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ORIGINAL PAPER

Association between the *HTR1A* rs6295 gene polymorphism and suicidal behavior: an updated meta-analysis

Yazmin Hernández-Díaz[1] · Carlos Alfonso Tovilla-Zárate[2] · Rosa Giannina Castillo-Avila[3] · Isela Esther Juárez-Rojop[3] · Alma Delia Genis-Mendoza[4] · María Lilia López-Narváez[5] · Guillermo Efrén Villar-Juárez[6] · Thelma Beatriz González-Castro[1]

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Abstract

Several association studies have indicated that the *HTR1A* gene is associated with suicidal behavior (SB). Thus, a systematic assessment of the association of *HTR1A* was performed based on a literature review and pooled analysis. Four electronic databases were comprehensively searched to find and pinpoint all case–control articles related to this study. When analyzing the genetic association with SB, data were divided into: (A) SB cases vs. healthy controls and (B) SB cases vs. psychiatric controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were assessed as measures of association. Heterogeneity among included studies was analyzed using sensitivity test and Q statistics. Publication bias was also explored by Egger and rank correlation test. Thirteen case–control studies were selected in this meta-analysis, involving 2817 SB patients, 2563 healthy controls and 545 psychiatric controls. In the overall comparison between SB cases and healthy controls, result showed that the rs6295 polymorphisms of *HTR1A* gene was associated with SB, but only when using the recessive model (OR = 2.21, 95% CI = 1.80–2.71, $P < 0.001$). In the smaller sample size comparison between SB and psychiatric controls, no significant association was detected with rs6295 in any of the five genetics models tested. The present meta-analysis suggests that rs6295 polymorphism of *HTR1A* gene could increase the risk for SB. Well-designed studies with more patients will be required to validate these results.

Keywords HTR1A · rs6295 · Polymorphism · Suicidal behavior · Meta-analysis

✉ Thelma Beatriz González-Castro
thelma.glez.castro@gmail.com

[1] División Académica Multidisciplinaria de Jalpa de Méndez, Universidad Juárez Autónoma de Tabasco, Carretera Estatal Libre Villahermosa-Comalcalco Km. 27+000 S/N Rancheria Ribera Alta, 86205 Jalpa de Méndez, Tabasco, Mexico

[2] División Académica Multidisciplinaria de Comalcalco, Universidad Juárez Autónoma de Tabasco, Comalcalco, Tabasco, Mexico

[3] División Académica de Ciencias de La Salud, Universidad Juárez Autónoma de Tabasco, Villahermosa, Tabasco, Mexico

[4] Laboratorio de Genómica de Enfermedades Psiquiátricas Y Neurodegenerativas, Instituto Nacional de Medicina Genómica, Ciudad de México, Mexico

[5] Hospital Chiapas Nos Une Dr. Gilberto Gómez Maza, Secretaría de Salud de Chiapas, Tuxtla Gutiérrez, Chiapas, Mexico

[6] Escuela de Ciencias de La Salud, Universidad Anahuac Querétaro, Querétaro, Mexico

Introduction

Suicidal behavior (SB) means any self-inflicted action that could cause the death of a person [20]. SB is complex in etiology due to several risk factors including the presence of co-occurring psychiatric disorders, social stresses and complex gene–environment interactions [25]. In this sense, SB has been associated with the serotonergic system.

Serotonin has been extensively studied in several psychiatric disorders, such as SB. Serotonin (5-HT) is a monoamine neurotransmitter that is synthesized from the hydroxylation of tryptophan. The 5-HT_{1A} receptors are responsible for mediating serotonin action. Moreover, 5-HT1A autoreceptor is a key component of serotonin circuity, which functions as the major somatodendritic autoreceptor on 5-HT neurons to inhibit the activity of the entire serotonergic system [18, 19].

The *HTR1A* gene encodes the 5-HT_{1A} receptor and is located on chromosome 5q11.2–13. *HTR1A* is an intronless gene approximately 2200 bp in size, including an

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approximately 1200-bp coding sequence known to code for 422 amino acid [24]. A number of single nucleotide polymorphisms (SNPs) have been identified for *HTR1A*. One of the most common SNPs of the *HTR1A* that is important and has been proposed as a candidate for psychiatric disorders is the SNP rs6295 (C-1019G). This SNP is located in the promoter region and is known to be a functional polymorphism that regulates *HTR1A* transcription and expression [3, 4]. Specifically, possessing the G-allele or having G/G homozygosity has been considered a risk genotype, as these variants have been found to be associated with schizophrenia, major depression, bipolar disorder and suicide [13, 24, 28]. Previous meta-analyses have reported negative associations between rs6295 polymorphism and SB [5, 10]. Subsequently, more number of association studies have been reported. Therefore, we performed an updated meta-analysis of available case–control studies to systematically evaluate the potential association between the rs6295 SNP of *HTR1A* gene and SB risk. However, to the best of our knowledge, no evidence from quantitative analysis has evaluated the association of *HTR1A* gene variation considering psychiatric controls with the risk of SB. Due to the above, we conducted a second meta-analysis to increase the precision of effect estimates, thereby clarifying the relationship between the rs6295 SNP and SB risk.

