Genetics in Concussion

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Alexa E. Walter

Concussion and the Role of Genetics

Concussion, or mild traumatic brain injury (mTBI), is a heterogenous brain trauma that is currently challenging to clinically diagnose and treat. mTBI, or sport-related concussion (SRC), is defined as a traumatic brain injury induced by biomechanical forces with common features including (a) a direct blow to the face, head, neck, or body with force transmitted to the head; (b) rapid onset of short-lived impaired neurological function that resolves spontaneously; and (c) a range of clinical symptoms that may or may not involve the loss of consciousness [1]. These injuries are diagnosed by medical providers, typically using the individual's subjective reporting of symptoms as the vast majority of computerized tomography and magnetic resonance imaging findings are negative [2]. The large majority of individuals recover from the injury within 7–10 days [3]; however, there is a growing population (10–20%) whose recovery is more delayed and develops into post-concussion syndrome [4].

Premorbid status has been shown to affect both risk [5] and recovery of SRC [6]. Risk of concussion has been associated with prior concussion history, participation in collision sports for men, participation in soccer for women, being female, age, and previous history of migraine headache (for a review see [5]). More well studied are premorbid characteristics and their role in recovery; however, these findings are very mixed (for a review see [6]).

Due to the heterogeneity of this injury, it has been assumed that genetic variability may play a role in the evolution of injury. The increased susceptibility to injury or different patterns of recovery after an injury has become a recent area of research in this field. The role of genetics has been well documented in Alzheimer's disease [7], Parkinson's disease [8], amyotrophic lateral sclerosis [9], and severe traumatic brain injury [10], but the link to concussion or mTBI is still relatively unknown.

A. E. Walter (✉)
Department of Kinesiology, Pennsylvania State University, University Park, PA, USA

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Therefore, this chapter only focuses on the link of genetics to concussion or mTBI, including both the link to the previous history of injury/risk of injury or to an individual's recovery after injury.

Brief Biology of Genetics

Individuals inherently have variation in their DNA, called polymorphisms, due to alterations in the sequence. These polymorphisms are defined as one of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair, termed single-nucleotide polymorphisms (SNPs) (Fig. 14.1). The majority of polymorphisms do not affect gene function; however, some can change gene expression or function.

SNPs are the simplest form of genetic differences, altering one single nucleotide pair and commonly occur in an individual's DNA (one in every 1000 nucleotides). These SNPs can occur in the exons (coding regions) or introns (non-coding regions) thereby affecting the resulting protein in different ways (Fig. 14.2). While SNPs are

