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TITLE

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

SHORT TITLE

Genetics of intracranial volume

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ABSTRACT

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 novel loci for intracranial volume and confirmed two known signals. Four of the loci are 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 ($\rho_{genetic}$=0.748), which indicated a similar genetic background and allowed for the identification of four additional loci through meta-analysis ($N_{combined}$ = 37,345). Variants for intracranial volume were also related to childhood and adult cognitive function, Parkinson's disease, and enriched near genes involved in growth pathways including PI3K-AKT signaling. These findings identify biological underpinnings of intracranial volume and provide genetic support for theories on brain reserve and brain overgrowth.

The intricate genetic control of the human brain, complemented by environmental factors, leads to the observed variations in brain size in human populations[1]. Intracranial volume is closely related to brain volume in early life as the brain grows.[2,3] However, it becomes stable after the brain has fully developed and remains unaffected by later age-related changes such as brain atrophy[4,5], thus 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[6-9].

Here, we performed genome-wide association studies in populations from the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)[10] and Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)[11] consortia on intracranial volume measured by magnetic resonance imaging. Genotypes were imputed to the 1000 Genomes reference panel (phase 1, version 3). Meta-analysis revealed five novel 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 are involved in specific pathways.

RESULTS

Genome-wide association studies

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

The discovery meta-analysis (N = 26,577) yielded seven genome-wide significant ($p < 5 \times 10^{-8}$) loci, five of them novel (**Figures 1-2; Table 1**). The quantile-quantile plot showed inflation ($\lambda = 1.092$; **Supplementary Figure S1**), which we determined to be mainly due to polygenicity rather than cryptic relatedness or population stratification using LD score regression[12]. 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 had the same direction of effect in the additional European samples (*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,* $P = 0.039$). Five nominally significant associations were detected across all three ethnicities.

Next we were able to map the association to novel variants for two previously identified loci at chromosome 17q21 (rs199525; $P = 3.8 \times 10^{-21}$) and 6q22 (rs11759026; $P = 2.2 \times 10^{-20}$)[6,7]. The five novel loci were on chr 6q21 (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 S4.**

Height-adjusted analyses

Four of the seven loci for intracranial volume were previously discovered for height (17q21, 6q22, 6q21, and 12q14), prompting us to investigate genome-wide overlap between the two traits. As height and intracranial volume are correlated (weighted average Pearson's $r = 0.556$; **Supplementary Table S5**) and 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**

564 **Methods**), we found that there is considerable genetic correlation between intracranial volume and
565 height ($\rho_{genetic}$ = 0.241, P = 2.4 x 10^{-10}), which disappears after adjusting for height ($\rho_{genetic}$ = 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 variants[13]. 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 ($\rho_{genetic}$ = 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 ($\rho_{genetic}$ < 0.3), which attenuated after
585 adjusting for height. Additionally, intracranial volume was genetically correlated with cognitive
586 function in childhood ($\rho_{genetic}$ = 0.277, P = 2.2x10^{-3}) as well as general cognitive function in middle-
587 aged and older adults ($\rho_{genetic}$ = 0.202, P = 6.3x10^{-4}). Furthermore, we found a positive genetic
588 correlation with Parkinson's disease ($\rho_{genetic}$ = 0.315, P = 6.6 x 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 (β = .031 per SD, P = 0.010). Furthermore, the effect of the polygenic score was
613 age-dependent and more prominent in older children (β = 0.0080 per SD polygenic score per year age,
614 $P_{interaction}$ = 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

circumference becomes apparent postnatally and increases towards six years, whereas the 12q14 locus exerts an effect from early pregnancy to one year of age, but is 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 genome-wide association studies of intracranial volume. We discovered five novel 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, HMGA2*), 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, and also with Parkinson's disease, indicating that the genes underlying brain development have far-reaching effects well beyond the initial years of life.

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

The significant variants at chr 6q21 span *FOXO3*, a gene associated with longevity[21], height[13], and serum IGF1 levels[22]. *FOXO3* regulates the proliferation of neural stem cells, and knockout mice show larger brains resulting from increased proliferation immediately after birth[23], followed by a decrease 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 infants[25]. 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 children[26],
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 report[7]. It has also previously been associated with height[13] and is
652 essential for growth[27]. 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 rRNA[28]. A variant in LD (rs7894407) has recently been identified in
655 a GWAS of cerebral white matter hyperintensities[29]. The top chr3q28 variant is located upstream of
656 *GMNC*, which codes for the geminin coiled-coil domain-containing protein essential for DNA
657 replication[30].

