Türk Biyokimya Dergisi [Turkish Journal of Biochemistry–Turk J Biochem] 2010; 35 (3) ; 163–171.

Opinion [Görüş]

Yayın tarihi 6 Eylül, 2010 © TurkJBiochem.com

[Published online 06 September, 2010]

APOE Epsilon4 Allele Frequency in Patients with Dementia in Different Ethnic and Geographic Groups

[Farklı Etnik ve Coğrafik Gruplardaki Demanslı Hastalarda APOE Epsilon4 Allel Sıklığı]

Diler Aslan[1],
Funda Ercan[1],
Hülya Aybek[1],
Türker Şahiner[2]

Departments of [1]Biochemistry, [2]Neurology, Faculty of Medicine, Pamukkale University, 20070 Denizli/Turkey

Yazışma Adresi
[Correspondence Address]

Prof. Dr. Diler Aslan

Pamukkale University, Faculty of Medicine
Dept. of Biochemistry P.K. 33 KINIKLI
20o70 Denizli/Turkey
Tel: 090 258 296 2455
Fax: 090 258 373 7060
E-mail: daslan@pau.edu.tr

Registered: 8 January 2010; Accepted: 28 April 2010

[Kayıt Tarihi : 8 Ocak 2010 ; Kabul Tarili : 28 Nisan 2010]

ABSTRACT

The APOE ε4 allele polymorphism is associated with the increased risk of behavioral and psychological signs and symptoms of dementia. Treatment strategies based on APOE genotypes are being developed. In this study, we aimed to assess the frequencies of APOE4 alleles in patients with Alzheimer's disease (AD) and vascular dementia (VaD) in different ethnic and geographic groups, and compare them with our results.

Method: We determined APOE polymorphisms in patients with VaD, AD, and in controls. For comparison, the literature was searched systematically. Out of 80 papers, 42 papers were assessed for APOE genotype and allele frequencies from several regions of America, Asia and Europe.

Results: There were marked variations in the APOE allele and genotype frequencies in all groups. The strength of association between AD and APOE ε4 allele carrying was found significant [OR:2.905 (95%CI: 1.237-6.823)]. APOE ε4 allele frequencies (%) showed gradual increase from controls to the AD patients (Control: $n_{studies}$=42; 11.33±5.95; VaD: n=7; 15±5.7; AD: n=21; 28.5±8.83).

Conclusion: Although there are more risk factors which accelerate the onset of AD or VaD, these results of comparison confirmed that having APOE ε4 allele was one of risk factors for accelerating the onset of AD. The regional determination of frequencies can be invaluable tool for planning the healthcare policy, and also disease management at the individual basis.

Key Words: APOE4, polymorphism, alzhiemer, disease, vascular dementia

ÖZET

APOE ε4 allel polimorfizmi Alzheimer olmak üzere demans hastalıklarının gelişmesiyle ilişkilidir. APOE genotipine göre tedavi stratejileri geliştirilmektedir. Bu yayında, farklı etnik ve coğrafik gruplardaki Alzheimer hastaları (AD), vasküler demans hastaları (VaD) ve sağlıklı bireylerin APOE4 allel sıklıklarının değerlendirilmesi ve Denizli'deki AD ve VaD hastalarının ve sağlıklı bireylerin sonuçlarıyla karşılaştırılması amaçlandı.

Yöntem: Denizli'deki AD ve VaD hastaları ile sağlıklı bireylerde APOE allel ve genotip dağılımı belirlendi. Karşılaştırma için literatür sistematik olarak tarandı ve değerlendirildi. Değerlendirmeye alınan 80 yayından 42'si Amerika, Asya ve Avrupa kıtalarının çeşitli bölgelerindeki APOE allel ve genotip sıklığı açısından incelendi.

Sonuçlar: Tüm gruplarda APOE allel ve genotip dağılımları arasında farklılıklar gözlendi. Beklendiği gibi APOE4 alleli taşıyanlarla AD arasında güçlü ilişki saptandı. [OR:2.905 (95%CI: 1.237-6.823)]. APOE4 sıklıklarında (%) kontrollerden AD'ye doğru artış saptandı (kontrol: $n_{çalışmalar}$=42; 11.33±5.95; VaD: n=7; 15±5.7; AD: n=21; 28.5±8.83).

Sonuç: AD veya VaD'ye neden olan ve hızlandıran çok sayıda etken olmasına karşın, bizim ve diğer çalışmaların çoğunun sonuçları APOE4 alleli taşımanın AD açısından risk faktörü olduğunu desteklemektedir. Bölgesel dağılımlarda farklılıkların gözlenmesi de APOE4 alleline sahiplik derecesinin bölgesel olarak belirlenmesi sağlık politikasının planlanmasında çok yararlı bilgiler sağlayabilecektir.

Key Words: APOE4, polimorfizm, alzhiemer hastalığı, vasküler, demans

Introduction

A great number of studies have been performed in order to evaluate polymorphisms in apolipoprotein E (APOE) gene as genetic risk factors for dementia, especially Alzheimer's Disease (AD) [1-17]. Most of them have shown that the APOE ε4 allele polymorphism was associated with the increased risk of AD, and also behavioral and psychological signs and symptoms of dementia.

As a results of studies which showed that apolipoprotein E (APOE) gene was susceptibility gene most clearly linked to late – onset Alzheimer's disease (AD) [1-3,6-9,11-16], the APOE genotyping is becoming useful indicator in the combination of genetic, neuropsychological, and neuroimaging findings which are useful to identify asymptomatic adults who will go on to develop late-onset AD [1,18-20].

Treatments are also being developed in order to prevent or delay the onset of symptoms of AD [21-25], and some studies have suggested that APOE e4 allele might also modify effects of some drugs [21,25,26).

According to these findings and practices, it may be necessary and helpful to determine the APOE genotype in each population especially for patients with AD and their family. Although there are some ethical problems for this genotyping issue, the new treatment strategies have been promising for preventing or delay the symptoms for individuals who are at risk for late-onset AD by virtue of their APOE genotype and family history.

