Special Article

Genetic Testing for Inherited Cardiac Arrhythmias

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Research into the identification of cardiac genes has facilitated a progressive understanding of the pathophysiology of inherited arrhythmogenic diseases (IADs).[1-2] Rapid advances in genetic sequencing technology coincident with a reduction of cost promise to significantly impact modern practice with regard to heritable arrhythmia. Most importantly, epidemiological evidence supports the idea that knowledge of the type of DNA abnormality is not only a diagnostic tool, but also bears prognostic and therapeutic implications. However, the integration of genetic analysis into clinical cardiology requires specific expertise and no simplified method exists for handling genetic information on these complex disease states. In this article we will review the appropriate use of genetic testing in those patients suspected of having IADs, with specific focus on the indications for testing and the expected probability of positive genotyping.

Genetic testing: which diseases and why?

Heritable arrhythmogenic diseases are primarily caused by mutations of genes that encode for cardiac ion channels or their regulators.[3] The long-QT syndrome was the first to enter the genetic fray[4-5] and several genes were associated with IADs in the years that followed (Table 1). This information has been instrumental in the collection of a large cohort of patients in whom the establishment of genotype-phenotype correlations was set, with the final goal of utilizing the genotype as a metric for risk stratification and as a tool to support therapeutic decisions.

A general concept, independent of the specific condition, is that a positive genetic test allows one to confirm diagnosis, to identify silent carriers within families (i.e. diagnosis in asymptomatic individuals lacking clinical diagnostic criteria of a disease) and to guide reproductive counseling (Table 2). Furthermore, in selected conditions, the identification of a mutation has a further impact on risk stratification and treatment.[6] The following review will address the role of genetic testing for those IADs in which there is more experience and information available, specifically: long-QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy.

Long-QT syndrome (LQTS)

LQTS is characterized by an abnormally prolonged QT interval leading to life-threatening arrhythmia in the presence of a structurally normal heart.[7] The mean age at onset of symptoms (syncope or sudden death) is 12 years and an earlier onset is usually associated with a more severe outcome.[8] The estimated prevalence is between 1: 5,000 and 1:7,000. However, there are several fac-

Table 1. Genetic loci and genes associated with arrhythmogenic diseases.

Gene symbol	Locus Name	Chromosomal locus	Inheritance	Protein	Functional effect	Phenotype
KCNQ1	LQT1	11p15.5	AD	I_{Ks} potassium channel alpha subunit (KvLQT1)	Loss of function	Long QT
	JLN1		AR		Loss of function	Long QT, deafness
	SQT2		AD		Gain of function	Short QT
	AF1		AD		Gain of function	Atrial fibrillation
KCNH2	LQT2	7q35-q36	AD	I_{Kr} potassium channel alpha subunit (HERG)	Loss of function	Long QT
	SQT1		AD		Gain of function	Short QT
	AF2		AD		Gain of function	Atrial fibrillation
SCN5A	LQT3	3p21	AD	Cardiac sodium channel alpha subunit (Nav 1.5)	Gain of function	Long QT
	BrS1		AD		Loss of function	Brugada syndrome
	AF3		AD		Loss of function	Atrial fibrillation
	PCCD		AD		Loss of function	Conduction defect/blocks
	SSS		AD		Loss of function	Sick sinus syndrome
KCNJ2*	AND/LQT7	17q23.1-q24.2	AD	I_{K1} potassium channel (Kir2.1)	Loss of function	Long QT, potassium sensitive periodic paralysis, dysmorphic features
	SQT3		AD		Gain of function	Short QT
	AF4		AD		Gain of function	Atrial fibrillation
KCNE1	LQT5	21q22.1-q22.2	AD	I_{Ks} potassium channel beta subunit (MinK)	Loss of function	Long QT
	JLN2		AR		Loss of function	Long QT, deafness
	AF5		AD		Gain of function	Atrial fibrillation
ANK2*	LQT4	4q25-q27	AD	Ankyrin B, anchoring protein	Loss of function	Long QT, atrial fibrillation
KCNE2	LQT6	21q22.1-q22.2	AD	I_{Kr} potassium channel beta subunit (MiRP)	Loss of function	Long QT
	AF6		AD		Gain of function	
CACNA1c	TS/LQT8	12p13.3	AD/ mosaicism	Calcium channel alpha subunit	Gain of function	Timothy syndrome: Long QT, syndactyly, septal defect, patent foramen ovale
	BrS3		AD		Loss of function	Brugada syndrome with short QT
CACNB2b	BrS4	10p12	AD	Calcium channel alpha subunit		Brugada syndrome with short QT
Cav3	LQT9	3p24	AD	Caveolin	Gain of function of sodium current	Long QT
SCNb4	LQT10	11q23.3	AD	Sodium channel beta subunit	Gain of function of sodium current	Long QT
AKAP9 (yotiao)	LQT11	7q21-q22	AD	A-kinase-anchoring protein	Reduced IKs current due to loss of camp sensitivity	Long QT
SNTA1	LQT12	20q11.2	AD	alpha1-syntrophin	Increased sodium current due to S-nitrosylation of SCN5A	Long QT syndrome
GPD1-L	BrS2	3p22.3	AD	glycerol-3-phosphate dehydrogenase 1 like	Reduced sodium current	Brugada syndrome
RyR2	CPVT1	1q42-43	AD	Cardiac ryanodine receptor	Diastolic calcium release	Catecholaminergic tachycardia
CASQ2	CPVT2	1p13.3-p11	AR	Cardiac calsequestrin	Diastolic calcium release	Catecholaminergic tachycardia

