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European Journal of Cardio-thoracic Surgery 35 (2009) 931—940

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Review

Inherited diseases and syndromes leading to aortic aneurysms and dissections

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Received 8 October 2008; received in revised form 6 January 2009; accepted 7 January 2009; Available online 23 February 2009

Summary

Genes affect virtually all human characteristics and diseases. These influences can be ascertained in individual patients through a review of the family history, physical examination and the use of medical diagnostics. Aneurysms and dissections are a leading cause of morbidity and mortality, in addition to medical expense, and, on the whole, their specific molecular mechanisms are beginning to be identified. Over the past decade, genetic tests have become available for numerous heritable disorders especially inherited with mendelian models. An important fact is that the results of genetic tests may also be useful beyond the individual affected by the genetic disorder. Depending upon the disorder, knowledge of carrier status may be important. Because of these facts, some essential information regarding basic genetics of aneurysm and dissection has been presented in this study.
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Keywords: Aneurysms; Dissections; Genetics

1. Inherited diseases of the aortic aneurysm and dissection

Aneurysms and dissections are the major diseases affecting the aorta and are a leading cause of morbidity, mortality and medical expense [1]. The incidence of thoracic aortic aneurysm is estimated to be 5.9/100,000 a year [2] and acute aortic dissection occurs in 5—30 per million people a year [3]. The incidence rate of combined aortic aneurysm and dissection is difficult to determine because many go undiagnosed. Aneurysms and dissections result from a weakening of the arterial wall. Aortic aneurysm is defined as a localized abnormal dilation of the aorta with a diameter at least 1.5 times that of the expected normal diameter [4]. The most common location for aortic aneurysms is in the infrarenal abdominal aorta, followed by the ascending thoracic aorta. Aortic dissection is characterized by the separation of aortic media caused by the flow of extraluminal blood, which creates a false lumen within the layers of the aortic wall. Aortic dissection may exist alone and with or without aortic aneurysm [5].

2. Genetics: why is it important?

Serial imaging of the aorta is an essential component of the long-term treatment and follow-up of patients with aortic aneurysm and dissection, because more than 40% of patients with thoracic aortic aneurysms are asymptomatic at the time of diagnosis. Such aneurysms are typically discovered accidentally through routine examination. Once one aneurysm has been discovered, the patient is at increased risk for developing another [6,7]. Therefore, lifelong follow-up is required in such patients. If any mutation is found in the people affected, this mutation is then researched in relatives and genetic counseling should be given. Because of this, according to target diseases, chromosomal and gene analysis are essential in selected cases with aneurysms or dissections, especially in inherited forms.

3. Major causes of medial necrosis of proximal aorta with aneurysms/dissections

Many syndromic and non-syndromic causes exist (Tables 1 and 2). At least 20% of aneurysms result from inherited disorders [8]. Medial necrosis of the proximal aorta with aneurysms/dissections is associated with a number of conditions, including inherited connective tissue disorders

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doi:10.1016/j.ejcts.2009.01.006

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Table 1
Genes responsible for non-syndromic aortic aneurysm and dissection.

	Locus name (gene cards)	Gene symbol	Chromosomal localization	Protein name
Affected genes	TAAD1 (AAT2)	Unknown	5q13–14	Unknown
	FAA1 (AAT1)	Unknown	11q23.3–24	Unknown
	TAAD2 (AAT3)	*TGFBR2*	3p24–25	TGF-beta receptor type-2
	MYH11	MYH11	16p13.13–p13.12	Myosin-11
Positional candidate genes	FBLN2	FBLN2	3p25.1	Fibulin-2
	TIMP4	TIMP4	3p25	Tissue inhibitor of metalloproteinases 4
Candidate genes	MMP3	MMP3	11q22.3	Matrix metalloprotease 3
	COL1A1	COL1A1	17q21.3–q22	Collagen alpha-1(I) chain
	COL1A2	COL1A2	7q22.1	Collagen alpha-2(I) chain

Human MYH11 gene mutations provide the first example of a direct change in a specific SMC protein leading to an inherited arterial disease [92]. The *TAAD2* locus encompasses the *MFS2* locus, raising the possibility that these conditions are allelic. Data are compiled from the following standard references: gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

such as Marfan syndrome and Ehlers–Danlos syndrome type IV, as components of other mendelian disorders, including Loeys–Dietz syndrome, Noonan syndrome, osteogenesis imperfecta, and homocystinuria, also can present along with bicuspid aortic valve, coarctation of the aorta, adult polycystic kidney disease, Turner syndrome and familial forms of thoracic aneurysm and dissection [8,9].

