Genetic Testing in Inherited Heart Diseases

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Inherited heart diseases include numerous conditions, from the more prevalent hypertrophic cardiomyopathy (HCM) and familial hypercholesterolaemia (FH), to the comparatively less common inherited arrhythmia syndromes, such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT) and Brugada syndrome (BrS). Genetic testing has evolved rapidly over the last decade and is now considered a mainstream component of clinical management of inherited heart diseases. Cardiac manifestations can also be part of wider syndromes, and genetic testing can play a critical role in clarifying the underlying aetiological basis of disease in some cases. The greatest utility of a genetic diagnosis, however, comes from the ability to elucidate disease risk amongst asymptomatic at-risk family members. Given the nuances and challenges, cardiac genetic testing is best performed in a multidisciplinary specialised clinic with access to cardiac genetic counselling.

Keywords Inherited heart diseases • Genetic testing • Genetic counselling

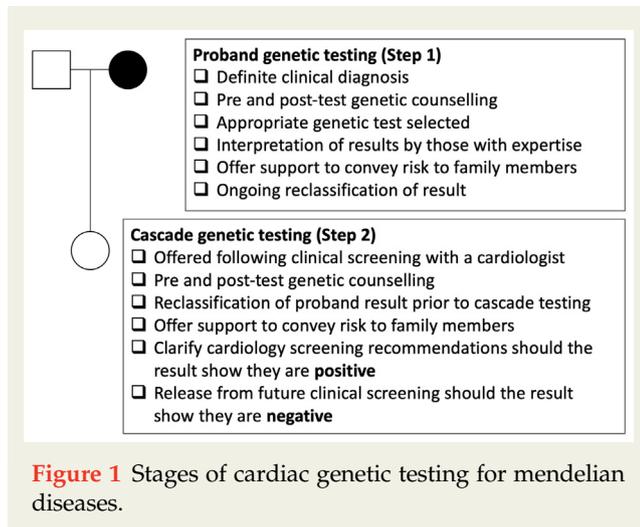## Genetic Testing in the Cardiology Clinic

Genetic testing for inherited heart diseases has considerable utility in the cardiology clinic. It is generally a two-step process, with genetic counselling integral at each step (Figure 1). Firstly, sequencing of causal genes is performed in a DNA sample from a clinically affected individual (the proband). Second, if a causative variant is identified, genetic testing for this variant (or variants) can be offered to asymptomatic at-risk relatives (cascade genetic testing). Determining the presence or absence of the variant can be a powerful tool for family management in asymptomatic or unaffected relatives. There are, however, challenges at each step, and the general consensus is that the best outcomes for the patient and their family are achieved when genetic testing is offered in a specialised multidisciplinary clinic with access to genetic counselling. Here, we describe the value and challenges of genetic testing in the cardiology clinic. Further, we provide a glossary of commonly used genetic testing vocabulary (Table 1).

Family History

Despite its value, the family history is often overlooked in clinical practice. Through this process, additional affected individuals as well as at-risk family members can be identified, both essential for genetic counselling. Inherited heart diseases are most often autosomal dominant (AD) traits, although autosomal recessive (AR), X-linked and maternal mitochondrial conditions are also described. With documentation of affected (or suspected affected) relatives, a pattern of inheritance may be inferred and preliminary screening recommendations that could be further adjusted

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Proband genetic testing (Step 1)
☐ Definite clinical diagnosis
☐ Pre and post-test genetic counselling
☐ Appropriate genetic test selected
☐ Interpretation of results by those with expertise
☐ Offer support to convey risk to family members
☐ Ongoing reclassification of result

Cascade genetic testing (Step 2)
☐ Offered following clinical screening with a cardiologist
☐ Pre and post-test genetic counselling
☐ Reclassification of proband result prior to cascade testing
☐ Offer support to convey risk to family members
☐ Clarify cardiology screening recommendations should the result show they are **positive**
☐ Release from future clinical screening should the result show they are **negative**

Figure 1 Stages of cardiac genetic testing for mendelian diseases.

with informative genetic testing made for first degree family members of affected individuals.

