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Genetic Basis of Congenital Cardiovascular Malformations

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Abstract

Cardiovascular malformations are a singularly important class of birth defects and, due to dramatic improvements in medical and surgical care, there are now large numbers of adult survivors. The etiologies are complex, but there is strong evidence that genetic factors play a crucial role. Over the last 15 years there has been enormous progress in the discovery of causative genes for syndromic heart malformations and in rare families with Mendelian forms. The rapid characterization of genomic disorders as major contributors to congenital heart defects is also notable. The genes identified encode many transcription factors, chromatin regulators, growth factors and signal transduction pathways— all unified by their required roles in normal cardiac development. Genome-wide sequencing of the coding regions promises to elucidate genetic causation in several disorders affecting cardiac development. Such comprehensive studies evaluating both common and rare variants would be essential in characterizing gene-gene interactions, as well as in understanding the gene-environment interactions that increase the susceptibility to congenital heart defects.

Keywords

Congenital Heart Defect; Cardiac Development; Chromosomal and single gene disorders; Genomic Disorder

Introduction

Congenital cardiovascular malformations (CVMs) present some of the most interesting and difficult challenges in medicine. They are exceptionally common (Hoffman and Kaplan, 2002; Hoffman et al., 2004) affecting 0.5–0.7% of all live born infants. The prevalence for severe CVMs at birth is reported to be ~1.5 cases per 1000 live births (Hoffman and Kaplan, 2002). Repair of heart defects requires advanced technological interventions, and they are among the most costly birth defects to manage. Even in the era of modern surgery, some cardiac defects continue to have very poor prognosis (Hoffman et al., 2004), and constitute the largest fraction of infant mortality attributable to birth defects (Boneva et al., 2001).

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Nevertheless, it is estimated that there are now more than 1 million adults with a history of significant CVM (Marelli et al., 2007; van der Bom et al., 2011).

In trying to define the origin of heart defects one might consider two very broad and non-exclusive models. In the ‘**embryonic insult**’ model a single inciting event in a specific developmental field or process is followed by a cascade of disturbed anatomic relationships, abnormal flow-, oxygen- and pressure-dependent remodeling, and abnormal maintenance of the cardiac muscle, valve, and vessel tissues. This abnormal cascade leads to a range of anatomic outcomes that are then classified by their clinical implications and management. Embryonic insults could involve genetic and/or environmental agents. There are a handful of well-established teratogens that greatly increase the chance of heart defects. These include maternal diabetes, first trimester rubella infection, and isotretinoin (Accutane) exposure (Jenkins et al., 2007). The second model invokes ‘**developmental pleiotropy**’ i.e. the inciting factor(s) affect multiple independent processes in heart development. In this model the anatomic outcome reflects the specificity of the disturbed developmental process e.g. tetralogy of Fallot resulting from direct impairment of pulmonary subinfundibulum growth rather than some earlier abnormality in cardiac precursor differentiation or growth. Genetic factors, either causal mutations or risk-increasing variants, could easily operate through either of these mechanisms.

Genetic disorders make up the most complex and numerically significant category of known causes of CVM. A broad range of genetic mechanisms are either known to participate or strongly suspected in causing cardiovascular malformations. Like most traits that exhibit complex inheritance, there are still many unknowns and the relative importance of various genetic factors (common variants, rare variants, copy number variations (CNVs), *de novo* mutations, epistasis, epigenetics, etc.) remains to be defined.

Despite important advances over the last 15 years, the etiology of the vast majority of CVM cases is unknown. There is a distinct lack of data concerning molecular mechanisms that are required for normal human cardiac development and very little direct observation of abnormal human embryos and fetuses. There is additional difficulty in making the connection between normal cardiac development and CVMs because there are no direct methods for determining in any single affected individual which developmental step(s) were disturbed. Many CVMs have an ambiguous embryologic origin and they may be interpreted as arising from multiple alternative early events or later and more specific processes.

Genetic Epidemiology of Congenital Cardiovascular Malformations

About 20% of infants born with a CVM have non-cardiac malformations or neurodevelopmental delays (Ferencz et al., 1989). These children are considered to have either ‘multiple congenital anomalies’ or ‘syndromic CVM’ to contrast them with those who have only ‘isolated’ CVM. Epidemiology studies usually distinguish between these groups but the published literature is inconsistent in the criteria that are applied. The high birth incidence together with the substantial sibling recurrence risk (1–4%) has suggested the hypothesis that CVMs have a multifactorial etiology (Burn et al., 1998; Gill et al., 2003). Supporting this supposition is the fact that a much larger number of infants have minor

anomalies of the heart at birth such as small atrial and ventricular septal defects, if imaging studies are performed without regard to symptoms. Bicuspid aortic valve (BAV) is a very common anomaly with studies in healthy adults indicating a prevalence of 1.3% (Roger et al., 2011). BAV does not cause symptoms in early life; however, it is an important risk factor for subacute bacterial endocarditis, late onset aortic valve calcification/stenosis, aortic aneurysm and dissection (Michelena et al., 2008; Tzemos et al., 2008).

There are generally very similar rates of CVM in all major geographical regions. For some CVM there are measurable differences in rates between population groups (Canfield et al., 2006; Fixler et al., 1990; Grech, 1998; Grech, 1999; Ho, 1991; McBride et al., 2005; Muir, 1960; Pradat et al., 2003; Schrire, 1963; Shann, 1969). The most likely explanation for these differences lies in the distinctive genetic history of different populations. There may be some increase in rate of CVM over the last decade (Oyen et al., 2009). This will require verification as previous studies are consistent with stable birth prevalence rates of CVM over the last 60 years (Hoffman and Kaplan, 2002). Changes in rates over relatively short time frames have typically been interpreted as reflecting environmental factors. However, the rapid change in mean parental age must also be accounted for and this could still involve increased rates of single gene mutation mechanisms.

High heritability of congenital heart defects means that genetic factors have a very large role in the overall occurrence of heart defects in the population and that the aggregate impact of genetic factors is apparently far larger than all environmental factors combined. Studies of some types of CVM have been consistent with heritability of 50–90% (Burn et al., 1998; Cripe et al., 2004; Hinton et al., 2007; Insley, 1987; McBride et al., 2005). Several factors cause heritability to be underestimated in CVM: (1) heart defects are approximately 10-fold more common in miscarried pregnancies and, as a consequence, many affected offspring may not be counted in population surveys; (2) affected individuals have fewer children than people without heart defects; (3) families whose first born is affected may decide against having further offspring. Family history of CVM is one of the most consistently identified risk factors in CVM (Loffredo et al., 2000; Loffredo et al., 2001; Oyen et al., 2009; Wollins et al., 2001; Zavala et al., 1992); the rate of occurrence in close relatives of affected individuals being substantially (5 - to 40-fold) higher than the general population rate. Across all CVM, sibling and or offspring recurrence risk is estimated at 1–4% (Burn et al., 1998; Digilio et al., 2001; Gill et al., 2003; Hoess et al., 2002; Hoffman, 1990; Lewin et al., 2004; Meijer et al., 2005; Oyen et al., 2009; Oyen et al., 2011; Piacentini et al., 2005; Siu, 1998; Whittemore et al., 1994). Several studies have also demonstrated increased rates of cardiovascular malformations in populations with increased inbreeding and consanguineous parentage (Badaruddoza et al., 1994; Becker and Al Halees, 1999; Becker et al., 2001; Chehab et al., 2007; Nabulsi et al., 2003; Ramegowda and Ramachandra, 2006). This is most likely to result from autosomal recessive inheritance of CVM-causing mutations. Inbreeding and the consequent reduced effective population size also makes it more likely that CVM risk increasing genetic variants could be present in one or both parents, thus increasing the occurrence of oligogenic traits.

