

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

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129

130 **Rupture of an intracranial aneurysm leads to subarachnoid hemorrhage, a severe type**  
131 **of stroke. To discover new risk loci and the genetic architecture of intracranial**  
132 **aneurysms, we performed a cross-ethnic, genome-wide association study in 10,754 cases**  
133 **and 306,882 controls of European and East Asian ancestry. We discovered 17 risk loci,**  
134 **11 of which are new. We reveal a polygenic architecture and explain over half of the**  
135 **disease heritability. We show a high genetic correlation between ruptured and**  
136 **unruptured intracranial aneurysms. We also find a suggestive role for endothelial cells**  
137 **using gene mapping and heritability enrichment. Drug target enrichment shows**  
138 **pleiotropy between intracranial aneurysms and anti-epileptic and sex hormone drugs,**

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

143

144 An intracranial aneurysm is a balloon-shaped dilatation, usually located at a branch of an  
145 intracranial artery. It is present in 3% of the population<sup>1</sup>. Rupture of an intracranial aneurysm  
146 causes an aneurysmal subarachnoid hemorrhage (aSAH), a severe type of stroke.

147 Approximately one third of patients die, and another third remain dependent for daily life  
148 activities<sup>2</sup>. Intracranial aneurysms occur in relatively young people with a mean age of 50  
149 years and is twice as common in women over 50 years old compared to men of that age.

150 Genetic predisposition plays an important role in the disease with an aSAH heritability of  
151 41%, as estimated in a twin study<sup>3</sup>.

152 Much is still unknown about the genetic architecture of intracranial aneurysms<sup>4,5</sup>.

153 Family-based studies identified a number of variants with Mendelian inheritance<sup>6-10</sup>, but  
154 genome-wide association studies (GWAS) have identified multiple common variants,  
155 suggesting a polygenic model of inheritance<sup>5,11-13</sup>. The largest GWAS published to date,  
156 involving 2,780 cases and 12,515 controls, identified six risk loci<sup>11,13</sup>. Based on that GWAS,  
157 the explained single nucleotide polymorphism (SNP)-based heritability of intracranial  
158 aneurysms was estimated as being only 4.1-6.1%, depending on population<sup>5</sup>.

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

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

169

## 170 Results

171 **GWAS of intracranial aneurysms.** Our GWAS meta-analysis on intracranial aneurysms  
172 consisted of two stages. The Stage 1 meta-analysis included all European ancestry individuals  
173 and consisted of individual-level genotypes from 23 different cohorts that were merged into  
174 nine European-ancestry strata based on genotyping platform and country. These strata were  
175 each analyzed in a logistic mixed model<sup>14</sup> and then meta-analyzed, while also including  
176 summary statistics from a population-based cohort study: the Nord-Trøndelag Health Study  
177 (the HUNT Study). This resulted in 7,495 cases and 71,934 controls and 4,471,083 SNPs  
178 passing quality control (QC) thresholds (Online Methods, Supplementary Table 1). Stage 2  
179 was a cross-ethnic meta-analysis including all Stage 1 strata and summary statistics of East  
180 Asian individuals from two population-based cohort studies: The Biobank Japan (BBJ) and  
181 the China Kadoorie Biobank (CKB). This totaled 10,754 cases and 306,882 controls and  
182 3,527,309 SNPs in Stage 2 (Supplementary Table 1).

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

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

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

209

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

213 and transcriptome-wide association study (TWAS, <http://gusevlab.org/projects/fusion/>) to  
214 annotate potential causative genes in these loci (Supplementary Tables 5-9 and  
215 Supplementary Fig. 2). A description of this annotation process is described in the  
216 Supplementary Note. Since SMR, eCAVIAR and TWAS all require LD reference panels, we  
217 limited the annotation to the loci identified in the European ancestry Stage 1 GWAS meta-  
218 analysis. This resulted in 11 potential causative genes at six unique loci:  
219 *SLC22A5/SLC22A4/P4HA2* (chr5), *NT5C2/MARCKSLIP1* (chr10), *FGD6/NR2C1* (chr12),  
220 *PSMA4* (chr15), and *BCARI/RP11-252K23.2* (chr16) (Table 1 and Supplementary Table 5).  
221 Although we did not find evidence for involvement of *SOX17* in the chr8 locus, previous  
222 studies did find functional evidence for *SOX17*<sup>19,20</sup>. Therefore, we annotated the chr8 locus as  
223 *SOX17*.