Materials and methods

Literature retrieval

Based on the guidelines for the Preferred Reporting Item of Systematic Review and Meta-Analysis (PRISMA), a comprehensive literature search was conducted in English databases, including PubMed, Scopus, EBSCO and Science Direct (the latest literature was updated to November 30, 2021).

The search process in the above-mentioned databases was conducted using the keywords: ("serotonin receptor 1A gene" OR "HTR1A gene" OR "HTR1A polymorphism" OR "-1019C/G HTR1A" OR "rs6295 HTR1A") AND ("SB" OR "suicide" OR "suicide attempt" OR "suicide ideation" OR "completed suicide"). Furthermore, we refined the search results of related studies by looking at the list of references included in each article.

Selection criteria

Relevant studies were included in accordance with the inclusion criteria and exclusion criteria. The inclusion criteria in this meta-analysis were set as follows: (1) human studies; (2) English-written studies; (3) studies with a case–control group not biologically related (cases group included patients with SB and the control group included healthy controls or psychiatric controls); (4) studies on the relationship between HTR1A gene rs6295 polymorphism and SB susceptibility; and (5) studies with sufficient specific data for case and control group to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

The exclusion criteria were set as follows: animal model studies, reviews, studies where their full text were not available, case reports and conference summaries. All the retrieved studies were screened by two reviewers according to the inclusion criteria and exclusion criteria. If there were numerous studies that gave overlying outcomes and data, we would make three attempts to reach the authors by e-mail for their raw data.

Data extraction

To improve the reliability of our results, two investigators (YHD, TBGC) used a standardized form to independently extract data. Any divergences of opinion were resolved by consensus with the senior authors (CATZ).

The following data from each selected article were collected: the surname of the first author, the publication year, country, age, gender, ethnicity, diagnostic, methods of genotyping, number of cases and controls, genotype and allele frequency.

Assessment of study quality and bias risk

The quality of eligible case–control studies was estimated using the Newcastle–Ottawa Scale (NOS). The score of each study ranged from 0 (worst) to 9 (best). Study quality was ranked as high, moderate, or low (score categories 7–9, 4–6, 0–3, respectively). The risk of bias assessment was performed using the ROBINS-I tool that evaluates the risk of bias in "Low risk", "Moderate risk" and "High risk". Two authors independently performed and study quality and risk of bias assessments. Conflicts were resolved by consensus or by consultation with a third author.

Statistical analysis

The presence of Hardy–Weinberg equilibrium (HWE) was tested using Pearson's goodness-of-fit chi-squared test. The relationship between *HTR1A* rs6295 SNP and SB risk was evaluated using odds ratios (ORs) and 95% confidence intervals (CI) under five genetic models: allele model (G versus C), homozygous model (GG versus CC), heterozygous model (GC versus CC), dominant model (GG + GC versus CC) and recessive model (GG versus GC + CC). When analyzing the genetic association with SB, data were divided into: A) SB cases vs. healthy controls and B) SB cases vs. psychiatric controls. As

the number of genetic models studied increase the risk of false positive results due to the high number of comparisons, Bonferroni's corrections were applied and set at $P < 0.01$ ($P_{\text{correction}} = 0.05/5 = 0.01$). A power analysis was performed using Quanto V.1.2.4 software with an allelic frequency of 0.48 additive mode of inheritance, assuming a disease prevalence of 0.08, at 0.01 significant level. We obtained a power of 0.99 ($n = 5925$) with odds ratio of 2.

The heterogeneity test between studies was performed based on the Q and I^2 statistics of all studies in each model. When $P < 0.01$ and $I^2 \geq 50\%$, it was considered that a large heterogeneity existed. The model used was the fixed-effects. In addition, we evaluated publication bias by drawing a funnel plot, and further confirmed using Begg or Egger tests. $P < 0.01$ was defined as significant publication bias.

