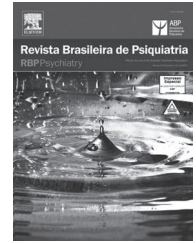




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### ORIGINAL ARTICLE

## No association between the HTR1A gene and suicidal behavior: a meta-analysis

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#### DESCRIPTORS

Suicide;  
Serotonin;  
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Meta-Analysis.

#### Abstract

**Objective:** Dysfunction of serotonin 1A receptors (HTR1A) may play a role in the genesis of suicidal behavior. We studied the association between a functional polymorphism in the HTR1A gene and suicidal behavior. **Method:** We performed a meta-analysis of published genetic association studies by searching through Medline, PubMed, and Web of Science databases to analyze a possible correlation between the rs6295 polymorphism and suicidal behavior in different populations. **Results:** Four studies comprising a total of nine hundred and fifty seven patients with suicidal behavior and nine hundred and fifty seven controls were the eligible. The G allele of the rs6295 polymorphism may not be associated with suicidal behavior (Random-effects model: OR = 1.08; 95% CI: 0.80-1.45;  $p(Z) = 0.80$ ) in presence of heterogeneity ( $Q = 17.84$ ,  $df = 4$ ,  $p = 0.0013$ ). In a second analysis that presented no heterogeneity, a negative association was also observed (OR = 0.94; 95%CI: 0.79-1.13;  $p(Z) = 0.99$ ). **Conclusion:** To our knowledge, the present study is the first meta-analysis searching for a correlation between rs6295 of HTR1A and suicidal behavior. Our results showed no association between HTR1A and suicidal behavior. However, more studies assessing different populations, as well as larger samples, are needed.

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**DESCRITORES:**

Suicídio;  
 Serotonina;  
 Receptor 1A de  
 Serotonina;  
 Metanálise.

**A não associação entre o gene HTR1A e comportamento suicida: uma metanálise****Resumo**

**Objetivo:** É possível que uma disfunção nos receptores 1A de serotonina (HTR1A) desempenhe um papel na origem do comportamento suicida. Estudamos a associação entre um polimorfismo funcional no gene HTR1A e comportamento suicida. **Método:** Realizamos uma metanálise de estudos de associação genética já publicados através de uma busca nos bancos de dados do Medline, PubMed e Web of Science para identificar uma possível correlação entre o polimorfismo rs6295 e comportamento suicida em diferentes populações. **Resultados:** Foram selecionados quatro estudos com um total de 957 pacientes com comportamento suicida e 957 controles. O alelo G do polimorfismo rs6295 não pôde ser associado a comportamento suicida (modelo de efeitos aleatórios: OR = 1,08; 95%CI: 0,80-1,45; p(Z) = 0,80) na presença de heterogeneidade (Q = 17,84, df = 4, p = 0,0013). Em uma segunda análise, sem heterogeneidade, também foi observada uma associação negativa (OR = 0,94; 95%CI: 0,79-1,13; p(Z) = 0,99). **Conclusão:** Pelo que nos consta, trata-se da primeira metanálise cujo objetivo é identificar uma correlação entre o polimorfismo rs6295 do HTR1A e comportamento suicida. Os nossos resultados não demonstraram existir uma correlação entre o HTR1A e comportamento suicida. No entanto, são necessários estudos adicionais que incluam outras populações, assim como amostras maiores.

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**Introduction**

Suicidal behavior is a major health problem worldwide. Several lines of evidence suggest that suicide has a genetic component.<sup>1</sup> Attempted and completed suicides are familiar behaviors with an inheritability of about 40-50%.<sup>2-4</sup> To date, many studies have suggested that at least three neurobiological systems are involved in the pathogenesis of suicidal behavior: serotonergic system (5-HT) deficiency,<sup>5</sup> hypothalamic-pituitary-adrenal axis hyperactivity,<sup>6</sup> and an excess release of norepinephrine followed by a deficiency of this neurotransmitter.<sup>7</sup> There is strong neurobiological evidence showing that serotonergic dysfunction is implicated in suicidal behavior.

Brain 5-HT<sub>1A</sub> receptors can be found both pre- and post-synaptically. Somatodendritic 5-HT<sub>1A</sub> autoreceptors are located on serotonergic neurons in the dorsal and medial raphe nuclei providing a negative feedback mechanism in serotonergic systems.<sup>8</sup> These autoreceptors control the firing rate of the serotonergic neurons resulting in the regulation of serotonin synthesis and release.<sup>9,10</sup>

The 5-HTR1A gene is located on the long arm of chromosome 5 (5q11.2-13).<sup>11</sup> A functional C(-1019)G variant has been reported.<sup>12,13</sup> This polymorphism (rs6295) is a common SNP in the promoter region of the gene, within a 26 bp palindromic region, which binds the nuclear DEAF-1-related (NUDR) proteins and Hess5. The G allele abolishes repression by NUDR to produce higher expression of 5-HTR1A, which in turn enhances the negative feedback inhibition exerted by 5-HTR1A autoreceptors on serotonergic raphe neurons, thus leading to a decrease in serotonergic neurotransmission.<sup>14</sup>

