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## Apolipoprotein E polymorphisms in frontotemporal lobar degeneration: A meta-analysis

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### Abstract

**Objective:** Case–control studies have not been consistent in showing association between apolipoprotein E (APOE) polymorphisms and frontotemporal lobar degeneration (FTLD), producing contradictory findings. The study objective was to define and quantify further the disease risk associated with the carriage of different APOE alleles to determine whether APOE gene polymorphism is a risk factor for FTLD.

**Methods:** A systematic review of all case–control studies investigating the association between the APOE gene and FTLD up to December 2011 was conducted. Case–control studies using clinical or pathological criteria for FTLD and reporting APOE allelic or genotypic data were included. Pooled odds ratios (ORs) were estimated using a random effects model, and 95% confidence intervals (CIs) were calculated.

**Results:** Twenty-eight case–control studies met the inclusion criteria. Carriage of the  $\epsilon 2$  allele had no effect on disease risk. On the contrary, carriage of the  $\epsilon 4$  allele was associated with a significantly increased disease risk ( $\epsilon 4$  carriers vs non- $\epsilon 4$  carriers: OR, 1.94; 95% CI, 1.43–2.64;  $\epsilon 4$  vs  $\epsilon 3$  allele: OR, 1.83; 95% CI, 1.34–2.52). Furthermore, a gene–dosage effect for the  $\epsilon 4$  allele was found. There was no evidence of publication bias, but heterogeneity between the studies was high.

**Conclusions:** Our study provides evidence for an association between the APOE  $\epsilon 4$  allele and frontotemporal lobar degeneration.

**Keywords:** Frontotemporal lobar degeneration; Case–control study; APOE; Polymorphism; Meta-analysis

### 1. Introduction

Frontotemporal lobar degeneration (FTLD) is a clinically, pathologically, and genetically heterogeneous disorder that accounts for up to 20% of dementia cases [1]. To date, FTLD has been linked to several disease-causing genes (CHMP2B, MAPT, PGRN, TARDBP, UBQLN2, VCP, SQSTM1, and C9orf72) [2,3]. The first genomewide association study performed in patients with FTLD identified TMEM106B as a genetic risk factor for FTLD with TAR DNA-binding protein 43 (TDP-43) inclusions [4]. Nevertheless, there is evidence of additional genetic heterogeneity in the disease, and several other genes probably modulate the risk of developing FTLD.

The apolipoprotein E (APOE) gene is located on chromosome 19q13.2 and it codes for a polymorphic protein— a product of alleles  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ —that performs isoform-dependent neurotrophic and antioxidant functions. The APOE gene has been known since 1993 as a major gene involved in late-onset Alzheimer's disease (AD) [5]. However, many researchers have wondered whether the APOE  $\epsilon 4$  allele may also increase the risk for the development of other neurodegenerative disorders such as Lewy body dementia and Parkinson's disease.

Several research groups investigated the role of the APOE gene in FTLD risk with inconclusive results. Much of this disagreement undoubtedly revolves around the use of relatively small studies with a low power to detect the association. In 2002, Verpillat and colleagues [6] performed a meta-analysis, including studies published until November 2001, showing that APOE  $\epsilon 2$  allelic frequency was significantly increased in the overall FTLD patients compared with control subjects.

To define and quantify the disease risk associated with the carriage of different APOE alleles further, we performed an updated meta-analysis of all existing studies, evaluating allelic and genotypic frequencies of the polymorphisms in FTLD.

## 2. Methods

### 2.1. Study selection

We identified eligible studies by searching Medline for all publications about the APOE genotype and FTLD up to December 2011. We used the search index terms APOE, apolipoprotein E, and APOE polymorphism, in combination with FTLD, FTD, frontotemporal dementia, lobar degeneration, and frontotemporal lobar degeneration. We also performed a separate search to identify FTLD subgroups using the terms APOE, apolipoprotein E, and APOE polymorphism, in combination with SD, semantic dementia, bv FTD, behavioral frontotemporal dementia, PPA, PA, primary progressive aphasia, PNFA, and progressive nonfluent aphasia. We also carried out an additional search of the references cited in the retrieved articles. We included in our meta-analysis all case-control studies with extractable data, published either as full-length articles or letters in peer-reviewed journals. Diagnosis of FTLD was made according to currently validated criteria [7–10]. In case of duplicate studies, the smaller data set was excluded. Fig. 1 shows the flowchart of study selection.

