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Genetic determinants of survival in patients with Alzheimer's disease

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Abstract

There is a strong genetic basis for late-onset of Alzheimer's disease (LOAD) and thus far >20 genes/loci have been identified that affect the risk of LOAD. In addition to disease risk, genetic variation at these loci may also affect components of the natural history of AD, such as survival in AD. In this study, we first examined the role of known LOAD genes with survival time in 983 AD patients. We then performed genome-wide single-nucleotide polymorphism (SNP) and gene-based association analyses to identify novel loci that may influence survival of AD. Survival analysis was conducted using Cox proportional hazards regression under an additive genetics model. We found multiple nominally significant associations ($P<0.01$) either within or adjacent to known LOAD genes. Genome-wide SNP analysis identified multiple suggestive novel loci and two of them were also significant in gene-based analysis (*CCDC85C* and *NARS2*) that survived after controlling for false-discovery rate (FDR) at 0.05. In summary, we have identified two novel genes for survival in AD that need to be replicated in independent samples. Our findings highlight the importance of focusing on AD-related phenotypes that may help to identify additional genes relevant to AD.

Keywords

LOAD; GWAS; Survival; Gene-Based Analysis

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Conflict of Interest

The authors declare no conflict of interest.

Introduction

Alzheimer's disease (AD), especially the late-onset form (LOAD), is a complex multifactorial neurodegenerative disease and the leading cause of dementia among the elderly [1]. Currently, there are approximately 5 million AD cases in the United States, and about 81.1 million cases worldwide [2]. Due to its long clinical course, AD is a major public health problem. Genetic susceptibility at multiple genes and interactions among them and/or environmental factors likely influence the risk of AD, which has a strong genetic basis with heritability estimates up to 80% [3]. Previous studies have shown that the mean survival in patients with AD ranges from 4 to 9 years [4–18]. While demographic, clinical and environmental factors associated with survival in AD patients have been implicated [19–21], the role of genetic factors affecting survival in AD has not been explored extensively. The effect of *APOE*4* allele of *APOE* on survival in AD has been explored in previous studies [22–26]; however, results have not been conclusive. To date, genome-wide association studies (GWAS) have identified >20 additional susceptibility loci, including *BIN1, INPP5D, MEF2C, CD2AP,HLA-DRB1/ HLA-DRB5,TREM2,EPHA1,NME8, ZCWPW1, CLU, PTK2B, CELF1, MS4A6A/MS4A4E, PICALM, SORL1, FERMT2, SLC24A4/ RIN3, DSG2, ABCA7, CD33,TRIP4,TP53INP1, IGHV1-67* and *CASS4* [27–34]. In addition to AD risk, genetic variations at these loci may also affect the survival in AD. We have tested this hypothesis by examining the role of known LOAD genes in AD survival. In addition, studies focusing on AD-related phenotypes, like survival in AD, may help to identify additional AD-relevant genes [35] Thus, we have also examined a genome-wide data set to determine if genomic regions contain novel loci associated with AD survival. We have performed genome-wide single-nucleotide polymorphism (SNP) and gene-based association analyses and have identified two novel loci for AD survival.

Materials and Methods

Subjects

The AD patients were recruited from Alzheimer's Research Program (ARP; 1983–1988) and the Alzheimer's Disease Research Center (ADRC) at the University of Pittsburgh (1988 to present). A total of 1,886 Probable AD patients were examined between April 1983 and December 2005; details of the cohort are described elsewhere [36]. All subjects received an extensive neuropsychiatric evaluation including medical history and physical examination, neurological history and examination, semi-structured psychiatric interview, neuroimaging, and neuropsychological assessment. Among these patients, 983 had available follow-up data and they are included in this study. Table 1 shows the demographic and clinical characteristics of these 983 patients. The overall survival time was calculated from the study entry.

Genotyping and quality control of genotype data

Samples were genotyped using the Illumina Omni1-Quad chip as described previously [37, 38]. SNPs with call rate <98% and minor allele frequency (MAF<1%), and failing to adhere to the Hardy-Weinberg equilibrium (HWE) test (P<1E-06) were removed. Genotypes for

two *APOE* SNPs, rs429358 (*E*4*) and rs7412 (*E*2*) were determined either as previously described [39] or using TaqMan SNP genotyping assays. For GWAS, a total of 803,323 QC-passed SNPs were selected for analysis.

