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APOE associations with severe CAA-associated vasculopathic changes – collaborative meta-analysis

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Abstract

Objectives—Cerebral amyloid angiopathy (CAA) is associated with lobar intracerebral haemorrhage (ICH). While only the ε4 allele of the apolipoprotein E gene (APOE) is associated with the presence of CAA, both APOE-ε4 and ε2 are associated with lobar ICH. The generally accepted explanation is that APOE-ε4 promotes vascular amyloid deposition, while APOE-ε2 promotes progression to severe CAA with associated vasculopathic changes that cause vessel rupture and ICH. We assessed the evidence for these allele-specific effects.

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Kristiina Rannikmäe: design and conceptualization of the study, acquisition, analysis and interpretation of the data, drafting and revising the manuscript; Rajesh N Kalaria: acquisition, analysis and interpretation of the data, revising the manuscript; Steven M Greenberg: acquisition, analysis and interpretation of the data, revising the manuscript; Helena C Chui: acquisition, analysis and interpretation of the data, revising the manuscript; Frederick A Schmitt: acquisition, analysis and interpretation of the data, revising the manuscript; Neshika Samarasekera: design and conceptualization of the study, analysis and interpretation of the data, revising the manuscript; Rustam Al-Shahi Salman: design and conceptualization of the study, analysis and interpretation of the data, revising the manuscript; Cathie LM Sudlow: senior supervision and co-ordination of the study, design and conceptualization of the study, acquisition, analysis and interpretation of the data, drafting and revising the manuscript.

Ethics approval: In accordance with NRES and MRC guidance, this study does not require ethics approval as it does not directly involve human participants. The data used in the systematic review and meta-analysis has come from studies which have previously satisfied regulatory requirements and been peer reviewed.

COMPETING INTERESTS: Authors report no competing interests.

Methods—We systematically identified published studies with data on APOE genotype and histopathological assessment of post-mortem brains for CAA severity. We obtained unpublished data from these for meta-analyses of the effects of $\epsilon 4$ -containing ($\epsilon 4+$) and $\epsilon 2$ -containing ($\epsilon 2+$) genotypes on progression to severe CAA.

Results—Of six eligible studies (543 eligible participants), data were available from five (497 participants, 353 with CAA). Meta-analyses showed a possible association of $\epsilon 4+$ genotypes with severe CAA ($\epsilon 4+$ versus $\epsilon 4-$: severe versus mild/moderate CAA, odds ratio [OR] 2.5, 95% confidence interval [CI] 1.4 to 4.5, $p=0.002$; severe versus moderate CAA, OR 1.7, 95% CI 0.9 to 3.1, $p=0.11$). For $\epsilon 2+$ versus $\epsilon 2-$ genotypes, there was no significant association, but the very small number of participants with $\epsilon 2+$ genotypes (22) precluded reliable estimates.

Conclusions—We found a possible association of severe CAA with APOE- $\epsilon 4$ but not APOE- $\epsilon 2$. However, our findings do not exclude a biologically meaningful association between APOE- $\epsilon 2$ and severe CAA. Further work is needed to elucidate fully the allele-specific associations of APOE with CAA and their mechanisms.

Keywords

Cerebral Amyloid Angiopathy; Apolipoproteins E; Cerebral Hemorrhage; Systematic Review

INTRODUCTION

Sporadic cerebral amyloid angiopathy (CAA) is characterised by deposition of amyloid β -protein (A β) in leptomeningeal and cortical blood vessels, with a prevalence in population-based autopsy studies of 20-40% in non-demented and 50-60% in demented elderly people. [1] Neuropathological case-control and cross-sectional studies, as well as the increased incidence of ICH in patients with Alzheimer's disease, suggest that CAA causes lobar intracerebral haemorrhage (ICH).[2,3]

