ApoE genotype in Amyotrophic Lateral Sclerosis

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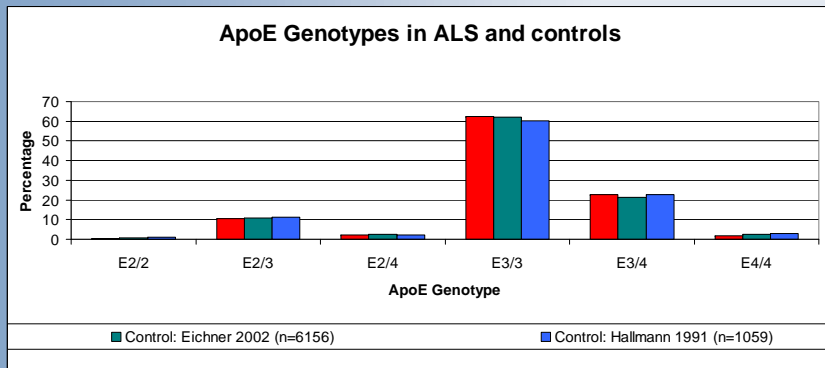
INTRODUCTION

Apolipoprotein E (APOE) genotype is known to reduce the age of onset for Alzheimer's disease and is associated with alterations in the clinical course of many other neurodegenerative conditions. Previous studies which investigated the effect of selective APOE genotypes on disease course of Amyotrophic Lateral Sclerosis (ALS) have lead to variable results.

METHODS

- 862 patients recruited from the Baylor College of Medicine MDA/ALS Outpatient Clinic
- Diagnosis of probable/definite ALS (El Escorial criteria)
- Measured motor disease variables included age at onset, rate of disease progression according to Appel ALS scale and disease duration.
- The patients' cognitive abilities were evaluated through a comprehensive neuropsychological battery. Measures included the American version of the National Adult Reading Test (AMNART); modified (Satz-Mogel) version of the Wechsler Adult Intelligence Scale Revised (WAIS-R); Stroop Color and Word Test; Verbal Series Attention Test (VSAT); Logical Memory (LM) and Visual Reproduction (VR) subtests from the Wechsler Memory Scale–Revised (WMS-R); Symbol Digit Modalities Test (SDMT), Rey Auditory Verbal Learning Test (RAVLT), Rey Ostrich Complex Figure Test (Rey O Complex), lexical fluency (COWA-FAS), semantic fluency (Animals) and Trail Making Test, parts A & B.
- ApoE genotype was determined using standard testing of venous blood. Participants who had genotypes ApoE2/2 and ApoE2/3 were classified as ApoE2 carriers; those with genotypes ApoE3/4 and ApoE4/4 were classified as ApoE4 carriers. In addition, those with ApoE3/3 were classified as ApoE3 carriers. ApoE2/4 were excluded due to their small number (n=10).
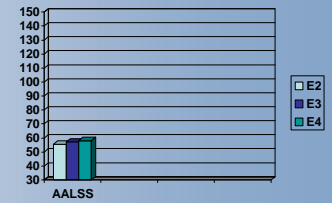
RESULTS

ApoE Genotypes in ALS and controls

Control: Eichner 2002 (n=6156)   Control: Hallmann 1991 (n=1059)

The distribution and frequencies of ApoE genotypes in ALS patients were the same as in controls

Comparison of motor disease variables among different ApoE carriers.

	ApoE			p-value
	E2 (2/2,2/3) (n=93)	E3 (3/3) (n=537)	E4 (3/4,4/4) (n=212)	
Age of onset (years) Mean(SD)	57.5 (13.5)	57.3 (13.7)	57.7 (13.2)	0.97
Rate of disease progression Mean(SD)	2.91 (2.66)	2.67 (2.66)	2.61 (2.47)	0.89
Length of disease (years) Mean(SD)	3.79 (3.70)	3.16 (2.38)	3.05 (1.75)	0.85

*Patients with genotype Apo E2/4 were excluded from this analysis.
No significant difference between groups on *Kruskal-Wallis* test

Motor impairment at the time of diagnosis did not differ among different ApoE genotypes.

Comparison of performance on neuropsychological tests among different ApoE carriers.

