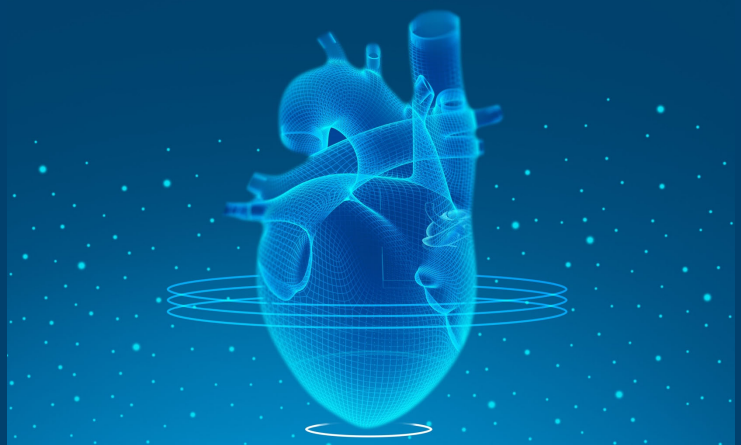
Minneapolis Heart Institute Foundation

GRAND ROUNDS



1

Minneapolis Heart Institute Foundation

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 International Scholar
Joseph F. Novogratz Family Heart Rhythm Center

Allison Berg
MS, CGC

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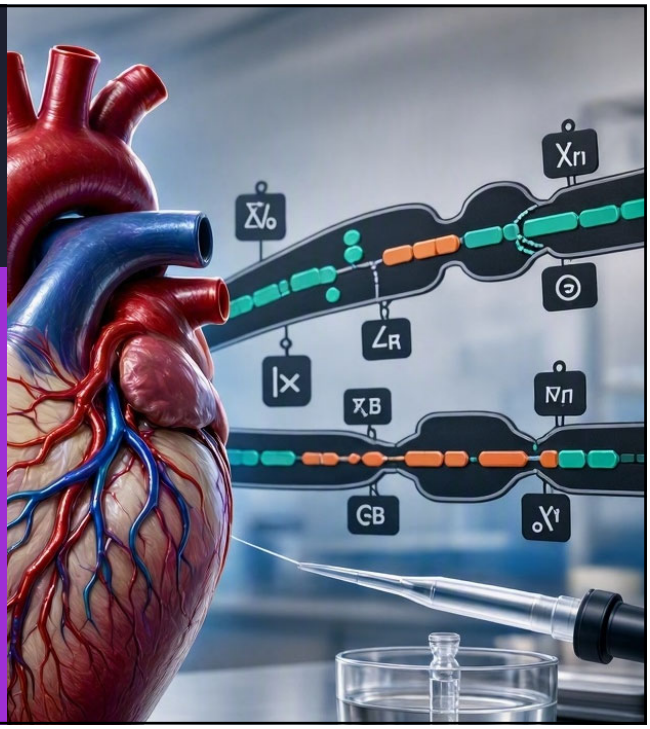
2

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



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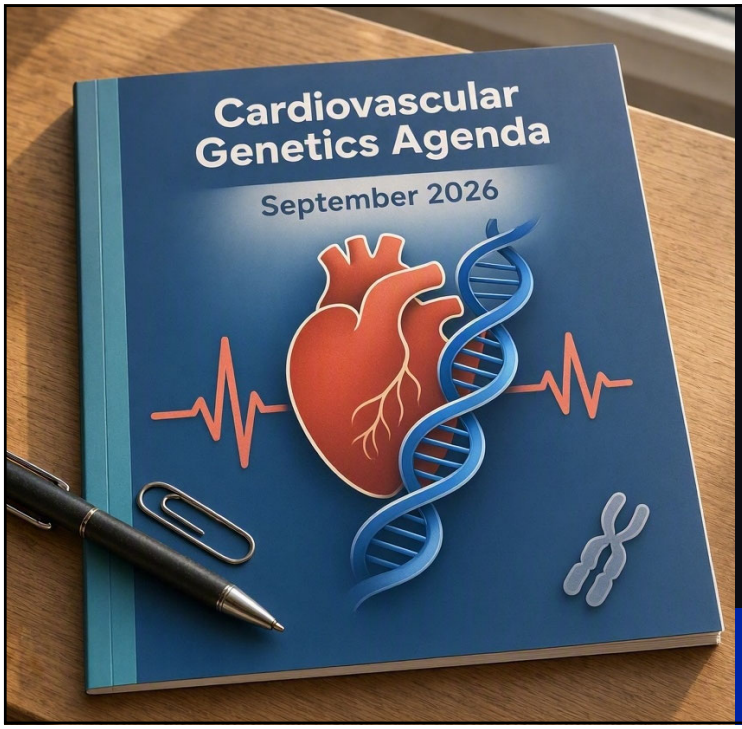


Agenda

- 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

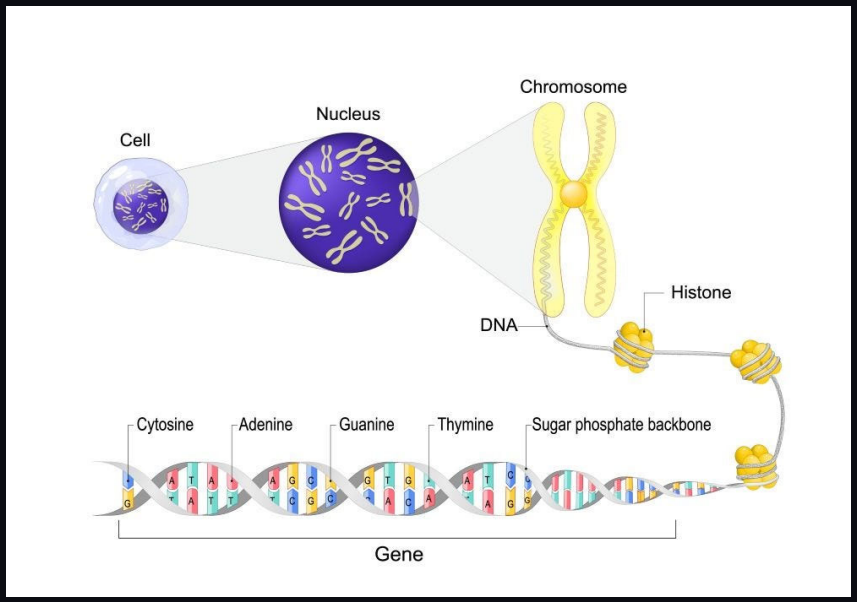
Estimated 20,000 genes

- Small portion characterized

Two copies of every gene – paternal gene and maternal gene

Genetic Terminology

- Penetrance
- Variable expressivity



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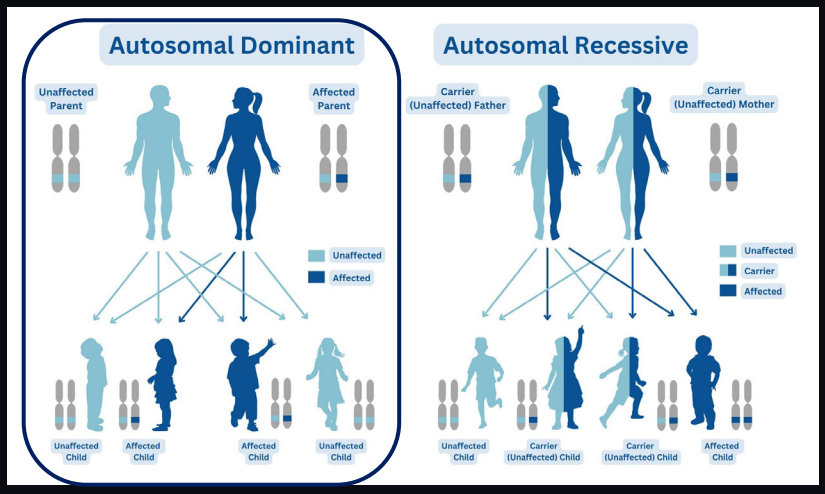
Inheritance

Dominant

Recessive

X-linked



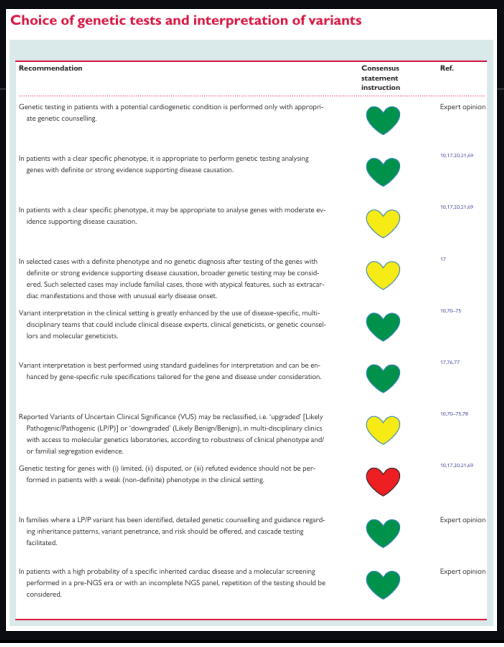
7

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.		10,17,20,21,69
In patients with a clear specific phenotype, it may be appropriate to analyse genes with moderate evidence supporting disease causation.		10,17,20,21,69
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, multidisciplinary teams that could include clinical disease experts, clinical geneticists, or genetic counsellors and molecular geneticists.		10,70–75
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 (LP/P)] 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.		10,70–75,78
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.		10,17,20,21,69
In families where a LP/P 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

