Planar cell polarity pathway and development of the human visual cortex

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The radial unit hypothesis provides a framework for global (proliferation) and regional (distribution) expansion of the primate cerebral cortex[1]. Using principal component analysis (PCA), we have identified cortical regions with shared variance in their surface area and cortical thickness, respectively, segmented from magnetic resonance images obtained in 19,171 participants. We then carried out meta-analyses of genome-wide association studies of the first two principal components for each phenotype. For surface area (but not cortical thickness), we have detected strong associations between each of the components and single nucleotide polymorphisms in a number of gene loci. The first ("global") component was associated mainly with loci on chromosome 17 ($8.8\times10^{-26} \leq p \leq 2.3\times10^{-14}$), including those detected previously as linked with intracranial volume[2,3]. The second (regional) component captured shared variation in the surface area of the primary and adjacent secondary visual cortices and showed a robust association with polymorphisms in *a* locus on chromosome 14 containing *Disheveled Associated Activator of Morphogenesis 1* (*DAAM1*; $p=3.0\times10^{-32}$). *DAAM1* is a key component in the planar-cell-polarity signaling pathway[4,5]. In follow-up studies, we have focused on the latter finding and established that: (1) *DAAM1* is highly expressed between 12th and 22nd post-conception weeks in the human cerebral cortex; (2) genes co-expressed with *DAAM1* in the primary visual cortex are enriched in mitochondria-related pathways; and (3) volume of the lateral geniculate nucleus, which projects to regions of the visual cortex staining for cytochrome oxidase (a mitochondrial enzyme), correlates with the surface area of the visual cortex in major-allele homozygotes but not in carriers of the minor allele. Altogether, we speculate that - in concert with thalamocortical input to cortical subplate - *DAAM1* enables migration of neurons to cytochrome-oxidase rich regions of the visual cortex, and, in turn, facilitates regional expansion of this set of cortical regions during development.

Using magnetic resonance imaging, one can derive a number of metrics informative with regard to development and aging of the human cerebral cortex, including cortical surface area and cortical thickness. The two measures provide insights into different developmental processes, each with a different timeline. Cortical surface area reflects primarily the tangential growth of the cerebral cortex during prenatal development; the phase of *symmetric division of progenitor cells* in the proliferative zones during the first trimester is particularly important for the tangential growth through additions of ontogenetic columns[1]. The subsequent phase of *asymmetric division* continues to increase the number of ontogenetic columns (and thus surface area) but it also begins to

contribute to the thickness of cerebral cortex formed by post-mitotic neurons migrating from the proliferative zones to the cortical plate in the inside-out manner[1]. Ionizing radiation of the (monkey) fetus during early gestation reduces surface area (sparing cortical thickness) while the same radiation applied in midgestation affects both the surface area and cortical thickness[6]. While surface area remains stable after early childhood, cortical thickness continues to change, in particular during puberty and aging. Furthermore, both surface area and cortical thickness vary across individuals in global and regional manner.

Here we report findings obtained in 19,171 participants assessed across 13 cohorts from the CHARGE Consortium and the UK Biobank (Table E1 in Extended Data). To identify genetic loci associated with global and regional variations in each cortical phenotype, i.e., the surface area and thickness of the cerebral cortex, we have first carried out principal component analysis of regional values (34 regions segmented by FreeSurfer) in each cohort. For each phenotype, the first (PC1) and second (PC2) components loaded in similar sets of cortical regions across all 13 cohorts (Figures E1 [surface area] and E2 [cortical thickness] in Extended Data). Figure 1 illustrates the loadings for each of the 34 cortical regions in PC1 (Fig. 1A) and PC2 (Fig. 1B) for surface area. Note that PC2 includes only a handful of cortical regions in the medial aspect of the occipital lobe, including the pericalcarine (primary visual) cortex.

