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The Moderating Effect of the Ankyrin Repeat and Kinase Domain Containing One Gene on the Association of Family Environment with Longitudinal Executive Function following Traumatic Brain Injury in Early Childhood: A Preliminary Study

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Abstract

This study examined whether the ankyrin repeat and kinase domain containing 1 gene (ANKK1) C/T single-nucleotide polymorphism (SNP) rs1800497 moderated the association of family environment with long-term executive function (EF) following traumatic injury in early childhood. Caregivers of children with traumatic brain injury (TBI) and children with orthopedic injury completed the Behavior Rating Inventory of Executive Function (BRIEF) at post-injury visits. DNA was collected to identify the rs1800497 genotype in the ANKK1 gene. General linear models examined gene-environment interactions as moderators of the effects of TBI on EF at two times post-injury (12 months and 7 years). At 12 months post-injury, analyses revealed a significant three-way interaction of genotype with level of permissive parenting and injury type. *Post hoc* analyses showed genetic effects were more pronounced for children with TBI from more positive family environments, such that children with TBI who were carriers of the risk allele (T-allele) had significantly poorer EF compared with non-carriers only when they were from more advantaged environments. At 7 years post-injury, analyses revealed a significant two-way interaction of genotype with level of authoritarian parenting. *Post hoc* analyses found that carriers of the risk allele had significantly poorer EF compared with non-carriers only when they were from more advantaged environments. These results suggest a gene-environment interaction involving the ANKK1 gene as a predictor of EF in a pediatric injury population. The findings highlight the importance of considering environmental influences in future genetic studies on recovery following TBI and other traumatic injuries in childhood.

Keywords: ANKK1; childhood; executive functions; genetics; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the leading causes of morbidity and mortality in children in the United States, with over $1 billion in total annual health care costs[1] and affecting approximately 1.14 million children and young adults ages 0–24 years annually.[2] Long-term impairments following pediatric TBI often involve cognitive deficits and behavioral problems.[3] Deficits in executive function (EF) skills, such as working memory, inhibitory control, and planning, are particularly pervasive and problematic, affecting academic, social, and functional outcomes.[4] A barrier to providing optimal care following pediatric TBI is lack of understanding of the sources of variability in the expression of these impairments and in responsiveness to therapeutic interventions, even in children who sustain seemingly similar TBI.[3] Therefore, recent research efforts have focused on understanding how such variability may be related to moderating factors, such as genetics[5] and the family environment.[6]

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A variety of individual and environmental factors influence recovery following pediatric TBI, including the family environment.[6] Parental mental health,[7,8] caregiver burden,[7] family functioning,[7,9,10] and chronic caregiver life stressors,[11,12] have all been associated with recovery of function after injury. These findings suggest that socioeconomic resources, social supports, and higher levels of family functioning buffer the adverse effects of TBI on EF[10] and predict more positive EF outcomes.[7,11,13] Parenting practices also impact recovery of EF in children with TBI, with more authoritarian and permissive parenting styles associated with greater executive dysfunction.[14,15] Greater parent-reported family burden after injury and a more permissive parenting style also have been associated with greater EF impairment over time following both TBI and orthopedic injury (OI).[16] A double-hazard injury model has been proposed in which the effect of more severe early injury is exacerbated by environmental risks.[11,7,17] These findings highlight the importance of evaluating both injury severity and environmental risk factors when assessing recovery following pediatric TBI.

A growing body of evidence suggests that an individual's genetic makeup may also affect recovery. While most current pediatric research on genetics in TBI has focused on the apolipoprotein E (ApoE) gene[5,18,19] and catechol-O-methyltransferase (COMT),[20] research from the adult literature suggests that genes related to pre-injury cognitive capacity and reserve also may be associated with EF following TBI.[21] Much of the current research has focused on genes involved in the dopaminergic and serotonergic pathways, which are pathways often implicated in post-TBI cognitive and social impairments.[21,22]

