Genetic Conditions Influencing Myocardial Function

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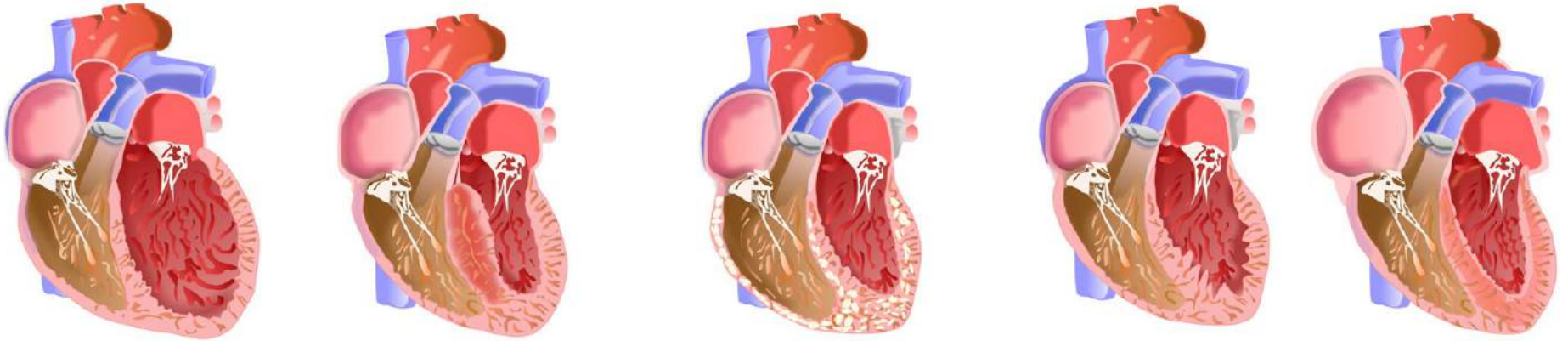
Many slides courtesy of Abigail Yesso, MS, CGC



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Disclosures

- None

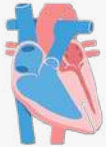
Common Causes of Myocardial Dysfunction

- **Congenital**
  - Metabolic/Storage disorders (e.g. Pompe)
  - RASopathies (e.g. Noonan syndrome)
  - Primary cardiomyopathy (e.g. HCM due to sarcomeric variants)
  - Syndromic aortopathy (e.g Marfan syndrome)
  - Mitochondrial syndromes (e.g. MELAS)
- **Acquired**
  - Myocarditis/post myocarditis
  - Ischemic cardiomyopathy
  - Hypertensive cardiomyopathy
  - Tachycardia-induced cardiomyopathy
  - Post-chemotherapy
  - Nutritional deficiencies

Classic types of cardiomyopathy

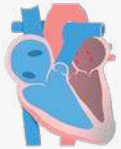
DCM

- Most common type
- 20-30% have fam hx
- **~35% testing yield**



HCM

- Most common genetic form
- Sarcomere genes
- **40-60% testing yield**

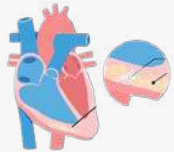


RCM

- Infection
- Storage/infiltration
- **10-60% testing yield**

LVNC

- LV Trabeculations
- **20% testing yield**
- 50% sporadic/ multifactorial



ARVC

- Arrhythmias prior to structural changes
- Desmosome genes
- Low penetrance/Digenic
- **50-60% testing yield**

https://www.ohsu.edu/doernbecher/pediatric-cardiomyopathy-program

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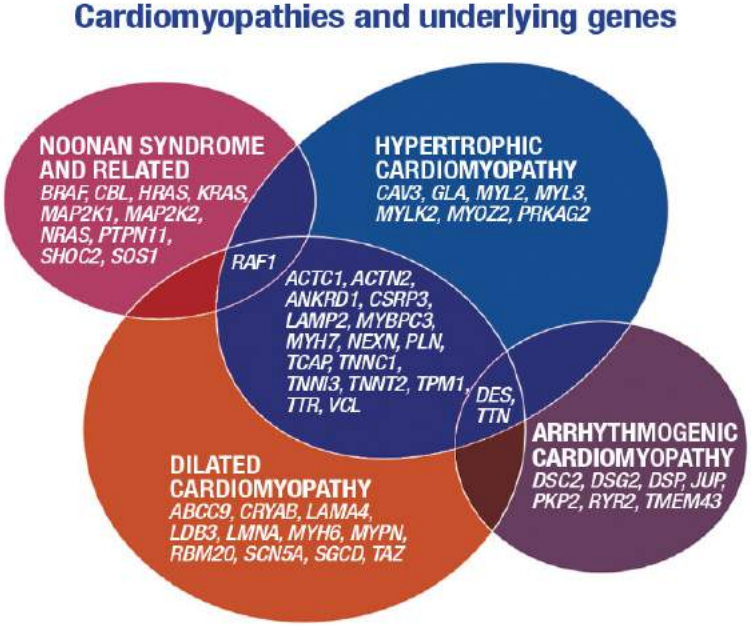
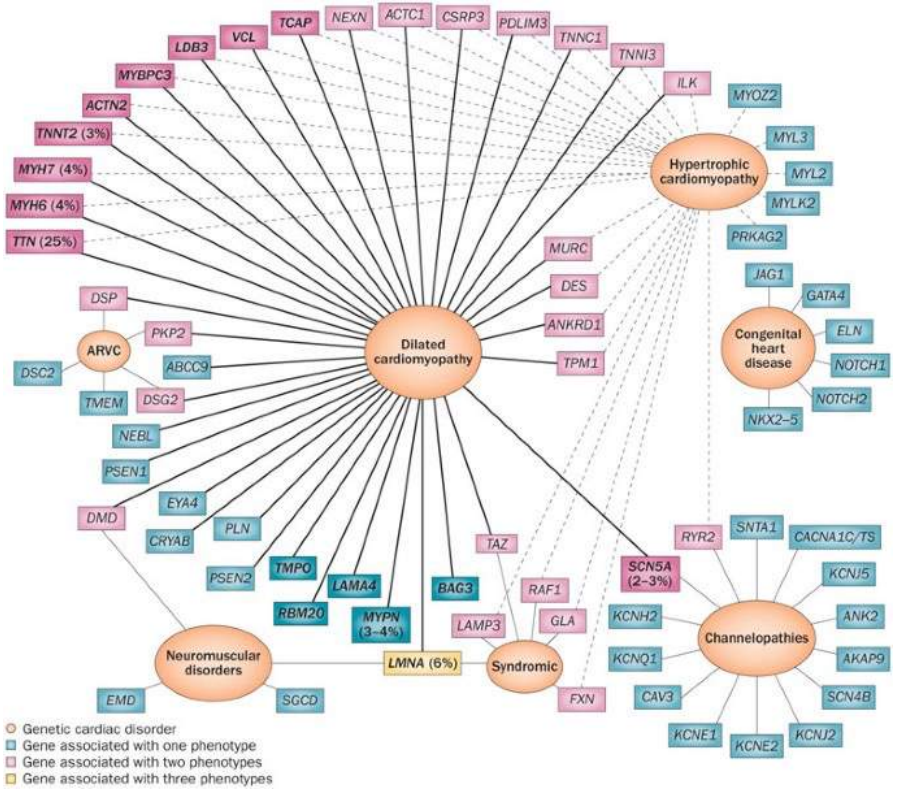
Genetics of cardiomyopathy