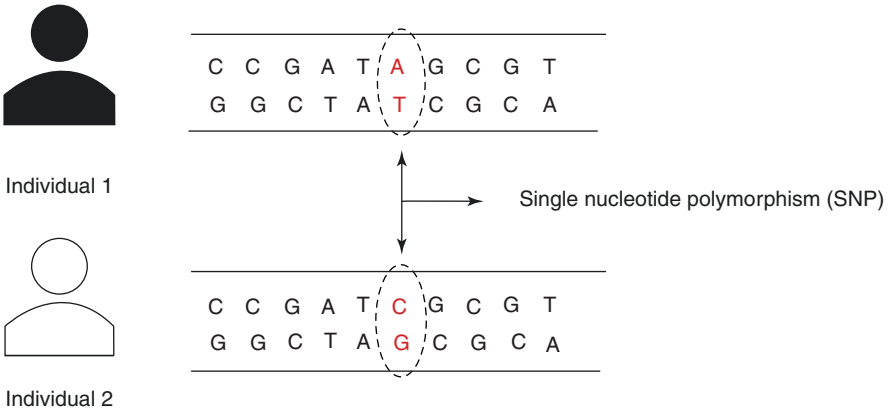

Fig. 14.1 Representation of a single-nucleotide polymorphism

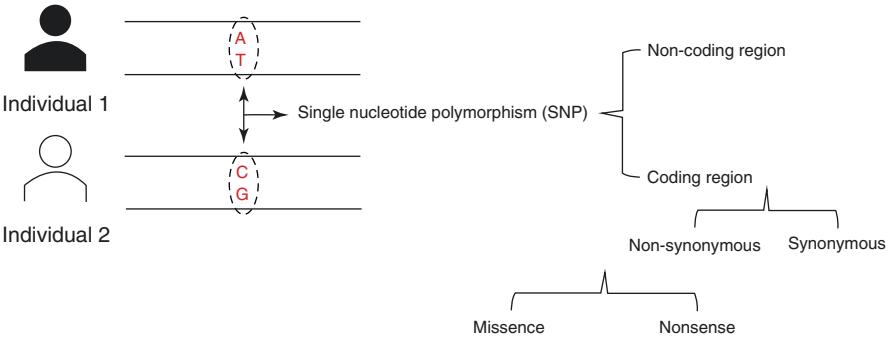

Fig. 14.2 Types of SNPs based on their location on the exon or intron

commonly used when studying genetics, other methods exist as well. Variable number tandem repeats (VNTRs) are short sequences of DNA (20–100 bp) repeated in tandem, while short tandem repeats (STRs) are sequences of DNA, normally 2–7 bp, that are repeated in tandem. Genome-wide association studies (GWAS) study the entire genome and identify all variable SNPs. GWAS is currently the most inclusive way to study genetics.

While all of these methods are feasible experimental techniques, the use of SNP analysis in this field is by far the most common. To our knowledge, no GWAS studies have been done to date on mTBI or concussion, somewhat limiting the potential utility of these findings in the larger context of understanding injury. The following text aims to summarize the current status of the literature involving SNP or VNTR genotypes and their association with concussion or mTBI in both athletic and military populations.

APOE

Apolipoprotein E (*APOE*) is the most studied gene in relation to concussion and mTBI. apoE (the protein) binds to various fats to form a lipoprotein which then packages cholesterol and other fats and carries them through the bloodstream. It is the major apolipoprotein produced in the central nervous system and is synthesized by astrocytes and microglial and during times of stress, neurons [11]. It exists in three isoforms coded by three alleles (ε2, ε3, ε4) [12, 13], and ε4 has been the focus of much neurological research.

In regard to the risk of obtaining a concussion or mTBI, there are mixed findings on the involvement of *APOE*. When examining the role of ε4 (rs7412 and rs429358) in military populations, Dretsch and colleagues ran two studies, one studying 231 soldiers [14] and the other on 438 soldiers [15], and found no link between genotype and previous mTBI history. There are numerous studies examining the link between ε4 and concussion history in college-aged athletes. The majority found no significant link [16–21], while one study ($n = 1056$) found that the ε4 allele was associated with a reduced risk of concussion [22]. Only one study, however, reported a significant association between a history of concussion and having all of the *APOE* rare alleles [18].

When examining the *APOE* G-219T promoter region (rs405509) in college athletes, Cochrane and colleagues found no relationship to previous concussion history [20]. However, Abrahams and colleagues when studying rugby players found that the TT genotype was associated with reduced concussion susceptibility [19]. Contradictory, Terrell and colleagues demonstrated in 195 college athletes that the TT genotype was associated with a threefold increase in risk for the history of concussion and a fourfold increased odds of concussion with loss of consciousness [17]. Tierney and colleagues also reported an association between the promotor minor allele (T allele) and experiencing more than two previous concussions [18].

Additional work has been done examining the link between the presence of the ε4 allele and recovery after injury. A study examining outcomes in children and

adolescents demonstrated a link between ε4 allele and lower GSC scores but no difference in neurocognitive ability or symptom presentation [23]. In studies on college athletes, Cochrane and colleagues ($n = 250$) demonstrated that individuals with the ε4 allele had slower reaction time, as measured by the ImPACT test, compared with non-ε4 carriers. There were no differences in cognitive results with the SNP for *APOE* G-219T promotor [20].

Work by Merritt and colleagues also demonstrated changes in neurocognitive scores with the presence of the ε4 allele. There were no differences when examining mean neurocognitive standardized scores; however, individuals with the ε4 allele had a greater number of impaired scores post-injury and had greater variability in their scores [24]. Furthermore, the same group of researchers showed that the presence of the ε4 allele can affect symptoms presentation post-injury, with those individuals with ε4 allele presenting with a higher severity of symptoms [25, 26].

