RESEARCH PAPER

Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis

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ABSTRACT

Background and purpose Cerebral amyloid angiopathy (CAA) is common in the ageing brain and is associated with dementia and lobar intracerebral haemorrhage. We systematically reviewed genetic associations with CAA to better understand its pathogenesis.

Methods We comprehensively sought and critically appraised published studies of associations between any genetic polymorphism and histopathologically confirmed CAA. We assessed the effects of genotype by calculating study specific and pooled odds ratios (ORs) in meta-analyses, and assessed small study bias.

Results 58 studies (6855 participants) investigated apolipoprotein E (APOE) genotype and sporadic CAA. Meta-analysis of 24 (3520 participants) of these showed an association of APOE ε4 with CAA (ε4 present vs absent, pooled OR 2.7, 95% CI 2.3 to 3.1, p<0.00001), which was dose dependent, robust to potential small study biases and occurred irrespective of dementia status. There was no significant association between APOE ε2 and CAA. Among 24 studies (4703 participants) of other genetic polymorphisms, there was preliminary evidence of an association with CAA of polymorphisms in the transforming growth factor β1 gene (two studies, 449 participants), translocase of outer mitochondrial membrane 40 gene (one study, 723 participants) and the complement component receptor 1 gene (one study, 544 participants). There were insufficient data to draw conclusions from 24 studies (~200 participants) of APOE and hereditary CAA or familial Alzheimer's disease.

Conclusions There is convincing evidence for a dose dependent association between APOE ε4 and sporadic CAA. Further work is needed to better understand the mechanism of this association and to further investigate other genetic associations with CAA.

INTRODUCTION

Cerebral amyloid angiopathy (CAA) is characterised by peptide deposition, mainly amyloid β, in cortical and leptomeningeal arteries. CAA is associated with increasing age, dementia, lobar intracerebral haemorrhage (ICH), lobar brain microbleeds, leukoaraiosis, small cortical infarcts and superficial siderosis.[1–4] ICH is usually attributed to CAA when pathological examination reveals extensive CAA deposition and related vasculopathic changes.[5]

Identifying genetic polymorphisms associated with histopathologically confirmed CAA should increase understanding of the mechanisms leading to CAA and associated diseases. Polymorphisms in the apolipoprotein E gene (APOE)[6] are associated with many conditions in which CAA may be involved, including subarachnoid haemorrhage, ICH, lobar brain microbleeds and Alzheimer's disease (AD).[4 7–12] In vitro studies have shown that APOE influences Aβ conformation, fibril formation and toxicity[13 14] while in vivo mouse studies have confirmed a critical role for APOE in Aβ deposition, toxicity and possibly clearance.[15 16] The currently favoured view is that APOE ε4 enhances deposition of amyloid β in cerebral blood vessel walls while ε2 promotes haemorrhage from amyloid laden blood vessels by increasing specific CAA related vasculopathic changes.[17–19]

A clear association between APOE and histopathologically confirmed CAA would explain many of the observed associations between APOE and clinical outcomes. There is robust large scale evidence for an association of APOE with ICH attributed to CAA on the basis of clinical criteria. However, studies suggesting an association of APOE with histopathologically confirmed CAA have been limited by various methodological shortcomings, including small size. Furthermore, the possibly contrasting effects of the different APOE alleles on CAA have remained unclear. No systematic evaluation has been performed of the association of APOE or of other polymorphisms with histopathologically confirmed CAA. We therefore aimed to assess the evidence for associations between genetic polymorphisms in any gene and histopathologically confirmed CAA by carrying out a systematic review, incorporating a comprehensive search strategy, a thorough assessment of study quality, a series of meta-analyses and an evaluation of the robustness of any positive findings to small study and other methodological biases.

METHODS

Study identification and inclusion/exclusion criteria

We sought all studies of adult humans published in any language in which participants had been genotyped for any genetic polymorphism and had CAA assessed pathologically (using autopsy or biopsy), regardless of whether any association was reported on.

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 (see online supplementary appendix S1). We also checked the bibliographies of all relevant studies and reviews identified, and searched Google Scholar for studies citing relevant studies.

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We wished to study genetic associations across the range of CAA severity and so included studies of genetic associations with: the presence versus absence of CAA pathology; more versus less severe CAA; or average CAA score. We excluded studies that assessed genetic associations with CAA associated ICH (CAAH) versus CAA free controls because these would not be able to distinguish a genetic association with CAA from an association with ICH. However, we included studies that had recruited participants with CAAH as an unselected part of the spectrum of CAA severity.[5] Two authors independently selected eligible studies, resolving disagreements by discussion.

We classified studies into three partly overlapping groups, according to the association investigated: APOE and sporadic CAA; APOE in any type of hereditary CAA (HCAA) or familial Alzheimer's disease (FAD); any other (non-APOE) genetic polymorphism and sporadic CAA. When two or more studies included overlapping sets of participants, we included only the study providing most data about the association among the largest number of participants. To avoid undue effort on relatively small studies, we further excluded studies with <35 participants from the APOE and sporadic CAA group thus excluding <3% of the total participants in eligible studies in this group.

Data extraction

APOE and sporadic CAA studies

For each study included, we extracted information on: first author; publication year; country in which the study was conducted; and participant source and characteristics. We also 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,[20 21] and the quality and characteristics of CAA pathology assessment (see online supplementary methods).

Where possible, we extracted data on the numbers of participants with ε4 or ε2 allele containing (ε4+ or ε2+) genotypes and their CAA status, in dichotomous (present or absent) or continuous (mean (and SD) severity score) format. In studies without such data available, we recorded any qualitative statement about the association between APOE and CAA. At least two authors extracted these data, resolving disagreements by discussion.

Studies of APOE in HCAA/FAD and of other genetic polymorphisms and sporadic CAA

For these smaller groups of studies, we extracted information on: first author; publication year; number of participants; polymorphism(s) studied; and any data about the association between the polymorphism studied and CAA.

Statistical analyses (APOE and sporadic CAA)

We used Cochrane RevMan (V.5) software. For studies presenting data in a dichotomous format, we calculated an unadjusted OR for the presence versus the absence of CAA among those with ε4+ versus ε4− and ε2+ versus ε2− genotypes. For studies presenting continuous data, we calculated standardised mean differences (SMD) in CAA scores. Then, to analyse the data from dichotomous and continuous studies together, we used the method described by Chinn to convert SMDs to ORs.[22] We also compared ε4 homozygous and heterozygous genotypes. We calculated pooled ORs using the generic inverse variance fixed effects method, and repeated all analyses using a random effects model. We assessed heterogeneity with I^2 and χ^2 statistics. We considered $p<0.05$ to imply statistical significance.

We assigned each included study a quality score, based on study size, participant recruitment method (prospective vs other), blinding, quality of genotyping and pathology assessment, and data format (considering continuous data superior due to potential bias in selecting cutoffs for dichotomous data). We conducted prespecified subgroup analyses based on: dementia status; ethnicity; study quality score; and each quality criterion separately. For any statistically significant result, we assessed the potential effect of unpublished negative studies or studies not reporting the data required for meta-analysis (ie, publication and reporting biases), using a modified 'failsafe N' method: we determined the size of a notional study with a null result (OR=1) required to bring any significant result ($p<0.05$) to a just non-significant level ($p=0.05$), assuming the overall prevalence of CAA and distribution of genotypes to be the average of these for the studies included.[23] We used the size of this notional study as a guide to whether there might plausibly be enough participants in unpublished, unreported or otherwise unretrieved null studies to make an apparently significant result non-significant if data from such studies were available for inclusion in our meta-analyses. We also inspected funnel plots.

