Protein-altering and regulatory genetic variants near GATA4 implicated in bicuspid aortic valve

Bicuspid aortic valve (BAV) is a heritable congenital heart defect and an important risk factor for valvulopathy and aortopathy. Here we report a genome-wide association scan of 466 BAV cases and 4,660 age, sex and ethnicity-matched controls with replication in up to 1,326 cases and 8,103 controls. We identify association with a noncoding variant 151 kb from the gene encoding the cardiac-specific transcription factor, GATA4, and near-significance for p.Ser377Gly in GATA4. GATA4 was interrupted by CRISPR-Cas9 in induced pluripotent stem cells from healthy donors. The disruption of GATA4 significantly impaired the transition from endothelial cells into mesenchymal cells, a critical step in heart valve development.