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NTRK2 Gene and Suicidality

Full Title: Association of *NTRK2* Gene with Suicidality: A Meta-analysis
Short title: *NTRK2* Gene and Suicidality

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Abstract

Background: Previous studies have shown that genes in brain development pathways may have important roles in affecting risk of suicidal behaviors, with our previous meta-analysis supporting a role of the brain-derived neurotrophic factor (*BDNF*) gene. *NTRK2* is a gene that encodes the neurotrophic receptor tyrosine kinase 2, which is a receptor for BDNF. In the current study, we aim to examine the potential association between *NTRK2* single nucleotide polymorphism (SNPs) and suicidal ideation/behaviors.

Methods: We first conducted a literature search using keywords like “*NTRK2*”, “*TRKB*”, and “suicid*” to identify papers on *NTRK2* SNPs and suicidal ideation/ behaviors. In addition, we have individual-level genotype data for all the identified SNPs in literature search. We used the R *meta* package to perform meta-analyses on both the genotype count and the allele count data. Moreover, we performed meta-analyses on specific haplotypes within each haplotype block.

Main Results: Following our literature search and meta-analyses on 20 *NTRK2* SNPs across up to 8467 samples, we found three SNPs, rs10868235 (N=5318, Odds Ratio (OR)=1.34, $p = 0.02$), rs1867283 (N=5134, OR=0.73, $p = 0.04$), and rs1147198 (N=5132, OR=1.36, $p = 0.03$) to be nominally associated with suicidal attempts. However, those three findings did not survive multiple-testing corrections. Also, none of the haplotype blocks showed significant involvement in suicidality.

Conclusion: Our results suggest that the *NTRK2* gene may not have a major role in suicidality. However, future efforts should explore gene-gene interaction and pathway analyses.

Keywords:

NTRK2, TrkB, Suicide, Meta-analysis, Haplotype, Genetics

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Introduction

According to The World Health Organization (WHO), 700,000 people died by suicide in 2021 worldwide, and according to Suicide Awareness Voices of Education (SAVE), for every suicidal death, there are approximately 25 suicide attempts. A major risk factor of suicide is the presence of psychiatric disorders including major depressive disorder, bipolar disorder, or schizophrenia (Conwell et al., 1996, Harris and Barraclough, 1997). Biological factors likely play an important role in suicide, with studies on postmortem brain samples from suicide completers or suicide attempters versus non-psychiatric controls suggesting that serotonin signaling, hypothalamic-pituitary-adrenal (HPA) axis, neurotrophins and neurotrophin receptors could play a role in suicide risk (reviewed in Pandey, 2013). Moreover, genetic studies including case-control studies, family-based association studies, and genome-wide association studies (GWAS), have supported a prominent genetic component in suicide (Docherty et al, 2023, Zai et al, 2012, reviewed in Mirkovic et al., 2016).

NTRK2, localized to chromosomal location 9q21.33, is a gene that encodes the Tropomyosin receptor kinase B/Tyrosine receptor kinase B (TrkB) protein, which is a receptor for Brain-derived neurotrophic factor (*BDNF*). The functional *BDNF* gene polymorphism Val₆₆Met (rs6265) has been associated with suicide attempt (Zai et al., 2012; Wang et al., 2015). Moreover, neurodevelopmental pathways have been implicated in GWASs of suicide attempt and suicide completion (Sokolowski et al., 2016; Pulay and Rethelyi, 2016). Thus, since TrkB is a receptor of *BDNF*, the *NTRK2* gene has been associated with substance use disorder (Yang et al., 2015), and substance use disorder has been associated with increased risk of suicidal ideation, suicide attempt, and suicide completion (Poorolajal et al., 2016), it is reasonable to hypothesize *NTRK2* as a potential contributor to suicidality, which encompasses suicidal ideation, suicide attempt, and suicide completion.

In the current research field, many studies have examined for the possible role of *NTRK2* gene variants on suicidality, each targeting different sets of *NTRK2* single nucleotide polymorphisms (SNPs) with mixed findings. However, there have not been a summary report of each variant's effect on suicidality risk across these studies. Furthermore, none of these studies have considered the potential possibility of the involvement of *NTRK2* haplotypes in suicidality.

