Association of lectin-like oxidized low density lipoprotein receptor 1 (*OLR1*) polymorphisms with late-onset Alzheimer disease in Han Chinese

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Background: Lectin-like oxidized low density lipoprotein receptor 1 (OLR1) locates within the area of chromosome 12p, which has been identified as the AD-susceptible region, and plays a role in lipid metabolism. Therefore, it has been suggested to be a good candidate gene for Alzheimer's disease (AD). Several SNPs within OLR1 have been reported to have association with AD among Caucasians.

Methods: We selected and genotyped three SNPs (rs1050283, rs1050286, rs17808009) in OLR1 to investigate its possible relationship with the onset of late-onset Alzheimer disease(LOAD) in 984 LOAD cases and 1,354 healthy controls among northern Han Chinese.

Results: No significant association was found between the OLR1 (rs1050283, rs1050286, rs17808009) polymorphisms and LOAD, even after adjustment for gender and age and stratification for apolipoprotein E (APOE) status.

Conclusions: Our study showed that the SNPs (rs1050283, rs1050286, rs17808009) located in the 3'UTR of OLR1 may not involve in the mechanism of LOAD in Han Chinese population.

Keywords: Alzheimer's disease (AD); genetics; oxidized low density lipoprotein receptor 1(OLR1); polymorphism association study

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Introduction

Alzheimer's disease (AD) is a common cause for dementia among old people. It could cause progressive cognitive impairment, accumulation of amyloid plaques (AP) and intracellular neurofibrillary tangles (NFTs), and neuronal loss in brain (1,2). The pathogenesis of AD is very complex. A number of studies have suggested that the onset of AD was influenced by genetic risk factors (3). Presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*), and amyloid precursor protein (*APP*) gene mutations bear responsibility for most familial AD cases (4). The ε4 allele of apolipoprotein E (*APOE*) is widely recognized for the more common sporadic late-onset AD (LOAD). *APOE* has been identified as a major transporter of cholesterol both in the blood and central nervous system (5). Based on the role of *APOE*

for the pathogenesis of AD and some other findings, we hypothesized that imbalanced cholesterol levels may influence the risk of AD, and statins and other cholesterol-modifying medications may be useful in AD's treatment and prevention (6-16).

Chromosome 12p has been recognized as a region associated with AD by Genome-wide linkage analyses. It includes lipoprotein receptor-related protein 1 (*LRP1*), α-2-macrogobulin (*A2M*), as well as *OLR1* (17). *OLR1*, a class E scavenger receptor, is a trans-membrane glycoprotein. It could mediate the uptake and internalization of oxidized low-density lipoprotein (oxLDL) (18). In vitro factors such as oxLDL, oxidative stress and inflammatory cytokines, and in vivo proatherogenic stimuli such as diabetes mellitus, hyperlipidaemia, as well as hypertension could induce its expression (19-21). Increased level of oxLDL induces endothelial cell activation, dysfunction, apoptosis and impaired vasorelaxation, thus contribute causally to atherosclerosis development and progression (22-28). Indeed, epidemiologic and clinical literature has consistently reported an association between atherosclerosis, vascular risk factors and AD (29,30). Therefore, it is possible that variations in *ORL1* could lead to oxLDL being removed less efficiently, and this, with increased amyloid beta peptide (Aβ) might result in death of neurons (31-33).

MicroRNAs (miRNAs) are 19–24 nt single-stranded RNA molecules. It can down-regulate gene expression through binding to a complementary sequence in the 3'UTR of target genes, thus resulting in translational inhibition or mRNA cleavage and subsequent degradation (34). Clinical and research evidence showed that a number of miRNAs are dysregulated in AD patients and AD animal models (35-39). The single-nucleotide polymorphism rs1050283 (also known as +1073 C/T) located in the 3'UTR of *OLR1* may influence its regulator miRNA binding and subsequent protein homeostasis. Several studies have explored the association between *OLR1* +1073 C/T and AD. However, the results are inconsistent (17,40-43). Recently, a meta-analysis confirmed the association of *OLR1*+1073 C/T with a decreased risk of AD among Caucasians (44). Moreover, Papassotiropoulos *et al.* investigated a cluster of cholesterol-related genes and identified rs1050286 polymorphism in *OLR1* conferring significant susceptibility for AD (45). Given the potential importance of *OLR1* in the pathogenesis and development of AD, we performed a case-control study consisting of 984 patients with LOAD as compared to 1,354 age-matched healthy subjects among northern Han Chinese, by analyzing the potentially association of three functional SNPs (rs1050283, rs1050286, rs17808009) located in 3'UTR of *OLR1* with LOAD in Han Chinese population.