4. Marfan syndrome

Marfan syndrome (MFS, OMIM 154700) is an autosomal dominant heritable disorder of the connective tissue that involves primarily the skeletal, ocular and cardiovascular systems. Variable expression in Marfan syndrome is the rule, but complete non-penetrance has not been definitively documented. Approximately one-quarter of affected individuals arise as new mutations: a paternal age effect is present, on average, in sporadic cases (Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Baltimore, MD), and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/, 2007). The leading cause of premature death in MFS patients is progressive dilatation of the aortic root and ascending aorta, causing aortic incompetence and dissection [10,11]. MFS has an incidence of at least 1:10,000 [12]. The most common cardiovascular manifestations of MFS affect the atrioventricular valves and the aorta. Mitral valve disease may be the earliest of the cardiovascular manifestations of MFS. Progressive dilatation of the aortic root is responsible for most cases of aortic incompetence. Usually, there is a gradual dilatation that starts at the aortic root, which may extend into the ascending aorta. This may then lead to the sudden onset of aortic dissection, which can cause acute aortic regurgitation or aortic rupture with sudden death [11]. Generalized aortic root dilatation [13], in addition to a family history of severe cardiovascular disease in relatives with MFS [14], is associated with a greater risk factor in aortic complications. The diagnosis of MFS can be made according to the criteria of the Ghent nosology; this formulation requires involvement of three systems with two major diagnostic manifestations. It provides for major skeletal manifestations and considers affected first-degree relatives or molecular data as major diagnostic criteria [15]. Marfan syndrome is the result of a mutation in the FBN1 gene [16].

4.1. FBN1 mutations in Marfan syndrome

The gene encoding type 1 fibrillin (FBN1) lies on the long arm of chromosome 15 at 15q15–q21.1. The locations of the mutation are spread throughout the FBN1 gene. The majority of mutations are missense mutations (about two-thirds of all FBN1 mutations) that alter one single amino acid out of the 2871 amino acids that constitute the protein [17]. About 20% of all reported mutations cause a frameshift with a downstream premature termination codon, and approximately 12% of all mutations found to date are splice site mutations. Genotype–phenotype correlations in Marfan syndrome are complicated by the large number of unique mutations reported, as well as by clinical heterogeneity among individuals with the same mutation [18]. Even today, it is still not possible to find a mutation satisfying the Ghent criteria in approximately 10% of patients with a definite diagnosis of Marfan syndrome [19,20]. These patients were observed to have mutations in the TGFBR2 gene, which encodes the transmembrane receptor type II of TGFβ [21]. Actually, this is a controversial area and many experts believe that TGFBR2 mutations lead to different condition, namely Loeys–Dietz aneurysm (LDS) syndrome that is mentioned later in this review. Moreover, mutations in the FBN1 gene have also been found in patients with other fibrillinopathies. Hutchinson et al. [22] suggested that differences in normal FBN1 expression could contribute to the clinical variability seen in families with Marfan syndrome, and should be considered as a potential modifier of phenotype.

4.2. FBN1 mutations in type 1 fibrillinopathies

The mutations identified to date have been found in almost all exons of the fibrillin-1 gene. Clear genotype–phenotype correlations have been slow to emerge. In light of the high intrafamilial variability, it is to be assumed that environmental, and perhaps epigenetic, factors play a significant role in determining the severity of the phenotype in a patient with a given mutation. In addition to mutations found in patients with classic MFS phenotypes, *FBN1* mutations have been found in a series of related connective tissue disorders, termed type 1 fibrillinopathies, including

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Table 2
Genes responsible for aortic aneurysm and dissection in frequent syndromes.

