TRANSCRIPTOME SIGNATURES AND SIGNALING PATHWAYS

IN HEART FAILURE

by

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ABSTRACT

Current heart failure treatment is based on targeting symptoms and left ventricle dysfunction severity, relying on a common HF pathway paradigm to justify common treatments for HF patients. This common strategy may belie an incomplete understanding of heterogeneous underlying mechanisms and could be a barrier to more precise treatments. We hypothesized we could use RNA-sequencing in human heart tissue to delineate HF etiology-specific and subphenotype-specific gene expression signatures. RNA-seq was performed in 64 human left ventricular samples: 37 dilated, 13 ischemic, and 14 non-failing. The dilated samples were also stratified by sub-phenotype and included 19 arrhythmogenic and 16 non-arrhythmogenic samples. Using a multi-analytic approach including covariate adjustment for age and sex, differentially expressed genes were identified characterizing HF, disease-specific, and subphenotype-specific expression. Pathway analysis investigated enrichment for biologically relevant pathways and functions. Our results demonstrate the commonality of mitochondrial dysfunction in end-stage HF but more importantly reveal key etiology- and phenotype-specific signatures. Dysfunctional cell-cell and cell-matrix adhesion signatures typified general dilated cardiomyopathy whereas signals related to immune and fibrotic responses were seen in ischemic cardiomyopathy. Arrhythmogenic dilated cardiomyopathy was characterized by fibrosis and upregulation of TGFβ1 and TP53 signaling activation, which were not recapitulated in an induced pluripotent stem cell-derived cardiomyocyte LMNA^{+/-} model. These findings suggest that transcriptome signatures may distinguish end-stage heart failure, shedding light on underlying biological

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differences between HF etiologies and sub-phenotypes, and that further characterization of the $LMNA^{+/-}$ cardiomyocytes will be necessary for its use as an accurate model system.

The form and content of this abstract are approved. I recommend its publication.

Approved: Matthew R. G. Taylor

DEDICATION

This dissertation is dedicated to my dad, who taught me how to be patient and loving by example; who valued my education and happiness above all else; who was always encouraging and supportive; who always made time; and who instilled in me an incessant curiosity about the world and always encouraged me to explore it.

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CHAPTER I

INTRODUCTION¹

Each day the average adult heart beats 100,000 times and pumps 2,000 gallons of blood throughout the human body. This encompasses the main function of the heart: to circulate blood throughout the body so that all tissues receive the oxygen they need to survive. A variety of genetic and environmental factors can affect how the heart functions. Sometimes, this can lead to drastically reduced heart function by way of mechanisms that are still incompletely defined.

Heart failure

Heart failure (HF) occurs when the heart muscle weakens from disease or injury and cannot pump enough blood to meet the body's oxygen needs. HF results from a variety of both primary as well as secondary causes, including coronary artery disease, heart attack, high blood pressure, abnormal heart valves, congenital heart defects, chemotherapy, diabetes, obesity, and heart muscle diseases or cardiomyopathies.

HF poses a significant public health burden, both in the number of people it affects as well as its associated costs; over the next decade, this burden is predicted to increase substantially. Currently, HF affects more than six million adult Americans each year, which accounts for approximately 2% of the population, and it incurs an annual health expenditure of

¹ Portions of this chapter were previously published in Encyclopedia of Life Sciences 2014 (http://www.els.net), Expert Opinion on Orphan Drugs 2015, 3(8): 869-876 and *Cardioskeletal myopathies in children and adults* 2016, chapter 12: Diseases of the nuclear membrane (pp. 233-248). These are included with the permission of the copyright holder.

more than \$30 billion. Every person regardless of sex has a one in five chance of developing HF by the age of 40^1 . By 2030, projections show that the number of Americans with HF will increase to more than eight million due to the ageing population, and annual health expenditures for HF will more than double to nearly \$70 billion².

Broadly, HF can be divided into two types that each account for approximately half of HF cases^{2,3}. In both types, the amount of blood that is pumped out of the left ventricle is reduced, but by different mechanisms. Instead, these types differ based on left ventricular ejection fraction, or the proportion of blood that is pumped out of the left ventricle with each heartbeat. HF with preserved ejection fraction (HFpEF) maintains a normal proportion, but the left ventricle walls thicken or stiffen, causing a decrease in the overall amount of blood the ventricle can intake. HF with reduced ejection fraction (HFrEF) results when the heart cannot contract efficiently, so the proportion of blood it outputs is severely decreased; a normal left ventricular ejection fraction is 52-72% for men and 54-74% for women, but a person with HFrEF has an output less than 40%⁴. Clinical presentation, causes, treatment, and outlook characterizing HFpEF and HFrEF subsets of patients are distinct⁵. Unless indicated, the term "HF" throughout this work will refer specifically to HFrEF.

Despite decades of research to develop new therapeutics and treatment strategies for HF, the overall impact on HF mortality has been relatively small. The five-year mortality rate for HF is nearly 50%, which has only decreased by 9% over the past four decades^{1,6}, and pharmacological treatment for acute HF has remained generally static since the 1970s^{7,8}. Moreover, although new therapeutic targets have been discovered, many of those that have positive results in Phase II trials often fail to replicate in Phase III trials, largely owing to poor understanding of HF pathophysiology and unrecognized heterogeneity of patient populations^{7,9}.



Figure 1. Proposed paradigm shift in HF treatment. Currently, HF treatment is symptombased on a severity scale (Class I – Class IV) with no regard to etiology or underlying biology of the disease. A proposed precision medicine model includes classification based on biology of the disease for a precision-medicine-directed approach to treatment.

Historically, most studies have focused on understanding and treating HF as a single entity with a "final common pathway" approach. This is evident particularly in the ways that HF severity is classified and treatment options are approached. Currently, HF is classified on the New York Heart Association (NYHA) severity scale originally established in 1928¹⁰. Patients are classified on a scale from Class I - Class IV, with severity of symptoms increasing with classification. As the symptoms of the patients worsen, they receive different medications to treat their symptoms. The focus is on treating the final common pathways of HF in a "one-size-fits-all" treatment model^{7,9} despite the fact that HF is a complex clinical syndrome with a myriad of primary and secondary causes (Figure 1, top panel). This disregards HF etiology and the potential pathological contribution of etiology-specific mechanisms. The residual high mortality rate of HF may reflect subgroups of patients that are not benefitting, or are potentially deteriorating, from therapies typically advised to all HF patients. In a more ideal, precision medicine model of HF therapy, the underlying biology of etiology-specific mechanisms would instruct treatment rather than severity of common HF symptoms for a more personalized approach to treatment; in this way, HF could be treated according the collective biology of different types of HF (Figure 1, bottom panel). This treatment model would require an in-depth understanding of HF mechanisms and how to rectify them clinically.

Gene expression analyses to interrogate disease mechanisms

One way to better characterize and understand the driving mechanisms in etiologyspecific HF progression is by studying gene expression. The central dogma of molecular biology as proposed by Francis Crick in 1957 described the flow of information from DNA to RNA to proteins. DNA is transcribed into RNA, and RNA is translated into protein¹¹. Six decades later, the scientific community has made great strides in showing that although this idea is oversimplified by current standards, it still represents the basic foundation of information necessary for a cell to function.

The transcriptome is comprised of all the RNA in a cell or tissue within a given timeframe or condition. Variations in the genome are reflected in the transcriptome, and alterations in the epigenome and the environment can lead to changes in the transcriptome. By studying the transcriptome, it is possible to quantify and analyze gene expression. Transcriptomes between cell and tissue types are unique and dynamic, changing throughout developmental and pathological stages. In fact, the transcriptome has been used to characterize the various cell types that comprise organs^{12,13} and how cell type composition of tissue changes over time,¹⁴ as well as to categorize disease stages¹⁵ and subtypes¹⁶.

The advantage of studying the transcriptome in disease is the potential connection between gene expression and phenotype. In cardiology, changes in expression of a handful of genes associated with pathological hypertrophy and sometimes referred to as the "fetal gene program" classify failing from non-failing hearts. These include increased expression of *MYH7*, *NPPA* and *NPPB* and decreased expression of *MYH6* and *ATP2A2*, among others¹⁷⁻²¹. *NPPB* specifically has been utilized clinically as a biomarker of HF, and it is a significant predictor of cardiovascular mortality.²² However, attempts to classify distinct types of disease within HF has failed to identify single, high-impact genes or groups of genes that stratify disease types. As a result, there has been a shift in the field from searching for single, high-impact genes to larger groups of moderate-to-small impact genes that act together in pathways.

This approach has been effective at elucidating biological mechanisms in other disease areas. Perhaps the field where the transcriptome-phenome has been most actively studied is cancer. Researchers have been able to molecularly classify sub-types of cancer based on differences in gene expression in order to identify clinically useful signatures²³. For example, cancers originating from different tissues can share molecular characteristics, so many studies have focused on characterizing cancer types not only by tissue-of-origin, but also by perturbed signaling pathways²⁴⁻³⁴. This sub-typing of cancers has led to improved prediction algorithms of clinical outcomes^{25,28,33} like chemosensitivity^{30,35}, survival³⁴, and biomarker development^{23,36}. Cancer is likely to have a substantially more diverse array of causal mechanisms than HF, mainly due to the fact that the nature of the disease is based on accumulation of cellular mutations leading to unrestrained proliferation or survival, which can occur in any organ system. However, one barrier cardiology researchers are currently facing is recognizing that diverse phenotypes may have diverse causal disease mechanisms. This is particularly relevant in dilated cardiomyopathy, which has a diverse genetic foundation and disease course despite common pathogenic features.

Mechanisms in dilated cardiomyopathy

DCM is a severe disease of the heart muscle that is characterized by dilation of the left ventricle and diminished systolic function. The wall of the left ventricle progressively weakens and thins, and the heart cannot pump blood efficiently to meet physiological needs. DCM is the most common form of cardiomyopathy³⁷ and a leading cause of HF, transplantation, and death.³⁸⁻⁴⁰. It has a prevalence of at least 1 in 2500 individuals^{41,42}, however, due to inconsistent use of diagnostic criteria⁴³ and lack of a well-designed large-scale epidemiological study, this is likely a grossly underestimated statistic; the true prevalence may be as high as 1 in 500 individuals^{44,45}.

Clinical presentation of DCM can be variable, ranging from patients who are

asymptomatic to patients who have severe progressive HF requiring transplantation. It can also present with arrhythmias, conduction system disorders and sudden death⁴⁰. Patients commonly live with DCM for several years before experiencing symptoms. Pre-symptomatic diagnosis by echocardiogram would demonstrate an enlarged diastolic left ventricular diameter and reduced diastolic function. Specifically, DCM is defined by the presence of two major clinical criteria: left ventricular end diastolic diameter greater than 117% of the predicted value corrected for age and body surface area based on Henry's formula (corresponding to two standard deviations from the expected normal limit plus 5%)⁴⁶ and left ventricular fractional shortening less than 25% and/or left ventricular ejection fraction less than 45%. DCM is only diagnosed in the absence of any other known cause of myocardial disease⁴⁶⁻⁴⁸. Primary DCM results when all acquired factors have been excluded and can be either 'idiopathic' or 'familial', depending on whether or not additional family members are affected^{44,49,50}.

Familial cases account for 20-35% of DCM. However, the frequency of familial forms is likely underestimated due to small pedigrees and families with undiagnosed members, where an underlying genetic cause may be less apparent and more difficult to elucidate due to variable expressivity and reduced penetrance of the disease gene.^{46,51-53} The most common form of inheritance pattern of DCM is autosomal dominant, but autosomal recessive and X-linked forms have also been described⁵⁴. As a result of significant progress in genome sequencing technology, genetic studies in families have led to the discovery of more than 50 genes and hundreds of mutations that cause DCM, most of them 'private' mutations that are unique to an individual or family^{44,50,55}. Despite recent success in discovering genetic causes of DCM, identified mutations account for only 40% of all familial cases, suggesting many more genetic causes remain unknown⁴⁴.

Molecular genetics

DCM is characterized by allelic heterogeneity, meaning that a variety of different mutations within the same gene contribute to a common DCM phenotype. Furthermore, DCM causing mutations have been discovered in multiple CM proteins and cellular pathways, with most mutations representing rare causes of DCM and each contributing a low frequency of the overall prevalence of DCM^{50,56}. These compounding factors make a statistical genotype-phenotype prediction complicated and reduce the likelihood that a sufficient relationship can be established between any particular mutation and measures of prognosis. This is further complicated by the relationship between DCM and HCM. For example, mutations within the same gene can yield either a DCM or HCM phenotype, depending on the location of the mutation. And in some cases, even the same mutation can yield distinct DCM or HCM phenotypes in different individuals of the same family, indicating possible unidentified genetic modifiers⁴⁴.

Molecular mechanisms of DCM are widespread and diverse but all result in a common dilated left ventricle phenotype. Most mutations associated with DCM are nonsynonymous missense mutations, resulting in a single amino acid change in the downstream protein, but frameshift, nonsense, insertions and deletions have also been associated with DCM⁵⁷. Genes causing DCM may be classified according to their structure and how proposed functional abnormalities contribute to disease development⁵⁸, but the genes involved are widespread and disparate. Here we will describe a number of disease genes that encode a diverse array of

proteins including the sarcomere, cytoskeleton and ion channels, with special focus on the nucleus, where the lamin A/C protein resides.

Sarcomeric genes. The sarcomere is the most basic component of cardiac muscle and includes the protein structures that initiate and sustain cardiac contraction. Mutations in sarcomeric genes lead to dysfunctional contraction and are the most common causes in both HCM and DCM⁵⁰. Mutations discovered within sarcomeric genes include myosin proteins (*MYH6*, *MYH7* and *MYBPC3*), actin proteins (*ACTC1* and *ACTN2*), actin cross-linking proteins (*FLNC*)^{59,60} troponin (*TNNC1* and *TNNI3*) tropomyosin (*TPM1*)⁵⁰, and the giant protein titin (*TTN*).

TTN stands out as is one of the largest genes in the human genome, producing the largestknown human protein with a size approximately 35000 amino acids⁶¹. The titin protein is highly expressed within the heart and serves as a spring-like protein within the sarcomere, providing passive force while modulating contractile force⁶². *TTN* is the most commonly mutated DCM gene, with heterozygous *TTN* truncating variants (TTNtv) accounting for 15-20% of DCM patients, making TTNtv the most common genetic cause of DCM. However, TTNtv are also found in 2-3% of the general population, which poses a significant challenge for clinical interpretation of TTNtv^{61,63,64}. This, along with the sheer size of TTN, has prompted deeper characterization of the location and pathogenesis of TTNtv. Generally, TTNtv located in constitutive exons are pathogenic; those located in exons that are minimally expressed or that can be rescued by differential splicing have reduced penetrance, but specific variants may be position-dependent with respect to proximal or distal ends of the protein⁶⁵. TTNtv in DCM are overrepresented in the A-band and in constitutive exons relative to the general population, and variants affecting minor isoforms are enriched in control subjects^{61,64,65}.

Cytoskeletal genes. Mutations in cytoskeletal proteins may cause DCM by preventing effective force transmission within and between cells thus disrupting the intricate coordination required for CMs to effectively maintain heart function. Important cytoskeletal genes that cause DCM are *DES, LDB3/ZASP*, and *DAG. DES* encodes desmin, an intermediate filament that stabilizes the sarcomere, bridges adjacent myofibrils, and attaches z-bands to the plasma membrane and nuclear envelope⁶⁶. *LDB3/ZASP* encodes a structural protein that plays an integral role in bridging the sarcomere to the network of cytoskeletal proteins. Clinically, mutations in *LDB3/ZASP* lead to DCM with severe left ventricular hypertrophy⁶⁷. *DAG* encodes the dystrophin-associated glycoprotein, an important complex that creates a structural link between the extracellular matrix and the intracellular cytoskeleton. Mutations in *DAG* causing DCM may present with skeletal manifestations^{56,58}.

Ion channel genes. In addition to dysfunction in the CM contracting unit and structural components of the cell, several mutations in genes that encode ion channel proteins can also cause DCM. Mutations in phospholamban (*PLN*) have been described in association with familial DCM⁶⁸. Phospholamban is a transmembrane protein that controls a calcium pump (SERCA2a) and thus regulates calcium reuptake from the CM⁶⁸. Mutations in *PLN* lead to inhibition of the SERCA2a pump and dysregulated cellular calcium levels. Further, they demonstrated that a DCM phenotype is recapitulated in mice by mutating PLN.⁶⁸ Similarly, mutations in *SCN5A*, which codes for a cardiac sodium channel, also cause DCM⁶⁹. Although mutations in *SCN5A* are more commonly associated with a Brugada syndrome, mutations related to DCM are associated with atrial fibrillation and conduction abnormalities. Mutations in these ion channel genes support that uncoordinated ion levels can lead to DCM^{69,70}.

Other genes. Development of DCM has also been attributed to several other genes involved in a variety of cellular functions, such as membrane, signaling and ion channels genes, including *ABBC9, TAZ, KCNJ2, PSEN1* and *PSEN2*⁵⁸. Mutations in genes encoding mitochondrial proteins have also been associated with DCM, including *TAZ, SDHA, MTT1, MTTL1* and *MTTH*⁵⁰. Additionally, extracellular matrix proteins have recently been described as genetic causes of DCM including lamin alpha-4 (*LAMA4*) and fukutin (*FKTN*)^{71,72}. For LAMA4, knockdown of the gene in zebrafish identified a phenotype consistent with DCM, and subsequent screening of the gene mutations in a panel of DCM patients identified the gene as a novel cause of the disease. It is proposed in this study that *LAMA4* mutations disrupt signaling pathways, cause a reduction in cardiomyocyte (CM) survival, and ultimately lead to cardiomyopathy⁷². BCL2-associated athanogene 3 (*BAG3*) mutations have recently been discovered as a cause of DCM and such mutations have been associated with up to 2.8% of DCM in Japanese patients⁷³⁻⁷⁵. Cellular studies suggest that *BAG3* plays a role in z-disc assembly, and mutations increase CM sensitivity to stress-induced apoptosis, which leads to loss of tissue and development of DCM⁷³.

The nuclear LMNA gene

The nuclear lamina is comprised of both A- and B-type lamins, which are intermediate filament proteins localized to the nucleus. A-type lamins are encoded by the *LMNA* gene, containing twelve exons that undergo alternative splicing to produce four isoforms: A, A Δ 10, C, and C2 ^{76,77}. Of these four, lamins A and C (lamin A/C) are most relevant to disease pathology because they are expressed in all differentiated somatic cells^{76,78}. Lamin A/C is particularly abundant in the basal epidermis, upper dermal layer, skeletal muscle, and cardiac tissue⁷⁸⁻⁸⁰ The expression of lamin A/C correlates with tissue elasticity; stiffer tissues like muscle and bone, which frequently undergo high amounts of mechanical stress, have higher expression than softer tissues⁸¹.

Lamin A/C share their first 566 amino acids but diverge in their C-terminus, where Lamin A has an additional 98 amino acids⁷⁶. Lamins are known to self-associate into coiled homodimers⁸² and provide a structural meshwork in the inner layer of the nuclear envelope in order to connect the nuclear envelope to the nuclear matrix and chromatin⁸³. LMNA also plays a role in cell division, nuclear growth, and attachment of other important proteins to the nuclear envelope⁸⁴.

Mutations in genes that encode proteins of the nuclear envelope, which consists predominantly of lamin but includes a few other lamin-associated proteins, cause a group of diseases called laminopathies. Mutations in *LMNA* are associated with at least 11 different diseases characterized by a large spectrum of phenotypes that can be classified as either tissue-specific or system-wide, and nine of which have either a primary or a secondary cardiac and/or skeletal muscle involvement^{76,85,86}. Tissue-specific laminopathies affect the striated muscle, adipose tissue, or peripheral nerve, while system-wide disorders are usually characterized by a progeria, or premature ageing, phenotype ^{76,85,87}. Perhaps the widespread role of lamin in so many cellular processes from structural integrity to chromatin organization and gene expression leads to its diversity in disease pathogenesis. Understanding how single mutations in a specific protein lead to this broad heterogeneity is challenging, and three distinct yet inclusive proposals have been made to explain the variability of lamin pathology: the structural hypothesis, the gene expression hypothesis, and the cell toxicity hypothesis.

The structural hypothesis is based on the idea that lamin, along with other nuclear envelope proteins and complexes that connect the inner and outer membranes, provide the

necessary structural network and support for the nucleus to maintain integrity. When the nuclear lamina is weakened, the cell has a reduced ability to withstand mechanical stress. This hypothesis is supported by the fact that a large proportion of the diseases resulting from mutations in *LMNA* have striated muscle phenotypes. Contracting cells undergo high frequencies of mechanical stress, which would be particularly damaging to cells with weakened structural framework^{77,87}.

The gene expression hypothesis focuses on the role of lamin and its associated proteins in the spatial organization of chromatin and resulting gene expression. A-type lamins and associated proteins are known to interact with transcription factors, chromatin, and histones to effect changes in cell signaling, mRNA expression, protein levels, and epigenetic elements. Mutations that lead to alterations in binding domains, dysfunctional or mislocalized proteins, and dominant negative effects all alter transcriptome dynamics and regulation. This variation can subsequently result in changes in gene expression^{77,87,88}.

The cell toxicity hypothesis proposes that mutated lamins or proteins involved in the nuclear lamina can build up over time and disrupt cell function. Accumulation of dysfunctional protein leads to toxicity and may eventually lead to cell death⁸⁷. These three hypotheses are not mutually exclusive. Because of the array of phenotypes associated with lamin, and overlap between diseases, it is thought that all of these hypotheses can be applied differentially to the laminopathies.

With regard to lamin mutations in cardiomyopathy, patients are at a high risk for sudden death due to ventricular arrhythmias ⁸⁹⁻⁹¹. Many long-term studies have attempted to analyze the relationship between types of mutations, cardiovascular symptoms, and prognosis in an effort to provide better clinical assessment and treatment counseling of *LMNA*-related cardiomyopathy

patients. For example, *LMNA* mutation carriers with cardiomyopathy are more likely than noncarriers to present with supraventricular arrhythmias, conduction disease, and elevated creatine kinase levels ⁸⁹. Carriers have also demonstrated a significantly worse prognosis compared to non-carriers, with a higher relative risk for cardiovascular-related death, cardiac transplant, or major cardiovascular events ⁸⁹. Risk stratification of malignant ventricular arrhythmia events shows that non-sustained ventricular tachycardia, left ventricular ejection fraction <45%, male sex, and non-missense or splice mutations are risk factors for *LMNA* cardiomyopathy patients ^{92,93}. Additionally, it has been reported that lamin mutations account for 33% of DCM cases with atrioventricular block, suggesting that this occurrence is more common in *LMNA*-related DCM than other causes ⁹⁴. Identifying risk factors in this particular cohort of patients has supported the clinical use of risk stratification to identify high-risk patients for preventative, potentially lifesaving implantable cardioverter defibrillator (ICD) implantation ^{44,93,95}.

Mouse models of laminopathies have been particularly useful to better understand the roles of lamin and lamin-associated proteins. Investigations into cell signaling pathways of *LMNA* defective mice show a number of disrupted pathways, which may prove useful therapeutic targets. Cardiac expression profiles of *LMNA*^{H222P/H222P} mice, which model Emery-Dreifuss muscular dystrophy and develop DCM, show upregulation of MAPK pathways, specifically the ERK, JNK, and p38α subfamilies ^{96,97}. This activation occurs prior to onset of cardiac defects⁹⁶. Inhibition of all three of these signaling pathways independently has been shown to improve cardiac function and survival rates⁹⁷⁻⁹⁹. An inhibitor of MAPK, ARRY-371797, is currently the subject of a Phase III clinical trial in *LMNA* patients.

Additional investigation into activated pathways of *LMNA*^{H222P/H222P} mice demonstrates that AKT/mTOR signaling is also hyperactive and precedes other detectable clinical symptoms.

Blockage of mTORC1 using temsirolimus, which specifically targets the mTOR pathway, prevents cardiomyopathy progression, presumably by reactivating autophagy. Treatment with temisirolimus daily for two weeks reduced heart size, decreased left ventricular end-diastolic and end-systolic diameters, and increased fractional shortening¹⁰⁰. These results were also confirmed in the *lmna*^{-/-} mouse, where rapamycin treatment reversed the upregulation of mTORC1 signaling by improving autophagy rates ¹⁰¹. The fact that aberrations in MAPK and AKT/mTOR pathways can be detected prior to all other clinical symptoms suggests that dysfunctional lamin perturbs signaling, which results in deterioration of cardiac function.

Studies focusing on single missense mutations have also been performed, and they help to extrapolate information on how a single residue change can affect lamin protein performance. A knock-in mouse model of *LMNA*^{*N195K*} successfully recapitulates the disease as seen in humans. This particular mutation, Asn195Lys, has been discovered in multiple families¹⁰². Like many mouse models of laminopathies and cardiomyopathies in general, heterozygous mice appeared unaffected, both by clinical and histological observation. Homozygous mutants typically died within 12 weeks due to arrhythmia, and histological examination of cardiac tissue revealed a disruption of sarcomere and intercalated disk organization. The transcription factor Hf1b/Sp4 was downregulated, indicating the mutant lamin affected gene expression¹⁰². Lamin and its associated proteins constitute a highly complex network in the cell. Their pathway involvement is extensive, intricate, and incompletely understood, particularly in the context of disease. Further investigation into lamin function, downstream effects of lamin dysfunction, and signaling pathways combined with ongoing animal models and exploration of therapeutic avenues will lead to a greater understanding of the role of lamin A/C in disease.

Туре	Source	#NF	#DCM	Findings	Ref
microarray	explanted tissue	5	7	Upregulation of genes in sarcomere, cytoskeleton, stress response, and transcription/translation regulators. Downregulation of cell-signaling channels and mediators, calcium signaling.	103
microarray	biopsy	4	10	Upregulation of genes in protein and lipid metabolism, energy production, muscle contraction, apoptosis, cell-cell matrix adhesion	
microarray	explanted tissue	5	6	Differential regulation of genes in apoptosis and oxidant stress, cell growth, maintenance, cytoskeleton, extracellular matrix, DNA replication and repair, ion transport, metabolism, mitochondria, RNA processing, signal transduction, translation and protein modification, and transcription factors	105
microarray	explanted tissue	6	21 NICM	Differential expression of genes in metabolism, cell growth, maintenance, signal transduction, and binding. Upregulation of genes in inflammation and immune response, cell adhesion, apoptosis, and development.	106
microarray	explanted tissue	20	20	Upregulation of genes in protein biosynthesis, Z-disc, and collagen. Downregulation of genes in immune system, inflammatory response, and chemokine activity. Differential regulation in genes in extracellular matrix.	107
microarray	explanted tissue	15	16 NICM	NICM classifier genes showed dysregulation of cytoskeleton, major histocompatibility complex, and antigen processing and presentation pathways.	108
microarray	explanted tissue	4	5	Dysregulation of genes in the tricarboxylic acid cycle, angiogenesis, apoptotosis, MAPK pathway, inorganic cation transporter, catabolism, energy metabolism, oxidative phosphorylation, and Alzheimer's disease pathways.	109
microarray	explanted tissue	5	12	Differential expression of ion channel genes involved in cardiac contraction	
microarray	explanted tissue	5	12	Differential expression of nucleocytoplasmic transport-related genes	111
RNA-seq	explanted tissue	8	13	Differential expression of nucleocytoplasmic transport-related genes	112
RNA-seq	explanted tissue	6	10	Enrichment for genes in muscle contraction, regulation of heart contraction, cell motion, and cell adhesion genes	113
RNA-seq	explanted tissue	3	2	Enrichment for genes in focal adhesion, the plasma membrane, and extracellular matrix.	114
RNA-seq	pre- LVAD biopsy	8	8 NICM	Enrichment for genes in the regulation of small molecule metabolic processes and transforming growth factor beta receptor binding. Analysis of differentially regulated miRNAs showed enrichment for small molecule metabolic processes and synaptic transmission.	115,116

Table 1. Summary of literature related to prior human transcriptome studies of DCM

NICM = nonischemic cardiomyopathy

Summary of gene expression studies

As outlined above, the diverse array of 50+ genes that can cause DCM, combined with the lack of an identifiable causal mutation in ~50-60% of cases, have made understanding disease mechanisms difficult and complex. Previous studies of the human cardiac transcriptome in DCM have attempted to better understand DCM HF pathways by analyzing differentially expressed genes (DEGs) between non-failing (NF) and DCM hearts. Most of these studies have predominantly been done with microarrays, modest sample sizes, and straightforward comparisons of healthy versus disease, and analyses between or among different groups of DCM have not been performed. These studies are summarized in Table 1.

Purpose of this dissertation

The research in the following chapters focuses on identifying disease-specific HF mechanisms. Current HF therapy is symptom-based without regard to the disease etiology or the underlying pathobiology that is causing the heart to fail. We propose there are gene expression signatures that characterize HF that can potentially be used to develop disease-specific HF treatments. This research focuses on the following specific aims: 1) Identify transcriptome signatures that differentiate ischemic cardiomyopathy (ICM) from DCM, 2) Identify transcriptome signatures that distinguish sub-phenotypes within DCM, and 3) Evaluate activation of p53 signaling, an enriched pathway identified in Aim 2, in an induced pluripotent stem cell-derived cardiomyocyte (iPSC-CM) model of aDCM. We used RNA-sequencing (RNA-seq) to evaluate gene expression in a set of 64 human explanted hearts from heart transplant patients. We show that distinct causes of HF and clinical sub-phenotypes within HF have distinct gene expression signatures, suggesting distinct biological mechanisms. We use one of these

signatures to evaluate a potential disease model and demonstrate that gene expression signatures differ between end-stage failing human hearts and our iPSC-CM model. This work is significant in that it provides a foundation for future investigations into the molecular basis of disease-specific HF mechanisms. Furthermore, a more personalized approach to therapy development to target these mechanisms will require robust disease models that accurately recapitulate human disease.

CHAPTER II

TRANSCRIPTOME ANALYSIS IN DILATED CARDIOMYOPATHY AND ISCHEMIC CARDIOMYOPATHY

Introduction

HF affects an estimated 6.5 million adult Americans. Although survival rates have improved by 10% between 1979 and 2000, the current 5-year mortality rate is still ~50%^{1,6}. A long-standing paradigm is that later-stage HF evolves via a "final common pathway" despite having diverse etiologies and genetic contributions^{117,118}. Clinical trial results and current guidelines for HF management reflect this viewpoint and direct therapy based largely on the degree of left ventricular dysfunction, assessed by ejection fraction, and clinical severity using the NYHA classification¹¹⁹. Despite HF due to ICM having a worse prognosis than DCM^{120,121}, current therapies are relatively indifferent to disease etiology, potentially reflecting an incomplete understanding of the heterogeneous biological mechanisms contributing to HF. Animal and cell-based HF models have provided key insights into general HF biology but have rendered a more limited contribution into subtypes of HF and into the substantial variation that is present in patient populations as compared to homogenous strains in animal and cell-based models. An improved understanding of underlying human HF biology could provide insight into diverse mechanisms and pave the way for new precision medicine strategies. We employed a global transcriptomics approach to uncover biological pathways that characterize human HF of general ICM or DCM etiology.

Prior microarray studies suggested distinct gene expression signatures between HF etiologies ^{106,108,122-125}; but others failed to find distinctions^{126,127}. RNA-seq provides superior

quantification of transcripts compared to microarrays and has been used to identify expression signatures between HF and NF hearts¹¹⁴, novel transcriptional regulators and perturbed miRNA networks in ICM or DCM ^{116,128}, pre- and post-left ventricular assist device (LVAD) transcriptomes¹¹⁵, common HF genes in pediatric cardiomyopathy¹²⁹, and splicing, eQTL, and allelic expression in DCM¹³⁰. Less progress has been made in refining differential expression between different adult HF etiologies, particularly in human tissue models where access is often limited and sample sizes are small. Additionally, prior studies focused on comparing end-stage diseased hearts and NF hearts, which allows for little intra-disease resolution. Overcoming the challenges of accessing human tissues, the previous largest RNA-seq study of HF etiologies consisted of 13 ICM, 13 DCM, and 10 NF, but the analyses focused on cytoskeletal and transport genes as translational targets in HF rather than distinguishing disease-specific pathways within HF^{112,113,131}.

We used RNA-seq in human left ventricles to resolve distinct etiologies within HF, specifically between ICM and DCM. Our hypothesis was that etiology-specific transcriptome signatures exist and can distinguish disease-specific HF mechanisms. Our analysis gives insight into a potentially etiology-specific pathogenesis of HF, providing evidence that a single final common pathway may not fully characterize HF and that HF can be sub-classified into etiologyspecific expression signatures. We performed RNA-seq on 64 explanted human hearts, using a multi-analytic approach to demonstrate there are common HF pathways as well as diseasespecific signatures in DCM and ICM (Figure 1a). Our results support shared and unique mechanisms in disease etiologies that contribute to HF.

Experimental procedures

Tissue collection

Explanted failing hearts were collected from adult patients undergoing heart cardiac transplantation at the University of Colorado Hospital as part of the Division of Cardiology Cardiac Tissue Biobank under a long-standing protocol approved by the Colorado Multiple Institutional Review Board (COMIRB, protocol 01-568) where transplant-listed patients signed written consent for use of their explanted hearts for research purposes. NF left ventricular samples were obtained from organ donors whose hearts could not be placed for transplantation due to size, ABO mismatch or other factors. Family members of organ donors signed written consent for research use of explanted cardiac tissue, obtained by the local organ procurement agency. Immediately upon explantation, left ventricular free wall aliquots of approximately 1 gram and remote from tissue scarring or infarcted segments were immersed in liquid nitrogen, transported to the laboratory, and stored at -80°C.

Patient cohorts

General clinical etiology (DCM or ICM) of patients transplanted for HF was determined by medical history, based on the absence or presence of significant previously documented obstructive coronary artery disease or myocardial infarction. NF organ donor hearts were defined by no major cardiac history and a left ventricular echocardiography-based shortening fraction of $\geq 25\%$. Statistical differences between cohort clinical characteristics were calculated by either Mann-Whitney U Test or Fisher's Exact Test, where appropriate, using a 0.05 significance level and a two-sided p-value.

RNA extraction

Frozen tissue was placed in liquid nitrogen and broken up using mortar and pestle to obtain a piece approximately 2 x 2 x 2 mm in size, macroscopically free of fatty infiltration, fibrosis, and blood. Tissue was placed immediately in TRIzol reagent (Thermo Fisher Scientific, Waltham, MA) and mechanically homogenized using an IKA T25 Ultra-Turaxx homogenizer. Tissue was homogenized for approximately 60 seconds, or until no visible chunks of tissue remained. RNA was extracted using the *mir*Vana miRNA isolation kit (Thermo Fisher Scientific) enriched for total RNA isolation according to manufacturer's instructions with the exception of replacing the Lysis/Binding Buffer with TRIzol. All samples were DNase treated using TURBO DNA-free Kit (Thermo Fisher Scientific). RNA was quantified at 260nm using a NanoDrop1000 (Thermo Fisher Scientific), and RNA integrity (RIN) was measured using an Agilent 2100 Bioanalyzer with the RNA 6000 Nano Assay (Agilent, Santa Clara, CA). All samples were required to demonstrate RIN \geq 7.0, and ranged from 7.0-9.3.

RNA sequencing

PolyA transcripts were isolated from 1µg total RNA using oligo-dT beads and the cDNA libraries were constructed using the TruSeq Stranded mRNA Library Prep Kit and protocol from Illumina (Illumina Inc., San Diego, CA). To minimize lane and batch effects, bar-coded libraries prepared from DCM, ICM, and NF samples were mixed and pooled across multiple lanes. Libraries were sequenced single-read with an Illumina HiSeq 2500 for 50 cycles at the University of Colorado Genomics and Microarray Core. The average number of reads per sample ranged from approximately 36 million to 66 million with an average of approximately 48 million (Appendix A: Table S2). Reads were filtered for quality and aligned to the GRchr37/hg19 version of the reference human genome using gSNAP ¹³² with an average of 95% of aligned reads (Appendix A: Table S2). Expression in terms of RPKM (reads per kilobase of transcript per million reads mapped) was derived using Cufflinks ¹³³ and Ensembl's GRch37.82 GTF. Due to the high proportion of cardiac mRNA reads known to map to the mitochondria, ¹¹⁵ mitochondrial genes were removed from the GTF file for a final set of 57,974 annotations.

Principal component analysis

Principal components were calculated in R using the svd (singular value decomposition) package and visualized in ggplot2. Principal components were used to visualize how the samples cluster for the most variably expressed genes: those genes with RPKM \geq 5 and a difference in RPKM between disease (ICM and DCM) and NF \geq 5 were included in the analysis.

DEG analysis

Expressed genes were defined as genes with mean RPKM \geq 5 in both groups. Differential expression was analyzed using Linear Model ANOVA in R. DEGs were defined as genes with a difference in RPKM between groups \geq 5 and a p-value adjusted for Benjamini-Hochberg false discovery rate (FDR) \leq 0.05. A multiple linear regression model was used to adjust for covariates of gene expression in R. Data was transformed log2(RPKM+1). Disease status and sex were categorical variables and age was a continuous variable. We identified: 1) genes shared between DCM *vs* NF and ICM *vs* NF, comprising the HF transcriptome signature or "HF-DEGs," 2) unshared, DCM- or ICM-specific genes, and 3) DEGs between DCM and ICM. We used Ingenuity Pathway Analysis (IPA; Qiagen, Redwood City, CA) on each gene list to investigate enrichment for pathways or functions biologically relevant to each disease. IPA uses up- and down-regulation of genes to predict activation or inhibition of pathways, so gene lists were not separated by fold change.

To validate our findings, we downloaded the processed gene count data from GSE55296 and microarray probe data from GSE1145 on NCBI GEO and extracted expression data for our genes of interest.

Random sample permutation

For each comparison we randomly permuted groups of the same size as each cohort, without replacement, and applied our DEG pipeline, repeating 1,000 times. Statistics between the observed and random sample distribution of DEGs were calculated using a one sample T-test. To graph the permutation counts logarithmically, a value of 0.1 was added to each count.

Data visualization

Genes were clustered using Spearman rank correlation and average linkage in either Cluster 3.0¹³⁴ or using the "cor" function with the pheatmap package in R. Clustering results were visualized in either Java TreeView¹³⁵ or pheatmap. Circos plots were created using the circlize package in R¹³⁶.

Pathway analysis

DEGs were interpreted using IPA. A dataset of Ensembl gene identifiers and fold changes was uploaded for Core Analysis.

Characteristics	DCM (n=37)	ICM (n=13)	p-value
Male sex, n (%)	30 (81)	10 (77)	0.71
Age at transplant	49 ± 13	56 ± 4	0.10
Race			
Caucasian, n (%)	31 (84)	13 (100)	0.32
Black/African American, n (%)	3(8)	0 (0)	0.56
unknown, n (%)	3(8)	0 (0)	0.56
Ethnicity			
Not Hispanic or Latino, n (%)	26 (70)	7 (54)	0.32
Hispanic or Latino, n (%)	5 (14)	1 (8)	1.00
unknown, n (%)	6 (16)	4 (31)	0.42
NYHA	3.3 ± 0.6	3.3 ± 1	0.67
*LVEF (%)	18 ± 8	13 ± 5	0.09
Comorbidities			
Coronary artery disease, n (%)	4 (11)	13 (100)	< 0.0001
Diabetes, n (%)	6 (16)	8 (62)	0.004
Hyperlipidemia, n (%)	8 (22)	9 (69)	0.005
*History of smoking, n (%)	17 (49)	8 (67)	0.33
Hypertension, n (%)	16 (43)	8 (62)	0.34
$^{*}BMI \ge 30, n (\%)$	5 (16)	2(22)	0.64
Medications			
Inotropes, n (%)	11 (30)	3 (23)	0.73
Statins, n (%)	10 (27)	12 (92)	< 0.0001
Antiarrhythmics, n (%)	32 (86)	12 (92)	1.00
Amiodarone, n (%)	11 (30)	3 (23)	0.73
Aspirin, n (%)	8 (62)	15 (41)	0.22
Beta Blockers, n (%)	20 (54)	8 (62)	0.75
ACE inhibitor, n (%)	17 (46)	8 (62)	0.52
Device Therapy			
ICD, n (%)	32 (86)	8 (62)	0.10
LVAD/BiVAD, n (%)	16 (43)	4 (31)	0.52

Table 1. Clinical characteristics of DCM and ICM cohorts

^{*}unknown for some patients. Plus-minus values are means ± one SD. P-values determined by Mann-Whitney U Test or Fisher's Exact Test (at significance levels of 0.05, 2-tailed hypothesis) where appropriate. ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; LVAD/BiVAD, left/biventricular assist device; NYHA, New York Heart Association



Figure 1. Schematic of RNA-seq analyses. A) mRNA from 64 human hearts was extracted, sequenced, and adjusted for covariates. By comparing DEGs at an FDR of 5%, three pathway analyses were conducted. Analysis 1 considered all shared DEGs between DCM *vs* NF and ICM *vs* NF as HF-DEGs (green-blue). Analysis 2 considered non-overlapping DEGs as DCM-specific (green) or ICM-specific (blue). Analysis 3 directly compares diseases (pink). B) Principal component analysis of all three cohorts, ICM (blue), DCM (green), and NF (grey). On the first two principal components, each of the three groups clusters together with overlap between ICM and DCM. ICM clusters further away from NF than DCM.

Results

Clinical characteristics of patients

Sixty-four hearts were investigated: 37 from DCM patients, 13 from ICM patients, and 14 NF (Appendix A: Table S1). Table 1 summarizes clinical characteristics between the patient groups. The ICM cohort had a significantly greater proportion of patients taking statins (p < 0.0001) and having coronary artery disease (p < 0.0001), hyperlipidemia (p = 0.005) and diabetes (p = 0.004).

Principal components of the cohorts

To investigate gene expression differences between HF etiologies, we performed single replicate poly-A RNA-seq on left ventricular tissue samples (Figure 1A, Appendix A: Table S2). We used principal component analysis to broadly understand gene expression relationships between cohorts and visualize sample clustering for the most variably expressed genes (Figure 1B). Using the first two components, the samples cluster distinctly between disease and NF and by disease with some overlap. ICM samples cluster further away from NF than DCM.

Random sample permutation

To test the strength of our disease classifications, we conducted a random sampling analysis. We show that our classifications achieve the highest number of DEGs of any random classifications and are highly significant within a 99.99% confidence interval. In DCM *vs* NF 96.4% of combinations had 5 or less DEGs, and the maximum combination had 1,105 DEGs (compared to the observed 3,649: M = 8.50, SD = 76.03, $p < 2.2e^{-16}$; Appendix A: Figure S1). In


Figure 2. Correlation matrix between samples. The heatmap matrix shows the Spearman correlation coefficient between samples for all expressed genes following adjustment. Samples cluster by phenotype. Cooler colors (blues, greens) represent relationships between samples that are most similar; warmer colors (reds, oranges) represent samples that are more dissimilar with lower coefficients.



Figure 3. Pathway analysis in HF-DEGs. A) Venn diagram of DCM *vs* NF and ICM *vs* NF DEGs highlighting 2,934 overlapping genes used in this analysis. B) Top 20 enriched pathways. Bars are filled according to z-score: teal indicates higher (activated), orange indicates lower (inhibited). Pathways without a z-score are grey, and pathways with a z-score of zero are white. The ratio of the number of enriched genes to the number of total genes in the pathway is listed on the right side. C) Circos plot of enriched biofunctions and their corresponding DEGs according to IPA. DEGs are colored by mean fold change from DCM or ICM *vs* NF D) Scatter plot of mean RPKM values of DCM against ICM logarithmically (R^2 =0.98) for the 2,934 HF-DEGs.

ICM *vs* NF, 98.1% of combinations had 5 or less DEGs, and the maximum combination had 1,940 DEGs (compared to the observed 4,150: M = 9.59, SD = 106.29, $p < 2.2e^{-16}$; Appendix A: Figure S1). In ICM *vs* DCM, 96.8% of combinations had 5 or less DEGs, with the maximum combination having 560 DEGs (compared to the observed 874: M = 5.51, SD = 42.63, $p = 4e^{-12}$; Appendix A: Figure S1). No combination produced as many DEGs as our NF and disease cohorts, suggesting our original clinical classifications were rigorous.

Multiple linear regression to adjust for covariates

Because age and sex are known to contribute to HF risk, we used multiple linear regression to adjust the gene expression for these confounding effects. Spearman correlation between the samples demonstrated that following covariate adjustment, the samples clustered into three distinct phenotypic groups with the NF and ICM groups being the most dissimilar (Figure 2). Before adjustment, DCM *vs* NF had 3,649 DEGs; after applying the model to adjust the expression for differences in age and sex, there were 3,495 DEGs. A majority (3,419; 98%) were significant before the model. ICM *vs* NF had 4,150 DEGs and 4,137 after the model was applied. A majority (3,808; 92%) were significant before the model. ICM *vs* NF had 499 (93%) were significant before the model. The adjusted gene expression values were used for the remaining analyses.

Analysis 1: HF-DEGs

There are 2,934 HF-DEGs (1472 upregulated, 1462 downregulated; Figure 3A). Many of these genes agree with previous HF gene expression literature, including decreased *MYH6* (fold change = DCM, -1.5; ICM, -2.0) expression and increased *NPPA* (fold change = DCM, 18.1;



Figure 4. Pathway analysis in disease-specific DEGs. A) Venn diagram of DCM vs NF and ICM vs NF highlighting 561 DCM-specific (green) and 1203 ICM-specific (blue) DEGs in this analysis. B) Unsupervised clustering heatmap of DCM- and ICM-specific DEGs. Samples cluster according to etiology. C) Enriched pathways ($p \le 0.005$). DCM-specific (left) and ICM-specific (right).

ICM, 11.2) and *NPPB* (fold change = DCM, 15.0; ICM, 22.4) expression^{18,19}. The four most significant pathways are Mitochondrial Dysfunction, Oxidative Phosphorylation, EIF2 Signaling, and Protein Ubiquitination Pathway (Figure 3B). Toxicity annotation in IPA revealed significant enrichment of well-characterized HF pathologies including cardiac fibrosis, hypertrophy, and necrosis/cell death. The genes involved in these pathologies that are dysregulated in the HF-DEGs are illustrated in Figure 3C.

The fold change direction for HF-DEGs was the same in both diseases for all genes. When plotting the average RPKM values for one disease against the other logarithmically, R^2 =0.98 (Figure 3D), indicating correlation of the relative magnitude of gene expression. This suggests these genes represent an expression pattern common to a failing heart irrespective of disease phenotype.

Analysis 2: Disease-specific

Identifying disease-specific DEG.s By removing the HF-DEGs from each comparison, DCM *vs* NF had 561 DCM-specific DEGs (202 upregulated, 359 downregulated) and ICM *vs* NF had 1203 ICM-specific DEGs (814 upregulated, 389 downregulated; Figure 4A, Appendix B: Table S1 and Table S2). To validate the disease specificity of these 561 and 1203 gene profiles, we performed hierarchical clustering of the combined genes for all samples to visualize gene expression clustering. The samples segregate into three large distinct clusters by NF, DCM, and ICM (Figure 4B). The NF and ICM samples cluster relatively homogenously compared to DCM, which clusters into smaller heterogeneous groups.



Figure 5. Pathway analysis in disease-specific DEGs. A) Network of genes involved in the predicted decrease of extracellular matrix adhesion in DCM. The absolute fold change of each gene is indicated by the size of its oval. E) Circos plot of predicted activated biofunctions in ICM for three categories: quantity, infection, and migration. Connection sizes correlate to the number of genes involved in each sub-category, which are listed on the outside of the circle.

Disease-specific DEG validation. To independently validate the disease specificity of the DCMand ICM- gene profiles, we used the previously published datasets GSE55296 and GSE1145 that are publicly available in the NCBI GEO database ^{112,113,131}. We were able to extract 1,548 corresponding genes from GSE55296 and 3,618 corresponding probes from GSE1145. Using the same hierarchical clustering methods, we demonstrated that this disease-specific expression profile was able to accurately segregate 10/13 DCM and 9/13 ICM samples from GSE55296 (Appendix B: Figure S2), and 14/15 DCM and 10/11 ICM samples from GSE1145 (Appendix B: Figure S2).

Pathway analysis for DCM-specific DEG.s At $p \le 0.05$, 47 pathways were predicted to be enriched. Those with $p \le 0.005$ are listed on the left side of Figure 4D. The most significantly enriched pathways are Germ Cell-Sertoli Cell Junction Signaling, implicating involvement of intercellular adhesion, and AMPK, which aids in monitoring heart energy consumption¹³⁷. Functional annotation of DEGs revealed decreases in adhesion, cell survival, and metabolism of reactive oxygen species. The differential expression of genes involved in the extracellular matrix are predicted to decrease extracellular matrix adhesion (Figure 5A).

Pathway analysis for ICM-specific DEGs. At $p \le 0.05$, 153 enriched pathways were predicted. Those pathways with $p \le 0.005$ are listed on the right side of Figure 4d. The most enriched pathways are ILK and Integrin Signaling and the most significantly activated pathways are RhoA and Death Receptor signaling. Many enriched pathways involve the immune system, including Antigen Presentation, CD28 in T Helper Cells, IL-6, CD40, JAK/Stat, fMLP in Neutrophils, and role of NFAT in Regulation of Immune Response. There is also enrichment for activation of



Figure 6. Pathways enriched in ICM *vs* **DCM.** A) Diagram highlighting 535 DEGs from ICM *vs* DCM. B) Top 20 enriched pathways. C) Graded activation of Antigen Presentation Pathway from relative low expression in NF, moderate expression in DCM, and high expression in ICM.

cytoskeletal regulation pathways: ILK, Integrin, Rho Family GTPases, RhoA, RhoGDI, Actin Cytoskeleton, Rac, and Remodeling of Epithelial Adherens Junctions. Functional annotation revealed increased infection and quantity and migration of multiple immune cells (Figure 5B). One pathway is shared between the disease-specific comparisons: EIF2, which is predicted to be activated in ICM and inhibited in DCM.

Analysis 3: ICM vs DCM direct transcriptome comparison

Lastly, we confirmed these results reflected significant differences in gene expression between the two HF general etiologies by directly comparing the DCM and ICM transcriptomes. We identified 535 DEGs (Figure 6A). 356 (67%) are upregulated in ICM relative to DCM. Using IPA, 121 pathways are significantly enriched ($p \le 0.05$), and Figure 6B illustrates the 20 most significant pathways. Thirteen of these pathways (Integrin, Clathrin-mediated Endocytosis, Antigen Presentation, Rho Family GTPases, RhoA, RhoGDI, CD28 in T Helper Cells, Actin Cytoskeleton, mTOR, Rac, Remodeling of Epithelial Adherens Junctions, Tight Junction, and Role of NFAT) were enriched in the ICM-specific Analysis 2 in the same z-score directions, suggesting their significance in this comparison is due to upregulated genes in ICM rather than downregulated genes in DCM.

Antigen Presentation Pathway. The Antigen Presentation Pathway was a significantly enriched pathway in all four analyses. We investigated its gene expression more deeply. The heatmap in Figure 6C depicts the average expression of each significant gene from the pathway in the three cohorts. It demonstrates a graded activation of Antigen Presentation Pathway genes, with relatively low NF expression, moderate DCM, and high ICM expression.

Discussion

There is a common HF transcriptome signature characterized by general metabolic dysfunction

Our HF-DEG analysis confirmed the hallmark fetal gene expression of HF controlled by β 1-adrenergic receptor signaling ^{20,138} and revealed additional critical common HF pathways supporting overall metabolic dysfunction in the failing heart. All 2,934 HF-DEGs were in the same fold change direction at similar expression magnitudes for both diseases compared to NF, suggesting these genes are characteristic of a failing heart (Figure 3D). Many of these genes also correspond to known HF pathologies (Figure 3C), The top four pathways enriched in this gene set were Mitochondrial Dysfunction, Oxidative Phosphorylation, EIF2 Signaling, and Protein Ubiquitination Pathway (Figure 3B). When comparing gene expression of HF to NF, mitochondrial pathways have commonly been disrupted, not only in microarrays of human tissue ^{139,140} but also in microarray and RNA-seq of animal models of HF ^{65,141,142}. Insufficient energy production in the failing heart has long been known to contribute to left ventricular dysfunction. Oxidative phosphorylation is decreased in chronic HF 30-50%¹⁴³ and decreased mitochondrial enzyme levels have been associated with HF severity ¹⁴⁴ and mortality ¹⁴⁵. Targeting mitochondrial function in HF has been recognized as having tremendous untapped potential and is currently a forefront target for novel HF therapies ¹⁴⁶. EIF2 signaling is required for translation, but is inhibited, suggesting decreased protein production. The Protein Ubiquitination Pathway is enriched, suggesting an increase in protein degradation due to cell death or tissue necrosis.

Cell-cell and cell-matrix adhesion is perturbed in DCM

The DCM-specific pathway analysis showed the top enriched pathway for DCM was Germ Cell-Sertoli Cell Junction Signaling (Figure 4D, left side). Germ cell-sertoli cell junctions in the testis are desmosome-like, comprised of many of the same proteins as cardiac desmosomes, and are essential for cell-cell adhesion and intercellular signal transduction ¹⁴⁷. In this pathway, genes encoding microtubule subunits, or tubulins, are downregulated: *TUBA1B* encoding an α tubulin, *TUBB4B* encoding a β -tubulin, and *TUBG1* encoding a γ -tubulin. In NF, *TUBA1B* and *TUBB4B* are two of the three highest expressed tubulins. This agrees with a recent publication reporting that *TUBA3D* and *TUBA3E* were significantly downregulated in DCM ¹³⁰. Evidence suggests microtubules are responsible for transporting gap junction protein connexin-43 to the cell surface ¹⁴⁸, and gap junction remodeling, including reduced expression of connexin-43 in myocytes, occurs in DCM ^{149,150}. This junction signaling pathway was also confirmed as being enriched in the direct comparison between ICM *vs* DCM.

Increased expression of *MYOC*, *POSTN*, *SGCE*, and *VCAN* (fold changes = 2.1, 2.7, 1.2, 1.7 respectively) and decreased expression of *ADAM9*, *EMP2*, *NID1*, and *SPP1* (fold change = - 1.5, -1.2, -1.3, -3.6, respectively) may contribute to decreased cell-matrix adhesion (Figure 5A). *SGCE* encodes the epsilon component of the sarcoglycan transmembrane complex, which connects the CM to the extracellular matrix. *MYOC*, *POSTN*, *VCAN*, *ADAM9*, *NID1*, and *SPP1* all reside primarily in the extracellular space. In particular, *SPP1* expression plays a protective role in cardiac dilation, possibly by promoting fibroblast growth and adhesion ¹⁵¹. *POSTN* encodes periostin, which is known to be highly expressed in HF caused by DCM. Overexpression of *POSTN* inhibits myocyte spreading and fibroblast adhesion, and it contributes to cardiac dysfunction ¹⁵². Additionally, cell adhesion and cytoskeletal processes have been

previously implicated in DCM ^{114,128} and mutations in cytoskeletal genes are known to cause DCM ⁴⁴, potentially through disrupted mechanotransduction.

The immune system and cytoskeleton are activated in ICM

The ICM-specific pathways can be categorized into two main types, immune response and cytoskeletal regulation (Figure 4D, right side). Involvement of these in ICM may stem from response to two stimuli, which are not mutually exclusive: the damaged, infarcted myocardium, to which the immune system responds through inflammation followed by fibrotic scar formation, and atherosclerosis, which is the buildup of cholesterol on artery walls, currently believed to be a chronic inflammation of arterial walls eliciting a similar immune response ^{153,154}. Myocardial infarctions are caused by coronary artery obstruction due to atherosclerosis, buildup of cholesterol-laden plaques on artery walls and subsequent plaque rupture with thrombus formation. In both cases, inflammation from infarcted tissue or plaque buildup and rupture induces proinflammatory cytokines like IL-1β, TNFα, CD40LG, and IL-6¹⁵⁴⁻¹⁵⁶, which are all predicted to be activated in our IPA regulator analysis (p = 0.001, z-score = 2.7; p = 0.001, zscore = 4.0; $p = 9e^{-6}$, z-score = 1.8; p = 0.007, z-score = 3.3 respectively, data not shown). The TNF α membrane receptor is also upregulated (*TNFRSF1B*, fold change = 2.2) and CD40 and IL-6 Signaling are predicted to be activated. This cytokine production stimulates cell adhesion molecules like ICAM-1 (*ICAM1*, fold change = 2.9) to translocate to endothelial cell surfaces, either at inflamed atherosclerotic plaques or arteries in proximity to damaged tissue, to recruit and interact with leukocytes ^{153,154}. Leukocyte accumulation involves a controlled process of tethering to the endothelium and migrating through the endothelium to infarcted tissue. This migration requires Rho signaling activation^{155,157}. RhoA and Signaling by Rho Family GTPases

are both predicted to be activated, and RhoGDI, an inhibitor of these pathways, is predicted to be inhibited. This is supported by the IPA functional annotation of DEGs, which showed increased immune cell quantity and migration, specifically lymphocytes and leukocytes (Figure 5B). A number of previous studies have shown Rho kinase inhibitors reduce ischemia/reperfusion injury by reducing infarct size, ¹⁵⁸ apoptosis, proinflammatory cytokines, and neutrophil response ^{159,160}. However, Rho signaling is also a mechanism in fibrosis, and ROCK1 haploinsufficient and knockout mice demonstrated decreased fibrosis and fibroblast differentiation following myocardial stress ^{161,162}. These findings are supported by previous transcriptome studies showing ICM enrichment for extracellular matrix-receptor interaction, actin filament processes, chemotaxis, inflammatory response, and cytokine activity ^{113,114}.

The ICM transcriptome signature is more distinct from NF than DCM

Overall, the expression profile of ICM is more extreme compared to NF than DCM. This is evident in two aspects: 1) the principal component plot (Figure 1B) demonstrated although the gene expression of ICM and DCM is distinct from NF, ICM was more dissimilar; this is even more evident following covariate adjustment (Figure 2). 2) in the disease-specific analysis, there were more than twice as many ICM-specific genes as DCM-specific (1203 *vs* 561), which demonstrated more genes characterize ICM-specific expression. This is contrary to transcriptome comparisons following LVAD support, where mRNA profiles between ICM and NICM were not distinct ¹¹⁵. This difference may be due to the fact that our samples were obtained from a later stage of HF. We also note that the DCM samples show greater heterogeneity in their transcriptomes than ICM samples (Figure 1B, Figure 2). This heterogeneity could be attributed to differences in pathogenic mutations in the DCM samples; as genotyping was not performed in

this study, the contribution of genetic heterogeneity to the transcriptome patterns remains speculative.

A specific example of this observation that ICM is more distinct from NF than DCM is related to our consistent discovery of enrichment for the Antigen Presentation Pathway, which was significant in every transcriptome comparison. Antigen presentation is an adaptive immune response where cells use Human Leukocyte Antigens (HLAs) to present endogenous or exogenous antigens for T cells to recognize. Figure 6C displays differentially regulated genes within this pathway. Graded activation from low expression in NF, moderate in DCM, and high expression in ICM suggests this pathway is important in HF but may play a larger role in ICM, where additional inflammation, injury, and tissue necrosis are involved. Transcriptome analyses from earlier microarray studies revealed immune system enrichment for antigen processing and presentation pathways and HLA gene expression ^{107,108}. However, more recent RNA-seq analyses of human tissue have failed to replicate this finding ¹¹³. Additionally, a variant residing within a non-protein-coding gene within the chromosome 6 major histocompatibility complex was identified via GWAS in DCM patients. Presence of this variant influenced expression of HLA-C, HLA-DRB5, HLA-DRB1, and HLA-DQB1¹⁶³, all of which were DEGs in DCM vs NF, ICM vs NF, or both.

