SORL1 and Converging Neural Risk for Alzheimer's Disease Across the Lifespan


Background
The sortilin-related receptor, LRRK1 (LRRK1) type. A repeat-containing (SORL) has been repeatedly implicated in late-onset Alzheimer’s disease (AD). SORL1
- gene variation has been associated with AD diagnosis
- shows decreased expression in the AD and MCI brain
- binds isofoms of APOE, a well-known AD risk factor
- regulates amyloid precursor protein processing
Recent studies have found a correlation of a SORL1 5' haplotype (TAT) with white matter hyperintensities, as well as hippocampal volume. While matter tracts connecting to the temporal lobe show reduced fractional anisotropy (FA) in AD patients and the subtle deterioration of brain structure and buildup of pathogenic proteins (i.e. “early brain signatures”) may be present decades before the emergence of clinical symptoms.

Our study is the first to examine effects of SORL1 on white matter using diffusion tensor imaging of SORL1 expression, as well as tau and Aβ pathology using a lifespan approach.

Methods
1) Diffusion Tensor Imaging - CAMH sample: 118 HC subjects (age 18-86, mean=46, SD=11), underwent DTI (1.5T GE Excite HD, 23 dir.: B = 1000 s/mm², 2.5 ms slices, 2.5 mm isotropic voxels, average of 3 acquisitions). Zucker Hillside sample: 68 HC subjects (age 18-84, mean=22, B = 71) underwent DTI (1.5T GE Signa HD, 31 dir.: B = 1000 s/mm², 2.5 s slices, 2.5 mm x 2.5 mm x 1.98 mm voxels). Exclusion criteria for both samples included any history of psychiatric illness, serial head trauma, or first-degree relative with major psychiatric disorder. All subjects were genotyped for 3 SNPs in the S' SORL1 risk haplotype: rs686887, rs689921, and rs641129.

2) Postmortem Tau and Aβ Pathology - Rush Memory and Aging Project (MAP); 788 autopsied Caucasian brains from elderly subjects (245 HC, 198 MCI, 341 AD) genotyped for rs686887 were analyzed for amyloid plaque and tau tangle count in the neocortex and temporal lobe separately.

3) SORL1 mRNA Expression - BrainCloud (data from dbGaP - Coalitiont et al., Nature 2012; 269 HC postmortem brains ranging from fetal to elderly, with genotypic (rs689921) and gene expression data for the prefrontal cortex.

Statistical Analysis
1) DTI: The 5' haplotype was in perfect LD in both imaging samples. For the CAMH and Zucker Hillside samples, tracts-based spatial statistics (TBSS) was carried out using general linear models to analyze SORL1 rs689921 genotypic group differences (minor allele (A) homoz to major allele (G) carriers) in white matter fractional anisotropy (FA). Covariates were age, sex, and APOE ε4 status (not available for Zucker Hillside sample).

2) Postmortem Tau and Aβ Pathology - HC, MCI, and AD groups were analyzed using ANCOVA for associations of genotype with cognitive and neurobehavioral measures. The SORL1 and tau pathology together separately for the both the neocortex and temporal lobe were analyzed for the entire sample.

3) SORL1 mRNA Expression - BrainCloud gene expression data. Caucasian and African-American subgroups were assessed for associations with prefrontal SORL1 mRNA levels across age, covarying for sex, postmortem interval, and sample pH. Linear models including restricted cubic splines for non-linear age effects were applied for each analysis.

Results
Figure 1A. Imaging - T55 FA Analysis. rs689921 A/A < G Carriers

Figure 1B. Imaging - Peak Voxel FA From TBSS

Figure 2. Prefrontal SORL1 mRNA

Table 1. Tau and Aβ Pathology: rs688387 T/T > C Carriers

Conclusions
When taken together, our neuroimaging results suggest that this risk gene impacts brain structure across the lifespan from childhood through late-life, likely manifesting as an ‘early hit’. Our in vivo results are supported by the prominent effects of the SORL1 variant on SORL1 mRNA expression during childhood and adolescence. Finally, the effects of this variant on amyloid and tau postmortem brain suggest that SORL1 confers neural risk through classic AD pathology mechanisms.

Our findings support the hypothesis that the SORL1 gene may influence risk for AD via an early neural hit. Determining the impact of other genetically-mediated early neural hits may permit accurate precclinical disease staging and targeted treatment interventions specifically aimed at those individuals at high risk for late onset AD.

References
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