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Mendelian Forms of Structural Cardiovascular Disease

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Abstract

Clinical and molecular genetics are inextricably linked. In the last two decades genetic studies have revealed the causes of several forms of structural heart disease. Recent work is extending the insights from inherited arrhythmias and cardiomyopathies to other forms of heart disease. In this review we outline the current state of the art for the genetics of adult structural heart disease, in particular the cardiomyopathies, valvular heart disease and aortic disease. The general approaches are described with a focus on clinical relevance, while potential areas for imminent innovation in diagnosis and therapeutics are highlighted.

Keywords

Mendelian Forms; Structural Cardiovascular Disease; Genetics; Cardiomyopathies; Valvular heart disease; Aortic disease

Introduction

The classification of cardiovascular diseases has been transformed by the advent of objective testing ranging from cardiac catheterization and echocardiography to MRI. As novel modalities have resolved novel structural features in arterial or ventricular anatomy, redefined cardiac physiology and begun, through magnetic resonance and molecular imaging, to define tissue characteristics in vivo so our understanding of the biology underlying most clinical conditions has been disrupted^{1, 2}.

Pathologic studies classified ventricular remodeling with dilatation or hypertrophy as distinctive adaptive responses of the myocardium to volume or pressure overload respectively. These phenomena were initially thought to represent the primary homeostatic responses driving maladaptive physiology, and leading eventually to congestive heart failure. With the emerging waves of innovative technologies, we have been able to follow for the first time the evolving nature of different forms of structural heart disease often non-invasively. Over time it has become apparent that in many forms of heart disease there is no evidence of prior myocardial injury or ongoing physiologic stressors^{2, 3}. The progressive dissemination of diagnostic tools to lower risk settings, and ultimately to asymptomatic individuals has allowed the definition of familial forms of many forms of myocardial and

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Compliance with Ethics Guidelines

Conflict of Interest

Calum A. MacRae has received royalties for genetic testing for HCM.

Human and Animal Rights and Informed Consent

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valvular disease. Despite these insights, most primary cardiovascular structural defects are often considered the consequence of occult insults, and this perception remains for many disorders—for example in the case of dilated cardiomyopathy where viral injury is still considered the dominant etiology⁴. Clearly injury does play a major role in many syndromes, but even here, the substantial variation in individual responses strongly suggests inherited contributions to the outcomes of acquired injury⁵.

Using human and model system genetics, the last three decades have seen tremendous advances in our understanding of the genetic basis of multiple forms of structural heart disease⁶. Although routine genetic testing is already appearing in many clinical settings, it will require a close collaboration between geneticists and clinical cardiologists and to fully realize the potential of the human genome in the management of structural heart disease. Clinical investigators will have to move beyond overly simplistic and deterministic views of genetic testing despite recent opinions to the contrary⁷. This review will outline the evolving relationship between molecular genetics and clinical investigation, emphasizing recent developments in the genomics of the major forms of structural heart disease.

Specific disorders

Dilated cardiomyopathy

Clinical genetics—Even in the earliest descriptions of DCM, an inherited basis was suspected from the occasional observation of extended families. Michels *et al.* studied the role of genetic factors in DCM by systematically evaluating the first-degree relatives of probands with DCM for evidence of the same disease⁸. There was evidence of DCM in 25% of ‘at risk’ first-degree relatives. Subsequent work from other investigators has confirmed the prevalence of DCM in relatives and demonstrated that when sub-clinical phenotypes are included up to 40% of DCM probands have affected relatives⁹. These findings, in the context of the successes of positional cloning approaches in HCM and other syndromes, led to an explosion in the number of genetic studies in DCM. Initial anticipation of early and unequivocal etiologic insights in DCM has been tempered by the consistent finding of small kindreds with relatively few definitively affected individuals¹⁰. Autosomal dominant patterns of inheritance predominate. The large numbers of individuals with subclinical disease have complicated linkage analyses and are one important reason for the high ratio of mapped loci to cloned genes (see Table 1). The high prevalence of subclinical disease raises the possibility of unmeasured genetic or environmental factors in the emergence of overt DCM, and several investigators have hypothesized that the underlying trait in DCM is susceptibility to adverse remodeling in the face of specific myocardial insults¹¹.