Statins, coronary artery disease, diabetes, and hyperlipidemia are not associated with strong gene expression changes

In addition to sex and age, we considered other possible covariates that may affect gene expression. As noted before, statins, coronary artery disease, diabetes, and hyperlipidemia are statistically significant between our cohorts. These data are not available for the majority of the

NF controls, which are derived from heart transplant donors; many of whom experience surgical harvesting at external hospital sites. Thus, including these covariates in the overall model is not possible due to missing data. Considering these covariates in a DCM-ICM only analysis is problematic because they are highly correlated with disease group, leading to multicollinearity and unstable coefficient estimates. As an alternative exploration of the degree to which these may affect expression, we fit a regression model with age, sex, and each potential covariate individually to predict expression for ICM and DCM subjects. With statins and coronary artery disease, only 15 and 7 genes (FDR ≤ 0.05) were significantly associated with each respectively. No genes were significantly associated with diabetes or hyperlipidemia. These results indicated that in our data statin use, coronary artery disease, diabetes, and hyperlipidemia were not strongly associated with gene expression changes.

It is interesting to note 12/13 of our ICM patients were on statins at time of transplantation, and the most recent lipid results for most patients were within normal ranges. Total cholesterol results for the ICM cohort prior to transplantation ranged from 81-168mg/d (average = 123mg/dL), which is within normal (<200mg/dL). LDL cholesterol results for the ICM cohort prior to transplantation ranged from 22-105 mg/dL (average = 64mg/dL), which is also within normal (<100mg/dL). Although this would indicate the statins worked to reduce cholesterol, statins are known to have anti-inflammatory effects. These include reducing the expression of genes encoding proinflammatory cytokines and adhesion molecules, like ICAM1, and reducing downstream signaling pathways like Rho ¹⁶⁴, all of which are increased or activated compared to DCM and NF. Perhaps statins are working in these patients to decrease cholesterol, but not effective in their anti-inflammatory properties.

Study limitations

Accessing human cardiac tissue specimens and developing large tissue banks are timeintensive and costly activities, circumstances that have likely limited prior analyses. In our simulation analysis >95% of random permutation datasets identified five or fewer DEGs, strongly supporting that our findings of 3,649, 4,150, and 874 DEGs are unlikely due to chance (Figure S1; DCM vs. NF, ICM vs. NF, and ICM vs. DCM, respectively). Our study of DCM and ICM captured mRNA of the HF left ventricle in an advanced disease state, which may be distinct from mRNA at disease onset or throughout disease progression. Thus, while our data provides inferences about end-stage HF, the biology of HF initiation and progression were not directly evaluated in our data. Because clinical cardiac biopsies yield small tissue volumes, most frequently target the right ventricle, and are performed in only a subset of HF patients, studying the transcriptome in early-stage HF and in HF progression poses additional challenges beyond those of studying explanted hearts. Furthermore, while our transcriptome analyses identified statistically significant transcriptome differences between NF, DCM, and ICM, and did not take into account groups of genes that demonstrate similar directionality without statistical significance. The RNA-seq data are limited by lack of sufficient sequence depth to address differences in alternative splicing the poly-A capture limits interrogation of many noncoding RNAs. Additional studies will be necessary to identify the key epigenetic, noncoding, and protein drivers in these pathways.

The NF donor hearts we studied are distinct from normal healthy hearts as they were harvested from persons who experienced acute and ultimately fatal events that rendered them transplant donors. Although a majority of the cell volume of myocardial tissue is from cardiac myocytes, the heart is comprised of many different cell types, and although we macroscopically

controlled for tissues free of overt fibrosis, our results may reflect differences in tissue composition or pathways enriched in specific cell types.

CHAPTER III

TRANSCRIPTOME ANALYSIS IN AN ARRHYTHMOGENIC SUBPHENOTYPE IN DILATED CARDIOMYOPATHY

Introduction

Cardiac arrhythmias frequently result from underlying cardiac pathology, causing physical symptoms, a need for medications and/or device therapy, and sudden cardiac death¹⁶⁵. In DCM, life-threatening arrhythmias can present early in disease,¹⁶⁶ and approximately one-third of patients experience frequent ventricular arrhythmias, which may occur independent of left ventricular dysfunction¹⁶⁷. Although arrhythmia-prone patients can be identified and stratified clinically once arrhythmias develop, there is a significant knowledge gap in understanding the biological mechanisms that contribute to ventricular arrhythmias in arrhythmogenic DCM patients.

Molecular and histological studies of human heart tissue from DCM patients with and without histories of ventricular arrhythmias showed that patients with a positive history had increased hypertrophy, evidence of oxidative stress, and fibrosis. Microarray analysis showed differences in gene expression that included increased expression of select genes encoding extracellular matrix proteins (*FGF18, COL4A2, COL12A1*) and ion channels (*KCNN2, TRPM7*); a formal analysis for enrichment of DEGs in key biological pathways has not been performed and prior results were not compared against NF controls.¹⁶⁸

We previously showed that although there is a common HF gene expression signature, there are also distinct gene expression signatures that distinguish DCM from ischemic cardiomyopathy that suggest distinct disease mechanisms. Here, we hypothesized that within

DCM, sub-phenotypic gene expression signatures exist that distinguish the arrhythmogenic DCM (aDCM) from the non-arrhythmogenic DCM (naDCM) state. We performed RNA-seq on 49 explanted human hearts and used a multi-analytic approach to discern aDCM- and naDCMspecific expression profiles. Using pathway analysis, these profiles suggest several biological mechanisms exist that distinguish aDCM from naDCM, including activation of TGFβ1 and TP53 signaling. Our results support that distinct disease mechanisms exist within DCM that separate arrhythmogenic and non-arrhythmogenic biological sub-phenotypes of DCM.

Experimental procedures

Tissue collection

Heart tissues were collected as described previously (Chapter II). Briefly, explanted failing hearts were collected at the University of Colorado Hospital as part of the Division of Cardiology Cardiac Tissue Biobank under a long-standing protocol approved by the Colorado Multiple Institutional Review Board (COMIRB, protocol 01-568). Donor hearts were obtained from the local organ procurement agency following signed research consent by family members of organ donors.

Patient cohorts

General clinical etiology of DCM in patients transplanted for HF was determined by medical history. Arrhythmogenic patients had histories of VT requiring ICD placement. Each patient had at least one appropriate shock within one year prior to transplant. The nonarrhythmogenic had no report of VT at any point throughout their medical history. NF organ

donor hearts were defined by no major cardiac history and a left ventricular echocardiographybased shortening fraction of \geq 25%. Statistical differences between cohort clinical characteristics were calculated by either Mann-Whitney U Test or Fisher's Exact Test, where appropriate, using a 0.05 significance level and a two-sided p-value.

RNA extraction

RNA was extracted from heart tissue as reported in Chapter II. Briefly, approximately 20mg of tissue, macroscopically free of fat, fibrosis, and blood, was mechanically homogenized in TRIzol reagent (Thermo Fisher Scientific, Waltham, MA). Total RNA was extracted, samples were DNase treated, and RNA was quantified at 260nm. RNA integrity (RIN) was measured and all samples were required to demonstrate RIN \geq 7.0, with a range from 7.0-9.3.

RNA sequencing

RNA sequencing was performed as reported previously in Chapter II. Briefly, PolyA transcripts were isolated from 1µg total RNA using oligo-dT beads and cDNA libraries were constructed using the TruSeq Stranded mRNA Library Prep Kit and protocol from Illumina (Illumina Inc., San Diego, CA). Libraries were sequenced single-read with an Illumina HiSeq 2500 for 50 cycles. Reads were filtered for quality and aligned to the GRchr37/hg19 version of the reference human genome using gSNAP¹³². Expression in terms of RPKM (reads per kilobase of transcript per million reads mapped) was derived using Cufflinks¹³³ and Ensembl's GRch37.82 GTF. Due to the high proportion of cardiac mRNA reads known to map to the mitochondria,¹¹⁵ mitochondrial genes were removed from the GTF file for a final set of 57,974 annotations.

Statistical analysis

Statistical analyses were performed in R. Expressed genes were defined as genes with mean RPKM ≥ 5 in all groups. Differential expression was analyzed using Linear Model ANOVA. DEGs were defined as genes with a difference in RPKM between groups ≥ 5 and a pvalue adjusted for Benjamini-Hochberg FDR ≤ 0.05 . A multiple linear regression model was used to adjust for age and sex covariates of gene expression in R. Data was transformed log2(RPKM+1). Disease status and sex were categorical variables and age was a continuous variable. For all other experiments, Student's t-test (qRT-PCR) or one-way ANOVA with Tukey Method were used. Error bars represent means \pm one standard deviation, and $p \leq 0.05$ was considered significant. Sample sizes are indicated in figure legends.

Unsupervised hierarchical clustering and data visualization

Genes were clustered using Kendall rank correlation and average linkage using the "hclust" function with the heatmap.2 package in R.

Pathway analysis

DEGs were interpreted using Ingenuity Pathway Analysis (IPA; Qiagen, Redwood City, CA). A dataset of Ensembl gene identifiers and fold changes was uploaded for Core Analysis. Association between upstream regulators was assessed and visualized in STRING v10¹⁶⁹ with the exception of the addition of the interaction between TGF β 1 and mir-193¹⁷⁰.

qRT-PCR

cDNA was synthesized from total RNA using the High Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific). The mRNA levels of selected targets were quantified by qRT-PCR using SYBR Select Master Mix (Thermo Fisher Scientific) and normalized to *GAPDH* and *18s*.

Second harmonic generation (SHG) and two-photon excitation fluorescent (TPEF) microscopy

Heart tissues were fixed in 10% formalin (Fisher) and embedded in paraffin. 5 mm thick sections were scanned in 20 random regions of interest. Images were acquired at 20x using a Zeiss 780 microscope (Carl Zeiss, Jena, Germany) equipped with a titanium:sapphire Chameleon Ultra II laser (Coherent, Santa Clara, CA). The average laser power of 7% at 800 nm (tuned for SHG) with 140 fs pulse duration and 80 MHz repetition rate was used. SHG signal was detected on a non-descanned detector (NDD) following transmission through a filter cube containing a narrow band 390 – 410 nm emission filter (hq400/20m-2p, Chroma Technology, Bellows Falls, VT). Quantification of collagen was done using ImageJ (NIH, http://imagej.nih.gov/ij/). The green (autofluorescence) and red (fibrillar collagens) channels were separated and a threshold was set for the collagen. The mean intensity and percent area was quantified using the threshold value.

Western blotting

Tissues or cells were homogenized in RIPA buffer (150mM sodium chloride, 1% NP-40, 0.5% sodium dyoxycholate, 0.1% SDS, 50mM Tris pH 7.6) with a 1:100 protease inhibitor cocktail (Sigma P8340). Tissues were mechanically homogenized using a IKA T25 Ultra-Turaxx

homogenizer and lysed with gentle agitation at 4°C for one hour. Samples were denatured in 1x Laemmli buffer. A total of 35mg (for anti-TP53) or 100mg (for anti-MDM2) of protein per sample was resolved by SDS-polyacrylamine gel electrophoresis (10% gel) and transferred to a PVDF membrane. Membranes were blocked for one hour with 5% milk in TBST. They were incubated overnight at 4°C in anti-TP53 (Santa Cruz Biotechnology sc-6243, 1:200) and anti-MDM2 (Santa Cruz Biotechnology sc-56154, 1:500) primary antibodies or with anti-GAPDH (Invitrogen AM4300, 1:8000) primary antibody at room temperature for one hour. These were followed by a one-hour incubation with secondary antibodies anti-mouse IgG peroxidase (Sigma-Aldrich A2554, 1:5000) or anti-rabbit IgG peroxidase (Sigma-Aldrich A0545, 1:5000). Protein bands were visualized using a FluorChem 8900 (Alpha Innotec). Densiometric quantification of blots was performed using ImageLab (Bio Rad Laboratories).

Validation of signatures in public datasets

GSE8000, GSE36052, and GSE82290 microarray datasets were downloaded from the gene expression omnibus (GEO, https://www.ncbi.nlm.nih.gov/geo/). Raw .CEL files were available for GSE8000, so these were processed using Bioconducter in R and normalized using the RMA method. Raw .CEL files were not available for GSE36502 or GSE82290, so RMA-normalized values were downloaded instead. The Ensembl Biomart (https://www.ensembl.org/biomart) was used to convert *Homo sapiens* Ensembl gene IDs to *Mus musculus* IDs. NIH David Gene ID Conversion was used to convert Ensembl gene IDs to official gene symbols. Additional TGFβ1 and TP53 gene sets were downloaded from the Broad Institute's GSEA database (http://software.broadinstitute.org/gsea/msigdb/genesets.jsp) and converted as described above. These sets included PLASARI_TGFB1_TARGETS_10HR_DN

Characteristics	naDCM	aDCM	n voluo
	(n=16)	(n=19)	p-value
Male sex, n (%)	12 (75)	16 (84)	0.68
Age at transplant	47 ± 14	51 ± 12	0.29
Race			
Caucasian, n (%)	13 (81)	16 (84)	1.00
Black/African American, n (%)	2 (13)	1 (5)	0.58
Unknown, n (%)	1 (6)	2 (11)	1.00
Ethnicity			
Not Hispanic or Latino, n (%)	13 (81)	11 (59)	0.17
Hispanic or Latino, n (%)	1 (6)	4 (21)	0.35
Unknown, n (%)	2 (13)	4 (21)	0.67
NYHA*	3.2 ± 0.7	3.3 ± 0.6	0.79
LVEF (%)*	19 ± 9	17 ± 6	0.45
Medications			
Antiarrhythmic therapy, n (%)	13 (81)	17 (89)	0.64
Amiodarone, n (%)	2 (13)	9 (64)	0.04
Beta Blockers, n (%)	10 (63)	8 (42)	0.22
ACE inhibitor, n (%)	8 (67)	9 (64)	1.00
Device Therapy			
ICD, n (%)	11 (69)	19 (100)	0.01
LVAD/BiVAD, n (%)	8 (50)	8 (42)	0.74
Comorbidities			
History of smoking, n (%)	8 (50)	8 (47)*	1.00
Diabetes, n (%)	1 (6)	5 (26)	0.19
*BMI ≥ 25, n (%)	6 (40)	10 (67)	0.5
LVIDs (cm)*	5.4 ± 1.3	5.8 ± 1.4	0.76
LVIDd (cm)*	6.1 ± 1.5	6.5 ± 1.4	0.74
QRS duration (ms)	144 ± 37	137 ± 49	0.68
QT interval (corrected)	505 ± 76	498 ± 57	0.90
Ventricular Tachycardia**	0 (0)	19 (100)	< 0.00001

Table 1. Clinical characteristics of aDCM and naDCM cohorts

*unknown for some patients. **within 1 year of explant (aDCM) or never in medical record (naDCM). Plus-minus values are means ± one SD. P-values determined by Mann-Whitney U Test or Fisher's Exact Test (at significance levels of 0.05, 2-tailed hypothesis) where appropriate. BMI, body mass index; ICD, implantable cardioverter defibrillator; LVAD/BiVAD, left/biventricular assist device; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association

(M2445), PLASARI_TGFB1_TARGETS_10HR_UP (M2446), and the

HALLMARK_P53_PATHWAY (M5939). The *Lmna^{-/-}* RNA-seq dataset was processed as described above with the exception that it was aligned to Ensembl's *Mus musculus* GRCm38.p6.

WGCNA and enrichment analysis

To avoid correlation artefacts, we used an average RPKM threshold of \geq 5 for each group (NF, all DCM) to filter expressed genes. The weighted correlation network was constructed by Pearson pairwise correlation between all expressed genes. We performed a sensitivity analysis of scale-free topology in order to determine the power parameter threshold, which we set to 7 and used to transform the correlation matrix into a matrix of connection strengths^{171,172}. Hierarchical clustering with average linkage was used to group genes on the basis of their connection overlap; connections were merged using a threshold of 0.25, so that groups with a correlation > 75% would be merged. Using these methods, 24 modules were detected. The module containing *LMNA* was comprised of 891 genes, which were submitted to GSEA's MSigDB (http://software.broadinstitute.org/gsea/msigdb/index.jsp) and evaluated for enrichment using the Hallmark gene sets, which represent well-characterized biological activities.

Results

Clinical characteristics of patients

Forty-nine hearts were investigated: 19 from aDCM patients, 16 from naDCM patients, and 14 NF (Appendix A: Table S1). Table 1 summarizes clinical characteristics between the



Figure 1. Schematic of RNA-seq analysis. mRNA from 49 human hearts was extracted, sequenced, and adjusted for covariates. 14 NF (grey), 19 arrhythmogenic DCM (blue) and 16 non-arrhythmogenic DCM (green) explanted left ventricles were analyzed. By comparing DEGs at an FDR of 5% between each sub-phenotype and the NF control, sub-phenotypic genes were identified and used in pathway analysis.



Figure 2. Global and sub-phenotype-specific gene expression clustering. A) Kendall pairwise correlation heatmap of all expressed genes demonstrates global gene expression clustering of both NF *vs* DCM and aDCM *vs* naDCM. B) Unsupervised hierarchical clustering by 590 aDCM-specific and 797 naDCM-specific genes demonstrates clustering by sub-phenotypes.

patient groups. As expected the aDCM cohort had a significantly greater proportion of patients taking amiodarone (p = 0.04), having an implantable cardioverter defibrillator (ICD; p = 0.01), and experiencing ventricular tachycardia (p < 0.00001).

Correlation analysis of the cohorts

To investigate gene expression differences between arrhythmogenic and nonarrhythmogenic sub-phenotypes in DCM, we performed poly-A RNA-seq on explanted left ventricular tissue samples (Figure 1, Appendix A: Table S2). To broadly understand gene expression relationships between cohorts and visualize global sample clustering for all expressed genes, we calculated Kendall correlation between samples (Figure 2A). The samples cluster distinctly by NF and DCM, and within the DCM group they cluster completely by aDCM while naDCM clusters into two groups. The data suggest that globally, there are different transcriptomes that characterize NF from DCM and also aDCM from naDCM.

Identifying phenotype-specific DEGs

We hypothesized that aDCM and naDCM patients would exhibit distinct transcriptome signatures. By removing DEGs shared between each sub-phenotype and the control, aDCM *vs* NF had 590 aDCM-specific DEGs and naDCM *vs* NF had 797 naDCM-specific DEGs (Figure 1, Appendix C: Table S1, Table S2). To validate the disease specificity of these gene profiles, we performed unsupervised hierarchical clustering of the combined genes for all samples to visualize gene expression clustering. The samples segregate into three large distinct clusters by NF, aDCM, and naDCM (Figure 2B). This shows that the unshared DEGs are sufficient to cluster the samples by sub-phenotype.



Figure 3. Pathway analysis in sub-phenotype-specific DEGs. A) Enriched IPA pathways ($p \le p$ 0.05) with aDCM-specific (left) and naDCM-specific (right) analyses. Bars are filled according to z-score: teal indicates higher (activated), orange indicates lower (inhibited). Pathways without a z-score are grey, and pathways with a z-score of zero are white. B) Enriched upstream regulators in aDCM. C) Network of enriched upstream regulators adapted from STRING. Nodes represent regulators and edges represent biological actions or effects that connect each node.

A

Canonical pathway analysis for phenotype-specific DEGs

We used IPA to investigate if the 590 aDCM-specific and 797 naDCM-specific genes were enriched for biologically relevant pathways. Enriched pathways were defined as those that met a p-value stringency of $p \le 0.05$. A total of 30 pathways were predicted as enriched in aDCM and 35 in naDCM. The more significant pathways with $p \le 0.01$ are listed in Figure 3a. The three most significantly enriched pathways in each analysis are significant in both subphenotypes: Mitochondrial Dysfunction, Oxidative Phosphorylation, and Sirtuin Signaling. (Figure 3A). These three pathways all relate to dysregulated energy metabolism in the mitochondria, which we have shown previously is a characteristic common to distinct HF etiologies (Chapter II).

Upstream regulator analysis for phenotype-specific DEGs

Because mitochondrial dysregulation could be a downstream effect in HF rather than a primary causative DCM mechanism, we considered upstream regulators that might explain the gene expression changes within the sub-phenotypes. Using IPA, we investigated whether our gene lists were enriched for biologically relevant upstream regulators. Using a cutoff of $p \le 0.05$ and an absolute activation z-score ≥ 2 , there are 11 significant regulators in naDCM (3 activated, 8 inhibited) and 20 in aDCM (14 activated, 6 inhibited; Figure 3B). We used these significant regulators in aDCM to generate a connectivity network, where TP53 and TGF β 1 directly interact with a majority of the other regulators (Figure 3C).



Figure 4. Heatmap of TGF\beta1 targets. Unsupervised hierarchical clustering of TGF β 1 targets identified as enriched by IPA clusters the samples by sub-phenotype except for two aDCM samples that cluster with naDCM.



Figure 5. Increased expression of TGF β **1 targets and collagen accumulation in aDCM.** A) qRT-PCR validation of TGF β 1 targets *COL1A1, POSTN*, and *VIM* in mRNA from NF (n = 4) and aDCM (n = 3) left ventricle. B) Representative images from second generation harmonic imaging of collagen in left ventricle tissue from naDCM (n = 10) and aDCM (n = 13) demonstrating increased collagen signal, quantified in C.

Increased expression of TGF β 1 targets and collagen accumulation in aDCM

Because TGF β 1 is a known regulator of cardiac fibrosis and increased cardiac fibrosis has previously been reported in DCM patients with VT¹⁶⁸, we sought to validate its role as a distinguishing mechanism between aDCM and naDCM. Unsupervised hierarchical clustering demonstrates that samples cluster by sub-phenotype according to TGF β 1 target gene expression from IPA (Figure 4). To validate upregulation of TGF β 1 targets, we confirmed that *POSTN*, *COL1A1*, and *VIM*, which are all cardiac fibroblast markers¹⁷³, had increased expression in aDCM relative to NF hearts (Figure 5A). To see whether increased cardiac fibrosis also distinguished our aDCM and naDCM cohorts, we used second harmonic generation imaging to quantitate the collagen in left ventricular explanted heart tissue (Figure 5B, Figure 5C)^{174,175}. aDCM patients showed significantly higher levels of collagen (p = 0.006; Figure 5C). Interestingly, the two aDCM samples that cluster with the naDCM samples in Figure 4 represent two of the three lowest collagen scoring aDCM samples in this analysis.

TP53 signaling is activated in aDCM

TP53 is a tumor suppressor that responds to cellular stresses by regulating gene expression to control the cell cycle, apoptosis, and DNA repair. Activated TP53 has previously been noted in DCM, specifically associated with mutations in *LMNA*,¹⁷⁶ which can cause $aDCM^{177}$. This activation was studied in a transgenic *Lmna*^{D300N} mouse where TGF β 1 is also activated. Interestingly, crossing this mouse with a TP53-null mouse partially rescues the phenotype, including reduction of TGF β 1 signaling (unpublished data). Furthermore, TP53 was an enriched pathway in an RNA-seq from biopsy tissue in patients with atrial fibrillation compared to normal sinus rhythm¹⁷⁸. Unsupervised hierarchical clustering demonstrates that



Figure 6. Heatmap of TP53 targets. Unsupervised hierarchical clustering of TP53 targets identified as enriched by IPA clusters the samples by sub-phenotype.



Figure 7. TP53 signaling is activated in aDCM. A) qRT-PCR validation of TP53 targets *CCNG2, CDKN1A, SERPEINE2,* and *XPC* in mRNA from NF (n = 4) and aDCM (n = 3-5) left ventricle. B) Western blot of TP53 and MDM2 in NF, aDCM, and naDCM left ventricle protein extracts. Blots are normalized to GAPDH and quantified in C.

samples cluster by sub-phenotype according to TP53 target gene expression (Figure 6). We further validated these findings by confirming upregulation of targets in aDCM relative to NF: *CDKN1A* (p21), a cyclin-dependent kinase inhibitor and primary mediator of p53-induced cell cycle response; CCNG2, involved in cell cycle progression; XPC, involved in nucleotide excision in response to DNA damage; and SERPINE2, involved in proliferation (Figure 7A). TP53 signaling is tightly regulated in normal cells, where TP53 protein is typically present at low levels because MDM2 targets it for ubiquitination and destruction. However, stressors like DNA damage trigger rapid stabilization and activation of TP53, resulting in changes in gene expression. Stabilized TP53 induces expression of MDM2 in a feedback loop so that the pathway remains tightly regulated. Although neither TP53 nor MDM2 mRNA was differentially expressed in the RNA-seq, TP53 protein was significantly more expressed in aDCM compared to both naDCM and NF (p = 0.02 and 0.007, respectively; Figure 7B, C), and MDM2 protein was significantly less expressed in aDCM compared to NF (p = 0.04; Figure 7B, C) but was also significantly less expressed in naDCM compared to NF (p = 0.003; Figure 7B, C). In aDCM, these results together suggest that MDM2 may be inhibited, allowing TP53 levels to remain higher than normal.

Recapitulation of aDCM, TP53, and TGF β 1 signatures in expression datasets of LMNA mutations

Mutations in *LMNA* account for 6-11% of DCM and can cause aDCM due to symptoms of frequent ventricular arrhythmias^{89,177,179}. As described above, previous unpublished experiments in the lab suggest an interesting relationship between *LMNA*, TP53, and TGFβ1. To further investigate this relationship and the significance of our findings in *LMNA*-related
aDCM signature



Figure 8. aDCM signature in *LMNA* **expression datasets.** Each heatmap represents extracted gene expression data for the genes in the aDCM signature for each dataset. NF control samples are indicated in grey and *LMNA* models are indicated in blue.

TGFβ1 aDCM signature



Figure 9. TGFβ1 signatures in *LMNA* expression datasets. Each heatmap represents extracted gene expression data for the genes in the TGFβ1 signature derived from the aDCM-specific analysis (A) or from the GSEA TGF β 1 signature gene set (B) for each dataset.

65

High

Low

cardiomyopathy, we used our aDCM-specific, TGFβ1, and TP53 signatures and unsupervised hierarchical clustering in publicly available datasets. We hypothesized that these three signatures would be recapitulated in datasets from *LMNA* mutation models. We interrogated four datasets for these signatures: GSE8000, a microarray on whole heart extracts from wildtype (WT), Lmna^{H222P/+}, and Lmna^{H222P/H222P} mice⁹⁶; GSE36502, a microarray on left ventricle extracts from WT and Lmna^{N195K/N195K} mice; GSE82290, a microarray on fibroblasts isolated from human skin biopsies from control and LMNA^{S143P/+} patients¹⁸⁰; and an RNA-seq on left ventricle extracts from WT and Lmna^{-/-} mice (shared by AJ Marian, our Leducq Foundation collaborator at the University of Texas Health Science Center). For GSE8000, heterozygous and homozygous samples were divided into two separate analyses.

Using our 590-gene aDCM-specific expression signature, we observe phenotypic clustering to some extent in all datasets except GSE82290, which originated from human fibroblasts (Figure 8). With the TGF β 1 signature, we did not observe any distinct patterns of clustering (Figure 9A). We hypothesize that this could be due to either the small number of genes that comprise our TGF β 1 signature (n = 26) relative to the number of genes that TGF β 1 is known to trigger or to the fact that our signature is not reproducible in *Lmna* mouse models. To address the first concern, we expanded our TGF β 1 signature to include a larger, GSEA curated gene set known to be experimentally induced by TGF β 1 stimulation in mouse embryonic fibroblasts¹⁸¹. Using this list of 443 genes, we observe that there is still a lack of distinct clustering between NF controls and *LMNA* models except in the *Lmna*^{-/-} model, where the *Lmna* knockouts cluster together distinct from 2-3 of the NF samples (Figure 9B). Lastly, we used our TP53 signature of 54 genes to cluster the datasets. As with the aDCM signature, all but dataset

TP53 aDCM signature



Figure 10. TP53 signatures in *LMNA* **expression datasets.** Each heatmap represents extracted gene expression data for the genes in the TP53 signature derived from the aDCM-specific analysis (A) or from the GSEA Hallmark TP53 sgene set (B) for each dataset.

А

Hallmark Gene Set Name	# Genes in Gene Set (K)	Description	# Genes in Overlap (k)	k/K	p-value	FDR
MYC_TARGETS_V1	200	A subgroup of genes regulated by MYC - version 1 (v1).	21	0.11	4.13E-11	2.06E-09
UNFOLDED_PROTE IN_RESPONSE	113	Genes up-regulated during unfolded protein response, a cellular stress response related to the endoplasmic reticulum.	16	0.14	9.80E-11	2.45E-09
MYC_TARGETS_V2	58	A subgroup of genes regulated by MYC - version 2 (v2).	12	0.21	2.30E-10	3.83E-09
APOPTOSIS	161	Genes mediating programmed cell death (apoptosis) by activation of caspases.	13	0.08	4.20E-06	5.25E-05
E2F_TARGETS	200	Genes encoding cell cycle related targets of E2F transcription factors.	13	0.07	4.26E-05	4.26E-04
UV_RESPONSE_UP	158	Genes up-regulated in response to ultraviolet (UV) radiation.	11	0.07	8.85E-05	7.37E-04
PROTEIN_SECRETI ON	96	Genes involved in protein secretion pathway.	8	0.08	2.37E-04	1.69E-03
DNA_REPAIR	150	Genes involved in DNA repair.	9	0.06	1.11E-03	6.93E-03
PI3K_AKT_MTOR_S IGNALING	105	Genes up-regulated by activation of the PI3K/AKT/mTOR pathway.	7	0.07	2.14E-03	9.83E-03
APICAL_JUNCTION	200	Genes encoding components of apical junction complex.	10	0.05	2.36E-03	9.83E-03

Table 2. GSEA Hallmark enrichment analysis for LMNA module from WGCNA analysis

GSE82290 cluster mostly by phenotype, suggesting that TP53 signaling is an important distinguishing factor between NF and *Lmna* model gene expression in the heart but not in skin fibroblasts (Figure 10A). We extended this signature to a larger gene list of GSEA's "Hallmark TP53" gene list, which includes 200 genes involved in TP53 signaling networks. We observe similar patterns as with the smaller TP53 signature derived from this current study, and GSE82290 still fails to cluster by phenotype (Figure 10B).

WGCNA and pathway analysis for genes co-expressed with LMNA

Lastly, we used our transcriptome dataset to perform a weighted gene co-expression network analysis (WGCNA) with the goal of determining which set of genes are highly correlated with LMNA expression in the heart. Pairwise correlation between genes determines which genes have highly correlated expression. We hypothesized that the network of genes associated with LMNA expression would inform our knowledge of the role of lamin A/C in the cell. WGNCA identified 24 distinct clusters of genes in the RNA-seq. The module containing LMNA was comprised of 891 genes and was not significantly associated with disease status, although 19 genes and 42 genes were differentially expressed in the aDCM-specific and naDCM-specific analyses, respectively. GSEA Hallmark gene set enrichment analysis identified MYC targets as the first and third most enriched gene sets (FDR = 2.06×10^{-9} , FDR = 3.83×10^{-9} ; Table 2). MYC is a proto-oncogene transcription factor involved in proliferation. Activated MYC elicits activation of cell cycle checkpoints, including those that occur through TP53 to promote apoptosis or cell cycle arrest¹⁸². Interestingly, MYC and lamin A/C are reported to interact directly. When MYC is phosphorylated at serine 62, it co-localizes and physically associates with lamin A/C, both at the nuclear periphery as well as the intra-nuclear space, to induce

proliferative and DNA-damage responses¹⁸³. The enrichment analysis also identified Apoptosis, UV Response Up, and DNA Repair as significant processes (FDR = 5.25×10^{-5} , FDR = 7.37×10^{-4} , FDR = 6.93×10^{-3}), which is intriguing given the direct role of TP53 in all three processes. DNA damage from a stressor like UV radiation stimulates the TP53 pathway, which regulates the DNA repair and apoptosis processes¹⁸⁴. Lastly, E2F Targets and PI3K/AKT/mTOR signaling were also enriched (FDR = 4.26×10^{-4} , FDR = 9.83×10^{-3}). E2F represents a family of transcription factors involved in the temporal regulation of the cell cycle¹⁸⁵. E2Fs are controlled by RB1, which was identified as an inhibited upstream regulator in our aDCM-specific analysis (Figure 3B). PI3K/AKT/mTOR signaling is relevant as its activation has been implicated in *LMNA*-related cardiomyopathy models, in particular prior to any clinical signs of cardiomyopathy. Notably, inhibition of the pathway prevents cardiomyopathy progression^{100,101}.

Discussion

aDCM and naDCM have distinct gene expression signatures

Many studies have shown the gene expression changes that occur in the failing human heart that distinguish it from a healthy heart, and failing hearts share common gene expression signatures. However, subtle differences in gene expression exist that can accurately classify hearts by disease etiology. Here, we showed that once the common, overlapping expression shared by all DCM patients is removed, we can identify biologically relevant signatures specific to DCM patients with (590 genes) and without VT (797 genes).

Upstream regulators may play a role in gene expression changes that distinguish aDCM from naDCM mechanisms

Several enriched upstream regulators were predicted to be activated or inhibited in aDCM relative to naDCM (Figure 3B). Mir-193 levels have been negatively correlated with fibrosis, and TGFβ stimulates downregulation of mir-193¹⁷⁰. Downregulation of mir-193 has also been negatively associated with cardiac fibrosis¹⁸⁶. BRD4 is an epigenetic regulator that binds acetylated chromatin to promote transcription. In CMs, BRD4 promotes expression of genes associated with pathological hypertrophy and TGF β -mediated fibrosis in response to stress¹⁸⁷⁻¹⁸⁹. *CTNNB1* encodes β -catenin, a protein involved in signal transduction. It duel-functions at the intercalated disc in cell-cell adhesion and in the nucleus as an effector of gene transcription in Wnt signaling. Although inhibition of Wnt/β-catenin has been demonstrated in ARVC,¹⁹⁰ activation has been associated with cardiac fibrosis^{191,192}. HDAC6 is a histone deacetylase that controls acetylation of α -tubulins, which are structural cytoskeletal polymers. Increased HDAC6 activity in atrial fibrillation models causes α -tubulin deacetylation, depolymerization, and degradation, which was confirmed in human tissue from patients with atrial fibrillation. Further, in vivo HDAC6 inhibition prevents electrical remodeling and contractile dysfunction¹⁹³. MAPK3 and MAPK1 are also known as ERK1/2 and are important regulators of cell cycle progression, proliferation, and survival. Activation of ERK1/2 has previously been reported in LMNA-related cardiomyopathy models,^{96,99} and pharmacological inhibition improves cardiac function^{98,100,194}. Activation of ERK1/2 also crosstalks with RB1, which is the tumor suppressor retinoblastoma 1 predicted to be inhibited. Interestingly, A-type lamins and RB1 directly interact and this is required for proper localization and stability of RB1^{195,196}. This association can be disrupted by ERK1/2, which can inactivate RB1 and induce cell cycle entry and proliferation¹⁹⁷.

$TGF\beta 1$ signaling is activated in aDCM

TGFβ1 is a master regulator of fibrosis in many tissues^{198,199} through induction of myofibroblast differentiation²⁰⁰. In the heart, TGFβ1 can alter the electrophysiology of cardiac myofibroblasts by promoting pro-arrhythmic intercellular interactions between myofibroblasts and CMs²⁰¹. A transgenic mouse model of TGFβ1 overexpression results in cardiac hypertrophy and interstitial fibrosis,²⁰² and a heterozygous knockout protects against age-associated cardiac fibrosis²⁰³. TGFβ1 was predicted to be activated in our aDCM cohort, and we showed that aDCM patients have higher levels of collagen on average than naDCM (Figure 5B, Figure 5C). Additionally, TGFβ1 is known to interact with a number of the other predicted upstream regulators, including activating the non-canonical ERK1/2 (MAPK3 and MAPK1) map kinase pathway (Fig3C)^{198,204,205}. ERK1/2 activation has previously been reported in *LMNA*-related cardiomyopathy^{96,99}.

TP53 signaling is activated in aDCM

TP53 is a transcriptional regulator and a prominent tumor suppressor. Its role in the heart, in either a healthy state or a pathogenic one, has not been well characterized. In endothelial cells and macrophages, activation of the sympathetic nervous system via β 2-adrenergic signaling increased expression of p53, resulting in cardiac inflammation²⁰⁶. P53 accumulation has been described in failing human hearts from DCM patients, but clinical characteristics including arrhythmia were not described²⁰⁷. A transgenic mouse model of an *ACTC1* missense mutation demonstrated accumulation of TP53 and irregular calcium handling. Arrhythmia was suggested as a potential cause of death.²⁰⁸ In accordance with our findings, in a zebrafish *LMNA*

knockdown model *TP53* and *CDKN1A* are both upregulated, supporting TP53 activation. ²⁰⁹ Recently, CM-specific conditional knockout of TP53 in mice led to hypertrophy and decreased contractile function²¹⁰. This was accompanied by repression of extracellular matrix and fibrosisrelated genes (including *TGFB1*, *TGFB2*, *TGFB3*, *POSTN*, and numerous collagens, including *COL1A1*) and increased expression of genes related to mitochondrial biogenesis and oxidative phosphorylation²¹⁰. Similarly, our results showed that activation of TP53 is accompanied by corresponding changes in *TGFB1*, fibrosis, and mitochondrial dysfunction.

aDCM-specific and TP53 expression signatures, but not the TGFB1 signature, cluster LMNA models by phenotype

Using the aDCM-specific, TP53, and TGFB1 signatures derived from the current study, we used unsupervised hierarchical clustering to observe how these expression signatures cluster the samples in a variety of datasets from human and mouse *LMNA/Lmna* models. We observed globally that our aDCM-specific and TP53 signatures were sufficient to cluster all samples (except GSE82290) by phenotype (Figure 8, Figure 10), but the TGFB1 signature was not adequate (Figure 9). GSE82290 is a microarray from fibroblasts derived from skin biopsies of patients, and thus represents the only non-cardiac-derived expression data in this analysis. *LMNA* is expressed in all differentiated somatic cells^{76,78} and non-cardiac phenotypes due to *LMNA* mutations can have skin phenotypes²¹¹⁻²¹³. However, the finding that TP53 signaling is enriched in all datasets except the one derived from fibroblasts suggests that mechanisms that lead to a phenotype in skin are distinct from cardiac mechanisms.

Despite expansion of the TGFB1 gene list, it did not characterize gene expression differences between NF and *LMNA*. Interestingly, significant cardiac fibrosis was reported for all

three *Lmna* mouse models associated with GSE8000⁹⁶, GSE36502¹⁰², and *Lmna^{-/-}*. Muchir *et al* (2007) reported fibrosis in the *Lmna^{H222P/H222P}* mice but not their heterozygous counterparts. They also reported significant enrichment of fibrosis pathways, specifically VEGF, in the homozygous but not the heterozygous microarray analysis. Potential explanations for this difference is that cardiac fibrosis signaling in mice is distinct from humans or that VEGF signaling may be up or downstream of TGFB1.

Both the TP53 gene list derived from the current study as well as a hallmark TP53 signaling gene list were sufficient to cluster samples by phenotype, suggesting that TP53 is a valid signaling pathway in *LMNA*-related aDCM. Additionally, this supports our finding that a signaling pathway identified originally in our aDCM cohort, which genetically-heterogeneous but phenotypically-homogenous, is valid.

Genes involved in TP53 and LMNA-relevant signaling pathways are coordinately expressed with LMNA in human heart tissue

Our WGCNA analysis focused specifically on *LMNA* revealed a module of 891 genes that are coordinately expressed with *LMNA* across human heart tissue. This module is not significantly associated with disease; nonetheless, these genes are enriched for relevant signaling pathways that have been previously associated with *LMNA*, not only in *LMNA* models of disease but also in molecular studies of transcription factor activity in the nucleus. This finding is significant because it demonstrates that *LMNA* is co-expressed with genes that belong to pathways that become perturbed in a disease state and further validates the involvement of these pathways in *LMNA*-related disease.

Study limitations

While the limitations concerning RNA-seq studies in end-stage, explanted human heart tissue have been described in detail and also apply to the current study (Chapter II), there are several clinical limitations specific to this study. Significantly more aDCM patients were receiving amiodarone than naDCM (Table 1; n = 9 and n=2, p = 0.04) and had ICDs (n=19 and n=11, p = 0.01), which could potentially impact gene expression between the groups. To our knowledge, no studies have sought to evaluate changes in gene expression in hearts with ICDs. Amiodarone on the other hand has been reported to decrease expression of Na+/K+ ATPase subunits $\alpha 2$ and $\beta 2 (ATP1A2$ and $ATP1B2)^{214}$, various sodium channels (SCN4A, SCN5A, SCN1B), connexin43 (GJA1), the calcium channel CACNA1C, various potassium channels (KCNA5, KCNB1, KCND2) and increase expression of other potassium channels including KCNA4, KCNK1, KCNAB1, KCNE3,²¹⁵ and KCNJ2²¹⁶. Our aDCM-specific DEGs do not include any of these genes. Moreover, in our unsupervised hierarchical clustering analyses with both TGFB1 and TP53 target genes, we do not see any distinct clustering differences between patients with ICDs or taking amiodarone. Additionally, a study of the effect of amiodarone on non-CMs demonstrated that amiodarone treatment does not affect expression of TP53²¹⁷, and long-term amiodarone therapy does not affect left ventricular remodeling or interstitial fibrosis²¹⁸. Lastly, our clinical cohorts were selected based on patients that had never experienced VT or that had experienced VT within a year of transplant, but does not negate naDCM patients who may have been at risk of developing VT.

CHAPTER IV

TP53 AND TGFβ1 SIGNALING IN AN ARRHYTHMOGENIC DILATED CARDIOMYOPATHY CELL MODEL²

Introduction

LMNA encodes lamin A/C, an intermediate filament protein that polymerizes to form a dense network within the nuclear matrix. Lamin A/C maintains a complex, fibrous structure by directly interacting with individual chromosomes and linker complexes connecting the inner nuclear space to the cytoskeleton to provide a stable nuclear envelope infrastructure^{219,220}. Mutations in *LMNA* account for approximately 6-11% of all DCM cases^{89,179}. In addition to DCM, they cause a generalized conduction system defect that often results in arrhythmias, leading to sudden cardiac death in nearly half of patients⁹¹. Because of this high risk of sudden cardiac death, it is recommended that *LMNA* patients receive ICD therapy as a primary preventative measure⁹⁵.

The mechanism by which mutations in *LMNA* cause DCM and arrhythmia remains unclear. Previous work has relied mostly on knock-in, knockout, and transgenic mice models. In the knock-in *Lmna*^{H222P/H222P} mouse, the ERK/JNK/p38 branches of the MAPK pathway and the AKT/mTOR pathway are activated^{96-100,194}. Elevated mTOR signaling was also prominent in the *LMNA*^{-/-}mice,¹⁰¹ but elevated MAPK signaling was not recapitulated in the *LMNA*^{+/-} model²²¹. Current unpublished work by the lab and collaborators has shown that TP53 and TGFβ1

² Portions of this chapter were previously published in *Cardioskeletal myopathies in children and adults* 2016, chapter 12: Diseases of the nuclear membrane (pp. 233-248). These are included with the permission of the copyright holder.

signaling are activated in a transgenic mouse model of *LMNA*^{D300N}. Gene expression changes in the left ventricle, measured by RNA-seq, demonstrate that this activation occurs at least as early as 16 weeks of age, prior to clinical signs of cardiomyopathy. This finding suggests that these pathways become activated in the early stages of disease.

In recent years, iPSC models have offered a unique opportunity to study human CMs *in vitro*. It is becoming increasingly common to transform fibroblasts from skin biopsies or peripheral blood mononuclear cells (PBMCs) from blood samples into iPSCs. This creates an unprecedented opportunity for developing disease-specific or even patient-specific models that have the potential to be used in drug screens to discover new therapeutics²²². This has a unique advantage over many animal models of cardiomyopathy, which often fail to recapitulate human phenotypes²²³. This disconnect is likely due to innate physiological differences like beating rate, electrophysiology, calcium handling, and cardiac myosin structure²²⁴. For example, mice are the most common cardiomyopathy model but display fundamental differences in heart tissue architecture; although *MYH7* is the predominant isoform in humans over *MYH6*, in mice it is the opposite^{225,226}.

In addition to offering a possibly more robust disease model for certain research questions, iPSCs also provide an opportunity to study human disease at an earlier stage. Much of what is currently known about the cellular and molecular characteristics of diseased human heart tissue is derived from research using end-stage explanted hearts from heart transplant patients. These hearts are useful for understanding what disease looks like in its final stages but may not be representative of the earlier stages and the cellular and molecular changes that originally occurred to cause HF.

Previously, we've used RNA-seq in 49 explanted human heart tissues to delineate gene expression signatures and enriched pathways that distinguish arrhythmogenic from nonarrhythmogenic forms of DCM. We found that TP53 and TGF β 1 were activated in arrhythmogenic DCM, suggesting they play a role in arrhythmogenicity in end-stage disease. We hypothesized that TP53 and TGF β 1 would be activated in a human iPSC-derived CM model of arrhythmogenic DCM, which represents an earlier stage of disease. Specifically, we used a CRISPR-Cas9-derived *LMNA*^{+/-} iPSC line differentiated into CMs. We predicted that the iPSC-CM would recapitulate the signals previously identified in our RNA-seq of explanted human heart tissue.

Experimental procedures

Culture, maintenance, and differentiation of iPSCs

iPSCs were maintained in feeder-free mTeSR1 medium (STEM CELL Technologies, Vancouver, CA) on Matrigel-coated (BD Bioscience, San Jose, CA) plates at 37°C with 5% (vol/vol) CO2. iPSCs were passaged at least 5 times post unfreezing before differentiation was started. iPSCs were differentiated into iPSC-CMs using a previously published protocol²²⁷ with the following exceptions. To inhibit WNT pathway signaling and induce cardiogenesis, each cell line was optimized with different drugs that worked most efficiently for that line. For Control cells, 6 μ M IWP-2 (Sigma) was used and for the *LMNA*^{+/-} line, 9-12 μ M IWR-1 (Sigma) was used. iPSC-CMs were not glucose starved and were re-plated at approximately day 21 using TrypLE (Thermo Fisher Scientific) to dissociate cells into a single-cell suspension and re-seed them on Matrigel-coated plates. Cells were differentiated and matured to either day 30 or day 60

as indicated. Cells were treated for 24 hours with 100mM/L of norepinephrine as indicated. Only wells with approximately >50% contracting cells were used for experiments.

RNA extraction, cDNA synthesis, and qRT-PCR

Cells were lysed in TRIzol reagent (Thermo Fisher Scientific, Waltham, MA). Chloroform was added and the aqueous phase was extracted. Total RNA was extracted from the aqueous phase using the RNeasy Plus Mini per manufacturer's instructions with the exception of replacing the lysis buffer with TRIzol. RNA was quantified at 260nm using a NanoDrop1000 (Thermo Fisher Scientific) and cDNA was synthesized using the High Capacity cDNA Reverse Transcription Kit (Thermo Fisher Scientific) per the manufacturer's instructions. The mRNA levels of selected targets were quantified by qRT-PCR using SYBR Select Master Mix (Thermo Fisher Scientific) and normalized using the $\Delta\Delta$ Ct method, using *GAPDH* or the geometric mean of *GAPDH* and *18s* as housekeeping genes.

Statistical analysis

qRT-PCR results between $LMNA^{+/-}$ and control were analyzed by a standard two-tailed ttest. Multiple comparisons between $LMNA^{+/-}$ and control at days 30 and 60 were analyzed by ANOVA followed by post-hoc Tukey HSD test in R. A p-value threshold of ≤ 0.05 was used to define significance. For the Tukey test at days 30 and 60, only significant differences for the following comparisons are reported: Control *vs* $LMNA^{+/-}$ day 30, Control *vs* $LMNA^{+/-}$ day 60, Control day 30 *vs* Control day 60, and $LMNA^{+/-}$ day 30 *vs* $LMNA^{+/-}$ day 60.



Figure 1. Expression of *LMNA* **in iPSC-CM** *LMNA*^{+/-}. *LMNA* mRNA expression A) and protein expression B) are decreased in *LMNA*^{+/-}cells.



Figure 2. Expression of fetal gene program in iPSC-CM *LMNA*^{+/-} and Control at day 30.

Results

mRNA and protein expression of LMNA

An iPSC line was derived from a skin biopsy from a healthy male control. This line was then used with CRISPR-Cas9 technology to generate an 11-nucleotide deletion in *LMNA* (c.689_699del), predicted to cause haploinsufficiency. This was confirmed by downregulation of the *LMNA* transcript (48-70% decreased expression, p = 0.001; Figure 1A) and downregulation of lamin A/C protein (54-62% decreased expression, p = 0.03; Figure 1B).

The fetal gene program is activated in iPSC-CM LMNA^{+/-}

First, we tested whether the fetal gene program was activated, thus confirming our model induces HF signaling. We investigated gene expression of *ATP2A2*, *MYH6*, *MYH7*, *NPPA*, and *NPPB* at day 30 (Figure 2). Expression of *ATP2A2* and *MYH6* were significantly depressed in *LMNA*^{+/-} (0.51-fold change, p = 0.002 and 0.39-fold change, p = 0.0006) while expression of *NPPB* was significantly increased (5.7-fold change, p = 0.0004). Although not significant, there was a trend towards increased expression of *MYH7* and *NPPA*. These findings corroborate typical fetal gene expression patterns observed in human heart tissue as well as expression patterns reported previously for iPSC-CM HF models²²⁸, indicating that our model is accurately depicting established markers of HF.



Figure 3. TP53 and TGF\beta1 target gene expression. Expression of TP53 A) and TGF β 1 B) target genes in iPSC-CM *LMNA*^{+/-} and Control at days 30 and 60.

TP53 and TGF β 1 are inhibited in iPSC-CM LMNA^{+/-}

Next, we tested whether the signals discovered in our RNA-seq were recapitulated in our *iPSC-CM LMNA*^{+/-} model. At day 30, we investigated gene expression of TP53 targets *CCNG2*, CDKN1A, SERPINE2, and XPC. In our previous RNA-seq, these genes were all upregulated, indicating TP53 activation. However, in our iPSC-CM LMNA^{+/-} model we observed the opposite: *CDKN1A* and *XPC* were significantly downregulated (0.10-fold change, $p = 4x10^{-5}$ and 0.56-fold change, p = 0.0004) and CCNG2 and SERPINE2 trended towards downregulation (these were significant using student's t-test but not significant using post-hoc Tukey HSD test for multiple comparisons (Figure 3A). Gene expression in iPSC-CMs is known to change drastically over time due to CM maturation^{229,230}, so we hypothesized that a more mature CM would better recapitulate the expression patterns seen in human tissue. To test this, we matured the CMs to day 60 and examined gene expression again. From day 30 to day 60, all four genes significantly increased in the Control, and all but SERPINE2 significantly increased in LMNA^{+/-}. This demonstrates that as CMs mature, gene expression changes; in this case, expression of genes downstream of TP53 signaling increase from day 30 to day 60 regardless of disease status. At day 60, *CDKN1A* and *SERPINE2* were significantly downregulated (0.08-fold change, $p = 5x10^{-1}$ ⁶ and 0.12-fold change, p = 0.004) but *CCNG2* and *XPC* were unchanged between Control and $LMNA^{+/-}$. As the cells mature, targets of TP53 are still either downregulated or equal between Control and LMNA^{+/-}.

We also tested whether targets of TGF β 1 were upregulated as observed in the RNA-seq. At day 30, *COL1A1* is significantly downregulated in *LMNA*^{+/-} (0.44-fold change, p = 0.007) and *POSTN* and *VIM* are not significantly changed. At day 60, *COL1A1* is significantly downregulated in *LMNA*^{+/-} (0.19-fold change, p = 0.001), and it is also significantly



Figure 4. Expression of MAPK targets in iPSC-CM *LMNA*^{+/-}and Control at day 30.

downregulated from day 30 to day 60 in both Control and *LMNA*^{+/-}. Gene expression of *POSTN* does not significantly change in any comparison, and expression of *VIM* decreases from day 30 to day 60 in both cell lines but is not significantly different between lines (Figure 3B). These results show that *COL1A1* expression is reduced in iPSC-CM *LMNA*^{+/-} but also that it decreases in iPSC-CMs as cells mature from day 30 to day 60. Likewise, expression of *VIM* decreases over time as well.

iPSC-CM LMNA^{+/-} *does not recapitulate previously reported ERK/JNK/p38 MAPK target gene expression*

Activation of the ERK/JNK/p38 branches of the MAPK pathway has been reported in the *Lmna*^{H222P/H222P} mouse and confirmed in human tissue from patients with *LMNA* mutations^{96-100,194}. Subsequently, a MAPK inhibitor, ARRY-371797, is the subject of a Phase III clinical trial in *LMNA* patients. We tested whether our iPSC-CM *LMNA*^{+/-} would recapitulate gene expression characteristic of activated MAPK. We measured Control and *LMNA*^{+/-} iPSC-CMs at day 30 for expression differences in six genes: *ATF2, ELK1, DDIT3,* and *JUN* which are MAPK transcription factors shown to be upregulated in *Lmna*^{H222P/H222P} mice^{96,97,194}; *MAX,* which is a Myc-associated transcription factor downstream of p38; and *MAPKAPK3,* a kinase activated by p38. Of these six genes, only expression of *ATF2* and *ELK1* were significantly different between Control and *LMNA*^{+/-} (0.83-fold change, p = 0.02 and 0.76-fold change, p = 0.004; Figure 4). These two genes have been previously reported as significantly overexpressed, but in our *LMNA*^{+/-} iPSC-CM they are decreased. At day 60, this downregulation remains significant for *ATF2* (0.51-fold change, p = 0.02) but not *ELK1* (data not shown).



Figure 5. TP53 and TGF\beta1 target gene expression following NE treatment. Expression of TP53 A) and TGF β 1 B) target genes in iPSC-CM *LMNA*^{+/-} and Control at day 30.

Stressing iPSC-CMs does not cause them to increase expression of TP53 or TGF^β1 targets

As the failing heart deteriorates, it enters a chronic state of hyperadrenergic signaling. This activation is an effort to stimulate the heart to increase output and restore normal cardiac function²³¹. This hyperadrenergic response can be stimulated by exposing the cells to norepinephrine (NE). This activates both the $\alpha 1$ and $\beta 1$ adrenergic receptors and has been shown to increase contraction force and rate in 30-day iPS-derived CMs²³². We hypothesized that aggravating the cells with NE, which mimics the human body's stress response, would induce a disease state more representative of what was observed in explanted heart tissue. Comparison of gene expression between iPSC-CM *LMNA*^{+/-} and *LMNA*^{+/-} + NE shows that the addition of NE invokes significant decreases of *SERPINE2, XPC,* and *POSTN* (0.06-fold change, p = 0.05; 0.30-fold change, p = 0.006; 0.22-fold change, p = 0.004, respectively) but not *CDKN1A, COL1A1,* or *VIM* (Figure 5). Thus, NE did not stress the cells into a state that better mimics our results observed in heart tissue.

Discussion

iPSC-CM LMNA^{+/-} *does not recapitulate expected gene expression*

CMs are terminally differentiated cells, so iPSC-CMs represent the only human-derived cardiac cell line readily available to researchers. Many iPSC-CM models described in recent years have been successful in providing robust disease models for other cardiomyopathies including Long QT Syndrome^{233,234}, patient specific models of *RYR2* mutations^{235,236}, ARVC^{237,238}, HCM²³⁹, and DCM²⁴⁰. Likewise, iPSC-CMs are beginning to be used in high-

throughput drug screening experiments to identify effective therapeutic compounds for novel treatments, with the ultimate goal of providing disease-specific or even patient-specific therapy²⁴¹⁻²⁴⁴. Based on the success of these previous models, we anticipated that our *LMNA*^{+/-} model would recapitulate the gene expression described in our aDCM patients and would thus be a valuable resource for better understanding and testing aDCM mechanisms and treatments. However, we found that gene expression in our model did not mirror our findings in human heart tissue. There are a number of potential reasons for this including: 1) iPSC-CMs represent an earlier disease stage, 2) the cells had not yet entered a representative disease state due to lack of stress signaling, and 3) the cell types confined to a petri dish are not representative of heart tissue.

First, it has been previously reported that the maturity of day 30 iPSC-CMs represent gene expression similar to embryonic day 14.5-18.5 mice.¹⁴ The earliest expression studies performed in *Lmna* mouse models have occurred at 6 weeks (GSE36052)¹⁰², when gene expression is likely vastly different than an embryonic state; subsequently, there is currently no data available to compare whether our findings are due to signaling that occurs at the earliest stages of disease. Kuppusamy *et al* (2015) performed RNA-seq in day 20 and 1-year old human embryonic stem cell-derived CMs (hESC-CMs) and compared the results to adult human tissues; at 1-year, expression profiles of the hESC-CMs were remarkably more similar to adult human tissue than hESC-CMs at day 20, but no comparison was made to pediatric human tissue²³⁰. Our gene expression analysis at days 30 and 60 revealed that downregulation of TP53 and TGF β 1 targets either does not change or stabilizes, but there is still a possibility that expression of these genes could continue to change over time.

Second, we attempted to stress the iPSC-CM *LMNA*^{+/-} by culturing them with NE for 24 hours in order to stimulate a stress response. Although hyper-adrenergic signaling is the body's

response to increase cardiac output, which is temporarily effective, prolonged hyper-adrenergic signaling is maladaptive and blocking this signaling pathway is a common therapy in HF^{245,246}. Previous research shows that changes in CM beating rate are observed < 1 hour after NE treatment, and beating rate at 24 hours post treatment is not significantly different than 96 hours²⁴⁰. After 24 hours of NE treatment, iPSC-CM *LMNA*^{+/-} demonstrated further either further downregulation (*SERPINE2, XPC, POSTN*) or no change (*CDKN1A, COL1A1, VIM*) of target genes. If inhibition of TP53 and TGF β 1 targets is truly characteristic of an early disease stage of *LMNA*^{+/-}, then further inhibition of these pathways in response to stress may be a valid physiological response.

Lastly, although our cultures are not 100% pure CMs, CMs do represent a significant proportion of the cultured cells as detected by immunohistochemistry for cardiac-specific proteins (data not shown). There are two ways that cell types could be significant in this case. First, it is possible that the TP53 and TGF β 1 changes detected in the RNA-seq do not originate from CMs, but instead represent pathogenic signaling in other cell types. Although this is possible, it is not likely; the *Lmna*^{D300N} mouse (unpublished data) is a cardiac-specific transgenic line, meaning that the *Lmna*^{D300N} transgene is only present in CMs. The CM-specific mutation is sufficient to cause disease in this animal and elicit activation of TP53 and TGF β 1. Second, adult heart tissue is comprised of only ~20-40% CMs;^{247,248} and it is likely that cardiomyopathy results from intercellular mechanisms and is not confined solely to intracellular perturbations. Thus, it may be possible that the non-CM portion of cells in the heart is essential for representative perturbation of TP53 and TGF β 1 signaling pathways.

Our experiments here demonstrate that our iPSC-CM *LMNA*^{+/-} model does not recapitulate gene expression changes observed in end-stage human heart tissue. Although it may

represent gene expression characteristic of early-stage disease, more experiments will be needed to confirm this. Further maturation of the iPSC-CMs for 1 year, as previously published, would confirm whether this model will exhibit gene expression changes characteristic of end-stage human tissue over time. Likewise, comparison of the gene expression changes reported here to an embryonic day 14.5-18.5 mouse model of $Lmna^{+/-}$ would confirm whether gene expression between our model and an early-stage model of $Lmna^{+/-}$ are similar. In its current state, the iPSC-CM $LMNA^{+/-}$ model at days 30 and 60 is not an accurate model for late-stage HF.

