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Genome-wide association study identifies a susceptibility locus for thoracic aortic aneurysms and aortic dissections spanning *FBN1* at 15q21.1

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AUTHOR CONTRIBUTIONS

S.A.L., J.W.B. and D.M.M. were the principal investigators who conducted the study. S.A.L. and D.M.M. coordinated and oversaw the study. L.R., R.J.J., C.C.M., D.M.M., S.A.L., J.S.C., H.J.S. and A.L.E. participated in study enrollment for stages 1 and 2, helped gather related detailed clinical information and biological samples, and helped carry out the clinical analysis. R.E.P., J.E.B., R.D., C.M., K.W.H., K.E., S.C.B., C.S., J.G.S. and E.M.I. participated in study enrollment for stages 2 and 3 and helped gather related detailed clinical information and biological samples. D.G. and M.N. participated in the preparation of biological samples. M.B., J.W.B., M.R.B. and L.M.F. carried out the genotyping. M.-L.N.M. and S.M.L. were responsible for bioinformatics and all statistical analyses. S.A.L., M.-L.N.M., D.G., S.M.L. and D.M.M. wrote the manuscript.

COMPETING FINANCIAL INTERESTS

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Abstract

Although thoracic aortic aneurysms and dissections (TAAD) can be inherited as a single-gene disorder, the genetic predisposition in the majority of affected people is poorly understood. In a multistage genome-wide association study (GWAS), we compared 765 individuals who had sporadic TAAD (STAAD) with 874 controls and identified common SNPs at a 15q21.1 locus that were associated with STAAD, with odds ratios of 1.6–1.8 that achieved genome-wide significance. We followed up 107 SNPs associated with STAAD with $P < 1 \times 10^{-5}$ in the region, in two separate STAAD cohorts. The associated SNPs fall into a large region of linkage disequilibrium encompassing *FBN1*, which encodes fibrillin-1. *FBN1* mutations cause Marfan syndrome, whose major cardiovascular complication is TAAD. This study shows that common genetic variants at 15q21.1 that probably act via *FBN1* are associated with STAAD, suggesting a common pathogenesis of aortic disease in Marfan syndrome and STAAD.

The natural history of aneurysms involving the aortic root and ascending thoracic aorta is progressive, asymptomatic enlargement over time, ultimately leading to life-threatening acute ascending aortic dissection (termed type A dissection in the Stanford classification) or rupture. Less deadly aortic dissections can originate in the descending thoracic aorta just distal to the origin of the left subclavian artery (type B dissections). All of these conditions are part of the TAAD disease spectrum. Risk factors for TAAD include poorly controlled hypertension and congenital cardiovascular abnormalities, such as a bicuspid aortic valve (BAV) and aortic coarctation. In addition, genetic predisposition has a prominent role in the etiology of TAAD. Thoracic aortic disease is inherited in families in an autosomal-dominant manner in the presence or absence of syndromic features. Marfan syndrome is an example of a genetic syndrome in which essentially all affected individuals have TAAD, in addition to skeletal and ocular complications[1]. Marfan syndrome results from heterozygous mutations in *FBN1*, which encodes an extracellular matrix protein (fibrillin-1) that is a component of the elastic fibers in the medial layer of the aorta.

Family aggregation studies indicate that up to one-fifth of individuals with TAAD who lack features of a genetic syndrome have family histories of TAAD; in these cases, TAAD is also inherited in an autosomal-dominant manner. The underlying genetic heterogeneity in familial TAAD results in substantial clinical heterogeneity in aortic disease presentation and associated vascular diseases; to date, seven genes have been identified that account for 20% of familial TAAD[2–5].

Although most TAAD is sporadic, the genetic basis of STAAD has not been fully explored. We performed a three-stage GWAS. For stage 1, we used samples from 765 affected individuals of European descent who presented for treatment of an ascending thoracic aortic aneurysm and/or a type A or B aortic dissection, who were more than 30 years old, and who

had no family history of TAAD or evidence of a syndromic form of TAAD on examination (Supplementary Table 1). The samples were genotyped with Illumina CNV370-Quad BeadChip arrays, and also analyzed were 1,355 controls from the Wellcome Trust Case-Control Consortium (WTCCC) 1958 Birth Cohort (C58), as well as 874 controls whose data were obtained from the US National Institute of Neurological Disorders and Stroke (NINDS) Repository's Neurologically Normal Control Collection.

