Introduction

- Over 35 million people around the world live with Alzheimer’s disease (AD), one of the most common forms of dementia.
- The Genetics Core of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) collected genomic and phenotypic data from cognitively normal (CN), mild cognitive impairment (MCI), and AD subjects.
- Amyloid-β plaques (Aβ) and neurofibrillary tangles (tau) are pathological hallmarks of AD.
- Around 10% of AD cases with noticeable cognitive decline do not have typical AD pathology. Also, high amounts of biomarkers do not always translate to cognitive decline.
- Previously, Roostaei et al. identified several genetic variants that affect the relationship between AD formation and cognitive decline using measurements from positron emission tomography (PET) scans.
- This study performed downstream analyses of several significant interactions between single nucleotide polymorphisms (SNPs), Aβ, and tau affecting cognitive function measured via immediate and delayed recall logical memory test scores (LMT and LMDT).
- Subjects were separated by stage because the effects of genetic variants and AD pathology differ by stage.
- The hypothesis of this study was that genetic variants change how AD-related endophenotypes affect cognitive decline.

Objectives

- Perform a genome-wide interaction study to identify novel loci affecting cognitive functions.
- Identify genes that may potentially be used as targets for drug therapy to treat AD in the future.

Methods

- Subjects: Data from ADNI participants was analyzed in downstream analyses following an initial genome-wide association study (GWAS). Analyses using ADNI data focused on CN subjects that remained after quality control (n=315).
- Phenotypic evaluation: This study analyzed interactions between significant SNPs and AD pathology to predict cognitive outcomes.
- Cerebral fluid (CSF) endophenotypes included amyloid-β (Aβ42) and total phosphorylated tau (t-tau).
- Cognitive outcome was measured through LMT and LMDT scores.
- Regional association: The software LocusZoom allows for visualization of GWAS results and was used to create regional association plots for statistically and biologically significant SNPs and surrounding SNPs.
- Expression SNP analysis: The Genotype-Tissue Expression (GTEX) portal was used to determine the amount of transcript-level expression of significant genes in the 13 different regions of the healthy human brain.
- Differential gene expression analysis: Data from the Religious Orders Study and Rush Memory and Aging Project (ROS/MAP) was used to examine whether genes within or close to the significant SNPs have different levels of expression depending on cognitive status. Boxplots were generated using Rstudio, an integrated development environment for R, a programming language used for statistical computing and graphics. A linear regression model that accounted for age and sex covariates was used.
- Bivariate correlation: Scatterplots generated in Rstudio visualize bivariate correlations in ADNI CN subjects stratified by genotype. Error is indicated by the shaded grey areas.
- Functional analysis: After identifying significant SNPs, the function of the associated gene was investigated in order to explain the mechanism by which the SNP-biomarker interaction contributes to AD.

Results

- Two significant SNP-biomarker interactions in CN subjects: r1238584 and gene ATP8A2 on chromosome 11 and r77369535 in gene ZNF804A on chromosome 2.
- ATP8A2: ATP8A2 codes for a protein involved in lipid flipping, a process in which phospholipids are moved inwards from the exoplasmic (outer) leaflet to the cytosolic (inner) leaflet of a cellular membrane. Lipid flipping plays a role in the synthesis of glycolconjugates by rapidly flipping lipid intermediates. Glycolconjugates have previously been shown to protect against metal-induced amyloid aggregation, which suggests a mechanism by which ATP8A2 affects the development of AD.
- ATP8A2 is highly expressed in the brain but expressed far less outside the brain, confirming its significance in the brain. Aβ and LMT show positive correlation in CN subjects with genotypes CC or CG but show negative correlation in CN subjects with the genotype GG. G is the minor (less common) allele. These findings suggest that an increase in Aβ is correlated with lower cognitive function only in individuals with a GG genotype. Additionally, the p-value from the differential gene analysis is insignificant, there is a downward trend in expression as cognitive function declines.

Discussion

- ZNF804A: ZNF804A codes for a zinc finger binding protein that binds to ATP1K1, the ataxin-1 protein which forms aggregations similar to those formed by tau and Aβ. Mutations can also cause spinocerebellar ataxia type 1, distinguished by a progressive loss of cerebellar neurones. Previously, other SNPs in ZNF804A have been identified as risk factors for bipolar disorder, heroin addiction, and especially schizophrenia.
- ZNF804A is also highly expressed in the brain, suggesting that the gene has a significant effect on the brain. According to the graphs displayed, Analyses of regional correlation, t-tau and LMDT show positive correlation in CN subjects with genotypes AA or AG. G is the minor allele. There is a slight downward trend from the differential expression analysis, but it is not significant, which might be due to the sample size and heterogeneity of brain tissues measured.

Conclusion

- Two loci (ATP8A2 and ZNF804A) were identified to have significant interaction effects on cognitive function with CSF measures of Aβ and p-tau.
- These findings warrant further genome-wide interaction studies for AD.

References


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