Since AD is one of the most common dementias among older people [22,27-29], it causes high expenses to the national healthcare expenditures as well as affects the quality of life in elderly. Although there are tools for scaling and determining of dementias [30-32], APOE ε4 is one of the risk factors of AD, determination of APOE polymorphism in the population may be valuable tool for establishment of regional and national healthcare policy, especially for older population.

Our aim is to assess the APOE allele and genotype frequencies obtained from the other related studies, and compare with our results from patients with AD which were previously published [33] and from patients with VaD. One of our objectives was to provide a database for future studies for making decision about what strategy should be improved for prevention or delay the onset of symptoms of AD in the regional basis in Turkey.

Methods

APOE genotyping was performed in patients with VaD (n= 53 (M/F: 29/24); mean age: 73.3 +7.54), [57-91]. Sample preparation, neuropsychological examination, and APOE genotyping were described in our study for AD patients which was published previously [33]. For comparison, the literature was searched by the key words, "ApoE4 AND polymorphism AND alzheimer AND disease", and "ApoE4 AND polymorphism AND vascular AND dementia", in the PubMed with the limitations of "English" and "any date". The "Google", and Turkish Journals also were searched. The total number of papers accessed was 600. The papers were screened individually by title and abstract searching. Among 600 papers, 80 papers were reviewed, and the APOE genotype and allele frequencies were assessed in 42 papers which have the results from several regions of America, Asia and Europe.

Analysis of distribution of APOE alleles and genotype frequencies in different populations

We evaluated the allele and genotype frequencies from the studies which investigated the role of APOE gene polymorphism in the development of AD, VaD, and the studies which had the values of populations without VaD and AD [2,3,5,7-9,12,14-16,18-20,26,34-36,38-49]. The distribution graphics of alleles and genotypes for controls, VaD and AD patients; and also the forest plots of ODDS ratios obtained from studies were produced according to the populations and countries: Af. Ame_His_Wh, Hispanic, Caucasian, US [2,5,15], Asia/East [12], Belgian [14], Cau_E.As, Cau_S.EU_E.As [12,45], Caucasian [12,38], Croatia, Europe, France Germany/North Ireland/North, Italy, Macedonia, Scotland, Serbia, Spain [16], Europe/Southern [12], Greece [48], Iran [8], Koreans [3,12], Netherlands [50], Saudi Arabia [41], Slovakia [20], Swed_Fin_Canada [26], Turkey, Turkey/East, Turkey/Ist, Turkey/South,Turkey/West [7,9, 35,36,40,43,44,46,47].

Statistical Analysis

We used χ^2 Statistics, one-way ANOVA: Post Hoc Multiple Comparisons (LSD), and nonparametric Kruskal Wallis test for comparisons. The correlations were evaluated by using Spearman's rank order test.

Whether APOE genotypes were in Hardy-Weinberg equilibrium among cases and controls were tested.

We computed odds ratios (ORs) for carriers of APOE ε4 alleles versus non-APOE e4 carriers for VaD, AD patients groups, and all patients. A p value less than 0.05 was considered as statistically significant. Statistical analysis was made by using the Statistical Package for Social Sciences (SPSS) for Window (version 11.0 SPSS Inc., Chicago, IL, US), and Comprehensive Meta-Analysis Program (version 2.0, Biostat, USA) for construction of Forest Plot.

Results

The distributions of APOE allele, and APOE genotype frequencies, gender, ages, cognitive function measurement scores, and APOE ε4 allele carrying in the control, VaD and AD patients groups are listed in the Table 1.

APOE allele frequencies and genotype distributions was found as APOE ε2: 8.5%, APOE ε3: 74.9%, APOE ε4: 16.7%, and E2E2: 0.6%, E2E3: 13.5%, E2E4: 1.8%, E3E3: 54.4%, E3E4: 28.7%, E4E4: 1.2% in the study population [n= 171; age: 72.5 (55-91)].

Table 1. Cognitive function scores and APOE allele and genotype frequencies of our study group.

	Groups		
	Controls	Vascular Dementia	Alzheimer's Disease
n (M/F)	56 (30/26)	53 (29/24)	62 (24/38)
	p=0.559	p=0.492	p=0.075
Age at inclusion Years (SD) (Min-max)	70.8 (7.65)	73.3 (7.54)	73.3 (6.85)
	56-88	57-91	55-87
Age onset Years (SD) (Min-max)		70.5 (7.84)	70.8 (6.74)
		54-87	52-84
Cognitive function Score Mean (SD) min-max			
MMSE	>25	18.0 (3.19)	17.9 (6.0)
		11-24	3-27
ADAS-Cog		25.4 (9.58)	31.4 (13.4)
		13-48	9-64
GDS		1.83 (0.727)	2.9 (1.41)
		1-3	1-6
Allele frequency n (%)			
E2	8 (7.1)	10 (10.4)*	10 (8.1)*
E3	94 (83.9)	75 (70.8)**	87 (70.2)**
E4	10 (8.9)	20 (18.9)***	27 (21.8)***
Genotype frequency n (%)			
E2E2 (n=1)	-	1 (1.9)	-
E2E3 (n=23)	8 (14.3)	7 (13.0)	8 (12.9)
E2E4 (n=3)	-	1 (1.9)	2 (3.2)
E3E3 (n=93)	38 (67.9)	25 (47.2)	30 (48.4)
E3E4 (n=49)	10 (17.9)	19 (35.8)	20 (32.2)
E4E4 (n=2)	-	-	2 (3.2)
E4 Carriers n (%)	10 (17.0)	20 (37.7)	24 (38.7)
Non E4 carriers n (%)	46 (82.1)	33 (62.2)	38 (61.3)

*no significant differences between patients (both VaD and AD) and controls (p>0.05)
**significant differences between patients and controls (p values are 0.012, 0.02, 0.007; AD *vs* C, VaD *vs* C, and VaD+AD *vs* C, respectively)
***significant differences between patients and controls (p values are 0.007, 0.033, and 0.007, AD *vs* C, VaD *vs* C, VaD+AD *vs* C, respectively)

APOE allele and genotype distributions in male and female subjects were not different in all groups (p>0.05). The age-onset of AD and VaD didn't show significant difference between two groups (p>0.05), and there was no correlation between age-onset of dementia and having APOE ε4 allele (r=-0.037, p=0.579).

