



# Gene Commonality in Arterial Circuits Throughout the Body

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## Abstract

### Keywords

- thoracic aortic aneurysm
- thoracic aortic dissection
- abdominal aortic aneurysm
- intracranial aneurysm
- spontaneous coronary artery dissections
- genetics
- dissection
- arterial circuits

The common genetic underpinnings of thoracic aortic aneurysms and aneurysms and dissections of several other major arterial circuits have been described in the literature. These include thoracic and abdominal aortic aneurysms, thoracic and intracranial aneurysms, thoracic aortic aneurysms, and spontaneous coronary artery dissections. In this study, we provide a unified report of these observations and investigate any genetic commonality between the above four arterial circulations.

## Introduction

We have previously described an overlap in the causative genes for aneurysms and dissections in various distributions in the human body. Specifically, we have described the overlapping genes known or suspected to be involved in the following pairings, (1) aneurysms of the thoracic aorta and the abdominal aorta,<sup>1</sup> (2) aneurysms of the thoracic aorta and intracranial aneurysms (ICAs), and (3) aneurysms of the thoracic aorta and spontaneous coronary artery dissections (SCADs).<sup>2</sup>

Our primary reports on those aneurysm pairings have been previously published separately. In this review paper, we present these findings succinctly in a single report, unifying the observations for an overall assessment throughout the body, and making the overlaps available in a single publication.

In this report, we additionally examine whether there is any gene commonality between *all four* arterial circulations in the body: thoracic aorta, abdominal aorta, intracranial arteries, and coronary arteries.

The Venn Diagram that we produce shows all overlaps visually. In our narrative specification of overlap between specific distributions, we pinpoint exclusively those overlaps between the zones being compared (and no others).

## Results

We found significant overlap between the genes responsible for thoracic aortic aneurysms (TAAs), abdominal aortic aneurysms (AAAs), and ICAs, as well as SCAD. The specific commonalities are listed in **–Fig. 1**.

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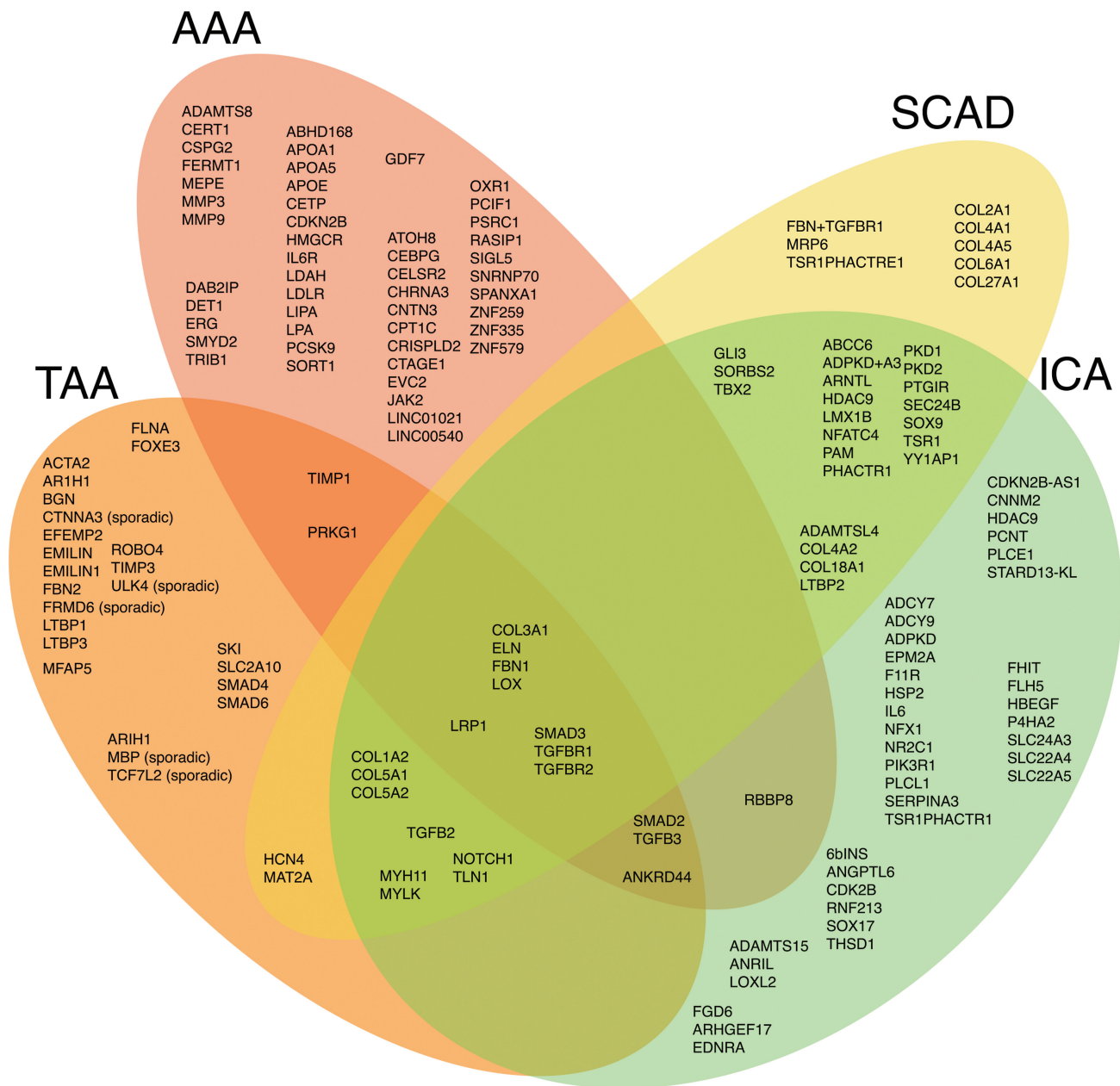
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**Fig. 1** Venn diagram combining the genetic overlap of TAA, AAA, SCAD, and ICA. AAA, abdominal aortic aneurysm, ICA, intracranial aneurysm, SCAD, spontaneous coronary artery dissection; TAA, thoracic aortic aneurysm.

