

2 **TITLE**

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

4 **SHORT TITLE**

5 Genetics of intracranial volume

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509 **ABSTRACT**

510 **Intracranial volume reflects the maximally attained brain size during development, and remains**
511 **stable with loss of tissue in late life. It is highly heritable, but the underlying genes remain**
512 **largely undetermined. In a genome-wide association study of 32,438 adults, we discovered five**
513 **novel loci for intracranial volume and confirmed two known signals. Four of the loci are also**
514 **associated with adult human stature, but these remained associated with intracranial volume**
515 **after adjusting for height. We found a high genetic correlation with child head circumference**
516 **($\rho_{\text{genetic}}=0.748$), which indicated a similar genetic background and allowed for the identification**
517 **of four additional loci through meta-analysis ($N_{\text{combined}} = 37,345$). Variants for intracranial**
518 **volume were also related to childhood and adult cognitive function, Parkinson's disease, and**
519 **enriched near genes involved in growth pathways including PI3K-AKT signaling. These**
520 **findings identify biological underpinnings of intracranial volume and provide genetic support**
521 **for theories on brain reserve and brain overgrowth.**

522 The intricate genetic control of the human brain, complemented by environmental factors, leads to the
523 observed variations in brain size in human populations¹. Intracranial volume is closely related to brain
524 volume in early life as the brain grows.^{2,3} However, it becomes stable after the brain has fully
525 developed and remains unaffected by later age-related changes such as brain atrophy^{4,5}, thus
526 representing the maximal attained brain size. Discovering genetic variants that influence intracranial
527 volume can contribute to our understanding of brain development and related diseases, but prior
528 studies have only identified two influential genetic loci⁶⁻⁹.

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

537 RESULTS

538 Genome-wide association studies

539 Detailed information on the population characteristics, image acquisition and processing, and genetic
540 quality control can be found in the **Online Methods** and **Supplementary Tables S1-3**.

541 The discovery meta-analysis ($N = 26,577$) yielded seven genome-wide significant ($p < 5 \times 10^{-8}$) loci,
542 five of them novel (**Figures 1-2; Table 1**). The quantile-quantile plot showed inflation ($\lambda = 1.092$;
543 **Supplementary Figure S1**), which we determined to be mainly due to polygenicity rather than
544 cryptic relatedness or population stratification using LD score regression¹². Next we analyzed
545 European samples ($N = 2,362$; not included in the discovery sample) and generalization samples with
546 African ($N = 938$), Asian ($N = 955$), and Hispanic ($N = 1,605$) ancestries (**Table 1**). All variants had
547 the same direction of effect in the additional European samples (*sign test*, $P = 0.0078$), and three
548 variants replicated, at nominal significance. Although sample sizes were generally small for the non-
549 Europeans, here too, the direction of effect was generally concordant with the discovery (*sign test*, $P =$
550 0.039). Five nominally significant associations were detected across all three ethnicities.

551 Next we were able to map the association to novel variants for two previously identified loci at
552 chromosome 17q21 (rs199525; $P = 3.8 \times 10^{-21}$) and 6q22 (rs11759026; $P = 2.2 \times 10^{-20}$)^{6,7}. The five
553 novel loci were on chr 6q21 (rs2022464; $P = 3.7 \times 10^{-11}$), chr 10q24 (rs11191683; $P = 1.1 \times 10^{-10}$), chr
554 3q28 (rs9811910; $P = 2.0 \times 10^{-9}$), chr 12q14 (rs138074335/ rs7312464; $P = 6.2 \times 10^{-9}$), and chr 12q23
555 (rs2195243; $P = 1.5 \times 10^{-8}$). Functional annotation of the variants and those in LD ($r^2 > 0.8$) can be
556 found in **Supplementary Table S4**.

557 Height-adjusted analyses

558 Four of the seven loci for intracranial volume were previously discovered for height (17q21, 6q22,
559 6q21, and 12q14), prompting us to investigate genome-wide overlap between the two traits. As height
560 and intracranial volume are correlated (weighted average Pearson's $r = 0.556$; **Supplementary Table**
561 **S5**) and this could drive association signals, we performed a GWAS of intracranial volume adjusted
562 for height in the studies that had measured height ($N = 21,875$). Findings were compared to the
563 corresponding subset of studies without adjustment ($N = 22,378$). Using LD score regression (**Online**

564 **Methods**), we found that there is considerable genetic correlation between intracranial volume and
565 height ($\rho_{\text{genetic}} = 0.241$, $P = 2.4 \times 10^{-10}$), which disappears after adjusting for height ($\rho_{\text{genetic}} = 0.049$, $P =$
566 0.21) (**Table 2**). The associations of the seven intracranial volume loci, however, remained significant
567 after adjusting for height (**Supplementary Table S6**). To investigate whether more height loci were
568 associated with intracranial volume independently of height, we analyzed all 697 genome-wide
569 significant height variants¹³. An additional 73 variants (10.7%; 14 variants not available) showed
570 nominally significant associations with intracranial volume but were not attenuated after adjustment
571 for height, although none survived Bonferroni correction (**Supplementary Table S7**). For some
572 variants, the direction of effect was discordant, i.e. positive for height and negative for intracranial
573 volume. Furthermore, a polygenic score of the 697 variants predicted intracranial volume, and this
574 was also the case after adjustment for height in a subset of the studies (**Supplementary Table S8**).

575 **Genetic correlation**

576 In addition to height, we examined the genome-wide genetic overlap between intracranial volume and
577 other anthropometric traits, cognitive function, and neurodegenerative diseases (**Table 2**). We found a
578 strong genetic correlation with child head circumference ($\rho_{\text{genetic}} = 0.748$), which validates intracranial
579 volume as a measure of brain growth during early development. Since this high correlation indicates
580 that the genetic determinants of intracranial volume and child head circumference are largely shared,
581 we aimed to leverage this information by performing a meta-analysis of both traits. The meta-analysis
582 (combined $N = 37,345$) led to the identification of four novel loci (**Figure 3; Supplementary Table**
583 **S9**).