Wilde et al. Nature Reviews 2014

Hershberger et al. Nature Reviews 2013

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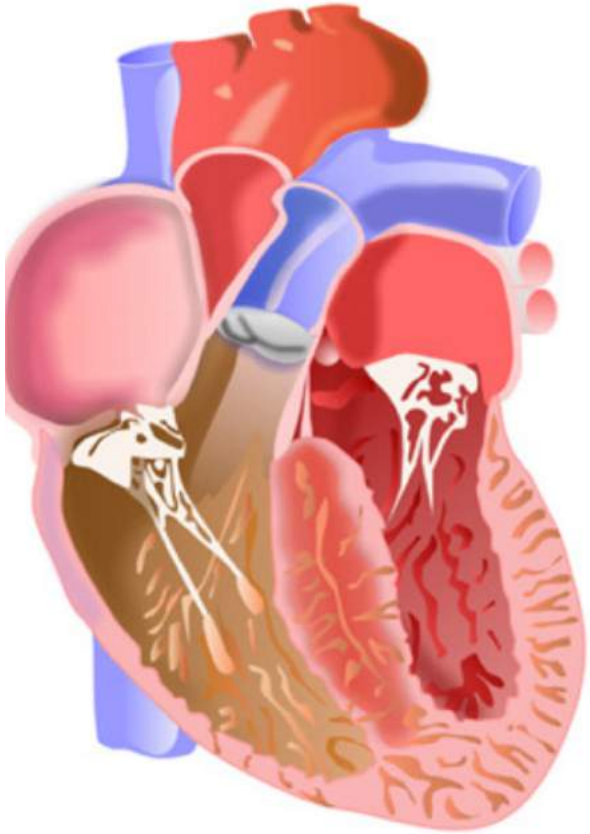

Hypertrophic Cardiomyopathy

Yogasundaram et al. Can J Cardiology 2021

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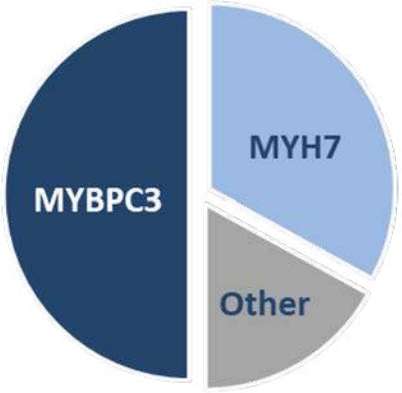
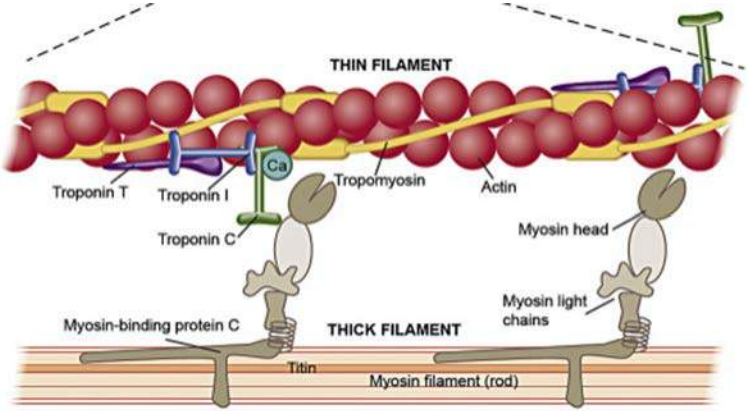
Genetic Testing in HCM

- Current detection rate of panel testing is ~60% (with fam hx)



Other Genes: ACTC1, ACTN2, AGL, BAG3, CACNA1C, CAV3, CSRP3, DES, FHL1, FLNC, GAA, GLA, LAMP2, MYL2, MYL3, PLN, PRKAG2, TCAP, TNNC1, TNNI3, TNNT2, TPM1, TTR, VCL



Mainly <u>sarcomere</u> proteins
MYH7 and *MYBPC3* account for 80%
3-5% compound het/digenic

