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Abstract

Objectives: Amnestic mild cognitive impairment (aMCI), a subtype of mild cognitive impairment, is characterized by memory impairment often accompanied by deficits in executive functioning, particularly in planning. While it is well established that individuals with aMCI experience planning difficulties, the neural mechanisms underlying these impairments remain largely unexplored. Understanding the genetic and molecular factors contributing to amyloid-related cognitive impairment (aMCI) is essential for advancing treatment strategies. This study aimed to investigate the association between specific gene polymorphisms (NKPD1, APOE, XRCC1, PEMT) and the risk of developing aMCI, as well as the influence of gender differences on aMCI susceptibility.

Methods: We examined the relationship between gene polymorphisms and aMCI risk in a cohort of 263 individuals with aMCI and 83 with non-amnestic MCI (naMCI). Polymorphisms in the APOE, XRCC1, NKPD1, and PEMT genes were genotyped, and gender differences were analyzed.

Results: Our findings revealed that the CC and CT genotypes of the APOE rs429358 polymorphism were associated with an increased risk of aMCI. Notably, the ε4 allele was more prevalent in the aMCI group (22.5%) compared to the naMCI group (3.5%). Additionally, three SNPs (rs7946, rs25489, rs28469095) were linked to a higher aMCI risk. The XRCC1 rs7946 polymorphism, specifically the TC and CC genotypes, was associated with an elevated risk of age-related macular degeneration among older individuals.

Conclusions: The APOE rs429358 and XRCC1 rs7946 polymorphisms may influence the susceptibility to aMCI in elderly Korean populations, suggesting a potential genetic basis for aMCI risk. Further research is warranted to explore these associations and their implications for aMCI treatment.

Introduction

Amnestic mild cognitive impairment (aMCI) is widely regarded as a precursor to Alzheimer's disease (AD), with a significant proportion of individuals with aMCI progressing to AD dementia. Approximately 10–15% of aMCI patients develop dementia each year, and within six years, up to 80% of aMCI cases transition to AD dementia [1] Given that aMCI represents a subtype of mild cognitive impairment (MCI) most strongly associated with AD progression [2, 3]. Early diagnosis and intervention are critical for improving outcomes in patients at risk of cognitive decline. Treatment with acetylcholinesterase inhibitors has been shown to potentially slow the progression of aMCI to AD dementia [4, 5], emphasizing the importance of early detection and therapeutic intervention.

The progression of aMCI can be further understood by categorizing the condition into early and late phases, which may provide valuable insights into its underlying pathophysiology and prognosis [6, 7]. A range of genetic factors,

including polymorphisms in genes such as PEMT, XRCC1, APOE, and NKPD1, have been implicated in the susceptibility to aMCI [8-11]. Understanding the genetic basis of aMCI is crucial for identifying individual risk factors, improving diagnostic accuracy, and potentially guiding personalized treatment strategies.

The apolipoprotein E (APOE) gene, which encodes a 299-amino acid protein involved in lipid transport in both the plasma and the central nervous system, plays a significant role in neurodegenerative diseases. APOE is integral to synaptic plasticity and the regulation of synaptic proteins [12]. Variations in the APOE gene are associated with a range of neurological conditions, including AD, Parkinson's disease (PD), multiple sclerosis (MS), and depression [13]. The ε4 allele of the APOE gene has been identified as a strong risk factor for early-onset AD and cognitive decline, while the ε2 allele may offer a degree of protection against neurodegenerative disorders [14] [15].

APOE is increasingly recognized as playing a crucial role in the development and progression of aMCI. It influences lipid homeostasis and inflammatory responses in the brain, and a correlation between cerebrospinal fluid levels of phosphorylated tau and APOE has been observed in individuals with cognitive impairment [16]. Research suggests that APOE polymorphisms, particularly the ε4 allele, are significantly associated with aMCI susceptibility [17]. This study focuses on the rs429358 polymorphism in the APOE gene and its influence on aMCI risk in a Korean population.

Recent advances in whole-exome sequencing (WES) technology have enabled detailed characterization of individual genetic landscapes, facilitating the identification of both common and rare variants that may be associated with disease risk. WES offers promising opportunities for uncovering the genetic basis of aMCI, providing insights into pathogenesis and guiding therapeutic interventions. The aim of this study is to identify causal genetic variants contributing to aMCI susceptibility, using WES data to uncover potential targets for treatment and management.

