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ABCA7 and EphA1 Genes Polymorphisms in Late-Onset Alzheimer's Disease

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Abstract

Large-scale genome-wide studies have revealed the role of several genes and their respective single-nucleotide polymorphisms (SNPs) in the pathophysiology of late-onset Alzheimer's disease (LOAD). Here, the frequencies of ABCA7 SNPs rs3764650 and rs4147929 and EphA1 SNP rs11771145 were assessed and compared in LOAD patients and healthy subjects. In a case-control study, 110 patients with LOAD (case) and 88 healthy unrelated age- and gender-matched individuals (control), both from Azeri descent, were enrolled. DNA was extracted from blood samples using the salting out method, and the genotyping was performed by RFLP-PCR for rs3764650, rs4147929, and rs11771145 polymorphisms. Electrophoresis was carried out on agarose gel. Sequencing was utilized for confirmation of the results. No differences were found in the frequencies of ABCA7 SNP rs3764650 and EphA1 SNP rs11771145 between healthy subjects and LOAD patients. However, a significant difference was revealed in the frequencies of AA ($p = 0.042$, OR = 0.150; 95%CI = 0.005–1.410) and GG ($p = 0.009$, OR = 1.716; 95%CI = 0.918–3.218) genotypes of ABCA7 SNP rs4147929 between the mentioned groups. This study showed that ABCA7 SNP rs4147929 might be a predisposing factor for LOAD. However, such an association was not found between ABCA7 SNP rs3764650 as well as EphA1 SNP rs11771145 and LOAD. These results must be confirmed in other ethnic groups.

Keywords Late-onset Alzheimer's disease · ABCA7 · EPHA1 · Single-nucleotide polymorphism · Association

Introduction

Alzheimer's disease (AD) is a progressive age-related neurodegenerative disorder, leading to dementia and death within 3 to 6 years after the presentation of the first symptoms (Sadigh-Eteghad et al. 2015). More than 3.5 million people suffer from AD all around the world, which would be expected to rise to 66 million by 2030 (Patterson 2018; Sadigh-Eteghad et al. 2014).

AD is traditionally classified into early-onset AD (EOAD) (< 65 years old) and late-onset Alzheimer's disease (LOAD) (≥ 65 years old) groups (Braak and Braak 1991). On the one hand, the vital role of genetics, i.e., APOE ε4 allele, has been revealed in EOAD. On the other hand, emerging evidence indicates the importance of genetic factors in LOAD (Gatz et al. 2006). Accordingly, 3124 differentially expressed genes have been found, many of which are highly associated with cerebral atrophy and Braak stage of the disease (Li et al. 2015). Also, large-scale genome-wide association studies (GWAS) have established the impact of several genes, including ABCA7 and EphA1, and their respective polymorphisms across the genome on LOAD initiation and progression (Hollingworth et al. 2011; Naj et al. 2011). However, a large part of the genetic influence on LOAD persists to be inexplicable.

ATP-binding cassette (ABC) transporter superfamily is involved in the cellular export of several groups of molecules, including cholesterol and lipids (Chan et al. 2008; Wilkens 2015). ABCA7 activates cellular efflux of cholesterol to APOE particles and modulates amyloid precursor protein (APP) metabolism leading to the prevention of amyloid-β (Aβ) production (Kim et al. 2005; Chan et al. 2008). ABCA7 knocked-out mice also show signs of escalated Aβ aggregation in the brain (Kim et al. 2013; Wildsmith et al. 2013). GWAS has confirmed that single-nucleotide polymorphisms (SNPs) near ABCA7, such as

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rs4147929 and rs3764650, may be important genetic factors in the pathophysiology of LOAD. However, their exact role remains to be elucidated (Karch et al. 2012; Vasquez et al. 2013). Further, evidence suggests an association between rs3764650 polymorphism in ABCA7 gene and neurotic plaque burden in AD patients (Shulman et al. 2013). The mentioned SNP is also thought to increase AD susceptibility in allele, dominant, recessive, and additive models (Liu et al. 2014).

