

The association of chr17q21 inversion with CSF-biomarkers and AD



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Background



- **Tau is one of the major hallmarks of AD**
- **In CSF, pTau levels associate with AD**

- **The genetics of tau in AD remain unclear**
- **MAPT lies in an inversion on chr17 (H1 and H2)**
- **Recently, this inversion has been associated with intracranial volume in older adults and head size measures in children**

Common variants at 6q22 and 17q21 are associated with intracranial volume

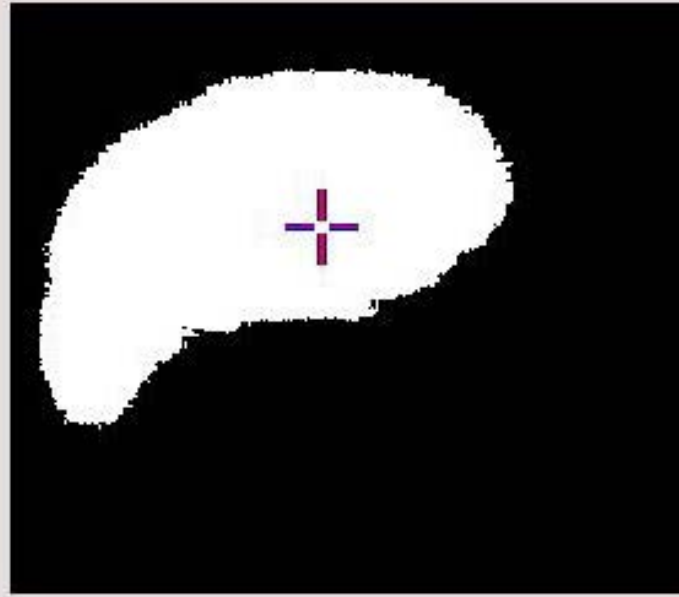
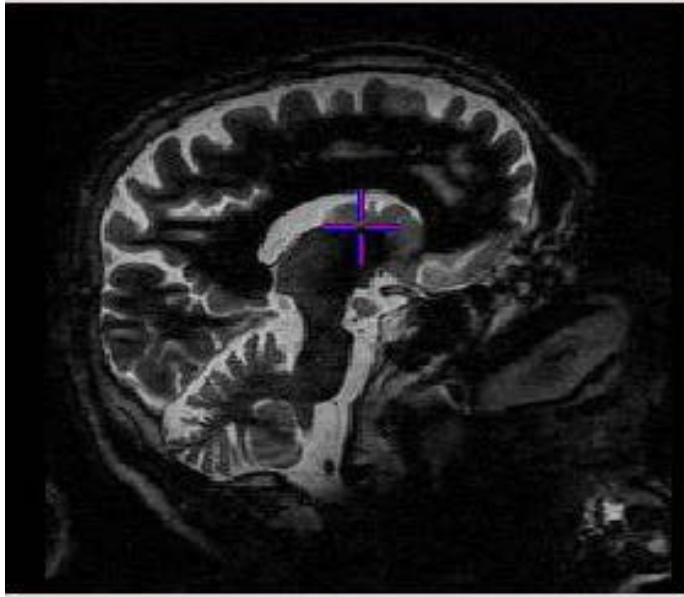
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Participating Cohorts



