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Assessment of the Correlation of rs7920721 in the *ECHDC3* Gene with Alzheimer's Disease in the Iranian Population

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Abstract

Alzheimer's disease is the most common cause of dementia in the elderly. One of the polymorphisms in Alzheimer's disease is rs7920721 in the *ECHDC3* gene, which has not been studied in the population of Iranian Alzheimer's patients and was evaluated in the present study. In 2021, 100 patients with Alzheimer's disease and 100 healthy controls performed the current case-control analysis. Following blood sampling and DNA extraction, rs7920721 polymorphism was examined using Tetra ARMS PCR. The frequency of AA, AG and GG genotypes in rs7920721 in the control group was 89, 10, and 1%, respectively; in people with Alzheimer's disease, they were 73, 23, and 4%, respectively (P = 0.014). The frequency of A and G alleles in the control group was 94% and 6%, respectively, and in people with Alzheimer's disease, they were 84.5% and 15.5%, respectively (P = 0.046). The value (OR = 2.874) (CI 95% = 1.43-5.77) indicated an increased probability of disease in the presence of polymorphism. Both the case and control populations were also in the Hardy-Weinberg equilibrium. The results of the present study showed that the presence of the G allele in rs7920721 of the *ECHDC3* gene could be associated with an increased risk of Alzheimer's disease in the Iranian population. As a result, this polymorphism can be introduced as a potential biomarker for Alzheimer's disease.

Keywords: Alzheimer's disease; Single nucleotide polymorphism; *ECHDC3* gene; rs7920721.

Introduction

Alzheimer's Disease (AD) is a progressive neurological disorder that causes the brain to atrophy and cells to die. AD is the most common cause of dementia. Dementia means a continuous decline in intellectual, behavioral, and social skills that affect a person's ability to function independently. In the United States, an estimated 5.8 million people over 65 have AD. Of those, 80% are aged 75 or over. Among the approximately 50 million people living with dementia worldwide, between 60% and 70% suffer from AD.

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Medications may temporarily improve or slow the progression of symptoms. These therapies may sometimes help AD patients to enhance their function and remain independent for some time (1, 2). Researchers believe that for most people, AD is caused by a combination of genetic, lifestyle, and environmental factors that affect the brain over time. Several types of mutations or genetic disorders have been identified in AD patients, including dysfunctional mutations, single nucleotide polymorphisms (SNPs), mitochondrial mutations, and epigenetic changes (3).

Dyslipidemia is known to be a risk factor for AD. This refers to abnormal levels of lipids or lipoproteins in the blood, including high levels of low-density lipoprotein (LDL-C), low levels of high-density lipoprotein (HDL-C), total cholesterol (TC), and triglycerides (TG) (4). Over the last decade, the relationship between cholesterol and AD has been widely studied, especially in longitudinal epidemiological studies (5). Evidence suggests that elevated blood cholesterol levels in the middle and end of life are associated with dementia (6-9). In addition, another study shows that if TC increases in the membrane of the brain, synapses do not form and therefore affect cognitive degeneration in AD (10).

Enoyl-CoA hydratase (ECH) is an enzyme that catalyzes the second step in the essential physiological pathway of fatty acid β-oxidation. This enzyme facilitates the simultaneous addition of a water molecule between the double bonds of a thioester called trans-2-enoyl-CoA, resulting in the formation of a thioester called beta-hydroxy acyl-CoA (11). Enoyl-CoA Hydratase Domain Containing 3 (ECHDC3) encodes a mitochondrial enzyme with a crotonase-like domain similar to enoyl-CoA hydratase. In addition, ECHDC3 is thought to be involved in β-oxidation, the most essential and well-known pathway for fatty acid oxidation (12). Over the past few years, studies have identified rs7920721 single nucleotide polymorphism in *ECHDC3*, which is associated with AD. It has also been shown to be involved in the level of plasma lipids or other lipid properties. The researchers showed the pleiotropic effects of rs7920721 polymorphism of the *ECHDC3* gene for AD, plasma C-reactive protein, and lipid levels (13). Accordingly, the present study evaluated the frequency of rs7920721 polymorphism of the *ECHDC3* gene in the Iranian population and its relationship with AD.

