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

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BACKGROUND

Alzheimer’s disease (AD) is genetically complex, resulting in neurodegeneration and progressive cognitive decline. Recently, a number of genome-wide association studies (GWAS) have implicated several loci as novel Alzheimer’s disease risk genes in addition to APOE (see www.alzgene.org). Eleven additional putative AD loci are reported at this meeting (Lambert et al. 2013 [F1-01-01]). In work related to the project presented here, we showed that the AD-associated risk alleles near PICALM, but not those near GLU or CRI, correlate with reduced levels of Aβ42 in the cerebrospinal fluid (CSF) of AD patients and healthy controls (1). We have now extended these CSF-biomarker analyses to include single-nucleotide polymorphisms (SNPs) in a number of additional GWAS loci – including those that emerged from a recent GWAS using CSF tau levels as quantitative trait (2) – in a substantially extended dataset, currently including more than 1,600 individuals.

RESULTS

Figure 1. Association analyses of SNPs in APOE and CSF-Aβ42 & CSF-tau levels.

Table 2: Results of the most significant association analyses between CSF-Aβ42 or CSF-t-tau levels and CSF-Aβ42 or CSF-t-tau levels and APOE.

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr</th>
<th>Gene</th>
<th>A1/A2</th>
<th>SE</th>
<th>P (significant)</th>
<th>SE</th>
<th>P (significant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs429358</td>
<td>1</td>
<td>APOE</td>
<td>E3/ε4</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

METHODS

STUDY SUBJECTS: All subjects were recruited at the respective collaborative sites (see Table 1). SNP Selection: The SNPs investigated in this study were chosen based on several GWAS published in AD since 2009. The CD22 locus (here analyzing SNP rs2333352) was originally identified by Bertram et al (3); the ABC7 locus (rs7603874 and rs825843) was identified in Hollingworth et al (4); and the CD2AP locus (rs3764650 and rs3752246) and ZNF14 (rs11475577) were identified in Naj et al (5) and BN7 (rs1445731) was identified in Sehlke et al (6). The SNPs were chosen based on their association with APOE-ε4 carriers or AD patients, but not those near GLU or CRI. Genotyping: Genotyping was performed using SNPlex on DNA samples provided by the collaborating sites derived from blood or saliva using standard extraction procedures. All SNPs were genotyped in 384-well format using TaqMan singleplex assays according to manufacturer’s instructions. Genotyping efficiency was 98.2% with an error rate below 0.1%, based on genotyping samples from the International HapMap Consortium (~5% on each 384-well plate). None of the markers violated HWE at P ≤ 0.05. The strongest Aβ42 and t-tau levels associated with CSF biomarker data

CONCLUSIONS

We have assembled a large, independent sample of >6,000 subjects (healthy, AD, MCI) with DNA & CSF biomarker data

References


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