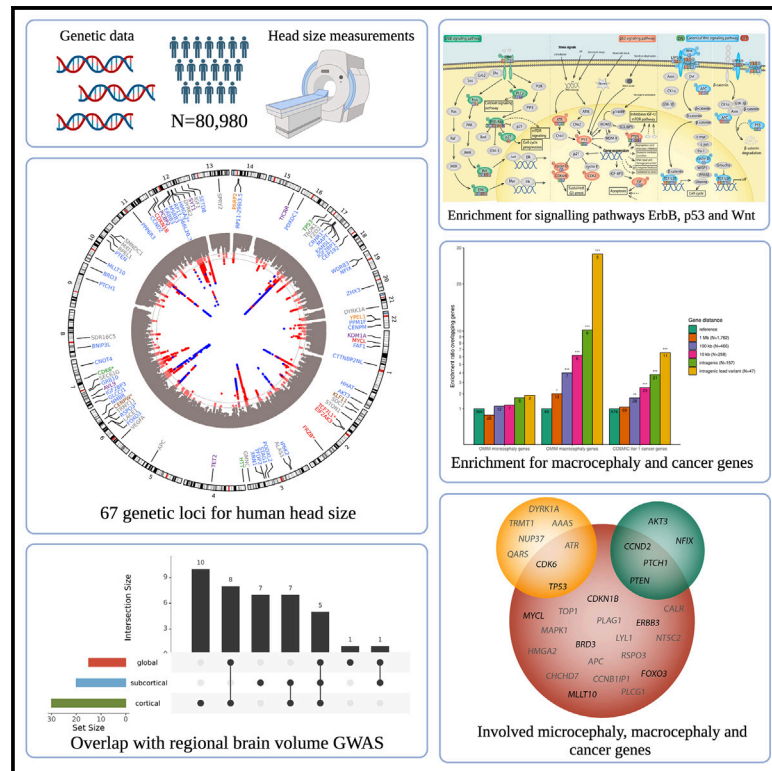


Genetic variants for head size share genes and pathways with cancer

Graphical abstract



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In brief

Knol, Poot, et al. identify 67 loci for human head size in a genome-wide association study. Genes harboring the lead variants enrich for cancer genes and pathways, which was not seen for height variants. These findings suggest a potential link between a larger head and a higher cancer risk.

Highlights

- Knol, Poot, et al. identify 67 genetic loci associated with human head size
- Genes harboring or near head size genetic variants enrich for macrocephaly genes
- Head size genetic variants preferentially locate to cancer genes and pathways
- Further research is needed on the potential link between head size and cancer risk



Report

Genetic variants for head size share genes and pathways with cancer

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SUMMARY

The size of the human head is highly heritable, but genetic drivers of its variation within the general population remain unmapped. We perform a genome-wide association study on head size ($N = 80,890$) and identify 67 genetic loci, of which 50 are novel. Neuroimaging studies show that 17 variants affect specific brain areas, but most have widespread effects. Gene set enrichment is observed for various cancers and the p53, Wnt, and ErbB signaling pathways. Genes harboring lead variants are enriched for macrocephaly syndrome genes (37-fold) and high-fidelity cancer genes (9-fold), which is not seen for human height variants. Head size variants are also near genes preferentially expressed in intermediate progenitor cells, neural cells linked to evolutionary brain expansion. Our results indicate that genes regulating early brain and cranial growth incline to neoplasia later in life, irrespective of height. This warrants investigation of clinical implications of the link between head size and cancer.

INTRODUCTION

The size of the human head, measured by head circumference or intracranial volume, correlates closely with brain size. Head size is

determined by growth in the first years of life and is largely completed by 6 years of age, whereas the rest of the body typically grows until early adulthood.¹ Head size is highly genetically determined, ranging from near 90% during childhood to 75% during



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adulthood.² Rare genetic syndromes have revealed individual genes strongly affecting head size.³ Nevertheless, genetic determinants of its variation within the general population are still poorly characterized, with no coherent and well-supported picture of associated biological pathways.

A previous genome-wide association study (GWAS) on 47,000 individuals identified 18 genetic loci for intracranial volume,⁴ while another GWAS on head size in 46,000 children and adults identified 17 loci for head size including low-frequency variants in *TP53*.⁵ Here, we increased the sample size to a total GWAS discovery sample size of 80,890 individuals, and validated the results in an independent sample of 25,088 individuals. Our GWAS analyses show strong enrichment for genes and multiple pathways involved in cancer, macrocephaly genes, and show preferential expression of genes near variants in intermediate progenitor cells.

RESULTS

We performed a meta-analysis of GWASs for head size, as proxied by intracranial volume from brain imaging, or head circumference (Tables S1–S3 and S4; STAR Methods). Compared with previous efforts,^{5,6} we nearly doubled the sample size ($N = 80,890$), in majority from European ancestry ($N = 75,309$). We identified 90 independent genetic variants in 67 loci associated with human head size in the European sample (Figure 1A; Tables S6–S8; Data S1, S2, and S3), of which 50 loci were novel. Although the results showed some bias (linkage disequilibrium [LD] score regression intercept 1.056; Table S5), the identified variants remained genome-wide significant after correction for this amount of bias. Most variants ($N = 48$) showed consistent directions of association among the European, African ($N = 1,356$), and Asian ($N = 4,225$) ancestry samples (Figure 1B; Table S6), suggesting population-specific genetic effects on head size in these loci. Since we had limited non-European samples, we also tested the combined effect of the lead variants, which showed positive associations in African and East Asian ancestry samples ($\beta_{\text{African}} = 0.34$, confidence interval [CI] 0.08–0.60; $\beta_{\text{East Asian}} = 0.40$, CI 0.24–0.57). In the European validation sample ($N = 25,088$), 20 of the 89 lead variants were associated with head size at a Bonferroni significance level ($p < 5.6 \times 10^{-4}$) and 54 at a nominal significance level, while all lead variants showed the same direction of effect. In the UK Biobank validation sample ($N = 23,046$), the 89 available lead variants together explained 2.3% of the phenotypic head size variance. A meta-analysis combining the European discovery and validation sample ($N = 101,241$) identified 102 genomic loci with 126 lead vari-

ants (Table S8), of which 60 loci overlapped with the 67 genomic loci identified by the discovery meta-analysis.

Head-specific growth vs. general growth

We investigated whether variants affecting head size are specific for growth of the human head or are driven, at least in part, by an effect on human body height. Accordingly, we performed a height-adjusted head size GWAS ($N = 50,424$). The genetic correlation between head size and height ($\rho_{\text{genetic}} = 0.26$, $p = 2.1 \times 10^{-30}$) disappeared in this model ($\rho_{\text{genetic}} = -0.02$, $p = 0.58$) (Figure 1C), confirming the removal of height-associated effects. Importantly, there was no significant reduction for any of the lead variants' effect sizes with head size (Table S6). We further explored the effect of these variants on the size of other body parts using area measures obtained from bone density scans ($N = 3,313$). As expected, a polygenic score of the lead variants was associated with the skull area, even after adjusting for height ($p = 2.1 \times 10^{-12}$). One lead genetic variant (rs12277225) was significantly associated with the L1–L4 spine area ($p = 1.3 \times 10^{-5}$), but the other lead variants did not affect bone area measures of arm, leg, and spine (Table S9). Altogether, this indicates that the effect of the identified variants on head size is predominantly head-specific.

