Inherited cardiac diseases

- Cardiomyopathies
- Arrhythmic diseases in structuraly normal heart

Combined estimated prevalence of 3% in the general population

From very frequent (1 in 500 for HCM) to rare (1 in 10000 for CPVT)

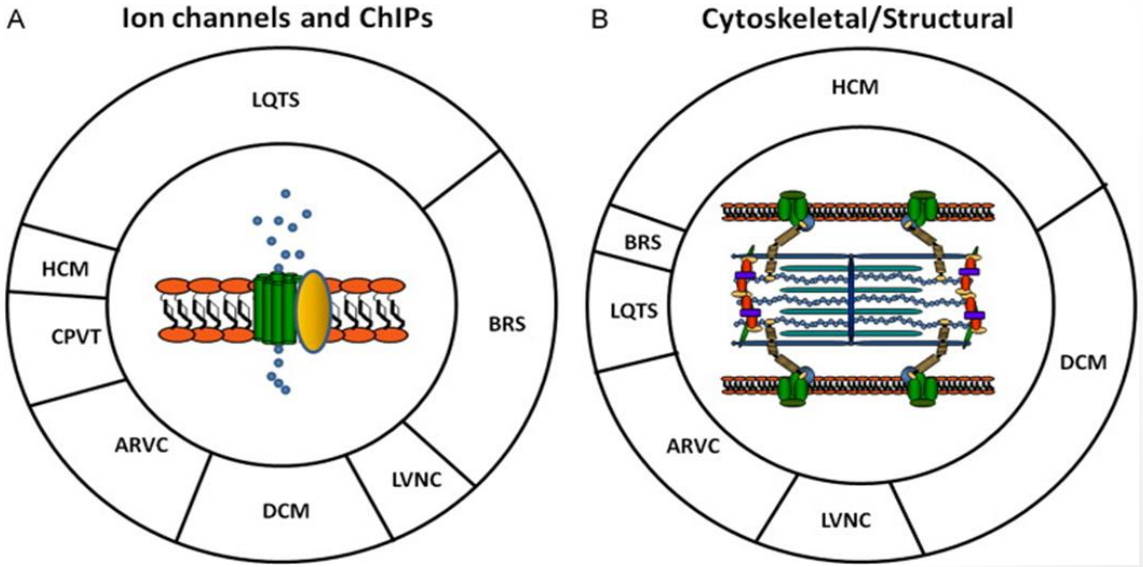
May account for 13-50% of SD, particularly in previously healthy young people

Classification of Cardiomyopathies:

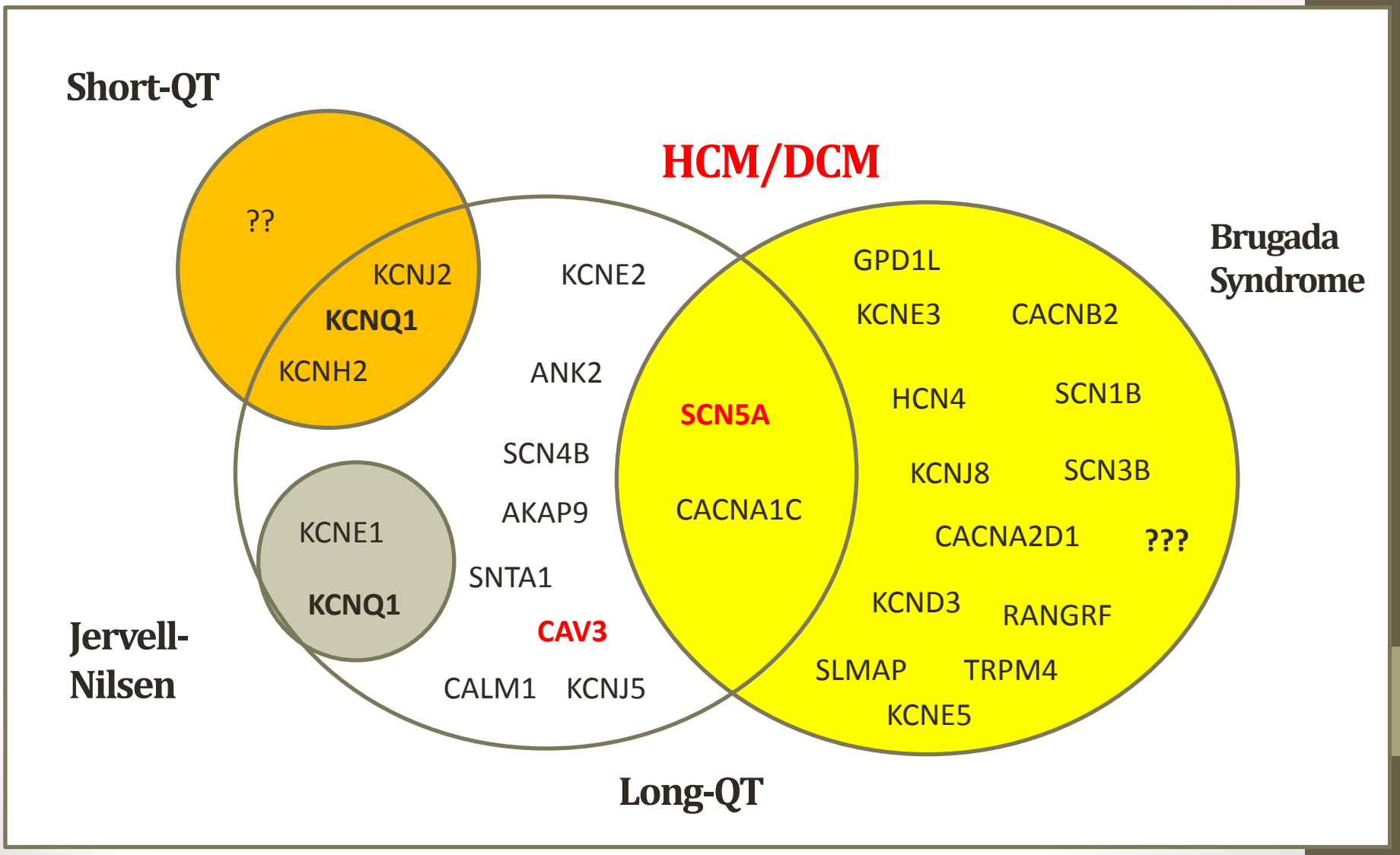
- ESC: DCM, HCM, ARVC, Restrictive, Unclassified, Hypokinetic non-dilated CM (recently added)
- AHA (gene – based): disease of the sarcomere (HCM…but other phenotypes also), disease of the intercellular junction (ARVC…but other genes also –see LMNA)……DCM far more heterogeneous … large overlap

Classification of Channelopathies (mostly genes of cardiac ion channels- structural-regulatory):

- LQTS and SQTS, BrS, CPVT, IVF, PCCD



Heart Diseases With Mendelian inheritance
Overlapping Phenotypes



Clinical guidelines and position article 2018

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

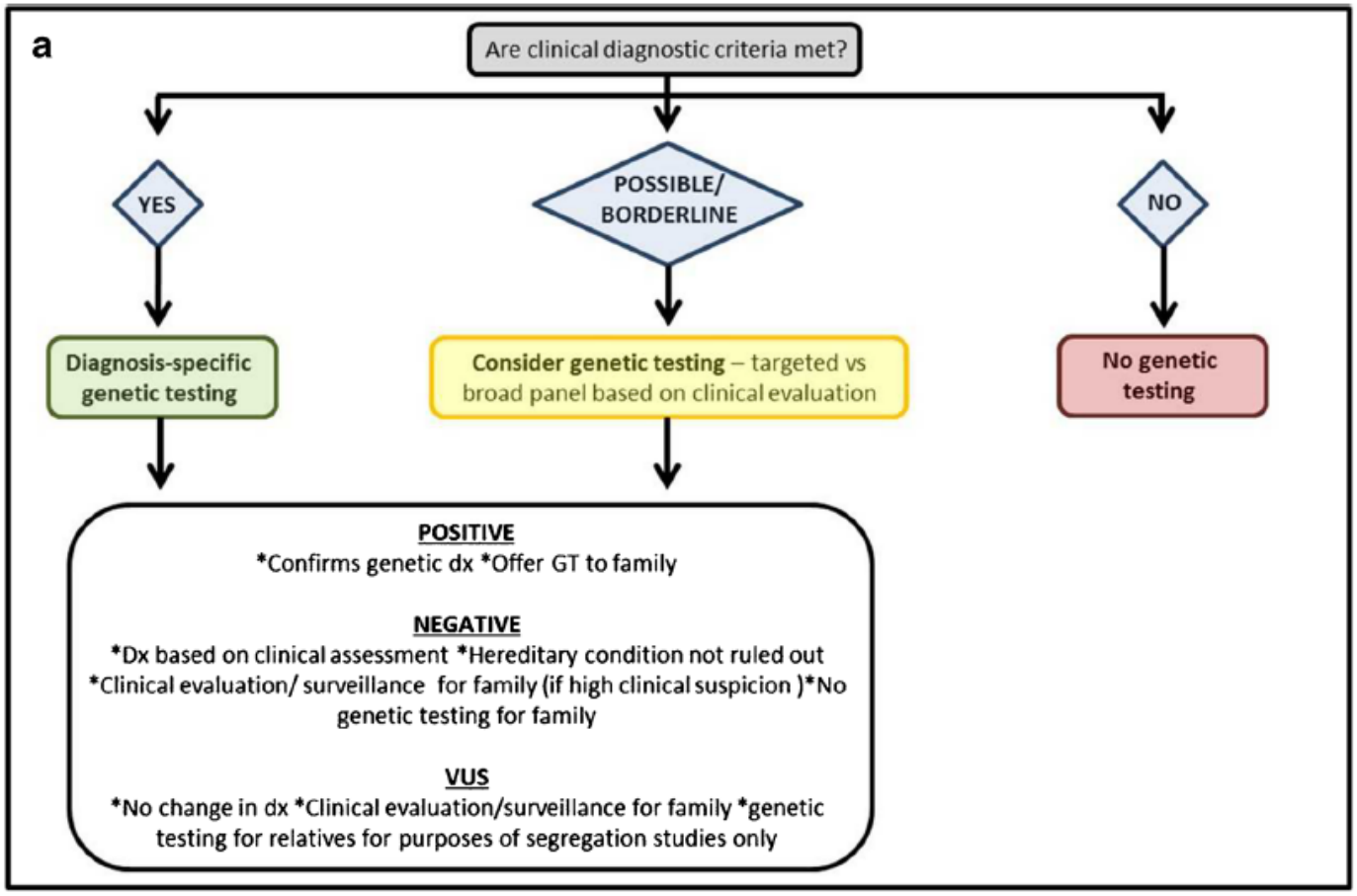
OPEN

Contemporary genetic testing in inherited cardiac disease: tools, ethical issues, and clinical applications

Table 2 When, where, and how to perform genetic testing in patients/families affected by inherited cardiac disease

When	Where	How
Genetic testing should be offered to index patients who fulfil diagnostic criteria for familial cardiovascular disease	In dedicated cardiogenetic services	Genetic tests are usually performed on DNA extracted from a blood sample
Probands with a precise clinical diagnosis (or reasonable suspicion) Family members only when a gene mutation has been already identified Careful consideration is needed when family members are asymptomatic children or adolescents	DNA testing should be performed in certified laboratory Counselling should be performed by trained healthcare professionals working within multidisciplinary teams	Pre-test counselling should be offered to: draw family pedigrees, collect information on family history, and help patients comprehend the procedure, benefits and limitations of the test and the possible consequences of the test results Post-test counselling should be offered: to discuss genetic results directly with the patient in presence of a cardiologist and a geneticist

Genetic testing in the symptomatic patient



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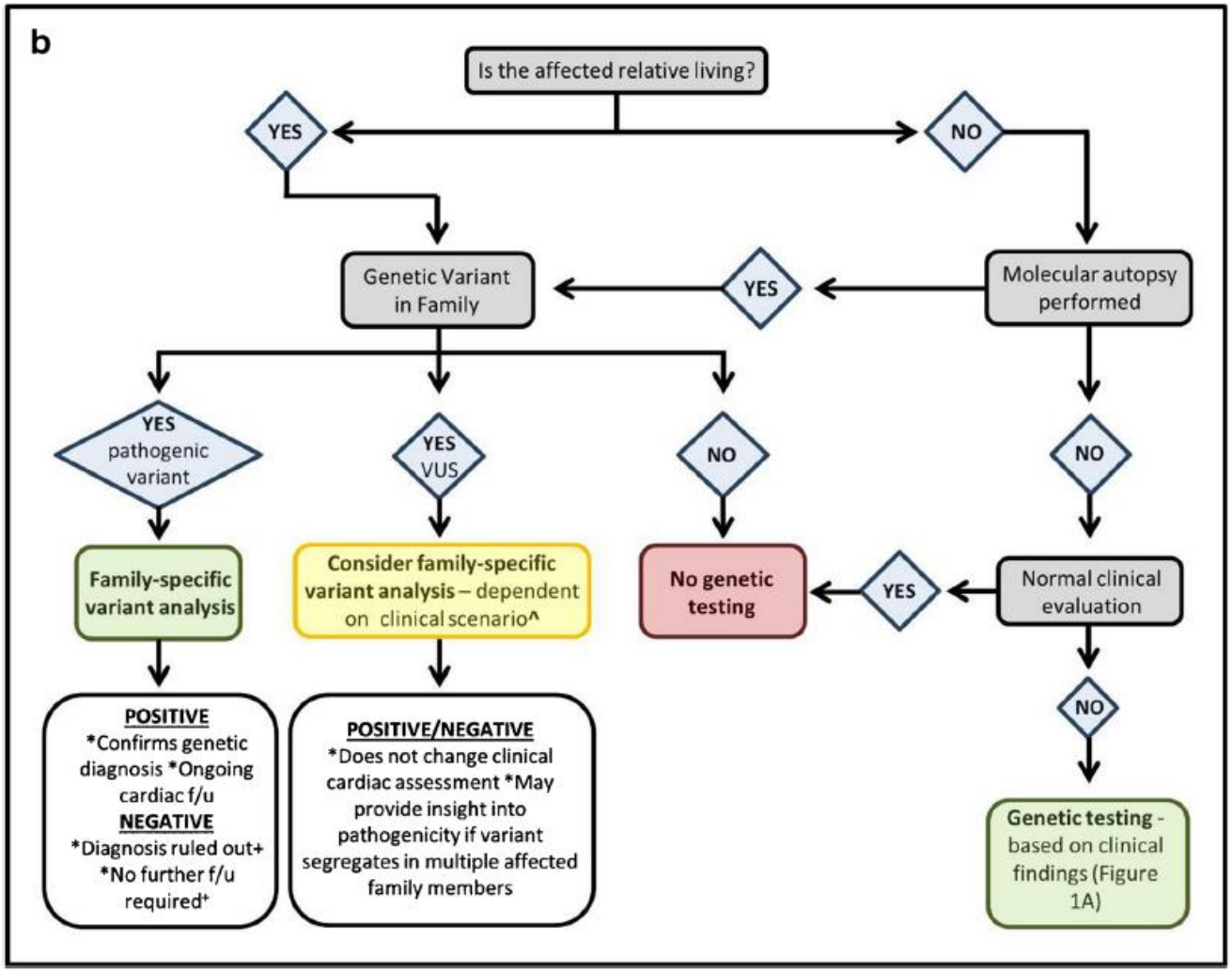
CrossMark

INVASIVE ELECTROPHYSIOLOGY AND PACING (EK HEIST, SECTION EDITOR)

Genetic Testing in Inherited Heart Diseases: Practical Considerations for Clinicians

Genetic testing in relatives



Need for combined expert cardiac evaluation and genetic counselling

Molecular Autopsy

ESC guidelines: Targeted postmortem genetic analysis should be considered in all SD victims in which a specific inherited cardiac diseases in suspected (class of recommendation IIa and level of evidence C)

Association for European cardiovascular pathology guidelines: recommended preliminary genetic couselling of family members before performing post-mortem genetic testing.

Costs not yet supported by the National Health Service in Italy

Morte Cardiaca Improvvisa

Task Force Multidisciplinare per la diagnosi, la gestione e la prevenzione

DIAGNOSI E PREVENZIONE DELLA MORTE IMPROVVISA GIOVANILE IN EMILIA ROMAGNA: DALLA ANATOMIA PATOLOGICA E DALLA MEDICINA LEGALE FINO ALLO SCREENING DELLE FAMIGLIE

Hic mors gaudet succurrere vitae

11 Maggio 2018

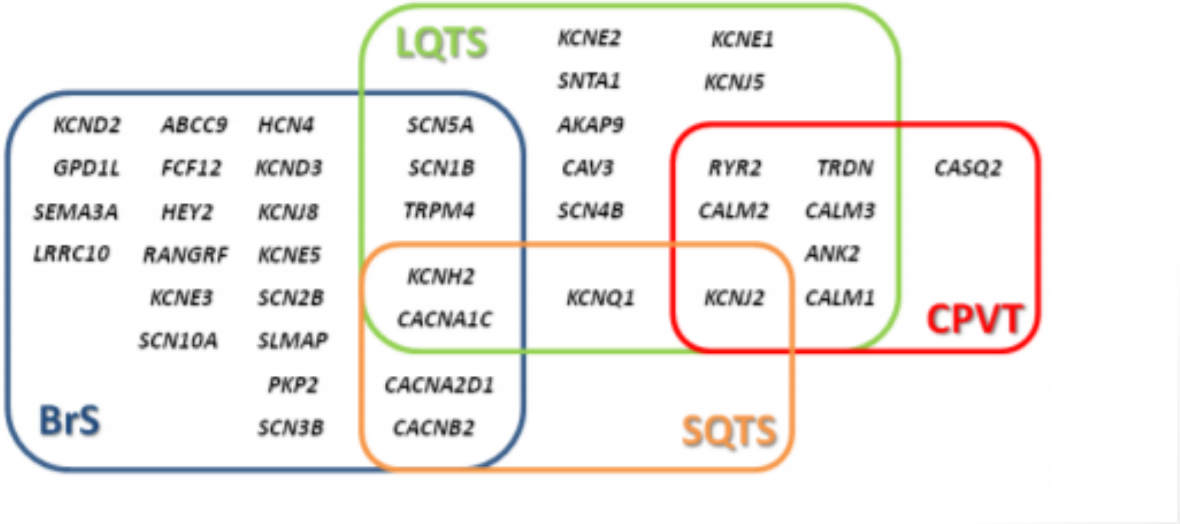
Sala della Cultura
Palazzo Pepoli
Museo della Storia di Bologna

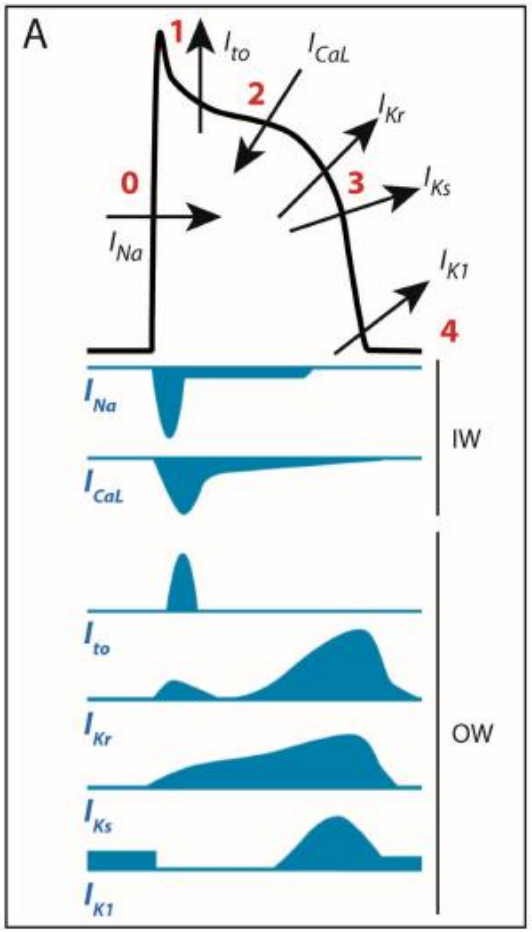
Via Castiglione,8
Bologna

Channellopathies

Hereditary **primary electrical disorders** that may account for up to 30% of all SCD in the young, and primarily include the long QT syndrome (LQTS), the short QT syndrome (SQTS), the Brugada syndrome (BrS) and the catecholaminergic polymorphic ventricular tachycardia (CPVT).

Most commonly respond to a mutation(s) in a gene(s) encoding cardiac ion channels or receptors and/or their regulatory proteins, the consequence in all cases being a modification in the cardiac action potential or in the intracellular calcium handling that leads to electrical instability and predisposition to life-threatening ventricular arrhythmias.



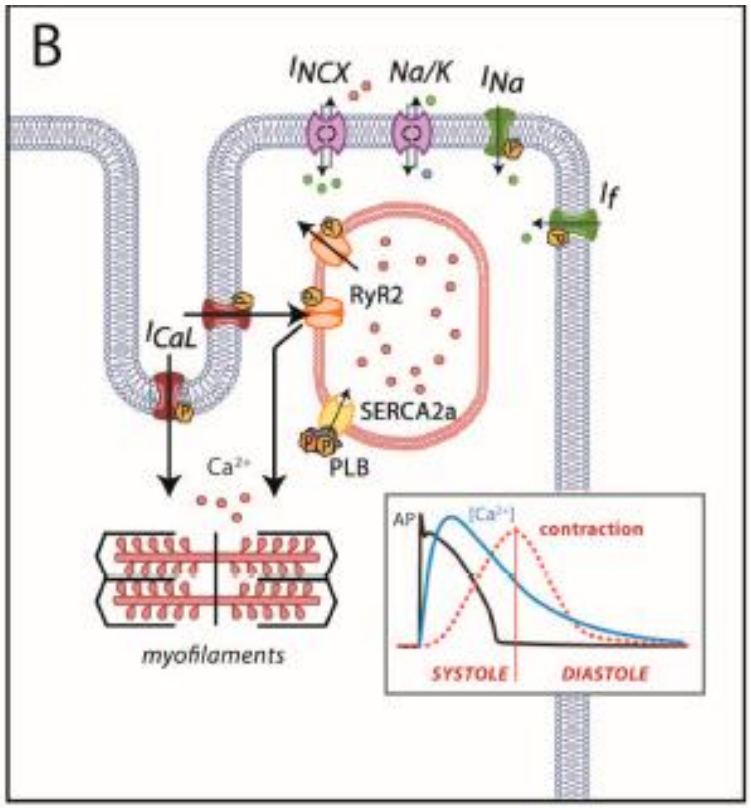


In contractile myocytes, APs are triggered by the acute entrance of sodium ions (Na+) inside the cell, resulting in an inward current (INa) that shifts the membrane potential from its resting state (-90 mV) to a depolarization state (+20 mV).

This phase is followed by the efflux of potassium (K+) ions through an outward current named Ito, which initiates cell repolarization.

In the plateau phase, a short period of constant membrane potential due to the balance between inward calcium (Ca2+) currents (ICaL) through the L-type voltage-dependent calcium channels (LTCC) and time-dependent delayed-rectifier outward K+ currents (mainly slow delayed-rectifier IKs and rapid delayed-rectifier IKr).

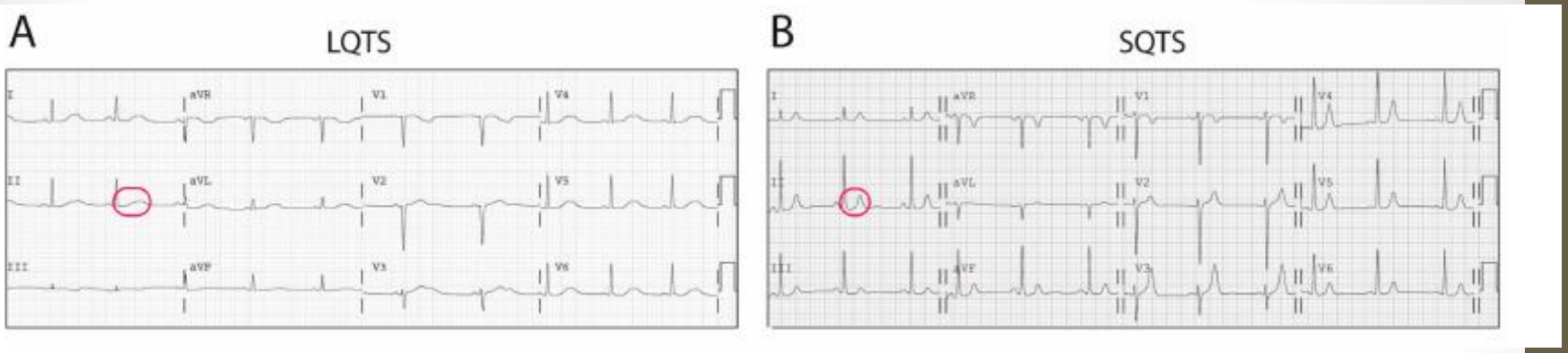
The balance between Ca2+ and K+ currents, therefore, determines the AP duration.
The basal and acetylcholine-dependent inward-rectifier K+ currents (IK1 and IKACh) control final repolarization and determine the resting membrane potential



Excitation-contraction coupling:

during action potential, Ca2+ entry in phase 2 induces a large release of Ca2+ from the sarcoplasmic reticulum through the RyR2 receptor that allows cell contraction.

After repolarization, Ca2+ is extruded from the cell through the Na+/Ca2+ exchanger (NCX) or taken back into the sarcoplasmic reticulum through SERCA2a to allow cell relaxation.



