npg

ARTICLE

Apolipoprotein E gene in frontotemporal dementia: an association study and meta-analysis

Patrice Verpillat*[,1,2], Agnès Camuzat[3], Didier Hannequin[4,5],
Catherine Thomas-Anterion[6], Michèle Puel[7], Serge Belliard[8], Bruno Dubois[9],
Mira Didic[10,11], Lucette Lacomblez[12,13], Olivier Moreaud[14], Véronique Golfier[8],
Dominique Campion[4], Alexis Brice[3,9,15] and Françoise Clerget-Darpoux[1]

[1]INSERM U535, Le Kremlin Bicêtre, France; [2]Département d'Epidémiologie, de Biostatistique et de Recherche
Clinique, Centre Hospitalier Universitaire Bichat-Claude Bernard, AP-HP/Université Paris VII, Paris, France;
[3]INSERM U289, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France; [4]INSERM EPI 9906, Rouen, France;
[5]Service de Neurologie, Centre Hospitalier Universitaire, Rouen, France; [6]Service de Neurologie, Centre Hospitalier
Universitaire, Saint-Etienne, France; [7]Service de Neurologie, Centre Hospitalier Universitaire Purpan, Toulouse,
France; [8]Service de Neurologie, Centre Hospitalier Universitaire Pontchaillou, Rennes, France; [9]Fédération de
Neurologie, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France; [10]Service de Neurologie et
Neuropsychologie, Centre Hospitalier Universitaire de la Timone, Marseille, France; [11]INSERM EMI U9926, Marseille,
France; [12]Fédération de Neurologie Mazarin, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France;
[13]Département de Pharmacologie, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France; [14]Service de
Neurologie, Centre Hospitalier Universitaire, Grenoble, France; [15]Département de Génétique, Cytogénétique et
Embryologie, Centre Hospitalier Universitaire Pitié-Salpêtrière, Paris, France

No definite genetic risk factor of non-monogenic frontotemporal dementia (FTD) has yet been identified. Several groups have examined the potential association of FTD with the apolipoprotein E (APOE) gene, but the results are inconsistent. Our objective was to determine whether APOE is a risk factor of FTD, using the largest series of patients with FTD and controls analysed so far (94 unrelated patients and 392 age and sex-matched controls), and a meta-analysis. Homozygosity for the E2E2 genotype was significantly associated with FTD (odds ratio (OR)=11.3; P=0.033, exact test). After stratification on familial history (FH) for FTD, the OR for E2E2 was still found significant when analysing only patients with a positive FH (OR=23.8; P=0.019). The meta-analysis, using 10 case–control studies with available genotype or allele information, comprising a total of 364 FTD patients and 2671 controls, including the patients of the present study, did not reach statistical significance even if the E2E2 genotype was more frequent in patients than in controls (0.018 vs 0.006, respectively). Because of studies heterogeneity (Mantel-Haenszel statistics: P=0.004), we analysed on one hand the neuropathologically-confirmed studies, and on the other hand the clinical-based studies. In the neuropathologically-confirmed studies (Mantel–Haenszel statistics: P=ns), we found a significant increase of the E2 allele frequency in FTD patients (OR[E2 vs E3]=2.01; 95% CI=1.02–3.98; P=0.04). The same result was found in the clinical-based studies, but studies heterogeneity remained. No result was significant with the E4 allele. The E2 allele

seems so to be a risk factor of FTD whereas this allele is associated with the lowest risk in Alzheimer's disease. If this finding was confirmed, it could provide new insights into the mechanisms of differential risk related to APOE in neurodegenerative diseases.

