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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.
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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,

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AP, and SP) in the emergency departments. All psychiatrists on the research team had at least 5 years of clinical experience and underwent training for the semi-structured interviews and data-gathering procedures of the study. The semi-structured interview included questions specific to clinical and demographic variables. The Mini International Neuropsychiatric Interview (MINI) [34] and the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) [35] were used for diagnostic purposes. Participant history of sexual abuse, history of SA, age of first SA, hospitalizations due to SA, and family history of suicidal behavior and psychiatric illness were assessed during this interview. The Columbia-Suicide Severity Rating Scale (C-SSRS) [36] was used to obtain further details related to a participant's lifetime and most recent SB. To assess impulsivity, participants were administered the Barratt Impulsiveness Scale (BIS)-11 [37]. The BIS-11 is composed of 30 items describing common impulsive or non-impulsive (for reverse scored items) behaviors and preferences. The BIS-11 yields three second-order factor scores: attentional impulsiveness (ie, intrusive thoughts and racing thoughts), motor impulsiveness (ie, tendency to act on the spur of the moment and consistency of lifestyle), and nonplanning impulsiveness (ie, difficulties with careful thinking and planning or enjoyment of challenging mental tasks). The Buss-Durkee Hostility Scale (BDHS) was used to evaluate the different aspects of hostility [38]. It consists of 75 items that are grouped into seven subscales of hostility and one subscale of guilt. The items are of "true and false" dichotomous response. It provides a total score and scores on each of the eight subscales; from the clinical point of view, the total score is more relevant. The Beck Hopelessness Scale (BHS) was used to assess aspects of hopelessness [39]: the negative expectations that a person has about his future and well-being as well as his ability to overcome difficulties and achieve success in his life. It is a 20-item self-report inventory to which an individual answers "true or false." Recent stressors were assessed with the Brugha Stressful Life Events Scale (List of Threatening Experiences [LTE]) [40]. The LTE is an instrument designed to collect the existence of stressful life events that occurred during a specific time period (recommended to be 6 months prior). It is a self-applied instrument that consists of a list of 12 categories of stressful life events to which individuals must answer "Yes" (1 point) or "No" (0 points). A global score is obtained that consists of the sum of the scores obtained in each of the 12 items.

At the end of the baseline assessment, blood samples were collected into EDTA blood collection tubes (BD Vacutainer) and transported to the laboratory in the Pharmacology Institute of the School of Medicine of the University of Buenos Aires, Argentina.

2.3.2. Follow-ups

Two trained psychiatrists (DR and LG) performed the telephone follow-ups. Participants were contacted by telephone at 6 months following their baseline assessment. If participants could not be reached, calls were made on alternate hours and days for one week. If contact was still not achieved, interviewers contacted two reference numbers that was provided upon enrollment. If contact was still not possible, an e-mail was sent. If contact was not established after three attempts, the participant was declared as "loss to follow-up."

When interviewers contacted the participants or the reference person, they assessed whether participants experienced a new SA during the follow-up period.

2.4. Genetic analysis

Genomic DNA was obtained from EDTA anti-coagulated peripheral blood using the ReliaPrep Blood gDNA (Promega) and DNeasy Blood and Tissue Kit (Quiagen) columns according to manufacturer specifications. Polymerase chain reaction (PCR) amplification of 5-HTTLPR polymorphism was carried out in a total volume of 50 μl containing 10 μl buffer, 1.5 mM MgCl, 10 μl 5X-PCR enhancer (PCR MAX, Biodynamics), 5 pmol of each primer (Sigma Aldrich), 0.3 mM dNTP mix, 0.5 units of GoTaq Hot Start DNA Polymerase (Promega) and 50–100 ng DNA sample. We amplified the 5-HTT regulatory region using the following primers: 5′-GAGGGACTGAGCTGGACAACCAC-3′ (reverse) and 5′-GCGTTGCCGCTCTGAATGC-3′ (forward). The PCR was performed as follows: an initial denaturation step of 94 °C for 3 min, followed by 38 cycles of 94 °C for 1 min, 55 °C for 1 min, and 72 °C for 1 min, and a final extension step at 72 °C for 7 min. PCR products were separated on 2% agarose gel stained with Gel Red (Biotium) to allow identification of the L allele (572 bp) and the S allele (528 bp). Genotyping procedures were conducted by researchers (ARA and AEE) who were blinded to the clinical status of the patients.

