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A dopamine D2 receptor gene polymorphism and physical activity in two family studies

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Abstract

A role for dopamine neurotransmission in the regulation of motor activity and reinforcement of behavior is supported by considerable evidence. We studied the association between a marker in the dopamine D2 receptor gene (DRD2) and physical activity level in two cohorts. A first cohort consisted of 721 participants from 161 families of the Quebec Family Study (QFS). Physical activity phenotypes were obtained from a three-day diary and a questionnaire probing physical activity during the past year. The second cohort was the HERITAGE Family Study (HERITAGE), which included 275 Black and 497 White participants from 228 families, among whom past year leisure time and occupational physical activity were probed. A fragment length polymorphism in exon 6 of the DRD2 gene was detected by the polymerase chain reaction (PCR) and NcoI digestion. Frequencies for the T and C alleles were 28% and 72% in the QFS. In the QFS, TT homozygote women had 25% and 34% lower age and BMI-adjusted physical activity level during the past year, compared to CC homozygotes and CT heterozygotes ($F=4.42$, $P=.016$). The DRD2 genotype was not associated with the QFS phenotypes obtained from the three-day diary. In the HERITAGE, the frequency of the T allele was 30% among Whites and 63% among Blacks. Similarly, the TT homozygote White women had 29–38% lower sports index ($F=4.09$, $P=.023$) and 27–33% lower work index ($F=6.23$, $P=.004$) than the CC homozygotes and CT heterozygotes. The results suggest that DNA sequence variation in the DRD2 gene is associated with physical activity levels among White women.

Keywords: Genetics; Polymorphism; Exercise; Inactivity; Heredity

1. Introduction

Physical activity levels have shown a pattern of familial aggregation [1–5] suggesting that participation in physical activity is explained not only by environmental factors, but also by shared family environment and perhaps genetic covariation. However, so far there has not been any evidence of specific genes involved in determining physical activity participation in humans. The dopamine D2 receptor gene (DRD2) is clearly a candidate gene for physical activity level because of its role in movement control [6] as well as in reward mechanisms [7–10].

In animal studies, the DRD2 gene has been found to be responsible for controlling both movement patterns and overall locomotor activity level. D2 receptor-deficient mice have shown decreased initiation of spontaneous movement [11]. DRD2 knockout mice have shown even more severe locomotor deficiencies characterized by lack of spontaneous movement, akinesy, abnormal gait, and posture [12]. Decreased locomotor activity level as well as impaired locomotor ability can be induced also pharmacologically by D2-like receptor antagonists [11,13]. In humans, abnormalities in the dopamine systems have been implicated in

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Table 1
Mean (±S.D.) characteristics in the QFS ($N=721$)

	Men	Women
Age	41.2±15.3 $n=319$	40.1±14.2 $n=402$
BMI	27.2±6.3 $n=317$	27.5±8.2 $n=398$
Past year PA (hours per week)	3.4±4.1 $n=317$	2.9±3.4 $n=402$
Three-day diary		
Total PA	705.6±122.4 $n=283$	664.3±91.3 $n=350$
Inactivity	464.3±86.7 $n=283$	475.0±71.2 $n=350$
Moderate to strenuous PA	238.8±178.6 $n=282$	189.4±141.5 $n=350$

PA = physical activity; BMI = body mass index.

several neurologic disorders characterized by locomotor impairment [14–16].

It has been proposed that dopamine plays a role in a range of behavioral phenotypes particularly related to rewarding mechanisms [10], since addictive behavior, such as alcoholism [17–19], drug abuse [8,20], and obesity [21] have shown suggestive associations with DRD2 polymorphisms. Similarly, a rewarding effect may be associated with exercise behavior. In fact, one factor thought to be a crucial determinant of exercise participation is a feeling of pleasure as a consequence of an exercise bout [22,23]. Some evidence for an exercise-induced pleasure comes from animal studies on brain neurotransmitter physiology. In rats, endurance training alters the number of brain dopamine binding sites [24] and the metabolism of brain dopamine [24,25]. Increased plasma dopamine level has been observed during short [26,27] and prolonged [26–28] exercise bouts in humans. However, the response of brain dopamine levels to endurance training in humans is not quite clear, since one study with Positron Emission Tomography (PET) scans was unable to detect any effect on brain dopamine metabolism after a 30-min maximal exercise test [29].

