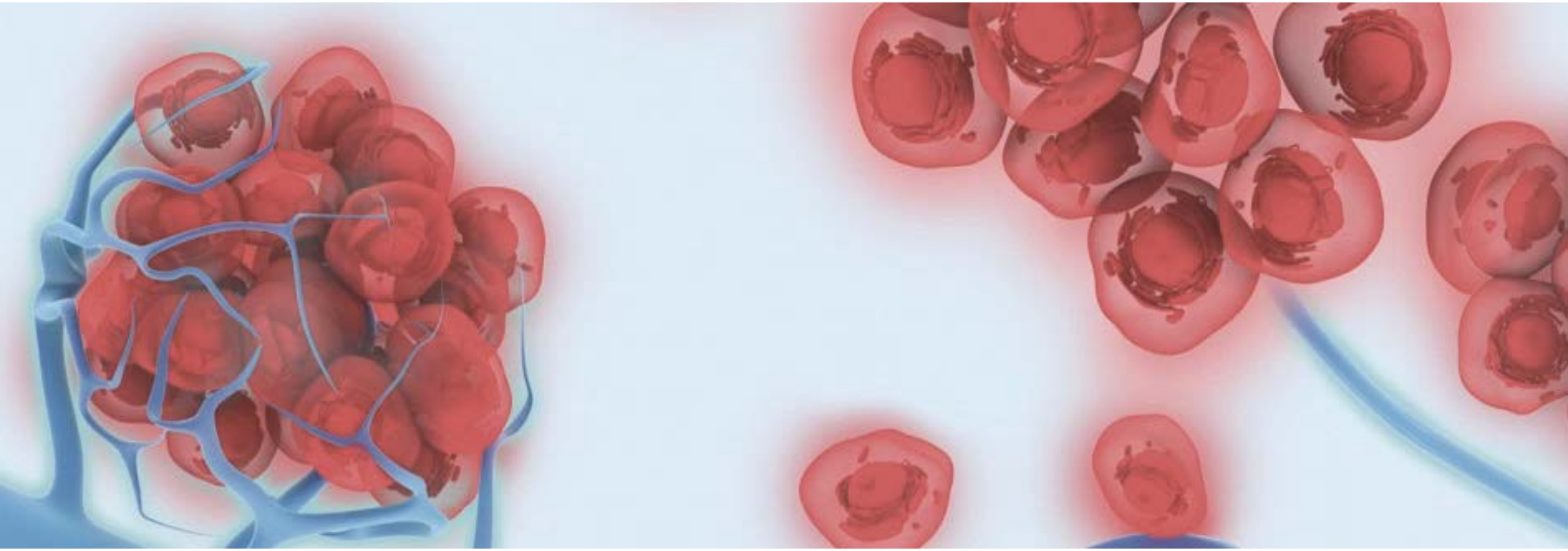

Cardiomyopathy: A heart starved of energy and choked with fibrosis

Shawn Prince, Senior Field Application Scientist, QIAGEN Bioinformatics

Analyzing heart development and heart disease datasets with OmicSoft and IPA bioinformatics solution.

Legal disclaimer

QIAGEN products shown here are intended for molecular biology applications. These products are not intended for the diagnosis, prevention or treatment of a disease.

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Position Available: Field Application Scientist, Boston Area
NGS Software Data Analysis

- ☐ Exciting role interacting with, and enabling, a wide range of researchers, across different scientific disciplines, using QIAGEN's bioinformatics analysis software.
- ☐ Become an expert on QIAGEN'S bioinformatics analysis and interpretation software
- ☐ Deliver scientific software demonstrations and product trainings
- ☐ Focused on gene expression analysis, sequence variant analysis, pathway analysis, microbial metagenomics analysis
- ☐ Field-based (home office with travel) role

- Stop by at a break or see QIAGEN Careers (will be posted Wednesday)

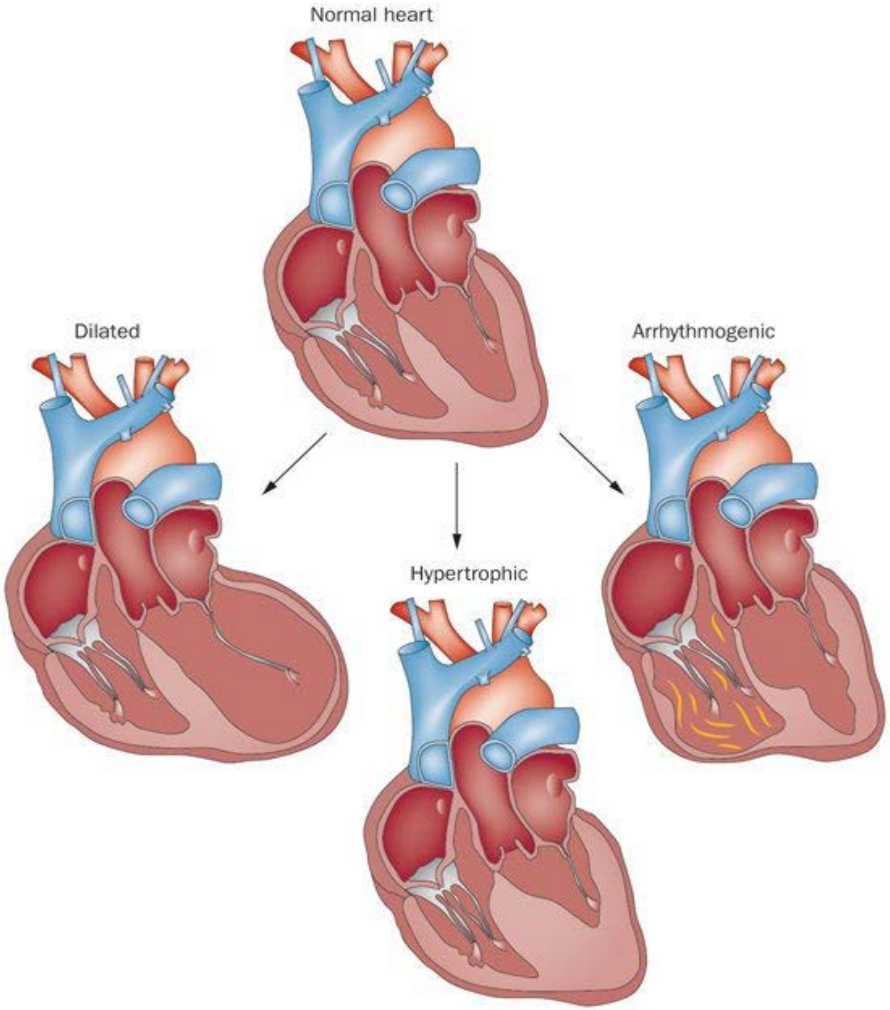
Cardiomyopathy Case Study

- Why did I choose this topic
- What is Hypertrophic Cardiomyopathy
- How data was processed
- Insights and findings

Why did I choose this project

What is Hypertrophic Cardiomyopathy

What is Hypertrophic Cardiomyopathy



Hershberger, R. E. *et al. Nat. Rev. Cardiol.* 10, 531–547 (2013); published online 30 July 2013; doi:10.1038/nrcardio.2013.105

Treatments and Lifestyle Changes

Medications

- beta-blockers and calcium channel blockers relax the heart muscle

Implantable Cardioverter Defibrillators (ICD)

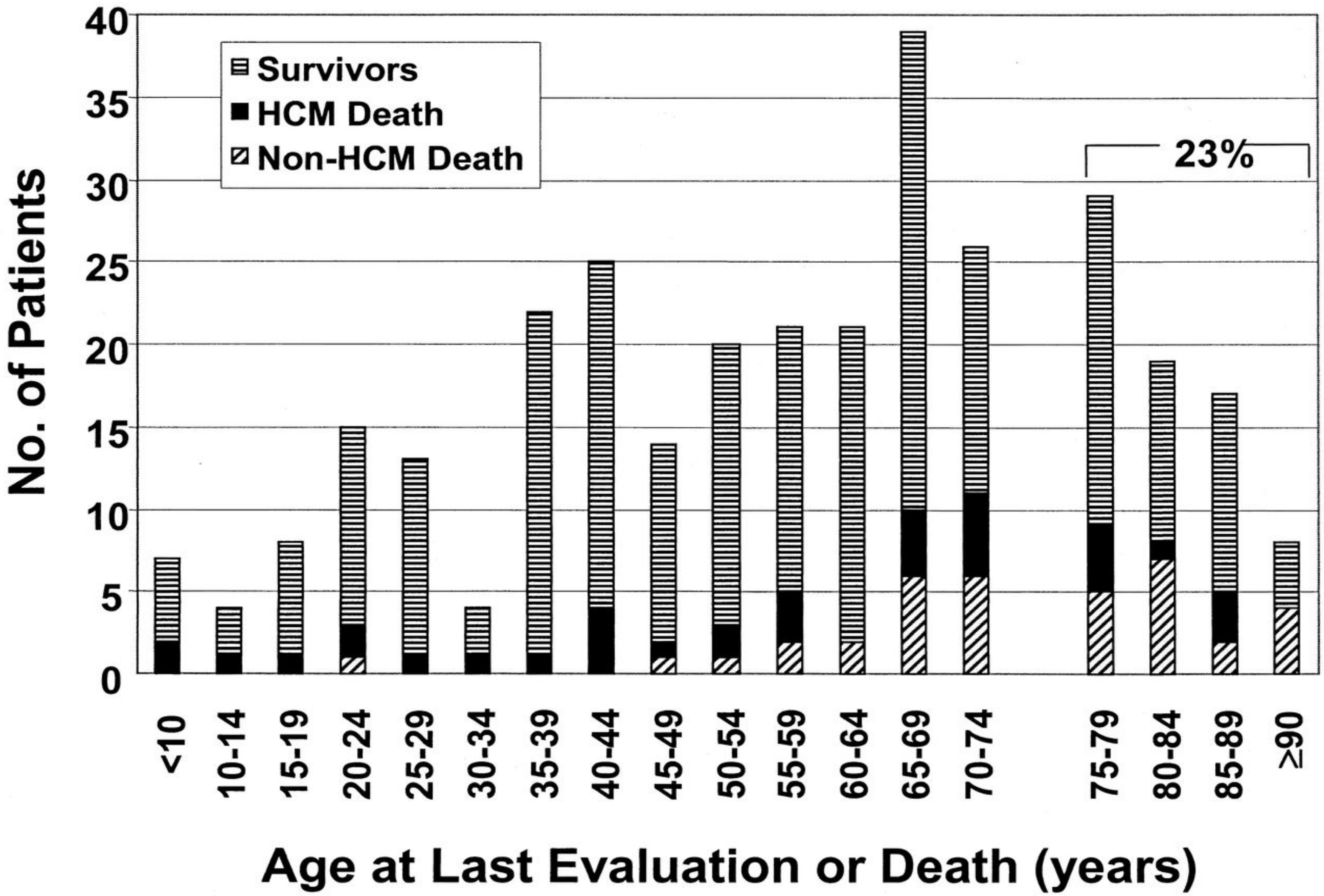
Procedures

- Septal Myectomy, Ethanol Ablation, Heart Transplant

Lifestyle changes

- Fluid and sodium restrictions
- Exercise limitations
- Regular Follow-Up Visits
- Reducing the Risk of Infection

Survival statistics

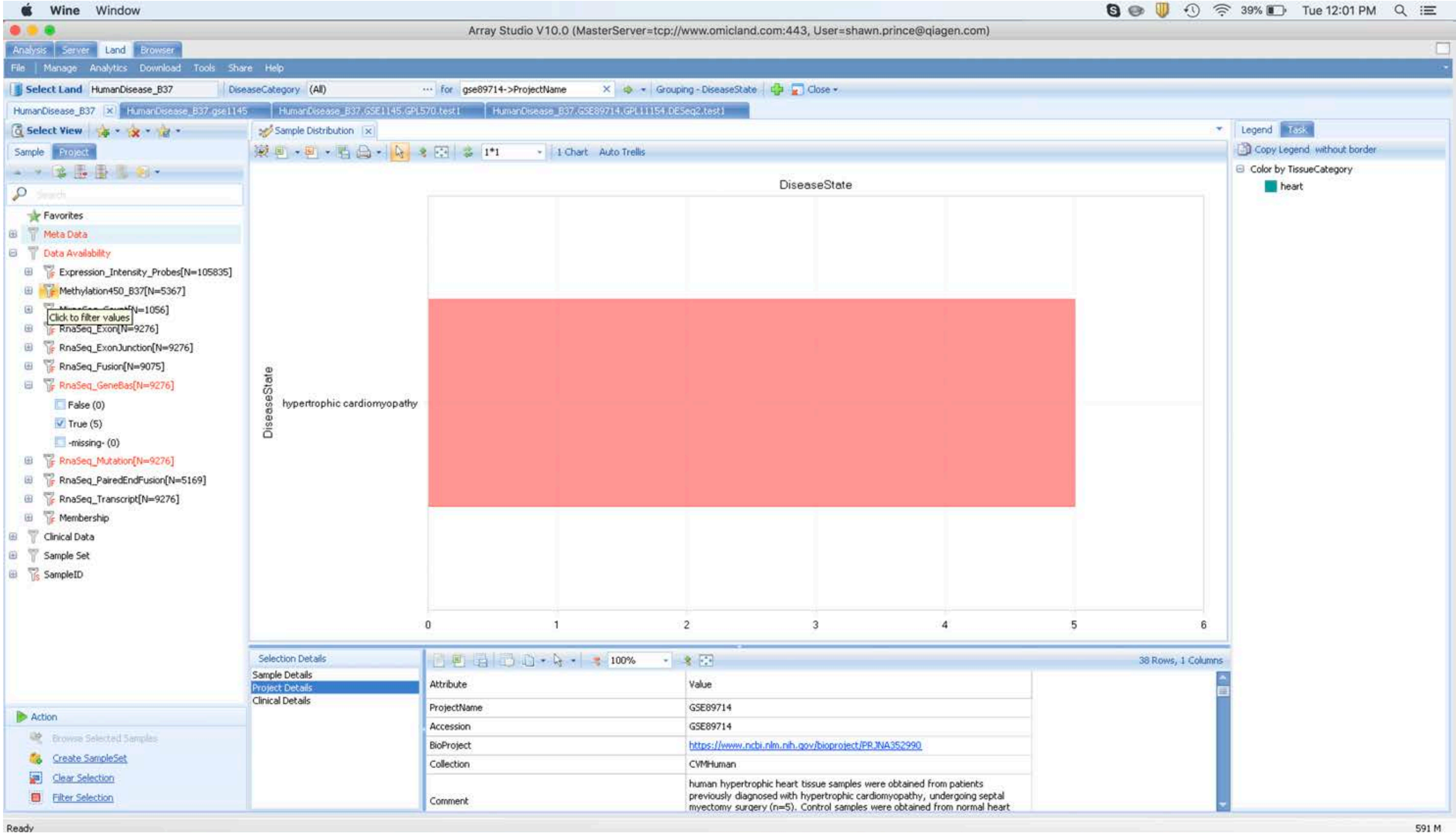


Clinical course of hypertrophiccardiomyopathy with survival to advanced age

Barry J Maron, Susan A Casey, Robert G Hauser and Dorothee M Aeppli

Searching for data

Diseaseland search

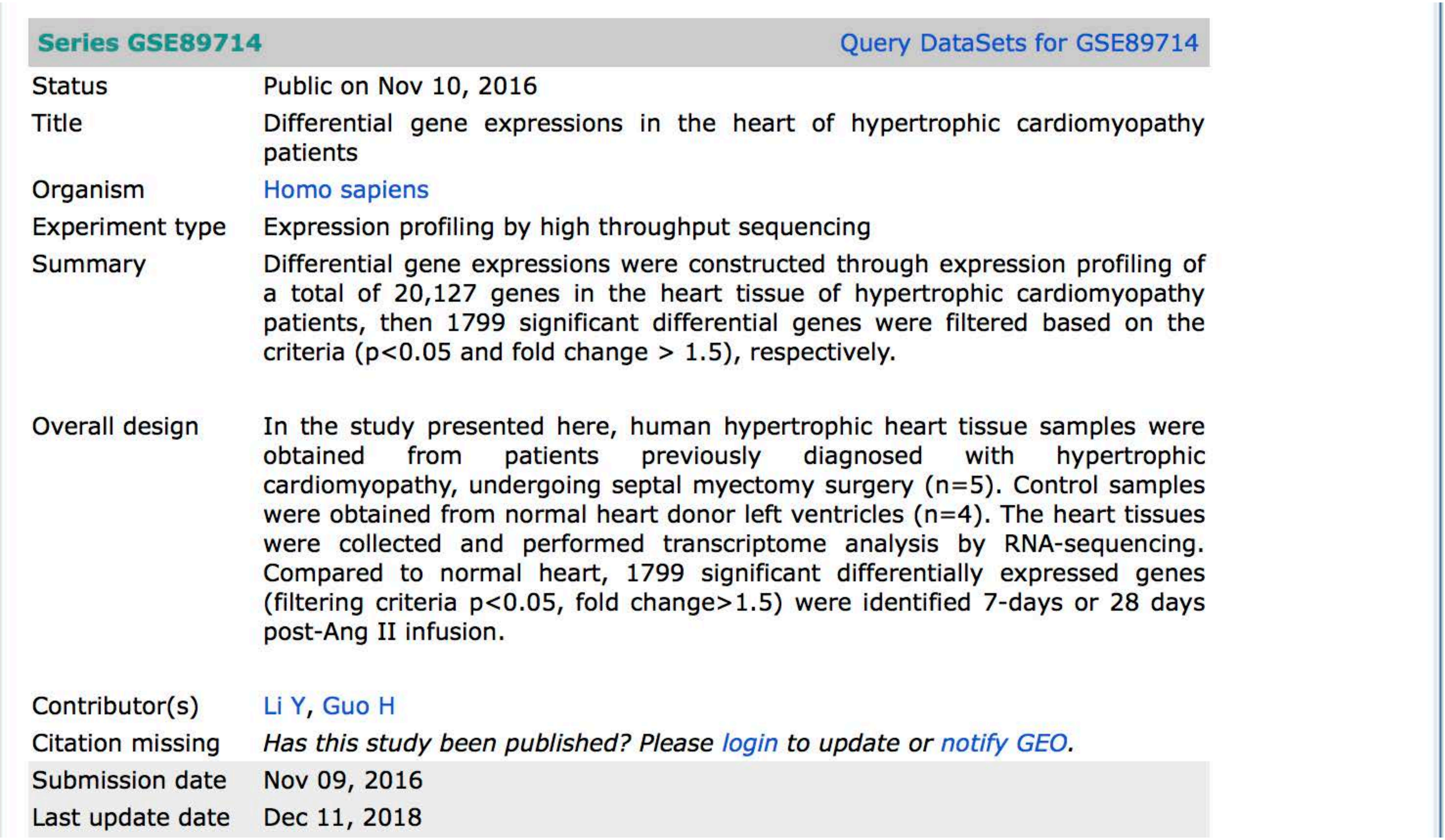


Array Studio V10.0 (MasterServer=tcp://www.omicland.com:443, User=shawn.prince@qiagen.com)

Select Land HumanDisease_B37 DiseaseCategory (All) for gse89714->ProjectName Grouping - DiseaseState Close

Attribute	Value
ProjectName	GSE89714
Accession	GSE89714
BioProject	https://www.ncbi.nlm.nih.gov/bioproject/PRJNA352990
Collection	CVMHuman
Comment	human hypertrophic heart tissue samples were obtained from patients previously diagnosed with hypertrophic cardiomyopathy, undergoing septal myectomy surgery (n=5). Control samples were obtained from normal heart

Study information

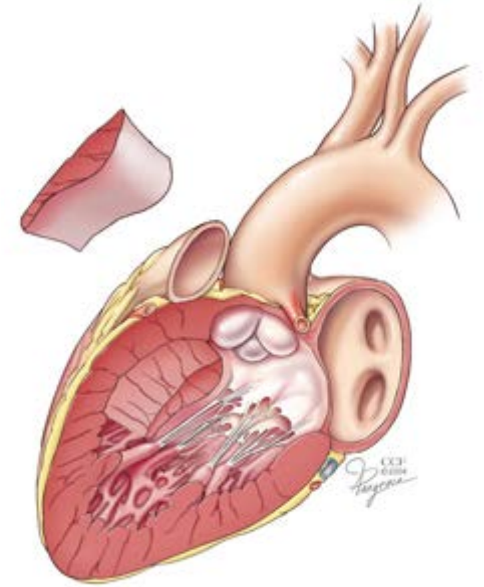


Series GSE89714	Query DataSets for GSE89714
Status	Public on Nov 10, 2016
Title	Differential gene expressions in the heart of hypertrophic cardiomyopathy patients
Organism	Homo sapiens
Experiment type	Expression profiling by high throughput sequencing
Summary	Differential gene expressions were constructed through expression profiling of a total of 20,127 genes in the heart tissue of hypertrophic cardiomyopathy patients, then 1799 significant differential genes were filtered based on the criteria ($p<0.05$ and fold change > 1.5), respectively.
Overall design	In the study presented here, human hypertrophic heart tissue samples were obtained from patients previously diagnosed with hypertrophic cardiomyopathy, undergoing septal myectomy surgery (n=5). Control samples were obtained from normal heart donor left ventricles (n=4). The heart tissues were collected and performed transcriptome analysis by RNA-sequencing. Compared to normal heart, 1799 significant differentially expressed genes (filtering criteria $p<0.05$, fold change>1.5) were identified 7-days or 28 days post-Ang II infusion.
Contributor(s)	Li Y, Guo H
Citation missing	*Has this study been published? Please login to update or notify GEO.*
Submission date	Nov 09, 2016
Last update date	Dec 11, 2018

Study overview

Samples derived from septal myectomy surgery patients with HCM (n =5)

Normal heart donor left ventricles (n =4)



During the septal myectomy procedure, the surgeon removes a small amount of the thickened septal wall to widen the outflow tract from the left ventricle to the aorta.

