Reading news headlines could lead someone to believe that playing contact sports such as football will lead to a degenerative neurological condition in early adulthood. Indeed, participation in sports such as high school football has declined as the number of news reports of concussion in sports has increased (11). However, research indicates that although higher than the normal population, only a low percentage of former athletes such as NFL players are reporting such problems (20). Since most of these players were likely exposed to thousands of subconcussive (and some concussive) impacts over a career, why are only some athletes exhibiting problems? The answer may lie in intrinsic factors such as genetics in combination with their environment (repetitive head impacts). Thus, risk of poor mental or cognitive health may not come from playing contact sports alone, but playing them in addition to having a specific genetic predisposition. In this chapter, we will explore genes and polymorphisms potentially associated with sport concussion.

Concussion pathomechanics and pathophysiology

Traumatic brain injury (TBI) can be viewed along a continuum (Figure 27.1) with high head-impact acceleration events (e.g., high-speed car accident) yielding severe TBI and low head accelerations (e.g., soccer heading) eliciting seemingly no injury (i.e., subconcussion). Concussion and subconcussion are on the low end of the continuum and are the most common impact types encountered in sports. The level of injury is determined through clinical assessment and, when appropriate, includes diagnostic imaging assessment. Subconcussion is a head impact (or head acceleration event) that does not result in any outward signs (e.g., unsteadiness) or subjective reporting of symptoms (e.g., headache) (4). A concussion is a head impact (or head acceleration event) that does result in signs and symptoms (37). A concussion would not yield any remarkable signs on diagnostic imaging (e.g., magnetic resonance imaging), which helps differentiate concussion from a moderate or severe brain injury.

To understand the role genetics may play in predisposing someone to a concussion, it is important to further understand concussion injury pathomechanics and pathophysiology. A concussion is an injury to the brain caused by acceleration forces (15). These forces can occur from something hitting the head, the head hitting something, or an indirect blow to the
body causing whiplash (3). The brain, which is floating in cerebrospinal fluid, moves rapidly within the skull creating tensile, compressive, or shear forces on the brain tissue producing cell deformation (i.e., pathomechanics) (45). The two main cell types in the brain are neurons, the conducting cells, and glia, the supporting cells. Identifying structures that manage stress and strain within these cells is important to finding a possible genetic predisposition to concussion (Figure 27.2).

A number of neuronal structures can help manage mechanical stress including the cell membrane, microtubules, and intermediate filaments. The cell membrane is stabilized by cholesterol embedded, in part, by the function of apolipoprotein. Neuronal microtubules give cells form and help transport cellular material, and are stabilized by the protein tau. Neuronal intermediate filaments are composed of proteins such as neurofilament heavy (NEFH) and light (NEFL), and form an internal cell scaffolding that helps create form and resist changes in cell shape. In astrocytes, the predominant glial cell comprising a large percentage of brain volume, a main component of intermediate filaments is glial fibrillary acidic protein (GFAP). These structures help resist cell deformation in response to mechanical stress. If deformation is large enough (e.g., > 5% of resting length), this axonal stretch can lead to neurometabolic events and cell dysfunction (i.e., concussion pathophysiology) (13).

Concussion pathophysiology involves a neurometabolic cascade of cellular events that occur post insult and trigger neuron dysfunction. These events have been described previously (16) and can include ion flux (e.g., Na⁺, Ca⁺) and glutamate release, cytoskeletal damage to microtubules and neurofilaments, altered neurotransmission due to glutamate and calcium channel disruption, inflammation, and potential cell death. Therefore, proteins involved in cytoskeleton stabilization (e.g., tau), cell membrane channel function, and glutamate regulation may play key roles in attenuating concussion pathophysiology. The ability of the proteins mentioned above to function properly to help withstand mechanical stress and restore proper neuronal function is largely due to their structure. In the next sections, we will review some of the genes that code for these proteins (see Tables 27.1 and 27.2), in particular distinguishing studies that have focused on pathomechanical and pathophysiological outcomes.

