Genetic influences on outcome following acute neurological insults
Ryan J. Waters and James A. R. Nicoll

Purpose of review
To examine the evidence for a genetic influence on clinical outcome after a variety of acute neurologic events.

Recent findings
Clinical outcome after brain injury is variable and cannot easily be predicted. It has been proposed that genetic polymorphisms may have an important role in determining outcome from a number of conditions, including acute neurologic events. Apolipoprotein E, an important mediator of cholesterol and lipid transport in the brain, is coded by a polymorphic gene (APOE). The APOE ε4 allele has been associated with unfavorable outcome after traumatic brain injury (TBI), hemorrhagic stroke and subarachnoid hemorrhage (SAH). Genes involved in other pathophysiological processes, such as cytokine genes in neuroinflammation, are now being implicated. For example interleukin-6 (IL-6) promoter polymorphisms are a risk factor for poor outcome after ischemic stroke, and may have an effect after traumatic brain injury. The emerging importance of a number of other gene polymorphisms is outlined in the review.

Summary
There is evidence demonstrating the ε4 allele of APOE predisposes to poor outcome after TBI, hemorrhagic stroke and SAH, but not ischemic stroke. The reason for this difference is unclear but it suggests there may be differences in the key mechanisms underlying the response to different types of insult. The role of other gene polymorphisms is being increasingly explored but there is still a need for larger prospective studies looking at larger panels of gene polymorphisms.

Keywords
genetics, head injury, outcome, stroke, subarachnoid hemorrhage

Introduction
The nervous system is at risk from many acute insults. The pathophysiology of acute neurologic events encompasses traumatic, ischemic, hemorrhagic and infective mechanisms that may all result in significant mortality, morbidity and disability. Patients who experience a poor outcome often require long-term care and place a burden upon health care and social welfare systems. Outcome from traumatic and nontraumatic brain injury is variable and cannot be predicted purely on the basis of clinical features or radiologic findings [1,2]. Prognosis of outcome is important for clinical decision-making, rehabilitation planning and communication with patients and their families.

It is now recognized that genetic polymorphism plays an important role in the susceptibility to, and outcome from, neurologic disease. Polymorphism occurs as a result of mutation, and can be defined as a genetic locus where the most common allele occurs with a frequency of less than 100% in the general population. The most common polymorphisms are single nucleotide polymorphisms (SNPs), resulting from a single base variation. Other polymorphisms occur due to the insertion or deletion of sections of DNA, forming both ‘minisatellites' and ‘microsatellites' [3]. The ε4 allele of the polymorphic apolipoprotein E gene (APOE) on chromosome 19 is an important susceptibility factor for Alzheimer’s disease [4,5]. Polymorphism of tumor necrosis factor-α (TNF-α) has been shown to cause a sevenfold increase in the relative risk of death from cerebral malaria [6]. If a genetic polymorphism is associated with outcome it will be present at a higher frequency in those patients who have a better or worse outcome. By targeting genes with known biologic activity, and investigating polymorphisms within the coding regions (which may affect protein structure, and thus function) or promoter regions (which may affect transcription rates) associations may become apparent.

Polymorphisms in a number of different genes have now been associated with poor outcome after different types of acute neurologic events and are summarized in this review.

Head injury
In the UK one million people present to Accident & Emergency units every year having suffered a head injury [7]. The morbidity from head injury is significant. It is estimated that the lifetime cost of providing care to a person
who has suffered a severe traumatic brain injury (TBI) in the United States approaches $2 million, although this does not include lost earnings and the cost to social services [8].