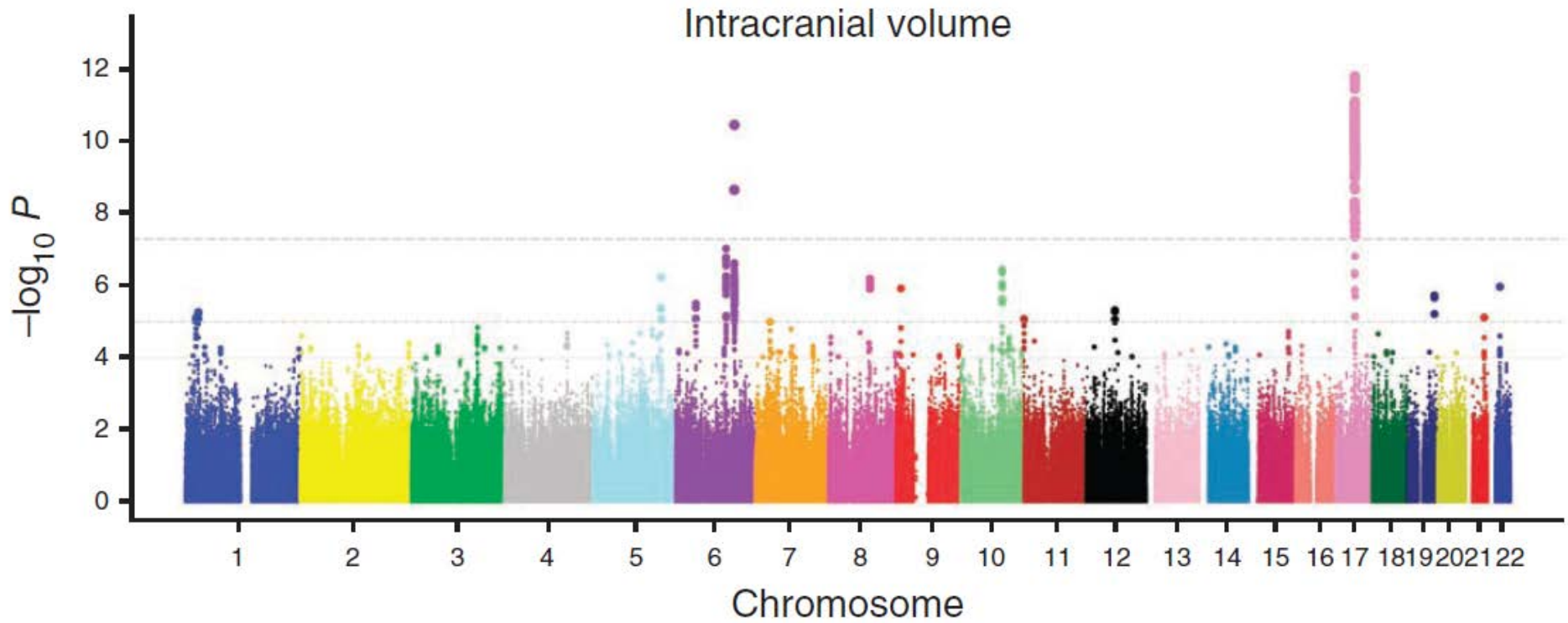
• AGES	2671
• ARIC	359
• ASPS	---
• FHS	2319
• RSSI	421
• RSSII	679
• RSS III	1726
•	Total-8,175

Intracranial Volume