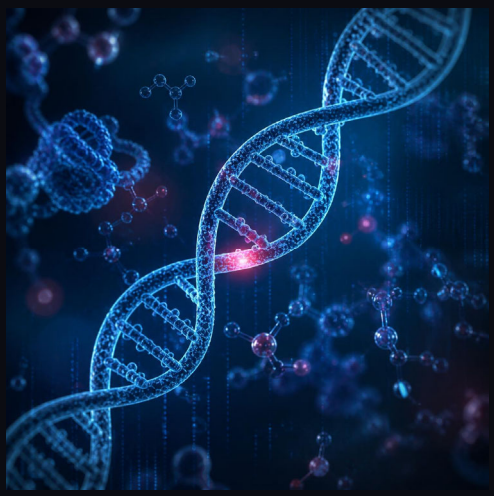
11

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%

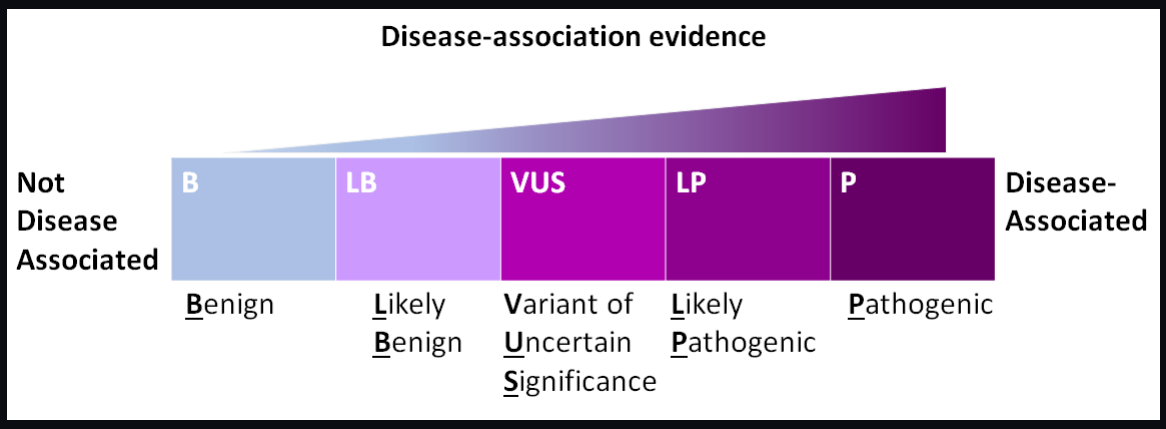
Lipidemias 20%-95%

** 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

2015 ACMG Guidelines for the Interpretation of Sequence Variants

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder *BA1/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*			

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

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.

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

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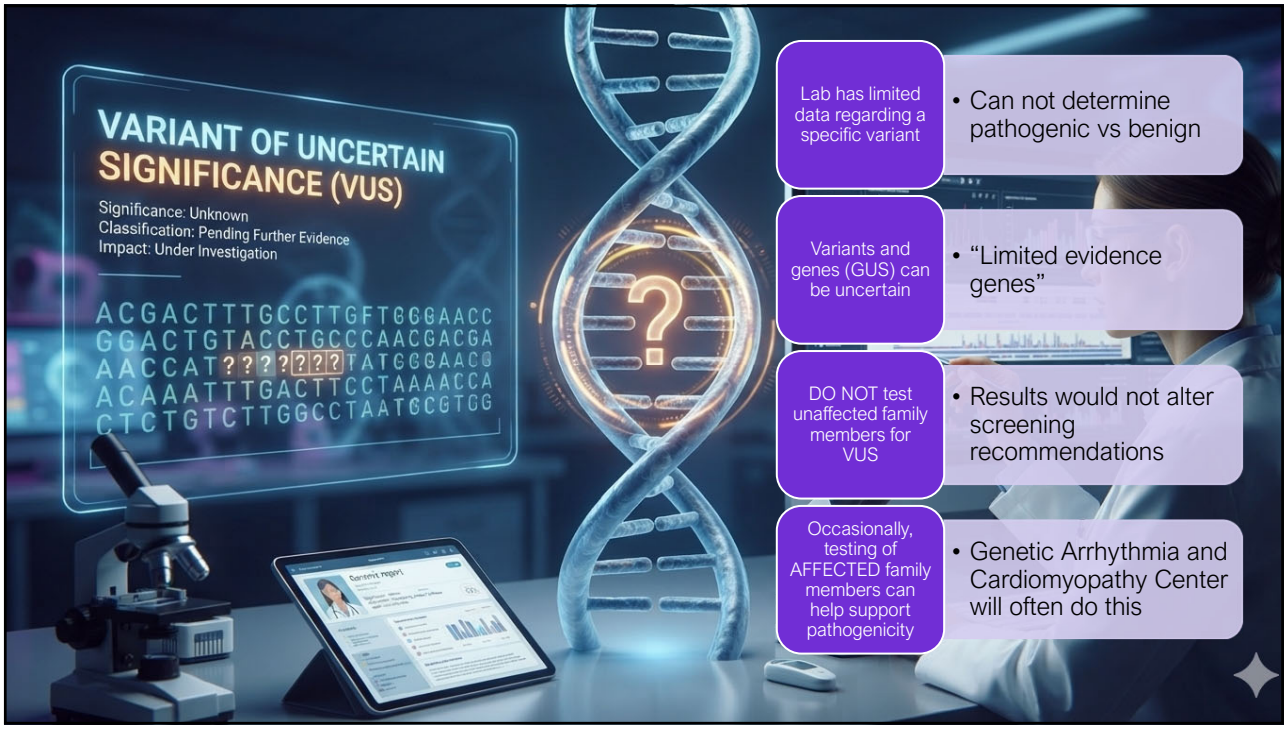

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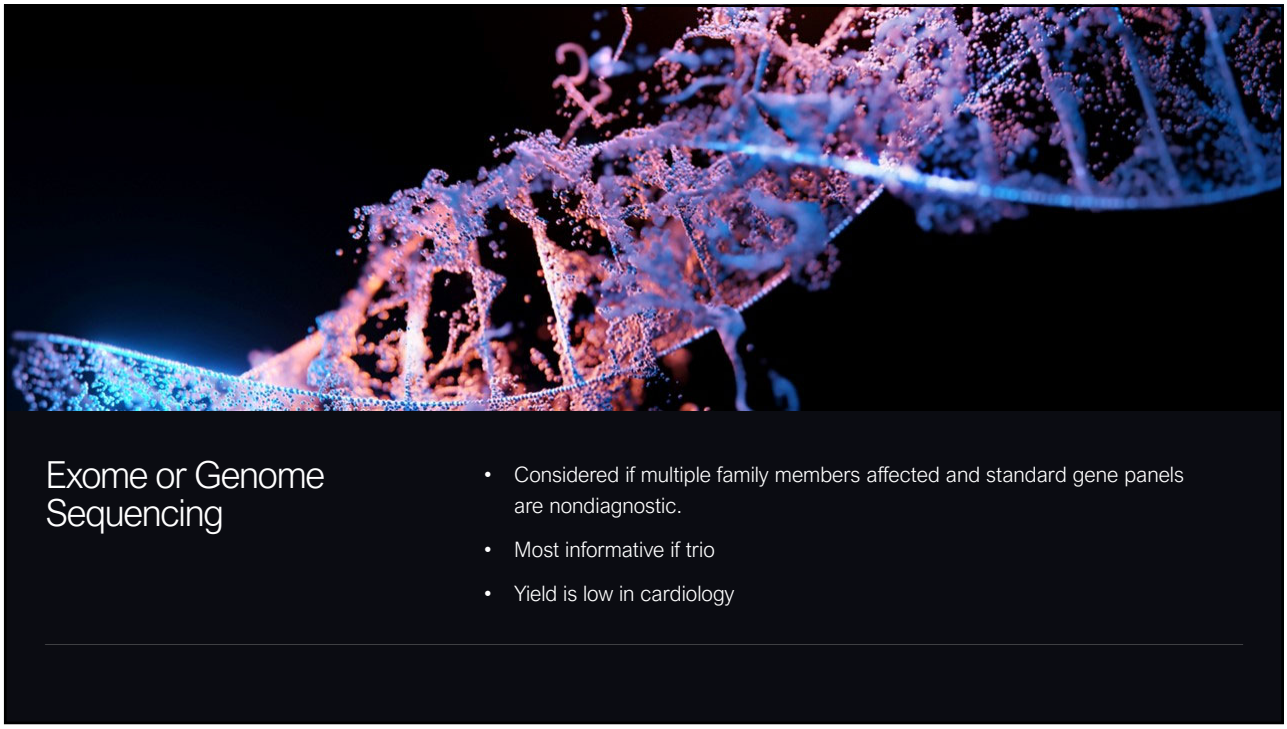