To investigate the associations between the DRD2 gene locus and physical activity levels in humans, we assessed a DRD2 polymorphism among 712 participants from the Quebec Family Study (QFS). Four physical activity phenotypes were available in the QFS, three of which reflected current physical activity and one indexed activity levels during the past year. As a replication, we used the HERITAGE Family Study (HERITAGE), in which three phenotypes representing sports, other leisure time activities, and occupational physical activity were probed among 275 Blacks and 497 Whites, all known to be sedentary participants.

2. Methods

2.1. Quebec family study

2.1.1. Participants

A total of 712 French Canadian parents and children from the Phase 2 of the QFS (Table 1) were available for the study [30]. The sample of 192 nuclear families included 161 fathers, 192 mothers, 158 sons, and 210 daughters. The study was approved by the Medical Ethics Committee of Laval University, and written informed consent was obtained from the participants.

2.1.2. Physical activity phenotypes

Using a three-day activity diary, which included one weekend day, participants were instructed to record the dominant activity for each 15-min period during 24 h using a list of categorized activities. Each categorical value was weighted by the category number (from 1 to 9), scaled to increasing energy expenditure, for the final summary score [31]. Three different phenotypes were formed on the basis of the diary information [32]. The summation score of all reported daily activities (Categories 1 to 9) was one of the phenotypes. In addition, a score based on resting or very light activities (Categories 1 to 4) was used to reflect the level of physical inactivity such as sleeping, driving a car, or taking a shower. Finally, a score based on moderate to strenuous physical activities (Categories 5 to 9) included light manual work such as carpentry, moderately fast walking, as well as strenuous exercise modes or intense manual work. The activity records were collected throughout the year and no seasonal variation was observed in the activity levels. The test–retest reliability of the activity record among 61 participants indicated an intraclass correlation coefficient of .96 for mean energy expenditure over repeated three-day periods of assessment [31]. Furthermore, the daily energy expenditure was positively related to PWC_{150} and negatively correlated with fatness [31].

In addition, participants were probed for their past year involvement in physical activity and sports using a ques-

Table 2
Associations between physical activity (PA) levels and DRD2 genotypes (controlled for age and BMI) in QFS

	Men					Women				
	C/C $n=165$	C/T $n=131$	T/T $n=23$	F	P value	C/C $n=197$	C/T $n=180$	T/T $n=25$	F	P value
Time spent in PA	1.13±0.11	1.27±0.11	1.13±0.16	1.14	.333	1.24±0.03	1.33±0.06	0.99±0.12	4.42	.016
Total PA	712.18±14.24	723.66±11.70	729.75±36.07	0.33	.722	663.49±5.73	658.31±8.20	666.59±22.10	0.18	.836
Inactivity	431.59±10.79	436.26±8.89	434.70±22.04	0.10	.903	476.37±5.77	477.38±7.88	464.50±17.02	0.28	.754
Moderate to strenuous PA	5.18±0.12	5.24±0.10	5.07±0.39	0.14	.868	4.91±0.07	5.02±0.10	5.09±0.21	0.50	.609

Table 3
Relative T allele frequencies (*n*) in the lowest and highest quartiles of the physical activity (PA) level phenotypes in the QFS

Phenotype	Men				Women			
	Lowest quartile	Highest quartile	χ^2	*P* value	Lowest quartile	Highest quartile	χ^2	*P* value
Past year PA (hours per week)	0.25 (39)	0.30 (45)	1.26	.262	0.33 (52)	0.29 (53)	0.37	.543
Total PA	0.26 (37)	0.32 (46)	0.90	.344	0.30 (48)	0.27 (43)	0.38	.536
Inactivity	0.29 (39)	0.23 (32)	0.93	.336	0.27 (46)	0.31 (50)	0.49	.486
Moderate to strenuous PA	0.29 (41)	0.29 (40)	0.02	.895	0.33 (52)	0.26 (42)	1.90	.169

tionnaire. Based on this information, the past year participation in physical activity (hours per week) was calculated for the most common exercise mode.