Family history information may be collected by questionnaire, or by drawing a pedigree. The information obtained should be targeted [1] to identify family members with the same or similar condition as the proband. Sudden cardiac death can be the presenting symptom and details of any suspicious deaths should be sought, ideally including a postmortem report. Information from a minimum of three generations should be collected, including both sets of the proband's grandparents. The integrated, specialised skills of cardiac genetic counsellors in this setting ensure adequate working data, good communication of inheritance risks, genetic testing options and frequency of clinical surveillance, as well as better psychosocial adjustment [2].

Cardiac Genetic Testing for Inherited Heart Diseases

Here we describe the specifics of genetic testing in each disease setting. Table 2 illustrates the minimum gene set that should be sequenced by disease.

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy is a disease most often caused by variants in genes that encode the cardiac sarcomere [3]. Genetic testing should include a minimum of eight sarcomere genes (*MYH7, MYBPC3, TNNT2, TNNI3, TPM1, ACTC1, MYL2, MYL3*). Analysis of genes which cause rare syndromic diseases that can present with isolated left ventricular hypertrophy mimicking HCM, is also considered to have clinical utility; these include *GLA* (Fabry disease), *PRKAG2* (*PRKAG2*-glycogen storage disease), *LAMP2* (Danon disease), amongst others shown in Table 2 [4]. The diagnostic yield when testing the index case (proband) with a definite clinical diagnosis of HCM is approximately 30–40%, with truncating variants in *MYBPC3* and missense

variants in *MYH7* accounting for the vast majority of cases. The highest yield of genetic testing will be amongst those with a demonstrated positive family history, severe left ventricular hypertrophy or young age at diagnosis, without concurrent hypertension [5].

Dilated Cardiomyopathy (DCM)

Dilated cardiomyopathy is a clinically heterogeneous condition and can present either as an isolated phenotype, or as part of a syndrome. Non-syndromic, isolated DCM may be caused by genetic and non-genetic factors, the latter including infectious aetiologies and cardiotoxic drug exposure. Over 100 genes are implicated, encoding proteins which perform a range of structural and functional roles within the cardiac myocyte (e.g., sarcomere, nuclear membrane, desmosome, sarcoplasmic reticulum, cytoskeleton) [6]. Amongst individuals with non-syndromic DCM, the diagnostic yield for a causative variant is approximately 20–30%, and a relatively small number of genes account for the majority of cases (Table 2) [6,7]. In recent years, truncating variants in the A-band (and possibly, other specific regions) of the *TTN* gene have been shown to account for disease in approximately 25% of probands [8]. *TTN* encodes the sarcomere protein titin, and, due to the high degree of truncating variants in normal populations, ascertaining causative from benign variants can be problematic [8,9]. Variants in the *LMNA* gene are detected in around 4–6% of probands, causing a distinct phenotype characterised by progressive conduction system disease, arrhythmia and systolic impairment [10]. As such, pathogenic *LMNA* variants are detected more frequently in individuals with DCM and conduction disease [11]. Given many DCM cases can have overlap with ARVC genes, the below section should also be considered in this group.

Arrhythmogenic Cardiomyopathies, Including ARVC

Given the phenotypic heterogeneity amongst ARVC families, with many showing preponderance to biventricular or predominantly left-sided disease, there has been a move to consider the broader group as arrhythmogenic cardiomyopathies [12]. Here, we discuss ARVC and the gene specific sub-types of cardiomyopathies.

ARVC is caused by pathogenic variants in genes encoding protein components of the cardiac desmosome. A causative variant is detected in up to 50% of individuals referred for genetic testing who meet 2010 taskforce criteria [13]. Truncating variants in *PKP2* are the most common cause of ARVC, accounting for 20–30% of cases. Variants in four other desmosomal genes (*DSC2, DSG2, DSP, JUP*) account for a smaller proportion of cases (Table 2); the majority of pathogenic variants in these genes are truncating variants [14]. It is well described that the desmosomal genes have a high rate of "noise", meaning rare missense variants occur frequently in unaffected control populations, therefore

Table 1 Definitions of commonly used genetics vocabulary.