We also performed subgroup analyses and a sensitivity analysis to explore sources of heterogeneity. Subgroup analyses stratified studies by type of SB (suicide attempt or completed suicide), ethnicity (Caucasian), genotyping method (PCR-RFLP or sequencing) and source of the biological sample (blood). Sensitivity analysis was performed by excluding individual studies. Data were meta-analyzed using the Comprehensive Meta-analysis software (Biostat, Englewood, NJ, USA version 3).

Results

Characteristics of included studies

Initially, 278 papers related to the keywords were identified. Subsequently, 13 case–control studies [6, 7, 10–12, 14, 17, 21–23, 26, 29, 30] were selected in this meta-analysis, involving 2817 SB patients, 2563 healthy controls and 545 psychiatric controls. A flow diagram of the process of study selection was presented in Fig. 1.

The genotype frequencies were consistent with the HWE in all studies except three in the control groups [10, 12, 21]. The general features and the genotype distributions are summarized in Table 1. Of them, there were eight case–control studies conducted in Caucasians, three in Asians, one in mixed populations and the other in Latin Americans. Blood samples were collected and sequencing-based genotyping was used to detect the polymorphism in the most eligible studies.

Data were divided into: (A) SB cases vs. healthy controls and (B) SB cases vs. psychiatric controls. First, for the meta-analysis for SB cases vs. healthy controls, patients met the criteria for a depressive disorder, affective spectrum, schizophrenia spectrum, borderline personality disorder, bipolar disorder, obsessive–compulsive disorder, anxiety disorder or alcohol dependence. Second, for meta-analysis SB cases

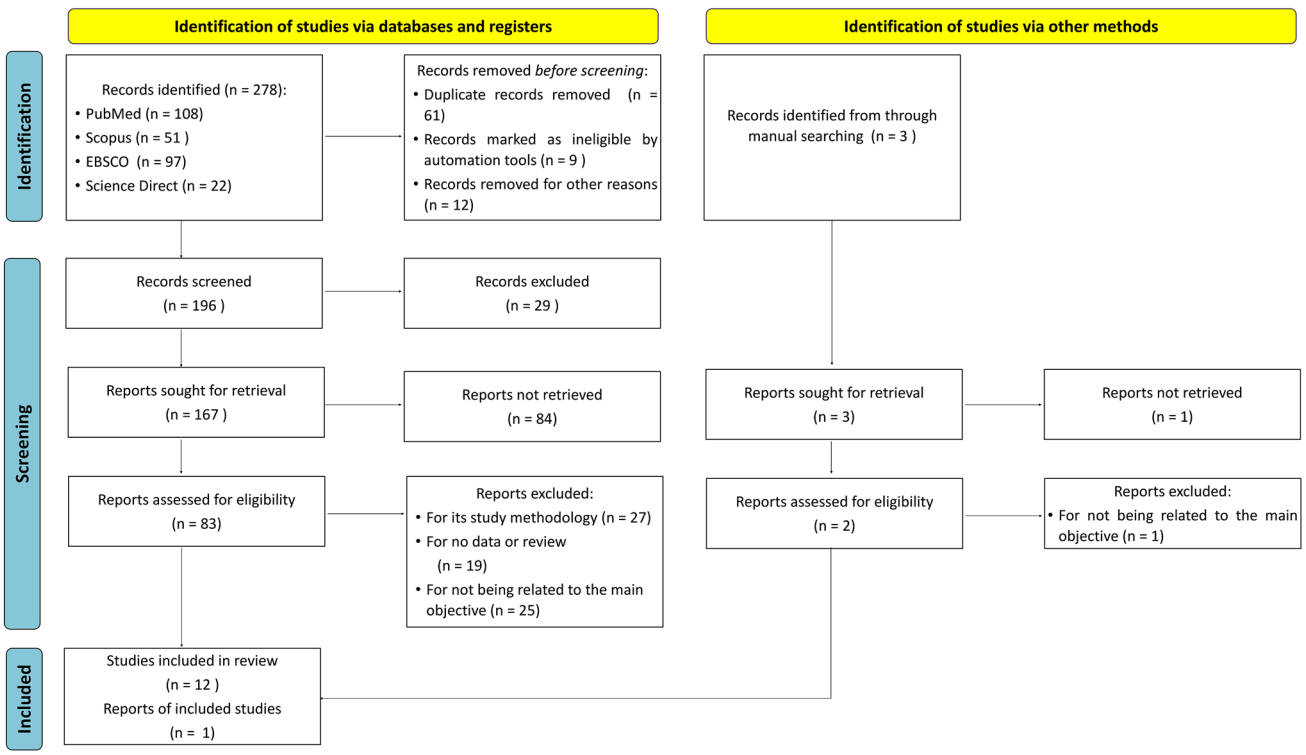

Fig. 1 Flow diagram of study selection

Table 1 Main characteristics of the included studies and genotype frequencies of cases and controls