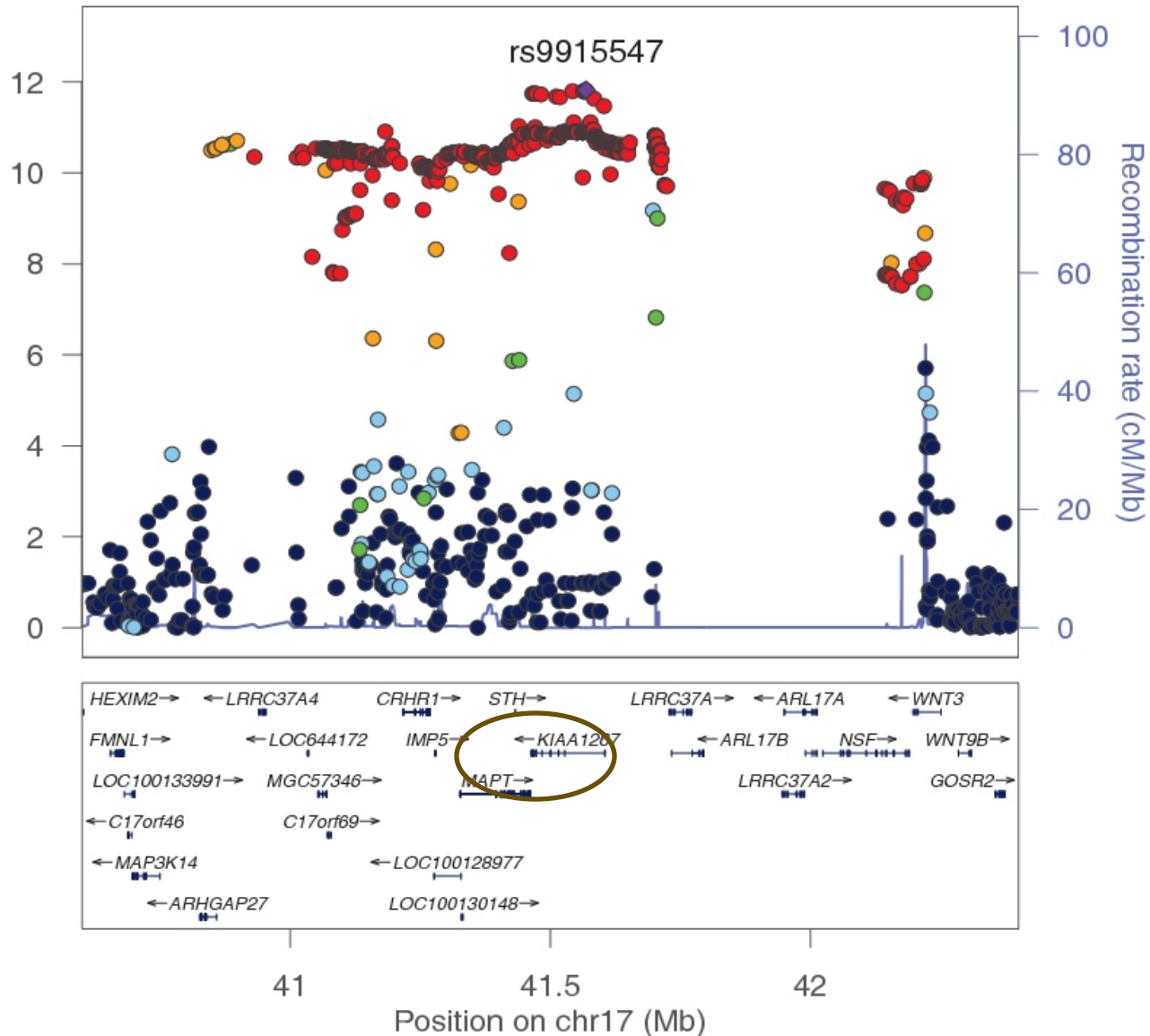
- A proxy for head size
- Remains constant throughout life
- Associated with height
- Associated with early life brain growth

