Genome-wide association study of intracranial aneurysms identifies 17 risk loci and genetic overlap with clinical risk factors

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Rupture of an intracranial aneurysm leads to subarachnoid hemorrhage, a severe type of stroke. To discover new risk loci and the genetic architecture of intracranial aneurysms, we performed a cross-ethnic, genome-wide association study in 10,754 cases and 306,882 controls of European and East Asian ancestry. We discovered 17 risk loci, 11 of which are new. We reveal a polygenic architecture and explain over half of the disease heritability. We show a high genetic correlation between ruptured and unruptured intracranial aneurysms. We also find a suggestive role for endothelial cells using gene mapping and heritability enrichment. Drug target enrichment shows pleiotropy between intracranial aneurysms and anti-epileptic and sex hormone drugs,

providing insights into intracranial aneurysm pathophysiology. Finally, genetic risks for smoking and high blood pressure, the two main clinical risk factors, play important roles in intracranial aneurysm risk and drive most of the genetic correlation between intracranial aneurysms and other cerebrovascular traits.

An intracranial aneurysm is a balloon-shaped dilatation, usually located at a branch of an intracranial artery. It is present in 3% of the population[1]. Rupture of an intracranial aneurysm causes an aneurysmal subarachnoid hemorrhage (aSAH), a severe type of stroke. Approximately one third of patients die, and another third remain dependent for daily life activities[2]. Intracranial aneurysms occur in relatively young people with a mean age of 50 years and is twice as common in women over 50 years old compared to men of that age. Genetic predisposition plays an important role in the disease with an aSAH heritability of 41%, as estimated in a twin study[3].

Much is still unknown about the genetic architecture of intracranial aneurysms[4,5]. Family-based studies identified a number of variants with Mendelian inheritance[6-10], but genome-wide association studies (GWAS) have identified multiple common variants, suggesting a polygenic model of inheritance[5,11-13]. The largest GWAS published to date, involving 2,780 cases and 12,515 controls, identified six risk loci[11,13]. Based on that GWAS, the explained single nucleotide polymorphism (SNP)-based heritability of intracranial aneurysms was estimated as being only 4.1-6.1%, depending on population[5].

We aimed to further characterize the genetic architecture of intracranial aneurysms by performing a cross-ethnic GWAS meta-analysis on a total of 10,754 cases and 306,882 controls from a wide range of European and East Asian ancestries. We included both cases with unruptured intracranial aneurysm and aSAH (i.e. with ruptured intracranial aneurysm), enabling us to identify potential risk factors specific for intracranial aneurysm rupture. We

also looked for genetic similarities between intracranial aneurysms and related traits, including other types of stroke, vascular malformations and other aneurysms, and analyzed whether known risk factors for intracranial aneurysms play a causal genetic role. Further, we investigated enrichment of genetic associations in functional genetic regions, tissue subtypes, and drug classes to provide insight into intracranial aneurysm pathophysiology.

Results

GWAS of intracranial aneurysms. Our GWAS meta-analysis on intracranial aneurysms consisted of two stages. The Stage 1 meta-analysis included all European ancestry individuals and consisted of individual-level genotypes from 23 different cohorts that were merged into nine European-ancestry strata based on genotyping platform and country. These strata were each analyzed in a logistic mixed model[14] and then meta-analyzed, while also including summary statistics from a population-based cohort study: the Nord-Trøndelag Health Study (the HUNT Study). This resulted in 7,495 cases and 71,934 controls and 4,471,083 SNPs passing quality control (QC) thresholds (Online Methods, Supplementary Table 1). Stage 2 was a cross-ethnic meta-analysis including all Stage 1 strata and summary statistics of East Asian individuals from two population-based cohort studies: The Biobank Japan (BBJ) and the China Kadoorie Biobank (CKB). This totaled 10,754 cases and 306,882 controls and 3,527,309 SNPs in Stage 2 (Supplementary Table 1).

The Stage 1 association study resulted in 11 genome-wide significant loci ($P \leq 5 \times 10^{-8}$; Fig. 1 and Supplementary Table 2). Transethnic genetic correlation analysis showed a strong correlation between the Stage 1 meta-analysis of European ancestry and an analysis including only East Asian ancestry samples ($\rho_g = 0.938 \pm 0.165$, standard error (SE) for genetic impact and 0.908 ± 0.146 for genetic effect; Supplementary Table 3). Stage 2

increased the number of genome-wide significant loci to 17 (Table 1 and Fig. 1). All but two loci (8q11.23, rs6997005 and 15q25.1, rs10519203) were also associated with intracranial aneurysms in the samples of East Asian ancestry added in Stage 2 ($P < 0.05/11$), and two loci were monomorphic in East Asians (Table 1). The Stage 2 loci included 11 novel risk loci and six previously reported risk loci[11]. We used conditional and joint (COJO, GCTA v1.91.1beta)[15] analysis to condition the Stage 1 GWAS summary statistics on the lead SNP in each locus. We found that none of the loci consisted of multiple independent SNPs and that each locus tagged a single causal variant (data not shown). Genomic inflation factors ($lambda_{GC}$) were 1.050 for the Stage 1 meta-analysis and 1.065 for Stage 2 (Supplementary Fig. 1 and Supplementary Table 4). The linkage disequilibrium score regression (LDSR) intercept was 0.957 ± 0.008 (SE) for the Stage 1 meta-analysis and 0.982 ± 0.008 for the East Asian subset. This indicated that, in all GWAS analyses, observed inflation was due to polygenic architecture.

Conditioning the Stage 1 GWAS summary statistics on GWAS summary statistics for systolic and diastolic blood pressure (BP, Neale lab summary statistics, http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank) using multi-trait conditional and joint (mtCOJO)[16] analysis resulted in one additional genome-wide significant locus (rs2616406, $P = 6.22 \times 10^{-8}$ in the Stage 1 GWAS, $P = 4.50 \times 10^{-9}$ after mtCOJO with BP). mtCOJO with smoking pack-years summary statistics or including genetic risk scores (GRSs) for smoking (cigarettes per day)[17] or blood pressure related traits[18] did not result in additional loci (data not shown).

Characterization of GWAS loci. An overview of the genic position, alleles, effect size and *P*-value of the strongest association per locus is shown in Table 1. We used summary statistics-based Mendelian randomization (SMR), co-localization analysis using eCAVIAR,

and transcriptome-wide association study (TWAS, http://gusevlab.org/projects/fusion/) to annotate potential causative genes in these loci (Supplementary Tables 5-9 and Supplementary Fig. 2). A description of this annotation process is described in the Supplementary Note. Since SMR, eCAVIAR and TWAS all require LD reference panels, we limited the annotation to the loci identified in the European ancestry Stage 1 GWAS meta-analysis. This resulted in 11 potential causative genes at six unique loci: *SLC22A5*/*SLC22A4*/*P4HA2* (chr5), *NT5C2*/*MARCKSL1P1* (chr10), *FGD6*/*NR2C1* (chr12), *PSMA4* (chr15), and *BCAR1*/*RP11-252K23.2* (chr16) (Table 1 and Supplementary Table 5). Although we did not find evidence for involvement of *SOX17* in the chr8 locus, previous studies did find functional evidence for *SOX17*[19,20]. Therefore, we annotated the chr8 locus as *SOX17*.

