University of Zurich[UZH]

Institute of Medical Molecular Genetics

Genetic Heterogeneity and Clinical Variability of Cardiomyopathies and Cardiac Arrhythmias

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Classification of Monogenic Cardiomyopathies

- dilated cardiomyopathy (DCM), ~ 1 in 2,500
- hypertrophic cardiomyopathy (HCM), ~ 1 in 500
- left ventricular non-compaction cardiomyopathy (LVNC)
- restrictive cardiomyopathy (RCM)
- arrhythmogenic right ventricular cardiomyopathy (ARVC), ~ 1 in 2,000 - 5,000
- non-syndromic and syndromic forms (combination with symptoms in other organs / tissues)

Indications for a Genetic Cause

Any of the following findings in the family history should be reason for further assessment:

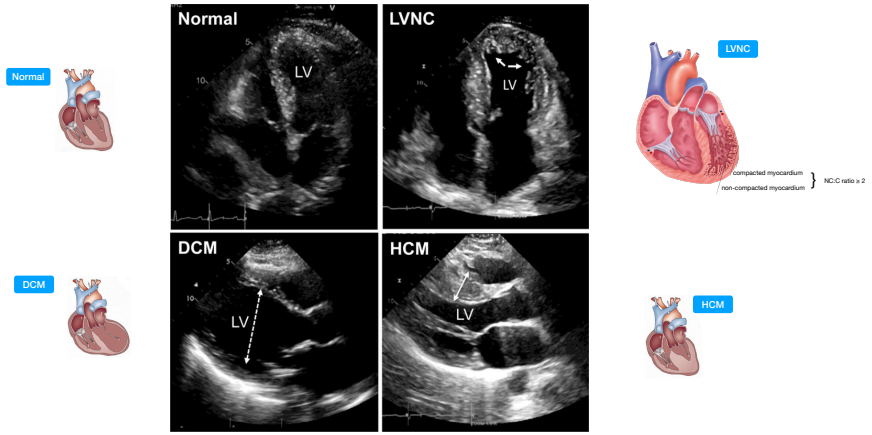
- Sudden cardiac death (SUD), e.g. athletes, sportspersons
- Sudden infant death syndrome (SIDS)
- Unexplained syncopes
- Heart transplantation in the absence of coronary artery disease
- Presence of a pacemaker and/or implantable defibrillator at age <60 years
- Muscle weakness or myopathy
- Drowning of an experienced swimmer

Rosenbaum AN et al. (2013) Nat Rev Cardiol

Clinical Tools for Diagnosis

- **Echocardiography:** ultrasound imaging of the heart
- **Electrocardiography (ECG):** measuring electrical impulses from the heart, can detect enlarged chambers of the heart and abnormal heart rhythms
- **Cardiac MRI:** cardiac MRI is often used in addition to echocardiograms to evaluate people with hypertrophic cardiomyopathy
- **Cardiac catheterization:** in addition to measuring pressures, cardiac catheterization is used to obtain X-ray images (angiograms) of the heart and blood vessels; a dye is injected through the catheter to help visualize the heart and blood vessels

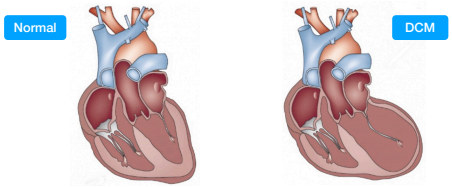
Clinical Diagnosis of Cardiomyopathies Using Echocardiography



- McNally EM & Mestroni L (2017) Circ Res
- https://www.saooleecp.com/cardiomyopathy/
- https://www.cincinnatichildrens.org/service/c/cardiomyopathy/types/left-ventricular-non-compaction-cardiomyopathy

McNally EM & Mestroni L (2017) Circ Res

Dilated Cardiomyopathy (DCM): Definition



Left ventricular enlargement

Enlargement is most commonly assessed in adults by either echocardiography or cardiac MRI. Because of rapid growth in children, expert cardiovascular assessment is recommended to assess left ventricular enlargement in the pediatric population.

Systolic dysfunction, a reduction in the myocardial force of contraction

An ejection fraction of less than 50% is considered a systolic dysfunction. The left ventricular ejection fraction is the most commonly used clinical measure of systolic function, and is usually estimated from a two-dimensional echocardiogram or from cardiac MRI.

