British Journal of Anaesthesia **99 (1):** 43–8 (2007)
doi:10.1093/bja/aem142 Advance Access publication June 6, 2007

BJA

Impact of genetic factors on outcome from brain injury

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Most human phenotypic characteristics are determined by the interplay of environmental factors (whether external, or related to the internal milieu) with the unique genetic attributes of the individual. The same is true for predisposition to and outcome from most disease states, with acute brain injury being no exception. A greater understanding of this interplay is likely to allow improved risk stratification of patients, the development of new preventative and therapeutic modalities, and the possibility of 'individualizing' patient management based upon their genetic inheritance.

Br J Anaesth 2007; **99**: 43–8

Keywords: complications, neurological; genetic factors; head, injury

Head injury is the most common cause of trauma-related death. Each year, between 0.5 and 1 million people present to Emergency Departments across the UK with traumatic brain injury (TBI),[44] of whom seven in every one hundred thousand will die.[18] A great many more fail to achieve full functional recovery, carrying with them a substantial economic and social burden. Mortality and morbidity related to brain injury also derives from an array of other insults, including the prevalent vascular causes such as cerebrovascular occlusion or subarachnoid haemorrhage. Understanding the physiological responses to brain injury, whether injurious or protective, offers the prospect of developing new therapeutic modalities which may have generic application. One means of exploring such physiological and pathophysiological pathways is through the use of genetic tools.

Humans all share the same 20 000-or-so genes and it is this common inheritance that defines us as a species. However, this genetic inheritance, our DNA, also varies between individuals. Sections vary in 'copy number'. Alternatively, common variants, called polymorphisms, may exist when small 'extra lengths' of DNA may be present ('insertion' variants) or removed ('deletion' variants), or the genetic code may vary at a single nucleotide 'code letter' (the so-called 'single nucleotide polymorphisms' or 'SNPs'). Some variants may alter the function of the gene ('functional polymorphism'), either by changing the amount of protein it makes in response to a stimulus or by changing the functional characteristics of that protein.

Human phenotypes ('the way we are') are determined by the interaction of environmental stimuli with this genetic inheritance. As, an example, angiotensin-converting enzyme (ACE) plays an axial role in the endocrine renin–angiotensin system (RAS): it yields pressor angiotensin II (Ang II) from angiotensin I and degrades vasodilator kinins. However, such systems are also present within a wide variety of cells and tissues including human myocardium. A polymorphic variant of the human ACE gene has been identified in which the absence (deletion, D) rather than the presence (insertion, I) of a 284 bp fragment is associated with raised ACE activity in circulating inflammatory cells[6] and also in the myocardium.[37] When individuals are exposed to exercise training as a uniform myocardial hypertrophic stimulus, the D-allele is found to be associated with a far greater myocardial growth response.[33] Further studies have demonstrated an association of the ACE D-allele (and hence increased myocardial ACE) with impaired outcome in the context of impaired cardiac systolic performance.[32] Studies such as this confirm the impact of genetic factors on both the aetiology and the outcome from diverse disease processes, and offer the prospect of identifying mechanistic pathways and therapeutic targets which might otherwise have remained concealed.

Genetic factors can influence the risk of developing some conditions which lead to brain injury, such as cerebral arterial aneurysms, and also influence the outcome after such injury. However, the identification of these genetic elements is not as easy as it is in other, simpler, phenotypes because a variety of environmental factors may be at work in both disease pathogenesis and outcome determination. Many of these issues are likely to remain unidentified, and even those that are known will vary in both duration and intensity, often in unquantifiable ways. For example, the

magnitude of a blow to a skull may vary, as may the nature of that blow, its location and the nature and extent of associated injuries. The ultimate injury to the brain will also depend on the thickness of the skin, subcutaneous tissue and the skull, and blood vessel friability. These factors, and a great many more, will therefore determine the actual physical extent and location of the cerebral injury. The level of *neuronal* injury will also be influenced by factors much less readily quantified, such as intracranial pressure and cerebral blood volume, cytokine and inflammatory response, tissue oxygen tension, temperature, drug therapies, and so forth. Each of these factors may interact with a variety of different genetic factors to influence ultimate outcome. The identification of genetic elements of interest is therefore much more difficult in multi-factorial diseases.

