Relationship between Taq1A Dopamine D2 Receptor Polymorphism and Motivation to Exercise and levels of Voluntary Physical Activity

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ABSTRACT: Aims: The purpose of this study was to examine the genetic basis underlying voluntary physical activity. This study explores to an association, if exists, between motivation to exercise, levels of voluntary physical activity and Taq1A gene polymorphisms. **Method:** 122 participants (age=24.4±5.7 yrs., 55 males & 67 females) completed the Behavioral Regulation in Exercise Questionnaire – 2 (BREQ-2) to assess their motivation to exercise and the International Physical Activity Questionnaire (IPAQ) to assess their level of physical activity. DNA was isolated from a cheek cell sample. The Taq1A genotype was identified using PCR with gene specific primers. **Results:** Our study included 85 normal-weight, 30 overweight, and 7 obese subjects. Three variants of DRD2 taq1A -CC (n=77, 63.1%), CT (n=35, 7.28%), and TT (n=10, 2.8%) - were identified. Internal motivation to exercise was significantly higher in the CC genotype compared to the other two genotypes (P=0.017). **Conclusion:** In general, intrinsic regulation factors of motivation, as well as the type of genotype, may play a major role in determining the level of physical activity. Taq1A polymorphism of the DRD2 gene is related to physical activity and body weight in young men and women.

KEYWORDS: Polymorphism, Motivation, Physical activity, Phenotype

Manuscrito recibido: 03/20/2020
Manuscrito aceptado: 05/20/2020

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INTRODUCCIÓN

Obesity is defined as the over-accumulation of fat in the subcutaneous tissue, around the organs, and sometimes in the visceral organs. Increased fat accumulation is considered as a risk factor leading to degenerative diseases such as diabetes mellitus, coronary heart disease and hypertension (O'Rourke, 2009). It is also characterized by an imbalance of the energy between the calories consumed and the calories cost in the long run, which is affected by the environmental and genetic factors (Kanaya and Vaisse, 2011). Having a healthy lifestyle is the best way to maintain health and enjoy a long and healthy life. In order to reduce this public health epidemic, the American College of Sports Medicine (ACSM) has supported physical activities for weight loss and long-term maintenance of weight successfully (Donnelly *et al.*, 2009). Healthy lifestyle, such as participation in regular physical activity, can reduce the risk of heart disease, stroke, type 2 diabetes, and depression (Federation, 2015). Several possible factors explain the low level of physical activity among communities, such as inadequate time, inadequate resources or the negative effects of physical activity or exercise and so on (Kinney, 2017).

Additionally, it has been proven that complex biological pathways regulate motivational behaviors, including eating, drinking and sleeping. Any physical activity that can involve spontaneous planning or spontaneous interaction is also considered as a motivational behavior. Dopaminergic pathways in the central nervous system are involved in rewarding, motivating, motor activity and affection. These pathways are ideal goals for genetic control of intrinsic motivation of physical activity. Intrinsic motivations are thought to involve the dopamine transmission in the brain. Dopamine is a neurotransmitter part of the central nervous system that stimulates the pleasure and regulates the motivation to gain a pleasure (Goldfield *et al.*, 2013). Human are naturally pleasure seeking due to the central reward sensation that dopamine causes (Kinney, 2017). Several studies have indicated that genetic variations in the dopamine pathway affect the level of voluntary physical activity in mice. Kinney has shown that dopamine and/or its type 1 receptor is involved in maintaining high levels of physical activity in mice(Kinney, 2017). Moreover, a mouse that voluntarily had highrunning activity on wheels showed significantly lower dopamine type 1 receptor expression (Knab *et al.*, 2009). It has been proven that complete depletion of brain dopamine (Leng *et al.*, 2004) as well as treatment with dopamine receptor antagonists, reduces running activity on a wheel in rodents (Rhodes and Garland, 2003).