Word	Meaning
Genetic testing	Process of sequencing DNA.
Genome sequencing	Sequencing of entire genome (including coding and non-coding regions).
Exome sequencing	Sequencing of just the coding regions (exons), including approximately 22,000 genes.
Proband	The index case in the family, usually the first or the most severely affected.
Genetic diagnosis	When a genetic variant can be confidently attributed to a disease in an individual.
Phenotype	The clinical manifestations of a genetic trait.
Variant	A change in the DNA sequence. This may be disease-causing or just part of normal variation.
Pathogenic	Describes a variant with >99% confidence that it is disease-causing. There is sufficient evidence to offer cascade genetic testing to family members.
Likely pathogenic	Describes a variant with >90–95% confidence that it is disease-causing. There is sufficient evidence to offer cascade genetic testing to family members.
Variant of uncertain significance (VUS)	There is insufficient or conflicting evidence for pathogenicity and the variant is therefore considered uncertain. Cascade genetic testing cannot be offered to family members.
Likely benign/benign	Describes a variant with sufficient evidence to say this is not the cause of disease.
Cascade genetic testing	Genetic testing of asymptomatic relatives to determine the presence or absence of the causative variant in their family.
Pathogenicity	The process of determining whether a variant is causative or not, most often involves collating evidence against systematic criteria.
Penetrance	How many individuals with the genetic variant will have the disease or trait. A highly penetrant disease will be evident in nearly all genetic carriers.

Table 1 (continued).

Word	Meaning
Variable expression	In those with disease, there can be variation in how it manifests. This can include variation in disease severity, age at onset, but also difference in disease characteristics.

interpretation of missense variants should be cautiously approached [15]. Variants in non-desmosomal genes have also been implicated though with less evidence, for example *CDH2*.

Other gene specific sub-types that may be considered under the broad term of arrhythmogenic cardiomyopathies include those due to variants in *TMEM43*, *LMNA*, *FLNC*, *TTN*, *DES*, *RBM20* and *PLN.* This list is likely to expand as further genetic sub-types are elucidated.

Left Ventricular Non-Compaction (LVNC)

LVNC, characterised by a non-compacted left ventricular wall with trabeculations, has gained recognition in clinical practice with increased use of cardiac magnetic resonance imaging. There is no consensus as to whether LVNC should be classified as a cardiomyopathy, as individuals with LVNC usually have associated findings, including systolic dysfunction, left ventricular enlargement, or congenital heart defects. The genetics of LVNC are poorly understood. Studies have reported variants mostly in genes associated with other cardiogenetic phenotypes in 29–41% of cases, although neither the phenotype definition or pathogenicity of the variants identified is clear [16]. In a paediatric cohort, the yield of genetic testing for LVNC was reported to be 9%, however, no variants were identified in cases with isolated LVNC. On the other hand, cases involving LVNC and other cardiomyopathy findings had a 12% yield, supporting the idea that isolated LVNC may be a phenotype, not a disease [17,18]. In light of this, we suggest that comprehensive cardiomyopathy or congenital heart disease genetic testing panels may be most informative when LVNC is not isolated or when the family history is consistent with cardiomyopathy or congenital heart defect.

Restrictive Cardiomyopathy (RCM)

Restrictive cardiomyopathy is clinically heterogeneous, with multiple aetiologies known, including infiltrative, storage disease, non-infiltrative, and endomyocardial, many of which are associated with specific genes [19]. Variants in HCM and DCM genes have been reported in non-infiltrative RCM. In these rare cases, family members may have RCM,

Table 2   Genes with robust evidence for disease causation.

