

# Novel genetic loci underlying human intracranial volume identified through genome-wide association

Intracranial volume reflects the maximally attained brain size during development, and remains stable with loss of tissue in late life. It is highly heritable, but the underlying genes remain largely undetermined. In a genome-wide association study of 32,438 adults, we discovered five previously unknown loci for intracranial volume and confirmed two known signals. Four of the loci were also associated with adult human stature, but these remained associated with intracranial volume after adjusting for height. We found a high genetic correlation with child head circumference ( $\rho_{\text{genetic}} = 0.748$ ), which indicates a similar genetic background and allowed us to identify four additional loci through meta-analysis ( $N_{\text{combined}} = 37,345$ ). Variants for intracranial volume were also related to childhood and adult cognitive function, and Parkinson's disease, and were enriched near genes involved in growth pathways, including PI3K-AKT signaling. These findings identify the biological underpinnings of intracranial volume and their link to physiological and pathological traits.

The intricate genetic control of the human brain, complemented by environmental factors, leads to the observed variations in brain size in human populations<sup>1</sup>. Intracranial volume is closely related to brain volume in early life as the brain grows<sup>2,3</sup>. However, it becomes stable after the brain has fully developed and remains unaffected by later age-related changes such as brain atrophy<sup>4,5</sup>, thereby representing the maximal attained brain size. Discovering genetic variants that influence intracranial volume can contribute to our understanding of brain development and related diseases, but prior studies have only identified two influential genetic loci<sup>6-9</sup>.

We carried out genome-wide association studies (GWAS) in populations from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)<sup>10</sup> and Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)<sup>11</sup> consortia on intracranial volume, as measured by magnetic resonance imaging. Genotypes were imputed to the 1000 Genomes reference panel (phase 1, version 3). Meta-analysis revealed five previously unknown loci associated with intracranial volume. We also discovered genome-wide overlap between intracranial volume and other key traits, including height, cognitive ability and Parkinson's disease. Furthermore, we found relatively enriched patterns of association for certain functional categories of variants and near genes that were involved in specific pathways.

## RESULTS

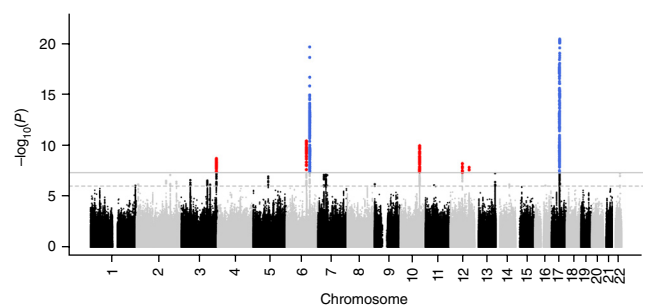
### GWAS

Detailed information on the population characteristics, image acquisition and processing, and genetic quality control can be found in the Online Methods and **Supplementary Tables 1–3**.

The discovery meta-analysis ( $N = 26,577$ ) yielded seven genome-wide significant ( $P < 5 \times 10^{-8}$ ) loci, five of which were previously unknown (**Figs. 1 and 2**, and **Table 1**). The quantile-quantile plot showed inflation ( $\lambda = 1.092$ ; **Supplementary Fig. 1**), which we determined to be mainly a result of polygenicity rather than cryptic relatedness

or population stratification using linkage disequilibrium score regression<sup>12</sup>. Next we analyzed European samples ( $N = 2,362$ ; not included in the discovery sample) and generalization samples with African ( $N = 938$ ), Asian ( $N = 955$ ) and Hispanic ( $N = 1,605$ ) ancestries (**Table 1**). All variants in the additional European samples had the same direction of effect (sign test,  $P = 0.0078$ ), and three variants replicated, at nominal significance. Although sample sizes were generally small for the non-Europeans, here too, the direction of effect was generally concordant with the discovery (sign test,  $P = 0.039$ ). We detected five nominally significant associations across all three ethnicities.

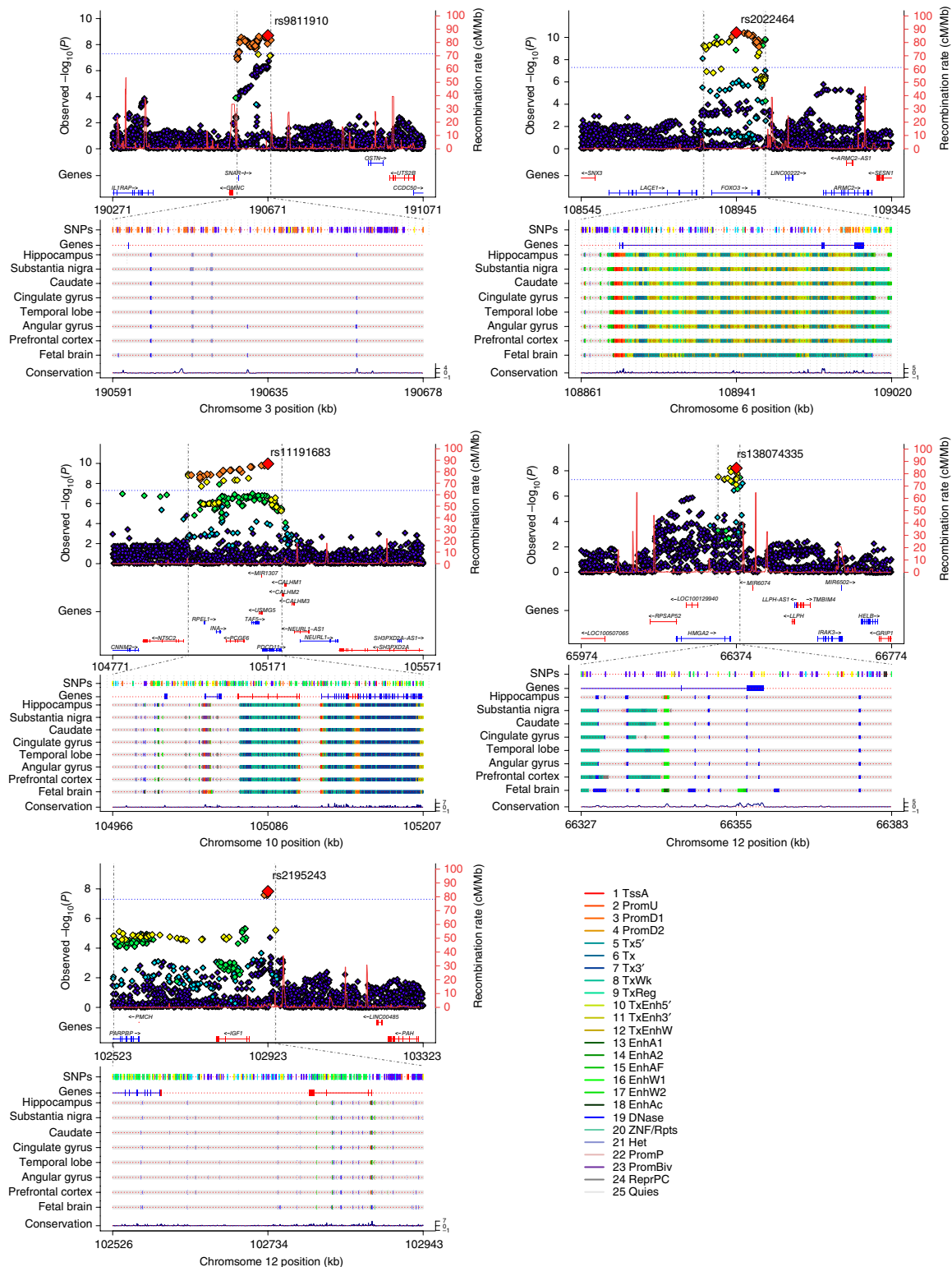
Next we mapped the association to new variants for two previously identified loci at chromosome 17q21 (rs199525;  $P = 3.8 \times 10^{-21}$ ) and 6q22 (rs11759026;  $P = 2.2 \times 10^{-20}$ )<sup>6,7</sup>. The five loci were located on chr 6q21



