



Comparison of Genes Associated with Thoracic and Abdominal Aortic Aneurysms

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Abstract

Keywords

- abdominal aortic aneurysm
- thoracic aortic aneurysm
- genetics
- mutation
- polymorphism

Aneurysms impacting the ascending thoracic aorta and the abdominal aorta affect patient populations with distinct clinical characteristics. Through a literature review, this paper compares the genetic associations of ascending thoracic aortic aneurysm (ATAA) with abdominal aortic aneurysms (AAA). Genes related to atherosclerosis, lipid metabolism, and tumor development are associated specifically with sporadic AAA, while genes controlling extracellular matrix (ECM) structure, ECM remodeling, and tumor growth factor β function are associated with both AAA and ATAA. Contractile element genes uniquely predispose to ATAA. Aside from known syndromic connective tissue disease and poly-aneurysmal syndromes (Marfan disease, Loeys–Dietz syndrome, and Ehlers–Danlos syndrome), there is only limited genetic overlap between AAA and ATAA. The rapid advances in genotyping and bioinformatics will elucidate further the various pathways associated with the development of aneurysms affecting various parts of the aorta.

Introduction

Abdominal aortic aneurysm (AAA) is a common disease, with an estimated global prevalence of 4 to 7% in men over 65 years old. Clinical predisposing factors for AAA include smoking, hypertension, male sex, and increasing age, which overlap with risk factors for atherosclerosis.¹ Clustering of cases in families suggests that these aneurysms are at least partly driven by genetic factors.² On the contrary, ascending thoracic aortic aneurysm (ATAA) seem to be more strongly genetically driven and far less associated with the classic risk factors for atherosclerosis.³

Most genetic studies have previously focused on single nucleotide polymorphisms (SNPs) associated with AAA or ATAA separately, with little emphasis on delineating any common pathways in their genetic associations. This paper provides a review of the genetic variants associated with AAA or ATAA, with an emphasis on the common mechanisms underlying their pathogenesis. Understanding similarities and differences between ATAA, a well-characterized genetic disease, and AAA, a disease with a more nebulous genetic background, may improve our understanding of both pathologies.

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Interestingly, AAA is very similar morphologically to descending thoracic aortic aneurysms (DTAA). Both AAA and DTAA, however, are morphologically very different from ATAA. Atherosclerosis is not associated with ATAA, whereas it affects both AAA and DTAA development.⁴ While the ascending aorta, in the case of ATAA, is usually smooth, noncalcified, and lacks thrombus, the opposite is true for AAA and DTAA.⁵ These morphological differences suggest different pathophysiologic forces driving aneurysms at different anatomical locations along the aorta, which, in turn, implies a different genetic background behind each aneurysm type. This paper presents a literature review of the genetic underpinnings of ATAA and AAA, the two most addressed genetic diseases of the aorta, focusing on the common genetic pathways underlying their pathogenesis.

Genetic Inheritance of Aneurysmal Disease at Different Sites Along the Aorta

Several studies have previously demonstrated the significance of genes following an autosomal dominant pattern in the pathogenesis of ATAA, rendering a more straightforward identification of affected individuals across generations.^{6,7} In the case of AAA, however, rarely does one single allele suffice for the development of AAA, with the notable exception of certain rare connective tissue syndromes, such as Marfan and Loeys-Dietz syndrome (LDS). Rather, as for coronary artery disease, many different, relatively common, alleles contribute additive small amounts of risk (e.g. *IL6R*, rs12133641: cases = 41.7% and controls = 38.6%).^{8,9} Therefore, the cumulative risk of developing an aneurysm could potentially be assessed by a genetic risk score, which certain studies have attempted to derive.^{10,11} Similarly, the same multigene concept could apply to derive genetic risk scores to predict aneurysm behaviors, such as growth rate and risk of rupture at a small size (<5.5 cm). In addition, clinical risk factors (e.g., smoking, atherosclerosis, and hypertension) often amplify the effect of common predisposing variants (effect modification).¹²⁻¹⁴ In other words, ATAA seems to follow a “rare, strong variant” causation, whereas sporadic AAA development is polygenic.

However, with the advent of new genetic technologies, whole exome sequencing and deep learning computational algorithms, the literature on thoracic aortic aneurysms, particularly isolated sporadic ATAA, is becoming even more detailed and comprehensive. One study compiling magnetic resonance images of the ascending aorta from over 36,000 individuals, used machine learning to identify 41 loci carrying alleles with a genome-wide association with isolated ATAA and create a polygenic risk score to predict their development. Among those genes, *ELN* (elastin) and *FBN1* (fibrillin 1) have a well-established causal relationship to known connective-tissue disease syndromes (Cutis laxa and Marfan syndrome, respectively).¹⁵ Moreover, Li et al recently utilized whole exome sequencing to derive a polygenic risk score predicting isolated ATAA development in selected patients, yielding promising results.¹⁶ Furthermore, despite being less extensively addressed in the bibliography

than both ATAA and AAA, a recent study has attempted to explore the genetics of DTAA, isolating 47 variants, 14 of which were also associated with ATAA.¹⁷

Previous studies have emphasized the cooccurrence of AAA and thoracic aortic aneurysms. In a study involving 324 AAA patients, Hultgren et al found that concurrent aortic pathology was more prevalent among female and elderly patients, with 94 participants having DTAA and 12 ATAAs, at the time of AAA diagnosis.^{18,19} Similarly, Dombrowski et al recommended that all patients diagnosed with AAA undergo a chest CT to screen for concurrent thoracic aortic aneurysms.¹⁹ With the advent of new technologies in genetic research, our understanding of the intricate genetic relationships between different types of aortic aneurysms is constantly increasing. As genome sequencing is becoming more widely available, along with the appropriate imaging to detect either concomitant or heterochronic aortic pathology, patients diagnosed with AAA will soon be given the choice to detect variants that increase their risk of developing aneurysms elsewhere along the aorta.