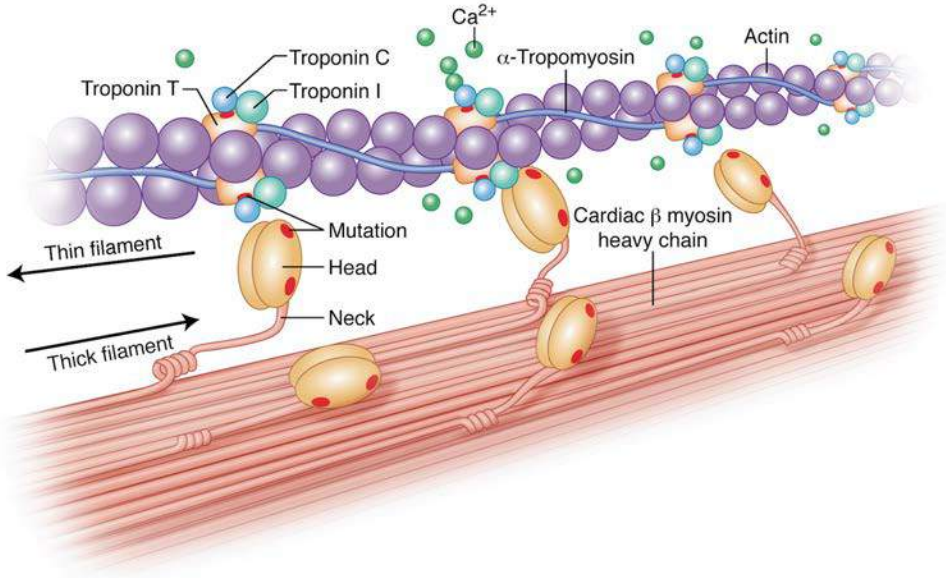
Sarcomere

A sarcomere is the basic unit of muscle tissue in both cardiac and skeletal muscle.

Individual sarcomeres are composed of long, fibrous proteins that slide past each other when the muscles contract and relax.

The two most important proteins within sarcomeres are myosin, which forms a thick, flexible filament, and actin, which forms the thin, more rigid filament.

Disruption of the protein product of genes that code for sarcomere proteins may lead to cardiomyopathy over time



Source: https://hypertrophiccardiomyopathy.com/

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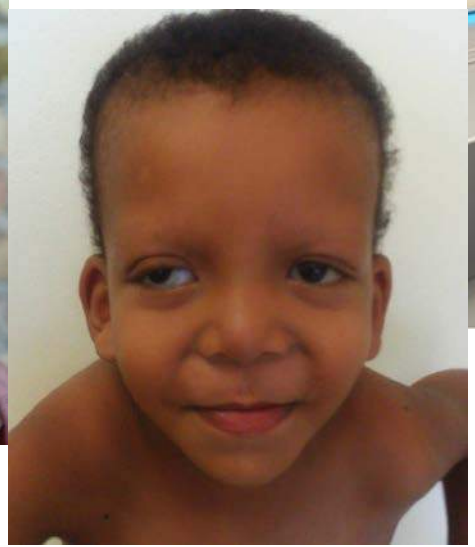
Dysmorphology Checkpoint



RASopathies

Cardiovascular

- Pulmonary stenosis
- Hypertrophic cardiomyopathy
- Atrial septal defects

Development

- Variable degree of developmental delay

Other Features

- Short stature
- Broad, webbed neck
- Pectus abnormality
- Wide set nipples
- Cryptorchidism in males
- Coagulation abnormalities

- **Noonan Syndrome** *(BRAF, KRAS, LZTR1, MAP2K1, MRAS, NRAS, PTPN11 (50%), RAF1, RASA2, TIR1, RRAS2, SOS1, SOS2)*
- **Noonan Syndrome with Multiple Lentigenes (NSML)**
- **Costello Syndrome** *(HRAS)*
- **Cardiofaciocutaneous syndrome** (*KRAS, BRAF, MEK1, MEK2)*

HCM Metabolic Phenocopies

Danon disease

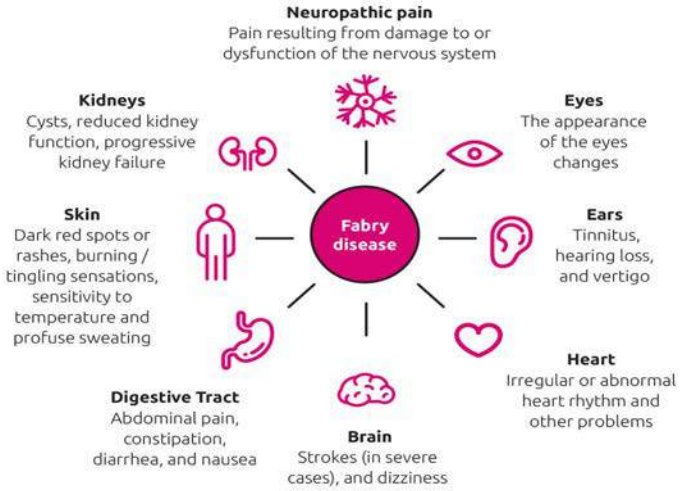
- lysosomal storage disorder,
- X-linked dominant, *LAMP2* gene
- Symptoms: cardiomyopathy, skeletal muscle weakness, intellectual disability, GI issues, difficulty breathing, visual abnormalities

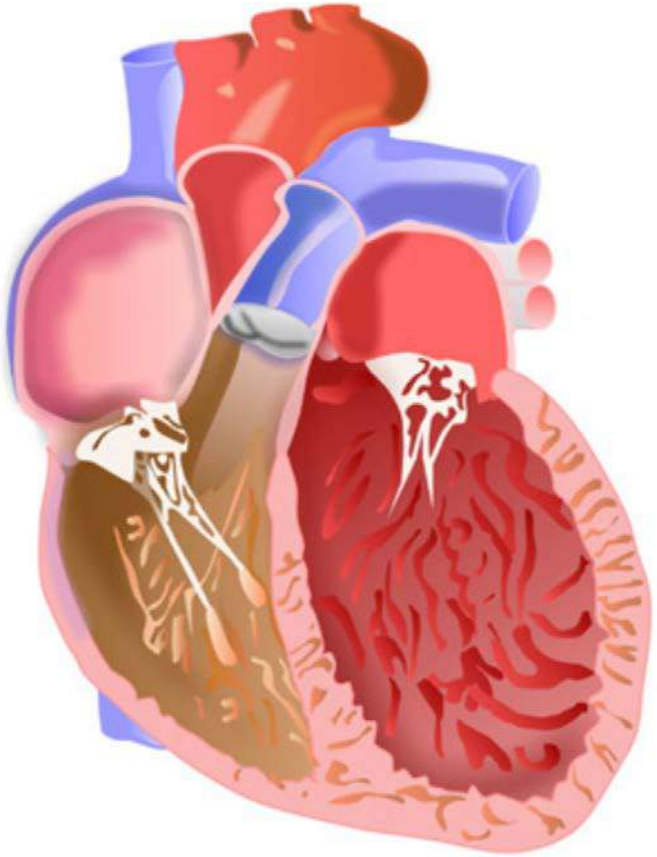
Pompe disease

- glycogen storage disorder, alpha glucosidase deficiency
- Autosomal recessive, *GAA* gene
- Symptoms: Shortness of breath, lung infections, enlarged liver, enlarged tongue that makes it hard to chew and swallow, stiff joints, cardiomyopathy

