



1



**Cardiovascular
Grand Rounds**



Monday, September 14 – 7AM CDT
in the MHIF Learning Center

**Genes, Rhythm, and Risk: Inside the Genetic Arrhythmia and
Cardiomyopathy Clinic**

Speakers



Jay Sengupta
MD
*Director, Joseph F. Novogratz
Family Heart Rhythm Center*



Kerollos Abdelsayed
MD
*Pierce Heart Rhythm Scholar
Joseph F. Novogratz Family
Heart Rhythm Center*

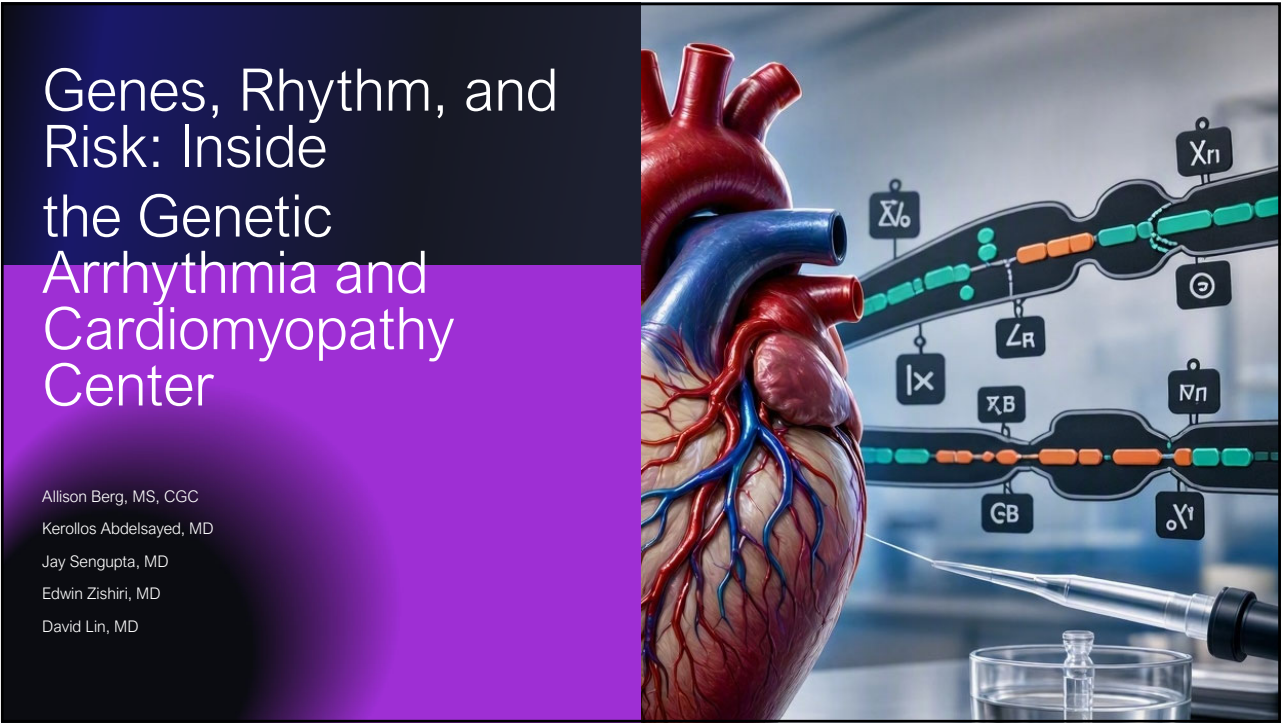


Allison Berg
MS, CGC
*Genetic Counselor
Allina Health Minneapolis
Heart Institute*



World-Class Cardiovascular Research & Education

2



Genes, Rhythm, and Risk: Inside the Genetic Arrhythmia and Cardiomyopathy Center

Allison Berg, MS, CGC
Kerollos Abdelsayed, MD
Jay Sengupta, MD
Edwin Zishiri, MD
David Lin, MD

3

Agenda

- History of the Genetic Arrhythmia and Cardiomyopathy Center (GACC)
- Genetics Refresher
- Genetic Counseling at MHI
- Genetic test results
- Case examples from the Genetic Arrhythmia and Cardiomyopathy Center

4

Learning Objectives

Participants will:

- Recognize patients who may benefit from genetic counseling and testing
- Understand benefits and limitations of genetic testing
- Appreciate the complexity of genetic test results and the implications for patients and their family members
- Recognize the importance of a team approach to inherited cardiac conditions
 - Lessons from the Genetic Arrhythmia and Cardiomyopathy Center (GACC)

5

Genetics Refresher

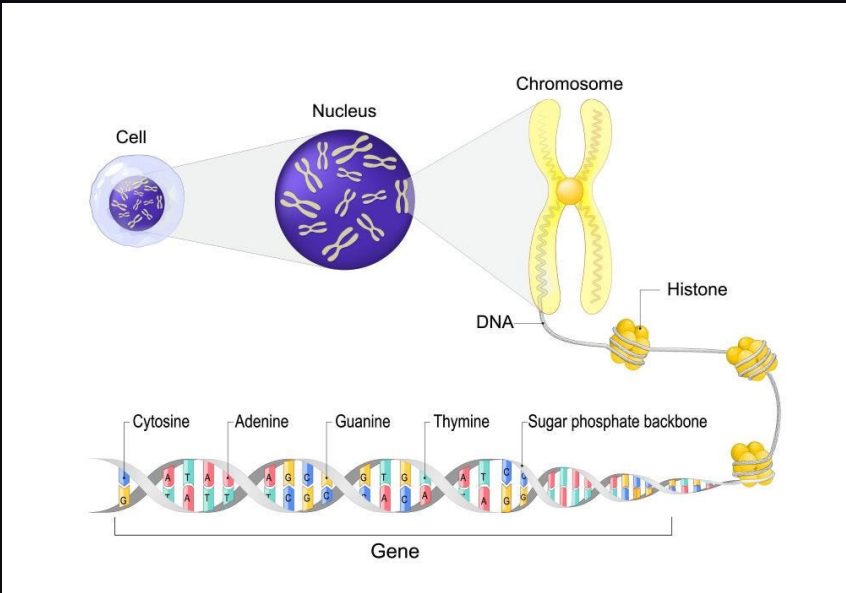
Estimated 20,000 genes

- Small portion characterized

Two copies of every gene – paternal gene and maternal gene

Genetic Terminology

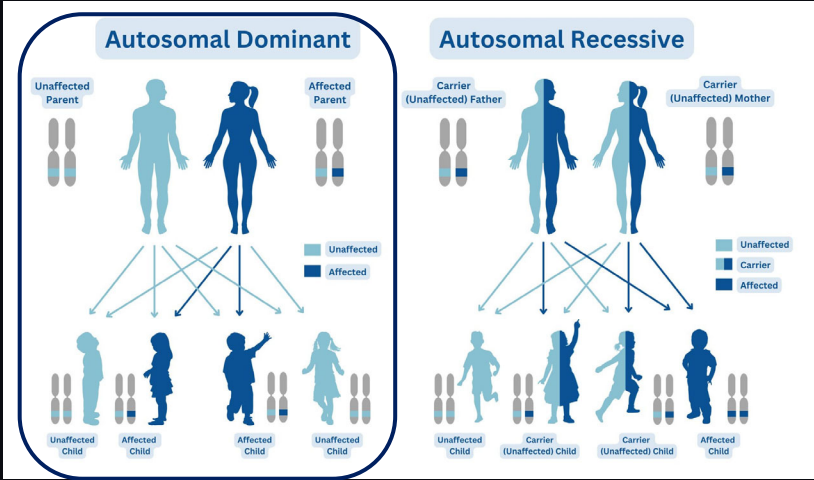
- Penetrance
- Variable expressivity



6

Inheritance

- Dominant
- Recessive
- X-linked



7

Common Indications for Cardiovascular Genetic Testing

Non-ischemic cardiomyopathy	Arrhythmogenic cardiomyopathy (ARVC)	Family or personal history of SCD/SCA	ATTR Amyloidosis
Family history of gene mutation	Concern for inherited arrhythmia	Aortic aneurysm/dissection	Hyperlipidemia