### 2.2. Data extraction and quality assessment

The following data were extracted from each study: first author, journal, year of publication, ethnicity of study population, genotyping method, allelic and genotypic frequencies of polymorphism, diagnosis of subgroups, number of patients and control subjects, age, sex, and number of neuropathologically confirmed cases. When allelic frequencies were lacking, we calculated them using genetic standard formulae. Data were extracted independently and in duplicate by two investigators (E.R. and I.R.).

### 2.3. Statistical analysis

Comprehensive Meta-Analysis Version 2.2.064 (Biostat, Englewood, NJ, USA) 2 was used to analyze our data [11]. Because the heterogeneity between studies was high, we used random effects (RE) to calculate the pooled odds ratio (OR). A funnel plot was drawn, using the Egger regression test for funnel plot asymmetry to assess small-study and publication biases. In addition, the Kendall's tau with continuity test was used [12]. To assess the association between APOE polymorphisms and the risk of developing FTLD, we compared the allelic and genotypic frequencies of APOE between FTLD patients and healthy control subjects. Afterward, because FTLD presentation is heterogeneous, we compared control subjects vs patients with behavioral frontotemporal dementia (bvFTD) and patients with deficits of linguistic functions (language variant of frontotemporal dementia [lvFTD]), including those previously diagnosed with progressive nonfluent aphasia, semantic dementia, or primary progressive aphasia (PPA). For this last group, a diagnosis of probable sporadic AD disease was excluded in all the studies selected for this analysis.

We analyzed the effect of the  $\epsilon 4$  and  $\epsilon 2$  alleles as risk factors for developing the disease. According to other metaanalyses for allele analysis, the Q test for heterogeneity was performed separately for two odds ratio:  $\epsilon 2$  allele vs  $\epsilon 3$  allele and  $\epsilon 4$  allele vs  $\epsilon 3$  allele, assigning  $\epsilon 3$  as the reference allele. The effect size of the  $\epsilon 4$  or  $\epsilon 2$  allele on the risk of developing FTLD was expressed for each study in terms of OR and 95% confidence interval (CI), newly calculated using our genetic data. Furthermore, comparisons between  $\epsilon 2$  vs non- $\epsilon 2$  carriers and  $\epsilon 4$  vs non- $\epsilon 4$  carriers were performed. For genotype analysis, when possible we performed separate pregenotyped analyses between homozygotes  $\epsilon 2\epsilon 2$  vs  $\epsilon 3\epsilon 3$ ,  $\epsilon 4\epsilon 4$  vs  $\epsilon 3\epsilon 3$ , and heterozygotes  $\epsilon 3\epsilon 4$  vs  $\epsilon 3\epsilon 3$ , explored by assigning  $\epsilon 3\epsilon 3$  as the reference group. We investigated a dose-dependent effect as well.

## 3. Results

### 3.1. Study inclusion and characteristics

A Medline search revealed 52 articles; a manual search of cited references provided three additional articles on the relationship between the APOE polymorphism and FTLD. Two additional studies compared PPA patients and control subjects. Data from 33 articles met the inclusion criteria [6,13–44]. Stevens and colleagues [44], Pickering-Brown and associates [43], Ingelson and coworkers [42], Boccardi and colleagues [41], and Acciarri and associates [40] were excluded because the cohorts of patients they analyzed were later included in papers by Rosso and coworkers [25], Srinivasan and colleagues [30], Fabre and associates [21],

Boccardi and coworkers [27], and Seripa and colleagues [37], respectively. Table 1 summarizes the clinical characteristics of the populations included in the meta-analysis.

In the first meta-analysis (FTLD patients vs control subjects), 28 case–control studies with allelic information about carrying or not carrying the  $\epsilon 4$  allele, and 21 studies with genotypic distribution were used. Only two studies divided genotypic and allelic frequencies according to sex. In the subgroups analysis, we used eight studies for lvFTD, two of which were used in the analysis of bvFTD.

### 3.2. Meta-analysis

Twenty-eight studies were used for the comparison of  $\epsilon 4$  allelic frequency between patients and control subjects [6,13–39]. The studies included 1630 FTLD patients and 6740 control subjects genotyped for APOE. In all studies, the genotypic distribution in control subjects was in Hardy-Weinberg equilibrium. The heterogeneity for most of the comparisons between FTLD patients and control subjects was high (I<sup>2</sup> . 50%). Table 2 shows the OR and heterogeneity results for APOE polymorphisms in patients with FTLD vs control subjects. The association of allele  $\epsilon 2$  and the risk of developing FTLD, in comparison with the  $\epsilon 3$  allele, did not show any significance; the RE OR was 1.24 (95% CI, 0.89–1.75; P 5.21; I<sup>2</sup> 5 67.49%). Conversely, when comparing the  $\epsilon 4$  allele vs the  $\epsilon 3$  allele, the pooled OR was significant (OR, 1.83; 95% CI, 1.34–2.52; P , .001; I<sup>2</sup> 5 77.62%). More interestingly, when we compared the  $\epsilon 2$  allele vs the  $\epsilon 4$  allele, the pooled OR was also significant (RE OR, 0.62; 95% CI, 0.40–0.97; P , .04; I<sup>2</sup> 5 70.93%) and, inversely, when we compared the  $\epsilon 4$  allele vs the  $\epsilon 2$  allele, subjects carrying  $\epsilon 4$  have a 1.60 increased risk to develop FTLD with respect to control subjects (RE OR, 1.60; 95% CI, 1.03–2.47; P , .04; I<sup>2</sup> 5 70.93%).