Introduction

Frontotemporal dementia (FTD) is one of the most common cause of neurodegenerative dementia after Alzheimer's disease (AD).[1] Since the Lund and Manchester groups consensus conference in April 1994,[2] clinical and neuropathological criteria for FTD have been well established. This has lead to a better distinction of FTD from AD, which is the most frequent misdiagnosis of FTD.[3,4] Recently, mutations in the tau gene localised to 17q21 have been identified in several families with autosomal dominant inheritance.[5–8] To date, ten missense mutations, two deletions, and three transition mutations not altering the encoded amino-acid sequence have been identified in exons of the tau gene.[9] In addition, six intronic mutations have also been found in the 5′ splice donor site of exon 10.[9,10] These mutations were detected in 25 to 40% of families with FTD that have autosomal dominant inheritance.[6,8,11] However, genetic heterogeneity has been demonstrated, since another locus for FTD has been mapped on chromosome 3 in a single large pedigree.[12] The genetics of non-monogenic FTD has been less studied, although several groups have examined the potential association of FTD with the apolipoprotein E (APOE) gene, with inconsistent results.[13–26]

The E4 allele of the APOE gene is now undeniably the most important risk factor in non-monogenic forms of AD. Although findings have not been as consistent as in AD, an increase in the APOE E4 allele frequency has been variably observed in other forms of dementia, including diffuse Lewy body disease[27–29] and vascular dementia.[30,31] But it does not appear to be an important risk factor in several other neurodegenerative processes, like progressive supranuclear palsy[32] and Parkinson's disease.[33,34] Some reports have suggested that APOE might also be a risk factor in FTD. Initially, Gustafson et al[13] reported a higher E4 allele and E4E4 genotype frequency in patients with FTD than in controls, and an even more significant increase of the E2 allele. Stevens et al[14] have also found a significantly increased risk for the E4 allele and E4E4 genotype in FTD. Subsequently, the results of a further study have suggested that the E2 allele, rather than the E4 allele, could be the risk factor for FTD.[15] Finally, a recent study has shown a significant increase of the E4 allele in an FTD population compared to healthy controls.[26] But ten other studies have not replicated this association.[16–25]

Because all previous studies have been based on relatively small samples (less than 35 except one study with 88 FTD patients), we have re-examined the role of APOE in a larger case–control study of 94 FTD patients and 392 controls. We performed also a meta-analysis using all published findings of similar case–control studies conducted until November 2001 to evaluate the effect of APOE as a risk factor for FTD.

Methods
Subjects

All patients were ascertained over a 3-year period through consecutive admissions to 10 university hospitals in France. In this sample, we analysed the tau gene in probands with autosomal dominant inheritance by direct sequencing (exons 1–5, 7 and 9–14, and the corresponding flanking intronic sequences). The same mutation, P301L, was found in six patients.[8] After excluding these six patients with autosomal dominant inheritance and mutation of tau, our sample for the present study was thus composed of 94 unrelated patients with FTD (41.5% men). All patients with FTD underwent a thorough clinical examination, including personal and familial medical history, neurological and psychiatric investigations, psychometric testing (Mini-Mental State Examination[35], Mattis Dementia Rating Scale[36], Verbal Learning Test[37] and Frontal Assessment Battery[38]), laboratory tests, computed tomography and magnetic resonance imaging, regional cerebral blood flow measurement (single-photon emission computed tomography) and electroencephalography. The diagnosis of FTD was established according to the Lund-Manchester clinical consensus criteria for FTD.[2] Age at onset was assessed by interviewing a next of kin and was defined as the age at which relevant symptoms first appeared according to the family (mean±SD age at onset, 60.6±8.5 years; range, 43–77 years). In our study, we identified 31 patients with one or more first- or second-degree relatives with FTD (33%; 35.5% men; mean±SD age at onset, 60.2±7.9 years; range, 45–77 years), but without clear autosomal dominant inheritance and without mutation in the tau gene.

Patients with FTD were compared with 392 age- and sex-matched controls (44.9% men; mean±SD age at examination, 62.5±8.7 years; range, 38–77 years). Control subjects were the patients' spouses or healthy blood donors or individuals living in nursing homes. None of the controls showed cognitive deficits or behavioural disturbance.

All participants in this study were white and were living in France. Informed written consent was obtained for all participants, either directly or from the legal tutor.