These results suggest that the dopaminergic system plays a role in the reward related to the voluntary running. The dopaminergic system is complex and regulation of the physical activity seems to be multifaceted. Variations such as receptor expression and downstream signaling pathways and the variations in the expression of the transcription factors and other factors affecting the gene expression are found throughout the system that may regulate the physical activity. Thus, we focus on the dopamine receptor and the genetic variations in the dopamine 2 receptor. The dopamine receptor naturally acts as a controller of dopamine activity (Ergun *et al.*, 2010). The dopamine receptor D2 is a G protein-coupled receptor, which is highly expressed in the central nervous system striatum. D2 Receptor also mediates a set of fundamental functions of the brain, including reward behavior, movement regulation, learning and memory, and attention. Moreover, D2 receptor is clinically important for the treatment of psychosis, Parkinson's disease, brain injuries, and restless legs syndrome (Gluskin and Mickey, 2016). Various studies have proven that the dopamine 2 receptor, especially the Taq1A polymorphism, is involved in obesity risk factors. Taq1A polymorphism decreases the D2 receptor in the brain and thus decreases dopamine function, leading to a reduction in the ability to inhibit negative behaviors such as eating and motivation to participate in physical activity (Volkow *et al.*, 2008).

Hence, as genetic variations in the dopamine pathway affect the voluntary physical activity, a few studies have examined these genetic variations and the level of the physical activity in humans. Thus, it is crucial to examine the potential relationships between the genetic differences of the dopaminergic pathway, the level of physical activity, and the specific motivational states of the participation in the human physical activity as a tool for understanding the biological basis of the participation in the physical activity. Hence, the present study was conducted to evaluate the relationship between Taq1A polymorphism of dopamine receptor D2 (DRD2) and body mass index and physical activity level in young men and women.

MATERIALS AND METHODS

Participants

This study was conducted after obtaining permission from the Ethics Committee of the Sport Sciences Research Institute of Iran (SSRI). Individuals who were willing to participate in this research were asked to complete and sign an informed consent. A total of 122 young subjects, including 55 men and 67 women with a mean age of 24.4±5.7 years old participated in this cross-sectional study. The research inclusion criteria were lack of a restrictive disease making the physical activity impossible.

Measurements

Phenotype:The height and weight of the subjects were measured using a digital scale with a maximal capacity of 150 kg and a height of 200 cm. Percentage of body fat was measured using body composition analyzer system (Bomeitong, Gs model, China).

Level of Voluntary Physical Activity: The voluntary physical activity level was measured using the International Physical Activity Questionnaire (IPAQ)- short form. IPAQ was developed by an international expert group in Geneva in 1998, and its validity and reliability have been confirmed in 12 countries(Booth*et al.* 2004)as well as inIran (Hazavehei *et al.*, Estebsari*et al.*, 2010). Total score was calculated according to a standard procedure and subjects were categorized to a level of low or sedentary (<600 MET-min/week), moderate (600-3000 MET-min/week) or high (>3000 MET-min/week) level (Seyed Emami *et al.*, 2010).

Motivation to exercise: The Behavioral Regulation in Exercise Questionnaire-2 (BERQ-2 questionnaire) was used to assess the motivation for engaging in a sport activity. BERQ-2 is a revised version of the original BREQ that was originally developed by Markland and Colleagues (2004).

The questionnaire includes 19 items on a 5-point Likert scale ranging from 0 (not true for me) to 4 (very true for me). The reliability and validity of this questionnaire have been previously confirmed (Sicilia *et al.*, 2014). It has been also reported to be valid and reliable in Iran (Farmanbar *et al.*, 2011). The questionnaire relates to 5 categories of motivation (subunit), including self-determination theory, motivation (4 items), external regulation (4 items), interjected regulation (4 items), identified regulation (3 items), and intrinsic regulation (4 items) (Deci and Ryan, 2000).