Syndrome (inheritance)	Gene symbol	Chromosome localization	Protein name	Gene function	Affected aortic segments
Marfan (autosomal dominant)	*FBN1*	15q21.1	Fibrillin-1	*FBN1* encodes fibrillin-1, a large glycoprotein that is a component of extracellular matrix structures called microfibrils	Dilatation of the ascending aorta involving the sinuses of Valsalva; dissection of the ascending aorta
	TGFβR2[a]	3p24–25	Transforming growth factor-beta receptor type II	TGF signaling plays an important role in cellular proliferation, differentiation and extracellular matrix production	Predominantly ascending aortic disease; however, significant descending aortic disease and aneurysms of other vessels also occurred in affected family members
Ehlers–Danlos syndrome type IV (autosomal dominant)	*COL3A1*	2q31	Collagen alpha-1(III) chain	The *COL3A1* gene encodes the chains of type III procollagen, a major structural component of skin, blood vessels, and hollow organs	Proximal branches of the aortic arch, the descending thoracic aorta and the abdominal aorta. The distal branches of the aorta, especially the renal, mesenteric, iliac and femoral arteries, are also particularly affected [102]
Turner syndrome (chromosomal)		45X			Aortic root dilatation with or without dissection has been incidentally noted in 6%-9% of patients with Turner syndrome [103,104]
Noonan syndrome (autosomal dominant)	*PTPN11*	12q24.1	Tyrosine-protein phosphatase non-receptor type 11 (SHP-2)	The protein is expressed throughout the body and it is an important player in cellular response to growth factors, hormones, cytokines and cell adhesion molecules	Coarctation of aorta
	KRAS	12p12.1	GTPase KRas	Their proteins regulate cell fates and they are key regulators of the RAS-RAF-MEK-ERK pathway, which is important for proliferation, growth and death of cells	
	RAF1	3p25	RAF proto-oncogene serine/threonine-protein kinase		
	SOS1	2p22–p21	Son of sevenless homolog 1		
Osteogenesis imperfecta (autosomal dominant)	*COL1A1*	17q21.3–q22	Collagen alpha-1(I) chain	They encode the chains of type I procollagen, the major protein in bone and most other connective tissues	Ascending aorta
	COL1A2	7q22.1	Collagen alpha-2(I) chain		
Homocystinuria (autosomal recessive)	*CBS*	21q22.3	Cystathionine beta-synthase	CBS is a pyridoxal 50-phosphate (PLP)–dependent enzyme and condenses homocysteine and serine to cystathionine, an irreversible step in transsulfuration	Abdominal aorta (especially elderly patients)
Autosomal dominant polycystic kidney disease (autosomal dominant)	*PKD1*	16p13.3	Polycystin 1	Cell cycle regulation and intracellular calcium transport	Thoracic aortic aneurysms
	PKD2	4q21–q22	Polycystin 2	Member of the family of voltage-activated calcium channels	
Pseudo xanthoma elasticum (autosomal recessive)	*ABCC6 (MRP6)*	16p13.1	ATP-binding cassette transporter C6 (multidrug resistance associated protein 6)	Cellular transport protein	Especially abdominal, sometimes arch and thoracic aortic aneurysms
Hurler syndrome (autosomal recessive)	IDUA	4p16.3	Alpha-L-iduronidase	Lysosomal degradation of glycosaminoglycans (heparan and dermatan sulphate)	Coarctation of aorta
Loeys–Dietz syndrome (autosomal dominant)	*TGFBR1* and *TGFBR2*	9q33–q34 and 3p24–p25	Transforming growth factor β receptors 1 and 2	TGF signaling plays an important role in cellular proliferation, differentiation and extracellular matrix production	Affected patients have a high risk of aortic dissection or rupture at an early age and at aortic diameters that ordinarily would not be predictive of these events

[a] Germline *TGFBR2* mutations are responsible for the inherited predisposition to familial TAAD in 5% of these cases.

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Marfan syndrome [23], neonatal MFS (nMFS) [24], Shprintzen–Goldberg syndrome [25], familial arachnodactyly [26], ectopia lentis [27], ascending aortic aneurysm and dissection without classical MFS (ascending aortic aneurysm and dissection, no ectopia lentis, no specific skeletal findings) [28,29], MASS phenotype (mitral valve prolapse, aortic root dilatation without dissection, skeletal and skin abnormalities) [30], new variant of the MFS (skeletal features of MFS with joint contractures and knee joint effusions, ectopia lentis and no cardiovascular manifestations) [31,32], and isolated skeletal features (tall stature, scoliosis, pectus excavatum and arachnodactyly) [33].