Meta-analysis

For the meta-analysis we searched through Medline for all studies performed for APOE in FTD until November 2001, and reviewed the references in the retrieved articles. Fourteen association studies were found.[13–26] Two different meta-analysis were performed: one with the genotypes, and another with the alleles. For the first meta-analysis, we included only the seven studies with available information on exact genotype frequencies.[14,15,18,20,22–24] For the second meta-analysis, three additional studies with available information on allele frequencies only were included.[13,17,21] Four studies could not be included in any meta-analysis because no information on exact genotype or allele frequencies was provided.[16,19,25,26] In all selected studies, we have verified that the controls were in Hardy–Weinberg Equilibrium (HWE). Table 1 provides the clinical descriptions and design of the studies included in the meta-analysis.

Genetic analysis

DNA was extracted from blood lymphocytes using standard methods. APOE genotypes were determined by restriction enzyme digestion according to the method of Hixson and Vernier.[39]

Statistical analysis

Power computations were made with nQuery Advisor® Release 4.0. Statistical analysis were performed using SAS software release 8.0 (SAS Institute, Cary, NC, USA). For initial comparisons, the two-sided χ^2 test or Fisher exact test when appropriate was used to determine potential differences in the distribution of the APOE genotypes and alleles between groups. Student *t*-test was employed to compare differences between mean age at onset and mean age at examination in the two groups, and non parametric Mann–Whitney test to compare differences between mean age at onset in the group with FTD according to APOE genotypes. Mantel–Haenszel–Peto statistics was performed to test for heterogeneity between studies selected for the meta-analysis and to compute weighted odds ratio.[40,41]

Results

Association study

No deviation from the HWE was observed among controls. Assuming a two-sided significance level (α) of 0.05 and a power (1-β) of 80%, the size of our sample was sufficient to detect an OR of at least 1.8 when bearing the E4 allele and 2.2 when bearing the E2 allele.

Genotype and allele frequencies in the control group were similar to frequencies reported in Caucasian populations (Table 2). The distribution of the APOE genotypes among patients with FTD and controls was significantly different (P=0.041, exact test). We found that the E2E2 frequency was more than 10-fold higher in patients than

Table 2 APOE genotype and allele frequencies in patients with FTD and controls

	FTD patients	Controls	
Genotypes	(*n*=94)	(*n*=392)	
E2E2	3.2 (3)	0.3 (1)	
E2E3	13.8 (13)	13.0 (51)	
E2E4	2.1 (2)	3.3 (13)	
E3E3	63.8 (60)	57.6 (226)	
E3E4	14.9 (14)	24.5 (96)	
E4E4	2.1 (2)	1.3 (5)	P=0.041 (exact test)
Alleles	(*n*=188)	(*n*=784)	
E2	11.2 (21)	8.4 (66)	
E3	78.2 (147)	76.4 (599)	
E4	10.6 (20)	15.2 (119)	P=0.171

Table 1 Clinical description of the populations included in the meta-analysis

					Case samples					Control samples		
Study	Country (region)	n	Sample type	% FH+	% M	Age, years mean ± SD	Diagnostic criteria	% NP	n	Clinical status	% M	Age, years mean ± SD
Farrer *et al.*[22]	USA (MA)	10	C	58	100	60.4±5.4*	AC	100	1204	–	–	§-1
Geschwind *et al.*[20]	USA (CA)	33	C	42	48	55±11*	L-M/AC	33	30	AC	43	73±14
Gomez-Isla *et al.*[24]	USA (MA)	31	C	–	52	68.3±13.3†	AC	100	129	–	40	77.8±13.5
Gustafson *et al.*[13]	Sweden	21	C	52	29	59±10.5*	L-M	0	29	C	–	§-2
Helisalmi *et al.*[18]	Finland	9	C	–	33	66±8*	–	–	60	–	47	69±8
Lehmann *et al.*[15]	UK (Oxford)	11	P	0	45	65.7‡	L-M/AC	82	136	C	43	77.5
Pickering-Brown *et al.*[17]	UK (Manchester)	27	C	–	–	–	L-M/AC	48	35	–	–	–
Pickering-Brown *et al.*[21]	UK (Manchester)	88	C	34	53	56.9±10.1*	L-M/AC	56	35	–	–	–
Schneider *et al.*[23]	USA (GA)	6	C	–	–	–	AC	100	95	–	–	–
Stevens *et al.*[14]	The Netherlands	34	P	0	35	52.1±9.2*	L-M	0	561	C	43	59.9±2.8
Current study	France	94	C	33	41	60.6±8.5*	L-M/AC	3	392	C	45	62.5±8.7

