Direct Inspection of Primary Aortic Cell Transcriptomes Identifies Candidate Causative Variants in Patients with Thoracic Aortic Aneurysm

Alexa V. Mederos[1], Benjamin J. Landis[1, 2]

[1]Indiana University School of Medicine; [2]Departments of Pediatrics and Medical and Molecular Genetics

Background: Thoracic aortic aneurysm (TAA) is an aortopathy that predisposes to life-threatening aortic dissection. Autosomal dominant disorders associated with TAA include Marfan syndrome (*FBN1*), Loeys-Dietz syndrome (*TGFBR1/2*, *SMAD3*, *TGFB2*), and vascular type Ehlers-Danlos syndrome (*COL3A1*). Our objective was to identify single nucleotide variants (SNVs) in these six genes within the transcriptomes of primary aortic cells acquired from patients with aortopathy.

Methods: Primary aortic cell lines were cultured directly from the medial layer of surgically explanted aortic tissues in 63 unrelated aortopathy patients. RNA samples were extracted from aortic cells for mRNA sequencing. RNA reads aligning to the 6 selected TAA genes were directly inspected using Integrative Genomics Viewer (Broad Institute), and the identified SNVs were filtered for downstream analysis.

Results: Study patients were predominantly male and of European ancestry with a mean age of 52±18 years. Thirty-three (52%) patients had a bicuspid aortic valve, and 10 (16%) had family history of TAA or dissection. A total of 3740 SNVs were identified in patient transcriptomes, and these occurred at 905 distinct genomic coordinates. There were 115 SNVs that were unique within the cohort, not located within a 3'-untranslated region, and had ≥20 aligned reads at the SNV's position. Using the application Franklin (Genoox) to estimate clinical interpretation, 8 unique SNVs were classified as pathogenic (P) or likely pathogenic (LP). Five of these P/LP SNVs were associated with reduced allelic expression, and gene expression level was below the 20th percentile of study samples for 6 P/LP SNVs. Eighty-six unique SNVs were classified as variants of uncertain significance (VUSs). A total of 39 patients (62%) had at least one SNV classified as P/LP/VUS.

Conclusion: Transcriptomic analysis of primary aortic cells identified candidate causative SNVs and their relative allelic expression. Further analyses will investigate additional TAA-associated genes and integrate transcriptional abnormalities with genetic variants.