8

2022 Consensus Statement on Genetic Testing for Cardiac Diseases

Choice of genetic tests and interpretation of variants		
Recommendation	Consensus statement instruction	Ref.
Genetic testing in patients with a potential cardiogenetic condition is performed only with appropriate genetic counselling.		Expert opinion
In patients with a clear specific phenotype, it is appropriate to perform genetic testing analysing genes with definite or strong evidence supporting disease causation.		16,17,20,21,49
In patients with a clear specific phenotype, it may be appropriate to analyse genes with moderate evidence supporting disease causation.		16,17,20,21,49
In selected cases with a definite phenotype and no genetic diagnosis after testing of the genes with definite or strong evidence supporting disease causation, broader genetic testing may be considered. Such selected cases may include familial cases, those with atypical features, such as extracardiac manifestations and those with unusual early disease onset.		17
Variant interpretation in the clinical setting is greatly enhanced by the use of disease-specific, multi-disciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists.		16,76-78
Variant interpretation is best performed using standard guidelines for interpretation and can be enhanced by gene-specific rule specifications tailored for the gene and disease under consideration.		17,76,77
Reported Variants of Uncertain Clinical Significance (VUS) may be reclassified, i.e. 'upgraded' [Likely Pathogenic/Pathogenic (LPP)] or 'downgraded' [Likely Benign/Benign], in multi-disciplinary clinics with access to molecular genetics laboratories, according to robustness of clinical phenotype and/or familial segregation evidence.		16,76-78,79
Genetic testing for genes with (i) limited, (ii) disputed, or (iii) refuted evidence should not be performed in patients with a weak (non-definite) phenotype in the clinical setting.		16,17,20,21,49
In families where a LPP variant has been identified, detailed genetic counselling and guidance regarding inheritance patterns, variant penetrance, and risk should be offered, and cascade testing facilitated.		Expert opinion
In patients with a high probability of a specific inherited cardiac disease and a molecular screening performed in a pre-NGS era or with an incomplete NGS panel, repetition of the testing should be considered.		Expert opinion

Table 5 Impact of genetic testing for the proband			
Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	-	+	-
Atrial fibrillation	-	+	-
Early repolarization syndrome	-	-	-
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic cardiomyopathy	+++	++	++
Left ventricular non-compaction	+	+	-
Restrictive cardiomyopathy	+	+	+
Congenital heart disease			
Syndromic CHD	+++	+	-
Non-syndromic CHD	++	-	-
Familial CHD	++	-	-

+++ is recommended/is indicated or useful.
++ can be recommended/can be useful.
+ may be considered/may be useful.
- is not recommended/is not indicated nor useful.

Wilde AAM, Semsarian C, Márquez MF, et al. European Heart Rhythm Association (EHRA)/Heart Rhythm Society (HRS)/Asia Pacific Heart Rhythm Society (APHRS)/Latin American Heart Rhythm Society (LAHRS) Expert Consensus Statement on the state of genetic testing for cardiac diseases. Europace. 2022;24(8):1307-1367. doi:10.1093/europace/euac030

9

Genetic Arrhythmia and Cardiomyopathy Center (GACC)



- Patients with suspected or confirmed diagnosis of inherited cardiomyopathy or arrhythmia
- Team approach
 - Physician consultation
 - EP and advanced heart failure backgrounds
 - Genetic counseling and testing
 - Imaging
 - cMRI and echocardiogram
 - Advanced imaging specialists
 - Cardiac rhythm monitoring
 - Research
 - Heart Rhythm Science Center
 - GACC Registry
- Opportunity for family members to be evaluated together
- Longitudinal screening and follow up
- Collaborative review
- Post-Mortem genetic testing
 - Sudden cardiac arrest network (Children's Heart Clinic)
 - Jesse Edwards

10

Genetic Counseling Visit: Pre-Test



- Family History
 - SCD, SCA, syncope, seizures, stillborn, muscle weakness, ancestry, pacemaker/ICD, MI
- Determine most appropriate gene panel based on personal and family histories
- Potential results
 - Positive
 - Negative
 - Uncertain
- GINA – Genetic Information Nondiscrimination Act
- Limitations
 - Negative result does not eliminate a genetic etiology or suspected clinical diagnosis
- Insurance coverage
- Sponsored testing options
- Sample collection – blood, saliva, buccal

11



Genetic Counseling is Essential

- Many misconceptions about genetic testing
- Address concerns regarding privacy
- Elicit family history details that may suggest diagnosis
- Discuss family member recommendations
- Interpret complex results
- Knowledge of genetic specific resources/databases

12

Genetic Testing Yield (pathogenic or likely pathogenic)



Cardiomyopathies

- HCM 30%-60%
- Arrhythmogenic cardiomyopathy 40%-60%
- Dilated cardiomyopathy 20%-35%

Channelopathies

- Long QT syndrome 60%-75%
- CPVT 60%-65%
- Brugada 20%-25%

Aortopathies 20%-40%

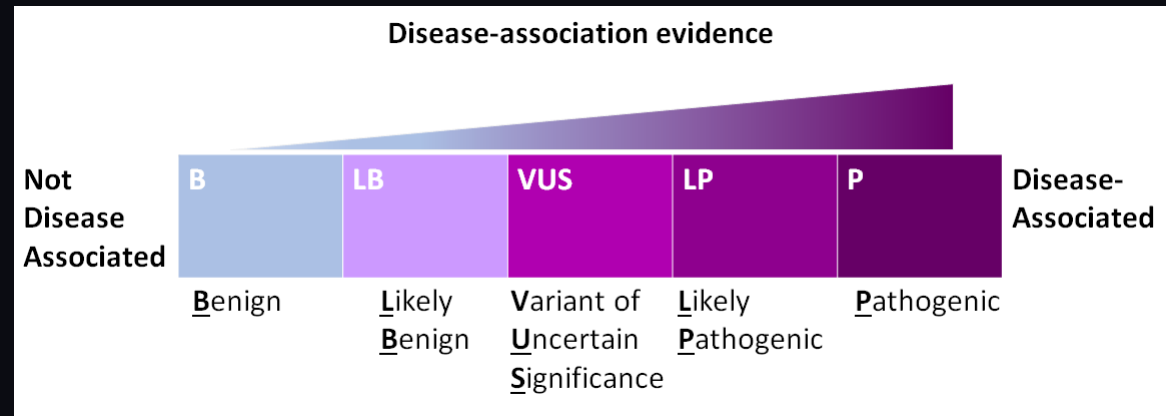
Lipidemias 20%-95%

** Yield will be higher with earlier age of onset and significant family history.

** Yield is also likely higher for patients seen in GACC because of available resources and multidisciplinary approach.

13

Gene Variant Classification



14

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder BAI/BS1 OR observation in controls inconsistent with disease penetrance BS2			Absent in population databases PM2	Prevalence in affecteds statistically increased over controls PS4	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product BP4 Missense in gene where only truncating cause disease BP1 Silent variant with non predicted splice impact BP7	Multiple lines of computational evidence support a deleterious effect on the gene /gene product PP3	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before PM5 Protein length changing variant PM4	Same amino acid change as an established pathogenic variant PS1	Predicted null variant in a gene where LOF is a known mechanism of disease PVS1
Functional Data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation Data	Non-segregation with disease BS4		Co-segregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo Data				De novo (without paternity & maternity confirmed) PM6	De novo (paternity & maternity confirmed) PS2	
Allelic Data		Observed in trans with a dominant variant BP2 Observed in cis with a pathogenic variant BP2		For recessive disorders, detected in trans with a pathogenic variant PM3		
Other Database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other Data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

Richards et al; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID: 25741868; PMCID: PMC4544753.

