Genetic association studies in patients with traumatic brain injury

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Traumatic brain injury (TBI) constitutes a major cause of mortality and disability worldwide, especially among young individuals. It is estimated that despite all the recent advances in the management of TBI, approximately half of the patients suffering head injuries still have unfavorable outcomes, which represents a substantial health care, social, and economic burden to societies.

Considerable variability exists in the clinical outcome after TBI, which is only partially explained by known factors. Accumulating evidence has implicated various genetic elements in the pathophysiology of brain trauma. The extent of brain injury after TBI seems to be modulated to some degree by genetic variants.

The authors’ current review focuses on the up-to-date state of knowledge regarding genetic association studies in patients sustaining TBI, with particular emphasis on the mechanisms underlying the implication of genes in the pathophysiology of TBI. (DOI: 10.3171/2009.10.FOCUS09215)

Key Words • genetic association study • polymorphism • genes • traumatic brain injury

Pathophysiology of TBI

Clinical and experimental data have demonstrated that several complex and multifactorial pathophysiological cascades are initiated in the brain after a traumatic event. Primary brain damage is induced by direct impact to the brain parenchyma leading to focal or diffuse tissue distortion, destruction, tearing, and/or hemorrhage. After initial trauma, cerebral edema, increased intracranial pressure, tissue hypoxia-ischemia, and disruption of the blood-brain barrier may occur. Secondary brain changes, which appear either immediately after TBI or in the following hours or days, include cellular, neurochemical, and molecular responses to TBI, such as neuronal cell death, apoptosis, excitotoxicity, inflammatory infiltration, Aβ-peptide deposition, disruption of calcium homeostasis, oxidative stress, and cytoskeletal and mitochondrial dysfunction. Expression studies have shown that several genes are implicated in the pathophysiology of secondary brain damage. Secondary processes were found to dramatically worsen primary damage, leading to the activation of a cascade of neuronal and axonal pathologies, which in turn determine the patient’s overall clinical outcome.

Genetic Association Studies

Recent evidence from genetic association studies supports the view that genetic factors play an important role in the outcome of various CNS disorders including TBI. Genetic association studies are useful tools in investigating possible relationships between gene polymorphisms and disease outcome. Recent advances in genotyping technologies have greatly expanded the number of studies that can test possible associations between gene polymorphisms and certain phenotypes. Genetic variations include insertions, deletions, duplications, or SNPs. Genetic polymorphisms may affect the clinical phenotype by altering the function of the encoded protein, either by changing the structure of this protein or by modifying the expression of a gene. Increased frequency of an allele in a phenotype (favorable...
ApoE is a plasma lipoprotein implicated in transporting cholesterol and lipids throughout tissues including the CNS. In the brain, ApoE is synthesized primarily by the astrocytes and the microglia and plays a vital role in the maintenance of neuronal membranes, neuronal tissue repair, remodeling, and synaptic neurotoxicity and neurodegeneration, inflammation, mitochondrial dysfunction, impairment of the antioxidative defense system, increased intracellular calcium, disruption of cholinergic transmission, dysregulation of the neuronal signaling pathways, and apoptosis.

Evidence from epidemiological and pathological studies has linked TBI to Alzheimer disease.72 Deposition of Aβ was detected in approximately 30% of individuals dying shortly after severe TBI,111 and this may imply a genetic predisposition to Aβ accumulation. In head-injured individuals, Aβ deposition was shown to be determined, though in part, by the presence of the ApoE4 allele.100 Furthermore, immunostaining of amyloid deposits, which appear early after head injury, was positive for ApoE, whereas the number of immunoreactive plaques was associated with the ApoE4 allele in a dose-dependent manner.43

Several association studies have investigated the role of the ApoE gene polymorphism in patients sustaining TBI.55 The design and results of each study are summarized in Table 1. Despite all the possible limitations, these studies provide valuable information concerning the implication of the ApoE genotype in the pathophysiology of TBI.

