Role of apolipoprotein E polymorphism as a prognostic marker in traumatic brain injury and neurodegenerative disease: a critical review

Tanmoy Kumar Maiti, MCh, Subhas Konar, MCh, Shyamal Bir, MD, PhD, Piyush Kalakoti, MD, Papireddy Bollam, MD, and Anil Nanda, MD, MPH

Department of Neurosurgery, LSU Health Shreveport, Louisiana

OBJECT The difference in course and outcome of several neurodegenerative conditions and traumatic injuries of the nervous system points toward a possible role of genetic and environmental factors as prognostic markers. Apolipoprotein E (Apo-E), a key player in lipid metabolism, is recognized as one of the most powerful genetic risk factors for dementia and other neurodegenerative diseases. In this article, the current understanding of *APOE* polymorphism in various neurological disorders is discussed.

METHODS The English literature was searched for various studies describing the role of *APOE* polymorphism as a prognostic marker in neurodegenerative diseases and traumatic brain injury. The wide ethnic distribution of *APOE* polymorphism was discussed, and the recent meta-analyses of role of *APOE* polymorphism in multiple diseases were analyzed and summarized in tabular form.

RESULTS Results from the review of literature revealed that the distribution of *APOE* is varied in different ethnic populations. *APOE* polymorphism plays a significant role in pathogenesis of neurodegeneration, particularly in Alzheimer's disease. *APOE* ϵ 4 is considered a marker for poor prognosis in various diseases, but *APOE* ϵ 2 rather than *APOE* ϵ 4 has been associated with cerebral amyloid angiopathy-related bleeding and sporadic Parkinson's disease. The role of *APOE* polymorphism in various neurological diseases has not been conclusively elucidated.

CONCLUSIONS Apo-E is a biomarker for various neurological and systemic diseases. Therefore, while analyzing the role of *APOE* polymorphism in neurological diseases, the interpretation should be done after adjusting all the confounding factors. A continuous quest to look for associations with various neurological diseases and wide knowledge of available literature are required to improve the understanding of the role of *APOE* polymorphism in these conditions and identify potential therapeutic targets.

<http://thejns.org/doi/abs/10.3171/2015.8.FOCUS15329>

KEY WORDS apolipoprotein E; Alzheimer's disease; traumatic brain injury; neurodegenerative disease

THE limited effectiveness of available interventions for neurodegenerative diseases has led researchers to focus on identifying genetic and modifiable predisposing factors that may be useful in prognosis as well as in developing possible therapeutic targets. Alteration of lipid metabolism has been implicated in various neurodegenerative diseases. Apolipoprotein E (Apo-E), a glycoprotein, plays a major role in the redistribution of cholesterol from cells during membrane synthesis, neuritic extension, growth, and repair.^{5,18,48,56,69} In various cell lines, Apo-E3 has been shown to increase growth and

branching of neurites, whereas Apo-E4 was found to have an opposite effect.^{5,48} These associations, however, are not consistent in several similar diseases, and their prevalence varies among different ethnic populations. Research over the last 3 decades has revealed the importance of variation in the promoter regions apart from the traditional polymorphisms of ϵ 2, ϵ 3, and ϵ 4. The evolving knowledge has paved the way for a novel therapeutic target. In this article, we discuss the current understanding of the role of *APOE* polymorphism as a prognostic marker in traumatic brain injury (TBI) and other neurodegenerative conditions.

ABBREVIATIONS A β = amyloid β protein; AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; APOE = apolipoprotein E; CAA = cerebral amyloid angiopathy; GOS = Glasgow Outcome Scale; ICH = intracerebral hemorrhage; PD = Parkinson's disease; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury.

SUBMITTED July 1, 2015. **ACCEPTED** August 4, 2015.

INCLUDE WHEN CITING DOI: 10.3171/2015.8.FOCUS15329.

Apolipoprotein E Structure and Its Biophysical Properties

Apolipoprotein E is a polymorphic 299–amino acid protein (molecular weight 34,200).³⁸ The 3 common isoforms, Apo-E2, Apo-E3, and Apo-E4, are encoded by 3 alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) of the same gene on chromosome 19. Therefore, 3 homozygous (*APOE* $\epsilon 2/\epsilon 2$, $\epsilon 3/\epsilon 3$, and $\epsilon 4/\epsilon 4$) and 3 heterozygous (*APOE* $\epsilon 3/\epsilon 2$, $\epsilon 4/\epsilon 3$, and $\epsilon 4/\epsilon 2$) genotypes can occur in humans. The *APOE* $\epsilon 3$ allele is the most common form (70%–80%), followed by *APOE* $\epsilon 4$ (10%–15%) and *APOE* $\epsilon 2$ (5%–10%).³⁸

Apo-E3 has cysteine at 112 and arginine at 158 positions, whereas Apo-E4 has arginine and Apo-E2 has cysteine at both positions. Although the existence of E5 (further divided into E5f and E5s based on fast and slow migration in SDS-PAGE) and E7 isoforms is known,⁸¹ their present roles are not well defined. The polymorphism affects 2 key properties of Apo-E: domain interaction and protein stability or molten globule (stable folded intermediate of unstable unfolded protein) formation. Apo-E2 is the most stable isoform, followed by Apo-E3 and Apo-E4,^{44,45} and the isoforms are prone to molten globule formation in the reverse order. The *APOE* genotype is an important determinant of plasma and CSF Apo-E and lipid levels. The *APOE* $\epsilon 2$ allele is associated with high concentrations of Apo-E, while the *APOE* $\epsilon 4$ allele is associated with lower Apo-E levels.⁶⁸ It is generally speculated that the enhanced instability of Apo-E4 leads to altered intradomain interactions, increased susceptibility to proteolysis, increased lipid and membrane binding, membrane disruption, and translocation across membranes. There are 2 structural domains in Apo-E: a 22-kD amino-terminal domain containing the low-density lipoprotein receptor binding region and a 10-kD carboxyl-terminal domain containing the major lipid-binding region.^{1,79} In Apo-E4, arginine-112 induces arginine-61 into a characteristic conformation, which may constitute a potential therapeutic target.³⁹

