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Research Paper

The Relationship Between Bridging Integrator 1 Gene Polymorphism and Susceptibility to Alzheimer's Disease

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ABSTRACT

Background: Alzheimer's Disease (AD) is the most common type of dementia. The role of genetic factors in AD development remains non-demonstrated.

Objectives: In this study, we aimed to investigate the association between one of the BIN1 gene's single-nucleotide polymorphisms(SNP) rs744373 and Late-Onset Alzheimer's Disease (LOAD) in an Iranian population in Guilan Province.

Materials & Methods: In this case-control study, 110 patients with LOAD and 110 unrelated healthy controls were recruited. Polymerase chain reaction-restriction length polymorphism (PCR-RFLP) was performed for genotyping the BIN1 gene's SNP rs744373. Electrophoresis was thereafter conducted using agarose gel and DNA-safe stain, and the gels were visualized under an Ultraviolet (UV) trans-illuminator. The allelic and genotypic frequencies were determined.

Results: The frequency of allele T (Wild-type allele) in the control and the LOAD groups was 70.9% (n=159) and 58.6% (n=129), respectively (P=0.007). The frequency of allele C in the LOAD group (41.4%) (n=91) was significantly higher than that of the control group (29.1%) (n=64) (P=0.007). BIN's homozygous genotype (CC) frequency was significantly higher in the LOAD group than in the control group (P=0.043).

Conclusion: The rs744373 SNP of the BIN1 gene is significantly associated with the risk of developing AD in the studied population.

Keywords: Alzheimer's disease, Polymorphism, Single-nucleotide polymorphism, BIN1 protein, Human

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Highlights

- In total, 110 patients with LOAD and 110 unrelated healthy controls were recruited.
- Having performed PCR-RFLP for genotyping, we performed gel electrophoresis.
- The studied population suggested that polymorphism rs744373 of the BIN1 gene was significantly associated with LOAD.

Introduction

Alzheimer's Disease (AD) is the most prevalent dementia in the elderly. The Hallmark of AD is the accumulation of amyloid plaques and the neurofibrillary tau protein tangles in the brain cortex [1]. Amyloid plaques are formed by the accumulation of Amyloid-Beta (Aβ) peptides resulting from the decomposition of Aβ Precursor Protein (APP). Furthermore, tau protein hyperphosphorylation leads to the polymerization of double-helical filaments, creating neurofibrillary tau tangles [2]. Genetic changes are involved in neurodegenerative diseases such as Parkinson's disease [3], Multiple Sclerosis [4, 5], and AD [6]. The mutations of APP and Presenilin 1 and 2 for familial AD or early-onset familial Alzheimer's Disease and ε4 allele of Apolipoprotein E (APOE) gene (APOE ε4) for sporadic cases were demonstrated [7, 8]. Polymorphism of TERM2 [9], MS4A6A [10], d, and CD33 [11]; they were found to be associated with AD.

A defect in the Bridging Integrator 1 (BIN1) gene is also an essential genetic risk factor suggested for Late-Onset Familial Alzheimer's Disease (LOAD) [12]. Moreover, BIN1 regulates endocytosis, inflammation, calcium homeostasis, and apoptosis [13]. The Single-nucleotide Polymorphism (SNP) rs744373 of the BIN1 gene, placed more than 25 kb before the encoding area of this gene, is the most important variation of the gene associated with AD [14]. Rs744373 polymorphism affects gene expression and interferes with tau metabolism. AD patients with this polymorphism may have high levels of tau accumulation in brain imaging studies and cerebrospinal fluid [15].

Seshadri et al. conducted a meta-analysis of more than 35000 individuals, including 8371 AD patients, and found, for the first time, the association between SNP rs744373 polymorphism of BIN1 on chromosome 2 and AD [16]. They also confirmed the association of this polymorphism with AD [Odds Ratio (OR)=1.13, P<0.05].

Gharesouran et al. studied the association between rs744373 polymorphism and LOAD in Iran's Turkish Azeri ethnicity [17]. They investigated the distribution of 11 polymorphisms in 160 patients with LOAD and 163 healthy controls. The results revealed that alleles and genotypes of BIN1 gene rs744373 polymorphism were significantly different between LOAD and control groups.

