AST AMERICAN SOCIETY OF TRANSPLANTATION

Use of Genetic Information to Direct Personalized Care of Individuals with Cardiovascular Disease

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Northwestern Medicine

CEOT CUTTING EDGE of **TRANSPLANTATION**

TRANSPLANT SUMMIT 2019

NO SIZE FITS ALL: *Uncovering the Potential of Personalized Transplantation*

FEBRUARY 21–23, 2019 • ARIZONA BILTMORE • PHOENIX, AZ

Disclosures

Paid consultant to:
Invitae, Inc
AstraZeneca
Exonics
Tenaya Therapeutics

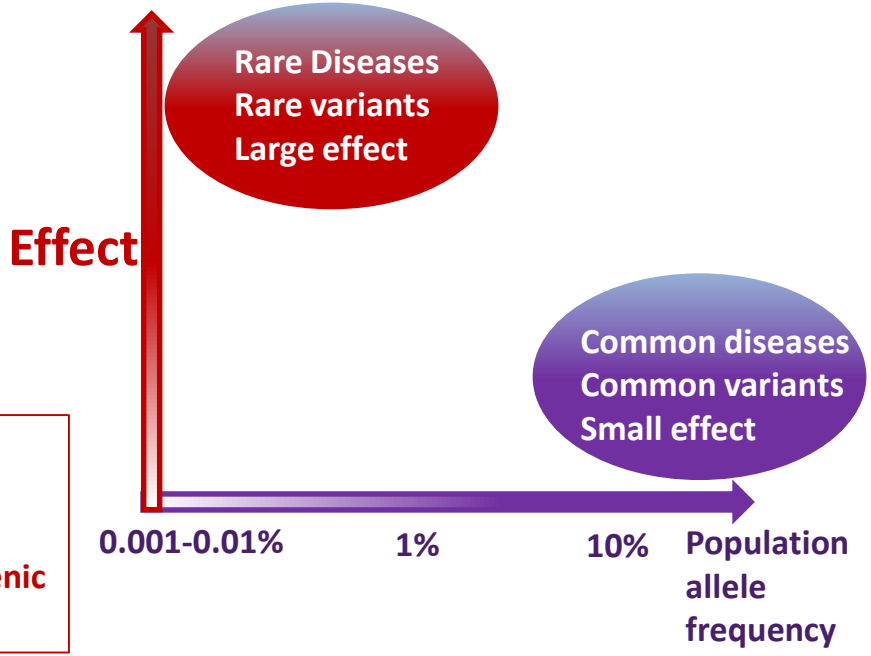
Founder: Ikaika Therapeutics

Grant support: Solid Biosciences, NIH, Department of Defense

Learning Objectives

1. Review genetic testing principles and practices with focus on cardiovascular diseases
2. Discuss medically actionable genes in personal health care
3. Explain proactive genetic screening for personalized risk assessments

Rare vs Common Genetic Variation



Rare variation
Direct sequence
Gene Panels
Pathogenic/Likely Pathogenic
Medically actionable

Common variation
Array testing
SNP Chips
Ancestry/Risk assessment/
Genetic Risk Scores
Pharmacogenetics

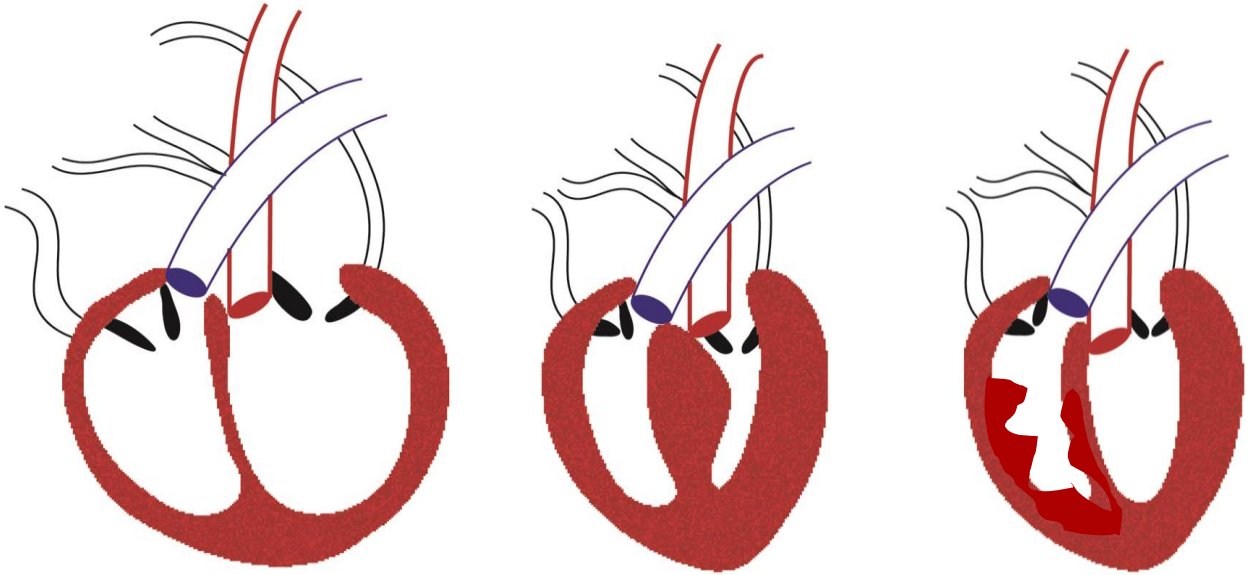
Genetic testing

- Gene panels fully sequence coding region of genes
- Gene panel testing is available for cardiomyopathies, arrhythmias, familial hypercholesterolemia, neuromuscular disease, aortopathies and other cardiovascular diseases

Genetic risk scores

- Genetic risk scores assess high frequency variation
- Each variant has small effect and is summed together for risk assessment
- Similar to ancestry testing
- Uses array-based strategy (SNP chips)

