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Catechol-O-Methyltransferase Genotypes and Parenting Influence on Long-term Executive Functioning after Moderate to Severe Early Childhood Traumatic Brain Injury: An exploratory study

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Abstract

Objective—To examine Catechol-O-methyltransferase (COMT) rs4680 genotypes as moderators of the effects of parenting style on post injury changes in parent behavior ratings of executive dysfunction following moderate to severe early childhood traumatic brain injury (TBI).

Setting—Research was conducted in an outpatient setting.

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Participants—Participants included children admitted to hospital with moderate to severe TBI ($n = 55$) or orthopedic injuries (OI; $n = 70$) between ages 3–7 years.

Design—Prospective cohort followed over seven years post injury.

Main Measures—Parenting Practices Questionnaire (PPQ) and the Behavior Rating Inventory of Executive Functioning (BRIEF) obtained at baseline, six, 12, and 18 months, and 3.5 and 6.8 years post injury. DNA was collected from saliva samples, purified using the Oragene (DNA Genotek, Ottawa, Ontario, Canada) OG-500 self-collection tubes, and analyzed using TaqMan (Applied Biosystems) assay protocols to identify the COMT rs4680 polymorphism.

Results—Linear mixed models revealed a significant genotype $\times$ parenting style $\times$ time interaction ($F = 5.72$, $p = .02$), which suggested the adverse effects of authoritarian parenting on post injury development of executive functioning were buffered by the presence of the COMT AA genotype (lower enzyme activity, higher dopamine levels). There were no significant associations of executive functioning with the interaction between genotype and authoritative or permissive parenting ratings.

Conclusion—The lower activity COMT rs4680 genotype may buffer the negative effect of authoritarian parenting on long-term executive functioning following injury in early childhood. The findings provide preliminary evidence for associations of parenting style with executive dysfunction in children and for a complex interplay of genetic and environmental factors as contributors to decreases in these problems after traumatic injuries in children. Further investigation is warranted to understand the interplay among genetic and environmental factors related to recovery after TBI in children.

Keywords

Traumatic Brain Injury; Genetic Factors; Pediatric Brain Injury; Behavior; Cognitive Function

Background

The estimated economic cost of traumatic brain injury (TBI), including direct and indirect costs, likely currently exceeds \$76.5 billion.¹ Childhood TBI is one of the leading causes of morbidity and mortality in children and results in approximately 2,685 deaths, 37,000 hospitalizations, and 435,000 emergency department visits yearly in the United States.^{2–4} Because injuries most commonly occur at a young age, they have a lifelong impact. Currently, the meager amount of scientific evidence available for prognosis, management, and treatment of pediatric TBI is disproportionate to the large societal and medical impact of this condition.

Recovery after injury is related to multiple factors, including age at injury, severity of injury, and time post injury; however, individuals with very similar brain injuries often have disparate trajectories of recovery.^{5–7} Differential trajectories of recovery, in part, are likely a result of variation in individual (i.e., genetic) and environmental influences. The quality of the child's environment, including parenting behavior, resources in the home, and family functioning, is an important determinant of both short- and long-term cognitive, behavioral, and social recovery after pediatric TBI.^{5,8–18} Greater socioeconomic resources, more social

supports, and better family functioning buffer or reduce the adverse effects of severe TBI on executive functions, behavior, and social and academic skills.^{9,19–21} The consequences of TBI are more pronounced in younger than older children and vary across time post injury, as a function of both TBI severity and environmental factors.¹⁶ Genetic factors have also been examined in relation to outcomes of pediatric TBI, with most studies focusing on the effects of Apolipoprotein E (APOE) genetic variants on survival and global functioning.^{22–27} The variety and breadth of candidate gene variants analyzed in prior adult studies highlight the potential for different genes to be important in recovery at various stages after TBI.²⁸ However, few studies have investigated the influence of variants in genes other than APOE on outcomes of pediatric TBI and we are not aware of any studies that have considered the joint influences of genetic and environmental factors on the post injury development of this population.

