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# Meta-analysis of the Association Between Variants in *SORL1* and Alzheimer Disease

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## Abstract

**Objective—**To reexamine the association between the neuronal sortilin-related receptor gene (*SORL1*) and Alzheimer disease (AD).

**Design—**Comprehensive and unbiased meta-analysis of all published and unpublished data from case-control studies for the *SORL1* single-nucleotide polymorphisms (SNPs) that had been repeatedly assessed across studies.

**Setting—**Academic research institutions in the United States, the Netherlands, Canada, Belgium, the United Kingdom, Singapore, Japan, Sweden, Germany, France, and Italy.

**Participants—**All published white and Asian case-control data sets, which included a total of 12 464 cases and 17 929 controls.

**Main Outcome Measures—**Alzheimer disease according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association).

**Results—**In the white data sets, several markers were associated with AD after correction for multiple testing, including previously reported SNPs 8, 9, and 10 ($P<.001$). In addition, the C-G-C haplotype at SNPs 8 through 10 was associated with AD risk ($P<.001$). In the combined Asian data sets, SNPs 19 and 23 through 25 were associated with AD risk ($P<.001$). The disease-associated alleles at SNPs 8, 9, and 10 (120 873 131-120 886 175 base pairs [bp]; C-G-C alleles), at SNP 19 (120 953 300 bp; G allele), and at SNPs 24 through 25 (120 988 611 bp; T and C alleles) were the same previously reported alleles. The SNPs 4 through 5, 8 through 10, 12, and 19 through 25 belong to distinct linkage disequilibrium blocks. The same alleles at SNPs 8 through 10 (C-G-C), 19 (G), and 24 and 25 (T and C) have also been associated with AD endophenotypes, including white matter hyperintensities and hippocampal atrophy on magnetic resonance imaging,

cerebrospinal fluid measures of amyloid β-peptide 42, and full-length *SORL1* expression in the human brain.

**Conclusion—**This comprehensive meta-analysis provides confirmatory evidence that multiple *SORL1* variants in distinct linkage disequilibrium blocks are associated with AD.

The neuronal sortilin-related receptor gene (*SORL1*) is a susceptibility gene for late-onset Alzheimer disease (AD),[1–7] is located on chromosome 11q23.2-q24.2, and encodes a 250-kDa membrane protein expressed in neurons of the central and peripheral nervous system.[8] The biological evidence for a role of *SORL1* in AD is compelling: *SORL1* is part of the VPS10 vacuolar protein–sorting receptor family,[9,10] which in turn belongs to a group of protein-trafficking molecules in the endocytic and retromerpathways.[9,10] These subcellular domains are important sites for the generation of the amyloid β–peptide (Aβ), the main putative culprit in AD. In patients with AD and persons with the amnesic form of mild cognitive impairment, an early stage of AD, the expression of *SORL1* is reduced in neurons but not glia in the brain.[11,12] However, this reduction is not a consequence of AD because *SORL1* expression is not altered in patients with presenilin 1 mutations.[11,12] Cell biological experiments suggest that underexpression of *SORL1* modulates amyloid precursor protein processing, leading to overproduction of Aβ.[6]

We previously explored a series of 29 *SORL1* SNPs, which we referred to by sequential numbers (SNPs 1-29).[6] Information with regard to numbering, location, orientation, and type of these SNPs is given in Table 1. We identified 2 clusters of SNPs in the 3′ and 5′ ends of *SORL1* that were associated with familial and sporadic forms of AD: (1) SNPs 8 through 10 (alleles C-G-C; 120 873 131-120 886 175 base pairs [bp]) in the 5′ end of the gene among Caribbean Hispanics (family study), whites (case-control study), and Israeli Arabs (case-control study) and (2) SNPs 22 through 25 (alleles T-T-C; 120 962 172-120 988 611 bp) in the 3′ end of the gene among multiple white samples (family and case-control studies) and African Americans (family study). In that study we reported that suppression of *SORL1* led to elevation of Aβ levels in human embryonic kidney cells.[6] Twelve studies[1–4,7,13–19] among different ethnic groups subsequently replicated the association of AD with clusters of SNPs in the same 2 regions of *SORL1* and with different AD-associated allelic variants in other ethnic groups. However, 6 studies reported weak or no association with AD.[5,20–24]