Genes Associated with both Ascending Thoracic Aortic Aneurysm and Abdominal Aortic Aneurysm

This section provides an overview of the genes and molecular pathways associated with both ATAA and AAA, as illustrated in the Venn diagram (► Fig. 1). Despite the paucity of data from genome-wide association studies (GWAS) for many of these genes, their mutations were linked to AAA and/or ATAA in case-control or family sequencing studies.

Extracellular Matrix Structural Genes

Genes that code for enzymes involved in the ECM structure and remodeling were found to cause both sporadic AAA and sporadic ATAA, as well as heritable AAA and ATAA. Fibrillin is known to form a scaffold around elastin, with both of those constituents contributing to the ECM structure. Where elastin offers extensibility, collagen confers strength and durability to the ECM. With regard to AAA, Dobrin et al showed that defects in the structure of elastin are associated with aneurysm expansion, whereas collagen structure defects increase the risk of aneurysm rupture.²⁰ However, weakening of the walls of the aorta can result from a defect in any of its vital connective tissue components.

FBN1 has classically been associated with Marfan syndrome. Mutations in this gene, however, have also been associated with hereditary nonsyndromic cases of the disease. In addition, a recent study by Ashvetiya reported seven new aneurysm loci in *FBN1* correlated with sporadic ATAA.²¹ With regard to AAA, a smaller case series by MacSweeney et al found a polymorphism in *FBN1* to be positively associated with AAA, even after accounting for clinical and hemodynamic risk factors.²² At a GWAS level, one study has found a mutation in *FBN1*, significantly associated with sporadic AAA. The same mutation was also associated with intracranial aneurysm (IA): a large meta-analysis was conducted using 1,000 Genome Project's GWAS data from four cohorts as well as data from six previously published case-control studies.²³ The authors found that two SNPs in *FBN1* were