Only one locus, at chromosome 15q21.1, harbored SNPs that were associated with STAAD with a genome-wide significance (GWS) level of $P < 5 \times 10^{-8}$ (Fig. 1, Table 1 and Supplementary Table 2). Five SNPs were associated with an increased risk of disease after adjustment for sex and population substructure; odds ratios (ORs) ranged from 1.4 to 1.8. To confirm that our findings were not biased by the different sources of cases and controls, we showed that rs2118181 was associated with STAAD with GWS whether the NINDS ($P_{\text{stage 1}} = 4.6 \times 10^{-8}$) or the C58 ($P_{\text{stage 1}} = 9.4 \times 10^{-9}$) controls were used. The STAAD cases had less evidence of population substructure with the NINDS controls ($\lambda_{\text{sex, C1}} = 1.005$) than with the C58 controls ($\lambda_{\text{sex, C1}} = 1.06$), so we report the results that were obtained using the NINDS controls.

To validate these findings, we genotyped the five GWS 15q21.1 SNPs, along with 99 imputed SNPs and three genotyped 15q21.1SNPs that were associated ($P_{\text{stage 1}} < 1 \times 10^{-5}$) in two independent STAAD cohorts (stages 2 and 3). Stage 2 comprised 385 individuals with STAAD, 192 (49.9%) of whom also had BAV, and 159 controls (Supplementary Table 1). Stage 3 comprised 163 people with sporadic nondissection ascending aortic aneurysms, 157 (96.3%) of whom had BAV, and 476 controls (Supplementary Table 1). In both replication stages, all five GWS SNP-STAAD associations replicated with no evidence of heterogeneity between the stages (Table 1). Of the 99 imputed SNPs, 62 SNPs were associated with STAAD with GWS in stage 1. In stages 2 and 3, the association was replicated ($P < 0.05$) for 51 of these imputed SNPs (Fig. 2a and Supplementary Table 3). The meta-analysis of data from stages 1, 2 and 3 identified rs2118181 as the stage 1–genotyped SNP that was most highly associated with STAAD ($\text{OR}_{\text{meta}} = 1.8$, $P_{\text{meta}} = 5.9 \times 10^{-12}$); of the imputed SNPs, rs1036476 was most highly associated with STAAD ($\text{OR}_{\text{meta}} = 1.9$, $P_{\text{meta}} = 5.9 \times 10^{-13}$; Supplementary Table 3). An association plot of the 15q21.1 region showed that the associated SNPs fall into a large linkage disequilibrium region approximately 305 kb in size that encompasses the entire *FBN1* gene, and *FBN1* is the only gene in this linkage disequilibrium region. *FBN1* mutations that cause Marfan syndrome are typically private, rare variants that lead to missense and nonsense mutations and splicing errors. In contrast, the association between 15q21.1 and STAAD is probably mediated by one or more common variants within *FBN1*.

The individuals with STAAD had a spectrum of thoracic aortic disease presentations. A subset had BAV, the most common congenital heart defect, which is found in 1% to 2% of the general population[6]. Among patients referred for surgical treatment of BAV, 20% have concurrent ascending aortic aneurysms[7,8], and approximately 15% of patients with acute aortic dissections have BAV[9], indicating a strong association between BAV and risk for STAAD. We investigated whether the 15q21.1 SNPs are associated with STAAD in the presence or absence of BAV. In stages 1 and 2, all five GWS 15q21.1 SNPs were associated with TAAD without BAV. This association was strongest for rs1036477 and rs2118181, but met GWS for all five SNPs in the meta-analysis ($\text{OR}_{\text{no BAV, meta}} = 1.9$, $P_{\text{no BAV, meta}} = 9.9 \times 10^{-10}$; Table 2 and Supplementary Table 4). Similarly, 16 imputed 15q21.1 SNPs were associated (meeting GWS) with STAAD without BAV in stage 1, and the associations were replicated in stage 2. Meta-analysis identified rs1036476 as the SNP most significantly associated with STAAD in the absence of BAV ($\text{OR}_{\text{no BAV. meta}} = 2.0$, $P_{\text{no BAV, meta}} = 3.3 \times 10^{-10}$; Supplementary Table 5 and Supplementary Fig. 1a).