*Age at onset; †age (not specified); ‡age at death or last examination; §only the range of age is specified (for 1: 22 to 71, for 2: 25 to 50). FH+=positive familial history; %M=% of males; %NP=% of neuropathological confirmation; C=clinical-based sample; P=population-based sample; AC=autopsy confirmed; L-M=Lund-Manchester clinical consensus criteria for FTD[2]; –=not available.

in controls (OR[E2E2 vs E3E3]=11.3; P=0.033, exact test). Heterozygosity did not involve a significantly increased risk. The allele distribution was not significantly different between patients and controls, even if we observed a non-significant increase of the E2 allele frequency in patients. After stratification on the absence (FH−) or presence (FH+) of familial history of FTD, the result was even more significant in the group with a positive familial history (FH+) of FTD (E2E2 vs E3E3: in FH+ group, OR=23.8; P=0.019, exact test; in FH− group, OR=5.5; P=0.29, exact test). This result remained significant even after a Bonferroni correction for multiple testing (corrected P-value=0.038). Further analysis of the APOE genotype in the whole sample of patients with FTD showed that the three patients with the E2E2 genotype had a lower mean age at onset than the 91 patients lacking this genotype (54.7±8.4 and 60.7±8.4, respectively), but this difference was not statistically significant, probably because of the small sample size. The same tendency was found in the FH+ group, but not in the FH− group (data not shown).

The same analyses were performed with the E3E4 and E4E4 genotypes, and the E4 allele. None was significant.

Meta-analysis

For the meta-analysis of the APOE polymorphism in FTD, we were able to pool seven case–control studies with genotype information (total of 228 FTD patients and 2607 controls including ours),[14,15,18,20,22–24] and three more with allele information (total of 364 FTD patients and 2671 controls including ours).[13,17,21] Some studies included only neuropathologically-confirmed patients,[22–24] when others were mainly clinical-based,[13–15,17,18,20,21] as ours. All populations were Caucasian.

We have first used the studies with available information on the genotype distribution among patients with FTD and controls. There was no significant difference between patients and controls (Table 3). The E2E2 genotype was more frequent in patients than in controls but this difference failed to reach statistical significance (OR[E2E2 vs E3E3]=3.08; P=0.06, exact test). We next investigated the association with the E2 allele in the 10 selected studies (Table 3). We found a significant increase of the E2 allele frequency in patients with FTD compared to controls (OR[E2 vs E3]=1.64; P=0.004) (Figure 1). But the Mantel–Haenszel statistics to test heterogeneity among studies was significant (P=0.004). Instead of considering one or more of the data sets as an outlier based on APOE genotype distribution and excluding it or them from the meta-analysis, we decided to reduce the heterogeneity of the meta-analysis in discriminating the studies according to the mode of recruitment (autopsy or clinic). Considering the 10 studies selected for the meta-analysis, three[22–24] were based only on neuropathologically-confirmed FTD patients, and another[21] provided allelic information on a subgroup of autopsied patients. For the latter, we have so added this

Table 3 Meta-analysis of APOE distribution in patients with FTD and controls

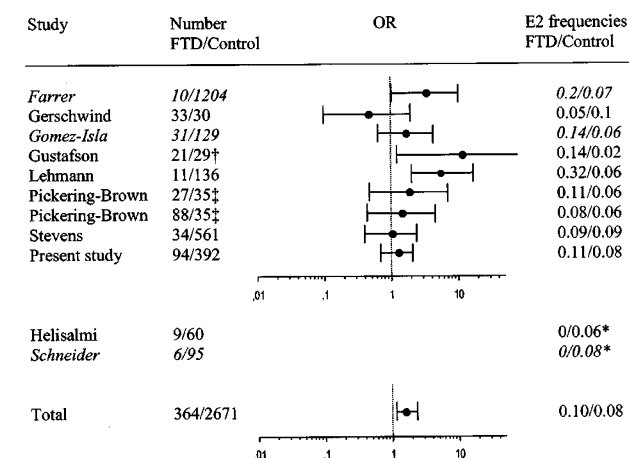*(a) Pooled genotype distribution of the 7 case-control studies[14,15,18,20,22–24] and the present study*