**Figure 1** Common genetic variants associated with intracranial volume. Manhattan plot in which every point represents a single genetic variant plotted according to its genomic position (x axis) and its  $-\log_{10}(P)$  for association with intracranial volume (y axis). Variants in blue were genome-wide significant in a previously known locus, whereas red variants reached genome-wide significant for the first time in that locus. The dashed horizontal line represents a significance threshold of  $P < 10^{-6}$  and the solid horizontal line represents genome-wide significance of  $P < 5 \times 10^{-8}$ . Variants surpassing these thresholds are indicated by larger points.

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**Figure 2** Regional association and functional annotation of previously unknown genome-wide significant loci. Regional association plots for the five genome-wide significant loci of intracranial volume with gene models below (GENCODE version 19). Annotation tracks below from the Roadmap Epigenomics Consortium<sup>46</sup> highlight the genomic region that likely harbors the causal variant(s) ( $r^2 > 0.8$  from the top SNP). See Online Methods for detailed track information. Plots were generated using the LocusTrack software (<http://gump.qimr.edu.au/general/gabrieC/LocusTrack/>). Color key: 1) Active transcription start site (TSS), 2) Promoter Upstream TSS, 3) Promoter Downstream TSS 1, 4) Promoter Downstream TSS 2, 5) Transcribed - 5' preferential, 6) Strong transcription Transcribed - 3' preferential, 7) Weak transcription, 8) Transcribed Regulatory (Prom/Enh), 9) Transcribed 5' preferential and Enh, 10) Transcribed 3' preferential and Enh, 11) Transcribed and Weak Enhancer, 12) Active Enhancer 1, 13) Active Enhancer 2, 14) Active Enhancer Flank, 15) Weak Enhancer 1, 16) Weak Enhancer 2, 17) Primary H3K27ac possible Enhancer, 18) Primary DNase, 19) ZNF genes and repeats, 20) Heterochromatin, 21) Poised Promoter, 22) Bivalent Promoter, 23) Repressed Polycomb, 24) Quiescent/Low.

**Table 1 Association of genome-wide significant loci for intracranial volume in European, African, Asian and Hispanic populations**

| Genetic variant | Locus | Position  | A1 | A2 | Freq | European discovery<br>( <i>N</i> = 26,577) |                       | European replication<br>( <i>N</i> = 2,363) |                      | African generalization<br>( <i>N</i> = 938) |                      | Asian generalization<br>( <i>N</i> = 955) |          | Hispanic generalization<br>( <i>N</i> = 1,605) |          |
|-----------------|-------|-----------|----|----|------|--|-----------------------|---|----------------------|---|----------------------|---|----------|--|----------|
|                 |       |           |    |    |      | $\beta$                                    | <i>P</i>              | $\beta$                                     | <i>P</i>             | $\beta$                                     | <i>P</i>             | $\beta$                                   | <i>P</i> | $\beta$  | <i>P</i> |
| rs199525        | 17q21 | 44847834  | T  | G  | 0.80 | 0.102                                      | $3.8 \times 10^{-21}$ | 0.024                                       | 0.407                | 0.358                                       | $1.3 \times 10^{-3}$ | 0.264                                     | 0.406    | 0.035  | 0.493    |
| rs11759026      | 6q22  | 126792095 | A  | G  | 0.76 | -0.095                                     | $2.2 \times 10^{-20}$ | -0.019                                      | 0.528                | -0.131                                      | 0.194                | -0.071                                    | 0.123    | -0.046   | 0.209    |
| rs2022464       | 6q21  | 108945370 | A  | C  | 0.30 | -0.063                                     | $3.7 \times 10^{-11}$ | -0.090                                      | $4.7 \times 10^{-3}$ | -0.060                                      | 0.233                | -0.105                                    | 0.035    | -0.088   | 0.013    |
| rs11191683      | 10q24 | 105170649 | T  | G  | 0.33 | 0.059                                      | $1.1 \times 10^{-10}$ | 0.040                                       | 0.174                | 0.187                                       | 0.021                | 0.085                                     | 0.075    | -0.005   | 0.911    |
| rs9811910       | 3q28  | 190670902 | C  | G  | 0.08 | 0.096                                      | $2.0 \times 10^{-9}$  | 0.075                                       | 0.010                | 0.346                                       | 0.020                | 0.101                                     | 0.621    | -0.148   | 0.187    |
| rs138074335     | 12q14 | 66374247  | A  | G  | 0.59 | 0.051                                      | $6.2 \times 10^{-9}$  | 0.106                                       | $2.9 \times 10^{-4}$ | -0.016                                      | 0.735                | -0.004                                    | 0.951    | 0.001  | 0.984    |
| rs2195243       | 12q23 | 102922986 | C  | G  | 0.22 | -0.059                                     | $1.5 \times 10^{-8}$  | -0.044                                      | 0.132                | 0.037                                       | 0.585                | -0.020                                    | 0.774    | -0.093   | 0.101    |

A1, effect allele; A2, reference allele; Freq, frequency of the effect allele; *N*, sample size.