However, Chen et al. could not validate the association of rs744373 polymorphism with AD in 17 AD cases and 34 controls from the Xinjiang Chinese population [18]. Moreover, Kaya et al. did not find an association between AD and BIN1 gene polymorphism in 53 AD patients and 56 controls from the Turkish population [19].

Given the need to identify genetic factors involved in the pathogenesis of AD in various populations, we sought to investigate the association of rs744373 polymorphism of BIN1 gene with LOAD in Guilan Province in the north of Iran.

Materials and Methods

We recruited 110 patients with LOAD and 110 unrelated healthy subjects in this case-control study. Patients over 65 years of age diagnosed with probable AD according to the National Institute on Aging and Alzheimer's Association criteria [20] were included in the study. Patients with a history of head trauma, stroke, hereditary dementia, Central Nervous System (CNS) infection, neuropsychiatric systemic lupus erythematosus, sarcoidosis, multiple sclerosis, and other neurodegenerative diseases were excluded from the study. Moreover, 110 age- and gender-matched unrelated healthy subjects were recruited.

DNA was extracted from blood samples of study subjects using the salting-out method. Polymerase Chain Reaction (PCR) was performed using a standard protocol. The PCR products (Figure 1) were incubated with the HinfI enzyme, and the genotypes of the cut samples were determined using 3% agarose gel electrophoresis

Table 1. Primers, restriction enzyme, restriction site, and restriction products for polymerase chain reaction of rs744373 polymorphism.

Forward primer	5'-CACCAGGGACAGGCAGGTCTGAGAC-3'
Reverse primer	5'-CACATCTTAGCCACAGAACAGG-3'
Restriction enzyme	HinfI
Restriction site of the enzyme	CTCTCGG
Size of restriction products after RFLP	TT: 225 bp and 26 bp TC: 251 bp, 225 bp, 26 bp CC: 251 bp

and DNA-safe stain (Figure 2). The gels were visualized under an Ultraviolet (UV) trans-illuminator.

In rs744373 polymorphism of the BIN1 gene, a nucleotide T is replaced with nucleotide C (CTCTCGG). G^ANTC is the sequence of restriction sites by the HinfI restriction enzyme. The band sizes after restriction fragment length polymorphism (RFLP) are displayed in Table 1.

Using SPSS, the obtained data were compared and evaluated by Chi-square and logistic regression analyses.

Results

We studied 110 patients with LOAD and 110 healthy unrelated healthy control. The LOAD group consisted of 77 (70%) women and and 33 (30%) men with a mean±SD of the age of 77.4±7.8 years. Besides, the control group consisted of 69 women (62.7%) and 40 men (36.4%) with a mean±SD age of 76.9±9.6 years. There were no significant differences between age (P=0752) and gender (P=0.348) of the 2 studied groups.

The Allelic frequency of the BIN1 gene polymorphism

The frequency of allele T (Wild-type allele) in the control group and the LOAD group was 70.9% (n=159) and 58.6% (n=129), respectively. Additionally, the frequency of allele C in the LOAD group (41.4%) (n=91) was significantly higher than that of the control group (29.1%) (n=64). The allelic frequency of rs744373 polymorphism in the LOAD and control groups is illustrated in Figure 3.

Further, there was a significant relationship between the allelic frequency of rs744373 polymorphism and LOAD [OR=1.71, 95% Confidence Interval (CI)= 1.15-2.55, P=0.007)].

The genotypic frequency of rs744373 polymorphism in LOAD

The TT genotype was found in 65 (59.1%) and 54 (49.1%) of the control and LOAD, respectively. TC genotype was seen in 26(23.6%) and 21(19.1%) of the control and the AD, respectively. The frequency of genotype CC was higher in the LOAD group (n=35, 31.8%) than in the control group (n=19, 17.3%). Figure 4 shows the genotypic frequency of the rs744373 polymorphism in LOAD and control groups. There was a significant association between the polymorphism and LOAD (P=0.043).

