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Genetics of Valvular Heart Disease

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Abstract

Valvular heart disease is associated with significant morbidity and mortality and often the result of congenital malformations. However, the prevalence is increasing in adults not only because of the growing aging population, but also because of improvements in the medical and surgical care of children with congenital heart valve defects. The success of the Human Genome Project and major advances in genetic technologies, in combination with our increased understanding of heart valve development, has led to the discovery of numerous genetic contributors to heart valve disease. These have been uncovered using a variety of approaches including the examination of familial valve disease and genome-wide association studies to investigate sporadic cases. This review will discuss these findings and their implications in the treatment of valvular heart disease.

Keywords

Heart valve; Heart valve development; Genetics; Bicuspid aortic valve; Aortic valve stenosis; Mitral valve prolapse; Myxomatous valve disease; Pulmonic valve stenosis; Ebstein anomaly; Aortic valve calcification; Valvular heart disease

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Compliance with Ethics Guidelines

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Introduction

Valvular heart disease (VHD), which encompasses both congenital and acquired forms, results in significant morbidity and mortality [1]. Over the past several decades, there has been a significant change in the subtypes of VHD with rheumatic heart disease becoming less common and calcific (or degenerative) disease being more prevalent in light of the increased lifespans in industrialized populations. The incidence of congenital valve defects has remained relatively constant and accounts for 10 % of all congenital heart defects (CHD) and found in over 50 % of CHD cases [1, 2]. Regardless of the etiology, therapies for diseased heart valves are limited and severe dysfunction ultimately requires surgical replacement with mechanical or bioprosthetic valves. The downside to this is the lack of durability of bioprosthetic valves that often need replacing, and the requirement of anticoagulation therapy for patients receiving mechanical valves [3]. Increased understanding of the mechanisms underlying cardiac valve development along with recent advances in sequencing of the human genome, have resulted in the identification of numerous genetic etiologies for congenital valvular malformations in humans. In addition, there is increasing evidence to suggest that adult-onset VHD has origins during embryonic development.

The emphasis of this review will be on the genetic contributors of congenital valvular malformations, and accordingly includes a brief overview of heart valve development. We have focused on the most common congenital anomalies of each of the 4 heart valves: bicuspid aortic valve, mitral valve prolapse, pulmonary valve stenosis, and Ebstein anomaly of the tricuspid valve. For each these lesions, there have been recent discoveries into their genetic basis and these etiologic human genetic mutations will be discussed. In addition, this review will include a discussion on the recent mutant mouse models that mimic human disease phenotypes, as these provide additional genetic links to disease onset. Finally, we will review recent studies investigating the genetic contributors to adult-onset VHD.

Development of the Cardiac Valves

Heart valve development is a complex process that involves the interplay of several cell lineages and cellular process all tightly controlled by multiple genetic programs [4, 5]. Development of the atrioventricular (AV) valves precedes semilunar valve development but both begin with the formation of swellings, referred to as endocardial cushions, within the wall of the linear heart tube of the outflow tract (OFT) and AV regions. The AV cushions rise to the mature mitral and tricuspid valves, whereas the OFT cushions will go on to form the aortic and pulmonary valves (Fig. 1A).

Endocardial cushion formation is first evident at human embryonic day (E)31–E35 and in the mouse around E9.5 [7, 8] and begins with endothelial to mesenchymal transformation (EMT). This process is initiated by signals emanating from the endocardial cells and adjacent myocardium that promote a subset of endocardial cells to lose cell-cell contacts and undergo transformation and migrate into the hyaluronan-rich matrix within the developing cushion. The resulting population of mesenchyme cells contributes to the progenitor cell pool that, in addition to other cell lineages, will give rise to the mature valve structures.

Previous studies have shown that members of the Tgf-β family are required for EMT, and secretion of BMP2 from the myocardium acts synergistically with endothelial derived Tgf-β to enhance mesenchyme cell formation [9–11]. In addition to these growth factors, the Notch and Ras signaling pathways have also been implicated in endocardial cushion development of the AVC and OFT [12, 13].