4.3. The fibrillin-2 gene (*FBN2*)

The fibrillin-2 gene (*FBN2*, previously *Fib5*) on chromosome 5q23–q31 is closely related to fibrillin-1. Fibrillin-1 and fibrillin-2 are differentially expressed, both in terms of developmental stages and tissue distribution [33,34]. Fibrillin-2 is found preferentially in elastic tissues, such as the elastic cartilage, the tunica media layer of the aorta and along the bronchial tree [35]. The two fibrillins may therefore have differing functional roles: fibrillin-2 may possess a major functional role during early morphogenesis in directing elastic fibre assembly [36]. In contrast, the predominance of fibrillin-1 in stress and load bearing structures, like the aortic adventitia, the ciliary zonules and the skin, suggests that fibrillin-1 may be mainly responsible for the structural function of the microfibrils [35]. Mutations in *fibrillin-2* (*FBN-2*) cause congenital contractural arachnodactyly variably associated with aortic disease (OMIM).

5. Ehler–Danlos syndrome

Ehlers–Danlos syndrome (EDS) comprises a heterogeneous group of connective tissue diseases of which the major clinical features are hyperextensibility of the skin, hypermobility of the joints and generalized connective tissue fragility [36]. The latest classification of EDS, Villefranche Nosology [37] recognizes six subtypes for which major and minor diagnostic criteria have been defined: classical, hypermobility, vascular, kyphoscoliosis, arthrochalasia and dermatosparaxis.

The vascular type of EDS (vEDS, EDS type IV; OMIM# 130050) is an autosomal dominantly inherited disorder caused by abnormal type III collagen, which is a major component of the cardiac and vascular extracellular matrix [38,39], resulting from heterogeneous mutations of the type III procollagen gene (*COL3A1*) [40]. In the United States, the incidence is estimated at 1 in 5000–20,000 live births [37]. Type III collagen is a homotrimer formed by an association of 3 alpha 1 (III) chains derived from a gene (*COL3A1*), which is large and contains 52 exons [41]. The core of the molecule is a triplehelix region with an amino acid sequence characterized by (Gly(glycine)-X-Y) 343 repeats [40]. To ensure the proper assembly of the alpha monotrimers, the Gly-X-Y repeats must not contain skips, and the length of the triple helix must be the same for each alpha chain. The molecular defects described previously in vEDS individuals include two types of mutations of *COL3A1* [42]. Most (approximately two-thirds) of the base changes are substitution of other amino acids for glycine in the (Gly-X-Y) 343 repeats in the triple helix region of *COL3A1* [41].

vEDS differs from other types of EDS because individuals with vEDS are at risk from arterial rupture, aneurysm and/or dissection; gastrointestinal perforation or rupture; and uterine rupture during pregnancy, which may lead to sudden death [43]. A correct diagnosis of vEDS may prevent complications and influence the treatment of patients with unexpected bowel or arterial rupture, especially regarding surgery and patients with a family history of similar events. Although necessary, clinical awareness and timely diagnosis of vEDS is still inadequate, as the disease is often diagnosed only after life-threatening complications or death [42,44,45]. To improve the likelihood of a good outcome, physicians must be made more aware of the existence of vEDS [45]. A family history is important for the interpretation of vEDS, which has an autosomal dominant inheritance pattern, although approximately 50% of affected individuals who have a de novo disease-causing mutation seem to be sporadic cases [42]. A dominant pattern is thus considered straightforward; namely, affected individuals have a 50% chance of passing the mutated gene to each child. A mutation analysis of *COL3A1* is the best method available for the diagnosis of vEDS and should be performed in all affected individuals when there is a suspicion of vEDS, despite negative findings in the collagen protein analysis. Owing to the recent biotechnological advances in gene diagnosis, clinical geneticists should therefore be consulted in order for affected individuals to receive appropriate genetic counseling.

