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# The influence of the serotonin transporter gene 5-HTTLPR polymorphism on suicidal behaviors: a meta-analysis

Giuseppe Fanelli, Alessandro Serretti*

*Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy*

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ABSTRACT

Suicidal Behavior (SB) is the second leading cause of death among youths worldwide and the tenth among all age groups. Inherited genetic differences have a role in suicidality with heritability ranging from 30 to 55%. The *SLC6A4 5-HTTLPR* gene variant has been largely investigated for association with SB, with controversial results.

In this work, we sought to determine whether the results of previous meta-analyses were confirmed or modified subsequent to the inclusion of more recent literature data.

An electronic literature search was performed to identify relevant studies published until July 2018. Data were analysed through RevMan v5.3. Subgroup and sensitivity meta-analyses were performed considering different SB sub-phenotypes, ethnicity, gender and psychiatric diagnostic categories.

Our literature search yielded 1186 articles; among these, we identified 45 pertinent case-control studies (15,341 subjects). No association was found between low-expressing alleles or genotypes (S + $L_G$ alleles or S′ carrier genotypes) and SB in the primary analyses. However, low-expressing alleles (S + $L_G$) were associated with an increased risk of Violent Suicide Attempt (OR = 1.44, C.I. 1.17–1.78, $p$ = .0007). An effect of the same alleles on SB was found in a subpopulation of substance abusers, but this result was not confirmed after the exclusion of healthy subjects from the control group. The other sensitivity meta-analyses did not show any significant effect.

Our findings contribute to clarify the conflicting previous evidence by suggesting an association between the 5-*HTTLPR* and Violent SB. Nonetheless, many other modulators, including environmental factors and epigenetic mechanisms may act to further increase the level of complexity.

## 1. Introduction

According to World Health Organization (WHO, 2014) Suicidal Behavior (SB) may be defined as "a range of behaviors that include thinking about suicide (or ideation), planning for suicide, attempting suicide and suicide itself". Every year, about 800,000 people die by suicide worldwide (WHO, 2018) with an estimated age-adjusted rate of 13.4 per 100,000 population (21.3 for males and 6 for females) (CDC, 2016) and many more people attempt suicide. Therefore, suicide may be considered a serious public health issue, as it is the second leading cause of death among people aged 10 to 34 and the tenth among all age groups (CDC, 2016; WHO, 2018). SB does not exclusively concern the most developed nations, as more than 78% of suicides occur in low and middle-income countries (WHO, 2018) with a substantial variation across ethnicities.

Inherited genetic differences have a relevant role in suicidality, as shown by family, adoption and twin studies (Brent and Melhem, 2008; Tidemalm et al., 2011), with heritability ranging from 30 to 55% (Voracek and Loibl, 2007). In fact, in a large case-control study, Mittendorfer-Rutz et al. (2008) pointed out an increased risk of suicide attempts (in a range from 2.7 to 9.8 times) in the presence of family members with a previous history of SB. Furthermore, a meta-analysis showed that monozygotic twins' concordance for the completed suicide is notably higher than in dizygotic twin pairs (respectively, 24.1% and 2.8%) (Voracek and Loibl, 2007). These data suggest that the likelihood of occurrence of SB is significatively greater in those who share a similar genetic background than in the general population. It should be noted that, although a genetic effect may explain the higher concordance among monozygotic twin pairs, a concordance approaching 100% would be expected if suicide was only due to a genetic aetiology. It means that the environmental component also plays at least an equal role in the onset of SB. Indeed, distal (predisposing) factors seem to interact with proximal (precipitating) factors in determining the suicidal event; in this way, genetic predisposition as well as early-life

* Corresponding author at: Department of Biomedical and Neuromotor Sciences, University of Bologna, Viale Carlo Pepoli 5, 40123 Bologna, Italy.
*E-mail address:* alessandro.serretti@unibo.it (A. Serretti).

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adversities and associated epigenetic modifications, which together modulate behavior and personality traits, provide the basis for the intervention of proximal triggers, such as recent life events and acute major psychiatric disorders episodes (Mann, 2003; Turecki, 2014). Noteworthy, roughly 90% of suicide completers may be diagnosed with a mental disorder prior to their death (Arsenault-Lapierre et al., 2004); however, it is worth considering that the family clustering of suicide, although partially coincident, is independent of that of psychopathology (Brent et al., 1996; Kim et al., 2005; McGirr et al., 2009).

In the last decades, many efforts have been made in order to disentangle the genetics and the neurobiological basis underpinning SB. Particular attention has been paid to the serotonergic system (Antypa et al., 2013). Earlier studies demonstrated a lower concentration of the serotonin metabolite 5-hydrxyindolacetic acid (5-HIAA) in the cerebrospinal fluid of depressed patients prone to develop SB (Asberg et al., 1976) as well as lower levels of serotonin (5-HT) and 5-HIAA in the brainstem of suicide victims (Mann et al., 1989). Moreover, a pharmacologic challenge with Fenfluramine, a serotonin agonist which provokes an increase of the serotonin in brain synapses (DrugBank, http://www.drugbank.ca/drugs/DB00574), has shown blunted patterns of prefrontal cortex (PFC) activation in SB (Desmyter et al., 2011), suggesting an impaired function of the serotonin neurotransmission.