	APOE genotype					
	E2E2	E2E3	E2E4	E3E3	E3E4	E4E4
FTD patients (n=228)	1.8 (4)	14.9 (34)	2.6 (6)	56.6 (129)	19.7 (45)	4.4 (10)
Control (n=2607)	0.6 (16)	12.3 (322)	2.3 (60)	60.9 (1587)	21.3 (555)	2.6 (67)

P=ns

(b) Pooled allele distribution of the 10 case–control studies[13–15,17,18,20–24] and the present study

	APOE allele		
	E2	E3	E4
FTD patients (n=364)	10.2 (74)	73.1 (532)	16.7 (122)
Controls (n=2671)	7.8 (419)	77.8 (4155)	14.4 (768)

P=0.014.

Study	Number FTD/Control	OR	E2 frequencies FTD/Control
Farrer	10/1204		0.2/0.07
Gerschwind	33/30		0.05/0.1
Gomez-Isla	31/129		0.14/0.06
Gustafson	21/29†		0.14/0.02
Lehmann	11/136		0.32/0.06
Pickering-Brown	27/35‡		0.11/0.06
Pickering-Brown	88/35‡		0.08/0.06
Stevens	34/561		0.09/0.09
Present study	94/392		0.11/0.08
Helisalmi	9/60		0/0.06*
Schneider	6/95		0/0.08*
Total	364/2671		0.10/0.08

Figure 1 Meta-analysis of the E2 allele in FTD. Mantel–Haenszel statistics: χ^2=25.7, 10 df, P=0.004. OR: odds ratios for the E2 allele vs E3 allele. Horizontal lines represent the 95% CI for the OR. †The OR 95%CI was 1.37−105.41. ‡The control group was the same for the two studies and was therefore included only once in the pooled control group. *No OR estimation was possible because of division by 0. The studies which were completely based on neuropathologically-confirmed patients are indicated in italics.

subgroup to the three others studies with neuropathological cases, and included the clinical-based subgroup of this study with the seven other clinical-based studies. In the studies with neuropathologically-confirmed FTD patients, we found a significant increase of the E2 allele frequency in patients (OR[E2 vs E3]=2.01; 95%CI=1.02–3.98; P=0.04). The same result was found in the clinical-based

studies (OR[E2 *vs* E3]=1.53; 95%CI=1.06–2.23; *P*=0.02). Moreover, heterogeneity disappeared in the neuropathological-based group (Mantel–Haenszel statistics: *P*=ns), but remained significant in the clinical-based group (*P*=0.004).

The meta-analysis was also performed to test the role of the E4 allele. No significant difference was found (OR[E4 *vs* E3]=1.19; 95%CI=0.92–1.54 including all studies; OR[E4 *vs* E3]=1.20; 95%CI=0.71–2.01 in the neuropathologically-confirmed studies; OR[E4 *vs* E3]=1.19; 95%CI=0.89–1.58 in the clinical-based studies).