2.5. Data analysis

Categorical measures are reported as frequencies or percentages, and continuous measures are reported as means ± standard deviations (SD). Comparisons between groups depend on the type of variable: categorical measures were compared with contingency tables (x^2) and Fisher's exact test, continuous measures by ANOVA methods (t-test), or Wilcoxon rank-sum test (Mann-Whitney U-statistic) for non-normally distributed continuous data.

Odds ratios (OR) and 95% confidence intervals (CI) were used to evaluate the association between suicide reattempt and genetic status via multivariable-adjusted logistic regression models. Independent variables were included stepwise and alpha (α) to enter was set at 0.20. Beta (β) coefficients and their 95% CI from logistic regression modeling are reported, with significance evaluated using t-test. Statistical significance was set at two-tailed $P < 0.05$. Assumptions were tested, and a robust analysis was performed to adjust our model to account for heteroscedasticity. All statistical analyses were conducted using SPSS software version 25.

3. Results

One hundred thirty-six participants (aged 37.1 ± 13.1 years with 66.2% women) fulfilled all the specified inclusion criteria and consented to the study. Of the total population, 85 (64%) participants met DSM-IV diagnostic criteria for current major depressive disorder (MDD), 25 (19%) for schizophrenia, and 20 (15%) for bipolar disorder (BD). A comorbid borderline personality disorder (BPD) was reported in 46% of the population, and substance abuse in 21%. Allele frequencies were 163 (59.9%) for the S-allele and 109 (40.1%) for the L-allele. Distribution of the genotypes were 57 (42%) for SS homozygotes, 49 (36%) for SL heterozygotes, and 30 (22%) for LL homozygotes. The distribution of genotype frequencies of 5-HTTLPR did not show any divergence from the Hardy-Weinberg equilibrium ($x^2 = 5.03$, $P = 0.08$).

At baseline, we found no significant differences in genotype status among patients with SI (SS-genotype, 41.3%, SL-genotype, 39.1%, LL-genotype, 19.6%), single suicide attempters (SS-genotype, 58.8%, SL-genotype, 23.5%, LL-genotype, 17.6%), and multiple suicide attempters (SS-genotype, 32.1%, SL-genotype, 41.1%, LL-genotype, 26.8%) ($P = 0.16$). When comparing baseline allele status among groups with SI (S-allele, 60.9%, L-Allele, 39.1%), single suicide attempters (S-allele, 70.6%, L-Allele, 29.4%), and multiple suicide attempters (S-allele, 52.7%, L-Allele, 47.3%) we observed a statistical tendency ($P = 0.06$) towards a higher frequency of the L-allele in the group of subjects with multiple suicide attempts.

Participants who were lost during follow-up differed from those available for the analysis, specifically in the diagnosis of bipolar disorder ($P = 0.03$) and family history of suicide attempts

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($P = 0.02$). Other clinical and demographic variables are shown in Table 1.

At 6 months of follow up, 26 (21%) subjects reported a new suicide attempt. Reattempters differ from non-reattempters with respect to age (33.0, 95% CI: 28.5 to 37.5 vs 38.5, 95% CI: 35.8 to 42.3, $P = 0.05$), history of previous suicide attempts (84.6% vs 62.5%, $P = 0.04$), and age of first suicide attempt (23.4, 95% CI: 19.0 to 27.8 vs 29.8, 95% CI: 26.8 to 32.9, $P = 0.05$). Furthermore, the frequency of L-allele was higher in reattempters when compared with non-reattempters (55.8% vs 35.4%, $P = 0.01$). L-carriers' genotypes were different in reattempters when compared with non-reattempters (76.9% vs. 54.2%, $P = 0.04$). Of the different psychopathological traits evaluated, only impulsivity was higher in subjects with suicide reattempts and trended towards statistical significance (69.3, 95% CI: 66.4 to 72.2 vs 73.6, 95% CI: 67.4 to 79.84, $P = 0.19$). There were no significant differences in other clinical or demographic variables between both groups as shown in Table 2.

