Investigating the Effect that Polygenic Risk Score has on Heritability of Mental Disorders

Nicky Kotler, Talya Koschitzky, Laura Schultz, Ph.D., Laura Almasy, Ph.D., and COGA Collaborators
Department of Biomedical and Health informatics at the Children's Hospital of Philadelphia, UPenn School of Medicine

BACKGROUND

- Beta waves are brain waves that are measured by an electroencephalogram (EEG).
- A previous study (Rangaswamy et al) found that people with AUD had higher Beta EEG values.
- Beta EEG are brain waves of the frequency 13-30 Hz (monitored while subject at rest).
- "Fast" Beta EEG is an endophenotype correlated with risk of AUD (Beta EEG helps highlight the heritability of alcoholism).
- Additional study of Beta EEG PRS found high heritability peaks (Almasy & Borecki)on Chromosomes 6 and 8 for families 20059 and 30018 respectively.

Could polygenic risk explain these linkage peaks?

METHODS

- The data was from the Collaborative Studies on Genetics of Alcoholism Study (COGA)
  - Family study with both families that have received medical treatment for alcoholism and control families

Clinical

- COGA focused specifically AUD (Alcohol use disorder).
  - Families must have had at least one member seek treatment for AUD.
  - The controls were taken from representative families in the same communities (primarily white Europeans).

Genetics

- Both Genome wide Beta EEG PRS and the Beta EEG PRS for Chromosomes 6 and 8 were previously calculated by Laura Schultz.

*__PRS__ = Score based on cumulation of variation in genetic loci and their predictive weights
*__GWAS__ = Searches genome for SNPs that coincide with increased risk for a certain disease

- All three PRS were regressed out top 10 principle components (PC) of ancestry
- The calculation of PRS was from unpublished leads, however, it was based off similar data to A Genome Wide Association Study of Fast Beta EEG in Families of European Ancestry (Meyers et al.)

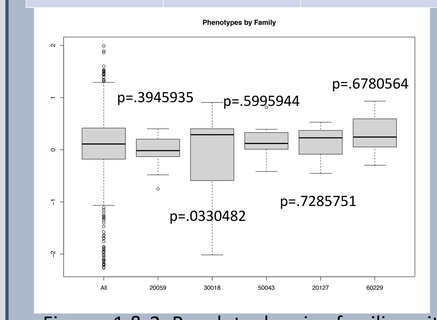
Analysis

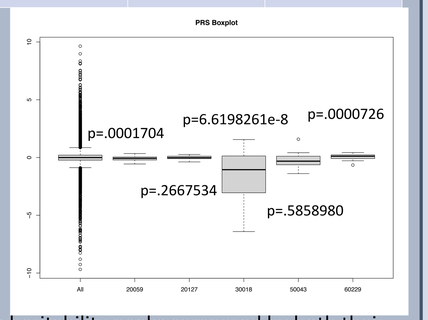
- Regression of PRS was run in R
  - Both the genome wide and chromosome specific PRS were regressed
- Additionally, the PC 1 and PC 2 data (the ethnicity data that accounts for the majority of variation) of families 20059 and 30018 were plotted vs. the total sample to confirm that ethnicity was not affecting the PRS.
- Solar Eclipse was used to calculate p-values of heritability for the families with heritability peaks. R studio would not account for the samples being from the same family and thus overcount and produce higher p-values.

RESULTS

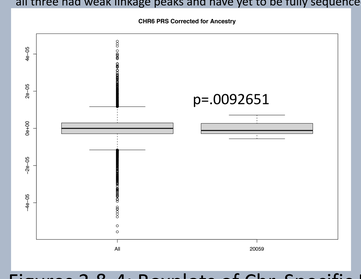
Table 2: Demographic breakdown of Beta EEG data (from COGA).

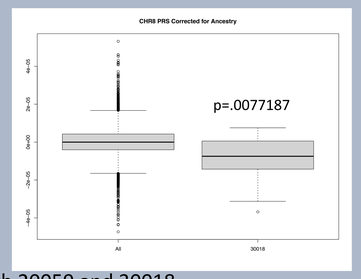
Sample Size	# of Families	Avg. Family Size (with data)	Avg. Age	% Female	% Male
1564	117	13.4	31.6	52.7	47.3





Figures 1 & 2: Boxplots showing families with heritability peaks compared by both their Beta EEG values (fig.1) and genome wide PRS (fig.2). Families 50043, 20127, and 60229 were not further explored as all three had weak linkage peaks and have yet to be fully sequenced.





Figures 3 & 4: Boxplots of Chr. Specific PRS for both 20059 and 30018

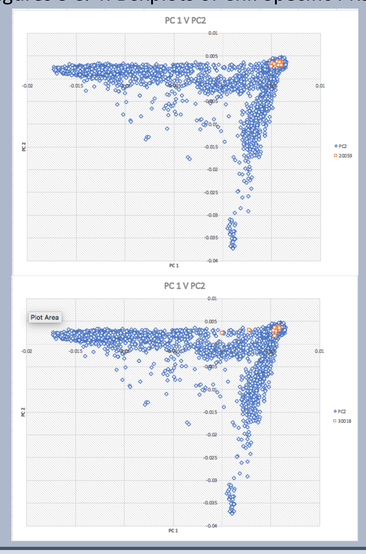


Figure 5: PC 1 and PC 2 of family 20059 vs. PC 1 and PC2 of the full sample. This confirms that differing ethnicity is not to blame for the low PRS.

Figure 6: PC 1 and PC 2 of family 30018 vs. PC 1 and PC2 of the full sample. This confirms that differing ethnicity is not to blame for the low PRS.

CONCLUSION

- Genome wide Beta EEG PRS is lower for both 20059 and 30018 compared to the full sample.
- Polygenic Risk Score does not seem to account for the high heritability peaks on Chromosome 6 and 8.
- Despite the PRS boxplots being consistent on there being a variant of large effect causing heritability, using exome to further study the variants present on these chromosomes in the families does not show any evidence of variant of large effect.

This study does not find any correlation between PRS and the linkage peaks present on chromosomes 6 and 8.

DISCUSSION

Due to the large linkage peaks present on chromosomes 6 and 8 for families 20059 and 30018 respectively, PRS was expected to be higher for these two families, specifically on chromosomes 6 and 8. This was not the case.

Some potential explanations include:

- A rare variant of large effect currently unknown to us.
- A significant lack of protecting variants present on chromosomes 6 and 8.

FUTURE STEPS

- The linkage study is currently be rerun conditional on PRS to see how the peaks are effected.
- Once the effects are seen, the study will either go back to exome (if not contingent on PRS) or do more work on PRS

ACKNOWLEDGEMENTS

Thank you to Dr. Almasy and Dr. Merikangas whose help and mentorship were invaluable this summer. Thanks to the NIH and National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute on Drug Abuse (NIDA) for supporting COGA.