Manhattan Plot



Association with headsize – Ikram et al. Nat Genet 2012

chr17q21



Chr 17 inversion



- Consists of two haplotypes: H1 and H2
- H2 is associated with smaller head size
 - Possible risk for late life dementia
 - New evolutionary development versus founder effect
 - ✦ Found almost only in Caucasians
- H2 has very little recombination (high LD)
- H1 shows considerable recombination with many SNPs present

Aim of this study



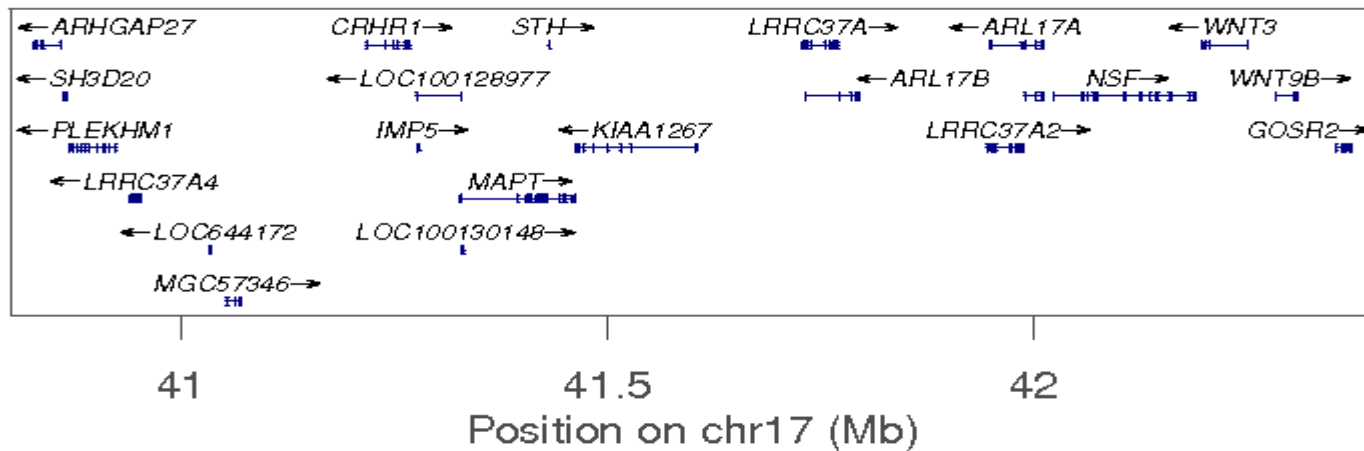
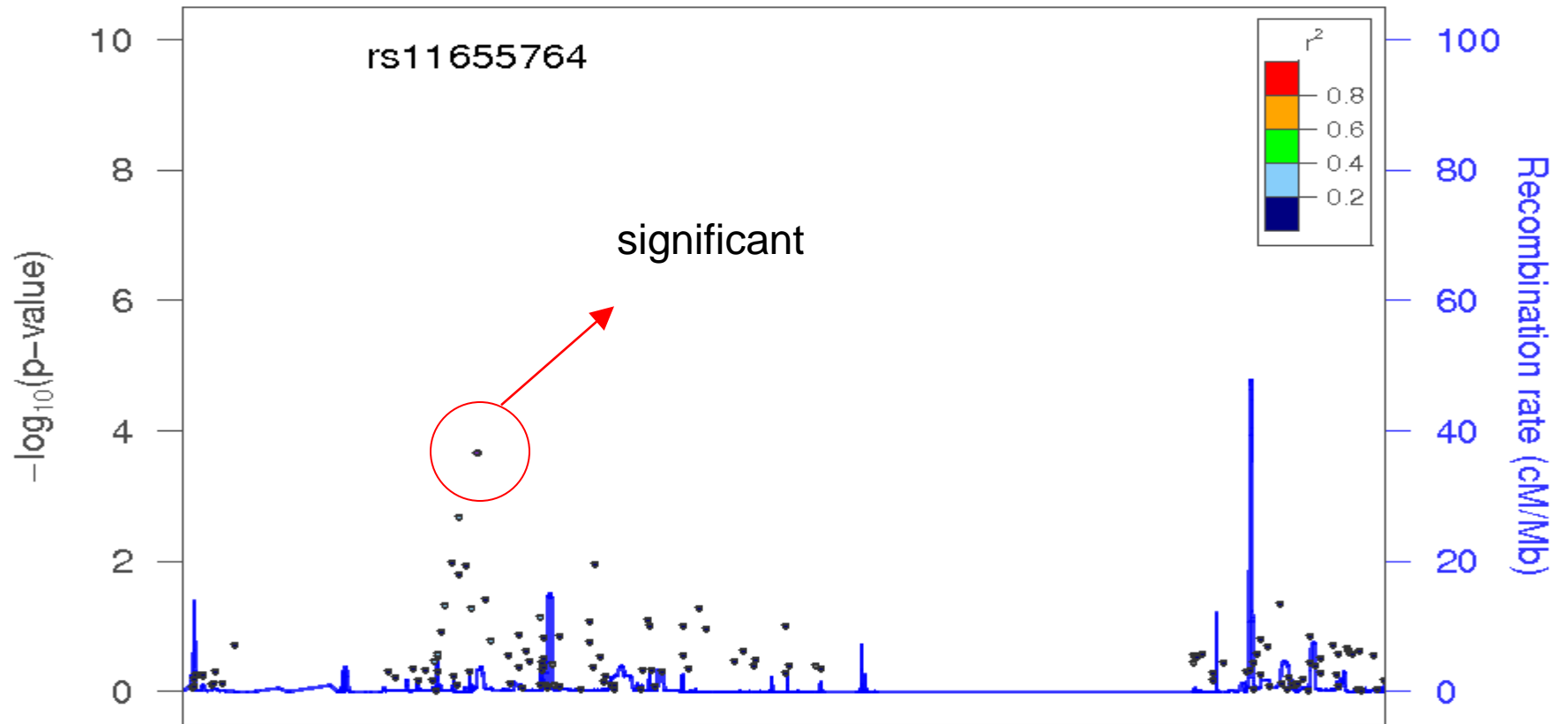
- To investigate association of chr17 inversion with CSF levels of tau and ptau
- To investigate association of chr17 inversion with AD