CHAPTER V

CONCLUSIONS

Dissertation summary

We used RNA-seq and pathway analysis in the largest cohort of human heart tissue from distinct etiologies, which is an incredibly rare and unique dataset. First, we stratify our analysis by two distinct cardiomyopathies, ICM and DCM, and compare gene expression in each to NF controls. We use this comparison to derive a HF gene signature; this demonstrated that HF in left ventricles of DCM *vs* ICM general etiology have a common gene expression signature. We then derived disease-specific gene expression signatures from each disease to show that although they share HF genes and signaling pathways, they also exhibit disease-specific expression signatures. Although the expression data does not reveal any single drivers of disease etiology, it does demonstrate that a collection of dysregulated pathways distinguishes DCM from ICM.

Next, we used a similar RNA-seq approach combined with pathway analysis, histology, and molecular studies to demonstrate that clinical distinctions in DCM arrhythmogenic subphenotypes result in biologically relevant differences. aDCM and naDCM have distinct gene expression signatures, including significant differences in the TGFβ1 and TP53 pathways. Analysis of publicly available datasets and co-expression of *LMNA* validates the importance of TP53 in aDCM. These results suggest that disease mechanisms may differ between DCM patients with and without VT. The results of these two studies are summarized in Figure 1.

The discovery of these key pathways in each HF clinical etiology and arrhythmogenic subtype are an important step forward in HF genomics, and they set the stage for future



Figure 1. Disease-specific, subtype specific, and shared HF pathways. Specific events can lead NF hearts towards DCM or ICM, and both diseases have common HF responses. Dysregulated cell-cell and decreased cell-matrix adhesion contributes to DCM. An activated innate immune response, activation of proinflammatory cytokines, and increases in immune cell quantity, movement, and migration are characteristic of ICM. Both DCM and ICM have responses common to HF, including reduced translation, increased fetal gene expression and antigen presentation, and dysregulated mitochondria and protein degradation. DCM can further be subtyped by activation of TGF β 1 leading to fibrosis, and activation of TP53 signaling.

functional research. These data also offer the possibility of a new taxonomic classification of HF, one of the key early steps to developing precision medicine paradigms as detailed by the National Research Council ²⁴⁹. Potentially, this strategy could yield findings relevant for monitoring HF progression and designing future treatments. The RNA-seq dataset discussed in this thesis has been deposited in NCBI's Gene Expression Omnibus (GEO) and are accessible through GEO series accession number GSE116250.

My research in the context of HF biology

The failing heart transcriptome is so distinct from NF that Liu *et al* (2014) was able to utilize RNA-seq from 3 failing and 2 NF hearts to predict HF status accurately in 98% of 313 additional samples. The 3 failing hearts came from two disease etiologies, demonstrating that the common pathways shared by HF etiologies account for an overwhelming proportion of gene expression that is consistently characteristic of HF. Developing therapeutics to target common pathways that result in shared signs and symptoms in a large patient population is a practical approach, because it as encompasses as many HF patients as possible. As such, the underlying heterogeneity in HF pathology has largely been ignored. Although this approach has led to the development of a number of useful therapies that are recommended for all HF patients, including β -adrenergic receptor antagonists, angiotensin-converting enzyme inhibitors, and aldosterone receptor antagonists, and although these therapies improve symptoms and clinical outcomes in many patients^{9,250}, it largely ignores valuable information about why the heart entered a state of disease in the first place. The effect of relying on therapies that target final common pathways of HF is that even if these have an overall benefit in the HF population, there are certainly

subgroups of patients for which these have no effect or actually worsen outcomes.

Acknowledgement of underlying pathophysiological mechanisms in HF cohorts and population stratification of these groups will be an essential step in improving the rate of successful clinical trials²⁵¹. The work presented in this thesis is a significant step forward in supporting the idea that distinct pathophysiological mechanisms exist in end-stage HF.

The studies presented in this thesis represent the first RNA-seq study of HF to specifically compare gene expression differences between diseases. Many gene expression studies have focused on identifying expression signatures that distinguish failing from NF hearts or have used global expression differences between different diseases and NF to determine if diseases have unique transcriptomes. These approaches, while contributing to our understanding of the transcriptomes of failing and NF hearts, have failed to provide clear disease signatures.^{106,108,122,124-126,130,252} The study presented here is unique for two main reasons. First, we used a linear regression model to adjust for age and sex in our patient cohorts, which are known to affect gene expression in the heart²⁵³⁻²⁵⁵. Second, our approach focused on first identifying commonalities of HF and subtracting them in order to assess differences more directly. We analyzed them separately to gain the most insight into common and disease-specific HF mechanisms.

The studies presented here also represent the first RNA-seq study of an arrhythmogenic sub-phenotype within DCM. Aside from the reasons mentioned above, this study was unique in that it is the first to investigate sub-phenotypes in DCM using RNA-seq. DCM patients with ventricular arrhythmias have been recognized as a distinct clinical population of patients within DCM¹⁶⁷, but it was unknown whether there are underlying biological differences between these groups of patients that contribute to such a clinical phenotype.



В

comparison	power		
NF vs HF	0.951		
NF vs ICM	0.890		
NF vs DCM	0.394		
DCM vs ICM	0.995		
aDCM vs naDCM	0.994		

Figure 2. RNA-seq power analysis. A) A power analysis of failing vs NF left ventricles based on prior RNA-seq data demonstrates that as the sample size increases, so does the power, until a plateau occurs at approximately 100 samples B) Using 100 samples per group, the predicted power is listed for each comparison.

Α

Future directions and recommendations

Understanding disease mechanisms in HF and how they can relate to improved or novel therapeutics will require a better understanding of how end-stage disease relates to earlier stages of disease. Gene expression signatures identified in end-stage human hearts are not necessarily indicative of the molecular changes that occurred upstream. One way to address this is to study tissue or models from an earlier stage of disease. The work in this thesis attempted to establish an early-stage disease model of iPSC-CM LMNA^{+/-}, but this effort was not successfully. Biopsies represent another resource of early-stage disease, but these are rare and precarious to extract RNA from due to their small size. Fortunately, the Division of Cardiology Cardiac Tissue Biobank has collected more than 100 LVAD core tissue samples which could be utilized to better understand HF progression. These are left ventricular tissues collected at the time of LVAD implantation, which is a procedure that sometimes occurs as a bridge to transplantation. The LVAD ensures that the heart continues to pump and circulate blood. LVAD cores represent a stage of disease prior to heart transplant; although some patients who receive LVADs go on to also get transplanted, others do not. Future work in the lab is already focused on using RNA-seq to investigate gene expression differences between LVAD cores and explanted hearts, using patients from the work in this thesis that also have LVAD core tissue available.

The lab recently received a TOPMed grant to perform RNA-seq and whole-genome sequencing in approximately 700 explanted human hearts. Using the RNA-seq data generated for this thesis, we were able to perform a power analysis and sample size calculation to determine how many samples per disease group will maximize data output. We calculated that by comparing 100 failing to 100 NF hearts, at an FDR of 5% and a fold change cutoff of 1.5, we will be able to detect ~95% of DEGs (Figure 2A). As the sample size increases from 100, the

power plateaus, demonstrating that adding additional samples will not necessarily provide valuable information. Based on the disease comparisons we have already performed, selecting ~100 samples per group is predicted to detect ~90-99% of DEGs for all comparisons except NF vs DCM (Figure 2B). This comparison in particular has a relatively low predictive value compared to the other calculations. An intriguing but not surprising finding from the first RNAseq study comparing DCM and ICM is that DCM gene expression is more heterogeneous than ICM. Although we explored one potential causal factor of this in the second RNA-seq study comparing aDCM and naDCM, it is likely that arrhythmogenicity is only one of the many factors contributing to heterogeneity in DCM. Another factor that likely contributes to this heterogeneity is underlying genetic mutations, as DCM is often an autosomal dominant disease resulting from a mutation in a single gene while ICM is characterized by some genetic predispositions but mostly by environmental factors. Although causal mutations are known for a handful of DCM patients in the study, it is likely that other patients carry causal mutations as well because we would expect to identify them in approximately 40% of DCM patients⁴⁴. Perhaps mutations in a single gene or a set of functionally related genes have distinct mechanisms; samples could be stratified into groups based on these mutations and analyzed for gene-specific mechanisms. Given our modest sample size of 37 DCM, a 40% discovery rate, and >50 disease genes, this approach was impractical for the studies described here; however, with the TOPMed grant, will be performing RNA-seq and whole-genome sequencing on ~200 DCM patients, so for some of the genes that account for a higher proportion of known genetic causes (LMNA, 6-11%^{89,179}; truncating mutations in *TTN*, $15-20\%^{61,63,64}$) this type of analysis may be feasible. Other genes could be grouped into similar functions, like the sarcomere, ion channels, nucleus, desmosome, and cytoskeleton to investigate if these share similar mechanisms as well. Alternatively, or

preferably in combination, an unsupervised or machine learning approach could be employed. This type of analysis would define the groups agnostically based solely upon gene expression, and a post-hoc analysis of clinical phenotype would reveal any shared etiology.

One of the biggest obstacles in studying gene expression in tissue is the inability to disentangle signals from different cell types. For example, if there is a gene in one cell type that is upregulated but it is downregulated in another cell type, these will cancel each other out. Additionally, pathways that are predicted to be activated or inhibited may not actually be so; alternatively, decreased or increased proportions of a particular cell type could also account for this signal. Adult heart tissue is comprised of only ~20-40% CMs;^{247,248} the remaining non-CMs is estimated to be 65% endothelial cells, 15% fibroblasts, 10% leukocytes, and 10% "other"²⁵⁶. Even among these cell "types," heterogeneity exists; global expression profiles of single cells in heart tissue demonstrate that for some groups, cells are characterized by a gradient of expression from one type to another instead of distinct clustering with well-defined boundaries. This means that cells are not always definable by gene expression alone or that our current technology cannot resolve such subtle differences²⁵⁵. Single cell RNA-seq has not been reported in human heart, and thus no failing vs NF comparison exists. Such a study would be technically challenging, as the tissue would have to be fresh. Still, work done in comparing single cell RNAseq between a healthy and ischemic mouse heart suggests that such a study would likely yield interesting results. As expected, the findings demonstrated that not only does global gene expression change with disease, but cell subpopulation ratios change as well²⁵⁷.

The goal of better understanding HF mechanisms, and how differences in etiology or phenotype contribute to differences in mechanisms, is of course to be able to provide improved treatment options for patients. With ~50% of HF patients dying within 5 years of diagnosis, there
is ample room for improvement^{1,6}. In order to transition from transcriptome signatures that are suggestive of distinct biological mechanisms to therapeutics, there are a number of hurdles to overcome. First, the mechanisms would have to be confirmed, either in a cell or an animal model. Second, a therapy, directed at the defined mechanism, would have to be demonstrated as an effective treatment. Lastly, a biomarker platform would have to be designed to detect a biological signal that would inform therapy. Any biomarkers destined for clinical use would have to first demonstrate three abilities: analytical validity, clinical validity, and clinical utility; that is, the technology the test uses must be accurate and reproducible, it must have a validated clinical prediction, and it must provide clinically useful information.²⁵⁸ With current technologies, any biomarkers would have to be validated in blood in order to be clinically useful; heart tissue biopsies are invasive and typically saved as a last diagnostic resort after other prognostic avenues have been exhausted²⁵⁹.

Transcriptome data of human heart tissue is a rare and valuable asset, but its true potential will only be realized when combined with mechanistic studies and other omic technologies for a truly systematic approach. The work in this thesis establishes the importance of considering disease-specific and sub-type specific analyses in transcriptome research in HF, and it provides a groundwork for further investigation into defining mechanisms of HF, which will aid in moving the field from a "one-size-fits-all" approach towards a more personalized treatment philosophy.

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APPENDIX A

RNA-seq supplemental materials

Table S1 Sample table. Characteristics including sex, race, ethnicity, age, cause of death (if applicable) and RNA integrity (RIN) score are listed.

Sample	Sample subtype	Sex	Race	Ethnicity	Age at Transplant	Cause of Death (NF only)	RNA integrity (RIN)
NF8	NA	Male	Unknown	Hispanic/Latino	46	CVA	8.5
NF7	NA	Male	White	Unknown	31	CVA	7.6
NF6	NA	Male	White	Unknown	54	CVA	8.4
NF5	NA	Male	White	Unknown	40	Blunt head trauma	7.7
NF4	NA	Male	White	Unknown	46	CVA	8.7
NF3	NA	Male	White	Unknown	60	Respiratory Arrest	8.5
NF2	NA	Male	White	Unknown	46	Subarachnoid hemorrhage	8.2
NF15	NA	Male	White	Unknown	52	Gun shot wound	8.2
NF14	NA	Male	White	Unknown	60	CVA	8.5
NF13	NA	Female	White	Unknown	58	Cerebrovascular Stroke	8.5
NF12	NA	Female	White	Unknown	56	Intercranial Hemorrhage/Stroke	8.9
NF11	NA	Female	White	Not Hispanic/Latino	41	Anoxia, seizure	8.6
NF10	NA	Male	White	Unknown	54	CVA	9.3
NF1	NA	Male	White	Unknown	43	Hanging, Suicide	8.8
ICM64	NA	Male	White	Not Hispanic/Latino	58	NA	8
ICM63	NA	Female	White	Not Hispanic/Latino	55	NA	9
ICM61	NA	Male	White	Not Hispanic/Latino	61	NA	8.1
ICM59	NA	Male	White	Not Hispanic/Latino	49	NA	7.3
ICM58	NA	Male	White	Unknown	62	NA	7.5
ICM56	NA	Male	White	Not Hispanic/Latino	56	NA	7.6
ICM55	NA	Female	White	Unknown	60	NA	7.1
ICM54	NA	Female	White	Unknown	56	NA	7.1
ICM53	NA	Male	White	Not Hispanic/Latino	54	NA	7.2
ICM52	NA	Male	White	Not Hispanic/Latino	49	NA	7.9
ICM50	NA	Male	White	Unknown	55	NA	7.1
ICM49	NA	Male	White	Unknown	56	NA	7
ICM47	NA	Male	White	Hispanic/Latino	63	NA	7.6
DCM8	aDCM	Male	White	Unknown	57	NA	7.8
DCM78	naDCM	Female	White	Not Hispanic/Latino	57	NA	8.5
DCM77	naDCM	Male	Unknown	Unknown	44	NA	7.2
DCM76	naDCM	Male	White	Not Hispanic/Latino	47	NA	7.9
DCM75	naDCM	Female	White	Not Hispanic/Latino	43	NA	7.4
DCM74	aDCM	Male	White	Not Hispanic/Latino	55	NA	8.1

Sample	Sample subtype	Sex	Race	Ethnicity	Age at Transplant	Cause of Death (NF only)	RNA integrity (RIN)
DCM73	aDCM	Male	Unknown	Hispanic/Latino	49	NA	7.6
DCM72	aDCM	Male	White	Not Hispanic/Latino	61	NA	7.8
DCM6	aDCM	Female	White	Not Hispanic/Latino	66	NA	7.1
DCM46	naDCM	Female	White	Not Hispanic/Latino	46	NA	8.3
DCM44	aDCM	Male	White	Hispanic/Latino	66	NA	7.1
DCM43	NA	Male	White	Not Hispanic/Latino	28	NA	8.1
DCM4	aDCM	Male	White	Unknown	26	NA	7.8
DCM39	naDCM	Male	White	Not Hispanic/Latino	65	NA	7.5
DCM38	naDCM	Male	White	Not Hispanic/Latino	52	NA	7.7
DCM35	naDCM	Female	White	Not Hispanic/Latino	57	NA	7.8
DCM34	NA	Male	White	Not Hispanic/Latino	59	NA	8
DCM33	aDCM	Male	White	Not Hispanic/Latino	64	NA	7.3
DCM32	naDCM	Male	Black or African American	Unknown	21	NA	7.9
DCM31	naDCM	Male	White	Hispanic/Latino	20	NA	7.2
DCM3	aDCM	Male	White	Unknown	66	NA	7
DCM29	naDCM	Male	White	Not Hispanic/Latino	41	NA	7.4
DCM28	naDCM	Male	White	Not Hispanic/Latino	43	NA	7.8
DCM26	aDCM	Male	White	Not Hispanic/Latino	39	NA	8.2
DCM24	aDCM	Male	White	Not Hispanic/Latino	63	NA	7.8
DCM22	naDCM	Male	White	Not Hispanic/Latino	65	NA	7.9
DCM21	naDCM	Male	Black or African American	Not Hispanic/Latino	52	NA	7.8
DCM20	naDCM	Male	White	Hispanic/Latino	45	NA	8.2
DCM2	aDCM	Male	White	Not Hispanic/Latino	38	NA	7.6
DCM19	aDCM	Male	White	Not Hispanic/Latino	57	NA	7.6
DCM18	aDCM	Male	White	Not Hispanic/Latino	29	NA	8.4
DCM17	aDCM	Male	Unknown	Hispanic/Latino	49	NA	8.2
DCM16	aDCM	Female	White	Unknown	51	NA	7.5
DCM14	aDCM	Male	White	Not Hispanic/Latino	47	NA	8
DCM13	naDCM	Male	White	Not Hispanic/Latino	27	NA	7.5
DCM12	aDCM	Male	Black or African American	Not Hispanic/Latino	51	NA	7.3
DCM11	aDCM	Female	White	Not Hispanic/Latino	59	NA	7.3

Sample	Sample subtype	Raw reads	Reads after QC	Percent yield after QC	Reads aligned	Percent yield after alignment
NF8	NA	57,720,015	57,285,773	99.25%	55,346,152	95.89%
NF7	NA	44,028,320	43,712,883	99.28%	42,105,154	95.63%
NF6	NA	55,524,901	55,125,616	99.28%	52,940,483	95.35%
NF5	NA	50,842,363	50,468,172	99.26%	48,549,009	95.49%
NF4	NA	53,646,936	53,269,546	99.30%	51,325,392	95.67%
NF3	NA	45,100,274	44,779,014	99.29%	43,035,675	95.42%
NF2	NA	42,564,384	42,263,328	99.29%	40,882,177	96.05%
NF15	NA	55,840,407	55,431,532	99.27%	53,551,987	95.90%
NF14	NA	46,963,851	46,619,695	99.27%	44,945,987	95.70%
NF13	NA	59,874,095	59,415,820	99.23%	57,269,228	95.65%
NF12	NA	64,882,190	64,403,196	99.26%	62,088,842	95.69%
NF11	NA	65,692,706	65,214,181	99.27%	62,645,616	95.36%
NF10	NA	49,689,489	49,328,352	99.27%	47,628,289	95.85%
NF1	NA	49,439,511	49,097,905	99.31%	47,545,579	96.17%
ICM64	NA	51,441,459	51,100,543	99.34%	49,000,107	95.25%
ICM63	NA	42,951,721	42,668,968	99.34%	40,829,541	95.06%
ICM61	NA	41,525,949	40,852,027	98.38%	39,069,828	94.09%
ICM59	NA	45,696,316	45,403,968	99.36%	43,627,273	95.47%
ICM58	NA	41,746,672	41,465,960	99.33%	39,740,426	95.19%
ICM56	NA	36,062,946	35,823,914	99.34%	33,887,389	93.97%
ICM55	NA	43,031,907	42,743,543	99.33%	40,966,204	95.20%
ICM54	NA	40,338,610	40,070,124	99.33%	38,436,755	95.29%
ICM53	NA	52,425,366	52,121,308	99.42%	50,071,561	95.51%
ICM52	NA	48,743,281	48,439,448	99.38%	46,685,229	95.78%
ICM50	NA	43,137,716	42,866,911	99.37%	41,185,591	95.47%
ICM49	NA	57,271,297	56,949,744	99.44%	54,565,934	95.28%
ICM47	NA	53,194,185	52,825,958	99.31%	50,607,502	95.14%
DCM8	aDCM	45,791,213	45,480,370	99.32%	43,654,529	95.33%
DCM78	naDCM	43,789,366	43,438,536	99.20%	41,973,980	95.85%
DCM77	naDCM	42,763,413	42,458,250	99.29%	40,762,829	95.32%
DCM76	naDCM	51,157,785	50,786,729	99.27%	48,893,295	95.57%
DCM75	naDCM	43,482,252	43,170,922	99.28%	41,604,894	95.68%
DCM74	aDCM	48,268,291	47,922,689	99.28%	46,121,660	95.55%
DCM73	aDCM	49,423,951	49,077,569	99.30%	47,238,521	95.58%
DCM72	aDCM	48,492,947	48,151,996	99.30%	46,318,457	95.52%
DCM6	aDCM	52,038,373	51,716,651	99.38%	49,575,238	95.27%
DCM46	naDCM	45,599,797	45,301,724	99.35%	43,562,967	95.53%

Table S2 RNAseq quality control table. Raw read counts ranged from ~36-66 million. Readcounts show a 99% retention after base quality quality control and a 94-96% alignment rate.

Sample	Sample subtype	Raw reads	Reads after QC	Percent yield after QC	Reads aligned	Percent yield after alignment
DCM44	aDCM	49,226,109	48,887,895	99.31%	46,805,277	95.08%
DCM43	NA	46,004,873	45,703,613	99.35%	43,826,417	95.26%
DCM4	aDCM	48,958,404	48,677,580	99.43%	46,738,867	95.47%
DCM39	naDCM	54,888,402	54,530,170	99.35%	52,279,663	95.25%
DCM38	naDCM	57,631,945	57,201,067	99.25%	54,915,437	95.29%
DCM35	naDCM	49,672,640	49,323,920	99.30%	47,324,702	95.27%
DCM34	NA	46,905,250	46,598,487	99.35%	44,809,543	95.53%
DCM33	aDCM	47,277,674	46,982,740	99.38%	45,012,740	95.21%
DCM32	naDCM	45,616,500	45,324,504	99.36%	43,715,536	95.83%
DCM31	naDCM	52,044,823	51,734,053	99.40%	49,599,016	95.30%
DCM3	aDCM	46,190,701	45,914,223	99.40%	44,100,222	95.47%
DCM29	naDCM	44,245,913	43,801,387	99.00%	41,660,791	94.16%
DCM28	naDCM	56,406,403	56,079,470	99.42%	53,827,588	95.43%
DCM26	aDCM	54,266,242	53,947,566	99.41%	51,922,999	95.68%
DCM24	aDCM	48,507,535	48,213,278	99.39%	46,313,412	95.48%
DCM22	naDCM	49,929,195	49,611,282	99.36%	47,650,801	95.44%
DCM21	naDCM	44,302,843	44,022,182	99.37%	42,168,065	95.18%
DCM20	naDCM	43,472,457	43,138,943	99.23%	41,338,660	95.09%
DCM2	aDCM	44,041,982	43,753,958	99.35%	41,918,897	95.18%
DCM19	aDCM	40,303,118	40,013,291	99.28%	38,322,579	95.09%
DCM18	aDCM	39,095,341	38,818,597	99.29%	37,367,289	95.58%
DCM17	aDCM	49,233,042	48,867,438	99.26%	46,967,178	95.40%
DCM16	aDCM	45,927,210	45,586,193	99.26%	43,698,108	95.15%
DCM14	aDCM	58,658,866	58,286,590	99.37%	56,011,446	95.49%
DCM13	naDCM	42,049,580	41,752,854	99.29%	40,026,135	95.19%
DCM12	aDCM	40,562,720	40,300,289	99.35%	38,728,485	95.48%
DCM11	aDCM	43,066,279	42,791,026	99.36%	40,866,215	94.89%

APPENDIX B

Chapter II supplemental materials



Figure S1. Empirical distribution of FDR values ≤ 0.05 for 1,000 permutations. Histogram with the number of genes in each permutation that had an FDR less than or equal to 0.05 is in logarithmic scale on the x-axis with frequency in logarithmic scale on the y axis. A value of 0.1 was added to each count to display it logarithmically. Red dotted lines indicate the observed number of DEGs in the comparison for A) DCM *vs* NF, B) ICM *vs* NF, and C) ICM *vs* DCM.

Table S1: DCM-specific adjusted gene expression.

ENSG	DR≤0.05 Gene	NF mean	DCM mean	FC	nval Age	nval Sex	nval DCM v NE	EDR DCM v NE
ENSG00000175899	A2M	950.89	754.34	-1.26	0.905204443	0.140249193	0.00153915	0.003060773
ENSG00000266967	AARSD1	88.48	97.16	1.10	0.637376368	0.065172388	0.009764095	0.015443713
ENSG00000183044	ABAT	8.42	14.51	1.72	0.594298218	0.516880667	0.000687672	0.00149971
ENSG0000006071	ABCC8	5.10	11.09	2.17	0.778445384	0.922473022	9.41E-05	0.000270208
ENSG00000154175	ABI3BP	45.89	76.12	1.66	0.025608343	0.932518783	0.00642503	0.010765464
ENSG00000266210	AB182	10.46	16.33	1.56	0.034664403	0.795014966	0.001362481	0.026206265
ENSG00000250347	AC005740.4	18.84	13.17	-1.43	0.9290782	0.320593735	2.75E-06	1.32E-05
ENSG00000229695	AC011242.5	17.19	7.51	-2.29	0.66501546	0.239690752	1.64E-08	1.99E-07
ENSG00000234520	AC018464.3	159.34	107.69	-1.48	0.560549768	0.399946034	0.013127189	0.019991827
ENSG00000181495	AC026703.1	9.60	22.13	2.30	0.074774873	0.673155551	4.69E-05	0.000147324
ENSG00000143429	AC027612.6	15.77	21.06	1.34	0.779069493	0.484790261	0.002738128	0.005047019
ENSG00000234638 ENSG00000230979	AC053503.6 AC079250.1	23.33	5.67	-4.11	0.645439472	0.494113	4.38E-08 0.014274073	4.31E-07 0.021522947
ENSG0000235997	AC109642.1	8.33	14.43	1.73	0.183691623	0.769516221	0.000194498	0.000500389
ENSG00000131584	ACAP3	97.98	84.72	-1.16	0.885593804	0.580114737	0.008897517	0.014245091
ENSG00000100813	ACIN1	97.26	88.58	-1.10	0.937476867	0.773023353	0.036150384	0.048825282
ENSG00000131473	ACLY	28.41	21.65	-1.31	0.886668593	0.748085839	0.000107065	0.00030156
ENSG00000134575	ACP2	52.17	44.91	-1.16	0.274992143	0.942422569	0.016032696	0.023816686
ENSG00000131069	AC352 ACTR1A	132.03	128.20	-1.19	0.754187609	0.210781952	0.000177627	0.000/67031
ENSG00000170634	ACYP2	67.73	76.95	1.14	0.23453923	0.005513441	0.015659885	0.023358544
ENSG00000168615	ADAM9	58.08	39.42	-1.47	0.540705865	0.754873601	0.026301407	0.03686419
ENSG00000174233	ADCY6	124.05	149.93	1.21	0.125585793	0.152498496	0.009680874	0.015332657
ENSG00000197894	ADH5	155.58	176.60	1.14	0.854534221	0.022805154	0.024676527	0.034793608
ENSG00000173209	AHSAZ	37.01	51.06	1.38	0.448287784	0.476423446	0.000190482	0.000491583
ENSG00000151520	AKIRIN1	40.09	49.97	-1.25	0.462026819	0.695198735	0.006139327	0.010345578
ENSG00000166199	ALKBH3	27.49	21.38	-1.29	0.956196501	0.60055028	0.000137826	0.000374122
ENSG00000178038	ALS2CL	37.25	31.82	-1.17	0.171577743	0.873133611	0.034844155	0.047251098
ENSG00000114019	AMOTL2	28.79	37.66	1.31	0.963193867	0.785759401	0.020880591	0.02991758
ENSG00000145020	AMT	44.63	55.94	1.25	0.740971777	0.682425473	0.001232816	0.002509813
ENSG00000129055	ANAPC13	101.88	115.46	1.13	0.133066731	0.258727486	0.014924756	0.02237527
ENSG00000118194	ANGPTE1 ANK1	181.90	126.05	-1.45	0.105777181	0.914857076	0.005735849	0.009724749
ENSG00000106524	ANKMY2	23.79	29.84	1.25	0.241290011	0.568246731	0.000603174	0.001341615
ENSG00000182718	ANXA2	168.49	121.18	-1.39	0.887632142	0.052894106	0.002524517	0.004708504
ENSG00000213406	ANXA2P1	31.48	21.35	-1.47	0.606895434	0.469245131	0.000258742	0.00064074
ENSG0000265590	AP000275.65	13.64	5.79	-2.36	0.448459801	0.103929931	4.74E-08	4.61E-07
ENSG00000254614	AP003068.23	12.34	5.94	-2.08	0.621677746	0.237904894	1.20E-06	6.60E-06
ENSG00000134262	AP4B1	22.28	27.74	1.25	0.680755867	0.398266017	7.31E-06	3.02E-05
ENSG00000166313	APBB1	84.43	74.73	-1.13	0.972305296	0.512815903	0.02983051	0.041222408
ENSG00000100823	APEX1	109.73	97.46	-1.13	0.610176278	0.911337258	0.017839787	0.02609823
ENSG00000189058	APOD	949.90	601.52	-1.58	0.27969264	0.878497461	0.004316695	0.007566252
ENSG00000165272	AQP3	20.69	12.64	-1.64	0.989116991	0.287711057	0.019701637	0.028503596
ENSG00000120318 ENSG00000111348	ARAP3	15.25	20.37	1.34	0.13/851/05	0.587790872	3.9/E-U6 0.012787516	1.79E-05 0.019556645
ENSG00000177479	ARIH2	118.72	143.54	1.21	0.449094642	0.189792556	0.008032873	0.013033378
ENSG00000134108	ARL8B	45.53	52.92	1.16	0.615472941	0.594217812	0.018009451	0.026330097
ENSG00000114098	ARMC8	53.31	67.26	1.26	0.663002749	0.966892967	0.008174058	0.013235125
ENSG00000137486	ARRB1	22.51	17.47	-1.29	0.671403318	0.546824043	0.009441026	0.014998126
ENSG00000105643	ARRDC2	15.99	26.58	1.66	0.328245211	0.39602248	0.01881371	0.027370146
ENSC00000113309	ARRDUS	24.22	10.46	1.00	0.55265926	0.109556955	0.000805685	0.00172751
ENSG00000239388	ASB14	11.51	6.46	-1.78	0.947293129	0.491014223	0.001269338	0.002573056
ENSG00000166669	ATF7IP2	30.60	25.13	-1.22	0.050784653	0.412468959	0.007210407	0.011907905
ENSG00000198925	ATG9A	88.48	77.48	-1.14	0.246422192	0.205727678	0.016885178	0.024887032
ENSG00000174437	ATP2A2	1527.73	1107.69	-1.38	0.000466906	0.10666243	4.66E-06	2.04E-05
ENSG00000159720	ATP6V0D1	104.09	95.18	-1.09	0.031933684	0.000139457	0.020122814	0.028979557
ENSG00000171953 ENSG00000087152	ATYN713	67.75	36.98	-1.12	0.240079955	0.535848232	0.029199645	0.040469232
ENSG00000177191	B3GNT8	73.05	45.51	-1.61	0.224621222	0.413335416	0.018422985	0.02686804
ENSG00000108641	B9D1	9.43	15.28	1.62	0.207092563	0.367448241	2.44E-08	2.73E-07
ENSG0000002330	BAD	118.96	91.98	-1.29	0.230676063	0.058565864	0.000612816	0.001357814
ENSG00000137936	BCAR3	27.42	20.04	-1.37	0.804238987	0.750608237	0.017709248	0.025963652
ENSG00000099968	BCL2L13	77.15	52.64	-1.47	0.732553045	0.439192995	0.036707541	0.049535219
ENSG00000133169	BDH2 BEX1	5.78	42.68	2.69	0.271746594	0.330023873	0.001107974	0.002287258
ENSG00000176171	BNIP3	192.50	165.48	-1.16	0.879066463	0.420430873	0.021059333	0.030123326
ENSG00000163170	BOLA3	124.35	107.65	-1.16	0.434756518	0.31543421	0.021986958	0.031348203
ENSG00000137274	BPHL	15.44	21.67	1.40	0.275900934	0.171898349	2.43E-07	1.77E-06
ENSG0000166164	BRD7	41.90	47.30	1.13	0.279333231	0.2294646	0.027399345	0.038266562
ENSG00000107738	C10orf54	80.19	64.93	-1.24	0.338441417	0.801515919	0.014383272	0.021666814
ENSG00000123144	C1orf123	66.56	72.82	1.09	0.68104	0.925402562	0.005461632	0.009299962
ENSG00000187642	C1orf170	131.07	85.85	-1.53	0.435570267	0.403224002	0.000364643	0.00085854
ENSG00000116667	Clorf21	61.18	76.54	1.25	0.456244902	0.823532723	0.020834621	0.029867813
ENSG00000173369	C1QB	65.86	44.96	-1.46	0.591152963	0.640394002	0.034480097	0.046810728
ENSG0000089101	C20orf26	50.26	71.22	1.42	0.217396351	0.06047842	0.002697486	0.004981844
ENSG000001123730	Coorf6?	/80.23	555.69 71.40	-2.34	0.134525479	0.262045625	2.23E-U5 0.001256157	7.78E-U5 0.002549626
ENSG00000198663	C6orf89	40.60	33.91	-1.20	0.336643635	0.255486515	0.000298611	0.000724627
ENSG00000162909	CAPN2	81.44	70.39	-1.16	0.544064776	0.1772411	0.020625097	0.029594441
ENSG00000153048	CARHSP1	35.50	28.58	-1.24	0.746718666	0.734206928	0.011072558	0.017231358
ENSG00000121691	CAT	61.74	80.06	1.30	0.419231627	0.109733159	0.001496444	0.002980876
EN5G00000119916	CCNB1IP1 CCNI	107.10	127.12	1.19	0.489750507	0.079342265	0.024790952	0.034934052
ENSG00000170458	CD14	21.30	14.79	-1.44	0.816320101	0.46104283	0.032037562	0.043873687
ENSG00000177575	CD163	168.98	72.35	-2.34	0.193682357	0.959037774	0.001443392	0.002884948
ENSG00000103855	CD276	31.53	26.09	-1.21	0.906448361	0.697288675	0.035525589	0.048084262
ENSG00000215039	CD27-AS1	33.20	40.33	1.21	0.226360646	0.468082449	0.022014392	0.031377829
EN5G0000151455	CDC122	107.21	83.72 cc en	-1.28	0.438330717	0.240285491	0.016797228	0.024796158
ENSG00000151405	CDCA7I	49.34	34.86	-1.14	0.624193452	0.914085103	0.016808747	0.024805397
ENSG0000008128	CDK11A	44.88	37.34	-1.20	0.444579108	0.216388376	0.007639574	0.01249847
ENSG00000111328	CDK2AP1	100.71	81.71	-1.23	0.595916145	0.704167809	0.000266011	0.000654273
ENSG00000129355	CDKN2 D	17.11	11.31	-1.51	0.404570879	0.766800464	3.80E-12	3.14E-10
ENSG00000130695	CEP85	51.05	40.00	-1.28	0.982976245	0.13278243	0.010418779	0.016353044
ENSG00000258890	CEP95	27.13	35.07	1.29	0.0285556684	0.5//768135	0.001864951	0.003620109
ENSG00000128849	CGNL1	5.10	45.24	2.07	0.304569095	0.497100992	1.30F-06	7.00F-06
ENSG00000100288	СНКВ	87.90	105.77	1.20	0.712708303	0.550515939	0.006137458	0.010345578
ENSG00000258289	CHURC1	95.89	116.83	1.22	0.182277513	0.409625899	0.007650129	0.012511397
ENSG0000005194	CIAPIN1	85.94	73.95	-1.16	0.649353966	0.445088351	0.003253126	0.00589262
ENSG00000230055	CISD3	61.98	53.99	-1.15	0.394090526	0.138967078	0.023769946	0.033646141
ENSG0000169375	COAS	430.04	599.71 37.66	-1.37	0.33019/242	0.3408/268/	0.002212643	0.004201616
ENSG00000168434	COG7	17.38	22.59	1.30	0.444668848	0.614879136	1.49E-05	5.53E-05
ENSG00000144810	COL8A1	11.76	19.13	1.63	0.032195872	0.726269303	0.00516212	0.008860355
ENSG00000149600	COMMD7	55.95	50.87	-1.10	0.066297306	0.758065194	0.009868276	0.015582358
ENSG00000145244	CORIN	67.99	32.34	-2.10	0.007281021	0.477907585	0.004298714	0.00754617
ENSG00000213025	COX20P1	20.85	14.96	-1.39	0.546369618	0.566542899	0.001139294	0.002336569
ENSG0000111775	COX411P1 COX6A1	15.54	7.49	-2.08	0.305130191	0.749204784	7.65E-08 0.032026482	6.92E-07 0.043871256
ENSG00000161281	COX7A1	5708.97	6773.68	1.19	0.600520975	0.239978159	0.02612996	0.036645676
ENSG00000243453	COX7BP1	28.17	9.86	-2.86	0.019909845	0.983953809	0.008020103	0.01302162
ENSG00000160111	CPAMD8	34.07	23.76	-1.43	0.154631106	0.849867372	0.025922524	0.036376399

DCM-specific DEGs at F	DR≤0.05							
ENSG ENSG00000106024	Gene	NF_mean	DCM_mean	FC 1.62	pval_Age	pval_Sex	pval_DCM_v_NF	FDR_DCM_v_NF
ENSG00000214078	CPNE1	131.70	151.93	1.02	0.559930237	0.523250363	0.018185096	0.026562183
ENSG00000205560	CPT1B	328.40	410.49	1.25	0.889246494	0.095672522	0.004457961	0.007784921
ENSG00000157184	CPT2 CPER2L1	16.78	22.90	1.36	0.370483278	0.103402432	1.43E-05	5.36E-05
ENSG00000150938	CRIM1	20.22	30.92	1.53	0.02585902	0.500217029	0.000555654	0.00124936
ENSG00000103653	CSK	27.15	22.09	-1.23	0.743087288	0.827152533	0.007498654	0.012293517
ENSG00000264868	CTB-167B5.2	12.14	6.88	-1.77	0.065247146	0.253571657	6.20E-06	2.61E-05
ENSG00000264281	CTD-2031P19.4	38.46	10.87	-3.54	0.201467055	0.481663714	0.013811682	0.02088585
ENSG00000175826	CTDNEP1	104.78	91.52	-1.14	0.732583053	0.875492483	0.000106937	0.000301436
ENSG00000109861 ENSG00000147113	CTSC CXorf36	34.35	21.75	-1.58	0.77819154	0.45053802	0.006968237	0.011548414
ENSG0000071967	CYBRD1	30.19	41.05	1.36	0.023071344	0.393840466	0.016780011	0.0247785
ENSG00000179091	CYC1	399.46	354.07	-1.13	0.080981337	0.175921628	0.014614341	0.021951774
ENSG00000108669	CYTH1	44.15	34.06	-1.30	0.060526314	0.601183962	0.000162714	0.000430284
ENSG00000130311	DDA1	46.10	40.35	-1.20	0.826582988	0.169257204	0.033869677	0.046141441
ENSG00000198171	DDRGK1	49.04	43.73	-1.12	0.234030015	0.047777331	0.015895103	0.023657011
ENSG00000100201	DDX17	296.94	332.59	1.12	0.389497513	0.566468621	0.013059513	0.019904881
ENSG00000198231	DDX23 DDX42	43.24	49.71	1.15	0.134959368	0.840764384	0.008399153	0.013548411
ENSG00000182108	DEXI	90.74	73.96	-1.23	0.395336478	0.030349928	0.000595781	0.001326928
ENSG0000058866	DGKG	23.00	34.60	1.50	0.055095876	0.910147843	0.000579661	0.001295923
ENSG00000174953	DHX36	48.45	62.58	1.28	0.487801539	0.012381999	7.76E-05	0.000228821
ENSG00000211448	DIO2	14.16	27.57	1.95	0.156106089	0.399854284	0.001392639	0.002792979
ENSG00000162595	DIRAS3	7.90	17.75	2.25	0.971652937	0.142782687	0.001666224	0.003289885
ENSG00000130818	DPY19L2	40.68	29.44 50.89	1.25	0.117099322	0.659063309	0.007208968	0.011907905
ENSG00000175550	DRAP1	123.75	104.68	-1.18	0.558701425	0.035982272	0.008204985	0.013276082
ENSG00000151914	DST	501.43	603.49	1.20	0.257306751	0.262151215	0.007573021	0.012402499
ENSG00000250182	EEF1A1P13	89.38	78.64	-1.14	0.168544429	0.976741024	0.0001727698	0.001471012
ENSG00000269858	EGLN2	43.76	38.29	-1.14	0.842391731	0.962095493	0.025859596	0.036309707
ENSG0000086232	EIF2AK1 FIF3G	71.78	64.88	-1.11	0.363070283	0.199630826	0.011647652	0.017953148
ENSG00000156976	EIF4A2	488.00	572.82	1.17	0.680410974	0.988566381	0.018369045	0.026797663
ENSG00000224781	EIF4A2P4	27.53	35.30	1.28	0.840702159	0.142437682	0.000660887	0.00145069
ENSG00000114867	EIF4G1	203.54	163.85	-1.24	0.725601246	0.299726038	0.00020143	0.000513652
ENSG00000127774	EMC6	29.42	48.45	-1.24	0.480654036	0.956737924	0.003237696	0.000297235
ENSG00000213853	EMP2	83.30	70.59	-1.18	0.476381091	0.825394171	0.009668189	0.015317712
ENSG0000086289	EPDR1	29.28	37.32	1.27	0.393491879	0.510186744	0.003456653	0.006218283
ENSG00000157036	EXOG	24.20	29.88	-1.17	0.236350843	0.371712329	0.012221236	0.005571033
ENSG00000124491	F13A1	51.88	27.84	-1.86	0.852062142	0.41876709	0.001678694	0.003308344
ENSG00000234964	FABP5P7	110.48	77.59	-1.42	0.101251766	0.878972077	0.002703074	0.004990209
ENSG00000221968 ENSG00000189350	FAD53 FAM179A	174.47	133.52	-1.31	0.353474246	0.1265/3/18	0.002777779	0.003917876
ENSG0000047346	FAM214A	43.59	55.90	1.28	0.990874975	0.288749997	0.010427087	0.016360637
ENSG0000169710	FASN	24.47	15.56	-1.57	0.440653662	0.642422211	0.012878083	0.019656899
ENSG00000162458 ENSG00000112787	FBLIM1 FBRSI 1	55.00	39.57	-1.39	0.39334041	0.003519255	0.000577204	0.001292268
ENSG00000158869	FCER1G	43.41	22.37	-1.94	0.488158821	0.693256182	3.34E-05	0.000109973
ENSG00000203747	FCGR3A	15.07	8.02	-1.88	0.273564584	0.258775123	0.001949348	0.003755037
ENSG00000113578 ENSG00000168386	FGF1 FILIP1I	53.18	68.65	1.29	0.085925644	0.310164555	0.004914203	0.008474933
ENSG00000173486	FKBP2	100.49	78.13	-1.29	0.588149262	0.025855335	0.000587684	0.001311372
ENSG0000004478	FKBP4	39.81	33.53	-1.19	0.76181467	0.353308159	0.020624539	0.029594441
ENSG00000177731 ENSG00000219507	FLII FTH1P8	20.25	12.05	-1.10	0.971164851	0.548944456	0.030578808	0.003520508
ENSG00000140564	FURIN	40.15	28.84	-1.39	0.827451216	0.258269714	0.000109004	0.000305925
ENSG00000139112	GABARAPL1	333.99	404.91	1.21	0.850704596	0.479841976	0.016615871	0.024574602
ENSG00000266010	GABRA4 GATA6-AS1	93.40	19.80	1.97	0.13153807	0.084952685	0.03469935	0.000489473
ENSG00000143140	GJA5	9.37	15.34	1.64	0.074014844	0.752827233	0.022607633	0.032165054
ENSG00000224051	GLTPD1 GMPR	42.49	33.01	-1.29	0.792846777	0.041037375	0.001077251	0.002232632
ENSG00000163938	GNL3	45.65	33.17	-1.19	0.794304074	0.947016669	0.000551051	0.001240194
ENSG00000120053	GOT1	891.59	783.40	-1.14	0.002990166	0.269955443	0.021351678	0.030488541
ENSG00000125772	GPCPD1 GPR157	13.25	21.00	1.58	0.182793105	0.570867264	2.28E-07	1.68E-06
ENSG00000166123	GPT2	12.34	7.21	-1.71	0.234091106	0.380564713	1.12E-06	6.26E-06
ENSG00000177885	GRB2	114.20	80.99	-1.41	0.071656899	0.911027809	0.000114863	0.000319704
ENSG00000134202	GSTM3	183.09	124.08	-1.48	0.431970194	0.112481342	0.002368087	0.004444877
ENSG00000189060	H1F0	70.70	46.70	-1.20	0.564756905	0.682829518	0.025301565	0.035611009
ENSG00000164032	H2AFZ	86.15	65.69	-1.31	0.827476129	0.047573379	2.94E-05	9.87E-05
ENSG00000103253	HAGHL	49.34	23.75	-2.08	0.849860884	0.090340383	0.015242213	0.022769434
ENSG0000051620	HEBP2	116.19	128.75	1.11	0.274880624	0.243022051	0.036119895	0.048798082
ENSG00000138411	HECW2	21.88	14.26	-1.54	0.693835027	0.57447691	0.026688071	0.037350625
ENSG00000135547 ENSG00000117305	HEY2 HMGCI	24.86	11.73 51 76	-2.12	0.094009547	0.976939828	3.20E-05 0.002142476	0.000105955
ENSG00000134240	HMGCS2	24.04	8.48	-2.83	0.63181723	0.190871409	0.024550549	0.034656753
ENSG00000189159	HN1	36.43	25.31	-1.44	0.301689624	0.846416049	0.000573478	0.00128637
ENSG00000169813 ENSG00000152197	HNRNPF	63.22	54.84	-1.15	0.79968705	0.033953094	0.006589857	0.011002541
ENSG00000261701	HPR	84.39	53.61	-1.57	0.841880612	0.193316088	0.02589566	0.03634952
ENSG00000173641	HSPB7	4970.82	4411.41	-1.13	0.116773617	0.148262278	0.01567749	0.023377408
ENSG00000167862 ENSG00000115732	ICT1 ID2	59.60 47.86	50.64	-1.18	0.177719313	0.536057609	0.005548008	0.027719086
ENSG00000216490	IFI30	15.88	8.69	-1.83	0.95978269	0.712651398	0.001745084	0.003419813
ENSG00000137965	IF144	20.96	30.66	1.46	0.917691043	0.927773838	0.011869462	0.018265181
ENSG0000027697	IFII M3 IFNGR1	411.48 139.12	347.69 117.72	-1.18 -1 18	0.171717599	0.501787452	0.030510832 0.023187506	0.042086748
ENSG00000214706	IFRD2	117.54	90.60	-1.30	0.882020433	0.195195145	6.17E-05	0.000187566
ENSG00000100360	IFT27	40.81	46.04	1.13	0.102656168	0.084386558	0.009596759	0.015219885
ENSG00000178035	IMPDH2	11/.00	103.30	-1.13	0.957253869	0.1/0468224	0.007351702	0.012103099
ENSG00000132849	INADL	53.31	63.55	1.19	0.813496822	0.521152235	0.024881147	0.035040206
ENSG00000165458	INPPL1	207.76	175.32	-1.19	0.819615703	0.618374865	0.005020367	0.008639062
ENSG00000171105 ENSG00000065150	INSK IPO5	30.47 47.92	36.43 55.75	1.20	0.265118202	0.024527	0.012111004	0.018606512
ENSG00000184216	IRAK1	64.68	48.95	-1.32	0.529115339	0.35118816	0.001328516	0.002680339
ENSG00000177508	IRX3	41.16	70.77	1.72	0.034680478	0.498553555	0.006525575	0.010914539
ENSG00000111203	ITFG2	6.34 22.35	13.49 27.53	2.13	0.038248324	0.424857064	0.001155235	0.002366174
ENSG00000269378	ITGB1P1	88.79	74.52	-1.19	0.655197763	0.13773605	0.029073531	0.040306292
ENSG00000161999	JMJD8	70.00	63.37	-1.10	0.309837877	0.35170511	0.025978204	0.036443687
ENSG0000018//15	KCMF1	48.83	43.28	-1.13	0.369881484	0.205445219	0.013516336	0.020478639
ENSG00000187486	KCNJ11	24.27	16.97	-1.43	0.302450883	0.273518631	0.003840827	0.006826046
ENSG00000121361	KCNJ8	75.11	57.19	-1.31	0.107512555	0.131177393	0.004427344	0.007734319
ENSG00000136240 ENSG00000115548	KDELR2 KDM3A	84.40 32.33	70.03 38.77	-1.21 1 20	0.253704809	0.498153903	0.002191052	0.004172379
ENSG0000007202	KIAA0100	57.75	50.50	-1.14	0.737822686	0.741915544	0.003484499	0.006258824
ENSG0000079616	KIF22	29.51	35.89	1.22	0.112565932	0.040084982	0.025509357	0.035871345
ENSG0000075945 ENSG00000103550	KIFAP3 KNOP1	51.06 13.88	73.74 8.84	1.44 -1 57	0.043163319	0.652106914	0.000679558	0.001903885
ENSG00000126790	L3HYPDH	20.52	14.89	-1.38	0.23880753	0.602625613	0.004026016	0.007106951
ENSG00000115365	LANCL1	32.10	38.12	1.19	0.556436283	0.37888891	0.010300825	0.016194862

DCM-specific DEGs at F	DR≤0.05	NF man	DCM more		and Ass	and Can	and DCM is NO	
ENSG ENSG00000162511	LAPTM5	27.24	19.35	-1.41	0.20664273	0.454653927	0.029493643	0.040828693
ENSG00000213626	LBH	85.34	109.72	1.29	0.082518006	0.478430427	0.021379206	0.030518606
ENSG00000187922	LCN10	31.28	13.82	-2.26	0.958219955	0.972166564	0.008771451	0.014071926
ENSG00000214110	LDHAP4	78.75	54.20	-2.20	0.970363856	0.463680288	0.002080974	0.003978829
ENSG00000213574	LDHAP5	34.86	20.62	-1.69	0.88466754	0.717481207	2.97E-05	9.96E-05
ENSG00000232662 ENSG00000050426	LDHBP1	17.09	22.78	1.33	0.238305455	0.086208727	0.000309581	0.000747019
ENSG00000260032	LINC00657	85.03	98.64	1.16	0.098134675	0.152224484	0.021027189	0.030098117
ENSG00000233117	LINC00702	40.05	72.63	1.81	0.02472108	0.420858606	0.003788556	0.00674841
ENSG00000241135 ENSG00000186001	LINC00881 LRCH3	86.27 30.93	50.91 39.97	-1.69 1.29	0.260895267	0.739431137	0.008979011 0.000650237	0.014356065
ENSG00000137821	LRRC49	53.09	73.38	1.38	0.279272624	0.64312892	0.00548009	0.009328023
ENSG0000003056	M6PR MAE1	245.09	221.90	-1.10	0.08507495	0.287515847	0.004869929	0.008407805
ENSG00000145495	MARCH6	55.86	63.99	1.15	0.40369066	0.056741818	0.024337777	0.034367361
ENSG00000127241	MASP1	161.53	229.99	1.42	0.183390475	0.927297945	0.006304196	0.010586156
ENSG00000103495 ENSG00000198125	MAZ	57.97	47.19	-1.23	0.557789031	0.419278523	0.019272513	0.027959969
ENSG00000160294	МСМЗАР	61.89	49.83	-1.24	0.272781065	0.261757192	0.001432361	0.00286533
ENSG00000116353	MECR MEMO1	48.94	57.88	1.18	0.210636237	0.060756288	0.001695235	0.00333599
ENSG00000162959	MFF	82.61	44.52	-1.20	0.163320632	0.986771857	0.000888546	0.001882919
ENSG00000111341	MGP	845.44	1305.79	1.54	0.022057595	0.677633321	0.017464498	0.025660676
ENSG00000133816 ENSG00000165175	MICAL2 MID1 IP1	70.73	85.39	-1.21	0.318688567	0.481696435	0.030518471	0.042086748
ENSG00000089693	MLF2	191.36	175.33	-1.09	0.555038974	0.049722496	0.002769333	0.005098557
ENSG00000115648	MLPH	45.21	31.14	-1.45	0.594169348	0.681197748	0.008350421	0.013474413
ENSG00000234801	MOCS1 MORF4	33.87	26.78	-1.26	0.389358794	0.623917065	2.09E-07	1.57E-06
ENSG00000185787	MORF4L1	114.85	126.62	1.10	0.239053179	0.723708285	0.023044159	0.03272687
ENSG00000218283	MORF4L1P1	117.97	131.85	1.12	0.256442431	0.961102299	0.010615263	0.01660616
ENSG00000129255	MPDU1	33.13	27.89	-1.19	0.519820716	0.944764237	0.00681495	0.01132223
ENSG00000196199	MPHOSPH8	23.59	29.13	1.24	0.54020887	0.796606217	0.004768908	0.008263654
ENSG00000130830 ENSG00000174547	MPP1 MRPL11	45.67 62.33	40.40 55.79	-1.13	0.046991509	0.396702017 0.799791462	0.022177547	0.031581738 0.034260136
ENSG00000197345	MRPL21	123.72	107.72	-1.15	0.197507681	0.871686831	0.031012632	0.0426435
ENSG0000082515	MRPL22	82.80	72.43	-1.14	0.65514279	0.777064814	0.013213772	0.020104206
ENSG00000256222	MTRNR2L1	24.69	33.47	1.36	0.695188988	0.884145995	0.008197569	0.013268636
ENSG00000255633	MTRNR2L9	22.31	28.72	1.29	0.928458725	0.442700055	0.009067393	0.014477737
ENSG00000157601	MX1 MXBBP1A	9.25	14.63	1.58	0.82923169	0.975688893	0.025342429	0.035657879
ENSG00000132382 ENSG00000104177	MYEF2	17.20	23.82	1.38	0.006009382	0.994575605	0.000196491	0.000503554
ENSG00000133026	MYH10	22.81	29.84	1.31	0.024314391	0.608740967	0.031459935	0.043145315
ENSG00000160808 ENSG0000034971	MYL3 MYOC	8660.85	7146.79	-1.21	0.01386556	0.66109905	0.011381041	0.01762286
ENSG00000101605	MYOM1	1123.79	1367.88	1.22	0.842493679	0.226226762	0.033995689	0.046286363
ENSG00000263155	MYZAP	731.04	839.45	1.15	0.756816076	0.939397005	0.02802203	0.039009115
ENSG00000102030 ENSG00000122390	NAA10 NAA60	105.96	88.49 38.76	-1.20	0.734044668	8.71E-05 0.268622997	9.59E-05 0.001656372	0.000274707
ENSG00000138744	NAAA	18.60	26.54	1.43	0.804236875	0.705143897	0.000268855	0.000659548
ENSG00000188554	NBR1	45.77	51.07	1.12	0.526346805	0.655644048	0.013800134	0.020875082
ENSG00000109390	NDUFC1	734.36	675.32	-1.29	0.755356971	0.963502007	0.035088616	0.047566277
ENSG00000125967	NECAB3	78.24	90.25	1.15	0.50687756	0.523481592	0.011663802	0.017972166
ENSG0000066136 ENSG00000182768	NFYC	77.76	90.92 139.91	1.17	0.899696407	0.607076141	0.003260299	0.005903345
ENSG00000116962	NID1	58.53	45.21	-1.29	0.591499305	0.863601536	0.026869143	0.037581729
ENSG00000243678	NME1-NME2	209.54	171.00	-1.23	0.188593286	0.559724724	0.007252273	0.011951928
ENSG00000153406 ENSG00000182117	NMRAL1 NOP10	40.75	27.63	-1.47	0.452985049	0.655576311	0.003039105	0.005541522
ENSG00000048162	NOP16	64.95	50.17	-1.29	0.985196011	0.446404584	0.007924515	0.01289306
ENSG00000141279	NPEPPS	59.17	53.17	-1.11	0.234365435	0.208741402	0.016362333	0.024236288
ENSG00000115389 ENSG00000197893	NRAP	536.47	675.77	1.56	0.767988352	0.21905422	0.008848841	0.014186428
ENSG00000147383	NSDHL	19.08	12.44	-1.53	0.300938526	0.666723475	0.003970917	0.007028106
ENSG00000103274 ENSG00000015676	NUBP1 NUDCD3	52.81	44.63 91.56	-1.18	0.821510572	0.147597135	0.005668429	0.009620822
ENSG00000140876	NUDT7	44.86	58.34	1.30	0.516997406	0.148234791	0.000608142	0.00135071
ENSG00000167799	NUDT8	51.09	38.37	-1.33	0.128161136	0.010697839	0.013395949	0.020335447
ENSG00000110713 ENSG00000099330	NUP98 OCFL1	66.57	59.50 17.29	-1.12	0.264173723	0.382258973	0.023903225	0.033824642
ENSG00000127083	OMD	7.19	16.72	2.32	0.021729649	0.401241905	1.67E-05	6.10E-05
ENSG00000178814	OPLAH	53.12	44.58	-1.19	0.742380975	0.243785567	0.013233331	0.02012747
ENSG00000228474 ENSG0000083454	P2RX5	482.81 21.49	440.16	-1.10	0.016972933	0.157228936	0.030574345	0.04214452
ENSG0000072682	P4HA2	62.18	51.23	-1.21	0.326454825	0.288312376	0.002059185	0.003941964
ENSG00000185624	P4HB PARPCA	903.37	794.38	-1.14	0.689031314	0.391902793	0.01893237	0.027517301
ENSG00000158006	PAFAH2	15.21	25.37	1.67	0.665933598	0.947087349	0.00014608	0.000393132
ENSG00000175193	PARL	65.24	73.11	1.12	0.796993011	0.448976533	0.014610383	0.021951774
ENSG0000166228 ENSG00000180628	PCBD1 PCGF5	187.18 47.73	164.75 37.91	-1.14 -1.26	0.36537147 0.549648854	0.749523254 0.906709628	0.007981641 0.010510165	0.012977047
ENSG00000140479	PCSK6	32.78	48.33	1.47	0.473584919	0.248506101	0.003587422	0.006426556
ENSG00000186642 ENSG0000004799	PDE2A PDK4	40.02	31.03	-1.29	0.063680533	0.7133829	0.035097153	0.047566277
ENSG00000162734	PEA15	307.54	253.25	-1.21	0.696775916	0.158127951	0.022888066	0.032514984
ENSG00000229833	PET100	90.02	74.08	-1.22	0.62831744	0.69825187	0.020920772	0.029963985
ENSG00000162735 ENSG00000143256	PEX19 PEDN2	118.69	130.05 96.01	1.10	0.610329761	0.435714069	0.027895219	0.038870693
ENSG00000143236	PFKFB2	52.14	37.22	-1.40	0.542034646	0.699151067	0.03074946	0.042331008
ENSG00000170525	PFKFB3	16.53	10.53	-1.57	0.676410914	0.849341881	0.010063043	0.015852739
ENSG0000152556 ENSG00000108518	PENI PEN1	915.46 224.21	769.99 191.91	-1.19	0.003273643 0.587409532	0.744383989 0.515685593	0.002229925	0.004225923
ENSG0000070087	PFN2	105.44	80.44	-1.31	0.851934671	0.490024555	0.001350426	0.002719888
ENSG00000134686	PHC2	120.66	104.60	-1.15	0.554544577	0.912421959	0.013450988	0.020386181
ENSG00000087111	PIGS	53.13	47.50	-1.12	0.282254995	0.554769181	0.016016364	0.023801885
ENSG00000176485	PLA2G16	220.57	195.21	-1.13	0.318733111	0.717458554	0.031153557	0.042812306
ENSG0000104886 ENSG00000167676	PLEKHJ1 PLIN4	64.80 101.16	56.68 80.34	-1.14 -1.26	0.944839164	0.032136926	0.027950596	0.038932662
ENSG00000114698	PLSCR4	14.66	20.52	1.40	0.056072198	0.838161845	0.016106948	0.023904394
ENSG00000196576	PLXNB2	99.98	81.90	-1.22	0.968718955	0.612511284	0.008752134	0.014053744
ENSG0000160783 ENSG00000143442	PIVIF1 POGZ	54.93 33.66	47.39 42 12	-1.16	0.583512014	0.623650375	0.004206814	0.00740393
ENSG00000106628	POLD2	297.33	245.41	-1.21	0.540483056	0.964921242	0.002737238	0.005047019
ENSG00000186184	POLR1D	70.07	58.47	-1.20	0.638522787	0.786302679	0.013948915	0.021066347
ENSG00000167272	POLK2J3 POP5	48.44	45.49	1.44	0.250758033	0.335023039	0.00898249	0.01396557
ENSG00000133110	POSTN	47.78	128.88	2.70	0.054907018	0.423282971	0.004401159	0.007697131
ENSG00000127125	PPCS	40.89	46.38	1.13	0.413911534	0.748859389	0.03630236	0.049016503
ENSG00000160972	PPP1R16A	62.27	52.71	-1.18	0.942113886	0.023016053	0.021495638	0.030667189
ENSG00000120910	PPP3CC	39.15	26.48	-1.48	0.897642717	0.755199434	0.014120139	0.021311285
ENSG00000113593 ENSG00000167815	PPWD1 PRDX2	17.87 811 27	23.13	1.29	0.933528286	0.341331254	0.002496028	0.004659055
ENSG00000117592	PRDX6	352.38	274.90	-1.28	0.029325064	0.868795678	0.00048954	0.00111525
ENSG00000188783	PRELP	19.47	47.44	2.44	0.061539569	0.920182461	0.000223272	0.00056386
ENSG0000184500	PROS1	196.94 36.79	1/9.17 72.80	-1.10	0.312940101 0.002715277	0.333293269	0.031839578 5.27F-06	0.043640584 2.28F-05
ENSG00000189002	PROSP	12.30	36.95	3.00	0.238791972	0.235917055	0.000125812	0.000347106

