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Impact of Mendelian Inheritance in Cardiovascular Disease

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Abstract

Cardiovascular disease is a leading cause of mortality worldwide. While the etiology for the majority of cardiovascular disease is presumed to be a combination of genetic and environmental factors, developments in our understanding of the basic biology of cardiac disorders have been greatly advanced through discoveries made studying heart diseases that exhibit Mendelian forms of inheritance. Most of these diseases primarily affect children and young adults and include cardiomyopathies, arrhythmias, aortic aneurysms and congenital heart defects. The discovery of the genetic etiologies for these diseases have had significant impact on our understanding of more complex forms of cardiovascular disease and in some cases led to novel diagnostic and treatment modalities. In this review, we will summarize these seminal genetic discoveries, highlighting a few that have resulted in significant impact on human disease, and discuss the potential utility of studying Mendelian-inherited heart disease with the development of new genetic technologies and our increased understanding of the human genome.

Introduction

Diseases of the cardiovascular system are a leading cause of death in both children¹ and adults.² Adult onset cardiovascular disease – hypertension, atherosclerotic heart disease, valvar disease – remain significant health problems and leading causes of death in developed countries,² and the prevalence is increasing in developing countries.³ Inherited cardiomyopathies and arrhythmias are among the most common human genetic disorders. In addition, congenital malformations of the heart and great vessels are the most common cause type of birth defect and are the leading cause of death in infants less than one year of age, despite recent advancements in medical and surgical therapy.⁴ Improved treatments have led to a greater number of adult survivors, such that there are now more adults than children with a congenital cardiovascular malformation (CVM).⁵ Survivors of these defects encounter significant life-long morbidity, and frequently have a shortened lifespan.⁶ These cardiovascular diseases that affect children and young adults have a strong genetic contribution and accordingly attracted interest from researchers to identify disease-causing genes.

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A significant amount of effort has been spent on identifying the genetic contributors to cardiovascular disease. A number of genome-wide association studies for complex genetic diseases that affect adults such as stroke, hypertension, and atherosclerosis have been performed, with limited success in identifying the underlying genetic susceptibility.⁷ In contrast, many classes of cardiovascular disease that affect children and young adults that are due to single gene disorders (cardiomyopathies, arrhythmias) are now well worked out, while those occupying a continuum from single gene through oligogenic to complex genetic etiologies (CVMs, aortopathies) are just now being elucidated. With the knowledge of individual causative genes for these disorders exhibiting Mendelian inheritance, much insight has been gained in disease pathophysiology and resulted in novel treatments.

In this review, we will demonstrate the importance of single gene defects in cardiovascular disease, focusing on cardiomyopathies, aortopathies, arrhythmias, and CVMs. Recent advances in clinical diagnostic testing and novel therapies will be highlighted. While cardiovascular diseases in both children and adults have a strong genetic contribution, our review will focus primarily on diseases first presenting in children and young adults where the majority of significant genetic discoveries have occurred.

Cardiomyopathy

In this section, we have focused on hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM), as major advances in understanding the genetic basis of these diseases have been made and have impacted clinical care.

Hypertrophic Cardiomyopathy

Familial HCM is defined as left ventricular thickening, which occurs in the absence of a syndrome or other cardiovascular conditions that increase afterload (i.e. aortic stenosis or hypertension), and possess the characteristic histology of myocyte disarray.⁸ Manifestations include dyspnea, chest pain, syncope, palpitations or sudden death. Symptoms may present from infancy to old age but are most apparent in adolescence. HCM is among the most common genetic disorders, with a prevalence of 1/500.⁹ It remains the most frequent cause of sudden cardiac death (SCD) in young competitive athletes in the US, accounting for 1/3.¹⁰

While first described as a clinical entity in the 1950's,¹¹ the familial nature of the disease was not elucidated until the 1980's. This was confirmed in 1990 with the description of the first gene implicated in HCM, *MYH7*.¹² Over 20 genes have now been characterized as causing familial HCM (Table IA), and in the process demonstrated that HCM is a disease of the sarcomere.¹³ Four of these genes, *MYH7*, *MYBPC3*, *TNNT2* and *TNNI3*, account for roughly 80% of all HCM for which a specific gene mutation can be identified.¹⁴ Over 900 different mutations have been found, with many mutations unique to individual families. The most common mutation, *MYBPC3* p.Arg502Trp, occurs in only 2.4% of individuals of European ancestry with HCM.¹⁵

With this increased knowledge of the genetics of HCM, it was thought that genotype-phenotype correlations could be identified. What was discovered was wide variability in presentation between families with the same mutation and even within a family with the same mutation.¹⁶ Only a few specific genotype-phenotype correlations exist, and only broad generalizations can be made. *MYBPC3* mutations tend to result in a later onset of symptoms.¹⁷ Mutations in *MYH7* tend to have a somewhat earlier age of onset, and the p.Arg403Gln and p.Arg453Cys mutations appear to confer more severe disease.¹⁸ However, these mutations have proven to be very rare (<1%) among those with HCM.¹⁹ *TNNT2* mutations cause less hypertrophy, but impart a higher risk of sudden cardiac death.^{20–22}

