RUNNING HEAD: COMT COMPETITIVE PERFORMANCE

Title:

Association between COMT Val158Met polymorphism and competition results of competitive swimmers.

Authors: Daisuke Abe[1], Hirokazu Doi[1], Taishi Asai[1],Mayuko Kimura[2], Tadashi Wada[3], Yuusuke Takahashi[4], Takaaki Matsumoto[5], Kazuyuki Shinohara[1]

Affiliations:

[1]Graduate School of Biomedical Sciences, Nagasaki University, [2]Kokushikan University Wellness Research Center, [3]School of Science and Engineering, Kokushikan University, [4]School of Science and Engineering, Chuo University, [5]School of Physical Education, Kokushikan University

Corresponding Author: Kazuyuki Shinohara

Affiliation: Graduate School of Biomedical Sciences, Nagasaki University

Address: 1-12-4 Sakamoto-cho, Nagasaki City, Nagasaki 852-8523 Japan

E-mail: kazuyuki@nagasaki-u.ac.jp

TEL: +81-95-819-7035

FAX: +81-95-819-7036

Abstract

Recent studies have shown the contribution of genetic determinants to athletes' physical ability. However, despite the fact that cognitive abilities like self-control and stress-tolerance influence athletes' competitive performance, few studies to date have investigated the association between genetic polymorphism, which is linked to cognitive ability and athletic performance. The present study investigated the link between single-nucleotide polymorphisms (SNPs), which are known to exert influences on dopaminergic neural function and competitive performance of swimmers. The results have revealed superior competitive performance in competitive swimmers with Met allele of catechol-O-methyltransferase Val158Met polymorphism than those with Val/Val genotype. The investigated SNPs of DRD2 and DRD3 were not associated with swimmer's competitive performance. This finding indicates that genetic polymorphism linked to cognitive ability influences the athletes' performance.

Keywords: Competitive Performance, SNP, COMT, Dopamine

1. Introduction

Research on biomechanics and physiology has greatly contributed to elucidating the determinants of athletes' competitive performance. For example, biomechanical studies on swimming have revealed the influence of starting motions and drag resistance on swimming speed (Craig & Pendergast, 1979; Toussaint & Beek, 1992). On the basis of these empirical findings, the previous studies on swimming have revealed effective training methods, like the improvement of swimming speed by high-resistance training and tapering (Inigo, Jean, Thierry, Andre, Frederc, & Lucien 1995; Joseph, Houmard, & Anderson 1994).

With regard to the factors that determine the competitive performance of individual athletes, recent studies have revealed association between the physiological characteristics of individual athletes and specific genetic polymorphisms. A well-known genetic polymorphism affecting physical ability is that in the *ACTN3* gene, which encodes α-actinin-3, a protein found in the muscle that affects muscular contraction speed and endurance. Yang et al (2003). reported that among athletes, those with the explosive power-type polymorphism of *ACTN3* showed significantly higher physical performance in several sports, including swimming, water polo, and wrestling.

Existing literatures in the field of sports psychology have identified cognitive abilities, such as motivation, stress tolerance and self-regulation, as the most important determinants of athletes' competitive performance (Tod, Thatcher, & Rahman, 2010; Orlick & Partington, 1988). Furthermore, recent studies have revealed genetic polymorphisms that determine individual differences in cognitive ability (Doi, Nishitani, & Shinohara, 2016; Savitz, Solms, & Ramesar, 2006; Surguladze et al., 2012). Taking these into consideration, it seems possible that genetic polymorphisms linked to individual differences in cognitive

ability may also exert influences on the competitive performance of competitive athletes. However, there are few studies on the link between athletes' competitive performance and genetic polymorphisms associated with cognitive ability.

One of intracerebral neurotransmitters affecting cognitive ability is dopamine. Dopamine belongs to the class of catecholamines including adrenaline and noradrenaline essential for the function of the reward system and the prefrontal region, which play pivotal roles in motivation and executive-control (Schultz, 1998). Among the components of the dopamine system, single nucleotide polymorphisms (SNPs) have been identified in the genes encoding catechol-O-methyltransferase (COMT) (Opmeer et al., 2013; Zhang et al., 2013), dopamine receptor D2 (DRD2) (Ernest, 2000; Tompson et al., 1997), and dopamine receptor D3 (DRD3) (Savitz et al., 2013).

COMT regulates the activities of the dopamine system by degrading dopamine (Axelrod, Senoh, & Witkop, 1958). A SNP resulting in substitution of the amino acid encoded at codon 158 of the COMT gene from valine to methionine (COMT Val158Met) has been shown to reduce the activity of the enzyme by one third to one fourth of that of the valine-type COMT (Savitz et al., 2006), thereby increasing the extracellular level of dopamine. It has been suggested that the COMT Val158Met polymorphism may be associated with individual differences in emotional response, motivation and executive-control ability (Drabant et al., 2006; Jaspar et al., 2014; Lancaste, Linden, & Heerey, 2012).