Ethnic Variation of *APOE* Polymorphism

The *APOE* ϵ alleles show a peculiar distribution throughout the world. The *APOE* $\epsilon 3$ allele is the most frequent in all human societies. Corbo and Scacchi¹⁰ found that *APOE* $\epsilon 3$ seems to be more prevalent in populations with a long-established agricultural economy, such as those of the Mediterranean basin, where the allele frequency is 0.849–0.898. On the other hand, *APOE* $\epsilon 4$ can be considered as an ancestral allele, with higher frequency in Pygmies (0.407), Khoi San (0.370), Papuans (0.368), and Native Americans (0.280). The frequency of the *APOE* $\epsilon 2$ allele fluctuates with no apparent pattern (0.145–0.02) and is absent in Native Americans and very uncommon (< 1%) in southern Europeans, according to population-based studies.^{10,64,68,71} Interestingly, the pooled data show that *APOE* $\epsilon 3$ is prevalent in European and Asian populations and *APOE* $\epsilon 4$ is markedly higher in Oceanians and Africans (Table 1).¹⁰

Role of *APOE* in Dementia

APOE in AD

The association of overrepresentation of *APOE* $\epsilon 4$ and

TABLE 1. Ethnic distribution of *APOE* polymorphism*

Ethnicity	N	<i>APOE</i> Allele		
		$\epsilon 2$	$\epsilon 3$	$\epsilon 4$
African	1618	0.072	0.685	0.240
European	24,262	0.068	0.813	0.119
Asian	2938	0.075	0.816	0.109
Native American	1045	0.008	0.796	0.195
Oceanian	285	0.099	0.599	0.302

* Based on Corbo and Scacchi.¹⁰

underrepresentation of *APOE* $\epsilon 2$ with sporadic and familial early- and late-onset Alzheimer's disease (AD) has been widely discussed. However, ethnic variation exists with respect to the magnitude of association. In Caucasians, the frequency of the $\epsilon 4$ allele has been found to be increased from approximately 14% in controls to around 40% in the AD population in both the sporadic and familial forms of the disease.^{40,54} The risk increased from 20% when no *APOE* $\epsilon 4$ alleles were present to 90% when 2 copies of the *APOE* $\epsilon 4$ allele were present in another study.¹² The *APOE* $\epsilon 4$ allele was shown to exert the worst effect on AD between the ages of 60 and 79 years.¹⁷ It was associated with more rapid memory decline in individuals without dementia¹³ and preclinical memory impairment in asymptomatic middle-aged individuals.⁸ *APOE* $\epsilon 4$ also carried an increased risk for AD following trauma²³ resulting from increased accumulation of A β .⁸³ Similar findings were noted in boxers, where those possessing an *APOE* $\epsilon 4$ allele had more severe cognitive deficits than those with no *APOE* $\epsilon 4$ alleles.³⁰ The presence of herpes simplex virus type 1 in combination with an *APOE* $\epsilon 4$ allele was found to be a strong risk factor for AD.²⁸ Long-term survivors of human immunodeficiency virus (HIV) infection with the *APOE* $\epsilon 4$ allele were found to be at higher risk for AD, and gene-virus interactions were postulated to speed AD development.¹¹ On the other hand, *APOE* $\epsilon 2$ alleles were associated with a delayed age of onset of AD,^{57,78} even in carriers of *APP* mutations.⁶⁹ These findings suggest that a protective role is conferred by *APOE* $\epsilon 2$.

The pathological association seems multifactorial. The association of *APOE* with amyloid plaque density is more conclusively established⁵² than the association with density of neurofibrillary tangles,⁶² although many other reports have raised questions regarding these observations.^{6,43} It is hypothesized that the *APOE* $\epsilon 4$ allele enhances the progression of cerebral amyloid angiopathy (CAA), possibly via diminished clearance of amyloid β (A β),⁸² which may be an important pathophysiological mechanism in development of AD. *APOE* $\epsilon 4$ had a dose-dependent relationship with CSF levels of A $\beta 42$, but not tau (A $\beta 42$ and tau are the 2 most important CSF biomarkers of AD with a decrease in former and increase in later is seen in AD).¹⁹ The presence of *APOE* $\epsilon 4$ was seen associated with dose-dependent greater risk of hippocampal volume loss and a greater rate of atrophy even before the clinical presentation. The marked reduction in temporal cortical and hippocampal choline acetyltransferase activity³ and reduction of acetylcholinesterase-positive cell density in the nucleus basalis of Meynert and the diagonal band of Broca⁵³ in

patients with *APOE* $\epsilon 4$ may also predispose them to the development of AD. The reduced antioxidant activity and impaired neuronal metabolism in individuals with the *APOE* $\epsilon 4$ allele may subject them to added risk. In a recent meta-analysis of 14 studies published from 1996 to 2014 seeking the association of *APOE* $\epsilon 4$ with a neuroimaging marker of AD, the authors concluded that *APOE* $\epsilon 4$ was associated with atrophic hippocampal volume ($p = 0.007$) and increased cerebral amyloid deposition ($p = 0.0006$) and decreased cerebral metabolism, especially in the right middle frontal gyrus³⁶ (Table 2).

Nevertheless, polymorphism at the 112 and 158 positions does not seem to be the only explanation of the variable response. Researchers have found polymorphisms in the promoter region of *APOE* leading to variable expression of Apo-E, therefore modulating the risk of developing AD; the -491 A/T promoter polymorphism has been studied more extensively than the -219 T/G (Th1/E47cs), $+113$ G/C, and -427 T/C polymorphisms.³⁴

APOE in Non-AD Dementias

The association of *APOE* polymorphism and other dementias is less well studied, and the results are more variable. Hardy et al.²⁵ noticed a strong association between the *APOE* $\epsilon 4$ allele and AD and no association between the *APOE* $\epsilon 4$ allele and Parkinson's disease (PD). Senile

Lewy body dementia was associated with a frequency of the $\epsilon 4$ allele that was intermediate between that of AD and that of PD. Egensperger et al.¹⁵ did not find the *APOE* $\epsilon 4$ allele to be a risk factor that influences the development of AD lesions in patients with PD. However, the relationship seems to be stronger in AD and other dementias developing after TBI. Tang et al. observed a 10-fold increase in the risk of AD among patients who were *APOE* $\epsilon 4$ carriers and had a history of TBI.⁷² Luukinen et al. found that fall-related TBI predicted earlier onset of dementia in *APOE* $\epsilon 4$ carriers.³⁷ The frequency of the *APOE* $\epsilon 4$ allele has been found to be increased in vascular dementia as well.⁵¹ Interestingly, the *APOE* $\epsilon 2/\epsilon 3$ genotype has been associated with a significantly earlier age of onset of Huntington's disease,³¹ and *APOE* $\epsilon 2/\epsilon 2$ has been associated with frontotemporal dementia, whereas *APOE* $\epsilon 4$ was not found to have any such association.⁷⁵