Genetic mapping—Genetic linkage studies have identified at least 20 loci at which DCM is a prominent component of the phenotype. Many genetic loci are represented by only a single published family (see Table 2). These data suggest a high degree of genetic heterogeneity. The detection of any allelic heterogeneity will require the identification of the responsible genes at these loci. The genetic heterogeneity is only partly reflected in clinical or phenotypic heterogeneity^{10, 12}. At least two more specific patterns of disease have been identified, each of which may represent a distinct etiologic pathway. There are several recessive or X-linked muscular dystrophies that are associated with significant cardiomyopathy, often disproportionate to the extent of the skeletal involvement^{10, 12}. The second phenotypic group is represented by families with autosomal dominant atrio-ventricular conduction block, intraventricular conduction disease and DCM. These appear to be manifestations of a syndrome which may also include arrhythmogenic right ventricular cardiomyopathy, or in some cases, limb-girdle muscular dystrophy^{10, 13, 14}. Even these clinical entities are themselves known to be genetically heterogeneous. The vast majority of DCM families are small kindreds with two or three clearly affected individuals in a

distribution consistent with autosomal dominant inheritance, with no obvious extracardiac features¹⁵.

Molecular genetics and pathophysiology—The genes responsible for several forms of DCM have been identified, and investigation of the basic mechanisms of disease has been initiated. These genes belong to several different gene families, with at present no unifying theme to unite them (Table 3).

Dystrophin and associated proteins: The cloning of the dystrophin gene responsible for Duchenne and Becker variants of muscular dystrophy, both of which have significant cardiac involvement, suggested this protein and other members of the dystrophin-associated glycoprotein complex (DGC) as potential candidates for other forms of DCM. So far only occasional families with X-linked DCM have been directly linked to mutations in the dystrophin gene, and other recessive cardiomyopathies have been found to result from mutations in the sarcoglycan genes^{16, 17}. Several screens of multiple affected probands have effectively excluded this protein complex as a common cause of DCM when unselected for mode of inheritance.

Mutations in this pathway are presumed to cause DCM through the role of the large dystroglycan associated glycoprotein complex in the structural integrity of the link between cytoskeleton and extracellular matrix. However, recent work implicating the DGC in membrane cycling, aggregation of signaling molecules into local, functionally important, clusters, and in adenoviral pathobiology suggests a much more complicated picture. Secondary abnormalities of the smooth muscle, affecting the circulation, have also been implicated in both skeletal myopathy and cardiomyopathy¹⁸.

Among the most interesting developments in recent years has been the emergence of several strategies for the treatment of skeletal and cardiac involvement with myopathy involving this prototypic pathway. Several approaches have proven useful in preclinical studies, most notably membrane stabilizing agents¹⁹ and small molecules or genetically delivered splicing RNAs that lead to read through of mutated exons²⁰. Importantly, these data suggest that, though there may be a considerable lag, fundamental discoveries in structural heart disease genetics may be as likely to lead to innovative and specific therapies as they have been in clonal disorders such as cancer.

Nuclear membrane proteins: The discovery of mutations in the lamin A/C gene in families with conduction disease and DCM recently suggested that such nuclear membrane proteins may represent a distinct pathway in cardiomyopathy¹⁴. These results built on the demonstration of a very similar cardiac phenotype with mutations in emerin, another nuclear membrane protein²¹. While it is possible that this pathway results in DCM through defects in the mechanical integrity of the nucleus, the biological functions of these genes are only beginning to be understood. Interestingly, lamin A/C is widely expressed, yet the diverse phenotypes associated with mutations in this gene appear tissue-specific. Several other loci exist where the discrete phenotypes of conduction disease and DCM co-segregate. The cloning of mutated genes at these loci will add further potential pathway members and may elucidate the mechanisms of disease in this subset²².

Interestingly, there is increasing evidence that the physical relationships among organelles in cardiomyocytes are important for the physiologic performance of the heart at baseline and in response to injury. Mutations in the giant sarcomeric protein titin, implicated in a significant proportion of dilated cardiomyopathy, have also been associated with perturbations of subcellular architecture²³. Beyond such organelle rearrangements, there is also evidence of substantial effects on signaling, which to date does not fit any particular paradigm²⁴.

