

Genetic variants for head size share genes and pathways with cancer

Authors and affiliations

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Correspondence

Hieab H.H. Adams, MD, PhD

Department of Clinical Genetics

Department of Radiology and Nuclear Medicine

Erasmus MC University Medical Center

Wytemaweg 80, 3015 CE, Rotterdam, the Netherlands

Telephone number: +31 10 70 33559

Fax number: +31 10 70 43489

E-mail address: h.adams@erasmusmc.nl

Abstract

The size of the human head is determined by growth in the first years of life, while the rest of the body typically grows until early adulthood¹. Such complex developmental processes are regulated by various genes and growth pathways². Rare genetic syndromes have revealed genes that affect head size³, but the genetic drivers of variation in head size within the general population remain largely unknown. To elucidate biological pathways underlying the growth of the human head, we performed the largest genome-wide association study on human head size to date (N = 79,107). We identified 67 genetic loci, 50 of which are novel, and found that these loci are preferentially associated with head size and mostly independent from height. In subsequent neuroimaging analyses, the majority of genetic variants demonstrated widespread effects on the brain, whereas the effects of 17 variants could be localized to one or two specific brain regions. Through hypothesis-free approaches, we find a strong overlap of head size variants with both cancer pathways and cancer genes. Gene set analyses showed enrichment for different types of cancer and the p53, Wnt and ErbB signalling pathway. Genes overlapping or close to lead variants – such as *TP53*, *PTEN* and *APC* – were enriched for genes involved in macrocephaly syndromes (up to 37-fold) and high-fidelity cancer genes (up to 9-fold), whereas this enrichment was not seen for human height variants. This indicates that genes regulating early brain and cranial growth are associated with a propensity to neoplasia later in life, irrespective of height. Our results warrant further investigations of the link between head size and cancer, as well as its clinical implications in the general population.

Main

To gain more insight into the genetic underpinnings of the human head size, we performed a meta-analysis of genome-wide association studies (GWAS) by including samples measuring head size using intracranial volume from magnetic resonance imaging or computed tomography, and tape measured head circumference (**Table S1-S4; Online Methods**). Compared to previous efforts^{4,5}, we nearly doubled the sample size (N = 79,107), of which the majority were of 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; Table S5-S7**), of which 50 loci were novel. Most variants (N = 48) showed consistent directions of association between the European, African (N = 1,356), and Asian (N = 1,335) ancestry samples (**Figure 1B**), while nominally significant heterogeneity was observed for five variants (**Table S6**), suggesting population-specific genetic effects on head size in these loci.

Head-specific growth versus general growth

Head growth coincides with growth of the entire body, prompting us to investigate whether variants affecting head size are specific for growth of the human brain and cranium or whether this is driven at least partly by an effect on human body height. We therefore performed an additional height-adjusted head size GWAS in European studies for which height measures were also available (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 second model ($\rho_{\text{genetic}} = -0.02$, $P = 0.58$) (**Figure 1C**), confirming the removal of height-associated effects. Importantly, there was no significant attenuation for any of the lead variants' effect sizes for their association 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 S8**). Altogether, this indicates that the effect of the identified variants on head size is predominantly cranium-specific.

Regional brain volumetric effects

Height is an overall measure reflective of growth in various body parts. Accordingly, head size itself may also 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 S9**). We further screened all loci previously associated with these regional brain volumes, and found 16 of those 132 loci to be significantly related with head size in our data set after multiple testing correction (**Table S10**). To determine if the current findings can be localized to specific brain regions, we systematically 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 S11**). Twenty-nine variants were associated with multiple cortical, subcortical, and global brain regions, and for the other 51 variants there was no apparent predilection to influence particular brain regions. However, seventeen variants were preferentially associated with one or two specific cortical or subcortical regions. For example, rs111939932 was associated with nucleus accumbens volume. This intronic variant in *PCBP2* is an eQTL for different genes in multiple tissues, including *ATP5G2* in the nucleus accumbens and basal ganglia of the brain. Further analysis additionally revealed localized effects of this variant on the shape of this structure (**Figure 2C; Table S12**). In the largest GWAS on nucleus accumbens volume to date⁶, this variant was nominally significant ($P = 0.02$), underlining the improved power of the current study to identify novel loci for brain morphometry. Overall, these results suggest that most head size variants are important for generalized brain or cranial growth, while a minority influences regional brain growth.

Pathway analysis

To obtain novel insights into the biological mechanisms underlying variation in human head size, we performed a hypothesis-free gene set enrichment analysis of all KEGG⁷ gene sets and found 14 to be significantly enriched (**Figure 3A; Table S13**). 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 signalling pathways, which are all involved in tumorigenesis including in the above cancer types⁸. Remarkably, the lead variants were often intragenic for the overlapping 7 genes in the p53 pathway, 8 genes in the Wnt pathway and 6 genes in the ErbB-EGFR pathway (**Figure 3C**), suggesting that modulation of these pathways plays an important role in head size variation.

P53 signalling pathway

The signalling pathway showing the strongest enrichment was the p53 signalling pathway ($P_{\text{adjusted}} = 7.6 \times 10^{-4}$) (**Figure 3C**). The tumour 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 the *TP53* 3'-UTR variant rs78378222 with predicted deleterious effects (CADD = 15.93), which was identified previously⁵. Three other genes in this pathway (*ATR*, *CDK6* and *PTEN*) also contained 3'-UTR or exonic variants in LD ($r^2 > 0.6$) with the identified lead variants. As we identified genes involved in cell cycle arrest and cellular senescence (*CDK6*, *CDK2* and *CCND2*), apoptosis (*IGF1*) and inhibition of the IGF-1/mTOR pathway (*PTEN*), our results suggest a comprehensive involvement of the p53 signalling pathway in cranial growth. This finding is in line with evidence that p53 signalling regulates both normal and malignant neural stem cell populations⁹⁻¹¹.

Wnt signalling pathway

The Wnt signalling pathway has extensive links to carcinogenesis, but also plays pivotal roles in the developing and adult central nervous system^{12,13}, as well as in bone development including cranial growth¹⁴. 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*). The Wnt signalling 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 ($r^2 > 0.6$), among which 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. Altogether, these observations suggest that this pathway is critical for brain and cranial growth in humans.

ErbB signalling pathway

The third enriched signalling pathway was the ErbB pathway ($P_{\text{adjusted}} = 0.014$), also known as the EGFR signalling pathway, with six overlapping genes. Overlapping genes near head size variants are involved in the downstream calcium signalling (*PLCG1*), MAPK signalling (*NCK1* and *MAPK1*) and PI3K-AKT signalling (*ERBB3*, *AKT3* and *CDKN1B*) pathways. In addition, five genetic variants are eQTLs for *EGFR* in the cerebellum. Interestingly, both *AKT3* and *CDKN1B* have been linked to clinical head size syndromes and cancer risk¹⁵⁻¹⁸ and contain, respectively, 3'-UTR variants and an exonic variant that reached genome-wide significance in the current study. This ErbB signalling is also increasingly recognized for its involvement in neurodevelopment¹⁹⁻²¹, making it a plausible pathway involved in head size variations.

P53, Wnt and ErbB signalling pathway in general growth

Since these signalling pathways have universal roles in cell growth, and thus are not specific for head size, we determined the enrichment for these pathways in the height GWAS. We found that from these three signalling pathways, only the Wnt signalling pathway was significantly enriched in the height GWAS ($P_{\text{adjusted}} = 3.8 \times 10^{-2}$), suggesting that the p53 and ErbB signalling pathways are more specifically involved in processes for head growth rather than generalized body growth.

Enrichment analyses

Because pathway analyses aggregate all genes in the vicinity of the lead variant, it becomes difficult to discern actual target genes. Given that target genes of GWAS variants are often close to the lead variant²², we determined the enrichment of different categories of genes located nearby head size variants stratified by their distance (**Table S14**).

OMIM macro- and microcephaly genes

First, we investigated genes mutated in OMIM syndromes associated with abnormal head size, i.e. macrocephaly or microcephaly (**Table S15-16**). 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. In contrast, microcephaly genes did not enrich upon shorter distance from lead variants (**Figure 4A**). The striking enrichment of macrocephaly genes did not change in the height-adjusted GWAS (**Table S17**). 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 S17**). Macrocephaly genes with intragenic lead variants include *AKT3* (Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 2), *PTCH1* (Basal cell nevus syndrome), *PTEN* (Cowden syndrome 1), *CCND2* (Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome 3) and *NF1X* (Sotos syndrome 2). We conclude that common genetic variation in genes associated with macrocephaly syndromes, but not microcephaly syndromes, contributes to variation in head size in the general population. Reciprocal to this, genes identified through our GWAS of head size may therefore also identify currently unknown causal genes for macrocephaly. Accordingly, we observed a patient in a previously described intellectual disability cohort²³ who presented with macrocephaly and had a mutation in *TICRR*, a gene for which a lead variant and variants in LD were eQTLs in twelve different tissues. This gene is involved in the initiation of DNA replication and interacts with *CDK2*²⁴, one of the genes nearby

another lead variant. Thus, *TICRR* is an interesting candidate for further study in currently undiagnosed macrocephaly syndromes.

Autosomal dominance score

We did not observe a significant enrichment for microcephaly genes (**Figure 4A**). This lack of enrichment is likely due to differences between the microcephaly and macrocephaly gene sets. Notably, macrocephaly typically results from mutations with an autosomal dominant inheritance pattern (64.6%, **Table S15**), whereas microcephaly predominantly involves mutations with an autosomal recessive inheritance pattern (72.3%, **Table S16**). 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 S17**) 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.

COSMIC tier 1 cancer genes

As our KEGG analysis showed a strong enrichment for cancer pathways (**Figure 3A**), we determined whether cancer genes are also enriched among genes closer to the lead variants (**Figure 4A**). Indeed, there was a 9-fold enrichment for high-fidelity cancer genes (first tier COSMIC²⁵) among genes with an intragenic lead variant, which persisted after adjusting for height (**Table S17**). There was only a modest enrichment of cancer genes close to variants from the height GWAS, providing additional evidence that cancer-related genes are specifically important for head size.

Gain of function and loss of function

We found that macrocephaly-associated genes were more enriched for high-fidelity cancer genes than microcephaly-associated genes (enrichment ratio 12.9 vs. 3.2, **Table S17**). We therefore investigated whether the same mutation type, i.e. gain of function or loss of function, causes both macrocephaly syndromes as a germ line 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 S15**), i.e. the same type of mutation associates with both macrocephaly and cancer. Moreover, germ line 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 S15**). Our GWAS data and these observations therefore suggest that subtle up-regulation of oncogenes and oncogenic pathways or down-regulation of tumor suppressor genes and pathways may increase head size in the general population.

Implications of the head size and cancer link

The link between cancer and head size is intriguing, with some of the high-fidelity cancer genes being known macrocephaly genes (**Figure 4C**). Germline mutations in two genes are known to be related to clinical syndromes causing both abnormal head sizes and an increased cancer risk, namely the genes *PTEN* (Cowden syndrome) and *PTCH1* (Gorlin syndrome). For both syndromes, patients are routinely screened for macrocephaly as part of the diagnostic criteria, but this relationship is not yet known for other syndromes such as Li-Fraumeni syndrome (*TP53*) or familial adenomatous polyposis syndrome (*APC*), both of which are near lead variants. Our GWAS, however, was performed in the general population, prompting the interesting question whether the link between head size and cancer extends beyond rare genetic syndromes.

