

No relationship between dopamine D3 receptor gene Ser9Gly polymorphism (rs6280) and schizophrenia: a meta-analysis of family-based association studies

Xiao-na Li

China Medical University

Bao-jie Wang

China Medical University

Jun Yao (✉ yaojun198717@163.com)

China Medical University <https://orcid.org/0000-0003-0781-5694>

Research article

Keywords: Dopamine receptor D3; Schizophrenia; Meta-analysis; Family study

Posted Date: July 28th, 2019

DOI: <https://doi.org/10.21203/rs.2.12020/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at BMC Medical Genetics on April 21st, 2020.

See the published version at <https://doi.org/10.1186/s12881-020-01018-w>.

Abstract

Background Ser9Gly (rs6280) is a functional single nucleotide polymorphism (SNP) in the human dopamine receptor D3 gene (*DRD3*). It is still controversial that whether Ser9Gly is involved in the occurrence of schizophrenia. Thus, a meta-analysis of family-based studies was performed to explore the role of Ser9Gly in the etiology of schizophrenia. Methods The published family-based association studies were searched from the relevant literature databases according to the established inclusion criteria. We generated odds ratios and 95% confidence intervals in order to determine the strength of the relationship between Ser9Gly SNP and the occurrence of schizophrenia. Results We finally pooled up 13 family-based association studies between Ser9Gly SNP and schizophrenia. It contained 11 transmission disequilibrium test (TDT) studies with 1219 informative meioses and 5 haplotype-based haplotype relative risk (HHRR) studies. There were no statistical significance for the heterogeneity in TDT and HHRR studies. Therefore, the fixed effect model was used to measure the pooled effect size. The results showed that neither of the associations between Ser9Gly and the risk of schizophrenia were observed in TDT and HHRR studies, except for the significantly preferential transmission of *DRD3* Ser9 allele in East Asian in TDT studies. Conclusions Our meta-analysis found no association between *DRD3* gene Ser9Gly polymorphism and the risk of schizophrenia. However, more effects need to further confirm the function of *DRD3* Ser9Gly SNP in the occurrence of schizophrenia.

1. Introduction

Schizophrenia is a complex mental disorder and affects approximately 1% of the population all over the world.¹ Multiple genetic and environmental factors are involved in the susceptibility of schizophrenia. Its heritability is almost up to 80%.² Despite the extensive efforts for many years, the precise etiology of this disease is still unclear.^{3,4} So far, although the etiology of schizophrenia is still not clear, the dysregulated dopaminergic neurotransmission is reported to play a role in the pathogenesis of schizophrenia.⁵⁻⁸ The genes related to the dopaminergic pathways are considered as the candidate susceptible genes of the disease.

As an endogenous neurotransmitter, dopamine plays a regulatory function by binding to the dopamine receptors. Its regulatory roles are mediated by two families of G protein-coupled receptors: the D1 and D2 receptor families. Presently, the known subtypes of dopamine receptors include the D1-like receptors, such as D1 and D5 receptors; and the D2-like receptors, such as D2, D3 and D4 receptors.⁹ Dopamine receptor D3 (*DRD3*) is a candidate susceptible gene for the risk of schizophrenia. *DRD3* is located on the chromosome 3 in the q13.3 band and its global homology is 52% with the D2 receptor band. It is primarily expressed in the limbic areas of human brain¹⁰ and involved a remarkable role in the emotional, cognitive, as well as endocrine functions.¹¹

Ser9Gly variant (rs6280) is a polymorphic site in the first exon, which corresponds to a serine to glycine amino acid substitution at position 9 in the extracellular N-terminal domain of *DRD3*. Ser9Gly SNP has

been involved in the alternation of dopamine binding affinity.¹² The substituted glycine allele is thought to yield D3 autoreceptors owning a higher affinity for dopamine and more robust intracellular signaling.¹³ Presently, Ser9Gly polymorphisms are reported to be associated with acute pain in sickle cell disease, bipolar disorder, Parkinson's disease, and suicidal behaviors.¹⁴⁻¹⁷ Recently, huge amount of molecular epidemiologic studies have addressed the association between Ser9Gly and schizophrenia risk. However, some reporters suggested that Ser9Gly was associated with the disease,^{18,19} whereas the others found no association.²⁰⁻²² These contradictory results may be due to small sample size, inclusion of various genetic backgrounds, and other potential confounding bias.²³

