Comparison of Genes Associated with Thoracic and Abdominal Aortic Aneurysms

Argyrios Gyftopoulos, MD[1] Bulat A. Ziganshin, MD, PhD[2] John A. Elefteriades, MD, PhD (Hon)[2]
Cassius I. Ochoa Chaar, MD, MS[3]

[1] National Kapodistrian University of Athens, School of Medicine, Athens, Greece
[2] Aortic Institute, Yale University School of Medicine, New Haven, Connecticut
[3] Division of Vascular Surgery and Endovascular Therapy, Department of Surgery, Yale University School of Medicine, New Haven, Connecticut

Address for correspondence Cassius I. Ochoa Chaar, MD, MS, Division of Vascular Surgery and Endovascular Therapy, Department of Surgery, Yale University School of Medicine, Boardman 204, 333 Cedar Street, New Haven, CT 06510 (e-mail: cassius.chaar@yale.edu).

Aorta (Stamford) 2023;11:125–134.

Abstract

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.

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

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.

received
June 23, 2022
accepted after revision
December 9, 2022
article published online
June 6, 2023

DOI https://doi.org/10.1055/s-0043-57266.
ISSN 2325-4637.

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

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 DTAAs 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

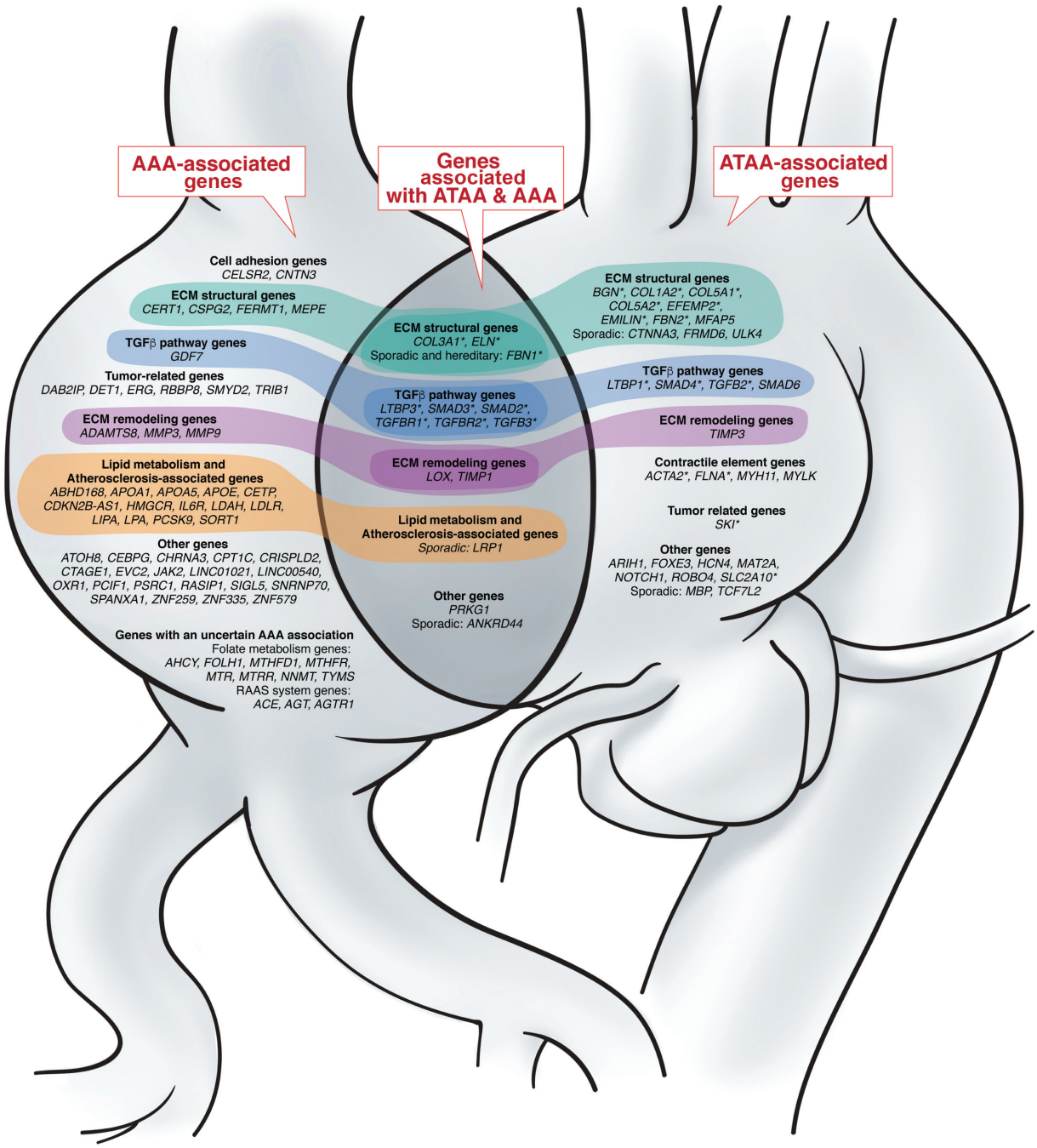

Fig. 1 Venn diagram of pathways and genes associated with ascending thoracic aortic aneurysm (ATAA) and with abdominal aortic aneurysm (AAA). Note: Common genes are displayed in central overlap zone. RAAS: renin–angiotensin–aldosterone system. ''*'' denotes the association of a gene with a known genetic 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 (TGFβ) pathway genes play a role in vessel wall inflammation in aneurysm formation. When secreted, TGBβ forms an inactive, latent complex with other proteins, such as *LTBP* (latent TGFβ-associated protein). Once TGFβ binds its receptor, it activates a downstream pathway that leads to *SMAD* (an intranuclear transcription factor) activation and gene expression regulation.[35]