224 In the Stage 2 GWAS, six additional loci were identified: 6q16.1, 10q23.33, 11p15.5,  
225 12p12.2, 12q21.22, and 20p11.23. Due to the combined European and East Asian LD  
226 structures, these loci cannot reliably be mapped to genes using the above-mentioned  
227 techniques. Of the six additional loci, four have previously been linked to blood pressure,  
228 namely 6q16.1 (rs11153071)<sup>21</sup>, 10q23.33 (rs11187838)<sup>22</sup>, rs11044991 (12p12.2)<sup>23</sup>, and  
229 rs2681492 (12q21.22)<sup>23,24</sup>. A detailed description of the genes and loci is found in the  
230 Supplementary Note.

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

238

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

256

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

263 conversion to the liability scale. Since this GWAS was an admixture of patients with ruptured  
264 and unruptured intracranial aneurysms, this prevalence may not be representative of the  
265 whole study population. Therefore, we calculated liability scale heritability using a range of  
266 prevalence values (Supplementary Fig. 3a). This shows that, also when using lower  
267 prevalence estimates (K), the explained SNP-based heritability is substantial (K = 0.02:  $h^2 =$   
268  $19.3 \pm 2.5\%$  (LDSC),  $26.8 \pm 4.8\%$  (SumHer); K = 0.01:  $16.3 \pm 2.1\%$  (LDSC),  $22.6 \pm 4.1\%$   
269 (SumHer)).

270 A substantial SNP-based heritability is also found for ruptured intracranial aneurysms  
271 (SAH-only,  $h^2 = 0.140 \pm 0.020$ ) and unruptured intracranial aneurysms (uIA-only,  $h^2 = 0.223$   
272  $\pm 0.044$ ). The difference between the heritability estimates could suggest differences in  
273 genetic architecture, but estimates depend on the prevalence estimate (Supplementary Fig.  
274 3b,c), meaning these differences should be interpreted with caution.

275

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

285 Tissue-specific LDSR did not show enrichment for any tissue (Supplementary Tables  
286 10 and 11). We then performed cell-type enrichment analysis using single-cell RNA-  
287 sequencing (scRNAseq) reference data derived from mouse brain<sup>36</sup>. No enrichment was

288 found using a scRNAseq dataset of mouse brain blood vessels<sup>37</sup> (Supplementary Table 12).  
289 Using a larger dataset defining cell-types in the mouse brain<sup>36</sup>, we found enrichment in  
290 ‘endothelial mural cells’, which is a combined set of vascular endothelial and mural cells  
291 (enrichment =  $2.31 \pm 0.41$  (SE),  $P = 1.65 \times 10^{-3}$ , Fig. 2c), and in midbrain neurons  
292 (enrichment =  $2.23 \pm 0.37$ ,  $P = 6.56 \times 10^{-4}$ ).