In the Stage 2 GWAS, six additional loci were identified: 6q16.1, 10q23.33, 11p15.5, 12p12.2, 12q21.22, and 20p11.23. Due to the combined European and East Asian LD structures, these loci cannot reliably be mapped to genes using the above-mentioned techniques. Of the six additional loci, four have previously been linked to blood pressure, namely 6q16.1 (rs11153071)[21], 10q23.33 (rs11187838)[22], rs11044991 (12p12.2)[23], and rs2681492 (12q21.22)[23,24]. A detailed description of the genes and loci is found in the Supplementary Note.

The product of the potentially causative gene *FGD6*[25] plays a role in angiogenesis, and defects may lead to a compromised formation of blood vessels. *FGD6* is a vascular endothelial cell (vEC) signaling gene involved in stress signaling in vECs[26]. Loss-of-function mutations in *THSD1* and *SOX17* lead to subarachnoid hemorrhage in animal models. Products of these genes both have key roles in vECs[7,19,27]. *BCAR1* is a ubiquitously expressed gene whose protein product is a sensor for mechanical stress[28]. The *PSMA4* locus is known for associations with a number of smoking and respiratory system traits[29-32].

Predictors of intracranial aneurysm rupture. We assessed whether genetic risk factors differed between ruptured and unruptured intracranial aneurysms using stratified GWAS analysis. The number of cases with unruptured intracranial aneurysm was small (n = 2,070). Therefore, in addition to performing a stratified GWAS on patients with a ruptured aneurysm versus patients with an unruptured intracranial aneurysm (aSAH-vs-uIA), we also performed a stratified GWAS on only patients with ruptured intracranial aneurysm versus controls (aSAH-only) and a stratified GWAS on only patients with an unruptured intracranial aneurysm versus controls (uIA-only) (Supplementary Table 4 and Supplementary Fig. 1e-j). Overall, 69% of intracranial aneurysm cases had a ruptured intracranial aneurysm and 28% an unruptured intracranial aneurysm, while 3.8% had an unknown rupture status. The aSAH-only and uIA-only GWASs identified a number of genome-wide significant loci, all of which reached genome-wide significance in the Stage 1 and 2 GWAS meta-analyses of intracranial aneurysms. In the aSAH-vs-uIA GWAS, we found no genome-wide significant loci. Furthermore, genetic correlation analysis showed a high correlation of 0.970 ± 0.133 (SE) between ruptured and unruptured intracranial aneurysms (Supplementary Table 3). Together these findings indicate a strong similarity in genetic architecture between ruptured and unruptured intracranial aneurysm.

SNP-based heritability. We estimated the SNP-based heritability of intracranial aneurysms to be 21.6 ± 2.8% (SE) on the liability scale with LD score regression (tool named LDSC[33], https://github.com/bulik/ldsc) and 29.9 ± 5.4% using SumHer[34] (http://dougspeed.com/sumher/) (Table 2). This corresponds to an explained fraction of the twin-based heritability (h^2 = 41%)[3] of 53-73% depending on the method used (LDSC or SumHer). We used a prevalence for unruptured intracranial aneurysms of 3%[1] for the

conversion to the liability scale. Since this GWAS was an admixture of patients with ruptured and unruptured intracranial aneurysms, this prevalence may not be representative of the whole study population. Therefore, we calculated liability scale heritability using a range of prevalence values (Supplementary Fig. 3a). This shows that, also when using lower prevalence estimates (K), the explained SNP-based heritability is substantial (K = 0.02: h^2 = 19.3 ± 2.5% (LDSC), 26.8 ± 4.8% (SumHer); K = 0.01: 16.3 ± 2.1% (LDSC), 22.6 ± 4.1% (SumHer)).

A substantial SNP-based heritability is also found for ruptured intracranial aneurysms (SAH-only, h^2 = 0.140 ± 0.020) and unruptured intracranial aneurysms (uIA-only, h^2 = 0.223 ± 0.044). The difference between the heritability estimates could suggest differences in genetic architecture, but estimates depend on the prevalence estimate (Supplementary Fig. 3b,c), meaning these differences should be interpreted with caution.

Enrichment of genomic regions. To understand the disease mechanisms of intracranial aneurysms, we applied several heritability enrichment analyses using LD-score regression (LDSR). Partitioning on functional genomic elements showed a clear enrichment of heritability in regulatory elements, including enhancer and promoter histone marks H3K4me1, H3K27Ac and H3K9Ac, super enhancers, and DNAse I hypersensitivity sites (Fig. 2a). Such enrichment of regulatory elements in the genome is also seen in other polygenic traits and indicates that the architecture of intracranial aneurysms is polygenic[35]. Partitioning heritability per chromosome further supported a polygenic architecture as heritability was associated with the number of SNPs on a chromosome (Fig. 2b).

Tissue-specific LDSR did not show enrichment for any tissue (Supplementary Tables 10 and 11). We then performed cell-type enrichment analysis using single-cell RNA-sequencing (scRNAseq) reference data derived from mouse brain[36]. No enrichment was

found using a scRNAseq dataset of mouse brain blood vessels[37] (Supplementary Table 12). Using a larger dataset defining cell-types in the mouse brain[36], we found enrichment in 'endothelial mural cells', which is a combined set of vascular endothelial and mural cells (enrichment = 2.31 ± 0.41 (SE), $P = 1.65 \times 10^{-3}$, Fig. 2c), and in midbrain neurons (enrichment = 2.23 ± 0.37, $P = 6.56 \times 10^{-4}$).

LD-pruned enrichment analysis using GARFIELD showed that genes specific for blood vessels were enriched (Fig. 2d and Supplementary Table 13), further supporting the role of promoters and enhancers (Fig. 2e).

Causal genetic roles of blood pressure and smoking. To assess which phenotypes causally influence the risk of intracranial aneurysms, we performed generalized summary statistics-based Mendelian randomization (GSMR) using summary statistics for all phenotypes available in the UK Biobank (Supplementary Table 14). We used the Stage 1 summary statistics excluding the UK Biobank data as outcome. In this analysis, we chose a stringent value for the multiple testing threshold of 376, which was the number of traits passing the GSMR quality control parameters. Sixteen traits were statistically significant after correction for multiple testing (Fig. 3a). All statistically significant traits were related to either smoking or blood pressure (BP), which are the two main clinical risk factors for unruptured intracranial aneurysms and aSAH[1,38,39]. To determine whether genetic predisposition for smoking and BP were causal genetic risk factors independent of one another, we conditioned the Stage 1 GWAS summary statistics on GWAS summary statistics for smoking and BP using multi-trait conditional and joint analysis (mtCOJO). We used summary statistics for both systolic BP (SBP) and diastolic BP (DBP) combined to condition on BP and summary statistics for pack-years to condition on smoking (Fig. 3a and Supplementary Table 14). All GSMR effects diminished after conditioning on either BP or pack-years and remained when

conditioning on the other risk factor. The mtCOJO method itself did not affect the effect size estimates as conditioning on standing height did not affect the estimates. These findings provide strong evidence that the genetic predisposition for BP and smoking are independent genetic causes of intracranial aneurysms (Fig. 3b).