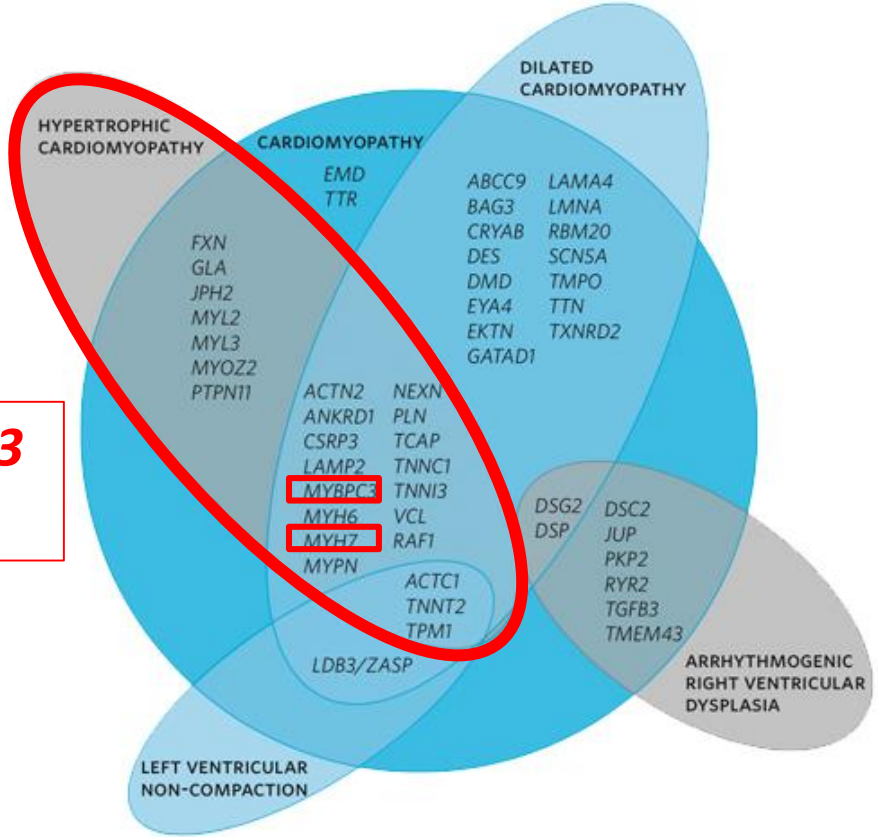
Cardiomyopathy subtypes



DILATED **HYPERTROPHIC** **ARRHYTHMOGENIC**

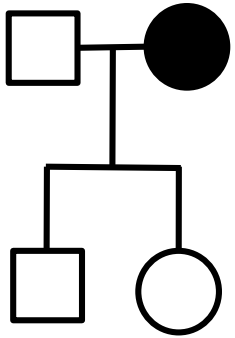
Genetic spectrum of cardiomyopathy: Hypetrophic Cardiomyopathy (HCM)

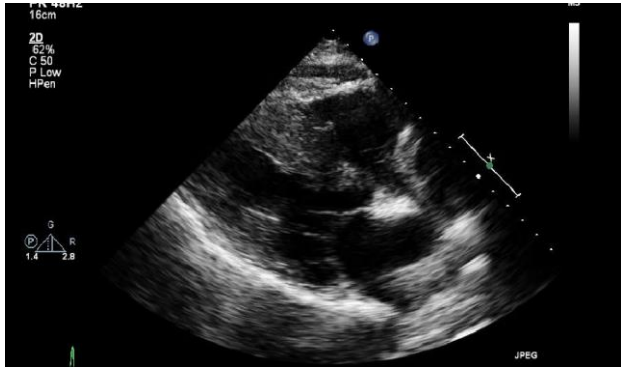
MYBPC3
MYH7

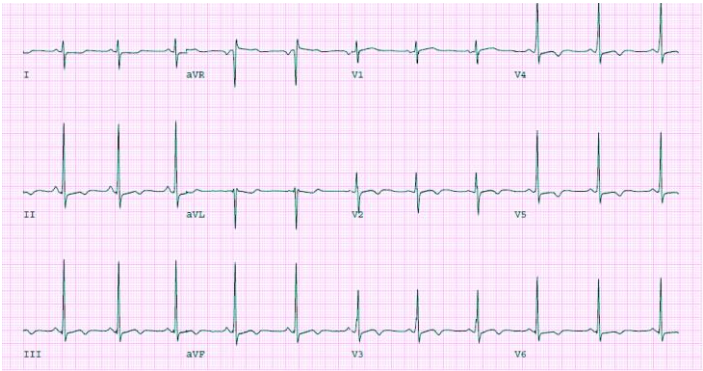


Ambry: http://www.ambrygen.com/tests/cmnext

40 yo F with progressive dyspnea and fatigue, systolic murmur increased on inspiration





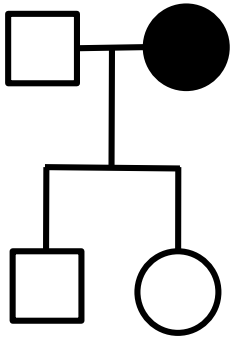


PMSHx: G2P2

Fam Hx: thinks some relatives had “heart problems”

ROS: palpitations, lightheaded episodes

Genetic testing identified *MYH7* p.Ala797Thr



Gene panel:
MYH7 A797T +

ClinVar: Database of Genetic Variants

NCBI Resources How To emcnally@era commons My NCBI Sign Out

ClinVar ClinVar Search ClinVar for gene symbols, HGVS expressions, conditions, and more Search

Advanced Help

Home About Access Help Submit Statistics FTP

NM_000257.3(MYH7):c.2389G>A (p.Ala797Thr)

Variation ID: 42901

Review status: ★★☆☆ criteria provided, multiple submitters, no conflicts

Interpretation

Go to:

Clinical significance: Pathogenic/Likely pathogenic

Last evaluated: Jun 13, 2017

Number of submission(s): 9

Condition(s):

- Familial hypertrophic cardiomyopathy 1 [MedGen - OMIM]
- Primary familial hypertrophic cardiomyopathy [MedGen - Orphanet - Orphanet - OMIM]
- VARIANT OF UNKNOWN SIGNIFICANCE [MedGen]
- Hypertrophic cardiomyopathy [MedGen - Orphanet - Human Phenotype Ontology]

See supporting ClinVar records

1 Affected gene

myosin heavy chain 7 (MYH7) [Gene - OMIM - Variation Viewer]

Haploinsufficiency - *No evidence available* (Nov 15, 2015)

Triplosensitivity - *No evidence available* (Nov 15, 2015)

Search ClinVar for variants within MYH7

Search ClinVar for variants including MYH7

Variant frequency in dbGaP

No dbGaP data has been submitted for this variant.