The potential association of apolipoprotein E gene (APOE) polymorphism with head injury outcome was postulated almost 10 years ago [9]. Apolipoprotein E is a key protein facilitating lipid transport and metabolism within the nervous system and has a role in neuronal maintenance and repair. It exists in three isoforms, coded by three alleles (e2, e3 and e4) that result in amino acid substitutions within the protein. A small study by Sorbi et al. [10] showed the e4 allele of APOE was a prognostic factor for posttraumatic coma. A preliminary study of 93 patients by Teasdale et al. [11] demonstrated a significant association between APOE e4 and poor outcome after head injury. Patients with the e4 allele were more than twice as likely to have an unfavorable outcome 6 months post head injury than those without. Subsequent studies have shown a similar association, although in all cases the subject numbers have been small (see Table 1). Friedman et al. [12] reported that only 3.7% of patients with the e4 allele had a good recovery, compared with 31% of patients without the allele. It should be noted that only patients who survived their injury and were referred for rehabilitation were included in this study. The outcome of patients who were able to complete a course of neurorehabilitation after TBI was also found to be associated with APOE genotype [13]. Overall and motor recovery, as assessed by the Functional Independence Measure, were both significantly lower in patients who possessed the e4 allele than those without. In addition to this, Crawford et al. [14], while demonstrating poorer outcome in e4 patients, found memory post TBI was worse in these subjects. In their study, 110 active and veteran American military personnel were assessed using a number of memory measures (FIM) at discharge. Treatment of mild head injury (mTBI) is more controversial. The clinical prediction rule (CPR) is an evidence-based approach to managing mTBI [15].

