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Significant effect of APOE Epsilon 4 genotype on the risk of Alzheimer's disease and mortality In persons with Down syndrome

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Abstract

Objective—Virtually all adults with Down syndrome (DS) have neuropathological manifestations of Alzheimer's disease (AD) but not all develop the condition. The effect of allelic variants of Apolipoprotein (APOE) gene in the development and progression of AD and mortality in people with DS is examined.

Methods—Participants with DS recruited through local clinical services and voluntary organizations underwent 2 to 14 sequential assessments over a follow up period of 5 years on average. Blood samples were collected for determination of the APOE genotype. Dementia status of each participant was confirmed as recommended by the Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability.

Results—At the end of the study APOE genotype results were available for 252 individuals and thus included in the analysis. Participants with APOE ε4 allele had a significantly higher risk of developing AD (Hazard ratio = 1.8, 95% CI: 1.12–2.79), had an earlier onset of AD (55.0 vs. 57.0 years; p = .0027) and a more rapid progression to death compared with participants with ε3 allele. In those who did not have AD, presence of ε4 allele was associated with early mortality (Hazard ratio = 5.9, 95% CI: 1.7–21.3).

Conclusions—This study highlights the relationship of APOE genotype to morbidity and mortality in people with DS which may have important clinical implications in terms of early identification of individuals at risk. We recommend screening for APOE genotype for individuals with DS early in their life.

Keywords

Apolipoprotein E; Alzheimer's Disease; Down Syndrome; Mortality

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Introduction

The gene for apolipoprotein E (APOE), on chromosome 19, is encoded for by three alleles, ε2, ε3 and ε4 and is involved in cholesterol transport and lipid metabolism in plasma (Dupuy *et al*., 2001). In the general population, the presence of the ε4 allelic variant of apolipoprotein gene (APOE) has been linked to an earlier onset of Alzheimer's disease (AD) as well as a rapidly deteriorating course and these effects increase with increasing number of ε4 alleles (heterogeneous vs. homogeneous) (Corder *et al*., 1993; Mayeux *et al*., 1993; Saunders *et al*., 1993; Meyer *et al*., 1998; Khachaturian *et al*., 2004).

The presence of the least common allele, APOE ε2 has been associated with an increased age of onset of AD as well as a decease in the overall risk of developing AD (Corder *et al*., 1994, Roses *et al*., 1994); however one study (van Duijn *et al*., 1995) has presented data suggesting that the APOE ε2 allele is associated with an increased risk of familial or early onset AD. The exact mechanism by which APOE influences the development of AD remains unknown. It has been suggested that it may influence the deposition of beta-amyloid (Aβ) and the hyperphosphorylation of tau protein which leads to development of neurofibrillary tangles (Ilyas, 1995), or that it has a role in repair functions in the brain, as the APOE gene has been found to be related to the maintenance, repair and growth of neurons (Houlden and Greenwood, 2006).

Virtually all adults with Down syndrome (DS) have the neuropathological manifestations of AD, including neurofibrillary pathology and deposition of Aβ in neuritic plaques (Mann, 1988; Wisniewski *et al*., 1985), attributable, at least in part, to the overexpression of the gene for Aβ precursor protein located on chromosome 21 (Rumble *et al*., 1989). Despite the near universal presence of AD neuropathology by age 40 (Malamud, 1972), a wide variation in the age of onset of dementia (i.e., 40 to 70 years of age) has been observed (Lai et al., 1999; Schupf, 2002), with some adults with DS in their 60's and 70's remaining non-demented (Krinsky-McHale *et al*., In Press), suggesting that other factors influence age at onset (Schupf, 2002).

The association between *APOE* genotype and AD in adults with DS generally mirrors the pattern of results found in the general population (Schupf *et al*., 198; Deb *et al*., 2000; Sekijima *et al*., 1998). Some conflicting results have been reported (Lai *et al*., 1999; Prasher *et al*., 1997; van Gool *et al*., 1995). Whether these reflect true findings or methodological issues remains to be determined. Sekijima *et al*. (1998) found that the link between the ε4 allele and AD in DS was stronger in a younger age group (less than 50 years) than in those over 50 years of age.

