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Relationship between the apolipoprotein E gene and headache following sports-related concussion

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ABSTRACT

Introduction: Headache is one of the most commonly reported and longest lasting symptoms that concussed athletes report, yet the etiology of headache symptoms following concussion is not entirely clear. The purpose of this study was to determine whether the e4 allele of the apolipoprotein E (APOE) gene influences the presence and severity of postconcussion headache. **Method:** Participants were composed of 45 concussed athletes and 43 healthy/nonconcussed athletes who were involved in a clinically based sports concussion management program. All athletes completed the Post-Concussion Symptom Scale (PCSS). The “headache” symptom from the PCSS was the primary outcome variable. Buccal samples were collected and analyzed to determine APOE genotype. **Results:** A significantly greater proportion of concussed e4+ athletes than e4– athletes endorsed headache. Furthermore, concussed e4+ athletes endorsed more severe headaches than e4– athletes. When examining the healthy/nonconcussed sample (i.e., athletes at baseline), results showed no differences between e4 allele groups with respect to the presence and severity of headache. **Conclusions:** These findings show that when compared to concussed e4– athletes, e4+ athletes are more likely to (a) endorse postconcussion headache and (b) report more severe headache symptoms following concussion. Conversely, it appears that the e4 allele does *not* influence baseline reports of headache. Thus, results suggest that those with the e4 genotype may be at a higher risk for experiencing headache-related difficulties only after a concussion is sustained.

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Concussed athletes often report many symptoms immediately following concussion, generally falling within the realm of physical/somatic, cognitive, affective, and sleep-related difficulties (Kontos et al., 2012; Pardini et al., 2004). When the broad range of symptoms expressed after a concussion is considered, headaches appear to be the most common symptom endorsed, with reports ranging from 57% to 93% (Erlanger et al., 2003; Guskiewicz, Weaver, Padua, & Garrett, 2000; Makdissi et al., 2010; Meehan, d’Hemecourt, & Comstock, 2010). In addition to headaches being the most frequently endorsed symptom, headaches are often the most severe (Merritt, Rabinowitz, & Arnett, 2015) and longest enduring (Conidi, 2012; Makdissi et al., 2010; Seifert, 2013) symptom reported following concussion. Given that this symptom is so widely experienced and often very

debilitating, and it occurs in the context of other neuropsychological consequences of concussion, understanding the etiology and manifestation of postconcussion headache is of principal concern.

The term “posttraumatic headache” (PTH) is applied to headache symptoms that occur following a traumatic brain injury (TBI) or concussion (Seifert & Evans, 2010). PTH has been further classified into (a) “acute PTH,” meaning that the headache symptoms developed within one week of the initial concussive event and resolved within three months of the injury, and (b) “chronic PTH,” meaning that the headache symptoms developed within one week of the initial concussive event and persisted for more than three months after the initial injury (Packard, 2005). Unfortunately, little is understood about risk for

acute or chronic PTH, but it has been hypothesized that headache symptoms may develop as a result of physiological changes that are associated with the concussive injury (Maugans, Farley, Altaye, Leach, & Cecil, 2012; Mayer, Huber, & Peskind, 2013; Seifert, 2013).

Further complicating our understanding of PTH is the occurrence of headaches in nonconcussed athletes (Ramadan, 2004; Sabin, Van Boxtel, Nohren, & Broglio, 2011) and in the general, uninjured, healthy population (Crystal & Robbins, 2010; Seifert, 2013). Preexisting headache symptoms also create ambiguity about the manifestation of PTH and likely confound our understanding of the true etiology and pathogenesis of PTH. Given our limited knowledge regarding concussion and the experience of headache symptoms, it would be meaningful to improve our understanding of the risk factors associated with headache presence, severity, and duration. One possibility is to examine the role of specific genetic factors that may be associated with the development and presentation of headache symptoms following concussion.

