Gene-Gene Interactions Within an Early Risk Pathway for Alzheimer’s Predict White Matter Integrity and Cortical Thickness

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Background

Common variants within three known Alzheimer’s disease risk genes (The Sortilin-Related Receptor, LDLR Type, A Repeat-Containing (SORL1), Apolipoprotein E (APOE), and Brain Derived Neurotrophic Factor (BDNF)) independently predict differences in disease-related neuroimaging and postmortem phenotypes across the lifespan [1-3].

These three genes are intimately related:

- SORL1 expression is increased 10-fold in the presence of BDNF [4].
- BDNF ability to clear beta-amyloid from cultured neurons is SORL1-dependent [4].
- SORL1 is a receptor for APOE and modulates activity of lipoprotein lipase [5,6].

The nature of these biological interactions suggests that this gene system may confer risk for Alzheimer’s through both amyloidogenic and cardiovascular mechanisms.

Genetic interactions may explain greater quantities of disease risk than any single variant alone [7,8]. We therefore hypothesized that genetic variation within SORL1, APOE, and BDNF would be interdependent in predicting imaging biomarkers of cortical thickness and white matter microstructure.

Methods

Subjects: 135 healthy subjects (age 18-86) were recruited at the Centre for Addiction and Mental Health (CAMH) and underwent full imaging-genetics procedures. Exclusion criteria included any history of psychiatric illness, serious head trauma, or first-degree relative with major psychotic disorder (see Table 1 for demographic summary).

White Matter Microstructure: All scans were performed on the same 1.5 T GE Echospeed scanner. DTI acquisition included 23 directions (B=1000 s/mm2), 57 slices, 2 isotropic voxels; 3 repetitions averaged. Whole brain tractography was performed using Slicer 3D software and fiber clusters belonging to major tracts were selected manually. Matlab was then used to calculate fractional anisotropy (FA) values for each tract.

Cortical Thickness: T1 images (0.78x0.78x1.5mm voxels) were processed using the CIVET pipeline which calculates the distance between gray and white matter surfaces at over 40,000 vertices across the cortex. Average thickness values were then calculated for each lobe (frontal, parietal, temporal, occipital).

Genetics: All subjects were genotyped for SORL1 rs689021, APOE ε4, and BDNF val66met (rs2420785). SORL1*APOE and SORL1*BDNF were used to model interactions.

Statistical Analysis

White Matter Microstructure: Genetic variants were coded as binary factors: SORL1 rs689021 grouped as G-carriers or A/A homozygotes, APOE ε4 grouped as ε4 carriers (+) or ε4-ε4- carriers (-), and BDNF val66met grouped as Val/Val carriers or Met carriers or Val carriers. Two interactions were tested for each outcome: SORL1*APOE and SORL1*BDNF. General linear models were applied for each interaction and each tract separately, with tract FA as the outcome measure and sex and age as covariates.

Cortical Thickness: The same methodology was applied as above, except that the outcome of each model was the average lobar cortical thickness and all models co-varied for total brain volume.

Conclusions

This is the first study of the genetic interaction between SORL1 and BDNF, and the first use of the intermediate phenotype approach in analyzing the interaction of variants in APOE and SORL1. SORL1*BDNF interaction predicted white matter fractional anisotropy in the right inferior longitudinal fasciculus and uncinate fasciculus. SORL1*APOE interaction predicted cortical thickness, primarily in frontal, parietal, and occipital lobes, though no effect withstood correction for multiple comparisons.

The results suggest that variants within these three genes exert effects in an interdependent manner and may confer greatest risk for Alzheimer’s when present in certain combinations. Further study is required to evaluate these interactions in Alzheimer’s populations and on neuropathological markers of disease that are modulated by this risk pathway.

References

1. Felsky D et al., Periventricular white matter is modulated by the HLA-C*04:01 and ERAP1. Nat Genet. 2010 Nov;42(11):985-90