Phenotype	Key genes	Diagnostic yield of genetic testing
Inherited cardiomyopathies		
Hypertrophic cardiomyopathy	*ACTC1, MYBPC3, MYH7, MYL2, MYL3, TNNI3, TNNT2, TPM1*	30–50%
Isolated LV hypertrophy	*ACTN2, FLNC, GLA, LAMP2, PLN, PRKAG2, TTR*	<5%
Dilated cardiomyopathy	*BAG3, DES, DMD, DSP, EYA4, FLNC, LMNA, MYH7, PLN, RBM20, SCN5A, TNNC1, TNNI3, TNNT2, TTN, TPM1, VCL*	20−30%
Arrhythmogenic right ventricular cardiomyopathy	*DSC2, DSG2, DSP, JUP, PKP2, PLN, TMEM43*	50%
Inherited arrhythmia syndromes		
Long QT syndrome	*KCNQ1, KCNH2, SCN5A,*	60−70%
Catecholaminergic polymorphic ventricular tachycardia	*RYR2, CASQ2*	50−60%
Brugada syndrome	*SCN5A*	∼20%
Familial hypercholesterolaemia		
Familial hypercholesterolaemia	*LDLR, APOB, PCSK9*	30−40%
Familial aortopathies		
Thoracic aortic aneurysms; Loey-Deitz; Marfan syndrome	*ACTA2, COL3A1, FBN1, LOX, MYH11, MYLK, PRKG1 SMAD3, TGFB2, TGFBR1, TGFBR2.*	∼ 20%

HCM or HCM with a restrictive pattern [20]. Genetic testing for RCM should therefore include HCM and DCM genes.

Long QT Syndrome (LQTS)

LQTS is caused by variants in genes which encode cardiac ion channel proteins. While many genes have been implicated in the past decade, only a small number of genes show robust gene−disease association. Causative variants in three genes, *KCNQ1, KCNH2* and *SCN5A*, are detected in approximately 60–70% of individuals with a clinical diagnosis of long QT syndrome [21]. Variants in other genes implicated in LQTS (*KCNE1, KCNE2, CACNA1C, CALM1, CALM2, CALM3, CAV3*) appear to be rare, accounting for less than 1% of cases. Rare multi-system syndromic disorders with prolonged QTc include Timothy syndrome (*CACNA1C*), Andersen-Tawil syndrome (*KCNJ2*), and recessive disorders Jervell and Lange–Nielsen syndrome (*KCNQ1* and *KCNE1*) and Triadin knockout syndrome (*TRDN*).

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Causative variants in the *RYR2* gene, which encodes ryanodine receptor-2, a cardiac calcium ion channel protein, account for 50–60% of individuals with a clinical diagnosis of CPVT [11]. Most causative variants are missense, with nonsense and splice variants having insufficient evidence at present. Approximately 1–2% of cases have autosomal recessive CPVT caused by pathogenic variants in the *CASQ2* gene [22]. Genetic testing has a very favourable yield in those with a clear diagnosis. In rare cases, variants in other genes can be identified which have phenotypic overlap which

suggests a misdiagnosis, for example *KCNJ2, CALM1, CALM2, CALM3* and *TRDN*.

Brugada Syndrome (BrS)

Causative variants in *SCN5A* account for 15–30% of individuals with a clinical diagnosis of BrS [23]. While a number of genes have been implicated in BrS at present there is limited evidence to support disease causality [24]. The genetic basis of BrS is poorly understood and there is growing evidence that many cases are polygenic [25], with familial inheritance rarely reported. Genetic testing in the clinical setting should be carefully considered and confined to *SCN5A*. Patients with a positive family history of disease, a spontaneous type 1 ECG pattern and symptomatic presentations may have a greater genetic yield though this is an area requiring further research.

Familial Hypercholesterolaemia (FH)

Causative variants in three key genes are detected in 60–80% of probands with a definite clinical diagnosis of FH [26]. The majority of cases have a variant in the *LDLR* gene, which encodes the low density lipoprotein receptor. Variants in the *APOB* gene, which encodes apolipoprotein B, and *PCSK9*, encoding proprotein convertase subtilisin/kexin 9 are detected in a smaller proportion of cases. In cases with a possible clinical diagnosis, the diagnostic yield is lower (25–30%) [27]. The *ABCG5, ABCG8* and *LIPA* genes may also be included in FH test panels; with variants in these genes causing rare autosomal recessive lipid conditions with phenotypic overlap with FH [27]. There is clear benefit of identifying individuals with FH and genetics in this setting is a powerful tool for identifying cases and at-risk relatives.