Materials and Methods

Type of study and inclusion and exclusion criteria: The present study was a case-control study that was performed to determine the frequency of rs7920721 polymorphism in the *ECHDC3* gene in AD patients and compare it with the control group was conducted in the spring and summer of 2021. The census survey included 100 AD samples. Control samples were collected from 100 healthy people with no prior AD in a first-degree relative in the same age range of patients. Inclusion criteria in this study included age over 60 years, AD, and the satisfaction of the individual (or their family). Exclusion criteria also included dissatisfaction, congenital genetic diseases, and systemic diseases such as cardiovascular disease, diabetes, and hypertension.

Sampling: With the consent of the cases and controls, each one takes 5 ml of venous blood. Blood samples were collected in EDTA-containing tubes for molecular tests. Their serum was separated from the clot using a centrifuge at 3000 rpm (10 minutes) and stored at -70 °C until the appropriate time.

DNA extraction: DNA extraction from serum samples was performed using a GeneAll DNA extraction kit by the manufacturer's instructions. The quantity and quality of the extracted DNA were evaluated by spectroscopy. It uses NanoDrop™ 2000/2000c Spectrophotometer and electrophoresis on 1% agarose gel.

Tetra ARMS PCR: Tetra ARMS PCR was performed using 2 µl of DNA template, 1 µl of each of the internal and external primers (Table 1), and 10 µl of master mix 2X, which reached a final volume of 18 µl with distilled water. The temperature cycle started with a denaturation step at 95 °C for 3 minutes and 35 bikes. It denaturation at 95 °C for 30 seconds, annealing at 64 °C for 30 seconds, and the expansion was continued at 72 °C for 60 seconds. The Tetra ARMS PCR was completed with an expansion step at 72 °C for 5 min.

Table 1. Primers designed to perform Tetra ARMS PCR reaction

Primers	Sequences	Product length (bp)
rs7920721 F outer	GAAACCGCAGCCCATGAGCCA	666
rs7920721 R outer	GGATCACAAGGTCACAAGGTCAAGAGA	
rs7920721 F inner	AGTCACCCTCAGCTGTTCACCTG	481 / 230
rs7920721 R inner	GCCTGAAAGCAGCCACAGACCAT	

The reaction product was observed on 1.5% agarose gel. A 666 bp band was considered as the accuracy of the reaction. Individuals with a 481 bp band were considered as GG genotype, individuals with both 481 and 230 bp bands were considered AG genotype, and individuals with a 230 bp band were considered AA genotype.

Sequencing: Samples were sequenced to ensure genotyping results by Tetra ARMS PCR. The resulting sequences were blasted in the NCBI database to determine whether they were related to the gene investigated in this study.

Statistical analysis: SPSS v.22 statistical software was used for data analysis. The Chi-square test and logistic regression were used to compare the frequency of polymorphisms. A p-value <0.05 was considered a significant level. The calculated and expected allelic frequencies (based on the percentage of genotypic frequency) were used to evaluate the Hardy-Weinberg equilibrium. Both groups were compared using the chi-square test. Pearson correlation test was used to study the correlation between the studied polymorphism and AD.

Results

Demographic characteristics of test participants: The demographic characteristics of participants, including age, sex, and family history of AD, were assessed. In this study, in the case group, 58 women and 42 men with a mean age of 87.44 ± 6.73 years (range 72-102 years) were present, and in the control group, 48 women and 52 men with a mean age of 86.16 ± 3.50 (range 78-102 years) participated. Statistical analysis showed no significant difference in age and sex between cases and controls (P> 0.05), and the study population was homogeneous.

Family history: The presence of AD family history was studied, and the results showed that in the patient group, 44% had a family history of AD, while the control group had a 32% family history of AD, which was statistically significantly lower than the patient group (P = 0.044). Family background is involved in AD.

Results of Tetra ARMS PCR: The reaction product of Tetra ARMS PCR was loaded on an agarose gel. The genotypes determined each individual based on the band formation pattern (Figure 1). As mentioned earlier, individuals with 481 bp bands were considered GG genotypes, individuals with both 481 and 230 bp bands were considered AG genotypes, and individuals with 230 bp bands were considered AA genotypes.