Developmental Epidemiology

A major problem is to explain why severe CVM are so common given that there should be severe selective constraints on the persistence of causal variants in the population. There are several potential explanations:

Dosage Sensitivity—Developmental pathways are exquisitely sensitive to the amount of gene product available at specific times and in very specific locations in the embryo. A prominent role for mutation in transcription factors and chromatin modulators in cardiovascular malformations has emerged. With few exceptions these cause defects through either haploinsufficiency or imbalanced expression. The sensitivity of cardiac development to these dosage imbalances makes both *de novo* mutation and dominant transmission the most common modes of inheritance.

Large Mutation Target—We know from the study of animal models that more than 300 genes are required for normal heart development (Bentham and Bhattacharya, 2008). Even though mutations in each individual gene might be quite rare, the large number of potential causal mutations might make heart defects very common.

Genetic Loci with High Mutation Rates—We know of a few examples of genomic regions that experience much higher than average mutation rates. The deletion of 22q11 (which underlies the DiGeorge/Velocardiofacial syndrome, observed in about 1 in 4000 live born children) is an example of this mechanism. If there are more such genomic regions or mutation-prone loci that have yet to be uncovered, they might be contributing to an important fraction of total cases.

Genetic Architecture of CVM

It is useful to consider the classes of genetic aberrations and the allele frequency spectrum of gene and genomic variants that contribute to cardiovascular malformations. The complex embryology of the heart, including cell commitment, growth, looping, and chamber specification suggests the involvement of numerous genes in normal cardiac development and, therefore, several chromosomal loci. Chromosomal abnormalities detected by conventional karyotyping account for approximately 10–12% of all CVMs in live born infants (Hartman et al., 2011). Within this group, trisomy 21 is the most common cause, constituting about half of cases (Hartman et al., 2011). The prevalence of CVM in Down syndrome is ~50% (Jaiyesimi and Baichoo, 2007). Although the most common defect in Down syndrome is a complete atrioventricular canal defect, other lesions are also seen such as ASD, VSD, PDA, and TOF. Less common defects include CoA, pulmonary valve stenosis, vascular ring, and defects of single ventricle physiology (Irving and Chaudhari, 2012; Lin et al., 2008). Other frequent cytogenetic abnormalities include trisomy 18 and trisomy 13 accounting for a significant fraction (~20%) within this group. CVM is found in greater than 90% of patients with trisomy 18, with VSD and PDA the most common abnormalities. The presence of polyvalvular disease is frequently a useful echocardiographic assessment related to trisomy 18, pending definitive diagnosis by karyotype study (Balderston et al., 1990). About half of the affected individuals with Wolf-Hirschhorn syndrome (4p minus) have structural malformations of the heart including ASD, PS, VSD,

and PDA (Battaglia et al., 2008). Cardiac anomalies have been estimated to affect 10%–20% of children with Cri-du-chat syndrome (5p terminal deletion) (Niebuhr, 1978). Sex chromosome abnormalities including Turner syndrome make up approximately 3% of G-banded cytogenetic abnormalities observed in CVM.

Genomic disorders resulting from instability of regional genomic architecture are an important cause of CVM (Breckpot et al., 2010; Greenway et al., 2009; Lalani et al., 2013; Symou et al., 2013). The use of array-comparative genomic hybridization (Array-CGH) has been pivotal in identifying causal submicroscopic aberrations in a significant fraction of cases with CVM. The 22q11 deletion syndrome is the most frequent genomic disorder associated with CVM, occurring in about 1 in 4000 live births (Burn and Goodship, 1996). The burden of functionally relevant CNVs ascertained as microdeletions and microduplications is reported between 3% and 20% in CVM cases, depending on the assertion of non-syndromic or syndromic classification respectively (Breckpot et al., 2011; Derwinska et al., 2012; Thienpont et al., 2007). To date, there are over 40 clinically delineated deletion and duplication syndromes with specific association to CVM (Table 1). One of these syndromes is Kleeftstra syndrome, which is caused by microdeletion of 9q34.3 in ~75% of cases. The dosage sensitive gene within this region, *EHMT1* (euchromatic histone-lysine *N*-methyltransferase 1) has been implicated in the disease, with 25% of cases having point mutations in the gene (Kleeftstra et al., 2006). About 50% of individuals with this syndrome have CVM. The cardiac abnormalities that have been reported include ASD/VSD, TOF, CoA, BAV, and pulmonic stenosis (Kleeftstra et al., 2006; Stewart and Kleeftstra, 2007).

Private mutations are the norm for single gene *de novo* mutations that cause severe syndromes such as CHARGE, Mowat-Wilson, Kabuki or Sotos syndromes. To date, defects in single genes are estimated to account for 3–5% of all cases (van der Bom et al., 2011) (Table 2). However the use of genome-wide sequencing of the coding regions in large affected cohorts is rapidly changing this landscape. Recent studies indicate that the frequency of *de novo* mutations may be much higher in severe CVM, accounting for approximately 10% of cases (Zaidi et al., 2013). A spectrum of causal genes and mutant alleles is predicted by standard population genetics theory (Pritchard and Cox, 2002). Common low penetrance genetic variants may have a weak to moderate effect in raising an individual's chance of having a heart malformation. Because such variants are common, the attributable fraction could be significant. At this time a model involving both rare and common variants, possibly with gene-gene and gene-environmental interactions, is the most likely explanation for the high frequency of CVM.

Classification of Heart Defects

The developmental origins of most heart defects are poorly understood. One approach is to consider the known steps in normal cardiac development and investigate how abnormalities in particular genes and pathways may impact those processes. This approach also leads to an effective hierarchical method to classify defects that can be used for both mechanistic and population-based epidemiological studies of CVM (Barriot et al., 2010). Heart defects are anatomically, clinically, epidemiologically, and developmentally heterogeneous. Basing

classification on clinical type alone can lead to so many groups that specific genetic associations may be obscured. It is also useful to consider all heart defects per case rather than treating each anatomic defect separately. Botto et al (Botto et al., 2007) implemented an individual case classification method in which there is first identification of detailed cardiac malformations (including 89 specific defects) and then grouping based on similarity, complexity, and suspected embryologic origin. In their classification there are eight major (Level III) groupings of human heart malformations. These are: (1) Conotruncal; (2) Atrioventricular Septal Defects (AVSD); (3) Anomalous Pulmonary Venous Return (APVR); (4) Left Ventricular Outflow Tract Obstruction (LVOTO); (5) Right Ventricular Outflow Tract Obstruction (RVOTO); (6) Septal; (7) Heterotaxy; and (8) Complex. There are obstacles to applying this approach. Many potential mechanisms of embryologic disturbance may operate to cause defects within each Level III class. It is equally clear that specific molecular mechanisms may cause defects across Level III classes.