Meta-analyses are proven to be the powerful tool for ascertaining associations of gene polymorphisms with disease.^{24,25} Since 1998, the meta-analysis have been performed to assess the association between Ser9Gly SNP and schizophrenia risk.²⁶⁻³² However, all of the pooled results were based on the case-control studies, but not the family-based studies. The family-based studies are more powerful to detect risk factors of schizophrenia, considering that the ability to exploit the cosegregation of variants with schizophrenia within families helps distinguish causal from noncausal factors.³³ Therefore, we perform a meta-analysis of family-based association studies to better evaluate the relationship between *DRD3* Ser9Gly SNP and the risk of schizophrenia.

2. Materials And Methods

2.1. Literature search

To identify studies eligible for this meta-analysis, the computerized search was conducted on three online electronic English databases (PubMed, Embase, and Web of Science) and one online Chinese CNKI database using the following key words: "*DRD3*", "dopamine receptor 3", "dopamine D3 receptor", "dopamine receptor D3", "schizophrenia", and "Ser9Gly". We also used the reference lists of the accessed articles and of potentially relevant review articles to get additional studies.

2.2. Inclusion criteria

Only the studies examining Ser9Gly SNP were included in the present meta-analysis. Moreover, the studies needed to meet the following inclusion criteria: (1) family-based design (transmission disequilibrium test (TDT) or haplotype-based haplotype relative risk (HHRR)); (2) original data, or available data to calculate an effect; (3) independent from other studies (i.e., studies that contained the same or overlapping data were reported by the same authors, the most recent article was selected).

2.3. Meta-analytic methods

The meta-analysis of the family-based association studies was divided into two parts: TDT and HHRR. For the TDT study, each study provided the two-by-two transmission disequilibrium table, which classifies heterozygous parental alleles (informative meioses) by transmission status (Ser9 allele transmitted to the

schizophrenic offspring) and data type (the number of observed transmission vs. the number of theoretic transmission).³⁴ For the HHRR studies, each study provided the two-by-two HHRR table, which classifies parental alleles by type of allele (Ser9 or Gly9) and transmission status (transmitted to the schizophrenic offspring or not).³⁴

Odds ratios (ORs) with accompanying 95% confidence intervals (CIs) were used to assess the strength of the association in the two-by-two tables. The degree of heterogeneity between studies was determined by means of the Q statistic.^{35,36} Specifically, $P > 0.05$ by the Q test indicated the absence of heterogeneity, and $P < 0.05$ indicated heterogeneity. I^2 was defined as the proportion of observed variance in effect sizes attributable to true differences among studies. Conventional interpretations of I^2 include limits for low (<25%), moderate (approximately 50%), and high (>75%) heterogeneity.³⁷ A random effect model was used when heterogeneity was present ($p < 0.05$ and/or $I^2 > 50%$); otherwise, a fixed effect model was applied.³⁵ Pooled calculations of ORs were obtained and compared using test statistic z and 95% CIs. Subgroup analysis was carried out by ethnicity (ie, East Asian, Caucasian, and other populations).

Publication bias was assessed by the funnel plot (the standard normal deviate of the OR is regressed on the precision of the OR). When there is no publication bias, the regression line should pass through the origin, and the expected value of intercept will be zero.³⁴ All the calculations of the meta-analysis were conducted by Comprehensive Meta Analysis V2 software.

3. Results

A total of 13 articles were included in the present meta-analysis.^{26,38-49} Among them, 11 studies were for TDT and 5 studies were for HHRR.

Table 1 showed the ORs and 95% CIs for the 11 TDT studies. There was no statistical significance for the heterogeneity ($I^2=28.3%$) and the fix effect model was selected. The pooled results showed that there were no association between Ser9Gly SNP and schizophrenia (OR=1.005, 95% CI = 0.898-1.125, Z-value = 0.086, $p = 0.932$). Furthermore, we performed the subgroup analysis to further explore the association of Ser9Gly in Caucasian and East Asian populations, respectively. The results showed the significantly preferential transmission of *DRD3* Ser9 allele in East Asian (OR=0.744, 95% CI = 0.564-0.980, Z-value = -2.104, $p = 0.035$), but not in Caucasian (OR=1.053, 95% CI = 0.923-1.202, Z-value = 0.771, $p = 0.441$).