Dilated Cardiomyopathy (DCM)
Management / Treatment

- **Medications:** drugs that have proved useful in the treatment of heart failure and dilated cardiomyopathy include:
  - **Angiotensin-converting enzyme (ACE) inhibitors,** widen or dilate blood vessels (vasodilator) to lower blood pressure, improve blood flow and decrease the heart's workload. ACE inhibitors may improve heart function
  - **Angiotensin II receptor blockers,** have many of the beneficial effects of ACE inhibitors and may be an alternative for people who can't tolerate ACE inhibitors
  - **Beta blockers,** slow heart rate, reduce blood pressure and may prevent some of the harmful effects of stress hormones, beta blockers may reduce signs and symptoms of heart failure and improve heart function
  - **Diuretics,** remove excess fluid and salt from the body
  - **Digoxin,** strengthens heart muscle contractions, also tends to slow the heartbeat
  - **Blood-thinning medications,** help prevent blood clots
- **Devices:** implantable devices used to treat dilated cardiomyopathy include:
  - **Biventricular pacemakers,** use electrical impulses to coordinate the actions of the left and right ventricles
  - **Implantable cardioverter-defibrillators (ICDs),** monitor heart rhythm and deliver electrical shocks when needed to control abnormal, rapid heartbeats, including those that cause the heart to stop, can also function as pacemakers
  - **Left ventricular assist devices (LVADs),** mechanical devices implanted into the abdomen or chest and attached to a weakened heart to help it pump
- **Heart transplantation:** if medications and other treatments are no longer effective

https://www.mayoclinic.org/diseases-conditions/dilated-cardiomyopathy/diagnosis-treatment/drc-20353155

Genetic Basis of Dilated Cardiomyopathies

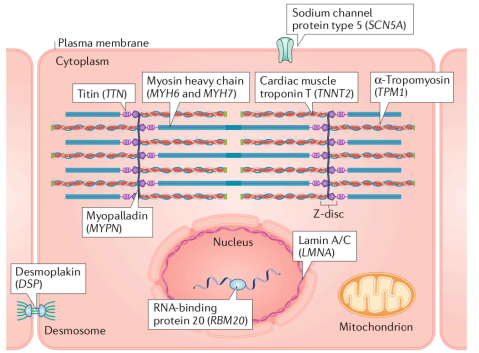
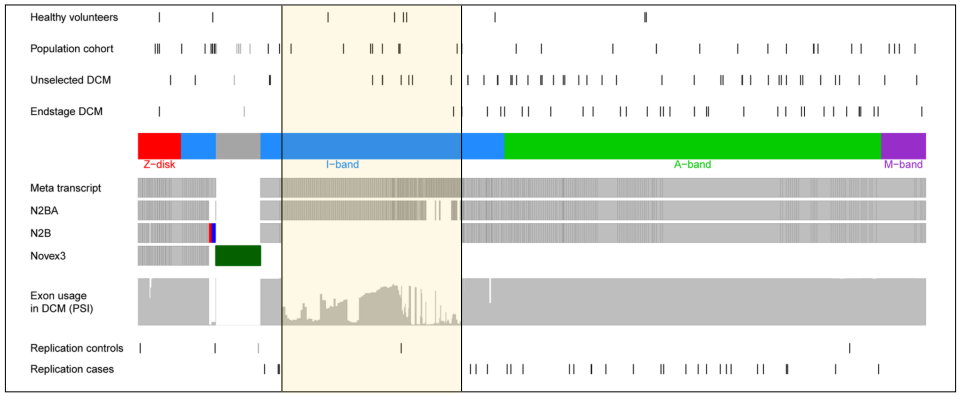


Fig. 1 | **Cellular locations of proteins associated with DCM.** The graphic shows the approximate cellular locations of the ten proteins and their respective genes in which dilated cardiomyopathy (DCM)-causing pathogenic variants most commonly occur (see TABLE 1).

Rosenbaum AN et al. (2013) Nat Rev Cardiol

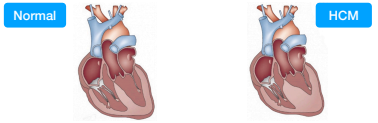
Distribution of TTN truncating variants in healthy individuals and DCM patients & TTN exon usage in the heart

Genomic size: 281.5 kbp; exons: 364; amino acids: 35,991



Roberts et al. (2015) Sci Transl Med

Hypertrophic Cardiomyopathy (HCM): Definition



- Hypertrophic cardiomyopathy (HCM) is defined by the presence of unexplained left ventricular hypertrophy (LVH) with a maximum **wall thickness ≥15 mm** in adults.
- If there is a family history of HCM, or if genetic testing confirms that a relative has inherited the family's pathogenic sarcomere variant, a maximum LV wall thickness ≥13 mm supports diagnosis.
- The differential diagnosis for HCM includes increased left ventricular wall thickness due to **acquired**, **syndromic** (with other systemic involvement), and **nonsyndromic** (without other systemic involvement) disorders.

