Supplemental Material

METHODS IN DETAIL

Clinical evaluation of patients

We performed transcriptomic analysis of heart tissue in matched cohorts of patients with IDCM (n=32) and myocarditis (n=16) selected from a biorepository containing samples from patients with new onset heart failure (HF; n=350). Patients underwent EMB as part of a comprehensive diagnostic evaluation of heart dysfunction that included history and physical exam, right-heart cardiac catheterization and echocardiography. All patients with history suggestive for ischemic heart disease or at least two standard risk factors for atherosclerosis were further evaluated with coronary angiography. Blood tests were performed for cardiac enzymes, thyroid-function and antinuclear antibodies.

Four to six biopsy specimens were obtained from each patient and examined by an experienced cardiac pathologist. In addition to standard staining, Congo red was used to identify amyloidosis and Prussian blue if hemochromatosis was suspected. If the diagnosis was unclear, additional special antibody stains were performed, such as immunofluorescence for IgG, IgM, IgA, C1q, C3d, C4d, fibrinogen, stains for AFB, fungi, elastosis, glycogen or iron accumulation.

Myocarditis was defined according to Dallas criteria[1, 2], without additional tests for presence of viral RNA, such as PCR.

After this extensive evaluation, idiopathic dilated cardiomyopathy (IDCM) was a diagnosis of exclusion. In addition to diagnostic biopsies, one entirely independent sample was obtained and flash frozen in liquid nitrogen for microarray analysis. All participants gave written informed consent for collection of samples and clinical data. Right ventricular septal

EMBs were obtained by advancing a disposable bioptome (Argon; Jawz) via the right jugular vein under fluoroscopic guidance.

Selection of patients

A total of 115 samples were used for microarray analysis, of which 81 were newly processed and 34 were obtained from a previously published study[3]. Forty-eight samples were selected for our first transcriptomic study. These included samples from patients with myocarditis (n=16) defined by the Dallas criteria[1, 2] and idiopathic dilated cardiomyopathy (IDCM, n=32) selected in a case-control fashion based on age, gender, functional parameters from echocardiography and right heart catheterization, and medication usage. In addition, we identified samples from 6 patients with myocarditis with divergent baseline criteria, from which we independently tested the diagnostic accuracy of the biomarker. Finally, the molecular signature was tested in secondary cardiomyopathies, such as stress induced cardiomyopathy (n=4), sarcoidosis (n=9), peripartum cardiomyopathy (n=6), arrhythmogenic right ventricular dysplasia (ARVD, n=3), giant cell myocarditis (n=3) and systemic lupus erythematosus (n=2). Data from a previous study[3] was used as an additional validation set, containing samples from normal heart (n=11), ischemic cardiomyopathy (n=8) and IDCM (n=15). These samples were analyzed with a prototype microarray, the Affyetrix U133A Gene Chip to evaluate for intraplatform reproducibility.

RNA extraction and microarray hybridization

Total RNA was extracted from biopsies as previously described[4, 5]. Quality control of integrity of RNA was performed with the 2100 Bioanalyzer (Agilent). MIAME guidelines were followed for all steps of the procedure. The extracted RNA (average 568 ± 88ng; Standard Error of the Mean (SEM)) was preprocessed with the Ovation Biotin RNA Amplification and Labeling System (NuGen, Cat. No. 2300-12) for subsequent hybridization with the Human Genome U133 Plus 2.0 Array from Affymetrix without additional amplification step.

Microarray data was normalized with Robust Multiarray Average (RMA) and analyzed with Significance Analysis of Microarrays (SAM) to identify differentially expressed genes in patients with myocarditis (n=16) vs IDCM (n=32). The resulting gene list was further processed with Meta Core pathway analysis incorporated in GeneGo (bioinformatics software, St. Joseph, MI). Organ- and species-specific pre-filtering was performed before network analysis, in order to extract solely pathways that are truly interrelated in the human heart. Each network was provided with a p-value, using the basic formula for hypergeometric distribution. This formula provides a value that represents the probability for a particular mapping of an experiment to a map (or network/process) to arise by chance, considering the numbers of genes in the experiment vs the number of genes in the map within the "full set" of all genes on maps. In addition, a z-score was calculated for each network, which reflects the saturation with genes from the experiment. A high z-score indicates a network that contains a large amount of genes from the experiment.