LQTS

13% may

experience SCD

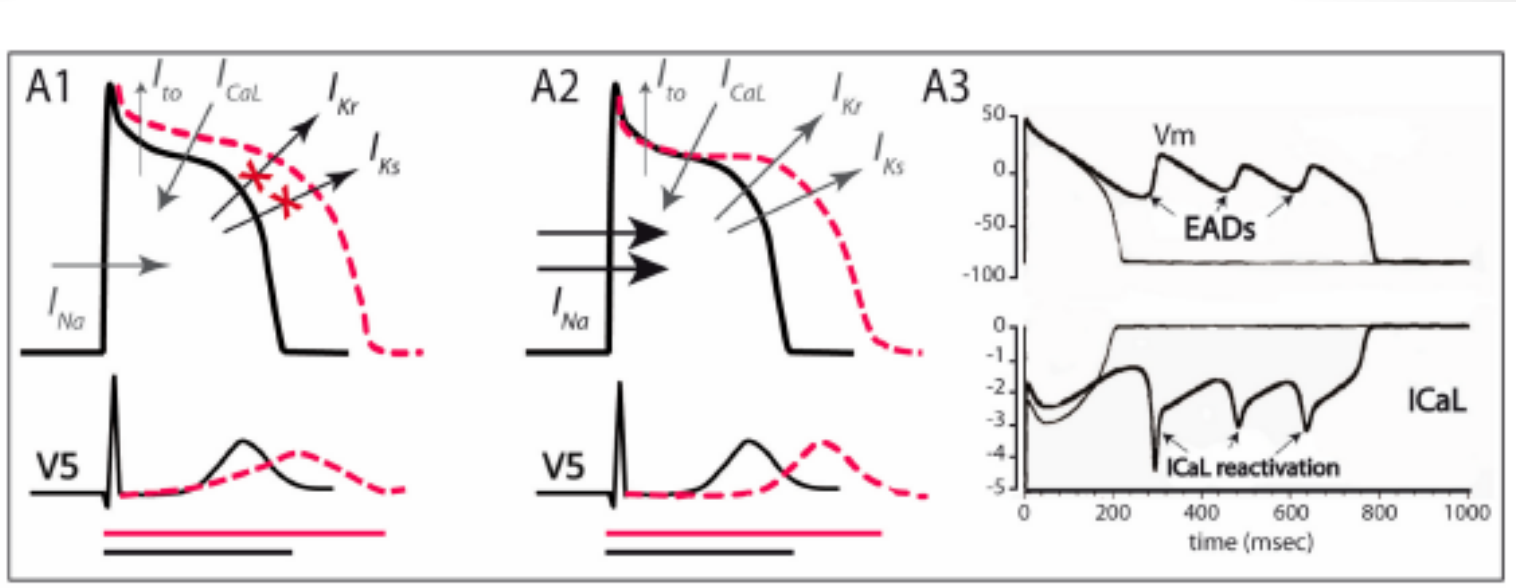
Schawartz-Moss score for Long-QT clinical diagnosis

FINDING	SCORE
ELECTROCARDIOGRAPHIC[†]	
Corrected QT interval, msec	
≥ 480	3
460–470	2
450 (in males)	1
Torsades de pointes[‡]	2
T-wave alternans	1
Notched T-wave in 3 leads	1
Low heart rate for age[§]	0.5

CLINICAL HISTORY	
Syncope[‡]	
With stress	2
Without stress	1
Congenital deafness	0.5
FAMILY HISTORY[¶]	
Family members with definite LQTS	1
Unexplained SCD in immediate family members < 30 yrs old	0.5

SCORE	PROBABILITY OF LQTS
≤ 1	Low
2–3	Intermediate
≥ 4	High

Schwartz et al., Circulation, 1993.



In LQTS, either by a **decrease in K+ currents** (A1) or an **increase in Na+ currents** (A2), AP duration is prolonged, and so is the QTc interval on the ECG.
This situation favors the development of early afterdepolarizations, the trigger of ventricular arrhythmias in LQTS patients.

Mutations in 20 different genes encoding direct or indirect mediators of these currents have been found in one or several families with LQTS.

Long-QT genes: ion channels subunits

Table 1. Mutations associated with the LQTS.

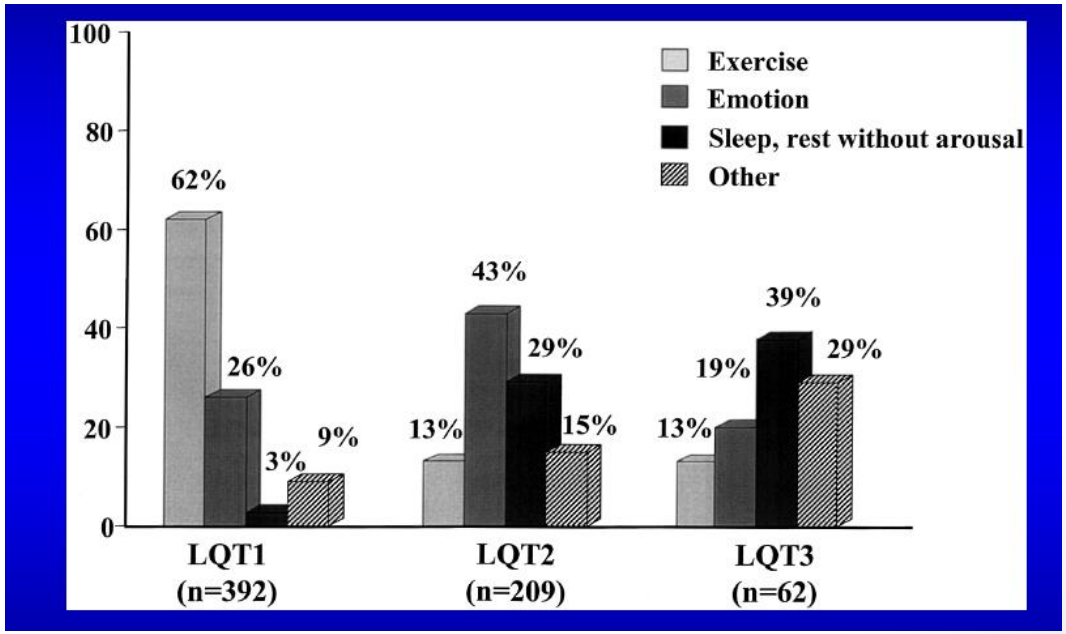
Gene	Protein	Current	Effect	Function	Prevalence
GENES ENCODING ION CHANNEL SUBUNITS					
1. Major LQTS-susceptibility genes					
KCNQ1	$K_V7.1$ (α-subunit of the voltage-dependent K^+ channel)	$\downarrow I_{Ks}$	loss-of-function	mediator of the slow component of the delayed rectifying potassium I_{Ks} current	≈40% (LQT1)
KCNH2	$K_V11.1$/hERG (α-subunit of the voltage-dependent K^+ channel)	$\downarrow I_{Kr}$	loss-of-function	mediator of the rapid component of the delayed rectifying potassium I_{Kr} current	≈30% (LQT2)
SCN5A	$Na_V1.5$ (α-subunit of the voltage-dependent Na^+ channel)	$\uparrow I_{Na}$	gain-of-function	mediator of the depolarizing inward sodium I_{Na} current	≈10% (LQT3)
2. Rare LQTS-susceptibility genes					
By reducing outward currents					
KCNE1	minK (β1-subunit of the voltage-dependent K^+ channel)	$\downarrow I_{Ks}$	loss-of-function	auxiliary protein modulator of $K_V7.1$ and the I_{Ks} current	<1%
KCNE2	MiRP1 (β2-subunit of the voltage-dependent K^+ channel)	$\downarrow I_{Kr}$	loss-of-function	auxiliary protein modulator of $K_V11.1$ and the I_{Kr} current	<1%
KCNJ2	Kir2.1 (inward rectifying K^+ channel)	$\downarrow I_{K1}$	loss-of-function, extra-cardiac manifestations	mediator of the inward rectifying potassium I_{K1} current	<1% (Andersen-Tawil syndrome, LQT7)
KCNJ5	Kir3.4 (G protein-activated inward rectifying K^+ channel 4)	$\downarrow I_{K,Ach}$	loss-of-function	mediator of the acetylcholine/adenosine-induced potassium $I_{K,Ach}$ current	<1%
By increasing inward currents					
SCN1B	β1-subunit of the voltage-dependent Na^+ channel	$\uparrow I_{Na}$	gain-of-function	auxiliary protein modulator of $Na_V1.5$ and the I_{Na} current	<1%
SCN4B	β4-subunit of the voltage-dependent Na^+ channel	$\uparrow I_{Na}$	gain-of-function	auxiliary protein modulator of $Na_V1.5$ and the I_{Na} current	<1%
CACNA1C	$Ca_V1.2$ (α1C-subunit of the voltage-dependent L-type Ca^{2+} channel)	$\uparrow I_{CaL}$	gain-of-function, extra-cardiac manifestations	mediator of the inward calcium I_{CaL} current	<1% (Timothy syndrome, LQT8)

Long-QT: genotype-phenotype

Patients with **LQT1** experience arrhythmias during exercise, particularly swimming, and often have broad-based T waves (IKs currents respond to progressive adrenergic stimulation such as that present during exercise).

Patients with **LQT2** have arrhythmias triggered by emotion, sudden or auditory stimuli, as well as low-amplitude or notched T waves. (IKr plays an important role in brisk increases in heart rate, LQT2 patients are prone to present arrhythmia-related symptoms in stress or emotional circumstances) .

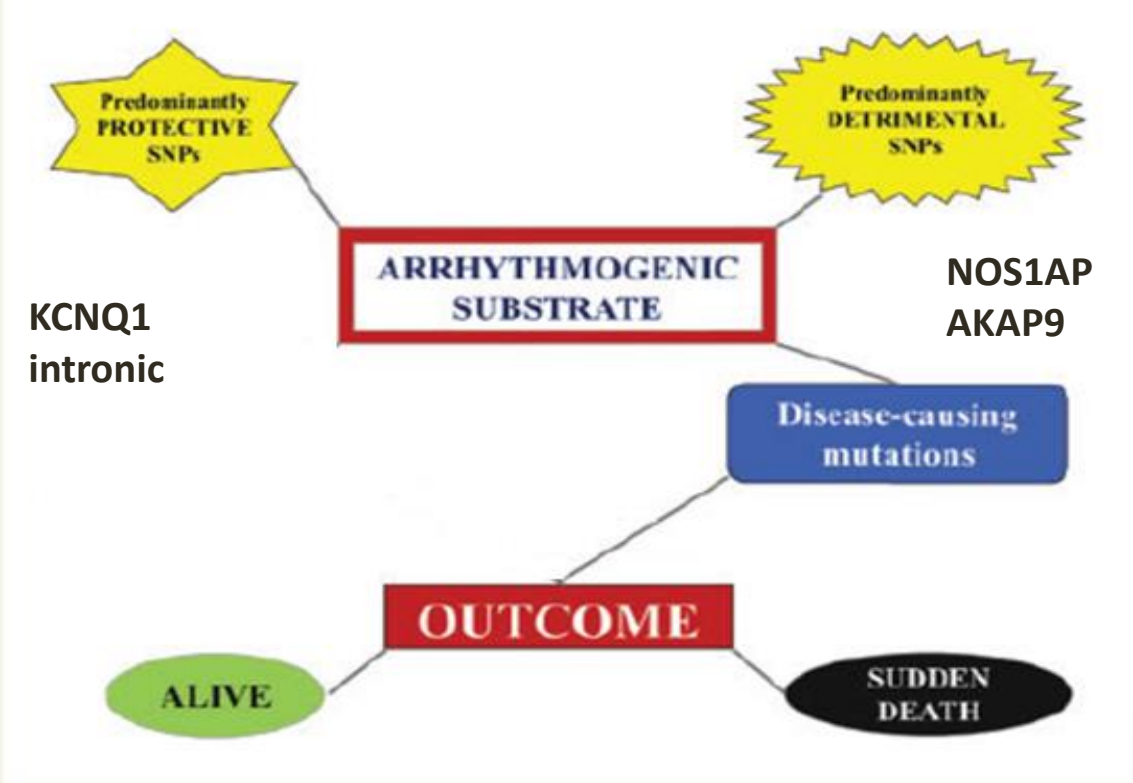
LQT3 carriers are often bradycardic with long, flat ST segments and SCD occurring during sleep. (The defect in INa becomes more evident with slow heart rates, so it is common that these patients develop arrhythmia-related symptoms in circumstances of bradycardia and typically during sleep) .



Long-QT genotype-phenotype: modifiers

The QTc is longer and the risk of cardiac events is higher in individuals with **digenic** or **compound mutations** than in monogenic carriers.

Synonymous single nucleotide polymorphisms (SNPs), known to modulate the QT interval in the general population can influence the severity of the phenotype.



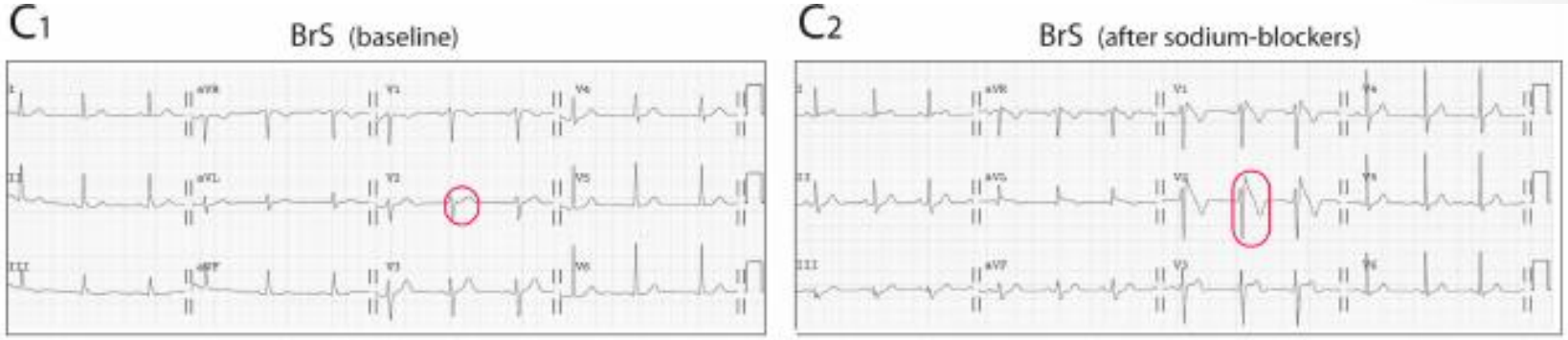
Long-QT genes: ion channels auxiliary proteins

Table 1. *Cont.*

Gene	Protein	Current	Effect	Function	Prevalence
			GENES ENCODING AUXILIARY PROTEINS		
			By reducing outward currents		
AKAP9	A-kinase anchor protein-9	$\downarrow I_{Ks}$	disruption of $K_V7.1$/PKA interaction	scaffolding protein assembling PKA and $K_V7.1$	<1%
			By increasing inward currents		
ANK2	ankyrin B	$\uparrow I_{CaL}$	disruption of Na^+/K^+ exchanger, Na^+/Ca^{2+} exchanger/IP_3 interaction	scaffolding protein assembling Na^+/K^+ exchanger, Na^+/Ca^{2+} exchanger and IP_3 receptor	<1%
CALM1	calmodulin (CaM)	$\uparrow I_{CaL}$	disorder in $Ca_V1.2$ functioning	essential Ca^{2+} sensor, signal-transducing protein modulator of $Ca_V1.2$ (and others)	<1%
CALM2	calmodulin (CaM)	$\uparrow I_{CaL}$	disorder in $Ca_V1.2$ functioning	essential Ca^{2+} sensor, signal-transducing protein modulator of $Ca_V1.2$ (and others)	<1%
CALM3	calmodulin (CaM)	$\uparrow I_{CaL}$	disorder in $Ca_V1.2$ functioning	essential Ca^{2+} sensor, signal-transducing protein modulator of $Ca_V1.2$ (and others)	<1%
SNTA1	α1-syntrophin	$\uparrow I_{Na}$	disruption of $Na_V1.5$/NOS-PMCA4b complex interaction	scaffolding protein that associates $Na_V1.5$ channels with the NOS-PMCA4b complex	<1%
TRDN	triadin	$\uparrow I_{CaL}$	reduction of I_{CaL} inactivation	regulator of ryanodine receptors and $Ca_V1.2$	<1%
			Less established mechanisms		
CAV3	caveolin-3	$\uparrow I_{Na}?/\downarrow I_{K1}?$	changes in membrane expression of $Na_V1.5$/Kir2.1	scaffolding protein regulating ion channels in caveolae	<1%
TRPM4	Transient receptor potential melastatin 4		loss-of-function	regulator of conduction and cellular electrical activity which impact heart development	<1%
RYR2	ryanodine receptor 2 (RyR2)		*not described*	mediator of Ca^{2+} release from the SR	<1%

↑: increased current; ↓: decreased current; ?: suspected but not confirmed mechanism.

Brugada Syndrome



The **BrS** is diagnosed in patients with a characteristic pattern of **ST-segment elevation** (defined as coved-type or type 1) 2 mm in 1 leads from V1 to V2 positioned in the second, third, or fourth intercostal space .

The ECG may be observed either spontaneously or after being unmasked by a provocative drug test with a sodium-channel blocker (test ajmalina, test flecainide) .

Sodium-channel blockers are antiarrhythmic agents that, by inhibiting INa, increase the imbalance between inward and outward currents in early phases of the AP, and therefore may exacerbate the phenotypic expression of the BrS

Brugada Syndrome

The **prevalence of the BrS** is highly variable in different geographical areas, but it has been estimated in 5/10,000 inhabitants.
BrS could be responsible for 4–12% of all SCD and for up to **20% of SCD in subjects without structural heart disease .**

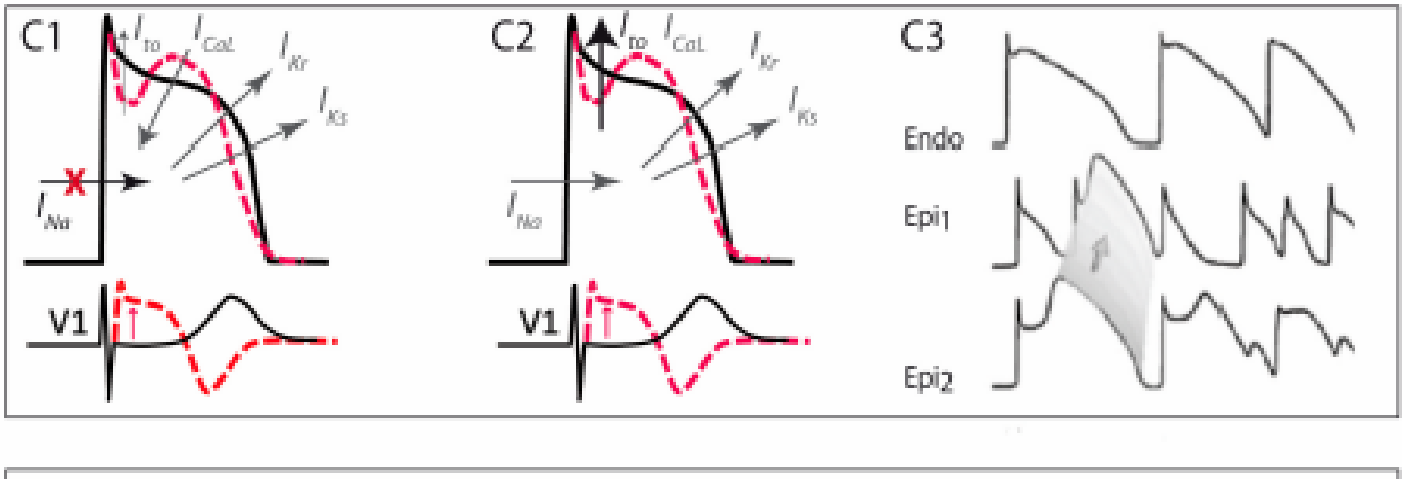
Patients with BrS usually remain asymptomatic, but syncope or SCD due to ventricular arrhythmias have been described in 17–42% of diagnosed individuals .
Age at presentation is around the **third-fourth decade** of life.

For SCN5A-mutation carriers (the gene most commonly affected in BrS patients), like in the case of LQT3 patients, **symptoms typically appear during rest or sleep** .

Gender differences have been reported, with the BrS being 8–10 times more prevalent in **men**, in whom the syndrome entails a worse prognosis.

A history of previous syncope, a spontaneous (not-induced) type-1 ECG and the inducibility of ventricular arrhythmias during programmed electrical stimulation (a catheter-based invasive test to test arrhythmia susceptibility) are all predictors of future SCD in BrS patients.

Brugada Syndrome



In BrS, a **decrease in Na+ currents** (C1) or, less commonly, an **increase in Ito currents** (C2); produces a ionic imbalance in early repolarization, giving rise to the characteristic ST-segment elevation seen in the ECG.

The consequent epicardial and transmural dispersion of repolarization favors ventricular arrhythmias by a mechanism of phase-2 reentry (C3).

Brugada Syndrome genes

Table 3. Mutations associated with the BrS.

Gene	Protein	Current	Effect	Function	Prevalence
GENES ENCODING ION CHANNEL SUBUNITS					
1. Major BrS-susceptibility genes					
SCN5A	$Na_V1.5$ (α-subunit of the voltage-dependent Na^+ channel)	↓ I_{Na}	loss-of-function	mediator of the depolarizing inward sodium I_{Na} current	≈25% (BrS1)
2. Rare BrS-susceptibility genes					
By decreasing inward currents					
SCN1B	β1-subunit of the voltage-dependent Na^+ channel	↓ I_{Na}	loss-of-function	auxiliary protein modulator of $Na_V1.5$ and the I_{Na} current	<1%
SCN2B	β2-subunit of the voltage-dependent Na^+ channel	↓ I_{Na}	loss-of-function	auxiliary protein modulator of $Na_V1.5$ and the I_{Na} current	<1%
SCN3B	β3-subunit of the voltage-dependent Na^+ channel	↓ I_{Na}	loss-of-function	auxiliary protein modulator of $Na_V1.5$ and the I_{Na} current	<1%
SCN10A	$Na_V1.8$ (α-subunit of the neuronal voltage-dependent Na^+ channel)	↓ I_{Na}	loss-of-function	mediator of the depolarizing phase of the neural AP, associated with pain perception	≈10%?
CACNA1C	$Ca_V1.2$ (α1C-subunit of the volatge-dependent L-type Ca^{2+} channel)	↓ I_{CaL}	loss-of-function, combined phenotype of BrS and SQTS	mediator of the inward calcium I_{CaL} current	<1%
CACNB2b	β2-subunit of the voltage-dependent L-type Ca^{2+} channel	↓ I_{CaL}	loss-of-function, combined phenotype of BrS and SQTS	auxiliary protein modulator of $Ca_V1.2$ and the I_{CaL} current	<1%
By increasing outward currents					
KCND3	$K_V4.3$ (α-subunit of the voltage-dependent K^+ channel)	↑ I_{to}	gain-of-function	mediator of the transient outward K^+ I_{to} current	<1%
KCNE3	minK-related peptide 2 (β-subunit of the voltage-dependent K^+ channel)	↑ I_{to}	gain-of-function	regulator of $K_V4.3$	<1%
KCNAB2	β2-subunit of the voltage-dependent K^+ channel	↑ I_{to}	gain-of-function	interaction with $K_V4.3$	<1%
KCND2	$K_V4.2$ (voltage-dependent K^+ channel)	↑ I_{to}	gain-of-function	contributor to the transient outward K^+ I_{to} current	<1%
KCNE5	minK-related peptide 4 (β-subunit of the voltage-dependent K^+ channel)	↑ I_{to}	gain-of-function	inhibitor of the delayed rectifying $K_V7.1$ channel and modulator of $K_V4.3$	<1%

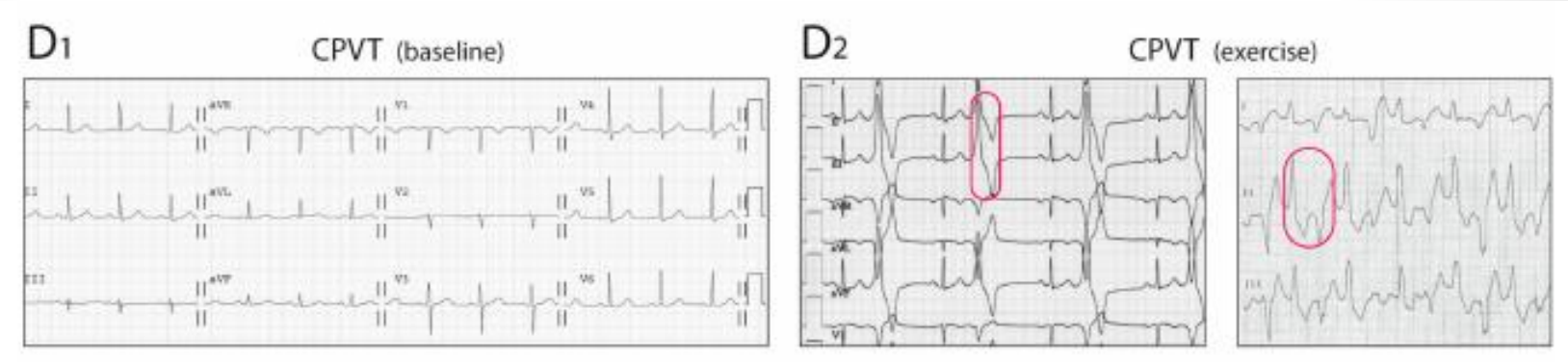
Brugada Syndrome genes

Table 3. *Cont.*

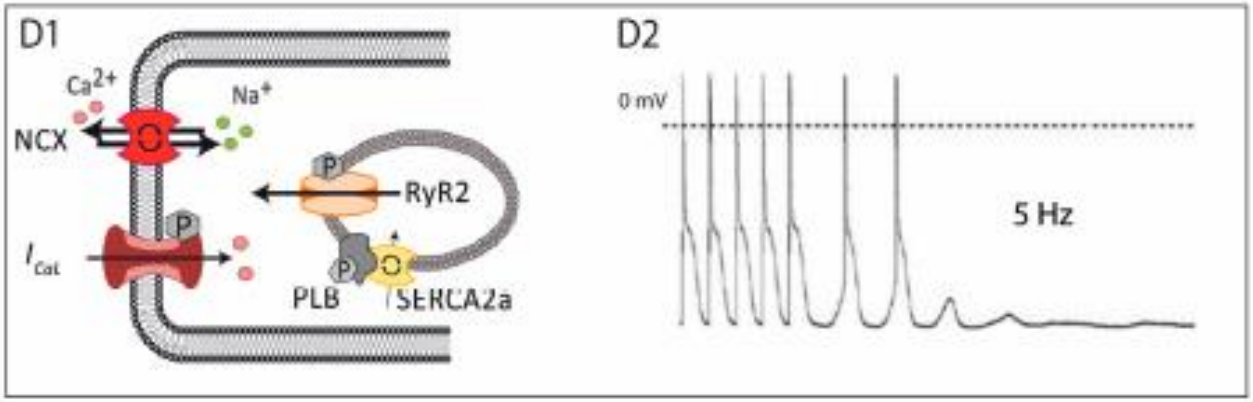
Gene	Protein	Current	Effect	Function	Prevalence
KCNJ8	Kir6.1 (inward-rectifier K^+ channel, subunit of the ATP-sensitive K^+ channel)	↑ $I_{K\text{-}ATP}$	gain-of-function	mediator of the $I_{K\text{-}ATP}$ currents	<1%
ABCC9	SUR2 (sulfonylurea receptor, subunit of the ATP-sensitive K^+ channel)	↑ $I_{K\text{-}ATP}$	gain-of-function	modulator of $I_{K\text{-}ATP}$ currents	<1%
KCNH2	K_V11.1/hERG (α-subunit of the voltage-dependent K^+ channel)	↑ I_{Kr}	gain-of-function	mediator of the rapid component of the delayed rectifying potassium I_{Kr} current	<1%
			Less established mechanisms		
CACNA2D1	α2/δ subunit of the volatge-dependent L-type Ca^{2+} channel	↓ I_{CaL}?	loss-of-function?, combined phenotype of SQTS and BrS	auxiliary protein modulator of Ca_V1.2 and the I_{CaL} current	<1%
HCN4	hyperpolarization-activated, cyclic nucleotide-gated ion channel 4	↓ I_f?	loss-of-function?	mediator of the pacemaker current, I_f	<1%
TRPM4	Transient receptor potential melastatin 4		loss-of-function/gain-of-function	regulator of conduction and cellular electrical activity which impact heart development	<1%
			GENES ENCONDING AUXILIARY PROTEINS		
FGF12	fibroblast growth factor 12	↓ I_{Na}	interaction with Na_V1.5 trafficking	modulator of Nav1.5 and the I_{Na} current	<1%
GPD1L	glycerol-3-phosphate dehydrogenase 1-like	↓ I_{Na}	interaction with Na_V1.5 trafficking	modulator of Na1.5 and the I_{Na} current	<1%
SLMAP	sarcolemma associated protein (striatin-interacting phosphatase and kinase complex)	↓ I_{Na}	interaction with Na_V1.5 trafficking	present in the T-tubules, regulator of excitation-contraction coupling	<1%
PKP2	plakophillin-2	↓ I_{Na}	changes in Na_V1.5 expression in intercalated disc	binds to and modulates Na_V1.5 and the I_{Na} current	<1%
SEMA3A	semaphorin-3A	↑ I_{to}	loss-of-function	inhibitor of the K_V4.3 channel	<1%
			Less established mechanisms		
RANGRF	MOG1 (multicopy suppressor of *Gsp1*)	↓ I_{Na}?	interaction with Na_V1.5 trafficking	involved in nuclear protein import—regulates cell surface location of Na_V1.5	<1%
HEY2	CHF1 (cardiovascular helix-loop-helix factor 1)	↑ I_{to}?	interaction with KCNIP2	transcriptional regulator of cardiac electrical function	<1%

↑: increased current; ↓: decreased current; ?: suspected but not confirmed mechanism.