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

296

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

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

317 Since the phenotype values of the exposure traits were inverse rank-normalized, the  
318 GSMR effect size of SBP ( $\beta_{xy} = 1.058 \pm 0.187$ ) and pack-years ( $\beta_{xy} = 0.973 \pm 0.236$ ) cannot  
319 easily be interpreted. Therefore, we performed an additional GSMR analysis for BP with an  
320 updated version of the UK Biobank GWAS (<http://www.nealelab.is/uk-biobank/>), including  
321 raw phenotype values for quantitative traits (Supplementary Table 15). For BP traits, the  
322 GSMR analysis resulted in an effect size estimate of  $0.095 \pm 0.019$  for DBP and  $0.047 \pm$   
323  $0.011$  for SBP, meaning an 8-12% increase in intracranial aneurysm risk per mmHg increase  
324 of DBP and a 3.7-6% increase in intracranial aneurysm risk per mmHg increase of SBP,  
325 assuming a linear effect of BP on intracranial aneurysm liability. In addition, age at high BP  
326 diagnosis had a significant GSMR effect ( $P = 1.79 \times 10^{-4}$ ,  $\beta_{xy} = 0.163 \pm 0.044$ ), indicating an  
327 increase in intracranial aneurysm risk of 13-23% for each year of additional high BP  
328 exposure. We did not include smoking quantitative traits because these were not normally  
329 distributed (data not shown) and could, therefore, lead to a biased effect estimate.

330 We then tested whether the effects of smoking and BP were different between  
331 ruptured (SAH-only) and unruptured intracranial aneurysms (uIA-only, Supplementary Table  
332 16). The GSMR effect sizes followed the same trend for all phenotypes, but 'Hypertension  
333 (Self-reported)' had a stronger effect on ruptured intracranial aneurysms (SAH-only:  $\beta_{xy} =$   
334  $6.74 \pm 0.61$  (SE), all intracranial aneurysms:  $2.97 \pm 0.42$ , uIA-only:  $2.38 \pm 0.70$ ), while  
335 amlodipine use had a weaker effect on unruptured intracranial aneurysms and became  
336 statistically non-significant (uIA-only:  $\beta_{xy} = 4.77 \pm 3.90$ ,  $P = 0.22$ , all intracranial aneurysms:  
337  $\beta_{xy} = 11.4 \pm 2.10$ ,  $P = 5.25 \times 10^{-8}$ , SAH-only:  $\beta_{xy} = 13.1 \pm 2.60$ ,  $P = 5.25 \times 10^{-7}$ ). Although

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

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

348

349 **Drivers of genetic correlation with vascular traits.** To identify traits correlated with  
350 intracranial aneurysms, we analyzed Stage 1 summary statistics using LDHub<sup>41</sup>. LDHub  
351 includes a subset of the summary statistics used for GSMR and a number of summary  
352 statistics from publicly available sources. Traits that showed correlations that reached the  
353 Bonferroni threshold for multiple testing ( $P = 0.05/464$ ) included several blood pressure  
354 (BP)-related traits, including diastolic BP (DBP) ( $\rho_g = 0.223$ ,  $P = 5.40 \times 10^{-9}$ ) and systolic BP  
355 (SBP) ( $\rho_g = 0.256$ ,  $P = 1.34 \times 10^{-8}$ ) and smoking traits, such as pack-years ( $\rho_g = 0.330$ ,  $P =$   
356  $7.87 \times 10^{-8}$ ) (Supplementary Table 17).

357 We used LDSR to calculate the genetic correlation of intracranial aneurysms with  
358 other stroke subtypes (ischemic stroke (IS)<sup>42</sup> and intracerebral hemorrhage (ICH)), with other  
359 vascular malformation types (intracranial arteriovenous malformation (AVM)<sup>43</sup> and cervical  
360 artery dissection<sup>44</sup>), and with abdominal aortic aneurysm (AAA)<sup>45</sup>. For IS, a correlation of  
361  $0.195 \pm 0.079$  ( $P = 0.014$ ) was found with intracranial aneurysms (Fig. 3c and Supplementary  
362 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<sup>1,38,39,46</sup>, the correlation  
364 was no longer statistically significant and reduced to  $0.121 \pm 0.081$  for BP and  $0.147 \pm 0.084$   
365 for pack-years. The correlation disappeared after conditioning on both risk factors ( $\rho_g = 0.009$   
366  $\pm 0.083$ ,  $P = 0.916$ ). When conditioning on an unrelated but heritable trait (standing height),  
367 the correlation remained ( $\rho_g = 0.238 \pm 0.081$ ,  $P = 0.003$ ). 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 ( $\rho_g = 0.447 \pm 0.184$ ,  $P = 0.015$ ), which was mainly driven by deep ICH ( $\rho_g = 0.516 \pm$   
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<sup>47</sup>,  
373 the correlation with deep ICH decreased ( $\rho_g = 0.288 \pm 0.189$  for BP and  $0.234 \pm 0.192$  for  
374 pack-years) and was no longer statistically significant. Conditioning on height had a much  
375 smaller effect ( $\rho_g = 0.380 \pm 0.196$ ).

