Association between \textit{TPH1} polymorphisms and the risk of suicide behavior: An updated meta-analysis of 18,398 individuals

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\textbf{Objectives:} We aimed to examine the association of \textit{TPH1} polymorphisms with the risk of suicide behavior (SB).

\textbf{Design:} Systematic review and meta-analysis.

\textbf{Method:} All relevant studies that evaluated the association between the A218C (rs1800532), A779C (rs1799913) and A6526G (rs4537731) polymorphisms and the susceptibility to SB published up to September 2021 were identified through a comprehensive systematic search in PubMed, Scopus, EBSCO and Science Direct electronic databases. The association between \textit{TPH1} gene polymorphisms and SB was evaluated using inheritance models by odds ratio (OR) and 95\% confidence interval (CI). Subgroup analyses, heterogeneity analyses, and publication bias were also tested in this meta-analysis.

\textbf{Results:} The meta-analysis for \textit{TPH1} A218C revealed an increased risk of SB in the dominant model (OR = 1.11, 95\%CI 1.01–1.22). We also observed a positive association in the allelic (OR = 1.13, 95\%CI 1.05–1.21), homozygous (OR = 1.22, 95\%CI 1.06–1.40), heterozygous (OR = 1.21, 95\%CI 1.08–1.37) and dominant (OR = 1.21, 95\%CI 1.09–1.34) inheritance models with the suicide attempt. Additionally, in the heterozygous (OR = 0.84, 95\%CI 0.73–0.97) and dominant (OR = 0.79, 95\%CI 0.68–0.91) inheritance models we detected an association with completed suicide. Based on ethnicity, an association of SB in the European population also was observed (OR = 1.29, 95\%CI 1.12–1.51). However, for both A779C and A6526G polymorphisms we did not find evidence of an association with SB.

\textbf{Conclusion:} This meta-analysis suggests that the A218C polymorphism of \textit{TPH1} gene could be a possible risk factor of SB. Future large-scale studies...
are required to analyze the molecular mechanisms by which affect the susceptibility of developing suicide behavior.

**KEYWORDS**

tryptophan hydroxylase, meta-analysis, suicide behavior, polymorphism, risk allele

**Introduction**

Human behavior is governed by a complex interplay of numerous biological, genetic, psychological, cultural, social and family determinants. In particular, suicide behavior (SB) ranges from suicide ideation to suicide attempts and completed suicide and constitutes a multifactorial public health issue. The understanding of the genetic system that causes vulnerability to develop SB is largely incomplete, as its etiology is complex and diverse; however, epidemiological studies show that suicide behavior is partly heritable and polygenic (1, 2).

Serotonin, also known as 5-hydroxytryptamine (5-HT), is produced by generating 5-hydroxytryptophan out of tryptophan and the downstream decarboxylation using aromatic amino acid decarboxylase (3). Tryptophan hydroxylase (TPH) is the rate limiting enzyme in the biosynthesis of serotonin. Serotonin is synthesized in the central nervous system (CNS) as well as gastrointestinal system, and it is produced by TPH, which can be present in two isoforms, TPH1 and TPH2 (4, 5).

The serotonergic system is implicated in the etiology and pathogenesis of several psychiatric disorders. Serotonergic pathways associated with mood disorders and SB include the inflammatory processes related to serotonin processing (6). The neuroimmunological kynurenine pathway has been implicated in major depressive disorder and suicide in adults. Kynurenine is formed from its precursor, tryptophan, if kynurenine levels are associated with tryptophan concentrations, these pathways are argued to have the ability to influence levels of serotonin. It has been reported that the kynurenine production is higher among individuals with a history of suicide attempts (1, 7).

The TPH1 gene has been extensively studied as a candidate for suicide behavior due to its role in serotonergic neurotransmission (1, 8). This gene is located on chromosome 11p15.3-p14 and has two common polymorphisms in intron 7 consisting of A for C substitution at nucleotides 779 (A779C; rs1799913) and at 218 (A218C; rs1800532), plus one polymorphism in the promoter region consisting of A for G substitution at nucleotides 6526 (A6526G; rs4537731). These polymorphisms have been associated with suicide for they may influence the level of serotonin metabolites and their functionality (9, 10).