In order to determine the minimum number of differentially expressed genes required for detection of patients with myocarditis compared to IDCM, we used Prediction Analysis of Microarrays (PAM) to obtain a biomarker based upon a nearest shrunken centroid. The classifier was developed from a train set (n=33), consisting of 2/3 of data, and applied to an independent test set (n=15) containing 1/3 of data.

After developing the transcriptomic biomarker with a case-control design, we tested its performance in unmatched samples, to test its generalizability independent of age, gender, heart function or drug therapy. To test this hypothesis, we used samples from patients with myocarditis (n=6), who presented with higher ejection fractions (65± 4.7%).

In order to test, if previously established classification algorithms can further reduce the number of genes necessary for accurate prediction, we applied misclassification-penalized posteriors classification (MiPP), which successfully predicts rejection in liver transplant recipients[6]. The MiPP package is an application in the R environment, which employs the libraries MASS for lda/qda (linear/quadratic discriminant analysis and e1071 for SVM (support vector machine). This software sequentially adds genes to a classification model based upon the Misclassication-Penalized Posteriors principle, which takes into account the likelihood that a sample belongs to a given class by using posterior probability of correct classification.

First we used MiPP, to test several different classification rules, to further reduce the novel molecular signature, consisting of 62 genes. We subsequently applied support vector machine with radial basis function (SVM-rbf) and lineal function (SVM-lin), quadratic discriminant analysis (qda), linear discriminant analysis (lda) and a combination of lda, qda and svm-rbf. When support vector machine algorithms are used for classification, the input data is plotted as two vectors in an n-dimensional space and a virtual hyperplane is created that best separates the two phenotypes. This hyperplane is then used to classify samples with unknown phenotypes. Linear discriminant analysis uses a linear combination of features, which best separate two or more classes. Quadratic discriminant analysis is closely related to lda, however there is no assumption that the covariance of each of the classes is identical. Models were developed based upon 5-fold cross validation in a train set (2/3 of data) and subsequent validation in an independent test set (1/3 of data).

In order to evaluate, if distinct models are generated from additional random splits, we performed 50 random divisions to develop individual classification models, which were then validated in 200 independent splits. As an additional confirmatory test, we performed principal components analysis (PCA) to illustrate how well patients with myocarditis can be separated from patients with IDCM based on the original 62 genes molecular signature, and to test if genes that we identified by MiPP analysis to be the most robust classifiers, would also be discovered to be important when PCA was applied. PCA is a method that depicts the importance of genes for phenotypic classification by means of illustration through Eigen vectors towards a phenotype, in which the gene is overexpressed. If genes are less robust as classifiers, the corresponding vector directs towards the center with close to vertical direction. Important classifiers are depicted with vectors having endpoints far from the center.

Validation of microarrays with quantitative realtime RT-PCR

Validation with realtime RT-PCR was performed in a randomly selected subset of patients (IDCM: n=10, myocarditis: n=10), with triplicates replication. First-strand cDNA was synthesized with a High-Capacity cDNA Reverse-Transcription Kit (Applied Biosystems Inc., CA, USA) from 100ng total RNA, which was amplified with MessageAmp II Amplification Kit (Applied Biosystems Inc., CA, USA). TaqMan probes, labeled with 6-carboxyfluorescein (FAM) were designed for a subset of 13 differentially expressed genes identified by microarray analysis: CD14, FCER1G, TLR1, TLR2, TLR7, ITGB2, SIGLEC 1, ADCY7, MEGF9, PTPLAD1, SWAP70, MSI1, and LCE1E, as well as the housekeeping gene 18S RNA. Data were analyzed by the threshold cycle (Ct) relative-quantification method (error bars = mean standard error). Finally, this molecular signature consisting of 13 genes was illustrated as a heatmap by an unsupervised hierarchical clustering approach in R based on Euclidean distance.

