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Genetic association of *ABCA7* and *PSEN1* polymorphisms with Alzheimer's disease in the northeast Algerian population: Exploring risk factors

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder with a strong genetic component. This research aims to identify the relationship between *ABCA7* rs3764650, *PSEN1* rs165932, and AD in the northeast Algerian population and investigate genetic risk factors contributing to disease susceptibility. A case-control study was performed with 98 patients and 156 controls. DNA was isolated from blood samples by salting out. Genotyping of *ABCA7* and *PSEN1* polymorphisms was conducted using PCR-RFLP. Significant associations were observed between *ABCA7* rs3764650 and AD under dominant and additive models. Similarly, *PSEN1* rs165932 was associated with a higher risk of AD under dominant, recessive, and additive models. The frequency of the *ABCA7* G allele was significantly associated with *PSEN1* T allele carriers (P=0.033), with no significant association observed in non-carriers. In contrast, the *PSEN1* T allele frequency was significant in both *ABCA7* G allele carriers (P=0.006) and non-carriers (P=0.001). Allelic frequencies for *ABCA7* and *PSEN1* were higher in late-onset cases (P=0.003; P< 0.001) and females (P=0.006; P< 0.001). This study highlights the association of the *ABCA7* rs3764650 G and *PSEN1* rs165932 T alleles with AD susceptibility, particularly in females and late-onset cases, suggesting their relevance as genetic markers of disease risk.

Keywords: Alzheimer's disease, polymorphisms, *ABCA7*, *PSEN1*, northeast Algerian population

INTRODUCTION

Alzheimer's disease (AD) is a prevalent form of dementia defined by a neurological process that advances over time. This condition manifests as a decline in cognitive functions, impaired reasoning, and behavioral changes caused by hippocampal alterations and the loss of nerve cells and synapses, ultimately leading to cerebral atrophy [1].

The major physiological mechanisms underlying AD follow the amyloid cascade hypothesis [2]. β-amyloid (Aβ) peptides form extracellular plaques that disrupt neuronal connections and contribute to damage [3]. Concurrently, abnormal hyperphosphorylation of Tau protein leads to intracellular deposits that impede nutrient transport, resulting in neuronal death [4]. Furthermore, recent investigations have highlighted the role of inflammatory responses, particularly involving immune cells activated by Aβ plaques and neurofibrillary tangles, that release various proinflammatory molecules leading to the disease progression [5,6].

AD is a complicated disorder caused by various factors. An established risk factor is age, with a significant increase in risk after 65 [7]. Several other factors can affect the probability of acquiring AD, including education, mental and physical activity, diet, blood pressure, smoking, and social engagement [8].

In terms of genetic components, the genetic basis of AD varies depending on its type. Familial or

early-onset AD affects individuals under 65 years and accounts for 1 to 5% of all AD cases. It is caused by autosomal dominant mutations in three key genes: *Amyloid Precursor protein* (*APP*), *Presenilin 1* (*PSEN1*), and *Presenilin 2* (*PSEN2*) [9]. *PSEN1* mutations are the most common, accounting for 30-70% of cases, followed by *APP* mutations at 10-15% and *PSEN2* mutations in 5% of cases. These mutations lead to the overproduction of amyloid-beta peptides, contributing to the formation of amyloid plaques [10]. For the more prevalent sporadic or late-onset AD, which affects individuals aged 65 and over and constitutes 95% of AD cases, the strongest genetic risk factor is the *Apolipoprotein E* (*APOE)* ε4 allele [9]. Carrying one copy of the ε4 allele increases the risk of developing AD by 3-7 times, while two copies can increase the risk by up to 12 times compared to those without this allele. However, this allele is neither necessary nor sufficient to cause the disease, as other genetic factors (such as *ABCA7*, *CR1*, *CLU*, *CD33*, *CD2AP*, and *TREM2*) play important roles [10-12].

The *ATP-binding cassette subfamily A member 7* (*ABCA7*) gene, located at position 19p13.3 on chromosome 19, encodes the ABCA7 protein expressed in brain tissue, particularly in the hippocampus [13]. This protein plays a vital role in accumulating Aβ and forming plaques, similar to that of APOE [14]. Several single nucleotide polymorphisms (SNPs) within *ABCA7* have been linked to an elevated risk of AD, including rs3764650, rs3752246, rs4147929, and rs78117248 [15]. Among these, the intronic rs3764650 (T>G) is notable for its consistent association with AD across diverse populations and genetic models [15,16].