Although one meta-analysis (10) has already addressed the issue of the association between the TPH1 polymorphisms and SB, the sample sizes used were relatively small. Also, in the last years, the TPH1 polymorphisms have been attracting attention and more studies have explored the association of TPH1 polymorphisms and suicide behavior. Therefore, it is important to summarize the results from more studies to further validate the association of TPH1 polymorphisms with the risk of suicide behavior. In this study, a systematic review and updated meta-analysis was performed on all eligible case-control studies to estimate the overall SB risk associated with three polymorphisms of the TPH1 gene: A218C, A779C and A6526G. Additionally, we conducted subgroup analyses stratified by ethnicity and diagnostic. The results of this meta-analysis can provide an opportunity to unveil the role that the TPH1 gene plays in the susceptibility to suicide.

**Materials and methods**

The search strategy follows the PRISMA (http://www.prisma-statement.org/) reporting guidelines.

**Search strategy**

The following terms were used for searching potential studies: (“suicide” OR “suicidal”) AND (“TPH1” OR “tryptophan hydroxylase 1”). We searched for articles were searched in PubMed, Scopus, EBSCO and Science Direct databases, dated up to September 2021. To find other potential studies, we examined the references of the eligible studies. The process of the study selection in the preset work is detailed in a flow diagram; Figure 1.

**Eligible inclusion/exclusion criteria**

The criteria applied for eligible studies were: 1- studies that evaluated the association between TPH1 A218C, A779C and A6526G polymorphisms and suicide risk, 2- cases-controls designs studies, 3- individuals with a suicidal behavior...
which identified by a specialist; we included all the suicidal behavior spectrum (attempt, ideation and completed suicide) addressed in the published studies, 4- sufficient data available to obtain genotypic frequencies to calculate odds ratio (OR) and 95% confidence interval (95%CI), 5- articles published in English. These data were not always available for all studies, but when needed, we contacted the authors to clarify the information not included in the papers. Reviews, meta-analysis, duplicates, case reports, book chapters, and animal studies were all excluded.

Data collection

The relevant data from each study were extracted by reviewers (Hernandez-Díaz and Castillo-Avila) using standardized and structured forms. The following data were extracted: first author, year of publication, country, main outcome, criteria diagnostic, source of DNA, genotyping method, ethnicity, gender, sample size, genotype distribution for the cases and controls. Once encountering discrepancies, other authors re-checked the original articles until an agreement was achieved by all of them.

Assessment of methodological quality

The Newcastle-Ottawa Scale (NOS) was used to examine the quality of each study. Quality scores range from 0 to 9, and higher scores mean better quality of the study. Studies scoring six or higher were considered as high-quality studies. The qualities of the includes studies were evaluated by the same two investigators. Disagreements were resolved through discussion by a third investigator (Gonzalez-Castro).
| References  | Country           | Sample | Males | Mean age | SB | Genotypes | Alleles | P for HWE | NOS |
|-------------|-------------------|--------|-------|----------|----|------------|---------|-----------|-----|
|             |                   | Case   | Control | Case   | Control | Case | Control | Case | Control | Scale |
| **A218C**   |                   |        |        |          |     |            |         |           |     |
| Bellivier F (12) | France | 52     | 94     | -       | 57  | -         | 43.7    | SA        | 17  |
| Kunugi H (14) | Japan            | 46     | 208    | -       | 95  | 55        | 32.1    | SA        | 10  |
| Geijer T (19) | Sweden           | 165    | 98     | 57      | 64  | 41        | 38      | SA        | 30  |
| Paik I (21)  | Korea            | 27     | 236    | -       | 124 | 30        | 29.6    | SA        | 4   |
| Ono H (20)   | Japan            | 132    | 132    | 90      | 90  | 48.3      | 47.2    | CS        | 29  |
| Souery D (25) | Belgium, Bulgaria, Croatia, Germany, Greece, Israel, Italy, Sweden, United Kingdom | 167    | 167    | -       | -   | -         | -      | SA        | 29  |