There are several potential explanations for the different results among studies. Alzheimer disease is complex; thus, it is possible that multiple different pathogenic variants occura cross multiple domains of *SORL1* (allelic heterogeneity), that the causative variants are absent or underrepresented in some data sets (locus heterogeneity), or that the effect of genetic variation in *SORL1* on AD risk is not large enough to be detected across multiple data sets. In fact, among the negative studies, Lietal[20] performed a 2-stage genome-wide association study first examining 753 case individuals and 736 control individuals in Canadian samples and then further examining the top 120 candidate SNPs using 418 cases and 249 controls from a United Kingdom Medical Research Council data set. The investigators had 48 SNPs in *SORL1* but did not observe an association with AD. In a separate study, Li et al[5] examined 3 sets of cases and controls totaling approximately 2000 samples from the United Kingdom or the United States. They found a weak association for *SORL1* SNPs 19 ($P$=.04) and 24 ($P$=.02) for the first UK data set but no association when all 3 data sets were combined. On close rexamination, SNPs19 and 24 were weakly associated with AD in 2 of 3 data sets. The SNP associations in the second UK data set differed from those for the other 2 data sets (first UK data set and Washington University School of Medicine), suggesting that sampling heterogeneity may have affected the results. Shibata et al[23] initially reported that the assessed variants in *SORL1* were not associated with AD in a Japanese cohort comprising 180 cases and 130 age-matched controls, but a subsequent reanalysis found associations of SNPs 8 and 24, supporting a role of *SORL1* in AD.[25]

The objective in the present study was to reexamine the association between *SORL1* and AD by performing a comprehensive and unbiased meta-analysis of all published and unpublished data from case-control studies for the *SORL1* SNPs that had been repeatedly assessed across studies (ie, SNPs 4, 5, 8, 9, 10, 12, 19, and 22–25). The combined data sets provided sufficient statistical power to validate the association and to identify SNPs worthy of further investigation. We focused the meta-analyses on white and Asian populations because multiple data sets were available in these ethnic groups. We excluded 3 case-control data sets from African Americans,[3] Caribbean Hispanics,[6] and Israeli Arabs[6] because there was only 1 data set each available for these ethnic groups and thus we could not perform separate meta-analyses.

# METHODS

## SELECTION OF STUDIES

The primary sources of the studies addressing the risk for AD associated with the *SORL1* gene polymorphisms were the AlzGene database (updated September 1, 2009) and the PubMed database. The keywords used for searching PubMed were *SORL1*, *SORLA*, *LR11*, *Alzheimer disease*, and *Alzheimer's disease*. The retrieved abstracts were read to identify studies examining the genotype association between SNPs within the *SORL1* gene and AD. We also performed a manual search of references cited in published articles. The studies were read in their entirety to assess their appropriateness for inclusion in the meta-analysis. Criteria for the inclusion in the analysis were diagnosis of AD according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) and the National Institute of Neurological Disorders and Stroke–Alzheimer Diseases and Related Disorders Association Working Group criteria[26]; genotyping data for *SORL1* SNPs 4, 5, 8, 9, 10, 12, 19, and 22 through 25; case-control study design; and control population in Hardy-Weinberg equilibrium. We did not include studies that imputed SNP data. This led to inclusion of all published white* (n=14) and Asian (n=3) data sets.[15,18,23] In addition to the published studies, 1 white study[28] was included in which the authors had obtained the SNP genotypes but had not published those specific results. Autopsy confirmation was available in 1 study.[2] One Israeli Arab,[6] 1 Caribbean Hispanic,[6] and 1 African American[3] case-control study were eliminated because of lack of additional case-control data sets in these ethnic groups.