**Table 1. Summary of association studies**

<table>
<thead>
<tr>
<th>Injury</th>
<th>First author</th>
<th>Ref</th>
<th>Gene</th>
<th>Outcome measure</th>
<th>Time of assessment</th>
<th>Effect</th>
<th>n</th>
</tr>
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<tbody>
<tr>
<td>TBI</td>
<td>Sorbi 10</td>
<td>APOE</td>
<td>Coma duration</td>
<td>1 year</td>
<td>e4 predictor of outcome</td>
<td>16</td>
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<td>TBI</td>
<td>Teasdale 11</td>
<td>APOE</td>
<td>GOS</td>
<td>6 months</td>
<td>e4 associated with unfavourable outcome</td>
<td>93</td>
<td></td>
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<tr>
<td>TBI</td>
<td>Friedman 12</td>
<td>APOE</td>
<td>Functional &amp; cognitive assessment</td>
<td>6-8 months</td>
<td>e4 associated with poorer clinical outcome</td>
<td>69</td>
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<tr>
<td>TBI</td>
<td>Lichtman 13</td>
<td>APOE</td>
<td>Functional Independence Measures (FIM)</td>
<td>6 months</td>
<td>e4 associated with poorer rehabilitation</td>
<td>31</td>
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<tr>
<td>TBI</td>
<td>Crawford 14</td>
<td>APOE</td>
<td>Learning/fluency test</td>
<td>6 months</td>
<td>e4 had poorer memory outcome</td>
<td>110</td>
<td></td>
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<tr>
<td>TBI</td>
<td>Chiang 15</td>
<td>APOE</td>
<td>GOS</td>
<td>6 months</td>
<td>e4 associated with unfavourable outcome</td>
<td>100</td>
<td></td>
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<tr>
<td>TBI</td>
<td>Nathoo 16</td>
<td>APOE</td>
<td>GOS</td>
<td>6 months</td>
<td>No correction</td>
<td>110</td>
<td></td>
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<tr>
<td>TBI</td>
<td>Sundstrom 17</td>
<td>APOE</td>
<td>Neuropsychological tests</td>
<td>unclear</td>
<td>e4 bearers had worse post-injury performance</td>
<td>34</td>
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<tr>
<td>TBI</td>
<td>Lieberman 18</td>
<td>APOE</td>
<td>Neuropsychological tests</td>
<td>6 weeks</td>
<td>No consistent pattern</td>
<td>87</td>
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<tr>
<td>TBI</td>
<td>Millar 21</td>
<td>APOE</td>
<td>GOS/Neuropsychological tests</td>
<td>mean 18 years</td>
<td>No clear relationship</td>
<td>396</td>
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<tr>
<td>TBI</td>
<td>Liaquat 22</td>
<td>APOE</td>
<td>Hematoma volume/GOS</td>
<td>6 months</td>
<td>e4 associated with larger haematoma volume and poorer outcome</td>
<td>129</td>
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<tr>
<td>TBI</td>
<td>Diaz-Arastia 23</td>
<td>APOE</td>
<td>GOS+/- posttraumatic seizures</td>
<td>6 months</td>
<td>e4 associated with increased risk of seizures, independent of outcome</td>
<td>106</td>
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<td>TBI</td>
<td>Lendon 25</td>
<td>APOE</td>
<td>GOS</td>
<td>6 months</td>
<td>Slight association of -219 with outcome</td>
<td>92</td>
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<td>TBI</td>
<td>Minambres 26</td>
<td>IL6</td>
<td>GOS</td>
<td>6 months</td>
<td>No correlation between -174C and outcome</td>
<td>62</td>
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<tr>
<td>Stroke</td>
<td>McCarron 27</td>
<td>APOE</td>
<td>Good if alive at home, otherwise poor</td>
<td>3 months</td>
<td>e4 showed trend towards unfavourable outcome in ICH</td>
<td>714</td>
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<tr>
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<td>McCarron 28</td>
<td>APOE</td>
<td>Barthel Index &amp; Rankin scale</td>
<td>3 months</td>
<td>e4 had no major influence</td>
<td>189</td>
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<td>MacLeod 29</td>
<td>APOE</td>
<td>Rankin scale</td>
<td>unclear</td>
<td>No association between e4 and outcome</td>
<td>266</td>
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<td>Stroke</td>
<td>Treger 30</td>
<td>APOE</td>
<td>NIHSS &amp; FIM</td>
<td>at discharge</td>
<td>e4 did not predict outcome</td>
<td>100</td>
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<td>Stroke</td>
<td>McCarron 31</td>
<td>APOE</td>
<td>In-hospital mortality</td>
<td>inpatient stay</td>
<td>Possible association with poor outcome</td>
<td>176</td>
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<tr>
<td>Stroke</td>
<td>McCarron 32</td>
<td>APOE</td>
<td>Hematoma volume/ in-hospital mortality</td>
<td>inpatient stay</td>
<td>No association of e4 with haematoma volume</td>
<td>102</td>
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<td>Stroke</td>
<td>Weir 33</td>
<td>APOE</td>
<td>Coagulation studies/ survival</td>
<td>unclear</td>
<td>e4 dose associated with improved survival (ischaemic pts)</td>
<td>578</td>
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<td>Stroke</td>
<td>Greisenegger 34</td>
<td>IL6</td>
<td>Rankin scale</td>
<td>3 months</td>
<td>174GG associated with severe stroke</td>
<td>214</td>
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<td>Stroke</td>
<td>Hoy 36</td>
<td>Myeloperoxidase</td>
<td>Rankin scale</td>
<td>median 11 days</td>
<td>463GA associated with poorer outcome</td>
<td>450</td>
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<td>SAH</td>
<td>Leung 37</td>
<td>APOE</td>
<td>GOS</td>
<td>6 months</td>
<td>e4 associated with worse outcome</td>
<td>72</td>
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<td>SAH</td>
<td>Niskakangas 38</td>
<td>APOE</td>
<td>GOS</td>
<td>mean 7.5 months</td>
<td>e4 associated with unfavourable outcome</td>
<td>160</td>
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<td>SAH</td>
<td>Tang 39</td>
<td>APOE</td>
<td>GOS</td>
<td>3 months</td>
<td>e4 associated with unfavourable outcome</td>
<td>104</td>
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<tr>
<td>SAH</td>
<td>Dunn 40</td>
<td>APOE</td>
<td>GOS</td>
<td>6 months</td>
<td>No significant association</td>
<td>100</td>
<td></td>
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<td>SAH</td>
<td>Morris 41</td>
<td>APOE</td>
<td>Neuropsychological tests/GOS</td>
<td>mean 16 months</td>
<td>No significant association</td>
<td>70</td>
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<td>SAH</td>
<td>Vergouwen 42</td>
<td>PAI-1</td>
<td>GOS</td>
<td>3 months</td>
<td>4G allele increase risk for poor outcome</td>
<td>126</td>
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<tr>
<td>SAH</td>
<td>Khurana 43</td>
<td>eNOS</td>
<td>Vasospasm</td>
<td>in-hospital</td>
<td>788TC predicts susceptibility vasospasm</td>
<td>141</td>
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</tbody>
</table>

Ref, reference number; n, number of subjects; GOS, Glasgow Outcome Scale.
and cognitive measures. Although all patients displayed impaired performance, those who had the ε4 allele were significantly worse.