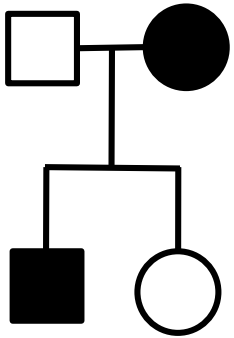
Browser views

RefSeqGene

Variation Viewer [GRCh38 - GRCh37]

https://www.ncbi.nlm.nih.gov/clinvar/variation/42901/

Cascade testing for family members

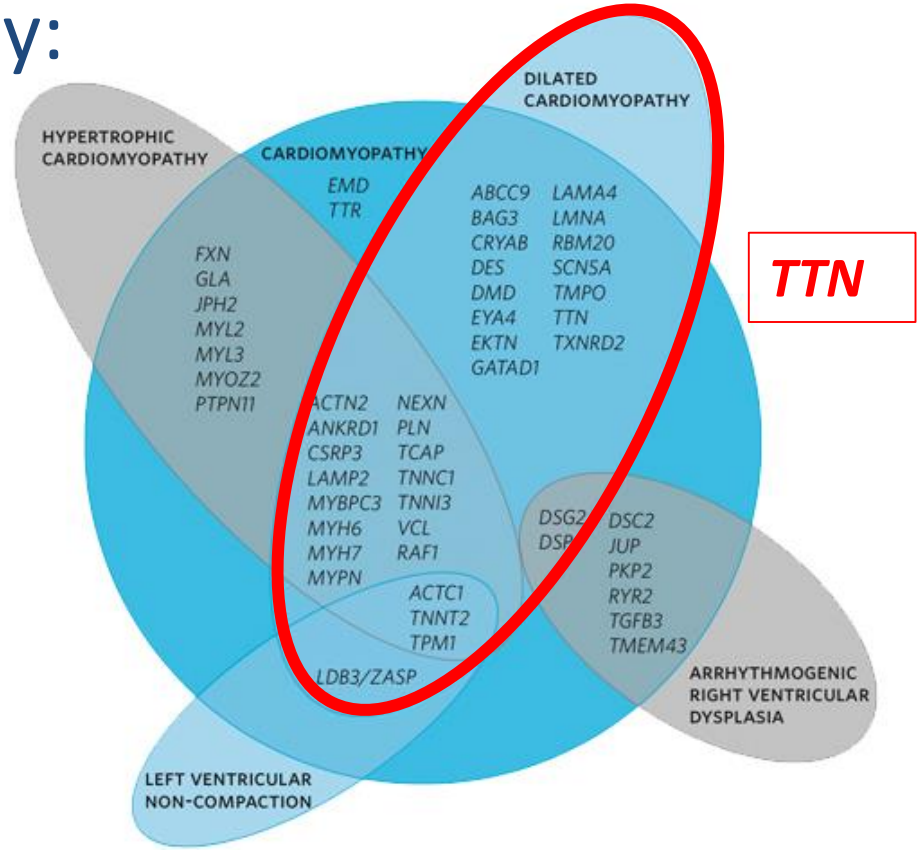


Gene panel:
MYH7 A797T +

Site specific testing:
MYH7 A797T +

Site specific testing:
MYH7 A797T -

Dilated cardiomyopathy: more genes, more mutations



Ambry: http://www.ambrygen.com/tests/cmnext

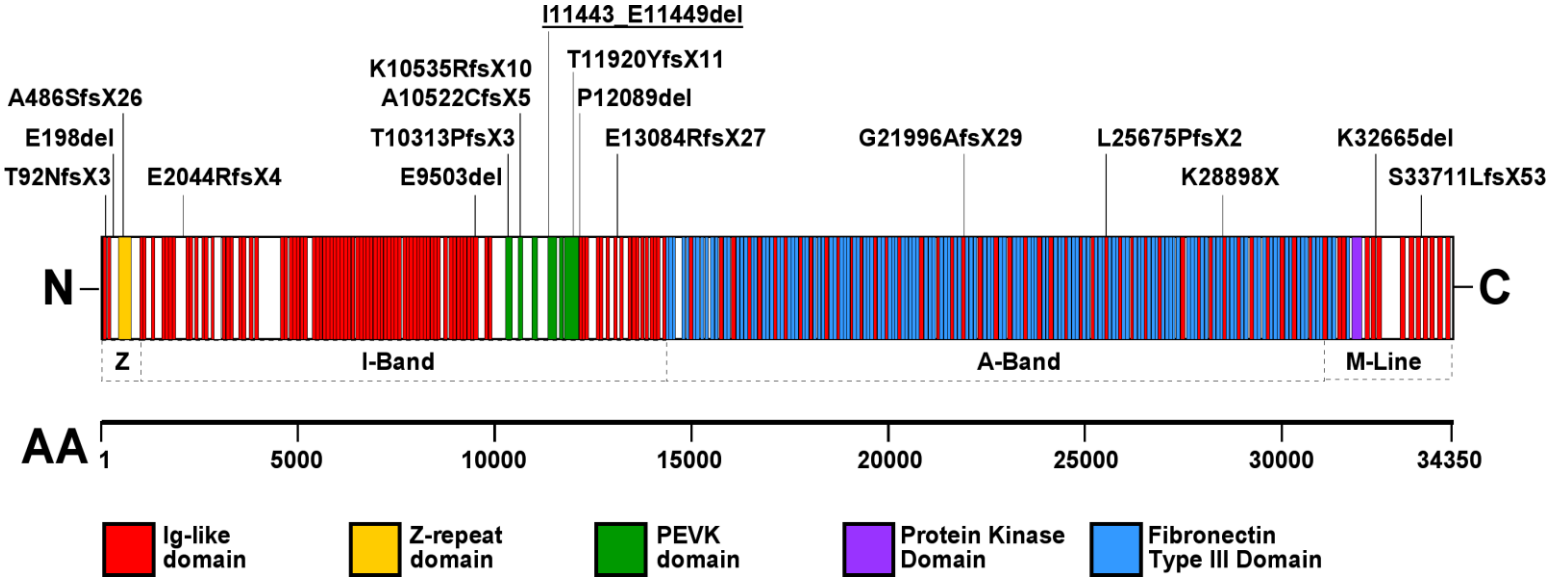
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Truncations of Titin Causing Dilated Cardiomyopathy