CPVT



CPVT. ECG is normal at baseline (D1), but premature ventricular complexes and occurrence of bidirectional tachycardia appear with exercise (D2).



The molecular basis of CPVT relies on an **abnormal release of Ca2+ from the SR in response to adrenergic stimulation.** Excess Ca2+ is handled by the cell membrane Na+/Ca2+-exchanger, which transports three Na+ ions into the cell per single Ca2+ ion extruded, creating a net depolarizing current that can lead to arrhythmogenesis by a mechanism called delayed afterdepolarizations.

CPVT

CPVT: Estimated prevalence of **1 in 10,000**

CPVT is an inherited disorder with both autosomal dominant and recessive patterns of transmission.

An **incomplete penetrance** has been reported (around 15% of all patients are silent carriers), but CPVT is usually an aggressive disorder, with symptoms likely appearing during childhood and a high incidence of cardiac events in follow-up (around **80% of untreated patients will experiment an arrhythmia, and up to 30% SCD**) .

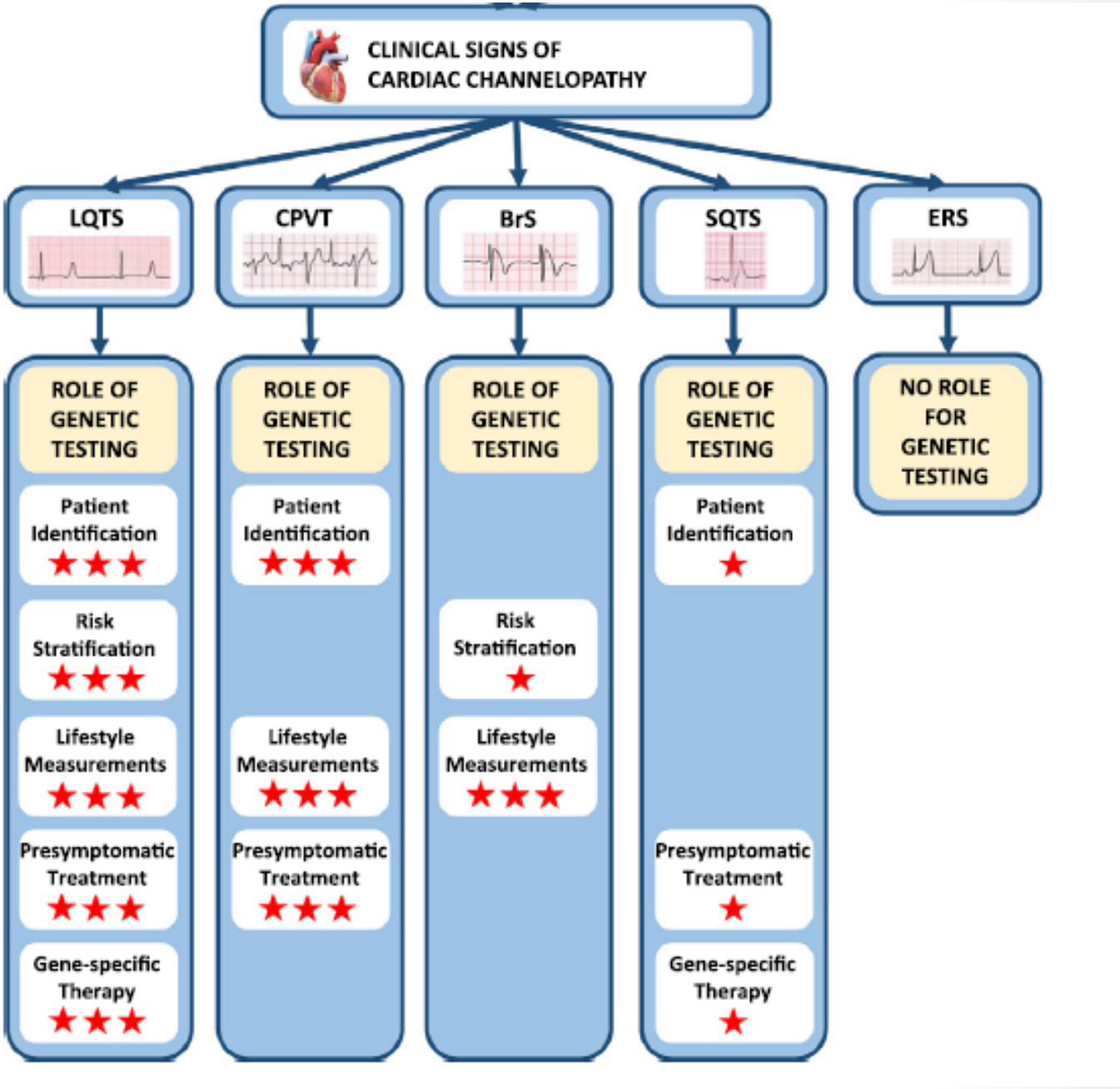
Arrhythmia-related symptoms such as syncope typically occur in adrenergically mediated circumstances such as **exercise or emotional stress**.

Male-sex seems to be a risk factor in patients carrying mutations in RYR2.

CPVT genes

Table 4. Mutations associated with the CPVT.

Gene	Protein	Effect	Function	Prevalence
GENES ENCODING ION CHANNELS AND AUXILIARY PROTEINS				
1. Major CPVT-susceptibility genes				
RYR2	ryanodine receptor 2 (RyR2)	cytoplasmic Ca^{2+} overload, due to Ca^{2+} leak from the SR	mediator of the release of stored Ca^{2+} ions from the SR	≈50–60% (CPVT1)
CASQ2	calsequestrin 2	decreased Ca^{2+} content in the SR and abnormal Ca^{2+} regulation	Ca^{2+} storage protein, controls Ca^{2+} release from the SR	≈5%
2. Rare CPVT-susceptibility genes				
TRDN	triadin	cytoplasmic Ca^{2+} overload, due to Ca^{2+} leak from the SR	regulator of ryanodine receptors, controls the Ca^{2+} release from the SR	<1%
CALM1	calmodulin (CaM)	Ca^{2+} leak from the SR due to loss of interaction CaM-RyR2	essential Ca^{2+} sensor, signal-transducing protein modulator of $Ca_V1.2$ or RyR2 (and others)	<1%
CALM2	calmodulin (CaM)	reduction in Ca^{2+}-binding affinity in the CaM C-domain	essential Ca^{2+} sensor, signal-transducing protein modulator of $Ca_V1.2$ or RyR2 (and others)	<1%
CALM3	calmodulin (CaM)	reduction in Ca^{2+}-binding affinity in the CaM C-domain and leak from the SR	essential Ca^{2+} sensor, signal-transducing protein modulator of $Ca_V1.2$ or RyR2 (and others)	<1%
TECLR	trans-2,3-enoyl-CoA reductase- like	decreased Ca^{2+} content in the SR and abnormal Ca^{2+} regulation	participates in the synthesis of fatty acids	<1%


CLINICAL SIGNS OF CARDIAC CHANNELOPATHY
LQTS
CPVT
BrS
SQTS
ERS
ROLE OF GENETIC TESTING
Patient Identification
Risk Stratification
Lifestyle Measurements
Presymptomatic Treatment
Gene-specific Therapy
ROLE OF GENETIC TESTING
Patient Identification
Lifestyle Measurements
Presymptomatic Treatment
ROLE OF GENETIC TESTING
Risk Stratification
Lifestyle Measurements
ROLE OF GENETIC TESTING
Patient Identification
Presymptomatic Treatment
Gene-specific Therapy
NO ROLE FOR GENETIC TESTING

International position statements recommend genetic test **in LQTS and CPVT as a class I indication** (a causative mutation can be identified in 70-80% and 60-70% of probands)

Cascade genetic screening strongly indicated (**class I**): preclinical diagnosis and prevention

Classes of Recommendations	Definition	Suggested wordiing to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

In LQTS arrhythmogenic triggers, response to therapy and prognosis differ based on disease causing gene and sometimes to specific mutation

LQT1 (KCNQ1): high risk during physical activity but very well protected by beta-blockers
LQT2 (KCNH2): high risk with sudden noise and post-partum period; reasonably good response to beta-blockers
LQT3 (SCN5A) a theraphy with sodium channel blockers can be considered in addition to beta blockade.
CALM1-3 (Calmodulin genes): very severe phenotype and poor response to therapies

In **SQTS** a disease causing mutation is identified in less than **5-10% of cases** with limited impact on clinical management.
Genetic testing is a Class IIb recommendation.

Classes of Recommendations	Definition	Suggested wordiing to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended/is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	*Weight of evidence/opinion is in favour of usefulness/efficacy.*	Should be considered
Class IIb	*Usefulness/efficacy is less well established by evidence/opinion.*	May be considered
Class III	Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful.	Is not recommended

In **BrS Genetic testing is a Class IIa recommendation**

Cascade genetic screening strongly indicated(class I) in all channelopathies :preclinical diagnosis and prevention

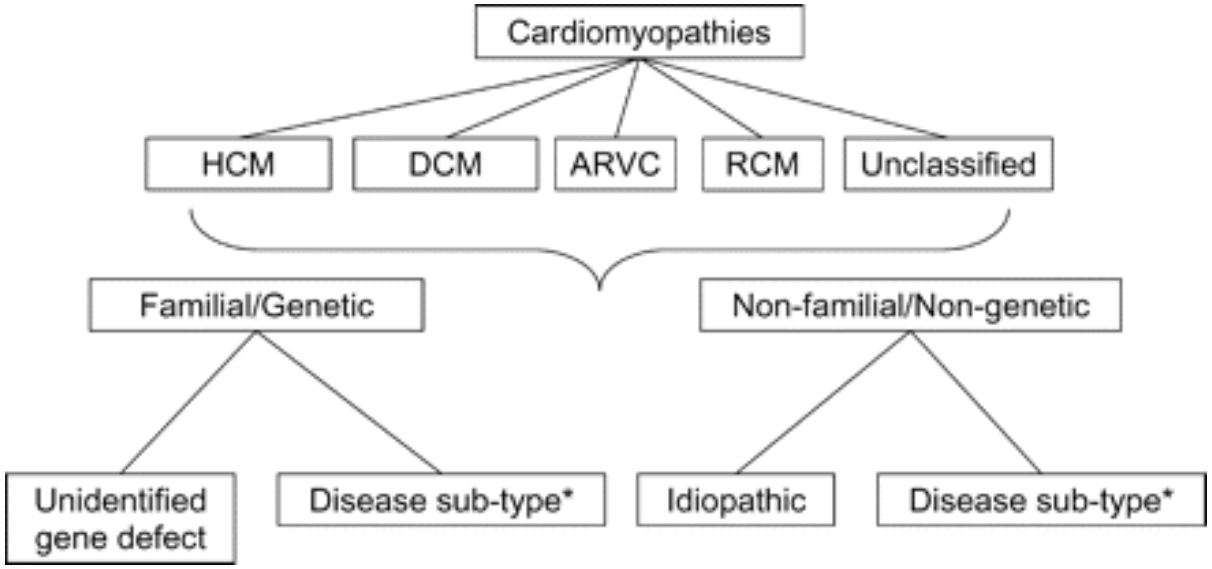
Carefull consideration in **asyntomatic and children or adolescent**:

Genetic testing is recommended under the age of 4 years in families with channellopathies and after the age of 10 years in families with structural progressive cardiomyopathies, unless condition of anxiety and the need for realistic lifestyle planning and clinical follow-up might advise earlier testing.

Cardiomyopathies

Position statement from the european society of cardiology (ESC) - 2008

DEFINITION: myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.



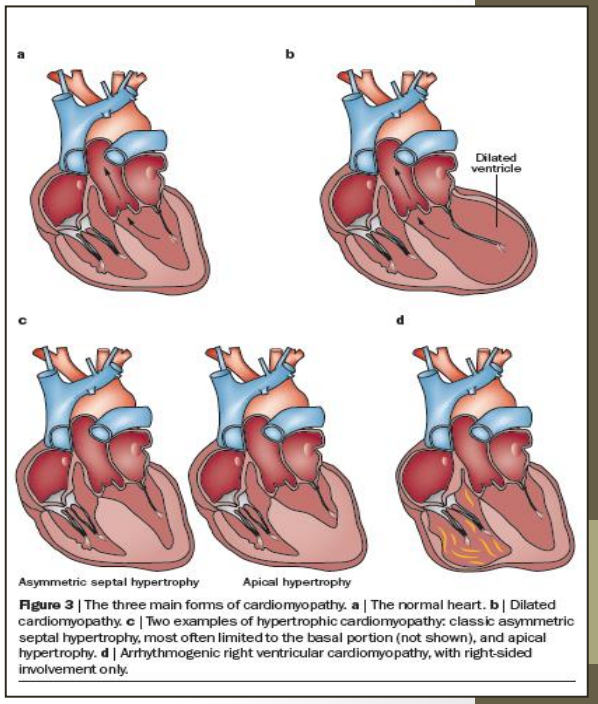


Figure 3 | The three main forms of cardiomyopathy. **a** | The normal heart. **b** | Dilated cardiomyopathy. **c** | Two examples of hypertrophic cardiomyopathy: classic asymmetric septal hypertrophy, most often limited to the basal portion (not shown), and apical hypertrophy. **d** | Arrhythmogenic right ventricular cardiomyopathy, with right-sided involvement only.

The recommendation for clinical genetic testing in CMP is variable.

The **Heart Rhythm Society and the European Heart Rhythm Association** recommend clinical genetic testing for all patients with a clinical diagnosis of HCM, and for DCM patients with significant cardiac conduction disease.

The **European Society of Cardiology** recommends genetic testing for patients with HCM who fulfill diagnostic criteria when it enables cascade screening of their relatives.

The **American College of Cardiology Foundation** and the **American Heart Association** recommend genetic testing only for patients with an atypical presentation of HCM or when another genetic condition is expected to be the cause.

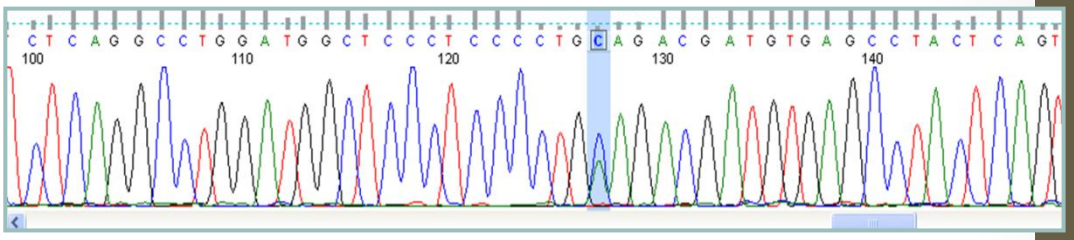
Genetic testing in cardiomyopathies often impact families even more than the affected individual.

Identification of causative mutations facilitates pre-symptomatic diagnosis of family members, clinical surveillance and reproductive advice.

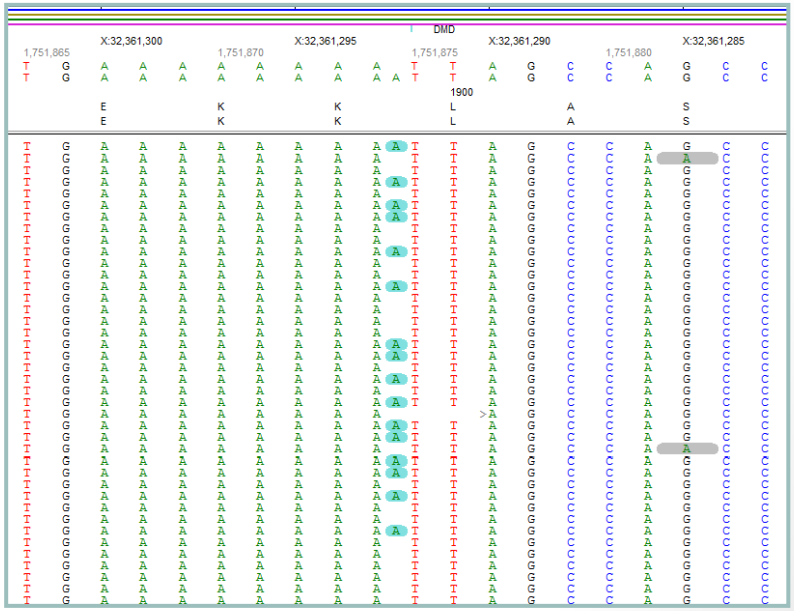
Genetic Counselling by trained professionals is recommended for family approach and for correct interpretation of genetic tests

Genetic analysis in CMP is mainly based on sequencing

Gene-by-gene Sanger sequencing



<u>Massively parallel sequencing (MPS)</u> using high throughput sequencing technologies allows to interrogate several genes simultaneously



The choice of the methodology for genetic analysis in CMP depends on PREVALENCE, CLINICAL FEATURES and DEGREE OF HETEROGENEITY of the specific CMP subtype, MOLECULAR STRUCTURE of involved genes, LABORATORY SKILLS

Cardiomyopathies are frequent and medically important diseases with high genetic and allelic heterogeneity

Population Prevalence of major cardiomyopathies:

- HCM - 1:500
- DCM - 1:2,500
- ACM – 1- 5,000

Genetic heterogeneity: more than 100 genes implicated in clinical and research studies with majority being sarcomeric or cytoskeletal genes

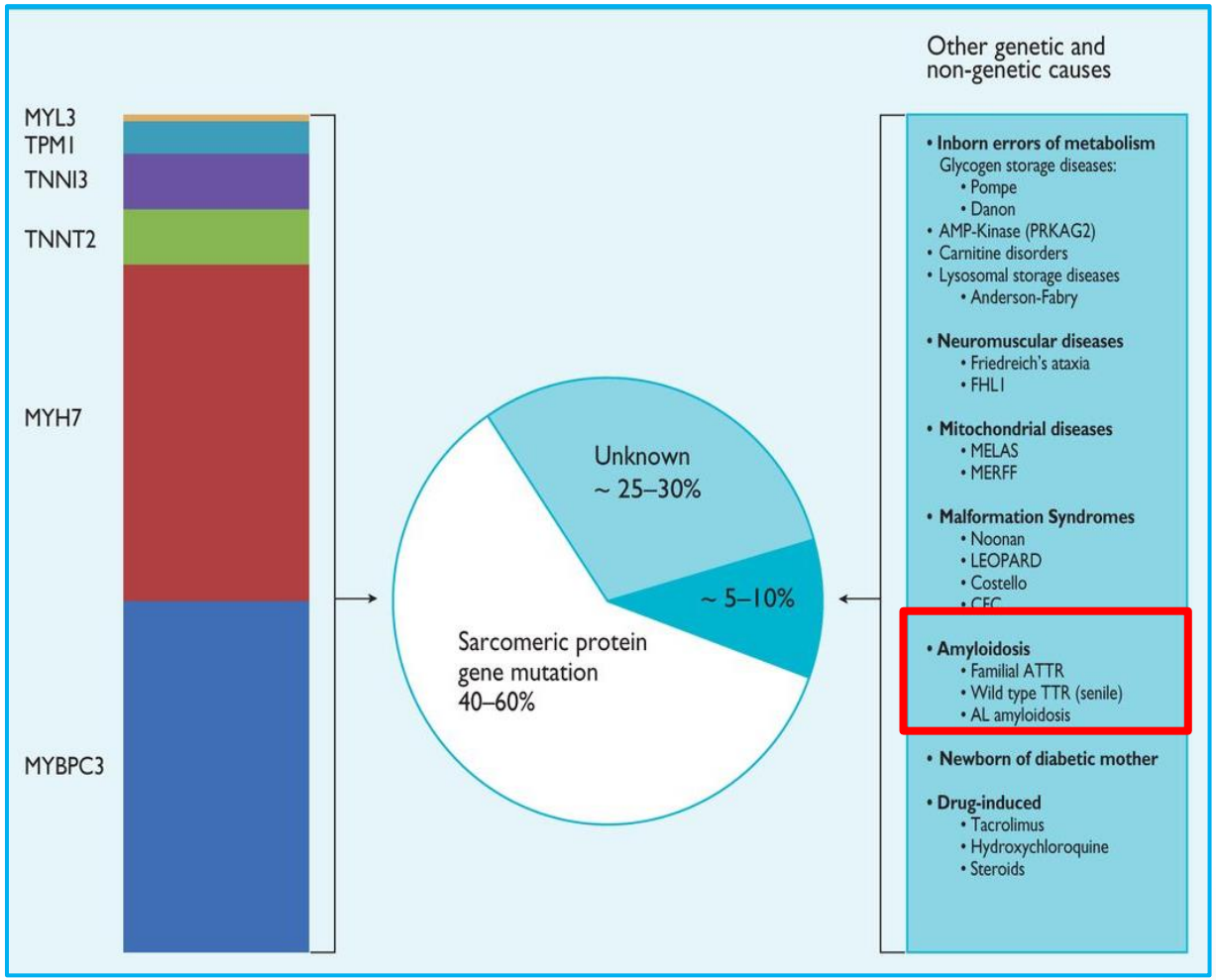
Allelic heterogeneity: approximately 1000 unique variants associated with HCM

Gene-by-Gene analysis trought Sanger Sequencing : when

- Distinctive clinical features (mTTR- related cardiomyopathy; Fabry disese…)
- Small single gene with multiple phenotypes (phenotypic heterogeneity) (TTR; DMD; LMNA…)
- Time restriction (prenatal, therapeutic choices) (LMNA,DMD,GAA…)

In HCM

5-10% of adult cases are caused by other genetic disorders (metabolic, neuromuscular, chromosomic, genetic syndromes).