|             |                   |        |        |          |     |            |         |           |     |
| Abbar M (22) | France           | 231    | 281    | 105     | 170 | 36        | 43      | SA        | 43  |
| Zalsman G (27) | Israel | 84     | 172    | 40     | 74  | 17.4      | 40.9    | SA        | 16  |
| Turecki G (26) | Canada | 101    | 129    | -      | -   | 32.2      | 34      | CS        | 18  |
| Hong CJ (23)  | Germany          | 140    | 251    | -      | 123 | 35.3      | 33.8    | SA        | 42  |
| Rujescu D (28) | Germany | 86     | 154    | 27     | 66  | 39        | 48      | SA        | 10  |
| Rujescu D (30) | Germany | 147    | 326    | 52     | -   | 40        | -       | SA        | 18  |
| Jernej B (31) | Croatia          | 185    | 358    | 144    | 298 | 52        | 43      | CS        | 84  |
| Okhtani M (32) | Japan       | 132    | 214    | 94     | 114 | 55.4      | 63.5    | CS        | 30  |
| Stefuli J (34) | Croatia | 160    | 284    | 160    | 284 | 48        | 44      | CS        | 21  |
| Stefuli J (36) | Croatia | 247    | 320    | 247    | 320 | 65        | 65      | CS        | 33  |
| Viana MM (37) | Brazil           | 248    | 63     | 142    | 36  | 37.2      | 34.3    | SA        | 45  |
| Liu X (35)    | China            | 297    | 174    | 171    | 98  | 46.1      | 42.8    | SA        | 72  |
| Yoon H K (38) | Korea            | 191    | 193    | 70     | 73  | 40.5      | 41.4    | SA        | 49  |
| Baud P (39)   | Switzerland and France | 544    | 1,027  | 166    | -   | 39.1      | -       | SA        | 99  |
| Wilson ST (40) | USA             | 71     | 101    | -      | 39  | 34.2      | 40.5    | SA        | 13  |

(Continued)
Statistical analysis

The relationship between TPH1 gene polymorphism and SB risk was determined by calculating OR and 95% CI. To measure this association, we evaluated the effect by five genetic models: allelic (A vs. C), dominant (AA + AC vs. CC), recessive (AA vs. AC + CC), heterozygous (AC vs. CC) and homozygous (AA vs. CC).

Z-test was used to determine the significance of the OR ($P < 0.05$ was considered statistically significant). Cochrane Q-test and $I^2$ test was conducted to assess the between studies heterogeneity. Significant heterogeneity was defined with a $P$-value $< 0.05$ and $I^2 \geq 50\%$ and a random effect model (DerSimonian–Laird) was used in this case. Otherwise, a fixed effect model (Mantel–Haenszel) was applied. Subgroup analysis was used to further identify the factors influencing heterogeneity. Publication bias was assessed by funnel diagram that produces a diagram according to its OR and the standard error of each study, moreover, Egger’s test was calculated ($P < 0.05$ was considered statistically significant). The data were analyzed using Comprehensive Meta-Analysis (CMA) software v.2.

Results

Literature search and study characteristics

A total of 441 potentially relevant studies emerged from the first search in PubMed, EBSCO, Science Direct, Scopus and manual searching. After excluding 351 unrelated publications, we screened 90 publications for eligibility of inclusion. Finally, thirty-six studies met the selection criteria and were finally enrolled for pooled analyses (11–47). The PRISMA flow diagram used for study selection process is summarized in Figure 1.

There were 6,214 cases and 12,184 controls in these 36 studies, 16 studies were conducted in European populations, 13 in Asian populations, 5 in American populations, 1 in Turkish and 1 in mixed populations (USA and Italy). In terms of the SB type, some studies evaluated suicide attempt ($n = 27$), suicide ideation ($n = 1$), and completed suicide ($n = 8$). The age of the individuals studied ranged from 17.4 to 65 years old. There were statistically significant deviations from the HWE in the control groups ($n = 3$); therefore, these studies were excluded from the meta-analysis.

According to the Newcastle–Ottawa scale, the quality score of each included study was >6, indicating good quality overall. Tables 1, 2 displays the main characteristics and quality assessment results of the eligible studies.
TABLE 2 The characteristics of included studies in this meta-analysis for A779C and A6528G polymorphisms.

