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Shared Genetic Risk Factors of Intracranial, Abdominal, and Thoracic Aneurysms

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***Background*—**Intracranial aneurysms (IAs), abdominal aortic aneurysms (AAAs), and thoracic aortic aneurysms (TAAs) all have a familial predisposition. Given that aneurysm types are known to co-occur, we hypothesized that there may be shared genetic risk factors for IAs, AAAs, and TAAs.

***Methods and Results*—**We performed a mega-analysis of 1000 Genomes Project-imputed genome-wide association study (GWAS) data of 4 previously published aneurysm cohorts: 2 IA cohorts (in total 1516 cases, 4305 controls), 1 AAA cohort (818 cases, 3004 controls), and 1 TAA cohort (760 cases, 2212 controls), and observed associations of 4 known IA, AAA, and/or TAA risk loci (9p21, 18q11, 15q21, and 2q33) with consistent effect directions in all 4 cohorts. We calculated polygenic scores based on IA-, AAA-, and TAA-associated SNPs and tested these scores for association to case-control status in the other aneurysm cohorts; this revealed no shared polygenic effects. Similarly, linkage disequilibrium–score regression analyses did not show significant correlations between any pair of aneurysm subtypes. Last, we evaluated the evidence for 14 previously published aneurysm risk single-nucleotide polymorphisms through collaboration in extended aneurysm cohorts, with a total of 6548 cases and 16 843 controls (IA) and 4391 cases and 37 904 controls (AAA), and found nominally significant associations for IA risk locus 18q11 near *RBBP8* to AAA (odds ratio [OR]=1.11; $P=4.1\times10^{-5}$) and for TAA risk locus 15q21 near *FBN1* to AAA (OR=1.07; $P=1.1\times10^{-3}$).

***Conclusions*—**Although there was no evidence for polygenic overlap between IAs, AAAs, and TAAs, we found nominally significant effects of two established risk loci for IAs and TAAs in AAAs. These two loci will require further replication. **(*J Am Heart Assoc*. 2016;5:e002603 doi: 10.1161/JAHA.115.002603)**

Key Words: abdominal aortic aneurysm • genome wide association study • intracranial aneurysm • thoracic aortic aneurysm

Intracranial aneurysms (IAs), abdominal aortic aneurysms (AAAs), and thoracic aortic aneurysms (TAAs) are 3 different forms of arterial vessel wall dilatations, which can all lead to rupture with a high case fatality rate.[1–3] A co-occurrence of AAA and TAA is known,[4,5] and a weak co-occurrence of IA and AAA has also been suggested.[6,7]

The authors' affiliations are provided on page 16 of the article.

*A complete list of the Aneurysm Consortium and the Vascular Research Consortium of New Zealand can be found in an Appendix at the end of the article.

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Furthermore, IA, TAA, and AAA cluster within affected families,[8,9] suggesting a shared genetic background of these 3 diseases.

Genome-wide association studies (GWASs) have revealed a handful of genetic risk factors for IA,[10–12] AAA,[13–16] and TAA,[17] and of these identified loci, locus 9p21 near *CDKN2A*, *CDKN2B*, and *CDKN2BAS* appears to be shared by IA and AAA.[11,18] However, the heritability explained by the risk loci identified to date is low for all 3 diseases, suggesting that many aneurysm risk loci remain to be discovered. Among these unknown and known risk loci, there could be shared risk loci for multiple types of aneurysms.

In this study, we searched for shared genetic risk factors for aneurysms. We combined individual participant GWAS data from a Dutch and a Finnish IA cohort,[12] a Dutch AAA cohort,[14] and a TAA cohort from the United States[17] for a GWAS mega-analysis across these traits. In a complementary approach, we performed a polygenic analysis to test groups of single-nucleotide polymorphisms (SNPs) for a joint effect on risk across diseases. Finally, we tested the effect of bona-fide risk SNPs from previously published IA, AAA, and TAA GWASs on the other aneurysm types by meta-analyzing summary statistics in the GWAS cohorts of IA, AAA, and TAA, extended by association results of additional IA and AAA GWAS cohorts.

Methods

Study Populations

For the GWAS mega-analysis and polygenic analysis, we used data of subjects genotyped in previously published GWAS cohorts of aneurysm cases and controls: 2 IA cohorts, 1 from the Netherlands[12,19,20] and 1 from Finland,[11,12,21,22] 1 AAA cohort from the Netherlands[14,18] and 1 TAA cohort from the United States.[17] All studies were approved by the relevant medical ethical committees, and all participants provided written informed consent. All study populations were previously described in detail.[12,17,19,20] Below is a brief description of each study population.

IA cases in the Dutch cohort (n=786) were admitted to the University Medical Center Utrecht, (Utrecht, The Netherlands) between 1997 and 2011. All cases were genotyped on Illumina CNV370 Duo BeadChips (Illumina, San Diego, CA). Controls (n=2089) were ascertained by the Rotterdam Study, a population-based cohort of subjects age 45 years and older recruited from a district in Rotterdam (The Netherlands). These controls were genotyped on Illumina HumanHap550 BeadChips.[23]

The Finnish IA cohort consisted of 790 cases treated at the Helsinki and Kuopio University hospitals and 2396 controls that were genetically matched to cases.[24] Of these, 1666 controls were extracted from the Helsinki Birth Cohort Study (HBCS).[21] Additionally, 651 controls were extracted from anonymous donors from Kuopio University Hospital and Helsinki and from the Health 2000 study (H2000).[22] All cases were genotyped on Illumina CNV370 Duo BeadChips, and controls were genotyped on Illumina HumanHap550 BeadChips (HBCS) and on Illumina CNV370 Duo BeadChips (anonymous donors and H2000).

The Dutch and the Finnish IA cohort both included cases with ruptured and unruptured IA. Ruptured IA cases were defined by symptoms suggestive of subarachnoid hemorrhage (SAH) combined with subarachnoid blood on a computed tomography (CT) scan and a proven IA at angiography (conventional angiogram, CT- or magnetic resonance [MR] angiogram). Unruptured IA cases were identified by CT or MR angiography or conventional angiography in the absence of clinical or radiological signs of SAH. Patients with fusiform IA, possible traumatic SAH, and polycystic kidney disease were excluded.

The AAA cohort consisted of 859 cases, predominantly with unruptured AAA. These cases were recruited from 8 medical centers in The Netherlands, mainly when individuals visited their vascular surgeon in the outpatient clinic or, in some cases, during hospital admission for elective or emergency AAA surgery. An AAA was defined as an infrarenal aorta diameter of ≥30 mm. Mean AAA diameter was 58.4 mm. Of these patients, 530 had undergone surgery, including 43 with rupture. Genotyping was performed on Illumina HumanHap610 chips.[14] As controls, we included 3110 Dutch subjects who were recruited as part of the Nijmegen Biomedical Study (n=1832) and the Nijmegen Bladder Cancer Study (n=1278).[19,20] These controls were genotyped on Illumina CNV370 Duo BeadChips.

The TAA cohort consisted of 765 cases with either an ascending TAA without dissection (n=401) or with a type A and/or type B aortic dissection (n=364). All cases were more than 30 years old, did not have a first-degree relative with TAA or dissection, and had no evidence of a syndromic form of TAA or dissection. Samples were genotyped with Illumina CNV370-Quad BeadChips. Controls (n=2229) were included from the Wellcome Trust Case-Control Consortium (WTCCC) 1958 Birth Cohort (n=1355), and from the US National Institute of Neurological Disorders and Stroke (NINDS) Repository's Neurologically Normal Control Collection (n=874).

Quality Control

We performed quality control (QC) in each of the 4 cohorts separately, using PLINK software (version 1.07).[25] After removal of SNPs with A/T or C/G alleles and SNPs that

were not called in any individual, we performed sample QC and SNP QC.

Sample QC was performed after merging cases and controls, using a subset of common, high-quality SNPs (as defined by SNPs without deviation from Hardy-Weinberg equilibrium [HWE; P>0.001], with high minor allele frequency [MAF; >20%], and with low rate of missing genotypes [<1%]). Linkage disequilibrium (LD) pruning (r^2>0.5) was performed. Subjects were removed based on the following 3 criteria: missing genotypes (subjects with a call rate below 95% were removed); heterozygosity (subjects were excluded if the inbreeding coefficient deviated more than 3 SDs from the mean); and cryptic relatedness (by calculating identity-by-descent [IBD] for each pair of individuals). In each pair with an IBD proportion of >20%, a subject was excluded, if it exhibited distant relatedness with more than 1 individual. For case-control pairs, we removed the control subject. In the case-case or control-control pairs, the subject with the lowest call rate was excluded.