APOE allele and genotype frequencies were in Hardy-Weinberg equilibrium in control, VaD, and AD groups (p>0.05).

There were no significant differences for APOE allele distribution between age groups (50-55, 56-60, and so on) in control, VaD, and AD patients groups (p>0.05).

APOE ε2 allele distributions showed no difference between three groups (p>0.05). APOE ε3 and APOE ε4 allele distributions in VaD and AD patients were significantly different compared with controls as shown in the Table 1. There were no significant differences for APOE allele distributions between VaD and AD patient groups (p>0.05).

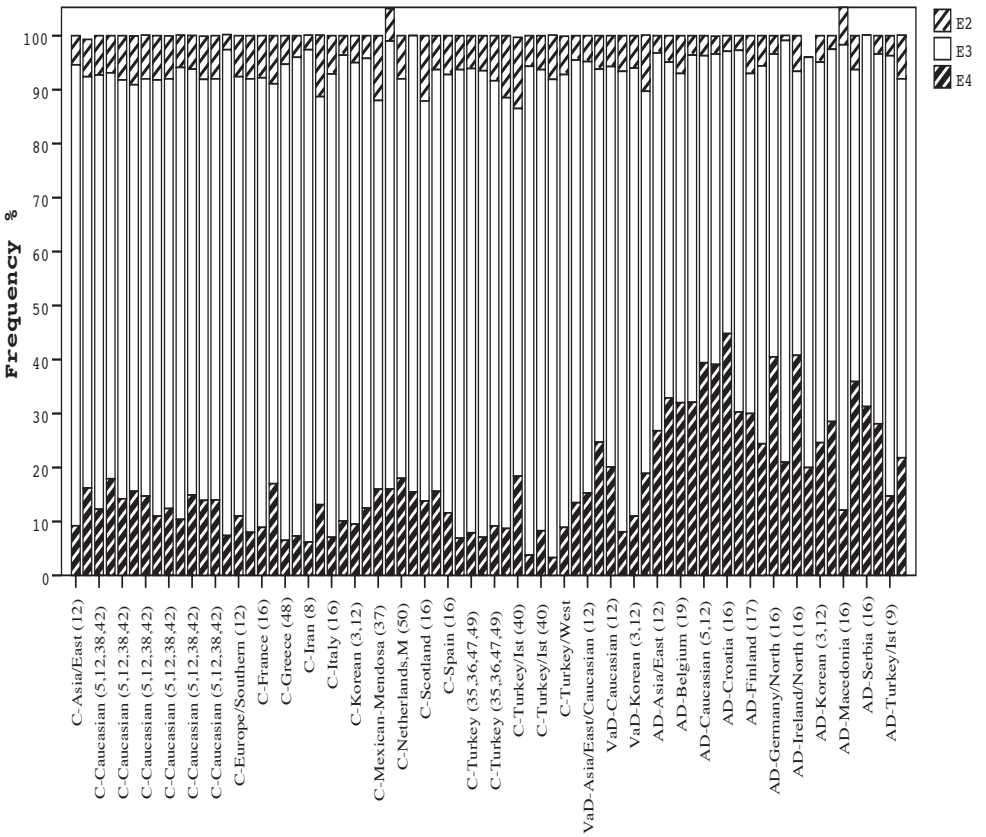
The APOE ε4 allele carriers to the non-APOE ε4 allele carriers ratios were 10/46, 20/33, and 24/38 for controls, VaD nad AD patients groups. There were only two homozygous for APOE ε4 in AD patients group.

Cognitive functions according to the MMSE, ADAS-Cog and GDS scores showed no significant differences comparing to APOE ε4 carriers with non-APOE ε4 carriers (p>0.05) in both VaD and AD patients. The ADAS-Cog and GDS scores showed significant difference between VaD and AD patients groups, p=0.047, p=0.0001, respectively.

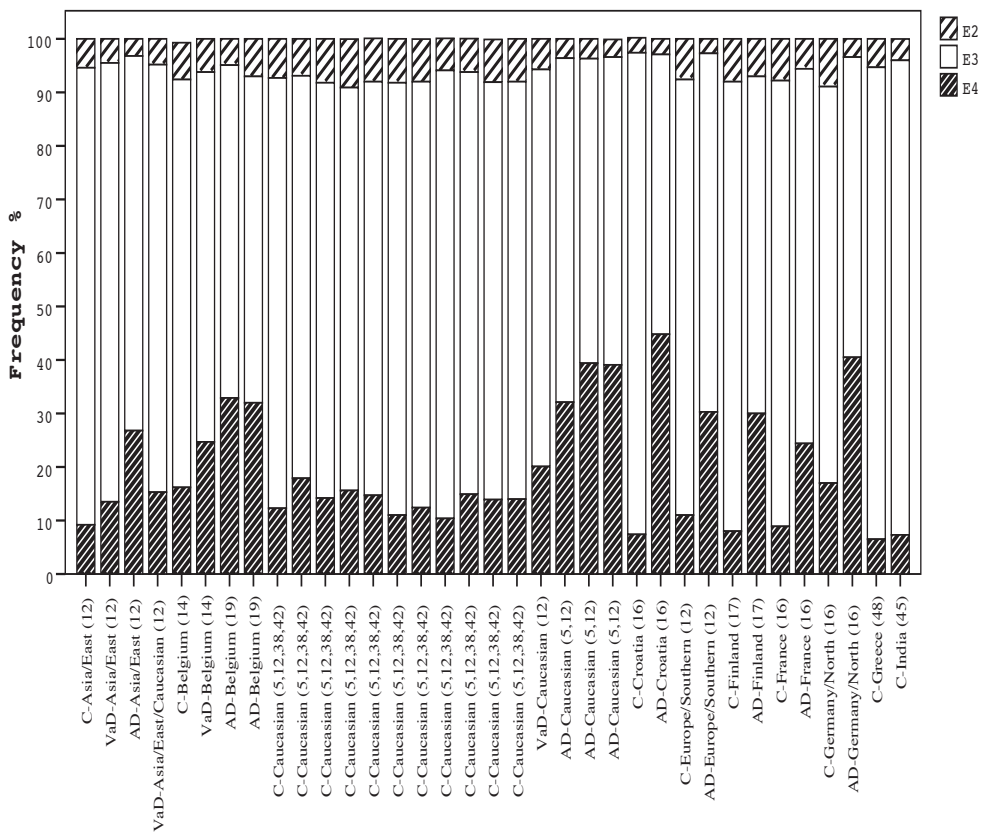
The strength of association between AD and APOE ε4 allele carrying was significant for AD patients [OR: 2.905 (95%CI: 1.237-6.823)].

