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Genetic determinants of disease progression in Alzheimer's disease

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Abstract

There is a strong genetic basis for late-onset of Alzheimer's disease (LOAD); thus far 22 genes/loci have been identified that affect the risk of LOAD. However, the relationships among the genetic variations at these loci and clinical progression of the disease have not been fully explored. In the present study, we examined the relationships of 22 known LOAD genes to the progression of AD in 680 AD patients recruited from the University of Pittsburgh Alzheimer's Disease Research Center. Patients were classified as "rapid progressors" if the MMSE changed ≥3 points in 12 months and "slow progressors" if the MMSE changed ≤2 points. We also performed a genome-wide association study in this cohort in an effort to identify new loci for AD progression. Association analysis between SNPs and the progression status of the AD cases was performed using logistic regression model controlled for age, gender, dementia medication use, psychosis, and hypertension. While no significant association was observed with either *APOE*4* (p=0.94) or *APOE*2* (p=0.33) with AD progression, we found multiple nominally significant associations (p<0.05) either within or adjacent to seven known LOAD genes (*INPP5D, MEF2C, TREM2, EPHA1, PTK2B, FERMT2* and *CASS4*) that harbor both risk and protective SNPs. Genome-wide association analyses identified four suggestive loci (*PAX3, CCRN4L, PIGQ* and *ADAM19*) at p<1E-05. Our data suggest that short-term clinical disease progression in AD has genetic basis. Better understanding of these genetic factors could help to improve clinical trial design and potentially affect the development of disease modifying therapies.

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Conflict of Interest
The authors declare no conflict of interest.

Keywords

LOAD; GWAS; MMSE; AD progression

Introduction

Late-onset Alzheimer's disease (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 due to multiple genes and interactions among them influence the risk of AD, which has a strong genetic basis with heritability estimates up to 80% [3].

APOE is the major susceptibility gene for LOAD. Genome-wide association studies (GWAS) have identified 21 additional susceptibility loci including BIN1, INPP5D, MEF2C, CD2AP,HLA-DRB1/HLA-DRB5, TREM2, EPHA1,NME8, ZCWPW1, CLU, PTK2B, CELF1, MS4A6A, PICALM, SORL1, FERMT2, SLC2A4, DSG2, ABCA7, CD33, and *CASS4*[4-9]. Recently rare variants in *TREM2* have also been reported to be associated with LOAD risk [10]. In addition to AD risk, genetic variation at these loci may also affect components of the natural history of the clinical dementia. However, the relationship between these known loci and dementia progression has not been explored extensively, highlighting the need to use other approaches in order to identify additional genes involved in the clinical and pathological manifestations of AD.

Large populations of well-characterized and longitudinally followed cases are necessary for such analyses. AD is characterized by gradual cognitive and functional decline, relating to the progressive degeneration of structure and chemistry of the brain over time. The patients' ability to remember, understand, communicate and reason gradually declines, with largely non-uniform rates of progression[11]. Many factors can affect the rate of clinical progression, including brain atrophy rates[12-14], patterns of regional brain atrophy[15], ventricular enlargement[16], neuropsychological and cerebral profiles[17], vascular factors[18], and immunological factors[19].

Genetic factors may also affect the rate of AD progression [20, 21]. The known AD risk genes are good candidates for assessing whether their genetic variation affects the natural history of AD. In this study we used the rate of AD clinical progression, as indexed by change in MMSE score after 12 months follow-up as a phenotype and hypothesized that like disease risk, disease progression also has a genetic basis. We used our previously described GWAS data set [23, 24] to 1) examine the role of 22 known LOAD genes with AD progression in 680 well-characterized and longitudinally followed-up AD patients, and 2) to perform a GWAS analysis in an effort to identify additional loci for AD progression, irrespective if they are genome-wide significant or not, for hypothesis generation.

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 [22]. 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.

Follow-up measurements, definition of Rapid Progression

For the purpose of this study, the rate of progression was defined by the change in the Mini Mental State Examination (MMSE) score from baseline evaluation to the clinic visit approximately 1 year later. Subjects whose MMSE scores changed ≥3 points/year were classified as "rapid progressors" and those whose scores change ≤2 points/year were classified as "slow progressors" [22].