RESULTS

Of 1754 publications identified for screening, 136 were relevant (figure 1).

Studies of APOE ε2/ε3/ε4 polymorphism and sporadic CAA

From 107 relevant publications we excluded 61 (49 because they included participants overlapping with included studies and 12 because of very small size (< 35 participants)),[s1–s61] leaving 46 studies, including 6645 participants overall (figure 1).[19 24 s62–s105] (See online supplementary tables S1b, S1c and results.)

Study characteristics and quality

All studies used autopsy brains from a brain bank, clinical autopsies or a population based prospective study. The median number of participants per study who were both genotyped and assessed pathologically was 100. Mean age was 70–85 years in most studies. About half of all participants were male. Nineteen studies (2660 participants) were conducted in white populations in Europe, 21 (3225 participants) in white subjects in the USA, five (714 subjects) in Asian populations (three in Japan, two in Japanese–Americans in the USA) and for one study this information was unavailable. About 30% of participants had clinical dementia (mainly AD), about 10% were known not to be demented and dementia status was not specified for about 60% (see online supplementary table S1a).

Genotyping quality was generally limited when assessed against current reporting standards,[20 21] and methods for pathological assessment were very variable (see online supplementary tables S1b, S1bc and results). There was substantial variation in overall study quality. For the studies in the meta-analysis, we calculated quality scores based on our pre-set criteria. No study fulfilled all of the criteria but larger studies tended to have higher quality scores (table 1).

Association between APOE ε4 and CAA

Twenty-four studies out of 46 (3520 of 6645 participants) provided sufficient quantitative data for meta-analysis (14 dichotomous and 10 continuous format) (figure 2). Twenty-two studies could not be included in our meta-analysis: six (443 participants) of these made a qualitative statement while 16 (2682 participants) provided no data about the association.

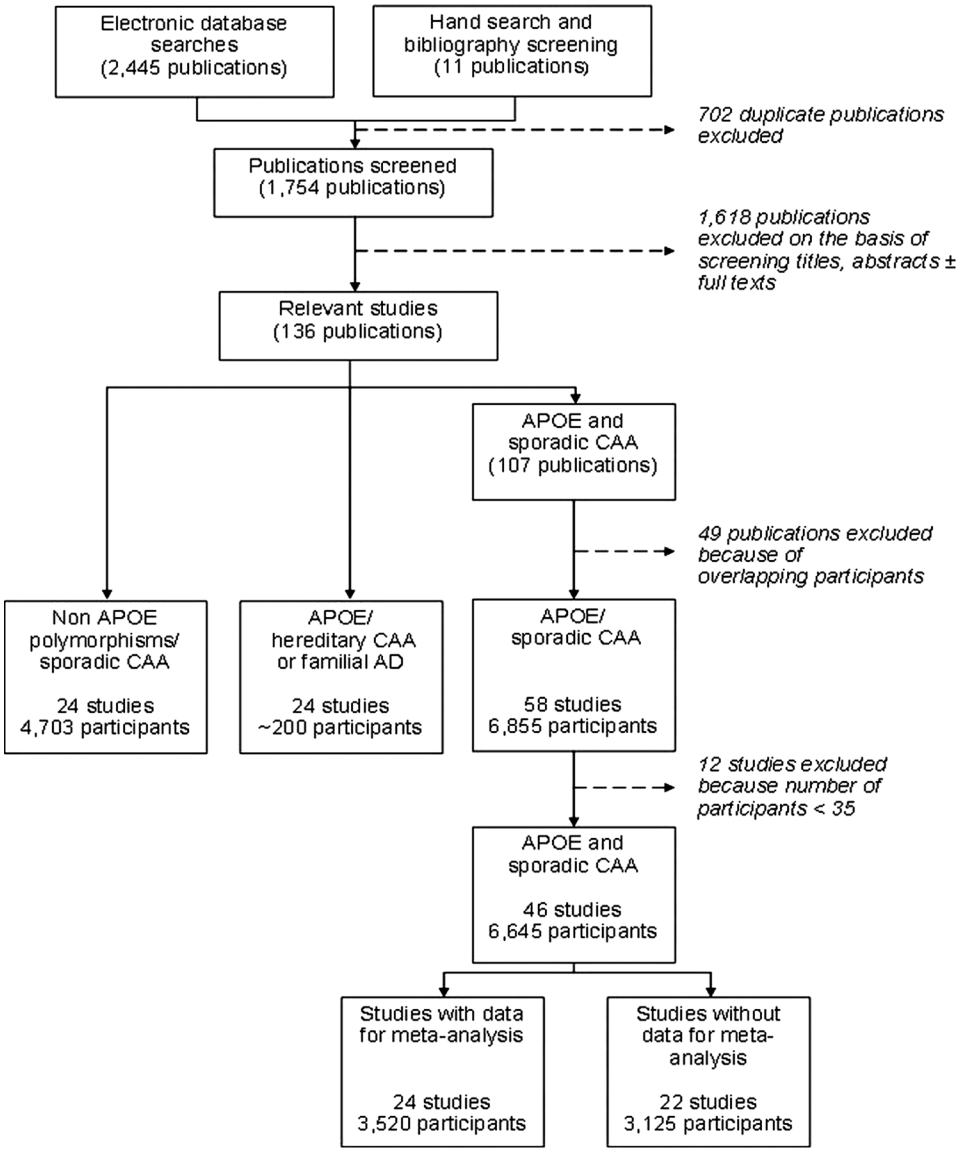


Figure 1 Selection of included studies. AD, Alzheimer's disease; APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy.

Figure 2 shows study specific and pooled ORs for ε4+ versus ε4 − genotypes. The pooled OR showed a significantly increased odds of having CAA for ε4+ genotypes (OR 2.67, 95% CI 2.31 to 3.08) with significant heterogeneity between the results of the studies (I^2=69%; χ^2_{28df}=89; p<0.00001). When we meta-analysed studies providing continuous and dichotomous data separately, pooled results were in the same direction as the overall pooled OR and were separately significant (continuous studies: SMD 0.48, 95% CI 0.38 to 0.59, p<0.00001; dichotomous studies: OR 4.15, 95% CI 3.23 to 5.34, p<0.00001). Subgroup analysis based on dementia status showed no significant subgroup differences (I^2=0%; χ^2_{2df}=1.91; p=0.38), with similar results when we limited the dementia subgroup to neuropathologically verified AD cases only. We detected no significant differences in subgroup analyses based on ethnicity (data not shown). The association did not vary significantly by study quality score (figure 3). Nor did we detect significant subgroup differences based on the individual quality criteria of study size, blinding or quality of genotyping. The association was slightly larger in studies with prospective recruitment of participants (OR 3.66, 95% CI 2.87 to 4.68 vs OR 2.56, 95% CI 2.15 to 3.05; I^2=82%; χ^2_{1df}=5.5; p_{diff}=0.02), in studies presenting data in a dichotomous versus a continuous format (OR 3.64, 95% CI 2.91 to 4.55 vs OR 2.48, 95% CI 2.06 to 2.98; I^2=85%; χ^2_{1df}=6.8; p_{diff}=0.009) and in studies with higher quality of pathology assessment (2 points: OR 3.07, 95% CI 2.46 to 3.83 vs 1 point: OR 2.22, 95% CI 1.84 to 2.67; I^2=80%; χ^2_{1df}=4.9; p_{diff}=0.03).