Following active stages of EMT, newly transformed mesenchymal cells within the AV region continue to proliferate resulting in expansion of the endocardial cushions and elongation into valve primordia (Fig. 1B). The expanding endocardial cushions divide the common atrioventricular canal, first by growth of the superior (anterior) and inferior (posterior) endocardial cushions and then by growth of the 2 lateral cushions (Fig. 1B). Finally, the AV canal is divided into the left and right AV valve orifices when the superior and inferior cushions fuse [4]. In addition to endothelial-derived cells, there is evidence that cells from the epicardium populate the cushions and parietal leaflets of the valve primordia and cells from the dorsal mesenchymal protrusion, a derivative of the second heart field, contribute to atrioventricular septation [14–16]. The final morphogenetic steps that lead to formation of the mature atrioventricular septum and valve leaflets is less defined, but NFAT signaling is involved [17, 18].

Development of the OFT cushions involves not only EMT but also requires contribution from a population of migratory neural crest cells, referred to as the cardiac neural crest (CNC), which arise from the neural tube between the otic placode and third somite [4]. The CNC cells populate the aortic sac after migrating through the pharyngeal arches. In the aortic sac, the CNC cells are required for the proper septation of the common outflow tract (truncus arteriosus) into the aorta and pulmonary artery. The CNC cells also contribute to the development of the semilunar valve leaflets and the superior aspect of the ventricular septum. As semilunar valve development occurs in a synchronized manner with OFT development, the CNC cells contribute to formation of the truncal swellings. A small eminence on each swelling, along with a third precursor region, will grow to form the valve cusps in the aorta and pulmonary artery (Fig. 1C).

Individual valve leaflets are initially evident in human fetuses at around weeks 5 and 6 of development and in mice at around E13.5. The valve primordia will continue to develop by a process of thinning, reshaping, and elongation, as well as remodeling of the ECM. This occurs well into postnatal development, until the valve has become well organized with a stratified trilaminar structure made up of organized ECM layers, which contains elastin, which makes up the atrialis of the AV and the ventricularis of the OFT, fibrillar collagen that form the fibrosa, and proteoglycans, which make up the spongiosa [19–21].

Genetics of Bicuspid Aortic Valve

Bicuspid aortic valve (BAV) is the most common valvular malformation, and it affects between 1 % and 2 % of the population [22, 23]. BAV occurs when there are 2 cusps, rather than the 3 that are found in a normal aortic valve. Over 35 % of affected individuals will develop severe complications from BAV, such as aortic valve stenosis and regurgitation, infective endocarditis, ascending aortic aneurysms, and dissection [24, 25]. BAV has the

largest health burden of all other CHD. BAVs are known to prematurely calcify leading to calcific aortic valve disease (CAVD), the second most common cause of aortic valve stenosis. In addition, BAV predisposes affected individuals to aortic aneurysms and infective endocarditis [26]. BAV has strong genetic components, as evidenced by reports of familial clustering and calculated heritability [27, 28]. In the past few years, mutations in several genes have been linked to BAV in humans and numerous mouse models with BAV have been identified.

Although the initial potential genetic link for human BAV was mutations in the gene *KCNJ2* in the setting of Anderson syndrome, no mutations in this gene had been reported in nonsyndromic BAV. The first genetic etiology of nonsyndromic BAV was identified through the use of genome-wide linkage analysis by studying families with autosomal-dominant disease. *NOTCH1* is a transmembrane receptor known to function in highly conserved signaling pathways that play important roles in cell fate and cardiovascular developmental processes [29, 30]. Interestingly, mutations in *NOTCH1* were found to segregate with affected individuals, and direct sequencing of the gene in another unrelated family also showed segregation of the mutation with individuals affected with aortic valve disease [23]. Following this study, several mutations in *NOTCH1* have been found to be associated with aortic valve disease [31–33]. These findings demonstrate evidence for *NOTCH1* haploinsufficiency as a causative agent in a subset of familial aortic valve disease.

In addition to *NOTCH1*, rare sequence variants in 2 genes implicated from murine studies have also been implicated in human BAV. *GATA5* belongs to the family of GATA transcription factors, and several of these factors have been implicated in human disease. It was recently shown that targeted deletion of *GaTa5* in mice leads to a partially penetrant BAV phenotypes [34]. Examination of a cohort of 100 unrelated individuals with BAV identified 4 individuals with rare sequence variations that predicted nonsynonymous amino acid substitutions of highly conserved residues [35•]. Our group has performed similar studies in a well-phenotyped population of BAV and demonstrated similar results (Bonachea and Garg, unpublished data). Mutations in *SMAD6*, a member of the Bmp signaling pathway, display functional deficits in vitro and have been found in humans with BAV [36, 37•]. Consistent with this, cardiac cushion abnormalities have also been observed in *Smad6*-null mice [36].