2.2. Heritage family study

2.2.1. Participants

A total of 275 Blacks from 127 family units and 497 Whites from 99 family units of the HERITAGE were available. The study is a multicenter one involving five universities [33]. In short, participants were healthy but sedentary over the previous 6 months. Sedentary was defined as the absence of participation in physical activities at a metabolic rate seven times or more over resting metabolic rate, for more than once a week, and lasting 30 min or more. The HERITAGE included an exercise intervention, but only the baseline values are used in this report. The protocol was approved by each of the Institutional Review Boards of the HERITAGE research consortium and written informed consent was obtained from all participants.

2.2.2. Physical activity phenotypes

Physical activity in the past year during leisure time and at work was measured using the ARIC questionnaire, which is a modification of the Baecke questionnaire [34]. The questionnaire graded activity levels in five categories in an increasing order of physical demands and frequency of the activity. Each index ranged from 1 to 5. The sports index is a sum of scores of the four most common physical activities (intensity level, hours per week, and months per year in an activity). The leisure time index consists of physical activity related to commuting, biking, walking, and watching television. The work index is comprised of the principal occupation, and includes information on the physical demands of the job (low, medium, high) as well as eight additional five-category choices related to sitting, standing, walking, lifting, sweating, and subjective exhaustion in the job.

2.3. Genotype determination

The DRD2 polymorphism, as described by Sarkar et al. [35], has a silent polymorphism at amino acid His^{313} as a result of a C to T transition. A 454-bp DNA fragment containing the polymorphic site was amplified using polymerase chain reaction (PCR). Genomic DNA was extracted from lymphoblastoid cell lines using phenol/chloroform technique followed by dialysis. Each 10-μl reaction contained 120 ng genomic DNA, 300 nM of each primer, 200 μM each dNTPs, 0.5% formamide, 1 U Taq polymerase, and 1 x buffer (Qiagen, Valencia, CA) according to the manufacturer's protocol. The reactions were incubated at 94 °C for 1 min, 49 °C for 2 min, 72 °C for 3 min, followed by 35 cycles at 94 °C for 30 s, 49 °C for 30 s, 72 °C for 30 s, and finally 72 °C for 10 min using a thermal cycler (Eppendorf Mastercycler gradient). The resulting PCR products were digested with 5 U of NcoI restriction endonuclease (Beverly, MA, USA) for 18 h at 37 °C. The DNA fragments were separated by electrophoresis on a 2.5% agarose gel and visualized with ethidium bromide under UV light. Ambiguous or unidentifiable results were reamplified and rescored, and samples that continued to amplify poorly were excluded. The amplified fragment was a 454-bp DNA fragment of the DRD2 gene that includes exon 6. The forward primer was ATTGTCCGGCTTTACC and the reverse primer was ATCCTGCAGCCATGG. The C allele corresponded to a 443-bp band while the T allele had two bands of 166 and 274 bp.

2.4. Statistical analyses

A χ^2 test was used to verify that genotype frequencies were in Hardy–Weinberg equilibrium. Skewed distributions of the time spent in physical activity and moderate to strenuous physical activity (skewness and/or kurtosis $> |1|$) were normalized with logarithmic transformations. A χ^2 test was also used to compare the allele frequency differences between the most sedentary and the most active participants. Associations between phenotypes and genotypes were analyzed using a MIXED procedure in the SAS software

Table 4
Participant characteristics and physical activity levels (mean ± S.D.) in the HERITAGE ($N = 772$)

Variable	Blacks	Whites
Age	33.6 ± 11.7 (275)	35.9 ± 14.6 (497)
BMI	27.9 ± 6.0 (275)	25.9 ± 5.0 (497)
Sports index	1.6 ± 0.8 (275)	1.9 ± 1.0 (497)
Leisure time index	2.0 ± 0.5 (274)	2.3 ± 0.5 (495)
Work index	2.2 ± 0.9 (269)	2.2 ± 1.0 (486)

Table 5
Associations between the DRD2 polymorphism and physical activity phenotypes in the HERITAGE by sex and race (mean ± S.E.)

