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Ke-Sheng Wang
East Tennessee State University

Xuefeng Liu

Liang Wang

David Briones

Chun Xu
The University of Texas Rio Grande Valley

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Research Article

Genetic Variants in the *SORL1* Gene Are Associated with Age at Onset of Alzheimer Disease: A Survival Analysis

Ke-Sheng Wang,[1] Xuefeng Liu,[1] Liang Wang,[1] David Briones,[2] and Chun Xu[2]

[1] *Department of Biostatistics and Epidemiology, College of Public Health, East Tennessee State University, P.O. Box 70259, Lamb Hall, Johnson City, TN 37614-1700, USA*
[2] *Departments of Psychiatry and Neurology and the Center of Excellence in Neuroscience, Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX 79905, USA*

Correspondence should be addressed to Ke-Sheng Wang; wangk@etsu.edu

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Few studies focused on the association of *SORL1* with the age at onset (AAO) of Alzheimer disease (AD). This study investigated the association of 43 SNPs in *SORL1* with the AAO of AD by using the Kaplan-Meier survival analysis and the Cox proportional hazards model in SAS version 9.2 and linear regression model in PLINK software (791 AD patients and 782 controls). Both logrank test and Cox regression model showed that five SNPs (rs1784934, rs676759, rs560573, rs593769, and rs11218313) were associated with the AAO of AD in the male sample, while one SNP (rs17125558) was associated with the AAO of AD in the female sample ($P < 0.05$). SNP rs560573, previously associated with the risk of late-onset AD, showed the most association with the AAO in the male sample ($P = 0.0077$ for logrank test and $P = 0.0117$ in the Cox model). The mean AAO was approximately 2.5 years earlier in individuals who were homozygous for the minor allele compared with those who had at least one major allele. Linear regression model showed that rs2282649 and rs726601 were associated with AAO in the whole sample ($P = 0.0374$ and 0.0367, resp.). These findings provide evidence of several genetic variants in *SORL1* influencing the AAO of AD.

1. Introduction

Alzheimer disease (AD) is the most common form of dementia. Most often, AD is diagnosed in people over 65 years of age, although the less-prevalent early-onset Alzheimer's can occur much earlier [1]. In the United States, the prevalence of AD in 2000 was estimated to be about 1.6% in the 65–74 age group, with the rate increasing to 19% in the 75–84 age group and to 42% in the greater than 84 age group [2]. The World Health Organization estimated that, in 2005, 0.379% of people worldwide had dementia, and the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030 [3]. Another study estimated that, in 2006, 0.40% of the world population (about 26.6 million) was afflicted by AD, which is predicted to affect 1 in 85 people globally by 2050 [4].

In addition to the disease risk, age at onset (AAO) of AD is also genetically influenced with an estimated heritability of about 42% [5, 6]. Genetic effects account for 57%–78% of the variance of AAO [7], while twin studies suggest that the heritability of AD exceeds 60% [8]. AD has a strong genetic predisposition (60–80% of the attributable risk) [9].

The sortilin-related receptor (*SORL1*) gene is located at 11q23.2-q24.2 and is expressed as a 10.5 kb transcript in brain, spinal cord, and testis [10]. Rogaeva et al. [11] reported that inherited variants of the *SORL1* neuronal sortilin-related receptor were associated with late-onset AD. Lee et al. [12] reported associations between various SNPs and haplotypes in the *SORL1* gene and AD among a total of 296 AD patients comprising 3 cohorts of African American, Caribbean Hispanic, and non-Hispanic white individuals. Their results suggested extensive allelic heterogeneity in *SORL1*, with specific SNPs associated with specific groups. Cellini et al. [13] concluded that their findings confirmed the association between *SORL1* and late-onset AD. Reitz et al. [14] also reported that their findings provided confirmatory evidence of the association of multiple *SORL1* variants with AD risk. However, few studies have focused on the association of *SORL1* with the AAO of AD [12, 15]. This study explored

Table 1: Descriptive characteristics of cases and controls.