Numerous additional genes have also been implicated as potential contributors to human BAV from animal models. Although one of the most studied animal models is the inbred Syrian hamster model, which exhibits BAVs with a fusion of the right and left coronary aortic leaflets, the genetic etiology for the malformation in hamsters remains unknown [38, 39]. One of the first mouse models of BAV was the observation that mice with targeted deletion of endothelial nitric oxide synthase (*Nos3*) displayed partially penetrant right-noncoronary fusion leaflet fusion BAV along with a broad spectrum of CHD [40]. Interestingly, the BAV phenotype displayed an almost 100 % penetrance when mice were null for *Nos3* and heterozygous for *NOTCH1* ($Nos3^{-/-};NOTCH1^{+/-}$), demonstrating that the nitric oxide and *NOTCH1* signaling pathways displayed a genetic interaction during aortic valve development [41•]. Recently, deletion of the proteoglycanase *Adamts5* in mice has also been shown to lead to BAV. This model demonstrates the ability of uncleaved

versican and insufficient *Smad2* phosphorylation to cause bicuspid aortic and pulmonic valves [42]. Another member of the Bmp signaling pathway has also been implicated in BAV in mice as recent studies have also shown that the tissue specific deletion of Activin Receptor Type I (*Alk2*), in the endocardial cushion mesenchyme at post-EMT stages, resulted in BAV [43]. Additional investigations of nitric oxide and Bmp signaling pathways are required to determine if these findings will translate to the genetics of human BAV.

Genetics of Mitral Valve Prolapse

Mitral valve prolapse (MVP) is a common cardiac valvular disorder that affects about 2 %–3 % of the general population, and occurs when there is abnormal bulging and displacement of the mitral valve leaflets during ventricular systole. The mitral valve is a bi-leaflet atrioventricular valve on the left side of the heart. It allows blood to flow from the left atria to the left ventricle during diastole. MVP predisposes the affected individual to a greater risk for mitral valve regurgitation, congestive heart failure, arrhythmia, and infective endocarditis [44–47]. In MVP, fibromyxomatous degeneration occurs in the valve leaflets, causing them to become thickened and lengthened, therefore unable to properly function. These thickened leaflets, combined with weakened or ruptured chordae tendineae, are able to abnormally protrude superiorly into the left atrium during systole, leading to mitral regurgitation and cardiac insufficiency [48]. Normal mitral valves are composed of a trilaminar ECM structure: the fibrosa, which is tensile and composed of collagen fibers, the spongiosa, which is compressive and composed of collagen and proteoglycans, and the atrialis, which has the ability to stretch and is composed of elastic fibers. In contrast, diseased myxomatous valves show an abnormal expansion of the spongiosa caused by excess proteoglycan deposition that contributes to the ‘floppy’ functional phenotype. This is accompanied by diminished collagen fibers, elastin fragmentation, myofibroblast activation, and overexpression of proteolytic enzymes such as matrix metalloproteinase (MMP)-1, MMP-2, and MMP-13, that together leads to pathologic remodeling of the valve connective tissue [49, 50].

The genetic basis of MVP in humans has primarily occurred through investigation of MVP associated with Marfan syndrome, a well-known connective tissue disorder affecting multiple tissues including the heart, blood vessels, eyes, bones, and lungs [51]. Marfan syndrome, is caused by mutations in Fibrillin 1 (*FBN1*), a key component of ECM microfibrils [51–53]. Originally thought to be a structural disorder, subsequent investigation elegantly demonstrated that the primary pathophysiology is due to alterations in Tgf-β signaling, which plays key roles in the embryonic development of valves as well as in adult valve disease [54]. FBN1 limits the activation of Tgf-β through its interaction and stabilization with a large latent complex containing latent Tgf-β binding proteins (LTBPs), latency associated peptides (LAPs), and bound Tgf-β. The loss of function mutations, present in Marfan syndrome patients, prevent the interaction and the stabilization of Tgf-β with the large latent complex, thereby allowing excessive amounts of active Tgf-β [55]. Ng et al have described a mouse model carrying a C1039G mutation in *Fbn1*, which exhibit thickened valves soon after birth associated with increased Tgf-β activity indicated by Smad2 phosphorylation. The valve phenotype in these mice was rescued by pharmacologic Tgf-β antagonism further supporting a role for Tgf-β dysregulation in Marfan syndrome and

MVP [55, 56]. A similar syndrome that has been associated with MVP is Loeys-Dietz (LDS). LDS has a similar phenotype to Marfan syndrome and interestingly is caused by mutations in *TGF-β* receptors 1 and 2 (*TGFBR1* and *TGFBR2*), further implicating Tgf-β signaling in MVP [57].

