Pathogenic variants in *THSD4*, encoding the ADAMTS-like 6 protein, predispose to inherited thoracic aortic aneurysm

PURPOSE: Thoracic aortic aneurysm and dissection (TAAD) is a life-threatening disease with often unrecognized inherited forms. We sought to identify novel pathogenic variants associated with autosomal dominant inheritance of TAAD.

METHODS: We analyzed exome sequencing data from 35 French TAAD families and performed next-generation sequencing capture panel of genes in 1114 unrelated TAAD patients. Functional effects of pathogenic variants identified were validated in cell, tissue, and mouse models.

RESULTS: We identified five functional variants in THSD4 of which two heterozygous variants lead to a premature termination codon. THSD4 encodes ADAMTSL6 (member of the ADAMTS/L superfamily), a microfibril-associated protein that promotes fibrillin-1 matrix assembly. The THSD4 variants studied lead to haploinsufficiency or impaired assembly of fibrillin-1 microfibrils. Thsd4+/- mice showed progressive dilation of the thoracic aorta. Histologic examination of aortic samples from a patient carrying a THSD4 variant and from Thsd4+/- mice, revealed typical medial degeneration and diffuse disruption of extracellular matrix.

CONCLUSION: These findings highlight the role of ADAMTSL6 in aortic physiology and TAAD pathogenesis. They will improve TAAD management and help develop new targeted therapies.