Meta-analyses of prospective observational studies found associations between height and increased risk of various forms of cancer²⁶, and the few studies on body length and head circumference at birth have shown similar results²⁷⁻²⁹. Our results also indicate that particularly genes associated with early growth rather than later adolescent growth may be associated to neoplasia, since cranial growth is completed around the 6th to 7th year of age whereas height is primarily determined by peripubertal growth. In combination with our findings, the relationship between head size and cancer risk warrants further study, as well as an exploration of its clinical implications.

Online methods

Study population

Most studies participate in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE)³⁰ or the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA)³¹ consortium. We also included the results of the most recent head circumference GWAS⁵. A complete overview of the population characteristics is presented in **Table S1**. 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 S2**). Quality control was performed using the EasyQC software³². 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 57,186 individuals, and using head circumference in 20,524 individuals (**Table S3**). These measures have previously shown to be phenotypically and genetically correlated^{4,5,33}, allowing us to perform a combined meta-analyse of different measures of head size.

Genome-wide association studies

GWAS were performed for each study adjusted for age, age² (if significant), sex, eigenstrat PC1-4 (if significant), study-specific adjustments and case-control status (if applicable). In a second model, additional adjustment for height was made. The METAL software³⁴ 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 previously³⁵. Genomic inflation and polygenic heterogeneity were assessed using the LD score regression software³⁶ by comparing the genomic control inflation factor and the LD score regression intercept (**Table S4**).

Functional annotations

Regional association plots were made with the LocusZoom software³⁷. The Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA GWAS) platform³⁸ was used to derive the independent genomic loci and genetic lead variants, and to functionally annotate the identified genetic variants. Additionally, enrichment for KEGG⁷ 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 ($r^2 > 0.6$).

Effects on anthropomorphic measures and regional brain volumes

The LD score regression software^{36,39} was used to assess genetic correlations with adult height⁴⁰, 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, age², sex 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 (GWAS) on brain volumes^{6,41-44}. We also analysed the associations between the identified lead genetic variants and volumes of four brain lobes, the lateral ventricles, eight subcortical structures and 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, age², sex 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 / (number of independent outcomes x number of lead genetic variants).

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) database⁴⁵ was used to retrieve information on genes related to heritable phenotypes affecting head size. Second, the Catalogue of Somatic Mutations in Cancer (COSMIC) database²⁵ 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, DOMINO⁴⁶, a previously developed machine learning tool, was used to assess if the genes in the different gene sets were more often predicted to harbour 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 GWAS⁴⁰. 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.

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Display items

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

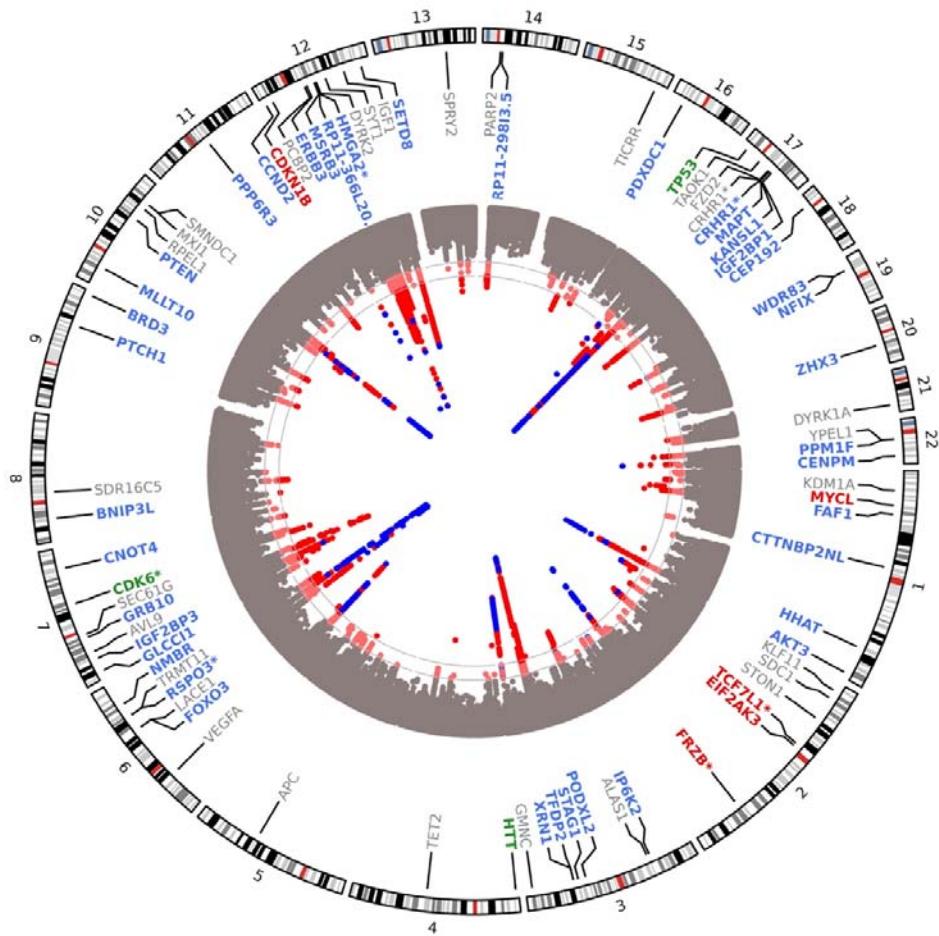


Figure 1A. Circos Manhattan plot of the European ancestry GWAS on head size, with the grey horizontal lines corresponding to a genome-wide significant ($P < 5 \times 10^{-8}$) or sub-significant ($P < 1 \times 10^{-6}$) P value threshold. Known genetic variants are depicted in blue, whereas novel variants are depicted in red. For each lead genetic variant, the nearest gene is shown with their corresponding location on the genome. The colour of each gene corresponds 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 (grey). Genes that are the nearest gene for more than one locus are denoted with an asterisk (*).

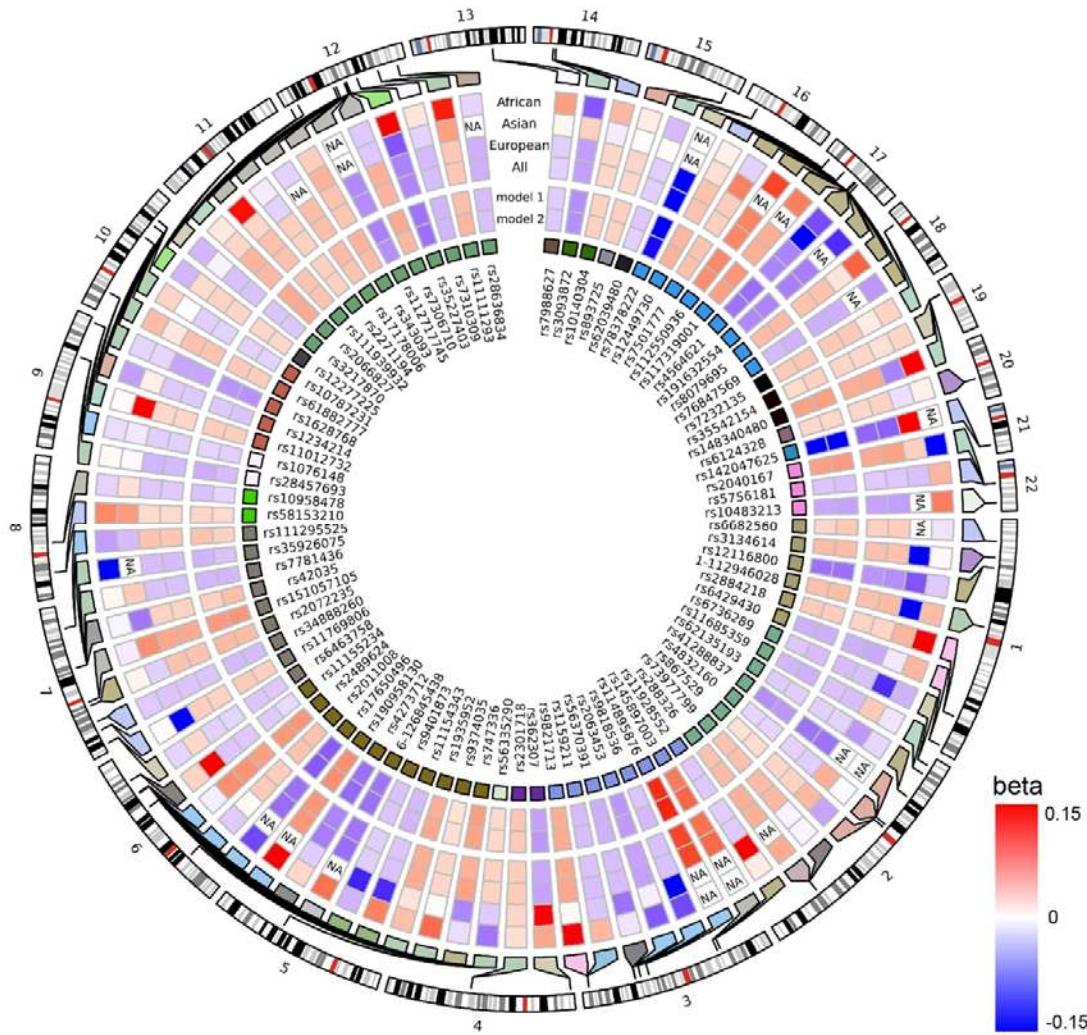


Figure 1B. Circos heatmap showing the betas of the 90 identified lead genetic variants in African, Asian and European ancestry sample meta-analysis, as well as the transancestral meta-analysis. In addition, the differences between the height-unadjusted (model 1) and height-adjusted (model 2) meta-analysis is shown. Positive associations are depicted in red, negative associations are depicted in blue.

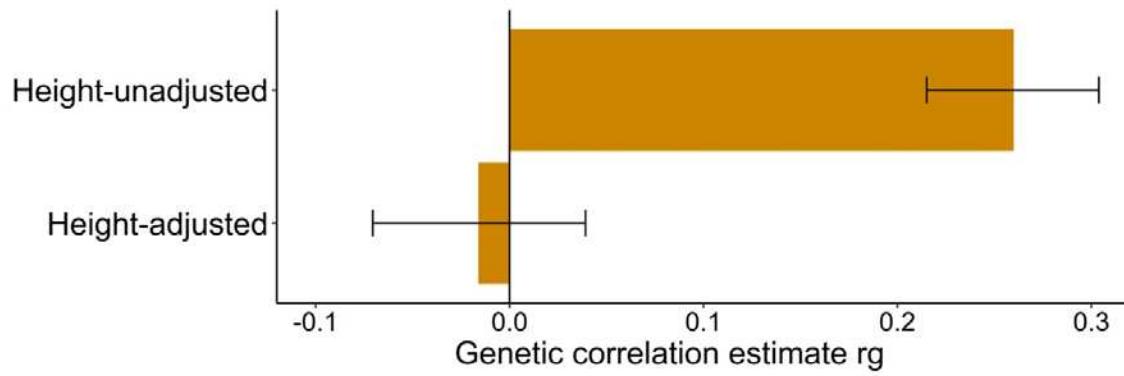


Figure 1C. Barplot of the genetic correlation coefficient ($rg_{genetic}$) of the height-unadjusted and height-adjusted head size genome-wide association study with the height genome-wide association study, with their accompanying 95% confidence intervals.

