

# Systematic Review of Genetic Risk Factors for Sustaining a Mild Traumatic Brain Injury

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## Abstract

This systematic review examined the association between genetics and risk for sustaining a traumatic brain injury. We retrieved articles published in English from 1980 to July 2016 obtained from the online databases PubMed, PsycINFO®, MEDLINE®, Embase, and Web of Science. In total 5903 articles were identified, 77 underwent full-text screening, and 6 were included in this review. Five studies examined the risk of concussion associated with apolipoprotein E alleles (APOE- $\epsilon$ 2,  $\epsilon$ 3,  $\epsilon$ 4), and polymorphisms of the APOE promoter (rs405509), brain derived neurotrophic factor (BDNF, rs6265), and dopamine receptor D2 (DRD2, rs1800497) were each considered in two studies. Microtubule associated protein tau (TAU exon 6 polymorphisms His47Tyr [rs2258689] and Ser53Pro [rs10445337]), and neurofilament heavy (NEFH, rs165602) genotypic variants, were the focus of single studies. No study showed an increased risk associated solely with the presence of the APOE- $\epsilon$ 4 allele, nor were there any significant findings for the NEFH, TAU, or DRD2 genotypic variants. Two studies examined the APOE promoter -219G/T polymorphism in athletes, and both found an association with concussion. Both BDNF studies also found a significant association with concussion incidence; United States soldiers with the Met/Met genotype were more likely to report a history of concussion prior to deployment and to sustain a concussion during deployment. We conclude that the APOE promoter -219G/T polymorphism and the BDNF Met/Met genotype might confer risk for sustaining a TBI. Based on research to date, the APOE- $\epsilon$ 4 allele does not appear to influence risk. More research is needed to determine if these findings replicate.

**Keywords:** apolipoprotein E; concussion; genotype; mild traumatic brain injury; risk

## Introduction

THERE IS CONSIDERABLE INTEREST in determining the extent to which genetic factors influence the outcome from traumatic brain injury (TBI) in children<sup>1,2</sup> and adults.<sup>3</sup> Most of the studies have examined the apolipoprotein E4 allele (APOE- $\epsilon$ 4) and its association with outcome from injury.<sup>4,5</sup> The gene (APOE) has three main alleles, APOE- $\epsilon$ 2, APOE- $\epsilon$ 3, and APOE- $\epsilon$ 4. APOE- $\epsilon$ 3 is the most common; APOE- $\epsilon$ 2 and APOE- $\epsilon$ 4 are considered the rare alleles. Decades of literature, including several meta-analyses, confirm that the presence of APOE- $\epsilon$ 4 correlates with worse long-term outcome from TBI.<sup>5–8</sup> The literature on whether genetics influence acute outcome, or the initial severity of injury is, however, mixed and contradictory, and when aggregated and meta-analyzed

there was no significant association.<sup>5</sup> There is also an interest in how genetics might influence the underlying pathophysiology of injury,<sup>9</sup> neuroplasticity,<sup>10</sup> as well as individual differences in cognitive, social, and emotional functioning that could relate to outcome following injury.<sup>11</sup>

Far less research has been devoted to whether genetics influence risk for sustaining a TBI in athletes, civilians, or active duty military service members. Mechanisms by which genetics could be associated with risk for sustaining a TBI include 1) influencing underlying brain physiology and susceptibility to neurotrauma; 2) increasing the risk for specific diagnoses that also are associated with increased risk for sustaining a TBI, such as attention-deficit/hyperactivity disorder (ADHD),<sup>12</sup> and substance abuse;<sup>13,14</sup> and 3) influencing behaviors that might increase risk for TBI, such as

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impulsivity, risk-taking, and aggression.<sup>13,15,16</sup> The purpose of this systematic review is to examine the world literature on the association between genetics and risk for sustaining a TBI in athletes, civilians, active duty service members, and veterans.