Unadjusted and adjusted ORs for the association of suicide reattempt with genetic status are presented in Table 3. In unadjusted models, the OR for suicide reattempt was almost 3 times higher in L-carrier (those with L allele in their genotype: LL or LS) when compared to SS genotype (OR = 2.8, 95% CI: 1.0–7.6). A multivariable logistic regression modeling was then performed to evaluate the role of impulsivity on the relation between genetic status and suicide reattempt. After adjusting for impulsivity, age, and sex, the OR for LL genotype was not significantly different (OR = 3.3; 95% CI: 1.1–9.8). Moreover, the interaction term between L-carrier and impulsivity was not significant ($p = 0.18$).

4. Discussion

The present findings indicate that the L-carrier genotypes of the 5-HTTLPR polymorphism predict short-term suicide reattempt in high-risk suicidal patients. This relation was not mediated or moderated by impulsivity. In addition, subjects who reattempted suicide at 6 months of follow-up were more likely to be younger, have a history of previous SA, and experienced their first SA at younger age.

Epidemiological studies suggest that suicide and SB is, at least partially, genetically determined with a pattern of transmission independent of the genetic transmission of psychiatric disorders [41]. Although the pathological mechanisms that lead to SB have not yet been elucidated, one of the most consistent findings is the observation of a reduced serotonergic function [13,42]. Abnormalities in serotonergic function have been observed in post-mortem autoradiography studies showing a decrease in 5-HTT binding and an increases in 5-HT_{1A} receptor binding together with a reduction in the 5-HIAA metabolite, suggesting reduction in serotonergic function, specifically in the anterior cingulate and ventral prefrontal cortex (PFC) regions involved in behavioral inhibition and decision making [14]. This observation has been supported by recently published in vivo studies using positron emission tomographic (PET) imaging, showing that individuals with MDD who attempt suicide have lower midbrain serotonin transporter binding compared with those who do not attempt suicide and that higher 5HT1 A binding in raphe nuclei is associated with higher lethality of SB [43]. Moreover, longitudinal prospective studies using PET shown that greater 5-HT_{1A} binding predict higher SI and more lethal suicidal behavior in a 2-year follow-up period [44]. Altogether, these findings confirm the initial observations associating reduced serotonergic function with SB. For this reason, many studies with candidate genes are focused on the associations among genes, the serotonergic system, and SB. Among those genes, the one encoding for the 5-HTT has captured the most attention since it regulates the duration and the magnitude of the serotonergic signal [45]. The

Table 1
General characteristics of the suicidal patients at index admission.