CAA is thought to be responsible for up to a third of all ICH in elderly people.[4] The prevalence of ICH in cases with CAA in a recent systematic review was about 11%.[2] It is unknown why only a few people with CAA pathology develop an ICH, but it seems likely to involve biological pathways additional to and distinct from those involved in vascular amyloid deposition. Cases of CAA with ICH not only have a greater proportion of amyloid-laden blood vessels,[5] but also more often demonstrate severe CAA with associated vasculopathy (Figure 1).[5-8] Apolipoprotein E genotype (APOE) is associated with both histopathologically-confirmed CAA and CAA-related clinical phenotypes, including lobar ICH. Our recent systematic review demonstrated a dose-dependent association between histopathologically-confirmed CAA and $\epsilon 4$ - but not $\epsilon 2$ -containing genotypes.[9] However, a recent large-scale genetic association study found that both $\epsilon 4$ - and $\epsilon 2$ -containing genotypes were associated with lobar ICH, particularly when attributed to CAA.[10] Furthermore, APOE- $\epsilon 2$ but not $\epsilon 4$ predicted initial hematoma volume, hematoma expansion, increased mortality and poor functional outcome of lobar ICH.[11,12] The generally accepted explanation for these findings is that while APOE- $\epsilon 4$ promotes vascular amyloid deposition, $\epsilon 2$ promotes progression to severe CAA with associated vasculopathy leading to vessel rupture and ICH (Figure 1).[5,13] We aimed to assess the evidence for this

hypothesis through a systematic review and meta-analyses of all available, relevant, published, histopathological studies.

METHODS

Study identification and inclusion/exclusion criteria

We sought all studies of adult humans published in any language, which had conducted both APOE genotyping and histopathological assessment for CAA, including assessment for severe CAA with associated vasculopathic changes (blood vessel dilatation, microaneurysm formation, fibrinoid degeneration, cracking and double-barrelling of the vessel wall, and paravascular leakage of blood) (Figure 1). The assessment for severe CAA could have occurred either as part of the Vonsattel grading scale, which includes such changes in its 'severe' category (Appendix e-1) or through specifically reporting on some or all of the relevant histopathological characteristics. From now on when using the term 'severe CAA', we are referring to severe CAA with associated vasculopathic changes.

To avoid the effects of possible reporting bias (whereby positive results are more likely to be included within publications than negative ones) and to increase the size of the relevant dataset, we considered studies to be eligible for inclusion whether or not they actually reported on any association of APOE with severe CAA.

We searched OVID *Medline* (1950 to March 2012) and *Embase* (1980 to March 2012), using a combination of search terms for APOE, genes and CAA (appendix e-2). We also checked the bibliographies of all relevant studies and reviews identified, and searched *Google Scholar* for other studies citing relevant studies.

Our focus was on assessing the potential influence of APOE genotypes (in particular APOE-ε2) on severe CAA preceding rupture. Because APOE-ε2 is already known to be associated with CAA-related ICH (perhaps - but not definitely - causally), and severe CAA is more commonly found in such cases, we reasoned that including brains with ICH in our analyses would inevitably yield an association of APOE-ε2 with severe CAA, without necessarily meaning that APOE-ε2 influences risk through promoting the most severe stages of CAA pathology that precede rupture. Hence, to avoid selection bias, we excluded studies that had selected participants on the basis of having had a CAA-related ICH. For the same reason, we excluded participants selected on the basis of having had a CAA-related ICH from the included studies. We also excluded studies of hereditary CAA cases and those with less than 10 eligible participants (thereby excluding <3% of overall eligible participants). Two authors independently selected studies for inclusion, resolving disagreements by discussion.