A more recent study of outcome after head injury involving a much larger number of patients (n = 984) (Teasdale et al., unpublished) has shown a much smaller difference in outcome between ε4 carriers and noncarriers. However, the effect of ε4 carriage was more marked in children and young adults than at an older age. This emphasizes the need for studies of this type to involve large numbers of patients.

An important point in studies of genetic variation is the ethnicity of the population. Chiang et al. [15*] extended the findings of the above studies to a Chinese population, in whom the ε4 allele is relatively uncommon in comparison to European and North American populations. One hundred consecutive patients admitted with TBI were prospectively followed until 6 months post injury. More than twice as many patients with ε4 had an unfavorable outcome at that stage than those without (52.6% vs. 24.1%).

The APOE ε4 allele is most frequently seen in people of African descent. The only study to have used a cohort of exclusively African subjects is that of Nathoo et al. [16*]. In a sample of 110 black Zulu-speaking patients with cerebral contusions, demonstrated by CT scanning, there was a nonsignificant trend between the ε4 allele and outcome. This may be because other gene interactions or expression are important in African populations, or because of gene-environment interactions that modify the response to TBI in this population.

The ε4 allele adversely affects outcome even after mild head injury. Sundstrom et al. [17*] were able to perform a series of neuropsychological tests on a small cohort of individuals both pre- and post-head injury. Those with the ε4 allele performed significantly worse in three tests post head injury, while those without the ε4 allele performed no different. This confirms the findings of an earlier study [18], which showed ε4-carriers had lower neuropsychological outcome scores than non-ε4 carriers at 3 and 6 weeks post mild TBI.

Amyloid β-protein (Aβ) is a protein that can form plaques within the brain and is involved in the pathogenesis of Alzheimer’s disease. This protein may be identified in the brains of patients with severe head injury [19], and its presence is associated with possession of the APOE ε4 allele [9]. Of potential relevance to this is a synergistic effect between the ε4 allele and a prior head injury in patients with Alzheimer’s disease [20]. It is therefore important to determine whether the ε4 allele affects long-term outcome. Results from longer-term follow-up [21*], studying patients 15 to 25 years after head injury, are available. Although these data confirmed a late decline in function after TBI, a relation to APOE genotype was not shown. The mean age of the cohort was still too young to assess the risk of Alzheimer’s disease. This raises the possibility that ε4 only exerts short-term effects, such as by worsening the initial injury, or that other genes have a greater importance in determining long-term outcome.

It is still unclear why ε4-carriers should have poorer short-term outcomes. The ε4 allele may predispose carriers to pathologies that result in worse outcomes. After trauma, patients with the ε4 allele are prone to larger intracranial hematomas [22] and seizures [23], both of which may adversely affect outcome. It is suggested that APOE ε4 promotes production of Aβ aggregates, cytoskeleton alterations and oxidative damage [24], while also impairing the ability of the brain to repair and regenerate.

Polymorphisms within the promoter region may increase APOE expression and exacerbate the response to TBI. A recent small study [25*] investigated three promoter polymorphisms. A poorer outcome was found in ~219 G/T carriers, but this may be confounded by evidence of linkage disequilibrium between this polymorphism and the ε4 allele.

There is increasing interest in how neuroinflammation, and especially cytokine levels, may affect outcome after TBI. To date there is little information attempting to correlate cytokine gene polymorphism with outcome. Minambres et al. [26*] were unable to demonstrate a role for the −174 G/C interleukin-6 (IL-6) promoter polymorphism (which is known to affect IL-6 levels) in influencing survival at 6 months.

In summary, most published literature supports the view that the ε4 allele of APOE adversely affects outcome after TBI in the first 6 months post injury. Its effects over a much longer period are less clear. The evidence for a role for other genes is beginning to appear but further work is required before any conclusions can be drawn.

