Genetic testing for inherited heart diseases

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A genetic diagnosis for an inherited heart disease enables cascade screening of at-risk family members. A positive gene result identifies asymptomatic gene carriers at the earliest preclinical stages of disease development, and a negative gene result provides reassurance and eliminates years of unnecessary clinical surveillance. Commercial genetic tests are available for most inherited heart diseases.

Key points

- **Most inherited heart diseases have an autosomal dominant inheritance.**
- **Inherited heart diseases are clinically and genetically diverse.**
- **The key role of genetic testing for inherited heart diseases is cascade screening of at-risk family members.**
- **Pre- and post-test genetic counselling is required in all cases.**
- **The optimal model of care is a specialised multidisciplinary clinic approach.**

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Over the past 25 years major advances have been made in defining the genetic basis of inherited heart diseases, and more than 40 different cardiovascular diseases have now been identified as being directly caused by mutations in genes that encode cardiac proteins. These cardiovascular diseases include inherited cardiomyopathies, primary arrhythmogenic diseases (also known as cardiac ion channelopathies), metabolic and vascular disorders, and congenital heart diseases. Identification of the genetic causes of inherited disease has led to improved and earlier diagnosis of at-risk individuals, and in some cases is helping to guide therapy and inform prognosis.

The development of new genetic testing technologies, particularly in the past five years, has led to rapid progress in the availability of commercial genetic tests. These tests now often comprise panels of genes (from 50 to 100 genes) to cover the various genetic disorders, and have short turn-around times and decreasing costs. The main utility of cardiac genetic testing is the ability to perform cascade genetic testing in at-risk family members.[1] A positive gene result has the potential to identify people who are asymptomatic gene carriers at the earliest preclinical stages of disease development, while a negative gene result will provide reassurance and eliminate years of unnecessary clinical surveillance. The benefits of genetic testing must always be considered in the setting of clinical, lifestyle, ethical and psychosocial implications of such testing, especially in children.

What are the inherited heart diseases?

More than 40 inherited heart diseases are currently known. A major subgroup is the inherited cardiomyopathies, which include

hypertrophic cardiomyopathy (HCM), familial dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM) and left ventricular noncompaction (LVNC). The other major subgroup is the primary arrhythmogenic disorders, which include familial long QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), cardiac conduction disease (CCD) and idiopathic ventricular fibrillation (IVF). The more common disease genes in inherited heart diseases are summarised in the Table.[1]

Inherited heart diseases have several common features: collectively, they are most often inherited as autosomal dominant traits (i.e. one in two risk of inheriting the disease gene), show marked variability in onset and severity of symptoms, have similar limitations regarding genetic testing (suboptimal pick-up rates, multiple mutation genotypes and difficulty interpreting gene test results) and require ongoing clinical surveillance of at-risk family members. Their most notable common feature, however, is the occurrence of sudden cardiac death.

Patients and families with inherited heart diseases need specialised multidisciplinary care (Figure 1).[2] This care includes prevention strategies such as clinical screening of at-risk relatives, prevention therapies such as antiarrhythmic medications and implantable cardioverter defibrillator (ICD) therapy, thorough investigation of the family history, structured long-term family follow up and general support.[3]

Two of the more common inherited heart diseases, HCM and LQTS, are discussed below.

Hypertrophic cardiomyopathy

HCM has an estimated prevalence of up to one in 200 of the general population and is a primary disorder of the myocardium characterised by left ventricular hypertrophy in the absence of other loading conditions such as hypertension.[4] HCM remains the most common structural cause of sudden cardiac death in individuals aged younger than 35 years, including competitive athletes.[5] Mutations in at least 14 causative genes, all encoding sarcomere or sarcomere-related proteins, have been identified as causing HCM, with a genetic diagnosis in 40 to 50% of families.[4]

In general, a genetic diagnosis in a proband has little prognostic or therapeutic value in HCM, but subsequent cascade genetic testing of asymptomatic relatives has significant benefit. For this reason, HCM genetic testing is widely advocated as a key component of family management.

