On the genetic bases of incomplete hippocampal inversion: a genome-wide association study

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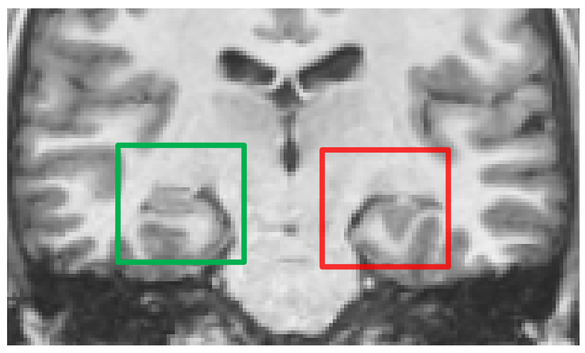
Introduction

Incomplete hippocampal inversion (IHI), is an anatomical variant of the hippocampus present in about 20% of healthy individuals (Baulac et al., 1998; Bajic et al, 2008, Bernasconi et al, 2005, Cury et al, 2015).

No IHI :

Hippocampus flat, properly inverted



IHI

- Rounded shape
- Medial position
- Deep and vertical collateral sulcus

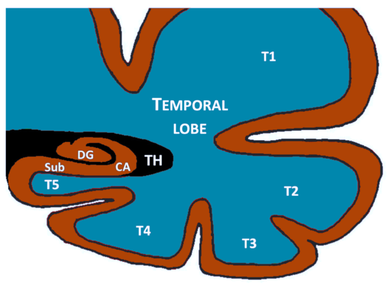
→ We performed the first genome-wide association study (**GWAS**) of **IHI** to unveil the **genetic factors** that may contribute **to incomplete inversion** during brain development.

Methods

Data	Discovery cohort: IMAGEN (N = 1381)	Validation cohort: PING (N = 161)
Description	mean age=14.5 years 49.7% females	mean age=16.1 years 48.4% females
Genotyping	blood samples on 610-Quad SNP and 660-Quad SNP arrays from Illumina	saliva samples on Human660W-Quad arrays from Illumina
Ancestry	European	European
IHI	26.1%	23.6%

IHI scoring (Cury et al. 2015):

- Manual scoring of the IHI using individual criteria (Cury et al 2015)
- A cut off at 4 was used to classify hippocampi in the IHI group or in the non-IHI.



Pre-processings steps :

- Raw genotyping data were prepared for imputation and haplotype reference consortium (HRC) v1.1
- SNPs were imputed on the Sanger imputation server[1] using EAGLE2 for pre-phasing and PBWT for imputation.
- QC was conducted on SNP level leaving 6,742,645 SNPs across the autosomes for the association analysis.

GWAS with Plink v1.9 :

- assuming an additive genetic model
- correcting for sex, age and five principal components for population structure and with a standard genome-wide threshold of p<5e-8.

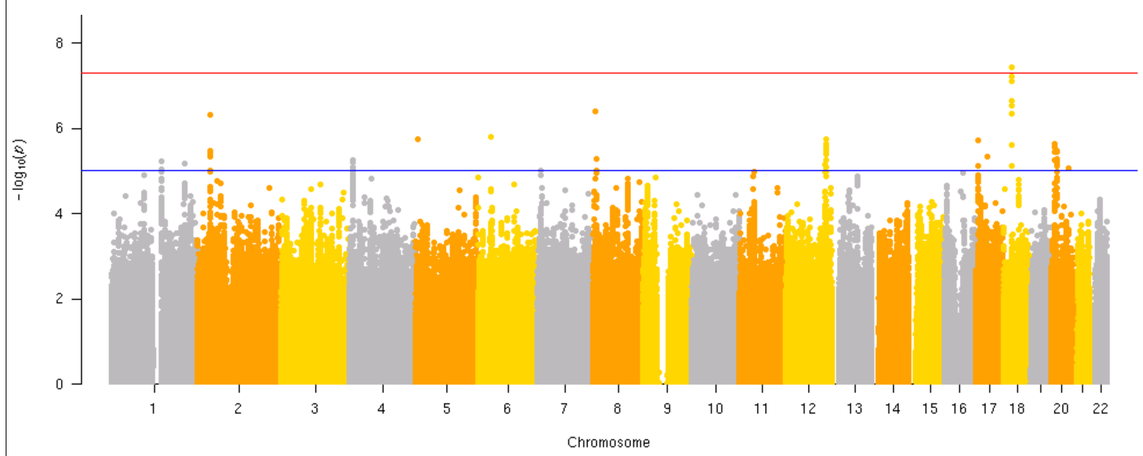
SNPs selection for validation:

- Validation cohort: SNPs exceeding the threshold for suggestive association with **IHI** (p<1e-5).
- If the **top SNP not genotyped** in PING, LDlink[2] was used to identify a proxy in linkage disequilibrium LD (r^2) within +/- 50kb of its location.