Most genetic studies in TBI have investigated possible association between ApoE polymorphism and functional outcome after TBI measured by the GOS.2,12,15,17,25,40,69,87,98,130,131,135 In a recent meta-analysis of 14 cohort studies (of 23 relevant studies identified from the literature) and 2427 participants, it was found that the ApoE4
### TABLE 1: Previously published association studies of patients who had suffered TBI*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Gene</th>
<th>Polymorphism</th>
<th>Methodology</th>
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<th>Comments</th>
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<tbody>
<tr>
<td>Nicoll et al., 1995</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>90 autopsy TBI cases (23 Aβ+)</td>
<td>Aβ deposition</td>
<td>pos</td>
<td>ApoE4 allele, p&lt;0.00001</td>
</tr>
<tr>
<td>Sorbi et al., 1995</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>16 young pts w/ TBI</td>
<td>posttraumatic unawareness</td>
<td>pos</td>
<td>ApoE4 allele, p&lt;0.01</td>
</tr>
<tr>
<td>Mayeux et al., 1995</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>236 community-dwelling elderly persons w/ Hx of TBI</td>
<td>risk of AD</td>
<td>pos</td>
<td>10-fold increase for AD in presence of ApoE4 allele &amp; Hx of TBI</td>
</tr>
<tr>
<td>Katzman et al., 1996</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>160 pts w/ AD, 69 controls w/ Hx of TBI</td>
<td>risk of AD</td>
<td>pos</td>
<td>ApoE4 allele &amp; TBI increased the risk of AD, OR 13.5 (95% CI 2.63–69.12), p&lt;0.0018</td>
</tr>
<tr>
<td>Teasdale et al., 1997</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>89 pts w/ TBI</td>
<td>poor GOS score at 6 mos</td>
<td>pos</td>
<td>ApoE4 allele, OR 0.23 (95% CI 0.06–0.82), p=0.024</td>
</tr>
<tr>
<td>Jordan et al., 1997</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>30 boxers</td>
<td>neurological impairment (CBI scale)</td>
<td>pos</td>
<td>high-exposure boxers w/ ApoE4 allele had increased severity of neurological deficits p&lt;0.01</td>
</tr>
<tr>
<td>Friedman et al., 1999</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>69 pts w/ TBI</td>
<td>poor clinical outcome</td>
<td>pos</td>
<td>ApoE4 allele</td>
</tr>
<tr>
<td>Mehta et al., 1999</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>797 participants of a population-based cohort w/ Hx of TBI</td>
<td>risk of dementia &amp; AD after mean 2.1-yr follow-up</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>Plassman et al., 2000</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>46 w/ AD, 356 non-AD military men w/ Hx of TBI</td>
<td>risk of AD</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>Lichtman et al., 2000</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>31 TBI pts w/ diffuse axonal injury</td>
<td>functional independence measures</td>
<td>pos</td>
<td>ApoE4 allele carriers had lower scores in functional independence measures, p=0.05</td>
</tr>
<tr>
<td>Guo et al., 2000</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>942 probands w/ AD &amp; Hx of TBI, 327 controls</td>
<td>risk of AD</td>
<td>pos</td>
<td>TBI increased risk of AD in the absence of ApoE4 allele, OR 3.3 (95% CI 2.0–5.5)</td>
</tr>
<tr>
<td>Kutner et al., 2000</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>53 active football players</td>
<td>neuropsych assessments</td>
<td>pos</td>
<td>older players w/ ApoE4 allele had lower cognitive test scores, p=0.004</td>
</tr>
<tr>
<td>Liaquat et al., 2002</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>129 pts w/ TBI</td>
<td>hematoma volume</td>
<td>pos</td>
<td>E4 associated w/ larger hematomas, p=0.0056</td>
</tr>
<tr>
<td>Crawford et al., 2002</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>110 pts w/ TBI</td>
<td>memory performance w/in 6 mos of injury</td>
<td>pos</td>
<td>ApoE4 allele carriers had worse memory performance</td>
</tr>
<tr>
<td>Liberman et al., 2002</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>87 pts w/ mild or moderate TBI</td>
<td>neuropsych tests at 3 &amp; 6 wks</td>
<td>pos</td>
<td>ApoE4 allele carriers had lower test scores at first visit</td>
</tr>
<tr>
<td>Chiang et al., 2003</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>100 pts w/ TBI</td>
<td>poor GOS score at 6 mos</td>
<td>pos</td>
<td>ApoE4 allele, OR 3.01 (95% CI 1.02–8.88), p=0.04</td>
</tr>
<tr>
<td>Nathoo et al., 2003</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>110 black Zulu-speaking pts w/ TBI</td>
<td>poor GOS score at 6 mos</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>Diaz-Arrastia et al., 2003</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>106 pts w/ moderate or severe TBI</td>
<td>posttraumatic seizures increased risk in E4, OR 2.41 (95% CI 1.15–5.07), p=0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Millar et al., 2003</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>396 pts w/ TBI</td>
<td>GOS score at 6 mos, neuropsych outcome of 18 yrs later</td>
<td>neg</td>
<td></td>
</tr>
<tr>
<td>Kerr et al., 2003</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>91 pts w/ severe TBI</td>
<td>concentrations of amino acid neurotransmitters (aspartate, glutamine) &amp; energy metabolites L/P ratio</td>
<td>pos</td>
<td>those w/ ApoE4 allele had significant increased &amp; sustained levels of aspartate &amp; L/P ratio post-TBI</td>
</tr>
<tr>
<td>Chamelian et al., 2004</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>90 pts w/ mild to moderate TBI</td>
<td>GOS score, neuropsych outcome</td>
<td>neg</td>
<td></td>
</tr>
</tbody>
</table>