658 Prior efforts to identify variants affecting intracranial volume were much smaller and critically did not
659 adjust for height[6-9]. We found that 4 out of 7 loci were already discovered for height[13], 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 disproportionally affect either leg length or
663 spine/head length[31] and may be a marker for pathological development[32]. 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 height[13]. 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

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, 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 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[5].

The brain reserve hypothesis states that premorbid brain size can modify resilience to age-related brain pathology[33], 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 that rather points to a brain "overgrowth" hypothesis. Interestingly, 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[34]. 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 larger GWAS might reveal genetic correlation with other traits as well.

It is not yet known if variance in intracranial volume, within 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. While not definitive, these are novel 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-phase) and various growth factor signaling pathways. PI3K-AKT signaling has a well described role in brain overgrowth disorders[35,36], and was the only significant 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 syndromes[37], whereas duplications give rise to
701 macrocephaly[38]. Similar to *FOXO3*, it is part of the IGF1 signaling pathway, which is important for
702 human longevity[39]. 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
714 these will provide better insight into brain development, but also into related neuropsychiatric traits
715 such as cognitive functioning and even for neurodegeneration late in life. Uncovering the remaining
716 heritability will advance our understanding of the brain's complex genetic architecture.
717

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Published GWASs used for genetic correlation analysis

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

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FIGURE LEGENDS

Figure 1. Common genetic variants associated with intracranial volume.

Manhattan plot where every point represents a single genetic variant plotted according to its genomic position (*x*-axis) and its –log10(p-value) for association with intracranial volume (*y*-axis). Variants in blue are genome-wide significant in a previously known locus, whereas red variants reach genome-wide significant for the first time in that locus. The dashed horizontal line represents a significance threshold of p-value < 10^{-6} and the full horizontal line represents genome-wide significance of p-value < 5 x 10^{-8}. Variants surpassing these thresholds are indicated by larger points.

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

Regional association plots for the five novel genome-wide significant loci of intracranial volume with gene models below (GENCODE version 19). Annotation tracks below from the Roadmap Epigenomics Consortium[57] highlight the genomic region that likely harbors the causal variant(s) (r2 > 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/).

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 grey (alternating light and dark between chromosomes). The most significant association of the variant-pair is plotted in red if is from the combined analysis (i.e., the association became more significant after meta-analyzing with the child head circumference GWAS) and in turquoise if it is from the discovery analysis (i.e., the association became less significant after meta-analyzing with the child head circumference GWAS). The dashed horizontal line represents a significance threshold of p-value < 10^{-6} and the full horizontal line represents genome-wide significance of p-value < 5 x 10^{-8}. Variants surpassing these thresholds are indicated by larger and brighter points.

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

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

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 is 2,824.

TABLES

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

						European discovery (N=26,577)		European replication (N=2,363)		African generalization (N=938)		Asian generalization (N=955)		Hispanic generalization (N=1605)	
Genetic variant	**Locus**	**Position**	**A1**	**A2**	**Freq**	**β**	**P**	**β**	**P**	**β**	**P**	**β**	**P**	**β**	**P**
rs199525	17q21	44847834	T	G	0.80	.102	$3.8x10^{-21}$	.024	0.407	.358	$1.3x10^{-3}$	.264	0.406	.035	0.493
rs11759026	6q22	126792095	A	G	0.76	-.095	$2.2x10^{-20}$	-.019	0.528	-.131	0.194	-.071	0.123	-.046	0.209
rs2022464	6q21	108945370	A	C	0.30	-.063	$3.7x10^{-11}$	-.090	$4.7x10^{-3}$	-.060	0.233	-.105	0.035	-.088	0.013
rs11191683	10q24	105170649	T	G	0.33	.059	$1.1x10^{-10}$	.040	0.174	.187	0.021	.085	0.075	-.005	0.911
rs9811910	3q28	190670902	C	G	0.08	.096	$1.2x10^{-9}$	.075	0.010	.346	0.020	.101	0.621	-.148	0.187
rs138074335	12q14	66374247	A	G	0.59	.051	$6.2x10^{-9}$	.106	$2.9x10^{-4}$	-.016	0.735	-.004	0.951	.001	0.984
rs2195243	12q23	102922986	C	G	0.22	-.059	$1.5x10^{-8}$	-.044	0.132	.037	0.585	-.020	0.774	-.093	0.101