DCM-specific DEGs at FD	R≤0.05							
ENSG	Gene	NF_mean	DCM_mean	FC 1.10	pval_Age	pval_Sex	pval_DCM_v_NF	FDR_DCM_v_NF
ENSG00000161542 ENSG00000116132	PRPSAP1 PRRX1	43.85	57.46	-1.18	0.002621625	0.6/5482/11	0.0004479191	0.007816205
ENSG00000100911	PSME2	112.60	88.22	-1.28	0.230223142	0.527746228	0.000817916	0.001748175
ENSG00000131467	PSME3	66.40	56.66	-1.17	0.737852179	0.471296005	0.001770833	0.003458773
ENSG00000110958	PTGES3	105.67	117.21	1.11	0.711898672	0.405907047	0.027558588	0.038466176
ENSG00000165996 ENSG00000179295	PTPLA PTPN11	261.31	226.65	-1.15	0.731278789	0.529650857	0.014757761	0.022153086
ENSG00000175354	PTPN2	32.67	27.24	-1.20	0.855280716	0.758387948	0.015224098	0.022751703
ENSG00000141378	PTRH2	18.45	13.06	-1.41	0.429971938	0.502916182	2.84E-06	1.35E-05
ENSG00000184924	PTRHD1	52.74	46.06	-1.14	0.372470047	0.110951056	0.03414413	0.046408064
ENSG00000176894 ENSG0000068976	PXMP2 PXGM	53.02	43.83	-1.21	0.092534404	0.762030865	0.020417486	0.02933371
ENSG00000111737	RAB35	36.97	30.47	-1.21	0.372097183	0.071948277	0.000226485	0.000570142
ENSG00000152061	RABGAP1L	70.00	90.51	1.29	0.350132901	0.26022174	0.020418502	0.02933371
ENSG00000128581	RABL5	33.45	40.84	1.22	0.645812731	0.608014088	0.000160045	0.000424416
ENSG00000203867	RBM20	51.22	41.27	-1.24	0.758363377	0.989050398	0.024284555	0.03430248
ENSG00000163743	RCHY1	37.45	43.15	1.15	0.627486523	0.275977088	0.009838849	0.015541096
ENSG0000049449	RCN1	38.65	29.10	-1.33	0.367693368	0.908587483	0.017723034	0.025975787
ENSG00000214455	RCN1P2	18.79	11.67	-1.61	0.977972079	0.938065753	0.000895563	0.001895003
ENSG00000131378	RFTN1	42.28	32.13	-1.32	0.436339247	0.001226544	0.000254936	0.000632977
ENSG00000173156	RHOD	28.32	19.44	-1.46	0.862171082	0.16351007	0.00017048	0.00044706
ENSG00000139725	RHOF	22.36	16.72	-1.34	0.2662527	0.051794372	0.000676961	0.001481147
ENSG00000265150	RN7SL2 RNASE1	17.96	30.61	1.70	0.456900829	0.9689131	0.015161693	0.022680007
ENSG00000239305	RNF103	69.99	60.52	-1.16	0.798411741	0.705132579	0.034132456	0.046405574
ENSG00000113269	RNF130	59.71	52.75	-1.13	0.154357117	0.575762815	0.017013743	0.025045207
ENSG00000255135	RP11-111M22.3	29.37	35.54	1.21	0.418917033	0.129094493	0.022110759	0.031496142
ENSG00000236404 ENSG00000253173	RP11-125B21.2 RP11-152C15.1	8.23	15.67	1.90	0.866440691	0.220877477	2.85E-06 3.05E-07	1.36E-05 2.12E-06
ENSG00000251235	RP11-156N15.1	27.89	22.19	-1.26	0.477005743	0.863633173	0.000903283	0.001903885
ENSG00000264112	RP11-159D12.2	14.63	22.23	1.52	0.752065643	0.113315978	1.75E-06	9.04E-06
ENSG00000250982	RP11-159J3.1	63.79	75.88	1.19	0.707196572	0.503874509	0.034043182	0.046324272
ENSG00000255248	RP11-166D19.1 RP11-175R9 3	52.24 116.57	/1.88	-1.38	0.000487554	0.105134322	0.000106217	0.000300068
ENSG00000228366	RP11-18B3.3	11.77	5.98	-1.97	0.887751164	0.252632322	8.02E-07	4.76E-06
ENSG00000262248	RP11-235E17.5	11.62	5.94	-1.96	0.063736212	0.122891504	4.57E-06	2.01E-05
ENSG00000230626	RP11-286H14.4	20.58	15.00	-1.37	0.727996818	0.249341432	2.71E-05	9.17E-05
ENSG00000236360	RP11-326A19.5	47.57	40.65	1.42	0.359720784	0.060521311	0.00808414	0.013112047
ENSG00000213036	RP11-365D23.4	62.66	54.99	-1.14	0.239771366	0.070982731	0.036924542	0.049813796
ENSG00000226900	RP11-432J24.5	92.05	62.27	-1.48	0.663504689	0.248990144	0.006220228	0.010466943
ENSG00000270213	RP11-452D24.1	47.61	26.81	-1.78	0.426358323	0.537710508	0.015361632	0.022928172
ENSG00000254771	RP11-50B3.1	13.95	6.80	-2.05	0.422366502	0.753115147	0.002534483	0.004725222
ENSG00000251141	RP11-53019.1	15.84	22.19	1.40	0.047591473	0.419569609	0.011401344	0.017648502
ENSG00000259413	RP11-5023.1	22.47	7.66	-2.93	0.750348455	0.321781139	1.65E-10	5.64E-09
ENSG00000267653	RP1-193H18.3 RP11.077G10.10	12.99	5.66	-2.29	0.163688324	0.336028551	0.011166651	0.017353579
ENSG00000257337	RP11-983P16.4	12.13	18.27	1.51	0.070065896	0.238894547	0.000165168	0.000435796
ENSG00000272114	RP1-261G23.7	16.85	5.42	-3.11	0.666348774	0.32857057	0.000100503	0.000286327
ENSG00000259613	RP13-608F4.6	7.66	28.68	3.74	0.692451966	0.319351451	0.006400203	0.010727678
ENSG00000235501 ENSG00000269968	RP4-639F20.1 RP5-94015 9	8.70	13.76	1.58	0.081624597	0.294074442	1.83E-05 2.54E-08	6.58E-05 2.80E-07
ENSG00000213307	RPL18P11	27.69	22.50	-1.23	0.368098446	0.709138299	0.01862161	0.027115779
ENSG00000163584	RPL22L1	34.18	25.71	-1.33	0.202992466	0.39892133	0.013412066	0.020348705
ENSG00000230364	RPL4P3	41.68	36.46	-1.14	0.424499898	0.047170403	0.021271225	0.030392068
ENSG0000089157 ENSG00000213553	RPLP0 RPLP0P6	240.45	185.94	-1.29	0.848027337	0.1093214	0.000200154	0.000510951
ENSG00000124614	RPS10	135.25	103.07	-1.31	0.738360111	0.695728432	0.01973904	0.028548949
ENSG00000187051	RPS19BP1	76.96	64.12	-1.20	0.99648356	0.047466207	0.001873423	0.003633562
ENSG00000140988	RPS2	255.52	216.98	-1.18	0.637960138	0.051448048	0.028787147	0.039979793
ENSG00000230829	RPSAP58	405.59	230.93	-1.70	0.733747718	0.039480886	0.019604835	0.02838968
ENSG00000176783	RUFY1	28.35	22.59	-1.26	0.211193994	0.702252326	0.000933356	0.001960255
ENSG00000143546	S100A8	62.63	26.39	-2.37	0.218483934	0.510199079	0.001116408	0.00230064
ENSG00000163220	\$100A9	88.14	32.58	-2.71	0.082980275	0.868258086	2.43E-05	8.32E-05
ENSG00000101347	SAT2	142.65	123.55	-1.39	0.4304485	0.634920085	0.030060657	0.041503952
ENSG00000165689	SDCCAG3	38.94	30.74	-1.27	0.433184836	0.929250636	0.000123517	0.000341975
ENSG00000224183	SDHDP6	61.07	71.10	1.16	0.139895357	0.009064208	0.004644491	0.00807477
ENSG00000198843	SELT	120.97	157.55	1.30	0.232532084	0.010451167	0.006670572	0.011121551
ENSG00000168385	SEPT2	266.39	304.84	-1.99	0.224061678	0.34132729	0.017048886	0.025089107
ENSG00000227850	SEPT2P1	144.20	176.67	1.23	0.062873789	0.408515973	0.004572654	0.007955743
ENSG00000140264	SERF2	787.53	679.70	-1.16	0.82562525	0.204948783	0.008099965	0.013133196
ENSG0000021355 ENSG00000135919	SERPINE1 SERPINE2	58.00	44.07	-1.32	0.78503749	0.406571612	0.000920897	0.001936677
ENSG00000132386	SERPINF1	331.41	444.78	1.34	0.0518044	0.798383179	0.032712034	0.044719409
ENSG00000168066	SF1	229.57	254.18	1.11	0.744688681	0.017914621	0.027647393	0.038567295
ENSG00000104332	SFRP1	21.67	35.77	1.65	0.552992382	0.167450634	0.017137403	0.025211499
ENSG00000127990 ENSG00000156463	SH3RF2	72.84 370 12	90.88	-1.34	0.07922339	0.046242243	0.012798361 0.010785973	0.019566885
ENSG00000198892	SHISA4	121.87	82.79	-1.47	0.784585746	0.876035337	0.000246309	0.000614609
ENSG00000147955	SIGMAR1	33.54	27.17	-1.23	0.357415016	0.560876633	7.51E-05	0.000222422
ENSG00000168575	SLC12A7 SLC20A2	91.98 113.51	75.56	-1.22	0.47631637	0.932896148	0.031365585	0.017784609
ENSG00000125454	SLC25A19	17.05	10.69	-1.59	0.946918355	0.383179393	1.97E-06	1.00E-05
ENSG00000153291	SLC25A27	33.93	48.98	1.44	0.244038292	0.814447858	0.000412481	0.000959945
ENSG00000117394	SLC2A1	33.44	25.26	-1.32	0.315839756	0.307706679	0.017602368	0.025843184
ENSG0000134294 ENSG00000143570	SLC38AZ SLC39A1	119.08 51.79	87.43 42.74	-1.36	0.9682424 0.717018952	0.30236417	0.0018557613	0.027030938
ENSG00000141873	SLC39A3	27.24	22.13	-1.23	0.283646881	0.704279923	0.000242213	0.000605533
ENSG00000114544	SLC41A3	57.53	48.41	-1.19	0.637135671	0.654805471	0.003168239	0.005749903
ENSG0000070214 ENSG00000100170	SLC44A1 SLC5A1	9.95	15.07	1.52	0.107445351	0.996323117	6.54E-06	2.73E-05
ENSG00000131389	SLC6A6	11.09	31.24	2.82	0.040940346	0.819014367	0.000588931	0.001313533
ENSG00000176463	SLCO3A1	44.87	39.49	-1.14	0.861213653	0.760866367	0.032058328	0.043889378
ENSG0000080503	SMARCA2	47.18	53.58	1.14	0.945989142	0.660470289	0.024249396	0.034263081
ENSG00000099940	SNAP29	52.48	46.54	-1.13	0.694878969	0.565237784	0.009721678	0.015392113
ENSG00000145335	SNCA	13.86	27.35	1.97	0.083561758	0.141420742	0.000175914	0.000460286
ENSG00000245910	SNHG6	329.39	274.18	-1.20	0.344586425	0.026210966	0.005756732	0.009753141
ENSG00000199753	SNORD104	45.63	159.58	3.50	0.922546946	0.061440132	0.009026714	0.014417668
ENSG0000161981	SNRNP25	104.10	249.92	2.4U -1.21	0.289012371	0.647028543	0.003805131	0.017560116
ENSG00000124562	SNRPC	164.94	132.61	-1.24	0.719205275	0.23417065	0.00015946	0.000423341
ENSG00000154556	SORBS2	983.74	1260.60	1.28	0.115857195	0.970198453	0.0134249	0.020359731
ENSG00000196141	SPATS2L	90.40	66.39	-1.36	0.423486	0.811520942	0.006537454	0.010922879
ENSG0000118785	SPP1	68.56 29.29	78.30	-3.65	0.869921023	0.110343336	0.008109027	0.001314337
ENSG00000138600	SPPL2A	65.57	54.87	-1.20	0.419528634	0.160063097	0.012316297	0.018884989
ENSG00000100104	SRRD	21.82	15.82	-1.38	0.85502368	0.626948767	0.017767048	0.026021018
ENSG00000100650	SRSF5	442.31	529.97	1.20	0.905328033	0.773732465	0.008878573	0.014224421
ENSG00000271303 ENSG00000073849	ST6GAL1	33.20 34.46	26.91 28.56	-1.23	0.282693509	0.918499976	0.02988921	0.041291423
ENSG00000127954	STEAP4	25.93	16.55	-1.57	0.11458243	0.226306218	0.001265655	0.002566694
ENSG00000168439	STIP1	108.22	83.86	-1.29	0.366977771	0.260698008	0.00046724	0.001070995
ENSG00000115694	STK25 STK40	198.32	182.90	-1.08	0.650646221	0.543208576	0.006537511	0.010922879
ENSG00000196182	STX10	46.78	35.73 52.29	-1.31	0.040306818	0.149568025	3.26E-US 0.005045663	0.000107564
ENSG00000137573	SULF1	7.47	15.00	2.01	0.019131136	0.787994477	0.002272455	0.00428585

DCM-specific DEGs at F	DR≤0.05							
ENSG	Gene	NF_mean	DCM_mean	FC	pval_Age	pval_Sex	pval_DCM_v_NF	FDR_DCM_v_NF
ENSG00000100242	SUN2	117.18	97.18	-1.21	0.262246177	0.537216016	0.015067413	0.022546129
ENSG00000197321	SVIL	433.73	523.00	1.21	0.673047831	0.454047419	0.003764873	0.006711295
ENSG00000169895	SYAP1	13.10	7.88	-1.66	0.823707452	0.006519464	8.03E-05	0.00023531
ENSG00000171992	SYNPO	420.53	354.66	-1.19	0.486835206	0.350615256	0.020283585	0.029184346
ENSG00000137501	SYTL2	8.41	15.61	1.85	0.048860992	0.983474569	0.002221078	0.004214239
ENSG00000171148	TADA3	64.12	57.41	-1.12	0.258861371	0.354161571	0.017005658	0.025041124
ENSG00000177156	TALDOI	164.14	144.72	-1.13	0.311411613	0.04574458	0.030022801	0.041463827
ENSG00000204267	TAP2	36.86	27.69	-1.33	0.439647983	0.100493138	0.027674838	0.038594162
ENSG00000113407	TAKS TRC1D1	80.72	65.61	-1.23	0.942166448	0.623777087	0.004274962	0.00/51825/
ENSC00000145070	TBC1D1	100.00	152.10	-1.10	0.730030807	0.004449003	0.01518/228	0.020070297
ENSG00000145979	TRC1D0P	56.97 92.45	40.51	1.24	0.030100113	0.004446092	0.013034975	0.022554009
ENSG00000137220	TRRCA	92.16	72 20	1 12	0.929898051	0.16000044	0.007803043	0.000013609
ENSC00000130270	TCTN1	29.10	25 21	1.15	0.423333303	0.445609660	0.003833200	0.005512008
ENSG00000204832	TESC	185.96	140.41	-1.2.5	0.001540675	0.317739176	0.005733002	0.010912774
ENSG00000163513	TGFBR2	81.54	65.59	-1.24	0.406056956	0.350750182	0.003980698	0.007037492
ENSG00000176946	THAPA	100.18	85.87	-1.17	0.259409496	0.719281869	0.003805467	0.006773415
ENSG00000145365	TIFA	15.85	7.35	-2.16	0.023274046	0.09930938	3.25E-07	2.24F-06
ENSG00000150779	TIMM8B	206.84	180.18	-1.15	0.100285648	0.267828674	0.029774759	0.041157429
ENSG0000104067	TIP1	69.37	84.40	1.22	0.111084562	0.179263083	0.003104521	0.005645128
ENSG0000065717	TLE2	63.80	56.05	-1.14	0.116050195	0.85990338	0.018460419	0.026903171
ENSG00000169908	TM4SF1	102.10	74.80	-1.36	0.674131858	0.681184397	0.01089296	0.016987135
ENSG0000064115	TM7SF3	50.49	62.63	1.24	0.149222387	0.88582474	0.018987343	0.027580198
ENSG0000099203	TMED1	49.89	42.30	-1.18	0.572126653	0.673105966	0.005000552	0.00861125
ENSG00000240849	TMEM189	30.71	21.63	-1.42	0.055019154	0.887411678	1.02E-05	4.02E-05
ENSG00000165152	TMEM246	25.86	31.92	1.23	0.002207175	0.099910802	8.64E-06	3.50E-05
ENSG00000126106	TMEM53	18.31	12.72	-1.44	0.142141092	0.73567056	6.63E-07	4.07E-06
ENSG00000164983	TMEM65	29.95	23.76	-1.26	0.528436143	0.611528097	0.029586337	0.040944989
ENSG00000129925	TMEM8A	60.01	52.83	-1.14	0.942279477	0.201386217	0.023185372	0.032910623
ENSG00000164897	TMUB1	36.30	28.24	-1.29	0.943765258	0.405665545	1.39E-05	5.24E-05
ENSG00000168884	TNIP2	24.47	19.19	-1.28	0.587246983	0.616517149	0.00136676	0.002748091
ENSG00000175768	TOMM5	86.40	77.22	-1.12	0.851084661	0.757255435	0.006825076	0.011335059
ENSG00000196683	TOMM7	603.29	681.83	1.13	0.389380274	0.647218436	0.016672759	0.024635556
ENSG00000182165	TP53TG1	21.69	27.89	1.29	0.037433623	0.966997928	0.002237575	0.004235314
ENSG00000111907	TPD52L1	62.01	84.84	1.37	0.441718918	0.124293307	0.001185335	0.002421514
ENSG00000132481	TRIM47	55.49	39.33	-1.41	0.727608813	0.794720853	0.003295711	0.005958312
ENSG00000174173	TRMT10C	23.61	18.37	-1.29	0.339340629	0.052888953	9.17E-05	0.000264444
ENSG00000157514	TSC22D3	101.63	182.94	1.80	0.566909018	0.238009379	0.017744407	0.02599903
ENSG00000157570	TSPAN18	39.70	50.72	1.28	0.076746967	0.801624097	0.002637486	0.004888265
ENSG00000140391	TSPAN3	145.29	132.07	-1.10	0.423222549	0.144/133/6	0.009378788	0.014909301
ENSG00000123416	TUBRIB	349.02	241.94	-1.44	0.885013174	0.212556591	5.3/E-U5	0.000166466
ENSC00000121462	TUBD4D	2/1.65	197.50	1.30	0.554580407	0.782219708	0.001255759	0.002545854
ENS00000131402	TAKES	120.25	07.71	1.23	0.142473008	0.171450050	0.000183070	0.000481023
ENSG00000126910	TYN	76.33	57.71	1 20	0.944616346	0.927414073	0.0003511320	0.000444522
ENSG00000110810	TYNIP	767.74	1120.03	1.30	0.412182563	0.342975523	0.000103324	0.006437649
ENSG00000228236	TYNP5	30.92	25.73	-1.20	0.568993213	0.648808156	0.031849629	0.043641674
ENSG00000160087	LIBE212	55.65	45.54	-1.22	0.970462901	0.277795543	1.63E-05	5.98F-05
ENSG0000078140	UBE2K	43.32	38.11	-1.14	0.842304549	0.907254041	0.002403876	0.00450667
ENSG00000185651	UBE2L3	41.16	28.40	-1.45	0.554430738	0.338028617	0.019332706	0.028030046
ENSG00000175931	UBE2O	30.08	24.97	-1.20	0.507572899	0.887486144	0.010366871	0.016276989
ENSG00000108312	UBTF	47.34	41.31	-1.15	0.245492445	0.471918213	0.010236056	0.016109147
ENSG00000167671	UBXN6	183.41	146.51	-1.25	0.336352249	0.197484509	0.000171631	0.000449828
ENSG00000143222	UFC1	92.34	80.88	-1.14	0.768642025	0.290555071	0.016864242	0.024871724
ENSG00000140474	ULK3	39.72	32.93	-1.21	0.11340025	0.00256796	2.14E-06	1.07E-05
ENSG00000267059	UQCR11	29.66	7.00	-4.24	0.50170163	0.855026558	3.13E-07	2.17E-06
ENSG00000166348	USP54	28.76	39.66	1.38	0.581028937	0.605674715	0.008237248	0.013314578
ENSG00000126756	UXT	138.05	123.63	-1.12	0.837572411	0.373631021	0.017662595	0.025919432
ENSG0000038427	VCAN	14.07	23.75	1.69	0.00693532	0.909319726	0.015293646	0.022833927
ENSG00000131871	VIMP	5943.92	4847.80	-1.23	0.959793807	0.423112161	0.015220858	0.022751703
ENSG0000048707	VPS13D	90.79	54.73	-1.66	0.081489883	0.459686923	0.0002215	0.000559685
ENSG00000156931	VPS8	30.52	39.07	1.28	0.201801331	0.939402738	0.001080598	0.002238585
ENSG00000185274	WBSCR17	23.24	30.59	1.32	0.452907407	0.679778669	0.020933604	0.029973259
EN5GUUUUUU/1127	WDR1	367.01	2/2.58	-1.55	0.768808244	0.356684356	3.66E-05	0.000119013
ENSG0000176871	WIPII	160.93	189.64	1.18	0.94/502481	0.312/651/9	0.021168605	0.024807229
ENSG000001708/1	¥V3D2 ¥AF1	64.19 34.44	/5.04	1.11	0.000103526	0.24697413	0.001108096	0.04282063
ENSG00000132330	V RNA	54.44	19.87	-2 71	0.08851322	0.98199296	0.035938647	0.000002182
ENSG0000065978	YBX1	194.31	170.51	-1.14	0.704800038	0.009608515	0.013664358	0.020682969
ENSG00000188706	ZDHHC9	16.47	11.34	-1.45	0.181342229	0.062271266	0.000136816	0.000371808
ENSG00000166432	ZMAT1	9,61	14.98	1.56	0.375979834	0.575439498	4.76E-05	0.000149126
ENSG00000136870	ZNF189	14.01	21.03	1.50	0.183323635	0.133220829	0.030641024	0.04219405
ENSG00000198816	ZNF358	67.80	55.97	-1.21	0.186609902	0.201864468	0.006793414	0.01129441
ENSG00000173545	ZNF622	78.07	64.60	-1.21	0.479945791	0.96258879	0.023464479	0.033230705

Table S2: ICM-specific adjusted gene expression.

ICM-specific DEGs at F	DR≤0.05							
ENSG	Gene	NF_mean	ICM_mean	FC	pval_Age	pval_Sex	pval_ICM_v_NF	FDR_ICM_v_NF
ENSG00000127837	AAMP	108.32	120.19	1.11	0.700221979	0.815279397	0.034612831	0.047482028
ENSG00000131043 ENSG00000154265	AAR2 ABCA5	9.75	15.88	-1.63	0.514/9289	0.554505939	0.017746433	9.03E-08
ENSG00000154265	ABCAS	24.74	25.99	-1.50	0.581574008	0.754082792	0.017746433	0.0201758052
ENSG00000154252	ABCA9	40.08	25.99	-1.54	0.203415748	0.578438168	0.012513197	0.019131439
ENSG00000131269	ABCB7	42.64	35.21	-1.21	0.046814787	0.791964895	0.011476182	0.017767741
ENSG00000197150	ABCB8	14.77	20.91	1.42	0.612232646	0.569878795	1.99E-05	7.21E-05
ENSG00000161204	ABCF3	58.72	73.71	1.26	0.922741672	0.571829455	7.83E-05	0.00022751
ENSG00000144827	ABHD10	30.04	24.81	-1.21	0.32807258	0.334035166	0.009866702	0.01560174
ENSG00000204427	ABHD16A	36.59	50.15	1.37	0.447412354	0.323997551	9.71E-08	8.63E-07
ENSG00000129968	ABHD17A	7.45	16.19	2.17	0.20014689	0.991856742	1.78E-10	5.93E-09
ENSG0000097007	ABL1	14.78	21.79	1.47	0.159072278	0.628184019	3.63E-05	0.000118835
ENSG00000268568	AC007228.9	8.55	14.41	1.68	0.141559864	0.202550598	0.000590297	0.001312444
ENSG00000214696	AC007347.1	6.49	12.77	1.97	0.13411371	0.973126461	4.37E-07	2.88E-06
ENSG00000237930	AC007563.4	37.80	27.95	-1.35	0.722352855	0.606226372	0.007063666	0.011585646
ENSG00000218682	AC010150.1	17.12	26.66	1.56	0.59920975	0.143815781	0.00525511	0.008915173
ENSG00000174077	AC012379.1	05.08	34.23	-1.92	0.664699796	0.425095814	0.022145355	0.031942378
ENSG00000174977	AC026271.5	102.76	19.15	-1.27	0.962/11945	0.281062854	0.001757882	0.00541514
ENSG0000000971 ENSG00000102977	ACAAL	192.76	18.06	-1.10	0.078402374	0.230031155	1 225-07	1.03F-06
ENSG00000123983	ACSI 3	49.21	33.37	-1.47	0.758607002	0.63963506	0.000430218	0.000991755
ENSG00000107796	ACTA2	141.35	234.17	1.66	0.1972385	0.246012291	0.033309506	0.045828024
ENSG00000159251	ACTC1	14311.14	18306.06	1.28	0.984024909	0.414070801	0.026187544	0.037145172
ENSG00000184009	ACTG1	405.41	629.19	1.55	0.947860228	0.189602391	0.000314667	0.000758269
ENSG00000113812	ACTR8	31.34	24.84	-1.26	0.421552421	0.129606027	0.000786871	0.001690782
ENSG00000139567	ACVRL1	20.89	27.05	1.29	0.523709124	0.670053794	0.027970563	0.039372123
ENSG00000154734	ADAMTS1	45.48	81.29	1.79	0.273066325	0.583278406	0.025595765	0.03639741
ENSG00000143382	ADAMTSL4	16.79	24.02	1.43	0.55486165	0.021765455	0.002308454	0.004335277
ENSG00000105963	ADAP1	8.02	13.67	1.70	0.171764084	0.311488006	0.00010135	0.000283659
ENSG0000087274	ADD1	149.54	178.42	1.19	0.374867581	0.813969643	0.001956509	0.00374931
ENSG00000148700	ADD3	113.07	69.97	-1.62	0.151942152	0.241150772	8.24E-U5	0.000236737
ENSG00000120007	ADIPOR2	10.05	20.00	1.27	0.061/4504	0.280052505	6.095.05	0.001301035
ENSG00000120907	ADRRK1	61.58	71.40	1 16	0.598665552	0.351313553	0.032453559	0.033614182
ENSG00000204310	AGPAT1	50.86	58.85	1.16	0.883005064	0.979324191	0.012480145	0.019086085
ENSG00000135744	AGT	84.63	106.69	1.26	0.419700471	0.423014599	0.003521237	0.006291992
ENSG00000126705	AHDC1	13.03	18.26	1.40	0.343492716	0.044131731	0.000823091	0.001759217
ENSG00000106305	AIMP2	30.63	39.01	1.27	0.079096107	0.490642403	0.000107632	0.000299456
ENSG00000250115	AK3P2	22.36	17.22	-1.30	0.688034802	0.090981877	0.005267368	0.008933279
ENSG00000256492	AL118508.1	82.35	137.09	1.66	0.337581276	0.766537919	0.000205798	0.000522989
ENSG00000226209	AL138764.1	8.83	14.39	1.63	0.980782123	0.031926506	0.000740286	0.001602036
ENSG00000255831	AL139385.1	15.97	21.47	1.34	0.953967752	0.997755051	0.001935695	0.003718277
ENSG00000264604	AL158069.1	6.46	32.41	5.02	0.534556582	0.00288455	0.012293276	0.018830973
ENSG00000213018	AL590762.11	5.32	11.47	2.16	0.52540283	0.073641191	1.84E-07	1.42E-06
ENSG00000119711	ALDHEAT	60.84	46.85	-1.30	0.72127649	0.734125768	0.001381631	0.028951178
ENSG00000116337	ALKBH5	74.24	90.64	1.22	0.44109/945	0.154577001	0.001281946	0.002583149
ENSC00000164221	ANKRAZ	26.22	20.07	1.07	0.778695616	0.375103415	0.000255191	0.000051918
ENSG00000104331	ANKRD10	109.68	91.80	-1.24	0.042623174	0.323037818	0.022883917	0.032887741
ENSG00000172932	ANKRD13D	13.93	20.87	1.50	0.752165601	0.090324807	0.000341081	0.000813914
ENSG00000163516	ANKZF1	45.64	38.37	-1.19	0.643901993	0.499288252	0.03508494	0.04802169
ENSG00000140350	ANP32A	167.02	141.17	-1.18	0.234107061	0.585978748	0.01086247	0.016905844
ENSG00000231991	ANXA2P2	13.51	23.63	1.75	0.798758418	0.744036637	4.36E-05	0.00013839
ENSG00000131471	AOC3	5.43	13.43	2.47	0.62891298	0.832416231	4.39E-06	2.00E-05
ENSG00000196961	AP2A1	33.91	44.74	1.32	0.942028388	0.457877873	0.000934524	0.001952933
ENSG00000185009	AP3M1	27.64	21.83	-1.27	0.781278203	0.889314786	0.000340653	0.000813287
ENSG00000242802	AP5Z1	6.27	14.03	2.24	0.868493642	0.538991233	1.32E-09	2.68E-08
ENSG00000101474	APMAP	32.97	40.93	1.24	0.183206667	0.590808166	3.22E-05	0.000108049
ENSG00000130203	APOE	23.36	42.26	1.81	0.347234506	0.989980078	0.024743756	0.03529274
ENSG00000142192	APP	520.49	460.66	-1.13	0.351040673	0.655112082	0.01890826	0.027691483
ENSG00000157500	APPL1	22.46	16.15	-1.39	0.155170713	0.53270679	0.000332575	0.000797331
ENSC000000136044	APPLZ	70.08	39.18	-1.55	0.5255/5045	0.126630674	0.004459945	0.007698321
ENSG0000004033	ARES	14.66	23 52	1.24	0.219307773	0.599879716	3 745-06	1 745-05
ENSG00000105527	ARHGAP23	15.40	20.81	1.00	0.467308644	0.739002203	0.008264724	0.013330505
ENSG00000198844	ARHGEF15	17.67	28.34	1.60	0.94524649	0.045196182	0.003536478	0.006315219
ENSG00000165801	ARHGEF40	13.05	19.63	1.50	0.254666784	0.640188591	0.004276269	0.007445148
ENSG00000129675	ARHGEF6	43.85	38.07	-1.15	0.017942017	0.892307766	0.02521572	0.035884154
ENSG00000131089	ARHGEF9	42.91	35.82	-1.20	0.007511587	0.38633709	0.001565199	0.003090898
ENSG00000150347	ARID5B	6.57	12.54	1.91	0.560086711	0.77056138	0.003638463	0.006476809
ENSG00000152219	ARL14EP	39.56	30.51	-1.30	0.814511755	0.876535363	0.010030804	0.015821263
ENSG00000182196	ARL6IP4	179.57	203.24	1.13	0.866919174	0.063719489	0.032650021	0.045122419
ENSG00000241685	ARPC1A	75.47	99.54	1.32	0.67232831	0.713357482	0.000211065	0.000533486
ENSG00000130429	ARPC1B	50.17	78.87	1.57	0.620503533	0.926017055	0.001038098	0.002147868
ENSG00000241553	ARPC4	57.42	76.00	1.32	0.890494816	0.818631553	0.001947697	0.003737508
ENSG00000136950	ARPC5L	32.78	41.36	1.26	0.400965124	0.399639275	0.003820497	0.006/51/82
ENSG00000197070 ENSG00000153317	ARRUCI ASAP1	20.85	30.89	-1.48	0.332750702	0.138914854	5.U3E-U7 0.000885133	3.24E-U6 0.001871734
ENSG0000015551/	ASH11	39.21	14.60	-1.42	0.332/39/93	0.130314034	0.000000100 0.000000100	0.0018/1254
ENSG00000101440	ASIP	12.79	18.20	1.30	0.81023446	0.094142824	0.03482396	0.047725174
ENSG00000198356	ASNA1	44.25	50.98	1.15	0.741310799	0.360291296	0.014387516	0.021702614
ENSG00000169696	ASPSCR1	26.34	34.29	1.30	0.983124829	0.316407406	0.000252471	0.000626066
ENSG00000156802	ATAD2	15.52	8.72	-1.78	0.11429931	0.692903324	0.009437092	0.014985506
ENSG00000162772	ATF3	18.69	38.40	2.05	0.176984042	0.511553743	0.022911332	0.032895822
ENSG00000149311	ATM	15.78	9.88	-1.60	0.156514376	0.495585747	8.13E-05	0.000234174
ENSG00000177556	ATOX1	85.22	99.99	1.17	0.818886028	0.145195386	0.016723146	0.024853127
ENSG00000105726	ATP13A1	27.15	33.22	1.22	0.750790031	0.906852325	0.012385526	0.01895682
ENSG00000143153	AIP1A1	132.81	176.44	1.33	0.576170406	0.635122302	0.010539757	0.000720002
ENSG00000145155	ATP183	210.05	108.26	1 78	0.95521400059	0.419569842	0.003844031	0.00078808
ENSG00000009849	ATP5C1	681 72	703.00	1 14	0.555214020	0.913303043	0.00028/95/	0.00070379
ENSG00000224004	ATP5C1P1	30.45	23.08	-1.32	0.385425832	0.198766867	0.012799739	0.019529091
ENSG00000261679	ATP5HP1	6.29	11.41	1.81	0.782615836	0.141920623	8.56E-08	7.82E-07
ENSG00000249256	ATP5LP3	79.45	94.41	1.19	0.206548065	0.987935193	0.012754472	0.019473901
ENSG00000100554	ATP6V1D	439.28	339.58	-1.29	0.390527636	0.284670304	0.002064293	0.003929131
ENSG00000131100	ATP6V1E1	272.01	238.43	-1.14	0.940434598	0.555163948	0.01110318	0.017237618
ENSG00000128524	ATP6V1F	81.00	109.58	1.35	0.308195611	0.103988962	0.00068758	0.001500901
ENSG0000136888	ATP6V1G1	69.31	81.48	1.18	0.409552904	0.382439771	0.022693837	0.032683302
ENSG00000143515	ATP8B2	6.12	13.43	2.19	0.029172426	0.397006634	4.62E-05	0.000145414
ENSG00000166377	ATP9B	9.50	14.66	1.54	0.682580831	0.736391823	2.46E-06	1.23E-05
ENSG00000253719	ATXN7L3B	22.70	29.32	1.29	0.889645601	0.426458294	3.63E-06	1.69E-05
ENSG00000148090	AUH	66.38	56.16	-1.18	0.811507813	0.803449811	0.01/647921	0.026042008
ENSG00000166710	B2M B2GAT2	2446.33	3639.30	1.49	0.950572257	0.483484265	0.001158772	0.002361983
ENSCO0000170340	DOUALS R2CNT2	10.11	17.06	1.09	0.125(07272	0.337010432	1.44E-07	1.16E-U6
EN5G000000000000	B3GN1Z R4GALT1	8.77	15.13	1.72	0.135687372	0.829040586	1.34E-05	5.08E-05
ENSG0000037847	B4GALTT	36.73	48.91	1.53	0.797036712	0.9258073	0.014941776	0.02244254
ENSG00000193340	BACE2	9.32	20.46	1 60	0.430/23029	0.900004334	0.02/102505	0.000100289
ENSG00000095739	BAMBI	9.64	16.83	1.05	0.472528968	0.850014282	0.004681573	0.008047891
ENSG00000087088	BAX	37.42	52.85	1.41	0.457076191	0.998179558	0.008154188	0.013178627
ENSG00000125124	BBS2	37.42	32.65 114.07	-1 21	0.392088410	0.3301/9336	0.000104100	0.00131/602/
ENSG00000125124	BCAP31	246.99	105 33	1 27	0.352088419	0.563581084	0.000145599	0.000388032
ENSG00000050820	BCAR1	48.56	61.97	1.28	0.488324928	0.411089212	0.002425634	0.004519187
ENSG00000116752	BCAS2	40.91	33.54	-1.22	0.766446542	0.469236492	0.012713289	0.019421548
ENSG00000126453	BCL2L12	7.79	14.57	1.87	0.683266235	0.193528451	8.96E-08	8.13E-07
ENSG0000074582	BCS1L	81.66	93.40	1.14	0.078578677	0.93760061	0.004678795	0.008046499
ENSG00000177951	BET1L	17.73	24.98	1.41	0.607125844	0.566415795	7.29E-07	4.43E-06
ENSG00000132840	BHMT2	13.91	7.35	-1.89	0.346791551	0.761656805	0.001954611	0.003746947

ICM-specific DEGs at FDRs	60.05	NF mean	ICM mean	FC	nval Age	nual Sex	oval ICM v NE	EDR ICM V NE
ENSG00000259040	BLOC1S5-TXNDC5	15.27	8.89	-1.72	0.374115193	0.765986493	0.000726985	0.001576533
ENSG00000204217	BMPR2	8.17	13.65	1.67	0.148150088	0.49858195	0.00024053	0.000599357
ENSG0000038219 ENSG00000162813	BOD1L1 BPNT1	52.37 29.37	39.69	-1.32	0.154114663	0.724074132	0.006969207 7 85E-06	0.01144738
ENSG00000106009	BRAT1	10.77	17.07	1.59	0.485745397	0.803124633	9.69E-08	8.62E-07
ENSG00000204256	BRD2	95.48	118.77	1.24	0.882269938	0.438163647	0.010525882	0.01647429
ENSG00000164713 ENSG00000134717	BTF3L4	96.72 14.98	20.43	1.37	0.456320552	0.539049478	0.000125331	0.000341613
ENSG00000227118	BTF3P13	14.86	21.90	1.47	0.765055288	0.595408774	2.75E-05	9.44E-05
ENSG00000154640	BTG3	7.85	13.68	1.74	0.626642393	0.475393622	0.000159422	0.000418734
ENSG00000110696	C11orf58	154.76	119.02	-1.30	0.368177772	0.612295483	0.000210785	0.000533257
ENSG00000166352	C11orf74	47.72	38.39	-1.24	0.555347155	0.539881146	0.021874014	0.031583341
ENSG00000187479	C11orf96 C12orf22	6.32	22.31	3.53	0.350903993	0.649589488	4.79E-05	0.000149678
ENSG00000111412	C12orf49	6.98	12.22	1.75	0.536695338	0.343565453	1.84E-08	2.18E-07
ENSG00000179933	C14orf119	31.26	38.69	1.24	0.907653878	0.523595695	0.000389413	0.000911867
ENSG00000185504 ENSG00000108666	C17orf70 C17orf75	10.93	16.21	1.48	0.396681341	0.395317387	3.04E-06 0.009697647	1.46E-05 0.015360288
ENSG00000141452	C18orf8	16.02	23.44	1.46	0.447896664	0.607479822	0.000158083	0.000416187
ENSG00000228300	C19orf24	11.91	17.55	1.47	0.71898825	0.618590837	0.007690295	0.012500612
ENSG00000119559 ENSG00000142444	C190rf25 C190rf52	9.23	20.66	1.35	0.381244478	0.427917418	4.14F-08	4.16F-07
ENSG00000204377	C1orf134	16.62	11.00	-1.51	0.709029791	0.447527172	0.01934856	0.028284844
ENSG00000174407	C20orf166	26.27	50.05	1.91	0.942710213	0.242106462	0.01668195	0.024798445
ENSG00000111731	C2CD5	27.81	22.13	-1.26	0.886622371	0.053580545	0.013476829	0.020454864
ENSG00000163608	C3orf17	32.81	24.37	-1.35	0.966480478	0.090907683	5.75E-05	0.000174451
ENSG00000056050	C4orf27 C7orf26	37.66	28.87	-1.30	0.408947138	0.910674087	0.000611144	0.001352922
ENSG00000243317	C7orf73	33.11	42.43	1.28	0.832443433	0.036122762	8.25E-05	0.000236904
ENSG00000151893	CACUL1	18.16	12.90	-1.41	0.856046571	0.590764966	1.49E-05	5.60E-05
ENSG0000084774 ENSG00000182985	CAD CADM1	5.15	10.83	2.10	0.161738863	0.702215528	1.62E-07 0.006670804	1.27E-06 0.011011811
ENSG00000145349	CAMK2D	209.83	181.03	-1.16	0.102180567	0.723396342	0.024823598	0.035397659
ENSG00000130559	CAMSAP1	18.23	12.98	-1.40	0.242772428	0.844870672	2.71E-05	9.33E-05
ENSG00000171302	CANTIAZ CANTI	72.21	88.32 22.43	1.22	0.345635569 0.633095917	0.014649107 0.510535434	0.001583318	0.003117936
ENSG00000127022	CANX	451.66	373.55	-1.21	0.162884239	0.312020437	0.008222976	0.013266966
ENSG00000103326	CAPN15	8.20	14.81	1.81	0.982723737	0.776678645	2.82E-05	9.63E-05
ENSG00000127995	CAPS2 CASD1	16.85 8.91	10.32 14.01	-1.63 1.57	0.350474851 0.136176379	0.186679413	1.30E-06 0.000422044	7.14E-06 0.000974906
ENSG00000164305	CASP3	11.81	17.49	1.48	0.57124383	0.349685657	0.003879417	0.006843029
ENSG00000153113	CAST	399.75	312.59	-1.28	0.660735955	0.298007202	0.001625032	0.003187824
ENSG00000105971 ENSG00000183741	CBX6	177.69	234.44 18.74	1.32	0.253098771 0.120992057	0.498959278	0.00586623	0.009836411 0.001516101
ENSG0000060339	CCAR1	57.40	44.56	-1.29	0.948510771	0.772068006	0.012804484	0.019529091
ENSG00000176476	CCDC101	13.24	19.52	1.47	0.665032813	0.106328222	9.03E-05	0.000256556
ENSG00000104957	CCDC107	48.98	38.75	1.31	0.649331188	0.826507708	0.000411702	0.000954146
ENSG00000180329	CCDC43	31.00	23.94	-1.30	0.600994672	0.477884805	6.05E-06	2.59E-05
ENSG00000176155	CCDC57	15.40	21.44	1.39	0.664966918	0.770416095	0.012630759	0.01930594
ENSG00000133773 ENSG00000015133	CCDC88C	33.65	26.76	-1.26	0.390023892	0.855334258	0.006634717	0.005677335
ENSG00000137500	CCDC90B	52.35	40.74	-1.29	0.66386425	0.994434834	0.005857362	0.009824465
ENSG00000137077	CCL21	10.40	28.89	2.78	0.523488834	0.19064518	0.002229109	0.004205894
ENSG00000158281 ENSG00000161649	CD300LG	14.58	21.60	1.48	0.009432763	0.98221175	0.022031418	0.031794316
ENSG0000026508	CD44	16.12	28.88	1.79	0.521277926	0.125366512	0.013868402	0.020981358
ENSG00000143119 ENSG00000099804	CD53 CDC34	12.32	18.22	1.48	0.133611388	0.583014764	0.031892763	0.04421354
ENSG00000143776	CDC42BPA	21.06	145.25	-1.36	0.52165872	0.403340625	0.000168759	0.000440792
ENSG00000128283	CDC42EP1	9.64	21.84	2.26	0.904651149	0.664372753	7.71E-05	0.000224719
ENSG00000134371	CDC73	9.93	15.33	1.54	0.217292858	0.789531923	2.24E-05	7.93E-05
ENSG00000221869	CEBPD	25.28	47.03	1.86	0.694376732	0.433533776	0.026140281	0.03708747
ENSG0000093072	CECR1	29.39	50.48	1.72	0.951654762	0.707522472	0.010089354	0.015873616
ENSG00000167123 ENSG00000090661	CERCAM	6.37	12.81	2.01	0.011715551	0.356323107	0.004233347	0.007382592
ENSG00000153140	CETN3	41.40	33.66	-1.23	0.926120185	0.98153797	0.023011885	0.033031582
ENSG00000197766	CFD	48.49	110.26	2.27	0.653006746	0.227082212	0.003538703	0.00631719
ENSG00000153922 ENSG0000085872	CHD1 CHERP	21.81	16.77	-1.30	0.522930989	0.880270656	0.032223232 1.28F-06	0.04460582 7.06F-06
ENSG00000255112	CHMP1B	20.33	28.09	1.38	0.825840884	0.608837067	0.000255083	0.000631916
ENSG0000033100	CHPF2	8.92	15.88	1.78	0.070339221	0.722576803	3.66E-07	2.48E-06
ENSG00000122863 ENSG00000147119	CHST3 CHST7	6.71	14.14	1.78	0.803986333	0.885208041	0.00013696	0.025445306
ENSG0000079432	CIC	13.08	18.10	1.38	0.513011284	0.936052422	0.001612227	0.003169326
ENSG00000138615	CILP	14.86	36.44	2.45	0.509355699	0.761168455	0.006816513	0.011231283
ENSG00000141076	CIRL CIRH1A	36.89 14.21	29.48 21.04	-1.25	0.910921754 0.388811193	0.445215421 0.894672857	0.023919375	0.0034198443
ENSG00000217555	CKLF	8.89	14.50	1.63	0.955739192	0.988582538	0.000558213	0.001255979
ENSG00000104859	CLASRP	51.46	64.76	1.26	0.381101707	0.206977497	0.031206987	0.04340167
ENSG00000113240	CLK4	40.19 29.97	23.68	-1.25	0.513537907	0.477482125	0.010240529	0.020811151
ENSG0000049656	CLPTM1L	71.47	82.07	1.15	0.665447118	0.872520002	0.011978334	0.018423678
ENSG00000139182 ENSG00000141367	CLSTN3 CLTC	8.50 88.07	18.69 106 74	2.20	0.635625533	0.95564418	3.20E-05 0.026280907	0.00010757
ENSG00000153815	CMIP	6.29	14.36	2.28	0.464142943	0.734317163	1.53E-08	1.91E-07
ENSG0000091317	CMTM6	11.18	16.18	1.45	0.208136851	0.465752197	0.001385308	0.002763748
ENSG00000137200 ENSG00000133313	CNTR1 CNDP2	18.96	25.37	1.34	0.882671647	0.430636656	1.49E-06 0.000384937	8.03E-06
ENSG00000143771	CNIH4	18.94	27.14	1.43	0.978977417	0.509639385	0.000159336	0.000418703
ENSG00000153721	CNKSR3	14.56	21.13	1.45	0.356611227	0.480735835	0.004250932	0.007407903
ENSG0000088038	CNNM4 CNOT3	13.88 14.54	19.26 20.25	1.39	0.44623849	0.532201209	0.010970522	0.017041059
ENSG0000068120	COASY	26.01	35.68	1.37	0.753814876	0.891302992	0.001862065	0.003589078
ENSG00000166685	COG1	35.28	43.57	1.23	0.741276827	0.558470024	0.004041716	0.007103864
ENSG00000134871	COL4A1 COL4A2	91.40 67.28	105.96	1.28	0.805004535	0.526393996	0.025995245 9.02E-05	0.03690028
ENSG00000170619	COMMD5	10.63	16.16	1.52	0.723692992	0.397896917	5.70E-10	1.36E-08
ENSG00000169019 ENSG00000105669	COMMD8 COPF	14.95	20.62	1.38	0.255620053	0.130498095	0.023976551	0.034259165
ENSG00000168090	COPS6	195.02	130.82	1.10	0.826768762	0.711758431	0.034887843	0.024313205
ENSG00000102879	CORO1A	13.97	22.73	1.63	0.070175107	0.568656093	0.008951643	0.014299279
ENSG00000172725	CORO1B CORO7	37.95	55.16	1.45	0.534370364	0.753006981	0.004196982	0.007329345
ENSG00000165934	CPSF2	19.23	12.36	-1.56	0.345031967	0.49589707	1.73E-05	6.35E-05
ENSG00000113851	CRBN	65.68	50.92	-1.29	0.401967272	0.042787345	0.003206286	0.005780549
ENSG00000118260 ENSG00000107175	CREB1 CREB3	14.67	8.28	-1.77	0.670095702	0.549205088	2.79E-06	1.36E-05
ENSG00000005339	CREBBP	35.58	26.68	-1.32	0.421132216	0.601548145	0.002429731	0.004522174
ENSG0000095794	CREM	50.97	71.37	1.40	0.845479316	0.433437906	0.002758174	0.005053513
ENSG00000103196 ENSG00000080200	CRISPLD2 CRYBG3	12.21	20.83	1.71	0.161347059	0.432908979	0.004944059	0.008440857
ENSG00000205758	CRYZL1	66.62	50.48	-1.32	0.537490397	0.081255365	0.000140603	0.000376859
ENSG00000141551	CSNK1D	82.98	99.55	1.20	0.791851423	0.334954791	0.008933766	0.014278819
ENSG00000133275	CSNK1G2 CSPG4	42.07	52.17	1.24	0.280261935	0.316066277	0.025334297	0.036043795
ENSG00000239622	CTA-242H14.1	9.96	14.50	1.65	0.291906998	0.303623209	9.75E-05	8.65E-07
ENSG00000248930	CTC-250P20.1	14.99	9.21	-1.63	0.370413109	0.439424354	2.29E-06	1.16E-05
ENSG0000249921 ENSG00000268205	CTC-329H14.1 CTC-444N24 11	6.25 6.55	11.34 14.75	1.81 2.25	0.685155547 0.311685708	0.818774372	2.27E-07 1.21F-09	1.69E-06 2.50F-08

ICM-specific DEGs at FI	DR≤0.05 Gene	NF mean	ICM mean	FC	nval Age	nval Sex	oval ICM v NF	FDR ICM v N
ENSG00000267660	CTC-479C5.17	7.65	14.04	1.84	0.302325459	0.220979894	5.22E-08	5.11E-0
ENSG00000248966	CTD-2089024.1	11.61	5.17	-2.25	0.565808167	0.397167314	4.27E-10	1.11E-0
ENSG00000232864	CTD-2090113.2 CTD-2210P15.2	15.35	8.52	-1.80	0.521192338	0.10712549	0.000210714	9.91E-1 0.00053325
ENSG00000225138	CTD-2228K2.7	5.56	10.93	1.97	0.928589159	0.365146673	0.012079472	0.01855391
ENSG00000230502	CTD-2230M5.1	16.54	7.99	-2.07	0.308535528	0.31974602	0.032856383	0.04535968
ENSG00000273420	CTD-2540B15.13	5.57	11.45	2.06	0.185706774	0.492805466	3.30E-05	0.00011001
ENSG00000267422 ENSG00000249026	CTD-2554C21.1 CTNNAP1	10.50	15.53	-1.48	0.453059913	0.811442548	3.52E-07 3.22E-09	2.40E-0 5.30E-0
ENSG00000163131	CTSS	20.79	34.82	1.68	0.446094634	0.915159117	0.010088266	0.01587361
ENSG00000174177	CTU2	9.88	15.10	1.53	0.120420298	0.493051862	0.001196569	0.00243023
ENSG00000139842	CUL4A	106.64	86.54	-1.23	0.642213779	0.17192878	0.001624769	0.00318782
ENSG00000112659	CUL9	9.77	15.08	1.54	0.225674843	0.259650116	0.000111024	0.00030733
ENSG00000112514	CXCI16	6.84	145.91	2.28	0.549094968	0.289695969	2.28E-05	0.0455596 8.04F-0
ENSG00000051523	CYBA	65.42	106.14	1.62	0.525771682	0.626600568	0.000200243	0.00051094
ENSG00000187954	CYHR1	51.30	59.13	1.15	0.760849956	0.027060139	0.019268394	0.02818959
ENSG00000135929	CYP27A1	6.49	13.03	2.01	0.408490762	0.208235187	7.29E-06	3.02E-0
ENSG00000129562 ENSG00000178149	DAURD3	233.88	275.13	1.18	0.851077599	0.162315916	0.01224582 6.31E-05	0.01877870
ENSG00000132676	DAP3	193.52	208.45	1.08	0.034468707	0.755776936	0.027333982	0.0385288
ENSG00000213088	DARC	9.66	30.45	3.15	0.970165638	0.446586467	5.66E-06	2.45E-0
ENSG00000137992	DBT	21.66	13.72	-1.58	0.522209719	0.091334726	4.95E-05	0.00015348
ENSG00000143164	DCAF6	143.98	119.45	-1.21	0.779144613	0.116376738	0.001893782	0.00364149
ENSG00000110005	DCP3	38.75	31.63	-1.75	0.515339014	0.244874413	0.000445983	0.00102641
ENSG00000179958	DCTPP1	34.08	40.93	1.20	0.287383057	0.861012589	0.004233787	0.00738259
ENSG00000043093	DCUN1D1	24.75	18.05	-1.37	0.917070173	0.573695228	0.000404083	0.00093958
ENSG00000109184	DCUN1D4	22.15	16.62	-1.33	0.195299858	0.320056541	0.005330127	0.00902070
ENSG00000203797	DDO	29.12	22.19	-1.31	0.59245044	0.305116938	0.002420425	0.00451097
ENSG00000123136	DDX39A	28.92	34.02	1.18	0.745280391	0.90874662	0.029260712	0.0409276
ENSG00000145833 ENSG00000110367	DDX46	27.13	21.18	-1.28	0.737141333	0.936547652	0.006281799	0.01044609
ENSG00000185000	DGAT1	60.12	73.30	1.22	0.122457286	0.885545355	0.001091576	0.00224041
ENSG0000065357	DGKA	15.35	24.58	1.60	0.496872215	0.654270786	0.001531567	0.00303298
ENSG00000077044	DGKD	28.20	40.54	1.44	0.595610409	0.15143148	0.030690249	0.0427568
ENSG00000149091	DGKZ	46.33	55.52	1.20	0.116892962	0.260014542	0.021429586	0.0309972
ENSG00000157379	DHRS1	11.10	17.27	1.56	0.651754154	0.604508868	0.000217726	0.00054835
ENSG00000132153	DHX30	24.60	32.39 29.07	1.32	0.898985522	0.199838894	0.004345335 3.87F-05	0.00754330
ENSG00000140829	DHX38	39.90	47.73	1.20	0.568632835	0.292842761	0.026310422	0.03727254
ENSG0000067596	DHX8	11.03	19.87	1.80	0.362473033	0.659316793	2.85E-08	3.06E-0
ENSG0000069345	DNAJA2	90.99	84.13	-1.08	0.915738777	0.040437228	0.021460913	0.03102779
ENSG00000137094	DNAJB5	48.79	82.29	1.69	0.7426272	0.489678599	0.009895888	0.015643
ENSG00000105993	DNAJB6	77.93	92.70	1.19	0.486758785	0.895301812	0.021326784	0.03087232
ENSG00000103821	DNAGC2 DPH2	13.06	19.03	-1.52	0.641609569	0.520591929	3 145-05	0.01407200
ENSG00000136908	DPM2	13.40	18.56	1.38	0.73117806	0.355726423	9.75E-06	3.88E-0
ENSG00000176978	DPP7	197.57	232.29	1.18	0.28834635	0.754887795	0.027654717	0.03895166
ENSG00000151640	DPYSL4	23.55	35.18	1.49	0.708418725	0.217390297	0.034636155	0.04750245
ENSG00000248593	DSTNP2	7.77	14.88	1.92	0.37203794	0.042393924	2.39E-07	1.77E-0
ENSG00000184545	DUSP8	14.72	21.94	1.49	0.965979564	0.14/040888	0.0023774463	0.04034726
ENSG00000181202	DYNC1112	126.05	42.50	-1.26	0.133085058	0.163780456	0.009188326	0.01462345
ENSG00000205250	E2F4	25.27	33.54	1.33	0.50314991	0.920035724	0.00038462	0.00090327
ENSG00000129518	EAPP	34.29	27.18	-1.26	0.937641231	0.893906435	0.000406517	0.00094446
ENSG0000038358	EDC4	44.88	55.66	1.24	0.385349962	0.293371759	0.015423995	0.0231236
ENSG00000132394	EEFSEC	11.10	17.78	1.60	0.850023694	0.221964925	1.04E-06	5.93E-0
ENSG00000159658 ENSG00000183690	EFCAB14 EFHC2	45.84	35.97	-1.27	0.59188783	0.896853943	9.325-05	0.00197685
ENSG00000142634	EFHD2	8.98	14.93	1.66	0.92968736	0.142873863	3.48E-07	2.39E-0
ENSG00000113790	EHHADH	27.71	17.25	-1.61	0.302325029	0.237233797	0.000490635	0.00111596
ENSG00000236698	EIF1AXP1	126.74	99.87	-1.27	0.329550112	0.952781296	0.001949888	0.00374043
ENSG00000104408	EIF3E	303.53	244.69	-1.24	0.459801014	0.891018916	0.012727014	0.01943724
ENSG00000161960	EIF4A1	158.53	240.92	1.52	0.811949175	0.444140424	0.000728556	0.00157933
ENSG00000075151	EIF403 EIF54	40.05	124 79	1.51	0.1988880098	0.122193201	0.000347203	0.00082726
ENSG00000138080	EMILIN1	8.59	17.85	2.08	0.275286317	0.208647517	0.000341662	0.00081495
ENSG00000145293	ENOPH1	9.49	15.61	1.65	0.45136663	0.493606959	1.27E-07	1.06E-0
ENSG00000167302	ENTHD2	14.20	21.29	1.50	0.495324744	0.702574584	0.000135024	0.00036468
ENSG00000159023	EPB41	20.67	14.01	-1.48	0.64890652	0.589728551	0.00040605	0.00094376
ENSG00000129595	EPB41L4A	21.73	16.46	-1.32	0.917677575	0.2919813	0.006491932	0.01075118
ENSG00000198411 ENSG00000112425	EPHB4 EPM2A	21.40	27.80	-1.30	0.259448291	0.322479689	0.02483188 8.81F-06	0.05559890 3.54F-0
ENSG00000136628	EPRS	75.36	63.19	-1.19	0.937451746	0.776510231	0.020103323	0.02922893
ENSG00000151491	EPS8	48.39	37.43	-1.29	0.63047955	0.561973761	0.028311058	0.03981640
ENSG00000132591	ERAL1	54.26	67.11	1.24	0.175642646	0.575002774	0.000975355	0.00202922
ENSG00000105722	ERF	44.12	54.73	1.24	0.375848371	0.305343935	0.026993087	0.03809595
ENSG00000106492	ESERG	5.36	12.24	2.28	0.35199164	0.595423671	7.39E-08	6.89E-0
ENSG00000196482	ETHE1	16.70	20.96	-1./1	0.15954/811 0.807385792	0.0301/15/3	2.09E-U5 0.000235946	9.276-0
ENSG00000157557	ETS2	21.59	35.95	1.67	0.450582527	0.513720521	0.03276735	0.04524785
ENSG00000139083	ETV6	5.87	11.84	2.02	0.783257941	0.44851395	0.012249679	0.01877950
ENSG00000142694	EVA1B	5.71	13.39	2.35	0.196279212	0.639532781	5.59E-07	3.53E-0
ENSG0000187000	EVALC EXD3	19.47	33.85	1.74	0.652423767	0.724183885	0.028698968	0.04025142
ENSG00000180104	EXOC3	21.82	28.34	1.30	0.603680914	0.676678173	0.000339132	0.0008109
ENSG00000070367	EXOC5	39.32	28.30	-1.39	0.369105133	0.02209905	0.002527224	0.00468210
ENSG0000077348	EXOSC5	19.64	25.14	1.28	0.888516768	0.504330735	0.00959304	0.01520314
ENSG00000134824	FADS2	11.26	20.78	1.85	0.556652837	0.565420665	0.003810717	0.00673872
EN5G00000175182	FAM131A	18.20	23.54	1.29	0.378056508	0.003929227	0.001812748	0.00350509
ENSG00000174132	FAM189A7	16.24	22.79	1.40	0.096961621	0.210945869	0.000259304	0.00064019
ENSG00000163946	FAM208A	24.38	18.97	-1.29	0.414976396	0.020693653	0.007445371	0.01215861
ENSG00000196227	FAM217B	12.62	6.75	-1.87	0.572271986	0.805680469	0.000620427	0.00137131
NSG00000164970	FAM219A	18.32	24.84	1.36	0.245777373	0.82054913	2.38E-05	8.32E-0
NSG00000143409	FAM63A	42.76	36.29	-1.18	0.620827296	0.220650902	0.025684672	0.03650540
INSG0000176072	FAM/3B FAM/89B	20.85	28.03	1.34	0.761658579	0.141070665	0.000228164	0.0005710
NSG00000006607	FARP2	8 35	13.54	1.55	0.294530016	0.778825562	6.29F-06	0.0009748i 2.67F-
NSG00000138399	FASTKD1	106.06	79.22	-1.34	0.784208648	0.66165418	0.004325294	0.00751409
ENSG00000149806	FAU	822.61	952.33	1.16	0.82874286	0.862479204	0.005597948	0.0094258
ENSG00000105202	FBL	93.19	110.39	1.18	0.268436474	0.168293583	0.025619769	0.03642235
NSG00000156860	FBRS	19.46	27.48	1.41	0.706387349	0.345171516	7.86E-05	0.0002280
INSG00000127452	FBXL12 FBXL22	10.98	18.51	1.69	0.733607355	0.577975018	1.59E-12	1.79E-:
NSG00000197361	FBAL22	0.0 PC	14.U3 81 DE	-1.75	0.213/869/8	0.160704015	0.002046233	0.00390002
ENSG00000182325	FBXL6	6.76	12.72	1.88	0.723809215	0.169938658	8.10E-10	1.76F-0
ENSG00000110429	FBXO3	73.35	62.32	-1.18	0.63558614	0.04409483	0.025130757	0.035772
ENSG00000145868	FBXO38	41.25	34.07	-1.21	0.441574283	0.572916068	0.01695575	0.0251325
NSG0000037637	FBXO42	21.73	26.89	1.24	0.210841144	0.304323619	0.022879645	0.0328877
ENSG00000137478	FCHSD2	38.83	28.98	-1.34	0.080802501	0.09870493	0.000546496	0.0012330
NSG00000149781	FERMT3	7.51	13.79	1.84	0.082088843	0.857268994	0.001607371	0.00316088
ENSG00000182511	FES	9.52	15.42	1.62	0.112297896	0.135435861	6.37E-06	2.70E-0
ENSG00000171055	FGL2	07.02 7.04	15.26	2 17	0.551496154	0.88647367	0.020301301	0.02930024
ENSG00000135723	FHOD1	45.75	57.34	1.25	0.934040143	0.423991554	0.013122605	0.0199545
ENSG00000165197	FIGF	12.88	7.31	-1.76	0.022941561	0.374041382	0.0091358	0.01454807
ENSG0000088832	FKBP1A	129.38	165.50	1.28	0.88281289	0.056715481	0.002828374	0.00516366
ENSG00000198225	FKBP1C	6.62	12.69	1.92	0.933686668	0.494114592	0.000389092	0.00091149
ENSG00000122522	FKBP7	21.47	15.69	-1.37	0.760697219	0.238128868	0.004257969	0.00741787
ENSG00000162076	FLYWCH2	17.54	207.02	1 39	0.421823925	0.756491837	1 295-05	4.925-0