Daniel S. Herman, Ph.D., Lien Lam, Ph.D., Matthew R.G. Taylor, M.D., Ph.D., Libin Wang, M.D., Ph.D., Polakit Teekakirikul, M.D., Danos Christodoulou, B.S., Lauren Conner, B.S., Steven R. DePalma, Ph.D., Barbara McDonough, R.N., Elizabeth Sparks, R.N.P., Debbie Lin Teodorescu, M.A., Allison L. Cirino, C.G.C., Nicholas R. Banner, F.R.C.P., Dudley J. Pennell, M.D., Sharon Graw, Ph.D., Marco Merlo, M.D., Andrea Di Lenarda, M.D., Gianfranco Sinagra, M.D., J. Martijn Bos, M.D., Ph.D., Michael J. Ackerman, M.D., Ph.D., Richard N. Mitchell, M.D., Ph.D., Charles E. Murry, M.D., Ph.D., Neal K. Lakdawala, M.D., Carolyn Y. Ho, M.D., Paul J.R. Barton, Ph.D., Stuart A. Cook, M.D., Luisa Mestroni, M.D., J.G. Seidman, Ph.D., and Christine E. Seidman, M.D.

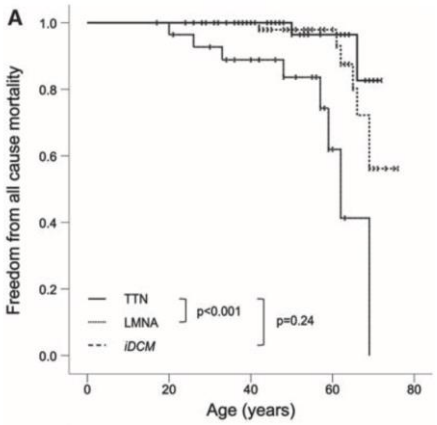
Protein disrupting variation in *TTN* is present in the general population

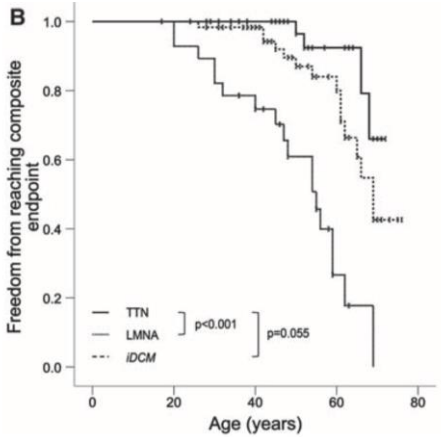


Golbus et al. Circulation Cardiovasc Gen 2012

Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy

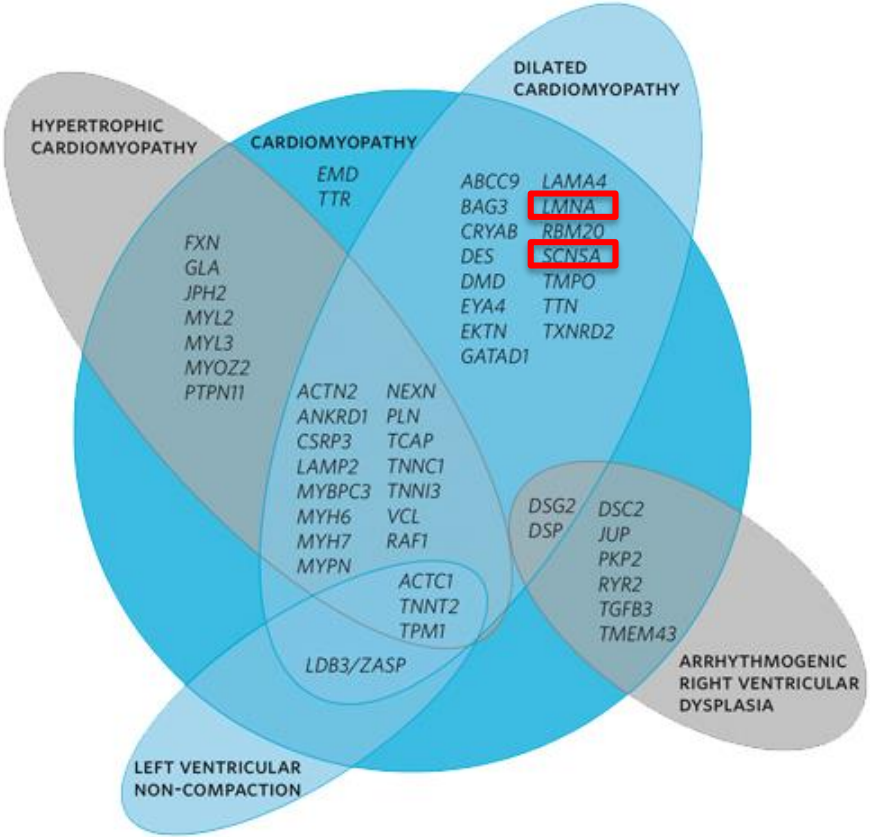
Joeri A. Jansweijer[1†], Karin Nieuwhof[2†], Francesco Russo[3], Edgar T. Hoorntje[2], Jan D.H. Jongbloed[2], Ronald H. Lekanne Deprez[3], Alex V. Postma[4], Marieke Bronk[3], Ingrid A.W. van Rijsingen[1], Simone de Haij[3], Elena Biagini[5], Paul L. van Haelst[6], Jan van Wijngaarden[7], Maarten P. van den Berg[8], Arthur A.M. Wilde[1], Marcel M.A.M. Mannens[3], Rudolf A. de Boer[8], Karin Y. van Spaendonck-Zwarts[3†], J. Peter van Tintelen[2,3†], and Yigal M. Pinto[1†*]





