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Original article

Serotonin transporter gene polymorphism as a predictor of short-term risk of suicide reattempts

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ABSTRACT

Objective: The serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphisms are associated with suicidal behavior; however, prospective studies are scarce. Herein we aim to determine if 5-HTTLPR polymorphisms predict risk of short-term suicide reattempt in a high-risk suicidal sample. We also explore possible mediators or moderators of this relationship.
Methods: A multicenter prospective cohort study was designed to compare data obtained form 136 patients admitted to the emergency department for current suicidal ideation or a recent suicide attempt. Subjects were clinically evaluated, genotyped, and monitored for a new suicide attempt for 6 months.
Results: At 6 months of follow up, 21% of the subjects had a new suicide attempt. The frequency of L-allele and L-carrier was higher in reattempters when compared with non-reattempters (55.8% vs. 35.4%, $p = 0.01$ and 76.9% vs. 54.2%, $p = 0.04$, respectively). Reattempters also differ from non-reattempters patients with respect to age, history of previous suicide attempts, and age of onset of suicidal behavior. The logistic regression model showed that L-carriers had an odds ratio of 2.8 (95% CI: 1.0–7.6) for reattempts when compared to SS genotype. The adjusted model indicates that this association is not mediated or moderated by impulsivity.
Conclusion: The 5-HTTLPR polymorphisms predicted short-term risk of suicidal reattempt independently of age and sex. L-carriers have almost three times more risk of relapse when compared with SS carriers.

1. Introduction

Suicide and suicidal behavior (SB) have been classified as among the leading causes of death and injuries worldwide. Approximately 800,000 deaths by suicide occur annually with 10–20 times more individuals attempting suicide, indicating that both suicide and non-fatal SB are prevalent problems that need to be addressed [1]. More than two thirds of patients completing suicide did so on the first attempt [2]. As such, interventions should focus on early detection and prevention of suicide attempts (SA). The study of subjects with SB is highly relevant to suicide mortality since a history of SA confers a 42-fold increased risk for suicide [3]. A limitation in assessing suicide risk among patients is that clinicians must rely on information provided by patients, and for different reasons, patients oftentimes may not provide accurate information about their suicidal status. Therefore, a need exists for the development of genomic, biochemical, molecular, imaging, and neuropsychological predictors for suicide risk.

Efforts to understand and predict SB must start with the study of potential contributing factors. Based on the stress–diathesis model, SB can be understood as a result of an interaction between state-dependent (environmental) stressors and trait-like diathesis [4,5]. The term diathesis or susceptibility is thought to include heritable factors among others, which could increase risk of SB. Twin and adoption studies have demonstrated that suicide has a heritable genetic component [6]. It has been estimated that the heritability for suicide ranges between 21–50% and between 30–55% for a broader phenotype of suicidal behavior and ideation [7].

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Offspring of probands who have attempted suicide are also at a nearly 5-fold higher risk of attempting suicide themselves. Although other psychiatric conditions associated with SB are also heritable, severe SB appears to be transmitted independently [8,9]. Since suicide and SB have a hereditary component, the first genetic studies used candidate gene association approaches to identify one or several genes variants that may increase the risk of SB, with most studies focused on biological systems linked to SB. Over the past decade, the field shifted to genome-wide association studies (GWAS), which use a less biased approach based on gene discovery. However, despite a great deal of enthusiasm and the potential to uncover novel genetic contributors to SB, GWAS studies collectively showed a lack of significant and reproducible findings [10], implying that individual gene variants are likely to account for only a small proportion of the total phenotypic variability [11]. Recent studies provided evidence that epigenetic mechanisms such as hypermethylation of brain derived neurotrophic factor (BDNF) could explain the missing link between heritability of SB and interaction with the environment [12].

Candidate genes studies for SB have been selected based on established biological correlates since alterations in serotonergic transmission have been observed in patients with SB [13–15] Genes involved in the synthesis (tryptophan hydroxylase, TPH), transport (serotonin transporter, 5-HTT), transmission (serotonin 1 A receptor, 5-HT_{1A}; serotonin 2C receptor, 5-HT_{2C}) and degradation (monoamine oxidase A; MAO-A) of serotonin have been used in association studies [16].