Environmental context may moderate the effect one particular gene has on the expression of a particular phenotype.²⁹ Adverse effects of a given genotype may be negated by a favorable environment and/or exacerbated by a poor environment. For example, dopamine-receptor, dopamine pathway, serotonin transporter, and catechol-O-methyltransferase genetic variants interact with environmental factors to influence cognitive and behavioral functioning in various childhood populations.^{30–41} These findings suggest that a complex interplay occurs between genetic and environmental factors that ultimately influences recovery from TBI. Thus, gene-environment interactions need to be considered to fully understand genetic influences on recovery after pediatric TBI.

The dopamine and catecholamine systems are believed to play an important role related to neurocognitive and behavioral recovery after TBI.^{42–48} Dopamine receptors are located in areas of the brain, including the frontal cortex, striatum, and hippocampus, that are commonly affected by TBI and important to neurocognitive and behavioral functioning.⁴⁸ Alterations in dopamine release, receptor expression, and metabolism influence neurocognitive and behavioral recovery after injury. Catechol-O-Methyltransferase (COMT) is an enzyme involved in degradation of dopamine and is primarily expressed in the prefrontal cortex and hippocampus.^{49–53} Variation of a common genetic variant (rs4680) in the COMT gene has direct functional implications and is associated with pre-frontal mediated working memory.^{49,50,54–58} The AA genotype codes for methionine homozygotes and results in lower enzyme activity, whereas the GG genotype codes for valine homozygotes and results in higher enzyme activity. Low COMT enzyme activity (i.e., decreased degradation of catecholamines) results in higher levels of neurotransmitters while high activity of COMT (i.e., increased degradation of catecholamines) results in lower levels of neurotransmitters.^{49,54} Because of the importance of catecholamine function in recovery after TBI^{42–48}, understanding associations of the COMT rs4680 genotypes with recovery after TBI is of particular interest. Preliminary studies suggest that variations in the COMT rs4680 genotype are related to outcomes after adult and pediatric TBI.^{59–62} Recent work with the same cohort studied in this study has demonstrated an association of the COMT rs4680 genotype with executive function outcomes up to 18 months after moderate to severe TBI and orthopedic injury (OI) in children age 3–7 years at the time of injury.⁶²

To our knowledge, prior work has not reported on the potential interaction of genetic and environmental influences of recovery after pediatric TBI. The objective of this study is to build upon our prior COMT rs4680 genotype research by examining the COMT rs4680 genotype as a moderator of associations between environmental factors and behavioral changes after TBI. We hypothesized that the COMT rs4680 genotype would moderate the association of parenting style and post injury executive function.

Methods

Design

This was a prospective, longitudinal (over ~7 years post injury) observational, cohort study of the moderating effect of a functional COMT variant (rs4680) on the association of parenting style with post injury changes in parent-reported executive dysfunction in young children with TBI and OI.

Participants

Participants were recruited from an ongoing, prospective, long-term descriptive study evaluating children who sustained a TBI between age 3 and 7 years and a comparison group of age-matched children with OI.⁶² Two-hundred and thirteen participants who were enrolled in the original study were eligible for the current genetic study. The only difference between participants included in the analysis compared to those not included in demographic characteristics and study measures was that participants had slightly lower permissive parenting practices scores (Mean(SD) = 30.95(6.86) versus 32.86(6.20), $p = .04$) (see Table 1). Recruitment took place at three children's hospitals and one general hospital in Ohio from 2003 to 2006. Participants completed assessments at multiple time points, including the immediate post-acute period (0 to 3 months after injury), six, 12, and 18 months post injury, and an average of approximately 3.5 and 6.8 years post injury. Additional inclusion criteria included hospitalization overnight for traumatic injury (TBI or OI), no evidence of child abuse as the cause of the injury, no history of documented neurological problems or developmental delays preinjury, and English as the primary language in the home. The severity of TBI was characterized using the lowest post resuscitation Glasgow Coma Scale (GCS) score.⁶³ Severe TBI was defined as a GCS score less than or equal to eight. The moderate TBI group had a GCS score of nine to 12 or a GCS score of 13 to 15 in association with abnormal brain imaging. Nine children in the sample with genetic data ($n=9$) who had mild TBI, defined as a GCS of 13 to 14 without evidence of abnormal brain imaging were excluded from analyses to limit heterogeneity of TBI severity. The OI group included children who sustained a bone fracture (not including skull or facial fractures), had an overnight stay in the hospital, and did not exhibit alterations in consciousness or other signs or symptoms of head trauma or brain injury.