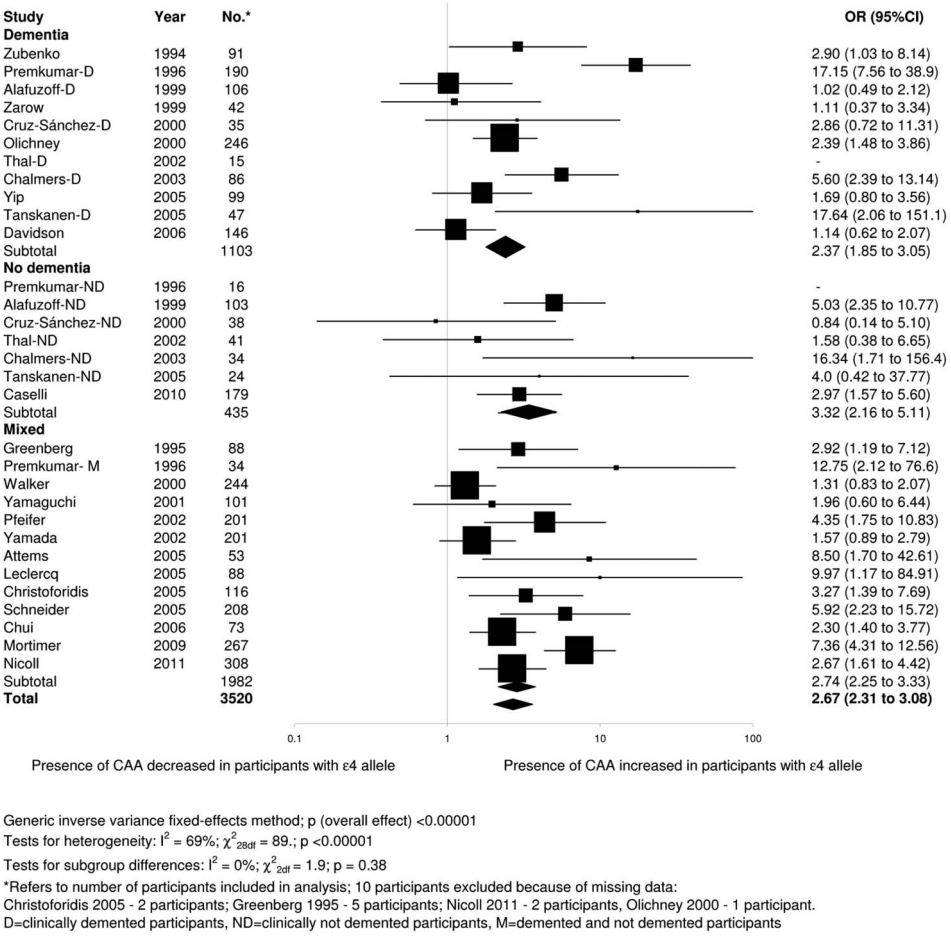
Failsafe N calculations showed that a null study of >137 000 participants would be required to bring the association of ε4+ genotypes with CAA to a just statistically non-significant level (ie, p=0.05). The funnel plot was only slightly asymmetrical. Studies providing only qualitative data reported either no significant association or a trend towards association with APOE ε4 (see online supplementary table S2).[s62–s67]

Twelve studies (1706 participants) provided quantitative data for meta-analysis of the association of APOE ε4 allele dose with CAA, showing a significant increase in the odds of having CAA with increasing dose of the ε4 allele (figure 4). Two studies (117 participants) providing a qualitative statement about the association supported this result (see online supplementary table S2).[s67, s102] Failsafe N calculations showed that it would require a null study of >7000 participants to bring the stronger association with CAA of ε4 homozygous versus heterozygous genotypes to a just non-significant level.

Table 1 Study quality scores

Study (first author)	Study size* (No of participants) ≤139 0	140–239 1	≥240 2	Blinding† None 0	Any 1	Complete 2	Study design‡ R 0	P 1	Data format§ D 0	C 1	Pathology assessment¶ 0	1	2	Genotyping reporting** 0	1	N††	Total score (0–9)
Cruz-Sanchez[s83]	✓			✓			✓		✓			✓			✓	73	2
Thal *et al*[24]	✓			✓			✓		✓			✓			✓	56	2
Yamaguchi[s84]	✓			✓			✓		✓			✓		✓		101	1
Nicoll[s85]			✓		✓			✓	✓				✓		✓	310	7
Schneider[s86]		✓		✓				✓	✓				✓		✓	208	5
Pfeifer[s87]		✓			✓			✓	✓				✓		✓	201	6
Premkumar[s88]			✓		✓		✓		✓				✓		✓	240	6
Walker[s89]			✓		✓		✓			✓		✓			✓	244	6
Caselli[s90]		✓		✓				✓		✓		✓		✓		179	4
Olichney[s91]			✓	✓			✓			✓		✓			✓	247	5
Yamada[s92]		✓		✓			✓			✓		✓			✓	201	4
Zarow[s93]	✓			✓			✓			✓			✓		✓	42	4
Yip[s94]	✓			✓			✓			✓		✓		✓		99	2
Alafuzoff[s95]		✓		✓			✓			✓		✓			✓	209	4
Chalmers[s96]	✓			✓			✓			✓			✓		✓	120	4
Davidson[s97]		✓		✓			✓			✓		✓			✓	146	4
Mortimer[s98]			✓		✓			✓		✓			✓		✓	267	8
Attems[s99]	✓			✓			✓		✓			✓			✓	53	2
Christoforidis[s100]	✓			✓			✓		✓			✓			✓	118	2
Chui[s101]	✓				✓			✓	✓				✓	✓		73	4
Greenberg[s102]	✓				✓		✓		✓				✓		✓	93	4
Leclercq[s103]	✓				✓		✓		✓			✓			✓	88	3
Zubenko[s104]	✓			✓			✓		✓			✓			✓	91	2
Tanskanen[s105]	✓			✓				✓	✓			✓			✓	71	3

*Study size: cut-offs chosen to divide study participants into three roughly equal groups.
†Blinding: genotypers to pathology data, pathologists to genotyping data, pathologists to clinical information (0, no blinding; 1, blinding at least one way; 2, blinding all three ways).
‡Study design (prospective (P) or retrospective (R)).
§Data format (dichotomous (D) or continuous (C)).
¶Pathology assessment based on: method for assessing CAA reported, neuropathologist rated CAA, >1 brain location examined (0, no criteria fulfilled; 1, one to two criteria fulfilled; 2, all three criteria fulfilled).
**Genotyping reporting: source of DNA and genotyping method reported (0, none or one criterion reported; 1, both criteria reported).
††Total study size—number of participants.
CAA, cerebral amyloid angiopathy.

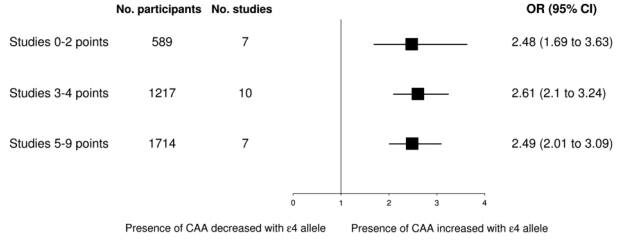


Generic inverse variance fixed-effects method; p (overall effect) <0.00001
Tests for heterogeneity: I^2 = 69%; χ^2_{28df} = 89.; p <0.00001
Tests for subgroup differences: I^2 = 0%; χ^2_{2df} = 1.9; p = 0.38
*Refers to number of participants included in analysis; 10 participants excluded because of missing data:
Christoforidis 2005 - 2 participants; Greenberg 1995 - 5 participants; Nicoll 2011 - 2 participants, Olichney 2000 - 1 participant.
D=clinically demented participants, ND=clinically not demented participants, M=demented and not demented participants

Figure 2 Meta-analysis of association of apolipoprotein E ε4+ versus apolipoprotein ε4− genotypes with cerebral amyloid angiopathy (CAA) by participants' dementia status. The squares represent study specific ORs, with their size proportional to their statistical weight by the generic inverse variance method. Horizontal lines represent 95% CIs. Diamonds represent pooled ORs and their width represents 95% CI.