Data Extraction

For each study included, we extracted information on: first author; publication year; country in which the study was conducted; source of participants; and methodological characteristics. We assessed the quality of reporting of genotyping based on the STREGA (Strengthening the Reporting of Genetic Association Studies) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) recommendations[14,15] and the quality and characteristics of CAA pathology assessment using our own previously published criteria.[9]

For our planned meta-analyses, we required summary data on the numbers of participants with each APOE genotype ($\epsilon 3\epsilon 3$, $\epsilon 2\epsilon 3$, $\epsilon 3\epsilon 4$, $\epsilon 4\epsilon 4$, $\epsilon 2\epsilon 2$, $\epsilon 2\epsilon 4$) and whether or not CAA was present or absent. For those with CAA, we required, for each genotype, their CAA severity on the Vonsattel scale and/or data on the presence or absence of specific vasculopathic changes associated with severe CAA. These data were not all provided in the publications we identified. To facilitate the sharing and analysis of the unpublished data required, we therefore formed a collaborative group including the principal investigators of the relevant studies. We created a structured data extraction form and completed it as far as possible by entering data from the relevant publication(s). Principal investigators then checked the information entered, made any necessary corrections, and entered additional unpublished data if required and available.

Statistical analyses – APOE genotype and CAA severity on the Vonsattel scale

We used Cochrane RevMan (V.5) software. In our primary analyses, we included only individuals with CAA present on histopathological assessment, calculating study-specific and random effects pooled, unadjusted odds ratios (ORs) for severe versus mild or moderate CAA among $\epsilon 4$ carriers ($\epsilon 4+$) versus those with other genotypes ($\epsilon 4-$) and among $\epsilon 2$ carriers ($\epsilon 2+$) versus others ($\epsilon 2-$). In secondary analyses, we repeated the primary analyses: comparing severe versus moderate CAA (but excluding mild CAA and so focussing on the severe end of the CAA spectrum); and comparing severe versus mild/moderate CAA, and severe versus moderate CAA among $\epsilon 4+$ versus the wild-type $\epsilon 3\epsilon 3$ and among $\epsilon 2+$ versus $\epsilon 3\epsilon 3$ to avoid potential confounding by mixed effects of $\epsilon 2$ and $\epsilon 4$ in the comparison group. In a further analysis, we included individuals both with and without CAA, comparing the presence versus absence of CAA among $\epsilon 4+$ versus $\epsilon 4-$ and among $\epsilon 2+$ versus $\epsilon 2-$ genotypes. To assess robustness of the methods, we repeated all the above analyses using the fixed effects method. We assessed heterogeneity with I^2 and χ^2 statistics. We considered $p < 0.05$ to imply statistical significance.

RESULTS

From 1754 publications identified by our search, we identified eight relevant studies. We excluded two with < 10 eligible participants,[16,17] leaving six eligible studies. These six studies included 645 unique participants, of whom 102 had been selected on the basis of having had an ICH, leaving 543 that were eligible for our study (Figure 2).[5,13,18-21] Only one of the six studies had previously reported on the association between the APOE genotype and severe CAA (assessed using Vonsattel scale), finding a significantly greater frequency of APOE- $\epsilon 2$ in severe versus moderate CAA cases.[13] This study and four others that had rated CAA on the Vonsattel scale, between them including 497 eligible participants (92% of all 543 potentially eligible participants),[18-21] were able to share their unpublished data in collaborative meta-analyses. Data were unavailable from one additional study (46 eligible participants) that had assessed various different CAA-associated vasculopathic changes (double barrelling of the vessel wall, fibrinoid necrosis and microaneurysm formation), including those that are not part of the Vonsattel scale.[5]

Characteristics and quality of studies included in meta-analyses

All of the five studies included in our meta-analyses used autopsy brains from brain tissue banks or a population-based prospective study with an autopsy component. There were between 57 and 227 eligible participants per study. Mean age at death was between 78 and 84 years and about half of all participants were male. Three studies (357 participants) were conducted in predominantly white populations in the USA while information on ethnicity was unavailable for two studies (140 participants). About 50% of participants had clinical dementia (mainly neuropathologically confirmed AD), about 20% were known not to be demented and in the remaining 30% dementia status was unknown (Table 1). The quality of genotyping and of pathology assessment was generally very good when assessed against current reporting standards.[14,15] Methods for pathological assessment were variable, reflecting a lack of agreed standards for CAA pathology assessment at the time these studies were conducted (Table 2).