Next steps

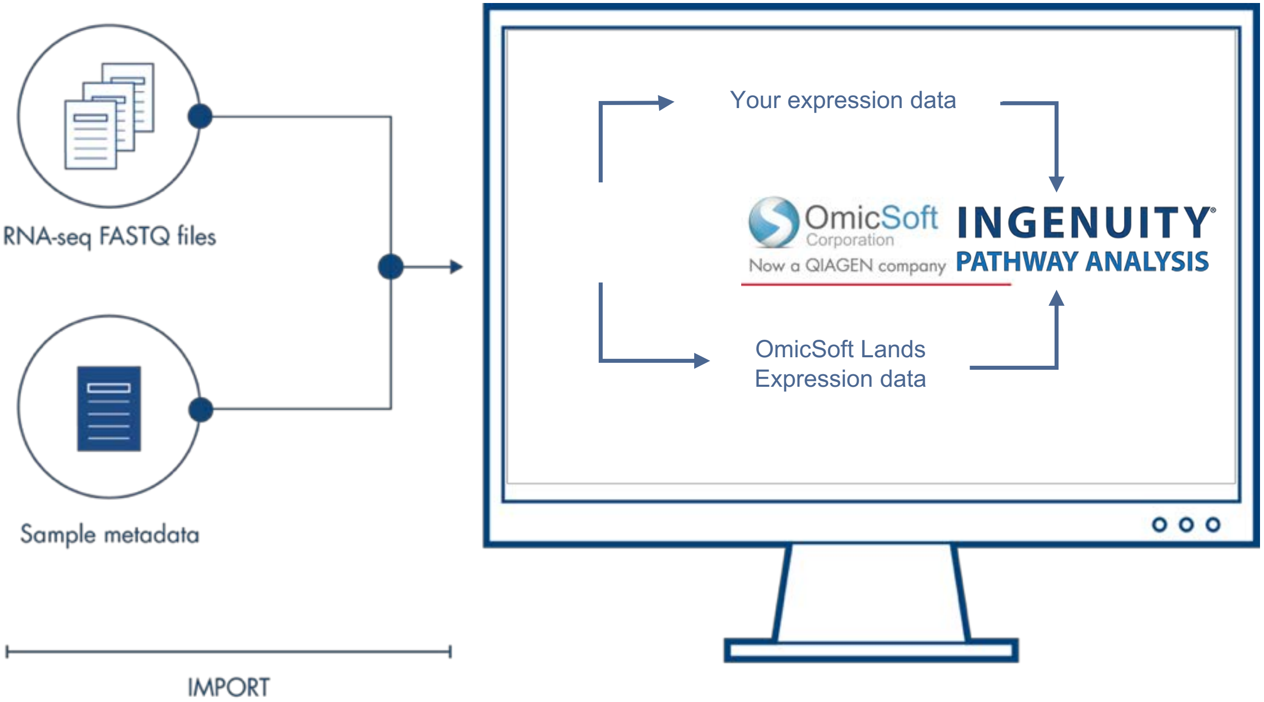
Process data in Omicsoft ArrayStudio

- Downloaded Sra data to run my own analysis
- Run RNA-seq Pipeline, calculated differential expression and called variants
- Exported variants in VCF for analysis in IVA
- Push differential expression results to IPA

Filtered variants in IVA and exported to IPA

Analyzed differential expression and variant function in IPA

Integration Array Studio – IPA (FASTQ to insight)



RNA-seq FASTQ files

Sample metadata

IMPORT

Your expression data

OmicSoft Corporation

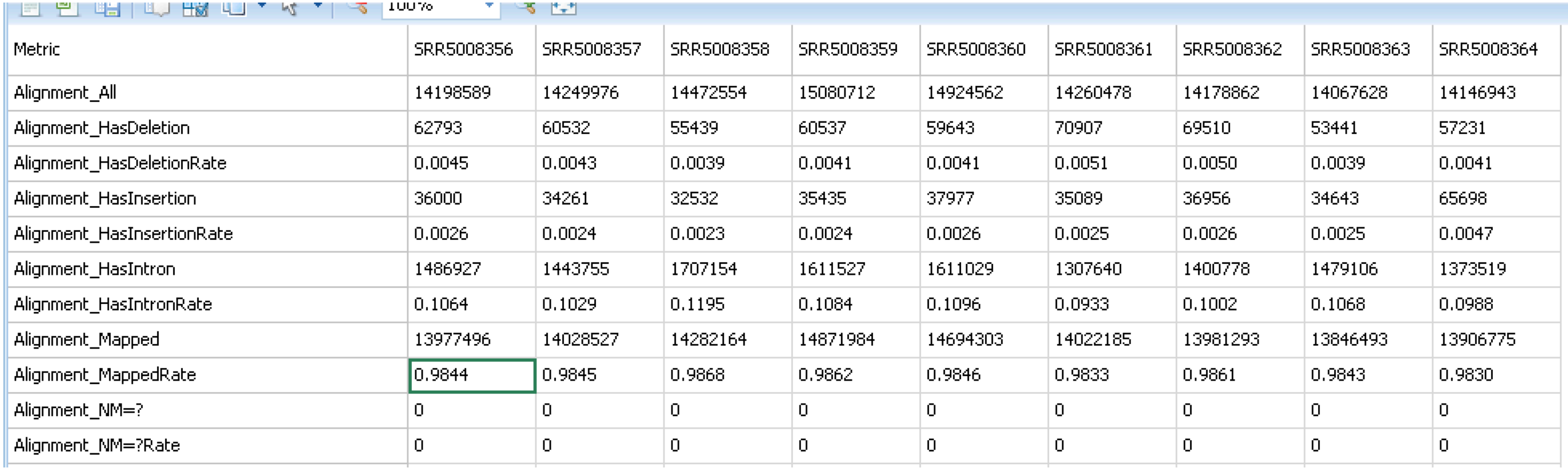
Now a QIAGEN company

INGENUITY PATHWAY ANALYSIS

OmicSoft Lands Expression data

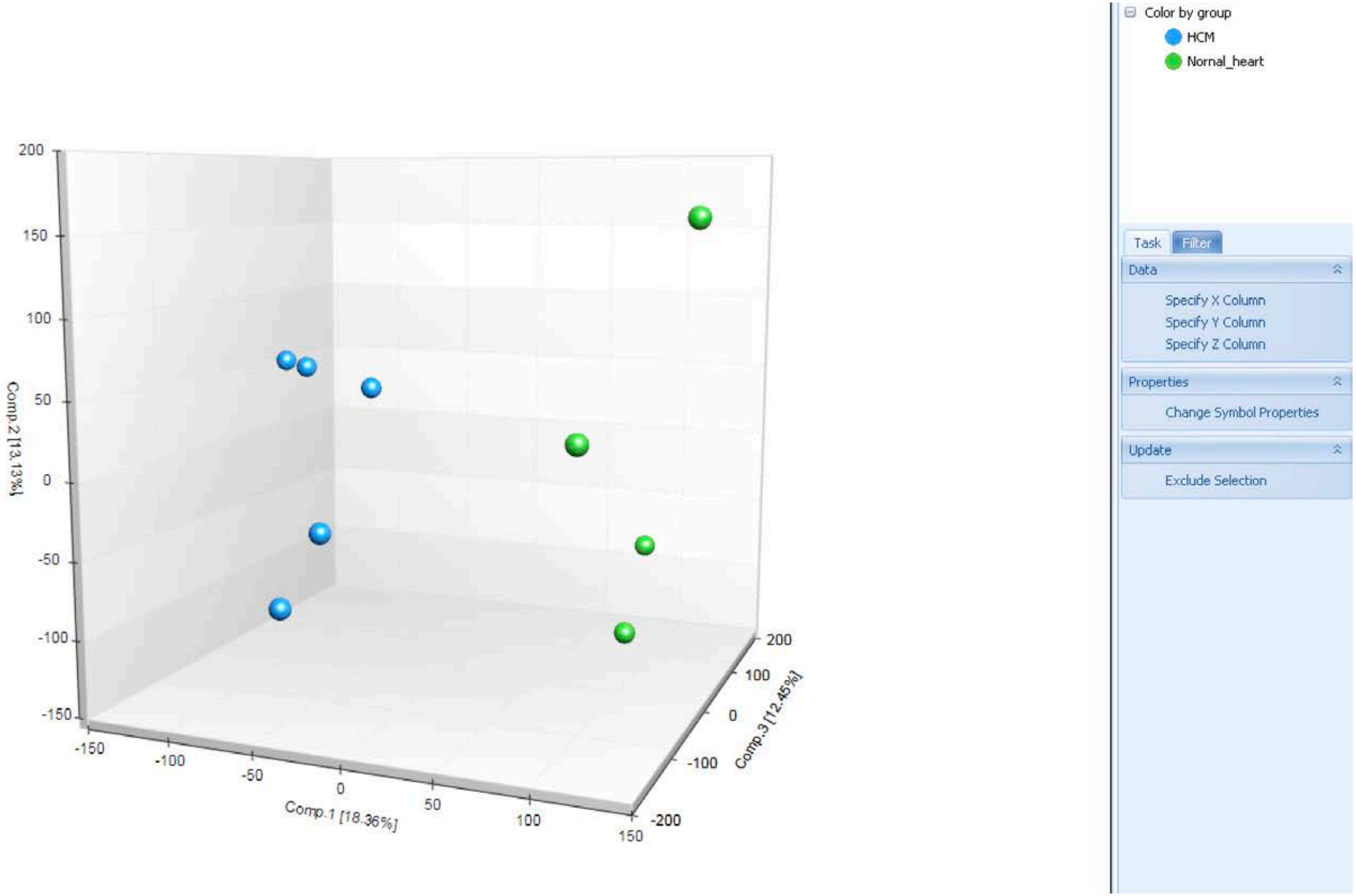
Secondary Analysis review

Quick QC of the mapping

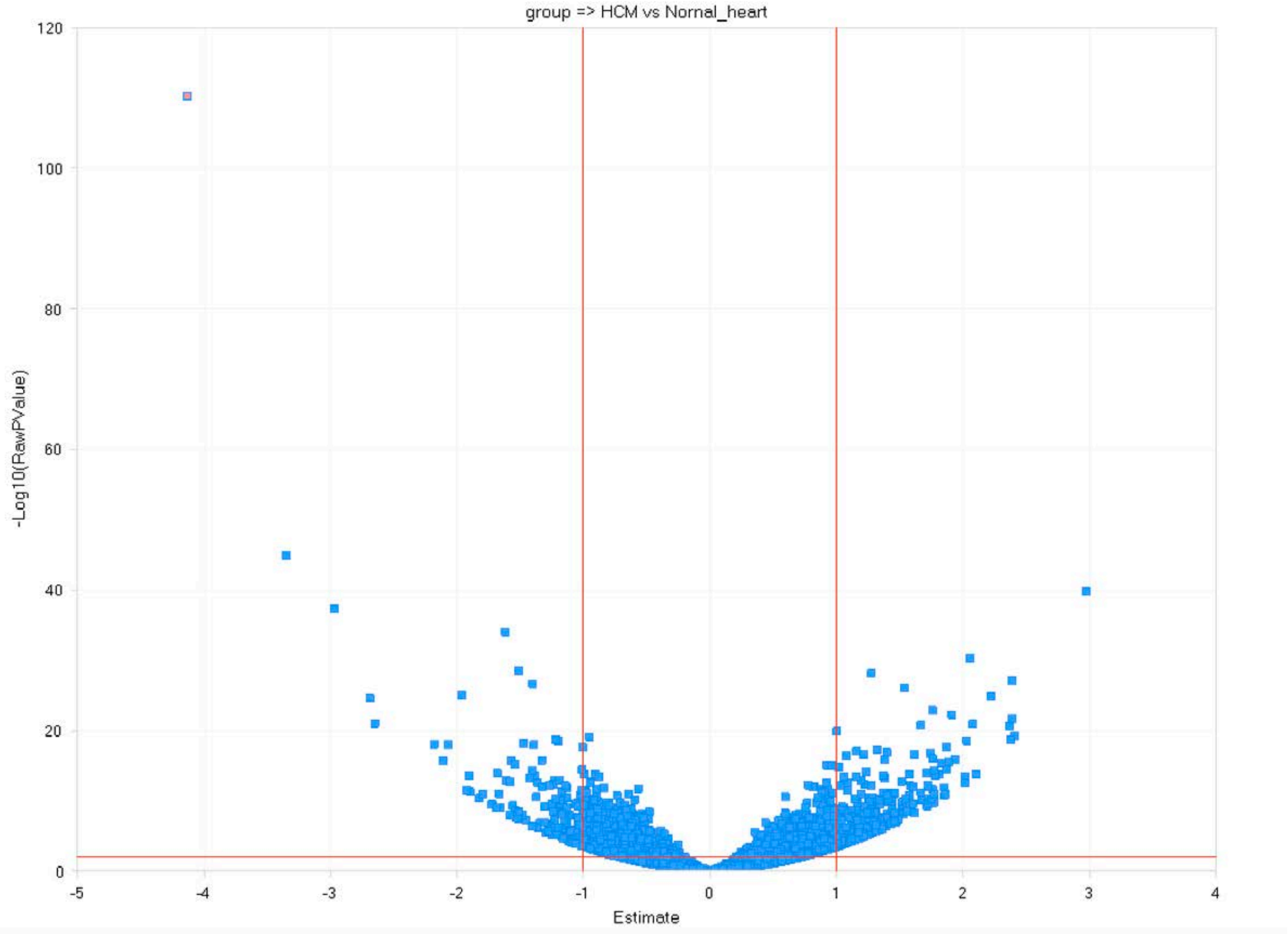


Metric	SRR5008356	SRR5008357	SRR5008358	SRR5008359	SRR5008360	SRR5008361	SRR5008362	SRR5008363	SRR5008364
Alignment_All	14198589	14249976	14472554	15080712	14924562	14260478	14178862	14067628	14146943
Alignment_HasDeletion	62793	60532	55439	60537	59643	70907	69510	53441	57231
Alignment_HasDeletionRate	0.0045	0.0043	0.0039	0.0041	0.0041	0.0051	0.0050	0.0039	0.0041
Alignment_HasInsertion	36000	34261	32532	35435	37977	35089	36956	34643	65698
Alignment_HasInsertionRate	0.0026	0.0024	0.0023	0.0024	0.0026	0.0025	0.0026	0.0025	0.0047
Alignment_HasIntron	1486927	1443755	1707154	1611527	1611029	1307640	1400778	1479106	1373519
Alignment_HasIntronRate	0.1064	0.1029	0.1195	0.1084	0.1096	0.0933	0.1002	0.1068	0.0988
Alignment_Mapped	13977496	14028527	14282164	14871984	14694303	14022185	13981293	13846493	13906775
Alignment_MappedRate	0.9844	0.9845	0.9868	0.9862	0.9846	0.9833	0.9861	0.9843	0.9830
Alignment_NM=?	0	0	0	0	0	0	0	0	0
Alignment_NM=?Rate	0	0	0	0	0	0	0	0	0

PCA Plots help determine differentiation of data



Volcano plot to determine if there is any significant genes

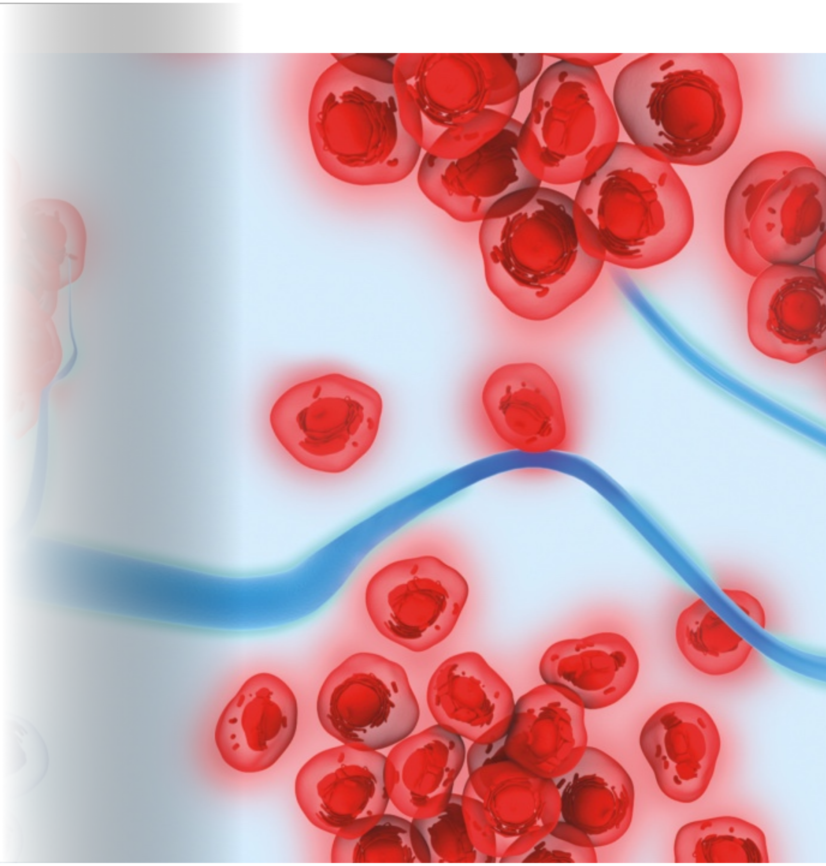


Secondary Analysis Conclusion

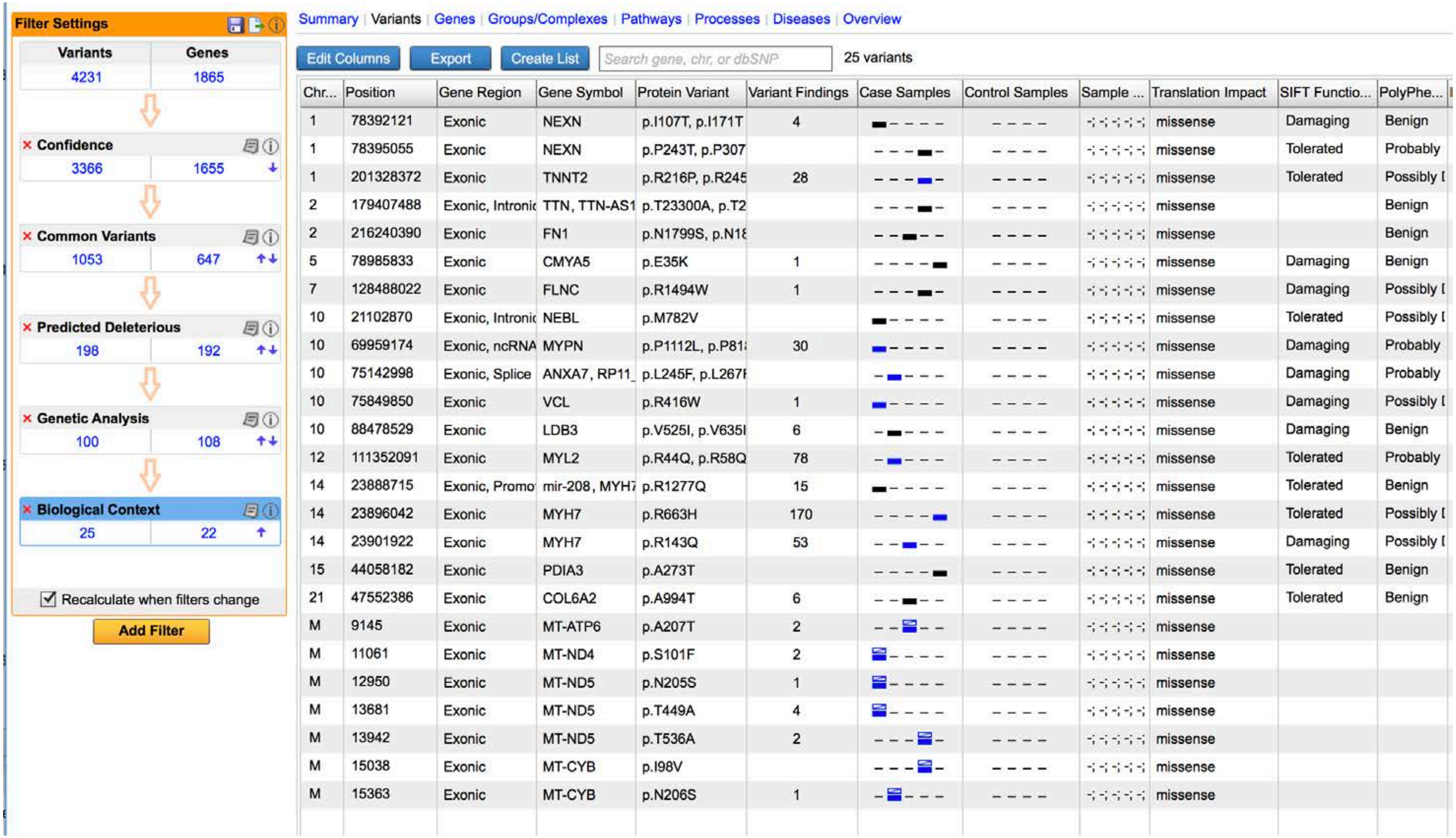
- Mapped reads were high and consistent
- PCA plot of HCM and NF hearts show that most samples within each group have similar expression patterns
- Volcano plot shows significant genes are differentially expressed
- Variants for each sample were called Annotation and filtering will be done in Ingenuity Variant analysis

Helping you uncover new insights in heart disease with OS and IPA

Determining the impact of mutation on Cardiomyopathy



Variants in the data



Filter Settings

Variants	Genes
4231	1865

× Confidence	
3366	1655

× Common Variants	
1053	647

× Predicted Deleterious	
198	192

× Genetic Analysis	
100	108

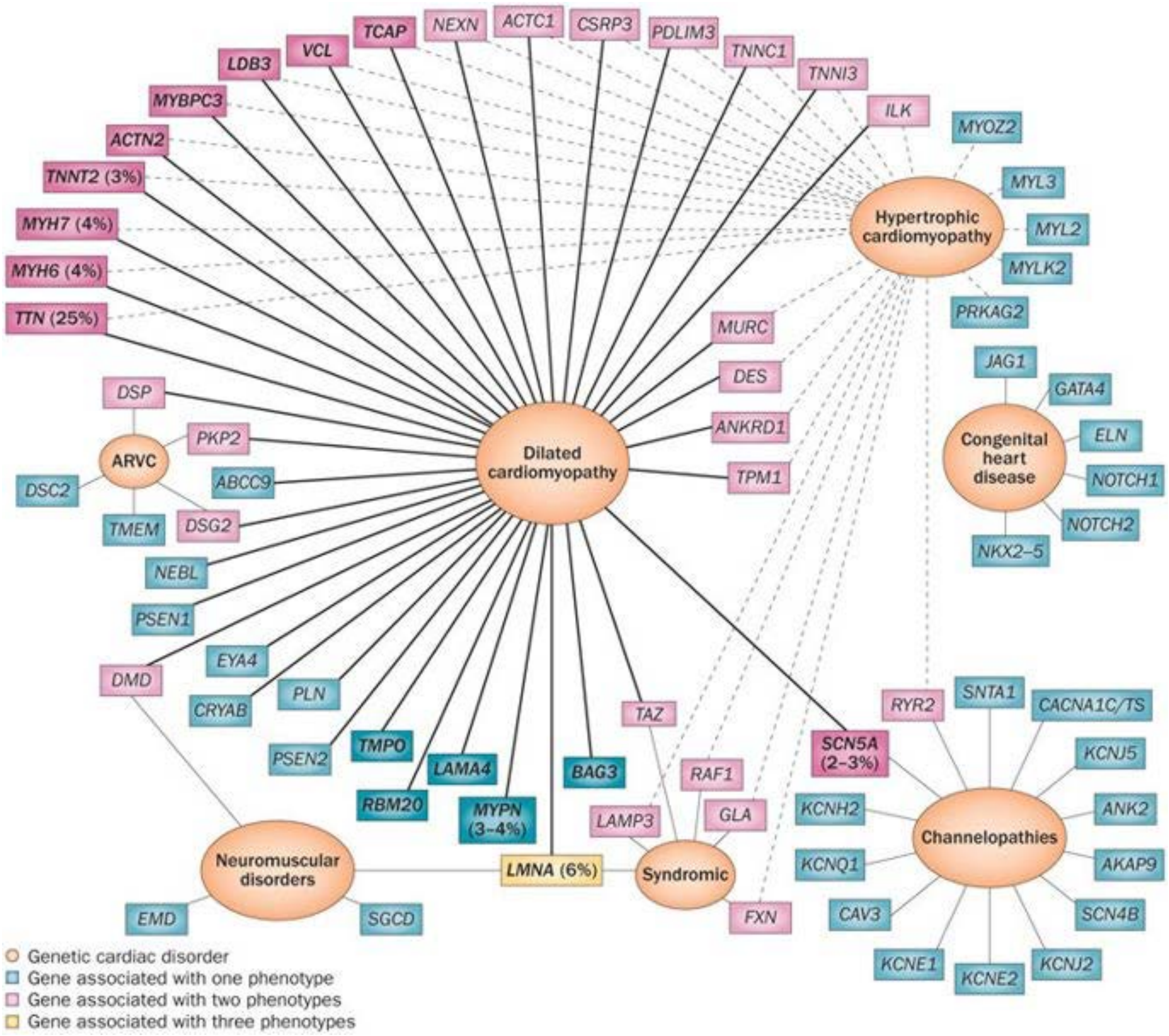
× Biological Context	
25	22

☑ Recalculate when filters change

25 variants

Chr...	Position	Gene Region	Gene Symbol	Protein Variant	Variant Findings	Case Samples	Control Samples	Sample ...	Translation Impact	SIFT Functio...	PolyPhe...
1	78392121	Exonic	NEXN	p.I107T, p.I171T	4	▬ – – – –	– – – –	-;-;-;-;-	missense	Damaging	Benign
1	78395055	Exonic	NEXN	p.P243T, p.P307		– – – ▬ –	– – – –	-;-;-;-;-	missense	Tolerated	Probably
1	201328372	Exonic	TNNT2	p.R216P, p.R245	28	– – – ▬ –	– – – –	-;-;-;-;-	missense	Tolerated	Possibly
2	179407488	Exonic, Intronic	TTN, TTN-AS1	p.T23300A, p.T2		– – – ▬ –	– – – –	-;-;-;-;-	missense		Benign
2	216240390	Exonic	FN1	p.N1799S, p.N1		– – ▬ – –	– – – –	-;-;-;-;-	missense		Benign
5	78985833	Exonic	CMYA5	p.E35K	1	– – – – ▬	– – – –	-;-;-;-;-	missense	Damaging	Benign
7	128488022	Exonic	FLNC	p.R1494W	1	– – – ▬ –	– – – –	-;-;-;-;-	missense	Damaging	Possibly
10	21102870	Exonic, Intronic	NEBL	p.M782V		▬ – – – –	– – – –	-;-;-;-;-	missense	Tolerated	Possibly
10	69959174	Exonic, ncRNA	MYPN	p.P1112L, p.P81	30	▬ – – – –	– – – –	-;-;-;-;-	missense	Damaging	Probably
10	75142998	Exonic, Splice	ANXA7, RP11_	p.L245F, p.L267		– ▬ – – –	– – – –	-;-;-;-;-	missense	Damaging	Probably
10	75849850	Exonic	VCL	p.R416W	1	▬ – – – –	– – – –	-;-;-;-;-	missense	Damaging	Possibly
10	88478529	Exonic	LDB3	p.V525I, p.V635I	6	– ▬ – – –	– – – –	-;-;-;-;-	missense	Damaging	Benign
12	111352091	Exonic	MYL2	p.R44Q, p.R58Q	78	– ▬ – – –	– – – –	-;-;-;-;-	missense	Tolerated	Probably
14	23888715	Exonic, Promo	mir-208, MYH7	p.R1277Q	15	▬ – – – –	– – – –	-;-;-;-;-	missense	Tolerated	Benign
14	23896042	Exonic	MYH7	p.R663H	170	– – – – ▬	– – – –	-;-;-;-;-	missense	Tolerated	Possibly
14	23901922	Exonic	MYH7	p.R143Q	53	– – ▬ – –	– – – –	-;-;-;-;-	missense	Damaging	Possibly
15	44058182	Exonic	PDIA3	p.A273T		– – – – ▬	– – – –	-;-;-;-;-	missense	Tolerated	Benign
21	47552386	Exonic	COL6A2	p.A994T	6	– – ▬ – –	– – – –	-;-;-;-;-	missense	Tolerated	Benign
M	9145	Exonic	MT-ATP6	p.A207T	2	– – ▬ – –	– – – –	-;-;-;-;-	missense		
M	11061	Exonic	MT-ND4	p.S101F	2	▬ – – – –	– – – –	-;-;-;-;-	missense		
M	12950	Exonic	MT-ND5	p.N205S	1	▬ – – – –	– – – –	-;-;-;-;-	missense		
M	13681	Exonic	MT-ND5	p.T449A	4	▬ – – – –	– – – –	-;-;-;-;-	missense		
M	13942	Exonic	MT-ND5	p.T536A	2	– – – ▬ –	– – – –	-;-;-;-;-	missense		
M	15038	Exonic	MT-CYB	p.I98V		– – – ▬ –	– – – –	-;-;-;-;-	missense		
M	15363	Exonic	MT-CYB	p.N206S	1	– ▬ – – –	– – – –	-;-;-;-;-	missense		