*Continued...*
TABLE 1: Previously published association studies of patients who had suffered TBI* (continued)

<table>
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<tr>
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<th>Polymorphism</th>
<th>Methodology</th>
<th>Phenotype</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sundström et al., 2004</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>34 pts w/ mild TBI pre- &amp; postinjury</td>
<td>neuropsych tests</td>
<td>pos</td>
<td>ApoE4 allele associated w/ decreased postinjury performance</td>
</tr>
<tr>
<td>Quinn et al., 2004</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>106 autopsy cases (2–19 yrs old)</td>
<td>brain swelling</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Koponen et al., 2004</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>60 pts w/ TBI</td>
<td>dementia</td>
<td>pos, neg</td>
<td>ApoE4 allele increased risk of dementia, p=0.028</td>
</tr>
<tr>
<td>Teasdale et al., 2005</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>1094 pts w/ TBI</td>
<td>GOS score at 6 mos</td>
<td>neg</td>
<td>ApoE4 allele associated w/ poor outcome only in pts &lt;15 yrs, OR 3.06 (95% CI 1.22–7.65)</td>
</tr>
<tr>
<td>Leclercq et al., 2005</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>88 TBI autopsies</td>
<td>cerebral amyloid angiopathy</td>
<td>pos</td>
<td>ApoE4 allele associated w/ cerebral amyloid angiopathy, p=0.021</td>
</tr>
<tr>
<td>Ariza, Pueyo et al., 2006</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>77 pts w/ TBI</td>
<td>neuropsych tasks ≥6 mos post-TBI</td>
<td>pos</td>
<td>ApoE4 allele increased risk of worse performance</td>
</tr>
<tr>
<td>Smith et al., 2006</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>239 cases of fatal TBI</td>
<td>moderate/severe contusions</td>
<td>pos, neg</td>
<td>ApoE4 allele increased risk of contusions, p=0.05, p=0.08</td>
</tr>
<tr>
<td>Jiang et al., 2006</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>110 pts w/ TBI</td>
<td>clinical deterioration in acute stage (&lt;7 days post-TBI)</td>
<td>pos</td>
<td>ApoE4 allele increased risk of clinical deterioration, OR 4.84 (95% CI 1.44–16.21), p=0.011</td>
</tr>
<tr>
<td>Isoniemi et al., 2006</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>58 pts w/ TBI</td>
<td>hippocampal vol, brain atrophy on average 31.3 yrs post-TBI</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Kerr et al., 2006</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>54 pts w/ severe TBI</td>
<td>CBF detected by Xe-CT w/in 24 hrs postinjury</td>
<td>pos</td>
<td>ApoE4 allele associated w/ higher CBF</td>
</tr>
<tr>
<td>Ponsford et al., 2007</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>120 pts w/ moderate or severe TBI</td>
<td>cognitive performance at 3, 6, &amp; 12 mos</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Han et al., 2007</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>78 pts w/ mild to moderate TBI</td>
