Association of glyceraldehyde-3-phosphate dehydrogenase locus variant with late-onset Alzheimer's disease

Mariet Allen1, Claire Cox2, Olivia Belbin3, Li Ma4, Gina D. Biscoglio5, Samantha L. Wilcox3, Chanley C. Howell6, Talisha A. Hunter3, Oliver Culley7, Louise P. Walker3, Minerva M. Carrasquillo5, Dennis W. Dickson8, Ronald C. Petersen9, M.P. Neill R. Grant-Radford10, Steven G. Yoomkin, Nifiur Effekh-Taper1

1Department of Neuroscience, Mayo Clinic College of Medicine, Jacksonville, FL, USA, Genetics and Molecular Medicine, Medical Research Council, and Molecular Medicine, Medical Research Council, Edinburgh, United Kingdom, 3Department of Neurology, Mayo Clinic College of Medicine, Rochester, MN, USA.

Background: Previous studies have implicated variants in glyceraldehyde-3-phosphate dehydrogenase gene (GAPDH) and its paralogs in late-onset Alzheimer's disease (LOAD), although the strength and direction of association have not been consistent. Our objective is to explore the associations between GAPDH, its paralogs and LOAD.

Methods: We genotyped three previously reported SNPs (rs3741916 in GAPDH, rs2029721 in GAPDH and rs4808173 in GAPDH) and 22 additional SNPs, at the GAPDH and GAPDHS loci, in three case-control series collectively composed of 2112 cases and 3808 controls. We tested these SNPs for association with LOAD using multivariable logistic regression analysis adjusting for age, gender and APOE. We performed meta-analysis of the most significant rs3741916 SNP using previously published series and ours. Results: GAPDH variant rs3741916, which resides in the 5'UTR of this gene, showed the strongest evidence of association with LOAD (OR = 0.93, p = 0.003). None of the other SNPs were as significant. The minor G allele showed a protective effect. Our combined series (OR = 0.87, 95% confidence interval (CI) = 0.79-0.96). This result is consistent with all of the published follow-up series but is in the opposite direction to three of the four series from the original report. Combined meta-analysis of all published series with available data and ours suggests presence of heterogeneity (Breslow-Day p < 0.0001). Meta-analysis of the 4 follow-up series with available data, including ours, revealed a significant protective effect for the minor G allele of rs3741916 (OR = 0.85, 95% CI = 0.76-0.96, p = 0.0094). Conclusions: Our results provide suggestive evidence for the presence of LOAD risk variants in the vicinity of GAPDH. The most promising variant (rs3741916) is unlikely to be the functional variant given opposing effects in different series. To provide greater understanding of the AD association at this heterogeneous locus, we intend to genotype this SNP in additional case-control series to further increase our sample size. Identification of the functional variant(s) in this region likely awaits deep variant discovery efforts.

Results

Table 1. The results of logistic regression analysis under an additive model in the Mayo Clinic series (rs3741916) and a dominant model in the other samples, plus our Mayo series.

Table 2. Replication analysis of previous reports: Chr = Chromosome, C = AD case, Cn = Control subject, N = number of subjects in series that have genotype data. MAF = minor allele frequency. OR = Odds Ratio, CI = Confidence Interval. Logistic regression includes Age, Gender and presence of an APOE4 allele as covariates. “Age” and AAE/D refers to Age at Diagnosis, Examination or Death. Nominal significantly p-values (<0.05) are highlighted in bold.

References


Figure 1. Linkage disequilibrium in the combined Mayo Clinic series at the GAPDH locus. LD was estimated and haplotype blocks were defined using the “Solid Spine” method implemented in HAPLOVIEW. Darker shades of red indicate increasing strength of LD (D’). Exons are represented with blue boxes and SNPs are represented with red lines. SNP rs3741916 (aka rs1136666) is highlighted by a red box.

Figure 2a. GAPDH rs3741916 (aka rs1136666) Meta Analysis of all series with reported counts and frequencies. Breslow-Day p-value = 0.0001.

Figure 2b. Meta Analysis of all previously reported series with counts and frequencies. Breslow-Day p-value = 0.0004.