Genotypic frequency of rs7920721 in cases and controls: Using the obtained patterns and calculated identified genotypes, the frequency of each genotype for rs7920721 in controls and AD patients. As shown in

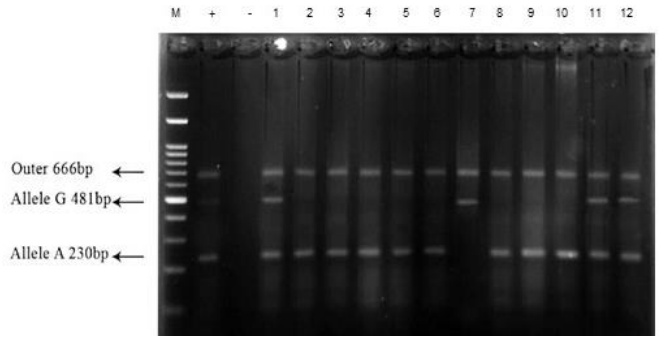

Figure 1. Bands of electrophoresis of Tetra ARMS PCR products to study rs7920721 polymorphism in *ECHDC3* gene (M lane: 100 bp molecular marker, + lane: positive control, - lane: negative control, lanes 2 to 6 and 8 to 10: homozygous dominant genotype AA, lanes 1, 11 and 12: heterozygous genotype AG, lanes 7: homozygous recessive genotype GG)

Table 2. Genotypic frequency of rs7920721 polymorphism in *ECHDC3* gene in case and control individuals

			Genotype			Total
			AA	AG	GG	
Group	Normal	Count	89	10	1	100
		% within Group	89.0%	10.0%	1.0%	100.0%
	Alzheimer	Count	73	23	4	100
		% within Group	73.0%	23.0%	4.0%	100.0%
Total		Count	162	33	5	200
		% within Group	81.0%	16.5%	2.5%	100.0%

Table 2, the prevalence of AA, AG, and GG genotypes in the control group was 89%, 10%, and 1%, respectively, while in the AD group, it was 73%, 23%, and 4%, respectively. The Chi-square test also showed a significant difference between case and control individuals regarding the genotypic frequency of rs7920721 polymorphism in the *ECHDC3* gene (P = 0.014).

Allelic frequency of rs7920721 in cases and controls: According to the identified genotypes, calculated the allelic frequency of rs7920721 polymorphism in the *ECHDC3* gene in patients and controls. As shown in Table 3, the frequency of alleles A and G in the control group was 94% and 6%, respectively, while it was 84.5% and 15.5%, respectively, in the case group. The Chi-square test also showed a significant difference between case and control individuals regarding the allelic frequency of rs7920721 polymorphism in the *ECHDC3* gene (P = 0.046). On the other hand, determining the risk level found that the OR value equals 2.874. OR more significant than 1 indicates an increased risk of disease in the presence of polymorphism. It means that people with G alleles are 2.874 times more likely to develop AD than people with A alleles. The 95% CI was calculated between 1.43 and 5.77.

Correlation between genotype and disease severity: The disease severity in AD patients was determined, and evaluated its correlation with their genotype. As shown in Table 4, of the individuals with mild AD, 81% had the AA genotype, 14.3% had the AG genotype, and 4.8% had the GG genotype. All of the patients with progressive AD had the AA genotype. Also, 64.8% of the AA genotype, 31.5% of the AG genotype, and 3.7% of the GG genotype were observed in severe AD. According to the Pearson correlation test, there was no correlation between disease severity and the genotype of individuals for rs7920721 polymorphism in the *ECHDC3* gene (P = 0.171).

Hardy-Weinberg equilibrium: The calculated allelic frequency and the expected allelic frequency (based on the percentage of genotypic frequency) in the control group were compared, and the chi-square test results showed a significant difference between the

Table 3. Allelic frequency of rs7920721 polymorphism in *ECHDC3* gene in case and control individuals

			Group		Total
			Normal	Alzheimer	
Allele	A	Count	188	169	357
		% within Group	94.0%	84.5%	89.3%
	G	Count	12	31	43
		% within Group	6.0%	15.5%	10.8%
Total		Count	200	200	400
		% within Group	100.0%	100.0%	100.0%