Regional brain volumetric effects

Head size may reflect growth of specific brain regions. Indeed, 15 lead genetic variants or variants in LD ($r^2 > 0.6$) from 12 genetic loci were previously reported to affect volumes of subregions of the brain (Figure 2A; Table S10). We screened all loci previously associated with these regional brain volumes, and found 16 of those 132 loci significantly related with head size after multiple testing correction (Table S11). To determine if the current findings can be localized to specific brain regions, we investigated the 90 independent head size variants in relation to more fine-grained measures of brain morphometry—corrected for head size—in 22,145 individuals (Figure 2B; Table S12). Thirty-nine variants were associated with one or multiple cortical, subcortical, and global brain regions of which 17 variants were preferentially associated with one or two specific cortical or subcortical regions. For example, rs111939932, an intronic variant in *PCBP2*, is associated with nucleus accumbens volume and is an expression quantitative trait locus (eQTL) for several genes, including *ATP5G2* in the nucleus accumbens and basal ganglia. Further analysis revealed its localized effects on this structure's shape (Figure 2C; Table S13). In the largest GWAS on nucleus accumbens volume,⁷ this variant was nominally significant ($p = 0.02$), showing the improved power of our

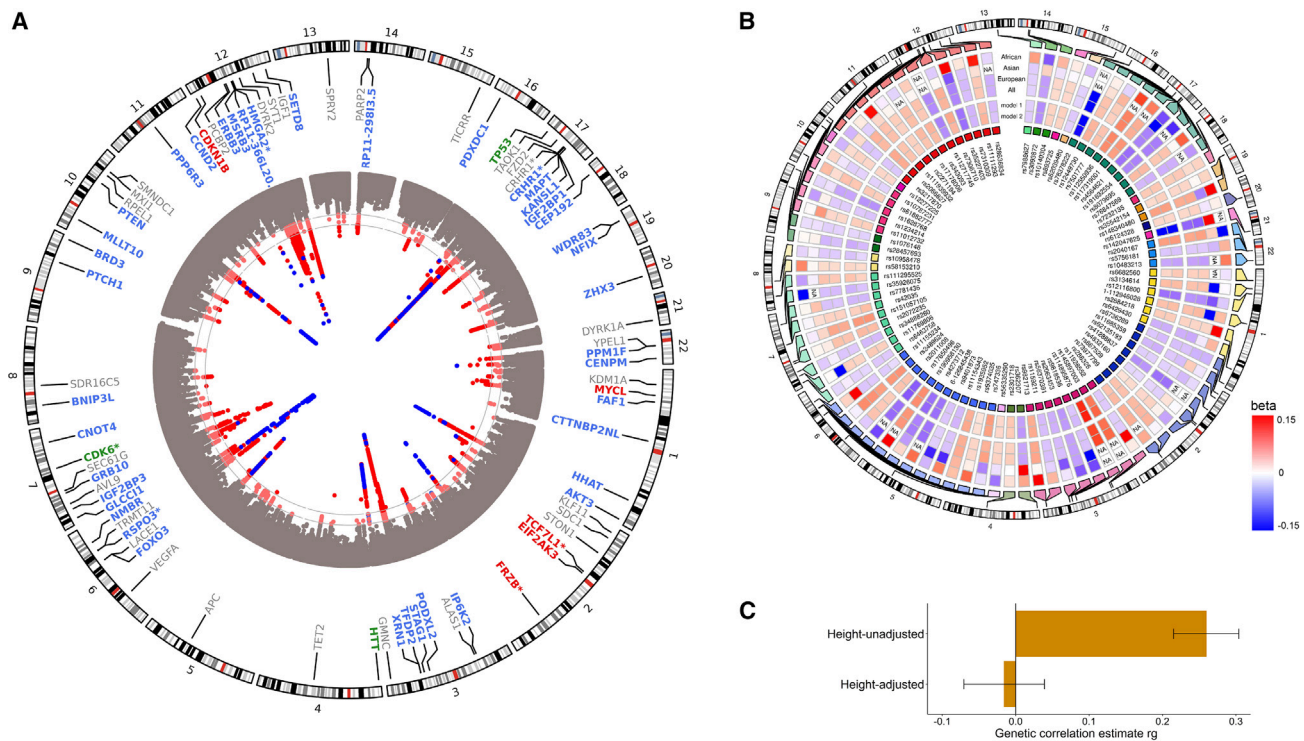


Figure 1. Genome-wide association studies on human head size

(A) Circos Manhattan plot of the European ancestry head size GWAS, with gray lines corresponding to genome-wide significant ($p < 5 \times 10^{-8}$) or sub-significant ($p < 1 \times 10^{-6}$) p value thresholds. Known variants are in blue, novel ones in red. For each lead variant, the nearest gene is presented, with the color corresponding to its position to the lead variant: exonic (red), 3'-UTR (green), intronic (blue), intergenic including up- and downstream, exonic and intronic non-coding RNA (gray). Nearest genes for more than one locus are denoted with an asterisk (*).

(B) Circos heatmap showing the betas of lead variants in African, Asian, and European ancestry meta-analyses, as well as the transancestral meta-analysis. Differences between the height-unadjusted (model 1) and -adjusted (model 2) meta-analysis are also shown.

(C) Bar plot of the genetic correlation coefficient (ρ_{genetic}) of the height-unadjusted and -adjusted head size GWAS with the height GWAS, with their accompanying 95% confidence intervals.

current study to identify novel brain morphometry loci. For the other 51 variants there was no apparent association with particular brain regions. Overall, these results suggest that most head size variants affect generalized brain or cranial growth, while a minority influence regional brain growth.

Genetic correlation with neuropsychiatric traits

Genetic correlation analyses with neuropsychiatric traits have been conducted previously.^{5,6} We replicated positive genetic correlations with cognitive functioning and Parkinson's disease, also when only including new samples (Figure S1; Table S14). The replicated correlation with Parkinson's disease provides independent evidence for the proposed brain overgrowth hypothesis in this disorder.⁸ Novel genetic correlations were found with multiple psychiatric traits; negative correlations with attention-deficit hyperactivity disorder ($\rho_{\text{genetic}} = -0.18, p = 4.5 \times 10^{-7}$), insomnia ($\rho_{\text{genetic}} = -0.19, p = 1.8 \times 10^{-5}$), major depressive disorder ($\rho_{\text{genetic}} = -0.11, p = 2.6 \times 10^{-4}$), and neuroticism ($\rho_{\text{genetic}} = -0.11, p = 5.4 \times 10^{-4}$) (Figure S1; Table S14). Since psychiatric disorders themselves are genetically correlated, incorporating head size and other brain anatomy traits could aid in disentangling underlying genetic factors.