## GENOTYPING AND STATISTICAL ANALYSES

Genotyping methods for each data set are described in the original publications.[1–3,5,6,15–18,23] We performed separate meta-analyses of the white and Asian data sets. To determine the strength of associations between the individual *SORL1* SNPs and AD, we calculated a pooled odds ratio (OR) for each marker using fixed- and random-effects models as implemented in PLINK. We first performed meta-analyses of unadjusted results from the individual data sets and then repeated the meta-analyses using the results from the individual data sets adjusted for age, sex, and apolipoprotein E (*APOE*) genotype. The *P* values for each SNP were corrected for multiple testing (ie, analysis of 11 SNPs) using the false discovery rate.[29] Between–data set heterogeneity was quantified using the $I^2$ metric for inconsistency,[30] and its statistical significance was tested with the $\chi^2$ distributed Q statistic.[31] $I^2$ is determined by the formula $(Q - df)/Q$, where *df* is the number of degrees of freedom (1 less than the number of combined data sets); it is considered large for values above 50%, and Q is considered statistically significant for $P=.10$.[30,31] Possible publication bias was assessed by constructing individual funnel plots for most consistently significant SNPs (8, 9, and 10).[32] These SNPs were chosen because they had a high genotyping frequency and homogeneity across data sets and constitute the risk haplotype C-G-C

*References 1–3, 5, 6, 13, 16, 17, 19, 21, 22, 24, 27, 28.

identified in the present meta-analysis and the initial study.[6] Finally, we performed haplotype analyses of the individual data sets with a sliding window of 3 contiguous SNPs using PLINK and subsequently performed meta-analyses of these results.

## RESULTS

The combined data sets of all available white studies included a total of 11 592 cases and 17 048 controls, and the combined data sets of all available Asian studies comprised 872 cases and 881 controls. The main characteristics of the individual data sets are given in Table 2.

Table 3 gives the results of the meta-analyses for the combined white and Asian studies. Because there was no evidence for between–data set heterogeneity of fixed-effects estimates and the random-effects estimates across data sets were similar, we adopted the pooled estimate derived by the fixed-effects model for SNPs showing no heterogeneity and adopted the OR derived by the random-effects model for SNPs showing heterogeneity. Notably, in the meta-analysis of all published white data sets (n=11 592 cases and 17 048 controls), 7 of the 11 assessed markers (ie, SNPs 4, 5, 8, 9, 10, 12, and 19) were significantly associated with AD after correction for multiple testing (Table 3). Importantly, the most significant associations were the C-G-C alleles at SNPs 8, 9, and 10 ($P<.001$) and the G allele at SNP 19 that were shown to be associated with AD in the initial report.[6] Of note, SNPs 4, 5, 8 through 10, 12, and 19 through 25 belong to distinct linkage disequilibrium (LD) blocks, with a low D′ between the blocks (eFigure 1; http://www.archneurol.com).

A meta-analysis of haplotypes at SNPs 8, 9, and 10 further confirmed C-G-C as a risk haplotype (OR, 1.2; $P<.001$; haplotype frequency, 0.56). Incomplete genotyping of SNPs 22 through 25 across the individual studies in combination with low haplotype frequencies of the putative risk haplotypes C-T-T and T-T-C at SNPs 22, 23, and 24 and 23, 24, and 25, respectively, did not allow us to perform meta-analyses of these putative risk haplotypes. Adjustment for age, sex, and *APOE* in each data set did not change these meta-analysis results. When the data sets of the initial report were excluded from the analysis (Canadian and Mayo Clinic data sets), the results for SNPs 8, 9, 10, and 12 remained essentially unchanged (Table 4). The eTable gives the allelic association test results for SNPs 8 through 10 in the individual white data sets.