AD = autosomal dominant; AR = autosomal recessive; * may cause CPVT phenocopy

tors that make a correct estimate of expected prevalence difficult: incomplete penetrance (10-35% of LQTS patients present with a normal QTc);[8] multiple mutations in 4-6% of patients;[9-10] and the fact that there may be a delay in diagnosis via misclassification as epilepsy.[11] Consequently, the actual prevalence in the population is possibly higher.

The list of LQTS-causing genes is continuously expanding and has reached a count of 12 (Table 1). Interestingly, while LQTS was initially thought to be a pure cardiac channelopathy, it is now clear that non-ion–channel encoding genes may also cause the disease.[12] Yet the concept that LQTS genes ultimately affect ionic currents, either directly (ion channel

Table 2. Clinical applicability of genetic testing in inherited monogenetic diseases.

	Expected Success Rate	Identification of silent carriers/ Diagnosis	Reproductive Risk Assessment	Prognosis	Therapy
LQTS	60-70%	+	+	+	+
CPVT	50-70%	+	+	±	–
BrS	20%	+	+	–	–
ARVC	40%	+	+	–	–
SSS	?	+	+	–	–
ATS	50-60%	+	+	+	±
SQTS	?	+	+	–	–

LQTS – long QT syndrome; CPVT – catecholaminergic polymorphic ventricular tachycardia; BrS – Brugada syndrome; ARVC – arrhythmogenic right ventricular cardiomyopathy; SSS – sick sinus syndrome; ATS – Anderson-Tawil syndrome; SQTS – short QT syndrome.

mutations) or indirectly (chaperones and/or other modulators), still holds true.

Despite the remarkable genetic heterogeneity, three genes dominate the picture: *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) cover >90% of LQTS patients with identified mutations.[13]

Knowledge of the underlying mutation has a direct clinical impact in LQTS: gene-specific differences have been described in terms of morphology of the ST-T wave complex,[14-15] triggers for cardiac events,[16] and risk of cardiac events.[8,10,17] Based on these findings, there is consensus that LQT2 and LQT3 genotypes show a worse prognosis and poor response to beta-blocker therapy. Prophylactic ICD implant may be considered in these LQTS variants when associated with QTc >500 ms and an early onset of cardiac events (<7 years of age).

Analysis of cardiac event rate with respect to the location of mutations has shown that *KCNH2* pore mutation and *KCNQ1* C-terminal mutations are independent predictors of a malignant and benign prognosis, respectively.[18-19] Though conceptually interesting, these latter findings have not been replicated and await confirmation. Additional evidence suggests that biophysical characterization of mutants may also provide important clues. For example, our group has demonstrated that the clinical response to mexiletine (a gene-specific therapy for LQT3) may be predicted on the basis of *in vitro* characterization of the underlying *SCN5A* mutation,[20] since the mutation-specific response to the drug is related to identifiable biophysical properties. This study proves the intriguing concept that *in vitro* expression can identify responders versus non-responders and directly impact care decisions; it also puts forth the idea that functional assay of mutants may become an important tool for the correct use/implementation of the results of genetic testing in the clinical setting.

Catecholaminergic polymorphic ventricular tachycardia (CPVT)

Mutations in the cardiac ryanodine receptor (*RYR2*) and calsequestrin (*CASQ2*) are responsible for the autosomal dominant and recessive variants of CPVT, respectively.[21-22] Both the *RYR2* and *CASQ2* genes are involved in the same intracellular metabolic pathway that is devoted to the control of calcium release from the sarcoplasmic reticulum.[23] The clinical presentation encompasses an unremarkable resting ECG, exercise- or emotion-induced syncopal events, and a distinctive pattern of reproducible, stress-related, bidirectional ventricular tachycardia in the absence of structural heart disease.[24] The mortality rate in untreated individuals is 30-50% by age 40 and the estimated prevalence is 1:7,000-1:10,000.[25]

Approximately 65% of genotyped CPVT patients carry an *RYR2* mutation, while the prevalence of *CASQ2* mutations is low–estimated at ~3-5% in our cohort.[26] Genetic screening allows the identification of mutations in up to 70% of patients;[24] however, genetic analysis is complicated by the fact that *RYR2* is one of the largest genes in the human genome, impacting turnaround time and comprehensive test availability.