The genotype comparisons between  $\epsilon 2\epsilon 2$  vs  $\epsilon 3\epsilon 3$  and  $\epsilon 2\epsilon 2$  1  $\epsilon 2\epsilon 3$  vs  $\epsilon 3\epsilon 3$  showed no difference. Comparing  $\epsilon 2$  carriers vs non- $\epsilon 2$  carriers, the pooled RE OR was 1.06 (95% CI, 0.75–1.48; P 5.75; I<sup>2</sup> 5 62.42%).

On the contrary, during the comparison between subjects with the  $\epsilon 3\epsilon 4$  genotype vs the  $\epsilon 3\epsilon 3$  genotype, the pooled RE OR was 1.75 (95% CI, 1.18–2.59; P 5 .01; I<sup>2</sup> 5 76.45%). When we compared  $\epsilon 4\epsilon 4$  vs  $\epsilon 3\epsilon 3$ , the RE OR was significantly higher (RE OR, 3.30; 95% CI, 2.03–5.35; P ,.001; I<sup>2</sup> 5 0.00%), showing a dose effect of the APOE  $\epsilon 4$  allele. Comparing  $\epsilon 3\epsilon 4$  1  $\epsilon 4\epsilon 4$  vs  $\epsilon 3\epsilon 3$ , the OR was 1.69 (95% CI, 1.21–2.36; P 5.01; I<sup>2</sup> 5 69.01%). Analyzing  $\epsilon 4$  carriers vs non- $\epsilon 4$  carriers, the RE OR was also significant (RE OR, 1.94; 95% CI, 1.43–2.64; P ,.001; I<sup>2</sup> 5 76.93%; Fig. 2).

Graphical analysis of the funnel plots did not provide evidence for selection and publication bias, and did not suggest an overrepresentation of smaller positive studies at the bottom of the graph (Fig. 3). Furthermore, there was no significant publication bias as evidenced by the Egger test (P 5.29) and Kendall's tau with continuity test (one tailed, P 5.35). The I<sup>2</sup> statistic describes a high percentage of variation between the studies in most of the comparisons. Furthermore, the classic measure of heterogeneity calculated by the Q value again showed a high heterogeneity between the studies.

### 3.3. Meta-analysis of pathologically confirmed FTLD

We then restricted the analysis to neuropathologically confirmed cases (five studies) [13,15,16,19,30]. No significant difference was found in the comparison between  $\epsilon 2$  allele carriers vs allele  $\epsilon 3$  carriers or in the comparison between  $\epsilon 4$  allele carriers vs  $\epsilon 3$ allele carriers. Furthermore, we did not find any significant difference when analyzing subjects carrying the  $\epsilon 2$  allele vs those carrying the  $\epsilon 4$  allele. Analyzing  $\epsilon 4$  carriers vs non- $\epsilon 4$  carriers, the RE OR was also not significant, as well as when comparing  $\epsilon 2$  carriers vs non- $\epsilon 2$  carriers. The only significant evidence was found when comparing homozygous  $\epsilon 2\epsilon 2$  vs homozygous  $\epsilon 3\epsilon 3$  (RE OR, 8.86; 95% CI, 1.74–45.13; P ,.001; I<sup>2</sup> 5 0.00%) and homozygous with  $\epsilon 4\epsilon 4$  vs homozygous with  $\epsilon 3\epsilon 3$  (RE OR, 3.44; 95% CI, 1.26–9.39; P , .001; I<sup>2</sup> 5 0.02%). Interestingly, when we compared  $\epsilon 2\epsilon 2$  homozygous subjects vs  $\epsilon 4\epsilon 4$  homozygous subjects, we did not find any significant difference (RE OR, 3.02; 95% CI, 0.43–21.01; P ,.26; I<sup>2</sup> 5 0.00%).