376 A genetic correlation was found between intracranial aneurysms and AAA ( $\rho_g = 0.302$   
377  $\pm 0.105$ ,  $P = 0.004$ ). Conditioning on pack-years strongly reduced the correlation between  
378 intracranial aneurysms and AAA ( $\rho_g = 0.173 \pm 0.117$ ,  $P = 0.138$ ), whereas BP did not ( $\rho_g =$   
379  $0.264 \pm 0.117$ ,  $P = 0.024$ ).

380 There was no genetic correlation between intracranial aneurysms and carotid artery  
381 dissection ( $\rho_g = 0.151 \pm 0.180$ ,  $P = 0.401$ ), 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 ( $\rho_g = 0.281 \pm 0.159$ ,  $P = 0.077$  and  $\rho_g = 0.174 \pm 0.149$ ,  $P =$   
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

387 intracranial aneurysm GWAS in the summary statistics of the AVM GWAS<sup>43</sup> but were  
388 unable to replicate any of these SNP associations ( $P < 0.05/17$ ) (Supplementary Table 18).  
389  
390 **Drug target enrichment.** To identify pleiotropic pathways between intracranial aneurysms  
391 and other diseases that contain known drug targets, we assessed enrichment in genes targeted  
392 by drugs and drug classes<sup>48</sup>. Gene-based  $P$ -values were calculated with MAGMA, resulting  
393 in 29 genes that passed the Bonferroni threshold for multiple testing ( $P < 0.05/18,106$ ,  
394 Supplementary Table 19). The anti-hypertensive drugs ambrisentan and macitentan showed a  
395 statistically significant enrichment ( $P = 1.35 \times 10^{-5}$ , Supplementary Table 20), which was  
396 driven by a single gene (*EDNRA*). Drug class enrichment analysis showed that drugs in the  
397 classes ‘anti-epileptics’ were enriched (area under the curve (AUC) = 0.675,  $P = 8 \times 10^{-5}$ ;  
398 Supplementary Table 21). The most statistically significant enriched drugs within this class  
399 are blockers of Na<sup>+</sup> and Ca<sup>2+</sup> channels, namely phenytoin, zonisamide, and topiramate<sup>49</sup>  
400 (Supplementary Table 20). These channels are important in blood pressure regulation, as well  
401 as in several other biological mechanisms. The other enriched drug class is ‘sex hormones +  
402 modulators of the genital system’ (AUC = 0.652,  $P = 2.02 \times 10^{-4}$ ). We also used MAGMA to  
403 study enrichment in gene pathways but found no statistically significant results  
404 (Supplementary Table 22).

405

## 406 Discussion

407 We identified 11 novel risk loci for intracranial aneurysms and confirmed six previously  
408 identified risk loci, yielding a total of 17 risk loci for intracranial aneurysms. A SNP-based  
409 heritability of 21.6% was found, explaining over half of the total heritability. We showed  
410 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<sup>1</sup>. 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

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

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

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

460 The heritability of unruptured intracranial aneurysms has never been studied in twins  
461 and may therefore not be an optimal estimate for intracranial aneurysm heritability. One twin  
462 study estimated the heritability of aSAH at 41%<sup>3</sup>. Our finding that the genetic architecture of  
463 uIA and aSAH are similar suggests that this heritability estimate may also be accurate for  
464 unruptured intracranial aneurysms. This means that, in European ancestry populations, 53-  
465 73% of the heritability of intracranial aneurysms can be explained by variants tagged in this  
466 GWAS.