DRD2 gene located on chromosome 11 at q22-q23 has been associated with several genetic polymorphisms (Ernest, 2000). Among them, the TaqIA polymorphism has been shown to reduce the amount of DRD2 in the striate bodies of the basal ganglia (Thompson et al., 1997). Consequently, it has been suggested the DRD2 TaqIA polymorphism may be

associated with individual differences in dependence and impulsivity (Ernest, 2000; Thompson et al., 1997).

Finally, DRD3 is an autoreceptor that inhibits the release of dopamine from dopaminergic neurons, which are mainly expressed in the nucleus accumbens (Bouthenet et al., 1991; Diaz et al., 2000; Savitz et al., 2013). A SNP in the DRD3 gene resulting in substitution of the amino acid encoded by codon 9 from serine to glycine (DRD3 Ser9Gly) has been associated with depression (Schosser et al., 2011), as well as with motivation and emotional response (Savitz et al., 2013).

On the basis of these, the present study examined the association of COMT Val158Met , DRD2 TaqIA, DRD3 Ser9Gly polymorphisms with the levels of competitive performance in competitive swimmers to gain further insight into the genetic basis affecting athletes' competitive performance . In the present study, we recruited only male swimmers in order to avoid the possible influences of sex-difference in the phenotypic expression of genetic polymorphisms; several studies have found sex-difference in the effects of COMT Val158Met polymorphism on neural function (White et al, 2014) and behavior (De Castro-Catala et al, 2015).

2. Methods

2.1. Participants

The participants were 57 Japanese male competitive swimmers (mean age, 19.14 , SD=0.89 years). Their levels of competitiveness ranged from a class ineligible for the Japanese national championship to a class that qualified for the national team (dispatch standard, a world ranking of 16th or above). They participated in the present study after giving written informed-consent according to the declarations of Helsinki. The breakdown of

participants according to swimming style was as follows; 23 freestyle swimmers, 5 backstroke swimmers, 10 breaststroke swimmers, 11 butterfly swimmers, and 8 individual medley swimmers. The procedure of this study had been approved by the ethical committee of Nagasaki University.

2.2 Indicator of Competitive Performance

In competitive swimming, swimmers compete in 5 different styles (i.e., freestyle, backstroke, breaststroke, butterfly, and individual medley) for various distances. In this study, the point scoring system devised by the Federation International de Natation Amateur (FINA) was used to compare the competitive performance of the participants regardless of the different styles and distances. FINA scale provides a measure of competitive performance derived from the comparison between personal records and the world records in corresponding style and distance. The point is calculated from *eq* (1) (FINA Points formula available at: http://www.fina.org/H2O/docs/FINApoints/FINA_Points_Table_20150205.pdf. Accessed 6 August 2015) with the world record in each style given 1000 points:

$$\text{FINA point} = 1000 \times (\text{world record [sec]}/\text{personal record [sec]})^3 \qquad eq\ (1)$$

Because the world records change regularly, the competitive performance of the participants in this study was calculated with respect to their personal records and the world records at the time of buccal swab sample collection for DNA sampling.

2.3. Extraction of DNA and Analysis of Genetic Polymorphisms

DNA was extracted from the samples of the buccal mucosa from the participants using the QIAamp DNA mini extraction kit (Qiagen, Inc.). SNPs were analyzed by real-time polymerase chain reaction with Light Cycler (Light Cycle 480, Roche, Inc.) using TaqMan probes corresponding to the COMT Val158Met (rs4680), DRD2 TaqIA (rs1800497), and DRD3 Ser9Gly (rs6280) polymorphisms.

3. Results

The number of participants in each genotype of COMT Val158Met , DRD2 TaqIA, DRD3 Ser9Gly polymorphisms are summarized in Table 1.

****Table 1 near here****

3.1 COMT Val158Met polymorphism

The chi-squared test was performed to examine whether the allelic distribution of each genotype of COMT Val158Met polymorphism agreed with Hardy-Weinberg equilibrium, and no significant deviation was observed ($\chi^2_{2,} = 0.25$, $p > .10$).