Fabry disease:

- metabolic disease caused by improper breakdown of alpha-galactosidase A
- X-linked dominant, *GLA* gene





Dilated Cardiomyopathy

Yogasundaram et al. Can J Cardiology 2021

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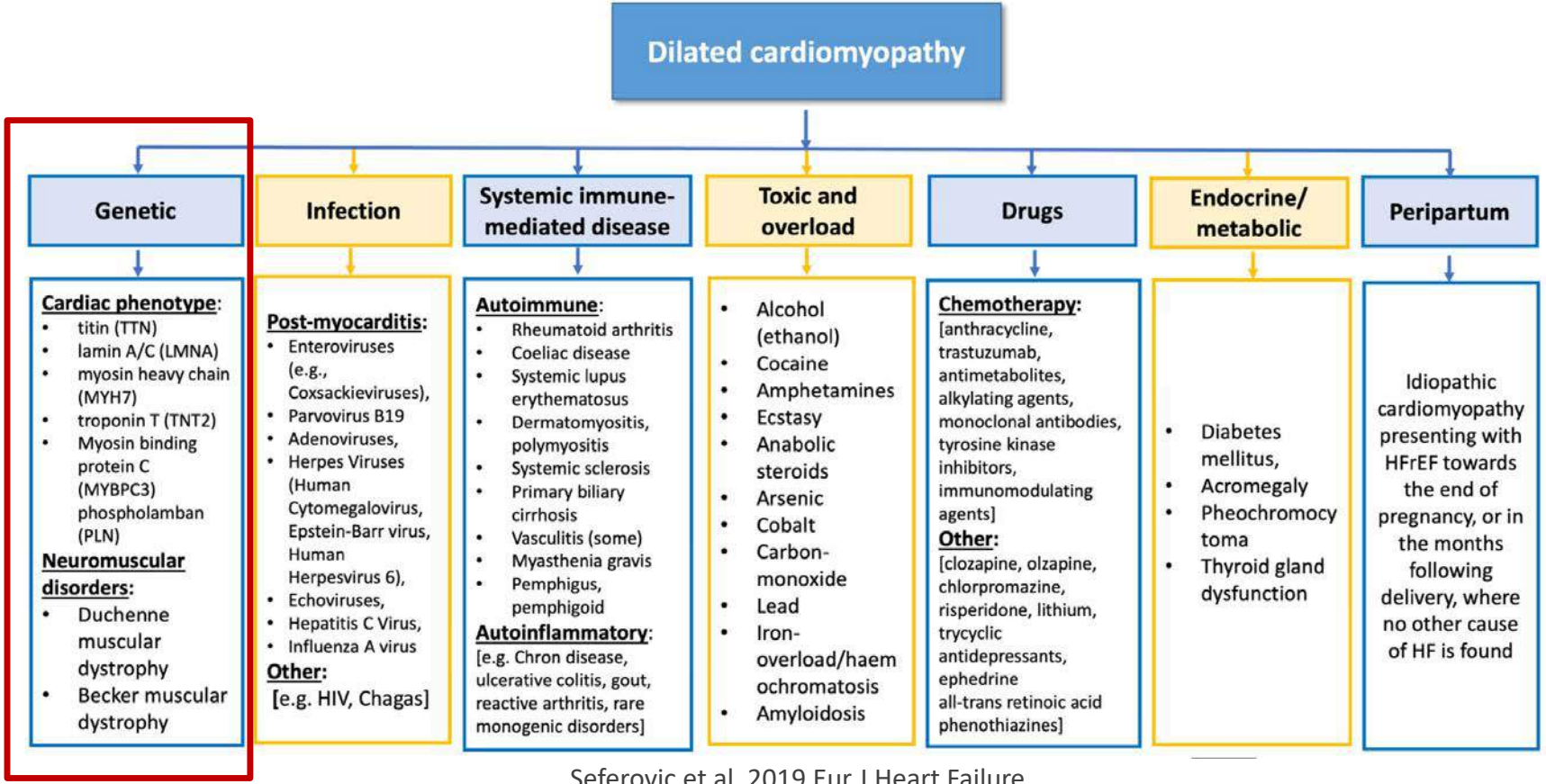
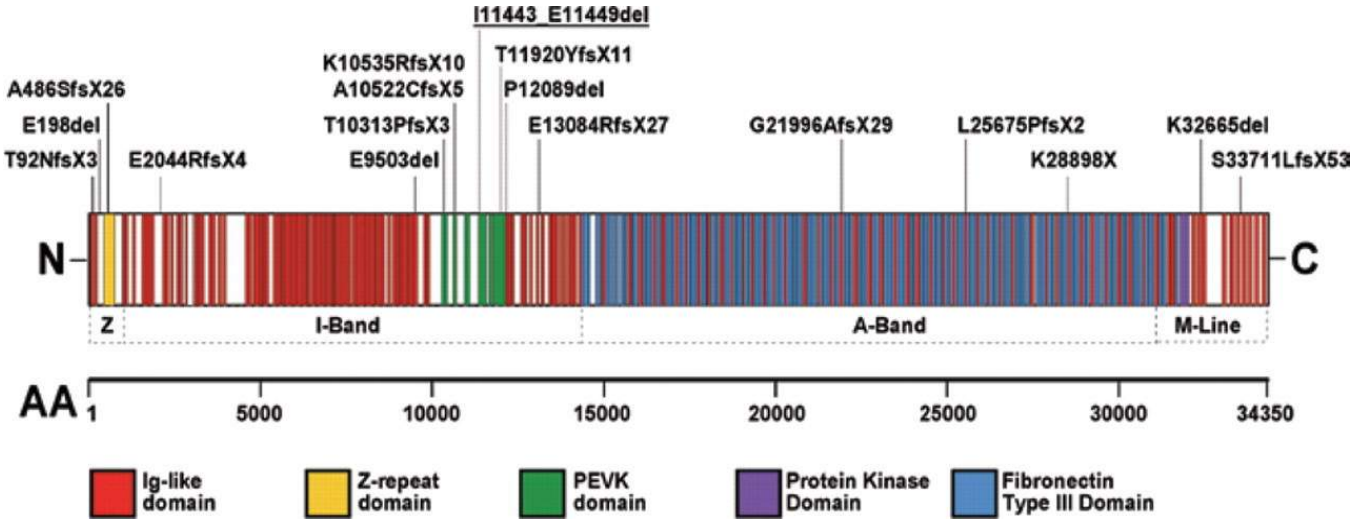
DCM Causes