467 Using transethnic genetic correlation, we found a remarkable similarity of genetic  
468 architecture between the European ancestry and East Asian ancestry GWASs of more than  
469  $90.8 \pm 14.6\%$  (SE). This indicates that the majority of common-variant genetic causes are the  
470 same, regardless of ancestry. However, since the LD structures remain distinct, current  
471 methods for summary statistic-based enrichment analysis cannot effectively account for  
472 population-specific variation in a cross-ethnic GWAS.

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

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

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

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656 Drug-target and MAGMA pathway enrichment analyses: J.R.I.C., G.B.

657 Critiquing the output for important intellectual content: D.J.W.

658

## 659 Competing Interests

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

661

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663

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## 794 Figure legends

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

804

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

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

823

824 **Figure 3 | Cross-trait analyses. a**, GSMR analysis of UK Biobank predictors on the Stage 1  
825 intracranial aneurysm GWAS, conditioned on traits depicted by column labels with mtCOJO.  
826 Numeric values are the GSMR effect sizes. The top 13 traits are blood pressure-related traits.  
827 The bottom three traits are smoking-related. Statistical significance was defined as  $P\text{-value} <$   
828  $0.05$  divided by the number of traits that passed quality control (376). Square fill colors  
829 indicate  $-\log_{10}(P\text{-value})$  of the GSMR effect. All 16 traits that pass the multiple testing  
830 threshold for significance in the unconditioned analysis are shown. BP, blood pressure.  
831 Presented  $n$  is sample size in UK Biobank GWAS. For intracranial aneurysms, effective  $n$  per  
832 SNP was used.  $P$ -values from two-sided linear regression, unadjusted. **b**, Causality diagram  
833 further explaining the analyses of **a**: GSMR analysis showed that genetic risk for smoking  
834 and BP are causative of intracranial aneurysms. Using mtCOJO, it was found that the genetic  
835 factors associated with BP and smoking cause intracranial aneurysms through independent  
836 mechanisms. Statistics are the same as used for **a**. BP,  $n = 317,754$  samples; smoking,  $n =$   
837  $101,726$  samples. **c**, Genetic correlation analysis with LDSR. Genetic correlation estimates  
838 are indicated by color and numeric value. Axis labels on the left denote the trait correlated  
839 with intracranial aneurysms. Labels on the top denote the trait for which the Stage 1