Long QT syndrome

LQTS is less common than HCM, with a prevalence of up to one in 2500 of the general population.[6] LQTS is a primary arrhythmogenic disorder and patients are often identified by QT prolongation on electrocardiography during clinical evaluation of unexplained syncope or palpitations, or as part of clinical screening due to a new diagnosis of a family member. The clinical course of patients with LQTS is variable and is influenced by the length of the corrected QT interval, gender, environmental factors, therapy and, importantly, genotype.

LQTS is caused by mutations in cardiac ion channel genes and is inherited mainly as an autosomal dominant trait. A causative mutation is identified in 75 to 80% of patients. Mutations in the three main genes *KCNQ1*, *KCNH2* and *SCN5A* account for up to 90% of genotyped LQTS patients (genotypes LQT1, LQT2 and LQT3, respectively). Importantly, unlike with other genetic heart diseases such as HCM, a genetic diagnosis can have prognostic and therapeutic implications for patients with LQTS. For example, the different LQT genotypes respond differently to beta-blocker therapy and have different overall prognoses, although genotype typically is never considered alone.

Who should have cardiac genetic testing and what are the benefits?

Genetic testing should be considered in all patients with inherited heart disease. As a general rule, the family member with the most definite clinical phenotype and most symptomatic disease should be selected for genetic testing. A clear phenotype, coupled with a definite family history of disease, will maximise the pre-test probability of obtaining a positive (informative) genetic result with a pathogenic (disease-causing) mutation. A complete cardiogenetic evaluation is required, which includes being certain of the clinical diagnosis in the proband. A positive gene result in the proband will facilitate cascade genetic testing in other family members.

The pathway of genetic testing in a specialised cardiac genetic clinic is summarised in the flowchart. In a proband with an autosomal dominant inherited heart disease, there will be a 50% chance of a first-degree relative having a positive genetic test. In those who carry

Table. Common disease genes in major inherited heart diseases*

Disease	Gene	Protein	Percentage of disease
Cardiomyopathies			
Hypertrophic cardiomyopathy (HCM)	*MYBPC3*	Cardiac myosin-binding protein C	20 to 45%
	MYH7	β-Myosin heavy chain	15 to 20%
	TNNT2	Cardiac troponin T type 2	1 to 7%
	TNNI3	Cardiac troponin I type 3	1 to 7%
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	*PKP2*	Plakophilin 2	25 to 40%
	DSG2	Desmoglein 2	5 to 10%
	DSP	Desmoplakin	2 to 12%
	DSC2	Desmocollin 2	2 to 7%
Dilated cardiomyopathy (DCM)	*TTN*	Titin	15 to 20%
Dilated cardiomyopathy with cardiac conduction defect (DCM + CCD)	*SCN5A*	Cardiac sodium channel alpha subunit (NaV1.5)	5 to 10%
	LMNA	Lamin A/C	10 to 15%
Left ventricular non-compaction (LVNC)	*MYBPC3*	Cardiac myosin-binding protein C	~10%
	MYH7	β-Myosin heavy chain	~10%
	LBD3	LIM binding domain 3	~5%
Restrictive cardiomyopathy (RCM)	*MYH7*	β-Myosin heavy chain	~5%
	TNNI3	Cardiac troponin I type 3	~5%
Primary arrhythmogenic disorders			
Long QT syndrome (LQTS)	*KCNQ1* (LQT1)	IKs potassium channel alpha subunit (Kv7.1)	30 to 35%
	KCNH2 (LQT2)	IKr potassium channel alpha subunit (Kv11.1 or hERG)	25 to 40%
	SCN5A (LQT3)	Cardiac sodium channel alpha subunit (NaV1.5)	5 to 10%
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	*RYR2* (CPVT1)	Ryanodine receptor 2	60%
Brugada syndrome (BrS)	*SCN5A*	Cardiac sodium channel alpha subunit (NaV1.5)	20 to 30%
Cardiac conduction disease (CCD)	*SCN5A*	Cardiac sodium channel alpha subunit (NaV1.5)	5%

* Adapted from Ackerman, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Heart Rhythm 2011; 8: 1308-1339.[1]

the gene mutation, regular clinical surveillance as per the disease-specific guidelines is followed. In those who have a negative cascade genetic test, no further clinical evaluation is required and the individual can be released from potentially decades of clinical screening, as can their children. This relies on a high level of certainty in the pathogenicity of the variant in question. Therefore, it is always important in cascade cardiac genetic testing that the benefits outweigh the harms and that decisions are made in a fully informed and patient-centred process.[6]

What does cardiac genetic testing involve?

