COLUMBIA
MAILMAN SCHOOL OF PUBLIC HEALTH
BIOSTATISTICS

Candidate Genes Study of Major Psychiatric Disorders

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BACKGROUND

- The rising prevalence of mental disorders in today's society is a public health concern because mental health patients are suffering from prolonged and debilitating pain.
- Major Depressive Disorder (MDD) affects more than 6.7% of the U.S population[1], while schizophrenia and bipolar disorder each affect about 1.5–3% of the U.S population[2,3].
- Heritability has been long hypothesized to play a factor in development of mental disorders and specific genetic variants have been recently linked to the risk of MDD[4], schizophrenia[5] and bipolar disorders[6], with some of them overlapping each other.
- 16 genes explored in this study include oxytocin receptors, serotonin receptors, integrases and transporter proteins, X-box binding protein, regulatory proteins, promoters, as well as polymorphisms that had been associated with major psychiatric disorders in past studies. Each gene was represented by one SNP.

ROLE & LEARNING OBJECTIVES

- The study objective was to investigate the relationships between candidate genes and patients' mental disorder diagnoses using the data collected by New York State Psychiatric Institute (NYSPI) from 1990 – 2017.
- My responsibilities covered the statistical analysis and interpretation of results, as well as data visualization and reporting.
- All statistical programming was done in RStudio.

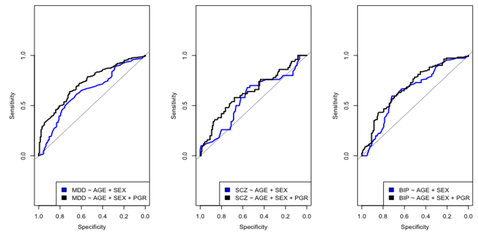
METHODS / DATA / STATISTICAL ANALYSIS

- The study focused on 1,021 subjects diagnosed with one of three mental disorders: Major Depression Disorder (MDD), schizophrenia, and bipolar disorder, and from three race groups: Caucasian, African American, and Asian.
- Control groups of each disorder in each race group were checked for Hardy-Weinberg equilibrium on each SNP.
- The three diagnoses were tested for association with sex, race group, and each of the sixteen genes using χ^2-test or Fisher's Exact test, depending on the number of subjects in each category.
- Genes found to be associated with each disorder in each race group were combined into one variable, a polygenic risk score (PGR), by adding up the number of risk alleles.
- Multi-predictor logistic regression were used with PGR as a predictor, besides age and sex, to predict each mental disorder and the results were visualized using ROC curves and quantified using AUC values in order to assess if PGR was a significant predictor for the three mental disorders in the three race sample groups.
- For each analysis, a model using only demographic predictors (age and sex) was used as a comparison for the ROC curves and the AUC values.

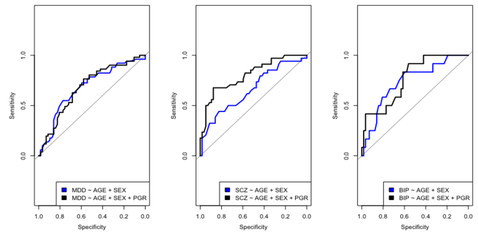
RESULTS/OUTCOMES

- The study included 1,021 subjects: 469 males and 552 females, average age of 28.21 years old.
- The control group comprised 251 subjects: 139 males and 112 females, average age of 25.17 years old.
- MDD group comprised 406 subjects: 155 males and 251 females, average age of 30.46 years old.
- Schizophrenia group comprised 121 subjects: 78 males and 43 females, average age of 23.75 years old.
- Bipolar group comprised 145 subjects: 61 males and 84 females, average age of 30.62 years old.

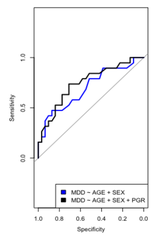
- Among the Caucasian, for MDD one significant SNP was found on the OXTR_RS53576. AUC for the blue model was 0.638, 95% CI [0.5816, 0.6943] and for the black model was 0.726, 95% CI [0.6773, 0.7749].
- Significant SNPs for schizophrenia were on BDNF V66M, COMT158, TPH2PR and XBP1. AUC for the blue model was 0.5757, 95% CI [0.4803, 0.6712] and for the black model was 0.6359, 95% CI [0.5421, 0.7296].
- Significant SNP for bipolar was on OXTR_RS53576. AUC for the blue model was 0.645, 95% CI [0.575, 0.715] and for the black model was 0.6898, 95% CI [0.6233, 0.7563].



- Among the African American, significant SNPs for MDD were on BDNF V66M, GSK3BPR, OXTR_RS53576, TPH7INT, and XBP1. AUC for the blue model was 0.6816, 95% CI [0.579, 0.7842] and for the black model was 0.6808, 95% CI [0.5789, 0.7826].
- Significant SNPs for schizophrenia were on BDNF V66M, COMT158, HTR1B861 and XBP1. AUC for the blue model was 0.6597, 95% CI [0.5415, 0.7779] and for the black model was 0.8039, 95% CI [0.7098, 0.898].
- Significant SNPs for bipolar were on BDNF V66M, COMT158, HTR1B861, OXTR_RS53576, and XBP1. AUC for the blue model was 0.7383, 95% CI [0.5834, 0.8932] and for the black model was 0.7683, 95% CI [0.634, 0.9025].



- Among the Asian, significant SNP for MDD was on HTR1APR. AUC for the blue model was 0.6978, 95% CI [0.5422, 0.8534] and for the black model was 0.7462, 95% CI [0.6025, 0.8899].



RESULTS/OUTCOMES

- Demographic predictors: there were significant associations between sex and MDD (p = 1.645 e-05) and between sex and bipolar disorder (p = 0.01071), but no association between sex and schizophrenia (p = 0.09593).
- There were significant associations between race group and the three diagnoses (MDD p = 1.926 e-08, schizophrenia p = 0.0456, bipolar p = 3.555 e-06).
- Generally, the models with sex, age and PGR as predictors (black models) had larger AUC values and ROC curves above the models with sex and age only (blue models).

CONCLUSIONS

- PGR was found to be a significant predictor for the three psychiatric disorders in each race group.
- The PGRs for the models mostly corroborated the findings from past papers.
- BDNF V66M has been found to be associated with increased susceptibility to neuropsychiatric disorders.
- COMT158, which polymorphism has been hypothesized to increase the susceptibility to schizoaffective disorders.
- OXTR_RS53576, the oxytocin receptor, which is theorized to be involved in the development of neuropsychiatric disorders that affect social performances.
- HTTLPRLS, TPH2PR ,TPH7INT, HTR1APR and HTR1B861 are all involved with the hormone serotonin, which is commonly believed to be the hormone that regulates mood and social functioning.

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