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

590 **Enrichment analyses**

591 Next, we assessed whether particular subsets of genetic variants were enriched for association with
592 intracranial volume using partitioned heritability and pathway analyses (**Online Methods**). Overall,
593 we found that common variants genotyped from across the whole genome explained 25.42% (S.E.
594 2.73%) of the variation in intracranial volume. Partitioning heritability by chromosome showed that
595 chromosome 22 contributed twofold more to variation in intracranial volume than would be expected
596 by its size (**Figure 4A**), which was not seen for any of the other complex traits from the genetic
597 correlation analysis (**Supplementary Figure S2**). Partitioning by functional elements showed an
598 enrichment for introns and several histone codes that are found in actively transcribed promoters
599 (**Figure 4B**). The enrichment for intronic variants was specific to intracranial volume, whereas the
600 other functional classes were also enriched in other complex traits (**Supplementary Figure S3**). We
601 also found that loci associated with intracranial volume cluster around genes involved in specific
602 pathways, with 94 pathways significantly enriched (**Figure 4C**; full list in **Supplementary Table**
603 **S10**). These pathways included all cell cycle components – the M-, G1-, S-, and G2-phases – and
604 various growth factor signaling pathways, including PI3K-AKT.

605 **Head growth trajectories**

606 Although intracranial volume reflects brain development until maturation, and we identified
607 influences of many growth-related processes contributing to its variation, all loci were still discovered
608 via cross-sectional associations in adults. Therefore, we tested whether a polygenic score of the 7 loci
609 could predict head growth in a longitudinal cohort of 2,824 children of European ancestry followed
610 prenatally until 6 years of age (**Online Methods**). We found that a higher polygenic score,
611 representing a genetically larger intracranial volume in adults, was also associated with a larger child
612 head circumference ($\beta = .031$ per SD, $P = 0.010$). Furthermore, the effect of the polygenic score was
613 age-dependent and more prominent in older children ($\beta = 0.0080$ per SD polygenic score per year age,
614 $P_{\text{interaction}} = 0.0091$). When investigating the individual loci separately, both 17q21 and 12q14 showed
615 significant associations with child head circumference, but they influenced the trajectories of head
616 growth differently (**Figure 4A-B**). For 17q21, the negative impact of the G allele on head

617 circumference becomes apparent postnatally and increases towards six years, whereas the 12q14 locus
618 exerts an effect from early pregnancy to one year of age, but is less prominent later in life.

619 **DISCUSSION**

620 Genes contributing to variation in the size of the human brain remain challenging to discover. In a
621 worldwide project of unprecedented scale, we performed the largest-ever meta-analysis of genome-
622 wide association studies of intracranial volume. We discovered five novel genetic loci associated with
623 intracranial volume, and replicated two known signals. The discovery sample included Europeans
624 only, but the direction of effect was similar in other ethnicities. The genes in these loci provide
625 intriguing links between maximal brain size and various processes, including neural stem cell
626 proliferation (*FOXO3*), neurodegeneration (*MAPT*), bone mineralization (*CENPW*), growth signaling
627 (*IGF1*, *HMGA2*), DNA replication (*GMNC*), and rRNA maturation (*PDCD*). On a genome-wide
628 scale, we discovered evidence of genetic correlation between intracranial volume and other key traits
629 such as height and cognitive function, and also with Parkinson's disease, indicating that the genes
630 underlying brain development have far-reaching effects well beyond the initial years of life.

631 The 17q21 locus tags a 1Mb inversion that is under positive selection in Caucasians¹⁴. It contains
632 multiple genes including the *MAPT* and *KANSLI*. The *MAPT* gene is consistently implicated in
633 various neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, and
634 frontotemporal dementia^{15,16}, and microduplications have been reported to cause microcephaly¹⁷.
635 *KANSLI* causes the reciprocal 17q21.31 microdeletion syndrome - a multisystem disorder with
636 intellectual disability, hypotonia and distinctive facial features¹⁸. The signal at 6q22 is intergenic to
637 *CENPW* and *RSPO3*, but now lies 172kb closer to *CENPW*. Interestingly, multiple variants at this
638 locus independently influence bone mineral density^{19,20}, and our signal particularly overlaps with the
639 variant showing high specificity for the skull²⁰.

640 The significant variants at chr 6q21 span *FOXO3*, a gene associated with longevity²¹, height¹³, and
641 serum IGF1 levels²². *FOXO3* regulates the proliferation of neural stem cells, and knockout mice show
642 larger brains resulting from increased proliferation immediately after birth²³, followed by a decrease
643 in adult neural stem cell renewal^{23,24}. The rs3800229 variant in strong LD with our top variant ($r^2 =$

644 0.84) contains chromatin promoter marks in the fetal brain (**Supplementary Table S4**), and regulates
645 serum IGF1 levels in infants²⁵. This provides a link to the genome-wide significant locus on chr12q23
646 near *IGF1*, pointing to a potential mechanism through which these loci may affect brain growth.
647 Chr12q23 lies 20Mb from one of two loci previously detected for head circumference in children²⁶,
648 but that region was not associated with intracranial volume in our study (rs7980687; P = 0.06). The
649 other reported child head circumference locus, however, corresponded to our chr12q14 signal, with
650 the top variant lying 14kb downstream of *HMGA2*, and already showed suggestive association with
651 intracranial volume in a previous report⁷. It has also previously been associated with height¹³ and is
652 essential for growth²⁷. The chr10q24 LD-block covers multiple genes, but an intronic variant within
653 *PDCD11* is most significant. *PDCD11* encodes an NF-kappa-B-binding protein required for rRNA
654 maturation and generation of 18S rRNA²⁸. A variant in LD (rs7894407) has recently been identified in
655 a GWAS of cerebral white matter hyperintensities²⁹. The top chr3q28 variant is located upstream of
656 *GMNC*, which codes for the geminin coiled-coil domain-containing protein essential for DNA
657 replication³⁰.