Seferovic et al, 2019 Eur J Heart Failure

Genetic Causes of Isolated DCM

Gene	Protein	% of cases of genetic DCM	Other associated conditions
TTN	Titin	10-20%	LGMD2J (AR)
LMNA	Lamin A	6%	Arrhythmogenic DCM, Emery-Dreifuss (AR), *LMNA*-related muscle disease
MYH7	Myosin 7	4.2%	Hypertrophic cardiomyopathy , Noncompaction cardiomyopathy
MYH6	Myosin 6	3-4%	Hypertrophic cardiomyopathy
SCN5A	Sodium channel protein type 5 subunit alpha	2-4%	Arrhythmogenic DCM, LQTS, Brugada , Cardiac conduction disease
MYBPC3	Myosin binding protein C	2-4%	Hypertrophic cardiomyopathy
TNNT2	Troponin T	2.9%	Hypertrophic cardiomyopathy , Noncompaction cardiomyopathy , Restrictive cardiomyopathy
BAG3	BAG family molecular chaperone regulator 3	2.5%	Progressive myofibrillar myopathy



Golbus et al. 2012

TTN (Titin)

- Encodes very large protein called titin. Titin plays an important role in skeletal and cardiac muscle structure.
- Interacts with other muscle proteins, including actin and myosin, to keep the components of sarcomeres in place as muscles contract and relax.
- The size of this gene makes it a mutational hotspot; truncating variants are more common in affected individuals >50y.o. With the majority of individuals having variants in the A-band of the gene

Syndromic Causes of DCM

Muscular Dystrophies

- **Emery Dreifuss**
  - Contractures
  - Muscle weakness (humeroperoneal muscles first)
  - DCM
  - AD and AR (LMNA), XL (EMD, FHL1)
- **Limb Girdle type 1**
  - AD and AR, *LMNA*
  - Progressive limb girdle weakness (pelvic then humeral)
  - DCM + CCD
  - NO contractures
  - CAV3 - HCM
- **DMD**
  - XL, females carriers at risk for DCM

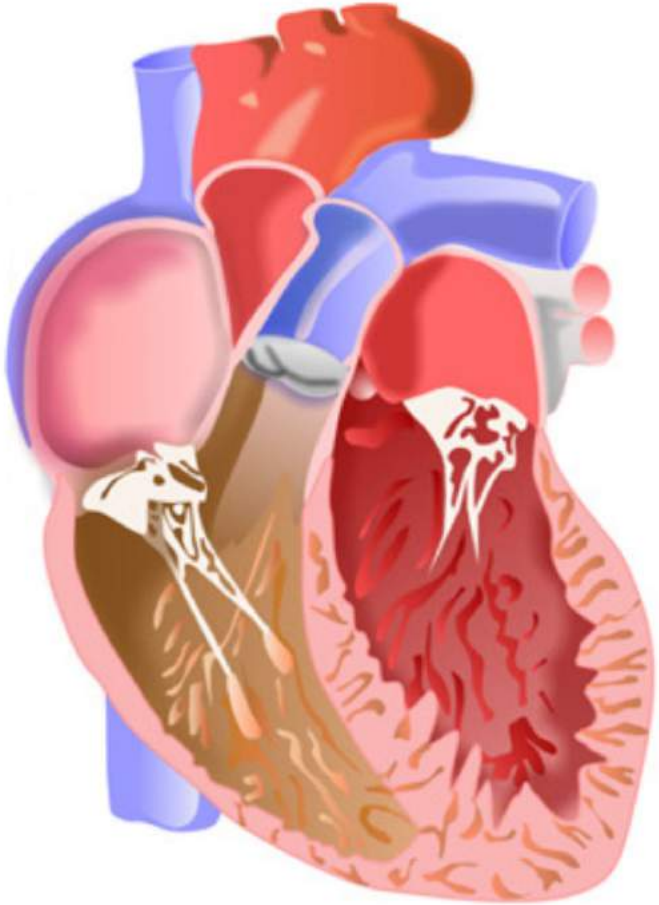
Metabolic

- **Barth**
  - XL mitochondrial disorder
  - Mutations in *TAZ*
  - DCM/LVNC (infantile onset)
  - Neutropenia
  - Hypotonia (DD)/SS
- **Congenital disorders of glycosylation**
- **Primary carnitine deficiency**

