Psychiatry

KEYWORDS: Genetic Polymorphism, Dopamine, Behavior, c.957C>T polymorphism; c.-585A> G polymorphism

DOPAMINE D2 RECEPTOR GENE POLYMORPHISMS AND EXTERNALIZING BEHAVIORS IN CHILDREN AND ADOLESCENTS

Volume-2, Issue-10, October - 2017

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Article History
Received: 11.07.2017
Accepted: 29.08.2017
Published: 10.10.2017

ABSTRACT:

Dopamine is involved in several cerebral physiological processes, and single nucleotide polymorphisms (SNP) in the dopamine D2 receptor gene (DRD2) have been associated with numerous neurological and mental disorders. The aim of this study was to evaluate the association between the SNPs c.957C>T (rs6277) and c.-585A> G (rs1799978) of the DRD2 gene and behavioral characteristics of children and adolescents based on an inventory of the Child Behavior Checklist (CBCL). Eighty-five patients between 8 and 20 years old were assessed overall, and the presence of the T allele (C/T and T/T) polymorphism of DRD2 c.957C> T was found to be significantly associated with the occurrence of defiant and oppositional problems and with attention and hyperactivity problems. There were no associations detected with polymorphism DRD2 c.-585A> G. Specifically, the presence of the T allele (C/T, T/T) in SNP c.957C>T was associated with difficulty in impulse control, self-control of emotions, and conduct adjustment, which can contribute to improving the identification of mental and behavioral phenotypes associated with gene expression.

Introduction

The dopamine D2 receptor gene (DRD2), located at chromosome 11q23.1, is involved in several cerebral physiological processes, including behavior inhibition and externalizing conditions, i.e., aggression and symptoms such as oppositional defiance, conduct problems, and attention deficit/hyperactivity– .

The single nucleotide polymorphism (SNP) c.957C>T (rs6277) is located on the Pro319 codon on the seventh exon of the DRD2 gene . Individuals with DRD2 C957T C/C homozygous genotypes, associated with a higher density of extrastriatal D2 receptors, were shown to be more efficient in inhibiting unwanted action tendencies and showed increased reward responsiveness after stress induction compared to T/– carriers . The presence of the T allele is associated with a reduction of the translation and stability of the messenger RNA (mRNA), and with a reduction in protein synthesis by up to 50% in comparison with activity of the C allele– .

The functional consequence of SNP c.-585A>G (rs1799978) is currently unknown; however, it is suspected to regulate the expression of the DRD2 gene due to its location on the promoter region . The G allele has been associated with conditions related to impulsiveness .

In this study, we tested the hypothesis that the T allele of the c.957C>T (rs6277) polymorphism and/or the G allele of the c.-585A>G (rs1799978) polymorphism are associated with the occurrence of externalizing behaviors among children and adolescents under psychiatric treatment.

Subjects and Methods

This was a descriptive cross-sectional study, with a sample composed of patients attending the Psychiatric Outpatient Clinic of Children and Adolescents, Department of Medical Psychology and Psychiatry, Clinical Hospital and School of Medical Sciences, University of Campinas (Unicamp) from March 2014 to August 2015. The center provides a service that typically cares for severe cases, most of whom are under a regime of psychotropic drugs, requiring a more complex level of mental health attention than those receiving primary health care.

All parents/caregivers of the subjects who participated in the study provided written informed consent in accordance with the Research Ethics Committee of the Unicamp (Concurring opinion 44199, Certificate of Presentation for Ethic Appreciation 04369612.8.0000.5404; 26.06.2012). All of the children and adolescents provided oral consent and assent to participate.

