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

Claire Curv1,2, Marzia Antonella Scelsi2, Roberto Torn2, Vincent Frouin3, Eric Artiges1, Andreas Heinz2, Henrik Walter2, Hervé Lemaitre1, Jean-Luc Martinot2, Jean-Baptiste Poline2, Michael Smolka16, Gunter Schumann11, Andre Allmann2, Olivier Colliot11

1 Inria/IRISA Rennes, France. 2 University College London, UK. 3 Institut Pasteur, France. 4 CEA, Neurospin, France. 5 INSERM Unit 1000, France. 6 Charité-Universitätsmedizin, Germany. 8 Hôpital Necker, Paris, France. 9 McGill University, Canada. 10 Technische Universität Dresden, Germany. 11 King’s College London, UK. 12 Aramis Lab, ICM, France.

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, Curv 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 (Curv et al., 2015):

- Manual scoring of the IHI using individual criteria (Curv 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 FUncional Mapping and Annotation (FUMA)3.
- IHI heritability estimated from GWAS statistics using LD score regression method (Bulka-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 study.
- 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.