What the practicing cardiologist needs to know about genetics and heart disease

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Abstract

As the inherited basis of some cardiovascular diseases have begun to be uncovered, a practical understanding of genetics has become important for the cardiologist. The advent of new studies on the inherited contributions to common traits and the emergence of genetic testing for a broad range of cardiac and vascular conditions will only increase the need for fluency in genetics. In this article we have outlined the genetic concepts likely to be most useful to the practicing cardiologist, focussing the discussion around the inherited conditions most likely to be identified in general clinical cardiology. ■ *Heart Metab.* 2008;41:11–15.

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Introduction

Genetic diseases lie along a continuum ranging from simple monogenic Mendelian disorders to complex traits, which arise from the interaction of a number of genetic and environmental factors. The concept of penetrance captures the distinction between genetic variants contributing to Mendelian disorders and complex disease traits. Penetrance for a genetic mutation is defined as the proportion of individuals carrying a particular genetic mutation who also demonstrate the disease phenotype. The mutations that lead to Mendelian disorders have high penetrances (approaching 100%), whereas for most variants contributing to complex disease the penetrance is quite low. The concept of genetic architecture describes the number of genes contributing to a disease trait, the number of variants per gene, and the magnitude of effect that each variant has on development of the trait. Although Mendelian disorders usually arise from inheritance of a single genetic mutation, many different individual genes may, when mutated, lead to a common disease phenotype (genetic heterogeneity). In addition, for any gene, many different mutations may also lead to the same disease phenotype (allelic heterogeneity*). Both genetic and allelic heterogeneity introduce complexity when one goes about designing a genetic screening program for heart disease. Furthermore, although the penetrance of a disorder may be high, the exact manifestation of disease may vary from individual to individual, despite their inheriting the same mutation (variable expressivity). A final level of complexity arises from the fact that several distinct diseases may share a common ''low-resolution'' phenotype, but in fact have a different pathologic basis (termed phenocopies*), with potentially different disease course and treatment.

Genetic screening

When should genetic screening be used? An example may help illustrate the approaches used for potentially heritable disorders. Consider an individual with a disease that does not appear to be arising from any

known environmental cause – in genetic studies, this individual is called the proband. An initial step should be to establish whether the disease is familial, as this has relevance to pursuing a genetic diagnosis for the individual, and on managing risk within family members. In addressing familiality, we must construct a careful family pedigree, asking about the health and manner of death of every relative. We need to be careful to distinguish two apparently similar situations with considerably different ramifications: one in which detailed pedigree information is available and no disease is apparent, and another in which there does not appear to be any other relative with the disorder but an inadequate family history is obtained. Only in the former case could we conclude that the disease is not familial, but either sporadic or attributable to environmental factors.

If the genetic architecture of the disease is such that there are a relatively small number of genes (low genetic heterogeneity) involved and there are causal genetic variants of moderate to high penetrance, genetic screening can be useful. Because many Mendelian disorders show significant allelic heterogeneity, screening for a single mutation tends to be unsuccessful, and sequencing of the gene is required to find likely causal variants. Several limitations exist with genetic testing of a single proband. Sequencing errors can occur, resulting in false positive and false negative results. Even with careful sequencing, a variant may be found in one of the candidate genes, but may not actually be causal for the disease. To establish a sequence variant as a potential mutation would require that it have the potential to have a deleterious effect. A mutation that is falsely assigned causality and used for genetic screening in family members would lead to both false reassurance and false alarm, as the inheritance of the variant would have no bearing on the likelihood of developing the disease.

How useful would the identification of a genetic variant be? Because of the bewildering genetic and allelic heterogeneity of most Mendelian disorders, the individualized prognostication and treatment that it was once hoped would follow genetic diagnoses have not materialized. We simply do not have enough prognostic information for individual mutations to provide mutation-specific predictions with any accuracy. As a result, the current utility of identifying a causal mutation in a proband is almost exclusively limited to facilitating screening of family members.

We can apply the above considerations to any disease with a heritable component. Below, we will address the approaches to hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM), highlighting how the known genetic architecture of the trait guides screening.

Hypertrophic cardiomyopathy

The genetic architecture of HCM (*Table I*) makes it amenable to genetic diagnosis. HCM appears to be familial in a large proportion of cases and the pattern of inheritance is almost always autosomal dominant with high penetrance [1,2]. There are 12 known genes responsible for this disorder (not including several phenotypic mimics [3]), and mutations in one of eight sarcomeric genes explain approximately 60% of cases [4]. In the USA, there are various commercial tests available for genetic screening, at costs ranging from $500 to $3000, but the prevalence of HCM is too low to justify screening of the general population.