2015 ACMG Guidelines for the Interpretation of Sequence Variants

- Several factors are considered to determine variant classification
- These are all factors a genetic counselor will consider when reviewing a patient's result

15

Genetic Test Result

Positive

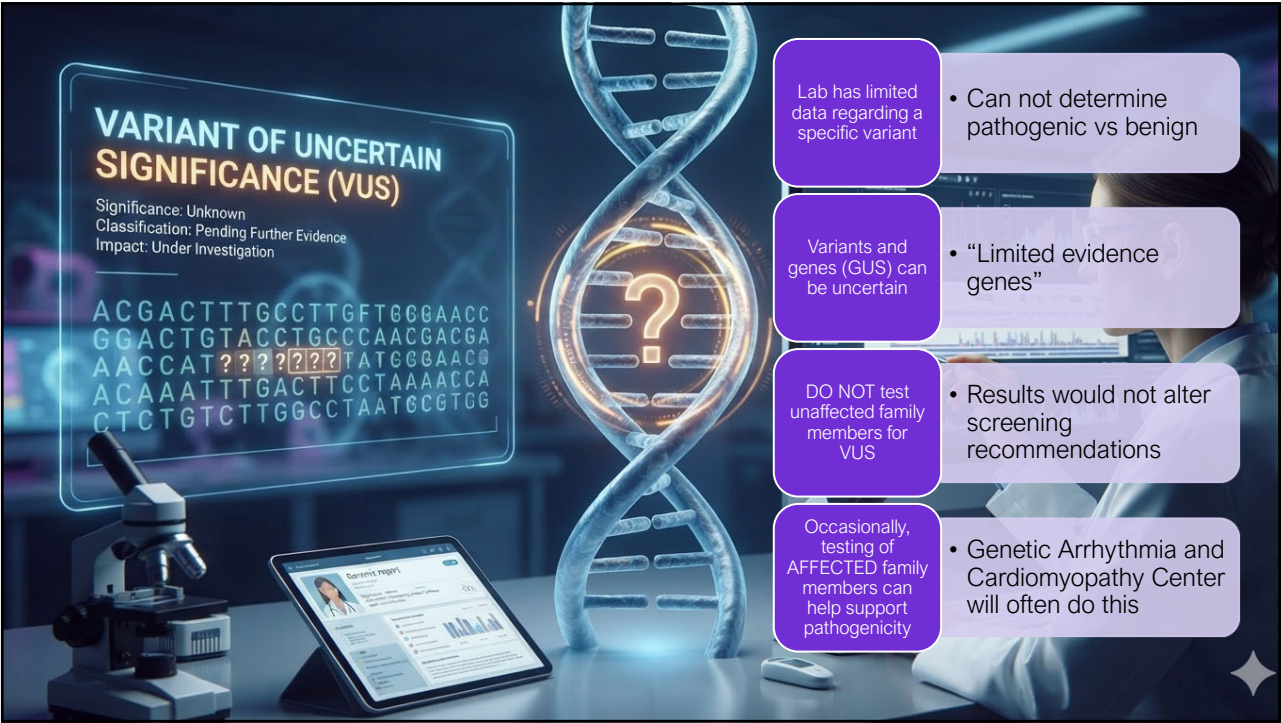
- Pathogenic or likely pathogenic variant
- Diagnostic (or carrier status)
- Helps guide management
- Gene Therapy Trials
- Family member testing

Negative

- Reduces the likelihood of genetic etiology
- Clinical screening for first degree relatives
- Repeat genetic testing in 3-5 years

16

Page 8 of 22



VARIANT OF UNCERTAIN SIGNIFICANCE (VUS)
Significance: Unknown
Classification: Pending Further Evidence
Impact: Under Investigation

ACGACTTTGCCTTGFTGGGAACC
GGACTGTACCTGCCCAACGACGA
AACCAT????TATGGGAACG
ACAAATTTGACTTCCTAAAACCA
CTCTGTCTTGGCCTAATCGGTGG

Lab has limited data regarding a specific variant

• Can not determine pathogenic vs benign

Variants and genes (GUS) can be uncertain

• “Limited evidence genes”

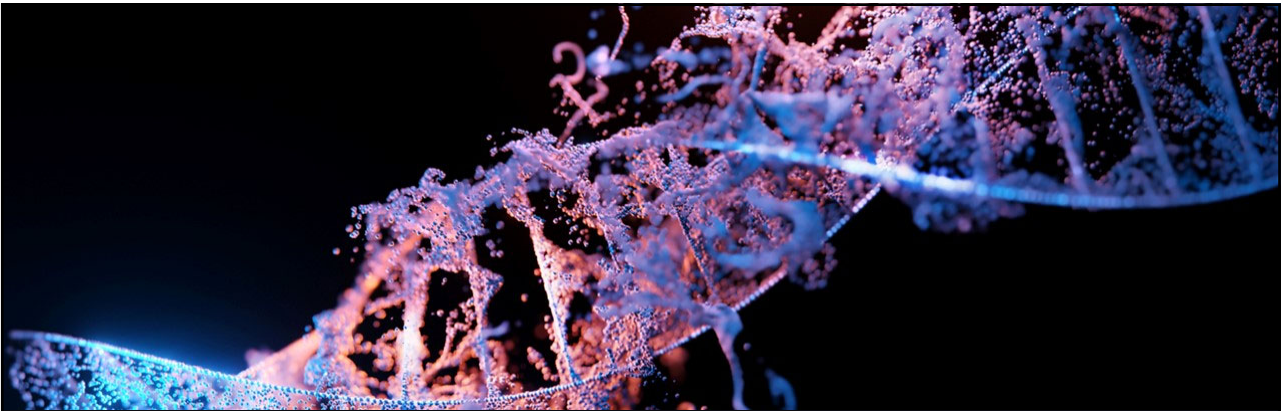
DO NOT test unaffected family members for VUS

• Results would not alter screening recommendations

Occasionally, testing of **AFFECTED** family members can help support pathogenicity

• Genetic Arrhythmia and Cardiomyopathy Center will often do this

17



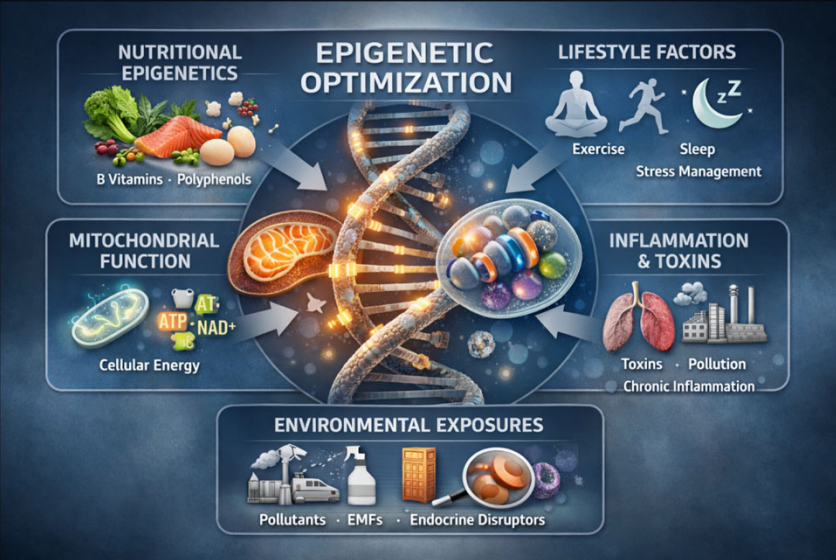
Exome or Genome Sequencing

- Considered if multiple family members affected and standard gene panels are nondiagnostic.
- Most informative if trio
- Yield is low in cardiology