**Pathomechanical genetic associations**

**Apolipoprotein E**

Apolipoprotein E (APOE) is one of the most studied genes associated with concussion and manifests multiple genetic polymorphisms. The APOE gene is located on chromosome 19 and produces the apolipoprotein E (ApoE) glycoprotein. This protein is involved in the redistribution of lipids to maintain and restore the neuronal membrane after an injury (7). ApoE exists in three isoforms, ApoE2, ApoE3, and ApoE4 encoded by three common alleles ε2, ε3, and ε4, respectively, and result in changes in different single amino acid changes (34). The three allelic variants
Figure 27.2  Cellular structures involved in concussion pathomechanics and pathophysiology.
### Table 27.1 Concussion pathomechanical genetic associations

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene</th>
<th>Variant</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein E</td>
<td>Apolipoprotein E (APOE)</td>
<td>ε4</td>
<td>30 professional boxers (23–76 years of age) underwent neurological examination using the chronic brain injury scale. Authors found the ε4 allele was associated with worse cognition scores in high-exposure boxers (22)</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
<td>Apolipoprotein E (APOE)</td>
<td>ε4</td>
<td>318 collegiate athletes (~52% male) were prospectively followed after a concussion. Authors found after adjusting for sex, weight, height, and team type that there was no association with ε4 and concussion risk (28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ε4</td>
<td>195 collegiate athletes (163 football and 33 female soccer players) self-reported the number of previous concussions (72 with concussion, 123 with no concussion). After adjusting for age, school, and years of sport experience, carrying the ε4 allele was not associated with concussion history (49)</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
<td>Apolipoprotein E (APOE)</td>
<td>G(−219)T-promoter SNP</td>
<td>196 collegiate athletes (163 football and 33 female soccer players) self-reported the number of previous concussions (48 with concussion, 148 with no concussion). Authors found carrying the T promoter allele and X alleles were associated with history of concussion (52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G(−219)T-promoter SNP</td>
<td>196 collegiate athletes (163 football and 33 female soccer players) self-reported the number of previous concussions (48 with concussion, 148 with no concussion). Authors found an increased risk of two or more concussions when carrying the minor T allele (52)</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
<td>Apolipoprotein E (APOE)</td>
<td>G(−219)T-promoter SNP</td>
<td>195 collegiate football and female soccer athletes self-reported previous history of concussion (72 with concussion, 123 with no concussion). After adjusting for age, school, and years of sport experience, carrying the APOE promoter TT was associated with increased concussion risk (49)</td>
</tr>
</tbody>
</table>
are distinguished by single nucleotide polymorphisms (SNPs) in exon 4 of the APOE gene. SNP rs7412C>T is present in alleles ε3 and ε4. SNP rs429358T>C is present in allele ε4. The most common allele is ε3 (65–70% frequency), with two others being rarer variants (ε2, 5–10%, and ε4, 15–20%); (35). The rs7412C>T SNP that causes a change of an amino acid in ApoE2 effects binding to the low-density lipoprotein receptor, while the rs429358T>C SNP that produces the ApoE4 polypeptide results in preferential binding of very low density lipoprotein particles and reduced ApoE4 stability (35). Previous studies attributed these effects to altered interactions between two functional domains within the ApoE polypeptide chain (35,54).
The effect of ApoE allelic variants on TBI outcome are likely modulated by mechanical force, age, or time post TBI. Several studies have indicated an association between APOE genotype and moderate/severe TBI poor outcome. Several studies have also demonstrated that the rare APOE variants are associated with greater risk of concussion, greater severity of symptoms, or poor outcomes following a concussion injury.

Recent meta-analyses of studies investigating the role of ApoE4 on moderate and TBI indicate an association with an increased risk of poor outcome in pediatric carriers of at least one ApoE4 allele (29). Such an association presents differently depending on trauma severity. In mild concussion, ApoE4 was not associated with post-concussion outcomes in 58.3% of the studies, while in more severe TBI, the role of ApoE4 was hazardous in 63.6% of the studies. Another meta-analysis of six studies including a total of 358 cases of pediatric TBIs revealed that at 6 months, there was over two times higher odds of poor outcome following TBI in children with at least one APOE ε4 allele, compared with children without an ε4 allele (26). In a meta-analysis of 12 studies on ApoE and functional outcome after TBI revealed an association with increased risk of unfavorable long-term functional outcome (≥6 months) (30). Due to the wide spectrum of brain injury severity, it is difficult to ascertain if TBI is different from concussion or repeated head impacts. Several studies are trying to bridge this gap; however, there are controversial findings.