The allelic heterogeneity of HCM, which includes more than 400 causal mutations, makes individualization of treatment and prognosis on the basis of genetics implausible. It is unlikely that, for any mutation, adequate samples will ever be assembled for a reliable estimate of risk. Furthermore, the presence of incomplete penetrance and variable expressivity* within families erodes confidence in the predictive utility of mutations. Attempts to prognosticate on the basis of genetic mutations have been difficult to replicate, and designations of mutations as ''benign'' or ''malignant'' are often the result of observational studies in small numbers of families [5]. It is, of course, expected that some mutations will have a more deleterious impact on protein function than

Table I. Genetic architecture of hypertrophic (HCM) and dilated (DCM) cardiomyopathies, and arrhythmogenic right ventricular dysplasia (ARVD).

	HCM	DCM	ARVD
Prevalence	1:500	1:2500	1:1000–1:5000
Number of known causal genes	12	20	7
Number of known variants	>400	>50	>70
Familiality (%)	50	35	30–50
Predominant patterns of inheritance	Autosomal dominant	Autosomal dominant Autosomal recessive X-linked	Autosomal dominant Autosomal recessive
Potential preventive treatment	AICD	ACEI, β-blocker, AICD	Avoidance of exercise AICD

ACEI, angiotensin-converting enzyme inhibitor; AICD, automatic implantable cardioverter-defibrillator.

others – but extrapolation of the clinical impact of a single mutation in a small number of individuals to others with different genetic and environmental backgrounds should be undertaken with caution.

Thus, at present, a genetic diagnosis is most useful for screening relatives in a family bearing a known mutation. Clinical screening also can be carried out using the electrocardiogram (ECG) and echocardiography, and may be as useful in many instances. Echocardiography has greater specificity, although ECG abnormalities, even in the absence of left ventricular hypertrophy on echocardiography, are suggestive for affected status, given the high pretest probability of disease in first-degree relatives.

In view of the concern for sudden death in child athletes, an early diagnosis of HCM in children has clear relevance to mitigating risk. Furthermore, as several variants of HCM can show clinical onset late in life [6], it is unclear if screening can be stopped confidently at any age. Maron et al [6] have made specific screening recommendations, which, while offering a rational approach, have yet to be validated for cost-effectiveness or influence on morbidity or mortality.

A preclinical diagnosis of HCM, through either genetic or clinical screening, offers an opportunity to make therapeutic decisions before the onset of disease. Unfortunately, there are no clear options for treatment to alter the course of disease. Sudden death is certainly the most dreaded sequela, but we are not confident which HCM patients will benefit most from therapy. At present, the best predictor of sudden death in patients with HCM is a personal history of cardiac arrest: 59% of individuals with one episode of cardiac arrest have a second one within 5 years [7]. However, in the absence of a prior cardiac arrest, the criteria for risk prediction become less clear. A personal history of unexplained syncope or a family history of sudden cardiac death [8] has modest additional predictive utility. The caveats described above that apply to establishing familiality also apply to establishing a family history for sudden death – one must be concerned if there are simply not enough family members on which to base a negative conclusion.

Dilated cardiomyopathy

DCM is considerably more complex than HCM, in terms of both genetic architecture and known contributing environmental factors. Coronary artery disease, nutritional deficiency, viral infection, and toxins such as alcohol all can cause DCM. The prevalence of idiopathic DCM may be as high as 1 : 2500 adults [9], but the diagnosis requires an extensive work-up to exclude other causes, some of which may prove to be reversible [10].

More than 20 genes have been implicated in the pathogenesis of DCM, with autosomal dominant, recessive, and X-linked patterns of inheritance [11] (*Table I*). Penetrance is often low, and expressivity varies considerably. DCM can be syndromic, with other abnormalities such as the skeletal muscle dystrophies and retinal disease [12]. Given the fact that mutations in DCM are distributed widely over a large number of different potential causal genes, there is usually too low a likelihood of success to recommend genetic sequencing or genetic screening. Associated cardiac and non cardiac findings can help narrow the diagnosis. For example, in one small study, if atrioventricular block accompanied DCM, there was a mutation found in the lamin A/C gene in one-third of cases [13]. As with all cardiomyopathies, it is challenging to predict risk for particular mutations [14].

Although the complexity of DCM precludes genetic screening, clinical screening by ECG or echocardiography can often be very useful. An early diagnosis in asymptomatic family members of the proband allows the initiation of treatment with potentially disease-modifying agents such as angiotensin-converting enzyme inhibitors (ACEIs; see below). Individuals with mildly depressed systolic ejection fraction or mild left ventricular enlargement should be followed with more frequent screening. For every affected individual, care must be taken to exclude age-appropriate, potentially reversible causes, as these may contribute to disease even in the context of an inherited tendency [15].