Connective tissue dysplasias caused by mutations in a variety of collagen genes are also characterized by MVP and include Ehlers-Danlos (EDS), Stickler, and osteogenesis imperfecta [58–60] (Table 1). Collagen is one of the main components of valvular ECM [61, 62]. Deletion of collagen genes, *ColVa1*$^{+/-}$ and *ColXa1*$^{-/-}$, in mice mutant mice recapitulate the EDS phenotype and also exhibit thickened valves with disorganized ECM [63]. Although the family of collagen genes represents exciting candidate genes for nonsyndromic MVP, human genetic studies do not support this, although studies have identified linkage to regions on chromosomes 11, 13, and 16 [64–66].

To date, the only gene linked to nonsyndromic myxomatous valve disease in humans is *Filamin A* (*FLNA*). By studying families with an X-linked form of valvular dystrophy, which predominantly affects the mitral and aortic valves in multiple families, *FLNA* was identified as having a role in nonsyndromic MVP [67, 68]. *FLNA* is a ubiquitous cytoplasmic phosphoprotein that has a structural role in the cytoskeleton and interacts with ECM bound cell-surface integrins [68]. *FLNA* has also been shown to affect TGF-β signaling through its association with Smads [68, 69•, 70]. *FLNA*-null mice exhibit a range of cardiovascular abnormalities including valve defects, OFT septation defects, and atrial and ventricular septal defects, as well as embryonic lethality [71, 72]. *FLNA* is expressed in the endocardium, epicardium, and interstitial cells of the valves throughout development, and mouse cell lineage studies have demonstrated that loss of endothelial *FLNA* expression leads to myxomatous mitral valves [69•]. Loss of *FLNA* leads to an impaired contractile phenotype with failed compaction and tissue remodeling of the valve leaflets. Further, a direct interaction has been shown between *FLNA* and serotonin during the fetal stage, which is considered to be an important time point for valvular remodeling and maturation required for proper valvular organization [69•].

In addition to these human studies, murine models for myxomatous mitral valve disease have been recently described. Mice haploinsufficient for *Adamts9*, which encodes a versican cleaving protease, exhibit abnormal myxomatous phenotypes with an abundance of proteoglycans along with other cardiovascular abnormalities involving the aortic valve and wall and ventricular myocardium. The thickened valves have an increase in uncleaved versican, as well as activated valve interstitial cells, which are normally quiescent in the absence of disease [73]. MVP phenotypes are also observed in mice overexpressing the ECM-degrading enzyme, matrix metalloproteainase-2 (MMP-2) in cardiac myocytes. Affected mice exhibit severely myxomatous mitral valves characterized by a disorganization of collagen bundles and a substantial accumulation of glycosoaminoglycans within the spongiosa [74]. It has been postulated that if the mechanism by which MMP-2 expression leads to MVP can be determined, then inhibition could be an alternative effective therapy for MVP patients [75]. Although yet to proven in vivo, the bHLH transcription factor Scleraxis is sufficient to promote proteoglycan secretion of valve interstitial cells in vitro and increased expression was observed in myxomatous valves from human patients and *Fbn1*

mutant mice [75]. By using these and other mouse models the molecular pathways that regulate the myxomatous changes will become increasingly defined.

Genetics of Pulmonary Valve and Tricuspid Valve Disease

The genetic contributors to disease involving the pulmonary and tricuspid valves are not as well defined. Pulmonary valve stenosis (PVS) occurs because of thickening of the valve leaflets causing stenosis, and is one of the more common types of CHD after cardiac septal defects [76]. The most well-studied genetic contributor to pulmonary valve stenosis in humans is in the setting of Noonan syndrome; a pleomorphic autosomal dominant disorder that is characterized by cardiac defects, typically pulmonary valve stenosis and hypertrophic cardiomyopathy, as well as cognitive disability, characteristic facies, and bleeding disorders [77]. Initially, mutations in *PTPN11*, which encodes protein tyrosine phosphatase SHP-2 involved in Ras signaling, were identified to be the cause of 50 % of Noonan Syndrome cases [78, 79]. Analysis of a knock-in mouse harboring a human associated mutation in *PTPN11* recapitulates the human syndrome and exhibits abnormal endocardial cushion development and pulmonary stenosis [80]. Further analysis has determined that this mutation functions in the endocardium and the potential disease mechanism involves increased MAPK activation [81]. Subsequent studies have found that mutations of other genes involved in the Ras signaling pathway including *RAF1*, *SOS1*, and *KRAS* are also associated with Noonan syndrome in addition to LEOPARD and Costello syndromes, which exhibit similar phenotypes as a result of *RAS* mutations [82–84].