Dopamine is a neurotransmitter that contributes to several critical functions, including motor control, cognition, reward processing, and emotion.[23,24] The relationship between dopamine and EF is well-established.[25] Bales and colleagues[26] have proposed that alterations in dopaminergic function may be partially responsible for persistent cognitive dysfunction following TBI. In support of this hypothesis, they summarized findings suggesting altered dopamine transporter gene DAT1 expression following TBI and improved cognitive outcomes with pharmacotherapies targeting dopamine. Within a pediatric TBI population, a recent study examined 32 single-nucleotide polymorphisms (SNPs) in dopamine-related genes and their association with short- and long-term neurobehavioral recovery.[27] The investigators found preliminary evidence that genetic variation in several SNPs significantly influenced outcomes. One gene specifically associated with DRD2 expression and density, ankyrin repeat and kinase domain containing 1 (ANKK1), was associated with poorer EF 6 months post-injury for T-allele carriers of the SNP rs1800497.

The ANKK1 gene C/T SNP rs1800497 is located on chromosome 11q23.1 in exon 8. In the past, it was referred to as the Taq1A polymorphism and was previously believed to be the dopamine receptor D2 (DRD2) gene. This portion of the ANKK1 gene has been found to affect dopamine binding in healthy controls.[28] The T allele is thought to confer risk and studies have found that the presence of a single T allele is associated with 30–40% fewer dopamine D2 receptors in the striatum compared with homozygous C/C carriers.[29,30]

The ANKK1 gene has been previously studied in the adult TBI population with preliminary significant findings. McAllister and colleagues[31] reported an association with the Taq1A (ANKK1) T allele and poorer verbal memory overall, as well as a significant diagnosis by allele interaction, whereby adults with mild TBI ($n=39$) showed worse attention compared with healthy controls ($n=27$) when they were carriers, but no group differences were found among non-carriers. These findings were replicated in a larger follow-up study ($n=141$) that added 54 participants with mild and moderate TBI.[32] Further support for ANKK1 involvement in cognitive outcomes following TBI was found by Yue and colleaugues[33] in a study that included a larger, more diverse adult TBI population ($n=492$). They found a dose–dependent effect for the T allele, with T/T homozygotes scoring lowest on a task of verbal memory (California Verbal Learning Test Second Edition). Another study found support that ANKK1 heterozygotes (C/T) performed better across several cognitive domains than homozygotes (CC or TT) at both 6 and 12 months post-injury, although this group difference was only evident for adults with severe TBI, suggesting ANKK1 may interact with injury severity to affect cognitive recovery.[34]

Given the previous findings suggesting both environmental and genetic influences on recovery following TBI, a better understanding of how gene-environment interactions may influence outcomes is needed. To our knowledge, no study has yet examined the ANKK1 SNP rs1800497 T allele and its association with environmental factors in predicting outcome in a pediatric TBI population. Because of the allele's relationship with dopaminergic functioning and its association with cognitive dysfunction following TBI, it is a particularly salient target for pediatric TBI research. Our primary aim was to examine whether variation in the ANKK1 gene involved in EF moderated the association of family environment with EF over time following pediatric TBI. Preliminary studies suggest that a complex interplay between genetic and environmental factors could impact functional outcomes in childhood after TBI, such that negative outcomes associated with the risk allele may be negated by positive environmental factors or exacerbated when combined with environmental disadvantage.[35,36] We hypothesized that children with TBI who were carriers of the risk allele (ANKK1 rs1800497 T) would be rated as having poorer EF relative to children who were non-carriers with TBI and children with OI regardless of carrier status. We also predicted that the effects of risk alleles on children's functioning post-TBI would be exacerbated in the context of a poor family environment as characterized by maladaptive parenting style or a poor quality home environment.

Methods

Participants

Children who had sustained a TBI between the ages of 36 and 84 months (3–7 years) were recruited from a cohort of participants that were enrolled previously in a multi-center study of cognitive and behavioral outcomes of early childhood TBI (three sites: Cincinnati, Cleveland, and Columbus, OH). The study prospectively evaluated child outcomes. Pre-injury functioning was assessed at an initial baseline visit ($\sim$1 month post-injury) and current functioning was assessed at 6, 12, and 18 months post-injury. Additional follow-ups were completed two or more years post-injury (average 3 1/2 years) and when the child entered middle school (average 7 years). Only post-acute (12 month) and long-term (7 year) outcomes were examined in this study.

