Non-syndromic thoracic aortic aneurysms and dissections-a genetic review

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1. ABSTRACT

Thoracic aortic aneurysm and dissections (TAADs) are associated with both high mortality and medical expense. Poor outcomes are preventable by surgical repair; however, identifying individuals at-risk is difficult. Researchers are scanning the human genome to characterize the genetic determinants of TAADs by identifying chromosomal regions, gene mutations, single nucleotide polymorphism (SNP), genomic copy number variants and micro-RNA variants, with the purpose of analyzing the risk of TAADs associated with these predisposing genes. The goal of this review is to develop screening tests to identify individuals at risk for non-syndromic TAADs. This genetic survey has significant clinical implications because high-risk individuals can be closely monitored and can benefit from preventative surgical repair.

2. INTRODUCTION

Thoracic aortic aneurysms and dissections (TAADs) have distinct classification systems based on anatomic location. Thoracic aortic aneurysms (TAA) are classified according to the portion of the aorta that is involved. Aortic dissections (ADs) are categorized on the basis of the location of the intimal tear and the length of the false lumen. Type A dissections initiate in the ascending thoracic aorta just above the aortic valve, whilst type B dissections originate in the descending thoracic aorta just beyond the junction of the subclavian artery. Progressive enlargement of an ascending thoracic aortic aneurysm develops a type A dissection; thus, thoracic aortic aneurysms and type A dissections are associated conditions. The incidence of TAADs is 2.7 per 100,000 person-years (1). Despite progress in TAADs therapy with cardiovascular surgery, postoperative complications and

surgical mortality remain high after operation in the case of TAADs, especially acute aortic dissection type B (AADB) (2). The mortality rate for ruptured TAADs has been reported to be up to 70% (3). Thus, it is important to monitor and take preventative action in patients having a high risk of TAADs.

Though the causes of TAADs are multiple, with genetic, environmental, and physiologic influences, gene abnormality plays an important role in the pathogenesis of TAADs. Genetic abnormalities can explain 95% of patients with TAA, whilst Marfan's disease explains only the remaining 5%. Previous studies have indicated a strong genetic component in patients with TAADs amongst those patients without Marfan's disease (4). In addition to the classic Mendelian connective tissue disorders such as Marfan or Ehlers-Danlos vascular-type syndromes (5-7), several loci have been associated with nonsyndromic TAADs. We have reviewed the gene polymorphisms and micro-RNA variants associated with non-syndromic TAADs to help to identify individuals at high risk of TAADs.

3. FAMILY HISTORY IS IMPORTANT IN TAADS

TAADs are frequently familial diseases. An inherited pattern for TAA was present in 21.5% of non-marfan syndrome (MFS) patients (8). Familial TAADs (FTAADs) are inherited in an autosomal dominant manner. The majority of familial TAAD patients have an affected parent. When a parent is affected, the children are at a 50% risk of inheriting the mutant allele and the disorder. If there are other affected individuals in the extended family, siblings could be at risk even if the parents are unaffected, and the possibility of developing TAAD is increased. Furthermore, patients with familial TAA are generally younger at the time of diagnosis (56.8 years) than are patients with sporadic TAA (64.3 years) (9). Patients who have a close relative with an aneurysm tend to seek medical attention earlier than patients with sporadic thoracic aortic aneurysm (9). In the absence of a syndromic cause, it has been estimated that 19-20% of TAAD cases have a genetic component leading to familial TAADs (10,11).

4. CHROMOSOMAL REGIONS AND TAAD

Researchers have been scanning the human genome to identify genetic defects responsible for TAADs. In a study of chromosomal regions predisposed to TAAD, the first locus 11q23.3-q24 was identified in Northern European TAA families (12). In a second study, a major locus on 5q13-14 was found in 9 of 15 families originating from mainly diverse Caucasian populations, but including one Japanese family (13). In a subsequent study 5q13-q14 locus (TAAD1) was confirmed by examining 11 Finnish families (with 115 family members genotyped), lending support to evidence that this chromosomal region is a prominent genetic determinant of the disease (14). Recently, a genome-wide analysis showed that familial non-syndromic TAADs are strongly associated with the FBN1 gene locus 15q21 (15).