### 3.4. Meta-analysis of subgroups

To assess the role of APOE polymorphisms in FTLD clinical subtypes, we performed two separate metaanalyses for each FTLD subgroup (lvFTD and bvFTD), comparing  $\epsilon 4$  carriers vs non- $\epsilon 4$  carriers and  $\epsilon 2$  carriers vs non- $\epsilon 2$  carriers.

For the first analysis, we used eight studies, with 328 patients and 2461 control subjects. We found a significant OR in  $\epsilon 4$  carriers vs non- $\epsilon 4$  carriers (RE OR, 2.21; 95% CI, 1.45–3.37;  $P = .001$ ; I<sup>2</sup> 54.55%). Comparison between  $\epsilon 2$  carriers vs non- $\epsilon 2$  carriers was not significant (Table 3).

No significant OR was found in the meta-analysis investigating exclusively subjects with bvFTD, which included only three studies.

#### 4. Discussion

This comprehensive meta-analysis suggests that APOE gene polymorphisms are associated significantly with FTLD, with allele  $\epsilon 4$  being a risk factor for developing the disease. Subjects carrying the  $\epsilon 4$  allele showed an approximate twofold increased disease risk in comparison with non- $\epsilon 4$  carriers. In addition, subjects homozygous for the same allele presented a higher risk of FTLD, suggesting a gene dosage effect. The comparison between APOE  $\epsilon 4$  and  $\epsilon 2$  allele carriers confirms these findings. In the analyses of FTLD subgroups, a significant association with APOE  $\epsilon 4$  was found only in patients with the language variant of the disease. However, these findings must be viewed cautiously because of the clinical heterogeneity of the disease. Last, we performed a meta-analysis with only pathologically proved cases but, because of the small number of patients involved in the studies, the results are inconsistent. Overall, our data provide evidence that the APOE  $\epsilon 4$  allele may represent a genetic risk factor for FTLD whereas carriage of the APOE  $\epsilon 2$  allele had no effect on disease risk.

There are some limitations to our study that deserve mention and suggest caution in the interpretation of the results. First of all, only a small number of studies had autopsyconfirmed diagnoses of FTLD, and the meta-analysis on these studies yielded inconsistent results. Therefore, when analyzing only the pathologically proved cases, no significant association between APOE and FTLD was found. To extend our investigation further, we explored APOE polymorphisms in patients with progressive supranuclear palsy and corticobasal degeneration. However, because of the small number of available studies, all comparisons between patients and control subjects were found to be lacking in significance (data not shown). Supposedly, the APOE gene plays a major role mainly in TDP-43 proteinopathies. Intriguingly, APOE has been suggested to have a role in modifying the clinical expression of amyotrophic lateral sclerosis, a disease that shows a significant clinical, genetic, and pathological overlap with FTLD. However, further investigations are required to solve this issue. Last, most of the studies included in this meta-analysis are small or medium-size case-control studies. There is evidence in the literature that smaller studies tend to overstate genetic effects in comparison with larger studies [45].

To date, neurobiological mechanisms concerning the possible role of APOE  $\epsilon 4$  in FTLD pathogenesis remain to be clearly established. Different pathways can be hypothesized to support a role for the  $\epsilon 4$  allele of the APOE gene in the disease. A first effect seems to be a rather general increase in brain vulnerability, with subjects carrying the  $\epsilon 4$  allele having a reduction in neuronal repair mechanisms. This effect is consistent with the hypothesis that  $\epsilon 4$  is the ancestral human APOE allele, from which the others have evolved in the direction of prolonging healthy aging. Accordingly, several studies have shown an association between the APOE  $\epsilon 4$  allele and cognitive impairment in several neurological diseases.

Additional mechanisms by which apoE could influence FTLD, as inferred from in vitro and animal studies, include modulation of neuroinflammation, neuronal toxicity, and synaptic plasticity. Studies in experimental mice have shown that the APOE gene modulates neuroinflammation because it is closely linked with both proinflammatory and anti-inflammatory cytokines. In patients with FTLD, neuroimaging and genetic studies suggested that an enhanced inflammatory response might be involved in disease risk and progression [46,47]. Intriguingly, a role for apoE in the regulation of the microtubule-associated protein tau has also been shown. In transgenic mice, overexpression of human APOE  $\epsilon 4$  in neurons resulted in tau hyperphosphorylation. APOE  $\epsilon 4$  knock-in mice showed higher concentrations of hyperphosphorylated tau than APOE  $\epsilon 3$  knock-in mice [48]. Therefore, variation in both inflammation and tau phosphorylation, related to different alleles, may explain the results observed in our meta-analysis.