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

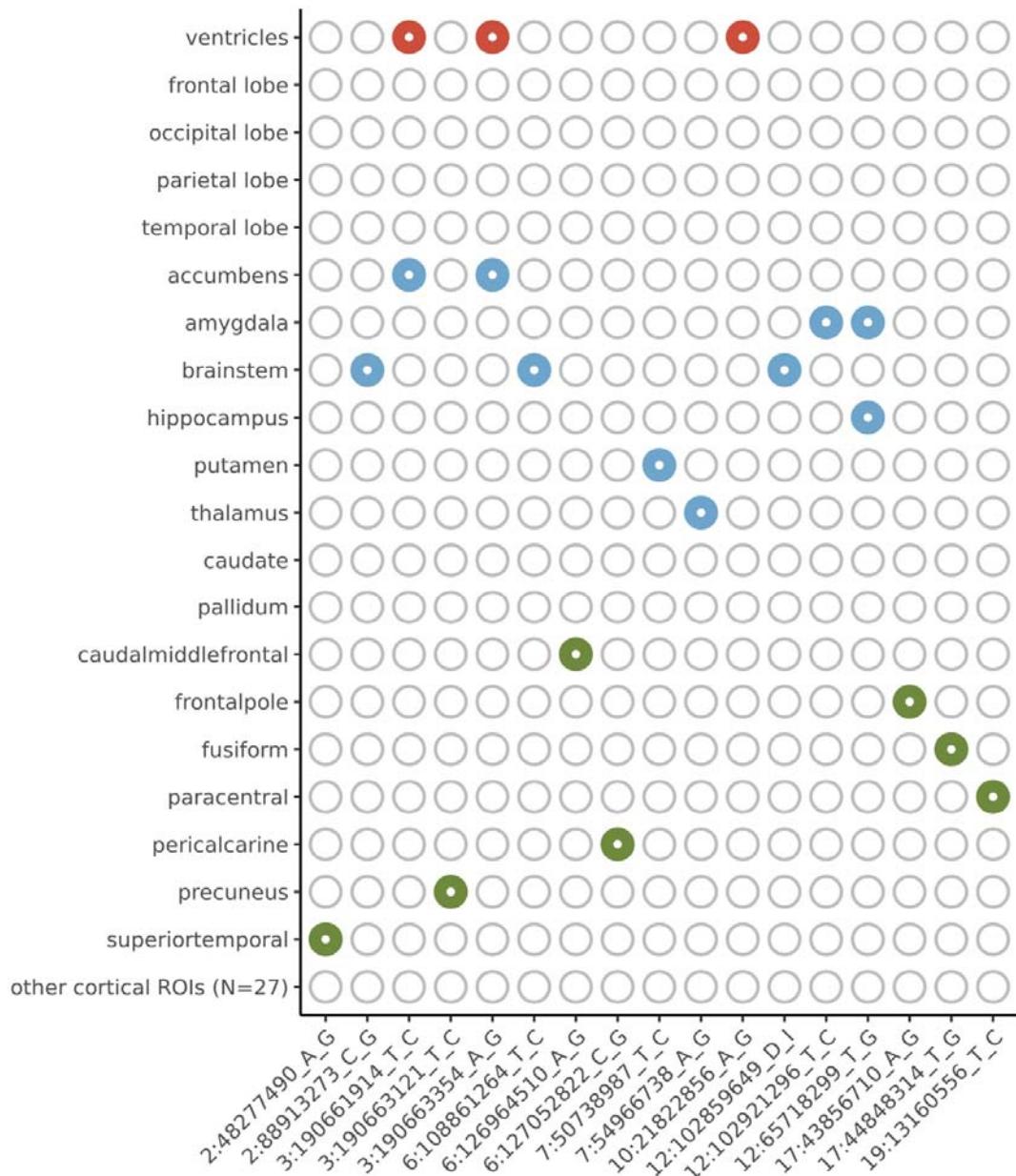


Figure 2A. Heatmap showing the genetic loci identified for human head size that overlap with previously identified genetic loci for global brain volumes (depicted in red), subcortical brain volumes (depicted in blue) and cortical regional of interest volumes (depicted in green).

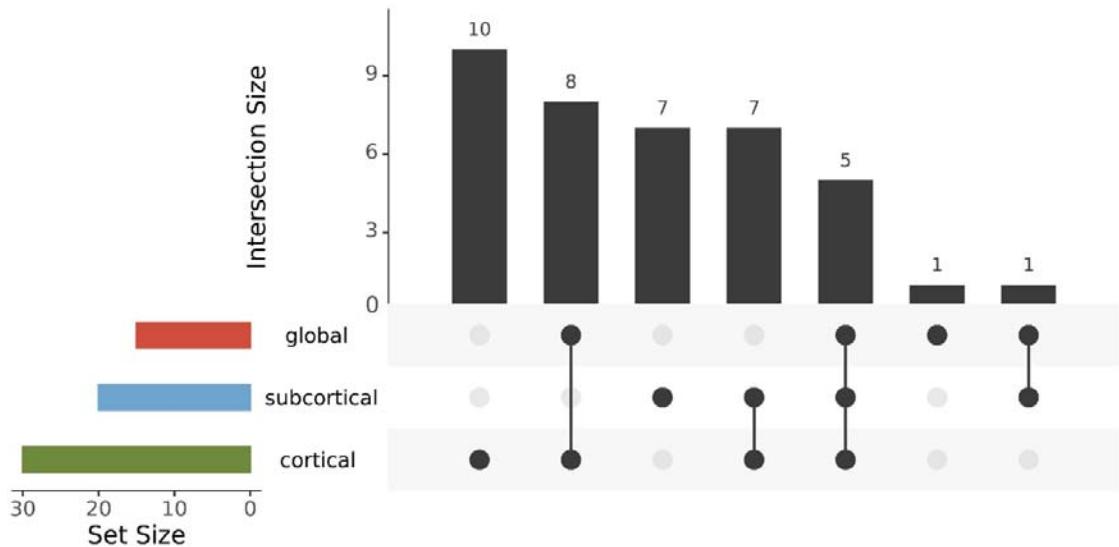


Figure 2B. UpSet plot of the different combinations of associations of the identified genetic variants for human head size and regional brain volumes. The intersection size corresponds to the frequency of the combination depicted below the bar. The set size corresponds to the frequency of associations with one of the structures belonging to the brain volume category (i.e., global, subcortical or cortical). Global volumes include the volumes of four brain lobes and the lateral ventricle volumes (depicted in red), subcortical volumes include the volumes of eight subcortical structures (depicted in blue), and the cortical volumes include the volumes of 34 cortical regions of interest (depicted in green).

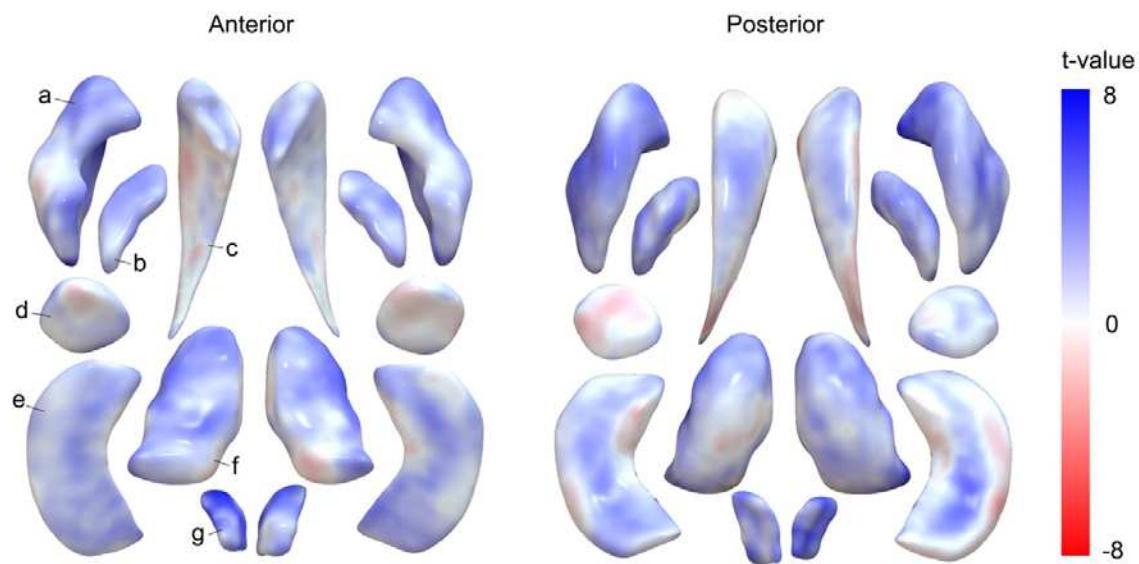


Figure 2C. Plot showing the results of the subcortical shape analysis of rs111939932 using log Jacobian determinants. Colours correspond to t-values, with positive associations depicted in blue, and negative associations depicted in red. The letters point to the different subcortical structures: a – putamen; b – pallidum; c – caudate; d – amygdala; e – hippocampus; f – thalamus; g – accumbens.

Figure 3. Gene sets enriched in human head size loci.

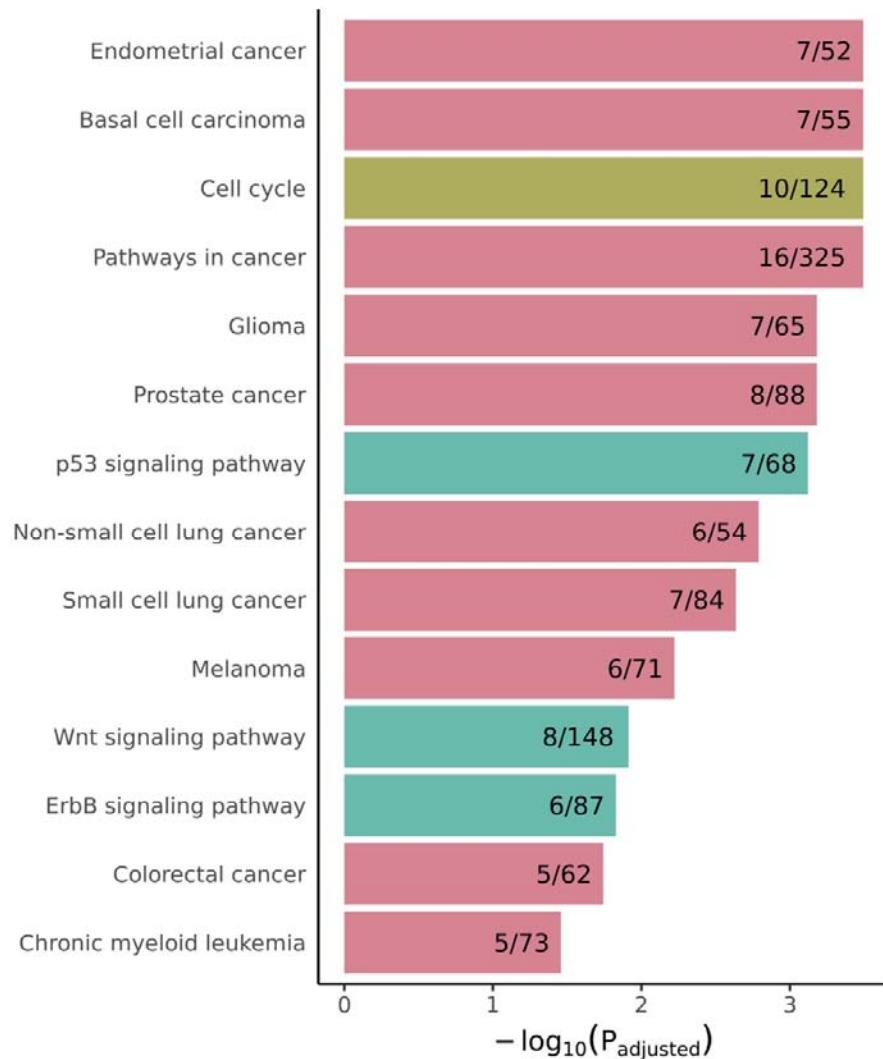


Figure 3A. Barplots presenting the significantly enriched KEGG gene sets. On the x-axis the $-\log_{10}$ of the adjusted p-value is presented, and the proportion of genes in the gene set that overlap with the genes nearby the genetic loci are shown inside the bars. Colours correspond to different categories of gene sets: cancer gene sets are depicted in pink, cell growth and death gene sets in yellow-green, and signal transduction gene sets in turquoise.