In the combined Asian data sets containing all available Asian data (n=872 cases and 881 controls), several SNPs in the 3′ end (SNPs 19 and 23–25), which lie within 1 LD block (eFigure 2), were associated with AD (Table 5). Among these, the strongest ORs and *P* values were observed for SNPs 19 ($P=.001$), 23 ($P<.001$), and 24 ($P<.001$). Of note, consistent with the meta-analyses of the white data set and the original report, the disease-associated alleles included the G allele at SNP 19 and the T and C alleles at SNPs 24 and 25. There was no association of SNPs 4, 5, 8, 9, 10, or 12 with AD in the combined Asian data sets. Also, these meta-analysis results remained unchanged after adjustment for age, sex, and *APOE* in each data set. Funnel plots of SNPs 8, 9, and 10 did not show evidence of publication bias (Figures 1, 2, and 3).

## COMMENT

We obtained all available white and Asian data on the *SORL1*-AD association, which allowed us to perform unbiased, comprehensive meta-analyses of data of 30 393 individuals (12 464 cases and 17 929 controls). Our findings confirm that variants in *SORL1* are associated with risk for AD in white and Asian populations and that there are likely to be multiple causative genetic variants in distinct regions in *SORL1*. Although in the combined white data sets, markers in multiple regions of the gene were associated with AD risk, in the

Asian data sets, markers in the 3′ end were predominantly related to AD risk. Importantly, the variants associated with AD in the combined white data sets occur in several distinct LD blocks. These observations suggest that the negative findings of previously published, individually analyzed data sets were likely related to underpowered studies with small sample sizes, allelic or locus heterogeneity, or both. It is also likely that many of the complex genetic factors for late-onset AD, such as *SORL1* and other loci identified in large genome-wide association studies (eg, *CLU, CR1*, or *PICALM*),[33,34] play only a modest role and are observable only in very large sample sizes or meta-analyses of several data sets.

Of note, the disease-associated alleles in the white and Asian data sets (including the C-G-C alleles at SNPs 8, 9, and 10, the G allele at SNP 19, and the T and C alleles at SNPs 24 and 25) were identical to those observed in the initial report[6] and replicated by 11 subsequent studies.[1–3,7,13–19] In addition, haplotype meta-analyses in the combined white data sets confirmed the finding in the initial report[6] that the C-G-C haplotype at SNPs 8, 9, and 10 is associated with increased risk of AD. There is only 1 published case-control study of the *SORL1*-AD association in African Americans, Caribbean Hispanics, and Israeli Arabs, to our knowledge. Thus, we could not perform separate meta-analyses for these ethnic groups. However, as described in this study, the C-G-C haplotype at SNPs 8 through 10 was also associated with AD risk in both the 228 Caribbean Hispanic families[6] and in the 111 cases and 144 controls from a community-based sample of Israeli Arabs.[6] In addition, SNPs 22 through 25, including the T and C alleles at SNPs 24 and 25, were associated with AD in 238 African American sibships[6] and an independent African American case-control data set (n=280).[3]

There is biological evidence suggesting that variants in *SORL1*, including the T allele at SNP 4, the C-G-C alleles at SNPs 8 through 10, the G allele at SNP 19, and the T and C alleles at SNPs 24 and 25 influence other AD endophenotypes. The SNPs in *SORL1* were found to be associated with magnetic resonance imaging endophenotypes of AD (general cerebralatrophy, hippocampalatrophy, white matter hyperintensities, and cerebrovascular disease) in 44 African American and 182 white sibships from the Multi-Institutional Research in Alzheimer's Genetic Epidemiology and with analogous pathological traits in 69 autopsy-confirmed white AD patients.[35] In the white sibships and autopsy sample, the C-G-C haplotype at SNPs 8 through 10 was associated with white-matter disease, and the T and C alleles at SNPs 24 and 25 were associated with hippocampal atrophy. In a study that explored *SORL1* expression in 29 AD vs 28 non-AD brains,[36] the expression of *FL-SORL1* but not δ-*2-SORL1* was associated with AD, neuropathologic AD, and synaptophysin expression. Consistent with the present meta-analysis, *SORL1* expression was also associated with the T allele at *SORL1* SNP 4. The SNPs 19, 21, 23, and 25 in *SORL1* were also associated with cerebrospinal fluid levels of $A\beta_{42}$ in 153 white AD patients ($P$=.003)[37] and age at onset of AD in 349 white AD patients (hazard ratio, 1.53; 95% confidence interval, 1.12–2.09; $P$=.007).[17] Finally, in the study by Seshadri et al,[14] *SORL1* SNP 29 was significantly associated with abstract reasoning ability as measured by the similarity test ($P$<.001) in 705 stroke- and dementia-free Framingham Study participants, indicating an association between *SORL1* and cognitive function.