Cytoskeletal and sarcomeric proteins: Given the specialized role of cardiac myocytes, and the adaptation of the cytoskeletal apparatus in the sarcomere, many of these genes became candidates in the search for the causes of DCM²⁵. The screening of large numbers of probands for mutations in the cardiac actin gene resulted in the identification of mutations in a very small fraction of these patients. Subsequent screening of series of probands has only confirmed the extreme rarity of actin mutations as causal factors in DCM²⁶. Interestingly, mutations in other sarcomeric protein genes, previously implicated in hypertrophic disease, have now been shown to cause DCM on occasion^{27, 28}. These genes potentially implicate several pathways in the development of DCM, including contractile dysfunction, inefficient energetics and myocardial sensing of stretch or other stimuli^{29, 30}.

As mentioned above, the advent of more efficient sequencing techniques has heralded the screening of massive genes which had long been suspected of playing a role in structural heart disease³¹. Using next generation sequencing strategies, it has been possible to screen 393 exons of the titin gene in disease cohorts. This has revealed that up to 25% of DCM is a result of truncating mutations or other variants in the titin gene²³. These findings suggest that it may ultimately be feasible to undertake a molecular classification of DCM, though the utility of parsing the syndrome in this manner remains to be determined.

Myotonic dystrophy: Occasionally myotonic dystrophy will present with DCM or conduction disease as a prominent component, although it is unusual for this to be the case throughout a single pedigree. The mutated gene appears to be a protein kinase, but the mutation, an expanded triplet repeat in the 3' untranslated region of the coding sequence, may also affect transcription of neighboring loci through effects on splicing³². This triplet repeat is unstable as it is transmitted meiotically, and so disease will often become more severe with each progressive generation, a phenomenon known as anticipation. The mechanism by which the mutation results in cardiomyopathy is unknown, but abnormal levels or localization of the myotonin kinase have been hypothesized. Here too, nuclear membrane effects have been postulated³³. In the last few years more extensive genomic analyses have suggested that there may be a more general defect in RNA transcription mediated directly by the trinucleotide repeats and involving the localization of specific transcription factors^{34, 35}.

Splicing factors: Recent work in both animal models and human genetics has implicated mutations in a splicing factor, known as RNA Binding Motif protein 20 (RBM20), in as many as 5–10% of patients with DCM. There is some evidence that mutations in this gene may be more common in families where sudden death is prominent, and that in some of these families extensive interstitial and subendocardial cardiac fibrosis may be common. Interestingly, this splicing factor appears to be required for the transition from fetal to adult isoforms for many proteins of diverse function (sarcomeric, cytoskeletal, metabolic, transmembrane transport) within the heart. Whether this pathway is a true mechanistic link between inherited and acquired forms of heart failure remains to be seen, but understanding the regulation of the fetal gene program will undoubtedly shed insight into all forms of ventricular dysfunction. There is some evidence that the mutations in this form of DCM lead to a persistent fetal splicing repertoire in myocardium particularly of titin isoforms, offering yet another link between monogenic forms of heart failure and the acquired remodeling seen more commonly in response to ischemia, infarction and other injuries³⁶.

Disease models—The identification of the causal human genes in DCM offers a definitive starting point for the generation of true disease models. The production of genetically modified organisms bearing the corresponding mutations allows investigators to unravel the mechanisms of cardiomyopathy from the initial insult through to the final phenotype³⁷. Insights may also travel in the opposite direction with model organism

phenotypes implicating previously unsuspected genes as candidates for DCM²⁸. Importantly, such inferences require confirmation through human molecular work, as null mutants or tissue specific transgenics may not reflect any naturally occurring human genotype. For example, mouse models of DGC-related DCM confirmed initial hypotheses suggesting that force transmission is somehow disrupted, but importantly have also revealed many other pathways that may be involved in the abnormal myocardial function seen. Clearly, it will be crucial to understand these multiple mechanisms of disease if we are to be able to design specific therapies for primary myocardial disease.

Specific models for other heritable forms of DCM do not yet exist, although there are intense efforts to generate such models, not only in mouse but in larger animals and in smaller more tractable organisms such as the zebrafish and the fruitfly³⁸. These model systems will enable the detailed pathophysiology of each gene defect to be explored, the causative pathways to be defined, and ultimately allow screening at increasingly higher throughput to directly identify modifier loci or novel therapies. The disparate phenotypes already identified in DCM suggest that no single pathway is the sole culprit in this syndrome. The dissection of the fundamental biology of these conditions should illuminate not only such differences, but also the commonalities that may well be shared with acquired forms of heart failure.

