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Associations between the dopamine D4 receptor gene polymorphisms and personality traits in elite athletes

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ABSTRACT: Personality traits and temperament may affect sports performance. Previous studies suggest that dopamine may play an important role in behavior regulation and physical exercise performance. The aim of this study is to determine associations between dopamine D4 receptor gene (DRD4 Ex3) polymorphisms and personality traits (such as neuroticism, extraversion, openness, agreeability and conscientiousness) in elite combat athletes. A total of 302 physically active, unrelated, self-reported Caucasian participants were recruited for this study. The participants consisted of 200 elite male combat athletes and 102 healthy male participants (control group). For personality trait measurements, the NEO Five-Factor Personality Inventory (NEO-FFI) and the State-Trait Anxiety Inventory questionnaires were used. For the genetic assays, blood was collected and all samples were genotyped using the real-time PCR method. A 2 x 3 factorial ANOVA revealed statistically significant differences on the Openness NEO Five Factor Inventory scale for both examined factors, i.e. sport status and genetics DTD4 Ex3. Combat athletes achieved higher scores on the Conscientiousness NEO-FFI scale when compared to controls (7.18 vs 5.98). On the other hand, combat athletes scored lower on the Openness scale in comparison with control group (4.42 vs. 4.63). Subjects with the DRD4 Ex3 s/s genotype had lower results on the openness scale in comparison with participants with the DRD4 Ex3 s/1 genotype (4.01 vs. 4.57) and higher DRD4 Ex3 1/1 genotype (4,01 vs. 3,50). In conclusion, we found an association between the dopamine D4 receptor gene in variable number tandem repeat (VNTR) polymorphisms and athletic status for two NEO-FFI factors: Openness and Conscientiousness. The *DRD4* exon 3 polymorphism may be associated with the selected personality traits in combat athletes, thereby modulating athletes' predisposition to participate in high risk sports.

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INTRODUCTION

Dopamine is the hormone of “motivation, thrill and adventure seeking” [1]. The influence of dopamine is associated with making so called “risky decisions”. The next element that should be acknowledged as important is the so called “mesolimbic reward system” which mediates the reward psychopharmacology response to physical effort or other factors. Dopamine, described as a “pleasure neurotransmitter,” is functionally connected with the “pleasure center,” located in the ventral tegmental area of the brain in which there are

neurons of the dopaminergic system and nucleus accumbent [2]. Hence, the system seems to be one of the key factors in starting and continuing training. It seems that the interactions between genetically conditioned temperament and environmentally conditioned character, are factors influencing will to participate in and continue with sport training, which consequently affect achievement of success in this area [3,4]. Hence, ontogenetic differences result from the modulatory influence of the neurotransmitter system on expression

of particular personality traits among others. This example of such modification could be a shortage of dopamine that results in significantly influencing “novelty-seeking” behaviors expressed in the form of constantly searching for new “thrills”. The effect is functional modification of dopaminergic system [5,6,7,8]. Another factor which exerts influence by modulating the dopaminergic pathway, and consequently sporting achievement, is visual perception, which is probably one of the key determinants in combat sports. Dopamine, which is a chemical analogue of light, affects the paracrine neurotransmitter in the retina, whereas receptors D2 and D4 of photoreceptor cells control illumination-related processes, among which melatonin biosynthesis, opsin expression in cone cells or the level of cAMP inside receptors [9] are included.

Personality significantly influences behavior, life-style and also the maintenance of healthy habits in a lifetime. Current research concerning personality concentrates on the model that is constructed of the so called Big Five [10,11,12,13], which consists of: Openness, Conscientiousness, Extraversion, Agreeableness and Neuroticism domains. These 5 traits isolate differences among people which influence emotions, motivation and cognition [14]. Currently, to analyze these personality traits, the NEO personality inventory (NEO-FFI) is employed.

The high novelty-seeking or ‘risk-taking’ personality trait was previously correlated with genetic variants within genes encoding dopamine receptors [15]. These dopamine receptors, including D2 and D4 receptor subtypes, are involved in dopamine neurotransmission and may modulate memory, behaviour and executive function [16]. It has also been suggested that dopamine neurotransmission is connected with novelty-seeking [17,18], which is defined as “excitement to novel stimuli” in relation with dependence [19,20] and relapse [21]. Also, extraversion is a trait connected with the functioning of the dopaminergic system. As dual research shows, the traits are related with genetics in different ranges – from 25% to 61% [21, 22]. Both novelty-seeking and extraversion are correlated with receptor 4 of the dopamine gene (*DRD4*) as indicated in research on healthy [23] and research dependent [24] subjects. However, other research does not seem to confirm this association [25].