EphA1 is a tyrosine kinase receptor which encodes the erythropoietin-producing hepatocellular receptor A1 and plays a vital role in cell behavior and morphology, axonal conduction, and synaptic plasticity (Yamazaki et al. 2009). Non-coding forms of EphA1 demonstrate a high association with AD in large GWAS (Ager et al. 2016). rs11767557 and rs11771145 are two SNPs near EphA1 that have been revealed in GWAS to reduce LOAD risk (Hollingworth et al. 2011; Lambert et al. 2009; Naj et al. 2011). These findings are not, however, definite.

Here, the correlation of ABCA7 and EphA1 genes polymorphisms, i.e., rs4147929, rs3764650, and rs11771145, respectively, with LOAD was assessed in a population-based study in Northwestern Iran.

Subjects and Methods

Patients and Design

In a case-control study, the correlation of ABCA7 and EphA1 genes polymorphisms, i.e., rs4147929, rs3764650, and rs11771145, respectively, with LOAD was assessed. The case group involved 110 patients with LOAD, and the control group comprised 88 healthy unrelated age- and gender-matched subjects. Subjects in both groups were older than 65 years old from Azari descent in Northwestern Iran. The control group included healthy individuals who did not have any past/current neurodegenerative disorders and familial history of AD. The case group consisted of patients with probable AD referred to the Neurology Clinic of Imam Reza Medical Research & Training Hospital of Tabriz University of Medical Sciences (TUOMS) between 2013 and 2017. Probable AD was diagnosed using the NINCDS–ADRDA criteria (Dubois et al. 2007). All patients underwent appropriate physical and neurological examination, and mini-mental state examination (MMSE) was used to assess cognitive ability in both groups.

Inclusion and Exclusion Criteria

On the one hand, subjects with informed self-consent for participation, probable AD diagnosis according to NINCDS–ADRDA criteria (case group), and absence of symptoms and family history of AD or other neurodegenerative disorders (control group) were enrolled. On the other hand, subjects with no informed self-consent, other disorders that mimic dementia such as hypothyroidism, vitamin E, B1, B12 deficiencies, alcoholism, major depressive disorder, hepatic and renal failure, spastic lesions, subdural hematoma, traumatic brain injury, encephalitis, normal pressure hydrocephalus, frontal lobe dementia, and Lewy body dementia were excluded from this study.

DNA Extraction

For this purpose, blood samples from both groups were mixed with anticoagulation substance (ethylenediaminetetraacetic acid or EDTA). Then, genomic DNA from peripheral blood leucocytes was extracted using the phenol-chloroform method previously explained by Ghatak et al. (2013). Briefly, 1000 μL of lysis buffer (10 mM Tris-HCl, 10 mM EDTA, 50 mM NaCl, 10% SDS, pH 7.5) was added to 500 μL of the blood samples. The resulting solution was centrifuged at 12000 rpm for 1 min at 4 °C and washed in a consequential manner. Accordingly, 0.7 mL of TRIAZOL reagent was added to the resulting precipitation and incubated for 5 min. Then, 0.15 mL of chloroform was added to the supernatant and incubated for another 3 min. Afterward, the supernatant was centrifuged at 12000 rpm for 15 min at 4 °C. Two milliliters of ethanol 70% was then used to extract DNA. The solution containing DNA was diluted with pure water, and its photo absorption was measured in the wavelength of 260 nm using spectrophotometry for evaluation of the extracted DNA.