18

Epigenetic Testing

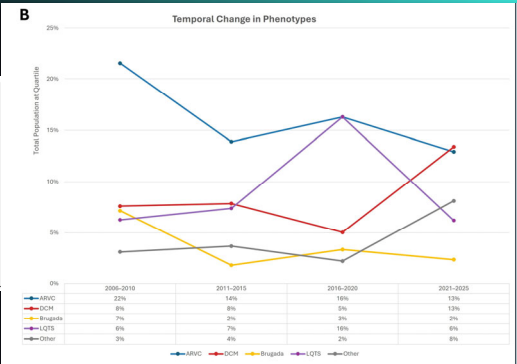
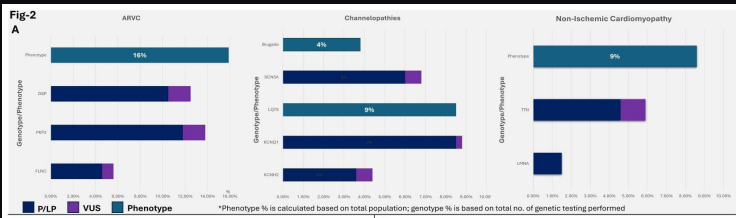
- Used to predict risk by analyzing molecular modifications that accumulate or change over time
- Might predict early disease before other labs or imaging studies can detect it
- Nondiagnostic



19

20 year experience of GACC

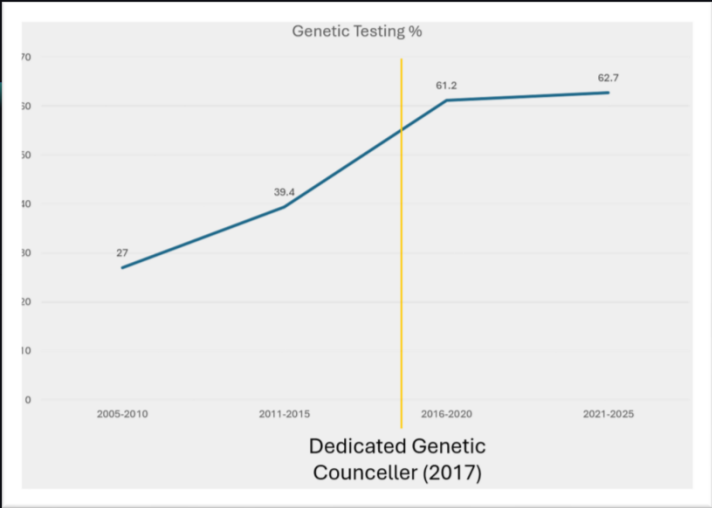
850 patients



20

20 year experience of GACC

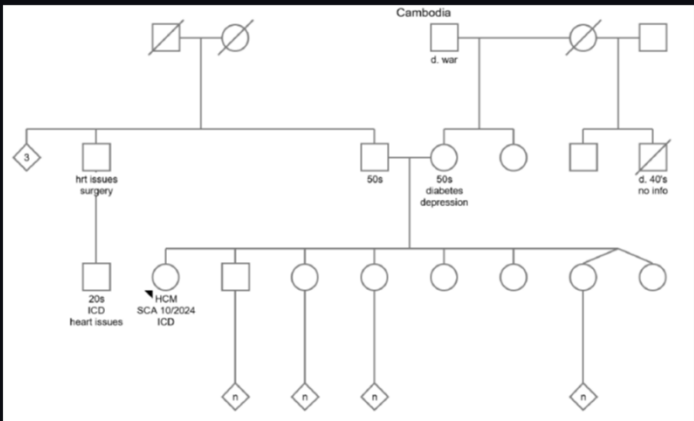
Introduction of genetic
counselling in 2017



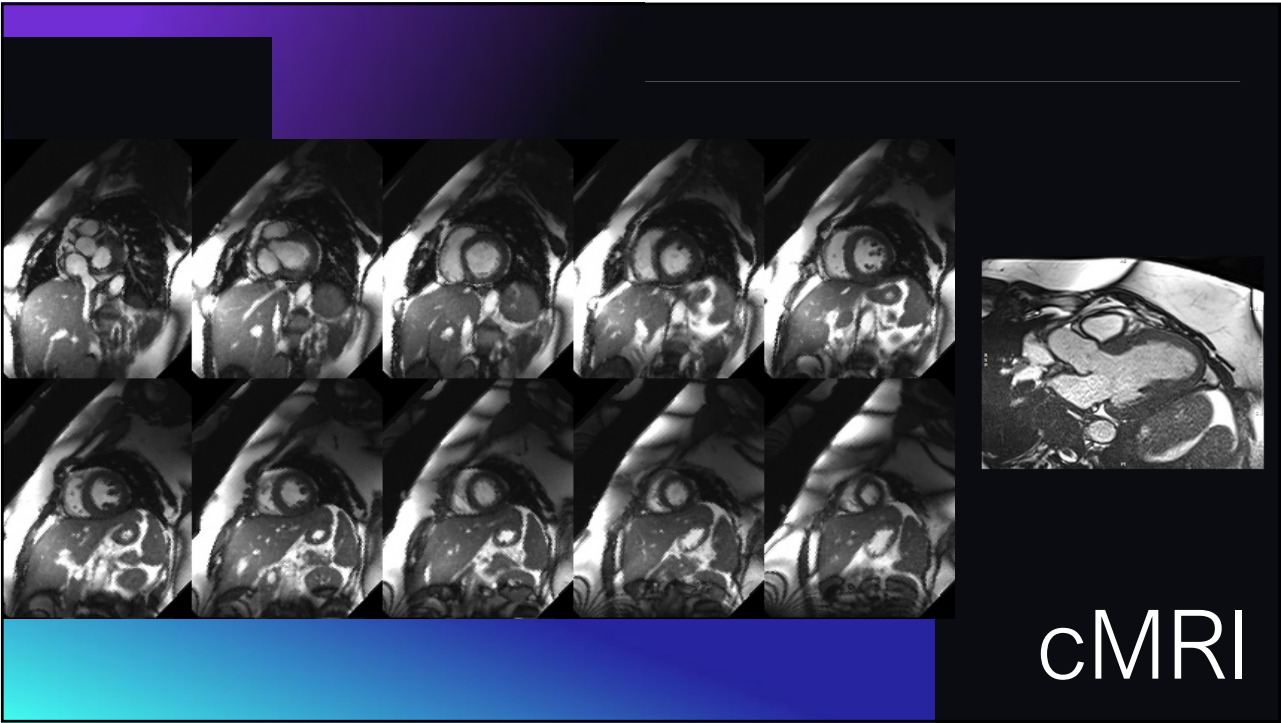
21

Case Example 1

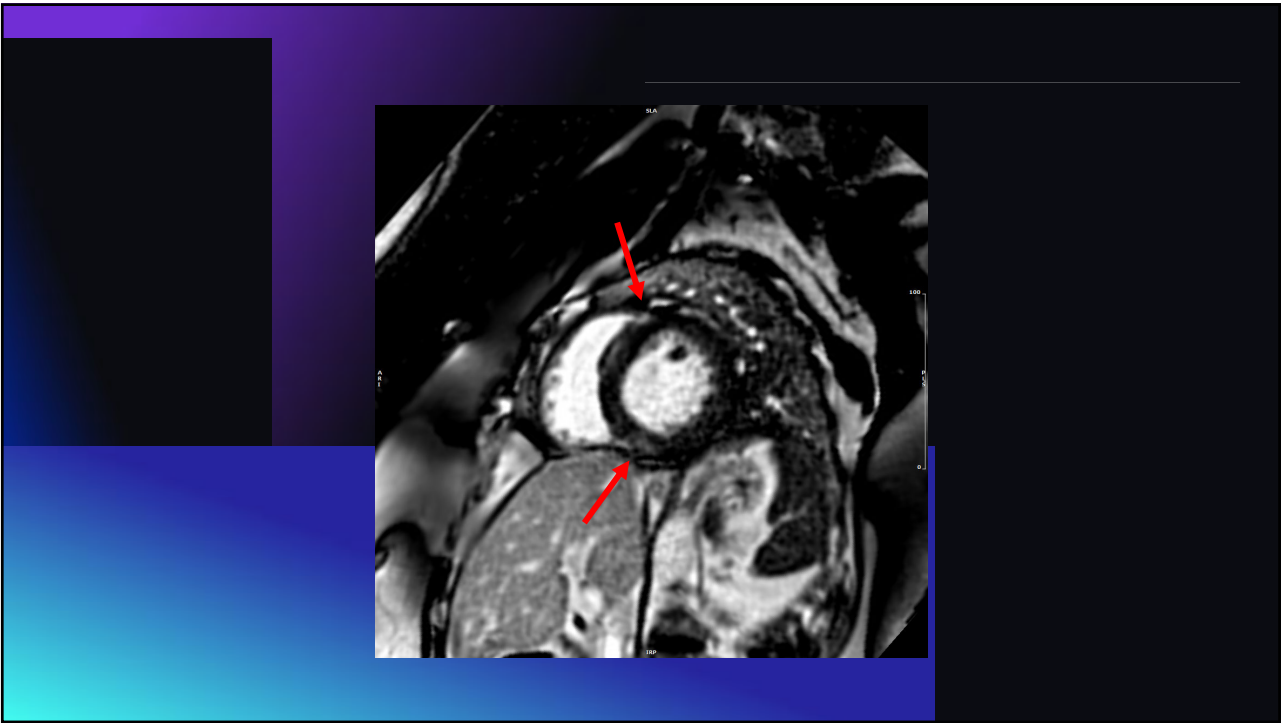
- Presented to ED at 36 yo with anxiety and palpitations
- Dx with HCM (vs hypertensive LVH), a fib, HTN and type 2 diabetes
- SCA at 37 yo, ICD placed
- Prolonged QT interval during admission