## Methods

The review was conducted in three stages. In stage 1, articles were retrieved via online database searching, hand-searching reference lists, and performing cited reference searches (see Fig. 1). The current review examined all articles published in English from 1980 up to July 2016 pertaining to genetic risk and TBI. The online databases of PubMed, PsycINFO®, MEDLINE®, Embase, and Web of Science were searched, using the key search terms: genotype, genetics, apolipoprotein E, APOE, APOE-ε4, ε4 allele, brain-derived neurotrophic factor, BDNF, Dopamine D2, DRD2, met genotype, met; in combination with injury terms: craniocerebral trauma, brain injuries, brain concussion, concuss\*, traumatic brain injury, TBI, mild traumatic brain injury, mTBI; in combination with risk-related terms: risk, risk\*, risk factors, risk reduction behavior, risk assessment. The reference lists of articles retrieved for inclusion in the review were hand searched to identify other relevant articles. Key articles retrieved via online databases and through hand searching reference lists were also used for further searches using the Web of Science Cited Reference function. During stage 2, the titles and abstracts of articles were reviewed to

assess eligibility for inclusion in this review. Articles were regarded as relevant and warranting inclusion if they were experimental studies examining genetic risk factors for traumatic brain injury of any severity, through any mechanism, and in humans. Studies were included whether they were conducted with acute or long-term TBI patients (i.e., there were no restrictions placed on time elapsed since injury) and regardless of examination techniques used to assess these individuals (e.g., neuroimaging, symptom checklist, balance testing, or neuropsychological testing). Where there was uncertainty about whether a study should be included based on the review of the title and abstract, the full article was retrieved. All eligible articles were independently assessed for quality using a standardized quality assessment checklist selected for its generic comprehensiveness and currency,<sup>17–19</sup> and supplemented with additional genetic measures (see Table 1).

## Data extraction

Subsequent to the process described, we extracted from the identified studies the data that pertained to 1) participant demographics; 2) characteristics of participants (sport, exposure to concussion, concussive history); 3) methodological details (technique and data collection); 4) time lapsed (immediate [minutes to hours], acute [1–14 days], subacute stage [2–4 weeks], prolonged and chronic stages [> 4 weeks]); and 5) results of the study.