Logistic regression analysis indicated that the odds of genotype CC were almost twice as high as that of genotype TT (normal homozygote) in the LOAD (Table 2). The CC genotype was associated with LOAD (P=0.019).

Investigating the relationship between different genotypes of polymorphism and AD according to the inheritance model and through nominal logistic regression indicated that the codominant and recessive models could play roles in the inheritance of polymorphism rs744373. Both models yielded similar associations between genotype and AD.

Discussion

The present study examined the association between rs744373 polymorphisms of the BIN1 gene and LOAD in a population in Guilan Province in the north of Iran.

The only study on the association between this polymorphism and LOAD in Iran was conducted by Gharesouran et al. [17] on a population of Iranian Azeris. The authors examined 11 polymorphisms, including rs744373, rs11554585, and rs7561528 polymorphisms in the BIN1

Table 2. Relationship between rs744373 polymorphism genotype and Alzheimer's disease

Gene	Genotype	No. (%)		Regression coefficient	OR	95%CI	P
		LOAD	Controls				
BIN1	CC	35(31.8)	19(17.3)	0.796	2.22	(1.14 -4.31)	0.019
	TC	21(19.1)	26(23.6)	-0.028	0.972	(0.49- 1.92)	0.935
	TT	54(49.1)	65(59.1)	-	-	-	-

gene in 160 patients with LOAD and 163 healthy controls. The frequency of allele C of rs744373 in the patient group (12.8%) was significantly greater than that in the control group (5%), and the polymorphism was associated with LOAD (OR = 2.847, P<0.001). However, the results of these studies should be interpreted with caution due to their limited sample sizes.

The odds of genotype CC were almost twice as high as that of genotype TT (normal homozygote) in the LOAD in the present study. CC genotype was also associated with LOAD (P=0.019).

BIN1 plays a role mainly through interaction with protein tau in AD [21]. Tau protein, a highly-soluble protein in the cytoplasm that maintains the stability of microtubules, is hyper-phosphorylated in AD, precipitates, and creates a dual string helix structure that ultimately leads to the creation of neurofibrillary tangles. Accumulation of these tangles inside the cell is neurotoxic and considered a mechanism of neurodegeneration [22]. Recent studies hypothesized that polymorphisms of BIN1 increase the neurotoxicity of the hyper-phosphorylated protein tau by interfering with the interaction between proteins tau and bin1, thereby changing the synapses [23].

Seshadri et al. conducted an international three-stage meta-analysis in which more than 35,000 individuals (including 8371 AD patients) participated. For the first time, they found the association between single nucleotide rs744373 polymorphism near the BIN1 gene on chromosome 2. They also confirmed the association of this polymorphism with AD [16].

In a study in 3 contrasting European populations from Finland, Italy, and Spain, Lambert et al. evaluated the association between BIN1 gene rs744373 polymorphism (OR=1.26, 95%CI=1.15-1.38, P=2.9×10-7) [14].

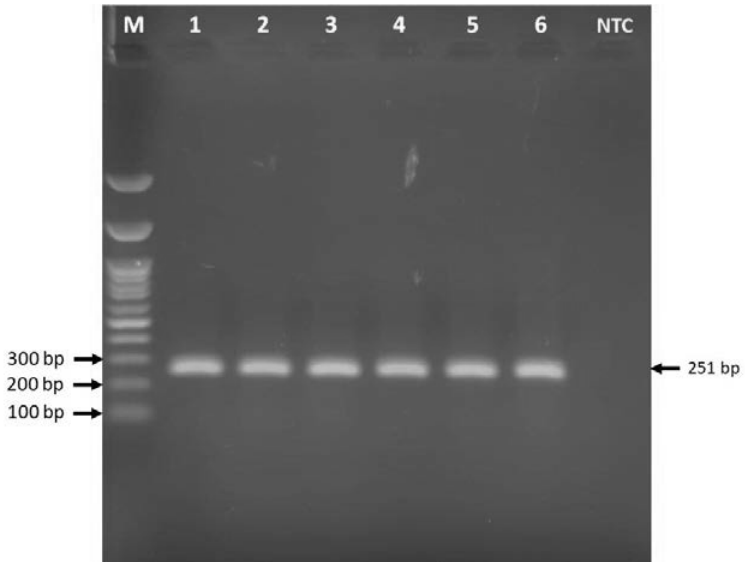

Figure 1. PCR products of BIN1 gene following electrophoresis using Agarose gel

Specific primers for the BIN1 gene proliferate a 251 bp fragment (M = 100-bp DNA ladder, NTC = non-template control).