Jansweijer et al. Eur J Heart Failure 2017

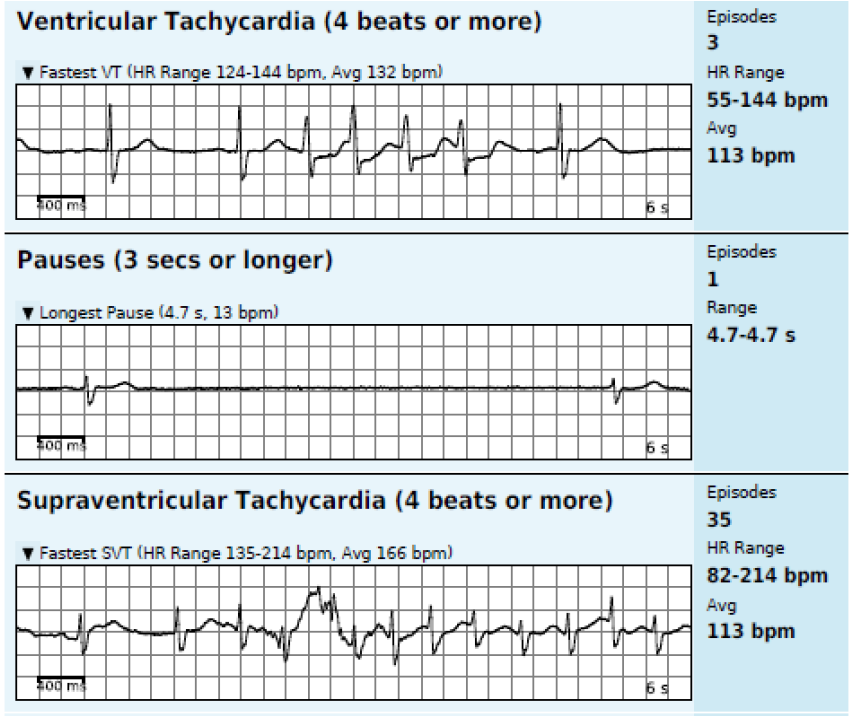
LMNA and *SCN5A* associate with increased arrhythmia risk



Ambry: http://www.ambrygen.com/tests/cmnext

52 yo male with cardiomyopathy and palpitations.
LVEF 36% by MRI, no LGE.
Treated with sacubitril/valsartan with recovery to LVEF 50-55%.
Holter with NSVT 9 bt run.

LMNA p.Ala242Val



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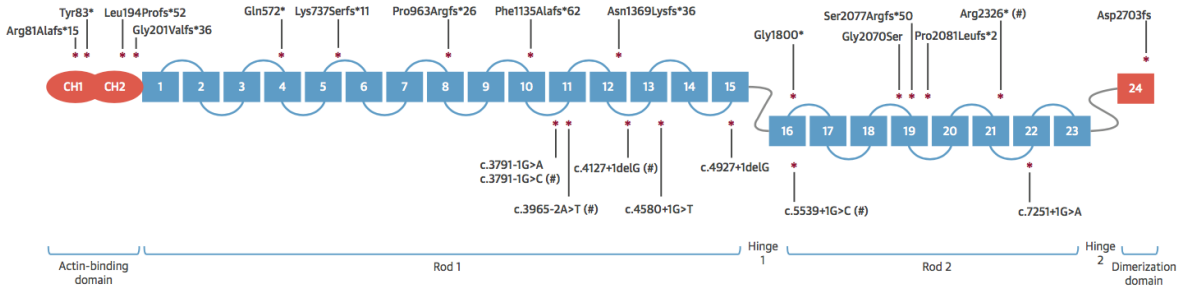
VOL. 68, NO. 22, 2016

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jacc.2016.09.927

Truncating *FLNC* Mutations Are Associated With High-Risk Dilated and Arrhythmogenic Cardiomyopathies

FIGURE 1 Spatial Distribution of Truncating Mutations in Filamin C Protein

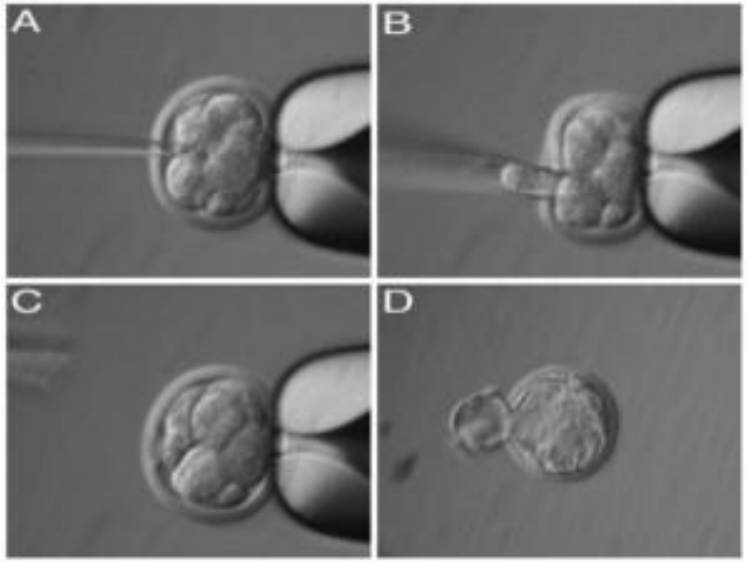


Mutations affecting coding exonic regions are shown above and mutations affecting intronic canonical splicing sites are shown below the diagram of **boxes with numbers** representing the 24 immunoglobulin-like repeats of filamin C. #Mutations identified in 2 unrelated families. CH1 = calponin homology domain 1; CH2 = calponin homology domain 2.