DNA Collection

DNA was collected from saliva samples from the participants, purified using the Oragene (DNA Genotek, Ottawa, Ontario, Canada) OG-500 self-collection tubes, and analyzed using TaqMan (Applied Biosystems) assay protocols to identify the COMT rs4680 genotypes as described previously.⁶² Genotypes identified were AA (methionine/methionine homozygote;

low COMT enzyme activity; higher catecholamine levels), GA (valine/methionine heterozygote; intermediate COMT enzyme activity, intermediate catecholamine levels) and GG (valine/valine homozygote; high COMT enzyme activity; lower catecholamine levels).⁶² COMT genotypes were dichotomized into low COMT enzyme genotype (AA) versus intermediate/high COMT enzyme genotypes (GA+GG) for analyses.

Measures

Parent ratings of the child on the Behavior Rating Inventory of Executive Function (BRIEF) targets problems in executive function (i.e., executive dysfunction) as evident in everyday behavior, with higher scores reflecting more executive dysfunction.^{64–68} The BRIEF preschool version was used for children 2–5 years and school age BRIEF version was used for children 6–18 years at the time of assessment.^{67,68} Baseline ratings were based on the parent's retrospective recall of the child's executive behavior prior to the injury. The six, 12, and 18 month, and 3.5 year, and 6.8 year evaluations reflected the parent's ratings of the child's executive behavior at the time of form completion. We used the global executive composite T-score (BRIEF GEC) to assess global executive function behaviors.

The Parenting Practices Questionnaire (PPQ) was used to assess the extent that parents rate themselves as engaging in authoritative, authoritarian, and permissive parenting behaviors.⁶⁹ The PPQ is a 62-item instrument that uses a five-point Likert scale. We used the raw total score for each of these dimensions to characterize parenting behaviors, which were originally described by Baumrind.^{70,71} Scores were included in statistical models as continuous variables. A permissive parent allows their child to regulate his/her own activities, avoids control, and uses reason and manipulation, but not power, to parent the child. An authoritarian parent shapes and controls their child in accordance with a strict and punitive standard and often restricts the child's autonomy. An authoritative parent directs their child in a rational manner, encourages discussion, and values both autonomy and disciplined conformity. Permissive and authoritarian parenting styles are generally considered ineffective, whereas authoritative parenting is considered an effective parenting style.

Analysis

Simple statistics such as means, standard deviations, and frequencies were used to summarize the data. Group comparisons were conducted using independent *t*-, Analysis of Variance, and Fisher exact tests as appropriate. COMT genotypes were tested for Hardy-Weinberg equilibrium using JMP genomics software as part of the SAS program as described previously.⁶² Mixed model linear regression was used to evaluate the moderating effect of genotype on associations of parenting style with post injury developmental change in parent ratings of executive dysfunction. Parenting style ratings on the PPQ were used to assess each of three parenting styles, with each style considered in a separate model. Each parenting style rating (permissive, authoritarian, and authoritative) was used as a continuous variable in the models. Participants were considered as random effects to account for correlation among data collected from participants in longitudinal designs. Baseline BRIEF GEC was included as a covariate in the models to control for preinjury executive functioning. We included the rs4680 genotypes and injury group as categorical variables. To

examine the moderating effect of genotype on the association of parenting behavior with executive function over time, we initially analyzed the four-way interaction of genotype, parenting behavior, time since injury, and group (severe TBI, moderate TBI, and OI), as well as all lower-level interaction terms. Initial models also controlled age at injury, race (white versus non-white), and socioeconomic status (defined as Z-score that combined parental education and median census tract income by zip code). Models were trimmed using systematic backward elimination and a p value threshold of .1. Higher interactions terms were trimmed first, followed by lower interaction terms and individual variables. The main effects for genotype, group (severe TBI, moderate TBI, and OI), and parenting behavior were forced into all models regardless of associated p values. When a significant ($p < .05$) genotype interaction was detected, post hoc analyses examined differences in executive dysfunction at each time point, with Holm-Bonferroni adjustment⁷² for multiple comparison based on a priori contrasts. Continuous variables were standardized to allow for computation of effect sizes based on the least squared mean estimates for group comparisons. We reported the effect sizes, the associated 95% confidence interval, and the associated adjusted p -values. P values of $< .05$ were considered statistically significant. All statistical analyses were conducted using SAS 9.3.