<td>neuropsych measures at 1 mo</td>
<td>pos</td>
<td>ApoE4 carriers associated w/ better performance in some tests</td>
</tr>
<tr>
<td>Alexander et al., 2007</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>123 pts w/ severe TBI</td>
<td>GOS score at 3, 6, 12, &amp; 24 mos postinjury</td>
<td>pos</td>
<td>ApoE4 allele carriers had a slower recovery rate</td>
</tr>
<tr>
<td>Hiekkanen et al., 2007</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>33 pts w/ nontrivial TBI</td>
<td>brain lesions determined w/ MRI ~1 wk &amp; 1 yr post-TBI</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Zhou et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>meta-analysis: 14 studies, 2427 participants</td>
<td>initial GCS score poor GOS score at 6 mos</td>
<td>neg, pos</td>
<td>ApoE4 allele, RR 1.36 (95% CI 1.04–1.78)</td>
</tr>
<tr>
<td>Willemse-van Son et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>79 pts w/ moderate or severe TBI</td>
<td>GOS score at 3, 6, 12, 18, 24, &amp; 36 mos postinjury</td>
<td>pos</td>
<td>ApoE4 allele pts had better recovery OR 0.26 (95% CI 0.02–0.51), p=0.037</td>
</tr>
<tr>
<td>Tanniverdi et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>93 pts w/ TBI, 27 healthy controls</td>
<td>risk of pituitary dysfunction post-TBI</td>
<td>pos</td>
<td>lower risk of pituitary dysfunction in ApoE3/E3 individuals, OR 0.29 (95% CI 0.11–0.78), p=0.01</td>
</tr>
<tr>
<td>Brichtová &amp; Kozák, 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>70 children w/ TBI</td>
<td>GCS score at admission, GOS score at 1 yr</td>
<td>pos</td>
<td>children w/ ApoE4 genotype had unfavorable neurological outcome after TBI</td>
</tr>
<tr>
<td>Luukinen et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>134 pts &gt;70 yrs, 28 w/ head injury w/o explicit TBI</td>
<td>risk of dementia after 9-yr follow-up</td>
<td>pos</td>
<td>increased risk of dementia in pts carrying the ApoE4 allele, OR 2.70 (95% CI 1.02–7.16)</td>
</tr>
<tr>
<td>Ost et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>96 pts w/ severe TBI</td>
<td>death 1 yr postinjury</td>
<td>pos</td>
<td>males w/ ApoE4 had enhanced 1-yr mortality; females did not, p=0.0079</td>
</tr>
<tr>
<td>Authors &amp; Year</td>
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<tr>
<td>Rapoport et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>49 pts w/ mild TBI, 68 controls</td>
<td>neuropsych performance at 1 &amp; 2 yrs postinjury</td>
<td>neg</td>
<td>—</td>
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<tr>
<td>Kristman et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>318 student athletes (28 w/ concussion)</td>
<td>risk of concussion</td>
<td>neg</td>
<td>—</td>
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<tr>
<td>Ashman et al., 2008</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>54 older adults w/ TBI, 40 controls</td>
<td>neuropsych tests, reexamination 2–5 yrs later</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Han et al., 2009</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>46 military participants w/ mild to moderate TBI</td>