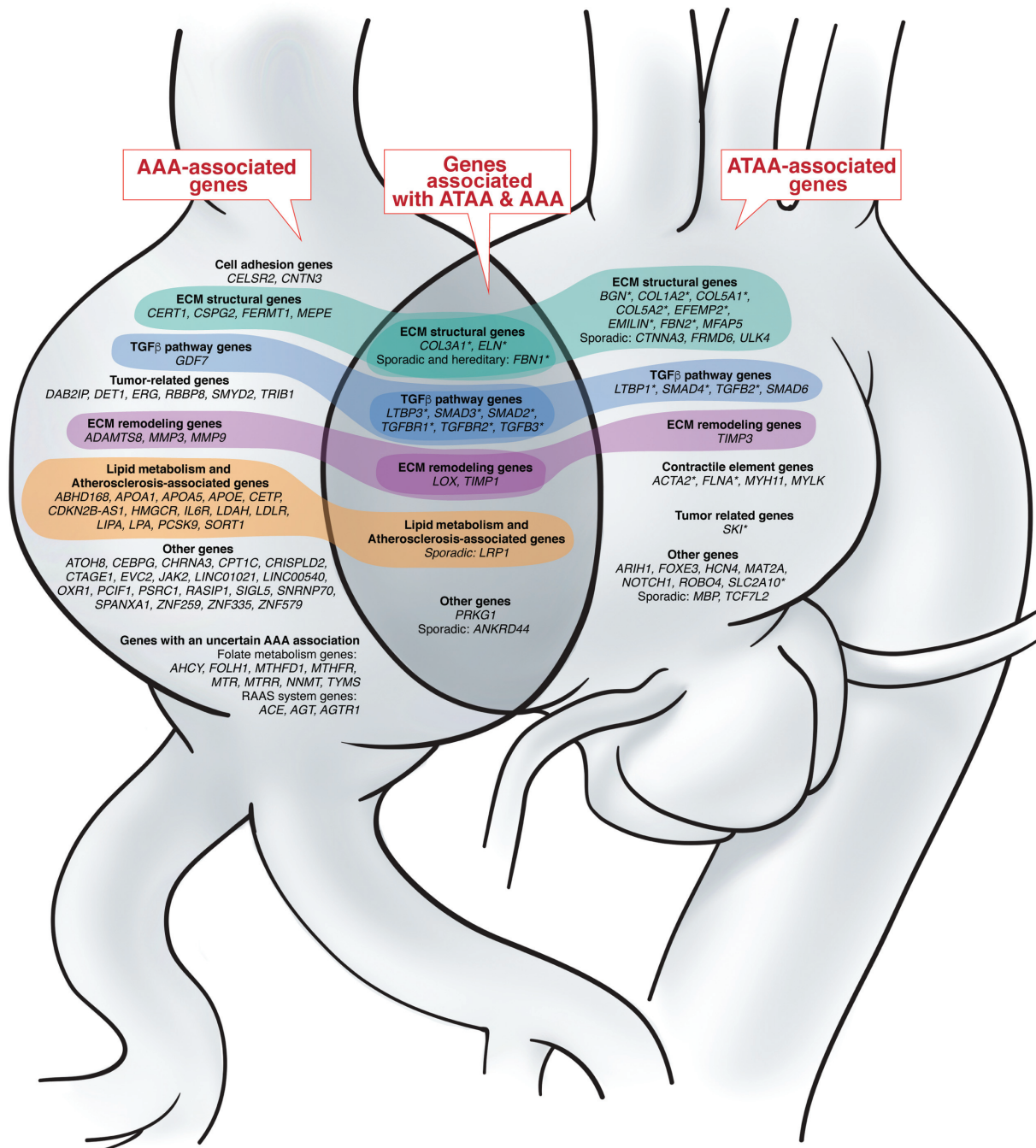


Fig. 1 Venn diagram of pathways and genes associated with ascending thoracic aortic aneurysm (ATAA) and with abdominal aortic aneurysm (AAA). Note: Common genes are displayed in central overlap zone. RAAS: renin-angiotensin-aldosterone system. “*” denotes the association of a gene with a known genetic syndrome (see ►Table 2). “Sporadic” denotes the association of a gene, or group of genes, with sporadic ATAA. Unless otherwise stated, all ATAA genes are associated with hereditary ATAA. Genes with an uncertain AAA association: Genes for which more studies (e.g., genome-wide association studies and meta-analyses) need to be undertaken to establish a strong level of significance to sporadic AAA.

associated with both AAA and ATAA (rs10519177 and rs2118181), and one SNP (rs595244) was associated with all three AAA, IA, and ATAA. AAA cases investigated were primarily isolated and sporadic.

The collagen (*COL3A1*) gene has been implicated in Ehlers–Danlos syndrome, characterized by generalized connective tissue pathology that may include AAA as well as other types of aneurysms. *COL3A1* mutations are strongly

associated with the hereditary form of ATAA. Earlier sequencing studies did report polymorphisms associated with AAA clustering in families with polyaneurysmal phenotypes, such as Ehlers–Danlos type IV, as well as other types of aneurysms, including ATAA.^{24–26} AAA cases investigated by such sequencing studies were all familial and syndromic. Thus, despite involving AAA in syndromic cases, these genes did not predispose to isolated sporadic AAA.

A polymorphism in the *ELN* gene (rs2071307) was found to be associated with AAA in a single case-control study. This included a total of 846 patients and controls with no family history of AAA.²⁷ *ELN* gene mutations have also been found to be associated with both intracranial and ATAA.^{6,28} However, to date, no definitive association has been found between heritable or sporadic ATAA and *ELN* mutations.²⁹

Extracellular Matrix Remodeling Genes

LOX (lysyl oxidase), *TIMP* (tissue inhibitor of metalloproteinases), *MMP* (matrix metalloproteinases), and *ADAMTS* (a disintegrin and metalloproteinase with thrombospondin motifs) are genes involved in ECM remodeling and, when mutated, have been implicated in aneurysm pathogenesis. Out of all ECM remodeling genes, however, only *LOX* and *TIMP* have been found to harbor mutations associated with both AAA and ATAA.

LOX mutations have been associated with both thoracic and AAA. Lee et al in 2016 reported a family with multiple aneurysms harboring a mutation in *LOX*, associated with ATAA as well as AAA in its members. A strong association exists between heritable ATAA and *LOX* according to a review by Renard et al but there have been no GWAS-level data with regard to the association between *LOX* loci and sporadic ATAA or sporadic AAA.²⁹

The various *TIMP* subtypes (*TIMP1*, 2, and 3) seem to have a weaker AAA/ATAA association, based on recent studies. Tilson et al first identified (in 1993) a substitution (434C > T) in *TIMP1* that resulted in a mutation, associated with increased risk of AAA in a small group of patients.³¹ *TIMP1* mutations are X-linked traits (Xq11.3); thus, they may show overexpression in male populations. Subsequent case-control studies proved that other polymorphisms in *TIMP1* were associated with AAA but had opposite effects, either increasing or decreasing the risk of developing the disease.^{32–34} According to some studies, *TIMP1* and *TIMP3* are known to harbor ATAA causative mutations, but a recent review was not able to detect a strong association between *TIMP* mutations and hereditary ATAA.^{6,29} In addition, no GWAS has demonstrated a relationship between sporadic ATAA and any of the proposed *TIMP* mutations, pointing toward a weaker genetic association.