Materials and Methods

Patient demographics

The discovery dataset comprised 346 participants, including 263 aMCI patients (167 females, 96 males) and 83 healthy older adults, all of Korean ancestry, recruited from Soon Chun Hyang University Bucheon Hospital, South Korea, between January 2020 and July 2021. All participants were over 60 years of age (mean age: 74 ± 8 years; range: 60–85 years) and had at least 8 years of education (mean: 14 years, range: 9–18 years).

The aMCI patients met the diagnostic criteria proposed by the Mayo Clinic Alzheimer's Disease Research Center, including: (1) subjective memory impairment corroborated by the patient and an informant; (2) objective memory impairment documented by AVLT-delayed recall scores ≤1.5 SD below age- and education-adjusted norms (cutoff ≤4/12 correct responses for ≥8 years of education); (3) normal general cognitive functioning with an MMSE score of ≤24; (4) a Clinical Dementia Rating (CDR) of 0.5, with at least 0.5 in the memory domain; (5) minimal or no impairment in activities of daily living; and (6) absence of dementia according to the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria.

Participants were excluded if they had a history of stroke (HIS score ≥4), alcoholism, head injury, Parkinson's disease, epilepsy, major depression, other neurological or psychiatric conditions, major medical illnesses (e.g., cancer, anemia, thyroid dysfunction), or severe visual or hearing impairments. All assessments were conducted by a neuropsychiatrist experienced in structured interviews with both participants and informants.

All participants provided written informed consent for human-derived material research, and the study was approved by the Institutional Review Board (IRB) of Soon Chun Hyang University Hospital, Bucheon. This study complies with the ethical standards outlined in the Declaration of Helsinki.

Exome sequencing and bioinformatics Analysis

Genomic DNA was extracted from peripheral blood, and concentration was measured using a Qbit 4.0 fluorometer (Thermo Fisher Scientific). DNA quality was confirmed by gel electrophoresis. Coding exons were captured using the xGen Exome Research Panel V2 (Integrated DNA Technologies), and libraries were sequenced at over 100x coverage on the NovaSeq 6000 platform (Illumina) to generate 151 bp paired-end reads. Reads were aligned to the human genome reference (hg19) using Burrows-Wheeler Aligner. Duplicates were removed with Picard MarkDuplicates, and the Genome Analysis Toolkit (GATK) v4.1 was used for INDEL realignment, base-quality recalibration, and mutation calling via HaplotypeCaller. Variants were annotated with snpEff, and copy number variants were identified using XHMM. Read depth and coverage were validated with Integrative Genome Viewer (IGV).

The selection of SNPs associated to aMCI

All reported SNVs and INDELs from exome sequencing were initially filtered using DisGeNET with the keyword 'Alzheimer' (DisGeNET; Name: Alzheimer's Disease; CUI: C0002395). Variants with an allele frequency greater than 5% in the KRGDB database (http://152.99.75.168:9090/KRGDB/menuPages/intro.jst) were selected for further analysis. Finally, quality control was performed using PLINK 1.9b with the following parameters: --mind 0.1, --hwe 0.001, --geno 0.1, and --maf 0.05.

Statistical Analysis

Differences in age and education level between aMCI and naMCI patients were assessed using an independent samples t-test, conducted with SPSS 26.0 (SPSS Inc., Chicago, IL, USA). Gender, allele, and genotype frequency differences between the groups were evaluated using the Pearson chi-square test.

Hardy-Weinberg equilibrium, allele frequency, and genotype frequency analyses were performed using PLINK 1.9 software (https://www.cog-genomics.org/plink/). Bonferroni correction was applied to control for multiple comparisons and reduce the false discovery rate. The association between single nucleotide polymorphisms (SNPs) and the risk of aMCI was examined using PLINK's model option, under five inheritance models: codominant, dominant, recessive, overdominant, and log-additive. Adjustments were made for potential confounders, including Mini-Mental State Examination (MMSE) score, education level, and age. Statistical significance was defined as a two-tailed p-value < 0.05.