### Thoracic Aortic Aneurysm, Intracranial Aneurysm, Abdominal Aortic Aneurysm, and Spontaneous Coronary Artery Dissection

The genes found to impact all four disorders are linked to syndromes previously associated with TAA, such as Ehlers–Danlos syndrome (*COL3A1*), Marfan's syndrome (*FBN1*), and Loeys–Dietz syndrome (*SMAD3*, *TGFB1*, *TGFB2*). Lysyl oxidase (*LOX*) is also involved in the pathophysiology of all four arterial circuit disorders; this gene affects the cross-linking of elastin and collagen in the extracellular matrix.<sup>1,3,4</sup> Low-density lipoprotein receptor-related protein 1 (*LRP1*), which is linked to endocytosis and intracellular signaling, is associated with atherosclerosis.<sup>1,2</sup> The elastin (*ELN*) gene involves genetic deletions in Williams–Beuren syndrome.<sup>1,5,6</sup> It can be observed that several syndromes associated with an

increased risk of TAA also involve genes that increase the risk for other arterial vascular disorders. Furthermore, genes related to the extracellular matrix and atherosclerosis can be found in all four arterial circuit diseases.

### Thoracic Aortic Aneurysm, Intracranial Aneurysm, and Spontaneous Coronary Artery Dissection

Genes involved in the mutual development of TAAs, ICAs, and SCAD include collagen genes (*COL1A2*, *COL5A1*, and *COL5A2*), smooth muscle myosin heavy chain 11 (*MYH11*), MYLK ( $\text{Ca}^{2+}$ /calmodulin [CaM]-dependent myosin light chain (MLC) kinase),<sup>4</sup> TGF- $\beta$  type II receptor (*TGFB2*),<sup>7</sup> notch homolog 1 (*NOTCH1*), and Talin 1 (*TLN1*).<sup>2</sup> These genes are responsible for linking the actin cytoskeleton to the extracellular matrix and their downregulation is known to weaken the vascular wall.<sup>2,7</sup>

### Thoracic Aortic Aneurysm, Abdominal Aortic Aneurysm, and Intracranial Aneurysm

Mutations in *SMAD2*, involved in TGF- $\beta$  signaling,<sup>8</sup> a TGF- $\beta$  3 ligand (*TGFB3*), causing a syndromic type of aneurysm associated with Loews–Dietz syndrome,<sup>9</sup> and ankyrin repeat domain 44 (*ANKRD44*), involved in endocytosis,<sup>1</sup> produce TAAs, AAAs, and ICAs.

