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Research Article

Dopamine DRD4 gene polymorphism as a risk factor for epilepsy in autism spectrum disorder

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Abstract

Background: Epilepsy can co-occur in Autism Spectrum Disorder (ASD) patients and impact the individual's behavior, socialization, and language development. Polymorphisms in the dopamine D4 receptor gene - *DRD4* - have been studied as a potential biomarker for co-occurrence and severity of these disorders. In this study, we evaluated the prevalence of the polymorphisms of the *DRD4* gene, its effects on clinical characteristics of ASD, and its association with epilepsy in ASD patients. Clinical investigations of 53 ASD patients aged between 2 and 16 years old were conducted to assess their health history and comorbidities. Genotyping of these patients was performed through the molecular analysis of the *DRD4* gene polymorphisms.

Results: ASD and control subjects did not differ in the prevalence of *DRD4* gene polymorphisms. However, heterozygous samples for *DRD4* polymorphism of 7 repetitions presented greater association with epilepsy. Combining homozygous and heterozygous samples for *DRD4* polymorphism of 7 repetitions resulted in no significant difference. The relative risk for epilepsy in heterozygous for *DRD4* polymorphism with 7 repetitions increased 3.5-fold.

Conclusion: ASD patients with *DRD4* gene polymorphism of heterozygous alleles with 7 repetitions are associated with a higher frequency of epilepsy.

Introduction

Autism Spectrum Disorder (ASD) is a disorder of child development characterized by deficits in communication and social interaction associated with patterns of behavior, interests or restricted and repetitive activities [1]. Individuals with ASD may present language and/or cognitive impairment, including Intellectual Disability. Furthermore, they also can have associated comorbidities, such as epilepsy and anxiety disorders, behavioral problems and aggressiveness, among others [2-4].

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The co-occurrence of ASD and epilepsy is well established, and is mainly associated with increased age, worse cognitive levels, reduced language development, history of regression in development, and more severe symptoms of ASD [5]. The mean prevalence of epilepsy in children with ASD between 2 and 17 years old is 12.5%, less than 10% in children under 10 years old and cumulative of 26.5% in teenagers up to 17 years old [6]. The association between ASD and epilepsy can be explained as both resulting from altered cortical and subcortical connections on a large scale. Molecular and cellular mechanisms are also involved in the increase of epileptogenesis, thus affecting social behavior and changes in language. These factors can be directly influenced by genes associated with early brain development and the release of neurotransmitters, thus disturbing neuronal inhibitory-excitatory balance [7-9].

Although the etiology of ASD has not yet been fully elucidated, its genetic influence is clear. Several genes are listed as possible candidates for the vulnerability to develop ASD [10]. Most of them with extremely complex neurobiological explanations, but none has yet proved to be a single determinant [11-13]. Genetic influence does not follow a specific pattern or a Mendelian inheritance, but contribute to the patients' phenotype and may be associated with specific comorbities. Among these, the DRD4 gene (NCBI Gene ID: 1815, OMIM: 126452) that encodes the dopamine D4 receptor comprises one of the most variable regions of the genome. It is located in the chromosome 11 (11p.15.5) and is composed of 4 exons and a variable number of tandem repeats (VNTR) in the third exon. Figure 1 shows DRD4 gene structure elements, as well as the amplicon region investigated in this study.

Figure 1 introduces DRD4 gene structure. This gene is shown on chromosome 11 (Chr 11) in the p15.5 region. DDR4 gene is composed by 4 exons (black boxes, E1 to E4) and the studied amplicon region is found in exon 3. The position of the start codon ATG and the stop codon TGA are described in E1 and E4, respectively. Grey bar represents 5'-UTR, 3'-UTR and introns numbered 1 to 4 (I1-I4).

There are seven repetitions of the VNTRs in the dopamine D4 receptors that increase the length of the alleles in the third intracellular loop, thus impairing the activation of the receptor. With the lower sensitivity of the D4 receptor to dopamine, activation of regions where it is highly expressed, such as the prefrontal cortex, anterior cingulate, and limbic areas [14-16], becomes less facilitated. The lower effectiveness provided by the polymorphism may be related, for example, to the decrease in the amount of D4 receptors in individuals with ASD [17].