Statistical analysis

The proportional hazard model was used to examine the risks associated with time to death. The survival analysis was conducted using Cox proportional hazards regression under an additive genetics model with adjustments for baseline MMSE score, gender, psychosis (the presence or absence of psychotic symptoms; psychosis was included as a time-dependent covariate), education level and the first four principle components. Single SNP association analyses were performed first in candidate genes and then on the genome-wide data. We also performed the versatile gene-based association (VEGA) analysis [40], which incorporates information from a full set of SNPs within a gene region and accounts for linkage disequilibrium (LD) between SNPs and it may provide more power than single SNP analysis to detect novel associations[33]. Survival analyses were done in R. We applied Benjamini-Hochberg procedure to control false-discovery rate (FDR) for multiple testing correction[41] and used a FDR threshold at 0.05.

Results

Demographic and Clinical Risk factors of AD Survival

The base-line MMSE scores were strongly associated with time to death with hazard ratios (HR) of 0.95 (95% CI: 0.93 to 0.96, P=1.09E-10, Table 2), indicating that AD patients with a higher MMSE score at baseline would have a better survival than patients with a lower baseline MMSE score. Females had a longer survival than males (HR=0.72, 95% CI: 0.60 to 0.86, P=2.76E-04, Table 2). AD patients who had diabetes (HR=1.41, 95% CI: 1.04 to 1.91; P=2.73E-02) and experienced more psychotic symptoms (psychosis) (HR=1.37, 95% CI: 1.14 to 1.65, P=7.63E-04) had a shorter survival than patients without diabetes and psychosis. Age, education level, blood pressure, heart disease, and depression did not relate to survival (Table 2).

Single SNP association analysis in known LOAD genes

We first examined the associations of AD survival with genetic variations in known 27 LOAD genes and the results are presented in Table 3. SNPs in 7 genes (*BIN1, INPP5D, HLA-DRB1, RIN3, TRIP4, APOE* and *CASS4*) were associated with AD survival at P<0.01. While SNPs in 4 genes were associated with shorter survival (*BIN1*/rs12476995, HR=1.25, P=4.75E-04; *INPP5D*/rs3792117, HR=1.55, P=4.53E-04 *RIN3*/rs7160605, HR=1.35, P=4.05E-03, and *TRIP4*/rs1163552, HR=1.46, P=6.61E-03), SNPs in 3 genes were associated with longer survival (*HLA-DRB1*/rs9392025, HR=0.83, P=2.76E-03, *APOE*/rs429358, HR=0.83, P=5.02E-03 and *CASS4*/rs2426622, HR=0.83; P=4.61E-03). However, none of these associations were significant after controlling for FDR at 0.05.

Genome-wide single SNP association analysis

Next we examined our genome-wide data in order to identify potential novel loci for survival in AD patients. Quantile-quantile plot of the observed and expected P values is

shown in Supplementary Figure 1, and the Manhattan plot showing association signals is presented in Supplementary Figure 2. In the genome-wide SNP analysis, the genetic inflation factors with and without principal components as covariates, were 1.021 and 1.023, respectively, which indicates that population stratification did not inflate the significance of the test statistics in our data. The top SNP, rs2243170 (P=6.62E-07), was located in the intronic region of *IL19* on chromosome 1. There were 4 additional SNPs with P<0.05 in this region (Table 4). Supplementary Figure 3 shows the Linkage disequilibrium (LD) structure of *IL19*. The other top SNPs were, *NCKAP5*/rs7588354 (P=1.37E-06) on chromosome 2, *CCDC85C*/rs2400749 (P=2.25E-06) on chromosome 14, *NARS2*/rs4474465 (P=3.41E-06) on chromosome 11, *PKNOX2*/rs11601321 (P=8.03E-06) on chromosome 11, *SDR9C7*/rs840163 (P=2.42E-06) on chromosome 12, and *ALDH4A1*/rs6695033 (P=3.245E-06) on chromosome 1(Table 4). The regional association plots containing SNPs within 500kb on either side of the top SNP in the top loci are shown in Supplementary Figures 4–10.