6. Turner syndrome

Originally described in 1938 by Turner [46], Turner syndrome (TS), or monosomy X, results from complete or partial monosomy of the X chromosome. This is a relatively common chromosomal disorder, affecting approximately 1 in 2500 live female births. While the most common features are short stature and gonadal dysgenesis, the most serious clinical aspect of the syndrome is due to congenital cardiovascular anomalies that include, most critically, aortic coarctation and dissection [47–52]. Cardiovascular malformations are present in at least 25% of patients with TS [53]. The malformations predominantly involve the vessels of the left side of the heart, although right-sided malformations have also been documented. A recent study using MRI described partial anomalous pulmonary venous return (13%) and persistent left superior vena cava (13%), in addition to the well-known left-sided malformations [54].

A bicuspid aortic valve is the most common cardiovascular finding in TS, and is seen in 13–34% of patients, compared with only 1–2% of the general population. Coarctation of the aorta is present in 4–14% of all patients with TS. Most patients with aortic coarctation are diagnosed early, because of the relative severity of the condition. Aortic dilation/aneurysm is present in 3–42% of all patients with TS [53]. Other malformations, including mitral valve prolapse or regurgitation, cardiac dextroposition, ventricular septal defect, atrioventricular septal defect, pulmonary valve abnormality (stenosis, regurgitation), persistent ductus

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arteriosus, interrupted inferior vena cava with continuation of azygos vein, and hypoplastic aortic arch, have also been reported [47,54,55–57]. The cause of congenital heart defects in TS remains unknown. To date, no biochemical or specific genetic abnormalities of the aortic wall have been identified in TS [53]. An increased aortic-root diameter, a risk factor for developing aortic dilatation and later rupture, is often seen and probably depends primarily on blood pressure [58], although other factors might also contribute. Prospective studies are required in order to determine how the risk of aortic dissection can be reduced. Currently, the approach is to reduce blood pressure and monitor the aortic-root diameter. Recently, Matura et al. showed that the risk for aortic dissection is greatly increased in young women with TS. Because of their stature, when ascending aortic diameters under 5 cm aortic dissection may occur. Thus, they suggest that, the use of aortic size index must be preferred [59]. Echocardiography should be performed in all patients at diagnosis. If this is normal, or near-normal, repeat echocardiography should then be performed in adolescence, in adulthood and probably every 5 years thereafter. A close working relationship with a cardiologist with knowledge of Turner syndrome is of great value. An evaluation of the aorta should be performed, with emphasis on aortic dilatation and the subsequent risk of aortic dissection. Cardiac monitoring should be performed prior to assisted reproductive therapy or unassisted pregnancy, and during pregnancy. Blood pressure should be monitored at every visit to the physician.

7. Bicuspid aortic valve

Bicuspid aortic valve (OMIM# 109730) is the most common type of cardiac malformation. In an estimated 1–2% of the population, the aortic valve is bicuspid and has only two leaflets instead of three [60–65]. The bicuspid aortic valve (BAV) is frequently found underlying aortic stenosis; in pediatric patients 70–85% of stenotic aortic valves are bicuspid [66] and at least 50% of adults with aortic stenosis have BAV [60]. The bicuspid aortic valve is also recognized in association with other cardiovascular malformations, including coarctation of the aorta (50–80%), interruption of the aorta (36%), and isolated ventricular septal defect (20%) [60,62,66]. However, BAV occurs infrequently with other forms of cardiovascular (CV) disease in the young. The importance of genetic factors involved in the development of aortic valve disease has become more apparent. BAV shows familial clustering and an autosomal dominant inheritance pattern [60,62].

The first reported genetic cause of BAV in humans was in the setting of Anderson syndrome, which is characterized by ventricular arrhythmias, periodic paralysis, dysmorphic facies, cleft palate and scoliosis [67]. The majority of BAVs occur as an isolated birth defect, but recently, a novel genetic cause of non-syndromic BAV in humans has been discovered. Garg et al. reported mutations in NOTCH1 gene in two families with BAV (R1108X; H1505del) that were associated with the calcification phenotype in BAV [68], and the authors have provided important insights into the cause of a common human developmental malformation. Aortic valve disease is a complex multifactorial process and recent molecular and genetic findings support that aortic valve malformations and calcific aortic valve disease may share a common genetic cause. More recently, Mohamed et al. suggested that NOTCH1 gene mutations do not only play a role in familiar BAV, but can also be observed in approximately 4% of sporadic cases [69]. Bicuspid aortic valve is often considered a benign lesion early in life, but complications of BAV, including aortic stenosis, aortic regurgitation, infective endocarditis and aortic dilation and dissection, result in considerable morbidity and mortality later in life [70–73].