Since the phenotype values of the exposure traits were inverse rank-normalized, the GSMR effect size of SBP ($\beta_{xy} = 1.058 \pm 0.187$) and pack-years ($\beta_{xy} = 0.973 \pm 0.236$) cannot easily be interpreted. Therefore, we performed an additional GSMR analysis for BP with an updated version of the UK Biobank GWAS (http://www.nealelab.is/uk-biobank/), including raw phenotype values for quantitative traits (Supplementary Table 15). For BP traits, the GSMR analysis resulted in an effect size estimate of 0.095 ± 0.019 for DBP and 0.047 ± 0.011 for SBP, meaning an 8-12% increase in intracranial aneurysm risk per mmHg increase of DBP and a 3.7-6% increase in intracranial aneurysm risk per mmHg increase of SBP, assuming a linear effect of BP on intracranial aneurysm liability. In addition, age at high BP diagnosis had a significant GSMR effect ($P = 1.79 \times 10^{-4}$, $\beta_{xy} = 0.163 \pm 0.044$), indicating an increase in intracranial aneurysm risk of 13-23% for each year of additional high BP exposure. We did not include smoking quantitative traits because these were not normally distributed (data not shown) and could, therefore, lead to a biased effect estimate.

We then tested whether the effects of smoking and BP were different between ruptured (SAH-only) and unruptured intracranial aneurysms (uIA-only, Supplementary Table 16). The GSMR effect sizes followed the same trend for all phenotypes, but 'Hypertension (Self-reported)' had a stronger effect on ruptured intracranial aneurysms (SAH-only: $\beta_{xy} = 6.74 \pm 0.61$ (SE), all intracranial aneurysms: 2.97 ± 0.42, uIA-only: 2.38 ± 0.70), while amlodipine use had a weaker effect on unruptured intracranial aneurysms and became statistically non-significant (uIA-only: $\beta_{xy} = 4.77 \pm 3.90$, $P = 0.22$, all intracranial aneurysms: $\beta_{xy} = 11.4 \pm 2.10$, $P = 5.25 \times 10^{-8}$, SAH-only: $\beta_{xy} = 13.1 \pm 2.60$, $P = 5.25 \times 10^{-7}$). Although

the effect of self-reported hypertension on SAH-only was stronger, conditioning on blood pressure using mtCOJO mitigated the effect ($\beta_{xy} = 1.02 \pm 0.45$, $P = 0.024$, data not shown). Since the power to detect GSMR effects in the uIA-only sample is much lower compared to all intracranial aneurysms and SAH-only due to limited sample size, further investigation is required to make inferences about genetic risk factors for rupture.

Traits influencing female hormones are suggested to play a role in aSAH risk[40]. Only two female hormone-related traits had enough genome-wide significant risk loci to pass GSMR quality control. These were 'age when periods started (menarche)' and 'had menopause'. Neither of these showed a causal relationship with intracranial aneurysms in the GSMR analysis (Supplementary Table 14).

Drivers of genetic correlation with vascular traits. To identify traits correlated with intracranial aneurysms, we analyzed Stage 1 summary statistics using LDHub[41]. LDHub includes a subset of the summary statistics used for GSMR and a number of summary statistics from publicly available sources. Traits that showed correlations that reached the Bonferroni threshold for multiple testing ($P = 0.05/464$) included several blood pressure (BP)-related traits, including diastolic BP (DBP) ($\rho_g = 0.223$, $P = 5.40 \times 10^{-9}$) and systolic BP (SBP) ($\rho_g = 0.256$, $P = 1.34 \times 10^{-8}$) and smoking traits, such as pack-years ($\rho_g = 0.330$, $P = 7.87 \times 10^{-8}$) (Supplementary Table 17).

We used LDSR to calculate the genetic correlation of intracranial aneurysms with other stroke subtypes (ischemic stroke (IS)[42] and intracerebral hemorrhage (ICH)), with other vascular malformation types (intracranial arteriovenous malformation (AVM)[43] and cervical artery dissection[44]), and with abdominal aortic aneurysm (AAA)[45]. For IS, a correlation of 0.195 ± 0.079 ($P = 0.014$) was found with intracranial aneurysms (Fig. 3c and Supplementary Table 3). After conditioning the intracranial aneurysm GWAS on either BP or on pack-years,

363 which are clinical risk factors for both IS and intracranial aneurysms[1,38,39,46], the correlation
364 was no longer statistically significant and reduced to 0.121 ± 0.081 for BP and 0.147 ± 0.084
365 for pack-years. The correlation disappeared after conditioning on both risk factors (ρ_g = 0.009
366 ± 0.083, P = 0.916). When conditioning on an unrelated but heritable trait (standing height),
367 the correlation remained (ρ_g = 0.238 ± 0.081, P = 0.003). No genetic correlation was found
368 for any of the IS subtypes.
369 We found a statistically significant genetic correlation between intracranial aneurysms
370 and ICH (ρ_g = 0.447 ± 0.184, P = 0.015), which was mainly driven by deep ICH (ρ_g = 0.516 ±
371 0.198, P = 0.009), and not by lobar ICH (P = 0.534). After conditioning the intracranial
372 aneurysm GWAS on either BP or pack-years, which are also important risk factors for ICH[47],
373 the correlation with deep ICH decreased (ρ_g = 0.288 ± 0.189 for BP and 0.234 ± 0.192 for
374 pack-years) and was no longer statistically significant. Conditioning on height had a much
375 smaller effect (ρ_g = 0.380 ± 0.196).
376 A genetic correlation was found between intracranial aneurysms and AAA (ρ_g = 0.302
377 ± 0.105, P = 0.004). Conditioning on pack-years strongly reduced the correlation between
378 intracranial aneurysms and AAA (ρ_g = 0.173 ± 0.117, P = 0.138), whereas BP did not (ρ_g =
379 0.264 ± 0.117, P = 0.024).
380 There was no genetic correlation between intracranial aneurysms and carotid artery
381 dissection (ρ_g = 0.151 ± 0.180, P = 0.401), whereas for vertebral artery dissection and the
382 combined set of vertebral and carotid artery dissection, a larger, albeit non-statistically
383 significant, estimate was observed (ρ_g = 0.281 ± 0.159, P = 0.077 and ρ_g = 0.174 ± 0.149, P =
384 0.066, respectively) (Supplementary Table 3). For AVM, a negative SNP-based heritability
385 was estimated, which could be due to the small sample size of this GWAS (1,123 cases and
386 1,935 controls). Therefore, we performed a lookup of all SNPs identified in the Stage 1 and 2

intracranial aneurysm GWAS in the summary statistics of the AVM GWAS[43] but were unable to replicate any of these SNP associations ($P < 0.05/17$) (Supplementary Table 18).

Drug target enrichment. To identify pleotropic pathways between intracranial aneurysms and other diseases that contain known drug targets, we assessed enrichment in genes targeted by drugs and drug classes[48]. Gene-based *P*-values were calculated with MAGMA, resulting in 29 genes that passed the Bonferroni threshold for multiple testing ($P < 0.05/18{,}106$, Supplementary Table 19). The anti-hypertensive drugs ambrisentan and macitentan showed a statistically significant enrichment ($P = 1.35 \times 10^{-5}$, Supplementary Table 20), which was driven by a single gene (*EDNRA*). Drug class enrichment analysis showed that drugs in the classes 'anti-epileptics' were enriched (area under the curve (AUC) = 0.675, $P = 8 \times 10^{-5}$; Supplementary Table 21). The most statistically significant enriched drugs within this class are blockers of Na^{+} and Ca^{2+} channels, namely phenytoin, zonisamide, and topiramate[49] (Supplementary Table 20). These channels are important in blood pressure regulation, as well as in several other biological mechanisms. The other enriched drug class is 'sex hormones + modulators of the genital system' (AUC = 0.652, $P = 2.02 \times 10^{-4}$). We also used MAGMA to study enrichment in gene pathways but found no statistically significant results (Supplementary Table 22).