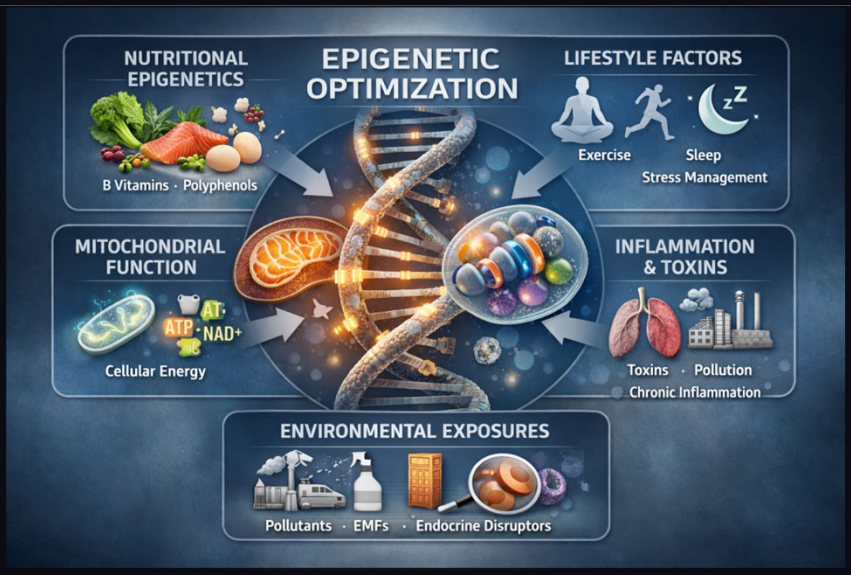
Exome or Genome Sequencing

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

18

Epigenetic Testing

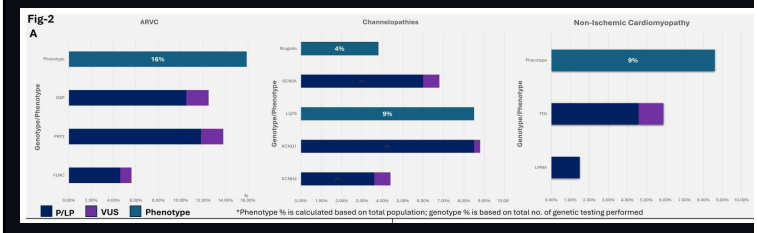
- Used to predict risk by analyzing molecular modifications that accumulate or change over time
- Might predict early disease before other labs or imaging studies can detect it
- Nondiagnostic

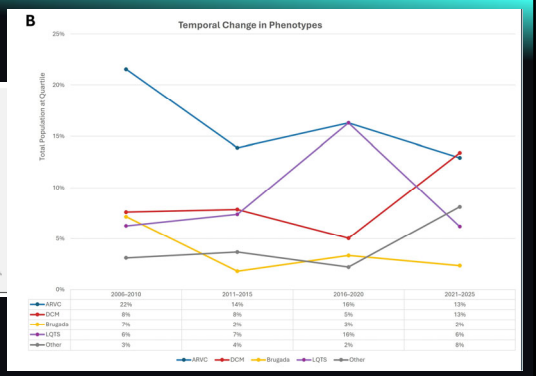


19

20 year experience of GACC

850 patients





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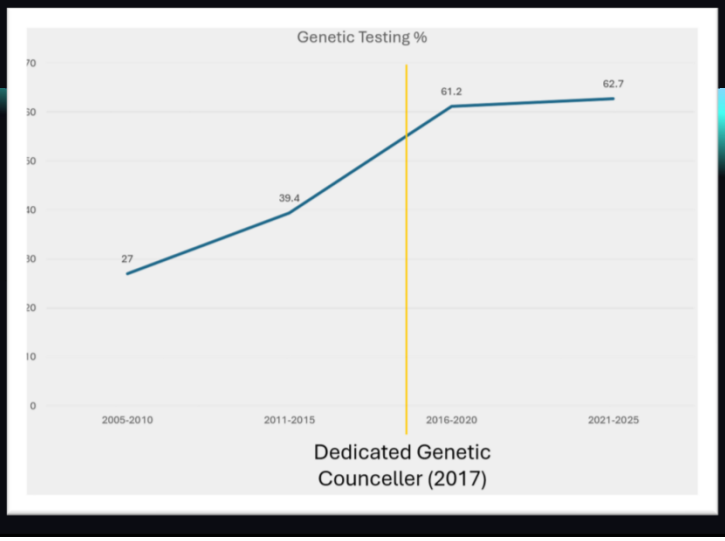
20 year experience of GACC

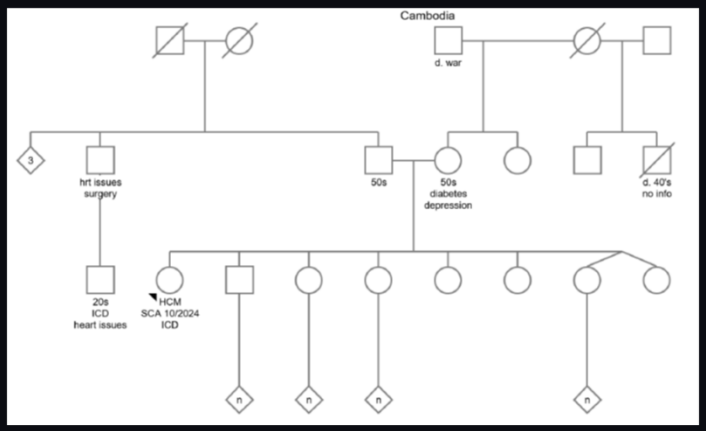
Introduction of genetic counselling in 2017



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



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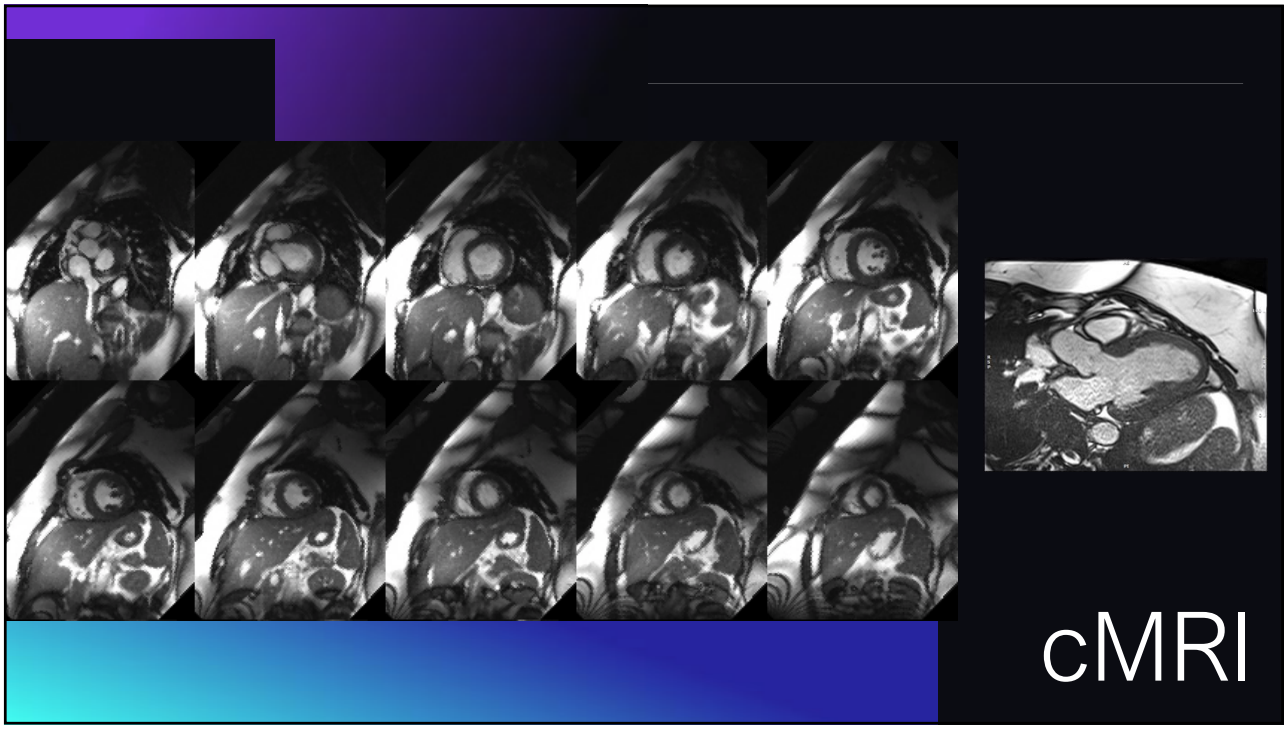