To date, the majority of genetic studies in brain injury have been 'candidate gene association studies', most often seeking a difference in allele frequency between different groups such as cases *vs* controls, or 'worst affected and best affected'. However, care should be taken in the interpretation of such data, as *association* does not necessarily infer *causation* of the measure being assessed. For example, an allele may be found with excess frequency among cases not because it is causal for the disease state, but because the alternative allele is associated with early mortality from that disease (the so-called 'survivor bias'). In addition, unless expression of a specific gene is known to occur solely in cerebral tissue, an allelic association may be attributed to either local or systemic effects, and this cannot be readily inferred. Finally, a genetic variant may be in close proximity to a neighbouring gene with which it is 'carried'—the two exhibit 'linkage'. The association of an allele with an effect may therefore be causally attributable to unidentified functional variation in a neighbouring gene, and not to the gene in which the *recognized* variation lies.

For these reasons, the current literature relating genetic variation to cerebral injury is not extensive, although it is likely to expand enormously in the coming years. This review discusses the current knowledge of genes that are believed to be involved with the development of brain injury and those believed to be associated with outcome after head injury.

Genes and causation of disease

The genetic origin of some diseases affecting the brain is well recognized. Examples include the autosomal dominant Huntington's disease and autosomal recessive Hurler's syndrome, both of which are related to alterations in genes on chromosome 4. However, evidence is now accumulating that genetic variation can also play a role in the pathogenesis and outcome of other 'complex' cerebral disease states.

Interleukin-6

Interleukin (IL)-6 is a pro-inflammatory cytokine, orchestrating the synthesis of acute-phase proteins and mediating chemokine and adhesion molecule release from endothelium. The transcranial IL-6 gradient, as measured from arterial and jugular samples, correlates well with the severity of traumatic brain injury (TBI),[29] and peak plasma IL-6 level with brain infarct volume, stroke severity, and outcome after cerebral ischaemic events.[42] Increasing evidence suggests that IL-6 plays a cerebral neuropathic role,[12 13] and it is therefore likely that IL-6 levels are not mere markers of the extent of cerebral injury but causative in mediating ongoing damage.

Two common 'single nucleotide' polymorphisms exist in the promoter region, where a cytosine (C) may be substituted for a guanine (G) at positions −572 and −174. The −174C and −572C alleles are associated with greater IL-6 synthesis in an inflammatory state.[4]

Increasing evidence suggests that the development of cerebral arterial aneurysms may be partly driven by local inflammation within the vessel wall, to which IL-6 may be a key contributor. Morgan and colleagues[30] investigated the prevalence of the two common functional polymorphisms of the IL-6 gene promoter in 91 Caucasian patients with ruptured aneurysms compared with 2720 controls patients. When compared with controls, cases had a higher C-allele frequency at position −572 and position −174; C-allele homozygotes were also more prevalent among controls than cases. The combination of a −572C allele with a −174G allele was associated with an increased relative risk of aneurysms of 1.89, whereas the −572G/174C combination had a reduced relative risk of 0.58. Such data suggest that IL-6 genotype influences either the development of aneurysms themselves or their predisposition to rupture. However, IL-6 genotype may also influence outcome once rupture has taken place. IL-6 is a potent vasoconstrictor of the canine cerebral artery[35] and raised IL-6 levels are strongly associated with a poor outcome after subarachnoid haemorrhage.[10]

In keeping with such observations, premature birth is associated with a significant risk of neurological impairment in which IL-6 may play a causative role. Since the C-allele at position −174 is associated with greater IL-6 production, Harding and colleagues[13] postulated that neurological outcome in preterm infants born before 32 weeks gestation might be worse in those with CC genotype. One hundred and forty-eight Caucasian preterm infants, with a median gestational age of 31 weeks, were successfully genotyped. When compared with those carrying one or more G-alleles, those with CC genotype had an increased incidence of haemorrhagic brain insults (19% *vs* 6%), ventriculomegally or white matter damage (26% *vs* 7%), and disability (31% *vs* 13%). In addition, carriage of one or more C-alleles at position −572 was associated with impaired cognitive development.[12]