Variable	Total patients	Male patients	Female patients	Control
Sample size (n)	791	334	457	782
Mean AAO (years ± SD)	72.3 (±8.5)	71.8 (±8.3)	72.6 (±8.6)	NA
Median AAO (years)	73	73	73	NA
Range of age at onset (years)	40–97	44–90	40–97	NA
Mean age at entry (years ± SD)	77.6 (±8.6)	77.5 (±8.4)	78.2 (±8.7)	73.4 (±7.9)
Median age at entry (years)	79	79	79	79
Range of age at entry (years)	43–100	49–94	43–100	48–94

the association of *SORL1* with the AAO of AD in a Canadian sample by using the Kaplan-Meier survival analysis, the Cox proportional hazards model, and linear regression model.

2. Materials and Methods

2.1. Subjects. Seven hundred and ninety-one patients with AD and 782 controls with complete genotype and phenotype information in a Canadian sample were selected from the Multi-Site Collaborative Study for Genotype-Phenotype Associations in Alzheimer's Disease and the Longitudinal Follow-Up of Genotype-Phenotype Associations in Alzheimer's Disease and the Neuroimaging Component of Genotype-Phenotype Associations in Alzheimer's Disease (dbGaP Study Accession: phs000219.v1.p1). The details about these subjects were described elsewhere [16, 17]. Genotyping was conducted using the Affymetrix 500 K Set comprising the Mapping250 K_Nsp and Mapping250 K_Sty Arrays (total 262,264 SNPs). We investigated the genetic associations of 43 single-nucleotide polymorphisms (SNPs) within the *SORL1* gene with the AAO of AD.

2.2. Statistical Methods. Hardy-Weinberg equilibrium was tested for all SNPs using the controls by using Haploview software [18]. Then, minor allele frequency (MAF) was determined for each SNP. The assessment of the association between genotypes of each SNP and AAO was initially performed using the logrank test (a nonparametric test) in Kaplan-Meier (KM) survival analysis. The KM survival curves were used to plot the survival function. When a significant value was obtained in the KM testing, the Cox proportional hazards model (a semiparametric model) was used to confirm the findings of KM analysis. Hazard ratio (HR) and 95% CI were calculated with Cox proportional hazards analysis of SNPs. Descriptive statistics for AAO and survival analyses were conducted with SAS statistical software, version 9.2 (SAS Institute, Cary, NC, USA).

To test for association with AAO as a quantitative trait, linear regression analysis was performed by PLINK 1.07 [19] to obtain the regression coefficient (β) and Wald test asymptotic P value. For statistical significance, empirical P values were generated by 100,000 permutation tests using Max (T) permutation procedure implemented in PLINK. This procedure allows calculation of the pointwise estimates of an individual SNP's significance (empirical pointwise P values). Pairwise linkage disequilibrium (LD) statistics (D') were assessed for the controls using Haploview [18]. We identified haplotype blocks based on solid spine of LD using Haploview [18]. Then we chose several SNPs within blocks including the associated SNPs for further analyses. Haplotype analysis based on a slide-window was performed using PLINK. To perform gene-based analysis, we constructed SNP sets based on haplotpye blocks; then we perform set-based tests using PLINK.

3. Results

3.1. Subjects Characteristics. The demographic characteristics of the subjects in the study are detailed in Table 1. The mean AAO for the cases was 72.3 years (71.8 years for the males and 72.6 years for the females, resp.). The mean age at entry into study was 77.6 years for cases (77.5 years for the males and 78.2 years for the females, resp.) and 73.4 years for the controls.

3.2. Survival Analyses. Of the 43 SNPs, none was associated with the AAO of AD in the whole sample using the logrank test. Interestingly, five SNPs were associated with the AAO of AD in the male sample, while one SNP was associated with the AAO of AD in the female sample ($P < 0.05$). The results of the top 6 associated SNPs based on the logrank test are summarized in Table 2. All 6 SNPs were in Hardy-Weinberg equilibrium in the controls. The most statistically significant associated SNPs were rs560573 ($P = 0.0077$) and rs593760 ($P = 0.0077$) in the male sample.