The *DRD4* gene encodes the dopamine D4 receptor and is expressed in the cognitive and emotional areas of the limbic system and is located on chromosome 11 (locus p15.5). A variable number of tandem repetitions (VNTR) located in the 3rd exon is one of the most frequently investigated polymorphisms of the gene. To date, association has been demonstrated for 2 of the 10 repeated 48bp sequence variants, showing influence on length of the third intracellular loop receptor D4. Interestingly, polymorphic variants influence the expression of these genes in a different manner [26]. Asghari [27], in his work, indicates diversified sensitivity in relation to endogenous dopamine depending on the length of the variant coding for the particular receptor. Dopamine transporter gene *DAT1*, which is another key element of the dopaminergic system, is located in chromosome 5 (p15.3). The most frequently investigated variant is the VNTR

polymorphism located in 3’ UTR region. The 40bp sequence of 3 to 13 repetitions was identified, however, the most frequently occurring variants had 9 or 10 repeated sequences [28]. Nevertheless, contradictory reports concerning polymorphic variants and *DAT1* transcription level were also observed in this case [29,30].

The goal of the present study was to investigate the personality traits in elite combat athletes and healthy controls with respect to variable number of tandem repeats (a 48 bp unit) in the third exon of the *DRD4* gene.

MATERIALS AND METHODS

Materials

The study was conducted among healthy (non-dependent and non-psychosis) 200 Polish male combat athletes aged 22.9 ± 4.2 (judo, $n = 51$; wrestling, $n = 38$; boxing, $n = 50$, kickboxing, $n = 32$; karate, $n = 29$). All of them were ranked in the top 10 nationally in their respective disciplines. The study population included 16 athletes classified as ‘top-elite’ (gold medalists in the World and European Championships, World Cups or Olympic Games) and 68 athletes classified as ‘elite’ (silver or bronze medalists in the World and European Championships, World Cups or Olympic Games). The others ($n=69$) were classified as ‘sub-elite’ (participants in international competitions, with no less than 8 years experience). Various methods were used to obtain the samples, including targeting national teams and providing information to national coaching personnel and athletes attending training camps.

Controls included 102 unrelated, healthy (non-dependent and non-psychosis) Polish male volunteers aged 21.6 ± 2.6 . All athletes and controls were Caucasian to reduce the possibility of racial gene skewing and to overcome any potential problems due to population stratification.

Ethical approval

The procedures followed in the study were conducted in accordance with the principles of the World Medical Association Declaration of Helsinki and were approved by the Bioethics Committee for Clinical Research at the Regional Medical Chamber in Gdansk, Poland. All participants were provided with an information sheet concerning study particulars, including the purpose of the study and the procedures involved, in addition to the possible risks and benefits associated with participation. All participants provided written informed consent to genotyping with the understanding that it was anonymous and that the obtained results would be confidential.

Methods

Personality Traits

All participants were tested using the NEO Five-Factor Personality Inventory (NEO-FFI) and, the State-Trait Anxiety Inventory (STAI) questionnaires. The results of these were both given on the sten scale.

The NEO Five Factor Inventory questionnaire is used to diagnose personality traits, which are included in the five-factor model defined

by the Big Five model (neuroticism, extraversion, openness, conscientiousness and agreeableness). The questionnaire consists of 60 statements (of self-reported character), which require the participant to examine one's attitude toward one's own self. The

Anxiety Inventory (STAI) questionnaire is used to examine anxiety, which is understood as conditionally and transiently conditioned condition of the individual and anxiety, understood as a relatively constant personality trait. The STAI questionnaire consists of two

TABLE 1. Hardy-Weinberg's law for the athletes subjects.

Hardy-Weinberg equilibrium calculator including analysis for ascertainment bias		Observed (Expected)		Test χ^2	
				χ^2	p
DRD4 Ex3	I/I	6 (10.1)	s allele freq = 0.78 I allele freq = 0.22	2.80	>0,05
	s/I	78 (69.7)			
	s/s	116 (120.1)			

TABLE 2. Hardy-Weinberg's law for the control subjects.