Polymerase Chain Reaction (PCR)

SNPs of ABCA7 and EphA1 genes were assessed using blood samples obtained from both groups. The gene sequence, annealing temperature, and product size of primers of the assessed genes are shown in Table 1. After the extraction phase, PCR was done on the extracted DNA samples of both groups using the designed primers to investigate the mentioned SNPs on ABCA7 and EphA1 genes. After PCR, the electrophoresis of products in 2% agarose gel was performed to make sure the existence of the exclusive bands to continue tests (Gulkovskyi et al. 2015). All of the enzymes were prepared from Thermo Fisher Company (Thermo Fisher Scientific, Waltham, MA, USA), and their serial number will be given in parenthesis in what follows.

Investigation of rs3764650 Variant of ABCA7 Gene Polymorphism

The products of PCR were cut by TaaI (ER1361) enzyme to survey rs3764650 variant of ABCA7 gene polymorphism. The solution for PCR amplification consisted of 10 mL of PCR reaction mixture (0.1–0.5 μg of DNA), 18 mL of nuclease-free water, 2 mL of 10× buffer tango, and 1–2 mL of TaaI enzyme. The solution was incubated at 37 °C for 5

Table 1 Sequences of PCR-RFLP primers used in genotyping reactions

Primer	Sequence (5′–3′)	Annealing temperature (°C)	Enzyme	Product size (bp)	Splicing products' size (bp)
ABCA7-F	CCCACCACACTATGTCCCA	59.5	TaaI (ER1361)	318	129, 189
ABCA7-R	AGATCCCATAAGCAAGGCC	57.3			
ABCA7-F	CTATGTGGACGACGTGTGAG	60.5	SduI (FD0654)	351	34, 297
ABCA7-R	CTCAAGGCGGGAAGATTT	53.9			
EphA1-F	TTACCACTTATTACAGCACCTACGC	64.2	DraI (FD0224)	122	17, 105
EphA1-R	CGTAACGGTAAATGAAAGAA CTCGGA	64.7			

bp, base pair

min. Then, the digestion reaction was stopped by heating for 5 min at 82 °C. The primary length of the gene product was 318 bp, and where rs3764650 SNP was detected, gene excision by TaaI led to two 129 and 189 bp segments. These segments were detected by electrophoresis on the produced samples.

Investigation of rs4147929 Variant of ABCA7 Gene Polymorphism

The products of PCR were cut by Bsp1286I (SduI) or (FD0654) enzyme to survey rs4147929 variant of ABCA7 gene polymorphism. The solution for PCR amplification consisted of 10 mL of PCR reaction mixture (0.1–0.5 μg of DNA), 17 μL of nuclease-free water, 2 μL 10× buffer tango, and 1 mL of SduI enzyme. The solution was incubated at 37 °C for 5 min. Then, the digestion reaction was stopped by heating for 5 min at 82 °C. The primary length of the gene product was 351 bp, and where rs3764650 SNP was detected, gene excision by SduI led to two 34 and 297 bp segments. These segments were detected by electrophoresis on the produced samples.

Investigation of rs11771145 Variant of EphA1 Gene Polymorphism

The product of PCR was cut by DraI (FD0224) enzyme for investigation of rs11771145 variant of EphA1 gene polymorphism. The solution for PCR amplification comprised 10 μL of PCR reaction mixture (0.1–0.5 μg of DNA), 17 mL of nuclease-free water, 2 mL of 10× FastDigest or 10× FastDigest Green Buffer, and 1 mL of FastDigest enzyme. The solution was incubated at 37 °C for 5 min. Then, the digestion reaction was stopped by heating for 5 min at 82 °C. The length of the primary product of PCR was 122 bp, which was then cut by DraI enzyme, and the two 17 and 105 bp segments were produced. These segments were detected by electrophoresis on the provided samples.

Ethical Considerations

The Ethics Committee of TUOMS approved the design and concept of this study (TBZMED.REC.1394.71). All the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from the participants or their first-degree relatives. All data were analyzed anonymously.

