

AORTIC VALVE STENOSIS AND GENETIC DISORDERS: A SHORT REVIEW

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ABSTRACT:

Aortic valve stenosis (AS) is the most common valvular heart disease in developed countries and a leading cause of cardiovascular morbidity and mortality among older adults. Traditionally considered a passive degenerative condition, AS is now recognized as an active disease involving inflammation, fibrosis, lipid deposition, and osteogenic calcification of the aortic valve. While aging and conventional cardiovascular risk factors contribute to disease development, genetic predisposition plays an important role, particularly in patients with early-onset disease or congenital valve abnormalities. Bicuspid aortic valve (BAV), the most common congenital cardiac malformation, is strongly associated with premature AS. Genome-wide association studies have also identified common variants, particularly in the LPA gene, that increase susceptibility to calcific aortic valve disease. Advances in molecular genetics have improved understanding of disease mechanisms and may facilitate earlier diagnosis, family screening, and targeted therapeutic approaches. This review summarizes the current evidence regarding the genetic basis of AS and discusses its clinical implications.

KEYWORDS: aortic valve stenosis; calcific aortic valve disease; bicuspid aortic valve; genetic disorders

INTRODUCTION

Aortic valve stenosis (AS) is characterized by progressive narrowing of the aortic valve, resulting in obstruction of left ventricular outflow and increased cardiac workload. If untreated, severe symptomatic AS is associated with heart failure, arrhythmias, and high mortality (1). Calcific aortic valve disease (CAVD) is the most common cause of AS in adults, particularly in developed countries, where increasing life expectancy has led to a growing prevalence of the disease (2). The prevalence of AS rises markedly with age, affecting approximately 2–4% of individuals older than 65 years and up to 5% of those over 75 years (3). Major risk factors include hypertension, diabetes mellitus, hyperlipidemia, smoking, chronic kidney disease, and advanced age (2). Nevertheless, these factors alone do not fully explain the considerable variability in disease onset and progression observed among patients, suggesting an important contribution from genetic factors (4).

Historically, CAVD was viewed as a passive consequence of aging and mechanical wear of the valve leaflets. However, research over the last two decades has demonstrated that the disease is an active and highly regulated biological process involving endothelial dysfunction, chronic inflammation, extracellular matrix remodeling, fibrosis, and osteogenic differentiation of valvular interstitial cells (5). These mechanisms resemble those observed in atherosclerosis but also involve unique molecular pathways responsible for pathological calcification.

Among the strongest genetic risk factors for AS is bicuspid aortic valve (BAV), which affects approximately 1–2% of the general population (6). Individuals with BAV frequently develop calcific stenosis one to two decades earlier than those with a normal tricuspid valve and are at increased risk of aortic aneurysm and dissection (7). In addition, advances in molecular genetics and genome-wide association studies (GWAS) have identified several genes associated with AS susceptibility, including NOTCH1, SMAD6, GATA5, and LPA, providing new insights into disease pathogenesis and potential therapeutic targets (8–10).

Genetic Basis of Aortic Valve Stenosis

Genetic factors contribute to both congenital and acquired forms of AS. Although most cases occur sporadically, familial clustering and twin studies support a significant heritable component (4). Genetic variants influence valve development during embryogenesis, regulate inflammatory and osteogenic signaling pathways, and modify the rate of calcification throughout adult life.

Bicuspid Aortic Valve

Bicuspid aortic valve is the most common congenital heart defect, occurring in approximately 1–2% of the population (6). Instead of three cusps, the valve has only two, resulting in abnormal blood flow patterns and increased mechanical stress on the valve leaflets. These altered hemodynamic forces accelerate fibrosis and calcification, leading to AS at a younger age than in patients with tricuspid valves (7).

BAV demonstrates an autosomal dominant pattern of inheritance with incomplete penetrance and variable expressivity, indicating that multiple genes and environmental factors contribute to its development (11). Approximately 20–30% of first-degree relatives of affected individuals have some form of cardiovascular abnormality, supporting the importance of family screening (11).

NOTCH1

The NOTCH1 gene is the best-characterized genetic determinant of BAV and inherited AS. In 2005, Garg and colleagues identified NOTCH1 mutations in families with autosomal dominant aortic valve disease and severe valve calcification (8). NOTCH1 plays a crucial role during cardiac development by regulating endothelial-to-mesenchymal transition and valvular morphogenesis.