Tumor Growth Factor β Pathway Genes

Tumor growth factor β (TGF β) pathway genes play a role in vessel wall inflammation in aneurysm formation. When secreted, TGF β forms an inactive, latent complex with other proteins, such as *LTBP* (latent TGF β -associated protein). Once TGF β binds its receptor, it activates a downstream pathway that leads to *SMAD* (an intranuclear transcription factor) activation and gene expression regulation.³⁵

TGF β pathway genes with a proposed role in both thoracic and AAA development include *LTBP3*, *SMAD2* (small mothers against decapentaplegic 2), *SMAD3*, *TGFB3*, *TGFB1* (TGF β receptor 1), and *TGFB2* (TGF β receptor 2). Mutations in some of the aforementioned genes are part of known connective tissue disease syndromes, including Loeys–Dietz types I (*TGFB1*), II (*TGFB2*), III (*SMAD3*), and V (*TGFB3*), as

well as an “osteoarthritis-aneurysms syndrome” (*SMAD2*). *LTBP3* was not found to be associated with any known connective tissue disease syndrome but was associated with both types of aneurysms in one family.⁶ Strong association between hereditary, nonsyndromic ATAA and TGF β pathway-related mutations only exists regarding *SMAD3*, *TGFB1*, and *TGFB2*, but not *TGFB2* mutations. Regarding AAA, there have been no GWAS-level data supporting a strong sporadic disease-TGF β pathway association. Two major case-control studies investigating AAA-associated mutations in a subset of the aforementioned genes primarily included familial-syndromic cases; Baas et al located 11 SNPs associated with increased AAA risk: 3 in *TGFB1* (rs10819634, rs1571590, and rs1626340), and 8 in *TGFB2* (rs3087465, rs1036095, rs4522809, rs13075948, rs9831477, rs1346907, rs9843143, and rs304839); Thompson found one SNP in *TGFB3* (rs11466414) associated with slower AAA growth.^{13,36} The role of these mutations in the development of sporadic AAA remains unclear.

Lipid Metabolism and Atherosclerosis-Related Genes

A strong association exists between lipid metabolism-loci and sporadic AAA, as multiple GWAS have established. On the contrary, Guo et al showed that rs11172113 in *LRP1* is associated also with sporadic ATAA in a GWAS including 753 patients. *LRP1* is the only atherosclerosis-associated gene associated with any form of ATAA, consistent with ATAA's being a nonarteriosclerotic process.³⁷

Other Genes

Finally, SNPs in two other genes are reportedly associated with both types of aneurysms, but their pathways did not fit into any of the above functional categories. These include *PRKG1* (protein kinase cyclic guanine monophosphate dependent 1), a protein involved in the nitric oxide pathway associated with vasodilation, and *ANKRD44* (ankyrin repeat domain 44) that plays a role in endocytosis.^{13,27,38} Only *PRKG1*, however, seems to have a strong association with hereditary nonsyndromic ATAA.⁶ Its association with AAA, however, is uncertain outside the context of small, family sequencing studies. The converse seems to be true regarding *ANKRD44*, a gene with a GWAS-level association with sporadic AAA, but no strong evidence linking it to either sporadic or hereditary, syndromic or nonsyndromic, ATAA.²³

Genes Associated with Abdominal Aortic Aneurysm Only

As illustrated in the Venn diagram (►Fig. 1), we have grouped genes associated with AAA only into seven categories. The following section will focus on genes associated with sporadic AAA only. ►Table 1 provides a summary of all the SNPs confirmed by GWAS as well as the corresponding odds ratios (ORs). Importantly, in this section, we only included genes associated with sporadic AAA.

Lipid Metabolism and Atherosclerosis-Associated Genes

While not associated with hereditary ATAA, atherosclerosis and AAA coexist in a large proportion of patients. Lipid