Reference List

(1) Aretz HT. Myocarditis: the Dallas criteria. *Hum Pathol* 1987;18:619-24.

(2) Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. *Circulation* 2006;113:593-5.

(3) Kittleson MM, Ye SQ, Irizarry RA, Minhas KM, Edness G, Conte JV, Parmigiani G, Miller LW, Chen Y, Hall JL, Garcia JG, and Hare JM. Identification of a gene expression profile that differentiates between ischemic and nonischemic cardiomyopathy. *Circulation* 2004;110:3444-51.

(4) Heidecker B, Kasper EK, Wittstein IS, Champion HC, Breton E, Russell SD, Kittleson MM, Baughman KL, and Hare JM. Transcriptomic biomarkers for individual risk assessment in new-onset heart failure. *Circulation* 2008;118:238-46.

(5) Heidecker B, Lamirault G, Kasper EK, Wittstein IS, Champion HC, Breton E, Russell SD, Hall JL, Kittleson MM, Baughman KL, and Hare JM. The gene expression profile of patients with new-onset heart failure reveals important gender-specific differences. *Eur Heart J* 2009. 31: 1188-96

(6) Martinez-Llordella M, Lozano JJ, Puig-Pey I, Orlando G, Tisone G, Lerut J, Benitez C, Pons JA, Parrilla P, Ramirez P, Brugera M, Rimola A, Sanchez-Fueyo A. Using transcriptional profiling to develop a diagnostic test of operational tolerance in liver transplant recipients. *J Clin Invest* 2008; 118:2845-57.

Supplemental table 1: Overexpressed genes in patients with myocarditis vs idiopathic dilated cardiomyopathy (q<5%, FC>2) and their biological function

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
1552302_at	FLJ77644,TMEM106A	similar to transmembrane protein 106A	NA
1552553_a_at	NLRC4	NLR family, CARD domain containing 4	apoptosis, caspase activation, defense response to bacterium ,interleukin-1 beta secretion
1552584_at	IL12RB1	interleukin 12 receptor, beta 1	cell surface receptor linked signal transduction, positive regulation of cell proliferation
1554899_s_at	FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	positive regulation hypersensitivity, phagocytosis, engulfment, immunoglobulin mediated immune response, positive regulation of interleukin-6 and 10 and TNF production, positive regulation of mast cell cytokine production
1555349_a_at	ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	apoptosis, inflammatory response, cell adhesion , leukocyte adhesion, integrin-mediated signaling pathway
1559584_a_at	C16orf54, hCG_1644884	chromosome 16 open reading frame 54	NA
1563245_at	MGST1	microsomal glutathione S-transferase 1	glutathione metabolic process
1565162_s_at	ANXA2	annexin A2	skeletal development
1568126_at	SPP1	Secreted phosphoprotein 1	ossification, cell adhesion
1568574_x_at	IFI30	interferon, gamma-inducible protein 30	oxidation reduction
201422_at	CTSC	cathepsin C	proteolysis, immune response
201487_at	LAPTM5	lysosomal multispanning membrane protein 5	transport
201721_s_at	CD14	CD14 molecule	response to molecule of bacterial origin , phagocytosis, apoptosis, inflammatory response
201743_at	CAPG	capping protein (actin filament), gelsolin-like	protein complex assembly, cell projection biogenesis
201850_at	PLTP	phospholipid transfer protein	lipid metabolic process, transport
202075_s_at	VAMP8	vesicle-associated membrane protein 8 (endobrevin)	vesicle-mediated transport