The apolipoprotein E (APOE) gene, located on chromosome 19, has previously been studied within the context of tension-type headaches and migraines (Gupta, Kumar, Luthra, Banerjee, & Bhatia, 2009; Pizza et al., 2012; Rainero et al., 2002) and thus could provide a starting point from which to explore PTH. Researchers have also begun to examine the APOE gene within the context of recovery and outcome following TBI, yet the relationship between this particular gene and headache symptoms in a brain-injured sample is not well understood. The APOE gene expresses a protein (apoE) that is involved in neuronal regrowth and repair following injury (Dardiotis et al., 2010; Finnoff, Jelsing, & Smith, 2011). The gene is composed of three primary alleles (e2, e3, and e4), each having a unique role in the recovery process; importantly, the e4 allele has been found to slow the process of neuronal regrowth/repair, whereas the e3 allele facilitates regrowth/repair (Finnoff et al., 2011; Silver, McAllister, & Yudofsky, 2011). Thus, the e4 allele may be a risk factor for neuropathology following injury or insult to the brain. Importantly, it has been estimated that the base rate of having at least one e4 allele in the general population is as high as 30% (Roses, 1996). Given the proposed mechanism of the APOE gene, as well as the research highlighted above, APOE is a sensible gene from which we

may begin to better understand the etiology of PTH.

Over the past two decades, researchers have examined the relationship between the APOE gene and TBI; however, a majority of published studies have explored gross functional outcomes in patients with more severe brain injuries. Consequently, very little is known about the relationship between the APOE gene and specific outcomes following brain injury, especially brain injuries that are on the mild end of the continuum. However, previous research by our lab has shown that there is a relationship between the e4 allele of the APOE gene and postconcussion symptom reporting following concussion (Merritt & Arnett, 2016). In this study we examined e4+ and e4-allele groups to determine whether there were differences in athletes' symptom reporting patterns across different symptom indices. Symptom clusters, including physical, cognitive, affective, and sleep, were examined (clusters identified based on previous factor analytic work), and results showed that concussed athletes with the e4 allele reported *greater* physical and cognitive symptoms than concussed athletes without the e4 allele. However, an important limitation of this study was that the physical symptom cluster did not include headache; thus, headache symptoms were not specifically evaluated. To our knowledge, no study to date has examined the relationship between the APOE gene and PTH following sports-related concussion.

The purpose of the present study was to determine whether the e4 allele of the APOE gene influences the presence and severity of headache following concussion. For the purpose of this study, we did not evaluate any symptoms beyond headache, including migraine-related symptomatology, as the central question of the study was to identify whether a relationship exists between the APOE gene and postconcussion headache. It was hypothesized that when compared to athletes without the e4 allele, a greater proportion of athletes with the e4 allele would endorse headaches, and that the e4 allele would be associated with more severe headache symptoms following concussion. Another aim of the study was to examine headache symptoms in a healthy/nonconcussed athlete group to determine whether there is any relationship between the e4 allele and the presence and severity of headache at baseline. Given our prediction about the e4 allele and its influence on

postconcussion sequelae, it was expected that there would be *no differences* between e4+ and e4- athletes with respect to headache symptoms reported at baseline.

Method

Participants and procedure

The present study utilized a prospective cohort design. Participants were composed of 45 concussed athletes and 43 healthy/nonconcussed athletes who were involved in a clinically based sports concussion management program at a Division I university in the United States. The concussion management program was designed to function according to the sports as a laboratory assessment model (Barth et al., 1989) wherein athletes are given a neuropsychological assessment prior to participating in college athletics (i.e., baseline evaluation) and are re-assessed following any concussions that are sustained during their collegiate athletic career. Team physicians diagnose concussions and refer athletes for postconcussion testing as soon as possible following the injury; however, in some cases, postconcussion referrals are made several days or weeks following the injury. The following criteria are used to determine whether a concussion, or mild TBI, was sustained: (a) loss of consciousness experienced for 30 minutes or less; (b) retrograde or anterograde amnesia surrounding the concussion, with anterograde amnesia lasting no longer than 24 hours; or (c) any alteration in mental status at the time of injury (Ruff, Iverson, Barth, Bush, & Broshek, 2009).

For the purpose of this study, concussed participants were selected based on the following criteria: (a) sustained a concussion according to the criteria described above; (b) underwent postconcussion neuropsychological testing within 3 months following the injury; and (c) provided a buccal (cheek cell) sample that could be analyzed to determine APOE genotype. The 3-month window was selected to balance our interest in evaluating relatively acute outcomes, while maintaining an adequate sample size. A proportion ($n = 30$; 67%) of the concussed athletes in our sample were also tested at baseline, but for the purpose of this study, their baseline data were not evaluated due to the smaller sample size. Instead, a separate group of athletes were selected to serve as a comparison group. This sample of healthy/nonconcussed

participants were selected based on the following criteria: (a) no concussions sustained while enrolled in our concussion management program; (b) underwent baseline neuropsychological testing; and (c) provided a buccal (cheek cell) sample that could be analyzed to determine APOE genotype.