Association between APOE ε2 and CAA

Eleven studies (1640 participants) provided quantitative data for meta-analysis of APOE ε2+ versus ε2− genotypes with CAA. The pooled OR showed a non-significantly decreased odds of CAA with APOE ε2+ genotypes (OR 0.73, 95% CI 0.53 to 1.00, p=0.05). When we meta-analysed studies providing continuous and dichotomous data separately, pooled results were in the same direction as the overall pooled OR but remained non-significant. Two studies (213 participants) provided a qualitative statement; neither reported a significant association (see online supplementary table S2).[s96,s102]



Generic inverse variance fixed-effects method
Test for subgroup differences: I^2=0%; χ^2_{2df}=0.1; p=0.95

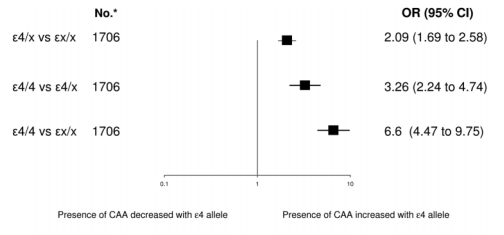
Figure 3 Subgroup analysis based on study quality scores. The squares represent pooled ORs and their width represents the 95% CI. CAA, cerebral amyloid angiopathy.

Random effects meta-analyses

Results were very similar when all of the above meta-analyses were repeated using a random effects model.

Studies of APOE ε2/ε3/ε4 polymorphism in cases of HCAA /familial AD

Of 24 relevant studies,[s60,s106–s128] only two reported on the association between the APOE genotype and severity of CAA. They found no effect of APOE ε4 on CAA in 16 HCHWA-D (hereditary cerebral haemorrhage with amyloidosis, Dutch type) patients[s106] or in 54 participants with FAD due to a presenilin-1 mutation.[s107]



Generic inverse variance fixed-effects method
*Refers to number of participants included in analysis.
Excluded due to missing data: Nicoll 2011- 2 participants; Davidson 2006 and Olichney 2000 - 1 participant

Figure 4 Meta-analysis of effects of apolipoprotein E ε4 dose (ε4−−/ε4+−/ε4++ genotypes) on the presence versus the absence of cerebral amyloid angiopathy (CAA). Notation as for figure 3.

Studies of other genetic polymorphisms and sporadic CAA

Few other polymorphisms had been studied in more than a few hundred participants or in more than one study and there were insufficient data for formal meta-analyses.[s4,s6–8,s11–13,s24,s35,s37–39,s41,s46,s71,s80–81,s97,s100,s129–133] However, there were some positive associations with CAA: a consistent trend to association with a single nucleotoide polymorphism (SNP) in the transforming growth factor β1 (TGF-β1) gene (two studies, 449 participants)[s13,s24]; significant associations with SNPs in the translocase of outer mitochondrial membrane 40 (TOMM40) gene (one study, 723 participants);[s132] and with a SNP in the complement component receptor 1 (CR1) gene (one study, 544 participants).[s133] Other studies found no overall significant associations although some reported associations in particular subgroups (table 2).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis of associations between genetic polymorphisms and pathologically proven CAA although there have been meta-analyses of genetic associations with deep and lobar ICH, ICH severity and outcome, and brain microbleeds.[9–11] We found a highly significant dose-dependent association between APOE ε4 and pathologically proven CAA, which did not vary significantly with dementia status, ethnicity or study quality. We found no overall association between APOE ε2 and the presence of CAA. No modifying effects of APOE on CAA were reported among cases of HCAA or of FAD, but because most of these participants have severe CAA anyway, modulation by APOE is very difficult to detect.[s109] Finally, there were too few studies and participants to draw firm conclusions about the effect of other genetic polymorphisms but there were some positive associations which merit replication in further larger studies or pooled datasets.

The prevalence of CAA in AD is over 70% but the relationship between CAA and AD is still poorly understood. Although the diagnostic criteria for dementia and the participant inclusion criteria varied between studies (with some excluding cases with severe dementia), demonstration of a similar association in those with and without clinical dementia suggests that the association of APOE ε4 with CAA is independent of its known association with dementia (mainly AD). This is further supported by similar results when we limited the dementia subgroup to neuropathologically verified AD cases only. Relative to other apoE isoforms, apoE4 is thought to increase aggregation or impair clearance of amyloid β, or both. While this mechanistic pathway is probably common to both CAA and AD, specific mechanisms might also occur. For example, apoE isoform specific neurotoxic effects may contribute to neurodegeneration in AD, independent of interactions with amyloid β.[25]

Our study benefited from thorough ascertainment and critical appraisal of pertinent studies including a large number of participants. Lack of variation in the effect of APOE ε4 by study size and the very large failsafe N show that this association cannot plausibly be explained by publication, reporting or any other small study bias. In addition, although study quality was generally limited when assessed against current reporting standards,[20 21] there were—reassuringly—no significant subgroup differences by study quality score.

There were some limitations. Pathological assessment was very variable. Indeed, there is no widely accepted standardised histopathological grading system for CAA,[26] and no comparative studies to determine the most accurate method for assessing CAA (although the suggested method is a combination of thioflavin S/T or Congo Red with immunohistochemistry).[27] CAA assessment location varied widely, possibly influencing the rate of CAA detection as a greater burden of CAA is generally reported in the occipital or parietal lobes, albeit with a higher frequency of frontal lobe involvement reported in studies from China and

Table 2 Summary of studies of non-apolipoprotein E polymorphisms and cerebral amyloid angiopathy

Gene	Location/polymorphism	No of studies	No of participants	Summary of results
TGF-β1(transforming growth factor β1)[s13,s24]	rs1800470	2	449	Consistent trend for positive association between T allele and CAA
TOMM40 (translocase of outer mitochondrial membrane 40)[s132]	rs2075650, rs34404554, rs11556505, rs769449, rs12972156, rs12972970, rs157582, rs184017, rs157581, rs283815, rs157580, rs439401, rs34095326, rs10119	1	723	SNPs associated with vascular amyloid burden
CR1 (complement component receptor 1) gene[s133]	rs6656401	1	544	Associated with severity of CAA pathology
LRP1 (low density lipoprotein receptor 1)[s38,s41,s100]	rs1799986	3	597	No overall significant associations (inconsistent trends and in some cases associations in subgroups)
ACT (α1 antichymotrypsin)[s7,s81]	Signal region of the gene → A/T alleles that determine the amino acid alanine or threonine*	2	235	
CYP46[s41,s129]	rs754203	2	524	
ACE (angiotensin 1 converting enzyme) [s35,s129]	Intron 16 insertion/deletion of a 287 bp sequence	2	239	
Other genes PS1 (presenilin-1)[s4];BCHE (butyrylcholinesterase)[s6];DXS1047 locus[s130];APOE promoter[s80,s129];A2M (α_2 macroglobulin)[s8];PON1 (paraoxonase)[s11];NEP (neprilysin)[s12];OLR1 (oxidised low-density lipoprotein receptor 1)[s38];LRP (low density lipoprotein receptor related protein)[s100];CYP46[s41];CH25H*1[s41];VEGF (vascular endothelial growth factor)[s37];IL-1A[s131];IL-1B[s131];IL-33[s39];GSTO1-1 (glutathione S-transferase omega-1)[s131];SORL1 (sortilin related receptor)[s46];CTSD (cathepsin D)[s97];AβPP and AβPppromoter[s71]		18	50–380†	

*Probably rs4943.
†Range of participant numbers in individual studies.
APOE, apolipoprotein E; CAA, cerebral amyloid angiopathy; SNP, single nucleotoide polymorphism.