As with other inherited forms of cardiac arrhythmia and sudden death, CPVT involves a high degree of genetic heterogeneity, with over 70 mutations reported so far–most being "private" (rare mutations isolated to a single family or few probands). Therefore, mutation scanning of the open reading frame regions of *RYR2* and *CASQ2* is the most frequently used approach for mutation detection; this is akin to sifting

through large areas to discover minor abnormalities. Most of the CPVT-*RYR2* mutations cluster in specific regions of the protein: primarily the *FKPB* binding domain (codons 2200-2500) as well as the transmembrane segments and C-terminus (starting from codon 3700). Therefore, some commercial laboratories only provide screening of select exons encompassing these critical regions. Preliminary observations from our CPVT cohort (personal communication with Priori, SG) show that 12% of *RYR2* probands have mutations *outside* of these clusters. Therefore, targeted exon analysis is likely to have lower detection sensitivity.

Aside from causing autosomal recessive CPVT, it is unclear whether *CASQ2* mutations may also cause an autosomal dominant transmission of the phenotype; cases of double heterozygosity in non-consanguineous families have been reported.[27] Therefore, it is rational to screen *CASQ2* in all *RYR2*-negative, sporadic CPVT patients.

A coherent *RYR2*/*CASQ2* screening approach has to include two additional important observations: 20% of mutation carriers have no phenotype (incomplete penetrance) and sudden cardiac arrest can be the first clinical presentation in up to 62%.[26] Therefore, CPVT may be regarded as a cause of adrenergically mediated idiopathic ventricular fibrillation (IVF), justifying genetic testing in such instances. Early CPVT genetic evaluation is very important for all family members of CPVT probands, facilitating pre-symptomatic diagnosis, diagnosis in silent carriers, and appropriate reproductive counseling. Furthermore, as beta-blockers are often an effective treatment, genetic diagnosis of CPVT is relevant in the prevention of life-threatening events.

More recently, based upon evidence that patients with Andersen-Tawil syndrome may have bidirectional ventricular tachycardia upon adrenergic stimulation,[28] it has been suggested that some CPVT cases can be explained by *KCNJ2* mutations. This point is particularly important to consider for *RYR2* and *CASQ2*-negative patients, since *KCNJ2* mutations are usually associated with a more benign prognosis and sudden death is considered an exceptional event in these cases.[29] Thus, molecular diagnosis may provide an important prognostic indication in these cases.

Brugada syndrome (BrS)

BrS is characterized by ST-segment elevation in the right precordial leads (V_1-V_3) and an increased risk of sudden cardiac death resulting from episodes of polymorphic ventricular tachycardia.[30] Although the disease is inherited as an autosomal dominant pattern, there is a striking male to female ratio of 8:1 of clinical manifestations. The estimated worldwide prevalence is 0.10%,[31] but it may reach as high as 3% in endemic areas of southeast Asia.[32] Chen et al reported the first *SCN5A* mutations identified in patients with BrS.[33] Now more than 90 *SCN5A* mutations are linked to BrS and account for 18-30% of clinically diagnosed cases.[34] Functional expression studies have shown a spectrum of biophysical abnormalities that all lead to a loss of sodium channel function.[35]

Other mutations linked to BrS include mutations in *CACNA1C* or *CACNB2*, the gene encoding the α1- or β2b-subunit of the L-type calcium channel, respectively, discovered in 3 probands with Brugada-like ST-segment elevation associated with a short QT interval.[36] Heterologous expression studies for the mutations revealed loss of function of I_{Ca}-L. Soon thereafter, mutation in a conserved amino acid of the glycerol-3-phosphate dehydrogenase 1-like (*GPD1-L*) gene was uncovered;[37] the GPD1-L mutation decreases *SCN5A* surface membrane expression and reduces I_{Na}.