Discussion

The results of our case–control study suggest that subjects who are homozygous for the APOE E2 allele are at increased risk for developing FTD. After stratification on familial history of FTD, the OR for E2E2 remains significant among patients with a positive FH (OR=23.8; *P*=0.019), even if the sample size is smaller (31 patients with FTD). Because E2 allele and E2E2 genotype frequencies are small in the general population (approximately 7% and 0.5% in the Caucasian population, respectively), our findings of a higher proportion of E2E2 genotype in patients compared to controls is marginally significant and predicated on very few subjects (three patients and one control). We have thus confirmed the genotype for these four subjects. Moreover, our data confirms some results of two previous studies.[13,15] Indeed, Gustafson *et al* have found a significantly higher E2 frequency in their 21 patients with FTD (14.3%) compared to 29 controls (1.7%),[13] as did Lehmann *et al*[15] who calculated an OR of 7.0 [2.5–19.5] for E2, using 11 patients with sporadic FTD (including nine patients with histopathological confirmation) and 136 controls from the cohort of the Oxford project to investigate memory and aging. In contrast, the implication of the E2 allele was not evidenced by a dozen studies which found either a significant increase of the E4 allele, or no significant difference in APOE allele or genotype frequency. These discrepancies could have many explanations. Firstly, the sample sizes of the previous studies were small (less then 35 except one study[21] with 88 patients with FTD, in which two different subgroups are identifiable, the one of 49 autopsy verified patients and the other of 39 clinical-based patients). Most of them probably did not have sufficient *a priori* statistical power to determine the effect of the relatively rare E2 allele. Our study with 94 FTD patients was sufficiently powerful to detect an effect of equivalent size to that reported by Stevens *et al*[14] for the E4 allele and by Lehmann *et al*[15] for the E2 allele (80% and >99%, respectively). Secondly, most studies relied on clinical diagnosis without reference to valid criteria for FTD. In these studies, the inclusion of patients with misdiagnosed AD could occur as a possible confounding factor. Besides, all the studies which have found an association with the E4 allele were performed exclusively with clinical-based patients. The inadvertent

inclusion of patients with AD would 'spuriously' inflate the E4 frequency and, on the contrary, decrease the E2 frequency. Since the Lund and Manchester consensus conference,[2] clinical criteria for FTD diagnosis are increasingly precise and allow to better distinguish between AD and FTD. If a significant number of patients with AD might have been inadvertently included in the first published studies, this has now become less likely. Although only a small proportion of the patients were examined neuropathologically (3%) which allowed confirmation of the diagnosis of FTD, misdiagnosis as AD in our study is un-likely given the criteria used to assess patients. Indeed, diagnosis of FTD was based on strict criteria: (a) clinical diagnosis according to the Lund–Manchester clinical consensus criteria for FTD[2], (b) neuropsychological confirmation of frontal lobe dysfunction, (c) frontal or frontotemporal atrophy on computed tomography or magnetic resonance images, (d) frontal or frontotemporal hypoperfusion on single-photon emission computed tomographic images and, (e) clinical and neuropsychological annual follow-up. Thirdly, studies often provide little information on case–control matching. Bickeböller *et al* have demonstrated that the frequency of the E4 allele was lower in males over 60 years of age than in females.[42] As the APOE allele frequency varies according to age and sex, it is crucial either to match patients and controls according to these two variables, or to take them into account by multivariate analyses.

In the meta-analysis, we examined seven case–control studies with genotype information[14,15,18,20,22–24] and three more with allele information[13,17,21] (total of 364 FTD patients and 2671 controls including ours). Using genotypes, the meta-analysis did not allow to reach statistically significant level even if the E2E2 genotype was more frequent in patients than in controls. We found a significant increase of the E2 allele frequency in FTD patients compared to controls, but also a heterogeneity between the different studies. We have then performed the meta-analysis in two more 'homogeneous' groups, based on the study design: on the one hand, the studies with available data in autopsy group of patients (neuropathologically-confirmed studies); on the other hand, the clinical-based studies. In the first group, an overall OR was then calculated which confirmed the role of the E2 allele in these patients with an accurate diagnosis of FTD. The same result was found in the clinical-based studies. Moreover, heterogeneity disappeared in the neuropathological-based group, but remained significant in the clinical-based group, showing the importance of the mode of recruitment for patients with FTD. We have also searched for an effect of the E4 allele in the meta-analysis. Any result was significant. Since we have found that the effect of APOE E2 is more marked in patients with positive family history, it would have been interesting to study the genotype and allele distributions according to FH. Unfortunately, even if it was indicated

in several previous studies, most of them did not provide enough information to stratify the meta-analysis on FH.

