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The power of collaboration: a case study on TNXB and it's clinical association

Background/Objectives: Biallelic alterations in TNXB are associated with Ehlers-Danlos, classic type; however, vascular aneurysms and dissections have not previously been associated.

Methods: Clinical exome sequencing at our academic medical center lab identified two TNXB variants in a patient with aortic aneurysm and vertebral artery dissections. A retrospective review of additional research exome sequencing found 5/350 cases with two or more TNXB variants in patients with vascular aneurysms or dissections. To evaluate the strength of this association, replication analysis on a cohort of 1844 individuals who underwent clinical testing for suspicion of vascular aneurysm and dissection syndromes was carried out using data from a diagnostic laboratory.

Results: Only 3/22 diagnostic laboratories identified offered genetic testing for aneurysms and dissections that included TNXB in their analysis due to its association with connective tissue disease. After incorporating data from one laboratory, there was a statistically significant difference ($p<0.01$) ein the presence of two or more TNXB variants between cases and controls, suggesting an expansion of phenotype associated with TNXB.

Conclusion: This project reinforces the value of transparent data sharing, within the confines of privacy regulations, between researchers, clinicians, and laboratories in the identification of candidate genes. It also illuminates the utility of broad panel testing and the lack of standardization of gene panel content between laboratories. The variability of panel content has implications for test selection, as clinicians sort through seemingly similar test offerings to identify the best one for patients.