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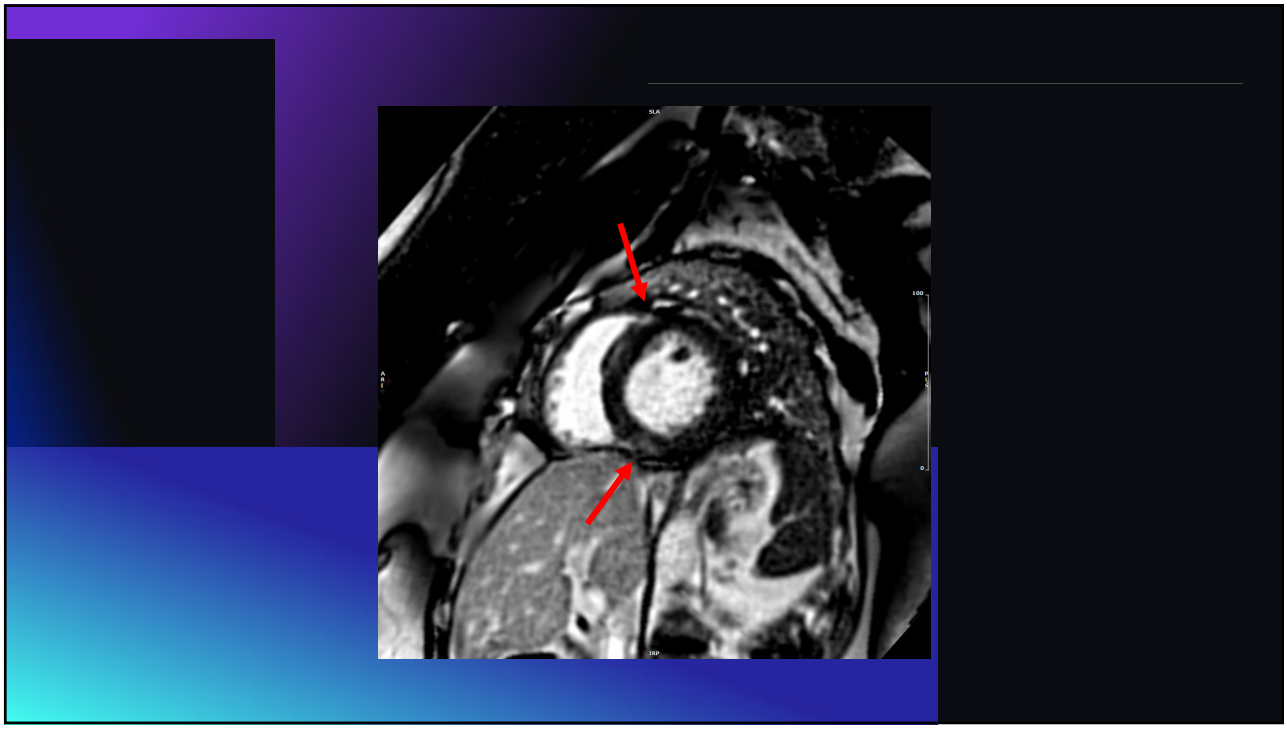

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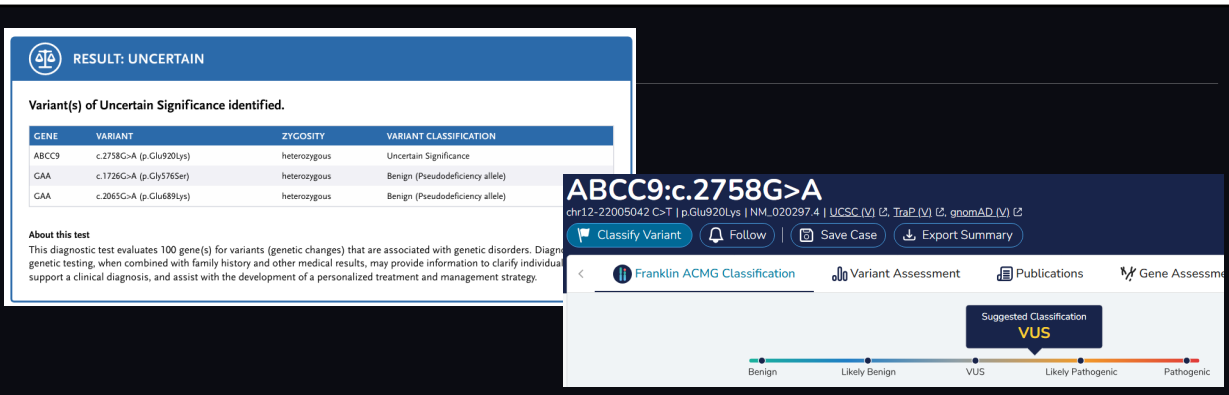


ABCC9, Exon 22, c.2758G>A (p.Glu920Lys), heterozygous, Uncertain Significance

- 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.

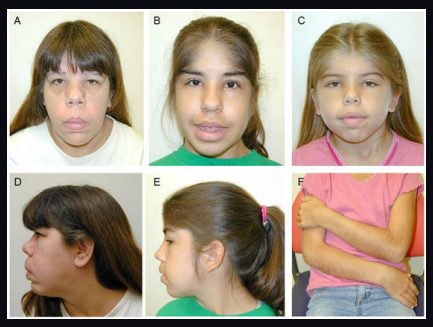
25

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



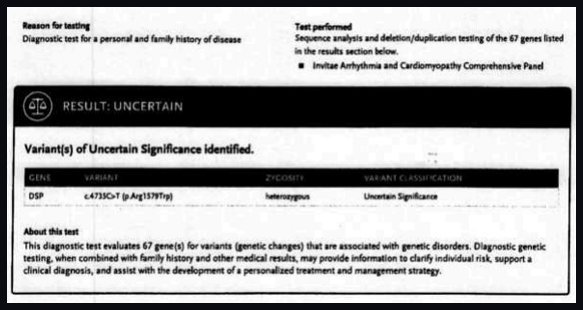
https://doi.org/10.1161/JAHA.122.027363

Cantú Syndrome - GeneReviews® - NCBI Bookshelf

26

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



Reason for testing
Diagnostic test for a personal and family history of disease

Test performed
Sequence analysis and deletion/duplication testing of the 67 genes listed in the results section below.
- Invitae Arrhythmia and Cardiomyopathy Comprehensive Panel

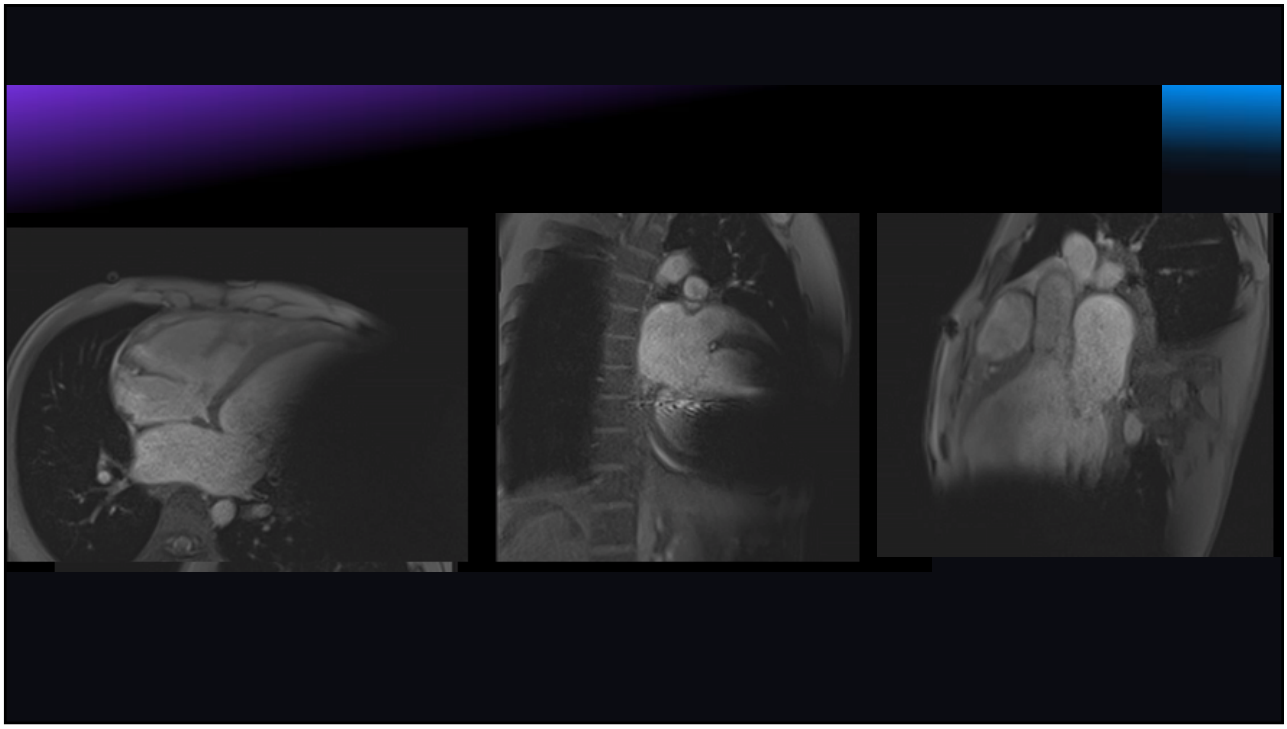
RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
DSP	c.4733C>T (p.Arg1579Trp)	heterozygous	Uncertain Significance