Variant Interpretation



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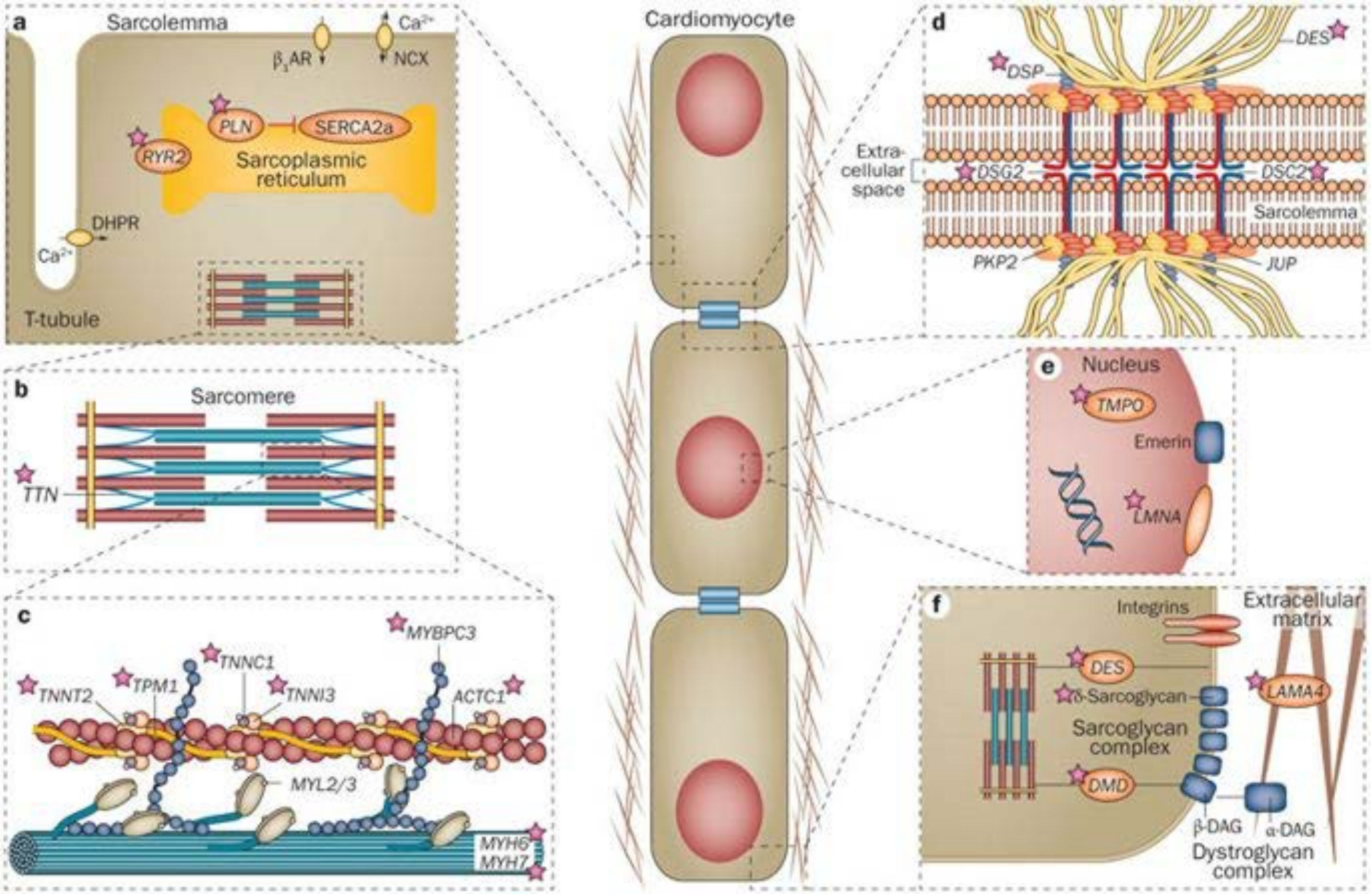


Hershberger, R. E. *et al. Nat. Rev. Cardiol.* 10, 531–547 (2013); published online 30 July 2013; doi:10.1038/nrcardio.2013.105

How The Variants Were Processed

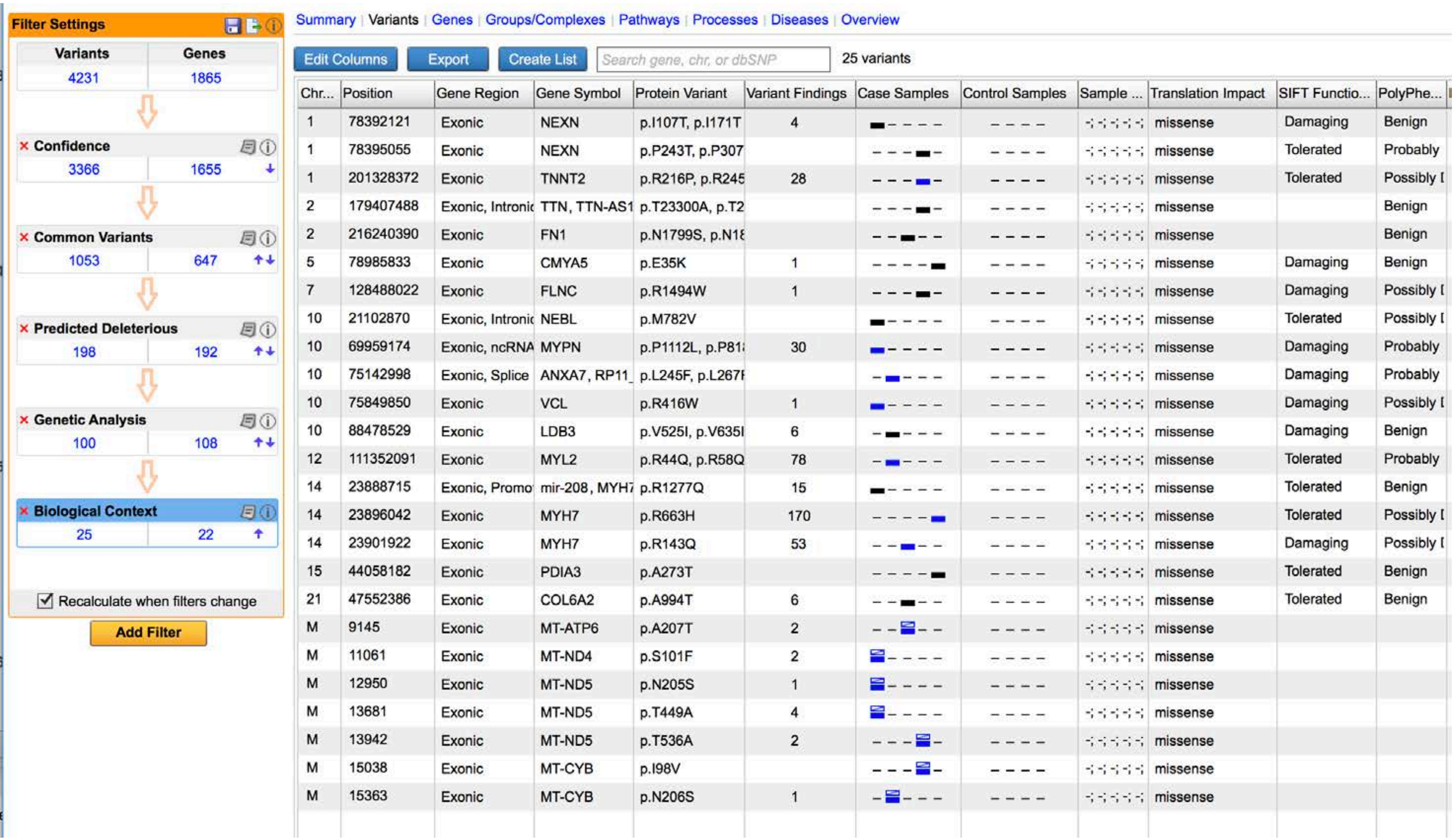
Variants were called in Arraystudio exported in VCF and uploaded to IVA

Analysis was setup as Case vs Control (as a way to control for experimental artifacts)

Variants were filtered for:

- Quality
- Population (remember its pretty common, use a 3% filter)
- removed Control variants
- predicted to be deleterious
- and is associated with HCM

Variants in the data



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1	78395055	Exonic	NEXN	p.P243T, p.P307					missense	Tolerated	Probably
1	201328372	Exonic	TNNT2	p.R216P, p.R245	28				missense	Tolerated	Possibly
2	179407488	Exonic, Intronic	TTN, TTN-AS1	p.T23300A, p.T2					missense		Benign
2	216240390	Exonic	FN1	p.N1799S, p.N1					missense		Benign
5	78985833	Exonic	CMYA5	p.E35K	1				missense	Damaging	Benign
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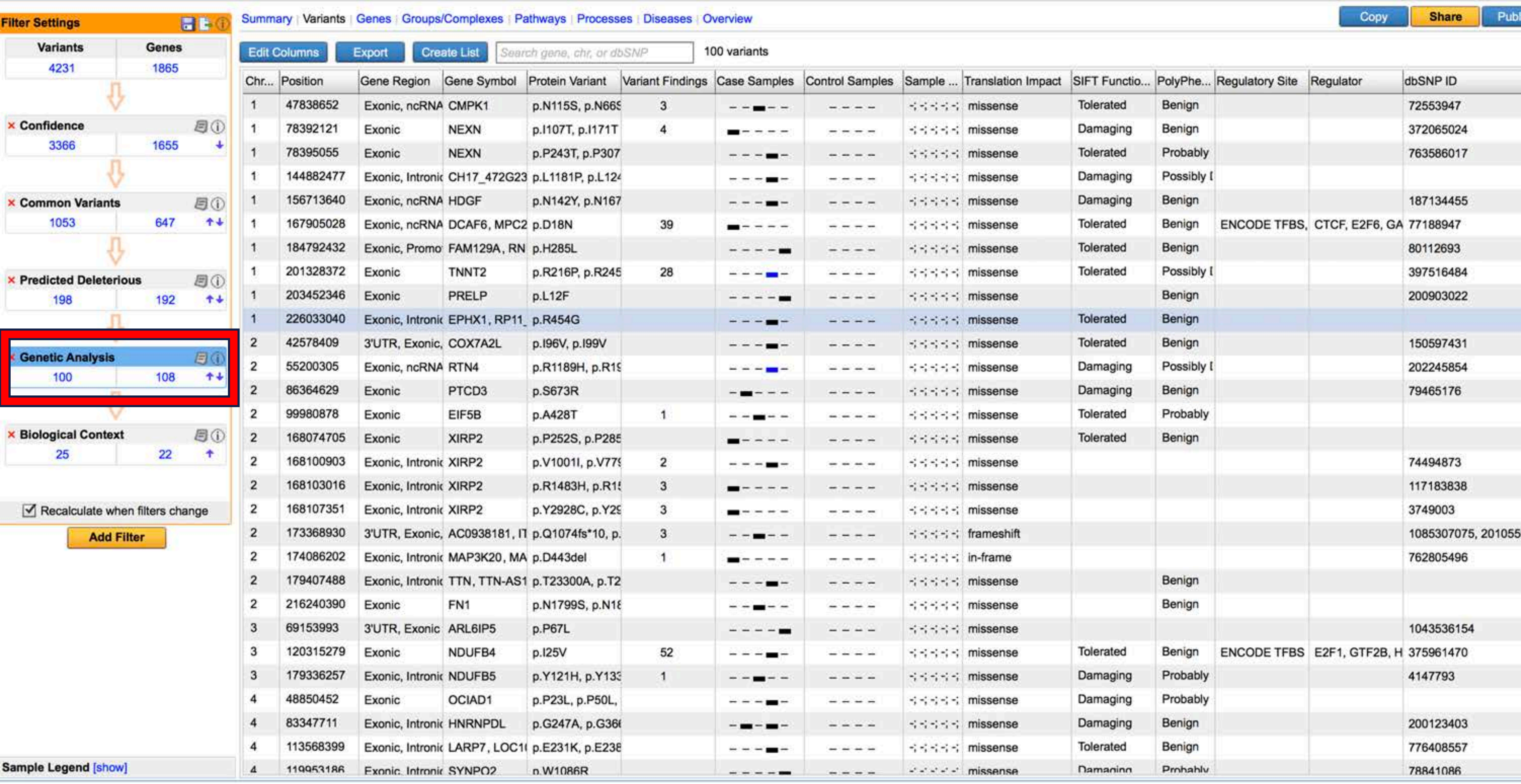
14	23896042	Exonic	MYH7	p.R663H	170				missense	Tolerated	Possibly
14	23901922	Exonic	MYH7	p.R143Q	53				missense	Damaging	Possibly
15	44058182	Exonic	PDIA3	p.A273T					missense	Tolerated	Benign
21	47552386	Exonic	COL6A2	p.A994T	6				missense	Tolerated	Benign
M	9145	Exonic	MT-ATP6	p.A207T	2				missense		
M	11061	Exonic	MT-ND4	p.S101F	2				missense		
M	12950	Exonic	MT-ND5	p.N205S	1				missense		
M	13681	Exonic	MT-ND5	p.T449A	4				missense		
M	13942	Exonic	MT-ND5	p.T536A	2				missense		
M	15038	Exonic	MT-CYB	p.I98V					missense		
M	15363	Exonic	MT-CYB	p.N206S	1				missense		

Exploring the Variant data in IPA



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100	108

× **Biological Context**

25	22

☑ Recalculate when filters change

Sample Legend [show]

100 variants

Chr...	Position	Gene Region	Gene Symbol	Protein Variant	Variant Findings	Case Samples	Control Samples	Sample ...	Translation Impact	SIFT Functio...	PolyPhe...	Regulatory Site	Regulator	dbSNP ID
1	47838652	Exonic, ncRNA	CMPK1	p.N115S, p.N66S	3	– – ▬ – –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign			72553947
1	78392121	Exonic	NEXN	p.I107T, p.I171T	4	▬ – – – –	– – – –	-; -; -; -; -;	missense	Damaging	Benign			372065024
1	78395055	Exonic	NEXN	p.P243T, p.P307		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Tolerated	Probably			763586017
1	144882477	Exonic, Intronic	CH17_472G23	p.L1181P, p.L124		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Damaging	Possibly [			
1	156713640	Exonic, ncRNA	HDGF	p.N142Y, p.N167		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Damaging	Benign			187134455
1	167905028	Exonic, ncRNA	DCAF6, MPC2	p.D18N	39	▬ – – – –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign	ENCODE TFBS,	CTCF, E2F6, GA	77188947
1	184792432	Exonic, Promo	FAM129A, RN	p.H285L		– – – – ▬	– – – –	-; -; -; -; -;	missense	Tolerated	Benign			80112693
1	201328372	Exonic	TNNT2	p.R216P, p.R245	28	– – – ▬ –	– – – –	-; -; -; -; -;	missense	Tolerated	Possibly [			397516484
1	203452346	Exonic	PRELP	p.L12F		– – – – ▬	– – – –	-; -; -; -; -;	missense		Benign			200903022
1	226033040	Exonic, Intronic	EPHX1, RP11_	p.R454G		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign			
2	42578409	3'UTR, Exonic,	COX7A2L	p.I96V, p.I99V		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign			150597431
2	55200305	Exonic, ncRNA	RTN4	p.R1189H, p.R19		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Damaging	Possibly [			202245854
2	86364629	Exonic	PTCD3	p.S673R		– ▬ – – –	– – – –	-; -; -; -; -;	missense	Damaging	Benign			79465176
2	99980878	Exonic	EIF5B	p.A428T	1	– – ▬ – –	– – – –	-; -; -; -; -;	missense	Tolerated	Probably			
2	168074705	Exonic	XIRP2	p.P252S, p.P285		▬ – – – –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign			
2	168100903	Exonic, Intronic	XIRP2	p.V1001I, p.V779	2	– – – ▬ –	– – – –	-; -; -; -; -;	missense					74494873
2	168103016	Exonic, Intronic	XIRP2	p.R1483H, p.R15	3	▬ – – – –	– – – –	-; -; -; -; -;	missense					117183838
2	168107351	Exonic, Intronic	XIRP2	p.Y2928C, p.Y29	3	▬ – – – –	– – – –	-; -; -; -; -;	missense					3749003
2	173368930	3'UTR, Exonic,	AC0938181, IT	p.Q1074fs*10, p.	3	– – ▬ – –	– – – –	-; -; -; -; -;	frameshift					1085307075, 201055
2	174086202	Exonic, Intronic	MAP3K20, MA	p.D443del	1	▬ – – – –	– – – –	-; -; -; -; -;	in-frame					762805496
2	179407488	Exonic, Intronic	TTN, TTN-AS1	p.T23300A, p.T2		– – – ▬ –	– – – –	-; -; -; -; -;	missense		Benign			
2	216240390	Exonic	FN1	p.N1799S, p.N18		– – ▬ – –	– – – –	-; -; -; -; -;	missense		Benign			
3	69153993	3'UTR, Exonic	ARL6IP5	p.P67L		– – – – ▬	– – – –	-; -; -; -; -;	missense					1043536154
3	120315279	Exonic	NDUFB4	p.I25V	52	– – – ▬ –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign	ENCODE TFBS	E2F1, GTF2B, H	375961470
3	179336257	Exonic, Intronic	NDUFB5	p.Y121H, p.Y133	1	– – ▬ – –	– – – –	-; -; -; -; -;	missense	Damaging	Probably			4147793
4	48850452	Exonic	OCIAD1	p.P23L, p.P50L,		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Damaging	Probably			
4	83347711	Exonic, Intronic	HNRNPDL	p.G247A, p.G366		– ▬ – ▬ –	– – – –	-; -; -; -; -;	missense	Damaging	Benign			200123403
4	113568399	Exonic, Intronic	LARP7, LOC10	p.E231K, p.E238		– – – ▬ –	– – – –	-; -; -; -; -;	missense	Tolerated	Benign			776408557
4	119953186	Exonic, Intronic	SYNPO2	p.W1086R		– – – – ▬	– – – –	-; -; -; -; -;	missense	Damaging	Probably			78841086

Core Analysis of Variant data

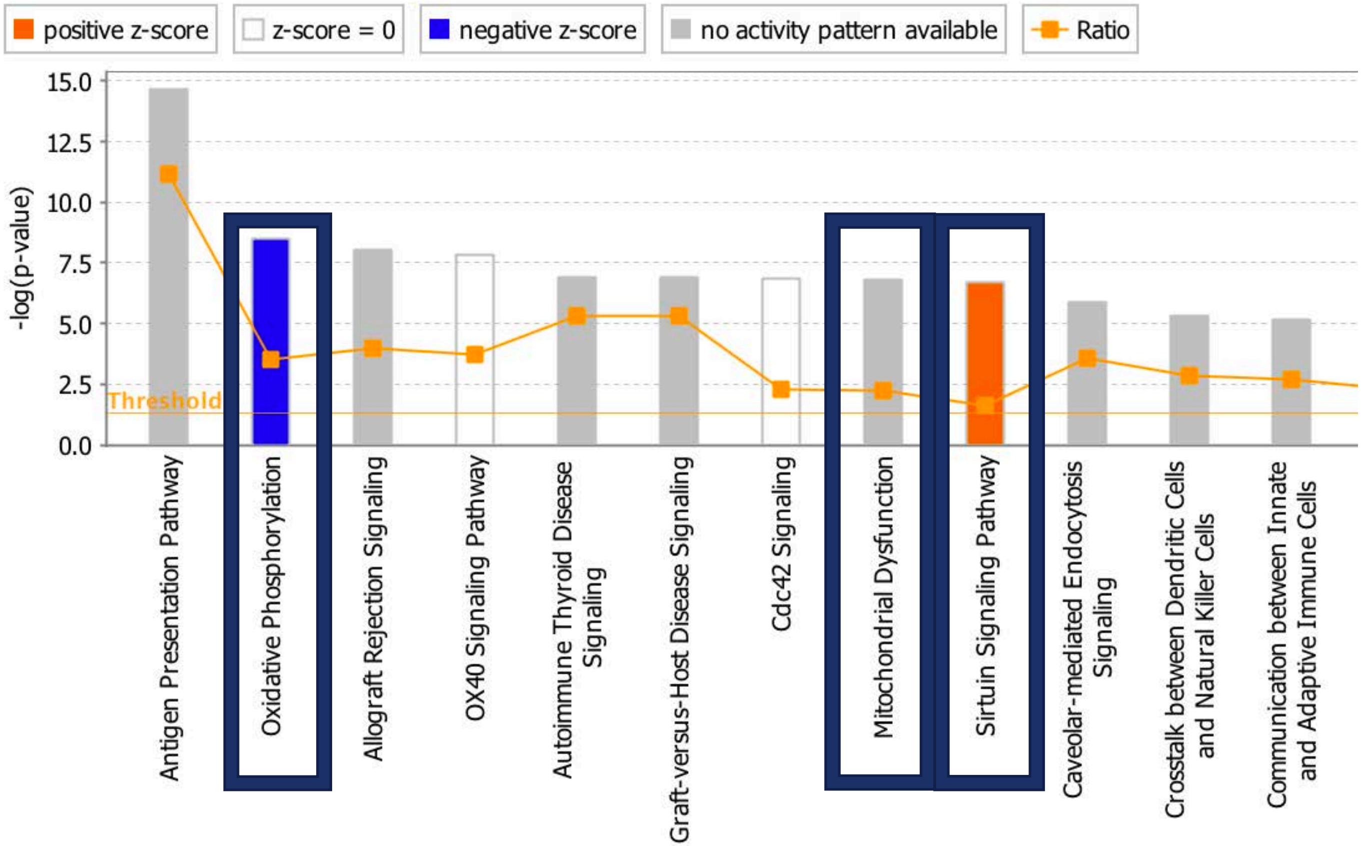
Variants from the Genetic filter were uploaded and Core analysis run in IPA