In the general population, the APOE ε4 allele has been directly related to early mortality in some studies as well as increased risk of AD, but the literature is inconsistent (Dal Forno *et al*., 2002; Lane *et al*., 2003; Koivisto *et al*., 2000). Conversely, the APOE ε2 allele has been associated with increased longevity (Schachter *et al*., 1994) in some, but not all, studies (van Duijn *et al*., 1995). An association between the APOE ε4 allele and increased mortality in demented (Hardy *et al*., 1994; Royston *et al*., 1994) and non-demented (Zigman *et al*., 2005) adults with DS has been reported. As has been reported for the general population, the presence of the APOE ε2 allele has been associated with increased longevity in adults with DS (Schupf, 2002).

In this study, we examined the relation of APOE genotype to age at onset of AD and mortality risk in a large cohort of adults with DS which has been followed for five years on average.

Methods

i) Participants

Adults with DS (16 years and above) known to the local clinical services and contacts including voluntary organizations were approached for the recruitment into the study. Consent or assent was obtained where appropriate. The enrollment period ranged from 1988 through 2006. All participants resided in one geographical region of the United Kingdom. Ethical Committee approval was obtained from the local authority with approval from the NHS Trust.

ii) Procedures

We employed a prospective cohort design, with a range of 2 to 14 sequential assessments over the course of the follow up. Baseline assessments included: (a) a standard full psychiatric history and mental state examination. Mental disorders were diagnosed using ICD-10 Symptom Checklist for Mental Disorders (WHO, 1994) according to ICD-10 research criteria (WHO, 1993) (b) an ascertainment of severity of ID according to ICD-10 criteria (WHO, 1992), (c) a physical examination (including an assessment of hearing and vision), (d) a comprehensive review of medical records, (e) hematological, biochemical, and thyroid screening, and (f) a comprehensive review of all prescribed medications. Participants diagnosed with mental or physical disorders were treated as appropriately and then followed up.

Blood samples for willing participants were collected in the morning. Two single nucleotide polymorphism (SNPs) within the APOE gene, 334T/C (rs 429358) and 472C/T (rs 7412) were genotyped, using TaqMan SNP Genotyping Assays (Applied Biosystems, Warrington, UK). Fluorescence was measured using an ABI 7900 Sequence Detection System (Applied Biosystems). The frequencies of the APOE isotype-specific alleles, ε2, ε3 and ε4 and APOE genotypes were obtained from nucleotide combinations of the 334 T/C and 472 C/T SNPs (Koch *et al*., 2002).

Record review and participant data over assessments were employed to confirm the dementia status of each participant as recommended by the Working Group for the Establishment of Criteria for the Diagnosis of Dementia in Individuals with Intellectual Disability (Aylward *et al*., 1997; Burt and Aylward, 2000).

iii) Statistical Analyses

We used chi-square tests for categorical variables and Student's t-tests and analysis of variance for continuous variables to compare demographic characteristics by APOE genotype group. Potential confounders were age, level of intellectual disability, sex and ethnicity, as they have been found to be related to mortality and dementia status in previous studies (Schupf, 2002; Zigman *et al*., 2005; Yang *et al*., 2002). Participants were classified into three separate groups, as a function of APOE ε4 dosage. The reference group included participants with no ε4 or ε2 alleles (i.e., ε3/ε3); the low-risk group included participants with at least one ε2 allele, (ε2/ε2, ε2/ε3, ε2/ε4 genotypes); and the high-risk group included participants with one or more ε4 alleles but no ε2 alleles (ε3/ε4 and ε4/ε4 genotypes). Allocation of the participants with ε2/ε4 genotypes (n= 4) to the high risk group made no significant difference to the results.

