Apolipoprotein E polymorphism and Age at onset of Alzheimer's disease in a Quadriethnic sample

Oh Dae Kwon, M.D.[ad], Aisha Khaleeq, M.D.[a], Wenyaw Chan, Ph.D.[c], Valory N. Pavlik, M.D.[b],Rachelle S. Doody, M.D.,Ph.D.[a]

Alzheimer's Disease and Memory Disorders Center,
Departments of [a]Neurology and [b]Family and Community Medicine, Baylor College of Medicine, Houston, TX, USA
[c]Department of Biometry, University of Texas Houston School of Public Health, Houston, TX., USA
[d]Department of Neurology, School of Medicine, Catholic University of Daegu, Daegu, Korea

ABSTRACT

•The relationship between ApoE genotype and AD is relatively well established in Caucasians but less established in other ethnicities This study examined the association between the ApoE genes and age at onset (AAO) of Alzheimer's disease (AD) in in quadriethnic community dwelling AD patients.

•AD patients were evaluated at two University-based outpatient memory disorder clinics. The ethnic distribution was: **Non-Hispanic Caucasians (C, n=1083), Hispanics (H, n=55), African-Americans (AA, n=84), and Koreans (KO, n=87).** All were diagnosed with probable AD according to NINCDS-ADRDA diagnostic criteria.

•Apo ε4 was associated with younger age at onset (AAO) for C (p<0.0001) followed by AA (p<0.03). There was no significant relationship between Apo ε4 allele and AAO in H (p=0.07) and KO (p=0.43). The Apo*E* ε3 was associated with older AAO in C (p<0.0002). After adjusting for ethnicity, Apo *ε4* was significantly associated with AAO of AD for the whole group (p<0.0001). However, after adjusting for Apo ε4, ethnicity was not significantly associated with AAO of AD (p=0.9969).

•When comparing the United States (US) group as a whole (C, H, AA) with the KO group, Apo ε4 and AAO were significantly correlated in the US group, with younger AAO in (p<0.0001). Furthermore, between the two regional groups, Apo ε3 was associated with older AAO in the US group (p<0.0001). However, there was no such significant relationship between AAO and Apo ε3 or Apo ε4 in KO group (p=0.85).

•The association between the Apo ε4 and younger AAO was most pronounced in Caucasians followed by African-Americans, with no significant relationship in Hispanics and Koreans, suggesting the impact of ApoE polymorphism on clinical phenotype may be different among distinct ethnic or regional groups.

BACKGROUND

•The relation between ApoE genotype and AD is relatively well established in no-Hispanic Caucasians but less established in other ethnicities.

•The current study examined the relationship between *Apo E* genotype and age at onset of AD as well as the genotypic differences among ethnicities in non-Hispanic Caucasians (C), Hispanics (H), African Americans (AA), and Koreans (KO).

OBJECTIVE & METHODS

- Cross sectional study
- Two memory disorder Centers
  - •ADMDC, Neurology, BCM, Houston TX, USA
  - •1989-2009
  - •Neurodeg. clinic, Neurology, DCUMC, Daegu, Korea
  - •2003-2009
- Diagnostic Criteria
  - •NINCDS-ADRDA and consensus conference
- Ethnic recruitment
  - •ADMDC(United States): C, H, AA
  - •Neurodeg. Clinic (Korea): KO.

RESULTS

Table 1. Clinical and demographic variables by ethnic group

	Hispanic	Caucasians	African-American	Korean	P-value
Number of patients	55	1083	84	87	
Gender (% female)	64	66	77	75	0.0694*
Education *mean (SD)*	12 (4.5)	14 (5.5)	13 (4.4)	5 (4.6)	<0.001**
MMSE(Initial visit) *mean (SD)*	16(7.1)	20(6.5)	15(7.8)	22(4.8)	<0.001**
Age at onset *mean (SD)*	70(9.1)	71(8.6)	70(10.0)	71(7.9)	0.6314**
ApoE Genotypes *n (%)*					<0.001†
ε4/ε4	5(9.1)	142(13.1)	16(19.0)	5(5.7)	
ε4/ε3	27(49.1)	500(46.2)	48(57.1)	23(26.4)	
ε4/ε2	-	34(3.1)	4(4.8)	4(4.6)	
ε3/ε3	23(41.8)	362(33.4)	13(15.5)	47(54.0)	
ε3/ε2	-	44(4.1)	3(3.6)	7(8.0)	
ε2/ε2	-	1(0.1)	-	1(1.1)	

Abbreviations: MMSE=mini-mental state examination, APOE=Apolipoprotein E

* Chi-square test

** One-way ANOVA test

† Fisher's exact test

Table 2. The Apo *E* allelic frequency in four populations.

