Possible Association between SORL1 and Alzheimer Disease?

Reanalysing the Data of Shibata et al.

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Shibata et al. [1] reported that the variants in neuronal sortilin-related receptor (*SORL1*) were not associated with Alzheimer disease (AD) in a Japanese cohort comprising 180 cases and 130 age-matched controls. The authors performed a genotypic association analysis using 7 single nucleotide polymorphisms (SNPs) that were previously reported to be statistically significant by Rogaeva et al. [2] and subsequently by others [3–5]. The authors reported no association with AD. However, they *did* observe a weak association ($p = 0.05$) for SNP 8 (rs668387) when restricted to APOE $\epsilon 4$ noncarriers.

We conducted an allelic association analysis of the same data, which shows that 2 SNPs (8 and 24) were significantly associated with AD with p values less than 0.05. Specifically, when all subjects were examined, SNP 24 (rs2282649) and SNP 8 (rs668387) were significant ($p < 0.05$).

However, using a model restricted to elderly APOE $\epsilon 4$ noncarriers, the association became somewhat stronger (SNP 8, $p = 0.0163$; SNP 24, $p = 0.0375$). More importantly, the associated variants in the study by Shibata et al. [1] were identical to those in the study by Rogaeva et al. [2]. For SNP 24, the T allele was associated with AD in Caucasians as well as in Japanese people. For SNP 8, the C allele was associated with AD in Caribbean Hispanics, Caucasians, Israeli Arabs, and Japanese people.

In contrast to the original conclusions, this study does support the association between variants in *SORL1* and AD in a Japanese population. Although the findings are only marginally significant given the small sample size, this study continues to support the association in both the 3' and 5' regions of *SORL1*.

References

- 1 Shibata N, Ohnuma T, Baba H, Higashi S, Nishioka K, Arai H: Genetic association between *SORL1* polymorphisms and Alzheimer's disease in a Japanese population. *Dement Geriatr Cogn Disord* 2008;26:161–164.
- 2 Rogaeva E, Meng Y, Lee JH, et al: The neuronal sortilin-related receptor *SORL1* is genetically associated with Alzheimer disease. *Nat Genet* 2007;39:168–177.
- 3 Bettens K, Brouwers N, Engelborghs S, De Deyn PP, Van Broeckhoven C, Sleegers K: *SORL1* is genetically associated with increased risk for late-onset Alzheimer disease in the Belgian population. *Hum Mutat* 2008;29:769–770.
- 4 Lee JH, Cheng R, Honig LS, Vonsattel JP, Clark L, Mayeux R: Association between genetic variants in *SORL1* and autopsy-confirmed Alzheimer disease. *Neurology* 2008;70:887–889.
- 5 Meng Y, Lee JH, Cheng R, St George-Hyslop P, Mayeux R, Farrer LA: Association between *SORL1* and Alzheimer's disease in a genome-wide study. *Neuroreport* 2007;18:1761–1764.