Presence of a mutation in any of the known genes that cause HCM is associated with more severe disease compared to those with HCM in whom a mutation is not identified.²³ Inheritance of mutations in two or more different genes known to cause HCM has been seen in a number of cases, and results in an earlier onset and more severe disease.^{14, 24–27}

Clinical gene testing for HCM has been available for over 5 years. Despite a reasonable rate of mutation identification (40% for isolated to 70% for familial cases), testing has not entered routine clinical practice. Many reasons exist for this, including high cost and limited utility for the individual patient as testing will have little impact on the prognosis or treatment. Most patients and their families are interested in testing once genetic counseling is provided.²⁸ The greatest benefit exists for relatives of the patient, as once the mutation in the family is identified, clinically unaffected at-risk relatives may be tested and those without the mutation may safely discontinue recommended clinical screening. While identification of a mutation in an unaffected individual may have negative psychological consequences, studies have demonstrated that the majority of individuals identified as carriers of disease-causing mutations positively value genetic counseling and predictive testing.^{29, 30}

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a much more clinically heterogeneous disorder. Individuals with DCM present with symptoms of heart failure, arrhythmias or conduction disturbance, and thromboembolic disease (from an intracardiac thrombus). DCM is defined by left ventricular enlargement and evidence of systolic dysfunction.³¹ A wide variety of acquired causes are known for DCM, including ischemic heart disease, valve disease, congenital heart disease, toxins, chemotherapy, infectious myocarditis, radiation and many others.³² Additionally, many specific genetic diseases present with DCM as a component of their manifestations, including muscular dystrophies and inborn errors of metabolism (IEM), making idiopathic DCM a diagnosis of exclusion. The incidence of idiopathic DCM for children is estimated at 0.57/100,000 while in adults it is 1/2500.^{33, 34} Most experts believe this is an underestimate as individuals with DCM may be asymptomatic for a prolonged time before heart failure becomes evident.

Familial DCM is defined as the occurrence of idiopathic DCM in two or more close relatives. Scattered case reports and small studies in the 1980's suggested DCM was a familial disease in only a small percentage of cases.³⁵ Full recognition that DCM could be a familial disease did not occur until a prospective echocardiography study on relatives of individuals with DCM in 1992,³⁶ which reported familial DCM in 20% of cases. It is now estimated that from 30–48% of individuals with DCM have an affected relative.^{37–39} This genetic knowledge has sparked investigation of seemingly sporadic DCM. Two recent studies demonstrated that half of pregnancy or peripartum DCM cases have a family history of DCM, and mutations can be identified in 5%.^{40, 41}

In contrast to HCM, the genetic etiology of DCM is varied and involves many structures or functions of the cardiomyocyte, that when perturbed, results in a loss of contractile force generation or transmission.⁴² Most genes implicated in familial DCM encode for cytoskeletal (dystrophin-sarcoglycan complex) or sarcomere proteins, but also include ion channels and transcription factors. Over 40 loci and more than 25 genes have been described (Table IB), many of which are implicated in syndromic forms of DCM or also cause HCM. It is likely that many more genes may be involved in DCM, as the currently known genes account for <40% of familial DCM.

The most commonly involved genes in DCM are *LMNA*, *MYH7*, and *TNNT2* which account for 5%, 4%, and 3% of all familial DCM, respectively, while other implicated genes

are found in <1%.^{43, 44} Combined, mutations in sarcomere genes account for up to 10% of mutations in DCM.⁴⁵

Unlike HCM, the role for genetic testing in DCM is limited due to the extensive genetic heterogeneity and low yield (currently 20%). The yield increases in families with DCM and conduction defects, where mutations in *LMNA* may be found in 40%.^{44, 46}

Other cardiomyopathies

Left ventricular non-compaction (LVNC) accounts for ~10% of all cardiomyopathies, and is characterized by spongy myocardial appearance with increased trabeculations.⁴⁷

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) consists of fibrofatty infiltration and dilation of the right ventricle.⁴⁸ Multiple disease loci and genes have been identified for LVNC and ARVC/D (Table IC). Many inherited disorders have secondary hypertrophic or dilated cardiomyopathy, including specific syndromes (Noonan and other Ras pathway syndromes), mitochondrial disorders,⁴⁹ IEM,⁵⁰ and muscular dystrophies⁵¹ and are beyond the scope of this review.

Novel technologies for clinical cardiomyopathy testing

Traditionally, gene testing is performed using Sanger sequencing technology. Analyzing multiple genes can quickly result in expensive test panels. Novel sequencing technologies have been used to lower cost, improve turnaround time, and perform more comprehensive testing by including more genes in the test panel. Oligonucleotide hybridization based resequencing DNA microarrays use 25 bp oligonucleotides that vary at a single central position.⁵² Four probes (A, C, G, and T) are constructed for each basepair in the gene. Fluorescently labeled patient DNA is added to the array, and the dye of maximal intensity identifies the base at the position interrogated. Resequencing arrays are easily scalable and amenable to quickly adding new genes to the test panel. They are currently used for HCM^{53, 54} and DCM⁵⁵ in clinical testing.

