

Imaging genomics reveals genetic architecture of the globular human braincase

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Abstract:

Compared with our fossil ancestors and Neandertal kin, modern humans have evolved a distinctive skull shape, with a rounder braincase and more delicate face. Competing explanations for this rounder skull have either linked it to changes in brain organisation, or seen it as a by-product of gracilization (evolution of thinner and lighter skeletal anatomy). Here, we combined palaeoanthropological data from hominin fossils and imaging genomics data from living humans to gain insight into evolutionary and developmental mechanisms shaping this uniquely modern human phenotype. We analysed endocranial globularity from magnetic resonance imaging (MRI) brain scans and genetic data of more than 33,000 adults. We discovered 28 genomic loci significantly associated with endocranial globularity. There was genetic overlap with the brain's ventricular system, white matter microstructure, and sulcal morphology, and with multivariate genetic analyses of reading/language skills, but not with general cognition. The associated genes exhibited enriched expression in the brain during prenatal development and early childhood. The connection to the ventricular system hints at a role for cerebrospinal fluid pressure in shaping the endocranium during development. Genes linked to endocranial globularity also showed enhanced expression in the cardiovascular and female reproductive systems. This finding suggests co-evolutionary pathways whereby changes impacting factors such as energy needs, pregnancy, or fertility concurrently shape the brain and its structure.

40 **Main Text:**

41 During foetal and infant development, the growing brain leaves an impression inside the skull.
42 Such endocranial imprints (endocasts) in fossil skulls document evolutionary changes in brain
43 volume, folding patterns, and brain shape. Modern humans have a distinct endocranial shape,
44 that is more globular than the elongated endocrania seen in all other fossil hominins and apes^{1,2}.
45 This endocranial globularity involves increased parietal bulging and an enlarged posterior cranial
46 fossa, which houses the cerebellum (Fig. 1A). This unique phenotype emerged within the *Homo*
47 *sapiens* lineage³, and is the most recently evolved anatomical trait of our species²⁻⁵.

48 Endocranial shape changes are not causally related to evolutionary changes in endocranial
49 volume, since the endocranial volumes of Neandertals and early *Homo sapiens* (~300 kya)^{2,3} fall
50 within the range of modern variation, but these fossils still have elongated endocrania. In present-
51 day humans, globularity emerges during early ontogeny⁶ – an important period for establishing
52 the white-matter networks of the brain. Consequently, endocranial globularity has been
53 associated with the timing and pattern of brain growth and development, especially the process
54 of myelination^{2,5}. Another theory suggests that evolutionary changes in facial size and robusticity,
55 possibly related to diet, were the main drivers of endocranial shape changes within the *Homo*
56 *sapiens* lineage⁷. However, it is not possible to uncover the underlying developmental processes
57 based on endocasts alone, as these represent only the brain's outer surface. Here, we combine
58 palaeoanthropology with archaic and neuroimaging genomics, and use interindividual variation in
59 present-day humans as a window into our evolutionary past. We investigate the biological
60 mechanisms underlying endocranial globularity to enhance our understanding of human brain
61 evolution.

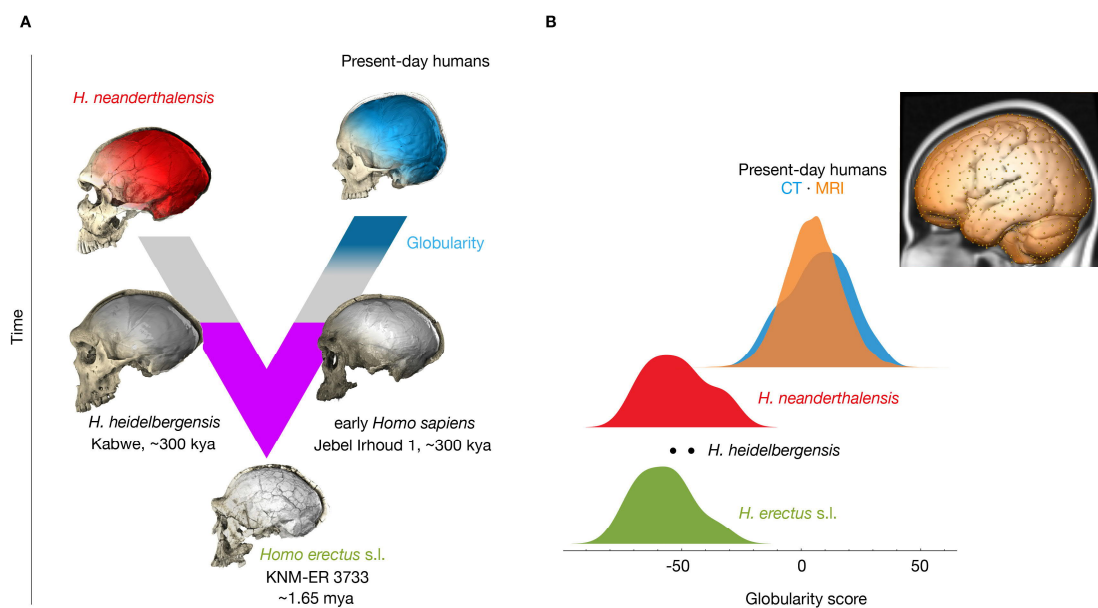
62 An earlier focused study, which used MRI brain scans and DNA data of around 4,500 healthy
63 adults to look specifically for effects of different introgressed Neandertal genetic fragments on
64 endocranial globularity, found associations with the expression of two genes involved in
65 neurogenesis and myelination, respectively⁵. Here, we performed a systematic investigation of
66 the biological bases of endocranial globularity, based on morphometric data from hominin fossil
67 endocasts, integrated with phenotypic and genomic data in a much larger sample.

68 We used a morphometric analysis of MRI data from lifespan and cross-sectional biobanking
69 cohorts to create a metric that quantifies endocranial globularity, and investigated possible
70 differences across age and sex. We then performed a genome-wide search to identify DNA
71 variants associated with interindividual variation in endocranial globularity in tens of thousands of
72 present-day individuals. Derived summary statistics were used to gain insight into the shared
73 genetic architecture of endocranial globularity and a range of anatomical brain imaging traits. We
74 moved beyond the brain to investigate genetically-mediated associations with disease
75 phenotypes and other complex traits. Finally, we studied the underlying biological mechanisms
76 revealed by enrichment and functional analyses of associated loci, and contributions of genes
77 and genomic regions that show evolutionary changes along the human lineage, on timescales
78 relevant for the emergence of this distinctive human trait.

79 **An evolutionarily derived quantitative index of present-day human endocranial shape**

80 We used geometric morphometrics⁸ to derive a summary-measure of endocranial globularity from
81 T1-weighted brain images of two independent epidemiological datasets comprising in total 34,595
82 individuals with European ancestry (Cambridge Centre for Ageing Neuroscience (CamCAN))^{9,10}

83 and UK Biobank (UKB)¹¹). We first digitized a mesh of 935 coordinates on virtual endocasts from
 84 computed tomographic (CT) scans of fossil and present-day human crania, as well as the MNI
 85 152 brain template. We used Procrustes superimposition to standardize for position, orientation,
 86 and scale, and then projected each individual onto the vector between the average shape of
 87 Neandertals and present-day humans. This yields a *globularity score*, an evolutionarily derived
 88 summary measure of overall endocranial shape⁵. While globularity scores of present-day humans
 89 derived from CT scans and structural MRI both show a high degree of interindividual variability,
 90 scores from these two modalities cluster together, displaying a minimal overlap with globularity
 91 scores of extinct humans, based on fossil data (Fig. 1B).



92 **Fig. 1. An evolutionarily derived globularity score captures interindividual variability in present-day human**
 93 **endocranial shape.** (A) Neandertals and present-day humans share a common ancestor that lived more than 500
 94 kya^{12,13} and likely evolved from *Homo erectus s.l.* in Africa. Purple: Fossils document an increase of endocranial
 95 volumes in the lineages leading to Neandertals, and to *Homo sapiens*, respectively. Early *Homo sapiens* like, e.g.,
 96 Jebel Irhoud 1, have endocranial volumes as large as present-day humans, but elongated endocrania. The emergence
 97 of the globularity phenotype in the *Homo sapiens* lineage is symbolized in blue. Virtual endocasts based on CT data
 98 are shown for a present-day human, a Neandertal (La Ferrassie 1), *Homo heidelbergensis* (Kabwe), early *Homo*
 99 *sapiens* (Jebel Irhoud 1), and *Homo erectus* (KNM-ER 3733). (B) Histograms of globularity scores computed from
 100 different modalities (orange: MRI-based scores of present-day humans, N = 34,595; blue: CT-based scores of present-
 101 day humans, N = 89; red: CT-based scores of Neandertals, N = 10; grey: CT-based scores of *H. heidelbergensis*, N =
 102 2; green: CT-based scores of *H. erectus*, N = 8; The endocranial measurement coordinates are shown on the endocast
 103 segmentation of the MNI 152 brain template).