Table 1 SNPS associated with AAA based on GWAS

Author, year (GWAS)	Locus/gene	SNP rs(id)	OR	p-Value	RAF ^{co}	RAF ^{ca}	Major allele	Ref allele	Functional consequence
Ashvetiya et al, 2021 ²¹	<i>LINC01021</i>	rs116390453	2.50	4.26×10^{-9}	NR	NR	C	T	Intergenic variant
	<i>JAK2</i>	rs193181528	2.78	3.26×10^{-8}	NR	NR	T	C	Intron variant
	<i>ATOH8</i>	rs113626898	2.71	9.06×10^{-9}	NR	NR	G	A	3' prime UTR variant
Klarin et al 2020 ¹⁰	<i>AC012065.7/ LDAH</i>	rs7255	1.10	8.58×10^{-13}	0.488	0.463	C	T	Noncoding transcript exon variant
	<i>MEPE</i>	rs10023907	1.09	1.90×10^{-8}	0.665	0.684	T	T	Downstream gene variant
	<i>CDKN1A</i>	rs3176336	1.10	9.50×10^{-11}	0.402	0.425	A	T	Intron variant
	<i>RP11-136O12.2/ TRIB1</i>	rs10808546	1.10	1.05×10^{-10}	0.564	0.587	C	C	Intron variant
	<i>LIPA</i>	rs1412445	1.10	1.46×10^{-10}	0.338	0.360	C	T	Intron variant
	<i>ZNF259/ APOA5</i>	rs964184	1.18	4.59×10^{-19}	0.139	0.160	C	G	3' prime UTR variant
	<i>ADAMTS8</i>	rs4936098	1.13	7.00×10^{-16}	0.629	0.657	G	G	Intron variant
	<i>CRISPLD2</i>	rs35254673	1.09	3.11×10^{-8}	0.254	0.270	A	G	Intron variant
	<i>CTAGE1</i>	rs4401144	1.11	3.63×10^{-14}	0.482	0.508	T	T	Regulatory region variant
	<i>APOE</i>	rs429358	1.17	1.16×10^{-15}	0.139	0.159	T	C	Missense variant
	<i>PCSK9</i>	rs11591147	1.58	6.43×10^{-11}	0.984	0.990	G	G	Missense variant
	<i>LPA</i>	rs118039278	1.28	3.64×10^{-18}	0.066	0.082	G	A	Intron variant
	<i>CHRNA3</i>	rs55958997	1.12	9.06×10^{-14}	0.367	0.393	C	A	Upstream gene variant
	<i>ABHD16B</i>	rs73149487	1.26	8.33×10^{-9}	0.957	0.965	G	G	Intergenic variant
Tang et al, 2019 ³⁴	<i>PCIF1/MMP9/ZNF335</i>	rs3827066	1.22	0.03	0.159	0.187	C	T	Intron variant
Harrison et al, 2017 ⁴²	<i>HMGCR</i>	rs12916	0.93	0.009	NR	NR	T	C	3' prime UTR variant
	<i>CETP</i>	rs3764261	0.89	3.7×10^{-7}	NR	NR	C	C	None
	<i>PCSK9</i>	rs11206510	0.94	0.04	NR	NR	T	C	None
Bradley et al, 2016 ⁴³	<i>APOA1</i>	rs964184	1.20	6.8×10^{-3}	NR	NR	NR	NR	NR
	<i>MMP3</i>	rs3025058	0.61	1.6×10^{-5}	NR	NR	NR	6A/6A	NR
van 't Hof et al, 2016 ²³	<i>CDKN2B-AS1</i>	rs7866503	1.26	2.06×10^{-13}	0.416	0.465	G	T	Intron variant
	<i>RNU6-1032P, RPS4XP18 (RBBP8)</i>	rs8087799	1.21	1.58×10^{-9}	0.327	0.367	G	A	Regulatory region variant
	<i>FBN1</i>	rs595244	1.35	1.01×10^{-8}	0.082	0.102	C	T	Intron variant
	<i>ANKRD44-IT1, ANKRD44</i>	rs919433	1.18	4.55×10^{-8}	0.410	0.416	G	A	Intron variant
	<i>RBBP8</i>	rs11661542	1.11	4.1×10^{-5}	NR	NR	C	C	NR
	<i>FBN1</i>	rs10519177	1.01	0.016	NR	NR	A	G	Intron variant
	<i>FBN1</i>	rs2118181	1.07	1.1×10^{-3}	NR	NR	T	G	Intron variant
Jones et al, 2016 ⁸	<i>IL6R</i>	rs12133641	1.12	3.1×10^{-6}	0.386	0.417	A	A	Intron variant
	<i>CDKN2B-AS1</i>	rs10757274	0.83	2.7×10^{-14}	0.555	0.511	A	A	Intron variant
	<i>DAB2IP</i>	rs10985349	1.18	2.0×10^{-7}	0.213	0.243	C	T	Intron variant
	<i>LRP1</i>	rs1385526	0.85	3.1×10^{-10}	0.419	0.395	G	C	Intron variant
	<i>SMYD2/ LINC02775</i>	rs1795061	1.15	3.3×10^{-7}	0.395	0.425	C	T	Intergenic variant
	<i>AL512484.1/ LINC00540</i>	rs9316871	0.86	1.23×10^{-6}	0.181	0.176	A	G	Intergenic variant
	<i>PCIF1</i>	rs58749629	1.22	1.9×10^{-10}	0.119	0.149	G	A	Intron variant
	<i>ERG</i>	rs2836411	1.14	2.5×10^{-8}	0.333	0.333	C	T	Intron variant
	<i>AL118505.1, FERMT1</i>	rs6516091	1.26	6.8×10^{-11}	0.094	0.096	G	A	Intergenic variant

(Continued)

Table 1 (Continued)