To fill this research gap, we aim to perform meta-analyses of *NTRK2* SNPs with suicidality, using all available data from published studies and additional unpublished data. We also aim to test for the possible association of *NTRK2* haplotypes with suicidality outcomes.

Methods

Literature Search

We performed a literature search in PubMed using the terms “*NTRK2*” OR “*TRKB*” AND “suicid*”, and in Web of Science using terms (*NTRK2* OR *TRKB* AND suicid*). Our selection criteria for the search results included: 1) articles being in the English language, 2) the results including specific genotype/allele count data for at least one *NTRK2* SNP, 3) the results having count data for both cases of suicidality and non-suicidal control subjects as comparison groups. With these criteria, we recorded the SNP name (rsID), type of genetic data (allele/genotype), type of suicidality outcome, the total number of cases of suicidality and non-suicidal control subjects, suicidality case and control count for each allele/genotype group, ethnicity, average age, and sex ratio for each study sample. Also, we used HaploReg (V4.1) to examine the potential pairwise linkage disequilibrium between *NTRK2* SNPs. For SNPs that had r^2 of 0.6 and

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above, we considered them as proxy SNPs and analyzed them together. We then included SNPs and their proxy SNPs with data from at least four samples for each meta-analysis. In addition, each paper's quality was examined using criteria from Q-Genie (Quality of genetic association studies) (Sohani et al., 2016).

Additional Data

Genotype data for participants of European ancestry were extracted for the clinical sample sets from the following studies: RADIANT (rad) major depressive disorder (MDD), Canada GSK bipolar (gbp), and UK GSK bipolar (iop; collected at the Institute of Psychiatry, Psychology & Neuroscience) from our recent suicidality GWAS (Zai et al., 2021), Toronto bipolar (tb) from our previous suicidality GWAS (Zai et al., 2015), Toronto schizophrenia (ts) from our schizophrenia GWAS (PGC-Schizophrenia, 2014), and Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD; step) from our recent GWAS of antidepressant-induced mania (Zai et al., 2023). Suicide attempt status was determined using the suicide severity item from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) for the rad, gbp, and iop samples (Zai et al., 2023), the suicide specifier from the SCID interview for ts and tb samples (Zai et al., 2015), and suicide attempt question within the past psychiatric history of the clinically rated affective disorders evaluation for the step sample.

Meta-Analysis

We performed meta-analyses on genotypes and alleles using the R meta package (version 5.5-0), together with sub-group analyses (among different suicidality outcomes), sensitivity analyses (leave-one-out analyses), and meta-regression analyses (with female percentage and average age), and publication bias tests with funnel plots). We have access to individual-level genotype data that were extracted from previous GWASs of suicidality or other phenotypes (Zai et al., 2015; Zai et al., 2021; Zai et al., 2023). These quality-controlled individual-level data were further processed and reformatted using the Python csv package (Python 3.11.2). For each meta-analysis, sub-group analysis, and sensitivity analysis, the Mantel-Haenszel method (Greenland and Robins, 1985; Robins et al., 1986) and the DerSimonian and Laird method (DerSimonian and Laird, 1986) was used respectively to calculate common and random effects estimates with binary outcome data. The common effect model (or fixed effect model) odd ratio was reported when heterogeneity was not significant, and the random effect model odds ratio was used when heterogeneity was significant at $p < 0.05$. The p-value threshold was calculated under Bonferroni correction, which was $0.05/\text{number of independent SNPs}$. For the funnel plot, the plot was drawn to inspect for potential publication bias.

Haplotype-Analysis

Using our five available individual-level data sets for all the previously identified SNPs in the haplotype analysis, we excluded individuals with larger than 50 percent missing genotype and ignore pairwise comparisons of markers further than 500kb apart. Also, we excluded any SNPs that were missing from at least one of the data sets. We performed haplotype analysis using Haploview (Barrett et al., 2005). The haplotype blocks were defined with a threshold of D' value of 0.9 from 5' end to 3' end of the *NTRK2* gene across all five sample sets. With each defined block, we retrieved the case and control count data for each of the specific haplotypes and performed meta-analysis using the method mentioned above.