APOE and Head Injury

The possible role of *APOE* polymorphism in predicting the outcome after TBI has drawn significant attention among researchers in last 2 decades. However, results varied here as well. Presence of the *APOE* $\epsilon 4$ allele has been suggested in various clinical studies to have a negative effect on outcome following closed head injury,¹⁸ but one of the largest studies (by Teasdale et al.,⁷³ involving 1094 patients) revealed that 36% of *APOE* $\epsilon 4$ carriers had

TABLE 2. Summary of available meta-analyses on role of *APOE* polymorphism in various diseases

Authors & Year	Disease	Population	Comment
Xin et al., 2010	AD	40 studies (pts: 9662; controls: 9696)	-491 A/T polymorphism (AA vs AT + TT: OR 1.49) & -219 T/G polymorphism (TT vs TG + GG: OR 1.30) showed significant association w/ AD susceptibility.
Sadigh-Eteghad et al., 2012	AD	21 studies (pts: 1480; controls: 6777)	<i>APOE</i> $\epsilon 4$ allele increases risk of sporadic late-onset AD ($p < 0.001$, OR 3.98).
Liu et al., 2015	AD	14 cross-sectional studies (n = 1628) comparing w/ neuroimaging marker of AD	<i>APOE</i> $\epsilon 4$ carrier status was associated w/ atrophic hippocampal volume ($p = 0.007$) & increased cerebral amyloid PET tracer ($p = 0.0006$).
Verpillat et al., 2002	FTD	10 cross-sectional studies (pts: 364; controls: 2671)	Significant increase of $\epsilon 2$ allele frequency in pts (OR [$\epsilon 2$ vs $\epsilon 3$] 2.01, $p = 0.04$). No correlation w/ <i>APOE</i> $\epsilon 4$.
Zhou et al., 2008	TBI	14 studies (n = 2527)	<i>APOE</i> $\epsilon 4$ allele is not associated w/ initial severity of brain injury following TBI but is associated w/ increased risk of poor long-term outcome at 6 mos after injury (RR 1.36).
Zeng et al., 2014	TBI	13 cohort studies (TBI w/ <i>APOE</i> $\epsilon 4$: 662; TBI w/o <i>APOE</i> $\epsilon 4$: 1614)	TBI pts w/ <i>APOE</i> $\epsilon 4$ had a worse prognosis in Asian populations ($p = 0.046$) but not in Caucasian populations ($p = 0.120$) & in severe TBI ($p = 0.020$) but not in other grades of TBI (all $p > 0.05$).
Sudlow et al., 2006	IS, ICH, SAH	IS: 26; ICH: 8; SAH: 3	<i>APOE</i> $\epsilon 4$ significantly associated w/ IS (OR 1.11, $p = 0.03$) & SAH (OR 1.42) but not w/ ICH. <i>APOE</i> $\epsilon 2$ was associated w/ ICH (OR 1.32, $p = 0.04$).
Schilling et al., 2013	CVD	42 studies (n = 29,965) <i>APOE</i> genotype & MRI markers of CVD	<i>APOE</i> $\epsilon 4$ was associated w/ increasing white matter hyperintensity burden & presence of cerebral microbleeds. <i>APOE</i> $\epsilon 2$ was associated w/ increasing white matter hyperintensity load & risk of brain infarct.
Zhang et al., 2014	ICH	11 case-control studies (6 in Asian population; 5 in Caucasian) (cases: 1238; controls: 3575)	ICH cases had a significantly higher frequency of <i>APOE</i> $\epsilon 4$ allele (OR 1.42, $p < 0.001$) (OR 1.52 for Asians, 1.34 for Caucasians); <i>APOE</i> $\epsilon 2$ not different from <i>APOE</i> $\epsilon 3$.
Govone et al., 2014		Cases: 4249; controls: 10,397	<i>APOE</i> $\epsilon 4$ allele was not associated w/ significantly increased disease risk.
Schürhoff et al., 2003		14 studies (cases: 1949; controls: 2354)	<i>APOE</i> polymorphism did not have any association w/ incidence of schizophrenia.

CVD = cerebrovascular disease; FTD = frontotemporal dementia; IS = ischemic stroke; pts = patients.

an unfavorable outcome at 6 months' follow-up compared with 33% of patients who did not carry this allele ($p = 0.23$). However, children and young adults under 15 years of age with the $\epsilon 4$ allele had less favorable outcomes.⁷³ Worse outcome in children has been observed by other researchers as well.⁷ The poorer cognitive outcome after TBI has been established in several studies in neuropsychological testing. Nevertheless, several groups of authors have expressed doubt about the correlation.^{42,49,56} In a detailed neuropsychological assessment of 90 adult patients with mild and moderate TBI at 6-month follow-up, investigators found no effect of *APOE* $\epsilon 4$ allele poor outcome.⁹ Some studies have even revealed that $\epsilon 4$ carriers performed better on measures of attention, executive functioning, and episodic memory encoding than do noncarriers.²⁴ No significant associations were found between *APOE* $\epsilon 4$ status and the Sickness Impact Profile-68 (SIP-68) and Community Integration Questionnaire (CIQ) results. Diaz-Arrastia et al. found that *APOE* $\epsilon 4$ was not associated with an unfavorable outcome (as indicated by GOS-E [Extended Glasgow Outcome Scale] scores), although they did find an association between *APOE* $\epsilon 4$ and late-onset posttraumatic seizure.¹⁴

In a meta-analysis of 14 eligible cohort studies between January 1993 and October 2007 including a total of 2527 participants (736 with and 1791 without the *APOE* $\epsilon 4$ allele) suggested that although the *APOE* $\epsilon 4$ allele does not influence the initial severity of TBI, it increases the risk of poor long-term outcome after TBI as measured by the Glasgow Outcome Scale (GOS) or GOS-E score at 6 months after injury.⁸⁷ The latest meta-analysis by Zeng et al.⁸⁴ in 2014, comprising 13 cohort studies (662 TBI patients with and 1614 TBI patients without *APOE* $\epsilon 4$), concluded that the *APOE* $\epsilon 4$ allele was associated with a poor prognosis in TBI patients (OR 0.68, $p = 0.027$). Subgroup analysis by ethnicity indicated that TBI patients with *APOE* $\epsilon 4$ had a worse prognosis than those with *APOE* $\epsilon 4$ in Asian populations (OR 0.46, $p = 0.046$), but not in Caucasian populations (OR 0.75, $p = 0.120$). A further subgroup analysis by TBI grade showed that the *APOE* $\epsilon 4$ allele was associated with poor prognosis in severe TBI (OR 0.43, $p = 0.020$), but not for other grades (Table 2).

