

M62. GABRA2 ASSOCIATION WITH ADDICTION-RELATED ENDOPHENOTYPES IS ENVIRONMENTALLY INFLUENCED

Margit Burmeister¹, Elisa Trucco¹, Shweta Ramdas¹, Stephen Parker¹, Mary Heitzeg¹, Sandra Villafuerte¹, Robert Zucker¹

¹University of Michigan

Background The GABRA2 gene contains more than 250 SNPs that in Caucasians form two major common “Yin-Yang” haplotypes - having either all or none of the non-ancestral (NA) alleles. Since 2004, association of the non-ancestral, slightly less common haplotype with alcohol use disorder (AUD) and with increased beta waves in EEG has been reported and replicated many times.

Methods In a longitudinal sample of >400 low SES families at high risk for AUD, we investigated the influence of these GABRA2 haplotypes on addiction related endophenotypes, and started to investigate potential functional implications.

We found that the NA haplotype is associated with impulsivity and with increased activation of the insula in response to reward expectation, both of which partially mediate the association of the NA alleles with alcoholism. Impulsivity was also associated with reward expectation, independent of genetics.

Results Moreover, the effect of parental monitoring on externalizing behavior trajectories across childhood and adolescence, i.e., consistently low, developmentally limited, and rising trajectories, was moderated by the NA alleles of GABRA2. Subjects with the NA alleles were more strongly influenced – both positively and negatively--by the extent of parental monitoring, while subjects with the ancestral alleles were not significantly influenced by the monitoring.

In addition to parents, peers are also known to influence addiction-related behaviors such as rule breaking during adolescence. Association with delinquent peers increased rule breaking, particularly in those with NA alleles of GABRA2, while association with peers who displayed positive behaviors (such as religious activity and scholastic competence) decreased externalizing behaviors. Subjects with the ancestral alleles of GABRA2 were less affected by peers.

Discussion Our results illustrate a more complex influence of genotypes on risk for common traits such as those associated with addiction. Our data suggest that the previously identified “risk” alleles impacts the strength of both adaptive and maladaptive environmental influences on risky behaviors such as rule breaking, and hence might be thought of as plasticity factors.

None of the alleles of the GABRA2 haplotypes change an amino acid, and they have no major influence on level of expression (eQTL) in several large brain expression samples. Allelic imbalance is more sensitive to slight expression differences.

Preliminary allelic imbalance RNASeq analyses of brain mRNA suggest that the NA alleles may increase expression. Our result is in contrast to a recent report of decreased expression of the risk alleles in iPSCs. Epigenetic modifications may be one pathway of how environmental influences on behavior are being molecularly mediated, and just as our results demonstrate plasticity at the behavioral level, plasticity may exist on the molecular level, in that expression of GABRA2 haplotypes may be influenced molecularly by different environments.

Disclosure: Nothing to Disclose.