Level of intellectual disability was classified into two groups: mild/moderate (IQ 35–70) and severe/profound (IQ ≤34), based on assessments of intellectual disability before onset of dementia. Ethnicity was coded as Caucasian or non-Caucasian. We used Cox proportional hazards models to estimate cumulative incidence and the hazard rate (HR) of dementia as a function of APOE genotype group, adjusting for age, sex, ethnicity and level of intellectual disability. Age at onset of dementia or age at last assessment (for those without dementia) was

the time-to-event variable. We also used Cox proportional hazards modeling to examine risk of death by APOE genotype group. Age at death or age at last assessment was the time-to-event variable. Because the presence of dementia is associated with early mortality (Evans *et al*., 1991; Coppus *et al*., 2006), we first estimated cumulative incidence and the HR of death as a function of APOE genotype for the entire sample, and then separately for participants who remained non-demented throughout the study period.

Results

Overall 390 individuals with DS were recruited during the study period. At the end point of the study results of the APOE genotype were available for 252 individuals (age 16 to 76 years at the beginning of the study) and thus included the analysis. The rest were either lost to follow up or the testing for APOE was not accessible during the individual's lifetime. Cytogenetic confirmation of the trisomy 21 karyotype was available for 206 (82%), non-trisomy 21 karyotype for 18 (7%) and clinical and phenotypic confirmation for the remaining 28 (11%) individuals.

i) Demographic data:

The mean age of the participants at baseline was 45.2 (SD = 11.6) years and 58.3% were male. Mean follow-up was 6.2 years (SD = 5.2) for the entire sample. There were 100 participants with either prevalent (n=60) or incident (n=40) dementia and 152 who did not develop dementia over the course of follow-up. Demented participants were older at baseline (52.2 vs. 40.5 years, p<.001) and more likely to be female (Table 1).

ii) *APOE* and onset/duration of dementia

APOE allele frequencies were: ε2, 8.3%; ε3, 78%; ε4, 13.7% comparable to those reported for Caucasian populations (Corder *et al*., 1994). In multivariable Cox proportional hazards analyses, adjusting for age, sex, ethnicity and level of intellectual disability, participants in the high-risk group (i.e., 3/4 or 4/4 genotypes) had a significantly higher risk of dementia compared with participants in the reference group (i.e., 3/3 genotype) (HR = 1.8, 95% CI: 1.12–2.79) (Table 2).

The median age of risk for dementia was 2 years earlier for participants in the high risk group compared with participants in the reference group (55.0 vs. 57.0 years, p = .0027). Neither the risk of dementia (HR=1.1, 95% CI: 0.63–2.0) nor the median age of risk for dementia differed significantly in participants in the low risk group (i.e., 2/2, 2/3, 2/4 genotypes) compared with participants with the 3/3 genotype (57.0 10 years vs. 57 years). Sex, level of intellectual disability and ethnicity were not associated with risk for dementia.

iii) APOE and mortality

Sixty-nine participants died over the course of the study, Table 3 presents the demographic characteristics of participants who died compared with participants who remained alive. Participants who died were older at baseline (52.2 vs. 42.5 years) and more likely to be demented (71% vs. 27.9%) than participants who remained alive, but did not differ in the distribution of sex, level of intellectual disability, ethnicity. or the presence of an ε4 allele.

Time from onset of dementia to death was shorter in those with the high risk genotypes (3/4, 4/4) compared with participants in reference group (4.2 years vs 5.4 years, respectively, p= . 048), but did not differ between participants in the low risk group and those in the reference group (5.1 years vs. 5.4 years, respectively, p = .66)., suggesting a more aggressive course of disease progression in those with high risk genotypes (3/4, 4/4). In multivariable Cox proportional hazards models, adjusting for age, sex, ethnicity and level of intellectual disability,

