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Perspective

Genetic and Aneurysms Osteoarthritis Syndrome

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INTRODUCTION

The segregation reflected autosomal dominant inheritance and variable disease gene expression. On chromosome 15 q22.33, a genome-wide linkage analysis using 250 k SNP arrays yielded a significant multipoint LOD (logarithms (base 10) of odds) score of 3.6. The fine-mapping-identified 12.8-Mb candidate region contained an intriguing candidate gene involved in the transforming growth factor-beta (TOF-(3) signaling pathway, namely the *SMAD3* gene. A heterozygous *SMAD3* mutation-c. 859C>T (p.Arg287ArgTrp)-was found to segregate with the phenotype in the family which is sequenced all SMAD3 exons in 99 people with thoracic aortic aneurysms and dissections and features similar to those seen in patients with Marfan Syndrome (MFS) but without *FBNI*, *TGFBRI*, or *TGFBR2* mutations to assess the frequency of *SMAD3* mutations.

Later, our *SMAD3* sequence analysis of 393 patients with thoracic aortic aneurysms and dissections (without mutations in the *FBNI*, *TGFBR1*, or *TGFBR2* genes) revealed five additional novels heterozygous *SMAD3* mutations c.3 I 3deIG (p.A1a105ProfsX1 I), c.539 540insC (P.I 80 ThrfxX7) four computerized algorithms predicted that all missense mutations that segregated with the phenotype and were affected by highly conserved amino acids were pathogenic and were absent in controls. Other pathogenic mutations caused a frame shift or a stop codon to be introduced. Because *SMAD3* mutations were found in only 1%-2% of our cohort, the incidence of *SMAD3* mutations in the thoracic aortic aneurysms and dissections cohort appears to be quite low. This rate is comparable to the 2% frequency of mutations in a cohort of non-syndromic familial thoracic aortic aneurysm and dissection patients. Recent studies, however, have revealed a slightly higher incidence (3%-4%) of *SMAD3* mutations in a large cohort of patients with both Syndromic and nonsyndromic thoracic aortic aneurysm and dissection There have been 36 different *SMAD3* gene mutations published in the literature so far, but many more unpublished *SMAD3* mutations have been identified. reported a small interstitial deletion of chromosome 15, causing the *SMAD3* gene to be disrupted The *SMAD3* gene has three major functional domains: The MH 1 and MH2 domains, as well as the linker region, with mutations occurring throughout the entire gene with 9 exons. These mutations are most likely to cause a loss of function, with TGF-13 signals not being transmitted *via SMAD3*. There has yet to be a clear genotype and phenotype correlation established.

DESCRIPTION

The *SMAD3* gene encodes the SMAD3 protein, a TGF-I3 pathway member required for TGF-I3 signal transmission. To determine how *SMAD3* mutations affected the aortic wall, we examined the histology and immunohistochemistry of aorta fragments obtained during surgery or autopsy. Tunica lateral due to lack of organization with elastic fiber fragmentation and loss, mucoid medial degeneration, and collagen accumulation in the media were all observed in varying degrees of severity. We also used immunohistochemistry to look at the expression of several TGF-P pathway members, including total SMAD3 (non-phosphorylated and phosphorylated forms), phosphorylated SMAD2 (pSMAD2), TGF-P 1, and Connective Tissue Growth Factor (CTGF). Although the *SMAD3* mutations were loss-of-function, the patient-derived aortic tissues showed evidence of increased (rather than decreased) TGF-P signaling was observed as increased labelling intensity of all markers studied.

TGF-D 1 was found to be expressed throughout the aneurismal aortic media, whereas controls only showed significant expression in the media adjacent to the adventitia layer, which is normally the most active. *SMAD3* pull mice have the same trait as humans, with abnormal calcification of synovial joints with osteophytes (knee, vertebral bones, and sternum), loss of articular cartilage, inter vertebral degradation, and hyperplastic differentiation of articular chondrocytes. These findings support the importance of *SMAD3*-mediated signals in cartilage maintenance. Later studies in *SMAD3* knock-out mice revealed a vascular phenotype characterized by progressive age-induced aortic root, ascending aorta dilation, aneurysm rupture, and aortic dissection.

Binding of ligands TGF-I3 is a TGF-13 super family ligand that is found in three TGF-I3 and also found in humans TOF-131, TOF-132, and TOF-f33. TGF-13s are secreted inactively they are synthesized as propeptide precursors with a prodomain also known as a latency-associated peptide, or LAP and a mature

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domain, forming the Small Latent Complex (SLC). The Large Latent Complex (LLC) is formed by disulphide-bonding the Latent TGF-13-Binding Protein 1 (LTBP-1) to the LAP of the SLC. LTBP-1 has domains that interact with matrix molecules like micro fibrils, directing the LLC to the extracellular matrix. TGF-131 sequestration/release is determined by interactions between TGF-13 I and LTBP-1, as well as between LTBP-1 and matrix proteins. TGF-13 signaling is regulated by the extracellular matrix, which is an important regulatory mechanism.

CONCLUSION

Phosphorylation and receptor recruitment TGF-3 receptors have a cysteine-rich extracellular domain, a Trans membrane domain, and a serine/threonine-rich cytoplasmic domain. TGFBR 1 is one of seven types I receptors or activin-like receptor kinases described, and five different types II receptors, including TGFBR2. The TGF-I3 ligand binds to the constitutively active TGF-I3 type II receptor dimer, which recruits a TGF-13 type I receptor dimer to form a complex that allows the type I receptor to be phosphorylated and activated.