<td>change in job status post-TBI</td>
<td>pos</td>
<td>ApoE4 allele may affect change in job status after TBI</td>
</tr>
<tr>
<td>Müller et al., 2009</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>59 pts w/ mild TBI</td>
<td>neuropsych testing before &amp; 6 mos after discharge</td>
<td>pos</td>
<td>ApoE4 genotype associated w/ impaired cognitive performance, p=0.046</td>
</tr>
<tr>
<td>Hiekkanen et al., 2009</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>33 pts w/ TBI</td>
<td>injury symptom checklist, GOS extended version at 1 yr postinjury</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Lo et al., 2009</td>
<td>ApoE</td>
<td>ε2/ε3/ε4</td>
<td>65 critically ill children</td>
<td>CPP insult</td>
<td>pos</td>
<td>significantly less CPP insult among ApoE4 allele carriers w/ poor outcome, p=0.03</td>
</tr>
<tr>
<td>Lendon et al., 2003</td>
<td>ApoE</td>
<td>−219G/T−491A/T−427C/T</td>
<td>92 pts w/ TBI</td>
<td>GOS at 6 mos</td>
<td>neg</td>
<td>nonsignificant when adjusted by logistic regression</td>
</tr>
<tr>
<td>Jiang et al., 2007</td>
<td>ApoE</td>
<td>−219G/T−491A/T−427C/T</td>
<td>110 pts w/ TBI</td>
<td>clinical deterioration in acute stage (&lt;7 days after TBI)</td>
<td>neg</td>
<td>491AA genotype act synergistically w/ ApoE4 allele</td>
</tr>
<tr>
<td>Jiang et al., 2008</td>
<td>ApoE</td>
<td>−219G/T−491A/T−427C/T</td>
<td>110 pts w/ TBI</td>
<td>CT worsening in acute stage (&lt;7 days post-TBI)</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Terrell et al., 2008</td>
<td>ApoE</td>
<td>t23/ε4</td>
<td>195 active male football players &amp; male/female soccer players, 72 w/ Hx of concussions over the previous 8 yrs</td>
<td>risk of concussions</td>
<td>neg</td>
<td>—</td>
</tr>
<tr>
<td>Johnson et al., 2009</td>
<td>neprilysin</td>
<td>GT repeats in the promoter</td>
<td>81 TBI autopsies</td>
<td>Aβ plaques formation</td>
<td>pos</td>
<td>increased risk if total GT repeat number &gt;41, OR 10.1 (95% CI 3.1–32.5), p=0.0001</td>
</tr>
<tr>
<td>Martinez-Lucas et al., 2005</td>
<td>Arg72Pro</td>
<td>p53</td>
<td>90 pts w/ severe TBI</td>
<td>poor GOS score at discharge</td>
<td>pos</td>
<td>Arg/Arg, OR 2.9 (95% CI 1.05–8.31), p=0.039</td>
</tr>
<tr>
<td>Ariza, Matarin, et al., 2006</td>
<td>insertion/deletion</td>
<td>ACE</td>
<td>73 pts w/ moderate or severe TBI</td>
<td>neuropsych tests after resolution of posttraumatic amnesia</td>
<td>pos</td>
<td>D allele carriers had better performance on certain tests</td>
</tr>
<tr>
<td>Uzan et al., 2005</td>
<td>IL-1β</td>
<td>+3953 C/T−511 A/G</td>
<td>69 pts w/ TBI</td>
<td>poor GOS score at 6 mos</td>
<td>pos</td>
<td>allele 2, OR 0.25 (95% CI 0.12–0.55), p=0.004</td>
</tr>
<tr>
<td>Hadjiigeorgiou et al., 2005</td>
<td>VNTR</td>
<td>IL-1ra</td>
<td>151 pts w/ TBI</td>
<td>cerebral hemorrhage</td>
<td>pos</td>
<td>allele 2, OR 4.57 (95% CI 1.67–12.96), p = 0.004</td>
</tr>
</tbody>
</table>