The variation of distribution of APOE alleles and genotype frequencies obtained from studies which published the values in their controls, patients with VaD, and AD can be seen in the Figures 1 and 2, and the ODDS ratios in the Figure 3.

A


Frequency %
E2
E3
E4
C-Asia/East (12)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Europe/Southern (12)
C-France (16)
C-Greece (48)
C-Iran (8)
C-Italy (16)
C-Korean (3,12)
C-Mexican-Mendosa (37)
C-Netherlands,M (50)
C-Scotland (16)
C-Spain (16)
C-Turkey (35,36,47,49)
C-Turkey (35,36,47,49)
C-Turkey/Ist (40)
C-Turkey/Ist (40)
C-Turkey/West
VaD-Asia/East/Caucasian (12)
VaD-Caucasian (12)
VaD-Korean (3,12)
AD-Asia/East (12)
AD-Belgium (19)
AD-Caucasian (5,12)
AD-Croatia (16)
AD-Finland (17)
AD-Germany/North (16)
AD-Ireland/North (16)
AD-Korean (3,12)
AD-Macedonia (16)
AD-Serbia (16)
AD-Turkey/Ist (9)

B


Frequency %
E2
E3
E4
C-Asia/East (12)
VaD-Asia/East (12)
AD-Asia/East (12)
VaD-Asia/East/Caucasian (12)
C-Belgium (14)
VaD-Belgium (14)
AD-Belgium (19)
AD-Belgium (19)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
C-Caucasian (5,12,38,42)
VaD-Caucasian (12)
AD-Caucasian (5,12)
AD-Caucasian (5,12)
AD-Caucasian (5,12)
C-Croatia (16)
AD-Croatia (16)
C-Europe/Southern (12)
AD-Europe/Southern (12)
C-Finland (17)
AD-Finland (17)
C-France (16)
AD-France (16)
C-Germany/North (16)
AD-Germany/North (16)
C-Greece (48)
C-India (45)

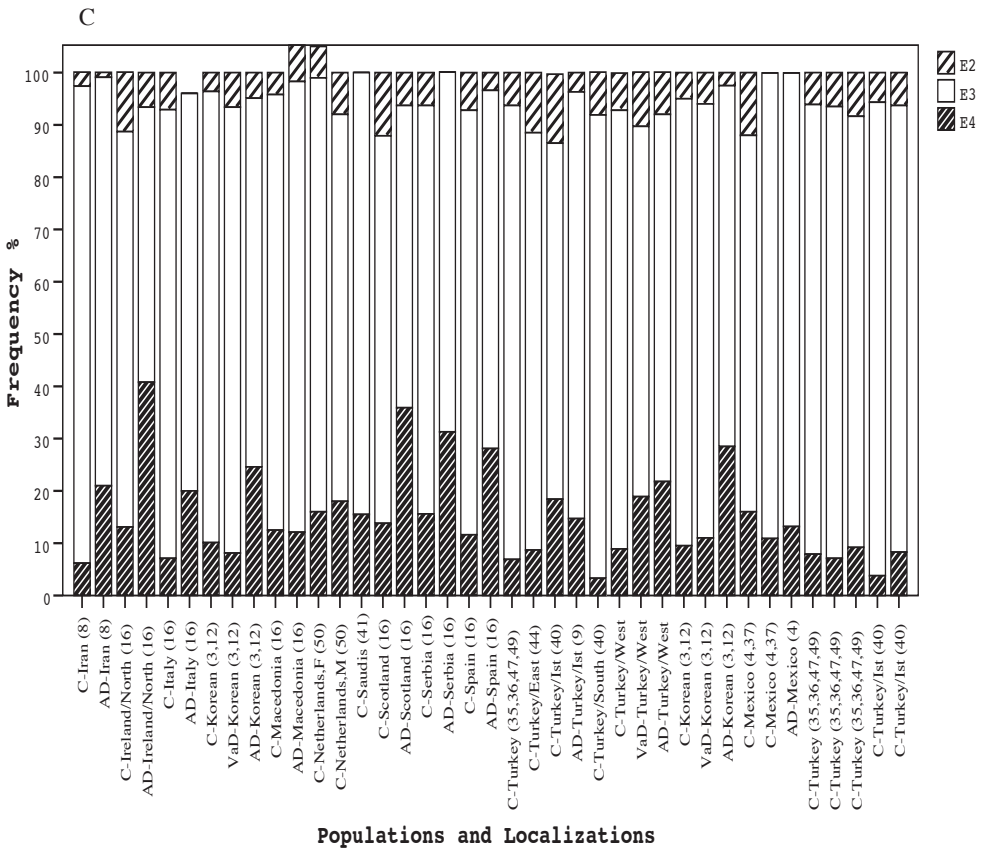


Figure 1. Frequencies of APOE alleles in several populations and people living in different localizations: (A) in groups of controls, patients with vascular dementia, and Alzheimer's disease; (B and C) in groups of controls and patients for each population of localization. C=Controls, VaD= patients with vascular dementia, AD=patients with Alzheimer's disease.