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
202546_at	LYN	v-yes-1 Yamaguchi sarcoma viral related oncogene homolog	protein amino acid phosphorylation, intracellular signaling cascade, positive regulation of cell proliferation, response to hormone stimulus, erythrocyte differentiation, interspecies interaction between organisms
202625_at	ITGB2	integrin, beta 2 (complement component 3 receptor 3 and 4 subunit)	apoptosis, inflammatory response, cell adhesion, leukocyte adhesion, integrin-mediated signaling pathway, neutrophil chemotaxis
202803_s_at	PCK2	phosphoenolpyruvate carboxykinase 2 (mitochondrial)	gluconeogenesis
202847_at	CSF1R	colony stimulating factor 1 receptor	protein amino acid phosphorylation, signal transduction, transmembrane receptor protein tyrosine kinase signaling pathway, multicellular organismal development, cell proliferation
203104_at	RASSF2	Ras association (RalGDS/AF-6) domain family member 2	cell cycle, signal transduction, negative regulation of cell cycle
203185_at	RPS6KA1	ribosomal protein S6 kinase, 90kDa, polypeptide 1	protein amino acid phosphorylation, signal transduction, protein kinase cascade
203379_at	CD53	CD53 molecule	signal transduction
203416_at	PLEK	pleckstrin	intracellular signaling cascade
203471_s_at	SEMA4D	sema domain, immunoglobulin domain (Ig), transmembrane domain (TM) and short cytoplasmic domain, (semaphorin) 4D	NA
203528_at	CD163	CD163 molecule	acute-phase response, inflammatory response
203645_s_at	PLA2G2A	phospholipase A2, group IIA (platelets, synovial fluid)	phospholipid metabolic process , lipid catabolic process
203649_s_at	CXCL9	chemokine (C-X-C motif) ligand 9	chemotaxis, defense response, inflammatory response, cellular defense response, G-protein coupled receptor protein signaling pathway
203915_at	CYBB	cytochrome b-245, beta polypeptide	superoxide metabolic process, ion transport, inflammatory response, superoxide release, innate immune response
203923_s_at	IRF8	interferon regulatory factor 8	transcription, immune response, myeloid cell differentiation

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
204057_at	CD48	CD48 molecule	defense response
204118_at	TYROBP	TYRO protein tyrosine kinase binding protein	cellular defense response, intracellular signaling cascade
204122_at	GLIPR1	GLI pathogenesis-related 1	NA
204222_s_at	FCER1G	Fc fragment of IgE, high affinity I, receptor for; gamma polypeptide	positive regulation of hypersensitivity, positive regulation of interleukin-10 and 6 and tumor necrosis factor production, mast cell activation
204232_at	PLEKHO2	pleckstrin homology domain containing, family O member 2	NA
204436_at	CD44	CD44 molecule	cell adhesion, cell-matrix adhesion
204490_s_at	SLC7A7	solute carrier family 7 (cationic amino acid transporter, y+ system), member 7	amino acid metabolic process, transport
204588_s_at	STC1	stanniocalcin 1	cellular calcium ion homeostasis, cell surface receptor linked signal transduction
204595_s_at	CD52	CD52 molecule	elevation of cytosolic calcium ion concentration, respiratory burst
204661_at	VSIG4	V-set and immunoglobulin domain containing 4	negative regulation of interleukin-2 production, negative regulation of T cell proliferation
204787_at	IL10RA	interleukin 10 receptor, alpha	NA
204912_at	SASH3	SAM and SH3 domain containing 3	NA
204923_at	TLR2	toll-like receptor 2	response to molecule of fungal origin, MyD88-dependent toll-like receptor signaling pathway, induction of apoptosis
204924_at	CSTA	cystatin A (stefin A)	peptide cross-linking
204971_at	CCR1	chemokine (C-C motif) receptor 1	chemotaxis, G-protein coupled receptor protein signaling pathway, response to wounding
205098_at 205269_at	LCP2	lymphocyte cytosolic protein 2 (SH2 domain containing leukocyte protein of 76kDa)	immune response, transmembrane receptor protein tyrosine kinase signaling pathway, mast cell activation, cytokine secretion
205270_s_at	GZMA	granzyme A (granzyme 1, cytotoxic T-lymphocyte-associated serine esterase 3)	proteolysis, apoptosis, cleavage of lamin, immune response , cytolysis
205488_at	CD86	CD86 molecule	immune response, positive regulation of cell proliferation, T cell activation