DNA Extraction: Saliva sampling was performed in this study. Saliva samples were collected from 5 individuals and preservative solution was added to them and they were transferred to the laboratory. DNA was extracted from CHEEK cells using a commercialkit (Oragene Co.). The following primers were used for the PCR:

5'-ACCCTTCCTGAGTGTCATCA-3 '(forward) and

5'-ACGGCTGGCCAAGTTGTCTA-3' (reverse)

Amplicons of 308 bp were visualized with 1% agarose gel. In this step, PCR reaction of temperature gradient was used for each pairs of primers designed in order to find the best primer annealing temperature. After completing the stopping steps, 3 µl of PCR product to ensure optimal replication on 1% Agarose gel was examined. After identifying the appropriate temperature for all three pairs of PCR synthesized primers of all samples, 2 µl of PCR product was brought to 0.1% Agarose gel to confirm the correct replication of the desired fragment.Restriction Fragment Length Polymorphism(RFLP) method was used for determining the genotype of the DRD2 gene. Above presents the restricting enzymes and the specifications of the fragments cut from the DRD2 gene. Enzymatic digestion at 65°C overnight consisted of 1 µl of the enzyme, 3 µl of PCR product, 2 µl of the specific buffer, and 15 µl of deionized water. After enzymatic digestion, the enzyme digestion product was electrophoresed on 12% polyacrylamide gel (PAGE) to observe the cut fragments, and three samples with different genotypes were sent to the lab for sequencing. Then, the digested DNA (TAQ1A CC: 130-178, Taq1A CT: 130-178-308, Taq1A TT: 308 bp) was visualized using a gel documentation system.

Data analysis

Kolmogorov–Smirnov statistical test was used to examine the normality of data. One-way analysis of variance (ANOVA) and Bonferroni post-hoc were used to compare the following variables in different genotypes: BREQ-2 questionnaire scores, physical activity level, and obesity phenotypes. The motivational categories of the BREQ-2 questionnaire among three different levels of physical activity were also analyzed using ANOVA. All statistical analysis were performed using SPSS 21 software and P<0.05 was considered as the significant level.

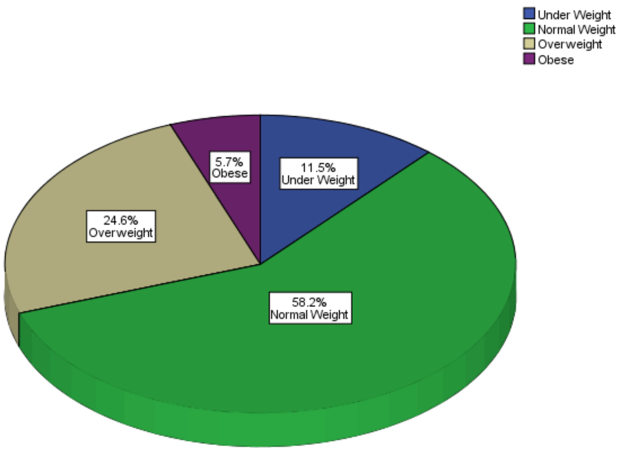
RESULTS

The Kolmogorov-Smirnov test showed a normal distribution in all variables, so parametric analysis was done.

Taq-1 Polymorphism and Obesity phenotypes

According to Chart 1, 85 subjects had normal weight, 30 subjects were overweight and 7 subjects were obese. Results showed that out of 122 subjects, 77 subjects had Taq1A polymorphism CC allele (63.1%), 35 subjects had Taq1A polymorphism CT allele (28.7%) and 10 subjects had TT allele (8.2%) (Chart 2). As a result, most of the research subjects had CC alleles.

Chart 1. Distribution of subjects based on BMI.



Significant differences were observed among the genotypes in body weight (F=4.733, P=0.011) and body fat percentage (F=3.892, P=0.023), while no significant difference was observed in body mass index and WHR, so that individuals carrying the TT genotype had higher weight, higher fat percentage and body mass index than those with other two genotypes (Table 1). Dopamine 2 receptor Taq-1A polymorphisms subjects with the TT genotype were more overweight and obese compared to the subjects with a normal weight, but the CC and CT genotypes were higher in the subjects with a normal weight.

Taq-1 Polymorphism and motivation

The mean of total scores of BREQ-2 showed no significant difference among the genotypes. Moreover, there was no significant difference in motivational categories among the genotypes, except for external motivation (F=3.807, P=0.025) and intrinsic motivation (F=4.223, P=0.017). The external motivation was higher in CT genotype (6.73) and individuals with genotype CC had higher intrinsic motivation (12.28) (Chart 3).

Chart 2. Distribution of subjects based on the type of genotype.