| References | Country          | Sample Case | Males Case | Mean age | SB | Genotypes | Alleles | P for HWE | NOS scale |
|------------|------------------|-------------|------------|----------|----|------------|---------|-----------|-----------|
|            |                  | Control     | Control    | Control  |    | AA AC CC   | A C     |           |           |
| Nielsen DA (11) | USA            | 102         | 232        | 31       | 32 | SA 17 57 28 | 91 113 204 | 0.186     | 0.268     |
| Rotondo A (15)  | Italy and USA  | 97          | 153        | 32       | 32 | SA 12 50 35 | 74 120 215 | 0.363     | 0.229     |
| Kunugi H (14)  | Japan           | 46          | 208        | 7        | 95 | SA 10 29 7  | 49 43 215 | 0.07      | 0.876     |
| Roy A (24)     | Sweden          | 24          | 158        | 15       | 77 | SA 2 12 10 | 16 32 156 | 0.54      | 0.264     |
| Rujescu D (28) | Germany         | 86          | 154        | 27       | 66 | SA 10 47 29 | 67 105 116 | 0.166     | 0.526     |
| Rujescu D (30) | Germany         | 147         | 326        | 52       | 148| SA 48 81 18 | 177 117 417 | 0.069     | 0.572     |
| Pooley EC (29) | United Kingdom  | 129         | 329        | 52       | 138| SA 20 67 42 | 107 151 223 | 0.427     | 0.126     |
| Ohnani M (32)  | Japan           | 134         | 325        | 95       | 171| SA 30 59 42 | 119 143 228 | 0.294     | 0.311     |
| Koller G (33)  | Germany         | 80          | 241        | 79       | 273| SA 15 38 27 | 68 92 186 | 0.801     | 0.975     |
| Liu X (35)     | China           | 266         | 164        | 117      | 98 | SA 77 126 63 | 280 252 171 | 0.414     | 0.622     |
| Pompili M (44) | Roma            | 57          | 54         | 36       | 34 | SA 8 25 21  | 41 67 53 | 0.899     | 0.717     |
| Lee SM (46)    | Korea           | 13          | 20         | 1        | 7  | SA 1 8 4  | 10 16 25 | 0.279     | 0.858     |
| Pan YF (47)    | China           | 712         | 739        | 235      | 247| SA 158 361 193 | 677 747 712 | 0.659     | 0.219     |
| Total         |                 | 1,893       | 3,103      |          |    |             |         |           |           |
| A6528G        |                  |             |            |          |    |             |         |           |           |
| Ono H (20)    | Japan           | 132         | 132        | 90       | 90 | SA 89 42 1  | 220 44 216 | 0.094     | 0.709     |
| Turecki G (26) | Canada          | 101         | 129        | -        | -  | SA 35 46 20 | 116 86 152 | 0.49      | 0.934     |
| Liu X (35)    | China           | 283         | 180        | 171      | 98 | SA 163 96 24 | 422 144 251 | 0.074     | 0.859     |
| Total         |                 | 516         | 441        |          |    |             |         |           |           |
| Systematic review |                  |             |            |          |    |             |         |           |           |
| Tsai SJ (16)  | China           | 41          | 200        | 91       | -  | SA 17 15 9  | 49 33 179 | 0.125     | 0.043     |
| Du L (18)     | Hungary         | 35          | 84         | 27       | 60 | SA 6 24 5  | 36 34 78 | 0.027     | 0.025     |
| Saetre P (41) | Denmark, Norway | 299         | 1,655      | 845      | 45 | SA 99 150 50 | 346 250 1,531 | 0.591     | 0.07      |
|    Norway and Sweden |                  |             |            |          |    |             |         |           |           |
| Total         |                 | 375         | 1,939      |          |    |             |         |           |           |
| A779C         |                  |             |            |          |    |             |         |           |           |
| Saetre P (41) | Denmark, Norway | 299         | 1,655      | 845      | 45 | SA 99 150 50 | 346 250 1,531 | 0.555     | 0.07      |
|    Norway and Sweden |                  |             |            |          |    |             |         |           |           |
| Total         |                 | 674         | 3,594      |          |    |             |         |           |           |
Meta-analysis of the association between A218C polymorphism and suicide behavior risk. (A) Forest plot of overall analysis in dominant comparison. (B) Funnel plot of overall analysis in dominant comparison.
TPH1 A218C polymorphism and the risk of SB

Twenty-seven studies (4,917 cases and 7,098 controls) assessed the relationship between TPH1 A218C polymorphism and the risk of suicide behavior (12, 14, 19–43, 45–47). The integrated analyses demonstrated that the AA/AC genotypes of A218C polymorphism was significantly associated with an increased risk of SB compared with the CC genotype (OR = 1.11, 95%CI 1.01–1.22; P = 0.026, Q test = 0.212, I² = 19.90) (Figure 2A).