22



23



24

RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
ABCC9	c.2758G>A (p.Glu920Lys)	heterozygous	Uncertain Significance
GAA	c.1726G>A (p.Gly576Ser)	heterozygous	Benign (Pseudodeficiency allele)
GAA	c.2065G>A (p.Glu689Lys)	heterozygous	Benign (Pseudodeficiency allele)

About this test

This diagnostic test evaluates 100 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

ABCC9:c.2758G>A

chr12-22005042 C>T | p.Glu920Lys | NM_020297.4 | UCSC (V) | TraP (V) | gnomAD (V)

Classify Variant | Follow | Save Case | Export Summary

Franklin ACMG Classification | Variant Assessment | Publications | Gene Assessment

Suggested Classification
VUS

Benign | Likely Benign | VUS | Likely Pathogenic | Pathogenic

Franklin.genoox.com

ABCC9, Exon 22, c.2758G>A (p.Glu920Lys), heterozygous, Uncertain Significance

- This sequence change replaces glutamic acid, which is acidic and polar, with lysine, which is basic and polar, at codon 920 of the ABCC9 protein (p.Glu920Lys).
- This variant is not present in population databases (gnomAD no frequency).
- This variant has not been reported in the literature in individuals affected with ABCC9-related conditions.
- Invitae Evidence Modeling of protein sequence and biophysical properties (such as structural, functional, and spatial information, amino acid conservation, physicochemical variation, residue mobility, and thermodynamic stability) has been performed for this missense variant. However, the output from this modeling did not meet the statistical confidence thresholds required to predict the impact of this variant on ABCC9 protein function.
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

25

ABCC9 Gene

The ABCC9 gene is associated with autosomal dominant Cantu syndrome and dilated cardiomyopathy (DCM) and with autosomal recessive intellectual disability and myopathy syndrome. Additionally, the ABCC9 gene has preliminary evidence supporting a correlation with autosomal dominant Brugada syndrome.

Cantu Syndrome

- Congenital hypertrichosis
- Craniofacial dysmorphic features
- Cardiac features
 - Increased ventricular mass – persistent through life and may progress to heart failure
 - High-output hypertrophy caused by low systemic vascular resistance, and the potential for progression to high-output heart failure.
- PDA
- Dilated aortic root and ascending aorta
- Pericardial effusion

A

B

C

D

E

F

<https://doi.org/10.1161/JAHA.122.027363>

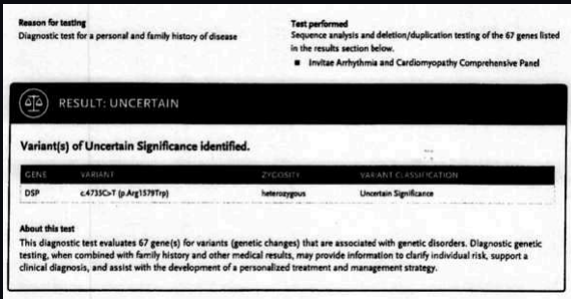
Cantú Syndrome - GeneReviews® - NCBI Bookshelf

26

Page 13 of 22

Case Example 2

- 19 yo male presented to GACC with history of SCA at age 16 , cardiomyopathy
- Mom and several maternal family members with cardiomyopathy
- Brother died suddenly at age 19
- Previous genetic testing performed at another facility
 - RYR2 variant in 2016
 - DSP uncertain variant 2019
 - family was in the process of tracking the variant and considering Exome/Genome sequencing

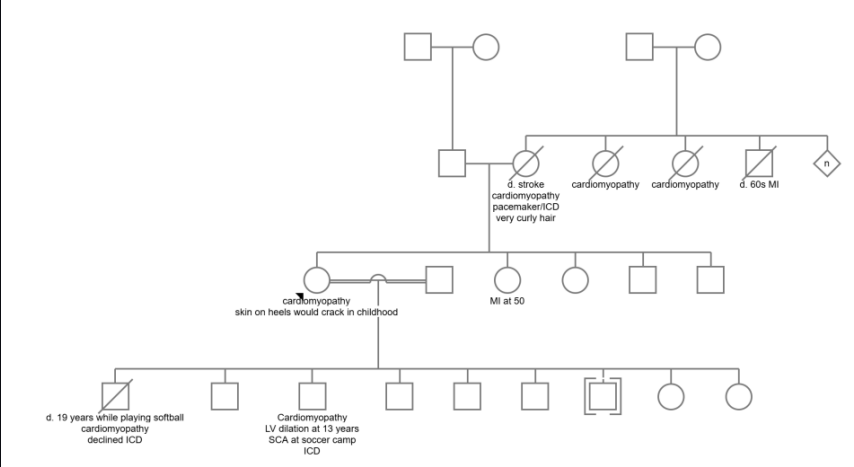


27



28

Family History



29

RESULT: POSITIVE

One homozygous Pathogenic variant identified in PCCB. PCCB is associated with autosomal recessive propionic acidemia.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PCCB	c.1606A>G (p.Asn536Asp)	homozygous	PATHOGENIC

About this test

This diagnostic test evaluates 2 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