### Thoracic Aortic Aneurysm and Spontaneous Coronary Artery Dissection

Hyperpolarization-activated pacemaker current channel 4 (*HCN4*), involved in the electrical conduction of the sinoatrial node but additionally responsible for structural cardiac abnormalities,<sup>10</sup> and methionine adenosyltransferase IIA (*MAT2A*), part of the DNA repair pathway,<sup>11</sup> were found to be affected in TAAs and SCAD.

### Thoracic Aortic Aneurysm and Abdominal Aortic Aneurysm

The only genes found to be involved in both TAAs and AAAs were tissue inhibitor of metalloproteinase 1 (*TIMP1*) and protein kinase cyclic guanine monophosphate-dependent 1 (*PRKG1*). *PRKG1* is known to be involved in nonsyndromic hereditary TAAs and is part of the nitric oxide pathway leading to vasodilation.<sup>1,6,12</sup> Of the TIMP subtypes, only *TIMP1* was found to be associated with both TAAs and AAAs, as *TIMP3* is singularly involved in the development of TAAs.

### Spontaneous Coronary Artery Dissection and Intracranial Aneurysm

There was an extensive overlap between the genes involved in the pathophysiology of SCAD and ICAs. We found overlap in *ADAMTSL4*, suspected to cause early termination of protein-synthesis and subsequent nonsense-related decay,<sup>13</sup> collagen IV (*COL4A2*)<sup>14</sup> and XVIII (*COL18A1*), associated with Knobloch syndrome,<sup>15</sup> *GLI3*, T-box transcription factor (*TBX2*), and yin yang 1 (YY1)-associated protein 1 (*YY1AP1*) thought to be involved in TGF- $\beta$ -dependent cell proliferation and signaling,<sup>16</sup> *SORBS2*, part of the sarcomeric Z-line and causing a reduction in myocytes,<sup>17</sup> ATP-binding cassette subfamily C member 6 (*ABCC6*) involved in a connective tissue disorder due to elastin degradation,<sup>16</sup> genes involved in autosomal dominant polycystic kidney disease (*APDKD* + *A3*, *PKD1*, and *PKD2*),<sup>18,19</sup> *ARNTL*, a vascular smooth muscle cell proliferation gene,<sup>16</sup> histone deacetylase 9 (*HDAC9*) leading to increased tunica media calcification and decreased contractile protein expression,<sup>16</sup> *LMX1B*, associated with Nail-patella syndrome,<sup>20</sup> latent TGF- $\beta$ -binding protein 2 (*LTBP2*),<sup>1</sup> nuclear factor of activated T cells 4 (*NFATC4*), peptidyl-glycine  $\alpha$ -amidating monooxygenase (*PAM*),<sup>16</sup> *PHACTR1*, enhancing the upstream gene for endothelin 1,<sup>16</sup> *PTGIR*, associated with fibromuscular dysplasia,<sup>2</sup> *SEC24B*, involved in the export of collagen,<sup>16</sup> SRY-Box transcription factor 9 (*SOX*),<sup>16</sup> and *TSR1* (ribosome maturation factor).<sup>16</sup>

### Abdominal Aortic Aneurysm and Intracranial Aneurysm

Only one gene, retinoblastoma-binding protein 8 (*RBBP8*), was found to affect both AAAs and ICAs, but not interact with

the pathophysiology of the other vascular pathologies, which is part of the DNA repair pathway.<sup>11,21</sup>