**Stroke**

Of the acute neurologic insults, stroke is a major cause of death and disability. Due to its role in response and recovery from CNS injury, and its role in head injury outcome, the ε4 allele of APOE may be a determinant of stroke outcome. Evidence now suggests there is a divergent influence of ε4 on ischemic and hemorrhagic stroke outcome.

McCarron et al. [27] retrospectively studied over 700 patients who had suffered a stroke and were able to demonstrate that the ε4 allele did not influence dichotomized 3-month outcome (good if alive at home, bad if dead or in care) after ischemic stroke. However in those patients who had suffered a hemorrhagic stroke there was a nonsignificant trend towards poorer outcome in those patients with
the ε4 allele. The findings of this study have been confirmed by more recent studies. The Glasgow group prospectively followed a new group of ischemic stroke patients and again the ε4 allele was not associated with 3-month outcome [28]; this was also shown in a second Scottish cohort [29]. TIEGER et al. [30] demonstrated the ε4 allele did not predict outcome after ischemic stroke at the time of discharge from an inpatient rehabilitation program.

McCaron's early findings that outcome after hemorrhagic stroke was worse in ε4-carriers still require further investigation. The same group recently published data confirming that the ε4 allele was associated with poor survival after intracerebral hemorrhage [31]. One hundred seventy six patients with intracerebral hemorrhage from two centers in Scotland and America were recruited and the in-hospital mortality determined. In a multiple logistic regression model increasing age and the presence of the ε4 allele were significantly associated with worse in-hospital survival. Although the outcome measures are different, it appears APOE ε4 does have a role to play in outcome after intracerebral hemorrhage. The ε4 allele is not associated with larger hematomas [32] but may be associated with relatively prolonged coagulation times [33].

In a similar manner to TBI, an inflammatory response is provoked by brain ischemia/hypoxia. Raised plasma IL-6 levels are associated with worse outcome from acute vascular events. In a group of 214 patients, who suffered an ischemic stroke before the age of 60, those with severe disability at 3 months post insult were significantly more often carriers of the −174GG genotype of the IL-6 promoter region [34*]. This interesting finding has yet to be validated by other studies, but warrants further investigation, as this study demonstrated IL-6 to be associated with stroke severity but not with stroke risk. This is in contrast to other studies that do implicate IL-6 as a risk factor for stroke [35].

Myeloperoxidase polymorphisms may also affect outcome after ischemic stroke. Myeloperoxidase has a strong oxidative activity and may increase tissue damage. HOY et al. [36*] discovered the A allele of the −129G/A polymorphism was associated with the size of brain infarction and the A allele of the −463G/A polymorphism was associated with a poorer outcome at around 11 days post infarct. This finding is worthy of further study.

The gene polymorphisms that have a role in determining outcome after ischemic and hemorrhagic stroke are beginning to be explored and further new developments in this area can be expected in the near future.

**Subarachnoid hemorrhage**

Outcome after subarachnoid hemorrhage (SAH) cannot be predicted purely by current prognostic factors. Between a third and a half of survivors have major neurologic deficits, so the ability to predict outcome is important. As has been discussed above, APOE genotype is one of the most investigated potential influences on neurologic outcome after acute neurologic events. The effect of APOE genotype on outcome after SAH is unclear.

Three papers have demonstrated the ε4 allele predisposes a patient to poor outcome after SAH. LEUNG et al. [37] demonstrated a significant influence on 6-month outcome in a study of 72 patients. NISKAKANGAS et al. [38] showed 40% of patients with the ε4 allele had an unfavorable outcome, compared with 19% of those without, while TANG et al. [39] found 28% of those with the ε4 allele had an unfavorable outcome compared with 8% without.

Two linked studies [40,41*] have not demonstrated an association between the APOE ε4 allele and outcome after SAH. Although no significant association was found in the preliminary study of 96 patients [40] the confidence intervals were wide, and may have masked a slight effect. Interestingly there was under-representation of the ε4 allele in the cohort, raising the possibility that the ε4 allele may be associated with early (i.e. pre-hospital) mortality after SAH. Seventy of these patients had further detailed neuropsychological assessment approximately 16 months after their bleed [41*]. Again no overall association with outcome could be detected. However, in those patients who sustained the most severe hemorrhage (Fisher Grade 4), there was a trend towards poorer outcome in ε4-carriers. This may be because they shared similar pathophysiology to ICH patients, where ε4 does seem to have an effect.