All participants individually completed a 2-hour neuropsychological test battery administered by trained graduate students or undergraduate research assistants who were under the supervision of a PhD-level clinical neuropsychologist between 2002 and 2015. However, required procedures for this study took approximately 30 minutes. The study was approved by the university's Institutional Review Board, and all participants signed an informed consent form prior to participation in research-related activities.

Laboratory procedures

DNA extraction on buccal samples was performed as outlined by Freeman et al. (2003). APOE genotype was determined by using two Taqman® Single Nucleotide Polymorphism (SNP) assays for the SNPs APOE112 and APOE158, rs429358 and rs7412, respectively. These Taqman® assays for APOE genotypes have previously been correlated with the original restriction fragment length polymorphism (RFLP) method to determine the genotypes (Rihn et al., 2009). An allelic discrimination assay protocol was used to determine the SNPs. The determination of the genotype is based on the two different SNPs in the APOE gene. The SNP will determine the amino acid sequence of the APOE protein at sites 112 and 158 of the gene. The procedures outlined in Christensen et al. (2008) and Ingelsson et al. (2003) were used to define the different genotypes based on these calls. The final genotyping results could be any combination (homozygous or heterozygous) of pairs of e2, e3, and e4 alleles.

Measures

All athletes completed the Post-Concussion Symptom Scale (PCSS), administered as part of the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) computer program (Lovell, Collins, Podell, Powell, & Maroon, 2000; Lovell et al., 2006). The PCSS is a self-report measure composed of 22 common postconcussion symptoms, including headache. Participants are

shown a series of symptoms and are instructed to rate how they *currently* feel using a scale ranging from 1–6, representing symptom severities of mild to severe, or they have the option of checking a box indicating that they are not currently experiencing the symptom. The PCSS has been widely used in the assessment of symptoms following sports-related concussions, and the reliability and validity of the measure have been well established (Lovell et al., 2006). For the purpose of this study, “headache” was the only symptom from the PCSS that was evaluated. The possible range of the symptom was 0–6, with higher scores representing greater symptom severity.

Approach to data analysis

Descriptive statistics were used to evaluate the overall sample, and chi-square analyses were used to test for differences between the concussed and nonconcussed athlete groups on APOE genotype status and the presence of headache. The concussed and nonconcussed groups were then independently divided into e4+ and e4– groups, and chi-square analyses and independent-sample *t* tests were used to verify group equivalences across demographic and injury severity variables. Finally, the concussed and nonconcussed groups were analyzed separately using chi-square and Mann–Whitney *U* tests (due to non-normality of data), respectively, to determine whether the APOE e4 allele influences the *presence* and *severity* of headache.

Results

Participant demographic characteristics

The overall sample ($N = 88$) was composed of 63 males and 25 females with a mean age of 19.3 ($SD = 1.5$) years and a mean education level of 12.9 ($SD = 1.2$) years. The majority of the sample self-identified as Caucasian (70.5%), followed by African American (22.7%), biracial or multiracial (5.7%), and Asian American (1.1%). The data include athletes from the following sports: basketball (22.7%), soccer (19.3%), football (18.2%), lacrosse (17.0%), hockey (9.1%), wrestling (6.8%), rugby (4.5%), and other (2.3%). When the sample as a whole is considered, 37.5% had an e4 allele, and 38.6% reported a headache at the time of testing. With respect to premorbid or preexisting headache/migraine

symptoms, 17.0% of the entire sample reported having received prior treatment for headaches and 13.6% for migraines.

Within the concussed sample ($n = 45$), 35.6% ($n = 16$) had an e4 allele, and 53.3% ($n = 24$) endorsed headache. Within the nonconcussed sample ($n = 43$), 39.5% ($n = 17$) had an e4 allele, and 23.3% ($n = 10$) endorsed headache. There were no differences between the concussed and nonconcussed groups with respect to the proportion of participants who were e4+, $\chi^2(1, N = 88) = 0.15, p = .70, \phi = .04$. However, as expected, a significantly greater proportion of the concussed than of the nonconcussed group reported headaches, $\chi^2(1, N = 88) = 8.39, p = .004, \phi = .31$.

