

# Genetic testing in specific cardiomyopathies

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## Abstract

An increasing number of genetic tests for cardiomyopathies are becoming available for clinical use. This commentary will give a short overview of indications and challenges concerning genetic testing for these conditions.

## Introduction and context

Over the last decade, we have witnessed a number of cardiomyopathies entering the genetic era. Considerable knowledge of pathophysiology in these diseases has originated from the discovery of mutations in genes encoding ion channel proteins and structural cellular proteins. Pathophysiological considerations have led to a redefinition of cardiomyopathies [1]. There are several cardiomyopathies for which genetic diagnostics are available and should be considered in a clinical setting, such as the electrical cardiomyopathies, including the long and short QT syndrome (LQTS and SQTs), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT), and the cardiomyopathies with structural alterations, including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Genetic tests for these diseases have varying degrees of accessibility and sensitivity. Before genotyping is initiated, a clinical phenotype has to be present. Genotyping may confirm the diagnosis and provide additional risk information. Most of the inherited cardiomyopathies are autosomal dominantly inherited. Having a mutation carrier in the family implies that the risk for a sister, brother, child, or parent to carry the family mutation is 50%. Family screening targets these family members. Genetic screening can identify individuals who may develop cardiomyopathy and has the

additional substantial benefit of assuring approximately 50% of the tested relatives of their negative mutation status.

## Recent advances

Molecular genetic studies continually demonstrate additional genes and loci associated with different cardiomyopathies (Table 1). Consequently, more patients receive a molecular genetic diagnosis and more family members are involved in screening procedures.

Genotype data have been known for a limited time and in a restricted number of populations. Therefore, genotype-phenotype data still have to be collected to guide the clinician in managing mutation carriers and their family members. Indeed, there appear to be differences between the phenotypic consequences of mutations in different genes and also between different mutations in the same gene [2]. An illustration of the advantage of genotyping is to detect *lamin A/C* carriers among patients with idiopathic DCM. These mutation carriers have increased risk of conduction disorders and arrhythmic events in addition to ventricular dilatation and heart failure [3]. Therefore, every *lamin A/C* mutation carrier has to be risk-stratified regarding malignant arrhythmias. In this setting, knowing the genotype allows one to focus the clinical resources on the high-risk individuals among DCM patients. Recent insight has raised the awareness of the risk of malignant arrhythmias and sudden cardiac death in individuals who carry a mutation for a cardiomyopathy

**Table 1. Specific cardiomyopathies and genes available for screening in a clinical setting**

Disease	Genes
Arrhythmogenic right ventricular cardiomyopathy	<i>PKP2, DSP, DSG2, DSC2, JUP</i>
Hypertrophic cardiomyopathy	<i>MYH7, MYL3, MYL2, ACTC, TNNT2, TPM1, TNNI3, MYBPC3, TTN</i>
Dilated cardiomyopathy	<i>LMNA, MYH7, TNNT2, TPM1, TNNI3</i>
Long QT syndrome	<i>KCNQ1, HERG, SCN5A, KCNE1, KCNE2, KCNJ2</i>
Short QT syndrome	<i>KCNQ1, HERG, KCNJ2</i>
Catecholaminergic polymorphic ventricular tachycardia	<i>RyR2, CASQ2</i>
Brugada syndrome	<i>SCN5A, CACNA1C, CACNB2b, CACNA2D1</i>

with structural alterations but who have not yet developed any structural changes. This is applicable for DCM and ARVC mutation carriers, who have increased risk for sudden cardiac death even before the development of clinical, manifest, structural changes.

### Implications for clinical practice

Patients with cardiomyopathies should be treated in specialized centers that have access to genetic analyses and genetic counselling. Genetic testing is indicated in patients with LQTS and CPVT phenotypes [4]. Particularly in LQTS, the genotype provides additional information about risk for arrhythmias [5]. Concomitant use of several drugs for other diseases (for example, erythromycin) represents an additional risk factor for arrhythmias. Genotype information is also helpful in decisions regarding implantable cardioverter defibrillator (ICD) therapy. In the large majority of LQT patients, beta-blocker therapy is obligatory as the first-choice option to reduce mortality and life-threatening events. In LQT2, the arrhythmic events are usually fewer than in LQT1 but are often severe. In both LQT1 and LQT2 patients (which together account for about 90% of LQT patients), ICD therapy should be considered in case of insufficient response on beta-blocker therapy and is obligatory after cardiac arrest. In LQT3 syndrome, beta-blocker therapy is doubtful since arrhythmic events usually occur at rest. ICD is the therapy of choice in LQT3 patients. Furthermore, genetic testing is important for identifying family members who are mutation carriers and at risk of cardiac arrhythmias. For relatives carrying an LQTS- or CPVT-associated mutation, prophylactic beta-blocker treatment should be offered after individual risk assessment.

SQTS has been described in few patients [6-8]. Genetic testing has a potential clinical role [4]. Treatment is limited to ICD implantation, although medical treatment with quinidine may be considered [9].

In Brugada syndrome, genetic testing has a potential clinical role [4]. Genetic testing allows the identification of a mutation in 15-20% of patients [10]. Preventive ICD therapy should be considered in mutation carriers with

syncope or with a malignant family history. Silent mutation carriers may benefit from prophylactic pharmacological treatment with quinidine [11-13]. Prospective trials regarding quinidine treatment are in progress [14].

Genetic testing is indicated in HCM patients. About 60% of index cases with HCM are heterozygous for mutations in a known disease-causing gene [15]. In normotensive HCM patients who are mutation-negative, the clinician may consider rare diseases like amyloidosis or Fabry disease. In clinical practice, however, HCM usually is not diagnosed by genetic testing, but with imaging techniques. In HCM mutation-positive patients, genotyping so far has contributed only modestly to risk assessment, although mutations in the *MYH7* gene may carry some prognostic information [4]. Family members of mutation-positive HCM patients should be screened for the family mutation as this allows a presymptomatic diagnosis and facilitates the allocation of resources to high-risk individuals.

DCM in association with conduction defects indicates a higher probability of *lamin A/C* mutations. Genetic screening in this subgroup of DCM patients therefore is simple and cost-efficient [4]. Implications for family members are considerable as mentioned above [3]. In patients with DCM without conduction defects, current guidelines propose genetic testing in the presence of a family history of cardiomyopathy or a relative with sudden unexplained death before age 35, indicating a genetic etiology [16]. However, the decision of when to start prophylactic treatment is still a challenge.

Genetic testing should be considered in ARVC patients [17]. Relatives carrying the family mutation have increased risk of arrhythmias and should be examined with electrocardiogram, Holter recording, exercise testing, imaging, and (if needed) electrophysiologic studies and biopsies for risk stratification. Onset is rare during childhood but is common during adolescence [17]. A recommendation of avoiding long-time endurance sports may be indicated as such athletes appear to have more severe forms of the disease [15].

In conclusion, the value of genetic testing for cardiomyopathies is specific to each disease. Genotyping should be performed when a clinical phenotype is present and may confirm diagnosis and provide added value in risk stratification. The management of each patient is based on clinical criteria. Family genetic screening identifies mutation carriers among relatives, and preventive treatment can be provided in high-risk individuals.

### Abbreviations

ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; LQT, long QT; LQTS, long QT syndrome; SQTS, short QT syndrome.

### Competing interests

The authors declare that they have no competing interests.

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