Genome-wide gene-based association analysis

Supplementary Figure 11 presents the Manhattan plot of the gene-based P-values. We identified two genes which remained significant after controlling for FDR at 0.05: *CCDC85C* (P=4.00E-06, FDR=0.03) and *NARS2* (P=4.00E-06, FDR=0.03). Interestingly, these two genes are also suggestive loci in genome-wide SNP analysis (see Table 4). Supplementary Figures 12–13 show the LD structure of these two genes. Gene-based analysis also identified *ANLN* as a suggestive gene (P=8.20E-05, FDR=0.13), but this was not among the top hits in genome-wide SNP analysis (*ANLN*/rs2392436, P=1.76E-04).

Discussion

In this study we have used a recently described GWAS data of LOAD to examine: 1) if variants in known LOAD genes are associated with survival in AD patients, 2) if additional novel variants in the genome also affect AD survival, irrespective if they are genome-wide significant or not, for hypothesis generation, and 3) if gene-wide analysis provides better power than genome-wide SNP analysis to detect new genes for AD survival. In our primary analysis, we observed 7 significant associations at P<0.01 with survival in AD in known LOAD genes (*BIN1*, *INPP5D*, *HLA-DRB*, *RIN3*, *TRIP4*, *CASS4* and *APOE*). These data suggest that at least some of the known LOAD genes may be relevant to affecting survival in AD patients; however, none of these associations remained significant after controlling for FDR at 0.05. Previously, the effect of *APOE*4* on survival of AD has been explored in several studies, however, the results were conflicting. Male *APOE*4* carriers were found to have a shorter survival than non-carriers but not in females[22], while others found longer survival among *APOE*4* carriers [23, 42]. However, in other studies *APOE*4* was not found to be related to survival of AD [25, 26]. We found that *APOE*4* was significantly associated with longer survival (P=5.02E-03, HR=0.83) in our sample after adjusting for sex, baseline MMSE score, education level and psychosis. A previous study has suggested that the processes increasing the risk of AD may differ from those that determine its clinical course [43]. Thus, although the presence of *APOE*4* increases the risk of AD, it may have a different effect on survival among AD patients. This seems to be a plausible interpretation of our findings in which *APOE*4* was associated with longer survival among AD patients.

In our genome-wide SNP analysis, we identified multiple novel suggestive loci associated with AD survival, including the top hit at P=6.62E-07 (*IL19* on chromosome 1) and 6 loci at P<1E-05 *(CCDC85C* on chromosome 14 *NARS2* on chromosome 11, *NCKAP5* on chromosome 2, *PKNOX2* on chromosome 11, *SDR9C7* on chromosome 12, and *ALDH4A1* on chromosome 1). Although these loci are not genome-wide significant and wait confirmation in future studies, we believe they provide insight for future studies as many of them may affect survival through their known associations with AD and other diseases. Especially the top hit, *IL19* is a cytokine that belongs to the *IL10* cytokine subfamily, which may modulate AD progression[44]. A systemic meta-analysis has suggested an association between *IL110* polymorphisms and AD [45, 46]. Furthermore, significant associations between AD and *IL10* polymorphism have been reported in Chinese and Italian populations [47, 48]. Polymorphisms in the *IL10* gene cluster have also been found to be involved with major depressive disorder [49].

Interestingly, in the genome-wide gene-based analysis, two of these suggestive genes (*CCDC85C* and *NARS2*) were gene-wide significance at FDR <0.05. This indicates that gene-based analysis provides additional useful information not captured in the genome-wide SNP analysis, as has also been recently shown in another study [33]. The two genes are biologically relevant to AD. The *CCDC85C* (coiled-coil domain containing 85C) gene is highly expressed in different brain regions and may play important role in cortical development, especially in the 7 maintenance of radial glia [50]. *NARS2* is located immediately adjacent to the *GAB2* gene, which has been previously reported to be associated with AD [51]. The *NARS2* and *GAB2* genes occur in a strong LD block that spans the full lengths of both transcripts.