Cox proportional models further confirmed the associations of these 6 SNPs (Table 3). SNPs rs560573 and rs593769 showed the most association with AAO in the Cox model with HR = 1.47 (95% CI = 1.09–1.97). The mean AAO was approximately 2.5 years earlier for individuals (TT for rs560573 and CC for rs593769) who were homozygous for the minor allele compared with those (AA or AT for rs560573 and CT + TT for rs593769) who had at least one major allele. Figure 1 shows the survival function for different genotypes of SNP rs560573. The median of AAO was 71 years for individuals with TT genotype and 73 years for individuals with AA or AT genotypes.

3.3. Linear Regression Analysis. The results of linear regression model are summarized in Table 4. Single-marker analysis showed that rs2282649 and rs726601 were associated with AAO in the whole sample ($P = 0.0374$ and 0.0367, resp.) and rs11218313 was associated with AAO in the male sample ($P = 0.0318$). For the rs11218313 ($\beta = 2.82$), the mean AAO in male was approximately 2.8 years earlier for the minor allele G

Table 2: Top 6 SNPs associated with the age at onset of Alzheimer's disease using the logrank test.

SNP	Position	A1[a]	MAF[b]	HWE[c]	Logrank-all[d]	Logrank-male[e]	Logrank-female[f]
rs1784934	121467284	C	0.36	0.35	0.288	0.040	0.96
rs676759	121488556	G	0.40	0.49	0.154	0.008	0.933
rs560573	121490175	T	0.39	0.59	0.176	0.0077	0.836
rs593769	121493294	C	0.39	0.84	0.152	0.0077	0.933
rs11218313	121512162	G	0.09	0.38	0.185	0.0317	0.89
rs17125558	121003094	T	0.03	0.71	0.0715	0.758	0.039

[a]Minor allele; [b]minor allele frequency; [c]Hardy-Weinberg equilibrium P value; [d]P value was based on logrank test for the whole sample; [e]P value was based on the logrank test for the males; [f]P value was based on the logrank test for the females.

Table 3: Top 6 SNPs associated with the age at onset of Alzheimer's disease using the Cox proportional hazards model.

SNP	Male	Mean	HR[a]	95% CI[b]	P	Female	Mean	HR	95% CI	P
rs1784934										
AA	42	70.6	1.39	1.00–1.93	0.049	59	72.9	1.01	0.76–1.32	0.962
AG + GG	292	72.0	1.00			398	73.5	1.00		
rs676759										
GG	53	69.8	1.46	1.09–1.97	0.0121	65	73.4	0.99	0.76–1.29	0.937
AA + AG	281	72.2				392	72.5	1.00		
rs560573										
TT	53	69.7	1.47	1.09–1.97	0.0117	63	73.5	0.97	0.74–1.27	0.845
AA + AT	281	72.2	1.00			394	72.4	1.00		
rs593769										
CC	53	69.7	1.47	1.09–1.97	0.0117	65	73.4	0.99	0.76–1.29	0.937
CT + TT	281	72.2	1.00			392	72.5	1.00		
rs11218313										
AG + GG	45	74.2	0.72	0.53–0.99	0.0459	80	72.6	0.98	0.77–1.26	0.897
AA	289	71.4	1.00			377	72.6	1.00		
rs17125558										
CT + TT	14	71.4	1.08	0.63–1.85	0.772	25	70.1	1.50	1.00–2.25	0.0494
CC	320	71.8	1.00			432	72.7	1.00		

[a]HR refers to hazard ratio; [b]CI refers to confidence interval.

Table 4: Association results for 8 SNPs and the age at onset of Alzheimer's disease using the linear regression model.