The Glasgow Coma Scale (GCS) score and imaging findings were used to define TBI severity, as follows: mild as GCS score of 13–15 with associated computed tomography and/or magnetic resonance imaging findings, moderate TBI as GCS score of 9–12, and severe TBI as GCS score of 3–8, with the former two groups combined into a single complicated mild-to-moderate TBI group (henceforth collectively referred to as ''moderate TBI''). The GCS score assigned to the child was the lowest one recorded. The initial study also recruited an orthopedic injury (OI) control group for comparison that was assessed at the same time-points post-injury as the TBI group. Inclusion in the OI group required a documented bone fracture in an area of the body other than the head that required an overnight hospital stay, as well as the absence of any evidence of loss of consciousness or other findings suggestive of

brain injury. Exclusion criteria included histories of child abuse, neurological disorder, autism, or intellectual disability prior to injury, or a language other than English as the primary language spoken in the home.

Of 213 participants enrolled in the original study, 135 provided DNA samples and were genotyped for the ANKK1 gene. Of those with genetic data, 15 had severe TBI, 50 moderate TBI, and 70 OI. The TBI and OI groups did not differ significantly in race, sex, age at injury, median family income, or level of maternal education (Table 1). Participants with genetic data did not differ significantly from those without genetic data in demographic characteristics or on other study measures.

DNA collection

Participants provided saliva samples for DNA extraction. The Oragene (DNA Genotek, Ottawa, Ontario, Canada) DNA Self-collection kit was used. Saliva was self-collected by spitting into an Oragene cup. DNA was extracted using the manufacturer's recommended procedure. ANKK1 rs1800497 genotyping was analyzed using TaqMan (Applied Biosystems) assay.

ANKK1 rs1800497 did not violate Hardy-Weinberg equilibrium ($p > 0.05$). Genotypes were collapsed into either 0 (absence of the T allele, non-carriers) or 1 (homo- or heterozygous T allele[s], carriers). There were 46 carriers and 78 non-carriers. Participants who were carriers did not differ significantly from those who were non-carriers in demographic characteristics, with the exception of race ($p \leq 0.01$), or on performance on study measures (Table 1); however, this difference appears to be consistent with findings in the general population.

Measures

Child EF. To assess behavioral outcomes related to attention and everyday EF, a parent-report of EF behaviors, the Behavior Rating Inventory of Executive Function (BRIEF),[37] was administered at all follow-ups. The BRIEF is widely used to assess behavioral manifestations of problems in EF in children following TBI.[38] Parent reports at baseline were based on retrospective recall of the child's function prior to injury to control for premorbid differences. For study analyses, the Global Executive Composite (GEC) score was used as a dependent variable.

Table 1. Participant Demographic Characteristics by Injury Group

	OI (n = *70*)	*TBI* (n = *65*)	p
Gender, *n* (%)			0.731
Male	36 (51.4)	36 (55.4)	
Female	34 (48.6)	29 (44.6)	
Race, *n* (%)			0.563
White	53 (75.7)	46 (70.8)	
Non-white	17 (24.3)	19 (29.2)	
Age at injury in years, M (SD)	5.07 (1.08)	5.21 (1.09)	0.471
Median family income, M (SD)	$60,736 (22,122)	$59,332 (23,002)	0.720
Highest maternal education, *n* (%)			0.172
<High school	5 (7.1)	10 (15.4)	
≥High school	65 (92.9)	55 (84.6)	
GCS, M (SD)		11.23 (4.42)	

OI, orthopedic injury; TBI, traumatic brain injury; M, mean; SD, standard deviation; GCS, Glasgow Coma Scale.