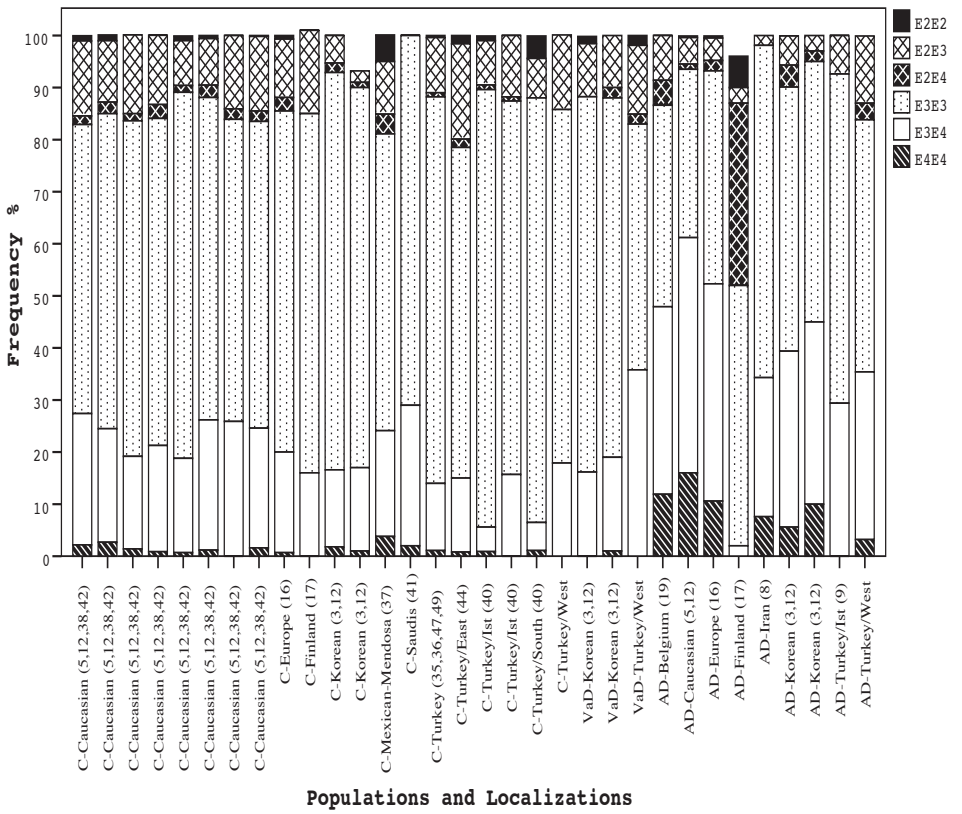


Figure 2. APOE genotype frequencies in several populations and people living in different localizations.

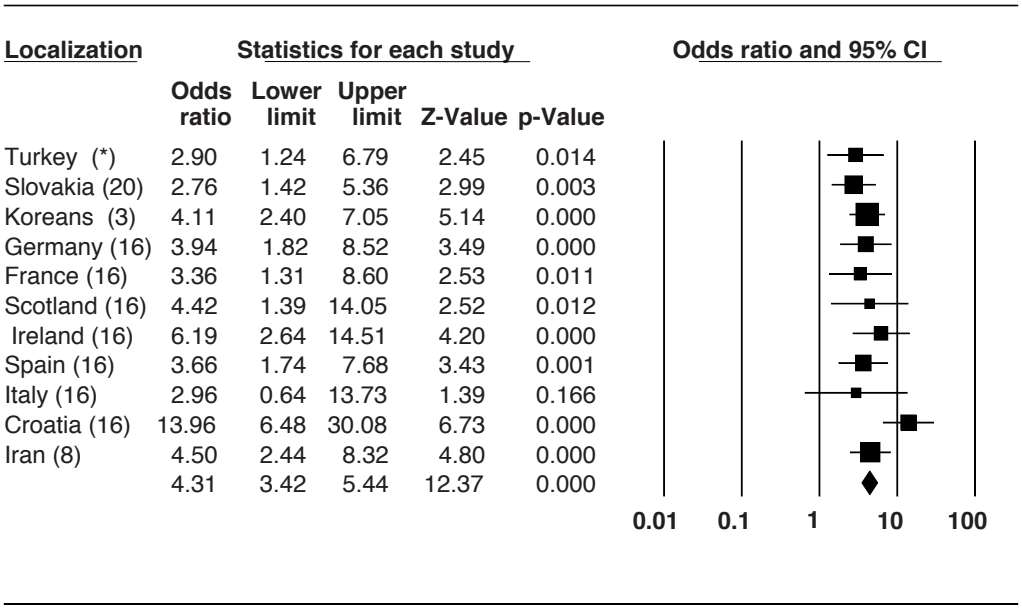


Figure 3. Forest plots of ODDS ratios for APOE ε4 allele in Alzheimer's Disease.

Discussion

We found high frequency of APOE ε4 allele in patients with AD (21.8%), and in patients with VaD (18.9%). Our results also confirmed that APOE genotype is a risk factor for AD (ODDS Ratio 2.905; 95% CI 1,237 – 6,823). Although there are more risk factors which accelerate the onset of AD or VaD, our results are consistent with most of the study results [2,5,6,9,10,12,19,20,26].

When APOE allele and genotype frequencies in all groups (controls, VaD and AD groups) between populations (Figure 1, and 2) are examined, it can be seen that there are great variations between populations according to their geographic localizations and also ethnic considerations, and in most of the studies have significant APOE ε4 allele frequencies of AD patients from those of controls [2,3,5,7-9,12,14-16, 18-20, 26,34-36,38-40,43-48]. The results of two studies, from Macedonia [16] and Mexico [4], show no differences in the APOE ε4 allele frequencies of AD patients from those of controls.