APOE in Multiple Sclerosis

Though studies from Italy⁶⁰ and Japan⁵⁰ did not show any association between *APOE* $\epsilon 4$ and progression of multiple sclerosis, a study from Austria (Enzinger et al.¹⁶) demonstrated a negative influence of *APOE* $\epsilon 4$ on brain volume, contributing to increasing brain atrophy in multiple sclerosis.

APOE and Neuromuscular Disease

The association of *APOE* polymorphism with peripheral nervous system diseases has been discussed in literature as well. However, the association, though significant, seems to be weaker than for CNS disease.⁴

Diabetic Neuropathy

In a study of 158 non-insulin-dependent diabetes patients from Japan, the prevalence of neuropathy was found

to be greater in patients with *APOE* $\epsilon 4$ (39%) than in patients with *APOE* $\epsilon 3$ (28%) or *APOE* $\epsilon 2$ (23%). Patients with *APOE* $\epsilon 4$ were also found to have an earlier onset of neuropathy as well as greater severity than patients without that allele.⁷⁴

Human Immunodeficiency Virus-Related Neuropathy

Although patients with the *APOE* $\epsilon 4$ allele were found to have more severe neuropathy after HIV, the association has not been thoroughly explored in the literature.¹¹

Amyotrophic Lateral Sclerosis

Despite multiple studies, the role of *APOE* in the prognosis of amyotrophic lateral sclerosis (ALS) remains controversial. In one of the initial reports, Mui et al.⁴⁷ suggested that age of onset and the duration of ALS did not correlate with *APOE* polymorphism status; however, that study's criteria for defining were later criticized.⁴ Al-Chalabi et al. noted that median survival was 35 months in patients with *APOE* $\epsilon 4$ and 49 months in patients without *APOE* $\epsilon 4$, but the difference was not statistically significant.² Moulard et al. found that although the allele frequency did not differ significantly between patients with ALS and controls, patients with the *APOE* $\epsilon 2/\epsilon 3$ genotype showed a significantly longer duration of the disease—median duration 51 months versus 28.5 for *APOE* $\epsilon 3/\epsilon 3$ and 27.5 for *APOE* $\epsilon 3/\epsilon 4$ ($p = 0.001$ and $p = 0.02$, respectively). In the bulbar group, patients with the *APOE* $\epsilon 4$ allele showed earlier onset of the disease.⁴⁶ Similarly, Praline et al.⁵⁵ found that the *APOE* $\epsilon 4$ allele was associated with an increased risk of bulbar-onset ALS in men. Nevertheless Siddique et al.⁶⁷ and Zetterberg et al.⁸⁵ found no significant relationship between *APOE* allele status and age of onset. In contrast, a study by Li et al.³⁵ provided support for a protective role of *APOE* $\epsilon 2$. This controversy is reflected in the recent meta-analysis by Govone et al.,²¹ in which the $\epsilon 4$ allele was not associated with a significantly increased disease risk of ALS.

Guamanian ALS/Parkinsonism-Dementia Complex

The available literature on the association of *APOE* with Guamanian ALS/parkinsonism-dementia complex is limited by a small sample size. Waring et al. did not find any difference in the distribution of *APOE* $\epsilon 4$ among patients and controls,⁷⁶ but they found that *APOE* $\epsilon 2$ had a protective role. Nevertheless, a recent study did not find any association.²⁰

Stroke

Cerebral Amyloid Angiopathy

Sporadic cerebral amyloid angiopathy (CAA) is characterized by the deposition of $A\beta$ protein in small to medium-sized leptomeningeal and cortical blood vessels.⁴¹ A minority of patients may develop single or multiple CAA-related hemorrhages. *APOE* $\epsilon 4$ allele was found to increase $A\beta$ deposition in the cerebral vasculature, whereas *APOE* $\epsilon 2$ was associated with rupture of $A\beta$ -laden blood vessels and resulting hemorrhage.⁴¹ Greenberg et al. found that the age at first CAA hemorrhage was earlier in patients with *APOE* $\epsilon 2$.²²

Ischemic Stroke, Intracerebral Hemorrhage, and Subarachnoid Hemorrhage

As with most of the other diseases, investigation of an association between *APOE* and ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage has produced varying results. In a study of stroke in a Japanese rural population, Kokubo et al.³² found that, compared with individuals with the *APOE* $\epsilon 3/\epsilon 3$ genotype, $\epsilon 2$ carriers had a 2-fold risk of cerebral infarction. The risk is greater for cortical infarction, but not for lacunar infarction. These individuals were also at risk for atherothrombosis and cardioembolism. Those with the *APOE* $\epsilon 2/\epsilon 2$ genotype had an increased risk of intracerebral hemorrhage (ICH) as well. *APOE* $\epsilon 4$ carriers had a 2.5-fold increased risk of subarachnoid hemorrhage (SAH). Individuals with the *APOE* $\epsilon 3/\epsilon 4$ genotype showed a 2-fold increased risk of atherothrombosis and ICH. The association between $\epsilon 2$ and stroke was accentuated in patients aged 70 years or older, but not in those aged 40–69 years. In a meta-analysis of 26 studies of ischemic stroke, 3 studies of SAH, and 8 studies of ICH, patients with the *APOE* $\epsilon 4$ allele were significantly more susceptible to ischemic stroke (OR 1.11) and SAH (OR 1.42) but not to ICH. Rather, *APOE* $\epsilon 2$ was found to be associated with ICH (OR 1.32) (more strongly for lobar than for deeper hemorrhages). However the strength of association was poor. The association appeared stronger for Asian populations compared with white populations.⁷⁰ However, a recent meta-analysis of 11 case-control studies with 1238 ICH cases and 3575 controls concluded that ICH patients had a significantly higher frequency of the *APOE* $\epsilon 4$ allele (OR 1.42, $p < 0.001$), but there was no significant association between ICH and the *APOE* $\epsilon 2$ allele. In the subgroup analysis by race, patients with ICH had a significantly higher frequency of the *APOE* $\epsilon 4$ allele in Asian ($p < 0.001$) as well as Caucasian ($p = 0.009$) groups. There was no significant relationship between the *APOE* $\epsilon 2$ allele and the risk of ICH.⁸⁶ The presence of *APOE* $\epsilon 4$ was found to increase the risk of delayed ischemic neurological deficit in one study.³³