The 7-fold VNTR present in the DRD4 gene has been associated with repetitive behaviors in autistic children as well as increased risk of autism symptoms in children and teenagers with Attention Deficit and Hyperactivity Disorder (ADHD). It has also been associated with other developmental disorders, such as schizophrenia, oppositional defiant disorder, and separation anxiety [14, 18-20]. In ASD, DRD4 polymorphism has been studied as a potential biomarker for severity and co-occurrence of associated symptoms, higher rates of behavioral problems and repetitive behaviors, and neuropsychiatric disorders [18,21].

Interestingly, investigation of the role of dopamine in ASD intensified after observing the beneficial effects of

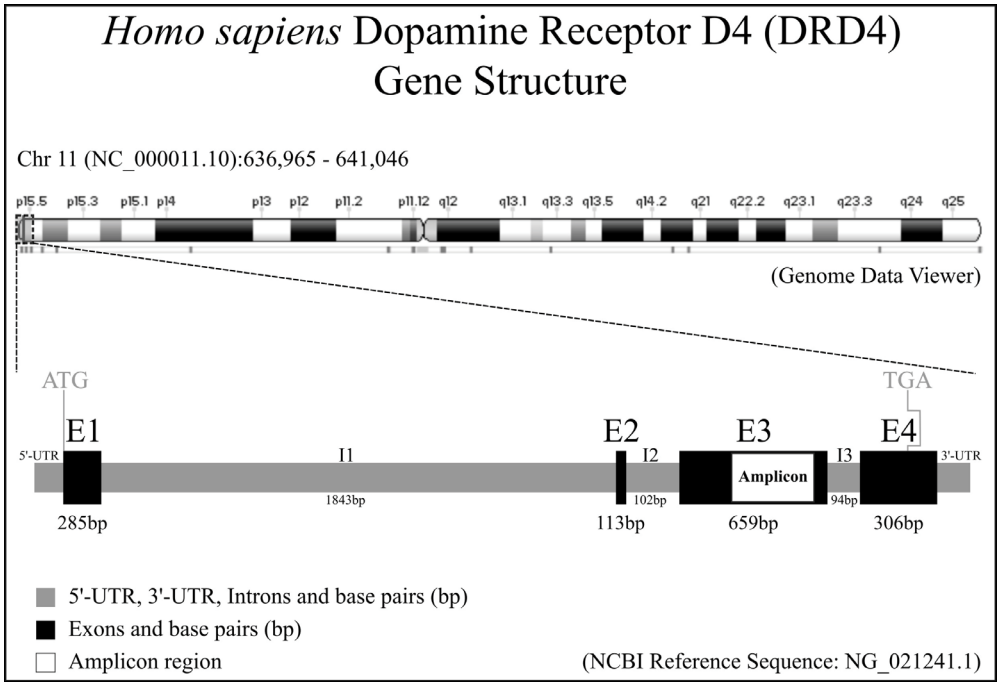

Figure 1: DRD4 gene structure.
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antipsychotics (dopaminergic antagonists) on aspects such as hyperactivity and aggressiveness. Studies have reported that different polymorphisms are associated to an increase or decrease in the activity of the dopaminergic system in the prefrontal cortex of autism individuals. The dysfunction of this system may still be related to behaviors of aggressiveness and impulsivity in adults with ASD [22-23].

Thus, the objective of this study was to evaluate the prevalence of polymorphisms of the *DRD4* gene and their clinical impact in patients with ASD. We have characterized the genotypic frequency of the DRD4 polymorphisms in order to demonstrate their potential association to ASD through the analysis of transmission and case-control disequilibrium. In addition, we tested the association of DRD4 polymorphisms with specific symptoms of ASD and individual comorbidities.

Materials and methods

This is an observational, analytical, cross-sectional study with prospective data collection. Procedures have been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) and were approved by the Independent Ethics Committee (IEC) of the Centro Universitário Autônomo do Brasil - UNIBRASIL, according to the opinion 002/2008 and acceptance of the Term of Informed Consent. All subjects gave their informed consent for inclusion in the study before enrollment.