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
205685_at	CD8A	CD8a molecule	immune response, transmembrane receptor protein tyrosine kinase signaling pathway, T cell activation
205758_at	ITGAM	integrin, alpha M (complement component 3 receptor 3 subunit)	cell adhesion, integrin-mediated signaling pathway
205786_s_at	LY86	lymphocyte antigen 86	apoptosis, humoral immune response, cell proliferation
205859_at	PTPN6	protein tyrosine phosphatase, non-receptor type 6	protein amino acid dephosphorylation, apoptosis, response to wounding
206687_s_at	CCR2, FLJ78302	chemokine (C-C motif) receptor 2	chemotaxis, inflammatory response, cellular defense response, JAK-STAT cascade, interspecies interaction between organisms
206978_at	PTPRC	protein tyrosine phosphatase, receptor type, C	negative regulation of T cell mediated cytotoxicity, positive regulation of B cell proliferation, defense response to virus
207238_s_at	SYK	spleen tyrosine kinase	serotonin secretion, leukocyte adhesion neutrophil chemotaxis, interspecies interaction between organisms , positive regulation of interleukin-3 biosynthetic process, positive regulation of B cell differentiation, positive regulation of gamma-delta T cell differentiation, positive regulation of alpha-beta T cell differentiation
207540_s_at	LILRB2	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 2	immune response, cellular defense
207697_x_at	LCP1	lymphocyte cytosolic protein 1 (L-plastin)	actin filament bundle formation
208885_at	CORO1A	coronin, actin binding protein, 1A	phagocytosis
209083_at	HLA-DQB1	major histocompatibility complex, class II, DQ beta 1	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II, immune response
209480_at	DLK1	delta-like 1 homolog (Drosophila)	multicellular organismal development
209560_s_at	CD44	CD44 molecule (Indian blood group)	cell adhesion, cell-matrix adhesion
209835_x_at	SPP1	secreted phosphoprotein 1	ossification, cell adhesion