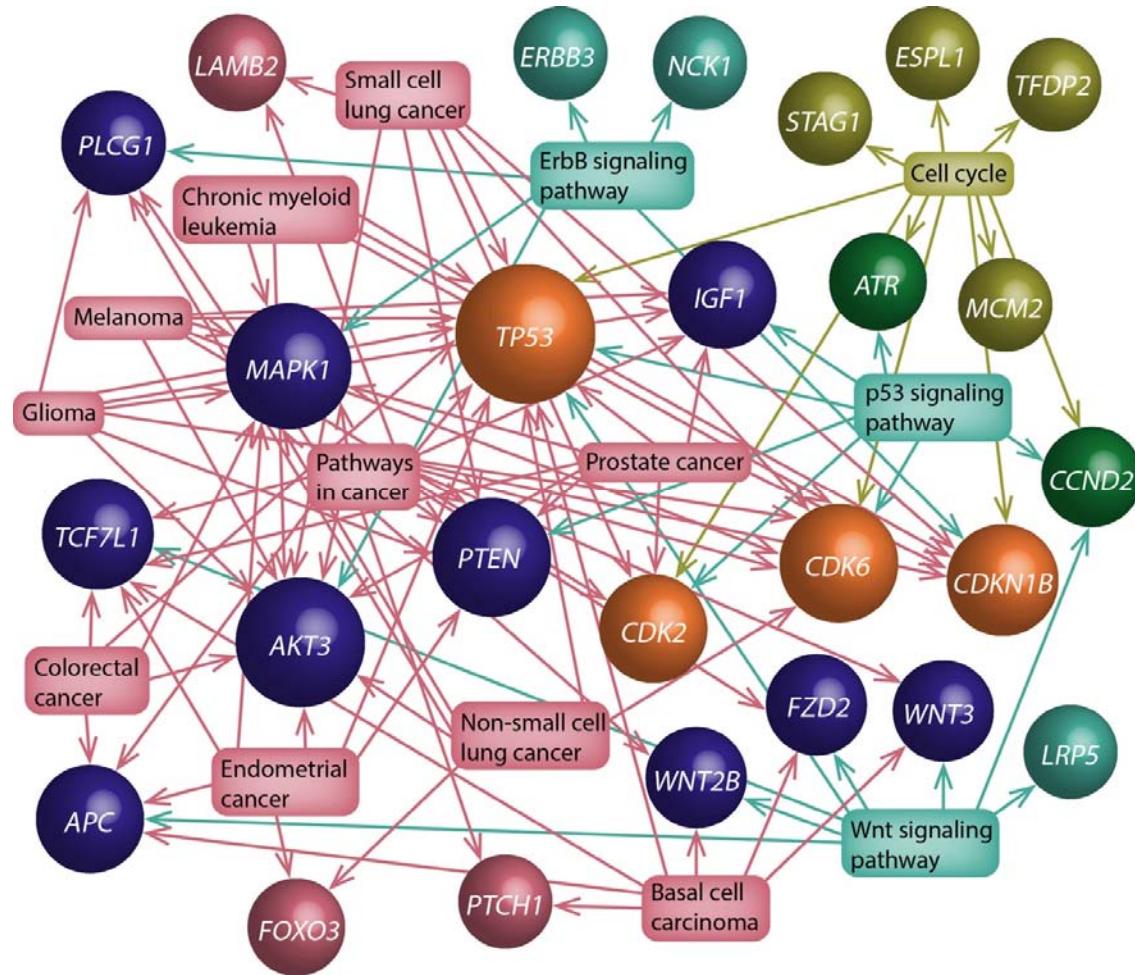


Figure 3B. Network graph showing the enriched KEGG gene sets and their included genes near genetic lead variants. Gene sets are shown in squares, with arrows connecting them to the overlapping genes presented as spheres. The colours of the spheres correspond to the gene set category the gene is linked to: 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 gene sets and signal transduction gene sets (green), or all three gene set categories (orange). The size of a sphere corresponds to the amount of gene sets linked to that gene.

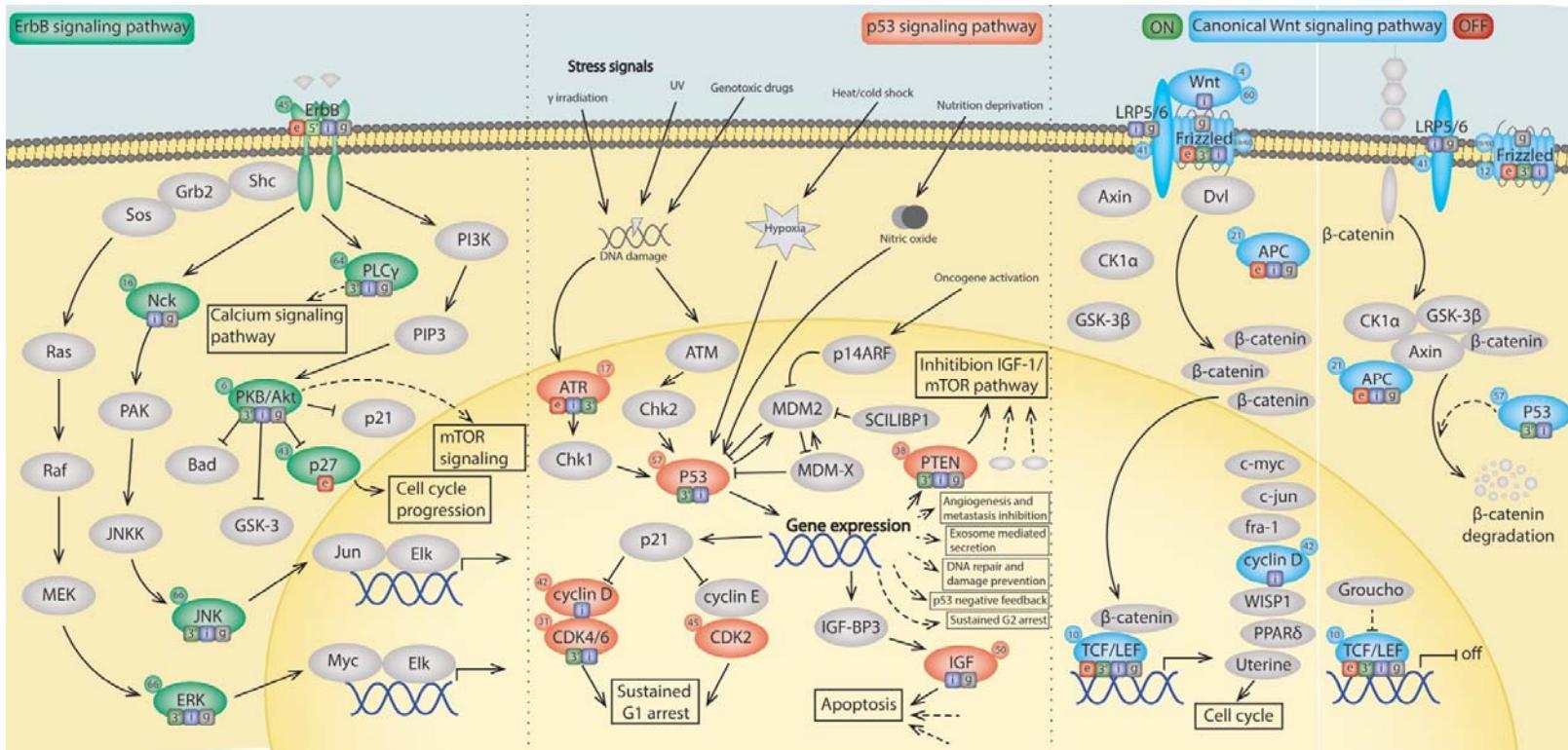


Figure 3C. Schematic overview of the significantly enriched signalling pathways with proteins encoded by genes near (< 10 kb) identified genetic loci. Proteins encoded by these genes are coloured (green – ErbB signalling pathway, red – p53 signalling pathway; blue – Wnt signalling pathway), whereas the other proteins are depicted in grey. The circle next to each protein name provides the locus number to which the encoding gene belongs. Locations of lead genetic variants and variants in linkage disequilibrium ($r^2 > 0.6$) are shown in the squares within each protein: 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; grey). For Frizzled, not only *FZD2* but also *FRZB* is taken into consideration.

Figure 4. Gene enrichment stratified by distance from lead variants.

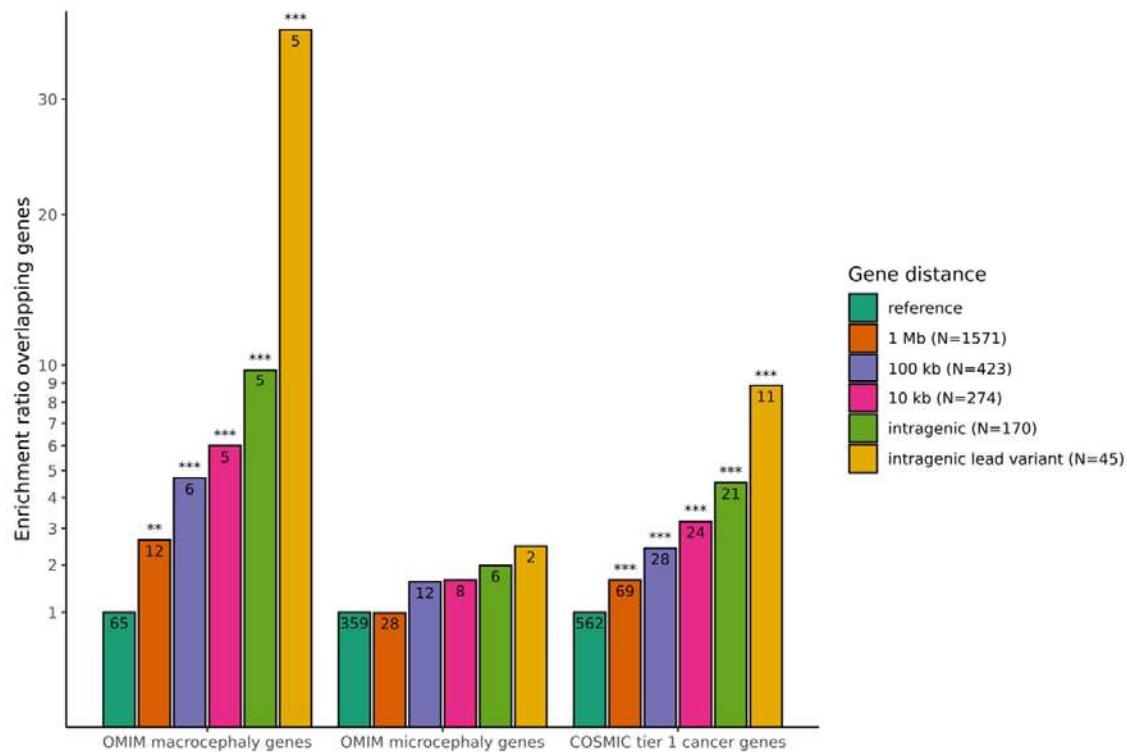


Figure 4A. Enrichment of genes nearby the identified genetic loci for OMIM macrocephaly genes, OMIM microcephaly genes and COSMIC tier 1 genes. Depicted are enrichment of genes within 1 Mb (orange), 100 kb (purple) or 10 kb (pink) of the identified genetic loci, genes within 10 kb of the identified genetic loci with intragenic genetic variants (light green), and genes with intragenic genetic lead variants (yellow), in comparison with genes in the reference genome (dark green). Significant results are denoted by asterisks: * $P < 0.05$; ** $P < 0.0125$ (0.05 / 4); *** $P < 0.0025$ (0.05 / 4 / 5).