When people with STAAD and BAV were compared to controls, a subset of the five 15q21.1 GWS SNPs were significantly associated in stages 1, 2 and 3; rs2118181 had the most significant association in the meta-analysis ($OR_{BAV,\ meta} = 1.8$, $P_{BAV,\ meta} = 2.2 \times 10^{-7}$; Table 2 and Supplementary Table 4). When the imputed SNPs were analyzed in stage 1, none of the 99 SNPs was associated with STAAD and BAV with GWS; however, in the meta-analysis, 20 of the SNPs were associated with STAAD and BAV with GWS, the most significant being rs689304 ($OR_{BAV,\ meta} = 2.0$, $P_{BAV,\ meta} = 1.7 \times 10^{-8}$; Fig. 2b and Supplementary Table 6). These data support the conclusion that the 15q21.1 locus confers susceptibility to STAAD whether or not the individual has BAV.

The spectrum of STAAD presentation included patients with ascending aortic aneurysms, who are typically referred for surgical repair when the aortic diameter reaches 5.5 cm or more[10], as well as patients who presented with type A or B aortic dissections. To determine whether the 15q21.1 locus was associated with both disease presentations, we initially analyzed the five GWS 15q21.1 SNPs in people with nondissection aneurysms (NDA) involving the root and/or ascending aorta. The SNPs rs1036477 and rs2118181 were the most significantly associated with such aneurysms ($OR_{NDA,\ stage\ 1} = 1.7$, $P_{NDA,\ stage\ 1} = 7.4 \times 10^{-5}$; Table 2 and Supplementary Table 4). Several of these associations were replicated in stages 2 and 3, and in the meta-analysis the SNP most significantly associated with aneurysm was rs2118181 ($OR_{NDA,\ meta} = 1.7$, $P_{NDA,\ meta} = 1.3 \times 10^{-7}$). Further investigation of the imputed SNPs in patients who presented with ascending aortic aneurysms revealed 13 SNPs that achieved GWS after meta-analysis of stages 1, 2 and 3; the SNP most significantly associated with nondissection aneurysm was rs636178 ($OR_{NDA,\ meta} = 1.7$, $P_{NDA,\ meta} = 3.5 \times 10^{-8}$; Supplementary Table 7 and Supplementary Fig. 1b).

Similarly, in stage 1, the five GWS 15q.21.1 SNPs were associated with aortic dissection (AD; $OR_{AD,\ stage\ 1} = 1.9$, $P_{AD,\ stage\ 1} = 2.7 \times 10^{-7}$). This association was replicated for all five SNPs in stage 2 ($OR_{AD,\ stage\ 2} = 4.1$, $P_{AD,\ stage\ 2} = 4.2 \times 10^{-6}$); the most significant meta-analysis result was $OR_{AD,\ stage\ 2} = 1.8$, $P_{AD,\ stage\ 2} = 6.6 \times 10^{-10}$ (Table 2 and Supplementary Table 4) for rs10519177. The OR in stage 2 for rs1036477 and rs2118181 was more than twice the OR in stage 1, and the null hypothesis of homogeneity was rejected ($P = 0.03$). This heterogeneity between stages may reflect differing linkage disequilibrium patterns between the tagged SNPs and the causal variant(s) or differences in the phenotype, or it may be due to chance. For SNPs failing the null hypothesis of homogeneity, a random-effects model was used to combine the stages. A total of nine SNPs were associated with aortic dissection with GWS in stage 1, including the genotyped SNP rs2289136. This result was replicated in stage 2, in which rs9806323 was the SNP most significantly associated with dissection in the meta-analysis ($OR_{AD,\ meta} = 2.1$, $P_{AD,\ meta} = 2.9 \times 10^{-12}$; Fig. 2c and Supplementary Table 8). Thus, the 15q21.1 locus is associated with presentation with an aneurysm or aortic dissection but is more significantly associated with aortic dissection.