ENSG ENSG00000161791	Gene FMNL3	NF_mean 7.80	ICM_mean 13.48	FC 1.73	pval_Age 0.243905539	pval_Sex 0.686256685	pval_ICM_v_NF 0.000138679	FDR_ICM_v_ 0.0003724
ENSG00000102081	FMR1	23.85	16.36	-1.46	0.410314157	0.869905171	0.034796037	0.047698
ENSG00000141560 ENSG00000165457	FN3KRP FOLR2	11.56 13.46	17.51 28.12	1.51	0.424530262	0.67670358	2.07E-06 0.000219823	1.07E 0.000552
ENSG00000170345	FOS	11.76	79.31	6.75	0.811927554	0.730372221	0.000423384	0.0009770
ENSG00000075426	FOSL2 FRMD8	22.11	41.97	1.90	0.950663018	0.404343138	0.008270315	0.013335 7 87F
ENSG00000213362	FTH1P12	17.21	39.37	2.29	0.144918556	0.334997656	0.00047391	0.001082
ENSG00000230204	FTH1P5	8.63	20.71	2.40	0.601032231	0.061021238	3.50E-06	1.64E
ENSG00000226608 ENSG00000140718	FTLP3 FTO	124.46 28.96	170.24	1.37	0.631805297	0.996909335	0.016167012	0.0241156
ENSG00000069509	FUNDC1	45.28	35.82	-1.26	0.86923964	0.394614063	0.001110111	0.002268
ENSG00000196968	FUT11	10.88	16.78	1.54	0.42010935	0.693941342	1.05E-05	4.11E
ENSG00000155760 ENSG00000105325	FZD7 FZR1	12.10	13.62	1.64	0.192117449	0.051059422	3.56E-U5 1.29E-06	0.000117. 7.10E
ENSG00000141349	G6PC3	28.69	38.33	1.34	0.625023812	0.703100719	3.97E-06	1.82E
ENSG00000109458	GAB1 GADD45R	50.61	35.91	-1.41	0.900664939	0.944658141	0.005877565	0.009852
ENSG00000178950	GAK GAK	25.15	36.50	1.94	0.212651167	0.849590963	1.64E-05	6.06E
ENSG0000054983	GALC	24.76	17.64	-1.40	0.950784124	0.800079195	0.000305437	0.000738
ENSG00000178234 ENSG00000143641	GALNT11 GALNT2	17.02	22.21	1.30	0.305733485	0.577829491	0.000589563 5.00E-05	0.001311
ENSG00000089597	GANAB	152.52	171.24	1.12	0.932647819	0.096680656	0.030737375	0.042801
ENSG00000111640	GAPDH	1808.74	2207.31	1.22	0.191798028	0.788829414	0.000423487	0.000977
ENSG00000248626 ENSG00000248180	GAPDHP40 GAPDHP60	21.99	28.73	1.26	0.120335614	0.443521734	4.50E-05	0.000767
ENSG00000239282	GATSL3	10.08	16.04	1.59	0.18491125	0.715888992	0.002571447	0.004753
ENSG00000117226	GBP3	13.97	8.59	-1.63	0.790871093	0.747966298	0.013561415	0.02056
ENSG00000239857 ENSG00000164347	GE14 GEM2	18.83	53.15	-1.16	0.379454814	0.281977267	3.87E-08 0.010073422	0.015861
ENSG00000198380	GFPT1	29.77	23.87	-1.25	0.026626125	0.172789906	0.012098326	0.018577
ENSG00000146830	GIGYF1	19.62	24.72	1.26	0.754457447	0.637616883	0.008783264	0.014062
ENSG00000204120 ENSG00000139436	GIGTE2	26.29	20.66	-1.27	0.980343424	0.546685936	0.001943971	0.000832
ENSG00000250571	GLI4	10.44	16.55	1.58	0.58818213	0.820922646	2.92E-07	2.078
ENSG00000109738	GLRB	7.73	13.41	1.73	0.301336735	0.426427983	7.15E-05	0.000210
ENSG00000197045	GMFB	118.76	101.57	-1.17	0.1096/2149	0.209934274	0.00786945	0.012/66
ENSG00000144591	GMPPA	22.20	31.02	1.40	0.308708142	0.770205673	0.002750447	0.005042
ENSG00000204628	GNB2L1	1285.84	1494.43	1.16	0.972859919	0.467190036	0.021905776	0.031621
ENSG00000127920 ENSG00000111670	GNG11 GNPTAB	42.39	25.38	-1.32	0.829566206	0.240442457	0.033408949 3.91E-05	0.045953
ENSG00000175265	GOLGA8A	46.20	33.80	-1.37	0.158193176	0.574824601	0.003701551	0.006568
ENSG00000173905	GOLIM4	60.33	48.64	-1.24	0.059975736	0.854254689	0.008563637	0.013753
ENSG00000020181	GPR124	5.12	11.03	2.15	0.160823068	0.950444769	0.00057965	0.001294
ENSG00000205336	GPR56	19.22	24.68	1.28	0.050823079	0.515765812	0.010042854	0.015835
ENSG00000170412 ENSG00000089351	GPRC5C GRAMD1A	25.16	34.35	1.37	0.171824595	0.276406124	0.002952644 6.61E-05	0.005367
ENSG00000030582	GRN	155.21	215.94	1.39	0.831202718	0.864972977	0.000655104	0.001437
ENSG0000084207	GSTP1	248.13	327.67	1.32	0.744871032	0.446696369	0.000914688	0.001920
ENSG00000100577 ENSG00000121964	GSTZ1 GTDC1	9.70	15.85	-1.35	0.479830014	0.873002604	4.29E-05 2.32E-05	0.000136
ENSG00000119041	GTF3C3	34.39	26.68	-1.29	0.870486754	0.066795045	0.003758597	0.006661
ENSG00000172432	GTPBP2	36.00	41.42	1.15	0.870221456	0.901744084	0.029110719	0.0407
ENSG00000136732 ENSG00000184897	GYPC H1FX	40.52	145.09 54.36	1.35	0.888913721 0.318561293	0.162285701 0.295052407	0.000920386	0.001929
ENSG0000049239	H6PD	10.42	15.63	1.50	0.250539976	0.146483291	2.34E-05	8.20E
ENSG0000084754	HADHA	507.11	390.44	-1.30	0.345369459	0.475896323	0.009277223	0.014760
ENSG00000138641	HERC3	30.43	23.26	-1.31	0.111648066	0.123994568	0.000387676	0.000908
ENSG0000010282	HHATL	1180.99	1471.65	1.25	0.252431847	0.379986886	0.019751489	0.028791
ENSG00000106049 ENSG00000167861	HIBADH HID1	113.25	96.10	-1.18	0.177165584	0.312052204	0.021380675 4.08E-05	0.03094
ENSG00000204257	HLA-DMA	37.37	64.94	1.74	0.738164393	0.564934268	0.001468275	0.002914
ENSG00000242574	HLA-DMB	13.42	24.61	1.83	0.915205098	0.374908776	0.00435698	0.007548
ENSG00000198502 ENSG00000253954	HMGN1P38	5.88	13.09	2.00	0.143901617	0.059557089	4.97E-06	2.206
ENSG00000182952	HMGN4	28.70	37.14	1.29	0.464983672	0.227168022	0.022134505	0.031934
ENSG00000113716	HMGXB3	9.31	15.41	1.66	0.336144376	0.53307586	0.002335393	0.00437
ENSG00000214753	HNRNPUL2	53.23	46.63	-1.14	0.771624422	0.74576293	0.014749274	0.022182
ENSG00000205100	HSP90AA4P	17.52	9.88	-1.77	0.429039786	0.547486562	1.52E-05	5.698
ENSG0000004776	HSPB6	1203.21	1837.13	1.53	0.708324535	0.940651408	0.015461162	0.023167
ENSG00000086758	HUWE1	73.75	82.47	1.12	0.326668017	0.209328985	0.021084174	0.030536
ENSG0000068001	HYAL2	50.65	80.92	1.60	0.401531458	0.765593179	0.011201954	0.017381
ENSG00000067704 ENSG0000005700	IARS2	72.68	59.05 30.62	-1.23	0.774035917	0.347059527	0.000895092	0.001887
ENSG00000090339	ICAM1	5.81	16.96	2.92	0.916653869	0.836282379	0.000206469	0.000524
ENSG0000010404	IDS	104.54	88.67	-1.18	0.013583528	0.356020111	0.008760616	0.014029
ENSG00000163565 ENSG00000119632	IFI16 IFI27L2	31.41	45.57	1.45	0.042545149	0.557509542	0.026709492	0.037780
ENSG00000068079	IFI35	13.67	21.37	1.56	0.398343904	0.951123073	0.002156347	0.004086
ENSG00000258664	IFRG15	19.37	13.18	-1.47	0.935603556	0.705851183	0.000581702	0.001298
ENSG0000068885 ENSG00000115457	IFT80 IGFBP2	24.85	16.37 218.02	-1.52	0.679410592	0.492256052	0.000469072	0.001072
ENSG00000141753	IGFBP4	83.47	142.26	1.70	0.778353571	0.485004897	3.43E-05	0.000113
ENSG00000163453	IGFBP7	695.86	888.57	1.28	0.647411824	0.234411645	0.01229052	0.018830
ENSG00000163702 ENSG00000077238	IL17RC IL4R	24.13 8.37	32.26 19.24	1.34 2.30	0.981178553	0.191430942	0.000155143 3.75F-05	0.000409
ENSG00000148950	IMMP1L	52.49	35.95	-1.46	0.869943632	0.993659095	0.001359275	0.002720
ENSG00000203485	INF2	20.79	30.28	1.46	0.504252108	0.697414279	0.000454281	0.001044
ENSG00000168395 ENSG00000115274	ING5 INO80B	9.94	15.11	1.52	0.804628874	0.859001833	0.002359518	0.004412
ENSG00000186480	INSIG1	6.58	11.89	1.81	0.44425261	0.171439606	0.000644224	0.001415
ENSG00000117408	IPO13	45.06	59.37	1.32	0.586298014	0.231989701	0.000343246	0.000818
ENSG00000133704 ENSG00000145703	IPU8 IQGAP2	20.69	14.98	-1.38	0.878601391	0.681002463	0.00035502	0.000843
ENSG00000125347	IRF1	17.14	26.35	1.54	0.821096876	0.589754363	0.020352293	0.029560
ENSG00000170604	IRF2BP1	9.38	14.41	1.54	0.226396205	0.28072152	5.12E-07	3.288
ENSG00000119669 ENSG00000167378	IRF2BPL IRGQ	13.49	19.15 21.44	1.42	0.077920732	0.741207704	0.008623495 6.79E-08	0.01384 6.40
ENSG00000135070	ISCA1	54.17	45.45	-1.19	0.938002171	0.725204273	0.001455486	0.002892
ENSG00000227653	ISCA1P6	35.38	29.84	-1.19	0.574469364	0.049182667	0.009864925	0.01560
ENSG00000063241	ISOC2	51.80	62.33	1.20	0.907941694	0.245725519	0.019995343	0.029079
ENSG00000132470	ITGB4	37.25	49.00	1.32	0.155151629	0.078451359	0.000186429	0.046964
ENSG00000115221	ITGB6	35.05	23.82	-1.47	0.119140282	0.314820582	0.002759128	0.005053
ENSG00000055955	ITIH4	9.40	19.81	2.11	0.680435302	0.806143347	2.39E-05	8.35
ENSG0000086544	ITM2C ITPKC	20.79	31.58 12.85	1.52	0.461824041 0.167138744	0.135817789 0.171487549	2.06E-05 0.00162124	7.408 0.003182
ENSG00000150995	ITPR1	10.13	15.22	1.50	0.095734488	0.118650449	0.004901388	0.008380
ENSG00000184916	JAG2	20.43	28.35	1.39	0.769171086	0.398455101	0.001568924	0.003095
ENSG00000100221	JOSD1	24.12	33.39	1.38	0.695378679	0.50552883	0.009561298	0.015161
ENSG00000186994	KANK3	a5.99 20.18	28.85	1.26	0.319561777	0.323419267	0.000775437	0.031543
ENSG00000120071	KANSL1	31.16	24.52	-1.27	0.191005319	0.09272668	0.023647111	0.033865
ENSG00000178695	KCTD12 KCTD15	17.83	28.02	1.57	0.760744288	0.85466578	0.003795908	0.006720
ENSG00000100379	KCTD17	9.05	17.42	1.80	0.056628539	0.916067521	0.030029797	0.041950
ENSG00000105438	KDELR1	87.16	101.46	1.16	0.995834935	0.561869133	0.006386429	0.010592
511000000000000000000000000000000000000	KDM2A	21.02	26.13	1.24	0.703767763	0.990914304	0.004851479	0.008305

ICM-specific DEGs at F	DR≤0.05 Gene	NF mean	ICM mean	FC	nval Age	nval Sex	oval ICM v NF	FDR ICM v NF
ENSG00000132510	KDM6B	8.33	16.11	1.94	0.703616141	0.1414698	0.000535709	0.001210178
ENSG00000131773	KHDRBS3	30.70	42.34	1.38	0.834501966	0.474396633	0.028444673	0.039964411
ENSG00000166783	KIAA0430	25.78	19.43	-1.33	0.705013718	0.544139786	0.000377942	0.000889814
ENSG0000047578	KIAA0556	6.58	12.53	1.91	0.751087033	0.633441683	2.37E-08	2.65E-07
ENSG00000196123 ENSG00000116685	KIAA0895L KIAA2013	20.11	26.66	1.33	0.987695555	0.135512686	0.002679231	0.004928106
ENSG00000183354	KIAA2026	16.13	9.16	-1.76	0.406086132	0.099715777	4.05E-11	2.00E-09
ENSG0000089177	KIF16B	15.45	9.13	-1.69	0.968714683	0.636341621	2.88E-07	2.05E-06
ENSG00000172059	KLF11	8.21	13.57	1.65	0.182796857	0.08143939	0.000118695	0.000324783
ENSG00000114796	KLHL24	61.02	38.42	-1.59	0.260535657	0.921265365	0.000313851	0.000756627
ENSG0000055609	KMT2C	20.75	15.34	-1.35	0.075782089	0.039701808	0.000290299	0.000708335
ENSG00000182481	KPNA2	16.43	26.04	1.59	0.951659366	0.880320548	0.005136538	0.008737698
ENSG00000262554	LA16c-360H6.2	12.37	5.07	-2.44	0.315485696	0.004965732	0.001093215	0.002242962
ENSG00000107929	LARP4B	40.01	33.99	-1.18	0.297123263	0.90121226	0.014241688	0.021505674
ENSG00000174720 ENSG0000002834	LARP7	127.01	91.06 27.58	-1.39	0.870109989	0.751450789	0.002430448	0.004522174
ENSG00000111716	LDHB	5869.92	4579.55	-1.28	0.285855699	0.357360475	0.021417263	0.030987381
ENSG00000130164	LDLR	5.20	14.44	2.78	0.58223064	0.292442726	1.85E-05	6.72E-05
ENSG00000183814	LIN9	18.37	12.49	-1.47	0.248389042	0.068988831	0.000826758	0.001763041
ENSG00000259330	LINC00984	26.69	35.16	1.64	0.851221307	0.389095006	0.009734975	0.025959552
ENSG00000107798	LIPA	21.58	27.44	1.27	0.250830059	0.967525449	0.01597855	0.023859833
ENSG00000160789	LMNA	157.05	225.45	1.44	0.18329815	0.782678769	0.001976528	0.003785098
ENSG00000196365 ENSG00000134013	LONPI	6.30	126.49	1.12	0.310444562	0.722110692	0.028629835	0.040164465
ENSG00000117114	LPHN2	40.81	32.91	-1.24	0.176635545	0.104053511	0.010900552	0.016960428
ENSG00000132793	LPIN3	19.57	25.05	1.28	0.717211713	0.910656283	0.020654993	0.029969155
ENSG0000077454	LRCH4	33.73	44.87	1.33	0.320842842	0.960177554	1.75E-05	6.41E-05
ENSG00000123384 ENSG00000197324	LRP1 LRP10	48.50	69.36	1.69	0.412878159	0.264773793	0.001087833	0.002212279
ENSG00000130881	LRP3	9.21	15.03	1.63	0.089700861	0.881287288	7.86E-07	4.71E-06
ENSG00000134569	LRP4	16.96	10.55	-1.61	0.840038249	0.601180678	4.49E-06	2.03E-05
ENSG00000136802	LRRC8A	41.19 13.28	52.32	1.59	0.289385169	0.525447294	0.005239371	0.00889321
ENSG00000164167	LSM6	21.15	15.97	-1.32	0.622979873	0.177196152	0.002785669	0.005098915
ENSG00000204482	LST1	11.77	20.97	1.78	0.43769301	0.087083739	0.006915826	0.011376281
ENSG00000111144	LTA4H	54.27	47.15	-1.15	0.476970004	0.623636058	0.016733768	0.0248558
ENSG00000269955	LUC7L2	36.24	42.40	-1.32	0.911088482	0.327470149	0.001580443	0.003207894
ENSG00000267697	LUZP6	202.23	388.98	1.92	0.582579989	0.729633117	0.005300248	0.008978231
ENSG00000011009	LYPLA2	18.26	24.60	1.35	0.698731121	0.684290831	8.19E-05	0.000235541
ENSG00000176018	LYSMD3	35.40	28.53	-1.24	0.145962381	0.495154786	0.001468042 7.89E-05	0.002914821
ENSG00000107816	LZTS2	19.80	28.98	1.46	0.280390618	0.660117534	6.28E-05	0.0001878
ENSG0000002822	MAD1L1	26.77	33.88	1.27	0.371975451	0.080020061	0.014547137	0.021914056
ENSG00000111885	MAN1A1	10.27	16.10	1.57	0.794383073	0.412152503	0.013892916	0.021012802
ENSG0000013288	MAN2B2	10.73	15.98	1.49	0.973848843	0.021007707	0.002302655	0.004327271
ENSG00000101363	MANBAL	19.06	25.99	1.36	0.63582453	0.340214624	5.03E-05	0.000155453
ENSG00000034152	MAP2K3	33.44	52.70	1.58	0.868282024	0.942373385	0.004347036	0.007543305
ENSG00000129680	MAP7D3	21.11	15.78	-1.34	0.894370391	0.640681369	0.012273808	0.01881138
ENSG00000155130	MARCKS	5.85	12.08	2.07	0.438482026	0.812341898	0.001344522	0.002697393
ENSG00000175130	MARCKSL1	14.68	22.29	1.52	0.818715949	0.862021184	0.01625897	0.024233608
ENSG00000158906	MATR3	94.84	136.98	-1.44	0.916814999	0.353480635	0.001095111	0.0022444
ENSG00000071655	MBD3	40.30	57.32	1.42	0.458388904	0.252180551	0.000259111	0.000640192
ENSG00000125505	MBOAT7	16.41	23.07	1.41	0.853520965	0.654121205	0.000774823	0.001668713
ENSG00000131844 ENSG00000126217	MCCC2 MCE2L	97.01	80.37	-1.21	0.846008428	0.551486753	0.004775556	0.008182933
ENSG00000137337	MDC1	13.59	19.66	1.45	0.311923011	0.156895598	0.000322908	0.000775805
ENSG00000111554	MDM1	14.79	9.71	-1.52	0.870653422	0.681656518	0.000301145	0.000729429
ENSG00000184634	MED12	11.76	18.15	1.54	0.645138458	0.967658278	0.019967131	0.029045912
ENSG00000133997	MED15 MED6	25.65	19.76	-1.30	0.59811957	0.38651502	1.25E-05	4.79E-05
ENSG00000141026	MED9	19.24	26.59	1.38	0.185379933	0.406692318	8.10E-06	3.28E-05
ENSG0000081189	MEF2C	28.17	19.97	-1.41	0.35526288	0.235295519	0.006318639	0.010495051
ENSG0000005102 ENSG00000146834	MEDX1	12.59	21.40	1.70	0.995102466	0.896483515	2.19F-06	0.037276603
ENSG00000165792	METTL17	67.08	81.86	1.22	0.840531033	0.945917997	0.004682461	0.008047891
ENSG00000181038	METTL23	21.74	29.84	1.37	0.689498782	0.600413396	8.62E-06	3.47E-05
ENSG00000170439	METTL7B	13.48	6.30	-2.14	0.840074775	0.687863394	0.007478933	0.012209884
ENSG00000100060	MENG	11.13	16.95	1.52	0.283730017	0.890868682	0.002187367	0.004136833
ENSG0000092931	MFSD11	16.18	22.77	1.41	0.733214344	0.014876321	3.01E-05	0.00010222
ENSG00000161091	MFSD12	19.55	26.62	1.36	0.378135849	0.766662163	0.002318375	0.004352457
ENSG00000131446	MGAT1	8.62	14.52 87.57	1.58	0.640603838	0.02842436	1.42E-07 0.003623754	1.15E-06 0.006456746
ENSG00000161013	MGAT4B	217.88	256.71	1.18	0.853186741	0.681992519	0.010402257	0.01630671
ENSG00000240972	MIF	119.19	240.13	2.01	0.276560254	0.89708369	0.02738523	0.038591392
ENSG00000079277	MIIP MKNK1	11.15	17.30	-1.55	0.352932645 0.06386154	0.283802277	0.000237179	0.000592054
ENSG00000178053	MLF1	139.03	103.59	-1.34	0.034654724	0.566116243	0.033178445	0.045737059
ENSG0000091436	MLTK	141.51	117.30	-1.21	0.034674334	0.164098479	0.01221635	0.01873861
ENSG00000157227	MOV10	12.50	18.72	1.50	0.399903455	0.1/1250727	0.002347056	0.00439021
ENSG00000103152	MPG	26.97	33.88	1.26	0.104967868	0.739060972	0.002150914	0.004078845
ENSG0000051825	MPHOSPH9	27.57	19.12	-1.44	0.514805369	0.585721887	0.000726449	0.001576394
ENSG00000173141	MRP63 MRPL27	15.68	22.32	1.42	0.745064402	0.720583774	1.01E-07	8.84E-07
ENSG00000204316	MRPL38	207.77	227.60	1.14	0.083755688	0.386969073	0.03239636	0.044834461
ENSG00000182154	MRPL41	108.53	140.95	1.30	0.820446588	0.053792455	0.003125689	0.005649705
ENSG00000174100	MRPL45	27.92	33.23	1.19	0.255562558	0.397538099	0.001601446	0.003150331
ENSG00000113048	MRPS27	59.43 150.16	126.56	-1.18	0.5728/9387	0.023586262	0.005151876	0.008/53218
ENSG00000125445	MRPS7	136.02	151.58	1.11	0.16903136	0.900117065	0.013012032	0.019813456
ENSG00000124532	MRS2	40.63	34.19	-1.19	0.586767513	0.022693178	0.010408267	0.016311593
ENSG00000147065	MK104 MSN	9.58 51.55	16.29 90.10	1.70	0.36283974 0.478485915	0.300753579	1.U9E-06 0.035239929	6.18E-06 0.048201447
ENSG00000251593	MSNP1	8.64	15.63	1.81	0.458241806	0.675195358	1.19E-06	6.63E-06
ENSG00000260549	MT1L	20.78	45.34	2.18	0.570772406	0.341980652	5.11E-05	0.000157407
ENSG00000233929	MT1XP1 MT2A	223.13	537.60	2.41	0.087213851	0.291529393	0.003785896	0.006705356
ENSG00000182979	MTA1	86.30	107.96	1.25	0.141152314	0.584738094	0.002114443	0.004016444
ENSG00000149480	MTA2	35.46	43.78	1.23	0.990643186	0.261236951	0.00852045	0.013688384
ENSG00000220113	MTCYBP4	28.10	16.14	-1.74	0.855464589	0.029278406	0.001213006	0.002459185
ENSG00000127989	MTERF MTHED2	13.21	7.35	-1.80	0.675972279	0.862619987	8.64E-11 0.001169791	3.45E-09
ENSG00000108389	MTMR4	22.69	16.48	-1.38	0.129098404	0.520241752	0.00166031	0.00324911
ENSG00000269028	MTRNR2L12	6782.44	4984.20	-1.36	0.904374084	0.56566746	0.001255319	0.002537663
ENSG00000255823	MTRNR2L8	5382.05	4385.36	-1.23	0.824885076	0.850693226	0.036182376	0.049334827
ENSG00000172732 ENSG00000141971	MUS81 MVR124	38.15	52.90 17.86	1.39	0.339355022	0.95/451747	0.000542024 5.92F-0F	0.001223858
ENSG00000179820	MYADM	44.34	78.70	1.78	0.241352113	0.300414595	0.00014205	0.000380195
ENSG00000136997	MYC	6.72	14.07	2.09	0.894863078	0.554092024	0.006844564	0.011272223
ENSG00000100345	MYH9 MYL9	150.38	199.78	1.33	0.473016978	0.429355664	0.011567514	0.01788457
ENSG00000007944	MYLIP	7.75	12.85	1.66	0.569553913	0.802351227	2.38E-05	8.32E-05
ENSG00000140795	MYLK3	131.47	84.68	-1.55	0.911186502	0.12765656	0.003453374	0.006176606
ENSG00000176658	MY01D	7.87	14.62	1.86	0.026973384	0 344916463	0.007003391	0.011496825

ICM-specific DEGs at F	DR≤0.05	NF men		50	and Ass	and fan		
ENSG0000066933	MYO9A	NF_mean 10.71	icivi_mean 5.11	-2.10	0.709633971	0.985592178	pvar_ICMI_V_NF 8.86E-08	8.05E-07
ENSG00000099331	MYO9B	30.93	43.65	1.41	0.624208186	0.780424271	0.001084867	0.002229894
ENSG00000173418	NAA20	56.41	65.11	1.15	0.387805208	0.093437583	0.035795434	0.048890055
ENSG00000166886	NAB2	6.23	13.32	2.14	0.324682838	0.80822279	6.53E-07	4.07E-06
ENSG0000008130 ENSG00000105402	NADK	48.86	364.88	1.36	0.076726475	0.261309689	0.010293602	0.005107693
ENSG00000137513	NARS2	33.18	25.57	-1.30	0.306453366	0.317360915	0.001818778	0.003515264
ENSG00000160796	NBEAL2	12.98	19.96	1.54	0.206234107	0.094998596	5.89E-05	0.000178218
ENSG00000270170	NCBP2-AS2	15.31	20.46	1.34	0.231770051	0.351017442	3.26E-05	0.000109261
ENSG00000125912 ENSG00000140396	NCLN NCOA2	21.47	34.62	-1.51	0.045539496	0.130918388	1.10E-06 0.000292711	6.22E-U6 0.000713293
ENSG00000101247	NDUFAF5	75.18	67.48	-1.11	0.276099807	0.793966177	0.01807503	0.026581759
ENSG00000183648	NDUFB1	1284.39	1039.78	-1.24	0.136964933	0.231046589	0.034477645	0.047319623
ENSG0000090266	NDUFB2	604.03	744.50	1.23	0.122687637	0.124129997	0.000981569	0.002039897
ENSG00000255526	NEDD8-MDP1	24.50	18.17	-1.35	0.923543709	0.018859044	0.028268503	0.039766478
ENSG00000185049	NELED	10.64	15.89	1.43	0.81552817	0.586104624	1.77E-08	2.12F-07
ENSG00000188986	NELFB	14.07	22.04	1.57	0.590816224	0.338585725	3.56E-08	3.65E-07
ENSG00000165525	NEMF	62.94	48.54	-1.30	0.646013972	0.553788206	0.007590744	0.012367337
ENSG00000176953	NFATC2IP	16.44	21.46	1.31	0.492451738	0.909394115	5.58E-05	0.000170302
ENSG00000077150 ENSG00000100906	NFKB2 NFKBIA	6.74 173.58	254 14	2.26	0.32297154	0.35988304	4.83E-05 0.0228054	0.000150593
ENSG00000104825	NFKBIB	12.69	17.86	1.40	0.588962394	0.300451723	0.001523701	0.003018471
ENSG00000134259	NGF	10.71	5.45	-1.97	0.601615738	0.548751582	3.89E-06	1.79E-05
ENSG0000087303	NID2	56.41	45.29	-1.25	0.091708489	0.998411533	0.012046127	0.018512788
ENSG00000100503	NIN	15.58	10.35	-1.51	0.015840851	0.943133374	0.000890251	0.001879464
ENSG00000168256	NKIRAS2	38.18	45.50	1.19	0.406343446	0.19590607	0.004862624	0.008322
ENSG00000140853	NLRC5	9.21	15.07	1.64	0.89453464	0.976166294	0.006260546	0.010416986
ENSG00000166741	NNMT	35.41	77.22	2.18	0.511890966	0.731304684	0.009285793	0.014770231
ENSG00000248092	NNT-AS1	28.82	23.57	-1.22	0.253812998	0.139120592	0.021461716	0.031027793
ENSG00000184967 ENSG00000130935	NOL4L NOL11	22.64	12.58	1.79	0.074705886	0.821426081	4.98E-07 0.001234608	3.21E-U6 0.002497588
ENSG00000198000	NOL8	25.87	20.62	-1.26	0.838888799	0.615524694	0.026932367	0.038029312
ENSG00000166197	NOLC1	19.37	25.90	1.34	0.759791447	0.866791192	0.001374566	0.002746207
ENSG00000196943	NOP9	12.26	17.59	1.43	0.986516539	0.693402044	1.65E-05	6.08E-05
ENSG00000164867	NOS3 NOTCH?	10.46	21.11	2.02	0.907698252	0.315466036	0.000803602	0.00172148
ENSG00000141458	NPC1	52.05 18.55	40.10	1.44	0.412334093	0.32862546	0.011070847	0.0116///64
ENSG00000120798	NR2C1	83.92	69.17	-1.21	0.153005023	0.581025821	0.01115747	0.017317131
ENSG00000151623	NR3C2	11.95	6.31	-1.89	0.275865546	0.545810879	2.22E-05	7.87E-05
ENSG00000123358	NR4A1	42.89	152.47	3.55	0.647031122	0.883321029	0.001703945	0.003322958
ENSG00000115216	NSL1	44.97	53.49 25.65	-1.23	0.369181597	0.203995203	0.01/8/10/3	0.026343/01
ENSG00000130305	NSUN5	10.82	16.99	1.57	0.262437984	0.874745815	3.03E-08	3.22E-07
ENSG00000125458	NT5C	42.60	52.47	1.23	0.380625974	0.034559101	0.017051176	0.025260669
ENSG00000178425	NT5DC1	41.53	32.96	-1.26	0.716542082	0.126322107	0.004250882	0.007407903
ENSG00000167005 ENSG00000105245	NUDT21 NUMBI	46.35	38.15	-1.22	0.616507971	0.097760801	0.000931423 1.275-05	0.001947898 4.855-05
ENSG00000258300	NUTF2P2	18.45	12.55	-1.47	0.667635202	0.784871872	0.001823957	0.003524065
ENSG00000124596	OARD1	40.29	33.43	-1.20	0.687883124	0.899751824	0.004381065	0.007580749
ENSG0000087263	OGFOD1	17.31	22.46	1.30	0.520743602	0.986348684	0.000380142	0.000893873
ENSG00000181396	OGFOD3	33.25	38.68	1.16	0.959247505	0.637865594	0.006961833	0.011438602
ENSG00000213790	ORC4	39.64	31.70	-1.44	0.687518508	0.011956012	0.008100974	0.01310014
ENSG00000123353	ORMDL2	18.68	28.23	1.51	0.9548992	0.595175107	0.000740451	0.001602036
ENSG0000091039	OSBPL8	14.13	8.79	-1.61	0.736930415	0.933012177	0.001803005	0.003490766
ENSG0000081087	OSTM1	61.61	51.49	-1.20	0.094104919	0.114255217	0.027262754	0.038447649
ENSG00000164830 ENSG00000175575	DAAF1	12 93	21.10	-1.40	0.042357989	0.211493104	0.000179593 5.22E-05	0.000465208
ENSG00000179364	PACS2	31.31	38.51	1.23	0.358629012	0.852976559	0.004413405	0.007629679
ENSG00000135473	PAN2	106.91	91.77	-1.17	0.155934617	0.350386789	0.006154411	0.010261602
ENSG00000116288	PARK7	354.64	405.65	1.14	0.941741515	0.757293488	0.016907889	0.025077696
ENSG00000140694	PARN	41.45	33.66	-1.23	0.351614556	0.081095763	0.002075576	0.003949272
ENSG00000178685 ENSG00000041880	PARP10 PARP3	13.92	19.52	1.40	0.938325221	0.830225742	0.0011342372	0.01/5/5062
ENSG00000197702	PARVA	56.93	71.35	1.25	0.824699926	0.089445179	0.029261025	0.04092766
ENSG00000163939	PBRM1	20.33	13.13	-1.55	0.2776034	0.1696489	2.06E-06	1.06E-05
ENSG00000132635	PCED1A	16.28	25.39	1.56	0.402288871	0.429614503	0.000339432	0.000811353
ENSG0000018674	PCM1 PCNVL2	116.28	91.05	-1.28	0.317045097	0.693806756	0.004161118	0.007276145
ENSG00000106333	PCOLCE	46.74	87.71	1.88	0.331508038	0.64978918	0.001065956	0.002196634
ENSG00000154678	PDE1C	92.56	70.41	-1.31	0.311118539	0.032040203	0.024021785	0.034315096
ENSG00000173517	PEAK1	26.49	21.17	-1.25	0.39206405	0.7633223	0.026233038	0.037190975
ENSG00000133027	PEMT PEV7	21.52	31.91	1.48	0.885851316	0.069420114	9.42E-05	0.000266026
ENSG00000247077	PGAM5	16.89	23.78	1.41	0.555383228	0.0731712	6.07E-06	2.70E-00 2.60E-05
ENSG00000119630	PGF	6.37	11.59	1.82	0.934218696	0.938397961	0.000925644	0.001938691
ENSG00000130313	PGLS	14.51	23.85	1.64	0.527924597	0.947470331	2.13E-05	7.61E-05
ENSG00000101856	PGRMC1	12.29	20.07	1.63	0.482640501	0.7203163	0.010546931	0.016487627
ENSG00000197724	PHF2	10.81	10.61	1.54	0.854019529	0.52/931135	1.68E-06 2.47F-05	8.91E-06 8.59E-05
ENSG00000232882	PHKA1P1	14.96	9.13	-1.64	0.0631077	0.950665473	0.000855391	0.001819967
ENSG00000155252	PI4K2A	6.84	12.90	1.89	0.995152276	0.618816385	1.05E-08	1.39E-07
ENSG00000131788	PIAS3	12.59	17.67	1.40	0.355434788	0.41342096	0.000549723	0.001238856
ENSG0000165195	PIGA	16.14	7.14	-2.26	0.256872976	0.012015309	0.005783281	0.00635966
ENSG00000145675	PIK3R1	82.73	56.84	-1.46	0.90107817	0.344361204	0.032662499	0.045125189
ENSG00000196455	PIK3R4	18.51	24.50	1.32	0.0751727	0.882570397	0.001364247	0.002729094
ENSG00000137193	PIM1	12.04	22.44	1.86	0.695370089	0.27761034	0.026603671	0.037650109
ENSG0000241979	PIPSKIC	20.06	28.22	1.41	0.768850338	0.709600151	1.41E-05	5.32E-05
ENSG00000254023	PKMP4	17.74	30.49	1.72	0.957594053	0.963888259	0.011579004	0.017897423
ENSG0000065243	PKN2	17.02	9.90	-1.72	0.536013916	0.656352702	5.24E-07	3.34E-06
ENSG00000103066	PLA2G15	25.20	31.78	1.26	0.757800464	0.459301121	0.034763614	0.047665661
ENSG00000104269	PLA2G4B PLAT	7.39	14.12	1.91	0.526020301	0.857326857	2.61E-05	9.02E-05
ENSG00000114508	PLAUR	9.75	13.54	1.94	0.3243336	0.907947731	0.019939595	0.029013347
ENSG00000151176	PLBD2	12.84	19.33	1.51	0.329772288	0.061831504	0.000105077	0.000292926
ENSG00000129219	PLD2	13.46	22.11	1.64	0.901178919	0.719414904	0.003262401	0.005874199
ENSG0000015762	PLEKHB2 PLEKHE1	18.02	24.66	1.37	0.407261453	0.566543048	0.000896792	0.001889501
ENSG00000116786	PLEKHM2	45.27	54.68	1.21	0.259397348	0.586234761	0.035762276	0.048871214
ENSG00000188313	PLSCR1	46.73	66.19	1.42	0.615944932	0.387189481	0.024837038	0.035398905
ENSG0000076356	PLXNA2	11.84	16.86	1.42	0.313234952	0.660843391	0.005149425	0.008751692
ENSG00000100417	PMM1	19.02	26.02	1.37	0.645812086	0.762570829	0.000224725	0.000563463
ENSG0000176902	PMPCA PNMA1	44.65	54.01 21.62	1.21	0.1/2707435	0.69126792	5.20E-06 0.006043181	2.29E-05 0.010001072
ENSG00000198805	PNP	7.05	13.95	1.98	0.617573248	0.608178375	0.002461291	0.004570505
ENSG00000146278	PNRC1	81.19	118.78	1.46	0.732318595	0.883801598	0.002606292	0.004808071
ENSG00000139323	POC1B	13.96	8.59	-1.63	0.717307297	0.589151634	7.09E-07	4.34E-06
ENSG00000115350	POLE4	45.09	63.67	1.41	0.445273691	0.462755079	0.000289151	0.000706145
ENSG00000121851	POLR2H POLR3C	31.67	42.07	1.33	0.894649912	0.70775563	0.000192624	0.000474772
ENSG00000121851	POMP	79.76	90.71	-1.18	0.905902777	0.005591225	0.024156799	0.034499216
ENSG00000130714	POMT1	21.29	30.73	1.44	0.324095884	0.245608313	7.78E-06	3.17E-05
ENSG00000105854	PON2	82.25	68.22	-1.21	0.402799031	0.756072579	0.0064367	0.010665991
ENSG00000127948	POR	73.62	97.14	1.32	0.633199327	0.589008449	0.023322617	0.033443529
ENSG00000130810	PPAN PPAPDC1P	16.59	22.67	1.37	0.709959543	0.243007052	0.001889563	0.003634619
ENSG00000110841	PPAPDC18 PPFIBP1	15.59	102.93	-1.52	0.024081881	0.480469001	0.000929024	0.018196435
ENSG00000138398	PPIG	21.63	15.89	-1.36	0.236224242	0.602677178	0.002506171	0.004646189
ENSG00000240344	PPIL3	50.48	36.67	-1.38	0.815189796	0.24525294	0.002542699	0.004705707
ICM-specific DEGs at FDR≤0.0	05 NE mos	n ICM moon	EC	nual Arro	nual Sax	aval ICM v NE	EDR ICM v NE	
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ENSG00000163644 PP	M1K 180.0	16 121.43	-1.48	0.846499923	0.505739402	0.006621445	0.010943157	
ENSG00000164088 PP	M1M 6.9	3 14.23	2.05	0.59735369	0.965566593	1.49E-06	8.03E-06	
ENSG00000214517 PP	ME1 22.1	9 27.40	1.24	0.792747829	0.869663772	0.002285554	0.004299436	
ENSG00000150722 PP	P1R1C 29.7	8 23.20	-1.28	0.199384603	0.4662113	0.036074788	0.049211951	
ENSG00000115685 PP	P1R7 101.9	6 116.96	1.15	0.621688492	0.746078063	0.01771348	0.026131905	
ENSG0000092020 PP	P2R3C 71.2 P2R4 93.0	7 58.95 9 118.27	-1.21	0.695052581	0.014468092	0.016406268	0.024420849	
ENSG00000154001 PP	P2R5E 17.0	4 11.92	-1.43	0.280332083	0.456427813	7.76E-06	3.17E-05	
ENSG00000148840 PP	RC1 6.9	9 15.22	2.18	0.56313825	0.963435676	2.33E-07	1.73E-06	
ENSG00000131238 PP ENSG00000162976 PO	11 52.6 ILC3 7.9	2 61.86 5 14.84	1.18	0.259890945 0.701750491	0.586292596	0.01079981 1.64E-05	0.016826916 6.06E-05	
ENSG0000085377 PR	EP 24.3	2 29.37	1.21	0.039490368	0.611074033	5.21E-05	0.000160137	
ENSG00000138078 PR	EPL 93.5	7 77.99	-1.20	0.406185607	0.956713456	0.032643822	0.045122419	
ENSG00000131791 PR ENSG00000126457 PR	MT1 102.4	1 25.62	-1.50	0.393585049	0.548732469	0.001996645	0.001275827	
ENSG00000130723 PR	RC2B 37.0	3 44.96	1.21	0.873299287	0.334420449	0.00834233	0.013434441	
ENSG00000143106 PSI	MA5 207.3	1 171.64	-1.21	0.879555831	0.506599519	0.001186929	0.002414136	
ENSG00000240065 PSI	MB9 11.6	1 20.22	1.40	0.728046193	0.641421781	0.0001428878	0.001862703	
ENSG0000011304 PT	BP1 55.3	9 78.89	1.42	0.673397772	0.731568482	0.000167052	0.000436941	
ENSG00000185920 PT	CH1 12.1	7 7.05	-1.73	0.401188519	0.604419491	2.79E-05	9.56E-05	
ENSG00000174915 PTI ENSG00000218902 PTI	MAP3 8.5	1 14.34	1.45	0.490299934	0.979961211	0.001107147	0.002264126	
ENSG00000214182 PT	MAP5 30.6	9 45.35	1.48	0.173483688	0.686844911	0.009904961	0.015649061	
ENSG00000254481 PTI	P4A2P2 17.9	1 12.81	-1.40	0.975005223	0.161582633	4.40E-05	0.000139267	
ENSG0000072135 PTI	PMAS 575.7 PN18 15.2	1 22.03	1.50	0.206206648	0.553123953	0.000337376	0.000807467	
ENSG00000204179 PT	PN20A 14.1	3 8.86	-1.60	0.102549333	0.024497585	0.014632323	0.022024715	
ENSG00000169410 PTI ENSG00000187024 PTI	PN9 12.0	6 19.40	1.61	0.499367531	0.670146176	0.000189947	0.000488686	
ENSG00000187024 P11 ENSG00000055917 PU	M2 35.5	5 29.21	-1.22	0.284736576	0.072646089	0.01083511	0.016872584	
ENSG00000048991 R3	HDM1 14.2	3 9.16	-1.55	0.189642982	0.463335934	0.001773573	0.00343851	
ENSG00000198858 R3	HDM4 18.7	3 28.20	1.51	0.58759689	0.587085051	3.55E-07	2.41E-06	
ENSG00000135631 RA	B11FIP5 25.6	i6 32.78	1.28	0.17672933	0.053241079	0.012856799	0.019592969	
ENSG00000174903 RA	B1B 67.8	4 82.12	1.21	0.471013789	0.529595745	0.003965587	0.00697973	
ENSG00000137502 RA ENSG00000197562 PA	B30 11.7 B40C 7	0 6.14 8 12.60	-1.90	0.455045556	0.191215938	3.36E-07 3.57E-05	2.31E-06 0.000117416	
ENSG00000196642 RA	BL6 39.2	4 45.51	1.67	0.624573695	0.516118628	0.011485539	0.017777343	
ENSG00000164754 RA	D21 112.5	9 87.35	-1.29	0.868621008	0.243984141	0.001345345	0.002697393	
ENSG00000179262 RA ENSG00000113522 PA	D23A 119.2 D50 20.0	9 140.62	1.18	0.945845822	0.784218102	0.006557463	0.010843777	
ENSG00000108384 RA	D51C 47.3	0 38.15	-1.45	0.562478467	0.878113353	0.015460992	0.023167071	
ENSG00000125970 RA	LY 98.4	9 117.63	1.19	0.940802148	0.835151422	0.01374248	0.020813208	
ENSG00000132341 RA	NIPS 23.9 N 1107	7 41.66 7 135.90	1.74	0.413825033	0.509533795	0.000637587	0.001402642	
ENSG00000131541 RA	NBP10 9.9	0 14.97	1.51	0.735262966	0.296814226	2.70E-08	2.94E-07	
ENSG00000137040 RA	NBP6 19.2	6 13.15	-1.47	0.689675305	0.145548865	0.000156499	0.000412209	
ENSG00000236603 RA ENSG00000213370 RA	NP1 20.2 NP6 33.5	0 30.03	1.49	0.900904976	0.513413851	1.60E-05 0.00460556	5.94E-05 0.007930234	
ENSG00000109756 RA	PGEF2 36.0	7 22.67	-1.59	0.888075941	0.165415778	8.05E-06	3.27E-05	
ENSG00000182872 RB	M10 14.9	5 23.57	1.58	0.998904413	0.40742553	0.012994659	0.019792352	
ENSG00000244462 RB ENSG0000086589 RB	M12 25.8 M22 30.9	7 38.88	-1.30	0.400967394	0.204507547	0.001756215	0.003413079	
ENSG00000173933 RB	M4 33.0	0 40.89	1.24	0.893543406	0.432465074	0.018255728	0.026819497	
ENSG00000100387 RB	X1 32.7	7 59.16	1.81	0.67325783	0.889856488	0.008657391	0.013896222	
ENSG00000179051 RC	C2 6.8	0 11.95	-1.42	0.659341649	0.64038275	6.55E-06	2.94E-03 2.76E-05	
ENSG0000068615 RE	EP1 22.7	0 17.54	-1.29	0.149044785	0.028685564	0.002412847	0.004499828	
ENSG00000157916 RE	R1 77.3	4 92.24	1.19	0.91851156	0.82327225	0.004098204	0.007183971	
ENSG00000148908 RG	S10 42.3	0 16.13	1.21	0.283994327	0.228283973	0.006903394	0.021379039	
ENSG00000159788 RG	S12 9.8	8 17.56	1.78	0.835532802	0.510248522	3.06E-05	0.000103544	
ENSG00000116741 RG	S2 12.7	6 29.79	2.33	0.846653329	0.056463467	0.001566399	0.003092184	
ENSG00000164292 RH	OBTB3 37.9	1 19.86	-1.40	0.364606448	0.92005729	0.001809484	0.003502107	
ENSG00000177105 RH	OG 23.4	7 34.52	1.47	0.905311231	0.574233237	1.07E-05	4.18E-05	
ENSG00000177963 RIC	CBA 62.9	8 82.97	1.32	0.496106596	0.974005253	0.001364547	0.002729094	
ENSG00000204227 RIM	VIG1 20.3	7 28.31	1.31	0.851472524	0.509153084	4.29E-05	0.000136553	
ENSG00000155906 RN	IND1 18.7	7 13.60	-1.38	0.883015718	0.129963205	0.000116237	0.000319609	
ENSG00000153561 RN	IND5A 59.6	5 48.53	-1.23	0.367758109	0.529120929	0.026697701	0.037773693	
ENSG00000263432 RN	7SL689P 11.2	9 6.02	-1.88	0.548202122	0.156860906	0.000173148	0.000450377	
ENSG00000172922 RN	ASEH2C 42.6	3 52.34	1.23	0.375638304	0.463221628	0.020972713	0.030391015	
ENSG0000026297 RN	ASET2 20.4	7 30.53	1.49	0.167260393	0.822077187	0.000906986	0.001908125	
ENSG00000133874 RN	IF122 8.5	8 16.55	1.93	0.537697963	0.53572273	0.005955077	0.009967589	
ENSG00000170881 RN	F139 11.5	7 17.34	1.52	0.993986102	0.222855807	4.19E-06	1.91E-05	
ENSG00000110315 RN ENSG00000137075 PN	F141 28.1	1 20.69	-1.36	0.293635388	0.017025621	9.82E-07	5.67E-06 0.000143451	
ENSG0000023191 RN	H1 134.2	1 158.27	1.49	0.390583532	0.483255535	0.033200322	0.045756021	
ENSG00000142327 RN	PEPL1 48.7	4 65.56	1.34	0.958721303	0.127783034	0.00040918	0.000949082	
ENSG0000253071 RN	1751 59.1 107-31P 350 f	.o 64.59 0 72.80	-4.82	0.948938301 0.9244421	0.972830922	0.031320072	0.043515977	
ENSG00000067900 RO	ICK1 13.8	5 8.55	-1.62	0.612346968	0.622352596	3.30E-05	0.000110013	
ENSG00000143365 RO	IRC 15.1	8 9.43	-1.61	0.877081151	0.476349535	0.034442647	0.04728464	
ENSG00000242660 RP	11-100W5.2 105.9 11-1094M14.1 120.9	7 79.04	-1.54	0.514593233	0.180909882	0.009015408	0.012766047	
ENSG00000225116 RP	11-137F15.1 17.1	6 11.92	-1.44	0.205606625	0.119351934	0.028974232	0.040586977	
ENSG00000269728 RP	11-145M9.4 9.8	6 15.81	1.60	0.321398176	0.958669839	0.036287767	0.049466557	
ENSG00000228929 RP	11-159C21.4 391.5	5 442.97	-1.60	0.462925205	0.442110918	9.16E-07 0.017950755	5.34E-06 0.026447321	
ENSG00000238102 RP	11-19D2.1 20.2	7 13.28	-1.53	0.008371107	0.268076061	0.013078436	0.019893064	
ENSG00000236636 RP	11-211A18.1 11.1 11-2110.2 42.2	9 6.02	-1.86	0.975838469	0.456323757	1.88E-05	6.82E-05	
ENSG00000255639 RP	11-234B24.6 15.7	1 21.85	1.39	0.002771238	0.169494651	1.02E-05	4.02E-05	
ENSG00000260490 RP	11-265N6.3 20.7	8 29.38	1.41	0.546065627	0.302196175	0.000218201	0.000549305	
ENSG00000260772 RP	11-311C24.1 8.7	7 17.55	2.00	0.510152037	0.389354485	6.03E-06	2.58E-05	
ENSG00000239219 RP	11-379K17.4 5.7	3 11.26	1.23	0.110956312	0.025196093	0.000834346	0.001777204	
ENSG00000213613 RP	11-380G5.3 38.1	2 46.79	1.23	0.376504328	0.200872373	0.036060997	0.049205051	
ENSG00000196951 RP	11-425113.3 13.9 11-427H3 3 27 2	9 8.05	-1.74	0.204128894	0.084460709	0.000597458	0.001325228	
ENSG00000249239 RP	11-428L21.2 6.9	6 16.05	2.31	0.958672446	0.11445343	4.99E-10	1.25E-08	
ENSG00000214380 RP	11-457K10.2 15.4	9 9.00	-1.72	0.17138913	0.008785563	7.84E-07	4.71E-06	
ENSG00000228844 RP ENSG00000176043 PP	11-467120.3 19.8 1-14613.1 94.1	1 103.92	-1.46	0.842934466	0.393938367	0.000402231	0.000936471	
ENSG00000261971 RP	11-473M20.7 6.0	103.82	2.04	0.992948793	0.332236646	1.95E-07	1.49E-06	
ENSG00000271207 RP	11-475J5.5 18.4	6 10.30	-1.79	0.486348949	0.721776189	0.000102881	0.000287516	
ENSG00000242951 RP	11-507E23.1 313.3	4 262.72	-1.19	0.566658022	0.963709456	0.031583731 5.17F_06	0.043828261 2 28FL0F	
ENSG00000235535 RP	11-532N4.2 436.9	6 278.68	-1.57	0.75020489	0.852700875	0.002733091	0.005014078	
ENSG00000218483 RP	11-554D15.2 5.0	8 13.19	2.59	0.437863003	0.016863385	5.49E-06	2.39E-05	
ENSG00000183298 RP	11-556K13.1 21.4 11-589M4.2 14.1	U 32.72	1.53	0.925994896	0.922282311	2.02E-05 0.035647925	7.28E-05 0.048735849	
ENSG00000226439 RP	11-621K7.1 10.4	6 5.39	-2.55	0.995892766	0.103572473	0.003657795	0.006505056	
ENSG00000204272 RP	11-622K12.1 36.1	6 69.52	1.92	0.227735582	0.713869897	0.01166498	0.018020427	
ENSG00000249741 RP ENSG00000264920 PP	11-6/3E1.3 22.0 11-6N17.4 1524	12 16.21 13 174.94	-1.36	0.286326162	0.276732394	0.000517331 0.015916967	0.00117101	
ENSG00000213331 RP	11-713C19.2 10.0	4 16.36	1.63	0.17161431	0.079320217	1.12E-05	4.35E-05	
ENSG0000260058	11-73M18.8 7	1 14.00	2.01	0 1105 20604	0 55177776*	3 675 00	2 025 07	