Discussion

We identified 11 novel risk loci for intracranial aneurysms and confirmed six previously identified risk loci, yielding a total of 17 risk loci for intracranial aneurysms. A SNP-based heritability of 21.6% was found, explaining over half of the total heritability. We showed strong evidence that the majority of intracranial aneurysm heritability is polygenic. Our

411 results further highlight several major features of the genetic architecture of intracranial
412 aneurysms. First, we identified endothelial cells as a key cell type in intracranial aneurysm
413 risk. Second, we showed that, out of 375 tested traits, smoking and BP predisposition were
414 the main genetic risk factors for intracranial aneurysms. Third, we showed that the main
415 drivers of the genetic correlation between intracranial aneurysms and other stroke types and
416 between intracranial aneurysms and abdominal aortic aneurysms are genetic predisposition
417 for smoking and blood pressure. Last, we found pleiotropic characteristics of anti-epileptic
418 drugs and sex hormones with intracranial aneurysms.

419 Through gene-mapping incorporating gene expression datasets and distinct
420 bioinformatics analyses, we were able to identify 11 potential causative genes within six of
421 the Stage 1 risk loci. Many of these genes have known or putative roles in blood vessel
422 function and blood pressure regulation. We found heritability enrichment in genes that are
423 specifically expressed in a combined set of endothelial and mural cells, and not in other
424 vascular cell types. Together, the identified potential causative genes and heritability
425 enrichment analyses suggest an important role of the vascular endothelial cell (vEC) in
426 intracranial aneurysm development and rupture.

427 Through genetic correlation and formal causal inference methods, we established that
428 genetic predisposition for smoking and BP are the most important independent genetic risk
429 factors for intracranial aneurysms[1]. First, using causal inference with GSMR, we showed that
430 genetic predisposition for these traits drives a causal increase in intracranial aneurysm risk.
431 Then, using multi-trait conditional analysis, we showed that smoking and high BP are
432 causative of intracranial aneurysms, independent of one another. By using non-transformed
433 continuous systolic blood pressure (SBP) and diastolic blood pressure (DBP) measures in the
434 UK Biobank, we estimated the increase in intracranial aneurysm risk per 1 mmHg increase of
435 SBP to be 3.7-6%, and that of DBP to be 8-12%. These strong effects provide genetic

evidence for clinical prevention by lowering blood pressure. Since smoking dose is not normally distributed, we were not able to estimate a quantitative effect of smoking on intracranial aneurysms, but this has been done before using non-genetic methods[50-52]. Future studies that model risk prediction using polygenic risk scores should determine whether the polygenic risks of genetic risk factors for intracranial aneurysms are clinically relevant risk factors for the disease.

We found that genetic correlations of intracranial aneurysms with ischemic stroke (IS) and deep intracerebral hemorrhage (ICH) are mainly driven by genetic predisposition for smoking and BP. For ICH, conditioning on smoking and BP did not completely mitigate the genetic correlation with intracranial aneurysms, suggesting additional shared genetic causes. For vertebral artery dissection, a substantial but not statistically significant correlation with intracranial aneurysms was found, whereas this was absent in carotid artery dissection. We showed that the genetic correlation between intracranial aneurysms and AAA was driven by smoking, but not by BP. This implies that intracranial aneurysms are more dependent on BP compared to AAA. This observation could be a result of different ratios of unruptured and ruptured aneurysms included in the two GWASs. The AAA GWAS consists of mainly unruptured AAA[45], and while the role of BP on AAA rupture is clear, the effect on developing AAA is a matter of debate[53].

One of the main aims of intracranial aneurysm research is to prevent rupture of intracranial aneurysms and thus avoid the devastating consequences of aSAH. We performed various analyses in an attempt to identify genetic predictors specific for intracranial aneurysm rupture. Instead, we found a very strong genetic correlation between ruptured and unruptured intracranial aneurysms. These analyses together indicate that the common variant genetic architecture of ruptured and unruptured aneurysms are strikingly similar.

The heritability of unruptured intracranial aneurysms has never been studied in twins and may therefore not be an optimal estimate for intracranial aneurysm heritability. One twin study estimated the heritability of aSAH at 41%[3]. Our finding that the genetic architecture of uIA and aSAH are similar suggests that this heritability estimate may also be accurate for unruptured intracranial aneurysms. This means that, in European ancestry populations, 53-73% of the heritability of intracranial aneurysms can be explained by variants tagged in this GWAS.

Using transethnic genetic correlation, we found a remarkable similarity of genetic architecture between the European ancestry and East Asian ancestry GWASs of more than 90.8 ± 14.6% (SE). This indicates that the majority of common-variant genetic causes are the same, regardless of ancestry. However, since the LD structures remain distinct, current methods for summary statistic-based enrichment analysis cannot effectively account for population-specific variation in a cross-ethnic GWAS.

Drug class enrichment showed pleiotropic characteristics of anti-epileptic drugs and sex hormones with the genetic association of intracranial aneurysms. It has been suggested that sex hormones might play a role in intracranial aneurysms[40], potentially explaining why women have a higher intracranial aneurysm risk than men[1]. However, as causal inference analysis with GSMR did not show evidence for the involvement of female hormones, further investigation is required. Enrichment of the anti-epileptic drug class may indicate shared disease mechanisms between intracranial aneurysms and epilepsy. The main mechanism of anti-epileptic drugs is through blocking Na^+ and Ca^{2+} ion channels[49]. Together with other ion channels, these play essential roles in contraction and relaxation of the blood vessels[54]. Mutations in the ion-channel gene *PKD2* (*TRRP2*) are known to cause intracranial aneurysms. This gene product, along with other members of the *TRP* gene family, regulates systemic blood pressure through vasoconstriction and vasodilation[55,56]. More research on the

effect of anti-epileptics on vascular tension and blood pressure will enhance our understanding of the disease-causing mechanisms. Furthermore, this could help to identify methods of intracranial aneurysm prevention using anti-epileptics or related drugs.

In conclusion, we performed a GWAS meta-analysis of intracranial aneurysms, identifying 11 new risk loci, confirming 6 previously identified risk loci, and explaining over half of the heritability of intracranial aneurysms. We found strong evidence for a polygenic architecture. Through gene-mapping and heritability enrichment methods, we discovered a possible role for endothelial cells in intracranial aneurysm development. We showed that the genetic architecture of unruptured and ruptured aneurysms are very similar. The well-known clinical risk factors, smoking and hypertension, were identified as main genetic drivers of intracranial aneurysms. These risk factors also explained most of the similarity to other stroke types, IS and deep ICH, which could open a window for clinical prevention. We also found pleiotropic effects between intracranial aneurysms and anti-epileptic drugs, which require further investigation to understand the shared mechanisms of intracranial aneurysms and epilepsy. Our findings represent a major advance in understanding the pathogenesis of intracranial aneurysms and an important step towards the development of effective genetic risk prediction and prevention of intracranial aneurysm development and subsequent aSAH in the future.