Hypertrophic cardiomyopathy

Clinical genetics—Early descriptions of HCM realized that a large proportion of cases appeared to be familial with prominent autosomal dominant inheritance. Studies based on less extreme echocardiographic phenotypes suggested lower rates of familial disease. Systematic family screening now suggests that as many as 90% of cases have evidence of autosomal dominant disease. The remaining ‘sporadic’ cases may represent true *de novo* mutations in the genes that cause Mendelian forms of the disease, or poorly penetrant forms of the underlying trait³⁹.

A large proportion of the genetic studies, and the majority of all clinical studies, in HCM are dominated by individuals from pedigrees with severe hypertrophic phenotypes or a high incidence of sudden death. Recent attempts to redress this balance have concentrated on non-referral populations, but virtually every study has failed to assess the potential relatedness of individual subjects from a single center. In a condition dominated by Mendelian forms the biases introduced by events or phenotypes in related individuals, genetic founder effects or other less obvious confounders make many current clinical investigations difficult to interpret. It is not surprising that conflicting data have appeared on the predictive value of most clinical indices including ECG and echocardiographic variables⁴⁰. There is an unmet need for proband-based clinical studies (and molecular studies), and the development of segregation-based approaches to the assessment of clinical risk within families. Despite more than two decades of investigation into the fundamental mechanisms of HCM, the majority of clinical investigators are reticent to incorporate genetic data into their work. There is a major need for more seamless integration across genetics and clinical research if robust measures for genotype-phenotype correlation or even simple clinical risk metrics are ever to be derived.

Clinical genetic studies identified discrete entities within the HCM syndrome several years prior to the use of molecular analyses. Braunwald’s initial description of familial HCM noted several large kindreds with evidence of ventricular pre-excitation and left ventricular hypertrophy³. In each family these conditions appeared to co-segregate tightly, and subsequent work has shown that pre-excitation, atrioventricular block and HCM are linked to a specific locus⁴¹. While pre-excitation is seen with other forms of HCM, spontaneous heart block has not been reported in other adult-onset families with autosomal inheritance.

Interestingly, pre-excitation and atrioventricular block are also seen in HCM due to mitochondrial disease⁴². Families in which both HCM and DCM co-segregate represent a second distinctive clinical entity. These kindreds contain multiple individuals with either phenotype, and importantly those with DCM do not appear to have progressed from HCM.

Although inbred families with heterozygous or more severe homozygous phenotypes have been reported⁴³, autosomal recessive HCM is uncommon. The most frequent form of recessive ventricular hypertrophy is observed in the context of Friedreich's ataxia, where there is cardiac involvement in the majority of cases⁴⁴. Other situations in which idiopathic cardiac hypertrophy is seen include Noonan's syndrome, and several of the glycogen storage disorders⁴⁵. In these instances, the phenotypes are usually very distinct, and the discordant clinical presentations and outcomes observed in such 'phenocopies' serve to highlight how important it is to have a comprehensive grasp on the etiologic heterogeneity in any studies of an inherited condition.

Molecular genetics—HCM is caused by mutations in at least 12 genes, the majority of which encode sarcomeric contractile proteins³⁷ (Table 4). While many hundreds of genes have been implicated in experimental forms of left ventricular hypertrophy, only this group of genes appears to cause human hypertrophic disease. Although there is tremendous variation in the expression of HCM even within a single family, some generalizations about the phenotypes seen with specific genes have emerged. Families with cosegregating HCM and DCM seem to be a particular feature of mutations in the cardiac actin gene on chromosome 15⁴⁶. Focal mid-cavity and disproportionate papillary muscle hypertrophy are associated with mutations in the myosin light chains⁴⁷. The syndrome of massive wall thickening, preexcitation and eventual atrioventricular block has been shown to be a result of activating mutations in the PRKAG2 gene⁴⁸. In this syndrome the increased wall thickening is due not only to true myocyte hypertrophy, but also to a significant component of inappropriate glycogen storage. Other data have suggested that myosin mutations may be associated with significantly more hypertrophy than troponin mutations⁴⁹, and myosin binding protein C mutations may be associated with later onset hypertrophic disease^{50, 51}. Most recently, mutations in the cardiac troponin I gene have been associated with families exhibiting both HCM and restrictive cardiomyopathy⁵².