Because many of these BAV-related complications can be predicted or prevented, the identification of BAV heritability supports the previous recommendation [62] that echocardiographic screening of first-degree relatives of patients with BAV is warranted in order to identify persons with structural cardiac abnormalities.

Recently Loscazo et al. confirmed autosomal dominant inheritance with incomplete penetrance for BAV/TAA in 13 families. Furthermore, they suggest that the component features, BAV and TAA, are independent manifestations of a single gene defect and to avoid the risk of early death, it is essential that all first-degree relatives receive echocardiographic follow-up at regular intervals regardless of the presence or absence of a BAV [74].

8. Genetic predisposition

Although the genetics of TAA in patients with Marfan syndrome are well documented, less is known about familial patterns of aneurysms not associated with any acknowledged vascular-collagen disease. Recent studies demonstrate that up to 19% of persons with TAAD do not have syndromes traditionally considered to predispose them to aortic disease. These individuals often have multiple relatives with TAAD, suggesting a strong genetic predisposition [75,76]. The inheritance and features of this familial syndrome are better characterized through aortic imaging of family members of patients with TAAD so as to identify asymptomatic aortic dilation [77]. Other cardiovascular manifestations of familial thoracic aortic aneurysms and aortic dissections (TAAD) may include: (1) dilatation of the aorta at the level of either the ascending aorta or the sinuses of Valsalva; and (2) aneurysms and dissections of the thoracic aorta involving either the ascending or descending aorta. Cardiovascular manifestations are usually the only findings. In most of the families ascertained to have multiple members affected by TAAD, the TAAD phenotype is mostly inherited in an autosomal dominant manner, commonly expressed in every generation with no gender bias. However, diagnosis is complicated by the observation of decreased penetrance (individuals who carry the predisposing gene mutations and, yet, do not develop TAAD), variable expression (the severity of TAAD varies among affected individuals within a family) and a variable age of onset of the aortic disease [76]. Familial TAAD is diagnosed based on the presence of dilatation and/or dissection of the thoracic aorta, absence of Marfan syndrome and other connective tissue abnormalities, and the presence of a positive family history. Predisposition is not known to be more prevalent in any ethnic or racial group.

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The mean age of presentation of individuals with familial TAAD is lower than that of individuals with non-familial TAAD but higher than the mean age of presentation of individuals with Marfan syndrome [6]. Aortic dissection is exceedingly rare in early childhood, although aortic dilatation may be present in childhood.

9. Chromosomal regions and genes predisposing to familial aortic aneurysm and dissection

9.1. Aortic aneurysm, familial thoracic 1 (AAT1, FAA1) (OMIM: 60706)

A gene defect for FAA disease is located on chromosome 11q23.3–q24 [78]. The *FAA1* gene defect can be inherited in an autosomal dominant fashion and result in aortic dilatation, aneurysm formation and dissection. Several clinical and genetic features distinguish FAA related to the *FAA1* locus from aortic aneurysms caused by defects at other genetic loci.

FAA related to this gene defect is an isolated vascular disorder. *FAA1*-related disease affects multiple aortic segments, with dilatation of the thoracic and abdominal aorta. Other large arterial vessels may also be affected by the *FAA1* gene defect [5]. Unlike other aortic aneurysm disorders, *FAA1*-related aortic disease is highly penetrant. Analysis of the *FAA1* disease gene may delineate molecular mechanisms for maintenance of vascular wall integrity.

9.2. Aortic aneurysm, familial thoracic 2 (AAT2; FAA2) (OMIM: 607087)

Guo et al. reported a number of families with clear autosomal dominant inheritance of thoracic aneurysms and dissections [79]. Kakko et al. genotyped 115 members of 11 Finnish families and segregated thoracic aortic aneurysms and dissections, and confirmed linkage to 5q13–q14 [80]. Gene map locus 5q13–q14 which causes TAAs and dissections inherited in an autosomal dominant manner with variable expression and reduced penetrance, primarily in women. The cardiovascular complications of the families with TAAD that are linked to 5q locus are similar to those observed in patients with Marfan syndrome. It is hypothesized by Guo et al. that the defective gene encodes a connective tissue protein.