Although familial forms of nonsyndromic PVS have been described in the literature, the genetic contributors have not been identified. We previously reported that mutations in *GATA4*, are linked to cardiac septation defects [85]. Interestingly, in 1 family with a specific mutation (G296S), there were several members who were affected with PVS and subsequent families with the same mutation were reported to have a similar valve anomaly in conjunction with atrial septal defect [85–87]. We recently generated a mouse harboring this knock-in human mutation and found that affected mice also displayed pulmonary and aortic valve stenosis [88]. Future work will determine if mutations in *GATA4* contribute to nonsyndromic isolated PVS in humans.

Anomalies of the tricuspid valve are quite uncommon but familial forms of Ebstein anomaly have been reported [89]. Ebstein anomaly of the tricuspid valve is characterized by downward displacement of the tricuspid valve into the right ventricle and is associated with varying degrees of valve dysfunction. Although the genetic basis of isolated Ebstein anomaly remains unknown, recent investigations have identified mutations in the *MYH7*, which encodes *β-myosin heavy chain*, in individuals with Ebstein anomaly that is associated with left ventricular noncompaction cardiomyopathy [90•, 91]. Future work is required to determine the role of *MYH7* in isolated Ebstein anomaly.

Genetics of Adult-Onset Valve Disease

Although the focus has been on the genetics of congenital valve abnormalities, there is increasing evidence pointing toward genetic contributors in valvular diseases in adults. The first evidence of this was based upon familial clustering of death because of aortic and mitral

valve diseases based upon a population based study [92]. The current evidence has focused on genetic contributors to calcific aortic valve disease (CAVD), in which valvular interstitial cells calcify preventing the valve from functioning properly, leading to valve stenosis and regurgitation [93]. Initial insights came from studying human families with *NOTCH1* mutations and BAV, which were discussed above. In these families, there were individuals who had normal tri-leaflet aortic valves but developed calcification suggesting a role for *NOTCH1*. *NOTCH1* was shown to interact with and activate hairy-like transcriptional repressors, which downregulate Runx2, a key transcriptional regulator of osteoblast fate [21, 94]. Subsequent studies have shown inhibition of Notch signaling prevents calcification in vitro and that *NOTCH1* regulates *Sox9*, a transcription factor that when deleted leads to valve calcification in mice [95]. Inhibition of *NOTCH1* causes a downregulation of Sox9, leading to an increase in calcification in vitro [96]. Along with these more molecular approaches, human genetic studies have attempted to identify potential genetic contributors to CAVD [97, 98]. Recently, a large genome-wide association study with 6942 participants with aortic valve calcification and 3795 participants with mitral valve calcification was performed [99••]. It led to the identification of 1 single nucleotide polymorphism (SNP) in the lipoprotein(a) (*LPA*) locus linked to CAVD. This finding was reproducible in multiple ethnicities and the SNP correlated with Lp(a) levels. Although potentially exciting, additional studies are required to confirm this association and determine if lowering of Lp(a) levels will serve as a new therapy.

Conclusions

The significant role that genetic factors play in human cardiac valve disease is becoming increasingly evident. Though only a handful of genetic mutations have been established as disease-causing, these findings have allowed a link to be created between congenital valvulopathies and human genetics. Mouse models have also been of great importance as the ability to recapitulate human disease will allow for the analysis of molecular pathways. In addition, the murine models allow for the elucidation of disease mechanisms and the identification of the roles that different cell types play in valve development and disease progression. The availability of new genetic technologies that allow for screening of whole exome/genomes and array comparative genome hybridization to identify subtle chromosomal deletions/duplications should allow for detection of additional genes implicated in human valvular disease.