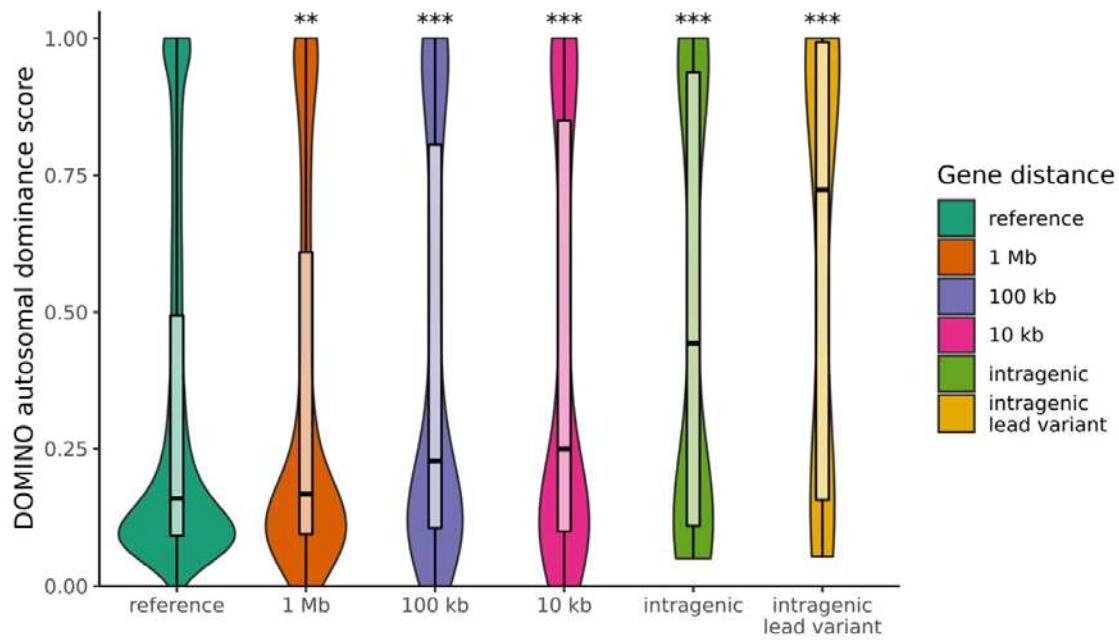


Figure 4B. Violin plots and boxplots showing the DOMINO autosomal dominance scores of genes within 1 Mb (orange), 100 kb (purple) or 10 kb (pink) of the identified genetic loci, genes within 10 kb of the identified genetic loci with intragenic genetic variants (light green), and genes with intragenic genetic lead variants (yellow), in comparison with genes in the reference genome (dark green). Significant results are denoted by asterisks: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

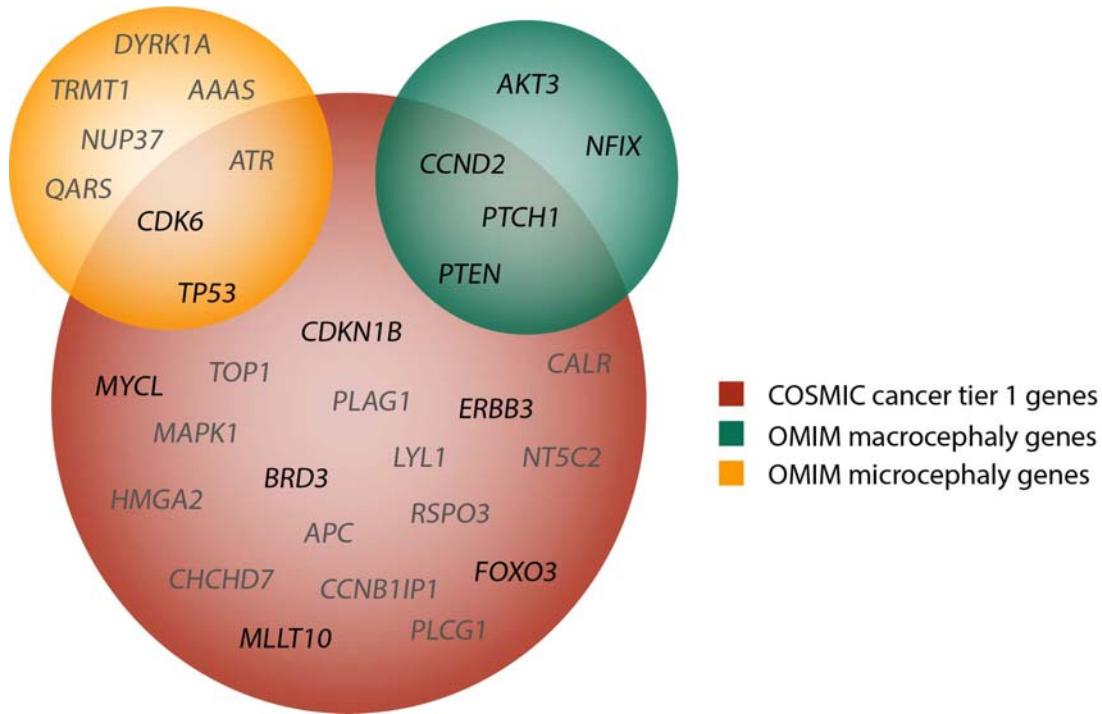


Figure 4C. Venn diagram showing the nearby (< 10 kb) genes that overlap with OMIM microcephaly genes (depicted in yellow), OMIM macrocephaly genes (depicted in green) and COSMIC cancer tier 1 genes (depicted in red), and their in-between overlap. Genes with intragenic genetic lead variants are depicted in black, and genes without intragenic genetic lead variants in grey.

Supplementary Materials

Supplementary Tables

See separate Excel file.

Table S1. List of all contributing studies.

Table S2. Population characteristics of new or updated contributing studies.

Table S3. Information on genotyping and quality control.

Table S4. Phenotyping information.

Table S5. Lambda genomic control, LD score regression intercept and ratio for different models.

Table S6. Lead genetic variants and their effects on human head size in samples of different ethnicities, with and without adjustment for height.

Table S7. Genome-wide significant genetic variants and variants in linkage disequilibrium ($r^2 > 0.6$), including functional annotations.

Table S8. Effects of lead genetic variants on bone size area measured using dual-energy X-ray absorptiometry (DXA).

Table S9. Overlap between identified loci and previously identified loci in genome-wide association studies of brain volumes.

Table S10. The effects of previously identified genetic variants for regional brain volumes in the current genome-wide association study.

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Table S12. Results of the subcortical shape analyses of seven lead genetic variants specifically associated with one or two subcortical structures.

Table S13. Kyoto Encyclopaedia of Genes and Genomes (KEGG) pathway analysis.

Table S14. Genes in or nearby identified genetic loci (< 1 Mb).

Table S15. List of genes linked to macrocephaly in the Online Mendelian Inheritance of Man (OMIM) database.

Table S16. List of genes linked to microcephaly in the Online Mendelian Inheritance of Man (OMIM) database.

Table S17. Enrichment of micro- and macrocephaly OMIM genes, COSMIC tier 1 cancer genes, intellectual disability trios and autosomal dominance DOMINO score.

Supplementary Figures

Figure S1. Forest plots presenting the study-specific associations of the identified lead genetic variants with human head size.

Figure S2. Regional plots of the identified genetic loci for human head size (± 100 kb).

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Authors and affiliations

Authors

Maria J. Knol^{1*}, Raymond A. Poot^{2*}, Tavia E. Evans^{3,4}, Claudia L. Satizabal^{5,6,7}, Aniket Mishra⁸, Sandra van der Auwera^{9,10}, Marie-Gabrielle Duperron⁸, Xueqiu Jian¹¹, Isabel C. Hostettler^{12,13}, Dianne H.K. van Dam-Nolen⁴, Sander Lamballais¹, Mikolaj A. Pawlak^{3,14}, Cora E. Lewis¹⁵, Amaia Carrion-Castillo¹⁶, Theo G.M. van Erp^{17,18}, Céline S. Reinbold^{19,20,21}, Jean Shin^{22,23}, Markus Scholz^{24,25}, Asta K. Håberg^{26,27}, Anders Kämpe^{28,29}, Gloria H.Y. Li³⁰, Reut Avinun³¹, Joshua R. Atkins^{32,33}, Fang-Chi Hsu³⁴, Alyssa R. Amod³⁵, Max Lam³⁶, Ami Tsuchida^{37,38,39}, Mariël W.A. Teunissen^{40,41}, Alexa S. Beiser^{6,7,42}, Frauke Beyer^{43,44}, Joshua C. Bis⁴⁵, Daniel Bos^{1,4}, R. Nick Bryan⁴⁶, Robin Bülow⁴⁷, Svenja Caspers^{48,49,50}, Gwenaëlle Catheline^{51,52}, Charlotte A.M. Cecil^{1,53}, Shareefa Dalvie³⁵, Jean-François Dartigues⁵⁴, Charles DeCarli⁵⁵, Maria Enlund-Cerullo^{56,57}, Judith M. Ford^{58,59}, Barbara Franke^{41,60,61}, Barry I. Freedman⁶², Nele Friedrich⁶³, Melissa J. Green^{64,65}, Simon Haworth^{66,67,68}, Catherine Helmer⁶⁹, Per Hoffmann^{19,20,70}, Georg Homuth⁷¹, M. Kamran Ikram^{1,72}, Clifford R. Jack⁷³, Neda Jahanshad⁷⁴, Christiane Jockwitz^{48,75}, Yoichiro Kamatani⁷⁶, Annchen R. Knodt³¹, Shuo Li⁴², Keane Lim³⁶, W. T. Longstreth^{77,78}, Fabio Macciardi⁷⁹, The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium[†], The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium[†], Outi Mäkitie^{28,29,56,57}, Bernard Mazoyer^{80,81}, Sarah E. Medland^{82,83,84}, Susumu Miyamoto⁸⁵, Susanne Moebus⁸⁶, Thomas H. Mosley^{87,88}, Ryan Muetzel^{1,53}, Thomas W. Mühleisen^{19,48,89}, Manabu Nagata⁸⁵, Soichiro Nakahara^{17,90}, Nicholette D. Palmer⁹¹, Zdenka Pausova^{22,23}, Adrian Preda⁹², Yann Quide^{64,65}, William R. Reay^{32,33}, Gennady V. Roshchupkin^{1,4}, Reinhold Schmidt⁹³, Pamela J. Schreiner⁹⁴, Kazuya Setoh⁷⁶, Chin Yang Shapland^{16,66,67}, Stephen Sidney⁹⁵, Beate St Pourcain^{16,61,66}, Jason L. Stein⁹⁶, Yasuharu Tabara⁷⁶, Alexander Teumer⁹⁷, Anne Uhlmann³⁵, Aad van der Lugt⁴, Meike W. Vernooij^{1,4}, David J. Werring¹², B. Gwen Windham^{87,88}, A. Veronica Witte^{43,44}, Katharina Wittfeld^{9,10}, Qiong Yang⁴², Kazumichi Yoshida⁸⁵, Han G. Brunner^{98,99}, Quentin Le Grand¹⁰⁰, Kang Sim^{101,102,103}, Dan J. Stein^{35,104}, Donald W. Bowden⁹¹, Murray J. Cairns^{32,33}, Ahmad R. Hariri³¹, Ching-Lung Cheung^{30,105,106}, Sture Andersson⁵⁶, Arno Villringer^{43,107}, Tomas Paus^{108,109}, Sven Cichon^{19,20,48}, Vince D. Calhoun¹¹⁰, Fabrice Crivello⁸⁰, Lenore J. Launer¹¹¹, Tonya White^{4,53}, Peter J. Koudstaal⁷², Henry Houlden¹², Myriam Fornage^{11,112}, Fumihiko Matsuda⁷⁶, Hans J. Grabe⁹, M. Arfan Ikram¹, Stéphanie Debette^{100,113}, Paul M. Thompson^{74**}, Sudha Seshadri^{5,6,7**}, Hieab H.H. Adams^{3,4**}✉.

