Onset of Dementia is Associated with Apolipoprotein E ε4 in Down's Syndrome

Nicole Schupf,*† Deborah Kapell,* Joseph H. Lee,*† Warren Zigman,‡ Basilisa Canto,† Benjamin Tycko,§ and Richard Mayeux†‖¶

We examined the influence of apolipoprotein E (apoE) genotype on risk of dementia in 82 adults with Down's syndrome (DS). Compared with those with an apoE 3/3 genotype, the group of adults with DS with apoE 2/4, 3/4, and 4/4 genotypes were 5 times more likely to become demented (*RR* = 4.7; 95% CI = 1.2, 17.9). We hypothesize that the increased risk of dementia may be mediated by exacerbation of β-amyloid deposition.

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By age 40, virtually all individuals with Down's syndrome (DS) have the neuropathological changes characteristic of Alzheimer's disease (AD), including deposition of β-amyloid in diffuse and neuritic plaques [1, 2]. However, the average age at onset of clinical dementia is 50 years [3] and varies widely. The neuropathologic manifestations have been attributed to triplication and overexpression of the gene for β-amyloid precursor protein (APP) [4], but the factors influencing age at onset of dementia are unresolved. The apolipoprotein E (apoE) ε4 allele has been associated with acceleration of the development of AD in the general population [5, 6], as well as greater accumulation of β-amyloid in the elderly with and without AD [7, 8]. Prior studies have shown that the apoE ε2 allele increases longevity and decreases risk of dementia in people with Down's syndrome [9, 10], but no clear association with the apoE ε4 allele has been established [9–11]. In this study, we examined the relation between apoE ε4 and risk of dementia among 82 adults with DS.

From the *Laboratory of Epidemiology and ‡Laboratory of Community Psychology, NYS Institute for Basic Research in Developmental Disabilities, Staten Island; and ‖Division of Epidemiology, Columbia University School of Public Health, ¶Departments of Neurology and Psychiatry, College of Physicians and Surgeons at Columbia University, and †Gertrude H. Sergievsky Center and §Department of Pathology, Columbia University, New York, NY.

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Address correspondence to Dr Schupf, NYS Institute for Basic Research in Developmental Disabilities, 1050 Forest Hill Road, Staten Island, NY 10314.

Subjects and Methods

Adults with Down's syndrome, residing in the nine-county downstate region of New York, were identified from a registry of persons with DS in New York State developed from the Developmental Disabilities Profile, a computerized database maintained by the New York State Office of Mental Retardation and Developmental Disabilities and supplemented by an independent survey of all state and voluntary service providers. We selected a random sample of adults with DS, 30 to 70 years of age. Informed consent to participate was provided by a responsible family member.

A semistructured interview was conducted with a close caregiver at the subject's residential or day-treatment facility. The interview obtained information on demographic characteristics and medical history. In addition to the history of dementia, we obtained information on history of onset of stroke, hypothyroidism, and other conditions that might result in dementia. Past and current medical records were reviewed for all subjects. Subjects were classified as demented if there was a diagnosis of AD by the subject's physician and a history of progressive memory loss, disorientation, and decline in activities of daily living skills over a period of at least 1 year. Subjects were not classified as demented if there was a history of stroke or other medical disorders that might result in dementia, if the duration of memory loss and difficulty in activities of daily living was less than 1 year, or if there was no physician diagnosis of AD. All diagnoses of dementia were made by physicians familiar with the subject and blind to the subject's genotype. We used age at physican diagnosis as the age at onset. Agreement between caregiver and physician ascertainment of dementia was substantial ($\kappa = 0.76$).

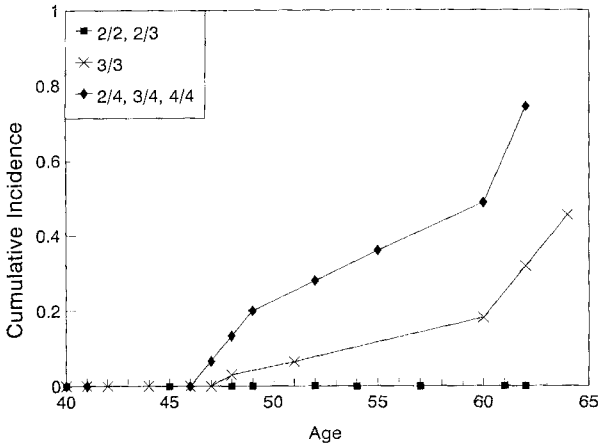
In addition, we examined change in function in a subsample of 20 subjects receiving four annual assessments of adaptative competence, using the AAMR's Adaptive Behavior Scale [12], as an independent index of the relation of apoE genotype and decline in adaptive competence.

All subjects were confirmed to have Down's syndrome by cytogenetic analysis. Eight subjects showed mosaicism for DS, ranging from 8 to 20% disomic cells. There was no relation of mosaicism to risk of dementia or to apoE genotype. Genomic DNA samples were prepared from peripheral white blood cells. ApoE genotyping was carried out as described in a previous study [6] and was performed on blood samples without knowledge of the subject's medical history or clinical diagnosis.

We used survival methods to assess risk of dementia. We compared cumulative incidence and rate ratios for dementia using the Kaplan–Meier life table and Cox proportional hazards models, adjusting for level of mental retardation and gender. We compared risk of dementia among those with any apoE ε4 allele (2/4, 3/4, and 4/4 genotypes) and among those with an apoE ε2 allele (2/2 and 2/3 genotypes) with those with the apoE 3/3 genotype. The relation of apoE ε4 to change in adaptive competence over four annual assessments was evaluated using a Mann–Whitney *U* test. All statistical procedures were run using SPSS 6.1 for Windows.