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 105 We first tested for potential effects of ageing on globularity scores using a lifespan dataset of
 106 healthy adult participants aged 18-88 years (CamCAN, N = 644), and found no association
 107 between age and endocranial globularity (Age: $t = 0.536$, $p = 0.592$; Age²: $t = -0.487$, $p = 0.626$)
 108 as well as no interaction of age and sex (Age*Sex: $t = -0.546$, $p = 0.585$; Age²*Sex: $t = 0.415$, $p =$
 109 0.678) (Supplementary Fig. 1A). Analysis of globularity scores derived from the UK Biobank (N =
 110 33,951), a large-scale cohort with a limited age-range clustering in the second half of life (mean
 111 + SD age 63.77 years \pm 7.52), showed a small effect that was statistically significant (Age: $t = -$
 112 3.822 , $p = 1.32 \times 10^{-4}$; Age²: $t = 3.709$, $p = 2.08 \times 10^{-4}$) with no significant interaction terms

113 (Age*Sex: $t = 1.695$, $p = 0.0900$; Age²*Sex: $t = -1.377$, $p = 0.169$), while overall only accounting
114 for 0.4% of the total variance ($F(5, 33945) = 25.1$, $p < 2.2 \times 10^{-16}$, $R^2_{\text{Adjusted}} = 0.0035$).

115 We also assessed possible sex effects on endocranial globularity and found a minor but
116 significant difference in globularity scores between males and females in the UK Biobank (t
117 $= 8.245$, $p < 2 \times 10^{-16}$, Cohen's $d = -0.0004$) (Supplementary Fig. 1B). Next, we investigated the
118 relationship with estimated total intracranial volume (eTIV) in UK Biobank ($N = 33,577$), finding a
119 statistically significant but subtle association, where eTIV explained 3.69% of the variance of
120 present-day endocranial globularity scores ($F(3, 33573) = 430.1$, $p < 2.2 \times 10^{-16}$, $R^2_{\text{Adjusted}} =$
121 0.0369) (Supplementary Fig. 1C). Lastly, using participant-specific health information available in
122 UK Biobank, we showed that globularity scores derived from people with distinct neuroanatomical
123 or neurodegenerative brain disorders ($N = 2,338$) do not differ from those of individuals without
124 such a diagnosis ($t = -0.039$, $p = 0.97$, Cohen's $d = -0.00084$) (Supplementary Fig. 1D).

125 **Genetics of interindividual differences in endocranial globularity**

126 Next, we performed a genome-wide association study (GWAS) to identify genetic variants
127 associated with interindividual differences in endocranial globularity. As age, neuroanatomical
128 and neurodegenerative disorders, and intracranial brain volume had either no or only marginal
129 influence on globularity scores, all 33,951 UK Biobank participants that passed genetic and
130 phenotypic quality control were included. These analyses identified 28 genome-wide significant
131 loci ($p \leq 5 \times 10^{-8}$), encompassing a total of 155 independent ($r^2 \leq 0.6$) genome-wide significant
132 single-nucleotide polymorphisms (SNPs) and insertions or deletions (indels), associated with
133 interindividual differences in endocranial globularity (Fig. 2A, Supplementary Fig. 2,
134 Supplementary Table 1).

135 The locus showing the most significant association (lead SNP rs9933149, $p = 1.58 \times 10^{-26}$) was
136 located in an intron of *C16orf95* on chromosome 16 (Supplementary Fig. 3). Previous studies
137 have associated this locus with individual variation in an array of neuroanatomical phenotypes
138 ranging from sulcal morphology to white-matter microstructure and ventricular volume^{14–24}.
139 Variants in the region have shown association with congenital heart defects²⁵ while multigene
140 deletions that encompass the coding region of *C16orf95* have been reported in cases of
141 microcephaly and neurodevelopmental disorders^{26,27}.

142 Most of the significantly associated variants showed small effect sizes, consistent with
143 expectations for a highly polygenic trait and in line with findings from other neuroimaging-based
144 traits^{28,29}. One notable exception was rs529711487, a rare variant (minor allele frequency =
145 0.002; European 1000 Genomes Phase 3 Reference Panel) on chromosome 3, which had a
146 strong effect on endocranial globularity with a Beta estimate of 6.68 (SE = 1.15) (Supplementary
147 Fig. 4A). The rs529711487 variant was in Hardy-Weinberg equilibrium (pexact test = 1) and had
148 a high imputation quality score (0.91). For this SNP, heterozygous carriers ($N = 114$) show larger
149 globularity scores compared to peers who are homozygous for the major allele (Supplementary
150 Fig. 4B); since there are no homozygous carriers of the minor allele in the UK Biobank
151 neuroimaging cohort, it was not possible to test whether it acts in an additive or dominant manner.

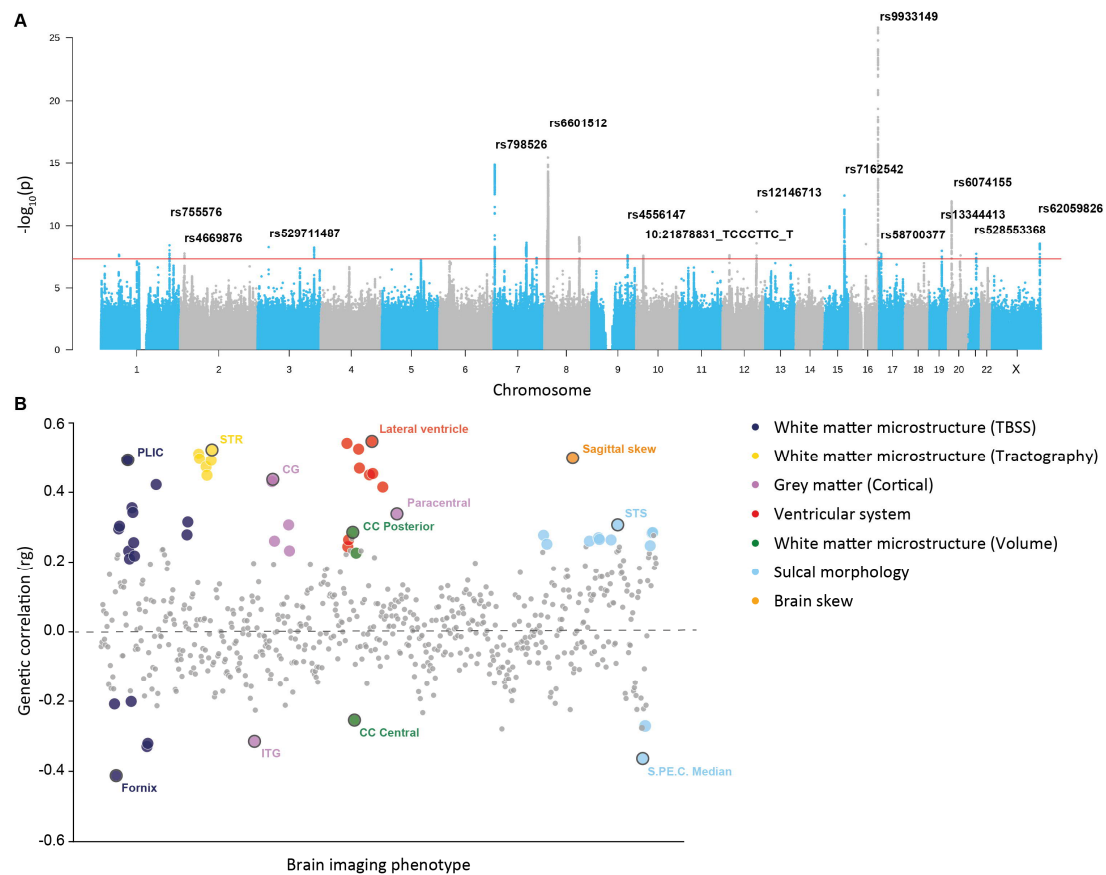


Fig. 2. Genetics of interindividual differences in endocranial globularity in a large cohort of present-day humans. (A) Manhattan plot of loci associated with interindividual variability in endocranial globularity ($N = 33,951$); the red line denotes genome-wide significance ($p < 5 \times 10^{-8}$). Per chromosome the respective top genome-wide significant loci are annotated with their lead SNP rsID. (B) Genetic correlations for endocranial globularity with 667 anatomical brain imaging phenotypes. Large coloured dots denote significant associations after Bonferroni correction, with top hits annotated per imaging category. CG = cingulate gyrus, ITG = inferior temporal gyrus, CC = corpus callosum, PLIC = posterior limb of the internal capsule, S.P.E.C Median = median precentral sulcus, STR = superior thalamic radiation, STS = superior temporal sulcus, TBSS = tract-based spatial statistics.