(rs2022464;  $P = 3.7 \times 10^{-11}$ ), chr 10q24 (rs11191683;  $P = 1.1 \times 10^{-10}$ ), chr 3q28 (rs9811910;  $P = 2.0 \times 10^{-9}$ ), chr 12q14 (rs138074335/rs7312464;  $P = 6.2 \times 10^{-9}$ ) and chr 12q23 (rs2195243;  $P = 1.5 \times 10^{-8}$ ). Functional annotation of the variants and those in LD ( $r^2 > 0.8$ ) can be found in **Supplementary Table 4**.

### Height-adjusted analyses

Four of the seven loci for intracranial volume have previously been discovered for height (17q21, 6q22, 6q21 and 12q14), prompting us to investigate genome-wide overlap between the two traits. Given that height and intracranial volume are correlated (weighted average Pearson's  $r = 0.556$ ; **Supplementary Table 5**), and the possibility that this could drive association signals, we performed a GWAS of intracranial volume adjusted for height in the studies that had measured height ( $N = 21,875$ ). Findings were compared to the corresponding subset of studies without adjustment ( $N = 22,378$ ). Using LD score regression (Online Methods), we found that there was considerable genetic correlation between intracranial volume and height ( $\rho_{\text{genetic}} = 0.241$ ,  $P = 2.4 \times 10^{-10}$ ), which disappeared after adjusting for height ( $\rho_{\text{genetic}} = 0.049$ ,  $P = 0.21$ ) (**Table 2**). The associations of the seven intracranial volume loci, however, remained significant after adjusting for height (**Supplementary Table 6**). To investigate whether more height loci were associated with intracranial volume independently

of height, we analyzed all 697 genome-wide significant height variants<sup>13</sup>. An additional 73 variants (10.7%; 14 variants not available) showed nominally significant associations with intracranial volume, but were not attenuated after adjustment for height, although none survived Bonferroni correction (**Supplementary Table 7**). For some variants, the direction of effect was discordant, that is, positive for height and negative for intracranial volume. Furthermore, a polygenic score of the 697 variants predicted intracranial volume, and this was also the case after adjustment for height in a subset of the studies (**Supplementary Table 8**).

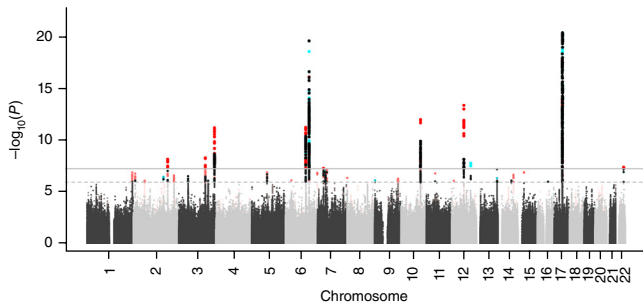
### Genetic correlation

In addition to height, we examined the genome-wide genetic overlap between intracranial volume and other anthropometric traits, cognitive function, and neurodegenerative diseases (**Table 2**). We found a strong genetic correlation with child head circumference ( $\rho_{\text{genetic}} = 0.748$ ), which validates intracranial volume as a measure of brain growth during early development. Given that this high correlation indicates that the genetic determinants of intracranial volume and child head circumference are largely shared, we aimed to leverage this information by performing a meta-analysis of both traits. The meta-analysis (combined  $N = 37,345$ ) led to the identification of four previously unknown loci (**Fig. 3** and **Supplementary Table 9**).

**Table 2 Genetic correlation between intracranial volume and other anthropometric traits, cognitive function, and neurodegenerative diseases**

| Phenotype                    | <i>N</i> total | <i>N</i> cases | Mean $\chi^2$ | Intracranial volume<br>Full sample ( <i>N</i> = 26,577) |       |   | Intracranial volume<br>Height subset ( <i>N</i> = 22,378) |       |   | Intracranial volume<br>Height adjusted ( <i>N</i> = 21,875) |       |  |
|------------------------------|----------------|----------------|---------------|---|-------|---|---|-------|---|---|-------|--|
|                              |                |                |               | $\rho_{\text{genetic}}$                                 | SE    | <i>P</i>                                | $\rho_{\text{genetic}}$                                   | SE    | <i>P</i>                                | $\rho_{\text{genetic}}$                                     | SE    | <i>P</i>                               |
| <b>Anthropometric traits</b> |                |                |               |   |       |   |   |       |   |   |       |  |
| Adult height                 | 253,280        | –              | 2.98          | 0.249   | 0.037 | <b><math>1.4 \times 10^{-11}</math></b> | 0.241   | 0.038 | <b><math>2.4 \times 10^{-10}</math></b> | 0.049   | 0.039 | 0.21                                   |
| Child head circumference     | 10,768         | –              | 1.04          | 0.748   | 0.121 | <b><math>5.5 \times 10^{-10}</math></b> | 0.758   | 0.124 | <b><math>1.1 \times 10^{-9}</math></b>  | 0.750   | 0.126 | <b><math>2.5 \times 10^{-9}</math></b> |
| Birth length                 | 28,459         | –              | 1.07          | 0.296   | 0.087 | <b><math>6.7 \times 10^{-4}</math></b>  | 0.278   | 0.087 | <b><math>1.3 \times 10^{-3}</math></b>  | 0.192   | 0.088 | <b>0.029</b>                           |
| Birth weight                 | 26,836         | –              | 1.06          | 0.285   | 0.081 | <b><math>4.4 \times 10^{-4}</math></b>  | 0.219   | 0.082 | <b><math>7.9 \times 10^{-3}</math></b>  | 0.160   | 0.086 | 0.062                                  |
| <b>Neurological traits</b>   |                |                |               |   |       |   |   |       |   |   |       |  |
| Childhood cognitive function | 12,441         | –              | 1.08          | 0.277   | 0.090 | <b><math>2.2 \times 10^{-3}</math></b>  | 0.277   | 0.091 | <b><math>2.5 \times 10^{-3}</math></b>  | 0.257   | 0.090 | <b><math>4.2 \times 10^{-3}</math></b> |
| Adult cognitive function     | 53,949         | –              | 1.15          | 0.202   | 0.059 | <b><math>6.3 \times 10^{-4}</math></b>  | 0.205   | 0.060 | <b><math>6.0 \times 10^{-4}</math></b>  | 0.198   | 0.059 | <b><math>6.9 \times 10^{-4}</math></b> |
| Alzheimer's Disease          | 54,162         | 17,008         | 1.11          | -0.070  | 0.097 | 0.47                                    | -0.049  | 0.097 | 0.61                                    | -0.043  | 0.098 | 0.66                                   |
| Parkinson's Disease          | 108,990        | 13,708         | 1.10          | 0.315   | 0.063 | <b><math>6.6 \times 10^{-7}</math></b>  | 0.316   | 0.070 | <b><math>5.5 \times 10^{-6}</math></b>  | 0.335   | 0.072 | <b><math>3.0 \times 10^{-6}</math></b> |
| White matter lesions         | 17,936         | –              | 1.07          | 0.112   | 0.075 | 0.13                                    | 0.111   | 0.078 | 0.16                                    | 0.096   | 0.079 | 0.23                                   |
| <b>Psychiatric traits</b>    |                |                |               |   |       |   |   |       |   |   |       |  |
| Autism                       | 10,263         | 4,949          | 1.07          | -0.011  | 0.069 | 0.87                                    | -0.036  | 0.074 | 0.63                                    | 0.026   | 0.071 | 0.72                                   |
| Bipolar disorder             | 11,810         | 6,990          | 1.14          | 0.070   | 0.071 | 0.33                                    | 0.007   | 0.075 | 0.93                                    | -0.004  | 0.076 | 0.95                                   |
| Major depressive disorder    | 16,610         | 9,227          | 1.07          | 0.002   | 0.100 | 0.98                                    | 0.025   | 0.098 | 0.80                                    | 0.005   | 0.096 | 0.96                                   |
| Schizophrenia                | 17,115         | 9,379          | 1.23          | 0.054   | 0.056 | 0.33                                    | 0.017   | 0.058 | 0.77                                    | -0.009  | 0.058 | 0.87                                   |
| Extraversion                 | 63,030         | –              | 1.08          | -0.041  | 0.092 | 0.65                                    | -0.101  | 0.095 | 0.29                                    | -0.097  | 0.092 | 0.29                                   |
| Neuroticism                  | 63,661         | –              | 1.08          | -0.017  | 0.109 | 0.87                                    | 0.035   | 0.106 | 0.74                                    | 0.070   | 0.111 | 0.53                                   |