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

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

			Intracranial volume Full sample (N=26,577)			Intracranial volume Height subset (N=22,378)			Intracranial volume Height adjusted (N=21,875)		
Phenotype	**N total**	**N cases**	**$\rho_{genetic}$**	**SE**	**P**	**$\rho_{genetic}$**	**SE**	**P**	**$\rho_{genetic}$**	**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

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.*
1261

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)[10] consortium and Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)[11] 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 S1**. 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 1×10^{-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, GenABLE). Variants that were poorly imputed (R^2 < 0.5) or uncommon (MAF < 0.5%) were removed prior to meta-analysis. Full details on the site-specific genotyping and quality control may be found in **Supplementary Table S2**.

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 mm3), 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 three standard deviations 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 S3**.

Genome-wide association studies

Genome-wide association studies of intracranial volume were performed for each site separately, controlling for age, sex, and, when applicable, age^2, 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[40]. 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[41] 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[12,42]. 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[43]. Additionally, 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).

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[26], birth weight[44], birth length[45], adult height[13], childhood cognitive function[46], adult cognitive function[47], Alzheimer's disease[48], Parkinson's disease[49], white matter lesions[50], psychiatric disorders[51], neuroticism[52], and extraversion[53].

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[42]. 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 (Finucane et al. page 4)[42]. Multiple testing thresholds were calculated accordingly: P_{thresh} = 0.05/(22 chromosomes) = 2.27 x 10^{-3} for the chromosomes and P_{thresh} = 0.05/(28 classes) = 1.79 x 10^{-3} for the functional classes.

Pathway analyses were performed using the KGG2.5[54] and MAGENTA[55] software packages. LD was calculated based with the 1000 Genomes Project European samples as a reference (see **URLs**). 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[54] without weighting *P*-values by predicted functional relevance. Pathway analysis was performed using the HYST test of association[56]. A multiple testing threshold accounting for the number of pathways tested resulting in a significance threshold of P_{thresh} = 0.05/(671 pathways) = 7.45 x 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.

URLs

ftp://pricelab:pricelab@ftp.broadinstitute.org/LDSCORE/

http://enigma.ini.usc.edu/protocols/genetics-protocols/

http://genenetwork.nl/bloodeqtlbrowser/

http://gump.qimr.edu.au/general/gabrieC/LocusTrack/).

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FIGURES

Figure 1. Common genetic variants associated with intracranial volume.