### Intracranial Aneurysm

Genes involving the cell cycle or the vascular endothelium appear only to be involved in the development of ICAs. Specific genes found are cyclin-dependent kinase inhibitor-2B-antisense RNA 1 (*CDKN2B-AS1*), a long noncoding RNA, which was shown to be involved in the pathogenesis of cerebral infarctions,<sup>22</sup> cyclin M2 (*CNNM2*), with increased expression being correlated to a higher risk of ICA formation,<sup>21,23</sup> *HDAC9*, which decreases transcription of estrogen receptors,<sup>24</sup> *PCNT*, involved in microtubule nucleation and found to bind another gene, *PKD2*, increasing the risk for ICAs,<sup>25,26</sup> Phospholipase C  $\epsilon$  1 (*PLCE1*), involved in cell messenger synthesis,<sup>27</sup> and StAR-related lipid transfer (START) domain containing 13 (*STARD13-KL*), influencing cell proliferation.<sup>23</sup> Genes involved in processes of the vascular endothelium are *endoglin* 6-bp insertion (*6bINS*), with increased expression in familial ICAs,<sup>28</sup> *ANGPTL6*, involved in endothelial permeability and cell migration,<sup>26</sup> *CDK2B*, ring finger protein 213 (*RNF213*), possibly involved in the construction of vascular walls,<sup>26,29</sup> *SOX17*, involved in determining the differentiation or senescence of progenitor cells,<sup>23</sup> and *TSHD1*, shown to be involved in vascular development and endothelial cells.<sup>26</sup>

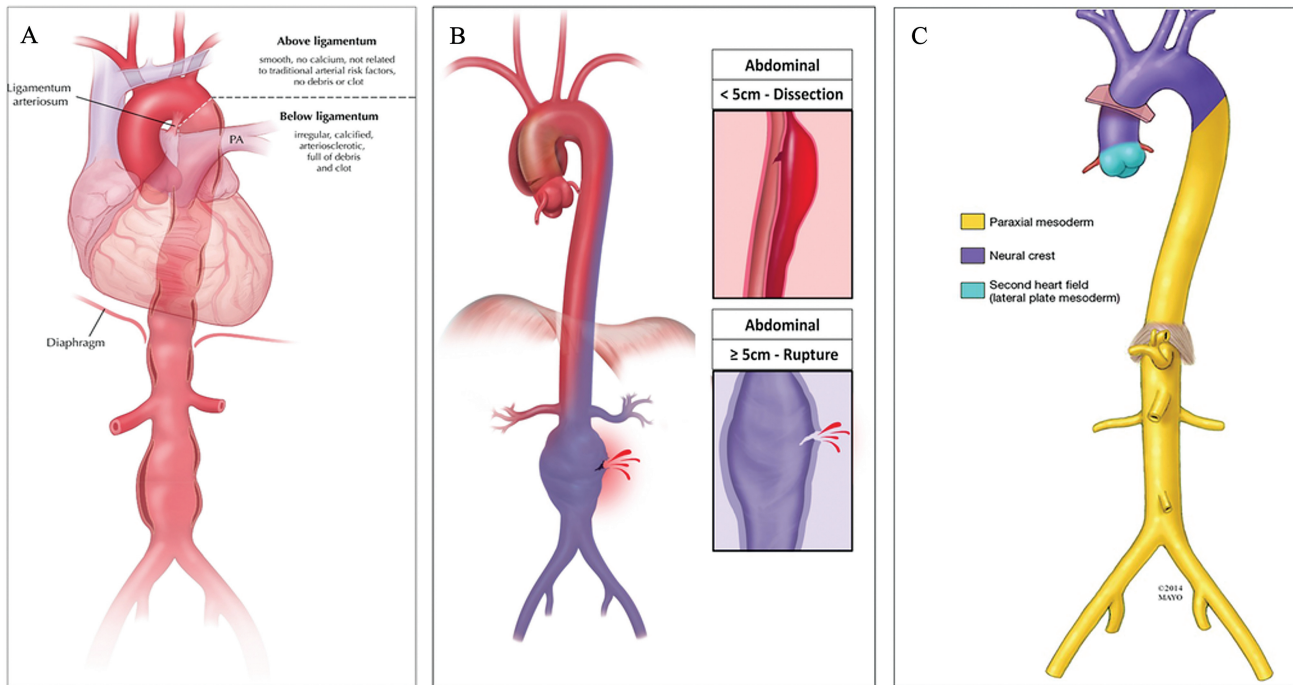
## Conclusion

Overlap in gene commonalities of four major disorders of the arterial circuit was identified. Genes uncovered to be responsible for pathophysiology in all four disorders include those responsible for the extracellular matrix, the TGF- $\beta$  pathways, and lipid metabolism, as well as being associated with extra aortic syndromic manifestations.

It is noteworthy that the development of ICAs and SCAD appears to have the most gene commonalities.

