Genetics in Cardiomyopathy

KHRS 2019

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No Disclosures

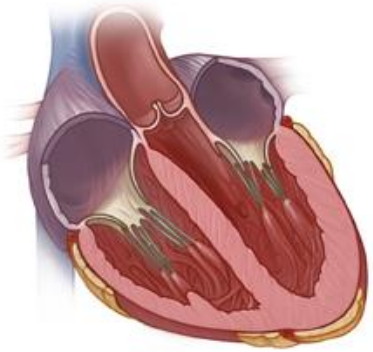
Centenary Institute life saving research

Cancer. Inflammation. Cardiovascular.

Inherited Heart Diseases

Cardiomyopathy
HCM, DCM, RCM, ARVC, LVNC

Arrhythmia
e.g. LQTS, CPVT, Brugada, SQT



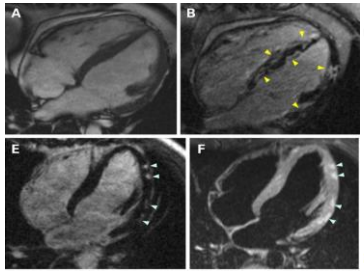
Vascular
e.g. Marfan, Ehler-Danlos IV

Metabolic
e.g. FH, homocystinuria

Congenital
e.g. ASD, TOF, myxomas

Common Features of Inherited Cardiomyopathies

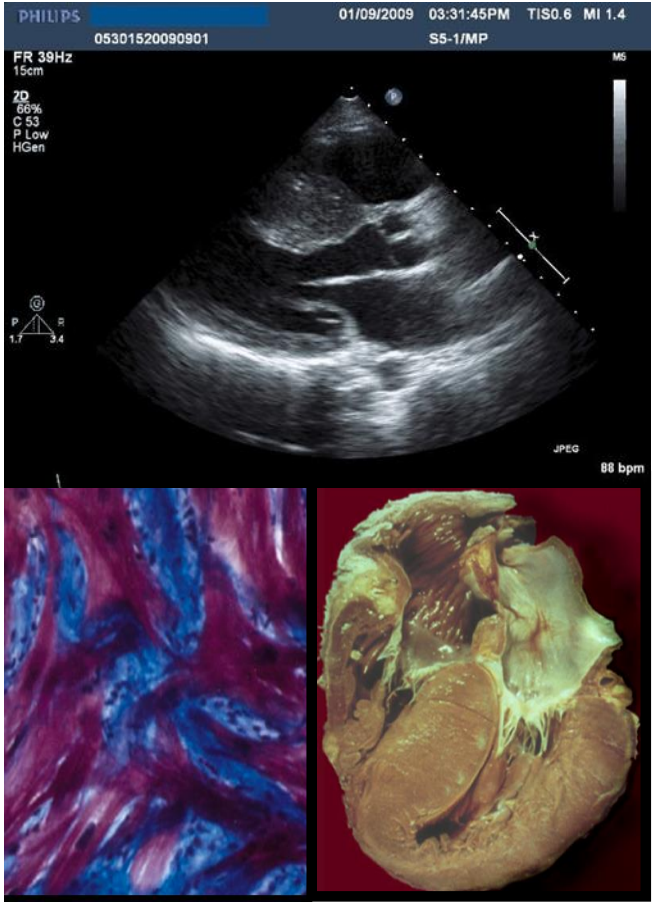
- Autosomal dominant inheritance
- Generally younger, often asymptomatic
- Clinical diversity – no symptoms to sudden death
- Genetically heterogeneous, i.e. many genes
- Specialised multidisciplinary clinic approach



1. Hypertrophic Cardiomyopathy

Hypertrophic Cardiomyopathy

- **Prevalence** up to 1:200 (Semsarian et al, JACC, 2015)
- **Clinical heterogeneity** - no symptoms to dyspnoea, syncope, sudden death
- **LV hypertrophy**, diastolic dysfunction, LVOT obstruction, AFib, VT, **heart failure**
- Important *structural* cause of **sudden death**, including competitive athletes