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
209875_s_at	AIF1	allograft inflammatory factor 1	response to stress, inflammatory response, cell cycle arrest, negative regulation of cell proliferation
209901_x_at	C3AR1	complement component 3a receptor 1	chemotaxis, inflammatory response, G-protein coupled receptor protein signaling pathway
209906_at	CD300A	CD300a molecule	immune response, cell adhesion
209933_s_at	NCF2	neutrophil cytosolic factor 2	cellular defense response
209949_at	LILRB2	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 2	immune response, cellular defense response, cell surface receptor linked signal transduction
210146_x_at	TLR1	toll-like receptor 1	inflammatory response, macrophage activation, positive regulation of tumor necrosis factor biosynthetic process, positive regulation of interleukin-6 biosynthetic process
210176_at	LAIR1	leukocyte-associated immunoglobulin-like receptor 1	immune response
210644_s_at	LILRB1	leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1	immune response, response to virus
211336_x_at	TRBC1, TRBC2, TRBV19	T cell receptor beta constant 1, T cell receptor beta constant 2, T cell receptor beta variable 19	immune response
211796_s_at	CD44	CD44 molecule	cell adhesion, cell-matrix adhesion
212063_at	PTPRC	protein tyrosine phosphatase, receptor type, C	negative regulation of T cell mediated cytotoxicity, cell surface receptor linked signal transduction, T cell differentiation, positive regulation of B cell proliferation, defense response to virus
212587_s_at			
212588_at	HLA-DQA1, HLA-DQA2	major histocompatibility complex, class II, DQ alpha 1,major histocompatibility complex, class II, DQ alpha 2	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II
212671_s_at	hCG_1998957, HLA-DQB1/B2, HLA-DRB1/2/3/4/5	major histocompatibility complex, class II, DQ beta 1 and 2; DR beta1,2,3,4 and 5	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
212999_x_at	AIF1	allograft inflammatory factor 1	response to stress, inflammatory response, cell cycle arrest
213095_x_at	DOCK2	dedicator of cytokinesis 2	actin cytoskeleton organization and biogenesis, lymphocyte chemotaxis
213160_at	HSPA6	heat shock 70kDa protein 6 (HSP70B')	response to stress
213418_at	RNASE6	ribonuclease, RNase A family, k6	RNA catabolic process, defense response
213566_at	RAC2	ras-related C3 botulinum toxin substrate 2 (rho family, small GTP binding protein Rac2)	chemotaxis, positive regulation of cell proliferation, regulation of respiratory burst
213603_s_at	MYO1F	myosin IF	NA
213733_at	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	antigen processing and presentation of peptide or polysaccharide antigen via MHC class II
213831_at	LYZ	lysozyme (renal amyloidosis)	tRNA aminoacylation for protein translation, inflammatory response, defense response to bacterium
213975_s_at	LOC648998	similar to Neutrophil cytosol factor 1 (NCF-1) (Neutrophil NADPH oxidase factor 1) (47 kDa neutrophil oxidase factor) (p47-phox) (NCF-47K) (47 kDa autosomal chronic granulomatous disease protein) (NOXO2)	NA
214084_x_at	CD163	CD163 molecule	acute-phase response, inflammatory response
215049_x_at	AIF1	allograft inflammatory factor 1	response to stress, inflammatory response, cell cycle arrest, negative regulation of cell proliferation
215051_x_at	ADA	adenosine deaminase	response to hypoxia, adenosine catabolic process, T cell activation
216705_s_at	FCGR1A, FCGR1C	Fc fragment of IgG, high affinity Ia, Ic, receptor (CD64)	phagocytosis, engulfment
216950_s_at	GLUL	glutamate-ammonia ligase (glutamine synthetase)	glutamine biosynthetic process, nitrogen compound metabolic process
217202_s_at	SNX10	sorting nexin 10	transport, cell communication
218404_at	MAFB	v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	transcription
218559_s_at	CCDC109B	coiled-coil domain containing 109B	NA
218802_at	BIN2	bridging integrator 2	NA

Probe Set ID	**Gene Symbol**	**Gene Title**	**GO biological process term**
219191_s_at	DOCK10	dedicator of cytokinesis 10	NA
219279_at	SLAMF8	SLAM family member 8	NA
219386_s_at	SIGLEC1	sialic acid binding Ig-like lectin 1, sialoadhesin	inflammatory response, cell adhesion, cell-matrix adhesion, cell-cell adhesion
219519_s_at	1-Mar	membrane-associated ring finger (C3HC4) 1	NA
219574_at	MS4A4A	membrane-spanning 4-domains, subfamily A, member 4	signal transduction
219607_s_at	MS4A6A		
219666_at	GAL3ST4	galactose-3-O-sulfotransferase 4	sulfur metabolic process, cell-cell signaling, biosynthetic process
219815_at	PSTPIP2	proline-serine-threonine phosphatase interacting protein 2	NA
219938_s_at	TLR7	toll-like receptor 7	inflammatory response, positive regulation of interferon-gamma biosynthetic process, positive regulation of interleukin-8 biosynthetic process, defense response to virus
220146_at	COTL1	coactosin-like 1 (Dictyostelium)	carbohydrate metabolic process
221059_s_at	NPL	N-acetylneuraminate pyruvate lyase (dihydrodipicolinate synthase)	carbohydrate metabolic process
221210_s_at	SH3BGRL3	SH3 domain binding glutamic acid-rich protein like 3	NA
221269_s_at	PYCARD	PYD and CARD domain containing	proteolysis, apoptosis, tumor necrosis factor-mediated signaling pathway, positive regulation of interleukin-1 beta secretion
221666_s_at	CLEC7A	C-type lectin domain family 7, member A	phagocytosis, recognition, inflammatory response, T cell activation, defense response to protozoan
221698_s_at	OBFC2A	oligonucleotide/oligosaccharide-binding fold containing 2A	NA
222872_x_at	CENTA2	centaurin, alpha 2	heart development
222876_s_at	MS4A7	membrane-spanning 4-domains, subfamily A, member 7	signal transduction
223343_at			
223344_s_at	MS4A6A	membrane-spanning 4-domains, subfamily A,	signal transduction