Japan.[26] Most included studies did not address the issue of potential confounding due to population stratification. However, such confounding is unlikely because these were not case control studies but cross sectional studies across a range of CAA severities. Finally, there was a large number of studies that we could not include in the meta-analysis because they did not report the necessary quantitative data about the association between the genetic polymorphism and CAA. However, our systematic review is strengthened by the identification and detailed characterisation of these studies. By contrast, many meta-analyses do not account for otherwise relevant studies without the necessary data within their publications and so risk undetected reporting bias as many studies report only significant findings and fail to mention non-significant ones. We have shown that our findings are robust to these missing data as our large failsafe N (>137 000) greatly exceeded the total number of participants excluded due to lack of available data (3125).

Several outstanding issues require more research. Genes other than APOE seem likely to influence CAA. Some preliminary positive findings merit replication in larger studies: the possible reported association between the TGF-β1 gene and CAA may be through an influence on Aβ clearance and deposition through activation of astrocytes and microglia; association of TOMM40 gene polymorphisms with vascular amyloid burden but not CAAH could be through interaction with APOE ε2 or affects on Aβ mitochondrial transport; association of a CR1 gene polymorphism with both CAA severity and CAAH may be via clearance of Aβ peptide.[28 s13 s132] As the effects of APOE on ICH may vary with ethnicity, there may be ethnic variation in genetic associations with CAA but these have not been widely studied in non-white populations.[29] Genetic associations may also differ by CAA location and subtype. For example, there is preliminary evidence that APOE ε4 may be associated with CAA type 1 (where CAA is found in cortical capillaries) and ε2 with CAA type 2 (where amyloid is deposited in leptomeningeal and cortical vessels with the exception of cortical capillaries).[24] Finally, the suggestion of different genetic influences on amyloid deposition in the vessel wall and advanced vasculopathic changes leading to ICH requires further investigation, in particular the proposed differential effects of ε4 and ε2 alleles.

In conclusion, despite study quality issues, a large body of evidence supports an association of APOE ε4 with the presence and severity of histopathologically confirmed CAA, at least in white populations. Future research efforts require methodologically robust studies adhering to current reporting standards, facilitating comparisons between studies and collaborative data pooling efforts. These should focus on the differential effects of APOE ε2 and ε4, variation in genetic effects by ethnicity and CAA location, and on the potential influence of other polymorphisms on this clinically important but as yet incompletely understood phenotype.

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Competing interests None.

Ethics approval In accordance with National Research Ethics Service and Medical Research Council 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 have come from studies which have previously satisfied regulatory requirements and been peer reviewed.

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ONLINE SUPPLEMENT

Title

Genetics of cerebral amyloid angiopathy: systematic review and meta-analysis

Online supplement:

- Supplemental methods and results
- 2 Supplemental tables:
    - Supplemental table S1(a) to (c): Characteristics of studies of APOE and sporadic CAA
    - Supplemental table S2: Summary of studies providing qualitative data about the association between APOE genotype and CAA
- Supplemental appendix S1
- Supplemental references S1-S134

Supplemental methods and results

Methods of assessing quality of genotyping and pathology assessment

With respect to genotyping, we extracted information on: source and storage of DNA; where genotyping was done; whether genotypes were assigned using all data simultaneously or in batches; number of participants in whom genotyping was attempted and in whom it was successful; genotyping method; whether genotypes were in Hardy-Weinberg equilibrium (HWE); blinding of genotyping staff to pathology data. With respect to pathology assessment, we extracted data on: method and consistency of assessment; qualification of CAA rater(s); brain locations examined; rating system used and its intra- and inter-rater reliability; blinding of raters to genotyping results and relevant clinical information.

Results of genotyping and pathology assessment quality

10 studies (1723 participants) did not report the source of DNA, 25 (2993 participants) used brain tissue, seven (1040 participants) used blood samples, three (632 participants) used both, and one used brain tissue or buccal cells. No study described how DNA was stored or how data were used to assign genotypes. Only two studies (350 participants) reported where genotyping had been done and two (294 participants) reported on the number of participants in whom genotyping had been attempted and in whom it had been successful. Six studies (1380 participants) did not report on the method of genotyping, while the rest used PCR-based techniques. In 22 studies (2884 participants) genotypes were either stated or calculated to be in HWE, for three (326 participants) they were not in HWE, 19 (3328 participants) provided no information on HWE and for two studies it was not applicable. Only two studies (333 participants) reported that genotypers were blind to pathology data (Supplemental table S1(b)).

With regard to CAA assessment, 34 studies (4570 participants) used immunohistochemistry (IHC) in all or some samples, 10 (1291 participants) used an alternative (Congo Red ± polarized light, Hematoxylin & Eosin, or Thioflavin S) and two (794 participants) did not report on staining method. 14 studies (2231 participants) specified that a neuropathologist rated CAA, but most did not report on this. A variety of CAA rating scales were used, including those devised by Olichney[s134], Vonsattel[5], and Attems[26]; 27 studies used an alternative severity rating measure or scale, five did not report the scale or severity measure used, and three did not rate CAA severity. Only two studies reported the inter- and intra-rater reliability of the scale used (or referenced a study of these). 31 studies (4600 participants) assessed CAA in occipital and/or parietal cortex, frequently in addition to other areas. Only eight studies (890 participants) reported that pathology raters were blind to genotyping results and six (1096 participants) that they were blind to relevant clinical information (Supplemental table S1(c)).

Supplemental table S1(a). Characteristics of studies of APOE and sporadic CAA

First author	Year published	Country*	Brief description of participants†	No. of non-overlapping participants genotyped & assessed for CAA	Mean/median‡ age or age range	Ethnicity	% male
Cruz-Sánchez[s83]	2000	n/k	Cases with clinically diagnosed dementia & controls without cognitive impairment	73	With dementia: 76 No dementia: 67	Caucasian§	60
Thal[s24]	2002	n/k	Cases with CAA & controls without	56	77	n/k	52
Yamaguchi[s84]	2001	Japan	People who died from cancer	101	65	Asian§	n/k
Nicoll[s85]	2011	UK	People from MRC CFAS neuropathology cohort of 456 participants (UK population-based study that started in early 1990s, and recruited people aged over 65 years from the community)	310	With dementia: 89‡ No dementia: 84‡	Caucasian§	40
Schneider[s86]	2005	USA	People from the Religious Orders Study (US-prospective study in older Catholic nuns, priests, and monks with no dementia at baseline)	208	86#	Majority Caucasian	45#
Pfeifer[s87]	2002	USA	Men from the Honolulu-Asia Aging Study (prospective study which recruited Japanese-American men born 1900-1919, living in Oahu at enrolment in 1965-1968)	201	85#	Japanese-American	100
Premkumar[s88]	1996	USA	People from an AD research programme	240	Normal controls: 70 Neurological controls: 73 AD participants: 79	Caucasian§	45
Walker[s89]	2000	Germany	Routine autopsy brains	244	67	Caucasian§	55
Caselli[s90]	2010	USA	Cognitively healthy adults mainly from retirement communities enrolled in the Sun Health Research Institute Brain Donation program 1991-2007	179	83	Majority Caucasian	55
Olichney[s91]	2000	USA	AD cases from an autopsy series	247	80#	Caucasian§	53#