Subgroup analyses were then performed based on ethnicity and diagnostic in order to investigate sources of heterogeneity (Table 3). We observed a positive association in the allelic (OR = 1.13, 95%CI 1.05–1.21; P = 0.000, Q test = 0.233, I² = 19.72), homozygous (OR = 1.22, 95%CI 1.06–1.40; n = 0.004, Q test = 0.117, I² = 30.77), heterozygous (OR = 1.21, 95%CI 1.08–1.37; P = 0.001, Q test = 0.186, I² = 23.60) and dominant (OR = 1.21, 95%CI 1.09–1.34; P = 0.000, Q test = 0.175, I² = 24.71) inheritance models with the suicide attempt; while a decreased risk of completed suicide was observed in the heterozygous model (OR = 0.84, 95%CI 0.73–0.97; P = 0.023, Q test = 0.153, I² = 33.09) and dominant model (OR = 0.79, 95%CI 0.68–0.91; P = 0.001, Q test = 0.317, I² = 14.38) (Figure 3A). In the subgroup analysis based on ethnicity, A218C was associated with increased SB risk in European populations according to the dominant model (OR = 1.29, 95%CI 1.12–1.51; P = 0.001, Q test = 0.117, I² = 43.22). However, no significant associations were found in Asian populations.

TPH1 A779C polymorphism and the risk of SB

Thirteen studies (1,893 cases and 3,103 controls) assessed relationship between TPH1 A779C polymorphism and the risk of suicide behavior (11, 14, 15, 24, 28–30, 32, 33, 35, 44, 46, 47). Overall, we did not observe an association between A779C polymorphisms of TPH1 gene in the allele frequencies or any genotype model with the overall SB risk (Table 3). Either in a subgroup analysis by ethnicity or by diagnostic, no significant SB risk was identified.

TPH1 A6526G polymorphism and the risk of SB

Three case–control studies with 516 patients and 441 controls were included in the present meta-analysis (20, 26, 35). The major outcomes in this study are summarized in Table 3. The TPH1 gene A6526G polymorphism was not significantly associated with suicide behavior under any genetic model.

Publication bias and sensitivity analysis

We estimated potential publication bias in this meta-analysis with funnel plots and Egger’s test. Funnel plots were found to be overall symmetrical (Figures 2B, 3B) and the P values for Egger’s test were >0.05 in all comparisons (Table 3). These results indicated that our quantitative pooled analysis results were not likely to be seriously influenced by publication biases. We carried out a sensitivity analysis to evaluate the influence of every study on the pooled OR by omitting an individual study at a time. The exclusion of any study did not alter the corresponding pooled OR; P-values demonstrated nonsignificant values ranging from 0.15 to 0.99.

Discussion

This meta-analysis, robustly estimated associations between gene polymorphisms in TPH1 gene and the risk of suicide behavior. Considerable evidence has shown that the TPH1 gene is a possible candidate involved in the etiology of suicide. Although one meta-analyses (10) has been conducted in the past 7 years evaluating the relationship between the TPH1 gene polymorphisms and SB, its findings were inconclusive. Hence, to resolve inconsistencies and to decrease heterogeneity, we performed an updated meta-analysis. Regarding the essential role of genetic factors in the pathogenesis of suicide behavior, we categorized our results according to ethnicity and diagnostic.

First, the pooled analyses results showed that the A218C polymorphism was significantly associated with the risk of SB. The A218C polymorphism was found to be associated with SB in Koreans and Caucasian populations; moreover, A218C has been associated with anger related traits (16, 21, 48). Subgroup analysis based on ethnicity rejected any association between A218C polymorphisms and the SB risk in Asian populations; nonetheless, a significant association between A218C polymorphism and SB susceptibility was detected in European populations. Many reasons might contribute to the conflicting results. First of all, environmental factors that individuals are exposed and different genetic backgrounds, which may have effects on suicide risk. Considering the polygenic effect on psychiatric disorders, the genetic factors that have impacted on the original diseases could share their contributions to suicide as well. In future, large number of case–control studies could provide more evidence for the role of this polymorphism with respect to susceptibility to SB. These findings are consistent with the results of Ono et al. (20), Liu et al. (35) and Abbar et al. (22).