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Competing Interests

When this study was conducted, C.L.M.S. was chief scientist for the UK Biobank study.

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Figure legends

Figure 1 | GWAS meta-analysis association results. SAIGE logistic mixed model association *P*-values of the Stage 1 (upwards direction) and Stage 2 (downwards direction) GWAS meta-analyses. The horizontal axis indicates chromosomal position. The vertical axis indicates -$\log_{10}$(*P*-value) of the association. The dotted lines indicate the genome-wide significance threshold of $P = 5 \times 10^{-8}$. Lead SNPs of each locus are highlighted with a diamond, and SNPs in close proximity (± 500 kb) are colored in pink or purple, depending on chromosome index parity. Labels are gene or locus names annotated using SMR, eCAVIAR and TWAS, or prior information of intracranial aneurysm-associated genes. Labels or loci identified only in the Stage 2 GWAS are shown in red.

Figure 2 | Heritability and functional enrichment analyses. a, Partitioned LDSR enrichment of regulatory elements. Labels indicate type of regulatory element or histone mark. On the horizontal axis, the enrichment is shown. Enrichment = 1 indicates no enrichment. Statistical significance was defined as *P*-value < 0.05 divided by the number of annotations (52). Effective *n* varies per SNP (see Methods). Points are estimates and error bars denote one standard error in the direction of no effect. Statistics derived from two-sided, weighted linear regression. No *P*-value adjustment. **b**, Partitioned LDSR heritability analysis per chromosome. On the horizontal axis, the proportion of SNPs on each chromosome is shown. On the vertical axis, the proportion of SNP-based heritability is shown. The linear regression line is shown in blue. Data are presented as point estimate ± standard error.

Statistics are the same as used for **a**. **c**, Partitioned LDSR enrichment analysis of scRNAseq brain cell types. Format and statistics are the same as used for **a**. **d**, GARFIELD analysis of tissues. On the horizontal axis, the enrichment of annotations is shown; on the vertical axis, the corresponding -$\log_{10}$(*P*-value) is shown. Dashed line indicates the significance threshold of $P = 0.05$ divided by the number of annotations. Odds ratios are derived by logistic regression. *P*-values are unadjusted, derived from two-sided test. **e**, GARFIELD analysis of regulatory regions defined by histone modifications. Format and statistics are the same as used for **d**.

Figure 3 | Cross-trait analyses. a, GSMR analysis of UK Biobank predictors on the Stage 1 intracranial aneurysm GWAS, conditioned on traits depicted by column labels with mtCOJO. Numeric values are the GSMR effect sizes. The top 13 traits are blood pressure-related traits. The bottom three traits are smoking-related. Statistical significance was defined as *P*-value < 0.05 divided by the number of traits that passed quality control (376). Square fill colors indicate -$\log_{10}$(*P*-value) of the GSMR effect. All 16 traits that pass the multiple testing threshold for significance in the unconditioned analysis are shown. BP, blood pressure. Presented *n* is sample size in UK Biobank GWAS. For intracranial aneurysms, effective *n* per SNP was used. *P*-values from two-sided linear regression, unadjusted. **b**, Causality diagram further explaining the analyses of **a**: GSMR analysis showed that genetic risk for smoking and BP are causative of intracranial aneurysms. Using mtCOJO, it was found that the genetic factors associated with BP and smoking cause intracranial aneurysms through independent mechanisms. Statistics are the same as used for **a**. BP, $n = 317{,}754$ samples; smoking, $n = 101{,}726$ samples. **c**, Genetic correlation analysis with LDSR. Genetic correlation estimates are indicated by color and numeric value. Axis labels on the left denote the trait correlated with intracranial aneurysms. Labels on the top denote the trait for which the Stage 1

intracranial aneurysm GWAS was conditioned using mtCOJO. More details are provided in Supplementary Table 3. Presented *n* is effective sample size for trait on the left, except for IS and ICH+IS, where an *n* per SNP was used and average *n* is shown. IS, ischemic stroke; ICH, intracerebral hemorrhage; AAA, abdominal aortic aneurysm.

Table 1 | Lead associations of genome-wide significant risk loci. Association statistics were derived by SAIGE logistic mixed model. *P*-values are unadjusted from a two-sided test. Risk loci reaching genome-wide significant threshold ($P < 5 \times 10^{-8}$) in the Stage 2 GWAS of European and East Asian ancestry individuals are shown. Chr, Chromosome; Position, basepair position on GRCh37; EA, effect allele; OA, other allele; Stage 1, European ancestry only GWAS meta-analysis; East Asian, subset of samples from Japan and China; Stage 2, meta-analysis of European ancestry and East Asian data; EAF, effect allele frequency; SE, standard error of beta. Annotated genes are potentially causative genes identified using summary statistics based Mendelian randomization (SMR), eCAVIAR and transcriptome-wide association study (TWAS). Associated traits are cardiovascular traits and stroke risk factors with which the lead SNP is associated. CAD, coronary artery disease; SBP, systolic blood pressure; IS, ischemic stroke; AAA, abdominal aortic aneurysm; DBP, diastolic blood pressure; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease. †Known locus, described in Hussain et al[11]. *Another SNP in this locus ($r^2 > 0.8$ with the Stage 2 lead SNP) has a lower *P*-value due to differences in LD patterns between European and East Asian populations. For locus 15q25.1, another SNP in that locus reaches genome-wide significance in Stage 1. **For two SNPs, no East Asian association statistics could be obtained because these SNPs are monomorphic in Japanese and Chinese populations (LDlink, https://ldlink.nci.nih.gov/).

SNP	Locus	Chr	Position	EA	OA	Stage	EAF	beta	SE	*P*-value	Annotated genes	Associated traits
rs6841581	4q31.22†	4	148401190	A	G	Stage 1	0.131	-0.262	0.031	1.08×10^{-17}*	-	CAD
						East Asian	0.297	-0.181	0.028	6.55×10^{-11}		
						Stage 2	0.222	-0.218	0.021	3.22×10^{-26}		
rs4705938	5q31.1	5	131694077	T	C	Stage 1	0.549	0.120	0.019	2.55×10^{-10}	*SLC22A5/SLC22A4/P4HA2*	Lung function
						East Asian	NA	NA	NA	NA**		
						Stage 2	0.549	0.120	0.019	2.55×10^{-10}		
rs11153071	6q16.1	6	97039741	A	G	Stage 1	0.185	0.158	0.032	5.86×10^{-7}*	-	SBP, migraine, sleep quality
						East Asian	0.113	0.143	0.041	5.29×10^{-4}		
						Stage 2	0.158	0.153	0.025	1.25×10^{-9}		
rs62516550	8q11.23†	8	55467028	T	C	Stage 1	0.389	0.169	0.023	1.44×10^{-13}*	*SOX17*	-
						East Asian	0.087	0.102	0.049	3.70×10^{-2}		
						Stage 2	0.335	0.157	0.021	3.44×10^{-14}		
rs1537373	9p21.3†	9	22103341	T	G	Stage 1	0.514	-0.186	0.019	2.60×10^{-22}	-	IS, AAA, CAD
						East Asian	0.342	-0.165	0.029	1.43×10^{-8}		
						Stage 2	0.462	-0.180	0.016	2.86×10^{-29}		