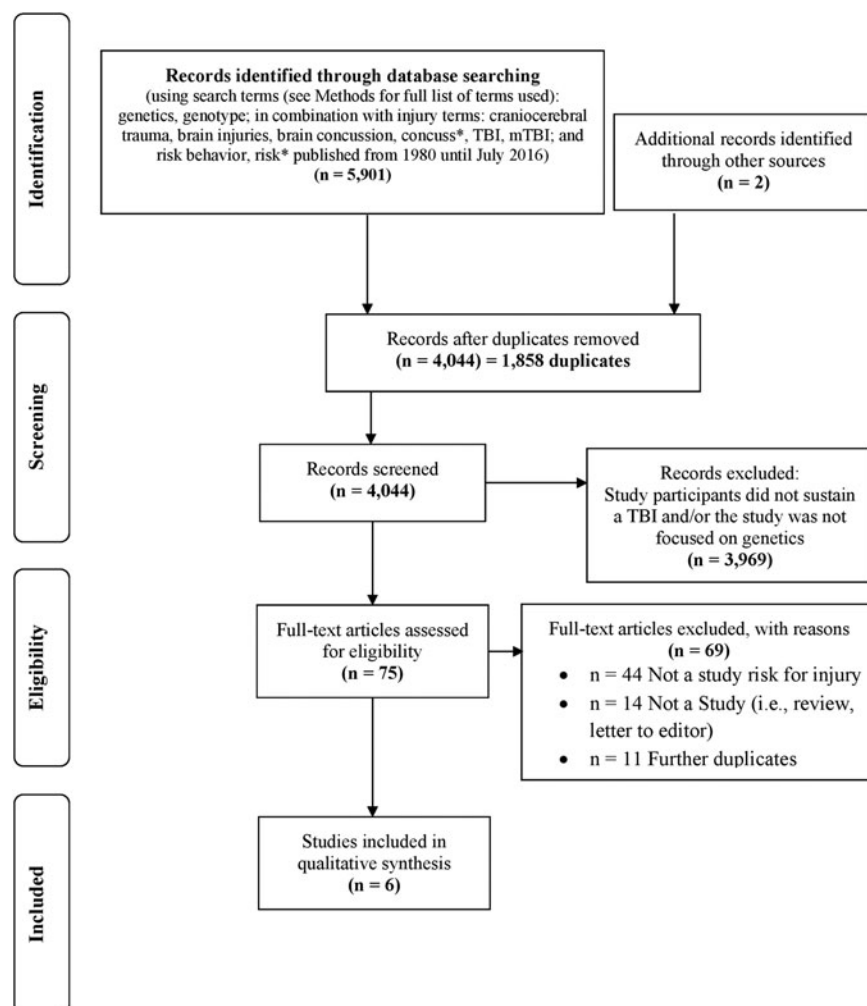


FIG. 1. PRISMA flow diagram.

TABLE 1. QUALITY ASSESSMENT RATINGS

Quality assessment rating criteria questions	Terrell <i>et al.</i> <sup>23</sup>	Kristman <i>et al.</i> <sup>25</sup>	Tierney <i>et al.</i> <sup>24</sup>	McDevitt <i>et al.</i> <sup>26</sup>	Dretsch <i>et al.</i> <sup>20</sup>	Dretsch <i>et al.</i> <sup>21</sup>
1. Was the research question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the selection of study subjects/patients free from bias?	Yes	Yes	Yes	Yes	Yes	Yes
3. Were study groups comparable?	Yes	Yes	No	Yes	Yes	Yes
4. Was method of handling withdrawals described?	Yes	Yes	Yes	Yes	Yes	Yes
5. Was blinding used to prevent introduction of bias?	Yes	Yes	Yes	Yes	Yes	Yes
6. Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Where intervening factors described?	Yes	Yes	Yes	Yes	Yes	Yes
7. Were outcomes clearly defined and the measurements valid and reliable?	No	Yes	No	Yes	Yes	Yes
8. Was Hardy–Weinberg equilibrium tested?	Yes	No	No	No	Yes	Yes
9. Was racial heterogeneity included in the analysis?	Yes	No	No	No	Yes	Yes
10. Was a validation group used?	No	No	No	No	No	No
11. Was the statistical analysis appropriate for the study design and type of outcome indicators? <sup>a</sup>	Yes <sup>a</sup>	Yes	Yes <sup>a</sup>	Yes	Yes <sup>a</sup>	Yes <sup>a</sup>
12. Were conclusions supported by results with biases and limitations taken into consideration?	Yes	Yes	No	Yes	Yes	Yes
13. Is bias resulting from the study's funding or sponsorship unlikely?	Yes	Yes	Yes	Yes	Yes	Yes
Overall Quality Rating	Neutral	Positive	Neutral	Positive	Positive	Positive

<sup>a</sup>However, statistical adjustment was not performed for the multiple comparisons tested.

## Results

A total of 5901 articles were identified using the search strategy outlined in Figure 1. After all the identified citations were screened, 75 were retrieved and further screened for eligibility. Of the 75 articles, 44 were excluded on the basis that they did not examine genetics as a risk for traumatic brain injury and 14 were excluded because they were review articles or commentaries; 11 duplicates were identified on closer inspection. The final outcome following this screening process resulted in the inclusion of four articles (see Fig. 1). One article was identified via hand searching. A final article, written by our research team and recently accepted for publication, also was included, bringing the total to six articles. The methodological quality of these six articles was reviewed by two authors (A.J.G. and W.J.P.) and is summarized in Table 1.