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Introgressed Neandertal alleles on chromosomes 1 and 18 that were associated with endocranial globularity in a prior targeted study of smaller cohorts⁵ exhibited the same direction of effect towards reduced globularity in UK Biobank (rs28445963, beta (SE) = -0.19 (0.22), $p = 0.37$; rs72931809, beta (SE) = -0.16 (0.21), $p = 0.45$) but associations were not significant.

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Next, we used the aggregated GWAS signal across the entire genome to gain further insights into the underlying biology. Estimates of SNP-heritability indicated that the captured genetic variation accounted for 32.6% (SE = 3.4%) of the observed phenotypic variation in endocranial globularity in the cohort. As genetic sex has distinct influences on brain (development), it is generally considered a possible confound in GWASs. To supplement the phenotypic analysis we also performed sex-stratified GWASs, finding a high genetic correlation between the male ($N = 16,148$) and female ($N = 17,803$) GWAS (rg (SE) = 0.9363 (0.0676)), $p = 1.245 \times 10^{-43}$ (Supplementary Fig. 5). Notably, with the exception of one indel (8:108402192_AGC_A, male GWAS), all

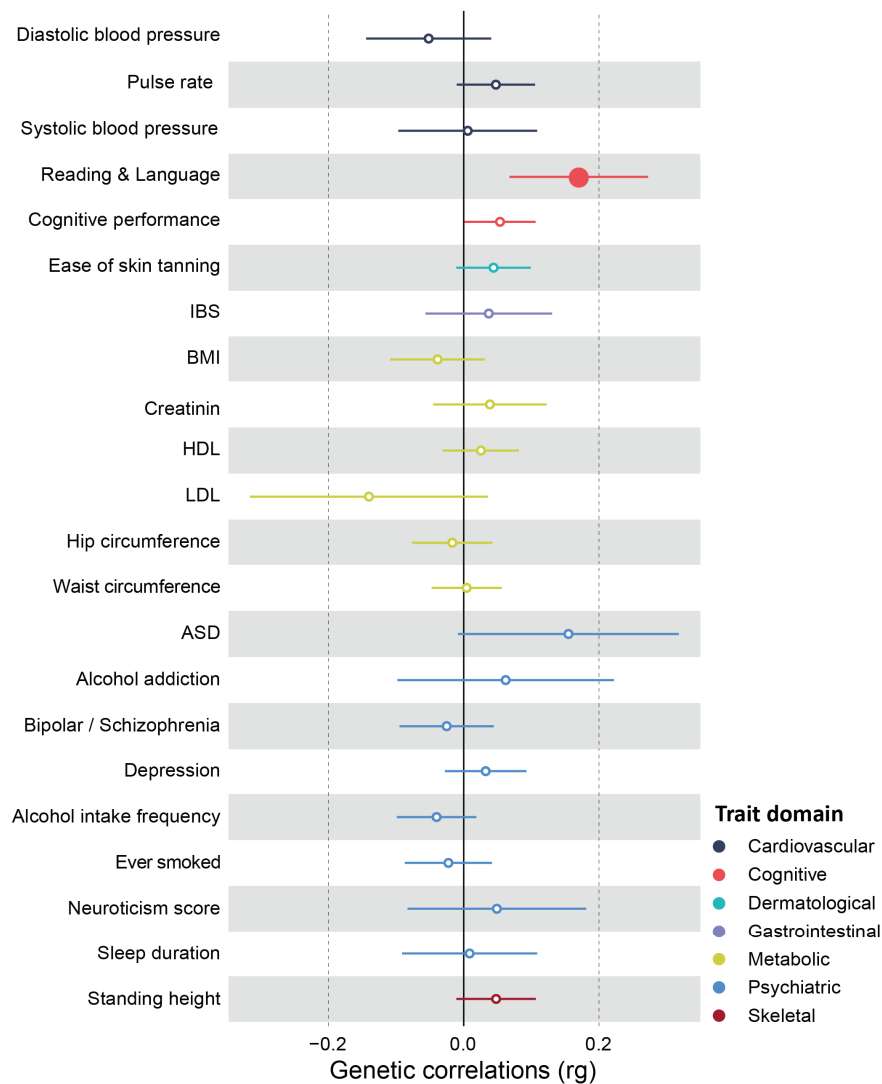
174 independent significantly associated variants in sex-stratified GWASs were also identified as
175 genomic regions associated with endocranial globularity (independent lead SNPs and SNPs in
176 LD ($r^2 > 0.6$)) in the primary GWAS (Supplementary Table 2). Thus, endocranial globularity shows
177 no pronounced sexual dimorphism, either phenotypically or genetically.

178 We went on to study relationships between endocranial globularity and a selection of other
179 relevant phenotypes, by estimating genetic correlations to measure the extent to which shared
180 genetic variation contributes to shared phenotypic variability across traits.

181 We used brain imaging derived phenotypes available in UK Biobank to assess whether certain
182 anatomical regions or specific metrics show significant genetic overlap with interindividual
183 variation of endocranial globularity, encompassing cortical and subcortical estimates as well as
184 white-matter microstructure estimates derived from tract-based spatial statistics (TBSS) and
185 probabilistic tractography. Further, we included metrics detailing sulcal brain morphology¹⁴ and
186 brain skew³⁰, traits with potential relevance to human evolution^{31–34} that are not part of the
187 standard UK Biobank processing pipeline. Of the 667 neuroanatomical phenotypes that we
188 analysed, 56 showed significant genetic correlations with endocranial globularity ($\alpha_{\text{Bonferroni}} = 0.05$
189 / 667 = 7.5×10^{-5}) (Fig. 2B, Supplementary Table 3), with strongest correlations for the ventricular
190 system, distinct white-matter tracts, certain sulcal width measures, and sagittal brain skew. Both
191 hemispheres contributed similarly to these correlations, while cortical (surface area, thickness)
192 and subcortical (volume) measures generally showed only small genetic overlaps with
193 endocranial globularity.

194 Because facial form was recently proposed to be a main driver of endocranial shape variation
195 during hominin evolution⁷ we tested whether any of the identified genomic regions associated
196 with endocranial globularity (independent lead SNPs and SNPs in LD ($r^2 > 0.6$)) were also
197 associated with individual differences in facial morphology in previous GWAS efforts^{35–51}. This
198 analysis highlighted four independent signals from four different genomic loci which showed both
199 an association here with endocranial globularity and in previous facial shape studies, mostly with
200 the morphology of the nose (Supplementary Table. 4).

201 Some have proposed links between the unique globularity of the human brain and the evolution
202 of cognitive capacities and emergence of complex human traits⁵². At the same time, evidence
203 from a range of sources supports a reappraisal of Neandertal capacities for complex behaviour,
204 suggesting that our archaic cousins had more cognitive sophistication than previously
205 appreciated^{53–56}. We tested for shared genetic underpinnings of endocranial globularity with a
206 curated set of complex human traits across several biological domains where an evolutionary
207 relevance was previously highlighted. Our choice was motivated by prior studies which highlighted
208 the phenotypic legacy of previous admixture events over trait domains linked to metabolism,
209 dermatology, the cardiovascular and gastrointestinal system, cognition, and skeletal features, as
210 well as neuropsychiatric disorders^{4,57–67} (Fig.3).



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Fig. 3. Genetic correlations between endocranial globularity and disease phenotypes and other complex traits. Large coloured dots denote significant associations after Bonferroni correction for the 22 phenotypes that were studied. Genetic correlation (rg) is presented as a dot, and error bars indicate the standard error. ASD = Autism spectrum disorder, BMI = Body mass index, HDL = high-density lipoprotein, IBS = Irritable bowel syndrome, LDL = low-density lipoprotein;

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A multivariate GWAS on reading- and language-related traits⁶⁸ was the only one to demonstrate a significant genetic correlation ($rg(SE) = 0.1704 (0.0523)$, $p = 0.0011$; $\alpha_{Bonferroni} = 0.05 / 22 = 0.0023$). In contrast, a measure of overall cognitive performance, as well as all other trait domains assessed here, exhibited no significant genetic overlap with endocranial globularity (Supplementary Table 5).