In addition to information about the use of medications and diagnoses registered on medical records, the inventory of the Child Behavior Checklist for the age range of 6–18 years old (CBCL/6-18) was used for qualification of the presence and severity of the mental and behavioral symptoms. The CBCL/6-18 is a standardized questionnaire designed by Achenbach in 1991, answered by the parents or caregivers, which is used to assess the behaviors of children or adolescents and was validated for application in the Brazilian population.. The CBCL/6-18 is widely recommended as one of the most effective tools for the qualification of parental responses related to childhood behavior. Such an inventory provides a profile of behavioral and emotional problems in syndromic groups, but has not been validated as a diagnostic instrument.

The emotional/behavior problem section of the CBCL/6-18 has 118 items. The respondent has to attribute the following scores to each problem: 0, not true; 1, somewhat true or rare; and 2, very true or very frequent over the last six months. Analysis of the CBCL/6-18 scores was conducted with the software of the Achenbach System of Empirically Based Assessment, and the results were grouped into three kinds of profiles: syndrome-based scores, which evaluate symptoms for each of the main clusters of mental health problems; scales that mainly group psychological symptoms according to internalizing and externalizing dimensions; and scales consistent with DSM-IV scales. The following DSM-oriented scales were used: "anxiety problems", "somatic problems", "attention deficit hyperactivity disorder problems", "opposition and challenging problems", and "conduct problems".

The results obtained from the CBCL/6-18 responses were used to classify the children/adolescents into the following categories: "normal" (behavior scores < 67, total scores < 60), "borderline clinical range" (behavior scores 67–70, total scores 60–63), and "clinical range" (behavior scores > 70, total scores > 63).

The genomic DNA samples were obtained from 8 mL of total peripheral blood collected in tubes with the anticoagulant ethylenediaminetetraacetic acid (0.6 M), pH 8.0. Genomic DNA extraction was performed using the technique standardized by the Human Genetics Lab of the Molecular Biology and Genetics Engineering Center (CBMEG) of Unicamp through lysis with K proteinase (Boehringer Mannhein, Germany). The determination of the SNPs c.957C>T (rs6277) and c.-585A>G (rs1799978) of the DRD2 gene was performed by real-time polymerase chain reaction using restriction enzymes or primer-specific alleles.

Statistical analysis was carried out using SPSS version 22 (IMB Co., Armonk, NY, USA). Hardy-Weinberg equilibrium was evaluated by the Haploview software (BROAD Institute) to determine if the allele frequencies of the SNPs assessed in the study population were balanced and therefore applicable for association studies. For the statistical analysis, the CBCL/6-18 results were grouped into two distinct groups of two categories each: in the first group, the results were compared between those without alterations ("normal") versus those with alterations ("borderline clinical range" plus "clinical range"); in the second group, the results were compared between those without alterations or with few alterations ("normal" plus "borderline clinical range") versus those with substantial alterations ("clinical range"). The chi-squared test was applied to evaluate the differences in the C and T allele frequencies for the polymorphism c.957C>T and in the A and G allele frequencies for the polymorphism c.-585A>G in relation to the grouped scores of the CBCL/6-18. The significance level adopted was 5%.

Results

This study comprised 85 patients with a mean age of 13.4 ± 2.7 years. Sixty-five patients (76.5%) were male. The sample was composed of 61 (71.8%) white, 15 (17.6%) bi-racial, 8 (9.4%) black, and 1 (1.2%) Asian individuals. The majority of the CBCL/6-18 assessment respondents were women (84.7%), 54 (75%) of which were the biological mothers. The other respondents included fathers, grandparents, and shelter caregivers that accompanied the child or adolescent.

All patients were receiving risperidone therapy, and 19 patients (22.7%) were on risperidone monotherapy. Antidepressants were involved in the treatment regimen of 46 (54.1%) cases, followed by psychostimulants in 23 patients (27.1%) and clonidine in 11 patients (12.9%). Anticonvulsants, lithium, benzodiazepines, and other associated antipsychotics accounted for 17.6% (15 patients) of the total use of medicines.