Family environment. To assess the quality of home environment, the Early Childhood-Home Observation for Measurement of the Environment (EC-HOME),[39] was administered at baseline. This instrument involved an in-home visit by an assessor who rated observed levels of parental stimulation and support for the child. Both objective observations of stimuli found within the home and discussions about child-related activities with parents were included in the scoring of the instrument. Domains assessed included learning materials, developmental stimulation, physical environment, and parental supportiveness. A total EC-HOME score is calculated by summing ratings across eight domains. Higher scores indicate greater levels of structure, stimulation, and support as rated in the home environment. Research has shown the EC-HOME to be a reliable and valid predictor of cognitive development in children that incorporates factors not wholly captured by socioeconomic status (SES).[39]

To assess self-reported parenting style, the Parenting Practices Questionnaire (PPQ) was administered at all follow-ups.[40] The PPQ assesses self-reported engagement in three types of parenting styles: authoritative, authoritarian, and permissive.[41] The authoritative parent directs the child in a rational manner, encourages give and take, and both autonomy and disciplined conformity are valued. The authoritarian parent shapes and controls the child in accordance with a set standard and often restricts the child's autonomy. The permissive parent allows the child to regulate his or her own activities, avoids control, and uses reason and manipulation, but not power, to parent the child. Permissive and authoritarian parenting styles are generally considered maladaptive, whereas authoritative parenting is considered effective. The instrument consists of 62-items presented in a 5-point Likert scale. We used the raw total score for each of the three dimensions to characterize parenting styles affecting the family environment.

Statistical analysis

All statistical analyses were conducted using SAS 9.3. Separate general linear model analyses (SAS GLMSELECT Procedure) were used to examine the moderating effect of carrier status (presence vs. absence of T allele) on associations of the three parenting styles (authoritarian, permissive, authoritative) and quality of the home environment with post-injury developmental change in EF, at 12 months and 7 years post-injury. Separate models were developed for each of the environmental factors: the three parenting styles and home environment. The two time-points were selected to examine both short-term and long-term recovery effects from early TBI. We initially examined the highest-level interaction of carrier status, family environment, group (TBI vs. OI), and time since injury, as well as all lower-level interaction terms involving carrier status. A backward elimination technique was used to remove effects based on significance level until effects in the model were significant at the 0.1 level.

Concurrent parent ratings of EF behaviors at the 12-month and 7-year follow-up were included in modeling the post-acute and long-term outcomes, respectively. Because baseline ratings represented pre-injury functioning, baseline EF ratings were included as a covariate in the models to control for pre-injury group differences in EF.

Initial models controlled for race (white vs. non-white) and SES, defined as a z-score that combined parental education and median census track income by zip code. Models were trimmed using backward elimination and a p value threshold of 0.1. Higher interactions terms were trimmed first, followed by lower interaction terms and individual variables. The main effects for carrier status, group, and family environment were included in all models. When a significant interaction involving carrier status was detected, *post hoc* analyses were done to characterize interpretation of group differences in outcome at low and high levels of family environment (defined at the 10th and 90th percentile for the sample). TBI carriers and non-carriers were compared with each other and to OI

carriers and non-carriers at each level of family environment. Therefore, interaction effects were examined in terms of variations in the effect of carrier status across injury groups and/or level of family environment quality.

In this exploratory study, the significance threshold was set at an alpha of 0.05 for interactions and main effects of interest despite multiple comparisons to reduce the risks of Type II error associated with tests of interactions in non-experimental designs[42] and because interactions were the primary focus of the study. Effect sizes were created by obtaining parameter estimates based on the final mixed model for each dependent variable and by standardizing all continuous predictors ($M = 0$, $SD = 1$) other than time since injury. The resulting coefficients are akin to standardized regression coefficients for continuous predictors and to standardized mean differences (e.g., *d*) for categorical variables. Because standardized regression coefficients can be scaled to correlations,[43] we used conventional definitions of effect size for correlations to characterize the magnitude of the standardized parameter estimates for continuous predictors and interactions involving only them (i.e., 0.1 is small, 0.3 is medium, and 0.5 is large). Likewise, we used conventional definitions of effect size for mean differences to characterize the magnitude of parameter estimates for categorical predictors and any interactions involving them (i.e., 0.2 is small, 0.5 is medium, 0.8 is large).