Author, year (GWAS)	Locus/gene	SNP rs(id)	OR	p-Value	RAF ^{co}	RAF ^{ca}	Major allele	Ref allele	Functional consequence
	<i>GDF7, LDAH</i>	rs13382862	0.86	8.8×10^{-9}	0.368	0.342	G	A	Regulatory region variant
	<i>PSRC1/ CELSR2/ SORT1</i>	rs602633	0.84	3.1×10^{-8}	0.209	0.194	G	T	Intergenic variant
	<i>EVC2</i>	rs10029392	1.33	1.4×10^{-6}	0.045	0.059	G	T	Intron variant
	<i>COL4A3BP (CERT1)</i>	rs12659791	1.19	2.6×10^{-7}	0.126	0.128	C	T	Intron variant
	<i>OXR1</i>	rs3110425	0.88	1.1×10^{-6}	0.387	0.348	C	T	Upstream gene variant
	<i>DET1</i>	rs17189674	1.21	3.6×10^{-7}	0.145	0.165	G	A	NR
	<i>ZNF579</i>	rs12980543	1.15	3.0×10^{-6}	0.094	0.096	G	A	NR
	<i>SPANXA1</i>	rs5954362	0.64	1.0×10^{-9}	0.287	0.200	G	G	2KB upstream variant
Bradley et al, 2013 ⁴¹	<i>LDLR</i>	rs6511720	0.76	2.08×10^{-10}	0.102	0.080	G	T	Intron variant
Bown et al, 2011 ⁵⁰	<i>LRP1</i>	rs1466535	1.15	4.52×10^{-10}	0.630	0.670	C	C	Intron variant
Gretarsdottir et al, 2010 ⁴⁰	<i>CDKN2B-AS1</i>	rs2383207	1.27	1.9×10^{-8}	0.457	0.524	G	G	Intron variant
	<i>CDKN2B-AS1</i>	rs1333040	1.25	1.6×10^{-7}	0.491	0.543	T	T	Intron variant
	<i>CDKN2B-AS1</i>	rs10116277	1.26	6.0×10^{-8}	0.418	0.470	T	T	Intron variant
	<i>DAB2IP</i>	rs7025486	1.21	4.6×10^{-10}	0.298	0.347	G	A	Intron variant
Baas et al, 2010 ³⁶	<i>CEBPG</i>	rs16968029	1.36	0.004	0.710	0.770	C	C	Intron variant
	<i>RASIP1</i>	rs281407	1.32	0.004	0.319	0.383	G	A	Intron variant
	<i>CPT1C</i>	rs1075453	1.32	0.004	0.589	0.663	G	C	Downstream transcript variant
	<i>SNRNP70</i>	rs4802552	1.54	0.004	0.120	0.810	C	A	Intron variant
	<i>SIGLEC5</i>	rs1530878	1.35	0.005	0.222	0.278	G	C	Intron variant
	None	rs285676	1.28	0.008	0.863	0.903	A	A	None
	None	rs576556	1.47	0.012	0.638	0.693	C	C	None
	None	rs6509496	1.26	0.013	0.573	0.629	C	C	None
Baas et al, 2010 ⁴⁹	<i>CSPG2 (VCAN)</i>	rs2652106	1.26	0.019	0.262	0.310	C	A	Intergenic variant
Elmore et al, 2009 ⁵²	<i>CNTN3</i>	rs7635818	1.33	0.003	0.417	0.480	G	C	Intergenic variant
Jones and van Rij, 2009 ⁵³	<i>CNTN3</i>	rs9876789	0.66	0.016	0.082	0.056	G	A	Intron variant (CNTN3 intron 2)
	<i>CNTN3</i>	rs6549604	0.71	0.033	0.091	0.067	C	T	Intron variant (CNTN3 intron 2)
	<i>CNTN3</i>	rs4076052	0.59	0.044	0.035	0.021	C	A	Intron variant (CNTN3 intron 2)

Abbreviations: AAA, abdominal aortic aneurysm; GWAS, genome-wide association study; NR, no reference; OR, odds ratio; RAF^{ca}, reference allele frequency in cases; RAF^{co}, reference allele frequency in controls; RefA, reference allele (risk or protective); SNP rs(id), single nucleotide polymorphism.

Note: ► **Table 1** lists authors and dates for all GWAS findings of association with AAA, as well as the gene name (or locus) and SNP specific id. The next seven columns list, in the following order: odds ratio by which the specific SNP increases the likelihood of AAA, p-value (statistical significance of the difference between reference allele frequency in cases and controls), reference allele frequency in cases and controls, major allele (the most common allele variation), the reference allele (risk or protective), and the functional consequence of the reference allele. Multiple genes or loci separated by “/” imply multiple genes in close proximity to that polymorphism.

metabolism and atherosclerosis-associated genes harbor numerous SNPs associated with sporadic AAA based on GWAS.⁶ Intramural lipid accumulation engenders luminal stenosis, which brings about compensatory expansion of the aortic wall via changes in the vessel media, thus favoring aneurysm formation.³⁹ First in 2010, Gretarsdottir identified three polymorphisms, rs2383207, rs1333040, and rs10116277 in *CDKN2B-AS1* (*CDKN2B* antisense RNA 1) associated with AAA.⁴⁰ In the following years, several

more genome-wide associations were made with receptors and enzymes involved in the lipid pathway, such as rs6511720 in *LDLR* (LDL receptor), rs11591147 in *PCSK9* (pro-protein convertase subtilisin/kexin type 9), and others (► **Table 1**).^{10,41,42} Bradley found one additional lipid metabolism-related locus with a significant AAA association, in *APOA1* (rs964184, apolipoprotein A1).⁴³ Most recently, a study through the Million Veteran Program identified seven additional SNPs associated with AAA including rs11206510

Table 2 Genes associated with syndromic thoracic aortic aneurysm and/or dissection