Cardiac genetic testing is not a simple blood test and requires several best practice approaches. Careful and detailed phenotyping is required to ensure the correct genetic test is chosen. There needs to be a clinical level of certainty that a patient has HCM and not left ventricular hypertrophy due to hypertension. Similarly, a complete clinical evaluation is needed to ensure a diagnosis of LQTS or BrS. Patients therefore need expert clinical evaluation at least at a specialist level, and in many cases at a tertiary referral centre that

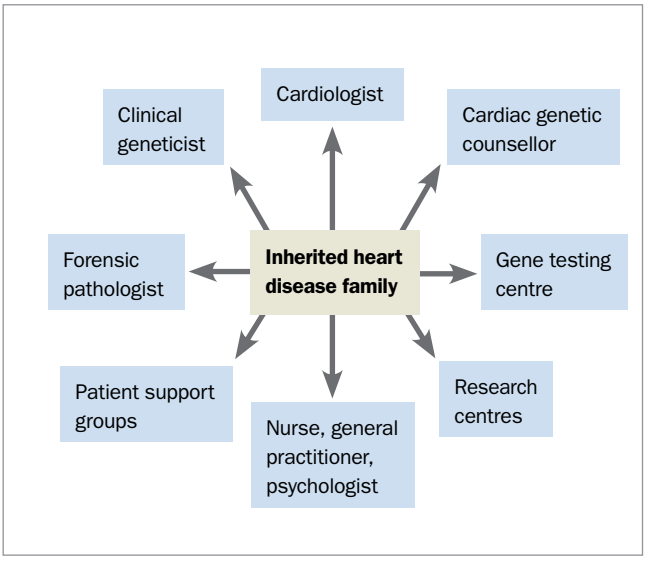

Figure 1. Specialised multidisciplinary approach to care of families with inherited heart diseases.

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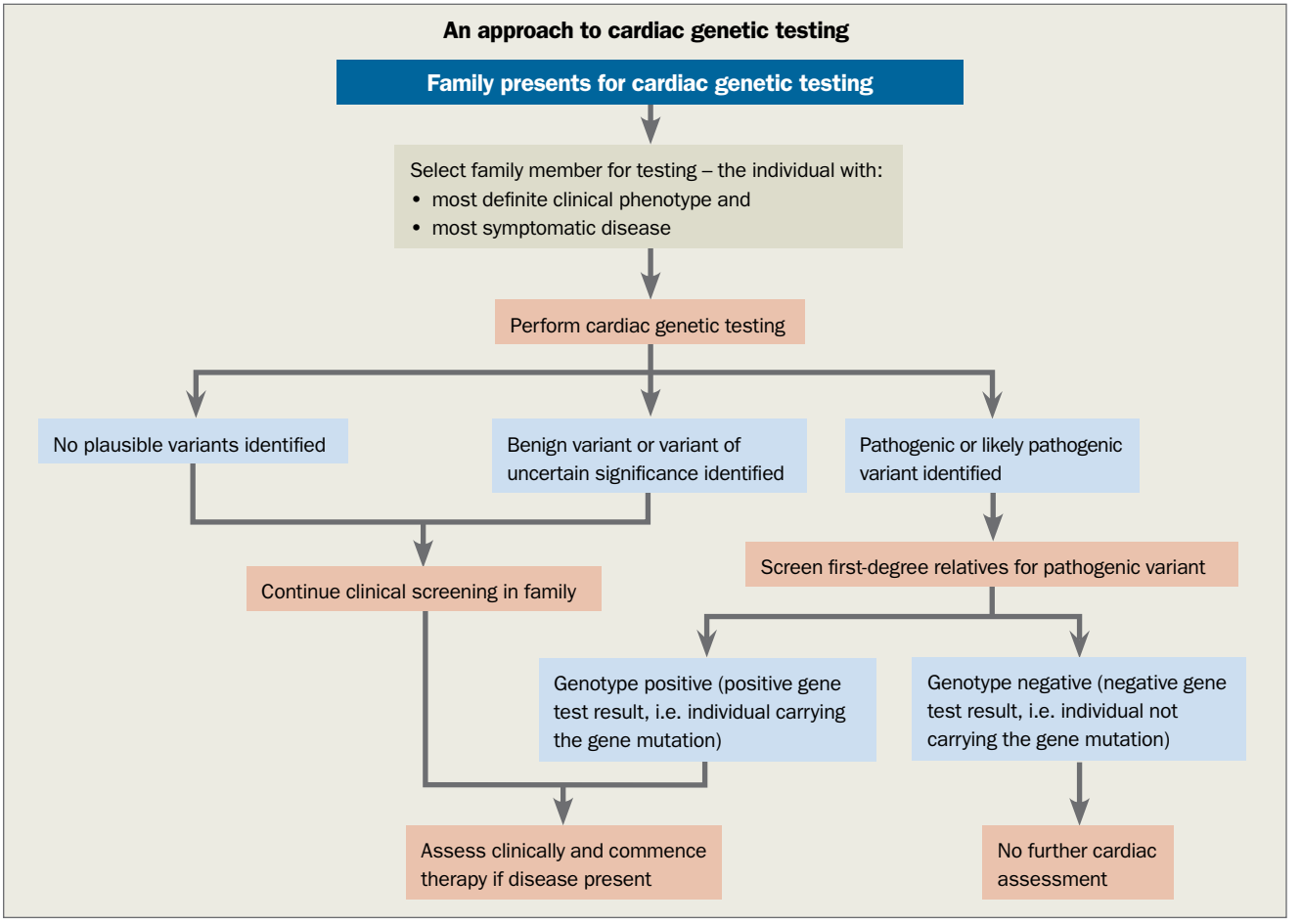
specialises in the evaluation of patients with inherited heart disease.

