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

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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 ε4 is considered a marker for poor prognosis in various diseases, but APOE ε2 rather than APOE ε4 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.

KEYWORDS 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. 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. 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 ε2, ε3, and ε4. 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 Aβ = 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.


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Apolipoprotein E Structure and Its Biophysical Properties

Apolipoprotein E is a polymorphic 299–amino acid protein (molecular weight 34,200). The 3 common isoforms, Apo-E2, Apo-E3, and Apo-E4, are encoded by 3 alleles (ε2, ε3, ε4) of the same gene on chromosome 19. Therefore, 3 homozygous (APOE ε2/ε2, ε3/ε3, and ε4/ε4) and 3 heterozygous (APOE ε3/ε2, ε4/ε3, and ε4/ε2) genotypes can occur in humans. The APOE ε3 allele is the most common form (70%–80%), followed by APOE ε4 (10%–15%) and APOE ε2 (5%–10%).

Apo-E 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, 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, 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 ε2 allele is associated with high concentrations of Apo-E, while the APOE ε4 allele is associated with lower Apo-E levels. 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. In Apo-E4, arginine-112 induces arginine-61 into a characteristic conformation, which may constitute a potential therapeutic target.

Ethnic Variation of APOE Polymorphism

The APOE ε alleles show a peculiar distribution throughout the world. The APOE ε3 allele is the most frequent in all human societies. Corbo and Scacchi found that APOE ε3 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 ε4 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 ε2 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. Interestingly, the pooled data show that APOE ε3 is prevalent in European and Asian populations and APOE ε4 is markedly higher in Oceanians and Africans (Table 1).

Role of APOE in Dementia

APOE in AD

The association of overrepresentation of APOE ε4 and underrepresentation of APOE ε2 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 ε4 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. The risk increased from 20% when no APOE ε4 alleles were present to 90% when 2 copies of the APOE ε4 allele were present in another study. The APOE ε4 allele was shown to exert the worst effect on AD between the ages of 60 and 79 years. It was associated with more rapid memory decline in individuals without dementia and preclinical memory impairment in asymptomatic middle-aged individuals. APOE ε4 also carried an increased risk for AD following trauma resulting from increased accumulation of Aβ. Similar findings were noted in boxers, where those possessing an APOE ε4 allele had more severe cognitive deficits than those with no APOE ε4 alleles. The presence of herpes simplex virus type 1 in combination with an APOE ε4 allele was found to be a strong risk factor for AD. Long-term survivors of human immunodeficiency virus (HIV) infection with the APOE ε4 allele were found to be at higher risk for AD, and gene-virus interactions were postulated to speed AD development. On the other hand, APOE ε2 alleles were associated with a delayed age of onset of AD, even in carriers of APP mutations. These findings suggest that a protective role is conferred by APOE ε2.

The pathological association seems multifactorial. The association of APOE with amyloid plaque density is more conclusively established than the association with density of neurofibrillary tangles although many other reports have raised questions regarding these observations. It is hypothesized that the APOE ε4 allele enhances the progression of cerebral amyloid angiopathy (CAA), possibly via diminished clearance of amyloid β (Aβ), which may be an important pathophysiological mechanism in development of AD. APOE ε4 had a dose-dependent relationship with CSF levels of Aβ42, but not tau (Aβ42 and tau are the 2 most important CSF biomarkers of AD with a decrease in former and increase in later is seen in AD). The presence of APOE ε4 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 activity and reduction of acetylcholinesterase-positive cell density in the nucleus basalis of Meynert and the diagonal band of Broca in

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>N</th>
<th>ε2</th>
<th>ε3</th>
<th>ε4</th>
</tr>
</thead>
<tbody>
<tr>
<td>African</td>
<td>1618</td>
<td>0.072</td>
<td>0.685</td>
<td>0.240</td>
</tr>
<tr>
<td>European</td>
<td>24,262</td>
<td>0.068</td>
<td>0.813</td>
<td>0.119</td>
</tr>
<tr>
<td>Asian</td>
<td>2938</td>
<td>0.075</td>
<td>0.816</td>
<td>0.109</td>
</tr>
<tr>
<td>Native American</td>
<td>1045</td>
<td>0.008</td>
<td>0.796</td>
<td>0.195</td>
</tr>
<tr>
<td>Oceanian</td>
<td>285</td>
<td>0.099</td>
<td>0.599</td>
<td>0.302</td>
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</table>

* Based on Corbo and Scacchi.10
patients with APOE ε4 may also predispose them to the development of AD. The reduced antioxidant activity and impaired neuronal metabolism in individuals with the APOE ε4 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 ε4 with a neuroimaging marker of AD, the authors concluded that APOE ε4 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 gyrus. Nonetheless, polymorphism at the 112 and 158 positions does not seem to be the only explanation of the variation of Apo-E, therefore modulating the risk of developing AD. The reduced antioxidant activity and impaired neuronal metabolism in individuals with the APOE ε4 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 ε4 with a neuroimaging marker of AD, the authors concluded that APOE ε4 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 gyrus. Nevertheless, polymorphism at the 112 and 158 positions does not seem to be the only explanation of the variation of Apo-E, therefore modulating the risk of developing AD. The reduced antioxidant activity and impaired neuronal metabolism in individuals with the APOE ε4 allele may subject them to added risk.