Genes	Genetic syndrome
<i>ACTA2</i>	Multisystemic smooth muscle dysfunction
<i>BGN</i>	Meester–Loeys syndrome
<i>COL1A2</i>	EDS, arthrochalasia type VIIb
<i>COL3A1</i>	EDS, vascular type IV
<i>COL5A1</i>	EDS, vascular type I
<i>COL5A2</i>	EDS, classical type II
<i>EFEMP2</i>	Cutis laxa, AR
<i>ELN</i>	Cutis laxa, AD
<i>EMILIN1</i>	CTD and peripheral neuropathy
<i>FBN1</i>	Marfan syndrome
<i>FBN2</i>	Contractural arachnodactyly
<i>FLNA</i>	Periventricular nodular heterotopia and otopalatodigital syndrome
<i>LTBP1</i>	Aortic dilation with associated musculoskeletal findings
<i>LTBP3</i>	Dental anomalies and short stature
<i>SKI</i>	Arterial tortuosity syndrome
<i>SLC2A10</i>	Unidentified CTD with arterial aneurysm/dissections
<i>SMAD2</i>	LDS type III
<i>SMAD3</i>	JP/HHT syndrome
<i>SMAD6</i>	AOVD
<i>TGFB2</i>	LDS type IV
<i>TGFB3</i>	LDS type V
<i>TGFBR1</i>	LDS type I
<i>TGFBR2</i>	LDS type II

Abbreviations: AD, autosomal dominant; AOVD, aortic valve disease; AR, autosomal recessive; CTD, connective tissue disease; EDS, Ehler–Danlos syndrome; HHT, hereditary hemorrhagic telangiectasia; JP, juvenile polyposis; LDS, Loeys–Dietz syndrome.

Note: Reproduced with permission from Vinholo et al.⁶

in PCSK9 (odds ratio = 1.58, $p = 6.43 \times 10^{-11}$) and rs118039278 in LPA (odds ratio = 1.28, $p = 3.64 \times 10^{-18}$; ▶ **Table 1**).⁶

Folate Metabolism and Renin Angiotensin Aldosterone-Associated Genes

Homocysteinemia resulting from folate deficiency has been associated with the formation of AAA, while hypertension resulting from renin–angiotensin–aldosterone (RAA) system dysregulation could contribute to AAA expansion. Case-control studies, but no GWAS to date, have found significant associations between AAA and RAA-system genes: rs4646994 in *ACE* (angiotensin-converting enzyme), rs5186 in *AGTR1* (angiotensin II receptor type 1), and rs699 in *AGT* (angiotensinogen).^{44,45} With regard to folate metabolism genes, case-control studies showed that rs8003379 in *MTHFD1* (methylenetetrahydrofolate dehydrogenase, cyclohydrolase, and formyltetrahydrofolate synthetase 1),

rs326118 in *MTRR* (5-methyltetrahydrofolate-homocysteine methyltransferase reductase), and rs2853523 in *MTR* (5-methyltetrahydrofolate-homocysteine methyltransferase) were associated with AAA.^{6,46–48}

Extracellular Matrix Structural and Extracellular Matrix Remodeling Genes

ECM genes can serve a structural or a functional role. With regard to structural ECM genes, Jones located two polymorphisms associated with AAA, rs6516091 in *FERMT1* (fermitin family member 1) and rs12659791 in *CERT1* (ceramide transporter 1). Bradley identified rs3025058 in *MMP3*.⁴³ Subsequent studies found rs2652106 in *CSPG2* (chondroitin sulphate proteoglycan 2) and rs10023907 in *MEPE* (matrix extracellular phosphoglycoprotein).^{10,49} Regarding ECM remodeling genes, Tang et al identified rs3827066 in *MMP9* and Klarin et al found rs4936098 in *ADAMTS8* (ADAM metalloproteinase with thrombospondin type 1 motif 8).^{10,34}

Tumor Growth Factor β Pathway Genes

With regard to TGF β pathway genes, so far only one polymorphism has been shown to have a significant association with sporadic AAA at a GWAS level; rs13382862 in *GDF7* (growth differentiation factor 7).⁸

Tumor-Associated Genes

Tumor-related genes include those with direct oncogenic or tumor suppressive properties or genes coding for molecules that regulate the function of such genes. Several genes have been identified, many of which have acquired a GWAS-level significance. van't Hof identified two polymorphisms in *RBBP8* (retinoblastoma binding protein 8), rs8087799 and rs11661542, in a GWAS-like meta-analysis that included a large patient population.²³ Rs8087799 in particular was found to be associated with AAA in addition to ATAA and IAs. Moreover, Gretarsdottir et al⁴⁰ identified rs7025486 in *DAB2IP* (disabled homolog 2-interacting protein), and Jones et al 2016 located rs10985349 in the same gene. Jones et al⁴⁵ in 2016 also found rs1795061 in *SMYD2* (SET and MYND domain containing 2), rs2836411 in *ERG* (ETS transcription factor), and rs17189674 in *DET1* (deetiolated 1). Finally, Klarin et al found rs10808546 in *TRIB1* (tribbles pseudokinase 1) to be an oncogenic gene with AAA association.¹⁰