	(1) All patients included in the study	(2) Patients that complete the follow-up	(3) Patients lost during the follow-up	*P*-Value (test) *(2)* vs. (3)
No. of participants	136	122	14	
Age (yrs.), mean (CI 95%)	37.1 (34.8 - 39.3)	37.3 (35.0 - 39.8)	34.6 (27.1 - 42.1)	0.46
Women (%)	90 (66.2%)	81 (66.4%)	9 (64.3%)	1.00
Diagnosis (%)				
Major depression	85 (64.4%)	79 (66.4%)	6 (46.1%)	0.22
Bipolar Disorder	20 (15.1%)	15 (12.6%)	5 (38.5%)	**0.03**
Schizophrenia	25 (18.9%)	23 (19.3%)	2 (15.4%)	1.00
Other	2 (1.5%)	2 (1.7%)	0 (0.0%)	1.00
Co-occurring disorders (%)				
Borderline personality	62 (46.3%)	56 (46.7%)	6 (42.8%)	1.00
Substance abuse	28 (21.2%)	23 (19.2%)	5 (41.7%)	0.13
Family history (%)				
Any psychiatric illness	107 (78.7%)	96 (78.7%)	11 (78.6%)	1.00
Suicide or suicide attempt	61 (44.8%)	59 (48.4%)	2 (14.3%)	**0.02**
Suicide history				
Attempted previously (%)	90 (66.2%)	82 (67.2%)	8 (57.1%)	0.55
Age at first attempt (yrs.), mean (CI 95%)	28.2 (25.8-30.6)	28.4 (25.8-31.0)	26.2 (19.9-32.4)	0.59
Rating scale scores, mean (CI 95%)				
Impulsivity (BIS)	70.4 (68.0-72.8)	70.2 (67.6-72.8)	72.6 (66.5-78.8)	0.53
Hopelessness (BHS)	10.0 (9.2-10.8)	9.9 (9.1-10.7)	10.4 (6.9-13.9)	0.82
Hostility (BDHI)	42.9 (41.1-44.6)	42.6 (40.8-44.5)	44.7(39.0-50.4)	0.48
Recent stressors (SLE)	311.3 (283.9-338.7)	306.1 (277.4-334.8)	355.4 (256.2-454.6)	0.28
History of Sexual abuse	64 (47.4%)	56 (46.3%)	8 (57.1%)	0.57
Allele *Status*				
S-Allele	163 (59.9%)	147 (60.2%)	16 (57.1%)	0.84
L-Allele	109 (40.1%)	97 (39.8%)	12 (42.8%)	
Genotype				
SS genotype	57 (41.9%)	50 (41.0%)	7 (50.0%)	0.16
SL genotype	49 (36.0%)	47 (38.5%)	2 (14.3%)	
LL genotype	30 (22.0%)	25 (20.5%)	5 (35.7%)	

Rating scales: BIS = Barratt Impulsiveness Scale; BHS = Beck Hopelessness Scale; BDHI = Buss-Durkee Hostility Inventory; SLE = Stressful Life Events Scale.

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Table 2
Estimated prevalence and 95% confidence intervals among reattempters and non-reattempters during the 6 month follow-up period.

Variables	Non-reattempters	Reattempters	*P*-Value
No. of study participants	96	26	
Age ('yrs.'), mean (CI 95%)	38.5 (35.8-42.3)	33.0 (28.5-37.5)	**0.05**
Sex (%)			
Women	63 (65.6%)	18 (69.2%)	0.82
Men	33 (34.4%)	8 (30.8%)	
Diagnosis (%)			
Major depression	62 (66.7%)	17 (65.4%)	1.00
Bipolar Disorder	13 (14.0%)	2 (7.7%)	0.52
Schizophrenia	16 (17.2%)	7 (26.9%) 0	0.27
Other	2 (2.1%)	(0.0%)	1.00
Co-occurring disorders (%)			
Borderline personality	44 (45.8%)	12 (50.0%)	0.82
Substance abuse	19 (20.0%)	4 (16.0%)	0.78
Family history (%)			
Any psychiatric illness	76 (79.2%)	20 (76.9%)	0.79
Suicide or suicide attempt	48 (50.0%)	11 (42.3%)	0.51
Suicide history			
Attempted previously (%)	60 (62.5%)	22 (84.6%)	**0.04**
Age at first attempt (yrs) mean (CI 95%)	29.8 (26.7-32.9)	23.4 (19.0-27.8)	**0.05**
Rating scale scores mean (CI 95%)			
Impulsivity (BIS)	69.3 (66.4-72.2)	73.6 (67.4-79.8)	0.19
Attentional	19.4 (18.5-20.4)	20.9 (18.8-23.0)	0.19
Motor	23.7 (22.4-25.0)	25.8 (23.0-28.74)	0.14
Nonplanning	26.2 (24.8-27.6)	26.8 (23.9-29.8)	0.67
Hopelessness (BHS)	9.8 (9.0-10.7)	10.2 (7.9-12.5)	0.73
Hostility (BDHI)	42.0 (40.0-44.1)	44.8 (40.3-49.2)	0.25
Recent stressors (SLE)	298.9 (268.7-329.1)	333.7 (277.4-334.8)	0.33
History of Sexual abuse	44 (46.3%)	12 (46.1%)	1.00
Allele *Status*			
S-Allele	124 (64.6%)	23 (44.2%)	**0.01**
L-Allele	68 (35.4%)	29 (55.8%)	
Genotype			
SS genotype	44 (45.8%)	6 (23.1%)	**0.05**
SL genotype	36 (37.5%)	11 (42.3%)	
LL genotype	16 (16.7%)	9 (34.6%)	
SS genotype	44 (45.8%)	6 (23.1%)	**0.04**
L-carrier	52 (54.2%)	20 (76.9%)	