Treatment of HCM

- **Medications:** beta blockers, calcium channel blockers, or medications to control heart rhythm
- **Implantable cardioverter-defibrillator (ICD):** an ICD is recommended in patients who have life-threatening heart rhythm disorders (arrhythmias) such as ventricular tachycardia or ventricular fibrillation
- **Septal myectomy:** surgical removal of part of the thickened, overgrown septum between the ventricles

https://www.mayoclinic.org/diseases-conditions/hypertrophic-cardiomyopathy/diagnosis-treatment/drc-20350204

Molecular Basis of Hypertrophic Cardiomyopathy

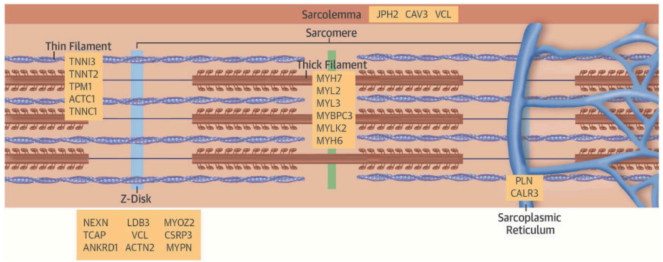
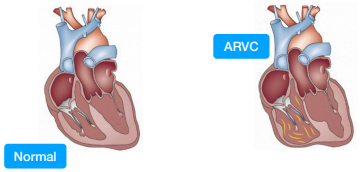


FIGURE 1. A Schematic of Definitive (Bolded) and Posited HCM Genes With the Subcellular Localization of the Encoded Proteins
All pathogenic genes encode sarcomere proteins. Putative HCM genes encode these and sarcomere-associated molecules. HCM = hypertrophic cardiomyopathy.

Burke MA et al. (2016) J Amer Coll Cardiol

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

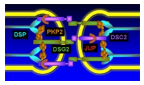


- previously referred to as arrhythmogenic right ventricular dysplasia (ARVD), abbrev. ARVC or ARVCM
- characterized by progressive fibrofatty replacement of the myocardium
- predisposes to ventricular tachycardia and sudden death in young individuals and athletes
- primarily affects the right ventricle, but may also involve the left ventricle
- presentation of disease is highly variable even within families
- some affected individuals may not meet established clinical criteria
- mean age at diagnosis is 31 years (±13; range: 4-64 years)

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Diagnosis / Testing

- diagnosis of ARVC is made using a combination of noninvasive and invasive tests to evaluate cardiac structure and rhythm
- common genetic causes known to be associated with ARVC are: *DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, and *TMEM43*
- less common genetic causes include *CTNNA3*, *DES*, *LMNA*, *PLN*, *RYR2*, *TGFB3*, and *TTN*
- a subset of these genes encode components of the desmosome



Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Management / Treatment

- management is individualized and focused on prevention of syncope, cardiac arrest, and sudden death
- use of antiarrhythmic medication and an implantable cardioverter-defibrillator (ICD)
- heart transplantation is considered when ARVC has progressed to right or left ventricular heart failure
- severe diffuse biventricular involvement simulating dilated cardiomyopathy and requiring heart transplantation appears to be rare

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Management / Treatment

- *Agents/circumstances to avoid:*
  - regular, vigorous athletic activity including competitive athletics should be discouraged because of the strain caused on the right heart and its promotion of ARVC and associated arrhythmias
- *Evaluation of relatives at risk:*
  - molecular genetic testing of at-risk relatives in families in which the pathogenic variant is known;
  - those with the family-specific pathogenic variant warrant annual clinical screening of cardiac function and rhythm between ages ten and 50 years.
  - clinical screening for cardiac involvement is recommended for asymptomatic at- risk first-degree relatives every three to five years after age ten years (if genetic testing was negative)