Conotruncal Defects and the Common Outflow Tract: Aorticopulmonary Septation - Contribution of the Second Heart Field and Cardiac Neural Crest

During the 5th week, ridges of the subendocardial tissue form in the **common outflow tract**. The spiral orientation of the ridges, results in a spiral aorticopulmonary septum when these ridges fuse. This septum divides the outflow tract into two channels, the aorta and the pulmonary trunk. The second heart field (SHF) plays a critical role in outflow tract development (Kelly and Buckingham, 2002; Mjaatvedt et al., 2001; Yutzey and Kirby, 2002). Descendants of the SHF give rise to the common outflow tract and anterior structures of the mature heart including the RV and proximal outflow tract before the migration and differentiation of the cardiac neural crest (CNC). The CNC, which extends from the otic placode to the 3rd somite, provides mesenchymal cells to the interventricular septum and outflow tract. This same population of cells plays a critical role in the development of the thymus and parathyroid glands. Patterning of the SHF at the arterial pole requires retinoic acid signaling.

Conotruncal defects

Several common defects have their origins in failure of development of the common outflow tract. These include Truncus Arteriosus (TA), Transposition of the Great Arteries (TGA), Double Outlet Right Ventricle (DORV), Tetralogy of Fallot (TOF – consisting of VSD, overriding aorta, pulmonic stenosis, and right ventricular hypertrophy), and Interrupted Aortic Arch Type B (IAA-B). Truncus arteriosus represents a failure of aorticopulmonary septation and consequently there is a single semilunar valve. As noted above, d-TGA may be associated with LR patterning defects but may also arise from a much later failure of the conotruncal septum to properly orient to the ventricles. Such failure leaves the aorta anterior and rightward of the pulmonary artery creating a connection of aorta to RV and pulmonary artery to LV. DORV is similar in that there is malposition of the aorta causing it to receive flow from the RV. IAA-B refers to an interruption of the aorta between the take-off positions of the carotid and subclavian arteries. The Velocardiofacial/DiGeorge syndrome (22q11 deletion) is the prototypical conotruncal disorder. About 75% of individuals with 22q11.2 deletion have CVM. The typical ~3 Mb deletion which encompasses ~60 known and predicted genes, is mediated by meiotic non-allelic recombination events. These events

occur due to the flanking segmental duplications termed LCR22, leading to aberrant interchromosomal exchanges. The deletion is also characterized by several extracardiac abnormalities including palatal abnormalities, hypocalcemia, immune deficiency, renal anomalies, and learning difficulties. It is estimated that 1 of every 8 cases of TOF, 1 of every 5 cases of truncus arteriosus, and 1 of every 2 cases of interrupted aortic arch type B in the population are attributable to the 22q11.2 deletion (Botto et al., 2003). Although most deletions occur *de novo*, approximately 7% are inherited from an affected parent. Rare mutations in *TBX1* indicate that haploinsufficiency of this transcription factor plays a major role in the occurrence of heart defects in 22q11 deletion (Yagi et al., 2003).

Recurrent duplications of 1q21.1 are often reported in conjunction with TOF (Soemedi et al., 2012). The *GJA5* gene encoding a gap junction protein Connexin40 has been proposed as a candidate gene within this ~1.5 Mb region. Conotruncal malformations have been demonstrated in Cx40-deficient mice (Gu et al., 2003). The reciprocal 1q21.1 deletions are associated with a more heterogeneous phenotype characterized by incomplete penetrance, with fewer reports of conotruncal abnormalities. It is estimated that in all cases of sporadic nonsyndromic TOF, *de novo* CNVs can be identified in about 10% of cases (Greenway et al., 2009).

Conotruncal heart defects are characteristic of CHARGE (*CHD7*), (Vissers et al., 2004) and Alagille (*JAG1*, *NOTCH2*) (McDaniell et al., 2006) syndromes. *JAG1* is a ligand for NOTCH-family receptors and the finding of mutations in this gene in patients with Alagille syndrome and isolated TOF (Bauer et al., 2010) demonstrates an important role for Notch signaling in outflow tract development. FOG2 specifically interacts with GATA4 and mutations in it lead to TOF (De Luca et al., 2010). Mutations in *GATA6* have been reported in truncus arteriosus and TOF (Lin et al., 2010). Rare mutations in *NKX2.5*, *TBX5*, *FOXH1* causing isolated TOF emphasize the variety of defects that may result from alterations in these key cardiac transcription factors. Other transcription factors have also been implicated as rare causes of syndromic conotruncal defects. These include mutation in *PROSIT240* (Muncke et al., 2003), and *HOXA1*. Bosley-Salih-Alorainy syndrome (BSAS) is an autosomal recessive disorder caused by *HOXA1* mutation (Bosley et al., 2008).

Atrioventricular Septal Defects (AVSD): Endocardial cushions and atrioventricular canal

Atrioventricular septal defects (AVSD) include a family of malformations that involve the inferior atrial septum and the superior ventricular septum. These have also been called endocardial cushion and AV canal defects. This class of anomalies is characteristic of Down syndrome. Larger studies estimate that more than two thirds of infants with AVSD have a cytogenetic abnormality, with trisomy 21 being the most common (Hartman et al., 2011). Patients with deletion of 8p23 which includes at least two transcription factors important in cardiac development, *GATA4* and *SOX7*, also typically have AV canal type defects (Giglio et al., 2000). Missense mutations in *GATA4* have been shown to cause AVSD in rare families (Garg et al., 2003). In addition, AVSD is the most common heart defect in patients with 3p25-26 deletion syndrome (Shuib et al., 2009). *CRELD1* within this region has been implicated in AVSD, with point mutations described in some studies (Maslen et al., 2006; Robinson et al., 2003). Mutations in *BMPR2* have been detected in several cases with

combined primary pulmonary hypertension and congenital heart defects (Roberts et al., 2004). Dominant negative mutation in another BMP/TGF- β receptor *ALK2* has been implicated in a single case (Smith et al., 2009). A locus for autosomal dominant familial AVSD has been mapped to chromosome 1p31-p21 (Sheffield et al., 1997), but a specific gene has not yet been identified.