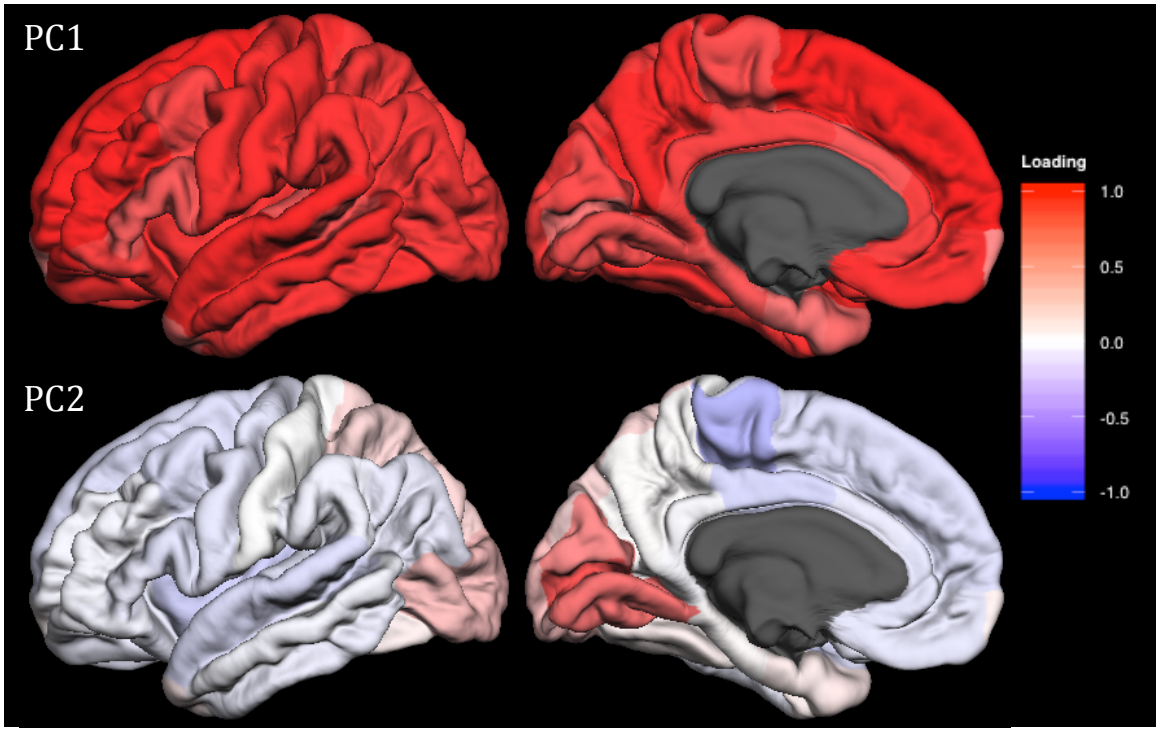

Figure 1. Lateral and medial views of median principal component (PC) loadings for the surface area of the 34 cortical regions in CHARGE consortium cohorts. Lateral (left column) and medial (right column) views of the median PC loadings are shown for PC1 (top) and PC2 (bottom). Each cohort estimated the surface area of the 34 cortical regions (left and right hemispheres summed), using FreeSurfer and carried out unrotated principal component analyses to obtain PC1 and PC2 loadings. Then, for each cortical region, median value of loadings was obtained across the cohorts. The red-to-blue color indicates the positive-to-negative loading values (i.e., correlation between PC scores and raw data) as indicated by the color bar. The median loading values were then used to derive the 'general' PC score for each individual and later used as the response variable in the GWAS meta-analyses.

We then executed a genome-wide association analysis (GWAS) in each of the 13 cohorts and, subsequently, meta-analyzed these cohort-based results (Supplementary Information) for each of the four phenotypes, namely PC1 and PC2 of surface area, and PC1 and PC2 of cortical thickness. For surface area, the first ("global") component was associated mainly with a number of loci on chromosome 17, including those detected previously as linked with intracranial volume[2,3] (Figure E3A and Table E2A in Extended Data). The second ("regional") component was associated mainly with a locus on chromosome 14 containing *DAAM1* (Figure 2, Figures E3B and E4, and Table E2B in Extended Data). For cortical thickness, meta-GWAS revealed a single locus associated with PC1 and a single locus associated with PC2 (Figure E5). The *DAAM1* locus (top hit: rs73313052) was associated with surface area (but not cortical thickness) of each of the four cortical regions loading on PC2 when examined on a region-by-region basis, as reported in the two companion reports from the CHARGE and ENIGMA Consortia (Table E3 in Extended Data).