Recent studies have highlighted the significant role of *ABCA7* polymorphisms in AD susceptibility, with various genetic variants influencing disease risk across populations. A meta-analysis by Ma et al. [17] analyzing 16 case-control studies confirmed that common *ABCA7* variants, particularly rs3764650, rs3752246, and rs4147929, are linked to increased AD risk, with loss-of-function (LOF) mutations posing an even greater susceptibility. The study also noted ethnic differences in risk levels, suggesting complex gene-environment interactions. Similarly, Le Guennec et al. [18] identified significant enrichment of rare LOF and damaging missense variants in French early-onset AD cases, leading to a 3.4-fold increased risk, with findings reinforced by a meta-analysis including Belgian data. On a functional level, Vasquez et al. [19] showed that the rs3764650 T allele, which reduces AD risk, is linked to increased *ABCA7* expression, though overall *ABCA7* levels remain elevated in AD patients likely as an insufficient compensatory response. Further highlighting population-specific dynamics, Wang et al. [20] reported that the rs3764650 G and rs4147929 A alleles are associated with heightened AD risk in the southern Chinese population, particularly among *APOE* ε4 carriers. These studies underscore the multifaceted role of *ABCA7* in AD pathogenesis, with both common and rare variants contributing to disease risk, and highlight its potential as a therapeutic target. However, the exact mechanisms by which *ABCA7* influences AD progression remain unclear, warranting further research.

PSEN1 gene is located on chromosome 14q24.2 and encodes a multifunctional protein implicated in cell surface reception, modulation of intracellular protein processing, and apoptosis [21]. While most associations involve early-onset AD cases, certain variants of the *PSEN1* gene such as rs165932 (G>T) are linked to late-onset AD [22,23].

This study explored the association between the rs3764650 and rs165932 variants with AD in the northeast Algerian population. Additionally, our goal was to identify and understand various risk factors that could contribute to susceptibility to AD.

MATERIALS AND METHODS

Ethics statement

This case-control study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Dr. Benbadis University Hospital Center of Constantine (Reference Number: CE/CHUC/10/12-2024). Informed consent was obtained from all participants to participate in the study.

Study population

A cohort of 254 participants, comprising 98 patients diagnosed with AD from the Department of Neurology at the University Hospital Center of Constantine in East

Algeria, and 156 healthy controls were included in this study. The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [24] and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS/ADRDA) [25] provided the guidelines for AD diagnosis. Cognitive function in AD patients was evaluated using the Mini-Mental State Examination (MMSE), employing a scale of 0-30, where a higher value indicates improved cognitive functioning. The study exclusively focused on individuals with confirmed AD, ensuring their exclusion from any other form of dementia or neurological disorders. Control subjects, including healthy volunteers, were in good health and free from neurodegenerative diseases or any other conditions that could potentially interfere with AD. The patients and controls were of the same ethnicity and originated from the same region of northeastern Algeria.

DNA extraction

Genomic deoxyribonucleic acid (DNA) was extracted from 4 ml of peripheral blood using the salting-out technique [26]. The isolated DNA was subsequently evaluated for purity and concentration using a Nanodrop (Thermo Scientific, NanoDrop 8000).

Molecular testing

Genotyping of ABCA7 rs3764650

The *ABCA7* rs3764650 SNP was genotyped using restriction fragment length polymorphism (PCR-RFLP) using the following primers: forward 5'ATCCGTGCTATGTGGACGAC3' and reverse 5'ACCTTGAGCACCAGAACCAG 3'. The PCR reaction was conducted in a total volume of 25 µl, containing 50 ng of genomic DNA, 1x PCR buffer, 1 mmol/L of dNTPs, 1.5 mM MgCl2, 3% DMSO, 0.5 U of Taq DNA polymerase, and 0.4 µM for each primer. The reaction conditions involved an initial denaturation at 95°C for 5 min, followed by 35 cycles at 95°C for 30 s, 59°C for 45 s, and 72°C for 30 s, with a final extension at 72°C for 7 min; 642 bp fragments from the PCR product were examined using 3% agarose gel electrophoresis and GelRed staining at 100 V for 30 min. The fragments were digested using HpyCH4III restriction enzymes (New England, BioLabs, #R0618L), incubated at 37°C for 60 min, and subsequently heated to 65°C for 20 min. Genotypes were identified through electrophoresis of the digested fragments on a 3% agarose gel at 100 V for 1 h, visualized using a molecular imager gel doc XR system, and analyzed with Image Lab software 6.1. Distinct band patterns enabled genotype interpretation: homozygous GG displayed three bands at 354 bp, 152 bp, and 136 bp; heterozygous GT showed four bands at 490 bp, 354 bp, 152 bp, and 136 bp; and homozygous TT was characterized by two bands at 490 bp and 152 bp.