Our study has few limitations. First, inferences from our results must be interpreted with caution because the actual cause of death was not investigated. Second, the procedure of disease death is very complex and many unknown demographic and clinical variables not included in this study could have confounded our results. Although our gene-based analysis has identified two novel genes that remained significant after controlling for FDR at <0.05, further studies in large and independent samples are needed to replicate these findings.

In summary, our results indicate that genetic variation in some genes associated with LOAD risk may also affect survival of AD. Our study also implicates two novel loci as possible genetic regions associated with overall survival among AD patients. Additional large independent studies are needed to confirm our findings and to further establish the genetic basis of survival in AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Demographic and Clinical Characteristics of 983 AD Patients

Age at onset (mean ± SD)	72.2 ± 6.6
Age at entry (mean ± SD)	77.3± 6.2
Education (mean SD)	12.6 ± 3.0
MMSE (mean SD)	18.1 ± 5.5
Gender (male/female)	346/637
Psychosis (Yes/No)	426/567
Diabetes Mellitus (Yes/No)	89/894
Heart disease (Yes/No)	200/783
Medication (Yes/No)	629/354
Depression (Yes/No)	182/801
Hypertension (Yes/No)	477/506

Table 2

Results of the Proportional Hazard Model Examining Risks Associated with AD survival

	Hazard Ratio (95% CI)	z	P
MMSE	0.95 (0.93, 0.96)	−6.45414	1.09E-10
Gender (female/male)	0.72 (0.60, 0.86)	−3.63687	2.76E-04
Psychosis (yes/no)	1.37 (1.14, 1.65)	3.365772	7.63E-04
Diabetes Mellitus (yes/no)	1.41 (1.04, 1.91)	2.207311	2.73E-02
Heart disease (yes/no)	1.18 (0.96, 1.46)	1.577429	1.15E-01
Medication (yes/no)	0.88 (0.74, 1.05)	−1.39636	1.63E-01
Depression (yes/no)	1.11 (0.88, 1.40)	0.873664	3.82E-01
Hypertension (yes/no)	1.06 (0.89, 1.27)	0.67541	4.99E-01
Education (years)	1.01 (0.98, 1.04)	0.534399	5.93E-01
Age (years)	1.00 (0.98, 1.01)	0.028572	9.77E-01

* Age: patients' age at entry; MMSE: the mean Mini-Mental state examination scores; Education: the years of getting education; Medication: taking any cholinesterase inhibitor (AChEI) treatment or not; psychosis: the presence or absence of psychotic symptom; Z: the log-rank test scores; P: P-values associated with testing the effect of the variables