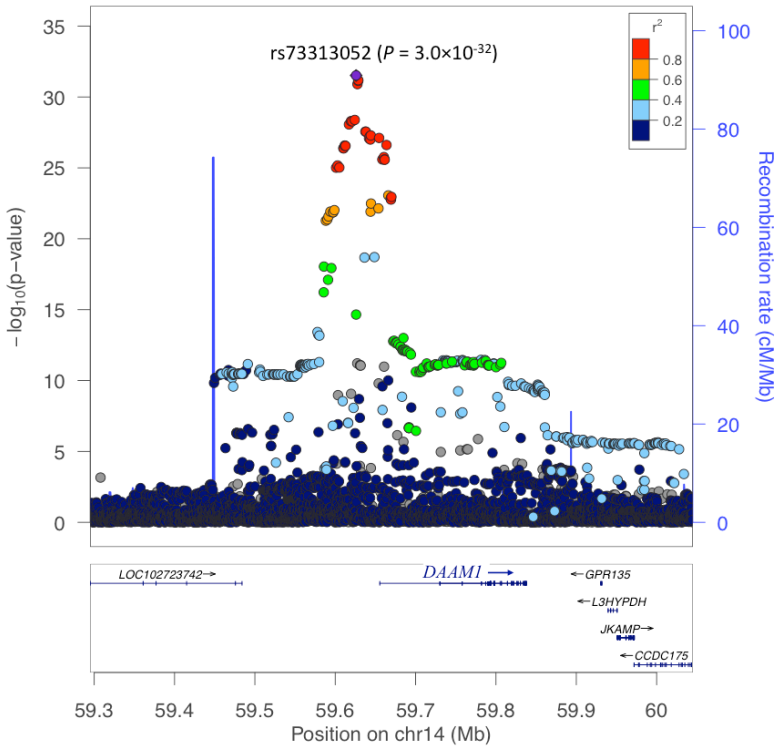

Figure2. Regional association plot for rs73313052, the top PC2 single nucleotide polymorphism (SNP). Each point indicates a SNP tested in the meta genome-wide association study (GWAS) of surface area PC2 within the shown genomic region. The top PC2 SNP is indicated by the purple diamond. The x-axis represents the genomic position on the human chromosome 14 (hg19). The left-vertical axis indicates the $-\log_{10}P$ values obtained from the GWAS meta-analysis (on the left side); and the right-axis, the estimated recombination rate from HapMap samples. The red-to-blue colors indicate the degree of linkage disequilibrium (LD) between each SNP and rs73313052. The LD was based on the pairwise squared allelic correlation r^2 estimated using the 1000 Genomes European reference panels (Nov 2014 EUR). The plot was created using LocusZoom (http://locuszoom.org/).

DAAM1 is a key component of the planar-cell-polarity signaling pathway[4,5]; it acts as a bridging factor between Disheveled, Rho-family GTPases and Rho-associated kinases[7], a molecular complex involved in organizing actin cytoskeleton[8].

In order to gain insights into possible mechanisms by which *DAAM1* contributes to the tangential expansion of the human visual cortex, we have carried out a number of follow-up studies. **First**, we examined *DAAM1* expression in the human brain using the BrainSpan dataset (Table E4 in Extended Data). *DAAM1* is expressed in the cerebral cortex between ~80 and ~150 post-conception days (280-day gestation); after birth, its expression is very low (Fig. 3, Table E4). Note that, in monkeys, neurogenesis of the primary visual cortex begins around embryonic day 40 (E40) and ends at E100 (165-day gestation)[1].