Patients

Subjects included in the study are patients from the Autism Outpatient Clinic of CENEP - Centro de Neuropediatria do Hospital de Clínicas da Universidade Federal do Paraná, with diagnosis of idiopathic ASD and who were followed from January 2012 to December 2014. The control group had 40 healthy individuals who were ethnically- and gender-matched to the ASD group. All samples from the control group were obtained from the DNA bank of the Centro Universitário Autônomo do Brasil - UNIBRASIL.

Patient inclusion and exclusion criteria

Patients diagnosed with idiopathic ASD whose caregivers agreed to participate in the study through A Term of Informed Consent and who performed regular follow-up at the outpatient clinic for at least one year were included in the study. Patients with genetic tests, brain imaging, or dimorphisms characterizing the diagnosis of specific genetic syndromes associated with ASD were excluded from the sample.

Fifty-eight patients were initially selected for participation and blood samples were collected. Subsequently, five patients were excluded from the clinical analysis because they failed to follow-up. Thus, a total of 53 patients whose blood samples were collected were included in the clinical and genetic analysis, and a total of 58 patients were genotyped for ASD vs control comparisons. The exclusion criteria for both groups consisted of the presence, or familial history, of genetic or non-genetic neurological diseases.

Procedures

Peripheral venous blood samples (5ml) were collected from each subject in an EDTA tube. Patient and control samples were submitted to DNA extraction by the method of Lahiri and Numberger [24].

All genetic tests were performed in the laboratory of Genetics and Molecular Biology of the Centro Universitário Autônomo do Brasil – UNIBRASIL.

For the *DRD4* gene, the alleles were divided as to their functionality since an allele with 7 repetitions reduces dopamine affinity for the D4 receptor and its inhibitory potency to 2 to 3 times lower. Therefore, they were divided in 3 categories: (i) No 7n - alleles without 7 repetitions with inhibitory power at the D4 receptor, (ii) Heterozygous 7n - heterozygous with an allele with 7 repetitions with lower inhibitory power and (iii) Homozygous 7n - homozygous for an allele with 7 repetitions with much lower inhibitory power at the D4 receptor [15].

The dependent variables analyzed were the presence of idiopathic ASD in the analysis of frequencies, and the presence of the following clinical characteristics and associated comorbidities:

- Diagnostic criteria for ASD: stereotypies, inflexibility, sensory dysfunctions;
- Associated characteristics: anxiety, psychomotor agitation, aggressiveness, regression in development;
- ASD specifications: language impairment and cognitive impairment;
- Comorbidities: epilepsy
- Level of impairment: levels 1, 2 or 3;
- Changes in exams: Electroencephalogram and imaging exams (Tomography or Brain Magnetic Resonance);
- Use of medications (mono and polytherapy)

For the *DRD4* gene, the genotyping process was performed to define the number of repetitions of the VNTR region presented by individuals in the third exon of the *DRD4* gene. The sequence of the primers used was described in Gadow et al., and the amplification by Polymerase Chain Reaction (PCR) agrees with the protocol suggested by the same authors [18].

The analysis of the genotypes was performed in agarose gel electrophoresis (concentration 2.5%) which observed allelic variations of 2 to 11 repetitions [18].

Statistical analysis

Measures of central tendency and dispersion are expressed as mean and standard deviation (mean + SD) for the symmetrical distribution of continuous variables and in medians, minimum and maximum values (median, minimum - maximum) for the asymmetric distribution variables.

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The estimation of the difference of continuous variables of normal distribution was performed by the parametric test, *Student-t test* and ANOVA (combined categorical and continuous variables). Asymmetrically distributed variables were analyzed by the non-parametric tests of Mann-Whitney and Kruskal-Wallis ANOVA.

Estimates of the difference between categorical variables were performed using Fisher's exact test and Pearson's chi-square test.

For all tests a minimum significance level of 5% and a minimum test power of 90% were considered.

Results

Genotyping of 58 patients with ASD and of 40 patients of the control group were performed. Alleles of the *DRD4* gene which vary between 2 and 8 repetitions in relation to the considered VNTR were found in this study. According to the genotypic characterization of the groups the allele and genotype frequencies were estimated in both populations, and the population was found to be in Hardy-Weinberg equilibrium (ASD: p=1.000; control: p=0.9999), as shown in Table 1.