The A218C polymorphism has also been associated with an increased risk of suicide attempt; nonetheless, a protective role was observed in individuals who completed suicide. This polymorphism is localized at intron 7, a site that is a potential GATA transcription factor-binding site. The...
TABLE 3 Integrated analyses for TPH1 gene polymorphisms and suicide behavior.

| Model                      | OR (CI 95%)  | Z   | P-value | Q-test P-value | I²   | Egger's test P-value |
|----------------------------|--------------|-----|---------|----------------|------|----------------------|
| A218C                      |              |     |         |                |      |                      |
| Overall                    |              |     |         |                |      |                      |
| A vs. C                    | 1.02 (0.96–1.08) | 0.456 | 0.175   | 22.29          | 0.343|
| AA vs. CC                  | 1.01 (0.89–1.13) | 0.875 | 0.109   | 27.65          | 0.989|
| AC vs. CC                  | 1.03 (0.94–1.13) | 0.482 | 0.122   | 27.29          | 0.191|
| AA vs. AC+CC               | 0.98 (0.88–1.08) | 0.690 | 0.281   | 13.17          | 0.807|
| AA+AC vs. CC              | 1.11 (1.01–1.22) | **0.026** | 0.212 | 19.90          | 0.212|
| Suicide attempt            |              |     |         |                |      |                      |
| A vs. C                    | 1.13 (1.05–1.21) | **0.000** | 0.233 | 19.72          | 0.444|
| AA vs. CC                  | 1.22 (1.06–1.40) | **0.004** | 0.117 | 30.77          | 0.199|
| AC vs. CC                  | 1.21 (1.08–1.37) | **0.001** | 0.186 | 23.60          | 0.228|
| AA vs. AC+CC               | 1.11 (0.98–1.25) | 0.091 | 0.128   | 29.49          | 0.765|
| AA+AC vs. CC              | 1.21 (1.09–1.34) | **0.000** | 0.175 | 24.71          | 0.145|
| Competed suicide           |              |     |         |                |      |                      |
| A vs. C                    | 0.92 (0.81–1.04) | 0.224 | 0.032   | 49.30          | 0.995|
| AA vs. CC                  | 0.86 (0.72–1.03) | 0.121 | 0.157   | 30.43          | 0.784|
| AC vs. CC                  | 0.84 (0.73–0.97) | **0.023** | 0.153 | 33.09          | 0.253|
| AA vs. AC+CC               | 0.88 (0.76–1.03) | 0.114 | 0.594   | 0.000          | 0.664|
| AA+AC vs. CC              | 0.79 (0.68–0.91) | **0.001** | 0.317 | 14.38          | 0.179|
| European population        |              |     |         |                |      |                      |
| A vs. C                    | 0.96 (0.88–1.05) | 0.392 | 0.146   | 38.99          | 0.702|
| AA vs. CC                  | 1.00 (0.83–1.20) | 0.975 | 0.345   | 11.04          | 0.620|
| AC vs. CC                  | 1.12 (0.98–1.28) | 0.084 | 0.102   | 41.52          | 0.372|
| AA vs. AC+CC               | 1.01 (0.86–1.18) | 0.846 | 0.118   | 39.17          | 0.284|
| AA+AC vs. CC              | 1.29 (1.12–1.51) | **0.001** | 0.117 | 43.22          | 0.107|
| Asian population           |              |     |         |                |      |                      |
| A vs. C                    | 1.01 (0.93–1.11) | 0.674 | 0.256   | 19.71          | 0.272|
| AA vs. CC                  | 1.06 (0.88–1.28) | 0.494 | 0.260   | 19.23          | 0.326|
| AC vs. CC                  | 1.00 (0.86–1.17) | 0.957 | 0.189   | 26.75          | 0.595|
| AA vs. AC+CC               | 1.01 (0.81–1.26) | 0.924 | 0.082   | 40.02          | 0.170|
| AA+AC vs. CC              | 1.00 (0.86–1.15) | 0.998 | 0.344   | 10.53          | 0.856|
| A779C                      |              |     |         |                |      |                      |
| Overall                    |              |     |         |                |      |                      |
| A vs. C                    | 0.98 (0.89–1.08) | 0.738 | 0.552   | 0.000          | 0.337|
| AA vs. CC                  | 0.97 (0.81–1.16) | 0.778 | 0.224   | 21.71          | 0.115|
| AC vs. CC                  | 1.05 (0.91–1.21) | 0.484 | 0.256   | 18.58          | 0.842|
| AA vs. AC+CC               | 0.89 (0.77–1.04) | 0.152 | 0.216   | 22.46          | 0.651|
| AA+AC vs. CC              | 1.02 (0.89–1.17) | 0.686 | 0.202   | 23.90          | 0.637|
| Suicide attempt            |              |     |         |                |      |                      |
| A vs. C                    | 0.92 (0.79–1.07) | 0.326 | 0.009   | 56.12          | 0.205|
| AA vs. CC                  | 0.94 (0.78–1.14) | 0.569 | 0.216   | 23.20          | 0.114|
| AC vs. CC                  | 1.07 (0.92–1.24) | 0.337 | 0.046   | 20.07          | 0.833|
| AA vs. AC+CC               | 0.90 (0.77–1.05) | 0.210 | 0.250   | 19.71          | 0.134|
| AA+AC vs. CC              | 1.03 (0.90–1.19) | 0.620 | 0.155   | 29.65          | 0.654|
| European population        |              |     |         |                |      |                      |
| A vs. C                    | 0.94 (0.79–1.13) | 0.566 | 0.336   | 11.36          | 0.857|
| AA vs. CC                  | 1.01 (0.73–1.41) | 0.925 | 0.121   | 42.65          | 0.105|