Genetic Basis of HCM

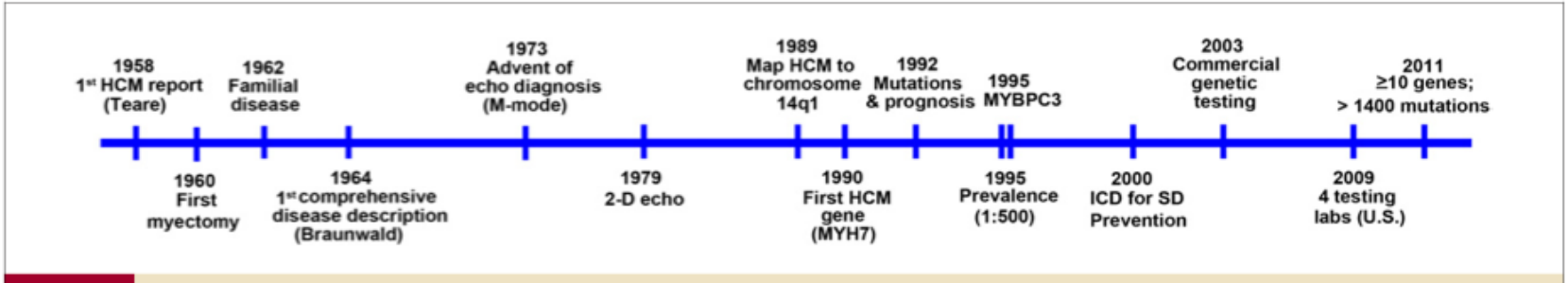
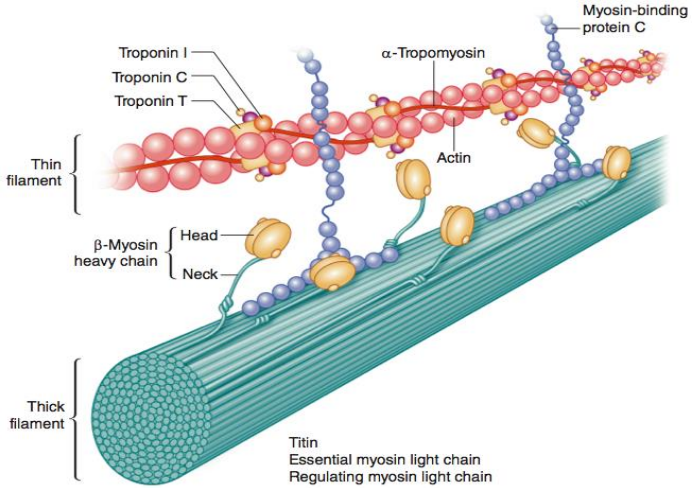


Figure 1 **HCM Landmarks** *Maron, Maron, Semsarian. J Am Coll Cardiol, 2012*

Sarcomere genes (top 5)

- β-myosin heavy chain (*MYH7*)
- Myosin-binding protein C (*MYBPC3*)
- α-tropomyosin (*TPM1*)
- Cardiac troponins (*TNNT2, TNNI3*)

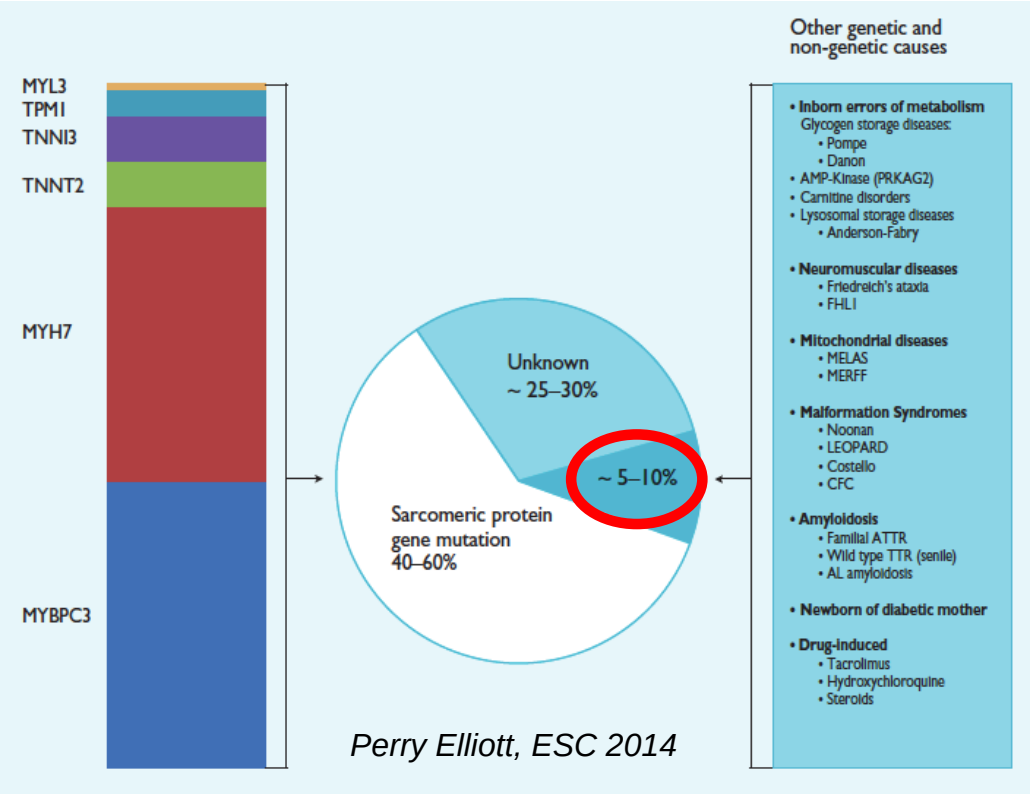
Pick up rate ~35-40% (>60% if Fam Hx)



Identification of “HCM Phenocopies”

- Expanded genetic testing identifies **HCM phenocopies**
  - *Glycogen storage (PRKAG2)*
  - *Fabry disease (GLA)*
  - *Danon disease (LAMP2)*
  - *Amyloidosis (TTR)*