658 Prior efforts to identify variants affecting intracranial volume were much smaller and critically did not
659 adjust for height⁶⁻⁹. We found that 4 out of 7 loci were already discovered for height¹³, but also that
660 over 10% of the known ‘height loci’ actually affect intracranial volume, even after regressing out
661 height. Interestingly, some variants showed discordant associations for height and intracranial volume
662 - in line with the recent finding that different height loci disproportionately affect either leg length or
663 spine/head length³¹ and may be a marker for pathological development³². Also, height might thus
664 serve as a proxy phenotype for intracranial volume, with the tenfold larger sample of the height
665 GWAS giving greater power to detect associations. Neural genes are also enriched in pathway
666 analyses of height¹³. However, to fully disentangle whether these identified genes are ‘height genes’,
667 ‘brain volume genes’, or ‘growth genes’ (i.e., pleiotropic), a large collaborative effort is needed that
668 examines the association of these variants with both intracranial volume and height under various
669 models.

670 When investigating genome-wide overlap with other traits, we found a strong correlation with child
671 head circumference, underlining that intracranial volume is valid measure for maximal attained brain

672 size. We were able to leverage this genetic link by meta-analyzing both traits, which led to the
673 identification of four additional loci (2q32.1, 3q23, 7p14.3, 22q13.2). The correlations with birth
674 length and weight were weaker and decreased further after adjusting for height, so a similar
675 phenotypic correlation between head size and body size at younger age may drive these correlations.
676 Intracranial volume was also genetically associated with cognitive function in childhood as well as
677 general cognitive function in middle-aged and older individuals. This indicates that variation in
678 maximally attained brain size during development shares a genetic basis with cognitive ability later in
679 life and supports intracranial volume as a measure of brain reserve⁵.

680 The brain reserve hypothesis states that premorbid brain size can modify resilience to age-related
681 brain pathology³³, but there was no indication of a genome-wide overlap with Alzheimer's disease.
682 However, we found a positive genetic correlation with Parkinson's disease that rather points to a brain
683 "overgrowth" hypothesis. Interestingly, the IGF1 and the PI3K-AKT pathways, key factors in both
684 growth signaling and our current study of intracranial volume, are neuroprotective in a model system
685 of Parkinson's disease³⁴. There were no correlations with other neurological or psychiatric traits,
686 indicating that this finding might be specific to Parkinson's disease. However, it is important to note
687 that there is a certain extent of variation in the sample size and power of these studies, and larger
688 GWAS might reveal genetic correlation with other traits as well.

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

695 The pathway analyses highlight cellular growth and proliferation and included all components of the
696 cell cycle (M-, G1-, S-, and G2-phase) and various growth factor signaling pathways. PI3K-AKT
697 signaling has a well described role in brain overgrowth disorders^{35,36}, and was the only significant
698 pathway using a different pathway analysis method (**Supplementary Table S11**). Interestingly, *AKT3*

699 intronic variants showed suggestive evidence for association with intracranial volume (rs7538011; P =
700 9.2×10^{-7}). Deletions of *AKT3* cause microcephaly syndromes³⁷, whereas duplications give rise to
701 macrocephaly³⁸. Similar to *FOXO3*, it is part of the IGF1 signaling pathway, which is important for
702 human longevity³⁹. The PI3K-AKT signaling pathway seems to have an important role in brain
703 growth, not only in pathological extremes, but also for normal variation at a population level. Other
704 pathways enriched for association with intracranial volume highlight neuronal functions such as
705 neurotransmission and axon guidance.

706 We identified novel loci all influencing intracranial volume and, at a genome-wide level, there seem
707 to be common pathways, but our longitudinal study reveals that their developmental effects are
708 complex. The loci influenced trajectories of head growth differently; it also would be interesting to
709 investigate whether their spatial profiles of effects are distinct, where certain loci promote growth of
710 particular brain regions.

711 Here we identified key genetic loci implicated in intracranial volume within a global collaborative
712 effort, followed by computational analyses to determine the important biological pathways and
713 functional elements. While the majority of the genetic variants are yet to be discovered, it is clear that
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717

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1082

1083 Published GWASs used for genetic correlation analysis

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1111

1112

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1114 The authors declare no competing financial interest related to any of the work described in this
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1116

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1213 **FIGURE LEGENDS**

1214 **Figure 1. Common genetic variants associated with intracranial volume.**

1215 Manhattan plot where every point represents a single genetic variant plotted according to its genomic
1216 position (*x*-axis) and its $-\log_{10}(\text{p-value})$ for association with intracranial volume (*y*-axis). Variants in
1217 blue are genome-wide significant in a previously known locus, whereas red variants reach genome-
1218 wide significant for the first time in that locus. The dashed horizontal line represents a significance
1219 threshold of $\text{p-value} < 10^{-6}$ and the full horizontal line represents genome-wide significance of p-value
1220 $< 5 \times 10^{-8}$. Variants surpassing these thresholds are indicated by larger points.

1221 **Figure 2. Regional association and functional annotation of novel genome-wide significant loci.**

1222 Regional association plots for the five novel genome-wide significant loci of intracranial volume with
1223 gene models below (GENCODE version 19). Annotation tracks below from the Roadmap
1224 Epigenomics Consortium⁵⁷ highlight the genomic region that likely harbors the causal variant(s) ($r^2 >$
1225 0.8 from the top SNP). See **Online Methods** for detailed track information. Plots were generated
1226 using the LocusTrack software (<http://gump.qimr.edu.au/general/gabrieC/LocusTrack/>).