Anomalous Pulmonary Veins (APVR)

Anomalous pulmonary veins (APVR) indicate malformations in which there is complete or partial failure of the establishment of the pulmonary vein connections to left atrium. There is a specific association of APVR with Cat Eye syndrome [tetrasomy 22q usually resulting from dicentric and bisatellited inv dup (22) supernumerary marker chromosome], but it is difficult to attribute this to a single gene. APVR has been described in rare genomic disorders involving ring 12p, deletion 11q24-ter, Williams syndrome and Smith-Magenis syndrome. Families have been found to segregate an autosomal dominant total anomalous pulmonary veins (TAPVR) linked to chromosome 4 (Bleyl et al., 1995). Using a very novel mapping procedure based on the likely single origin of the mutation, Bleyl *et al* (Bleyl et al., 2010) were able to identify the underlying mechanism as disrupted regulation of the *PDGFRA* gene. Disrupted regulation of the *ANKRD1* gene has also been demonstrated in an individual with APVR and bearing a *de novo* 10;21 balanced translocation (Cinquetti et al., 2008). There is insufficient data from model systems to determine whether these genetic disorders directly disturb pulmonary venous development i.e. represent pathway specificity. TAPVR has been reported in rare cases with *SEMA3D* mutation (Degenhardt et al., 2013). Total anomalous pulmonary venous return (TAPVR) and partial anomalous pulmonary veins (PAPVR) are frequently found in conjunction with left and right isomerism sequences, respectively, as a feature of heterotaxy. In those cases the APVR is clearly secondary to aberrant LR patterning.

Left Ventricular Outflow Tract Obstruction

Left Ventricular Outflow Tract Obstruction (LVOTO) type CVM include aortic valve stenosis (AS), coarctation of the aorta (CoA), hypoplastic left heart syndrome (HLHS), complicated mitral valve stenosis with HLHS and CoA (Shone complex), and Bicuspid Aortic Valve (BAV). Severe outflow obstruction caused by aortic valve or aortic abnormality are thought to lead to poor growth of the left ventricle in HLHS. CoA, AS, and HLHS are the most common CVMs in Turner syndrome (45,X), seen in about 30% of cases (Korpál-Szczyrska et al., 2005; van Egmond et al., 1988; Volkl et al., 2005). Aortopathy including dilatation of the ascending aorta, aortic aneurysms and aortic dissection has been exemplified in several studies, supporting vigilant cardiac follow up into adulthood for several individuals with Turner syndrome (Bondy, 2008; Carlson and Silberbach, 2007). Several single gene disorders are associated with LVOTO defects including Smith-Lemli-Opitz (*DHCR7*), X-linked heterotaxy (Ware et al., 2004) (*ZIC3*) and Holt-Oram syndrome (*TBX5*). Multiplex families have been reported with CoA (MIM21000). Families with multiple occurrences of HLHS, AS, CoA, and BAV strongly suggest the existence of one or more discrete susceptibility genes common to all these defects (Ferencz et al., 1997). Heritability and linkage studies however indicate that the inheritance is most often oligogenic and there is significant locus heterogeneity. Rare occurrences of familial AS and

sporadic LVOTO defects have been associated with mutations in *NOTCH1* (Garg et al., 2005). Notch signaling is apparently critical for normal valve leaflet development tying congenital aortic valve dysplasia with both BAV and late-onset aortic valve calcification. Deletions in 16q24 that affect a FOX gene cluster (*FOXF1*, *FOXL1*, and *FOXC1*) give a characteristic syndrome of alveolar capillary dysplasia and HLHS (Stankiewicz et al., 2009). The gene *FOXF1* is apparently required for lung development, but patients with point mutations in that gene do not exhibit cardiac defects. A report characterizing patients with deletion in 6q24 has identified the MAPK signaling cofactor *TAB2* as responsible for the associated aortic valve stenosis and BAV with aortic dilation (Thienpont et al., 2010). The 11q terminal deletions between 5–20 Mb (Jacobsen syndrome) occur in conjunction with CVM in about half of all cases (Grossfeld et al., 2004). Left sided obstructive lesions are frequently described in Jacobsen syndrome. A transcription factor, *ETS-1* within this region has been implicated in cardiac defects (Ye et al., 2010). Cytogenetically visible terminal deletions of 15q26 are frequently associated with LVOTO, including CoA, AS and HLHS (Davidsson et al., 2008; Tumer et al., 2004). At least two genes within this region, *COUP-TFII* (Pereira et al., 1999) and *MCTP2* (Lalani et al., 2013) have been linked to heart development. Kabuki syndrome is one of the most interesting syndromic associations with LVOTO defects (frequent occurrence of CoA and VSD), caused by mutations in the chromatin modifier *MLL2* and the lysine-specific demethylase 6A, *KDM6A* genes (Lederer et al., 2012; Ng et al. 2010). Supravalvar aortic stenosis is a rare form of LVOTO commonly observed in 7q11.23 deletion (Williams-Beuren syndrome) (Zalzstein et al., 1991). Duplication 17p11.2 syndrome (Potocki-Lupski syndrome) is the homologous recombination reciprocal of the Smith-Magenis syndrome, often presenting with BAV and dilated aortic root (Jefferies et al., 2012; Potocki et al., 2000). HLHS has also been reported in rare patients with Potocki-Lupski syndrome (Sanchez-Valle et al., 2011).

Right Outflow Tract Obstruction (RVOTO) Defects

Abnormal development of the pulmonary valve often leads to obstruction of flow from the right ventricle. The characteristic lesions are called pulmonary stenosis (PS) or atresia (PA). These lesions often occur in combination with other defects and are a component of TOF. Mutations in *TBX1* and *JAG1* have been observed in isolated PA/PS (Bauer et al., 2010) presumably representing the functions of these pathways in OFT more generally. Pulmonary Atresia with Intact Ventricular Septum (PA-IVS) has been observed in patients with Sotos syndrome caused by mutations in *NSD1* (Miyamoto et al., 2003). Isolated pulmonary valve dysplasia of Noonan syndrome is a well-known example of a specific association in which mutations in the intracellular phosphatase *PTPN11* lead to constitutive activation of MAPK signal transduction pathways presumably including the EGFR pathway mentioned above (Tidyman and Rauen, 2009). Similar mechanisms are likely operating in the Costello syndrome (*HRAS*) and Cardiofaciocutaneous Syndrome (*BRAF*, *MEK1*, *MEK2*, *KRAS*). The genes mutated in those diseases encode proteins which all play important roles in MAPK signaling. Pulmonary artery stenosis is a typical feature of Keutel Syndrome due to mutation in the extracellular matrix protein *MGP* (Munroe et al., 1999). Pulmonary artery stenosis is also clinically important in the arterial tortuosity syndrome. This disorder is caused by mutations in *SLC2A10* which encodes the GLUT10 transporter, one of only a handful of transporter and channel defects involved in CVM (Coucke et al., 2006).