Sports concussion in collegiate level young adults was the focus of four studies, and active duty US soldiers the focus of the other two. A total of 805 college athletes, the majority male, were represented in the sport studies. A total of 230 soldiers, including 221 men and 9 women, were included in one of the military studies,<sup>20</sup> and 458 in the other study of which 28 were women.<sup>21</sup> Five studies examined the risk of concussion associated with APOE polymorphisms (rs429358 and rs7412),<sup>20,22–25</sup> while genotypic variants of the APOE promoter (rs405509),<sup>23,24</sup> brain derived neurotrophic factor (BDNF, rs6265), and dopamine receptor D2 (DRD2, rs1800497)<sup>20,21</sup> were each considered in two studies. Microtubule associated protein Tau (TAU exon 6 polymorphisms His47Tyr [rs2258689] and Ser53Pro [rs10445337]),<sup>23</sup> and neurofilament heavy (NEHF) genotypic variants,<sup>26</sup> were the focus of single studies.

Two studies were prospective<sup>20,25</sup> and neither found an association between the presence of APOE-ε4 and the incidence of TBI. Kristman and coworkers<sup>25</sup> followed 318 athletes engaged in diverse collegiate sports for up to 4 years, ascertaining concussions with a locally developed concussion assessment tool, administered on field by a sport medicine specialist, and then confirmed by a

physician.<sup>25</sup> Supplementing this approach, the authors also elicited concussion history over the past season by querying if the athlete had experienced a concussion during play that was missed by the athletic team or not reported by the athlete. Using this protocol, a total of 28 concussions were documented, augmented with another 20 concussions that were elicited with the end of season self-report. The primary outcome measure was time to first concussion using a Kaplan–Meier survival curve analysis. Using a dominant genetic model, the adjusted hazard ratio for the presence of the APOE-ε4 on the time to medically documented concussion ( $n=28$ ) was not significant at 1.06 confidence interval (CI) (0.41, 2.72). The analysis was repeated with the inclusion of self-reported concussion ( $n=48$ ), and the finding remained nonsignificant (hazard ratio [HR] = 0.96 CI [0.5, 1.85]).

Dretsch and coworkers<sup>20</sup> prospectively followed 230 United States soldiers through a 1 year combat deployment to the Middle East during Operation Iraqi Freedom (OIF)/Operation Enduring Freedom (OEF). In addition to APOE-ε4 carrier status (rs429358 and rs7412), they also stratified concussions by common polymorphisms of the DRD2 (rs1800497) and BDNF (rs6265) genes using a co-dominant model.<sup>20</sup> There were 24 concussions in total, translating to an incidence of 10.6%. Concussions were ascertained following deployment by self-report using the Brief Traumatic Brain Injury Screen (BTBIS),<sup>27</sup> and at minimum, a TBI was operationalized as an injury-related event with a resultant altered state of consciousness. There were no significant associations between any of the APOE or DRD2 genotypes and concussion risk. There was a significant association between self-reported concussions in those soldiers with the BDNF Met/Met genotype (four concussions in 24 soldiers; 16.7%), as compared with those without this variant (nine concussions in 203 soldiers; 4.4%);  $\chi^2(1)=5.95$ ,  $p=0.015$ .

In a more recent study by Dretsch and coworkers,<sup>21</sup> the polymorphisms of APOE-ε4 (rs429358 and rs7412), DRD2 (rs1800497), and BDNF (rs6265), genes were stratified, using a co-dominant model, for 458 soldiers preparing for deployment (OIF/OEF). Self-report concussion history was collected using the BTBIS to explore

the frequency of the given genotypes based on the number of concussions. For those with BDNF Met/Met genotype, 57.9% (11/19) had a history of one or more prior concussions, which was significantly more than the 35.6% (154/432) of participants with prior concussion who did not possess the Met/Met genotype ( $\chi^2[1] = 3.88$ ,  $p = 0.049$ , odds ratio [OR] = 2.48). In contrast, APOE and DRD2 genotypes were not associated with risk for past concussions.