As the search for new HCM disease genes has slowed, so investigators have reported increasing numbers of individuals with mutations in multiple sarcomeric disease genes. These 'compound' mutations are very difficult to assess, as there is usually insufficient clinical or functional data to determine whether the primary mutation segregating within a family is definitively pathogenic, far less any of the secondary variants⁵³. Similarly, the incidence of potentially pathogenic missense mutations in coding sequences that is being reported in emerging whole exome or whole genome sequencing (100–200 per genome) implies that much larger studies will be required before any of these variants can be rigorously interpreted⁵⁴.

One other development in this arena has been the recognition that some forms of left ventricular non-compaction are a result of mutations in sarcomeric contractile protein genes⁵⁵. These findings again broaden the scope of potential overlap syndromes and reinforce the idea that current myocardial disease classification systems would benefit from reappraisal.

Disease Models—Murine models of HCM have been generated and recapitulate many of the features of the human disease³⁷. There is evidence that the most specific of these models, the Arg403Gln β -cardiac myosin 'knock-in' mouse, has significant abnormalities of myocyte cross-bridge cycling. The precise pathways involved have not yet been elucidated,

but clearly these mice offer the potential to dissect the fundamental mechanisms of hypertrophy most relevant to human disease. The temptation to invoke a single pathway is strong, but evidence of common genetic modifiers, and discrete hypertrophic disorders with distinctive clinical features suggest otherwise. It is possible even that different mutations in the same gene result in hypertrophy through completely different pathways. Inefficient energy utilization may act as an important downstream pathway, and might help reconcile some of the divergent effects of mutations on contractility^{56, 57}. The disease gene in Friedreich's ataxia is a mitochondrial protein, which appears to be a critical player in oxidative stress pathways⁵⁸. Many other processes might also be perturbed, such as sarcomere assembly or cellular transport pathways, and the systematic study of genetic models will be vital to unraveling the pathophysiology of primary cardiac hypertrophy.

Valvular Heart Disease

Investigators in valvular heart disease have also been active in the last few years, exploring the heritable contribution to aortic and mitral valve disease and embarking on the work to define the causal genes in the Mendelian forms. Initial genetic epidemiology studies revealed a significant genetic contribution to bicuspid aortic valve (BAV) and also inferred, though co-segregation, a common etiology with disorders on the hypoplastic left heart syndrome spectrum⁵⁹. Interestingly, extended study of some families suggests that calcific aortic valve disease also may have a significant heritable contribution⁶⁰.

To date only mutations in Notch 1 have been identified as causes of isolated BAV, though BAV is seen incidentally in TGF-beta related disorders⁶¹. Notch1 mutations are extremely rare, and usually are observed in the context of more extensive congenital defects⁶².

In the field of mitral valve prolapse (MVP), the difficulties in excluding subtle forms of involvement have slowed scientists' ability to define the causal genes. Several loci have been mapped, but to date no definitive causal genes have been identified^{63, 64}. Mutations in SMAD 3 have been associated with dysplastic mitral valves, though here the relationship with non-syndromic forms of disease remains unclear⁶⁵.

Aortic Disease

The pioneering work of Dietz' group has continued to redefine our understanding of Marfan syndrome and is moving inexorably towards specific therapies⁶⁶. The discovery that the mutant fibrillin defects previously presumed to have purely structural role in the Marfan aorta are in fact mediating many of their effects through aberrant TGFbeta signaling has transformed the field⁶⁷. In mouse models TGF-beta modulation has been shown to improve not only the vascular phenotypes but also abnormalities in lung parenchyma and skeletal muscle atrophy. Initial work demonstrated an anti-TGF beta effect from high dose losartan, and following some evidence of success in a small cohort of pediatric subjects with Loeys Dietz syndrome (caused by mutations in the TGF beta receptors), there are now ongoing trials of high dose angiotensin receptor blockers in Marfan syndrome⁶⁸.

Several new genes have subsequently been identified in other forms of aortopathy, and an emerging theme of structural proteins with regulatory effects is being developed^{65, 69, 70}. Ultimately, most genetic defects likely act through diverse signaling networks, but the potential unifying role of TGF-beta signaling has helped to drive current mechanistic investigation⁷¹.