BDNF

Brain-derived neurotrophic factor (*BDNF*) is involved with neuronal survival through its role in the growth and maturation of neurons [27]. Elevated *BNDF* activity level has the potential to restore neural connectivity and facilitate neuroplastic changes leading to adaptive repair [28]. In particular, the Met allele has been associated with abnormal storage and secretion of *BDNF* [29].

A study on college athletes ($n = 87$) revealed no relationship between *BDNF* and previous history of concussion [21]. Two studies involving military personnel demonstrated that individuals with the Met/Met genotype had an increased lifetime history of concussion ($n = 231$ [14] and $n = 458$ [15]).

DRD

Dopamine receptors (DRD) are G protein-coupled receptors involved with dopamine transmission and therefore are implicated in many processes including motivation, learning and memory, and fine motor control [30]. *DRD2* and *DRD4* are the more commonly studied variants of this gene. *DRD2* encodes the D2 subtype of the dopamine receptor, involved in the inhibition of adenylyl cyclase [31] and *DRD4* encodes the D4 subtype of the dopamine receptor, involved in the inhibition adenylyl cyclase [32]. They have been linked to various neurological and psychiatric concisions, including schizophrenia, Parkinson's disease, impulsivity, and attention-deficit hyperactivity disorder [33].

In a study on 250 college athletes, Cochrane and colleagues found no link between *DRD2* genotype (rs1800497) and concussion history or neurocognitive performance [20]. Similarly, in studies of military personnel, Drestsch and colleagues also found no association between *DRD2* genotype and prior concussions [14, 15].

A study by Abrahams and colleagues examined the role of both *DRD4* (rs1800955) and *DRD2* (rs12364283 and rs1076560) on previous concussion history; 301 rugby athletes from high school (junior) and professional (senior) teams demonstrated that the *DRD4* CC genotype was associated with decreased concussion susceptibility in the junior players. Furthermore, the TT and CT genotypes were associated with lower reward dependence behaviors in both the junior and senior players. The *DRD2* genotypes alone were not related to previous concussion history; however, when the combination of DRD2 alleles (A – C – C) was used they were associated with decreased concussion susceptibility in junior players [19].

COMT

Catechol-O-methyl transferase (*COMT*) is involved with the breakdown of dopamine in the prefrontal cortex [34, 35]. It plays a critical role in cell death, cellular dysfunction, and central nervous system inflammation and seems to be associated with impulsivity [20, 33].

When examining the link to previous concussion history, studies on college athletes revealed no link of genotype (rs4680) to previous concussion history [20, 21]. There was found to be a link to neurocognitive performance with individuals with Val/Val genotype having worse impulse control scores, as measured by ImPACT, as compared to Met-carrying individuals [20].

Interleukins

Interleukin 6 (*IL6*) is a pro-inflammatory cytokine and anti-inflammatory myokine secreted by T cells and macrophages. It is heavily involved in the immune responses as well as involved in encoding a pleiotropic cytokine involved in inflammation and maturation of B cells [36, 37]. The C allele has been associated with lower levels of *IL6* while the G allele is associated with higher levels [10, 38]. It has been implicated in mTBI pathology as it can suppress post-injury neuroinflammation, neuronal injury, and motor coordination deficits [39].

A study on 1056 college athletes demonstrated a significant association between the CC genotype for the IL-6 receptor (rs22281450) and increased concussion risk (3 times greater risk) [22]. There was no association between previous concussions and *IL6* (rs1800796). A study on 87 college athletes using rs1800795 also found no association between genotype and previous concussions [21].

Other work from Mc Fie and colleagues examined the role of *IL1B* (rs16944) and *IL6* (rs1800795) in 163 rugby players. There was no association with previous concussion history for either SNP; however, there was reduced symptom severity in both the rs16944 C allele and the rs1800795 C allele. When a combination of the two SNPs was used, the C-C inferred allele construct demonstrated higher symptom counts and prolonged symptom duration [40].