Rating scales: BIS = Barratt Impulsiveness Scale; BHS = Beck Hopelessness Scale; BDHI = Buss-Durkee Hostility Inventory; SLE = Stressful Life Events Scale.

gene that codes for the 5-HTT has a common functional promoter polymorphism (5-HTTLPR, rs4795541), which consists of a short (S) and a long (L) allele.

A cross-sectional design has been used in most studies aimed at exploring candidate genes to detect associations between 5-HTTLPR polymorphism and suicide or SA among patients with different psychiatric diagnoses or comorbidities or between patients and healthy controls [16]. Initial studies report an association between the L-allele of the 5-HTTLPR polymorphism and depressed patients who die by suicide when compared with control subjects [46]. However, subsequent studies failed to replicate these findings. For example, some studies found an association between the S-allele or S-carrier genotypes and SB [47–54], while other studies indicate no association at all [47,55–58]. A possible explanation for the discrepancies among association studies could be that a single gene polymorphism may not explain complex multi-determined behaviors such as SB. Certain gene expressions could be modified through epigenetic mechanisms such as DNA methylation or histone marks that modify expression levels and alter the response to stressors. Regulation of SLC6A4 gene expression may contribute to the inter-individual susceptibility or resilience [59]. Recent findings suggest a role of SLC6A4 AluJb methylation in MDD, amygdala reactivity, and stress reaction [60]; however, whether this mechanism is important in SB remains to be clarified. Future studies should not only address the presence or absence of one genetic polymorphism but also the possibility of epigenetic modifications.

The contradictory findings from candidate gene studies generated uncertainty about the usefulness of this polymorphism as a genetic marker of suicide or some type of specific SB (violent or lethal SB) because while 5-HTTLPR polymorphisms are some of the most studied, the underlying mechanism contributing to the variability in this relation is still unknown. However, some hypotheses have been proposed. In vitro studies with membrane preparations of lymphoblast suggested that the LL-genotype is associated with an increase in SLC6A4 transcription, resulting in increased transporter levels and more rapid serotonin uptake [45,61]. Taken together, it could be hypothesized that subjects with the L-allele or the LL-genotype have a reduction in extracellular serotonin and therefore, lower serotonin levels, which have been linked to SB as proposed by Du et al. 1999 [46]. A similar assumption has been used by those who found S-carriers to be associated with SB. In this case, the S-allele was associated with a decreased re-uptake of serotonin in individuals with SB [50]. Nonetheless, in vivo studies did not find the same

Table 3
Unadjusted and adjusted odds ratios (ORs) and % confidence intervals (95% CIs) for the association of risk factors for reattempters.

Risk factors	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[1]
Genetic Status (L-carrier)	*2.8 (1.0 – 7.6)*	*3.3 (1.1 – 9.8)*
Impulsivity (BIS score / 10)	*1.2 (0.9 - 1.8)*	*1.2 (0.8 – 1.8)*
Female	*1.2 (0.5 - 3.0)*	*1.1 (0.4 – 3.1)*
Age (decades)	*0.7 (0.5 - 1.0)*	*0.8 (0.5 – 1.1)*

[1] Adjusted for all significant variables. L-carrier represents those patients with LL or LS genotypes. BIS = Barratt Impulsiveness Scale.