Last, neuroimaging provided evidence that carriage of the APOE  $\epsilon 4$  allele is associated with loss of synaptic plasticity and regional atrophy. In middle-aged men, carriage of the APOE  $\epsilon 4$  allele was associated with a thinner cortex in the superior frontal and left rostral and right caudal midfrontal regions [49]. In addition, a research using voxel based magnetic resonance imaging showed that bvFTLD patients carrying the  $\epsilon 4$  allele have greater atrophy in the bilateral parietal cortex and right hippocampus in comparison with non- $\epsilon 4$



carriers [31]. This  $\epsilon 4$  effect supports the hypothesis that apoE may affect morphologic expression in different neurodegenerative diseases.

A recent neuropathological study provided evidence that, in FTLD patients, carriage of the APOE  $\epsilon 4$  allele is associated with a more severe atrophy in the right ventral striatum [27]. In bvFTD, the  $\epsilon 4$  allele influenced gray matter atrophy in a specific subset of frontal and insular regions, predominately in the right hemisphere. Furthermore, the prospective study by Engelborghs and colleagues [50] that investigated the effect of APOE genotype on clinical expression in FTLD showed a dose-dependent effect of apoE  $\epsilon 4$  on behavioral symptoms in frontal lobe dementia.

In conclusion, our study provides additional evidence that the APOE gene is a genetic risk factor for FTLD. However, the mechanism by which APOE  $\epsilon 4$  increases the risk of FTLD remains to be clearly established. Additional investigations are needed to define further the precise role of the APOE gene in neurodegeneration.

#### RESEARCH IN CONTEXT

##### 1. Systematic review:

There is a long-lasting discussion about the role of apolipoprotein E gene in frontotemporal lobar degeneration (FTLD). We screened the medical literature for all publications regarding this topic and found contradictory results. A systematic review for all case–control studies was then conducted.

2. Interpretation: Our data clearly showed that carriage of the  $\epsilon 4$  allele was associated with a significantly increased disease risk. Conversely, carriage of the  $\epsilon 2$  allele had no effect on the risk of developing FTLD.

3. Future directions: Neurobiological mechanisms linking apolipoprotein E functions and FTLD need further investigation.

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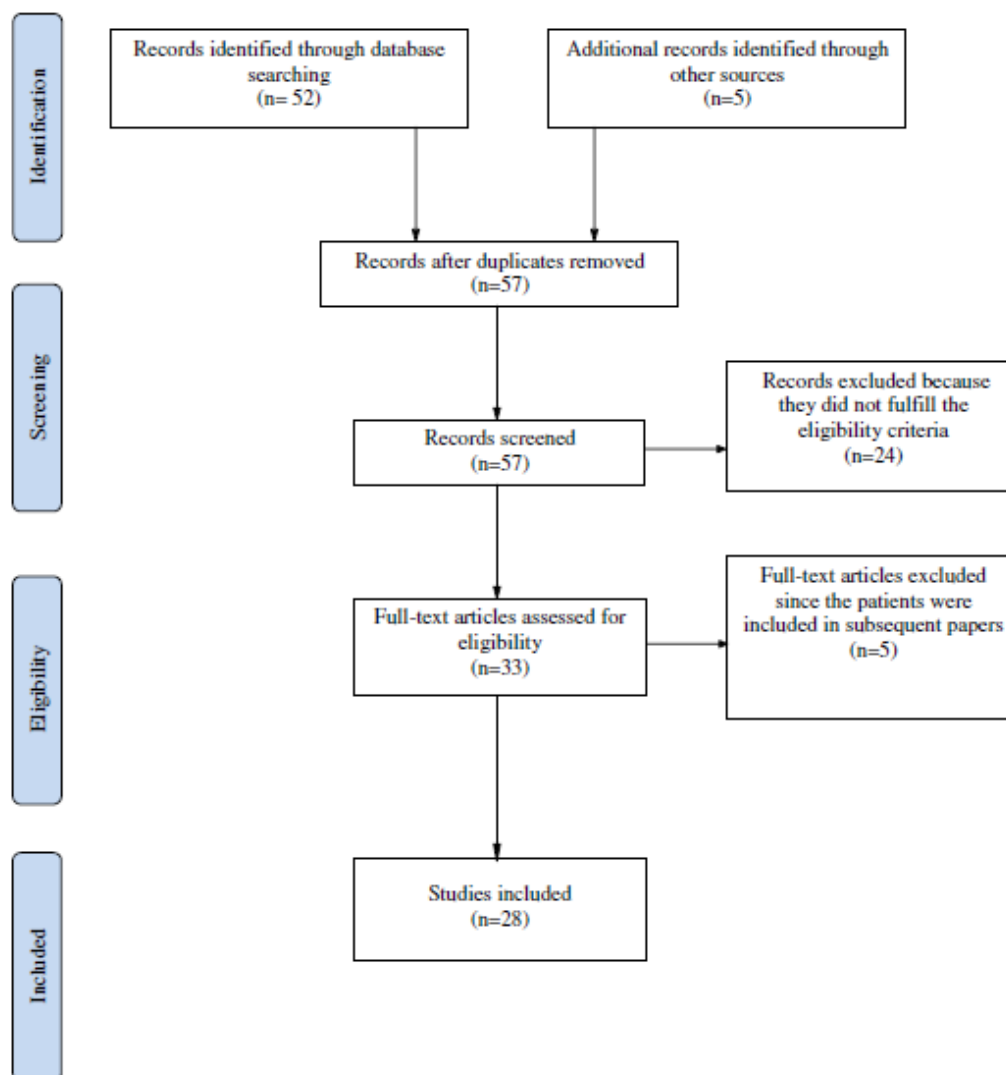


