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

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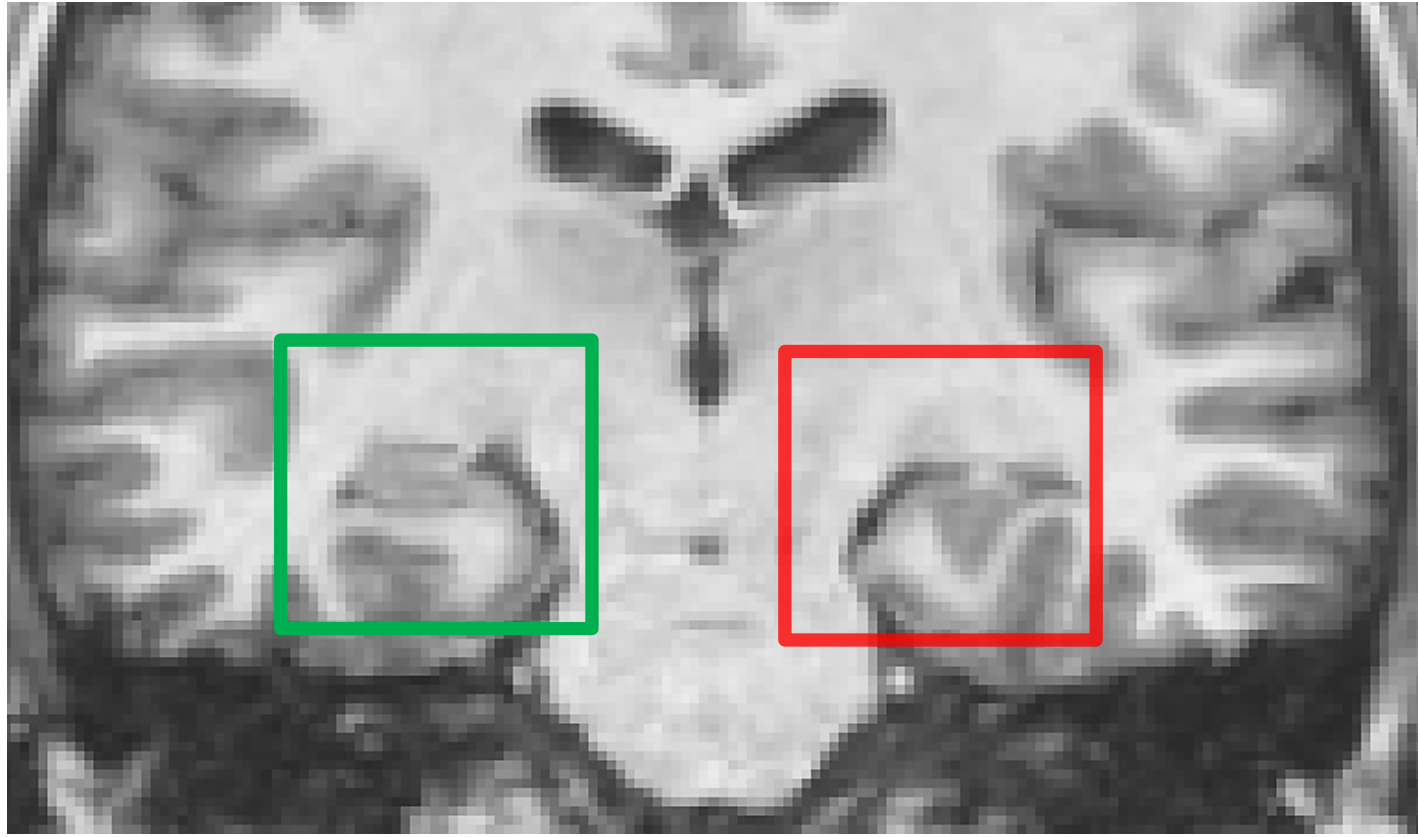


## INTRODUCTION

**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



IHI

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

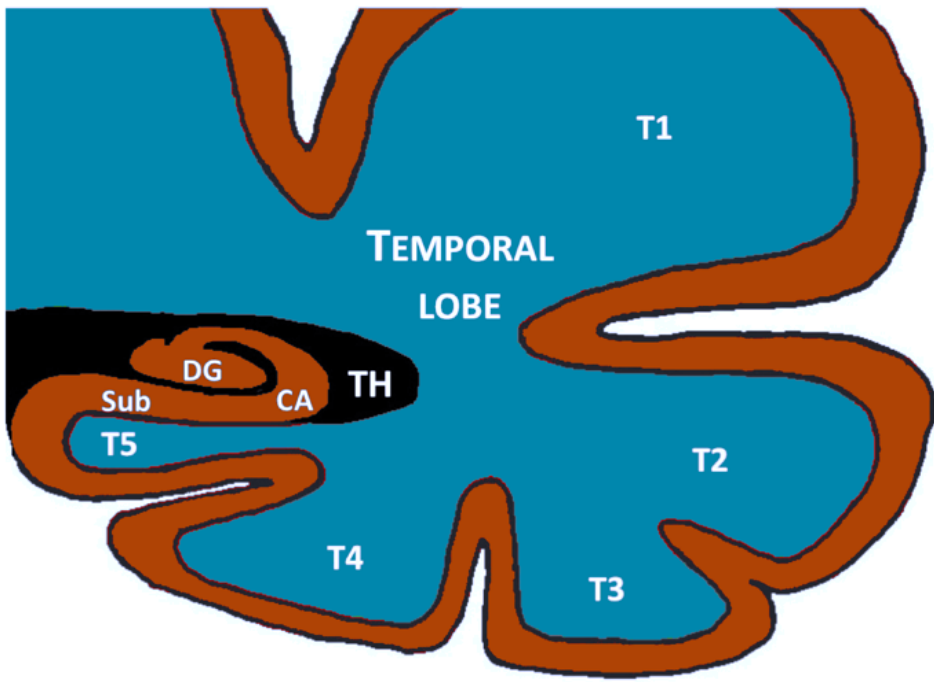
→ We performed the first genome-wide association study (**GWAS**) of **IHI** to unveil the **genetic factors** that may contribute to **incomplete inversion** during brain development.