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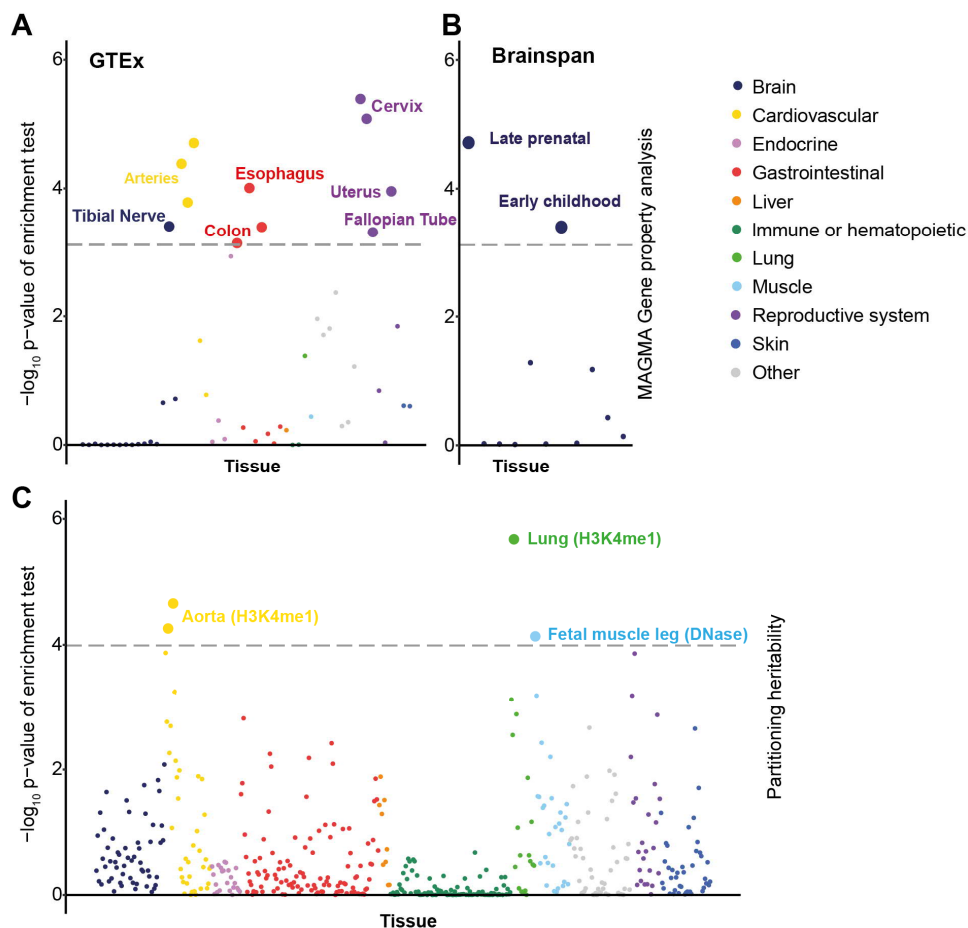
Functional enrichment in gene expression and chromatin data

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To gain insights into functions of genes related to endocranial globularity, we first examined gene-based associations using MAGMA's gene-based test as implemented in FUMA⁶⁹. 77 genes were

227 significantly associated with interindividual variation in endocranial globularity ($\alpha_{\text{Bonferroni}} = 0.05 /$
 228 $19,312 = 2.59 \times 10^{-6}$; Supplementary Table 6) with the top signal seen for *C16orf95*, in line with
 229 the SNP-based associations. We then performed MAGMA gene-property analysis to test for
 230 positive associations between tissue-specific gene expression profiles and gene-based p-values
 231 from the GWAS. Using two gene expression datasets (GTEx, Brainspan) ($\alpha_{\text{Bonferroni}} = 0.05 / (54 +$
 232 $11) = 7.69 \times 10^{-4}$) we identified significant enrichment in adult tissue (GTEx)⁷⁰ highlighting the
 233 tibial nerve as well as several non-brain tissues, mainly attributed to the cardiovascular,
 234 gastrointestinal (colon and oesophagus) and female reproductive systems (cervix, uterus,
 235 fallopian tube) (Fig. 4A, Supplementary Table 7). Further, enrichment in brain tissues sampled
 236 through development (Brainspan)⁷¹ highlighted late-prenatal and early childhood brain tissues
 237 (Fig. 4B, Supplementary Table 7).

238 We next tested for (brain) cell type enrichments using two single-cell RNA-sequencing datasets
 239 covering foetal and adult brain tissue which highlighted significant enrichments in endothelial cells
 240 of adult tissue (Supplementary Fig. 6, Supplementary Table 8).



241 **Fig. 4. Analyses of expression profiles in adult and brain developmental tissue as well as tissue-specific**
 242 **chromatin signatures.** Enrichment $-\log_{10}$ p-values of MAGMA gene-property analysis in gene expression data from
 243 (A) adult tissue and (B) brain tissue from different developmental time points. (C) Partitioned heritability enrichment -
 244 \log_{10} p-values in active regulatory elements across tissues and cell types. In all panels, the dashed line denotes the p-
 245 value threshold for significant enrichment after Bonferroni correction.
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247 To complement the gene expression analyses, we investigated enrichment of globularity
248 associations in tissue-specific chromatin signatures, using LDSC partitioned heritability
249 analysis^{72,73}. We found significant enrichment ($\alpha_{\text{Bonferroni}} = 0.05 / 489 = 1.02 \times 10^{-4}$) in regions with
250 DNase hypersensitivity, a marker for active chromatin, in foetal skeletal muscle (Fig. 4C,
251 Supplementary Table 9) and in regions with histone-3 lysine-4 monomethylation (H3K4me1), a
252 marker for enhancer regions, which again highlighted the cardiovascular system but also showed
253 enrichment in lung tissue (Fig. 4C, Supplementary Table 9).

254 **Partitioned heritability analysis with evolutionary annotations of the genome**

255 Focusing on the timescale over which endocranial globularity is thought to have emerged on the
256 *Homo sapiens* lineage (i.e., within ~300kya, see Figure 1A), we investigated relationships
257 between our association data and genomic annotations that tag relevant evolutionary events.

258 First, we used LDSC partitioned heritability analysis^{72,73} to test the contributions of archaic
259 admixture to the overall SNP-based heritability of the trait. Here, we analysed (i) Neandertal
260 introgressed alleles resulting from admixture events ~50-60k years ago⁷⁴ and (ii) archaic deserts,
261 which represent long stretches in the human genome that have a significant underrepresentation
262 of introgressed alleles⁷⁵. This analysis revealed a significant ($\alpha_{\text{Bonferroni}} = 0.05 / 2 = 0.025$)
263 heritability depletion in archaic deserts (enrichment = 0.61, SE = 0.14, $p = 0.0115$), indicating that
264 common DNA variants in these regions explain a lower proportion of the total SNP-based
265 heritability of endocranial globularity than expected under complete polygenicity (Supplementary
266 Table 10).

267 Next, we investigated links between endocranial globularity and two further sets of evolutionary
268 annotations that match the relevant timescale: (i) ancient selective sweeps, as defined by
269 extended lineage sorting⁷⁶, and (ii) anatomically modern human-derived differentially methylated
270 regions (AMH-derived DMRs) identified using skeletal DNA methylation maps of Neandertals,
271 Denisovans, and present-day humans⁷⁷. Since these annotations cannot be tested reliably with
272 existing LDSC heritability partitioning tools⁷⁸, we adopted a MAGMA gene-set approach⁷⁹ using
273 two custom gene-sets covering genes that fall within $\pm 1\text{kb}$ of the relevant evolutionary
274 annotations. We found that common variants associated with endocranial globularity are
275 significantly ($\alpha_{\text{Bonferroni}} = 0.05 / 2 = 0.025$) enriched in and near genes ($\pm 1\text{ kb}$) co-located with ancient
276 selective sweeps (Beta = 0.163, SE = 0.061, $p = 0.004$), but not in those co-located with AMH-
277 derived DMRs (Beta = 0.02, SE = 0.003, $p = 0.333$) (Supplementary Table 11).