rs11187838	10q23.33	10	96038686	A	G	Stage 1	0.415	-0.075	0.019	1.24×10^{-4}	-	SBP, migraine, fat free mass
						East Asian	0.473	-0.108	0.025	1.81×10^{-5}		
						Stage 2	0.436	-0.087	0.015	1.55×10^{-8}		
rs79780963	10q24.32†	10	104952499	T	C	Stage 1	0.078	-0.225	0.039	6.82×10^{-9}	*NT5C2/MARCKSL1P1*	-
						East Asian	0.371	-0.163	0.032	3.11×10^{-7}		
						Stage 2	0.254	-0.188	0.025	2.34×10^{-14}		
rs2280543	11p15.5	11	203788	T	C	Stage 1	0.041	0.162	0.053	2.19×10^{-3}	-	-
						East Asian	0.131	0.277	0.038	2.87×10^{-13}		
						Stage 2	0.101	0.238	0.031	1.16×10^{-14}		
rs11044991	12p12.2	12	20174364	A	G	Stage 1	0.038	-0.142	0.053	7.47×10^{-3}	-	Mean arterial pressure
						East Asian	0.476	-0.125	0.025	6.74×10^{-7}		
						Stage 2	0.395	-0.128	0.023	1.74×10^{-8}		
rs2681472	12q21.33	12	90008959	A	G	Stage 1	0.844	0.086	0.029	2.86×10^{-3}	-	SBP, DBP, pulse pressure, CVD, CAD
						East Asian	0.629	0.131	0.026	5.29×10^{-7}		
						Stage 2	0.719	0.116	0.020	6.71×10^{-9}		
rs7137731	12q22	12	95490999	T	C	Stage 1	0.647	-0.138	0.020	3.31×10^{-12}*	*FGD6/NR2C1*	-
						East Asian	0.640	-0.086	0.026	1.01×10^{-3}		
						Stage 2	0.644	-0.119	0.016	4.88×10^{-14}		
rs3742321	13q13.1†	13	33704065	T	C	Stage 1	0.764	-0.148	0.022	4.10×10^{-11}	-	-
						East Asian	0.756	-0.135	0.032	2.71×10^{-5}		
						Stage 2	0.762	-0.144	0.018	5.47×10^{-15}		
rs8034191	15q25.1	15	78806023	T	C	Stage 1	0.659	-0.115	0.022	1.22×10^{-7}*	*PSMA4*	Smoking behaviour, lung function, COPD
						East Asian	0.976	-0.161	0.091	7.69×10^{-2}		
						Stage 2	0.676	-0.117	0.021	2.75 × 10-8		
rs7184525	16q23.1	16	75437186	A	G	Stage 1	0.450	0.148	0.023	8.80×10^{-11}*	*BCAR1/RP11-252K23.2*	-
						East Asian	0.459	0.123	0.028	1.04×10^{-5}		

						Stage 2	0.453	0.138	0.018	5.60×10^{-15}		
rs11661542	18q11.2†	18	20223695	A	C	Stage 1	0.516	-0.166	0.021	5.74×10^{-16}	-	-
						East Asian	0.401	-0.087	0.026	6.82×10^{-4}		
						Stage 2	0.471	-0.135	0.016	3.17×10^{-17}		
rs4814863	20p11.23	20	19469685	A	G	Stage 1	0.248	0.096	0.024	6.71×10^{-5}	-	-
						East Asian	0.513	0.110	0.025	1.10×10^{-5}		
						Stage 2	0.375	0.103	0.017	3.22×10^{-9}		
rs39713	22q12.1	22	30343186	T	C	Stage 1	0.088	0.182	0.033	4.10×10^{-8}	-	-
						East Asian	NA	NA	NA	NA**		
						Stage 2	0.088	0.182	0.033	4.10×10^{-8}		

Table 2 | SNP heritability estimates. Values are given on the observed scale (h^2_{obs}) and liability scale (h^2_{liab}). Prevalence used for conversion to the liability scale is shown. Effective number samples was used for the conversion, as described in the Supplementary Note. For SumHer, two analyses were done: one with settings suggested by the SumHer authors, using LD reference data from the Health and Retirement Study (HRS), and one to mimic LDSC, with the same settings and reference panel (HapMap3, hm3). n_{eff}, effective sample size.

Trait	Method	h^2_{obs}	SE (h^2_{obs})	Prevalence	h^2_{liab}	SE (h^2_{liab})	Cases	Controls	n_{eff}
Intracranial aneurysms (Stage 1)	LDSC	0.295	0.038	0.03	0.216	0.028	7,495	71,934	24,253
Intracranial aneurysm (Stage 1)	SumHer	0.409	0.074	0.03	0.299	0.054	7,495	71,934	24,253
Intracranial aneurysm (Stage 1)	SumHer (LDSC)	0.276	0.037	0.03	0.202	0.027	7,495	71,934	24,253
aSAH-only	LDSC	0.296	0.043	0.005	0.140	0.020	5,140	71,952	17,019
uIA-only	LDSC	0.393	0.075	0.03	0.223	0.044	2,070	71,952	7,721

Online Methods

Recruitment and diagnosis. Detailed cohort descriptions are given in the Supplementary Note. In brief, all intracranial aneurysm cases have a saccular intracranial aneurysm. We included both cases with ruptured (thus with aSAH) and unruptured intracranial aneurysms confirmed using imaging. Patients with conditions known to predispose to intracranial aneurysms, including autosomal dominant polycystic kidney disease, Ehlers-Danlos disease and Marfan's syndrome, were excluded. All controls were unselected controls. Controls were matched by genotyping platform and country on cohort-level.

Genotype data quality control. Cohorts for which individual-level data were available are specified in Supplementary Table 1. An overview of inclusion and exclusion criteria, data collection and genotyping methods for each cohort are given in the Supplementary Note. Genotypes were lifted to reference genome build GRCh37. An extensive QC was performed on each cohort, described in detail in the Supplementary Note. Cohorts were merged into strata based on genotyping platform and country. An overview of strata compositions is given in Supplementary Table 1. Next, QC was performed on each stratum, outlined in the Supplementary Note. Genotypes were imputed against the Haplotype Reference Consortium (HRC) release 1.1. After imputation, another set of QC steps was taken, which is described in the Supplementary Note. An overview of the number of SNPs, cases and controls excluded in the QC is shown in Supplementary Table 1.