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. noticed a strong association between the APOE ε4 allele and AD and no association between the APOE ε4 allele and Parkinson’s disease (PD). Senile Lewy body dementia was associated with a frequency of the ε4 allele that was intermediate between that of AD and that of PD. Egensperger et al. did not find the APOE ε4 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 ε4 carriers and had a history of TBI. Luukinen et al. found that fall-related TBI predicted earlier onset of dementia in APOE ε4 carriers. The frequency of the APOE ε4 allele has been found to be increased in vascular dementia as well. Interestingly, the APOE ε2/ε3 genotype has been associated with a significantly earlier age of onset of Huntington’s disease, and APOE ε2/ε2 has been associated with frontotemporal dementia, whereas APOE ε4 was not found to have any such association.

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 ε4 allele has been suggested in various clinical studies to have a negative effect on outcome following closed head injury, but one of the largest studies (by Teasdale et al., involving 1094 patients) revealed that 36% of APOE ε4 carriers 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). APOE ε4 carriers 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).

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

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Disease</th>
<th>Population</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xin et al., 2010</td>
<td>AD</td>
<td>40 studies (pts: 9662; controls: 9969)</td>
<td>−491A/T polymorphism (AA vs AT + TT: OR 1.49) &amp; −219T/G polymorphism (TT vs TG + GG: OR 1.30) showed significant association w/ AD susceptibility.</td>
</tr>
<tr>
<td>Sadigh-Eteghad et al., 2012</td>
<td>AD</td>
<td>21 studies (pts: 1480; controls: 6777)</td>
<td>APOE ε4 allele increases risk of sporadic late-onset AD (p &lt; 0.001, OR 3.98).</td>
</tr>
<tr>
<td>Liu et al., 2015</td>
<td>AD</td>
<td>14 cross-sectional studies (n = 1628) comparing w/ neuroimaging marker of AD</td>
<td>APOE ε4 carrier status was associated w/ atrophic hippocampal volume (p = 0.007) &amp; increased cerebral amyloid PET tracer (p = 0.0006).</td>
</tr>
<tr>
<td>Verpillat et al., 2002</td>
<td>FTD</td>
<td>10 cross-sectional studies (pts: 364; controls: 2671)</td>
<td>Significant increase of ε2 allele frequency in pts (OR [ε2 vs ε3] 2.01, p = 0.04). No correlation w/ APOE ε4.</td>
</tr>
<tr>
<td>Zhou et al., 2008</td>
<td>TBI</td>
<td>14 studies (n = 2527)</td>
<td>APOE ε4 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).</td>
</tr>
<tr>
<td>Zeng et al., 2014</td>
<td>TBI</td>
<td>13 cohort studies (TBI w/ APOE ε4: 662; TBI w/o APOE ε4: 1614)</td>
<td>TBI pts w/ APOE ε4 had a worse prognosis in Asian populations (p = 0.046) but not in Caucasian populations (p = 0.120) &amp; in severe TBI (p = 0.020) but not in other grades of TBI (all p &gt; 0.05).</td>
</tr>
<tr>
<td>Sudlow et al., 2006</td>
<td>IS, ICH, SAH</td>
<td>IS: 28; ICH: 8; SAH: 3</td>
<td>APOE ε4 significantly associated w/ IS (OR 1.11, p = 0.03) &amp; SAH (OR 1.42) but not w/ ICH. APOE ε2 was associated w/ ICH (OR 1.32, p = 0.04).</td>
</tr>
<tr>
<td>Schilling et al., 2013</td>
<td>CVD</td>
<td>42 studies (n = 29,965) APOE genotype &amp; MRI markers of CVD</td>
<td>APOE ε4 was associated w/ increasing white matter hyperintensity burden &amp; presence of cerebral microbleeds. APOE ε2 was associated w/ increasing white matter hyperintensity load &amp; risk of brain infarct.</td>
</tr>
<tr>
<td>Zhang et al., 2014</td>
<td>ICH</td>
<td>11 case-control studies (6 in Asian population; 5 in Caucasian) (cases: 1238; controls: 3575)</td>
<td>ICH cases had a significantly higher frequency of APOE ε4 allele (OR 1.42, p &lt; 0.001) (OR 1.52 for Asians, 1.34 for Caucasians); APOE ε2 not different from APOE ε3.</td>
</tr>
<tr>
<td>Govone et al., 2014</td>
<td>Cases: 4249; controls: 10,397</td>
<td>APOE ε4 allele was not associated w/ significantly increased disease risk.</td>
<td></td>
</tr>
<tr>
<td>Schürhoff et al., 2003</td>
<td>14 studies (cases: 1949; controls: 2354)</td>
<td>APOE polymorphism did not have any association w/ incidence of schizophrenia.</td>
<td></td>
</tr>
</tbody>
</table>