Meta-analyses – APOE genotype and CAA severity on the Vonsattel scale

Meta-analysis of data from 353 participants with CAA included in five studies showed, for $\epsilon 4+$ versus $\epsilon 4-$ genotypes, a significant association with severe versus mild/moderate CAA (OR 2.5, 95% CI 1.4 to 4.5, $p=0.002$) but no significant association with severe versus moderate CAA (OR 1.7, 95% CI 0.9 to 3.1, $p=0.11$) (Figure 3A, figure e-1). There was no significant heterogeneity between individual studies' results ($I^2=0\%$; $\chi^2_{3df}=1.2$; $p=0.75$ and $I^2=0\%$; $\chi^2_{3df}=1.2$; $p=0.76$ respectively). For $\epsilon 2+$ versus $\epsilon 2-$ genotypes, the associations were non-significant (severe CAA versus mild/moderate CAA: OR 2.3, 95% CI 0.5 to 11.3, $p=0.3$; severe CAA versus moderate CAA: OR 2.7, 95% CI 0.6 to 11.4, $p=0.19$), with wide confidence intervals due to small numbers of participants, particularly in the $\epsilon 2+$ group, which included 22 individuals, only seven of whom had severe CAA (Figure 3B, figure e-2). There was moderate heterogeneity between individual studies' results for severe CAA versus mild/moderate CAA ($I^2=52\%$; $\chi^2_{3df}=6.2$; $p=0.1$) and minimal heterogeneity for severe versus moderate CAA ($I^2=11\%$; $\chi^2_{3df}=3.4$; $p=0.3$). Results were similar and conclusions unchanged for the $\epsilon 4+$ and $\epsilon 2+$ genotypes when we used $\epsilon 3\epsilon 3$ genotypes as the comparison group (rather than $\epsilon 4-$ or $\epsilon 2-$) (table e-1), and when we performed the analyses using the fixed effects method.

Associations with the presence versus absence of CAA were consistent with results from our previous published systematic review,[9] showing a clearly significant association with $\epsilon 4+$ ($\epsilon 4+$ versus $\epsilon 4-$: OR 4.8, 95% CI 3.0 to 7.6, $p<0.00001$) but not with $\epsilon 2+$ genotypes ($\epsilon 2+$ versus $\epsilon 2-$: OR 0.38, 95% CI 0.1 to 1.0, $p=0.05$).

DISCUSSION

After collecting and analysing data from five out of six existing relevant studies identified through a systematic search (including >90% of all eligible participants), our meta-analyses suggested a possible association of APOE- $\epsilon 4$ with progression to severe CAA as well as the expected association of $\epsilon 4$ (and not of $\epsilon 2$) with the presence of CAA.[9] However, we were unable to confirm a statistically significant association between APOE $\epsilon 2+$ genotypes and severe CAA. It should be emphasised that, although we included all available data from

relevant publications, the relative rarity of $\epsilon 2+$ genotypes (only 22 of 353 individuals with CAA in our collaborative dataset) made the $\epsilon 2$ -based analyses very imprecise.

The strengths of our study are the thorough search methods along with critical appraisal of the quality of included studies (which was generally good), inclusion of unpublished data through establishing a collaborative group to share data, and inclusion of these data in meta-analyses. In addition, we were careful to avoid selection bias by excluding cases selected on the basis of having had an ICH, since this phenotype has known associations both with severe CAA and with APOE- $\epsilon 2$ and $\epsilon 4$.