Septal Defects

Ventricular septal defects

Ventricular septal defects (VSD), while broadly the most common of all heart malformations, are anatomically heterogeneous. Although the cardiology literature is clear on this, animal models and human genetic studies most often fail to make important distinctions about anatomic details. Perimembranous VSDs, in contrast to the more common muscular VSDs, occur within and adjacent to the membranous septum (formed by the fusion of the endocardial cushion with the superior portion of the muscular septum). Perimembranous VSDs, themselves, are divided into 3 types: outlet; inlet (which are the AVSD type); and trabecular. Defects in the outlet septum are thought to be caused by failure of fusion of the conus septum. Inlet defects may be caused by failure of complete fusion of the right superior endocardial cushion with the muscular septum. Muscular defects in the trabecular septum are probably due to excessive remodeling of the interventricular wall or inadequate merger of the medial walls. Because VSD can arise from disparate cardiac elements and heterogeneous mechanisms, molecular interpretation of such defects is hazardous. VSDs have been observed in almost all genetic disorders affecting heart development and so convey the least specificity for studies of genetic causation. Some represent a continuum of defects of the common outflow tract e.g. Velocardiofacial syndrome or AV canal e.g. Down syndrome. Muscular VSDs are presumably due to defects in cardiomyocyte growth as in Holt-Oram Syndrome (*TBX5* mutation, (Basson et al., 1997)) and *GATA4* (Rajagopal et al., 2007), or defects in cardiomyocyte remodeling and survival, as in congenital cardiomyopathy such as Left Ventricular Noncompaction (Ichida et al., 2001). VSDs may also commonly accompany other single defects e.g. coarctation of the aorta plus VSD, or more complex cardiac defects. It is not known whether these associations represent a specific molecular subset or simply secondary defects perhaps caused by aberrant intracardiac flow. VSDs can also be the most common cardiac defect in multisystem syndromes. Examples of this include Rubinstein-Taybi syndrome (haploinsufficiency for *CREBBP*) and Simpson-Golabi-Behmel syndrome (*GPC3*).

Atrial Septal Defects

Common atrium is a severe early defect in atrial septation with apparent combined failure of the growth of both the septum primum and septum secundum. This anomaly is characteristic of the Ellis Van Creveld Syndrome due to mutations in either *EVC* or *EVC2* (Baujat and Le Merrer, 2007). The combination of atrioventricular canal and common atrium may be observed in Smith-Lemli-Opitz Syndrome, a condition that results from defective cholesterol biosynthesis. The complex developmental defects may result not only from defective cholesterol modification of SHH but also de-repression of SHH signaling (Koide et al., 2006).

Defects in the septum secundum, i.e. secundum ASD (ASD2), are the most common form of ASD, but abnormal valve-incompetent foramen ovale called primum ASD (ASD1) are also important. The Holt-Oram Syndrome is the prototype of genetic disorders causing septal defects. This condition, which is caused by mutations in the transcription factor *TBX5* (Basson et al., 1997; Stennard and Harvey, 2005), is almost always associated with thumb,

hand, or radial malformations. In the past few years additional ASD families have been identified with mutations in another key cardiac transcription factor *NKX2.5* (Schott et al., 1998). These individuals often have associated cardiac conduction defects. Mutations in other key cardiac transcription factors *GATA4* (Garg et al., 2003) and *TBX20* (Kirk et al., 2007) were also found in a few families with isolated ASD. An interesting observation is that some individuals in these families are also affected with cardiomyopathy, implying a continued requirement for these transcription factors in normal cardiomyocyte maintenance. All these transcription factors are known to be part of a complex which regulates cardiac gene expression or in the case of *TBX20* to act upstream of the specific components of the complex. Mutation in the *MYH6* gene has been observed in familial ASD (Ching et al., 2005). *MYH6* encodes a contractile protein that is a transcriptional regulatory target of *TBX5* establishing a potential functional connection between the 2 genetic disorders. Mutation in alpha-cardiac actin (*ACTC1*) in familial ASD further reinforces the link between contractile protein disorders and septal defects (Matsson et al., 2008). ASD is a common associated finding in many other Mendelian disorders suggesting that diverse pathways are involved in atrial septation or that ASD is a relatively non-specific outcome to early disturbance to cardiac development. ASD occurring in syndromic eye defects e.g. *MCOPS3* caused by mutation in *BCOR* (Hilton et al., 2009), and in the recognized TARP syndrome which is caused by mutations in *RBM10* (Johnston et al., 2010) illustrate the sensitivity of atrial septation to many unexpected factors. The finding of ASD in individuals with *CITED2* mutations, a gene product known to be involved in Nodal signaling and embryonic LR patterning (Sperling et al., 2005) also gives an indication that the anatomic consequences of early embryonic abnormalities are very diverse.

Heterotaxy—Heterotaxy or situs ambiguus means discordance in the relationship between the normally asymmetric organs of the thorax and abdomen. Heterotaxy arises from abnormal left right (LR) patterning with abnormal symmetry or reversals of cardiac chambers, vessels, lungs, and/or abdominal organs. An affected individual may have segmental discordances (e.g. transposition of the great arteries), loss of structures (e.g., asplenia), improper symmetry (e.g., right atrial isomerism in which left atrial development is concomitantly lost), or failure to regress symmetrical embryonic structures (e.g. persistent left superior vena cava). Heart defects may typically combine transposition of the great arteries (TGA) or double outlet right ventricle (DORV), atrial septal defects (ASD), ventricular septal defects (VSD), persistent left superior vena cava (LSVC), anomalous pulmonary venous return (APVR), common atrium, atrioventricular septal defects (AVSD), pulmonary valve atresia (PA) and stenosis (PS), coarctation of the aorta (CoA), hypoplastic left heart (HLHS), or single ventricle. It seems most likely that these complex combinations arise as a consequence of disturbed mesoderm induction rather than specific roles for left right patterning in all later stages of heart development. Dextro-transposition (d-TGA) is distinguished from levo-transposition (l-TGA, also called congenitally corrected transposition) in that the latter implies a leftward looping of the heart tube at the C-loop stage. L-looping clearly involves a disturbance in early LR axis patterning. The result is discordance of the outflow tract with the ventricles i.e. morphologically RV receives oxygenated blood and pumps to the systemic circulation via the aorta.

More than 80 genes associated with laterality defects in animal models and mutations in a few of these have been identified in humans (Levin, 2005). Abnormalities in monocilia presumably explain the association of heart defects with primary ciliary dyskinesia (PCD) caused by mutations in *DNAH5*, *DNAI1*, *RPGR*, *DNAH11* and *TXNDC3* (Escudier et al., 2009). The Bardet-Biedl Syndromes (BBS), which have a surprising degree of locus heterogeneity, are caused by mutations in genes required for cilia assembly or regulation and this could explain the occasional patient with BBS having dextrocardia or heterotaxy (Zaghloul and Katsanis, 2009). Heterotaxy and related isolated congenital heart defects have been associated with mutations in *ZIC3* (Gebbia et al., 1997), *ACVR2B* (Kosaki et al., 1999), *LEFTY1* (Kosaki et al., 1999), *CFC1* (Bamford et al., 2000), *GDF1* (Karkera et al., 2007), and *NODAL* (Mohapatra et al., 2009). All of these genes are known to be functionally connected to the NODAL signaling pathway. Rare CNVs in individuals with heterotaxy have revealed several other genes involved in human laterality defects including *NEK2*, *GALNT11*, *ROCK2*, *NUP188*, and *TGFBR2* (Fakhro et al., 2011). Observations of dextrocardia caused by mutation in very diverse genes such as *PQBPI* (Renpenning Syndrome) (Stevenson et al., 2005), *NKX2.5* (Hirayama-Yamada et al., 2005; Watanabe et al., 2002), *CITED2* (Yang et al., 2010), and *CRELD1* (Robinson et al., 2003) require further research. *CITED2* is a particularly promising candidate gene given that protein product alters Nodal-Pitx2 signaling, it has been associated with other heart defects (Sperling et al., 2005) and the mouse mutation models show typical LR patterning defects (Lopes Floro et al., 2011).