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
		member 6A	
223922_x_at			
224356_x_at	MS4A4A	membrane-spanning 4-domains, subfamily A, member 4	signal transduction
224357_s_at	COTL1	coactosin-like 1 (Dictyostelium)	NA
224583_at	BCAT1	branched chain aminotransferase 1, cytosolic	G1/S transition of mitotic cell cycle, metabolic process, cell proliferation, amino acid biosynthetic process
225285_at	C1QC	complement component 1, q subcomponent, C chain	phosphate transport, complement activation, classical pathway
225353_s_at	CTSC	cathepsin C	proteolysis, immune response
225646_at	CTSC		
225647_s_at	BCAT1	branched chain aminotransferase 1, cytosolic	G1/S transition of mitotic cell cycle, metabolic process, cell proliferation, amino acid biosynthetic process
226517_at	MPEG1	macrophage expressed gene 1	NA
226818_at			
226841_at	FYB	FYN binding protein (FYB-120/130)	carbohydrate metabolic process, protein amino acid phosphorylation, immune response, signal transduction
227266_s_at	RILPL2	Rab interacting lysosomal protein-like 2	NA
227983_at	OSR1	odd-skipped related 1 (Drosophila)	heart development
228399_at	C1orf162	chromosome 1 open reading frame 162	NA
228532_at	LILRB1	Leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 1	immune response, response to virus
230741_at	MRO	maestro	NA
231358_at	CTSS	cathepsin S	proteolysis, immune response
232617_at	DOCK8	dedicator of cytokinesis 8	NA
232843_s_at	OBFC2A	oligonucleotide/oligosaccharide-binding fold containing 2A	NA
233085_s_at	PARVG	parvin, gamma	cell adhesion, cell-matrix adhesion
234987_at	CPM	carboxypeptidase M	proteolysis, anatomical structure morphogenesis
235019_at	HAVCR2	hepatitis A virus cellular receptor 2	NA

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
235458_at	CCL18	chemokine (C-C motif) ligand 18 (pulmonary and activation-regulated)	chemotaxis, inflammatory response
32128_at	CD52	CD52 molecule	elevation of cytosolic calcium ion concentration, respiratory burst
34210_at	MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	response to stress, regulation of transcription
36711_at	SIGLEC1	sialic acid binding Ig-like lectin 1, sialoadhesin	inflammatory response, cell adhesion, cell-matrix adhesion

Supplemental table 2: Downregulated genes in patients with myocarditis vs idiopathic dilated cardiomyopathy (q<5%, FC>2) and their biological function

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
1552411_at	DEFB106A /B	defensin, beta 106A	defense response, defense response to bacterium
1556721_at	FLJ33706	hypothetical protein FLJ33706	NA
1559224_at	LCE1E	late cornified envelope 1E	keratinization
1562256_at	NLRP1	NLR family, pyrin domain containing 1	induction of apoptosis, caspase activation, defense response
1562257_x_at			
1562785_at	HERC6	Hect domain and RLD 6	protein modification process
1564281_at	LOC285708	hypothetical protein LOC285708	nucleotide and nucleic acid metabolic process, nervous system development
1564362_x_at	ZNF843	zinc finger protein 843	NA
1569568_at	NA	NA	NA
1569569_x_at	NA	NA	NA
213609_s_at	SEZ6L	seizure related 6 homolog (mouse)-like	NA
213791_at	PENK	proenkephalin	behavioral fear response, signal transduction, neuropeptide signaling pathway, sensory perception of pain
224209_s_at	GDA	guanine deaminase	nucleotide and nucleic acid metabolic process, nervous system development