According to the clinical evaluation made by experienced psychiatrists and collected from the patients' medical records, the psychiatric syndromes were described as: disruptive/aggressive (42 patients, 49.4%), hyperkinetic (35 patients, 41.2%), depressive (29, 34.1%), intellectual disability (24, 28.2%), autism (20, 23.5%), phobic-anxious (17, 20%), learning disturbances (13, 15.3%), and psychotic (6, 7.1%).

The DRD2 polymorphisms were in Hardy-Weinberg equilibrium [c.957C>T (rs6277) p = 0.4169, c.-585A>G (rs1799978) p = 0.246]. Table 1 shows the genotypic distribution, sample allele frequencies, and minor allele frequencies (MAFs) of the SNPs for the study sample and the global population according to the 1000 Genomes Project and HapMap databases. The MAFs of the study population were highly similar to those of the global population for both polymorphic alleles. The only significant associations between polymorphisms and the CBCL/6-18 results were between the c.957C>T (rs6277) polymorphism and the occurrence of oppositional defiant disorders, attention problems, and hyperactivity, which are summarized in detail in Table 2. There were no significant associations for the SNP c.-585A>G (rs1799978).

Table 1
Table I2

Discussion

In the present study, the possible associations of the polymorphisms c.957C>T (rs6277) and c.-585A>G (rs1799978) of the DRD2 gene with the emotional/behavior problem section of the CBCL/6-18 were investigated; a significant association was detected between the polymorphism c.957C>T (rs6277) and the occurrence of oppositional defiant disorders, attention problems, and hyperactivity.

The allele frequency of the SNP c.957C>T (rs6277) was similar to that of the general population. It is interesting to note that the genotype distributions of the African, Asian, and European populations differ from each other as well as from the population of the present study; in particular, in the Asian and African populations, the T/T genotype is extremely rare (6%) and there is a higher frequency of heterozygotes in the European population (54%), indicating heterogeneity among these populations, and similarity between the Brazilian and Amerindian populations. The allelic frequency of the SNP c.-585A>G (rs1799978) in the study population was similar to that of the general population, with a slightly higher MAF of the G allele in the global population (11.9% vs. 11.2%).

Pena et al. in 2011 showed that the race of individuals in Brazil cannot be predicted from their genomic ancestry alone. Understanding the heterogeneity and admixture of Brazilians within and between geographical regions has important clinical implications for the design and interpretation of clinical trials, practice of clinical genetics and genomic medicine, implementation

of pharmacogenetic knowledge in drug prescriptions, and extrapolation of data from other, more homogeneous populations. The admixture proportions vary greatly among Brazilian populations as well as across Latin America ²⁷(Rodrigues de Moura et al. 2015)(27). The pooled ancestry contributions in Brazil are reported to be 0.62 European, 0.21 African, and 0.17 Amerindian.

The results of the present study showed a higher frequency association amongst externalizing symptoms, which, according to Goodman, result in hyperactive, challenging, aggressive, or antisocial behaviors. These symptoms include conditions of difficulties in impulse control, emotion self-control, and behavior regulation. These conditions share a spectrum of externalization associated with personality dimensions named "disinhibition" and inversely, "retraction" –. The challenging and oppositional problems as well as the attention and hyperactivity problems are common and potentially harmful–. They frequently occur as comorbidities and share some common etiological factors. The dopaminergic system influences and regulates diverse neuronal and physiological activities such as the sleep/wake cycle, mechanisms of reward and reinforcement, and motivation and learning, besides modulating voluntary movement control. A previous study of the polymorphism c.957C>T showed that the presence of the T allele (C/T, T/T) promotes reduction in the mRNA translation of the DRD2 gene, with a consequent reduction of the density of DRD2 receptors and of the dopaminergic function.