(Continued)
TABLE 3 Continued

| Model                  | OR (CI 95%)      | Z   | P-value | Q-test P-value | I²  | Egger's test P-value |
|------------------------|------------------|-----|---------|----------------|-----|----------------------|
| AC vs. CC              | 1.20 (0.94–1.54) | 0.140 | 0.195   | 32.11          | 0.109 |
| AA vs. AC+CC           | 0.86 (0.66–1.12) | 0.286 | 0.330   | 13.26          | 0.593 |
| AA+AC vs. CC           | 1.23 (0.96–1.57) | 0.088 | 0.259   | 24.31          | 0.107 |
| **Asian population**   |                  |     |         |                |     |
| A vs. C                | 0.99 (0.88–1.11) | 0.917 | 0.382   | 4.411          | 0.475 |
| AA vs. CC              | 1.00 (0.79–1.27) | 0.951 | 0.366   | 7.189          | 0.552 |
| AC vs. CC              | 0.92 (0.75–1.12) | 0.412 | 0.575   | 0.000          | 0.699 |
| AA vs. AC+CC           | 1.05 (0.86–1.27) | 0.606 | 0.208   | 32.02          | 0.388 |
| AA+AC vs. CC           | 0.94 (0.78–1.13) | 0.549 | 0.608   | 0.000          | 0.998 |
| **A6526G**             |                  |     |         |                |     |
| A vs. G                | 1.12 (0.91–1.38) | 0.247 | 0.458   | 0.000          | 0.583 |
| AA vs. GG              | 1.14 (0.69–1.86) | 0.602 | 0.298   | 17.34          | 0.374 |
| AG vs. GG              | 0.90 (0.55–1.47) | 0.689 | 0.252   | 27.42          | 0.128 |
| AA vs. AG+GG           | 1.20 (0.92–1.56) | 0.175 | 0.378   | 0.000          | 0.108 |
| AA+AG vs. GG           | 1.01 (0.63–1.60) | 0.955 | 0.284   | 20.64          | 0.207 |

GATA transcription binding factors allow the initiation of transcription (49). The A218C polymorphism could affect the transcription level of TPH1. The TPH is an initial enzyme in the TRYCATs pathway, and its low expression may lead to stopping the pathway.