278 **Discussion**

279 Our results point to proximate developmental, and evolutionary causes underlying a uniquely
280 modern human anatomical phenotype. The origins of endocranial globularity have been much
281 debated, with some studies emphasizing roles of genes related to neurogenesis and
282 myelination^{2,5}, while others propose that endocranial shape changes in *Homo sapiens* are driven
283 by facial gracilization linked to dietary and lifestyle differences⁷. In the current study, we
284 approached this longstanding question by investigating interindividual differences in endocranial
285 globularity in nearly 34,000 present-day living participants, identifying 28 loci and 77 genes
286 associated with the trait, and revealing a SNP-heritability comparable to (and in some cases larger
287 than) other neuroanatomical traits which have been studied via brain imaging genomics^{15,21,80}.

288 We found that genetic variation associated with endocranial globularity is shared with that of
289 several neuroanatomical metrics covering a variety of brain regions, highlighting the multifactorial
290 nature of this evolutionarily-defined phenotype. Particularly prominent here is the shared genetic
291 make-up with the ventricular system, raising the possibility that rounder endocrania may in part
292 be due to increased hydrostatic pressure of cerebrospinal fluid during development. Moreover,
293 these results go beyond confirming prior hypotheses concerning a role for white-matter
294 changes^{2,5}, by revealing which white-matter tracts show the strongest genetic overlaps with
295 endocranial globularity (Supplementary Table 3).

296 While the globularization of the brain is thought to have contributed to the emergence of complex
297 human-specific traits^{52,53,81,82}, adaptive evolution might have increased our susceptibility to certain
298 (brain-related) disorders^{57,58,61}. In the present study, we tested 22 phenotypes in a range of
299 categories where prior studies have suggested an impact of previous admixture events. Across
300 all trait domains we found at most very subtle genetic relationships with endocranial globularity,
301 and only one of the traits that we tested met statistical significance. This is in line with recent
302 studies finding that Neandertal variants overall show little association with diseases seen in
303 present-day humans, specifically with psychiatric and neurological disorders^{58,63}. More generally,
304 our findings indicate that the trend towards a more globular brain is not per se linked to increased
305 disease susceptibility and seems fairly independent of other trait domains previously linked to
306 Neandertal introgression. While we did not expect straightforward correlations between brain
307 shape and complex human traits, the absence of shared genetic architecture of endocranial
308 globularity with traits previously linked to Neandertal introgression might in part also reflect the
309 focus on common variants in this study, given that a large percentage of Neandertal introgressed
310 fragments is rare with allele frequencies below 1%⁸³.

311 Reading- and language-related skills were the only cognitive traits that showed a significant
312 genetic correlation with endocranial globularity. However, this does not necessarily imply the
313 absence of language in archaic hominins. As our analysis revealed only a marginal, non-
314 significant genetic overlap with general cognitive abilities, this finding may rather indicate a
315 continuous refinement of language-related abilities in the *Homo sapiens* lineage after the split
316 from Neandertals. Indeed, based on data from an array of palaeoanthropological sources, it has
317 been suggested that Neandertals had more complex communication abilities than previously
318 appreciated, potentially reflecting a deeper evolutionary history for speech and language
319 capacities⁸⁴⁻⁸⁷. This is consistent with archaeological evidence of complex and sophisticated
320 Neandertal behaviours, suggesting cognitive and behavioural similarities between Neandertals
321 and contemporary fossil *Homo sapiens*⁵³⁻⁵⁶. Given both the shared and diverging genetic
322 architecture with anatomical brain traits, subtle differences in brain circuitry which might emerge
323 during the globularization phase of brain development^{2,5,6} may have refined key brain structures
324 important for language circuitry that has subsequently also been recruited for processes involved
325 in reading. Intriguingly, anatomical measures of the superior temporal sulcus, a key brain region
326 involved in linguistic processing, show high genetic correlations with both endocranial globularity
327 and reading-/language-related traits⁶⁸.

328 Focusing on functional implications of identified associations, gene-property analysis highlighted
329 an enrichment of variants associated with endocranial globularity in genes expressed in the brain
330 during prenatal development and in early childhood. This finding links directly to prior work on
331 skulls which places the ontogenetic emergence of this phenotype within early development^{5,6,88,89}.

332 Several lines of evidence point to an association between endocranial globularity, metabolic
333 supply and the circulatory system. First, endocranial globularity showed strong genetic
334 correlations with the ventricular system, including the choroid plexus. Second, via gene-property
335 analysis, we found that genes associated with this trait have enriched expression in tissues linked
336 to the cardiovascular system as well as in adult brain endothelial cells, a cell type also linked to
337 the brain's metabolite supply⁹⁰. Third, using heritability partitioning, we observed enrichment of
338 heritability within regulatory elements linked to the cardiovascular system. In addition to the
339 cardiovascular system, genes associated with endocranial globularity also showed significant
340 enrichment in female reproductive tissues. The association of endocranial globularity and the
341 cardiovascular system highlights the advantages of our approach to uncover novel associations
342 which open up unexpected avenues for further research. This is consistent with recent research
343 that has shown strong phenotypic and genetic links between the heart and the brain⁹¹ and even
344 uncovered possibly genetic causal links between cardiovascular endophenotypes and
345 neurological health.

346 While Gunz & Tilot et al.⁵, using a smaller cohort, identified a number of Neandertal introgressed
347 alleles associated with elongated endocranial shape in present-day humans, our genome-wide
348 approach revealed a broader signal of SNP-heritability depletion within archaic deserts. This may
349 suggest that archaic deserts lack the genetic loci and regulatory elements that contribute to the
350 formation of the globular shape of the human endocranium during early development, similar to
351 earlier findings⁷⁸ showing archaic desert heritability depletion for cortical surface area. Further,
352 the gene-set analysis indicated a significant enrichment of globularity-associated variants within
353 genes that are co-located with ancient selective sweeps. Thus, genes that are co-located with
354 haplotypes fixed on the human lineage after the split from Neandertals and Denisovans (~450-
355 750 kya)¹³, but before the split of modern human populations (~100-120 kya)⁶⁶, may have played
356 an important role in the evolution of human endocranial globularity. The implicated time period
357 partially overlaps with that observed from the fossil data, which suggests endocranial globularity
358 emerged in the *Homo sapiens* lineage over the last ~300 kya. Overall, combining fossil and
359 genetic data narrows down the presumable time window for the evolutionary emergence of
360 endocranial globularity to the last ~300-120 kya.

361 An inherent limitation of the GWAS approach is that it cannot directly assess the impact of genetic
362 changes that have become fixed over the course of hominin evolution, as the basis of the analysis
363 relies on both genetic and phenotypic interindividual variation present in the cohort under study.
364 In addition, for pragmatic reasons, our study focused on individuals of European ancestry,
365 highlighting the need for further research of well-powered neuroimaging genomics cohorts from
366 diverse population backgrounds (as they become available) to gain a comprehensive
367 understanding of the biological mechanisms underlying aspects of human neuroanatomy. It is
368 important to keep in mind ethical implications of research on fundamental human traits; Box 1
369 outlines key issues, highlighting the scope and limitations of GWAS and providing guidelines for
370 interpreting such genetic findings.

371 Our study leveraged the interindividual differences in an evolutionarily derived phenotype unique
372 to present-day humans through analyses of large-scale neuroimaging genetics, to gain novel
373 insights into biological processes underlying human variation and evolution. We uncovered
374 unexpected signals that lead to new, testable hypotheses for future work when more fine-grained
375 datasets become available. Using neuroimaging genomic data spanning perinatal and infant

376 development will then allow for more detailed insights into the ontogeny of endocranial shape
377 while the latest data from single-cell transcriptomics and epigenomics will help to further
378 disentangle the involvement of metabolic supply, the circulatory and female reproductive system.
379 Further, availability of large-scale exome and whole-genome sequencing data will shed more light
380 on the contribution of rarer variants with larger effect sizes, whose functional implications and
381 interplay with more common variants are not yet clear.