1227 **Figure 3. Meta-analysis of intracranial volume and child head circumference.**

1228 A ‘twin’ Manhattan plot shows every variant twice: once for the discovery analysis and once for the
1229 combined discovery plus replication analysis. The least significant association of the variant-pair is
1230 plotted in grey (alternating light and dark between chromosomes). The most significant association of
1231 the variant-pair is plotted in red if it is from the combined analysis (i.e., the association became more
1232 significant after meta-analyzing with the child head circumference GWAS) and in turquoise if it is
1233 from the discovery analysis (i.e., the association became less significant after meta-analyzing with the
1234 child head circumference GWAS). The dashed horizontal line represents a significance threshold of p-
1235 $\text{value} < 10^{-6}$ and the full horizontal line represents genome-wide significance of $\text{p-value} < 5 \times 10^{-8}$.
1236 Variants surpassing these thresholds are indicated by larger and brighter points.

1237 **Figure 4. Enrichment analyses of common variants associated with intracranial volume.**

1238 Enrichment of subsets of variants for association with intracranial volume: A) by chromosomes, B) by
1239 functional subtype, and C) by pathway. See **Online Methods** for additional information.

1240 **Figure 5. Temporal trends of intracranial volume loci during pre- and postnatal brain**
1241 **development.**

1242 Mean predicted values of standardized head circumference using linear mixed models with age, sex,
1243 and the rs199525 or rs138074335 variants. The blue line represents children not carrying the risk
1244 allele, purple only a single risk allele, and red with two risk alleles. See **Online Methods** for
1245 additional information. Total sample size is 2,824.

1246 TABLES

1247 **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 (N=26,577)		European replication (N=2,363)		African generalization (N=938)		Asian generalization (N=955)		Hispanic generalization (N=1605)	
						β	P	β	P	β	P	β	P	β	P
rs199525	17q21	44847834	T	G	0.80	.102	3.8×10^{-21}	.024	0.407	.358	1.3×10^{-3}	.264	0.406	.035	0.493
rs11759026	6q22	126792095	A	G	0.76	-.095	2.2×10^{-20}	-.019	0.528	-.131	0.194	-.071	0.123	-.046	0.209
rs2022464	6q21	108945370	A	C	0.30	-.063	3.7×10^{-11}	-.090	4.7×10^{-3}	-.060	0.233	-.105	0.035	-.088	0.013
rs11191683	10q24	105170649	T	G	0.33	.059	1.1×10^{-10}	.040	0.174	.187	0.021	.085	0.075	-.005	0.911
rs9811910	3q28	190670902	C	G	0.08	.096	1.2×10^{-9}	.075	0.010	.346	0.020	.101	0.621	-.148	0.187
rs138074335	12q14	66374247	A	G	0.59	.051	6.2×10^{-9}	.106	2.9×10^{-4}	-.016	0.735	-.004	0.951	.001	0.984
rs2195243	12q23	102922986	C	G	0.22	-.059	1.5×10^{-8}	-.044	0.132	.037	0.585	-.020	0.774	-.093	0.101

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1249 *Abbreviations: A1 = effect allele, A2 = reference allele, Freq = frequency of the effect allele, SE = standard error, N = sample size.*

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1256 **Table 2.** Genetic correlation between intracranial volume and other anthropometric traits, cognitive function, and neurodegenerative diseases.

Phenotype	N total	N cases	Intracranial volume Full sample (N=26,577)			Intracranial volume Height subset (N=22,378)			Intracranial volume Height adjusted (N=21,875)		
			ρ_{genetic}	SE	P	ρ_{genetic}	SE	P	ρ_{genetic}	SE	P
Anthropometric traits											
Adult height	253,280	-	.249	.037	1.4x10⁻¹¹	.241	.038	2.4x10⁻¹⁰	.049	.039	0.21
Child head circumference	10,768	-	.748	.121	5.5x10⁻¹⁰	.758	.124	1.1x10⁻⁹	.750	.126	2.5x10⁻⁹
Birth length	28,459	-	.296	.087	6.7x10⁻⁴	.278	.087	1.3x10⁻³	.192	.088	0.029
Birth weight	26,836	-	.285	.081	4.4x10⁻⁴	.219	.082	7.9x10⁻³	.160	.086	0.062
Neurological traits											
Childhood cognitive function	12,441	-	.277	.090	2.2x10⁻³	.277	.091	2.5x10⁻³	.257	.090	4.2x10⁻³
Adult cognitive function	53,949	-	.202	.059	6.3x10⁻⁴	.205	.060	6.0x10⁻⁴	.198	.059	6.9x10⁻⁴
Alzheimer's Disease	54,162	17,008	-.070	.097	0.47	-.049	.097	0.61	-.043	.098	0.66
Parkinson's Disease	108,990	13,708	.315	.063	6.6x10⁻⁷	.316	.070	5.5x10⁻⁶	.335	.072	3.0x10⁻⁶
White matter lesions	17,936	-	.112	.075	0.13	.111	.078	0.16	.096	.079	0.23
Psychiatric traits											
Autism	10,263	4,949	-.011	.069	0.87	-.036	.074	0.63	.026	.071	0.72
Bipolar disorder	11,810	6,990	.070	.071	0.33	.007	.075	0.93	-.004	.076	0.95
Major depressive disorder	16,610	9,227	.002	.100	0.98	.025	.098	0.80	.005	.096	0.96
Schizophrenia	17,115	9,379	.054	.056	0.33	.017	.058	0.77	-.009	.058	0.87
Extraversion	63,030	-	-.041	.092	0.65	-.101	.095	0.29	-.097	.092	0.29
Neuroticism	63,661	-	-.017	.109	0.87	.035	.106	0.74	.070	.111	0.53

1257

1258 Genetic correlation between various phenotypes and intracranial volume in the complete discovery sample (“Full sample”), adjusted for height in
1259 the studies that had measured height (“Height adjusted”), and the corresponding subset of studies without adjustment (“Height subset”).