First author	Year	Country	Ethnicity	Sample size		Mean age		Diagnostic	SB	Genotyping method	Tissue	Genotype distribution						HWE	
				Case	Control	Case	Control					Case			Control				
												GG	GC	CC	GG	GC	CC	Case	Control
Healthy controls																			
Lemonde et al. [14]	2003	Canada	Caucasian	102	116	32	34	Major depression	CS	Sequencing	Brain	17	30	55	5	26	85	0.001	0.118
Huang et al. [12]	2004	USA	Mixed	214	107	–	39	Major depression, schizophrenia or bipolar disorder	SA	ASA	Buccal mucosa and blood	64	97	53	23	50	34	0.182	0.566
Serreti et al. [23]	2007	German	Caucasian	259	312	39	48	Affective spectrum, schizophrenia spectrum, or borderline personality disorder	Mixed	Sequencing	Brain and blood	61	132	66	74	159	79	0.751	0.730
Serreti et al. [23]	2007	Italian	Caucasian	92	163	39	48	Affective spectrum, schizophrenia spectrum, or borderline personality disorder	SA	Sequencing	Blood	17	50	25	48	78	37	0.360	0.622
Videtic et al. [26]	2009	Slovenia	Caucasian	323	190	48	49	–	CS	PCR-RFLP	Blood	91	160	72	57	84	49	0.916	0.115
Serreti et al. [22]	2009	German	Caucasian	111	289	39	45	Affective spectrum, schizophrenia spectrum, or borderline personality disorder	SA	Sequencing	Blood	26	55	30	69	149	71	0.935	0.595
Yoon and Kim [30]	2009	Republic of Korea	Asian	181	176	40	40	Major depression	SA	PCR-RFLP	Blood	93	79	9	98	67	11	0.129	0.920

Table 1 (continued)

First author	Year	Country	Ethnicity	Sample size		Mean age		Diagnostic	SB	Genotyping method	Tissue	Genotype distribution						HWE	
				Case	Control	Case	Control					Case			Control				
												GG	GC	CC	GG	GC	CC	Case	Control
Benko et al. [6]	2010	Hungary	Caucasian	724	616	30	–	Obsessive–compulsive disorder, depression, or anxiety disorder	SA	MassARRAY	Buccal mucosa	193	368	163	89	438	89	0.621	0.001
Wrzose et al. [29]	2011	Poland	Caucasian	38	112	> 18	> 18	Alcohol-dependent	SA	Simple probe	Blood	10	16	12	29	53	30	0.337	0.571
Samadi et al. [21]	2012	Iran	Asian	191	218	47	45	–	CS	PCR–RFLP	Blood	56	53	82	26	42	150	0.001	0.001
González-Castro et al. [10]	2013	Mexico	Latin Americans	152	264	25	31	Schizophrenia spectrum or anxiety disorder	SA	TaqMan	Blood	26	58	68	55	115	94	0.321	0.756
Psychiatric controls																			
Huang [12]	2004	USA	Mixed	85	156	43	43	Major depression	CS	ASA	Brain	20	40	25	50	63	43	0.608	0.017
Hofer et al. [11]	2016	Austria, Israel, Belgium, Italy and France	Caucasian	142	100	–	–	Major depression	SB	–	Blood	32	75	35	33	45	22	0.498	0.373
Pompili et al. [17]	2017	Italy	Caucasian	63	57	36	55	Schizophrenia, schizoaffective disorder, bipolar disorder, major depression or personality disorder	SA	Pyrosequencing	Blood	16	29	18	16	31	10	0.533	0.450
Choi et al. [7]	2018	Republic of Korea	Asian	71	89	39	41	Depressive or bipolar disorder	SI	TaqMan	Blood	50	20	1	52	34	3	0.523	0.363
Choi et al. [7]	2018	Republic of Korea	Asian	69	143	39	45	Depressive or bipolar disorder	SA	TaqMan	Blood	44	22	3	87	51	5	0.905	0.453

SA suicide attempt, *SB* suicidal behavior, *CS* completed suicide, *ASA* allele-specific PCR amplification

vs. psychiatric controls, psychiatric subjects were divided as follows: presence or absence of SB as cases or controls, respectively. This meta-analysis included patients with schizophrenia, schizoaffective disorder, bipolar disorder, major depression or personality disorder. Finally, the diagnostic features of the study population are listed in Table 1.