(continued)
allele increases the risk of poor clinical outcome, which was evaluated 6 months after the injury.139

The ApoE polymorphism was also tested in patients who had suffered TBI in relation to several other neuropathological, laboratory, or imaging intermediate phenotypes, such as Aβ deposition,109 hippocampal volume and brain atrophy,58 cerebral blood flow,59 presence of brain lesions,41 hematoma volume,69 cerebral contusions, ischemic damage,101,121,132 brain swelling,107 cerebral amyloid angiopathy,85 concentrations of amino acid neurotransmitters,58 and CPP insult.25 Other phenotypes included clinical neurological impairment,32,40,51,56 mortality,101 functional independence measures,71 neuropsychological assessments,7,9,15,20,38,62,70,87,95,106,109,125 changes in work status,19 and risks of posttraumatic unawareness,121 Alzheimer disease,36,57,60,75,80,86,105 pituitary dysfunction,127 posttraumatic seizures,25 and psychiatric disorders.60

In addition to the aforementioned coding sequence polymorphisms, the ApoE gene is also polymorphic in the regulatory region. Promoter −219G/T and −491A/T polymorphisms were found to substantially alter the transcriptional activity of the ApoE gene.8 It has been reported that these polymorphisms confer susceptibility to Alzheimer disease,10 possibly by facilitating the Aβ deposition.64 However, in patients who have suffered TBI, the effects of promoter polymorphisms have remained inconclusive.50,52,68,132

Neprilysin

The accumulation of β-amyloid peptide in some patients shortly after TBI may be the result of an imbalance between production and clearance of Aβ. Of note, a major therapeutic strategy for Alzheimer disease is the activation of proteases involved in the Aβ degradation process. One such protease is neprilysin, which was found to play the most important role in the degradation of Aβ.49 Neprilysin levels were decreased in cerebral cortex and CSF in cases of early Alzheimer disease.79,113 In addition, knockout models for neprilysin were shown to have an increased burden of brain Aβ, while overexpression of neprilysin was associated with reduction in Aβ levels and retardation of plaque formation.49,90 However, it seems that neprilysin may not have an effect on the removal of already existing amyloid plaques but only on the prevention of forming new amyloid plaques.89

A GT repeat polymorphism in the neprilysin gene was shown to be associated with cerebral amyloid angiopathy and increased risk of Alzheimer disease.115,138 The polymorphism is located in the regulatory region of the neprilysin gene, and it may induce conformational changes in the DNA, influence gene expression, and the degree of the Aβ degradation. In a recent study, this polymorphism was tested in 81 fatal cases of TBI with available autopsy data and a 3.45-day mean survival after injury. It was found that TBI cases with longer GT repeats had increased risk of Aβ plaques,24 suggesting that neprilysin polymorphism may make patients who have suffered TBI more vulnerable to plaque formation.
Genetic association studies in TBI

The p53 Gene

Experimental and clinical studies have provided evidence of widespread local and remote apoptosis that can be detected from hours to days after TBI. These studies have indicated that apoptosis following TBI occurs in neurons and glia and may contribute to neurological dysfunction. Apoptotic cell death after TBI has been associated with decreased expression of survival-promoting proteins, such as Bcl-2 and extracellular signal-regulated kinase and increased expression of death-inducing proteins, such as Bax, c-Jun N-terminal kinase, p53, calpain, and caspases. Interestingly, minocycline, a tetracycline derivative currently being tested in spinal cord injury, has been reported to exert neuroprotective and antiapoptotic effects in TBI via inhibition of cytokine c release, inhibition of caspase-1 and -3, and expression and suppression of microglial activation. The p53 tumor suppressor factor is a key regulator of DNA repair, cell cycle progression, apoptosis, and neuronal damage; p53 is induced shortly after TBI, while its inhibition is assumed to offer neuroprotection. A functional polymorphism of the p53 gene in codon 72, which alters the properties of the produced protein, was studied in a group of 90 severely head-injured patients who were admitted to an intensive care unit. Patients with the Arg/Arg genotype were associated with unfavorable outcome at the time of discharge. However, 6 months later, no significant difference was found between the groups of patients with and without the Arg/Arg genotype, which may suggest a limited role of p53 in affecting the long-term clinical outcome of patients who have sustained TBI.