Comparison of the genotypic and allelic frequencies between the two groups resulted in non-significant values (genotypic: p=0.5685; alleles: p=0.4305), indicating that both genotypes and alleles are similarly distributed among these populations. The frequency observed in this study (adding the ASD and control groups due to the homogeneous distribution of the alleles between them) compared to the mean frequencies observed in the world population did not differ significantly (p= 0.9754).

Table 1 Allelic frequencies were divided according to their gene expression and functionality.

Table 2 The results of the allele comparison with the clinical characteristics of the sample are summarized in Table 3.

Heterozygous patients for polymorphism of 7 repetitions for the *DRD4* gene presented a higher frequency of association with epilepsy (p = 0.01). When grouped with homozygous for 7 repetitions, no statistical difference was observed (p = 0.09) with Relative Risk (RR) for epilepsy of 3.5 (95% CI = 0.95 to 13.08). Although the sample is small, with only 17 patients with at least one allele with 7 repetitions, this ratio may represent a risk factor for epilepsy in ASD patients. However, studies with a larger sample are necessary for the confirmation of this data.

For the other results, there was no significant difference between the groups with the different polymorphisms of the *DRD4* gene.

Discussion

In this study, we show that the prevalence of *DRD4* gene polymorphisms in ASD group was the same as in the control group. From a clinical perspective, in the ASD group the *DRD4* gene polymorphism with the presence of homozygous alleles with 7 repetitions was associated with a higher frequency of epilepsy in the ASD group.

The relatively similar distribution of the *DRD4* alleles in the ASD and control groups observed in this study was expected since the previous studies suggest that there is an allele ratio of 7 repetition of *DRD4* with some specific symptoms of ASD [18,25,26] or with associated comorbidities [20].

However, we did not find significant differences for specific symptoms (repetitive behaviors, anxiety, psychomotor agitation, inflexibility or aggressiveness). This fact may be related to the difficulty in clinically evaluating these symptoms since the analysis is subjective, and these data were not objectively quantified by specific questionnaires to investigate comorbidities. In addition, data analysis was shown to be complex due to sample heterogeneity relative to the degree of impairment and the low age of the sampled population (median of 7 years old). Another key factor hindering the analysis is the small sample size of patients with at least one allele with 7 replicates (n=17).

Table 1: Genotypic and allelic frequencies of the *DRD4* gene observed in the SAD and control groups.

Genotype frequencies *DRD4*

Genotype	n of patients (%)	n of controls (%)
2-2	0 (0)	1 (2.5)
2-4	8 (13.8)	2 (5.0)
2-7	1 (1.72)	1 (2.5)
3-3	0 (0)	1 (2.5)
3-4	2 (3.45)	3 (7.5)
4-4	27 (46.55)	21 (52.5)
4-5	1 (1.72)	0 (0)
4-6	1 (1.72)	1 (2.5)
4-7	13 (22.42)	7 (17.5)
4-8	0 (0)	1 (2.5)
7-7	5 (8.62)	2 (5)
Total	58 (100)	40 (100)
χ2	p=1.0000	p=0.9999

Allele frequencies.

Allele	Patient alleles n (%)	Control alleles n (%)	Observed population Frequency	World population frequency
2	9 (7.7)	5 (6.3)	7.14%	8.8%
3	2 (1.7)	5 (6.3)	3.57%	2.4%
4	79 (68)	56 (70)	68.88%	65.1%
5	1 (0.9)	---	0.51%	1.6%
6	1 (0.9)	1 (1.2)	1.02%	2.2%
7	24 (20.7)	12 (15)	18.37%	19.2%
8	---	1 (1.2)	0.51%	0.6%
Total	116 (100)	80 (100)		

Chi-square test.

Table 2: DRD4 allele frequency according to functionality.

Alleles	Inhibitory power in D4	n	%
No 7	Normal	36	67.9
Heterozygote 7 repetitions	Minor	12	22.7
Homozygous 7 repetitions	Much smaller	5	9.4

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Table 3: Results of genotype analysis with the clinical characteristics of the sample.