the hazard rate of death did not differ among participants in the APOE risk groups, when participants in the total group was considered (Table 4), nor when dementia status was added to the model (HR for participants in the high-risk group vs. participants in the reference group = 1.2, 95% CI: 0.64–2.1, HR for participants in the low-risk group vs. participants in the reference group = 1.3, 95% CI: 0.70–2.6; data not shown). However, a history of dementia was strongly associated with risk of death (HR= 3.3, 95% CI: 1.8–6.1; data not shown). When the analysis was restricted to those participants without dementia, there was a significant relationship between participants in the high-risk group vs. participants in the reference group and risk of death (HR = 5.9, 95% CI: 1.7–21.3). On average, age at death was 55.7 years for participants in the high-risk group compared with 72.7 years for participants in the reference group. Risk of death was also marginally increased for participants in the low-risk group compared with participants in the reference group (HR = 3.5, 95% CI: 0.94–12.8), but this increase failed to reach statistical significance.

Discussion

Prior studies on the effects of APOE genotype on AD in individuals with DS have been susceptible to several methodological issues, including small study sample size, few cases of dementia, accuracy of the clinical diagnosis of AD and failure to control age–effect. This prospective follow-up study of a large community sample representative of the DS population as a whole highlights the association between APOE genotype and AD. Persons with an ε4 allele had a significantly higher risk of AD than those with an ε2 or ε3 allele. Further, those with an ε4 allele had a significantly earlier onset of dementia and shorter life expectancy once the disease began. Findings from this study are consistent with those for the general population where a strong association between APOE ε4 genotype and risk for AD and reduction in age of onset of dementia has been well established (Corder *et al*., 1993; Mayeux *et al*., 1993; Saunders *et al*., 1993; Meyer *et al*., 1998; Khachaturian *et al*., 2004). The findings are also consistent with previous meta-analyses of studies of DS and AD which have shown a significantly higher frequency of ε4 in DS adults with dementia (Deb *et al*., 2000) and a lowering in age of onset of dementia in person with DS with an ε4 allele(Prasher *et al*., 1997).

The role of ε2 as a protective factor for AD is more controversial. In this study, presence of an ε2 allele was found not to reduce the risk of dementia or delay the age of onset. A number of studies in the general population have found an association of the ε2 allele with reduced risk for AD (Corder *et al*., 1994) whilst others have not supported this finding (van Duijn *et al*., 1995). For the DS population previous meta-analysis studies (Deb *et al*., 2000; Prasher *et al*., 1997) have not reported a significant delay in onset of dementia in persons with an ε2 allele, although a number of individual studies have reported such an association(Hardy *et al*., 1994; Royston *et al*., 1994; Schupf *et al*., 1996). Such differences may reflect methodological issues or suggest that the APOE effect in persons with DS is not of the magnitude as that seen in the general population due to the “overwhelming effect of triplication of the APP gene” (Prasher *et al*., 1997).

This study found a significant association between presence of an ε4 allele and increased risk of death for non-demented DS persons. A similar finding has been reported previously by Zigman *et al*. (2005) where they found that individuals with DS without dementia who had at least one ε4 allele were approximately 5 times more likely to die than persons with an ε3 allele. This may explain the few DS individuals with ε4/4 reported in the literature. The underlying reasons for earlier death in people with ε4 allele are uncertain but may relate to such findings in general population (Koivisto *et al*., 2000; Schachter *et al*., 1994; Ewbank, 2002).

The findings in this study may have important clinical implications in terms of early identification of people with DS at risk of developing AD which may follow a particularly aggressive course. We recommend that a screening for APOE genotype is done for individuals with DS early in their life. Though such screening measures may have ethical implications and require informed consent from the individual concerned, identification and management of a dementing process at an early stage may play substantial role in improving the outcome as well as quality of life of the individual concerned.

The pathogenesis of AD in persons with DS remains complex with many factors playing a possible significant role, in particular triplication and over-expression of the APP gene, APOE genotype, gender, oestrogen deficiency and levels of plasma beta1–40 and beta1–42 (Schupf, 2002). It is evident that over the next two decades many strides will be made in the identification of genes in the pathogenesis of AD in DS.