Next generation sequencing has just entered the clinical realm.⁵⁶ Various strategies have been devised to reduce the cost by sequencing specific targets through capture by microarray^{57, 58} or fluid methods,⁵⁹ rather than the whole genome. “Bait” sequence is used to capture the “target” region of interest in the patient’s DNA, which may then be sequenced on a variety of platforms. Clinical testing using this method is already available for HCM and DCM.

Thoracic aortic aneurysms

The thoracic aorta is a complex structure with elastic and contractile properties that allow it to receive blood, transmit the pulse wave, and reduce workload of the ventricle. Thoracic aortic aneurysms (TAA) occur due to a weakening of the arterial wall, and predispose to dissection. TAAs, particularly of the ascending aorta, represent an entity distinct from abdominal aortic aneurysms.⁶⁰ The incidence of TAA is 3.5/100,000 with rates increasing with advancing age, but frequent misdiagnosis suggests this is an underestimate.⁶¹ TAAs may be sporadic, familial or syndromic.

Marfan Syndrome

Marfan syndrome (MFS) is a well-known multisystem connective tissue disorder with a defining feature of aortic root enlargement at the sinuses of Valsalva that progresses to aortic dissection by 20–40 years of age.⁶² MFS accounts for only 5% of all TAAs. It is still diagnosed clinically using family history and the clinical features (Ghent criteria) to identify major involvement of at least two systems (skeletal, ophthalmologic, cardiovascular, dura)

and involvement of a third (the preceding and pulmonary, dermatologic).⁶³ Three groups converged on *FBN1* as the causative gene in 1991.^{64–66} Individuals meeting Ghent criteria will have a mutation in *FBN1* in 70–93% of cases.⁶⁷ Some genotype-phenotype correlation exists, as missense mutations eliminating or producing a cysteine are more likely to cause ectopic lentis, and mutations in exons 24–32 have a more severe phenotype, including neonatal MFS.⁶⁸ Originally thought to be a structural disorder, recent work has elegantly shown that the primary pathophysiology is due to alterations in TGF β signaling.⁶⁹ Loss of fibrillin-1 sequestration of TGF β in the extracellular matrix leads to an increase in active TGF β signaling that results in aortic root dilation, lung bullae formation and impaired muscle regeneration.

Loeys-Dietz Syndrome

Following the identification of *FBN1* as the causative gene for MFS, there were observations of individuals with a clinical overlap but without *FBN1* mutations. Several of these families were investigated by linkage analysis, and mutations in *TGFBR1* and *TGFBR2* were found.⁷⁰ Individuals with Loeys-Dietz syndrome have aortopathy (arterial tortuosity, aneurysms and dissections), skeletal abnormalities (pectus deformities, arachnodactyly, talipes equinovarus), translucent skin, and craniofacial abnormalities (bifid uvula, ocular hypertelorism). Compared to MFS, aneurysms may occur in any medium-sized artery, and the arterial disease is much more aggressive with earlier dissection and age of death.⁷¹ Mutations in either gene cause a similar phenotype.

Ehlers-Danlos Syndromes

The Ehlers-Danlos syndromes (EDS) are a collection of connective tissue disorders characterized by variably severe joint hypermobility and increased skin elasticity.⁷² With the exception of the kyphoscoliotic type, all are autosomal dominant in inheritance. EDS, vascular type (formerly EDS IV), is caused by mutations in *COL3A1*. It is characterized by joint hypermobility, increased skin translucency, and rupture of medium sized arteries, bowel and uterus. Although thoracic aortic aneurysms may occur, it is not the most common vessel involved. EDS, kyphoscoliotic form (formerly type VI), is due to mutations in *PLOD1*. It also may have arterial dissection of the medium-sized vessels or aorta. It is distinguished by severe neonatal hypotonia, early and progressive scoliosis, and rupture of the globe. EDS, classic type (types I and II) are due to mutations in *COL5A1* or *COL5A2*, and EDS, hypermobility type (type III or benign familial hypermobility) is likely genetically heterogeneous. Echocardiography observations indicate mild aortic root dilation may be present in up to 1/3 of individuals with the classic or hypermobility types.^{73, 74} In the absence of severe dilation, there does not appear to be a significant risk of aortic dissection; however there are currently no clinical guidelines on long-term management. Longitudinal studies are required to determine if the observed mild dilation is progressive.

Familial thoracic aortic aneurysm

The genetic contribution to non-syndromic TAA has only recently been defined. The first familial case of non-syndromic TAA was described 25 years ago,⁷⁵ but not until the late 1990's was the inheritance and segregation studied in detail.^{76–78} Family studies indicate roughly 20% of individuals with a TAA have a similarly affected relative, and in those families, individuals with TAA presented at an earlier age.^{77, 79} TAA families also have higher rates of aneurysms anywhere in the arterial tree. Aortic dilation is common among individuals with a BAV,^{80, 81} with multiple reports now demonstrating co-segregation of TAA and BAV in families.⁸² Families with TAA may be divided into two phenotypic groups by location, using the ligamentum arteriosum. TAA above the ligamentum is highly familial and not associated with atherosclerosis, while TAA below is associated with atherosclerosis.⁶⁰ This likely reflects the embryonic origin of the smooth muscle cells in the

aorta, as cardiac neural crest cells only contribute to the aortic arch above the ligamentum arteriosum.⁸³