OVERVIEW OF TTR AMYLOIDOSIS

- Amyloidosis is a disorder of protein folding
- Classification of amyloid type by precursor protein
- Transthyretin (TTR) aka prealbumin 55 k-Da protein synthesized by liver > 100 known SNPs
- Mutations alter thermodynamic properties of protein to favor mis-folding and aggregation as amyloid fibrils
  - Variant TTR amyloidosis
  - Autosomal dominant inheritance pattern (50% likelihood of transmission)

Variant TTR amyloidosis results from single nucleotide polymorphisms (SNPs) that cause nerve, cardiac, and soft tissue amyloid fibril deposition (alone or in combination)

Mutations vary by geographic distribution thus ancestry can predict mutation

Penetrance is incompletely understood however there are clear gender and age associations with phenotypic expression

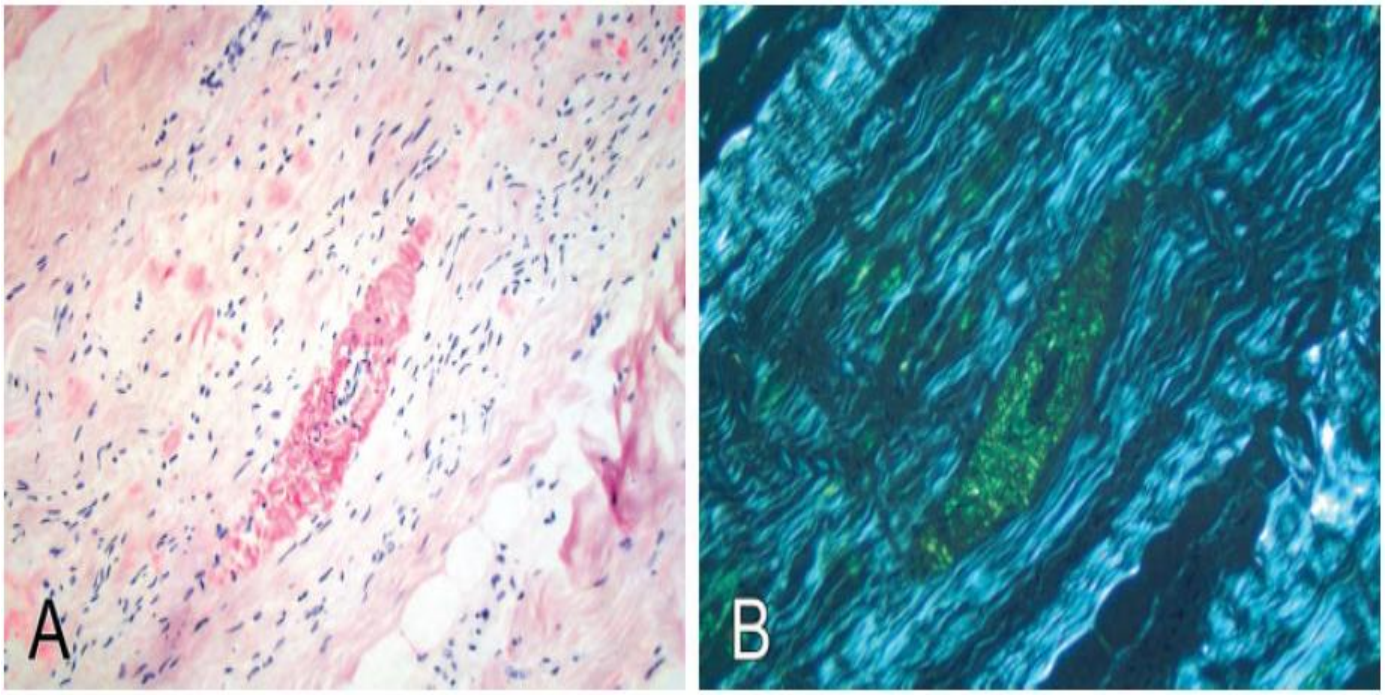
Clinically it can be difficult to distinguish variant TTR from ATTRwt, but easier to differentiate from AL

Novel approaches using TTR stabilization or suppression agents hold great promise to treat variant TTR disease

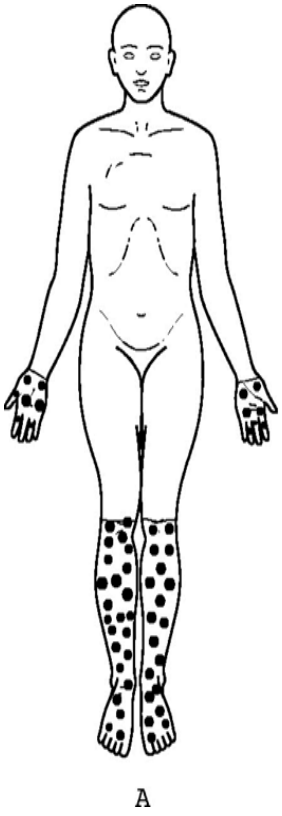
TTR amyloid deposition in nervous system

- Nerves
  - polyneuropathy
  - small nerve fiber neuropathy
    - pain & temperature sensation
    - autonomic functions
- Meningeal brain vessels (uncommon)

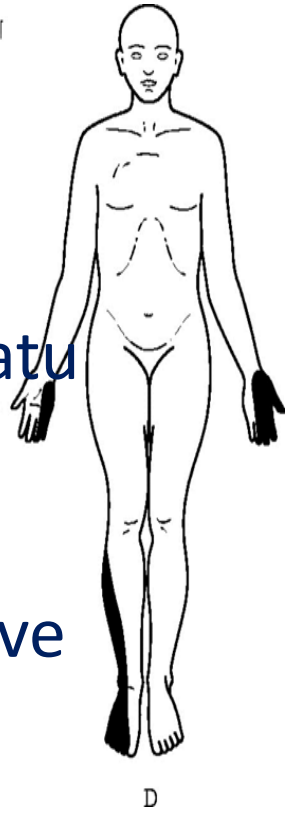
Amyloid deposition in nerves



Hereditary ATTR polyneuropathy (TTR-FAP)



- progressive
- painful*
- ↓muscle strength
- ↓ sensation
  - pain/temperatu re*
  - touch
  - vibration/move ment
- unsteadiness



* small nerve fibers: small fiber neuropathy

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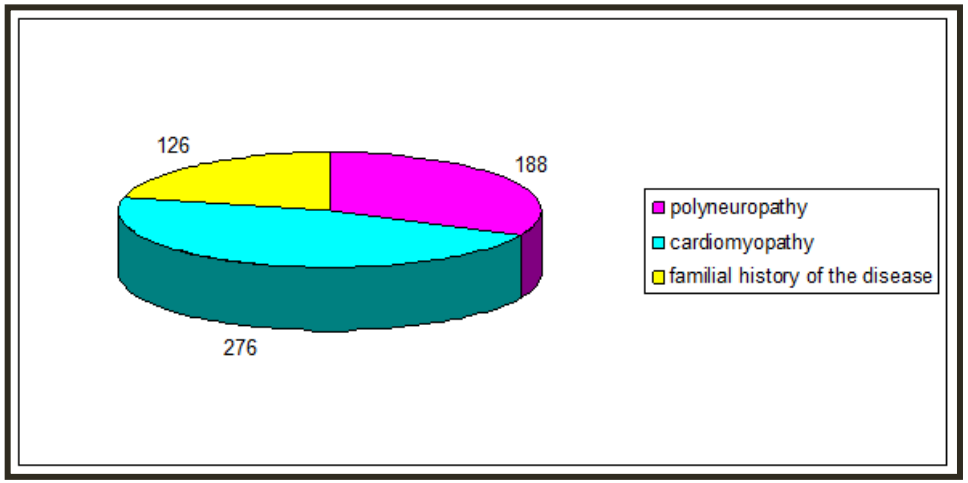
ATTR autonomic neuropathy*

- dizziness/light-headedness (orthostatic hypotension)
- urination problems
- erectile problems
- constipation, diarrhoea
- nausea, early satiety (gastroparesis)
- dry eyes/mouth (sicca)
- altered sweating
- irregular heartbeat, palpitations

* small nerve fibers: small fiber neuropathy

TTR analysis by sanger sequencing of the 4 gene exons in 590 patients with different prevalent phenotype.

Five mutations accounts for 86% of positive patients.
The mutation Ile68Leu represents 63% of our cohort of cases with cardiac involvement.



Distribution of TTR mutations in 100 index cases

Mutations	Ile 68 Leu	Phe 64 Leu	Val 30 Met	Glu 89 Gln	Thr 49 Ala	Ser 23 Asn	Val 122 Ile	Gly 47 Arg	Arg 34 Thr	Gly 53 Glu	Ala 81 Thr	Gln 92 Lys	Glu 54 Lys	Glu 62 Lys	Thr 59 Lys	Val 14 Leu Novel mutation
TOTAL 99	36 (36%)	20 (20%)	15 (14%)	11 (12%)	4 (4%)	2 (2%)	2 (2%)	2 (2%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	1 Cardiac amyloidosis

86%

INVESTIGATIONAL THERAPEUTICS FOR VARIANT TTR AMYLOID CARDIOMYOPATHY

Agent	Mechanism	Trial	Identifier	Design	Endpoint	Comments
Tafamidis	stabilization	ATTR-ACT/Pfizer	NCT 01994889	20 mg vs. 80 mg vs. placebo	All-cause mortality + cardiovasc. hospitalization	PO daily for 30 months
Revusiran	Suppression (RNAi)	ENDEAVOR/Alnylam	NCT 02319005	500 mg vs. placebo	6 min walk duration	SC weekly for 18 months
Patisiran	Suppression (RNAi)	APOLLO/Alnylam	NCT 01960348	Active drug vs. placebo	NIS+7 score	IV weekly for 18 months
ISIS-TTR-Rx	Suppression (Antisense ODN)	ISIS	NCT 01737398	300 mg vs. placebo	NIS+7 score	SC weekly for 65 weeks

N Engl J Med. 2018 Jul 5;379(1):22-31. doi: 10.1056/NEJMoa1716793.

Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis.

Benson MD[1], Waddington-Cruz M[1], Berk JL[1], Polydefkis M[1], Dyck PJ[1], Wang AK[1], Planté-Bordeneuve V[1], Barroso FA[1], Merlini G[1], Obici L[1], Scheinberg M[1], Brannagan TH 3rd[1], Litchy WJ[1], Whelan C[1], Drachman BM[1], Adams D[1], Heitner SB[1], Conceição I[1], Schmidt HH[1], Vita G[1], Campistol JM[1], Gamez J[1], Gorevic PD[1], Gane E[1], Shah AM[1], Solomon SD[1], Monia BP[1], Hughes SG[1], Kwoh TJ[1], McEvoy BW[1], Jung SW[1], Baker BF[1], Ackermann EJ[1], Gertz MA[1], Coelho T[1].

N Engl J Med. 2018 Jul 5;379(1):11-21. doi: 10.1056/NEJMoa1716153.

Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis.

Adams D[1], Gonzalez-Duarte A[1], O'Riordan WD[1], Yang CC[1], Ueda M[1], Kristen AV[1], Tournev I[1], Schmidt HH[1], Coelho T[1], Berk JL[1], Lin KP[1], Vita G[1], Attarian S[1], Planté-Bordeneuve V[1], Mezei MM[1], Campistol JM[1], Buades J[1], Brannagan TH 3rd[1], Kim BJ[1], Oh J[1], Parman Y[1], Sekijima Y[1], Hawkins PN[1], Solomon SD[1], Polydefkis M[1], Dyck PJ[1], Gandhi PJ[1], Goyal S[1], Chen J[1], Strahs AL[1], Nochur SV[1], Sweetser MT[1], Garg PP[1], Vaishnaw AK[1], Gollob JA[1], Suhr OB[1].

Treatment of TTR-FAP

- at present no cure
- symptom management (can be difficult)
- combat amyloid deposition
  - slow progression
  - prevention & delay (carriers)
- rehabilitation & supportive care
- multidisciplinary care

Ando et al. Orphanet Journal of Rare Diseases 2013, 8:31
http://www.ojrd.com/content/8/1/31

ORPHANET JOURNAL OF RARE DISEASES

REVIEW Open Access

Guideline of transthyretin-related hereditary amyloidosis for clinicians

Yukio Ando[1,13*], Teresa Coelho[2], John L Berk[3], Márcia Waddington Cruz[4], Bo-Göran Ericzon[5], Shu-ichi Ikeda[6], W David Lewis[7], Laura Obici[8], Violaine Planté-Bordeneuve[9], Claudio Rapezzi[10], Gerard Said[11] and Fabrizio Salvi[12]

SUPPLEMENT ARTICLE

OPEN

CURRENT OPINION

First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy

David Adams[a], Ole B. Suhr[b], Ernst Hund[c], Laura Obici[d], Ivailo Tournev[e,f], Josep M. Campistol[g], Michel S. Slama[h], Bouke P. Hazenberg[i], Teresa Coelho[j], from the European Network for TTR-FAP (ATTReuNET)

Curr Opin Neurol 2016 Feb; 29(Suppl 1): S14–S26

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Symptomatic treatment in TTR-FAP

- Neuropathic pain
  - amitriptyline*, duloxetin*
  - gabapentin*, pregabalin*
  - pain specialist

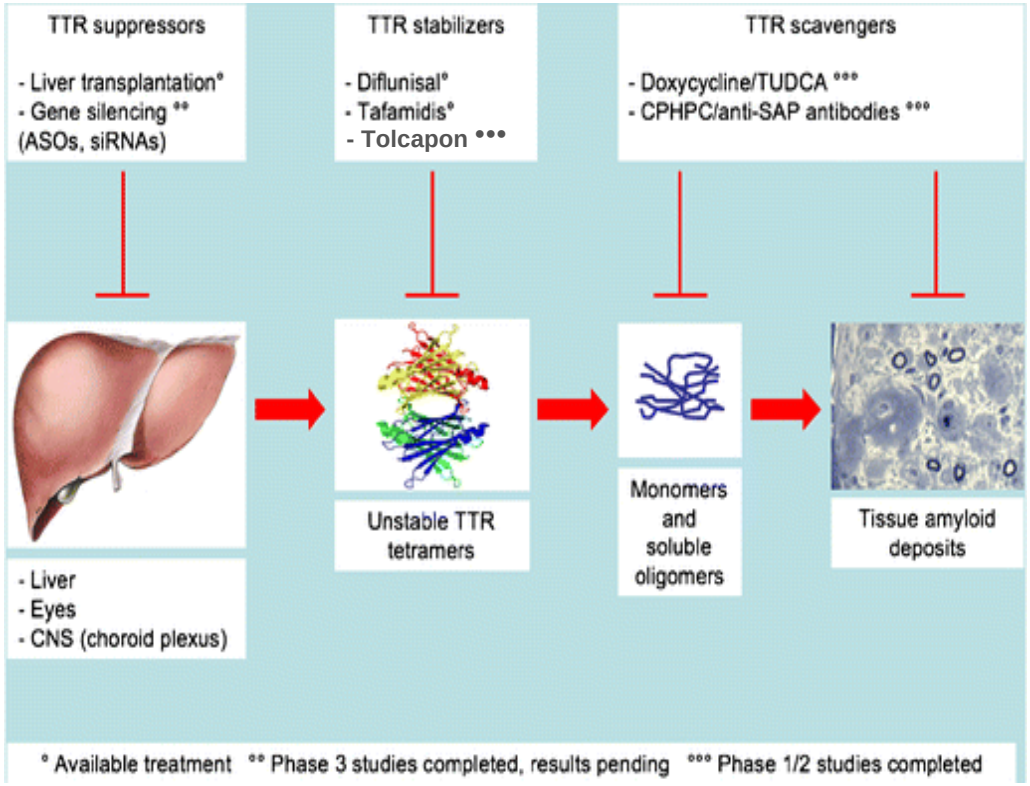
*Cochrane Database of Systematic Reviews

Symptomatic treatment in TTR-FAP

autonomic neuropathy	
orthostatic hypotension	salt, stockings, midodrine, fludrocortisone
nausea/satiety	domperidone, metoclopramide, erytrhromycin, feeding tube
constipation	laxatives
diarrhoea	loperamide
urination problems	distigmine, catheter, neurostimulator
impotence	sildenafil, tadalafil, vardenafil, phentolamine/papaverine, alprostadil
sicca	artificial tears/saliva

Treatment of TTR-FAP

- Combating amyloid deposition



Kerschen P, Planté-Bordeneuve V. Curr Treat Options Neurol 2016;18(12):53

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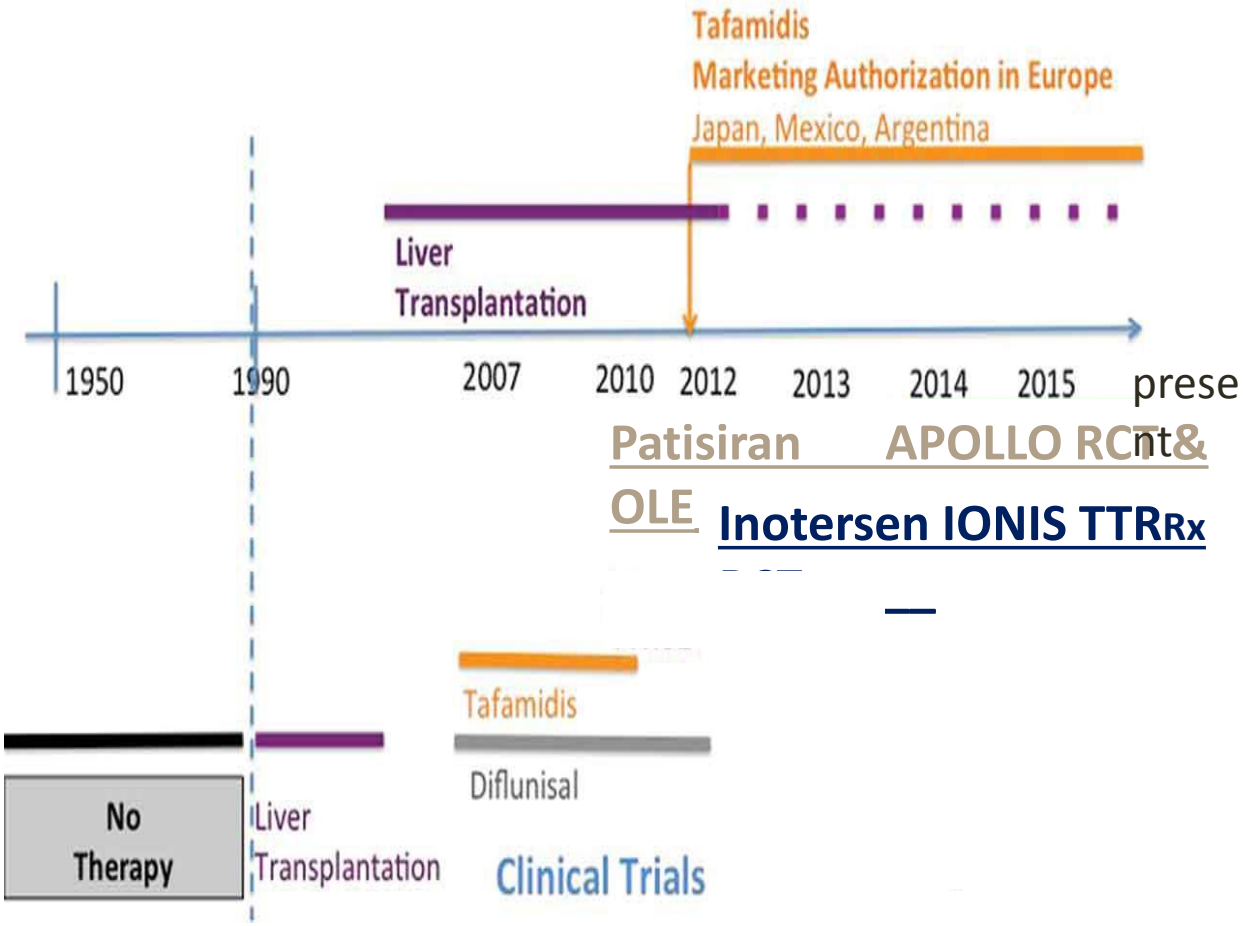
Treatment of TTR-FAP



Adams D et al. Exp Opin Pharmacother 2016;17(6):791-802

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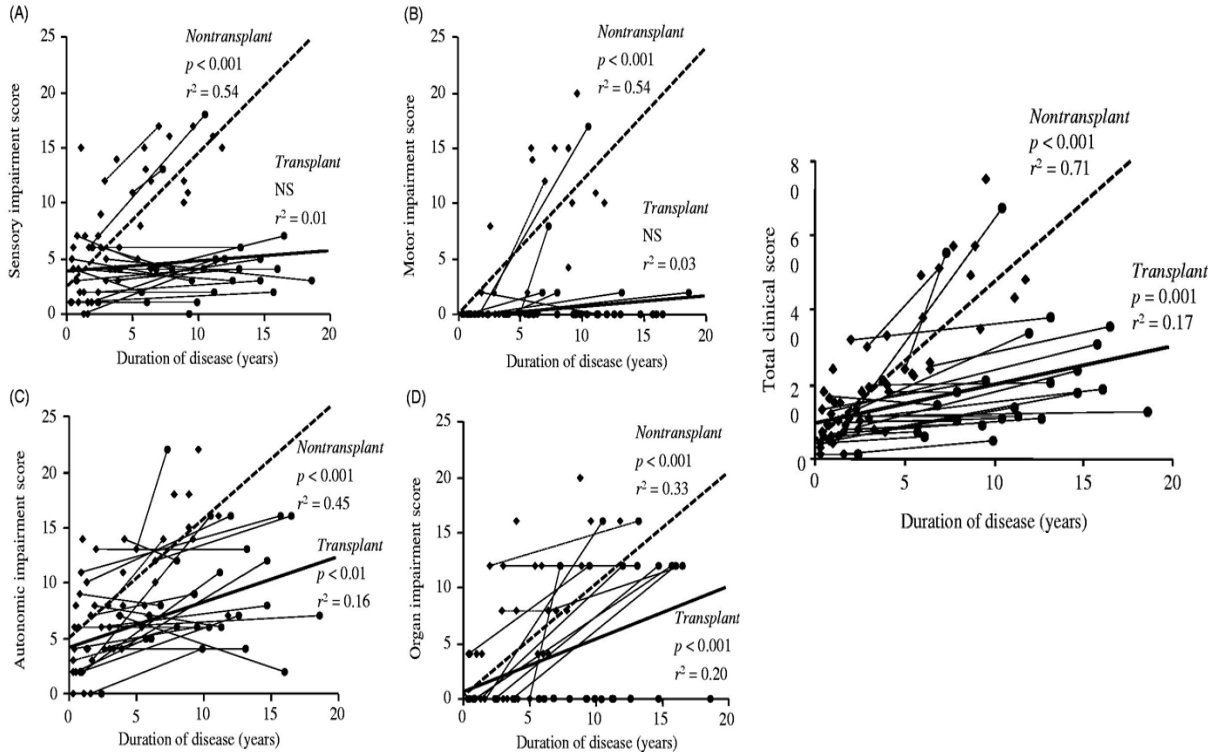
Treatment of TTR-FAP

- **liver transplantation**
- tafamidis
- diflunisal
- patisiran/inotersen
- other

Treatment of TTR-FAP

- Liver transplantation Japan



Okumura K et al. Amyloid 2016;23(1):39-45

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Treatment of TTR-FAP

- Liver transplantation Europe
  - most transplant recipients PND I-III / FAP 1-2
  - 33% (107/322) progression
  - 2.9 years average time to progression

Adams D et al. Orphan J Rare Dis 2015;10(Suppl1):P19

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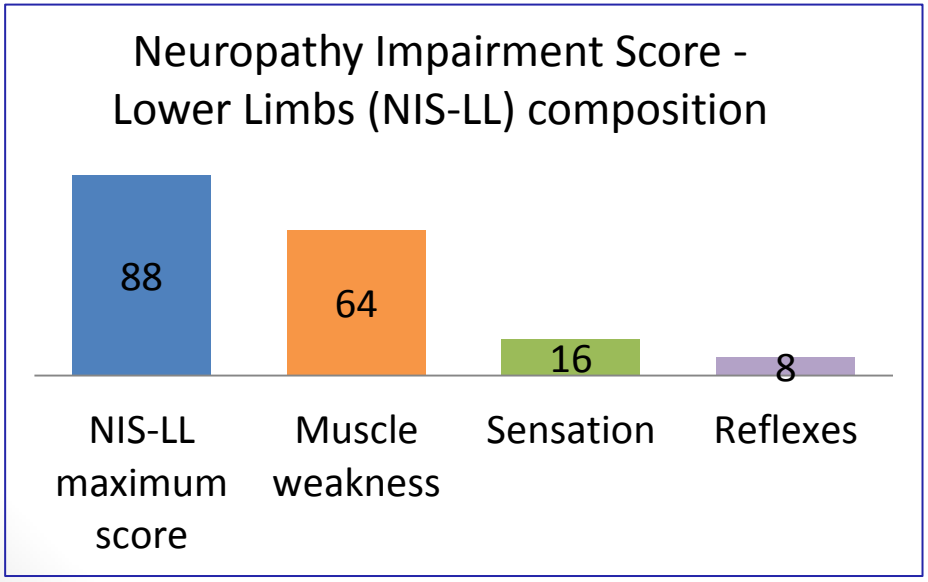
Scoring severity of TTR-FAP

- PND 0 = FAP 0: asymptomatic
- PND I-II = FAP 1: mild symptoms, independent walking
- PND IIIa&b = FAP 2: moderate symptoms, walking aids
- PND IV = FAP 3: severe symptoms, weelchair/bedridden



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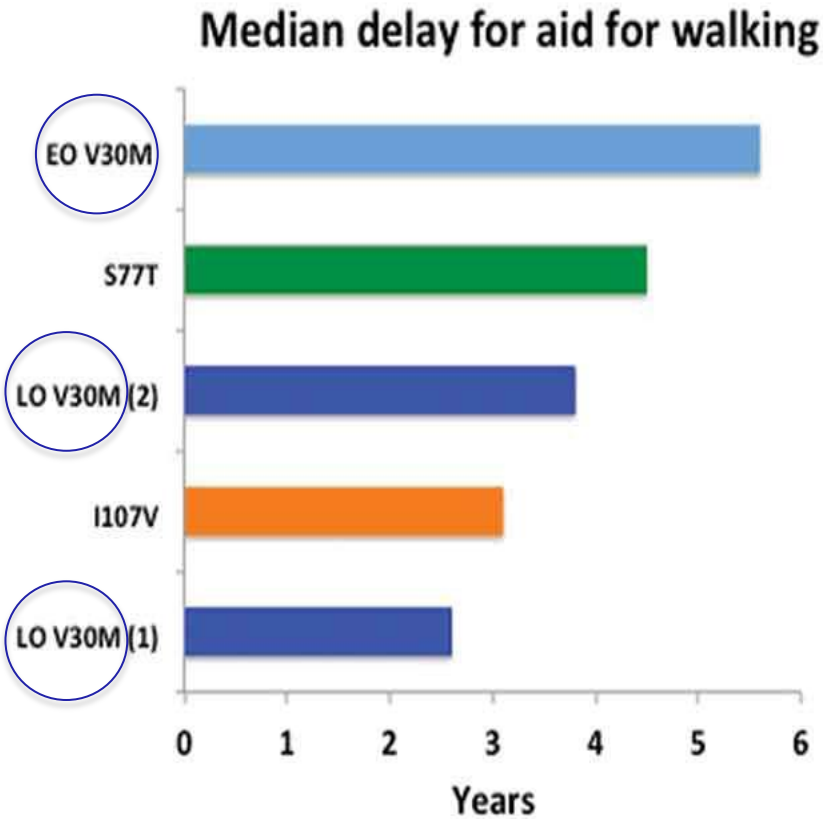
Walking ability in TTR-FAP



Adams D et al. Exp Opin Pharmacother 2016;17(6):791-802

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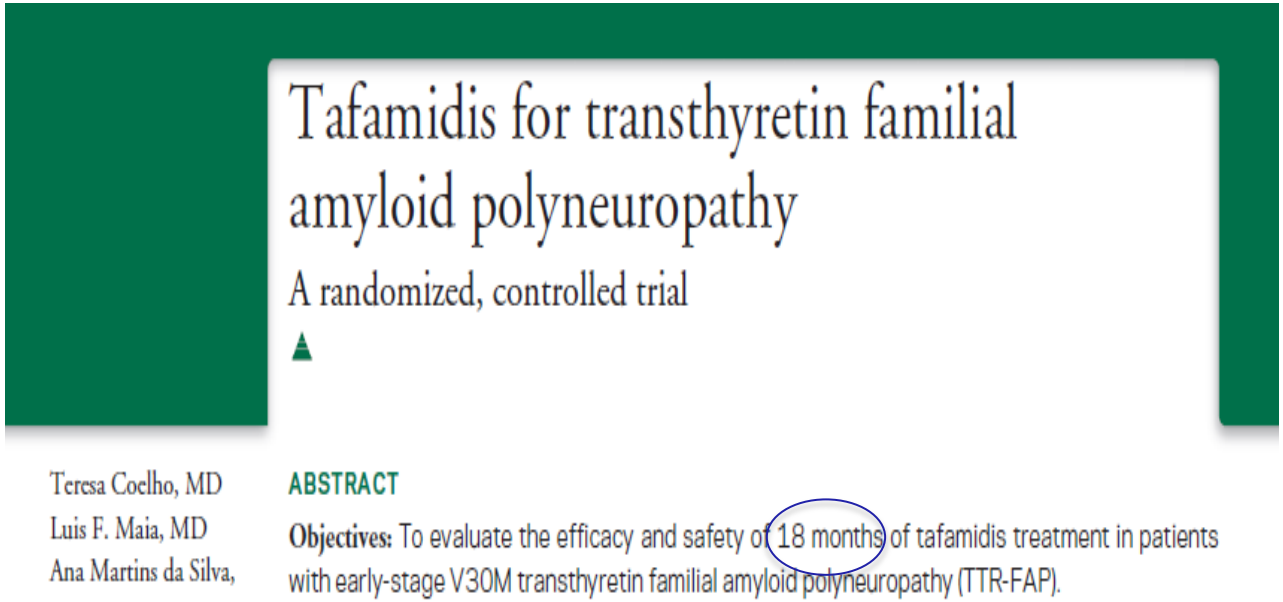
Treatment of TTR-FAP

- liver transplantation
- **tafamidis**
- diflunisal
- patisiran/inotersen
- other

Tafamidis for Val30Met TTR-FAP

- RCT effectiveness at 1.5 years
- most “early stage” Val30Met TTR-FAP



Tafamidis for transthyretin familial amyloid polyneuropathy

A randomized, controlled trial

Teresa Coelho, MD
Luis F. Maia, MD
Ana Martins da Silva,

ABSTRACT

Objectives: To evaluate the efficacy and safety of 18 months of tafamidis treatment in patients with early-stage V30M transthyretin familial amyloid polyneuropathy (TTR-FAP).

