Researchers discover genes that shape human brain surface

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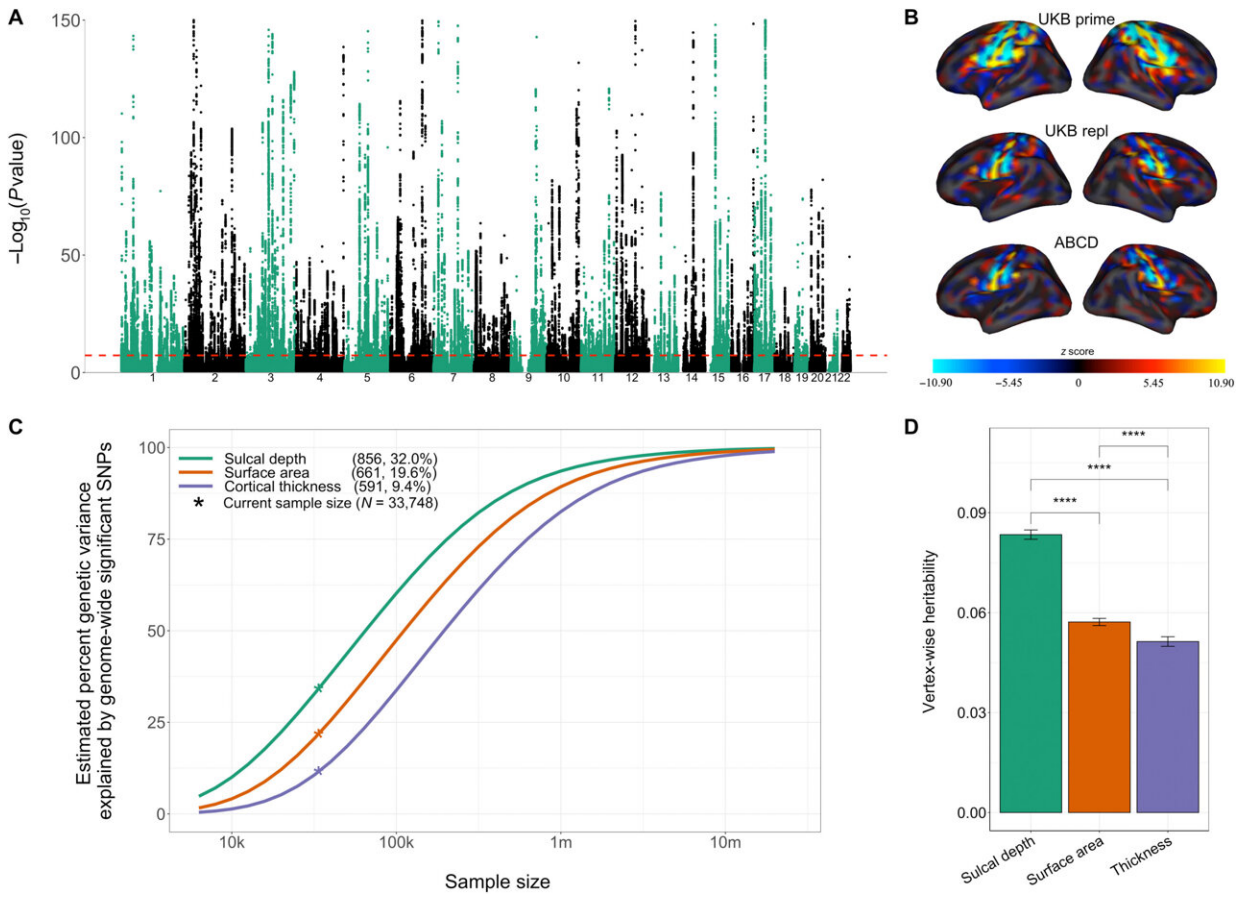

Fig. 1. Locus discovery.(A) Manhattan plot of the multivariate GWAS on sulcal depth, with the observed $-\log_{10}$(P value) of each SNP shown on the y axis. The x axis shows the relative genomic location, grouped by chromosome, and the red dashed line indicates the whole-genome significance threshold of 5×10^{-8}. The y axis is clipped at $-\log_{10}$(P value) = 150. (B) Lateral view of the cortex, depicting the color-coded vertex-wise z values for the top hit rs4924345 at chromosome 15, across the discovery sample (top) and the two replication samples (middle

and bottom). The left column corresponds to the left hemisphere, and the right column to the right hemisphere. (C) Power plot showing the relation between variance explained by genome-wide significant hits (y axis) and sample size (x axis). The number of hits discovered per modality and the percent explained genetic variance are indicated between brackets in the legend. (D) Bar plot of the mean SNP-based heritability (with 95% confidence interval) across vertices (on the y axis) per modality (x axis). In (C) and (D), sulcal depth is represented in green, surface area in orange, and cortical thickness in purple. ****P ≤ 0.0001. Credit: DOI: 10.1126/sciadv.abj9446

The surface of our brain, the cortex, is folded into an intricate pattern of bumps (gyri) and grooves (sulci). While individual differences in this pattern have been linked to brain disorders and cognitive performance, very little has been known about how the 'bumpiness and grooviness' of the cortex is determined. In a study recently published in *Science Advances*, an international research team conducted the first major genetic study into cortical folding patterns.

The researchers analyzed genetic and neuroimaging data from more than 45,000 people, in the UK and U.S.. Using advanced statistical methods, they discovered and characterized genetic variation linked to the extent of folding, and compared this to findings on the much more commonly studied measures of cortical surface area and thickness.

The investigation showed that cortical folding is substantially more heritable than the two other measures. This contributed to the identification of 856 significant genetic variants, the most discovered for any brain measure in a single study. The associated genes are known to be part of important brain developmental processes, such as neuronal migration, and were found to be expressed primarily before birth. A substantial number of the identified variants had also been previously coupled to a range of brain disorders, attesting to the clinical relevance

of cortical folding.

First author Dennis van der Meer explains: "Our findings certainly confirmed our impression that this is an under-investigated brain measure, one that can tell us a whole lot more about the brain, how it develops, and how this shapes our behavior, in health and disease."

The study provides fundamental insight into the human brain. "These findings enable experimental studies to identify the biological pathways involved," says professor Ole A. Andreassen, senior author and director of the NORMENT Centre of Excellence at the University of Oslo and Oslo University Hospital. "The strong pattern of results further suggests that it is possible to develop prediction tools that can ultimately have clinical utility, benefitting people with severe mental disorders," Andreassen adds.

More information: Dennis van der Meer et al, The genetic architecture of human cortical folding, *Science Advances* (2021). DOI: 10.1126/sciadv.abj9446

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