In this study, the presence of the T allele (C/T and T/T) was significantly associated with clinical attention and hyperactivity problems. Deregulation of the reward system has been proposed as a theoretical model contributing to attention deficit hyperactivity disorder, in which failure in the phasic liberation control of dopamine in the striate would result in injury of the cortico-striatal duct, influencing the connection between the cingulate anterior and parietal cortices with the caudate nucleus. According to Dichter et al., dopaminergic function reduction can be implicated with problems in learning and poor behavioral control, but has a reduced influence on rewards related to the behavior.

Oppositional defiant disorder involves the violation of others' rights and of the social rules, and is characterized by recurrent patterns of defiant behavior against authority figures, aggressiveness, and violence; it is frequently associated with attention deficit hyperactivity disorder and other kinds of impulsive behaviors. Dopaminergic polymorphisms have been associated with a variety of negative adaptive and antisocial phenotypes. It has also been suggested that a disability in impulse control is related to a higher tendency toward violence and aggressiveness. The hypo-reactivity of the orbitofrontal cortex and the reduction of dopaminergic function are related to hyposensitivity of the reward system, favoring transgressor behaviors, delinquency, and the abuse of psychoactive substances.

A limitation of the present study was the fact that all of the patients were under psychiatric pharmacological treatment during the CBCL assessment. In addition, the parents' and caregivers' evaluations regarding the children's or adolescents' behaviors tended to focus more on recent problems. The prescription of psychiatric medications as an attempt to decrease externalizing behavioral symptoms can have a positive effect on previously problematic behaviors, and may have influenced the perception in a minority of cases at the time of the CBCL assessment. Nevertheless, the scores of recorded behaviors were high, suggesting that the symptoms were still relevant by the time of the interviews, even with medication use.

The association of the T allele of the polymorphism c.957C>T (rs6277) with disruptive/aggressive symptoms, and problems of behavior, oppositional defiance, and attention/hyperactivity suggest that DRD2 gene expression changes can help with the identification of genetically associated behavioral and mental phenotypes. New studies analyzing the possible longitudinal association between these polymorphisms and the symptoms of more common occurrence in adults (manic psychotic, depressive symptoms) are encouraged to evaluate these relationships in more detail. In particular, more in-depth study of the SNPs are required for applications in not only improving diagnoses but also for preventive medicine. A broader view of the field of externalized behavioral conditions with respect to personalized medicine taking into account different genetic susceptibilities may facilitate the development of new drugs, as well as provide new ways of prescribing existing drugs, in a genetically oriented way according to the needs of each patient.

Acknowledgments

This work is supported by the São Paulo Research Foundation (FAPESP-Process no. 2012/14005-1).

Conflicts of interest

All authors of this study report no conflicts of interest.

Table 1 - Genotypic distribution and allele frequencies of DRD2 gene polymorphisms, and MAF values of the study population and the global population.

SNP	Genotype	Allele frequency	MAF of the study population	MAF from the global database
rs6277	C/C 43 (50.6%) C/T 37 (43.5%) T/T 5 (5.9%)	C =123 (72.35%) T = 47 (27.65%)	T = 27.65%	T = 24.4%
rs1799978	A/A 66 (77.6%) A/G 19 (22.4%)	A = 151 (88.82%) G = 19 (11.18%)	G = 11.18%	G = 11.9%

MAF = minor allele frequency

Table 2 – Significant associations between the results of the CBCL/6-18 and the rs6277 polymorphism of the DRD2 gene*

	Presence of the T allele (C/T e T/T)	Absence of the T allele (C/C)	p-value	χ^2
Challenging and oppositional problems according to the DSM-IV No alteration (0) With alteration (1 and 2)	14 (35.9%) 28 (60.9%)	25 (64.1%) 18 (39.1%)	0.022	5.265
Attention problems and hyperactivity by the DSM-IV Few alterations (0 and 1) Substantial alteration (2)	26 (61.9%) 16 (38.1%)	35 (81.4%) 8 (18.6%)	0.046	3.983

*There were no associations between the rs1799978 polymorphism of DRD2 and any of the CBCL/6-18 results.

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