Our study has a number of limitations. First, although our analysis includes data from >90% of eligible cases identified, we were unable to include cases from one small study.[5] In that study, APOE- $\epsilon 2$ allele-carriers had a statistically significant excess of fibrinoid necrosis compared with non- $\epsilon 2$ carriers, but CAA-related ICH cases were included in these analyses. Second, despite including data from almost all relevant cases from the published literature, total numbers were relatively small and confidence intervals wide, especially for analyses of the effects of APOE- $\epsilon 2$. Third, methods for histopathological assessment varied between studies, potentially introducing heterogeneity and reducing the likelihood of detecting a consistent effect across studies. Fourth, APOE allele-specific effects on severe CAA may differ according to the presence or absence of Alzheimer's disease, particularly for APOE- $\epsilon 2$, which has been associated with a decreased risk of Alzheimer's dementia.[22] We could not perform informative subgroup analysis, however, because of the small overall numbers of participants and because dementia status was unknown for a large number of participants. Fifth, while the studies included here assessed those severe CAA-associated vasculopathic changes that are specifically alluded to in the Vonsattel scale, other vasculopathic changes may also be relevant. Sixth, both APOE allele-specific and other genetic associations may differ by CAA subtype. For example, there is preliminary evidence that APOE- $\epsilon 4$ may be associated with CAA type 1 (where CAA is found in cortical capillaries), and $\epsilon 2$ with CAA type 2 (where amyloid is deposited in leptomeningeal and cortical vessels with the exception of cortical capillaries).[23] If CAA types 1 and 2 represent different pathological entities, the mechanisms and genetic risk factors for severe CAA and ICH could also differ. We did not have the necessary data to explore this in our study. Seventh, the issue of potential confounding due to population stratification was not addressed in the included studies. However such confounding is unlikely because these were not case control studies but autopsy series where comparison groups within each study came from the same population. Finally, there may be other genetic influences that interact with APOE- $\epsilon 2$ to increase risk of or protect against severe CAA and ICH.

Our study therefore confirms existing strong evidence that APOE- $\epsilon 4$ promotes cerebral amyloid angiopathy, and further suggests that $\epsilon 4$ may increase the risk of developing severe CAA among those with CAA. However, while our findings do not exclude a biologically meaningful association between the APOE- $\epsilon 2$ allele and progression to severe CAA, we did not find convincing evidence to support this. Much larger numbers of individuals will need to be included in CAA histopathology studies before reliable conclusions can be drawn about the specific effects of APOE- $\epsilon 2$ on CAA. In particular, the hypothesis that APOE- $\epsilon 2$ influences risk of ICH through promoting progression of CAA to its severe form is not

supported by the existing, relevant, unbiased data. Future research efforts in this area will also be helped substantially by the development and use of an internationally-agreed, standardised histopathological grading system for CAA (including assessment of CAA types 1 and 2), and by the consistent reporting of dementia – and specifically Alzheimer’s disease – status among individuals included in histopathology studies.[24]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference List

1. Charidiomou A, Gang Q, Werring DJ. Sporadic cerebral amyloid angiopathy revisited: recent insights into pathophysiology and clinical spectrum. *J Neurol Neurosurg Psychiatry*. 2012; 83:124–37. [PubMed: 22056963]
2. Samarasekera N, Smith C, Al-Shahi Salman R. The association between cerebral amyloid angiopathy and intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2012; 83:275–81. [PubMed: 22056966]
3. Chi NF, Chien LN, Ku HL, et al. Alzheimer disease and risk of stroke: a population-based cohort study. *Neurology*. 2013; 80:705–11. [PubMed: 23303851]
4. Pezzini A, Padovani A. Cerebral amyloid angiopathy-related hemorrhages. *Neurol Sci*. 2008; 29(Suppl 2):S260–263. [PubMed: 18690512]
5. McCarron MO, Nicoll JA, Stewart J, et al. The apolipoprotein E epsilon2 allele and the pathological features in cerebral amyloid angiopathy-related hemorrhage. *J Neuropathol Exp Neurol*. 1999; 58:711–8. [PubMed: 10411341]
6. Vonsattel JPG, Myers RH, Hedley-Whyte ET, et al. Cerebral amyloid angiopathy without and with cerebral hemorrhages: a comparative histological study. *Ann Neurol*. 1991; 30:637–49. [PubMed: 1763890]
7. Okazaki H, Reagan TJ, Campbell RJ. Clinicopathological studies of primary cerebral amyloid angiopathy. *Mayo Clin Proc*. 1979; 54:22–31. [PubMed: 759733]
8. Mandybur TI. Cerebral amyloid angiopathy: the vascular pathology and complications. *J Neuropathol Exp Neurol*. 1986; 45:79–90. [PubMed: 3941328]
9. Rannikmäe K, Samarasekera N, Martínez-González NA, et al. Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry*. 2013; 84:901–8. [PubMed: 23457231]