Meta-analysis for *HTR1A rs6295* between SB cases and healthy controls

The main result of the meta-analysis is displayed in Table 2. Ten case–control studies with 2387 patients and 2563 controls were included in the present meta-analysis [6, 10, 12, 14, 21–23, 26, 29, 30]. Our meta-analysis revealed a significantly increased risk of SB with *HTR1A* rs6295 under the recessive genetic model (OR = 2.21, 95% CI = 1.80–2.71, $P < 0.01$) (Fig. 2). There was no considerable heterogeneity detected between studies included in the analysis ($I^2 < 50\%$; $P > 0.01$). In the other genetic models, no association was observed.

Finally, we performed subgroup analyses to explore the association of *HTR1A* rs6295 only in the suicide attempt [6, 10, 12, 22, 23, 29, 30]. Contrary to that observed in SB overall, we found a significant protective association with suicide attempt (OR = 0.75, 95% CI = 0.63–0.90, $P = 0.002$) in the dominant model (Supplementary Table S1).

Table 2 Results of overall analyses for SB and healthy or psychiatric controls

Groups	Genetic models	No. of studies[a]	Sample size	Test of association		Test of heterogeneity		Test of publication bias
				OR (95% CI)	*P* value	*P* value	I^2%	*P* value
SB vs healthy controls								
Overall	Allelic	8	4545	0.97 (0.87–1.08)	0.625	0.400	3.495	0.622
	Homozygote	9	4694	1.08 (0.83–1.21)	0.939	0.302	15.32	0.450
	Heterozygote	9	4694	1.03 (0.86–1.23)	0.711	0.354	9.559	0.563
	Dominant	8	4545	0.96 (0.80–1.14)	0.673	0.402	3.460	0.862
	Recessive	4	2745	**2.21 (1.80–2.71)**	**0.000**	0.328	14.24	0.921
SB vs psychiatric controls								
Overall	Allelic	5	975	0.89 (0.73–1.08)	0.266	0.230	28.24	0.180
	Homozygote	5	975	0.69 (0.44–1.04)	0.070	0.762	0.000	0.112
	Heterozygote	5	975	0.93 (0.63–1.37)	0.713	0.687	0.000	0.825
	Dominant	5	975	0.82 (0.57–1.19)	0.310	0.748	0.000	0.674
	Recessive	3	643	0.30 (0.21–1.42)	0.066	0.104	55.04	0.100

Bold numbers means significant association

[a]The total studies analyzed was ten, the column represents the studies analyzed after excluding studies that favored heterogeneity

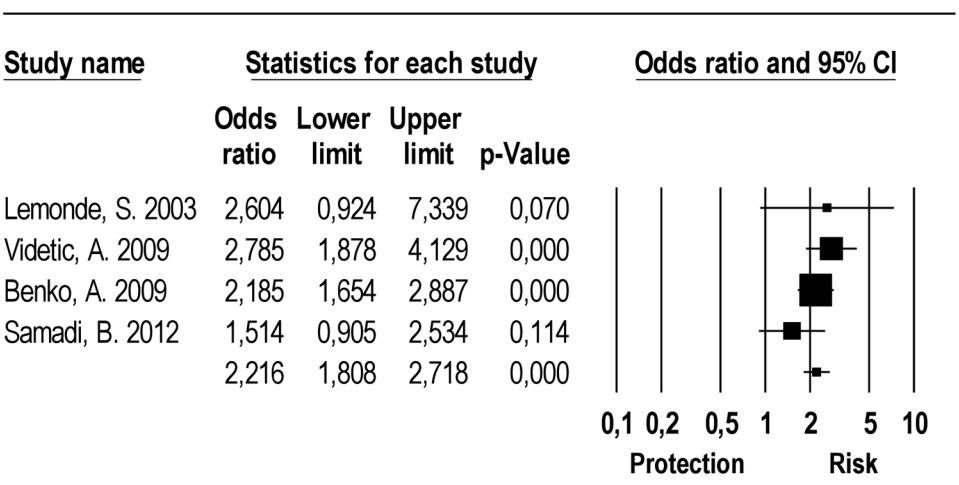

Fig. 2 Forest plot of *HTR1A* rs6295 polymorphism and SB in the recessive model

Meta-analysis for *HTR1A rs6295* between SB cases and psychiatric controls

To explore the probable effect of the clinical diagnostic of the control group, we performed a meta-analysis with a psychiatric control group. Consequently, four studies with 430 patients and 545 controls were enrolled in the meta-analysis [7, 11, 12, 17]. There was no significant association between this SNP and predisposition to SB in any of the models that were used (Table 2; Supplementary Table S2).