Hardy-Weinberg equilibrium calculator including analysis for ascertainment bias		Observed (Expected)		Test χ^2	
				χ^2	p
DRD4 Ex3	s/I	28 (32.1)	s allele freq = 0.8 I allele freq = 0.2	1.7	>0,05
	s/s	68 (65.9)			
	I/I	6 (3.9)			

TABLE 3. Frequency of genotypes and alleles of the DRD4 Ex3 genes polymorphisms in athletes and in controls.

Group	DRD4 Ex3				
	Genotypes			Alleles	
	s/I N(%)	s/s N(%)	I/I N(%)	s N(%)	I N(%)
Athletes N=200	78 (0.39)	116 (0.58)	6 (0.03)	310 (0.78)	90 (0.22)
Control N=102	28 (0.27)	68 (0.67)	6 (0.06)	164 (0.80)	40 (0.20)
χ^2		4.81		.67	
p value		.090		.413	

p-statistical significance χ^2 test, N- number of subjects

Significant between-group differences are marked in bold print.

TABLE 4. STAI and NEO Five Factor Inventory results between healthy control and athletes.

STAI / NEO Five Factor Inventory/ (sten scale)	Athletes (N = 200)	Control (N = 102)	t p value	Cohen's d
STAI ST	4.90± 2.22	4.73±2.14	.688	.08
STAI C	5.28±2.37	5.20±2.00	.848	.04
Neuroticism/scale	4.84±2.30	4.82±1.72	.967	.01
Extraversion/scale	6.20±1.88	6.14±1.78	.864	.03
Openness/scale	4.42±1.62	4.63±1.75	.538	.12
Agreeability/scale	5.18±2.13	5.51±1.88	.411	.16
Conscientiousness/scale	7.18±1.92	5.98±1.79	.002	.65

p-statistical significance t-Student's test, N- number of subjects

Significant between-group differences are marked in bold print.

TABLE 5. Differences in DRD4 Ex3 and STAI /NEO Five Factor Inventory between healthy control subjects and athletes.

STAI /NEO Five Factor Inventory (sten scale)	DRD4 Ex3					Main Effects ANOVA				
	Athletes (N = 200)	Control (N = 102)	s/l (N = 106)	s/s (N = 184)	l/l (N = 12)	full model	Main Effects			
						F (p value)	factor	F (p value)	η^2	power (alfa = 0,05)
STAI ST	4.90 ± 2.22	4.72 ± 2.14	4.45 ± 2.73	4.61 ± 2.65	3.75 ± 2.18	F5,296=.389 p=.865 R2=.007	intercept	F_{1,296}=223 (p=.000)	.430	1.000
							sport/control	F1,296=.0003 (p=.987)	1e-6	.050
							DRD4 Ex3	F2,296=.65 (p=.525)	.004	.158
							sport/control x DRD4 Ex3	F2,296=0.12 (p=.883)	.0008	.069
STAI C	5.28 ± 2.37	5.20 ± 2.00	4.93 ± 2.56	4.97 ± 2.91	4.25 ± 2.18	F5,296=.557 p=.733 R2=.009	intercept	F_{1,296}=252 (p=.000)	.460	1.000
							sport/control	F1,296=.34 (p=.560)	.001	.089
							DRD4 Ex3	F2,296=.31 (p=.735)	.0002	.099
							sport/control x DRD4 Ex3	F2,296=.08 (p=.922)	.0006	.062
NEO FFI Neuroticism /scale	4.84 ± 2.30	4.82 ± 1.72	4.63 ± 2.62	4.16 ± 2.44	3.25 ± 2.60	F5,296=1.14 p=.338 R2=.019	intercept	F_{1,296}=223 (p=.000)	.430	1.000
							sport/control	F1,296=.04 (p=.837)	.0001	.054
							DRD4 Ex3	F2,296=2.08 (p=.127)	.014	.426
							sport/control x DRD4 Ex3	F2,296=0.17 (p=.843)	.001	.076
NEO FFI Extraversion /scale	6.20 ± 1.88	6.14 ± 1.78	5.44 ± 2.64	5.40 ± 2.39	6.67 ± 3.03	F5,296=1.02 p=.406 R2=.017	intercept	F_{1,296}=473 (p=.000)	.615	1.000
							sport/control	F1,296=1.18 (p=.278)	.004	.192
							DRD4 Ex3	F2,296=1.57 (p=.209)	.011	.333
							sport/control x DRD4 Ex3	F2,296=0.13 (p=.878)	.0009	.070
NEO FFI Openness /scale	4.42 ± 1.62	4.63 ± 1.75	4.57 ± 2.39	4.01 ± 2.01	3.50 ± 2.54	F_{5,296}=4.48 p=.0006 R²=.070	intercept	F_{1,296}=331 (p=.000)	.528	1.000
							sport/control	F_{1,296}=16.3 (p=.00007)	.052	.981
							DRD4 Ex3	F_{2,296}=3.80 (p=.023)	.025	.689
							sport/control x DRD4 Ex3	F_{2,296}=5.01 (p=.007)	.033	.812
NEO FFI Agreeability /scale	5.18 ± 2.13	5.51 ± 1.88	5.03 ± 2.64	5.56 ± 2.56	5.00 ± 1.86	F5,296=0.684 p=.636 R2=.011	intercept	F_{1,296}=358 (p=.000)	.548	1.000
							sport/control	F1,296=.005 (p=.941)	.00002	.051
							DRD4 Ex3	F2,296=1.66 (p=.192)	.011	.349
							sport/control x DRD4 Ex3	F2,296=1.06 (p=.853)	.001	.074
NEO FFI Conscien- tiousness/ scale	7.18 ± 1.92	5.98 ± 1.79	6.10 ± 2.46	6.23 ± 2.59	6.33 ± 2.46	F_{5,296}=6.85 p=.000005 R²=.104	intercept	F_{1,296}=569 (p=.000)	.658	1.000
							sport/control	F_{1,296}=10.3 (p=.001)	.034	.892
							DRD4 Ex3	F2,296=0.14 (p=.868)	.0009	.072
							sport/control x DRD4 Ex3	F_{2,296}=4.18 (p=.016)	.027	.733