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

844 **Table 1 | Lead associations of genome-wide significant risk loci.** Association statistics were derived by SAIGE logistic mixed model. *P*-values  
845 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  
846 East Asian ancestry individuals are shown. Chr, Chromosome; Position, basepair position on GRCh37; EA, effect allele; OA, other allele; Stage 1,  
847 European ancestry only GWAS meta-analysis; East Asian, subset of samples from Japan and China; Stage 2, meta-analysis of European ancestry  
848 and East Asian data; EAF, effect allele frequency; SE, standard error of beta. Annotated genes are potentially causative genes identified using  
849 summary statistics based Mendelian randomization (SMR), eCAVIAR and transcriptome-wide association study (TWAS). Associated traits are  
850 cardiovascular traits and stroke risk factors with which the lead SNP is associated. CAD, coronary artery disease; SBP, systolic blood pressure;  
851 IS, ischemic stroke; AAA, abdominal aortic aneurysm; DBP, diastolic blood pressure; CVD, cardiovascular disease; COPD, chronic obstructive  
852 pulmonary disease. †Known locus, described in Hussain et al<sup>11</sup>. \*Another SNP in this locus ( $r^2 > 0.8$  with the Stage 2 lead SNP) has a lower *P*-  
853 value due to differences in LD patterns between European and East Asian populations. For locus 15q25.1, another SNP in that locus reaches  
854 genome-wide significance in Stage 1. \*\*For two SNPs, no East Asian association statistics could be obtained because these SNPs are  
855 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	$1.08 \times 10^{-17*}$	-	CAD
						East Asian	0.297	-0.181	0.028	$6.55 \times 10^{-11}$		
						Stage 2	0.222	-0.218	0.021	$3.22 \times 10^{-26}$		
rs4705938	5q31.1	5	131694077	T	C	Stage 1	0.549	0.120	0.019	$2.55 \times 10^{-10}$	SLC22A5/SLC22A4/P4HA2	Lung function
						East Asian	NA	NA	NA	NA**		
						Stage 2	0.549	0.120	0.019	$2.55 \times 10^{-10}$		
rs11153071	6q16.1	6	97039741	A	G	Stage 1	0.185	0.158	0.032	$5.86 \times 10^{-7*}$	-	SBP, migraine, sleep quality
						East Asian	0.113	0.143	0.041	$5.29 \times 10^{-4}$		
						Stage 2	0.158	0.153	0.025	$1.25 \times 10^{-9}$		
rs62516550	8q11.23†	8	55467028	T	C	Stage 1	0.389	0.169	0.023	$1.44 \times 10^{-13*}$	SOX17	-
						East Asian	0.087	0.102	0.049	$3.70 \times 10^{-2}$		
						Stage 2	0.335	0.157	0.021	$3.44 \times 10^{-14}$		
rs1537373	9p21.3†	9	22103341	T	G	Stage 1	0.514	-0.186	0.019	$2.60 \times 10^{-22}$	-	IS, AAA, CAD
						East Asian	0.342	-0.165	0.029	$1.43 \times 10^{-8}$		
						Stage 2	0.462	-0.180	0.016	$2.86 \times 10^{-29}$		

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

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

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857

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

Trait	Method	$h^2_{\text{obs}}$	SE ( $h^2_{\text{obs}}$ )	Prevalence	$h^2_{\text{liab}}$	SE ( $h^2_{\text{liab}}$ )	Cases	Controls	$n_{\text{eff}}$
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

862

## 863 Online Methods

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

871

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

883

884 **Individual-level association analysis.** For each stratum, single-SNP associations were  
885 calculated using SAIGE (0.29.3)<sup>14</sup>. SAIGE uses a logistic mixed model to account for  
886 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)<sup>57</sup> 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<sup>15</sup>. 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<sup>18</sup> and cigarettes per day

912 (CPD)<sup>17</sup> 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<sup>58</sup> 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<sup>59</sup>. 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<sup>60</sup> 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,

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

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

944

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

955

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

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

967

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

977

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

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

992

993 **Conditional genetic correlation.** We used mtCOJO<sup>16</sup> to condition Stage 1 intracranial  
994 aneurysm GWAS summary statistics on summary statistics from the Neale lab UK Biobank  
995 GWAS release 1 ([http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-](http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank)  
996 [phenotypes-for-337000-samples-in-the-uk-biobank](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)  
997 following a method described previously<sup>16</sup>. The resulting summary statistics were then used  
998 to calculate genetic correlation between intracranial aneurysms, conditioned on another trait,  
999 and other vascular diseases. LD scores supplied by LDSC (eur\_w\_ld\_chr/[chr].12.ldscore.gz)  
1000 were used. European ancestry control samples from stratum sNL2 (from the Doetinchem  
1001 Cohort Study) were used as an LD reference panel. All other settings were left as default.

1002

1003 **Trans-ancestry genetic correlation.** Popcorn version 0.9.9<sup>64</sup> was used to assess genetic  
1004 correlation between intracranial aneurysm cohorts of European and East Asian ancestry.  
1005 Popcorn uses separate LD score reference panels per ancestry to account for differences in  
1006 LD structure between cohorts. We used LD scores provided by the authors of the Popcorn  
1007 tool (<https://github.com/brielin/Popcorn>) for European and East Asian descent  
1008 (EUR\_EAS\_all\_gen\_[eff/imp].cscore). We calculated the genetic correlation for both genetic  
1009 impact and genetic effect.