Fig. 1. Flow chart of study selection process and included studies.

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

Study	Country	Patients with FTLD					Diagnostic criteria	Control subjects		
		n	FH, %	M, %	Age, years, mean $\pm$ SD	NP, %		n	M, %	Age, years, mean $\pm$ SD
Farrer et al [15]	USA (MA)	10	58	100	60.4 $\pm$ 5.4	AC	100	1204	–	–
Schneider et al [16]	USA (GA)	6	–	–	–	AC	100	95	–	–
Gomez-Isla et al [13]	USA (MA)	31	–	52	68.3 $\pm$ 13.3	AC	100	129	40	77.8 $\pm$ 13.5
Helisalmi et al [14]	Finland	9	–	33	66.0 $\pm$ 8.0	Clinic	0	60	47	69.0 $\pm$ 8.0
Minthon et al [17]	Sweden	25	–	40	61.0 $\pm$ 9.7	AC, Neary et al [8]	40	26	50	63.8 $\pm$ 6.4
Geschwind et al [18]	USA (CA)	33	42	48	55.0 $\pm$ 11.0	LM, AC	33	30	43	–
Kálmán et al [19]	Hungary	36	–	28	71.0 $\pm$ 8.4	AC	100	79	47	71.0 $\pm$ 7.9
Lehmann et al [20]	UK	11	0	36	65.7	AC, Neary et al [8]	82	136	56	77.5
Fabre et al [21]	Sweden	64	38	31	59.4 $\pm$ 9.1	LM, Neary et al [8]	–	47	30	70.2 $\pm$ 6.5
Kowalska et al [22]	Japan	24	21.4	35	49–74	LM	–	200	–	–
Masullo et al [23]	Italy	23	–	–	60.6 $\pm$ 12.1	Neary et al [8]	0	114	–	59.6 $\pm$ 6.9
Riemenschneider et al [24]	Germany	52	–	54	61.7 $\pm$ 7.7	AC, Neary et al. [8]	21	182	47	63.6 $\pm$ 9.3
Rosso et al [25]	Netherlands	98	–	–	–	LM	17	561	–	–
Short et al [26]	USA (FLA)	63	–	44	66.0 $\pm$ 8.7	Neary et al [8]	–	338	–	–
Verpillat et al [6]	France	94	33	41	60.6 $\pm$ 8.5	LM, AC	3	392	45	62.5 $\pm$ 8.7
Boccardi et al [27]	Italy	8	–	75	62.0 $\pm$ 5.0	Neary et al [8]	–	26	35	69.0 $\pm$ 9.0
Borroni et al [28]	UK	86	21	50	57.2 $\pm$ 7.7	Neary et al [8]	15	50	–	–
Bernardi et al [29]	Italy	100	46	50	65.1 $\pm$ 9.4	LM	–	180	50	65.2 $\pm$ 6.7
Srinivasan et al [30]	UK	198	0	52	57.4 $\pm$ 9.2	AC, Neary et al [8]	25	756	30	Over 50
Albani et al [32]	Italy	73	–	46	69.4 $\pm$ 9.7	Neary et al [8], McKhann et al [9]	–	151	40	67 $\pm$ 12
Agosta et al [31]	USA (CA)	31	–	–	29 to 80	Neary et al [8]	16	56	37.5	66.7 $\pm$ 8.5
Daniele et al [33]	Italy	127	–	–	67.3 $\pm$ 9.7	McKhann et al [9]	–	343	–	66 $\pm$ 12.3
Fehér et al [34]	Hungary	72	–	37.5	73.3 $\pm$ 7.7	Clinic, AC	80	164	38.4	71.7 $\pm$ 8.5
Steenland et al [35]	USA (GA)	72	–	54.3	65.7	Clinic	–	571	37.7	60.6
Lovati et al [38]	Italy	75	–	45.3	68.7 $\pm$ 1.97	Neary et al [8]	–	506	34.5	68.7 $\pm$ 0.6
Zintl et al [36]	Germany	73	35.6	–	62.3 $\pm$ 12.0	LM	–	54	–	–
Seripa et al [37]	Italy	86	–	42	69.4 $\pm$ 8.4	McKhann et al [9]	–	99	51	66.2 $\pm$ 7.3
Premi et al [39]	Italy	94	–	46	65.7 $\pm$ 9.1	Gorno-Tempini et al [10]	–	200	51	63.8 $\pm$ 7.6