In addition, in patients with both TAAD and PDA, of 40 subjects belonging to 3 generations in a large pedigree, the locus 16p12.2-p13.13 was identified. This is a unique locus responsible for both TAAD and PDA with aortic stiffness as an early hallmark of the disease (16). Recently, a novel locus 12q13-14 was identified for the mutant gene and causing disease in a large family with multiple members with TAADs. Until now it is the only locus for ascending TAA that has been associated with a low risk of aortic dissection (17).

5. GENE MUTATIONS AND TAAD

Gene mutations related to TAAD, including TGFBR1, TGFBR2, SMAD3, MYH11, ACTA2, FBN1, MYLK and MMP9, have been observed. TGFB1, TGFB2 and SMAD3 participate in the TGF-beta signal pathway, which plays an important role in cellular proliferation, differentiation and extracellular matrix production. MYH11 is the smooth muscle-specific isoform of the myosin heavy chain protein. ACTA2, or smooth muscle alpha-actin, is a smooth muscle cell-specific protein. Fibrillin-1 is an extracellular matrix protein that contributes to large structures called microfibrils. MYLK encodes myosin light chain kinase (MLCK), and proteins of the matrix metalloproteinase (MMP) family are involved in the breakdown of extracellular matrix in normal physiological processes.

5.1. TGFBR1 and TGFBR2

TGFBR1 is in the locus of 9q33-q34, and TGFBR2 is in the locus of 3p22. Transforming growth factor beta receptor TGFBR1 is a type I transmembrane receptor protein, and TGFBR2 is a type II transmembrane receptor protein. Both of TGFBR1 and TGFBR2 proteins have serine-threonine kinase activity, which binds TGF-beta and transduces the TGF-beta signal intracellularly by recruitment and phosphorylation of TGFBR1. Then the TGFBR1 phosphorylates receptor-regulated SMADs (R-SMADs) which can now bind the coSMAD SMAD4. R-SMAD/coSMAD complexes accumulate in the nucleus where they act as transcription factors and participate in the regulation of target gene expression (Figure 1).

Previous studies have described four missense mutations that effect the kinase domain of TGFBR1, causing familial TAADs (18). For TGFBR2, two recurrent missense mutations 1378C>T (Arg460Cys) and 1379G>A (Arg460His) can lead to familial TAADs (19), without Marfan syndrome. All these mutations effect the kinase domain, and implicate an important role for TGF-beta signaling in the pathophysiology of TAAD. These mutations occur in the intraceullular kinase domain of the protein, which is important in function. Thus, these mutations could lead to missing function. This has been demonstrated by functional analysis of mutant TGFBR2 in cell lines (20, 21). In aortic tissue of TAAD patients, the TGF-beta pathway can be upregulated with TGFBR1 and TGFBR1 mutations (22), whilst the precise function of the abnormal gene product is still unclear.

5.2. SMAD3

SMAD3 is in the locus of 15q21-q22. SMAD3 is a direct mediator of transcriptional activation by