1010

1011 **Mendelian randomization.** To infer causal genetic effects of exposure traits on intracranial  
1012 aneurysms (the outcome), we used GSMR<sup>16</sup>. We used a meta-analysis of all European  
1013 ancestry strata, except the UK biobank (stratum sUK2), as outcome. As exposures we used  
1014 summary statistics of 2,419 traits analyzed using UK Biobank data, prepared by the Neale  
1015 lab, release 2017 ([http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-](http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank)  
1016 [phenotypes-for-337000-samples-in-the-uk-biobank](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  
1017 quantitative phenotypes, we used the 2019 GWAS release from the same group. GSMR was  
1018 run using the GCTA wrapper (v1.92.2). More details on the method and settings are  
1019 described in the Supplementary Note.

1020         In order to determine which of the top significant GSMR traits were independent  
1021 genetic causes of intracranial aneurysms, the Stage 1 GWAS summary statistics were  
1022 conditioned on the top traits, i.e. smoking and blood pressure (BP). Conditioning was done  
1023 using mtCOJO (GCTA v1.92.2 beta) as described in the “Conditional genetic correlation”  
1024 section of the Online Methods.

1025

1026 **Drug target enrichment.** Drug target enrichment analysis was performed according to a  
1027 previously described method<sup>48</sup>. Gene-wise *P*-values were calculated with MAGMA v1.06  
1028 using a combined approach of average and top *P*-values per gene region. Gene-set analysis  
1029 was performed using MAGMA, with pathways curated from MSigDB<sup>65,66</sup>, TargetValidation  
1030 (<https://www.targetvalidation.org>), and with drug-target sets described previously<sup>48</sup>. Drug-  
1031 class enrichment analysis was performed using a Wilcoxon-Mann-Whitney test. Drug gene-  
1032 set *P*-values were tested for enrichment in drug-classes. Enrichment was expressed as the  
1033 area under the curve (AUC). AUCs were compared between drug gene-sets within a drug  
1034 class and all other drug gene-sets.

1035

1036 **Statistics.** The different statistical tests used in the different analysis methods are as follows:  
1037 (1) SAIGE: Logistic mixed model with saddle-point approximation for  $P$ -values. Resulting  
1038 beta values are on the logit scale. (2) METAL: Inverse-variance weighted meta-analysis.  
1039 Resulting betas are on the same scale as the input (here, logit scale). (3) eCAVIAR: Directly  
1040 calculates a colocalization posterior probability from expression and trait GWAS effect sizes  
1041 using Bayes' rule. (4) TWAS: Uses to calculate a  $Z$ -score, which is tested against a null-  
1042 distribution of mean zero and unit variance to calculate a  $P$ -value. (5) SMR: The Mendelian  
1043 randomization effect of exposure (gene expression)  $x$  on outcome  $y$  is the ratio of the estimate  
1044 of the effect of SNP  $z$  on outcome  $y$  and SNP  $z$  on exposure  $x$ . The SNP effect  $Z$ -scores are  
1045 used to calculate a  $\chi^2$ -statistic with one degree of freedom. (6) LDSC: Weighted linear  
1046 regression, where weights are the inverse of the LD score of a SNP. The slope is divided by  
1047 sample size and multiplied by the number of SNPs. Standard errors are obtained by jackknife  
1048 method. (7) GARFIELD: Calculates enrichment odds ratios using logistic regression,  
1049 accounting for LD, distance to transcription start site, and binary annotations. (8) POPCORN:  
1050 Maximum likelihood test. Standard error is calculated using a block jackknife method. (9)  
1051 GSMR: Two-sided linear regression after excluding pleiotropic SNPs using 'heterogeneity in  
1052 dependent instrument'-test. (10) MAGMA (gene test): Uses a multiple linear regression to  
1053 calculate gene effects. Subsequent  $P$ -value is derived from two-sided F-test. MAGMA (gene  
1054 set test): Drug  $P$ -values are calculated by comparing gene  $Z$ -scores (derived from  $P$ -values  
1055 reported in Supplementary Table 19) in the gene set to those outside the gene set.  $P$ -values  
1056 are derived from one-sided  $t$ -test. (11) SumHer: Conceptually similar to LDSC, but with  
1057 different weight based on linkage disequilibrium and minor allele frequency.  
1058