For example, carrying the ε4 allele has been associated with poor outcome following TBI. Within a small sample of 30 boxers, including high-exposure boxers (12 or more professional matches; 23–76 years of age), researchers examined the relationship between carrying the ε4 allele and their Chronic Brain Injury Scale scores. The Chronic Brain Injury Scale assesses motor function (gait), cognitive deficits, and behavioral abnormalities, where 0 is normal and above 4 is severely impaired. The authors found that carriers of the ε4 allele had worse Chronic Brain Injury Scale scores (37% had normal scores). Within the same study, all boxers with severe impairment were found to carry at least one ε4 allele, and had high exposure to boxing (60% participated in 12 or more professional bouts) (22). Other studies, which examined self-reported concussion history and APOE genotype, reported no association with carrying the ε4 allele or other APOE variants were significantly associated with poor outcomes (28, 49, 50, 52).

In a large cohort of 318 collegiate athletes (~20 years of age; 51% male; eight different sports) authors evaluated the association between APOE ε4 and concussion risk. The authors measured time to first concussion and calculated athletic exposures. The mean number of athletic exposures was approximately 100. Approximately 25% of the athletes carried the ε4 allele and 8% suffered a concussion during the course of the research study. The authors found no association between carrying the APOE ε4 allele and sustaining a concussion (28). In a multicenter study that included 195 college athletes (~19 years of age; male football, female soccer players) authors assessed self-reported concussion over an 8-year time period obtained via a questionnaire. The athletes reported a total of 97 documented concussions. None of the athletes with reported concussion carried the homozygous ε4 genotype; however, approximately 40% of the concussed cohort carried the G(−219)T SNP in the APOE promoter region. Therefore the authors demonstrated that homozygous carriers of the promoter G(−219)T SNP in the APOE promoter region were at increased risk for having a history of concussion, but did not find any difference between ε2, ε3, and ε4 allele carriers (49, 50).

In a similar multicenter study, the authors evaluated the self-reported history of documented concussions within a cohort of 196 collegiate athletes (163 football and 33 female soccer players). Twenty-five percent of the athletes suffered a concussion, of whom 32% carried the ε4 allele, and 50% carried the promoter allele. The authors found a significant association was reported between college athletes who carried all three alleles and history of concussion (i.e.,
heterozygous $\varepsilon 2/\varepsilon 4$ and carried the rare promoter allele G) (52). In the same study Tierney et al. also found a significant association between homozygous carriers of G($-219$)T SNP and athletes reporting two or more concussions. With only limited evidence suggesting the important role $APOE$ allelic variants play in concussion incidence and recovery, conflicting results do not allow us to make a formal confirmation of this hypothesis at this time. The ultimate confirmation would require prospective, multicenter studies with sufficient power and carefully selected inclusion/exclusion criteria (18, 51). For example, a genome-wide association study would be beneficial to identify if $APOE$ is a significant genetic marker for brain injury. For this type of research design, thousands of athletes’ genomes with a concussion history would be compared to thousands of those with no concussion history.

One of the reasons $APOE$ is targeted as a genetic marker is due to the fact that head injury is reported to trigger amyloid B protein deposition, which is also a key factor in the progression of Alzheimer’s disease (AD) (44). Similar to TBI, AD displays as a cognitive decline. A recent review found this cognitive decline seems to be accelerated in patients carrying the $APOE$ $\varepsilon 4$ allele (31). This was attributed to the $APOE4$ protein being not as efficient in delivering cholesterol to maintain synaptic transmission. Additionally, the authors of the review found that $APOE4$ protein promotes proinflammatory processes that further exacerbate the disease progression. Similar to genetic associations to brain injury, not everyone carrying the rare allele/genotype has poor outcomes. Approximately 34–65% of patients with AD carry the $APOE$ $\varepsilon 4$ allele, while it is present in about 20–30% of the nonaffected adult population (43).

