Bicuspid aortic valve (BAV) is a heterogeneous disease with variable phenotypes encompassing valvular disease and aortopathy. Although a majority of BAV patients are non-syndromic and have isolated BAV disease, it can also occur as a feature of certain genetic syndromes such as Turner syndrome. The genetic architecture of BAV is also complex and multifactorial with reduced penetrance and variable expressivity among families (1). Unlike most Mendelian type disorders, where single gene may cause the disease, BAV seems to be caused or affected by multiple genes in association with the environmental and epigenetic factors (1,2). Due to the complex polygenic and multifactorial nature of BAV, the genetics of BAV still largely remain unraveled.

The study by Zhao et al. (3) describes a potential association of MYBPC3 (myosin binding protein C) with BAV. They have reported heterozygous mutation (Ala58Val) of MYBPC3 (c.173 C>T) in a BAV pedigree consisting of an 11-year-old proband and her affected father (described as aortic stenosis but not defined as a BAV) while the mother was unaffected and negative for mutation. The proband's echocardiogram does demonstrate a BAV with right and non-coronary cusp fusion. The major limitation of this study is the absence of experimental validation of this mutation. However, authors have vigorously attempted to counter this limitation by utilizing systematic bioinformatics and protein modeling assays that demonstrated reduced stability of MYBPC3 protein with this reported mutation. Moreover, they have also reported the expression of MYBPC3 mutation in the family, demonstrating that the levels of mRNA and MYBPC3 protein in the proband and affected father were almost half as compared to the unaffected mother who was negative for the mutation.

The MYBPC3 gene has primarily been described among patients with hypertrophic cardiomypathy (4) in addition to left ventricular non-compaction (5) and dilated cardiomyopathy (6). The relationship to structural valve disease is not as easily explained. Although it has not been previously linked to BAV, recently emerging evidence has suggested some potential associations. Notably, Theis et al. (7) recently described a pathogenic MYBPC3 nonsense variant in a three generational family of a proband with hypoplastic left heart syndrome, father with left ventricular non-compaction, and two fourth-degree relatives with hypertrophic cardiomyopathy. Interestingly, the brother of this proband, who did not have genetic data available, had died during infancy from complications related to BAV, coarctation of the aorta and mild hypoplasia of left ventricle. Unfortunately, the lack of genetic or pathologic studies in this sibling leaves this observation only open to speculation.

Therefore, the reports by Theis et al. and Zhao et al. suggest a rare but potential role of MYBPC3 in the structural left heart lesions like BAV that needs to be further validated and studied in experimental models.

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Footnote

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