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TREM2 and Neurodegenerative Disease

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TO THE EDITOR

Guerreiro et al.[1] and Jonsson et al.[2] (Jan. 10 issue) report an association between the single-nucleotide polymorphism (SNP) rs75932628 in the gene encoding the triggering receptor expressed on myeloid cells 2 (*TREM2*) (predicting an R47H substitution) and Alzheimer's disease in persons of European ancestry.

We and other members of the Alzheimer's Disease Genetics Consortium assembled multiple data sets from a total of 5896 black patients (1968 cases and 3928 controls). First, the association of Alzheimer's disease with genotyped and imputed SNPs was individually assessed in each data set with the use of logistic regression for case–control data sets and generalized estimating equations for family-based data sets (with adjustment for age, sex, the presence or absence of the apolipoprotein E [*APOE*] ε4 allele, and population stratification). The results from the individual data sets were combined in a genomewide inverse-variance-weighted meta-analysis. Subsequently, a versatile gene-based association study (VEGAS)[3] was performed specifically to explore the association of the *TREM2* gene with Alzheimer's disease; the addition of 20 kb to each side yielded a list of SNPs (see the Supplementary Appendix, available with the full text of this letter at NEJM.org). With the use of simulation based on the linkage-disequilibrium structure of a group of reference samples from HapMap, VEGAS allowed us to calculate the empirical P value for associations between disease status and variants in *TREM2* while taking into account gene size and linkage disequilibrium between the markers.[3]

The *TREM2* SNP described by Guerreiro et al. and Jonsson et al. (rs75932628) did not pass quality control because of a low minor allele frequency (0.0009). However, in the genomewide meta-analyses of the results from the individual data sets, five SNPs in the *TREM2* region were associated with Alzheimer's disease at a P value of less than 0.009; the G allele of rs7748513 was most strongly associated with affected status (odds ratio ±SE, 1.16±0.05; P = 0.001). This SNP is located 1 kb downstream of and in linkage disequilibrium with rs75932628. In the VEGAS analyses in which linkage disequilibrium between the markers was taken into account, the *TREM2* gene was significantly associated with Alzheimer's disease (P<0.001). Also, in these analyses, the strongest single-marker association was observed for rs7748513 (P = 0.001). Finally, in VEGAS analyses that were restricted to the largest individual data set (907 cases and 1675 controls), the *TREM* gene remained significantly associated with Alzheimer's disease (P = 0.04). This genetic study of Alzheimer's disease in blacks provides support for a role of *TREM2* in Alzheimer's disease.

Members of the Alzheimer's Disease Genetics Consortium are listed in the Supplementary Appendix, available at NEJM.org.

No potential conflict of interest relevant to this letter was reported.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

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