Bicuspid Aortic Valve: Genetic and Clinical Insights

Idit Tessler, MD, MPH1,2,3 Juliette Albuisson, MD, PhD4 Guillaume Goudot, MD5
Shai Carmi, PhD2,3 Shoshana Shpitzen, MSc1 Emmanuel Messas, MD5 Dan Gilon, MD1,2
Ronen Durst, MD1,2

1 Department of Cardiology, Hadassah Medical Center, Jerusalem, Israel
2 Faculty of Medicine, The Hebrew University, Jerusalem, Israel
3 Braun School of Public Health and Community Medicine, The Hebrew University of Jerusalem, Jerusalem, Israel
4 Oncogenetics laboratory, Centre George François Leclerc, Dijon, France
5 Cardiovascular Department, Georges Pompidou European Hospital, Paris, France

Address for correspondence Idit Tessler, MD, MPH, Department of Cardiology, Hadassah Hebrew University Medical Center, Jerusalem, 91120, POB 12000, Israel (e-mail: idit.tessler@gmail.com).

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Abstract

Bicuspid aortic valve (BAV) is the most common valvular congenital heart disease, with a prevalence of 0.5 to 2% in the general population. Patients with BAV are at risk for developing cardiovascular complications, some of which are life-threatening. BAV has a wide spectrum of clinical presentations, ranging from silent malformation to severe and even fatal cardiac events. Despite the significant burden on both the patients and the health systems, data are limited regarding pathophysiology, risk factors, and genetics. Family studies indicate that BAV is highly heritable, with autosomal dominant inheritance, incomplete penetrance, variable expressivity, and male predominance. Owing to its complex genetic model, including high genetic heterogeneity, only a few genes were identified in association with BAV, while the majority of BAV genetics remains obscure. Here, we review the different forms of BAV and the current data regarding its genetics. Given the clear heritability of BAV with the potential high impact on clinical outcome, the clinical value and cost effectiveness of cascade screening are discussed.

Keywords

► bicuspid aortic valve
► genetics
► congenital heart disease
► thoracic aortic aneurysm
► aortic dissection

Introduction

Bicuspid aortic valve (BAV) is the most common valvular congenital heart disease, with a prevalence of 0.5 to 2% in the general population.1 BAV was first described more than 500 years ago by Leonardo da Vinci, illustrating the valve anatomy. Since data on BAV clinical significance have been established, a substantial proportion of aortic valve diseases were found to be due to BAV, regardless of a patient’s age.2 Patients with BAV have an increased risk of developing aortic valve diseases such as calcification and stenosis, regurgitation, and infective endocarditis. Aortopathies are also prevalent among BAV patients. These include coarctation of the aorta, aortic aneurysm, and dissection. BAV patients are prone to require aortic valve replacement (AVR) and aortic surgery, procedures that carry substantial risks and costs.3 Population-based studies have found a 53% risk for AVR and a 25% risk for aortic surgery during 25-year follow-up, and the risk for aortic dissection was eight times higher than in the general population.4 Moreover, the mean age for valve replacement or surgical intervention for aortic dilation is markedly younger for BAV patients compared with patients with tricuspid aortic valve.2,4 BAV was estimated to cause more morbidity and mortality than the combination of all other congenital heart defects, generating a considerable health burden to both patients and the health system.5

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Bicuspid Aortic Valve can be classified as sporadic BAV (sporadic isolated defect), familial nonsyndromic BAV (nsBAV; in clusters within families without associated anomaly), or syndromic BAV (considered familial and associated with other anomalies including cardiovascular defects). The method of choice for diagnosis and follow-up is echocardiography (Fig. 1).

BAV clinical presentation varies significantly from a silent disease to severe life-threatening complications, even at a young age. Little is known about most dimensions of BAV, including the identity of the biochemical pathways involved in its pathogenesis. The determinants of the valve morphology and of the wide spectrum of clinical presentations and complications over time are mostly unelucidated.

Genetic data provide a very powerful and unbiased tool for understanding the basic mechanisms culminating in valve dysfunction and disease. Better understanding of the molecular processes of the disease may lead to future development of novel personalized management approaches, ultimately leading to individual risk stratification, sparing unnecessary interventions to low-risk patients, and preventing potentially fatal complications for patients at high risk.

Here, we summarize the current data regarding BAV genetics and discuss its potential clinical implication.