This rs6295 polymorphism of the 5-HTR1A promoter has been associated with a number of disorders including anxiety,<sup>15,16</sup> major depression,<sup>16,17</sup> aggression, and impulsivity.<sup>18</sup> It has also been associated with suicidal behavior (attempted

or completed suicide). Its possible involvement in suicide has been suggested by the abnormal HT<sub>1A</sub> receptor signaling in brains of suicide victims or attempters.<sup>19,20</sup> Several studies have investigated the association between this functional polymorphism and suicidal behavior with contradicting results. Therefore, a meta-analysis of all published data was performed to investigate the true association between this polymorphism and suicidal behavior.

**Method***Identification and selection of publications*

A literature search was performed from April to June 2010. Relevant publications were identified using the following search terms in Medline, PubMed and Web of Science databases: "HTR1A and suicidal behavior", "HTR1A and suicide", "rs6295 and suicidal behavior", "rs6295 and suicide", and "HTR1A C-1019G and suicide". These words were combined to retrieve the summaries. The search also implicated the review of the bibliography cited at the end of various research articles. To be selected, the publications had to meet the following criteria: (1) be published in peer-reviewed journals, (2) contain independent data, (3) be case-control association studies in which the frequencies of three genotypes were clearly stated or could be calculated, and (4) use of healthy individuals as controls.

*Data extraction*

The following data were obtained for each of the studies: authors, year of publication, region, number of cases and controls, age, and ethnical origin.

The meta-analysis outcomes were built taking into consideration the following categories: (1) exposed sick, (2) exposed not-sick, (3) not-exposed sick, and (4) not-exposed

not-sick. The “sick” term refers to subjects exhibiting suicidal behavior and the “exposed” term refers to the risk allele.

### Data analysis

For the meta-analysis procedures, we used the EPIDAT 3.1 program (<http://dxsp.sergas.es>). This software is freely available for epidemiologic analysis of tabulated data. Data was analyzed with the random-effects model following the reports in literature.<sup>21,22</sup> Sample heterogeneity was analyzed with the Dersimonian and Laird’s Q test. The Q test result was complemented with graphs to help visualize those studies that favor heterogeneity. The meta-analysis results are expressed as an odds ratio (OR). To address the problem of publication bias, funnel plots were calculated by the EPIDAT 3.1 software. This plotting standardized the effect of each of the published studies on the vertical axis and its correspondent precision on the horizontal axis. Finally, a chi-squared ( $\chi^2$ ) analysis was used to calculate the Hardy-Weinberg equilibrium to evaluate genotype distribution.

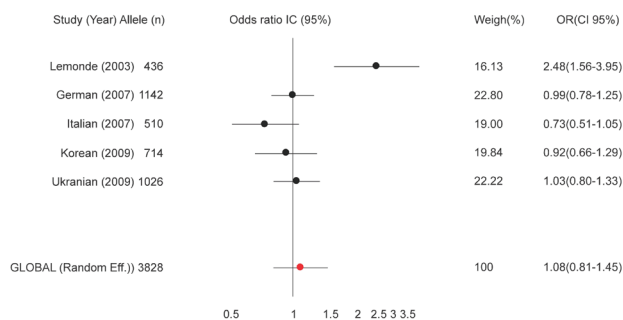
### Results

Regarding literature search, a total of 13 papers were identified, but only 4 were included in this meta-analysis.<sup>14,23-25</sup> The other nine studies were excluded for not complying with the inclusion criteria.<sup>8,26-33</sup> One of the selected studies consisted of two populations that were analyzed separately.<sup>25</sup>

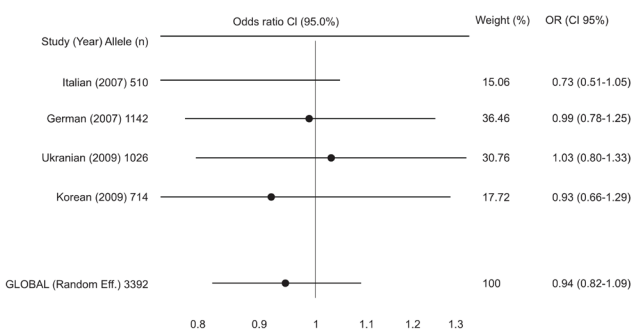
The selected studies comprised a total of nine hundred and fifty seven patients and nine hundred and fifty seven controls. All genotyped populations, both patients and controls, were in Hardy-Weinberg equilibrium ( $p > 0.05$ ), excluding the patients described by Lemonde et al.<sup>14</sup> ( $\chi^2 = 0.18$ ;  $p < 0.019$ ).

