Copy Number Variation Contributes to Sporadic and Familial Thoracic Aortic Aneurysms and Dissections

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Study Hypothesis
The genetic origins of thoracic aortic aneurysms and dissections (TAAD) are relatively unknown. Twenty percent of cases have similarly affected family members, but genes previously identified for familial TAAD have exhibited reduced penetrance and variable severity. The genes previously implicated in familial TAAD (ACTA2, MYH11, TGFBR1, TGFBR2) have all been found to be involved in vascular smooth muscle cell (SMC) contractility and adhesion. Copy number variations (CNVs) have been found previously to increase risk of several multifactorial diseases, such as autism and schizophrenia. The authors hypothesized that rare structural variants could contribute to risk of TAAD, and that such variants would be enriched with genes regulating SMC adhesion and contractility.

How Was the Hypothesis Tested?
Four hundred eighteen unrelated cases of sporadic TAAD (TAAD in patients not reporting a family history of vascular disease) were used as the discovery cohort for the sporadic disease; the replication cohort consisted of an additional 387 unrelated individuals with sporadic TAAD. All patients were non-Hispanic, of European descent, and had their condition confirmed by imaging. Patients aged <31 years were excluded because of higher prevalence of Mendelian disorders in this age group. The familial TAAD cohort consisted of 88 affected probands from families with multiple members who did not have a genetic mutation previously identified as the cause of their TAAD. Controls came from 5 publicly available data sets from the Database of Genotypes and Phenotypes and were confined to unrelated individuals of European descent aged >31 years with Illumina genotypes. Genotyping of cases was done using the Illumina HumanCNV370-Quad Bead Chip for the sporadic TAAD samples and the Illumina Human660W-Quad BeadChip for familial TAAD samples.

Principal Findings
In a genome-wide analysis of sporadic TAAD cases, a total of 2063 CNVs in 123 separate chromosomal regions were detected by both calling algorithms. Nine predicted CNV regions of interest were chosen for amplification and validation (involving MYH11, TGFBR1, TGFBR2) and were all found to be involved in vascular smooth muscle cell (SMC) contractility and adhesion. Copy number variations (CNVs) have been found previously to increase risk of several multifactorial diseases, such as autism and schizophrenia. The authors hypothesized that rare structural variants could contribute to risk of TAAD, and that such variants would be enriched with genes regulating SMC adhesion and contractility.

Additional information:
- CNV detection was restricted to 311 803 single-nucleotide polymorphisms that were common to the 370k and 660k platforms. Two algorithms were used for CNV detection: CNVPartition and PennCNV. Genes overlapping with TAAD-associated CNVs were identified with a regional association test in PLINK. To limit findings to rare CNVs, CNVs present in >1% of the samples were excluded from comparative analyses. Validation of identified CNVs was done using comparative genomic hybridization with custom Agilent oligonucleotide arrays. Gene ontology and network analysis were conducted using the GeneGo Meta-Core and Ingenuity Pathways databases.
- In case-control analyses of sporadic TAAD, 47 CNV regions were enriched or unique to the sporadic TAAD discovery patients compared with controls. In the replication cohort, the authors identified 57 rare CNV regions that were associated with sporadic TAAD. Overall, 5 CNV regions (4 gain, 1 loss) involving 31 genes (including MYH11) were present in both the replication and the discovery groups. Other than MYH11, none of the other loci have been previously reported to play a role in TAAD. In case-control analyses of familial TAAD, 20 unique or rare CNV regions (15 gains in base pairs, 5 losses in base pairs) involving 84 genes were identified. The overlap prevalence of rare CNVs was significantly increased in familial TAAD compared to sporadic TAAD (23% versus 13%, P=0.03).
- Gene ontology, expression profiling, and network analysis found that TAAD-associated CNVs were enriched for genes that regulate cell adhesion or the actin cytoskeleton through interaction with the smooth muscle-specific isoforms of actin and myosin. Mutations in the genes encoding these proteins have been previously associated with familial TAAD. Enrichment of genes with these functions was replicated in both the sporadic and familial TAAD discovery patients.
sporadic TAAD replication cohort and the familial TAAD cohort. The authors concluded that the findings support a common underlying mechanism for the pathogenesis of both familial and sporadic TAAD through which any one of multiple, individually rare variants can predispose to the disorder through disruption of SMC function, specifically cell adhesion and contraction.

**Implications**
Timely surgical repair of aneurysms can prevent death, but they often are asymptomatic until dissection. Determining the genetic origins of TAAD may allow for the prospective identification of patients at risk for TAAD and possibly prevent sudden death from the disease. These findings provide evidence that both familial and sporadic TAAD involve multiple rare CNVs that are enriched for genes involved in an interacting network that regulates vascular SMC adhesion and contractility.

**Disclosures**
None.
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