To date, a total of seven loci have been described and 4 genes identified for familial TAA (Table II).^{84–87} The 4 identified genes appear to explain roughly 20% of all familial TAA. In addition, families with BAV and aortic dilation or thoracic aortic aneurysm segregating with *NOTCH1* mutations have been identified.⁸⁸ Little genotype-phenotype correlation exists, but individuals with mutations in *ACTA2* may also be predisposed to stroke and exhibit moya-moya phenomenon on cerebral angiography.⁸⁹

Novel therapies for thoracic aortic aneurysm

Much excitement has been generated by the demonstration of nearly complete cessation of aortic root dilation in a mouse model of MFS with the use of losartan.⁹⁰ Losartan is an angiotensin II receptor blocker (ARB), but as demonstrated in the mouse model, it also acts to suppress TGF β signaling. Preliminary results on the use of losartan in patients with MFS appear promising. A small group of pediatric patients who were switched to losartan after treatment failure with beta-blockers demonstrated significant slowing of aortic root growth.⁹¹ Several trials are in progress comparing standard beta-blocker therapy to losartan in the US and Europe.^{92–94} The role ARBs might play in other syndromic, familial or sporadic TAA is unknown, as is the role of the TGF β pathway in these other diseases. The greatest promise may exist for LDS, which is also due to TGF β pathway dysregulation.

Ventricular Arrhythmias

Diseases of the cardiac conduction system are very prevalent in the world and affect an estimated millions of individuals in the United States alone.⁹⁵ The majority of these diseases are associated with adult cardiovascular disease, but the elucidation of the genetic causes of inherited arrhythmias, including long QT syndrome (LQTS), Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT) which exhibit Mendelian inheritance patterns, have resulted in an increased understanding of conduction system disease. While conduction system disease encompasses a spectrum of arrhythmias, those of ventricular origin have a propensity to be lethal and present in sudden cardiac death (SCD). Here, we highlight the discovery of the genetic etiologies of LQTS, Brugada syndrome and CPVT and how these findings have affected clinical management and care.

Long QT syndrome

Long QT syndrome (LQTS) is an inherited cardiac disease, which presents with syncope and SCD, due to the ventricular tachyarrhythmias (VT), torsade de pointes. It is characterized by prolongation of the QT interval on electrocardiogram. The diagnosis is made using clinical criteria⁹⁶ and the disease has an estimated prevalence of 1 in 2000–5000 individuals.^{97, 98} Four clinical subtypes of LQTS have been defined and include the more common Romano-Ward syndrome,^{99, 100} Jervell-Nielsen syndrome (with congenital deafness),¹⁰¹ Anderson syndrome (with periodic paralysis and malformations)^{102, 103} and Timothy syndrome (with cardiac and other birth defects, autism).¹⁰⁴

The etiology for LQTS had remained unknown until 1995, when two simultaneous publications identified mutations in *HERG* (LQTS1) and *SCN5A* (LQTS3) through linkage analysis of large kindreds.^{105, 106} These discoveries led to the concept of ion channelopathies as the cause of inherited arrhythmias. Since then, 12 LQTS subtypes have been identified (Table IIIA), with the first three subtypes comprising the majority of clinical cases.^{107, 108} For these three most common subtypes (LQTS1, LQTS2, and LQTS3), numerous features that tend to occur with each subtype have been identified. Each subtype has unique triggers: exercise for LQTS1, startling due to noises for LQTS2, and episodes of

bradycardia (i.e. sleep) for LQTS3.¹⁰⁹ In addition, each of these 3 subtypes has distinct electrocardiographic findings when examining T wave morphology and are often used to direct genetic testing.¹¹⁰ The subtypes also have variable responses in regards to drug therapy, as LQTS1 is more responsive to beta-blocker therapy when compared to LQTS3 where mexiletene (a sodium channel blocker) is often used, and have different prognostic implications with LQTS3 being highly lethal as compared to LQTS1.¹¹¹ This increased knowledge has led to the use of commercially available genetic testing, and allowed for screening of family members and improved clinical management. Although much knowledge has been gained, clear genotype-phenotype associations regarding SCD risk prediction and treatment efficacy remain elusive.

Brugada syndrome

With the discovery of ion channel mutations as a cause of VT, investigators began investigating other familial cases of idiopathic VT. The best described of these is Brugada syndrome which is characterized by ST-segment elevation in the right precordial leads (V1–V3) on electrocardiogram and an increased risk of SCD due to polymorphic VT.^{112, 113} The disease was known to have an autosomal dominant pattern of inheritance with incomplete penetrance, but the genetic cause was unclear until 1998. Using a candidate gene approach and studying several well-phenotyped small families with autosomal dominant disease, investigators identified mutations in *SCN5A* as the cause of Brugada syndrome.¹¹⁴ Since then additional molecular genetic studies have identified 7 molecular subtypes of Brugada syndrome but *SCN5A* mutations account for the majority of cases (Table IIIB).¹¹⁵ Similar to LQTS, these discoveries have resulted in commercially available genetic testing and improved genetic counseling but novel therapeutics and treatments are still under development.