Using these common, high-quality SNPs, we performed principal components (PCs) analysis using EIGENSTRAT on the remaining study subjects and HapMap-CEU subjects. We excluded SNPs from 3 regions with known long-distance LD: the major histocompatibility region (chr6: 25.8–36 Mbp); the chromosome 8 inversion (chr8: 6–16 Mbp); and a chromosome 17 region (chr17: 40–45 Mbp). We created PC plots with the first 4 PCs, using R software (version 2.11; R Foundation for Statistical Computing, Vienna, Austria).[26] Based on visual inspection of these plots, we excluded subjects that appeared to be outliers with respect to the CEU (Utah residents with ancestry from northern and western Europe) or the study population. After outlier removal, we recomputed PCs for them to be included as covariates in the logistic regression models. PC plots after outlier removal are shown in Figure 1.

After sample QC, we excluded SNPs with more than 2% missing genotypes, MAF <1%, missing genotype rate higher

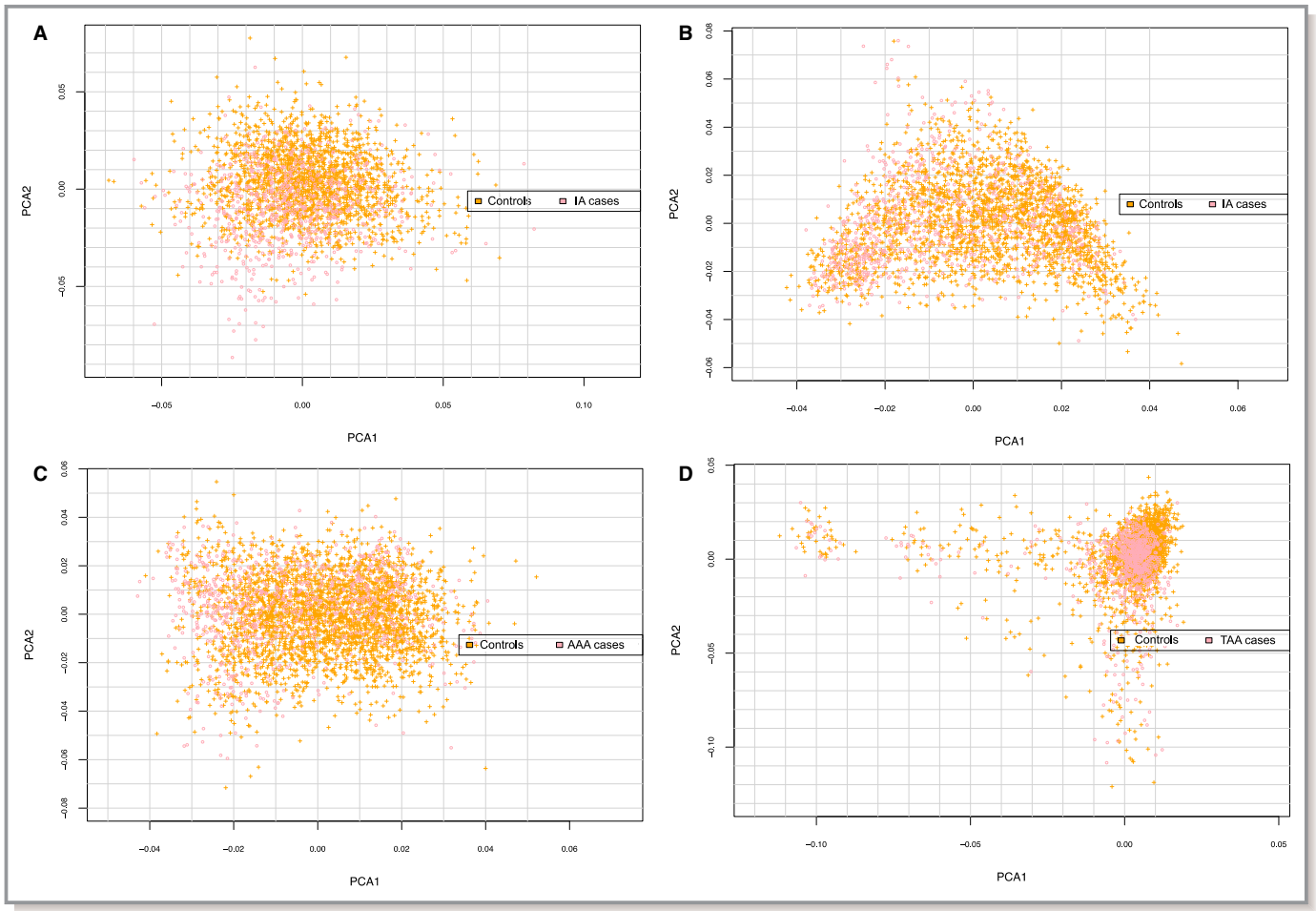


Figure 1. Principal component analysis (PCA) plots of IA, AAA, and TAA GWAS cohorts. (A) Dutch IA GWAS cohort; (B) Finnish IA GWAS cohort; (C) AAA GWAS cohort; (D) TAA GWAS cohort. These figures show PCA2 values plotted against PCA1 values for each individual in the 4 GWAS cohorts (Dutch IA and Finnish IA, AAA, and TAA) of the aneurysm mega-analysis, after removal of outliers from quality control. AAA indicates abdominal aortic aneurysm; GWAS, genome-wide association study; IA, intracranial aneurysm; TAA, thoracic aortic aneurysm.

than MAF, and HWE deviation ($P<0.001$). Because cases and controls had been genotyped separately, we performed these QC steps in each study cohort separately and again after merging cases and controls. We also removed SNPs with a differential degree of missing genotypes between cases and controls ($P<1\times10^{-5}$; chi-squared test).

Imputation

For each case-control data set, we performed genotype imputation using the prephasing/imputation step-wise approach implemented in IMPUTE2 and SHAPEIT (chunk size of 3 Mb and default parameters).[27,28] The imputation reference set consisted of 2184 phased haplotypes from the full 1000 Genomes Project data set (February 2012; 40 318 253 variants). All genomic locations are given in NCBI Build 37/UCSC hg19 coordinates. After imputation, SNPs with an imputation accuracy score <0.6 or MAF <0.5% were excluded.

GWAS Mega-Analysis Across IA, AAA, and TAA

We performed a mega-analysis on all 4 GWAS cohorts. Association testing was carried out in PLINK[25] using imputed SNP dosages. We included as covariates the first 4 PCs and an indicator variable to adjust for each case-control data set. SNPs with $P<5\times10^{-8}$ were considered as genome-wide significant. We also performed a GWAS on each cohort separately and a combined analysis of only the Dutch and Finnish IA cohort, which was needed for the polygenic analysis as described below. We calculated genomic inflation factors (λ_{GC}) for each GWAS and the mega-analysis, defined as the ratio of the median of the empirically observed distribution of the test statistic to the expected median.[29]

We calculated the statistical power for detecting a significant association ($P<5\times10^{-8}$) in the mega-analysis using the genetic power calculator.[30] In case of a risk allele frequency of 10%, the resulting power is 0.03% at a relative risk of 1.1 per allele, and 68.7% at a relative risk of 1.3 per allele, assuming additive effects. In case of a higher risk allele frequency of 20%, the power is 0.3% at a relative risk of 1.1 and 98.9% at a relative risk of 1.3 per allele.

Polygenic Analysis

We performed polygenic analysis as previously described.[31] We used the IA cohorts (Dutch and Finnish cohorts combined) as a discovery sample and the AAA and TAA cohorts as 2 separate target samples, and vice versa, in all possible combinations (6 in total).