Table 3

Results of Association Analysis Between LOAD Genes and AD Survival

CHR	Gene	Start	Stop	Total SNPs	Lead SNP	BP	Allele	MAF	HR	P	SNPs (P<0.05)
2	*BIN1*	127522076	127581334	34	rs12476995	127512490	G	0.20	1.25	**4.75E-04**	31
2	*INPP5D*	233633279	233781288	60	rs3792117	233780076	A	0.03	1.55	**4.53E-04**	8
5	*MEF2C*	88051921	88214780	29	rs11951031	88174487	A	0.14	0.72	**2.82E-02**	2
6	*CD2AP*	47553483	47702955	23	rs3818866	47657588	C	0.29	1.09	2.30E-01	0
6	*HLA-DRB1*	32654524	32665540	19	rs9392025	3924750	A	0.05	0.83	**2.76E-03**	7
6	*HLA-DRB5*	32593131	32605984	2	SNP6-32605940	32605940	G	0.18	0.86	1.32E-01	0
6	*TREM2*	41234223	41238900	5	rs12202176	41246027	A	0.23	1.19	4.84E-01	0
7	*EPHA1*	142798326	142816107	21	SNP7-142790182	142790182	A	0.18	0.72	8.94E-02	0
7	*NME8*	37854723	37906527	59	rs17171184	37867527	G	0.26	0.84	**2.57E-02**	7
7	*ZCWPW1*	99836430	99864238	12	rs5015756	99851393	A	0.24	1.06	3.38E-01	0
8	*CLU*	27510367	27528244	15	rs12680584	27502941	A	0.20	0.88	1.03E-01	0
8	*PTK2B*	27224915	27372820	99	rs7833348	27227403	A	0.05	0.66	**2.50E-02**	1
8	*TP53INP1*	96007375	96030791	14	rs524678	96033180	A	0.06	1.24	8.20E-02	0
11	*CELF1*	47444064	47531368	10	rs4752845	47496273	A	0.07	0.87	5.37E-02	0
11	*MS4A4E*	59725302	59767151	10	rs668134	59756902	G	0.31	0.84	0.179737	0
11	*MS4A6A*	59695655	59707250	6	rs610932	59695883	A	0.05	0.92	1.99E-01	0
11	*PICALM*	85346132	85457756	28	rs10501605	85421021	G	0.06	0.89	1.12E-01	0
11	*SORL1*	120828170	121009681	61	rs1784933	120994626	A	0.24	1.34	**3.67E-02**	1
14	*FERMT2*	52393742	52487460	27	rs11157934	52435566	A	0.12	1.06	3.48E-01	0
14	*RIN3*	92049877	92225087	75	rs7160605	92063089	C	0.10	1.35	**4.05E-03**	3
17	*SLC24A4*	7125777	7132091	12	rs222842	7132815	G	0.26	1.09	2.01E-01	0
15	*TRIP4*	62467055	62534555	11	rs11635527	62462366	G	0.05	1.46	**6.61E-03**	6
18	*DSG2*	27332024	27382812	30	rs7239805	27322066	A	0.05	0.90	1.07E-01	0
19	*ABCA7*	991101	1016570	32	rs2242436	1016945	A	0.18	0.84	**4.41E-02**	1
19	*APOE*	50100878	50104490	20	rs429358	50103781	A	0.14	0.83	**5.02E-03**	6
19	*CD33*	56420146	56435086	10	rs3865444	56419774	A	0.05	1.09	2.06E-01	0
20	*CASS4*	54420770	54467243	28	rs2426622	54410913	G	0.19	0.83	**4.61E-03**	1

[*] CHR: chromosome; Gene: candidate gene associated with AD; Start: the coordinate of the beginning of gene; Stop: the coordinate of the end of the gene; Total SNPs: the total number of the SNPs in the gene region; Lead SNP: most significant SNP associated with time to death in the gene region; Minor Allele: the minor allele; MAF: the frequency of minor allele; SNPs (P<0.05): total number of SNPs associated with time to death with P < 5E-02 in the gene region; HR: Hazard ratio; P: p-values associated with testing the effect of lead SNP.

Table 4

Novel top loci in Genome-Wide Single SNP and Gene-Based analyses Associated with AD Survival (P<1.00E-05).

					Single locus analysis							Gene-based analysis		
CHR	**Gene**	**Start**	**Stop**	**Total SNPs**	**Lead SNP**	**BP**	**Minor Allele**	**MAF**	**HR**	**P**	**SNPs (P<0.05)**	**Test**	**P**	**FDR**
1	*IL19*	205038837	205082948	24	rs2243170	205076533	A	0.10	1.65	6.62E-07	5	88.4654	3.76E-03	0.29
2	*NCKAP5*	133145841	134042501	282	rs7588354	134049231	A	0.21	0.66	1.37E-06	31	387.7963	7.46E-02	0.73
14	*CCDC85C*	99047355	99140480	35	rs2400749	99106771	G	0.46	0.72	2.25E-06	15	220.2165	4.00E-06	**0.03**
12	*SDR9C7*	55603204	55614456	15	rs840163	55606978	G	0.26	1.40	2.42E-06	10	95.3635	1.38E-03	0.14
11	*NARS2*	77824890	77963367	26	rs4474465	77882028	G	0.20	1.44	3.41E-06	22	421.4499	4.00E-06	**0.03**
1	*ALDH4A1*	19070512	19101659	41	rs6695033	19074506	G	0.03	2.71	3.24E-06	3	71.0355	9.30E-02	0.76
11	*PKNOX2*	124539768	124808495	125	rs11601321	124698806	G	0.07	1.63	8.03E-06	9	177.1226	1.12E-01	0.77