Keypoints

- Apolipoprotein E ε4 genotype is associated with higher risk of Alzheimer's disease in and an earlier onset of the dementing process in people with Down syndrome
- ε4 genotype is also associated early mortality in people with and without dementia.

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Table 1

Demographic Characteristics by Dementia Status in adults with Down syndrome

Characteristic	Non-demented	Demented	TOTAL
Sample size	152	100	252
Age at Baseline (mean ± S.D.)*	40.5 ± 11.6	52.2 ± 7.1	45.2 ± 11.6
Sex (n, %)			
Male	90 (59.2)	57 (57.0)	147 (58.3)
Female	62 (40.8)	43 (43.0)	105 (41.7)
Level of intellectual disability (n, %)			
Mild/Moderate	137 (90.1)	90 (90.0)	227 (90.1)
Severe/Profound	15 (9.9)	10 (10.0)	25 (9.9)
Ethnicity (n, %)			
Caucasian	148 (97.4)	100 (100)	248 (98.4)
Non-Caucasian	4 (2.6)	0 (0)	4 (1.6)
APOE ε4 Genotype (n, %)			
2/2, 2/3,2/4	26 (17.1)	15 (15.0)	41 (16.3)
3/3	95 (62.5)	54 (54.0)	149 (59.1)
3/4, 4/4	31 (20.4)	31 (31.0)	62 (24.6)

* $p < .001$

Table 2

Hazard Ratio for Alzheimer's disease by APOE genotype

APOE Genotype	N	AD (n,%)	Hazard Ratio*	95% CI
Genotype Group				
3/4, 4/4	62	31 (50.0)	1.8	1.12–2.79
2/2, 2/3, 2/4	41	15 (36.6)	1.1	0.63–2.0
3/3	149	54 (36.2)	1.0	reference

Adjusted for age, sex, level of intellectual disability, and ethnicity

*Cox proportional Hazards; Hazard Ratio with 95% Confidence Interval

Table 3

Demographic Characteristics by Vital Status

Characteristic	Alive	Deceased	TOTAL
Sample size	183	69	252
Age at Baseline (mean ± S.D.)*	42.5 ± 11.5	52.2 ± 8.5	45.2 ± 11.6
Sex (n, %)			
Male	109 (59.6)	38 (55.1)	147 (58.3)
Female	74 (40.4)	31 (44.9)	105 (41.7)
Level of intellectual disability (n, %)			
Mild/Moderate	167 (91.3)	60 (87.0)	227 (90.1)
Severe/Profound	16 (8.7)	9 (13.0)	25 (9.9)
Ethnicity (n, %)			
Caucasian	179 (97.8)	69 (100)	248 (98.4)
Non-Caucasian	4 (2.2)	0 (0)	4 (1.6)
APOE ε4 Genotype (n, %)			
2/2, 2/3,2/4	27 (14.8)	14 (20.3)	41 (16.3)
3/3	112 (61.2)	37 (53.6)	149 (59.1)
3/4, 4/4	44 (24.0)	18 (29.0)	62 (24.6)
Dementia Status (n, %)*			
Non-demented	132 (72.1)	20 (29.0)	152 (60.3)
Demented	51 (27.9)	49 (71.0)	100 (39.7)

*P < .001

Table 4

Hazard Ratio for Death by APOE genotype

	N	Deceased (n, %)	Hazard Ratio *	95% CI
TOTAL GROUP				
APOE Genotype				
3/4, 4/4	62	18 (29.0)	1.7	0.96–3.1
2/2,2/3,2/4	41	14 (34.1)	1.5	0.76–2.80
3/3	149	37 (24.8)	1.0	Reference
NONDEMENTED ONLY				
APOE Genotype				
3/4, 4/4	31	5 (16.1)	5.9	1.7–21.3
2/2,2/3,2/4	26	5 (19.2)	3.5	0.94–12.8
3/3	95	10 (10.5)	1.0	Reference

Adjusted for age, sex, level of intellectual disability, and ethnicity

*Cox proportional Hazards; Hazard Ratio with 95% Confidence Interval