Additional anecdotal reports identify *SCN1B* (sodium channel beta subunit) in a family with BrS and conduction disease[38] and a mis-sense mutation in *KCNE3*, which encodes the potassium channel β-subunit and interacts with Kv4.3 (transient outward current: I_{to}) channel to create a gain of function.[39] Since these results have not been confirmed and their relative prevalence is unknown (probably very low) the routine screening of these genes is currently not indicated. Furthermore, it is clear that approximately two thirds of Brugada patients have not yet been genotyped, suggesting the presence of additional genetic heterogeneity.[40]

Allelic disorders of *SCN5A* are found in long-QT syndrome (LQT3), progressive cardiac conduction defects, and sick sinus syndrome,[41-43] as well as myocardial abnormalities similar to those observed in arrhythmogenic right ventricular cardiomyopathy[44-45] and in dilated cardiomyopathy.[46] Approximately 65% of mutations identified in the *SCN5A* gene are associated with a BrS phenotype.[47]

Using carefully constructed clinical data to unmask the phenotype helps to facilitate decisions for genotyping. One of the key factors after recognition of the type I ECG pattern is the identification of concomitant conduction defects, as both prolonged PR ≥210 ms and HV ≥60 ms have been shown to

correlate with the presence of *SCN5A* mutations.[48] Therefore, all positive *SCN5A* patients, especially if harboring a truncated mutant, should be closely monitored for the onset of conduction abnormalities at follow up.

BrS is more frequent in southeast Asian countries and a possible explanation of the race-specific prevalence of the BrS phenotype has been suggested by Bezzina et al.[49] Resequencing of the *SCN5A* promoter region allowed these authors to identify an Asian-specific haplotype, not present among Caucasians, that is associated with lower transcription activity of the gene. The haplotype has a high frequency of 0.22 in the Asian population and it is associated with a reduced inward sodium current (I_{Na}). The clinical role of systematic genotyping of this haplotype is still undefined. Other analysis has also demonstrated that prolonged P-wave duration correlates with both *SCN5A* mutation status and inducibility of VT or VF during programmed electrical stimulation.[50,51] BrS patients have approximately a 20% incidence of supraventricular tachycardia and atrial fibrillation.[52] Overall, it appears that genotype-phenotype correlations will continue to be progressively unveiled and will continue to impact the clinical arena.

Hypertrophic cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is caused by mutations in genes encoding the sarcomeric elements of myocytes, with >90% of mutations being familial in nature.[53] To date, over 450 mutations in 21 sarcomere-related and myofilament-related genes have been identified in HCM (Table 3).[54] The resultant histopathological hallmarks of HCM –marked myocyte hypertrophy, fibrosis, and disarray– reflect the underlying pathophysiology of impaired ventricular contractility. Comparative functional analysis of HCM myectomy samples and end-stage heart failure samples has revealed a common molecular phenotype demonstrating deranged myosin phosphorylation, impaired motility, and reduced contraction amplitude and relaxation rates, irrespective of genotype.[55] Severe clinical complications, such as heart failure, supraventricular and ventricular arrhythmias, and sudden cardiac death (SCD), may ensue. Though the most prevalent (0.2%, 1:500)[56] and thus most reported and investigated of the heritable cardiomyopathies, the classification of SCD risk predictors and prognosis for HCM remains difficult and has not been definitively established. Noninvasive predictors of SCD risk include SCD in first-degree relatives, malignant genotype, unexplained syncope, abnormal blood pressure response to exercise, ectopic ventricular activity and massive septal hypertrophy (≥30 mm), as well as, more recently, scar by cardiac magnetic resonance imaging.[57]

Mutations in the genes encoding the beta-myosin heavy chain (*MYH7*), myosin-binding protein C (*MYBPC3*), and cardiac troponin-T (*TNNT2*) are responsible for more than 45% of familial HCM, and 88% of disease-causing genes reside on these three loci.[54] Analogous to what has been described for other heritable cardiac diseases, such as LQTS and BrS,[58] the consequence of mutations may vary in different carriers (incomplete penetrance and variable expressivity). It is not known what determines the severity of clinical manifestations in response to a mutation; the role of both causal mutations and of modifier genes and/or factors in the ultimate pattern of clinical expression has been advocated.

Despite such variability, some genotype/phenotype correlations have been reported for HCM-causing mutations. *MYH7* mutations, like A403G and A453C, often create highly penetrant disease phenotypes with severe myocardial hypertrophy at a young age, heart failure and unfavorable prognosis for SCD.[59] However, there are other mutations, located on the same gene, that portend a more favorable prognosis (i.e. N232S, G256E, V403Q), with less hypertrophy and less reported symptomatology.[59] These major allelic differences in disease expression have been linked to the electric charge of the missense amino acid or the specific β-subunit affected, but have yet to be substantiated.[60]

MYBPC3 mutations may produce a mild clinical course with a later age of onset, occurring in older adults and the elderly, often without displaying a strong familial history (low penetrance). The latter phenomenon may hide the heritable nature of the disease, though the gene is implicated in 30% of familial HCM cases.[61] More recently, reports have described a phenotype closer to that of *MYH7*, with adverse events occurring between the ages of 13-67 and in up to 51% of genotyped patients,[62] underlining the fact that the spectrum of clinical presentation is so broad that one single genetic factor is probably not enough to fully explain the clinical presentation.