1260 *Abbreviations: SE = standard error.*

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1263 **ONLINE METHODS**

1264 **Study population**

1265 This study reports data on 32,438 subjects from 52 study sites that are part of the Cohorts for Heart
1266 and Aging Research in Genomic Epidemiology (CHARGE)¹⁰ consortium and Enhancing
1267 NeuroImaging Genetics through Meta-Analysis (ENIGMA)¹¹ consortium. Briefly, the CHARGE
1268 consortium is a collaboration of predominantly population-based cohort studies that investigate the
1269 genetic and molecular underpinnings of age-related complex diseases, including those of the brain.
1270 The ENIGMA consortium brings together numerous studies, mainly with a case-control design, which
1271 performed neuroimaging in a range of neuropsychiatric or neurodegenerative diseases, as well as
1272 healthy normative populations. Studies participated in either the discovery cohort of European
1273 ancestry, the replication in European ancestry, or the generalization to other ethnicities. An overview
1274 of the demographics and type of contribution for each cohort is provided in **Supplementary Table**
1275 **S1**. Written informed consent was obtained from all participants. Each study was approved by the
1276 respective Institutional Review Board or Local Ethics Committee.

1277 **Genetics**

1278 Genotyping was performed using a variety of commercial arrays across the contributing sites. Both
1279 samples as well as variants underwent similar quality control procedures based on genetic
1280 homogeneity, call rate (less than 95%), minor allele frequency (MAF < 0.01), and Hardy-Weinberg
1281 Equilibrium (HWE p-value less than 1×10^{-6}). Good quality variants were used as input for
1282 imputation to the 1000 Genomes reference panel (phase 1, version 3) using validated software
1283 packages (MaCH/minimac, IMPUTE2, BEAGLE, GenABEL). Variants that were poorly imputed (R^2
1284 < 0.5) or uncommon (MAF < 0.5%) were removed prior to meta-analysis. Full details on the site-
1285 specific genotyping and quality control may be found in **Supplementary Table S2**.

1286 **Imaging**

1287 Magnetic resonance imaging (MRI) was obtained from scanners with a diversity of manufacturers,
1288 field strengths, and acquisition protocols. Images were used to estimate milliliters of intracranial

1289 volume from automated segmentations generated by freely available or in-house methods that have
1290 been described and validated earlier. Most sites measured intracranial volume for each participant by
1291 multiplying the inverse of the determinant of the transformation matrix required to register the
1292 subject's MRI scan to a common template by the template volume (1,948,105 mm³), using the
1293 FreeSurfer software. Visual inspections were performed to identify and remove poorly segmented
1294 images. Either all scans were visually inspected, or sites generated histogram plots to identify any
1295 outliers, which were defined as individuals with a volume more than three standard deviations away
1296 from the mean. Statistical outliers were only excluded if the segmentations were deemed improper. .
1297 More site-specific information related to the imaging is available in **Supplementary Table S3**.

1298 **Genome-wide association studies**

1299 Genome-wide association studies of intracranial volume were performed for each site separately,
1300 controlling for age, sex, and, when applicable, age², population stratification variables (MDS /
1301 principal components), study site (for multi-site studies only), diagnosis (for case-control studies
1302 only). Studies of unrelated individuals performed a linear regression analyses whereas studies of
1303 related individuals (ASPSFam, BrainSCALE, ERF, GeneSTAR, GOBS, NeuroIMAGE, NTR-Adults,
1304 OATS, QTIM, SYS) used linear mixed models to account for familial relationships. Summary
1305 statistics, including the effect estimates of the genetic variant with intracranial volume under an
1306 additive model, were exchanged to perform a fixed-effects meta-analysis weighting for sample size in
1307 METAL⁴⁰. After the final meta-analysis, variants were excluded if they were only available for fewer
1308 than 5,000 individuals. Meta-analyses were stratified by race and done separately for discovery,
1309 replication, and generalization samples. Beta coefficients were recalculated from Z-scores, allele
1310 frequencies, and the sample, as described earlier⁴¹ Site-specific quantile-quantile plots were generated
1311 to inspect the presence of genomic inflation. The variance explained by all variants in the GWAS was
1312 estimated using LD score regression^{12,42}. Sensitivity analyses were performed by excluding patients.

1313 **Functional annotation**

1314 All tracks of the regional association plots were taken from the UCSC Genome Browser Human hg19
1315 assembly. *SNPs (top 5%)* shows the top 5% associated variants within the locus and are colored by

1316 their correlation to the top variant. *Genes* shows the gene models from GENCODE version 19. The
1317 tracks give the predicted chromatin states based on computational integration of ChIP-seq data for 12
1318 chromatin marks in various human tissues derived from the Roadmap Epigenomics Consortium⁴³.
1319 Additionally, we used HaploReg version 3 for annotation of the top variants and all variants in LD (>
1320 0.80) (http://www.broadinstitute.org/mammals/haploreg/haploreg_v3.php).

1321 **Genetic correlation**

1322 The genetic correlation analyses were also performed using LD score regression. The GWAS meta-
1323 analysis of intracranial volume, as well as the height adjusted and height subset meta-analyses, were
1324 correlated with published GWAS of the following traits: Child head circumference²⁶, birth weight⁴⁴,
1325 birth length⁴⁵, adult height¹³, childhood cognitive function⁴⁶, adult cognitive function⁴⁷, Alzheimer's
1326 disease⁴⁸, Parkinson's disease⁴⁹, white matter lesions⁵⁰, psychiatric disorders⁵¹, neuroticism⁵², and
1327 extraversion⁵³.

1328 **Enrichment analyses**

1329 To determine whether the intracranial volume association results were enriched for certain types of
1330 genetic variants, we employed two strategies: partitioned heritability and pathway analyses.

1331 Partitioned heritability was calculated using a previously described method⁴². This was done by
1332 partitioning variants by chromosome and by 28 functional classes: coding, UTR, promoter, intron,
1333 histone marks H3K4me1, H3K4me3, H3K9ac5 and two versions of H3K27ac, open chromatin DNase
1334 I hypersensitivity Site (DHS) regions, combined chromHMM/Segway predictions, regions that are
1335 conserved in mammals, super-enhancers and active enhancers from the FANTOM5 panel of samples
1336 (Finucane et al. page 4)⁴². Multiple testing thresholds were calculated accordingly: $P_{\text{thresh}} = 0.05/(22$
1337 $\text{chromosomes}) = 2.27 \times 10^{-3}$ for the chromosomes and $P_{\text{thresh}} = 0.05/(28 \text{ classes}) = 1.79 \times 10^{-3}$ for the
1338 functional classes.