The tryptophan (TRY) metabolism has two large pathways: the methoxyindole pathway and the kynurenine pathway. Regarding the available TRYS in the body, approximately 1~5% are synthesized as serotonin through the methoxyindole pathway and 95~99% of TRYS are metabolized through the kynurenine pathway and form tryptophan catabolites (TRYCATs) (50, 51). These TRYCATs are important metabolites that may contribute to the pathophysiology of psychiatric disorders such as anxiety and depression (52). TRYCATs potentiate or antagonize relationships with various neurotransmission systems (53). TRYCATs could influence SB by directly contributing to neuroprotective-neurodegenerative changes in the brain. Activation of the TRYCAT pathway leads to the production of a range of neuroactive, neuroprotective and neurotoxic TRYCATs. For example, quinolinic acid act as potent neurotoxin which inhibit ATP production by mitochondria, provoke disrupt neuron glial communication, induce apoptosis of glial cells and directly damage neurons. Other TRYCATs also possess neurotoxic or neuroprotective properties via pro-oxidant and antioxidant effects (54, 55).

Moreover, this polymorphism could also influence individual differences in anger-related personality traits. Individuals carrying the AA genotype have a reduced capacity of controlling anger expression when they experience this emotion. Conversely, the alternative genotypes (AC and CC) can be considered as “protective” against the tendency to lose control when experiencing anger (39). Therefore, we suggest that suicide attempt and completed suicide could be under genetic control and regulated through capacity to control anger.

The observed differences in susceptibility, between suicide attempt and completed suicide, are likely due to the overall genetic background that modifies the SB prone risk factors. Moreover, this discrepancy in SB risk may be explained by daily lifestyle, geographic climate, dietary habits, ethnic diversity and so on. However, these results should be illustrated prudently and need further confirmation by more trials.

Second, A779C and A6526G polymorphisms were not associated with the risk of suicide behavior. Still, we cannot ignore the interaction between TPH1 and other genes on SB susceptibility, such as TPH2. Therefore, it is necessary to systematically screen for functional variants within the TPH1 gene and other related genes in the SB pathogenesis.

In González-Castro (10) meta-analysis in 2014, our results indicated that the A218C polymorphism was associated with SB, which is consistent with the present study. In comparison with the previous meta-analyses, some advantages of the current study should be addressed. Our study updated the data on TPH1 polymorphism and the risk of SB and analyzed the role A6526G polymorphism on suicide behavior for the first time. Methodological issues were well explored (e.g., publication bias, sensitivity analysis, heterogeneity analysis) in the present work. Last but not least, the present work was carried out with five genetic models and sub-analyses by population and diagnostic subgroups were performed. Suicide attempt and completed suicide were not analyzed in previous meta-analyses.

The current meta-analysis also has some limitations. First, only articles published in English-language journals...
Meta-analysis of the association between A218C polymorphism and completed suicide risk. (A) Forest plot of subgroup analysis in dominant comparison. (B) Funnel plot of subgroup analysis in dominant comparison.

were included. Second, inter-gene and gene–environment interactions might also influence the accuracy of our outcomes. A lack of the original data restricted further evaluations of the potential inter-gene and gene–environment interactions. Related to, we recognized as a limitation that considerable percent of the studies were performed in some specific population (e.g. Croatian or German), this possible overlap of clinic center and sample population could introduce bias in the outcome. Therefore, the findings should be taken with caution. Finally, in the suicide ideation group, the number of relevant original documents was limited, there was not enough data to identify the relationship between TPH1 and suicide ideation. Moreover, the inclusion of the studies that dealt with only ideation may have increased the heterogeneity of the analyzed data.

Conclusion

The current meta-analysis gives a comprehensive analysis of the available information for the association between the TPH1 polymorphisms and suicide behavior. This meta-analysis revealed a significant association between the A218C polymorphism of TPH1 gene and SB. However, neither in overall population nor in subgroup analysis was found a significant association between A779C and A6526G polymorphisms and
SB susceptibility. Therefore, the A218C polymorphism could be considered as one possible risk factor of SB. Further studies that investigate the relative contribution of TPH1 polymorphisms and the mechanisms by which they affect the pathogenesis of SB are required to corroborate these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

Conceptualization, investigation, methodology, validation, visualization, roles/writing—original draft, and writing—review and editing: YH-D, TG-C, CT-Z, ML-N, MR-M, and AG-M. Data curation: YH-D, TG-C, CT-Z, and RC-A. Formal analysis and resources: TG-C, CT-Z, ML-N, and AG-M. Funding acquisition: YH-D, TG-C, CT-Z, and ML-N. Project administration: YH-D, TG-C, and CT-Z. Software: YH-D, TG-C, and CT-Z. Supervision: CT-Z, RC-A, ML-N, MR-M, and AG-M. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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