Following a clear clinical diagnosis, the appropriate genetic test is chosen and performed, with both pre- and post-test genetic counselling to inform patients of both the benefits and potential harms of genetic testing.[8]

Once the genetic result is available, the genetic findings are interpreted to determine the pathogenicity of the variants identified and whether they are disease-causing. Genetic test results should not be considered a binary (yes/no) outcome, but rather a complex and carefully considered result placed somewhere along a continuum from benign variant to variant of uncertain significance (VUS) to likely pathogenic and pathogenic variants (Figure 2).[4] A pathogenic or likely pathogenic gene result can then be used for cascade testing in the patient's relatives. The genetic test result is therefore a probabilistic one, in which the weight of evidence for pathogenicity determines the probability of the specific variant being disease-causing.[2] Given the complexities of both clinical evaluation and interpretation of genetic findings, cardiac genetic testing is best performed in the setting of a specialised multidisciplinary genetic heart disease clinic, such as the first such clinic established in Australia at Royal Prince Alfred Hospital in Sydney, as well as other cardiac genetic clinics



around the country (www.heartregistry.org.au/patients-families/cardiac-genetic-services).

Are there any harms associated with cardiac genetic testing?

The greatest clinical utility of genetic testing is when a pathogenic mutation is identified, enabling cascade genetic testing to be undertaken in asymptomatic relatives. However, where there is uncertainty about the significance of a reported variant, the so-called VUS, that variant should not be used for cascade genetic testing. If cascade family screening is performed based on an incorrectly classified variant then there is the very real possibility of incorrectly releasing family members from clinical screening. Reports of pathogenic mutations being downgraded to benign polymorphisms commonly found in normal populations have made this a reality across a number of conditions.

Of crucial importance for the clinician is an understanding that genetic medicine is evolving at an incredible pace, and mass sequencing of control and disease populations is expanding current knowledge about the extent of normal variation within the human genome. Currently, there are more than 8000 publicly available human exomes (the protein-coding region of the genome) and genomes (the complete set of DNA, including all the genes), as part of the US National Heart, Lung and Blood Institute (NHLBI) GO Exome Sequence Project and the international 1000 Genomes Project, providing unprecedented volumes of genetic information. Thus, periodic reassessment of all variants is not only necessary but essential in ensuring family members are appropriately managed.[9]