SLC6A4, which is located on chromosome 17q11.1-q12 and encodes for the serotonin transporter (5-HTT), is the most studied candidate gene and is responsible for regulating the duration of the serotonergic signal in the central nervous system (CNS) [17]. Several polymorphisms have been described for SLC6A4, but most studies have focused on a common polymorphism in the 5′promoter region, referred to as the serotonin-transporter-linked polymorphic region (5-HTTLPR) [18]. Even though 3 polymorphisms have been reported [19], most research has focused on two variations in this region that generate a short (S) allele with 44 fewer base pairs than the long (L) allele. While *in vitro* studies provide evidence that variations in this region are associated with different basal activity of the transporter, which is most likely related to varying transcriptional activity [20], this has not been confirmed in *in vivo* studies [21].

Although the 5-HTTLPR is the most studied, studies employing this genetic marker use a cross-sectional design used to detect associations among these polymorphisms and SB in patients with different psychiatric diagnoses and comorbidities or between patients and control subjects [16]. Previous studies have shown contradictory results, with some suggesting an association between SB and L-allele or L-homozygotes while others report an association between SB and the S-allele or S-carriers [16].

Because one of the best predictors of a future SA and suicide is a previous SA [2], clinicians require tools to categorize high-risk suicidal subjects according to their potential risk and try to predict who may be more prone to relapse. To date, we lack robust genetic predictors that can help quantify suicide risk, and the only method to assess risk is using longitudinal cohort studies. To the best of our knowledge, only one prospective cohort study has assessed the role of 5-HTTLPR polymorphisms as a predictor of suicide events in high-risk suicidal patients in which SS genotype was associated with a higher risk of reattempts [22]. However, these results have not been replicated.

Impulsivity and aggression are two personality traits frequently associated with SB and meet the definition of endophenotype [23]. In addition, both impulsivity and aggressive behavior have been related to serotonergic abnormalities [24]. It has been proposed that these abnormalities in serotonergic function can influence neurobiological systems and cognitive functioning, resulting in personality developments, such as impulsivity and/or aggressive traits, that lead to SB, especially under the influence of acute stressors or psychopathological states [24]. Despite some inconsistencies, association studies have linked impulsive and aggressive behavior with 5-HTTLPR polymorphisms. An association between the S-allele and increased aggressiveness and impulsivity has been described in various cohorts including children [25,26], adolescents [27], adopted children [28], adolescent and young girls [29], cocaine-dependent individuals [30], and patients with personality disorders [31].

In the present study, we aimed to determine if the genetic status of 5-HTTLPR polymorphisms predicts the risk of short-term suicide reattempt in a high-risk suicidal patient sample. We also explored whether suicidal endophenotypes are mediators or moderators of this relationship. Taking into account prior studies, it was hypothesized that S-carrier status would predict short-term suicide reattempt.

2. Methods

2.1. Study design

The present study used blood samples obtained from patients enrolled in a multicenter prospective cohort study conducted in Buenos Aires, Argentina. The cohort was recruited from three different hospitals: the Braulio A. Moyano Neuropsychiatric Hospital, the Hospital Borda, and the Hospital de Clínicas "José de San Martin", in the city of Buenos Aires. All hospitals in the current study serve a large urban catchment area in Buenos Aires and predominantly treat low-income, uninsured patients. The cohort study began in 2012 with collection of baseline data finishing in December 2016. The current study utilized data obtained at 6 months of follow-up. The study protocol was approved by the institutional review board at each participating hospital.

2.2. Patients

Participants were patients who had been admitted to the emergency department of one of the three hospitals for current suicidal ideation (SI) or a recent SA. SI was defined as any current self-reported thought of engaging in suicide-related behavior [32], and SA was defined as a potentially self-injurious behavior with a nonfatal outcome, for which there was evidence (either explicit or implicit) that the person intended at some (non-zero) level to kill him or herself [33].

Eligible participants were aged 18–65 years, hospitalized for SI or a SA within 72 h, sufficiently alert and able to respond with fluency in Spanish, and could provide written informed consent to participate. Participants were excluded if they were unable to respond autonomously (ie, due to sedative effects of medication or language limitations), were transferred to another institution, or had a profession related to mental health.

All participants gave written informed consent to participate in the study. Participants were included in the study if all relevant measures were completed at the baseline assessment. After discharge, subjects who had been recruited as inpatients received treatment as usual in the community. Participants were evaluated 6 months after their hospitalization.

2.3. Measures

2.3.1. Baseline data

At baseline evaluation, each participant underwent a semi-structured interview conducted by one of three psychiatrists (LG,