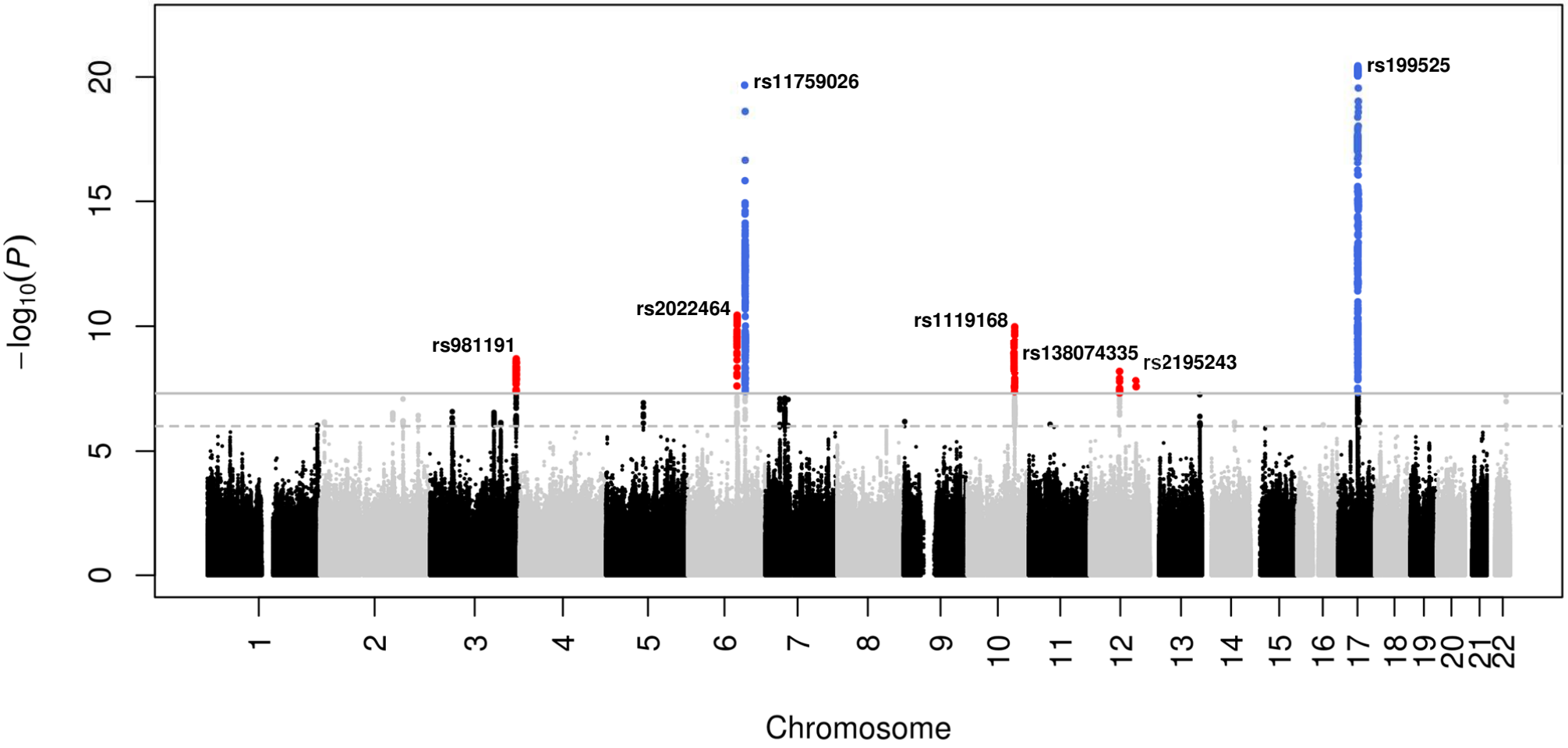
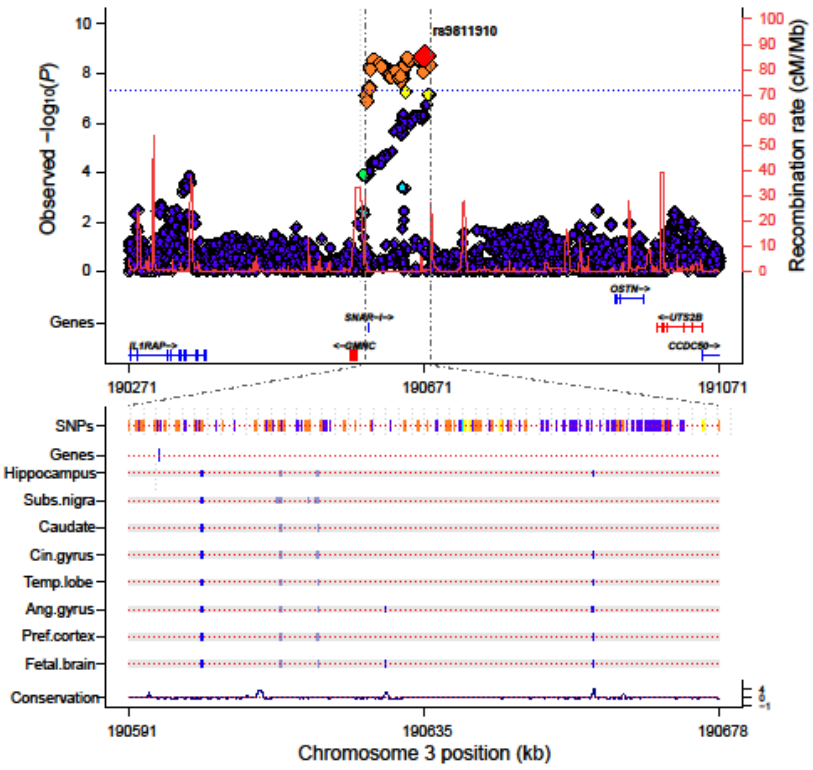
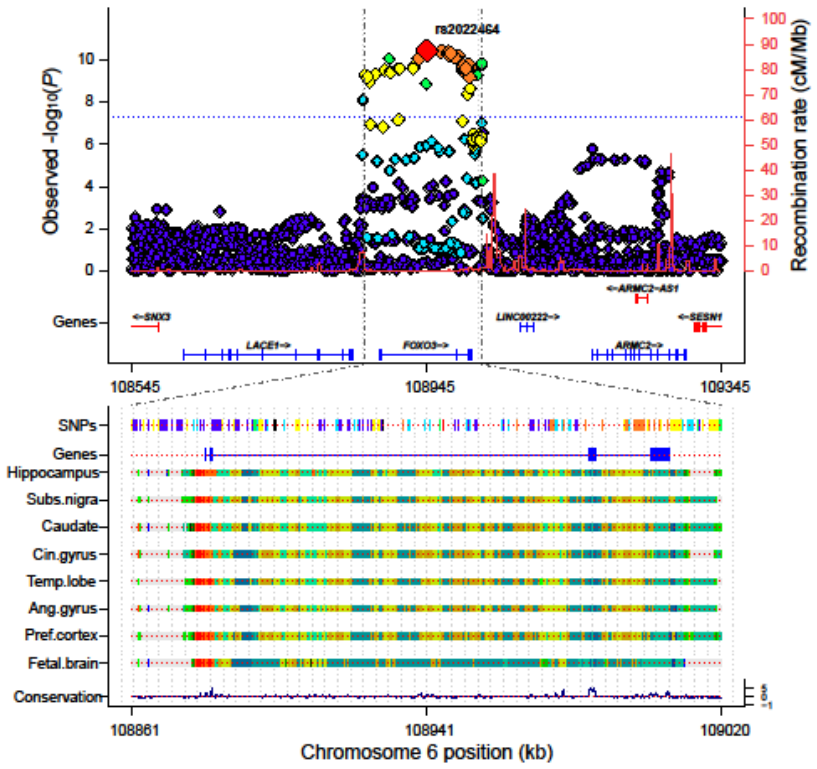