Methods

Subjects

Totally, 984 sporadic LOAD patients and 1,354 healthy controls were enrolled for the study. They were matched for age and sex. The cases came from several hospitals in Shandong Province. All participants were northern Han Chinese. The diagnosis of AD was carried out with standard clinical evaluation in accordance with NINCDS-ADRDA criteria (46). No patients had severe CNS diseases or a family history of dementia. The controls were confirmed healthy and neurologically normal by medical history, general examinations, laboratory examinations and Mini Mental State Examination MMSE (score ≥28). They were enrolled from the Health Examination Center of the Qingdao Municipal Hospital. The present study was carried out with approval by the Institute Ethical Committee of Qingdao Municipal Hospital and with informed consent of all the participants or their representatives. The ID number of informed consent is 2009-05-06-003.

SNP selection and genotype

Candidate SNPs meet the following criterion: (I) SNPs of miRNA binding sites located in the 3'UTR region of *OLR1*; (II) SNPs from the public databases and literatures; (III) SNPs with a minor allele frequency (MAF) ≥0.05 in Han Chinese. Finally, three SNPs (rs1050283, rs1050286, rs17808009) were chosen and genotyped.

Standard procedures were used for extraction of human genomic DNA. Genotyping of *OLR1* polymorphisms (rs1050286and rs17808009) and *APOE* polymorphisms (rs429358 and rs7412) were determined by a custom-by-design 2-×48-Plex SNPscan^{TM} kit (Genesky Biotechnologies Inc., Shanghai, China).

The sequence of probes in SNP scan reaction and sequence for the PCR reaction are available from the corresponding author. The improved multiplex ligase detection reaction (iMLDR) method was used for detection of genotyping of rs1050283 in the OLR1 gene (Shanghai Genesky Bio-Tech Co, Ltd; www.geneskies.com). Primers for rs1050283 are as follows: forward primer: CTTGATTTCGGAATGGCCTCTG; reverse primer:

Table 1 Characteristics of the study groups

Characteristic	Patients with AD (n=984)	Control subjects (n=1,354)	P value	OR (95% CI)
Age (years; mean ± SD)			0.186*	–
Age at examination	79.81±6.71	75.50±6.49		
Age at onset	75.15±6.08	–		
Gender, n (%)			0.068	–
Male	406 (41.3)	610 (45.1)		
Female	578 (58.7)	744 (54.9)		
MMSE score, mean ± SD	11.99±6.20	28.41±1.09	<0.001	–
APOEε4 status, n (%)			<0.001	2.422 (1.970–2.977)
APOEε4 (+)	280 (27.8)	191 (13.6)		
APOEε4 (–)	704 (72.2)	1,163 (86.4)		

*, P value was calculated with the age of onset for late-onset AD and age at examination for control subjects. *APOEε4* (+) refers to subject carrying at least one *APOEε4* allele; *APOEε4* (–) refers to subject carrying no *APOEε4* allele. Differences in the characteristics of age and MMSE score between the two groups were examined using the Student's *t*-test. Differences in gender and *APOEε4* status between patients with AD and control subjects were assessed using the χ^2 test. AD, Alzheimer disease; *APOE*, apolipoprotein E; CI, confidence interval; MMSE, Mini Mental State Examination; OR, odds ratio; SD, standard deviation.

CCTTTGCAGAAACTGGGGTTCC. Data analysis was performed via an ABI3130XL Sequencer and GeneMapper Software v4.1 (Applied Biosystems, USA).