10. Biffi A, Sonni A, Anderson CD, et al. Variants of APOE influence risk of deep and lobar intracerebral hemorrhage. *Ann Neurol*. 2010; 68:934–43. [PubMed: 21061402]
11. Biffi A, Anderson CD, Jagiella JM, et al. APOE genotype and extent of bleeding and outcome in lobar intracerebral haemorrhage: a genetic association study. *Lancet Neurol*. 2011; 10:702–9. [PubMed: 21741316]
12. Brouwers HB, Biffi A, Ayres AM, et al. Apolipoprotein E genotype predicts hematoma expansion in lobar intracerebral hemorrhage. *Stroke*. 2012; 43:1490–5. [PubMed: 22535266]
13. Greenberg SM, Vonsattel JP, Segal AZ, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. *Neurology*. 1998; 50:961–5. [PubMed: 9566379]
14. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000; 283:2008–12. [PubMed: 10789670]
15. Little J, Higgins JPT, Ioannidis JPA, et al. STrengthening the REporting of Genetic Association Studies (STREGA) – An Extension of the STROBE Statement. *PloS Med*. 2009; 6:e22. [PubMed: 19192942]
16. van Horsen J, de Jong D, de Waal RM, et al. Cerebral amyloid angiopathy with severe secondary vascular pathology: a histopathological study. *Dement Geriatr Cogn Disord*. 2005; 20:321–30. [PubMed: 16179828]
17. Eng JA, Frosch MP, Choi K, et al. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. *Ann Neurol*. 2004; 55:250–6. [PubMed: 14755729]
18. Greenberg SM, Rebeck GW, Vonsattel JP, et al. Apolipoprotein E epsilon 4 and cerebral hemorrhage associated with amyloid angiopathy. *Ann Neurol*. 1995; 38:254–9. [PubMed: 7654074]
19. Chui HC, Zarow C, Mack WJ, et al. Cognitive impact of subcortical vascular and Alzheimer's disease pathology. *Ann Neurol*. 2006; 60:677–87. [PubMed: 17192928]
20. Davis DG, Schmitt FA, Wekstein DR, et al. Alzheimer neuropathologic alterations in aged cognitively normal subjects. *J Neuropathol Exp Neurol*. 1999; 58:376–88. [PubMed: 10218633]
21. Kalara RN, Premkumar DRD. Apolipoprotein E genotype and cerebral amyloid angiopathy. *Lancet*. 1995; 346:1424. [PubMed: 7475834]
22. Verghese PB, Castellano JM, Holtzman DM. Apolipoprotein E in Alzheimer's disease and other neurological disorders. *Lancet Neurol*. 2011; 10:241–52. [PubMed: 21349439]
23. Thal DR, Ghebremedhin E, Rüb U, et al. Two types of sporadic cerebral amyloid angiopathy. *J Neuropathol Exp Neurol*. 2002; 61:282–93. [PubMed: 11895043]
24. Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*. 2013; 9:1118–27. [PubMed: 20934914]

Figure 1. Proposed theory about associations between APOE genotype and CAA phenotype
 APOE = apolipoprotein E; CAA = cerebral amyloid angiopathy; ε4+: ε4 allele containing genotypes; ε2+: ε2 allele containing genotypes;

The currently generally accepted explanation is that while APOE-ε4 promotes vascular amyloid deposition, ε2 promotes progression to severe CAA with associated vasculopathy leading to vessel rupture and ICH

Figure 2.
Selection of included studies

A. Meta-analysis of APOE- ϵ 4 associations with severe CAA

B. Meta-analysis of APOE- ϵ 2 associations with severe CAA

Figure 3. Meta-analyses of association of APOE $\epsilon 4+$ vs $\epsilon 4-$ and $\epsilon 2+$ vs $\epsilon 2-$ genotypes with severe CAA

The diamonds represent pooled OR across studies and the width of the diamonds represents 95% confidence intervals (CIs).