Pathway analysis

To obtain novel insights into the biological mechanisms underlying head size variation, we performed a gene set enrichment analysis of Kyoto Encyclopedia of Genes and Genomes (KEGG)⁹ gene sets and found 14 to be significantly enriched (Figure 3A; Table S15). Nine of those gene sets represent different cancer types that substantially overlap between each other and share underlying biological pathways (Figure 3B). The remaining gene sets represent the p53, Wnt, and ErbB signaling pathways, all involved in tumorigenesis including in the abovementioned cancer types.¹⁰ Remarkably, lead variants in our GWAS were predominantly intragenic for the seven genes in the p53 pathway, eight genes in the Wnt pathway, and six genes in the ErbB-EGFR pathway (Figure 3C), suggesting that modulation of these pathways plays an important role in head size variation.

The p53 signaling pathway showed the strongest enrichment ($\rho_{\text{adjusted}} = 7.6 \times 10^{-4}$) (Figure 3A; Table S15). Tumor suppressor protein p53, encoded by *TP53*, is activated by different stress signals to regulate the cell cycle and apoptosis. Our lead signal in this locus was *TP53* 3'-UTR variant rs78378222 with predicted deleterious effects (CADD = 15.93), which was identified previously.⁵ Three other genes in this pathway (*ATR*, *CDK6*, and

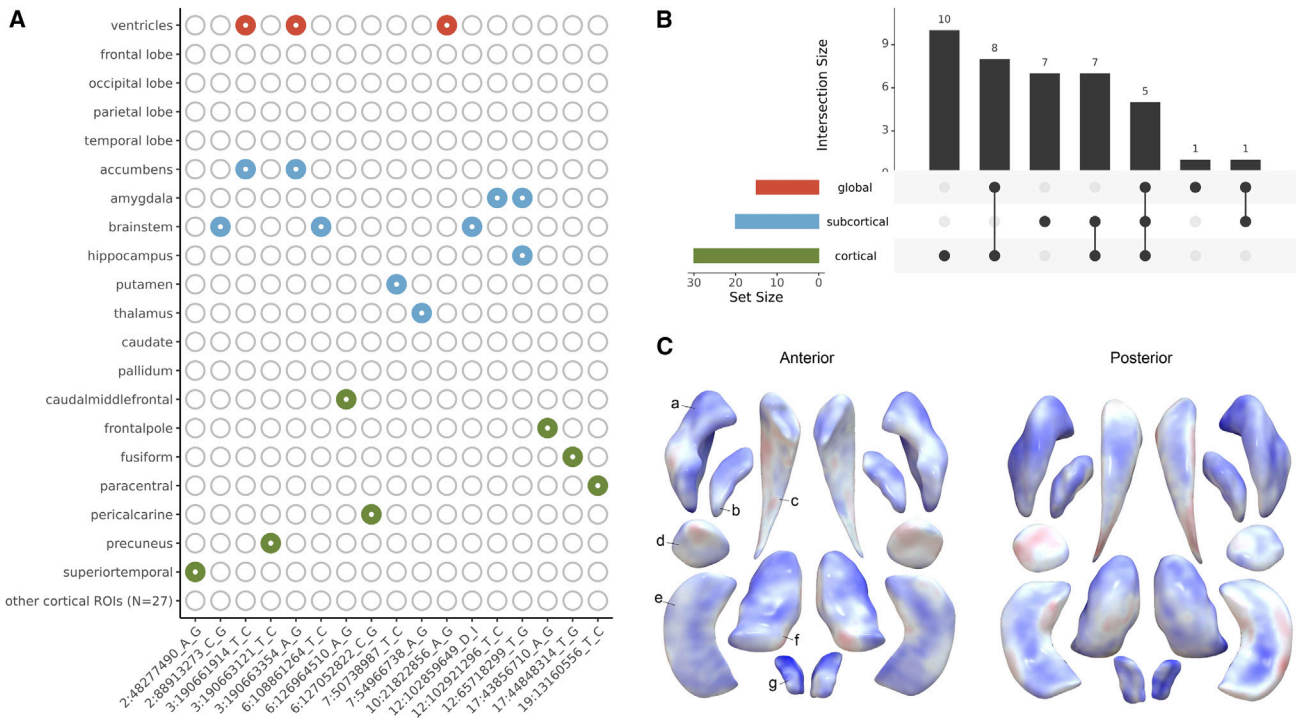


Figure 2. Genetic loci for head size and effects on regional brain volumes

(A) Heatmap showing head size loci that overlap with previously identified loci for global brain volumes (red), subcortical volumes (blue), and cortical region of interest volumes (green).

(B) UpSet plot of associations between head size lead variants and brain volumes. Intersection size corresponds to the frequency of the combination depicted below the bar. Set size corresponds to the frequency of associations with one of the brain volume categories (i.e., global, subcortical, or cortical).

(C) Plot showing the subcortical shape analysis of rs111939932 using log Jacobian determinants. Colors correspond to t values, with positive associations depicted in blue, and negative ones in red. Letters point to different subcortical structures: a, putamen; b, pallidum; c, caudate; d, amygdala; e, hippocampus; f, thalamus; g, accumbens.

PTEN) also contained 3'-UTR or exonic variants in LD ($r^2 > 0.6$) with lead variants. Identified genes act in cell-cycle arrest and cellular senescence (*CDK6*, *CDK2*, and *CCND2*), apoptosis (*IGF1*), or inhibition of the insulin growth factor (IGF)-1/mammalian target of rapamycin (mTOR) pathway (*PTEN*), suggesting comprehensive involvement of the p53 signaling pathway in head growth. This finding is in line with evidence that p53 signaling regulates both normal and malignant neural stem cell populations.^{11–13}

The Wnt signaling pathway has links to carcinogenesis and the developing and adult central nervous system,^{14,15} as well as to bone development including cranial growth.¹⁶ Of the eight overlapping genes, three contained exonic or 3'-UTR variants in LD ($r^2 > 0.6$) with identified lead variants (*APC*, *TP53*, and *TCF7L1*). Wnt signaling pathway gene *FRZB*, not annotated in KEGG, also contained exonic and 3'-UTR variants. In total, 1,948 genetic variants in LD with the identified lead variants ($r^2 > 0.6$), including 35 exonic variants, are eQTLs for *WNT3* in 27 different tissues including the cerebellar hemispheres. In addition, various exonic, 3'-UTR and 5'-UTR variants in LD with the lead variants are eQTLs for *TCF7L1* in brain tissues. These observations suggest that variants in this pathway affect brain and cranial growth in the human population.