Statistical analyses

Differences in the characteristics between two groups were assessed with the χ^2 test or Student *t*-test. Hardy-Weinberg equilibrium was examined with the χ^2 test. The χ^2 test was used to compare distributions of genotype and allele, and was also used to test differences between two groups stratified by *APOEε4* status. Differences in allele and genotype distribution between two groups were analyzed with logistic regression adjusted for gender, age and APOEε4 status in several genetic models. The models were defined as 0 (AA + Aa) versus 1 (aa) for recessive, 2 (aa) versus 1 (Aa) versus 0 (AA) for additive, and 0 (AA) versus 1 (Aa + aa) for dominant, (A: major allele; a: minor allele). STPLAN4.5 software was used to estimate statistical power. SPSS 16.0 software was used for data analysis. P<0.05 were considered to have statistical significance.

Results

Demographic and clinical characteristics of LOAD and healthy controls are shown in *Table 1*. The two groups were well-matched with regard to age (P=0.186) and gender (P=0.068). LOAD subjects had much lower MMSE scores than controls (P<0.001). Bearing of the APOE ε4 allele was related to an elevated risk for LOAD as expected (OR =2.422, 95% CI: 1.970–2.977, P<0.001).

Table 2 summarized the details of the SNPs detected in our study. The distributions of rs1050283, rs1050286 and rs17808009 in both groups were all in HWE (P>0.05). The genotypes and allele frequencies of rs1050283, rs1050286 and rs17808009 in LOAD patients and controls in the total sample and after stratification for *APOEε4* allele are presented in *Tables 3-5*. Though the frequencies of the minor alleles of all SNPs within *OLR1* were reduced in patients compared with control subjects, no statistically significant association was observed for genotypic (P=0.675, P=0.706, P=0.515 for rs1050283, rs1050286 and rs17808009, respectively) and allelic(OR =0.942, 95% CI: 0.822–1.078, P=0.384, OR =0.954, 95% CI: 0.833–1.093, P=0.497, OR =0.925, 95% CI: 0.808–1.059, P=0.261 for rs1050283, rs1050286 and rs17808009, respectively) frequencies between LOAD patients and controls. Moreover, no differences were found in the genotypic or allelic distributions between the two groups even after stratification by APOEε4 status (*Tables 3-5*). Furthermore, no significant difference was detected between LOAD patients and healthy controls by the multivariate logistic

Table 2 Allele frequencies of SNPs of the OLR1 gene among LOAD patients and healthy control subjects

SNPs	Alleles (1/2)	Chromosome	Function	Position	MAF		OR (95% CI)	P	PHWT	
					Cases	Controls			Cases	Controls
rs1050283	C/T	12	3'UTR	10159690	0.238	0.249	0.942 (0.822–1.078)	0.384	0.321	0.252
rs1050286	C/T	12	3'UTR	10311563	0.236	0.246	0.954 (0.833–1.093)	0.497	0.236	0.247
rs17808009	A/G	12	3'UTR	10311929	0.237	0.251	0.925 (0.808–1.059)	0.261	0.206	0.175

bp, base pairs; MAF, minor allele frequency; OR (95% CI), odds ratio with 95% confidence interval; P, P value calculated from χ^2 test; PHWT, P value from Hardy-Weinberg equilibrium test among control subjects; 1, major allele; 2, minor allele; 3'UTR, 3'-untranslated region.

Table 3 Distribution of the allele and genotype frequencies of the OLR1 polymorphisms stratified by *APOEε4* allele

rs1050283	Groups	N	Genotype				Allele		
			CC (%)	CT (%)	TT (%)	P	C (%)	T (%)	P
All	Cases	984	566 (57.52)	368 (37.40)	50 (5.08)	0.675	1,500 (76.22)	468 (23.78)	0.384
	Controls	1,354	756 (55.84)	522 (38.55)	76 (5.61)		2,034 (75.11)	674 (24.89)	
APOEε4 (+)	Cases	280	158 (56.43)	104 (37.14)	18 (6.43)	0.441	420 (75.00)	140 (25.00)	0.346
	Controls	191	97 (50.79)	82 (42.93)	12 (6.28)		276 (72.25)	106 (27.75)	
APOEε4 (–)	Cases	704	408 (57.95)	264 (37.50)	32 (4.55)	0.630	1,080 (76.70)	328 (23.30)	0.436
	Controls	1,163	659 (56.66)	440 (37.83)	64 (5.50)		1,758 (75.58)	568 (24.42)	

P, P value calculated from Pearson's χ^2 test or Fisher's exact test where is necessary.