- Targetted management and therapeutic options, e.g. enzyme replacement



Perry Elliott, ESC 2014

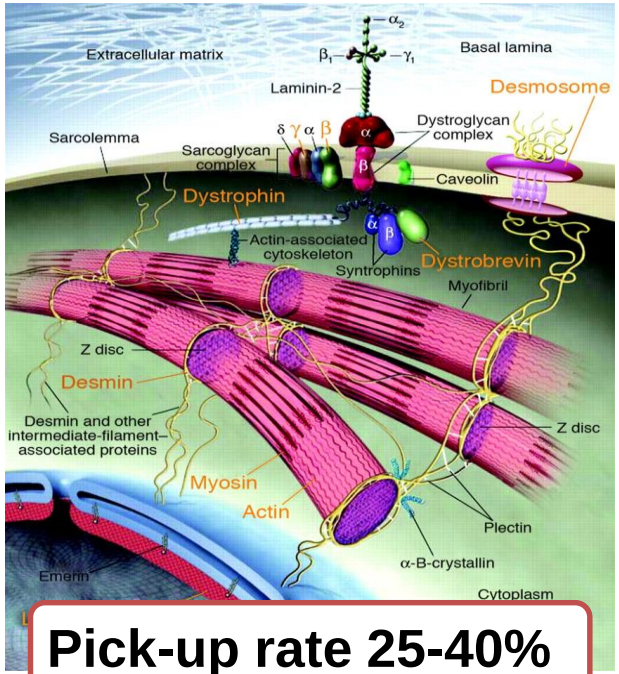
2. Familial Dilated Cardiomyopathy

Familial Dilated Cardiomyopathy

- 15-30% of DCM familial
- Dilated cardiac chambers with impaired systolic function
- Presentation with heart failure, arrhythmias, sudden death
- Treatment involves lifestyle factors, pharmacotherapy, device therapies, surgery

Genetic Basis of Familial DCM

15-30% of DCM familial



Pick-up rate 25-40%

LOCUS	GENE	PROTEIN
1p1-q21	***LMNA***	**Lamin A/C**
1q32	*TNTT2*	Cardiac troponin T
1q42-q43	*RYR2*	Cardiac RyR2
1q42-q43	*ACTN2*	α-actinin 2
2q31	**TTN**	**Titin**
2q35	*DES*	Desmin
3p21-p14	*TNNC1*	Cardiac troponin C
3p21	*SCN5A*	Cardiac Na^+ channel
5q33		
6q22		
10q22-q23		
10q22-q23		
11p11		
11p15		
12p12		
12q22		
14q12		
14q12		
15q14		
15q22		
17q12		

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Truncations of Titin Causing Dilated Cardiomyopathy

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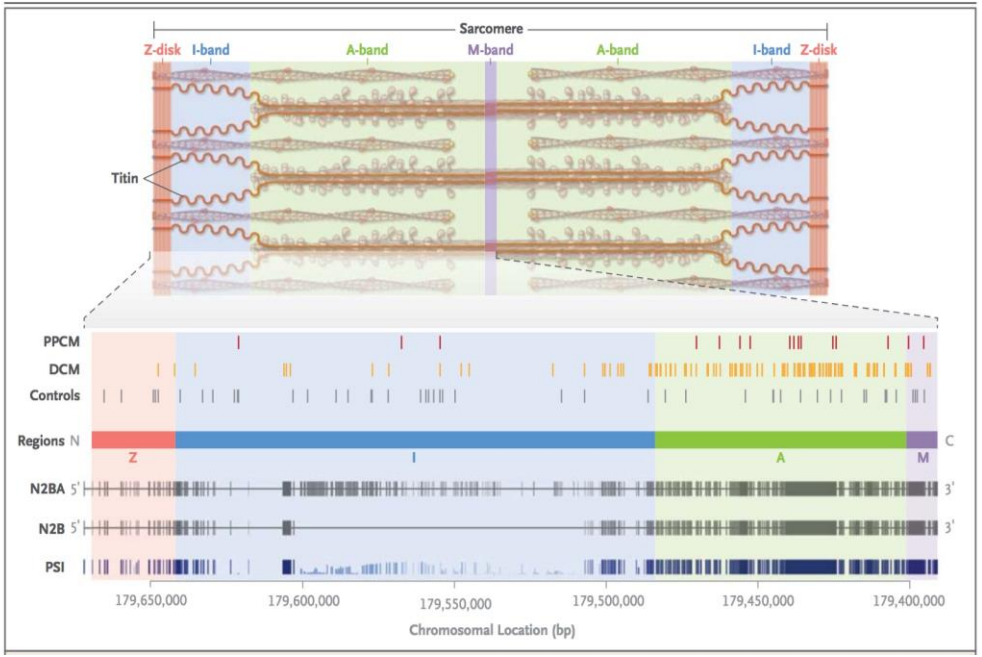
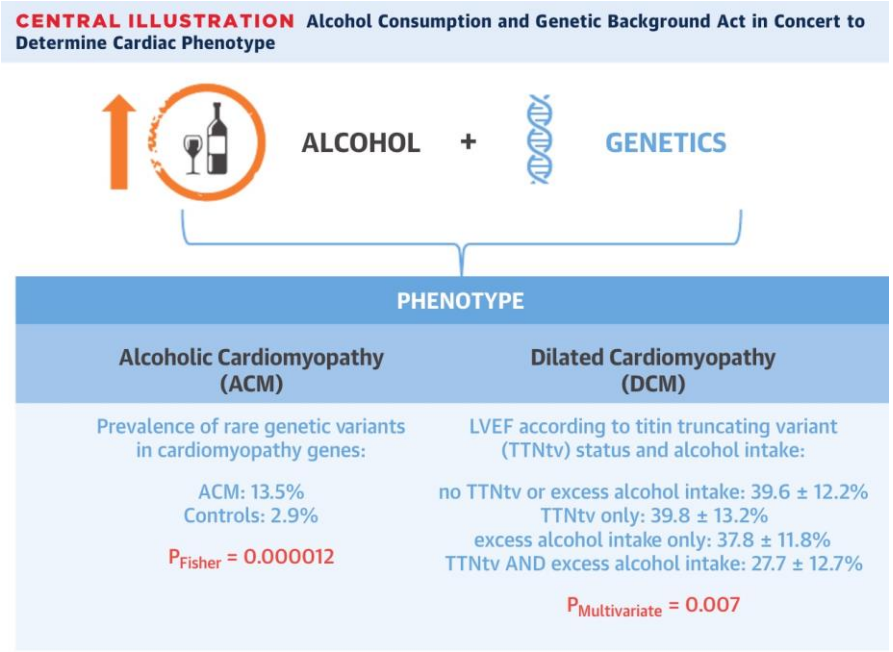
Role of Titin in Other Cardiomyopathies

