Cardiovascular Genetics: A News Round Up

Transforming Growth factor β2 Mutations and Familial Thoracic Aortic Aneurysms

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Study Hypothesis

Previous genetic studies of patients with thoracic aortic aneurysms have identified mutations in several genes involved in some way with transforming growth factor (TGF)-β signaling: FBN1 (encoding fibrillin-1, causing Marfan syndrome), TGFBRI and TGFBRII (encoding transforming growth factor-β receptors I and II, causing Loeys-Dietz syndrome), and SMAD3 (encoding Mothers against decapentaplegic homolog 3, causing aneurysms-osteoarthritis syndrome). Two groups (Boileau et al, Lindsay et al) sought to identify additional genes responsible for familial thoracic aortic aneurysms. They also sought to explain an apparent paradox: mutations in the aforementioned genes that would be predicted to result in reduced activity of the TGF-β pathway appear to cause vasculopathy via increased TGF-β signaling.

How Was the Hypothesis Tested?

Both groups started by identifying families with autosomal dominant transmission of thoracic aortic aneurysms and in whom mutations in FBN1, TGFBRI, TGFBRII, and SMAD3 had been ruled out. Each used modern genetic techniques to identify the presumptive causal gene mutations responsible for thoracic aortic aneurysms in each of the families, followed by resequencing of the implicated gene in unrelated probands to identify additional mutations in the gene to confirm its involvement in vascular disease. The groups then used patient tissues to characterize the effects of the mutations on TGF-β signaling in the human aorta. Lindsay et al extended the work by modeling the effects of the mutant gene in mice and unequivocally demonstrating the link to aortopathy.

Principal Findings

Notably, the 2 groups used different approaches to converge on the same gene. Boileau et al first performed linkage analyses in 2 distinct families (1 in the United States, 1 in France) that displayed autosomal dominant transmission of thoracic aortic aneurysms and found that both shared a modest linkage peak on chromosome 1q41. The investigators then performed exome sequencing of a few judiciously chosen members of each family and found that the only gene harboring rare variants in both families was TGFB2, which happens to be located in the 1q41 locus; there was a frameshift mutation in 1 family, a nonsense mutation in the other. Through resequencing of TGFB2 in unrelated individuals with thoracic aortic aneurysms, they identified an additional 2 heterozygous TGFB2 mutations (a nonsense mutation and a frameshift mutation). Lindsay et al used SNP array analysis in probands from two families and discovered each to harbor a microdeletion on chromosome 1q41, in each case resulting in heterozygous deletion of the entire TGFB2 gene (as well as other genes). With resequencing they identified an additional 6 heterozygous TGFB2 mutations in 6 families with thoracic aortic aneurysms (1 nonsense mutation, 3 missense mutations, 1 frameshift mutation, and 1 in-frame deletion).

Both groups examined aortic tissue from probands and found fragmentation of elastin fibers and deposition of collagen and proteoglycans, similar to what is observed in tissues from Marfan syndrome and Loeys-Dietz syndrome patients. Additionally, they assessed for altered TGF-β signaling, and both groups found evidence for increased signaling as judged by an increase in TGF-β1 or TGF-β2 protein expression and greater nuclear accumulation of phosphorylated SMAD2, despite many of the TGFB2 mutations clearly pointing to loss of gene function (eg, heterozygous deletion of the entire gene). Careful clinical phenotyping of TGFB2 mutation-bearing individuals identified a variety of vascular, musculoskeletal, and other features shared by patients with either Marfan syndrome or Loeys-Dietz syndrome.

Lindsay et al additionally studied TGFB2 heterozygous knockout (TGFB2+/-) mice and found these mice to have aortic root dilatation, consistent with the human disease presentation. Furthermore, the aortic tissue displayed signs of increased TGF-β signaling. Finally, the investigators showed...
that mutant alleles of *TGFB2* and *FBN1* have additive effects on aortic pathology.

**Implications**
The studies are noteworthy because 2 groups were able to use 2 different discovery strategies, followed by validation studies in humans and mice, to successfully identify *TGFB2* as a novel cause of familial aortopathy, adding this gene to the 4 previously characterized genes involved in various clinical syndromes with aortic aneurysms. They also confirmed previous observations that, at first blush, appear to be paradoxical—that aortic disease in these syndromes arises from increased TGF-β signaling despite apparent loss-of-function mutations occurring in genes that positively regulate TGF-β signaling. These studies open the door to future work that will test the hypothesis that compensatory mechanisms instigated by the initial loss of function result in overshoot activation of the TGF-β pathway and, by clarifying the disease pathogenesis, may yield new therapeutic strategies to prevent thoracic aortic aneurysms and other types of vascular disease.

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**Disclosures**
None.
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