382 Taken together, these findings suggest that human endocranial shape and brain function may
383 have co-evolved with both the circulatory and reproductive systems. In such a scenario, selection
384 acting on one system would also affect the other; thus, changes affecting, e.g., metabolite supply,
385 energy demand, pregnancy, or fertility would also affect brain structure and endocranial shape,
386 possibly as indirect by-products.
387

388 **Box 1 General ethical considerations and implications linked to brain shape and its genetic**
389 **underpinnings**

390 **Historical context of craniology and phrenology warrants a careful and vigilant ethical approach**

391 Endocranial imprints can provide direct empirical evidence of brain evolution revealing evolutionary
392 changes of brain size, shape and sulcal morphology in palaeoanthropology^{2,6,92–96}. However, given the
393 historical burden of craniometry, using endocranial metrics as phenotypes and correlating them with
394 anatomical or behavioural traits requires vigilant and thorough ethical considerations to avoid
395 misappropriation of presented results^{97,98}. Craniometry, the study of skull shape, size, and proportions, was
396 prevalent in anthropology during the 18th and early 19th centuries. It misused measurements, like the
397 cervical index (the ratio of a skull's maximum width to its length), to wrongly suggest racial differences in
398 intellectual capabilities. These ideas were absorbed into phrenology, which claimed to predict personality,
399 mental health, and criminal tendencies based on skull measurements, providing a pseudo-scientific basis
400 for racist beliefs, slavery, colonialism, and later, 20th-century eugenics^{99,100}. Despite being discredited as
401 pseudoscience^{101,102}, the remnants of racial craniology and phrenology still influence contemporary studies
402 linking brain and behaviour¹⁰³.

403 **Brain shape as a window into our evolutionary past**

404 In this study we make use of the latest advances in palaeoanthropology and endocranial shape analysis
405 from Neandertal fossils combined with brain imaging data from thousands of present-day living humans to
406 create a singular metric for endocranial globularity⁵. As the globular shape of the human braincase
407 represents one of the most distinct anatomical differences between *Homo sapiens* and our closest living
408 and extinct relatives, endocranial globularity functions here as an evolutionary phenotype^{2,6}. Investigating
409 associated genetic factors underlying this evolutionary phenotype offers a novel approach to study the more
410 elusive aspects of brain evolution and might lead to new insights into differences and similarities compared
411 to our closest extinct relatives, with no intent or scientific grounds to draw any conclusions for an individual
412 based on differences in their endocranial globularity.

413 **What can genetics tell us about human endocranial globularity today?**

414 Genome-wide association analyses of endocranial globularity highlight the polygenicity of this trait; that is,
415 there are thousands, if not tens of thousands, of DNA variants acting together to shape this particular aspect
416 of our anatomy. While identified associations do not inherently imply causal relationships, they can open
417 up new avenues of scientific inquiry for human evolution^{104,105}. Overall, endocranial globularity showed a
418 SNP-heritability (the proportion of interindividual variation that may be accounted for by common genetic
419 variants) of 30%, comparable to other brain morphological traits^{80,106,107}. Still, this means that only a third of
420 the interindividual variation in endocranial globularity can currently be explained by factors at the genetic
421 level. While larger sample sizes and a focus on rare variants might increase the genetic contribution, this
422 level of heritability indicates that a substantial proportion of variability in this trait is still unexplained and can
423 be attributed to non-genetic factors such as environmental influences¹⁰⁴ and developmental stochasticity.
424 Even though each identified genetic variant associated with endocranial globularity shows only minor
425 effects, the aggregated signal was correlated with a range of brain morphological traits, while most of the
426 health and complex human traits that we studied did not show significant genetic correlation. Overall, these
427 analyses can reveal the aetiological heterogeneity of endocranial globularity and other complex traits, and
428 help us to better understand their shared biology. Yet, it is important to note that genetic correlations do not
429 imply causal links between phenotypes¹⁰⁸.

430 We emphasize that our results and summary statistics do not provide a scientific foundation for deterministic
431 predictions of human endocranial shape. The findings represent statistical trends within the studied
432 population and cannot be applied to individuals. Additionally, given that different populations show
433 differences in allele frequencies and patterns of linkage disequilibrium (i.e. co-inheritance of neighbouring
434 DNA variants that lie close to each other on the same chromosome), this also means that the results should
435 not be taken out of context to make any inferences about other ancestry groups or to draw comparisons
436 between populations.

437

438 **Methods**

439 Dataset

440 For lifespan analyses we included 644 cognitively healthy adults (age range, 18 – 88 years) obtained from
441 the Cambridge Centre for Aging and Neuroscience (CamCAN) repository (available at <http://www.mrc-cbu.cam.ac.uk/datasets/camcan/>)^{9,10}. Ethical approval was obtained from the Cambridgeshire Research
442 Ethics Committee and participants gave written informed consent.
443

444
445 All data for the described neuroimaging genetics analysis were obtained from the UK Biobank (UKB) under
446 the research application 16066 with Clyde Francks as the principal investigator. Detailed descriptions of
447 the data used as well as sample-specific pre-processing and quality control (QC) are described below. The
448 UK Biobank received ethical approval from the National Research Ethics Service Committee North West-
449 Haydock (reference 11/NW/0382), and all of their procedures were performed in accordance with the World
450 Medical Association. Informed consent was obtained for all participants by UK Biobank with details about
451 data collection and ethical procedures described elsewhere^{11,109}.

452

453 Endocast segmentation and measurement protocol

454 Based on computed tomographic (CT) scans of recent and fossil crania, we used the endocranial shape
455 differences between present-day humans (N = 89) representing world-wide cranial shape variation², and
456 fossil humans (N = 20) as a framework for evolutionary shape changes⁵. The fossil sample comprises eight
457 *Homo erectus* s.l. (KNM-ER 3733, KNM-ER 3883, KNM-WT 15000, OH 9, Ngandong 14, Ngawi,
458 Sambungmacan 3, Sangiran 2), ten *Homo neanderthalensis* (Amud 1, Feldhofer 1, Gibraltar 1, Guattari 1,
459 La Chapelle aux Saints, La Ferrassie 1, Spy 1, Spy 2, Saccopastore 1, Le Moustier 1), and two *Homo*
460 *heidelbergensis* s.l. crania (Kabwe, Petralona). We first used semi-automated segmentation to create
461 virtual endocranial imprints in the software Avizo 3D (Version 9; FEI SAS, Thermo Fisher Scientific)
462 following protocols detailed in Neubauer et al.^{2,88}. We also segmented the endocranial surface of the MNI
463 152 template, an average of 152 normal MRI brain scans. On each endocranial surface we then digitized
464 a mesh of 935 anatomical landmarks, curve semilandmarks¹¹⁰ and surface semilandmarks following the
465 protocol described in Neubauer et al.²To establish geometric correspondence of the semilandmarks across
466 individuals we allowed curve semilandmarks to slide along tangents to the curves, and surface
467 semilandmarks to slide on tangent planes to the surface, minimizing the thin-plate spline bending energy
468 following Gunz et al.¹¹⁰. Missing landmarks or semilandmarks were estimated based on minimal bending
469 energy during this sliding step^{111,112}.

470

471 Sample level quality control and pre-processing of the neuroimaging data

472 For the lifespan analyses we used available T1-weighted images within the CamCAN data set. All details
473 regarding the MRI acquisition are described in detail in Taylor et al.⁹. All available T1-weighted images were
474 further pre-processed using *fs_l_anat* as part of the FSL toolbox (v 5.1.0) to reorient the images to MNI
475 standard orientation, automatically crop and bias-correct the images, and apply an initial brain extraction
476 which was followed by a secondary brain extraction using FSL *bet*. Images were subsequently aligned to
477 the MNI-T1-1mm standard template using FSL *flirt* to derive the inverse affine transformation matrix for
478 each of 644 individuals.
479

480

481 For UKB data we first applied genetic sample level quality control measures to derive a final study sample
482 that would also be suitable for further genetic analysis. As the first step, participants with available imaging
483 data (N = 40,681, release 2020) were extracted from the full UKB imputed genotype dataset¹¹. Subject-
484 level QC parameters were then applied to the 39,678 individuals for whom both neuroimaging and genotype
485 data were available. This involved excluding individuals with a mismatch of their self-reported (UKB data
486 field 31) and genetically inferred sex (UKB data field 22001), as well as individuals with putative
487 aneuploidies (UKB data field 22019), or individuals who were determined as outliers based on
heterozygosity (PC corrected heterozygosity >0.1903) or genotype missingness rate (missing rate >0.05)

488 (UKB data field 22027)¹¹. For all participants with self-reported 'White European' ancestry (UKB data field
489 21000) who passed the above described sample level quality control, a Bayesian outlier detection algorithm
490 ($\lambda = 40$) was applied (*abberant*¹¹³). This algorithm identified dense clusters of participants with similar
491 genetic ancestry along PC1-PC2, PC3-PC4 and PC5-PC6, where only participants at the intersection of all
492 three principal component clusters were subsequently included. Lastly, we identified pairs of individuals
493 with a kinship coefficient > 0.0442 (UKB data field 22021¹¹) and available imaging data, and excluded one
494 individual from each pair, prioritizing the exclusion of individuals related to a larger number of other
495 individuals to maximize the overall sample.