The ErbB pathway ($p_{\text{adjusted}} = 0.014$, Figure 3A), also known as the EGFR signaling pathway, has six overlapping genes near head

size variants, which are involved in calcium signaling (*PLCG1*), MAPK signaling (*NCK1* and *MAPK1*), and PI3K-AKT signaling (*ERBB3*, *AKT3*, and *CDKN1B*). In addition, five genetic variants are eQTLs for *EGFR* in the cerebellum. Interestingly, both *AKT3* and *CDKN1B* are linked to clinical head size syndromes and cancer risk^{17–20} and contain, respectively, 3'-UTR variants and an exonic variant that reach genome-wide significance. ErbB signaling is involved in neurodevelopment,^{21–23} making it a plausible pathway involved in head size variation.

Since the above signaling pathways also have universal roles in cell growth, we determined their enrichment in the height GWAS. We found that only the Wnt signaling pathway was significantly enriched in the height GWAS ($p_{\text{adjusted}} = 0.038$), suggesting that the p53 and ErbB signaling pathways are more specifically involved in head growth rather than generalized body growth.

Functional prioritization using gene expression

Using a transcriptome-wide association study (TWAS), we identified 156 head size-associated variants functioning as eQTLs, regulating the expression of 112 genes (eGenes) in relevant tissue types (Table S16). Genomic overlap with additional gene-regulatory and epigenetic features provides evidence for 67 eQTLs regulating the expression of 58 eGenes (RegulomeDB probability score >0.5), including *AKT3* in brain tissue and

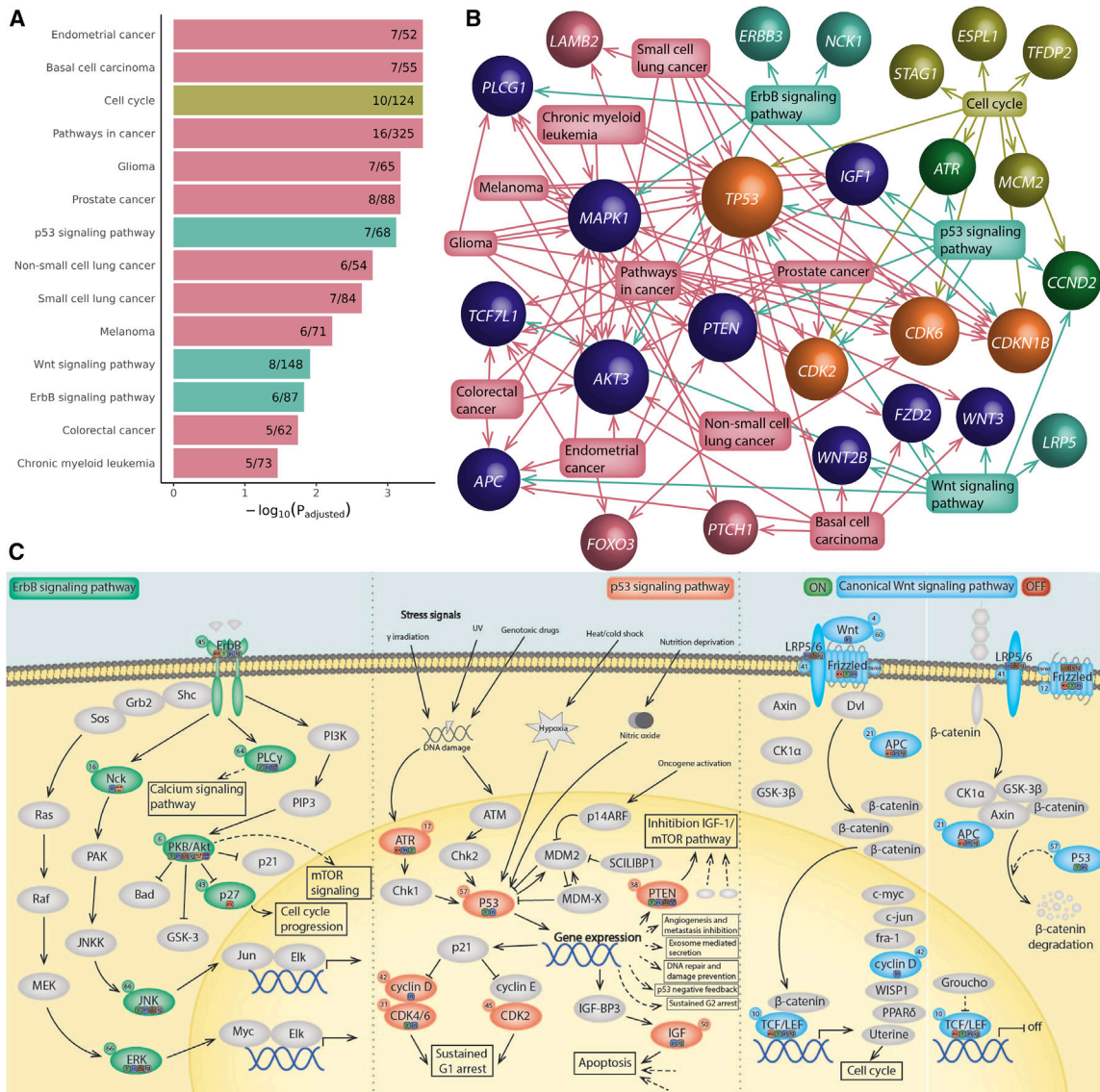


Figure 3. Gene sets enriched in human head size loci

(A) Bar plots presenting enriched KEGG gene sets. $-\log_{10}$ of adjusted p value and proportion of nearby genes overlapping with the gene set are presented. Cancer gene sets are depicted in pink, cell growth and death gene sets in yellow-green, and signal transduction gene sets in turquoise.

(B) Network graph showing enriched KEGG gene sets and their included genes near genetic lead variants. Gene sets are shown in squares with arrows to overlapping genes. Colors correspond to gene set categories: only cancer gene sets (pink), only cell growth and death gene sets (yellow-green), only signal transduction gene sets (turquoise), cancer gene sets and cell growth and death gene sets (dark blue), cell growth and death and signal transduction gene sets (green), or all three gene set categories (orange). Sphere size corresponds to the number of gene sets linked to that gene.

(C) Schematic overview of enriched signaling pathways with proteins encoded by genes near (<10 kb) identified genetic loci. Proteins encoded by these genes are colored (green, ErbB pathway; red, p53 pathway; blue, Wnt pathway), other proteins are depicted in gray. Circles next to protein names provide the locus number of the encoding gene. Locations of lead variants and variants in LD ($r^2 > 0.6$) are shown in squares next to the proteins: exonic (e; red), 3'-UTR (3'; green), 5'-UTR (5; light green), intronic (i; blue), intergenic including up- and downstream, exonic and intronic non-coding RNA (g; gray). For Frizzled, not only FZD2 but also FRZB is taken into consideration.

TCF7L1 in the cerebellum—part of the ErbB and Wnt pathway, respectively. In addition, 22 eGenes were suggested to be regulated by 22 splicing QTLs (sQTLs), including *AKT3*. The omnibus test revealed a shared effect for 80 eGenes across the tested gene expression panels (Table S17), including *WNT3*, *AKT3*, and *EGFR*.

Enrichment of Mendelian head size genes and cancer genes

Target genes of GWAS variants are often close to the lead variant.²⁴ Accordingly, we determined the enrichment of different categories of genes located nearby head size variants, stratified by their distance (Table S18).