Sample characteristics for the concussed and nonconcussed groups, divided by e4 allele status, are presented in Tables 1 and 2, respectively. With respect to the concussed sample, there were no significant differences between the e4+ and e4– allele groups on any of the demographic or injury severity variables evaluated (Table 1). Similarly, within the nonconcussed sample, there were no significant differences between the e4+ and e4– allele groups on any of the demographic variables evaluated (Table 2).

APOE e4 allele status and headache: Concussed sample

The concussed sample ($n = 45$) was tested, on average, 10 days post injury ($SD = 14.3, Mdn = 4.0$; range = 0–72 days), and 71.1% of these athletes were tested within 7 days of their injury. Descriptive statistics for headache severity in the concussed sample are reported in Table 3.

Chi-square analyses were used to determine whether the *presence* of headache symptoms varies as a function of e4 allele status. Results showed that there was a significant difference between the e4 allele groups with respect to the proportion of participants who reported headache, $\chi^2(1, N = 45) = 4.68, p = .030, \phi = .32$. Specifically, 75% (12 of 16) of e4+ participants endorsed headache at the time of testing, compared with only 41% (12 of 29) of e4– participants. A Mann–Whitney *U* test was then used to compare headache *severity* across e4+ and e4– participants within the concussed sample. Headache severity was greater for e4+ athletes ($Mdn = 1.5$) than for e4– athletes ($Mdn = 0$), $U = 141.50, p = .023, r = .34$. Figure 1 displays headache severity ratings among the concussed sample.

Table 1. Concussed sample characteristics by e4 allele group.

Variables	Positive e4 allele group (n = 16)				Negative e4 allele group (n = 29)				p
	M	SD	N	%	M	SD	N	%	
Age (years)	20.00	1.37			20.00	1.54			1.00
Education (years)	13.88	1.36			13.38	1.18			.208
Days tested post injury	8.75	12.05			10.69	15.57			.668
Sex									.347
Male			12	75.0			25	86.2	
Female			4	25.0			4	13.8	
Ethnicity									.492
Caucasian			10	62.5			21	72.4	
Other			6	37.5			8	27.6	
Concussion history									.897
0			5	31.3			9	31.0	
1			7	43.8			11	37.9	
2 or more			4	25.0			9	31.0	
Treatment for Ha/Mig									.492
Yes			2	12.5			6	20.7	
No			14	87.5			23	79.3	
Loss of consciousness									.427
Yes			3	18.8			3	10.3	
No			13	81.3			26	89.7	
Retrograde amnesia									.661
Yes			3	18.8			4	13.8	
No			13	81.3			25	86.2	
Anterograde amnesia									.373
Yes			5	31.3			13	44.8	
No			11	68.8			16	55.2	

Note. Ha = headache; Mig = migraine.

Table 2. Nonconcussed sample characteristics by e4 allele group.

Variables	Positive e4 allele group (n = 17)				Negative e4 allele group (n = 26)				p
	M	SD	N	%	M	SD	N	%	
Age	18.47	1.01			18.58	1.39			.787
Education	12.24	0.56			12.35	0.89			.651
Sex									.415
Male			9	52.9			17	65.4	
Female			8	47.1			9	34.6	
Ethnicity									.383
Caucasian			11	64.7			20	76.9	
Other			6	35.3			6	23.1	
Concussion history									.616
0			8	47.1			16	61.5	
1			6	35.3			6	23.1	
2 or more			3	17.6			4	15.4	
Treatment for Ha/Mig									.642
Yes			5	29.4			6	23.1	
No			12	70.6			20	76.9	

Note. Ha = headache; Mig = migraine.

Table 3. Headache severity characteristics by e4 allele status.

Group	N	APOE status	Mean	SD	Median	Min	Max
Concussed	16	e4+	1.75	1.48	1.5	0	4
	29	e4-	0.79	1.08	0	0	3
	45	Combined	1.13*	1.31	1.00	0	4
Nonconcussed	17	e4+	0.59	1.54	0	0	6
	26	e4-	0.46	0.95	0	0	4
	43	Combined	0.51*	1.20	0	0	6
Total	88	Combined	0.83	1.29	0	0	6

Note. Headache severity could range from 0–6, with 0 indicating no headache, and 6 indicating severe headache.