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Results

Literature search

From the initial literature search, we found a total of 53 studies from PubMed, and 51 studies from Web of Science. After the removal of 30 duplicate studies, 3 studies without available full text, and 65 studies not meeting our inclusion criteria, 6 studies remained (see PRISMA flow chart in Figure 1), which collectively examined 28 SNPs: rs10780691, rs10780695, rs10868235, rs11140714, rs11140800, rs1147198, rs117296760, rs11791090, rs1187272, rs1187286, rs1187323, rs1187352, rs1387923, rs1439050, rs1565445, rs1659400, rs17087710, rs1778933, rs1822420, rs1867283, rs2289656, rs2289657, rs2289658, rs3824519, rs4877289, rs56142442, rs6559838, and rs78963306.

After assessing linkage disequilibrium pairwise across SNPs using r^2 of 0.6, we found four sets of correlated SNPs, which included rs10780691, rs4877289, rs10868235, and rs11140800; rs1187323 and rs1147198; rs1659400 and rs1187352; as well as rs2289658 and rs2289657. Thus, we kept one SNPs from each linkage set and randomly removed rs10780691, rs4877289, rs11140800, rs1187323, rs1659400, and rs2289658 from the analysis. Moreover, SNPs rs56142442 and rs78963306 were examined in fewer than four studies; thus, we excluded them from further analyses. In all, we were left with 20 SNPs to be meta-analyzed.

The final set of data that we analyzed in the present meta-analysis came from 6 previously published studies plus six additional available sample sets. In total, we had 2629 cases of suicidality and 5838 controls. The demographic information of the included sample sets is displayed in Table 1, with one sample reporting on suicidal ideation (SI), three on suicide completion (SC), and the remaining eight on suicide attempt (SA).

Meta-Analysis

The results from the meta-analyses for genotype count data for all suicidality outcomes were displayed in Table 2a, and those for SA only were displayed in Table 2b. The results from meta-analyses for allele count data for all suicidality outcomes were displayed in Table 3a, and those for SA only were displayed in Table 3b.

From the results, SNP rs1147198 genotype G/G (Figure 2a: common-effects model $p = 0.02$; OR = 1.38; 95% CI = 1.06 - 1.80) was associated with the risk of all suicidalities. Moreover, the SNPs rs1147198 genotype G/G (Figure 2b: common-effects model $p = 0.03$; OR = 1.36; 95% CI = 1.03 - 1.80), rs1867283 genotype G/G (Figure 2c: random-effects model $p = 0.04$; OR = 0.73; 95% CI = 0.54 - 0.99), and rs10868235 genotype C/C (Figure 2d: random-effects model $p = 0.02$; OR = 1.34; 95% CI = 1.05 - 1.72) were associated with SA. These results did not survive correction for multiple testing. The sensitivity analysis results indicated that there was no significant influence of each sample set on the overall effect estimate, and the funnel plots showed no significant asymmetry or publication bias (Figure 3, Figure 4). Results for the meta-analyses of allele count data were not significant for all suicidality or SA only (Table 3).

The results of meta-regression with sex ratio showed that the OR for rs1187272 appeared to behave differently for males and females ($p = 0.02$ in genotype count, $p < 0.01$ in allele count) (Table 3) with a positive correlation between female percentage and OR (Figure 5). The result of meta-regression with age did not yield significant findings for either all suicidality or SA only.

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Haplotype-Analysis

The demographic information for data used for haplotype analysis could be found in Table 1, in which we used all the study samples with available individual-level data excluding Toronto bipolar sampleⁱ because Toronto bipolar sample did not have required SNPs to generate the same block definition as other samples. All the data reported on SA only.

The block definition is displayed in supplement block definition file (supplement file 3). There were 5 blocks identified among the five samples: block 1 (rs1140714, rs1147198, rs1187323); block 2 (rs1778933, rs1659400); block 3 (rs4877289, rs10780691, rs10868235); block 4 (rs6559838, rs3824519); block 5 (rs1565445, rs1387923). From three significant SNPs found in previous section, two SNPs (rs1147198 and rs10868235) were included in the defined blocks.

The result from meta-analysis for the defined haplotype blocks were displayed in Table 4. Results from fixed/common effects models were reported, with the exceptions of haplotypes with significant heterogeneity across studies, where results from the random effects models were reported instead. From the result, none of the haplotypes showed a significant association with the risk of SA.