- 100 or so variants

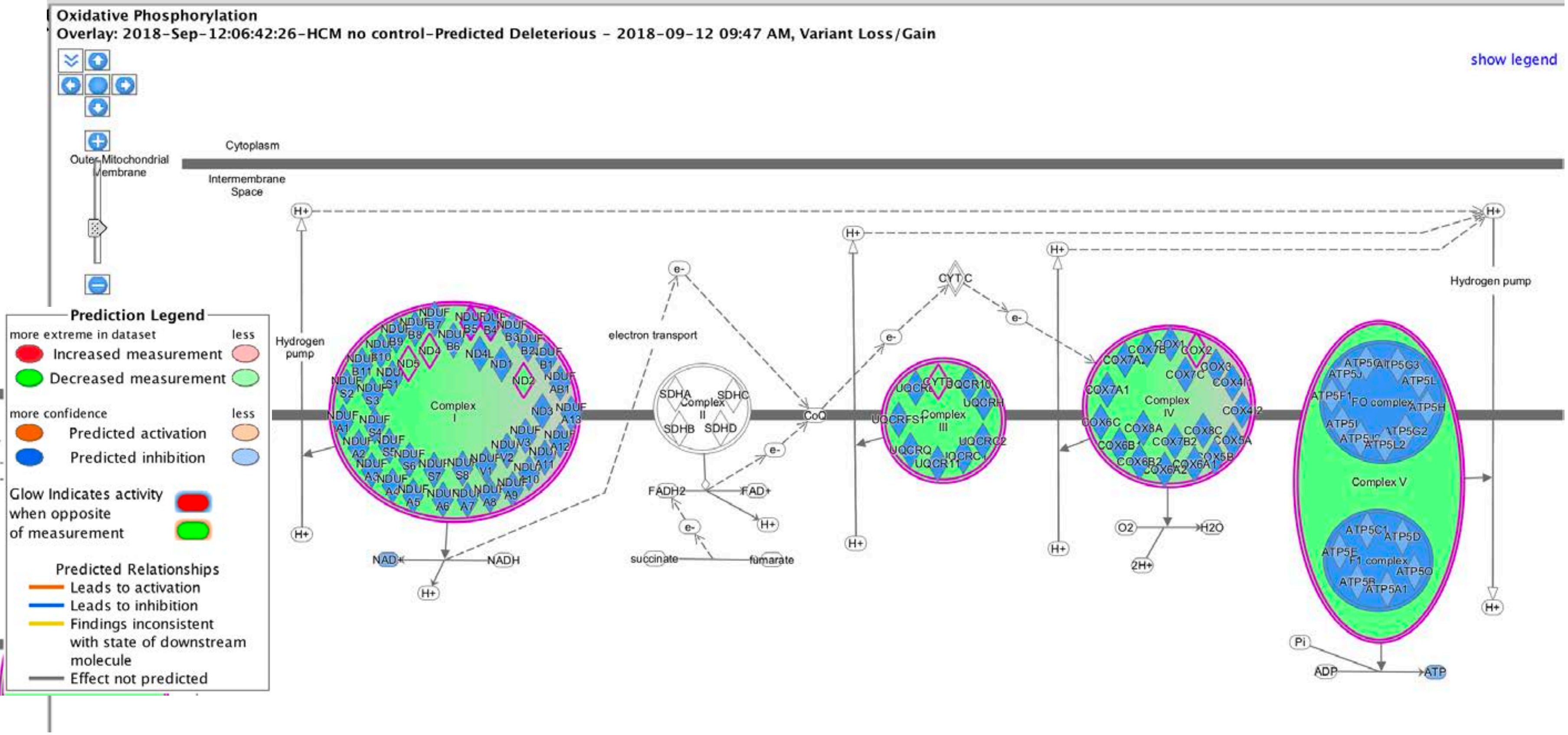
Two themes emerge

- Canonical Pathways
- Disease and function

Core Analysis Results



Oxidative Phosphorylation Pathway



Oxidative Phosphorylation

Overlay: 2018-Sep-12:06:42:26-HCM no control-Predicted Deleterious - 2018-09-12 09:47 AM, Variant Loss/Gain

show legend

Prediction Legend

more extreme in dataset — less

🟥 Increased measurement

🟩 Decreased measurement

more confidence — less

🟧 Predicted activation

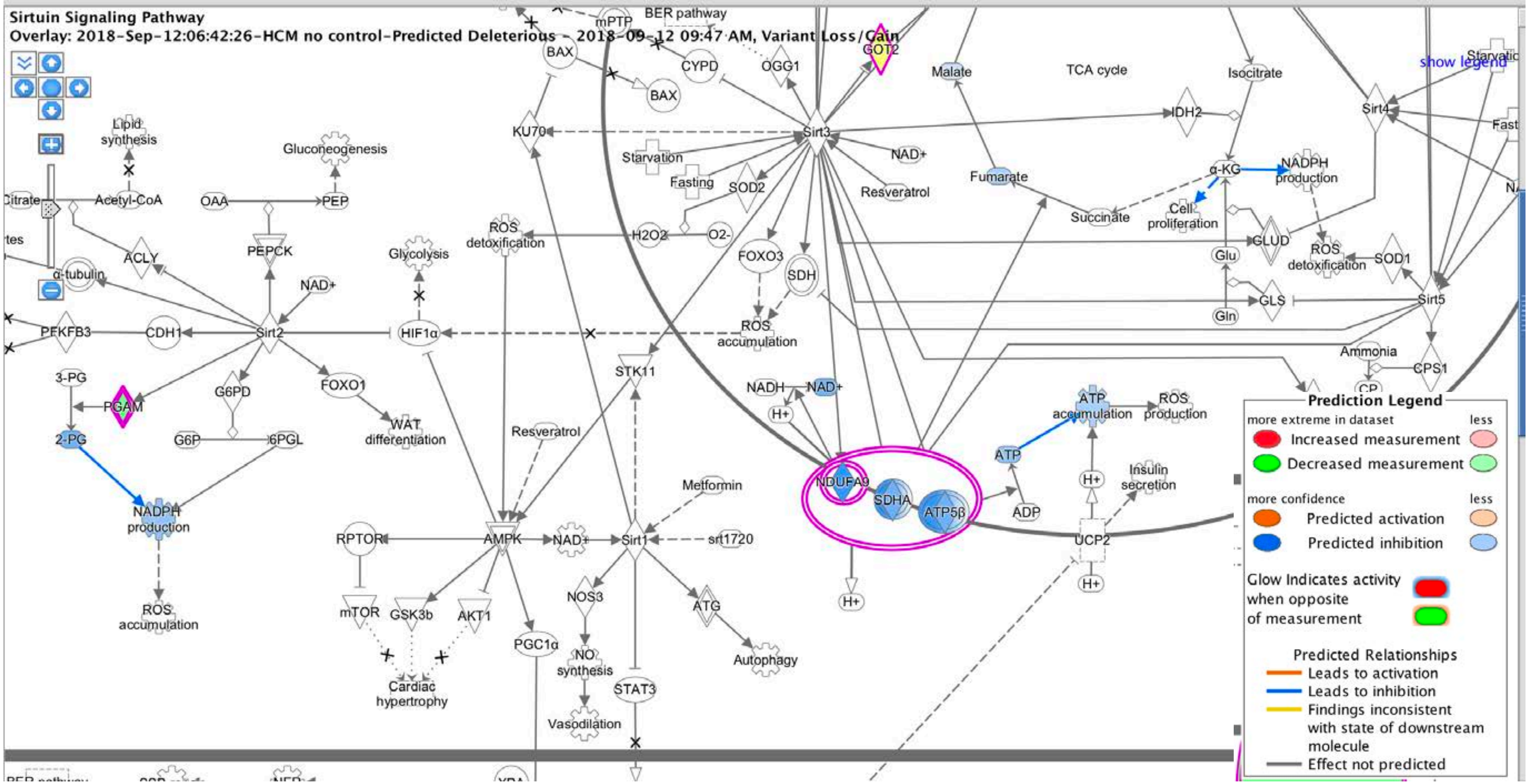
🟦 Predicted inhibition

Glow Indicates activity when opposite of measurement

Predicted Relationships

- Leads to activation
- Leads to inhibition
- Findings inconsistent with state of downstream molecule
- Effect not predicted

Sirtuin Pathway



Sirtuin Signaling Pathway

Overlay: 2018-Sep-12:06:42:26-HCM no control-Predicted Deleterious - 2018-09-12 09:47 AM, Variant Loss/Gain

show legend

Prediction Legend

more extreme in dataset — less

🟥 Increased measurement

🟩 Decreased measurement

more confidence — less

Predicted activation

Predicted inhibition

Glow Indicates activity when opposite of measurement

Predicted Relationships

Leads to activation

Leads to inhibition

Findings inconsistent with state of downstream molecule

Effect not predicted

Disease and Function

There are 10 unique molecules selected

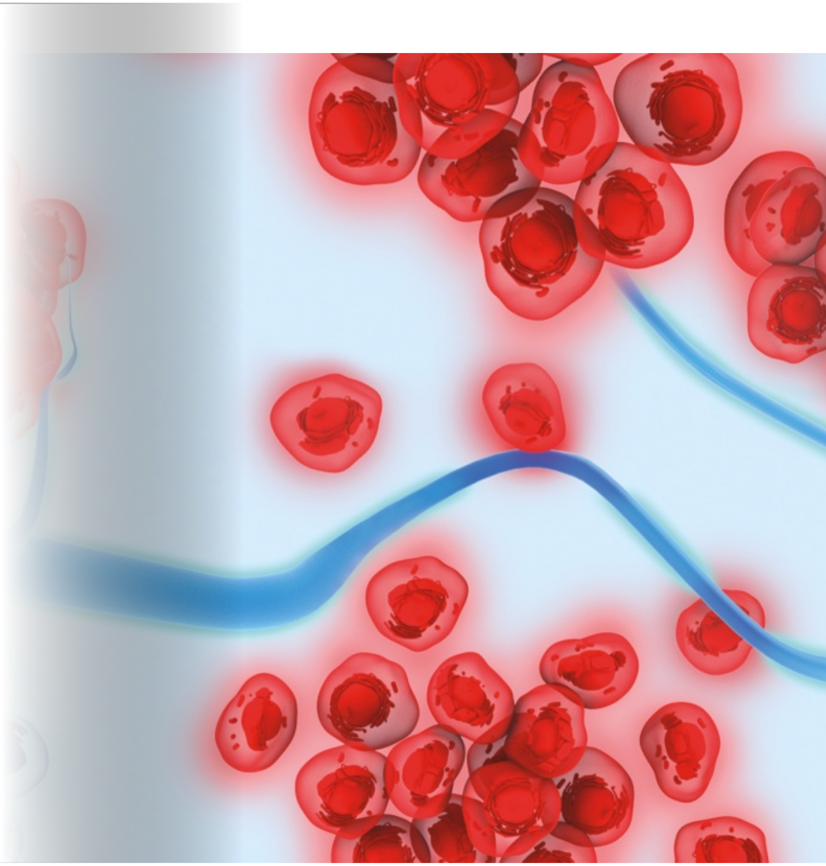
Categories	Diseases or Functions Annotation	p-Value	Predicted Activation ...	Activation z-score	Molecules	# Molecules
Hereditary Disorder,Organi...	Hereditary myopathy	4.06E-22			ADSSL1,AHNAK,...all 32	32
Skeletal and Muscular Disor...	Caveolinopathy	1.94E-14			ADSSL1,AHNAK,...all 14	14
Cardiovascular Disease,Her...	Familial hypertrophic cardiomyopathy	5.58E-12			FLNC,↓MYH7,↓......all 10	10
Cardiovascular Disease,Her...	Dilated cardiomyopathy 1S	1.08E-11			↓MYH7,↓MYL2, ...all 6	6
Cardiovascular Disease,Her...	Autosomal dominant cardiomyopathy	1.17E-11			FLNC,↓MYH7, ↓... ...all 9	9
Cardiovascular Disease,Her...	Familial dilated cardiomyopathy	2.17E-11			FLNC,↓MYH7, ↓... ...all 9	9
Neurological Disease	Movement Disorders	2.60E-11			ARL6IP5, ASAH1,...all 31	31
Cardiovascular Disease,Org...	Hypertrophic cardiomyopathy	4.44E-11			FLNC,↓MT-AT... ...all 11	11

Selected 1 / 500

Summary of Variant Analysis

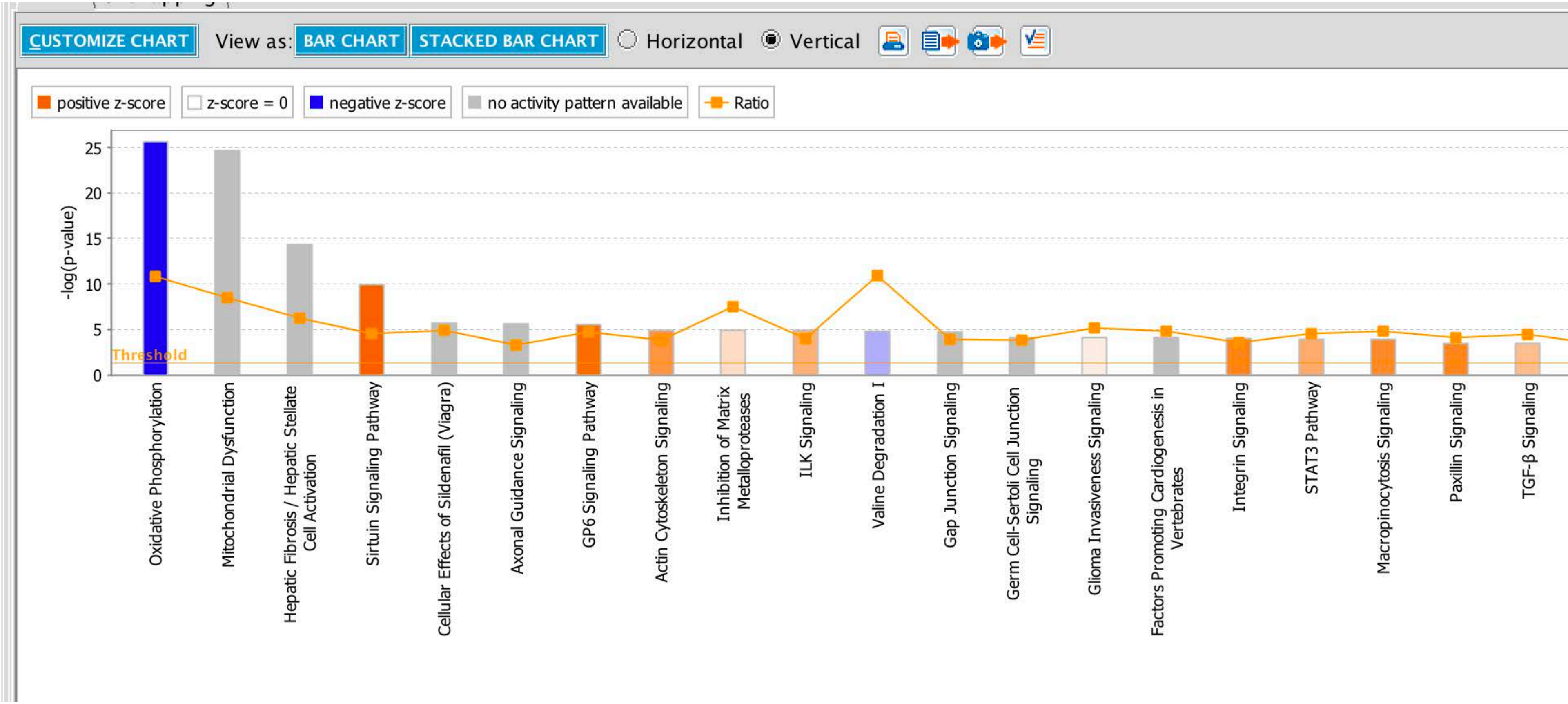
- Predicted decrease of Oxidative Phosphorylation
- Predicted activation of Sirtuin Pathway
- MT dysfunction
- Variants show enrichment of cardiovascular disease and hereditary disorder

Helping you uncover new insights in heart disease with OS and IPA

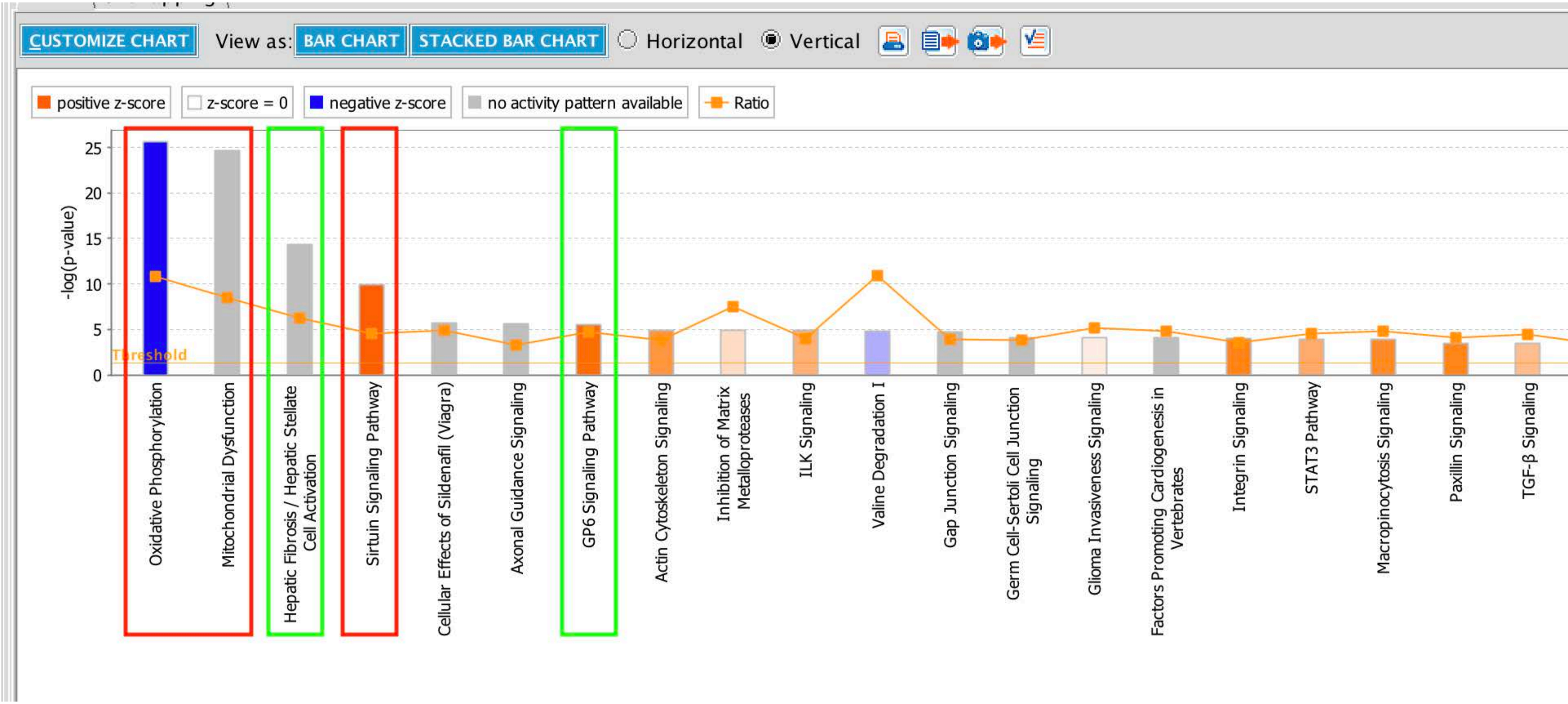


Exploring the results of expression data in IPA

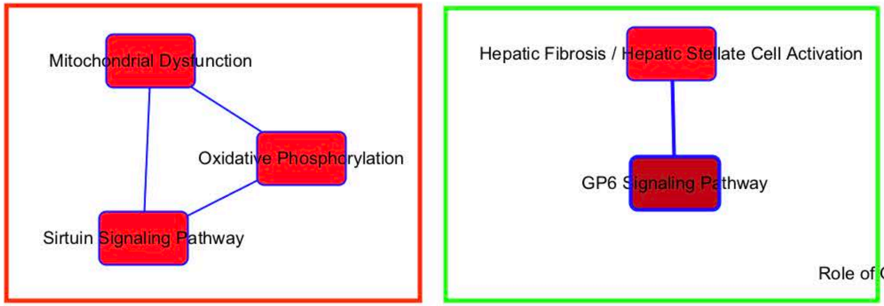
Interpretation With IPA

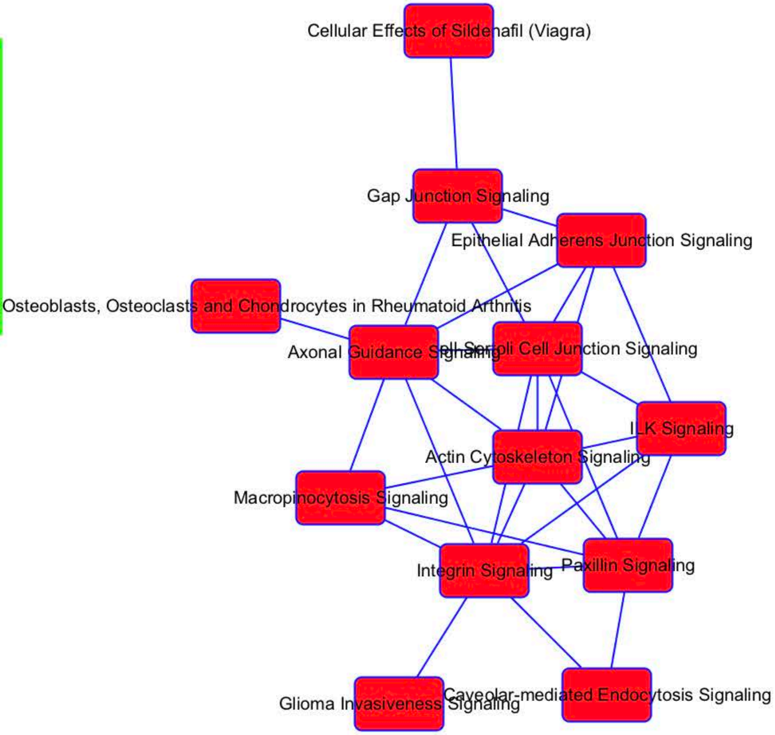


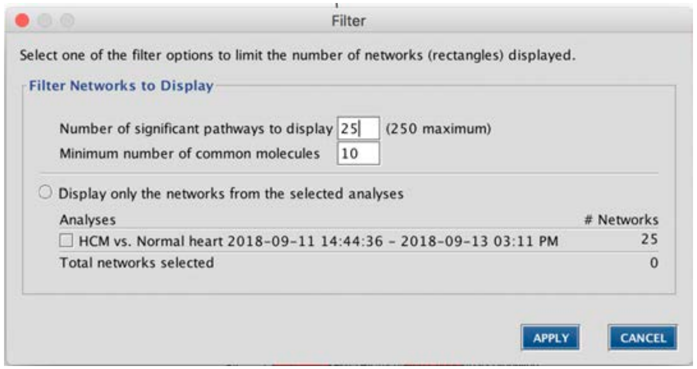
Interpretation With IPA



Canonical Pathway Overlap






Filter

Select one of the filter options to limit the number of networks (rectangles) displayed.