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 ε4 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 ε4 allele poor outcome.9 Some studies have even revealed that ε4 carriers performed better on measures of attention, executive functioning, and episodic memory encoding than do noncarriers.24 No significant associations were found between APOE ε4 status and the Sickness Impact Profile–68 (SIP-68) and Community Integration Questionnaire (CIQ) results. Diaz-Arrastia et al. found that APOE ε4 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 ε4 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 ε4 allele) suggested that although the APOE ε4 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. concluded that the APOE ε4 allele was associated with an unfavorable outcome (as indicated by GOS-E Extended Glasgow Outcome Scale scores), although they did find an association between APOE ε4 and late-onset posttraumatic seizure.14

APOE in Multiple Sclerosis

Though studies from Italy60 and Japan50 did not show any association between APOE ε4 and progression of multiple sclerosis, a study from Austria (Enzinger et al.16) demonstrated a negative influence of APOE ε4 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 ε4 (39%) than in patients with APOE ε3 (28%) or APOE ε2 (23%). Patients with APOE ε4 were also found to have an earlier onset of neuropathy as well as greater severity than patients without that allele.24

Human Immunodeficiency Virus–Related Neuropathy

Although patients with the APOE ε4 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 ε4 and 49 months in patients without APOE ε4, 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 ε2/ε3 genotype showed a significantly longer duration of the disease—median duration 51 months versus 28.5 for APOE ε3/ε3 and 27.5 for APOE ε3/ε4 (p = 0.001 and p = 0.02, respectively). In the bulbar group, patients with the APOE ε4 allele showed earlier onset of the disease.46 Similarly, Praline et al.55 found that the APOE ε4 allele was associated with an increased risk of bulbar-onset ALS in men. Nevertheless Siddique et al.59 and Zetterberg et al.83 found no significant relationship between APOE allele status and age of onset. In contrast, a study by Li et al.56 provided support for a protective role of APOE ε2. This controversy is reflected in the recent meta-analysis by Govone et al.,23 in which the ε4 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 ε4 among patients and controls,26 but they found that APOE ε2 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 Aβ 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 ε4 allele was found to increase Aβ deposition in the cerebral vasculature, whereas APOE ε2 was associated with rupture of Aβ-laden blood vessels and resulting hemorrhage.41 Greenberg et al. found that the age at first CAA hemorrhage was earlier in patients with APOE ε2.22
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. found that, compared with individuals with the APOE ε3/ε3 genotype, ε2 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 ε2/ε2 genotype had an increased risk of intracerebral hemorrhage (ICH) as well. APOE ε4 carriers had a 2.5-fold increased risk of subarachnoid hemorrhage (SAH). Individuals with the APOE ε3/ε4 genotype showed a 2-fold increased risk of atherothrombosis and ICH. The association between ε2 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 ε4 allele were significantly more susceptible to ischemic stroke (OR 1.11) and SAH (OR 1.42) but not to ICH. Rather, APOE ε2 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. 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 ε4 allele (OR 1.42, p < 0.001), but there was no significant association between ICH and the APOE ε2 allele. In the subgroup analysis by race, patients with ICH had a significantly higher frequency of the APOE ε4 allele in Asian (p < 0.001) as well as Caucasian (p = 0.009) groups. There was no significant relationship between the APOE ε2 allele and the risk of ICH. The presence of APOE ε4 was found to increase the risk of delayed ischemic neurological deficit in one study.

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 ε4 was found to be overrepresented and APOE ε2 was found to be underrepresented in comparison with frequencies in controls. No association was found in patients with familial amyloidic polyneuropathy. A meta-analysis of 22 studies of sporadic PD suggested an association with APOE ε2 rather than APOE ε4 (OR 1.2 and 0.99, respectively). The APOE ε4 allele (OR 1.41) was associated with an increased risk of Creutzfeldt-Jakob disease (CJD), and APOE ε3 (OR 0.81) tended to be protective against CJD in another meta-analysis of 11 case-control studies. 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 ε2 were found to have an increased risk of schizophrenia (although the increase was not statistically significant).

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 ε4 allele was associated with differences in neurological recovery and longer length of stay in a rehabilitation facility. Setzer et al. found that APOE ε4 was more prevalent in patients with cervical myelopathy than in controls. In an extension of this study they found that the presence of APOE ε4 was an independent predictor of poor outcome after anterior decompression surgery in these patients.

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 ε4 was associated with poorer outcome, subsequent studies have proven that the association is not straightforward. APOE ε2, 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.
References


Role of APOE polymorphism as a prognostic indicator


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.

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