ICM-specific DEGs at FI	DR≤0.05	NE moon	ICM moon	50	nual Arra	nual Sav	publicM v NE	
ENSG00000225484	RP11-773D16.1	34.78	22.04	-1.58	0.977593676	0.681432556	0.001298814	0.002611564
ENSG00000248113	RP11-791G16.4	14.26	7.70	-1.85	0.043699039	0.783418672	1.13E-06	6.37E-06
ENSG00000260104	RP11-817013.1	17.89	27.12	1.52	0.490905999	0.65227544	0.03602611	0.049169357
ENSG00000265982	RP11-927P21.4	7.30	47.84	6.55	0.041517044	0.204728299	0.03170216	0.043970943
ENSG00000250090	RP13-401N8.3	13.28	7.58	-1.75	0.956245111	0.703224971	0.015712836	0.02350667
ENSG00000261189	RP3-512B11.3	22.31	15.93	-1.40	0.883334563	0.05436697	0.001459963	0.002900364
ENSG00000230084	RP4-613B23.1	11.23	16.37	1.46	0.087747207	0.235893159	0.011806653	0.018207535
ENSG00000223745	RP4-717I23.3	14.09	19.81	1.41	0.810722209	0.70115732	0.012160224	0.018657599
ENSG00000213058	RP4-765C7.2	30.19	59.58	1.97	0.369324588	0.269104283	0.032555946	0.045033194
ENSG00000254539	RP4-791M13.3	19.34	25.85	1.34	0.79790899	0.362389483	0.0085004	0.013666047
ENSG00000255204	RP5-1009N12.1 RP5-1103G7.4	24.96	18.42	-1.36	0.755142155	0.05169285	4 715-06	2 12F-05
ENSG00000228436	RP5-864K19.4	6.00	11.34	1.89	0.410959386	0.666409858	0.000451039	0.001037206
ENSG00000225710	RP5-875013.6	16.76	10.33	-1.62	0.47555648	0.975842837	2.27E-07	1.69E-06
ENSG00000147403	RPL10	433.23	989.55	2.28	0.388501738	0.623903964	0.031747888	0.04402353
ENSG00000188873	RPL10AP2	5.17	10.45	2.02	0.833759392	0.732992942	0.000114295	0.000315038
ENSG0000063177	RPL18	627.62	743.54	1.18	0.8958813	0.461347503	0.012399301	0.018967598
ENSG00000105640	RPL18A	10.95	19.51	1.78	0.327109091	0.171364918	7.08E-06	2.95E-05
ENSG00000244485	RPLIOPIS RPI19	14.40	770.39	-1.08	0.758191995	0.099450717	0.001142884	0.002552955
ENSG00000037241	RPL26L1	20.10	13.97	-1.44	0.868443414	0.796865842	0.016727728	0.024853381
ENSG00000100316	RPL3	473.85	645.25	1.36	0.336207994	0.867776753	0.008501863	0.013666047
ENSG00000109475	RPL34	341.55	425.50	1.25	0.566720417	0.729474701	0.028065516	0.039490788
ENSG00000140986	RPL3L	211.45	181.69	-1.16	0.411681017	0.854675359	0.025494217	0.036262161
ENSG00000227939	RPL3P2	14.47	23.93	1.65	0.681449966	0.737572515	0.001634182	0.003204099
ENSG00000148505	RPD14	141.81	101.90	-1.26	0.752150959	0.405808459	0.002455267	0.004560114
ENSG00000148688	RPP30	25.44	30.49	1.20	0.069025535	0.796699048	0.000878813	0.001861366
ENSG00000142534	RPS11	971.06	1215.62	1.25	0.701753678	0.350619219	0.009696415	0.015360288
ENSG00000112306	RPS12	269.25	333.03	1.24	0.717574763	0.248633609	0.033483672	0.046045157
ENSG00000115268	RPS15	164.12	207.22	1.26	0.760001032	0.716069725	0.009458721	0.015012318
ENSG00000234093	RPS15AP11	51.93	70.66	1.36	0.927760917	0.051622456	0.023664587	0.033882156
ENSG00000237668	RP515AP38	38.56	47.92	1.24	0.573561131	0.811855607	0.01349668	0.02047692
EN3G00000240463 ENSG00000145425	RPS3A	5.50	12.93	2.35	0.636376092	0.053402392	1.83E-09 0.007522542	3.45E-08 0.012266862
ENSG00000244073	RPS4XP6	10.44	16.73	1.60	0.366608577	0.000679333	1.45E-07	1.16E-06
ENSG0000067533	RRP15	15.75	10.41	-1.51	0.355715659	0.308967703	0.0001617	0.000423905
ENSG00000136444	RSAD1	30.10	37.37	1.24	0.893646746	0.541947477	0.000224909	0.000563673
ENSG0000048649	RSF1	16.71	10.59	-1.58	0.763632319	0.031330187	4.32E-05	0.000137353
ENSG00000114993	RTKN	14.96	22.29	1.49	0.301299741	0.640252069	0.000498501	0.001132025
ENSG00000251222	RTN3P1	30.47	39.74	1.30	0.589784749	0.149769364	0.019302179	0.028231692
ENSG00000201000	RUNX1T1	10.29	10.00	-1.49	0.376820782	0.679784389	0.00081986/	0.001/55099
ENSG00000160753	RUSC1	10.57	15.74	1.49	0.172907826	0.485791697	0.000201832	0.000514302
ENSG00000198853	RUSC2	11.28	17.71	1.57	0.550664074	0.512684766	0.000177773	0.000461342
ENSG00000156253	RWDD2B	23.21	15.88	-1.46	0.653282777	0.004780319	0.000169913	0.000443395
ENSG00000175741	RWDD4P2	19.86	13.87	-1.43	0.311099294	0.277934437	3.47E-05	0.000114663
ENSG00000175467	SART1	39.68	50.95	1.28	0.750291051	0.088850839	0.004949195	0.008447066
ENSG00000126524	SBDS	452.84	378.63	-1.20	0.484743229	0.158508162	0.0175133	0.025873234
ENSG00000100241 ENSG00000064932	SBN02	16.22	28.54	1.24	0.503065271	0.526212903	7.33E-05	0.00021509
ENSG00000116521	SCAMP3	81.04	99.12	1.22	0.269801996	0.476390793	0.0002973	0.000722128
ENSG0000074660	SCARF1	11.41	17.12	1.50	0.959112404	0.753307606	2.28E-05	8.04E-05
ENSG0000010803	SCMH1	65.98	58.98	-1.12	0.049144365	0.540950803	0.008668672	0.013910367
ENSG00000121064	SCPEP1	81.75	100.68	1.23	0.443939663	0.806064488	0.029313876	0.040991407
ENSG00000136021	SCYL2	18.49	12.54	-1.47	0.510211618	0.870589916	0.000866286	0.001838981
ENSG00000198501	SDADI	12.40	20.14	-1.41	0.261950774	0.870303990	5.0/E-05	0.000120005
ENSG00000128228	SDE2L1	8.15	16.99	2.08	0.122682009	0.974713245	0.001354832	0.002714482
ENSG00000185986	SDHAP3	25.24	12.40	-2.04	0.12882742	0.912512764	0.002089171	0.003972457
ENSG00000214549	SDHCP2	14.27	9.12	-1.56	0.301860451	0.592650978	2.99E-06	1.44E-05
ENSG00000223380	SEC22B	21.09	27.03	1.28	0.11235326	0.34738271	0.000646395	0.001419248
ENSG00000176986	SEC24C	31.06	39.06	1.26	0.930661882	0.776122051	0.000185601	0.000479107
ENSG00000058262	SEC61A1	64.29	81.08	1.26	0.324311555	0.711230888	0.004907197	0.008388091
ENSG00000108805	SEPT9	74.96	94.94	1.28	0.254203939	0.18685524	0.003140491	0.005671002
ENSG00000106366	SERPINE1	8.13	23.89	2.94	0.813606821	0.409622414	0.031506142	0.04374214
ENSG00000149257	SERPINH1	34.95	52.78	1.51	0.477065422	0.487814684	0.02683413	0.037928622
ENSG00000197019	SERTAD1	6.98	12.51	1.79	0.454766134	0.469828305	2.73E-05	9.38E-05
ENSG00000181555	SETD2	21.45	15.41	-1.39	0.837600008	0.955218249	2.69E-06	1.32E-05
ENSG00000115524	SF3B1	361.56	307.59	-1.18	0.717512552	0.350703403	0.016577298	0.024655886
ENSG00000113128	5F5B14	24.75	21.49	-1.17	0.036260427	0.740428087	0.010754075	0.00244601
ENSG00000198818	SFT2D1	30.14	37.40	1.24	0.316216508	0.78162096	2.84E-05	9.70E-05
ENSG00000170624	SGCD	34.20	28.26	-1.21	0.193311052	0.382769349	0.029205515	0.040870311
ENSG00000102683	SGCG	93.11	114.52	1.23	0.942175777	0.898462341	0.018550423	0.027216949
ENSG00000198964	SGMS1	18.83	12.97	-1.45	0.104975682	0.042058294	0.000362575	0.000859019
ENSG00000104969	SGTA	64.92	73.50	1.13	0.460724998	0.133476352	0.030222412	0.04218857
ENSG0000141985 ENSG00000174705	SH3GL1 SH3PYD2R	22.86	30.05	1.31	0.303255731	0.996944716	0.006724655	0.011090956
ENSG0000114705	SHISAS	60.85	75.71	1 74	0.641340557	0.377371588	0.018717453	0.027447717
ENSG00000160410	SHKBP1	22.43	38.52	1.72	0.815852368	0.443368078	0.000118946	0.000325312
ENSG00000198053	SIRPA	8.79	15.51	1.77	0.15879811	0.414256275	0.000315136	0.000759075
ENSG00000101307	SIRPB1	12.47	20.00	1.60	0.20339307	0.631145531	0.000403015	0.000937484
ENSG0000077463	SIRT6	11.92	18.29	1.53	0.406949872	0.76287295	6.34E-08	6.01E-07
ENSG00000157933	SKIV2L2	15.47	23.0b 35.64	-1.49	0.20246174	0.248102411	0.001952168	0.005743538
ENSG00000139370	SLC15A4	15.20	21.19	1.39	0.789019173	0.41719043	0.001260016	0.002545332
ENSG00000117479	SLC19A2	16.78	30.41	1.81	0.293976951	0.373147966	0.012940617	0.019715369
ENSG0000079215	SLC1A3	101.57	72.36	-1.40	0.958384357	0.043549042	0.0168892	0.025073453
ENSG00000144136	SLC20A1	8.40	16.59	1.97	0.276885358	0.900970758	0.000191485	0.000491667
ENSG00000092096	SLC22A17	10.18	18.20	1.79	0.662200141	0.346373045	2.57E-05	8.90E-05
ENSG00000100075	SIC25A1	17.62	∠3.3b 40.28	-1 20	0.31132//99	0.440378439	0.001413401	0.002813817
ENSG00000160785	SLC25A44	20.84	26.97	1.20	0.758422507	0.262420719	0.013770182	0.020849558
ENSG0000005022	SLC25A5	143.76	285.38	1.99	0.464097245	0.521077258	0.036571599	0.049805267
ENSG0000059804	SLC2A3	5.91	16.69	2.82	0.80107895	0.877055441	0.000363623	0.00086114
ENSG00000136856	SLC2A8	10.52	17.33	1.65	0.233815009	0.306660154	1.05E-06	5.98E-06
ENSG0000014824	SLC30A9	61.41	47.19	-1.30	0.156388563	0.094519982	0.000308565	0.000744839
ENSG00000112473	SLC39A/	47.19	55.72 62.80	1.18	0.249405826	0.831236104	0.035788837	0.048890055
ENSG00000169241	SLC50A1	14.04	19.49	1.39	0.498024438	0.436207471	0.005030863	0.008576061
ENSG00000185803	SLC52A2	9.11	15.93	1.75	0.750109204	0.95322822	5.46E-06	2.38E-05
ENSG0000065054	SLC9A3R2	175.56	238.11	1.36	0.538652094	0.794432793	0.010377808	0.016281974
ENSG00000184347	SLIT3	8.21	15.52	1.89	0.606077337	0.532933533	0.001391572	0.00277428
ENSG00000164609	SLU7	100.86	70.27	-1.44	0.855182049	0.737195932	5.07E-06	2.24E-05
ENSG000001127616	SMARCA4	30.95	41.11	1.33	0.757239313	0.445597276	0.00039969	0.000931673
ENSG0000105771	SMG9	18.53	12.29	-1.51	0.539376056	0.57016450	0.001257193	0.00254054
ENSG00000166311	SMPD1	19.14	20.54 63.99	1.40	0.884121142	0.059669936	0.006513089	0.010779889
ENSG00000174365	SNHG11	7.94	13.51	1.70	0.241030853	0.580817452	2.25E-06	1.14E-05
ENSG00000197989	SNHG12	20.13	34.71	1.72	0.545290127	0.598640425	0.005135732	0.008737698
ENSG00000184602	SNN	17.79	24.04	1.35	0.34283172	0.460555644	0.023622232	0.033838712
ENSG00000199744	SNORD36A	296.77	36.85	-8.05	0.545370944	0.118573191	0.00484629	0.008299087
ENSG00000209482	SNURD83A	6.35	36.22	5.71	0.925461213	0.681820524	0.018085882	0.026590777
ENSG00000077312	SNRPA	21.24	28.52	1.34	0.967/35052	0.024395863	8.89E-05 0.001754	0.000253217
ENSG00000125835	SNRPB	51.34	64.57	1.26	0.782822192	0.233257494	0.002660478	0.004900011
ENSG00000256968	SNRPEP2	14.17	20.13	1.42	0.533796179	0.002749777	0.000305494	0.000738375
ENSG00000205302	SNX2	42.16	34.17	-1.23	0.838067617	0.587854423	0.026859443	0.037954879
ENSG00000106266	SNX8	23.79	29.55	1.24	0.687935605	0.334146308	0.016135028	0.024074351
ENSG00000184557	SOCS3	7,46	24.57	3.29	0.346027345	0.804316225	0.00414301	0.007248981

ENSG00000095637	SORBS1	528.51	414.51	-1.28	0.26767327	0.458896007	0.000913687	0.00192
ENSG00000134243	SORT1	86.96	73.12	-1.19	0.058899674	0.898557749	0.031219864	0.04340
ENSG00000100485	SOS2	29.17	22.46	-1.30	0.541511163	0.288800846	0.002230857	0.00420
ENSG00000143842	SOX13	8.56	15.16	1.77	0.718799592	0.963716453	5.78E-07	3.64
ENSG00000090487	SPG21	50.23	60.16	1.20	0.212010894	0.147873577	0.009476633	0.01503
ENSG00000183018	SPNS2	8.63	13.69	1.59	0.268241994	0.273333334	0.000571075	0.00127
ENSG00000198369	SPRED2	14.21	19.97	1.41	0.734320005	0.956516264	0.000117196	0.00032
ENSG00000133914 ENSG00000112658	SRF	50.54	66.65	1.32	0.467215336	0.25470821	0.014425917	0.00875
ENSG00000163486	SRGAP2	9.73	15.78	1.62	0.441881359	0.222683381	3.08E-05	0.00010
ENSG00000122862	SRGN	36.76	79.71	2.17	0.334177358	0.370435725	0.000110031	0.00030
ENSG00000224953	SRIP3	8.63	16.32	1.89	0.439870627	0.17086575	0.000111411	0.00030
ENSG00000174780 ENSG00000144867	SRP72 SRPRB	25.85	32.34	1.25	0.525910527	0.468467345	0.007582851	0.00450
ENSG00000145687	SSBP2	50.46	62.82	1.24	0.041413537	0.885080164	0.021016811	0.03044
ENSG00000176101	SSNA1	47.14	58.39	1.24	0.436245002	0.114499745	0.018964999	0.02776
ENSG00000126091	ST3GAL3	19.55	25.54	1.31	0.952342808	0.079788885	8.30E-05	0.00023
ENSG00000010327	STAB1	43.22	64.85	1.50	0.894879054	0.791437562	0.00817701	0.00730
ENSG0000010270	STARD3NL	17.01	23.29	1.37	0.07136559	0.313644582	0.000191553	0.00049
ENSG00000126561	STAT5A	6.70	13.17	1.96	0.603935307	0.950084471	3.20E-07	2.23
ENSG00000124214 ENSG00000144589	STAU1 STK11IP	52.28	16.19	1.10	0.153251514	0.17041383	0.000174463	0.04798
ENSG00000130413	STK33	31.46	25.00	-1.26	0.624279294	0.150815097	0.02571218	0.03653
ENSG0000067221	STOML1	20.56	25.78	1.25	0.922690015	0.486243331	0.016183426	0.02412
ENSG00000023734 ENSG00000115808	STRAP	132.57	150.98	-1.14	0.728777137	0.517405825	0.020852572	0.03023
ENSG00000196792	STRN3	35.00	26.84	-1.32	0.41873109	0.876719634	0.001741819	0.00338
ENSG00000134910	STT3A	82.96	103.16	1.24	0.072059302	0.961155693	0.015089687	0.02265
ENSG00000117758	STX12	16.73	22.36	1.34	0.590133658	0.820176281	0.006780938	0.0111
ENSG00000168818	STX18	43.13	36.28	-1.19	0.307076122	0.161973464	0.001569195	0.00309
ENSG00000064607	SUGP2	14.89	19.96 99.11	1.54	0.880733552	0.58436261	0.005007563	0.00078
ENSG00000109111	SUPT6H	26.06	31.13	1.19	0.832985401	0.473629721	0.005441121	0.00919
ENSG00000110066	SUV420H1	26.68	18.62	-1.43	0.65373602	0.436666434	3.12E-06	1.49
ENSG00000117614	SYF2 SYMPF	73.92	63.18	-1.17	0.707095995	0.956556528	0.000106202	0.03357
ENSG00000125755	SYNDIG1	9.25	40.04	1.25	0.551995557	0.921155814	1.39E-05	0.0005
ENSG00000213463	SYNJ2BP	30.69	21.82	-1.41	0.347934326	0.108237326	7.46E-06	3.07
ENSG00000132718	SYT11	6.33	11.37	1.80	0.147743182	0.510540182	3.03E-06	1.46
ENSG00000103168	TAF1C	40.76	47.21	1.16	0.009019707	0.82661543	0.023822061	0.03409
ENSG00000130699	TAGLN	20.22	423.91	-1.58	0.18177398	0.095767807	0.014299857	0.00435
ENSG00000253676	TAGLN2P1	44.00	55.73	1.27	0.925590762	0.134885354	0.036017107	0.04916
ENSG00000115183	TANC1	24.11	32.18	1.33	0.686904982	0.443796441	0.011730406	0.01810
ENSG00000168394	TAP1	20.48	31.22	1.52	0.601587339	0.699234553	0.001342643	0.00269
ENSG00000139192	TBC1D15	27.80	19.25	-1.44	0.81546744	0.20228139	0.0015941595	0.02381
ENSG00000105254	TBCB	91.18	114.47	1.26	0.552836811	0.655794285	0.01349863	0.0204
ENSG00000171703	TCEA2	36.95	71.55	1.94	0.677797988	0.987401712	0.006127502	0.01022
ENSG00000204219	TCEA3	82.37	62.58	-1.32	0.811616151	0.609999697	0.00908267	0.01447
ENSG00000214121	TDPX2	24.35	32.02	1.40	0.620793626	0.005565107	0.024426877	0.00011
ENSG00000205678	TECRL	1995.81	1277.63	-1.56	0.237472729	0.008935331	0.002301161	0.00432
ENSG00000172171	TEFM	19.31	12.96	-1.49	0.769625278	0.042215339	2.08E-06	1.0
ENSG00000257949	TEN1 TERE2	8.56	17.18	2.01	0.778654943	0.43129396	4.08E-05	0.00013
ENSG00000107140	TESK1	20.38	26.12	1.28	0.908955778	0.801135029	0.028907892	0.01051
ENSG00000114354	TFG	62.08	79.62	1.28	0.904425438	0.679184158	0.000139394	0.00037
ENSG00000100109	TFIP11	29.97	24.13	-1.24	0.776425083	0.198370399	0.01325161	0.02014
ENSG00000177426	TGIF1	9.27	15.31	1.65	0.910312466	0.539601732	0.00407037	0.00714
ENSG00000177683	THADA	22.86	16.02	-1.43	0.342364913	0.393177693	0.00024322	0.00060
ENSG00000137801	THBS1	36.43	74.17	2.04	0.377260182	0.813609094	0.016271286	0.0242
ENSG00000125676	THOC2	49.14	36.68	-1.34	0.533759444	0.461767173	0.000707049	0.00153
ENSG00000131652	THOC6	6.81	12.71	1.86	0.543599633	0.270309447	4.57E-06	2.06
ENSG00000137221	TLK1	14.90	10.79	-1.59	0.044275546	0.963918563	1.03E-07	0.00025
ENSG00000137076	TLN1	382.29	456.45	1.19	0.474730502	0.525170283	0.001589623	0.00312
ENSG00000162604	TM2D1	70.75	58.92	-1.20	0.67572759	0.842566743	0.005449694	0.0092
ENSG00000091947	TMEM101	15.06	20.36	1.35	0.804020933	0.003719367	5.57E-06	2.42
ENSG00000198270	TMEM126B	74.02	44.87	-1.29	0.787945907	0.18724173	0.011808721	0.0113
ENSG00000075568	TMEM131	35.85	29.09	-1.23	0.999068039	0.172772872	0.000399896	0.00093
ENSG00000149483	TMEM138	19.93	28.77	1.44	0.875907622	0.251765774	6.87E-06	2.87
ENSG00000244187	TMEM141	47.26	55.82	1.18	0.156547169	0.552703253	0.017987647	0.02649
ENSG0000064545	TMEM147	29.04	71.95	1.30	0.30639158	0.172851739	0.003762762	0.00039
ENSG00000185475	TMEM179B	27.04	33.52	1.24	0.981212024	0.483712844	0.018540459	0.02720
ENSG00000226479	TMEM185B	11.54	18.47	1.60	0.911894451	0.470294825	5.64E-11	2.6
ENSG00000188807	TMEM201	6.07	11.33	1.87	0.854694883	0.811870999	6.36E-11	2.87
ENSG00000187713	TMEM203 TMEM209	33.72	40.03	1.19	0.624097604	0.347526257	0.00169847	0.00331
ENSG00000089063	TMEM230	42.90	49.12	1.14	0.282405148	0.216747809	0.01463144	0.02202
ENSG00000106609	TMEM248	21.13	28.45	1.35	0.372852059	0.724866242	0.000357789	0.00084
ENSG00000184497	TMEM255B	6.94	12.90	1.86	0.969975373	0.218342717	0.000108894	0.0003
ENSG00000187838	TMEM256-PLSCR3	23.63	31.43	1.33	0.64499883	0.792416542	6.53E-05	0.00019
ENSG00000112697	TMEM30A	59.45	48.60	-1.22	0.090381639	0.202201971	0.017630335	0.02602
ENSG00000169964	TMEM42	6.78	12.40	1.83	0.424717477	0.286660384	6.87E-10	1.5
ENSG00000155099	TMEM55A	42.66	33.75	-1.26	0.132677935	0.034209238	0.006283603	0.01044
ENSG00000165782	TMEM55B TMEM88	44.69	52.35	1.17	0.532509757	0.531167181	0.016180427	0.02412
ENSG00000137103	TMEM88	8.97	45.55	1.69	0.326136179	0.500393816	6.81E-06	2.8
ENSG00000175348	ТМЕМ9В	59.66	69.26	1.16	0.065215019	0.8942751	0.00761653	0.01240
ENSG00000144747	TMF1	26.67	15.58	-1.71	0.522915702	0.910387584	0.000138314	0.0003
ENSG00000205542	TMSB4X	91.80	221.11	2.41	0.670720221	0.839097529	0.004285892	0.00745
ENSG00000166479	TMX3	36.11	23.26	-1.56	0.479548999	0.502294721	0.000418227	0.00096
ENSG00000041982	TNC	7.13	28.94	4.06	0.927214078	0.210558771	0.000748234	0.00161
ENSG00000109079	TNFAIP1	23.52	34.33	1.46	0.857230573	0.511787707	0.000471365	0.00107
ENSG00000185215	TNFAIP2	40.55	74.66	1.84	0.737202784	0.64223878	0.002326916	0.00436
ENSG00000120889 ENSG00000028137	INFRSF10B TNFRSF1B	20.49	28.20	1.38	0.386383022	0.616769941	0.003434614	0.00614
ENSG00000149115	TNKS1BP1	48.71	63.87	1.31	0.98194671	0.880819106	0.005088705	0.0086F
ENSG00000079308	TNS1	327.23	246.00	-1.33	0.344363048	0.932562441	0.001374045	0.0027
ENSG00000130204	TOMM40	17.21	23.45	1.36	0.058260208	0.806989129	3.05E-05	0.0001
ENSG00000163781	TOPBP1	19.52	11.87	-1.64	0.786734111	0.710419481	1.51E-06	8.12
ENSG00000115129	1P53I3 TPGS2	14.63	20.95	1.43	0.201245161	0.442845533	0.000994848	0.00206
ENSG00000134779	TPM1	51.47 18112 73	44.U7 22899 17	1.17	0.0194/612/	0.238980335	0.01093047	0.0169
ENSG00000163870	TPRA1	15.37	22.71	1.48	0.820253927	0.764740251	3.23E-06	1.5
ENSG00000197253	TPSB2	19.34	31.08	1.61	0.218626945	0.173398754	0.019794921	0.02884
ENSG00000170638	TRABD	10.68	16.02	1.50	0.253379013	0.936489365	0.025880465	0.03675
ENSG00000131653 ENSG00000135149	TRAF7	14.77	20.23	1.37	0.537882491	0.937068653	0.01053878	0.01648
ENSG00000115993	TRAK2	95.10	67.83	-1.40	0.01507657	0.058906425	7.19E-05	0.000202
ENSG00000181029	TRAPPC5	71.81	100.41	1.40	0.971975309	0.583938616	4.28E-05	0.00013
214500000010101015	TOIDA	0.00	10.00	2.11	0.532813638	0.235533011	0.000626602	0.0014
ENSG00000173334	TRIBI	9.00	19.00	1.20	0.00020202000	0.220521211	0.000030032	0.0014
ENSG00000173334 ENSG00000071575 ENSG00000132274	TRIB1 TRIB2 TRIM22	23.89	30.67	1.28	0.933138401	0.238521341	0.019871918	0.02894

ICM-specific DEGs at FE	0R≤0.05 Gene	NE mean	ICM mean	FC	nval Age	nval Sex	nval ICM v NE	EDR ICM V NE
ENSG00000183718	TRIM52	19.18	13.00	-1.48	0.724088688	0.132627069	0.000108655	0.000301855
ENSG00000100815	TRIP11	14.07	8.48	-1.66	0.591326932	0.979188177	5.97E-06	2.56E-05
ENSG00000205133	TRIQK	23.04	14.74	-1.56	0.103921637	0.708953099	0.001426079	0.002837051
ENSG0000099899	TRMT2A	41.52	52.95	1.28	0.864382951	0.370547059	0.000466378	0.001067252
ENSG0000187688	TRPV2	6.73	14.18	2.11	0.56769292	0.900227575	5.32E-07	3.38E-06
ENSG00000182173	TSEN54	8.06	13.78	1.71	0.54369369	0.198798574	2.62E-05	9.04E-05
ENSG00000108219	TSPAN14	22.64	28.18	1.24	0.413832008	0.90915661	0.005715431	0.00960356
ENSG00000156298	TSPAIN/	62.78	115 21	1.04	0.423009928	0.765514798	0.010528705	0.01647429
ENSG00000198677	TTC37	42.25	28.84	-1.46	0.284229961	0.100798194	3.12E-05	0.000105195
ENSG00000136295	ТТҮНЗ	5.03	10.18	2.02	0.625932975	0.925855394	1.76E-05	6.44E-05
ENSG00000176014	TUBB6	60.05	94.95	1.58	0.381469863	0.298071163	0.002429231	0.004522174
ENSG0000074935	TUBE1	47.88	32.32	-1.48	0.902726229	0.042979001	0.000409095	0.000949082
ENSG00000130640	TUBGCP2	36.56	43.73	1.20	0.73995029	0.532535998	0.000298667	0.000724361
ENSG00000128159	TUBGCP6	15.69	22.64	1.44	0.397482767	0.334208504	2.28E-06	1.15E-05
ENSG00000046E2	TUSC3	52.74	12 56	1.29	0.591124952	0.12112/344	2.075.07	1 575 06
ENSG0000004652	TXINB	112 29	15.56	-1 29	0.248092828	0.802/5256/	0.001886792	0.003631768
ENSG00000129235	TXNDC17	49.10	61.72	1.26	0.430164347	0.186582716	0.004164629	0.007280025
ENSG00000115514	TXNDC9	41.12	31.68	-1.30	0.531391778	0.067799747	0.005233068	0.008885806
ENSG00000221983	UBA52	494.87	641.81	1.30	0.898688758	0.678614971	0.001501719	0.002977018
ENSG00000153443	UBALD1	27.07	32.79	1.21	0.889322339	0.135113669	0.022911467	0.032895822
ENSG00000189136	UBE2Q2P1	15.14	9.03	-1.68	0.288026972	0.580557762	0.000277041	0.000679221
ENSG00000107341	UBE2R2	22.23	27.25	1.23	0.836336725	0.51706558	0.000138804	0.000372569
ENSG00000159202	UBEZZ	24.74	32.12	1.30	0.376274104	0.55596409	0.0002126833	0.000766041
ENSG00000133018 ENSG00000188021	UBOLN1	16 35	24.77	-1.24	0.158250842	0.853636907	0.00031881	0.000766941
ENSG00000163960	UBXN7	12.00	6.39	-1.88	0.576902774	0.802347057	1.03E-07	8.97E-07
ENSG00000143179	UCK2	7.25	12.72	1.76	0.058742125	0.690584611	0.002857	0.005212545
ENSG00000151116	UEVLD	16.51	11.16	-1.48	0.590671859	0.144284204	2.34E-05	8.20E-05
ENSG00000109775	UFSP2	113.08	92.34	-1.22	0.789770569	0.019609058	0.00388324	0.006847629
ENSG00000140553	UNC45A	11.74	19.46	1.66	0.670195743	0.624830545	5.62E-09	8.12E-08
ENSG0000076248	UNG	14.77	20.70	1.40	0.86514244	0.222799012	2.15E-05	7.66E-05
ENSG00000226085	UQCRFS1P1	7.68	15.20	1.98	0.36141018	0.826634226	0.00135619	0.002715272
ENSG00000105176	URII	49.59	38.74	-1.28	0.753891759	0.568055043	0.008/0392/	0.013955016
ENSG00000136878	USP20	11.05	16.73	1.55	0.449188639	0.651241833	9.50F-05	0.000267883
ENSG00000143258	USP21	17.05	22.89	1.34	0.227527813	0.387805465	0.000992849	0.002061058
ENSG00000103404	USP31	13.52	8.26	-1.64	0.959152826	0.772827013	4.00E-05	0.000128924
ENSG00000115464	USP34	87.60	64.76	-1.35	0.537170336	0.026894602	0.000122611	0.000334685
ENSG00000168883	USP39	47.04	53.05	1.13	0.104753515	0.230788656	0.034443763	0.04728464
ENSG00000108828	VAT1	64.81	86.72	1.34	0.711256907	0.744923455	0.010649008	0.016624137
ENSG00000144560	VGLL4	22.72	28.81	1.27	0.573695197	0.210964853	0.007645299	0.01244183
ENSG00000167397	VKORC1	47.23	59.80	1.27	0.644741691	0.843452322	0.018773004	0.027514855
ENSG00000197969	VPS13A	19.65	14.20	-1.38	0.610163355	0.196/52681	1 125 05	4 295 05
ENSG00000213305	VPS25	33.45	39.35	1.33	0.303194428	0.224043037	0.010595345	0.016544948
ENSG00000136100	VPS36	43.20	33.56	-1.29	0.915376674	0.224234673	0.007981812	0.012929709
ENSG00000155975	VPS37A	46.72	41.11	-1.14	0.967948065	0.91584107	0.020130336	0.029253111
ENSG0000006715	VPS41	54.19	42.48	-1.28	0.621240617	0.0507301	0.001167012	0.002377059
ENSG00000132612	VPS4A	45.59	55.20	1.21	0.580972865	0.530480515	0.006291276	0.010455767
ENSG00000119541	VPS4B	23.10	18.00	-1.28	0.373536217	0.458765427	0.003293451	0.005926318
ENSG00000105053	VRK3	29.77	24.49	-1.22	0.340525069	0.699436456	0.006524897	0.010796261
ENSG00000204396	VWA7	10.49	15.71	1.50	0.229798267	0.526880457	0.000104857	0.000292458
ENSC00000162625	V WDEV2	35.64	0.12	-2.09	0.54179476	0.458519200	0.002/18500 5 005 07	2 275 06
ENSG00000196998	WDR45	204.64	170.38	-1.20	0.244109784	0.845509966	0.003605793	0.006426776
ENSG00000227057	WDR46	39.44	48.32	1.23	0.893690731	0.096879898	0.005701528	0.009588779
ENSG00000164091	WDR82	45.29	53.59	1.18	0.275259502	0.324917675	4.58E-05	0.000144316
ENSG00000147548	WHSC1L1	19.31	13.98	-1.38	0.303738958	0.244457892	3.27E-05	0.000109401
ENSG00000124535	WRNIP1	26.88	32.46	1.21	0.231762614	0.734456296	0.009018568	0.014381719
ENSG00000146457	WTAP	24.97	32.19	1.29	0.80818603	0.931375965	0.005069818	0.008639853
ENSG0000076924	XAB2	20.05	26.37	1.32	0.533080786	0.430437524	1.77E-05	6.47E-05
ENSG00000136936	XPA	25.46	19.87	-1.28	0.632928529	0.37155793	0.001049566	0.002169206
ENSG00000108039	X PNPEP1	88.78	100.09	1.13	0.252317799	0.989390061	0.01/2165/9	0.0254/2218
ENSG0000015153	YAF2	204.05	87.39	-1.55	0.482640124	0.326797099	0.01053989	0.016481194
ENSG00000137207	YIPE3	134.24	150.44	1.12	0.521160118	0.302776114	0.019506078	0.028492933
ENSG0000083896	YTHDC1	61.07	48.39	-1.26	0.565551105	0.724745043	0.000813932	0.001742285
ENSG00000198492	YTHDF2	24.25	30.64	1.26	0.803935752	0.321428555	0.00483506	0.008282374
ENSG00000116809	ZBTB17	32.95	40.50	1.23	0.926868646	0.934735625	0.00544091	0.009191987
ENSG00000158545	ZC3H18	14.28	25.56	1.79	0.951940257	0.51015865	4.35E-09	6.71E-08
ENSG00000122299	ZC3H7A	76.75	63.91	-1.20	0.631966359	0.676572437	0.008060264	0.013045541
ENSG00000126247	ZDHHC11B	29.68	18.38	-1.61	0.55524431	0.04326151	0.02857197	0.04009327
ENSG0000156599	ZDHHC5	40.65	33.00	1.24	0.904727939	0.711853779	0.001491169	0.004705707
ENSG00000023041	ZDHHC6	41.15	32.20	-1 28	0.911896902	0.589595724	0.000919865	0.001929107
ENSG00000148516	ZEB1	37.85	31.47	-1.20	0.022902485	0.444777361	0.031950975	0.044283344
ENSG00000158552	ZFAND2B	20.94	28.01	1.34	0.182426991	0.429678436	0.004982852	0.008499361
ENSG00000185650	ZFP36L1	55.85	76.51	1.37	0.374827859	0.413652822	0.014640117	0.022030561
ENSG00000152518	ZFP36L2	37.68	56.38	1.50	0.812394075	0.702948941	0.001653716	0.003239581
ENSG0000056097	ZFR	68.71	52.88	-1.30	0.150291794	0.437128804	0.000290052	0.000708039
ENSG0000039319	ZFYVE16	33.36	25.98	-1.28	0.305928859	0.401128568	0.027091684	0.038225532
ENSG0000072121	ZETVE26	15.44	9.00	-1.72	0.442583491	0.541191453	1.73E-06	9.11E-06
ENSG00000166478	7NF143	18.46	12.43	-1.44	0.030198434	0.525989925	5.38F-05	0.000164913
ENSG00000163848	ZNF148	19.14	11.91	-1.61	0.317096186	0.644331195	0.000360961	0.000855555
ENSG00000204789	ZNF204P	13.71	8.40	-1.63	0.304882803	0.260902118	5.14E-05	0.000158245
ENSG0000010244	ZNF207	47.50	59.49	1.25	0.996534705	0.380385084	0.003867352	0.006826022
ENSG00000172466	ZNF24	26.28	20.38	-1.29	0.840761092	0.547864051	0.001335937	0.002683304
ENSG00000198105	ZNF248	17.28	11.70	-1.48	0.177629823	0.109181871	3.01E-05	0.00010222
ENSG00000257267	ZNF271	22.79	14.85	-1.53	0.566800585	0.061799886	1.31E-07	1.08E-06
ENSG00000119725	ZNF410	11.29	18.37	1.63	0.0664400922	0.250085356	5.06E-06	2.24E-05
ENSCO000074677	ZINF444	8.92	17.95	2.01	0.000440982	0.3431/891	1.78E-U9	5.4UE-U8
ENSG0000166770	ZNF55Z ZNF667-451	44.52	35.99	-1.24	0.010011000	0.920201272	0.011966048	0.016409807
ENSG00000171161	ZNF672	13.07	19.84	1.50	0.651755386	0.372827511	4.07E-06	1.86E-05
ENSG00000128000	ZNF780B	15.15	10.12	-1.50	0.66404976	0.173949725	0.000203382	0.000517549
ENSG00000235109	ZSCAN31	16.80	11.32	-1.48	0.734979424	0.981196444	0.004168202	0.007284011
ENSG00000214655	ZSWIM8	62.64	79.57	1.27	0.80860136	0.207479485	0.013618986	0.020642821
ENSG00000159840	ZYX	81.54	114.71	1.41	0.745489367	0.206355024	0.008692343	0.01394041



Figure S2 Disease-specific DEGs clusters samples by phenotype in publicly available

expression data. Expression values for the disease-specific genes identified in our analysis were extracted from publicly available A) RNA-seq and B) microarray data.

Appendix C

Chapter III supplemental materials

Table S1: aDCM-specific adjusted gene expression.

ENSG	Gene	NF_mean	aDCM_mean	FC	pval_Age	pval_Sex	pval_aDCM_v_NF	FDR_aDCM_v_M
ENSG00000094914	AAAS	63.33	74.39	1.17	0.388024163	0.670523825	0.0000972	0.00037040
ENSG00000183044	ABAT	8.46	15.16	1.79	0.768263767	0.144735983	0.001228941	0.00303220
NSG00000131269	ABCB7	42.64	36.73	-1.16	0.024105846	0.4011413	0.002224438	0.0049487
NSG00000114779	ABHD14B	17.44	23.85	1.37	0.756029569	0.319944223	0.0000652	0.00026980
NSG00000154175	ABI3BP	45.80	92.27	2.01	0.047981394	0.976596726	4.64E-04	1.33E-0
NSG00000166016	ABTB2	10.47	18.09	1.73	0.039884085	0.477164398	4.30E-04	0.0012584
NSG00000196295	AC005154.6	35.87	46.64	1.30	0.98327517	0.088375566	0.005624917	0.01066456
NSG00000256210	AC005255.3	29.69	39.46	1.33	0.366532211	0.456143052	1.81E-02	2.92E-0
NSG00000159186	AC007383.6	95.82	77.40	-1.24	0.122905416	0.207883143	6.25E-03	1.16E-0
NSG00000234520	AC018464.3	159.29	89.58	-1.78	0.961832188	0.451300318	6.15E-04	0.0016873
NSG00000235978	AC018816.3	7.17	12.71	1.77	0.044584313	0.655740321	0.012498941	0.0213000
NSG00000143429	AC027612.6	15.78	21.96	1.39	0.558762146	0.469448196	1.79E-03	4.13E-0
NSG00000212694	AC084018.1	19.67	27.32	1.39	0.208912858	0.661161213	0.000607409	0.0016742
NSG00000256586	AC091171.1	10.12	17.54	1.73	0.413912709	0.615743394	0.005162389	0.00993240
NSG00000072818	ACAP1	8.63	15.63	1.81	0.67487188	0.013740679	0.0000696	0.00028393
NSG00000131584	ACAP3	97.98	82.86	-1.18	0.644523779	0.651846767	0.006278065	0.0116574
NSG00000100813	ACIN1	97.26	87.19	-1.12	0.749202777	0.92605688	0.022400369	0.0349087
NSG00000151726	ACSL1	539.04	408.54	-1.32	0.713487342	0.402187384	1.92E-02	3.06E-
NSG00000107796	ACTA2	141.56	208.97	1.48	0.355282759	0.104960687	0.013930979	0.0234503
NSG00000075624	ACTB	881.19	1162.23	1.32	0.780479479	0.954738579	0.00208606	0.0046921
NSG00000184009	ACTG1	406.08	517.74	1.27	0.894084125	0.042254287	0.004772941	0.0092970
NSG00000136518	ACTL6A	41.24	51.45	1.25	0.444925276	0.883833476	0.004749503	0.0092597
NSG00000151320	AKAP6	40.12	51.53	1.28	0.682177299	0.267869816	0.003831856	0.007738
NSG00000159063	ALG8	36.30	44.05	1.21	0.566409122	0.323209452	0.002538313	0.0055358
NSG00000123505	AMD1	47.02	31.79	-1.48	0.861062277	0.842104877	0.000885759	0.0022955
NSG00000129055	ANAPC13	101.85	119.34	1.17	0.299160296	0.912798142	0.001709532	0.0039750
NSG00000116194	ANGPTL1	20.50	31.83	1.55	0.11307293	0.501517264	0.00823639	0.0147894
NSG00000106524	ANKMY2	23.78	31.60	1.33	0.88209368	0.434547503	0.0000121	0.00007
NSG00000165887	ANKRD2	228.14	123.81	-1.84	0.741911429	0.333597441	2.09E-02	0.0328483
NSG00000135046	ANXA1	45.23	58.60	1.30	0.729992929	0.467383404	0.032365562	0.048177
NSG00000138772	ANXA3	75.57	57.55	-1.31	0.485935392	0.831019021	1.79E-02	0.0288193
NSG00000196975	ANXA4	16.34	25.91	1.59	0.177720413	0.568213178	0.0000782	0.0003112
NSG00000070718	AP3M2	8.98	14.96	1.66	0.671459583	0.110457089	0.002780604	0.005987
NSG00000100823	APEX1	109.74	96.31	-1.14	0.460901628	0.74924905	0.022141306	0.0345510
NSG00000189058	APOD	949.53	560.43	-1.69	0.721251474	0.602484039	0.003118795	0.0065908
NSG00000184867	ARMCX2	51.80	71.62	1.38	0.633672965	0.065926966	0.004904533	0.0094948
NSG00000113369	ARRDC3	10.28	17.71	1.72	0.370532295	0.476647908	0.000564731	0.0015807
NSG00000198925	ATG9A	88.57	76.02	-1.17	0.558057668	0.039616443	0.015495963	0.0256478
NSG00000145246	ATP10D	6.75	12.19	1.81	0.128964148	0.906977874	0.0000163	0.0000
NSG00000133657	ATP13A3	44.77	76.30	1.70	0.193460455	0.031841535	0.001923269	0.0043934
NSG00000058668	ATP2B4	53.35	70.69	1.32	0.1496361	0.113420278	0.02926253	0.0441767
NSG00000224004	ATP5C1P1	30.51	24.29	-1.26	0.662873705	0.056956507	1.87E-02	2.99E-
NSG00000169020	ATP5I	3084.41	2507.37	-1.23	0.261041348	0.565884742	0.001772306	0.0040986
NSG00000237701	ATP5JP1	68.37	141.38	2.07	0.721896806	0.465350756	0.02048283	0.0323184
NSG00000241837	ATP5O	2594.63	1945.99	-1.33	0.117602565	0.132156451	0.002539191	0.0055358
NSG00000143515	ATP8B2	6.14	11.31	1.84	0.011455012	0.156243952	0.000198344	0.0006687
NSG00000174684	B3GNT1	38.18	44.10	1.16	0.755049452	0.125110377	0.029085236	0.0439374
NSG00000117411	B4GALT2	21.52	27.81	1.29	0.096443181	0.683938991	0.006106858	0.011384
NSG00000108641	B9D1	9.43	16.79	1.78	0.601353128	0.457712568	1.92E-08	0.000006
NSG00000237758	BANF1P3	364.25	273.88	-1.33	0.917872786	0.653552145	0.00957474	0.0168502
NSG00000140463	BBS4	13.11	20.15	1.54	0.58411287	0.937318382	1.58E-04	0.0005546
NSG00000197580	BCO2	144.04	110.72	-1.30	0.771650142	0.402469905	2.26E-02	3.51E-
NSG00000177951	BET1L	17.74	22.90	1.29	0.6708508	0.245251565	0.000029	0.0001420
NSG00000133169	BEX1	5.79	23.32	4.03	0.631716927	0.244366844	0.0000714	0.0002896
NSG00000182492	BGN	59.49	167.61	2.82	0.157027655	0.571689831	3.52E-03	7.21E-
NSG00000090013	BLVRB	127.75	106.83	-1.20	0.201844907	0.595332256	9.25E-03	0.0163690
NSG00000163170	BOLA3	124.39	104.04	-1.20	0.566175062	0.263507117	0.021734159	0.0340063
NSG00000106009	BRAT1	10.77	16.02	1.49	0.66497419	0.809554089	0.0000066	0.000007
NSG00000182685	BRICD5	11.66	17.94	1.54	0.749104306	0.645850753	0.001968514	0.0044641
NSG00000133639	BTG1	66.24	94.71	1.43	0.74273954	0.195113033	0.000520856	0.0014800
NSG00000112276	BVES	42.00	30.76	-1.37	0.721947737	0.483334455	0.001414859	0.0034048
NSG00000136261	BZW2	312.65	247.37	-1.26	0.531503523	0.592791367	5.44E-03	1.04E-
NSG00000211450	C11orf31	1218.79	1496.26	1.23	0.040580498	0.056639251	0.014395207	0.0241055
NSG00000170270	C14orf142	23.20	17.73	-1.31	0.723934937	0.177854379	0.0000128	0.00007
NSG00000166780	C16orf45	54.65	75.82	1.39	0.145221526	0.350329825	0.000526329	0.0014929
NSG00000231245	C1DP1	41.57	33.15	-1.25	0.687046323	0.196763015	0.005181408	0.0099649
NSG00000162384	C1orf123	66.56	74.03	1.11	0.686312552	0.890947619	0.003163489	0.0066605
NSG00000117616	Clorf63	174.60	208.07	1.19	0.760578364	0.277631541	0.019359514	0.0308264
NSG00000174407	C20orf166	26.19	46.52	1.78	0.766772893	0.607402956	0.032315955	0.0481347
NSG00000165233	C9orf89	23.48	28.91	1.23	0.032960045	0.554242296	0.007128804	0.0130508
NSG00000163618	CADPS	21.35	31.53	1.48	0.186373736	0.422015709	0.010771319	0.0186891
NSG00000122565	CBX3	31.11	36.83	1.18	0.150742695	0.372411104	0.02359156	0.0365825
NSG00000136710	CCDC115	17.29	22.67	1.31	0.909489385	0.273152215	0.0000458	0.0002060
NSG00000180329	CCDC43	31.00	25.46	-1.22	0.298954422	0.804493303	0.0000061	0.00004
NSG00000176155	CCDC57	15.40	21.12	1.37	0.883072534	0.944801591	9.87E-03	1.73E-
NSG00000138764	CCNG2	6.31	11.39	1.81	0.639559158	0.102946781	0.000238369	0.0007714
NSG00000118816	CCNI	403.12	506.91	1.26	0.470968305	0.743202424	2.37E-03	0.0052309
NSG00000177697	CD151	214.45	291.42	1.36	0.719661237	0.294430772	0.009747325	0.0171340
NSG00000215039	CD27-AS1	33.18	42.94	1.29	0.540743359	0.724257695	0.001747725	0.0040497
NSG00000128283	CDC42EP1	9.65	15.74	1.63	0.836811671	0.605498214	0.007348115	0.0133895
NSG00000167617	CDC42EP5	26.66	38.20	1.43	0.569694818	0.934307186	0.00271514	0.005867
NSG0000008128	CDK11A	44.88	34.97	-1.28	0.085951849	0.478549595	0.000396691	0.0011735
NSG00000124762	CDKN1A	45.11	74.45	1.65	0.850358282	0.791958135	2.43E-02	0.0374929
NSG00000091527	CDV3	73.46	62.69	-1.17	0.282055757	0.094043323	0.021725361	0.0340039
NSG00000102901	CENPT	34.96	42.10	1.20	0.636606732	0.227195602	0.002344231	0.0051807
NSG00000172824	CES4A	9.17	15.39	1.68	0.299153375	0.418003933	0.004699639	0.0091701
NSG0000000971	CFH	25.39	52.01	2.05	0.046200551	0.641660144	0.000447895	0.0012987
NSG00000003402	CFLAR	213.02	184.59	-1.15	0.561482483	0.361643573	0.012015981	0.0205818
NSG00000128849	CGNL1	5.11	11.15	2.18	0.362260518	0.265224879	0.00000227	0.000
NSG00000177830	CHID1	66.54	78.24	1.18	0.703905399	0.042234759	0.005379503	0.0102951
NSG00000122873	CISD1	178.88	157.20	-1.14	0.836336998	0.268797966	2.57E-03	5.59E-
NSG00000230055	CISD3	62.07	51.27	-1.21	0.201817134	0.016439751	0.002451261	0.0053769
NSG00000104879	CKM	4527.53	3394.90	-1.33	0.150716537	0.542457387	0.005644412	0.0106885
NSG00000141367	CLTC	88.09	101.34	1.15	0.542695813	0.332929953	0.020201863	0.0319828
NSG00000070371	CLTCL1	9.58	15.00	1.57	0.660138011	0.448670778	0.0000373	0.0001737
NSG00000103121	CMC2	182.66	146.98	-1.24	0.710795213	0.16473075	0.001956813	0.0044462
NSG00000184220	CMSS1	36.61	28.11	-1.30	0.901740338	0.887132601	4.96E-03	0.0095898
NSG00000140931	CMTM3	8.96	15.24	1.70	0.64109843	0.868251614	9.28F-05	3.57F-
NSG00000168275	COA6	33.54	27.23	-1.23	0.949507433	0.073337054	1.33E-02	2.25FJ
NSG00000108821	COLIAI	59.69	114 22	1.91	0.444352272	0.336048952	0.01809515	0 020110
NSG0000169547	01341	AD 71	00 20	2.02	0.791240205	0.436059172	0.010000000	0.025110
NSG00000188153	COL4A5	+3.71	11 95	1.88	0.414272174	0.503865201	1 55F-07	3 6FE -
NSG00000144810	COL8A1	11.74	22.23	1.89	0.0994191	0.746822744	1.57E-03	3 71 F-
NSG00000206561	010	863	20.00	3.46	0.427535679	0.154302302	0.0000586	0.0003/469
NSG00000148444	COMMD3	148.94	166.80	1.17	0.169007562	0.404564075	3 16F-07	0.0473904
NSG0000240444	COMMD3-BMI1	20.08	6 34	-3.16	0.125057364	0.351812994	0.003509972	0.0472090
NSG00001/0600	COMMD7	CC 0C	E0 61	-1 11	0 132062421	0 318267006	0.02010070	0.0210761
	CONTRID/	10.90	20.01	-1.11	0.132303421	0.310201030	0.02019079	0.0213/01

aDCM-specific DEGs at	FDR≤0.05	NE moon	aDCM moan	FC	mual Ago	nual Sox	nual aDCM v NE	EDR DOCM V NE
ENSG00000169019	COMMD8	14.93	20.23	1.36	0.614695948	0.511705044	0.004045143	0.008088559
ENSG00000165644	COMTD1	32.36	23.83	-1.36	0.318260409	0.057940855	0.007971531	0.014385618
ENSG00000129083	COPB1	44.76	52.33	1.17	0.709832116	0.260565421	0.001613247	0.003790684
ENSG00000214552	COPS8P2	21.26	26.86	1.26	0.397676204	0.215275918	0.002369582	0.005230925
ENSG00000132423	CORIN	67.95	42.79	-1.27	0.020659774	0.513596874	6.60F-03	1.22F-02
ENSG00000178741	COX5A	1544.69	1308.73	-1.18	0.148452047	0.074971375	0.008771841	0.015660896
ENSG00000258981	COX5AP2	59.49	52.49	-1.13	0.727848829	0.421770291	1.76E-02	2.84E-02
ENSG00000164919	COX6C	2349.47	1844.48	-1.27	0.526791795	0.159293735	0.00070082	0.00188142
ENSG00000112895	CREG1	2125.40	1009.58	-1.17	0.539151824	0.109840885	0.012838009	0.0021810989
ENSG00000095794	CREM	50.95	61.81	1.21	0.742817854	0.902958949	0.019865997	0.031533706
ENSG00000213145	CRIP1	47.08	81.62	1.73	0.26661886	0.085131355	1.30E-04	4.71E-04
ENSG00000170275	CRTAP	61.98	83.90	1.35	0.315225568	0.856095204	2.00E-03	4.53E-03
ENSG00000253683	CTB-79E8.3	69.15	46.42	-1.49	0.804021196	0.783671936	0.010232565	0.017873592
ENSG00000259340 ENSG00000249286	CTD-202/G2.1 CTD-2210P15 2	14.70	5.86	-2.51	0.169695255	0.135836139	0.0000653	0.019191202
ENSG00000230502	CTD-2230M5.1	16.46	8.78	-1.88	0.455945586	0.933753672	1.80E-02	2.90E-02
ENSG00000213315	CTD-3035D6.1	84.90	105.32	1.24	0.766043858	0.729338012	0.009464838	0.016700767
ENSG00000174080	CTSF	82.76	105.69	1.28	0.263226494	0.308289007	0.008814704	0.01572529
ENSG00000139842	CUL4A	106.61	93.70	-1.14	0.701588719	0.493712894	0.021709211	0.033990048
ENSG00000119929	CUTC	40.04	33.01	-1.21	0.712031891	0.929576346	0.007121189	0.013042052
ENSG00000179091	CYC1	399.28	326.05	-1.22	0.230557654	0.775987502	0.000216169	0.000338797
ENSG00000138061	CYP1B1	7.04	20.09	2.85	0.035568144	0.029661358	9.41E-06	5.94E-05
ENSG00000178149	DALRD3	12.29	17.71	1.44	0.498748847	0.647238778	0.0000433	0.000196781
ENSG00000244274	DBNDD2	278.15	235.50	-1.18	0.791200586	0.510338214	1.23E-02	2.10E-02
ENSG0000011465	DCN	2374.06	3265.42	1.38	0.029485638	0.41951821	0.023923706	0.037024031
ENSG00000129187	DCTD	40.63	45.86	1.13	0.470765126	0.79704999	0.013428765	0.022670118
ENSG00000244038	DD031	105.75	94.09	-1.12	0.122466146	0.765657941	0.022997465	0.035732292
ENSG00000100201	DDX17	296.94	339.54	1.14	0.66587629	0.43301969	2.47E-03	5.40E-03
ENSG00000198231	DDX42	43.25	49.76	1.15	0.068757419	0.548420308	0.017745152	0.028625748
ENSG0000067596	DHX8	11.03	16.46	1.49	0.551802167	0.701692608	0.000084	0.000330894
ENSG00000162595	DIRAS3	7.99	25.06	3.14	0.472747284	0.046480499	0.0000187	0.000100712
ENSG00000125164	DLAT DMTE1	96.28	81.30	-1.18	0.699494149	0.515994164	0.00374158	0.007595066
ENSG00000155104	DPCD	24.90	29.91	1.27	0.211057767	0.863956534	0.018149628	0.029177723
ENSG0000000419	DPM1	69.18	80.42	1.16	0.314125412	0.314289185	4.45E-03	8.78E-03
ENSG00000177990	DPY19L2	40.69	53.31	1.31	0.309791235	0.330455885	2.47E-03	0.005400399
ENSG00000175550	DRAP1	123.78	103.50	-1.20	0.5537902	0.062158096	1.70E-02	2.77E-02
ENSG00000120129	DUSP1	75.69	127.52	1.68	0.687126484	0.925085501	2.68E-02	4.09E-02
ENSG00000108861	DYNC2111	209.18	249.44	-1.10	0.200922438	0.175605477	0.021062305	0.055927951
ENSG00000107223	EDF1	522.49	447.59	-1.17	0.884940025	0.296454962	1.78E-02	2.87E-02
ENSG00000156508	EEF1A1	200.94	279.61	1.39	0.361297418	0.031025623	0.003580085	0.007311618
ENSG00000250182	EEF1A1P13	16.92	29.60	1.75	0.184599718	0.99056195	0.000117804	0.000436678
ENSG00000241404	EGFL8	13.12	18.57	1.42	0.241720889	0.292305482	0.000188096	0.000642491
ENSG00000144995	EIF1AXP1	126.86	111.39	-1.14	0.424950358	0.060900154	2.19E-02 4.17E-02	3.42E-02 9.22E.02
ENSG00000149100	EIF3M	197.41	176.26	-1.12	0.221803212	0.669828943	0.011841903	0.020320862
ENSG0000049540	ELN	32.24	54.95	1.70	0.140226695	0.27703651	0.005683862	0.010737202
ENSG00000127463	EMC1	95.82	72.28	-1.33	0.589486107	0.856380624	0.022990057	0.035732292
ENSG00000125746	EML2	88.47	117.52	1.33	0.81058418	0.566471371	0.000861172	0.002240482
ENSG00000167136	ENDOG	23.69	18.46	-1.28	0.42110099	0.02905334	0.002227102	0.004952288
ENSG00000120915	EPHA2 EPN1	102.04	34.20	-1.18	0.856774258	0.33036932	1.83F-02	0.037171742
ENSG00000254270	ERHP1	5.36	10.43	1.95	0.353906187	0.746997624	0.00000427	0.0000325
ENSG0000068912	ERLEC1	31.08	36.62	1.18	0.028211197	0.849559848	0.005841441	0.010968512
ENSG0000090989	EXOC1	21.12	26.12	1.24	0.374890229	0.862021473	4.96E-03	9.59E-03
ENSG00000121769	FADPS FAM214A	43 55	56.08	-1.20	0.495170487	0.047000822	0.010407139	0.026987928
ENSG00000158246	FAM46B	25.23	14.19	-1.78	0.396057099	0.123771946	0.009147307	0.016213791
ENSG00000153310	FAM49B	29.61	24.39	-1.21	0.825370034	0.215425305	0.019330148	0.030790165
ENSG00000130244	FAM98C	11.05	16.41	1.49	0.937915823	0.324312468	0.0000464	0.000208581
ENSG00000077942	FBLN1	36.50	83.46	2.29	0.179072405	0.992514796	0.006361833	0.011775677
ENSG00000140092	FBLN5	65.78	90.39	1.37	0.465298214	0.622870667	0.002073845	0.004669142
ENSG00000112787	FBXO3	73.31	64.86	-1.13	0.821900932	0.164110063	0.013968473	0.023504979
ENSG00000225733	FGD5-AS1	47.82	55.18	1.15	0.070326157	0.910935408	0.003169753	0.006665448
ENSG00000113578	FGF1	53.25	75.36	1.42	0.208001153	0.084787399	0.000531016	0.001502566
ENSG00000214253	FIS1	363.47	328.00	-1.11	0.355305605	0.875163113	2.64E-02	0.040321146
ENSG00000141756	FKBP10	15.24	23.88	1.57	0.074840136	0.298618571	1.72E-02	2.80E-02
ENSG0000004478 ENSG00000177731	FKBP4	39.83	32.37	-1.23	0.725566305	0.193831785	0.013427478	0.022670118
ENSG00000257365	FNTB	21.02	26.86	1.28	0.637915908	0.1525183	0.0085382	0.015296247
ENSG00000165060	FXN	37.41	44.12	1.18	0.297677777	0.003096535	0.003477142	0.007141867
ENSG0000089327	FXYD5	21.48	30.24	1.41	0.52651779	0.172946858	0.008986953	0.015977942
ENSG00000141013	GAS8	38.72	47.35	1.22	0.932129207	0.076128364	0.007194159	0.013165396
ENSG00000164949	GEM	14.36	23.64	1.65	0.2386507	0.096901981	0.017390201	0.028287014
ENSG00000250571	GLI4	9.50 10.45	19.78	1.48	0.548494844	0.479164771	1.69F-06	1.62F-05
ENSG00000182512	GLRX5	81.81	73.59	-1.11	0.905143959	0.077840929	0.014309211	0.023992136
ENSG00000224051	GLTPD1	42.61	30.63	-1.39	0.966757618	0.003291549	8.46E-05	3.33E-04
ENSG00000137198	GMPR	120.48	94.67	-1.27	0.923187165	0.657861656	0.006747191	0.012425125
ENSG00000120053	GPR157	691.48 27.67	/54.2/	-1.18	0.00496653	0.9491/9628	0.014800927	0.024692818
ENSG00000164294	GPX8	6.23	11.59	1.86	0.000354519	0.284147251	0.00165264	0.00386296
ENSG00000106070	GRB10	29.33	40.87	1.39	0.373203685	0.173011759	0.0000456	0.000205522
ENSG0000030582	GRN	155.23	195.88	1.26	0.504555219	0.862069873	0.007916536	0.014302909
ENSG00000000148308	GIF3C5	38.79	32.28	-1.20	0.23685438	0.083848725	0.000149876	0.003573672
ENSG00000163754	GYG1	154.78	187.37	1.40	0.553046022	0.479703049	0.017432642	0.028330048
ENSG00000213397	HAUS7	24.45	32.45	1.33	0.44589016	0.399119461	0.0000724	0.000293162
ENSG00000116478	HDAC1	26.03	31.62	1.21	0.740300803	0.427037581	0.002835174	0.006073705
ENSG00000184508	HDDC3	23.49	17.56	-1.34	0.221720638	0.734411771	4.71E-05	0.000210937
ENSG00000212014	HEPH	8.47	20.07	2.37	0.175839446	0.406451091	0.0000852	0.000334367
ENSG00000163909	HEYL	20.41	31.36	1.54	0.05419238	0.758719019	0.005045971	4.262-04
ENSG00000180573	HIST1H2AC	16.69	24.11	1.45	0.94961571	0.166436737	3.25E-03	6.80E-03
ENSG00000184678	HIST2H2BE	85.28	105.63	1.24	0.386231442	0.644786933	0.004642018	0.009088031
ENSG0000064961	HMG20B	33.73	26.72	-1.26	0.846773106	0.507657076	0.012061374	0.02065207
ENSG000001070144	HNRNPA3	14.50	19.55	1.35	0.37251863	0.463132313	0.0000662	0.000272843
ENSG00000197451	HPR	84.64	51.6/ 48.56	-1.18	0.1226/1969	0.399/28803	0.004650159	0.009096364
ENSG00000126803	HSPA2	15.13	39.06	2.58	0.037112716	0.716567125	0.0000266	0.000134392
ENSG00000256356	HSPA8P5	13.65	8.35	-1.63	0.672529978	0.731775195	0.001938948	0.004418536
ENSG00000173641	HSPB7	4968.93	4342.71	-1.14	0.176131161	0.889465703	0.01359792	0.022939143
ENSG00000167862	ICT1	59.60	49.13	-1.21	0.265983058	0.923978769	8.19E-03	0.014732427
ENSG00000115738	ID2	47.86	64.31	1.34	0.642778309	0.918405456	2.37E-02	3.68E-02
ENSG00000119632	IFIZ/LZ	10.90	96.28 14.27	-1 36	0.200/33028	0.832484079	0.005070668	0.009771991
ENSG00000101052	IFT52	10.62	16.27	1.53	0.86089745	0.849712702	0.00022756	0.000743661
ENSG0000073792	IGF2BP2	18.01	12.01	-1.50	0.658627223	0.139676897	0.00000715	0.0000483
ENSG00000146674	IGFBP3	82.56	120.36	1.46	0.649600616	0.954306516	0.026601322	0.040617538
ENSG00000163453	IGFBP7	695.92	837.18	1.20	0.691558821	0.260559205	3.31E-02	4.91E-02
ENSG00000137033	IL33	8.89	15.82	1.78	0.22774489	0.268582946	6.82E-04	1.84E-03
ENSG00000143621	IMPDH2	117.04	101.13	-1.16	0.790595084	0.068603121	0.005578959 2.20F-02	0.010590298
ENSG00000065150	IPO5	47.93	57.82	1.21	0.409050392	0.696081577	0.008674861	0.015511407
ENSG00000177508	IRX3	41.36	78.80	1.91	0.053959598	0.143632477	0.001739581	0.004034897
ENSG00000113430	IRX4	21.60	14.85	-1.45	0.987371901	0.587506156	0.0000671	0.000275225
ENSG00000111203	ITFG2	22.35	28.05	1.26	0.257420509	0.70002051	0.005636944	0.010683047

