

# Unearthing the Evolutionary History of Genetic Variants Influencing Human Sulcal Widening

Presented During: Posters Session

Wednesday, June 12, 2019: 12:45 PM - 02:45 PM

## Poster No:

W281

## Submission Type:

Abstract Submission

## Authors:

Herve LEMAITRE<sup>1</sup>, Yann Le Guen<sup>1</sup>, Amanda Tilot<sup>2</sup>, Jason Stein<sup>3</sup>, Cathy Philippe<sup>1</sup>, Jean-Francois Mangin<sup>1</sup>, Vincent Frouin<sup>1</sup>, Simon Fischer<sup>2</sup>, Stanislas Dehaene<sup>1</sup>

## Institutions:

<sup>1</sup>Neurospin CEA, Saclay, France, <sup>2</sup>Language and Genet. Dept., Max Planck Inst. for Psycholinguistics, Nijmegen, Netherlands, <sup>3</sup>Dept of Genet. & Neurosci. Ctr., UNC-Chapel Hill, Chapel Hill, NC

## Introduction:

One of the most distinctive changes in the evolution of the human brain was the enlargement of the cerebral cortex, with areal expansion and folding of cortical surfaces. Such expansion may have contributed to emergence of our capacities for high-order cognitive abilities such as language. Cortical folding starts very early in life and consists of the formation of gyri and their counterparts called sulci in a precise spatio-temporal order. As regards to sulci, it has been shown that sulcal pits - the locally deepest regions of sulci and the first to develop - are under tighter genetic control than the rest of the cortex (Le Guen et al., 2018). Molecular analysis of multiple human, archaic hominin, and non-human primate populations has allowed us to identify chromosomal regions showing evidence of selection along the human lineage at varying evolutionary time points. In this study, we aimed to assess the contributions of these chromosomal regions to the heritability of sulcal widening, using data from UK Biobank.

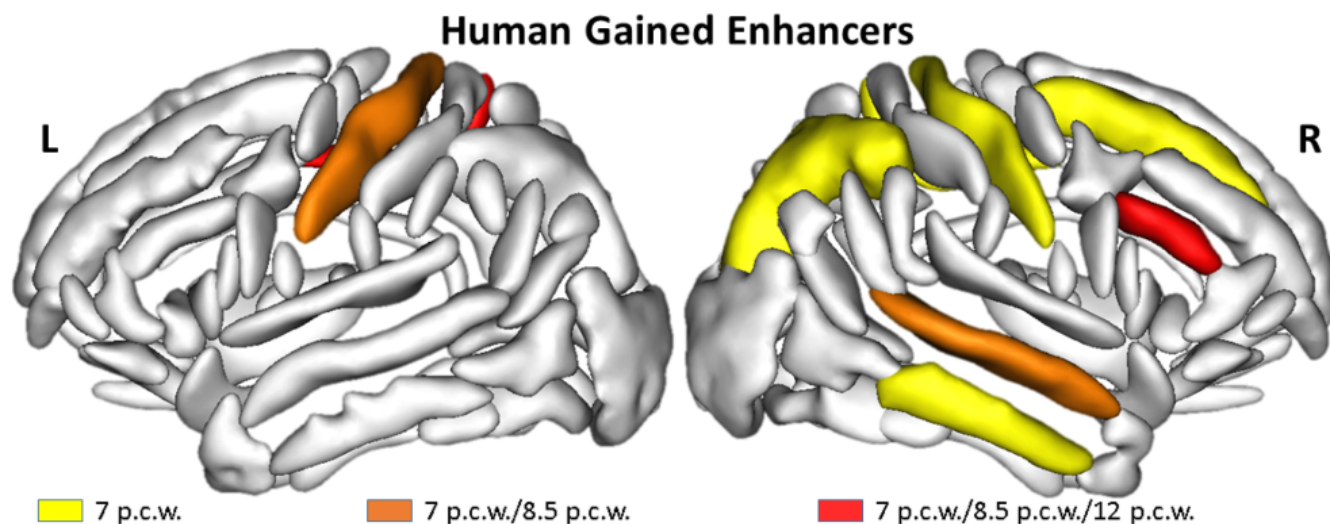
## Methods:

From the UK Biobank dataset, we obtained T1 MRI in more than 15,000 subjects and selected the British ancestry subset. Using Brainvisa (Riviere et al., 2009), the sulcal widening feature in twenty two main brain sulci was extracted and, the genome-wide association statistics using PLINK (Purcell et al., 2007) were derived with covariate accounting for the sex, genotyping array type and age. We studied five sets of genomic regions that experienced selective pressure at varying time points of primate and human evolution ranging from 30 Mya to 50 kya: Human gained enhancers (Reilly et al., 2015), Human accelerated regions (Capra et al., 2013), Selective Sweep (Peyr gne et al, 2017), Neanderthal introgression (Simonti et al., 2016), Neanderthal lineage depleted region (Vernot et al., 2016).