Sensitivity analysis, quality and risk bias measures

We carried out a sensitivity analysis to evaluate the influence of any study on the pooled OR by omitting an individual study in sequence. Sensitivity data analysis showed that no individual study altered the pooled ORs qualitatively, which provided evidence of the stability of the meta-analysis. The quality of included studies was assessed with an NOS scale and ranged from 6 to 8. The risk of bias was evaluated for the different studies chosen using the ROBINS-I tool. It was found that overall, a low risk of bias was obtained in 69.23% of the included studies (Fig. 3). Additionally, Table 2 includes the publication bias assessment with its respective *P* value for each test. In addition, the graphical representations of publication bias under the recessive model for healthy controls is shown in Fig. 4. The shape of Begg funnel plots and Egger linear regression tests showed no publication bias.

Discussion

In the present study, we evaluated the contribution of *HTR1A rs6295* SNP to the susceptibility to SB. First, the present meta-analysis, including 2387 patients and 2563 healthy controls, was conducted to evaluate the association between *HTR1A* rs6592 SNP and SB risk. Our results indicated that the variant genotypes were associated with a risk of SB.

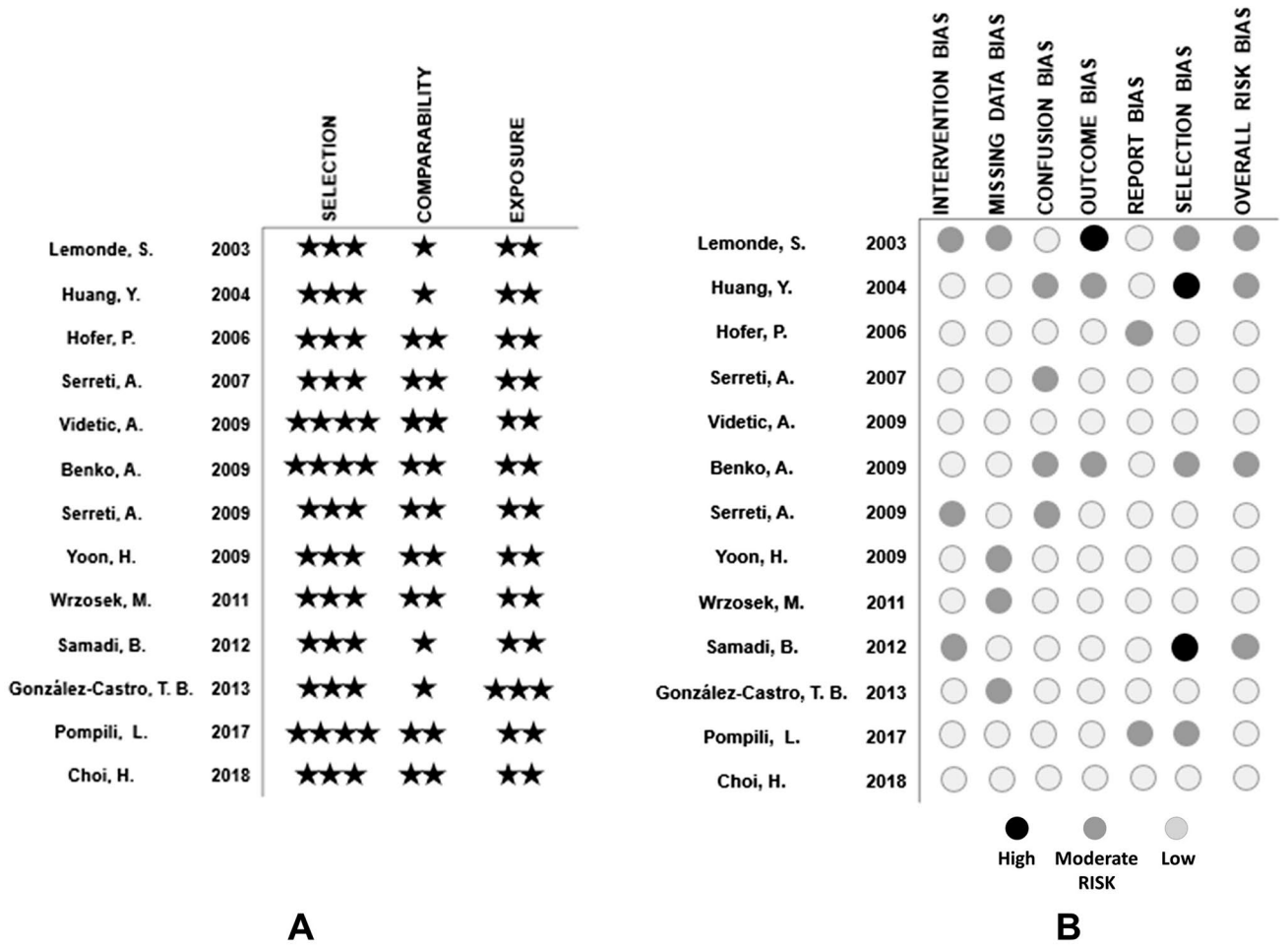

Fig. 3 Assessment of quality and risk of bias. **A** NOS scale. **B** ROBINS-I scale