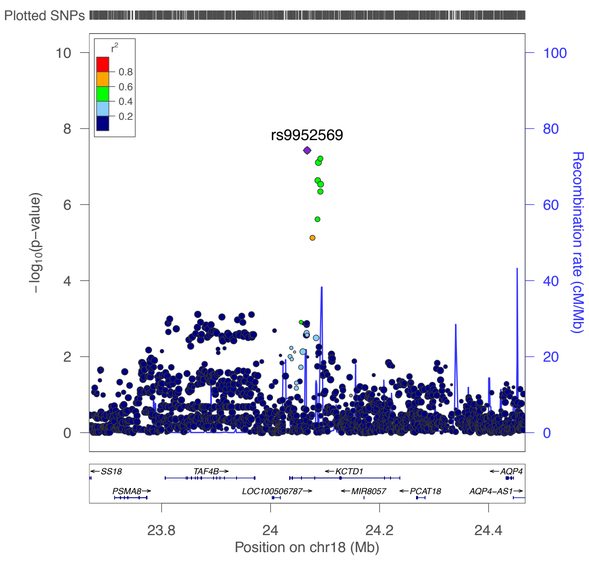
GWAS summary statistics:

- Statistics annotated using the FUnctional Mapping and Annotation (FUMA)[3].
- IHI heritability estimated from GWAS statistics using LD score regression method (Bulik-Sullivan et al, 2015)

Results



- A locus on 18q11.2 (rs9952569; OR=1.999; Z=5.502; P=3.755e-8) showed a **significant association with the presence of IHI**.
- Functional annotation of the locus implicated the genes **AQP4** (Aquaporin-4) and **KCTD1** (Potassium Channel Tetramerization Domain Containing 1).



- The gene **KCTD1 negatively regulates** the AP-2 family of transcription factors and the Wnt signaling pathway, which **controls normal embryonic development**, cellular proliferation and growth (Li et al., 2014).
- The gene AQP4 is a bidirectional water channel that is found on astrocytes throughout the central nervous system.
- Neither this locus nor the other 16 suggestive loci reached a significant p-value in the validation cohort.
- The inferred **heritability** was substantial with h^2=0.54 (sd: 0.30) and was significant (Z=1.8; P=0.036).

- We proposed **the first genome-wide association study of IHI**, where we identified a genome-wide significant locus.
- This locus was not significant in the validation cohort
- Additional exploration of the resulting summary statistics revealed a **high heritability.**

Baulac, M., De Grissac, N., Hasboun, D., Oppenheim, C., Adam, C., Arzimanoglou, A., … Berger, B. (1998). Hippocampal developmental changes in patients with partial epilepsy: magnetic resonance imaging and clinical aspects. Annals of Neurology, 44, 223–233. https://doi.org/10.1002/ana.410440213

Bernasconi, N., Kinay, D., Andermann, F., Antel, S., & Bernasconi, A. (2005). Analysis of shape and positioning of the hippocampal formation: an MRI study in patients with partial epilepsy and healthy controls. Brain : A Journal of Neurology, 128, 2442–2452. https://doi.org/10.1093/brain/awh599

Bajic, D., Wang, C., Kumlien, E., Mattsson, P., Lundberg, S., Eeg-Olofsson, O., & Raininko, R. (2008). Incomplete inversion of the hippocampus - A common developmental anomaly. European Radiology, 18(1), 138–142. https://doi.org/10.1007/s00330-007-0735-6

Cury, C., Toro, R., Cohen, F., Fischer, C., Mhaya, A., Samper-González, J., … Consortium, I. (2015). Incomplete Hippocampal Inversion: A Comprehensive MRI Study of Over 2000 Subjects. Frontiers in Neuroanatomy, 9, 160. https://doi.org/10.3389/fnana.2015.00160

Jernigan, T. L., Brown, T. T., Hagler, D. J., Akshoomoff, N., Bartsch, H., Newman, E., … Study, P. I. N. and G. (2016). The Pediatric Imaging, Neurocognition, and Genetics (PING) Data Repository. NeuroImage, 124(Pt B), 1149–1154.

Schumann, G., Loth, E., Banaschewski, T., Barbot, A., Barker, G., Büchel, C., … Consortium, I. (2010). The IMAGEN study: reinforcement-related behaviour in normal brain function and psychopathology. Molecular Psychiatry, 15(12), 1128–1139. https://doi.org/10.1038/mp.2010.4

1: https://imputation.sanger.ac.uk ; 2: https://analysistools.nci.nih.gov/LDlink/ : 3: http://fuma.ctglab.nl/