All five studies of APOE and outcome after SAH have used small sample populations, and these have resulted in mixed results. There are also different ethnicities included in the sample populations, and different time periods of follow-up. To clearly define the role of APOE it will be necessary to complete some much larger studies. We await the findings with interest.

Very recently a new gene polymorphism has been implicated as a risk factor for poor outcome after SAH. Plasminogen activator inhibitor-1 (PAI-1) is already known to influence outcome in a number of conditions, such as sepsis and burns, possibly by encouraging the formation of microthrombi. The 4G promoter polymorphism correlates with higher PAI-1 levels. In a cohort of 126 Dutch patients, those with the 4G genotype were more at risk of secondary ischemia after SAH and were more likely to have a poor outcome [42*]. This study is important, as it provides one mechanistic clue as to why nimodipine provides a degree of neuroprotection after SAH — it reduces PAI-1 levels in plasma — and it also suggests other treatments that enhance fibrinolysis may be effective as neuroprotective agents after SAH.
There is evidence that polymorphism in the endothelial nitric oxide synthase (eNOS) gene promoter region is a risk factor for susceptibility to SAH and post-SAH vasospasm [43]. Although direct association with functional outcome has not been shown, vasospasm is likely to result in a poorer outcome than if it had not occurred.

Other conditions
The effect of gene polymorphisms on outcome from a number of other acute neurologic conditions are being explored. TNF-α promoter polymorphism –308 is associated with a sevenfold increased risk of death or severe neurologic sequelae due to cerebral malaria in African children [6], while the –238 and –376 polymorphisms have also been associated with increased susceptibility to cerebral malaria in certain African populations [44]. Interleukin-12 (IL-12) polymorphisms have also been associated with increased mortality from cerebral malaria [45]. To date there is little evidence to support the role of gene polymorphisms in outcome from other bacterial or viral CNS infections, despite a host of evidence for systemic infection. APOE interacts with HSV-1, and may facilitate its transport within the CNS, but it does not appear to affect outcome from herpes simplex encephalitis [46].

There is no current evidence to support the role of genetic polymorphism in outcome from acute demyelination in the peripheral nervous system [47]. However there is some evidence that axonal loss is associated with the APOE e4 allele and may influence long-term outcome after central nervous system demyelination [48,49].

Conclusion
Study of the genetic influence on outcome after acute neurologic insults is still at an early stage. Clearly APOE polymorphisms play an important role but this is not the full story. Studies to date have suffered from a number of limitations. In general the populations studied have been small, so small influences may not be detected. In addition these small studies are prone to type I errors and require confirmation with larger independent studies. Ethnicity of the study population is important, as the polymorphisms may exert differing effects in different populations. The manner in which outcome is assessed requires more standardization, both in the manner of measurement and time of assessment. It is difficult to compare studies that have used entirely different outcome measures. Many other genes, such as those that modulate the neuroinflammatory response, require investigation. Gene–gene and polymorphism–polymorphism interactions must be explored to understand the underlying functional basis for the relationships discovered. Studies of multiple genes are needed, rather than the single gene studies currently available. Clinical studies of larger cohorts and larger panels of polymorphisms are required.

References and recommended reading
Paper of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest

22. A study examining the association of apolipoprotein E genotype and long-term outcome measures.

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Miambres E, Cemborain A, Sanchez-Velasco P, et al. Correlation between transcranial interleukin-6 gradient and outcome in patients with acute brain injury. Crit Care Med 2003; 31:933–938. An interesting study that measured serial arterial and jugular IL-6 levels and attempted to correlate these, as well as IL-6 genotypes, with outcome.


Morris PG, Lindsay Wilson JT, Dunn LT, Nicoll JAR. Apolipoprotein E polymorphism and neuropsychological outcome following subarachnoid haemorrhage. Acta Neurol Scand 2004; 109:205–209. A study in which patients outcome was assessed by a comprehensive panel of neuropsychological methods 14 to 23 months after SAH.