The studies distribution of the funnel plot was substantially symmetrical for the pooled effect size (Fig. 1). Thus, there was no publication bias for TDT studies.

Table 2 showed the ORs and 95% CIs for the 5 HHRR studies. There was no statistical significance for the heterogeneity ($I^2=30.372%$) and the fix effect model was selected. The pooled results showed that there were no association between Ser9Gly SNP and schizophrenia (OR=0.869, 95% CI = 0.713-1.059, Z-value = -1.395, $p = 0.163$). Furthermore, we performed the subgroup analysis to further explore the association of

Ser9Gly in Caucasian population. The results showed no significantly preferential transmission of *DRD3* Ser9 allele in Caucasian (OR=0.871, 95% CI = 0.604-1.254, Z-value = -0.744, $p = 0.457$).

The studies distribution of the funnel plot was slightly asymmetrical for the pooled effect size (Fig. 2). Thus, there was the moderate publication bias for HHRR studies.

4. Discussion

We conducted a meta-analysis of family-based association studies (11 for TDT and 5 for HHRR) to investigate the putative association of *DRD3* Ser9Gly SNP with the schizophrenia risk. Our final results suggested that no association were observed between Ser9Gly and the occurrence of schizophrenia in TDT and HHRR studies, except for the significantly preferential transmission of *DRD3* Ser9 allele in East Asian in TDT studies.

The previous meta-analyses have assessed the potential association of *DRD3* Ser9Gly with the risk of schizophrenia in case-control studies.^{27,28,30-32,50} The latest meta-analysis, which included seventy-three studies comprising 10,634 patients with schizophrenia (cases) and 11,258 controls, suggested that the Ser9Gly SNP is not associated with schizophrenia.³² Its finding was consistent with our study. Although the subgroup analysis of TDT meta-analysis observed the significant association between Ser9Gly and schizophrenia in East Asian population, it only included two studies with the limited sample size (204 meioses).^{43,44} Moreover, one study of HHRR in East Asian also found the significant association, but its sample size is still small (404 samples).⁴³ Thus, the positive results need to interpret cautiously and more work is required to validate the association in East Asian population.

Numerous candidate genes are involved in the susceptibility of the complex disease, such as schizophrenia. Family-based association studies can provide an informative way to investigate the putative susceptible genes. However, the genetic heterogeneity will complicate the etiology of schizophrenia because the allele distributions of *DRD3* Ser9Gly vary in different ethnicity population. Gly9 allele frequencies vary almost as much in the Japanese control populations (22%–34%) as they do in northern and western Caucasian control populations (30%–44%).^{28,32} Therefore, in order to reduce the genetic heterogeneity, it is necessary to study the homogeneous populations.

There are two limitations in our current meta-analysis. Initially, we detected a slight but significant publication bias in the HHRR studies. This bias might be due to only English- and Chinese-language studies included. Subordinately, we just evaluated the role of Ser9Gly SNP in the risk of schizophrenia. Nevertheless, only one variation just plays a minute role in the overall genetic susceptibility of the disease. Regrettably, the gene-gene interactions and epigenetics were not assessed without the sufficient information.

5. Conclusions

In conclusion, our meta-analysis of family-based association studies found no association between DRD3 Ser9Gly SNP and the risk of schizophrenia. The large sample homogeneous population studies need to further explore the role of DRD3 in the etiology of schizophrenia.

Abbreviations

SNP: single nucleotide polymorphism; **DRD3**: dopamine receptor D3; **TDT**: transmission disequilibrium test; **HHRR**: haplotype-based haplotype relative risk; **ORs**: Odds ratios; **CIs**: confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study was supported by National Natural Science Foundation of China (No.81601653) and Doctoral Research Start Foundation of Liaoning Province (201601115).for Dr. Jun Yao.

Competing interests

The authors declare that they have no competing interests.

Author Contributions

XNL and JY conceived and designed the experiments. XNL and BJW searched the literature, extracted and analyzed the data. JY wrote the paper.