Statistical Analyses

The sample size was calculated according to the previous studies and also considering the 1% prevalence of AD. The following formula was applied to calculate the sample size where p was 1%, and d was 0.02.

$$n = \left(\frac{2\sqrt{Pq}}{d}\right)^2$$

Data were analyzed with IBM SPSS® 20 software platform (SPSS Inc., Chicago). Descriptive data were expressed as frequency and mean ± standard deviation (SD). Deviations from Hardy-Weinberg equilibrium were assessed in both control subjects and patients to see if any violations exist. Chi-square test (if needed, Fisher's exact test) was used to compare qualitative variables, and independent t test or Mann Whitney U test was applied to compare quantitative variables. $p < 0.05$ was considered statistically significant.

Results

In a case-control study, 110 patients with probable AD and 88 healthy subjects were enrolled. No significant differences were found between groups in the age, gender, and education level ($p > 0.05$ for all comparisons). There was a significant difference between groups in

their respective MMSE score, where it was meaningfully lower in the AD group (Table 2) (p = 0.00).

rs3764650 Variant of ABCA7 Gene Polymorphism

The allelic frequency of TT genotype for rs3764650 polymorphism was 100% in both patient and control groups. However, the frequency of GT and GG genotypes was 0% in both groups. No significant difference in the frequency of rs3764650 variant of ABCA7 gene polymorphism was detected between groups (p = 1) (Table 3).

rs4147929 Variant of ABCA7 Gene Polymorphism

The allelic frequencies of AA, AG, and GG genotypes for rs4147929 polymorphism were 9%, 57.3%, and 41.8% in the AD group, respectively. However, the frequencies of these genotypes were 5%, 64.8%, and 29.5% in the control group. Significant differences in the frequencies of AA and GG genotypes were revealed between LOAD and control groups (p = 0.009 and p = 0.042, respectively) (Table 4).

rs11771145 Variant of EphA1 Gene Polymorphism

Distribution of GG, GA, and AA genotypes in the patient group was 64.5% (71 cases), 30.9% (34 cases), and 4.5% (5 cases), respectively, and in the control group, was 63.6% (56 cases), 30.6% (27 cases), and 5.6% (5 cases), respectively. No significant difference in the frequency of rs11771145 variant of EphA1 gene polymorphism was detected between groups (p = 1) (Table 5).

Table 2 The demographic information of the case and control groups and their respective MMSE scores

Variables	Control (%) n = 88	AD (%) n = 110
Gender		
Male	32 (36.36%)	47 (42.72%)
Female	56 (63.63%)	63 (57.27%)
Age group (years)		
65–69	46 (52.27%)	46 (41.81%)
70–74	13 (14.77%)	20 (18.18%)
75–79	18 (20.45%)	27 (24.54%)
≥ 80	11 (12.5%)	17 (15.45%)
Education (years)		
Illiterate	47 (53.40%)	56 (50.9%)
1–4 years	30 (34.09%)	35 (31.81%)
5–8 years	8 (9.09%)	14 (12.72%)
≥ 9 years	3 (3.40%)	5 (4.54%)
MMSE		
< 20 (moderate-to-severe)	0	42 (38.18%)
20–24 (mild)	0	68 (61.81%)
Normal	88 (100%)	0

MMSE, mini-mental status score; *AD*, Alzheimer's disease

Table 3 Genotypes and allelic frequency of rs3764650 variant of ABCA7 gene polymorphism in the study groups

Genotype	LOAD		Control	
	n	f(%)	n	f(%)
T	220	100	176	100
G	0	0	0	0
TT	110	100	88	100
GT	0	0	00	0
GG	0	0	00	0

n, number; f, frequency; *OR*, odds ratio; *CI*, confidence interval; *LOAD*, late-onset Alzheimer's disease

Discussion

It has been previously shown that common genetic mutations responsible for EOAD such as those occurring in the APP and presenilin1-2 (PSEN1-2) genes are not essential role players in LOAD (Gerrish et al. 2012). However, recent efforts using GWASs have helped scientists recognize newer risk genes for LOAD. Several studies have thus linked SNPs in ABCA7 and EPHA1 genes to LOAD (Hollingworth et al. 2011; Naj et al. 2011). SNPs in these genes might play a vital role in the pathogenesis of AD because of their impacts on the production and clearance of Aβ protein (Karch and Goate 2015).