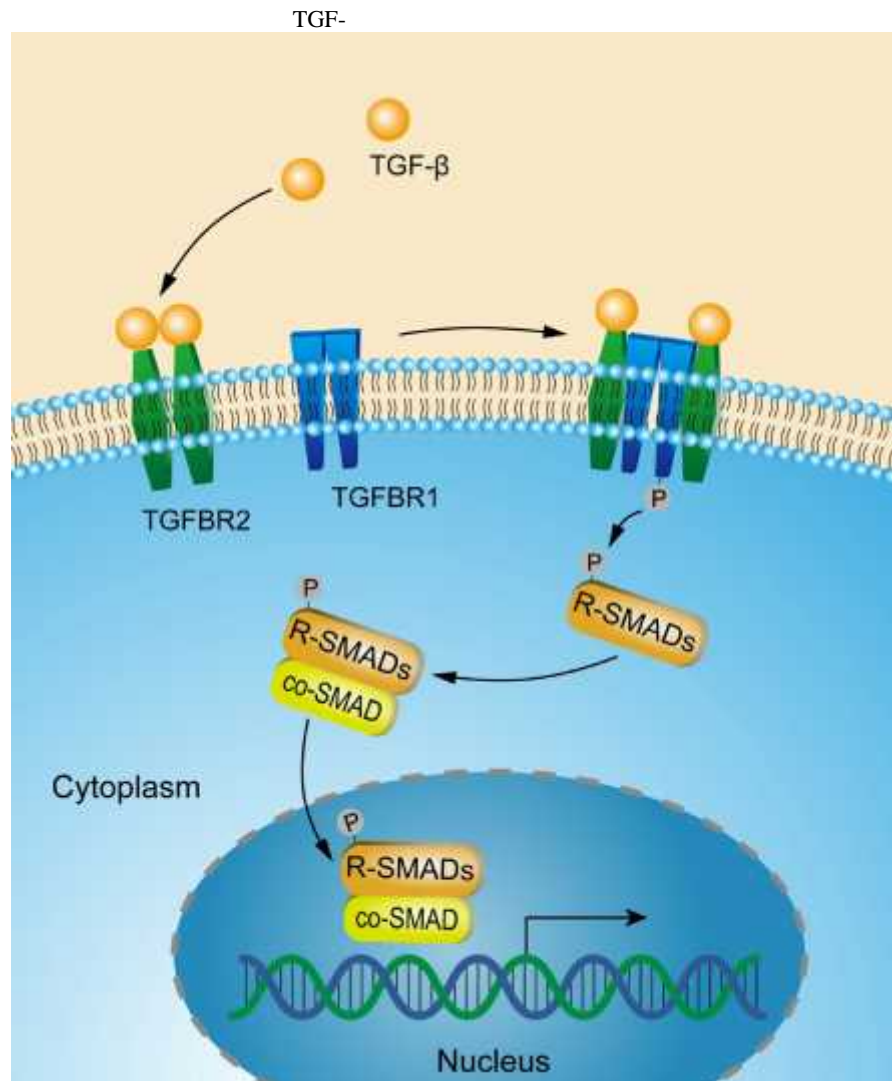the   TGF-

Figure 1.TGF-beta signal pathway. TGF-beta binds to transforming growth factor beta receptor 2 (TGFBR2), which recruits and phosphorylates TGFBR1. TGFBR then phosphorylates receptor-regulated SMADs (R-SMADs) which can then bind the coSMAD SMAD4. R-SMAD/coSMAD complexes accumulate in the nucleus where they act as transcription factors and participate in the regulation of target gene expression.

beta signaling pathway. The type 1 receptor kinase in this pathway phosphorylates SMAD3. Once phosphorylated, SMAD3 can form homomeric and heteromeric complexes with SMAD4, which accumulate in the nucleus and regulate expression of target genes (23, 24).

One frameshift mutation and three missense mutations were identified in individuals with FTAAD. The frameshift mutation c.652delA in exon 5 leads to premature termination of protein translation and probably to nonsense-mediated decay of the RNA. A c.335C>T alteration in exon 2 encodes the MH1 domain related with DNA binding. The other missense mutations, c.715G>A and c.836G>A, were both in exon 6 encoding the MH2 domain that is involved in protein-protein interactions

(25). Mutations in SMAD3 would disrupt TGF-beta signaling and transcription of target genes.

5.3. MYH11

MYH11 is in the locus of 16p13.13-p13.12. Mutations in MYH11 have been identified in two families with familial TAADs in whom the TAAD was associated with patent ductus arteriosus (PDA) in some family members: a splice donor site mutation (IVS32+1G>T) and a missense mutation (5273G>A) on the same allele and a 72-nucleotide deletion in exon 28   (3810_3881del)   (26). Two missense mutations, Leu1264Pro and Arg1275Leu, in the coiled-coil domain in one family and another missense mutation, Arg712Gln, in the *MYH11*ATPase head region in an unrelated family have also been reported (27).

5.4. ACTA2

ACTA2 is in the locus of 10q22-q24. Genotype-phenotype correlations have emerged based on initial data from ACTA2 families indicating that the Arg258 change predisposes to TAADs and premature stroke, whereas other mutations (Arg149 and Arg118) predispose to TAADs and coronary artery disease (28). A recurrent de novo ACTA2 mutation, c.536G>A (Arg179His), and other de novo mutations that alter Arg179, cause dysfunction of smooth muscle cells throughout the body, which is involved in TAADs (29, unpublished data).

5.5. FBN1

FBN1 is in the locus of 15q21.1. Although most FBN1 mutations are related to Marfan syndrome (30), a missense mutation, D1155N in exon 27 was found that could cause TAA in patients without Marfan syndrome (31).