1339 Pathway analyses were performed using the KGG2.5⁵⁴ and MAGENTA⁵⁵ software packages. LD was
1340 calculated based with the 1000 Genomes Project European samples as a reference (see **URLs**).

1341 Variants were considered to be within a gene if they were within 5 kb of the 3'/5' UTR based on

1342 chromosome positions (hg19) coordinates. Gene-based tests were done with the GATES test⁵⁴ without
1343 weighting *P*-values by predicted functional relevance. Pathway analysis was performed using the
1344 HYST test of association⁵⁶. A multiple testing threshold accounting for the number of pathways tested
1345 resulting in a significance threshold of $P_{\text{thresh}} = 0.05/(671 \text{ pathways}) = 7.45 \times 10^{-5}$.

1346 **Head growth trajectories**

1347 Head growth trajectory analyses were done within the Generation R study, a longitudinal cohort study
1348 situated in Rotterdam, the Netherlands. For this analysis we included 2,824 children of European
1349 ancestry followed prenatally until 6 years of age. Head size was measured at the following points:
1350 prenatally (using echo) during the first, second, and third trimester, and postnatally (measuring head
1351 circumference) at 0-2 months, 2 months, 3 months, 4 months, 5-10 months, 10-13 months, 13-17
1352 months, and 5 years of age. We tested whether a polygenic score of the 7 loci, as well as the 7 loci
1353 themselves separately, were related to head growth using linear mixed models and included an
1354 interaction term between time and the genetic score/variant (SAS software). Next, the predicted
1355 values were calculated for each person and plotted over time, stratified by genotype (0/1/2 risk alleles)
1356 using the R software package.

1357 **URLs**

1358 <ftp://pricelab:pricelab@ftp.broadinstitute.org/LDSCORE/>

1359 <http://enigma.ini.usc.edu/protocols/genetics-protocols/>

1360 <http://genenetwork.nl/bloodqtlbrowser/>

1361 <http://gump.qimr.edu.au/general/gabrieC/LocusTrack/>.

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FIGURES

Figure 1. Common genetic variants associated with intracranial volume.

