A PheWAS of rs279858, a GABRA2 SNP Previously Associated with Alcohol Use Disorder, Yields Associations with Risk-taking Behavior and Nervousness

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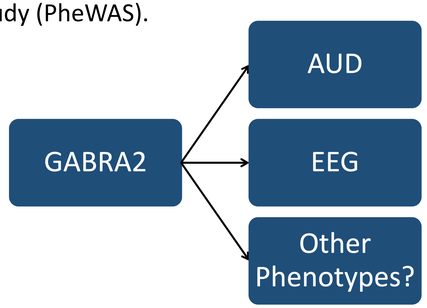
Background

- Alcohol use disorders (AUD) and electrophysiological endophenotypes (EEG) have been associated with single nucleotide polymorphisms (SNPs) in the GABRA2 gene.[1-4]
- The causal variants in GABRA2 and their mechanisms of influence on electrophysiologic parameters and AUD have not been established.
- Here we investigate the phenotypic spectrum of an AUD-associated GABRA2 coding variant (rs279858) through a phenome-wide association study (PheWAS).



PheWAS

- PheWAS are used to examine the association between a genetic variant and many phenotypes
- Originally described using electronic medical record (EMR) data by Denny et al. 2010[5]

Online Tools

- MRC IEU OpenGWAS[6] PheWAS queries a manually curated collection of eighteen GWAS summary datasets including the UKBB and other national databases e.g., the Japanese Biobank and FinnGen.
- Open Targets Genetics[7] is a public-private partnership that uses human genetics and genomics data for systematic drug target identification and prioritization, and the PheWAS tool queries the UKBB, FinnGen, and others.

Results

Phenome-wide rs279858 Associations

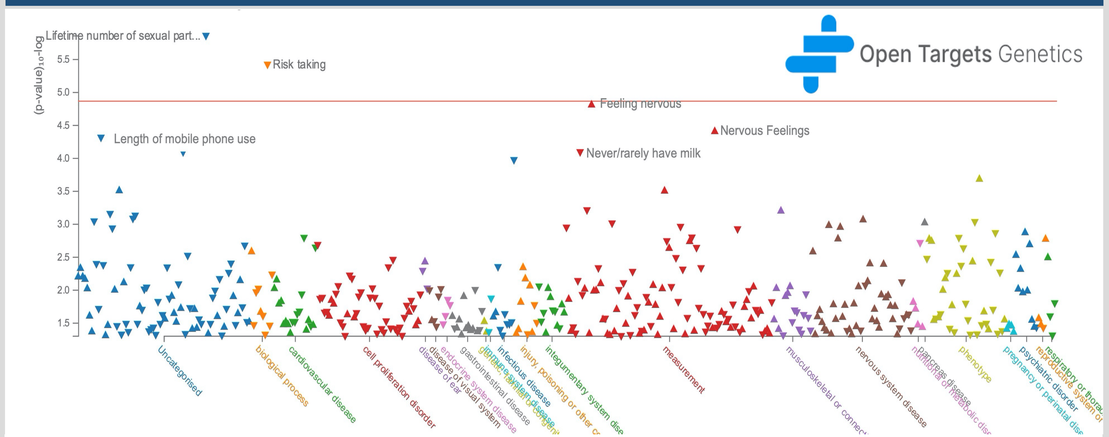


Figure 1: Phenome-wide Associations of rs279858. The x-axis lists the traits examined by body system groups. The y-axis shows the $-\log_{10}$ p-value for the trait. The up arrows represent a positive beta, while the down arrows represent a negative beta. The red line indicates a Bonferroni corrected statistical significance threshold, after adjusting for the number of independent phenotypes in the OpenTargets database. Only traits with p-value < 0.05 are shown.

Top rs279858-Associated Traits

Trait	Data Source	Total N	# SNPs	Effect Size	p-value
Risk taking	IEU UKBB[6]	446,279	9,851,867	-0.00515526	**2.10E-08**
Nervous feelings	IEU UKBB[6]	450,700	9,851,867	0.00450822	**4.60E-07**
Lifetime number of sexual partners	IEU UKBB[6]	378,882	9,851,867	-0.00904621	**1.10E-06**
Length of mobile phone use	IEU UKBB[6]	456,972	9,851,867	-0.0133956	**2.80E-06**
Natural Killer T Absolute Count	EBI Database[8]	3,653	15,195,758	0.1123	1.02E-05
HLA DR on HLA DR+ T cell	EBI Database[8]	3,060	14,891,166	-0.1071	4.10E-05
Natural Killer T %T cell	EBI Database[8]	3,669	15,198,020	0.1046	4.34E-05
Natural Killer T %lymphocyte	EBI Database[8]	3,669	15,198,020	0.102	7.47E-05
Milk type used: Never/rarely have milk	Neale Lab UKBB[9]	360,806	13,512,195	-0.0016503	8.08E-05
MAP kinase-activated protein kinase 2	Sun et al. 2018[10]	3,301	10,534,735	0.0941	1.35E-04

Table 1: Top ten associations of rs279858. For traits that appeared more than once, the instance with the smallest p-value was retained. Bonferroni-corrected significance threshold of $p<4.00\times10^{-6}$.

The strongest associations that survived correction for multiple comparisons were for novelty seeking phenotypes:
↓ risk taking, lifetime number of sexual partners, and length of mobile phone use
↑ nervous feelings

Discussion

- The negative associations with risk taking and number of sexual partners, and positive associations with nervous feelings may indicate that rs279858 may be related to novelty seeking behavior that has been identified as a trait in alcohol misuse
- The immune phenotypes may point to an inflammatory process that could be related to AUD
- The association with never/rarely having milk is puzzling and may be an index of another unmeasured social variable
- Replication efforts are underway

Strengths & Limitations

- Wide variety of biological and social phenotypes that extend beyond traditional EHR-based phenotypes
  - Can lead to interesting associations, but may be difficult to interpret
- Phenotypes can appear multiple times in the same database
  - Lack of independence in analyses

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