**Tau**

Tau is a microtubule-associated protein that stabilizes microtubules. The human tau gene ($MAPT$) is located on chromosome 17 and contains 16 exons (coding regions of the gene). Two different tau gene haplotypes have been identified (H1 and H2), consisting of eight common SNPs. H1 is the most common, and it is overexpressed in disorders such as progressive neurological disorders. In the central nervous system, alternative splicing of exons 2, 3, and 10 result in the appearance of six tau isoforms (2).

There is a paucity of research examining tau genotype and concussion. Terrell et al. (details of study reported above) (49, 50) reported that tau variants in exon 6 (Ser53Pro (TauSer), Hist47Tyr (TauHis)) were not associated with acute concussion. In spite of this, tau does seem to be an important protein to focus on for genetic predisposition to brain injury due to its association with chronic traumatic encephalopathy (CTE) and AD. CTE is a neurodegeneration characterized by the abnormal accumulation of hyperphosphorylated tau protein within the brain; however, CTE can only be definitively diagnosed postmortem (40). CTE is also thought to be associated with subconcussive blows to the head (14). Therefore, it is plausible that tau genetic polymorphisms may be key in determining the risk of CTE or AD in relation to contact sport participation. Currently, there are no genetic studies involving tau, contact sport participation, and CTE. In a postmortem study, authors examined numerous genes in 17 military personnel and football athletes with a history of repetitive brain injury and found that $MAP2$ is upregulated in brains with late-stage CTE (42). Similar to $MAPT$, $MAP2$ codes for microtubule-associated proteins involved in stabilizing the dendrite shape during neurodevelopment. The authors did not evaluate $MAPT$. Currently, many of the studies examining tau focus on cerebral spinal fluid and plasma tau protein concentrations following acute brain injury (56).
**Neurofilament**

The neuronal cytoskeleton is composed of 50% neurofilaments including light (NEFL), medium (NEFM) and heavy neurofilament (NEFH) (17, 53). These neurofilaments are composed of proteins that determine the quality of the cytoskeleton. The NEFH gene resides on chromosome 22, and several variants within this gene have been associated with neurodegenerative conditions, such as amyotrophic lateral sclerosis (1).

Only the NEFH has been examined to date in association with concussion outcomes. The authors of one study sought to determine an association between a SNP within a gene coding for a neuronal structural protein (i.e., neurofilament heavy) and previous occurrence and severity of concussions in college athletes (38). Using a case–control study design, 48 athletes with a reported history of concussion were matched by age, height, sport, and position to 48 athletes with no history of concussion (~19 years of age). The authors reported that 24% of the athletic cohort carried the NEFH rare allele, but there was no significant association between carrying the rare allele and concussion history or severity. Although the rare allele alters the NEFH protein sequence, this SNP does not seem to influence an athlete’s susceptibility to concussion (38).

**Pathophysiological genetic associations**

**Glutamate receptor ionotropic NMDA receptor 2A (GRIN2A)**

The primary function of the N-methyl-D-aspartate (NMDA) receptor is to act as synaptic connectivity between two neurons as well as to trigger postsynaptic potentials and dendritic spikes, where action potentials are formed. Mechanical stress activates NMDA receptors via overstimulation by the increased glutamate concentration within the synaptic cleft, and causes excitotoxicity (injury to the nerve due to excessive stimulation by glutamate). Ionotropic NMDA receptors are recognized as the major source of glutamate excitotoxicity dependent on the influx of Ca$^{2+}$ when glutamate binds to NMDA receptors. NMDA receptors are composed of four subunits forming a ligand-gated cation (e.g., Ca$^{2+}$) channel in which the NR1–NR2A heterodimer is the functional unit. The main NR2 subunits are NR2A and NR2B encoded by the GRIN2A and GRIN2B genes, respectively. GRIN2A is located on chromosome 16 and contains multiple SNPs in the coding, intronic, and promoter regions, and has been implicated in several cognitive brain diseases including dementia, AD, depression, and schizophrenia (21).