Postpartum Cardiomyopathy



Ware et al. *N Engl J Med,* 2016

Alcoholic Cardiomyopathy

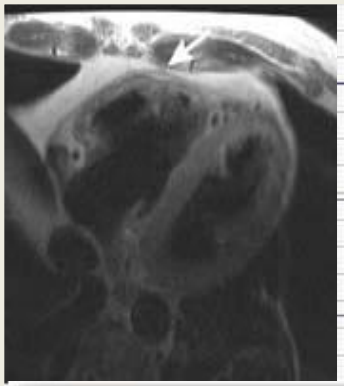


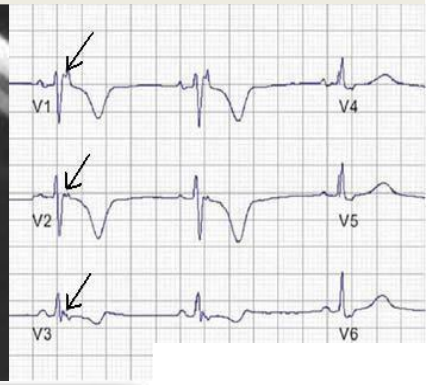
Ware et al. *J Am Coll Cardiol,* 2018

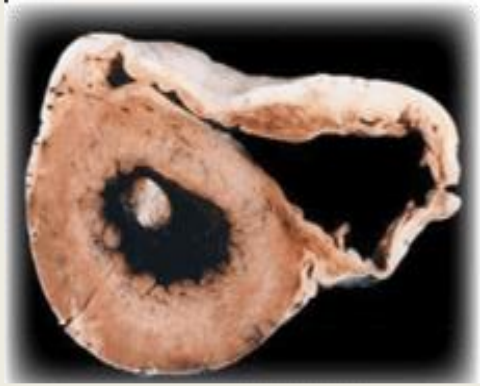
3. Arrhythmogenic RV Cardiomyopathy

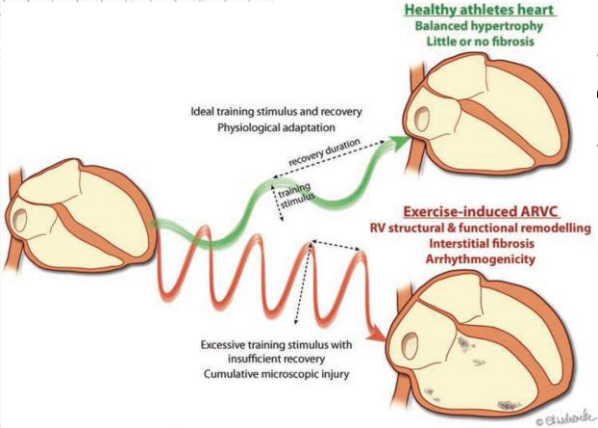
Phenotype of Arrhythmogenic RV Cardiomyopathy