Among the serotonin system candidate genes for SB, many genetic association studies have focused on the *SLC6A4* (Solute Carrier Family 6, Member 4) gene (Antypa et al., 2013; Gonda et al., 2011), located on chromosome 17 (17q11.2). This gene encodes for the serotonin transporter, a transmembrane presynaptic protein involved in the reuptake of the released serotonin from the synaptic cleft (Daws and Toney, 2007; Rudnick and Clark, 1993). In humans, the transcriptional activity of *SLC6A4* gene is modulated by a 44 base-pair insertion/deletion polymorphism, commonly known as *5-HTTLPR* (Serotonin Transporter Linked Polymorphic Region polymorphism - rs4795541), located upstream of the transcription start site. Most frequently, it is composed by the repetition of 14 (for the S - short - allele) or 16 (for the L - long - allele) repeated elements (Murphy et al., 2004). The S allele causes reduced expression of the *SLC6A4*, in a dominant way compared to the L allele, which is characterised, conversely, by higher levels of expression (Heils et al., 1996; Lesch et al., 1996). Nevertheless, the effect of rs25531 SNP (A- > G substitution), located within the L allele of the *5-HTTLPR* (Nakamura et al., 2000), may result in a similar transcription activity of the $L_G$ and S allele (Hu et al., 2006; Wendland et al., 2006). Thus, the $L_A$ and $L_G$ allele, together with the S allele, may be considered as the components of a triallelic *SLC6A4* locus. Post-mortem and in-vivo studies have also investigated the role of the *5-HTTLPR* on SB. Of note, it has been shown that depressed suicide victims had a smaller amount of serotonin transporters in the PFC, hypothalamus and brainstem (Purselle and Nemeroff, 2003). Moreover, a SPECT study pointed out a lower serotonin transporter availability in the frontal cortex of male suicide attempters carrying the S allele when compared to healthy controls (Bah et al., 2008). Most importantly, a number of studies have indicated an increased risk of SB among people carrying the S allele and reporting a previous history of stressful life events or early life adversities (Mandelli and Serretti, 2013); this is consistent to the existence of a reasonable gene-environment interaction effect.

Controversial results have been obtained from numerous case-control association studies, which have so far examined the influence of the 5-*HTTLPR* on SB. As a consequence, a number of meta-analytic studies have attempted to summarize previous single study data in order to elucidate the role of the *5-HTTLPR* polymorphism on SB. At first (Anguelova et al., 2003), a significant association for the S allele with SB was reported ($p = .009$); the association was particularly valid among attempters (SAs), though only three studies for suicide completers (SCs) were available at that time. A subsequent meta-analysis (Lin and Tsai, 2004), confuted the prior results and pointed out the lack of association between the 5-*HTTLPR* polymorphism and SB ($p = .379$); nevertheless, they found a significant association between the genotypes carrying the S allele and violent suicide, when cases were compared to healthy controls. A few years later, with an increased sample size, Li and He (2007) described a robust positive association ($p = .007$) of the 5-*HTTLPR* with SB, both for pooled and sub-grouped samples; the association was independent of the psychiatric diagnoses, as suggested by the stronger association obtained comparing SAs and non-attempter patients rather than with healthy controls. Noteworthy, Clayden and colleagues' meta-analysis (Clayden et al., 2012) showed a significant association between attempted suicide and the S allele, but not with the overall SB, suggesting that it would be better to consider SB as distinct phenotypes. A very small statistically significant effect of the 5-*HTTLPR* L/S on SB was achieved in Schild and coworkers' meta-analysis (Schild et al., 2013) only when cases were compared to healthy controls. Lastly, de Medeiros Alves et al. (2015), in another meta-analysis, confirmed an association between the 5-*HTTLPR* and SB, showing an increased risk of SB for the L allele among patients affected by psychiatric disorders.

Given the abovementioned discrepancies, we re-evaluated the possible modulatory effect of the 5-*HTTLPR* on SB with the inclusion of more recent literature data. Furthermore, we tested whether the effect of the 5-*HTTLPR* polymorphism may vary depending on gender, ethnicity, a shared psychiatric diagnosis or by using more specific suicidal phenotypes as an outcome. The clarification of the role of genetic variability in SB may be of particular importance in order to help clinicians to better stratify subjects based on their suicidal genetic risk as well as to develop better prevention and therapeutic strategies.

## 2. Methods

### 2.1. Search strategy

An electronic search of the literature was performed to identify association studies investigating the link between the 5-*HTTLPR* and SB. Medline/PubMed, Web of Science, Scopus and PsycINFO databases were searched for papers published until July 2018. We used search terms related to the serotonin transporter gene and its polymorphism, such as “5-HTTLPR” or “HTTLPR” or “SLC6A4” or “SERT gene” or “5-HTT gene” or “5HTT gene”, and terms referring to the outcomes, such as “suicide” or “suicidal” or “suicidal behavior” or “suicide attempt” or “suicide attempters” or “suicide completers” or “suicide completer” or “completed suicide” or “attempted suicide”, excluding reviews as publication type and including only papers written in English language. The reference lists of the selected articles were inspected to retrieve additional papers not indexed by the scientific literature databases.

### 2.2. Study selection and data extraction

The two reviewers independently screened searches to identify potentially relevant studies. The full text of the selected studies was obtained and evaluated to detect pertinent studies. Studies were included if: 1) they were genetic association studies evaluating the relationship between the 5-*HTTLPR* polymorphism and SB; 2) the study did not overlap with others taking into account a larger sample; 3) they were written in English. For each selected study, the following information was extracted: first author, publication year, location/ethnicity, sample size, characteristics of the control sample (presence of healthy or non-healthy subjects), 5-*HTTLPR* genotypic or allelic frequencies, triallelic or biallelic genotyping approach, gender ratio, psychiatric diagnosis and comorbidities, suicide phenotypes tested. Nevertheless, data were not available for some studies. When genotypic or allelic frequencies were partial or entirely not available in the research paper or the supplementary information, we extracted data from the presented graphs by g3data software (https://github.com/pn2200/g3data) or we requested data from the corresponding author.