

Analysis of genetic risk factors for alcohol related cognitive disorders

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- **Alcohol Use Disorders (AUD) adversely impact physical and mental health. 10% of people with AUD have some form of cognitive impairment.**
- **Uncovering the genetic risk effects of a disorder can rapidly progress understanding of its molecular basis and of resilience to disease. This can inform prevention, diagnosis and treatment strategies.**

We have examined the shared genetic liability between the risk of developing alcohol-related cognitive dysfunction and schizophrenia and Alzheimer's disease, two disorders known to impact cognitive processes.



Methods

GWAS of alcohol dependence syndrome in 2336 cases and 10417 controls with meta-analysis in data from Denmark, Germany and the UKBiobank.

GWAS of alcohol related cognitive disorders in 168 alcohol dependent subjects with cognitive disorders (one or more of Confusion, Nystagmus, Ataxia, Disorientation, Memory impairment, Confabulation and/or an MMSE<28) and 686 cognitively intact alcohol dependent subjects (none of the symptoms above and an MMSE>27).

Polygenic risk score (PRS) analysis using summary GWAS statistics from large consortium studies of schizophrenia (PGC SCZ2) and Alzheimer's disease (IGAP).

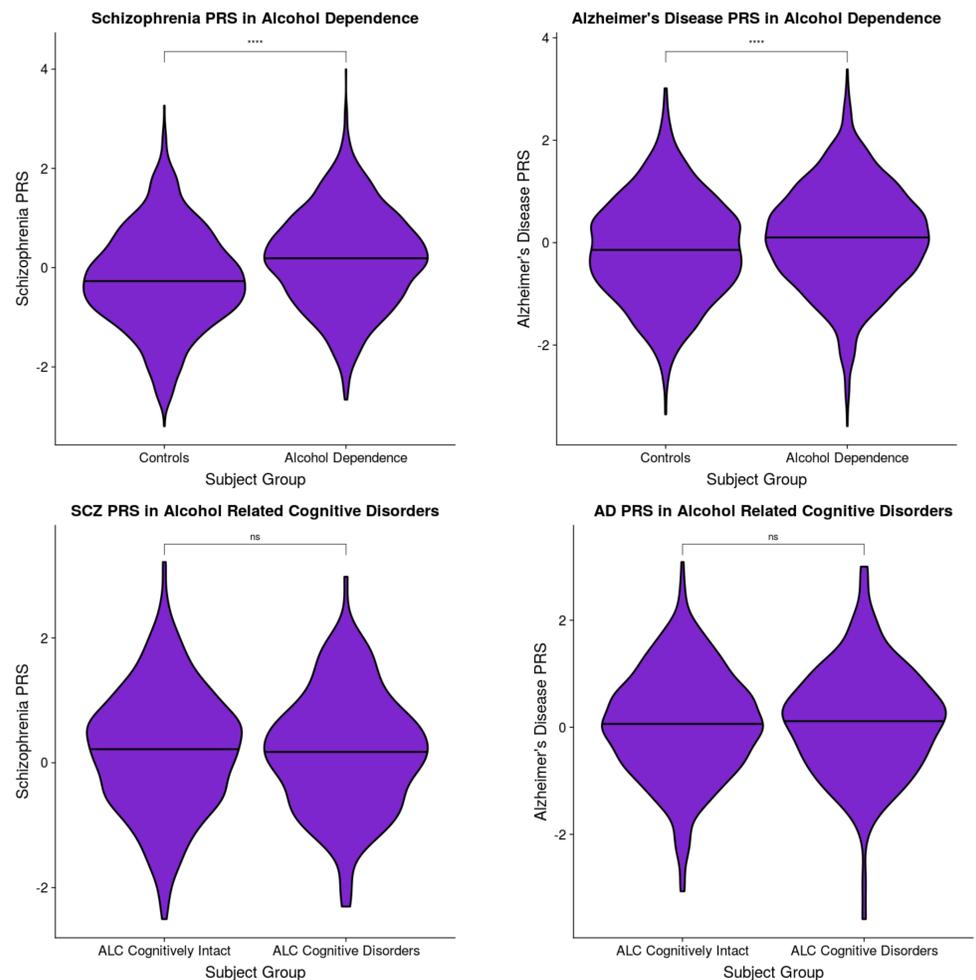
These PRS were analysed in GWAS data from the alcohol dependence study and from the alcohol related cognitive disorder study.