AAAs have the lowest gene commonality of all four disorders evaluated. This could suggest that different pathomechanisms are involved in the development of AAAs specifically. Our prior work (see ►Fig. 2) has highlighted the highly different biological behavior between the ascending and descending aortas, which we consider markedly “different” organs—in terms of both embryology and clinical manifestations. The ascending aorta arises from the neural crest, and the descending and abdominal aortas arise from the mesoderm. The wall of an ascending aortic aneurysm is generally smooth, noncalcified, and free from thrombus. In contradistinction, the wall of an AAA is typically irregular in contour, heavily calcified, and full of thrombus. In terms of behavior, the ascending aorta dissects but rarely ruptures without antecedent dissection. By contrast, the abdominal aorta rarely dissects but often ruptures without antecedent dissection.<sup>30</sup>

Examining the genetic overlaps among aneurysms in these four zones (TAA, AAA, ICA, and SCAD) demonstrates both commonalities and discrepancies and contributes to our scientific understanding of the diseases and their



**Fig. 2** (A) Illustration from Elefteriades and Farkas (2010) showing the divide of thoracic aneurysms by the ligamentum arteriosum. Illustration by Rob Flewell. PA, pulmonary artery.<sup>31</sup> (B) Illustration from Zafar et al (2019) showing the differences in behavior regarding rupture versus dissection in abdominal and thoracic aortic aneurysms.<sup>30</sup> (C) Illustration from Maleszewski (2015) showing the embryologic origin of the different aspects of the aorta.<sup>32</sup>

development. We do recommend that a complete assessment of TAA patients include imaging of the abdominal and intracranial vasculature. We recommend that AAA patients undergo imaging of the entire thoracic aorta. We recommend that ICA patients undergo imaging of at least the thoracic aorta (and preferably the abdominal as well). In this way, specialists in each field (TAA, AAA, and ICA) can avoid the “tunnel vision” of investigating only their own special vascular organ, while neglecting possible or even likely (and potentially lethal) disease in other segments of the vascular tree.

While SCAD has demonstrated some genetic overlaps, it tends to occur without aneurysmal dilatation of the underlying coronary artery, and we make no specific recommendation for extensive screening (for TAA or AAA) in patients presenting with SCAD. However, because of the specific overlap between SCAD and ICA, brain vessel screening may be recommended.

**Conflict of Interest**  
None declared.

## References

- 1 Gyftopoulos A, Ziganshin BA, Elefteriades JA, Ochoa Chara CI. Comparison of genes associated with thoracic and abdominal aortic aneurysms. *Aorta (Stamford)* 2023;11(03):125–134
- 2 Jeoffrey SMH, Kalyanasundaram A, Zafar MA, Ziganshin BA, Elefteriades JA. Genetic overlap of spontaneous dissection of either the thoracic aorta or the coronary arteries. *Am J Cardiol* 2023;205:69–74
- 3 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
- 4 Takeda N, Komuro I. Genetic basis of hereditary thoracic aortic aneurysms and dissections. *J Cardiol* 2019;74(02):136–143
- 5 Guemann AS, Andrieux J, Petit F, et al. ELN gene triplication is responsible for familial supravalvular aortic aneurysm. *Cardiol Young* 2015;25(04):712–717
- 6 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
- 7 Wei X, Sun Y, Wu Y, et al. Downregulation of Talin-1 expression associates with increased proliferation and migration of vascular smooth muscle cells in aortic dissection. *BMC Cardiovasc Disord* 2017;17(01):162
- 8 Micha D, Guo DC, Hilhorst-Hofstee Y, et al. SMAD2 mutations are associated with arterial aneurysms and dissections. *Hum Mutat* 2015;36(12):1145–1149
- 9 Bertoli-Avella AM, Gillis E, Morisaki H, et al. Mutations in a TGF- $\beta$  ligand, TGFB3, cause syndromic aortic aneurysms and dissections. *J Am Coll Cardiol* 2015;65(13):1324–1336
- 10 Vermeer AMC, Lodder EM, Thomas D, et al. Dilation of the aorta ascendens forms part of the clinical spectrum of HCN4 mutations. *J Am Coll Cardiol* 2016;67(19):2313–2315
- 11 Zhou Z, Liu Y, Gao S, et al. Excessive DNA damage mediates ECM degradation via the RBBP8/NOTCH1 pathway in sporadic aortic dissection. *Biochim Biophys Acta Mol Basis Dis* 2022;1868(02):166303
- 12 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
- 13 Wang Y, Starovoytov A, Murad AM, et al. Burden of rare genetic variants in spontaneous coronary artery dissection with high-risk features. *JAMA Cardiol* 2022;7(10):1045–1055