Value of genetic testing

- Cascade family screening
- Targeted monitoring
- Early diagnosis, early treatment
- Refined treatment recommendations
- Moving towards gene specific treatments
- Family planning

Pre-implantation Genetic Diagnosis



http://oncofertility.northwestern.edu/blog/2009/11/preimplantation-genetic-testing-and-oncofertility

Tetra Images/Alamy Stock Photo

GENE THERAPY

Human genome editing in heart disease

> There is now no question that human germline genome editing can be performed

Human germline genome editing with CRISPR–Cas9 was used with high efficiency, accuracy and safety to correct a heterozygous, autosomal dominant mutation in *MYBPC3* associated with hypertrophic cardiomyopathy, according to a new study in *Nature*.

CRISPR–Cas9 is a versatile tool for recognizing a specific genomic sequence and inducing a double-

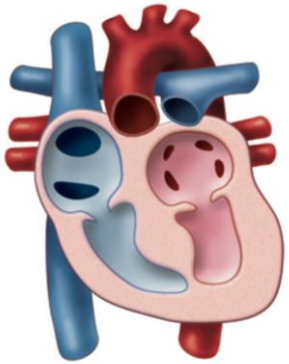
The researchers introduced a mixture of Cas9 protein, single-guide RNA (to target the specific *MYBPC3* deletion), and single-strand oligodeoxynucleotide (encoding the wild-type template) into the zygotes 18 h after fertilization. Injected zygotes and intact controls were cultured for 3 days before each embryonic blastomere was isolated and individually analysed. The overall targeting effi-

demonstrated that co-injection of CRISPR–Cas9 and sperm into the human oocyte during metaphase II of the cell cycle was more efficient than injection into zygotes and, importantly, eliminated the occurrence of mosaicism.

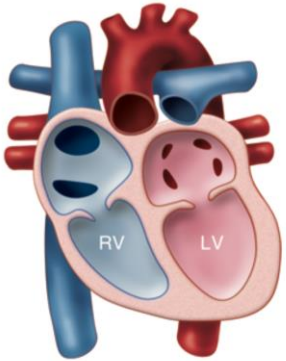
Another risk of CRISPR–Cas9 is the introduction of off-target mutations in the genome. However, comprehensive whole-genome and whole-exome sequencing did not detect off-target effects. Importantly, CRISPR–Cas9-treated human embryos developed normally into blastocysts and embryonic stem cells, with no cytogenetic abnormalities.

Human genome editing raises many ethical and safety concerns. "There is now no question that human germline genome editing can be performed," says Kiran Musunuru (University of Pennsylvania, USA), who was not involved in the study. "Further improvements can and will be made to the genome-editing technique, so we now need to start having those serious conversations about which circumstances, if any, would permit the clinical use of germline genome editing." Eric Olson is also cautious: "aside from the many ethical issues, this method is impractical for

Genotype→Phenotype

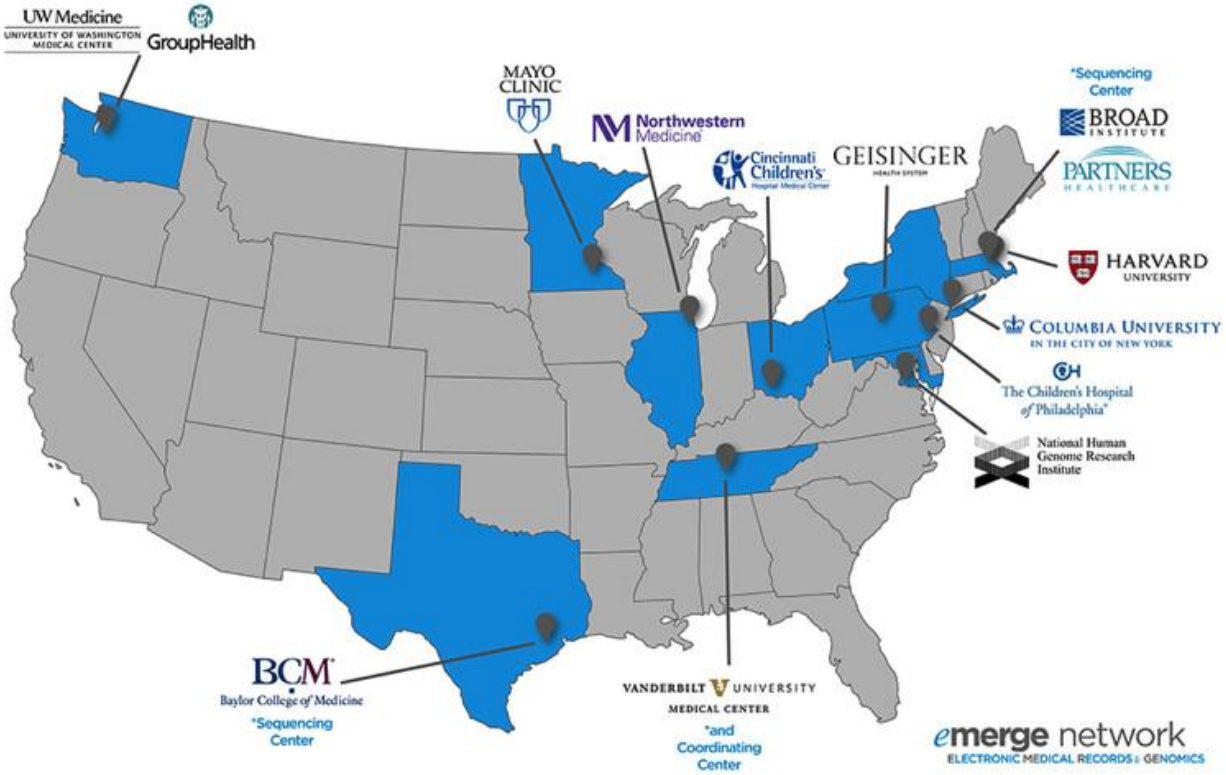


Hypertrophic Cardiomyopathy



Normal heart
Mild HCM
Risk relates to genotype?
Risks related to phenotype?