Filter Networks to Display

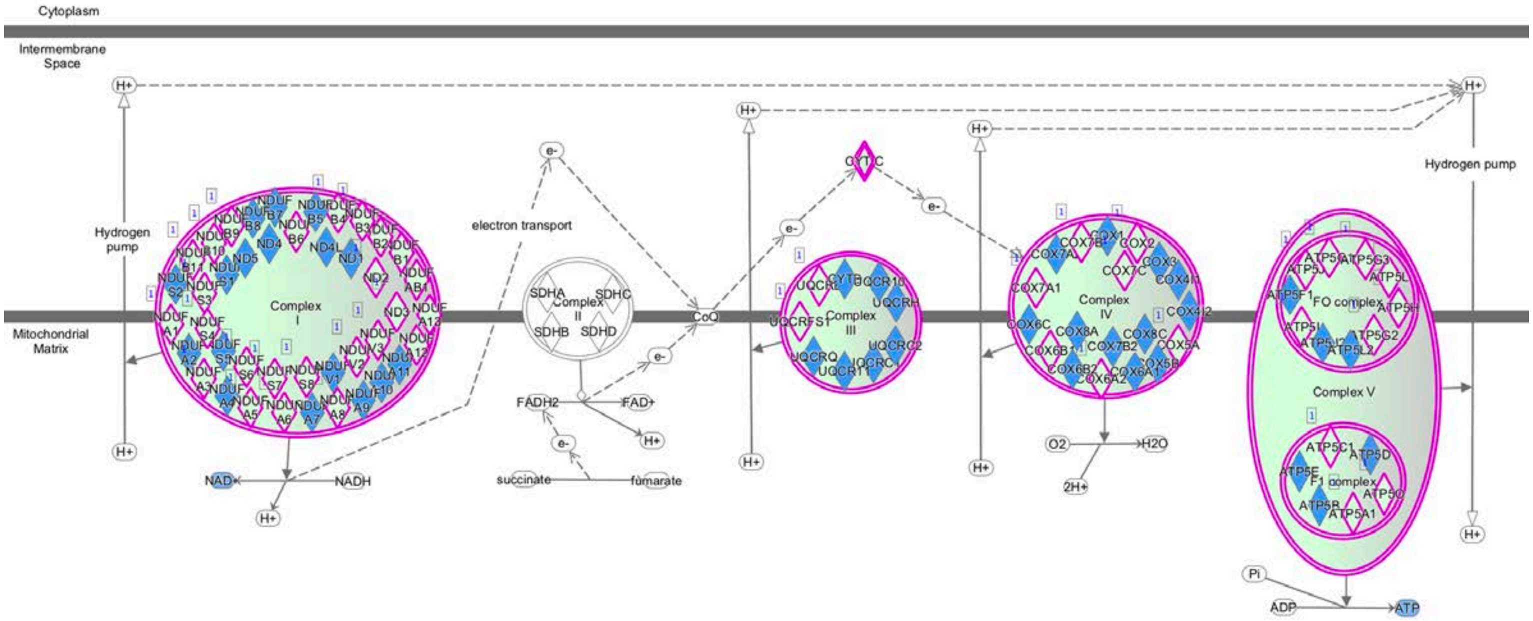
○ Number of significant pathways to display 25 (250 maximum)

Minimum number of common molecules 10

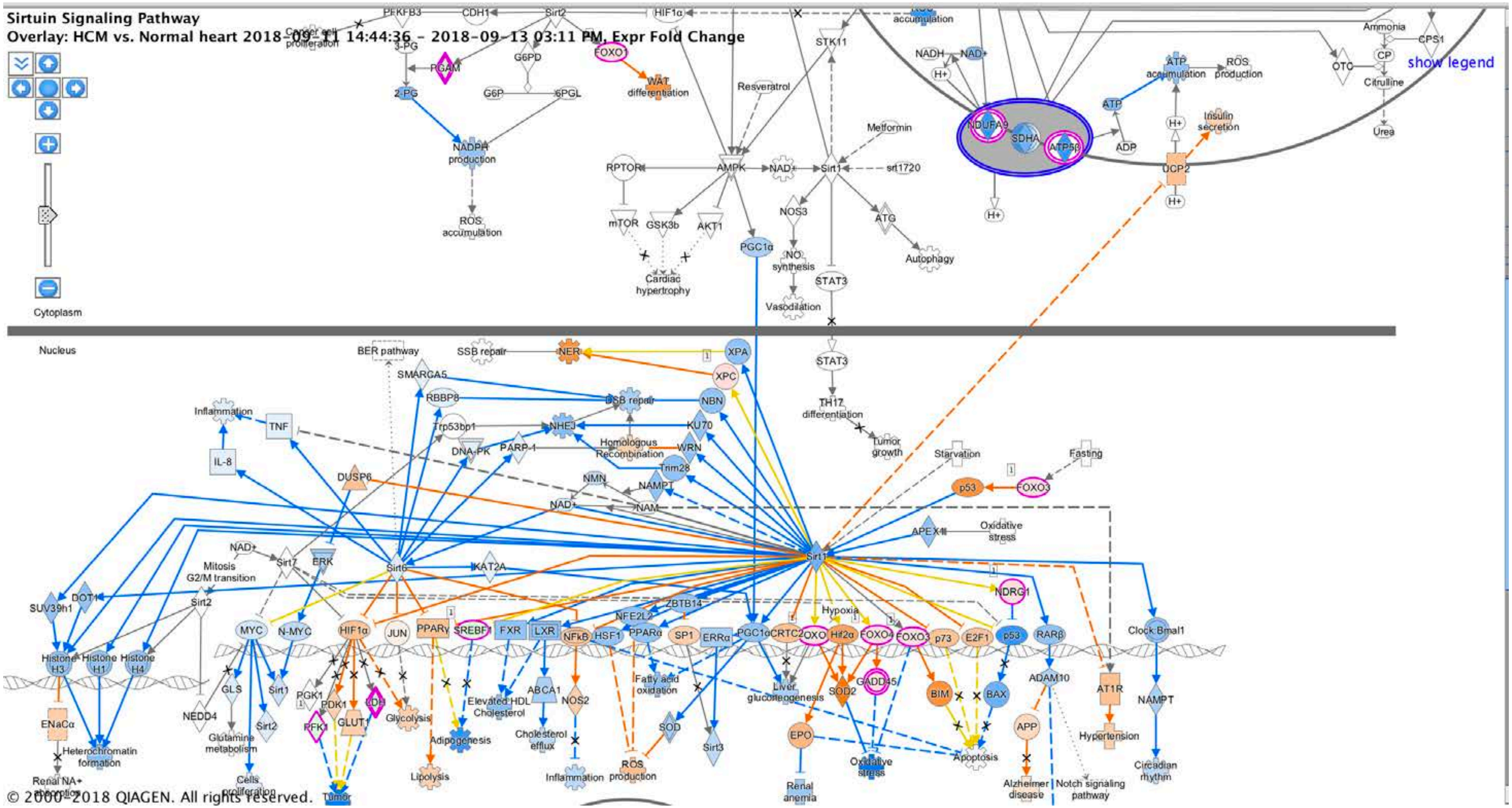
○ Display only the networks from the selected analyses

Analyses	# Networks
☐ HCM vs. Normal heart 2018-09-11 14:44:36 - 2018-09-13 03:11 PM	25
Total networks selected	0

Oxidative phosphorylation (expression)



Sirtuin Pathway (expression)



Sirtuin Signaling Pathway

Overlay: HCM vs. Normal heart 2018-09-11 14:44:36 - 2018-09-13 03:11 PM, Expr Fold Change

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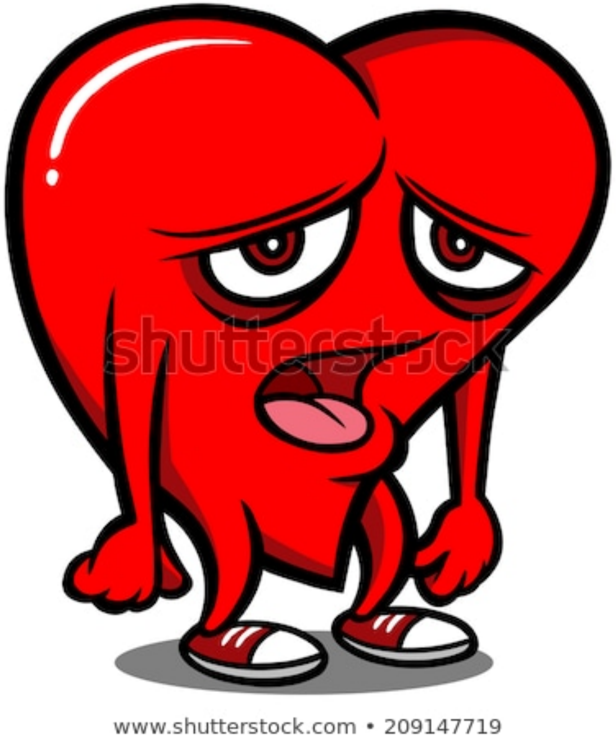
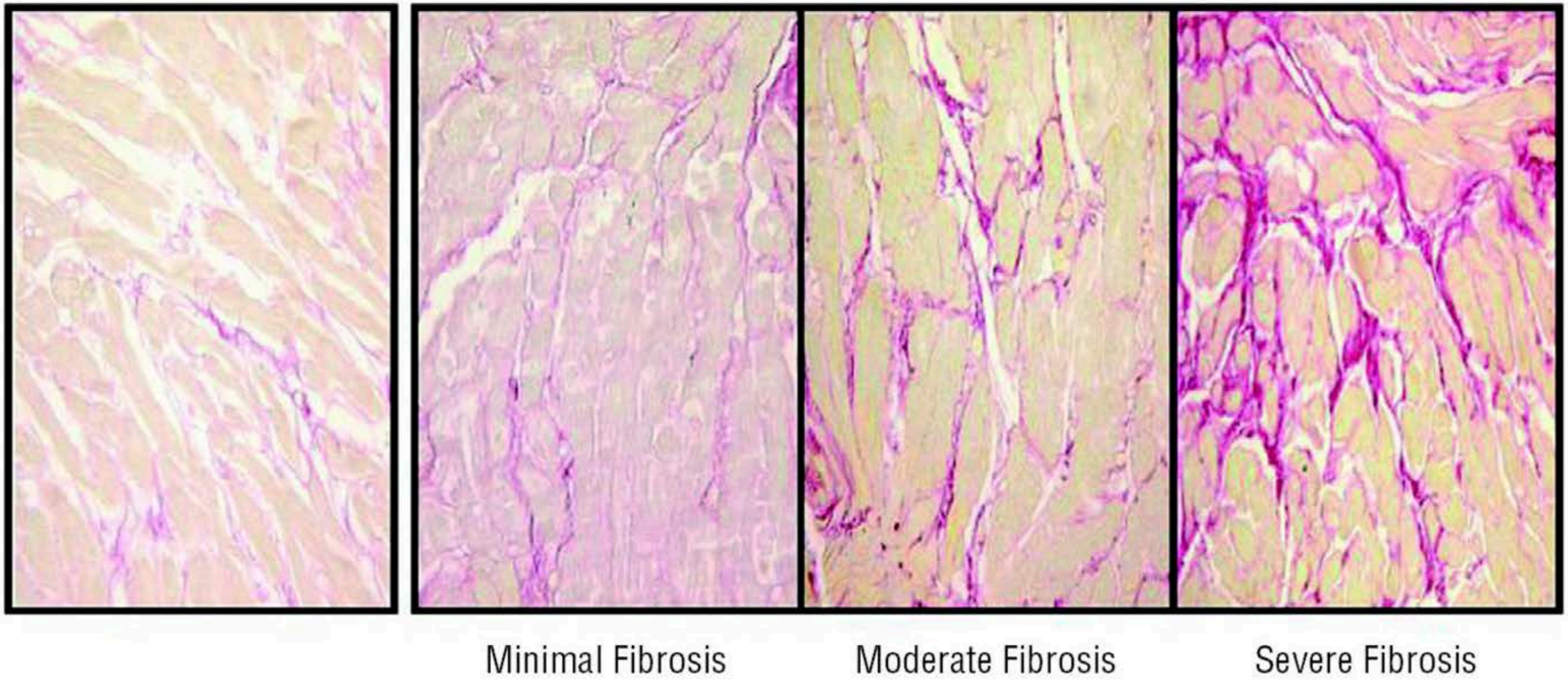
The Heart Is Lacking Energy!



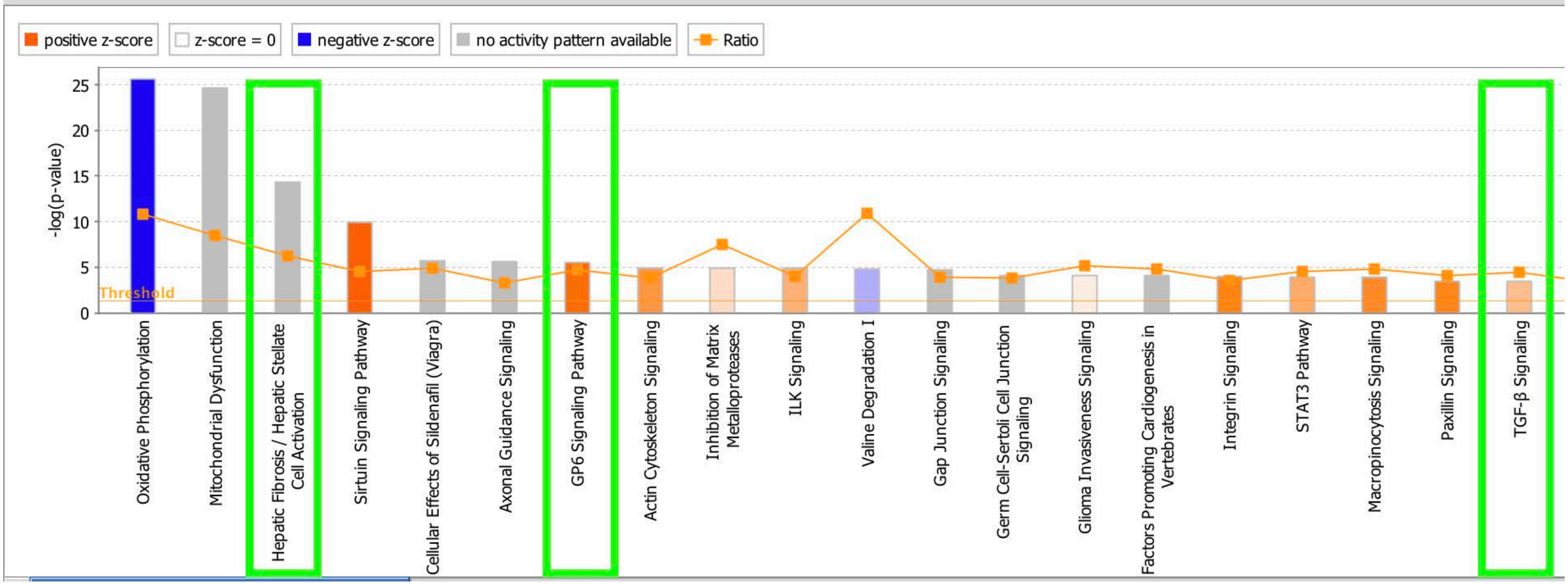
Fibrosis



Minimal Fibrosis Moderate Fibrosis Severe Fibrosis

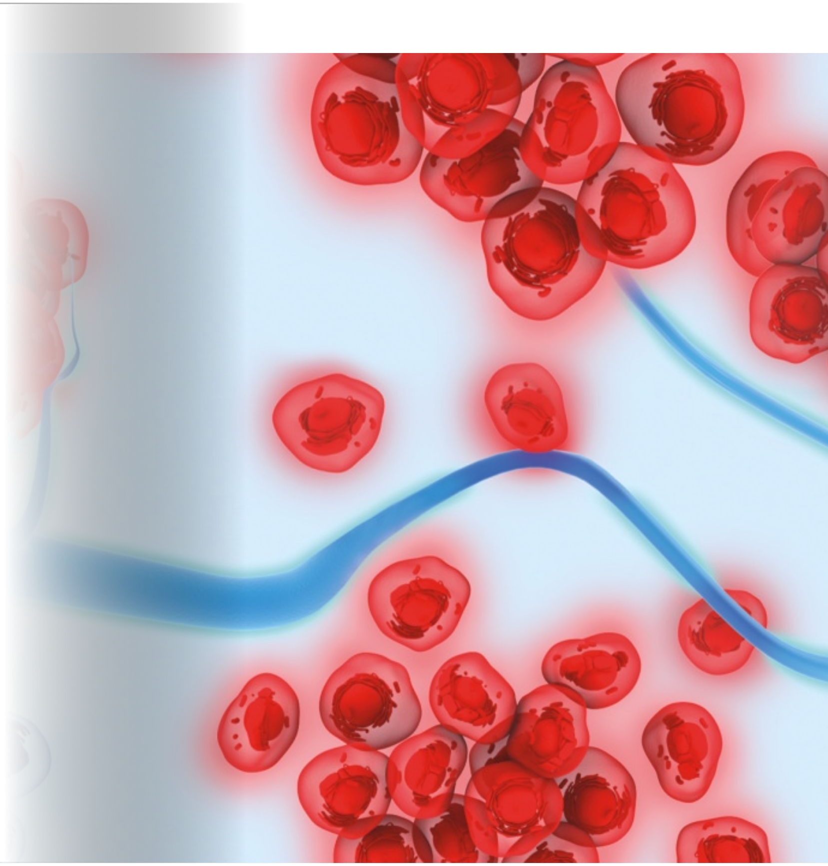
Rev Esp Cardiol. 2006;59:1047

Fibrosis


positive z-score
z-score = 0
negative z-score
no activity pattern available
Ratio
-log(p-value)
25
20
15
10
5
0
Threshold
Oxidative Phosphorylation
Mitochondrial Dysfunction
Hepatic Fibrosis / Hepatic Stellate Cell Activation
Sirtuin Signaling Pathway
Cellular Effects of Sildenafil (Viagra)
Axonal Guidance Signaling
GP6 Signaling Pathway
Actin Cytoskeleton Signaling
Inhibition of Matrix Metalloproteases
ILK Signaling
Valine Degradation I
Gap Junction Signaling
Germ Cell-Sertoli Cell Junction Signaling
Glioma Invasiveness Signaling
Factors Promoting Cardiogenesis in Vertebrates
Integrin Signaling
STAT3 Pathway
Macropinocytosis Signaling
Paxillin Signaling
TGF-β Signaling

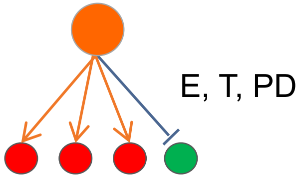
Explore the underlying transcriptional programs

Upstream Analysis



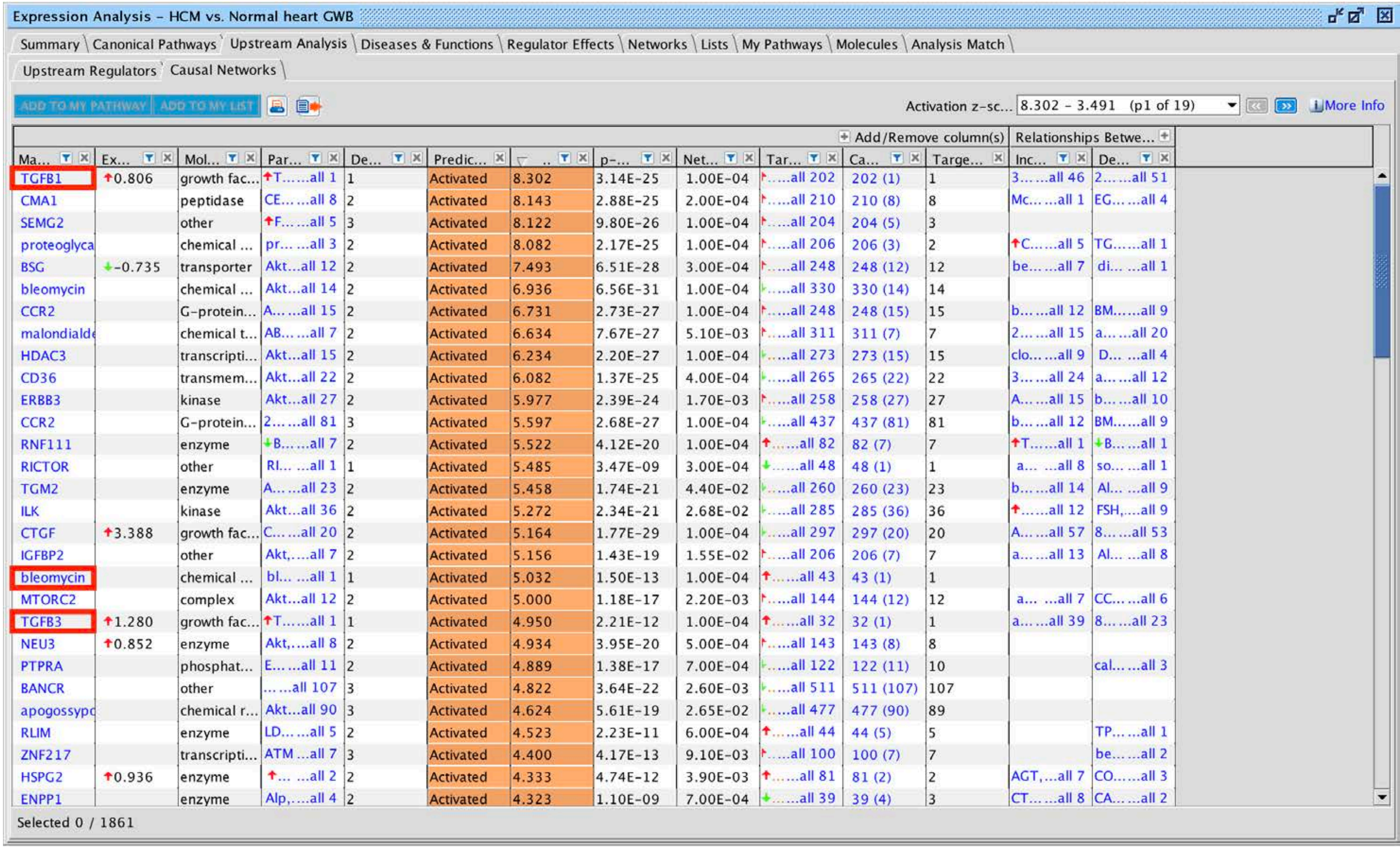
Network types in IPA

Upstream regulator



Dataset molecules

Upstream Regulators Associated with Fibrosis



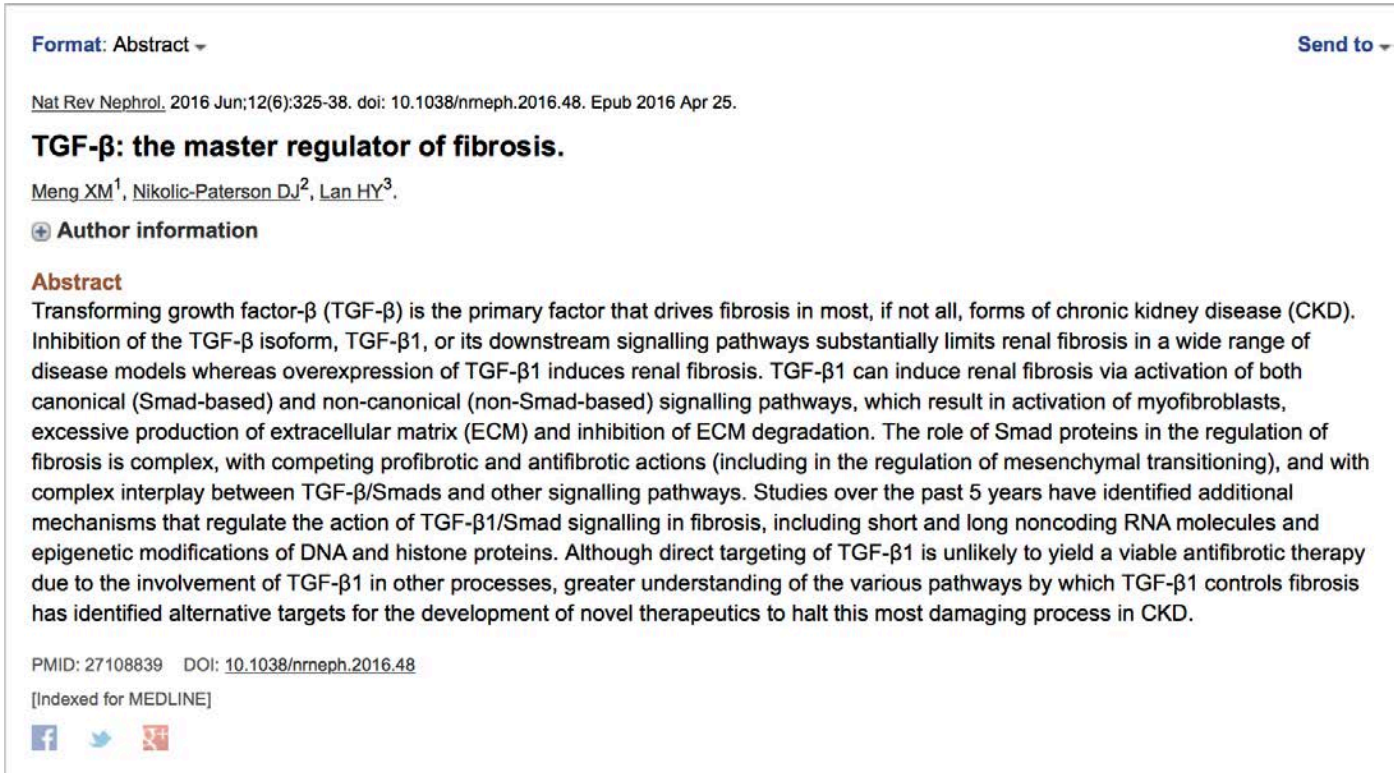
Expression Analysis - HCM vs. Normal heart GWB