Patent Ductus Arteriosus

The ductus arteriosus is a normal structure that allows flow of oxygenated blood from the venous circulation to enter the systemic circulation *in utero*. After birth and the inflation of the lungs, the ductus closes allowing for establishment of the separate venous and arterial circulations. Persistent patent ductus arteriosus (PDA) results when the ductus fails to undergo its normal physiologic closure and involution. PDA is seen in numerous genetic disorders and the causal mechanisms are very poorly understood. Char Syndrome (*TFAP2B*) (Mani et al., 2005) is an example of a relatively specific association in that other heart defects are not typically observed in that condition. Mowat-Wilson Syndrome patients caused by mutation in the transcription factor *ZEB2* (Zweier et al., 2005) often have PDA and it is the most specific CVM associated with that disorder. Rare families with thoracic aortic aneurysm plus PDA have been found to segregate mutations in the vascular smooth muscle contractile protein *MYH11* (Zhu et al., 2006).

Conclusion

In the last 15 years there has been a revolution in our understanding of the genetic basis of CVM. Extensive locus heterogeneity among the single gene forms provides strong support for the concept that there are a large number of loci that when mutated can give rise to a cardiac malformation. Whether there are any common variants that contribute to the high frequency of CVM should be determined by ongoing GWAS. Using other methods in human genetics such as genome-wide copy number analysis, exome and complete genome DNA sequencing will allow both testing of pathway candidate genes and unbiased

identification of rare variants. Because CVM follow simple patterns of Mendelian inheritance in only a minority of cases, one of the great challenges will be to reliably identify the genes that are involved in oligogenic inheritance, epistasis and gene-environment interactions. Experimental systems will play an essential role in determining how mutations and gene variants alter the normal network of growth, differentiation, and intercellular signaling required for normal cardiovascular development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary Points

1. Cardiovascular malformations (CVM) are the most common anatomic class of birth defects and are responsible for the single largest fraction of infant mortality attributable to birth defects.
2. CVM can result from chromosomal aberrations, genomic disorders, and single gene disorders.
3. Genomic disorders demonstrate the importance of *de novo* mutation in the etiology of heart defects.
4. Animal models suggest that there are a very large number of genes that when mutated can give rise to a heart malformation.
5. A large number of single gene disorders, mainly complex syndromes, may have heart defects as either common or occasional features.
6. There is some correlation between the anatomic classes of CVM and specific genetic loci, but milder lesions such as ASD and VSD can be seen associated with almost all known CVM genes.
7. Complex inheritance, including the influence of multiple genes and possible interactions with environmental factors, is thought to play the major role in causing heart malformations.

Future Issues

1. New whole exome and whole genome sequencing methods should determine whether there are loci with recurrent *de novo* mutations involved in both syndromic and non-syndromic CVM.
2. Because of the severity of CVM, rare variants may predominate in the pathogenic allele frequency spectrum.
3. Interpretation of oligogenic patterns of inheritance presents a difficult obstacle to understanding individual cases and families.
4. Investigation of gene-environment interactions will require large and well-organized epidemiologic studies.

Table I**Genomic Disorders Known to Cause Cardiovascular Malformations**

	OMIM#	Syndromes	Cardiac lesions
Deletions	607872	1p36 deletion	VSD, ASD, PDA, Aortopathy
	274000	1q21.1 deletion (TAR)	VSD, ASD, TOF, CoA
	612474	1q21.1 deletion	VSD, TA, TGA, BAV, CoA, PDA
	612530	1q41-q42 deletion	TOF, PDA
	612513	2p16.1-p15 deletion	BAV, MVP
	609425	3q29 deletion	PDA, PH
	194190	Wolf-Hirschhorn (4p16.3 deletion)	VSD, ASD
	123450	Cri-Du-Chat (5p15.2 deletion)	VSD, ASD, PS, TOF, AS, PDA
	117550	Sotos (5q35.2-q35.3 deletion)	ASD, VSD
	612582	6pter-p24 deletion	ASD, TOF, PDA
	612863	6q24-q25 deletion	VSD, ASD, PS
	194050	Williams-Beuren (7q11.23 deletion)	SVAS, PBS
	154230	9p24.3 deletion	VSD, ASD, CoA, PDA
	610253	Kleefstra (9q34.3 deletion)	VSD, ASD, PS, TOF, BAV, CoA, PDA
	147791	Jacobsen (11q23 deletion)	VSD, ASD, TA, DORV, BAV, AS, HLHS, MS, CoA
	NA	8p23.1 deletion	AVSD, ASD, TOF
	179613	Recombinant 8	VSD, ASD, PS, TOF, DORV
	600383	Mesomelia-synostoses (8q13 deletion)	VSD, ASD, CoA, PDA
	612242	10q23 deletion	VSD, ASD
	609625	10q26 deletion	ASD, PDA
	613457	14q11-q22 deletion	VSD, PDA
	612001	15q13.3 deletion	TOF
	613406	15q24 deletion	Aortopathy
	612626	15q26-qter deletion	VSD, ASD, CoA
	611913	16p11.2 deletion	BAV, AS
	136570	16p12.1 deletion	VSD, PS, DORV, BAV, HLHS, MA, APVR, HTX
	613604	16p12.2-p11.2 deletion	PA, TOF
	610543	16p13.3 deletion	HLHS
	247200	Miller-Dieker (17p13.3 deletion)	ASD, PDA
	182290	Smith-Magenis (17p11.2 deletion)	VSD, ASD, PS, PA, TOF, AS, MS, APVR
	610443	17q21.31 deletion	VSD, ASD, PS, BAV, Aortopathy
	613355	17q23.1-q23.2 deletion	ASD, BAV, PDA
	146390	18p deletion	VSD, AS, HLHS, PDA, HTX
	601808	18q deletion	VSD, ASD, PS, PA, AS, PDA, Aortopathy
	192430/188400	Digeorge/Velocardiofacial (22q11.2 deletion)	VSD, PA, TOF, DORV
	611867	Distal 22q11.2 deletion	VSD, PS, TA, BAV, PDA, hypoplastic aortic arch
Duplications			

	OMIM#	Syndromes	Cardiac lesions
	NA	Microduplication of 8q12	VSD, ASD
	613458	16p13.3 duplication	ASD, TOF
	610883	Potocki-Lupski (17q11.2 duplication)	VSD, ASD, BAV, HLHS, AS, aortopathy
	608363	22q11.2 duplication	TGA, DORV, CoA

Table 2

Genes Involved in Syndromic and Non-Syndromic Cardiovascular Malformations in Humans