Genetic correlation between various phenotypes and intracranial volume in the complete discovery sample (full sample), adjusted for height in the studies that had measured height (height adjusted), and the corresponding subset of studies without adjustment (height subset). Significant *P* values are shown in bold. SE, standard error.



**Figure 3** Meta-analysis of intracranial volume and child head circumference. A 'twin' Manhattan plot shows every variant twice: once for the discovery analysis and once for the combined discovery plus replication analysis. The least significant association of the variant-pair is plotted in gray (alternating light and dark between chromosomes). The most significant association of the variant-pair is plotted in red if it is from the combined analysis (that is, the association became more significant after meta-analyzing with the child head circumference GWAS) and in turquoise if it is from the discovery analysis (that is, the association became less significant after meta-analyzing with the child head circumference GWAS). The dashed horizontal line represents a significance threshold of  $P < 10^{-6}$  and the solid horizontal line represents genome-wide significance of  $P < 5 \times 10^{-8}$ . Variants surpassing these thresholds are indicated by larger and brighter points.

Weaker correlations were found with birth length and weight ( $\rho_{\text{genetic}} < 0.3$ ), which attenuated after adjusting for height. In addition, intracranial volume was genetically correlated with cognitive function in childhood ( $\rho_{\text{genetic}} = 0.277$ ,  $P = 2.2 \times 10^{-3}$ ), as well as general cognitive function in middle-aged and older adults ( $\rho_{\text{genetic}} = 0.202$ ,  $P = 6.3 \times 10^{-4}$ ). Furthermore, we found a positive genetic correlation with Parkinson's disease ( $\rho_{\text{genetic}} = 0.315$ ,  $P = 6.6 \times 10^{-7}$ ), but there was no significant genetic overlap with Alzheimer's disease, white matter lesions and psychiatric traits.

### Enrichment analyses

Next, we assessed whether particular subsets of genetic variants were enriched for association with intracranial volume using partitioned heritability and pathway analyses (Online Methods). Overall, we found that common variants genotyped from across the whole genome explained 25.42% (s.e.m., 2.73%) of the variation in intracranial volume. Partitioning heritability by chromosome revealed that chromosome 22 contributed twofold more to variation in intracranial volume than would be expected by its size (Fig. 4a), which was not seen for any of the other complex traits from the genetic correlation analysis (Supplementary Fig. 2). Partitioning by functional elements showed an enrichment for introns and several histone codes that are found in actively transcribed promoters (Fig. 4b). The enrichment for intronic variants was specific to intracranial volume, whereas the other functional classes were also enriched in other complex traits (Supplementary Fig. 3). We also found that loci associated with intracranial volume cluster around genes involved in specific pathways, with 94 pathways being significantly enriched (Fig. 4c; full list in Supplementary Table 10). These pathways included all of the cell cycle components—the M, G1, S and G2 phases—and various growth factor signaling pathways, including PI3K-AKT.

### Head growth trajectories

Although intracranial volume reflects brain development until maturation, and we identified influences of many growth-related processes contributing to its variation, all of the loci were still discovered via cross-sectional associations in adults. Thus, we tested whether

a polygenic score of the seven loci could predict head growth in a longitudinal cohort of 2,824 children of European ancestry followed prenatally until 6 years of age (Online Methods). We found that a higher polygenic score, representing a genetically larger intracranial volume in adults, was also associated with a larger child head circumference ( $\beta = 0.031$  per s.d.,  $P = 0.010$ ). Furthermore, the effect of the polygenic score was age dependent and more prominent in older children ( $\beta = 0.0080$  per s.d. polygenic score per year age,  $P_{\text{interaction}} = 0.0091$ ). When investigating the individual loci separately, we found significant associations between both 17q21 and 12q14 and child head circumference, but they influenced the trajectories of head growth differently (Fig. 5). For 17q21, the negative effect of the G allele on head circumference became apparent postnatally and increased toward 6 years of age, whereas the 12q14 locus exerted an effect from early pregnancy to 1 year of age, but was less prominent later in life.