Results

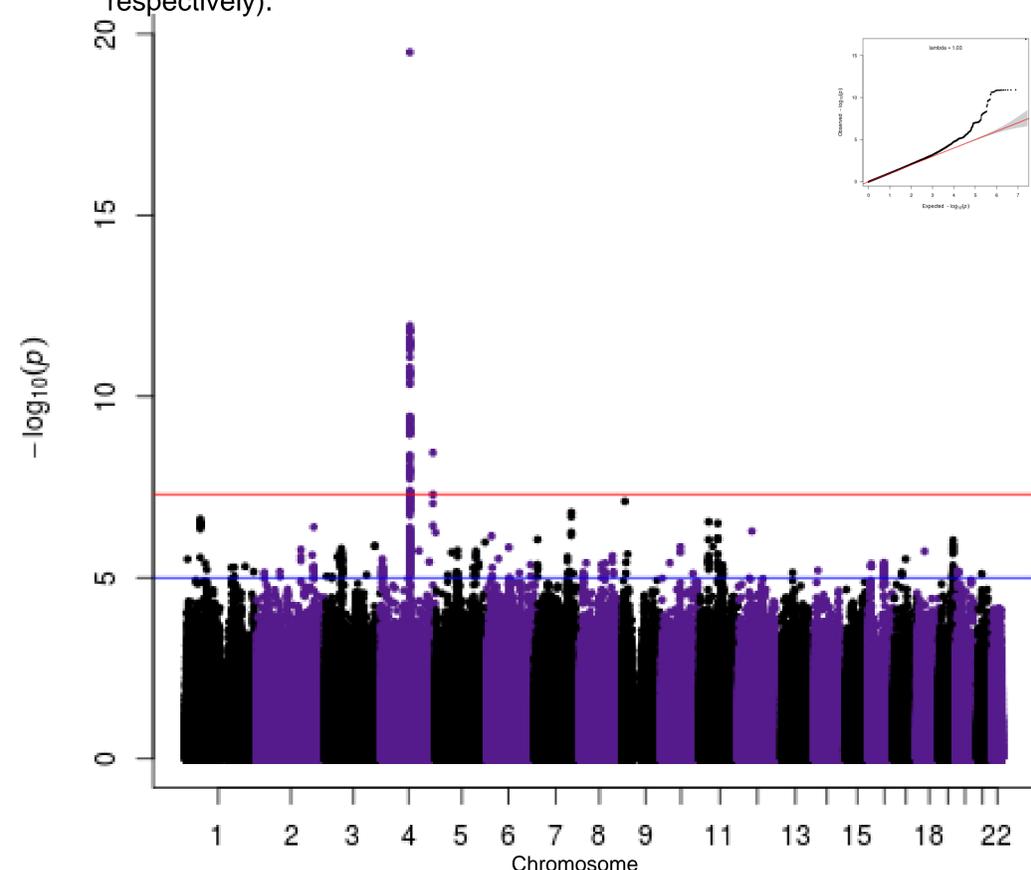
- Meta-analysis of alcohol dependence GWAS data confirmed a strong association with the *ADH1B* gene ($p=1.21 \times 10^{-17}$), and gave a second association signal in an intergenic region chromosome 4 also reaching genome wide significant levels of association ($p=2.42 \times 10^{-08}$).
- The GWAS of alcohol related cognitive disorders showed suggestive evidence for association with the *NRXN1* gene on chromosome 2 ($p=4.48 \times 10^{-06}$).
- Schizophrenia PRS analysis showed strong association with alcohol dependence and explained 5.96% of the variance between alcohol dependence cases and controls ($p=1.59 \times 10^{-29}$).
- Alzheimer's disease PRS also showed association with alcohol dependence and explained 1.26% of the variance between alcohol dependent cases and controls ($p=7.93 \times 10^{-10}$).
- Neither the schizophrenia or the Alzheimer's disease PRS scores, could distinguish between alcohol dependent subjects with cognitive impairment from alcohol dependent subjects without these problems ($p=0.85$ and $p=0.72$ respectively).