Overlap Syndromes

As clinical genetic evaluation and genetic testing has become more widely available, it has become all too apparent that our current nosology is simply inadequate. Extended kindreds

have been reported with well-documented AF, atrioventricular block and dilated cardiomyopathy due to mutations in SCN5A⁷². Similarly, other investigators have documented overlap between these syndromes and one characterized by incessant ectopy arising from the Purkinje system^{73, 74}. When combined with the known associations between other SCN5A mutations and either the Long QT syndrome, Brugada syndrome or both, the profound complexity of genotype phenotype relationships for even a single gene becomes apparent⁷⁵.

Phenotypic overlap has also been demonstrated for HCM and DCM, DCM and ARVC, and hypertrophy and ARVC^{6, 76, 77}. There is increasing recognition of a concomitant myopathy in some forms of aortic and mitral valve disease, while the association between BAV and aortic disease has been well-documented for decades, though attributed to hemodynamic forces until recently⁷⁸. In addition, as the intensity of non-invasive evaluation increases, so minor structural abnormalities are being reported in what were previously thought to be purely electrical disorders. Ultimately, as the physiologic phenotyping that is feasible accelerates, we may be able to resolve these apparent overlap syndromes into some more fundamental set of upstream abnormalities. These recent developments highlight the wave of translational innovation that will be required to fully reconcile the genome with its phenotypic outcomes.

Genetic Testing for Structural Heart Disease

The last few years have seen tremendous advances in the study of structural heart disease. The major pathways have been identified in HCM and ARVC, while similar inroads are beginning to be made in DCM, valve and aortic disease. The identification of molecular pathways is the first step in developing a mechanistic understanding of these Mendelian disorders, but also offers the potential for insight into more common types of heart and vascular disease. It is clear that the morphological classification of heart disease that has proven so useful for decades will be superseded by a molecular nosology. Currently panels of disease genes are re-sequenced by traditional Sanger methods or more recently by targeted capture and next generation sequencing technologies. In the very near future, cost-efficiency will mandate whole exome or whole genome sequencing as the primary tool for mutation detection⁷⁹. The scale of next generation sequencing serves to underline the importance of developing rigorous methodologies to interpret sequence variation⁸⁰. For the foreseeable future this will require coordinated clinical genetic evaluation.

There is still much investigation required before molecular diagnostics or prognostics are useful in the management of these disorders. Recent guidelines for genetic testing in inherited heart disease from a number of professional bodies have recognized the problems posed by using molecular genetics in a deterministic manner^{80, 81}. It is remarkably difficult to establish pathogenicity without extensive familial data or detailed animal modeling of the specific allele⁸⁰. Similarly, there are emerging data from whole genome and whole exome sequencing on the high frequency of different classes of 'mutation' in normal individuals that have led to a reappraisal of the stringency of defining disease causality. Indeed, there are also data suggesting that only a small proportion of those with sequence variants in sarcomeric disease genes previously thought disease-causing may develop the relevant phenotypes⁸². As a result, the most recent guidelines all recommend the cautious interpretation of genetic data in the context of a comprehensive clinical genetic evaluation⁸³. Extremely helpful insights can be gained from clinical investigation of all of the 'at risk' family members with an awareness of some basic genetic principles⁸³, and these insights may be more immediately applicable than molecular information. Nevertheless, genetic testing for both DCM and HCM is already widely available. The sensitivity and specificity are improving constantly, but remain at level where molecular diagnosis is often simply not

feasible. Allelic and genetic heterogeneity and variable expressivity render prognostication difficult. Negative genetic tests have little value in the presence of overt clinical disease, while the majority of 'positive' tests have few data to support a definitive causal role. In this setting, management decisions based on the results of genetic testing are fraught with uncertainty-already a prominent feature in the therapy of such patients.

Common alleles

The limited predictive utility of simple Mendelian genotypes implies relatively common and substantial genetic modifiers⁸⁴. In the last few years the availability of genetic arrays capable of genotyping hundreds of thousands of markers in a single experiment has popularized case cohort genetic studies known as genome-wide association studies (GWAS)⁸⁵. These studies have been able to detect genetic loci influencing LV mass, some echocardiographic structural LV or valvular parameters and even aortic dimensions on a population-wide basis⁸⁶. In general such GWAS loci explain only a limited proportion of the liability variance for the respective conditions^{87, 88}. These data also support prior evidence that inherited heart diseases are highly heterogeneous, each with multiple underlying disease genes and multiple new mutations in each disease gene further underlining the utility of integrated clinical assessment with molecular data to manage the entire kindred.³⁷.