Results

Genetic data were included from 55 children with moderate ($n=40$) and severe ($n=15$) TBI and 70 with OI (see Table 2). There were no differences between the TBI and OI groups with genetic data with regard to sex, race, age at injury, median family income, or level of maternal education.

After trimming higher order interactions, the authoritarian parenting model showed a significant genotype $\times$ parenting $\times$ time interaction ($F = 5.72$, $p = .02$, Table 3 and Figure 1). Because the four-way interaction including group was not significant, the gene $\times$ environment $\times$ time interaction applies to the entire cohort after controlling for group (i.e., severe TBI, moderate TBI, and OI). Children with the low COMT enzyme activity genotype (AA) exposed to high levels of authoritarian parenting demonstrated decreasing parent-reported executive dysfunction over time compared to the intermediate/high COMT enzyme activity genotypes (GA+GG). Among children whose parents reported low levels of authoritarian parenting, no differences in the trajectory of executive functioning were apparent as a function of genotype (AA versus GA+GG) over time. The findings suggest the AA genotype buffered the negative long-term effects of the authoritarian parenting style on longer-term development of executive functioning.

There was also a parenting $\times$ time $\times$ group interaction in the authoritarian model that met the p value threshold of .1 ($F = 2.73$, $p = .07$, Table 3), suggesting increasing executive dysfunction over time among parents who reported higher levels of authoritarian parenting that was specific to the moderate TBI group.

There were no significant interactions between genotype and permissive parenting ratings. Models examining permissive parenting showed a parenting $\times$ time interaction in the permissive parenting model that met the p value threshold of .1 ($F = 3.05$, $p = .08$, Table 3),

suggesting increasing executive dysfunction over time across the entire cohort, after controlling for group (i.e., severe and moderate TBI versus OI) and genotype, among children's parents who reported higher levels of permissive parenting.

There were no significant interactions identified between genotype and authoritative parenting ratings. Models examining authoritative parenting demonstrated only main effects for parenting across the entire cohort ($F=11.11$, $p = .0009$, Table 3), after controlling for group (i.e., severe and moderate TBI versus OI), time, and genotype, suggesting less executive dysfunction across the entire cohort and time since injury period among parents reporting higher levels of authoritative parenting.

Discussion

Findings from this exploratory study provide evidence for the potential combined association of genetic and environmental factors with changes over time in parent ratings of executive dysfunction after traumatic injuries in children. Across the entire cohort, the low activity enzyme (AA genotype) buffered the adverse effects of high levels of authoritarian parenting on children's executive behaviors, whereas intermediate/high enzyme activity (GA +GG genotypes) conferred risk. There were no significant interaction effects between genotype and permissive or authoritative parenting styles. In contrast to our initial hypothesis, moderating effects of genotype did not vary by injury type (severe TBI, moderate TBI, and OI). These findings, thus, do not suggest genetic effects on recovery are specific to TBI, but effects apply to development of executive behavior in children more generally or at least to those having sustained traumatic injuries. Due to the preliminary nature of the study, larger replication studies are needed to verify these associations in the future.

Prior work in adult and pediatric TBI indicates the COMT rs4680 genotypes may be associated with recovery of cognitive and behavioral functioning after injury;^{28,59,62} however, this prior work has not considered environmental factors also related to recovery. Similar to this prior work, results from the current study indicate that the low activity rs4680 COMT genotype (AA) is associated with improved executive functioning after traumatic injuries (i.e., TBI and OI), especially in the context of an authoritarian parenting behavior environment. Cognitive and behavioral outcomes in other pediatric populations have been influenced by interactions between COMT rs4680 genotypes and environmental factors. Hygen et al. found that, given a history of more serious life events, the high activity rs4680 genotype (GG) was associated with more aggression in children at a mean age of 54.8 months.⁷³ These findings indicate there is a greater susceptibility to poor behavioral outcomes in response to environmental adversity in children with the rs4680 COMT GG genotype.⁷³ Additionally, carriers of the low activity COMT rs4680 genotype (AA) perform better on tasks of dual cognitive load⁷⁴ and have increased cognitive flexibility when exposed to early childhood maltreatment⁷⁵, as compared to other rs4680 genotypes. These findings confirm the importance of considering the combined effects of genetic and environmental factors on long-term outcomes after traumatic injuries in children.