aDCM-specific DEGs at ENSG	FDR⊴0.05 Gene	NF_mean	aDCM_mean	FC	pval_Age	pval_Sex	pval_aDCM_v_NF	FDR_aDCM_v_NF
ENSG0000055955	ITIH4	9.40	15.11	1.61	0.822683118	0.756226321	0.000755456	0.00199763
ENSG00000198399 ENSG00000187486	ITSN2 KCNI11	27.17	21.27	-1.28	0.599917877	0.646181533	0.005656248	0.010697984
ENSG00000100379	KCTD17	8.18	14.32	1.75	0.168861966	0.540290363	0.005292348	0.010153244
ENSG00000105438 ENSG00000115548	KDELR1 KDM3A	87.16	97.25 39.63	1.12	0.850814635	0.676006793	1.59E-02 1.74E-02	2.62E-02 2.83E-02
ENSG00000126012	KDM5C	36.05	28.52	-1.26	0.532874068	0.00000107	8.20E-04	2.15E-03
ENSG00000100647 ENSG0000075945	KIAA0247	7.06	12.07 82.10	1.71	0.666563271	0.342951756	1.99E-09 4.84E-05	1.23E-07 2.15E-04
ENSG00000114648	KLHL18	21.63	29.03	1.34	0.184900126	0.754258473	9.75E-03	1.71E-02
ENSG0000005483	KMT2E	17.93	23.51	1.31	0.565059147	0.202996253	2.86E-03	6.12E-03
ENSG00000115365	LANCL1	32.09	39.37	1.23	0.944452684	0.659806649	0.005106995	0.009837951
ENSG00000133424	LARGE	91.24	76.03	-1.20	0.214681592	0.894929854	0.017465825	0.028343399
ENSG00000267206	LCN6	50.49	22.26	-2.27	0.893422092	0.748123479	1.71E-02	0.02787778
ENSG00000116977	LGALS8	68.98	56.20	-1.23	0.24072627	0.886606688	2.10E-02	3.30E-02
ENSG00000260032 ENSG00000204054	LINCO0657 LINCO0963	11.40	105.01	1.24	0.112027144	0.805989923	0.000246289	0.001235596
ENSG00000231721	LINC-PINT	73.73	102.90	1.40	0.165132842	0.394284819	1.25E-02	2.14E-02
ENSG00000129038	LOXL1	34.37	80.23	2.33	0.112634226	0.689584503	0.000600764	0.001659809
ENSG00000225787	LSM3P3	19.40	24.62	1.27	0.755072999	0.220308023	0.007853937	0.014211742
ENSG00000179632	MAF1	176.95	145.41	-1.00	0.392104513	0.74449828	0.001483153	0.003540064
ENSG00000102158	MAGT1	34.98	43.37	1.24	0.755552274	0.458016729	0.002332983	0.005158338
ENSG00000145495	MAP1A MARCH6	55.84	67.89	1.81	0.533361577	0.230225218	0.005776583	0.010864151
ENSG00000155254	MARVELD1	6.06	12.88	2.13	0.101789773	0.765907852	0.0000059	0.0000416
ENSG00000127241 ENSG00000198125	MASP1 MB	161.43 17206.35	250.89 21507.21	1.55	0.402166708	0.774095931 0.840920696	1.90E-03 0.008369376	0.004362345 0.015011026
ENSG0000076706	MCAM	69.11	101.04	1.46	0.150231142	0.643208816	4.91E-03	9.50E-03
ENSG00000131844 ENSG00000124370	MCCC2 MCEE	97.03 66.95	84.90 56.14	-1.14	0.996745057 0.565286528	0.297657577 0.373747383	1.69E-02 0.01286889	0.027650536 0.021858909
ENSG00000112139	MDGA1	10.19	5.17	-1.97	0.4851323	0.18271213	2.89E-03	6.17E-03
ENSG00000162959 ENSG00000164024	MEMO1 METAP1	53.13 45.53	43.27	-1.23	0.79011834	0.045721106	0.00473054	0.009226623
ENSG00000170439	METTL7B	13.49	5.39	-2.50	0.950347622	0.623847346	0.000198817	0.000669804
ENSG00000198408 ENSG00000111341	MGEA5 MGP	124.55	144.48 1527.77	1.16	0.521468016	0.835583155	0.006351031	0.011764984
ENSG00000133816	MICAL2	70.71	88.42	1.25	0.432757498	0.648522994	0.030431324	0.045734881
ENSG00000243156	MICAL3	83.73	65.23	-1.28	0.308559657	0.052310317	0.014904765	0.024848349
ENSG00000207652	MIR621	43.57	16.62	-2.62	0.235991196	0.276341332	0.031170502	0.046695924
ENSG00000146147	MLIP	342.88	239.40	-1.43	0.94664076	0.467539547	0.000578454	0.001614362
ENSG00000128003	MMRN2	27.76	36.19	1.24	0.200345202	0.513315127	0.005516341	0.010489012
ENSG00000171160	MORN4	15.31	22.15	1.45	0.578926513	0.096508685	0.001204947	0.002984013
ENSG00000101928 ENSG00000143158	MOSPD1 MPC2	340.07	301.62	-1.23	0.726875014	0.115682546	1.70E-02	0.02780563
ENSG00000129255	MPDU1	33.13	27.22	-1.22	0.686258868	0.720952622	0.004685513	0.009150233
ENSG00000130830	MPHOSPH8 MPP1	45.69	30.19	-1.15	0.015578899	0.35279619	0.025277661	0.038824299
ENSG00000174547	MRPL11	62.36	52.88	-1.18	0.64966161	0.174808486	0.002163274	0.004831003
ENSG00000180992 ENSG00000242485	MRPL14 MRPL20	42.87 275.66	37.46 236.81	-1.14	0.557892033 0.650593826	0.062953432	0.011115927 0.009948846	0.019223025
ENSG00000197345	MRPL21	123.75	103.48	-1.20	0.310790481	0.444792654	2.31E-02	0.035911037
ENSG00000082515 ENSG00000106591	MRPL22 MRPL32	82.83	68.95 66.58	-1.20	0.259523461 0.5051956	0.329899474 0.09720156	2.30E-03 0.00251319	5.10E-03 0.005491959
ENSG00000130312	MRPL34	179.50	139.76	-1.28	0.185403876	0.028855062	0.00065221	0.001770608
ENSG00000149792 ENSG00000182180	MRPL49 MRPS16	30.24	36.48 103.81	-1.11	0.844046985	0.256466137 0.00361348	2.14E-03 0.024046878	4.80E-03 0.037167003
ENSG0000096080	MRPS18A	63.71	56.34	-1.13	0.019575144	0.430210888	0.005665766	0.01071166
ENSG00000175110 ENSG0000062582	MRPS22 MRPS24	78.79	69.81 143.83	-1.13	0.004180212	0.090417352	0.013163189	0.022302176
ENSG0000090263	MRPS33	204.47	167.49	-1.22	0.51467585	0.214492624	0.00339137	0.007006894
ENSG00000135972 ENSG00000260549	MRPS9 MT1L	68.52	57.15	-1.20	0.009978747	0.321626684	0.000462324 2.43E-02	0.001333987
ENSG00000220113	MTCYBP4	27.96	19.23	-1.45	0.68458123	0.248647816	0.00530701	0.010173035
ENSG00000182534 ENSG00000172428	MXRA7 MXEOV2	266.79	326.24	1.22	0.416999384	0.378770988	1.64E-02 8.60E-04	0.027017521
ENSG00000133026	MYH10	22.80	33.43	1.41	0.061064597	0.535686844	0.003378194	0.00698767
ENSG00000160808	MYL3	8669.17	6648.36	-1.30	0.044146713	0.159326637	0.003205079	0.006724634
ENSG00000176658	MY01D	7.87	14.01	1.78	0.027945249	0.545009881	0.001000952	0.002554473
ENSG00000141052	MYOCD	7.42	13.14	1.77	0.033213912	0.666733116	0.003416766	0.00704567
ENSG00000095380	NANS	209.02	21.83	-1.42	0.486741387	0.659649856	0.0000224	0.000117053
ENSG00000137513	NARS2	33.17	27.70	-1.20	0.12211615	0.733381643	5.45E-03	1.04E-02
ENSG00000132780 ENSG00000188554	NBR1	45.77	57.34	-1.16	0.514159439	0.837700797	0.025840238	0.039583047
ENSG0000025770	NCAPH2	18.11	29.00	1.60	0.664124511	0.841487042	0.029009529	0.043837246
ENSG00000072864 ENSG00000104419	NDE1 NDRG1	10.65	16.81 216.06	1.58	0.172359201 0.615209422	0.915738971 0.06664553	0.0000948 3.74E-03	0.000363265 7.59E-03
ENSG0000004779	NDUFAB1	936.02	742.33	-1.26	0.323836261	0.030765711	0.003045269	0.006473443
ENSG00000101247 ENSG00000156170	NDUFAF5 NDUFAF6	75.20	68.58 28.54	-1.10	0.044863086	0.804528149 0.923733675	0.022731305 0.000234809	0.035365681 0.000763617
ENSG00000140990	NDUFB10	600.28	481.09	-1.25	0.619082817	0.701665102	0.000054	0.000233105
ENSG00000147123 ENSG00000119013	NDUFB11 NDUFB3	211.06 444.88	182.96 349.03	-1.15	0.540666703	0.04592993	3.04E-02 2.82E-04	4.57E-02 8.85E-04
ENSG0000065518	NDUFB4	996.00	808.95	-1.23	0.692079327	0.883283601	0.007255057	0.013245783
ENSG00000147684 ENSG00000109390	NDUFB9 NDUFC1	556.64 734.36	483.79 655.22	-1.15	0.655269966 0.933115337	0.103273706 0.933504785	0.025470658 0.016795062	0.03906947 0.027510661
ENSG00000168653	NDUFS5	742.93	568.86	-1.31	0.594048086	0.547883441	8.06E-04	2.12E-03
ENSG00000183091 ENSG00000125967	NEB NECAB3	6.65 78.24	23.05	3.46	0.038844288	0.686701963	0.000358486 3.52F-03	0.001074596 7.21E-03
ENSG00000111859	NEDD9	20.26	28.75	1.42	0.127347548	0.850047991	0.017079592	0.027868895
ENSG00000154328 ENSG0000008441	NEIL2 NEIX	8.63 45.71	14.25 58.56	1.65	0.120087147	0.446759823	0.0000191	0.000102779
ENSG00000169599	NFU1	202.05	163.14	-1.24	0.582965677	0.612303973	0.000528306	0.001497364
ENSG00000243678	NME1-NME2 NMRK2	209.61	169.38	-1.24	0.207467376	0.341438162	0.009081349	0.016127401
ENSG00000141279	NPEPPS	59.18	52.02	-1.14	0.3657191	0.180544062	0.021648255	0.033917289
ENSG00000113389 ENSG00000124599	NPR3 NOO2	11.90	22.06	1.85	0.086546889	0.751849444	0.001960884	0.004451196
ENSG00000160113	NR2F6	26.17	20.73	-1.46	0.360558216	0.013192007	3.49E-03	7.17E-03
ENSG00000123358	NR4A1	42.95	95.48	2.22	0.44911471	0.952656005	0.011792244	0.020254677
ENSG00000258300	NUTF2P2	18.45	34.26 13.27	-1.51	0.21806657	0.800288863	0.001912634	0.00909514
ENSG0000065154	OAT	44.81	53.24	1.19	0.266024594	0.886401144	1.59E-03	3.74E-03
ENSG00000178814	OPLAH	53.10	42.12	-1.41	0.5/96/25/4	0.105022123	0.002194398	0.004886526
ENSG00000175115	PACS1	30.82	43.31	1.41	0.185949539	0.21683628	0.008089256	0.01458121
ENSG00000124374 ENSG00000149269	PAIP2B PAK1	42.38 9.57	29.04 16.16	-1.46 1.69	0.467769552 0.040242421	0.168246157 0.414563412	7.29E-04 2.44E-04	0.001937958 7.85E-04
ENSG00000166228	PCBD1	187.26	162.23	-1.15	0.291868437	0.15601961	0.003549902	0.007262643
ENSG00000180628 ENSG00000105185	PCGF5 PDCD5	47.74 139.86	36.05 109.67	-1.32 -1.28	0.383133693 0.869091109	0.780032334 0.334952342	0.006030326 1.29E-04	0.011259975 4.67E-04
ENSG00000249915	PDCD6	42.41	50.28	1.19	0.911538577	0.572442717	0.006955685	0.012768903
ENSG00000115252 ENSG00000104213	PDE1A PDGFRL	11.28 5.95	21.90 11.06	1.94 1.86	0.234327615 0.069578314	0.77962681 0.683013217	0.007308838 0.0000336	0.013333576 0.000159701
ENSG00000168291	PDHB	287.13	237.62	-1.21	0.168579494	0.640966598	0.000163462	0.000570837
ENSG00000120913	PDLIM2	8.47	16.14	1.91	0.27209863	0.954969803	0.001221808	0.003016198

aDCM-specific DEGs at FDR≤0.05							500 0001 N
ENSG Gene ENSG00000196923 PDLIM7	NF_mean 54.55	98.37	FC 1.80	0.06682612	0.07918546	1.10F-04	4.11E-04
ENSG00000162734 PEA15	307.55	248.81	-1.24	0.3665505	0.31671944	0.030447264	0.045744158
ENSG00000229833 PET100	90.02	66.69	-1.35	0.969679667	0.733226023	0.002442636	0.005362805
ENSG00000162735 PEX19	118.68	133.75	1.13	0.751881777	0.901673644	0.011554667	0.019878951
ENSG0000034693 PEX3	23.50	29.34	1.25	0.959046294	0.998846763	0.0000818	0.000323555
ENSG00000204220 PFDN6	68.71	56.02	-1.23	0.908971464	0.706044977	0.013298197	0.022498358
ENSG00000141959 PFKL	20.34	33.01	1.62	0.422655984	0.630032822	0.01874785	0.029996685
ENSG00000152556 PFKM	915.09	697.34	-1.31	0.017661496	0.777428739	0.0000354	0.000166371
ENSG00000134686 PHC2	120.66	102.76	-1.17	0.795407664	0.777642302	1.77E-02	2.86E-02
ENSG000001/422/ PIGG ENSG00000087111 PIGS	16.14	21.98	-1.13	0.29514005	0.127021496	0.000117647	0.02576004
ENSG00000118495 PLAGL1	13.80	21.72	1.57	0.9748517	0.357583112	1.48E-04	5.24E-04
ENSG00000104368 PLAT	9.74	15.00	1.54	0.014427245	0.307419161	0.005068325	0.009771498
ENSG00000105223 PLD3	213.99	269.29	1.26	0.674286144	0.636568203	0.002947511	0.006285608
ENSG00000104999 PLEKHAZ	17.76	32.15	1.81	0.418414058	0.01126204	2 225 02	0.013963879
ENSG00000214456 PLIN5	81.09	58.80	-1.38	0.774276692	0.742625439	0.011794684	0.020254677
ENSG00000114698 PLSCR4	14.67	23.93	1.63	0.113294817	0.371999735	7.63E-04	2.02E-03
ENSG00000164050 PLXNB1	72.85	54.56	-1.34	0.366328539	0.406636287	0.000410978	0.001209879
ENSG00000160783 PMF1	54.93	44.17	-1.24	0.495525479	0.883287718	0.0000298	0.000144877
ENSG0000010417 PNNN1 ENSG0000006757 PNPLA4	54.67	46.00	-1.19	0.419621283	0.000938573	2 03F-02	3.21F-02
ENSG00000143442 POGZ	33.66	44.40	1.32	0.643423452	0.62301664	1.54E-03	0.00364716
ENSG00000256525 POLG2	17.22	22.52	1.31	0.041399664	0.696952898	1.60E-05	9.01E-05
ENSG00000186184 POLR1D	70.07	54.06	-1.30	0.883103402	0.842193865	1.47E-03	3.52E-03
ENSG00000099821 POLRMT	31.54	37.82	1.20	0.948504929	0.364783229	0.023484469	0.036428542
ENSG00000133110 POSTN	48.19	156.15	3.24	0.081764402	0.248640233	2 19F-03	4.88F-03
ENSG00000127125 PPCS	40.89	47.82	1.17	0.798017816	0.594674317	0.017473285	0.028343399
ENSG00000125534 PPDPF	190.78	560.47	2.94	0.585212269	0.997956892	0.003162837	0.006660511
ENSG00000160972 PPP1R16A	62.37	51.09	-1.22	0.895483802	0.009698035	1.10E-02	0.019116723
ENSG0000073711 PPP2R3A	42.02	32.52	-1.29	0.84592492	0.15767635	0.011293622	0.019494299
ENSG00000167393 PPP2R3B	210.86	183.96	-1.15	0.885551567	0.002006667	0.012823571	0.021799448
ENSG00000131238 PPT1	126.64	108.83	-1.16	0.191088356	0.250766876	0.01/434807 3.19F-02	0.028330048
ENSG00000113593 PPWD1	17.86	23.94	1.34	0.530376079	0.618290543	0.000471595	0.001355726
ENSG00000162976 PQLC3	7.94	13.54	1.70	0.934898081	0.960235355	0.0000151	0.000085
ENSG00000138073 PREB	63.57	77.74	1.22	0.775470246	0.91677462	2.06E-02	3.25E-02
ENSG00000257704 PRR24	6.22	11.23	1.81	0.04439733	0.129461158	0.00000121	0.000012
ENSG0000068878 PSME4	39.80	47.19	1.19	0.241716958	0.877642182	0.027155117	0.04132837
ENSG00000110958 PTGES3	105.66	118.27	1.12	0.600616672	0.946437654	0.019380229	0.0308489
ENSG00000165996 PTPLA	261.33	209.82	-1.25	0.469121678	0.542708784	0.000543316	0.001531816
ENSG00000179295 PTPN11	36.69	45.99	1.25	0.032082073	0.835014727	1.32E-02	2.23E-02
ENSG00000168994 PXDC1	26.60	34.57	1.30	0.029189213	0.485363209	5.64E-03	0.010688549
ENSG00000126894 PXMP2 ENSG00000126621 PAR115/05	53.01	38.37	-1.38	0.516255152	0.338461089	0.000273794	0.000862839
ENSG00000155651 RAB11FIP5 ENSG00000168461 RAB31	10.33	20.39	1.21	0.209271039	0.952444833	0.000140816	0.00050292
ENSG00000141084 RANBP10	9.90	15.22	1.54	0.577959304	0.191185841	1.62E-08	0.000000583
ENSG00000123728 RAP2C	29.06	22.85	-1.27	0.12841244	0.576971068	0.002997381	0.006380334
ENSG00000131759 RARA	9.20	15.13	1.64	0.302595483	0.519536041	2.84E-05	0.000140396
ENSG00000068831 RASGRP2	51.26	40.27	-1.27	0.975562026	0.05333937	0.003339213	0.006928459
ENSG00000162742 RBM6	133.33	102.51	-1.30	0.813039903	0.075920312	0.012366155	0.02109679
ENSG00000103743 RCH11 ENSG00000042445 RETSAT	37.44	44.29	-1.10	0.976937749	0.950805795	0.014484776	0.02422578
ENSG00000182175 RGMA	18.24	12.82	-1.42	0.614320107	0.034505324	0.000224183	0.000734159
ENSG0000007384 RHBDF1	44.51	55.11	1.24	0.414239738	0.295080418	0.00863758	0.015462456
ENSG00000072422 RHOBTB1	20.63	27.85	1.35	0.483968991	0.810413374	2.48E-02	0.038195035
ENSG00000166532 RIMKLB ENSG00000161920 RNASEK C17orf	17.63	22.72	1.29	0.681969649	0.049664464	0.008821226	0.01572529
ENSG00000121835 RNA3ER-C17017	771.87	679.71	-1.14	0.525828423	0.46374926	1.84F-02	0.029479929
ENSG00000185946 RNPC3	18.12	26.07	1.44	0.807090379	0.46342748	1.85E-02	2.97E-02
ENSG00000176393 RNPEP	17.52	23.64	1.35	0.864703963	0.392826856	0.0000746	0.000299768
ENSG00000255135 RP11-111M22.3	\$ 29.34	38.00	1.30	0.983097937	0.644778249	0.006305134	0.011693838
ENSG00000251235 RP11-156N15.1 ENSG00000250982 RP11 15912.1	27.89	20.82	-1.34	0.976652105	0.569345739	4.54E-04	1.31E-0:
ENSG00000250582 RF11-15555.1	98.98	76.01	-1.30	0.619793771	0.182791934	1.70F-02	0.02777979
ENSG00000169253 RP11-220D10.1	44.02	32.83	-1.34	0.841197462	0.486456182	0.019050779	0.03042796
ENSG00000234925 RP11-254B13.3	306.40	247.58	-1.24	0.163459302	0.756202053	0.005554444	0.01055231
ENSG00000225471 RP11-262D11.2	12.57	20.89	1.66	0.410564805	0.635958958	0.016431628	0.027005833
ENSG00000237807 RP11-400K9.4	15.71	9.55	-1.64	0.588101644	0.433878494	1.09E-02	0.01886176
ENSG00000245422 RP11-415E0.1 ENSG00000226900 RP11-432124.5	92.12	55 54	-1.91	0.557665542	0.557506795	0.00017987	0.000616400
ENSG00000220500 RF11-432124.5 ENSG00000235582 RP11-448G4.2	80.97	63.81	-1.27	0.59700141	0.446574392	0.006968525	0.01278746
ENSG00000270213 RP11-452D24.1	47.62	24.35	-1.96	0.37038598	0.935207685	1.99E-02	3.16E-02
ENSG00000251107 RP11-466P24.4	32.04	24.69	-1.30	0.58703433	0.237842273	0.005873582	0.01101967
ENSG00000271207 RP11-475J5.5	18.48	13.39	-1.38	0.437966541	0.382952147	0.010112028	0.01769604
ENSG00000204272 PP11-613F7.1	47.00	31.73	-1.48	0.326249144	0.374590894	1.06E-02	1.84E-0
ENSG00000223509 RP11-022K12.1 ENSG00000223509 RP11-632K20.7	12.93	6.93	-1.87	0.96608299	0.409362343	2.70E-02	4.11F-0
ENSG00000249460 RP11-665C14.2	5.10	13.89	2.72	0.120774393	0.273105701	0.03087899	0.04630365
ENSG00000224012 RP11-756G12.1	38.67	55.37	1.43	0.773061681	0.146041471	0.007859739	0.01421674
ENSG00000213630 RP11-772E11.1	42.65	26.61	-1.60	0.89133617	0.311327825	0.003769953	0.00763611
ENSOUUUUU249145 RP11-77403.2	17.51	10.01	-1.75	0.000074332	0.568744237	0.000321254	0.00097944
ENSG0000237897 RP11-0/9F14.2	39.26	33.17	-1.18	0.620353029	0.413623406	0.020294195	0.03208565
ENSG00000267653 RP1-193H18.3	13.09	5.19	-2.52	0.259985065	0.205978212	0.016737968	0.02743573
ENSG00000257337 RP11-983P16.4	12.11	20.36	1.68	0.247717096	0.657344659	0.0000872	0.00034030
ENSG00000255252 RP1-65P5.3	37.28	54.78	1.47	0.920423726	0.720580929	0.023769219	0.03682145
ENSG00000235501 RP4-613823.1	11.22	17.45	1.55	0.240890012	0.431552935	0.000147957	0.00052411
ENSG00000223745 RP4-717123.3	14.09	20.29	1.44	0.760092524	0.852086011	0.001845584	0.0042408
ENSG00000224415 RPL19P12	128.06	107.29	-1.19	0.801094888	0.695875663	0.028866481	0.0436633
ENSG00000163584 RPL22L1	34.16	25.36	-1.35	0.25942533	0.905308054	0.018399097	0.02952809
ENSG00000114391 RPL24	862.55	696.55	-1.24	0.855450208	0.733870264	0.006566141	0.01213466
ENSG00000100316 RPI 3	473.89	596.10	1.25	0.409429157	0.629771537	1.23E-02	0.02092424
ENSG00000172809 RPL38	1097.40	862.41	-1.27	0.832999204	0.759399438	0.020845142	0.0328016
ENSG00000140986 RPL3L	211.47	180.48	-1.17	0.28069826	0.398196168	0.001356945	0.00329423
ENSG00000174444 RPL4	1226.99	1379.75	1.12	0.566553706	0.808321814	2.79E-02	0.0423288
ENSG00000213051 RPL5P5 ENSG00000214612 RPS10P1	21.10	26.47	1.25	0.51618177	0.154760164	0.00152481	0.00361719
ENSG00000138326 RPS24	27.15	684.59	-1 27	0.746875602	0.0281635	0.009147258	0.0261420
ENSG00000116954 RRAGC	28.13	23.07	-1.22	0.506534396	0.347328109	0.007660893	0.01388388
ENSG00000143171 RXRG	5.42	10.53	1.94	0.944038206	0.177584775	0.013527566	0.02282868
ENSG00000141504 SAT2	142.72	114.23	-1.25	0.7381152	0.238348624	0.003285983	0.0068453
ENSG00000136193 SCAF11	79.28	87.34	1.10	0.840902708	0.012218199	0.025712091	0.0394268
ENSG0000150155 SURV1	13.41	17.14	1.35	0.674298009	0.308378370	0.000402775	0.00135446
ENSG00000179918 SEPHS2	64.63	57.92	-1.12	0.739683197	0.198310146	2.86E-02	4.33F-0
ENSG00000164402 SEPT8	31.28	37.52	1.20	0.381374918	0.791303002	1.54E-02	2.55E-0
ENSG00000140264 SERF2	787.86	667.17	-1.18	0.696071119	0.109594876	0.005859571	0.01099814
ENSG00000120742 SERP1	23.57	29.45	1.25	0.257782319	0.116928559	2.03E-03	4.57E-0
ENSG00000123286 SERPINE2	27.01	64.19	2.38	0.062460952	0.560631123	0.003164561	0.00666051
ENSG00000132360 SERPINE1 ENSG00000080546 SESN1	331.28 79.10	497.68	-1.50	0.054511541	0.807838989	0.005434324	0.0103/377
ENSG00000240489 SETP14	21.39	15.50	-1.38	0.878512513	0.133804033	0.000122519	0.00045071
ENSG00000168066 SF1	229.72	261.79	1.14	0.659431592	0.005295556	0.004805692	0.00934193
ENSG00000116560 SFPQ	191.16	213.33	1.12	0.924706171	0.029274929	0.028344854	0.04292980
ENSG00000107819 SFXN3	18.56	24.57	1.32	0.586353822	0.234158879	2.67E-02	4.07E-0
ENSCO0000156462 SU2852	/2.8/	97.03	-1.55	0.14554/37	0.24/541602	5.391-04	1.52E-0

aDCM-specific DEGs at	t FDR≤0.05							
ENSG	Gene	NF_mean	aDCM_mean	FC 1.20	pval_Age	pval_Sex	pval_aDCM_v_NF	FDR_aDCM_v_NF
ENSG00000107338	SHB	10.24	17.40	1.30	0.070186849	0.666088666	0.00000137	0.000014
ENSG00000185187	SIGIRR	48.29	40.21	-1.20	0.274760868	0.491788457	0.013147696	0.022283989
ENSG00000142178	SIK1	7.47	20.53	2.75	0.822416606	0.733760004	0.003364739	0.006965991
ENSG00000101307	SIRPB1	12.47	18.33	1.47	0.282106356	0.63538332	0.000753442	0.001994555
ENSG00000182628	SKA2	56.84	48.44	-1.17	0.389663591	0.553631875	0.007965812	0.01438084
ENSG00000157933	SKI	15.47	21.31	1.38	0.159483797	0.902342714	0.002186118	0.004877366
ENSG00000168575	SLC20A2	113.63	90.48	-1.26	0.446296599	0.037810128	0.026906663	0.040990209
ENSG00000151729 ENSG00000169100	SLC25A4 SLC25A6	152.91	1441.65	-1.11	0.16/3/2396	0.731269729	0.011089343	0.019191202
ENSG00000174502	SLC26A9	24.56	16.59	-1.48	0.923431659	0.193659224	0.014065437	0.023634174
ENSG00000115194	SLC30A3	10.83	16.53	1.53	0.638218968	0.668054831	0.01476531	0.024650961
ENSG00000145740	SLC30A5	31.77	39.30	1.24	0.032461267	0.872677056	0.002367898	0.005230598
ENSG00000157637	SLC38A10	36.05	46.30	1.28	0.020110493	0.010177335	0.0000558	0.000238945
ENSG0000070214	SLC44A1	9.95	15.98	1.61	0.174617045	0.685658495	0.0000386	0.000178818
ENSG00000114923	SLC4A3	309.71	271.93	-1.14	0.257750433	0.041088322	2.52E-02	3.87E-02
ENSG00000131389	SLC6A6	11.14	45.24	4.06	0.119756168	0.252235481	0.000013	0.0000771
ENSG00000090020	SLC9A1	18.37	26.70	1.45	0.447091273	0.735227625	0.004494624	0.008851271
ENSG00000119705	SLIRP	453.26	383.59	-1.18	0.995226349	0.576739995	1.55E-02	2.56E-U2
ENSG00000214097	SNHG6	329.62	260.15	-1.00	0.499295455	0.955275451	0.002895104	0.006185115
ENSG00000206680	SNORD21	6.51	24.94	3.83	0.006527015	0.010104062	0.001955848	0.004446231
ENSG00000238465	snoU13	12.62	50.81	4.03	0.608758063	0.597861463	0.003387316	0.007003445
ENSG00000106266	SNX8	23.80	28.96	1.22	0.521719266	0.170045723	0.019625427	0.031196834
ENSG00000154556	SORBS2	984.14	1329.73	1.35	0.193004565	0.525685933	0.009790572	0.017191319
ENSG00000152377	SPOCK1	20.57	36.72	1.79	0.134812839	0.164305004	0.027393712	0.041650894
ENSG00000138600	SPPL2A	65.56	53.90	-1.22	0.27512265	0.346906529	0.012480525	0.021276409
ENSG00000157837	SPPL3	30.61	36.61	1.20	0.352550993	0.498718423	0.004083482	0.008153757
ENSG00000198369	SPRED2 SDRV4	14.21	19.55	1.38	0.764222113	0.767594646	4 505 06	0.00013696
ENSG00000106028	SSBP1	133.73	115.45	-1.16	0.849752944	0.936707086	0.011225394	0.019397977
ENSG00000114850	SSR3	223.24	185.80	-1.20	0.392920664	0.025622529	2 32F-02	3.59F-02
ENSG00000225259	ST13P6	54.14	43.53	-1.24	0.138819988	0.163478832	0.021430539	0.033609918
ENSG0000004866	ST7	27.97	21.35	-1.31	0.381233298	0.326059999	0.0000495	0.000218099
ENSG00000165283	STOML2	136.54	115.89	-1.18	0.931997532	0.000658245	0.000344031	0.001039417
ENSG00000169689	STRA13	29.08	24.07	-1.21	0.498874575	0.057459432	0.01914727	0.030561236
ENSG00000104915	STX10	60.95	51.79	-1.18	0.574492708	0.034745866	0.006797783	0.012508454
ENSG00000261612	SUB1P3	71.58	59.16	-1.21	0.784208053	0.743434123	0.019679558	0.031261658
ENSG00000137573	SULF1	7.45	18.07	2.43	0.072386083	0.79257109	0.000739869	0.001963062
ENSG00000196562	SULF2	34.55	44.15	-1.28	0.0728/9246	0.23166609	0.008428168	0.015104903
ENSG00000100242	SVEP1	5 30	96.27 11.86	2 20	0.441012421	0.91/980505	0.029963936 3.17F_0F	0.045133841 2.50F.05
ENSG00000137501	SYTI 2	8.44	18.76	2.20	0.117985102	0.309575978	0.000318498	0.000972945
ENSG00000187325	TAF9B	14.89	20.02	1.34	0.84663288	0.289060022	0.0000536	0.000232187
ENSG00000149591	TAGLN	227.55	357.46	1.57	0.172212654	0.242500071	1.93E-02	3.07E-02
ENSG00000177156	TALDO1	164.14	138.70	-1.18	0.47091348	0.089819692	1.90E-02	3.04E-02
ENSG00000204267	TAP2	36.84	26.19	-1.41	0.499521641	0.210040262	0.031414002	0.046989703
ENSG0000065882	TBC1D1	156.50	131.18	-1.19	0.611212798	0.620333128	0.022188231	0.034612754
ENSG00000145979	TBC1D7	39.02	50.87	1.30	0.786282815	0.00858584	0.015358535	0.025486895
ENSG00000136270	TBRG4	83.19	71.37	-1.17	0.683283695	0.080845912	0.004095395	0.008171596
EN5G00000204852	TEEC	28.24	38.01	1.35	0.459009022	0.041260708	0.000191642	0.000651748
ENSC000001406932	TGER111	14.92	21.01	-1.40	0.009177591	0.40074275	0.005074544	0.010725926
ENSG00000140082	TGEBI	42.83	62.70	1.42	0.648346756	0.73713725	0.006398573	0.011839004
ENSG00000176946	THAP4	100.20	83.54	-1.20	0.338865226	0.43916701	2.67E-03	0.005787183
ENSG00000186340	THBS2	9.09	17.23	1.90	0.05231021	0.636451812	0.005818161	0.010933567
ENSG00000169231	THBS3	12.23	20.66	1.69	0.084459021	0.650017478	2.38E-04	0.000771461
ENSG00000159445	THEM4	33.55	27.88	-1.20	0.9705476	0.843027519	7.86E-06	0.0000518
ENSG00000134375	TIMM17A	86.55	73.87	-1.17	0.424975402	0.571275447	0.003171619	0.006666378
ENSG00000150779	TIMM8B	207.13	175.59	-1.18	0.141815876	0.058294482	0.027466143	0.041747468
ENSG0000064115	TM7SF3	50.48	67.28	1.33	0.220532907	0.955306808	0.003139771	0.006623221
ENSG00000171204	TMEM126B	73.98	64.49	-1.15	0.634805727	0.667482226	0.033281864	0.049369328
ENSCO0000164584	TMEN1195A	44.00	56.20	1.52	0.000997024	0.947366339	0.011202461	0.004270114
ENSG000001555504	TMEM246	25.85	33.17	1 28	0.026126349	0.281277292	0.00000242	0.000021
ENSG00000170876	TMEM43	26.93	37.73	1.40	0.100844019	0.154484059	0.009140553	0.016213791
ENSG00000164983	TMEM65	29.97	22.71	-1.32	0.468210806	0.417179618	0.018738981	0.029996685
ENSG00000129925	TMEM8A	59.99	52.25	-1.15	0.671501825	0.786233559	0.02263482	0.035227272
ENSG00000227372	TP73-AS1	24.37	30.89	1.27	0.400020608	0.312707992	0.000139432	0.000499587
ENSG00000143549	TPM3	125.54	217.85	1.74	0.011834451	0.487947627	0.005497652	0.010465652
ENSG00000183022	TPM3P8	6.10	11.39	1.87	0.014529813	0.492207513	0.001543976	0.003648053
ENSG0000047410	TPR TPADDC12	54.00	61.36	1.14	0.785587534	0.246238541	0.010014473	0.025046759
ENSG00000171853	TRAPPC12	99.86	87.34	-1.14	0.368937974	0.140170294	0.010212305	0.00001484359
ENSG00000134233	TRMT10C	10.92	10.19	-1 36	0.730350059	0.430590295	0.0000994175	0.000014648
ENSG00000157514	TSC22D3	102.35	191.55	1.87	0.535780751	0.108703731	0.014972325	0.024925489
ENSG00000157570	TSPAN18	39.70	52.77	1.33	0.08747315	0.959699902	0.003264269	0.006818275
ENSG00000113312	TTC1	94.33	76.31	-1.24	0.938838287	0.076816672	0.002191774	0.004883005
ENSG00000165533	TTC8	9.47	14.95	1.58	0.411038547	0.969646572	3.19E-06	2.59E-05
ENSG00000131462	TUBG1	23.00	17.12	-1.34	0.874140551	0.829275342	2.51E-04	8.03E-04
ENSG00000117862	TXN2	181.68	152.03	-1.20	0.247937134	0.507829097	0.001733271	0.004024248
ENSG00000117802	UACA	40.07	47.44	1 25	0.77392081	0.043026936	3.0000399972	4 875.02
ENSG00000150991	UBC	1619.53	1328.09	-1.22	0.111611958	0.526071406	0.010195393	0.017821958
ENSG00000131508	UBE2D2	68.63	62.37	-1.10	0.382625586	0.16451587	2.39E-02	3.70E-02
ENSG00000140367	UBE2Q2	33.98	51.79	1.52	0.199733846	0.841191001	0.0000236	0.000121365
ENSG00000175567	UCP2	19.75	28.48	1.44	0.351803475	0.269375152	0.030295606	0.045589435
ENSG00000105698	USF2	277.60	215.57	-1.29	0.085115484	0.473867036	0.000306617	0.00094778
ENSG00000103194	USP10	43.59	38.28	-1.14	0.447116218	0.218245512	2.49E-02	0.038311766
ENSG00000114216	USP11	33.00	66.01	2.00	0.470650248	0.013479405	0.004012716	0.00804248
ENSG00000114510	VAT1	27.00	00.00	1.10	0.333611225	0.047807128	1.40E-02	2.300-02
ENSG00000038427	VCAN	14.04	27.60	1 97	0.031389634	0.521157374	0.005275707	0.010129617
ENSG00000112715	VEGFA	124.73	152.72	1.22	0.32737796	0.023626647	0.000948182	0.002438406
ENSG00000144560	VGLL4	22.73	29.50	1.30	0.850841178	0.118202774	0.000701429	0.00188142
ENSG0000026025	VIM	237.31	392.06	1.65	0.323458683	0.373171596	0.000163396	0.000570837
ENSG00000179403	VWA1	8.12	14.76	1.82	0.290530267	0.505728242	0.000282301	0.000886068
ENSG00000116455	WDR77	45.57	52.48	1.15	0.723976275	0.003047814	0.019991343	0.031681521
ENSG00000164091	WDR82	45.29	50.40	1.11	0.370073703	0.474894244	0.004632735	0.00908505
ENSG0000070540	WIPI1	160.95	194.10	1.21	0.543603023	0.353056896	0.020265866	0.032062517
ENSG00000154767	XPL V RNA	13.29	18.99	1.43	0.734513483	0.256279264	0.00000854	0.0000552
ENSG00000252965	T_RINA YBX1	55.27 194.46	18.58	-2.97	0.963506271	0.006385580	0.005516643 2 R0F_02	0.010489012 6.01F-02
ENSG00000060139	YBX3	3482 73	2488 98	-1 40	0.578526852	0.182821106	0.015270726	0.0253681/9
ENSG00000130733	YIPF2	17.97	23.45	1.30	0.4600925	0.856650912	0.003284207	0.006844656
ENSG00000166913	YWHAB	80.11	91.31	1.14	0.735085114	0.78575508	0.024173462	0.037336517
ENSG00000114853	ZBTB47	50.04	68.59	1.37	0.024493376	0.223768922	0.030357165	0.045667395
ENSG00000166432	ZMAT1	9.65	15.65	1.62	0.826408496	0.022009984	0.00000195	0.0000178
ENSG00000198816	ZNF358	67.79	54.66	-1.24	0.079960183	0.731758844	0.007012469	0.012852992
ENSG00000173545	ZNF622	78.10	60.55	-1.29	0.899212417	0.422675541	0.008943874	0.015913436
ENSG00000166770	ZNF667-AS1	14.99	20.34	1.36	0.949782294	0.899846963	0.003132208	0.006613223
ENSG0000229809	ZNE688	34.85	28.42	-1.23	0.322590973	0.92/254366	2.16E-02	3.38E-02
ENSG00000107700	2111 03 75WIM7	51.20 46.58	41.00	-1 27	0.740802943	0.839751346	2 26F-02	3 51F-02

Table S2: naDCM-specific adjusted gene expression.

naDCM-specific DEGs a ENSG	Gene	NF mean	naDCM mean	FC	pval Age	nval Sex	pval naDCM v NF	FDR naDCM v NF
ENSG00000158122	AAED1	21.33	15.96	-1.34	0.901145373	0.007368774	0.000725688	0.001889513
ENSG00000115977	AAK1	25.17	15.27	-1.65	0.827586664	0.616885415	0.0000155	0.0000828
ENSG00000141338	ABCA8	96.57	64.60	-1.49	0.702200902	0.685191874	0.002682738	0.005595952
ENSG00000154258	ABCA9	30.84	21.89	-1.41	0.459799545	0.97035313	0.033830263	0.04898025
ENSG00000222482	AC005071.1	29.62	6.63	-4.47	0.52920669	0.400237494	0.025706517	0.038803496
ENSG00000233287	AC009362.2	15.86	22.72	1.43	0.739280358	0.072332341	0.000581464	0.001573906
ENSG00000218682	AC010150.1	17.21	24.12	1.40	0.834384053	0.034815822	0.027660665	0.041227805
ENSG00000240303	ACAD11	65.11	51.25	-1.27	0.451954958	0.145184863	0.000465535	0.00132511
ENSG0000075239	ACAT1	1243.99	1460.25	1.17	0.218742465	0.050893403	0.017147363	0.027238337
ENSG00000119673	ACOT2	17.11	24.49	1.43	0.238071521	0.385424591	0.00121668	0.002906148
ENSCO0000134575	ACP2	40.21	44.77	1.17	0.256540126	0.620436430	0.03312/265	0.048150449
ENSG00000123583	ACYP2	67.71	78.40	1.16	0.11880661	0.023947921	0.004734259	0.009101173
ENSG00000168615	ADAM9	58.10	33.85	-1.72	0.780363675	0.661234527	0.017026483	0.027099508
ENSG00000163638	ADAMTS9	15.44	9.64	-1.60	0.327528048	0.442323242	0.000616827	0.00165031
ENSG00000174233	ADCY6	124.37	151.73	1.22	0.095429693	0.04097223	0.024507524	0.037166938
ENSG00000087274	ADD1	149.55	169.95	1.14	0.482631798	0.547473393	0.020420106	0.031774498
ENSG00000197894	ADDS ADH5	155.89	181.76	-1.55	0.65142189	0.000397478	0.004165246	0.00815911
ENSG00000120907	ADRA1A	18.84	12.78	-1.47	0.316937428	0.782022907	0.007474189	0.013507503
ENSG00000146416	AIG1	50.12	63.41	1.27	0.471965248	0.129924292	0.001720292	0.00385854
ENSG00000106305	AIMP2	30.65	36.84	1.20	0.149414275	0.184506629	0.00444349	0.008596648
ENSG00000147952	AK1	1103./1	925.63	-1.19	0.050444794	0.301902351	0.000042225	0.002435862
ENSG00000117448	AKR1A1	50.95	61.10	1.20	0.517511155	0.377251735	0.01733701	0.027476671
ENSG00000151632	AKR1C2	16.96	7.80	-2.18	0.261414909	0.378375174	0.000826843	0.002105019
ENSG00000226209	AL138764.1	8.87	14.88	1.68	0.514579265	0.008200234	0.000129386	0.000458279
ENSG00000148218	ALAD	96.80	71.69	-1.35	0.137334953	0.472927831	0.008982048	0.015746146
ENSG00000111275	ALDH2	237.63	278.20	1.17	0.75972752	0.20330117	0.027191704	0.040653606
ENSG00000162066	ALDOC AMDHD2	402.78	17.49	-1.54	0.733800738	0.63315334	0.00031296	0.000951023
ENSG00000159461	AMFR	95.02	82.59	-1.15	0.574218466	0.071654375	0.030840168	0.045354288
ENSG00000114019	AMOTL2	28.79	42.77	1.49	0.772574141	0.803782728	0.000868815	0.002188259
ENSG0000088448	ANKRD10	109.80	88.86	-1.24	0.088448956	0.079522258	0.012127625	0.020384821
ENSG00000160746	ANO10	19.35	14.33	-1.35	0.389287212	0.510690664	0.000126245	0.000449119
ENSG0000182718 ENSG0000161202	ANXA2 AP2M1	169.18	109.04	-1.55	0.441332198	0.011933559	0.016122045	0.00079511
ENSG0000065000	AP3D1	84.22	75.11	-1.10	0.990062721	0.331969805	0.011414321	0.019366857
ENSG00000185009	AP3M1	27.65	22.02	-1.26	0.876362323	0.211715144	0.000182022	0.000611696
ENSG00000221838	AP4M1	15.76	21.88	1.39	0.326306158	0.134901214	1.13E-04	4.13E-04
ENSG00000242802	AP5Z1	6.28	11.89	1.89	0.632025287	0.250711569	0.00000392	0.00000505
ENSG00000164062	APEH	78.05	97.49	1.25	0.775815996	0.063171616	0.000133806	0.000471868
ENSG00000183382	APOAIBP APOI 2	52.39	99.12 41.84	-1.22	0.558085079	0.015867529	0.001176578	0.002825648
ENSG00000142192	APP	520.56	459.09	-1.13	0.788354585	0.275503944	0.014112329	0.023175337
ENSG00000157500	APPL1	22.51	16.82	-1.34	0.395531713	0.01982206	0.000366857	0.00108427
ENSG00000240583	AQP1	152.12	251.06	1.65	0.562557655	0.202527757	0.001431003	0.003328042
ENSG00000120318	ARAP3	15.25	20.79	1.36	0.053426339	0.86073939	0.0000138	0.0000757
ENSG0000004059	ARF5	70.97	80.57	1.14	0.917656613	0.257901787	0.025628695	0.038698054
ENSG00000242247	AREGEE1	31.94	25.33	-1.30	0.919310296	0.999293893	0.002406874	0.005125454
ENSG00000071205	ARHGAP10	31.04	37.29	1.20	0.868601872	0.31499009	0.017806649	0.02813833
ENSG00000107863	ARHGAP21	34.04	22.76	-1.50	0.767407766	0.829015418	0.000760237	0.001962633
ENSG00000111348	ARHGDIB	129.75	98.25	-1.32	0.259920027	0.429071233	0.000637153	0.00169535
ENSG00000076928	ARHGEF1	35.44	44.12	1.24	0.640796115	0.973031748	0.020421789	0.031774498
ENSG00000110237	ARHGEF17	118 84	149.92	1.22	0.049880759	0.163532659	0.024261645	0.007412401
ENSG00000162980	ARLSA	49.63	39.11	-1.27	0.565839959	0.734992739	0.000607955	0.001631967
ENSG00000134108	ARL8B	45.53	53.20	1.17	0.610182925	0.827408141	0.033549898	0.048646851
ENSG00000105676	ARMC6	17.38	23.20	1.33	0.929676094	0.929382595	0.000236965	0.00076004
ENSG00000114098	ARMC8	53.33	71.22	1.34	0.33690594	0.820866362	0.002110613	0.004589852
ENSG00000133794	ARNTL	25.51	15.05	-1.69	0.637544391	0.384342447	0.008542658	0.015062639
ENSG00000241885	ARRB1	22.52	16.07	-1.40	0.944098427	0.334584373	0.005077519	0.009665399
ENSG00000105643	ARRDC2	16.09	27.70	1.72	0.457023734	0.131605281	0.021805181	0.033540057
ENSG0000099889	ARVCF	31.06	40.01	1.29	0.794867825	0.938874937	0.019540863	0.030560525
ENSG00000153317	ASAP1	39.32	29.24	-1.34	0.718970893	0.02432527	0.003760124	0.007483263
ENSG0000088280	ASAP3	34.20	24.66	-1.39	0.313850853	0.732113766	0.001456835	0.003367469
ENSG00000166183	ASPG ASS1	18.64	10.09	-1.85	0.068953014	0.033804402	0.016973106	0.027023411
ENSG00000138138	ATAD1	93.17	73.44	-1.27	0.941481523	0.912602405	0.000654233	0.001735093
ENSG00000107669	ATE1	30.29	21.12	-1.43	0.175585795	0.022923431	0.002976695	0.006117151
ENSG00000168397	ATG4B	43.20	52.72	1.22	0.774257284	0.063200745	0.007467171	0.013499845
ENSG00000111676	ATN1	35.93	43.26	1.20	0.045812847	0.372639681	0.020736144	0.032150292
ENSG00000165629	ATP5C1 ATP5C2	681.78	789.41	1.16	0.289705499	0.267467447	0.01271359	0.021259364
ENSG00000249256	ATP5LP3	79.46	95.02	1.24	0.343952843	0.471030533	0.021286554	0.032856805
ENSG00000100554	ATP6V1D	439.25	390.76	-1.12	0.110349344	0.527887644	0.029809032	0.043997769
ENSG00000128524	ATP6V1F	80.95	99.92	1.23	0.7498015	0.230879619	0.011161946	0.018991734
ENSG00000130770	ATPIF1	454.02	544.45	1.20	0.539206387	0.29394164	0.016329087	0.026161018
ENSG00000177104	B2M B3GNT8	2445.60	3073.38	1.26	0.68097582	0.996139576	1.75E-02	2.77E-02
ENSG00000121578	B4GALT4	18.36	13.33	-1.38	0.162800683	0.413836438	0.000461922	0.001318453
ENSG00000204463	BAG6	281.73	335.87	1.19	0.923379326	0.339001367	0.000115271	0.000417416
ENSG00000125124	BBS2	149.00	129.41	-1.15	0.190716825	0.771615627	1.13E-02	1.93E-02
ENSG00000114439	BBX	18.66	11.00	-1.70	0.823276789	0.477538268	0.0000813	0.000314948
ENSG00000137936	BCAR3 BCS11	27.46	16.74	-1.64	0.740147504	0.283/41226	0.000788901	0.002026934
ENSG00000259040	BLOC155-TXNDC5	15.28	9.91	-1.54	0.262049919	0.782150446	0.002370807	0.005067183
ENSG00000140299	BNIP2	87.57	75.08	-1.17	0.858076671	0.37195028	2.65E-02	3.98E-02
ENSG00000176171	BNIP3	192.49	162.76	-1.18	0.678390897	0.659751684	0.032701214	0.047601047
ENSG00000162813	BPNT1	29.37	24.36	-1.21	0.561836426	0.876357052	0.006077013	0.011280571
ENSG00000166164	BRD7 BRI3	41.89	49.02	1.17	0.270540033	0.428390742	0.012557689	0.021013142
ENSG00000104713	C10orf128	30.57	24.20	-1.19	0.396882401	0.117750815	0.017490951	0.02528575
ENSG00000184601	C14orf180	49.66	74.50	1.50	0.407988872	0.32090649	0.004804823	0.009218577
ENSG00000108666	C17orf75	25.87	31.86	1.23	0.769330749	0.079714919	0.005715097	0.010698732
ENSG00000104979	C19orf53	129.12	153.40	1.19	0.356871544	0.951897047	0.009231577	0.016090646
ENSG00000120170	C10rt198	36.15	44.19	1.22	0.20753618	0.008938215	0.007742167	0.013898693
ENSG00000139178 ENSG00000162972	C2nrf47	17.04	10.91	-1.56	0.245582964	0.37576396	0.000115414	0.000417622
ENSG00000243317	C7orf73	33.11	38.32	1.16	0.889686876	0.064133413	0.010472964	0.018002376
ENSG00000148120	C9orf3	110.14	153.49	1.39	0.050605027	0.864782432	0.001335595	0.003121102
ENSG00000182985	CADM1	55.46	41.87	-1.32	0.774550777	0.259500131	0.00336326	0.006813513
ENSG0000064989	CALCRL	15.55	10.36	-1.50	0.452012435	0.922255333	0.007386086	0.013378156
ENSG00001630559	CANISAP1 CAPN2	18.23	11.70	-1.56	0.43801376	0.911981535	0.0000001	0.00000186
ENSG00000182909	CAPS2	16.84	11.56	-1.19	0.740148992	0.664238966	0.0000242	0.000117655
ENSG00000198898	CAPZA2	472.10	372.23	-1.27	0.743365695	0.79633808	3.09E-02	4.54E-02
ENSG00000105483	CARD8	36.97	29.23	-1.26	0.064169464	0.926791014	0.000851563	0.002154867
ENSG00000153048	CARHSP1	35.51	26.03	-1.36	0.545247193	0.61002563	0.002082012	0.004537813
ENSG00000177303	CASKIN2	18.91	24.36	1.29	0.72862109	0.550539734	0.015082794	0.024479294
EN5GUUU00118729	CASUZ	2403.54	1938.37	-1.24	0.260204363	0.908419126	0.014228823	0.023319327
ENSG0000159228	CBR1	18 44	11.01			···· ··· ··· ··· ··· ··· ··· ··· ···· ····		0.044165716
ENSG00000159228 ENSG00000160200	CBR1 CBS	18.44 14.70	9.00	-1.63	0.58537098	0.653438596	0.03023839	0.049183209
ENSG00000159228 ENSG00000160200 ENSG00000172785	CBR1 CBS CBWD1	18.44 14.70 15.45	9.00 8.40	-1.63	0.58537098 0.746230592	0.653438596 0.53259245	0.03023839 0.0000192	0.044577299 0.0000981