Table 4. Frequency of individuals with different genotypes for rs7920721 polymorphism in *ECHDC3* gene in different stages of AD

			Grade			Total
			Mild	Progressive	Severe	
Genotype	AA	Count	34	4	35	73
		% within Grade	81.0%	100.0%	64.8%	73.0%
	AG	Count	6	0	17	23
		% within Grade	14.3%	0.0%	31.5%	23.0%
	GG	Count	2	0	2	4
		% within Grade	4.8%	0.0%	3.7%	4.0%
Total		Count	42	4	54	100
		% within Grade	100.0%	100.0%	100.0%	100.0%

Table 5. Calculated allelic frequency and expected allelic frequency for rs7920721 polymorphism in *ECHDC3* gene

		Control Group			Alzheimer Group		
		Frequency		Total	Frequency		Total
		Observed	Expected		Observed	Expected	
Genotype	AA	89	88.5	177.5	73	71.5	144.5
	AG	10	11.2	21.2	23	26	49
	GG	1	0.3	1.3	4	2.6	6.5
Total		100	100	200	100	100	200

calculated allelic frequency and the expected allelic frequency. (P = 0.592) and as a result, Hardy-Weinberg equilibrium is established in this population. It compared and calculated allelic frequency and the expected allelic frequency (based on the percentage of genotypic frequency) in the AD group. The chi-square test showed no significant difference between the calculated and expected allelic frequency (P = 0.646). As a result, Hardy-Weinberg equilibrium is established in this population (Table 5).

Sequencing: To confirm the experiment, DNA was extracted and sequenced for one case of homozygous and one point of heterozygous. The sequencing results were blasted and controlled in the NCBI database,