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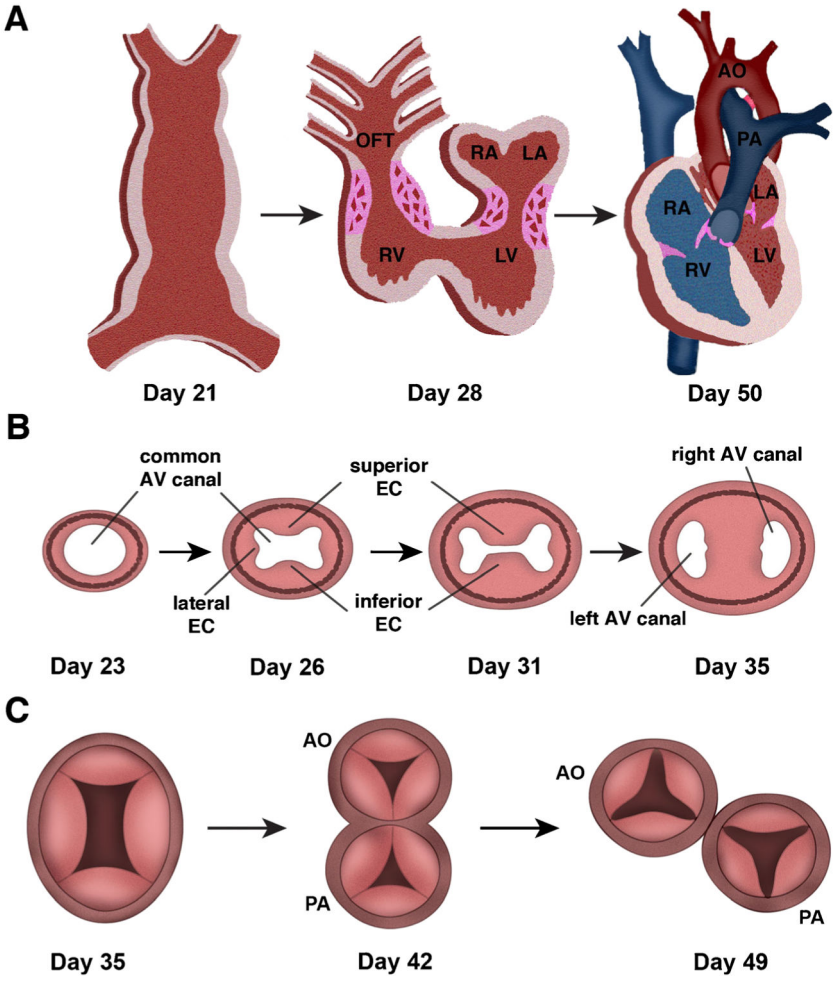

Fig. 1.

Cardiac valve development. **A,** At day 21 of gestation, the linear heart tube is formed and the primitive heart completes rightward looping by day 28 of human gestation. Significant remodeling of the inner curvature and growth of the ventricular chambers then occurs to result in the maturely developed heart with partitioned systemic (*red*) and pulmonary circulations (*blue*) by day 50. Regions of atrioventricular and outflow tract (OFT) cushion formation and development are shown in pink. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle. **B,** Growth of the superior, inferior, and lateral endocardial cushions in the common atrioventricular canal is shown. Days of human gestation are noted. By day 35, the superior and inferior cushions have fused to divide to result in 2 atrioventricular openings. *AV* atrioventricular, *EC* endocardial cushions. **C,** Transverse section through the common outflow tract (truncus arteriosus) with 4 truncal swellings at day 35 of gestation. At day 42 of gestation, the common outflow tract has started to divide into the aorta (AO) and pulmonary artery (PA) and leaflet formation has begun. By day 49, the aorta and pulmonary artery are septated and each has 3 leaflets. Adapted from: Garg V. “Growth of the Normal Human Heart” In: Preedy VR, editor. Handbook of Growth and Growth Monitoring in Health and Disease. New York: Springer; 2011; and Garg V.

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Table 1

Genetic etiologies of valvular heart disease in humans

Bicuspid aortic valve	
Syndromic	*KCNJ2*
Nonsyndromic	*NOTCH1, GATA5, SMAD6*
Myxomatous mitral valve	
Syndromic	*FBN1, TGFBR1, TGFBR2, Collagen types I–III, V, XI*
Nonsyndromic	*Filamin A*
Pulmonic valve stenosis	
Syndromic	*PTPN11, RAF1, SOS1, KRAS*
Nonsyndromic	*GATA4*
Ebstein anomaly	
Nonsyndromic	*MHY7*