First author	Year published	Country*	Brief description of participants†	No. of non-overlapping participants genotyped & assessed for CAA	Mean/median‡ age or age range	Ethnicity	% male
Yamada[s92]	2002	Japan	Brains from autopsy series of a large geriatric hospital in Japan, excluding brains with neurodegenerative diseases except AD	201	86	Asian	40
Zarow[s93]	1999	USA	Cases with definite AD	42	77#	Caucasian§	50#
Yip[s94]	2005	USA	AD cases	99	75	Majority Caucasian	97
Alafuzoff[s95]	1999	Finland	Brains from a brain bank	209	With dementia: 82 No dementia: 75	Caucasian§	33
Chalmers[s96]	2003	UK	Clinically diagnosed AD & 34 elderly normal controls from a brain bank	120	78#	Caucasian§	47#
Davidson[s97]	2006	UK	Neuropathologically confirmed AD cases	146	n/k	Caucasian	n/k
Mortimer[s98]	2009	USA	People from the Nun Study (prospective study which recruited members of the School Sisters of Notre Dame congregation 1991-1992)	267	91	Caucasian§	0
Attems[s99]	2005	Austria	Brains from a pathology department of a large hospital	53	84#	Caucasian§	39#
Christoforidis[s100]	2005	Germany	Routine autopsy brains	118	74	Caucasian	n/k
Chui[s101]	2006	USA	People from the Ischemic Vascular Dementia Programme (longitudinal study of subcortical ischemic vascular dementia, AD and cognitively normal elderly people)	73	83#	86 % Caucasian	57#
Greenberg[s102]	1995	USA	Brains selected from a brain tissue resource centre (713 brains) to provide cases each of CAA grade	93	79	Caucasian§	n/k
Leclercq[s103]	2005	UK	Traumatic head injury cases	88	30‡	Caucasian§	74
Zubenko[s104]	1994	USA	Neuropathologically confirmed AD cases	91	76	Caucasian§	39
Tanskanen[s105]	2005	Finland	People aged ≥ 95 years from the	71	97#	Caucasian§	18#

First author	Year published	Country*	Brief description of participants†	No. of non-overlapping participants genotyped & assessed for CAA	Mean/median‡ age or age range	Ethnicity	% male
			Vantaa 85+ study (Finnish population based study that recruited people from the community born before 1906 and living in Vantaa on April 1, 1991)				
Thomas[s62]	2000	n/k	Elderly Norwegian AD patients	50	86	Caucasian§	28
Stopa[s63]	2008	USA	Brains from a brain bank and AD research centre	75	78	Caucasian	38
Oyama[s64]	1995	Japan	Consecutive autopsy brains from a geriatric hospital and psychiatric hospital	37	50-101	Asian§	n/k
Jicha[s65]	2008	USA	AD patients from an AD research centre and a community-based study	81	88	Caucasian§	26
Berg[s66]	1998	USA	Brains from a consecutive autopsy series of prospectively studied probable AD or incipient dementia participants and controls	176	81#	Caucasian§	46#
Roher[s67]	2003	USA	Brains from a brain donation programme	24	82	Caucasian§	54
Greenberg[19]	1998	USA	Autopsy brains with moderate or severe CAA chosen from a brain tissue resource centre	47	79#	Majority Caucasian	n/k
Tiraboschi[s68]	2004	USA	Brains with a neuropathological diagnosis of AD	48	80	Caucasian§	42
Lewis[s69]	2006	UK	AD cases, vascular dementia cases, and controls from a brain tissue resource centre	98	81	Caucasian§	44
Sonnen[s70]	2010	USA	People from the Adult Changes in Thought Study (US prospective study that enrolled 3392 cognitively intact community-dwelling participants aged ≥ 65y in 1994-2003)	256	93 participants ≤ 75 157 participants: 76-85 43 participants: ≥ 86#	Majority Caucasian	42#
Peuralinna[s71]	2011	Finland	People from the Vantaa 85+ study (Finnish population-based study that	211	93#	Caucasian§	17#

First author	Year published	Country*	Brief description of participants†	No. of non-overlapping participants genotyped & assessed for CAA	Mean/median‡ age or age range	Ethnicity	% male
			recruited people from the community born before 1906 and living in Vantaa on April 1, 1991)				
Petrovitch[s72]	2008	USA	Men from the Honolulu-Asia Aging Study (prospective study which recruited Japanese-American men born 1900-1919, living in Oahu at enrolment in 1965-1968)	174	86#	Japanese-American	100
Alafuzoff[s73]	2009	Finland	Participants from a university hospital	492	74#	Caucasian§	46#
Attems[s74]	2008	Austria	Consecutive autopsied brains from 3 large hospitals	157	79#	Caucasian§	40#
Etiene[s75]	1998	USA	Participants with AD, some with symptomatically remote cerebral infarcts, from an AD research centre brain bank	100	80	Caucasian§	36
Honig[s76]	2005	USA	Demented and control participants	538	80	Majority Caucasian	47
Lashley[s77]	2008	UK	PD cases and normal control participants randomly selected from a brain bank	57	78#	Caucasian§	53#
Love[s78]	2003	UK	Brain donors without evidence of AD by CERAD criteria	118	60-102#	Caucasian§	51#
Nelson[s79]	2010	USA	Elderly participants from an AD centre autopsy cohort with a range of cognitive impairment	334	84	Majority Caucasian	41
Pahnke[s80]	2003	n/k	Routine autopsy brains of non-AD participants	30	67#	Caucasian§	54#
Durany[s81]	2000	n/k	AD patients, CAA cases without other AD features and non-neurological controls from a general hospital	15	74#	Caucasian	56#
Zipser[s82]	2007	USA	AD participants	7	51-97#	Caucasian§	39#

Light grey shading - studies providing data for ε4+ versus ε4- CAA meta-analysis; dark grey shading – studies providing a qualitative statement about ε4 association with CAA; no shading – studies providing no data about association between APOE genotype and CAA
* If country where study conducted was not stated, then assumed from authors' affiliations
† All were autopsy brains
‡ Median age
§ Ethnicity not explicitly stated, but assumed from context
# Data provided for a larger or smaller group of participants than the ones included
n/k – not known

Supplemental table S1(b). Characteristics of studies of APOE and sporadic CAA – genotyping characteristics