Mitochondrial syndromes

	General Features	CM	Other Cardiac involvement
MERRF	• Myoclonus, general seizures, ataxia	*Dilated*	
Kearns-Sayre syndrome	• Ophthalmoplegia • Retinitis Pigmentosa • Cerebellar ataxia, dementia • Calcifications at basal ganglia and thalamus • cortical or cerebellar atrophy	*Dilated*	• PR interval prolongation preceding 2nd or 3rd degree AV block • His-ventricular (H-V) interval prolongation WPW syndrome • Stokes-Adams syncope
Pearson syndrome	• Ophthalmoplegia, ptosis • Proximal muscle weakness and dysphagia	*Dilated*	
MELAS	• Stroke-like episodes with cortical lesions usually in posterior regions • Dementia and/or seizures • Proximal muscle limb weakness with RRF	*Hypertrophic or Dilated*	• Sudden death • WPW syndrome in both childhood and adult patients
Leigh syndrome	• Severe subacute psychomotor delay and necrotizing symmetrical lesions in the brainstem, thalamus, cerebellum, spinal cord and optic nerves • Elevated lactate in blood and CFS	*Hypertrophic or Dilated*	• Bradycardia
NARP	*Sensory-motor axonal neuropathy, ataxia, seizures, pigmentary retinopathy and dementia	*Hypertrophic or Peri-partum dilated*	• Ventricular pre-exitation

Adapted from Berardo et al 2011



Left Ventricular Noncompaction

Yogasundaram et al. Can J Cardiology 2021

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LVNC Genes

- Diagnostic yield of genetic testing in clinically identified cases of LVNC ~20%, primarily sporadic
- Due to low yield in index cases, the utility of genetic testing for diagnosis remains unclear
- Mutations in the X-linked gene taffazin (TAZ) causes Barth Syndrome (myopathy, short stature, neutropenia, LVNC) in young males
- Consider mitochondrial / metabolic disease in LVNC, requires a high index of suspicion for evaluation

Table 2
Genes associated with LVNC

Gene	Protein
ACTC1	α-Actinin-2
ACTN2	α-Cardiac actin
DTNA	α-Dystrobrevin
DYS/nZASP	Dystrophin
GLA	α-Galactosidase
LDB3	LIM-domain binding 3
LMNA	Lamin A/C
MYBPC3	Myosin-binding protein C
MYH7	β-Myosin heavy chain 7
TAZ	Tafazzin
TNNT2	Cardiac troponin T, type 2
TPM1	α-Tropomyosin
TNNI3	Cardiac troponin I

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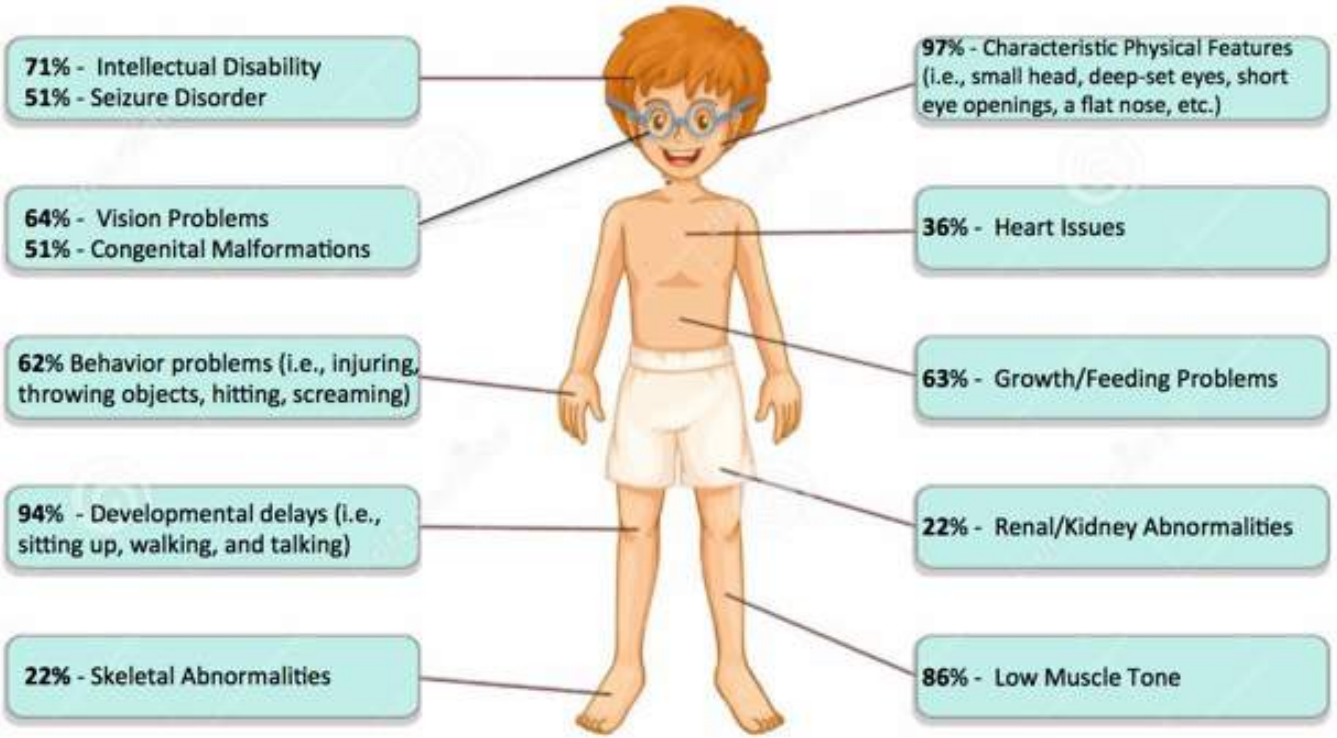
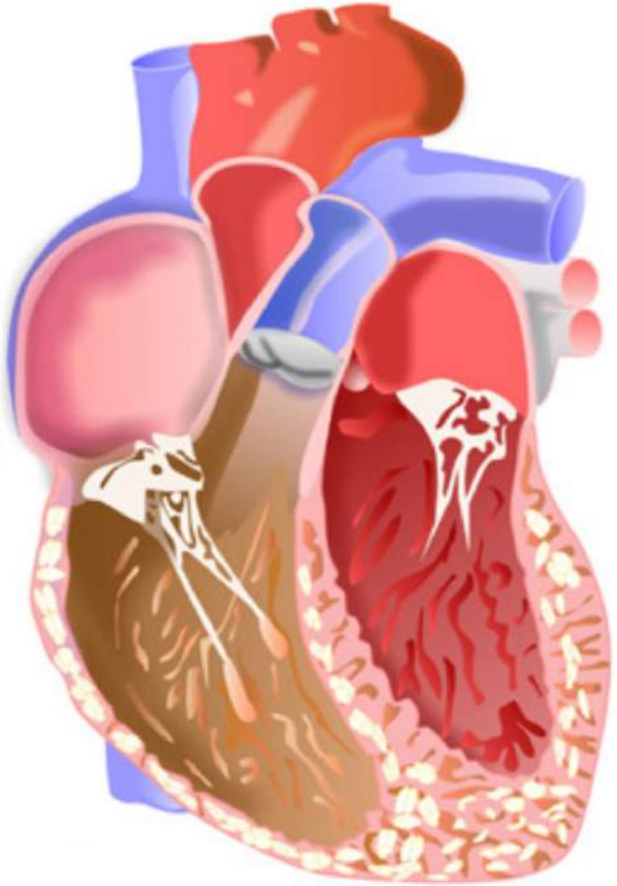
1p36 Deletion Syndrome