Individual-level association analysis. For each stratum, single-SNP associations were calculated using SAIGE (0.29.3)[14]. SAIGE uses a logistic mixed model to account for population stratification and saddle point approximation to accurately determine *P*-values

887 even in the presence of case-control imbalance. Details on how these steps were performed
888 are described in the Supplementary Note.
889
890 **Meta-analysis.** We meta-analyzed association statistics from our individual level SAIGE
891 analysis with association statistics prepared by other groups who used the same analysis
892 pipeline. There were two meta-analysis stages: Stage 1, including all individual level data and
893 the European ancestry summary statistics (HUNT Study), and Stage 2, including all
894 individual-level data and all summary statistics (HUNT Study, China Kadoorie Biobank,
895 Biobank Japan). Summary statistics that were generated by other groups were cleaned prior
896 to meta-analysis, as described in the Supplementary Note. We used METAL (release 2011-
897 03-25)[57] for the inverse-variance weighted meta-analysis across all studies. Only SNPs
898 present in at least 80% of the strata were included.
899
900 **Conditional analysis.** To investigate whether a genome-wide significant locus consisted of
901 multiple independent signals, we used GCTA-COJO[15]. COJO uses GWAS summary statistics
902 and the LD structure of a reference panel to iteratively condition GWAS summary statistics
903 on top SNPs. We used control samples from stratum sNL2 (Doetinchem Cohort Study) as a
904 reference panel for LD estimation. We used a stepwise approach to condition on the top
905 independent SNPs with $P < 5 \times 10^{-8}$ and minor allele frequency (MAF) > 0.01. In addition,
906 we conditioned the summary statistics on the identified top independent hits to determine if
907 any additional signal remained.
908
909 **Genetic risk score analysis.** To investigate the effect of genetic risk for blood pressure (BP)
910 and smoking on intracranial aneurysms, we used its genetic risk scores (GRS) as covariates in
911 a SAIGE association model. Summary statistics for BP-related traits[18] and cigarettes per day

912 (CPD)[17] were obtained. SNPs to include in the GRS models were determined using different
913 LD thresholds by clumping (r^2 of 0.1, 0.2, 0.5, 0.8 or 0.9). Individual-level GRSs were
914 calculated using plink v1.9 (https://www.cog-genomics.org/plink2/). The optimal models
915 were selected based on the highest fraction of variance explained (adj.r.squared from lm() in
916 R/3.6.1). An optimal r^2 of 0.1 and 0.9 were selected for BP and CPD, respectively. A set of
917 20,000 individuals from the UK Biobank, including all intracranial aneurysm cases, was used
918 to train the model. Individual levels GRSs using the optimized set of SNPs was used as a
919 covariate in an association analysis using SAIGE.
920
921 **eQTL-based gene mapping.** We used eCAVIAR[58] to determine colocalization of GWAS
922 hits with eQTLs. Vascular and whole blood eQTLs from GTEx v7 were used. eCAVIAR
923 used SNP Z-scores and LD correlation values to calculate a colocalization posterior
924 probability (CLPP) of a trait GWAS locus and an eQTL. eCAVIAR requires an LD matrix to
925 determine colocalization of eQTLs and GWAS hits. We calculated LD in SNPs 1 Mb on both
926 sides of the SNPs with lowest Stage 1 GWAS *P*-value, using European ancestry Health and
927 Retirement Study (HRS dbGaP accession code phs000428.v2.p2) samples as a reference.
928 Multiple causal SNPs were allowed.
929 TWAS is a method to perform differential expression analysis with eQTL-based
930 predicted transcript levels. We used a summary statistics-based approach integrated in
931 FUSION[59]. We used the 1000 Genomes LD weights provided by FUSION, and vascular and
932 blood eQTL datasets provided on the FUSION reference webpage
933 (http://gusevlab.org/projects/fusion/). Default settings were used for all other options.
934 SMR[60] was used to highlight genes for which expression has a causal influence on
935 intracranial aneurysm risk. eQTL reference datasets from vascular tissues and blood provided
936 by the creators of SMR were used. These include: CAGE, GTEx V7 (aorta, coronary artery,

tibial artery and whole blood) and Westra (https://cnsgenomics.com/software/smr/#DataResource). eQTLs with $P < 5 \times 10^{-8}$ were selected. The MAF cutoff was set at 0.01. European ancestry samples from the HRS were used as LD reference panel. Both the single SNP and multi-SNP approaches were used.

eCAVIAR, TWAS and SMR results were used to annotate genes to genome-wide significant GWAS loci identified in the Stage 1 GWAS meta-analysis. This approach is explained in more detail in the Supplementary Note.

SNP-based heritability. To calculate SNP-based heritability, we used LDSC (1.0.0)[33] to perform LD-score regression (LDSR), and we used SumHer[34]. LDSC makes the assumption that the contribution of each SNP to the total SNP heritability is normally distributed and not affected by MAF or LD. SumHer is the summary statistics based equivalent of an LD-adjusted kinship (LDAK) method to estimate SNP heritability and, instead, assumes that heritability is higher for low MAF variants and lower in high LD regions. In addition, SumHer models inflation due to residual confounding as a multiplicative parameter, whereas LDSC models this additively (the LDSR intercept). Heritability estimates were converted to the liability scale using effective sample size. More details and the rationale of these analyses are described in the Supplementary Note.

Functional enrichment analysis using LDSC. To assess enrichment of heritability in functional annotations, tissues, chromosomes and minor allele frequency (MAF) bins, we used stratified LD-score regression with LDSC[61]. When available, we used the publicly available partitioned LD scores for pre-defined annotations provided by the LDSC authors (https://data.broadinstitute.org/alkesgroup/LDSCORE/); otherwise, we calculated our own LD scores using European ancestry samples from the 1000 Genomes (1000G) project. To

further assess cell type-specific enrichment, we used a method introduced by Skene et al.[36]. For this analysis, we used single-cell RNA sequencing (scRNAseq) gene expression data derived from mouse brain to define gene sets specific to cell types in brain[36] and brain blood vessels[37]. A detailed description of the rationale and parameters is given in the Supplementary Note.

Functional enrichment analysis using GARFIELD. The GWAS functional enrichment tool GARFIELD v2[62] was used to explore regulatory, functional and tissue-specific enrichment of the GWAS summary statistics. It determines whether GWAS SNPs reaching a certain *P*-value threshold are enriched in annotations of interest compared to the rest of the genome while accounting for distance to nearest transcription start site, MAF and LD. We used the default annotations provided by the authors to test enrichment in tissues (https://www.ebi.ac.uk/birney-srv/GARFIELD/). We tested enrichment of SNPs passing *P*-value thresholds for every $\log_{10}$-unit between 0.1 and 10^{-8}. A more detailed description of the method is given in the Supplementary Note.

Genetic correlation. We assessed correlation between intracranial aneurysms and other traits using LDHub and LD-score regression (LDSR) with LDSC. To assess genetic correlation between intracranial aneurysms and many non-stroke-related traits, we used LD Hub[41]. This platform uses LDSR to assess genetic correlation with a large number of publicly available GWASs. For the correlation of intracranial aneurysms and other stroke subtypes, we obtained summary statistics for all stroke (AS), cardioembolic stroke (CE), any ischemic stroke (AnyIS), large artery stroke (LAS), small vessel disease (SVD)[42], deep, lobar, and combined intracerebral hemorrhage (ICH)[63], carotid- and vertebral artery dissection[44], arteriovenous malformation (AVM)[43], and abdominal aortic aneurysms (AAA)[45]. We used LDSC to

calculate genetic correlation. LD scores from European ancestry individuals from 1000G were calculated for SNPs in the HapMap 3 SNP set and used to calculate genetic correlation. Since the heritability estimate was negative for AVM, due to the small sample size, we performed a SNP lookup of the Stage 2 intracranial aneurysm loci that passed the multiple testing threshold ($P < 5 \times 10^{-8}$) from the GWAS of AVM[43].