Discussion

We report the first meta-analysis of *NTRK2* SNPs and haplotypes with suicidality outcomes. With all our results from all 12 studies, we found the rs1147198 G/G genotype to be nominally associated with all suicidalities. For SA, we found the rs1147198 G/G genotype ($p = 0.03$), rs1867283 G/G genotype ($p = 0.04$), and rs10868235 C/C genotype ($p = 0.02$) to be nominally associated with suicidal attempt. However, since we tested 20 SNPs in this paper, the Bonferroni corrected p -value threshold would have been $0.05/20 = 2.5 \times 10^{-3}$. None of the results for these three SNPs survived Bonferroni correction for multiple testing. Results from haplotype-analysis on block 1 and block 3, which were the blocks that include rs1147198 and rs10868235, did not show significant association with SA. Results from meta-regression analyses suggest that the association among the mentioned SNPs were not influenced significantly by age or sex ratios. Results from publication bias and leave-one-out analyses indicated minimum publication bias and no significant influence of individual sample sets on the overall effect estimates.

Our findings should be interpreted with some limitations. Firstly, we did not have individual-level data to perform haplotype meta-analysis on all the samples listed in Table 1. Our samples were exclusively from clinical studies of psychiatric patients of European ancestry; thus, our findings may not be generalizable to the general population or other ancestries.

Overall, our study results do not support *NTRK2* SNPs in playing a major role in suicidality. Our results agree with the most recent SA GWAS on 39,911 cases and 883,334 controls, where *NTRK2* SNPs were not among the top findings (Docherty et al, 2023). Furthermore, as observed by genome-wide association studies of suicidality, the total sample size of our meta-analyses may not be sufficient to detect moderate effect sizes. Larger sample sizes would also enable us to explore the effects of underlying psychiatric disorders, substance use, and environmental stressors. Nonetheless, our study demonstrated the feasibility of conducting meta-analyses of haplotypes, which may capture additional genetic variations that might have been missed by individual SNPs. *NTRK2* may still be involved in the risk of suicidality through its effects on neurodevelopment pathways. Future directions could include examining the

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combined effects of *NTRK2* SNPs and other neurodevelopment genes such as *BDNF* on suicidality.

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Statement of Interest

CCZ and JLK are authors on patents for suicide markers. JLK is a Scientific Advisory Board member of Myriad Neuroscience. CF was a speaker for Janssen.

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Reference

- BARRETT, J. C., FRY, B., MALLER, J. & DALY, M. J. (2005). Haploview: analysis and visualization of LD and haplotype maps. *Bioinformatics* 21:263-5.
- CHOJNICKA, I., STRAWA, K., FUDALEJ, S., FUDALEJ, M., PAWLAK, A., KOSTRZEWA, G., et al. (2012). Analysis of four genes involved in the neurodevelopment shows association of rs4307059 polymorphism in the cadherin 9/10 region with completed suicide. *Neuropsychobiology* 66:134-40.
- CONWELL, Y., DUBERSTEIN, P. R., COX, C., HERRMANN, J. H., FORBES, N. T. & CAINE, E. D. (1996). Relationships of age and axis I diagnoses in victims of completed suicide: a psychological autopsy study. *Am J Psychiatry* 153:1001-8.
- DEFLESSELLE, E., COLLE, R., RIGAL, L., DAVID, D. J., VIEVARD, A., MARTIN, S., et al. (2018). The TRKB rs2289656 genetic polymorphism is associated with acute suicide attempts in depressed patients: A transversal case control study. *PLoS One*, 13, e0205648.
- DERSIMONIAN, R., LAIRD, N. (1986). Meta-analysis in clinical trials. *Control Clin Trials* 7:177-88.
- DOCHERTY, A. R., MULLINS, N., ASHLEY-KOCH, A. E., QIN, X., COLEMAN, J. R. I., SHABALIN, A., et al. (2023). GWAS Meta-Analysis of Suicide Attempt: Identification of 12 Genome-Wide Significant Loci and Implication of Genetic Risks for Specific Health Factors. *Am J Psychiatry* 180:723-738.
- GREENLAND, S. & ROBINS, J. M. (1985). Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 41:55-68.
- GTEX CONSORTIUM. (2013). The Genotype-Tissue Expression (GTEx) project. *Nat Genet* 45:580-5.
- HARRIS, E. C. & BARRACLOUGH, B. (1997). Suicide as an outcome for mental disorders. A meta-analysis. *Br J Psychiatry* 170:205-28.
- KOHLI, M. A., SALYAKINA, D., PFENNIG, A., LUCAE, S., HORSTMANN, S., MENKE, A., et al. (2010). Association of genetic variants in the neurotrophic receptor-encoding gene NTRK2 and a lifetime history of suicide attempts in depressed patients. *Arch Gen Psychiatry* 67:348-59.
- MIRKOVIC, B., LAURENT, C., PODLIPSKI, M. A., FREBOURG, T., COHEN, D. & GERARDIN, P. (2016). Genetic Association Studies of Suicidal Behavior: A Review of the Past 10 Years, Progress, Limitations, and Future Directions. *Front Psychiatry* 7:158.
- PAGE, M. J., MOHER, D., BOSSUYT, P. M., BOUTRON, I., HOFFMANN, T. C., MULROW, C. D., et al. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*, 372, n160.
- PANDEY, G. N. (2013). Biological basis of suicide and suicidal behavior. *Bipolar Disord* 15:524-41.
- POOROLAJAL, J., HAGHTALAB, T., FARHADI, M., & DARVISHI, N. (2016). Substance use disorder and risk of suicidal ideation, suicide attempt and suicide death: a meta-analysis. *Journal of public health (Oxford, England)*, 38:282–291.
- PULAY, A. J. & RETHELYI, J. M. (2016). Multimarker analysis suggests the involvement of BDNF signaling and microRNA biosynthesis in suicidal behavior. *Am J Med Genet B Neuropsychiatr Genet* 171:763-76.