* These authors contributed equally to this work.

** These authors jointly supervised this work.

[†] A full list of the consortium authors is provided below.

The Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium

Philippe Amouyel¹¹⁴, Konstantinos Arfanakis^{115,116}, Benjamin S. Aribisala^{117,118,119}, Mark E. Bastin^{120,121}, Ganesh Chauhan^{8,122}, Christopher Chen¹²³, Ching-Yu Cheng^{124,125}, Philip L. de Jager¹²⁶, Ian J. Deary¹²⁷, Debra A. Fleischman^{116,128,129}, Rebecca F. Gottesman^{130,131}, Vilmundur Gudnason^{132,133}, Saima Hilal^{134,135,136}, Edith Hofer^{93,137}, Deborah Janowitz⁹, J. Wouter Jukema^{138,139,140,141}, David C.M. Liewald¹⁴², Lorna M. Lopez¹⁴³, Oscar Lopez¹⁴⁴, Michelle Luciano¹⁴², Oliver Martinez¹⁴⁵, Wiro J. Niessen^{4,146}, Paul Nyquist^{130,147}, Jerome I. Rotter¹⁴⁸, Tatjana Rundek¹⁴⁹, Ralph L. Sacco¹⁴⁹, Helena Schmidt¹⁵⁰, Henning Tiemeier^{53,151}, Stella Trompet¹⁵², Jeroen van der Grond¹⁵³, Henry Völzke⁹⁷, Joanna M. Wardlaw^{120,121,154}, Lisa Yanek¹⁴⁷, Jingyun Yang^{116,128}.

The Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium

Ingrid Agartz^{155,156,157}, Saud Alhusaini¹⁵⁸, Laura Almasy^{159,160}, David Ames^{161,162}, Katrin Amunts^{48,49,89}, Ole A. Andreassen^{163,164}, Nicola Armstrong¹⁶⁵, Manon Bernard¹⁶⁶, John Blangero^{167,168}, Laura M.E. Blanken⁵³, Marco P. Boks¹⁶⁹, Dorret I. Boomsma¹⁷⁰, Adam M. Brickman¹⁷¹, Henry Brodaty^{172,173}, Randy L. Buckner^{174,175,176}, Jan K. Buitelaar¹⁷⁷, Dara M. Cannon¹⁷⁸, Vaughan J. Carr^{64,65,179}, Stanley V. Catts^{180,181}, M. Mallar Chakravarty^{182,183}, Qiang Chen¹⁸⁴, Christopher R.K. Ching⁷⁴, Aiden Corvin¹⁸⁵, Benedicto Crespo-Facorro^{186,187}, Joanne E. Curran^{167,168}, Gareth E. Davies¹⁸⁸, Eco J.C. de Geus^{189,190}, Greig I. de Zubicaray¹⁹¹, Anouk den Braber¹⁷⁰, Sylvane Desrivière¹⁹², Allissa Dillman¹⁹³, Srdjan Djurovic^{194,195}, Wayne C. Drevets¹⁹⁶, Ravi Duggirala^{167,168}, Stefan Ehrlich¹⁹⁷, Susanne Erk¹⁹⁸, Thomas Espeseth^{21,199}, Iryna O. Fedko¹⁷⁰, Guillén Fernández⁶¹, Simon E. Fisher^{16,61}, Tatiana M. Foroud²⁰⁰, Tian Ge²⁰¹, Sudheer Giddaluru^{195,202}, David C. Glahn²⁰³, Aaron L. Goldman¹⁸⁴, Robert C. Green^{204,205,206}, Corina U. Greven^{177,207,208}, Oliver Grimm²⁰⁹, Narelle K. Hansell²¹⁰, Catharina A. Hartman²¹¹, Ryota Hashimoto²¹², Andreas Heinz¹⁹⁸, Frans Henskens^{213,214}, Derrek P. Hibar²¹⁵, Beng-Choon Ho²¹⁶, Pieter J. Hoekstra²¹⁷, Avram J. Holmes^{176,218,219}, Martine Hoogman⁶¹, Jouke-Jan Hottenga¹⁷⁰, Hilleke E. Hulshoff Pol²²⁰, Assen Jablensky²²¹, Mark Jenkinson^{222,223,224}, Tianye Jia^{225,226,227}, Karl-Heinz Jöckel²²⁸, Erik G. Jönsson^{157,229}, Sungeun Kim^{230,231}, Marieke Klein^{98,232}, Peter

Kochunov²³³, John B. Kwok^{234,235}, Stephen M. Lawrie²³⁶, Stephanie Le Hellard^{195,202}, Hervé Lemaître³⁸, Carmel Loughland^{237,238}, Andre F. Marquand⁶¹, Nicholas G. Martin²³⁹, Jean-Luc Martinot²⁴⁰, Mar Matarin²⁴¹, Daniel H. Mathalon^{242,243}, Karen A. Mather^{65,172}, Venkata S. Mattay^{130,184,244}, Colm McDonald¹⁷⁸, Francis J. McMahon²⁴⁵, Katie L. McMahon²⁴⁶, Rebekah E. McWhirter^{247,248}, Patrizia Mecocci²⁴⁹, Ingrid Melle^{155,250}, Andreas Meyer-Lindenberg²⁵¹, Patricia T. Michie²⁵², Yuri Milaneschi²⁵³, Derek W. Morris¹⁷⁸, Bryan Mowry^{210,254}, Kwangsik Nho²³¹, Thomas E. Nichols²⁵⁵, Markus N. Nöthen⁷⁰, Rene L. Olvera²⁵⁶, Jaap Oosterlaan^{257,258}, Roel A. Ophoff^{53,259}, Massimo Pandolfo^{260,261}, Christos Pantelis^{262,263,264}, Irene Pappa⁵³, Brenda Penninx²⁶⁵, G. Bruce Pike²⁶⁶, Paul E. Rasser^{238,267,268}, Miguel E. Rentería²⁶⁹, Simone Reppermund^{172,270}, Marcella Rietschel²⁷¹, Shannon L. Risacher²⁷², Nina Romanczuk-Seiferth¹⁹⁸, Emma Jane Rose²⁷³, Perminder S. Sachdev^{172,274}, Philipp G. Sämann²⁷⁵, Andrew J. Saykin^{200,272}, Ulrich Schall^{238,268}, Peter R. Schofield^{65,235}, Sara Schramm²²⁸, Gunter Schumann^{198,276,277}, Rodney Scott^{238,268,278}, Li Shen²⁷⁹, Sanjay M. Sisodiya^{280,281}, Hilkka Soininen²⁸², Emma Sprooten¹⁷⁷, Velandai Srikanth²⁸³, Vidar M. Steen¹⁹⁵, Lachlan T. Strike²¹⁰, Anbupalam Thalamuthu¹⁷², Arthur W. Toga²⁸⁴, Paul Tooney^{32,267,268}, Diana Tordesillas-Gutiérrez^{285,286}, Jessica A. Turner²⁸⁷, Maria del C. Valdés Hernández^{119,120,142}, Dennis van der Meer^{288,289}, Nic J.A. Van der Wee^{290,291}, Neeltje E.M. Van Haren^{53,169}, Dennis van 't Ent¹⁷⁰, Dick J. Veltman^{265,292}, Henrik Walter¹⁹⁸, Daniel R. Weinberger^{184,293}, Michael W. Weiner⁵⁹, Wei Wen^{172,274}, Lars T. Westlye^{21,163,294}, Eric Westman²⁹⁵, Anderson M. Winkler^{219,296}, Girma Woldehawariat²⁹⁷, Margaret J. Wright^{210,298}, Jingqin Wu³².

Affiliations

¹Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

²Department of Cell Biology, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

³Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

⁴Department of Radiology and Nuclear Medicine, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

⁵Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, UT Health San Antonio, San Antonio, TX, USA.

⁶The Framingham Heart Study, Framingham, MA, USA.

⁷Department of Neurology, Boston University School of Medicine, Boston, MA, USA.

⁸University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team VINTAGE, UMR 1219, Bordeaux, France.

⁹Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Germany.

¹⁰German Centre of Neurodegenerative Diseases (DZNE), Site Rostock/Greifswald, Greifswald, Germany.

¹¹Brown Foundation Institute of Molecular Medicine, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA.

¹²Stroke Research Centre, University College London, Institute of Neurology, London, UK.

¹³Department of Neurosurgery, Klinikum rechts der Isar, University of Munich, Munich, Germany

¹⁴Department of Neurology and Cerebrovascular Disorders, Poznań University of Medical Sciences, Poznań, Poland.

¹⁵Department of Epidemiology, School of Public Health, University of Alabama at Birmingham Shool of Medicine, Birmingham, AL, USA.

¹⁶Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands.

¹⁷Clinical Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, University of California Irvine, Irvine, CA, United States.

¹⁸Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, CA, USA.

¹⁹Department of Biomedicine, University of Basel, Basel, Switzerland.

²⁰Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland.

²¹Department of Psychology, University of Oslo, Oslo, Norway.

²²The Hospital for Sick Children, University of Toronto, Toronto, Canada.

²³Department of Nutritional Sciences, University of Toronto, Toronto, Canada.

²⁴Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany.

²⁵LIFE Research Center for Civilization Disease, Leipzig, Germany.

²⁶Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology (NTNU), Trondheim, Norway.

²⁷Department of Radiology and Nuclear Medicine, St. Olavs University Hospital, Trondheim, Norway.

²⁸Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden.

²⁹Department of Clinical Genetics, Karolinska University Hospital, Stockholm, Sweden.

³⁰Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.

³¹Laboratory of NeuroGenetics, Department of Psychology & Neuroscience, Duke University, Durham, NC, USA.

³²School of Biomedical Sciences and Pharmacy, The University of Newcastle, Callaghan, NSW, Australia.

³³Centre for Brain and Mental Health Research, Hunter Medical Research Institute, Newcastle, NSW, Australia.

³⁴Department of Biostatistics and Data Science, Wake Forest School of Medicine, Winston-Salem, NC, USA.

³⁵Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa.

³⁶Research Division, Institute of Mental Health, Singapore.

³⁷Groupe d'Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives, UMR5293, Université de Bordeaux, Bordeaux, France.

³⁸Groupe d'Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives, UMR5293, CNRS, Bordeaux, France.

³⁹Groupe d'Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives, UMR5293, CEA, Bordeaux, France.

⁴⁰Department of Neurology, Maastricht University Medical Center+, Maastricht, The Netherlands.

⁴¹Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands.

⁴²Department of Biostatistics, Boston University School of Public Health, Boston, MA, USA.

⁴³Department of Neurology, Max Planck Institute for Cognitive and Brain Sciences, Leipzig, Germany.