First, we investigated genes mutated in OMIM syndromes associated with abnormal head size, i.e., macrocephaly or microcephaly (Tables S19 and S20). We found increasing enrichment for macrocephaly genes with decreasing distance to the lead variants, culminating in a 37-fold enrichment of macrocephaly genes in genes containing an intragenic lead variant (Figure 4A). In contrast, microcephaly genes were not enriched with shorter distance from lead variants. The striking enrichment of macrocephaly genes did not change in the height-adjusted head size GWAS (Table S21). Furthermore, there was only a modest enrichment for macrocephaly genes in the height GWAS, even for the top 67 loci (i.e., the same number of loci as our GWAS; Table S21). Macrocephaly syndrome genes with intragenic lead variants include *AKT3*, *PTCH1*, *PTEN*, *CCND2*, and *NFIX* (Table S19). We conclude that common genetic variants near genes associated with macrocephaly syndromes, but not microcephaly syndromes, contribute to variation in head size in the general population. Our GWAS of head size may therefore identify novel macrocephaly genes. Accordingly, a patient with intellectual disability²⁵ presented with macrocephaly and a mutation in *TICRR*, a gene for which a lead variant and variants in LD were eQTLs in 12 different tissues. *TICRR* acts in initiation of DNA replication and interacts with *CDK2*,²⁶ a gene nearby another lead variant. *TICRR* is therefore an interesting candidate macrocephaly syndrome gene.

We determined whether cancer genes are enriched close to lead variants (Figure 4A). Indeed, there was a 9-fold enrichment for high-fidelity cancer genes (first-tier COSMIC²⁷) among genes with an intragenic lead variant, which persisted after height adjustment (Table S21). There was only a modest enrichment of cancer genes close to height GWAS variants, providing additional evidence that cancer-related genes are specifically relevant for head size variation.

At a variant-level, no genetic correlation was found with GWAS meta-analyses of various cancer types^{28–31} (Table S22).

Autosomal dominance score

We did not observe a significant enrichment for microcephaly genes (Figure 4A). This may be due to differences between the micro- and macrocephaly gene sets. Macrocephaly typically results from mutations with an autosomal dominant inheritance pattern (64.6%, Table S19), whereas microcephaly predominantly involves mutations with an autosomal recessive inheritance pattern (72.3%, Table S20). We observed a profound increase for genes with a predicted dominant inheritance pattern closer to our lead variants (Figure 4B). However, neither dominant nor recessive microcephaly genes were enriched (Table S21) and the predominant recessive inheritance patterns of microcephaly genes could not explain their lack of enrichment. An alternative explanation is that microcephaly syndromes are more clinically heterogeneous and the underlying mechanisms are less specific to brain and cranial growth.

Gain of function and loss of function

The overlap among macrocephaly genes, microcephaly genes, and cancer genes is shown in Figure 4C. Macrocephaly-associated genes were more enriched for high-fidelity cancer genes than microcephaly-associated genes (enrichment ratio 12.9 vs.

3.2, Table S21). We therefore investigated whether the same mutation type, i.e., gain of function or loss of function, causes both macrocephaly syndromes as a germline mutation but also associate with cancer as somatic mutations. We found that this was the case for the vast majority of macrocephaly-associated genes with a defined role in cancer (37 of 41 genes, Table S19), i.e., the same type of mutation associated with both macrocephaly and cancer. Moreover, germline mutations in 14 of these 37 genes, including our GWAS genes *PTEN*, *PTCH1*, and *SUFU*, are associated with a syndrome or condition with a suggested cancer predisposition (Table S19). Our GWAS data and these observations may therefore suggest that subtle up-regulation of oncogenes and oncogenic pathways or down-regulation of tumor suppressor genes and pathways increases head size in the general population.

Brain cell expression

As neural progenitors are the actively dividing cells in the developing brain, their expressed genes may explain the observed genetic variants for head size.³² Indeed, genes at or near the head size loci were enriched in differentially expressed neural progenitor cell genes (Figure 4D; Table S23). Subsequently, we looked at a single-cell RNA-sequencing (scRNA-seq) dataset from cell types in the human cortex.^{33,34} Intriguingly, we find that genes close to head size variants are strongly enriched for genes preferentially expressed in intermediate progenitor cells (IPCs) (Figure 4E; Tables S24 and S25; Figure S2). Increased proliferation of IPCs in a primate-specific area of the brain, the outer region subventricular zone, is believed to be responsible for the evolutionary expansion of the human brain.^{35,36} This suggests that genetic variation regulating the proliferation or neuronal differentiation of IPCs plays an important role in determining human head size. Indeed, Wnt pathway genes, p53 pathway genes, and *PTCH1*, *SUFU*, and *NFIX*, which we find near genetic variants determining head size, are examples of regulators of IPCs.^{37–43} To understand which type of variants influence head size, we performed a partitioned heritability analysis that classifies variants into categories based on functional elements. We found an enrichment for variants in the regulatory elements of both neural progenitors and their neuronal progenies (enrichment_{progenitors} = 12.7, $p = 8.3 \times 10^{-4}$; enrichment_{neurons} = 16.1, $p = 3.7 \times 10^{-4}$).

Finally, we assessed whether a similar pattern was seen for the Catalog of Somatic Mutations in Cancer (COSMIC) first-tier cancer genes. Indeed, our differential gene expression analysis dataset indeed showed an enrichment of cancer genes in the genes specific for neural progenitors (enrichment = 2.9, $p = 1.7 \times 10^{-6}$, Table S23). However, no significant enrichment was found for IPCs using the scRNA-seq data.

DISCUSSION

Here we performed the largest head size GWAS to date and found that associated genetic variants significantly locate to cancer genes and cancer-associated pathways. Genes near head size variants were enriched for high-fidelity cancer genes even after adjustment for height, suggesting a specific association of head growth with cancer, rather than general growth. Germline mutations in multiple macrocephaly syndrome genes