Results

Demographic information

A total of 346 unrelated participants were included in this study, consisting of 263 patients with aMCI and 83 with naMCI. The aMCI group comprised 163 females and 96 males, with a mean age of 65.40 ± 8.33 years (range: 50–80 years). The naMCI group included 59 females and 24 males, with a mean age of 66.30 ± 9.40 years (range: 50–80 years). There was no significant difference in gender distribution between the two groups ($P = 0.176$). (Table.1)

SNP Allele and Genotype Frequencies

Five SNPs associated with aMCI were identified and analyzed: rs7946 (PEMT), rs25489 (XRCC1), rs440446, rs429358 (APOE), and rs28469095 (NKPD1). The allele and genotype frequencies for each polymorphism are

presented in Table 2. The population distribution of all five aMCI-related polymorphisms was consistent with Hardy-Weinberg equilibrium (Table 3). A significant difference was observed in the rs429358 polymorphism of the APOE gene between the aMCI and naMCI groups (OR = 2.35, 95% CI = 1.276–4.354, P = 0.004861).

In a linear regression analysis evaluating the cumulative effect of all SNPs on age at onset, based on the genetic risk score, significant associations were found with PEMT (rs7946) and XRCC1 (rs25489). The PEMT rs7946 SNP showed a significant difference in genotype frequency between aMCI and naMCI patients (Beta = 1.86, P = 0.02162 in the additive model; Beta = 2.099, P = 0.04491 in the dominant model). Similarly, the XRCC1 rs25489 SNP demonstrated a significant association in the dominant model (Beta = 2.442, P = 0.04642). However, no significant differences were observed in the probability of aMCI with the APOE rs440446, rs429358, or NKPD1 rs28469095 polymorphisms with respect to age at onset (Table 4).

Relationship between APOE Genotypes and aMCI

Additionally, the frequencies of APOE ε4 genotypes and alleles were examined (P = 0.006). The frequency of the ε4+ allele was almost 7-fold higher in the aMCI group (22.5%) than in the naMCI group (3.5%)(Figure.1). Using logistic regression, the presence of the ε4 allele raised the probability of aMCI by a factor of 1.954. (Table5,6). Moreover, we separated the participants into their respective groups according to the APOE 4 status of each individual. Patients who had been diagnosed with naMCI had a much lower frequency of the A allele in their genomes than those who had been given a diagnosis of aMCI. This difference was discernible from a statistical point of view. After taking into account factors such as gender and age, the researchers found that PEMT rs7946 was associated with aMCI in both an additive and a dominant model (Table S1,S2). There were significant differences in the PEMT rs7946 allele or genotype distribution among the APOE 4 carriers between the aMCI patients and the controls (P = 0.01405). These differences were seen between the two groups. These changes were seen between the patients diagnosed with aMCI and the naMCI group. There is a substantial link between APOE 4 carriers and the XRCC1 rs25489 and the NKPD1 rs28469095 polymorphism respectively, a suitable genetic model was not supportive of this association (Table, S1-S3).

Discussion

In this present study, we identified APOE(rs440446, rs429358, repectively *P =0.03601, 0.004861*), PEMT(*P =0.04449*), XRCC1(*P =*0.02104), NKPD1(*P =*0.04098) and as a candidate causal gene potentially responsible for the one or two fold increased risk of aMCI by analysis of common variants. In the dominant model, the APOE rs429358 polymorphism was observed to enhance susceptibility to aMCI. Both of additive and dominant model, PEMT rs7946 polymorphism genotypes CC and TC were related with an elevated risk of aMCI by strified by aging in the Korean population. XRCC1 rs25489 polymorphism GC and CC in dominant model. and NKPD1 rs28469095 shows relationship with APOE E4 but no genetic model clearly explanation.

The ε4 allele of the APOE gene was overexpressed in aMCI compared to naMCIs, according to our findings. Using ε2 and ε3 allele carriers as a point of comparison, the presence of the ε4 allele increased the probability of aMCI. The allele for apolipoprotein epsilon 4 (Apo ε4) is the most often observed genetic risk factor for AD. Genome-wide association studies (GWAS) indicated that up to 40% of Alzheimer's disease (AD) patients possess the ApoE4 allele, and that the risk for AD rises further among ε4/ ε4 carriers[18]. Additionally, the APOE rs429358 polymorphism is overexpressed in the brains of PD patients

and greatly impacts the course of cognitive impairment[19]. Cognitive dysfunction is an important focus of research in PD and AD. While the concept of amnestic mild cognitive impairment (MCI) as a prodrome to AD has been recognized for many years, the construct of MCI in PD is a relative newcomer with recent development of diagnostic criteria. In this study, ε4 carriers had a significantly increased chance of acquiring aMCI, according to our findings.