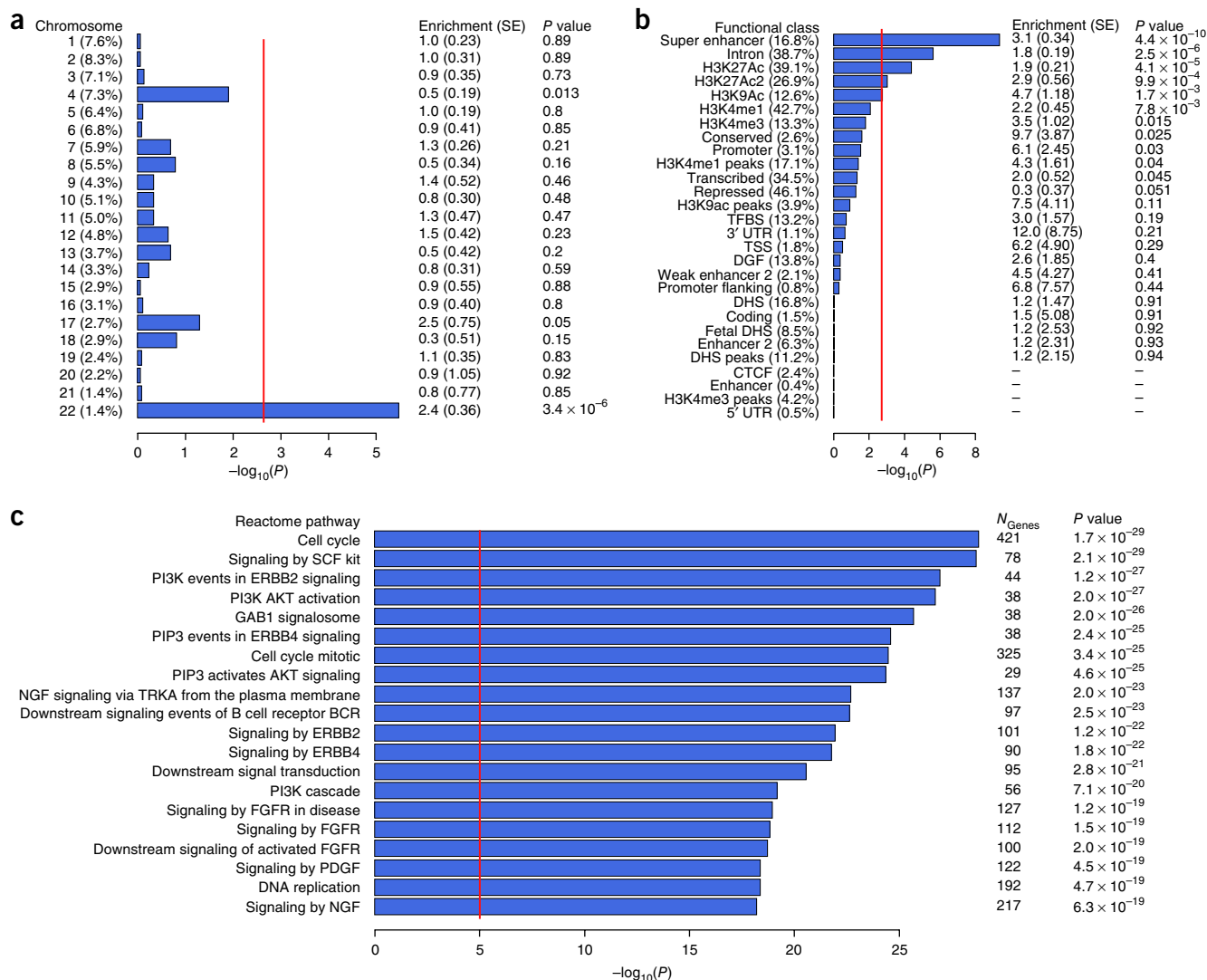
### DISCUSSION

Genes contributing to variation in the size of the human brain remain challenging to discover. In a worldwide project of unprecedented scale, we performed the largest-ever meta-analysis of GWAS of intracranial volume. We discovered five previously unknown genetic loci associated with intracranial volume, and replicated two known signals. The discovery sample included Europeans only, but the direction of effect was similar in other ethnicities. The genes in these loci provide intriguing links between maximal brain size and various processes, including neural stem cell proliferation (*FOXO3*), neurodegeneration (*MAPT*), bone mineralization (*CENPW*), growth signaling (*IGF1*, *HMG2*), DNA replication (*GMNC*) and rRNA maturation (*PDCD*). On a genome-wide scale, we discovered evidence of genetic correlation between intracranial volume and other key traits such as height and cognitive function, as well as with Parkinson's disease, indicating that the genes underlying brain development have far-reaching effects that extend well beyond the initial years of life.

The 17q21 locus tags a 1-Mb inversion that is under positive selection in Caucasians<sup>14</sup>. It contains multiple genes, including *MAPT* and *KANSL1*. The *MAPT* gene has been consistently implicated in various neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease and frontotemporal dementia<sup>15,16</sup>, and micro-duplications have been reported to cause microcephaly<sup>17</sup>. *KANSL1* causes the reciprocal 17q21.31 microdeletion syndrome: a multisystem disorder characterized by intellectual disability, hypotonia and distinctive facial features<sup>18</sup>. The signal at 6q22 is intergenic to *CENPW* and *RSPO3*, but now lies 172 kb closer to *CENPW*. Notably, multiple variants at this locus independently influence bone mineral density<sup>19,20</sup>, and our signal particularly overlapped with the variant showing high specificity for the skull<sup>20</sup>.

The significant variants at chr 6q21 span *FOXO3*, a gene associated with longevity<sup>21</sup>, height<sup>13</sup> and serum IGF1 levels<sup>22</sup>. *FOXO3* regulates the proliferation of neural stem cells, and knockout mice have larger brains, resulting from increased proliferation immediately after birth<sup>23</sup>, followed by a decrease in adult neural stem cell renewal<sup>23,24</sup>. The rs3800229 variant in strong LD with our top variant ( $r^2 = 0.84$ ) contains chromatin promoter marks in the fetal brain (Supplementary Table 4), and regulates serum IGF1 levels in infants<sup>25</sup>. This provides a link to the genome-wide significant locus on chr12q23 near *IGF1*, pointing to a potential mechanism by which these loci may affect brain growth. Chr12q23 lies 20 Mb from one of two loci previously detected for head circumference in children<sup>26</sup>, but that region was not associated with intracranial volume in our study (rs7980687,  $P = 0.06$ ). The other reported child head circumference locus, however, corresponded to our chr12q14 signal, with the top