In summary, both the genetic association study and the meta-analysis indicate that the E2 allele may be a risk factor for FTD. However, these data should be interpreted with caution because of the relatively small sample size of patients with FTD analysed and the rarity of the E2E2 genotype. As already stated by Lehmann *et al* in their article,[15] if this finding was confirmed, it could provide new insights to explore mechanisms of differential risk related to APOE in neurodegenerative diseases as AD and FTD.

Acknowledgements

References

1 Jackson M, Lowe J: The new neuropathology of degenerative frontotemporal dementias. *Acta Neuropathol* 1996; **91**: 127–134.

2 Clinical and neuropathological criteria for frontotemporal dementia. The Lund Manchester Groups. *J Neurol Neurosurg Psychiatry* 1994; **57**: 416–418.

3 Mendez MF, Selwood A, Mastri AR, Frey WH: Pick's disease versus Alzheimer's disease: a comparison of clinical characteristics. *Neurology* 1993; **43**: 289–292.

4 Gearing M, Mirra SS, Hedreen JC *et al*: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part X. Neuropathology confirmation of the clinical diagnosis of Alzheimer's disease. *Neurology* 1995; **45**: 461–466.

5 Spillantini MG, Murrell JR, Goedert M *et al*: Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci USA* 1998; **95**: 7737–7741.

6 Hutton M, Lendon CL, Rizzu P *et al*: Association of missense and 5′-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998; **393**: 702–705.

7 Poorkaj P, Bird TD, Wijsman E *et al*: Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* 1998; **43**: 815–825.

8 Dumanchin C, Camuzat A, Campion D *et al*: Segregation of a missense mutation in the microtubule-associated protein tau gene with familial frontotemporal dementia and parkinsonism. *Hum Mol Genet* 1998; **7**: 1825–1829.

9 Reed LA, Wszolek ZK, Hutton M: Phenotypic correlations in FTDP-17. *Neurobiol Aging* 2001; **22**: 89–107.

10 Miyamoto K, Kowalska A, Hasegawa M *et al*: Familial frontotemporal dementia and parkinsonism with a novel mutation at an intron 10+11-splice site in the tau gene. *Ann Neurol* 2001; **50**: 117–120.

11 Rizzu P, Van Swieten JC, Joosse M *et al*: High prevalence of mutations in the microtubule-associated protein tau in a population study of frontotemporal dementia in the Netherlands. *Am J Hum Genet* 1999; **64**: 414–421.

12 Brown J, Ashworth A, Gydesen S *et al*: Familial non-specific dementia maps to chromosome 3. *Hum Mol Genet* 1995; **4**: 1625–1628.

13 Gustafson L, Abrahamson M, Grubb A, Nilsson K, Fex G: Apolipoprotein-E genotyping in Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord* 1997; **8**: 240–243.

14 Stevens M, van Duijn CM, de Knijff P *et al*: Apolipoprotein E gene and sporadic frontal lobe dementia. *Neurology* 1997; **48**: 1526–1529.

15 Lehmann DJ, Smith AD, Combrinck M, Barnetson L, Joachim C: Apolipoprotein E epsilon2 may be a risk factor for sporadic frontotemporal dementia. *J Neurol Neurosurg Psychiatry* 2000; **69**: 404–405.

16 Czech C, Monning V, Tienari PJ *et al*: Apolipoprotein E-epsilon 4 allele and Alzheimer's disease. *Lancet* 1993; **342**:1309.

17 Pickering-Brown SM, Siddons M, Mann DM *et al*: Apolipoprotein E allelic frequencies in patients with lobar atrophy. *Neurosci Lett* 1995; **188**: 205–207.

18 Helisalmi S, Linnaranta K, Lehtovirta M *et al*: Apolipoprotein E polymorphism in patients with different neurodegenerative disorders. *Neurosci Lett* 1996; **205**: 61–64.

19 Minthon L, Hesse C, Sjogren M *et al*: The apolipoprotein E epsilon4 allele frequency is normal in fronto- temporal dementia, but correlates with age at onset of disease. *Neurosci Lett* 1997; **226**: 65–67.

20 Geschwind D, Karrim J, Nelson SF, Miller B: The apolipoprotein E epsilon4 allele is not a significant risk factor for frontotemporal dementia. *Ann Neurol* 1998; **44**: 134–138.