Tierney and coworkers<sup>24</sup> examined the relationship of concussion to the rare alleles of two APOE genotypes using a dominant genetic model in 196 athletes.<sup>24</sup> They ascertained concussion by self-report "operationally defined as an injury that was documented by a physician or certified athletic trainer." The rare alleles of interest were APOE- $\epsilon 2$  and APOE- $\epsilon 4$  in APOE (rs429358 and rs7412) and the T allele of APOE promoter -219G/T (rs405509). In their analysis, they investigated differences between carriers of these rare alleles versus non-carriers with respect to concussion history.

Tierney and coworkers found that carrying at least one copy of either the APOE- $\epsilon 2$  or APOE- $\epsilon 4$  allele, or at least one copy of these alleles in combination with the T allele of -219G/T was *not* associated with an increased risk of concussion; however, those few subjects possessing the APOE- $\epsilon 2/\epsilon 4$  genotype, *in addition to* the T allele appeared to be at increased risk ( $p = 0.05$ , OR = 9.8, CI [1.0–96.6]). In addition, the presence of the T allele of -219G/T was associated with an increased risk of multiple concussions, with eight of nine athletes who experienced more than two concussions carrying the T allele of -219 G/T ( $p = 0.04$ , OR = 8.4 CI [1.03–68.8]). A possible confound, however, was a trend toward increased potential for concussion exposure in subjects carrying the T allele, because they had more years of playing exposure ( $10.2 \pm 4.1$  years) than non-carriers ( $9.0 \pm 4.5$  years,  $p = 0.054$ ).

Terrell and coworkers<sup>23</sup> ascertained concussions in 195 athletes through an investigator-assisted concussion history questionnaire in which concussion was defined using the American Orthopedic Society for Sport Medicine Concussion Workgroup definition,<sup>28</sup> the salient component being "a transient alteration in neurological function that may last 15 seconds or more."<sup>23</sup> You may experience loss of consciousness, memory loss, confusion/disorientation, headache, dizziness, 'being in a fog', nausea, vomiting, increased fatigue, visual disturbances such as flashes of light or hear 'bells ringing.'" Through the questionnaire the investigators were also able to divide concussions by severity, using the Cantu<sup>29</sup> and American Academy of Neurology (AAN) grading scales.<sup>30</sup> They tested the effect of the APOE alleles ( $\epsilon 2$ ,  $\epsilon 3$ ,  $\epsilon 4$ ), the APOE promoter -219G/T variant, and TAU exon 6 polymorphisms His47Tyr (rs2258689) and Ser53Pro (rs10445337) on concussion risk using a co-dominant model. Only the APOE promoter TT genotype was significantly associated with a history of one or more concussions ( $p = 0.03$ , OR = 2.7 CI [1.1–6.8]), and this genotype also had a stronger association with more severe (AAN grade 3) concussions (OR = 7.2, CI [1.2–41.7]). Interestingly, when stratified by number of previous concussions, APOE promoter TT genotype was only significantly associated with a history of one prior concussion (OR = 4.2 CI [1.4–12.1]), but not to multiple concussions (OR = 1.5 [0.4–6.1]); although this finding is limited by small sample size (only five subjects with the TT genotype experienced more than one concussion).

