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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

<table>
<thead>
<tr>
<th>DATA</th>
<th>DISCOVERY COHORT: IMAGEN (N = 1381)</th>
<th>VALIDATION COHORT: PING (N = 161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESCRIPTION</td>
<td>mean age=14.5 years 49.7% females</td>
<td>mean age=16.1 years 48.4% 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>
</tr>
<tr>
<td>ANCESTRY</td>
<td>European</td>
<td>European</td>
</tr>
<tr>
<td>IHI</td>
<td>26.1%</td>
<td>23.6%</td>
</tr>
</tbody>
</table>

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 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 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 h2=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.