Functional involvement of NMDA receptors in the concussion stress response is supported by several lines of evidence (25, 41). An important role of polypeptide components of the NMDA receptor was demonstrated in experiments with genetically manipulated mice. Less brain ischemia was detected in NR2A or NR2A/NR2B knockout mice, after they were subjected to focal cerebral ischemia. The lack of NR2A is likely to alleviate glutamate excitotoxicity due to the decreased amount of blood volume, which could be explained by decreased NMDA channel activity (41). The reduced functionality of the NMDA receptors results in less Ca$^{2+}$ entering the cell (25). Taken together, the above data support the premise that variability in NMDA receptor expression could be a risk factor for concussion outcome. Therefore, variants of the genes coding for the components of the NMDA receptor complex are attractive candidates for association with concussion incidence or recovery.

One important type of genetic variability is the number of tandem repeats (i.e., GT) in the promoter region of the GRIN2A gene. GRIN2A expression is modulated by (GT)$n$ VNTR in the promoter region. The (GT)$n$ VNTR in the promoter region had been earlier associated with altered expression level of GRIN2A (23, 25). The length of (GT)$n$ repeat modulates
GRIN2A expression level, with longer alleles (≥25 repeats) associated with lower transcription of GRIN2A mRNA. In a study of 87 athletes (~19 years of age; 74% male) suffering with a concussion, homozygous carriers of the longer alleles (>25 repeats) were found to be six times more likely to recover in 60 or more days, compared with homozygous carriers of the shorter (<25 repeats) alleles (39). With athletes categorized to one of two groups (prolonged recovery vs. normal recovery), significant variation between the frequencies of longer alleles and shorter alleles was detected, where the carriers of longer alleles were two times more likely to be in the prolonged recovery group than those carrying shorter alleles. Moreover, homozygous carriers of longer alleles demonstrated a significant association with prolonged recovery when compared with homozygous carriers of shorter alleles (39).

Vesicle glutamate transporters

Uptake of glutamate at the synapse following a mechanical insult (e.g., concussion) is important for the restoration of normal neuron function. The synaptic uptake of glutamate is facilitated by vesicular transporters (i.e., vesicle glutamate transporter (VGLUT)-1, VGLUT2, and VGLUT3) encoded by the solute carrier subfamily of genes located on chromosomes 19 (SLC17A7), 11 (SLC17A6), and 12 (SLC17A8), correspondingly. VGLUT1 performs synaptic uptake of glutamate and deposits it into neurosecretory vesicles and is expressed in cerebrum, cerebellum, and hippocampus. Downregulation of VGLUT1 vesicular transport production was shown to cause severe changes in the neurological phenotype of experimental animals (12). Knockout studies demonstrated reduction of vesicle pool size accompanied by residually high concentrations of glutamate within the synaptic cleft (55). Another piece of evidence indicating that VGLUT activity could modulate synaptic efficacy came from the clinical studies of VGLUT expression in schizophrenic patients. VGLUT expression in the hippocampus and the dorsolateral prefrontal cortex was reduced in the brains of schizophrenic patients (9).

If the expression level of a protein responsible for reducing the amount of glutamate (e.g., VGLUT1) within the synaptic cleft is altered due to genetic variation, this may affect the severity of the concussive injury, and the recovery time. A study in 40 athletes (~20 years of age; 73% male) demonstrated that carriers of the rs74174284:G allele in the SLC17A7 promoter were five times more likely to exceed 20 days to recover from a concussion (33). These results are in parallel with the hypothesis that low expression of SLC17A7 encoding VGLUT1 probably reduces glutamate transport in the carriers of G allele (55).

Future directions

Sport concussion is its own entity within TBI science. Concussion is not severe TBI or a neurodegenerative disease. As we learn more about how these injuries and diseases overlap, it provides an opportunity to explore new genetic associations. Table 29.3 provides a summary of some genes (and proteins) studied in other conditions or that have a hypothetical role in the pathomechanics and/or pathophysiology of sport concussion. Genetic associations studied in other neurological conditions, in addition to our ever-growing understanding of concussion, are the key to enlightening the science of sport concussion genetics.