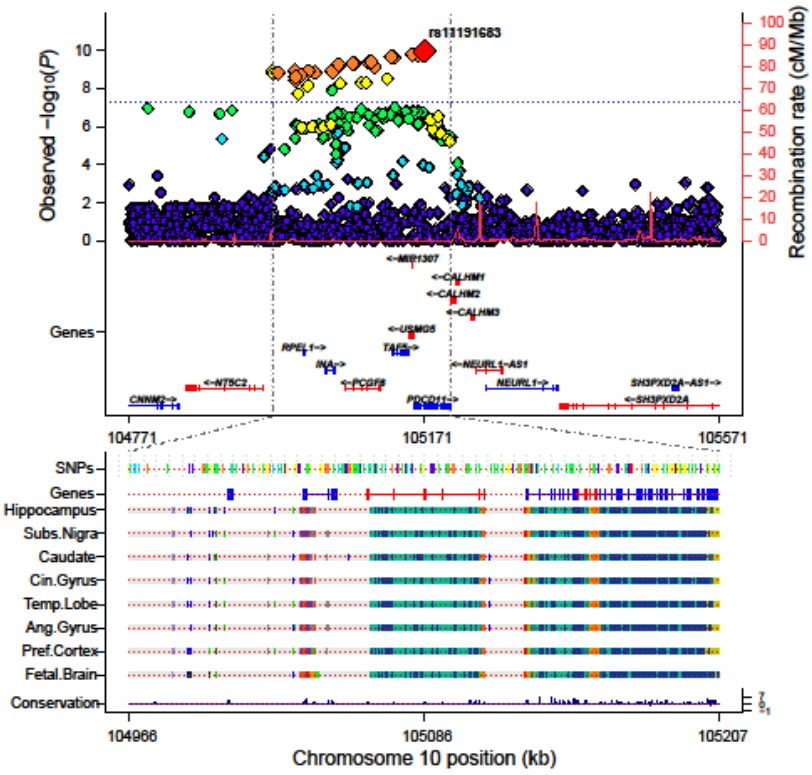
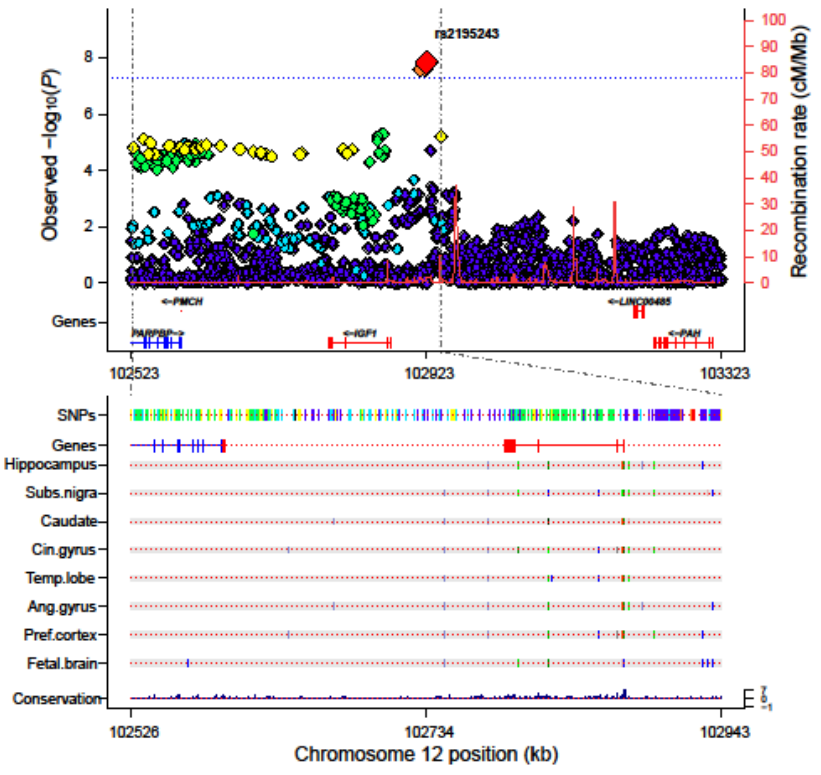