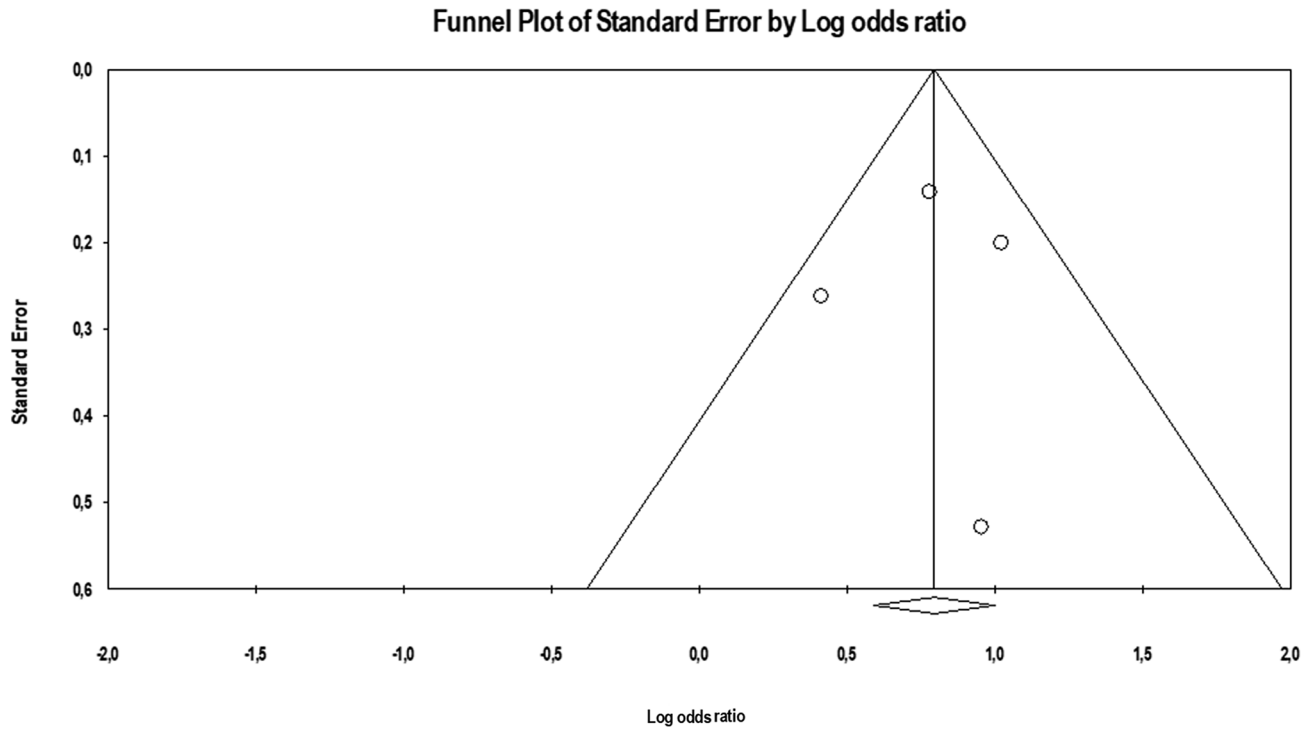

Fig. 4 Funnel plot of publication bias for the *HTR1A* rs6295 polymorphism and SB in the recessive model

5-HT_{1A} receptors are highly expressed in areas with strong involvement in emotional and affective processes. In vitro studies indicate that rs6295 SNP may functionally impact *HTR1A* transcription. Therefore, we propose the potential mechanism as follows: the G-allele should lead to higher HT1A receptor expression to reduce 5-HT neurons firing. Subsequently, this allows a reduction of the postsynaptic HT1A receptors, which decrease the serotonin neurotransmission [1, 2]. Nevertheless, it has been found in post-mortem samples of the prefrontal cortex (PFC) that the G-allele associated with decreased mRNA of *HTR1A* [8], likely due to the enhancer activity of NUDR/Deaf1 in the PFC. Therefore, it could be plausible to assume that the modulation of *HTR1A* expression is implicated in the predisposition to suicide [8].