According to the Parkinson's disease patients who exercised regularly were shown to completely avoid an increase in plasma homocysteine concentrations after L-DOPA treatment, in contrast to sedentary Parkinson's disease patients (PMID: 23153729). In patients who already have a diagnosis of Alzheimer's disease, the rate of cognitive decline positively correlated with the concentration of plasma homocysteine (PMID: 19484711). Furthermore, patients with moderate AD and elevated homocysteine concentrations experienced greater behavioral disturbances associated with major depressive disorder (PMID: 20808087). PEMT is an important catalyst involved in the production of homocysteine that increased concentrations of circulating homocysteine are associated with AD (PMID: 23153729). In addition, the functional single nucleotide polymorphism (rs7946) was related with plasma homocysteine concentrations in PEMT and the likelihood of sporadic Alzheimer's disease in a Han Chinese population (PMID: 21881829). We indicate that rs7946 is linked with progression from aMCI to AD in our sample.

The XRCC1 gene is located on chromosome 19q13.2 and consists of 17 exons and encodes a protein of 633 amino acids. Amino acid substitutions in the active protein binding domains may affect the function of this enzyme in mammalian orthologues. XRCC1 protein is recruited to the damage site of repair till the last stage of ligation, regulating and coordinating the whole process. XRCC1 plays a coordinating role for consecutive stages of base excision repair (BER) system and interacts with several proteins including human 8-oxoG DNA glycosylase (hOGG1), apurinic/apyrimidinic endonuclease (APE1), DNA polymerase β (POL β), DNA ligase III α and poly (ADP-ribose) polymerase 1 (PARP-1) [PMID: 17581577]. Because the various types of DNA damage could promote the development of human diseases thus those are illustrate how increasing knowledge of DNA-damage responses is providing opportunities for improving disease detection and management (PMID: 19847258). A few studies suggest that frequent BER gene polymorphisms, such as Arg194Trp on exon 6, Arg280His on exon 9, and Arg399Gln on exon 10, all of which result in nonsynonymous alterations, may have a role in AD neurodegeneration [PMID: 16221808, PMID: 19199873]. We observed in this cohort analysis that rs25489 is related with aMCI in the Korean population. Larger controlled studies are required to establish the impact of interaction with other genes and haplotypes or diplotypes of the XRCC1 gene on aMCI risk.

NKPD1 (hg38 chr19:45,149,744-45,160,982) is firstly reported large scaled genome-wide association study of AD that identified to have genome-wide significance for the rs597668(OR, 1.18; 95% CI, 1.07-1.29; P = 6.45×10−9) on chromosome 19q13.32(hg38 chr19:45,205,630) contains several other genes (NKPD1, TRAPPC6A, BLOC1S3, MARKL1, and MARK4) that could also represent the functional correlates underlying this association (PMID: 20460622, PMID: 22482448). It remains to be seen whether this region is genetically and functionally related as the associated SNP only maps ~300 kb distal to the APOE region that merely "tagging" the association with APOE and does not actually represent a novel AD locus in its own right. [PMID: 20955934] In a subsequent large AD cohort study, The exonic non-synonymous variant rs28469095 (MAF=0.091 and 1.97E-38) was linked with an increased risk for AD and

was predicted to have detrimental effects on gene function. [PMID: 30617256] In the FUMA gene-mapping study, a significant eQTL was observed for the APOE-locus, a change in expression for NKPD1 was reported in the hippocampus, and significant mQTLs were identified in the dorsolateral prefrontal cortex that are typically degenerated in the brains of Alzheimer's disease (AD) patients[PMID: 30617256].

Prior to the recent past, attempts to establish clinical predictors of progression to AD in individuals with MCI focused mostly on demographic characteristics, neurocognitive ability, and molecular markers. All of these factors were reported, and it was found that the development from MCI to AD was best predicted by ApoE status. Intriguingly, we have found aMCI-associated non-synonymous SNPs of rs440446 (APOE), rs429358 (APOE), rs7946 (PEMT), rs25489 (XRCC1), and rs28469095 (NKPD1) in the Korean population that have been previously linked to AD and dementia. In addition, the findings of this research might be used as a significant resource for the selection of prospective genes for functional follow-up tests, as well as the identification of targets for drug development and stratification strategies.