Table 1. Subject Characteristics by Genotype

Genotype	n	Age (yr) ($\bar{X} \pm$ SE)	n (%) Males	Level of Mental Retardation (n, %)		
				Mild/Moderate	Severe	Profound
2/2	1	61.0 (—)	1 (100)	—	—	1 (100)
2/3	6	49.7 (4.9)	4 (67)	4 (67)	2 (33)	—
2/4	4	47.0 (14.7)	3 (75)	2 (50)	2 (50)	—
3/3	53	49.6 (9.2)	28 (53)	17 (32)	26 (49)	10 (19)
3/4	15	53.4 (8.3)	7 (47)	6 (40)	6 (40)	3 (20)
4/4	3	48.7 (2.5)	1 (33)	1 (33)	2 (67)	—



Cumulative incidence of dementia in adults with Down's syndrome by apolipoprotein E genotype. (■) = 2/2, 2/3; (◆) = 2/4, 3/4, 4/4; (X) = 3/3.

Results

Table 1 presents subject characteristics by ApoE genotype. Because the sample was drawn from the NYS service system, there was a larger proportion of persons with severe mental retardation than would be found in the total population of individuals with DS. The frequencies of apoE genotypes were similar to those found in European and American populations [13] (see Table 1). Cumulative incidence of dementia to age 65 was 0.74 in those with any apoE ε4 genotype and 0.45 in those with the apoE 3/3 genotype (Fig). No individual with an apoE ε2 allele developed dementia. The age-adjusted risk of dementia was 5 times greater for individuals with any apoE ε4 genotype than for those with the apoE 3/3 genotype (Table 2, Rate Ratio = 4.7, 95% confidence interval [CI] = 1.2, 17.9). The age-adjusted risk associated with the ε4 allele increased to 7.4 (95% CI = 1.8, 31.1) if those with an apoE 2/4 genotype were omitted from the comparison. In addition, we found significantly greater decline in adaptative competence in those with an apoE ε4 allele compared with those without ($p < 0.05$), regardless of whether dementia was diagnosed.

Discussion

These findings are consistent with previous studies showing a protective effect of the apoE ε2 allele in adults with DS [9, 10]. In addition, we demonstrated a strong association between the apoE ε4 allele and risk of dementia. The apoE ε4 allele has been associated with increased deposition of β-amyloid in AD and other clinical conditions such as traumatic head injury and senile dementia of the Lewy body type [7, 14, 15]. Hyman and colleagues [8] have found that adults with DS with an apoE-ε4 allele have greater deposition of β-amyloid than those without apoE ε4. Our finding of an association between apoE ε4 and earlier age at onset of dementia in individuals with DS strengthens the evidence implicating an interactive role between β-amyloid deposition and the APOE4 protein in the etiology of AD.

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Table 2. Association of Apolipoprotein E Genotype and Dementia

Genotype	n	Affected (n, %)	Cumulative Risk to Age 65	Ratio Rate[a]	95% CI[b]
2/2, 2/3	7	0 (0.0)	0.0	—	
2/4, 3/4, 4/4	22	7 (31.8)	0.74	4.7	(1.2, 17.9)
3/3	53	6 (11.3)	0.45	1.0	(reference group)
Total	82	13 (15.8)	0.57		

[a]Adjusted for level of mental retardation and gender.
[b]CI = confidence interval.

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Confirmation of Linkage of Oculopharyngeal Muscular Dystrophy to Chromosome 14q11.2-q13

Jeffrey M. Stajich, MA, PA-C,* James M. Gilchrist, MD,† Felicia Lennon, BS,* Arnold Lee, BS,* Larry Yamaoka, PhD,* Barbara Helms, BA,* Perry C. Gaskell, PA-C,* Lauren Donald, BA,† Allen D. Roses, MD,* Jeffrey M. Vance, MD,* and Margaret A. Pericak-Vance, PhD*

Oculopharyngeal muscular dystrophy is a late-onset, autosomally dominant disorder characterized by progressive ptosis, dysphagia, and extremity weakness. Linkage of oculopharyngeal muscular dystrophy to 14q11.2-q13 has been reported in a series of French Canadian families. Haplotype analysis in these data shows a single segregating disease chromosome, suggesting a founder effect in this population. We ascertained and sampled for linkage studies 5 multigenerational American families with oculopharyngeal muscular dystrophy. Four of the 5 families have known French Canadian ancestry while the fifth is of English/Scottish origin. A peak multipoint lod score of 6.30 was obtained for the marker MYH7.1 in the families, confirming linkage to 14q11.2-q13. The English/Scottish family exhibited a different chromosomal haplotype for the oculopharyngeal muscular dystrophy alleles than did the families of French Canadian origin. These data suggest that this family may represent a second, possibly independent mutation in this disorder.

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Oculopharyngeal muscular dystrophy (OPMD) is a late-onset, autosomally dominant disorder characterized by progressive ptosis, dysphagia, and extremity weakness. It has a high prevalence in the French Canadian population, most likely as a result of a founder effect [1, 2]. Brais and his colleagues [3] recently reported linkage of OPMD to chromosome 14q11.2-q13. OPMD has been sublocalized further to an area

From the *Division of Neurology, Duke University Medical Center, Durham, NC, and †Department of Neurology, Rhode Island Hospital, Brown University, Providence, RI.

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Address correspondence to Dr Pericak-Vance, Duke University Medical Center, Division of Neurology, Bryan Research Building, Box 2900, Room 227, Durham, NC 27710.