Bicuspid Aortic Valve Genetics: Many Links Yet an Unsolved Riddle

It is well established that BAV has a significant genetic component. Various studies demonstrated familial clustering of BAV. The prevalence of BAV was found to be 10-fold higher among first-degree relatives of an affected individual compared with the general population. In family studies, the heritability index for BAV, representing the degree of phenotypic variance explained by inherited rather than environmental factors, was found to be as high as 89%, suggesting marked involvement of genetic factors on disease development. Among familial BAV, most pedigrees suggest an autosomal-dominant inheritance pattern with incomplete penetrance and male predominance in a 3:1 ratio (Fig. 2). According to Mendelian genetics, autosomal-dominant inheritance pattern implies that half of first-degree relatives are expected to carry the disease-causing allele. Accounting for 50% penetrance (i.e., half of the carriers will demonstrate clinical disease), 25% of first-degree relatives are expected to be clinically affected with BAV. However, the actual rate of BAV among first-degree relatives in family studies ranges from 6 to 30%. This large range, along with the wide spectrum of structural and clinical phenotypes, is thought to be the result of the complexity of the developmental mechanisms at play in aortic valve development, involving genetic, epigenetic, and environmental factors (Fig. 3).

A high prevalence rate of aortopathies, including aneurysm, dissection, and aortic coarctation, has been demonstrated among BAV patients and their relatives. Both the aortic root and the aortic valve have the same embryologic origin: the cardiac neural crest and the second heart field. Thoracic aortic aneurysm (TAA) frequently affects patients with BAV, or their first-degree relatives with a morphologically normal valve. TAA and BAV are thus thought to have a common genetic etiology. This observation adds support to the concept that BAV does not represent a dichotomous phenotype but would rather be integrated in a continuous spectrum of phenotypic expressions.

Nonsyndromic Bicuspid Aortic Valve Genetics

Since 2005, with the identification of NOTCH1 in nsBAV cases, few other genes were found to be associated with nsBAV with varying degrees of supporting evidence (Table 1). Each of these genes explains only a small percentage of the overall nsBAV prevalence and involves different molecular pathways that do not necessarily assemble into one common mechanism. In light of its high phenotypic and genotypic heterogeneity, establishing a genetic causality for BAV is challenging. Causality can only be determined when the mutation has a robust effect, the familial segregation and linkage analyses are strong, and when the association is supported by experimental and functional models.

NOTCH pathway: the first and currently single gene considered definitively causal for nsBAV is NOTCH1. NOTCH1 signaling is a highly conserved pathway of signal transduction, leading to transcription of endothelial and vascular smooth muscle cells. Altered NOTCH signaling is a well-known cause of human cardiovascular disease.

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**Fig. 1** Transthoracic echocardiogram of bicuspid aortic valve (BAV), short axis view. (A) Diastolic image demonstrating a raphe that may mimic tricuspid valve. (B) Systolic image demonstrating only two leaflets with elliptical opening pattern. Morphology assessment of BAV must include systolic imaging, as diastolic imaging may be misleading.

**Fig. 2** Transthoracic echocardiogram of bicuspid aortic valve (BAV), short axis view. (A) Systolic image demonstrating only two leaflets with elliptical opening pattern. Morphology assessment of BAV must include systolic imaging, as diastolic imaging may be misleading.

**Fig. 3** Transthoracic echocardiogram of bicuspid aortic valve (BAV), short axis view. (A) Diastolic image demonstrating a raphe that may mimic tricuspid valve. (B) Systolic image demonstrating only two leaflets with elliptical opening pattern. Morphology assessment of BAV must include systolic imaging, as diastolic imaging may be misleading.
Fig. 2 Examples of bicuspid aortic valve pedigrees, consistent with autosomal dominant inheritance, and low penetrance, as reflected by the limited number of clinically affected individuals.

Fig. 3 Illustration of the underlying process in bicuspid aortic valve (BAV) development. Involvement of one or more genes is the primary insult. This might be modulated by epigenetic factors, such as chromatin modifications and DNA methylation affecting genetic regulatory elements. Environmental factors, such as longstanding abnormal blood flow and hypertension, may also contribute to BAV outcome. The epigenetics illustration was modified from the ENCODE portal (https://www.encodeproject.org).
genetic variants were demonstrated to be associated with the development of calcific aortic valve stenosis, with or without BAV. Yet, this gene is estimated to be involved in only approximately 5 to 10% of nBAV cases, leaving the vast majority of the genetic causes of BAV unexplained. Other members of the NOTCH1 pathway (►Fig. 4) were linked to BAV and to other left-ventricular outflow tract obstruction pathologies, including mastermind-like transcriptional coactivator 1 (MAML1), rho GTPase activating protein 31 (ARHGAP31), jumonji and AT-rich interaction domain containing 2 (JARID2), and SWI/SNF-related matrix-associated actin-dependent regulator of chromatin, subfamily A, member 4 (SMARCA4).\textsuperscript{12}