Taken together, these meta-analyses provide confirmatory evidence that multiple *SORL1* alleles in distinct LD blocks are associated with AD risk. However, *SORL1* may account for only a modest degree of the genetic variance of AD, similar to that of *CR1*, *CLU*, or *PICALM*.[33,34] Moreover, the ability to demonstrate association between *SORL1* and AD may be even more difficult than these other genes, given the intralocus heterogeneity.

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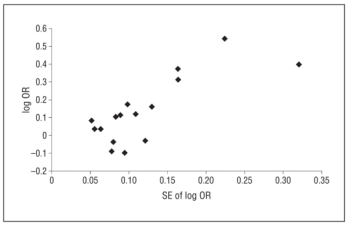


**Figure 1.**
Funnel plot of single-nucleotide polymorphism 8 (white and Asian data sets). OR indicates odds ratio.

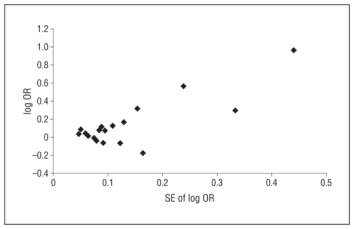


**Figure 2.**
Funnel plot of single-nucleotide polymorphism 9 (white and Asian data sets). OR indicates odds ratio.

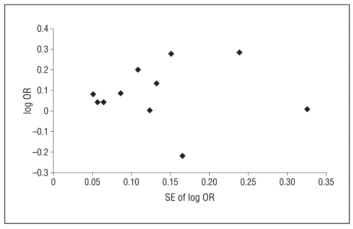


**Figure 3.**
Funnel plot of single-nucleotide polymorphism 10 (white and Asian data sets). OR indicates odds ratio.

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**Table 1**

*SORL1* SNPs

| SNP No. | dbSNP rs No. | Location, bp | Distance From Previous Marker, bp | Alleles | Orientation/Strand | SNP Type |
|---|---|---|---|---|---|---|
| 1 | rs4935774 | 120 826 964 | | A/G | Rev/T | Upstream of 5′ UTR |
| 2 | rs578506 | 120828 687 | 1723 | C/G | Fwd/B | Intron |
| 3 | rs582446 | 120 833 069 | 4382 | A/G | Fwd/T | Intron |
| 4 | rs661057 | 120 834 164 | 1095 | C/T | Fwd/B | Intron |
| 5 | rs11218304 | 120 854 321 | 20 157 | C/T | Rev/B | Intron |
| 6 | rs560573 | 120 866 094 | 11 773 | A/T | Fwd/B | Intron |
| 7 | rs12364988 | 120 872 836 | 6742 | A/G | Rev/T | H269H |
| 8 | rs668387 | 120 873 131 | 295 | C/T | Rev/B | Intron |
| 9 | rs689021 | 120 876 330 | 3199 | A/G | Rev/T | Intron |
| 10 | rs641120 | 120 886 175 | 9845 | C/T | Fwd/B | Intron |
| 11 | rs4935775 | 120 894 712 | 8537 | C/A | Rev/T | Intron |
| 12 | rs12285364 | 120 898 436 | 3724 | C/T | Fwd/B | Intron |
| 13 | rs2298813 | 120 898 894 | 458 | A/G | Fwd/T | T528A |
| 14 | rs11600231 | 120 911 918 | 13 024 | C/T | Fwd/B | Intron |
| 15 | rs2276346 | 120 919 686 | 7768 | G/T | Fwd/B | Intron |
| 16 | *SORL1*-T833T | 120 931 165 | 11 479 | A/T | Fwd/T | T833T |
| 17 | rs556349 | 120 931 417 | 252 | G/T | Rev/B | Intron |
| 18 | rs11218340 | 120 936 564 | 5147 | A/T | Fwd/B | Intron |
| 19 | rs2070045 | 120 953 300 | 16 736 | G/T | Fwd/B | S1187S |
| 20 | rs3824966 | 120 953 393 | 93 | C/G | Fwd/T | Intron |
| 21 | *SORL1*-18ex26 | 120 959 359 | 5966 | C/G | Fwd/T | (−18) 5′ of exon 26 |
| 22 | rs1699102 | 120 962 172 | 2813 | C/T | Fwd/B | N1246N |
| 23 | rs3824968 | 120 981 132 | 18 960 | A/T | Rev/T | A1584A |
| 24 | rs2282649 | 120 984 168 | 3036 | C/T | Fwd/B | Intron |
| 25 | rs1010159 | 120 988 611 | 4443 | C/T | Rev/B | Intron |
| 26 | rs1784933 | 120 994 626 | 6015 | A/G | Fwd/T | Intron |
| 27 | rs1614735 | 120 998 211 | 3585 | C/A | Rev/T | Intron |
| 28 | rs1133174 | 121 006 965 | 8754 | A/G | Fwd/T | Downstream of 3′ UTR |
| 29 | rs1131497 | 121 007 955 | 990 | C/G | Fwd/B | Downstream of 3′ UTR |

Abbreviations: bp, base pair; dbSNP, Single-Nucleotide Polymorphism Database; fwd, forward; rev, reverse; rs, reference number; SNP, single-nucleotide polymorphism; *SORL1*, sortilin-related receptor gene.

