

TITLE:

Assessment of Alzheimer's Disease Risk Genes With CSF-Biomarker Levels

AUTHORS:

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BACKGROUND:

Recent genome-wide association studies (GWAS) have implicated ten loci as novel Alzheimer's disease risk genes in addition to APOE (see www.alzgene.org). We previously showed that the AD-associated risk alleles near PICALM, but not those near CLU or CR1, correlate with reduced levels of Ab42 in the cerebrospinal fluid (CSF) of AD patients and healthy controls (Schjeide et al [2011] Arch Gen Psychiatry 68(2):207-13). We have now extended the CSF-biomarker analyses to include single-nucleotide polymorphisms (SNPs) in the remaining GWAS loci in a substantially extended dataset.

METHODS:

Our sample currently includes a total of 1,111 individuals (732 AD cases, 245 healthy controls, 134 MCI or other dementias) from Germany, Sweden, Spain, and Croatia, in whom we have measured CSF Ab42 and tau protein concentrations. These samples were genotyped for disease-associated SNPs in the ten currently established AD risk genes ABCA7, APOE, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A6A, and PICALM. These data are currently being extended by genotyping additional AD risk SNPs emerging from GWAS meta-analyses performed by our group, as well as SNPs emerging from independent CSF biomarker GWAS. All signals are compared with data from the Alzheimer's Disease Neuroimaging Initiative (ADNI).

RESULTS:

The currently available genotype data from ten AD susceptibility genes suggest that risk allele dosage of SNPs in APOE, PICALM, and ABCA7 correlates with decreased CSF-Ab42 levels in the complete dataset (P-values ranging from $<1 \times 10^{-15}$ to 0.08). Conversely, CSF-tau concentrations were associated with SNPs in APOE and BIN1 (P-values ranging from $<1 \times 10^{-5}$ to 0.1). Interestingly, gene ontology analysis reveals that the loci showing association with CSF biomarker levels in our dataset are all linked to "vesicle endocytosis", a process also emerging in similar analyses on other neurodegenerative diseases.

CONCLUSION:

We have assembled a large dataset including more than 1,100 individuals with CSF-biomarker data relevant for AD. With the exception of APOE, current AD risk genes only show marginal correlations with CSF biomarkers. The loci that did emerge as associated with CSF Ab42 or tau are all involved in endocytotic processes. Additional analyses are ongoing and up-to-date results will be presented at the meeting.