*A Mann-Whitney *U* test indicated that headache severity was significantly higher for the concussed group (*Mdn* = 1.5) than for the nonconcussed group (*Mdn* = 0), *U* = 667.00, *p* = .004, *r* = .31.

Group means, as opposed to mean ranks or median values, are displayed in the figure for the purpose of clinical interpretation.

APOE e4 allele status and headache: Nonconcussed sample

Descriptive statistics for headache severity in the nonconcussed sample are reported in Table 3. As done previously with the concussed sample, chi-square analyses were used to determine whether the presence of headache symptoms varies as a

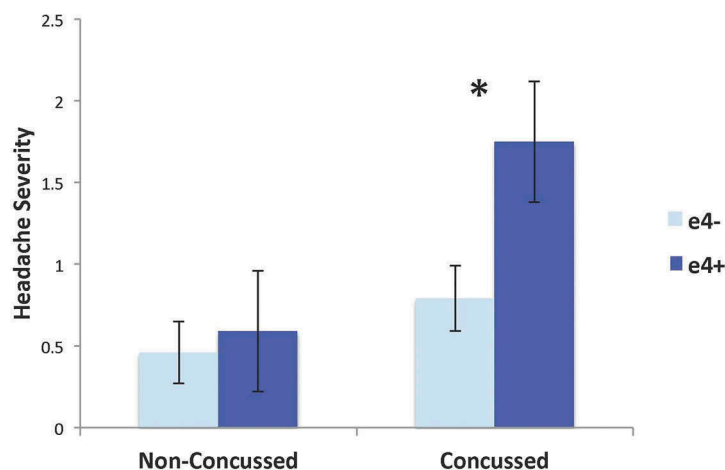


Figure 1. Headache severity ratings (mean scores \pm standard error) across concussed and nonconcussed athletes by e4 allele group. Nonconcussed sample ($n = 43$): 17 e4+ participants and 26 e4- participants. Concussed sample ($n = 45$): 16 e4+ participants and 29 e4- participants. Headache severity could range from 0–6, with greater scores representing more severe headaches. * $p < .05$. To view a color version of this figure, please see the online issue of the Journal.

function of e4 allele status among the nonconcussed group. This time, there were no significant differences between the e4 allele groups with respect to the proportion of participants who reported headache, $\chi^2(1, N = 43) = 0.50, p = .481, \phi = .11$; only 18% (3 of 17) of e4+ participants endorsed headache at the time of testing (i.e., at baseline), and 27% (7 of 26) of e4- participants endorsed headache symptoms. Finally, a Mann-Whitney U test was used to compare headache severity across e4+ and e4- participants within the nonconcussed sample. This revealed no significant differences in headache severity between e4+ athletes ($Mdn = 0$) and e4- athletes ($Mdn = 0$), $U = 207.00, p = .638, r = .07$. Figure 1 displays headache severity ratings among the nonconcussed sample. As before, group means are displayed in the figure for the purpose of clinical interpretation.

Discussion

Although headache is one of the most commonly reported symptoms after a concussion, the understanding of factors that contribute to the experience and severity of headache has previously been limited. This study furthers our knowledge of postconcussion headache by showing that genetic factors may play a role. In particular, in our sample of athletes who had sustained concussions, those with the APOE e4 allele were more likely to (a) report headache symptoms and (b) report more severe headaches than those who did not have the e4 allele. We also examined the impact of the e4 allele on headache in a

nonconcussed sample with a similar frequency of the e4 allele as the concussed group. In this sample of participants who had not sustained concussions, the presence and severity of headache did *not* differ as a function of e4 status. Taken together, these findings indicate a potentially meaningful relationship between APOE genotype and headache, wherein APOE e4 allele status plays an important role in the presence and severity of headache only *after* the traumatic event of a concussion.

One complicating factor in understanding PTH has been the question of its relationship to “baseline” headache symptoms (i.e., headaches experienced by nonconcussed athletes) or the experience of headache in the general, uninjured, healthy population. Since there were no differences in the report of headache symptoms between e4+ and e4- groups in our nonconcussed sample of collegiate athletes—a presumably healthy group of participants—this particular allele does not appear to influence the universal experience of headache. However, knowledge of genetic status was valuable for predicting which athletes would experience PTH, suggesting that there may be an interactive relationship between possessing an e4 allele and sustaining a concussive injury.