Other Cranial Diseases

An association has been sought in several other diseases as well. In a small sample of patients with inclusion body myositis, *APOE* $\epsilon 4$ was found to be overrepresented and *APOE* $\epsilon 2$ was found to be underrepresented in comparison with frequencies in controls.²⁶ No association was found in patients with familial amyloidotic polyneuropathy.⁵⁹ A meta-analysis of 22 studies of sporadic PD suggested an association with *APOE* $\epsilon 2$ rather than *APOE* $\epsilon 4$ (OR 1.2 and 0.99, respectively).²⁷ The *APOE* $\epsilon 4$ allele (OR 1.41) was associated with an increased risk of Creutzfeldt-Jakob disease (CJD), and *APOE* $\epsilon 3$ (OR 0.81) tended to be protective against CJD in another meta-analysis of 11 case-control studies.⁷⁷ A meta-analysis of *APOE* in schizophrenia did not support a major role for the *APOE* gene in that disease as a whole, but male patients with *APOE* $\epsilon 2$ were found to have an increased risk of schizophrenia (although the increase was not statistically significant).⁶³

Spinal Cord Injury and Degeneration

Surprisingly, there have been fewer studies of *APOE*

polymorphism in spinal cord injury and degenerative conditions of the cord than in cranial disease, although the injury mechanism remains same. In patients with cervical cord injuries, the *APOE* $\epsilon 4$ allele was associated with differences in neurological recovery and longer length of stay in a rehabilitation facility.²⁹ Setzer et al. found that *APOE* $\epsilon 4$ was more prevalent in patients with cervical myelopathy than in controls.⁶⁵ In an extension of this study they found that the presence of *APOE* $\epsilon 4$ was an independent predictor of poor outcome after anterior decompression surgery in these patients.⁶⁶

Comments

Since the initial reports of the association of *APOE* with various neurological diseases, much enthusiasm has been noted among the researchers in last 3 decades. Although the initial reports almost universally suggested that *APOE* $\epsilon 4$ was associated with poorer outcome, subsequent studies have proven that the association is not straightforward. *APOE* $\epsilon 2$, which may be protective for AD, is found to be associated with increased risk for other diseases like amyloid angiopathy-related hemorrhage and sporadic PD. The literature shows plenty of reports in which *APOE* polymorphism did not have any correlation with pathogenesis and outcome, despite the fact that negative reports are generally less published. Though there is tantalizing evidence of an association with *APOE* polymorphism in AD studies and in most of the studies of TBI, similar conclusions cannot be drawn for other diseases. Also, the extent of association with specific diseases varied from study to study. This discrepancy is hard to understand, especially when there are similarities between the cellular pathologies of the various diseases. One possible explanation for this ambiguity may be small sample sizes and lack of proper control groups. The ethnic variation of different populations in the world may also explain some findings. The results show some variation according to age and gender as well. As *APOE* has been found to affect many nonneurological diseases like hypertension, coronary artery disease, and diabetes mellitus, nonadjustment for these comorbidities led to methodological flaws in much of the available literature. Again, the role of genetic and epigenetic factors affecting *APOE* expression (as, for example, in the above-mentioned studies of promoter regions of *APOE* for AD) has not been studied extensively for diseases other than AD. Finally, a continuous search for other genetic markers and knowledge of interaction between genetic markers may give new insight into our understanding of the pathogenesis of these diseases.

Conclusions

In summary, the understanding of the role of *APOE* may be still preliminary for diseases other than AD. Further studies should involve larger sample sizes, rigid and objective definitions of the diseases being studied, and proper at-risk and disease-free control groups to minimize methodological flaws. An ongoing search for other genes involved in the variability of *APOE* expression and study of the newer genes in relation to established factors and periodic meta-analyses in various diseases are needed to solidify this relationship.⁴