Assessed item	Alleles DRD4			
	No 7 n (%) n=36	Heterozygous 7 n (%) n=12	Homozygous 7 n (%) n=5	P
Stereotypes	16 (44.4)	3 (25)	1 (20%)	0.36
Inflexibility	9 (25)	2 (16.7)	1 (20)	0.81
Anxiety	11 (30.6)	3 (25)	1 (20)	0.9
Psychomotor agitation	11 (30.6)	2 (16.7)	2 (40)	0.81
Aggressiveness	4 (11.1)	1 (8.3)	0	0.90
Regression	11 (30.6)	4 (33.3)	3 (60)	0.43
Level 1	15 (41.7)	9 (75)	2 (40)	0.31
Level 2	8 (22.2)	2 (16.7)	1 (20)	0.31
Level 3	13 (36.1)	1 (8.3)	2 (40)	0.31
Language Impairment	18 (50)	3 (25)	3 (60)	0.25
Cognitive impairment	19 (52.8)	3 (25)	3 (60)	0.20
Epilepsy	3 (8.3)	2 (16.7)	3 (60)	0.01**

Nonetheless, the potential risk of a greater association of epilepsy and ASD in patients with at least one allele with 7 repetitions needs to be highlighted and further investigated. Traditionally, the occurrence of epilepsy may be explained by the imbalance between excitatory (glutamate) and inhibitory (GABA) neurotransmitters. Currently, the SFARI database presents 943 genes considered to predispose autism in individuals [27]. Among these genes, some include the dopamine and serotonin neurotransmitter systems that are also involved in epileptogenesis. Dopamine D4 receptors belong to the D2-like dopamine receptors and can be found in post-synaptic glutamatergic and GABAergic neurons with an inhibitory action by activating Gi protein. The association between the dysfunctional dopaminergic system and epilepsy is evidenced by pro-convulsants and anti-convulsants agents that bind to dopaminergic receptors. Additionally, animal studies demonstrated that receptors with D2-like action have a crisis-regulating effect, as is the case with D4 [28]. As we have observed in our results, DRD4 polymorphism with 7 repetitions presents a higher association of epilepsy in ASD patients. As this polymorphism makes the D4 receptor less functional by lowering its sensitivity to dopamine, thus decreasing its inhibitory action [29,30], it is likely that epileptogenesis might be increased by an incapability of dopamine to properly regulate glutamatergic and GABAergic systems. Further studies are necessary to demonstrate this mechanism.

In D2 receptor deficiency, for example, there is an accumulation of dopamine in the synaptic cleft which generates a reduction or even inhibition of dopamine synthesis and release by negative feedback [23]. This condition, by mechanisms not yet clarified, results in the activation of noradrenergic neurons in the locus coeruleus and consequent release of noradrenaline. Considering this evidence along with the idea of dopamine actions in conjunction with other neurotransmitter systems point to the possibility that an analogous process may occur in individuals in whom dopamine D4 receptors are less sensitive to dopamine [31].

It is necessary to emphasize that the small number of subjects included in the genetic analysis is the main limitation of the present study. This derives from the rigid inclusion criteria used to recruit patients. The sample analyzed is small, but it is very well characterized in terms of the type and number of standardized diagnostic scales the patients underwent. This limitation certainly prevents further conclusions on the association between the DRD4 polymorphisms with 7 repetitions and epilepsy in patients with ASD. However, the diagnostic reliability present in the individuals included in the analysis and the finding of higher frequency of epilepsy in individuals with DRD4 polymorphisms with 7 repetitions raise an intriguing question regarding the role of the dopaminergic system in mediating epileptogenesis in individuals with and without ASD.

Taken together, it is evident that further investigation is needed to explore different genes and polymorphisms that may be acting on certain behaviors or diseases such as ASD. For example, a large sample of subjects and joint analysis of different polymorphisms in genes of complementary action on the nervous system could shed light into the hypothesis discussed in this study. The relevance of a well-characterized sample regarding symptomatology, as used in this study, highlighting each particularity in a more quantitative way added to the genetic characteristics can justify behaviors that are difficult to understand and help in the development of drugs employed in the search for the well-being of the individuals affected by ASD.