SNP	Position	A1[a]	β-all[b]	P-all[c]	EMP1[d]	β-male[e]	P-male[f]	EMP-male[g]	β-female[h]	P-female[i]	EMP-female[j]
rs1784934	121467284	C	0.08	0.865	0.865	−0.71	0.296	0.295	0.65	0.261	0.258
rs676759	121488556	G	0.14	0.749	0.752	−0.78	0.240	0.242	0.85	0.144	0.147
rs560573	121490175	T	0.13	0.764	0.767	−0.77	0.238	0.24	0.85	0.148	0.15
rs593769	121493294	C	0.12	0.784	0.788	−0.79	0.223	0.225	0.83	0.152	0.157
rs11218313	121512162	G	0.96	0.225	0.225	2.82	0.0326	0.0318	−0.09	0.93	0.935
rs2282649	121608249	T	0.97	0.0394	0.0374	0.67	0.359	0.365	1.15	0.0636	0.0637
rs726601	121610698	T	0.96	0.0382	0.0367	0.77	0.287	0.296	1.06	0.083	0.0844
rs17125558	121003094	T	−1.78	0.648	0.653	−0.46	0.881	0.883	−2.61	0.67	0.657

[a]Minor allele; [b]β refers to the regression coefficient of the linear regression for all patients; [c]P value refers to the Wald test asymptotic P value for all patients; [d]empirical P value for all patients generated by 100,000 permutation tests using Max (T) permutation procedure; [e]β refers to the regression coefficient of the linear regression for male patients; [f]P value refers to the Wald test asymptotic P value for male patients; [g]empirical P value for male patients generated by 100,000 permutation tests using Max (T) permutation procedure; [h]β refers to the regression coefficient of the linear regression for female patients; [i]P value refers to the Wald test asymptotic P value for female patients; [j]empirical P value for female patients generated by 100,000 permutation tests using Max (T) permutation procedure.

Table 5: Haplotype analysis for the whole sample.

Haplotype		Frequency[a]	β[b]	P value[c]
rs2282648	rs2282649			
T	T	0.30	0.97	0.0394
T	C	0.02	−0.48	0.744
C	C	0.68	−0.89	0.0554
rs2282649	rs726601			
T	T	0.29	1.03	0.0294
C	T	0.02	−0.30	0.842
C	C	0.69	−0.91	0.0502

[a]Haplotype frequency in the sample.
[b]β refers to the regression coefficient of the linear regression.
[c]P value for the haplotype.

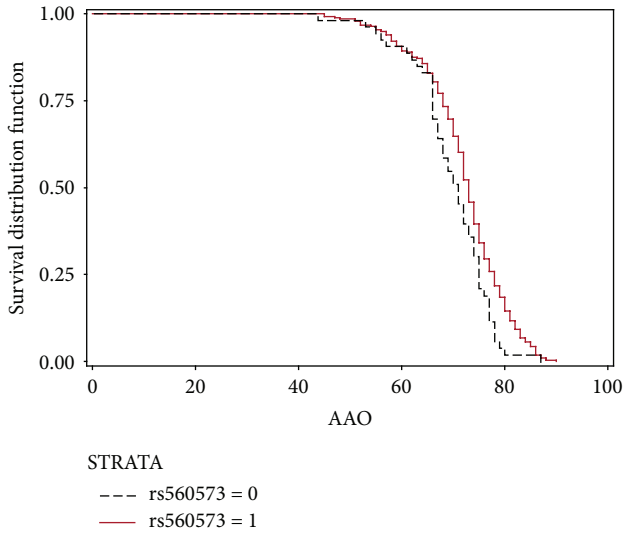

Figure 1: Survival function by genotype of rs560573 0 = TT Genotype, 1 = AA + AT Genotypes.

compared to major allele. All 3 SNPs had empirical pointwise P values < 0.05 using a permutation procedure (Table 4).

Using Haploview software, we identified 4 haplotype blocks for 43 SNPs. Haplotype analyses for the whole sample (Table 5) showed that the T-T haplotype from rs2282648 and rs2282649 ($D' = 1$) was associated with AAO ($P = 0.0394$), and the T-T haplotype from rs2282649 and rs726601 ($D' = 0.98$) was associated with AAO ($P = 0.0294$). Furthermore, haplotype analyses for the male sample (Table 6) showed that the C-G haplotype from rs668387 and rs12218313 ($D' = 1$) was associated with AAO ($P = 0.0326$), and the C-G haplotype from rs1218313 and rs626885 ($D' = 0.91$) was associated with AAO ($P = 0.0326$).