TNNT2 mutations behave paradoxically to other sarcomeric protein genes, in that they are associated with relatively little hypertrophy (mean septal thickness of 16 mm), but a proportionately higher number of SCD events.[63] This is corroborated by evidence at

the cellular level of marked disorganization *without* hypertrophy or fibrosis,[64] an arrhythmogenic substrate that allows for slowing and inhomogeneous electrical conduction leading to re-entrant arrhythmias. The sudden death of a relative with HCM whose heart weight is normal or near normal should raise suspicion of *TNNT2* involvement.

Using HCM as the hallmark heritable cardiomyopathy, and noting the complex genotype-phenotype correlations, genetic screening is the only method which may enable the recognition of mutation carriers in the *preclinical* phase of the disease. Genotyping may also help to distinguish pathologic from normal variants, such as the athletic heart, hypertensive heart disease, or asymmetric septal hypertrophy. Implicit is the appropriate clinical evaluation prior to testing, which will help to eliminate the rare non-sarcomeric variants (termed 'phenocopies'), in which thickening of the left ventricular wall resembling HCM occurs.[65] These variations include metabolic disorders, mitochondrial cytopathies and syndromes (i.e. Noonan's syndrome, Friedrich's ataxia, Anderson-Fabry disease, amyloidosis, etc.) that may present with hypertrophy and make clinical diagnosis difficult to reconcile. Phenocopies may express more conduction disease and progression to cavitary dilatation and heart failure, as well as more extracardiac manifestations of disease, including musculoskeletal and neurologic involvement.[66]

Given the high yield of analysis for HCM, in which ~90% of patients with an identifiable mutation may be identified by screening only 4 of the 21 known genes, genotyping is recommended for the most affected individual in a given family, in order to facilitate family screening and exact disease management.[67] A reasonable expectation for positive genotyping is ~60% of affected patients, with *MYH7*, *MYBPC3*, and *TNNT2* accounting for 25-35%, 20-30%, and 3-5%, respectively.[68]

Arrhythmogenic right ventricular cardiomyopathy (ARVC)

ARVC is a disorder of the cardiac desmosome, a protein complex responsible for supporting structural stability through cell-cell adhesion, regulating transcription of genes involved in adipogenesis and apoptosis, and maintaining proper electrical conductivity through regulation of gap junctions and calcium homeostasis.[69] The estimated prevalence of the disease is 1:5000 and it is thought to be a major contributor to SCD in young people and athletes, with a mortality rate of 2-4% per year.[70] ARVC is a predominantly autosomal dominant disease characterized by myocardial degeneration and fibrofatty infiltration of the right ventricular free wall, the sub-tricuspid region, and the outflow tract. A rare autosomal recessive variant (Naxos disease), characterized by typical myocardial involvement, palmar keratosis, and woolly hair has also been described.[71]

The histopathophysiology of ARVC involves the progressive replacement of myocardial tissue with fibro-fatty tissue, predominantly in the right ventricle, but often also involving the left (in up to 25%), resulting in malignant arrhythmia of ventricular origin.[72] Seminal research by Asimaki et al has recently demonstrated that immunohistochemical analysis of human myocardial tissue obtained by routine endomyocardial biopsy can be used as a highly sensitive (91%) and specific (82%) test to delineate alterations in desmosomal proteins, diagnostic of ARVC.[73]

Mutation in genes encoding any of the five major components of the desmosome can result in ARVC, but *PKP2* (encoding plakophilin-2), *DSG2* (encoding desmoglein-2), and *DSP* (encoding desmoplakin) account for the majority: 27%, 26%, and 11% of mutations, respectively[74] (Table 3). In pooled analysis, 39.2% of individuals with ARVC who have undergone full sequence analysis of all the desmosome genes have a single, heterozygous mutation identified.[75] Currently, there is no clear risk stratification that may be gleaned from genotyping ARVC; recent studies have shown that *PKP2* genotype positive patients have symptom and arrhythmia onset at an earlier age, but prospective defibrillator events were not significantly different from the *PKP2* negative cohort.[76]

However, owing to the age-related penetrance and variable expressivity found in ARVC, enabling cascade screening in relatives becomes the principal issue, as it may avert a lifetime of clinical reassessment in extended ARVC families. Therefore, genotyping in ARVC may be recommended for confirmation of select index cases –to facilitate further family screening– but is best left to expert medical centers. The ARVC Task Force clinical criteria, in the final process of being updated, provide the best diagnostic tool for ARVC screening.[77] First-degree relatives should be screened clinically with 12-lead ECG, echocardiography, and cardiac magnetic resonance imaging.