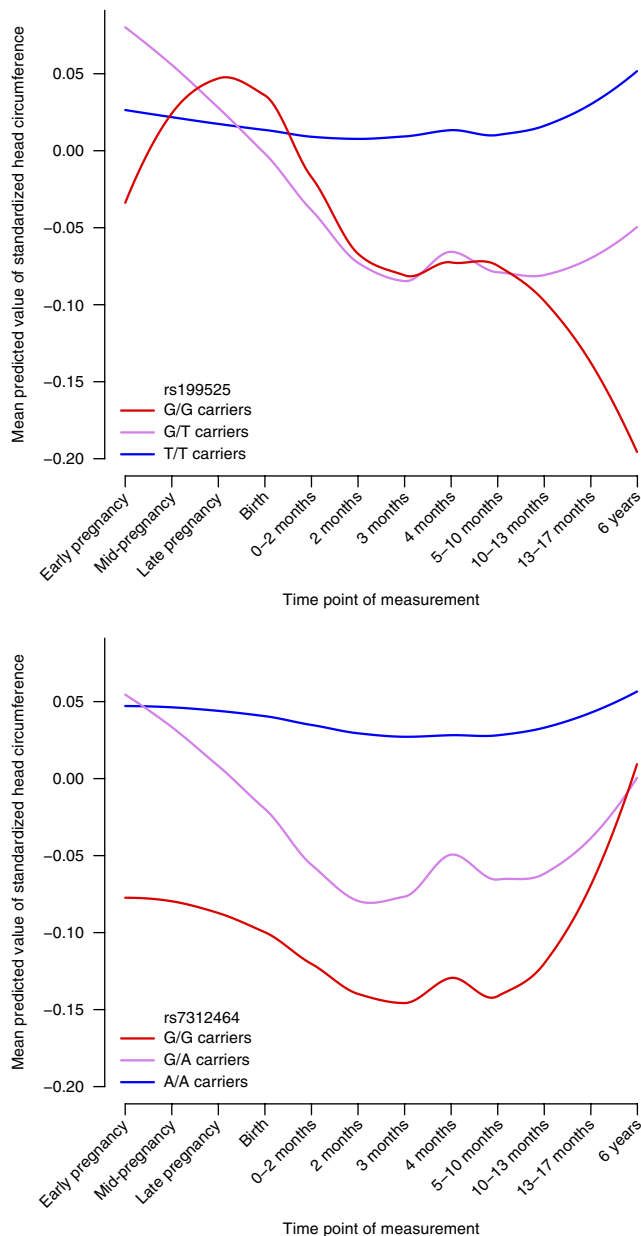
**Figure 4** Enrichment analyses of common variants associated with intracranial volume. Enrichment of subsets of variants for association with intracranial volume by chromosomes (a), functional subtype (b) and pathway (c). See Online Methods for additional information. TFBS, transcription factor binding site; TSS, transcription start site; DGF, DNase genomic footprinting; DHS, DNase I hypersensitive sites; CTCF, CCCTC-binding factor.

variant lying 14 kb downstream of *HMGA2*, and already showed suggestive association with intracranial volume in a previous report<sup>7</sup>. It has also previously been associated with height<sup>13</sup> and is essential for growth<sup>27</sup>. The chr10q24 LD-block covered multiple genes, but an intronic variant in *PDCD11* was most significant. *PDCD11* encodes an NF- $\kappa$ B-binding protein that is required for rRNA maturation and generation of 18S rRNA<sup>28</sup>. A variant in LD (rs7894407) has recently been identified in a GWAS of cerebral white matter hyperintensities<sup>29</sup>. The top chr3q28 variant is located upstream of *GMNC*, which encodes the geminin coiled-coil domain-containing protein essential for DNA replication<sup>30</sup>.

Prior efforts to identify variants affecting intracranial volume were much smaller and did not adjust for height<sup>6–9</sup>. We found that four of seven loci had already been discovered for height<sup>13</sup>, and that over 10% of the known ‘height loci’ actually affected intracranial volume, even after regressing out height. Interestingly, some variants showed discordant associations for height and intracranial volume, consistent with the recent finding that different height loci disproportionately affect either leg length or spine and head length<sup>31</sup>, and may be a marker for pathological development<sup>32</sup>. In addition, height might

therefore serve as a proxy phenotype for intracranial volume, with the tenfold larger sample of the height GWAS giving greater power to detect associations. Neural genes are also enriched in pathway analyses of height<sup>13</sup>. However, to fully disentangle whether these identified genes are ‘height genes’, ‘brain volume genes’ or ‘growth genes’ (that is, pleiotropic), a large collaborative effort is needed that examines the association of these variants with both intracranial volume and height in various models.

When investigating genome-wide overlap with other traits, we found a strong correlation with child head circumference, underlining the notion that intracranial volume is a valid measure for maximal attained brain size. We were able to leverage this genetic link by meta-analyzing both traits, which led to the identification of four additional loci (2q32.1, 3q23, 7p14.3 and 22q13.2). The correlations with birth length and weight were weaker and decreased further after adjusting for height, so a similar phenotypic correlation between head size and body size at younger age may drive these correlations. Intracranial volume was also genetically associated with cognitive function in childhood, as well as general cognitive function in middle-aged and older individuals. This indicates that variation in



**Figure 5** Temporal trends of intracranial volume loci during pre- and postnatal brain development. Mean predicted values of standardized head circumference using linear mixed models with age, sex, and the rs199525 or rs138074335 variants. The blue line represents children not carrying the risk allele, purple only a single risk allele and red with two risk alleles. See Online Methods for additional information. Total sample size was 2,824.

maximally attained brain size during development shares a genetic basis with cognitive ability later in life and supports intracranial volume as a measure of brain reserve<sup>5</sup>.

The brain reserve hypothesis states that premorbid brain size can modify resilience to age-related brain pathology<sup>33</sup>, but there was no indication of a genome-wide overlap with Alzheimer's disease. However, we found a positive genetic correlation with Parkinson's disease, which instead points to a brain 'overgrowth' hypothesis. Notably, the IGF1 and the PI3K-AKT pathways, key factors in both growth signaling and our current study of intracranial volume, are neuroprotective in a model system of Parkinson's disease<sup>34</sup>. There were no

correlations with other neurological or psychiatric traits, indicating that this finding might be specific to Parkinson's disease. However, it is important to note that there is a certain extent of variation in the sample size and power of these studies, and a larger GWAS might reveal genetic correlation with other traits as well. For schizophrenia, we also tested the latest GWAS (36,989 cases and 113,075 controls), but here too there was no significant correlation ( $\rho_{\text{genetic}} = 0.01$ ,  $P = 0.79$ ).

It is not yet known whether variance in intracranial volume, in the normal range, contributes to disease risk or brain reserve. There is no doubt that in the pathological extremes of the distribution, size can matter, as in disorders such as microcephaly or macrocephaly. Here we found evidence for a shared genetic background between intracranial volume and cognitive function, and risk of Parkinson's disease. Although not definitive, these are new pieces of empirical evidence in the debate on whether or not whole brain size matters.