APOE allele and genotype frequencies showed differences between VaD patients and controls in all populations in the studies reviewed [3,14], however, we estimated a significant difference in APOE ε4 allele frequencies between controls and VaD groups (p=0.033) while the significant differences were found in the frequencies of APOE ε2, ε3 and ε4 alleles (for all groups p=0.000), and of E2E3 (p=0.011), E3E3 (p=0.002), E3E4 (p=0.000), and E4E4 (p=0.003) genotypes between controls and AD patients (Figures 1, and 2).

The VaD and AD patients in Denizli showed significant differences from controls in APOE ε3 and APOE ε4 frequencies (for APOE ε3: p=0.02, p=0.012; for APOE ε4: p= 0.033, p=0.007, respectively). We also found significant difference in genotype frequencies for E2E3 (p=0.002 for both patient groups), and for E3E4 (p=0.002 in VaD, p=0.008 in AD patients) between controls and both VaD and AD patients. The differences are consistent with the findings of the other studies in different populations and in ethnic groups except a study from Macedonia [16], and one from Mexico [4] (Figure 1,2). The Koreans show lower APOE allele frequencies in VaD patients than controls or similar pattern [3]. As seen in the Figures 1 and 2, there are marked variations in the APOE allele and genotype frequencies in all groups between populations. These variations are also seen between different regions of Turkey [9,35,36,40,47,49].

If these variations in the distributions of APOE allele and genotype frequencies between populations are combined with the importance of ApoE protein in lipoprotein metabolism and lipid transport, the determination of APOE polymorphism in a population may be useful tool for monitoring the demented patients, managing the intervention after brain damages, and planning the healthcare policy, especially for elderly. This is also true in country basis because the variations are determined between different regions of Turkey as seen in the Figures 1-2.

ODDS ratios for APOE ε4 allele carriers against non-carriers in patients with AD (3,8,16) except Mexicans

(OR 1.15 (0.54-2.47 CI 95%) (4) have been shown that APOE ε4 allele is a strong risk factor for AD, especially late-onset AD. According to the OR's (between 0.34-1.27) of having APOE ε4 allele against VaD from the present study and other studies [3,12,20], it can be suggested that demented subjects who carried the APOE ε4 allele had greater probability of AD than VaD.

Cognitive functions according to the MMSE, ADAS-Cog and GDS scores showed no significant differences comparing to APOE ε4 carriers with non-APOE ε4 carriers ($p>0.05$) such as the finding of Kleiman et al [51]. Blazer et al [13] found no significant association between the ε4 allele presence and quality of life in the group of individuals who were at age 72 or higher by evaluating the five states (social, economic, mental and physical health and functional status).

They also found that some conditions such as diabetes (22%), hypertension (69%), stroke (9%), and heart attack (18%) in their sample group had related to the presence of APOE ε4 allele. In their study, the frequencies of ε4 allele were estimated as 29% in diabetes, 31% in hypertension, 32% in stroke, 16% in heart attack.

Although most of the studies have shown that APOE ε4 allele is a risk factor for dementia, especially AD in elderly, the reality is that having APOE ε4 allele doesn't mean that AD will be developed even if there is familial predisposition. Therefore there is no consensus whether APOE polymorphism should be performed for every person who is at risk for VaD and AD. This is an ethical issue when we think about only one individual concerned. But the other consequences due to the APOE ε4 presence such as being at risk of coronary artery disease (CAD), and having no response to some drugs may be a strong reason for performing regional APOE polymorphism studies in large groups. Then ethical issue may be solved in this manner.

But in the light of studies which have been showing that APOE ε4 allele is one of causes for not responding the drugs, and responsible for poor prognosis after brain damages, it may be needed to determine APOE polymorphism in individual basis.

Conclusion

Although there are more risk factors which accelerate the onset of AD or VaD, this results of comparison confirmed that having APOE ε4 allele was one of risk factors for accelerating the onset of AD. The regional determination of frequencies can be invaluable tool for planning the healthcare policy, and also disease management at the individual basis.

Grant/funding support

This study was supported by a grant from the Scientific Research Commission of Pamukkale University (Project No: 2004TPF016).

References

[1]. Cosentino S, Scarmeas N, Helzner E, Glymour MM, Brandt J, Albert M, Blacker D, Stern Y. (2008) APOE epsilon 4 allele predicts faster cognitive decline in mild Alzheimer disease. Neurology. 70:1842-189.

[2]. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. (1997) Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. JAMA. 278(16):1349-56.

[3]. Kim KW, Youn JC, Han MK, Paik NJ, Lee TJ, Park JH, Lee SB, Choo IH, Lee DY, Jhoo JH, Woo JI. (2008) Lack of association between apolipoprotein E polymorphism and vascular dementia in Koreans. J Geriatr Psychiatry Neurol. 21(1):12-7.

[4].. Villalpando-Berumen JM, Mejia-Arango S, Ordonez-Sanchez ML, Gutierrez-Robledo LM. (2008) Apolipoprotein E e4, Alzheimer's Disease, and Cognitive Performance in Elderly Mexican Mestizos. J Am Geriatr Soc 56:677–682.

[5].. Davidson Y, Gibbons L, Pritchard A, HardicreJ, Wren J, Stopford C, Julien C, Thompson J, Payton A, Pickering-Brown SM, Pendleton N, Horan MA, Burns A, Purandare N, Lendon CL, Neary D, Snowden JS, Mann DMA. (2007) Apolipoprotein E _ 4 Allele Frequency and Age at Onset of Alzheimer's Disease. Dement Geriatr Cogn Disord. 23:60–66.

[6].. Baum L, Lam LCW, Kwok T, Lee J, Chiu HFK, Mok VCT, Wong A, Chen X, Cheung WS, Pang CP, Ma SK, Tang NLS, Wong KS, Keung H. (2006) Apolipoprotein E ε4 Allele Is Associated with Vascular Dementia Dement Geriatr Cogn Disord. 22:301-305.

[7].. Mahley RW, Weisgraber KH, Huang Y. (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A. 103(15):5644-51.