The ACE Gene

Angiotensin converting enzyme plays an important role in regulating both the production of angiotensin II and the degradation of bradykinin at the endothelial surface. Angiotensin II, which is the main active product of the renin-angiotensin system, has been linked to vascular remodeling, inflammation, and endothelial dysfunction. The ACE insertion/deletion polymorphism has been extensively studied in various diseases. It has been associated, among others, with atherosclerosis and Alzheimer disease. The ACE insertion/deletion polymorphism appears to be of particular clinical significance as it alters the ACE plasma levels and the local tissue production. However, the polymorphism only partially (47% in the study group) determines the variation in plasma ACE levels and it is uncertain if it represents a functional polymorphism. Actually, despite considerable efforts, the precise location of the ACE gene functional polymorphism among the several polymorphic sites that have been described remains unknown. Ariza et al. studied 73 patients who suffered moderate or severe TBI and reported worse neuropsychological performance in the D allele carriers of the ACE insertion/deletion polymorphism. The authors attributed this association to changes in the blood flow and cerebrovascular tone mediated by the local production of angiotensin II. Angiotensin II can also induce neuronal damage because it was found to have proinflammatory properties and to be implicated in the generation of reactive oxygen species.

The IL-1 Genes

Brain injury induces a complex sequence of inflammatory processes, which are believed to contribute to the pathogenesis of TBI. The level of these processes determines the patient’s clinical presentation and outcome. Interleukins are induced in response to brain injury and have multiple actions and targets, and often overlapping biological effects. Interleukin-1α and -1β are proinflammatory cytokines with pleiotropic activities, including growth and differentiation of T and B cells, and induction of other interleukins, adhesion molecules, histamine, and thrombocyte. Interleukin-1 receptor antagonist (IL-1ra) is a naturally occurring competitive inhibitor of IL-1α and IL-1β and, as such, plays an important role in regulating the inflammatory process. In experimental TBI models, rapid induction of IL-1β was reported after brain trauma (increased mRNA concentration occurred 15 minutes after the injury, while increased concentration of the involved protein occurred 6 hours after the injury). Similarly, IL-1ra was upregulated after head injury in the same experimental study (increased concentration of mRNA was observed 6 hours after the injury). Furthermore, administration of exogenous IL-1β markedly exacerbates brain injury, whereas injection or overexpression of IL-1ra significantly inhibits neuronal damage. Additionally, increased IL-1 expression is also detected in CSF in patients with head injury. A randomized phase II study of IL-1ra in acute stroke patients has reported promising results. The IL-1 gene cluster contains genes encoding IL-1α, IL-1β, and IL-1ra and lies on 2q13 within the 430-kb region in humans. A variable number tandem repeat (VNTR) polymorphism in intron 2 of the IL-1ra gene appears to be of particular clinical significance, as it has been associated with a variety of inflammatory diseases. Carriers of the 2-repeat allele (IL-1RN*2) have increased IL-1ra plasma levels, enhanced IL-1β production, and decreased local production of IL-1ra in various tissues. Two polymorphisms of the IL-1β gene have been studied extensively in the +3953 and −511 positions. The minor alleles of both polymorphisms are considered to be high producers of IL-1β protein.

Uzan et al. first provided evidence of an association between IL-1β +3953 and −511 polymorphisms and unfavorable prognosis in patients who had sustained TBI. In another study, the IL-1RN*2 allele carriers were associated with an increased risk of posttraumatic hemorrhagic events, which were used as an intermediate phenotype. Surprisingly, the IL-1RN*2 allele was associated with more severe initial clinical presentation (p = 0.045) and better clinical outcome (p = 0.02). These results may suggest that the increased inflammatory processes in IL-1RN*2 allele carriers may be deleterious in the acute postinjury period, but may participate in neuronal survival and repair in the intermediate and chronic postinjury period, possibly reflecting the dual role of cytokines in neurodegeneration and neuroprotection.