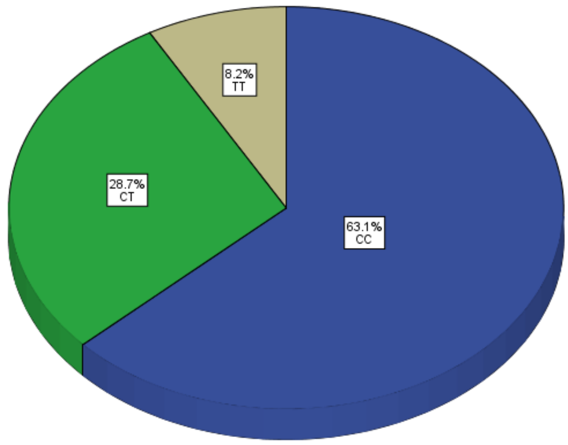
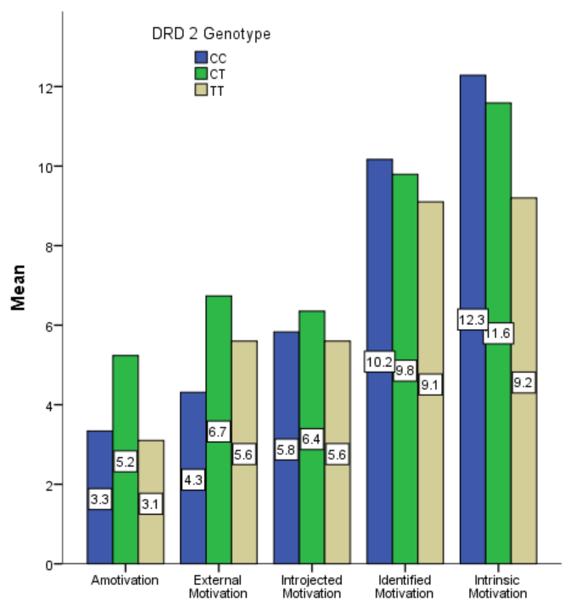


Table 1. Obesity phenotypes based on the genotype of the subjects.

Genotype	Body Weight (kg)	WHR	BMI (kg/m^2)	Body Fat (%)
CC	11.65 ± 66.68	0.07±0.84	3.25 ± 22.87	5.93 ± 23.21
CT	62.57 ± 10.03	0.85 ± 0.08	23.09 ±4.08	25.86 ±7.05
TT	20.92 ± 75.77	0.09± 0.87	6.66 ± 26.56	6.89 ± 28.01
P value	**0.011**	**0.61**	**0.019**	0.023

Chart 3. BREQ-2 scores based on the genotype of subjects.



Taq-1 polymorphism and the level of physical activity

Physical activity was measured in MET-min per week, and ANOVA showed that individuals carrying the TT genotype had lower physical activity per week than those carrying other two genotypes, although this difference was not significant (F=1.054, P= 0.352) (Chart 4). The dopamine 2 receptor Taq-1A polymorphisms in this study showed that the subjects with the TT genotype had a lower activity level compared to the subjects with the CC and CT genotype.

Subjects were categorized according to their physical activity level: Low (<600 MET-min/week), Moderate (600-3000 MET-min/week), and High (>3000 MET-min/week). One-way ANOVA showed a significant difference in WHR among the subjects with different level of physical activity (F=5.166, P=0.012) (Table 2). BREQ-2 questionnaire scores are presented in Chart 5 based on the physical activity level. No significant difference was found among the subjects in the BREQ-2 scores based on the level of physical activity.

*Chart 4.*The physical activity level of subjects based on the type of genotype.