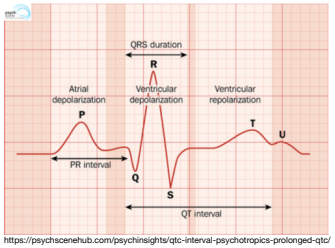
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Genetic Counselling

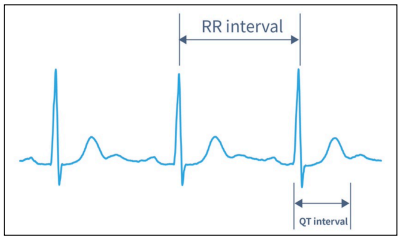
- ARVC is typically inherited in an autosomal dominant manner
- a patient with autosomal dominant ARVC may have the disorder as a result of a *de novo* pathogenic variant
- proportion of cases caused by a *de novo* variant is unknown
- child of an individual with autosomal dominant ARVC has a 50% risk of inheriting the pathogenic variant
- ARVC may also be inherited in a digenic manner (i.e., a single allele of two different genes has a pathogenic variant)
- prenatal diagnosis for pregnancies at increased risk is possible if the pathogenic variant(s) have been identified in the family

Clinical Diagnosis of Long QT Syndrome

Electrocardiography (ECG)



https://psychscenehub.com/psychinsights/qtc-interval-psychotropics-prolonged-qtc/



- Q wave: arises from the spread of excitation from the apex to the base of the heart (beginning of ventricular excitation)
- R wave: depolarization of both ventricles of the myocardium
- T wave: repolarization of the ventricles
- QT time: time of ventricular systole, depends on heart rate
- QTc: corrected QT duration (corrected for RR interval = heart rate), i.e. corrected for the heart rate

Bazett's Formula:

$$QTc = \frac{QT}{\sqrt{RR}}$$

Long QT Syndrome

Clinical findings

- cardiac electrophysiologic disorder, characterized by QT prolongation (males > 450 ms, females > 470 ms, > 460 in children < 15 years) and T-wave abnormalities on the ECG
- associated with tachyarrhythmias, typically the ventricular tachycardia *torsade de pointes* (TdP)
- TdP is usually self-terminating, thus causing a syncopal event, the most common symptom in individuals with LQTS
- cardiac events typically occur during exercise and emotional stress, less frequently during sleep, usually without warning.
- TdP may also degenerate to ventricular fibrillation and cause aborted cardiac arrest (if the individual is defibrillated) or sudden death
- approximately 50% of untreated individuals with a pathogenic variant in one of the genes associated with LQTS have symptoms, usually one to a few syncopal events
- cardiac events may occur from infancy through middle age, they are most common from the preteen years through the 20s
- Prevalence / frequency: 1 in 2,500

Long QT Syndrome

Diagnosis / Testing

- diagnosis of LQTS is established by prolongation of the QTc interval in the absence of specific conditions known to lengthen it (for example QT-prolonging drugs)
- molecular genetic testing identifies a diagnostic change (or changes) in one or more of the 15 genes known to be associated with LQTS
- *KCNQ1* (LQT1), *KCNH2* (locus name LQT2), and *SCN5A* (LQT3) are the most commonly mutated genes
- approximately 20% of families meeting clinical diagnostic criteria for LQTS do not have detectable pathogenic variants in a known gene
- LQTS associated with biallelic pathogenic variants or heterozygosity for pathogenic variants in two different genes (i.e., digenic pathogenic variants) is generally associated with a more severe phenotype with longer QTc interval

Long QT Syndrome

Treatment of manifestations and prevention

- beta blocker medication is the primary treatment for LQTS
- possible implantable cardioverter-defibrillators (ICD), also prophylactic
- left cardiac sympathetic denervation (LCSD) for those with beta-blocker-resistant symptoms, inability to take beta blockers, and/or history of cardiac arrest
- sodium channel blockers can be useful as additional pharmacologic therapy for patients with a QTc interval >500 ms

Long QT Syndrome

Genetic Counselling

- LQTS is typically inherited in an **autosomal dominant** manner (exception: LQTS associated with sensorineural deafness, known as Jervell and Lange-Nielsen syndrome)
- most individuals diagnosed with LQTS have an affected parent
- proportion of LQTS caused by a *de novo* pathogenic variant is small
- each child of an individual with autosomal dominant LQTS has a **50% recurrence risk** of inheriting the pathogenic variant
- **penetrance** of the disorder may vary
- prenatal testing for pregnancies at increased risk and preimplantation genetic diagnosis are possible once the pathogenic variant(s) have been identified in the family