Neurology
2012;79(8):785-92

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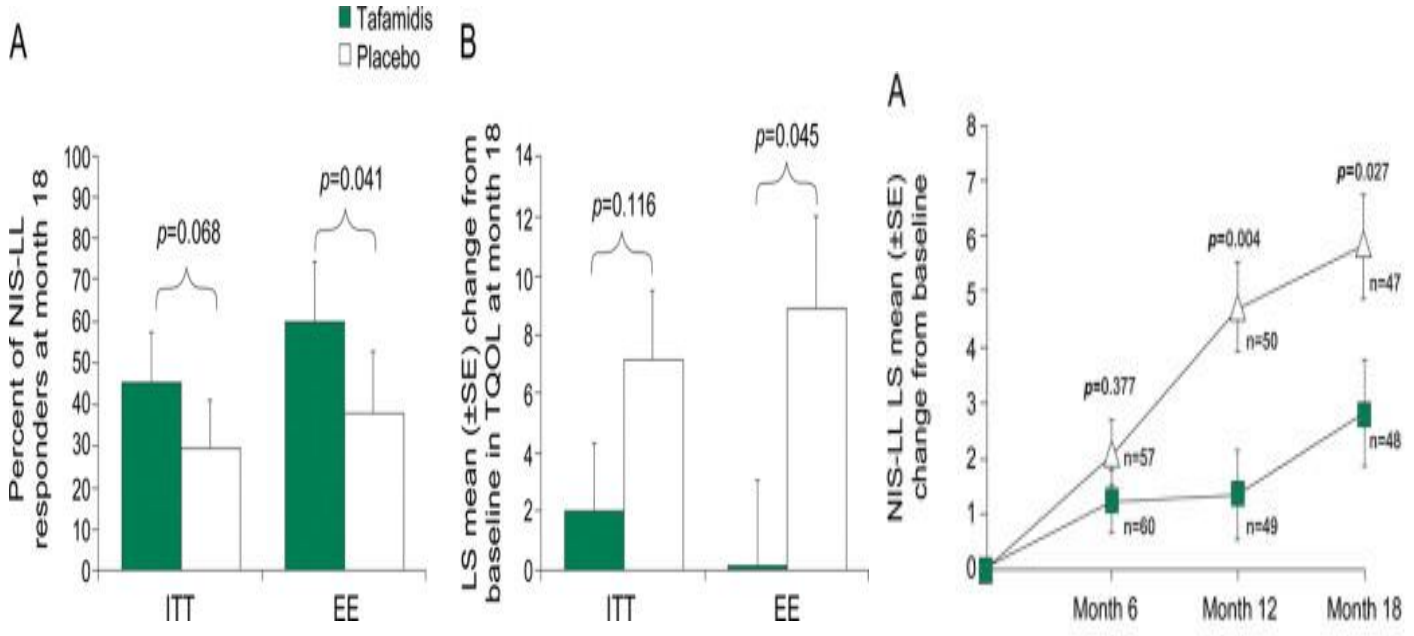
Tafamidis for Val30Met TTR-FAP

- Drop-out rate (liver transplatation) rate 25% equal for placebo and tafamidis



Coelho T et al. Neurology 2012;79:785-92

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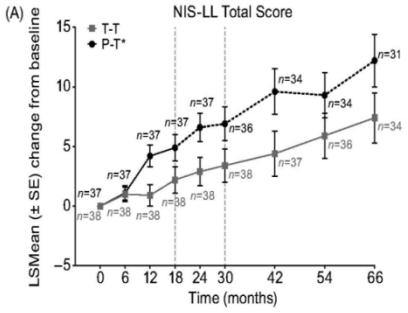
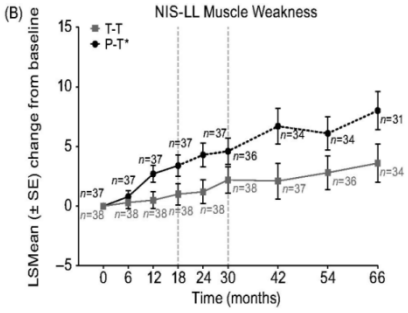
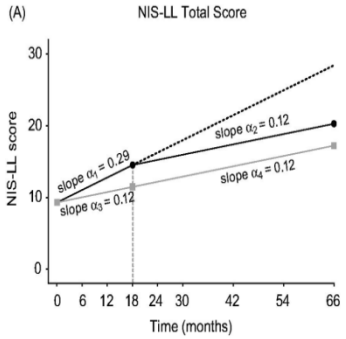
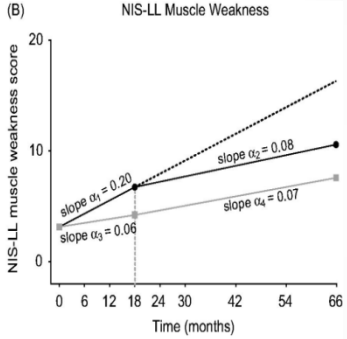
Tafamidis for Val30Met TTR-FAP

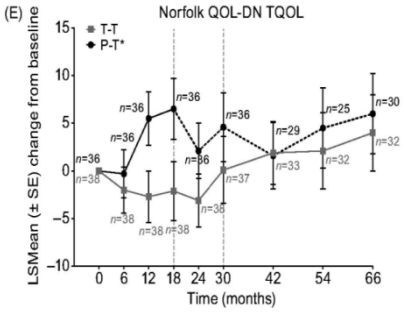
- Open label effectiveness at 6 years

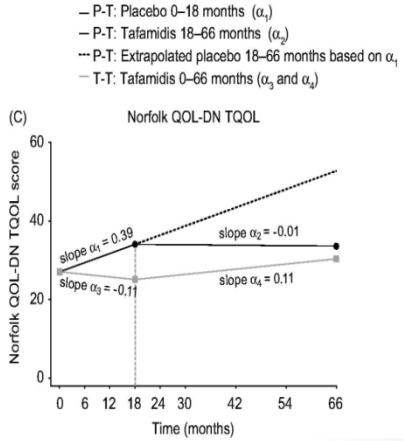












Barroso FA et al. Amyloid 2017;24(3):194-204

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Tafamidis for late onset/stage 2-3 Val30Met TTR-FAP

- Open label effectiveness at 1 year
  - frequently non-responders
  - on average no clear change of disease progression
  - individual patients may benefit

Lozeron P et al. Eur J Neurol 2013;20(12):1539-1545

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Tafamidis for non-Val30Met TTR-FAP

- Open label effectiveness at 1-4 years
  - frequently non-responders
  - on average
    - less effectiveness on disease progression
    - no effectiveness on quality of life

Barroso FA et al. Amyloid 2017;24(3):194-204
Planté-Bordeneuve V et al. J Neurol 2017;

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Treatment of TTR-FAP

- liver transplantation
- tafamidis
- **diflunisal**
- patisiran/inotersen
- other

Diflunisal for TTR-FAP

- RCT effectiveness at 2 years
  - Val30Met & non-Val30Met
  - PND stages I-IV/FAP stages 1-3
  - 31% use of walking aid

Research

Original Investigation

Repurposing Diflunisal for Familial Amyloid Polyneuropathy
A Randomized Clinical Trial

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JAMA 2013;310(24):2658-2667

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Diflunisal for TTR-FAP

- Drop-out rate (liver transplantation) placebo 21% more often than

Outcomes	Mean (95% CI) Placebo Change From Baseline	Diflunisal Change From Baseline	Difference, Placebo–Diflunisal	*P* Value
NIS+7 score				
At 1 year	12.5 (8.6 to 16.4)	6.2 (2.8 to 9.6)	6.4 (1.2 to 11.6)	.02
At 2 years	26.3 (20.2 to 32.4)	8.2 (2.9 to 13.6)	18.0 (9.9 to 26.2)	<.001
NIS score				
At 1 year	10.1 (6.9 to 13.3)	4.1 (1.2 to 6.9)	6.0 (1.7 to 10.3)	.007
At 2 years	23.2 (17.8 to 28.5)	6.4 (1.6 to 11.2)	16.8 (9.6 to 24.0)	<.001
NIS-LL score				
At 1 year	6.0 (3.9 to 8.2)	3.2 (1.3 to 5.2)	2.8 (−0.1 to 5.7)	.06
At 2 years	12.1 (8.9 to 15.3)	3.8 (0.9 to 6.6)	8.3 (4.1 to 12.6)	<.001
Kumamoto score				
At 1 year	4.1 (2.1 to 6.2)	1.9 (0.1 to 3.7)	2.3 (−0.5 to 5)	.10
At 2 years	8.0 (5.8 to 10.3)	3.1 (1.1 to 5.1)	5.0 (1.9 to 8.0)	.002
Modified BMI[b]				
At 1 year	−38.5 (−74.9 to −2.1)	−18.7 (−51.6 to 14.1)	−19.8 (−68.8 to 29.2)	.43
At 2 years	−67.9 (−108.1 to −27.7)	−33.7 (−69.3 to 1.8)	−34.1 (−87.8 to 19.5)	.21
SF-36 physical component score				
At 1 year	−1.9 (−3.9 to 0.2)	0.7 (−1.1 to 2.5)	−2.6 (−5.3 to 0.1)	.06
At 2 years	−4.9 (−7.6 to −2.1)	1.2 (−1.2 to 3.7)	−6.1 (−9.8 to −2.5)	.001

Berk JL et al. JAMA 2013;310(24):2658-2667

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Diflunisal for TTR-FAP

- Open label effectiveness at >3-4 years
  - on average no change of clinical FAP score per year

Sekijiama Y et al. Amyloid 2015;22(2):1744-83

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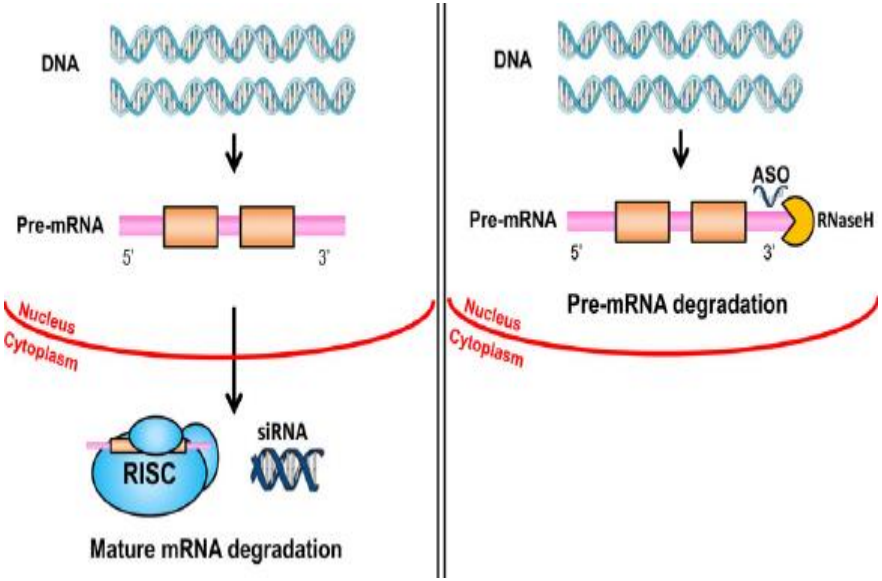
Treatment of TTR-FAP

- liver transplantation
- tafamidis
- diflunisal
- **patisiran/inotersen**
- other

Treatment of TTR-FAP

- Genetic modifying therapy
  - siRNA antisense oligonucleotides (ASO)

    patisiran inotersen



Beaudet RL, Meng L.. Human Molecular Genetics 2016; 25(R1):R18-26

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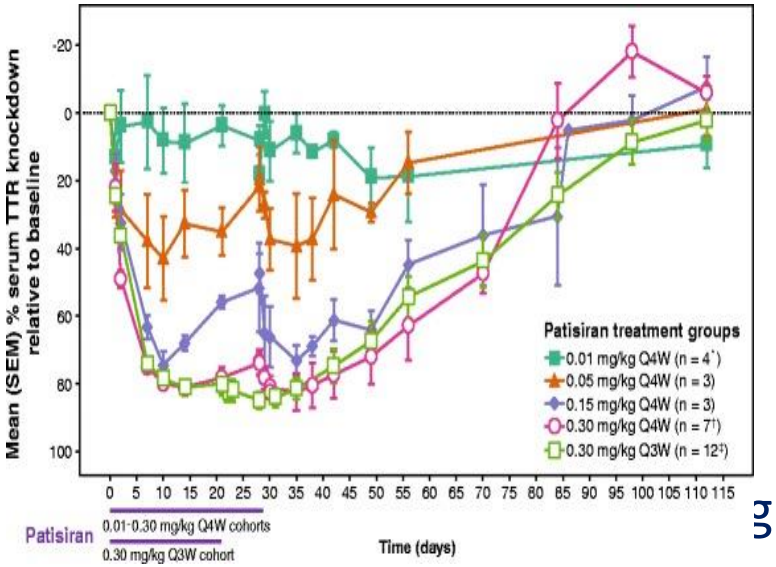
Patisiran for TTR-FAP

- phase 1 / 2 studies (open label)



gression

- APOLLO RCT data at this meeting: effectiveness at 1.5 yr on all endpoints

Suhr OB et al. Orphanet J Rare Dis 2015;10:109
Adams D et al. Value in Health 2017;20:5 (A211-A212)

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Inotersen for TTR-FAP

- RCT IONIS-TTRRx effectiveness at 15 months
  - less progression of polyneuropathy
  - less reduction in quality of life

http://ir.ionispharma.com/news-releases/news-release-details/ionis-pharmaceuticals-announces-phase-3-neuro-ttr-study

Treatment of TTR-FAP

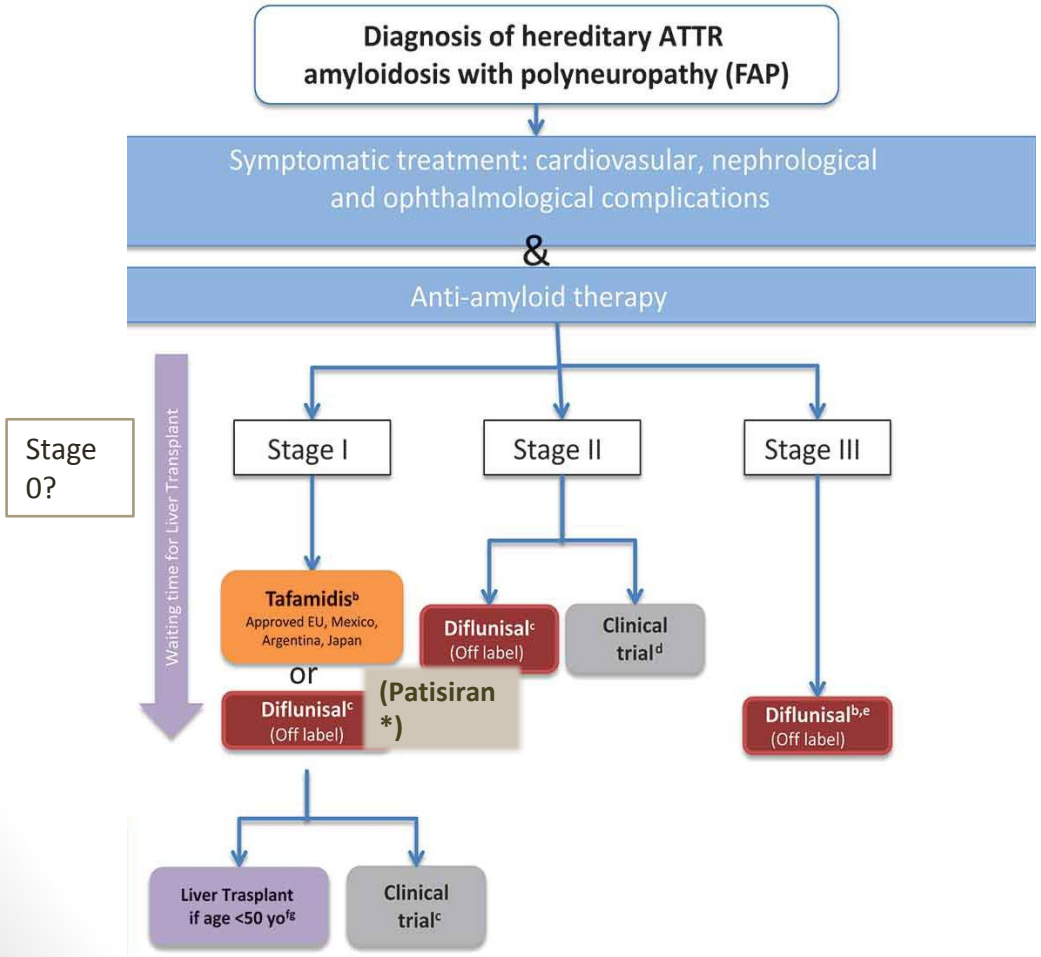
- liver transplantation
- tafamidis
- diflunisal
- patisiran/inotersen
- **other**

Treatment of TTR-FAP

Other TTR stabilizers

- open label phase 1/2 studies (dose-finding, toxicity, tolerability,…)
- inhibitors of fibril/amyloid formation, clearance of TTR amyloid
  - doxycycline + (tauro)ursodeoxycholzuur/(T)UDCA
  - tolcapone
  - epigallocatechin-3-gallate (green tea component)
  - curcumin
  - antibodies
  - ……

Treatment of TTR-FAP



Adams D et al. Exp Opin Pharmacother 2016;17(6):791-802

***patisiran is not yet available**

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Brain Center Rudolf Magnus

Treatment of TTR-FAP

The earlier the better, 3 pillars:

- symptom management
- anti-amyloid deposition

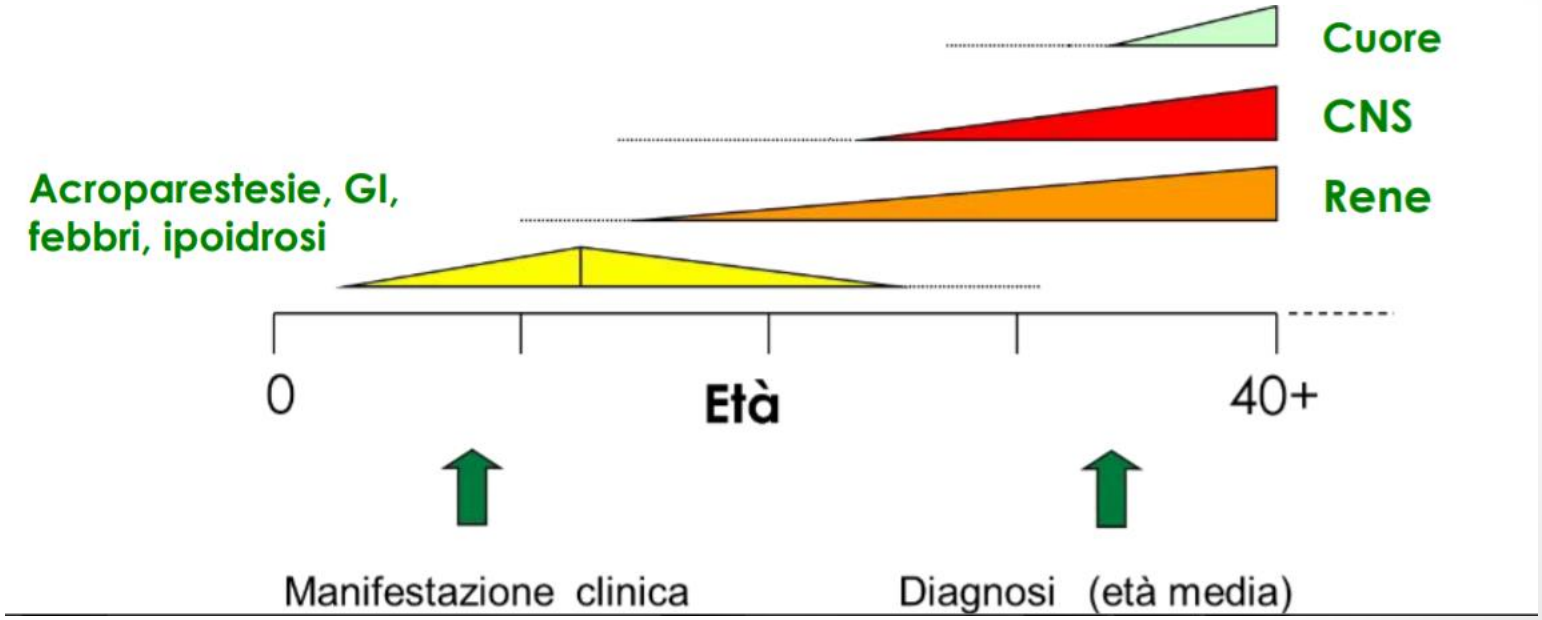
Medicine	Clinical FAP stage	Availability	Side-effects
✓ tafamidis	1	Europe, Japan,….	few/mild
✓ diflunisal	1-3	depends on country	gastric, kidneys
✓ patisiran(/inotersen)	1 & 2 (3?)	not yet available	few/mild

Treatment of TTR-FAP

Your texte here

Anderson-Fabry disease (AFD)

- an X-linked lysosomal storage disorder caused by mutations in the GLA gene that result in deficiency of the enzyme α-galactosidase A.
- The worldwide incidence of Fabry's disease is reported to be in the range of 1 in 40,000–117,000, although this value may be a significant underestimate given under recognition of symptoms and delayed or missed diagnosis
- The prevalence in selected patient cohorts is even higher and reported to be between 0.25–3.5% in male haemodialysis patients, **0.9–3.9%** in male patients with **hypertrophic cardiomyopathy (HCM**) and 3–5% in patients with cryptogenic stroke.



Enzyme replacement therapy

ERT aims to compensate for the reduced α-galactosidase levels and to reduce accumulation of glycosphingolipids in tissues. Two formulations of ERT are licenced, both administered as an intravenous infusion fortnightly, agalsidase-α (Replagal, Shire) and agalsidase-β (Fabrazyme, Sanofi-Genzyme).

Data on the impact of ERT on changes in left ventricular hypertrophy are conflicting with some studies showing a reduction in LV mass and improved myocardial function as assessed by systolic radial strain rate whereas others fail to show significant changes in ventricular wall thickness

Chaperone therapy

More recently, oral chaperone therapy has become available for use in patients. Migalastat is a small molecule chaperone that reversibly binds to the active site of α-galactosidase and thereby stabilises mutant enzyme and promotes α-galactosidase-based catabolism of cellular products.

Migalastat has been shown in case reports to reduce left ventricular hypertrophy and decrease LGE and associated cardiac serum biomarkers.

MPS analysis with Single gene/Small Gene Panels : when

- Single gene MPS: large gene, multiple phenotypes, laboratory skills (DMD)
- High coverage - CNVs detection (mutation spectrum)

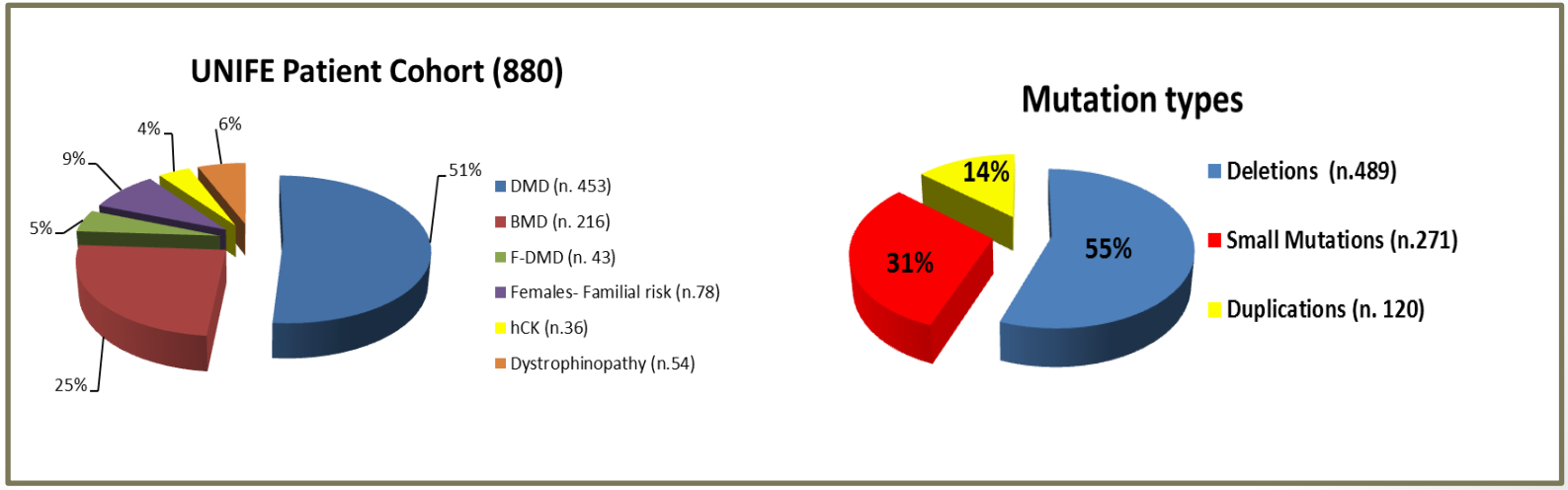
- Small MPS panels: frequent disease with a few major genes (HCM-ACM)
- Time restriction (prenatal, therapeutic choices) (LMNA,DMD,GAA…)

DMD-MPS single gene

Product Name	Genomic Target	Contents	Reactions
DMD MASTR	DMD, SNV+CNV (118 amplicons)	4 PCR mixes, Taq, AR1	8

MASTR (Multiplex Amplification of Specific Targets for Resequencing): a primer library for PCR amplification of all 79 DMD exons and exon-introns boundaries (with at least 30 bp flanking regions).