independent subscales, each of which contains 20 statements, one (X-1) measures anxiety-state and the other (X-2) measures an anxiety-trait.

Genetic analyses

For the genetic assays, blood was collected into tubes with EDTA (anticoagulant). Data Collection Genomic DNA from peripheral blood leukocytes was extracted using a High Pure Polymerase Chain Reaction (PCR) Template Preparation extraction kit (Roche Diagnostics, Mannheim, Germany). The extraction was performed according to the manufacturer’s instructions. DNA sample were stored at 4°C for further analysis.

The genomic DNA was isolated from venous blood according to standard procedures. Samples were genotyped using the PCR method. The *DRD4* genotypes were grouped based on the presence of the short (2–5 repeat) and long (6–11 repeat) variants. Genotyping was performed using the PCR-VNTR method, using primers: F: 5 0 -GCG ACT ACG TGG TCT ACT CG 3 0, R: 5 0 -AGG ACC CTC ATG GCC TTG 3 0; in the final volume of 25 µL PCR mix per reaction, with 100 ng genomic DNA, 10 pmol of primers, 50 mM KCl, 10 mM TrisHCl, 1.5 mM MgCl₂, 200 µM dATP, dCTP, dTTP, dGTP and 0.8 U of the Tag polymerase. Conditions for reaction: 3 min. of initial denaturation in 95°C, cycling 30 s. of denaturation in 95°C, 1 min. of primers hybridization in 63°C and 30 s. of elongation in 72°C, repeated in 35 cycles, 5 min. of final elongation in 72°C. The amplified products were visualized using ethidium bromide stained gel electrophoresis (3% agarose) and UV photography. The products ranged from 379 bp (2 repeats) to 811 (11 repeats). The products were divided into 2 groups: short alleles (S, 2–5 repeats) and long alleles (L, 6–11 repeats).

Statistical analysis

Concordance between the genotype frequency distribution and Hardy-Weinberg equilibrium (HWE) was tested with the HWE software (<http://www.oege.org/software/hwe-mr-calc.html>) [31]. *DRD4* genotype frequencies between control subjects and cases were tested using Chi square test. The relationship between *DRD4* variant, group assignment (elite athletes vs controls) and NEO Five Factor Inventory (NEO-FFI) or STAI sten scores were analyzed using 2 x 3 factorial ANOVA. The Tukey HSD post-hoc tests were conducted to determine if the interaction term was significant. All computations were performed using STATISTICA 13 (Tibco Software Inc, Palo Alto, CA, USA) for Windows (Microsoft Corporation, Redmond, WA, USA).