Tau

Microtubule-associated protein tau (MAPT) is encoded by the *MAPT*, or *TAU*, gene and is involved with tau protein regulation and binding to microtubules [41]. Two SNPs, rs2435211 and rs2435200, were examined in work by Abrahams and colleagues. Studying 303 rugby players from high school (junior) and professional (senior) levels, they found that rs2435200 AA genotype was associated with reduced susceptibility to multiple concussions (66%) and rs2435200 AG genotype was associated with increased susceptibility (134%) in senior players. rs2435211 was not associated with concussion history. The inferred haplotype using both SNPs (T-G) was associated with increased susceptibility for concussion in the senior players [42].

Work in 195 college athletes demonstrated no link between *Tau* Ser53Pro (rs2258689) or *Tau* His47Tyr (rs10445337) and previous concussion history [17]. This was further confirmed in a study of 1056 college athletes where neither *Tau* Ser53Pro nor *Tau* His47Tyr were associated with previous concussion [22].

Single Study Genes Examined

The following genes were only examined in 1 published study to our knowledge and are briefly summarized.

KIAA0319 *KIAA0319* is involved in the regulation of neuronal migration and cell adhesion, especially in the cerebral cortex [43, 44]. Using the SNP rs4504469, a study by Walter and colleagues on 87 college athletes demonstrated a significant association between genotype and previous concussion history. Individuals with the TT genotype had the lowest risk for previous concussion [21].

SLC17A7 The synaptic uptake of glutamate involves vesicular transporters, which are encoded by a subfamily of genes located on chromosome 19 (*SLC17A7*) and chromosomes 11 and 12. A study by Madura and colleagues found that the *SLC17A7* promotor (rs74174284) was not linked to the history of previous injury but was linked with recovery. Individuals with the G allele were 6.33 times more likely to have prolonged recovery rates and perform worse on motor speed tests, as measured by ImPACT, than individuals with the CC phenotype [45].

CACNA1A Calcium voltage-gated channel subunit alpha1 (*CACNA1A*) is involved with altering the configuration of Ca^{2+} pore-forming component and is primarily expressed in neuronal tissue. It is essential for proper neuron communication. A study by McDevitt and colleagues examined 40 athletes and found that individuals with the *CACNA1A* (rs704326) GG genotype had a prolonged recovery. The rs35737760 SNP had no association with the severity of injury [46].

NEFH Neurofilament heavy (*NEFH*) is important for mature axon function and may be involved in forming neuronal filamentous networks. In a study on 96 athletes, McDevitt and colleagues found no association between the rare allele, using rs165602, and history of concussion or symptom recovery [47].

GRINA2A N-methyl-D-aspartate receptor 2A sub-unit (*GRIN2A*) is an NMDA glutamate receptor subunit which has been implicated in influencing the magnitude of neuron dysfunction. A study on 87 athletes using rs3219790 examined the long allele (≥25 repeats) and the short allele (<25 repeats), and found that LL carriers were 6 times more likely to have a longer recovery compared to SS carriers [48].

CASP8 Caspase 8 (*CASP8*) encodes a cysteine-aspartic acid protease and is involved in the execution of cell apoptosis. A study by Mc Fie and colleagues examined rs3834129 in 163 rugby players and found no link between genotype and concussion history or severity [40].

DARC Duffy antigen receptor of chemokines (DARC) encodes a glycosylated membrane protein that is a non-specific receptor for many chemokines and is expressed on Purkinje cells [49, 50]. It has been shown to be upregulated at the BBB [51] and transports inflammatory chemokines across the BBB. In a study on 87 college athletes, using rs2814778, it was found to have no relation to previous concussion history [21].

PARP1 Poly(ADP-ribose) polymerase 1 (*PARP1*) modifies various nuclear proteins by poly ADP-ribosylation. This modification is DNA-dependent and is involved in the regulation of various cellular processes including differentiation, proliferation, tumor transformation, and cell damage and death [52, 53]. In a study on 87 college athletes, using rs3219119, there was no link between genotype and previous concussion history [21].

TPH2 Tryptophan hydroxylase 2 (TPH2) is involved in regulating the production of serotonin and has a role as a trans-synaptic messenger in axonal and dendritic growth [54, 55]. It has been linked to various psychiatric disorders as well as impulsivity and impaired response inhibition [33]. In a study on 87 college athletes, using rs1386483, there was no link between genotype and previous concussion history [21].