The pathway analyses highlight cellular growth and proliferation and included all components of the cell cycle (M, G1, S and G2 phases) and various growth factor signaling pathways. PI3K-AKT signaling has a well-described role in brain overgrowth disorders<sup>35,36</sup>, and was the only significant pathway using a different pathway analysis method (**Supplementary Table 11**). Interestingly, *AKT3* intronic variants showed suggestive evidence for association with intracranial volume (rs7538011;  $P = 9.2 \times 10^{-7}$ ). Deletions of *AKT3* cause microcephaly syndromes<sup>37</sup>, whereas duplications give rise to macrocephaly<sup>38</sup>. Similar to *FOXO3*, it is part of the IGF1 signaling pathway, which is important for human longevity<sup>39</sup>. The PI3K-AKT signaling pathway seems to have an important role in brain growth, not only in pathological extremes, but also for normal variation at a population level. Other pathways enriched for association with intracranial volume highlight neuronal functions such as neurotransmission and axon guidance.

We identified previously unknown loci that influence intracranial volume, and, at a genome-wide level, there seemed to be common pathways, but our longitudinal study revealed that their developmental effects are complex. The loci influenced trajectories of head growth differently; it would also be interesting to investigate whether their spatial profiles of effects are distinct, such as certain loci promoting growth of particular brain regions.

Here we identified key genetic loci that have been implicated in intracranial volume in a global collaborative effort, followed by computational analyses to determine the important biological pathways and functional elements. Although the majority of the genetic variants are yet to be discovered, it is clear that these will provide better insight into brain development, as well as into related neuropsychiatric traits such as cognitive functioning and even for neurodegeneration late in life. Uncovering the remaining heritability will advance our understanding of the brain's complex genetic architecture.

**URLs.** LD score software: <ftp://pricelab:pricelab@ftp.broadinstitute.org/LDSCORE/>, ENIGMA protocols: <http://enigma.usc.edu/protocols/genetics-protocols/>, eQTL browser: <http://genetnet-work.nl/blooddeqtlbrowser/>, LocusTrack software: <http://gump.qimr.edu.au/general/gabrieC/LocusTrack/>.

## METHODS

Methods, including statements of data availability and any associated accession codes and references, are available in the [online version of the paper](#).

*Note: Any Supplementary Information and Source Data files are available in the online version of the paper.*

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Buitelaar<sup>13,14,61</sup>, Kazima B Bulayeva<sup>145</sup>, Wiepke Cahn<sup>20</sup>, Vince D Calhoun<sup>146,147</sup>, Dara M Cannon<sup>94,148</sup>, Gianpiero L Cavalleri<sup>22</sup>, Christopher Chen<sup>69,70</sup>, Ching-Yu Cheng<sup>82,149,150</sup>, Sven Cichon<sup>151–153</sup>, Mark R Cookson<sup>140</sup>, Aiden Corvin<sup>105</sup>, Benedicto Crespo-Facorro<sup>103,104</sup>, Joanne E Curran<sup>135</sup>, Michael Czisch<sup>73</sup>, Anders M Dale<sup>154–158</sup>, Gareth E Davies<sup>159–162</sup>, Eco J C De Geus<sup>49</sup>, Philip L De Jager<sup>56,162,163</sup>,



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Guelfi<sup>85</sup>, Narelle K Hansell<sup>9,117</sup>, John Hardy<sup>85</sup>, Catharina A Hartman<sup>125</sup>, Ryota Hashimoto<sup>180,181</sup>, Katrin Hegenscheid<sup>182</sup>, Andreas Heinz<sup>171</sup>, Stephanie Le Hellard<sup>58,59</sup>, Dena G Hernandez<sup>85,140,183</sup>, Dirk J Heslenfeld<sup>184</sup>, Beng-Choon Ho<sup>185</sup>, Pieter J Hoekstra<sup>125</sup>, Wolfgang Hoffmann<sup>18,118</sup>, Albert Hofman<sup>1</sup>, Florian Holsboer<sup>73,186</sup>, Georg Homuth<sup>187</sup>, Norbert Hosten<sup>182</sup>, Jouke-Jan Hottenga<sup>49</sup>, Hilleke E Hulshoff Pol<sup>20</sup>, Masashi Ikeda<sup>188</sup>, M Kamran Ikram<sup>1,69,70,82,149</sup>, Clifford R Jack Jr<sup>189</sup>, Mark Jenkinson<sup>130</sup>, Robert Johnson<sup>190</sup>, Erik G Jönsson<sup>32,130</sup>, J Wouter Jukema<sup>10</sup>, René S Kahn<sup>20</sup>, Ryota Kanai<sup>191–193</sup>, Iwona Kloszewska<sup>194</sup>, David S Knopman<sup>195</sup>, Peter Kochunov<sup>196</sup>, John B 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Ohi<sup>180</sup>, Rene L Olvera<sup>177</sup>, Roel A Ophoff<sup>20,95</sup>, Massimo Pandolfo<sup>166</sup>, Tomas Paus<sup>219–221</sup>, Zdenka Pausova<sup>36,222,223</sup>, Brenda W J H Penninx<sup>111</sup>, G Bruce Pike<sup>224,225</sup>, Steven G Potkin<sup>127</sup>, Bruce M Psaty<sup>226–229</sup>, Simone Reppermund<sup>30,230</sup>, Marcella Rietschel<sup>63</sup>, Joshua L Roffman<sup>51</sup>, Nina Romanczuk-Seiferth<sup>171</sup>, Jerome I Rotter<sup>231</sup>, Mina Ryten<sup>85,101</sup>, Ralph L Sacco<sup>17,107,108,232</sup>, Perminder S Sachdev<sup>30,233</sup>, Andrew J Saykin<sup>77,79,176</sup>, Reinhold Schmidt<sup>71</sup>, Peter R Schofield<sup>197,198</sup>, Sigurdur Sigurdsson<sup>114</sup>, Andy Simmons<sup>234–236</sup>, Andrew Singleton<sup>140</sup>, Sanjay M Sisodiya<sup>75</sup>, Colin Smith<sup>237</sup>, Jordan W Smoller<sup>51,55–57</sup>, Hilikka Soininen<sup>238,239</sup>, Velandai Srikanth<sup>240</sup>, Vidar M Steen<sup>58,59</sup>, David J 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## ONLINE METHODS

**Study population.** This study reports data on 32,438 subjects from 52 study sites that are part of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)<sup>10</sup> consortium and Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)<sup>11</sup> consortium. Briefly, the CHARGE consortium is a collaboration of predominantly population-based cohort studies that investigate the genetic and molecular underpinnings of age-related complex diseases, including those of the brain. The ENIGMA consortium brings together numerous studies, mainly with a case-control design, which performed neuroimaging in a range of neuropsychiatric or neurodegenerative diseases, as well as healthy normative populations. Studies participated in either the discovery cohort of European ancestry, the replication in European ancestry, or the generalization to other ethnicities. An overview of the demographics and type of contribution for each cohort is provided in **Supplementary Table 1**. Written informed consent was obtained from all participants. Each study was approved by the respective institutional review board or local ethics committee.