According to COMT Val158Met genotype, the participants were divided into those with the valine homozygous genotype (Val/Val) and the methionine carrier (Met carriers). Several previous studies on the association between this SNP and neural or behavioral functions have adapted this grouping method (Colzato, van den Wildenberg & Hommel, 2014; He et al., 2012). Figure 1(a) shows the mean FINA points of each group. Comparison between the groups revealed that the mean FINA point of the Met carrier group was significantly higher than that of the Val/Val group ($t_{55} = 2.16$, $p = .036$, $d = 0.57$, $M = 48.7$, 95% Cl [10.7, 86.6]), indicating that competitive performance was higher in the Met carrier

group. Age was significantly different between the groups ($t_{55} = 2.11$, $p = .04$), with the averaged age of Met carrier group being significantly higher than that of Val/Val group. Therefore, analysis of covariance was performed with age as a covariate. As a result, the effect of the genetic polymorphism was still found to be significant even after adjustment for the effects of age ($F_{1,54}=5.25$, $p = .026$).

****Figure 1 near here****

3.2 DRD2 TaqIA polymorphism

The chi-squared test was performed to examine whether the allelic distribution of each genotype of DRD2 TaqIA polymorphism agreed with Hardy-Weinberg equilibrium, and no significant deviation was observed ($\chi^2_2 = 0.24$, $p > .10$).

According to DRD2 TaqIA genotype, the participants were divided into the A1 carriers (A1 carrier) and the A2 homozygous genotype (A2/A2). Several previous studies on the association between this SNP and behavioral functions have adapted this grouping method (Esposito-Smythers, Spirito, Rizzo, Mcgeary, & Knopik, 2009; Sieminska, Buczkowski, Jassem, Niedoszytko, & Tkacz, 2009). Figure 1(b) shows the mean FINA points of each group. There was no significant difference in the FINA points between these groups ($t_{55} = 0.17$, $p > .10$ $d = 0.05$, $M = 4.09$, 95% CI [-37.3, 45.4]). There was no significant difference in age between the groups ($t_{55} = 0.06$, $p > .10$).

3.3 DRD3 Ser9Gly polymorphism

Data from one participant was discarded from the analysis of DRD3 Ser9Gly polymorphism, due to the failure in genotyping. The chi-squared test was performed to examine whether the allelic distribution of DRD3 Ser9Gly polymorphism agreed with Hardy-Weinberg equilibrium, and no significant deviation was observed ($\chi^2_2 = 5.65$, $p > .05$).

According to DRD3 Ser/Gly genotype, the participants were divided into those with the serine homozygous genotype (Ser/Ser) and the heterozygous genotype (Ser/Gly) , because there was no participant with the glycine homozygous genotype. Figure 1(c) shows the mean FINA points of each group. There was no significant difference in FINA points between these groups ($t_{54} = 0.07$, p > .10, $D = 0.02$, $M = 1.7$, 95% Cl [-41.9, 38.4]). There was no significant difference in age between the groups ($t_{54} = 0.96$, $p > .10$).

4. Discussion

The present study investigated the association between genetic polymorphisms influencing dopaminergic functions and competitiveness of swimmers. The results showed that the mean value of FINA point, which indicates the competitiveness of competitive swimmers, was significantly higher in the Met carrier group than in the Val/Val group regarding COMT Val158Met polymorphism. On the other hand, no effect of either DRD2 TaqIA or DRD3 Ser9Gly polymorphism on FINA point was observed. These results suggest that the function of COMT is likely to affect the competition results of competitive swimmers.

In Met carriers with COMT Val158Met polymorphism, reduced COMT enzymatic activities lead to an increased amount of extracellular dopamine in the brain (Savitz et al., 2006), and consequently enhance the function of the prefrontal cortex (PFC), where

dopaminergic neurons are abundantly distributed (Drabant et al., 2006; Jaspar et al., 2014) The PFC governs emotional- and self-regulation as the seat of executive-control, possibly through functional connectivity with subcortical regions (Drabant et al., 2006). On the basis of these, we tentatively think that the emotional- and self-regulation ability enhanced by an increased amount of dopamine in the PFC might improve the competitive performance of the Met carriers. In relation to this interpretation, Stroth et al (2010) have revealed that adults with Val/Val genotype showed larger improvement in their executive-control ability after aerobic exercise training than Met-carriers. On the basis of this, if the above interpretation is correct, it might be possible to improve the athletic performance of swimmers with Val/Val genotype by intensitive training to increase their aerobic capacity.

In contrast to COMT, DRD2 and DRD3 are mainly distributed in the subcortical regions, predominantly in the basal ganglia and nucleus accumbens (Bouthenet et al., 1991; Diaz et al., 2000; Thompson et al., 1997). The lack of association between polymorphisms of the DRD2/DRD3 genes and competition results is likely due to the fact that these polymorphisms do not play prominent roles in the dopaminergic neuronal activities in the PFC.