We pruned the SNPs genotyped or imputed in the discovery sample, using an LD threshold of $r^2>0.1$. For each genomic region, we chose SNPs with the lowest P values in the GWAS of the discovery sample, in order to retain a set of independent, maximally associated SNPs. Next, we created sets of SNPs with disease association in the discovery sample at 12 different significance thresholds, increasing from $P<5\times10^{-8}$ to $P<0.5$. For each SNP set, we calculated a polygenic risk score in each individual of target sample as follows:

$$\text{Genetic score} = \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n,$$

where x_i is the estimated allele dosage (between 0 and 2) in a given individual, and β_i is the effect size from the GWAS in the discovery sample for the i^{th} SNP. We tested the association between these polygenic risk scores and case-control status in the target sample using logistic regression, adjusting for the first 4 PCs in the target sample. For analyses involving the combined IA cohort as target sample, we also adjusted for population (Finnish or Dutch). For analyses involving the IA and AAA cohorts as target and discovery sample, we also adjusted for the genotype of the known shared IA/AAA risk SNPs on locus 9p21.[11,18]

Table 1. Overview of Study Populations Used for the Specific Lookup of Known IA, AAA, and TAA Risk SNPs

Cohort	Cases (n)	Controls (n)
IA		
Netherlands	717	1987
Finland	799	2317
Japan 1	288	194
Japan 2	1383	5484
USA+	2617	2548
@neurIST	717	3296
Total	6548	16 843
AAA		
Netherlands	812	2998
Iceland	430	27 712
USA	724	1604
Aneurysm Consortium	1846	5605
New Zealand 1	608	612
New Zealand 2	400	384
Total	4391	37 904
TAA		
USA	760	2212

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; SNPs, single-nucleotide polymorphisms; TAA, thoracic aortic aneurysm.

LD Score Regression: Heritability Estimation and Genetic Correlation Analyses

We used LD score regression (LDSC) for heritability estimation and genetic correlation analysis.[32] These analyses were applied to the same 4 GWAS datasets as used in the GWAS mega-analysis and polygenic analysis described above (Dutch IA and Finnish IA, AAA, and TAA), but for this analysis we only included genotyped SNPs (after QC), and not imputed SNPs.

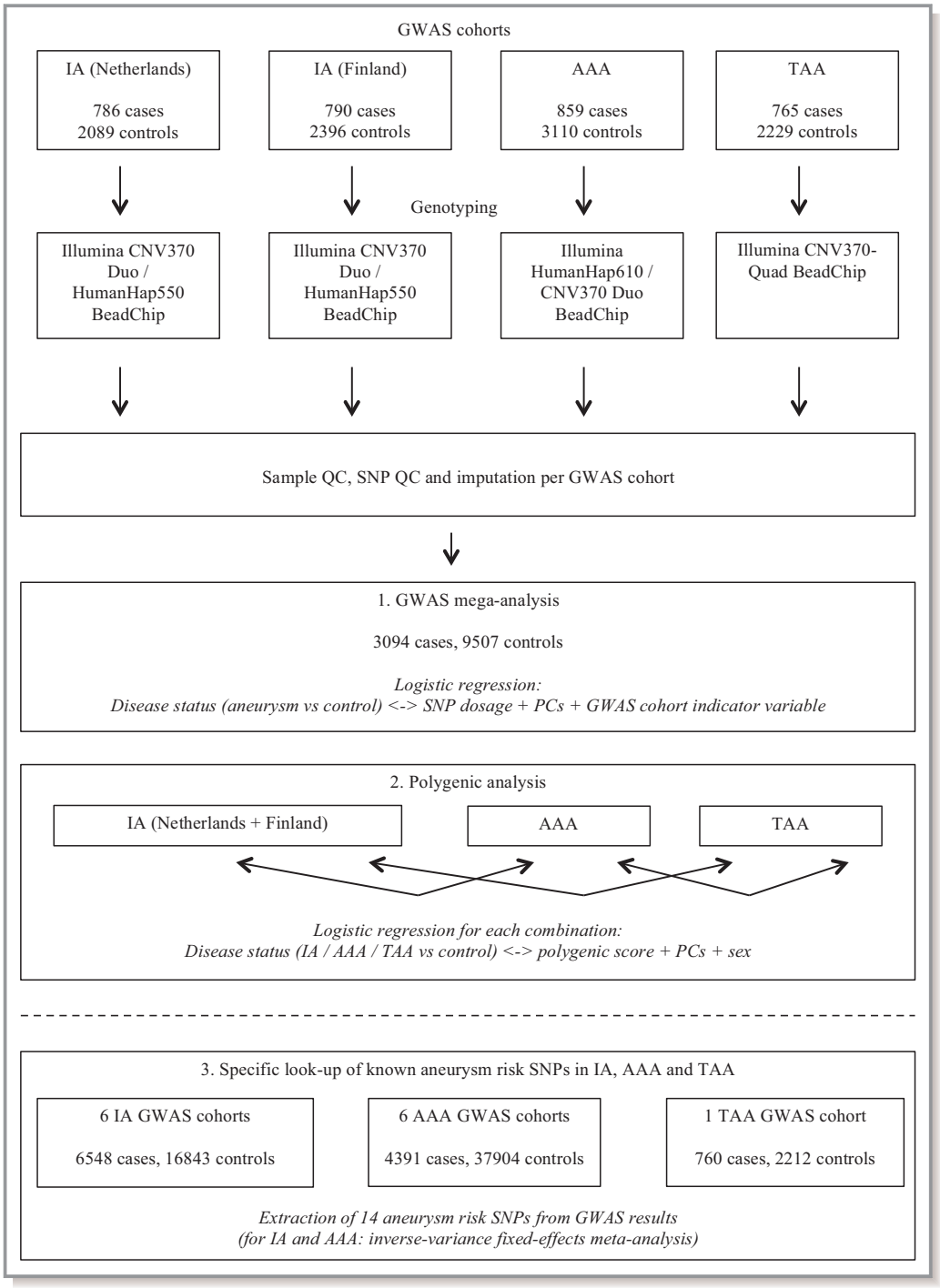


Figure 2. Work-flow figure. This figure gives an overview of the study methods. AAA indicates abdominal aortic aneurysm; CNV, copy number variation; GWAS, genome-wide association study; IA, intracranial aneurysm; PCs, principal components; QC, quality control; SNP, single-nucleotide polymorphism; TAA, thoracic aortic aneurysm.

LDSC is a new approach that implements LD-score weighted linear regression methods to estimate the variance (and covariance) explained by all SNPs on the whole genome for a complex trait. This method can distinguish true polygenicity from confounding effects attributed to population structure and cryptic relatedness. Under a polygenic model, the more-genetic variants an index variant tags, the more the probability that the index variant will be significant.[32] Under this reasoning, the expected χ^2 statistic of variant j can be constructed as follows:

$$E[\chi^2|\ell_j] = Nh^2\ell_j/M + Na + 1,$$

where N is the sample size; M is the number of SNPs, so that h^2/M is the average heritability per SNP; *a* measures the contribution of confounding biases, like cryptic relatedness and population stratification; and $\ell_j = \sum_k r_{jk}^2$ is the sum of the r^2 values to all variants that a variant j tags, which is called the LD score of variant j. The LD score can be calculated using reference panel containing whole genome information of the population. For the analysis of the European population, we used the LD estimates that are from the European-ancestry samples in the 1000 Genomes Project.[33] Details were elaborated from the LDSC's GitHub repository.[32]

In addition to estimating heritability using LDSC, we also used LDSC to estimate genetic correlation (ρ) between each pair of 3 diseases (AAA, IA, and TAA).[34] We investigated the Dutch and Finnish IA cohort separately in this analysis, and also tested the correlation between these two IA data sets, to evaluate the genetic correlation within 1 disease.

Effects of Previously Established Risk SNPs

We investigated the effect of established IA,[10–12] AAA,[13–16] and TAA[17] risk SNPs from previous GWASs in each of the other aneurysm types. We looked up the effect sizes and significance of these SNPs in separate case-control data sets for IA, AAA and TAA beyond the individual-participant data sets already described above. We did not have access to all genotype data of these data sets, but we obtained association results for these candidate SNPs only. For IA, we used GWAS results of 2 Japanese cohorts,[11] a combined cohort of several previously IA studies that recruited subjects from mainly North America, but also Poland and Australia (further referred to as "USA+"),[35] and the @neurIST study.[11] For AAA, we used GWAS results of a cohort from Iceland, the United Kingdom, the United States, and 2 cohorts from New Zealand.[15,16,36,37] For TAA, no additional GWAS cohorts are currently available, to our knowledge. The sample sizes and other details per cohort are listed in Table 1. In total, the target samples available for this lookup analysis contained 6548 cases and 16 843 controls for IA, 4391 cases and 37 904 controls for AAA, and 760 cases and 2212 controls for TAA.