Limitation

Our research has significant limitations. First of all, since our research was cross-sectional, we did not investigate the order of exposures, the timing of outcomes, or the causal link between exposures and outcomes. Also, the limits of our sample size resulted in less accurate or convincing results. Consequently, these results should be regarded with care. In the future, we will increase our sample size to improve our results even more. Finally, our research did not account for linkage disequilibrium (LD) between SNPs. LD may influence the function of adjacent genes. Therefore, it is vital to have a deeper comprehension of the impact of LDs on samples. Since aMCI is a complex illness, other factors such as marital, mental, and nutritional condition should be included in the gathering of clinical data.

Conclusion

In conclusion, several genes and their polymorphism genotypes contribute to the etiology of aMCI. In the Korean population, our research indicates that the APOE gene and PEMT play a major role in the etiology of aMCI. Age variations also impact aMCI susceptibility. These findings are very important for comprehending the role and effect of several polymorphism genes in aMCI. We hope that these findings will contribute to the development of novel diagnostic and therapeutic approaches for aMCI.

Availability Statement

Ethics Statement

The Human Research and Ethics Committee of Soon Chun Hanyg University Hospital Bucheon examined and authorized the research projects that included subjects from the general population. In order to take part in this investigation, the patients and volunteers all gave their informed permission in writing form.

Author Contributions

Funding

Conflict of Interest

The authors report no conflicts of interest associated with this work.

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Table.1 Characteristics of the investigated groups of people.

	aMCI Patients (N=263)	*Control (N=83)*	*chi squared*	*P-value*
Age, Mean +-SD (yr.)	74.42±8.33	65.27±9.40	NA	0.001
MMSE	22.61±4.42	27.34±1.87	NA	0.001
CDR Score	57	285	33.759	0.001
Gender,male	96(28.9%)	24(37.1%)	1.833	0.176
APOE-ε4	77(22.5%)	12(3.5%)	7.615	0.006

P-value < 0.05

Table.2 allele frequency and genotype frequency.

GENE	*SNP*	*Alt Allele Count*		*chisq*	*P Value*	*OR*	*SE*	*95% CI*	*KRGDB Minor Allele freq.*	*Reference*
		aMCI	*naMCI*							
PEMT	rs7946	155	36	4.038	0.04449	1.53	0.2125	1.009-2.32	0.266705	
XRCC1	rs25489	69	11	5.324	0.02104	2.149	0.3382	1.107-4.169	0.106768	
APOE	rs440446	223	55	4.397	0.03601	1.486	0.1896	1.025-2.155	0.379942	
APOE	rs429358	88	13	7.93	0.004861	2.359	0.3124	1.279-4.352	0.0921283	
NKPD1	rs28469095	39	5	4.177	0.04098	2.6	0.484	1.007-6.713	0.0594752	

P-Value < 0.05, CI : Confidence Interval, KRGDB : Korean Reference Genome DataBase MAF > 0.05

Table.3 Hardy-Weinberg equilibrium test of the SNPs

SNP	*GROUP*	*Genotype (Ref_Hom/Hetero/Alt_Hom)*	*P-Value*
rs7946	aMCI+naMCI	28/135/169	0.8937

	aMCI	24/107/121	1
	naMCI	4/28/48	1
rs25489	aMCI+naMCI	1/78/254	0.06443
	aMCI	1/67/185	0.05866
	naMCI	0/11/69	1
rs440446	aMCI+naMCI	54/171/108	0.3679
	aMCI	45/134/75	0.309
	naMCI	9/37/33	1
rs429358	aMCI+naMCI	10/81/241	0.2929
	aMCI	9/70/174	0.5154
	naMCI	1/11/67	0.4153
rs28469095	aMCI+naMCI	2/40/291	0.6436
	aMCI	2/35/216	0.6475
	naMCI	0/5/75	1

P-Value > 0.05 (In accordance with HWE)

Table. 4 Association between genetic variants and aMCI risk stratified by age

SNP	***GENE***	***REF***	***ALT***	***Model***	***NMISS***	***BETA***	***Coefficient (T-test)***	***P***
rs7946	PEMT	T	C			1.868	2.308	0.02162*
rs25489	XRCC1	T	C			2.181	1.821	0.06956
rs440446	APOE	T	C	ADD	332	1.156	1.505	0.1333
rs429358	APOE	T	C			0.9537	0.9497	0.343
rs28469095	NKPD	T	C			0.01466	0.009983	0.992

rs7946	PEMT	T	C			2.099	2.013	0.04491*
rs25489	XRCC1	G	C			2.442	1.999	0.04642*
rs440446	APOE	G	C	DOM	332	1.991	1.792	0.0741
rs429358	APOE	G	C			1.457	1.243	0.2149
rs28469095	NKPD	C	T			-0.1078	-0.06843	0.9455
rs7946	PEMT	C	T			3.199	1.703	0.08958
rs25489	XRCC1	C	T			-10.24	-1.074	0.2836
rs440446	APOE	C	T	REC	332	0.7037	0.4963	0.62
rs429358	APOE	C	T			-1.048	-0.3418	0.7327
rs28469095	NKPD	C	T			2.301	0.3401	0.734