eMERGE: electronic Medical Records and Genomics



ACMG STATEMENT | Genetics inMedicine

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics

Sarah S. Kalia, ScM[1], Kathy Adelman[2], Sherri J. Bale, PhD[3], Wendy K. Chung, MD, PhD[4,5], Christine Eng, MD[6], James P. Evans, MD, PhD[7], Gail E. Herman, MD, PhD[8], Sophia B. Hufnagel, MD[9], Teri E. Klein, PhD[10], Bruce R. Korf, MD, PhD[11], Kent D. McKelvey, MD[12,13], Kelly E. Ormond, MS[10], C. Sue Richards, PhD[14], Christopher N. Vlangos, PhD[15], Michael Watson, PhD[16], Christa L. Martin, PhD[17], David T. Miller, MD, PhD[18]; on behalf of the ACMG Secondary Findings Maintenance Working Group

Benign	Likely Benign	Variant of Uncertain Significance	Likely Pathogenic	Pathogenic

Recommended to report known pathogenic and likely pathogenic

Medically Actionable Genes

ACMG Cardiac Genes	ACMG Cardiac Genes	ACMG Cancer Genes	ACMG Cancer Genes	Other ACMG Genes
ACTA2	*MYH7*	*APC*	*SDHB*	*ATP7B*
ACTC1	*MYL2*	*BMPR1A*	*SDHC*	*CACNA1S*
APOB	*MYL3*	*BRCA1*	*SDHD*	*OTC*
COL3A1	*PCSK9*	*BRCA2*	*SMAD4*	*RYR1*
DSC2	*PKP2*	*MEN1*	*STK11*	
DSG2	*PRKAG2*	*MLH1*	*TP53*	
DSP	*RYR2*	*MSH2*	*TSC1*	
FBN1	*SCN5A*	*MSH6*	*TSC2*	
GLA	*SMAD3*	*MUTYH*	*VHL*	
KCNH2	*TGFBR1*	*NF2*	*WT1*	
KCNQ1	*TGFBR2*	*PMS2*		
LDLR	*TMEM43*	*PTEN*		
LMNA	*TNNI3*	*RB1*		
MYBPC3	*TNNT2*	*RET*		
MYH11	*TPM1*	*SDHAF2*		

58 yo male with *MYH7* p.Arg870Cys

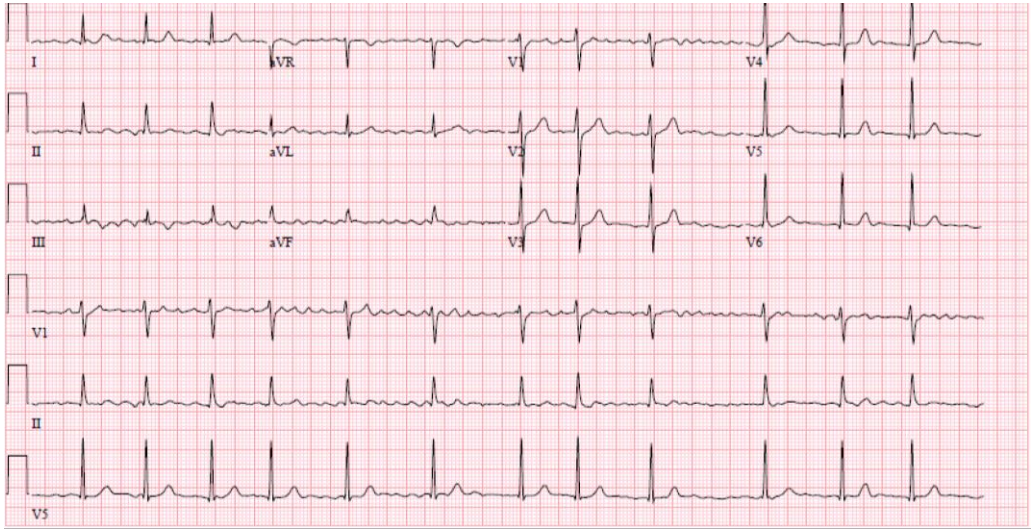
NM_000257.3(MYH7):c.2609G>A (p.Arg870His) Cite this record

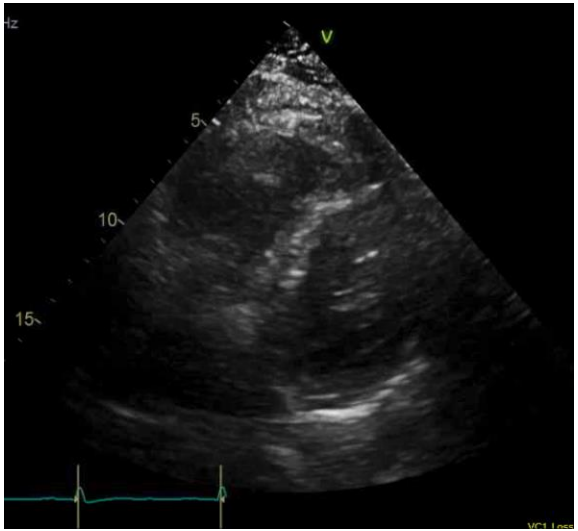
Interpretation:	**Pathogenic**
Review status:	★★★☆ reviewed by expert panel
Submissions:	9 (Most recent: Nov 28, 2017)
Last evaluated:	Dec 15, 2016
Accession:	VCV000014120.2
Variation ID:	14120
Description:	single nucleotide variant

Pathogenic (Dec 15, 2016)	reviewed by expert panel (ACMG variant classification (MYH7)) Method: curation	Primary familial hypertrophic cardiomyopathy (Autosomal dominant inheritance)	ClinGen Inherited Cardiomyopathy Expert Panel Accession: SCV000564434.2 Submitted: (Jul 28, 2017)	Evidence details Publications PubMed (1)
Pathogenic (Feb 16, 2015)	criteria provided, single submitter (LMM Criteria) Method: clinical testing	Primary familial hypertrophic cardiomyopathy (Autosomal dominant inheritance)	Laboratory for Molecular Medicine,Partners HealthCare Personalized Medicine Accession: SCV000059458.4 Submitted: (Apr 26, 2016)	Evidence details Publications PubMed (15) Comment: The p.Arg870His variant in MYH7 has been (more...)
Pathogenic (Apr 23, 2015)	criteria provided, single submitter (Variant Classification) Method: clinical testing	Primary familial hypertrophic cardiomyopathy	Blueprint Genetics Accession: SCV000207099.2 Submitted: (Jan 15, 2016)	Evidence details Publications PubMed (3)
Pathogenic (Aug 22, 2017)	criteria provided, single submitter (GeneDx Variant Classification (06012015)) Method: clinical testing	Not Provided	GeneDx Accession: SCV000208490.11 Submitted: (Nov 28, 2017)	Evidence details