To realize a full precision medicine approach for pediatric TBI, a more complete understanding of environmental influences is needed. In this study, gene environment interaction effects were found in relation to only one aspect of parenting; however, gene environment interactions were not identified for authoritative or permissive parenting. Although this finding concurs with previous work in pediatric TBI identifying environmental factors as critical determinants of long-term outcomes,^{9,12,16,19–21} more work is needed to fully understand how various environmental factors interact with other injury- and non-injury characteristics in determining developmental changes after injury. More broadly, significant work is needed to understand how genetic information may be used to develop precision medicine^{76,77} approaches for individuals after TBI.

Limitations

Although the present study is one of the largest investigations of the association of genetic factors with developmental change after pediatric TBI, it may be underpowered to detect group differences in recovery between the TBI and OI groups in regards to COMT rs4680 genetic variability. Larger sample sizes are needed to replicate the findings and more definitively elucidate the conjoint effects of genetic variants and environmental factors on long-term outcomes. Additionally, use of an uninjured control group would help to elucidate whether findings are specific to injured children or children in general. Because the candidate gene approach used evaluated only the COMT rs4680 polymorphism, this study did not explore the potential role of other polymorphisms within the COMT gene or consider polymorphisms in other genes on recovery after pediatric TBI. Future studies evaluating potential genetic influences more broadly are needed. Additionally, the influence of other environmental factors besides parenting practices was not explored in this study. A further limitation is the measure of executive function used in the study was based on parent report and both this measure and parenting style were based on parent self-report, thus shared rater variance is a potential problem. Although retrospective ratings of preinjury behavioral problems were included in models to control for preinjury function, due to the age of enrollment (3–7 years), behavioral problems that typically develop later (e.g., ADHD) may not have declared themselves at time of enrollment. Therefore, controlling for developmental disorders that typically present in later childhood was not possible. Finally, because the study population consisted primarily of moderate injuries and all children were injured during early childhood, sample size limitations precluded investigation of potential differences in genetic moderation in relation to injury severity or age at injury.

Conclusion

Prior research has demonstrated potential links between several candidate gene variants with global outcomes, secondary medical complications, and cognitive and behavioral recovery after TBI in adults. Studies evaluating the association of genetic variants with recovery after pediatric TBI are limited to primarily APOE variants. Developing a comprehensive model of recovery and subsequent development after TBI should also consider the role of the home and family environment, and their interrelationships with individual characteristics such as genes. Findings from the current study revealed moderating effects of a COMT rs4680 genotype on associations between authoritarian parenting and post injury development of

executive behaviors following early childhood traumatic injuries broadly. The findings provide preliminary evidence for a complex interplay among genetic and environmental factors as contributors to development after injury. Further investigation is warranted to understand the interplay among genetic and environmental factors related to recovery after TBI in children.

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Figure 1. Executive Function ratings over seven years post injury by genotype and authoritarian parenting behavior

Over time after injury, individuals with the COMT rs4680 AA genotype have less executive dysfunction in environments with high levels of authoritarian parenting. Post-hoc analysis of least square means over time in high authoritarian environments demonstrates widening differences between executive dysfunction scores in low activity genotype (AA) and intermediate/high activity genotypes (GA+GG): 6 months: Estimate(std error)= $-.84$ (2.31) with 95% Confidence Interval (CI) of -5.38 to 3.69 , effect size estimate(std error) = $.06$ (.17) with 95% CI of $.28$ to $.41$, $p=1$; 12 months: Estimate(std error)= -1.52 (2.21) with 95% CI of -5.86 to 2.82 , effect size estimate(std error) = $.11$ (.16) with 95% CI of $.21$ to $.44$, $p=1$, 18 months: Estimate(std error)= -2.19 (2.14) with 95% CI of -6.40 to 2.01 , effect size estimate(std error) = $.16$ (.16) with 95% CI of $.15$ to $.48$, $p=1$, 3.5 years: Estimate(std error)= -4.90 (2.15) with 95% CI of -9.11 to $-.68$, effect size estimate(std error) = $.37$ (.16) with 95% CI of $.05$ to $.68$, $p=.21$, 6.8 years: Estimate(std error)= -9.36 (3.02) with 95% CI of -15.29 to -3.43 , effect size estimate(std error) = 0.70 (.23) with 95% CI of 0.26 to 1.14 , $p=0.02$. Note that parenting ratings were divided into low and high (defined as one standard deviation above and below the sample mean) for development of figure, but were used as continuous variables in the analytic models. *P* values represent multiple testing corrected values.