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impact of genetic polymorphism on serotonin neurotransmission as compared to in vitro studies [21]. Therefore, the "static hypothesis" on how 5-HTTLPR polymorphisms could be linked to SB by affecting serotonin bioavailability may not be useful. Another hypothesis that may explain a possible mechanism by which different genotypes may affect SB derives from the influence of the 5-HTTLPR allele status on brain development and neurogenesis. Evidence demonstrates that serotonergic neurons are among the first neurons generated and that serotonin plays an important role in brain development [62]. The importance of serotonin in neurogenesis has also been demonstrated [63], and this effect is potentially mediated through the interaction of the serotonergic system with BDNF. It has been demonstrated that during brain development, serotonin influences cortical development [64] and has neurotrophic effects on the hippocampus and frontal cortex [65]. The main finding of this study is that independent of age and sex, patients with L-allele in their genotype (L-carrier) are almost three times more at risk of a new suicide attempt after 6 months following hospitalization for SI or SA. Furthermore, we observed that participants who reattempt suicide during follow-up have a history of previous SA and start their SB at a younger age. Altogether, these observations are better explained by a "developmental hypothesis" in which sustained changes in the morphology and connections of certain brain regions could explain SB rather than a "statistic hypothesis" that explains circumstantial availability of serotonin. Alterations in gray matter brain volume [66] and connectivity [67] in the CNS have been associated with the L-allele of 5-HTTLPR polymorphism.

To our knowledge, the predictive value of 5-HTTLPR polymorphisms has only been studied in one genetic follow-up study with a cohort of high-risk subjects [22]. In that study, the S-carriers were characterized by a higher risk of repeated SB [22]. Taking into account prior published studies, it was hypothesized that the S-carriers status would predict short-term suicide reattempt. However, based on the results of this study, our initial research hypothesis was rejected. In our cohort, S-carrier status did not predict relapse but L-allele and L-carrier status did. This is consistent with the finding that at baseline multiple suicide attempters showed a higher frequency of L-allele when compared with participants with SI or single suicide attempt. A possible explanation for this discrepancy is that in the study of Courtet et al, only 76 patients (85% women) were included, and only 2 patients with the LL-genotype reattempted suicide. In this study, the total population included 60% more participants, and almost one-third identified as male.

5-HTTLPR polymorphisms have also been associated with endophenotypes, or categories of SB such as impulsive suicides [52]. In this study, we compared different characteristics of the SB of participants included in the sample population. Among all of these characteristics, impulsivity was the only one that exhibited a trend to be related to suicide reattempt; therefore, a logistic regression model was built to determine its role as mediator or moderator. Impulsivity, measured with the BIS-11, was neither a mediator nor a moderator of the relation between L-carrier genotypes and suicide reattempt.

Suicide behavior is determined by a combination of genetic and environmental interactions. In the last years, the 5-HTTLPR polymorphism was also found to increase the risk of developing SB following exposure to environmental factors such as child abuse [68] and stressful life events [69]. Therefore, in the present study, we explored if child sexual abuse or stressful life events in the year prior to hospitalization differed between those with or without reattempts at 6 month. Our results showed no differences between the groups.

The strength of this study relied on its prospective longitudinal design that allows exploring predictors of a SA. Furthermore, this study included several key factors that were measured using validated instruments, which might explain the relationship between the 5-HTTLPR polymorphism and SB. Despite these strengths, some limitations should be considered when interpreting the results because this study was limited to a unique patient sample hospitalized for severe SI or SA, which limits generalization of the results. Furthermore, we employed a biallelic approach; however, it is worth noting that there are additional polymorphic variants in the 5-HTTLPR. Recently, a single nucleotide polymorphism rs25531 (A → G) has been described for the L-allele, giving rise to variants of this allele denoted LA and LG [70]. The LG variant results in a reduction of the transcriptional efficiency of SLC6A4 in a similar manner to the S-allele. This could lead to a misclassification' however, the LG variant is absent or near absent in Caucasians and Hispanics population [71]. Moreover, an additional limitation was the limited assessment of early life stress; information was only gathered regarding childhood sexual abuse, and patients may have suffered another type of stressors.

In conclusion, patients hospitalized for SB includes those with a high risk of short-term relapse, and they are characterized by younger age, a history of previous SA, younger age at their first SA, and a higher frequency of the L-allele in the 5-HTTLPR. Therefore, this polymorphism can potentially be used as a predictive biomarker of this population.

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Disclosures

No author or immediate family member has financial relationships with commercial entities that might appear to represent a potential for conflicts of interest. All authors have approved the final article.

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