* $\epsilon 4+$ and $\epsilon 2+$: number of subjects with an $\epsilon 4$ or $\epsilon 2$ allele respectively and severe CAA / total number of subjects with an $\epsilon 4$ or $\epsilon 2$ allele respectively and any severity of CAA **or** severe/moderate CAA

$\epsilon 4-$ and $\epsilon 2-$: number of subjects without an $\epsilon 4$ or $\epsilon 2$ allele respectively and severe CAA / total number of subjects without an $\epsilon 4$ or $\epsilon 2$ allele respectively and any severity of CAA **or** severe/moderate CAA

Results of two studies conducted in one centre were combined for the analyses^{13,18}

Table 1

Study characteristics

First author, publication year and country	Source of participants	N*	Clinically demented/AD†	Mean age (SD)	Ethnicity	% male
Davis 1999 USA[20]	Prospective study of > 60 year old cognitively normal volunteers from community	57	0/0	83.9 (7.4)	Caucasian	46%
Greenberg 1995 & 1998 USA[13,18]	Brains selected from a brain tissue resource centre	140	?	78.9 (8.9)‡	?	46%
Chui 2006 USA[19]	People from a longitudinal study of ischaemic vascular dementia, AD and cognitively normal elderly people	73	42/34§	82.8	86% Caucasian	57%
Kalaria 1995 USA[21]	Brains from research based brain tissue banks	227¶	211/177	77-79	Caucasian	45%

?: not known

* N: number of eligible participants genotyped & assessed for CAA

† AD: clinically diagnosed and neuropathologically confirmed Alzheimer's disease

‡ Mean age for 138 participants

§ 42/79 participants were clinically demented and 34/79 had clinically diagnosed and neuropathologically confirmed Alzheimer's disease

¶ authors provided unpublished data for additional 34 controls not included in the original publication

Table 2

Study genotyping and pathology characteristics and quality

First author	Source of DNA	Genotyping attempted/successful*	Genotyping method	CAA method†	G to P	Blinding‡	CAA rater§	Locations examined¶
Davis[20]	Blood or brain tissue	57/57	PCR	IHC	✓	✓	NP	F,T,P,O,LM
Greenberg[13,18]**	Brain tissue	?	PCR	CR (all) H&E (some) IHC (some)	✓	✓	NP	F,T,P,O,C
Chui[19]	Blood	73/73	PCR	H&E (all) IHC (some) CR (some)	✓	✓	NP	F,T,P,O
Kalaria[21]	Brain tissue	227/227	PCR	CR (PL) ThS	✓	✓	NP	F,T,P,O

* number of participants in whom genotyping attempted and in whom successful

† method for assessing CAA from the pathology samples; IHC = immunohistochemistry; CR = Congo Red; H&E = Hematoxylin and Eosin; PL = polarised light; ThS = Thioflavin S

‡ Blinding: G to P = genotypers to pathology data; P to G = pathologists to genotyping data; P to C = pathologists to relevant clinical information; “✓” done; “-” not done

§ CAA rater: qualification of the person rating CAA; NP = neuropathologist

¶ Locations examined for CAA vasculopathic changes: F= frontal cortex; T= temporal cortex; P= parietal cortex; O= occipital cortex; C= cerebellar cortex; LM= leptomeninges

minimal clinical information available to pathologists

** data applies to both Greenberg 1995 and 1998 publications; ? = not known