We combined the GWAS results for the selected SNPs in the extended IA and AAA cohorts using an inverse-variance fixed-effects meta-analysis. For each SNP, we first calculated *z* scores from the provided *P* values of each GWAS, and summed the *z* scores across all studies using the effective sample size of each study as weights.[38] The resulting *z* scores were converted into chi-square values and 2-sided *P* values. We applied Bonferroni correction for performing 28 association tests (14 selected SNPs tested in 2 aneurysm types) and considered associations with $P<1.8\times10^{-3}$ (0.05/28) as significant. Figure 2 gives an overview of the methods described above.

Results

Study Populations

Table 2 shows the numbers of cases, controls, and SNPs of all 4 cohorts after QC and imputation. Quantile-quantile (QQ) plots for each GWAS per cohort are shown in Figure 3.

Table 2. Baseline Characteristics After Quality Control and Imputation of the Study Populations Used for the Mega-Analysis and Polygenic Analysis of IA, AAA, and TAA GWAS Data

	Study Cohort			
Characteristics	IA (Netherlands)	IA (Finland)	AAA	TAA
Cases, n	717	799	818	760
Women, %	64.3	57.8	10.5	34.3
Controls, n	1988	2317	3004	2212
Women, %	56.2	57.2	37.7	53.0
SNPs, n	10 683 725	10 524 028	10 684 772	10 750 239
Genomic inflation factor	1.10	1.06	1.04	1.05

AAA indicates abdominal aortic aneurysm; GWAS, genome-wide association study; IA, intracranial aneurysm; SNP, single-nucleotide polymorphism; TAA, thoracic aortic aneurysm.

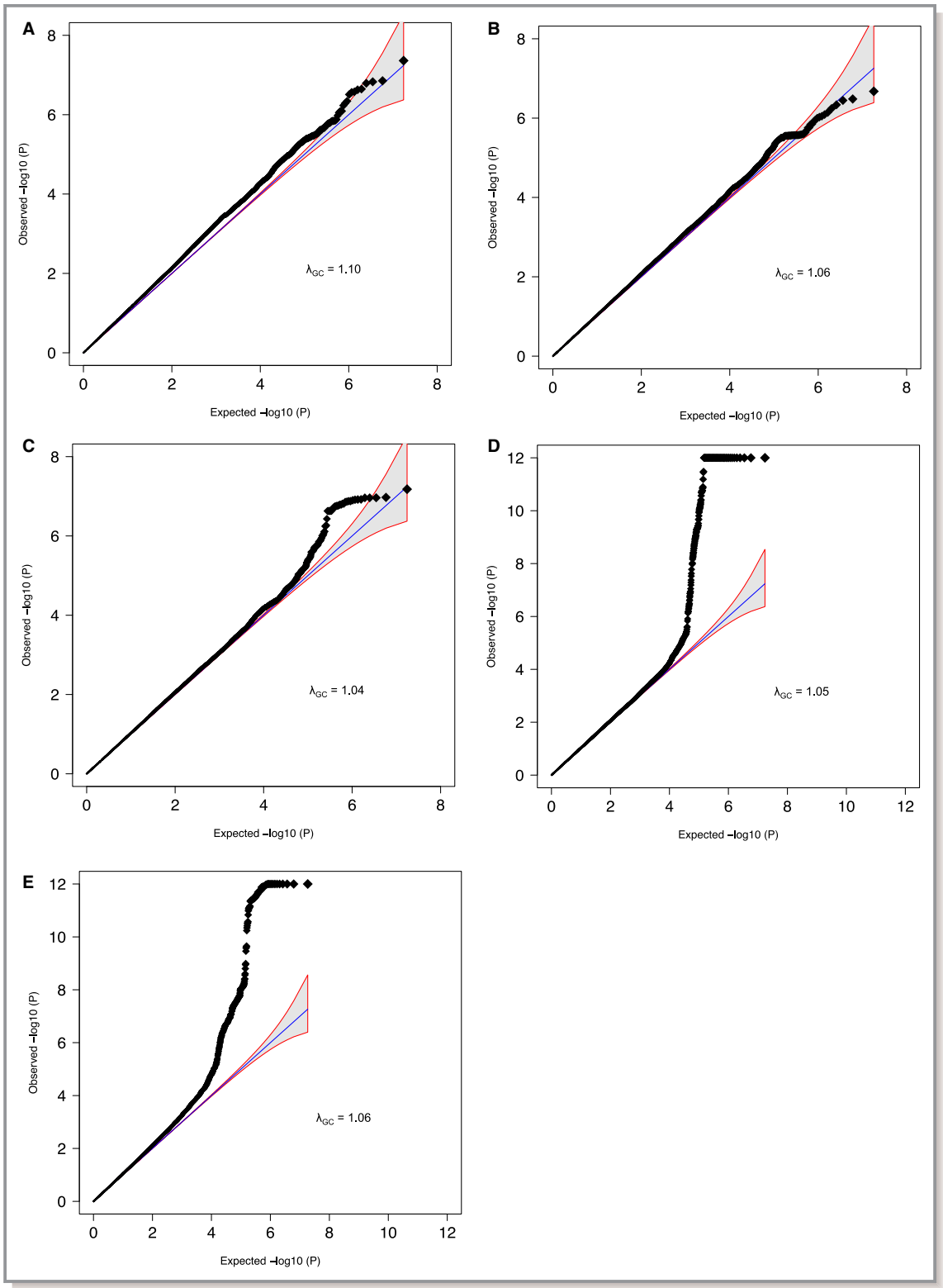


Figure 3. Quantile-quantile (QQ) plots of IA, AAA, and TAA GWAS and the aneurysm mega-analysis. A, Dutch IA GWAS; (B) Finnish IA GWAS; (C) AAA GWAS; (D) TAA GWAS; (E) aneurysm mega-analysis. These QQ plots show the observed distribution of *P* values (black dots) plotted against the expected distribution of *P* values (blue line) on a negative $\log_{10}$ scale, for each of the 4 GWAS (Dutch IA and Finnish IA, AAA, and TAA) and for all cohorts combined in the aneurysm mega-analysis. Genomic inflation factors (λ_{GC}) per study, defined as the ratio of the median of the empirically observed distribution of the test statistic to the expected median, are also shown. AAA indicates abdominal aortic aneurysm; GWAS, genome-wide association study; IA, intracranial aneurysm; TAA, thoracic aortic aneurysm.

GWAS Mega-Analysis Across IA, AAA, and TAA

In total, 3094 cases, 9507 controls, and 9 245 988 SNPs were available for the mega-analysis across all 4 aneurysm cohorts (λ_{GC}=1.06). The results of this mega-analysis are shown in a Manhattan plot (Figure 4). We found 4 genome-wide significant loci, though all these loci were previously described as risk loci for IA, AAA, and/or TAA. The direction of effect for these loci was consistent across all four aneurysm cohorts (see forest plots in Figure 5). First, SNPs at the known IA and AAA risk locus 9p21 near *CDKN2A*, *CDKN2B*, and *CDKN2BAS* were associated.[11,18] The strongest association at this locus was found for rs7866503, with $P=2.1\times10^{-13}$. The second association was found for SNPs at the known IA risk locus 18q11 near *RBBP8*,[11] with the strongest association for rs8087799 ($P=1.6\times10^{-9}$). The third association was found for SNPs at the known TAA risk locus 15q21 near *FBN1*,[17] with the strongest association for rs595222 ($P=1.0\times10^{-8}$). The fourth association was found for rs919433 ($P=4.6\times10^{-8}$), which is located at 2q33 near *ANKRD44*. The same SNP was previously found to be associated with IA in a Finnish and Dutch population.[24] This SNP is also in strong LD (r^2=0.7) with a nearby SNP (rs700651), which was previously found to be associated with IA in a Dutch, Finnish, and Japanese population,[12] but did not reach genome-wide significance after adding other populations of IA patients.[11]

Polygenic Analysis

Next, we investigated whether groups of SNPs associated with 1 type of aneurysm (eg, IA) were also associated with the other types (eg, AAA or TAA). The results of these polygenic analyses with the IA, AAA, and TAA GWAS cohorts are shown in Tables 3 through 8 and in Figure 6. No SNP sets with a significant joint effect on another aneurysm type were observed, except for a small group of 7 SNPs associated with IA with $P<10^{-6}$. This SNP set was associated with AAA with $P=5\times10^{-3}$ (Table 7). When taking a closer look at this SNP set, it appears that the polygenic association is driven by 2 SNPs (rs36071109 at 2q33; $P_{AAA}=2.3\times10^{-3}$; and rs4330012 at 18q11; P (cursive)$_{AAA}=1.3\times10^{-2}$), both in very strong LD to genome-wide significant SNPs in our mega-analysis described above. (The pleiotropic 9p21 locus shared by IA and AAA had already been adjusted for.)