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Author contributions

Conceptualization, Lilian Pereira Ferrari, Salmo Raskin and Sergio A. Antuniuk; Methodology, Mariane Wehmuth, Liya Regina Mikami, Karine Bittencourt da Silva Alcantud; Formal Analysis, Adriana de Oliveira Christoff, Henrique Ravanhol Frigeri, Suelen Lucio Boschen; Writing – Original Draft Preparation, All Authors; Writing – Review & Editing, all authors.

References

1. APA (2013) American Psychiatric Association. Diagnóstic and Statistical Manual of Mental Disorders.5 ed. (DSM – V). Arlington: APA 50-59.

2. Maski KP, Jeste SS, Spence SJ (2011) Common Neurological Co-Morbidities in Autism Spectrum Disorders. Curr Opin Pediatr 23: 609-615. Link: https://bit.ly/2VgVRLG

3. Mcpartland J, Volkmar FR (2012) Autism and Related Disorders. Clin Neurol Neurosurg 106: 407-418. Link: https://bit.ly/2CH6pgD

4. Ung D, Wood JJ, Ehrenreich-May J, Arnold EB, Fuji C, et al. (2013) Clinical Characteristics of High Funcioning Youth with Autism Spectrum Disorder and Anxiety. Neuropsichyatry. Link: https://bit.ly/3dzXjyZ

5. Shen HI, Huang N, Reemmer J, Xiao L (2012) Adenosine Actions on Oligodendroglia and Myelination in Autism Spectrum Disorder. Front Neurosci 482: 12. Link: https://bit.ly/2YusJm1

6. Berg AT, Plioplys S, Tuchman R (2011) Risk and Correlates of Autism Spectrum Disorder in Children with Epilepsy: a Community-Based Study. J Child Neurol 26: 540-547. Link: https://bit.ly/3fYce7H

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7. Gadia CA, Tuchman R, Rotta NT (2004) Autism and pervasive developmental disorders. J Pediat 80: 83-94. Link: https://bit.ly/2ZbsFH5

8. Tuchman R, Moshe SL, Rapin I (2009) Convulsing Toward the Pathophysiology of Autism brain development. Brain Dev 31: 95-103. Link: https://bit.ly/3fW8XFV

9. Viscidi EW, Triche EW, Pescosolido MF, McLean RL, Joseph RM (2013) Clinical Characteristics of Children with Autism Spectrum Disorder and Co-Occurring Epilepsy. PLoS One 8: e67797. Link: https://bit.ly/2Nvh6Vy

10. Wiśniowiecka-Kowalnik B, Nowakows BA (2019) Genetics and epigenetics of autism spectrum disorder—current evidence in the field. J Appl Genet 60: 37-47. Link: https://bit.ly/2Zc0DeF

11. Rubinstein M, Cepeda C, Hurst RS, Flores-Hernandez J, Ariano MA, et al. (2001) Dopamine D4 Receptor-Deficient Mice Display Cortical Hyperexcitability. J Neurosci 21: 3756-3763. Link: https://bit.ly/2VkaQ7D

12. Geschwind DH (2011) Genetics of Autism Spectrum Disorders. Trends Cogn Sci 15: 409-416. Link: https://bit.ly/3dz9tYK

13. Veenstra-Vanderweele J, Blakely RD (2012) Networking in Autism: leveraging genetic, biomarker and model system findings in the search for new treatments. Neuropsychopharmacology 37: 196-212. Link: https://bit.ly/3dzsevp

14. Gehricke JG, Swanson JM, Duong S, Nguyen J, Wigal TL, et al. (2015) Increase brain activity to unpleasant stimuli in individuals with the 7R allele of the DRD4 gene. Psychiatry Res 231: 58-63. Link: https://bit.ly/2VhSLa4

15. Marques FZC (2006) Polimorfismos nos genes DAT1 e DRD4 e transtorno de déficit de atenção e hiperatividade (TDAH) em adultos. Braz J Psychiatry 22: 38-40. Link: https://bit.ly/2YyiRI1

16. Rodrigues LT (2010) Receptor de dopamina D4: estudo da variabilidade e evolução em populações Ameríndias. Universidade Federal do Rio Grande do Sul, Porto Alegre. Link: https://bit.ly/2Nt4sqf