Probe Set ID	Gene Symbol	Gene Title	GO biological process term
231628_s_at	NA	NA	NA
243909_x_at	GUSBL2	glucuronidase, beta-like 2	NA
244891_x_at	NA	NA	NA

Supplemental table 3: Overexpressed pathways in patients with myocarditis vs idiopathic dilated cardiomyopathy

Network	GO Processes	Total nodes	Root nodes	p-Value	zScore
MafB, MafF, MHC class II, CD44, BCAT1 (Homo sapiens)	system development (66.0%; 2.241e-13), response to stimulus (74.5%; 1.751e-12), multicellular organismal development (68.1%; 7.914e-12), organ development (55.3%; 2.289e-11), positive regulation of cellular process (51.1%; 9.353e-11)	50	10	2.43E-17	29.34
CCR2, BCAT1, ADA, Annexin II, Pleckstrin (Homo sapiens)	response to external stimulus (53.8%; 2.384e-09), intracellular signaling cascade (57.7%; 1.087e-08), behavior (38.5%; 4.275e-08), response to chemical stimulus (53.8%; 8.258e-08), MAPKKK cascade (26.9%; 1.123e-07)	50	7	1.97E-12	24.29
p47-phox, CCR2, p67-phox, Pleckstrin, IL-12 receptor (Homo sapiens)	protein kinase cascade (48.8%; 2.208e-20), intracellular signaling cascade (68.3%; 6.669e-18), response to chemical stimulus (61.0%; 1.232e-14), regulation of cell migration (29.3%; 3.132e-14), MAPKKK cascade (31.7%; 3.194e-14)	50	7	1.53E-11	21.11
C1q, CD44, CD14, SLAP-130(ADAP), alpha-4/beta-1 integrin (Homo sapiens)	cell-matrix adhesion (30.4%; 2.499e-10), cell-substrate adhesion (30.4%; 4.574e-10), positive regulation of biological process (69.6%; 1.047e-09), cell adhesion (47.8%; 2.037e-08), biological adhesion (47.8%; 2.037e-08)	24	4	2.85E-07	16.72
Plastin, IRT-1 (Homo sapiens)	actin filament bundle formation (100.0%; 1.902e-05), actin filament organization (100.0%; 5.224e-05), actin cytoskeleton organization (100.0%; 4.702e-04), actin filament-based process (100.0%; 5.330e-04), macrophage activation (50.0%; 2.438e-03)	2	2	5.36E-06	29.3
CD163, HP/HB complex (Homo sapiens)	acute inflammatory response (100.0%; 1.664e-04), response to L-ascorbic acid (50.0%; 4.879e-04), nitric oxide transport (50.0%; 4.879e-04), inflammatory response (100.0%; 1.161e-03), response to magnesium ion (50.0%; 1.341e-03)	2	1	4.64E-03	14.62
Complement component C1, Complement C4 = Complement component C4a + Complement component C4b, Complement C2 = Complement component C2a + Complement component C2b, Complement component C4a, C4a (Homo sapiens)	complement activation, classical pathway (100.0%; 3.660e-03), glial cell differentiation (100.0%; 3.904e-03), humoral immune response mediated by circulating immunoglobulin (100.0%; 4.026e-03), activation of plasma proteins during acute inflammatory response (100.0%; 4.819e-03), complement activation (100.0%; 4.819e-03)	8	1	1.16E-02	9.18

PLTP, ABCA1, CREB1, Cholesterol extracellular region, Cholesterol + ATP + H(,2)O = Cholesterol + ADP + PO(,4)('3-) (Homo sapiens)	response to drug (60.0%; 7.494e-05), platelet dense granule organization and biogenesis (20.0%; 3.050e-04), response to vitamin K (20.0%; 3.050e-04), response to menaquinone (20.0%; 3.050e-04), positive regulation of growth (40.0%; 3.354e-04)	19	1	3.88E-02	4.84