⁴⁴Collaborative Research Center 1052 Obesity Mechanisms, Faculty of Medicine, University of Leipzig, Leipzig, Germany.

⁴⁵Cardiovascular Health Research Unit, Department of Medicine, University of Washington, Seattle, WA, USA.

⁴⁶The University of Texas at Austin Dell Medical School, Austin, TX, USA.

⁴⁷Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, Greifswald, Germany.

⁴⁸Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany

⁴⁹JARA-BRAIN, Jülich-Aachen Research Alliance, Jülich, Germany

⁵⁰Institute for Anatomy I, Medical Faculty, Heinrich Heine University Duesseldorf, Duesseldorf, Germany

⁵¹University of Bordeaux, CNRS, INCIA, UMR 5287, team NeuroImagerie et Cognition Humaine, Bordeaux, France.

⁵²EPHE-PSL University, Bordeaux, France.

⁵³Department of Child and Adolescent Psychiatry, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

⁵⁴University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team SEPIA, UMR 1219, Bordeaux, France.

⁵⁵Department of Neurology and Center for Neuroscience, University of California at Davis, Sacramento, CA, USA.

⁵⁶Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

⁵⁷Folkhälsan Research Center, Helsinki, Finland.

⁵⁸San Francisco Veterans Administration Medical Center, San Francisco, CA, USA.

⁵⁹University of California San Francisco, San Francisco, CA, USA.

⁶⁰Department of Psychiatry, Radboud University Medical Center, Nijmegen, The Netherlands.

⁶¹Donders Institute for Brain, Cognition and Behaviour, Radboud University, Nijmegen, The Netherlands.

⁶²Department of Internal Medicine, Section on Nephrology, Wake Forest School of Medicine, Winston-Salem, NC, USA.

⁶³Institute of Clinical Chemistry and Laboratory Medicine, University Medicine Greifswald, Greifswald, Germany.

⁶⁴School of Psychiatry, the University of New South Wales, Sydney, NSW, Australia.

⁶⁵Neuroscience Research Australia, Sydney, NSW, Australia.

⁶⁶MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK.

⁶⁷Population Health Sciences, University of Bristol, Bristol, UK.

⁶⁸Bristol Dental School, University of Bristol, Bristol, UK.

⁶⁹University of Bordeaux, Inserm, Bordeaux Population Health Research Center, team LEHA, UMR 1219, Bordeaux, France.

⁷⁰Institute of Human Genetics, University of Bonn Medical School, Bonn, Germany.

⁷¹Interfaculty Institute for Genetics and Functional Genomics, University Medicine Greifswald, Greifswald, Germany.

⁷²Department of Neurology, Erasmus MC University Medical Center, Rotterdam, the Netherlands.

⁷³Department of Radiology, Mayo Clinic, Rochester, MN, USA.

⁷⁴Imaging Genetics Center, Mark & Mary Stevens Neuroimaging & Informatics Institute, Keck USC School of Medicine, CA, USA.

⁷⁵Department of Psychiatry, Psychotherapy and Psychosomatics, RWTH Aachen University, Medical Faculty, Aachen, Germany.

⁷⁶Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.

⁷⁷Department of Neurology, University of Washington, Seattle, WA, USA.

⁷⁸Department of Epidemiology, University of Washington, Seattle, WA, USA.

⁷⁹Laboratory of Molecular Psychiatry, Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine, CA, USA.

⁸⁰Groupe d'Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives, Centre National de la Recherche Scientifique, Commissariat à l'Energie Atomique, et Université de Bordeaux, Bordeaux, France.

⁸¹Centre Hospitalo-Universitaire de Bordeaux, Bordeaux, France.

⁸²Psychiatric Genetics, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia.

⁸³School of Psychology, University of Queensland, Brisbane, QLD, Australia.

⁸⁴Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia.

⁸⁵Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan.

⁸⁶Institute for Urban Public Health, University of Duisburg-Essen, Essen, Germany.

⁸⁷Department of Medicine, Division of Geriatrics, University of Mississippi Medical Center, Jackson, MS, USA.

⁸⁸Memory Impairment and Neurodegenerative Dementia (MIND) Center, Jackson, MS, USA.

⁸⁹C. and O. Vogt Institute for Brain Research, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

⁹⁰Unit 2, Candidate Discovery Science Labs, Drug Discovery Research, Astellas Pharma Inc, 21, Miyukigaoka, Tsukuba, Ibaraki 305-8585, Japan.

⁹¹Department of Biochemistry, Wake Forest School of Medicine, Winston-Salem, NC, USA.

⁹²Department of Psychiatry, University of California Irvine, Irvine, CA, USA.

⁹³Clinical Division of Neurogeriatrics, Department of Neurology, Medical University of Graz, Graz, Austria.

⁹⁴University of Minnesota School of Public Health, Minneapolis, MN, USA.

⁹⁵Kaiser Permanente Division of Research, Oakland, CA, USA.

⁹⁶Department of Genetics & UNC Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.

⁹⁷Institute for Community Medicine, University Medicine Greifswald, Greifswald, Germany.

⁹⁸Department of Human Genetics, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, the Netherlands.

⁹⁹Department of Clinical Genetics MUMC+, GROW School of Oncology and developmental biology, and MHeNs School of Mental Health and Neuroscience, Maastricht University, The Netherlands.

¹⁰⁰Bordeaux Population Health, University of Bordeaux INSERM U1219, Bordeaux, France.

¹⁰¹West Region, Institute of Mental Health, Singapore.

¹⁰²Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

¹⁰³Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

¹⁰⁴MRC Unit on Risk and Resilience, University of Cape Town, Cape Town, South Africa.

¹⁰⁵Centre for Genomic Sciences, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.

¹⁰⁶Department of Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong.

¹⁰⁷Day Clinic for Cognitive Neurology, University Hospital Leipzig, Leipzig, Germany.

¹⁰⁸Bloorview Research Institute, Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada.

¹⁰⁹Departments of Psychology and Psychiatry, University of Toronto, Toronto, Canada.

¹¹⁰Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Atlanta, GA, USA.

¹¹¹Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute of Aging, The National Institutes of Health, Bethesda, MD, USA.

¹¹²Human Genetics Center, School of Public Health, University of Texas Health Science Center at Houston, Houston, TX, USA.

¹¹³Department of Neurology, Bordeaux University Hospital, Bordeaux, France.

¹¹⁴Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1167 - RID-AGE - Risk Factors and Molecular Determinants of Aging-Related Diseases and Labex Distalz, Lille, France.

¹¹⁵Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, USA.

¹¹⁶Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA.

¹¹⁷Brain Research Imaging Centre, University of Edinburgh, Edinburgh, UK.

¹¹⁸Department of Computer Science, Lagos State University, Lagos, Nigeria.

¹¹⁹Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) Collaboration, Department of Neuroimaging Sciences, University of Edinburgh, Edinburgh, UK.

¹²⁰Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK.

¹²¹Edinburgh Imaging, University of Edinburgh, Edinburgh, UK.

¹²²Centre for Brain Research, Indian Institute of Science, Bangalore, India.

¹²³Memory Aging & Cognition Centre, Departments of Pharmacology and Psychological Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

¹²⁴Duke-NUS Medical School, Singapore.

¹²⁵Singapore Eye Research Institute, Singapore.

¹²⁶Center for Translational and Computational Neuroimmunology, Department of Neurology and the Taub Institute for Research on Alzheimer's disease and the Aging brain, Columbia University Irving Medical Center, New York NY, USA.

¹²⁷Lothian Birth Cohorts, Department of Psychology, University of Edinburgh, Edinburgh, UK.

¹²⁸Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA.

¹²⁹Department of Psychiatry and Behavioral Sciences, Rush University Medical Center, Chicago, IL, USA.

¹³⁰Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

¹³¹Department of Epidemiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

¹³²Icelandic Heart Association, Kopavogur, Iceland.

¹³³Faculty of Medicine, University of Iceland, Reykjavik, Iceland.

¹³⁴Saw Swee Hock School of Public Health, National University of Singapore, Singapore.

¹³⁵Department of Pharmacology, National University of Singapore, Singapore.

¹³⁶Memory Aging and Cognition Center, National University Health System, Singapore.

¹³⁷Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria.

¹³⁸Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands.

¹³⁹Netherlands Heart Institute, Utrecht, the Netherlands.

¹⁴⁰Netherlands Consortium of Healthy Ageing.

¹⁴¹Durrer Center for Cardiogenetic Research, Amsterdam, the Netherlands.

¹⁴²Centre for Cognitive Ageing and Cognitive Epidemiology, Psychology, University of Edinburgh, Edinburgh, UK.

¹⁴³Department of Biology, Maynooth University, Maynooth, Co. Kildare, Ireland.

¹⁴⁴Department of Neurology and Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

¹⁴⁵Imaging of Dementia and Aging (IDeA) Laboratory, University of California at Davis, Davis, CA, USA.

¹⁴⁶Faculty of Applied Sciences, Delft University of Technology, Delft, the Netherlands.

¹⁴⁷GeneSTAR Research Program, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

¹⁴⁸Institute for Translational Genomics and Population Sciences, the Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA, USA.

¹⁴⁹University of Miami Miller School of Medicine, Miami, FL, USA.

¹⁵⁰Research Unit Genetic Epidemiology, Gottfried Schatz Research Center, Division of Molecular Biology and Biochemistry, Medical University Graz, Graz, Austria.

¹⁵¹Department of Social and Behavioural Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

¹⁵²Department of Internal Medicine, Section of Gerontology and Geriatrics, Leiden University Medical Center, Leiden, the Netherlands.

¹⁵³Department of Radiology, Leiden University Medical Center, Leiden, the Netherlands.

¹⁵⁴UK Dementia Research Centre, University of Edinburgh, Edinburgh, UK.

¹⁵⁵NORMENT (Norwegian Centre for Mental Disorders Research), Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

¹⁵⁶Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway.

¹⁵⁷Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet & Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden.

¹⁵⁸Neurology Department, Yale University School of Medicine, New Haven, CT, USA.

¹⁵⁹Department of Genetics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA.

¹⁶⁰Department of Biomedical and Health Informatics , Children's Hospital of Philadelphia, Philadelphia, PA, USA.

¹⁶¹Academic Unit for Psychiatry of Old Age, University of Melbourne, St George's Hospital, Kew, Australia.

¹⁶²National Ageing Research Institute, Parkville, Victoria, Australia.

¹⁶³CoE NORMENT, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway.

¹⁶⁴Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

¹⁶⁵Mathematics & Statistics, Murdoch University, Perth, WA, Australia.

¹⁶⁶Translational Medicine, Hospital for Sick Children, University of Toronto, Toronto, Canada.

¹⁶⁷Department of Human Genetics, Brownsville, TX, USA.

¹⁶⁸South Texas Diabetes and Obesity Institute, University of Texas Rio Grande Valley School of Medicine, Brownsville, TX, USA.

¹⁶⁹Department of Psychiatry, UMC Utrecht, Utrecht, the Netherlands.

¹⁷⁰VU university Amsterdam, Department of Biological Psychology & Netherlands Twin Register, Amsterdam, Netherlands.

¹⁷¹Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA.

¹⁷²CHeBA (Centre for Healthy Brain Ageing), School of Psychiatry, UNSW Sydney, Sydney, Australia.

¹⁷³Dementia Centre for Research Collaboration, University of New South Wales, Sydney, Australia.

¹⁷⁴Department of Psychology and Center for Brain Science, Harvard University, Boston, MA, USA.

¹⁷⁵Department of Radiology, Massachusetts General Hospital, Boston, MA, USA.

¹⁷⁶Department of Psychiatry, Massachusetts General Hospital, Boston, MA, USA.