TGFβ pathway genes with a proposed role in both thoracic and AAA development include *LTBP3*, *SMAD2* (small mothers against decapentaplegic 2), *SMAD3*, *TGFB3, TGFBR1* (TGFβ receptor 1), and *TGFBR2* (TGFβ receptor 2). Mutations in some of the aforementioned genes are part of known connective tissue disease syndromes, including Loeys–Dietz types I (*TGFBR1*), II (*TGFBR2*), 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 TGFβ pathway-related mutations only exists regarding *SMAD3*, *TGFBR1*, and *TGFBR2,* but not *TGFB2* mutations. Regarding AAA, there have been no GWAS-level data supporting a strong sporadic disease-TGFβ 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 *TGFBR1* (rs10819634, rs1571590, and rs1626340), and 8 in *TGFBR2* (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]	*LINC01021*	rs116390453	2.50	4.26×10^{-9}	NR	NR	C	T	Intergenic variant
	JAK2	rs193181528	2.78	3.26×10^{-8}	NR	NR	T	C	Intron variant
	ATOH8	rs113626898	2.71	9.06×10^{-9}	NR	NR	G	A	3′ prime UTR variant
Klarin et al 2020[10]	*AC012065.7/ LDAH*	rs7255	1.10	8.58×10^{-13}	0.488	0.463	C	T	Noncoding transcript exon variant
	MEPE	rs10023907	1.09	1.90×10^{-8}	0.665	0.684	T	T	Downstream gene variant
	CDKN1A	rs3176336	1.10	9.50×10^{-11}	0.402	0.425	A	T	Intron variant
	RP11-136O12.2/ TRIB1	rs10808546	1.10	1.05×10^{-10}	0.564	0.587	C	C	Intron variant
	LIPA	rs1412445	1.10	1.46×10^{-10}	0.338	0.360	C	T	Intron variant
	ZNF259/ APOA5	rs964184	1.18	4.59×10^{-19}	0.139	0.160	C	G	3′ prime UTR variant
	ADAMTS8	rs4936098	1.13	7.00×10^{-16}	0.629	0.657	G	G	Intron variant
	CRISPLD2	rs35254673	1.09	3.11×10^{-8}	0.254	0.270	A	G	Intron variant
	CTAGE1	rs4401144	1.11	3.63×10^{-14}	0.482	0.508	T	T	Regulatory region variant
	APOE	rs429358	1.17	1.16×10^{-15}	0.139	0.159	T	C	Missense variant
	PCSK9	rs11591147	1.58	6.43×10^{-11}	0.984	0.990	G	G	Missense variant
	LPA	rs118039278	1.28	3.64×10^{-18}	0.066	0.082	G	A	Intron variant
	CHRNA3	rs55958997	1.12	9.06×10^{-14}	0.367	0.393	C	A	Upstream gene variant
	ABHD16B	rs73149487	1.26	8.33×10^{-9}	0.957	0.965	G	G	Intergenic variant
Tang et al, 2019[34]	*PCIF1/MMP9/ZNF335*	rs3827066	1.22	0.03	0.159	0.187	C	T	Intron variant
Harrison et al, 2017[42]	*HMGCR*	rs12916	0.93	0.009	NR	NR	T	C	3′ prime UTR variant
	CETP	rs3764261	0.89	3.7×10^{-7}	NR	NR	C	C	None
	PCSK9	rs11206510	0.94	0.04	NR	NR	T	C	None
Bradley et al, 2016[43]	*APOA1*	rs964184	1.20	6.8×10^{-3}	NR	NR	NR	NR	NR
	MMP3	rs3025058	0.61	1.6×10^{-5}	NR	NR	NR	6A/6A	NR
van 't Hof et al, 2016[23]	*CDKN2B-AS1*	rs7866503	1.26	2.06×10^{-13}	0.416	0.465	G	T	Intron variant
	RNU6-1032P, RPS4XP18 (RBBP8)	rs8087799	1.21	1.58×10^{-9}	0.327	0.367	G	A	Regulatory region variant
	FBN1	rs595244	1.35	1.01×10^{-8}	0.082	0.102	C	T	Intron variant
	ANKRD44-IT1, ANKRD44	rs919433	1.18	4.55×10^{-8}	0.410	0.416	G	A	Intron variant
	RBBP8	rs11661542	1.11	4.1×10^{-5}	NR	NR	C	C	NR
	FBN1	rs10519177	1.01	0.016	NR	NR	A	G	Intron variant
	FBN1	rs2118181	1.07	1.1×10^{-3}	NR	NR	T	G	Intron variant
Jones et al, 2016[8]	*IL6R*	rs12133641	1.12	3.1×10^{-6}	0.386	0.417	A	A	Intron variant
	CDKN2B-AS1	rs10757274	0.83	2.7×10^{-14}	0.555	0.511	A	A	Intron variant