Genotyping of PSEN1 rs165932

The PCR-RFLP technique was employed to genotype the *PSEN1* rs165932 SNP using the primer sequences: forward 5′ CACCCATTTACAAGTTTAGC 3' and reverse 5′ CACTGATTACTAATTCAGGATC 3′. The PCR reaction was conducted in a total volume of 25 µl, including 50 ng of genomic DNA, 1x PCR buffer, 0.6 mmol/L of dNTPs, 2 mM MgSO4, 2% DMSO, 2 U of Taq DNA polymerase, and 0.2 µM for each primer. The PCR conditions involved an initial denaturation at 94°C for 5 min, followed by 35 cycles at 94°C for 30 s, 45°C for 1 min, and 72°C for 30 s, with a final extension at 72°C for 7 min. The PCR products were subjected to 3% agarose gel electrophoresis at 100 V for 30 min. The products were digested for 15 min at 37°C using BamH1 restriction enzymes (New England, BioLabs, #R0136S) and visualized through 3% agarose gel electrophoresis at 100 V for 1 h. We identified three genotypes: homozygotes GG and TT showed single bands at 182 bp and 199 bp, respectively, while heterozygotes TG displayed two bands at 199 bp and 182 bp.

Statistical analysis

Microsoft Excel 2020 and SPSS software version 27.0 (IBM SPSS) were used for statistical analysis. The chi-square test ($\chi 2$) was applied to determine the Hardy-Weinberg equilibrium (HWE), analyze qualitative variables with data presented as frequencies and percentages, and evaluate allelic and genotypic frequencies under various genetic models. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each genetic model using $\chi 2$. Additionally, logistic regression analysis was employed to compute ORs (95% CI) for different genetic models, adjusting

Table 1. Descriptive features of AD and control groups

Descriptive features	AD cases n (%) n = 98	Controls n (%) n = 156	P
Age (mean and SD)	69.60±9.40	69.65±10.12	0.957
Sex			
Female	59 (60.20)	90 (57.69)	0.692
Male	39 (39.80)	66 (42.31)	
Education			
Illiterate	40 (40,82)	53 (33,97)	0.271
Literate	58 (59.18)	103 (66,03)	
MMSE	13.65±4.44	29.50±1.26	< **0.001***
Hypertension	57 (58.16)	48 (30.77)	< **0.001***
Diabetes	37 (37.76)	36 (23.08)	**0.012***

SD – standard deviation, MMSE – mini-mental status examination. The P values for quantitative variables were assessed using the Mann-Whitney U-test for non-parametric and asymmetrically distributed variables, while the χ^2 test was used for qualitative variables. A P<0.05 was considered significant.

for age and sex. Quantitative variables were compared between the two groups using the Mann-Whitney U non-parametric test, with results reported as mean values and standard deviations (SD). Statistical significance was defined as P< 0.05.

RESULTS

Descriptive characteristics in Alzheimer's: Cases vs. controls

This study included a total of 98 AD patients and 156 healthy controls. The descriptive characteristics of the participants are summarized in Table 1. The mean ages of the AD patients and the control group were comparable at 69.60±9.40 years and 69.65±10.12 years, respectively, with a predominance of females in both groups. No significant differences were observed between the two groups regarding age at onset, sex distribution, or educational level (P≥0.05). Additionally, MMSE scores were statistically significant (P<0.001), indicating that patients with AD had lower scores than healthy controls. Moreover, significant associations were observed with hypertension and diabetes, at P<0.001 and 0.012, respectively.