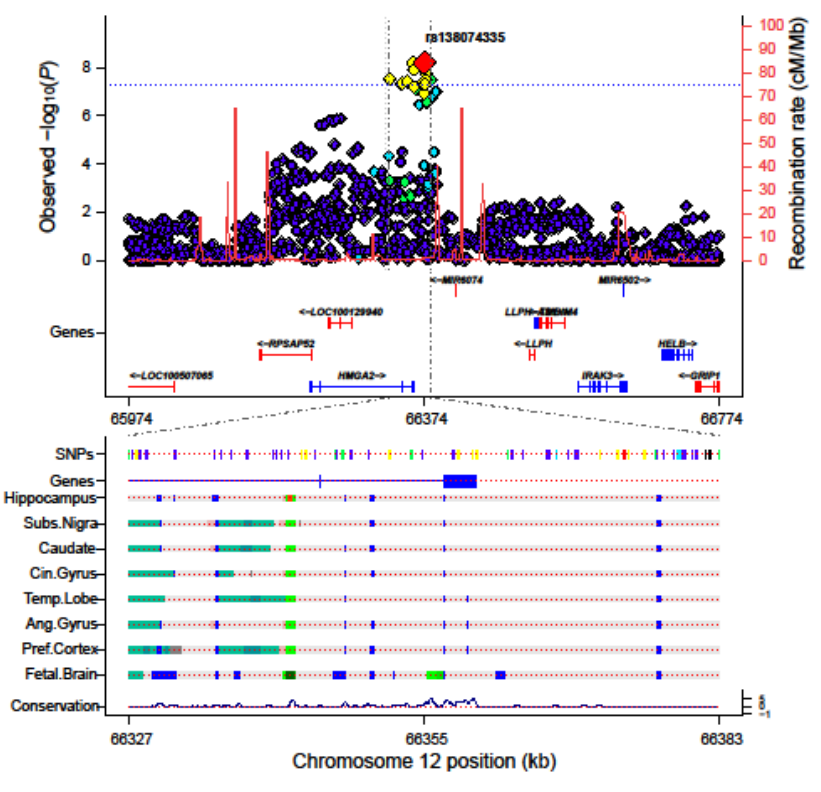
Figure 2. Regional association and functional annotation of novel genome-wide significant loci.