9.3. Aortic aneurysm, familial thoracic 3 (AAT3, FAA3) (OMIM; 608967)

The third locus responsible for familial autosomal dominant thoracic aortic aneurysm and dissection TAAD (*TAAD2*) that maps to 3p25–p24 may be caused by mutations in the TGFBR2 gene (encoding transforming growth factor beta receptor type II) [81]. *TAAD2* locus overlaps with a controversial locus for a MFS-like connective tissue disorder, the *MFS2* locus, increasing the possibility that these conditions are allelic [82,83]. Hasham et al. commented that the variable expression and decreased penetrance of this and other familial aortic aneurysm loci make it necessary to continue to monitor aortic dimensions throughout an at-risk individual's lifetime, and to do so even if the parent is unaffected [81]. In most adults, the risk of aortic dissection or rupture becomes significant when the maximal aortic dimension reaches about 5.5 cm. However, in individuals with *TGFBR2* mutations, dissection of the aorta may occur before the aorta extends to 5.0 cm [84]. Even patients with LDS syndrome, both TGFBR1 and two mutations have been described and dissections may occur under 5.0 cm. Pannu et al. estimated that germline TGFBR2 mutations are responsible for the inherited predisposition to familial TAAD in 5% of cases [85]. The cardiovascular phenotype associated with *TGFBR2* mutations is predominantly ascending aortic disease, although significant descending aortic disease and aneurysms of other vessels also occurred in affected family members. The majority of individuals with TAAD resulting from *TGFBR2* mutations present initially with aortic disease; however, the risk for aneurysms and dissections of other vessels including cerebral aneurysms is increased.

More aggressive surgical repair may be indicated for individuals with a family history of aortic dissection without significant aortic root enlargement, and in individuals with *TGFBR2* mutations.*TGFB* geneThe coding region of *TGFBR2* consists of eight exons. TGF signaling plays an important role in cellular proliferation, differentiation and extracellular matrix production. *TGFBR2* mutations leading to aneurysms and dissections occur predominantly in the functionally important kinase domain and are predicted to cause loss of function. However, evidence also suggests that the TGF pathway might be upregulated in aortic tissue from individuals with *TGFBR2* mutations [83]. The precise function of the abnormal gene product is currently under investigation. In addition, several missense mutations that cause syndromic TAAD in association with Marfan syndrome, Loeys–Dietz aortic aneurysm syndrome (LDAS is an aortic aneurysm syndrome characterized by widely spaced eyes (hypertelorism)), bifid uvula and/or cleft palate, and generalized arterial tortuosity with ascending aortic aneurysm and aortic dissection. This syndrome shows autosomal dominant inheritance and variable clinical expression. Other findings in multiple systems include craniosynostosis, structural brain abnormalities, mental retardation, congenital heart disease and aneurysms with dissection throughout the arterial tree), or related syndromes have been described [21,85–88]. Even nowadays, a lot of authorities believe that dysregulation and oversignaling in TGFR pathway I is the primary mechanism for the pathophysiology of MFS.

11. Myosin, heavy chain 11, smooth muscle; MYH11 (AAT4, FAA4)

Mutations in *MYH11* have been identified in two families with TAAD in whom the TAAD was associated with patent ductus arteriosus (PDA) in some family members [89–91]. Zhu et al. concluded that MYH11 heterozygous mutation leads to an early and severe decrease in the elasticity of the aortic wall, consistent with the role of smooth muscle cells in maintaining the mechanical properties of the thoracic aorta [92].

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12. Positional candidate genes predisposing to aortic aneurysm and dissection

A candidate gene is a gene whose effect is known to be related to the biological systems, which might affect the trait(s) of interest. This information usually comes from research into other species, such as humans and mice. Once a disease-related gene has been mapped, a database search will reveal the genes in that region. Analyzing the predicted products of these genes and their possible functions, as deduced by comparing their aminoacid sequences against aminoacid sequences of proteins with known functions, will establish the most promising candidates for the disease. Each of these candidate genes will then be studied in normal and affected individuals in order to determine which one is associated with the disease.

13. Fibulin-2 (FBLN2)

Fibulin-2 (FBLN2) is an extracellular matrix protein known to interact with the fibrillin-1 protein, and its gene mapped to 3p25–p24 [93,94]. Screening of the FBLN2 promoter (the upstream regulatory information that directs the timing and dosage of the FBLN2 gene expression) is required before this gene can be excluded formally as a cause of TAAD in these kindred.