NGB Neuroglobin encodes oxygen-binding proteins expressed in the central and peripheral nervous system where it may be involved in facilitating oxygen transfer across the BBB and increase oxygen availability [56, 57]. In 87 college athletes, using rs3783988, there was no link between genotype and previous concussion history [21].

Implications and Future Work

The use of individuals' genetics for health purposes has been a growing area of research and it can be assumed that there is a link between concussion and genetics. However, at this time, the findings are still fairly limited. Studies involving genetics often are aiming to address susceptibility to concussion or risks associated with recovery from injury. While individual studies employ different techniques and gene selection, in combination they reveal some core findings that will be discussed.

Overall, there is limited evidence of a genotype predicting previous concussion history. *NGB, TPH2, PARP1, DARC, CASP8, GRINA2A, NEFH, CACNA1A*, and *SLC17A7* were all examined by single studies and showed no association with the risk of injury. However, *SLC17A7* (G allele), *CACNA1A* (GG phenotype), and *GRINA2A* (long allele, LL) were all associated with longer recoveries after injury. The only gene to predict previous concussion history was *KIAA0319,* with the TT genotype having the lowest risk of previous concussion [21]. In animal models, reduced expression of *KIAA0319* negatively affected the adhesion of neurons to the glial skeleton, impacting neuronal migration [43]. These findings, or lack of findings, should be replicated with further work and could suggest future theoretical frameworks to consider when studying the underlying physiology of injury or the role of genetics in susceptibility to concussion.

More commonly studied genes also revealed limited, and sometimes contradictory, findings in regard to risk of injury. *Tau* genotypes were found to be both not related [17, 22] and related to the susceptibility of injury [19]. *COMT* genotypes were found to be not related to the risk of injury [20, 21] but were related to worse outcomes after injury, specifically in individuals with the Val/Val genotype [20]. *BDNF* genotypes were found to have no association with concussion risk in college athletes [21] but did have an association in military populations. Specifically, individuals with the Met/Met genotype had increased history of concussion [14, 15]. *DRD2* also had no link to concussion risk both in athletic [19, 20] or military populations [14, 15]. *DRD4* was found to have an association with concussion risk with the CC genotype having decreased susceptibility to injury [19]. *IL6* was found to have no association with concussion risk [21, 40] and an increased risk for concussion specifically individuals with the CC genotype [22]. In regards to outcome, the C allele of *IL6* was associated with reduced symptom severity [40].

APOE is the most commonly studied gene in association with concussion risk and recovery. However, most studies show no link between *APOE*, specifically ε4, and concussion risk. Only one study [22] demonstrated that the ε4 allele was associated with a reduced risk of concussion. Use of the promoter region SNP of *APOE* also revealed highly mixed findings: one study shows no association [20], one shows reduced risk [19], and one shows increased risk [17].

Findings on recovery after injury and the association of *APOE* are more in agreement. Typically, the presence of ε4 is associated with worse outcomes after injury, specifically lower GCS scores [23], slower reaction times [20], and greater variability in neurocognitive testing results and more severity of symptoms [24–26].

As with the single study genes, these genes also reveal limited findings in regard to the risk of injury and warrant further exploration. Much larger sample sizes are needed as the sample sizes in the studies included are small for a genetic study (largest $n = 1056$) and this could be contributing to some of the mixed findings demonstrated. Ideally, more comprehensive and rigorous examinations of genotypes should be done instead of focusing on single SNPs. Using GWAS technology would provide a more comprehensive look at genetic susceptibility and the potential interactions that may exist as it is highly unlikely that one individual SNP is a risk factor. Instead, it is more likely that it is an interaction of many, maybe hundreds of, SNPs that is contributing to the high variability in risk of and recovery after injury.

Overall, these studies highlight the beneficial use of genetics as a growing field to consider when understanding injury susceptibility. However, the findings should be interpreted with some caution. Primarily these studies are done on college-aged male, contact sport athletes, and are done in small sample sizes. Additionally, as well as little diversity in sex, there is often little diversity in race. This limits the generalizability of results to other sports teams as well as the general population. Furthermore, the use of an individual's premorbid status as a binary screening tool for participation is currently cautionary. Each of these factors, at this time, should not be used in isolation, but instead should be evaluated to shed light on the observed variability seen and to gain insights into potential physiological consequences of injury.

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