Activation z-sc... 8.302 - 3.491 (p1 of 19)

Ma...	Ex...	Mol...	Par...	De...	Predic...	..	p-...	Net...	Tar...	Ca...	Targe...	Inc...	De...
TGFB1	↑0.806	growth fac...	↑T......all 1	1	Activated	8.302	3.14E-25	1.00E-04	↑.....all 202	202 (1)	1	3... ...all 46	2......all 51
CMA1		peptidase	CE... ...all 8	2	Activated	8.143	2.88E-25	2.00E-04	↑.....all 210	210 (8)	8	Mc... ...all 1	EG... ...all 4
SEMG2		other	↑F... ...all 5	3	Activated	8.122	9.80E-26	1.00E-04	↑.....all 204	204 (5)	3		
proteoglyca		chemical ...	pr... ...all 3	2	Activated	8.082	2.17E-25	1.00E-04	↑.....all 206	206 (3)	2	↑C... ...all 5	TG......all 1
BSG	↓-0.735	transporter	Akt...all 12	2	Activated	7.493	6.51E-28	3.00E-04	↑.....all 248	248 (12)	12	be... ...all 7	di... ...all 1
bleomycin		chemical ...	Akt...all 14	2	Activated	6.936	6.56E-31	1.00E-04	↓.....all 330	330 (14)	14		
CCR2		G-protein...	A... ...all 15	2	Activated	6.731	2.73E-27	1.00E-04	↑.....all 248	248 (15)	15	b... ...all 12	BM......all 9
malondialde		chemical t...	AB... ...all 7	2	Activated	6.634	7.67E-27	5.10E-03	↑.....all 311	311 (7)	7	2... ...all 15	a... ...all 20
HDAC3		transcripti...	Akt...all 15	2	Activated	6.234	2.20E-27	1.00E-04	↓.....all 273	273 (15)	15	clo... ...all 9	D... ...all 4
CD36		transmem...	Akt...all 22	2	Activated	6.082	1.37E-25	4.00E-04	↓.....all 265	265 (22)	22	3... ...all 24	a... ...all 12
ERBB3		kinase	Akt...all 27	2	Activated	5.977	2.39E-24	1.70E-03	↑.....all 258	258 (27)	27	A... ...all 15	b... ...all 10
CCR2		G-protein...	2... ...all 81	3	Activated	5.597	2.68E-27	1.00E-04	↓.....all 437	437 (81)	81	b... ...all 12	BM......all 9
RNF111		enzyme	↓B... ...all 7	2	Activated	5.522	4.12E-20	1.00E-04	↑......all 82	82 (7)	7	↑T......all 1	↓B... ...all 1
RICTOR		other	RI... ...all 1	1	Activated	5.485	3.47E-09	3.00E-04	↓......all 48	48 (1)	1	a... ...all 8	so... ...all 1
TGM2		enzyme	A... ...all 23	2	Activated	5.458	1.74E-21	4.40E-02	↓.....all 260	260 (23)	23	b... ...all 14	Al... ...all 9
ILK		kinase	Akt...all 36	2	Activated	5.272	2.34E-21	2.68E-02	↓.....all 285	285 (36)	36	↑......all 12	FSH,....all 9
CTGF	↑3.388	growth fac...	C... ...all 20	2	Activated	5.164	1.77E-29	1.00E-04	↓.....all 297	297 (20)	20	A... ...all 57	8... ...all 53
IGFBP2		other	Akt,....all 7	2	Activated	5.156	1.43E-19	1.55E-02	↑.....all 206	206 (7)	7	a... ...all 13	Al... ...all 8
bleomycin		chemical ...	bl... ...all 1	1	Activated	5.032	1.50E-13	1.00E-04	↑......all 43	43 (1)	1		
MTORC2		complex	Akt...all 12	2	Activated	5.000	1.18E-17	2.20E-03	↑.....all 144	144 (12)	12	a... ...all 7	CC... ...all 6
TGFB3	↑1.280	growth fac...	↑T......all 1	1	Activated	4.950	2.21E-12	1.00E-04	↑......all 32	32 (1)	1	a... ...all 39	8... ...all 23
NEU3	↑0.852	enzyme	Akt,....all 8	2	Activated	4.934	3.95E-20	5.00E-04	↑.....all 143	143 (8)	8		
PTPRA		phosphat...	E... ...all 11	2	Activated	4.889	1.38E-17	7.00E-04	↓.....all 122	122 (11)	10		cal... ...all 3
BANCR		other	... ...all 107	3	Activated	4.822	3.64E-22	2.60E-03	↓.....all 511	511 (107)	107		
apogossypc		chemical r...	Akt...all 90	3	Activated	4.624	5.61E-19	2.65E-02	↓.....all 477	477 (90)	89		
RLIM		enzyme	LD... ...all 5	2	Activated	4.523	2.23E-11	6.00E-04	↑......all 44	44 (5)	5		TP... ...all 1
ZNF217		transcripti...	ATM ...all 7	3	Activated	4.400	4.17E-13	9.10E-03	↑.....all 100	100 (7)	7		be... ...all 2
HSPG2	↑0.936	enzyme	↑... ...all 2	2	Activated	4.333	4.74E-12	3.90E-03	↑......all 81	81 (2)	2	AGT,...all 7	CO... ...all 3
ENPP1		enzyme	Alp,....all 4	2	Activated	4.323	1.10E-09	7.00E-04	↓......all 39	39 (4)	3	CT... ...all 8	CA... ...all 2

Selected 0 / 1861

TGF-B Regulates Fibrosis



Nat Rev Nephrol. 2016 Jun;12(6):325-38. doi: 10.1038/nrneph.2016.48. Epub 2016 Apr 25.

TGF-β: the master regulator of fibrosis.

Meng XM[1], Nikolic-Paterson DJ[2], Lan HY[3].

Author information

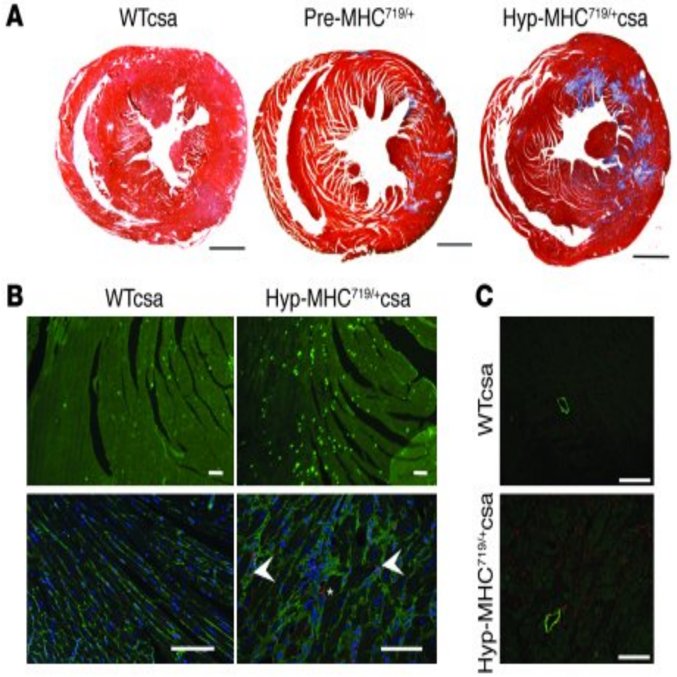
Abstract

Transforming growth factor-β (TGF-β) is the primary factor that drives fibrosis in most, if not all, forms of chronic kidney disease (CKD). Inhibition of the TGF-β isoform, TGF-β1, or its downstream signalling pathways substantially limits renal fibrosis in a wide range of disease models whereas overexpression of TGF-β1 induces renal fibrosis. TGF-β1 can induce renal fibrosis via activation of both canonical (Smad-based) and non-canonical (non-Smad-based) signalling pathways, which result in activation of myofibroblasts, excessive production of extracellular matrix (ECM) and inhibition of ECM degradation. The role of Smad proteins in the regulation of fibrosis is complex, with competing profibrotic and antifibrotic actions (including in the regulation of mesenchymal transitioning), and with complex interplay between TGF-β/Smads and other signalling pathways. Studies over the past 5 years have identified additional mechanisms that regulate the action of TGF-β1/Smad signalling in fibrosis, including short and long noncoding RNA molecules and epigenetic modifications of DNA and histone proteins. Although direct targeting of TGF-β1 is unlikely to yield a viable antifibrotic therapy due to the involvement of TGF-β1 in other processes, greater understanding of the various pathways by which TGF-β1 controls fibrosis has identified alternative targets for the development of novel therapeutics to halt this most damaging process in CKD.

PMID: 27108839 DOI: 10.1038/nrneph.2016.48

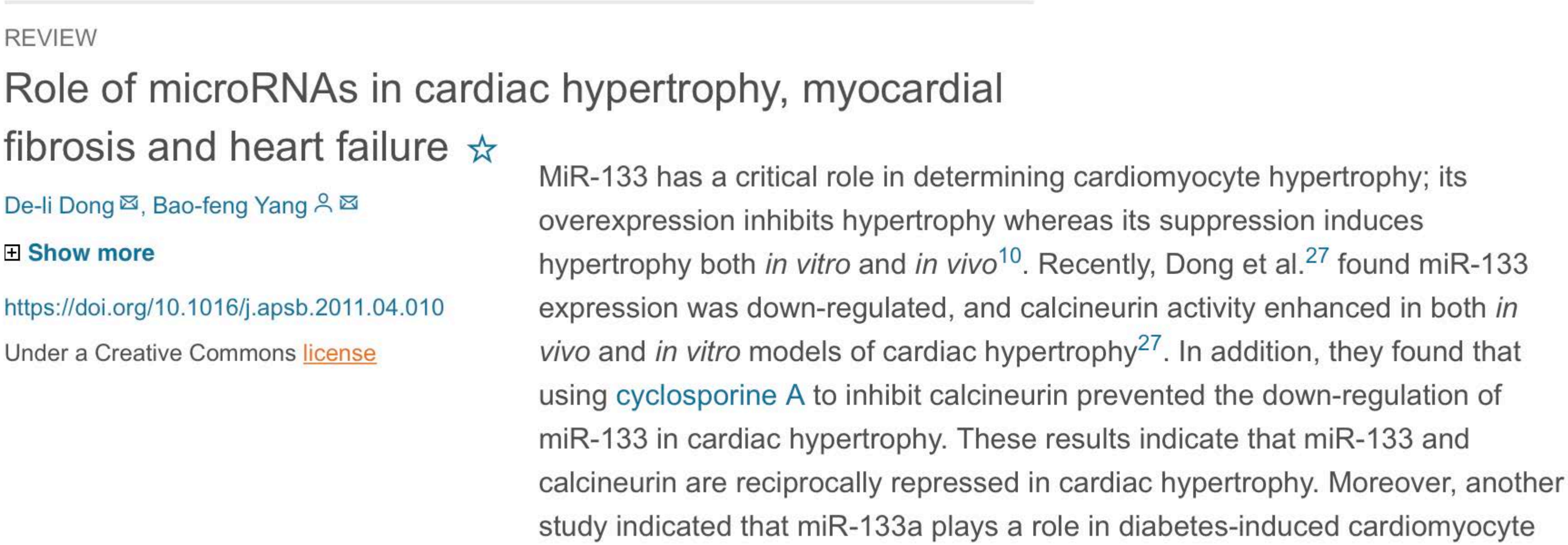
[Indexed for MEDLINE]

Cardiac fibrosis in mice with hypertrophic cardiomyopathy is mediated by non-myocyte proliferation and requires Tgf-β



J Clin Invest DOI: 10.1172/JCI42028

Mir-133 Role in HCM



REVIEW

Role of microRNAs in cardiac hypertrophy, myocardial fibrosis and heart failure ☆

De-li Dong, Bao-feng Yang

⊞ **Show more**

https://doi.org/10.1016/j.apsb.2011.04.010

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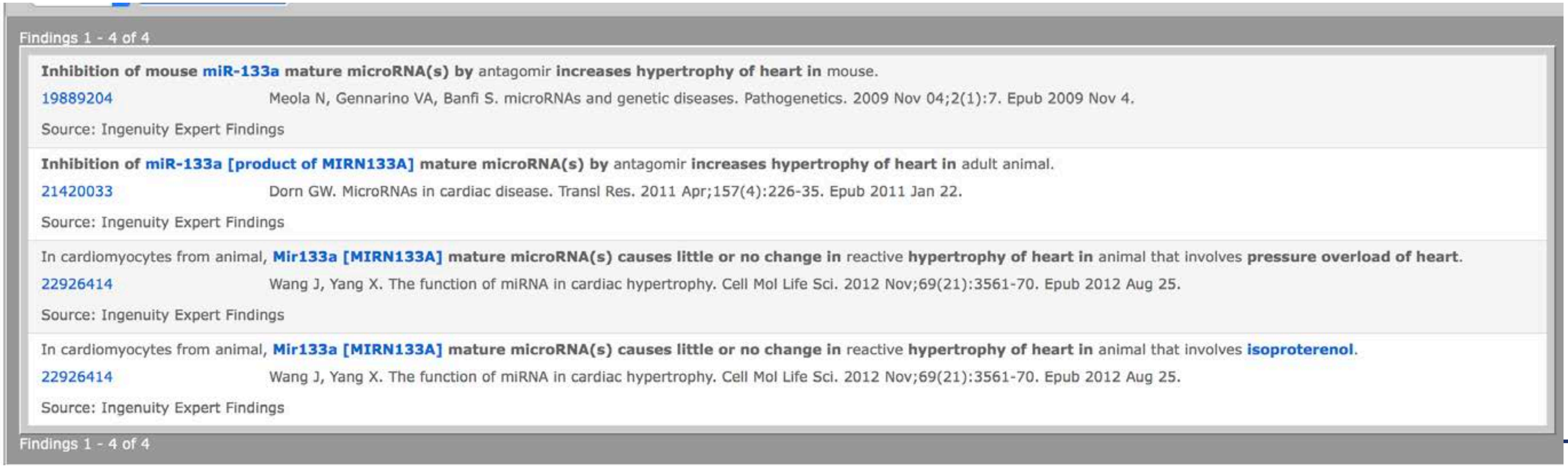
MiR-133 has a critical role in determining cardiomyocyte hypertrophy; its overexpression inhibits hypertrophy whereas its suppression induces hypertrophy both *in vitro* and *in vivo*[10]. Recently, Dong et al.[27] found miR-133 expression was down-regulated, and calcineurin activity enhanced in both *in vivo* and *in vitro* models of cardiac hypertrophy[27]. In addition, they found that using cyclosporine A to inhibit calcineurin prevented the down-regulation of miR-133 in cardiac hypertrophy. These results indicate that miR-133 and calcineurin are reciprocally repressed in cardiac hypertrophy. Moreover, another study indicated that miR-133a plays a role in diabetes-induced cardiomyocyte



Findings 1 - 4 of 4

Inhibition of mouse miR-133a mature microRNA(s) by antagomir **increases hypertrophy of heart in** mouse.
19889204 Meola N, Gennarino VA, Banfi S. microRNAs and genetic diseases. Pathogenetics. 2009 Nov 04;2(1):7. Epub 2009 Nov 4.
Source: Ingenuity Expert Findings

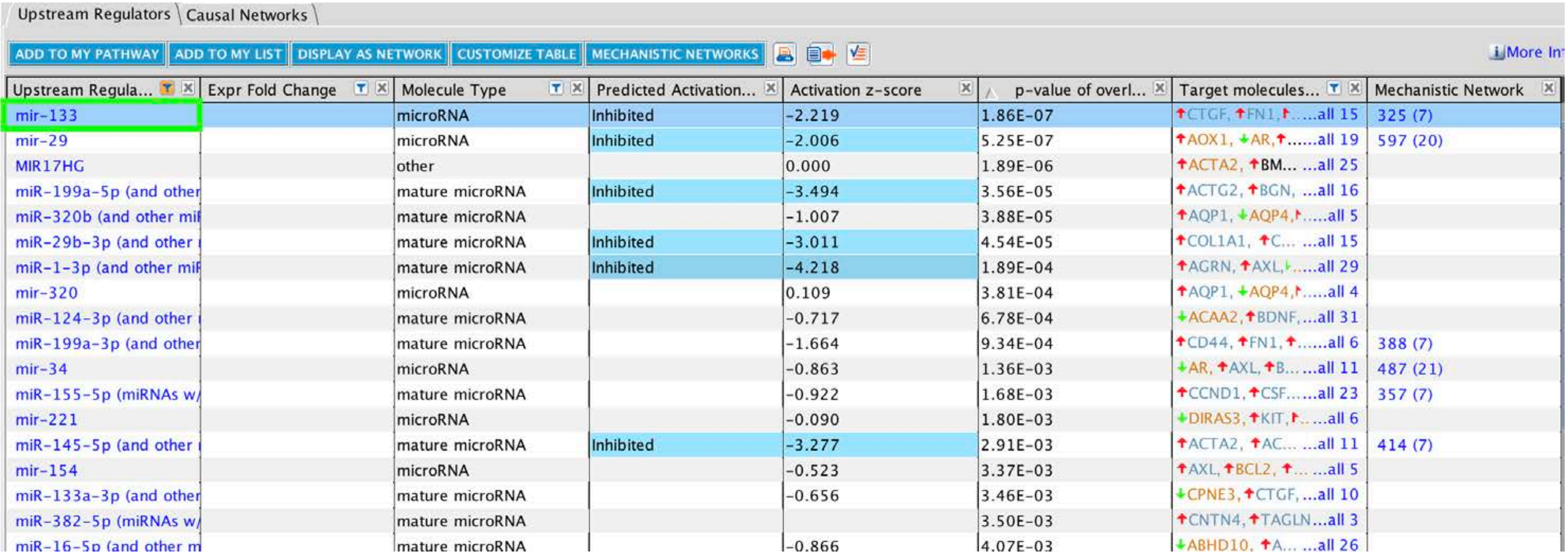
Inhibition of miR-133a [product of MIRN133A] mature microRNA(s) by antagomir **increases hypertrophy of heart in** adult animal.
21420033 Dorn GW. MicroRNAs in cardiac disease. Transl Res. 2011 Apr;157(4):226-35. Epub 2011 Jan 22.
Source: Ingenuity Expert Findings

In cardiomyocytes from animal, **Mir133a [MIRN133A] mature microRNA(s) causes little or no change in** reactive **hypertrophy of heart in** animal that involves **pressure overload of heart**.
22926414 Wang J, Yang X. The function of miRNA in cardiac hypertrophy. Cell Mol Life Sci. 2012 Nov;69(21):3561-70. Epub 2012 Aug 25.
Source: Ingenuity Expert Findings

In cardiomyocytes from animal, **Mir133a [MIRN133A] mature microRNA(s) causes little or no change in** reactive **hypertrophy of heart in** animal that involves **isoproterenol**.
22926414 Wang J, Yang X. The function of miRNA in cardiac hypertrophy. Cell Mol Life Sci. 2012 Nov;69(21):3561-70. Epub 2012 Aug 25.
Source: Ingenuity Expert Findings

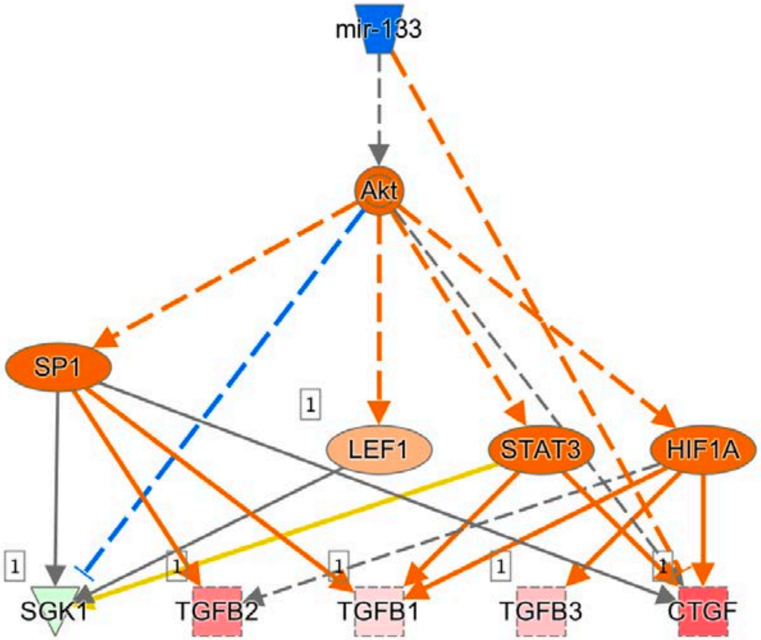
Findings 1 - 4 of 4

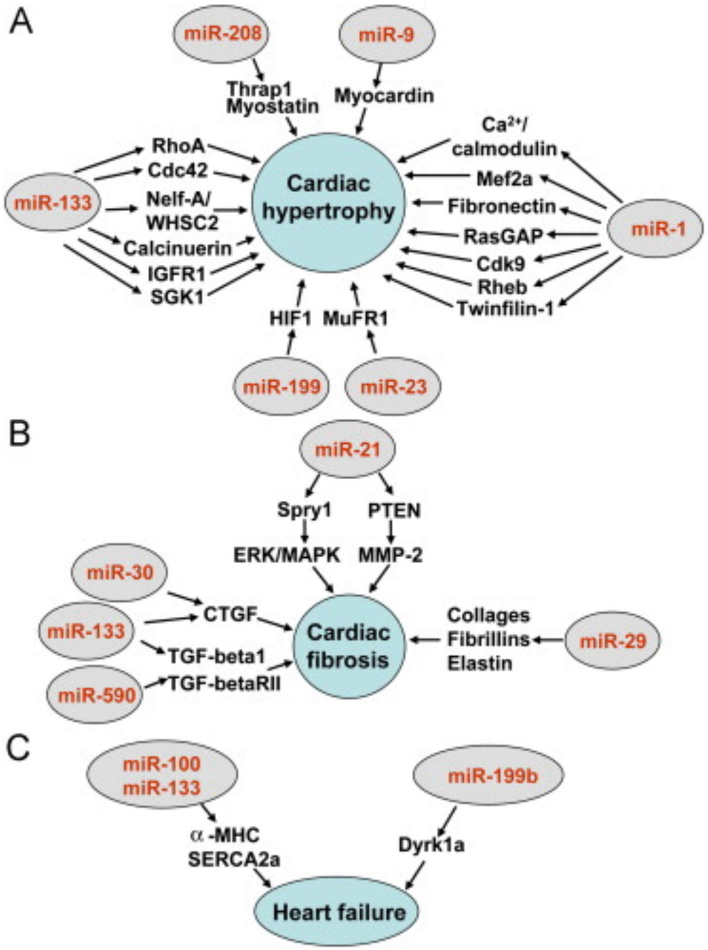
Mir-133 Role in HCM



Upstream Regula...	Expr Fold Change	Molecule Type	Predicted Activation...	Activation z-score	p-value of overl...	Target molecules...	Mechanistic Network
mir-133		microRNA	Inhibited	-2.219	1.86E-07	↑CTGF, ↑FN1,↑......all 15	325 (7)
mir-29		microRNA	Inhibited	-2.006	5.25E-07	↑AOX1, ↓AR,↑......all 19	597 (20)
MIR17HG		other		0.000	1.89E-06	↑ACTA2, ↑BM... ...all 25	
miR-199a-5p (and other		mature microRNA	Inhibited	-3.494	3.56E-05	↑ACTG2, ↑BGN, ...all 16	
miR-320b (and other mi		mature microRNA		-1.007	3.88E-05	↑AQP1, ↓AQP4,↑.....all 5	
miR-29b-3p (and other		mature microRNA	Inhibited	-3.011	4.54E-05	↑COL1A1, ↑C... ...all 15	
miR-1-3p (and other mi		mature microRNA	Inhibited	-4.218	1.89E-04	↑AGRN, ↑AXL,↓.....all 29	
mir-320		microRNA		0.109	3.81E-04	↑AQP1, ↓AQP4,↑.....all 4	
miR-124-3p (and other		mature microRNA		-0.717	6.78E-04	↓ACAA2,↑BDNF,...all 31	
miR-199a-3p (and other		mature microRNA		-1.664	9.34E-04	↑CD44, ↑FN1, ↑......all 6	388 (7)
mir-34		microRNA		-0.863	1.36E-03	↓AR, ↑AXL, ↑B... ...all 11	487 (21)
miR-155-5p (miRNAs w/		mature microRNA		-0.922	1.68E-03	↑CCND1,↑CSF......all 23	357 (7)
mir-221		microRNA		-0.090	1.80E-03	↓DIRAS3,↑KIT,↑.. ...all 6	
miR-145-5p (and other		mature microRNA	Inhibited	-3.277	2.91E-03	↑ACTA2, ↑AC... ...all 11	414 (7)
mir-154		microRNA		-0.523	3.37E-03	↑AXL,↑BCL2, ↑... ...all 5	
miR-133a-3p (and other		mature microRNA		-0.656	3.46E-03	↓CPNE3,↑CTGF, ...all 10	
miR-382-5p (miRNAs w/		mature microRNA			3.50E-03	↑CNTN4,↑TAGLN...all 3	
miR-16-5p (and other m		mature microRNA		-0.866	4.07E-03	↓ABHD10, ↑A... ...all 26	