	DAB2IP	rs10985349	1,18	2.0×10^{-7}	0.213	0.243	C	T	Intron variant
	LRP1	rs1385526	0.85	3.1×10^{-10}	0.419	0.395	G	C	Intron variant
	SMYD2/ LINC02775	rs1795061	1.15	3.3×10^{-7}	0.395	0.425	C	T	Intergenic variant
	AL512484.1/ LINC00540	rs9316871	0.86	1.23×10^{-6}	0.181	0.176	A	G	Intergenic variant
	PCIF1	rs58749629	1.22	1.9×10^{-10}	0.119	0.149	G	A	Intron variant
	ERG	rs2836411	1.14	2.5×10^{-8}	0.333	0.333	C	T	Intron variant
	AL118505.1, FERMT1	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
	GDF7, LDAH	rs13382862	0.86	8.8×10^{-9}	0.368	0.342	G	A	Regulatory region variant
	PSRC1/ CELSR2/ SORT1	rs602633	0.84	3.1×10^{-8}	0.209	0.194	G	T	Intergenic variant
	EVC2	rs10029392	1,33	1.4×10^{-6}	0.045	0.059	G	T	Intron variant
	COL4A3BP (CERT1)	rs12659791	1.19	2.6×10^{-7}	0.126	0.128	C	T	Intron variant
	OXR1	rs3110425	0.88	1.1×10^{-6}	0.387	0.348	C	T	Upstream gene variant
	DET1	rs17189674	1.21	3.6×10^{-7}	0.145	0.165	G	A	NR
	ZNF579	rs12980543	1.15	3.0×10^{-6}	0.094	0.096	G	A	NR
	SPANXA1	rs5954362	0.64	1.0×10^{-9}	0.287	0.200	G	G	2KB upstream variant
Bradley et al, 2013[41]	*LDLR*	rs6511720	0.76	2.08×10^{-10}	0.102	0.080	G	T	Intron variant
Bown et al, 2011[50]	*LRP1*	rs1466535	1.15	4.52×10^{-10}	0.630	0.670	C	C	Intron variant
Gretarsdottir et al, 2010[40]	*CDKN2B-AS1*	rs2383207	1.27	1.9×10^{-8}	0.457	0.524	G	G	Intron variant
	CDKN2B-AS1	rs1333040	1.25	1.6×10^{-7}	0.491	0.543	T	T	Intron variant
	CDKN2B-AS1	rs10116277	1.26	6.0×10^{-8}	0.418	0.470	T	T	Intron variant
	DAB2IP	rs7025486	1.21	4.6×10^{-10}	0.298	0.347	G	A	Intron variant
Baas et al, 2010[36]	*CEBPG*	rs16968029	1.36	0.004	0.710	0.770	C	C	Intron variant
	RASIP1	rs281407	1.32	0.004	0.319	0.383	G	A	Intron variant
	CPT1C	rs1075453	1.32	0.004	0.589	0.663	G	C	Downstream transcript variant
	SNRNP70	rs4802552	1.54	0.004	0.120	0.810	C	A	Intron variant
	SIGLEC5	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]	*CSPG2 (VCAN)*	rs2652106	1.26	0.019	0.262	0.310	C	A	Intergenic variant
Elmore et al, 2009[52]	*CNTN3*	rs7635818	1.33	0.003	0.417	0.480	G	C	Intergenic variant
Jones and van Rij, 2009[53]	*CNTN3*	rs9876789	0.66	0.016	0.082	0.056	G	A	Intron variant (CNTN3 intron 2)
	CNTN3	rs6549604	0.71	0.033	0.091	0.067	C	T	Intron variant (CNTN3 intron 2)
	CNTN3	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
ACTA2	Multisystemic smooth muscle dysfunction
BGN	Meester–Loeys syndrome
COL1A2	EDS, arthrochalasia type VIIb
COL3A1	EDS, vascular type IV
COL5A1	EDS, vascular type I
COL5A2	EDS, classical type II
EFEMP2	Cutis laxa, AR
ELN	Cutis laxa, AD
EMILIN1	CTD and peripheral neuropathy
FBN1	Marfan syndrome
FBN2	Contractural arachnodactyly
FLNA	Periventricular nodular heterotopia and otopalatodigital syndrome
LTBP1	Aortic dilation with associated musculoskeletal findings
LTBP3	Dental anomalies and short stature
SKI	Arterial tortuosity syndrome
SLC2A10	Unidentified CTD with arterial aneurysm/dissections
SMAD2	LDS type III
SMAD3	JP/HHT syndrome
SMAD6	AOVD
TGFB2	LDS type IV
TGFB3	LDS type V
TGFBR1	LDS type I
TGFBR2	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 metallopeptidase with thrombospondin type 1 motif 8).[10,34]