17. Taurines R, Grünblatt E, Schecklmann M, Schwenck C, Albantakis L, et al. (2011) Altered mRNA expression of monoaminergic candidate genes in the blood of children with attention deficit hyperactivity disorder and autism spectrum disorder. World J Biol Psychiatry 12: 104-108. Link: https://bit.ly/3eCJtx6

18. Gadow KD, DeVincent CJ, Pisarevskaya V, Olvet DM, Xu W, et al. (2010) Parent-Child DRD4 Genotype as a Potential Biomarker for Oppositional, Anxiety, and Repetitive Behaviors in Children with Autism Spectrum Disorder. Prog Neuropsychopharmacol Biol Psychiatry 34: 1208-1214. Link: https://bit.ly/3i7TuVp

19. Holmboe K, Nemoda Z, Fearon RM, Sasvari-Szekely M, Johnson MH (2011) Dopamine D4 receptor and serotonin transporter gene effects on the longitudinal development of infant temperament. Genes Brain Behav 10: 129-136. Link: https://bit.ly/2CG7iGg

20. Szekely A, Balota DA, Duchek JM, Nemoda Z, Vereczkei A, et al. (2010) Genetic factors of reaction time performance: DRD4 7-repeat allele associated with slower responses. Genes Brain Behav 10: 129-136.

21. Sánchez-Soto M, Yano H, Cai NS, Casadó-Anguera V, Moreno E, et al. (2019) Revisiting the Functional Role of Dopamine D4 Receptor Gene Polymorphisms: Heteromerization-Dependent Gain of Function of the D4.7 Receptor Variant. Mol Neurobiol 56: 4778-4785. Link: https://bit.ly/2VyhHKT

22. Nakamura K, Sekine Y, Ouchi Y, Tsujii M, Yoshikawa E, et al. (2010) Brain Serotonin and Dopamine Transporter Bindings in Adults With High-Functioning Autism. Arch Gen Psychiatry 67: 59-68. Link: https://bit.ly/2YxoyGg

23. Palaniyappan L, Batty MJ, Liddle PF, Liddle EB, Groom MJ, et al. (2019) Reduced Prefrontal Gyrification in Carriers of the Dopamine D4 Receptor 7 Repeat Allele With Attention Deficit/Hyperactivity Disorder: A Preliminary Report. Front Psychiatry 10: 235. Link: https://bit.ly/37Xqaw3

24. Lahiri DK, Nurnberger JR (1991) A rapid non-enzymatic method for the preparation of HMW DNA from blood for RFLP studies. Nucleic Acids Res 19: 5444. Link: https://bit.ly/2AZBewH

25. Gangi D, Messinger DS, Martin ER, Cuccaro ML (2016) Dopaminergic Variants in Siblings at High Risk for Autism: Associations With Initiating Joint Attention. Autism Res 9: 1142-1150. Link: https://bit.ly/2Yv0svy

26. Gehrickea JG, Swansona J, Duonga S, Nguyenb J, Wigala T, et al. (2015) Increased brain activity to unpleasant stimuli in individuals with the 7R allele of the DRD4 gene. Psychiatry Res 231: 58–63. Link: https://bit.ly/3i2W6DV

27. Autism Research Community (2017) Sfari gene [data base]. Link: https://bit.ly/2AZAYhd

28. Thipathi PP, Bozzi Y (2015) The role of dopaminergic and serotoninergic systems in neurodevelopmental disorders: a focus on epilepsy and seizure susceptibility. Bioimpacts 5: 97-102. Link: https://bit.ly/2Nt3NFh

29. Chang FM, Kidd JR, Livak KJ, Pakstis AJ, et al. (1996) The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. Hum Genet 98: 91-101. Link: https://bit.ly/2NrAaE6

30. Wang E, Ding YC, Flodman P, Kidd JR, Kidd KK, et al. (2004) The Genetic Architecture of Selection at the Human Dopamine Receptor. Am J Hum Genet 74: 931–944. Link: https://bit.ly/387sCQI

31. Ptáček R, Kuzelová H, Stefano GB (2011) Dopamine D4 receptor gene DRD4 and its association with psychiatric disorders. Med Sci Monit 17: RA215-RA220. Link: https://bit.ly/3g1mj3B

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