Analyzing the association between SNPs and AD

As detailed in Tables 2 and 3, the genotype distribution of *ABCA7* and *PSEN1* adheres to HWE for AD cases (P=0.841; P=0.812) and controls (P=0.074; P=0.111).

For genotypic frequencies, *ABCA7* rs3764650 exhibited a significant association (P=0.009), whereas *PSEN1* rs165932 displayed a stronger association (P<0.001). Similarly, for allelic frequencies, *ABCA7* rs3764650 was associated with AD (P=0.012), while *PSEN1* rs165932 demonstrated a stronger association (P<0.001).

Both genotypic and allelic frequencies revealed a statistically significant variation between controls and AD patients. However, *PSEN1* rs165932 showed a stronger association compared to *ABCA7* rs3764650 in terms of both genotypic and allelic frequencies.

For the rs3764650, the dominant (DOM) and additive (ADD) both showed a notable association with the disease (DOM: P=0.031; ADD: P=0.024), indicating that patients possessing the GG genotype have an increased likelihood of acquiring AD compared to individuals with GT and TT genotypes.

Furthermore, for rs165932, all models (DOM, recessive (REC), and ADD) demonstrated a high level of statistical significance (DOM: P<0.001; REC: P=0.005; ADD: P<0.001), indicating an elevated risk of AD in individuals carrying the T allele, particularly under the DOM and ADD genetic models.

Hence, the data were stratified based on both *PSEN1* allele T status to assess its influence on the relationship between *ABCA7* rs3764650 SNP and susceptibility to AD, and based on *ABCA7* allele G status to evaluate its effect on the relation between *PSEN1* rs165932 variant and susceptibility to the disease.

As shown in Table 4a, for individuals carrying the *PSEN1* allele T a notable difference was observed in the allele frequency within rs3764650 for *ABCA7* when compared to cases with controls (P=0.033), although the genotype frequencies were not significantly different. The G allele appeared more frequently in patients (26.5%) compared to controls (17%). Logistic regression revealed a higher association for the DOM and ADD following age and sex adjustments, (DOM: P=0.001; ADD: P<0.001).

In the stratification by ABCA7 allele G, as detailed in Table 4b, the genotype and allele frequencies were statistically significant for both carriers and non-carriers of the ABCA7 G allele (P < 0.05). However, the

Table 2. Genotypic, allelic frequencies and genetic models of *ABCA7* rs3764650 in AD cases and controls

***ABCA7* rs3764650**	**AD cases n (%) n=98**	**Controls n (%) n=156**	**P**	**OR (95% CI)**
Genotype			**0.009***	1.896 (1.187-3.029)
TT	54 (55.10)	107 (68.59)		
GT	38 (38.78)	48 (30.77)		
GG	6 (6.12)	1 (0.64)		
Allele			**0.012***	**1.753 (1.129-2.720)**
T	146 (74.49)	262 (83.97)		
G	50 (25.51)	50 (16.03)		
Dominant model				
GG+ GT vs TT	44 (44.90)	49 (31.41)	**0.031***	1.779 (1.055-2.999)
Recessive model				
GG vs GT+ TT	92 (93.88)	154 (98.72)	0.051	5.022 (0.993-25.402)
Additive model				
GT vs TT	38 (38.78)	48 (30.77)	0.100	1.569 (0.917-2.683)
GG vs TT	6 (6.12)	1 (0.64)	**0.024***	11.889 (1.396-101.265)

n – number of individuals, OR – odds ratio, CI – confidence interval, P was examined by the $\chi 2$ test and considered significant at <0.05.

Table 3. Genotypic, allelic frequencies and genetic models of PSEN1 rs165932 in AD cases and controls