Because gene by environment interactions are the focus of the present paper, we report significant results only for main effects or interactions involving carrier status; significant findings involving the moderating effect of the family environment alone have been reported in other papers from our group.[15,44]

Results

EF at 12 months post-injury

Analysis of the BRIEF GEC at 12 months revealed a significant 3-way interaction among carrier status, level of permissive parenting, and injury type, ($F[1, 98] = 2.08$, $p = 0.04$; Fig. 1). *Post hoc* contrasts revealed, for children exposed to low levels of permissive parenting, carriers with TBI showed significantly worse EF compared with carriers with OI ($p = 0.04$) and non-carriers with OI ($p = 0.04$). Effect sizes were large for both comparisons (standardized estimates = 0.70 and 0.53, respectively). For those exposed to high levels of permissive parenting, only non-carriers with TBI showed significantly worse EF compared with non-carriers with OI ($p = 0.01$), with a large effect size (standardized estimate = 0.72). No other *post hoc* contrasts were significant.

Analyses did not reveal significant main effects or interactions involving ANKK1 status in models involving authoritative or authoritarian parenting or quality of the home environment as predictors.

EF at 7 years post-injury

Analyses revealed a significant 2-way interaction among carrier status and level of authoritarian parenting ($F[1, 112] = 2.53$, $p = .01$; Fig. 2). Planned *post hoc* contrasts revealed that, among those exposed to low levels of authoritarian parenting, carriers showed significantly worse EF compared with non-carriers ($p = 0.02$), with a medium effect size (standardized estimate = 0.42). There was no significant difference between groups for those exposed to high levels of authoritarian parenting.

Analysis did not reveal significant main or interaction effects involving ANKK1 status in models that included type of injury, authoritative or permissive parenting, or the quality of the home environment as predictors.

Discussion

The current study sought to examine the potential joint influences of the ANKK1 rs1800497 T allele and environmental factors