Abbreviations: FTLD, frontotemporal lobar degeneration; FH, familial history; M, male; SD, standard deviation; NP, neuropathological confirmation; AC, autopsy confirmed; LM, Lund Manchester criteria; –, not available.

Table 2  
Odds ratio and heterogeneity results for apolipoprotein E polymorphism in patients with FTLD vs control subjects

Comparisons	Subjects, n			Effect size and 95% CI	Heterogeneity					
	Studies, n	df, Q	FTLD patients	Control subjects	Random effects OR (95% CI)	z Value	P value	Q value	P value	I <sup>2</sup>
Alleles $\epsilon$ 2 vs $\epsilon$ 3	21	20	2063	9021	1.24 (0.89–1.75)	1.26	.21	61.52	<.001	67.49
Alleles $\epsilon$ 4 vs $\epsilon$ 3	21	20	2316	9441	1.83 (1.34–2.52)	3.76	<.001	89.36	<.001	77.62
Alleles $\epsilon$ 2 vs $\epsilon$ 4	21	20	635	1973	0.62 (0.40–0.97)	2.11	.04	68.80	<.001	70.93
$\epsilon$ 2 carriers vs non- $\epsilon$ 2 carriers	21	20	1250	5029	1.06 (0.75–1.48)	0.32	.75	53.22	<.001	62.42
$\epsilon$ 4 carriers vs non- $\epsilon$ 4 carriers	28	27	1630	6740	1.94 (1.43–2.64)	4.23	<.001	117.06	<.001	76.93
$\epsilon$ 2 $\epsilon$ 2 vs $\epsilon$ 3 $\epsilon$ 3	13	12	534	2704	1.73 (0.80–3.74)	1.40	.16	10.01	.62	0.00
$\epsilon$ 2 $\epsilon$ 2 + $\epsilon$ 2 $\epsilon$ 3 vs $\epsilon$ 3 $\epsilon$ 3	21	20	841	3888	1.02 (0.75–1.38)	0.13	.90	32.81	.04	39.05
$\epsilon$ 3 $\epsilon$ 4 vs $\epsilon$ 3 $\epsilon$ 3	21	20	1032	4200	1.75 (1.18–2.59)	2.79	.01	84.93	<.001	76.45
$\epsilon$ 4 $\epsilon$ 4 vs $\epsilon$ 3 $\epsilon$ 3	20	19	750	3305	3.30 (2.03–5.35)	4.84	<.001	13.91	.79	0.00
$\epsilon$ 3 $\epsilon$ 4 + $\epsilon$ 4 $\epsilon$ 4 vs $\epsilon$ 3 $\epsilon$ 3	21	20	1074	4280	1.69 (1.21–2.36)	3.10	.01	64.53	<.001	69.01

Abbreviations: CI, confidence interval; FTLD, frontotemporal lobar degeneration; OR, odds ratio.