496 This process resulted in 34,861 participants passing the described genetic sample level QC, of which
497 33,996 also had usable imaging data (T1 folder not declared 'unusable'). From this sample, we then made
498 use of imaging-derived phenotypes and pre-processed image data generated by an imaging-processing
499 pipeline developed and run on behalf of the UK Biobank. All details regarding image acquisition and
500 subsequent applied processing pipelines are available on the UK Biobank website
501 (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=2367>), and in the respective brain imaging documentation
502 (<http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977>), as described elsewhere^{114,115}. We used the
503 provided linear affine transformation matrices of each individual, which was part of the standard T1-
504 weighted MRI processing pipeline (UKB data field 20252; T1_to_MNI_linear.mat). We further used FSL
505 (v5.1.0, *convert_xfm*) to derive the inverse affine transformation matrix for each of the 33,996 participants.
506

507 Globularity scores derived from structural MRI scans and quality control

508 To quantify the endocranial shape differences between modern humans and Neandertals, we combined
509 geometric morphometrics⁸ using scripts in Mathematica (Version 12; Wolfram Inc.) with standard
510 neuroimaging data. In Mathematica, we applied the derived inverse affine transformation matrices for each
511 individual from both datasets (CamCAN, UKB) to the 3D coordinates of the dense mesh of 935 landmarks
512 and semilandmarks on the MNI 152 template, thereby bringing these coordinates into the native anatomical
513 space of each individual. Using Procrustes superimposition¹¹⁶ we standardized position, orientation, and
514 scale. From these Procrustes shape coordinates we then computed the difference between the mean
515 endocranial shape of Neandertals, and the mean endocranial shape of present-day humans. To calculate
516 the globularity scores, we projected each individual onto that multivariate vector, and multiplied the resulting
517 scalars by 1000. In this summary metric, more elongated (Neandertal-like) endocrania have low values,
518 and more globular endocrania have high values.
519

520 Quality control of the derived phenotype

521 For both datasets (CamCAN, UKB) we manually checked the respective T1-weighted image of any
522 individuals presenting with extreme globularity scores (Q1/Q3 +/- 1.5 IQR) for crude deviations in brain
523 shape from derived globularity scores. Further, the created inverse transformation matrix for all outliers was
524 applied to the MNI 152 standard template using FSL *flirt* and the derived image overlaid on each individual's
525 initial T1-weighted image, respectively. All overlays were manually inspected and individuals with crude
526 misalignments (N = 45) excluded from subsequent analysis, resulting in 644 and 33,951 individuals for
527 CamCAN and UKB, respectively.
528

529 Characterization of phenotype

530 Previous work suggested a subtle relationship between age and globularity scores⁵. We refined this
531 characterization and systematically assessed the relationship between age and endocranial globularity
532 during adulthood within the CamCAN lifespan dataset (N = 644) as well as the UKB dataset (N = 33,951),
533 also accounting for possible interactions with sex. To do so, we used a univariate linear regression
534 implemented in R [*lm*], including both age at time of scanning (UKB data field 21003; instance 2.0) and
535 age² terms and sex (UKB data field 31) as covariates, as well as possible interaction term (sex*age,
536 sex*age²) in our model. For a more detailed description of possible sex dimorphism, we assessed the effect
537 of sex on endocranial globularity using a univariate linear regression, where sex was included as the main

538 binary predictor ($N_{\text{Male}} = 16,148$; $N_{\text{Female}} = 17,803$), while controlling for age. We extracted the t-statistic
539 for the 'sex' term to calculate Cohen's d effect sizes and 95% confidence intervals using the psych package
540 (version 2.1.9) in R¹¹⁷.

541 Further, we investigated relationships with estimated total intracranial volume (UKB data field 26521,
542 instance 2.0, $N = 33,577$), and subject-specific health data (UKB Category 100074 and 2002). As before,
543 we applied a univariate linear regression to assess relationships between brain size and endocranial
544 globularity, using both age and sex as covariates. For subject-specific health data, we screened provided
545 health information for distinct neuroanatomical and neurodegenerative disorders that might potentially have
546 an influence on human brain shape, combining both supplied ICD9/10 information (UKB data fields 41202,
547 41203, 41204, 42205) and self-reported data (UKB data field 200002) which were collected in a verbal
548 interview at the assessment centre. In each case, all instances up to the imaging visit (instance 2) were
549 screened. This screen highlighted 27 participants with an ICD9 diagnosis and 1022 individuals with an
550 ICD10 diagnosis, while 1808 individuals indicated a neuroanatomical or neurodegenerative diagnosis in
551 the self-reported health screen. As some participants had multiple records, this led to a total of 2,338 unique
552 diagnosed participants while the rest of the cohort ($N = 31,613$) were treated as control participants. We
553 assessed the relationship with these disorders using a univariate linear regression, where diagnosis (case-
554 control status) was included as the main binary predictor, while controlling for sex and age. We extracted
555 the t-statistic for the 'diagnosis' term to calculate Cohen's d effect sizes and 95% confidence intervals using
556 the psych package (version 2.1.9) in R¹¹⁷.

557

558 Genome-wide association analysis

559 For all individuals in the UKB sample ($N = 33,951$), imputed single-nucleotide polymorphism (SNP)
560 genotype data (UKB Category 263, bgen files; imputed data v3-released March 2018) were extracted and
561 variant level QC and SNP statistics were computed using qctool v2.0.2
562 (https://www.well.ox.ac.uk/~gav/qctool_v2/). We excluded variants with a minor allele frequency below
563 0.001, Hardy-Weinberg equilibrium test p-value $< 1 \times 10^{-6}$, imputation quality INFO score < 0.7 (included in
564 the imputed UKB data) and multi-allelic SNPs. As recommended, for the X chromosome only Hardy-
565 Weinberg equilibrium p-values based on the female dataset were checked¹¹⁸. This procedure resulted in
566 15,030,319 SNPs, of which 499,719 were located on the X chromosome.

567 A linear regression model as implemented in PLINK 2.0 (www.cog-genomics.org/plink/2.0/)^{119,120} was used
568 to test for the association of endocranial globularity with sample specific dosages, using an additive model.
569 Here, PLINK converted the raw probabilities stored in the .bgen files to dosages. Covariates were scaled
570 to have unit variance, by using the `--covar-variance-standardiz` flag. To account for dosage compensation
571 (DC) due to X chromosome inactivation in females, we assumed full DC and treated males as homozygous
572 females with genotypes coded as (0,2) which represents the default model in PLINK 2.0¹²¹. We included
573 age (UKB data field 21003-2.0), age², sex (UKB data field 31-0.0), sex-by-age and age² interactions, the
574 first 10 genetic principal components (UKB data fields 22009-0.1 to 22009-0.10), genotype measurement
575 array (UKB data field 22000-0.0), and dummy variables for assessment centre (UKB data field 54-2.0), as
576 well as several imaging-related covariates, namely scanner position parameters (X, Y and Z position: UKB
577 data fields 25756-2.0, 25757-2.0 and 25758-2.0), T1 signal-to-noise ratio (UKB data field 25734-2.0), and
578 T1-contrast-to-noise ratio (UKB data field 25735-2.0) as co-factors.

579 For sex-stratified analysis we used the `--keep-male` or `--keep-female` flags as implemented in PLINK 2.0,
580 which decreased the overall sample size to 16,148 and 17,803 individuals, respectively. The sex-stratified
581 association tests were not adjusted for sex or any interaction terms thereof. The Manhattan plot was
582 generated using the "qqman" R function¹²² (qqman package v0.1.8), while QQ plots were added with a
583 custom function (https://genome.sph.umich.edu/wiki/Code_Sample:_Generating_QQ_Plots_in_R by
584 Matthey Flickinger). For sex-stratified GWAS, the Miami plot was created with the custom R function gmirror
585 ([https://github.com/RitchieLab/utility/blob/master/personal/ana/hudson-paper/hudson-paper-figures-
586 code.R](https://github.com/RitchieLab/utility/blob/master/personal/ana/hudson-paper/hudson-paper-figures-code.R)).

587 Subsequently, LD score regression (v1.0.0)¹²³ was used to estimate SNP heritability for endocranial
588 globularity and to calculate genetic correlation estimates between the male and female GWAS. For all these
589 analysis streams and any following analysis using *ldsc*, only autosomes were included, since the X
590 chromosome is not supported by the *ldsc* software.