References

- Aggerbeck LP, Wetterau JR, Weisgraber KH, Wu CS, Lindgren FT: Human apolipoprotein E3 in aqueous solution. II. Properties of the amino- and carboxyl-terminal domains. **J Biol Chem** **263**:6249–6258, 1988
- Al-Chalabi A, Enayat ZE, Bakker MC, Sham PC, Ball DM, Shaw CE, et al: Association of apolipoprotein E epsilon 4 allele with bulbar-onset motor neuron disease. **Lancet** **347**:159–160, 1996
- Arendt T, Schindler C, Brückner MK, Eschrich K, Bigl V, Zedlick D, et al: Plastic neuronal remodeling is impaired in patients with Alzheimer's disease carrying apolipoprotein epsilon 4 allele. **J Neurosci** **17**:516–529, 1997
- Bedlack RS, Strittmatter WJ, Morgenlander JC: Apolipoprotein E and neuromuscular disease: a critical review of the literature. **Arch Neurol** **57**:1561–1565, 2000
- Bellosta S, Nathan BP, Orth M, Dong LM, Mahley RW, Pitas RE: Stable expression and secretion of apolipoproteins E3 and E4 in mouse neuroblastoma cells produces differential effects on neurite outgrowth. **J Biol Chem** **270**:27063–27071, 1995
- Brat DJ, Gearing M, Goldthwaite PT, Wainer BH, Burger PC: Tau-associated neuropathology in ganglion cell tumours increases with patient age but appears unrelated to ApoE genotype. **Neuropathol Appl Neurobiol** **27**:197–205, 2001
- Brichtová E, Kozák L: Apolipoprotein E genotype and traumatic brain injury in children—association with neurological outcome. **Childs Nerv Syst** **24**:349–356, 2008
- Caselli RJ, Osborne D, Reiman EM, Hentz JG, Barbieri CJ, Saunders AM, et al: Preclinical cognitive decline in late middle-aged asymptomatic apolipoprotein E-epsilon 4 homozygotes: a replication study. **J Neurol Sci** **189**:93–98, 2001
- Chamelian L, Reis M, Feinstein A: Six-month recovery from mild to moderate traumatic brain injury: the role of APOE-epsilon 4 allele. **Brain** **127**:2621–2628, 2004
- Corbo RM, Scacchi R: Apolipoprotein E (APOE) allele distribution in the world. Is APOE*4 a 'thrifty' allele? **Ann Hum Genet** **63**:301–310, 1999
- Corder EH, Robertson K, Lannfelt L, Bogdanovic N, Eggersten G, Wilkins J, et al: HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. **Nat Med** **4**:1182–1184, 1998
- Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al: Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. **Science** **261**:921–923, 1993
- Deary IJ, Whiteman MC, Pattie A, Starr JM, Hayward C, Wright AF, et al: Cognitive change and the APOE epsilon 4 allele. **Nature** **418**:932, 2002
- Diaz-Arrastia R, Gong Y, Fair S, Scott KD, Garcia MC, Carlile MC, et al: Increased risk of late posttraumatic seizures associated with inheritance of APOE epsilon 4 allele. **Arch Neurol** **60**:818–822, 2003
- Egensperger R, Bancher C, Kösel S, Jellinger K, Mehraein P, Graeber MB: The apolipoprotein E epsilon 4 allele in Parkinson's disease with Alzheimer lesions. **Biochem Biophys Res Commun** **224**:484–486, 1996
- Enzinger C, Ropele S, Smith S, Strasser-Fuchs S, Poltrum B, Schmidt H, et al: Accelerated evolution of brain atrophy and "black holes" in MS patients with APOE-epsilon 4. **Ann Neurol** **55**:563–569, 2004
- Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al: Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. **JAMA** **278**:1349–1356, 1997
- Friedman G, Froom P, Sazbon L, Grinblatt I, Shochina M, Tsentur J, et al: Apolipoprotein E-epsilon 4 genotype predicts a poor outcome in survivors of traumatic brain injury. **Neurology** **52**:244–248, 1999
- Galasko D, Chang L, Motter R, Clark CM, Kaye J, Knopman D, et al: High cerebrospinal fluid tau and low amyloid beta 42 levels in the clinical diagnosis of Alzheimer disease and relation to apolipoprotein E genotype. **Arch Neurol** **55**:937–945, 1998
- Galasko D, Salmon D, Gamst A, Olichney J, Thal LJ, Silbert L, et al: Prevalence of dementia in Chamorro on Guam: relationship to age, gender, education, and APOE. **Neurology** **68**:1772–1781, 2007
- Govone F, Vacca A, Rubino E, Gai A, Boschi S, Gentile S, et al: Lack of association between APOE gene polymorphisms and amyotrophic lateral sclerosis: a comprehensive meta-analysis. **Amyotroph Lateral Scler Frontotemporal Degener** **15**:551–556, 2014
- Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, et al: Association of apolipoprotein E epsilon 2 and vasculopathy in cerebral amyloid angiopathy. **Neurology** **50**:961–965, 1998
- Guo Z, Cupples LA, Kurz A, Auerbach SH, Volicer L, Chui H, et al: Head injury and the risk of AD in the MIRAGE study. **Neurology** **54**:1316–1323, 2000
- Han SD, Drake AI, Cessante LM, Jak AJ, Houston WS, Delis DC, et al: Apolipoprotein E and traumatic brain injury in a military population: evidence of a neuropsychological compensatory mechanism? **J Neurol Neurosurg Psychiatry** **78**:1103–1108, 2007
- Hardy J, Crook R, Prihar G, Roberts G, Raghavan R, Perry R: Senile dementia of the Lewy body type has an apolipoprotein E epsilon 4 allele frequency intermediate between controls and Alzheimer's disease. **Neurosci Lett** **182**:1–2, 1994
- Harrington CR, Anderson JR, Chan KK: Apolipoprotein E type epsilon 4 allele frequency is not increased in patients with sporadic inclusion-body myositis. **Neurosci Lett** **183**:35–38, 1995
- Huang X, Chen PC, Poole C: APOE-epsilon 2 allele associated with higher prevalence of sporadic Parkinson disease. **Neurology** **62**:2198–2202, 2004
- Itzhaki RF, Dobson CB, Shipley SJ, Wozniak MA: The role of viruses and of APOE in dementia. **Ann N Y Acad Sci** **1019**:15–18, 2004
- Jha A, Lammertse DP, Coll JR, Charlifue S, Coughlin CT, Whiteneck GG, et al: Apolipoprotein E epsilon 4 allele and outcomes of traumatic spinal cord injury. **J Spinal Cord Med** **31**:171–176, 2008
- Jordan BD, Relkin NR, Ravdin LD, Jacobs AR, Bennett A, Gandy S: Apolipoprotein E epsilon 4 associated with chronic traumatic brain injury in boxing. **JAMA** **278**:136–140, 1997
- Kehoe P, Krawczak M, Harper PS, Owen MJ, Jones AL: Age of onset in Huntington disease: sex specific influence of apolipoprotein E genotype and normal CAG repeat length. **J Med Genet** **36**:108–111, 1999
- Kokubo Y, Chowdhury AH, Date C, Yokoyama T, Sobue H, Tanaka H: Age-dependent association of apolipoprotein E genotypes with stroke subtypes in a Japanese rural population. **Stroke** **31**:1299–1306, 2000
- Lantern LA, Rigoldi M, Tredici G, Biroli F, Cesana C, Gaini SM, et al: APOE influences vasospasm and cognition of non-comatose patients with subarachnoid hemorrhage. **Neurology** **64**:1238–1244, 2005
- Laws SM, Hone E, Gandy S, Martins RN: Expanding the association between the APOE gene and the risk of Alzheimer's disease: possible roles for APOE promoter polymorphisms and alterations in APOE transcription. **J Neurochem** **84**:1215–1236, 2003
- Li YJ, Pericak-Vance MA, Haines JL, Siddique N, McKenna-Yasek D, Hung WY, et al: Apolipoprotein E is associated with age at onset of amyotrophic lateral sclerosis. **Neurogenetics** **5**:209–213, 2004
- Liu Y, Yu JT, Wang HF, Han PR, Tan CC, Wang C, et al:

- APOE genotype and neuroimaging markers of Alzheimer's disease: systematic review and meta-analysis. **J Neurol Neurosurg Psychiatry** 86:127–134, 2015
37. Luukinen H, Viramo P, Herala M, Kervinen K, Kesäniemi YA, Savola O, et al: Fall-related brain injuries and the risk of dementia in elderly people: a population-based study. **Eur J Neurol** 12:86–92, 2005
38. Mahley RW: Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. **Science** 240:622–630, 1988
39. Mahley RW, Huang Y: Apolipoprotein (apo) E4 and Alzheimer's disease: unique conformational and biophysical properties of apoE4 can modulate neuropathology. **Acta Neurol Scand Suppl** 185:8–14, 2006
40. Martins RN, Clarnette R, Fisher C, Broe GA, Brooks WS, Montgomery P, et al: ApoE genotypes in Australia: roles in early and late onset Alzheimer's disease and Down's syndrome. **Neuroreport** 6:1513–1516, 1995
41. McCarron MO, Nicoll JA, Ironside JW, Love S, Alberts MJ, Bone I: Cerebral amyloid angiopathy-related hemorrhage. Interaction of APOE ε2 with putative clinical risk factors. **Stroke** 30:1643–1646, 1999
42. Mehta KM, Ott A, Kalmijn S, Slooter AJ, van Duijn CM, Hofman A, et al: Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. **Neurology** 53:1959–1962, 1999
43. Morris CM, Massey HM, Benjamin R, Leake A, Broadbent C, Griffiths M, et al: Molecular biology of APO E alleles in Alzheimer's and non-Alzheimer's dementias. **J Neural Transm Suppl** 47:205–218, 1996
44. Morrow JA, Hatters DM, Lu B, Hochtl P, Oberg KA, Rupp B, et al: Apolipoprotein E4 forms a molten globule. A potential basis for its association with disease. **J Biol Chem** 277:50380–50385, 2002
45. Morrow JA, Segall ML, Lund-Katz S, Phillips MC, Knapp M, Rupp B, et al: Differences in stability among the human apolipoprotein E isoforms determined by the amino-terminal domain. **Biochemistry** 39:11657–11666, 2000
46. Moulard B, Sefiani A, Laamri A, Malafosse A, Camu W: Apolipoprotein E genotyping in sporadic amyotrophic lateral sclerosis: evidence for a major influence on the clinical presentation and prognosis. **J Neurol Sci** 139 Suppl:34–37, 1996
47. Mui S, Rebeck GW, McKenna-Yasek D, Hyman BT, Brown RH Jr: Apolipoprotein E ε4 allele is not associated with earlier age at onset in amyotrophic lateral sclerosis. **Ann Neurol** 38:460–463, 1995
48. Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas RE: Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. **Science** 264:850–852, 1994
49. Nathoo N, Chetry R, van Dellen JR, Connolly C, Naidoo R: Apolipoprotein E polymorphism and outcome after closed traumatic brain injury: influence of ethnic and regional differences. **J Neurosurg** 98:302–306, 2003
50. Niino M, Kikuchi S, Fukazawa T, Yabe I, Tashiro K: Polymorphisms of apolipoprotein E and Japanese patients with multiple sclerosis. **Mult Scler** 9:382–386, 2003
51. Noguchi S, Murakami K, Yamada N: Apolipoprotein E genotype and Alzheimer's disease. **Lancet** 342:737, 1993
52. Olichney JM, Hansen LA, Galasko D, Saitoh T, Hofstetter CR, Katzman R, et al: The apolipoprotein E epsilon 4 allele is associated with increased neuritic plaques and cerebral amyloid angiopathy in Alzheimer's disease and Lewy body variant. **Neurology** 47:190–196, 1996
53. Poirier J: Apolipoprotein E: a pharmacogenetic target for the treatment of Alzheimer's disease. **Mol Diagn** 4:335–341, 1999
54. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S: Apolipoprotein E polymorphism and Alzheimer's disease. **Lancet** 342:697–699, 1993
55. Praline J, Blasco H, Vourc'h P, Garrigue MA, Gordon PH, Camu W, et al: APOE ε4 allele is associated with an increased risk of bulbar-onset amyotrophic lateral sclerosis in men. **Eur J Neurol** 18:1046–1052, 2011
56. Pruthi N, Chandramouli BA, Kuttappa TB, Rao SL, Subbakrishna DK, Abraham MP, et al: Apolipoprotein E polymorphism and outcome after mild to moderate traumatic brain injury: a study of patient population in India. **Neurol India** 58:264–269, 2010
57. Roses AD: Apolipoprotein E genotyping in the differential diagnosis, not prediction, of Alzheimer's disease. **Ann Neurol** 38:6–14, 1995
58. Sadigh-Eteghad S, Talebi M, Farhoudi M: Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer's disease. A meta-analysis. **Neurosciences (Riyadh)** 17:321–326, 2012
59. Saunders AM, Schmechel K, Breitner JC, Benson MD, Brown WT, Goldfarb L, et al: Apolipoprotein E ε4 allele distributions in late-onset Alzheimer's disease and in other amyloid-forming diseases. **Lancet** 342:710–711, 1993
60. Savettieri G, Andreoli V, Bonavita S, Cittadella R, Caltagirone C, Fazio MC, et al: Apolipoprotein E genotype does not influence the progression of multiple sclerosis. **J Neurol** 250:1094–1098, 2003
61. Schilling S, DeStefano AL, Sachdev PS, Choi SH, Mather KA, DeCarli CD, et al: APOE genotype and MRI markers of cerebrovascular disease: systematic review and meta-analysis. **Neurology** 81:292–300, 2013
62. Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, et al: Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. **Proc Natl Acad Sci U S A** 90:9649–9653, 1993
63. Schürhoff F, Krebs MO, Szöke A, Loze JY, Goldberger C, Quignon V, et al: Apolipoprotein E in schizophrenia: a French association study and meta-analysis. **Am J Med Genet B Neuropsychiatr Genet** 119B:18–23, 2003
64. Seet WT, Mary Anne TJ, Yen TS: Apolipoprotein E genotyping in the Malay, Chinese and Indian ethnic groups in Malaysia—a study on the distribution of the different apoE alleles and genotypes. **Clin Chim Acta** 340:201–205, 2004
65. Setzer M, Hermann E, Seifert V, Marquardt G: Apolipoprotein E gene polymorphism and the risk of cervical myelopathy in patients with chronic spinal cord compression. **Spine (Phila Pa 1976)** 33:497–502, 2008
66. Setzer M, Vrionis FD, Hermann EJ, Seifert V, Marquardt G: Effect of apolipoprotein E genotype on the outcome after anterior cervical decompression and fusion in patients with cervical spondylotic myelopathy. **J Neurosurg Spine** 11:659–666, 2009
67. Siddique T, Pericak-Vance MA, Caliendo J, Hong ST, Hung WY, Kaplan J, et al: Lack of association between apolipoprotein E genotype and sporadic amyotrophic lateral sclerosis. **Neurogenetics** 1:213–216, 1998
68. Siest G, Pillot T, Régis-Bailly A, Leininger-Muller B, Steinmetz J, Galteau MM, et al: Apolipoprotein E: an important gene and protein to follow in laboratory medicine. **Clin Chem** 41:1068–1086, 1995
69. Sorbi S, Nacmias B, Piacentini S, Repice A, Latorraca S, Forleo P, et al: ApoE as a prognostic factor for post-traumatic coma. **Nat Med** 1:852, 1995
70. Sudlow C, Martínez González NA, Kim J, Clark C: Does apolipoprotein E genotype influence the risk of ischemic stroke, intracerebral hemorrhage, or subarachnoid hemorrhage? Systematic review and meta-analyses of 31 studies among 5961 cases and 17,965 controls. **Stroke** 37:364–370, 2006
71. Takeda M, Martínez R, Kudo T, Tanaka T, Okochi M, Tagami S, et al: Apolipoprotein E and central nervous system