## 1059 Data availability statement

1060 Summary statistics for the Stage 1 and Stage 2 GWAS meta-analyses, the SAH-only, and  
1061 uIA-only GWAS, and a meta-analysis consisting of only East Asian samples, including  
1062 effective sample size per SNP, can be accessed through Figshare  
1063 (<https://doi.org/10.6084/m9.figshare.11303372>) and through the Cerebrovascular Disease  
1064 Knowledge Portal (<http://www.cerebrovascularportal.org>). Detailed information on access to  
1065 publicly available data is given in the Life Sciences Reporting Summary.

1066

## 1067 Ethical Statement

1068 All participants provided written informed consent. The Biobank Research Ethics Committee  
1069 of the University Medical Center Utrecht reviewed and approved the study protocol (TCBio  
1070 17-087). The following local data access and ethics committees approved collection and use  
1071 of genetic data for this study. @neurIST: Medisch Ethische Toetsings Commissie Erasmus  
1072 MC (METC), Research Committee of the Hospital Clinic de Barcelona, Central Office for  
1073 Research Ethics Committees (COREC) NHS, and Commission centrale d'éthique de la  
1074 recherché sur l'être humain de la république et canton de Genève. ARIC: NHLBI Data  
1075 Access Committee (through dbGaP). Busselton: GABRIEL Consortium Data Access  
1076 Committee (through EGA). Utrecht 1: University Medical Center Utrecht Ethics Committee.  
1077 Netherlands (EGA): Wellcome Trust Case-Control Consortium Data Access Committee  
1078 (through EGA). Utrecht 2: University Medical Center Utrecht Ethics Committee.  
1079 Doetinchem Cohort Study: Scientific Advisory Group of the Netherlands National Institute  
1080 for Public Health and the Environment. Project MinE: Project MinE GWAS Consortium.  
1081 French Canadian: Comité d'éthique de la recherche du Centre hospitalier de l'Université de  
1082 Montréal and McGill University ethics. Finland (EGA): Wellcome Trust Case-Control

1083 Consortium Data Access Committee (through EGA). Finland: The ethics committee of  
1084 Kuopio University Hospital and Helsinki University Hospital. NFBC1966: Ethics Committee  
1085 of Northern Ostrobothnia Hospital District, Finland. ICAN: Institutional Review Boards  
1086 (Comité consultatif sur le traitement de l'information en matière de recherche dans le  
1087 domaine de la santé, Commission Nationale de l'Informatique et des Libertés) and Groupe  
1088 Nantais d'Ethique dans le Domaine de la Santé (GNEDS). PREGO: Research Ethics  
1089 Committee (CPP of Nantes). GAIN: NHLBI Data Access Committee (through dbGaP). FIA:  
1090 University of Cincinnati ethics committee. nonGAIN: NHLBI Data Access Committee  
1091 (through dbGaP). Poland: Institutional review board of the Jagiellonian University. NBS:  
1092 Wellcome Trust Case-Control Consortium Data Access Committee (through EGA). UK  
1093 Biobank: UK Biobank Data Access Committee. GOSH controls: Central London REC 3  
1094 committee. GOSH cases: Central London REC 3 committee. NBS+1958BBC: Wellcome  
1095 Trust Case-Control Consortium Data Access Committee (through EGA). HUNT study: The  
1096 Norwegian Data Inspectorate, the Norwegian Board of Health, and the Regional Committee  
1097 for Ethics in Medical Research. China Kadoorie Biobank: Oxford University ethical  
1098 committee and the China National CDC. Biobank Japan: Research ethics committees at the  
1099 Institute of Medical Science, the University of Tokyo. More details can be found in the Life  
1100 Sciences Reporting Summary.

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