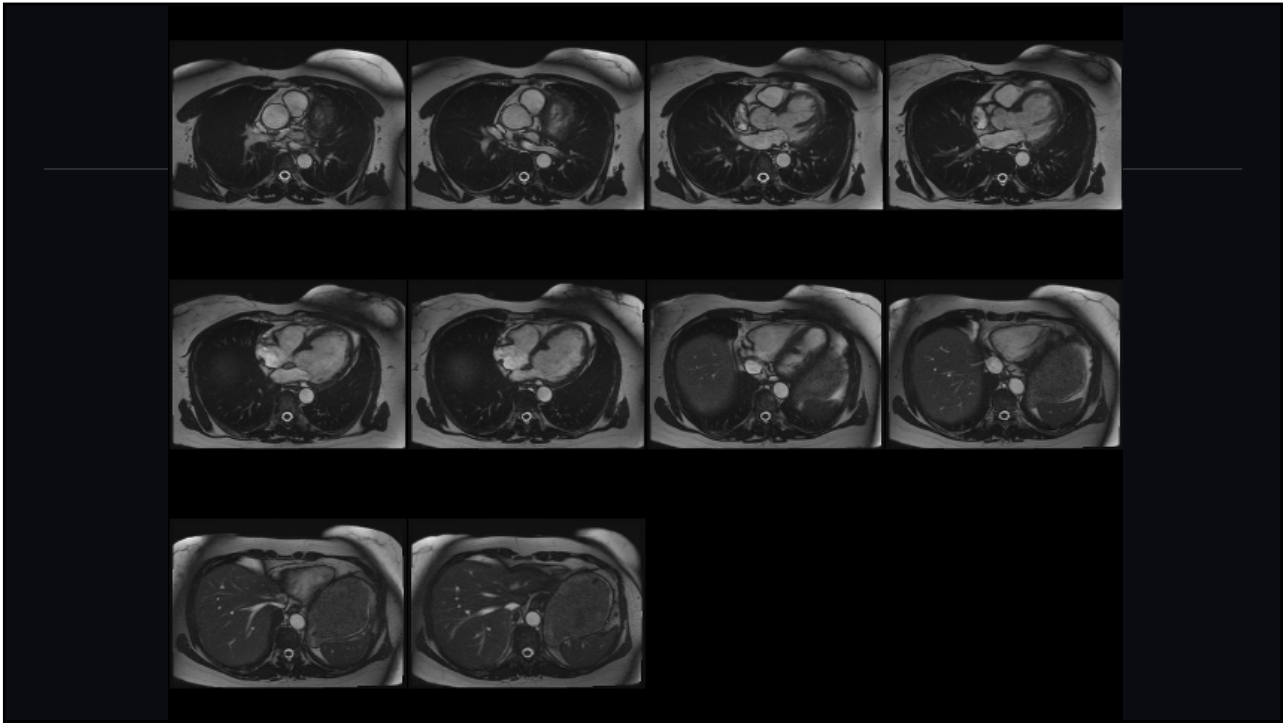
- 1. Mennonite
- 2. Consanguinity
- 3. Review of family records

*Consideration of these important clues lead to diagnosis of Propionic Acidemia, which would not have been diagnosed by the Comprehensive Arrhythmia and Cardiomyopathy Gene Panel.

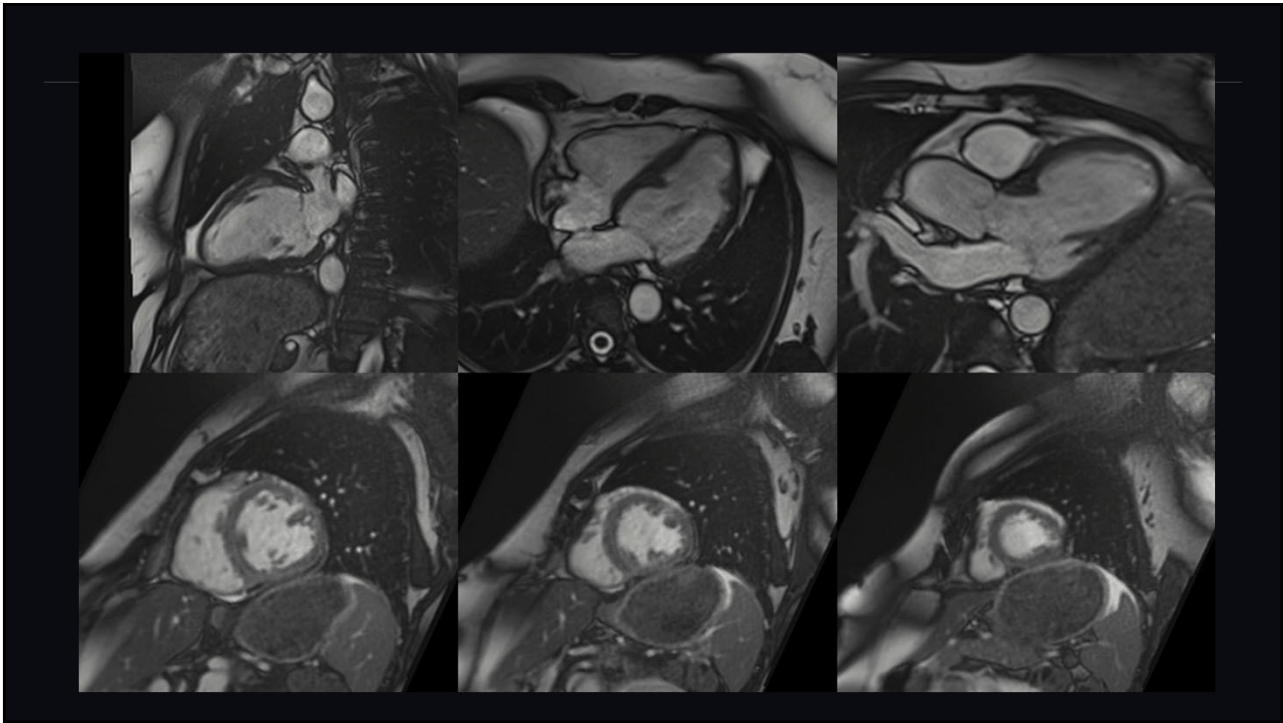
Mom had a separate genetic cardiomyopathy - DSP pathogenic gene variant identified on Comprehensive Panel