Heritable Thoracic Aortic Aneurysm/ Dissection (HTAAD)

Causal variants in genes encoding protein components of smooth muscle cells (*ACTA2, MYL11, MYLK*), the transforming growth factor beta (TGFB) signalling pathway (*SMAD3, TGFB2, TGFBR1, TGFBR2*), and the extracellular matrix (*FBN1, COL3A1*), are detected in approximately 20% of individuals presenting with HTAAD [28]. Variants in *ACTA2, MYL11, MYLK* cause non-syndromic HTAAD, whereas variants in other definitive HTAAD genes cause rare syndromic disorders which can present with isolated aortopathy: Loeys-Dietz syndrome (*SMAD3, TGFB2, TGFBR1, TGFBR2*), Marfan syndrome (*FBN1*); vascular Ehlers-Danlos syndromes (*COL3A1*). Genetic testing is useful in distinguishing non-syndromic versus syndromic aortopathy.

The Practical Steps

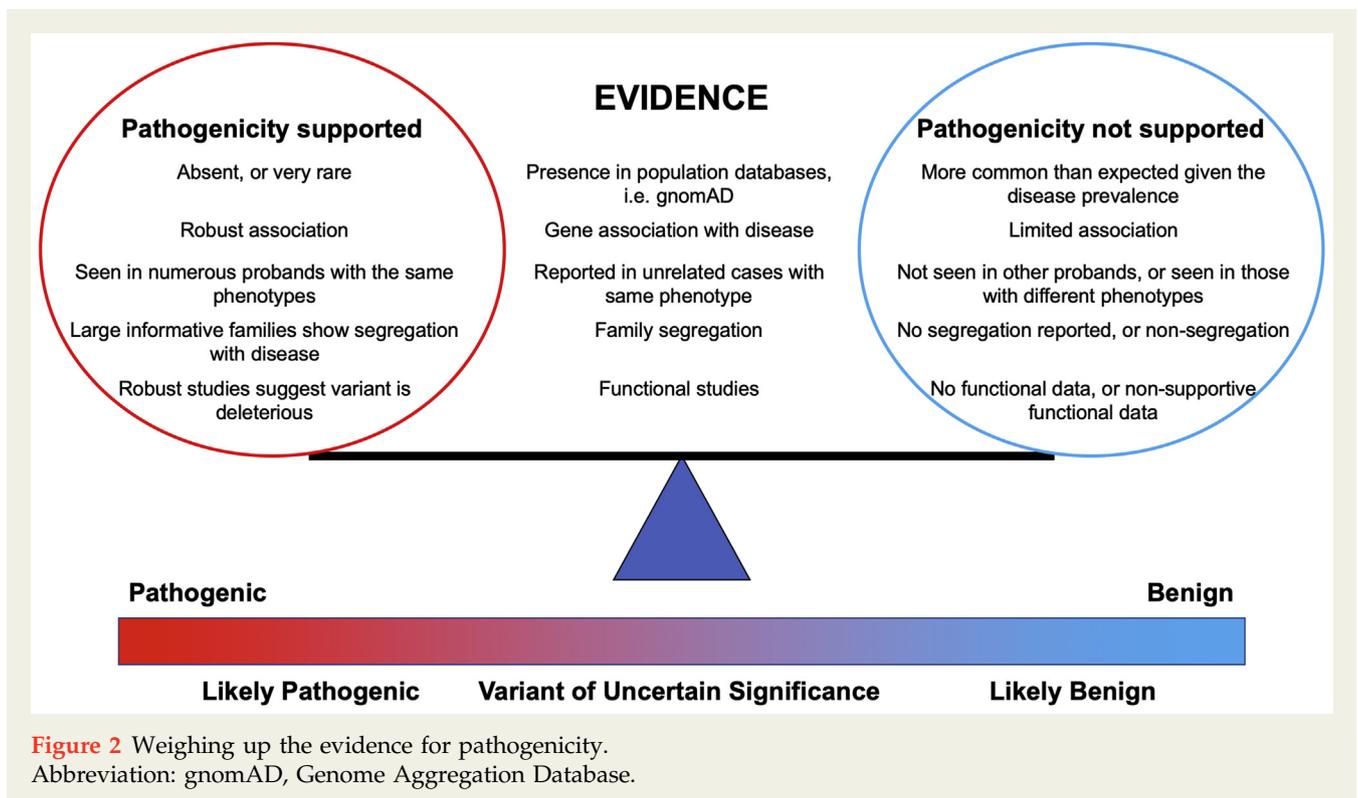## Who Should Get Genetic Testing?