1p36 Deletion Syndrome



1p36 deletion support and awareness group



Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Yogasundaram et al. Can J Cardiology 2021

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Arrythmogenic Cardiomyopathy genes

James et al. E ur Heart J 2020

Gene[a]	Protein	Prevalence in ACM	Phenotype
Desmosomal			
PKP2	Plakophilin-2	20–46%	ARVC
DSP	Desmoplakin	3–20%	ALVC; also associated w/ DCM. Rare homozyg.-Carvajal Syndrome
DSG2	Desmoglein-2	3–20%	ACM, also associated with dilated cardiomyopathy
DSC2	Desmocollin-2	1–15%	ACM. Can be recessive
JUP	Plakoglobin	0–1% (higher in Naxos, Greece)	Naxos disease (cardiocutaneous). Autosomal recessive
Founder variants			
PLN	Phospholamban	0–4% (higher in Netherlands)	ACM. Worse outcomes in females.
TMEM43	Transmembrane protein 43	0–2% (higher in Newfoundland)	ACM. Younger male onset w/ lethal ventricular arrhythmias in males
Overlap syndromes			
SCN5A	$Na_V1.5$	2%	ARVC. Also associated w/ Brugada, DCM, long QT syndrome
LMNA	lamin A/C	0–4%	ACM; overlap with DCM
TTN	Titin	0–10%	ACM; overlap with DCM
FLNC	Filamin C	0–3%	ACM; left predominant
DES	Desmin	0–3%	ACM
Emerging genes			
CTNNA3	Alpha T-catenin	0–2%?	ARVC—few cases reported
CDH2	Cadherin-2	0–2%?	ARVC—few cases reported
TJP1	Tight junction protein 1	0–4%?	ACM—few cases reported
ANK2	Ankyrin-B	0–5%?	ACM—few cases reported
TP63	p63	0–2%?	ACM—singe case

DCM and ARVC Overlap

DES (desmin)

- Isolated DCM
  w/ conduction defects and arrhythmias
  Autosomal dominant
- Skeletal myopathy with CM + CCD (AVB)
  (**DCM**, RCM, HCM)

LMNA (laminopathies)

- DCM + CCD
  AVB may be presenting sign
  SCD common
  Autosomal dominant
- Emery Dreifuss MD
  Limb Girdle MD
  Familial partial lipodystrophy
  Hutchinson-Gildford progeria
  CMT2

SCN5A

- DCM (ARVC)
  +
  Progressive CCD
  +
  Supraventricular or ventricular arrhythmias
- Brugada
  LQTS 3
  HB, SSS, Vfib, Afib

Some genes that cause DCM have an increased risk for malignant arrhythmias that may proceed any structural heart disease or be out of proportion with the structural disease/LV dilation. These are sometimes referred to as 'left-dominant ARVC'. More recently, the term 'arrhythmogenic cardiomyopathy' is being used to encompass ARVC and other genes that have a significant arrhythmogenic phenotype (DES, LMNA, SCN5A, RBM20, FLNC, DSP).

Genetic Evaluation of Cardiomyopathy—A Heart Failure Society

Table 3. Selected Genes in Association With Cardiomyopathy

Cardiomyopathy	Core Genes*	Estimates of Genetic Testing Diagnostic Yield	ACMG Secondary Findings Gene List	Metabolic Causes of Cardiomyopathty	Examples of Genetic Syndromes
HCM	*MYH7*, *MYBPC3*, *TNNT2*, *TNNC1*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, *ACTN2*, *CSRP3*, *PLN*, *TTR*, *PRKAG2*, *LAMP2*, *GLA*	30%–60%	*MYBPC3*, *MYH7*, *TNNT2*, *TNNI3*, *TPM1*, *MYL3*, *ACTC1*, *PRKAG2*, *GLA*, *MYL2*, *LMNA*	*GAA* (Pompe); Mitochondrial disease genes	RASopathies (eg, Noonan syndrome, others); Friedreich ataxia
DCM	*TTN*,† *LMNA*, *MYH7*, *TNNT2*, *BAG3*, *RBM20*, *TNNC1*, *TNNI3*, *TPM1*, *SCN5A*, *PLN*. For testing, all HCM and ARVC genes are recommended to be included.	10%–40%		Mitochondrial disease genes	Muscular dystrophies; Alström syndrome
ARVC	*DES*, *DSC2*, *DSG2*, *DSP*, *JUP*, *LMNA*, *PKP2*, *PLN*, *RYR2*, *SCN5A*, *TMEM43*, *TTN*†; consider full DCM panel	10%–50%	PKP2, DSP, DSC2, TMEM43, DSG2, RYR2 SCN5A		Naxos syndrome; Carvajal syndrome
RCM	Consider HCM or DCM gene panel	10%–60%			
LVNC	Use the gene panel for the cardiomyopathy identified in association with the LVNC phenotype	Unknown		Mitochondrial disease genes, including *TAZ* in Barth syndrome	1p36 deletion syndrome; RASopathies