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- ROBINS, J., BRESLOW, N. & GREENLAND, S. (1986). Estimators of the Mantel-Haenszel variance consistent in both sparse data and large-strata limiting models. *Biometrics* 42:311-23.
- ROPRET, S., ZUPANC, T., KOMEL, R. & VIDETIC PASKA, A. (2015). Investigating the associations between polymorphisms in the NTRK2 and NGFR genes and completed suicide in the Slovenian sample. *Psychiatr Genet* 25:241-8.
- SCHIZOPHRENIA WORKING GROUP OF THE PSYCHIATRIC GENOMICS CONSORTIUM (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, 511: 421–427.
- SOHANI, Z. N., SARMA, S., ALYASS, A., DE SOUZA, R. J., ROBIOU-DU-PONT, S., LI, A., et al. (2016). Empirical evaluation of the Q-Genie tool: a protocol for assessment of effectiveness. *BMJ Open*, 6, e010403.
- SOKOLOWSKI, M., WASSERMAN, J. & WASSERMAN, D. (2016). Polygenic associations of neurodevelopmental genes in suicide attempt. *Mol Psychiatry* 21:1381-90.
- VOEGELI, G., RAMOZ, N., SHEKHTMAN, T., COURTET, P., GORWOOD, P. & KELSOE, J. R. (2016). Neurotrophin Genes and Antidepressant-Worsening Suicidal Ideation: A Prospective Case-Control Study. *Int J Neuropsychopharmacol* 19.
- WANG, J. Y., WANG, X. T., WANG, L. L. & JIA, C. X. (2015). Association of Brain-Derived Neurotrophic Factor G196A and Attempted Suicide: A Case-Control Study in Rural China. *Neuropsychobiology* 72:91-6.
- YANG, J., WANG, S., YANG, Z., HODGKINSON, C. A., IARIKOVA, P., MA, J. Z., et al. (2015). The contribution of rare and common variants in 30 genes to risk nicotine dependence. *Mol Psychiatry* 20:1467-78.
- ZAI, C. C., DE LUCA, V., STRAUSS, J., TONG, R. P., SAKINOFSKY, I., & KENNEDY, J. L. (2012). Genetic Factors and Suicidal Behavior. In Y. Dwivedi (Ed.), *The Neurobiological Basis of Suicide*. CRC Press/Taylor & Francis.
- ZAI, C. C., FABBRI, C., HOSANG, G. M., ZHANG, R. S., KOYAMA, E., DE LUCA, V., et al. (2021). Genome-wide association study of suicidal behaviour severity in mood disorders. *World J Biol Psychiatry* 22:722-731.
- ZAI, C. C., GONCALVES, V. F., TIWARI, A. K., GAGLIANO, S. A., HOSANG, G., DE LUCA, V., et al. (2015). A genome-wide association study of suicide severity scores in bipolar disorder. *J Psychiatr Res* 65:23-9.
- ZAI, C. C., MANCHIA, M., DE LUCA, V., TIWARI, A. K., CHOWDHURY, N. I., ZAI, G. C., et al. (2012). The brain-derived neurotrophic factor gene in suicidal behaviour: a meta-analysis. *Int J Neuropsychopharmacol* 15:1037-42.
- ZAI, C. C., SQUASSINA, A., TIWARI, A. K., PISANU, C., PINNA, M., PINNA, F., et al. (2023). A genome-wide association study of antidepressant-induced mania. *Prog Neuropsychopharmacol Biol Psychiatry* 127:110800.
- ZARRILLI, F., AMATO, F., CASTALDO, G., TOMAIUOLO, R., KELLER, S., FLORIO, E., et al. (2014). Tropomyosin-related kinase B receptor polymorphisms and isoforms expression in suicide victims. *Psychiatry Res* 220:725-6.