Cell Adhesion Molecule-Associated Genes

Cell adhesion molecules constitute another category that has reached GWAS level association with sporadic nonsyndromic AAA.⁶ Intercellular adhesion molecules within the wall layers of the abdominal aorta contribute to the organ's structural integrity, and dysfunctional adhesions can contribute to aneurysm formation. Polymorphisms associated with *CNTN3* (contactin 3), namely rs9876789, rs6549604, rs4076052, and rs7635818 (200kbp upstream of the gene's transcription start site) and rs602633 in *CELSR2* (cadherin epidermal growth factor laminin G seven-pass G-type receptor 2) were associated with sporadic nonsyndromic AAA on a GWAS level.^{52–54}

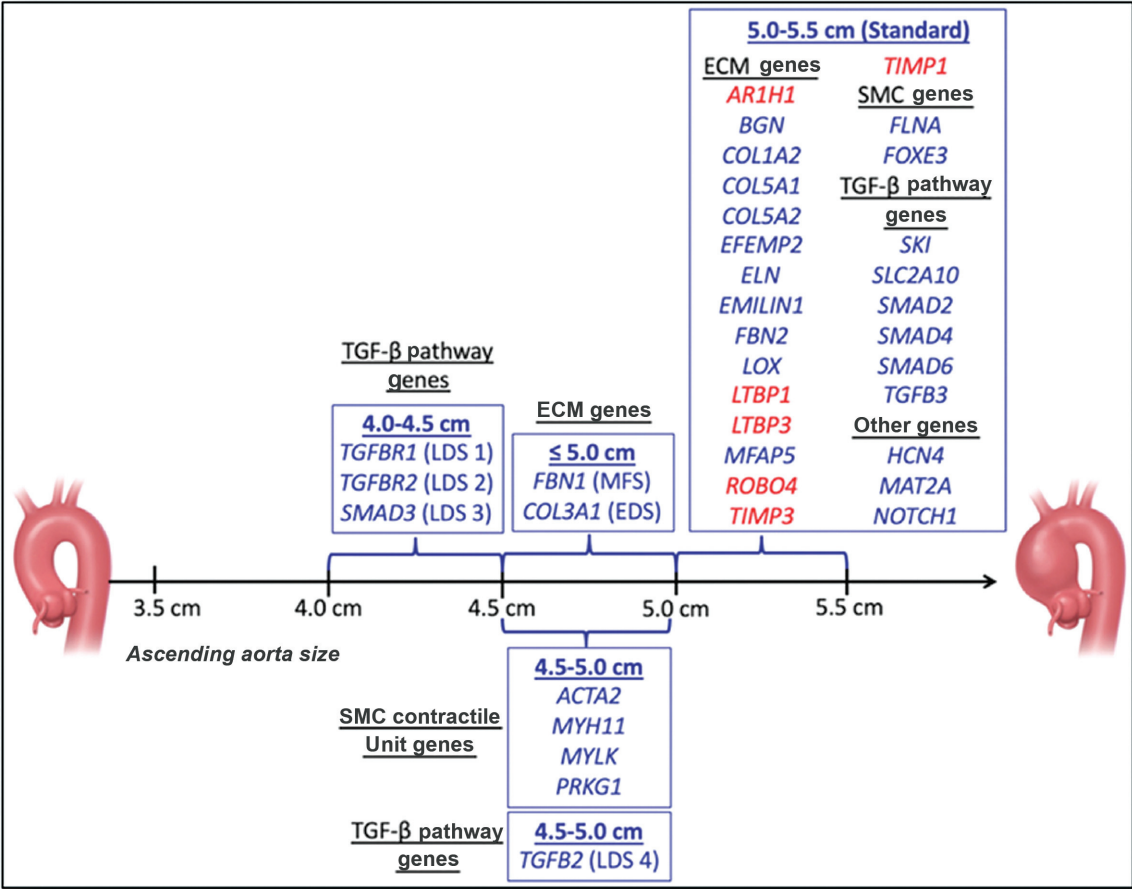


Fig. 2 Genes involved in thoracic aortic aneurysm. Genes associated with thoracic aortic aneurysm, showing also the recommended aortic sizes for surgical intervention. Reproduced with permission from Vinholo et al.⁶

Other Genes

There are numerous other genes harboring SNPs with a GWAS-level AAA association that do not fit into any of the prior categories. These genes code for various molecules including proteins involved in MHCII (major histocompatibility complex II) presentation, β oxidation, and cellular energy management, as well as lectins or transcription factors regulating the expression of other genes; these genes are organized in ►Fig. 1, and their associated SNPs, ORs and p-values are listed in ►Table 1.

Genes Associated with Ascending Thoracic Aortic Aneurysm Only

Several genes responsible for ATAA have been identified over the last decades. An extensive detailed review can be found in a recent article by Vinholo et al.⁶ For the sake of completion, ►Fig. 2 provides a visual summary with grouping according to the biological system affected by each gene.

Conclusion

This paper provides a broad overview of the genetics of AAA and ATAA focusing on the overlapping SNPs and pathways. Genetic discoveries to date reflect the clinical observation

that AAA and ATAA, as well as their subtypes (sporadic, hereditary syndromic, and hereditary nonsyndromic) are separate disease entities. Genes harboring mutations for both AAA and ATAA seem to be limited largely to connective tissue syndromes and mutations in genes causing pan-aneurysmal disease. There seems to be minimal overlap between sporadic forms of AAA and ATAA, especially in atherosclerosis-related genes.

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