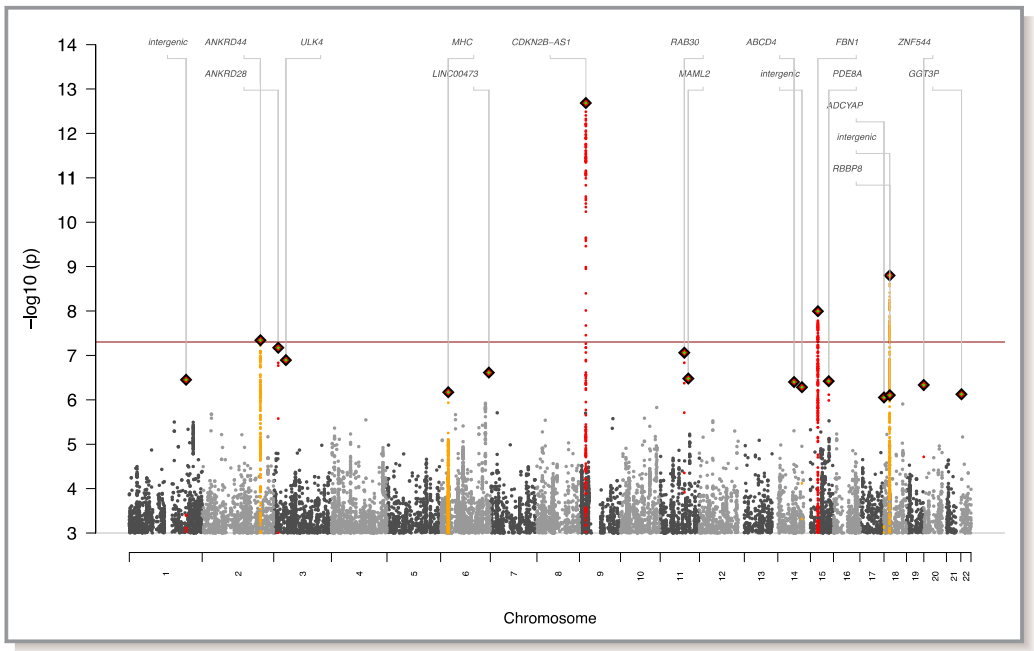


Figure 4. Manhattan plot of the aneurysm GWAS mega-analysis. This Manhattan plot shows the *P* values of all SNPs with an association with $P<10^{-4}$ to disease (IA, AAA, or TAA). *P* values on the *y*-axis are presented on an inverse log scale. The *x*-axis represents the genomic position of each SNP. The red horizontal line represents $P=5\times10^{-8}$, the cut-off value for genome-wide association. Index SNPs with $P<1\times10^{-6}$ are depicted as diamonds, whereas SNPs in the same LD block as these SNPs are depicted as yellow and red dots. AAA indicates abdominal aortic aneurysm; GWAS, genome-wide association study; IA, intracranial aneurysm; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism; TAA, thoracic aortic aneurysm.

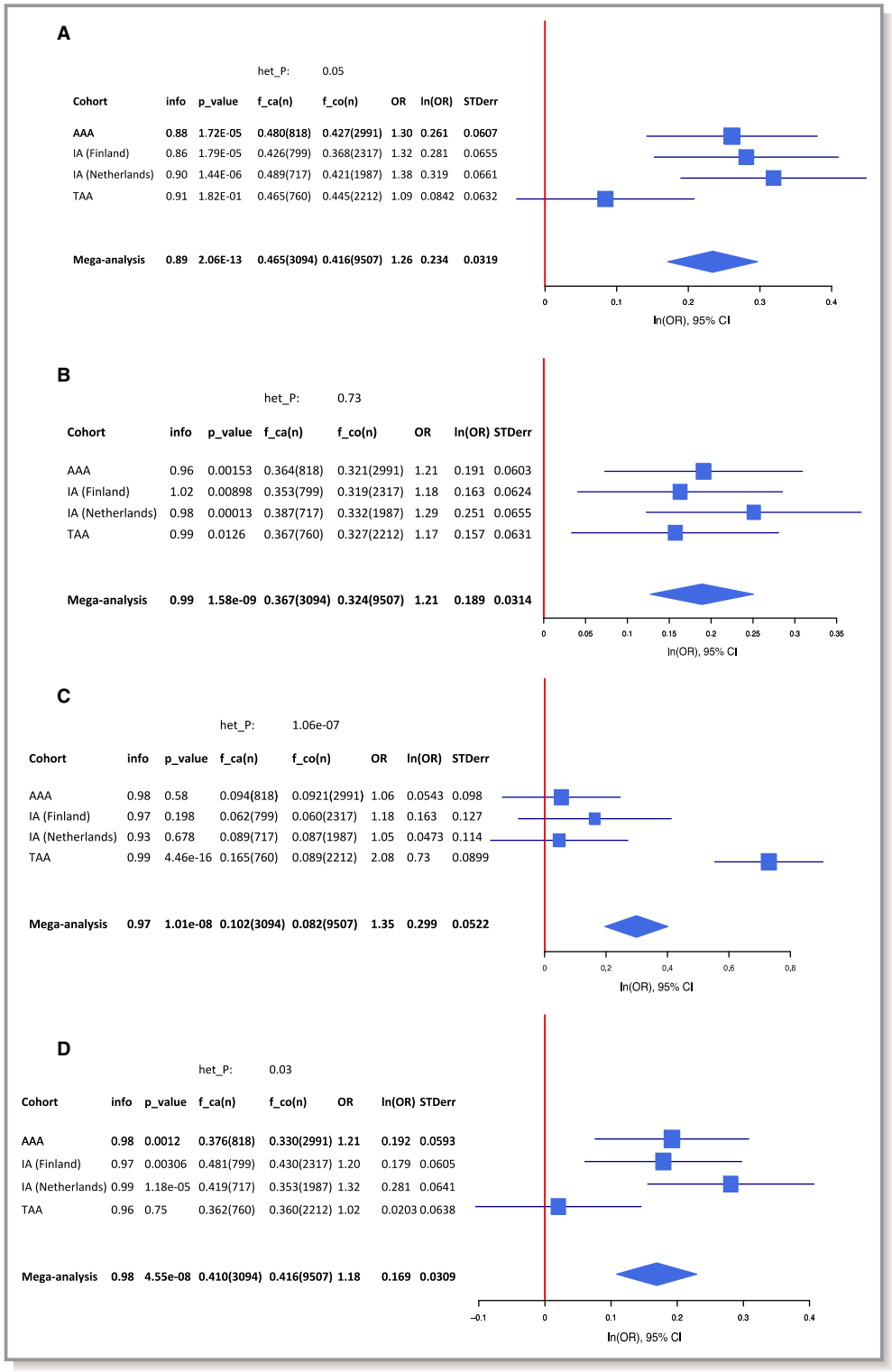


Figure 5. Forest plots of significant SNPs from the aneurysm mega-analysis. A, rs7866503 (risk allele T) at locus 9p21; (B) rs8087799 (risk allele A) at locus 18q11; (C) rs595244 (risk allele T) at locus 15q21; (D) rs919433 (risk allele A) at locus 2q33. These figures show forest plots for each of the 4 genome-wide significant SNPs from the mega-analysis of IA, AAA, and TAA GWAS cohorts. AAA indicates abdominal aortic aneurysm; f_ca(n), risk allele frequency in cases (number of cases); f_co(n), risk allele frequency in controls (number of controls); het_P, *P* value for heterogeneity; IA, intracranial aneurysm; info, imputation accuracy score; ln(OR), natural log of odds ratio; OR, odds ratio; *P*_value, *P* value for association of risk allele in aneurysm cohort; SNP, single-nucleotide polymorphism; STDerr, standard error; TAA, thoracic aortic aneurysm.