When the genotypes of all populations were combined, they still remained in equilibrium ( $\chi^2 = 0.92$ ; OR = 1.06;  $p = 0.33$  and  $\chi^2 = 0.92$ ; OR = 0.94;  $p = 0.33$  for patients and controls, respectively). Four populations were Caucasians and one Asian. The proportion of the least common genotype in Caucasians was GG (24%), whereas for the Asian population it was CC (6%).

The pooled OR derived from all studies indicated a non-significant association of the G allele of rs6295 with suicidal behavior (Random effects model: OR = 1.08; 95%CI: 0.80-1.45;  $p(Z) = 0.80$ ) – Figure 1. Heterogeneity was observed in all studies ( $Q = 17.84$ ;  $df = 4$ ;  $p = 0.0013$ ). Subsequently, we performed a second analysis, which only included studies inside the heterogeneity curve (Italian, German, Ukrainian, and Korean populations). However, we could not find an association (OR = 0.94; 95%CI: 0.82-1.09;  $p(Z) = 0.30$ ;  $Q = 2.54$ ;  $df = 3$ ;  $p = 0.46$ ) – Figure 2. In addition, when we included an explorative analysis of each of the Caucasian samples, no significant heterogeneity was found ( $Q = 2.51$ ;  $df = 2$ ;  $p = 0.28$ ). Also, we could not detect a significant association between G allele and suicidal behavior (OR = 0.94; 95%CI: 0.79-1.13;  $p(Z) = 0.99$ ). Finally, in an analysis of the studies containing only suicide victims (Ukrainian, Koran, and French-Canadian population), the results were also negative (OR = 1.29; 95%CI 0.78-2.13;  $p(Z) = 0.40$ ) in presence of heterogeneity ( $Q = 13.02$ ;  $df = 2$ ;  $p = 0.0015$ ).



**Figure 1** Odds ratios for the G allele of the rs6295 polymorphism in the HTR1A gene of individuals with suicidal behavioral.



**Figure 2** Random-effects model, 95% CI, and OR of each of the studies with no heterogeneity and of the meta-analysis comprising the studies of G allele of the rs6295 polymorphism in the HTR1A gene and suicidal behavior.

### Discussion

In the present study, we could not find an association between the rs6295 of the HTR1A gene and suicidal behavior. To our knowledge, this is the first meta-analysis considering HTR1A and suicidal behavior. A search for trends in PubMed showed only a few publications analyzing this gene and suicidal behavior. These reports involve populations of European descent and only one study considered an Asian population. Therefore, to analyze a possible correlation between HTR1A and suicidal behavior, studies including populations from Asia, Latin America, and Africa must also be taken into consideration.

Currently, serotonin is probably the most studied neurotransmitter involved in suicidal behavior. Experiments have shown that 5-HTR1A receptors are upregulated in prefrontal cortex; this could be a compensatory mechanism to the low activity of serotonergic neurons.<sup>33</sup> A functional polymorphism in the gene encoding for this receptor has been investigated. However, only few reports have analyzed the association of this regulatory region and suicidal behavior.

In association studies, contradicting results have been obtained, which makes it hard to speculate the true association between this polymorphism and suicidal behavior.

One must bear in mind that these association studies were conducted in various populations, different criteria were used for the phenotype definition, and sample sizes were relatively small. Although our meta-analysis consisted of a considerable sample, no association between the G allele of rs6295 and suicidal behavior could be obtained. Hence, we decided to test the probability association with completed suicide. As a result, we found that G allele of rs6295 was not associated with completed suicide. Though the OR value is 1.29, the CI contains values smaller than 1, which indicates no association. The sample sizes of the studies included in our meta-analysis are in the low range compared to genetics studies for other diseases. Therefore, future studies comprising larger samples of completed suicide are important to determine this association. We also consider that, given the small number of studies available, the association is not observable.

In a first approach we observed heterogeneity; however this variation was given by a sole study reporting a positive association. A second analysis, in which the study that gave rise to heterogeneity was discarded, also presented no association between rs6295 and suicidal behavior (Figure 2).

Our study presents some limitations, publication bias has to be considered, as negative studies are less likely to get published; moreover, there might be an overrepresentation of the results showing an association between the polymorphism and the investigated disorder.<sup>34</sup> Although, in the case of the polymorphism rs6295 and suicidal behavioral, most reports show negative associations, the present analysis includes positive and negative reports. Other limitations are inherent in many meta-analysis of association, including this one: their retrospective nature and the inclusion of study-level data.

In conclusion, our results suggest that the G allele of the rs6295 polymorphism in the 5HTR1A gene is not associated with suicidal behavioral. However, more comprehensive studies and larger samples are necessary to determine conclusively an association between 5HTR1A and suicidal behavior.

## Disclosures

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\* Modest

\*\* Significant

\*\*\* Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author. For more information, see Instructions for Authors.

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