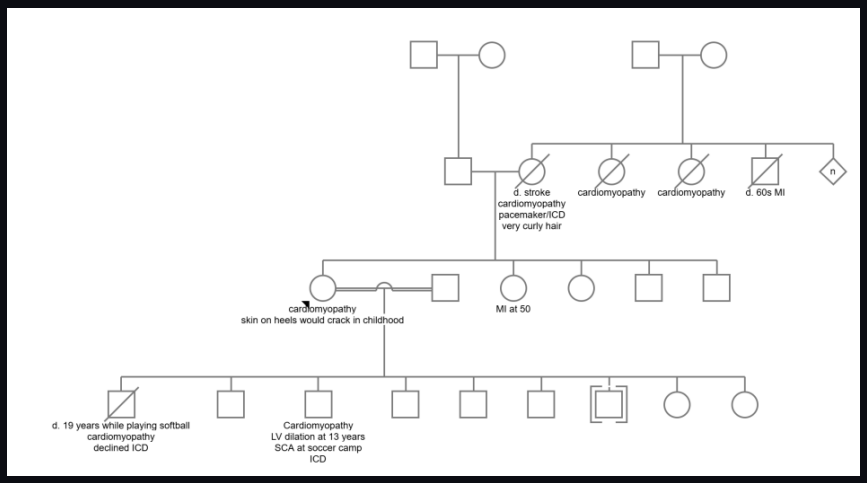
About this test
This diagnostic test evaluates 67 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

27



28

Family History



Obtained hospital records – biochemical studies suggested PPA

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.

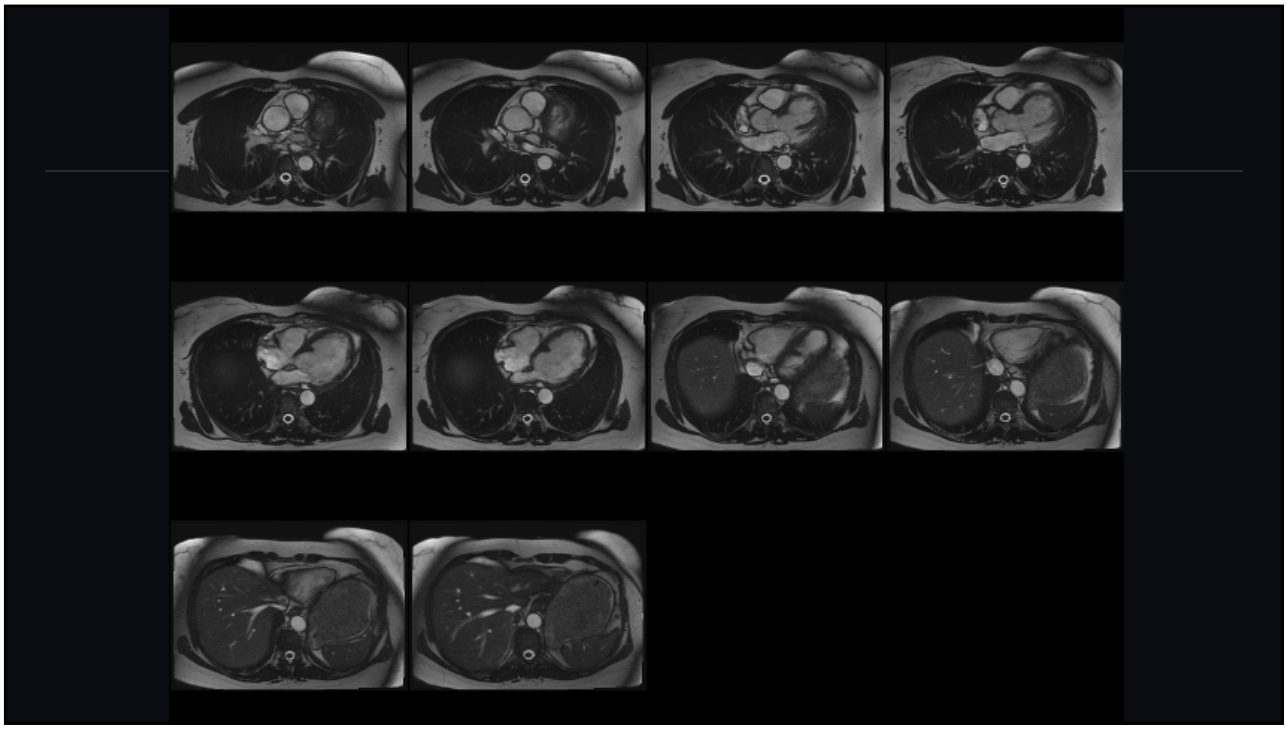
Family History is Essential

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

30



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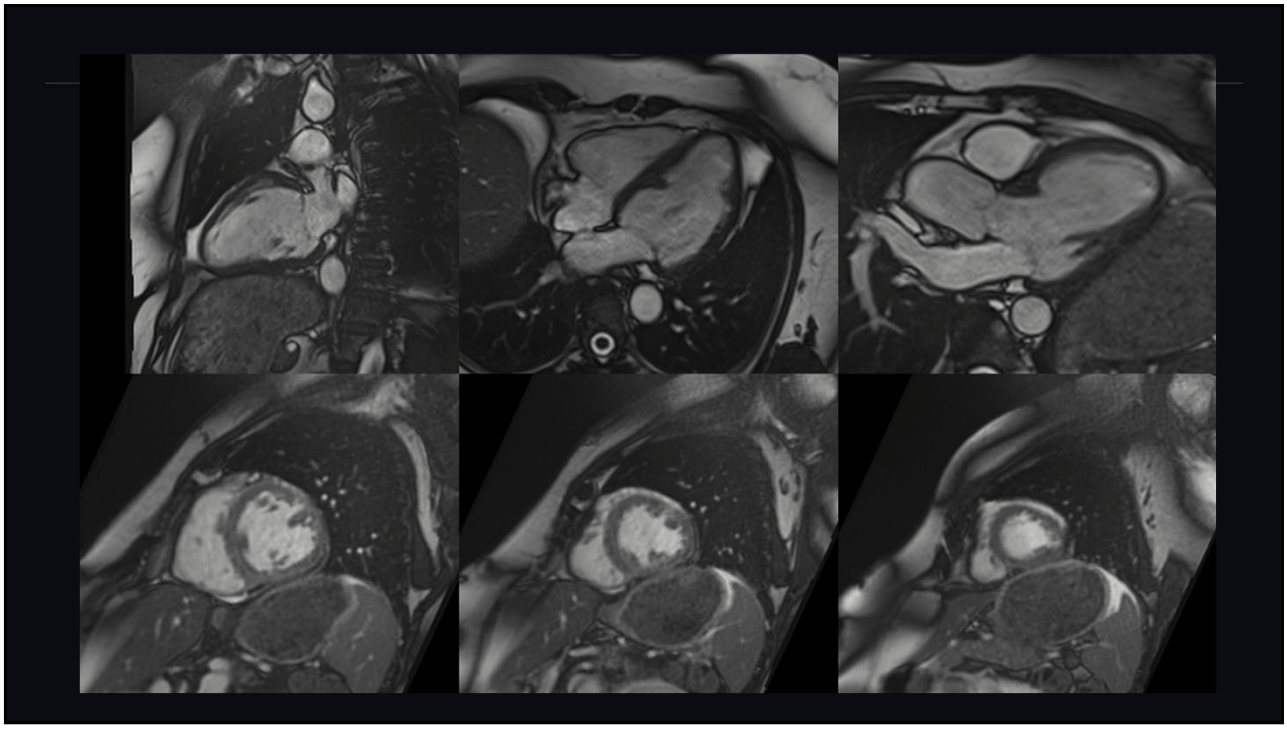