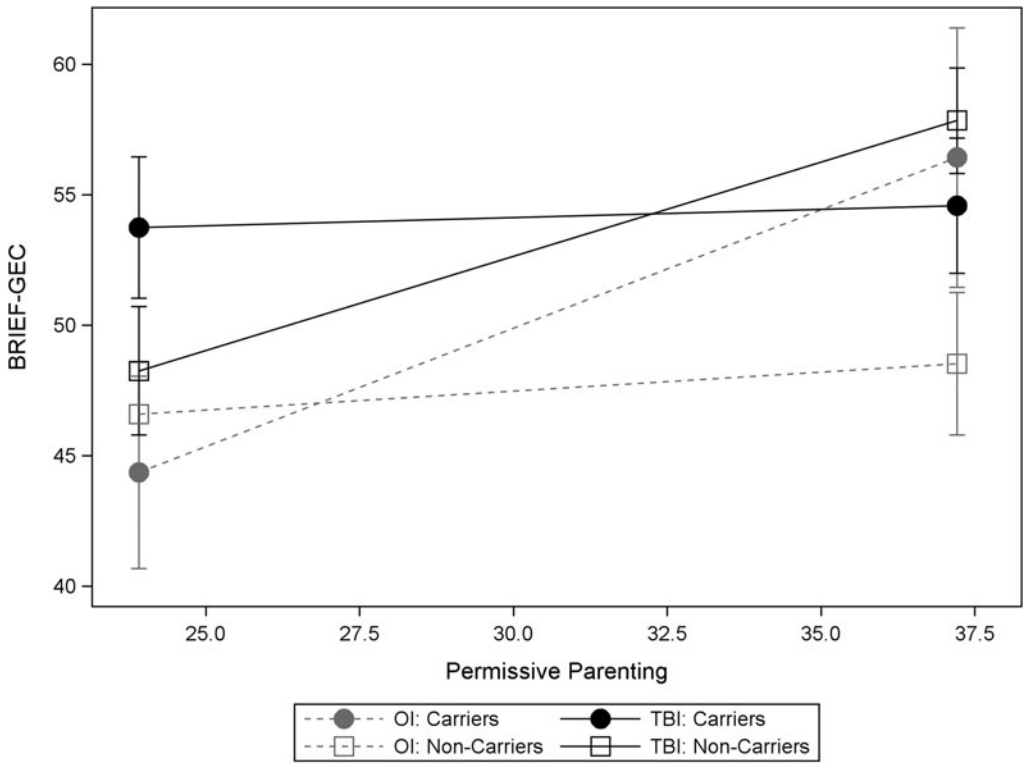

FIG. 1. Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite outcomes at 12 months revealed a significant three-way interaction among carrier status, level of permissive parenting, and injury type.

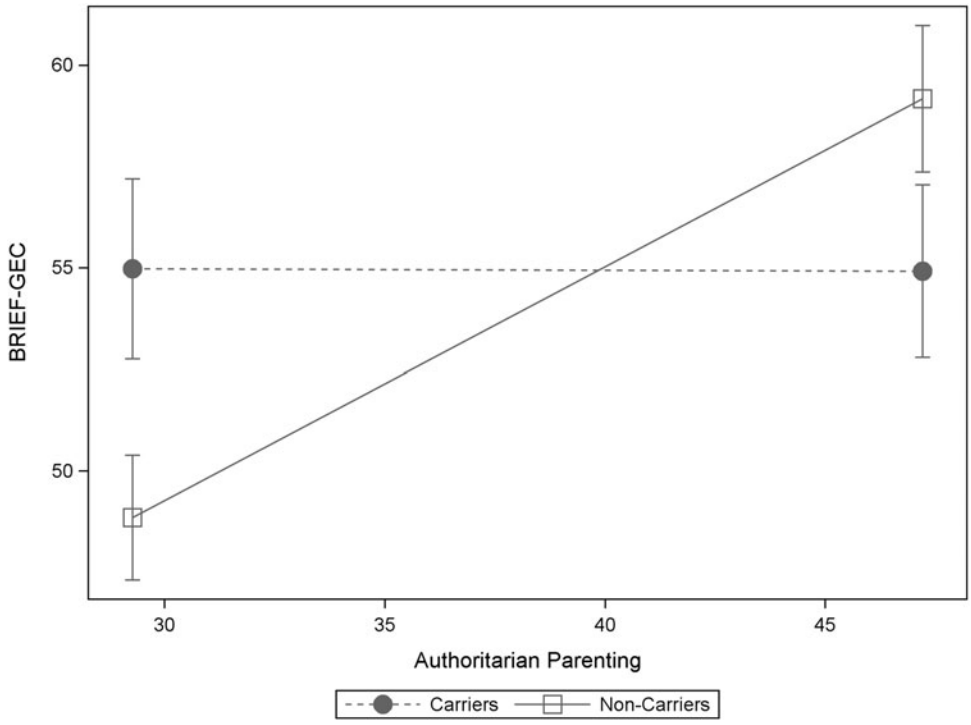

FIG. 2. Behavior Rating Inventory of Executive Function (BRIEF) Global Executive Composite outcomes at 7 years revealed a significant two-way interaction among carrier status and level of authoritarian parenting.

(i.e., parenting style or quality of the home environment) on short- and long-term EF outcomes for a pediatric TBI population. For short-term EF outcomes, children with TBI who were carriers of the T allele had poorer EF compared with the OI group in a better parenting environment (i.e., low levels of permissive parenting). When exposed to a more negative parenting environment (i.e., high levels of permissive parenting), the presence of the T allele was no longer associated with poorer EF scores; only children with TBI who were non-carriers had significantly poorer EF compared with children with OI who were non-carriers. From an injury perspective, TBI was associated with poorer EF than OI; however, when considering both genetic and parenting factors, the relationship became more complicated. In a positive parenting environment (low permissiveness), the combination of TBI and carrier status was associated with worse EF; however, in a negative parenting environment (high permissiveness) the combination of TBI and carrier status was associated with similar EF to non-carriers with TBI and carriers with OI.