In adults, NOTCH1 signaling inhibits osteogenic differentiation of valvular interstitial cells. Loss-of-function mutations reduce this inhibitory effect, allowing increased expression of osteogenic transcription factors such as RUNX2, ultimately promoting pathological calcification of the valve (5,8). Although pathogenic NOTCH1 variants account for only a minority of BAV cases, they represent one of the strongest examples of a direct genetic cause of AS.

SMAD6 and Bone Morphogenetic Protein Signaling

Another important gene implicated in bicuspid aortic valve (BAV) and aortic valve disease is SMAD6, which encodes an intracellular inhibitor of bone morphogenetic protein (BMP) signaling. BMP pathways play a critical role in embryonic valve development and later contribute to pathological calcification through activation of osteogenic pathways (12).

Variants in SMAD6 have been identified in patients with BAV, aortic valve calcification, and associated thoracic aortic aneurysm. Loss of SMAD6 function results in excessive BMP activity, promoting differentiation of valvular interstitial cells into osteoblast-like cells and accelerating calcium deposition within valve tissue (12). These findings highlight the importance of developmental signaling pathways in both congenital valve abnormalities and adult-onset calcific disease. The relationship between SMAD6 mutations and AS also demonstrates the overlap between congenital and degenerative forms of valve disease. Abnormal valve formation during fetal development may create a substrate that predisposes individuals to accelerated calcification decades later.

GATA5 and Other Developmental Genes

The transcription factor GATA5 is essential for cardiac development and regulation of genes involved in valve formation. Experimental studies have demonstrated that disruption of GATA5 expression can interfere with normal valve morphogenesis and contribute to congenital valve abnormalities (13).

Although mutations in GATA5 are relatively uncommon, several studies have identified variants in individuals with BAV and familial aortic valve disease. These findings support the concept that AS is genetically heterogeneous, with multiple genes contributing to abnormal valve development and later calcification.

Other developmental genes, including NKX2-5, ROBO4, and ACTA2, have also been associated with congenital aortic valve abnormalities and thoracic aortic disease (14). However, their contribution to isolated AS appears limited compared with NOTCH1 and SMAD6. The identification of these genes has improved understanding of cardiac embryogenesis and provided insight into why some individuals develop severe disease at a young age.

Genome-Wide Association Studies and Common Genetic Variants

While rare mutations explain some familial cases of AS, most cases are likely caused by the combined effects of multiple common genetic variants. Genome-wide association studies (GWAS) have identified several genetic loci associated with calcific aortic valve disease susceptibility and progression.

One of the strongest and most consistently replicated associations involves the LPA gene, which encodes apolipoprotein(a), a major component of lipoprotein(a) [Lp(a)] (9). Elevated plasma Lp(a) levels are genetically determined and have been associated with increased risk of aortic valve calcification and clinically significant AS.

Lp(a) contributes to valve calcification through several mechanisms. It transports oxidized phospholipids into the valve tissue, promoting inflammation and stimulating osteogenic differentiation of valvular interstitial cells (9). Unlike traditional cardiovascular risk factors, Lp(a)-associated risk appears to be particularly relevant for calcific valve disease. The discovery of the LPA-AS association has important therapeutic implications. Novel therapies targeting Lp(a), including antisense oligonucleotides and small interfering RNA-based treatments, are currently being investigated as potential strategies to prevent or slow progression of calcific AS.

Another important susceptibility locus identified through GWAS is PALMD (palmdelphin), which is involved in cytoskeletal organization and extracellular matrix regulation within valvular cells. Variants in PALMD have been associated with increased risk of aortic valve calcification, supporting the role of cellular remodeling pathways in disease development (15).

Other identified loci include genes involved in inflammatory regulation, lipid metabolism, and calcium signaling. Together, these findings indicate that AS is a complex polygenic disorder in which numerous genetic variants interact with environmental factors and aging processes.

Genetic Syndromes Associated with Aortic Valve Stenosis

Although most AS occurs as an isolated condition, several inherited syndromes are associated with increased risk of aortic valve abnormalities. These disorders provide important insights into the molecular pathways involved in valve development and connective tissue integrity.

Turner Syndrome

Turner syndrome is a chromosomal disorder caused by complete or partial absence of one X chromosome. Cardiovascular abnormalities are among the most important clinical features of this condition, with BAV occurring in approximately 25–30% of affected individuals (16).

Patients with Turner syndrome have an increased risk of progressive aortic valve dysfunction, aortic dilation, and aortic dissection. Because of this increased cardiovascular risk, lifelong cardiac surveillance with imaging is recommended. The

association between Turner syndrome and BAV demonstrates the importance of genetic factors beyond individual gene mutations.