Clinical guidelines recommend the use of ACEIs and β-blockers for all cases of DCM, independent of cause [16], and implantation of an implantable cardioverter-defibrillator in symptomatic individuals with severe left ventricular dysfunction. It is unclear if early initiation of treatment with ACEIs or β-blockers mitigates the disease course in individuals with mild echocardiographic abnormalities, or exclusively ECG abnormalities.

Arrhythmogenic right ventricular cardiomyopathy

ARVC is a genetically heterogeneous disorder, for which 12 genetic loci are currently identified [17] (*Table I*). Causal genes corresponding to eight of these loci have been found, with five encoding desmosomal proteins. The prevalence of ARVC is unknown, but has been estimated at 1 : 1000 to 1 : 5000 individuals [18]. ARVC is familial in nearly 50% of cases [19], and inheritance is usually autosomal dominant, with variable expressivity and incomplete penetrance.

The routine diagnostic work-up of a patient suspected to have ARVC includes ECG, Holter monitoring, signal-averaged ECG, echocardiography, and, potentially, cardiac magnetic resonance imaging [20]. If the clinical and family history and these

initial studies raise a high suspicion for ARVC, endomyocardial biopsy is often performed for confirmation, and an electrophysiological study may be performed to exclude benign right ventricular outflow tract tachycardia. The above diagnostic tests have been incorporated into criteria for the diagnosis of ARVC proposed by the Task Force of the Working Group on Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology [21].

A large percentage (up to 43%) of cases of ARVC can be explained by mutations in the plakophilin 2 (*PKP2*) gene [22,23], with more than 50 *PKP2* mutations currently known [17]. The penetrance* of ARVD appears to be low, possibly because of the insensitivity of the Task Force criteria [19,24]. Sequencing of the most commonly mutated genes may be useful in identifying family members of the proband who require long-term clinical follow-up, especially because correct identification of affected individuals may be useful in prevention of sudden cardiac death. Testing for the four most common genes mutated in ARVC is available in the USA for a cost of $3000.

The relevance of genetic diagnosis to prognostication or individualization of treatment is limited by the fact that most mutations identified to date are rare, and ''private'' to individual families [25]. Given incomplete penetrance and variable expressivity within families, it is unclear to what extent we can extrapolate the risk of sudden death from one family with a given mutation to another, even if they share the same mutation. It is highly unlikely that we will be able to define a common risk profile for all mutations of a single gene [26–28].

If a genetic diagnosis cannot be made for the proband, then clinical screening of family members would occur, but those who appear to be ''negative'' for disease should continue to be screened at some regular interval [29]. The late appearance of ARVC in some individuals [30] requires that screening should continue throughout adult life.

Placement of an implantable cardioverter-defibrillator in patients with the diagnosis of ARVC remains an area of uncertainty [31]. As with HCM, attempts have been made to identify high-risk diagnostic features [32,33].

Restrictive cardiomyopathy

RCM demonstrates several rare hereditary variants, including familial idiopathic restrictive cardiomyopathy, and hereditary amyloidosis. Familial idiopathic RCM is extremely rare, with reports only from a small series of cases [34,35]. As yet, no gene has been identified. Furthermore, in some families with HCM, individual members can show a pattern of restrictive filling with little or no left ventricular hypertrophy [36,37]. In a systematic analysis of 1226 relatives of HCM probands, this ''restrictive phenotype'' of HCM was seen in 1.5% of individuals, and the diagnosis was accompanied by a high rate of dyspnea and mortality.

Hereditary amyloidosis represents a more common form of heritable RCM and typically involves a genetic defect in the transthyretin protein or apolipoprotein A-I protein, leading to misfolded proteins and infiltration of the myocardium with amyloid fibrils. RCM shows allelic heterogeneity, with multiple transthyretin mutations identified to date [38]. The pattern of inheritance is usually autosomal dominant.

Conclusions

General principles of the architecture of genetic disease can guide screening and diagnostic approaches for all the cardiomyopathies – and, in fact, for all inherited diseases. At present, the primary benefit of identifying a causal mutation in a proband is to facilitate screening in family members. A preclinical diagnosis achieved through screening programs can allow initiation of further monitoring programs for disease development, avoidance of high-risk behaviors, and potential implementation of disease-mitigating therapies. Although there is considerable incentive to offer genotype-based forecasting for patients, allelic and genetic heterogeneity and variable expressivity have rendered such individualization of care highly unlikely. Our ultimate desire for tailored prognostication and treatment is likely to be realized only when we can generate phenotypic profiles that can integrate individual genotypic and environmental information and yet be sufficiently common to allow accuracy in prediction and classification.

*See glossary for definition of these terms. ■

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