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# Research in Autism Spectrum Disorders

journal homepage: <http://ees.elsevier.com/RASD/default.asp>

## Psychomotor agitation and mood instability in patients with autism spectrum disorders: A possible effect of *SLC6A4* gene?



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### ARTICLE INFO

#### Article history:

Received 25 September 2015

Received in revised form 25 February 2016

Accepted 1 March 2016

Available online 10 March 2016

#### Keywords:

ASD  
Serotonin transporter gene  
Clinical symptoms  
Sex differences  
Association  
Family-based test

### ABSTRACT

Autism spectrum disorders (ASD) are a group of neurodevelopmental conditions characterized by impairments in communication and social interaction and repetitive and stereotyped behaviors. Serotonergic transmission has been suggested as an important neuronal pathway in ASD. In this study, we analyzed four polymorphisms (5HTTLPR, rs2066713, STin2, rs1042173; 5' → 3' end) at the serotonin transporter gene (*SLC6A4*) in a sample of 209 ASD children and their biological parents. Both single markers and haplotypes were tested for association with ASD diagnosis and with clinical symptoms (aggression, echolalia, seizures, mood instability, psychomotor agitation, repetitive behaviors and sleep disorders) commonly present in ASD patients. The family-based analyses showed a significant result for one haplotype (H4: S-G-12R-T), which did not hold in global analyses. In male patients, a nominal association between the rs1042173 GG genotype and a diminished psychomotor agitation was observed; a trend for an association between the 5HTTLPR LaLa genotype and mood instability was also verified. Through interesting results that are mainly related to clinical manifestations and gender differences, our study adds to knowledge of ASD. Future investigations may corroborate the relevance of our data to upcoming clinical and pharmacological interventions.

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## 1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental conditions of childhood onset with a worldwide occurrence. Combined epidemiological studies from different countries showed a prevalence of 69 ASD cases per 10,000 (Hill, Zuckerman, & Fombonne, 2015), while in United States, the most recent data estimated 147 ASD cases per 10,000 (CDC, 2014). These disorders are characterized by impairments in communication and social interaction and repetitive and stereotyped behaviors (American Psychiatric Association, 2013). The clinical heterogeneity encompasses a range of

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comorbidities and other behaviors, including epilepsy, echolalia, mood instability, psychomotor agitation and aggression (Bishop et al., 2013; Grossi, Marcone, Cinquegrana, & Gallucci, 2012; Kanemura, Sano, Tando, Sugita, & Aihara, 2013; Mazefsky, McPartland, Gastgeb, & Minshew, 2013; Rutter, 2013). Clinical differences according to gender are also present. Some studies reported that females present more social problems and advanced receptive language skills than boys, while repetitive and stereotyped behaviors are more common in males (Bolte, Duketis, Poustka, & Holtmann, 2011; Holtmann, Bolte, & Poustka, 2007). These differences may be relevant to the epidemiology of these disorders since ASD are more common in males than in females, with a male:female ratio of 4.3:1 (Fombonne, 2003).

Serotonergic transmission has been suggested as an important neuronal pathway in ASD. Studies have shown higher serotonin blood levels in patients (Cook & Leventhal, 1996; Hranilovic et al., 2008). On the other hand, the effective treatment of some symptoms commonly seen in the disorder (e.g., aggression and anxiety) with selective serotonin reuptake inhibitors (SSRIs) suggests that diminished serotonin transmission can be also present (Hollander et al., 2005). These biological changes can be explained at least in part by different genetic and environmental factors, featuring the multifactorial origin of ASD. In this context, the contribution of genetics is probably substantial, given its high heritability of around 80% (Ronald & Hoekstra, 2011). The search for genetic factors has mainly focused on studies with candidate genes defined from biological hypothesis. Given the evidence indicating the importance of the serotonin system in ASD etiology, the possible influence of the serotonin transporter (5-HTT) has been studied. Through the reuptake of serotonin to pre-synaptic neurons, 5-HTT represents the major control mechanism of serotonergic function (Amara & Pacholczyk, 1991), suggesting its coding gene (*SLC6A4*) is a good candidate for molecular studies in ASD.

The main investigated polymorphism in the *SLC6A4* gene is the 5-hydroxytryptamine transporter linked polymorphic region (5HTTLPR), located at the proximal 5' promoter region. Several studies in ASD showed promising findings, although different alleles concerning this polymorphism were associated with the disorder. One meta-analysis highlighted this inconsistency, with negative results (Huang & Santangelo, 2008). The investigation of other polymorphisms in *SLC6A4* gene is less common, but some studies presented associations (Brune et al., 2006; Coutinho et al., 2007; Gadow et al., 2013; Huang & Santangelo, 2008; Kistner-Griffin et al., 2011; Ma et al., 2010; Nijmeijer et al., 2010; Valencia et al., 2012). Considering its putative importance in ASD, new investigations comprising different variants and diverse methodological strategies are worthy. Our aims were to investigate the possible impact of the *SLC6A4* gene on ASD diagnosis and on specific clinical symptoms commonly seen in these disorders, in a sample of ASD probands and their biological parents. To improve the analyses, subsets of patients defined according to gender were also analyzed. Polymorphisms in different regions of the gene (5HTTLPR, rs2066713, STin2 and rs1042173, from 5' to 3' end) were evaluated in an attempt to cover the whole gene.

## 2. Material and methods

### 2.1. Subjects

The complete description of research protocol and clinical and socio-demographic data was already reported (Schuch et al., 2014). Briefly, the sample consisted of 209 idiopathic ASD probands and their biological parents. Fragile X syndrome and other genetic syndromes, chromosomal abnormalities and lesional abnormalities of CNS were used as exclusion criteria. ASD diagnosis was made according to DSM-IV by clinical observations in regular appointments at the Neuropediatric Outpatient Unit from Hospital de Clínicas de Porto Alegre (HCPA), a teaching hospital of Federal University of Rio Grande do Sul (UFRGS). This process was always conducted by one neuropediatrician, with a second one participating in the clinical observations and confirming the diagnosis. Data about clinical symptoms and comorbidities observed in patients were also collected. The symptoms included aggression (both unprovoked and recurrent aggressive behavior toward self and/or others); echolalia; epilepsy (at least two unprovoked seizures); seizures (one or more episodes); mood instability (excessive and disabling variations in mood); psychomotor agitation (excessive activity not always related to the occasion, which can be manifested due to changes in the environment or in the individual's routine); repetitive behaviors; and sleep disorders. This information was obtained during the regular appointments by asking the parents and/or caregiver if the condition was present or absent in the proband, after a brief explanation about the context in which the behavior occurs. For each patient, data were confirmed through hospital medical records. The proportion of patients presenting each behavior listed above is

**Table 1**  
Frequencies<sup>a</sup> of clinical symptoms in ASD patients.

Symptoms	All (n = 209)	Male (n = 170)	Female (n = 39)
Aggression	61.8% (128)	61.2% (104)	64.9% (24)
Echolalia	60.4% (125)	60.0% (102)	62.2% (23)
Epilepsy	11.1% (23)	12.4% (21)	5.4% (2)
Seizures	28.0% (58)	25.3% (43)	40.5% (15)
Mood Instability	49.5% (102)	48.5% (82)	54.1% (20)
Psychomotor agitation	60.9% (126)	60.0% (102)	64.9% (24)
Repetitive behaviors	75.4% (156)	75.9% (129)	73.0% (27)
Sleep disorders	55.8% (115)	53.3% (90)	67.6% (25)

<sup>a</sup> Percentages (and numbers) of patients presenting each symptom.

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