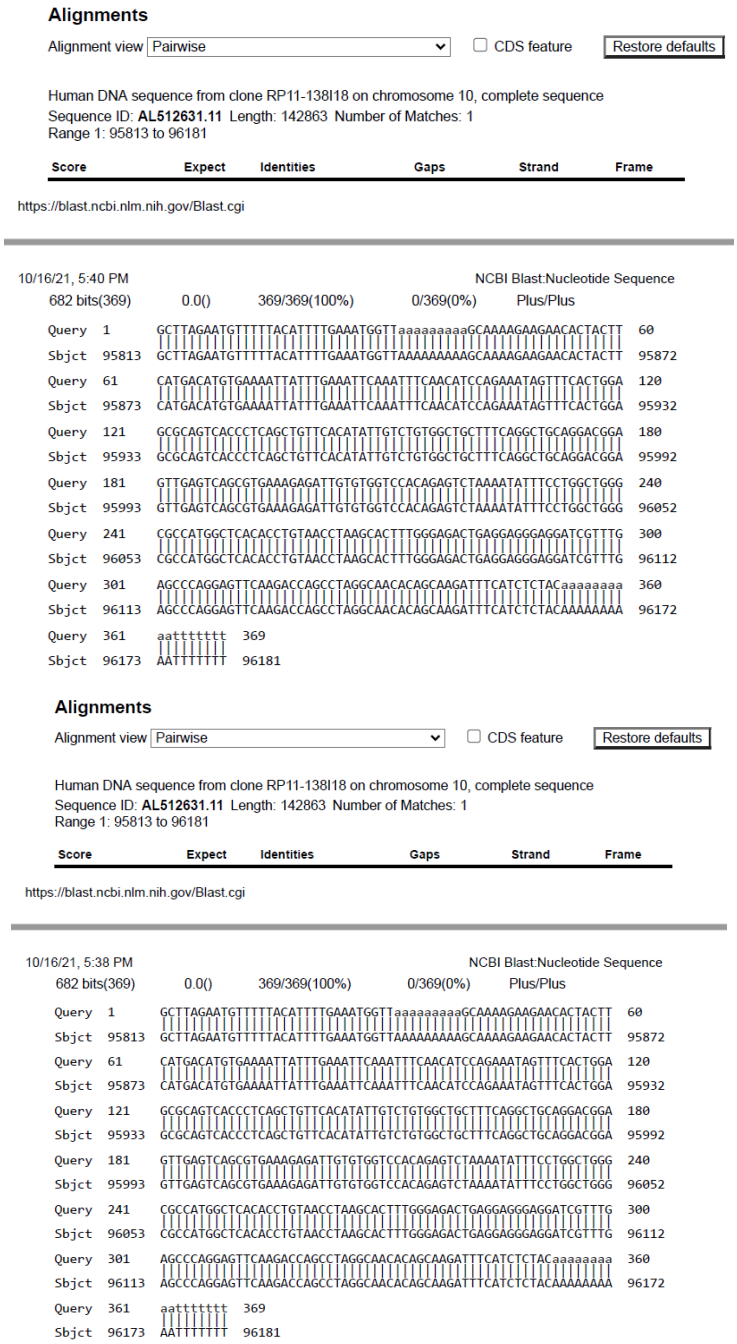

Figure 2. Blast of sequences in NCBI (A: AA homozygous dominant sample, B: GG homozygous recessive sample, C: AG heterozygous sample)

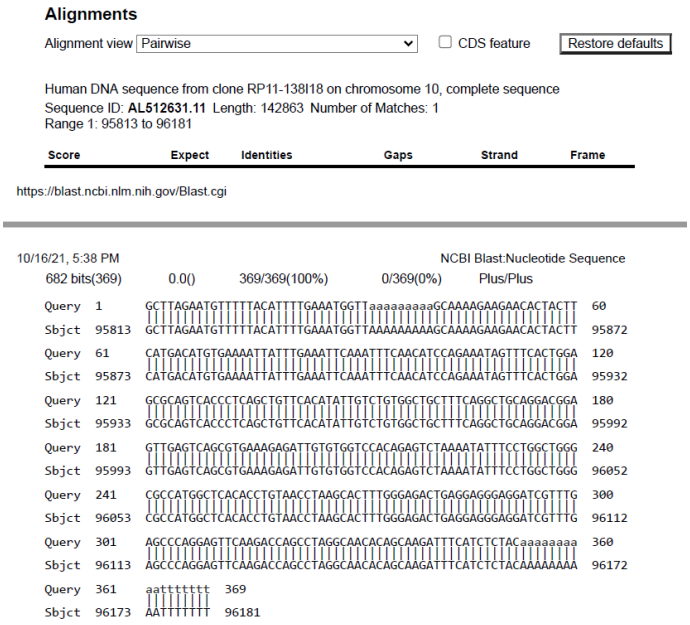

Figure 2. Continued

confirming the effects of the Tetra ARMS PCR genotype (Figure 2).

Discussion

The present study investigated the correlation between the rs7920721 polymorphism in the *ECHDC3* gene and AD by Tetra ARMS PCR. The results showed a significant difference in this polymorphism's genotypic and allelic frequency between healthy individuals and AD patients. The results of experiments and statistical analyzes showed that the G allele compared to the A allele, may significantly increase the risk of AD.

It has been demonstrated that the *ECHDC3* gene influences plasma lipid levels (14). In addition, upregulation of the *ECHDC3* gene has been reported in patients with acute myocardial infarction, and the product of this gene has been associated with fatty acid biosynthesis in mitochondria (15). *ECHDC3* regulation is impaired in the brains of AD patients (16). A genomic-wide association study has also recently reported that rs7920721 is mainly associated with individuals lacking the APOE ε4 allele (17). The risk locus rs7920721 has also been reported through case-control and AD-related meta-analyzes (18, 19).

Although the brain has very high concentrations of long-chain omega-3 and omega-6 fatty acids, there is no definitive explanation for how these fatty acids contribute to different signaling cascades in AD (20, 21). However, studies of AD pathology have confirmed a decrease in docosahexaenoic acid (DHA) levels in the brain, mainly in the hippocampus. Hippocampus lesions are associated with learning and memory problems, a sign of the onset of AD (22). As it is increasingly proven that AD is associated with altered fatty acid metabolism, fatty acid concentrations can be potential biomarkers of the disease (23). Other biomarkers are polymorphisms. Given the role of genes in lipid metabolism in AD, it appears that polymorphisms of these genes can be considered biomarkers of AD.

As mentioned, the *ECHDC3* gene encodes an enzyme that affects levels of plasma lipids, and mutations or changes in its expression have been observed in vascular diseases and AD. The present study investigated the relationship between rs7920721 single nucleotide polymorphism in this gene and the incidence of AD. The results showed the role of this polymorphism in increasing the risk of AD. In this respect, similar research was conducted, which is explained below.