Conditional genetic correlation. We used mtCOJO[16] to condition Stage 1 intracranial aneurysm GWAS summary statistics on summary statistics from the Neale lab UK Biobank GWAS release 1 (http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank) for smoking and blood pressure (BP) following a method described previously[16]. The resulting summary statistics were then used to calculate genetic correlation between intracranial aneurysms, conditioned on another trait, and other vascular diseases. LD scores supplied by LDSC (eur_w_ld_chr/[chr].l2.ldscore.gz) were used. European ancestry control samples from stratum sNL2 (from the Doetinchem Cohort Study) were used as an LD reference panel. All other settings were left as default.

Trans-ancestry genetic correlation. Popcorn version 0.9.9[64] was used to assess genetic correlation between intracranial aneurysm cohorts of European and East Asian ancestry. Popcorn uses separate LD score reference panels per ancestry to account for differences in LD structure between cohorts. We used LD scores provided by the authors of the Popcorn tool (https://github.com/brielin/Popcorn) for European and East Asian descent (EUR_EAS_all_gen_[eff/imp].cscore). We calculated the genetic correlation for both genetic impact and genetic effect.

Mendelian randomization. To infer causal genetic effects of exposure traits on intracranial aneurysms (the outcome), we used GSMR[16]. We used a meta-analysis of all European ancestry strata, except the UK biobank (stratum sUK2), as outcome. As exposures we used summary statistics of 2,419 traits analyzed using UK Biobank data, prepared by the Neale lab, release 2017 (http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank). For a second GSMR run with raw quantitative phenotypes, we used the 2019 GWAS release from the same group. GSMR was run using the GCTA wrapper (v1.92.2). More details on the method and settings are described in the Supplementary Note.

In order to determine which of the top significant GSMR traits were independent genetic causes of intracranial aneurysms, the Stage 1 GWAS summary statistics were conditioned on the top traits, i.e. smoking and blood pressure (BP). Conditioning was done using mtCOJO (GCTA v1.92.2 beta) as described in the "Conditional genetic correlation" section of the Online Methods.

Drug target enrichment. Drug target enrichment analysis was performed according to a previously described method[48]. Gene-wise *P*-values were calculated with MAGMA v1.06 using a combined approach of average and top *P*-values per gene region. Gene-set analysis was performed using MAGMA, with pathways curated from MSigDB[65,66], TargetValidation (https://www.targetvalidation.org), and with drug-target sets described previously[48]. Drug-class enrichment analysis was performed using a Wilcoxon-Mann-Whitney test. Drug gene-set *P*-values were tested for enrichment in drug-classes. Enrichment was expressed as the area under the curve (AUC). AUCs were compared between drug gene-sets within a drug class and all other drug gene-sets.

Statistics. The different statistical tests used in the different analysis methods are as follows: (1) SAIGE: Logistic mixed model with saddle-point approximation for *P*-values. Resulting beta values are on the logit scale. (2) METAL: Inverse-variance weighted meta-analysis. Resulting betas are on the same scale as the input (here, logit scale). (3) eCAVIAR: Directly calculates a colocalization posterior probability from expression and trait GWAS effect sizes using Bayes' rule. (4) TWAS: Uses to calculate a *Z*-score, which is tested against a null-distribution of mean zero and unit variance to calculate a *P*-value. (5) SMR: The Mendelian randomization effect of exposure (gene expression) *x* on outcome *y* is the ratio of the estimate of the effect of SNP *z* on outcome *y* and SNP *z* on exposure *x*. The SNP effect *Z*-scores are used to calculate a χ^2-statistic with one degree of freedom. (6) LDSC: Weighted linear regression, where weights are the inverse of the LD score of a SNP. The slope is divided by sample size and multiplied by the number of SNPs. Standard errors are obtained by jackknife method. (7) GARFIELD: Calculates enrichment odds ratios using logistic regression, accounting for LD, distance to transcription start site, and binary annotations. (8) POPCORN: Maximum likelihood test. Standard error is calculated using a block jackknife method. (9) GSMR: Two-sided linear regression after excluding pleiotropic SNPs using 'heterogeneity in dependent instrument'-test. (10) MAGMA (gene test): Uses a multiple linear regression to calculate gene effects. Subsequent *P*-value is derived from two-sided F-test. MAGMA (gene set test): Drug *P*-values are calculated by comparing gene *Z*-scores (derived from *P*-values reported in Supplementary Table 19) in the gene set to those outside the gene set. *P*-values are derived from one-sided *t*-test. (11) SumHer: Conceptually similar to LDSC, but with different weight based on linkage disequilibrium and minor allele frequency.

Data availability statement

Summary statistics for the Stage 1 and Stage 2 GWAS meta-analyses, the SAH-only, and uIA-only GWAS, and a meta-analysis consisting of only East Asian samples, including effective sample size per SNP, can be accessed through Figshare (https://doi.org/10.6084/m9.figshare.11303372) and through the Cerebrovascular Disease Knowledge Portal (http://www.cerebrovascularportal.org). Detailed information on access to publicly available data is given in the Life Sciences Reporting Summary.

Ethical Statement

All participants provided written informed consent. The Biobank Research Ethics Committee of the University Medical Center Utrecht reviewed and approved the study protocol (TCBio 17-087). The following local data access and ethics committees approved collection and use of genetic data for this study. @neurIST: Medisch Ethische Toetsings Commissie Erasmus MC (METC), Research Committee of the Hospital Clinic de Barcelona, Central Office for Research Ethics Committes (COREC) NHS, and Commission centrale d'éthique de la recherché sur l'être humain de la république et canton de Genève. ARIC: NHLBI Data Access Committee (through dbGaP). Busselton: GABRIEL Consortium Data Access Committee (through EGA). Utrecht 1: University Medical Center Utrecht Ethics Committee. Netherlands (EGA): Wellcome Trust Case-Control Consortium Data Access Committee (through EGA). Utrecht 2: University Medical Center Utrecht Ethics Committee. Doetinchem Cohort Study: Scientific Advisory Group of the Netherlands National Institute for Public Health and the Environment. Project MinE: Project MinE GWAS Consortium. French Canadian: Comité d'éthique de la recherche du Centre hospitalier de l'Université de Montréal and McGill University ethics. Finland (EGA): Wellcome Trust Case-Control

Consortium Data Access Committee (through EGA). Finland: The ethics committee of Kuopio University Hospital and Helsinki University Hospital. NFBC1966: Ethics Committee of Northern Ostrobotnia Hospital District, Finland. ICAN: Institutional Review Boards (Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé, Commission Nationale de l'Informatique et des Libertés) and Groupe Nantais d'Ethique dans le Domaine de la Santé (GNEDS). PREGO: Research Ethics Committee (CPP of Nantes). GAIN: NHLBI Data Access Committee (through dbGaP). FIA: University of Cincinatti ethics committee. nonGAIN: NHLBI Data Access Committee (through dbGaP). Poland: Institutional review board of the Jagiellonian University. NBS: Wellcome Trust Case-Control Consortium Data Access Committee (through EGA). UK Biobank: UK Biobank Data Access Committee. GOSH controls: Central London REC 3 committee. GOSH cases: Central London REC 3 committee. NBS+1958BBC: Wellcome Trust Case-Control Consortium Data Access Committee (through EGA). HUNT study: The Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee for Ethics in Medical Research. China Kadoorie Biobank: Oxford University ethical committee and the China National CDC. Biobank Japan: Research ethics committees at the Institute of Medical Science, the University of Tokyo. More details can be found in the Life Sciences Reporting Summary.

Methods-only references

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