Our study showed that the frequency of rs4147929 G>A SNP is significantly higher in LOAD patients than that of healthy subjects in Iran. Evidence indicates that ABCA7 is linked to AD via various pathways, such as lipid metabolism, phagocytosis, and Aβ metabolism (Zhao et al. 2015). It has been found that rs4147929 SNP in ABCA7 gene is associated with LOAD (Lambert et al. 2013; Hollingworth et al. 2011). rs4147929 SNP in ABCA7 gene is also found to be a major determinant of the left postcentral gyrus morphology (which is involved in

Table 4 Genotypes and allelic frequency of rs4147929 variant of ABCA7 gene polymorphism in the study groups

Genotype	LOAD		Control		OR (95% CI)	p value
	n	f(%)	n	f(%)		
A	65	29.5	67	38.1	0.680 (0.361–1.278)	0.099
G	155	70.5	109	61.9	1.471 (0.782–2.770)	0.080
AA	1	9	5	5	0.150 (0.005–1.410)	0.009
AG	63	57.3	57	64.8	0.729 (0.396–1.342)	0.159
GG	46	41.8	26	29.5	1.716 (0.918–3.218)	0.042

n, number; f, frequency; *OR*, odds ratio; *CI*, confidence interval; *LOAD*, late-onset Alzheimer's disease

Table 5 Genotypes and allelic frequency of rs11771145 variant of EphA1 gene polymorphism in the study groups

Genotype	LOAD		Control		OR (95% CI)	*p* value
	n	*f*(%)	*n*	*f*(%)		
G	176	80	139	78.9	1.07 (0.51–2.24)	0.366
A	44	20	37	21.1	0.94 (0.44–1.97)	0.5
GG	71	65.5	56	63.6	1.04 (0.56–1.93)	0.436
GA	34	30.9	27	30.6	1.01 (0.53–1.93	0.531
AA	5	4.5	5	5.6	0.79 (0.18–3.25)	0.362

n, number; *f*, frequency; *OR*, odds ratio; *CI*, confidence interval; *LOAD*, late-onset Alzheimer's disease

AD pathogenesis) in healthy subjects (Roshchupkin et al. 2016). A large meta-analysis of GWAS showed that rs4147929 variant in an ABCA7 intron increased the risk of AD in subjects of European ancestry (OR = 1.15; 95% CI = 1.11–1.19) (Hollingworth et al. 2011). Another meta-analysis assessed the association between different SNPs of ABCA7 gene and LOAD. This study found a significant relationship between various SNPs of ABCA7 gene such as rs4147929 among others and LOAD. However, this association varied among different ethnic backgrounds (Ma et al. 2018). Similarly, Cuyvers et al. conducted a study on 772 Belgian patients with AD and found that rs4147929 SNP is linked to an escalated risk of AD (Cuyvers et al. 2015). In a close association with these studies, Kjeldsen et al. assessed the association between ABCA7 gene polymorphisms and risk of dementia in the178,304 Danish individuals and revealed that one allele ABCA7 rs4147929 increased the risk of LOAD by 1.15 (1.12–1.18) (Kjeldsen et al. 2017). In line with that, a study performed by Moreno-Grau on a Spanish population showed that A*BCA7* rs4147929:G>A was significantly higher in AD patients than that of healthy subjects indicating its role in the pathogenesis of AD (odds ratio (OR) = 1.15, 95% confidence interval (95% CI) = 1.12–1.19; $P = 1.60 \times 10^{-19}$) (Moreno-Grau et al. 2018). These findings were in line with the results of our study, indicating a link between this SNP and AD pathogenesis.