Tumor Growth Factor β Pathway Genes

With regard to TGFβ 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 al[40] identified rs7025486 in *DAB2IP* (disabled homolog 2-interacting protein), and Jones et al 2016 located rs10985349 in the same gene. Jones et al[45] 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]

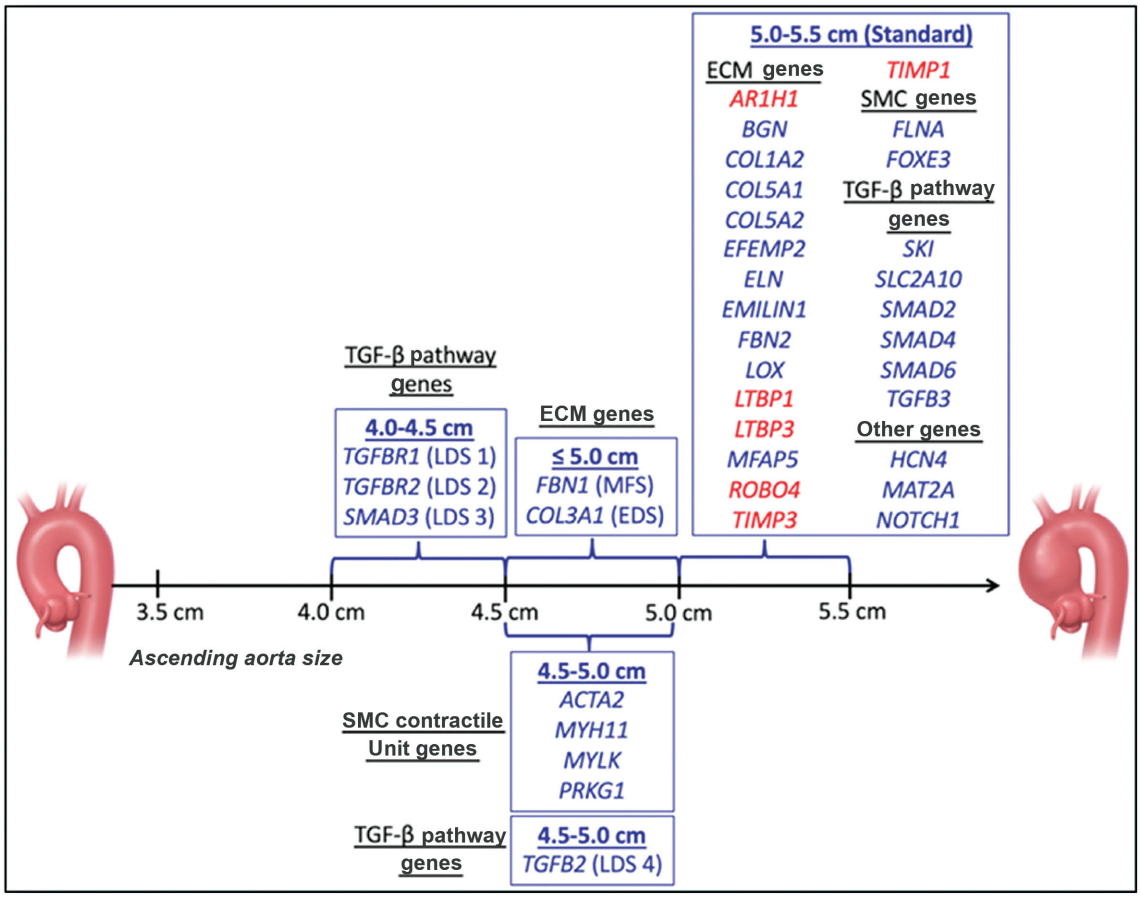

Fig. 2 Genes involved in thoracic aortic aneurysm. Genes associated with thoracic aortic aneurysm, showing also the recommended aortic sizes for surgical intervention. Reproduced with permission from Vinholo et al.[6]

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.

Funding
None.

Conflict of Interest
A.G.: None.
B.A.Z.: None
J.A.E.: Principal, CoolSpine; Consultant: Tissium
C.I.O.C.: None.

Acknowledgments
None.