We also sought to determine whether the 15q21.1 locus was associated with aortic dissections originating in the ascending aorta (type A) and descending aorta (type B). The SNPs most significantly associated with type A aortic dissection in stages 1 and 2 were rs1036477 and rs2118181 ($OR_{AD,\ A,\ stage\ 1} = 2.1$, $P_{AD,\ A,\ stage\ 1} = 7.7 \times 10^{-7}$; $OR_{AD,\ A,\ stage\ 2} = 5.3$, $P_{AD,\ A,\ stage\ 2} = 4.5 \times 10^{-7}$). In the meta-analysis of the type A dissection data from stages 1 and 2, rs10519177 was the most significant SNP ($OR_{AD,\ A,\ meta} = 1.8$, $P_{AD,\ A,\ meta} = 1.2 \times 10^{-8}$; Table 2 and Supplementary Table 4). The null hypothesis of homogeneity between stages 1 and 2 was rejected ($P = 0.0094$) for rs1036477 and rs2118181; therefore, the random-effects model was used to combine the stages. Among the 99 SNPs that were genotyped after being imputed in stage 1, rs9806323 was the one most significantly associated with dissection in the meta-analysis ($OR_{AD,\ A,\ meta}$

= 2.4, $P_{AD, A, meta} = 4.9 \times 10^{-13}$; Supplementary Table 9 and Supplementary Fig. 1c). Although several SNPs were associated with type B dissection in stages 1 and 2, the meta-analysis of the 15q GWS SNPs and imputed SNPs did not indicate GWS for the most significant SNP, rs682938 ($OR_{AD, B, meta} = 1.7$, $P_{AD, B, meta} = 2.0 \times 10^{-5}$; Table 2, Supplementary Tables 4 and 10 and Supplementary Fig. 1d). Although the 15q21.1 locus was associated with type A dissection, the association with type B dissection did not reach GWS, possibly because there were fewer type B dissection cases.

We have shown that 15q21.1 SNPs lying in a linkage-disequilibrium region containing the entire *FBN1* gene are associated with STAAD. The 15q21.1 locus association remains robust across various STAAD subphenotypes, including STAAD occurring in the presence or absence of BAV, and presentation with either an aneurysm or type A aortic dissection. It is unlikely that the associations identified in this study were caused by a synthetic association with multiple rare variants, as this would require that these rare variants fall on the same haplotype in all three stages of the study. More likely, the association is due to one or more common variants in *FBN1* that alter fibrillin-1 expression or function. Previous studies have established that *FBN1* mutations can predispose individuals to TAAD in the absence of other phenotypic manifestations of Marfan syndrome[11,12]; therefore, it is not surprising that the possible functional variant in *FBN1* predisposes people to thoracic aortic disease in the absence of the skeletal and ocular features of Marfan syndrome.

Our GWAS data identified one locus associated with STAAD with GWS. This is in contrast to the several Mendelian genes known to predispose individuals to TAAD, in which substantial genetic heterogeneity is evident for both syndromic and nonsyndromic disease. Similarly, copy-number variant (CNV) analysis of STAAD has identified 47 CNVs enriched or unique in people with STAAD compared with controls[13]. Both single-gene mutations and a recurrent CNV involving duplication of 16p13.1 are associated with specific thoracic aortic disease presentations[14,15]. The 15q21.1 locus is associated with all disease presentations except type B dissections, which probably allowed its identification in the discovery phase of this study. Future GWAS of thoracic aortic disease need to have subject cohorts of sufficient size to detect loci associated with specific subphenotypes.

