A Candidate Gene Approach to Identify Genetic Variants Associated with Individual Concussion Symptoms During Recovery

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INTRODUCTION: Concussion represents a complex neurological injury resulting in acute neuropathological changes, which manifest as a diverse array of clinical symptoms. Symptoms present acutely and may evolve in the days to weeks after injury. The development of persisting symptoms after concussion (PSaC) can lead to additional time loss from athletics, decreased academic engagement, decreased peer interactions, and increased health care utilization. Little is known about the biologic factors that predispose certain individuals to worsening or persisting symptoms during and after the acute concussion recovery phase. Single nucleotide polymorphisms (SNPs) within neurometabolic, neurochemical, oxidative stress, and neurovascular pathways have been hypothesized to play a role in concussion pathophysiology and are hypothesized to influence concussion recovery. The purpose of this study was to test whether genetic variants identified in prior studies as being related to concussion risk and/or outcomes following concussion (*BDNF*[1], *APOE*[2,3] , *NGB*[4], *ANKK1*[5], and *COMT*[6], Table 1) were associated with individual concussion symptoms during the concussion recovery period.

METHODS: We conducted a secondary analysis of data collected from adolescents (13-18 yrs.) with a recent concussion in a prospective, IRB approved multi-site study of concussion led by Penn State University. DNA was extracted from frozen saliva samples. Candidates SNPs, *BDNF* (rs6265), *APOE* (rs405509), *NGB* (rs3783988), *ANKK1* (rs1800497), and *COMT* (rs4680), were genotyped using custom TaqMan® SNP genotyping assays (Applied Biosystems). Of the 244 participants, 55 participants were excluded due to missing data: genetic (n=65), sex (n=1), race and ethnicity (n=3), current sports participation (n=35), and incomplete post-concussion symptom scale (PCSS) data at all follow-up visits (n=16). The final dataset included 189 participants. Concussion symptom data and assessments of postural stability and reaction time were collected at three timepoints: enrollment visit (<48-hours post-injury), 7-days post-injury, and 30-days post-injury. Individual concussion symptoms were assessed with the PCSS, a self-reported symptom inventory that quantifies the severity of 22 concussion symptoms based on an ordinal scale from 0 (None) to 6 (Severe). Multivariable logistic regression models with Firth's Penalized Likelihood Method were used to test the correlation between the candidate variants and (1) presence of severe symptoms (individual symptom rating>4) for each of the 22 PCSS symptoms at enrollment, and (2) worsening of symptom severity between enrollment and day 7 or day 30. Linear regression models were used to test the correlation between candidate variants and (1) total Balance Error Scoring System (BESS) score at enrollment, (2) total symptom severity at enrollment, (3) percentage (0-100%) of 'Feeling Normal' at enrollment, (4) average reaction time. Age, sex, race, ethnicity, enrolling site, and current participation in sports were adjusted for in all models.

RESULTS: The average age among the 189 participants (n=113; 59.8% male and n=76; 40.2% female) was 14.8 ($\pm$3.4) years. Concussions more frequently occurred during sports participation (135/189, 71.4%). The median total PCSS symptom score across all participants was 32 (Interquartile Range: 0 to 129) at enrollment. *ANKK1* (rs1800497) was significantly correlated with severe 'Irritability' (Table 1). *APOE* (rs405509) was significantly correlated with severe 'Headache', 'Nausea and Vomiting', and 'Dizziness' symptom ratings at enrollment. *APOE* was also correlated with worsening of the 'Don't Feel Right' symptom following the enrollment visit (Table 1). *NGB* (rs3783988) was significantly correlated with total BESS score at enrollment (Table 1). Genetic variants for *BDNF* and *COMT* were not correlated with any of the 22-item PCSS symptoms during concussion recovery, balance, and/or reaction time.

DISCUSSION: Genetic variants mapped to *ANKK1* and *APOE* demonstrated correlations with individual PCSS symptom severity within 48 hours of concussion in adolescents. Presence of the A allele for *ANKK1* was correlated with increased symptoms of 'Irritability' acutely post-concussion, while presence of the G allele for *APOE* decreased susceptibility to severe 'Headache', 'Nausea and Vomiting', and 'Dizziness' symptoms acutely post-concussion and decreased susceptibility to worsening of the 'don't feel right' symptom during recovery. For *NGB*, presence of the C allele was associated with increased postural instability acutely post-concussion. Additional work is needed to replicate these findings in a large independent population, and to comprehensively test similar genetic markers across the genome

SIGNIFICANCE/CLINICAL RELEVANCE: The identification of objective genetic markers that may increase susceptibility to specific concussion symptoms has important implications for risk stratification and development of personalized therapeutic strategies. Additional work is needed to evaluate whether these genetic variants also influence responsiveness to concussion treatment options including aerobic exercise, neuromuscular training, and/or vestibular therapies.

Table 1. Genetic Variants Associated with Concussion Symptoms

Variant and Symptom	Allele	Effect	95% CI	p-Value
rs1800497 (ANKK)				
Irritability at Enrollment (Severe vs. Not Severe)	A	3.05†	1.12-8.33	0.030
rs405509 (APOE)				
Headache at Enrollment (Severe vs. Not Severe)	G	0.57†	0.35-0.93	0.024
Nausea and Vomiting at Enrollment (Severe vs. Not Severe)		0.29†	0.10-0.86	0.025
Dizziness at Enrollment (Severe vs. Not Severe)		0.42†	0.20-0.87	0.020
'Don't Feel Right' (Worsening at Day 7 or Day 30 vs Improvement/No Change)		0.46†	0.21-0.99	0.048
rs3783988 (NGB)				
Total BESS at Enrollment	C	0.20*	0.65-7.70	0.021

†Odds ratio; * Standardized Slope: standard deviation change in outcome per 1 allele increase in variant.

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