Table 4 Distribution of the allele and genotype frequencies of the OLR1 polymorphisms stratified by *APOEε4* allele

rs1050286	Groups	N	Genotype				Allele		
			AA (%)	AG (%)	GG (%)	P	A (%)	G (%)	P
All	Cases	984	568 (57.72)	368 (37.40)	48 (4.88)	0.706	1,504 (76.42)	464 (23.58)	0.497
	Controls	1,354	762 (56.28)	518 (38.26)	74 (5.46)		2,042 (75.41)	666 (24.59)	
APOEε4 (+)	Cases	280	160 (57.14)	104 (37.14)	16 (5.72)	0.330	424 (75.71)	136 (24.29)	0.309
	Controls	191	97 (50.79)	84 (43.98)	10 (5.23)		278 (72.77)	104 (27.23)	
APOEε4 (–)	Cases	704	408 (57.95)	264 (37.50)	32 (4.55)	0.660	1,080 (76.70)	328 (23.30)	0.547
	Controls	1,163	665 (57.18)	434 (37.32)	64 (5.50)		1,764 (75.84)	562 (24.16)	

P, P value calculated from Pearson's χ^2 test or Fisher's exact test where is necessary.

regression with adjustment for non-genetic and the bearing of at least one *APOEε4* allele (*Table 6*).

Discussion

As an endothelial receptor for oxLDL, *OLR1* has been suggested to regulate lipid metabolism, and thus being an intriguing candidate gene for AD susceptibility. We sought to determine whether SNPs in *OLR1* are involved with AD. In our research, we investigated three SNPs (rs1050283, rs1050286, rs17808009) for miRNA binding sites of 3'UTR in *OLR1*. Notably, we describe a novel

Table 5 Distribution of the allele and genotype frequencies of the OLR1 polymorphisms stratified by *APOEε4* allele

rs17808009	Groups	N	Genotype				Allele		
			CC (%)	CT (%)	TT (%)	P	C (%)	T (%)	P
All	Cases	984	566 (57.52)	370 (37.60)	48 (4.88)	0.515	1,502 (76.32)	466 (23.68)	0.261
	Controls	1,354	750 (55.39)	528 (39.00)	76 (5.61)		2,028 (74.89)	680 (25.11)	
APOEε4 (+)	Cases	280	158 (56.43)	106 (37.86)	16 (5.71)	0.357	422 (75.36)	138 (24.64)	0.213
	Controls	191	95 (49.74)	84 (43.98)	12 (6.28)		274 (71.73)	108 (28.27)	
APOEε4 (–)	Cases	704	408 (57.95)	264 (37.50)	32 (4.55)	0.594	1,080 (76.70)	328 (23.30)	0.369
	Controls	1,163	655 (56.32)	444 (38.18)	64 (5.50)		1,754 (75.41)	572 (24.59)	

P, P value calculated from Pearson's χ^2 test or Fisher's exact test where is necessary.

Table 6 Logistic regression analysis of OLR1 polymorphisms adjusted for age, gender and *APOEε4* status

SNP	Model	OR (95% CI)	P
rs1050283	Dom	1.091 (0.922–1.292)	0.31
	Add	1.081 (0.940–1.244)	0.275
	Rec	1.134 (0.781–1.648)	0.508
rs1050286	Dom	1.085 (0.916–1.285)	0.344
	Add	1.074 (0.933–1.237)	0.322
	Rec	1.112 (0.761–1.624)	0.585
rs17808009	Dom	1.115 (0.942–1.320)	0.207
	Add	1.101 (0.957–1.268)	0.179
	Rec	1.164 (0.798–1.698)	0.431

SNP, single nucleotide polymorphism; Dom, dominant model; Rec, recessive model; Add, additive model; OR (95% CI), odds ratio with 95% confidence interval.

polymorphism rs17808009. However, we are unable to replicate the findings in a case-control sample with adequate power to detect the risk ratio observed in previous studies. No significant differences in the genotypic or allelic distributions of these three SNPs (rs1050283, rs1050286, rs17808009) between LOAD subjects and controls was found in a Han Chinese population, even after statistical adjustment for non-genetic and *APOEε4* status and stratification for *APOEε4* status.