	ApoE			p-value
	E2(2/2,2/3) (n=93)	E3(3/3) (n=537)	E4(3/4,4/4) (n=212)	
amNART (raw) Mean(SD)	109 (8.30)	113 (14.2)	107 (8.50)	0.09
Verbal IQ (raw) Mean(SD)	101 (8.80)	103 (15.2)	95.6 (17.3)	0.08
Performance IQ (raw) Mean(SD)	104 (13.1)	104 (15.3)	93.8 (14.4)	**0.00**
Full IQ (raw) Mean(SD)	99.8 (12.5)	103 (15.4)	93.2 (16.8)	**0.01**
Information Mean(SD)	0.32 (0.94)	0.13 (0.96)	-0.05 (1.16)	0.15
Comprehension Mean(SD)	-0.01(1.13)	0.02 (1.02)	-0.13 (1.09)	0.56
Vocabulary Mean(SD)	0.78 (0.90)	0.12 (1.13)	0.22 (1.10)	0.25
Arithmetic Mean(SD)	0.22 (0.91)	0.10 (1.16)	0.09 (0.90)	0.93
Similarities Mean(SD)	0.10 (1.06)	-0.01 (1.05)	-0.17 (0.93)	0.31
Matrix Reasoning Mean(SD)	-0.22 (1.02)	0.07 (1.14)	0.33 (1.48)	0.81
Picture Completion Mean(SD)	1.09 (1.01)	0.46 (1.26)	0.15 (1.24)	0.06
Picture Arrangement Mean(SD)	0.92 (0.96)	0.74 (1.13)	0.71 (1.11)	0.88
Block Design Mean(SD)	0.14 (0.82)	0.00 (0.97)	-0.36 (0.99)	**0.01**
Object Assembly Mean(SD)	0.70 (1.11)	-0.13 (1.02)	-0.43 (0.98)	**0.01**
VSAT-time Mean(SD)	-0.72 (1.34)	-0.95 (1.70)	-1.43 (2.23)	0.07
VSAT-error Mean(SD)	-0.59 (1.61)	-0.68 (2.05)	-1.15 (2.83)	0.25
Stroop-word Mean(SD)	-0.76 (0.96)	-0.71 (1.10)	-0.90 (0.99)	0.40
Stroop-color Mean(SD)	-0.82 (0.91)	-0.73 (0.99)	-0.98 (0.88)	0.15
Stroop color-word Mean(SD)	-0.43 (1.09)	-0.37 (1.23)	-0.74 (1.13)	0.07
Symbol Digit - oral Mean(SD)	-0.50 (1.03)	-0.42 (1.02)	-0.72 (1.14)	0.17
Symbol Digit - written Mean(SD)	-0.50 (1.06)	-0.51 (1.10)	-0.69 (1.09)	0.49
Trails A Mean(SD)	-0.83 (1.79)	-0.57 (1.53)	-0.79 (1.37)	0.67

	ApoE			p-value
	E2 (2/2,2/3) (n=93)	E3 (3/3) (n=537)	E4 (3/4,4/4) (n=212)	
Logical Memory I Mean(SD)	0.20 (1.02)	0.03 (1.06)	0.00 (1.22)	0.64
Logical Memory II Mean(SD)	0.36 (0.95)	0.15 (1.02)	0.06 (1.13)	0.33
Visual Reproduction I Mean(SD)	0.07 (1.11)	-0.02 (1.13)	-0.17 (1.13)	0.53
Visual Reproduction II Mean(SD)	0.16 (1.08)	-0.17 (1.16)	-0.27 (1.17)	0.21
RAVLT-total Mean(SD)	0.00 (0.99)	-0.10 (1.10)	-0.33 (1.36)	0.54
RAVLT-immediate Mean(SD)	0.42 (1.39)	0.27 (1.18)	-0.66 (1.20)	**0.01**
RAVLT-delay Mean(SD)	0.24 (1.26)	0.19 (1.02)	-0.49 (1.00)	0.06
RAVLT-recognition Mean(SD)	0.82 (0.48)	0.68 (0.63)	0.14 (1.27)	**0.01**
Rey copy Mean(SD)	-1.01 (1.47)	-1.80 (2.76)	-2.09 (2.16)	0.32
Rey immediate Mean(SD)	0.52 (1.71)	-0.40 (1.23)	-0.26 (1.18)	0.52
Rey delay Mean(SD)	-0.12 (1.00)	-0.64 (1.20)	-0.49 (1.17)	0.78
FAS Mean(SD)	-0.76 (0.86)	-0.89 (1.04)	-0.78 (1.13)	0.64
Animals Mean(SD)	-0.35 (1.22)	-0.29 (1.18)	-0.34 (1.06)	0.93
BNT Mean(SD)	0.13 (1.32)	-0.21 (1.72)	-0.47 (1.78)	0.47
Trails B Mean(SD)	-0.96 (1.55)	-0.62 (1.48)	-1.52 (2.69)	0.07

Multiple pair-wise comparison of significant measures

	group I	group J	I-J	p value	95% CI
Performance IQ	E4(3/4,4/4)	E2(2/2,2/3)	-10.8	0.05	-21.7,0.08
		E3(3/3)	-11.3	0.00	-18.7,-3.85‡
Full IQ	E4(3/4,4/4)	E2(2/2,2/3)	-6.61	0.44	-17.5,4.36
		E3(3/3)	-9.87	0.01	-17.3,-2.43‡

CONCLUSIONS

- ApoE genotype distribution does not differ between ALS and control groups suggesting that genotype does not alter the risk of having ALS.
- ApoE genotype does not associate with the age of onset, rate of motor disease progression or disease duration in ALS.
- ApoE4 genotype is associated with lower performance on some neuropsychological measures of intelligence.