¹⁷⁷Department of Cognitive Neuroscience, Donders Institute for Brain, Cognition and Behavior, Radboudumc, Nijmegen, the Netherlands.

¹⁷⁸Centre for Neuroimaging & Cognitive Genomics (NICOG), Clinical Neuroimaging Laboratory, NCBES Galway Neuroscience Centre, College of Medicine Nursing and Health Sciences, National University of Ireland Galway, Galway, Ireland.

¹⁷⁹Department of Psychiatry, School of Clinical Sciences, Monash University, Melbourne, Victoria, Australia.

¹⁸⁰University of Queensland, Brisbane, QLD, Australia.

¹⁸¹University of Sydney, Sydney, Australia.

¹⁸²Computational Brain Anatomy (CoBrA) Laboratory, Cerebral Imaging Centre, Douglas Research Centre, Montreal, QC, Canada.

¹⁸³Departments of Psychiatry and Biological and Biomedical Engineering, McGill University, Montreal, QC, Canada.

¹⁸⁴Lieber Institute for Brain Development, Baltimore, MD, USA.

¹⁸⁵Department of Psychiatry, Trinity Translational Medicine Institute, Trinity College, Dublin, Ireland.

¹⁸⁶Hospital Universitario Virgen del Rocío, Department of Psychiatry, IBISS, University of Sevilla, Sevilla, Spain.

¹⁸⁷CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Sevilla, Spain.

¹⁸⁸Avera Institute for Human Genetics, Sioux Falls, SD, USA.

¹⁸⁹Department of Biological Psychology, Vrije Universiteit Amsterdam, Amsterdam, the Netherlands.

¹⁹⁰Amsterdam Public Health Research Institute, Amsterdam UMC, Amsterdam, the Netherlands.

¹⁹¹Faculty of Health and Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia.

¹⁹²MRC-SGDP Centre, Institute of Psychiatry, King's College London, London, UK.

¹⁹³Cell Biology and Gene Expression Section, Laboratory of Neurogenetics, National Institute on Aging, National Institutes of Health, Bethesda, Maryland, USA.

¹⁹⁴Department of Medical Genetics, Oslo University Hospital, Oslo, Norway.

¹⁹⁵NORMENT, Department of Clinical Science, University of Bergen, Bergen, Norway.

¹⁹⁶Janssen Research & Development, LLC, of Johnson & Johnson, San Diego, CA, USA.

¹⁹⁷Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU Dresden, Germany.

¹⁹⁸Department of Psychiatry and Psychotherapy, Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany.

¹⁹⁹Bjørknes College, Oslo, Norway.

²⁰⁰Indiana University School of Medicine, Department of Medical and Molecular Genetics, Indianapolis, IN, USA.

²⁰¹Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA.

²⁰²Dr Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway.

²⁰³Department of Psychiatry, Boston Children's Hospital and Harvard Medical School, Boston, MA, USA.

²⁰⁴Brigham and Women's Hospital, Boston, MA, USA.

²⁰⁵The Broad Institute, Boston, MA, USA.

²⁰⁶Harvard Medical School, Boston, MA, USA.

²⁰⁷Karakter, Child and Adolescent Psychiatry, University Center, Nijmegen, the Netherlands.

²⁰⁸King's College London, Social, Genetic and Developmental Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, London, UK.

²⁰⁹Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital, Goethe University, Frankfurt, Germany.

²¹⁰Queensland Brain Institute, University of Queensland, Brisbane, Australia.

²¹¹University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation, Groningen, the Netherlands.

²¹²Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan.

²¹³School of Medicine & Public Health, University of Newcastle, Callaghan, NSW, Australia.

²¹⁴Health Behaviour Research Group, University of Newcastle, Callaghan, NSW, Australia.

²¹⁵Genentech, Inc., South San Francisco, CA, USA.

²¹⁶Department of Psychiatry, University of Iowa Carver College of Medicine, Iowa City, IA, USA.

²¹⁷University of Groningen, University Medical Center Groningen, Department of Child and Adolescent Psychiatry, Groningen, Netherlands.

²¹⁸Department of Psychology, Yale University, New Haven, Connecticut, USA.

²¹⁹Department of Psychiatry, Yale University, New Haven, Connecticut, USA.

²²⁰Brain Center Rudolf Magnus, Department of Psychiatry, UMC Utrecht, Utrecht, the Netherlands.

²²¹University of Western Australia, Perth, Australia.

²²²Wellcome centre for Integrative Neuroimaging (WIN), Nuffield Department of Clinical Neurosciences, University of Oxford, John Radcliffe Hospital, Oxford, UK.

²²³Australian Institute of Machine Learning (AIML), Department of Computer Science, University of Adelaide, SA, Australia.

²²⁴South Australian Health and Medical Research Institute (SAHMRI), North Terrace, Adelaide, SA, Australia.

²²⁵Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China.

²²⁶Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Fudan University), Ministry of Education, China.

²²⁷Centre for Population Neuroscience and Precision Medicine, MRC SGDP Centre, IoPPN, King's College London, London, UK.

²²⁸Institute of Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, Germany.

²²⁹NORMENT – TOP study, Institute of Clinical Medicine, Psychiatry section, University of Oslo, Oslo, Norway.

²³⁰Electrical and Computer Engineering, State University of New York, Oswego, NY, USA.

²³¹Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA.

²³²Department of Psychiatry, University of California San Diego, CA, USA.

²³³Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA.

²³⁴Brain and Mind Centre, The University of Sydney, Camperdown, NSW, Australia.

²³⁵School of Medical Sciences, University of New South Wales, Sydney, Australia.

²³⁶Division of Psychiatry, University of Edinburgh, Royal Edinburgh Hospital, Edinburgh, Scotland, UK.

²³⁷Hunter New England Health, New Lambton, NSW, Australia.

²³⁸University of Newcastle, Callaghan, NSW, Australia.

²³⁹QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia.

²⁴⁰INSERM U A10 "Trajectoires développementales & psychiatrie", Université Paris-Saclay, Ecole Normale Supérieure Paris-Saclay, CNRS, Centre Borelli, Gif-sur-Yvette, France.

²⁴¹UCL Institute of Neurology, London, United Kingdom and Epilepsy Society, UK.

²⁴²Department of Psychiatry and Behavioral Sciences and Weill Institute for Neurosciences, University of California, San Francisco, CA, USA.

²⁴³Veterans Affairs San Francisco Healthcare System, San Francisco, CA, USA.

²⁴⁴Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

²⁴⁵Genetic Basis of Mood & Anxiety Section, Human Genetics Branch, NIMH Intramural Research Program, NIH, Bethesda, MD, USA.

²⁴⁶School of Clinical Sciences, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia.

²⁴⁷Menzies Institute for Medical Research, University of Tasmania, Hobart, Tasmania, Australia.

²⁴⁸Centre for Law and Genetics, Faculty of Law, University of Tasmania, Hobart, Tasmania, Australia.

²⁴⁹Section of Gerontology and Geriatrics, Department of Medicine, University of Perugia, Perugia, Italy.

²⁵⁰NORMENT Centre, Oslo University Hospital, Oslo, Norway.

²⁵¹Clinical Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany.

²⁵²School of Psychology, University of Newcastle, Callaghan, NSW, Australia.

²⁵³Department of Psychiatry, Amsterdam Public Health and Amsterdam Neuroscience, Amsterdam UMC/Vrije Universiteit & GGZinGeest, Amsterdam, the Netherlands.

²⁵⁴Queensland Centre for Mental Health Research, The University of Queensland, Brisbane, QLD, Australia.

²⁵⁵Oxford Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, Nuffield Department of Population Health, University of Oxford, Oxford, UK.=

²⁵⁶Departments of Psychiatry and Pediatrics, UT Health San Antonio, San Antonio, TX, USA.

²⁵⁷Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Emma Neuroscience Group, department of Pediatrics, Amsterdam Reproduction & Development, Amsterdam, the Netherlands.

²⁵⁸Vrije Universiteit, Clinical Neuropsychology section, Amsterdam, the Netherlands.

²⁵⁹UCLA Center for Neurobehavioral Genetics, Los Angeles, California, USA.

²⁶⁰Department of Neurology, Hopital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

²⁶¹ULB Laboratory of Experimental Neurology, Brussels, Belgium.

²⁶²Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia.

²⁶³NorthWestern Mental Health, Sunshine Hospital, Sunshine, Victoria, Australia.

²⁶⁴Florey Institute for Neuroscience and Mental Health, Parkville, Victoria, Australia.

²⁶⁵Department of Psychiatry, Amsterdam UMC, Vrije Universiteit, Amsterdam, the Netherlands.

²⁶⁶Departments of Radiology and Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada.

²⁶⁷Priority Research Centres for Brain and Mental Health Research and Stroke and Brain Injury, University of Newcastle, Newcastle, Australia.

²⁶⁸Hunter Medical Research Institute, Newcastle, NSW, Australia.

²⁶⁹Department of Genetics & Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia.

²⁷⁰Department of Developmental Disability Neuropsychiatry, School of Psychiatry, University of New South Wales, Sydney, Australia.

²⁷¹Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Mannheim, Germany.

²⁷²Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA.

²⁷³Program for Translational Research on Adversity and Neurodevelopment (P-TRAN), Edna Bennett Pierce Prevention Research Center, The Pennsylvania State University, Pennsylvania, USA.

²⁷⁴Neuropsychiatric Institute, The Prince of Wales Hospital, Sydney, Australia.

²⁷⁵Max Planck Institute of Psychiatry, Munich, Germany.

²⁷⁶Centre for Population Neuroscience and Stratified Medicine (PONS), Institute of Psychiatry, Psychology and Neuroscience, SGDP-Centre, King's College London, London, UK.

²⁷⁷Institute for Science and Technology of Brain-Inspired Intelligence (ISTBI), Fudan University, Shanghai, China.

²⁷⁸NSW Health Pathology, Newcastle, NSW, Australia.

²⁷⁹Department of Biostatistics, Epidemiology and Informatics, Institute for Biomedical Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

²⁸⁰UCL Queen Square Institute of Neurology, London, UK.

²⁸¹Chalfont Centre for Epilepsy, Bucks, UK.

²⁸²Institute of Clinical Medicine, Neurology, University of Eastern Finland, Kuopio, Finland.

²⁸³Peninsula Clinical School, Central Clinical School, Monash University, Australia.

²⁸⁴Laboratory of Neuro imaging, USC Stevens Neuroimaging and Informatics Institute, University of Southern California, Los Angeles, CA, USA.

²⁸⁵Neuroimaging Unit, Technological Facilities, Valdecilla Biomedical Research Institute IDIVAL, Spain.

²⁸⁶Centro Investigación Biomédica en Red de Salud Mental (CIBERSAM), Spain.

²⁸⁷Psychology Department & Neuroscience Institute, Georgia State University, Atlanta, GA, USA.

²⁸⁸NORMENT, KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

²⁸⁹School of Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, the Netherlands.

²⁹⁰Department of Psychiatry, Leiden University Medical Center, Leiden, the Netherlands.

²⁹¹Leiden Institute for Brain and Cognition, Leiden University Medical Center, Leiden, the Netherlands.

²⁹²Amsterdam Neuroscience, Amsterdam, the Netherlands.

²⁹³Departments of Psychiatry, Neurology, Neuroscience and Genetic Medicine, Johns Hopkins University, Baltimore, MD, USA.

²⁹⁴KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo, Oslo, Norway.

²⁹⁵Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden.

²⁹⁶National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA.

²⁹⁷Human Genetics Branch, National Institute of Mental Health (NIMH), National Institute of Health (NIH), Bethesda, MD, USA.

²⁹⁸Centre for Advanced Imaging, University of Queensland, Brisbane, Queensland, Australia.