Table 3. Polygenic Analysis: AAA-Associated SNPs Tested for Association With TAA Case-Control Status

Threshold (*P*)*	SNPs (n)†	*P* Value‡	Direction of Effect
5×10^{-8}	0	NA	NA
1×10^{-7}	1	0.269	+
1×10^{-6}	4	0.262	+
1×10^{-5}	21	0.481	+
1×10^{-4}	181	0.979	+
1×10^{-3}	1417	0.815	+
0.01	10 075	0.294	+
0.05	38 528	0.549	+
0.1	67 187	0.614	–
0.2	113 644	0.823	–
0.3	151 807	0.773	–
0.4	183 891	0.765	–
0.5	211 723	0.611	–
10^{-4} to 10^{-3}	1236	0.787	+
10^{-3} to 0.01	8658	0.273	+
0.01 to 0.05	28 453	0.972	–
0.05 to 0.1	28 659	0.964	–
0.1 to 0.2	46 457	0.115	–
0.2 to 0.3	38 163	0.745	–
0.3 to 0.4	32 084	0.904	–
0.4 to 0.5	27 832	0.0915	–

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; NA, not applicable; SNPs, single-nucleotide polymorphisms; TAA, thoracic aortic aneurysm.
**P* value threshold for inclusion of IA-, AAA-, or TAA-associated SNPs in each polygenic model.
†Number of SNPs included in each polygenic model.
‡*P* value for association of the polygenic model with IA, AAA or TAA case-control status.

Table 4. Polygenic Analysis: TAA-Associated SNPs Tested for Association With AAA Case-Control Status

Threshold (*P*)*	SNPs (n)†	*P* Value‡	Direction of Effect
5×10^{-8}	1	0.581	+
1×10^{-7}	1	0.581	+
1×10^{-6}	1	0.581	+
1×10^{-5}	25	0.853	+
1×10^{-4}	148	0.971	–
1×10^{-3}	1350	0.292	+
0.01	10 021	0.579	+
0.05	39 120	0.902	–
0.1	67 736	0.944	–
0.2	114 125	0.815	–
0.3	151 712	0.956	–
0.4	183 843	0.958	–
0.5	211 170	0.965	–
10^{-4} to 10^{-3}	1202	0.252	+
10^{-3} to 0.01	8671	0.877	–
0.01 to 0.05	29 099	0.801	–
0.05 to 0.1	28 616	0.953	–
0.1 to 0.2	46 389	0.643	+
0.2 to 0.3	37 587	0.255	–
0.3 to 0.4	32 131	0.997	–
0.4 to 0.5	27 327	0.422	+

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; SNPs, single-nucleotide polymorphisms; TAA, thoracic aortic aneurysm.
**P* value threshold for inclusion of IA-, AAA-, or TAA-associated SNPs in each polygenic model.
†Number of SNPs included in each polygenic model.
‡*P* value for association of the polygenic model with IA, AAA or TAA case-control status.

LD Score Regression: Heritability Estimation and Genetic Correlation Analyses

We attempted to analyze heritability of the 3 aneurysm subtypes using LDSC. The estimated heritability was 0.15 for AAA, 0.31 for the Finnish IA cohort, 0.34 for the Dutch IA cohort, and 0.40 for TAA (Table 9). These estimates are smaller than the twin-based estimates as reported in the literature (0.41 for IA,[39] 0.70 for AAA,[16] and unknown for TAA), but the SEs are large, so the differences are not statistically significant. Note that methods estimating heritability using SNP data can often underestimate the heritability if the SNP set does not tag all underlying causal variants.

We then performed genetic correlation analyses (Table 10). We found that all pairs did not show statistically significant genetic correlations ($P>0.05$). The direction of correlation was either close to zero or positive, but the SE values were large. As expected, we observed the largest genetic correlation between the 2 cohorts of the same IA disease ($\rho=1.59$). However, this correlation was also not significant ($P=0.09$; SE=0.93).

Effects of Previously Established Risk SNPs

Table 11 shows the results of the lookup of previously published aneurysm risk SNPs in IA, AAA, and TAA GWAS results. Besides the 2 IA and AAA risk SNPs at 9p21, which are associated with IA and AAA but not TAA, we observed 2 SNPs with significant associations to another aneurysm type after multiple testing correction. First, the IA risk SNP rs11661542 at 18q11 near *RBBP8* was associated with AAA (odds ratio [OR]=1.11; $P=4.1\times10^{-5}$). Second, the TAA risk SNP rs2118181 at 15q21 near *FBN1*

Table 5. Polygenic Analysis: IA-Associated SNPs Tested for Association With TAA Case-Control Status

Threshold (*P*)*	SNPs (n)†	*P* Value‡	Direction of Effect
5×10^{-8}	2	0.464	+
1×10^{-7}	3	0.459	+
1×10^{-6}	7	0.964	+
1×10^{-5}	36	0.361	–
1×10^{-4}	263	0.24	–
1×10^{-3}	1738	0.32	–
0.01	11 365	0.681	+
0.05	40 885	0.088	+
0.1	69 990	0.608	+
0.2	116 737	0.931	–
0.3	154 387	0.612	–
0.4	184 519	0.633	–
0.5	209 893	0.625	–
10^{-4} to 10^{-3}	1475	0.572	–
10^{-3} to 0.01	9627	0.318	+
0.01 to 0.05	29 520	0.04	+
0.05 to 0.1	29 105	0.0699	–
0.1 to 0.2	46 747	0.193	–
0.2 to 0.3	37 650	0.105	–
0.3 to 0.4	30 132	0.951	–
0.4 to 0.5	25 374	0.864	–

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; SNPs, single-nucleotide polymorphisms; TAA, thoracic aortic aneurysm.
**P* value threshold for inclusion of IA-, AAA-, or TAA-associated SNPs in each polygenic model.
†Number of SNPs included in each polygenic model.
‡*P* value for association of the polygenic model with IA, AAA or TAA case-control status.

Table 6. Polygenic Analysis: TAA-Associated SNPs Tested for Association With IA Case-Control Status

Threshold (*P*)*	SNPs (n)†	*P* Value‡	Direction of Effect
5×10^{-8}	1	0.245	+
1×10^{-7}	1	0.245	+
1×10^{-6}	1	0.245	+
1×10^{-5}	25	0.0957	–
1×10^{-4}	148	0.658	–
1×10^{-3}	1347	0.741	–
0.01	10 030	0.547	+
0.05	39 150	0.72	+
0.1	67 783	0.693	+
0.2	114 079	0.554	+
0.3	151 575	0.538	+
0.4	183 611	0.651	+
0.5	210 876	0.675	+
10^{-4} to 10^{-3}	1199	0.588	–
10^{-3} to 0.01	8683	0.592	+
0.01 to 0.05	29 120	0.965	+
0.05 to 0.1	28 633	0.813	+
0.1 to 0.2	46 296	0.487	+
0.2 to 0.3	37 496	0.761	+
0.3 to 0.4	32 036	0.409	+
0.4 to 0.5	27 265	0.84	+

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; SNPs, single-nucleotide polymorphisms; TAA, thoracic aortic aneurysm.
**P* value threshold for inclusion of IA-, AAA-, or TAA-associated SNPs in each polygenic model.
†Number of SNPs included in each polygenic model.
‡*P* value for association of the polygenic model with IA, AAA or TAA case-control status.

was associated with AAA (OR=1.07; $P=1.1\times10^{-3}$). The other TAA risk SNP rs10519177, which lies at the same locus but is independent from rs2118181, showed a suggestive, but not statistically significant, association to AAA (OR=1.01; $P=0.016$). For both significant associations, the direction of effect was concordant in all but 1 of the 6 AAA cohorts in the analysis, with no significant heterogeneity in the meta-analysis of the 6 cohorts ($P_{\text{Cochran's Q}}=0.11$ for rs11661542 at 18q11 and 0.45 for rs2118181 at 15q21).