Summary

- HCM, DCM, ARVC have high yield of genetics testing. Increasing evidence in LVNC. Varying estimates in RCM
- Think of syndromic and non-syndromic forms
- Consider mitochondrial involvement
- Complex field – work with genetic specialists
- Rapidly changing

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Genetic Evaluation of Cardiomyopathy—A Heart Failure Society of America Practice Guideline

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DCM	*TTN*,† *LMNA*, *MYH7*, *TNNT2*, *BAG3*, *RBM20*, *TNNC1*, *TNNI3*, *TPM1*, *SCN5A*, *PLN*. For testing, all HCM and ARVC genes are recommended to be included.	10%–40%		Mitochondrial disease genes	Muscular dystrophies; Alström syndrome

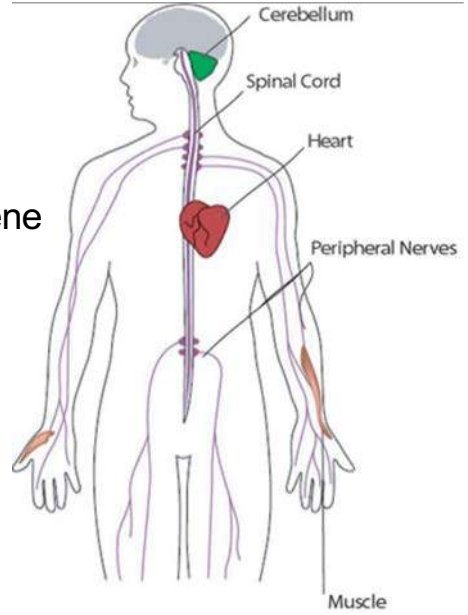
- For an affected proband, likelihood of a positive genetic test result influenced by family history. ~15-50% of individuals with idiopathic DCM have a positive family history
  - *Positive family history – 30-50% likelihood of a positive result*
  - *No known family history – 10-25%*
- Idiopathic DCM and systolic dysfunction without LV dilation have similar genetic risk assessments
- Consider genetic testing when LV ejection fraction <45% (situation dependent 45-50%)
- Genetic testing for DCM can have prognostic and therapeutic implications
  - *When to consider ICD*
  - *Neuromuscular/skeletal disease risk*
  - *Type of screening indicated for at-risk individuals (arrhythmia may precede dysfunction)*

Journal of Cardiac Failure Vol. 24 No. 5 2018

Syndromic Causes of HCM

Friedreich's Ataxia

- Most common hereditary ataxia
- Autosomal recessive, trinucleotide repeat (~ 96%) of GAA in the *FXN* gene
  - Nl: 5-33 repeats
  - Premuation: 34-65
  - Full mutation: 66-1300
- Can have progressive systolic dysfunction



Progressive ataxia (legs and torso)
Muscle weakness
Absent muscle stretch reflexes
Wheelchair bound typically by 15 years

Dysarthria
Pectus cavus
Scoliosis
Diabetes (30%)
Optic nerve atrophy
Dysphagia

ARVC Genotype/Phenotype Correlation

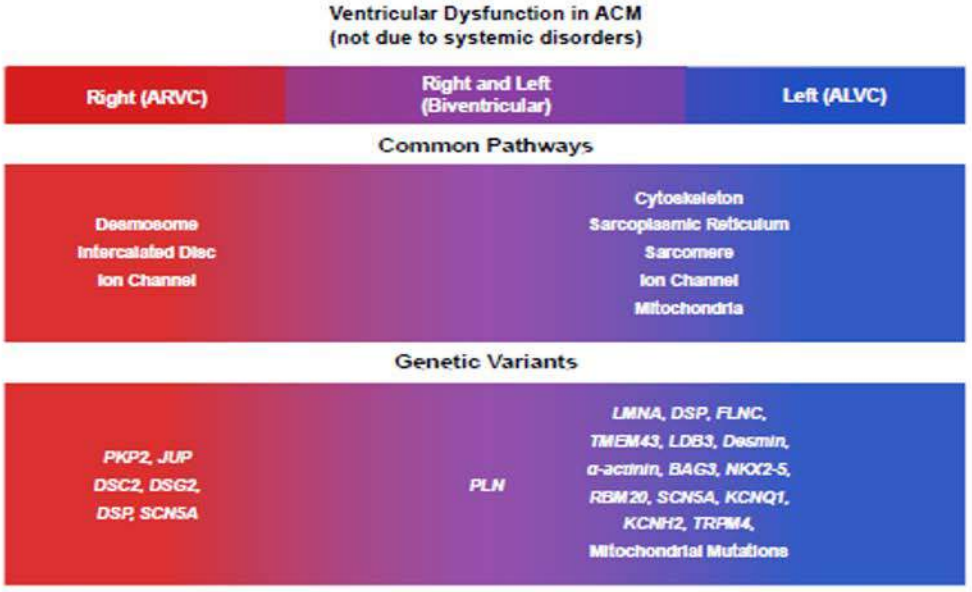


Figure 4 Approach to understanding the common pathway and genetic variants in a patient with arrhythmogenic cardiomyopathy (ACM) according to the predominant ventricular dysfunction. See also Table 3. ALVC = arrhythmogenic left ventricular cardiomyopathy; ARVC = arrhythmogenic right ventricular cardiomyopathy; *BAG3* = BCL2 associated athanogene 3; *DSC2* = desmocollin-2; *DSG2* = desmoglein-2; *DSP* = desmoplakin; *FLNC* = filamin-C; *JUP* = junction plakoglobin; *KCNH2* = potassium voltage-gated channel subfamily H member 2; *KCNQ1* = potassium voltage-gated channel subfamily Q member 1; *LDB3* = LIM domain binding 3; *LMNA* = lamin A/C; *NKX2-5* = NK2 homeobox 5; *PKP2* = plakophilin-2; *PLN* = phospholamban; *RBM20* = RNA binding motif protein 20; *SCN5A* = sodium voltage-gated channel alpha subunit 5; *TMEM43* = transmembrane protein 43; *TRPM4* = transient receptor potential melastatin 4.