Tábuas et al. (2020) examined loci associated with AD and found that several loci, including *ECHDC3*, were involved in AD (24). Yu et al. (2020) studied transcript profiles of functional brain networks at different stages of AD. The results showed 15 AD-related susceptibility genes. In particular, *ECHDC3* and *HS3ST1* showed the strongest positive and negative gene association, respectively (25). Tan et al. (2021)

examined the association of AD risk variants with (i) gene expression, (ii) amyloidosis, (iii) tauopathy, and (iv) neurodegeneration. In total, 27 variants were identified associated with regulating 21 adjacent genes in blood and brain samples. It found eleven variants (especially the new variants in *ADAM10*, *IGHV1-68*, and *SLC24A4*/*RIN3*) with cerebral amyloidosis. Also, find seven variants (especially in INPP5D and *PTK2B*) with cerebral tauopathy and eight variants (especially in *ECHDC3* and *HS3ST1*) with neurogenesis (26). The present study investigated the role of rs7920721 polymorphism in the *ECHDC3* gene (AD). It explores the Tetra ARMS PCR method and is similar to other studies in this field. Locus is associated with AD.

Lambert et al. (2013) conducted a meta-analysis of approximately 74,000 Europeans with AD and identified 11 new loci associated with the disease. They showed that rs7920721 is a locus associated with an increased risk of AD (18). This finding is consistent with the results of the present experiment. Desikan et al. (2015) showed that the pleiotropic effects of rs7920721 near the *ECHDC3* gene in AD patients affect plasma lipid and C-reactive protein levels. In their genomic association study, in more than 200,000 people, 55 loci were associated with an increased risk for AD. A meta-analysis of about 29,000 AD patients and 114,000 healthy individuals identified two SNPs affecting AD, including rs13113697 near the *HS3ST1* gene and rs7920721 near the *ECHDC3* gene. They also showed that the regulation of these two genes (*HS3ST1* and ECHDC3) in the brains of AD patients changed compared to healthy individuals. These genetic changes caused changes in plasma lipid and C-reactive protein levels in people with polymorphism (16). The present study, in line with the above research, showed the role of rs7920721 in the incidence of AD.

Jun et al. (2017) conducted a genome-wide study to find new AD-associated loci. People with AD from different European, African-American, Japanese and Israeli-Arab races participated in this study. Their results showed the presence of polymorphisms in *PFDN1*/*HBEGF*, *USP6NL*/*ECHDC3*, and *BZRAP1-AS1* genes that could be associated with AD. One of the SNPs they reported was rs7920721 (17), which is consistent with the present study.

Liu et al. (2017) conducted a case-control study of association mapping using proxies in families with a history of twelve common diseases, including AD. This study was performed on the profiles of about 116 thousand individuals in the UK Biobank. The results of their research identified four new loci for AD, eight loci for coronary artery disease, and five for type 2 diabetes. One of the risk loci identified for AD was rs7920721 (19). The rs7920721, based on the results present study, was introduced as a locus associated with the risk of AD.

Yin et al. (2019) examined the association of rs10164112 polymorphism in the *STARD6* gene and rs7920721 near the *ECHDC3* gene with AD patients carrying the APOE ε4 allele in the Chinese population. Their results showed that rs10164112 could be considered a risk factor in individuals carrying the APOE ε4 allele. However, their statistical results did not establish a significant relationship between rs7920721 and individuals having the APOE ε4 allele (13). This observed difference may be due to the number of participants in the experiment or the population being studied.

The relationship between rs7920721 polymorphism in the *ECHDC3* gene and AD in the Iranian popular has been reported. The findings are consistent with other studies in other areas and confirm the role of rs7920721 in increasing the risk of AD. The results of the present study generally showed that the genotypic and allelic frequencies in rs7920721 in the *ECHDC3* gene in AD patients are significantly different from healthy people, and the presence of the G allele may increase the risk of AD compared to the A allele. Since similar results have been reported in similar studies, rs7920721 can be used as a potential biomarker for AD. Its use at the clinical level requires further studies, which are expected to be considered in future research.

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