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FROM RESEARCH TO INDUSTRY

A Genetic Study of the Brain Cortical Sulci with the IMAGEN Cohort

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Challenge

- Central sulcus depth has already been studied in an extended-pedigree study was reported under genetic control [1].
- We propose to analyze the depth of all primary sulci, which are **specific landmarks of the brain cortical surface.**
- **Genome wide complex trait analysis (GCTA)** to estimate the variance of an observed phenotype which can be explained by the SNPs [2].

Materials & Methods

Imaging

- IMAGEN cohort composed of **1765 subjects** with T1 MR Images (ADNI-MPRAGE) and genotyping data.
- *Approach 1)* Extraction of the sulci using the **Morphologist pipeline available in Brainvisa** [3].
- *Approach 2)* Cortical dense sulcal depth obtained using **Freesurfer *recon-all*** command [4].

} *Extracting the sulcal depth related phenotypes*

- Subjects were quality checked using the following criterion: they need to have at least 2% of all their sulci features within $\mu \pm 3\sigma$.

Genetics

- 466,125 variants filtered using PLINK with the following thresholds: minor allele frequency 0.01, genotyping rate 0.99, threshold for Hardy-Weinberg equilibrium test 10^{-6}. Keep the SNPs in moderate linkage disequilibrium with variation inflation factor 10 within a window of 50 SNPs.
- Compute the genetic relationship matrix with GCTA using the **229.193 SNPs left**
- **Covariates:** sex, center of acquisition, 5 principal components of identity-by-state matrix, and ICV.
- Use **MEGHA** equivalent to GCTA to **compute the estimate of the heritability of the sulcal depth** [5].

Phenotype	h2	Pval
FCLp_left	0.643	0.0260
SC_left	0.548	0.0488
SFinf_left	0.648	0.0250
SOlf_left	0.586	0.0383
SPeCinf_left	0.835	0.0058
STs_left	0.610	0.0327
Stster-post_left	0.560	0.0453

Phenotype	h2	Pval
FIP_right	0.956	0.0019
SC_right	0.600	0.0348
SFinter_right	0.594	0.0364
SFsup_right	0.808	0.0073
SPasup_right	0.804	0.0076
SPeCsup_right	0.571	0.0422
Stster-ant_right	0.714	0.0153

Tab. 1 Heritability (h2) estimates of the maximum depth of primary sulci recognized on 1657 subjects, using Brainvisa.

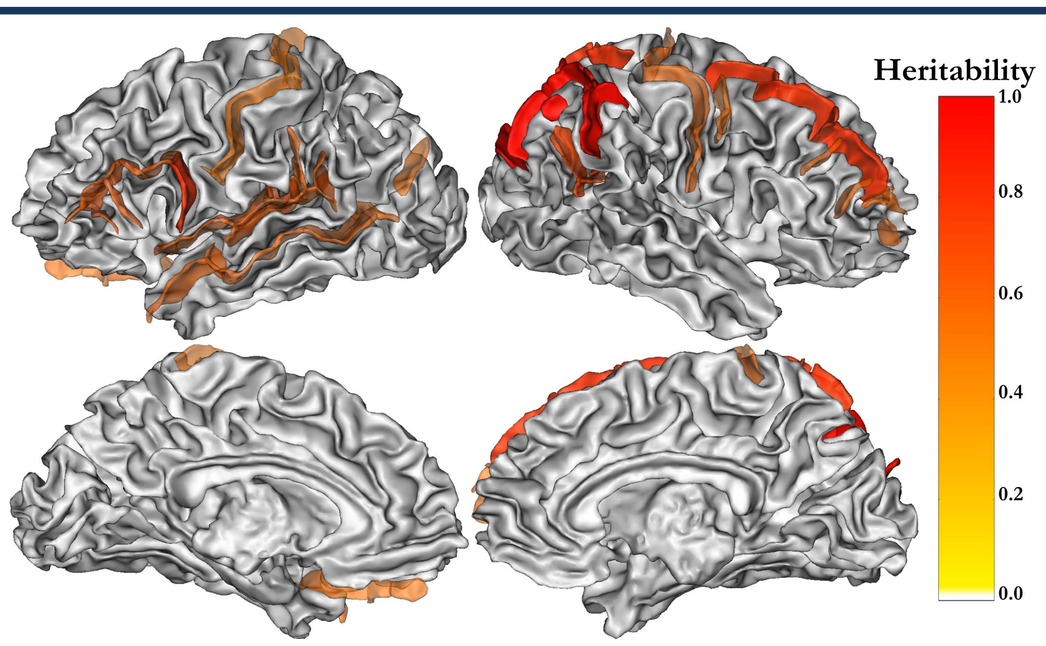

Fig. 1 Mapping of the heritability of the sulcal-based maximum depth for each sulcus having a p-val < 0.05, computed with MEGHA