ADNI dataset

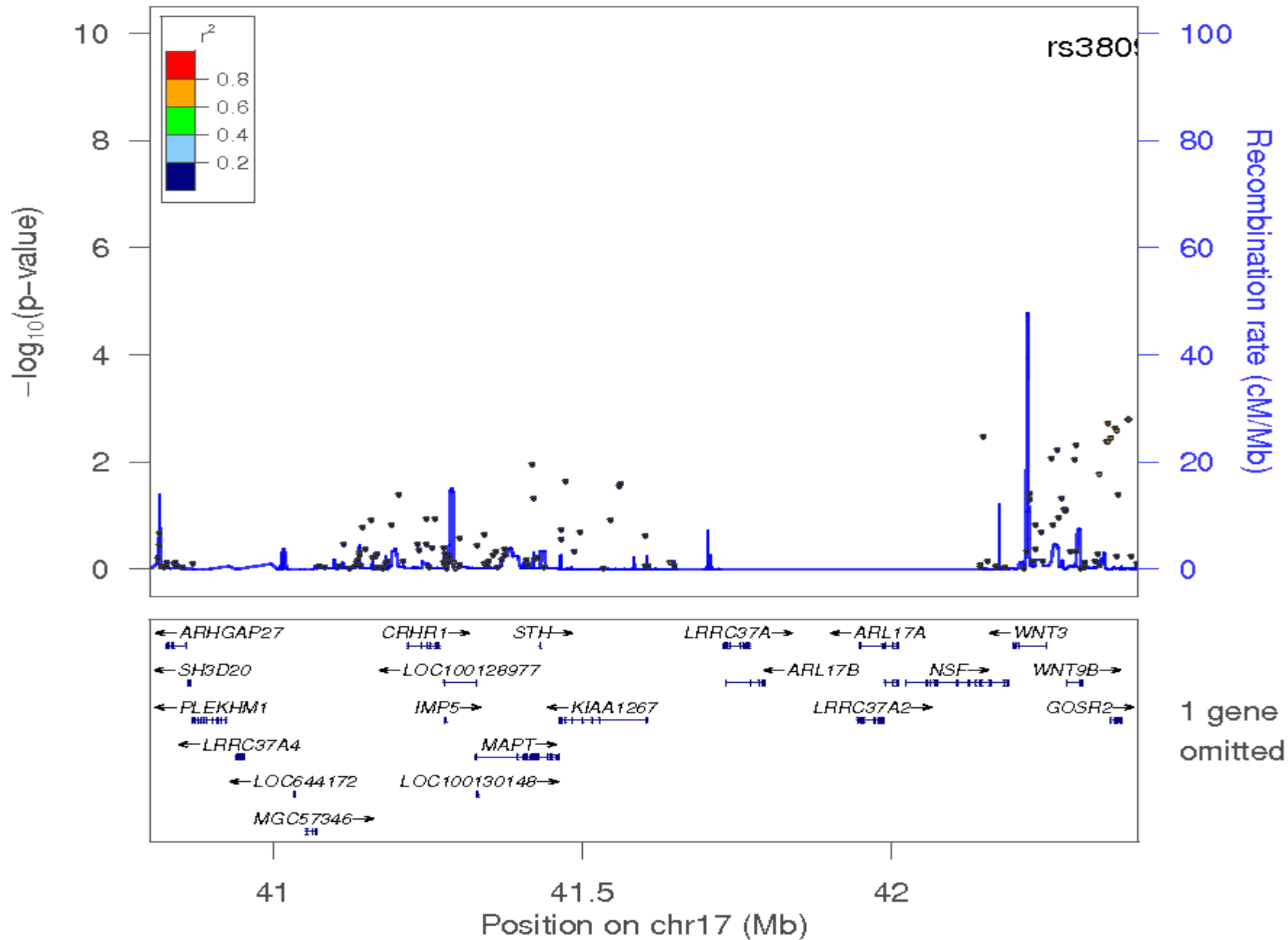


- Publicly available dataset
- Persons with genotype data and CSF markers
(n~390)
- “Inversion-wide” association study
- Associate significant SNP(s) with clinical diagnosis
(NC, MCI, AD)

P-TAU



ABETA



Association with AD



- **Rs11655764 is the 'top'-SNP associated with p-tau levels**
- **G-allele of rs11655764 associated with higher ptau-levels compared to A-allele**
- **However, Rs11655764 only shows variation in H1 carriers. H2 carriers do not show any variation and always carry the G-allele due to the primarily Caucasian population**

Potential “Haplotypes”