14. Tissue inhibitor of metalloprotease (TIMP) 4

This gene belongs to the TIMP gene family of four members, TIMP1–4, the proteins of which are endogenous inhibitors of matrix metalloproteinases (MMPs). TIMP4 is considered to be the most characteristic of cardiovascular structures [95], but its function in cardiovascular biology and pathology is still poorly understood.

15. Candidate genes predisposing to aortic aneurysm and dissection

15.1. Matrix metalloproteonase 3; MMP3 (Stromelysin I; STMY1; STR1)

Genes whose products participate in the structural organization and remodeling of the vasculature are logical candidates. Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that are known to play an important role in these processes because of their ability to collectively degrade all components of the ECM. It is divided into five classes: collagenases, gelatinases, stromelysins, membrane-type MMPs, and others, including a few of the most recently identified MMPs [96–98]. Although several MMPs (MMP-1, -2, 3, -9, and -12) are expressed at elevated levels compared to normal vessel walls in patients with abdominal aortic aneurysms [99], MMP3 alone appears to harbor genetic changes that directly contribute to these elevated levels. Medley et al. concluded that the MMP3 5A/6A genotype may be an important determinant of vascular remodeling and age-related arterial stiffening, with the heterozygote having the optimal balance between matrix accumulation and deposition [100].

16. *Collagen, type I, alpha-1; colla1*

Type I collagen is the main component of fibrils that provides tissues with tensile strength. To achieve the highly variable levels of type I collagen in different tissues during development, growth, ageing and tissue repair, the genes encoding the constituent α1 and α2 chains of type I collagen (*Col1a1* and *Col1a2*) are likely to be under complex transcriptional and post-transcriptional control.

17. Is genetic etiology associated with faster aortic dilatation?

Thoracic aortic aneurysm (TAA) is a lethal disease and the size of the aneurysm has a profound impact on aortic dissection and death [75]. The growth rate of TAA is highly variable ranging from 0.03 to 0.22 cm per year, and the genetic factors may play an important role in aortic growth rates. The data suggest that genetic etiology permits more rapid aortic dilation, thus increasing the risk for aortic dissection. Physicians must know how to distinguish between syndromic and non-syndromic forms of aortic aneurysm and dissection (Table 3). As a result family history is a most important issue in evaluating the patients who have aortic aneurisyms/dissection. Approximately 15% of patients with aortic aneurysm have a first-degree relative with an aortic aneurysm, and segregation analyses of such families have suggested a major gene defect [6,101–104]. When an aortic aneurysm ruptures it can cause serious bleeding and lead to sudden death. Therefore, when identifying individuals at risk, it is critical to obtain a family history of TAAD, including any unexplained sudden death, regardless of age and in the absence of any known genetic syndrome [75]. Coady et al. reported that patients with familial thoracic aortic aneurysm are younger at the time of diagnosis (56.8 years) than patients with sporadic thoracic aortic aneurysm (64.3 years),

Table 3
Comparison of syndromic and non-syndromic aortic aneurysm and dissection.

Features[a]	Syndromic or sporadic	Non-syndromic
The growth rate of aortic aneurysms	Less than non-syndromic type	High than syndromic type
Risk for aortic dissection	Less than non-syndromic type	More risk for aortic dissection than syndromic type
Age, at the time of TAAD diagnosis (approximately)	Sporadic thoracic aortic aneurysm-sixth decade Marfan syndrome – second decade	Fifth decade
Family history	Yes, in syndromic type	Yes

[a] This table is majority derived from clinical studies that were limited by ascertainment bias and research methods.

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but are older than patients with Marfan syndrome (24.8 years) [75]. Patients who have a close relative with an aneurysm ought to seek medical attention earlier than patients with sporadic thoracic aortic aneurysm [75].

In the near future, new genetic studies such as single nucleotide polymorphisms (SNP) and RNA expression studies may help underlie genetic based therapies and develop more useful, simple and cheap diagnostic genetics tests for the susceptible patients.

Acknowledgements

I would like to thank Cornelis vanBremen for his collaboration. I would like to apologize to colleagues whose work was not cited due to limited space.

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