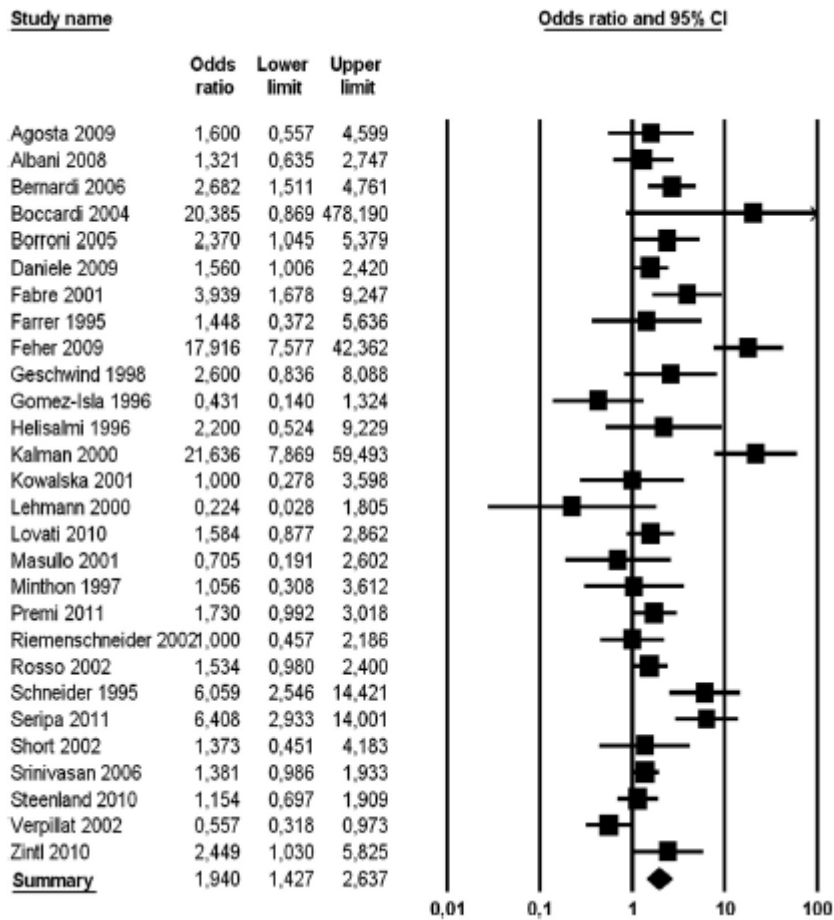


Fig. 2. Forest plot of estimated odds ratio for apolipoprotein E (APOE)  $\epsilon$ 4 allele carriers in patients with frontotemporal lobar degeneration.

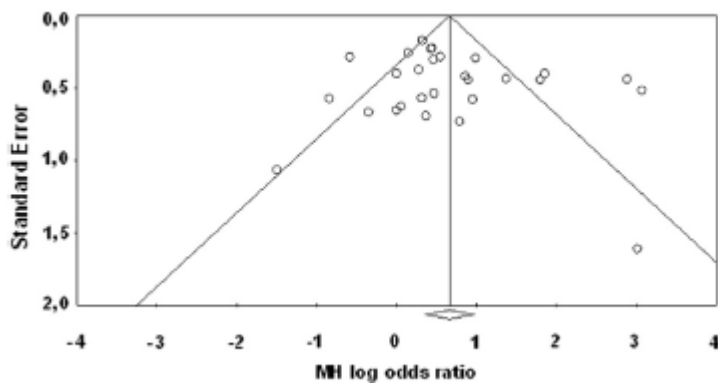


Fig. 3. Funnel plots of comparison of E4 carriers vs non-E4 carriers to determine publication bias. Abbreviation: MHlog odds ratio, Mantel-Haenszel log odds ratio

Table 3

Odds ratio and heterogeneity results for apolipoprotein E polymorphism in patients with frontotemporal lobar degeneration subgroups vs control subjects

Comparisons	Subjects, n				Effect size and 95% CI	Heterogeneity				
	Studies, n	<i>df</i> , <i>Q</i>	Patients	Control subjects	Random effects OR (95% CI)	<i>z</i> Value	<i>P</i> value	<i>Q</i> value	<i>P</i> value	<i>I</i> <sup>2</sup>
<b>lvFTD</b>										
Alleles $\epsilon$ 2 vs $\epsilon$ 3	5	4	371	2650	1.71 (0.96–3.02)	1.83	.07	7.67	.10	47.85
Alleles $\epsilon$ 4 vs $\epsilon$ 3	5	4	416	2815	1.97 (1.15–3.38)	2.48	.01	11.30	.02	64.60
Alleles $\epsilon$ 2 vs $\epsilon$ 4	5	4	117	583	0.80 (0.39–1.63)	0.61	.54	8.08	.09	50.49
$\epsilon$ 4 carriers vs non- $\epsilon$ 4 carriers	8	7	328	2461	2.21 (1.45–3.37)	3.67	<.001	15.40	.03	54.55
$\epsilon$ 2 carriers vs non- $\epsilon$ 2 carriers	5	4	226	1512	1.61 (0.86–2.99)	1.50	.13	8.24	.08	51.47
<b>bvFTD</b>										
$\epsilon$ 4 carriers vs non- $\epsilon$ 4 carriers	3	2	149	667	1.46 (0.96–2.24)	1.76	.08	1.16	.56	0.00

Abbreviations: CI, confidence interval; OR, odds ratio; lvFTD, language variant of frontotemporal dementia; bvFTD, behavioral frontotemporal dementia.