Table 1

Comparison of participants included and not included in the analysis

Demographics	Participants in analysis	Participants not in analysis	Total n for included and not included in analysis for each comparison variable		<i>p</i>
			Included	Not included	
Gender, n (%)			125	96	0.41
Male	69(55.20)	59(61.46)			
Female	56(44.80)	37(38.54)			
Race, n (%)			125	96	0.37
White	93(74.40)	66(68.75)			
Non-white	32(25.60)	30(31.25)			
Age at injury in years, mean (stdv)	5.14(1.09)	4.92(1.12)	125	96	0.15
Median family income, mean (stdv)	\$60,305.00 (22299.76)	\$60,654.76 (26896.49)	124	93	0.92
Education categorized by high school, n (%)			125	92	1.00
Less than high school	14(11.20)	11(11.96)			
Greater than or equal to high school	111(88.80)	81(88.04)			
Glasgow coma scale (GCS)	10.87(4.70)	11.81(4.07)	55	47	0.29
Socioeconomic status (Z-score)	0.01(0.96)	-0.01(1.05)	125	96	0.91
Parenting Practices: Authoritative raw	114.23(10.81)	114.61(9.23)	124	88	0.79
Parenting Practices: Authoritarian raw	39.50(7.94)	39.32(7.51)	124	88	0.87
Parenting Practices: Permissive raw	30.95(6.86)	32.86(6.20)	124	88	0.04
BRIEF: Global Executive Composite (T-Score)	48.83(12.96)	51.23(13.64)	125	83	0.20

Table 2

Participant Characteristics included the model by injury group

Participant Characteristics by Injury Group				
	OI	Moderate TBI	Severe TBI	p
	(n=70)	(n=40)	(n=15)	
Gender, n (%)				0.64
Male	36(51.43)	24(60.00)	9(60.00)	
Female	34(48.57)	16(40.00)	6(40.00)	
Race, n (%)				0.80
White	53(75.71)	30(75.00)	10(66.67)	
Non-white	17(24.29)	10(25.00)	5(33.33)	
Age at injury in years, M (SD)	5.07(1.08)	5.27(1.15)	5.12(0.97)	0.65
Median family income, M (SD)	\$ 60,735.67 (22121.68)	\$60,271.88 (24700.33)	\$58,246.29 [#] (16483.96)	0.93
Highest Maternal Educational Attainment, n (%)				0.23
< high school	5(7.14)	6(15.00)	3(20.00)	
high school	65(92.86)	34(85.00)	12(80.00)	
Glasgow Coma Scale		13.43(2.18)	4.07(1.94)	<.0001

[#] based on n of 14

Table 3

Final mixed effect models organized by parenting behavior

Variable	Authoritarian		Permissive		Authoritative	
	F-value	p-value	F-value	p-value	F-value	p-value
Preinjury GEC	99.16	<.0001	81.69	<.0001	103.79	<.0001
Group	2.88	.06	10.84	<.0001	13.55	<.0001
Genotype	.05	.82	.38	.54	.25	.62
Time since injury	1.42	.23	6.37	.01	5.34	.02
Parenting	4.13	.043	30.23	<.0001	11.11	.0009
Parenting x group	.67	.51	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Time since injury x genotype	4.17	.04	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Time since injury x group	2.10	.12	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Parenting x time since injury	.68	.41	3.05	.08	xxxxxx	xxxxxx
Parenting x genotype	.05	.83	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Parenting x time since injury x genotype	5.72	.02	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Parenting x time since injury x group	2.73	.07	xxxxxx	xxxxxx	xxxxxx	xxxxxx