- disorders: reviews of clinical findings. **Psychiatry Clin Neurosci** **64**:592–607, 2010
72. Tang MX, Maestre G, Tsai WY, Liu XH, Feng L, Chung WY, et al: Effect of age, ethnicity, and head injury on the association between APOE genotypes and Alzheimer's disease. **Ann N Y Acad Sci** **802**:6–15, 1996
73. Teasdale GM, Murray GD, Nicoll JA: The association between APOE ϵ 4, age and outcome after head injury: a prospective cohort study. **Brain** **128**:2556–2561, 2005
74. Tsuzuki S, Murano T, Watanabe H, Itoh Y, Miyashita Y, Shirai K: [The examination of apoE phenotypes in diabetic patients with peripheral neuropathy.] **Rinsho Byori** **46**:829–833, 1998 (Jpn)
75. Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, et al: Apolipoprotein E gene in frontotemporal dementia: an association study and meta-analysis. **Eur J Hum Genet** **10**:399–405, 2002
76. Waring SC, O'Brien PC, Kurland LT, Thibodeau SN, Tsai MS, Petersen RC, et al: Apolipoprotein E allele in Chamorro with amyotrophic lateral sclerosis/parkinsonism-dementia complex. **Lancet** **343**:611, 1994
77. Wei Y, Tang Y, He W, Qu Z, Zeng J, Qin C: APOE gene polymorphisms and susceptibility to Creutzfeldt-Jakob disease. **J Clin Neurosci** **21**:390–394, 2014
78. West HL, Rebeck GW, Hyman BT: Frequency of the apolipoprotein E ϵ 2 allele is diminished in sporadic Alzheimer disease. **Neurosci Lett** **175**:46–48, 1994
79. Wetterau JR, Aggerbeck LP, Rall SC Jr, Weisgraber KH: Human apolipoprotein E3 in aqueous solution. I. Evidence for two structural domains. **J Biol Chem** **263**:6240–6248, 1988
80. Xin XY, Ding JQ, Chen SD: Apolipoprotein E promoter polymorphisms and risk of Alzheimer's disease: evidence from meta-analysis. **J Alzheimers Dis** **19**:1283–1294, 2010
81. Yamanouchi Y, Arinami T, Tsuchiya S, Miyazaki R, Takaki H, Takano T, et al: Apolipoprotein E5 and E7 in apparently healthy Japanese males: frequencies and relation to plasma lipid levels. **Jpn J Hum Genet** **39**:315–324, 1994
82. Yang DS, Small DH, Seydel U, Smith JD, Hallmayer J, Gandy SE, et al: Apolipoprotein E promotes the binding and uptake of beta-amyloid into Chinese hamster ovary cells in an isoform-specific manner. **Neuroscience** **90**:1217–1226, 1999
83. Yang DS, Smith JD, Zhou Z, Gandy SE, Martins RN: Characterization of the binding of amyloid-beta peptide to cell culture-derived native apolipoprotein E2, E3, and E4 isoforms and to isoforms from human plasma. **J Neurochem** **68**:721–725, 1997
84. Zeng S, Jiang JX, Xu MH, Xu LS, Shen GJ, Zhang AQ, et al: Prognostic value of apolipoprotein E ϵ 4 allele in patients with traumatic brain injury: a meta-analysis and meta-regression. **Genet Test Mol Biomarkers** **18**:202–210, 2014
85. Zetterberg H, Jacobsson J, Rosengren L, Blennow K, Andersen PM: Association of APOE with age at onset of sporadic amyotrophic lateral sclerosis. **J Neurol Sci** **273**:67–69, 2008
86. Zhang R, Wang X, Tang Z, Liu J, Yang S, Zhang Y, et al: Apolipoprotein E gene polymorphism and the risk of intracerebral hemorrhage: a meta-analysis of epidemiologic studies. **Lipids Health Dis** **13**:47, 2014
87. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA: Meta-analysis of APOE4 allele and outcome after traumatic brain injury. **J Neurotrauma** **25**:279–290, 2008

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Nanda, Maiti, Konar, Bir. Acquisition of data: Maiti, Konar, Bir. Analysis and interpretation of data: Maiti, Konar, Bir. Drafting the article: Maiti, Konar, Bir. Critically revising the article: Nanda, Maiti, Konar, Bir. Reviewed submitted version of manuscript: Maiti, Konar, Bir, Kalakoti, Bollam. Administrative/technical/material support: Nanda.

Correspondence

Anil Nanda, Department of Neurosurgery, LSU Health Shreveport, 1501 Kings Hwy., Shreveport, LA 71130-3932. email: ananda@lsuhsc.edu.