Family History is Essential

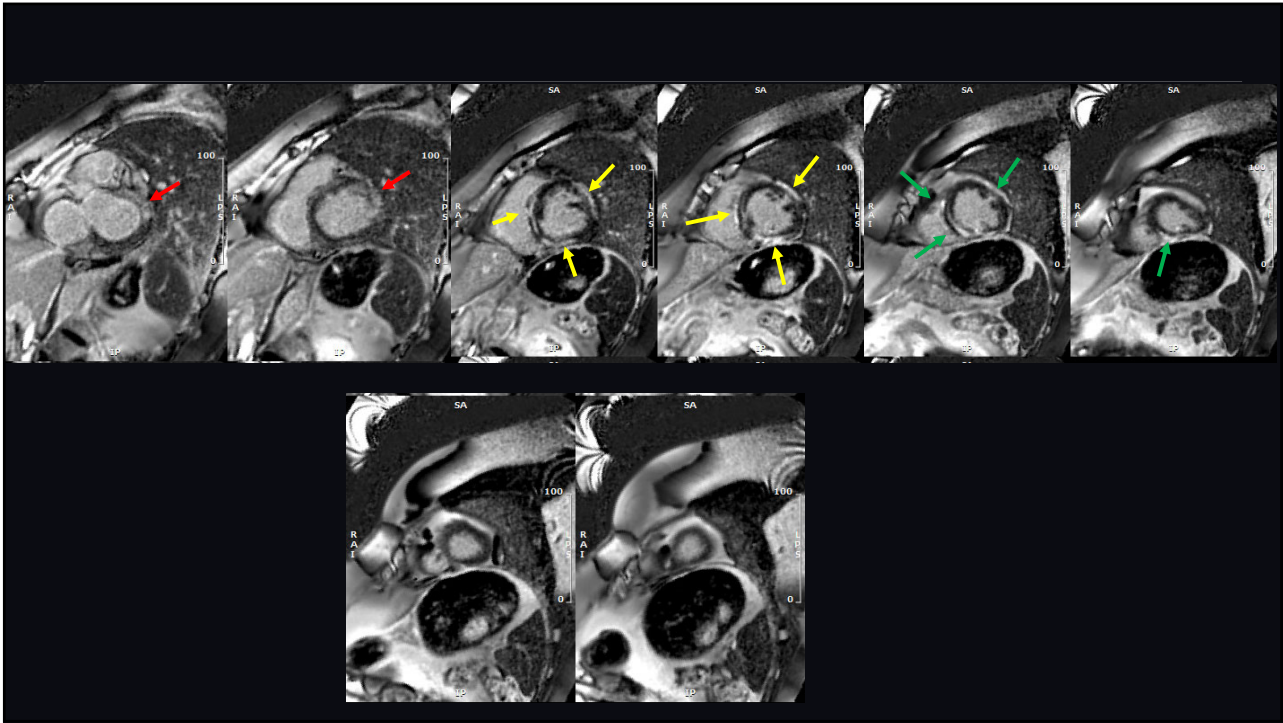
30



31



32



33

Case Example 3

35 yo with possible ARVC

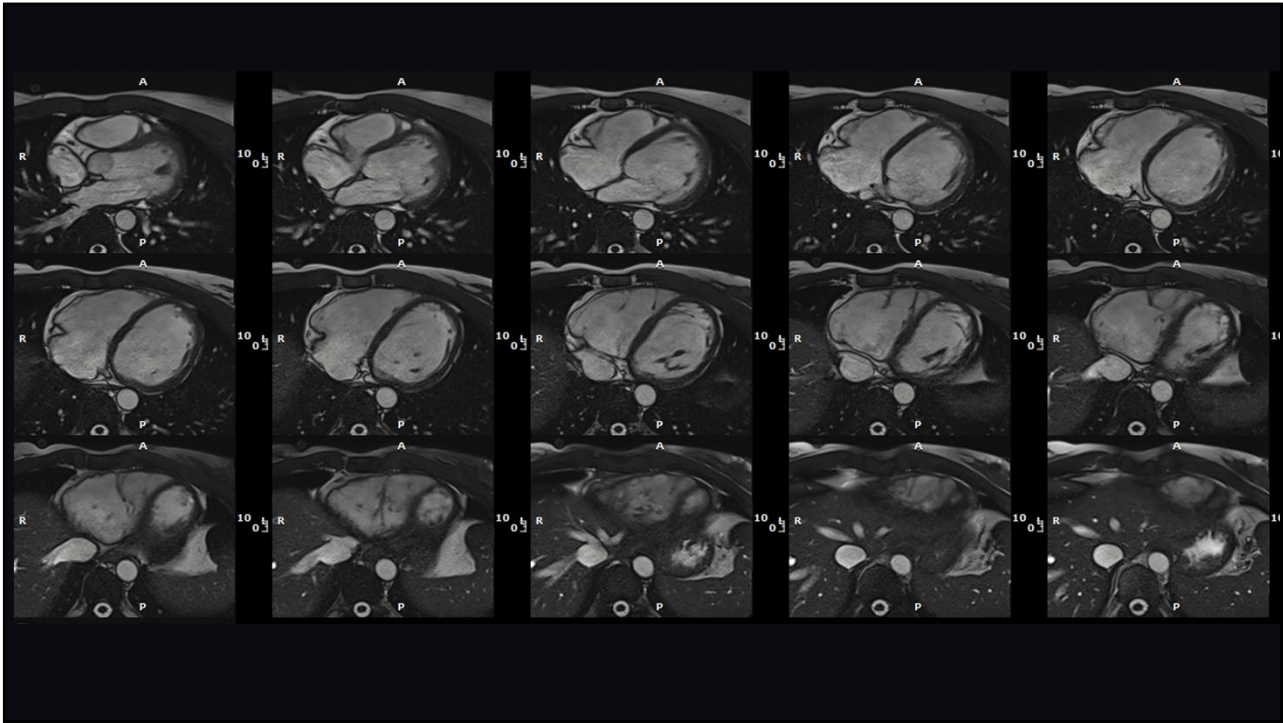
Frequent PVC's

BAV

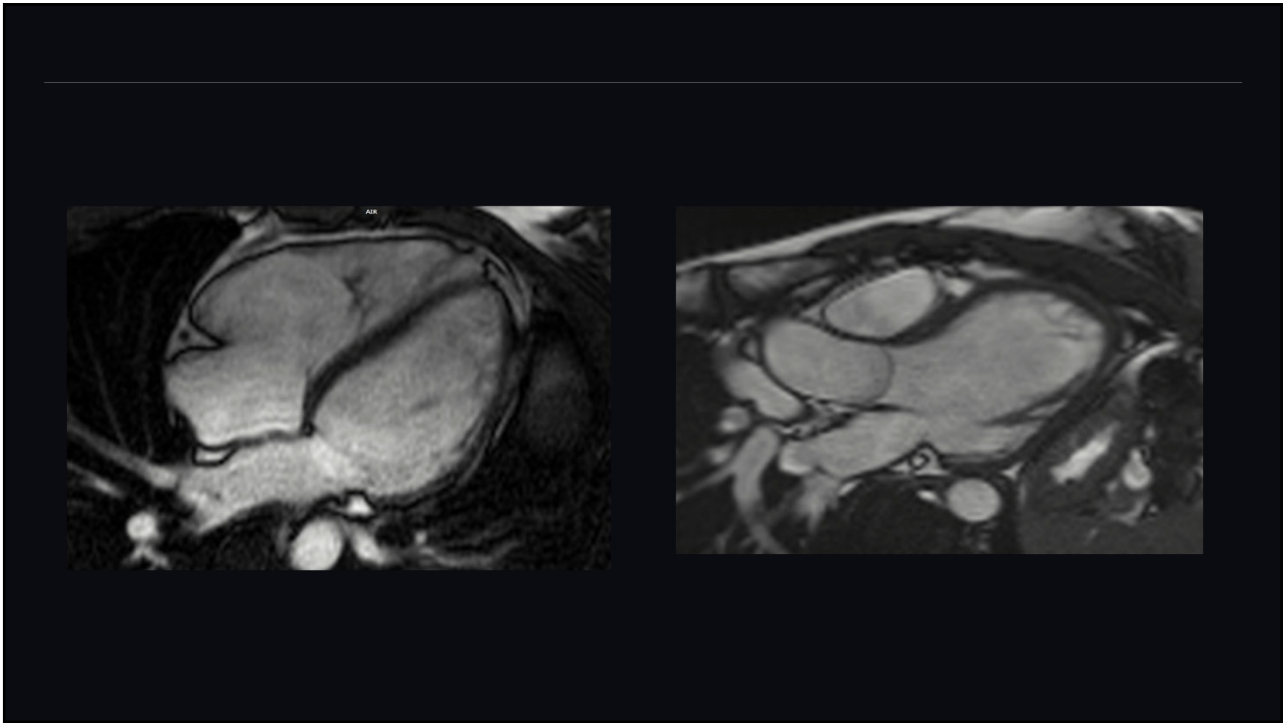
Father with hx of heart transplant in his 30's

German

34



35



36

1. Heart, removed during cardiac allotransplantation for idiopathic dilated cardiomyopathy, showing features of arrhythmogenic right ventricular dysplasia/cardiomyopathy:
 - a. 473 g biventricular specimen (expected, approximately 200-300 g).
 - b. Hypertrophy, biventricular, moderate to marked.
 - c. Dilation, biventricular, marked, with 5.5 cm short-axis internal diameter of left ventricle, without mural thrombus in either ventricle.
 - d. Wall thinning, due to effects of dilation, with ventricular thicknesses (in cm): left 0.9, septum 1.0, and right 0.3.
 - e. Valvular dilation, due to ventricular dilation, moderate, with annular circumferences (in cm): aortic 7.5, pulmonary 8.7, mitral 13.3, and tricuspid 14.2.
 - f. Interstitial fibrosis, right ventricular, focally moderate, and left ventricular, focally mild to moderate.
 - g. Interstitial adiposity, right ventricular, focally moderate to marked, and left ventricular, focal and mild.
 - h. Recurrent ventricular tachycardia (by history).
 - i. Lymphocytic myocarditis, microfocal, biventricular, minimal.
 - j. Coronary atherosclerosis, noncalcific and noncritical disease, with focal grade 1 (of 4) lesions, widely patent coronary ostiums, and right coronary dominance.