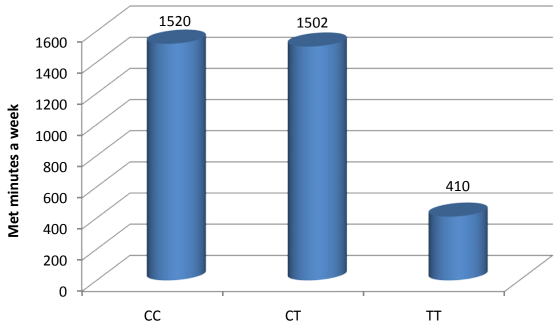
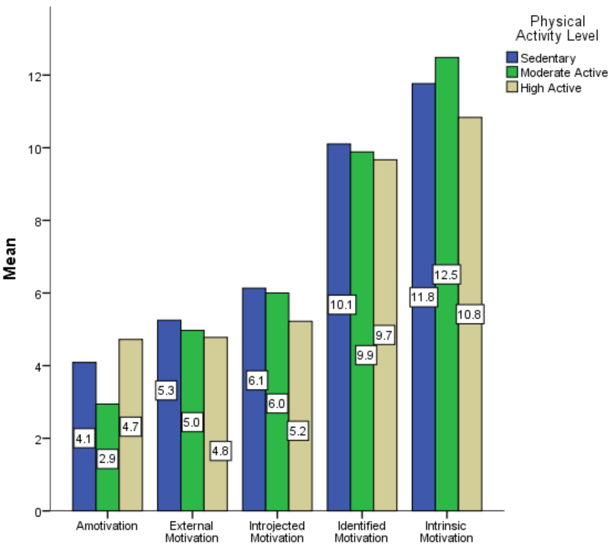


Table 2. Obesity phenotypes based on physical activity level.

physical Activity level	Body Weight (kg)	WHR	BMI (kg/m²)	Body Fat (%)
Sedentary	14.36±66.40	0.08 ± 0.85	23.29 ± 4.31	6.67 ± 24.58
Moderate Active	10.09 ± 67.06	0.93 ± 0.85	3.79 ± 23.91	6.86 ± 24.96
High Active	9.50 ± 64.85	0.51/± 0.81	2.23 ± 21.70	4.79 ± 22.37
P value	**0.83**	**0.012**	**0.15**	0.36

Chart 5. BREQ-2 Questionnaire scores based on physical activity level.



DISCUSSION AND CONCLUSIONS

In this study, three types of DRD2 Taq1A, 77 subjects with CC type (63.1%), 35 subjects with CT type (28.7%) and 10 subjects with TT type (8.2%) were observed. This study is consistent with the study conducted by (Sari and Wijaya, 2017; Yeh *et al.*, 2016) that observed three changes in the DRD2 Taq1A gene (Sari and Wijaya, 2017; Yeh *et al.*, 2016). In our study, the frequency of the CC genotype was higher than that of CT and TT, but in the two studies mentioned, the frequency of CT genotype was higher in Asian students than that of CC and TT genotypes. Pinto *et al.* (2015) observed higher TT genotype frequency than CC and CT. It might be due to differences in genotypes and alleles that give the ethnicity in populations caused by differences in race and diet (Pinto *et al.*, 2015). The results revealed that subjects with CT genotype had more external motivation than the other two genotypes, which this difference was significant between the groups carrying CT with CC alleles. Individuals with the CT genotype are affected by external motivation, and physical activity behavior may be less self-determined in these individuals.

This difference may also suggest that subjects with CT genotype are probably participating in physical activity to obtain reward or prevent punishment (Deci and Ryan, 2000).

However, individuals with the CC genotype are probably more voluntarily participating in physical activity based on self-determination theory, since when behavior is more self-determined and autonomous, it becomes more intrinsic. In confirming this issue, the results of intrinsic regulation showed that subjects with CC genotype had higher scores and this difference with the TT group was significant (P=0.015).

The study revealed that the level of voluntary physical activity in the TT genotype group was lower than that of the other two groups (410±281 versus 1520±2620 for CC group; 1502±1172 for CT group), although this difference was not significant. Hence, it seems that obesity phenotypes to be lower in this group. The results revealed that people with TT genotype had higher mean scores in all obesity phenotype indices (body weight, WHR, BM3z4I and body fat percentage) (Table 2).