***PSEN1* rs165932**	**AD n (%) n=98**	**Controls n (%) n=156**	**P**	**OR (95% CI)**
Genotype			**< 0.001***	2.124 (1.477-3.055)
GG	17 (17.35)	65 (41.67)		
TG	49 (50.0)	64 (41.03)		
TT	32 (32.65)	27 (17.31)		
Allele			**< 0.001***	2.238 (1.555-3.222)
G	83 (42.35)	194 (62.18)		
T	113 (57.65)	118 (37.82)		
Dominant model				
TT+ TG vs GG	81 (82.65)	91 (58.33)	**< 0.001***	3.403 (1.845-6.277)
Recessive model				
TT vs TG+ GG	66 (67.35)	129 (82.69)	**0.005***	2.316 (1.282-4.187)
Additive model				
TG vs GG	49 (50.0)	64 (41.03)	**0.001***	2.927 (1.527-5.612)
TT vs GG	32 (32.65)	27 (17.31)	**< 0.001***	4.532 (2.162-9.497)

n – number of individuals, OR – odds ratio, CI – confidence interval, P was examined by the $\chi 2$ test and considered significant at <0.05.

minor allele frequency (MAF) of the T allele remained unchanged between G allele carriers and non-carriers when comparing Alzheimer's disease cases and controls. However, after age and sex adjustments using logistic regression, the models for dominant, recessive, and additive traits were significant and linked to the possibility of acquiring AD for those carrying the G allele (DOM: P=0.001; REC: P=0.013; ADD: P<0.001).

To confirm the relationship between candidate gene SNPs and AD susceptibility, Table 5 provides evidence of a correlation between the rs3764650 variant of *ABCA7* and morbidity associated with AD. In the allele model, a significant association was identified without adjusting for age and sex (P=0.012). However, after adjustments, significant relationships were observed in the dominant (DOM, P=0.018), recessive (REC, P=0.048), and additive (ADD, P=0.004) models. Similarly, the rs165932 variant of the *PSEN1* gene showed a significant association within the allelic model (P=0.000) in the absence of adjustments for age and sex. After adjustments, notable associations were observed across the DOM (P<0.001), REC (P=0.005), and ADD (P<0.001). These results provide evidence of a relationship between the *ABCA7* rs3764650 and *PSEN1* rs165932 variants and the likelihood of AD morbidity.

Risk factors in AD

Interestingly, after stratifying by the age of onset, the genotypic and allelic frequencies of *ABCA7* rs3764650 showed significant associations with late-onset age

Table 4a. Association of *ABCA7* rs3764650 with risk of AD stratified by *PSEN1* allele T status

rs3764650	**Total**	***PSEN1* T+**	***PSEN1* T-**
MAF (AD/control)	0.255/0.164	0.265/0.170	0.206/0.146
Allele			
P	**0.012***	**0.033***	0.398
OR (95% CI)	1.753 (1.129-2.720)	1.760 (1.046-2.962)	1.515 (0.578-3.969)
Genotype (P)	**0.009***	0.054	0.346
DOM model (adjusted)			
P	**0.018***	**0.001***	0.160
OR (95% CI)	1.908 (1.115-3.263)	2.610 (1.448-4.703)	0.513 (0.202-1.301)
REC model (adjusted)			
P	**0.048***	0.061	-
OR (95% CI)	5.174 (1.018-26.312)	4.764 (0.928-24.459)	-
ADD model (adjusted)			
P	**0.004***	**<0.001***	0.160
OR (95% CI)	2.011 (1.242-3.256)	2.542 (1.499-4.312)	0.513 (0.202-1.301)

MAF – minor allele frequency, OR – odds ratio, CI – confidence interval. P for the genotype and allele were evaluated using the χ^2 test. DOM, REC, and ADD models were adjusted for age and sex using binary logistic regression.

Table 4b. Association of *PSEN1* rs165932 with risk of AD stratified by *ABCA7* allele G status

rs165932	**Total**	***ABCA7* G+**	***ABCA7* G-**
MAF (AD/control)	0.577/0.378	0.574/0.379	0.580/0.378
Allele			
P	**<0.001***	**0.006***	**0.001***
OR (95% CI)	2.238 (1.555-3.222)	2.273 (1.262-4.092)	2.213 (1.382-3.544)
Genotype (P)	<0.001*	0.022*	0.006*
DOM model (adjusted)			
P	**<0.001***	**0.001**	0.274
OR (95% CI)	3.617 (1.937-6.755)	2.610 (1.448-4.703)	1.341 (0.792-2.272)
REC model (adjusted)			
P	**0.005***	**0.013***	0.180
OR (95% CI)	2.385 (1.298-4.383)	3.382 (1.292-8.853)	1.641 (0.796-3.382)
ADD model (adjusted)			
P	**<0.001***	**<0.001***	0.168
OR (95% CI)	2.198 (1.514-3.190)	2.061 (1.344-3.160)	1.280 (0.901-1.820)

MAF – minor allele frequency, OR – odds ratio, CI – confidence interval. The P values for the genotype and allele were evaluated using the χ^2 test. DOM, REC, and ADD models were adjusted for age and sex using binary logistic regression.