Case Example 4

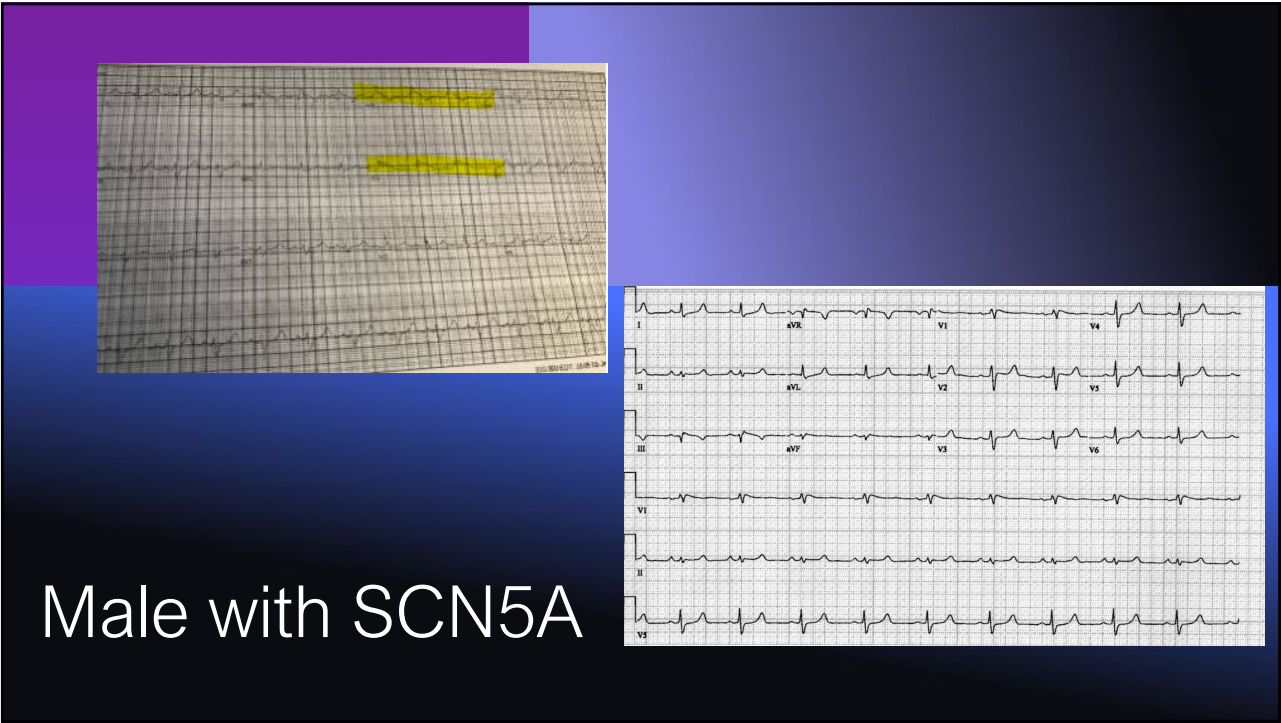
- 66 yo male presents to GACC with hx of SCA
- Brugada pattern
- Genetic Testing revealed SCN5A pathogenic variant
- Cascade testing

39



Female with SCN5A

40



41

Autosomal-dominant biventricular arrhythmogenic cardiomyopathy in a large family with a novel in-frame DSP nonsense mutation

 Sajya M Singh ¹, Susan A Casey ¹, Allison A Berg ², Raed H Abdelhadi ¹, William T Katsiyannis ¹, Mosi K Bennett ¹, Shannon Mackey-Bojack ³, Emily R Duncanson ³, Jay D Sengupta ¹

Affiliations [+ expand](#)
PMID: 30160835 DOI: 10.1002/ajmg.a.38719

Case Example 5

42

The Future of Cardiovascular Genetics

☐ NCT06109181
Active, not recruiting

Gene Therapy for ACM Due to a PKP2 Pathogenic Variant

conditions

No longer looking for participants

Arrhythmogenic Cardiomyopathy
PKP2
PKP2 ACM

Locations

Stanford, California, United States	Baltimore, Maryland, United States
Ann Arbor, Michigan, United States	Rochester, New York, United States

[View all 3 locations](#)

Display

Non-interventional study of Seroprevalence of Pre-existing Antibodies Against Adenovirus-associated Virus Vector (AAV9) and the Progression of Disease in Patients With Plakophilin 2 (PKP2)-Associated Arrhythmogenic...

[Find Contact Information](#)
[Check who can join](#)

Conditions

Arrhythmogenic Right Ventricular Cardiomyopathy

Locations

San Francisco, California, United States	Aurora, Colorado, United States
Baltimore, Maryland, United States	Boston, Massachusetts, United States

[View all 21 locations](#)

☐ NCT06282894

Open-label, Dose Escalation Study of Safety and Preliminary Efficacy of TN-019 Adults With PKP2 Mutation-associated ARVC

Conditions

Arrhythmogenic Right Ventricular Cardiomyopathy

Locations

San Francisco, California, United States	Aurora, Colorado, United States
Baltimore, Maryland, United States	Boston, Massachusetts, United States

[View all 7 locations](#)

[ClinicalTrials.gov](https://clinicaltrials.gov)


NCT05836259

Recruiting

Multi-center, Open-label, Single-ascending Dose Study of Safety and Tolerability of TN-201 in Adults With Symptomatic **MYBP3 Mutation-associated HCM**

Conditions

Hypertrophic Cardiomyopathy

Locations

- La Jolla, California, United States
- Atlanta, Georgia, United States
- San Francisco, California, United States
- Boston, Massachusetts, United States

[Show all 12 locations](#)

[Find Contact Information](#)

[Check who can join](#)

☐
NCT07218887

ALXN2350 in Adult Participants With **BAG3** Associated Dilated Cardiomyopathy

Conditions

BAG3 Mutation Associated Dilated Cardiomyopathy

Locations

Birmingham, Alabama, United States

Boston, Massachusetts, United States

Cincinnati, Ohio, United States

Portland, Oregon, United States

[Show all 10 locations](#)

Dilated Cardiomyopathy (DCM)

Conditions

BAG3 Mutation Associated Dilated Cardiomyopathy
Dilated Cardiomyopathy (DCM)

Locations

Miami, Florida, United States

Kansas City, Missouri, United States

Houston, Texas, United States

☐
NCT07137238

A Phase 1 AAV **Gene Therapy** Trial Evaluating Safety and Preliminary Efficacy of RP-AAV01 in Subjects With **BAG3** Dilated Cardiomyopathy

Conditions

Dilated Cardiomyopathy (DCM)

Locations

San Diego, California, United States

Rochester, Minnesota, United States

Charleston, South Carolina, United States

Recruiting

[Find Contact Information](#)

[Check who can join](#)

Display

[Show all 10 locations](#)

[Check who can join](#)

43

1 Genetics 101

- 20,000 genes
- 6000 characterized
- Two copies of every gene – paternal and maternal copy

2 Inheritance

- Dominant
- Recessive

3 Common Indications

- Nonischemic cardiomyopathy
- Arrhythmic cardiomyopathy
- Family or personal history of SCD/SCA
- Post-mortem testing
- ATRR amyloidosis
- Family history of gene mutation
- Concern for inherited arrhythmia
- Aortic aneurysm/dissection
- Hyperlipidemia

4 Genetic Counseling: Pre-Test

- Family history
- Determine gene panel
- Potential results
- GINA
- Limitations
- Insurance coverage
- Sample collection

5 Gene Variant Classification

- Benign: Not associated with disease
- Likely benign: Likely not associated with disease
- Uncertain: Insufficient evidence to determine significance
- Likely pathogenic: Likely associated with disease
- Pathogenic: Associated with disease

6 Genetic Test Result

- Positive: A pathogenic or likely pathogenic variant identified
- Negative: No pathogenic variant identified
- Uncertain: Variant of uncertain significance identified

7 Family History of Cardiac Disease

- Known familial variant: Targeted testing for variant
- No known familial variant: Consider comprehensive testing

8 Gene Therapies

- Viral vector delivers genetic material
- Restores or modifies gene function
- Potential to treat underlying genetic cardiovascular disease

9 Exome or Genome Sequencing

- DNA Sample
- Sequencing
- Data Analysis
- Comprehensive Variant Detection

THE GENETIC CONNECTION

Genetic variants can influence cardiac structure, electrical activity, and vascular integrity—impacting risk for cardiovascular disease across the lifespan.

DNA VARIANTS → ALTERED PROTEINS → CELLULAR EFFECTS → CLINICAL IMPACT

PERSONALIZED RISK ASSESSMENT | GUIDE MANAGEMENT | INFORM FAMILY | IMPROVE OUTCOMES

44