These results are in line with the results of the study conducted by Sari and Wijaya (2017), in which the frequency of individuals with CC genotype who had normal weight was more (Sari and Wijaya, 2017). We observed that there was no significant difference between the BREQ-2 total scores of individuals and the level of physical activity. However, individuals who were in the active group had higher mean scores on intrinsic regulation and lower scores in external regulation. These results suggest that people who are more intrinsically motivated are more likely to participate in physical activity, as a motivation in these individuals was lower than that of the inactive group. The lack of a significant difference between the active and inactive groups in the intrinsic and identified regulation suggests that other motivational factors such as adequate time play a role in physical activity level. The Taq1A allele of the dopamine 2 receptor gene in this study showed that there was a significant difference between individuals carrying different polymorphisms in terms of body weight. One study had already indicated a significant relationship between body weight and dopamine receptor access in the caudate brain (Dunn *et al.*, 2012). Another study has revealed that evidence for lower access to D2 / D3 receptors of the striatum in obesity confirms the role of the striatum dopaminergic reward system in obesity (de Weijer et al., 2011).

The reduction in the amount of D2 receptors is proportional to the increase in BMI in obese individuals with the A1 allele. Furthermore, the minor allele is associated with an increase in body fat percentage (Chen et al., 2012). The T allele against C is associated with a decrease in DRD2 mRNA levels as well as a decrease in translation of mRNA into the receptor protein (Duan et al., 2003). Research has confirmed that this reduction leads to lower levels of D2 receptors in the cortex of individuals with this allele and that receptors exhibit a lower binding affinity for dopamine (Hirvonen et al., 2004). Chen et al. Showed that the polymorphisms of GAD2 (+83897 T/A) and DRD2 (-243 A/G) are significantly associated with an increased risk of developing obesity (Chen *et al.*, 2012).

Individuals with dopamine Receptor D2 gene polymorphism have lower dopamine receptor levels and disorder in dopamine system causes addictive, impulsive, and compulsive behaviors and also makes the individual unable to make good judgments on food intake and physical activity levels. As a result, this disorder causes fat storage in adipose tissue. Moreover, dopamine has a greater role in regulating motor control related to the pleasure system in the brain. It also enhances the sense of pleasure and provides a source of motivation for active participation in specific activities. This theory links obesity and inactivity to Taq1A polymorphism of the dopamine 2 receptor genes (Alexxai *et al.*, 2016). Although dopamine regulates the physical activity, this question of whether a reduction in D2R due to genetic changes causes changes in energy and physical activities costs leading to obesity has remained unanswered. Research conducted by Beeler et al on a D2R knockdown (KD) mouse line showed that contribution of altered D2R signaling to obesity lies in altered energy expenditure rather than in the induction of compulsive overeating. (Beeler *et al.*, 2016)

In general, the scores of intrinsic motivation scores and physical activity levels were higher in CC genotype. It suggests that behavioral activity is intrinsic in individuals with the CC genotype. The interesting parent observed in this study was that two groups with higher physical activity levels also reported higher intrinsic motivation scores. Therefore, intrinsic factors, as well as the type of genotype, may play a major role in determining the level of physical activity. Hence, this study revealed that Taq1A polymorphism of the DRD2 gene affects physical activity and body weight in young men and women.

Exposure to obesity-related diets is associated with changes in physical activity levels and dopaminergic function. Changes caused by the Taq1A polymorphism in the dopamine system may be sufficient to explain the physical inactivity in obese people. Understanding obesity-related changes in dopamine and related systems may support evidence-based approaches to increase physical activity in obese individuals. Moreover, such an understanding may indicate genetic or environmental contributions to dopaminergic function and physical inactivity in obesity.

Limitations

One limitation of the study was low sample size of subjects. In addition, physical activity assessed via a questionnaire which answering the questions of the questionnaire can lead into errors. Hence, the use of interview or new technologies to assess the physical activity in terms of intensity, duration, and number of the sessions per week will be more useful to obtain more accurate results in this regard.

Recommendations for future studies

The study was conducted in a young population and deliberately focused on this group of the population, while considering other population groups that have different environmental conditions may provide a more general insight on the relationship between the genetic background and the physical activity. Finally, future studies should evaluate the genetic variations of other dopamine receptors to determine the relationship between the dopamine regulators and these genetic variations to gain a better picture of the role of dopamine in regulating the physical activity and creating a motivation to participate in the physical activity.

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