References

1 Cornuz J, Sidoti Pinto C, Tevaearai H, Egger M. Risk factors for asymptomatic abdominal aortic aneurysm: systematic review

and meta-analysis of population-based screening studies. Eur J Public Health 2004;14(04):343–349
2 Wahlgren CM, Larsson E, Magnusson PKE, Hultgren R, Swedenborg J. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. J Vasc Surg 2010;51(01):3–7, discussion 7
3 Achneck H, Modi B, Shaw C, et al. Ascending thoracic aneurysms are associated with decreased systemic atherosclerosis. Chest 2005;128(03):1580–1586
4 Saeyeldin AA, Velasquez CA, Mahmood SUB, et al. Thoracic aortic aneurysm: unlocking the "silent killer" secrets. Gen Thorac Cardiovasc Surg 2019;67(01):1–11
5 Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. J Am Coll Cardiol 2010; 55(09):841–857
6 Vinholo TF, Brownstein AJ, Ziganshin BA, et al. Genes associated with thoracic aortic aneurysm and dissection: 2019 update and clinical implications. Aorta (Stamford) 2019;7(04):99–107
7 Rohde S, Zafar MA, Ziganshin BA, Elefteriades JA. Thoracic aortic aneurysm gene dictionary. Asian Cardiovasc Thorac Ann 2021;29 (07):682–696
8 Jones GT, Tromp G, Kuivaniemi H, et al. Meta-analysis of genome-wide association studies for abdominal aortic aneurysm identifies four new disease-specific risk loci. Circ Res 2017;120(02): 341–353
9 Visscher PM, Brown MA, McCarthy MI, Yang J. Five years of GWAS discovery. Am J Hum Genet 2012;90(01):7–24
10 Klarin D, Verma SS, Judy R, et al; Veterans Affairs Million Veteran Program† Genetic architecture of abdominal aortic aneurysm in the million veteran program. Circulation 2020;142(17): 1633–1646
11 Ye Z, Austin E, Schaid DJ, Kullo IJ. A multi-locus genetic risk score for abdominal aortic aneurysm. Atherosclerosis 2016; 246:274–279
12 Eriksson P, Jones KG, Brown LC, Greenhalgh RM, Hamsten A, Powell JT. Genetic approach to the role of cysteine proteases in the expansion of abdominal aortic aneurysms. Br J Surg 2004;91 (01):86–89
13 Thompson AR, Cooper JA, Jones GT, et al. Assessment of the association between genetic polymorphisms in transforming growth factor beta, and its binding protein (LTBP), and the presence, and expansion, of abdominal aortic aneurysm. Atherosclerosis 2010;209(02):367–373
14 Bellamkonda KS, Nassiri N, Sadeghi MM, Zhang Y, Guzman RJ, Ochoa Chaar CI. Characteristics and outcomes of small abdominal aortic aneurysm rupture in the American College of Surgeons National Surgical Quality Improvement Program database. J Vasc Surg 2021;74(03):729–737
15 Tcheandjieu C, Xiao K, Tejeda H, et al; Regeneron Genetics Center VA Million Veterans Program FinnGen Project. High heritability of ascending aortic diameter and trans-ancestry prediction of thoracic aortic disease. Nat Genet 2022;54(06):772–782
16 Li Y, Song L, Rong W, et al. Exome risk score for predicting susceptibility to and severity of isolated thoracic aortic aneurysm. Hum Mol Genet 2022;31(21):3672–3682
17 Pirruccello JP, Chaffin MD, Chou EL, et al. Deep learning enables genetic analysis of the human thoracic aorta. Nat Genet 2022;54 (01):40–51
18 Hultgren R, Larsson E, Wahlgren CM, Swedenborg J. Female and elderly abdominal aortic aneurysm patients more commonly have concurrent thoracic aortic aneurysm. Ann Vasc Surg 2012; 26(07):918–923
19 Dombrowski D, Long GW, Chan J, Brown OW. Screening chest computed tomography is indicated in all patients with abdominal aortic aneurysm. Ann Vasc Surg 2020;65:190–195
20 Dobrin PB, Baker WH, Gley WC. Elastolytic and collagenolytic studies of arteries. Implications for the mechanical properties of aneurysms. Arch Surg 1984;119(04):405–409