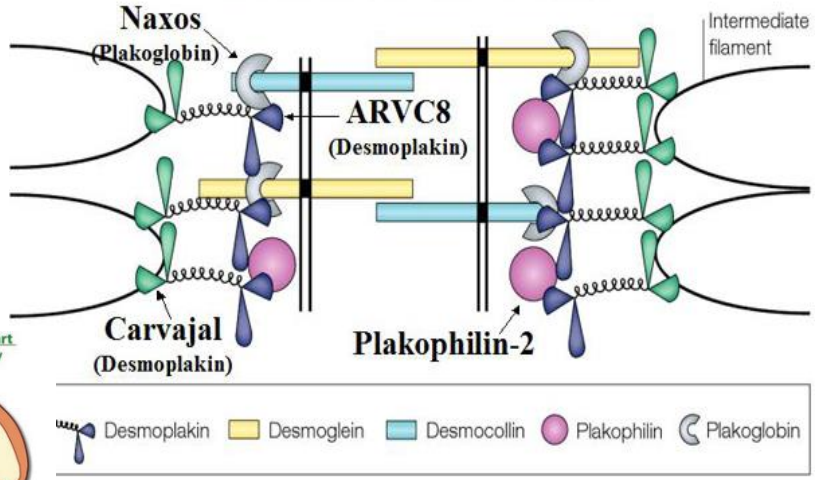
(ARVC, ARVD, ACM)







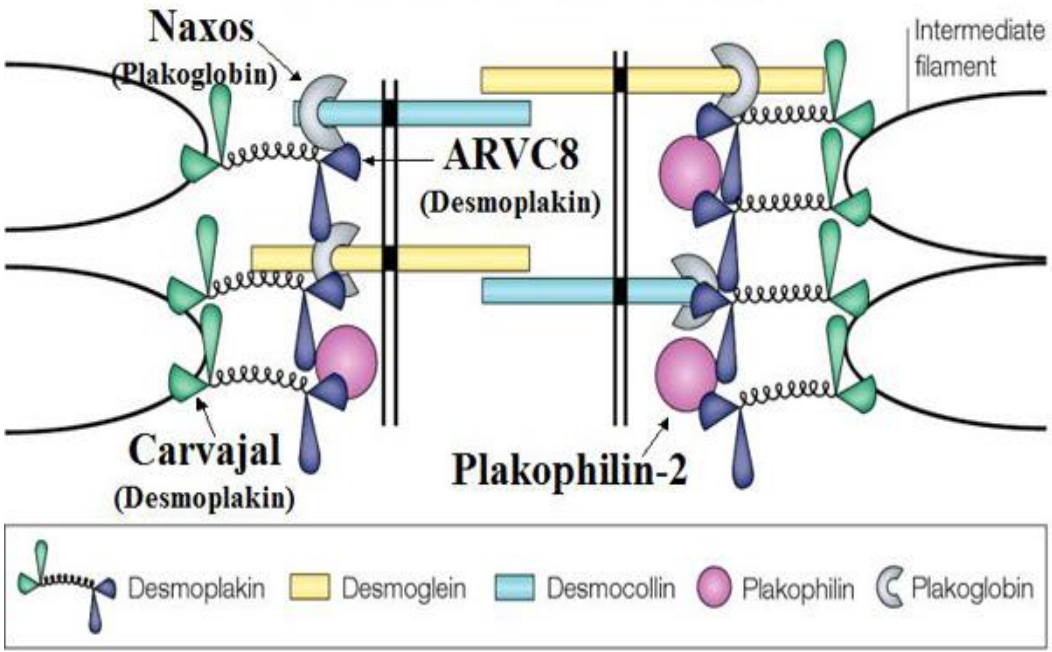




Exercise Increases Age-Related Penetrance and Arrhythmic Risk in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy–Associated Desmosomal Mutation Carriers

Cynthia A. James, ScM, PhD, Aditya Bhonsale, MD, Crystal Tichnell, MGC, Brittney Murray, MS, Stuart D. Russell, MD, Harikrishna Tandri, MD, Ryan J. Tedford, MD, Daniel P. Judge, MD, Hugh Calkins, MD

Genetic Basis of ARVC: The Desmosome



HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies

This document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA)

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Heart Rhythm 2011; 8: 1308-39

Pick-up rate 40-50%

Majority in *PKP2* gene

Clinical Phases of ARVC

“Concealed” Phase	• Asymptomatic, mild or absent RV features • Risk of sudden death event
Overt Electrical Disorder	• Symptomatic RV arrhythmias • Overt RV functional and structural changes
RV Failure	• Progressive loss of RV myocardium • Global RV dysfunction
Bi-ventricular Failure	• Significant LV involvement • Bi-ventricular heart failure

Concealed ARVC in Sudden Unexplained Cardiac Death Events

Circulation: Genomic and Precision Medicine

CLINICAL LETTER

Concealed Arrhythmogenic Right Ventricular Cardiomyopathy in Sudden Unexplained Cardiac Death Events

Plakophilin-2 (*PKP2*) is an integral component of the desmosome, important in cell-cell adhesion. Causative variants in *PKP2* are a well-established cause of arrhythmogenic right ventricular cardiomyopathy (ARVC). An inherited cardiomyopathy characterized by fibro-fatty replacement of the myocardium and propensity for ventricular arrhythmias. Importantly, sustained arrhythmias have been shown only to occur in mutation carriers with clear structural disease on imaging.[1] *PKP2* is important for transcription of genes that control intracellular calcium cycling, and it is hypothesized this newly described disease mechanism could lead to life-threatening arrhythmias in humans in the absence of structural disease.[2] Despite this, the arrhythmic risk is not reported before the development of an overt phenotype.[3,4] We report 4 unrelated probands who presented because of an unexplained sudden cardiac arrest with overt structurally normal hearts in early adulthood with causative loss of function variants in the *PKP2* gene subsequently identified.