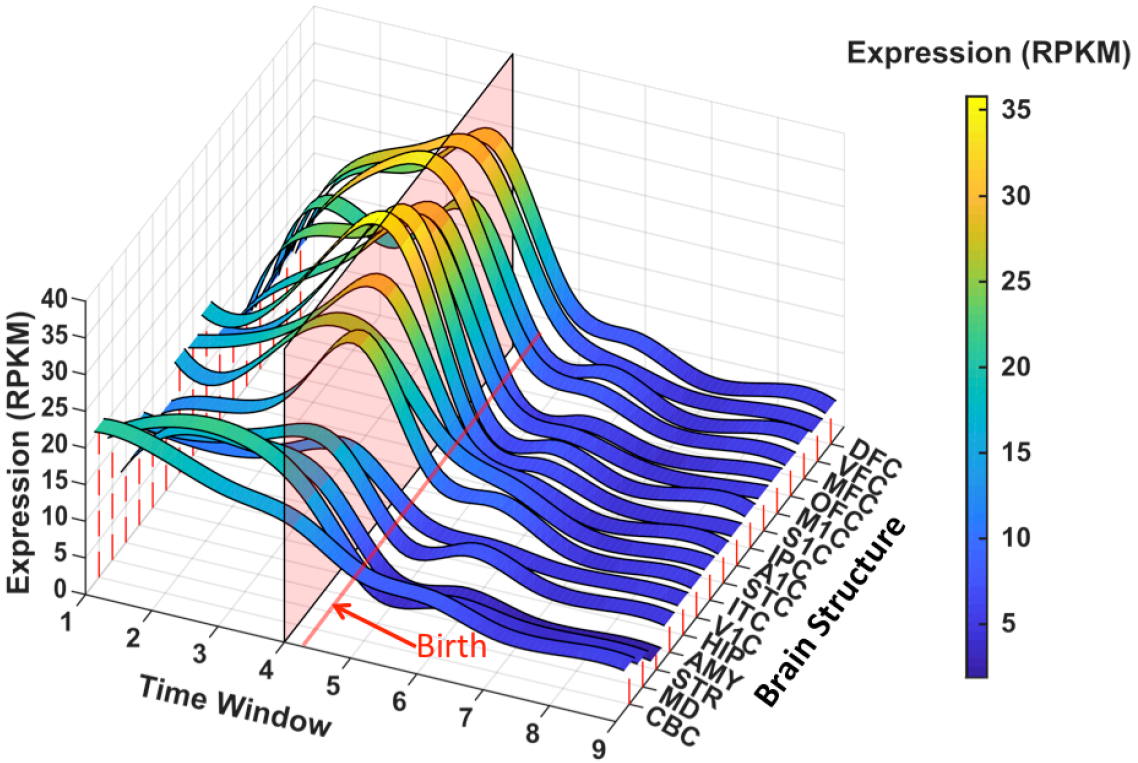

Figure 3. Spatial and temporal expression of *DAAM1* on BrainSpan mRNA-seq data. The mRNA expression levels were measured by RNA sequencing in 607 brain tissues from 18 female and 23 male donors available in BrainSpan database (http://www.brainspan.org/). For a given brain structure, *DAAM1* expression value was averaged and then fitted across differentiation windows using spline function implemented in MATLAB to get smooth *DAAM1* expression dynamics. Each colored band represents the fitted expression levels in RPKM (reads per kilobase per million) of *DAAM1*. Brain structure includes 11 cortical and 5 sub-cortical regions: dorsolateral prefrontal cortex (DFC), ventrolateral prefrontal cortex (VFC), medial frontal cortex (MFC), orbitofrontal cortex (OFC), primary motor cortex (M1C), primary sensory cortex (S1C), inferior parietal cortex (IPC), primary auditory cortex (A1C), superior temporal cortex (STC), inferior temporal cortex (ITC), primary visual cortex (V1C), hippocampus (HIP), amygdala (AMY), striatum (STR), mediodorsal nucleus of thalamus (MD) and cerebellar cortex (CBC). The human brain differentiation was split into 9 windows based on post conception days: 52-69 (Window 1), 70-111 (Window 2), 112-132 (Window 3), 133-167 (Window 4), 168-447 (Window5), 448 - 1299 (Window 6), 1300-4648 (Window 7), 4649-7570 (Window 8), and 7571-14876 (Window 8). The red line indicates the boundary between pre- and postnatal periods. The pink panel indicates the

time where *DAAM1* has peak expression in V1C. Blue-to-yellow colors represent low-to-high expression levels of *DAAM1* as indicated in the color bar.