First author	Year of publication	Source of DNA	Storage of DNA	Laboratory/centre where genotyping done	Genotypes assigned using all data simultaneously or in batches	No in whom genotyping attempted/in whom successful	Genotyping method	Genotypes in HWE	Genotypers blinded to pathology data
Cruz-Sánchez[s83]	2000	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Thal[24]	2002	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Yamaguchi[s84]	2001	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k
Nicoll[s85]	2011	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Schneider[s86]	2005	Blood	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Pfeifer[s87]	2002	Blood	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Premkumar[s88]	1996	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	Yes
Walker[s89]	2000	Brain	n/k	n/k	n/k	n/k	PCR-based	No	n/k
Caselli[s90]	2010	n/k	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Olichney[s91]	2000	Brain or blood	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Yamada[s92]	2002	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Zarow[s93]	1999	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Yip[s94]	2005	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k
Alafuzoff[s95]	1999	Brain or blood	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Chalmers[s96]	2003	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Davidson[s97]	2006	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Mortimer[s98]	2009	Brain or buccal cells	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Attems[s99]	2005	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Christoforidis[s100]	2005	Brain	n/k	n/k	n/k	118/125	PCR-based	Yes	n/k
Chui[s101]	2006	Blood	n/k	n/k	n/k	n/k	n/k	n/k	n/k
Greenberg[s102]	1995	Brain	n/k	n/k	n/k	n/k	PCR-based	n/a	Yes
Leclercq[s103]	2005	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Zubenko[s104]	1994	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k

First author	Year of publication	Source of DNA	Storage of DNA	Laboratory/centre where genotyping done	Genotypes assigned using all data simultaneously or in batches	No in whom genotyping attempted/in whom successful	Genotyping method	Genotypes in HWE	Genotypers blinded to pathology data
Tanskanen[s105]	2005	Blood	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Thomas[s62]	2000	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Stopa[s63]	2008	n/k	n/k	n/k	n/k	n/k	PCR-based	No	n/k
Oyama[s64]	1995	n/k	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Jicha[s65]	2008	Blood	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Berg[s66]	1998	Brain or blood	n/k	Stated	n/k	176/199	PCR-based	Yes	n/k
Roher[s67]	2003	Brain	n/k	n/k	n/k	n/k	PCR-based	n/a	n/k
Greenberg[19]	1998	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Tiraboschi[s68]	2004	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Lewis[s69]	2006	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Sonnen[s70]	2010	Blood	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Peuralinna[s71]	2011	Blood	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Petrovitch[s72]	2008	Blood	n/k	Stated	n/k	n/k	PCR-based	n/k	n/k
Alafuzoff[s73]	2009	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Attems[s74]	2008	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Etiene[s75]	1998	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Honig[s76]	2005	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k
Lashley[s77]	2008	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Love[s78]	2003	n/k	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Nelson[s79]	2010	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k
Pahnke[s80]	2003	Brain	n/k	n/k	n/k	n/k	PCR-based	Yes	n/k
Durany[s81]	2000	Brain	n/k	n/k	n/k	n/k	PCR-based	n/k	n/k
Zipser[s82]	2007	n/k	n/k	n/k	n/k	n/k	PCR-based	No	n/k

Light grey shading – studies providing data for ε4+ versus CAA meta-analysis; dark grey shading – studies providing a qualitative statement about ε4 association with CAA; no shading – studies not providing data about association between APOE genotype and CAA. n/k – not known; n/a – not applicable;

Supplemental table S1(c). Characteristics of studies of APOE and sporadic CAA - pathology assessment characteristics

First author	Year of pub.	Method for assessing CAA				Consistency of method*	Qualification of the person who rated CAA	Locations examined	Scale/ severity grading/ amyloid quantification system used used	Inter- and intra-rater reliability of the scale	Blinding to genotype	Blinding to relevant clinical information †
		IHC	CR	HE	ThS							
Cruz-Sánchez[s83]	2000	✓	✓			Yes	n/k	Ot; O; T;	n/a	n/a	n/k	n/k
Thal[24]	2002	✓				Yes	n/k	T; O; LM	Other	n/k	n/k	n/k
Yamaguchi[s84]	2001	✓				Yes	n/k	F	n/k	n/a	n/k	n/k
Nicoll[s85]	2011		✓			Yes	Neuro-pathologist	F; T; P; O; Ot; LM;	Other	n/k	n/k	Yes
Schneider[s86]	2005	✓				Yes	Neuro-pathologist	F; O; LM;	After Attems	n/k	n/k	n/k
Pfeifer[s87]	2002	✓				Yes	Neuro-pathologist	F; T; P; O; LM;	After Vinters	n/k	n/k	Yes
Premkumar[s88]	1996	✓	✓ some		✓ some	Yes	Neuro-pathologist§	F; T; P; O;	Other	n/k	Yes	n/k
Walker[s89]	2000	✓				Yes	n/k	Ot; T; LM;	Other	n/k	Yes	n/k
Caselli[s90]	2010			✓ some	✓ some	Yes	n/k	F; T; P; O;	Other	n/k	n/k	n/k
Olichney[s91]	2000			✓	✓	Yes	n/k	Ot; F; P; T; LM;	Olichney	n/k	n/k	n/k
Yamada[s92]	2002	✓some	✓			Yes	n/k	O; LM;	Other	n/k	n/k	n/k
Zarow[s93]	1999				✓	Yes	Neuro-pathologist	F; P; O; T; Ot; LM;	Other	intra-rater reliability κ 0,76; inter-rater reliability κ 0,77	n/k	n/k
Yip[s94]	2005	✓				Yes	Neuro-pathologist	O;	Other	n/k	n/k	n/k
Alafuzoff[s95]	1999	✓				Yes	n/k	P; LM;	Other	n/k	n/k	n/k

First author	Year of pub.	Method for assessing CAA				Consistency of method*	Qualification of the person who rated CAA	Locations examined	Scale/ severity grading/ amyloid quantification system used used	Inter- and intra-rater reliability of the scale	Blinding to genotype	Blinding to relevant clinical information †
		IHC	CR	HE	ThS							
Chalmers[s96]	2003	✓				Yes	Neuro-pathologist	F; T; P;LM;	Olichney	n/k	n/k	n/k
Davidson[s97]	2006	✓				Yes	n/k	F;	Other	looked at in a previous study and described as "good" but using methods that were unclear	n/k	n/k
Mortimer[s98]	2009	✓				Yes	Neuro-pathologist	F; P; T; O; Ot; LM;	Other	n/k	n/k	Yes
Attems[s99]	2005	✓				Yes	n/k	F; Ot; O; LM;	Olichney Attems	n/k	n/k	n/k
Christoforidis[s100]	2005	✓				Yes	n/k	T; O; LM;	Other	n/k	n/k	n/k
Chui[s101]	2006	✓ some	✓	✓		Yes	Neuro-pathologist	F; T; P; O; Ot;	Vonsattel	n/k	Yes	Yes
Greenberg[s102]	1995		✓			Yes	Neuro-pathologist	F; P; T; Ot; O; C;	Vonsattel	n/k	Yes	n/k
Leclercq[s103]	2005	✓	✓			Yes	n/k	F; T; LM;	Other	n/k	Yes| |	Yes| |
Zubenko[s104]	1994		✓			Yes	Neuro-pathologist	n/k	n/a	n/a	n/k	n/k
Tanskanen[s105]	2005	✓ some	✓			Yes	n/k	F; T; P; Ot; C; LM;	Other	n/k	n/k	n/k
Thomas[s62]	2000	√				Yes	Image analysis	T;	Other	n/k	n/k	n/k