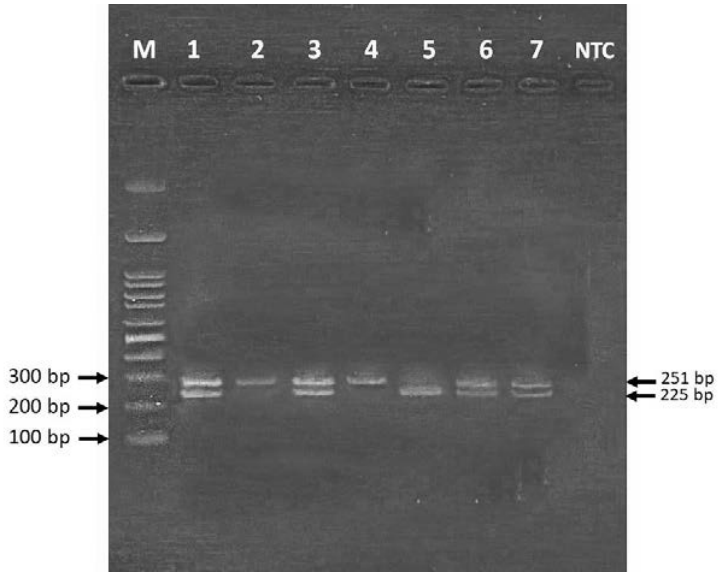

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Figure 2. Restriction products following PCR-RFLP and electrophoresis using Agarose gel After enzymatic treatment

three 251 bp, 225 bp, and 26 bp fragments are obtained. The 26 bp fragment is invisible in this picture. Individuals with wild-type homozygous genotypes have a 251 bp fragment (Samples No. 2 and 4). Individuals with heterozygous genotype are recognized by two 251 bp and 225 bp fragments (Samples No. 1, No. 3, No. 6, and No. 7), and individuals with homozygous mutant genotype are recognized by 225 bp fragment (Sample No. 5) (M = 100-bp DNA ladder, NTC = non-template control).

Moreno et al. conducted a case-control study in Colombia and found a significant association between polymorphism rs744373 in the BIN1 gene and AD (OR=1.42, 95%CI=1.07-1.88, P=0.015) [8].

Wang et al. found that rs744373 was significantly associated with AD in a population in East China (OR=1.256, 95%CI=1.028-1.535, P=0.038) [24]. The author found that such an association was not present in a population in Southwest China (OR=1.024, 95%CI =0.820-1.281, P=0.874). However, the relationship between rs744373 of the BIN1 gene with AD was confirmed after meta-analysis (OR=1.14, 95% CI=1.05-1.24, P=0.001).

Dos Santos et al. further conducted a case-control study on rs744373 polymorphism of the BIN1 gene in a Brazilian population [25]. Their findings indicated no association between rs744373 and AD in the Brazilian population (CC genotype of BIN1; OR=0.79, 95%CI=0.28-2.26, P=0.660), TT genotype of BIN1 (OR=1.20, 95%CI=0.66-2.19, P=0.547).

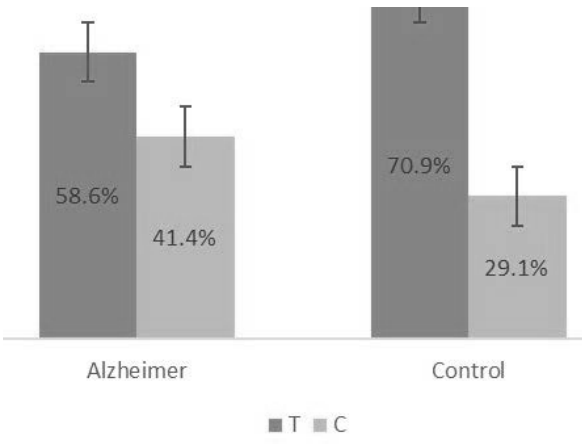

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Figure 3. Comparison of allelic frequency of rs744373 polymorphism between the healthy and LOAD groups