Other inherited arrhythmias

Genes for several additional IADs aside from those

Table 3. Genes associated with hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy.

Gene	Phenotype	Inheritance	Chromosome	Protein	Estimated prevalence	OMIM	Reference
MYH7	HCM	AD	14q12	Beta-myosin heavy chain	35-45%	192600	Van Driest, SL [2004]
TNNT2	HCM, DCM	AD	1q32	Cardiac troponin T	5-10%	115195	Richard, P [2003]
TPM1	HCM, DCM	AD	15q22.1	Alpha tropomypsin	1-5%	115196	Richard, P [2003]
MYBPC3	HCM, DCM	AD	11p11.2	Cardiac myosin-binding protein	20-50%	115197	Richard, P [2003]
PRKAG2	HCM, WPW	AD	7q36	AMP-az/activated protein kinase	<1%	600858	Arad, P [2002]
TNNI3	HCM, DCM	AD	19q12.2-q13.2	Cardiac troponin I	1-5%	191044	Kimura, A [1997]
MYL3	HCM	AD	3p21	Cardiac essential mysin light chain	1-5%	608751	Poetter, K [1996]
TTN	HCM, DCM	AD	2q31	Titin	<1%	590040	Satoh, M [1999]
MYL2	HCM	AD	12q23-24.3	Cardiac regulatory myosin light chain	<1%	160781	Poetter, K [1996]
ACTC	HCM, DCM	AD	15q14	Actin	<1%	102540	Mogensen, J [1999]
CSRP	HCM	AD	11p15.1	Cysteine and glycine rich protein 3	1%	612124	Geier, C [2008]
MYOZ2	HCM	AD	4q26-q27	Myozenin 2	unknown/rare	605602	Osio, A [2007]
TNNC1	HCM	AD	3p21.3-14.3	Cardiac troponin C	0.40%	191040	Kimura, A [1997]
MYH6	HCM	AD	14q12	Alpha-myosin heavy chain	<1%	160710	Carniel, E [2005]
MYLK2	HCM	AD	20q13.3	Myosin light chain kinase 2	unknown/rare	606566	Chaudoir, B [1999]
MYO6	HCM, deafness	AD	6q13	Myosin VI	unknown/rare	606346	Mohiddin, S [2004]
NDUFV2	HCM, encephalopathy	na	18p11.3-11.2	NADH dehydrogenase ubiquinone flavoprotein 2	unknown/rare	600532	Benit, P [2003]
MTTI	HCM, DCM	Matrilineal	Mitochondrial DNA	tRNA isoleucine and tRNA glycine	unknown/rare	590045	Prasad, G [2006]
MTTH	HCM, DCM	Matrilineal	Mitochondrial DNA	tRNA histidine	unknown/rare		Prasad, G [2006]
LAMP2	HCM, muscle weakness, mental retardation, glycogen storage	XD	Xq24	Lysosome-associated membrane protein 2	unknown/rare	300257	Arad, M [2005]
GLA	HCM, isolated or with Fabry phenotype	XD	Xq22	Alpha-galactosidase-A	unknown/rare	301500	Sachdev, B [2002]
JUP	ARVC	AD	17q21	Plakoglobin	<1%	173325	McKoy, G [2000]
DSP	ARVC	AD	6p24	Desmoplakin	6%-16%	125647	Rampazzo, A [2003]
PKP2	ARVC	AD	12p11	Plakophilin-2	11%-43%	602861	Dalal, D [2006]
DSG2	ARVC	AD	18q12.1-q12.2	Desmoglein-2	12%-40%	125671	Pilichou, K [2006]
DSC2	ARVC	AD	18q12.1	Desmocollin-2	<1%	125645	Syrris, P [2007]
RYR2	ARVC	AD	1q42.1-q43	Ryanodine receptor	<1%	180902	Tiso, N [2001]
TGFB3	ARVC	AD	14q24	Transforming growth factor Beta subunit 3	<1%	190230	Beffagna, G [2005]

OMIM – Online Mendelian Inheritance in Man database reference; HCM – hypertrophic cardiomyopathy; DCM – dilated cardiomyopathy; ARVC – arrythmogenic right ventricular cardiomyopathy; AD – autosomal dominant; XD – X-linked dominant

mentioned have been identified and reported in the literature (Table 1). Since many of these phenotypes are allelic to LQTS or Brugada (for example, all short QT syndrome genes are allelic to LQTS), the methodology to implement genetic screening for such conditions has been readily available upon initial gene discovery. A common denominator of these conditions is their infrequency and relatively limited knowledge of genotype-phenotype correlations. Therefore genetic screening may bear diagnostic implications, but it is currently of no value for risk stratification and therapeutic management.