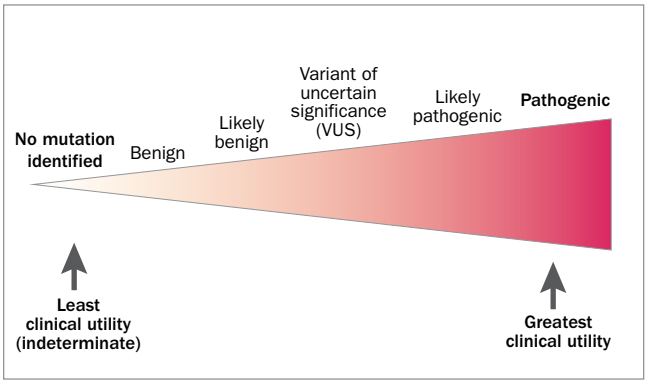


Figure 2. Probabilistic nature of genetic results, from benign variants to pathogenic mutations.

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The Australian Genetic Heart Disease Registry

The Australian Genetic Heart Disease Registry was established in 2007 by the authors JI and CS, with the goal of enrolling every family in Australia with a genetic heart disease.

The Registry's website (http://www.heartregistry.org.au) has useful information sheets about all major inherited heart diseases, and provides information for both patients and health professionals.

What is the role of cardiac genetic testing in the setting of sudden cardiac death?

Sudden cardiac death is a devastating outcome of almost all inherited heart diseases. In up to one-third of sudden cardiac deaths in young people (aged 1 to 40 years), a complete postmortem examination fails to reveal a cause of death; this is known as sudden unexplained death (SUD).[10]

Primary arrhythmogenic disorders, which do not cause structural abnormalities of the heart, are thought to be the underlying cause of the death in a significant proportion of cases of sudden unexplained death. Careful clinical evaluation of family members along with postmortem genetic testing of known genes can be performed. Clinical evaluation of the family can reveal a clinical phenotype in up to 40% of cases. The goal of the molecular autopsy is both to identify the underlying heart disease causing the death and to provide the option for family members to undergo genetic testing of the family mutation.[11] Commonly, a molecular autopsy includes testing four genes, *KCNQ1, KCNH2, SCN5A* and *RYR2*, incorporating the major LQTS, BrS and CPVT genes (Table). Mutation pick-up rates of molecular genetic testing of sudden unexplained death cases are, at best, 10 to 30%, and intense research efforts are focused on improving the understanding of the genetic causes of sudden unexplained death.

Regardless of genetic testing efforts, clinical evaluation of the surviving first-degree relatives is crucial, and indeed may contribute to identifying a clinical phenotype, or as a minimum reassure family members that they do not harbour a heart condition at that time.[10]

What does the future hold in terms of cardiac genetic testing?

Major advances have been made in our understanding of the genetic causes of inherited heart disease and widespread commercial availability has facilitated the incorporation of genetic testing into clinical cardiology practice. A useful resource for both health professionals and patients and their families is the Australian Genetic Heart Disease Registry (Box).

Overall, the greatest utility of genetic testing is in the screening and diagnosis of asymptomatic relatives through cascade genetic testing. Accurate interpretation of gene variants is a focus area as more genes are routinely tested. The introduction of clinical genome testing will be a major challenge in coming years, as cardiac genetic results form a part of global disease gene screening including for cancer risk, neuromuscular and degenerative diseases, and inherited metabolic disorders. This highlights the importance of continued research efforts focused on expanding our knowledge of the genetic basis of inherited heart diseases, and reinforces the key role of the specialised multidisciplinary team in caring for these families.

Conclusion

Genetic testing is an important part of the management of families with inherited heart diseases. Commercial genetic tests are available for most inherited heart diseases and increasing uptake among patients has contributed to a vastly improved knowledge of the genetic basis of these diseases. The major advances in genetic technologies have translated to faster, more comprehensive and inexpensive commercial genetic tests and have revolutionised the landscape of commercial genetic testing. Although there are enormous challenges, mostly relating to interpretation of genetic variants, the value of a genetic diagnosis is now established in cardiovascular disease. In almost all cases, the single greatest utility is for cascade genetic testing of family members, which then guides subsequent management and clinical surveillance. **CT**

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