Jodie Ingles, GradDipGenCouns, PhD, MPH
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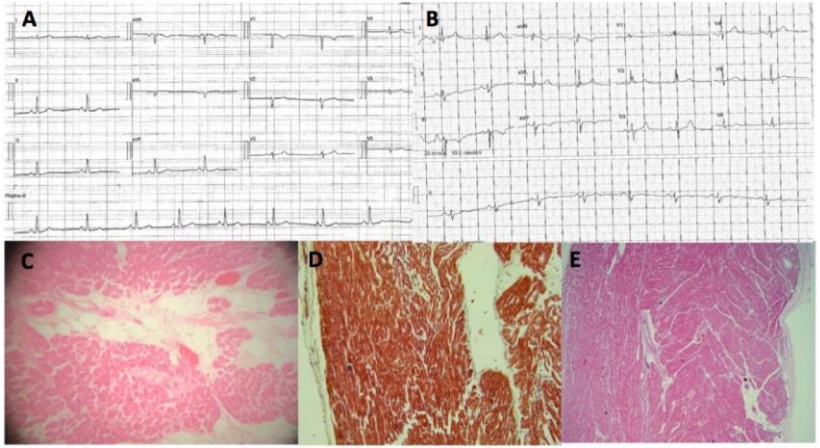
Laura Yeates, GradDipGenCouns
Michele McGrady, MBBS, PhD
Yemima Berman, MBBS
David Whalley, MBBS
Johan Duflou, MMed, FRCPA
Christopher Semsarian, MBBS, PhD, MPH

Ingles et al. *Circ Genom Prec Med,* 2018

- Four families with sudden death events with overt structurally normal hearts with **loss-of-function PKP2 variants**!



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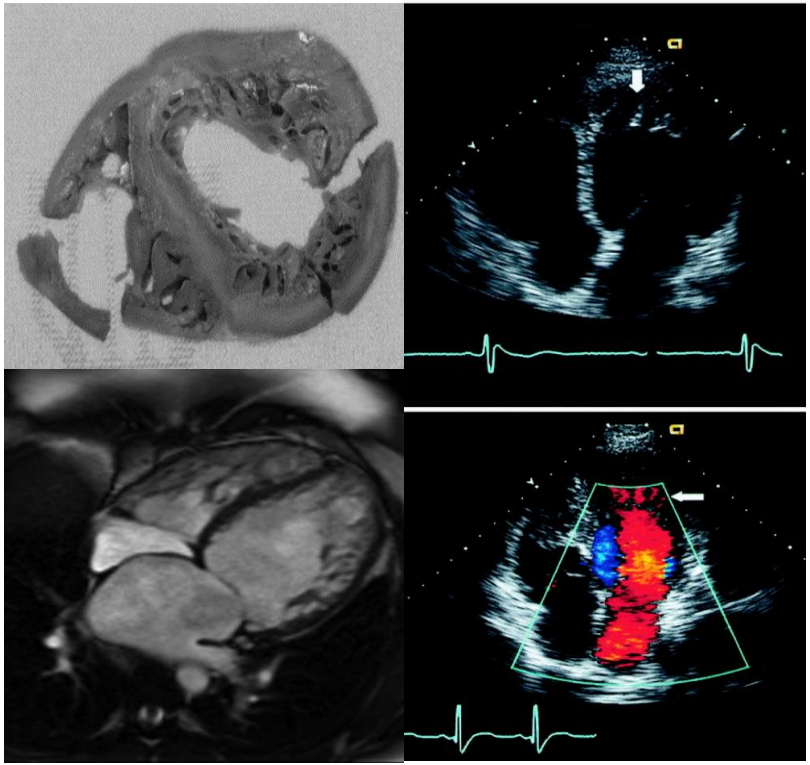
Patient	Variant details	gnomAD allele count	ACMG/AMP criteria	ACMG/AMP classification
AWF1	PKP2(NM_004572.3: c.2489+1G>A)	6	PVS1; PM2; PM7	Pathogenic
BTT1	PKP2(NM_004572.3: c.2229dupT; p.Leu744Serfs*3)	0	PVS1; PM2	Likely pathogenic
QW1	PKP2(NM_004572.3: c.2391C>A; p.Tyr797Ter)	0	PVS1; PS2; PM2	Pathogenic
AYD1	PKP2(NM_004572.3: c.253_256delGAGT; p.Glu85Metfs*26)	0	PVS1; PM2	Likely pathogenic

4. Left Ventricular Noncompaction

LV Noncompaction Cardiomyopathy (LVNC)

- **Familial** and **isolated** cases with variable age of presentation (children vs adults)
- Associated with other **cardiomyopathies**, e.g. HCM, DCM, and in physiological states such as in **athletes** or during **pregnancy**
- Complications include arrhythmias, heart failure, sudden death
- “True” genetic cause in < 10%