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Figure 1. PRISMA Flow Chart displaying the screening process and criteria for study selection. The “Identification” phase displayed the initial search result. The “Screening” phase displayed the number of records reviewed and criteria for selecting records. The “Included” phase displayed the number of records included in the meta-analyses.

Table 1. Characteristics of datasets that were included in the meta-analyses. The included data came from studies from our literature search as well as samples with available individual-level data . The total number of cases of suicidality and non-suicidal individuals, type of suicidality, average age, ethnicity, gender percentage, and the quality of each paper based on criteria from Q-Genie. In total, there were 2629 cases of suicidality and 5838 non-suicidal controls. **SC:** Suicide Completion; **SA:** Suicide Attempt; **SI:** Suicide Ideation; **D:** Discovery; **R:** Replicate; **step:** STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) Bipolar; **tb:** Toronto Bipolar; **ts:** Toronto Schizophrenia; **iop:** UK GSK Bipolar; **gbp:** Canada GSK Bipolar; **rad:** RADIANT UK Major Depression Disorder; **ns:** ethnicity not specified

Figure 2. Forest plots for Meta-analyses of NTRK2 SNPs: **a)** rs1147198 and suicidality under the common-effect model **b)** rs1147198 and SA under the common-effect model **c)** rs11867283 and SA under the random-effect model **d)** rs10868235 and SA under the random-effect model

Table 2. Meta-Analysis Results for Genotype Counts: the overall results of meta-analyses using genotype count data for all SNPs that have available data from more than four studies with **a)** all suicidality, **b)** only SA. The models were selected based on heterogeneity p-values, where the random-effect models were used in cases of significant heterogeneity. **P:** P Value; **Heter.P:** Heterogeneity P Value; **Reg:** Meta-regression P Value

Table 3. Meta-Analysis Results for Allele Counts: the overall results of meta-analyses using allele count data for all SNPs that have available data from more than four studies with **a)** all suicidality, **b)** only SA. The models were selected based on heterogeneity p-values, where the random-effect model were used in cases of significant heterogeneity. **P:** P Value; **Heter.P:** Heterogeneity P Value; **Reg:** Meta-regression P Value

Figure 3. Omit-One (Sensitivity) analysis of NTRK2 SNPs: **a)** rs1147198 and suicidality under the common-effect model **b)** rs1147198 and SA under common-effect model **c)** rs11867283 and SA under the random-effect model **d)** rs10868235 and SA under the random-effect model.

Figure 4. Funnel Plots of NTRK2 SNPs: **a)** rs1147198 and suicidality under the common-effect model **b)** rs1147198 and SA under common-effect model **c)** rs11867283 and SA under the random-effect model **d)** rs10868235 and SA under the random-effect model.

Figure 5. Bubble plots of odds ratio (OR) and female percentage of NTRK2 SNPs: **a)** rs1187272 and SA with genotype count under the common-effect model **b)** rs1187272 and SA with allele count under the common-effect model. The x-axis represents the female percentage, and the y-axis represents OR.

Table 4. Meta-Analysis Results for Haplotypes: the overall results of meta-analyses of haplotype blocks. The models were selected based on heterogeneity p-values, where the random-effect models were used in cases of significant heterogeneity. **P:** P Value; **Heter.P:** Heterogeneity P Value