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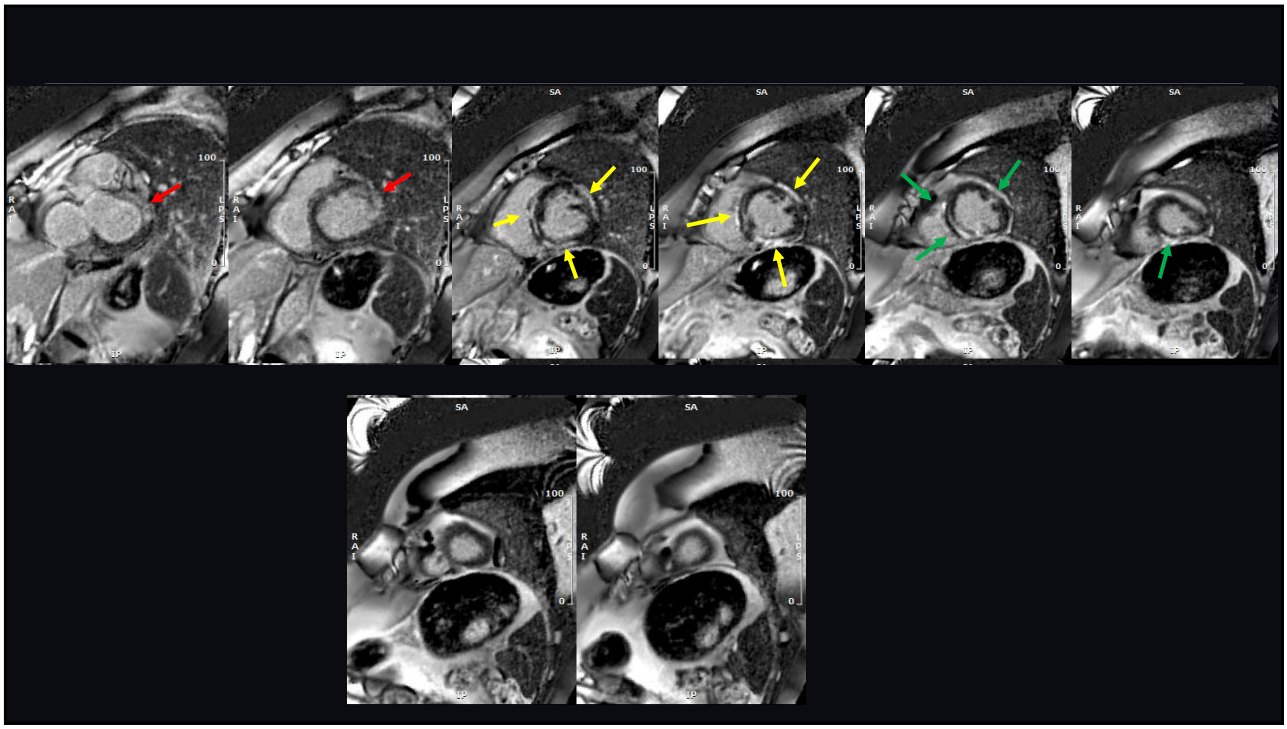


33

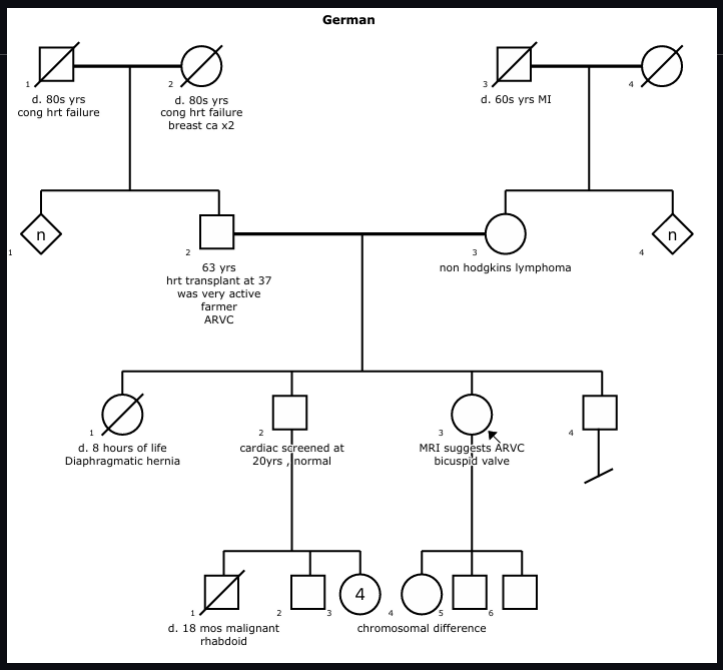
Case Example 3

35 yo with possible ARVC

Frequent PVC's

BAV

Father with hx of heart transplant in his 30's



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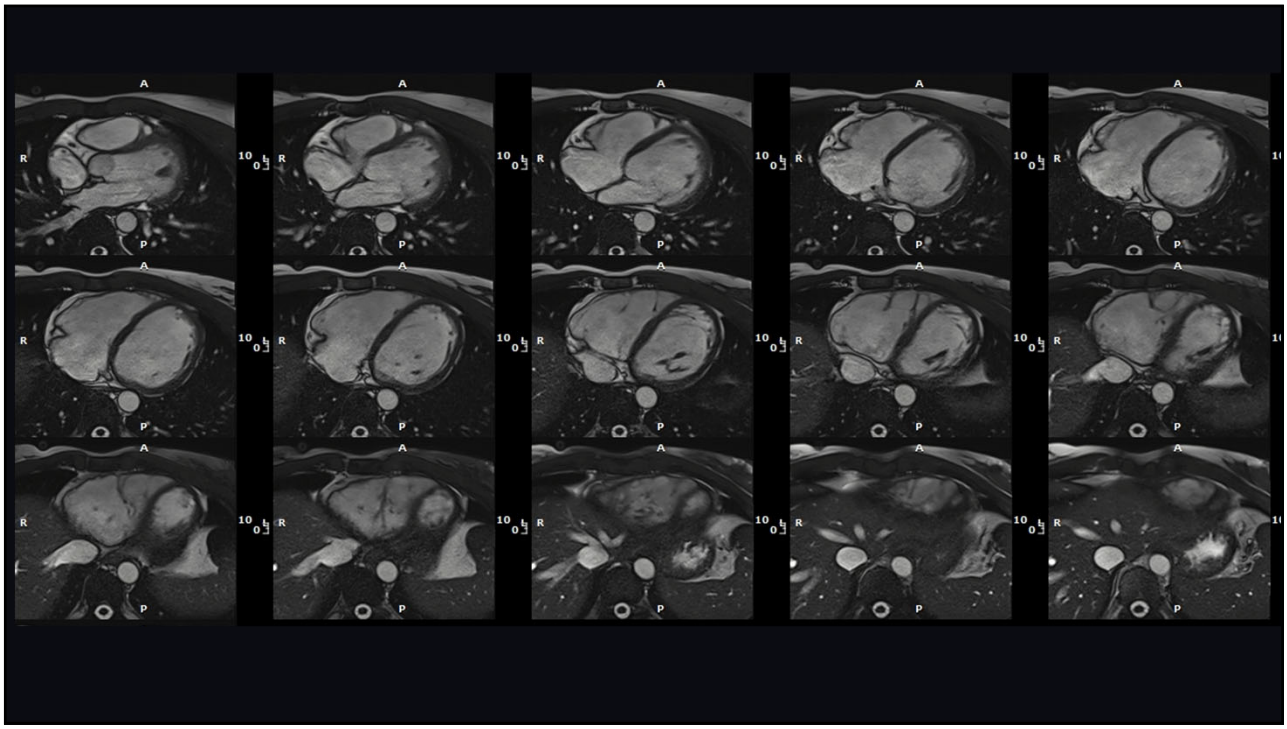