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a relatively rare but important cause of SCD in young children.¹¹⁶ The disease, which is characterized by adrenergically mediated VT has been described for over three decades.¹¹⁷ Individuals typically develop symptoms of syncope, VT, SCD with exercise and suffer from significant mortality prior to 40 years of age.¹¹⁸ It is a genetically inherited condition and presents in both an autosomal dominant and recessive condition (Table IIIC). The autosomal dominant form was mapped to a region on chromosome 1q42-43¹¹⁹ and subsequently mutations in the human cardiac ryanodine receptor (*RYR2*) were identified as the genetic etiology.^{120, 121} The autosomal recessive form had been mapped to a region on chromosome 1p13-p21 and the identification of *Ryr2* as the cause of the autosomal dominant form allowed investigators to focus on other genes critical for calcium handling on the sarcoplasmic reticulum. Calsequestrin 2 (*CASQ2*) was located in this 8Mb interval and mutations in this gene were found to segregate with the disease in families. These genetic discoveries led to a greater understanding of the biochemical effects of the mutations to cause sarcoplasmic reticulum leak of calcium^{122, 123} and the development of mouse models for CVPT.^{124, 125} These molecular insights and investigations have allowed for the recent discovery that flecainide, an FDA-approved antiarrhythmic drug, was efficacious in suppressing VT in mouse models of CVPT and humans with CVPT.¹²⁶ Larger clinical trials are currently being planned to determine if this is a novel therapy for this highly lethal disease.

These seminal discoveries have increased our understanding of SCD and opened a field of channelopathies. While these genetic discoveries have impacted patient care, a significant amount of research still needs to be done. For example, mutations in *SC5NA* cause both LQTS and Brugada syndrome and the reason for the phenotypic differences remain unclear. Of note, these discoveries have allowed us to expand into conduction system disease not

related to familial cases of SCD. For example, genetic polymorphisms in the LQTS genes likely result in drug-induced long QT¹²⁷ and a nucleotide variation in *SC5NA* results in increased arrhythmias in African American population.¹²⁸ These genetic discoveries have also assisted in the identification of the cause of SCD as approximately 25–35% of sudden unexplained deaths in children and young adults have no autopsy findings. It is estimated that up to 10% of sudden infant death syndrome (SIDS) cases can be attributable to a mutation in an LQTS or CPVT susceptibility gene.¹²⁹ An increased understanding of these molecular pathways regulating ion channels will help clarify the disease phenotype differences.

Cardiovascular Malformations

Cardiovascular malformations (CVMs) constitute the most common group of birth defects, accounting for ~25% of all birth defects. The birth prevalence for all CVMs is 6–8 per 1,000 live births, with rates increasing with advances in imaging technology that led to discovery of milder defects.^{130–132} Improved medical treatment and surgical palliation has led to a burgeoning population of adult survivors of CVMs, but deaths from CVMs still account for 40% of all deaths from birth defects.

Both birth defect registry studies and population based case-control studies have been performed for CVMs to define the epidemiology and identify specific etiologies. The Baltimore Washington Infant Study (BWIS) was instrumental in defining population-based risk factors for CVMs classified into specific mechanistic groups.¹³³ This study identified many important features of CVMs at a population level, such as sex and race differences for specific groups of defects, recurrence of specific CVMs within families, and the increased risk for CVMs in maternal diabetes. While a number of studies, including the BWIS, have searched for environmental factors at the population level, the resulting data has been less conclusive.¹³⁴ Only a limited number of prenatal exposures of the fetus are known environmental risk factors and they include alcohol, retinoic acid, and anticonvulsants, and maternal diseases such as rubella, influenza, diabetes, and phenylketonuria.

Multiple studies show CVMs possess high heritability and increased recurrence risk above the general population suggesting a role for genetic contributors.¹³⁵ Identified genetic causes include chromosomal microdeletions or microduplications (22q11), and aneuploidy (trisomies 13, 18, and 21, and monosomy X) (Table IV) and were uncovered by standard cytogenetic methodology. Although for the vast majority of cases, the underlying cause is unknown, it is clear that the complex process of heart development is guided by a combination of a carefully orchestrated genetic program and hemodynamic forces. This intricate process of cardiac morphogenesis with its multiple cellular contributors is controlled by a set of highly conserved molecular pathways. Studies using diverse species, from flies to mice, have led to the identification of many genes critical for normal cardiac development.^{136, 137} This knowledge of cardiac developmental biology has assisted investigators in the elucidation of the genetic contributors of human CVM. In this section, we discuss the genetic causes of syndromic and non-syndromic CVM that were discovered using Mendelian cases of disease and highlight how the knowledge of cardiac development genes assisted in gene discovery.