In summary, we have identified novel associations of polymorphic variants at the 15q21.1 locus, encompassing *FBN1*, with STAAD. These data suggest that one or more common variants in *FBN1* predispose individuals to STAAD, implying a common pathogenesis of thoracic aortic disease between Marfan syndrome and STAAD. Our current understanding of the molecular pathways that lead to thoracic aortic disease is driven by studies of Marfan-syndrome mouse models. Blocking the signaling of transforming growth factor-β with losartan attenuates aneurysm formation in the mouse models, and this observation has led to clinical trials of losartan to prevent aneurysm formation in people with Marfan syndrome[16]. In addition, inhibitors of matrix metalloproteinases and of the ERK signaling pathway have also shown efficacy in blocking aneurysm formation in mouse models of Marfan syndrome[17,18]. Finding a common pathologic pathway to thoracic aortic disease that is driven by genetic variants in *FBN1* (including mutations and common variants) may allow the effective treatments designed to slow or prevent thoracic aortic disease in patients with Marfan syndrome to be rapidly applied to patients with STAAD.

URLs

NINDS dbGAP database, http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap; WTCCC database, https://www.wtccc.org.uk/ccc1/access_to_data_samples.shtml; R script from Broad Institute website, http://www.broadinstitute.org/diabetes/scandinavs/figures.html.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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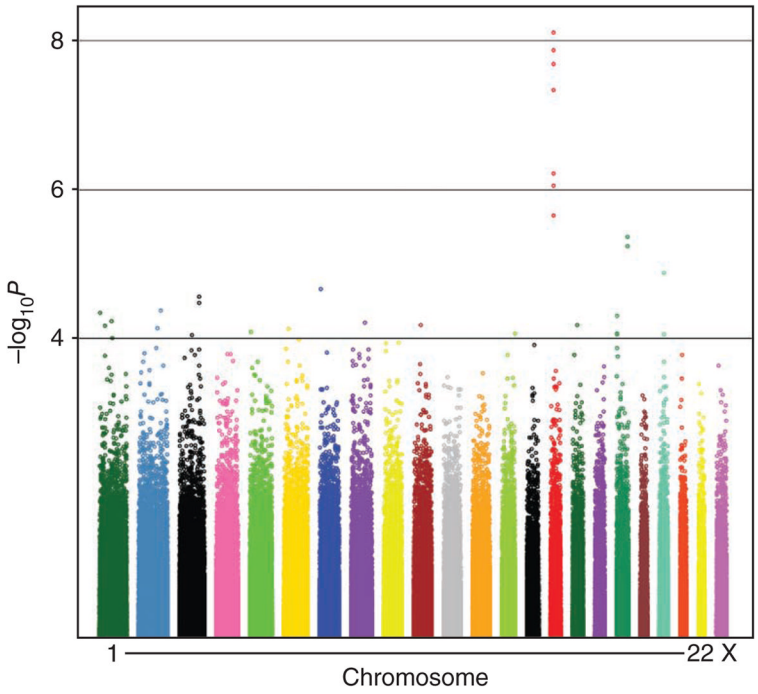

Figure 1.

A Manhattan plot of stage 1 genome-wide association results from comparison of STAAD cases to NINDS controls. For each tested marker, the significance is displayed on the *y*-axis as the $-\log_{10}$ of the *P* value. The $-\log_{10}$ results are ordered along the *x*-axis by chromosome, with each colored bar representing a different chromosome.

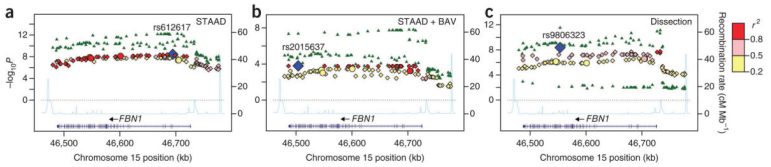

Figure 2.

FBN1 regional association plots. (**a**–**c**) Association plots are shown for STAAD (**a**), STAAD with BAV (**b**) and aortic dissection (**c**). The top-ranked stage 1 SNP for each phenotype is marked by a blue diamond. Red, pink and yellow shading denotes r^2 (see key), corresponding to the linkage disequilibrium between the top-ranked SNP and other SNPs in the region. The recombination rate according to HapMap CEU is plotted as a light blue line, with amplitude scaled to the right-hand *y*-axis. Circles denote the five SNPs genotyped in the *FBN1* region that were associated with TAAD in stage 1 with GWS. Dotted lines denote $-\log_{10} P = 0$. Green triangles denote the fixed-effects meta-analysis results for the combined stages. When the result of the Cochran *Q* test of homogeneity was <0.1, random-effects meta-analysis results are shown; otherwise fixed-effects meta-analysis was performed.