Our study found that there was a significant association between *HTR1A* and SB susceptibility, which differed from the meta-analyses reported by González-Castro et al. [10] and Angles et al. [5] and GWAS studies [9, 16]. Two previous meta-analyses had addressed the relationship of *HTR1A* gene variants and SB: the first with 957 patients/957 controls and the other with 2366 cases/2943 controls. The present analysis involved 2817 SB patients and 3108 controls. This meta-analysis evaluated the additional data from 451 cases and 165 controls [7, 11, 12]. Compared with previous meta-analyses, the current meta-analysis contained more number of samples and provided more valuable information such as the results of subgroup analysis. This study included literature conducted with a strict quality evaluation. Last, but not least, methodological issues have also been well explored (e.g., publication bias, sensitivity and heterogeneity).

In a GWAS with a 29,782 suicide attempt cases and 519,961 controls, the significance for the major histocompatibility complex and an intergenic locus on chromosome 7 was reported. Nevertheless, they failed to find an association of rs6295 or an SNP in the vicinity of the *HTR1A* gene. We recognize that GWAS has provided a powerful approach for identifying common disease SNP. Our meta-analysis found a positive association with rs6295, but GWAS studies did not replicate it, possibly explained by the fact that this SNP did not reach genome-wide significance. So a larger population-based study will need to be conducted to verify the relationship between the genetic variant of rs6295 and SB risk. Moreover, GWAS individually test for additive genetic effect of each locus. Single locus additive model approaches rarely explain more than a small proportion of the heritable variation and might fail to detect loci due to lack of controlling genetic background variants [15, 27].

Second, we summarized the relationship between rs6295 and SB in four studies with 430 patients and 545 psychiatric controls. To the best our knowledge, this is the first meta-analysis to assess the relation in *HTR1A* in psychiatric controls by combining all available literature up to date. Each genetic model had no association with

increased SB risk, which included allele, homozygote, heterozygote, dominant and recessive models. The possible reasons for negative results could be as follows: first, our results may be overestimated due to the limited sample size. Studies with larger sample sizes are required to confirm our findings further. Second, SB is a complex disorder, which involves multiple loci polymorphisms and environmental factors. Our results should be treated with caution. Nevertheless, it should be noted that observing an association with healthy controls, but not with psychiatric controls, presents a probable relation of this *HTR1A* gene variant with an increased risk for psychiatric illness per se, which could in turn increase suicidal risk. Therefore, the association of rs6295 with suicidality in the general population should be considered with caution. Related to this, there are reports which established that people with a present mental illness constitute a high-risk group. However, there are epidemiological reports showing that a considerable percentage of deaths by suicide were by people with no known psychiatric illness. Therefore, suicide as an independent psychiatric disorder should not be ruled out. Even more, there are genome-wide association studies that identify risks locus that contribute more strongly to SBs than other psychiatric phenotypes. This fact suggests that the shared underlying biology between suicide and known risk factors is not mediated by psychiatric disorders.

On the other hand, the present meta-analysis takes into consideration case–control studies that addressed the association of *HTR1A* as a candidate gene for SB. There is some criticism of candidate gene studies, due to in replication studies the findings varied. However, one important limitation of GWAS is the limited phenotyping in patients groups in these large-sample studies and the multiple-testing burden of these types of studies with the same diagnoses. Therefore, meta-analysis of case–control studies can expand the associated data from studies with genotypes data in samples with the same diagnostic. Furthermore, combining the results of multiple studies improve the statistical power, which is an important limitation of the case–control studies, decreasing the bias in the analysis.

In addition, we have to admit the limitations in the meta-analysis performed here. First, some relevant studies could not be included due to incomplete raw data provided or publication limitations. Second, our results may be overestimated due to the limited sample size, which may lead to not powerful enough estimation. The small sample size study may have a low power and the method of pooled odds ratio may affect the results. Third, multiple factors can influence the development of SB, such as age, sex, gene–gene interactions and gene-environment interaction, which were not analyzed here due to lack of sufficient data. Fourth, the literature retrieval strategy was limited by language, and only articles published in English were included.

Conclusion

Our meta-analysis of 13 case–control comprising 5925 individuals with SB, a healthy control group and a sample with psychiatric diagnoses provided evidence that carriers of the GG genotype of *HTR1A* rs6295 SNP showed an increased risk for SB in the general population. However, well-designed and multicenter studies, with larger sample size and different ethnic groups are needed to confirm these results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00406-022-01500-x.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by YH-D, CAT-Z, ADG-M, MLL-N, GEV-J and TBG-C. The first draft of the manuscript was written by YH-D, CAT-Z, RGC-A, IEJ-R and TBG-C and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Not applicable.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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