Overwhelmingly, comprehensive phenotyping to identify a patient who clearly meets diagnostic criteria for disease will give the greatest yield from cardiac genetic testing. Factors such as no alternative clinical explanation for the phenotype, young age at onset, severe disease and positive family history of disease may signal a greater chance that the underlying basis of disease is genetic, i.e., high pre-test probability. If cardiac genetic testing is performed on individuals with an unclear or borderline diagnosis, interpretation of the genetic

variants will be very difficult. Cardiac genetic testing should be avoided in those where the pre-test probability is low, due to the risk of misclassifying a variant as causative which may have important harms [29].

Interpretation of the Results

Rare variants occur in those with and without disease; ascertaining which variants are disease-causing and which are benign is a challenge. Classifying a variant is akin to detective work, whereby evidence is collected and a case is built (Figure 2). Where there is sufficient evidence for causation, a variant will be classified as likely pathogenic or pathogenic. Where the evidence supports the variant not being disease causing, then it will be classified as likely benign or benign. If there is insufficient or contradictory evidence regarding causality, then it will be classified as a variant of uncertain significance (VUS). In 2015, the American College of Medical Genetics and Genomics (ACMG) and the Association for Medical Pathologists (AMP) released a joint statement on the interpretation of sequence variants [30], and these have been widely adopted. Recent gene specific modifications have been published, including *MYH7* variants in cardiomyopathies [31]. Data from public repositories of curated variant information, such as ClinVar [32], can aid variant interpretation; however, it is important to assess the evidence on which previous classifications were based.

In addition to considering the evidence for a variant, whether or not the gene is robustly associated with a given phenotype is of even greater importance. Gene−disease

Figure 2 Weighing up the evidence for pathogenicity.
Abbreviation: gnomAD, Genome Aggregation Database.

associations are now considered routinely when curating genes, and this process involves assessing the clinical and experimental evidence linking the gene and the phenotype, with recent ClinGen gene curation working groups now published [5,24,28]. Where a gene does not have reasonable evidence for disease association, variants in this gene should not be classified as causative nor be used in a clinical setting.

Cardiac Genetic Counselling

Around the world, cardiac genetic counselling is often performed by a counsellor or genetic nurse, and focusses on providing information and emotional support relating to the cardiac genetic disease in their family. Some of the roles include taking a family history, explanation of inheritance risks, assistance with communication to relatives and organising clinical screening, pre and post-test genetic counselling to ensure good understanding and adjustment to genetic results, and psychosocial support where needed.

A Brief Note on Complex Genetic Diseases and Polygenic Risk Scores

Polygenic diseases are caused by numerous genetic and non-genetic factors, with coronary artery disease being a well-described example. By performing genome-wide association studies (GWAS), thousands of single nucleotide variants which each provide a small incremental increased risk of disease can be identified [33]. A polygenic risk score (PRS) is the predicted additive effect of these variants which can be used to predict the risk of developing disease. While not currently in clinical practice, the study reported by Khera and colleagues illustrated the potential for PRS to provide important prognostic value in the management of patients with coronary artery disease [34]. By combining millions of common variants, a PRS was calculated showing better prediction of coronary artery disease than any single traditional risk factor. While promising, these findings are yet to be associated with clear clinical interventions, and to date have the greatest predictive power in European individuals. In the future, used in tandem with clinical investigations and information, PRS may enhance our ability to predict those at greater risk of complex diseases or adverse outcomes, even further necessitating access to specifically trained genetic counsellors.

Summary

Cardiac genetic testing is an extremely useful addition to clinical management of patients with inherited heart diseases. For the most part, the value lies in cascade genetic testing of at-risk relatives, however there is a growing role in clarifying the diagnosis and potentially for management and prognosis in future. Given the nuances, cardiac genetic testing should be performed in centres with experience, including those with access to genetic counselling.

Acknowledgements

Disclosures

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