Cost-effectiveness

The science utilized in genotyping and mutational analysis carries considerable financial costs, although these are progressively diminishing as technique and technology advance. Reimbursement policies dealing with this issue are universally lacking, an impediment prohibiting further incorporation into clinical practice. The percentage of successfully identified patients (detected mutations) is not the only parameter to consider in the assessment of the indications for genetic testing. Several additional parameters (such as possibility of guiding therapy and risk stratification) should also be considered as inexorably linked to the cost-effectiveness definition. Unfortunately, as of today there have been few attempts to quantify the cost-effectiveness of genetic testing.

We have recently performed a survey of the performance of genetic screening and we estimated the cost for each detected mutation according to the clinical presentation.[78] This study outlines the fact that the performance of genetic diagnosis is directly linked to the entry criteria and can be performed at reasonable cost in individuals with a conclusive diagnosis –specifically, LQTS, CPVT, and BrS with atrioventricular block– a fact that would likely extend to both HCM and ARVC. In LQTS, the cost for one positive test is acceptable (US$13,402) but it varies dramatically if the patient has a "definite" LQTS diagnosis (yield 64%, US$8,418) or if one presents as an unselected family member of someone with IVF (yield 2%, US$221,400) (Figure 1A). The presence or absence of symptoms may also be a determinant of cost-effectiveness for LQTS genetic testing (US$2,500 per year of life saved) according to some authors.[79] A clear correlation between clinical presentation and performance is also evident in BrS and CPVT, although *RYR2* and *CASQ2* screening for adrenergically triggered IVF (without previous clinical diagnosis) demonstrated better performance (15% of detected CPVT mutations in adrenergic IVF, with US$21,560 per positive test). *SCN5A* screening in BrS has an unsatisfactory performance overall, unless atrioventricular block is also present (Figure 1B).

In summary, genetic testing for IAD may be cost-effective outside the research labs with a careful selection of patients based on clinical presentation. It is clear that careful phenotyping through disease and patient specific correlations are the key to controlling costs; arriving at a genetic diagnosis is not synonymous with ordering a "Familion test".[80] Moreover, the integrated expertise of a cardiogenetics team is best suited for the labor, time, and resource-intensive longitudinal care that necessarily ensues following a positive diagnosis of an inherited arrhythmogenic disease. Cost-effectiveness estimates are based on current technology and related costs. It is likely that future technological improvement will lead to significant reductions in cost and turnaround time.

Limitations

Only few years ago, genetic testing for inherited arrhythmogenic diseases was provided only within research labs; more recently, the increasing availability of commercial testing is making this service more accessible to the medical community. While in principle this is a positive advance, it is also clear that it poses some issues: the interpretation of genetic findings is *not* straightforward and expert opinion is often necessary in order to place the results of genetic testing in their proper place within the patient's clinical profile.

The identification of a previously reported mutation with clear co-segregation evidence, high penetrance and, even more, with known biophysical consequences (*in vitro* expression data), is very helpful for clinical management. On the other hand, the identification of novel mutants in sporadic cases or in families with low penetrance, in the absence of functional information, generates uncertainties in interpretation and requires evaluation in professional referral centers with specific expertise and experience in diagnosis and treatment of IADs and cardiovascular genetics –a notion supported by larger governing bodies.[67] Hurdles may arise from the interpretation of mutations detected on the less frequent genes (e.g. Caveolin in LQTS or GPD1-L in BrS) for which the underlying pathophysiology and genotype-phenotype correlation are less well understood.