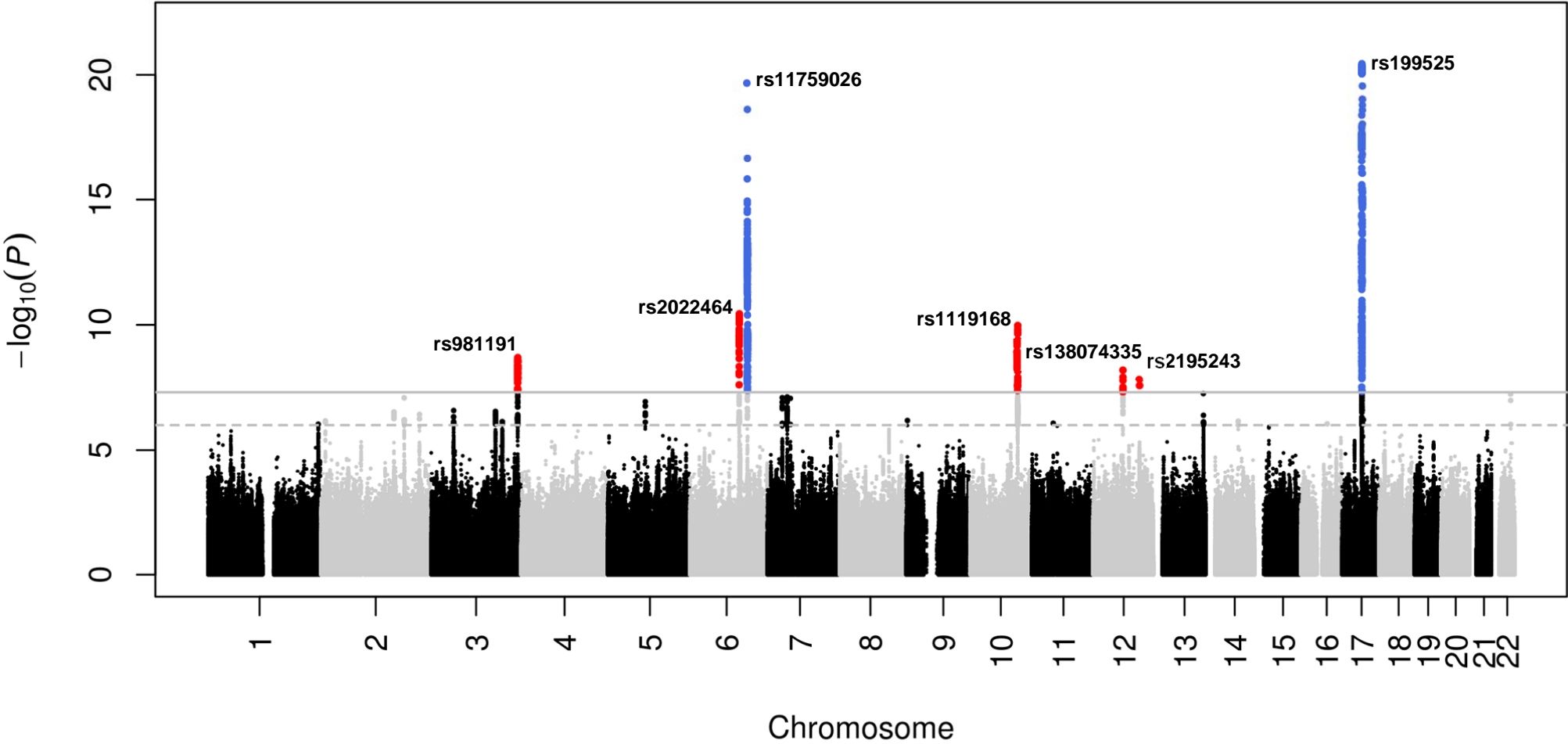
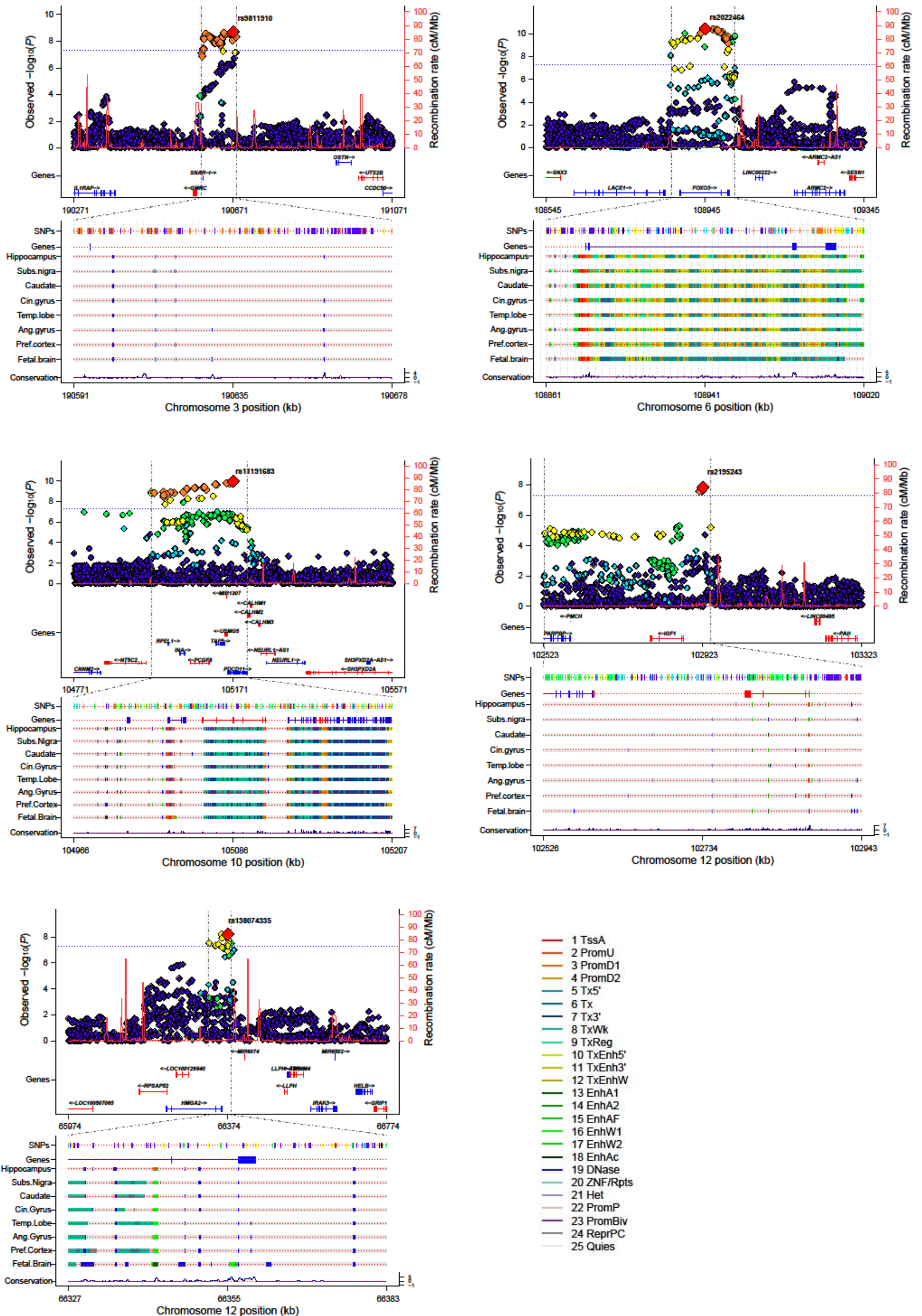


Figure 2. Regional association and functional annotation of novel genome-wide significant loci.



FIGURES

Figure 3. Meta-analysis of intracranial volume and child head circumference.