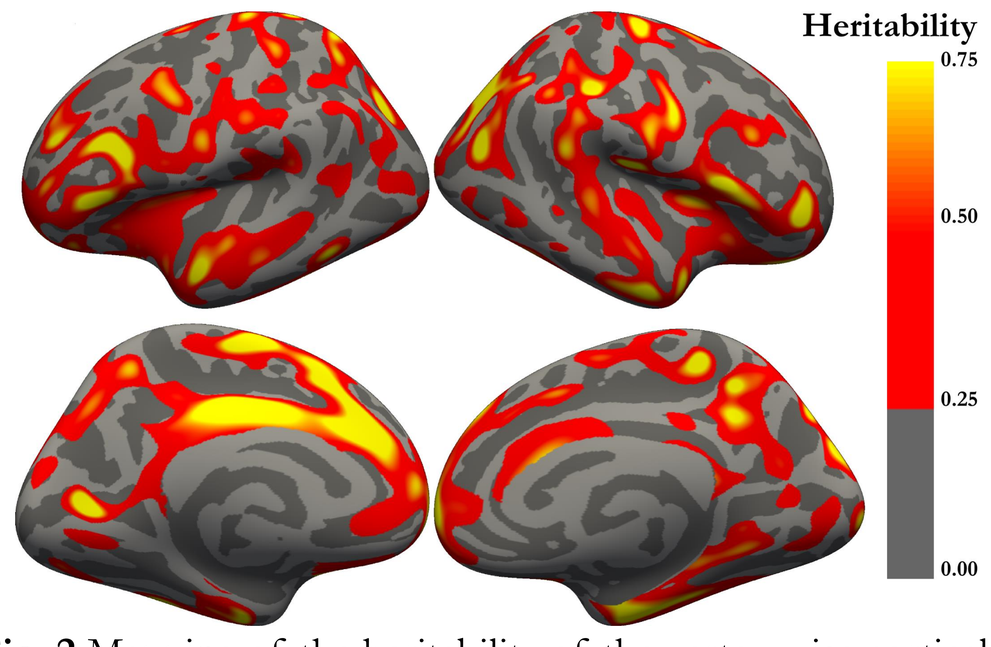

Fig. 2 Mapping of the heritability of the vertex-wise cortical sulcal depth on the whole brain on 1657 subjects, using MEGHA.

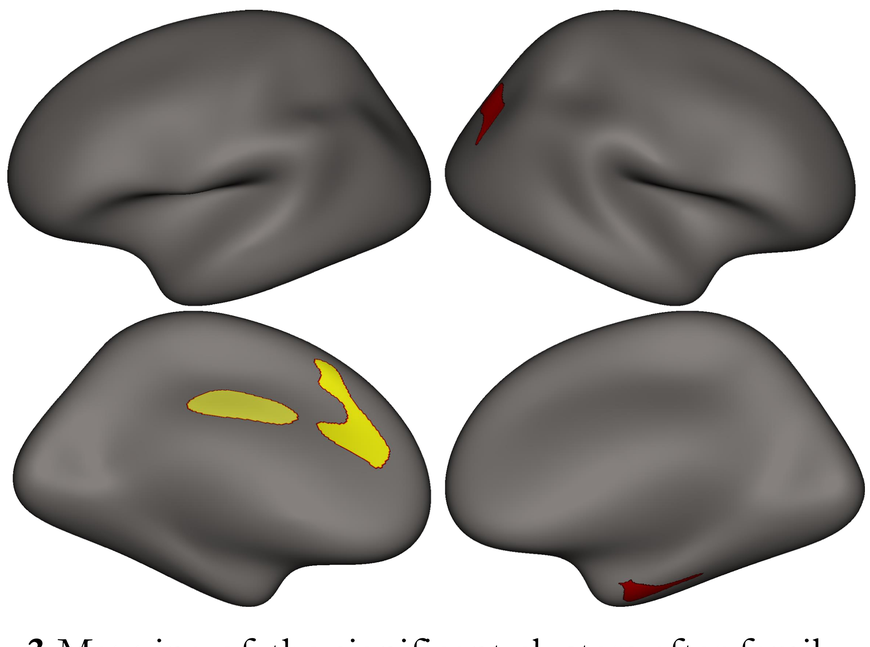

Fig. 3 Mapping of the significant clusters after family wise error correction of the pval, using MEGHA.

Conclusion

- Our findings emphasize **the sulcal depth as a phenotype under genetic control**. Yet, we would need 10k subjects to confirm this result.
- We compared two phenotypes, which contain a priori similar information on the brain structure, **one sulcal based maximum depth phenotype** and **one vertex-wise dense sulcal depth**. The relationship between these two phenotypes need to be further analyzed.

Remark: The genome-wide heritability of the cortical sulcal depth was estimated with only 50% statistical power to detect heritability values above 45% and presented results with uncorrected pval.

Perspective

- The sulci are specific landmarks of the brain that appear *in utero* and early year in development. The results presented here suggest that sulcal depth is a trait of interest to unveil **how genetics contribute to the brain structure development**. This phenotype is **a good candidate for finer genetic analyses** with either more powerful cohort or by using gene candidate or sulcus-candidate analysis.

References & Acknowledgment

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