National Center for Biotechnology Information. ClinVar; Variation ID 14120, https://preview.ncbi.nlm.nih.gov/clinvar/variation/14120

Two years prior presented with L facial droop

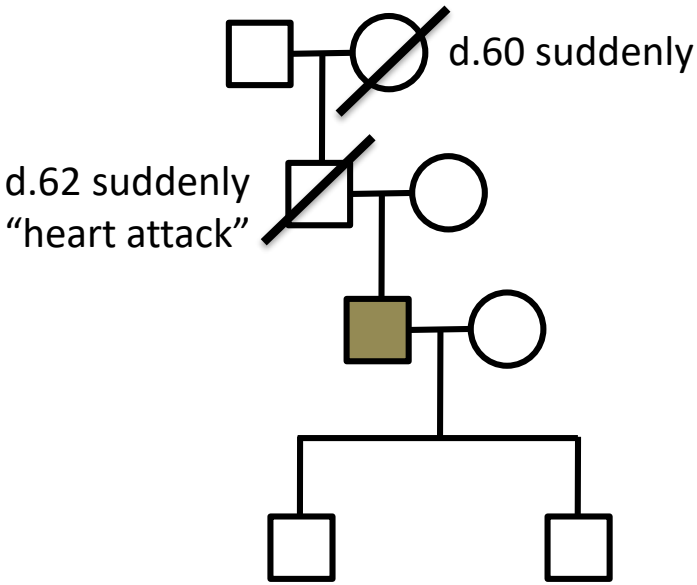




Thrombolytics, AF ablation

Echo: LVH, septal thickening, Enlarged left atrium
MRI: 1.4 cm septal thickness,Delayed enhancement
Enlarged atria

Family history



Prospective gene sequencing of medically actionable genes

- Patient or physician initiated ordering
- Cancer and/or cardiac genes
- Reports pathogenic/likely pathogenic
- Biobank prospective sequencing suggests 3-5% with actionable findings

Patient-initiated ordering/ Direct to consumer

- Saliva samples
- Common variants for ancestry and risk alleles
- Gene panels now available as “wellness screens”

sign in | register kit | 0

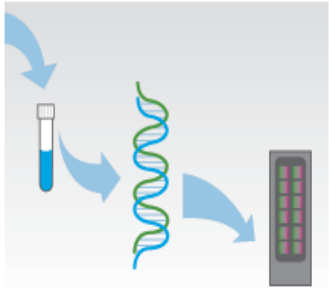
welcome | ancestry | health | how it works | store | search | help

Get to know your DNA. All it takes is a little bit of spit.

Here's what you do:

1. Order a kit from our online store.

2. Register your kit, spit into the tube, and send it to the lab.



3. Our CLIA-certified lab analyzes your DNA in 6-8 weeks.

4. Log in and start exploring your genome.

Ancestry testing

Health Related Testing

ANCESTRY FEATURES		
NOW WITH 150+ REGIONS Ancestry reports 5 reports including: Ancestry Composition, Maternal & Paternal Haplogroups, Neanderthal Ancestry, Your DNA Family	✓	✓
DNA Relative Finder (opt in) Find and connect with relatives in the 23andMe database who share DNA with you.	✓	✓
HEALTH FEATURES See full list of reports		
Genetic Health Risk reports* 5+ reports including: BRCA1/BRCA2 (Selected Variants), Hereditary Thrombophilia, Late-Onset Alzheimer's Disease, Parkinson's Disease		✓
Carrier Status reports* 40+ reports including: Cystic Fibrosis, Sickle Cell Anemia, Hereditary Hearing Loss		✓
Wellness reports 5+ reports including: Deep Sleep, Lactose Intolerance, Genetic Weight		✓
Traits reports 25+ traits including: Male Bald Spot, Sweet vs. Salty, Unibrow		✓
OTHER FEATURES		
Raw Data Access your raw, uninterpreted genetic data file.** Must not be used for medical or diagnostic purposes.	✓	✓

Patients may come to physicians with genetic information
Patient-initiated ordering

Amazon's Choice

60+ genes
across heart health, cancer risk and medication response

Genetic Risk Test for Common Cancers, Heart Conditions, and Medication Response - Analysis of 60+ Genes, Including BRCA1 and BRCA2 (Not Available in NY)

by Color

$249.00

✓prime

FREE Delivery by **Wed, Nov 21**

5

with coupon

Product Features

Tests are physician-ordered. Either your own doctor or an ...

Jb1017

Worth the peace of mind!

January 19, 2019

Verified Purchase | Early Reviewer Rewards (What's this?)

I have several family member who have been diagnosed with cancer. I was concerned about how much genetics played a part in their conditions. I was prepared to learn there for some genetic markers, but I wanted to know so I could do what I could to concentrate prevention on those areas. I was relieved to find I had no generic markers for cancer or heart disease. While I know it doesn't mean I won't have issues with these conditions. I at least know genetic do not appear to be the cause. The sense of relief is priceless. I would definitely recommend!

2 people found this helpful

Helpful | Comment | Report abuse

Genetic screening to consider

- **LDLR+,** familial hypercholesterolemia

→ statin, PSCK9 inhibitor

- **TTR,** amyloidosis risk

→ patisiran recently FDA approved

- **HFE,** hemochromatosis risk (cirrhosis, liver disease, cardiomyopathy)

→ reduce alcohol intake, avoid supplemental iron, reduce iron intake

- **Medically actionable genes**
  - Cardiomyopathy genes → consider treating stage 1 hypertension
  - LQTS genes → avoid QT prolonging drugs
  - Aortopathy genes → consider treating stage 1 hypertension

Thank You