[8].. Raygani AV, Zahrai M, Raygani AV, Doosti M, Javadi E, Rezaei M, Pourmotabbed T. (2005) Association between apolipoprotein E polymorphism and Alzheimer disease in Tehran, Iran. Neurosci Lett. 25;375(1):1-6.

[9].. Yokeş MB, Emre M, Harmancı H, Gürvit H, Hanağası H, Şahin H, Bilgiç B, Başak AN. (2005) The apolipoprotein E (APOE) genotype in a Turkish population with Alzheimer'd Disease. Balkan J. Med Genet. 8:57-63.

[10]..Huang W, Qiu C, Strauss EV, Winblad B, Fratiglioni L. (2004) APOE Genotype, Family History of Dementia, and Alzheimer Disease Risk. Arch Neurol. 61: 1930-1934.

[11]. Scarmeas N, Anderson KE, Hilton J, Park A, Habeck C, Flynn J, Tycko B, Stern Y. (2004) APOE-dependent PET patterns of brain activation in Alzheimer disease. Neurology. 63(5):913-915.

[12]. Bang OY, Kwak YT, Joo IS, Huh K. (2003) Important link between dementia subtype and apolipoprotein E: a meta-analysis. Yonsei Med J. 44(3):401-13.

[13]. Blazer DG, Fillenbaum GG, Gold DT, Burchett BM, Hays JC. (2003) APOE epsilon4 as a predictor of subjective quality of life in a biracial older person community sample. J Aging Health. 15(4):645-60.

[14]. Engelborghs S, Dermaut B, Goeman J, Saerens J, Mariën P, Pickut BA, Van den Broeck M, Serneels S, Cruts M, Van Broeckhoven C, De Deyn PP. (2003) Prospective Belgian study of neurodegenerative and vascular dementia: APOE genotype effects. J Neurol Neurosurg Psychiatry. 74(8):1148-51.

[15]. Mayeux R, Small SA, Tang M, Tycko B, Stern Y. (2001) Memory performance in healthy elderly without Alzheimer's disease: effects of time and apolipoprotein-E. Neurobiol Aging. 22(4):683-9.

[16]. Siest G, Bertrand P, Qin B, Herbeth B, Serot JM, Masana L, Ribalta J, Passmore AP, Evans A, Ferrari M, Franceschi M, Shepherd J, Cuchel M, Beisiegel U, Zuchowsky K, Rukavina AS, Sertic J, Stojanov M, Kostic V, Mitrevski A, Petrova V, Sass C, Merched A, Salonen JT, Tiret L, Visvikis S. (2000) Apolipoprotein E polymorphism and serum concentration in Alzheimer's disease in nine European centres: the ApoEurope study. ApoEurope group. Clin Chem Lab Med. 38(8):721-30.

[17]. Polvikoski T, Sulkava A, Haltia A, Kainulainen A, Vuorio A, Verkkoniemi U, Niinistö E, Halonen I, Kontula K. (1995) Apolipoprotein E, Dementia, and Cortical deposisition of b. N Engl J Med. 333:1242-7.

[18]. Cherbuin N, Leach LS, Christensen H, Anstey KJ. Neuroimaging and APOE genotype: a systematic qualitative review.Dement Geriatr Cogn Disord. 2007;24(5):348-62.

[19]. Engelborghs S, Dermaut B, Mariën P, Symons A, Vloeberghs E, Maertens K, Somers N, Goeman J, Rademakers R, Van den Broeck M, Pickut B, Cruts M, Van Broeckhoven C, De Deyn PP. (2006) Dose dependent effect of APOE epsilon4 on behavioral symptoms in frontal lobe dementia. Neurobiol Aging. 27(2):285-92.

[20]. Gdovinová Z, Habalová V, Novosadová Z. (2006) Polymorphism of Apolipoproteine E in Relation with Alzheimer and Vascular Dementia Cellular and Molecular Neurobiology 26:1219-224.

[21]. Sabbagh M. (2008) Commentary "The Atorvastatin/Donepezil in Alzheimer's Disease Study (LEADe): Design and baseline characteristics". Alzheimer and Dementia. 4(3);174-175.

[22]. Bird TD. (2007) Alzheimer Disease Overview. 1-22 (Accessed: December 2009, http://www.geneclinics.org/profiles/alzheimer/details.html).

[23]. Cedazo-Mínguez A. (2007) Apolipoprotein E and Alzheimer's disease: molecular mechanisms and therapeutic opportunities. J. Cell. Mol. Med. 11(6):1227-1238.

[24]. Sadowski MJ, Pankiewicz J, Scholtzova H, Mehta PD, Prelli F, David D, and Wisniewski T. (2006) Blocking the apolipoprotein E/amyloid- interaction as a potential therapeutic approach for Alzheimer's disease. PNAS. 103:18787–18792 (www.pnas.org_cgi_doi_10.1073_pnas.0604011103).

[25]. Sparks DL, Connor DJ, Sabbagh MN, Petersen RB, Lopez J, Browne P. (2006) Circulating cholesterol levels, apolipoprotein E genotype and dementia severity influence the benefit of atorvastatin treatment in Alzheimer's disease: results of the Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) trial. Acta Neurol Scand. 114 (Suppl. 185): 3–7.

[26]. Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, Hachinski V, Cedazo-Minguez A, Soininen H, Tuomilehto J, Nissinen A. (2008) Apolipoprotein E ε4 Magnifies Lifestyle Risks for Dementia: A Population Based Study. J Cell Mol Med. 12(6B):2762-71.

[27]. Gürvit H, Emra M, Tinaz S, Bilgic B, Hanagasi H, Sahin H, Gurola E, Kvaloy JT, Harmanci H. (2008) The prevalence of dementia in an urban Turkish Population. AJADD. 23(1):67-76.

[28]. Serretti A, Olgiati P, De Ronchi D. (2007) Genetics of Alzheimer's disease. A rapidly evolving field. JAD. 12 (1):73-92.