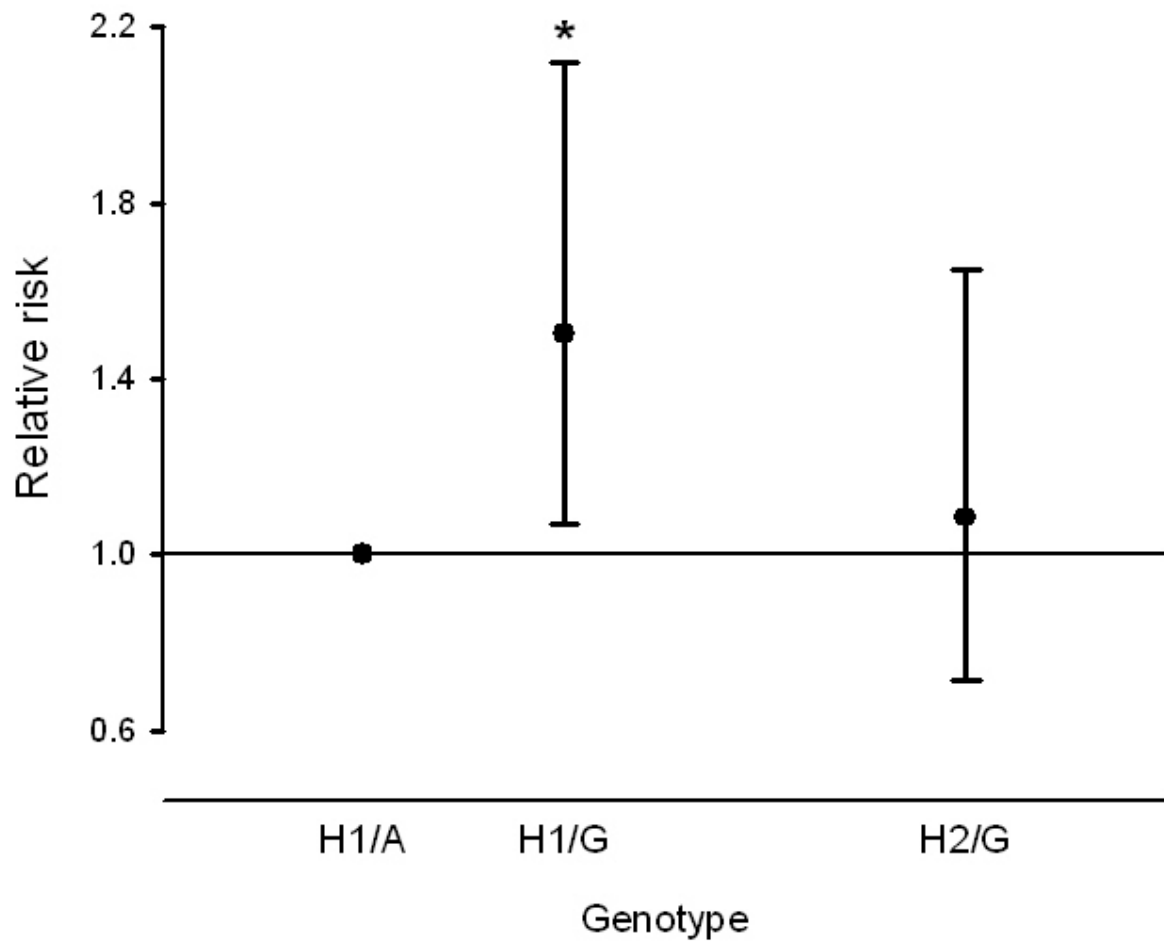
- **H1 carriers with A-allele of rs11655764**
- **H1 carriers with G-allele of rs11655764**
- **H2 carriers with G-allele of rs11655764**