**Table 2**

Studies Included in the Meta-analyses

| Source | Country | Ethnicity | No. of Cases (n=12 464) | No. of Control Individuals (n=17 929) | AAO | AALV | SNPs Studied |
|---|---|---|---|---|---|---|---|
| Rogaeva et al,[6] 2007 | Canada, Northern Europe | White | 177 | 224 | 76.1 (7.0) | 73.2 (8.1) | 4, 5, 8–10, 12, 19, 22–25 |
| Rogaeva et al, 2007 | United States | White | 549 | 477 | 77 (5.0) | 75 (6.0) | 4, 5, 8, 9, 12, 19, 22, 23, 24, 25 |
| Rogaeva et al, 2007 | United States | White | 443 | 1217 | 76 (6.0) | 77 (5.0) | 4, 5, 8, 9, 12, 19, 22, 23, 24, 25 |
| Rogaeva et al, 2007 | United States (autopsy series) | White | 423 | 430 | 76 (6.0) | 74 (6.0) | 4, 5, 8, 9, 12, 19, 22, 23, 24, 25 |
| Lee et al,[3] 2007 | United States | White | 30 | 76 | 84.4 (8.0) | 82.7 (7.2) | 4, 5, 8–10, 12, 19, 22–25 |
| Meng et al,[13] 2007 | United States (Translational Genomics Research Institute) | White | 859 | 552 | 76.9 (7.6) | 77.4 (7.3) | 8, 24, 25 |
| Lee et al,[2] 2008 | United States | White | 103 | 93 | 80.5 (7.2) | 79.7 (8.0) | 8–10, 22–25 |
| Minster et al,[22] 2008 | United States | White | 1009 | 1009 | 72.9 (6.2) | 74.1 (6.1) | 4, 8, 9, 10, 19, 23 |
| Kölsch et al,[17] 2009 | Germany | White | 348 | 487 | 71.9 (8.2) | 71.6 (8.2) | 4, 19, 23, 25 |
| Bettens et al,[1] 2008 | Belgium | White | 550 | 634 | 78.9 (5.2) | 61.9 (15.3) | 4, 5, 8–10, 12, 19, 22–25 |
| Shibata et al,[23] 2008 | Japan | Japanese | 180 | 130 | 68.1 (10.8) | 60.6 (6.9) | 8–10, 22–25 |
| Cellini et al,[19] 2009 | Italy | White | 350 | 358 | 76.2 (8.9) | 83.4 (17.9) | 4, 5, 8–10, 19, 22–25 |
| Beecham[a] et al,[28] 2009 | United States | White | 656 | 804 | 73.2 (7.1) | 73.2 (7.1) | 4, 9, 12, 19, 22–24 |
| Feulner et al,[16] 2009 | Germany | White | 486 | 492 | 72.4 (8.8) | 39.7 (11.1) | 4, 9, 19, 22 |
| Liu et al,[21] 2009 | The Netherlands | White | 490 | 6251 | 68.9 (8.7) | 69.5 (9.1)[b] | 8–10, 22–25 |