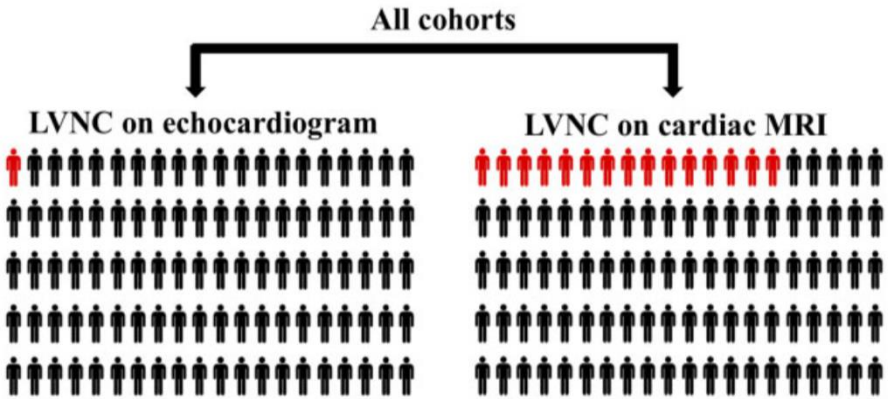
ESC European Society of Cardiology
European Heart Journal (2019) **0**, 1–11
doi:10.1093/eurheartj/ehz317

META-ANALYSIS
Myocardial disease

A systematic review and meta-analysis of the prevalence of left ventricular non-compaction in adults

Samantha B Ross[1,2], Katherine Jones[1], Bianca Blanch[1], Rajesh Puranik[2,3]
Kevin McGeechan[4,5], Alexandra Barratt[4,5], and Christopher Semsarian[1,2,3,5]*

- **No diagnostic gold standard**
- **Overdiagnosis** partly due to switch to CMR imaging
- Unclear phenotypes…
- Genetic testing limited…



Cohort	Echocardiogram ES (95% CI)	Cardiac MRI ES (95% CI)
Cardiac patient cohorts	0.90 (0.64, 1.20)	9.76 (4.59, 16.56)
Control cohorts	1.05 (0.00, 7.88)	15.03 (8.94, 22.24)
Population representative cohorts	-	19.72 (11.64, 29.28)
Athlete cohorts	3.16 (0.26, 8.48)	27.29 (13.58, 43.27)
Non-cardiac patient cohorts	2.21 (0.24, 5.46)	36.21 (23.64, 49.72)
Primigravida pregnancy cohort	18.63 (11.60, 27.55)	-
All cohorts	**1.28 (0.95, 1.64)**	**14.79 (8.85, 21.85)**

Echo ~ 1% MRI ~15%

Whole Genome Sequencing in Cardiomyopathy

Whole Genome Sequencing Improves Outcomes of Genetic Testing in Patients With Hypertrophic Cardiomyopathy

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ABSTRACT

BACKGROUND Whole genome sequencing (WGS) is a comprehensive genetic testing approach that reports most types of nucleotide variants.

OBJECTIVES This study sought to assess WGS for hypertrophic cardiomyopathy (HCM) in which prior genetic testing did not establish a molecular diagnosis, and as a first-line genetic test.

METHODS WGS was performed on 58 unrelated patients with HCM, 14 affected family members, and 2 unaffected parents of a severely affected proband. The authors searched for nucleotide variants in coding regions of 184 candidate cardiac hypertrophy genes. They also searched for nucleotide variants in deep intronic regions that alter RNA splicing, large genomic rearrangements, and mitochondrial genome variants. RNA analysis was performed to validate splice-altering variants.

RESULTS The authors found a pathogenic or likely pathogenic variant in 9 of 46 families (20%) for which prior genetic testing was inconclusive. Three families had variants in genes not included in prior genetic testing. One family had a pathogenic variant that was filtered out with prior exome sequencing. Five families had pathogenic variants in noncoding regions, including 4 with deep intronic variants that activate novel splicing, and 1 mitochondrial genome variant. As a first-line genetic test, WGS identified a pathogenic variant in 5 of 12 families (42%) that had never received prior genetic testing.

