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).

Methods

<table>
<thead>
<tr>
<th>Data</th>
<th>Discovery Cohort: IMAGEN (N = 1381)</th>
<th>Validation Cohort: PING (N = 161)</th>
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</thead>
<tbody>
<tr>
<td>Description</td>
<td>mean age=14.5 years 49.7% females</td>
<td>mean age=16.7 years 46.8% females</td>
</tr>
<tr>
<td>Genotyping</td>
<td>blood samples on 610-Quad SNP and 660-Quad SNP arrays from Illumina</td>
<td>saliva samples on Human660W-Quad arrays from Illumina</td>
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<tr>
<td>Ancestry</td>
<td>European</td>
<td>European</td>
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IHI scoring (Curie et al., 2015):
- Manual scoring of the IHI using individual criteria (Curie 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 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) tool.
- 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 analysis.

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 identify 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.