First author	Year of pub.	Method for assessing CAA				Consistency of method*	Qualification of the person who rated CAA	Locations examined	Scale/ severity grading/ amyloid quantification system used used	Inter- and intra-rater reliability of the scale	Blinding to genotype	Blinding to relevant clinical information †
		IHC	CR	HE	ThS							
Stopa[s63]	2008	✓				Yes	n/k	F;	Other	n/k	Yes	n/k
Oyama[s64]	1995	✓ #				yes	n/k	F; T; O;	Other	n/k	n/k	n/k
Jicha[s65]	2008			✓		Yes	n/k	n/k for CAA; but F; T; P; O; C; Ot; LM;	Other	n/k	n/k	n/k
Berg[s66]	1998				✓	Yes	n/k	n/k for CAA but F; T; P; LM;	Other	n/k	n/k	n/k
Roher[s67]	2003				✓	Yes	n/k	LM; P;	Other	n/k	n/k	n/k
Greenberg[19]	1998	✓ some	✓	✓		Yes	n/k	Cerebral cortex and cerebellum	Vonsattel	n/k	Yes	n/k
Tiraboschi[s68]	2004				✓	Yes	n/k	F; P; T; Ot; LM;	Other	n/k	n/k	n/k
Lewis[s69]	2006	✓				Yes	Image analysis	T; F;	Other	n/k	n/k	n/k
Sonnen[s70]	2010	n/k	n/k	n/k	n/k	n/k	Neuro-pathologist	n/k	n/k	n/k	n/k	n/k
Peuralinna[s71]	2011	✓	✓			Yes	n/k	F; P; T; O; Ot; C	Other	n/k	n/k	n/k
Petrovitch[s72]	2008	✓				Yes	Neuro-pathologist	F; T; P; O; Ot; LM;	Other	n/k	n/k	n/k
Alafuzoff[s73]	2009	✓				Yes	n/k	F; T; P;	n/a	n/a	n/k	n/k
Attems[s74]	2008	✓				Yes	n/k	F; Ot; O; LM;	Olichney	n/k	n/k	Yes
Etiene[s75]	1998	✓				Yes	n/k	T; LM;	Other	n/k	n/k	n/k
Honig[s76]	2005	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k	n/k
Lashley[s77]	2008	✓				Yes	Neuro-	F; T; P; O;	Olichney	n/k	n/k	n/k

First author	Year of pub.	Method for assessing CAA				Consistency of method*	Qualification of the person who rated CAA	Locations examined	Scale/ severity grading/ amyloid quantification system used used	Inter- and intra-rater reliability of the scale	Blinding to genotype	Blinding to relevant clinical information †
		IHC	CR	HE	ThS							
							pathologist	LM;				
Love[s78]	2003	✓				Yes	n/k	F; T;	Olichney	n/k	n/k	n/k
Nelson[s79]	2010	✓		✓		Yes	n/k	n/k for CAA	n/k	n/a	n/k	n/k
Pahnke[s80]	2003	✓				Yes	n/k	T; Ot; LM;	Other	n/k	Yes	n/k
Durany[s81]	2000	✓	✓	✓		Yes	n/k	O; T; Ot; LM;	Other	n/k	n/k	n/k
Zipser[s82]	2007	✓				Yes	n/k	F;	n/k	n/k	n/k	n/k

Light grey shading – studies providing data for ε4+ versus CAA meta-analysis; dark grey shading – studies providing a qualitative statement about ε4 association with CAA; white shading – studies providing no data about association between APOE genotype and CAA. Locations examined: F- frontal cortex; T- temporal cortex; P- parietal cortex; O- occipital cortex; Ot- other; C- cerebellar cortex; LM – leptomeninges (assumed leptomeninges were assessed when the scale used in the study included assessment of these vessels). If an included study referenced another study regarding how pathology assessment was done, then we generally assumed the method and scale used were the same; however, other details of pathology assessment had to be mentioned in the original study.

IHC – Immunohistochemistry; CR – Congo Red; HE – Hematoxylin and Eosin; ThS – Thioflavin S

* If there was no reason to assume that the pathological methods used were not consistent (i.e. was it the same method throughout the study or variable with time, recruting centre etc), ticked yes, even if this had not been specifically stated in the study

†Relevant clinical information for example includes dementia/AD status, ICH history, age etc of the participants

§ Premkumar 1996 – some rated by neuropathologist, n/k for some;

‖Leclercq 2005 – IHC assessed blind to genotype and clinical information

Oyama 1995 – assumed IHC based on a reference to a previous study on same participants;

n/k – not known

Supplemental table S2. Summary of studies providing qualitative data about the association between APOE genotype and CAA

First author & year	Participants´ dementia status	Number of participants*	Association between CAA and the APOE genotype
Stopa 2008[s63]	M	75	No overall association with APOE genotype
Jicha 2008[s65]	D	81	No overall association with APOE ε4 allele possession
Thomas 2000[s62]	D	50	No overall association with APOE ε4 allele possession
Berg 1998[s66]	M	176	APOE ε4 allele possession associated with increased severity of CAA in the neocortex but not in hippocampal or entorhinal regions
Oyama 1995[s64]	?	37	APOE ε4 allele possession associated with a trend towards increased severity of CAA
Greenberg 1995†[s102]	M	93	Homozygosity for the APOE ε4 allele associated with increased severity of CAA APOE ε2 allele possession associated with a trend towards less severe CAA
Roher 2003[s67]	D	24	Homozygosity for the APOE ε4 allele associated with increased severity of CAA
Chalmers 2003†[s96]	M	120	No association with homozygosity for the APOE ε2 allele

M- mixed demented and non-demented participants; D- clinically demented participants; ?- unknown

* Number of participants in the study for whom association between genotype and CAA assessed

†Study also provided data for meta-analysis of the association between APOEε4 allele and CAA

Appendix S1

Ovid Embase search strategy (1980 to March 2012)

1. exp vascular amyloidosis/
2. exp Congo Red/ or exp amyloid/ or exp amyloid beta protein/ or exp amyloid precursor protein/
3. exp cerebrovascular disease/
4. 2 and 3
5. (amyloid angiopath$ or congophil$ angiopath$ or cerebral amyloid$ or cerebral congo?red or cerebral A?beta or cerebral beta?amyloid).tw.
6. 1 or 4 or 5
7. exp genetics/ or exp genetic disorder/ or genetic epidemiology/ or exp genetic analysis/ or exp population genetic parameters/ or quantitative trait/ or exp molecular genetics/ or exp genetic parameters/ or exp gene mapping/ or exp APOLIPOPROTEIN E2/ or exp APOLIPOPROTEIN/ or exp APOLIPOPROTEIN E3/ or exp APOLIPOPROTEIN E/ or exp APOLIPOPROTEIN E4/
8. (polymorphi$ or genotype$ or gene or genes or genetic$ or allele$ or mutat$ or apolipoprotein$ or apoprotein$ or APO?E$).tw.
9. 7 or 8
10. 6 and 9
11. limit 10 to human

Ovid Medline search strategy (1950 to March 2012)

1. exp Cerebral Amyloid Angiopathy/
2. amyloidosis/ or amyloidosis, familial/ or exp Amyloid beta-Protein/ or exp Amyloid/ or exp Congo Red/
3. exp cerebrovascular disorders/
4. 2 and 3
5. (amyloid angiopath$ or congophil$ angiopath$ or cerebral amyloid$ or cerebral congo?red or cerebral A?beta or cerebral beta?amyloid).tw.
6. 1 or 4 or 5
7. exp genetics/ or exp genotype/ or exp inheritance patterns/ or exp linkage genetics/ or exp genes/ or exp genome/ or apolipoproteins/ or exp apolipoproteins e/
8. (polymorphi$ or genotype$ or gene or genes or genetic$ or allele$ or mutat$ or apolipoprotein$ or apoprotein$ or APO?E$).tw.
9. Cerebral Amyloid Angiopathy/ge [Genetics]
10. 7 or 8
11. 6 and 10
12. 9 or 11
13. limit 12 to humans

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