Table.5 Association between APOE ε4 carriers and aMCI

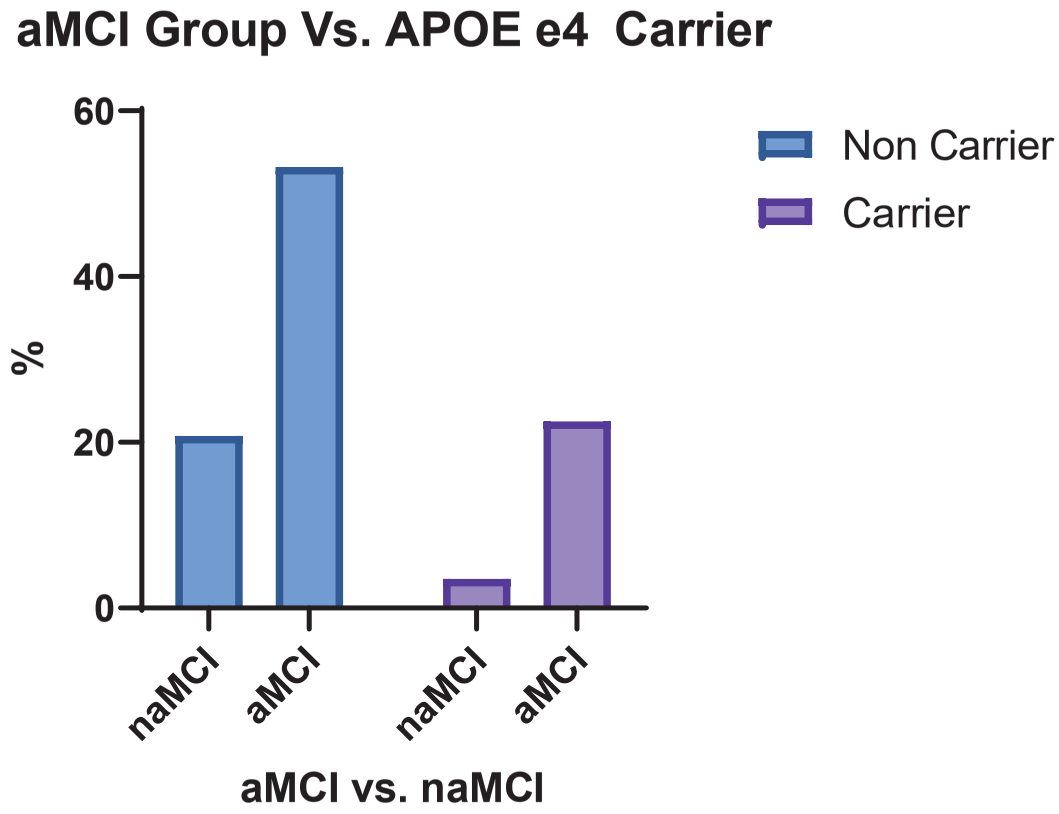
		Sample				TOTAL	chi sqaure	p-value
		naMCI		aMCI				
		Number	Percentage	Number	Percentage			
APOE(ε4)	Non Carrier	71_a	20.8%	182_b	53.2%	253	7.615	0.006
	Carrier	12_a	3.5%	77_b	22.5%	89		

P<0.05

Table. 6 Logistic regression analysis of APOE polymorphisms and aMCI risk.