	Hispanic	Caucasians	African-American	Korean	P-value
Allele N (%)					
ε2	-	80(3.7)	7(4.2)	13(7.5)	0.0629*
ε3	73(66.4)	1268(58.5)	77(45.8)	124(71.3)	<0.001*
ε4	37(33.6)	818(37.8)	84(50.0)	37(21.3)	<0.001*

Abbr.: N=Number of patients
*** Fisher's exact test**

Table 3. Age at onset of Alzheimer's disease by Apo ε allele status in four populations.

	Hispanic (n=55)		Caucasians (n=1083)		African-American (n=84)		Korean (n=87)	
	Age at onset mean(SD)	N	Age at onset mean(SD)	N	Age at onset mean(SD)	N	Age at onset mean(SD)	N
ε2 status*								
ε2=2			65(0.0)	1			75	1
ε2=1 or 2	-		72 (8.8)	79	75(7.6)	7	72 (5.9)	12
ε2=1			72(8.8)	78	75(7.6)	7	72(6.1)	11
ε2=0	70(9.1)	55	71(8.6)	1004	70(10.1)	77	71(8.2)	75
ε3 status**								
ε3=2	69(11.0)	23	72 (10.0)	362	73(12.0)	13	72 (9.0)	47
ε3=1 or 2	70 (9.0)	50	71(8.8)	906	71 (9.9)	64	71(8.3)	77
ε3=1	72(6.6)	27	71(7.9)	544	71(9.3)	51	71(7.1)	30
ε3=0	63(7.4)	5	69(7.1)	177	67(10.0)	20	71(4.5)	10
ε4 status**								
ε4=2	63(7.4)	5	68(6.5)	142	65(10.4)	16	72(4.6)	5
ε4=1 or 2	71(7.4)	32	71 (7.7)	676	69 (9.5)	68	70 (6.5)	32
ε4=1	72(6.6)	27	71(7.9)	534	70(9.0)	52	70(6.7)	27
ε4=0	69 (11.0)	23	72(9.9)	407	74(11.3)	16	72(8.6)	55

Abbreviations: N=Number of patient.

***Non-significant by General Linear Model (two-way ANOVA) adjusting for allele status or ethnicity**

**** Non-significat by General Linear Model(two-way ANOVA)adjusting for allele status, P<0.001 by General Linear Model(two-way ANOIVA)adjusting for ethnicity**

Table 4. Age at onset of Alzheimer's disease by Apo ε allele status in US vs. Korean populations.

	United States (n=1222)		Korean (n=87)	
	Age at onset mean(SD)	N	Age at onset mean(SD)	N
ε2 Carrier status*				
ε2=2	65	1	75	1
ε2=1 or 2	72(8.7)	86	72 (5.9)	12
ε2=1	73(8.7)	85	72(6.1)	11
ε2=0	71(8.7)	1136	71(8.2)	75
ε3 Carrier status**				
ε3=2	72(10.1)	398	72 (9.0)	47
ε3=1 or 2	71(8.8)	1020	71(8.3)	77
ε3=1	71(8.0)	622	71(7.1)	30
ε3=0	68(7.5)	202	71(4.5)	10
ε4 Carrier status**				
ε4=2	67(7.0)	163	72(4.6)	5
ε4=1 or 2	70(7.9)	776	70 (6.5)	32
ε4=1	71(7.9)	613	70(6.7)	27
ε4=0	72(10.0)	446	72(8.6)	55

DISCUSSION

- After adjusting for ethnicity , the Apo ε4 allele is significantly associated with AAO (p<0.0001, General Linear Model) for the whole group.
- After adjusting for Apo ε4, ethnicity is not significantly associated with AAO (p=.9969, General Linear Model) for the whole group.
- Education of the four populations showed regional differences (P<0.001), possibly due to socio-economic differences.
- Distribution of 6 genotypes were different among the 4 populations (P<0.001, Fisher's exact test)
- Allelic frequency among the four populations were different in terms of ε3(P<0.001), and ε4(P<0.001), but they were not different in reference to ε2 (P=0.0629).
  - –Apo*E* ε3 highest in KO(71.3%), and lowest in AA(45.8%).
  - –*ApoE* ε4 highest in AA (50.0%) and lowest in KO (21.3%).
- The mean AAO of the four populations showed no differences (P=0.6314)
- The association between the ε4 allele and earlier age at onset was most pronounced in C followed by AA, with no significance in H and KO patients
- Compared to the US group, the ε4 genotype did not appear to play a role in AAO in the Korean populations.
- The lack of association between ε4 and AAO in H and KO patients could reflect the small number of ε4 homozygotes in these two populations.
- The ε2 allele may be more prevalent in Koreans compared to the other ethnic groups.

CONCLUSIONS

- The impact of ApoE polymorphism on clinical phenotype may be different for distinct ethnic groups.
- The impact of ApoE polymorphism on clinical phenotype may be different for distinct regional groups
- Other genetic or environmental factors may modify the effect of ApoE gene in some populations.

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DISCLOSURE

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- *Rachelle S. Doody, M.D., Ph.D. :NONE*

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