Regarding the IL-1α gene, a polymorphism in the
promoter region (−889) has been studied in various diseases. Although the IL-1α (−889) allele 2 was associated with elevated IL-1α and IL-1β protein levels, the functional role of this polymorphism has been questioned.24 Two studies have investigated the role of this polymorphism in patients who have sustained a TBI, but these studies were not able to establish any positive association.24,128

In another study that included patients who had suffered severe TBI and provided autopsy data, Johnson et al.39 examined a possible association between IL-1α and IL-1β polymorphisms and the extent of programmed cell death. Interestingly, the amount of TUNEL positivity did not differ between genotypes.

Another cytokine that is implicated in TBI pathophysiology is IL-6. Interleukin-6 has regulatory, antiinflammatory, and neurotrophic effects and is associated with neuronal protection and survival.92 It has been demonstrated that IL-6−deficient mice have increased numbers of apoptotic neurons after brain injury.103 However, administration of IL-6 can either enhance or inhibit neuronal injury, probably depending on the time course and extent of expression.4 In patients who have suffered TBI, the concentrations of IL-6 in CSF were elevated, and this upregulation after injury was associated with better neurological outcome.18 However, a polymorphism in the promoter of IL-6 was not found to have any effect on the outcome of patients with TBI.88

Other Association Studies

Clinical studies in patients who have sustained TBI have investigated the role of genetic variants in genes that modulate neurotransmitters such as dopamine41 or serotonin.16 Traumatic brain injury induces excessive neurotransmitter release, and this may affect motor function, behavior, mood, and cognition.

Dopamine and noradrenaline are key neurotransmitters that regulate cognitive function and affective behavioral processes. Dopamine and noradrenaline interact with specific receptors or are inactivated by COMT. Catechol-O-methyltransferase Val158Met polymorphism is associated with variation in COMT activity. The 158Met allele, which decreases the activity of the enzyme, is associated with higher dopamine concentrations in the prefrontal cortex63 and possibly with better cognitive performance. In patients who have suffered TBI, the COMT genotype was associated with higher postinjury performance on tests of executive function.53 In another study, a polymorphism in the ANKK1 gene, which regulates the adjacent dopamine D2 receptor gene, causing a reduction in the expression of D2 receptors, was found to be associated with slower postinjury performance on response latency.82,83

Depression is among the most common postinjury sequelae and may contribute to posttraumatic disability. Depression after TBI may be the result of a disturbance in serotonergic neurotransmission.81 However, a polymorphism in serotonin transporter protein (SLC6A4 solute carrier family 6 member 4) was not associated with increased frequency of depression after TBI.16

Conclusions

Over the past years, there has been extensive research in elucidating the pathophysiology of TBI and the determinants of patient outcome, whereas it remains to be seen if this knowledge will lead to the induction of new treatment strategies and improved clinical outcome. Several association studies have revealed a number of genetic variants that confer susceptibility to poor outcome after TBI. Apart from providing insights into the pathophysiology of TBI, genetic studies may have some useful implications including the development of genetic markers for determination of specific molecular profiles in individuals and assessment of phenotype risk. Identification of ApoE alleles may determine which patients with TBI will respond, for example, to ApoE administration or to targeted therapies, such as bapineuzumab, which is currently being tested in patients with Alzheimer disease who have a specific ApoE genotype. It is also possible that detection of genetic markers, such as IL-6 high-risk alleles, may help in identifying those patients who have sustained TBI with a specific proinflammatory or antiinflammatory phenotype, who may benefit from an early antiinflammatory treatment. This may, in part, explain the lack of clear clinical efficacy in improving outcome of previous antiinflammatory-based treatment trials in patients suffering TBI.1

Furthermore, our better understanding of complex genetic pathways may lead to specific genetic manipulation, for example, by targeting genetic modulators such as promoter regions,47 in the near future. There is also the possibility of neutralizing pathological mRNA, protein products and secondary messengers.11 Genetic determination of patients’ functional alterations in metabolic enzymes may also have a clear beneficial effect on developing specific treatment strategies. It is possible that this pharmacogenomics approach may have a clear impact in determining the optimal therapeutic doses, minimizing the possibility of any side effects, and improving treatment adherence and efficacy.11 In the future, all of these approaches may offer the prospect of personalized risk assessment and novel, genomic-based, targeted therapies.

Disclosure

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

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