	B	S.E.	Wald	P	Exp(B)
APOE_E4	0.670	0.316	4.497	0.034	1.954
APOE_E3	-0.601	0.287	4.384	0.036	0.548
APOE_E2	-0.243	0.439	0.306	0.580	0.785

Figure. 1


aMCI Group Vs. APOE e4 Carrier
60
40
20
0
%
Non Carrier
Carrier
naMCI
aMCI
naMCI
aMCI
aMCI vs. naMCI

Supplementary

S.1 Logistic Regression analysis of Additive, Gender, APOE_ε4 polymorphisms and aMCI risk

SNP	A1	NMISS	TEST	OR	SE	L95	U95	STAT	P
rs7946	T	332	ADD	1.672	0.2335	1.058	2.643	2.203	0.02763
			Gender	0.592	0.3016	0.3278	1.069	-1.738	0.08221
			APOE	2.417	0.3593	1.195	4.887	2.456	0.01405
rs25489	T	333	ADD	1.909	0.3708	0.923	3.949	1.744	0.08118
			Gender	0.6641	0.3025	0.3671	1.202	-1.353	0.1761
			APOE	2.178	0.3569	1.082	4.383	2.18	0.02923
rs440446	G	333	ADD	1.207	0.2294	0.7699	1.892	0.8202	0.4121
			Gender	0.6247	0.2986	0.3479	1.122	-1.576	0.1151
			APOE	1.959	0.3948	0.9034	4.246	1.703	0.08864
rs429358	C	332	ADD	1.785	1.037	0.2339	13.62	0.5589	0.5763
			Gender	0.6319	0.2988	0.3518	1.135	-1.536	0.1244
			APOE	1.215	1.159	0.1253	11.78	0.1677	0.8668
rs28469095	C	333	ADD	2.478	0.4905	0.9476	6.481	1.85	0.06428
			Gender	0.6242	0.2999	0.3468	1.124	-1.571	0.1161
			APOE	2.301	0.3565	1.144	4.628	2.338	0.0194

S2. Logistic Regression analysis of Dominant, Gender, APOE_ε4 polymorphisms and aMCI risk

SNP	A1	NMISS	TEST	OR	SE	L95	U95	STAT	P
rs7946	T	332	DOM	1.884	0.2816	1.085	3.271	2.249	0.02451
			Gender	0.5871	0.3017	0.325	1.06	-1.765	0.0775

			APOE	2.448	0.3599	1.209	4.957	2.488	0.01286
rs25489	T	333	DOM	1.903	0.3738	0.9148	3.96	1.722	0.08513
			Gender	0.6618	0.3024	0.3659	1.197	-1.365	0.1722
			APOE	2.175	0.3569	1.081	4.379	2.177	0.02945
rs440446	G	333	DOM	1.277	0.3036	0.7045	2.316	0.8063	0.42
			Gender	0.6279	0.2988	0.3496	1.128	-1.558	0.1193
			APOE	2.017	0.3827	0.9526	4.271	1.833	0.0668
rs429358	C	332	DOM	NA	NA	NA	NA	NA	NA
			Gender	NA	NA	NA	NA	NA	NA
			APOE	NA	NA	NA	NA	NA	NA
rs28469095	C	333	DOM	2.478	0.5159	0.9015	6.812	1.759	0.07859
			Gender	0.62	0.2998	0.3445	1.116	-1.595	0.1107
			APOE	2.289	0.3563	1.139	4.602	2.324	0.0201

S.3 Logistic Regression analysis of Recessive, Gender, APOE_ε4 polymorphisms and aMCI risk

SNP	A1	NMISS	TEST	OR	SE	L95	U95	STAT	P
rs7946	T	332	REC	1.817	0.5822	0.5805	5.688	1.026	0.305
			Gender	0.6149	0.299	0.3422	1.105	-1.626	0.1039
			APOE	2.293	0.3555	1.142	4.602	2.334	0.01958
rs25489	T	333	REC	NA	NA	NA	NA	NA	NA
			Gender	NA	NA	NA	NA	NA	NA

			APOE	NA	NA	NA	NA	NA	NA
			REC	1.198	0.434	0.5118	2.806	0.4169	0.6767
rs440446	G	333	Gender	0.618	0.2981	0.3445	1.109	-1.614	0.1065
			APOE	2.141	0.3754	1.026	4.468	2.028	0.04261
			REC	1.526	1.128	0.1671	13.93	0.3744	0.7081
rs429358	C	332	Gender	0.6272	0.2984	0.3495	1.126	-1.563	0.118
			APOE	2.187	0.3645	1.071	4.467	2.147	0.0318
			REC	NA	NA	NA	NA	NA	NA
rs28469095	C	333	Gender	NA	NA	NA	NA	NA	NA
			APOE	NA	NA	NA	NA	NA	NA