**TGF-β Pathway:** The SMAD family member 6 (SMAD6) gene encodes a signal transduction protein highly expressed in the embryonic heart and involved in many pathways, including transforming growth factor beta (TGF-β). This pathway plays a key role in vascular matrix remodeling and was linked to connective tissue disorders (►Fig. 4). The association of SMAD6 with BAV was shown by targeted resequencing.**

**Table 1 Main genes associated with bicuspid aortic valve**

<table>
<thead>
<tr>
<th>Humans genes</th>
<th>Genetic approach</th>
<th>Mouse genes</th>
<th>Prevalence of BAV (%)</th>
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</thead>
<tbody>
<tr>
<td>NOTCH1\textsuperscript{11}</td>
<td>Linkage analysis</td>
<td>Acvr1/Alk1\textsuperscript{36}</td>
<td>78–83</td>
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<td>GATA4\textsuperscript{19}</td>
<td>Genome-wide association study</td>
<td>Gata5\textsuperscript{18}</td>
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<td>Target gene sequencing</td>
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<td>Family study</td>
<td>Matr3\textsuperscript{47}</td>
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<tr>
<td>NKX2–5\textsuperscript{22}</td>
<td>Family study</td>
<td>Nkx2–5\textsuperscript{35}</td>
<td>2–20</td>
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<tr>
<td>TBX20\textsuperscript{14}</td>
<td>Copy number variation analysis</td>
<td>Nos3\textsuperscript{32}</td>
<td>42</td>
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<tr>
<td>SMAD6\textsuperscript{13}</td>
<td>Candidate gene resequencing</td>
<td>Robo1/Robo2\textsuperscript{33}</td>
<td>100</td>
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<tr>
<td>ROBO4\textsuperscript{24}</td>
<td>Family study (whole exome sequencing)</td>
<td>Robo4\textsuperscript{24}</td>
<td>15</td>
</tr>
</tbody>
</table>

Abbreviation: BAV, bicuspid aortic valve.

**Fig. 4** Bicuspid aortic valve (BAV)–associated pathways. (A) NOTCH pathway. A graphical representation of NOTCH pathway activation: (1) NOTCH receptor extracellular domain binds to its ligand’s extracellular domain; (2) Notch ligand ubiquitination allowing endocytosis of the ligand in the signal-sending cell; (3) then, the notch receptor undergoes sequential proteolytic cleavages that result in the release of the Notch intracellular domain (NICD) and the notch extracellular domain; and (4) the NICD translocates to the nucleus and acts as a transcriptional regulator. *Genes associated with BAV: MIB1 KO mice developed; JAG1 was associated with BAV in family and mice studies; Variants in SMARCA4, JARID2 and MAML were identified in familial BAV. (B) TGF-β signaling pathway. The interaction between the TGF-β signaling pathway and the SMAD proteins: (1) TGF-β binding to its receptors triggering the signaling activation in the receiving cell; among others modifiers, the signal transduction is regulated by the SMAD proteins, while SMAD6 functions as the negative regulator; and (3) nuclear regulation affects cell proliferation, differentiation and growth. JARID2, jumonji and AT-rich interaction domain containing 2; MAML, mastermind-like transcriptional coactivator; MIB1, mindbomb 1 SMARCA4, SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily A, member 4; TGF-β, transforming growth factor beta 1. Image modified from Guo et al.\textsuperscript{98}
resequencing of individuals with BAV and TAA, contributing to the development of BAV/TAA in 2.5% of the cases. Recently, T-box transcription factor 20 (TBX20) was identified as a possible contributing gene for BAV using copy number variation analysis, explaining 1% of the BAV/TAA cases. This gene was found to be related to SMAD6 in in vivo studies, and was described in association to other congenital cardiac malformations. Of note, other components of the TGF-β pathway (TGFB2, TGFB-3, TGFB-R1, TGFB-R2, and SMAD3) are involved in syndromic aortopathies where BAV is present in 5 to 30% of the cases.