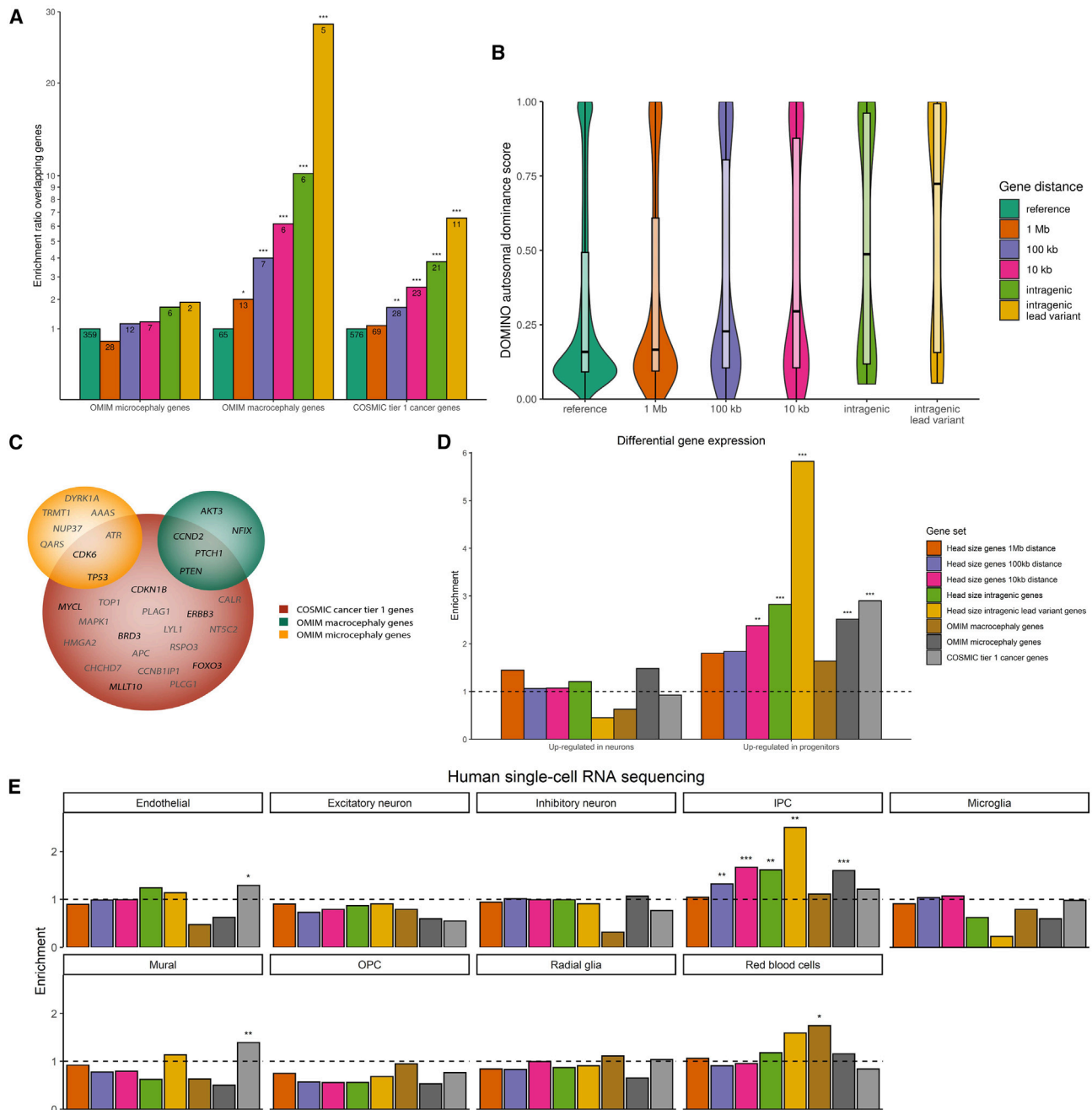


Figure 4. Gene enrichments stratified by distance from head size lead variants

(A) Enrichment of OMIM macro- and microcephaly genes and COSMIC tier 1 genes near identified genetic loci. Depicted are enrichments of genes within 1 Mb (orange), 100 kb (purple), or 10 kb (pink) of identified genetic loci, genes with intragenic genetic variants (light green) and genes with intragenic genetic lead variants (yellow) in comparison with genes in the reference genome (dark green). * $p < 0.05$; ** $p < 0.0125$ (0.05/4); *** $p < 0.0025$ (0.05/4/5).

(B) Violin plots showing DOMINO autosomal dominance scores of different gene sets. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

(C) Venn diagram showing genes within 10 kb of genetic loci that overlap with OMIM microcephaly genes (green) or COSMIC cancer tier 1 genes (red). Genes with intragenic lead variants are depicted in black, others in gray.

(D) Bar plot showing enrichments of gene sets for genes differentially expressed in neurons and progenitors. * $p < 0.05$; ** $p < 0.025$ (0.05/2); *** $p < 0.003$ (0.05/2/8).

(E) Bar plots showing enrichments of gene sets for the various cell types in the human cortical brain using single-cell RNA-sequencing data. * $p < 0.05$; **FDR < 0.05 ; *** $p < 0.0007$ (0.05/9/8).

are known to be an increased cancer risk, including *PTEN* (Cowden syndrome) and *PTCH1* (Gorlin syndrome) (Table S19). Our GWAS was performed in the general population, which prompts the question of whether the link between head size and cancer extends beyond rare genetic syndromes.

Previous meta-analyses of prospective observational studies found associations between adult height and increased risk for various forms of cancer.⁴⁴ Similarly, head circumference at birth has previously been positively associated with brain cancer during childhood,⁴⁵ and with different types of cancer later in life including stomach cancer and breast cancer,⁴⁶ with stronger associations than for respectively birth weight or birth length. The correlation between head size at birth and breast cancer later in life was further supported by a pooled analysis of 32 studies,⁴⁷ but not by another prospective cohort study.⁴⁸ Our study provides further evidence for this link between head size and cancer.

The abovementioned observational studies together with our genetic results suggest that early growth rather than later adolescent growth may be associated with neoplasia, since cranial growth is completed around the sixth year of age, whereas height is primarily determined by peri-pubertal growth. Head size at birth and its growth during early infancy in relation to cancer risk therefore deserves further studies to identify potential underlying pathophysiological mechanisms and its potential clinical implications.^{45,49,50}

Limitations of the study

Although this study suggests an association between head growth and cancer, further studies are needed to investigate whether head size is causally related to cancer development. In our study, we were not able to account for environmental factors such as socio-economic status and diet, especially during childhood, which would be important to adjust for in future studies. In addition, the clinical implications of the findings of our study need to be investigated, for example if patients with clinical macrocephaly syndromes need to be screened for cancer more extensively.

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STAR★METHODS

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

| REAGENT or RESOURCE | SOURCE | IDENTIFIER |
|--|--|---|
| Deposited data | | |
| Genome-wide association study summary statistics | CHARGE dbGaP and http://enigma.ini.usc.edu/research/download-enigma-gwas-results | phs000930 (dbGaP accession number) |
| Software and algorithms | | |
| EasyQC | Winkler et al. ⁵¹ | Software - Universität Regensburg (uni-regensburg.de) |
| METAL | Willer et al. ⁵² | METAL Documentation - Genome Analysis Wiki (umich.edu) |
| LD score regression | Bulik-Sullivan et al. ⁵³ | GitHub - bulik/ldsc: LD Score Regression (LDSC) |
| LocusZoom | Pruim et al. ⁵⁴ | LocusZoom - Create Plots of Genetic Data |
| FUMA GWAS | Watanabe et al. ⁵⁵ | Functional Mapping and Annotation of Genome-wide association studies (ctglab.nl) |
| TWAS-Fusion | Gusev et al. ⁵⁶ | TWAS/FUSION (gusevlab.org) |
| DOMINO | Quinodoz et al. ⁵⁷ | Domino (job.ch) |
| Other | | |
| OMIM database | Amberger et al. ⁵⁸ | Home - OMIM |
| Cortical organoids' scRNA-seq data | Bhaduri et al. ³⁴ | https://organoidreportcard.cells.ucsc.edu |
| e/sQTLs, and allele-specific expression in cultured primary human neural progenitors and their sorted neuronal progeny | Aygün et al. ³² | https://bitbucket.org/steinlabunc/expression_splicing_qtls_public/src/master/ |

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Hieab H.H. Adams (Hieab.Adams@radboudumc.nl).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The genome-wide summary statistics that support the findings of this study will be made available through the CHARGE dbGaP (accession number phs000930) and ENIGMA (<http://enigma.ini.usc.edu/research/download-enigma-gwas-results>) websites.

