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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

→ 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 group.

Pre-processings steps:

- Raw genotyping data were prepared for imputation and haplotype reference consortium (HRC) v1.1.
- SNPs were imputed on the Sanger imputation server1 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, LDlink2 was used to identify a proxy in linkage disequilibrium LD (r2) 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=3.75e-8) showed a significant association with the presence of IHI.
- Functional annotation of the locus implicated the genes AQP4 (Aquaporin-4) and KCNTD1 (Potassium Channel Tetramerization Domain Containing 1).
- The gene KCNTD1 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 h2=0.54 (sd: 0.30) and was significant (Z=1.8; P=0.036).

We propose 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.