5.6. MYLK

MYLK is in the locus of 3q21. MYLK encodes myosin light chain kinase (MLCK), which is a ubiquitously expressed kinase whose only known target of phosphorylation is the 20 kDa regulatory light chain of smooth and nonmuscle myosin II. One nonsense and four missense variants that were not present in matched controls were identified in MYLK. Two MYLK variants, c.4438C>T and c.5275T>C, segregated with TAADs in two families. Three additional MYLK variants were identified, c.5260G>A, c.3637G>A, and c.4195G>A, but additional affected family members were not available for segregation analysis (32). Since the mutation c.4438C>T (p.Arg1480X) locates in the MLCK kinase domain, this mutation can cause a truncated protein to miss the kinase and CaM binding domains, and then the kinase activity would be destroyed. Mutations c.5260G>A and c.5275T>C can disrupt amino acids in the -helix of the calmodulin-binding sequence, and can reduce the function of MLCK by disrupting CaM binding.

5.7. MMP9

MMP9 is in the locus of 20q11.2-q13.1. The MMP9-8202A/G polymorphism is also associated with TAAD such that patients with TAAD were nearly 5 times more likely to have the G allele than control subjects (33).

Other gene mutations, such as angiotensin-converting enzyme (ACE) gene and homeobox NKX2-5 gene mutations have also been studied. However, no association between ACE I/D polymorphism and type I aortic dissection was observed (34), as well as the association between NKX2-5 (239A>G) and ascending aortic aneurysm (35).

6. SNP AND TAAD

Gene analysis of the single nucleotide polymorphism (SNP) also showed association with TAAD. The A allele frequency for the SNP on 9p21, tagged as rs10757278, was found to be an independent susceptibility factor for TAD in men from the ethnic Chinese Han population (36). A previous study also found that the -340A>G polymorphism (rs514921) of MMP1 was significantly associated with the outcome of TAA, with the minor G allele being related to a favorable outcome. TAAD patients with the G allele of rs514921 of MMP1 have a more favorable outcome (37).

7. GENOMIC COPY NUMBER VARIANTS (CNVS) AND TAAD

Duplications of 16p13.1 has been identified in 8 out of 765 patients of European descent with adult-onset TAAD compared with 4 of 4,569 controls matched for ethnicity. Duplications of 16p13.1 were identified in 2 out of 130 patients with familial TAADs. Chromosomal deletions or reciprocal duplications of the 16p13.1 region have been implicated in a variety of neuropsychiatric disorders. This study suggested chromosome 16p13.1 duplications confer a risk for TAADs in addition to the established risk for neuropsychiatric disorders. It also indicates that recurrent CNVs may predispose to disorders involving more than one organ system (38).

8. MICRO-RNA AND TAAD

In addition to traditional genes, variants might be found in small noncoding micro-RNAs (miRNAs), which control gene expression either by inducing miRNA degradation or by blocking translation. In the vasculature, miRNAs are known to control apoptosis, angiogenesis and vessel remodeling (39). A study of TAAD patients, in which 18 miRNAs upregulated and 56 downregulated, showed that the miRNA-29 and miRNA-30 families are likely to play a role in the regulation of the focal adhesion and the mitogen-activated protein kinase (MAPK) signaling pathways, respectively (40). In a group of TAA patients, a significant relationship between miRNA expression levels (miRs -1, -21, -29a, and -133a) and aortic diameter was identified such that miRNA expression decreased as aortic diameter increased. In the same study, an inverse relationship between miR-29a and total MMP-2 was also identified in the clinical TAA specimens. This suggests that the loss of specific miR expression may allow for the elaboration of specific MMPs capable of driving aortic remodeling during TAA development (41).

9. CONCLUSIONS

Patients with TAAD are often asymptomatic and suffer a high annual mortality rate. Genetic analysis of TAADs will allow us to identify individuals at risk for non-syndromic TAADs. These high-risk individuals and families can be closely monitored and offered careful radiological follow-up and elective preemptive surgical intervention (42). Such identification of individuals at risk for TAADs is a potentially life-saving approach.

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Abbreviations: TAADs: Thoracic aortic aneurysm and dissections; SNP: single nucleotide polymorphism; TAA: Thoracic aortic aneurysms; Ads: Aortic dissections; AADB: acute aortic dissection type B; MFS: marfan syndrome; MLCK: myosin light chain kinase; MMP: matrix metalloproteinase; PDA: patent ductus arteriosus; ACE: angiotensin-converting enzyme; CNVs: copy number variants

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