Single Gene Defects Associated with Syndromic and Non-syndromic CVM

With advances in genetic technology and the completion of the Human Genome Project, single gene defects leading to syndromes associated with congenital heart disease have been elucidated and they are summarized in Table VA. Some of the earliest work was the discovery that mutation of *Fibrillin 1* (*FBNI*) was the cause of MFS (discussed earlier). Since then the genetic basis of numerous syndromes have been identified and each is

characterized by a unique constellation of birth defects. One of the first was Holt-Oram syndrome, which is characterized by atrial and ventricular septal defects, progressive atrioventricular conduction system disease, and radial limb and thumb anomalies. Classic positional approaches were utilized to first identify the genetic locus on chromosome 12q¹³⁸ and subsequently, disease-causing mutations were discovered in the transcription factor, *TBX5*.¹³⁹ Another common syndrome, which frequently exhibits CVMs, is Noonan syndrome. The phenotype consists of cardiac defects, typically pulmonary valve stenosis and HCM, as well as cognitive disability, characteristic facies, and bleeding disorders. Using small families with autosomal dominantly inherited disease, investigators used a candidate gene based approach to identify mutations in *PTPN11*, a gene involved in Ras signaling and implicated by murine studies to be critical for semilunar valvulogenesis, to be the cause of 50% of cases.^{140, 141} Subsequent studies have found that mutations of other genes involved in the Ras signaling pathway including *RAF1*, *SOS1*, and *KRAS* were also associated with a similar spectrum of disease. In addition, LEOPARD and Costello syndromes, which exhibit a similar phenotype as Noonan syndrome, are the result of mutations in Ras signaling pathway members.^{142, 143} Alagille syndrome is characterized by intrahepatic bile duct paucity and cardiovascular malformations, including peripheral pulmonic stenosis, pulmonary valve stenosis, and tetralogy of Fallot. Disease-segregating mutations in *JAG1*, a gene encoding a ligand in the Notch signaling pathway, were identified by studying several small families with autosomal dominant disease.^{144, 145} Consistent with this, mutations in a NOTCH receptor, *NOTCH2*, have also been identified in subjects with Alagille syndrome using a candidate gene approach.¹⁴⁶ A rare genetic syndrome that is characterized by dysmorphic facies and digit anomalies along with congenital heart disease (specifically patent ductus arteriosus) was found to be caused by mutations in the transcription factor, *TFAP2b* using traditional approaches after the identification of large kindreds.¹⁴⁷ Lastly, heterotaxy syndrome, which is randomization of cardiac, pulmonary and gastrointestinal situs, is frequently associated with CVMs, specifically atrioventricular septal defects, and transposed great arteries. Disease-causing mutations in *ZIC3* were identified in an X-linked form of heterotaxy.¹⁴⁸ After this discovery, *ZIC3* was shown to be critical in left-right development in vivo¹⁴⁹ and subsequently mutations in *CFC1*, *ACVR2B*, and *LEFTY4*, genes that regulate left-right asymmetry in the developing embryo were found to be associated with heterotaxy.¹⁵⁰

Over the past decade, single gene defects associated with isolated or non-syndromic congenital heart disease have been discovered (Table VB). The first gene identified to be associated with non-syndromic CVM was *NKX2.5*, which was identified by linkage analysis in families with autosomal dominant inherited atrial septal defects with atrioventricular conduction delay.¹⁵¹ Mutations in *GATA4*, a zinc finger transcription factor known to interact with *NKX2.5*, have been linked to isolated atrial septal defects without conduction system abnormalities using large multi-generation families. Interestingly, a mutation in *Gata4* specifically disrupted an interaction with *TBX5*¹⁵² and mutations in a common downstream target of *GATA4* and *TBX5*, myosin heavy chain 6 (*MYH6*), have been identified as another cause of atrial septal defects.¹⁵³ More recently, investigators have linked another *GATA* family member, *GATA6*, to truncus arteriosus using a candidate gene approach.¹⁵⁴ Similarly another T-box family member, *TBX20*, was identified to cause CVM, predominantly cardiac septal and valve defects, in several small families with autosomal dominant disease.¹⁵⁵ Additionally, mutations in *NOTCH1* have been identified as a cause of aortic valve malformations, including bicuspid aortic valve and early aortic valve calcification, via genome-wide linkage analysis of an affected family¹⁵⁶. Subsequent studies have expanded the phenotype to a spectrum of malformations that affect left-sided cardiac structures.¹⁵⁷ These discoveries that syndromic and non-syndromic CVM are caused by single gene defects were facilitated by studies in families with Mendelian inherited disease and even in those cases where candidate gene approaches were utilized, the availability of

small pedigrees allowed for increased confidence that disease-segregating mutations were truly causal. Ultimately, these initial discoveries will reveal more about the molecular pathways that are critical for cardiac morphogenesis and relevant to human CVMs.