FIGURES

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

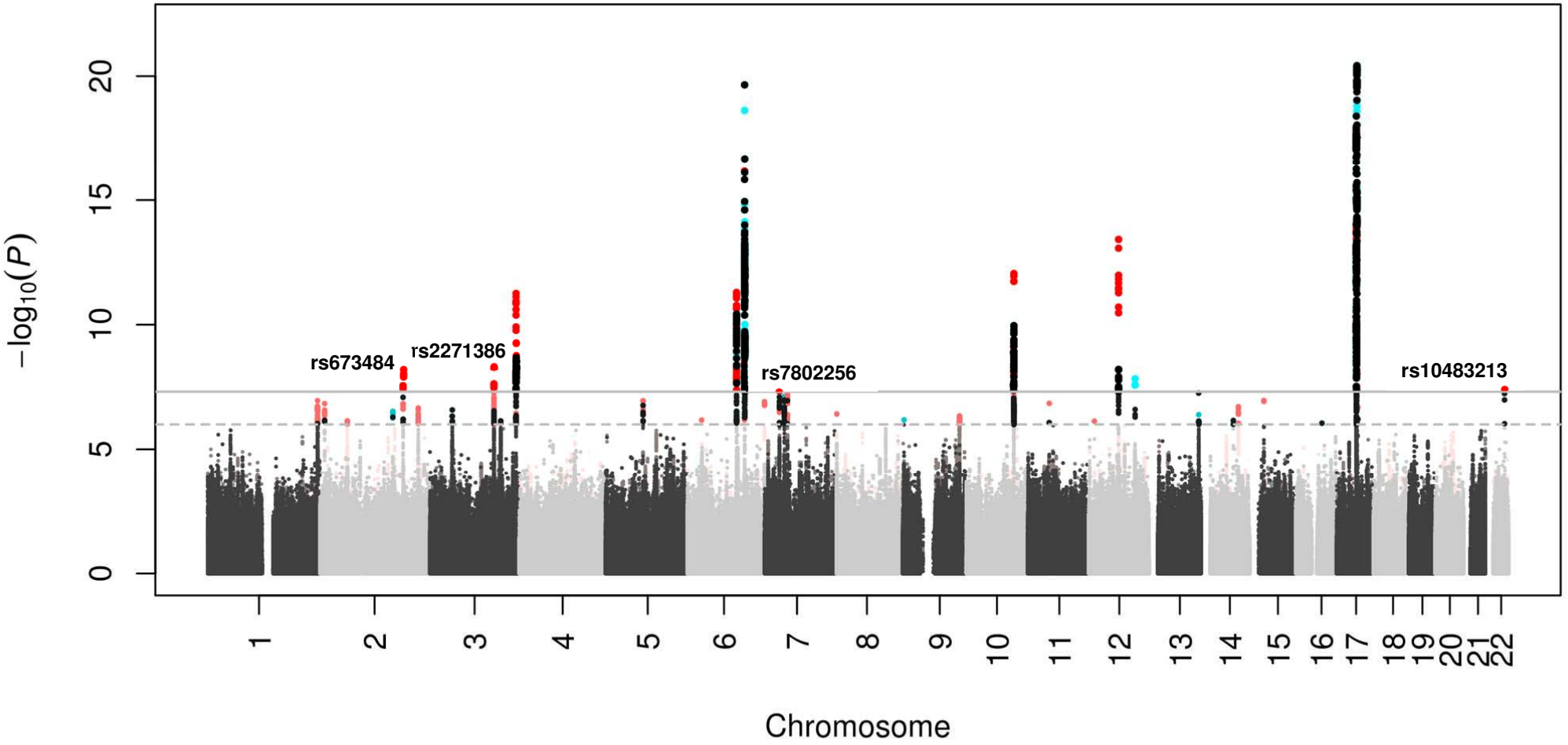


Figure 4. Enrichment analyses of common variants associated with intracranial volume.