| Tan et al,[15] 2009 | Singapore | Malay/Chinese | 255 | 300 | 71.2 (8.9) | 70.8 (8.5) | 8–10, 19, 22–24 |
| Kimura et al,[18] 2009 | Japan | Japanese | 437 | 451 | 71.9 (8.2) | 74.8 (5.8) | 4, 8, 9, 12, 19, 23–25 |
| Harold et al,[33] 2009 | United Kingdom | White | 3333 | 1225 | 73.1 (8.6) | 76.3 (6.8) | 4, 9, 19, 22 |
| Reynolds et al,[27] 2009 | Sweden | White | 1270 | 2180 | 74.5 (8.2) | 78.3 (9.0) | 8–10, 19, 23, 24 |
| Cousin et al,[24] 2009 | France | White | 516 | 539 | 63.4 (9.1) | 67.3 (10.9) | 4, 8–10, 12, 23–25 |

Abbreviations: AALV, age at last visit (unaffected only); AAO, age at onset of disease (cases only); SNP, single-nucleotide polymorphism.

[a] Includes previously unpublished SNP results.

[b] Age at last visit of whole cohort (cases and controls).

**Table 3**

Association Between *SORL1* SNPs and Alzheimer Disease in the Combined White Data Sets of 11 592 Cases and 17 048 Controls

| SNP | Allele 1 | Reference Allele | No. | OR (95% CI) | *P* Value | $I^2$ | *P* Value (Q)[a] |
|---|---|---|---|---|---|---|---|
| 4 | C | T | 16 753 | 0.94 (0.90–0.99) | .01 | 35.2 | .12 |
| 5 | C | T | 5924 | 1.1 (1.02–1.17) | .01 | 0 | .46 |
| 8 | C | T | 20 742 | 1.08 (1.03–1.13) | .001 | 31.6 | .15 |
| 9 | G | A | 26 308 | 1.06 (1.02–1.10) | .007 | 4.2 | .40 |
| 10 | C | T | 15 812 | 1.08 (1.03–1.13) | .002 | 0 | .78 |
| 12 | C | T | 6694 | 0.8 (0.68–0.96) | .006 | 8.2 | .36 |
| 19 | G | T | 19 206 | 1.08[b] (1.01–1.14) | .02[b] | 44.9 | .05 |
| 22 | C | T | 20 850 | 1.03 (0.98–1.08) | .21 | 0 | .69 |
| 23 | T | A | 20 247 | 1.02[b] (0.95–1.09) | .62[b] | 55.4 | .01 |
| 24 | C | T | 19 195 | 0.96 (0.90–1.02) | .22 | 26.5 | .19 |
| 25 | C | T | 16 120 | 1.01 (0.97–1.05) | .62 | 10.1 | .35 |

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism; *SORL1*, sortilin-related receptor gene.