DMD as a big gene (79 exons; >30Kb genomic sequence of exons and intron boundaries)
Specific phenotype (DMD>BMD); different phenotypes
Short time of analysis frequently needed (pregnancy and positive family history; novel available therapies)
Need for validated, robust and simple-to-use tools in diagnostic setting
Need for EU IVD (in vitro diagnostic) approval for medical devises and softwares (compliance with the In vitro diagnostic Directive (IVDD; directive 98/79/EC).



From Marian AJ et al., 2016

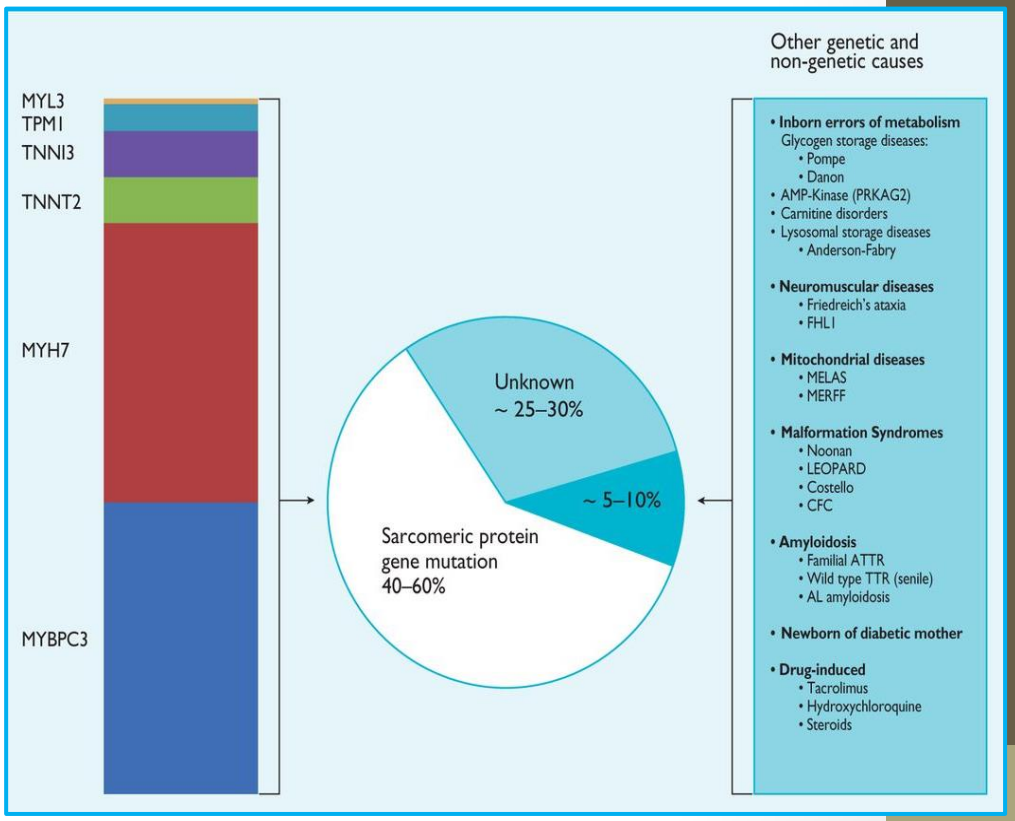
TABLE 4 Genetic Basis for HCM

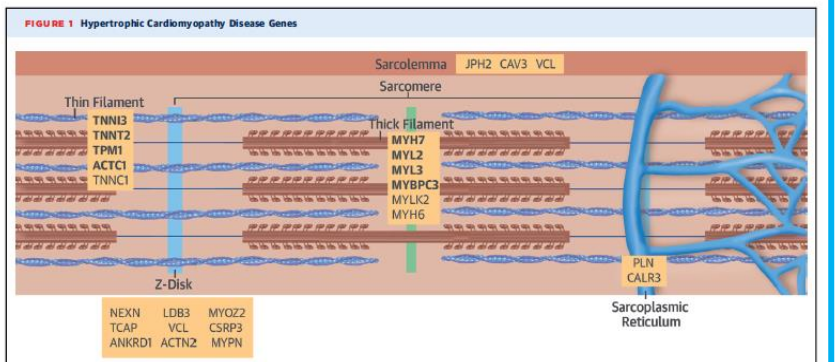
Protein	Gene	Locus	Frequency
Established causal genes			
β-myosin heavy chain	*MYH7*	14q1	~25%
Myosin binding protein C	*MYBPC3*	11q1	~25%
Cardiac troponin T	*TNNT2*	1q3	<5%
Cardiac troponin I	*TNNI3*	19p13.2	<5%
α-tropomyosin	*TPM1*	15q1	<5%
Likely causal genes			
Cardiac alpha-actin	*ACTC1*	15q11	<5%
Myozenin 2	*MYOZ2*	4q25-26	Rare
Tripartite motif containing 63	*TRIM63*	1p34-33	Rare
Myosin light chain 3	*MYL3*	3p	Rare
Myosin light chain 2	*MYL2*	12q	Rare
Titin	*TTN*	2q13-33	Rare
Telethonin	*TCAP*	17q12	Rare
Myosin light chain kinase 2	*MYLK2*	20q13.3	Rare
α-myosin heavy chain alpha	*MYH6*	14q12	Rare
Troponin C	*TNNC1*	3p21	Rare
Caveolin 3	*CAV3*	3p25	Rare
Phospholamban	*PLN*	6p22.1	Rare
Lamin A/C	*LMNA*	21.2-q21.3	Rare
Calsequestrin	*CASQ2*	1p13.1	Rare
Junctophilin 2	*JPH2*	20q13.12	Rare

HCM = hypertrophic cardiomyopathy.

In HCM a small set of core sarcomeric genes accounts for up to 60% of cases

5-10% of adult cases are caused by other genetic disorders (metabolic, neuromuscular, chromosomic, genetic syndromes).





From Burke MA et al., 2016

Table 1. Distribution and Frequency of Disease-Associated Mutations in Patients With HCM

Gene	No. of mutations found in this study (novel mutations)	No. of proband patients with mutations in this study (novel mutations)	% Frequency of mutations in familial HCM patients in this study (n=112)	% Frequency of mutations in the French familial HCM cohort* (n=172)	% Frequency of mutations in the US HCM cohort** (n=389)†
MYH7	12 (2)	12 (2)	10.7	26.2	15.2
MYBPC3	13 (7)	22 (7)	19.6	26.2	18.0
MYL3	0 (0)	0 (0)	0.0	0.0	0.0
MYL2	0 (0)	0 (0)	0.0	0.6	1.8
ACTC	0 (0)	0 (0)	0.0	0.0	0.0
TNNT2	7 (1)	10 (1)	8.9	2.9	2.3
TNNI3	1 (1)	1 (1)	0.9	4.7	1.3
TPM1	4 (2)	4 (2)	3.6	0.0	0.5
Total	37 (13)	49 (13)	43.8	60.6	39.4

*_Circulation_ 2003; **107:** 2227–2232. **_J Am Coll Cardiol_ 2004; **44:** 1903–1910. †120 familial cases and 269 sporadic cases.
HCM, hypertrophic cardiomyopathy.

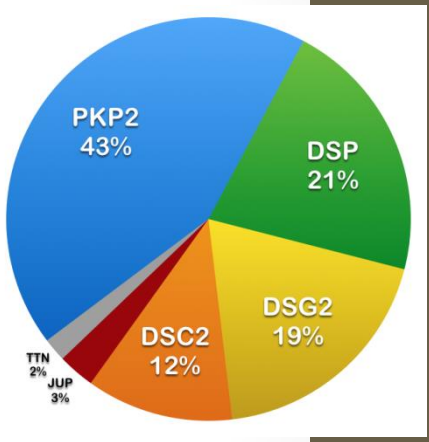
In ACM the 11 known genes accounts for only 50% of cases, with desmosomal genes as major genes.

Table 3 Genetic background of AC

MIM entry	Locus	Disease gene	Gene	Mode of transmission	Author, year [Reference]	Comment
Desmosomal genes						
#611528	17q21.2	Plakoglobin	JUP	AD/AR	McKoy et al. [43],	AR form: Cardiocutaneous syndrome
#601214						
#607450	6p24.3	Desmoplakin	DSP	AD/AR	Rampazzo et al. [46],	AR form: Cardiocutaneous syndrome
#605676						
#609040	12p11.21	Plakophilin- 2	PKP2	AD/AR	Gerull et al. [47],	
#610193	18q12.1	Desmoglein-2	DSG2	AD/AR	Pilichou et al. [48],	
#610476	18q12.1	Desmocollin-2	DSC2	AD/AR	Syrris et al. [49],	
Non-desmosomal genes						
#600996	1q43	Cardiac Ryanodine Receptor 2	RYR2	AD	Tiso et al. [58],	CPVT (AC phenocopy)
#107970	14q24.3	Transforming growth factor-beta-3	TGFB3	AD	Beffagna et al. [57],	Modifier?
#604400	3p25.1	Transmembrane Protein 43	TMEM43	AD	Merner et al. [51],	
	2q35	Desmin	DES	AD	Van Tintelen et al. [52],	Overlap syndrome (DC and HC phenotype, early conduction disease)
	6q22.31	Phospholamban	PLN	AD	Van der Zwaag et al. [53],	
	2q31.2	Titin	TTN	AD	Taylor et al. [54],	Overlap syndrome (early conduction disease, AF)
	1q22	Lamin A/C	LMNA	AD	Quarta et al. [55],	Overlap syndrome
#615616	10q21.3	alpha-T-catenin	CTNNA3	AD	Van Hengel et al. [56],	

Abbreviations. *AD*: autosomal dominant; *AF*: atrial fibrillation; *AR*: autosomal recessive; *CPVT*: catecholaminergic polymorphic ventricular tachycardia; *DC*: dilated cardiomyopathy; *HC*: hypertrophic cardiomyopathy

Mutated ACM cases



MiSeqDx instrument is certified as *in vitro* diagnostic (IVD) next-generation sequencing (NGS) system.

Multiplicom

51 genes underlying Primary Electrical Disorders (PED)

HCM genes MYBPC3, MYH7, TNNI3, TNNT2, MYL2

Application

- Identification of all SNVs and CNVs in the MYBPC3, MYH7, TNNI3, TNNT2, MYL2 genes

Genes analyzed	*MYBPC3, MYH7, TNNI3, TNNT2, MYL2*
Genomic region analyzed	*28.2 kb*
Number of amplicons	*131 including 16 control amplicons*
Amplicon length	*280-430 bp*
Number of plexes	*5*
DNA amount required	*20 ng per multiplex reaction*

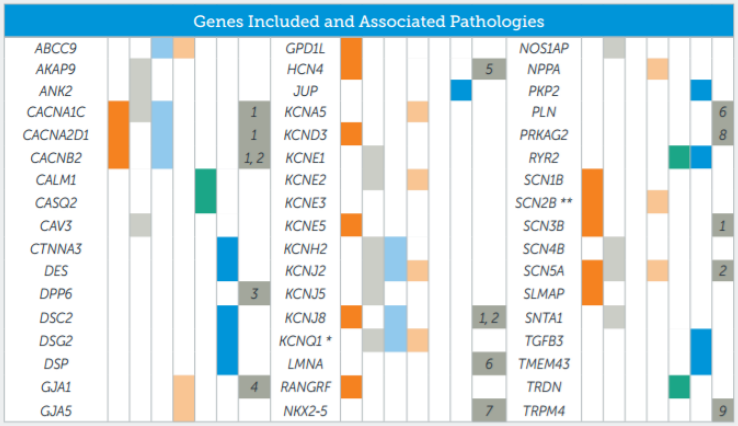


Table 1 Overview of inherited heart disease genes and genetic testing detection rates [2, 3, 5, 16–18]

Inherited heart condition	Associated genes			Genetic testing detection rate
	Autosomal dominant inheritance	Autosomal recessive inheritance	X-linked inheritance	
ARVC	*PKP2*[a], *DSP*[a], *DSG2*[a], *DSC2*, *TMEM43*, *JUP*, *PLN*, *RYR2*	*JUP*[b], *DSP*[b], *DSC2*[b]	NA	25–60%
BrS	*SCN5A*[a], *SCN10A*, *GPD1L*, *CACNA1C*, *PKP2*, *CACNB2*, *SCN1B*, *KCNE3*, *SCN3B*, *HCN4*, *CACNA2D1*, *RANGRF*, *TRPM4*, *SLMAP*, *KCNJ8*, *ABCC9*, *KCND3*, *KCNH2*, *FGF12*, *SEMA3A*	NA	*KCNE5*	25–30%
CPVT	*RYR2*[a], *KCNJ2*, *CALM1*, *CALM2*, *ANK2*	*CASQ2*, *TRDN*	NA	50–60%
DCM	*MYH7*[a], *TTN*[a], *LMNA*[a], *MYBPC3*, *ABCC9*, *ACTC1*, *ACTN2*, *BAG3*, *CAV3*, *CRYAB*, *CSRP3*, *DES*, *EYA4*[b], *FKRP*, *FLNC*, *PKP2*, *PLN*, *RAF1*[b], *RBM20*, *SCN5A*, *TCAP*, *TNNC1*, *TNNI3*, *TNNT2*, *TPM1*, *TTR*[b], *VCL*, *PSEN1*[b], *PSEN2*[b], *MYH6*, *ANKRD1*, *MYPN*, *PDLIM3*, *LDB3*, *LAMA4*, *KHL2*, *TMPO*, *GATAD1*	*SGCD*[b], *DOLK*[b], *TCAP*[b], *FKTN*[b], *SLC22A5*[b], *MYPN*[b], *GATAD1*	*DMD*[b], *TAZ*, *DES*[b], *EMD*[b], *LAMP2*[b]	10–30%
HCM	*MYBPC3*[a], *MYH7*[a], *TNNT2*, *TNNI3*, *ABCC9*, *ACTC1*, *ACTN2*, *CSRP3*, *MYL2*, *MYL3*, *MYOZ2*, *NEXN*, *TNNC1*, *TPM1*, *TTR*[b], *PRKAG2*, *CAV3*, *JPH2*, *PLN*, *CALR3*, *LDB3*, *TCAP*, *VCL*, *ANKRD1*, *MYPN*, *RAF*[b], *PTPN11*[b]	NA	*GLA*[b], *LAMP2*[b]	35–60%
LQTS	*KCNQ1*[a], *KCNH2*[a], *SCN5A*[a], *ANK2*, *KCNE1*, *KCNE2*, *KCNJ2*[b], *CACNA1C*[b], *CAV3*, *SCN4B*, *AKAP9*, *SNTA1*, *KCNJ5*, *CALM1*, *CALM2*, *CACNA2D1*	*KCNQ1*[b], *KCNE1*[b], *TRDN*	NA	75–80%
SQTS	*KCNH2*, *KCNQ1*, *KCNJ2*	NA	NA	UK
IVF	*DPP6*, *CALM1*, *RYR2*, *IRX3*	NA	NA	UK
PCCD	*SCN5A*, *TRPM4*, *SCN1B*, *SCN10A*, *KCNK17*, *NKX2.5*[c], *GATA4*[c], *LMNA*[b], *DES*[b]	NA	NA	UK

This table represents genes that have been reported in association with various clinical phenotypes; however, given the dynamic nature of disease-gene associations, it is not an exhaustive list. Genes that are included on individual genetic testing panels vary between laboratories and may not include all genes reported for a given clinical phenotype. In addition, testing for some of these reported genes may only be currently available as part of research studies and not through an accredited clinical laboratory

NA not applicable, *UK* unknown

[a] Accounts for >5% of cases

[b] May be associated with extra-cardiac features and/or genetic syndromes

[c] Associated with congenital heart disease

New diseses genes continue to be reported and added to panels; however this has not changed significantly the detection rate over time.

Curr Cardiol Rep (2017) 19: 88
DOI 10.1007/s11886-017-0885-3

CrossMark

INVASIVE ELECTROPHYSIOLOGY AND PACING (EK HEIST, SECTION EDITOR)

Genetic Testing in Inherited Heart Diseases: Practical Considerations for Clinicians

FIRST-TIER analysis for CHANNELLOPATHIES, AC and HCM

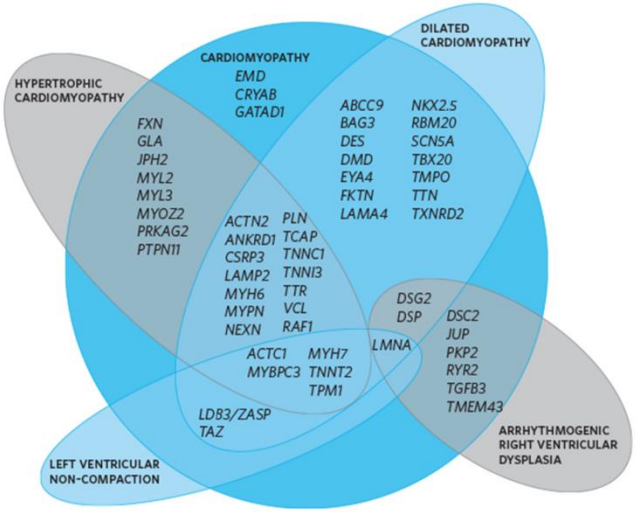
Genes			
CACNA1C	*HCN4*	*MYH6*	*SCN10A*
CACNA2D1	*KCNE1*	*MYH7*	*SCN5A*
CACNB2	*KCNE2*	*MYL2*	*TMEM43*
CASQ2	*KCNH2*	*NKX2-5*	*TNNI3*
CTNNA3	*KCNJ2*	*PKP2*	*TNNT2*
DSC2	*KCNQ1*	*PLN*	*TRDN*
DSG2	*LMNA*	*PRKAG2*	*TTR*
DSP	*MYBPC3*	*RYR2*	

+

GLA
ACTC1
LAMP2
MYL3
TPM1

MPS analysis with Large Gene Panels or Exome sequencing: when

- **Highly heterogeneous diseases, with large genes involved (DCM)**
- **Phenotypic overlap**



The impact of high-throughput sequencing in the diagnostic yield has been notable in cardiomyopathies , mainly DCM. Modest in ACM.

	SANGER SEQUENCING					HIGH-THROUGHPUT SEQUENCING					GAIN		
	Nº Genes	Estimated cost/gen*	Estimated cost	Estimated cost per positive result	Yield (%)	Nº Genes	Estimated cost/gen*	Estimated cost	Estimated cost per positive result	Yield (%)	% reduction cost	% reduct cost per positive result	% increase yield
HCM	2-4	700	1400-2800	3111-6222	45	16-20	98	1692	2351	72	86	64	27
DCM	14-19	700	7000-9000	50000-64286	14	23-96	48	2059	4118	50	93	96	36
ACM	5-8	700	3500-4500	6034-7759	58	14-53	77	1929	3507	60	89	72	2

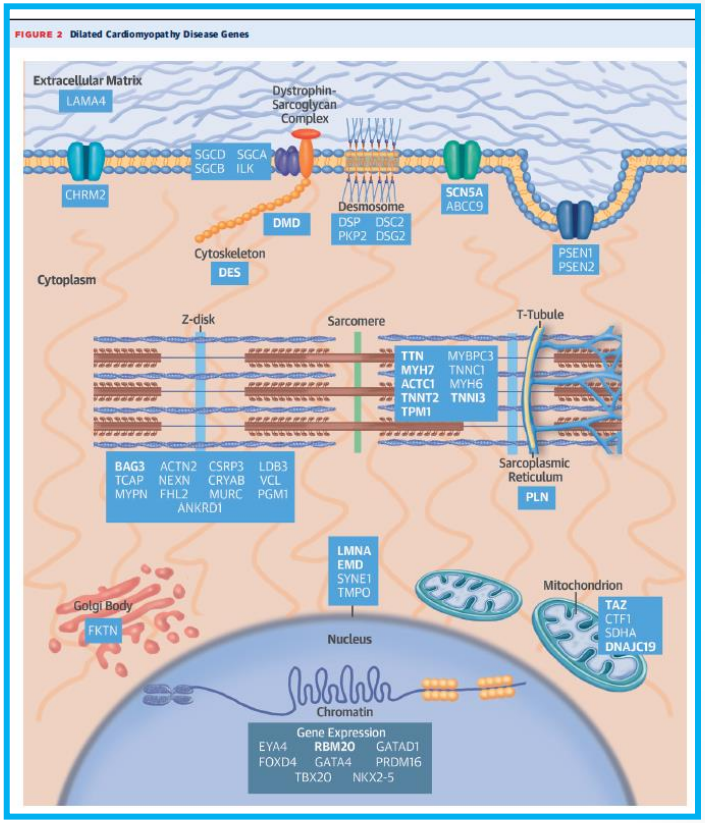
New sequencing technologies have led to a striking reduction of costs in all CMP.

More than 50 genes have been associated to DCM; a single gene (TTN-Titin) accounts for 25% of familial and 18% of sporadic cases. The other genes are rare and their pathogenic role often questioned.

TABLE 6 Causal Genes for Primary DCM

Gene	Protein	Comments/Phenotypic Plasticity
TTN	Titin	Giant sarcomere protein, responsible for ~25% of primary DCM, also causes HCM
MYH7	Myosin heavy chain 7 (β)	HCM
TNNT2	Cardiac troponin T	HCM
TNNI3	Cardiac troponin I	HCM
TNNC1	Cardiac troponin C	HCM
TPM1	α-tropomyosin	HCM
ACTC	Cardiac α-actin	HCM
TNNI3K	Troponin I interacting kinase	Conduction defect, atrial fibrillation
LMNA	Lamin A/C	Nuclear envelope protein responsible for over 1 dozen phenotypes
EMD	Emerin	Emery-Dreifuss syndrome
RBM20	RNA-binding motif protein 20	Targets splicing of several cardiac genes
SGCA	α-sarcoglycan	Involves skeletal muscle
SGCB	β-sarcoglycan	
SGCD	δ-sarcoglycan	
DMD	Dystrophin	Duchenne muscular dystrophy
CSRP3	Cysteine and glycine rich protein 3	
ANKRD1	Ankyrin repeat domain 1	
DES	Desmin	Desminopathy
CRYAB	αB-crystallin	Protein aggregation myopathy
ACTN2	Alpha-actinin 2	
TCAP	Telethonin (T-cap)	
LDB3	LIM domain binding 3 (Z-band alternatively spliced PDZ motif)	
VCL	Vinculin	
BAG3	BCL2-associated athanogene 3	Cochaperone
SCN5A	Sodium voltage-gated channel	Also causes Brugada syndrome and conduction defects
ABCC9	SUR2 subunit of potassium channels	
PLN	Phospholamban	Inhibits SERCA2
KCNQ1	Potassium channel	

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; RNA = ribonucleic acid; SERCA = sarco/endoplasmic reticulum calcium ATPase.



TTN is the largest gene in the human genome (386 exons; complex isoforms). Highly variable in control population

Only TTN truncating variants involving all isoforms are significantly enriched in DCM population (16%) vs controls (ExAc – 0.3%)

Data Sheet: DNA Sequencing

illumina

TruSight® Cardio Sequencing Kit

High-performance, affordable, accurate genetic profiling of 174 genes with known associations to 17 different inherited cardiac conditions.

Table 1: ICCs Covered by the TruSight Cardio Sequencing Kit

Cardiac Condition	No. of Genes Covered
Aortic Valve Disease	3
Marfan Syndrome	3
Loeys-Dietz Syndrome	4
Short QT Syndrome	4
Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)	6
Familial Hypercholesterolemia	7
Restrictive Cardiomyopathy	9
Non-Compaction Cardiomyopathy	10
Noonan Syndrome	11
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)	11
Brugada Syndrome	13
Structural Heart Disease	15
Long QT Syndrome	15
Familial Aortic Aneurysm	16
Familial Atrial Fibrillation	21
Hypertrophic Cardiomyopathy	47
Dilated Cardiomyopathy	59

The TruSight Cardio Sequencing Kit uses NGS for genetic profiling of 174 genes with known associations to 17 ICCs. For a complete gene list, visit www.illumina.com/cardio.