Second, we examined co-expression of *DAAM1* across all cortical regions and prenatal time points using the same BrainSpan dataset. As expression of *DAAM1* increases and decreases, so does expression of genes enriched in pathways involving neuron migration and cytoskeleton organization, among others (Table E5A in Extended Data). On the other hand, expression of a large number of genes varies in the direction opposite to that of *DAAM1*, including genes enriched in pathways involved in a number of metabolic processes (Table E5B in Extended Data). To ascertain the pattern of *DAAM1* co-expression *specific* to the primary visual cortex (V1), we have identified genes co-expressed highly (top 1%) in V1 but not in any other cortical region (i.e., not present among top 1% in any of the other eight regions). This analysis yielded striking enrichment for mitochondria-related genes co-expressed strongly in the same direction as *DAAM1* in V1 but not in the other cortical regions (Table E6 in Extended Data). This observation turned our attention to the well-known parcellation of the visual cortex to cytochrome-oxidase rich sub-regions, so-called “blobs” (V1) and “stripes” (V2/V3)[9]. We then examined co-localization of *DAAM1* and a mitochondrial marker ATP5A in the developing (22nd post-conception week) visual cortex (Figure E6); its co-localization is consistent with the co-expression analyses described above. It is known that post-mitotic neurons migrate, along radial glia, from proliferative (ventricular and subventricular) zones to subplate zones, which contain afferents from the thalamic radiation[1]. Activity carried by these afferents from the retina is critical for the development of the primate visual cortex; enucleation of the eyes during fetal development results in the reduction of the surface area (but not thickness) of the monkey primary visual cortex[10,11], as well as in a reduced size of the lateral geniculate nucleus (LGN)[11]. A tight relationship exists between the volume of LGN and surface area of the primary visual cortex in the human (adult) brain[12]. Furthermore, the koniocellular portion of LGN (which carries signals from short wavelength [blue] cones) appears to project specifically to cytochrome-oxidase rich areas of the visual cortex[13]. Therefore, we hypothesized that DAAM1 contributes to the migration of cytochrome-oxidase positive neurons in response to the LGN inputs in the subplate zones during fetal development. **Third**, to test this hypothesis in our data, we predicted that the expected relationship between the LGN volume (a proxy for retinal inputs during fetal development) and V1 surface area will be present only in *DAAM1* (rs73313052) major-allele homozygotes (GG) but not in the carriers of minor allele (GA or AA). This prediction was confirmed: an interaction between rs73313052 genotype and LGN volume vis-à-vis PC2 magnitude was significant when examined in a cohort with available LGN volumes (GG: $r=0.13$, $p=0.0006$, $n=694$; A carriers: $r=-0.06$, $p=0.37$, $n=206$; interaction: t ratio= -2.47, $p=0.014$, $n=900$; Figure E7 in Extended Data).

Finally, to examine similarities between the molecular architecture underlying global (PC1) and regional (PC2) expansion of the cortical surface area and that of other complex traits, we have calculated genetic correlations between these two brain phenotypes and a number of psychiatric disorders, personality characteristics, general cognitive function and educational attainment (Figures E8 through E20 in Extended Data). We find strong genetic correlations between the tangential growth of cerebral cortex and three behavioural traits, namely general cognitive function, educational attainment and schizophrenia (Figure 4). This shared molecular architecture is consistent with the importance of early cortical development for both normal[14] and abnormal cognitive functioning later in life.