	C/C	C/T	T/T	*F*	*P* value	C/C	C/T	T/T	*F*	*P* value
	Black men ($n=91$)					Black women ($n=184$)				
n	10	43	38			20	98	66		
Sports index	2.07 ± 0.37	2.13 ± 0.17	1.67 ± 0.19	2.64	.131	1.66 ± 0.17	1.61 ± 0.10	1.66 ± 0.12	0.13	.882
Leisure time index	2.14 ± 0.21	1.90 ± 0.06	2.01 ± 0.09	0.99	.413	2.05 ± 0.11	2.05 ± 0.06	1.95 ± 0.07	0.64	.536
Work index	2.78 ± 0.29	2.48 ± 0.17	2.43 ± 0.17	0.52	.617	2.00 ± 0.21	2.05 ± 0.11	2.07 ± 0.10	0.06	.938
	White men ($n=241$)					White women ($n=256$)				
n	116	109	16			119	115	22		
Sports index	2.06 ± 0.14	2.23 ± 0.10	2.16 ± 0.24	0.60	.551	1.65 ± 0.06	1.77 ± 0.10	1.28 ± 0.15	4.09	.023
Leisure time index	2.27 ± 0.058	2.24 ± 0.05	2.21 ± 0.11	0.11	.894	2.08 ± 0.06	2.21 ± 0.07	2.21 ± 0.12	2.64	.082
Work index	2.54 ± 0.11	2.48 ± 0.10	2.10 ± 0.25	1.19	.314	2.28 ± 0.13	2.38 ± 0.18	1.79 ± 0.21	6.23	.004

package (SAS 8.0). Nonindependence among family members was adjusted for using a "sandwich estimator," which asymptotically yields the same parameter estimates as ordinary least squares or regression methods, but the standard errors and consequent hypothesis tests are adjusted for the dependencies. The method is general, assuming the same degree of dependency among all members within a family.

3. Results

3.1. Quebec family study

The basic characteristics of the participants are presented in Table 1. Frequencies for the T and C alleles were 0.28 and 0.72, respectively. The observed genotype frequencies were in Hardy–Weinberg equilibrium. Age explained 0–11% and BMI 0–5% of the variation of the phenotypes, which were studied in six gender-by-generation subgroups.

In the whole cohort, a significant association ($F=4.02$, $P=.020$) was detected between the time spent being physically active in the last year and DRD2 genotype (not shown in tables). The TT homozygotes had a 22% lower physical activity level than the CT heterozygotes and a 9% lower physical activity level than the CC homozygotes. There were no significant differences between the genotypes in the physical activity level phenotypes as assessed from the three-day diary.

Among males, no differences in physical activity levels were found between the DRD2 genotypes (Table 2). However, the time spent in physical activity was significantly lower among TT homozygote women ($F=4.42$, $P=.016$) than CC homozygotes (25%) as well as among CT heterozygotes (34%). Again, no differences in physical activity phenotypes derived from three-day diary were found between genotypes. There were no allele frequency differences between the most sedentary and most active men or women when the upper and lower quartiles of each phenotype distributions were compared with the χ^2 test (Table 3).