591 Genetic correlations with brain imaging phenotypes

592 Publicly available GWAS summary statistics of brain imaging derived neuroanatomical traits were obtained
593 via the Oxford Brain Imaging Genetics Server¹⁵ (<http://big.stats.ox.ac.uk/>). Brain imaging derived
594 phenotypes (IDPs) encompassed surface T1 structural phenotypes (UKB Category 110), namely regional
595 grey matter volumes (FAST, UKB Category 1101), subcortical volumes (FIRST, UKB Category 1102),
596 Freesurfer ASEG (UKB Category 190) and Freesurfer DKT (UKB Category 196), as well as diffusion
597 imaging phenotypes (UKB Category 107), where we selected both fractional anisotropy (FA) and mean
598 diffusivity (MD) from the diffusion MRI skeleton measurements (UKB Category 134) and diffusion weighted
599 means measures (UKB Category 135), respectively. We also included summary statistics for two further
600 brain IDPs, namely sulcal morphology measures¹⁴ and brain skew³⁰. This resulted in 1017 traits, where
601 only those with a SNP-heritability larger than 0.1 were used, to avoid signal inflation, leading to a total of
602 667 final brain IDPs. A description of all IDPs used in this study can be found in Supplementary Table 3.
603 LD score regression¹²³ was used to assess genetic correlations between endocranial globularity and the
604 brain IDPs, with Bonferroni correction to adjust for multiple testing of 667 phenotypes.

605 As GWAS statistics for facial morphology traits were mostly available from multivariate screens and hence
606 lacked beta estimates, LD score regression was not applicable to test for possible genetic correlation. We
607 therefore used a lookup approach as an alternative, to determine if any of the genome-wide significant loci
608 associated with facial morphology (as reported in Supplementary Tables 1 and 3 of White et al.³⁵)
609 overlapped with identified genomic regions associated with endocranial globularity (independent lead SNPs
610 and SNPs in LD ($r^2 > 0.6$)).

612 Genetic correlation analysis with complex human traits

613 Several studies have highlighted potential relevance to human evolution for certain brain-related disorders
614 including depression, autism, schizophrenia, and addiction^{57,60,61,124}, inflammatory conditions⁶⁴, as well as
615 cognitive traits, with language being the most prominent^{66,86,87}. Further, the legacy of previous admixture
616 events was shown to influence trait variability in several categories, ranging from metabolism to
617 dermatological traits, as well as the cardiovascular and gastrointestinal system, and skeletal form. We
618 curated a list of 22 traits within these domains where high quality GWAS summary statistics were available
619 and used LD score regression¹²³ to estimate genetic correlations between endocranial globularity and
620 these traits. We made use of publicly available GWAS summary statistics for schizophrenia and bipolar
621 disorder¹²⁵, depression¹²⁶, autism spectrum disorder¹²⁷, alcohol dependence¹²⁸, inflammatory bowel
622 disease¹²⁹, cognitive performance¹³⁰, and a multivariate GWAS on reading- and language-related traits⁶⁸.
623 For all other traits, LDSC formatted summary statistics were downloaded from the Neal Lab heritability
624 server¹³¹ (https://nealelab.github.io/UKBB_ldsc/index.html). Bonferroni correction was used to correct for
625 multiple testing of 22 traits. A detailed overview of results and a description of all traits used in this study
626 can be found in Supplementary Table 5.

628 Functional Mapping and Annotation of GWAS analysis results

629 For functional annotation of GWAS results, we used the SNP2GENE function implemented in FUMA^{69,132}
630 (Functional Mapping and Annotation of Genome-Wide Association Studies; <https://fuma.ctglab.nl/>; version
631 v1.3.7) to highlight associated genomic loci and independent significant SNPs ($r^2 > 0.6$).

633 Gene and gene-property analysis in MAGMA

634 MAGMA⁷⁹ (version 1.08), integrated in the SNP2GENE function in FUMA, was used for gene-based, gene-
635 set, and gene-property analyses. For gene-based analysis (SNP-wide mean model) the European 1000

637 Genomes Phase 3 Reference Panel¹³³ was used and the gene window was set to 35 kb upstream and 10
638 kb downstream¹³⁴ to determine gene-based p-values, with other settings using default values. MAGMA
639 controls for gene size, the number of SNPs within a gene, and LD structure, by default.

640 We tested for enrichment of low gene-based p-values in specific tissue and cell types using MAGMA gene-
641 property analysis, where we selected adult tissue samples from GTEx V8
642 (<http://www.gtexportal.org/home/datasets>), as well as gene expression data of developmental brain
643 samples (<http://www.brainspan.org>). Additionally, we chose two single-cell RNA-sequencing datasets
644 covering fetal (prefrontal cortex, 8-26 weeks post conception; Gene expression omnibus (GEO) accession
645 number GSE104276) and adult (PsychENCODE Adult, <http://resource.psychencode.org/>) brain tissue for
646 the cell type-specific analysis, also implemented in FUMA¹³². Bonferroni correction was used in each case
647 to correct for multiple testing of bulk RNA-sequencing datasets (65 tissues) as well as for all single-cell
648 RNA-sequencing datasets (67 cell types), respectively.

649 Partitioning heritability of chromatin signatures

650 We used stratified LD score regression^{72,73} to test for enrichment of endocranial globularity SNP-heritability
651 in annotations of tissue-specific chromatin signatures reflecting regulatory and/or transcriptional activity.
652 The annotations used here were all based on data from the Roadmap Epigenomics project and ENTEX, as
653 described by Finucane et al.⁷². Bonferroni correction was used to correct for multiple testing of 489
654 annotations.

655 Analyses of contributions of Neandertal admixture

656 We used stratified LD score regression to determine if annotations of the human genome tagging signatures
657 of Neandertal ancestry show enrichment or depletion of the total SNP-heritability. We estimated the
658 contribution of evolutionary annotations associated with Neandertal ancestry, by using recently published
659 and enhanced genome annotations⁷⁸. These annotations were chosen based on their relevance for the
660 timing of the evolution of endocranial globularity in our ancestors (i.e. after the Neandertal-*Homo sapiens*
661 split), and the need for sufficient SNP-coverage to allow robust partitioned heritability analysis. Based on
662 these criteria, the following annotations were used: 1) Neandertal introgressed alleles (and SNPs in perfect
663 LD ($r^2 = 1$)), short genomic regions of Neandertal DNA which introgressed in to varying degree into the
664 genome of some present-day humans as a result from interbreeding events⁷⁴; and 2) archaic deserts, long
665 stretches of DNA that are significantly depleted of Neandertal sequences in modern human populations⁷⁵.
666 Both annotations were controlled for the baseline LD v2.2 model.

667 MAGMA gene-set analysis with custom evolutionary gene-sets

668 Two curated genome annotations with high evolutionary relevance were unsuitable for heritability
669 partitioning due to low SNP-coverage and were assessed instead via MAGMA gene-set analysis⁷⁹. These
670 annotations were: 1) Ancient Selective Sweeps, haplotypes that reached fixation after the split with archaic
671 humans (~450-750 kya), but before the differentiation of modern human populations (~100-120 kya)⁷⁶, 2)
672 Anatomically Modern Human-derived Differentially Methylated Regions (AMH-derived DMRs), regions with
673 unmethylated state in ancient and modern humans, but methylated in Neandertals and Denisovans,
674 reflecting chromatin-state differences that emerged between AMHs and archaic humans after they split
675 ~450-750 kya⁷⁷. We listed genes that fall within ± 1 kb of each loci locus tagged by one of these two
676 annotations, and filtered for protein coding genes using NCBI's hg19 genome annotation¹³⁵. We then
677 performed gene annotation by integrating SNP locations from GWAS summary statistics and gene locations
678 from NCBI hg19 genome annotation. We followed this with a gene-based analysis using SNP p-values and
679 1000 Genomes Phase 3 European Panel¹³³, and finally applied the gene-set analysis using results from
680 gene annotation, gene analysis, and the two evolutionary gene-sets that we curated. Bonferroni correction
681 was used to correct the enrichment p-value threshold for two tests.

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Data availability:

Imaging data across the adult lifespan are available from CamCAN (<http://www.mrc-cbu.cam.ac.uk/datasets/camcan>). Neuroimaging and genotype data used for GWAS are available from UK Biobank (<https://www.ukbiobank.ac.uk>). GWAS summary statistics of endocranial globularity will be made freely available through the GWAS Catalog (<https://www.ebi.ac.uk/gwas/>).

Code availability:

Coordinate-measurements on endocasts, and scripts used for the analyses are available on the project GitLab repository (<https://gitlab.gwdg.de/barmol/globularity>).

696

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974 Supplementary Information is available for this paper

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