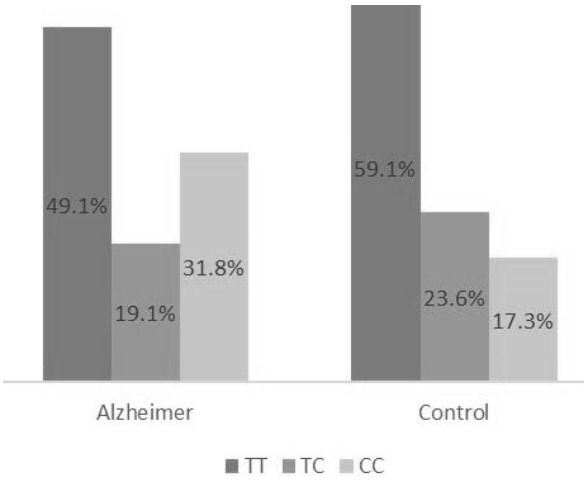

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Figure 4. Comparing the genotypic frequency of polymorphism genotype between healthy and Alzheimer's groups

Carrasquillo et al. genotyped rs744373 and rs597668 variants in a large (3,287 LOAD, 4,396 controls) series from the USA and Europe [26]. They outlined a significant association between BIN1 and LOAD (OR=1.17, 95%CI=1.08-1.26, P=1.1×10−4).

Miyashita et al. conducted a 3-stage genome-wide association study using three Japanese, Koreans, and Caucasians [27]. They reported a significant association between rs744373 of BIN1 gene with LOAD in Japanese (OR=1.25, 95%CI=1.11-1.4, P=1.39×10 -4) and Korean (OR=0.98, 95%CI=0.81-1.18, P=8.05×10-1).

Chen et al. investigated the association of the five AD-associated variants, 8-oxoguanine DNA glycosylase 1 rs1052133, BIN1 rs744373, sortilin-related receptor 1, rs1133174, presenilin 2 rs8383, and nerve growth factor rs6330, in the Xinjiang Chinese population [18]. They recruited 17 AD cases and 34 controls from the Xinjiang Chinese population. The authors were unable to validate the association of rs744373 polymorphism with AD. They declared this might be because of the limited sample size.

Kaya et al. examined the polymorphism and allele frequency of the APOE and BIN1 genes in 53 AD patients and 56 controls in a Turkish population [19]. There was no significant difference in CC genotype prevalence of the BIN1 gene between patients and controls (P>0.05). The authors concluded no association between AD and the BIN1 gene polymorphism.

Han et al. conducted a meta-analysis with 71,168 samples (22,395 AD cases & 48773 controls, from 37 studies of 19 articles) [28]. They identified a significant association between rs744373 polymorphism with AD in pooled populations (OR=1.12; 95%CI=1.07-1.17, P=5×10-07) and in Caucasian populations (OR=1.16, 95%CI=1.10-1.22, P=3.38×10-08). However, the association was not identified in the East Asian populations (OR=1.057, 95%CI= 0.95-1.15, P=0.393).

The association between rs744373 and LOAD has presented to be heterogeneous results. Its presence in the European populations (white), Colombia, Japan, China, and Iran was associated with an increased risk of LOAD [8, 14, 25-27]. Still, such an association did not exist in Brazil, Turkey, and the East Asian mixed population [18, 19, 25, 28].

Conclusion

The present study findings suggested that polymorphism rs744373 of the BIN1 gene was significantly associated with LOAD in the studied population. It is helpful to conduct further studies of this polymorphism with larger sample sizes. Further studies on the expression of the BIN1 gene are recommended.

Ethical Considerations

Compliance with ethical guidelines

All study procedures were done in compliance with the ethical guidelines of the Declaration of Helsinki, 2013. The present study was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1398.518).

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Authors contributions

All of the authors helped shape this collaborative research study and contributed to the project.

Conflict of interest

The authors declared no conflicts of interest.

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