The participants in this study included 7 world-class athletes who had reached the podium as members of the Japanese national team and in Japanese national championships. Regarding COMT Val158Met polymorphism, these 7 participants consisted of 6 Met carriers. Thus, the Met carrier group included more elite athletes than the Val/Val group. Unlike ordinary athletic events that record official times, the motivation and pressure for obtaining a higher-ranking position in selection races for the national team is extremely high. Taking these into consideration, it is assumed that one reason for superior performance in swimmers

with the Met-allele might be the ability to achieve their best under high-pressure thanks to their superior executive-control.

The present study has shown significant association between COMT Val158Met polymorphism and competitive performance in swimmers. However, this study has the following limitations. First, the present results alone do not tell us the mechanism through which COMT genotype influences swimmer's competitive performance . If COMT is somehow linked to emotional-regulation of stress reaction in competition as mentioned above, it is possible that the level of stress hormone just before actual competition should differ according to COMT genotype. To examine such possibilities, future studies need to compare stress hormone release just before competitions across groups with different COMT Val158Met polymorphism genotypes. Secondly, the results of this study suggest the possibility that individual differences in executive-control ability, which is greatly affected by COMT Val158Met polymorphism (Drabant et al., 2006; Jaspar et al., 2014), may influence competition results. However, executive-control ability was not directly assessed with any objective indicators in this study. Thus, in future studies, the executive-control ability and the PFC activation need to be assessed by behavioral indicators (Vestberg, Gustafson, Maurex, Ingnar, & Pertovic, 2012) or with non-invasive measurements of neural function. The third limitation is the recruitment of only male swimmers. The previous studies have shown sex-difference in the dopamine metabolism (Laakso et al, 2002; Munro et al, 2006), the affinity of D2 receptor to dopamine (Pohjalainen, Rinne, Någren, Syvälahti, & Hietala 1998), and the influences of COMT Val158Met polymorphism on neural function and behavior (De Castro-Catala et al., 2015; White et al., 2014). On the basis of these, it is highly conceivable that genetic polymorphisms linked to dopaminergic neural functions exert differential influences on competitive performance in female competitive swimmers.

5. Conclusions

This study evaluated the effects of COMT Val158Met , DRD2 TaqIA, DRD3 Ser9Gly polymorphisms on the competitive performance of competitive swimmers. The results revealed that competitive performance was significantly higher in the Met carrier group than in the Val/Val group regarding COMT Val158Met polymorphism. This finding indicates that genetic polymorphism linked to cognitive ability influences the athletes' competitive performance. To further elucidate the effects of COMT on athletes' performance, it would be important to examine whether similar influence of COMT Val158Met polymorphism is observed in athletic events other than competitive swimming.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Table 1. *Allelic distribution of each SNP.*

SNP	Genotype	N	Age
COMT Val158Met	Val/Val	28	18.9 (0.82)
	Val/Met	25	19.4 (0.89)
	Met/Met	4	19.5 (0.87)
DRD2 TaqIA	A1/A1	8	19.3 (0.99)
	A1/A2	29	19.1 (0.80)
	A2/A2	20	19.2 (0.96)
DRD3 Ser9Gly	Ser/Ser	29	19.0 (0.87)
	Ser/Gly	27	19.2 (0.83)
	Gly/Gly	0	

In the parenthesis are standard deviations of age.

Figure legends

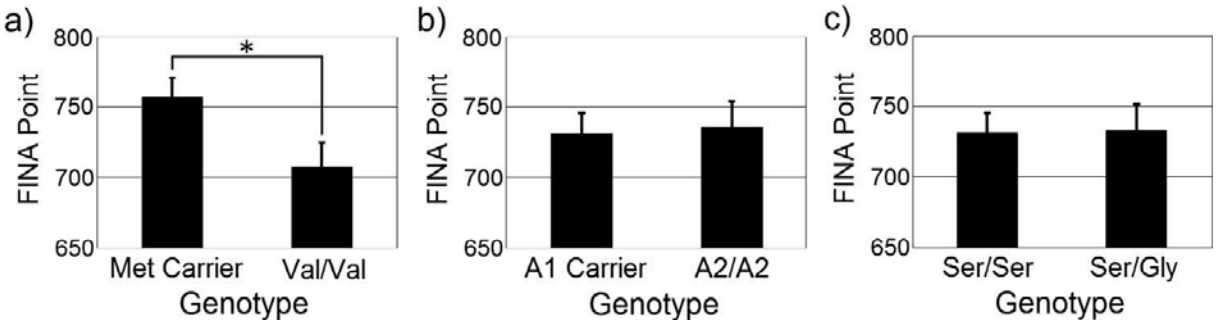

Figure 1. The averaged FINA point in each genotype of a) COMT Val158Met, b) DRD2 TaqIA, and c) DRD3 Ser9Gly polymorphisms. The error bar indicates standard error. *$p < 0.05$ for the group difference.