Genotyping and quality control (QC) of genotype data

Samples were genotyped using the Illumina Omni1-Quad chip as described previously [23, 24] 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 [25] or using TaqMan SNP genotyping assays. For GWAS, a total of 803,323 QC-passed SNPs were selected for analysis.

Statistical analysis

We used t-tests and χ^2-tests to analyze demographic and clinical differences between rapid progressors and slow progressors. The association between AD progression status and SNPs was tested using an additive logistic regression model that included age, dementia medication use (taking any cholinesterase inhibitor (AChEI) or memantine), psychosis (at any time during follow-up), hypertension and the top four principal components derived from our GWAS data as covariates. The Versatile Gene-based Associations (VEGA) analyses [26] were performed for the known 22 LOAD genes and 4 suggestive genes identified in this study. In these genes, LD -Select Tag SNP selection algorithm was implemented in Haploview [27] with an r^2 cutoff of 0.8 to select independent SNPs within each gene plus 10kb on either side of the gene. All statistical tests were two-sided. All analyses were done in R and/or PLINK[28].

Results

Characteristics of rapid and normal progressors

There were 373 slow progressors and 307 rapid progressors among the 680 patients included in this analysis. Table 1 shows the demographic and clinical characteristics of the patients by progression type. The rapid progressors were younger (p=0.05), had more hypertension

(p=0.04) and less psychotic symptoms (p=0.01) and used less dementia medications (p=6.5E-05) than patients who were classified as slow progressors. Since the effect of genetic factors on AD progression may have been confounded by those variables, they were included in the additive logistic regression model.

Association of known LOAD genes with AD Progression

The associations of AD progression with genetic variations in known 22 LOAD genes are presented in Table 2. SNPs in 7 genes (*INPP5D, MEF2C, TREM2, EPHA1, PTK2B, FERMT2*, and *CASS4*) were associated with AD progression at the nominal cutoff of p<0.05. While the top SNPs in 4 genes were associated with slow AD progression (*PERMT2*/rs7160582, OR=1.62; p=1.08E-02., *INPP5D*/rs1057258, OR=1.48; p=0.01, *PTK2B*/rs4732720, OR=1.34; p=0.01, and *TREM2*/rs7748777, OR=1.34; p=0.011), SNPs in 3 genes were associated with rapid progression (*MEF2C*/rs9293505, OR=0.275; p=0.03, *EPHA1*/rs11768549, OR=0.246; p=0.037, and *CASS4*/rs16979934, OR=0.596; p=0.033). In the gene-based analysis, 2 of these 7 genes remained significant (*PERMT2*, p=0.04) or had borderline significance (*INPP5D*, p=0.07).

New loci associated with AD Progression in GWAS

Next we examined our genome-wide association data in order to identify new loci for disease progression. Quantile-quantile (QQ) 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. We identified four suggestive novel loci with p<1E-05. The top SNP, rs348987 (p=3.32E-06), was located near *PAX3* on chromosome 2 at position 119kb. There were 19 additional SNPs with p<0.05 in this region (Table 3).The other three top SNPs were, *CCRN4L* /rs13116075, p=7.94E-06 on chromosome 4, *PIGQ* / rs2071979, p=8.17E-06 on chromosome 16 and *ADAM19* /rs2277027, p=9.55E-06 on chromosome 5. The regional association plots containing SNPs within 500kb on either side of the top SNP in the 4 suggestive loci are shown in Supplementary Figures 3-6. We also performed gene-based analyses on the four genes and three of them (*CCRN4L, PIGQ, ADAM19*) demonstrated significant associations with AD progression (p<0.05).

Discussion

Among the known LOAD genes, *INPP5D, MEF2C, TREM2, EPHA1, PTK2B, FERMT2* and *CASS4* revealed nominal associations (p<0.05) with dementia progression and two of them (*PERMT2* and *INPP5D*) survived in the gene-based analysis. Although none of the observed associations survived after adjusting for multiple comparisons, we believe they may provide insight for future studies as they are present in confirmed genes for LOAD, which in addition to affecting risk may also affect components of natural history of AD. Our findings, together with a recently published study showing association of *PICALM*/rs3851179 with dementia progression [29], supports this hypothesis ; Although we did not replicate this result in our samples for the same SNP (p =0.12), the direction of allelic effect was the same, suggesting that this may be a weak, but genuine association.