Short QT Syndrome (SQTS)

Diagnosis / Testing

- rare, familial, cardiac channelopathy characterised by an abnormally short QT interval & increased risk for atrial and ventricular arrhythmias but no structural heart disease
- clinical diagnosis is based on symptoms (syncope or cardiac arrest), family history and electrocardiogram (ECG) findings
- males with QTc ≤ 330 ms and females with QTc ≤ 340 ms have abnormally short QT and should be considered having SQTS, even if they are asymptomatic
- population studies revealed a relatively small number of individuals have QTc intervals < 360 ms (males) and < 370 ms (females), respectively, so that these values probably should be regarded as 'short'
- mutations in cardiac ion channel genes are responsible
- due to the malignant natural history of SQTS, implantable cardioverter defibrillator (ICD) is the first-line therapy in affected patients

Rudic B et al. (2014) Arrhythm Electrophysiol Rev

Short QT Syndrome (SQTS)

Management / Treatment

Table 1: Genes Associated with Short QT Syndrome

SQTS Subtype	Gene Name	Chromosomal Location	Protein Name	Function	SQTS Mechanism
SQT-1	*KCNH2*	7q35-7q36	Kv11.1	α-subunit I_{Kr}	Gain-of-function[17]
SQT-2	*KCNQ1*	11p15.5	Kv7.1	α-subunit I_{Ks}	Gain-of-function[18]
SQT-3	*KCNJ1*	17q23.1-17q24.2	Kir2.1	α-subunit I_{K1}	Gain-of-function[19]
SQT-4	*CACNA1C*	12p13.3	Cav1.2	α-subunit $I_{L,Ca}$	Loss-of-function[20]
SQT-5	*CACNB2*	10p12	Cavβ2	β2-subunit $I_{L,Ca}$	Loss-of-function[20]
SQT-6	*CACNA2D1*	7q21-7q22	Cavδ1	δ1-subunit $I_{L,Ca}$	Loss-of-function[21]

SQTS = short QT syndrome.

Rudic B et al. (2014) Arrhythm Electrophysiol Rev

- small number of reported cases, therefore treatment and management is poorly defined
- recommended that all patients with SQTS receive an ICD, especially those who have survived cardiac arrest or have had a prior syncopal episode
- Quinidine has shown promise in treatment by prolonging the QTc interval and decreasing the amplitude of the T wave

Genetic Testing in Cardiomyopathies and Arrhythmias

Disease	Number of Genes
HCM	> 15
DCM	> 30
ARVC	> 10
LQTS	>15
SQTS	> 5

- genetic testing by high throughput DNA sequencing (Next Generation Sequencing, NGS, HTS)
- three levels of HTS: gene panels, whole exome or whole genome sequencing (WES / WGS)
- interpretation of identified variants is a challenge (in particular amino acid substitutions)
- sequence variants in Titin are difficult to interpret, even premature stop codons and frameshifts
- testing laboratories offering HTS analyses for these diseases have to be accredited ISO17025:2017 until November 2027, then ISO15189:2022
- costs for genetic testing by HTS up to CHF 4'000.- (orphan disease regulation)

Interpretation of Genetic Testing Results

- filtering of variants according to frequency is an important criterion (most are autosomal dominant, frequency should be below 1 in 50,000 or 100,000 individuals)
- known mutations in known genes (ClinVar, Human Gene Mutation Database ®) or novel mutations in known genes
- segregation analysis in families (affected and unaffected family members)
- public databases for variant frequencies are important tools (gnomAD etc.)
- functional assays to characterise DNA sequence variants are the ultimate goal, but difficult to achieve
- disease modelling by using genome editing (CRISPR/Cas9) and iPSCs

Summary - Conclusions - Take Home Messages

- monogenic or Mendelian cardiomyopathies and arrhythmias are clinically variable and genetically heterogeneous diseases
- high throughput DNA sequencing is used for genetic testing in patients and families (WES and WGS)
- genetic testing is important for management and/or treatment of patients (clinical follow-up, recurrence risk, beta blockers, etc.)
- genetic counselling should be offered in families with a positive family history and a pathogenic sequence variant in an index patient
- interpretation of genetic testing results is not always straight forward (variants of unknown significance, VUS) and predominantly based on prediction algorithms (amino acid substitutions)