Previous human genetic association studies of the *OLR1* have yielded conflicting results (17,33,40,41,43,47,48). Luedecking-Zimmer *et al*. (17) found that in *APOEε4* bearers homozygosity of the T allele of the ORL1 rs1050283 polymorphism had an elevated risk for LOAD, while in non-ε4 carriers, homozygote of the T allele was over-represented in the controls. On the contrary, Lambert *et al*. (40) found that the expression of *OLR1* was decreased in AD cases carrying the CC and CT genotypes compared with controls with the same genotypes (OR =1.56, 95% CI: 1.19–2.04, P<0.001), which indicated C allele to be a risk factor for AD. This was supported by two other studies (41,43). Recently, a meta-analysis including 2,419 cases and 2,381 controls from five studies demonstrated a significantly lower AD risk in the recessive model (TT *vs.* TC + CC: OR =0.79, 95% CI: 0.65–0.96), however, they failed to conduct further study to confirm the influence of *APOEε4* on the association between rs1050283 polymorphism and AD (44). The results of an independent replication study by Pritchard *et al*. provided support to our research (48), they performed an association study of rs1050283 in a UK population of 356 LOAD patients and 358 healthy controls, and failed to find any association between rs1050283 and AD, even after stratification by *APOEε4* status, onset age and haplotype distributions. In addition, Papassotiropoulos *et al*. (45) investigated a cluster of cholesterol-related genes and identified rs1050286 polymorphism in *OLR1* conferring significant susceptibility to AD, which was inconsistent with our findings. Moreover, there is another SNP site known as +1071 T/A (not included in our study) within the *OLR1*3'UTR, being tested by three groups (40,41,48). However, no relationship was found between the +1071 T/A polymorphism and AD onset risk.

A number of studies have explored the reasons for the frequent failure of candidate gene studies for replication in other cohorts (49-52). Our study failed to detect any association does not mean invalidation of previous findings. There are some explanations. Firstly, the difference

between our study and previous research might be due to genetic variability in various ethnic populations, including differences in minor allele and MAF, as well as the complexity of the potential genetic structure (53,54). In Caucasians C allele was the minor allele of the rs1050283 polymorphism with a MAF of 0.482, while in our cohort T was the minor allele with a MAF of 0.238. Our information was similar to those from NCBI database (MAF: T=0.183). Candidate gene studies might differ in the study population and in the definition of the phenotype (55). Secondly, it is possible that our study is under-powered to detect small size effect in the Han Chinese population (56). In fact, our sample had a power of more than 90% to detect these variants with modest risk (MAF =0.25 and OR of ~1.5) at a significant level (alpha) of 0.05. However, we cannot deny that our results could be under-powered in case of weak effects. Thirdly, AD is not only a genetic disease, but also involves environmental components. Therefore, the effects of some SNPs detected by GWAS may vary in different populations owing to some undiscovered interactions between gene and environment (57). Moreover, variations in the clinical characteristics of the study cohort, as well as experimental and statistical methods could have caused statistical bias (58,59). More analyses with independent follow up are required to evaluate these possibilities.

To conclude, we failed to find any significant differences between SNPs (rs1050283, rs1050286, rs17808009) and LOAD in the Han Chinese population. As far as we know, this is the first study aimed at exploring the possible effects of the SNPs (rs1050283, rs1050286, rs17808009) in OLR1 to LOAD in non-Caucasians. Further and larger studies in Han Chinese and other ethnic groups are warranted to assess our results.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The present study was carried out with approval by the Institute Ethical Committee of Qingdao Municipal Hospital and with informed consent of all the participants or their representatives. The ID number of informed consent is 2009-05-06-003.

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