Unlike for the other cardiovascular diseases described earlier, the translation of the genetic discoveries for CVMs to the clinic is still in its early stages. The knowledge of genetic etiologies for syndromic cases has been utilized for genetic testing in only a subset of cases that are difficult to define. Often, determining the diagnosis in syndromic cases has significant prognostic implications, which are useful for the clinician especially in regards to neurodevelopmental outcomes. At this time, the genetic knowledge that has been gained from the discovery of genetic causes of non-syndromic CVM has focused on development of transgenic mouse models, which have allowed for an increased understanding of the molecular pathways regulating heart development. The information has been less useful clinically as the identified genetic causes have ultimately been found to represent only a small percentage of cases of CVM¹⁵⁸⁻¹⁶¹ and no clear genotype-phenotype correlations have been identified. At this time, the etiology for most isolated cases of non-syndromic CVM remains unknown and it is likely that rare functional sequence variations in genes critical for cardiac morphogenesis are present in affected individuals. Future studies utilizing new diagnostic methods, such as next-generation sequencing, may ultimately provide a more accurate genetic predisposition risk for CVM. Ultimately, the discovery of CVM-causing genes and associated animal models may allow us to test environmental influences on genetic predispositions and possibly devise novel preventive measures that reduce the incidence of congenital heart defects.

Summary

From chromosomal aneuploidy to single gene defects causing cardiovascular disease, genetics has a much greater influence on the development of various types of heart disease than previously appreciated¹³⁵. This review summarizes many genetic causes for cardiovascular diseases, which were identified by positional cloning approaches utilizing families with Mendelian inherited forms of disease. Several new methodologies hold great promise to identify many more disease-associated genetics variants. We are just beginning to understand the significance of copy number variations in cardiac disease.¹⁶²⁻¹⁶⁴ As the cost of DNA sequencing decreases, sequencing of entire genomes will lead to an increased rate of gene discovery in cardiovascular disease likely utilizing even smaller families with Mendelian disease.^{56, 165} Armed with these new cardiac disease-causing genes and the development of international collaborative databases with phenotypic information will allow for the study of clinical outcomes and prognosis based on genetic predispositions. This new genetic knowledge of cardiovascular diseases will lead to improved genetic counseling and the development of novel therapeutics to benefit future generations.

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Table I**Disease Genes for Cardiomyopathy**

IA. Disease genes for hypertrophic cardiomyopathy (HCM)			
Gene	Gene MIM	Chromosome location	Disease
ACTC1	102540	15q14	HCM
CSRP3	600824	11p15.1	HCM
MYBPC3	600958	11p11.2	HCM
MYH6	160710	14q12	HCM
MYH7	160760	14q12	HCM
MYL2	160781	12q23-q24	HCM
MYL3	160790	3p21.3-p21.2	HCM
PRKAG2	602743	7q36	HCM
TNNC1	191040	3p21.3-p14.3	HCM
TNNI3	191044	19q13.4	HCM
TNNT2	191045	1q32	HCM
TPM1	191010	15q22.1	HCM
TTN	188840	2q31	HCM
VCL	193065	10q22.1-q23	HCM

IB. Disease genes for dilated cardiomyopathy (DCM)			
Gene	Gene MIM	Chromosome location	Disease
ABCC9	601439	12p12.1	DCM
ACTC	102540	15q14	DCM
ACTN2	102573	1q42-q43	DCM
CSRP3	600824	11p15.1	DCM
DES	125660	2q35	DCM
DSG2	125671	18q12.1-q12.2	DCM
DSP	125647	6p24	DCM
EYA4	603550	6q23-q24	DCM
FCMD	607440	9q31	DCM
LAMP2	309060	Xq24	DCM
LDB3	605906	10q22-q23	DCM +/- LVNC
LMNA	150330	1q21.2	DCM with conduction defect
MYBPC3	600958		DCM
MYH6	160710	14q12	DCM
MYH7	160760	14q12	DCM
NEXN	613121	1p32-p31	DCM
PLN	172405	6q22.1	DCM
PSEN1	104311	14q24.3	DCM
PSEN2	600759	1q31-q42	DCM

IB. Disease genes for dilated cardiomyopathy (DCM)			
Gene	Gene MIM	Chromosome location	Disease
RBM20	613171	10q25.2	DCM
SCN5A	600163	3p	DCM
SGCD	601411	5q33	DCM
TCAP	604488	17q12	DCM
TMPO	188380	12q22	DCM
TNN	188840	2q31	DCM
TNNC1	191040	3p21.3-p14.3	DCM
TNNI3	191044	19q13.4	DCM
TNNT2	191045	1q32	DCM
TPM1	191010	15q22.1	DCM
VCL	193065	10q22-q23	DCM

IC. Disease genes for left ventricular noncompaction (LVNC) and arrhythmogenic right ventricular dysplasia (ARVD)			
Gene	Gene MIM	Chromosome location	Disease
DTNA	601239	18q12.1	LVNC
TAZ	300394	Xq28	LVNC
DSC2	125645	18q12.1	ARVD
DSG2	125671	18q12.1-q12	ARVD
DSP	125647	6p24	ARVD
JUP	173325	17q21	ARVD
PKP2	602861	12p11	ARVD
RYR2	180902	1q42-q43	ARVD
TGFB3	190230	14q23	ARVD
TMEM43	612048	3p23	ARVD

Table II

Disease Genes for Thoracic Aortic Aneurysms (TAA)

Gene	Gene MIM	Chromosome location	Disease
ACTA2	102620	10q22	TAA
MYH11	160745	16p13	TAA & PDA
TGFBR1	190181	9q22	TAA
TGFBR2	190182	3p22	TAA

