Association of Candidate Gene Susceptibility Alleles on Chromosome 10 with AD Risk and Endophenotypes


Background: Alpha-T calcium (VR22) is an excellent functional and positional candidate LOAD gene. We previously found two VR22 SNPs which showed significant association with plasma Aβ levels and accounted for our chromosome 10 linkage signal in LOAD families. Leucine-rich repeat transmembrane protein 3 (LRRTM3) resides on inv dup 7 of VR22. To identify AD susceptibility alleles within LRRTM3 and VR22, we genotyped SNPs within these genes in 3 independent case-control series collected at Mayo Clinic Rochester (5), Jacksonville (3), and an autopsy series (AUT). We tested for association with LOAD and Braak neurofibrillary tangle (NFT) staging. Results: We identified 6 MLGs within VR22 and 71 SNPs in LRRTM3 uniting SNP, haplotype and multilocus genotype (MLG) approaches. Analysis of combined risky VR22 and LRRTM3 MLGs yielded AD association with greater odds ratios (ORs) and stronger p values across all series, compared to only risky LRRTM3 MLGs or only risky VR22 MLGs alone. Combined risky VR22 and LRRTM3 MLGs also significantly associate with Braak neurofibrillary tangle (NFT) staging in AD brains.

A. NO SIGNIFICANT SINGLE SNP-AD ASSOCIATIONS FOR LRRTM3 OR VR22

B. HAPLOTYPIC AND GLOBAL MLG-AD ASSOCIATIONS FOR LRRTM3 AND VR22

C. MULTILEXUS GENOTYPE - AD ASSOCIATIONS FOR LRRTM3 AND VR22

D. BOTH LRRTM3 AND VR22 MLGS ASSOCIATE WITH AD

E. COMBINED LRRTM3-VR22 MLGS ASSOCIATE REPLICABLY WITH AD

F. COMBINED LRRTM3-VR22 MLGS ASSOCIATE WITH BRAAK NFT STAGE

G. CONCLUSIONS

Both LRRTM3 and VR22 genes have variants that associate replicably with AD. Combined Risky LRRTM3 and VR22 variants associates with AD and Braak NFT stage. This results strongly suggest that LRRTM3 and VR22 may have multiple AD susceptibility variants that influence disease pathology. Additional replication of these findings will be necessary for further confirmation. (*Equal contribution)