Mir-133 Role in HCM

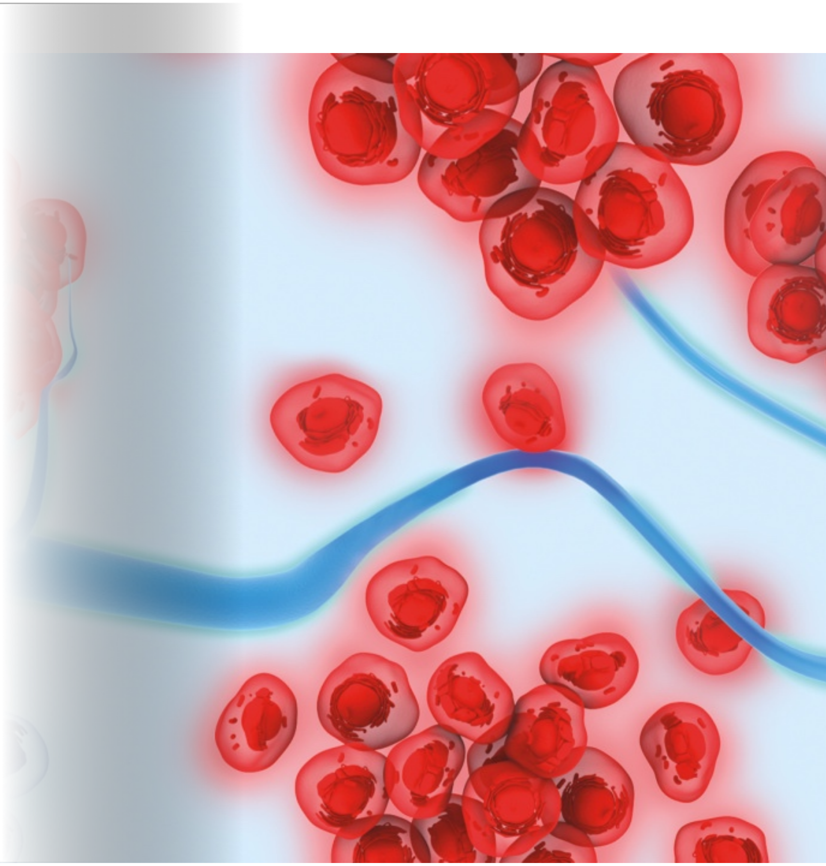




Role of microRNAs in cardiac hypertrophy, myocardial fibrosis and heart failure☆
Author links open overlay panelDe-liDongBao-fengYang

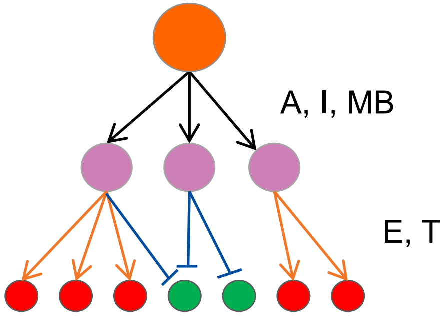
Generate hypotheses to validate in the lab

Causal Network

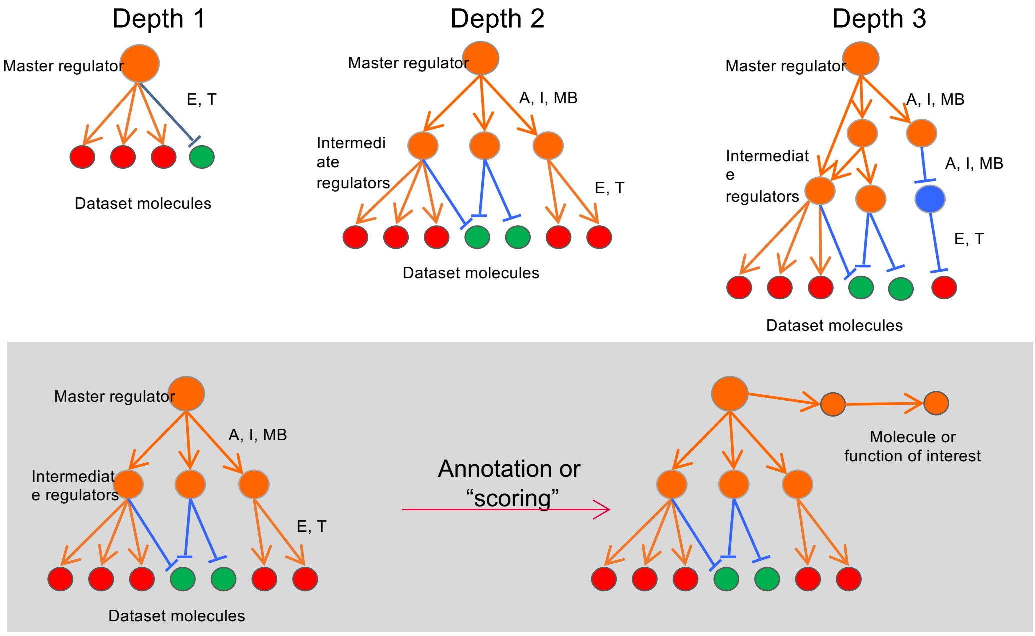


Network types in IPA

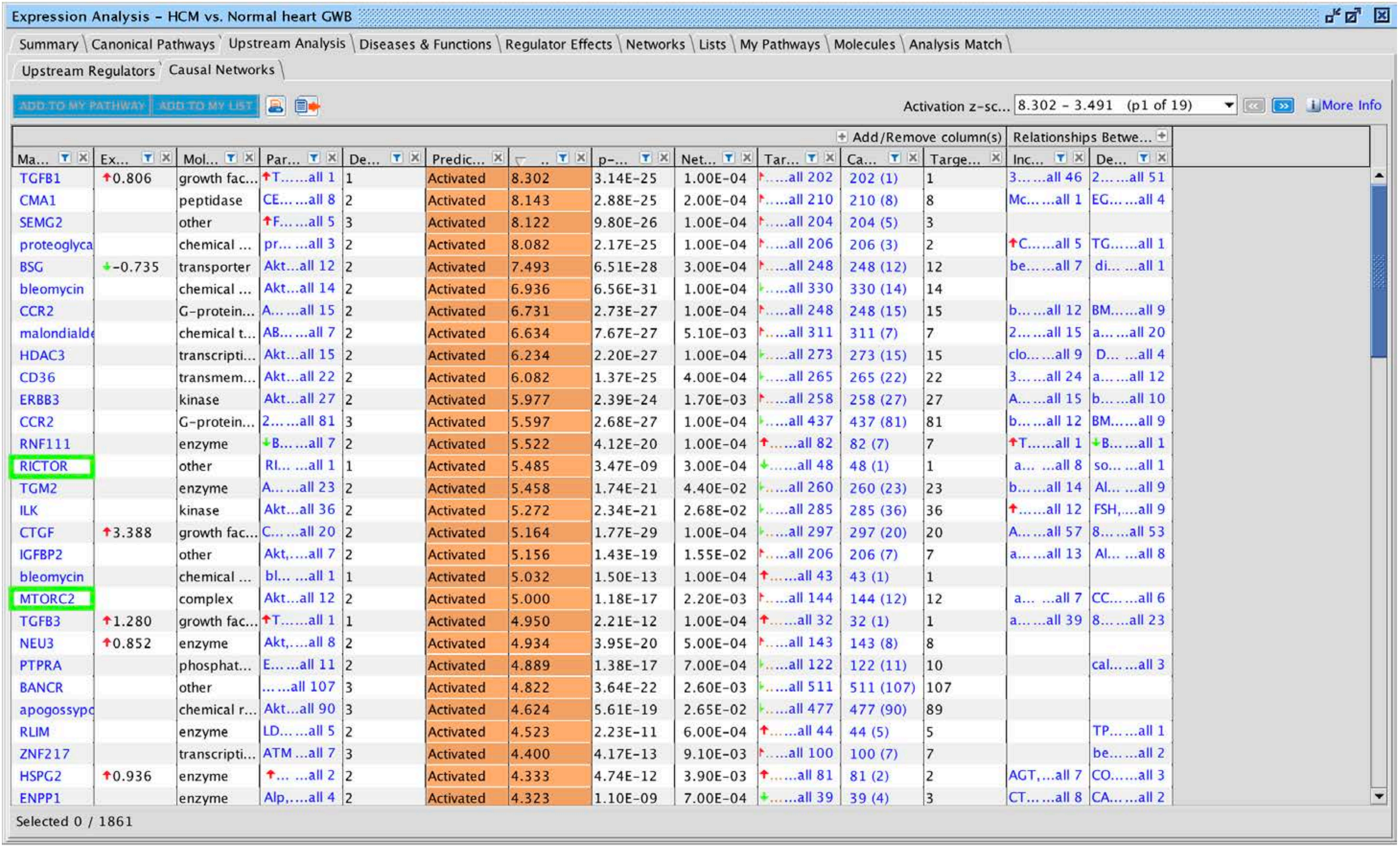
Causal network



Causal network analysis in IPA



Specific Regulators For HCM

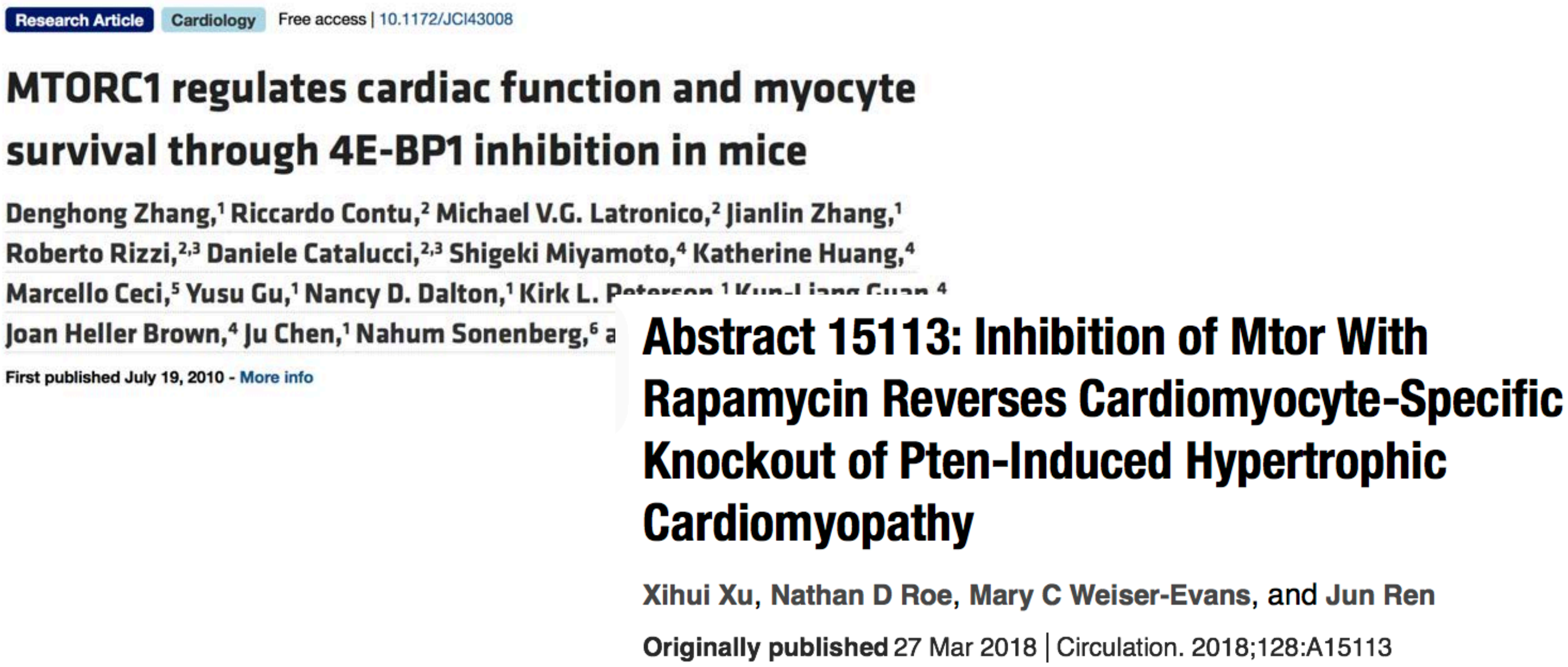


Activation z-sc... 8.302 - 3.491 (p1 of 19)

												Relationships Betwe...	
Ma...	Ex...	Mol...	Par...	De...	Predic...	..	p-...	Net...	Tar...	Ca...	Targe...	Inc...	De...
TGFB1	↑0.806	growth fac...	↑T... ...all 1	1	Activated	8.302	3.14E-25	1.00E-04	......all 202	202 (1)	1	3... ...all 46	2... ...all 51
CMA1		peptidase	CE... ...all 8	2	Activated	8.143	2.88E-25	2.00E-04	......all 210	210 (8)	8	Mc... ...all 1	EG... ...all 4
SEMG2		other	↑F... ...all 5	3	Activated	8.122	9.80E-26	1.00E-04	......all 204	204 (5)	3		
proteoglyca		chemical ...	pr... ...all 3	2	Activated	8.082	2.17E-25	1.00E-04	......all 206	206 (3)	2	↑C... ...all 5	TG... ...all 1
BSG	↓-0.735	transporter	Akt...all 12	2	Activated	7.493	6.51E-28	3.00E-04	......all 248	248 (12)	12	be... ...all 7	di... ...all 1
bleomycin		chemical ...	Akt...all 14	2	Activated	6.936	6.56E-31	1.00E-04	......all 330	330 (14)	14		
CCR2		G-protein...	A... ...all 15	2	Activated	6.731	2.73E-27	1.00E-04	......all 248	248 (15)	15	b... ...all 12	BM... ...all 9
malondiald		chemical t...	AB... ...all 7	2	Activated	6.634	7.67E-27	5.10E-03	......all 311	311 (7)	7	2... ...all 15	a... ...all 20
HDAC3		transcripti...	Akt...all 15	2	Activated	6.234	2.20E-27	1.00E-04	......all 273	273 (15)	15	clo... ...all 9	D... ...all 4
CD36		transmem...	Akt...all 22	2	Activated	6.082	1.37E-25	4.00E-04	......all 265	265 (22)	22	3... ...all 24	a... ...all 12
ERBB3		kinase	Akt...all 27	2	Activated	5.977	2.39E-24	1.70E-03	......all 258	258 (27)	27	A... ...all 15	b... ...all 10
CCR2		G-protein...	2... ...all 81	3	Activated	5.597	2.68E-27	1.00E-04	......all 437	437 (81)	81	b... ...all 12	BM... ...all 9
RNF111		enzyme	↓B... ...all 7	2	Activated	5.522	4.12E-20	1.00E-04	↑......all 82	82 (7)	7	↑T... ...all 1	↓B... ...all 1
RICTOR		other	RI... ...all 1	1	Activated	5.485	3.47E-09	3.00E-04	↓......all 48	48 (1)	1	a... ...all 8	so... ...all 1
TGM2		enzyme	A... ...all 23	2	Activated	5.458	1.74E-21	4.40E-02	......all 260	260 (23)	23	b... ...all 14	Al... ...all 9
ILK		kinase	Akt...all 36	2	Activated	5.272	2.34E-21	2.68E-02	......all 285	285 (36)	36	↑......all 12	FSH,....all 9
CTGF	↑3.388	growth fac...	C... ...all 20	2	Activated	5.164	1.77E-29	1.00E-04	......all 297	297 (20)	20	A... ...all 57	8... ...all 53
IGFBP2		other	Akt,....all 7	2	Activated	5.156	1.43E-19	1.55E-02	......all 206	206 (7)	7	a... ...all 13	Al... ...all 8
bleomycin		chemical ...	bl... ...all 1	1	Activated	5.032	1.50E-13	1.00E-04	↑......all 43	43 (1)	1		
MTORC2		complex	Akt...all 12	2	Activated	5.000	1.18E-17	2.20E-03	......all 144	144 (12)	12	a... ...all 7	CC... ...all 6
TGFB3	↑1.280	growth fac...	↑T... ...all 1	1	Activated	4.950	2.21E-12	1.00E-04	↑......all 32	32 (1)	1	a... ...all 39	8... ...all 23
NEU3	↑0.852	enzyme	Akt,....all 8	2	Activated	4.934	3.95E-20	5.00E-04	......all 143	143 (8)	8		
PTPRA		phosphat...	E... ...all 11	2	Activated	4.889	1.38E-17	7.00E-04	......all 122	122 (11)	10		cal... ...all 3
BANCR		other	... ...all 107	3	Activated	4.822	3.64E-22	2.60E-03	......all 511	511 (107)	107		
apogossypo		chemical r...	Akt...all 90	3	Activated	4.624	5.61E-19	2.65E-02	......all 477	477 (90)	89		
RLIM		enzyme	LD... ...all 5	2	Activated	4.523	2.23E-11	6.00E-04	↑......all 44	44 (5)	5		TP... ...all 1
ZNF217		transcripti...	ATM ...all 7	3	Activated	4.400	4.17E-13	9.10E-03	......all 100	100 (7)	7		be... ...all 2
HSPG2	↑0.936	enzyme	↑... ...all 2	2	Activated	4.333	4.74E-12	3.90E-03	↑......all 81	81 (2)	2	AGT,...all 7	CO... ...all 3
ENPP1		enzyme	Alp,....all 4	2	Activated	4.323	1.10E-09	7.00E-04	↓......all 39	39 (4)	3	CT... ...all 8	CA... ...all 2

Selected 0 / 1861

MTORC1 and HCM



Research Article **Cardiology** Free access | 10.1172/JCI43008

MTORC1 regulates cardiac function and myocyte survival through 4E-BP1 inhibition in mice

Denghong Zhang,[1] Riccardo Contu,[2] Michael V.G. Latronico,[2] Jianlin Zhang,[1] Roberto Rizzi,[2,3] Daniele Catalucci,[2,3] Shigeki Miyamoto,[4] Katherine Huang,[4] Marcello Ceci,[5] Yusu Gu,[1] Nancy D. Dalton,[1] Kirk L. Peterson,[1] Kun-Liang Guan,[4] Joan Heller Brown,[4] Ju Chen,[1] Nahum Sonenberg,[6] a

First published July 19, 2010 - More info

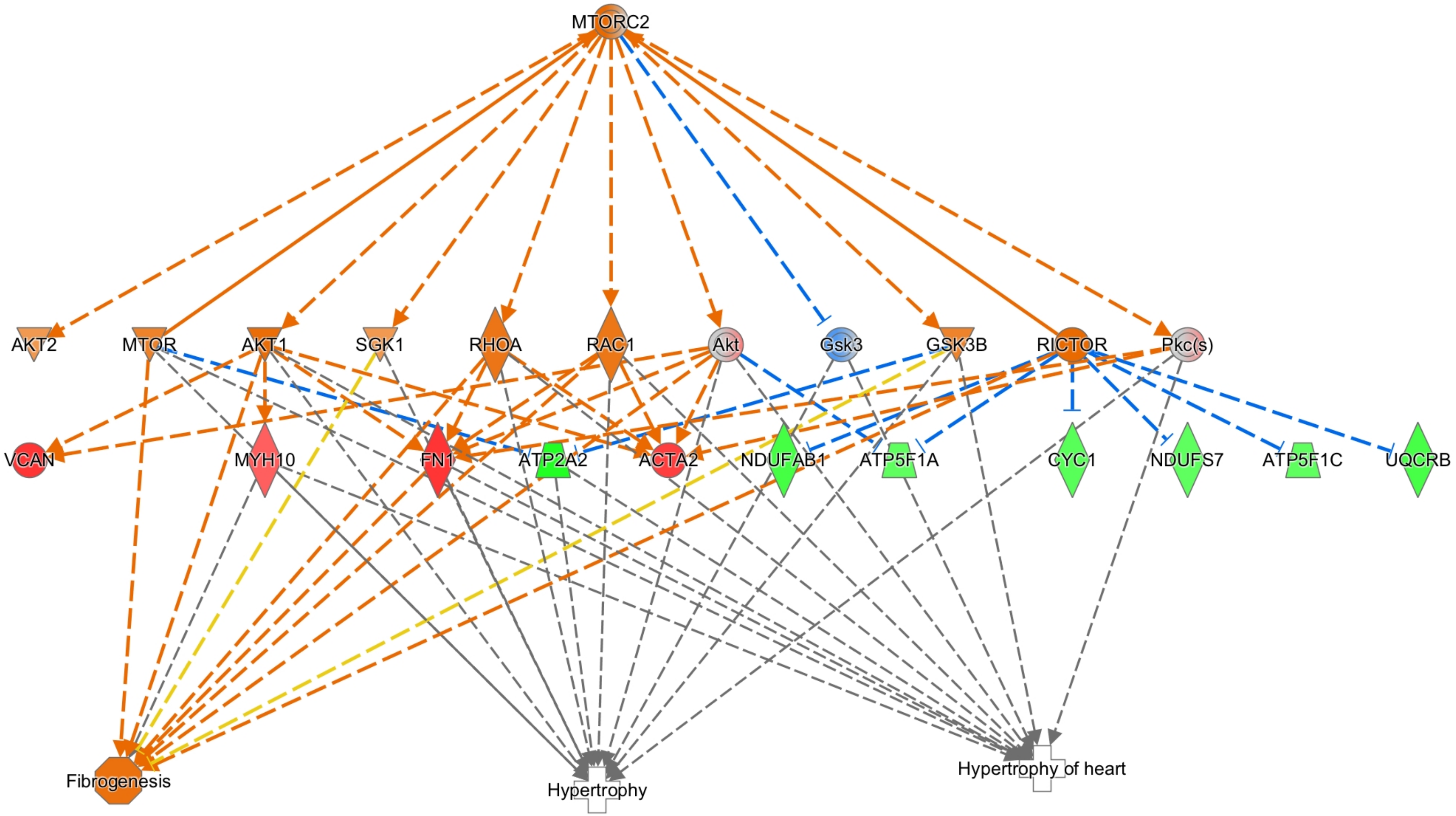
Abstract 15113: Inhibition of Mtor With Rapamycin Reverses Cardiomyocyte-Specific Knockout of Pten-Induced Hypertrophic Cardiomyopathy