Table 1

Genotyped SNPs associated with STAAD ($P < 5 \times 10^{-8}$) with variants within and flanking the *FBN1* gene in stage 1 samples

			Stage 1 sample[a]				Stage 2 sample[b]				Stage 3 sample[c]				Stage 1, 2 and 3 combined[d]		
SNP	**BP**	**Allele**	**MAF**	**OR**	**SE**	***P***	**MAF**	**OR**	**SE**	***P***	**MAF**	**OR**	**SE**	***P***	**OR**	***P***	***Q***
			(765 cases, 874 NINDS controls)				**(385 cases, 150 controls)**				**(163 cases, 476 controls)**				**(1,313 cases, 1,500 controls)**		
rs10519177	46544486	G	0.27	1.6	0.08	1.3×10^{-8}	0.27	1.4	0.16	0.02	0.26	1.5	0.15	0.0064	1.6	2.6×10^{-11}	0.80
rs4774517	46546582	A	0.27	1.6	0.08	2.0×10^{-8}	0.27	1.4	0.16	0.02	0.26	1.5	0.15	0.0064	1.5	3.8×10^{-11}	0.82
rs755251	46599311	G	0.27	1.6	0.08	7.8×10^{-9}	0.27	1.4	0.16	0.03	0.26	1.5	0.15	0.009	1.6	3.2×10^{-11}	0.69
rs1036477	46702217	G	0.13	1.8	0.11	4.6×10^{-8}	0.13	2.6	0.26	2.9×10^{-4}	0.13	1.6	0.18	0.0103	1.8	6.5×10^{-12}	0.30
rs2118181	46703175	G	0.13	1.8	0.11	4.6×10^{-8}	0.13	2.6	0.26	2.9×10^{-4}	0.13	1.6	0.18	0.0095	1.8	5.9×10^{-12}	0.30

MAF, minor allele frequency; OR, odds ratio; SE, standard error of the odds ratio; MDS, multidimensional scaling. BP denotes NCBI Build 36.1 SNP physical position. *Q* denotes *P* value for the Cochran *Q* statistic for homogeneity between stages 1 and 2.

[a] Adjusted for sex and first MDS component from stage 1 samples and NINDS controls.

[b] Adjusted for sex and first MDS component from stage 2 samples and controls.

[c] Adjusted for sex for stage 3 samples and controls.

[d] Fixed-effects meta-analysis results from stage 1 cases and NINDS controls, and from stage 2 and stage 3 samples. For $Q < 0.1$, the random effects OR and *P* are reported.

Table 2

Associations between STAAD subphenotypes and genotyped SNPs associated with STAAD ($P < 5 \times 10^{-8}$) with variants within and flanking the *FBN1* gene in stage 1 samples[a]