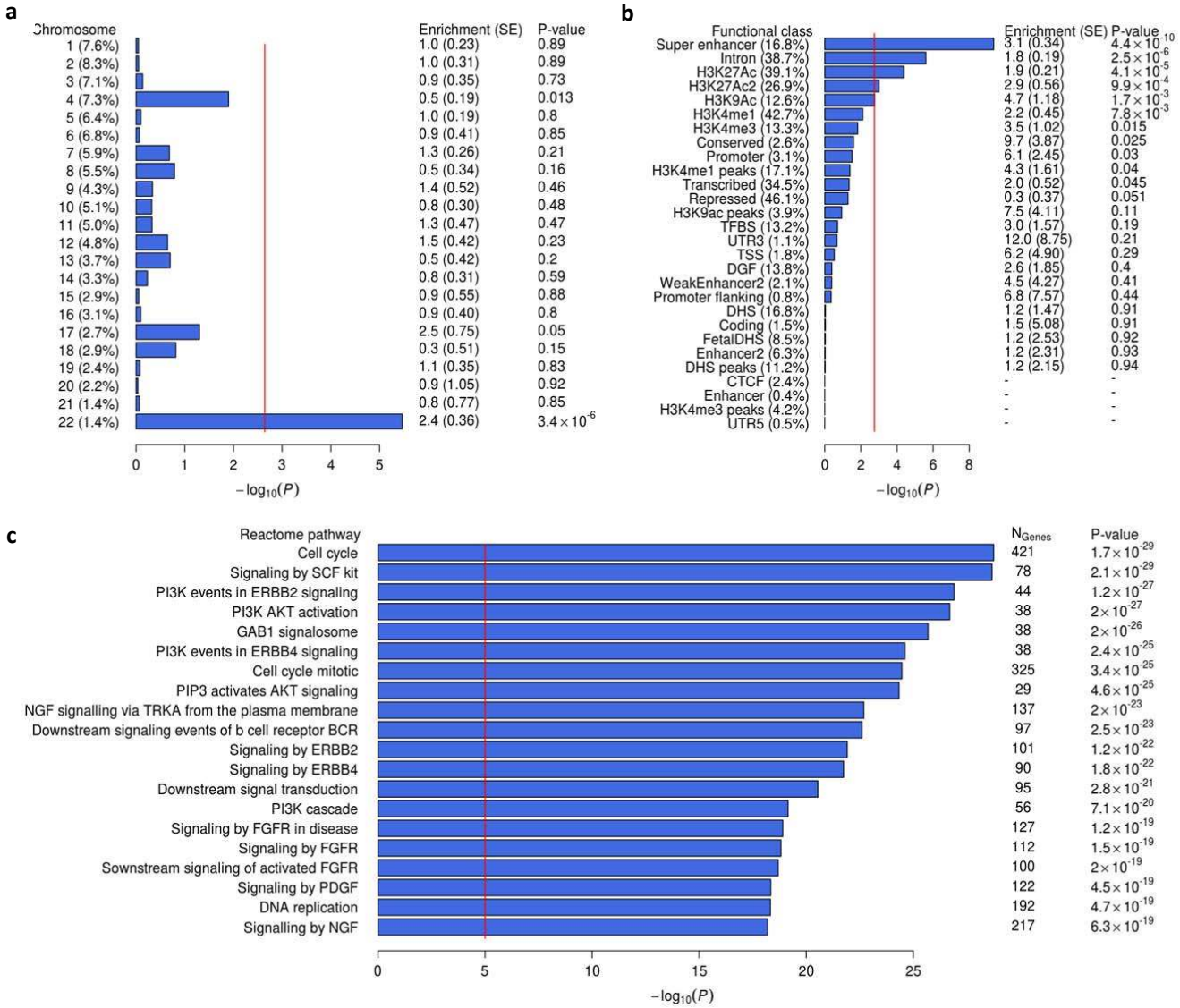


Figure 5. Temporal trends of intracranial volume loci during pre- and postnatal brain development.