PDA, patent ductus arteriosus

Table III**Disease Genes for Cardiac Conduction System Diseases**

IIIA. Disease genes for Long QT syndrome		
Type	Gene	Gene MIM
LQT1	KCNQ1	607542
LQT2	KCNH2	152427
LQT3	SCN5A	600163
LQT4	ANK2	106410
LQT5	KCNE1	176261
LQT6	KCNE2	603796
LQT7	KCNJ2	600681
LQT8	CACNA1C	114205
LQT9	CAV3	601253
LQT10	SCN4B	608256
LQT11	AKAP9	604001
LQT12	SNTA1	601017

IIIB. Disease genes for Brugada syndrome		
BrS Type	Gene Name	Gene MIM
BrS1	SCN5A	600163
BrS2	GPD1L	611778
BrS3	CACNA1C	114205
BrS4	CACNB2	600003
BrS5	SCN1B	600235
BrS6	KCNE3	604433
BrS7	SCN3B	608214

IIIC. Disease genes for catecholaminergic polymorphic ventricular tachycardia		
Type	Gene	Gene MIM
autosomal dominant	RYR2	180902
autosomal recessive	CASQ2	114251

Table IV**Common Syndromes Resulting from Anueploidy and Microdeletions**

Syndrome	Cardiac Anomalies	% with CHD
Trisomy 13	ASD, VSD, PDA, HLHS	80%
Trisomy 18	ASD, VSD, PDA, TOF, DORV, CoA, BAV	90–100%
Trisomy 21 (Down syndrome)	ASD, VSD, AVSD, TOF	40–50%
Monosomy X (Turner Syndrome)	CoA, BAV, AS, HLHS	25–35%
1p36 deletion	VSD, AVS, TOF, CoA, LVNC	70%
7q11.23 deletion (Williams-Beuren Syndrome)	Supravalvar AS, PPS	50–85%
11q23 deletion (Jacobsen)	VSD, AVS, CoA, HLHS	50–60%
22q11.2 deletion (DiGeorge Syndrome)	IAA Type B, aortic arch anomalies, truncus arteriosus, TOF	75%

CHD, congenital heart defect; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; HLHS, hypoplastic left heart syndrome; TOF, tetralogy of Fallot; DORV, double outlet right ventricle; CoA, coarctation of aorta; BAV, bicuspid aortic valve; AVSD, atrioventricular septal defect; IAA, interrupted aortic arch; AS, aortic stenosis; PPS, peripheral pulmonic stenosis; LVNC, left ventricular non-compaction.

Table V**Disease Genes for Cardiovascular Malformations**

VA. Disease genes for syndromic cardiovascular malformations			
Syndrome	Cardiac Anomalies	Causative Gene(s)	Gene MIM
Alagille Syndrome	PS, TOF, ASD, peripheral pulmonary stenosis	JAG1, NOTCH2	601920, 600275
Char Syndrome	PDA	<i>TFAP2β</i>	601601
CHARGE Syndrome	ASD, VSD, valve defects	<i>CHD7, SEMA3E</i>	608892, 608116
Costello Syndrome	PS, HCM, cardiac conduction abnormalities	HRAS	190020
Ellis van Creveld	ASD	<i>EVC, EVC2</i>	604831, 607261
Heterotaxy Syndrome	DILV, DORV, d-TGA, AVSD	<i>ZIC3, CFC1</i>	300265, 605194
Holt-Oram Syndrome	ASD, VSD, AVSD, progressive AV conduction system disease	<i>TBX5</i>	601620
LEOPARD Syndrome	PS and cardiac conduction abnormalities	PTPN11, RAF1	176876, 164760
Noonan Syndrome	PS with dysplastic pulmonary valve, AVSD, HCM, CoA	PTPN11, KRAS, RAF1, SOS1	176876, 190070, 164760, 182530
Rubinstein Taybi	ASD, VSD	<i>CREBBP, EP300</i>	600140, 602700
Smith Lemli Opitz	VSD, ASD, AVSD	<i>DHCR7</i>	602858

VB. Disease genes for non-syndromic cardiovascular malformations		
Cardiac Anomalies	Gene	Gene MIM
ASD, VSD	<i>GATA4</i>	600576
Truncus arteriosus	<i>GATA6</i>	601656
ASD, hypertrophic cardiomyopathy	<i>MYH6</i>	160710
ASD, atrioventricular conduction delay, TOF, tricuspid valve abnormalities	<i>NKX2.5</i>	600584
BAV, early valve calcification	<i>NOTCH1</i>	190198
ASD, VSD, cardiomyopathy, cardiac valve anomalies	<i>TBX20</i>	606061

PS, pulmonic valve stenosis; AVSD, atrioventricular septal defect; HCM, hypertrophic cardiomyopathy; CoA, coarctation of aorta; TOF, tetralogy of Fallot; ASD, atrial septal defect; VSD, ventricular septal defect; AV, atrioventricular; DILV, double inlet left ventricle; DORV, double outlet right ventricle; TGA, transposition of the great arteries; PDA, patent ductus arteriosus; BAV, bicuspid aortic valve; PHTN, pulmonary hypertension.