Table 5. Relationship of candidate gene SNPs to AD risk

Gene	***ABCA7***	***PSEN1***
SNP	rs3764650	rs165932
Minor allele	G	T
Allele model		
P	0.012*	<0.001*
OR (95% CI)	1.753 (1.129-2.720)	2.238(1.555-3.222)
DOM model (adjusted)		
P	0.018*	<0.001*
OR (95% CI)	1.908 (1.115-3.263)	3.617 (1.937-6.755)
REC model (adjusted)		
P	0.048*	0.005*
OR (95% CI)	5.174 (1.018-26.312)	2.385 (1.298-4.383)
ADD model (adjusted)		
P	0.004*	<0.001*
OR (95% CI)	2.011 (1.242-3.256)	2.198 (1.514-3.190)

OR – odds ratio, CI – confidence interval. The χ^2 test was used to evaluate the P for the allele, while P for the DOM, REC, and ADD was calculated through binary logistic regression.

(P=0.011; P=0.003) but not with early-onset age (P=0.137; P=0.518), as detailed in Supplementary Table S1a. For *PSEN1* rs165932, stratification by onset age revealed a significant association between genotype and allele frequencies in late-onset cases (P<0.001). However, no significant association was observed for genotype (P=0.393) or allele frequencies (P=0.185) in early-onset cases, as shown in Supplementary Table S1b.

When stratifying *ABCA7* SNP by sex, a significant association was found in females with genotypic (P=0.005) and allelic (P=0.006) frequencies for rs3764650, whereas no significant correlation was detected in males (genotypic P=0.762; allelic P=0.484), as summarized in Supplementary Table S2a. For the *PSEN1* SNP, a significantly stronger association was observed in females for both genotypic (P<0.001) and allelic frequencies (P<0.001) compared to males. However, in males, allele frequency showed a significant association (P=0.014), whereas genotype frequency did not (P=0.073), as outlined in Supplementary Table S2b.

DISCUSSION

This case-control study aimed to explore the relationship between SNPs rs3764650 in *ABCA7* and rs165932 in *PSEN1* and to study their potential impact on susceptibility to AD within the Northeast Algerian population. Additionally, we assessed the predisposition to AD while considering its correlation with other risk factors.

Our study revealed a notable correlation between the *ABCA7* rs3764650 T>G variant and susceptibility to AD. Subjects with the G allele showed a heightened likelihood of developing AD compared to those without this allele. This observation aligns with the findings of Hollingworth et al. [27], who identified the G allele of rs3764650 as a potential risk factor for AD, establishing it as a novel susceptibility locus. Supporting these findings, numerous genome-wide association studies (GWAS) and investigations across diverse populations, including Caucasian [7], Asian [28], and African American [29,30], have consistently demonstrated a significant correlation between this *ABCA7* variant and a higher likelihood of developing AD. In our control group, the frequency of the G allele aligns with that reported in Caucasian populations [7], appears lower than in African American controls [29,30], and higher than in Asian populations [28]. These interpopulation differences highlight the importance of considering ethnic diversity when evaluating genetic risk factors for AD and may help explain the variability in AD prevalence across populations. However, conflicting results have been reported in other studies, suggesting that the T allele plays a protective role against AD [14,19], whereas others have found no relationship between rs3764650 and susceptibility to this disease [1,31].

The identified link between the *ABCA7* rs3764650 T>G SNP and susceptibility to AD has stimulated the exploration of the underlying mechanisms. The *ABCA7* gene encodes the ABCA7 protein found in microglial cells, with specific localization in CA1 hippocampal neurons [5]. Recent studies have highlighted that a deficiency in *ABCA7* promotes the amyloidogenic process, contributing to the development of Aβ plaques by elevating the activity of β-secretase, causing Aβ to split apart from APP [7,32]. Research suggests that the intronic *ABCA7* variant influences its expression levels in the brain, with investigations revealing increased *ABCA7* mRNA expression in AD-affected brains compared to control individuals [14,33]. The presence of the G allele in rs3764650 is linked to the emergence of neuritic plaque pathology due to a functional deficiency of the *ABCA7* gene [34,35]. Conversely, possessing the T allele in this *ABCA7* variant exerts a protective effect against Aβ plaque formation in AD [13,19].