Our GWAS analysis identified four suggestive loci (*PAX3*, *CCRN4L*, *PIGQ* and *ADAM19*) with significance of $p<1E-05$. The most significant association was identified 119kb from the 3′ region of the *PAX3* gene on chromosome 2q35 (rs348987; $p=3.32E-06$). Although the associated SNPs were not present in an annotated gene in this region, the nearby *PAX3* is a reasonable candidate gene that codes for a transcription factor. Down-regulation of *PAX3* has been attributed to altered signaling pathways involving cell cycle, apoptosis, cell adhesion, cytoskeletal remodeling, and development [30]. Mutations in *PAX3* are associated with Waardenberg syndrome [31-33]. Furthermore, an intronic SNP in *CASS4*, a recently implicated gene for LOAD [9], has been suggested to affect the *PAX3* binding motif [34]. The next most significant SNP (rs13116075; $p=7.94E-06$) was located in the *CCRN4L* gene on chromosome 4q31, which is expressed in the brain [35], and genetic variation in this gene has been shown previously to affect body mass index [36]. The third top SNP resides on chromosome 16p13 near *PIGQ*/*RAB40C* (rs2071979; $p=8.17E-06$). RAB40C is a member of the Rab family of small GTPases that play important roles in neuronal and glial metabolism [37]. Another nearby gene in this region, *RAB11FIP3*, interacts with and regulates Rab GTPases, suggesting a potential combined significance of these functionally related genes in AD progression.

Limitations of our study include the relatively small sample sizes in both the rapid and slow AD progression groups, and variability of duration of time of follow-up of the cases for cognitive decline. Dementia medications affect individuals' rates of decline [22], although we adjusted for this in the logistic regression models. Further, clinical disease progression is very complex, and many unknown demographic and clinical variables (e.g. other medical illnesses and sources of disability) not assessed in this study may have confounded our results. Because of the relatively small sample size, our GWAS findings are meant for only hypothesis generation for future larger studies.

In conclusion, our data suggest that short-term clinical disease progression in AD has genetic basis as we observed nominal associations with some known LOAD genes. Our secondary GWAS analysis identified 4 suggestive loci that, although not meeting the genome-wide significant threshold of $p<5E-08$, are potential candidate genes for AD clinical progression that warrant follow-up studies in larger data sets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographic and clinical characteristics of rapidly progressive AD patients and normally progressive AD patients

	slower (n=373)	Rapid (n=307)	t-test/χ^2	p-value
Age	77. 6 + 6.0	76.6 + 6.3	2.0	**0.05**
Gender (male/female)	136/237	119/188	0.28	**0.59**
Education (years)	12.78 + 3.1	12.96 + 3.0	−0.75	**0.45**
Baseline MMSE	19.00+ 4.75	18.82 + 5.50	0.45	**0.65**
Medication (Yes/No)	291/82	196/111	15.95	**6.50E-05**
Psychosis (Yes/No)	125/248	133/174	6.47	**0.01**
Heart Disease (Yes/No)	74/299	68/239	0.41	**0.52**
Diabetes Mellitus (Yes/No)	29/344	27/280	0.11	**0.73**
Hypertension (Yes/No)	196/177	136/171	4.26	**0.04**
Depression Yes/No)	**59/314**	**52/252**	**0.08**	**0.77**