Enrichment of heritability explained by single-nucleotide polymorphisms (SNPs) within the relevant evolutionary regions was assessed through linkage disequilibrium (LD)-score partitioned heritability (Funicane et al., 2015).

### Results:

Human fetal enhancers regulating cortical development that are found in humans but absent from non-human primates (Reilly et al., 2015), show a significant enrichment in the heritability of sulcal widening in the left and right central sulci and callosal-marginal posterior fissures, and in the right inferior and superior frontal, anterior inferior and superior temporal, and intraparietal sulci (See Figure). Conversely, introgressed Neanderthal SNPs and human accelerated regions showed a depletion of variants impacting on sulcal widening, indicating that these segments of the genome could explain less of the heritability of this trait than expected by chance.



•Figure: Enrichment in heritability of sulcal widening with Human gained enhancers ( $p < 0.05$ ). p.c.w.: post conception weeks, L: left, R: right.

### Conclusions:

We show in this study that genetic variations in genomic regions that have experienced selective pressure over the last 30 million years of human evolution may impact on the shape of different human sulci. Integration of evolutionary signatures with data from neuroimaging genetics provides an exciting way to explore how these early developmental anatomical features relate to brain functions in modern humans.

### Genetics:

Genetic Association Studies <sup>1</sup>

### Imaging Methods:

Anatomical MRI <sup>2</sup>

### Neuroanatomy:

Cortical Anatomy and Brain Mapping

### Keywords:

Cortex

Development  
Phenotype-Genotype  
STRUCTURAL MRI

<sup>1|2</sup>Indicates the priority used for review

**My abstract is being submitted as a Software Demonstration.**

No

**Please indicate below if your study was a "resting state" or "task-activation" study.**

Other

**Healthy subjects only or patients (note that patient studies may also involve healthy subjects):**

Healthy subjects

**Was any human subjects research approved by the relevant Institutional Review Board or ethics panel? NOTE: Any human subjects studies without IRB approval will be automatically rejected.**

Yes

**Was any animal research approved by the relevant IACUC or other animal research panel? NOTE: Any animal studies without IACUC approval will be automatically rejected.**

Not applicable

**Please indicate which methods were used in your research:**

Structural MRI

**For human MRI, what field strength scanner do you use?**

3.0T

**Provide references using author date format**

- Capra, J. A., Erwin, G. D., McKinsey, G., Rubenstein, J. L. R., & Pollard, K. S. (2013). Many human accelerated regions are developmental enhancers. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 368(1632), 20130025.
- Finucane, H. K., Bulik-Sullivan, B., Gusev, A., Trynka, G., Reshef, Y., Loh, P.-R., ... Price, A. L. (2015). Partitioning heritability by functional annotation using genome-wide association summary statistics. *Nature Genetics*, 47(11), 1228-1235. <https://doi.org/10.1038/ng.3404>
- Le Guen, Y., Auzias, G., Leroy, F., Noulhiane, M., Dehaene-Lambertz, G., Duchesnay, E., ... Frouin, V. (2018). Genetic Influence on the Sulcal Pits: On the Origin of the First Cortical Folds. *Cerebral Cortex (New York, N.Y.: 1991)*, 28(6), 1922-1933.
- Peyrégne, S., Boyle, M. J., Dannemann, M., & Prüfer, K. (2017). Detecting ancient positive selection in humans using extended lineage sorting. *Genome Research*, 27(9), 1563-1572.
- Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., ... Sham, P. C. (2007). PLINK: a

tool set for whole-genome association and population-based linkage analyses. *American Journal of Human Genetics*, 81(3), 559-575.

Reilly, S. K., Yin, J., Ayoub, A. E., Emera, D., Leng, J., Cotney, J., ... Noonan, J. P. (2015). Evolutionary genomics. Evolutionary changes in promoter and enhancer activity during human corticogenesis. *Science (New York, N.Y.)*, 347(6226), 1155-1159.

Rivière, D., Geffroy, D., DENGHIEN, I., Souedet, N., & Cointepas, Y. (2009). BrainVISA: an extensible software environment for sharing multimodal neuroimaging data and processing tools. *Neuroimage*, 47.

[https://doi.org/10.1016/S1053-8119\(09\)71720-3](https://doi.org/10.1016/S1053-8119(09)71720-3)

Simonti, C. N., Vernot, B., Bastarache, L., Bottinger, E., Carrell, D. S., Chisholm, R. L., ... Capra, J. A. (2016). The phenotypic legacy of admixture between modern humans and Neandertals. *Science (New York, N.Y.)*, 351(6274), 737-741.

Vernot, B., Tucci, S., Kelso, J., Schraiber, J. G., Wolf, A. B., Gittelman, R. M., ... Akey, J. M. (2016). Excavating Neandertal and Denisovan DNA from the genomes of Melanesian