21 Pickering-Brown SM, Owen F, Isaacs A *et al*: Apolipoprotein E epsilon4 allele has no effect on age at onset or duration of disease in cases of frontotemporal dementia with pick- or microvacuolar-type histology. *Exp Neurol* 2000; **163**: 452–456.

22 Farrer LA, Abraham CR, Volicer L *et al*: Allele epsilon 4 of apolipoprotein E shows a dose effect on age at onset of Pick disease. *Exp Neurol* 1995; **136**: 162–170.

23 Schneider JA, Gearing M, Robbins RS, de l'Aune W, Mirra SS: Apolipoprotein E genotype in diverse neurodegenerative disorders. *Ann Neurol* 1995; **38**: 131–135.

24 Gomez-Isla T, West HL, Rebeck GW *et al*: Clinical and pathological correlates of apolipoprotein E epsilon 4 in Alzheimer's disease. *Ann Neurol* 1996; **39**: 62–70.

25 Neary D, Pickering-Brown S, Roberts DA, Owen F: Apolipoprotein E4 alleles and Non-Alzheimer's Disease forms of dementia. *Neurodegeneration* 1993; **2**: 300–301.

26 Fabre SF, Forsell C, Viitanen M *et al*: Clinic-based cases with frontotemporal dementia show increased cerebrospinal fluid tau and high apolipoprotein E epsilon4 frequency, but no tau gene mutations. *Exp Neurol* 2001; **168**: 413–418.

27 Pickering-Brown SM, Mann DM, Bourke JP *et al*: Apolipoprotein E4 and Alzheimer's disease pathology in Lewy body disease and in other beta-amyloid-forming diseases. *Lancet* 1994; **343**:1155.

28 Arai H, Higuchi S, Muramatsu T *et al*: Apolipoprotein E gene in diffuse Lewy body disease with or without co-existing Alzheimer's disease. *Lancet* 1994; **344**:1307.

29 St Clair D, Norrman J, Perry R *et al*: Apolipoprotein E epsilon 4 allele frequency in patients with Lewy body dementia, Alzheimer's disease and age-matched controls. *Neurosci Lett* 1994; **176**: 45–46.

30 Frisoni GB, Geroldi C, Bianchetti A *et al*: Apolipoprotein E epsilon 4 allele frequency in vascular dementia and Alzheimer's disease. *Stroke* 1994; **25**: 1703–1704.

31 Noguchi S, Murakami K, Yamada N: Apolipoprotein E genotype Alzheimer's disease. *Lancet* 1993; **342**: 737.

32 Anouti A, Schmidt K, Lyons KE *et al*: Normal distribution of apolipoprotein E alleles in progressive supranuclear palsy. *Neurology* 1996; **46**: 1156–1157.

33 Arai H, Muramatsu T, Higuchi S, Sasaki H, Trojanowski JQ: Apolipoprotein E gene in Parkinson's disease with or without dementia. *Lancet* 1994; **344**:889.

34 Marder K, Maestre G, Cote L *et al*: The apolipoprotein epsilon 4 allele in Parkinson's disease with and without dementia. *Neurology* 1994; **44**: 1330–1331.

35 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12**: 189–198.

36 Mattis S: *Dementia rating scale* Odessa, FL: Psychological Assessment Ressources Inc 1988.

37 Grober E, Buschke H: Genuine memory deficits in dementia. *Dev Neuropsychol* 1987; **3**: 13–36.
38 Dubois B, Slachevsky A, Litvan I, Pillon B: The FAB: a Frontal Assessment Battery at bedside. *Neurology* 2000; **55**: 1621–1626.
39 Hixson JE, Vernier DT: Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990; **31**: 545–548.

40 Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1959; **22**: 719–748.
41 Pignon JP, Poynard T: Meta-analysis of clinical trials. *Gastroenterol Clin Biol* 1991; **15**: 229–238.
42 Bickeböller H, Campion D, Brice A *et al*: Apolipoprotein E and Alzheimer disease: genotype-specific risks by age and sex. *Am J Hum Genet* 1997; **60**: 439–446.