The precise physiological mechanisms by which headaches develop following brain injury are poorly understood. Although it is beyond the scope of this manuscript to elucidate such mechanisms, it can be anticipated from our data that there may be an interactive relationship between the “metabolic cascade” (Giza & Hovda, 2001, 2014)

that ensues after brain injury and the deleterious effects of the e4 allele (Dardiotis et al., 2010; Jordan, 2007; Mahley, Weisgraber, & Huang, 2006) that results in the development of PTH. As reviewed above, after neurological insult (i.e., a concussion), the APOE gene is involved in neuronal tissue repair and synaptogenesis (Dardiotis et al., 2010; Finnoff et al., 2011). Importantly, the e2, e3, and e4 alleles of the gene differentially influence tissue regrowth/repair, with the e4 allele having a disadvantageous effect on the recovery process, including proposed functions such as inhibiting neurite outgrowth and causing neurodegeneration and cognitive decline (Finnoff et al., 2011; Jordan, 2007; Mahley et al., 2006). Thus, given our data, it is possible that initial damage to brain tissue when accompanied by the e4 allele leads to neurological symptoms such as headaches. Although speculative, it is also possible that the e4 allele may play a role in the microstructural damage that sometimes occurs following brain injury. Again, because the APOE gene is involved in the maintenance of neuronal tissue, as well as neuronal repair and plasticity following brain injury (Dardiotis et al., 2010; Silver et al., 2011), possession of at least one e4 allele may influence the extent of structural injury experienced, thereby leading to headache symptomatology. Further research is clearly needed to determine the exact mechanisms by which expression of the e4 allele could contribute to headache symptoms, but our data provide a starting point for thinking about such mechanisms.

Limitations

Our clinical sample contributed to some limitations of this study. As noted above, athletes receive baseline testing and then are referred again to our clinic in the event of a concussion; however, we do not control the window from time of injury to referral. Therefore, there was some variability with respect to how much time elapsed between the injury event and the time in which symptoms were assessed post concussion. Consequently, this limits specific conclusions about the time course for the development of headache symptoms. Relatedly, although our findings address the question of the presence and severity of relatively acute postconcussion headache, we were unable to determine the influence of the e4 allele on the duration of headache symptoms. Further research with a

chronic sample is needed to understand whether these relationships persist throughout the course of the recovery process.

In addition, for the purpose of this study “headache” was evaluated as a self-reported symptom on the PCSS. Thus, the experience of headache was subjective on the part of the athlete and may not reflect the clinical definition of a headache disorder. Furthermore, a definition of headache was not provided to the athlete, and so we do not have any information about the type of headache pain experienced. Nevertheless, it is common practice to assess self-reported symptoms in concussed athletes using a measure such as the PCSS (McCrory et al., 2013), and the PCSS has been demonstrated to have strong reliability and validity (Lovell et al., 2006). Finally, other limitations include a relatively small sample size in the concussed and nonconcussed athlete groups, as well as a smaller number of female athletes being evaluated. However, genetic studies have been published in the TBI literature using similar sample sizes (Ariza et al., 2006; Chamelian, Reis, & Feinstein, 2004; Han et al., 2007; Kutner, Erlanger, Tsai, Jordan, & Relkin, 2000; Liberman, Stewart, Wesnes, & Troncoso, 2002; Sundstrom et al., 2004).

Conclusions

This research furthers our understanding of how biological factors such as genetics uniquely contribute to individual differences in postconcussion symptoms. The findings from this study demonstrate the prevalence of headache in athletes at baseline and following a concussion and specifically indicate that the APOE e4 allele appears to be a risk factor associated with both the presence and severity of PTH. Such information may be useful in determining appropriate concussion management procedures and for ensuring the ongoing safety and well-being of athletes. For instance, having a better understanding of those at greater risk for postconcussion deficits such as PTH could facilitate the development of safer and more effective return to play guidelines. Moreover, concussions also can have an impact on collegiate athletes’ academic performance, so understanding risk factors for potentially a longer term recovery is valuable. It is also possible that as genetic relationships are identified, individually targeted treatments could be developed to mitigate persisting

postconcussion symptoms. It will be necessary for these findings to be replicated in a larger sample, but at present, these data show that collegiate athletes with the e4 genotype may be at a higher risk for experiencing headache-related difficulties following concussion.

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Disclosure statement

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