Our study uncovered a robust correlation between the G > T variant of *PSEN1* rs165932 and disease predisposition, highlighting the significant role of the T allele as a potential contributor to increased susceptibility in individuals with this neurodegenerative disorder. Notably, the risk associated with the TT genotype was twice as high in patients with AD than in the controls. This association was initially identified by Wragg et al. [36], who suggested that the TT genotype may be a potential contributor to late-onset AD. Our findings align with investigations conducted in Spanish [37], UK [21,38], Brazilian [39], Japanese [40], and Chinese [23] populations, consistently emphasizing the link between this variant and AD. Conversely, Brooks et al. highlighted a relationship between the G allele and elevated susceptibility to AD [41], while Ezquerra et al. found that the GG genotype protects against the disease [42].

PSEN1 variants impact AD by affecting the cleavage of APP, leading to increased Aβ aggregation and the creation of neuritic deposits [43]. Specifically, rs165932, located in intron 3′ between exons 8 and 9 of *PSEN1*, influences exon transcription by altering pre-mRNA splicing. This modification potentially regulates PSEN1 expression and function [22,23]. Janssen et al. reported mutations in exon 8 of *PSEN1* in early-onset AD patients, implying its function as a risk factor in AD development [44]. Furthermore, a study conducted by Brooks et al. identified mutations at the splice acceptor site preceding exon 9 of *PSEN1*, leading to the skipping of exon 9 during pre-mRNA splicing. This deletion results in an altered PSEN1 protein that may disrupt APP processing, thereby contributing to AD pathogenesis [41].

Nevertheless, divergent outcomes emerge across different populations, with certain studies indicating an absence of association between the *PSEN1* genetic variant and AD among Caucasian [45], Russian [46], African American [47], and Asian [48] populations.

Age and sex have proven to be critical contributors to AD susceptibility. Our research offers new perspectives on the genetic factors linked to the disease, particularly concerning the age of onset and sex. The identified

associations between the genetic variants rs3764650 and rs165932 and late-onset AD (≥65 years) emphasize the significance of these variations in the context of disease susceptibility. These findings align with those of previous GWAS studies [6,49], further strengthening the evidence regarding these specific genetic markers.

These results indicate that genes could influence AD risk differently in males and females, revealing sex-specific associations at various loci linked to the disease. Moreover, the correlation between female sex and *ABCA7* and *PSEN1* variants enhances our understanding of AD predisposition, which is consistent with previous research [50-52]. This observation further implies that specific genetic factors may exert distinct effects on cognitive resilience in males and females [50,52,53].

Additionally, we explored other potential risk factors associated with AD. One of these was hypertension, which was investigated and revealed as highly significant P<0.001. These findings highlight hypertension as a significant contributor to AD risk and are consistent with results reported by Ballard et al. [54], Kivipelto et al. [55], Qiu et al. [56], and a meta-analysis [8], all pointing towards high blood pressure significantly contributing to the likelihood of developing AD, due to disruptions affecting blood-brain barrier [57].

Furthermore, our findings revealed a notable relationship between diabetes and neurodegenerative disease (P=0.012). Consistent with our observations, other studies reported that diabetes could contribute to the risk of developing mild cognitive impairment or AD [58,59]. They also suggested that elevated blood sugar levels impact the aggregation and accumulation of Aβ protein within brain lesions [60].

Exploring the biological mechanisms underlying these associations is essential for further investigation, as it could unveil new and innovative therapeutic targets.