Aim II

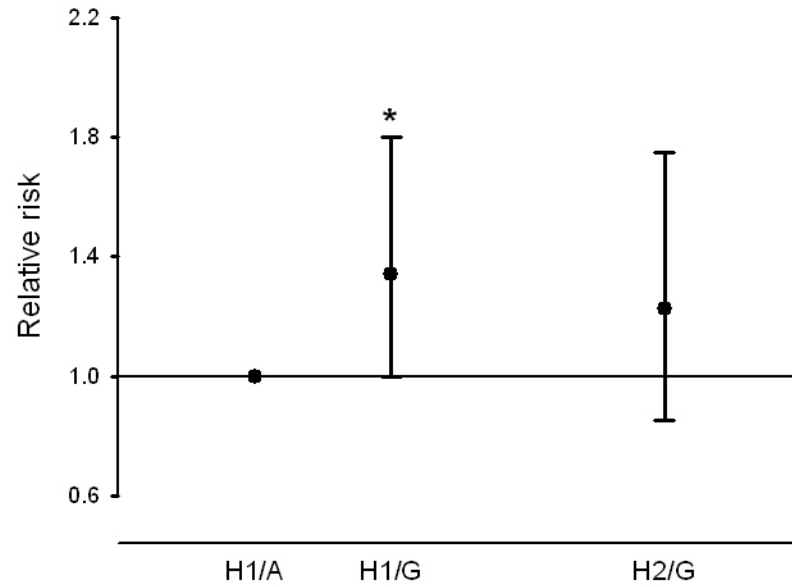


- **Examine the impact of Haplotype on risk for prevalent cognitive impairment**
 - **Hypotheses:**
 - ✦ rs11655764 G-allele will be associated with increased risk for cognitive impairment
 - ✦ H2 will be associated with increased risk for cognitive impairment
 - ✦ H2/ rs11655764G will be at greatest risk for cognitive impairment

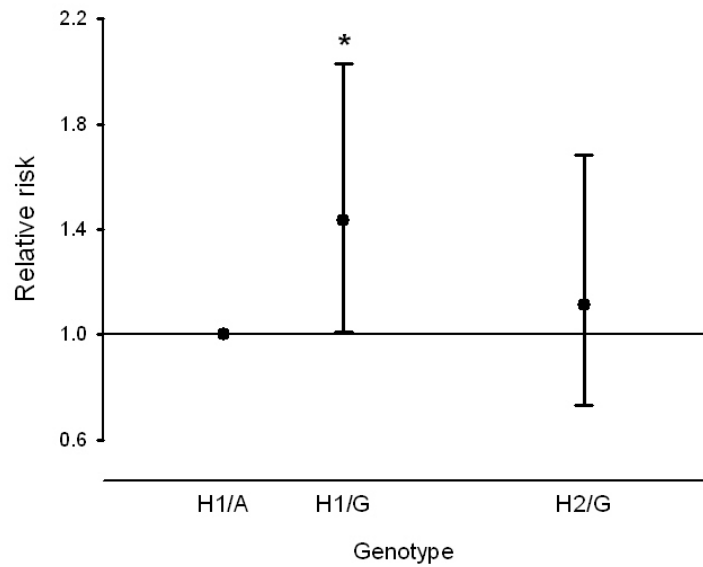
NC versus AD



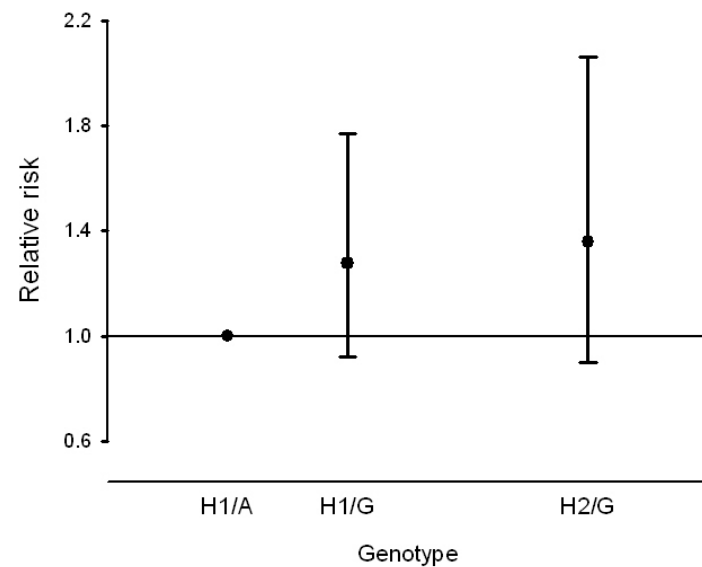
MCI versus AD



MCI-APOE- versus AD



MCI-APOE+ versus AD



Conclusion



- **Rs11655764, located in the chr17 inversion, is associated with higher p-tau levels**
- **The SNP also associates with higher risk of AD**
- **However, there is effect modification of this association by the H2-haplotype where the H2 unexpectedly is protective**

Future Directions



- **Larger datasets are needed**
 - AD Centers could contribute
 - ADNI II
- **Use amyloid imaging as marker of CSF amyloid**
- **Deep sequencing**