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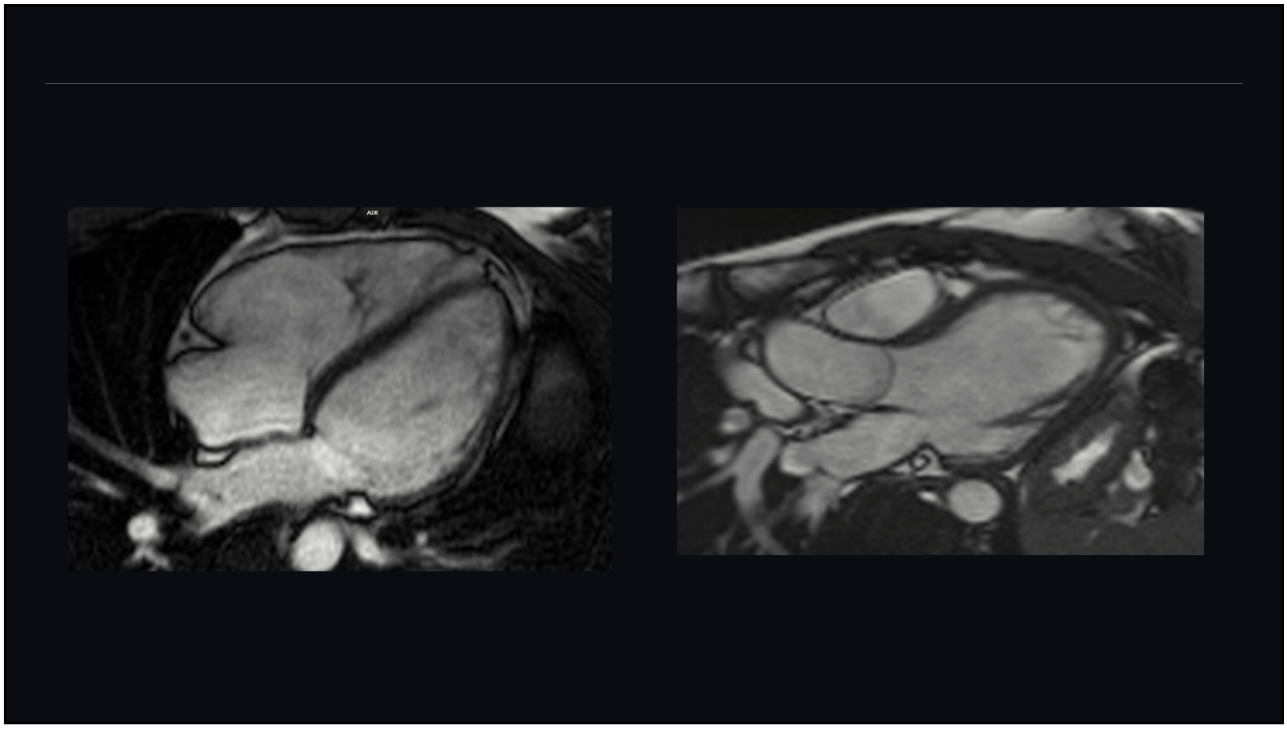


36

Case Example 3

Father's explanted heart pathology

DIAGNOSIS:
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.

37

RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
DES	c.833G>A (p.Arg278Gln)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 100 gene(s) for variants (genetic
genetic testing, when combined with family history and other r
support a clinical diagnosis, and assist with the development o

DES, Exon 4, c.833G>A (p.Arg278Gln), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with glutamine, which is neutral and polar, at codon 278 of the DES protein (p.Arg278Gln).
- This variant is present in population databases (rs761475402, gnomAD 0.006%).
- This variant has not been reported in the literature in individuals affected with DES-related conditions.
- ClinVar contains an entry for this variant (Variation ID: 1913006).
- Advanced 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 at Invitae 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 DES 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.

Search Page › DES:c.833G>A

DES:c.833G>A

chr2-220285314 G>A | p.Arg278Gln | NM_001927.4 | rs761475402 (V), UCSC (V), TraP (V), gnomAD (V)

Classify Variant | Follow | Save Case | Export Summary

Franklin ACMG Classification | Variant Assessment | Publications | Gene Assessment | Associated Cor

Suggested Classification
Likely Pathogenic

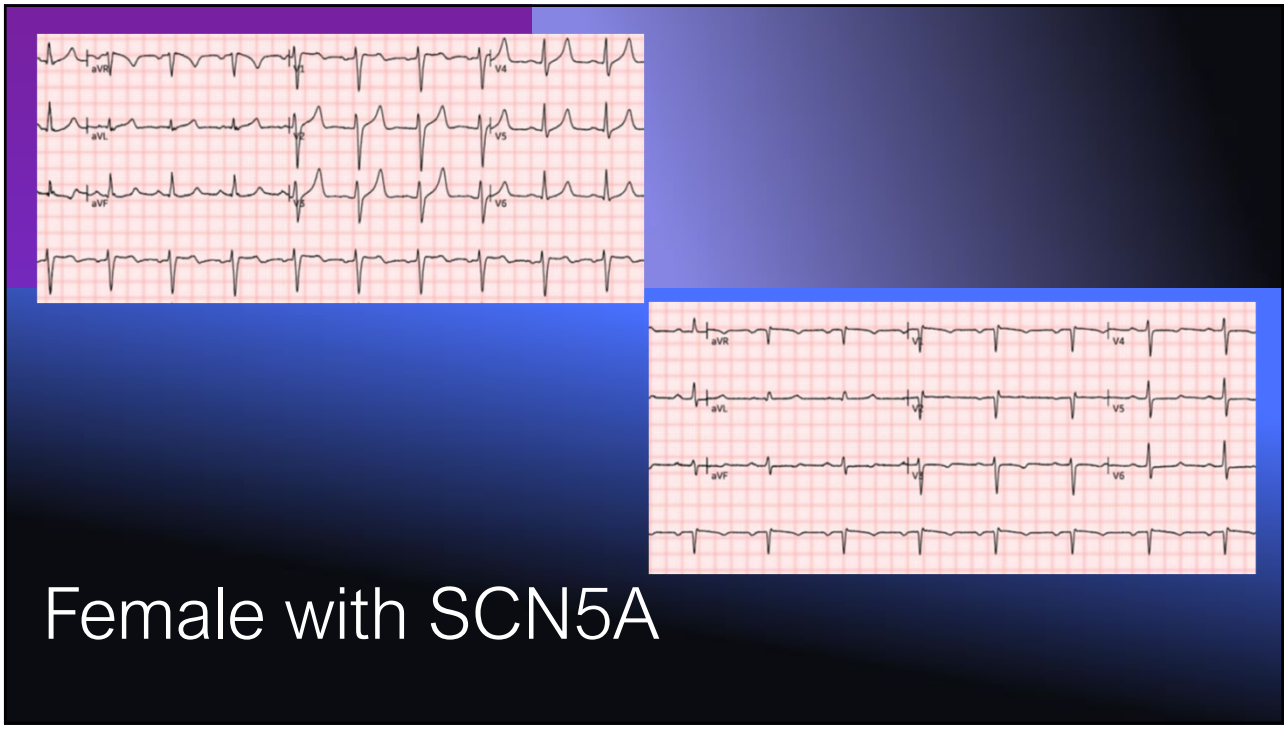
Benign | Likely Benign | VUS | Likely Pathogenic | Pathogenic