The results from four studies were aggregated to examine the association between APOE- $\epsilon 4$  and concussion. Data from the smaller study by Dretsch and coworkers,<sup>20</sup> although collected at a different time point (i.e., post-deployment), were not included

because these same subjects were included in the larger pre-deployment study.<sup>21</sup> This resulted in a total of 1147 participants, of whom 876 were APOE- $\epsilon 4$  negative and 271 carried at least one APOE- $\epsilon 4$  allele (APOE- $\epsilon 4$  positive). Stratifying concussion by APOE- $\epsilon 4$  carrier status revealed 533 participants who were APOE- $\epsilon 4$  negative and had no concussion history, 343 who were APOE- $\epsilon 4$  negative and had a history of at least one concussion, 155 who were APOE- $\epsilon 4$  positive with no concussion history, and 116 participants who were APOE- $\epsilon 4$  positive and had a history of concussion. For the aggregated data, there was no significant association between the presence of the APOE- $\epsilon 4$  allele and concussion ( $\chi^2[1, 1,147] = 1.15$ ,  $p = 0.28$ , OR = 1.16, 95% CI = 0.88–1.55).

McDevitt and colleagues<sup>26</sup> examined 48 National Collegiate Athletic Association division 1 football or soccer collegiate athletes with a self-reported concussion history, using a case-control methodology, to test an association between the NEFH gene polymorphism (rs165602) and concussion risk. Concussion was defined as trauma to the head requiring medical attention and resulting in restriction of athletic participation for at least 1 day. The authors found no association with one concussion, multiple concussions, duration of signs or symptoms after concussion, or time to return to play (all  $p > 0.15$ ).

## Discussion

This systematic review identified six studies that have reported on genetic risk for sustaining a TBI. Polymorphisms that were examined include those comprising the APOE, BDNF, TAU, DRD2, and NEFH genes. Most of these genetic polymorphisms were not associated with concussion risk, with the exception of genotypic variants of the APOE promoter and the BDNF gene, which were associated with a greater risk of concussion. Although traditionally thought to confer poor prognosis *following TBI*,<sup>5–8</sup> there is *no* study in the literature that supports the presence of APOE- $\epsilon 4$ , in isolation, as a risk factor for sustaining a TBI. Five studies included in this review examined this association and all found a null result.<sup>20,21,23–25</sup> Moreover, aggregating and analyzing the participants from four of these studies revealed no significant association. One study, by Tierney and coworkers,<sup>24</sup> reported an increase in risk if the  $\epsilon 4$  allele was paired with a highly rarefied combination of *both* an APOE- $\epsilon 2$  allele *and* the APOE -219G/T promoter variant (GT or TT). There should be caveats, however, to the authors' conclusion that this rare combination does indeed impart risk. First, this conclusion was based on a significant finding (at exactly  $p = 0.05$ ) in a total of only four subjects, three of whom had a concussion. Second, multiple statistical analyses were performed with no adjustments for multiple comparisons. Therefore, this finding requires replication.

Two studies examined the effect of the APOE -219G/T promoter polymorphism on concussion risk, and both found an association. Considering the -219G/T promoter TT genotype in isolation, Terrell and coworkers<sup>23</sup> found that it was associated with increased risk of sustaining a single concussion, but not multiple concussions. Following a dominant model, Tierney and coworkers<sup>24</sup> focused on T carriers and found the reverse, namely that the APOE -219G/T allele conferred a risk for a history of multiple injuries, but not a single concussion, unless paired with *both* an APOE- $\epsilon 2$  and APOE- $\epsilon 4$  allele.<sup>24</sup> Taken together, the literature does indicate some support for the theory that this promoter variation does incur a risk of concussion, but with a low level of certainty given the small samples studied.