- 14 Kuo DS, Labelle-Dumais C, Gould DB. COL4A1 and COL4A2 mutations and disease: insights into pathogenic mechanisms and potential therapeutic targets. *Hum Mol Genet* 2012;21(R1):R97–R110
- 15 Li Z, Zhou C, Tan L, et al. Variants of genes encoding collagens and matrix metalloproteinase system increased the risk of aortic dissection. *Sci China Life Sci* 2017;60(01):57–65
- 16 Bax M, Romanov V, Junday K, et al. Arterial dissections: common features and new perspectives. *Front Cardiovasc Med* 2022;9:1055862
- 17 Liang F, Wang B, Geng J, et al. *SORBS2* is a genetic factor contributing to cardiac malformation of 4q deletion syndrome patients. *eLife* 2021;10:e67481
- 18 Rutman AM, Wangaryattawanich P, Aksakal M, Mossa-Basha M. Incidental vascular findings on brain magnetic resonance angiography. *Br J Radiol* 2023;96(1142):20220135
- 19 Qian Q, Li M, Cai Y, et al. Analysis of the polycystins in aortic vascular smooth muscle cells. *J Am Soc Nephrol* 2003;14(09):2280–2287
- 20 Kaadan MI, MacDonald C, Ponzini F, et al. Prospective cardiovascular genetics evaluation in spontaneous coronary artery dissection. *Circ Genom Precis Med* 2018;11(04):e001933
- 21 Yasuno K, Bilguvar K, Bijlenga P, et al. Genome-wide association study of intracranial aneurysm identifies three new risk loci. *Nat Genet* 2010;42(05):420–425
- 22 Lei JJ, Li HQ, Mo ZH, et al. Long noncoding RNA CDKN2B-AS1 interacts with transcription factor BCL11A to regulate progression of cerebral infarction through mediating MAP4K1 transcription. *FASEB J* 2019;33(06):7037–7048
- 23 Bakker MK, van Straten T, Chong M, Paré G, Gill D, Ruigrok YM. Anti-epileptic drug target perturbation and intracranial aneurysm risk: Mendelian randomization and colocalization study. *Stroke* 2023;54(01):208–216
- 24 Lansdell TA, Fisher C, Demel S, Dorrance A. Increased HDAC9 expression is associated with decreased estrogen in female patients with intracranial aneurysm. *FASEB J* 2019;33(S1):828–835
- 25 Lorenzo-Betancor O, Blackburn PR, Edwards E, et al. *PCNT* point mutations and familial intracranial aneurysms. *Neurology* 2018;91(23):e2170–e2181
- 26 Bakker MK, Ruigrok YM. Genetics of intracranial aneurysms. *Stroke* 2021;52(09):3004–3012
- 27 Bell S, Tozer DJ, Markus HS. Genome-wide association study of the human brain functional connectome reveals strong vascular component underlying global network efficiency. *Sci Rep* 2022;12(01):14938
- 28 Hu X, Fang Y, Li YK, et al. Role of endoglin insertion and rs1800956 polymorphisms in intracranial aneurysm susceptibility: a meta-analysis. *Medicine (Baltimore)* 2015;94(45):e1847
- 29 Zhou S, Ambalavanan A, Rochefort D, et al. RNF213 is associated with intracranial aneurysms in the French-Canadian population. *Am J Hum Genet* 2016;99(05):1072–1085
- 30 Zafar MA, Chen JF, Wu J, et al; Yale Aortic Institute Natural History Investigators. Natural history of descending thoracic and thoracoabdominal aortic aneurysms. *J Thorac Cardiovasc Surg* 2021;161(02):498–511.e1
- 31 Elefteriades JA, Farkas EA. Thoracic aortic aneurysm clinically pertinent controversies and uncertainties. *J Am Coll Cardiol* 2010;55(09):841–857
- 32 Maleszewski JJ. Inflammatory ascending aortic disease: perspectives from pathology. *J Thorac Cardiovasc Surg* 2015;149(2 Suppl):S176–S183