Xihui Xu, Nathan D Roe, Mary C Weiser-Evans, and Jun Ren

Originally published 27 Mar 2018 | Circulation. 2018;128:A15113

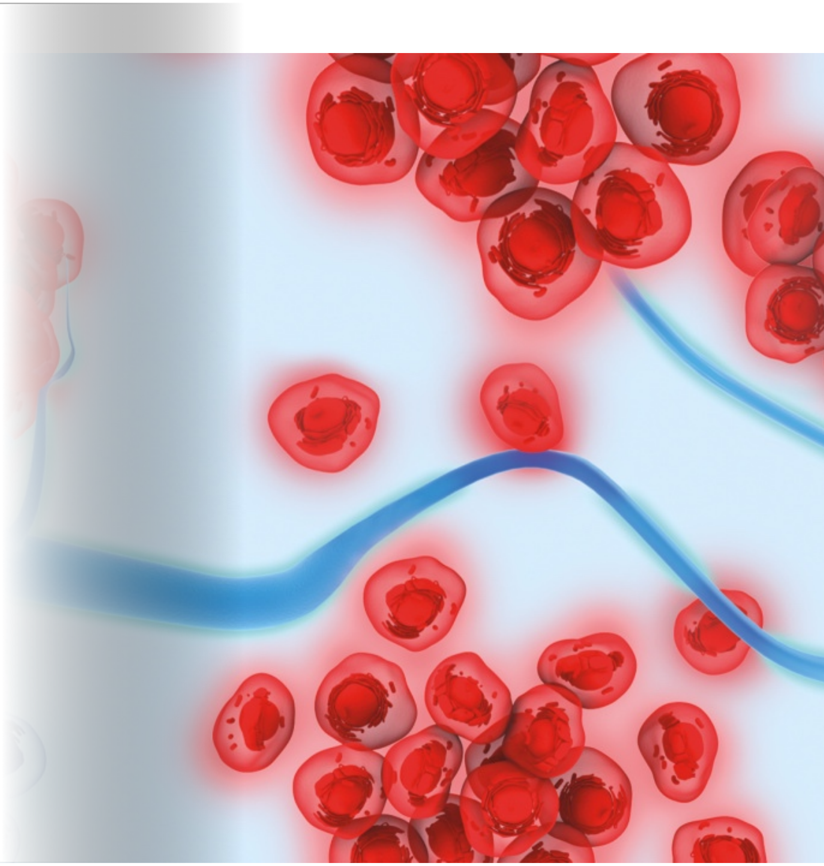
MTORC1 and HCM

MTORC2 1



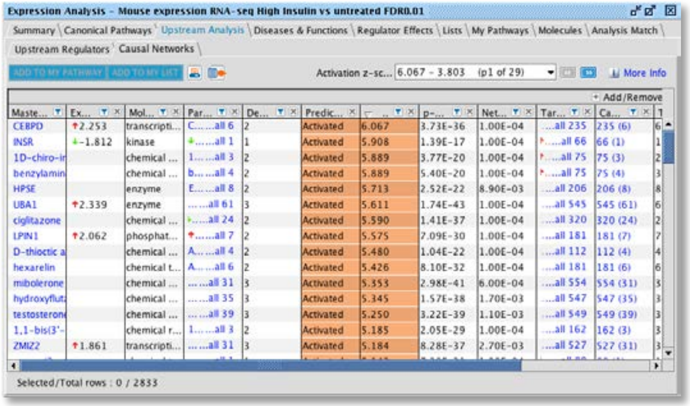
Compare your analysis to pre-computed datasets

Analysis Match – OmicSoft Lands



Introducing Analysis Match

How can you discover which analyses look like yours, to uncover insights from mechanistic similarities and differences?



Expression Analysis - Mouse expression RNA-seq High Insulin vs untreated FDR0.01

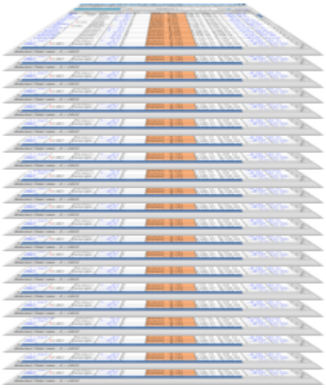
Activation z-sc... 6.067 - 3.803 (p1 of 29)

Maste...	Ex...	Mol...	Par...	De...	Predic...	..	p-...	Net...	Tar...	Ca...	T
CEBPD	↑2.253	transcripti...	C... ...all 6	2	Activated	6.067	3.73E-36	1.00E-04	....all 235	235 (6)	6
INSR	↓-1.812	kinase	↓... ...all 1	1	Activated	5.908	1.39E-17	1.00E-04	▸....all 66	66 (1)	1
1D-chiro-i		chemical ...	1... ...all 3	2	Activated	5.889	3.77E-20	1.00E-04	▸....all 75	75 (3)	2
benzylamin		chemical ...	b... ...all 4	2	Activated	5.889	5.40E-20	1.00E-04	▸....all 75	75 (4)	3
HPSE		enzyme	E... ...all 8	2	Activated	5.713	2.52E-22	8.90E-03	....all 206	206 (8)	8
UBA1	↑2.339	enzyme	... ...all 61	3	Activated	5.611	1.74E-43	1.00E-04	....all 545	545 (61)	6
ciglitazone		chemical ...	▸... ...all 24	2	Activated	5.590	1.41E-37	1.00E-04	....all 320	320 (24)	2
LPIN1	↑2.062	phosphat...	↑... ...all 7	2	Activated	5.575	7.09E-30	1.00E-04	....all 181	181 (7)	7
D-thioctic a		chemical ...	A... ...all 4	2	Activated	5.480	1.04E-22	1.00E-04	....all 112	112 (4)	4
hexarelin		chemical t...	A... ...all 6	2	Activated	5.426	8.10E-32	1.00E-04	....all 181	181 (6)	6
mibolerone		chemical ...	... ...all 31	3	Activated	5.353	2.98E-41	6.00E-04	....all 554	554 (31)	3
hydroxyflut		chemical ...	... ...all 35	3	Activated	5.345	1.57E-38	1.70E-03	....all 547	547 (35)	3
testosteron		chemical ...	... ...all 39	3	Activated	5.250	3.22E-39	1.10E-03	....all 549	549 (39)	3
1,1-bis(3'-		chemical r...	1... ...all 3	2	Activated	5.185	2.05E-29	1.00E-04	....all 162	162 (3)	3
ZMIZ2	↑1.861	transcripti...	... ...all 31	3	Activated	5.184	8.28E-37	2.70E-03	....all 527	527 (31)	3

Selected/Total rows : 0 / 2833

Match against

>52,000 analyses



Which analyses have similar Upstream Regulators, Canonical Pathways, Diseases and Functions, etc.?

Applications of Analysis Match

- Compare your analysis with *your other analyses* as well as analyses of datasets from *public domain* (TCGA, SRA, GEO, LINCS, etc.)

Mechanism of action

- Is there a shared biology across your samples?

Target discovery/validation

- What key regulators/pathways are similarly activated or inhibited across the groups?

Biomarker discovery through comparison analysis

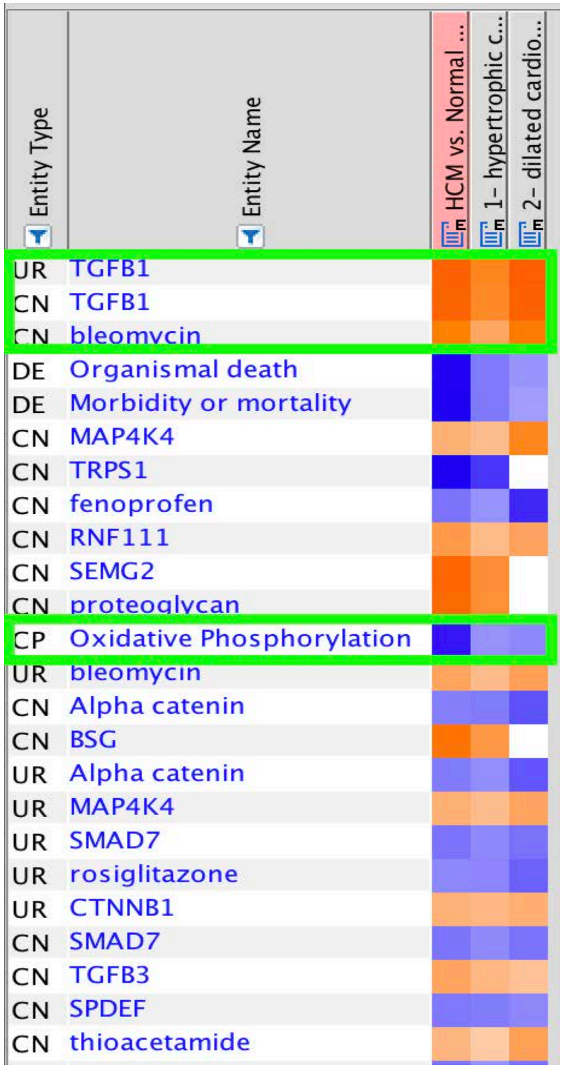
- Generate gene expression heatmap specific to cellular/molecular processes

Analysis Match

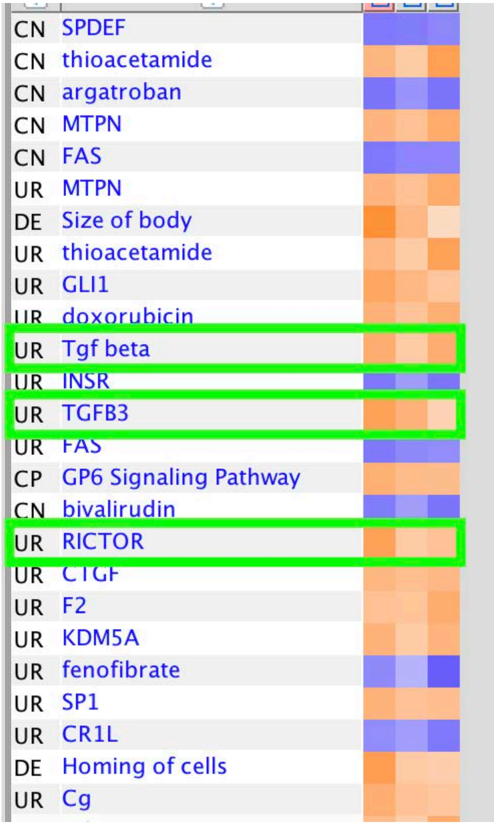
z-score overall... 100.0 - 33.51 (p1 of 200)

Analysis Name	Proj...	...	...	...	...	...	...	...	...	...	...	▽	...	...	...	...	...
HCM vs. Normal heart GWB	Jennifer P							100.00	100.00	100.00	100.00	100.00	3.92E-...	1.62E-...	5E-249	8.22E-...	89.20
HCM vs. Normal heart 2018-09	HCM_GWB...							100.00	100.00	100.00	100.00	100.00	3.92E-...	1.62E-...	5E-249	8.22E-...	89.20
lgm_hcm_vs_norm_omicsoft	hypertroph...							90.14	88.32	75.50	78.51	83.12	9.6E-19	1.08E-...	1.2E-98	1.66E-88	84.01
lgm_hcm_vs_norm_omicsoft	Jennifer P							90.14	88.32	75.50	78.51	83.12	9.6E-19	1.08E-...	1.2E-98	1.66E-88	84.01
GSE89714.hypertorphic_expres	Land.Com...							75.00	84.85	64.81	70.22	73.72	1.33E-...	1.17E-...	1.76E-...	8.1E-67	79.94
lgm_hcm_vs_NH.DESeq2_relaxe	hypertroph...							75.00	82.46	57.45	72.15	71.76	1.83E-...	4.74E-...	4E-45	7.33E-69	76.57
GSE89714_fc_1.7_fdr05	Land.Com...							55.90	82.46	62.45	80.24	70.26	4.79E-...	4.74E-...	3.91E-...	1.38E-95	77.16
1- hypertrophic cardiomyopathy	HumanDis...	hypertr...		heart	Disease...	Disease...	https://...	50.00	81.24	66.33	52.34	62.48	9.7E-05	5.99E-...	7.77E-...	1E-38	71.01
2- dilated cardiomyopathy [hea	MouseDise...	dilated ...		heart v...	Disease...	Clinical...	http://...	66.14	67.82	34.64	45.33	53.48	7.58E-...	2.54E-59	4.8E-11	1.44E-20	43.14
5- normal control [small intestin	MouseDise...	normal ...		small in...	Treatm...	TissueR...	https://...	50.00	60.00	43.59	54.90	52.12	1.6E-03	6.23E-41	7.46E-...	6.52E-31	46.66
2- normal control [embryo] rosi	MouseDise...	normal ...		embryo	Treatm...	Treatm...	http://...	50.00	64.81	36.06	53.63	51.12	8.79E-...	1.15E-51	2.49E-...	1.11E-31	47.81
1- liver cirrhosis [liver] NA 329	RatDisease	liver cir...		liver	CellTyp...	Disease...	https://...	55.90	59.16	40.00	43.79	49.71	4.91E-...	3.12E-39	1.99E-...	2.53E-17	37.06
17- normal control [spinal cord]	MouseDise...	normal ...		spinal c...	Tissue1...	Tissue ...	https://...	55.90	51.96	35.78	54.90	49.63	4.79E-...	1.45E-26	2.14E-...	1.24E-29	40.37
4- normal control [fetal brain] r	MouseDise...	normal ...		fetal br...	Treatm...	Treatm...	http://...	50.00	51.12	40.00	56.13	49.31	8.79E-...	4.07E-31	1.99E-...	3.53E-33	40.80
lgm_hcm_vs_NH.DESeq2_strict	hypertroph...								70.71	60.00	65.17	48.97	1.93E-...	2.19E-67	5.14E-...	1.63E-55	75.86
3- lung adenocarcinoma (LUAD)	OncoGEO	lung ad...		lung	Treatm...	TreatTi...	http://...	61.24	53.85	31.62	46.82	48.38	3.46E-...	1.42E-29	1.3E-08	1.05E-21	31.09
2- normal control [liver] NA 33	RatDisease	normal ...		liver	CellTyp...	Disease...	https://...	61.24	51.96	37.42	40.54	47.79	3.46E-...	1.45E-26	1.18E-...	9.99E-15	28.62
HCM vs. Normal heart - 2018-	Demo			heart					64.03	61.64	65.17	47.71	1.53E-...	8.2E-50	4.54E-...	1.63E-55	75.95
1- normal control [epididymal w	MouseDise...	normal ...		epididy...	CellTyp...	Tissue:...	https://...	55.90	57.45	33.17	43.79	47.58	1.52E-...	6.58E-36	8.35E-...	6.09E-17	32.15
2- normal control [vastus latera	HumanDis...	normal ...		vastus l...	Treatm...	Subject...	https://...	61.24	48.99	34.64	45.33	47.55	1.18E-...	2.91E-22	4.8E-11	6.84E-19	27.47
14045- prostate adenocarcinor	LINCS	prostat...	PI3K	prostate	Treatm...	Treatm...	https://...	50.00	44.72	37.42	53.63	46.44	2.66E-...	6.16E-17	1.18E-...	1.38E-28	29.79
1- atrial fibrillation [myocardium	HumanDis...	atrial fi...		myocar...	Disease...	Disease...	http://...	50.00	66.33	41.23	26.17	45.93	6.23E-...	1.92E-55	7.22E-...	1.08E-06	38.16
7- amyotrophic lateral sclerosis	MouseDise...	amyotr...		lumbar ...	Disease...	Disease...	http://...	50.00	52.92	26.46	52.34	45.43	6.23E-...	4.68E-28	2.38E-...	5.3E-26	30.22
1- interstitial lung disease (ILD);	HumanDis...	interstit...		skin	Disease...	Disease...	http://...	50.00	52.92	36.06	42.20	45.29	6.23E-...	4.68E-28	2.49E-...	1.41E-16	28.99
1- skin melanoma (SKCM) [skin]	Metastatic...	skin me...		skin	Disease...	Experi...	https://...	50.00	50.00	38.73	42.20	45.23	1.7E-04	1.14E-23	5.06E-...	2.88E-16	28.27
63- pancreas adenocarcinoma	TCGA	pancre...		pancreas	Other C...	CHEK2...	https://...	66.14	30.51	33.17	49.66	44.87	4.51E-...	4.69E-10	8.35E-...	1.42E-25	25.30

Analysis Match

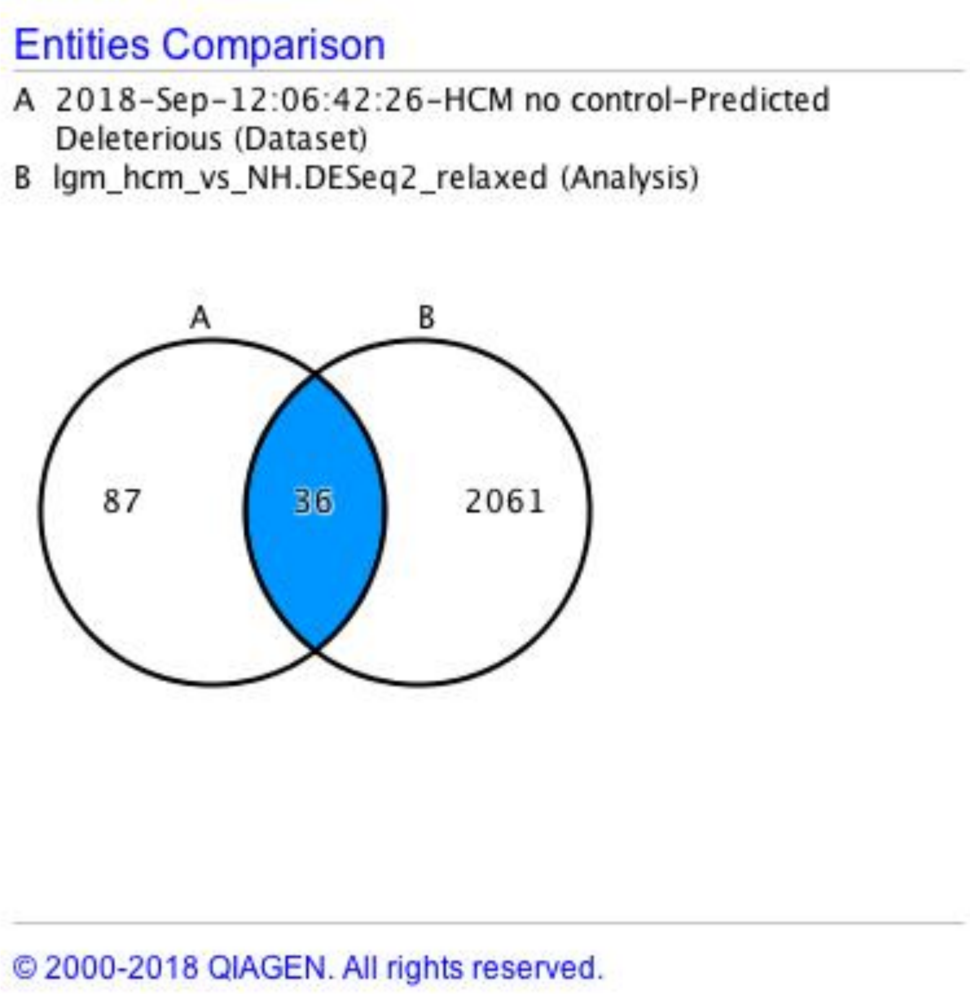


Entity Type	Entity Name	HCM vs. Normal ...	1- hypertrophic c...	2- dilated cardio...
UR	TGFB1	🟧	🟧	🟧
CN	TGFB1	🟧	🟧	🟧
CN	bleomycin	🟧	🟧	🟧
DE	Organismal death	🟦	🟦	🟦
DE	Morbidity or mortality	🟦	🟦	🟦
CN	MAP4K4	🟧	🟧	🟧
CN	TRPS1	🟦	🟦	⬜
CN	fenoprofen	🟦	🟦	🟦
CN	RNF111	🟧	🟧	🟧
CN	SEMG2	🟧	🟧	⬜
CN	proteoglycan	🟧	🟧	⬜
CP	Oxidative Phosphorylation	🟦	🟦	🟦
UR	bleomycin	🟧	🟧	🟧
CN	Alpha catenin	🟦	🟦	🟦
CN	BSG	🟧	🟧	⬜
UR	Alpha catenin	🟦	🟦	🟦
UR	MAP4K4	🟧	🟧	🟧
UR	SMAD7	🟦	🟦	🟦
UR	rosiglitazone	🟦	🟦	🟦
UR	CTNNB1	🟧	🟧	🟧
CN	SMAD7	🟦	🟦	🟦
CN	TGFB3	🟧	🟧	🟧
CN	SPDEF	🟦	🟦	🟦
CN	thioacetamide	🟧	🟧	🟧



CN	SPDEF	🟦	🟦	🟦
CN	thioacetamide	🟧	🟧	🟧
CN	argatroban	🟦	🟦	🟦
CN	MTPN	🟧	🟧	🟧
CN	FAS	🟦	🟦	🟦
UR	MTPN	🟧	🟧	🟧
DE	Size of body	🟧	🟧	🟧
UR	thioacetamide	🟧	🟧	🟧
UR	GLI1	🟧	🟧	🟧
UR	doxorubicin	🟧	🟧	🟧
UR	Tgf beta	🟧	🟧	🟧
UR	INSR	🟦	🟦	🟦
UR	TGFB3	🟧	🟧	🟧
UR	FAS	🟦	🟦	🟦
CP	GP6 Signaling Pathway	🟧	🟧	🟧
CN	bivalirudin	🟦	🟦	🟦
UR	RICTOR	🟧	🟧	🟧
UR	CTGF	🟧	🟧	🟧
UR	F2	🟧	🟧	🟧
UR	KDM5A	🟧	🟧	🟧
UR	fenofibrate	🟦	🟦	🟦
UR	SP1	🟧	🟧	🟧
UR	CR1L	🟦	🟦	🟦
DE	Homing of cells	🟧	🟧	🟧
UR	Cg	🟧	🟧	🟧

Intersection of Variants and Expression



Entities Comparison

A 2018-Sep-12:06:42:26-HCM no control-Predicted Deleterious (Dataset)

B lgm_hcm_vs_NH.DESeq2_relaxed (Analysis)

Molecule Name	Molecule Name
ADSSL1	LRP1
AHNAK	MPC2
ARL6IP5	MYH7
CALCOCO2	MYOZ2
CHCHD10	NDRG1
CHPT1	NDRG4
DCTN1	NDUFB4
ECH1	NDUFB5
ETFB	NEBL
FAM129A	OCIAD1
FLNA	PGAM2
FN1	PRELP
GOT2	RPL3L
HSD17B4	RTN4
IGFBP7	TNNT2
KTN1	TRDN
LAMA2	VCAN
LARP7	WEE1

Summary

Secondary analysis

- Data quality and samples were mostly consistent

Variant annotation and analysis in IVA

- Variants found in typical HCM Genes and many in the MT
- IPA analysis of Variants Supports a decrease in Oxidative Phosphorylation and and increase of Surtuin Pathway suggesting a lack of energy for cardiomyocytes

IPA analysis of the expression data

- Echoes the decrease in Oxidative Phosphorylation and and increase of Surtuin Pathway suggesting a lack of energy for cardiomyocytes
- Suggests an increase of Fibrosis
- Upstream Regulators support this with an increase in TGF-B
- Specific HCM regulators support increase in hypertrophy MTOR and Mir-133
- Disease and function show and increase in fibrosis and cellular movement
- Analysis Match helps support the same finding in other Cardiomyopathy studies