**Genetics.** Genotyping was performed using a variety of commercial arrays across the contributing sites. Both samples as well as variants underwent similar quality control procedures based on genetic homogeneity, call rate (less than 95%), minor allele frequency (MAF < 0.01), and Hardy-Weinberg Equilibrium (HWE p-value less than  $1 \times 10^{-6}$ ). Good quality variants were used as input for imputation to the 1000 Genomes reference panel (phase 1, version 3) using validated software packages (MaCH/minimac, IMPUTE2, BEAGLE, GenABEL). Variants that were poorly imputed ( $R^2 < 0.5$ ) or uncommon (MAF < 0.5%) were removed before meta-analysis. Full details on the site-specific genotyping and quality control may be found in **Supplementary Table 2**.

**Imaging.** Magnetic resonance imaging (MRI) was obtained from scanners with a diversity of manufacturers, field strengths, and acquisition protocols. Images were used to estimate milliliters of intracranial volume from automated segmentations generated by freely available or in-house methods that have been described and validated earlier. Most sites measured intracranial volume for each participant by multiplying the inverse of the determinant of the transformation matrix required to register the subject's MRI scan to a common template by the template volume (1,948,105 mm<sup>3</sup>), using the FreeSurfer software. Visual inspections were performed to identify and remove poorly segmented images. Either all scans were visually inspected, or sites generated histogram plots to identify any outliers, which were defined as individuals with a volume more than 3 s.d. away from the mean. Statistical outliers were only excluded if the segmentations were deemed improper. More site-specific information related to the imaging is available in **Supplementary Table 3**.

**GWAS.** GWAS of intracranial volume were performed for each site separately, controlling for age, sex, and, when applicable, age<sup>2</sup>, population stratification variables (MDS / principal components), study site (for multi-site studies only), diagnosis (for case-control studies only). Studies of unrelated individuals performed a linear regression analyses whereas studies of related individuals (ASPSFam, BrainSCALE, ERF, GeneSTAR, GOBS, NeuroIMAGE, NTR-Adults, OATS, QTIM, SYS) used linear mixed models to account for familial relationships. Summary statistics, including the effect estimates of the genetic variant with intracranial volume under an additive model, were exchanged to perform a fixed-effects meta-analysis weighting for sample size in METAL<sup>47</sup>. After the final meta-analysis, variants were excluded if they were only available for fewer than 5,000 individuals. Meta-analyses were stratified by race and done separately for discovery, replication, and generalization samples. Beta coefficients were recalculated from Z-scores, allele frequencies, and the sample, as described earlier<sup>48</sup>. Site-specific quantile-quantile plots were generated to inspect the presence of genomic inflation. The variance explained by all variants in the GWAS was estimated using LD score regression<sup>12,49</sup>. Sensitivity analyses were performed by excluding patients.

**Functional annotation.** All tracks of the regional association plots were taken from the UCSC Genome Browser Human hg19 assembly. SNPs (top 5%) shows the top 5% associated variants within the locus and are colored by their correlation to the top variant. Genes shows the gene models from GENCODE version 19. The tracks give the predicted chromatin states based on computational integration

of CHIP-seq data for 12 chromatin marks in various human tissues derived from the Roadmap Epigenomics Consortium<sup>46</sup>. In addition, we used HaploReg version 3 for annotation of the top variants and all variants in LD (>0.80) ([http://www.broadinstitute.org/mammals/haploreg/haploreg\\_v3.php](http://www.broadinstitute.org/mammals/haploreg/haploreg_v3.php)).

**Genetic correlation.** The genetic correlation analyses were also performed using LD score regression. The GWAS meta-analysis of intracranial volume, as well as the height adjusted and height subset meta-analyses, were correlated with published GWAS of the following traits: child head circumference<sup>26</sup>, birth weight<sup>50</sup>, birth length<sup>51</sup>, adult height<sup>13</sup>, childhood cognitive function<sup>45</sup>, adult cognitive function<sup>40</sup>, Alzheimer's disease<sup>52</sup>, Parkinson's disease<sup>43</sup>, white matter lesions<sup>29</sup>, psychiatric disorders<sup>44</sup>, neuroticism<sup>41</sup>, and extraversion<sup>42</sup>.

**Enrichment analyses.** To determine whether the intracranial volume association results were enriched for certain types of genetic variants, we employed two strategies: partitioned heritability and pathway analyses.

Partitioned heritability was calculated using a previously described method<sup>49</sup>. This was done by partitioning variants by chromosome and by 28 functional classes: coding, UTR, promoter, intron, histone marks H3K4me1, H3K4me3, H3K9ac5 and two versions of H3K27ac, open chromatin DNase I hypersensitivity Site (DHS) regions, combined chromHMM/Segway predictions, regions that are conserved in mammals, super-enhancers and active enhancers from the FANTOM5 panel of samples<sup>49</sup>. Multiple testing thresholds were calculated accordingly:  $P_{\text{thresh}} = 0.05/(22 \text{ chromosomes}) = 2.27 \times 10^{-3}$  for the chromosomes and  $P_{\text{thresh}} = 0.05/(28 \text{ classes}) = 1.79 \times 10^{-3}$  for the functional classes.

Pathway analyses were performed using the KGG2.5 (ref. 53) and MAGENTA<sup>54</sup> software packages. LD was calculated based with the 1000 Genomes Project European samples as a reference (see below). Variants were considered to be within a gene if they were within 5 kb of the 3'/5' UTR based on chromosome positions (hg19) coordinates. Gene-based tests were done with the GATES test<sup>53</sup> without weighting P values by predicted functional relevance. Pathway analysis was performed using the HYST test of association<sup>55</sup>. A multiple testing threshold accounting for the number of pathways tested resulting in a significance threshold of  $P_{\text{thresh}} = 0.05/(671 \text{ pathways}) = 7.45 \times 10^{-5}$ .

**Head growth trajectories.** Head growth trajectory analyses were done within the Generation R study, a longitudinal cohort study situated in Rotterdam, the Netherlands. For this analysis we included 2,824 children of European ancestry followed prenatally until 6 years of age. Head size was measured at the following points: prenatally (using echo) during the first, second, and third trimester, and postnatally (measuring head circumference) at 0–2 months, 2 months, 3 months, 4 months, 5–10 months, 10–13 months, 13–17 months, and 5 years of age. We tested whether a polygenic score of the 7 loci, as well as the 7 loci themselves separately, were related to head growth using linear mixed models and included an interaction term between time and the genetic score/variant (SAS software). Next, the predicted values were calculated for each person and plotted over time, stratified by genotype (0/1/2 risk alleles) using the R software package.

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