



Is there a genetic basis to the different morphological subtypes of bicuspid aortic valve?

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Comment on: Gharibeh L, Komati H, Bossé Y, *et al.* GATA6 regulates aortic valve remodeling, and its haploinsufficiency leads to right-left type bicuspid aortic valve. *Circulation* 2018;138:1025-38.

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Bicuspid aortic valve (BAV) is one of the most common congenital heart defects leading to a significant global financial health burden as a result of its complications (1). BAV can lead to premature aortic valve disease in the form of aortic valve stenosis or regurgitation requiring multitude of interventions on aortic valve, including transcatheter interventions or surgical valve replacement. BAV disease is a continuum of disease process that not only affects the aortic valve but also extends to the thoracic aorta leading to dilatation with risk of aortic aneurysm and dissection. Even though the impacts of BAV are far and wide spread and despite decades of research and investigation, we still lack a clear understanding of the genetic and molecular pathophysiology of BAV (2).

The study by Gharibeh *et al.* describes the role of GATA6 in regulation of aortic valve remodeling as a novel cellular and molecular mechanism underlying BAV (3). This is a very well-orchestrated study in which authors analyzed *GATA6* gene variants in 452 BAV cases and 1,849 controls from Framingham GWAS study. Authors also delved into the expression of GATA6; GATA6 haploinsufficiency leads to reduced levels of tissue inhibitor of metalloproteinase 1 (TIMP1), fibrillin 1 (FBN1), and Versican (VCAN), which play an important role in the integrity of extracellular matrix and could be a potential pathophysiological mechanism of abnormal valvulogenesis in BAV. Moreover, GATA6 haploinsufficiency also leads to an abnormal apoptosis and

thus abnormal valve remodeling.

The GATA family of zinc-finger transcription factors plays an essential role in cardiac embryogenesis especially GATA4, GATA5 and GATA6. They are expressed in the endocardial cushions, outflow tract and cardiac neural crest cells which are important in development of aortic valve. Variants with GATA5 and GATA6 have been observed in patients with BAV and indirectly provide a link to BAV formation (4). Interestingly all the BAVs in this study by Gharibeh *et al.* were RL in morphology, which leads to a strong association of GATA6 mutation with RL cusp fusion. In prior studies, Laforest *et al.* have demonstrated the association of GATA5 with RN cusp fusion morphology; where they generated GATA5 null mice models that showed a partial penetrance of BAV and all these cases of BAV demonstrated RN cusp fusion (5). This highly supports the idea of distinct genetic differences among the morphological subtypes of BAV possibly leading to variations in the developmental pathway of aortic valve formation. In order to comprehend these differences, we need to understand the embryogenesis of BAV and its morphological subtypes. The right and left cusps of aortic valve arise from the conotruncal cushions of outflow tract, while the non-coronary (LN) cusp arises from the right-posterior and left-anterior intercalated cushions of the outflow tract (4,6). Some recently published studies in mice and Syrian hamster also suggested that BAV with RN cusp

fusion results from defective development of the outflow tract cushions, while BAV with RL cusp fusion possibly results from abnormal septation of proximal outflow tract region (7,8). Therefore, morphological phenotypes of BAV may have distinct embryological origins.

Authors in this study also evaluated cardiac neural crest cell dysregulation which was normally regulated in *GATA6* haploinsufficient mice. Although this does not seem to be a mechanism in BAV with RL morphology, it could still be a potential mechanism of abnormal valvulogenesis in BAV with RN morphology. Recently Odelin *et al.* reported the loss of *Krox20* function, which has been implicated in cardiac neural crest cells regulation, resulting in partially penetrant BAV in *Krox20*^{-/-} mice. Interestingly, the phenotype of BAV in *Krox20*^{-/-} mice was either RN or left non-coronary (LN) cusp fusion. RN cusp fusion is also reported in patients with Down syndrome and atrioventricular septal defects, which is mainly caused by dysregulation of neural crest cells and may provide an indirect association (6). Considering the association of *GATA5* with RN cusp fusion, it will be valuable to examine cardiac neural crest cell dysregulation in *GATA5* haploinsufficient or null mice which could be another potential pathophysiological mechanism of abnormal valve formation in BAV with RN morphology (5,9).

Authors further validated the study by looking at the variants within the *GATA6* gene in human subjects which although did not reach the locus wide significance but showed a decreased expression of *GATA6* in valves and aorta of individuals with BAV in comparison to tricuspid aortic valves. We congratulate the authors on excellent study and development of an animal model which opens up the doors for further investigations, not only related to aortic valve but also aortopathy.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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