Discussion

In this study, we have applied multiple analytic approaches to detect a possible genetic overlap between IA, TAA, and AAA. By performing a GWAS mega-analysis and polygenic analysis, we considered both sharing of significant risk loci with individually large effects on disease risk, as well as a cumulative effect of many loci with individually weak effects. Although we did not find novel shared aneurysm risk loci that were previously not described as risk loci for IA, AAA, and/or TAA, we did find some evidence for a shared genetic background of IA, AAA, and TAA. In the GWAS mega-analysis across IA, AAA, and TAA, we detected genome-wide significant associations for SNPs at 4 loci: 9p21, 18q11, 15q21, and 2q33. These were all previously described to be associated with IA, AAA, or TAA, but in this study, they showed globally consistent effects across all 3 aneurysm types. Polygenic analysis did not reveal any groups of weakly IA-, AAA-, or TAA-associated loci with a joint effect on other aneurysm types. Similarly, LD-score regression analyses did not show significant correlations between any pair of aneurysm subtypes. The correlation between 2 cohorts of the same subtype (IA) was relatively

Table 7. Polygenic Analysis: IA-Associated SNPs (From Dutch and Finnish IA Cohorts Combined) Tested for Association With AAA Case-Control Status

Threshold (*P*)*	SNPs (n)†	*P* Value‡	Direction of Effect
5×10^{-8}	2	0.531	+
1×10^{-7}	3	0.016	+
1×10^{-6}	7	5.07×10^{-3}	+
1×10^{-5}	36	1.36×10^{-2}	+
1×10^{-4}	256	0.694	+
1×10^{-3}	1725	0.365	−
0.01	11 355	0.986	+
0.05	40 855	0.505	+
0.1	69 919	0.329	−
0.2	116 610	0.298	−
0.3	154 280	0.349	−
0.4	184 378	0.326	−
0.5	209 684	0.251	−
10^{-4} to 10^{-3}	1469	0.401	−
10^{-3} to 0.01	9630	0.673	+
0.01 to 0.05	29 500	0.343	−
0.05 to 0.1	29 064	0.291	−
0.1 to 0.2	46 691	0.503	−
0.2 to 0.3	37 670	0.929	+
0.3 to 0.4	30 098	0.568	−
0.4 to 0.5	25 306	0.085	−

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; SNPs, single-nucleotide polymorphisms; TAA, thoracic aortic aneurysm.
**P* value threshold for inclusion of IA-, AAA-, or TAA-associated SNPs in each polygenic model.
†Number of SNPs included in each polygenic model.
‡*P* value for association of the polygenic model with IA, AAA, or TAA case-control status.

Table 8. Polygenic Analysis: AAA-Associated SNPs Tested for Association With IA Case-Control Status

Threshold (*P*)*	SNPs (n)†	*P* Value‡	Direction of Effect
5×10^{-8}	0	NA	NA
1×10^{-7}	1	0.789	−
1×10^{-6}	4	0.589	+
1×10^{-5}	21	0.481	+
1×10^{-4}	181	0.826	+
1×10^{-3}	1420	0.914	−
0.01	10 094	0.362	+
0.05	38 571	0.72	+
0.1	67 304	0.596	+
0.2	113 818	0.827	+
0.3	152 058	0.874	+
0.4	184 216	0.700	+
0.5	212 087	0.585	+
10^{-4} to 10^{-3}	1239	0.834	−
10^{-3} to 0.01	8674	0.318	+
0.01 to 0.05	28 477	0.239	+
0.05 to 0.1	28 733	0.592	+
0.1 to 0.2	46 514	0.549	+
0.2 to 0.3	38 240	0.153	+
0.3 to 0.4	32 158	0.163	+
0.4 to 0.5	27 871	0.162	+

AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; NA, not applicable; SNPs, single nucleotide polymorphisms; TAA, thoracic aortic aneurysm.
**P* value threshold for inclusion of IA-, AAA-, or TAA-associated SNPs in each polygenic model.
†Number of SNPs included in each polygenic model.
‡*P* value for association of the polygenic model with IA, AAA, or TAA case-control status.

high, but also not significant. The absence of novel shared loci, a polygenic association or a genetic correlation can be attributed to the modest sample size and power, certainly in comparison to community-wide efforts for coronary artery disease.[40] It may therefore be premature to claim that there are genuinely no novel shared loci or shared polygenic effects for IA, AAA, and TAA.

After testing the association of bona-fide aneurysm risk loci in other aneurysm types in much larger aneurysm GWAS cohorts (consisting of the mega-analysis data plus additional IA and AAA GWAS cohorts), we found nominally significant associations of the IA risk locus 18q11 and the TAA risk locus 15q21 to AAA, both of which were previously unknown to be associated with AAA. The 15q21 locus has reported biological functions that could plausibly be related to aneurysm development, because it encompasses the *FBN1* gene, which encodes fibrillin-1, an extracellular matrix protein in the elastic fibers of the aortic wall. Mutations in *FBN1* cause Marfan syndrome, which is often associated with (mainly thoracic) aortic aneurysms.[17]

There are extensive differences in pathophysiology and epidemiological risk factors between the 3 diseases. IAs are mostly saccular-shaped dilatations, whereas AAAs and TAAs are more often fusiform; the vessel wall structure differs between the locations where IA, AAA, and TAA occur; and atherosclerosis has a clear role in AAA, in contrast to IA and TAA.[41–44] However, there have been previous reports of a co-occurrence of AAA and TAA[4,5] and, to a lesser extent, of IA and aortic aneurysms.[6,7] Also, IA mainly co-occurs with AAA and TAA within families,[8,9] so genetic sharing between IA, AAA, and TAA could theoretically be present in the familial form, but not in sporadic cases (which were primarily studied here). For example, mutations in *TGFBR1* and *TGFBR2* were found in families in which all 3 aneurysm