*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

Table 2

Results of Association Analysis between LOAD Genes and the Progression of AD

				Single locus analysis							Gene-based analysis	
CHR	**Gene**	**Total SNPs**	**Tagger SNPs**	**Lead SNP**	**BP**	**A**	**MAF**	**OR**	**P1**	**SNPs (p<0.05)**	**Test**	**P2**
2	*BIN1*	34	22	rs6750960	127551475	A	0.14	0.7467	0.07	0	26.24557	0.56
2	*INPP5D*	60	50	rs1057258	233780368	A	0.18	1.476	0.01	8	95.60424	0.07
5	*MEF2C*	33	25	rs9293505	88222225	A	0.02	0.2751	0.03	1	21.10667	0.58
6	*CD2AP*	23	11	rs2894740	47689800	G	0.40	1.202	0.12	0	21.57318	0.41
6	*HLA-DRB1 /HLA-DRB5*	45	34	rs6597017	3902270	A	0.28	1.222	0.13	0	27.95059	0.19
6	*TREM2*	5	5	rs7748777	41241784	A	0.46	1.34	0.01	1	9.091647	0.15
7	*EPHA1*	21	18	rs11768549	142805275	A	0.01	0.246	0.04	1	16.09665	0.57
7	*NME8*	59	29	rs12671838	37906849	A	0.03	1.857	0.06	0	47.42309	0.62
7	*ZCWPW1*	12	6	rs5015756	99851393	A	0.43	0.8638	0.19	0	10.45819	0.44
8	*CLU*	15	10	rs9331947	27510794	G	0.04	1.621	0.12	0	8.238591	0.74
8	*PTK2B*	99	36	rs4732720	27293625	G	0.49	1.336	0.01	14	147.9678	0.17
11	*CELF1*	10	5	rs2242081	47456843	G	0.46	1.174	0.16	0	9.485295	0.39
11	*MS4A6A*	6	4	rs12453	59702321	G	0.37	0.8959	0.34	0	3.104919	0.61
11	*PICALM*	28	16	rs17148741	85443439	A	0.02	0.5551	0.23	0	8.709003	0.93
11	*SORL1*	61	40	rs2276412	120966056	A	0.02	1.98	0.15	0	28.9085	0.92
14	*FERMT2*	27	12	rs7160582	52411195	A	0.10	1.629	0.01	9	68.89701	0.04
17	*SLC2A4*	12	6	rs3744404	7133916	A	0.02	1.376	0.51	0	1.059282	0.99
18	*DSG2*	30	14	rs12604517	27378422	A	0.24	1.25	0.09	0	18.37447	0.69
19	*ABCA7*	32	19	rs4147914	1000269	A	0.16	1.244	0.15	0	25.98096	0.56
19	*APOE*	20	14	lab_rs7412	50103919	A	0.03	0.7496	0.34	0	4.800756	0.98
19	*CD33*	10	6	rs1803254	56434956	C	0.07	0.6993	0.09	0	6.215891	0.62
20	*CASS4*	28	18	rs16979934	54460186	G	0.06	0.5956	0.03	1	18.45753	0.67

*CHR: chromosome; Gene:candidate gene associated with AD; Total SNPs: the total number of SNPs located in the region 10kb before and after the gene; Tagger SNPs: the number of tagger SNPs in the region; Lead SNP: most significant SNP in the gene region; BP: base-pair position of the lead SNP under building version 36; A: the minor allele of the lead SNP; MAF: minor allele frequency; OR: odds ratio; P1: the *p*-value in the single locus analysis; SNPs ($p<0.05$): total number of SNPs with $p < 5E-02$ in the gene region; Test: the test statistics in gene-based analysis; P2: the p-value in the gene-based analysis.

Table 3

Novel loci Associated with AD progression (P<1E-05)

				Single locus analysis							Gene-based analysis	
CHR	**Gene**	**Total SNPs**	**Tagger SNPs**	**Lead SNP**	**BP**	**A**	**MAF**	**OR**	**P1**	**SNPs (p<0.05)**	**Test**	**P2**
2	*PAX3*	50	26	rs348987	222653295	A	0.46	0.574	3.32E-06	20	64.71445	0.18
4	*CCRN4L*	4	4	rs13116075	140149482	G	0.15	0.496	7.94E-06	4	32.4932	0.0001
5	*ADAM19*	55	36	rs2277027	156864954	C	0.35	1.737	9.55E-06	18	192.15	0.002
16	*PIGQ*	10	4	rs2071979	564115	G	0.40	0.5918	8.17E-06	9	148.9967	0.00002