Based on the 4 haplotype blocks, we built 4 set SNPs. We performed set-based tests using PLINK for the whole sample and also for the male sample. We did not find any significant associations for the set-based analyses (data not shown).

Table 6: Haplotype analysis for the male sample.

Haplotype		Frequency[a]	β[b]	P value[c]
rs668387	rs11218313			
C	G	0.08	2.82	0.0326
T	A	0.45	−0.28	0.66
C	A	0.47	−0.35	0.51
rs11218313	rs626885			
A	C	0.43	−0.09	0.878
C	G	0.07	2.82	0.0326
A	G	0.5	−0.56	0.38

[a]Haplotype frequency in the sample.
[b]β refers to the regression coefficient of the linear regression.
[c]P value for the haplotype.

4. Discussion

In the present study we explored the association of 43 SNPs in the *SORL1* gene with the AAO of AD by using the Kaplan-Meier survival analysis, the Cox proportional hazard model, and the linear regression model. Using the Kaplan-Meier survival analysis and Cox proportional hazard we found that five SNPs were significantly associated with the AAO of AD in the male sample and one SNP was associated with the AAO of AD in the female sample ($P < 0.05$). Linear regression model showed that two SNPs (rs2282649 and rs726601) were associated with AAO in the whole sample. SNP rs11218313 was associated with AAO in the male sample using logrank test and Cox model was also associated with AAO in the male sample in the linear model. Haplotype analyses in the linear model further supported the associations of single-marker analyses.

It has been reported that *SORL1* gene is consistently downregulated approximately 2-fold in lymphoblasts from patients with AD, and the structure and function of *SORL1* as a mosaic ApoE receptor strongly suggest that it plays a role in AD [20]. Sager et al. [21] also found a correlation between decreased *SORL1* expression and impaired cognitive function among 34 individuals, including 10 patients with AD, 15 with mild cognitive impairment, and 9 controls, suggesting that decreased *SORL1* expression reflects cognitive performance and may predispose individuals with mild cognitive impairment to the development of AD.

Several previous studies have reported that *SORL1* gene is associated with the risk of AD [11, 12, 14]; however, few studies have focused on the association of *SORL1* with the AAO of AD. Lee et al. [12] examined the associations of 7 SNPs in *SORL1* gene with the AAO of AD and found that 2 SNPs (rs536360 and rs556349) were associated with the AAO of AD. Another study [15] investigated the association of 4 *SORL1* genetic variants (rs2070045, *SORL1*-18ex26, rs3824968, and rs1010159) with the AAO of AD and found that *SORL1*-18ex26 was associated with an earlier AAO of AD in a German population. In the present study, of the 43 SNPs, none was associated with the AAO of AD in the whole sample using the logrank test; however, two SNPs were associated with AAO in the whole sample in the linear model. Furthermore, we found that five SNPs (rs1784934, rs676759,

rs560573, rs593769, and rs11218313) were statistically significantly associated with the AAO of AD in the male sample, and one SNP (rs17125558) was associated with the AAO of AD in the female sample ($P < 0.05$) using survival analyses. Several studies examined rs560573 with the risk of AD [11, 12, 14, 22, 23] and one study found that rs560573 was associated with the risk of AD [23]. Previous studies did not find the associations of other SNPs (rs676759, rs593769, rs11218313, and rs17125558) with the risk of AD [22].

There are a number of strengths in this study. First, our sample size was relatively large for this type of study. Second, we used the logrank test to examine the association with the AAO and further confirmed the results using the Cox proportional model. Furthermore, we conducted linear regression analyses. In addition, we detected gender differences. We also realized some limitations in this study. First, our current findings might be spurious or subject to type I error. Second, these findings need to be replicated in additional samples.

5. Conclusions

Our results demonstrate that genetic variants in *SORL1* gene are associated with the AAO of AD. These findings may serve as a resource for replication in other populations. Future functional study of this gene may help to better characterize the genetic architecture of the AAO of AD.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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