Class	OMIM	Gene	Disorder or Syndrome	Heart Defects
	136760	<i>ALX3</i>	Frontonasal Dysplasia 1	TOF
Transcription Factor	300215	<i>ARX</i>	Lissencephaly, X-Linked, With Ambiguous Genitalia	VSD, PDA
	602937	<i>CITED2</i>	Isolated septal defect	ASD, VSD
	225500	<i>EVC, EVC2</i>	Ellis-Van Creveld	Common atrium, AVSD, HLHS
	166780	<i>EYA1</i>	Otofaciocervical Syndrome	TOF
		<i>FOXC1</i>	Axenfeld-Rieger Syndrome, Type 3	PDA, ASD, AS, MR
	153400	<i>FOXC2</i>	Lymphedema-Distichiasis	TOF, VSD, TAPVR
	265380	<i>FOXF1-FOXC2-FOXL1</i> deletion	Alveolar Capillary Dysplasia With Misalignment Of Pulmonary Veins	APVR, HLHS
	607941	<i>GATA4</i>	Familial ASD2	ASD
	200990	<i>GLI3</i>	Acrocallosal, Pallister-Hall	VSD, PS, ASD
	601536	<i>HOXA1</i>	Athabaskan Brainstem Dysgenesis	TOF
	169400	<i>LBR</i>	Pelger-Huet Anomaly	VSD
	309520	<i>MED12</i>	Lujan-Fryns Syndrome	ASD, VSD, aortic aneurysm
	164280	<i>MYCN</i>	Feingold	PDA
	108900	<i>NKX2.5</i>	ASD with Conduction Defect	ASD, TOF, Dextrocardia
	148820	<i>PAX3</i>	Waardenburg Type III	ASD
	107480	<i>SALL1</i>	Townes-Brocks	VSD, TOF
	607323	<i>SALL4</i>	Duane Radial Ray	VSD
	269150	<i>SETBP1</i>	Schinzel-Giedion Midface Retraction Syndrome	ASD
	212550	<i>SIX6</i>	Microphthalmia, Isolated, With Cataract Type 2	VSD, PDA
	601349	<i>SNX3</i>	Microcephaly, Microphthalmia, Ectrodactyly Of Lower Limbs, And Prognathism	VSD
	206900	<i>SOX2</i>	Microphthalmia And Esophageal Atresia	VSD, PDA
	114290	<i>SOX9</i>	Campomelic Dysplasia	Complex
	602054	<i>TBX1</i>	DiGeorge, Conotruncal Anomaly Face	TOF, PA, IAA(B), RAA, DORV VSD, TA
	181450	<i>TBX3</i>	Ulnar-Mammary	PS
	142900	<i>TBX5</i>	Holt-Oram	VSD, ASD, HLHS, TAPVR, TOF, DORV
	611363	<i>TBX20</i>	Familial ASD4	ASD
	169100	<i>TFAP2B</i>	Char	PDA, muscular VSD
	608771	<i>THRAP2, ZIC3</i>	Transposition of the Great Arteries	TGA
	106260	<i>TP73L</i>	Ankyloblepharon-Ectodermal Defects-Cleft Lip/Palate	VSD, PDA
	101400	<i>TWIST</i>	Saethre-Chotzen	VSD
	235730	<i>ZFH1B</i>	Mowat-Wilson	VSD, PDA
	603693	<i>ZFPM2/FOG2</i>	Tetralogy of Fallot	TOF
	306955	<i>ZIC3</i>	Heterotaxy 1, X-linked	Dextrocardia, TGA, PS, VSD, TAPVR, HLHS, CoA

Class	OMIM	Gene	Disorder or Syndrome	Heart Defects
	301040	<i>ATRX</i>	Alpha-Thalassemia/Mental Retardation, X-Linked	VSD
Chromatin Regulator	214800	<i>CHD7</i>	CHARGE	TOF, IAA(B), VSD, DORV+/-AVSD, TA
	180849	<i>CREBBP</i>	Rubenstein-Taybi	VSD, ASD, PDA, CoA, HLHS
	268300	<i>ESCO2</i>	Roberts, SC Phocomelia	PS, PA
	147920	<i>MLL2</i>	Kabuki	CoA, VSD, ASD
	275210	<i>LMNA</i>	Lethal Tight Skin Contracture	PDA, ASD
	300000	<i>MID1</i>	Opitz	VSD, Persistent LSVC, ASD, PDA, DORV
	122470	<i>NIPBL</i>	Brachman-De Lange	BAV, VSD, PS
	117550	<i>NSD1</i>	Sotos	ASD, VSD, PDA
	309500	<i>PQBP1</i>	Renpenning	ASD, Dextrocardia
	218600	<i>RECQL4</i>	Baller-Gerold	VSD, ASD
	273395	<i>ZMPSTE24</i>	Tetra-Amelia	PDA, ASD
	602730	<i>ACVR2B</i>	Heterotaxy	HLHS, AVSD, LSVC
	149000	<i>AGGF1</i>	Klippel-Trenaunay-Weber	PDA, ASD, PS, MVP
	300166	<i>BCOR</i>	Microphthalmia, syndromic Type 2	ASD, VSD, MVP
	178600	<i>BMPR2</i>	Primary Pulmonary Hypertensions with CHD	AVSD, ASD, VSD, PDA, PAPVR
	605376	<i>CFC1</i>	Heterotaxy 2	DORV, TA, TGA, Heterotaxy
	277300	<i>DLL3</i>	Jarcho-Levin	ASD, DORV
	305400	<i>FGD1</i>	Aarskog-Scott	ASD, VSD, PS, AS, CoA
	207410	<i>FGFR2</i>	Antley-Bixler	ASD
	101200	<i>FGFR2</i>	Apert	VSD
	187500	<i>JAG1, GDF1</i>	Tetralogy of Fallot	TOF
	218040	<i>HRAS</i>	Costello	HCM, PS, ASD, other valve dysplasia, dysrhythmias
	300472	<i>IGBP1</i>	Corpus Callosum, Agenesis Of, With Mental Retardation, Ocular Coloboma, and Micrognathia	VSD, PDA
Ligand, Receptor, Signal Transduction	118450	<i>JAG1, NOTCH2</i>	Alagille	TOF+/-PA, CoA, PS, ASD, VSD
	115150	<i>KRAS, BRAF, MEK1, MEK2</i>	Cardiofaciocutaneous	ASD, PS, HCM
	601877	<i>LEFTY2</i>	Heterotaxy	Heterotaxy, HLHS, AVSD, LSVC
	259770	<i>LRP5</i>	Osteoporosis-Pseudoglioma Syndrome	VSD
	162200	<i>NF1</i>	Neurofibromatosis-Noonan, Watson	PS, VSD, CoA
	109198	<i>NOTCH1</i>	Familial Calcific Bicuspid Aortic Valve	BAV, MS, VSD, TOF
	194200	<i>PRKAG2</i>	Wolff-Parkinson-White	Accessory Conduction Pathways
	255960	<i>PRKARIA</i>	Intracardiac Myxoma	ASD
	153480	<i>PTEN</i>	Bannayan-Zonana	ASD
	163950	<i>PTPN11, KRAS, SOS1, RAF1, NRAS, BRAF, SHOC2, CBL, NF1</i>	Noonan, LEOPARD	PS, HCM, CoA, ASD