No previously unreported custom computer code or mathematical algorithm was used to generate results central to the conclusions.

Any additional information required to re-analyse the data reported in this work paper is available from the [lead contact](#) upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Study population

Most studies participate in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)⁵⁹ or the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA)⁶⁰ consortium. We also included the results of the most recent head

circumference GWAS.⁵ A complete overview of the included studies is shown in Table S1 and their population characteristics are presented in Table S2. Each contributing study was approved by their institutional review boards or local ethical committees. Written informed consent was obtained from all study participants.

Genotyping

Genotyping of individuals was performed on commercially available arrays, and imputed to 1000 Genomes (1KG) or Haplotype Reference Consortium (HRC) imputation panels (Table S3). Quality control was performed using the EasyQC software.⁵¹ In each study, genetic variants with an imputation quality r^2 below 0.3 and a minor allele frequency (MAF) below 0.001 were excluded. Additionally, variants were filtered on study level requiring $(r^2 \times MAF \times N) > 5$.

Phenotyping

Different methods were used to measure human head size across studies. Briefly, either head circumference was measured, or intracranial volume was measured on computed tomography (CT) or magnetic resonance imaging (MRI) scans. In total, human head size was measured using intracranial volume measured on CT or MRI scans in respectively 1,283 and 84,171 individuals, and using head circumference in 20,524 individuals (Table S4). These measures have previously shown to be phenotypically and genetically correlated.^{5,6,61} Genetic correlations between our MRI scans and head circumference measurements was 0.75. Together, this allowed us to perform a combined meta-analysis of different measures of head size.

METHOD DETAILS

Genome-wide association studies

GWAS were performed for each study adjusted for age, age² (if significant), gender, eigenstrat PC1-4 (if significant), study-specific adjustments and case-control status (if applicable). In a second model, additional adjustment for height were made. The METAL software⁵² was used to perform a sample size weighted Z score meta-analysis. After meta-analysis, genetic variants available in less than 5,000 individuals were excluded. Comparable betas were derived using the formula $Zscore \times \sqrt{\frac{1}{N \times 2 \times MAF}}$ as was done previously.⁶² Genomic inflation and polygenic heterogeneity were assessed using the LD score regression software⁵³ by comparing the genomic control inflation factor and the LD score regression intercept (Table S5).

GWAS meta-analyses were performed separately for African, Asian and European samples. We also performed a transancestral meta-analysis. Since the analyses in non-European samples were underpowered, we additionally used an inverse-variance weighted method to test the combined effects of the lead variants in the non-European samples. This analysis was performed using the gtx package as implemented in R.

Functional annotations

Regional association plots were made with the LocusZoom software.⁵⁴ The Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA GWAS) platform⁵⁵ was used to derive the independent genomic loci and genetic lead variants, and to functionally annotate the identified genetic variants. Additionally, enrichment for KEGG⁹ biological pathways was assessed for genes located nearby the identified genetic loci using the default options in FUMA, using hypergeometric tests. Genotype-Tissue Expression (GTEx) v7 was used to identify expression quantitative trait loci (eQTL) for the lead genetic variants and variants in LD ($r^2 > 0.6$).

We performed a transcriptome-wide association study (TWAS) using the association statistics from the European-only head size GWAS summary statistics and weights from 21 publicly available gene expression reference panels. We focused on the gene expression weights from blood (Young Finns Study, YFS), arterial (GTEx), brain (GTEx, CommonMind Consortium (CMC)) and peripheral nerve tissues (GTEx). Precomputed SNP-expression weights in the 1-Mb window were obtained for each gene in the reference panel, including the highly-tissue specific splicing QTL (sQTL) information on gene isoforms in the dorsolateral prefrontal cortex (DLPFC, CMC). Using the SNP-expression weights, SNP-trait effect estimates and the SNP correlation matrix, we used the TWAS-Fusion⁵⁶ to estimate the association statistic between the predicted expression and head size (TWAS Z score). Transcriptome-wide significant genes (eGenes) and the corresponding QTLs (eQTLs) were determined using Bonferroni correction in each reference panel, based on the average number of features (4,320 genes) tested across all the reference panels.⁵⁶ Finally, using a prior association probability of 1.1×10^{-5} and colocalization analysis (COLOC)⁶³ for each locus we estimated the posterior probability of a shared causal variant ($PP4 > 0.75$) between the gene expression and trait association. eGene regions with eQTLs not reaching genome-wide significance in the head size GWAS were considered putatively novel TWAS signals. Furthermore, functional validation of the eGenes was performed by integrating eQTL with the functional genomics feature from the RegulomeDB.⁶⁴ A RegulomeDB probability score greater than 0.5 and closer to 1 indicates the likelihood of the eQTL having a gene-regulatory role. Finally, accounting for pairwise correlation between the gene expression features we conducted the multiple degree of freedom omnibus analysis, to test for the shared effect of eGenes across the different gene reference panels. A significance threshold of $p < 3.48 \times 10^{-6}$ accounting for the number of genes ($N = 14,385$) tested was used to identify significant eGenes in the omnibus test.

Effects on anthropomorphic measures and regional brain volumes

The LD score regression software^{53,65} was used to assess genetic correlations with adult height,⁶⁶ for both the height-unadjusted and height-adjusted model.

Dual-energy X-ray absorptiometry (DXA) measurements of the UK Biobank imaging subsample ($N = 3,313$) were used to examine the effect of the identified lead variants on anthropometric measures across the body, i.e., bone area of the arms, legs, pelvis, ribs, spine, trunk and vertebrae L1-L4. In these analyses values more than three standard deviations from the mean were considered outliers and removed from the analyses. We adjusted for age, age,² gender and principal components (model 1), and additionally for height (model 2) to correct for an overall growth effect.

To investigate the effects of the identified variants for head size on growth in specific brain regions, we investigated the overlap between the identified loci for head size and previous genome-wide association studies (GWASs) on brain volumes.^{7,67–70} We also analyzed the associations between the identified lead genetic variants and global volumes (i.e., four brain lobes and lateral ventricle volumes), subcortical volumes (i.e., volumes of eight subcortical structures) and cortical volumes (i.e., volumes of 34 cortical regions of interest) in the UK Biobank ($N = 22,145$). Volumes were derived using the FreeSurfer 6.0 software. Values more than 3.5 standard deviations away from the mean were considered outliers and removed from the analysis. In the first model, we adjusted for age, age,² gender and principal components, and in the second model additionally for intracranial volume.