naDCM-specific DEGs at ENSG	FDR≤0.05 Gene	NF_mean	naDCM_mean	FC	pval_Age	pval_Sex	pval_naDCM_v_NF	FDR_naDCM_v_NF
ENSG00000104957	CCDC130	29.51	35.06	1.19	0.525642423	0.73218074	0.012534825	0.020989348
ENSG0000024862 ENSG00000173588	CCDC28A CCDC41	8.34	13.36	1.60	0.490730763	0.539236658	0.00000254	0.0000203
ENSG00000120860	CCDC53	141.36	111.61	-1.27	0.759685722	0.046301031	0.0000481	0.000205928
ENSG00000186166	CCDC84	17.17	25.38	1.48	0.331648737	0.723670419	0.00000185	0.0000162
ENSG00000137500 ENSG00000100814	CCDC90B CCNB1IP1	52.40 107.19	43.88	-1.19 1.28	0.727316537	0.136606701 0.075308161	0.020287251 0.011753672	0.031606663
ENSG00000260916	CCPG1	127.06	98.13	-1.29	0.701179125	0.072268731	0.0000109	0.0000622
ENSG00000115484 ENSG00000146731	CCT4	110.30	130.56	1.18	0.757662549	0.562275099	0.00290716	0.005994552
ENSG00000170458	CD14	21.27	13.78	-1.54	0.818292208	0.796293676	0.02411678	0.036665963
ENSG00000103855	CD276	31.53	24.38	-1.29	0.770437558	0.90906536	0.014438415	0.023602494
ENSG00000161649 ENSG00000174059	CD300LG CD34	14.58	24.58	-1.36	0.040240673	0.294419183	0.016114781	0.025868884
ENSG00000151465	CDC123	75.09	64.17	-1.17	0.572184329	0.798738427	0.008517469	0.015034835
ENSG0000099804	CDC34	122.76	141.51	1.15	0.395776947	0.209274415	0.029577118	0.043708608
ENSG00000164649 ENSG00000058091	CDCA7L CDK14	49.36	33.72	-1.46 -1.61	0.446466481 0.341880108	0.948925583	0.022539404 0.002471973	0.034549036
ENSG0000059758	CDK17	22.67	14.90	-1.52	0.611616281	0.472873283	0.000351109	0.001047289
ENSG00000117266	CDK18 CER170	117.27	100.51	-1.17	0.909194389	0.007875374	0.020799456	0.032227874
ENSG00000143702 ENSG00000100422	CERK	70.22	52.72	-1.44	0.982783822	0.025649096	0.0000848	0.000324861
ENSG00000153774	CFDP1	82.88	66.51	-1.25	0.550014776	0.031967066	9.14E-03	1.59E-02
ENSG00000111642 ENSG00000100288	CHD4 CHKB	776.19	616.53 118.73	-1.26	0.818112665	0.298735486	0.028554951	0.042365671
ENSG00000258289	CHURC1	95.85	120.23	1.25	0.392524997	0.604525195	0.010310083	0.017753817
ENSG00000121940	CLCC1	36.94	31.19	-1.18	0.90692352	0.747614595	0.008656759	0.015236399
ENSG00000213719 ENSG00000125246	CLYBL	20.88	27.82	1.33	0.154883494	0.876893541	0.00171881	0.003856996
ENSG00000168405	CMAHP	21.90	16.44	-1.33	0.70713418	0.312888341	0.008206809	0.014592554
ENSG00000137200	CMTR1	18.97	24.05	1.27	0.419312077	0.139971404	0.00000699	0.0000436
ENSG00000068120	COASY	26.03	32.91	1.26	0.981094115	0.323632152	0.012983247	0.021583927
ENSG00000164597	COG5	46.39	38.35	-1.21	0.399629234	0.351423197	0.014694495	0.023953161
ENSG00000178449 ENSG00000131143	COX14 COX411	128.59	154.55	1.20	0.567957376	0.010647403	0.001103136	0.002677075
ENSG00000135940	COX5B	811.78	1016.18	1.25	0.922269544	0.065659873	0.000304863	0.000934251
ENSG00000161281	COX7A1	5721.98	7473.54	1.31	0.827737651	0.019572012	1.57E-03	0.003580218
ENSG00000243453 ENSG00000127184	COX76P1 COX7C	28.03 2057.40	6.02 2542.89	-4.66 1.24	0.034568612	0.348495862	0.001698675	0.003818872
ENSG00000205560	CPT1B	328.40	450.62	1.37	0.41789636	0.197301864	0.00078999	0.002027913
ENSG00000157184	CPT2	16.76	24.16	1.44	0.916313845	0.855828227	0.0000195	0.0000992
ENSG00000118280	CSK	27.15	20.80	-1.39	0.949616448	0.394827097	0.002772857	0.005751813
ENSG00000113712	CSNK1A1	159.88	129.13	-1.24	0.847883764	0.714497454	0.002963119	0.006096995
ENSG00000249192	CTB-3601.3	485568.71	375606.22	-1.29	0.07173393	0.341900439	0.004427006	0.00856817
ENSG00000244921 ENSG00000244331	CTB-3601.7 CTB-47B8.1	228.43	9211.38	-1.28	0.208033598	0.294987108	0.013951289	0.022926383
ENSG00000268032	CTB-5212.4	21.19	27.96	1.32	0.564218892	0.00894732	0.000482224	0.001360651
ENSG00000248930	CTC-250P20.1	14.99	9.28	-1.62	0.739937426	0.397033178	0.00000512	0.0000345
ENSG00000250222 ENSG00000268205	CTC-444N24.11	6.54	11.67	1.58	0.12191629	0.124847381	8.3E-09	0.00000344
ENSG00000175215	CTDSP2	107.82	91.05	-1.18	0.288153129	0.355277276	0.033729009	0.048862789
ENSG00000169862 ENSG00000085733	CTNND2 CTTN	9.54	15.67	1.64	0.00305035	0.577579689	2.94E-03	6.06E-03
ENSG0000008256	СҮТНЗ	35.98	28.99	-1.24	0.9449158	0.867212157	0.015242662	0.024689249
ENSG00000180902	D2HGDH	34.41	44.09	1.28	0.931804107	0.716225351	0.01328875	0.022023948
ENSG00000115866 ENSG00000204209	DARS	142.32	118.29 25.19	-1.20	0.322716967	0.70893534	0.000580359	0.001571791
ENSG00000136279	DBNL	32.66	40.24	1.23	0.465261307	0.919733876	0.015699451	0.02528575
ENSG00000132912	DCTN4	38.76	33.12	-1.17	0.422629801	0.187108584	1.74E-03	3.90E-03
ENSG00000198171	DDRGK1	49.05	43.64	-1.35	0.190946815	0.045793825	0.019438524	0.030459333
ENSG00000215301	DDX3X	84.42	47.76	-1.77	0.705281831	0.03859736	0.016127182	0.025871687
ENSG0000067048	DDX3Y	23.67	14.12	-1.68	0.807477433	2.62E-20	0.024133711	0.036680219
ENSG00000114956	DGUOK	21.63	26.85	1.24	0.244850361	0.515944462	1.78E-03	0.003975336
ENSG0000095059	DHPS	100.60	124.81	1.24	0.449405683	0.774594415	0.000079	0.00030855
ENSG00000184544 ENSG0000075711	DHRS7C	53.94	12.68	-4.25	0.051811023	0.68887631	0.000262518	0.000827247
ENSG00000119689	DLST	100.86	113.54	1.13	0.485734812	0.558744875	0.001853624	0.004113892
ENSG00000198947	DMD	115.43	85.22	-1.35	0.665661837	0.072686813	0.001244403	0.002950595
ENSG00000135924 ENSG00000137094	DNAJB2 DNAJB5	71.73	87.15	1.21	0.518160086	0.454744435	0.02062678	0.032013724
ENSG00000105821	DNAJC2	21.91	16.60	-1.32	0.619695376	0.286636164	0.000047	0.000201842
ENSG00000224165	DNAJC27-AS1	5.02	10.56	2.10	0.148843305	0.060560552	1.90E-05	9.73E-05
ENSG00000146425 ENSG00000105204	DYNLT1 DYRK1B	124.91	159.80	1.28	0.980947769	0.180137591	0.007064194	0.01286315
ENSG00000117298	ECE1	64.43	50.04	-1.29	0.398583438	0.769936374	5.88E-03	0.010961989
ENSG00000121310	ECHDC2	279.99	353.48	1.26	0.651119408	0.861123848	0.000776025	0.001998079
ENSG0000136160	EDNRB	20.67	151.04	-1.45	0.25134671	0.609287365	0.032845649	0.01431398
ENSG00000132394	EEFSEC	11.09	16.53	1.49	0.543081358	0.772685712	0.00000395	0.0000285
ENSG00000159658 ENSG00000113790	EFCAB14 EHHADH	45.84	37.04	-1.24	0.98185871 0.663832739	0.449825212 0.268060143	0.001887561 0.000886474	0.004181568 0.002225812
ENSG00000104408	EIF3E	303.89	274.89	-1.11	0.047607289	0.007485207	0.011272016	0.019165585
ENSG00000178982	EIF3K	642.21	721.95	1.12	0.941694632	0.455915385	0.020903809	0.032327673
ENSG00000110321 ENSG00000075151	EIF4G2 EIF4G3	40.59	2921.95	-1.16	0.90770825	0.076819303	0.004340897	0.008435132
ENSG00000120690	ELF1	23.14	29.42	1.27	0.912967761	0.32618112	0.01651052	0.026408131
ENSG0000062598	ELMO2	34.89	28.61	-1.22	0.357589194	0.981988842	0.000462566	0.001318977
ENSG00000128463	EMC4	104.76	120.60	-1.32	0.739750621	0.254444641	0.008458135	0.014962733
ENSG00000213853	EMP2	83.31	69.60	-1.20	0.368777623	0.749368608	0.014351343	0.023506365
ENSG00000167280 ENSG00000049283	ENGASE EPN3	17.21	23.36	1.36	0.822961191	0.492749618	0.000279522	0.000868989
ENSG00000136628	EPRS	75.41	65.91	-1.14	0.331351407	0.074727465	0.007433802	0.013444522
ENSG00000151491	EPS8	48.38	36.07	-1.34	0.952977213	0.6004911	0.001829952	0.00406977
ENSG00000132591 ENSG00000082805	ERC1	54.25 20.04	63.52 12.28	-1.63	0.444936782	0.792476503	0.018075121	0.028543996
ENSG00000197930	ERO1L	24.05	17.88	-1.35	0.069776781	0.024156851	0.00410277	0.008052972
ENSG00000196482	ESRRG	18.66	13.16	-1.42	0.153047774	0.290763111	0.002094604	0.004561165
ENSG00000134954	ETS1	34.10	27.93	-1.14	0.99197944	0.15130666	0.033970898	0.049139911
ENSG0000070367	EXOC5	39.23	30.28	-1.30	0.670313981	0.198423639	0.007133693	0.012974237
ENSG00000157036 ENSG00000171934	EXOG EXOSC10	24.20	32.11	1.33	0.168224067	0.3965152542	0.000601089	0.00161801
ENSG00000092820	EZR	189.27	161.47	-1.10	0.182186609	0.222492173	0.01679799	0.02679732
ENSG00000134824	FADS2	11.26	18.01	1.60	0.494079851	0.671271347	0.015431081	0.024936216
ENSG00000154153 ENSG00000163946	FAM134B FAM208A	279.16	205.14	-1.36	0.379925457	0.400121985	0.004180633 4.23E-03	0.008182649 8 27F-03
ENSG00000196227	FAM217B	12.63	6.80	-1.86	0.941602299	0.430171425	0.000739758	0.001920997
ENSG00000143409	FAM63A	42.77	34.90	-1.23	0.759009976	0.16402739	0.003191538	0.006500884
ENSG0000165716 ENSG00000148343	FAM73B	9.63 20.87	15.49 25.97	1.61	0.396553963 0.436579086	0.364417652 0.050010988	5.97E-08 0.002132013	1.27E-06 0.004623964
ENSG00000116120	FARSB	39.28	32.80	-1.20	0.064817504	0.791250135	0.000374418	0.00110259
ENSG00000169710	FASN	24.49	13.81	-1.77	0.363541529	0.661525335	0.009701693	0.016783548
ENSG00000127452	FBXL12	61.26 10.98	72.33	1.18	0.470004407	0.501869217	0.028232393 2.77F-09	0.000000155
ENSG00000138081	FBXO11	42.01	34.96	-1.20	0.829515917	0.461179814	0.000104529	0.000386884
ENSG0000037637	FBXO42	21.78	27.96	1.28	0.542316629	0.03559417	0.011052212	0.018818212
ENSG00000137478	FCHSD2	38.82	30.08	-1.29	0.098244738	0.203539163	0.00433426	0.008425607

naDCM-specific DEGs	at FDR≤0.05							
ENSG	Gene	NF_mean n	aDCM_mean	FC	pval_Age	pval_Sex	pval_naDCM_v_NF	FDR_naDCM_v_NF
ENSG00000149557	FDPS FEZ1	94.75 57.63	43.62	-1.32	0.820728877	0.745518681	0.014489577	0.023666796
ENSG00000171055	FEZ2	87.82	77.52	-1.13	0.172174685	0.006445706	0.0296007	0.043721823
ENSG00000156427	FGF18	6.41	12.19	1.90	0.448919496	0.746280814	0.008713389	0.015320036
ENSG00000139914	FITM1	95.50	130.86	1.32	0.93016646	0.895238091	0.001009692	0.002481307
ENSG00000106080	FKBP14	11.83	6.71	-1.76	0.133498674	0.48828238	0.0000162	0.0000856
ENSG00000079150	FKBP7	21.46	15.18	-1.41	0.621954046	0.920168919	0.000241351	0.000769533
ENSG00000122042	FLNC	259.75	429.54	1.65	0.609463134	0.943890844	0.002036027	0.004455587
ENSG00000110074	FOXRED1	28.20	35.26	1.25	0.680947236	0.714462633	0.000783164	0.002014325
ENSG00000219507 ENSG00000087086	FTH1P8 FTI	20.28	10.37 493.89	-1.96	0.821981553	0.426414325	0.001907524	0.004218094
ENSG00000137726	FXYD6	54.08	70.61	1.31	0.434757859	0.256060466	0.00125642	0.002973937
ENSG00000141349	G6PC3	28.70	34.64	1.21	0.97291386	0.192495691	0.001562438	0.003568767
ENSG00000054983 ENSG00000249489	GALC GAPDHP70	24.76	18.34 206.79	-1.35	0.588625319	0.361238734	0.0000805	0.000313658
ENSG00000107862	GBF1	20.36	26.02	1.28	0.763343496	0.44901402	0.00240757	0.005125454
ENSG00000117226	GBP3	13.97	8.95	-1.56	0.700360007	0.836033527	0.012415463	0.020811007
ENSG00000125447	GGA3	34.21	28.31	-1.13	0.80951451	0.401274024	0.012801974	0.022514008
ENSG00000141034	GID4	19.29	13.39	-1.44	0.97695068	0.762246752	0.000173347	0.00058989
ENSG00000146830	GIGYF1	19.64	26.18	1.33	0.62399047	0.140567768	0.000517914	0.001433043
ENSG00000187513	GJA4	22.90	27.54	1.21	0.718362243	0.776956628	0.027649429	0.041223711
ENSG00000109738	GLRB	7.74	12.80	1.65	0.202455227	0.667718462	0.0000243	0.000117954
ENSG00000197045 ENSG00000144591	GMFB	19.65	13.12	-1.50	0.155836212	0.092938553	0.000527725	0.001453967
ENSG00000087258	GNA01	12.63	6.31	-2.00	0.114709545	0.031176947	0.00063281	0.001686568
ENSG00000176533	GNG7	24.68	29.85	1.21	0.62422713	0.362769669	0.034181179	0.049354343
ENSG00000111670 ENSG00000175265	GNPTAB GOLGA8A	42.38	35.05	-1.21	0.537246846	0.966998942	0.0002836	0.000879975
ENSG00000125166	GOT2	400.20	460.24	1.15	0.369313462	0.032726949	0.022326731	0.03426631
ENSG00000119927	GPAM	13.49	7.89	-1.71	0.178972776	0.871718479	0.000241988	0.000771058
ENSG0000160360 ENSG00000137106	GPSW1 GRHPR	27.97 93.28	41.12 105.88	1.47	0.8689638 0.801949586	0.191212272 0.620752307	0.025475295	0.038513277
ENSG00000198873	GRK5	33.78	25.02	-1.35	0.746616093	0.205048083	0.001628694	0.003696528
ENSG00000133433	GSTT2B	13.56	7.48	-1.81	0.505110904	0.864258224	0.021078231	0.032576668
ENSG00000136732	GYPC	0.08 107.17	126.96	2.05	0.543152627	0.116323621	0.031521026	0.007428734
ENSG00000184897	H1FX	40.60	50.21	1.24	0.399671614	0.053341151	0.021585156	0.033233201
ENSG00000112855 ENSG00000112070	HARS2 HBEGE	28.73	35.95	1.25	0.649919002	0.259867477	0.000166686	0.000570018
ENSG00000164818	HEATR2	16.49	23.65	1.43	0.22569463	0.008720212	0.0000422	0.000184453
ENSG0000051620	HEBP2	116.18	135.84	1.17	0.151510564	0.708739935	0.006876515	0.012553518
ENSG00000173064 ENSG00000138641	HECTD4 HERC3	22.26	28.17	-1.27	0.672246769	0.809705671	0.001751125	0.003916842
ENSG00000185359	HGS	61.68	76.05	1.23	0.739963975	0.890734342	0.012433585	0.020834193
ENSG00000100644	HIF1A	64.09	49.90	-1.28	0.2176706	0.656492696	0.011368919	0.019303312
ENSG00000146066 ENSG00000197903	HIGD2A HIST1H2BK	157.45	211.02	-1.34	0.637787371	0.53572599	0.000121435	0.000435195
ENSG00000181666	HKR1	31.17	36.20	1.16	0.998569782	0.543706331	0.015228815	0.02467505
ENSG00000231389	HLA-DPA1	96.87	141.72	1.46	0.897949972	0.763668827	0.020606414	0.032010476
ENSG00000092199	HNRNPC	200.65	163.13	-3.60	0.347408019	0.01328748	0.006121811	0.011350712
ENSG00000125944	HNRNPR	99.62	89.08	-1.12	0.385369486	0.039752103	3.37E-02	4.89E-02
ENSG00000132541	HRSP12	57.09	48.06	-1.19	0.698864112	0.99898676	2.40E-02	0.036582432
ENSG00000204389	HSPA1A	35.10	52.07	1.41	0.451813352	0.385728837	0.004310567	0.008386263
ENSG00000170276	HSPB2	19.04	29.29	1.54	0.079768595	0.00863658	0.000928165	0.00231731
ENSG00000115541	HSPE1	53.14	69.23	1.30	0.306813123	0.0464842	0.001511986	0.003468125
ENSG00000122988	ICAM2	57.99	82.27	1.48	0.077908499	0.539560933	0.005060499	0.009636778
ENSG00000137965	IF144	20.96	33.49	1.60	0.879830311	0.94937834	0.011020992	0.018778224
ENSG00000100360 ENSG0000068885	IFT27 IFT80	40.81	47.22	1.16	0.022907695	0.268948949	0.012842466	0.021415871
ENSG00000131724	IL13RA1	14.30	8.89	-1.61	0.626483865	0.537075655	0.008157209	0.01452031
ENSG00000134352	IL6ST	126.42	53.63	-2.36	0.860488424	0.622247378	0.0000281	0.00013194
ENSG00000132849 ENSG00000117408	IPO13	45.09	51.74	1.24	0.999654852	0.942749053	0.014775949	0.024045579
ENSG00000205339	IPO7	87.19	51.56	-1.69	0.607012419	0.965196716	0.000197278	0.000652575
ENSG00000168310	IRF2	34.62	24.44	-1.42	0.828132137	0.481760182	0.000306874	0.000937818
ENSG00000126456 ENSG00000185507	IRF3	10.24	98.99 16.97	1.18	0.322370047	0.714834537	0.0031246116	0.001049905
ENSG00000213928	IRF9	42.83	55.31	1.29	0.780550699	0.558646792	0.012150041	0.020415432
ENSG00000167378	IRGQ	13.93	19.14	1.37	0.129527705	0.98636541	0.0000147	0.0000795
ENSG00000129636	ITFG1	151.83	121.01	-1.25	0.255919778	0.510076742	0.000254972	0.00080556
ENSG00000135916	ITM2C	20.77	26.25	1.26	0.681446622	0.645014516	0.00993005	0.017148052
ENSG00000161999 ENSG00000149596	JMJD8 IPH2	70.00	61.97 110.88	-1.13	0.255574827	0.56886491	0.027842157	0.041460139
ENSG00000130522	JUND	70.21	96.83	1.38	0.342053387	0.850467576	0.011432077	0.019383439
ENSG00000107104	KANK1	65.10	78.64	1.21	0.596749544	0.439323055	0.032528116	0.047405921
ENSG00000186994 ENSG00000114987	KANK3 KANSL3	20.19 26.99	26.97 32.01	1.34	0.431592439	0.213529246	0.007412749	0.013411442
ENSG00000103510	KAT8	41.85	54.37	1.30	0.113855542	0.41152667	0.0000298	0.000137615
ENSG00000187715	KBTBD12 KCTD10	16.39	24.50	1.49	0.433489337	0.459401592	0.002497635	0.005275819
ENSG00000110906	KIAA0040	32.10	24.49	-1.51	0.556726905	0.470863901	0.001894124	0.004194193
ENSG00000132680	KIAA0907	39.99	32.30	-1.24	0.927150897	0.134910237	2.70E-03	5.63E-03
ENSG00000164944	KIAA1429	39.17	46.02	1.17	0.323018898	0.090274812	0.017041979	0.027115285
ENSG00000089177	KIF16B	15.46	10.90	-1.53	0.403547754	0.494843874	0.00000297	0.0000227
ENSG00000139116	KIF21A	52.13	39.89	-1.31	0.592370705	0.402096053	0.002147948	0.004656444
ENSG0000079616	KIF22	29.59	39.54	1.34	0.311704266	0.008527798	0.005723654	0.010706496
ENSG00000162413	KLHL21	62.72	42.91	-1.46	0.918086441	0.491003804	0.00801068	0.010620068
ENSG0000055609	KMT2C	20.73	14.48	-1.43	0.154040405	0.329650169	0.0000658	0.000267404
ENSG00000133619 ENSG00000162511	KRBA1	16.74	34.78	2.08	0.593346501	0.177921467	0.000121025	0.000434686
ENSG00000001497	LAS1L	18.76	24.59	1.35	0.596439468	0.972064309	0.00000418	0.0000299
ENSG00000169744	LDB2	38.43	23.52	-1.63	0.417931216	0.718622504	0.001992193	0.004383366
ENSG00000214110 ENSG00000169961	LDHAP4	78.75	48.08	-1.64	0.471300957	0.715008324	0.000285365	0.000883757
ENSG00000153902	LGI4	14.04	20.26	1.44	0.717482844	0.871540994	0.002179968	0.004711136
ENSG00000183814	LIN9	18.34	12.70	-1.44	0.346831162	0.461618025	0.001217602	0.00290692
ENSG00000237854 ENSG00000241135	LINC00674	77.05	52.72 48.01	-1.46	0.652986925	0.710081734	0.000243223	0.000774487
ENSG00000189067	LITAF	46.56	30.98	-1.50	0.328319753	0.52206325	0.001456971	0.003367469
ENSG00000132793	LPIN3	19.57	25.06	1.28	0.606807576	0.67386971	0.007570661	0.013646299
ENSG00000163956 ENSG00000137821	LRPAP1	311.51	265.55	-1.17	0.8045628	0.748847323	0.025780959	0.038891686
ENSG00000185565	LSAMP	18.70	6.93	-2.70	0.063888559	0.019514035	0.000743413	0.001928426
ENSG00000106355	LSM5	55.38	63.65	1.15	0.279584245	0.370752329	0.017589983	0.027823114
ENSG00000111144	LTA4H	54.28	47.66	-1.14	0.085863037	0.348667226	0.001468685	0.003388091
ENSG00000176018	LYRIVI2 LYSMD3	35.32 16.09	30.07	-1.17	0.423592495	0.372345933 0.306413373	0.000232588	0.0000489 0.0000489
ENSG0000003056	M6PR	245.09	216.16	-1.13	0.193140145	0.280354969	0.003026792	0.00620959
ENSG00000101460	MAP1LC3A	55.44	67.46	1.22	0.869567029	0.057093409	0.016426675	0.026291343
ENSG00000137337	MARCH5 MDC1	28.27 13.59	35.69 19.26	1.26 1.42	0.904113856 0.449480958	0.343775877	0.020823634	0.032247948
ENSG00000112159	MDN1	20.56	26.40	1.28	0.746840432	0.001700209	0.000467345	0.001328103
ENSG00000124733	MEA1	45.69	38.87	-1.18	0.856048369	0.751874382	0.010518276	0.0180547

naDCM-specific DEGs at ENSG	FDR≤0.05 Gene	NF_mean	naDCM_mean	FC	pval_Age	pval_Sex	pval_naDCM_v_NF	FDR_naDCM_v_NF
ENSG00000141026	MED9	19.25	24.47	1.27	0.598124	0.159895741	0.000841261	0.002134359
ENSG0000081189 ENSG00000165792	MEF2C METTL17	28.29	19.93	-1.42	0.602433696	0.024006451	0.003392161	0.006852052
ENSG00000181038	METTL23	21.75	27.56	1.27	0.742503126	0.24672327	0.000117661	0.000425122
ENSG00000147324	MFHAS1	16.26	9.00	-1.81	0.399627887	0.496043351	0.0000905	0.000342129
ENSG00000116688 ENSG00000100060	MENG	320.03	3/3.55	1.17	0.223695099	0.24034584	0.001596928	0.003635576
ENSG00000154305	MIA3	79.33	67.69	-1.17	0.686863475	0.078603206	0.013534302	0.022347014
ENSG00000173436	MINOS1	204.55	254.85	1.25	0.799061994	0.002723172	0.000670951	0.001768806
ENSG00000224237 ENSG00000227671	MINUS1P3 MIR3916	40.17	20.24	-1.35	0.447232752	0.399096567	0.00713062	0.012973508
ENSG00000158411	MITD1	28.01	21.73	-1.29	0.997673108	0.070482957	0.00103874	0.002543681
ENSG00000159256	MORC3	16.00	10.02	-1.60	0.539955327	0.474634412	0.007864273	0.014086651
ENSG00000185787 ENSG00000218283	MORF4L1 MORF4L1P1	114.90	126.30	1.10	0.121043315	0.403195741	0.034190282 8.61E-03	0.049354343 1.52E-02
ENSG00000173141	MRP63	15.69	21.58	1.38	0.570370054	0.170657389	0.000000117	0.00000206
ENSG00000115364	MRPL19	33.99	39.77	1.17	0.491857732	0.61358684	0.00416834	0.008161878
ENSG00000116221 ENSG00000105364	MRPL37 MRPL4	41.92	49.88	1.14	0.988657198	0.122027659	0.003149592	0.006431631
ENSG00000183617	MRPL54	45.90	59.46	1.30	0.514494679	0.468376365	0.007621526	0.013727793
ENSG00000048544	MRPS10	59.41	51.73	-1.15	0.813751813	0.122960983	1.30E-02	2.16E-02
ENSG00000204568 ENSG00000243927	MRPS18B MRPS6	105.51	118.76	-1.13	0.241572026	0.040174334	0.02285048	0.019822391
ENSG00000169715	MT1E	86.27	176.90	2.05	0.624610372	0.446731551	7.21E-04	0.001880205
ENSG00000125148	MT2A	89.21	152.54	1.71	0.578221036	0.73076243	0.018106858	0.028575529
ENSG00000182979 ENSG00000117640	MTA1 MTER1I	86.32	98.99	1.15	0.108838435	0.267289808	0.010765186	0.018398195
ENSG00000225630	MTND2P28	90.96	40.75	-2.23	0.673323831	0.510040249	0.028005168	0.041690096
ENSG00000232177	MTND4P24	82.64	45.43	-1.82	0.905048521	0.728869087	0.016612657	0.026550248
ENSG00000248923	MTND5P11	7695.83	5854.90	-1.31	0.670282834	0.946858172	0.010572422	0.01814123
ENSG00000255633	MTRNR2L9	22.30	30.76	1.38	0.961586116	0.900224526	0.003912928	0.007742941
ENSG00000124275	MTRR	36.48	31.25	-1.17	0.499459718	0.541357065	0.032661733	0.047572098
ENSG00000170873	MTSS1	41.17	29.01	-1.42	0.59089921	0.74390626	0.013366101	0.022137034
ENSG00000111245	MYL2	32453.73	44539.43	1.26	0.557973035	0.2142/6838	4.59E-03	0.032696212 8.86E-03
ENSG00000196465	MYL6B	77.71	92.48	1.19	0.259472124	0.173591177	0.00845474	0.014962178
ENSG00000140795	MYLK3	131.36	95.83	-1.37	0.850606188	0.25305971	0.014204259	0.023294794
ENSG00000101605	MYOC MYOM1	5.27	11.75 1634 32	2.23	0.383565648	0.190933042	0.014590568	0.002381573
ENSG00000263155	MYZAP	731.13	864.28	1.18	0.848584112	0.577149696	0.030414295	0.044782236
ENSG00000121089	NACA3P	10.63	18.20	1.71	0.732130788	0.047580937	0.00000284	0.00000399
ENSG00000187109 ENSG00000141562	NAP1L1 NARE	307.18	265.49	-1.16	0.822341222	0.900262372	0.004939904	0.009447883
ENSG00000114503	NCBP2	55.29	47.19	-1.17	0.903885896	0.106744298	0.000279301	0.000868989
ENSG00000115053	NCL	567.56	493.74	-1.15	0.843118282	0.032754259	0.004679617	0.009017548
ENSG00000140396	NCOA2	18.24	13.02	-1.40	0.675095099	0.137473415	0.001179999	0.002831064
ENSG00000124151 ENSG00000174886	NCUA3 NDUFA11	18.88	673.16	-1.54	0.945435616	0.939714965	0.009651164	0.01649823
ENSG00000131495	NDUFA2	144.93	189.96	1.31	0.793245364	0.006614642	0.001318244	0.003093955
ENSG00000139180	NDUFA9	418.48	520.05	1.24	0.111809982	0.036182069	0.0001934	0.000642814
ENSG00000090266 ENSG00000099795	NDUFB2 NDUFB7	604.81 509.33	723.80	1.20	0.396537824	0.009522439	0.004294612	0.008361922
ENSG00000166136	NDUFB8	594.64	674.72	1.13	0.395119224	0.097417377	0.002767391	0.005747841
ENSG00000158864	NDUFS2	441.27	535.76	1.21	0.553521469	0.117353427	0.000427788	0.001237248
ENSG00000213619	NDUFS3	407.41	522.40	1.28	0.910597961	0.300546784	0.0000554	0.000230934
ENSG00000172260	NEGR1	13.86	8.57	-1.62	0.479115496	0.685502359	0.002649151	0.005533022
ENSG00000188986	NELFB	14.08	19.19	1.36	0.325816667	0.088844877	1.99E-05	1.01E-04
ENSG00000165525	NEME	63.06	53.65	-1.18	0.891911901	0.036839368	0.033287488	0.048309635
ENSG00000182768	NGRN	159.96	134.89	-1.19	0.963534502	0.886796351	0.023667307	0.036061639
ENSG00000100503	NIN	15.61	10.56	-1.48	0.057532962	0.073758989	0.00054652	0.00149703
ENSG00000131669	NINJ1	59.44	48.36	-1.23	0.290087195	0.001436037	0.015456344	0.024960427
ENSG00000165028 ENSG00000112992	NIPSNAP3B NNT	21.22	27.33	1.29	0.690988342	0.092100549	0.00239841	0.035974042
ENSG00000119655	NPC2	215.85	170.22	-1.27	0.388878567	0.494264614	0.007650621	0.013764882
ENSG00000249353	NPM1P27	90.38	103.35	1.14	0.400171856	0.334470345	0.027023119	0.04043891
ENSG00000131408 ENSG00000197893	NR1H2 NRAP	39.37 536.80	46.84	1.19	0.068553799	0.233414228	0.020862885	0.032284949
ENSG00000147383	NSDHL	19.09	11.66	-1.64	0.406716965	0.537681802	0.009552198	0.016578082
ENSG0000088833	NSFL1C	91.54	79.66	-1.15	0.865373808	0.064550534	0.006485089	0.011942204
ENSG00000141698	NT5C3B	40.15	34.51	-1.16	0.930931376	0.042512931	0.017589554	0.027823114
ENSG00000140538	NTRK3	5.97	11.18	1.87	0.316374384	0.329162564	0.007779976	0.013945944
ENSG0000015676	NUDCD3	100.45	88.23	-1.14	0.504697147	0.089512553	0.008156327	0.01452031
ENSG00000149761	NUDT22	54.45	68.89	1.27	0.282747025	0.058988733	0.000106917	0.000393326
ENSG00000110713 ENSG00000176046	NUP98 NUPR1	90.91	60.63	-1.22	0.157193997	0.328053615	0.007714793	0.00054806
ENSG00000198836	OPA1	125.00	76.13	-1.64	0.871764204	0.776484688	0.000198264	0.000654946
ENSG00000115947	ORC4	39.60	33.88	-1.17	0.249831111	0.052703418	0.008477409	0.014980457
ENSG00000021762 ENSG00000091039	OSBPLS OSBPL8	15.48	20.60	1.33	0.347994209	0.165987819	0.002244091	0.004828226
ENSG00000228474	OST4	482.95	421.16	-1.15	0.992974984	0.096621337	1.14E-02	1.94E-02
ENSG0000081087	OSTM1	61.54	49.20	-1.25	0.258457872	0.467802144	0.008890195	0.015613305
ENSG00000007168	PABPC4 PAFAH1R1	392.13 76.46	329.10 67.84	-1.19	0.382760577 0.634048522	0.543427672	0.009184375	0.016019873
ENSG00000175193	PARL	65.26	74.75	1.15	0.922781184	0.257008543	0.019914119	0.031104201
ENSG00000140694	PARN	41.47	35.49	-1.17	0.700967268	0.045125038	0.01718071	0.027282383
ENSG00000163939 ENSG00000204304	PBRM1 PBX2	20.31	13.98 26.38	-1.45	0.653947947	0.888509402	0.0000337 0.013586411	0.000152547 0.02241781
ENSG00000090097	PCBP4	58.21	68.43	1.18	0.69828323	0.872638775	0.023188882	0.035421582
ENSG0000081154	PCNP	89.59	75.91	-1.18	0.152278375	0.534212859	0.010482616	0.018012591
ENSG00000186642	PDE2A PDGEPP	39.99	29.44	-1.36	0.163806419	0.974462518	0.02754811	0.041110517
ENSG00000164951	PDP1	51.72	34.23	-1.51	0.718321454	0.88884224	0.003183834	0.006490637
ENSG00000121892	PDS5A	22.70	16.03	-1.42	0.877592098	0.608405723	0.000105381	0.000388725
ENSG00000133027	PEMT	21.55	26.82	1.24	0.865062668	0.031493123	0.016547916	0.026459229
ENSG00000125850	PFN1	224.18	190.64	-1.52	0.831505773	0.727215675	2.55E-02	3.85E-02
ENSG0000079739	PGM1	135.32	163.83	1.21	0.237819065	0.379115826	0.00066119	0.001748769
ENSG00000135365	PHF21A	49.00	36.30	-1.35	0.962233306	0.555634602	0.0000946	0.000355442
ENSG00000054148	PHPT1	212.03	257.38	1.20	0.832123728	0.011591	2.97E-03	2.46E-04 6.11E-03
ENSG00000073921	PICALM	151.50	116.47	-1.30	0.924297575	0.012541115	0.002463436	0.005221802
ENSG00000165195	PIGA	16.32	9.92	-1.65	0.416995918	0.010230386	0.027110144	0.040556642
ENSG00000142892 ENSG00000078142	PIGK PIK3C3	34.70	26.28 41.12	-1.32	0.802747521	0.994511248 0.964417267	0.000617	0.000252664
ENSG00000105355	PLIN3	30.23	21.40	-1.41	0.232288666	0.232899322	0.001374952	0.003208442
ENSG00000167676	PLIN4	101.22	78.13	-1.30	0.565344602	0.522858559	0.028537113	0.042361962
ENSG00000102007	PLP2	51.90	30.51	-1.70	0.489597976	0.262806213	0.027461052	0.041005802
ENSG00000128567	PODXL	58.33	46.13	-1.26	0.545701955	0.611849914	0.013586402	0.02241781
ENSG0000005075	POLR2J	49.59	59.03	1.19	0.313084554	0.076740373	0.009311494	0.016195062
ENSG00000168255	POLR2J3	31.63	46.96	1.48	0.064973083	0.184837469	1.37E-02	2.25E-02
ENSG00000121851 ENSG00000132963	POLR3GL POMP	79.75	72.12	-1.11	0.343495283	0.883285032	0.031447616	0.0460246
ENSG00000130714	POMT1	21.30	26.52	1.24	0.355552505	0.137828392	0.002229701	0.004799391
ENSG00000105854	PON2	82.26	70.24	-1.17	0.718891416	0.258213252	0.002100588	0.004570097
ENSG00000109819 ENSG00000143847	PPARGC1A PPFIA4	55.71 17.04	39.07	-1.43	0.753490606	0.635963072	0.007410433	0.013411442
ENSG00000166794	PPIB	229.25	170.27	-1.35	0.581271597	0.416525957	0.003967949	0.007842231
ENSG00000100034	PPM1F	21.17	15.90	-1.33	0.666033511	0.361756411	0.011811956	0.01991627

naDCM-specific DEGs at ENSG	FDR≤0.05 Gene	NF_mean	naDCM_mean	FC	pval_Age	pval_Sex	pval_naDCM_v_NF	FDR_naDCM_v_NF
ENSG00000163644	PPM1K	180.20	119.32	-1.51	0.248125157	0.366170832	0.000293269	0.000903626
ENSG00000077157 ENSG00000125503	PPP1R12B PPP1R12C	262.52	191.25	-1.37	0.597645169	0.965452397	0.011999388	0.020183245
ENSG00000184203	PPP1R2	54.27	45.09	-1.20	0.337837834	0.065060148	0.00070351	0.001841848
ENSG00000104695	PPP2CB	303.27	363.31	1.20	0.906479371	0.836489149	2.16E-02	3.33E-02
ENSG00000120910 ENSG00000167815	PPP3CC PRDX2	39.15 811.89	24.54 933.47	-1.60	0.929229571 0.893230826	0.76278394	0.026536279	0.039808518 0.015016405
ENSG0000085377	PREP	24.32	29.43	1.21	0.034544892	0.734371623	0.000384826	0.001128452
ENSG00000132356	PRKAA1	40.03	28.00	-1.43	0.615219139	0.330456894	0.001228105	0.002926241
ENSG00000072062	PRKACA	368.43	313.96	-1.17	0.505532902	0.288426613	0.006034395	0.011214322
ENSG00000100462	PRMT5	196.97	173.52	-1.14	0.269107828	0.37058843	0.021092707	0.032588668
ENSG00000108294	PSMB3 PSMD12	195.00	237.56	1.22	0.697204336	0.035454619	0.003875627	0.00768165
ENSG00000174915	PTDSS2	21.34	27.25	1.28	0.986982726	0.040285346	0.000363296	0.001076363
ENSG00000106853	PTGR1	55.75	45.20	-1.23	0.625073836	0.033196263	0.005337441	0.010077221
ENSG00000104960 ENSG00000184489	PTOV1 PTP4A3	85.25	106.58	1.25	0.402779771	0.09241448	2.78E-03 0.013449177	0.005758785
ENSG00000072135	PTPN18	15.21	20.36	1.34	0.109205677	0.954732334	0.003835052	0.007616773
ENSG00000175354	PTPN2	32.68	26.65	-1.23	0.922891061	0.244254497	0.000669457	0.001766784
ENSG00000150787 ENSG00000183255	PTS PTTG1IP	24.72	30.89 142.84	-1.14	0.083161486	0.270620438	0.003471203	0.006976889
ENSG00000055917	PUM2	35.51	28.90	-1.23	0.451563757	0.715841902	0.004462238	0.008629482
ENSG00000130202	PVRL2	25.42	31.50	1.24	0.28688587	0.572078909	0.013597375	0.022425993
ENSG00000145337	PYURF	54.10	59.97	1.20	0.141045693	0.084255216	0.021120731	0.032621588
ENSG00000206418	RAB12	63.20	71.27	1.13	0.46007586	0.633862177	0.032677557	0.047580874
ENSG00000138069	RABIA	175.06	158.84	-1.10	0.829488722	0.652652135	0.002559046	0.005381865
ENSG0000029725	RABEP1	38.51	31.46	-1.22	0.257044153	0.205411259	0.005622669	0.010550109
ENSG00000152061	RABGAP1L	69.98	96.85	1.38	0.520357167	0.263583622	0.005462696	0.010273761
ENSG00000113522 ENSG00000010017	RAD50 RANRP9	29.58	24.10	-1.23	0.717850048	0.236424774	0.016349985	0.026185859
ENSG00000236603	RANP1	20.20	25.24	1.25	0.785104028	0.365569793	0.005060387	0.009636778
ENSG00000109756	RAPGEF2	36.15	28.19	-1.28	0.747560699	0.024926641	0.003774959	0.007507543
ENSG00000244462	RBM12	70.26 25.85	85.95 20.00	-1.22	0.918200037	0.160665563	0.014732558	0.023999095
ENSG00000119446	RBM18	44.99	38.16	-1.18	0.285520401	0.72857749	0.001741797	0.003901369
ENSG00000203867	RBM20	60.47	75.73	1.25	0.459697696	0.756208286	4.69E-03	9.03E-03
ENSG00000132819	RBM39	40.55	31.60	-1.28	0.270452798	0.262232749	0.016104976	0.025868884
ENSG00000049449	RCN1	38.68	26.60	-1.45	0.583340172	0.36957664	0.004152623	0.008140952
ENSG00000102760	RGCC	112.78	175.91	1.56	0.163685017	0.118141111	0.030133047	0.044435493
ENSG00000205517 ENSG00000164292	RHOBTB3	27.60 37.92	18.90 28.27	-1.46	0.089269903 0.557303129	0.353593132	0.007619491 0.010603401	0.013727793
ENSG0000058729	RIOK2	38.93	31.00	-1.26	0.926211825	0.138738768	6.27E-03	0.011585812
ENSG00000137824	RMDN3	30.63	25.34	-1.21	0.469306228	0.895657199	0.001658408	0.003747411
ENSG00000239303	RNF105	54.91	77.92	1.42	0.984656932	0.274192569	0.007058574	0.012861702
ENSG0000013561	RNF14	66.55	53.29	-1.25	0.594420726	0.491950386	1.32E-03	3.10E-03
ENSG00000158717	RNF166	28.63	36.19	1.26	0.211061863	0.065819444	0.003997739	0.007894681
ENSG00000181852	RNF41	41.84	35.73	-1.17	0.083182871	0.098442274	7.32E-03	1.33E-02
ENSG00000114125	RNF7	60.75	74.11	1.22	0.275054209	0.059119359	0.002692337	0.005609897
ENSG00000142327	RNPEPL1	48.86	56.83	1.16	0.442019981	0.004034313	0.018442373	0.029055988
ENSG00000187186	RP11-195F19.5	25.39	32.43	1.28	0.272627258	0.701317766	0.001455765	0.003367469
ENSG00000257524	RP11-203J24.9	12.42	6.54	-1.90	0.710533184	0.882821826	0.002586396	0.005425287
ENSG00000174171 ENSG00000242140	RP11-23P13.6 RP11-262M14.2	27.65	38.11	1.38	0.847150127	0.625803879	0.012870655 1.74E-06	0.021451573
ENSG00000260490	RP11-265N6.3	20.78	26.15	1.26	0.668198341	0.324605612	8.52E-03	1.50E-02
ENSG00000224550	RP11-270C12.3	1823.86	2214.73	1.21	0.734689312	0.02986464	0.026962949	0.040361307
ENSG00000260260 ENSG00000233597	RP11-304L19.5 RP11-343R5.1	9.45	15.85 42.13	1.68	0.35413242	0.019858795	0.000136625	0.000480761
ENSG00000213036	RP11-365D23.4	62.61	53.00	-1.18	0.323492759	0.297822441	0.015466897	0.024966362
ENSG00000236739	RP11-370B11.1	32.89	21.00	-1.57	0.50694105	0.294838313	0.001739436	0.003899677
ENSG00000188971 ENSG00000249239	RP11-427H3.3 RP11-428L21.2	27.30	21.19	-1.29	0.731836807	0.440790659	0.005732803	0.010715354
ENSG00000226457	RP11-430L17.1	40.70	49.17	1.21	0.760860565	0.438397101	0.01453699	0.023736255
ENSG00000253993	RP11-451018.1	29.43	22.65	-1.30	0.427221361	0.876948962	0.005200908	0.009866269
ENSG00000214380 ENSG00000237931	RP11-457K10.2 RP11-469F19.1	15.46	10.09	-1.53	0.305625813	0.063504811	0.00000551	0.0000362
ENSG00000261971	RP11-473M20.7	6.06	11.21	1.85	0.958056786	0.167556649	7.92E-08	0.00000155
ENSG00000248648	RP11-485M7.1	357.19	488.38	1.37	0.859087136	0.009851923	0.002970495	0.006108817
ENSG00000251141 ENSG00000218483	RP11-53019.1 RP11-554D15.2	5.13	24.19	2.02	0.765172451	0.027767023	0.000324992	0.0106167
ENSG00000265542	RP11-60A24.3	11.01	5.01	-2.20	0.701077784	0.593921372	0.005808833	0.010840774
ENSG00000259291	RP11-617F23.1	32.28	46.10	1.43	0.336966278	0.390713415	0.000940097	0.002339882
ENSG00000238381 ENSG00000124399	RP11-663P9.2	156.59	188.91	1.90	0.970260499	0.383797387	0.0218638	0.033608931
ENSG00000263647	RP11-927P21.5	12.50	7.16	-1.75	0.953733247	0.152964407	0.001966038	0.004331707
ENSG00000144785	RP11-977G19.10	16.74	10.97	-1.52	0.866807098	0.496690153	0.0121703	0.0204424
ENSG00000253716	RP13-58209.5	14.64	21.24	1.45	0.797205983	0.011161821	7.17E-04	1.87E-03
ENSG00000259613	RP13-608F4.6	8.01	31.46	3.93	0.494561507	0.080631993	0.009676584	0.016752047
ENSG00000181227 ENSG00000235371	кР4-682C21.2 RP4-764D2.1	45.13	53.31 42.74	1.18	0.105287125	0.039601127 0.618369497	0.002949909	0.006074961
ENSG00000213058	RP4-765C7.2	30.78	78.42	2.55	0.738060274	0.04011026	0.003345066	0.006779484
ENSG00000254539	RP4-791M13.3	19.38	25.14	1.30	0.732943919	0.078555924	0.011295365	0.019198563
ENSG0000225377	RP5-875013.6	24.95	19.89	-1.25	0.245045347	0.5559996967	0.0000808	0.0000487
ENSG00000236552	RPL13AP5	83.57	109.55	1.31	0.865131108	0.311091768	0.005578228	0.010474817
ENSG00000105640 ENSG00000198242	RPL18A RPL23A	10.98	16.65	1.52	0.662918717	0.04824658	0.001548249	0.003541356
ENSG00000176343	RPL37AP8	41.40	56.32	1.40	0.904169991	0.104665726	0.002194045	0.008436209
ENSG00000198918	RPL39	86.13	107.26	1.25	0.797348352	0.018547584	0.025141245	0.038092319
ENSG00000148688 ENSG00000230629	RPP30 RPS23P8	25.43	31.34	1.23	0.85054744	0.743493129	0.000123731	0.030985680
ENSG00000185088	RPS27L	276.74	199.72	-1.39	0.766584774	0.048241889	0.0000826	0.000317513
ENSG00000240342	RPS2P5	10.57	18.82	1.78	0.685291822	0.315854607	0.0000485	0.000207316
ENSG00000214203 ENSG00000198208	RPS4XP1 RPS6KL1	18.69	25.03 27.64	1.34	0.749840744	0.675037569	0.000362746	0.001075394
ENSG00000171863	RPS7	24.04	31.39	1.31	0.493942128	0.135305331	0.003707525	0.007399811
ENSG00000183405	RPS7P1	91.47	127.37	1.39	0.532685374	0.070997546	0.001596015	0.003635201
ENSG00000143303	RRNAD1	17.63	43.11 24.14	1.37	0.575917649	0.626083927	4.70E-04	1.33E-03
ENSG0000052749	RRP12	13.23	21.62	1.63	0.495001508	0.379253983	9.00E-04	2.26E-03
ENSG00000175741	RWDD4P2	19.86	14.81	-1.34	0.278591618	0.957034353	0.000180067	0.000608916
ENSG00000153191	SAP18	183.92 303.16	134.89	-1.36	0.975156417	0.055309216	0.007539148	0.013602257
ENSG0000079332	SAR1A	71.23	60.79	-1.17	0.277193926	0.989003875	0.001028381	0.002520858
ENSG00000140386	SCAPER SDAD1	48.85	42.10	-1.16	0.022715964	0.128773832	0.029264803	0.043312979
ENSG00000140612	SEC11A	23.23 124.39	17.73	-1.31	0.920989068	0.82112915	0.016867346	0.026890293
ENSG0000008952	SEC62	60.28	51.07	-1.18	0.850869352	0.58286043	0.026425784	0.039704086
ENSG00000198843 ENSG00000143434	SELT SEMA6C	120.79	157.75	1.31	0.16618745	0.107263556	0.017128903	0.027217916
ENSG00000186522	SEPT10	52.27	40.69	-1.28	0.548972526	0.515781546	0.001172638	0.002818975
ENSG00000138758	SEPT11	27.75	19.80	-1.40	0.614729406	0.221980744	0.016267997	0.026071748
ENSG00000168385 ENSG00000227850	SEPT2 SEPT2P1	266.38	308.39 179.52	1.16	0.171599486 0.054981491	0.836347468	0.023055298 0.007972441	0.035228612
ENSG00000215900	SEPW1P	185.62	238.93	1.29	0.904180454	0.00385872	0.004083524	0.008023907
ENSG00000167565	SERTAD3	25.04	33.19	1.33	0.561702554	0.540260178	0.005211063	0.009877018

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SG00000197233 TMIN33 21.56 14.83 -1.45 0.83060347 0.2205084 0.00043143 (i) SG00000197233 TMIQK 23.07 15.79 -1.37 0.070364608 0.50032877 0.013739045 (i) SG00000149743 TMIQK 23.07 15.79 -1.37 0.070364608 0.50032877 0.013739045 (i) SG00000143743 TMIP1 114.23 140.76 1.23 0.01143702 0.66333383 0.00384894 SG00000143971 TFMI1 9.10 14.77 15.2 0.114462140 0.23349256 0.000123227 (i) SG0000014391 TSPANS 145.27 128.03 -1.13 0.71489237 0.00264944 0.00253178 (i) 0.001635704 SG0000143643 TTC13 15.64 9.21 -1.70 0.19839704 0.0000186 0.0000186 SG0000145454 TTC13 20.64 14.66 -1.38 0.210819787 0.00000186	00019723 TRINA3 21.56 14.83 -1.45 0.830680347 0.22062084 0.00043143 CO 000197233 TRINA 21.56 14.83 -1.45 0.830680347 0.22062084 0.00043143 CO 000105133 TRICK 23.07 16.79 -1.37 0.07036608 0.5032877 0.013789045 CO 000149743 TRPT1 114.23 140.76 1.23 0.011453702 0.665538328 0.003848946 00016382 TRNB1 9.10 14.77 1.62 0.174462146 0.823349256 0.000123217 CO 000164391 TSFNA13 145.27 12.80 1.13 0.71189237 0.040664494 0.00253178 CO 000143643 TSSC4 2.167 2.969 1.37 0.172145944 0.2025888 0.000552704 000143643 TC33 2.06.4 1.496 -1.38 0.7880750 0.000406055 CO 000191273 TC33 2.06.4 1.496 -1.88 0.78907109 <td< td=""></td<>
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Subscience: Immin 114.4.5 140.7b 1.25 0.011433702 0.06533328 0.003848946 SG000016382 TRUBI 9.10 14.77 16.26 0.213462146 0.000123227 (SG0000163931 TSPAN3 145.27 128.03 -1.13 0.718462146 0.0002593178 (0.00014391 TSPAN3 145.27 128.03 -1.13 0.7189237 0.0026808 0.00165704 SG0000143643 TTC13 15.64 9.21 -1.70 0.19837504 0.0000186 0.00000186 SG0000145454 TTC13 2.064 1.46 -1.38 0.78007310 0.310891978 0.00000186	UDDIT#778 INF11 14.4.5 140.76 1.2.3 0.01145/02 0.665358328 0.003848946 000165832 TRUB1 9.10 147.77 162 0.174462146 0.623349256 0.000143221 0.00013227 0 000140391 TSFAN3 145.27 128.03 -1.13 0.71189237 0.40266444 0.00529178 0 000140421 TSGA 2.167 2.669 1.37 0.121245944 0.005159777 0.0000665764 000146483 TCL3 1.564 9.21 -1.70 0.198837564 0.651527777 0.00000186 000114583 TCL3 2.064 1.466 -1.88 0.78997100 0.10891797 0.0000046265 C
Induit FLAG Lac. ULIMPEL49 0.023592/05 0.0001123227 C S600000143811 TSPANS 145.27 128.03 -1.13 0.71189237 0.0005293178 C S600000143811 TSSC4 21.67 29.69 1.37 0.712145944 0.20258308 0.001655704 S6000001384281 TTC13 15.64 9.21 -1.70 0.198837504 0.00000186 S6000001384543 TTC13 15.64 9.21 -1.70 0.198837504 0.00000186 S6000001384543 TTC13 20.64 1.49 -1.37 0.788072100 0.310819378 0.00000186	Display 14,77 1.62 0.1/4*05.49 0.06239172 0.00012321 Display 15,87 128,03 -1.13 0.71182327 0.020604344 0.005293178 0 D00114321 TSSC4 21,67 29,69 1.37 0.172145944 0.2025808 0.001655704 D00114341 TSC4 21,67 2.9,69 1.37 0.172145944 0.2025808 0.001655704 D00114363 TTC33 20,64 1.496 -1.38 0.78070109 0.310891799 0.000406295 D00114263 TTC33 20,64 1.496 -1.38 0.78070109 0.310891799 0.00046295
Control Control <t< td=""><td>Constraint Constraint Constra</td></t<>	Constraint Constra
SG0000143643 TTC13 15.64 9.21 -1.70 0.198837504 0.051527787 0.0000000186 SG00000113638 TTC33 20.64 14.96 -1.38 0.798073109 0.0018091979 0.000000186	000143643 TTC13 15.64 9.21 -1.70 0.198837504 0.051527787 0.000000166 00011368 TTC33 20.64 14.96 -1.38 0.789073109 0.31081979 0.000462455 0
SG00000113638 TTC33 20.64 14.96 -1.38 0.780073100 0.310801070 0.000405305 (000113638 TTC33 20.64 14.96 -1.38 0.789073109 0.310891979 0.000406295 0

naDCM-specific DEGs at FDRs0.05									
ENSG	Gene	NF_mean	naDCM_mean	FC	pval_Age	pval_Sex	pval_naDCM_v_NF	FDR_naDCM_v_NF	
ENSG00000228236	TXNP5	30.92	24.51	-1.26	0.77169539	0.969266624	2.76E-02	0.04112739	
ENSG0000025708	TYMP	13.59	21.82	1.61	0.594497651	0.184534176	0.002067289	0.0045118	
ENSG00000119048	UBE2B	229.66	265.90	1.16	0.813461733	0.764468232	0.015054107	0.024440904	
ENSG00000184787	UBE2G2	97.76	79.83	-1.22	0.798045325	0.175162105	1.43E-04	0.000501635	
ENSG00000185651	UBE2L3	41.23	24.48	-1.68	0.777677473	0.294469837	0.011971626	0.020164487	
ENSG00000189136	UBE2Q2P1	15.15	10.09	-1.50	0.693102958	0.252986829	0.004893016	0.009365584	
ENSG00000198258	UBL5	397.88	478.53	1.20	0.796033929	0.009344128	0.009058065	0.015839381	
ENSG00000135018	UBQLN1	137.06	118.95	-1.15	0.389331161	0.557948603	1.48E-02	2.40E-02	
ENSG00000108312	UBTF	47.34	39.52	-1.20	0.295949518	0.5917404	0.005259557	0.009961158	
ENSG00000151116	UEVLD	16.50	11.35	-1.45	0.910606976	0.445324173	0.0000257	0.000123287	
ENSG00000143222	UFC1	92.41	79.78	-1.16	0.820260407	0.115478571	0.028205386	0.041962425	
ENSG0000083290	ULK2	27.29	19.57	-1.39	0.294736089	0.049220807	0.001256697	0.002973937	
ENSG00000109103	UNC119	35.79	25.12	-1.42	0.464716633	0.233730941	0.00013551	0.000477182	
ENSG0000005007	UPF1	15.25	20.90	1.37	0.931362476	0.289280305	0.0000286	0.000133881	
ENSG00000151461	UPF2	17.82	12.37	-1.44	0.954356661	0.92907296	0.00000156	0.00000245	
ENSG0000010256	UQCRC1	1500.95	1748.31	1.16	0.234609735	0.017102293	0.016615775	0.026550248	
ENSG00000173660	UQCRH	404.16	523.88	1.30	0.724840417	0.131079433	0.0008175	0.002084969	
ENSG00000138768	USO1	114.57	97.04	-1.18	0.745724664	0.627596403	1.92E-02	3.01E-02	
ENSG0000058056	USP13	47.32	39.91	-1.19	0.279840114	0.904428727	0.008343277	0.014797281	
ENSG00000101557	USP14	34.22	28.70	-1.19	0.810314969	0.405198778	1.69E-02	2.70E-02	
ENSG00000155313	USP25	59.08	34.12	-1.73	0.718809379	0.463352095	0.015221477	0.024671392	
ENSG00000115464	USP34	87.51	76.48	-1.14	0.476532723	0.168413383	0.015686369	0.025281449	
ENSG00000137411	VARS2	13.77	20.59	1.50	0.619434193	0.252651391	0.000122604	0.00043906	
ENSG00000165280	VCP	339.14	410.59	1.21	0.890641464	0.040994971	0.000276544	0.000863043	
ENSG0000073905	VDAC1P1	35.76	21.43	-1.67	0.859403331	0.619322682	0.013483243	0.022277859	
ENSG00000165637	VDAC2	53.02	75.34	1.42	0.625764052	0.04078447	0.0000972	0.000363929	
ENSG00000271198	VDAC3P1	20.59	25.96	1.26	0.417526163	0.150364294	0.0000505	0.000213213	
ENSG00000173511	VEGFB	190.14	229.56	1.21	0.043355218	0.333922059	0.002060875	0.004501848	
ENSG00000131871	VIMP	5943.35	4541.23	-1.31	0.724590314	0.638163607	0.010191489	0.017568289	
ENSG00000147852	VLDLR	46.64	58.19	1.25	0.22291394	0.61919334	0.007778505	0.013945944	
ENSG00000132612	VPS4A	45.59	51.88	1.14	0.257154053	0.817082151	0.028062126	0.041762086	
ENSG0000075399	VPS9D1	56.57	33.35	-1.70	0.230457527	0.442194836	0.000769748	0.001984022	
ENSG00000105053	VRK3	29.78	24.65	-1.21	0.172419484	0.873970109	0.003423619	0.006893339	
ENSG00000163625	WDFY3	16.14	9.57	-1.69	0.320861141	0.803231667	0.00000275	0.0000217	
ENSG0000065268	WDR18	12.72	20.54	1.62	0.100395618	0.716986289	0.0000238	0.0000196	
ENSG00000103091	WDR59	61.78	52.26	-1.18	0.992012357	0.959738342	0.021616266	0.033262157	
ENSG00000165238	WNK2	119.83	101.48	-1.18	0.682313994	0.30290654	0.032369152	0.047216763	
ENSG0000018408	WWTR1	37.87	27.58	-1.37	0.995132464	0.731807918	0.009246586	0.016111023	
ENSG00000168334	XIRP1	322.83	545.36	1.69	0.892110904	0.109875355	0.033504008	0.048594821	
ENSG00000163092	XIRP2	105.19	183.52	1.74	0.594696717	0.71440493	0.00466597	0.00899482	
ENSG0000093100	XXbac-B461K10.4	9.88	16.54	1.67	0.109594557	0.646243587	1.01E-08	0.00000395	
ENSG00000200090	Y_RNA	204.01	133.54	-1.53	0.83259962	0.44910184	0.012102947	0.020350385	
ENSG0000058799	YIPF1	22.26	17.23	-1.29	0.06204143	0.38038305	0.0000294	0.000136119	
ENSG00000170027	YWHAG	152.23	182.20	1.20	0.654934295	0.699621932	0.01075591	0.018394845	
ENSG0000164924	YWHAZ	85.52	74.05	-1.15	0.121141131	0.651720479	0.020008935	0.031232205	
ENSG00000158545	ZC3H18	14.28	19.38	1.36	0.527792203	0.6786417	1.79E-04	6.06E-04	
ENSG00000144161	ZC3H8	21.05	15.09	-1.40	0.539244995	0.806885764	0.0000533	0.000223253	
ENSG0000206077	ZDHHC11B	30.30	21.32	-1.42	0.121113039	0.000893836	0.020825693	0.032247948	
ENSG00000188706	ZDHHC9	16.50	11.02	-1.50	0.145874926	0.027716779	0.000196952	0.000651944	
ENSG0000169554	ZEB2	42.25	30.88	-1.37	0.205190648	0.723342901	0.000638329	0.001697551	
ENSG00000160445	ZER1	45.91	40.03	-1.15	0.739302436	0.502381976	1.08E-02	1.84E-02	
ENSG0000056097	ZFR	68.72	57.91	-1.19	0.370408744	0.149457072	0.002412352	0.005133385	
ENSG0000015171	ZMYND11	58.80	46.26	-1.27	0.324750402	0.140164561	0.004121788	0.008087032	
ENSG00000101040	ZIMYND8	31.54	19.41	-1.62	0.504333136	0.526140928	0.005406581	0.010187542	
ENSG0000103994	2NF106	285.38	231.33	-1.23	0.17072967	0.936235857	0.008106985	0.014452099	
ENSG00000163848	ZNF148	19.13	13.88	-1.38	0.881160699	0.822845427	0.012291465	0.020631646	
ENSG00000167380	ZNF226	18.13	23.30	1.29	0.832342077	0.037470823	0.0000721	0.000285893	
ENSG0000257267	ZINF271	22.77	17.45	-1.30	0.667436498	0.575666761	0.0000278	0.000130957	
ENSG00000171606	ZNF274	13.58	19.24	1.42	0.767618746	U.552154455	0.0000258	0.000123392	
ENSG00000186918	ZNF395	21.37	15.67	-1.36	0.977181721	0.226016602	0.000882755	0.00221762	
ENSG0000133250	2NF414	26.90	32.62	1.21	0.856100753	0.440767603	0.020153771	0.031438071	
ENSG00000170954	ZNF415	34.00	26.40	-1.29	0.242075015	U.988967995	0.000307849	0.000937839	
ENSG00000167685	ZNF444	8.93	14.02	1.57	0.055807873	0.202629446	0.00000675	0.0000424	
ENSG0000065029	ZINF76	33.38	38.74	1.16	0.171083075	0.667763474	0.017304175	0.027442545	