CONCLUSIONS WGS identified additional genetic causes of HCM over targeted gene sequencing approaches. Extending genetic screening to deep intronic regions identified pathogenic variants in 9% of gene-elusive HCM. These findings translate to more accurate diagnosis and management in HCM families. (J Am Coll Cardiol 2018;72:419-29)
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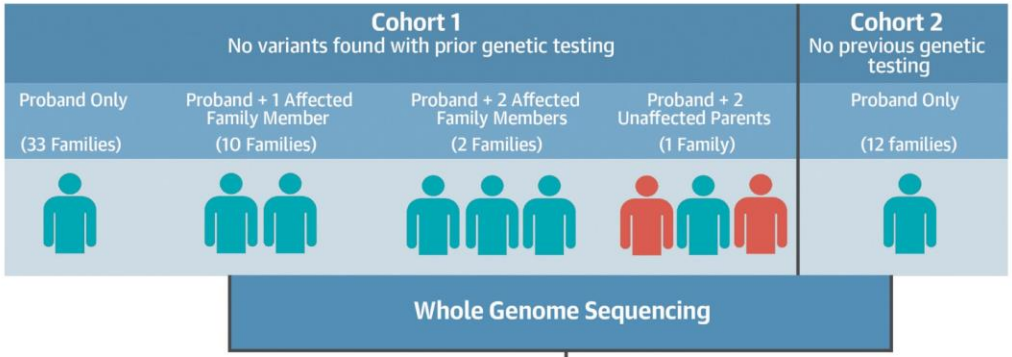
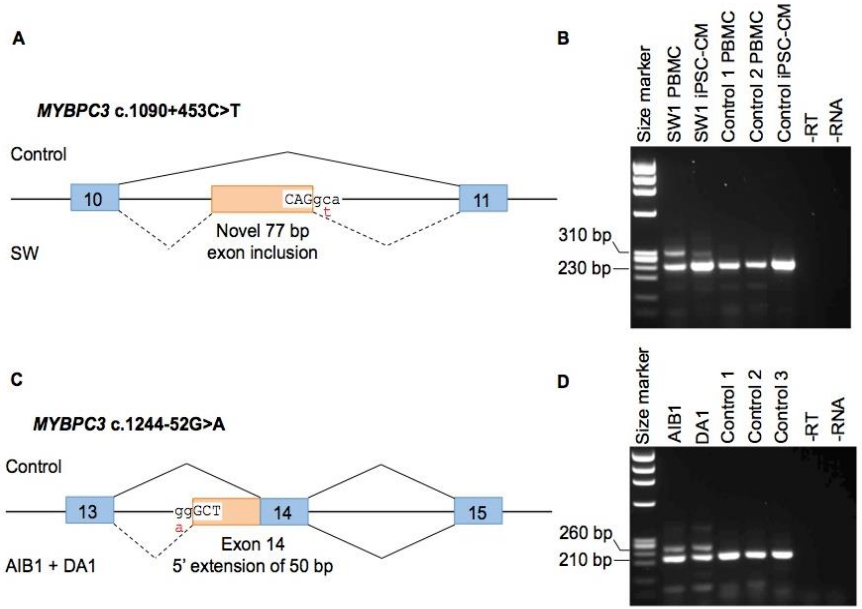
CENTRAL ILLUSTRATION Genome Sequencing Analysis of Hypertrophic Cardiomyopathy

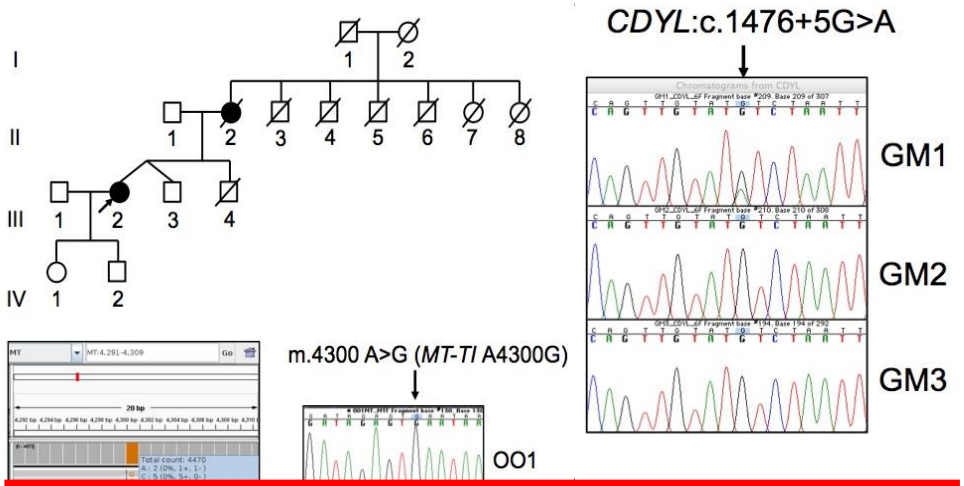


Genetic Analysis Performed	Cohort 1 Families Solved	Cohort 2 Families Solved
184 genes: Single nucleotide variant and short (<25 bp) indels	4 (9%)	5 (42%)
184 genes: Structural variants	0	0
11 genes: Deep intronic splice-gain	4 (9%)	0
Mitochondrial genome	1 (2%)	0
	Total solved = 9 (20%)	Total solved = 5 (42%)

Bagnall, R.D. et al. J Am Coll Cardiol. 2018;72(4):419-29.

Whole Genome Sequencing in HCM





We need to look harder at known sarcomere genes vs “new gene discovery”

- Deep intronic variants and alternate splicing, mitochondrial mutations
- WGS adds up to 15% pick up over panels and exomes

Bagnall et al, *J Am Coll Cardiol*, 2018

Take Home Messages

Genetic cardiomyopathies encompass many pathologies and are most commonly autosomal dominant

Family history and **detailed phenotype assessment** essential

Genetic testing is valuable in diagnosis, particularly in predictive testing of relatives

Specialised multidisciplinary clinic *optimal approach to care*

Major advances in **genetic technologies** will lead to greater understanding of inherited cardiomyopathies

Acknowledgements

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National

International

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Thank you

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