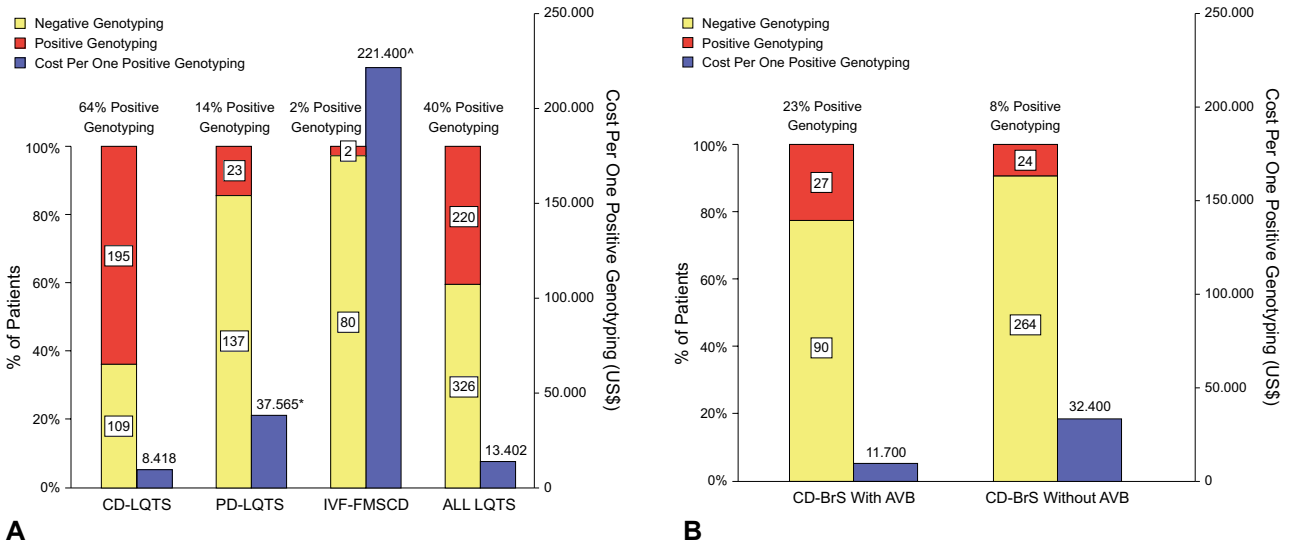

Figure 1. Cost-effectiveness data for long-QT syndrome (LQTS) and Brugada syndrome (BrS). A. LQTS: Yield of genetic testing, defined as percentage of patients with positive genotyping (left y-axis, red bars), and cost in US$ per 1 positive genetic screening (right y-axis, blue bars) in patients screened for mutations in genes associated with LQTS. The actual number of positively/negatively genotyped patients is also reported in the bars. (*p<0.0001 compared with CD-LQTS; †p<0.008 compared with PD-LQTS.) B. BrS: Yield (left y-axis, red bars) and cost in US$ per 1 positive genetic screening (right y-axis, blue bars) in patients with a conclusive diagnosis of BrS according to the presence/absence of atrioventricular block (AVB). The actual number of positively/negatively genotyped patients is also reported in the bars. (*p<0.0001 compared with CD-BrS with AVB.)

Additional factors that limit the current clinical applicability of genetic testing may also include: 1) low prevalence of a specific genetic variant preventing the collection of adequate study cohorts for genotype-phenotype correlation studies; 2) variability of phenotype in subjects with the same genetic defect; 3) variable and time-dependent expressivity; and 4) direct technical limitations.

The role of single nucleotide polymorphisms (SNPs) is attracting particular focus within the scientific community as a potential explanation of the reduced standardization capability as mentioned above. SNPs may act as modifiers of the clinical expressivity of IADs, modulate penetrance, and may create uncertainties in the interpretation of genetic testing. Many SNPs are known to exist in the LQTS genes.[81] Recent evaluation of 744 apparently healthy subjects found that 14% of white subjects and 25% of African American subjects had at least one rare SNP in the 4 LQTS genes (*KCNQ1*, *KCNH2*, *MinK*, or *MiRP1*).[82]

The role of SNPs in molecular electrophysiology is still open to debate: widespread occurrence indicates that they are neither necessary nor sufficient to cause a disease, but it is likely that at least some of them can lead to a reduced repolarization reserve. Several polymorphisms, like the T8A polymorphism in *MiRP1* and the S1102Y polymorphism in *SCN5A*, have been demonstrated to be involved in drug-induced QT prolongation and pro-arrhythmia, despite there being a normal QT interval in the absence of QT-prolonging drugs.[83-84] More recently, genetic association studies have highlighted the idea that several chromosomal loci, not strictly related to ion channel encoding genes (such as the case of *NOS1AP*), contribute to the definition of QT interval duration variability and the risk of sudden death in the population.[85] It is possible that these factors also play a role in IADs and that they will be included in both risk stratification algorithms and in routine genetic testing in the future.

It is important to note that the prevalence of technically undetectable mutations using DNA sequencing in the current IADs testing arena is unknown, but the take-home concept is that negative screening of a given gene cannot rule out the presence of a mutation with 100% certainty.

Conclusion

Indications for genetic testing of IADs are progressively expanding due to the identification of novel genes, improvement of genotype-based risk stratification algorithms and technological improvements. The

diagnostic and prognostic value of each identified mutation depends on the specific disease and must be viewed in the light of the clinical findings. The resultant integration between the expected yield of genetic screening and cost may allow the formation of criteria to prioritize access for those who could derive the greatest clinical benefit.

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