Williams-Beuren Syndrome

Williams-Beuren syndrome results from a deletion of chromosome 7q11.23 involving the ELN gene, which encodes elastin. The classic cardiovascular abnormality in this syndrome is supravalvular aortic stenosis caused by reduced elastin production and abnormal arterial wall structure (17).

Although supravalvular stenosis differs anatomically from valvular AS, Williams syndrome illustrates how abnormalities in extracellular matrix proteins can influence the structure and function of the aortic outflow tract.

Marfan Syndrome and Loeys-Dietz Syndrome

Marfan syndrome is caused by mutations in FBN1, encoding fibrillin-1, a structural component of connective tissue. The major cardiovascular manifestation is dilation of the ascending aorta, although mitral and occasionally aortic valve abnormalities may occur (18).

Loeys-Dietz syndrome, caused by mutations affecting the transforming growth factor- β (TGF- β) signaling pathway, including TGFBR1, TGFBR2, and related genes, is characterized by aggressive aortic disease and congenital cardiovascular abnormalities. While valve stenosis is not the primary manifestation, abnormalities in developmental signaling pathways demonstrate the close relationship between genetic regulation of the aorta and cardiac valves.

Clinical Implications of Genetic Findings

The identification of genetic contributors to AS has several important clinical applications. Patients with early-onset AS, BAV, associated aortopathy, or a strong family history of congenital heart disease may benefit from genetic evaluation and screening of first-degree relatives (11).

Echocardiographic screening of relatives of patients with BAV is increasingly recommended because early identification of valve abnormalities and aortic enlargement allows appropriate monitoring and preventive management.

Genetic information may also contribute to future precision medicine approaches. Current treatment of severe AS remains based mainly on surgical or transcatheter valve replacement, as no pharmacological therapy has yet been proven to halt disease progression (1,2). However, improved understanding of pathways involving NOTCH signaling, Lp(a) metabolism, inflammation, and osteogenic transformation may lead to disease-modifying therapies.

Future Perspectives

The increasing understanding of the genetic mechanisms involved in aortic valve stenosis (AS) has changed the perception of the disease from a simple age-related degenerative process to a complex disorder influenced by genetic, molecular, and environmental factors. Future research will likely focus on identifying individuals at increased genetic risk before the development of severe valve obstruction and on developing therapies capable of modifying disease progression.

One important area of investigation is the development of genotype-based risk stratification. Patients with bicuspid aortic valve (BAV), pathogenic variants in genes such as NOTCH1 or SMAD6, or elevated genetically determined lipoprotein(a) [Lp(a)] levels may represent groups requiring closer surveillance and earlier intervention. Integration of genetic information with imaging biomarkers and clinical parameters may improve prediction of disease progression (11,15).

Another promising field is the development of targeted pharmacological therapies. Despite extensive research, no medication has yet demonstrated the ability to reliably prevent or reverse established calcific aortic stenosis. Statins, despite their beneficial effects in atherosclerotic disease, have failed to significantly slow AS progression in clinical trials, suggesting that alternative pathways are involved (19). Current investigations focus on therapies targeting Lp(a), inflammation, osteogenic signaling, and molecular pathways involved in valve calcification.

Lp(a)-lowering therapies represent one of the most promising approaches because genetic studies have provided strong evidence linking elevated Lp(a) levels with calcific AS. Novel RNA-based therapies capable of markedly reducing Lp(a) concentrations may determine whether modification of this pathway can delay or prevent progression of valve calcification (9).

Furthermore, advances in genomic sequencing technologies may allow identification of additional rare variants responsible for familial disease. Combining genomic data with transcriptomic and epigenetic analyses may provide a more complete understanding of the molecular events leading to valve fibrosis and calcification.

CONCLUSION

Aortic valve stenosis is a complex cardiovascular disorder in which genetic susceptibility interacts with aging and environmental risk factors. Although degenerative calcification remains the predominant cause of AS in elderly individuals, genetic factors play a crucial role in congenital valve abnormalities, early disease onset, and progression.

Bicuspid aortic valve represents the most important inherited predisposition to AS, with mutations affecting developmental pathways such as NOTCH1, SMAD6, and GATA5 contributing to abnormal valve formation and accelerated calcification.

Recognition of the genetic basis of AS has important clinical implications, including improved family screening, earlier identification of high-risk individuals, and future development of personalized therapies. Continued research into genetic, molecular, and epigenetic mechanisms may ultimately transform management from treatment of advanced valve obstruction to prevention and modification of disease progression.

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