RESULTS

The observed *DRD4* Ex3 VNTR polymorphism frequencies did not differ from expectations based on Hardy-Weinberg theorem, neither in the elite athletes (Table 1, $p=0.094$), nor in the control group (Table 2, $p=0.192$). There were no significant differences between cases and controls with respect to genotypes ($p=0.090$) and alleles ($p=0.669$) (Table 3).

The results of 2x3 factorial ANOVA of the NEO Five-Factor Personality Inventory (NEO-FFI) and the State-Trait Anxiety Inventory (STAI) sten scales are summarized in Table 4. We found a significant result when comparing groups (elite athletes vs controls) for Openness ($F_{1,296}=16.3$, $p=0.00007$) and Conscientiousness ($F_{1,296}=10.3$, $p=0.001$), accounting for 5.2% and 3.4% of variance, respectively. In addition to those findings, we found group x *DRD4* genotype interactions: for Openness (Figure 1, $F_{2,296}=5.01$, $p=0.007$) and Conscientiousness (Figure 2, $F_{2,296}=4.18$, $p=0.016$) responsible for 3.3% and 2.7% phenotypic variation, respectively. Post-hoc analysis is shown in Table 5.

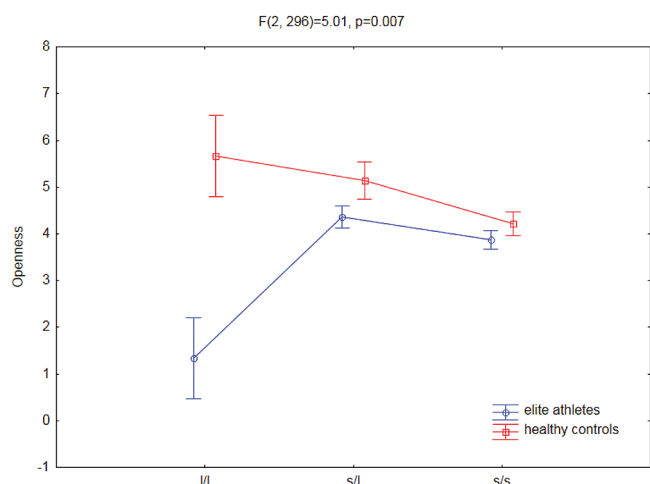


FIG. 1. The group (elite athletes vs healthy controls) x *DRD4* Ex3 polymorphism interaction for the NEO Five Factor Inventory scale of Openness.

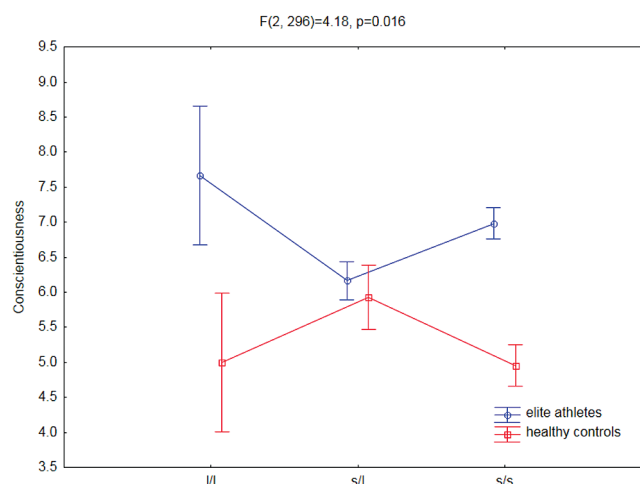


FIG. 2. The group (elite athletes vs healthy controls) x *DRD4* Ex3 polymorphism interaction for the NEO Five Factor Inventory scale of Conscientiousness.

DISCUSSION

In the present study, we demonstrated elite status in combat sports x *DRD4* genotype interactions in two domains of the five-factor model of personality: Openness and Conscientiousness. Specifically, Openness differed between *DRD4* Ex3 VNTR genotypes, but only in the elite athletes (1.33 ± 0.82 vs 4.36 ± 2.36 , for the L/L and S/L genotype, respectively, $p=0.031$), whereas Conscientiousness, although not statistically different between *DRD4* genotypes in both elite athletes and healthy controls, was significantly higher in the elite athletes compared with controls, especially in the S/S homozygotes (6.98 ± 2.34 vs 4.96 ± 2.49 , $p=0.00003$).