Class	OMIM	Gene	Disorder or Syndrome	Heart Defects
	268310	<i>ROR2</i>	Robinow, Brachydactyly Type B1	PS, PA
	609192	<i>TGFB2, TGFB1</i>	Loeys-Dietz	PDA, ASD, BAV
	243800	<i>UBR1</i>	Johanson-Blizzard	ASD, VSD, Dextrocardia
	300373	<i>WTX</i>	Osteopathia Striata With Cranial Sclerosis	ASD, VSD, PDA
	235510	<i>CCBE1</i>	Hennekam Lymphangiectasia-Lymphedema Syndrome	ASD, VSD, pericardial lymphangiectasia and effusion
	267750	<i>COL18A1</i>	Knobloch	PDA, VSD, TAPVR
	200610	<i>COL2A1</i>	Achondrogenesis Type II	ASD, AVSD
	606217	<i>CRELD1</i>	AVSD2	AVSD, Heterotaxy, PA
	606617	<i>DTNA</i>	Left Ventricular Noncompaction	LSVC, PDA, HLHS
Structural, or Cell Adhesion	185500	<i>ELN1</i>	Familial Supravalvar Aortic Stenosis	SVAS
	608328	<i>FBN1, ADAMTS10</i>	Weill-Marchesani	AS, MI, PS, PDA, VSD
	121050	<i>FBN2</i>	Congenital Contractural Arachnodactyly	ASD, VSD
	309350	<i>FLNA</i>	Melnick-Needles	TOF
	150250	<i>FLNB</i>	Larsen	ASD, VSD
	312870	<i>GPC3</i>	Simpson-Golabi-Behmel	VSD, PS, TGA, PDA, HCM
	607941	<i>MYH6</i>	Familial ASD	ASD
		<i>MYH11</i>	Familial Thoracic Aortic Aneurysm with PDA	PDA
	612794	<i>ACTC1</i>	Familial ASD5	ASD
	608688	<i>ATIC</i>	IMP Cyclohydrolase Deficiency	ASD
	261540	<i>B3GALT1</i>	Peters Plus Syndrome	ASD, VSD, subvalvar AS, PS, BAV
	602398	<i>DHCR24</i>	Desmosterolosis	TAPVR, PDA
	270400	<i>DHCR7</i>	Smith-Lemli-Opitz	AVSD, ASD, VSD, PDA, HLHS, CoA, PS, TAPVR
Metabolic	608799	<i>DPM1</i>	Congenital Disorder Of Glycosylation Type 1e	PDA
	612541	<i>G6PC3</i>	Neutropenia, severe congenital, autosomal recessive 4	ASD
	309801	<i>HCCS</i>	Microphthalmia, Syndromic 7; MCOPS7	ASD, VSD, cardiomyopathy
	212066	<i>MGAT</i>	Congenital Disorder of Glycosylation, type IIa	VSD
	308050	<i>NSDHL</i>	Congenital Hemidysplasia with Ichthyosiform Erythroderma and Limb Defects	ASD, VSD, Single ventricle, CoA, Shone Complex
	214100	<i>PEX genes</i>	Zellweger	VSD, PDA, HLHS
	201000	<i>RAB23</i>	Carpenter Syndrome	ASD, VSD, TOF, PS, TGA, PDA
	208085	<i>VPS33B</i>	Arthrogryposis, renal dysfunction, and cholestasis type 1	ASD, VSD
	601005	<i>CACNA1C</i>	Timothy	VSD, TOF, PDA, Long QT
	170390	<i>KCNJ2</i>	Andersen	BAV, CoA, Long QT
Ion Channel	612391	<i>SLC29A3</i>	Hyperpigmentation, cutaneous, with hypertrichosis, hepatosplenomegaly, heart anomalies, and hypogonadism with or without hearing loss	ASD, VSD, BAV, MVP
	227650	<i>FANC genes</i>	Fanconi	VSD, TOF

Class	OMIM	Gene	Disorder or Syndrome	Heart Defects
DNA Repair				
	209900	<i>BBS1</i> , -2, -4, -5, -9, -10, -12; <i>ARL6</i> , <i>BBS4</i> , <i>BBS5</i> , <i>MKKS</i> , <i>TTC8</i> , <i>TRIM32</i> , <i>MKSI</i> , <i>CEP290</i> , <i>C2ORF86</i> , <i>CCDC28B</i>	Bardet-Biedl	VSD, Dextrocardia
Monocilia	270100	<i>DNAH11</i> , <i>DNAH1</i> , <i>DNAH5</i>	Situs Inversus Viscerum, Kartagener	TGA, TA, VSD, ASD
	604896	<i>MKKS</i>	McKusick-Kaufman	TOF
	249000	<i>MKSI</i>	Meckel	ASD, VSD, CoA, PDA
	208540	<i>NPHP3</i>	Renal-Hepatic-Pancreatic Dysplasia	Dextrocardia, ASD, AS
	105650	<i>RPS19</i>	Diamond-Blackfan Anemia	VSD
RNA Binding	300080	<i>RBM10</i>	TARPS syndrome	ASD
Cell Cycle	300707	<i>FAM58A</i>	STAR Syndrome	ASD, VSD

* ASD – atrial septal defect, primum or secundum; AS – aortic stenosis; AVSD – atrioventricular septal defect; BAV – bicuspid aortic valve; CoA – coarctation of the aorta; DCM – dilated cardiomyopathy; DORV double outlet right ventricle; HCM – hypertrophic cardiomyopathy; HLHS – hypoplastic left heart; IAA(B) – interrupted aortic arch type B; LSVC – persistent left superior vena cava; MVP – mitral valve prolapse; PA – pulmonary atresia; PDA – patent ductus arteriosus; PPAS – peripheral pulmonary artery stenosis; PS – pulmonic stenosis; Shone complex – parachute mitral valve, aortic stenosis, coarctation; SVAS – supraaortic stenosis; TA – truncus arteriosus; TAPVR – total anomalous pulmonary venous return; TOF – tetralogy of Fallot; VSD – ventricular septal defect

Table 3

Acronyms of Cardiovascular Malformations

APVR	Anomalous Pulmonary Venous Return
AS	Aortic Stenosis
ASD	Atrial Septal Defect
AVSD	Atrioventricular Septal Defect
BAV	Bicuspid Aortic Valve
CoA	Coarctation of the Aorta
DORV	Double Outlet Right Ventricle
HLHS	Hypoplastic Left Heart Syndrome
LSVC	Left Superior Vena Cava
LVOTO	Left Ventricular Outflow Tract Obstruction
PA	Pulmonary Atresia
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PS	Pulmonic Stenosis
RVOTO	Right Ventricular Outflow Tract Obstruction
SVAS	Supravalvar Aortic Stenosis
TA	Truncus Arteriosus
TGA	Transposition of the Great Arteries
TOF	Tetralogy of Fallot
VSD	Ventricular Septal Defect