3.2. HERITAGE family study

Although participants included in the cohort were relatively sedentary, there was variability in physical activity level among them (Table 4). The DRD2 allele frequencies differed markedly between Blacks and Whites ($P<.0001$); the frequency of the T allele was 30% among Whites and 63% among Blacks. However, the genotype frequencies were in Hardy–Weinberg equilibrium in Blacks ($\chi^2=2.79$, $P=.095$) and in Whites ($\chi^2=2.40$, $P=.122$). Across eight sex, generation, and race groups, age and BMI explained 0–13%, 0–3%, 0–5%, and BMI 0–7%, 0–9%, and 0–19% of the variation of the sports, leisure time, and work indexes, respectively.

When the population was stratified by sex and race, associations between the DRD2 genotype and physical

Table 6
Relative T allele frequencies (n) in the low and high physical activity (PA) level groups[a] in the HERITAGE

Phenotype	Lowest PA level	Highest PA level	χ^2	*P* value	Lowest PA level	Highest PA level	χ^2	*P* value
	Black men				Black women			
Sports index (median)	0.72 (65)	0.59 (51)	3.27	.071	0.61 (142)	0.66 (83)	0.94	.332
Leisure time index (median)	0.65 (57)	0.67 (59)	0.10	.751	0.64 (153)	0.60 (72)	0.48	.488
Work index (quartiles)	0.71 (31)	0.64 (32)	0.44	.507	0.56 (50)	0.63 (52)	1.10	.295
	White men				White women			
Sports index (median)	0.28 (71)	0.30 (67)	1.18	.671	0.32 (83)	0.31 (74)	0.15	.704
Leisure time index (median)	0.28 (83)	0.31 (55)	0.55	.459	0.27 (86)	0.38 (71)	5.85	.016
Work index (quartiles)	0.29 (40)	0.25 (28)	0.40	.530	0.36 (47)	0.29 (36)	1.46	.226

[a] In the high and low PA levels, different determination of the contrast groups (median or quartiles) were used depending on the phenotype distributions.

activity levels were found for the sports index ($F=5.93$, $P=.005$) and work index ($F=3.61$, $P=.042$) among White women (Table 5). Among them, the TT homozygotes had 29% and 38% lower sports index than the CC homozygotes and CT heterozygotes, respectively. Furthermore, the White TT homozygote women also had 27% and 33% lower work index values than CC homozygotes and CT heterozygotes, respectively. There were no differences between the genotypes in the leisure time index. Among Black men, the T allele tended to be more frequent among inactive compared to the active for the sports index ($\chi^2=3.27$, $P=.071$) (Table 6). The relative proportion of T allele carriers was significantly higher ($\chi^2=5.85$, $P=.016$) in White women with a leisure time index above the median than among those below the median. No other allele frequency differences were observed between participants with low and high physical activity levels.

4. Discussion

The results of this study suggest that DNA sequence variation in the DRD2 gene is associated with physical activity level during the past year, but not with the current level. The association was particularly consistent among White women both in the QFS and HERITAGE cohorts. In the QFS, White women homozygotes for the T allele had 25–38% lower past year physical activity level compared with the C allele carriers. In addition, the TT homozygote White women had 27–33% lower occupational physical activity level than C allele carriers in the HERITAGE. It should be emphasized that no association between the DRD2 polymorphism and physical activity level was found for the phenotypes derived from three-day habitual current activity levels. The correlations between current activity levels and past year activity phenotypes ranged from −.10 to .08, indicating that they truly reflect different behavioral phenotypes.

The association between past year physical activity level and DRD2 genotype was found among females but not consistently among men. In the QFS cohort, intrafamilial correlations have been consistently higher between mother and daughter (.13) and between mother and son (.10) than between father and son (.04) or between father and daughter (.06) suggesting that the maternal genotype may have a slightly stronger impact on offspring's past year physical activity level [32]. It may be truly the case that the physical activity level and DRD2 genotype association can be detected only among women. Alternatively, a potential association among men could have been diluted due to a stronger role of environmental factors in determining physical activity participation in men than in women. As in earlier studies of the QFS cohort, the maximal heritability for the QFS physical activity phenotypes ranged from 16% to 25% [32]. Considering this moderate heritability and the assumption that physical activity is a polygenic trait, studies on such phenotypes need large cohorts to detect such gender-specific genotype effects.