[a] Heterogeneity (Cochran Q) *P* value (considered statistically significant for *P*=.10[30,31]).

[b] OR (*P* value) derived from random-effects model.

**Table 4**

Association Between *SORL1* SNPs and Alzheimer Disease in the Combined White Data Sets, Excluding the Data Sets From the Initial Study[6] (Canadian and Mayo Clinic Data Sets)

| SNP No. | Allele 1 | Reference Allele | No. | OR (95% CI) | *P* Value | $I^2$ | *P* Value (Q)[a] |
|---|---|---|---|---|---|---|---|
| 4 | C | T | 12813 | 0.97 (0.92–1.03) | .31 | 22.1 | .25 |
| 5 | C | T | 1984 | 1.13 (0.99–1.26) | .06 | 0 | .62 |
| 8 | C | T | 16802 | 1.07 (1.02–1.12) | .01 | 27.5 | .20 |
| 9 | G | A | 22368 | 1.05 (1.01–1.09) | .03 | 0 | .48 |
| 10 | C | T | 15411 | 1.08 (1.02–1.13) | .006 | 0 | .87 |
| 12 | C | T | 2754 | 0.75 (0.59–0.99) | .03 | 19.9 | .29 |
| 19 | G | T | 15266 | 1.05 (0.99–1.11) | .10 | 0 | .55 |
| 22 | C | T | 16910 | 1.02 (0.96–1.08) | .54 | 0 | .63 |
| 23 | T | A | 16307 | 0.99 (0.95–1.03) | .62 | 7.2 | .38 |
| 24 | C | T | 15255 | 0.99 (0.94–1.04) | .69 | 28.4 | .19 |
| 25 | C | T | 12180 | 0.98 (0.93–1.03) | .47 | 0 | .64 |

Abbreviations: CI, confidence interval; OR, odds ratio; SNP, single-nucleotide polymorphism; *SORL-1*, sortilin-related receptor gene.

[a] Heterogeneity (Cochran Q) *P* value (considered statistically significant for $P=10^{30,31}$).

**Table 5**

Association Between *SORL1* SNPs and Alzheimer Disease in the Combined Asian Data Sets of 872 Cases and 881 Control Individuals

| SNP | Allele 1 | Reference Allele | No. | OR (95% Confidence Interval) | *P* Value | $I^2$ | *P* Value (Q)[a] |
|---|---|---|---|---|---|---|---|
| 4 | C | T | 888 | 1.05 (0.87–1.23) | .61 | 0 | >.99 |
| 5 | C | T | NG | NG | NG | NG | NG |
| 8 | C | T | 1753 | >.99 (0.99–1.01) | .99 | 36.8 | .31 |
| 9 | G | A | 1753 | 0.99 (0.91–1.08) | .82 | 0.7 | .42 |
| 10 | C | T | 865 | 0.92 (0.75–1.12) | .42 | 9.47 | .33 |
| 12 | *C* | T | 888 | 0.82 (0.47–1.34) | .07 | 0 | >.99 |
| 19 | G | T | 1443 | 1.27 (1.10–1.41) | .001 | 0 | .72 |
| 22 | *C* | T | 865 | 0.78 (0.60–1.05) | .07 | 0 | .93 |
| 23 | T | A | 1753 | 0.79 (0.69–0.92) | <.001 | 0 | .72 |
| 24 | C | T | 1753 | 0.76 (0.67–0.89) | <.001 | 0 | .92 |
| 25 | C | T | 1198 | 1.21 (1.03–1.37) | .02 | 0 | .43 |

Abbreviations: CI, confidence interval; NG, not genotyped; OR, odds ratio; SNP, single-nucleotide polymorphism; *SORL-1*, sortilin-related receptor gene.

[a]Heterogeneity (Cochran Q) *P* value (considered statistically significant for *P*=.10[30,31]).