			Stage 1 sample[b]				Stage 2 sample[c]				Stage 3 sample[d]				Stages 1, 2 and 3 combined[e]		
SNP	**BP**	**Allele**	**MAF**	**OR**	**SE**	***P***	**MAF**	**OR**	**SE**	***P***	**MAF**	**OR**	**SE**	***P***	**OR**	***P***	***Q***
STAAD without BAV			**(618 cases, 874 NINDS controls)**				**(193 cases, 150 controls)**				**(6 cases, 476 controls)**				**(811 cases, 1,024 controls)**		
rs10519177	46544486	G	0.27	1.6	0.09	7.8×10^{-8}	0.28	1.6	0.18	7.5×10^{-3}	–	–	–	–	1.6	2.0×10^{-9}	0.98
rs2118181	46703175	G	0.13	1.8	0.11	2.3×10^{-7}	0.12	2.7	0.28	4.1×10^{-4}	–	–	–	–	1.9	9.9×10^{-10}	0.17
STAAD with BAV			**(147 cases, 874 NINDS controls)**				**(192 cases, 150 controls)**				**(157 cases, 476 controls)**				**(339 cases, 1,024 controls)**		
rs10519177	46544486	G	0.24	1.6	0.14	5.0×10^{-4}	0.25	1.3	0.19	0.19	0.26	1.5	0.15	0.008	1.5	8.9×10^{-6}	0.57
rs2118181	46703175	G	0.11	1.8	0.18	6.3×10^{-4}	0.11	2.9	0.31	7.4×10^{-4}	0.13	1.6	0.18	0.011	1.8	2.2×10^{-7}	0.26
Nondissection aneurysm			**(401 cases, 874 NINDS controls)**				**(253 cases, 150 controls)**				**(163 cases, 476 controls)**				**(817 cases, 1,500 controls)**		
rs10519177	46544486	G	0.26	1.3	0.1	1.3×10^{-5}	0.24	1.1	0.17	0.43	0.26	1.5	0.15	0.0064	1.4	6.2×10^{-7}	0.32
rs2118181	46703175	G	0.12	1.7	0.13	7.4×10^{-5}	0.1	1.9	0.28	0.016	0.13	1.6	0.18	0.0095	1.7	1.3×10^{-7}	0.83
Dissection			**(364 cases, 874 NINDS controls)**				**(132 cases, 150 controls)**				**(0 cases, 476 controls)**				**(496 cases, 1,024 controls)**		
rs10519177	46544486	G	0.26	1.7	0.1	7.2×10^{-7}	0.29	2.2	0.2	1.2×10^{-4}	–	–	–	–	1.8	6.6×10^{-10}	0.26
rs2118181	46703175	G	0.13	1.9	0.13	2.7×10^{-7}	0.13	4.1	0.31	4.2×10^{-6}	–	–	–	–	2.7	7.4×10^{-3}	0.03
Type A dissection			**(224 cases, 874 NINDS controls)**				**(84 cases, 150 controls)**				**(0 cases, 476 controls)**				**(308 cases, 1,024 controls)**		
rs10519177	46544486	G	0.25	1.7	0.12	6.1×10^{-6}	0.28	2.2	0.22	3.1×10^{-4}	–	–	–	–	1.8	1.2×10^{-8}	0.33
rs2118181	46703175	G	0.12	2.1	0.15	7.7×10^{-7}	0.13	5.3	0.33	4.5×10^{-7}	–	–	–	–	3.2	1.4×10^{-2}	0.01
Type B dissection			**(144 cases, 874 NINDS controls)**				**(53 cases, 150 controls)**				**(0 cases, 476 controls)**				**(197 cases, 1,024 controls)**		
rs10519177	46544486	G	0.24	1.6	0.15	8.0×10^{-4}	0.25	1.8	0.26	0.028	–	–	–	–	1.7	6.4×10^{-5}	0.79
rs2118181	46703175	G	0.11	1.8	0.18	1.4×10^{-3}	0.08	2	0.4	0.079	–	–	–	–	1.8	2.8×10^{-4}	0.78

MAF, minor allele frequency; BAV, bicuspid aortic valve; MDS, multidimensional scaling. BP denotes NCBI Build 36.1 SNP physical position. – denotes that SNP was not analyzed in stage 3 cases without BAV because of low sample size. *Q* denotes *P* value for the Cochran statistic for homogeneity between stages 1 and 2 or stages 1, 2 and 3, as appropriate.

[a] Results for two of the five GWS 15q21.1 SNPs (see Supplementary Table 4 for the other three SNPs).

[b] Adjusted for sex and first MDS component from stage 1 samples and NINDS controls.

[c] Adjusted for sex and first MDS component from stage 2 samples.

[d] Adjusted for sex for stage 3 samples.

[e] Fixed-effects meta-analysis results between stage 1 and 2 samples for STAAD without BAV, aortic dissection (including type A and type B), and between stage 1, 2 and 3 samples for STAAD, STAAD with BAV, and nondissection aneurysm. Stage 3 aortic dissection (including type A and type B) and STAAD without BAV were not analyzed because there were only a limited number of cases with these subphenotypes. For $Q < 0.1$, the random effects OR and P are reported.