An interesting finding of this study was that the association between the DRD2 gene variant and physical activity level was found only for the past year physical activity level in the QFS cohort but not for the current activity level, as assessed by the three-day diary. It may be that three days is not sufficient to give an accurate estimate of a participant's habitual physical activity level, since there is seasonal and weekly variation in physical activity patterns. Despite the fact that physical inactivity was an inclusion criterion, sports and work indexes showed similar trend in their association with DRD2 genotype among White women of the HERITAGE cohort. For example, 1–2 h/week of brisk walking for 7–9 months/year gives a sports index of 1.8, which is close to the mean sports index values in both races among HERITAGE participants. For comparison, in QFS, men and women exercised, on average, 3.4 and 2.9 h/week, respectively, during the past year.

Polymorphisms located in exon 2 (TaqIA1) and exon 3 (TaqIB1) of the DRD2 gene have also been reported. Pharmacological studies have shown that DRD2 allele A1+ carriers have reduced numbers of brain D2 receptors as well as diminished dopaminergic tone [9]. In addition, among the TaqIA1 allele carriers [36,37], as well as in TaqIB1 allele carriers [36], reduced dopamine receptor-binding density has been found in PET measurement. It is not known if the marker used in the present study, exon 6 of the DRD2 gene, has functional significance by itself, or whether it is in disequilibrium with other DNA variants within DRD2. It is also possible that the association of the DRD2 genotype with physical activity levels suggested in the present study is not due to the DRD2 gene itself but to a yet to be discovered variant in another gene in linkage disequilibrium with the DRD2 mutation.

The mechanisms of the way dopamine may affect physical activity level are still somewhat speculative. Two major hypotheses may be offered: dopamine has an effect on motor control effecting motor skills, or it is part of the rewarding mechanisms. Similarly to addictive drugs, participation in exercise may cause feelings of pleasure thus leading to exercise adherence. The dopaminergic neurons are located in the midbrain substantia nigra, the motor areas in the basal ganglia (affected in Parkinson's disease [38]), the frontal lobes (affected in attention deficit hyperactivity disorder [39]), and the limbic system (related to drug addiction [40] and locomotor overactivity in schizophrenia [41]).

The role of dopamine, dopamine receptors, and dopaminergic neurons on motor control is relatively well established [42]. Deficiency in the dopaminergic system may lead to diseases causing various degrees of locomotor impairment [15–17,43]. Also in animal studies, both D2 receptor-deficient mice [44] and DRD2 knockout mice [12] have reduced locomotor activity level. Therefore, it could be speculated that participants with dopamine receptor defi-

ciencies or alterations may also have impaired or subtly reduced motor skills and thus could be less inclined to be physically active.

According to the second hypothesis, increased dopamine levels in the brain due to exercise may cause pleasure and thus encourage seeking the feeling of pleasure through exercise. The role of dopamine in the search for reward through drugs [7,8,19] and alcohol [9,10] has been indisputably shown among rodents. Again, one may speculate that genetic differences among people may explain why exercise loses or enhances its reinforcing property and influences the habit formation. Endurance training increases the number of dopamine binding sites and metabolism of dopamine in rats [24]. As little as 1 h of exercise has increased striatal extracellular dopamine levels both in trained and in untrained rats [25]. Acute strenuous exercise has increased sulfoconjugated dopamine (dopamine metabolite) level in plasma among well-trained and minimally trained men [45] suggesting that endurance training may have an effect on dopamine metabolism and lead to behavioral and physiological changes among humans as well. However, this hypothesis remains to be tested.

In conclusion, an association between a DRD2 gene polymorphism and physical activity level over the past year was found among White women both in the QFS and HERITAGE cohorts. However, no association was found for current activity phenotypes. These results indicate that a genetic basis might be the reason some people are consistently physically active and others are not. The TT genotype was in both studies associated with lower long-term activity level. DNA sequence variation in the DRD2 locus may contribute to long-term participation to physical activity.

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