Conclusion

At present, the primary benefit of identifying a causal mutation in a proband with structural heart disease 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. Our ultimate desire for tailored prognostication and therapy is likely only to be realized when we are able to generate phenotypic profiles that can integrate individual genotypic and environmental information and yet be common enough to allow accuracy in prediction and classification.

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Figure 1.

The classic view of HCM and DCM as discrete biological pathways has been challenged by recent molecular genetic studies, although the physiologic profiles are clearly distinct. Hypertrophy is known to progress to dilatation in many situations, including in some familial cardiomyopathies. However, a single mutation in different individuals within the same family may cause hypertrophy or dilatation, as a result, it is presumed, of genetic or environmental modifiers. Understanding the mechanisms favoring the development of hypertrophy or dilatation will help in the dissection of acquired forms of ventricular remodeling.

Relating Genotype to Phenotype-Variable Expressivity

Figure 2.

Only the systematic assessment of family members of affected probands reveals the true genetic architecture of a syndrome which may be very homogeneous as in some of the cardiomyopathies, or highly heterogeneous as in this example from a study of atrial fibrillation.

Figure 3.

Apparently unrelated phenotypes may be mechanistically related from simple clinical observations in extended families. Here left ventricular hypertrophy and ventricular pre-excitation cosegregate in a single pedigree, in a manner consistent with a single autosomal dominant disorder. The study of individual parts of the pedigree, such as the highlighted nuclear family in which hypertrophy is prominent (enlarged symbols), may give a distorted view of the overall nature of the underlying trait.

Table 1**Basic genetic terminology**

Allele -Any one of the sequence variants of a particular gene.

Genome -The complete DNA sequence of an organism.

Haplotype -A series of sequence variations that are linked together on a single chromosome.

Introns and exons -Genes are initially transcribed as continuous sequences, but only some segments (the exons) of the resulting messenger RNA molecules contain information that encodes the gene's protein product. The intervening regions between exons (the introns), are excised (or spliced) from the RNA to generate the final RNA from which the protein is translated.

Messenger RNA (mRNA) -Following the initial transcription from a gene of a continuous RNA molecule, this molecule is then processed in a number of ways including splicing to generate the final messenger RNA which is then translated by the cells machinery into a protein.

Mutation -Any variation in sequence from a reference state.

Phenotype -The complete set of characteristics of an organism including morphology and function.

Proteome- The complete repertoire of proteins encoded by a genome.

Single nucleotide polymorphism (SNP)- Most of the variation in DNA sequence between individual members of a population is the result of changes in single nucleotides. These polymorphisms are known as SNPs.

Transcription -The copying of a gene's DNA into RNA.

Translation -The synthesis of a protein from the information encoded in a messenger RNA.

Table 2**Criteria for defining a causal mutation – discrimination from a polymorphism****I - The “mutation” should segregate perfectly with disease.**

The sequence anomaly must be present in all the affected individuals and absent from all the unaffected individuals. Ideally two independent means should be used to confirm that this is the case. The best statistical support for this segregation is a LOD or logarithm of the odds score (also used in anonymous mapping studies), which estimates the likelihood of random cosegregation as a function of the number of informative events.

II - The “mutation” should not be present in a normal population

Rare polymorphisms may be overrepresented in any given large family. These polymorphisms may have functional significance, yet not be responsible for disease. For example null alleles have been described for many genes including that encoding the cardiac beta myosin heavy chain, but when present in the heterozygous state may be of no import. It is necessary to screen a large normal population for any putative mutation to ensure that it is not simply an incidental polymorphism.

III - The “mutation” should effect substantial change on the gene sequence

There should be indirect evidence that the mutation will have a biological effect. This may be obvious for some mutations which disrupt the sense of the entire coding sequence of the gene. Other mutations will have more subtle effects, changing only a single amino-acid residue. The confirmation of these substitutions as disease-causing may require additional studies, such as comparative sequence analyses (with the same gene in other species, or similar genes in the same species, to see if a particular residue is highly conserved), *in vitro* structure function analysis or *in vivo* genetic analyses.

IV - The introduction of the “mutation” should be sufficient to cause disease

There should be direct evidence that the mutation has a biological effect. The ultimate proof of causality lies in the demonstration that the simple addition of the mutation is sufficient to recapitulate the disease. This is usually done in genetic model organisms, but the specific knock-in of a point mutation (the most common mutation calls in human disease) is rarely performed. Often a causal role is inferred from transgenic expression of a mutant gene or from knock-out of the gene. The demonstration of disease in association with a *de novo* mutation in humans is the logical equivalent.