This type of genetics research can be challenging for many reasons. For example, there are multiple outcomes with variable responses that could have genetic associations such as the acute and long-term response to repetitive subconcussion, acute concussion, or severe TBI. Further complicating matters is that each of these injuries are based on clinical decision-making and management. For example, a researcher studying concussion response (e.g., return to play
Table 27.3  Potential concussion genetic associations

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene (abbreviation)</th>
<th>Variant</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glial fibrillary acidic protein</td>
<td>Glial fibrillary acidic protein (GFAP)</td>
<td></td>
<td>10 different isoforms within exons 6, 7 and the 5’ UTR. A literature review revealed isoforms α, β, γ, δ, and ε were associated with a greater risk of Alexander’s disease (46)</td>
</tr>
<tr>
<td>S100 calcium binding protein B</td>
<td>S100 calcium binding protein (S100B)</td>
<td>rs9722</td>
<td>794 participants (396 ischemic stroke patients and 398 controls; ~58 years of age; ~61% male). Authors found carriers of the A allele had an increased S100B serum, which increased risk for ischemic stroke (32)</td>
</tr>
<tr>
<td>Calcium voltage-gated channel subunit alpha-1A (CACNA1A)</td>
<td>rs121908225</td>
<td></td>
<td>Within 3 participants with delayed severe edema and 152 nonaffected family members and controls, authors found that carriers of the T allele had increased brain swelling and coma after TBI (27) In a review of literature, authors found an increased risk of hemiplegic migraine and cerebral edema after minor head injury in carriers of the S218L mutation in exon 5 (48)</td>
</tr>
<tr>
<td>Calcium voltage-gated channel subunit alpha-1E (CACNA1E)</td>
<td>rs704326</td>
<td></td>
<td>1q31 and 1q32 provide genes that code for proteins such as ATPase, and proteins integral for active transport of sodium ions. This SNP within exon 43 lies within this region of the gene that is associated with migraines (10)</td>
</tr>
<tr>
<td>Glutamate receptor ionotropic NMDA type subunit 2B (GRIN2B)</td>
<td>rs228411</td>
<td></td>
<td>Using the FBAT program, the authors found the C allele carriers had greater symptoms scored and were associated with attention deficit disorder (8)</td>
</tr>
<tr>
<td>Glutamate ionotropic receptor AMPA type subunit 1–4 (GRIA1–4)</td>
<td>Tandem repeats in exons 4, 5, and 12</td>
<td></td>
<td>Associated with autism and intellectual disability (5, 6, 19) (continued)</td>
</tr>
</tbody>
</table>
(time) should consider factors such as: When was injury identified? Who identified the injury? What assessments were performed? Was rehabilitation implemented? What was the return to play protocol? and When was it initiated? Due to the number of factors affecting outcomes, large multicentered prospective studies involving a large number of participants are needed.

The largest study of sport concussion ever conducted began in 2015 by the Care Consortium (www.careconsotium.net). The Care Consortium is a joint effort by the National Collegiate Athletic Association (NCAA) and the US Department of Defense involving 30 NCAA institutions as data collection sites. The consortium aims to conduct prospective, longitudinal research to study the natural history of concussion and conduct advanced studies integrating biomechanics, neuroimaging, and neurobologic and genetic markers of injury. Over the initial 3-year period, more than 39,000 baseline and 2800 postinjury assessments have been performed. Additionally, researchers are looking to examine athletes over the long term, making this one of the most important research endeavors ever conducted. Projects such as this are the key to advancing the science of sport concussion genetics.

### Table 27.3 (Cont.)

<table>
<thead>
<tr>
<th>Protein</th>
<th>Gene (abbreviation)</th>
<th>Variant</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain–derived neurotrophic factor</td>
<td>Brain–derived neurotrophic factor (BDNF)</td>
<td>rs6562</td>
<td>113 participants (75 with mild TBI and 38 healthy; ~33 years of age; 61% male) were assessed using five different cognitive assessments. The authors found that the Met allele was associated with slower processing speed in the entire group, but not within the mild TBI group specifically. Other SNPS in linkage disequilibrium may increase risk of slower processing speeds after mild traumatic brain injury (36)</td>
</tr>
</tbody>
</table>

### References


11. Feudtner C and Miles SH. Traumatic brain injury news reports and participation in high school tackle football. *JAMA Pediatrics* 172: 492–494, 2018