CONCLUSIONS

This research has provided important findings regarding the relationship between the G allele at rs3764650 in *ABCA7* and the T allele at rs165932 in *PSEN1*, identifying them as significant risk factors contributing to increased susceptibility to AD within the northeastern Algerian population. Noteworthy correlations were observed between these genetic variations and late-onset age groups and among females. These findings show the genetic nuances of AD within this specific population, emphasizing the need for targeted research. Moving forward, rigorous validation with a larger Algerian population sample and multicentric studies are crucial to confirm and generalize the associations between *ABCA7*, *PSEN1* genes, and AD, thereby advancing our understanding of the genetic foundations of this complex neurodegenerative disorder.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1a. Association of *ABCA7* rs3764650 with AD cases stratified by age of onset

	N	Genotypes n (%)			P	Alleles n (%)		P	OR (95% CI)
ABCA7		TT	GT	GG		T	G		
Age < 65					0.137			0.518	1.286 (0.601-2.752)
AD cases	25	12 (48)	11 (44)	2 (8)		35 (70)	15 (30)		
Controls	48	24 (50)	24 (50)	0 (0)		72 (75)	24 (25)		
Age ≥ 65					**0.011***			**0.003***	2.304 (1.318-4.030)
AD cases	73	42 (57.53)	27 (36.99)	4 (5.48)		111 (76.03)	35 (23.97)		
Controls	108	83 (76.85)	24 (22.22)	1 (0.93)		190 (87.96)	26 (12.04)		

N – total, n- number of individuals, OR – odds ratio, CI – confidence interval, P was examined by χ2 test and considered significant <0.05.

Supplementary Table S1b. Association of *PSEN1* rs165932 with AD cases statified by age of onset

	N	Genotypes n (%)			P	Alleles n (%)		**P**	**OR (95% CI)**
PSEN1		GG	TG	TT		G	T		
Age < 65					0.393			0.185	1.595 (0.8-3.18)
AD cases	25	6 (24)	13 (52)	6 (24)		25 (50)	25 (50)		
Controls	48	19 (39.58)	21 (43.75)	8 (16.67)		59 (61.46)	37 (38.54)		
Age ≥ 65					< 0.001*			**< 0.001***	2.529 (1.643-3.891)
AD cases	73	11 (15.07)	36 (49.32)	26 (35.62)		58 (39.73)	88 (60.27)		
Controls	108	46 (42.59)	43 (39.81)	19 (17.59)		135 (62.5)	81 (37.5)		

N – total, n- number of individuals, OR – odds ratio, CI – confidence interval, P was examined by χ2 test and considered significant <0.05.

Supplementary Table S2a. Association of *ABCA7* genotypes and alleles with AD across sex.

	N	Genotypes n (%)			P	Alleles n (%)		P	OR (95% CI)
ABCA7		TT	GT	GG		T	G		
Female					0.005*			**0.006***	2.197 (1.247-3.873)
AD cases	59	30 (50.85)	24 (40.68)	5 (8.47)		84 (71.19)	34 (28.81)		
Controls	90	62 (68.89)	28 (31.11)	0 (0)		152 (84.44)	28 (15.56)		
Male					0.762			0.484	1.290 (0.631-2.638)
AD cases	39	24 (61.54)	14 (35.9)	1 (2.56)		62 (79.49)	16 (20.51)		
Controls	66	45 (68.18)	20 (30.3)	1 (1.52)		110 (83.33)	22 (16.67)		

Supplementary Table S2b. Association of *PSEN1* genotypes and alleles with AD across sex.

	N	Genotypes n (%)			P	Alleles n (%)		P	OR (95% CI)
PSEN1		GG	TG	TT		G	T		
Female					< 0.001*			**< 0.001***	2.406 (1.496-3.870)
AD cases	59	8 (13.56)	34 (57.63)	17 (28.81)		50 (42.37)	68 (57.63)		
Controls	90	39 (43.33)	37 (41.11)	14 (15.56)		115 (63.89)	65 (36.11)		
Male					0.073			**0.014***	2.033 (1.152-3.588)
AD cases	39	9 (23.08)	15 (38.46)	15 (38.46)		33 (42.31)	45 (57.69)		
Controls	66	26 (39.39)	27 (40.91)	13 (19.7)		79 (59.85)	53 (40.15)		

N – total, n - number of individuals, OR – odds ratio, CI - confidence interval, P was examined by χ2 test and considered significant <0.05.

RESEARCH DATASET

The raw data underlying this article is available as an online supplementary research dataset:
https://www.serbiosoc.org.rs/NewUploads/Uploads/Achou%20et%20al_Dataset.pdf