21 Ashvetiya T, Fan SX, Chen YJ, et al. Identification of novel genetic susceptibility loci for thoracic and abdominal aortic aneurysms via genome-wide association study using the UK Biobank Cohort. PLoS One 2021;16(09):e0247287
22 MacSweeney STR, Skidmore C, Turner RJ, et al. Unravelling the familial tendency to aneurysmal disease: popliteal aneurysm, hypertension and fibrillin genotype. Eur J Vasc Endovasc Surg 1996;12(02):162–166
23 van 't Hof FNG, Ruigrok YM, Lee CH, et al; Aneurysm Consortium; Vascular Research Consortium of New Zealand. Shared genetic risk factors of intracranial, abdominal, and thoracic aneurysms. J Am Heart Assoc 2016;5(07):e002603
24 Kontusaari S, Tromp G, Kuivaniemi H, Ladda R, Prockop D. Inheritance of an RNA splicing mutation (G+ 1 IVS20) in the type III procollagen gene (COL3A1) in a family having aortic aneurysms and easy bruisability: phenotypic overlap between familial arterial aneurysms and Ehlers-Danlos syndrome type IV. J Clin Invest 1990;86(05):1465–1473
25 Kontusaari S, Tromp G, Kuivaniemi H, Romanic AM, Prockop DJ. A mutation in the gene for type III procollagen (COL3A1) in a family with aortic aneurysms. J Clin Invest 1990;86(05): 1465–1473
26 Tromp G, Wu Y, Prockop DJ, et al. Sequencing of cDNA from 50 unrelated patients reveals that mutations in the triple-helical domain of type III procollagen are an infrequent cause of aortic aneurysms. J Clin Invest 1993;91(06):2539–2545
27 Saracini C, Bolli P, Sticchi E, et al. Polymorphisms of genes involved in extracellular matrix remodeling and abdominal aortic aneurysm. J Vasc Surg 2012;55(01):171–179.e2
28 Jelsig AM, Urban Z, Hucthagowder V, Nissen H, Ousager LB. Novel ELN mutation in a family with supravalvular aortic stenosis and intracranial aneurysm. Eur J Med Genet 2017;60(02):110–113
29 Renard M, Francis C, Ghosh R, et al. Clinical validity of genes for heritable thoracic aortic aneurysm and dissection. J Am Coll Cardiol 2018;72(06):605–615
30 Lee VS, Halabi CM, Hoffman EP, et al; Brigham Genomic Medicine. Loss of function mutation in LOX causes thoracic aortic aneurysm and dissection in humans. Proc Natl Acad Sci U S A 2016;113(31): 8759–8764
31 Tilson MD, Reilly JM, Brophy CM, Webster EL, Barnett TR. Expression and sequence of the gene for tissue inhibitor of metalloproteinases in patients with abdominal aortic aneurysms. J Vasc Surg 1993;18(02):266–270
32 Ogata T, Shibamura H, Tromp G, et al. Genetic analysis of polymorphisms in biologically relevant candidate genes in patients with abdominal aortic aneurysms. J Vasc Surg 2005;41(06): 1036–1042
33 Hinterseher I, Tromp G, Kuivaniemi H. Genes and abdominal aortic aneurysm. Ann Vasc Surg 2011;25(03):388–412
34 Tang W, Saratzis A, Pattee J, et al. Replication of newly identified genetic associations between abdominal aortic aneurysm and SMYD2, LINC00540, PCIF1/MMP9/ZNF335, and ERG. Eur J Vasc Endovasc Surg 2020;59(01):92–97
35 Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355 (08):788–798
36 Baas AF, Medic J, van't Slot R, et al. Association study of single nucleotide polymorphisms on chromosome 19q13 with abdominal aortic aneurysm. Angiology 2010;61(03):243–247
37 Guo DC, Grove ML, Prakash SK, et al; GenTAC Investigators BAVCon Investigators. Genetic variants in LRP1 and ULK4 are associated with acute aortic dissections. Am J Hum Genet 2016;99 (03):762–769
38 Guo DC, Regalado E, Casteel DE, et al; GenTAC Registry Consortium National Heart, Lung, and Blood Institute Grand Opportunity Exome Sequencing Project. Recurrent gain-of-function mutation in PRKG1 causes thoracic aortic aneurysms and acute aortic dissections. Am J Hum Genet 2013;93(02):398–404