Additionally, we took the lead variants specifically associated with one or two subcortical volumes, and investigated their effects on the shape of seven subcortical structures, i.e., amygdala, caudate nucleus, hippocampus, nucleus accumbens, pallidum, putamen and thalamus. The radial distances and log Jacobian determinants were derived using the ENIGMA-Shape package (<http://enigma.usc.edu/ongoing/enigma-shape-analysis/>). Volumetric outliers more than 3.5 standard deviations from the mean were removed from the analysis.

We performed 10,000 permutations to define the number of independent DXA, brain volumetric and subcortical shape outcomes. We used this number to define our multiple testing adjusted p value thresholds for significance, i.e., $0.05/(\text{number of independent outcomes} \times \text{number of lead genetic variants})$.

Genetic correlations

We investigated the genetic correlations with neuropsychiatric traits using the LD score regression software.^{53,65} Genetic correlation analyses were performed for educational attainment,⁷¹ general cognitive function,⁷² all stroke,⁷³ Alzheimer's disease,⁷⁴ frontotemporal dementia,⁷⁵ Parkinson's disease,⁷⁶ anorexia nervosa,⁷⁷ attention-deficit hyperactivity disorder,⁷⁸ autism spectrum disorder,⁷⁹ bipolar disorder,⁸⁰ extraversion,⁸¹ insomnia,⁸² major depressive disorder,⁸³ neuroticism,⁸⁴ obsessive compulsive disorder⁸⁵ and schizophrenia.⁸⁰ Analyses were performed in the entire GWAS dataset as well as in the GWAS set with newly included studies in comparison to the intracranial volume GWAS performed by Adams et al.⁶

We also performed genetic correlation analyses for publicly available cancer GWAS, namely for breast cancer,²⁸ ovarian cancer²⁹ and prostate cancer.³⁰ To obtain information on more cancer types, we additionally included GWAS of cancer registries from the UK Biobank and Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging (GERA).³¹ Of those, we excluded cancer types with less than 1,000 cases, which left the following cancer types to be analyzed: bladder cancer ($N_{\text{cases}} = 2,242$), breast cancer ($N_{\text{cases}} = 17,881$), cervical cancer ($N_{\text{cases}} = 6,563$), colon cancer ($N_{\text{cases}} = 3,793$), endometrial cancer ($N_{\text{cases}} = 2,037$), esophageal/gastric cancer ($N_{\text{cases}} = 1,091$), kidney cancer ($N_{\text{cases}} = 1,338$), lung cancer ($N_{\text{cases}} = 2,485$), malignant melanoma ($N_{\text{cases}} = 6,777$), non-Hodgkin's lymphoma ($N_{\text{cases}} = 2,400$), prostate cancer ($N_{\text{cases}} = 10,792$) and rectal cancer ($N_{\text{cases}} = 2,091$). Genetic correlations with oral cavity/pharyngeal cancer ($N_{\text{cases}} = 1,223$) and ovarian cancer ($N_{\text{cases}} = 1,259$) could not be calculated due to low heritability estimates.

Enrichment analyses

We performed enrichment analyses of different gene sets: genes within 1 Mb, 100 kb or 10 kb of the identified genetic loci, genes within 10 kb of the identified genetic loci with intragenic genetic variants, and genes within 10 kb of the identified genetic loci with intragenic genetic lead variants. As a reference, we used the rest of the protein-coding genome.

First, the Online Mendelian Inheritance in Man (OMIM) database⁵⁸ was used to retrieve information on genes related to heritable phenotypes affecting head size (Tables S19 and S20). Second, the COSMIC database²⁷ was used to extract Tier 1 cancer genes. Taking the rest of the genome as our reference gene set, we calculated the enrichment of these macrocephaly, microcephaly and cancer genes in the abovementioned gene sets.

Lastly, DOMINO,⁵⁷ a previously developed machine learning tool, was used to assess if the genes in the different gene sets were more often predicted to harbor dominant changes in comparison with genes in the rest of the genome.

Mean autosomal dominance scores were compared with the reference genome using a Mann-Whitney test. Differences in the proportions for the OMIM macro- and microcephaly genes, intellectual disability genes and COSMIC genes were calculated using a Pearson's χ^2 test.

We performed these analyses for the head size height-unadjusted GWAS results, but also the GWAS in the subset of studies for which height was available, the height-adjusted GWAS and the height GWAS.⁶⁶ For comparison, we also selected the top 67 loci for the height GWAS, so the results were not driven by a difference in the number of associated loci.

Experimental datasets of brain cells

To assess whether the identified genes in the current study are enriched for genes differentially expressed in human progenitors versus neurons, we utilized differential gene expression data of those cell lines, derived from a previously published sample population ($N_{\text{donor}} = 85$ in progenitors and $N_{\text{donor}} = 74$ in neurons).³² Using genes with at least 10 counts in more than 5% of the cell-type specific donors in either cell-type (resulting in 16,172 protein-coding genes out of 28,785 genes in total), we performed a paired differential gene expression analysis with design matrix: `model.matrix(~ CellType + as.factor(DonorID) + RIN, data)` as described previously,³² using the `limma` R package.⁸⁶ We detected 1,095/1,420 protein genes upregulated in progenitors/neurons, respectively, for $\text{abs}(\log\text{FC}) > 1.5$ and adjusted p value < 0.05 . Performing a hypergeometric test, we evaluated if multiple protein-coding gene sets: head size gene sets with different distances from the lead variants, OMIM macrocephaly and microcephaly genes, and COSMIC tier 1 cancer genes are enriched among the protein-coding genes upregulated in progenitors or neurons.

Using a different approach, scRNA-seq data were used to investigate whether our genes of interest were enriched for genes specific for certain cortical brain cell types. Specifically, scRNA-seq data from the developing human cortex (gestational week 6–22, more than 189,000 cells) were used to identify the top 10% of genes specific for a certain cell type.³⁴ Using this data, we first performed LD score regression⁵³ based enrichment analyses of the head size GWAS summary statistics, as previously described.^{33,87} Gene specificity was defined as the ratio of expression of a gene in a cell type by the total expression of that gene in all cell types. In parallel, we again tested the enrichment of various gene sets: head size gene sets with different distances from the lead variants, OMIM macrocephaly and microcephaly genes, and COSMIC tier 1 cancer genes, with the top 10% of cell specific genes for each cell type using hypergeometric tests. FDR correction was used to correct for the multiple gene sets tested for enrichment in each cell type.

To determine if regulatory elements of neural progenitors are enriched for the heritability of head size, we performed partitioned heritability analyses^{53,88} using chromatin accessibility profiles from a population of 76 primary human neural progenitor cells and 61 of their differentiated neuronal progenies, as was done previously.⁸⁹

QUANTIFICATION AND STATISTICAL ANALYSIS

Please see the statistical analyses and software in [method details](#).