The APOE promoter -219G/T polymorphism is a transversion of the common guanine nucleotide to a thymine nucleotide 219 base pairs upstream of the APOE gene, within the APOE promoter. This is thought to result in differential binding of nuclear proteins and subsequently lower levels of APOE transcription.<sup>31</sup> APOE promoter polymorphisms have been linked to worse outcome after TBI,<sup>32</sup> increased deposition of beta amyloid,<sup>33</sup> variant cortical anatomy,<sup>34</sup> central nervous system (CNS) vascular vulnerability to spasm and bleeding,<sup>35,36</sup> and lower cognitive performance in areas such as attention and executive function.<sup>37</sup> Theoretically, this promoter variant could be linked with 1) increased risk of sustaining an injury (via worse attention or executive function), 2) somehow amplifying the consequences of trauma such that the minimum clinical threshold for concussion is reached, or 3) being associated with vulnerable brain anatomy. Amplification, for example, could occur in the form of increased cerebral vasospasm after TBI. Cerebral vasospasm is a known immediate complication of TBI, and produces symptoms that overlap with traditional concussion such as confusion and headache, thus making the diagnostic threshold of concussion easier to meet. Anatomic vulnerability is also a possibility, because the APOE -219G/T promoter polymorphism has demonstrated anatomical correlations including decreases in cortical gray matter, which theoretically could decrease CNS reserve, resulting in less force being necessary to cause symptoms.

The studies with active duty soldiers examined the DRD2 gene (rs1800497).<sup>20,21</sup> These polymorphisms influence striatal D2 receptor density<sup>38</sup> and the minor allele (A1) has been associated with negative cognitive outcomes after TBI.<sup>39–41</sup> Variation in DRD2 could conceivably increase the risk of brain injury in civilians or service members in several ways. The D2 receptor is involved in a plethora of neuropsychiatric and cognitive processes, and has been ascribed both neuroprotective and neurotoxic roles.<sup>42</sup> Genetic studies have also linked variations in the DRD2 gene to substance use,<sup>43</sup> aggression,<sup>44</sup> and impulsivity,<sup>45</sup> all of which could increase the risk for brain trauma. Although ecologically there is reason to presuppose that DRD2 receptors might in some way be connected to risk of brain injury, so far the two studies in the literature examining the DRD2 gene did not find an effect.

The TAU gene has at least 50 known pathological mutations,<sup>46</sup> many of which have been shown, in animals, to influence outcome after TBI.<sup>47</sup> In humans TAU mutations are causally related to frontotemporal dementia, and likely many other neurodegenerative diseases.<sup>48</sup> Curiously, the only study to explore a link between TAU genotype and risk of concussion chose two nonpathogenic TAU polymorphisms with no known function; namely, His47Tyr and Ser53Pro on exon 6, and found no effect on concussion risk. The authors provide no rationale for choosing these particular polymorphisms. The appropriate inference, therefore, is that *these particular* TAU variants were not associated with increased concussion risk. Broader deductions about the role of the TAU protein, or the role of the many known pathological TAU mutations in concussion, cannot be meaningfully extrapolated.

Multiple neurodegenerative pathologies have been linked to neurofilament expression (for a review see the study by Wang and coworkers<sup>49</sup>). Neurofilaments are a major constituent of the neuronal cytoskeleton, and they provide protection against mechanical stress, play a role in organizing various cellular compartments and organelles, and are instrumental in growth and myelination.<sup>50</sup> Neurofilament taxonomy is weight based, with light, intermediate, and heavy (NEHF) forms. McDevitt and colleagues examined the NEHF polymorphism rs165602, which is a missense mutation at position 2414 on exon 4. This polymorphism was chosen because it

is prevalent in the population (> 20%) and has a substantial likelihood of meaningfully altering cytoskeletal integrity, but it is not associated with disease that would prevent participation in college athletics.<sup>26</sup> Although there was no association of this NEFH variant with concussion incidence or symptoms, the authors appropriately forward the caveat that, given the single polymorphism studied, the role of the NEFH gene in concussion remains unknown.