[29]. Harmanci, H, Emre M, Gurvit H, Bilgic B, Hanagasi H,Gurol E, Sahin H, Tinaz S. (2003) Risk Factors for Alzheimer Disease: A Population-Based Case-Control Study in Istanbul, Turkey. Alzheimer Dis Assoc Disord. 17:139–145.

[30]. Morris JC, Heyman A, Mohs RC, Hughes JP, Van Bell G, Fillenbaum G, Mellits ED, Clark C. (1989) The Consortium to Establish a Registry for Alzheimer's Disease (CERAD): Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology. 39:1159–65.

[31]. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. (2002) Standardize Mini Mental Test'in Türk Toplumunda Hafif Demans Tanısında Geçerlik ve Güvenilirliği. Türk Psikiyatri Derg. 13:273-281.

[32]. Rosen WG, Mohs RC, Davis KL. (1984) A new rating scale for Alzheimer's disease. Am J Psychiatry. 141:1356–64.

[33]. Aybek H, Ercan F, Aslan D, Şahiner T. (2007) Determination of malondialdehyde, reduced glutathione levels and APOE4 allele frequency in late-onset Alzheimer's disease in Denizli, Turkey. Clinical Biochemistry. 40:172–176.

[34]. Brichtová E, Kozák L. (2008) Apolipoprotein E genotype and traumatic brain injury in children—association with neurological outcome Childs Nerv Sys.t 24:349–356.

[35]. Sazci A, Akpinar G, Aygun C, Ergul E, Senturk O, Hulagu S. (2008) Apolipoprotein E polymorphisms in patients with non-alcoholic steatohepatitis. Dig Dis Sci. 53(12):3218-3224.

[36]. Onat A, Hergenç G, Ayhan K, Kaya Z, Küçükdurmaz Z, Bulur G, Can G, Ünaltuna NE. (2007) Serum apolipoprotein E concentrations among Turks: information additive to genotype relative to dyslipidemia and metabolic seydrom. Türk Kardiyol Dern. Araş. 35:449-457.

[37]. Mendes-Lana A, Pena G.G, Freitas S.N, Lima A.A, Nicolato R.L.C, Nascimento-Neto R.M, Machado-Coelho G.L.L, Freitas R.N. (2007) Apolipoprotein E polymorphism in Brazilian dyslipidemic individuals: Ouro Preto study. Braz J Med Biol Res. 40(1):49-56

[38]. Thakkinstian A, Bowe S, McEvoy M, Smith W, Attia J. (2006) Assosiation between apolipoprotein E polymorphism and age-related macular degeneration: a Huge review and Meta-Analysis. Am J Epidomiol. 164(9): 813-822.

[39]. Singh PP, Singh M, Mastana SS. (2006) APOE distribution in world populations with new data from India and the UK. Annals of Human Biology. 33(3): 279–308.

[40]. Attila G, Acartürk E, Eskandari G, Akpıinar O, Tuli T, Kanadaşi M, Kayrın L. (2001) Effects of apolipoprotein E genotypes and other risk factors on the development of coronary artery disease in Southern Turkey. Clin Chim Acta. 312(1-2):191-196.

[41]. Al-Khedhairy AA. (2005). Apolipoprotein E polymorphism in Saudis. Molecular Biology Reports. 31(4):257-260.

[42]. Baird PN, Guida E, Chu DT, Vu HTV, Guymer RH. (2004) The 2 and 4 Alleles of the Apolipoprotein Gene Are Associated with Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 45:1311–1315.

[43]. Duman BS, Oztürk M, Yilmazer S, Hatemi H. (2004) Apolipoprotein E polymorphism in Turkish subjects with Type 2 diabetes mellitus: allele frequency and relation to serum lipid concentrations. Diabetes Nutr Metab. 17(5):267-74.

[44]. Duzenli S, Pirim I, Gepdiremen A. Deniz O. (2004) Apoliprotein E polymorphism ans stroke in population from Eastern Turkey. Journal of Neurogenetics, 18:1, 365 — 375.

[45]. Thelma, B. K. (2001) "APOE Polymorphism in a Rural Older Population-Based Sample in India" Hum Biol. 73(1):135-144.

[46]. Isbir T, H Yilmaz, B Agachan, ZE Karaali. (2003) Cholesterol ester transfer protein, apolipoprotein E and lipoprotein lipase genotypes in patients with coronary artery disease in the Turkish population. Clin Genet. 64:228-234.

[47]. Brega A, Scacchi R, Cuccia M, Kirdar B, Peloso G, Corbo RM. (1998) Study of 15 protein polymorphisms in a sample of the Turkish population. Hum Biol. 70(4):715-28.

[48]. Sklavounou E, Economou-Petersen E, Karadima G, Panas M, Avramopoulos D, Varsou A, Vassilopoulos D, Petersen MB. (1997) Apolipoprotein E polymorphism in the Greek population. Clin Genet. 52: 216-218.

[49]. Mahley RW, Palaoğlu KE, Atak Z, Dawson-Pepin J, Langlois AM, Cheung V, Onat H, Fulks P, Mahley LL, Vakar F, Özbayrakçı S, Gökdemir O, Winkler W. (1995) Turkish Heart Study: lipids, lipoproteins, and apolipoproteins. J Lipid Res. 36(4):839-59.

[50]. Ribalta J, Halkes CJM, Salazar J, Masana L, Cabezas MC. (2005) Additive Effects of the PPARγ, APOE, and FABP-2 Genes in Increasing Daylong Triglycerides of Normolipidemic Women to Concentrations Comparable to Those in Men Clin. Chem. 51: 864 - 871.

[51]. Kleiman T, Zdanys K, Black B, Rightmer T, Grey M, Garman K, MacAvoy M, Gelernter J, van Dyck C. (2006) Apolipoprotein E 4 Allele Is Unrelated to Cognitive or Functional Decline in Alzheimer's Disease: Retrospective and Prospective Analysis-Dement Geriatr Cogn Disord. 22:73–82.