39 Golledge J, Norman PE. Atherosclerosis and abdominal aortic aneurysm: cause, response, or common risk factors? Arterioscler Thromb Vasc Biol 2010;30(06):1075–1077
40 Gretarsdottir S, Baas AF, Thorleifsson G, et al. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. Nat Genet 2010;42(08):692–697
41 Bradley DT, Hughes AE, Badger SA, et al. A variant in LDLR is associated with abdominal aortic aneurysm. Circ Cardiovasc Genet 2013;6(05):498–504
42 Harrison SC, Smith AJP, Jones GT, et al; Aneurysm Consortium. Interleukin-6 receptor pathways in abdominal aortic aneurysm. Eur Heart J 2013;34(48):3707–3716
43 Bradley DT, Badger SA, McFarland M, Hughes AE. Abdominal aortic aneurysm genetic associations: mostly false? A systematic review and meta-analysis. Eur J Vasc Endovasc Surg 2016;51(01): 64–75
44 Fatini C, Sofi F, Sticchi E, et al. eNOS G894T polymorphism as a mild predisposing factor for abdominal aortic aneurysm. J Vasc Surg 2005;42(03):415–419
45 Jones GT, Thompson AR, van Bockxmeer FM, et al. Angiotensin II type 1 receptor 1166C polymorphism is associated with abdominal aortic aneurysm in three independent cohorts. Arterioscler Thromb Vasc Biol 2008;28(04):764–770
46 Giusti B, Saracini C, Bolli P, et al. Genetic analysis of 56 polymorphisms in 17 genes involved in methionine metabolism in patients with abdominal aortic aneurysm. J Med Genet 2008;45 (11):721–730
47 Liu J, Jia X, Li H, et al. Association between MTHFR C677T polymorphism and abdominal aortic aneurysm risk: a comprehensive meta-analysis with 10,123 participants involved. Medicine (Baltimore) 2016;95(36):e4793
48 Strauss E, Waliszewski K, Pawlak AL. [The normotensive carriers of the MTHFR 677T allele, displaying the increased risk of development of the abdominal aortic aneurysm (AAA), occur at the highest frequency among the smoking patients]. Przegl Lek 2004;61(10):1086–1089
49 Baas AF, Medic J, van't Slot R, et al. The intracranial aneurysm susceptibility genes HSPG2 and CSPG2 are not associated with abdominal aortic aneurysm. Angiology 2010;61(03):238–242
50 Bown MJ, Jones GT, Harrison SC, et al; CARDIoGRAM Consortium Global BPgen Consortium DIAGRAM Consortium VRCNZ Consortium. Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. Am J Hum Genet 2011;89(05):619–627
51 Sampson UKA, Norman PE, Fowkes FGR, et al. Estimation of global and regional incidence and prevalence of abdominal aortic aneurysms 1990 to 2010. Glob Heart 2014;9(01):159–170
52 Elmore JR, Obmann MA, Kuivaniemi H, et al. Identification of a genetic variant associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association. J Vasc Surg 2009;49(06):1525–1531
53 Jones GT, van Rij AM. Regarding "Identification of a genetic variant associated with abdominal aortic aneurysms on chromosome 3p12.3 by genome wide association". J Vasc Surg 2009;50(05): 1246–1247, author reply 1247
54 Biros E, Norman PE, Jones GT, et al. Meta-analysis of the association between single nucleotide polymorphisms in TGF-β receptor genes and abdominal aortic aneurysm. Atherosclerosis 2011;219 (01):218–223