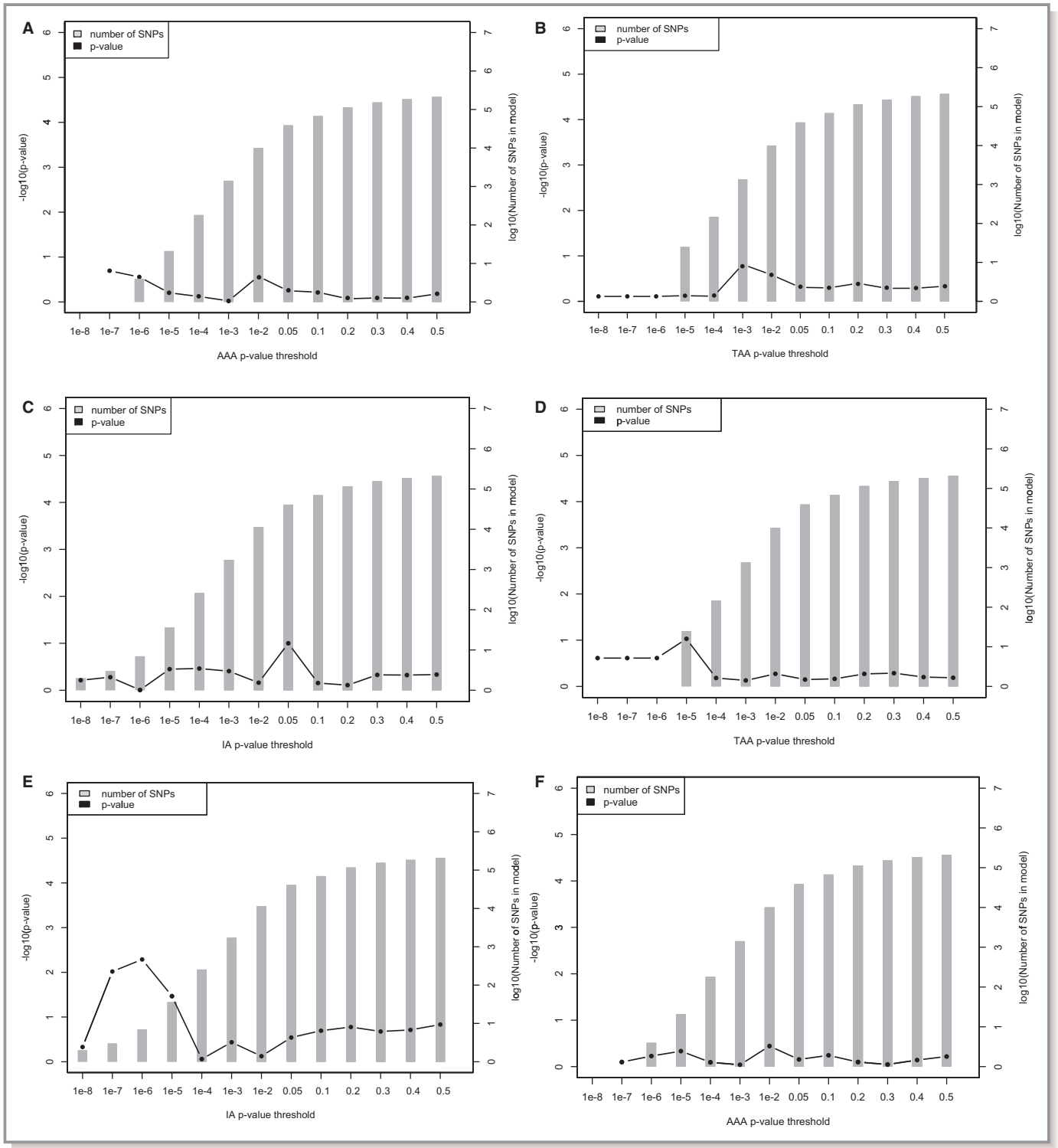


Figure 6. Polygenic analysis results. (A) AAA-associated SNPs tested for association with TAA case-control status; (B) TAA-associated SNPs tested for association with AAA case-control status; (C) IA-associated SNPs tested for association with TAA case-control status; (D) TAA-associated SNPs tested for association with IA case-control status; (E) IA-associated SNPs tested for association with AAA case-control status; (F) AAA-associated SNPs tested for association with IA case-control status. We created polygenic scores based on IA-, AAA-, and TAA-associated SNPs at different *P* value thresholds and tested these scores for association to case-control status in GWAS cohorts of IA, AAA, and TAA in each possible combination between these phenotypes. The figures show the resulting *P* values of the association tests (left *y*-axis) for each polygenic model (*x*-axis), with the corresponding number of SNPs in each model (right *y*-axis). AAA indicates abdominal aortic aneurysm; GWAS, genome-wide association study; IA, intracranial aneurysm; SNP, single-nucleotide polymorphism; TAA, thoracic aortic aneurysm.

Table 9. Heritability Analysis Results From LDSC

Cohort	h^2	SE (h^2)
AAA	0.160	0.179
IA (Finland)	0.314	0.258
IA (The Netherlands)	0.341	0.231
TAA	0.396	0.280

AAA indicates abdominal aortic aneurysm; h^2, proportion of phenotypic variance explained by genetic effects; IA, intracranial aneurysm; LDSC, linkage disequilibrium score regression; TAA, thoracic aortic aneurysm.

types occur.[8] Furthermore, a genetic linkage study in 26 families with both IA and AAA or TAA found linkage peaks at locus 6p23 and 11q24.[45] Independent linkage studies on IA, AAA, and TAA also found linkage peaks at 11q24.[46] We did not find associations of these loci in our study, which can be explained by our focus on the sporadic aneurysm cases, in contrast to the familial cases in the linkage studies.

In conclusion, our study results do not reveal new risk loci shared between IA, AAA, and TAA, but the effects of established IA, AAA, and TAA risk loci in other aneurysm types do suggest a shared genetic background. Future studies with larger sample sizes should increase the statistical power to detect common genetic variants with a smaller effect on disease risk, and to draw definitive conclusions on genetic correlation between aneurysm subtypes.

Appendix

Aneurysm Consortium

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Table 10. Genetic Correlation Analysis Results From LDSC (Linkage Disequilibrium Score Regression)

Cohorts	Correlation (ρ)	Standard Error (ρ)	*P* Value
AAA—IA (Finland)	−0.032	0.557	0.955
AAA—IA (Netherlands)	−0.384	0.658	0.560
AAA—TAA	0.243	0.777	0.754
IA (Finland)—TAA	0.685	0.509	0.179
IA (Netherlands)—TAA	0.847	0.740	0.253
IA (Finland)—IA (Netherlands)	1.591	0.928	0.086

The test evaluates the genetic correlation between diseases based on their common SNPs set corresponding to the structured LD from the reference panel. AAA indicates abdominal aortic aneurysm; IA, intracranial aneurysm; LDSC, linkage disequilibrium score regression; TAA, thoracic aortic aneurysm; ρ, genetic correlation.

Vascular Research Consortium of New Zealand

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Table 11. Specific Lookup of Previously Published Aneurysm Risk SNPs in 6 Case-Control Datasets of IA, 6 Case-Control Data Sets of AAA, and 1 Case-Control Data Set of TAA

				AAA				TAA			
SNP—IA	Gene	Chr	RA	*P* Value	OR	Dir*	$P_{Cochran's\ Q}$	*P* Value	OR	Dir*	$P_{Cochran's\ Q}$
rs6841581[10]	*EDNRA*	4	G	0.62	0.98	+−−−−+	0.45	0.43	1.07	NA	NA
rs10958409[12†]	*SOX17*	8	A	0.81	0.99	−−++−−	0.14	0.37	1.07	NA	NA
rs9298506[12†]	*SOX17*	8	A	0.81	0.99	−+−+−−	0.09	0.67	0.97	NA	NA
rs1333040[12]	*CDKN2BAS*	9	T	1.5×10^{-8}	1.15	+++++−	0.07	0.52	1.04	NA	NA
rs12413409[11]	*CNNM2*	10	G	0.69	1.02	+−−−++	0.70	0.95	1.01	NA	NA
rs9315204[11]	*STARD13-KL*	13	T	0.73	1.01	−−++++	0.21	0.79	1.02	NA	NA
rs11661542[11]	*RBBP8*	18	C	4.1×10^{-5}	1.11	++++−+	0.11	0.08	1.11	NA	NA
				IA				TAA			
SNP—AAA	Gene	Chr	RA	*P* Value	OR	Dir*	$P_{Cochran's\ Q}$	*P* Value	OR	Dir*	$P_{Cochran's\ Q}$
rs10757278[18]	*CDKN2BAS*	9	G	5.9×10^{-17}	1.30	+++...	0.81	0.42	1.05	NA	NA
rs1466535[13]	*LRP1*	12	C	0.95	1.00	−−++−+	0.66	0.07	1.12	NA	NA
rs7025486[14]	*DAB2IP*	9	A	0.25	1.03	+−++−+	0.36	0.70	0.97	NA	NA
rs599839[16]	*SORT1*	1	G	0.41	0.97	−+−...	0.76	0.42	0.94	NA	NA
rs6511720[15]	*LDLR*	19	G	0.15	1.07	+−+−..	0.09	0.05	1.21	NA	NA
				IA				AAA			
SNP—TAA	Gene	Chr	RA	*P* Value	OR	Dir*	$P_{Cochran's\ Q}$	*P* Value	OR	Dir*	$P_{Cochran's\ Q}$
rs10519177[17‡]	*FBN1*	15	G	0.99	1.00	++−−++	0.25	0.016	1.01	−+++−+	0.32
rs2118181[17‡]	*FBN1*	15	G	0.20	0.96	++−−−+	0.08	1.1×10^{-3}	1.07	+−++++	0.45

Lookup results in different cohorts were combined per subtype, using an inverse-variance fixed-effects meta-analysis. AAA indicates abdominal aortic aneurysm; Chr, chromosome; Dir, direction of effect; IA, intracranial aneurysm; OR, odds ratio; $P_{Cochran's\ Q}$, *P* value from Cochran's Q test; RA, risk allele; SNP, single nucleotide polymorphism; TAA, thoracic aortic aneurysm.
*Direction of effect per cohort. For AAA, directions correspond to the cohorts "Iceland," "Netherlands," "USA," "Aneurysm Consortium," "New Zealand 1," and "New Zealand 2," respectively. For IA, directions correspond to the cohorts "Netherlands," "Finland," "USA," "@neurIST," "Japan 1," and "Japan 2," respectively. "+" indicates same direction as previously published aneurysm risk SNP; "−" indicates opposite direction; "." indicates absence of the SNP in target cohort.
†These 2 SNPs are independent (r^2=0.06).
‡These 2 SNPs are independent (r^2=0.24).

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None.

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Shared Genetic Risk Factors of Intracranial, Abdominal, and Thoracic Aneurysms

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