Total Variants: **250-350**

Biological consequences (missense, frameshifting, Stop gained, stop loss, inframe del - ins, splice **100 -150**

MAF: <1% **5-15**

MPS analysis with large gene panels implies the identification of a large number of variants that have to be correctly classified

Target	Bases in the target	Median coverage	Bases to be sequenced	Expected variants (unfiltered)	Expected variants (filtered)
GS	3,100,000,000	30x	>120Gb	**3,000,000**	**30,000**
ES	50,000,000	100x	10Gb	**30,000**	**50–500**
Large panel	1,500,000	200x	1Gb	**1,000**	**300**
Small panel	50,000	300x	0.05Gb	**30**	**15**

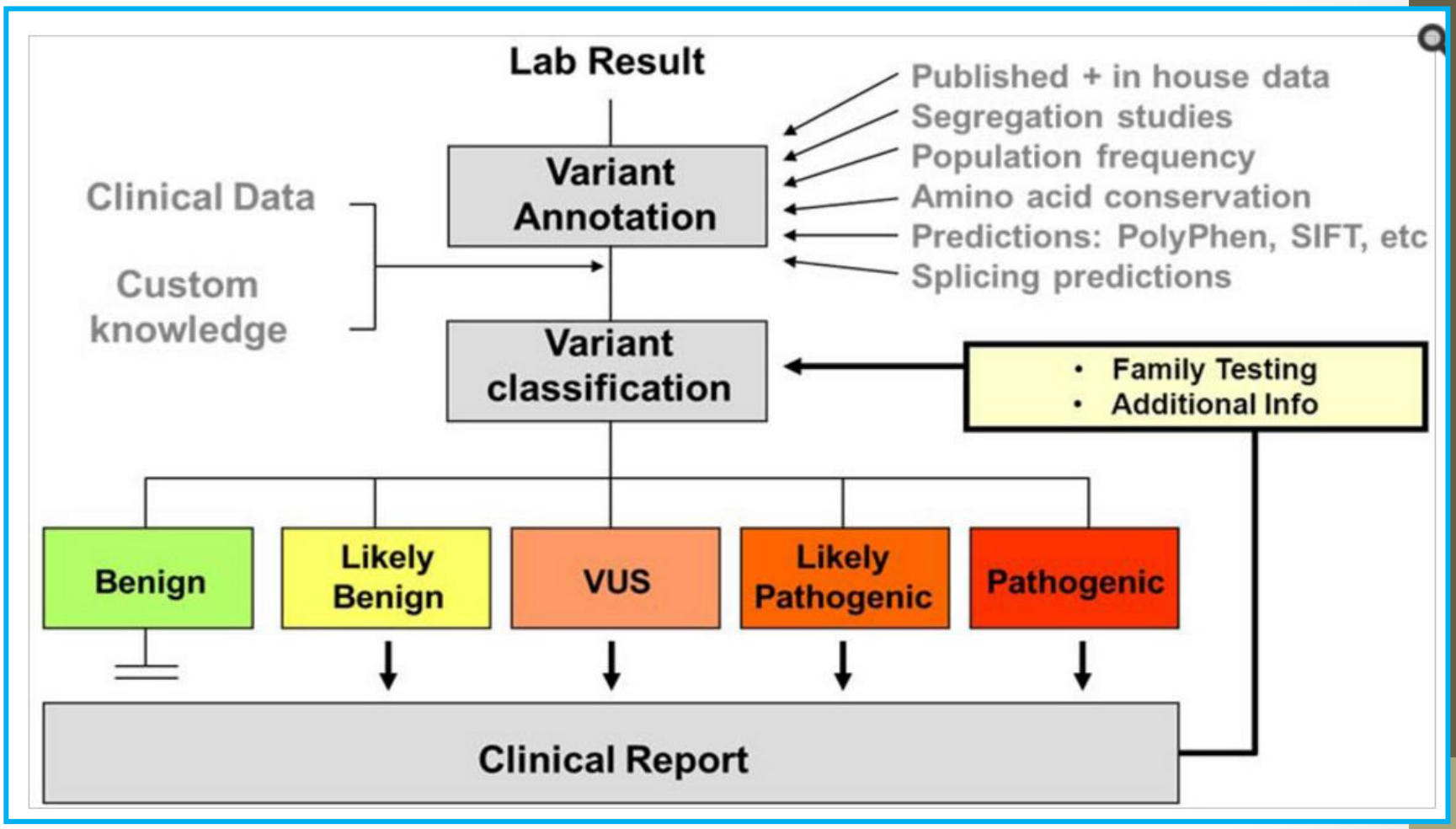
Criteria of pathogenicity and relative strenght

Type of evidence of pathogenicity

	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*			

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): 405–424. doi:10.1038/gim.2015.30.

When novel variants are identified, a complex post-test workflow is needed to prove disease causing significance.



Variant classification impacts clinical decision

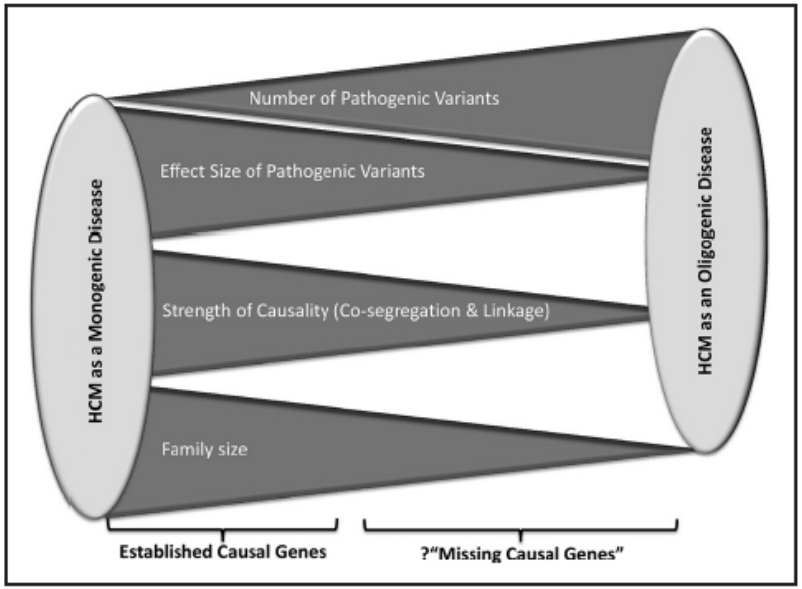
Table 2. Proposed classification for DNA sequence variants and correlation of clinical recommendation with probability that any given alteration is deleterious

DNA alteration class	Definition	Probability of being deleterious	Clinical testing	Surveillance recommendations
5	Definitely pathogenic	>0.99	Test at-risk relatives for the variant	Full high-risk surveillance
4	Likely pathogenic	0.95–0.99	Test at-risk relatives for the variant	Full high-risk surveillance
3	Uncertain	0.05–0.949	Do not use as predictive testing in at-risk relatives	Counsel based on family history and other risk factors
2	Likely not pathogenic	0.001–0.049	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected
1	Not pathogenic	<0.001	Do not use as predictive testing in at-risk relatives	Counsel as if no mutation detected

Table adapted from Plon et al. 2008 [8]. Note that for most variants, a quantitative probability is not yet available, as insufficient lines of evidence exist to generate the probability.

MPS analysis with large gene panels/exomes has revealed multiple pathogenic variants in aggregate in single affected subjects ,not perfectly cosegregating with the phenotype suggesting an oligogenic (Mutation Load) etiology.

For HCM, it has been recently proposed that a fraction of the so-colled missing causal genes (near 40% of cases) mainly in sporadic cases, might be because of an OLIGOGENIC INHERITANCE.



Li L et al., Circ.Res., march 2017

Figure 1. Hypothesis. The spectrum of genetic cause of hypertrophic cardiomyopathy (HCM) is illustrated. On one end of the spectrum, a single rare variant that exerts a large effect size leads to familial HCM with a high level of cosegregation. On the other end of the spectrum, HCM is caused by multiple pathogenic variants, each exerting a modest to moderate effect size and in aggregate cause HCM in sporadic cases and small families. In such scenario, the variants do not cosegregate with the phenotype. The latter group might explain, in part, the failure to identify the missing causal genes in HCM.

A sporadic case of BrS

CARDIOLOGY

Novel Insights from Clinical Experience

Cardiology 2017;137:256–260
DOI: 10.1159/000471792

Mutation Load of Multiple Ion Channel Gene Mutations in Brugada Syndrome

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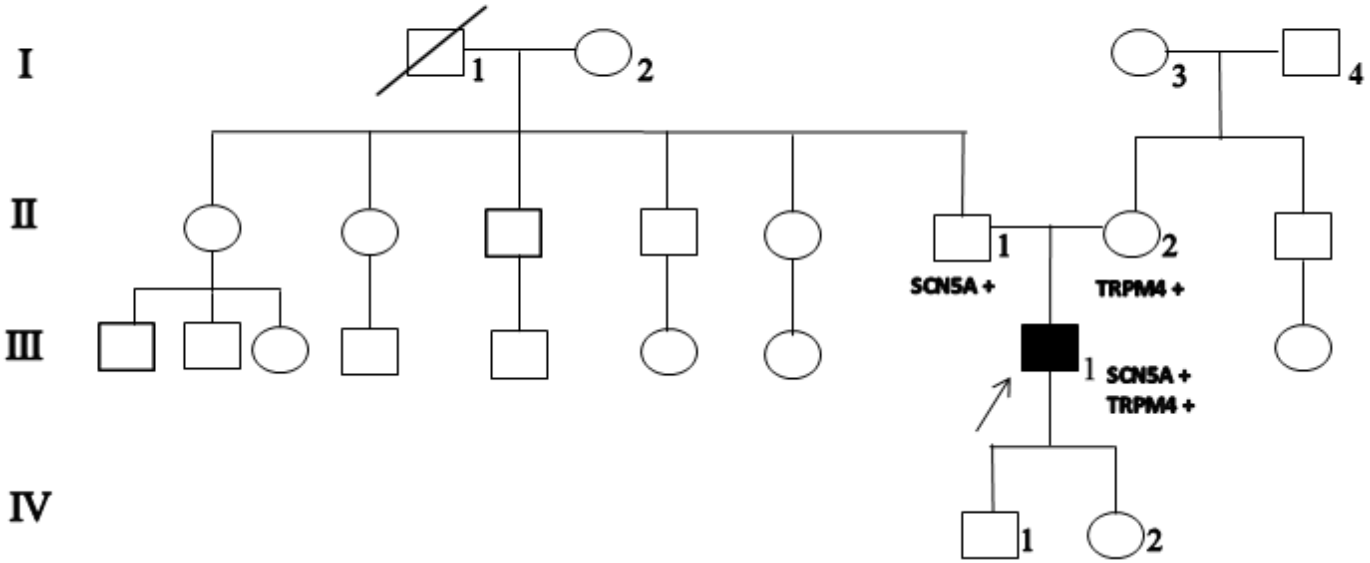


Besides interpretative challenges of VUS, large sequencing efforts are providing an invaluable opportunity to characterize the spectrum and importance of rare variations, increasing clinical utility of genetic analysis .

From the Exome Aggregation Consortium (ExAc) data set has emerged that the average exome contains 7.6 rare non-synonimous variants (MAF<0.1%) in well characterised dominant disease gene, with the majority being very rare or «private».

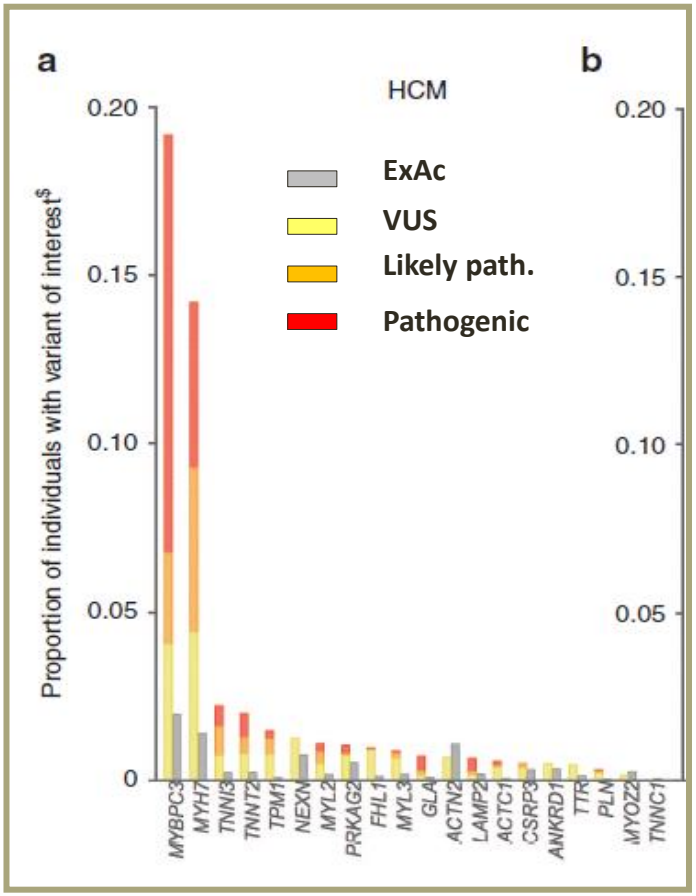
Genetics inMedicine | ORIGINAL RESEARCH ARTICLE Official journal of the American College of Medical Genetics and Genomics

Open

Walsh R. et al., 2017

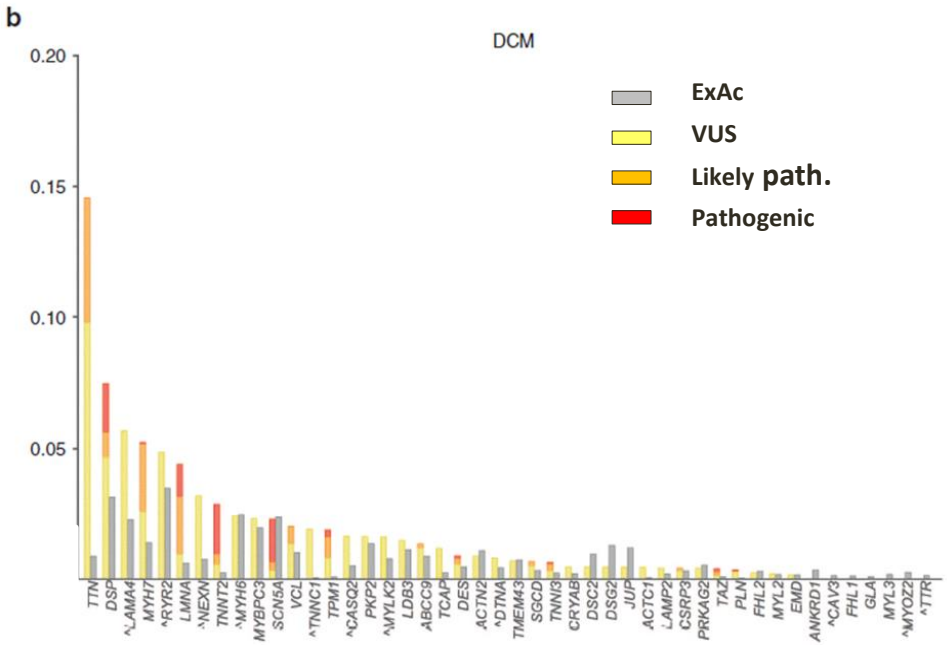
Reassessment of Mendelian gene pathogenicity using 7,855 cardiomyopathy cases and 60,706 reference samples

The burden of rare protein altering variants (MAF<0.1%) detected in **20 HCM genes**, **48 DCM genes** and **8 ARVC genes** in patients were compared with the burden in ExAc.



Rare variations in well characterized HCM genes are in a significant excess (P<0.05) in cases as compared with ExAc, confirming their association with disease.

For several recently reported HCM genes (NEXN,TNNCI, MYOZ2,ACTN2, ANKRD1) there was no significant excess of rare variations in HCM cases



The prevalence of rare variants in TTN (truncating-14%) and other well characterised DCM genes (MYH7, LMNA, TNNT2, TPM1, DSP truncating) are significantly enriched in cases as compared with ExAc, confirming their association with disease.

There was a limited burden and modest or no significant excess variation in the remaning 40 genes tested.

NB: In the gene robustly supported by a large excess of pathogenic and likely pathogenic variants, even VUS were seen in excess over ExAc , suggesting that clinical laboratory may be overly conservative.

MPS has dramatically changed the genetic analysis in cardiomyopathis, reducing time frame for analysis and costs and increasing the detection rate (DCM-HCM).

Big challenge in interpretation of the outcome of genetic analysis

Inheritance revised – novel models emerging (digenic, oligogenic, mutation load)

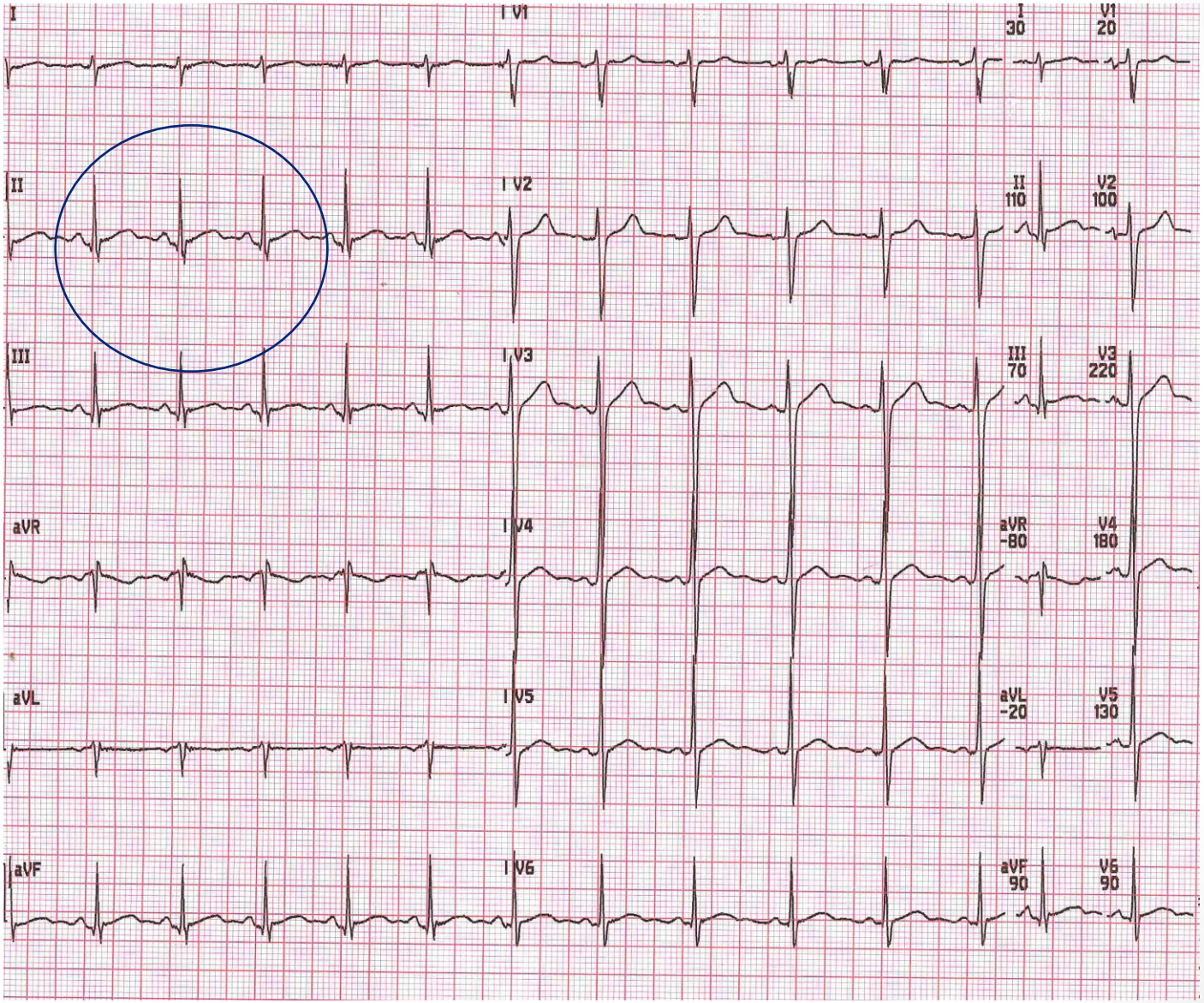
Genetic heterogeneity revised – few strongly associated genes

C.E. ♂ 14 anni

Riscontro di temporaneo allungamento del tratto QT (QT corretto) durante test ergometrico per idoneità sportiva agonistica.

- Storia famigliare muta per morte cardiaca improvvisa/malattie CV
- Non storia anamnestica di sincope, arresto cc, epilessia
- Terapia farmacologica: nessuna
- Esame obiettivo: ndd
- Asintomatico
- ECG basale: QTc nei limiti
- Esami bioumorali: parametri (elettroliti) nei limiti
- Ecocardiografia: funzione biventricolare conservata

QTc 440 msec



QT interval

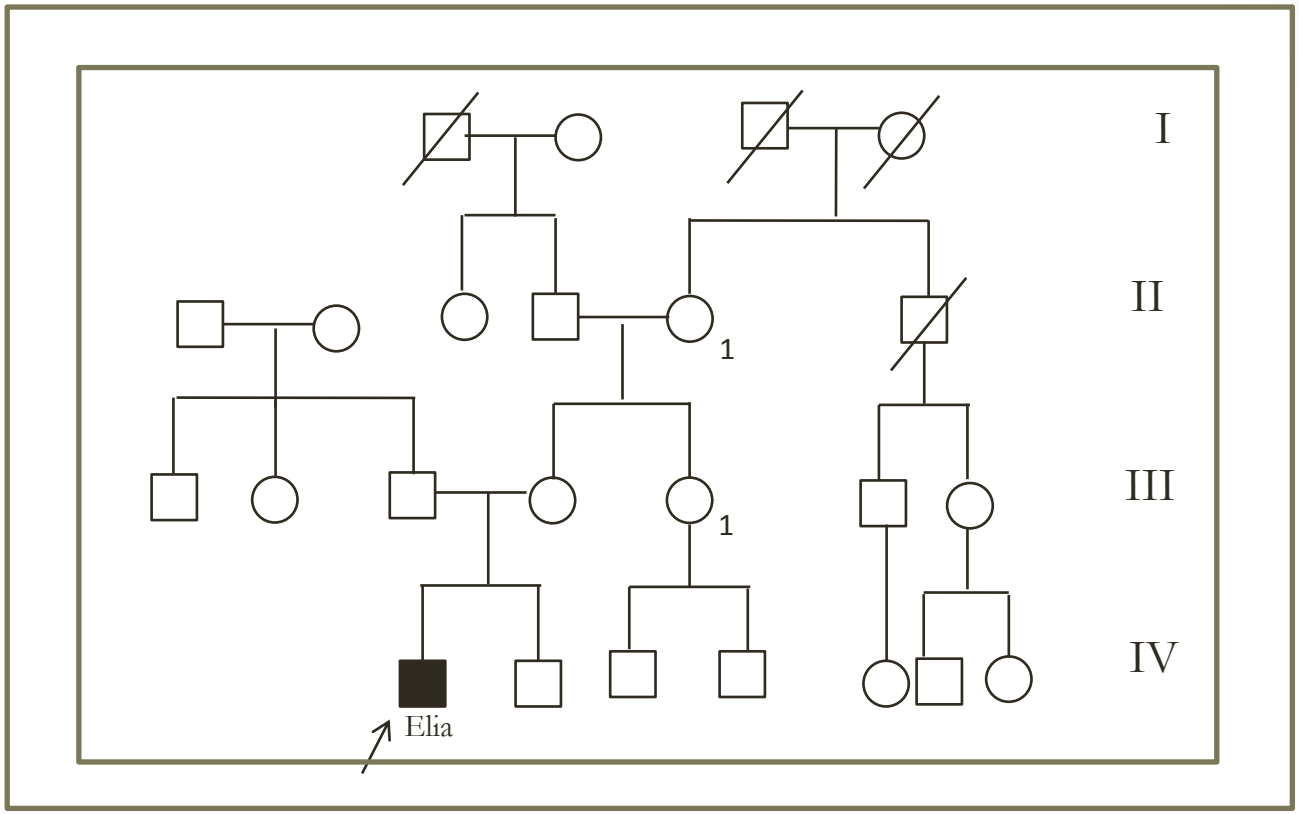
DECISIONE CLINICA:

inviare il paziente ad un approfondimento c/o il Centro della Genetica Medica

Consigli:

- Evitare situazioni scatenanti eventi cardiaci
  (stress psico-fisico importante, stimoli auditori)
  e farmaci/alterazioni elettrolitiche
- Sospensione temporanea dell'attività fisica agonistica in attesa del risultato della valutazione genetica

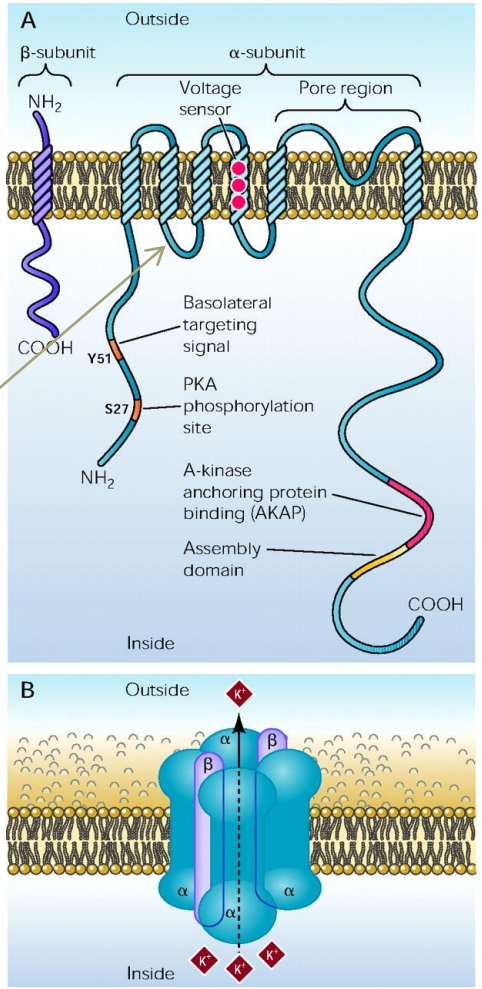
Albero genealogico



- II1: 75 anni. Riferiti episodi di cardiopalmo e affanno in montagna ad alta quota
- III1: effettuata ablazione cardiaca a 45 anni a seguito di episodi di cardiopalmo

KCNQ1 codifica per la subunità α del canale del potassio a risposta lenta (IKs)

La subunità α richiede l'assemblamento della subunità β per produrre una normale Iks (*KCNE1)*



Arg190Trp

La mutazione è tra il domain S2S3 della proteina

Per formare il canale del potassio è necessaria la cooperazione di 4 proteine KCNQ alfa e due o più beta

Jespersen T et al. The KCNQ1 Potassium Channel: From Gene to Physiological Function. Physiology 2005

KCNQ1: het ex3 c.568C>T;p.Arg190Trp

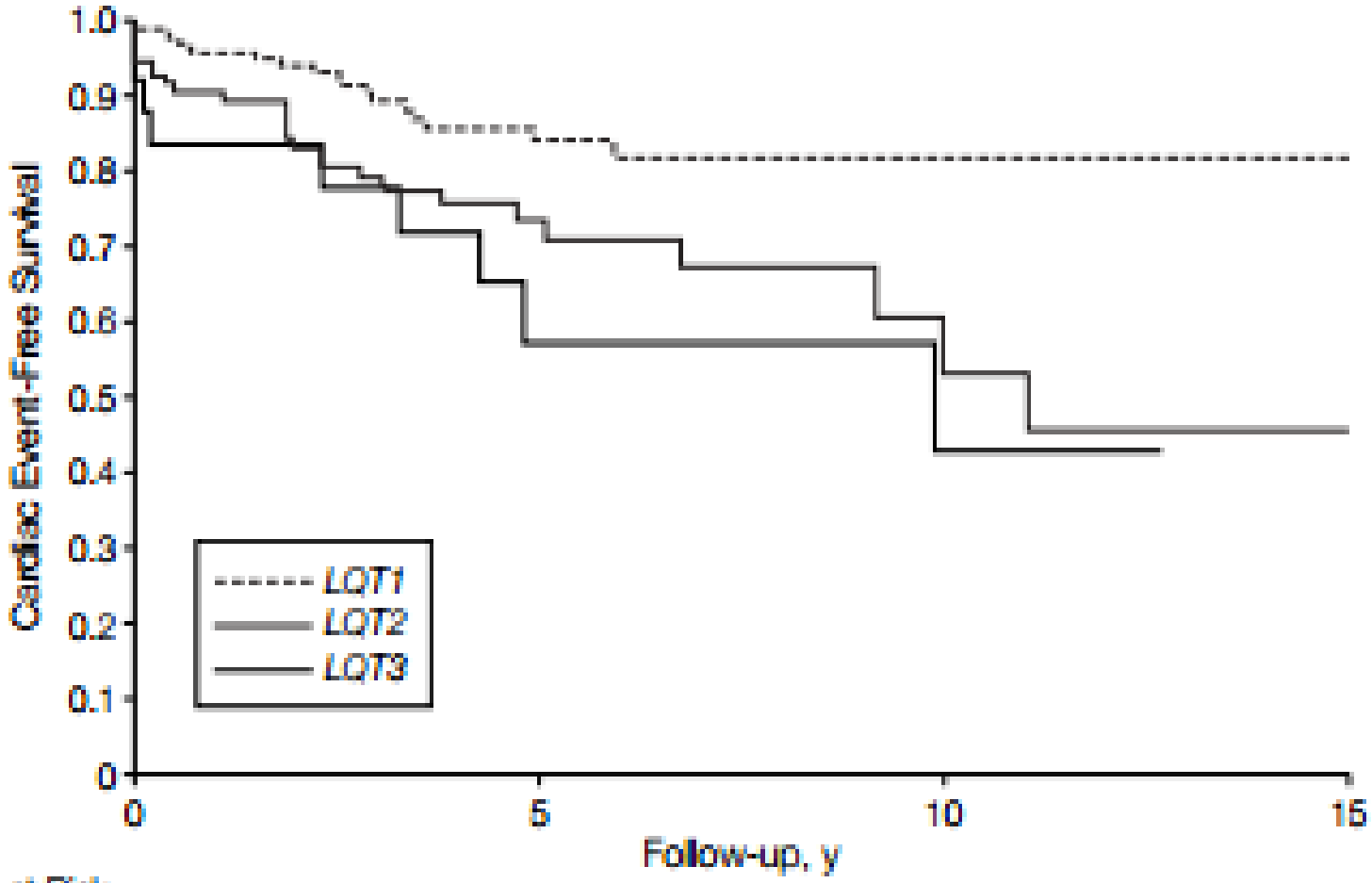
Si localizza a livello della regione S_2S_3 della proteina ed è stata identificata per la prima volta in un paziente con Long QT syndrome (Napolitano C et al., 2005); mutazione assente in 800 controlli.