Polygenic risk score analysis

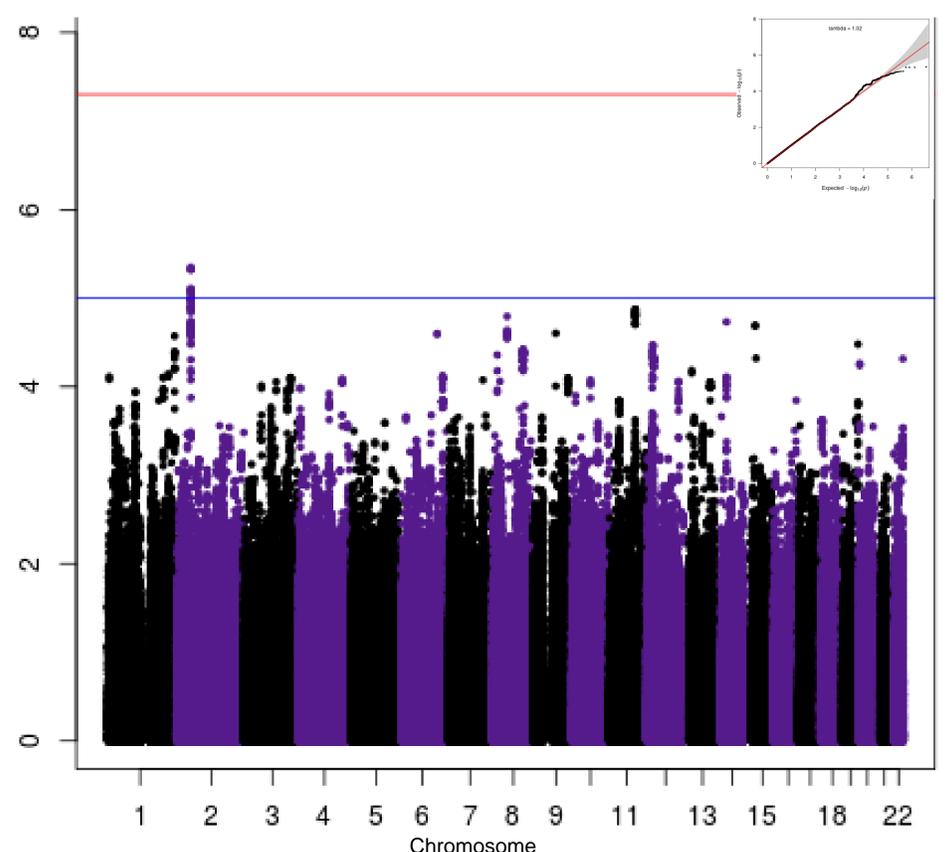


Discussion

- These data suggest a shared genetic aetiology between the risk of developing alcohol dependence and the risk of developing both schizophrenia and Alzheimer's disease.
- Whether this shared risk is as a result of comorbidity between disorders or of shared aetiological pathways remains to be determined.
- The results with alcohol related cognitive impairment may suggest that genetic aetiology for these problems is not related to schizophrenia or to Alzheimer's disease.
- However, reduced sample size for the alcohol related cognitive impairment analysis means that these findings are at best tentative. Replication of these findings in larger cohorts is required to further validate the findings reported here.



Alcohol Dependence Syndrome



Alcohol Related Cognitive Disorders