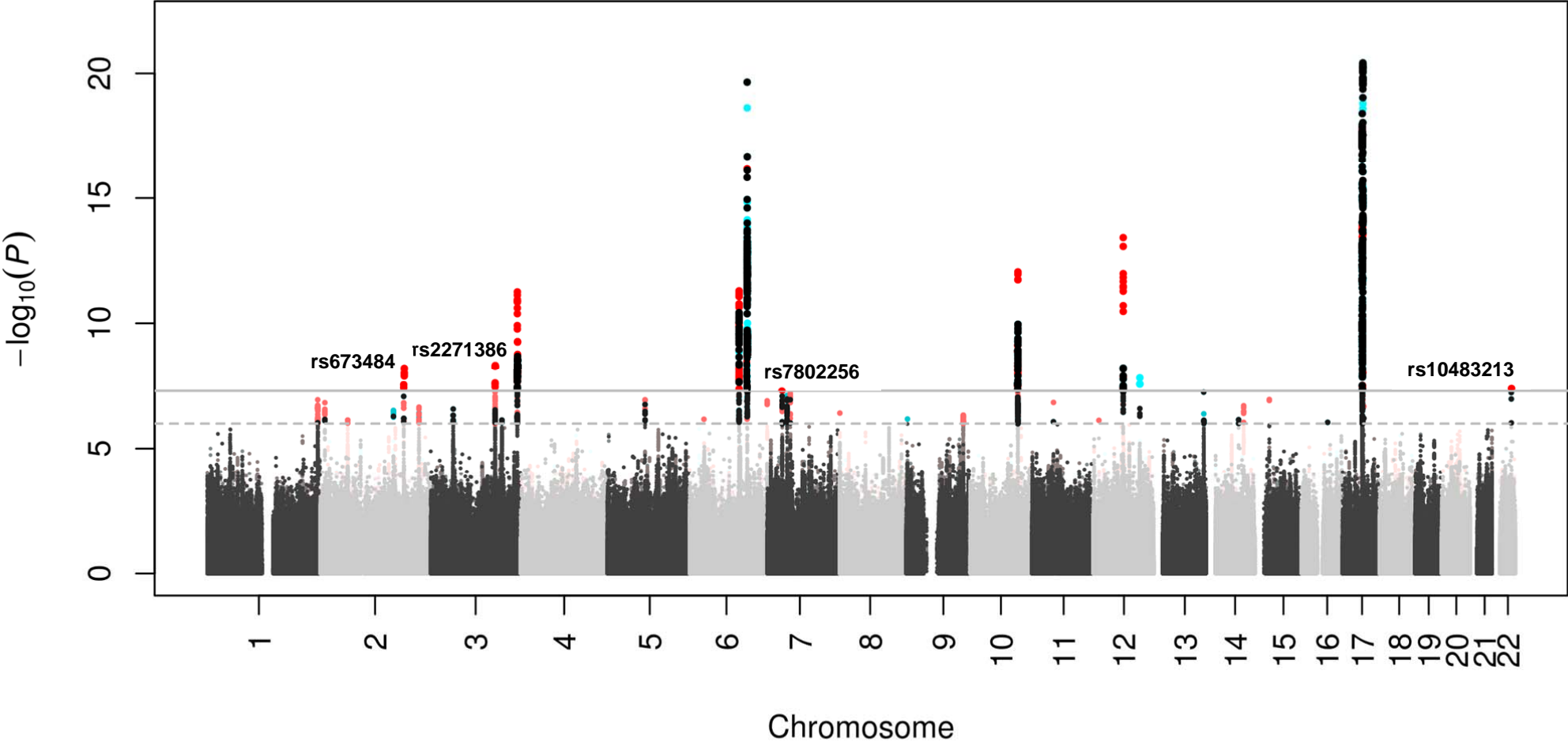


Figure 4. Enrichment analyses of common variants associated with intracranial volume.

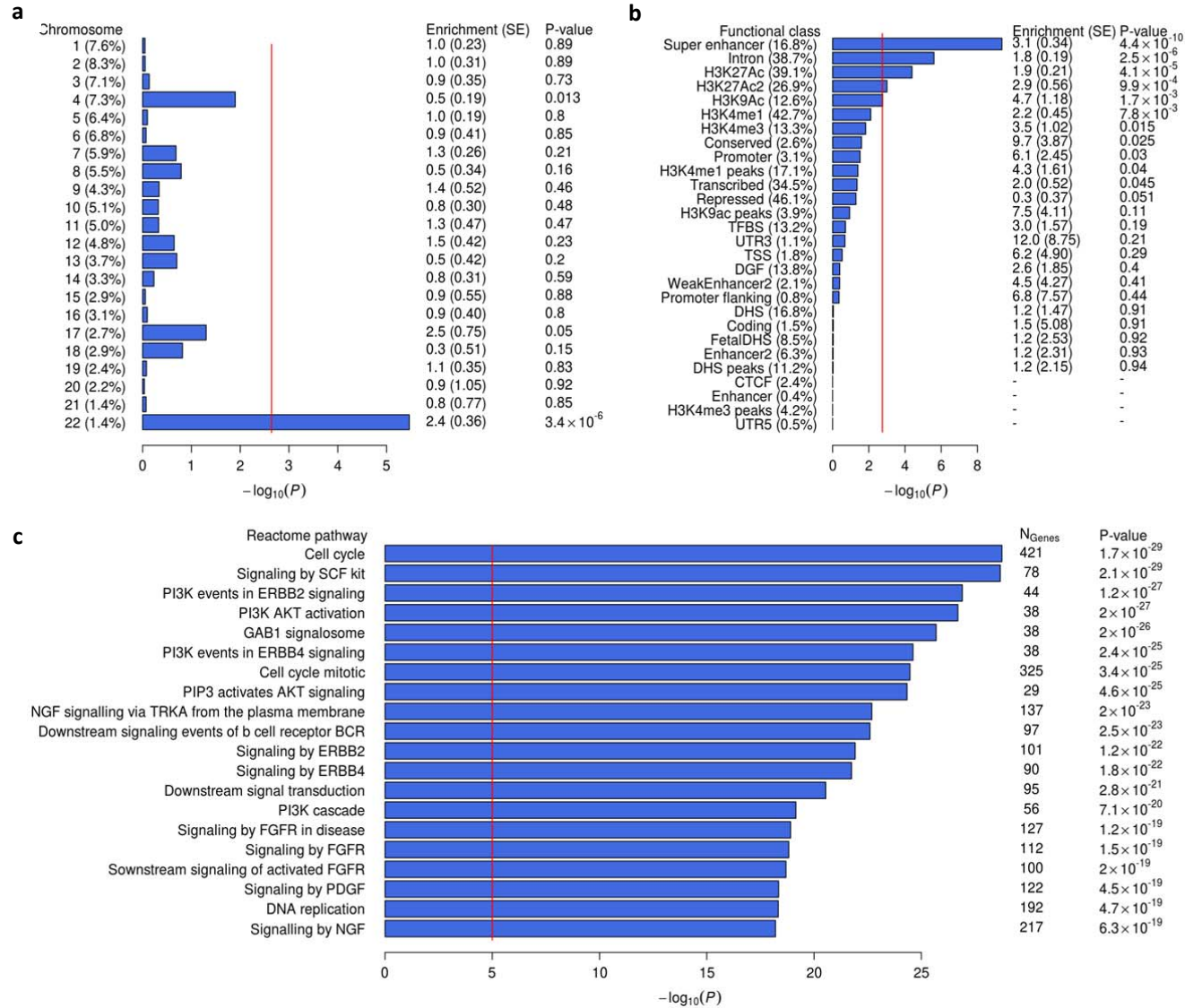


Figure 5. Temporal trends of intracranial volume loci during pre- and postnatal brain development.