38

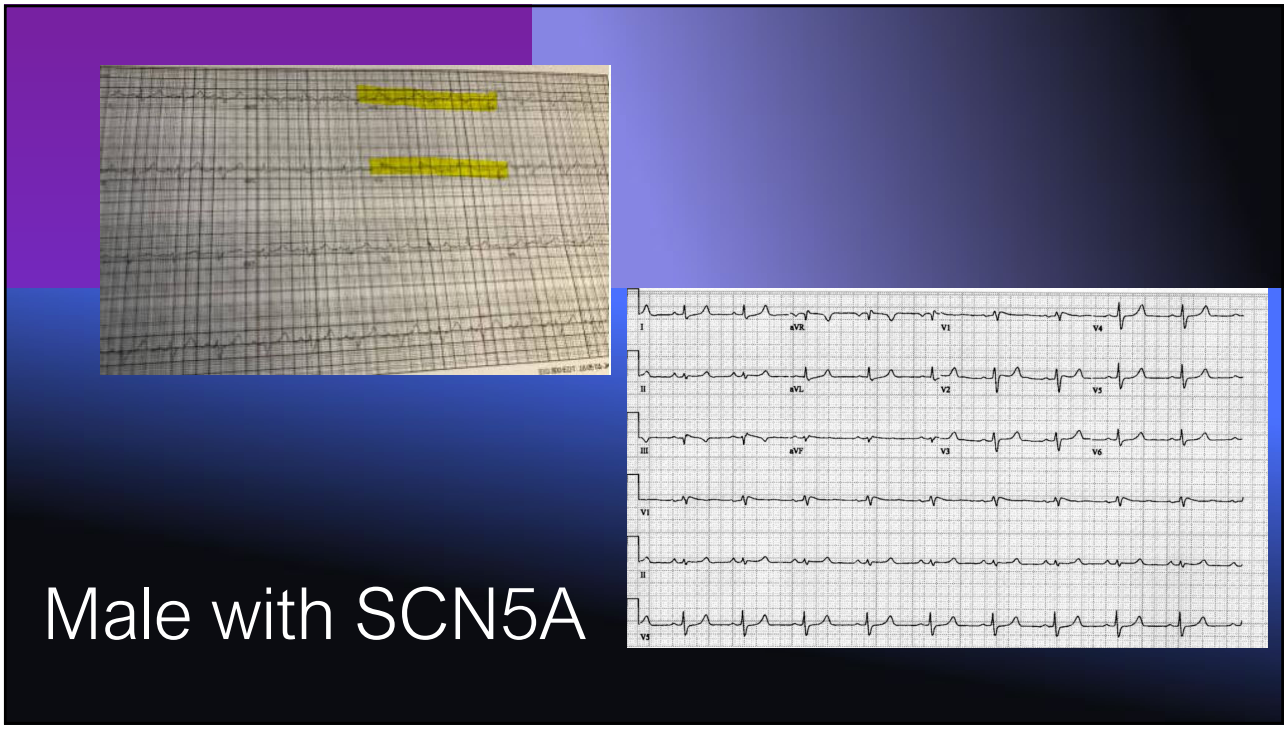
Case Example 4

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

39



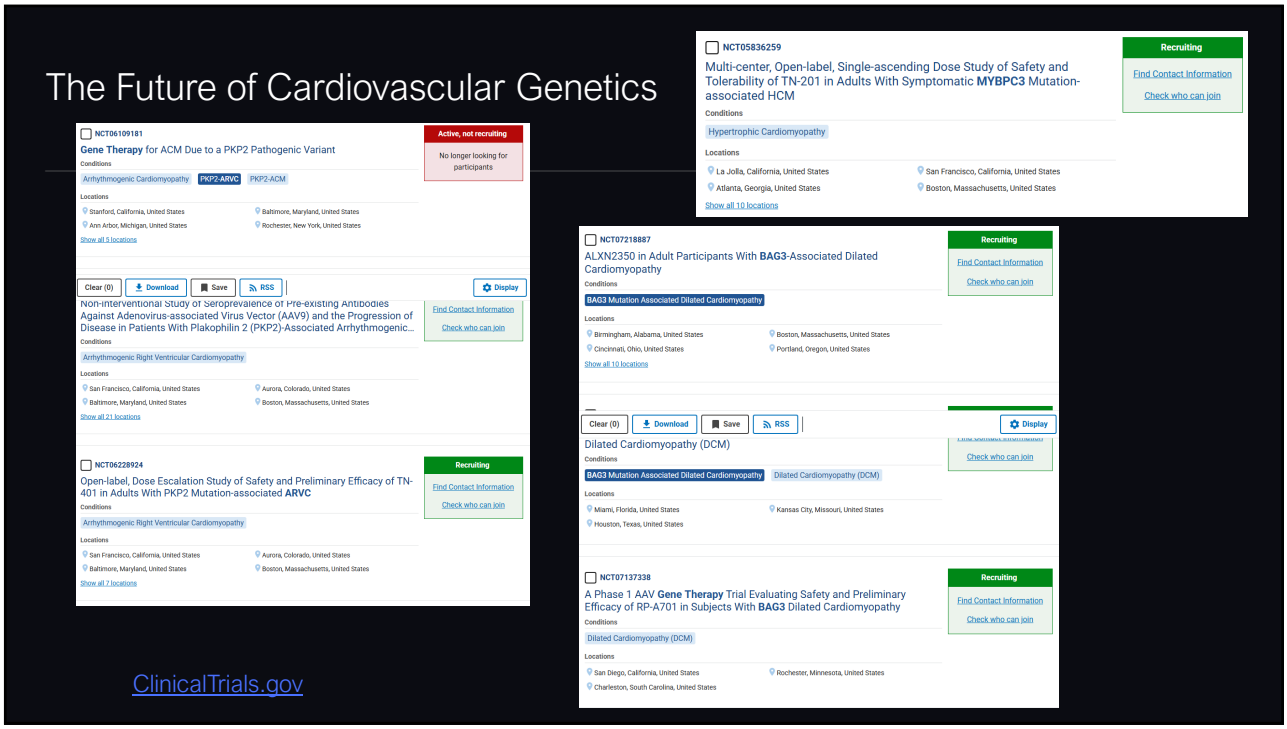
40


Male with SCN5A

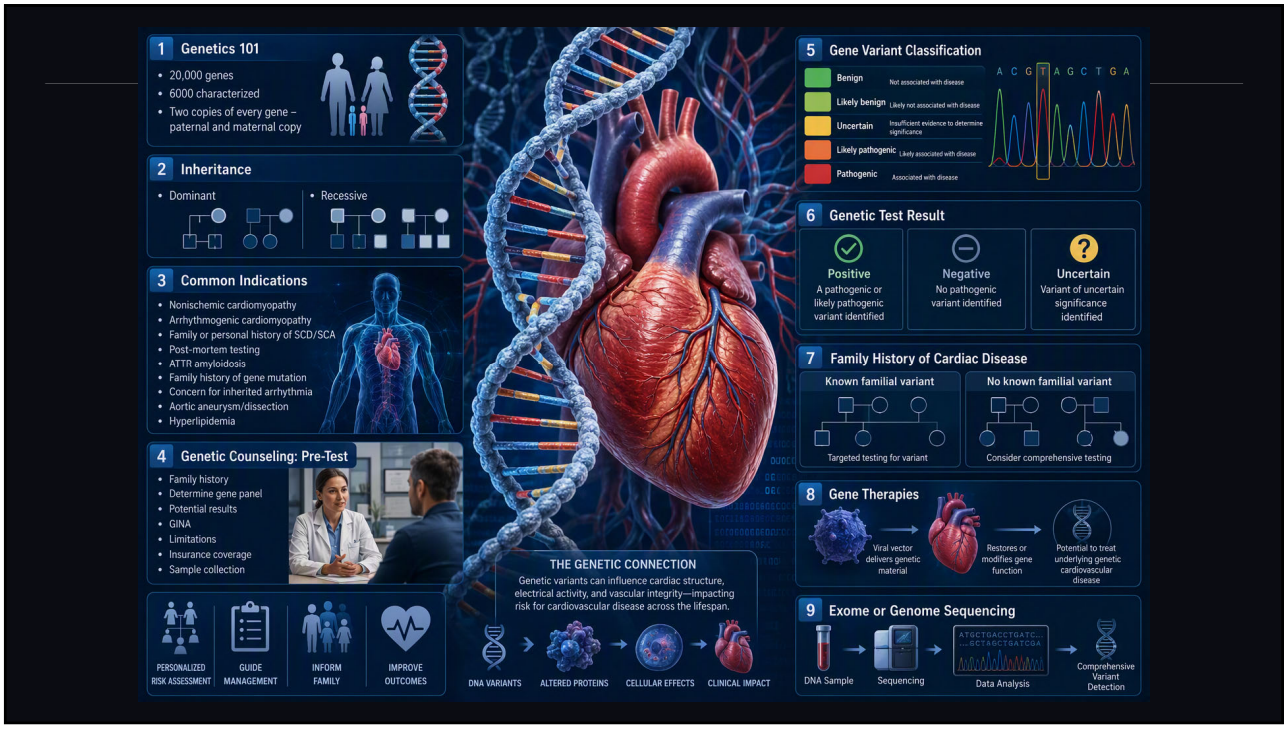
41


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 Katsiyiannis [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
Gene Therapy for ACM Due to a PKP2 Pathogenic Variant
Active, not recruiting
No longer looking for participants
Conditions
Arrhythmogenic Cardiomyopathy
PKP2-ARVC
PKP2-ACM
Locations
Stanford, California, United States
Baltimore, Maryland, United States
Ann Arbor, Michigan, United States
Rochester, New York, United States
Show all 9 locations
Clear (0)
Download
Save
RSS
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
Show all 21 locations
NCT06228924
Open-label, Dose Escalation Study of Safety and Preliminary Efficacy of TN-401 in Adults With PKP2 Mutation-associated ARVC
Recruiting
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
Show all 7 locations
ClinicalTrials.gov
NCT05836259
Multi-center, Open-label, Single-ascending Dose Study of Safety and Tolerability of TN-201 in Adults With Symptomatic MYBPC3 Mutation-associated HCM
Recruiting
Find Contact Information
Check who can join
Conditions
Hypertrophic Cardiomyopathy
Locations
La Jolla, California, United States
San Francisco, California, United States
Atlanta, Georgia, United States
Boston, Massachusetts, United States
Show all 10 locations
NCT07218887
ALXN2350 in Adult Participants With BAG3-Associated Dilated Cardiomyopathy
Recruiting
Find Contact Information
Check who can join
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
Clear (0)
Download
Save
RSS
Display
Dilated Cardiomyopathy (DCM)
Check who can join
Conditions
BAG3 Mutation Associated Dilated Cardiomyopathy
Dilated Cardiomyopathy (DCM)
Locations
Miami, Florida, United States
Kansas City, Missouri, United States
Houston, Texas, United States
NCT07137338
A Phase 1 AAV Gene Therapy Trial Evaluating Safety and Preliminary Efficacy of RP-A701 in Subjects With BAG3 Dilated Cardiomyopathy
Recruiting
Find Contact Information
Check who can join
Conditions
Dilated Cardiomyopathy (DCM)
Locations
San Diego, California, United States
Rochester, Minnesota, United States
Charleston, South Carolina, United States

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
Arrhythmogenic cardiomyopathy
Family or personal history of SCD/SCA
Post-mortem testing
ATTR 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
PERSONALIZED RISK ASSESSMENT
GUIDE MANAGEMENT
INFORM FAMILY
IMPROVE OUTCOMES
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
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
A C G T A G C T G A
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

44