## 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<sup>1</sup> 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  $p < 5e-8$ .

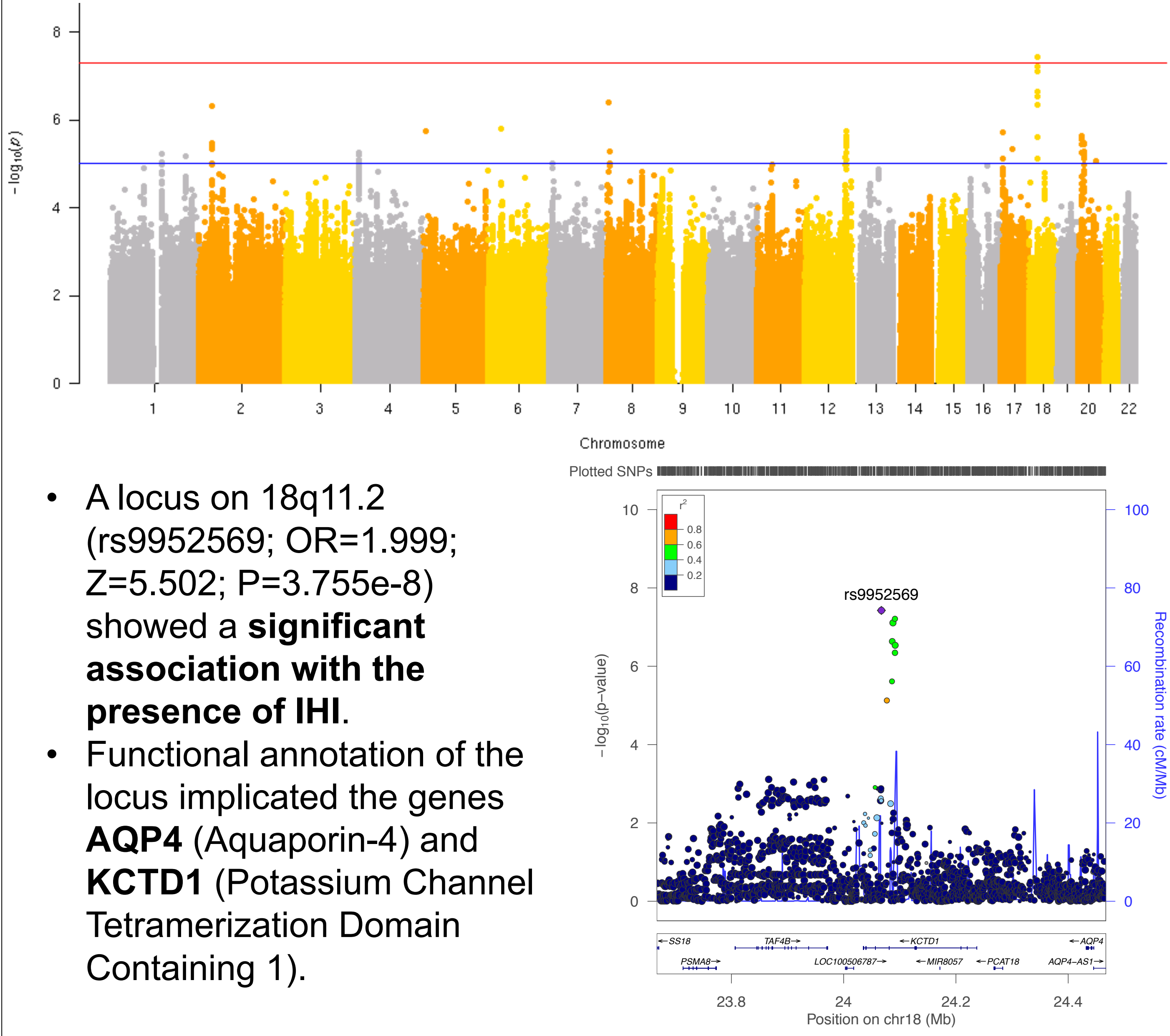
**SNPs selection for validation:**

- Validation cohort: SNPs exceeding the threshold for suggestive association with IHI ( $p < 1e-5$ ).
- If the **top SNP not genotyped** in PING, LDlink<sup>2</sup> 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)<sup>3</sup>.
- 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.**

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