BDNF is ubiquitously involved in neuropsychiatric disease, plays a central neuroplastic role in the adult brain, and has links to neurocognitive function. The Val66Met polymorphism represents a substitution of the common valine amino acid for a methionine amino acid at codon 66 of the BDNF gene. This substitution is thought to influence activity-dependent secretion of BDNF by perturbing intracellular trafficking.<sup>51</sup> The methionine substitution appears to function in a dose-dependent fashion so that the homozygous genotype (BDNF Met/Met) results in a greater reduction in BDNF secretion than the heterozygous genotype (BDNF Val/Met).<sup>52</sup> The literature examining the association of the Val66Met polymorphism with outcome after TBI is limited and mixed, with some studies reporting deleterious effects,<sup>41,53</sup> whereas others suggest a protective role in the recovery of executive function, general intelligence, and cranial nerve function.<sup>54–57</sup> BDNF polymorphisms have also been linked with character traits that may predispose individuals to greater risk of injury such as hyperactive-impulsivity,<sup>58</sup> proclivity to addictions,<sup>59,60</sup> high-risk sport participation,<sup>61</sup> and aggression.<sup>62</sup> One of the military studies<sup>21</sup> showed a link with BDNF Met/Met genotype and character traits; namely, greater aggression and hostility. However, these factors were not independent predictors of lifetime concussion. Theoretically, BDNF could also act to increase concussion ascertainment by lowering the threshold for loss of consciousness or memory impairment, because polymorphisms of the BDNF gene are known to affect autonomic nervous system function<sup>63</sup> and hippocampal function.<sup>51</sup> Therefore, there is a pathophysiological rationale for why the BDNF Met/Met genotype could predispose to either neurotrauma or to an aberrant neurochemical cascade leading to a lower threshold for mild TBI. Two military studies that stratified concussion risk by BDNF genotype found a significant association with the Met/Met polymorphism, although, as the authors stated, replication of the findings in a larger sample is needed.<sup>20</sup>

The extant literature on genetics and concussion risk is composed of only six studies, and those six studies provide some, albeit weak, support for an increased risk of concussion associated with the APOE promoter -219G/T polymorphism (rs405509) and the BDNF polymorphism (rs6265). Despite the well-known association with long-term outcomes, and some emerging evidence for an influence on acute symptoms,<sup>64,65</sup> there is currently no supportive evidence for a role of the APOE-ε4 allele in the risk for mild TBI. The field of genetics and concussion risk is in its formative phase, and clarity will only come with larger population and validation studies. In the interim, future research could consider a variety of mechanisms by which genetics might be associated with risk for sustaining a TBI including: 1) influencing underlying brain physiology and susceptibility to neurotrauma, 2) increasing the risk for specific diagnoses that also are associated with increased risk for sustaining a TBI, such as ADHD, and substance abuse, and 3) influencing behaviors that might increase risk for TBI, such as impulsivity, risk taking, and aggression.

#### Author Disclosure Statement

G.L.I. has been reimbursed by the government, professional scientific bodies, and commercial organizations for discussing or

presenting research relating to mild traumatic brain injury (mTBI) and sport-related concussion at meetings, scientific conferences, and symposiums. G.L.I. has a clinical practice in forensic neuropsychology involving individuals who have sustained mTBIs. G.L.I. has received honorariums for serving on research panels that provide scientific peer review of programs. G.L.I. is a co-investigator, collaborator, or consultant on grants relating to mTBI funded by several organizations. W.J.P. has a clinical practice in forensic neuropsychiatry involving individuals who have sustained mTBIs. A.J.G. has a clinical practice in neuropsychology involving individuals who have sustained sport-related concussion (including current and former athletes). He has operated as a contracted concussion consultant to the Australian Rugby Union (ARU) from July 2016. He has received travel funding from the Australian Football League (AFL) to present at the concussion in Football Conference in 2013. Previous grant funding includes the NSW Sporting Injuries Committee, the Brain Foundation (Australia), and the Hunter Medical Research Institute (HMRI), supported by Jennie Thomas. He is currently funded through the HMRI, supported by Anne Greaves, and the University of Newcastle's Priority Research Centre for Stroke and Brain Injury. All other authors report no conflict of interest. The opinions, interpretations, conclusions, and recommendations are those of the authors and are not necessarily endorsed by the United States Army and/or the United States Department of Defense.

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