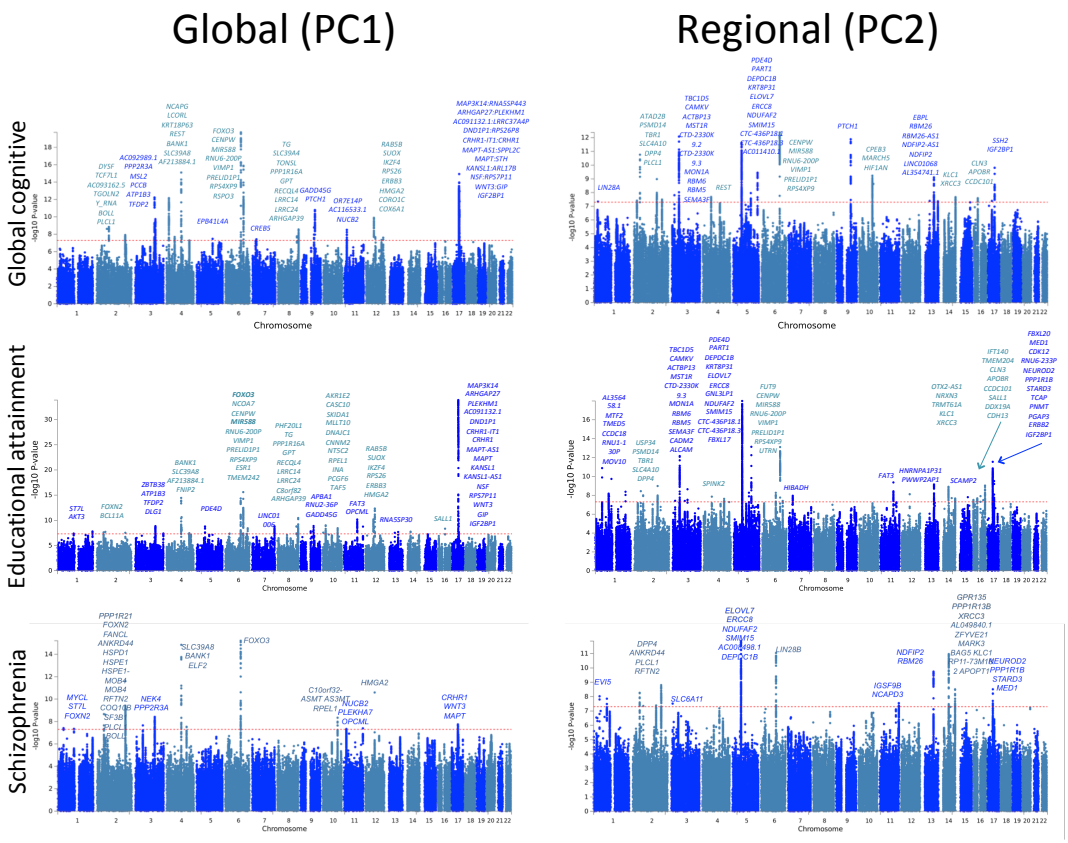

Figure 4. Genetic correlations between surface area principal component (PC) scores vs. global cognitive function (top), educational attainment (middle), and schizophrenia (bottom). PC1 and PC2 results are presented in the left and right columns, respectively. For this pleiotropy analysis, we examined whether there are any genetic loci associated with both surface area PC (e.g., PC1) *and* a given phenotype (e.g., global cognitive function), using GWAS summary statistics of the SNPs tested in both GWAS. The statistical significance was assessed by comparing the sum of the ranks of the observed pair of p-values (from the two GWAS) against the null distribution of the sum of ranks of p-values generated from the uniform distributions. The information on the sources of the GWAS results and pleiotropy analysis method used for obtaining the displayed results is presented in Extended Data Figures (Figures E8, E18 and E19).

In summary, we discovered a non-overlapping set of 74 'independent' single nucleotide polymorphisms within 22 genomic loci contributing to the global and regional tangential growth (surface area) of the human cerebral cortex (Table E7, in Extended Data). On the other hand, our meta-GWAS of cortical thickness, carried out in the same individuals, yielded only two loci. This negative finding is consistent with a very low number of loci associated with both global and regional values of cortical thickness reported in the two companion reports from the CHARGE and ENIGMA Consortia; it may reflect substantial dynamics of cortical thickness during puberty[15] and aging[16]. Through a series of follow-up studies, we formulated a working model by which *DAAM1* regulates tangential expansion of the visual cortex by interacting with LGN inputs, likely at the level of cortical subplate, during mid-gestation. This finding illustrates how specification of cortical areas, and their relative growth, might be guided by an interaction between fetal environment and generic developmental mechanisms, such as those constituting planar-cell-polarity signaling pathway.

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