For long-term EF outcomes, a similar pattern was found for the total sample (children with TBI and OI combined). In a more positive parenting environment (i.e., low levels of authoritarian parenting) carriers of the T allele had significantly worse EF outcomes compared with non-carriers, whereas no significant group differences were found in the negative parenting environment (i.e., high levels of authoritarian parenting). Therefore, regardless of injury type (TBI or OI), in the context of a positive parenting environment (low authoritarian), carrier status was associated with worse EF. Overall, these findings suggest that the effects of genetic factors on EF are more evident for children with pediatric injury from more favorable family environments, such that significant genetic effects of the T allele may either be muted or obscured under conditions of environmental disadvantage.

These findings add to the growing literature on genetic influences on recovery following pediatric TBI. Recent studies have found associations of the COMT genotype with long-term EF after TBI and OI[20] and of other dopamine-related genes with neurobehavioral recovery after early TBI, including ANKK1.[27] This study expands upon the limited literature by including the interaction of environment and genetic variation on outcomes of pediatric TBI. While identifying genetic factors associated with recovery after TBI is in the early stages, other work has highlighted the importance and complexity of environmental influences in genetic research.[36] Our study also adds to the literature by examining genetic effects in the context of both negative and positive environments. Belsky and Pluess[45] have argued for the importance of examining the effect of risk alleles when exposed to a stressor (e.g., negative environment), consistent with the diathesis-stress (vulnerability) model,[46,47] as well as to explore a differential susceptibility (plasticity) model. The latter model is hypothesized to account for associations of some risk alleles with more positive outcomes when the carrier is exposed to a positive environment, such that the carrier of the allele is more susceptible to both adverse and supportive environmental influences in a ''for-better-and-for-worse'' manner.[48] Such an effect has been found for the ANKK1 T allele in preliminary research on typically developing children examining the gene-environment interaction for the ANKK1 T allele in terms of early maternal influences and the prediction of later affective functioning[49] or vagal reactivity.[50] While the current findings are not consistent with a differential susceptibility model, the ways in which epigenetic or other TBI-related factors uniquely affect the gene-environment interaction in an injured pediatric population warrant further exploration.

The findings should be considered preliminary and interpreted in light of the study's limitations. More research is needed to

explore the robustness of the associations. Although the sample size was equal to or larger than that of other similar studies, larger sample sizes are needed to corroborate and further evaluate relationships. Because of the sample size, other analyses exploring injury severity or age at injury were not able to be included. These factors are related to recovery following pediatric TBI and should be considered in subsequent research with larger samples. Although *post hoc* adjustments for multiple comparisons were not made due to limited power, the medium-to-large effect sizes found in the present study and related findings in the adult TBI population suggest that these associations are reliable. EF outcomes were limited to parent report, which may be more ecologically valid than traditional neuropsychological tests, but may also introduce bias. It would be beneficial to explore gene–environment influences across a broad range of child outcomes, including measures of neuropsychological skills, academic achievement, and social–behavioral functioning. In addition, only a single SNP was included. Other genes related to dopamine have been associated with neurobehavioral outcomes following pediatric TBI[27] and evidence from the adult literature suggests the interaction of within-gene genotypes for ANKK1 (i.e., haploblocks) may better account for significant effects.[32]

In summary, this study represents one of the first to explore gene-environment interactions in a pediatric TBI population, and presents preliminary evidence that genetic influences on TBI recovery may vary across different environmental contexts. Knowledge of the underlying biological mechanisms influencing recovery following TBI could inform prognosis and promote individualized treatment protocols that could improve short- and long-term outcomes for children with TBI. Further work is needed to understand gene-environment interactions involving ANKK1 and other dopamine-related genes that may influence neurobehavioral recovery after early TBI.

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Author Disclosure Statement

No competing financial interests exist.

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