In seguito descritta in eterozigosi composta con la R518X in una femmina svedese di circa 5 anni sottoposta, sin dalla nascita, a terapia profilattica con beta-bloccanti in un lavoro condotto su 19 pazienti Svedesi con diagnosi di Jervell e Lange-Nielsen syndrome (Winbo A et al., 2012).

Poi identificata in una femmina di 24 anni con storia pregressa di problematiche psichiatriche (abuso di ecstasy, tentato suicidio) trovata morta nel proprio appartamento dalla figlia (non identificata causa di morte all'esame autoptico; screening tossicologico negativo).

In conclusione:

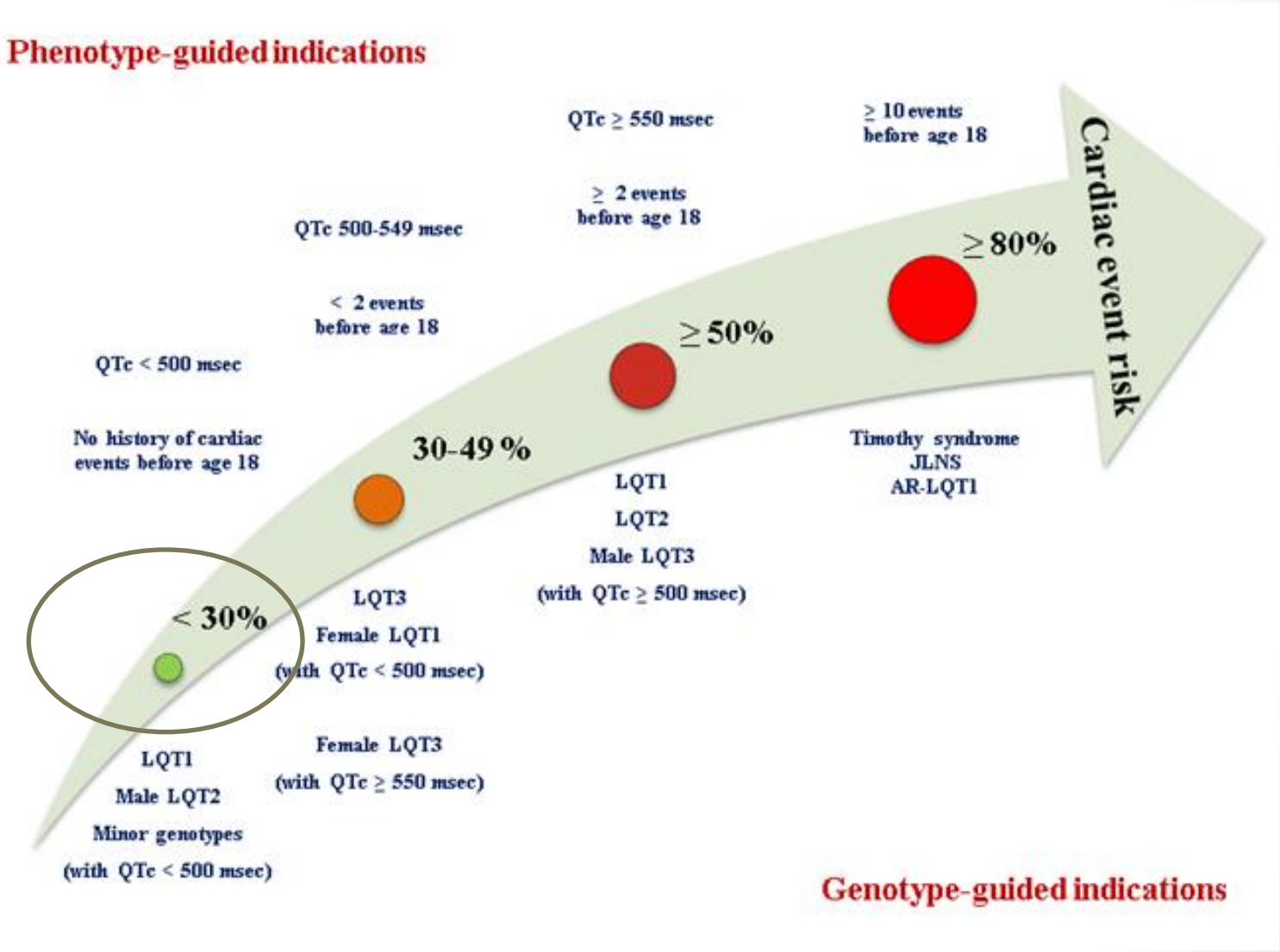
- Il rilievo della mutazione a carico gene KCNQ1 consente di porre nella sig.ra e in Elia la diagnosi di Sindrome QT lungo tipo 1.
- La gestione clinica di tale condizione è di pertinenza cardiologica e pertanto rimandiamo ai colleghi cardiologi per la programmazione di adeguata prevenzione, trattamento e follow up sia per la sig.ra che per Elia.
- Sulla base della eziologia autosomica dominante della condizione, sussiste per entrambi il 50% di probabilità di trasmettere tale condizione alla prole, indipendentemente dal sesso.
- É appropriata consulenza genetica specifica con ricerca della mutazione KCNQ1 identificata nella signora e in Elia nei familiari a rischio di essere portatori della medesima mutazione (in particolare i genitori, la sorella della signora e il figlio Lorenzo). Dati desumibili dalla letteratura sottolineano come infatti sussista un rischio di eventi cardiaci maggiori in soggetti portatori di mutazioni a carico del gene KCNQ1 con normale intervallo QTc valutabile come pari circa al 10% prima dei 40 anni di età, se non adeguatamente trattati. L'appropriatezza dell'esecuzione di tale indagine, in particolare per piccolo Lorenzo, in buona salute e ancora in minore età, verrà comunque valutata nell'ambito del colloquio in accordo con il collega Cardiologo.



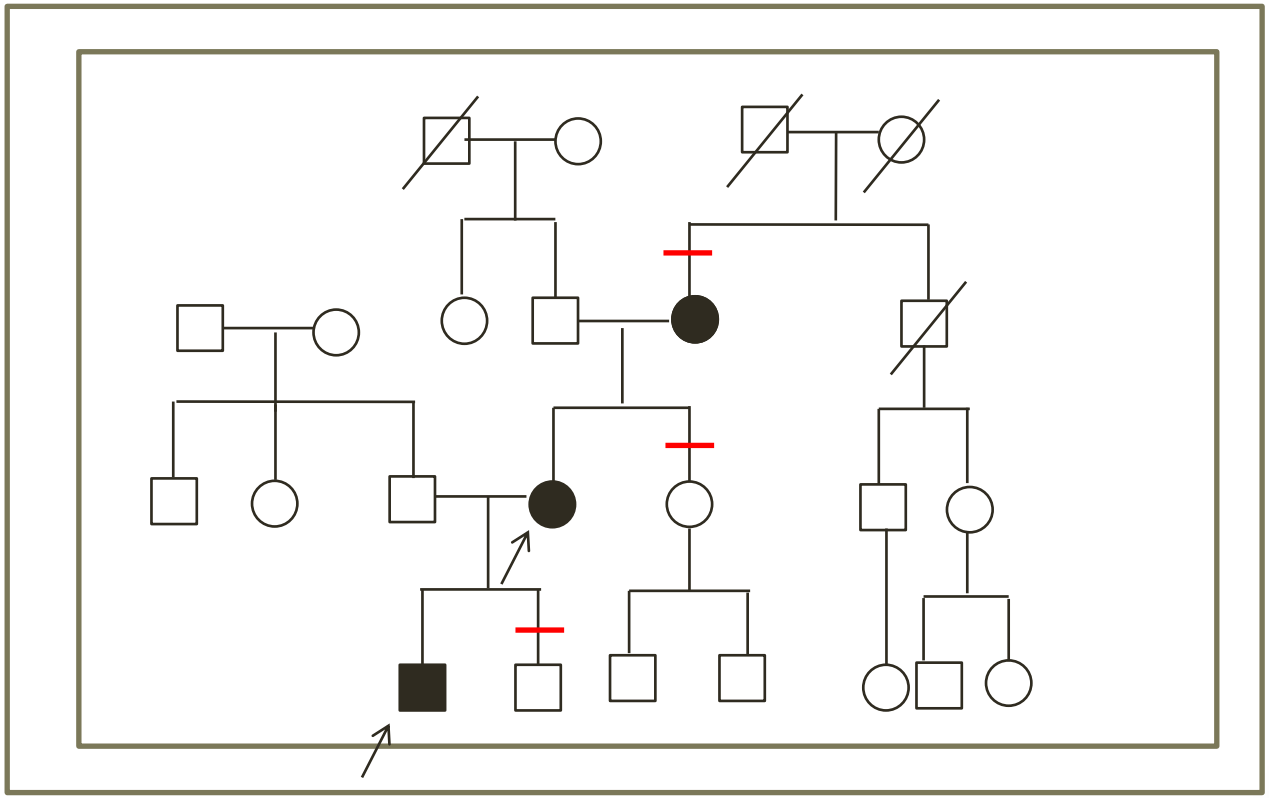
No. at Risk

LQT1	187	50	26	17
LQT2	120	30	8	4
LQT3	28	8	3	0

STRATIFICAZIONE DI RISCHIO



Studio dei familiari a rischio



Gestione clinica (ESC 2015 Guidelines):

- evitare esposizione a stress fisico (ad esempio: nuoto)
- evitare farmaci che inducano l'allungamento del tratto QTc e/o che inducano un'alterazione del livello sierico elettrolitico di potassio/magnesio/calcio
- analisi genetica ai famigliari
- Stratificazione di rischio??? Terapia? -> **beta-bloccante**

Mutazione *de novo* o in eredità?

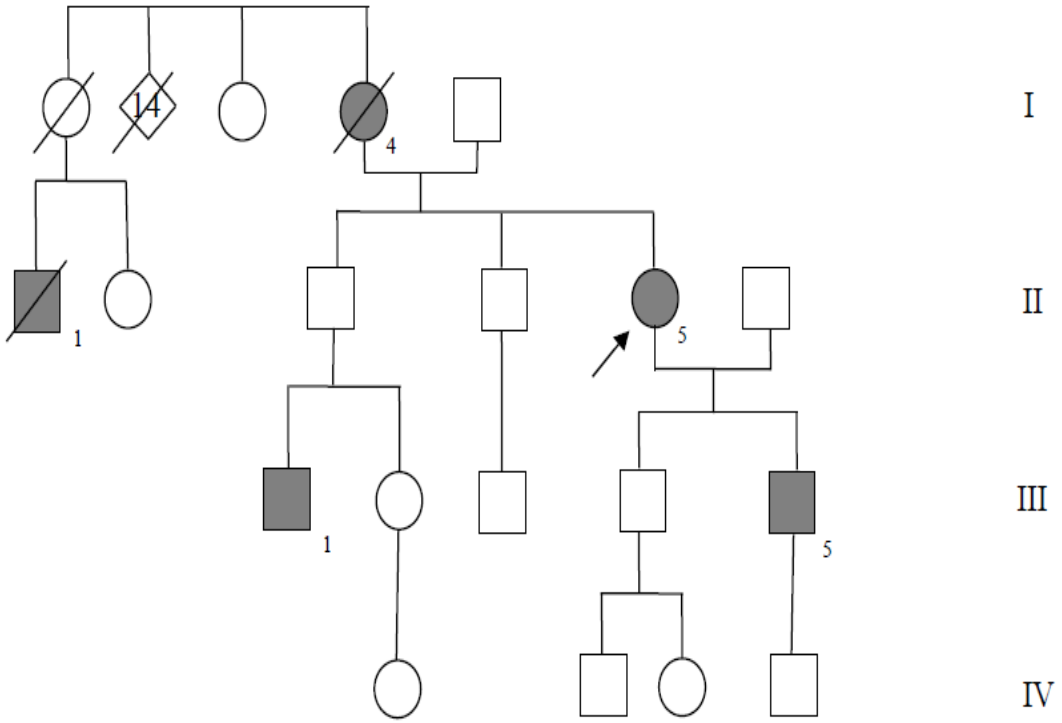
Riscontro di analoga mutazione per la **MADRE**

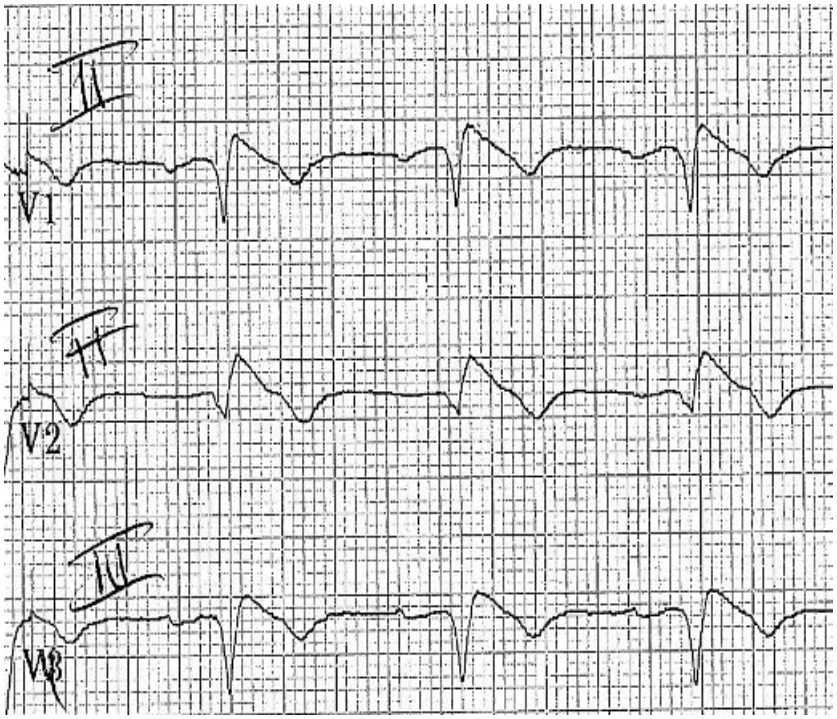
- Asintomatica
- Qtc allungato all'ECG in ortostatismo ed al monitoraggio ECG-grafico durante test ergometrico
- terapia farmacologica con beta-bloccante

La probanda (II5) è una donna di 66 anni, che all'età di 57 anni, ha avuto un episodio sincopale in corso di intervento chirurgico. In quella occasione, veniva riscontrato un pattern ECG Brugada tipo I e impiantato un defibrillatore.

Il figlio della probanda (III5) è stato valutato in relazione alla storia familiare, pur non avendo mai manifestato sintomi soggettivi. All'ECG è risultato presente un pattern Brugada tipo I e lo studio elettrofisiologico ha evidenziato inducibilità di aritmie. Vi è quindi stata l'indicazione ad impiantare un defibrillatore in prevenzione primaria per rischio aritmico.

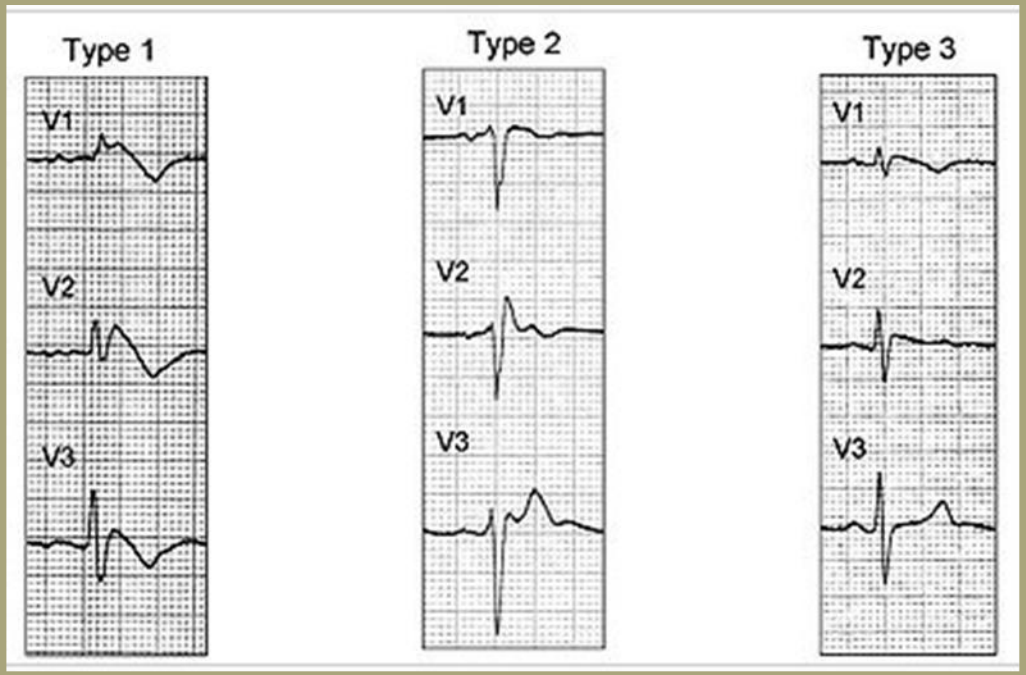
FAMIGLIA CON RICORRENZA DI SINDROME DI BRUGADA





ECG Brugada di tipo I della probanda della famiglia in analisi

Il tipo I è caratterizzato da un sopraslivellamento del punto J ≥ 2 mm, seguito da un tratto ST rapidamente discendente e un'onda T negativa (ST "coved") ed è l'unico pattern ECG Brugada considerato patologico.



Le alterazioni elettrocardiografiche sono visibili nelle derivazioni V1-V3 e sono di tre tipi, tuttavia è ritenuto diagnostico solo il tipo 1.

Gli eventi aritmici si manifestano prevalentemente nel sonno o dopo pasti abbondanti: si consiglia dunque di evitare un eccessivo introito di liquidi (soprattutto alcool) e i pasti abbondanti.

- Durante attività fisica-sportiva non si osserva un rischio di eventi aritmici, essa non è pertanto controindicata. Tuttavia, le attuali linee guida vietano lo sport a livello agonistico.

- La febbre rappresenta un elemento scatenante eventi aritmici in pazienti affetti da Sindrome di Brugada: è di fondamentale importanza intervenire prontamente in caso di febbre con farmaci antipiretici per evitare il protrarsi dell'iperpiressia.

- Alcuni farmaci interferendo con la funzione dei canali del sodio possono smascherare questi difetti elettrici cardiaci favorendo eventi aritmici; l'elenco sempre aggiornato dei farmaci da evitare è disponibile al sito: http://www.brugadadrugs.org

- E' estremamente importante, a conclusione dell'iter diagnostico, che anche i familiari vengano sottoposti ad un'accurata valutazione clinica e genetica.

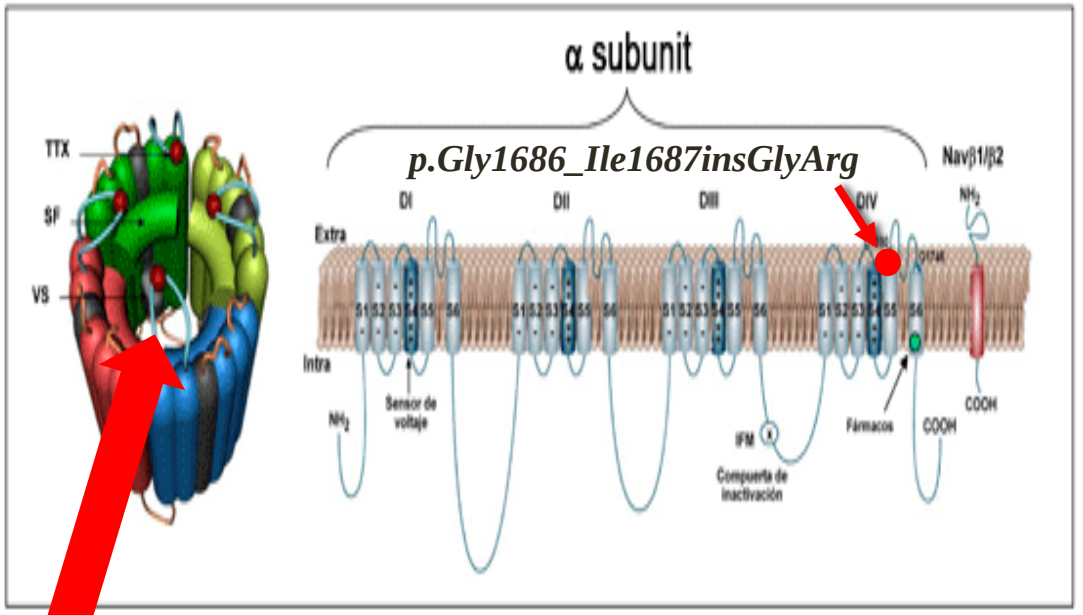

SOPHiA DDM
WORKSPACE
Requests
VDB
Variant Database Browser
ANALYSIS 1888-17PED
#20100-0030
Ospedale Sant'Anna di ...
PROJECT Interpretation 1
SAMPLE #103323 1888-17PED 17/18
RUN 07/08/2017 3.8.17
1888-17PED S17 - -
Simona Neri
PED
51 genes
Low Coverage
Patient's Disease (0)
REPORTED 0/0
PED MASTR Plus
germline
OVERVIEW SCREENING GENES SNVs/INDELs CNVs FUSION WARNINGS
Interpretation Scope: PED
Variant List - sorted by: PRED_CAT > PATHOGENICITY_CLASS > GENE
save column preferences
SOPHiA Filters
Retained Variants 258
Highly Pathogenic A 1
Potentially Pathogenic B 5
Unknown Significance C 236
Likely Benign D 16
Low Confidence Variants 170
Flagged Variants 0
Actionability T... Gene Coding consequence c.DNA Depth VF% ref alt Exon ID S...
N/A INDEL SCN5A inframe_6 c.5058_5059in... 1112 49.0 T TGCGGCC 28
Nuova mutazione identificata in SCN5A che consiste nella inserzione di 6 nucleotidi; ne consegue l'inserimento di due amminoacidi, glicina e arginina, nel dominio DIV del canale al confine tra il segmento S5 e l'ansa che collega i segmenti S5 e S6.
OVERVIEW DETAILS FLAGGING VIEWER SIMILAR PATIENTS WARNINGS SCREENING
reads 1112 DEPTH
frequencies 2/10 RUN 1% ACCOUNT .1% COMMUNITY
flagging predictions
transcript NM_000335 Exon rank 28 CDS rank
c.5058_5059insGG...
ref/alt T→TGCGGCC
sequence ATC→GGCCGCATC
amino acid I→GRI
protein p.Gly1686_Ile1687insGlyArg
Add To Report
Set To False +
strand dbSNP ID ClinVar
INDEL ins 6
inframe_
scores
POLYPHEN2 N/A
MutationTaster N/A
SIFT N/A
ESP N/A
G1000 N/A
ExAC N/A
Links
ExAC
ClinVar
COSMIC
IGV
NCBI
ALAMUT
Google
OMIM

Canale del sodio cardiaco (Nav1.5)

Il gene SCN5A è localizzato sul braccio corto del cromosoma 3 (3p21), contiene 28 esoni e codifica per la subunità α del canale del sodio cardiaco (Nav1.5), che è costituita da 2016 amminoacidi.
La subunità α di Nav1.5 costituisce il poro del canale e contiene:

- quattro domini omologhi transmembrana (DI-DIV);
- tre regioni di legame interposte tra questi.

Ciascun dominio è composto da sei segmenti transmembrana (S1-S6) legati da anse intra- ed extracellulari.



Il poro attraverso cui passano gli ioni Na^+ è delineato dai segmenti S5 e S6 e dalle anse interposte tra questi.

La nuova mutazione c.5058_5059insGCGGCC, p.Gly1686_Ile1687insGlyArg si trova nell'esone 28 del gene SCN5A e determina l'inserimento di due residui aminoacidici nel dominio DIV del canale al confine tra i segmenti S5 e S6.