Our study did not show such a difference in the frequency of rs3764650 T>G polymorphism between LOAD and healthy subjects, where all the samples of both control and patient groups had the homozygote TT allele. On the one hand, some studies have linked rs3764650 variant to hippocampal and cortical atrophy in mild cognitive impairment (MCI) patients and also healthy subjects (Ramirez et al. 2016). rs3764650 variant is also associated with memory impairment in MCI and LOAD patients (Carrasquillo et al. 2015). On the other hand, the findings of some other studies are in line with our results. Tan et al. recruited 612 patients with LOAD in a northern Han Chinese population. However, they could not draw an association between rs3764650 SNPs and risk of LOAD in the respective population (Tan et al. 2013).

EphA1 is found to be a risk gene locus for LOAD. This could be mediated by the effects of EphA1 on the blood-brain barrier integrity and neuroinflammation in LOAD patients. Intronic EphA1 LOAD SNP rs11771145 is situated within the EphA1-antisense RNA 1 gene and may play a vital role in the gene expression (Owens et al. 2018). Our results found no difference in the frequency of SNP rs11771145 between healthy subjects and LOAD patients. Similarly, Seshadri et al. found no significant association between rs11767557 variant in EphA1 promoter zone and AD. In this study, the allelic frequency of rs11771145 GA polymorphism was surveyed. Nevertheless, no meaningful difference was found in the frequency of homozygote and heterozygote alleles between the control and patient groups (Seshadri et al. 2010). Likewise, Lin et al. evaluated the effects rs11771145 SNP on AD predisposition in a Taiwanese population and found no association between rs11771145 variant and perceptual and cognitive decline in AD patients (Lin et al. 2017). On the other hand, in a meta-analysis performed by Lambert et al., it was found that EphA1 rs11771145 may be associated with decreased AD susceptibility, and thus, this variant may render protective effects on carriers (Lambert et al. 2013). Also, in a study by Gulkovskyi et al. conducted on 65 patients with mild (IQ score between 50 and 70) idiopathic intellectual disability from different regions of Ukraine, it was revealed that rs11771145 SNP in the EphA1 gene is linked to idiopathic mild intellectual disability (Gulkovskyi et al. 2015).

The observed difference between studies may stem from the fact that the formerly reported gene impacts may be unique to the studied populations. Thus, the same results may not be achieved using a different sample. Also, because linkage disequilibrium (LD) and the allele frequencies of SNPs may change from community to community, it is essential to appreciate the impacts of these variables in various samples. LD with other pathogenic SNPs, which have not been yet recognized, might be higher or lower in different populations, which will decrease the power of such population-based studies to notice such impacts (Tan et al. 2013).

The results of our study should be interpreted with caution. This study was conducted in a limited number of LOAD patients in Iran; thus, its conclusions may not be generalized to other populations. Indeed, the successful recapitulation of the novel GWAS-associated loci in different communities from multiple ethnic backgrounds is essential for the justification of these discoveries. As many GWAS studies have been performed in patients from European ancestry, their findings are not generalizable to the patients from other populations.

Conclusion

Identification of genetic factors which have an essential role in the pathogenesis of LOAD is the principal goal in the

development of modern therapeutic strategies for the disease. Investigation of genetic biomarkers for prediction of AD risk and identification of the molecular pathways involved in this disorder appears to be of vital importance. In this study, no differences were found in the frequencies of ABCA7 SNP rs3764650 and EphA1 SNP rs11771145 between healthy subjects and LOAD patients in Iranian Azeri population. However, a significant difference was revealed in ABCA7 SNP rs4147929 between the mentioned groups. These results are only hypothesis-generating and should be interpreted with caution. Future studies should assess these findings in other ethnic groups with larger sample sizes.

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Compliance with Ethical Standards All the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2013. Written informed consent was obtained from the participants or their first-degree relatives.

Conflict of Interest The authors declare that they have no conflict of interest.

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