In 1996, two independent papers showed an association between dopaminergically modulated personality trait novelty seeking and the *DRD4* gene [18,32]. The higher scores of novelty seeking assessed by Tridimensional Personality Questionnaire were found in carriers of the 7-repeat allele and those findings were subsequently confirmed by others [33,34]. Interestingly, in the present study, we found that the elite combat athletes homozygous for the L allele (defined as the 6-11 repeats of a 48 bp segment) had significantly lower Openness scores compared with S/L heterozygotes. It is difficult to compare our findings with previous observations, as we did not assess the novelty seeking, nor did we predict it by means of correlation (multiple regression models) between novelty seeking and NEO-FFI [35]. However, given the link between novelty seeking and openness to experience (and extraversion) [36] our results may seem contradictory to previous findings that suggest an association between novelty seeking and the long allele of the *DRD4* VNTR [11,32,33]. On the other hand, the correlation between novelty seeking and NEO-FFI openness domain may not be straightforward. According to Goctowska et al. [36], "both openness and extraversion are linked to novelty in a unique way, with each of the other traits explaining a somewhat different portion of variance in novelty seeking behavior". Also, many recent studies have not found any associations between the *DRD4* exon 3 polymorphism and novelty seeking or extraversion [37,38]. A recent meta-analysis of studies of the association between the *DRD4* VNTR and *DRD4* promoter polymorphism (-521 C/T) and several approach-related traits including novelty seeking, extraversion and impulsivity revealed that only a promoter variant may be associated with novelty seeking and impulsivity [39]. Moreover, in a genome-wide association study of the FFM of personality traits in young Korean women, none of the NEO-FFI major factors were associated with the *DRD4* gene [40]. Benjamin et al. [32] reported that the presence of the 7-repeat allele was also associated with lower NEO Conscientiousness scores. However, subsequent studies failed to confirm this initial finding [25,34]. Moreover, Paterson et al. [41] pointed out some methodological flaws in the original association studies. In the present study we did not find any *DRD4* VNTR genotype dependent differences in NEO Conscientiousness scores in the elite athletes or control individuals. However, this personality domain

was significantly higher in the athletes compared with control individuals, yet the difference was evident only in carriers of the S/S genotype. It is not clear whether this is only a statistical phenomenon or a reflection of true biological interaction. The relationship between personality and exercise capacity has long been of interest to sport psychologists [42]. Elite athletes competing at the national and international level were found to have lower levels of neuroticism than non-elite athletes, whereas the level of conscientiousness and agreeableness was higher [43]. In another study, athletes scored higher than non-athletes for conscientiousness, but other personality traits did not differ significantly between the groups [42]. Thus, although our study is similar to previous studies with respect to the association between Conscientiousness and elite status, it is not clear whether the S allele, linked to higher scores of Conscientiousness [32], plays any role in the observed interaction pattern.

Studies investigating the *DRD4* variants with respect to personality dimensions in a specialized cohort of athletes are scant [44,45,46]. In 2013, Thomson et al. [45] reported a significant association between the -521 C/T (rs1800955) polymorphism in the promoter region of the *DRD4* and sport-specific sensation seeking in a high-risk sport population (skiers and snowboarders). Interestingly, another study by the same authors, in which five polymorphisms were investigated (21106T/C, 2906T/C, 2809G/A, 2291C/T, 120-bp duplication) in the promoter region of the *DRD4* in a cohort of skiers and snowboarders, failed to reproduce the previous finding of association between the *DRD4* and sensation seeking [46]. In a recent study, Abrahams et al. [47] investigated associations of *DRD2* and *DRD4* genotypes with concussion susceptibility and personality in rugby players. The authors found the association between the -521 C/T *DRD4* variant and concussion susceptibility as well as socially detached behaviour.

CONCLUSIONS

Engaging in high-risk sport (e.g. snowboarding, parachuting, martial arts) may be associated with several personality characteristics. In the present study, we found an interaction between the dopamine D4 receptor gene VNTR polymorphism and athletic status in two major NEO-FFI factors: Openness and Conscientiousness. The *DRD4* exon 3 polymorphism may be associated with the NEO Openness and Conscientiousness domains in martial arts athletes, thereby modulating athletes' predisposition to participate in high risk sport. As a majority of personality traits have been linked to genetic factors, behavioral genetic studies and personality genetics represent a new promising area of research aimed at obtaining a better understanding of athletic motivation and behavior.

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