Table 3

Adult dilated cardiomyopathy loci

Locus	Inheritance mode	Disease gene	Specific clinical features	References
1q21 CDCD-1	AD	Lamin A/C	AVB, LGMD, CMT	[14]
1q31 CMD-1D	AD	Cardiac troponin T		[27]
2q14-22 CMD-1H	AD	Unknown		[89]
2q31 CMD-1G	AD	Titin		[31]
2q35 CMD-1I	AD	Desmin	RCM, Inclusion myopathy	[90]
3p21 CDCD-2	AD	SCN5A	AVB	[13, 91]
4q12	AR	β -sarcoglycan		[92]
5q33 CMD-1L	AD/AR	δ -Sarcoglycan		[93]
6p24	AR	Desmoplakin	ARVC, Woolly Hair	[94]
6q12-16 CMD-1K	AD	Unknown	Possibly allelic with AFib	[95]
6q22 CMD-1P	AD	Phospholamban		[96]
6q23 CDCD-3	AD	Unknown	AVB, LGMD	[97]
6q23-24 CMD-1J	AD	EYA-4	Sensorineural hearing loss	[98, 99]
9q13	AD	Unknown		[100]
10q21-23	AD	Vinculin		
10q21-23	AD	Unknown	Possibly allelic with AFib	[101]
10q22-23	AD	Lim Domain Binding 3		[102]
10q25	AD	RBM20	Fibrosis, SCD	[103]
11p15 CMD-1M	AD	CSRP3		[28]
11p11	AD	MYBP-C		[104]
12p12 CMD-1O	AD	ABCC9		[105]
14q12 CMD-1S	AD	β -Cardiac myosin heavy chain (MYH7)		[27]
15q14 CMD-1R	AD	α -cardiac actin	Cosegregating FHC	[25]
19q13	AD	Myotonic	Anticipation, AVB, arrhythmia	[32]
19q13	AD	TNNI3		[106]
Xp21	X-Linked	Dystrophin		[16]
Xq28	X-Linked	Emerin	AVB, Humero-peroneal MD	[21]

Abbreviations: AD-autosomal dominant; AR-autosomal recessive; AVB-atrioventricular block; MYBP-C-Myosin binding protein-C; LGMD-limb girdle muscular dystrophy; CMT-Charcot -Marie-Tooth; RCM-restrictive cardiomyopathy; AFib-atrial fibrillation; FHC-Familial hypertrophic cardiomyopathy; MD-muscular dystrophy. **Notes:** This table does not include some putative DCM disease genes where the absence of segregation or functional data precludes definitive attribution of causality. In addition, some contiguous loci may be allelic, but there is insufficient information to determine this at present

Table 4**Hypertrophic cardiomyopathy loci**

Locus	Inheritance mode	Disease gene	Specific clinical features	References
1q31	AD	Cardiac troponin T	Hypertrophy may be less marked	[107]
3p	AD/AR	Myosin light chain 3 kinase	Mid-cavity/PAP muscle hypertrophy	[47]
7q36	AD	PRKAG2	Glycogen storage AVB, WPW	[48]
9	AR	Frataxin	Ataxia	[58]
11p15	AD	Muscle LIM protein		[108]
11p11	AD	MYBP-C	Often later onset disease	[109]
14q12	AD	MYH7 and MYH 6		[110]
15q14	AD	α -cardiac actin	Cosegregating DCM	[46]
15q22	AD	α -Tropomyosin		[107]
19q13	AD	Cardiac Troponin I	Cosegregating RCM	[111]
20q13	AD	Myosin light chain kinase	Mid-cavity/PAP muscle hypertrophy	[47]
Xq24	X-linked	LAMP2	Lysosomal storage, SCD	[45]

Abbreviations: AD-autosomal dominant; AR-autosomal recessive; PRKAG2- Adenosine monophosphate activated protein kinase gamma-2 subunit; MYBP-C-Myosin binding protein-C; MYH-Myosin heavy chain; PAP- papillary; AVB-atrioventricular block; WPW-ventricular pre-excitation; DCM-dilated cardiomyopathy; RCM-restrictive cardiomyopathy