The GATA family: GATA binding protein genes encode zinc-finger transcription factors that play a role in heart valve differentiation. GATA4 was recently identified as a predisposing gene for BAV in a human genome-wide association study (GWAS) involving 466 BAV cases and 4,660 controls, with odds ratios ranging from 1.4 to 2.4 depending on the variant. Rare variants of the GATA5 gene, highly expressed in the endocardium, were also linked to nsBAV, although these results have not been consolidated in subsequent studies. A GATA6 disruptive variant was found in an nsBAV family, and in vitro studies demonstrated that GATA6 haploinsufficiency interrupts the aortic valve remodeling and extracellular matrix composition. Loss-of-function mutations in the NK2 Homeobox 5 (NKX2.5) gene, which encodes a homeodomain-containing transcription factor that is involved in the aortic valve development, was found in a nsBAV family to disrupt the interaction between NKX2.5 and GATA5, supporting involvement of both genes in the pathology.

The roundabout guidance receptor 4 (ROBO4) gene is involved in endothelial function. Rare variants in the gene were identified by whole exome sequencing in a BAV/TAA family study.

Genetic loci linked to BAV: linkage analyses demonstrated the involvement of human chromosomal regions 18q, 5q, and 13q in BAV alone, and between BAV/TAA and human chromosomal regions 15q25–26, suggesting that unelucidated genetic defects remain to be investigated.

### Syndromic Bicuspid Aortic Valve Genetics

BAV can be syndromic, that is, presenting within a constellation of cardiac and noncardiac anomalies. The highest occurrence of BAV is found in Turner’s syndrome. Turner’s syndrome results from complete or partial missing of one X chromosome (45X). This leads to a complex developmental disorder, including cardiovascular anomalies. BAV occurs in 15 to 30% of patients and often coexists with coarctation of the aorta. The high prevalence of BAV in Turner’s syndrome may be related to high diagnostic rate due to routine cardiac imaging performed in these patients, but may also suggest X-chromosome involvement in BAV formation. This is also supported by the 3:1 male predominance found in BAV, leading to the hypothesis that X chromosome gene hemizygosity (i.e., having one copy only) is involved in BAV development.

Marfan’s syndrome (MFS) is a rather common connective tissue disorder manifesting by aortic root dilation among other phenomena. BAV was initially considered more prevalent than in the general population. A recent larger study that included more than 1,400 MFS cases, has demonstrated that the prevalence of BAV was 1.8%, equivalent to the population prevalence. However, BAV presentation in MFS was associated with a more severe aortic aneurysm phenotype necessitating repair at an earlier age.

Loeys–Dietz syndromes are a group of connective tissue disorders close to MFS. These syndromic aortopathies are the consequence of abnormal TGF-β signaling, and association with BAV was demonstrated.

As illustrated here, the frequent cooccurrence of BAV and aortic aneurysms in nsBAV and in sporadic BAV, is also the rule in syndromic BAV, supporting the hypothesis that disruption of connective tissue homeostasis is related with BAV.

BAV was also described in Shone complex, a syndrome of multiple left heart obstructive lesions. Like nsBAV, it was also associated with NOTCH1 mutations.

### Animal Models

Animal models may serve as an additional approach for understanding BAV genetics and pathophysiology. There are several mouse and Syrian hamster models for BAV, some of which were developed to support candidate genes found in humans. Of note, similarly to family studies in humans, all animal models have demonstrated incomplete penetrance and, in most cases, presented with other cardiac malformations. In some, male predominance was also observed. The main human and mouse genes involved in BAV are listed in Table 1.

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genetic origin</th>
<th>Prevalence of BAV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turner’s syndrome</td>
<td>Monosomy X</td>
<td>15–30</td>
</tr>
<tr>
<td>Marfan’s syndrome</td>
<td>FBN1</td>
<td>1.8</td>
</tr>
<tr>
<td>Loeys–Dietz syndromes</td>
<td>TGF-β pathway</td>
<td>10–30</td>
</tr>
<tr>
<td>Shone’s complex</td>
<td>NOTCH1</td>
<td>50</td>
</tr>
<tr>
<td>Andersen’s syndrome</td>
<td>KCNJ2</td>
<td>10^4</td>
</tr>
</tbody>
</table>

A total of 10% genotype-positive family member presented with BAV.
null
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References


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association task force on practice guidelines. Circulation 2014; 129(23):2440–2492


46 Laforest B, Nemer M. GATA5 interacts with GATA4 and GATA6 in outflow tract development. Dev Biol 2011;358(02):368–378