Acknowledgements

Not applicable

References

1. Hoenders R, Bartels-Velthuis A, Vollbehr N, Bruggeman R, Knechtering R, de Jong J. Natural medicines in schizophrenia: a systematic review. *Journal of alternative and complementary medicine*. May 2014;20(5):A79. 2. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Archives of general psychiatry*. Dec 2003;60(12):1187-1192. 3. Mueser KT, McGurk SR. Schizophrenia. *Lancet*. Jun 19 2004;363(9426):2063-2072. 4. Heron EA, Cormican P, Donohoe G, et al. No evidence that runs of homozygosity are associated with schizophrenia in an Irish genome-wide association dataset. *Schizophrenia research*. Apr 2014;154(1-3):79-82. 5. Abi-Dargham A, Moore H. Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *The Neuroscientist : a review journal bringing neurobiology, neurology and psychiatry*. Oct 2003;9(5):404-416. 6. Fan H, Zhang F, Xu Y, et al. An association study of DRD2 gene polymorphisms with schizophrenia in a Chinese Han population. *Neuroscience letters*. Jun 21 2010;477(2):53-56. 7. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophrenia bulletin*. May 2009;35(3):549-562. 8. Davis J, Moylan S, Harvey BH, Maes M, Berk M. Neuroprogression in schizophrenia: Pathways underpinning clinical staging and therapeutic corollaries. *The Australian and New Zealand journal of psychiatry*. May 6 2014. 9. Yamamoto K, Fontaine R, Pasqualini C, Vernier P. Classification of Dopamine Receptor Genes in Vertebrates: Nine Subtypes in Osteichthyes. *Brain, behavior and evolution*. 2015;86(3-4):164-175. 10. Sokoloff P, Giros B, Martres MP, et al. Localization and function of the D3 dopamine receptor. *Arzneimittel-Forschung*. Feb 1992;42(2A):224-230. 11. Yang B, Niu W, Chen S, et al. Association study of dopamine receptor genes polymorphisms with the risk of schizophrenia in the Han Chinese population. *Psychiatry research*. Nov 30 2016;245:361-364. 12. Utsunomiya K, Shinkai T, Sakata S, et al. Genetic association between the dopamine D3 receptor gene polymorphism (Ser9Gly) and tardive dyskinesia in patients with schizophrenia: a reevaluation in East Asian populations. *Neuroscience letters*. Jan 17 2012;507(1):52-56. 13. Savitz J, Hodgkinson CA, Martin-Soelch C, et al. The functional DRD3 Ser9Gly polymorphism (rs6280) is pleiotropic, affecting reward as well as movement. *PloS one*. 2013;8(1):e54108. 14. Jhun E, He Y, Yao Y, Molokie RE, Wilkie DJ, Wang ZJ. Dopamine D3 receptor Ser9Gly and catechol-o-methyltransferase Val158Met polymorphisms and acute pain in sickle cell disease. *Anesthesia and analgesia*. Nov 2014;119(5):1201-1207. 15. Chang TT, Chen SL, Chang YH, et al. The DRD3 Ser9Gly Polymorphism Predicted Metabolic Change in Drug-Naive Patients With Bipolar II Disorder. *Medicine*. Jun 2016;95(24):e3488. 16. Xu S, Liu J, Yang X, Qian Y, Xiao Q. Association of the DRD2 CAn-STR and DRD3 Ser9Gly polymorphisms with Parkinson's disease and response to dopamine agonists. *Journal of the neurological sciences*. Jan 15 2017;372:433-438. 17. Zai CC, Manchia M, Sonderby IE, et al. Investigation of the genetic interaction between BDNF and DRD3 genes in suicidal behaviour in psychiatric disorders. *The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry*. Apr 2015;16(3):171-179. 18. Crocq MA, Mant R, Asherson P, et al. Association between schizophrenia and homozygosity at the dopamine D3 receptor gene. *Journal of medical genetics*. Dec 1992;29(12):858-860. 19. Nimgaonkar VL, Sanders AR, Ganguli R, et al. Association study of schizophrenia and the dopamine D3 receptor gene locus in two independent samples. *American journal of medical genetics*. Nov 22 1996;67(6):505-514. 20. Ayoub N, Jeyasekharan AD, Bernal JA, Venkitaraman AR. HP1-beta mobilization promotes chromatin changes that initiate the DNA damage response. *Nature*. May 29 2008;453(7195):682-686. 21. Chen CH, Liu MY, Wei FC, Koong FJ,

Hwu HG, Hsiao KJ. Further evidence of no association between Ser9Gly polymorphism of dopamine D3 receptor gene and schizophrenia. *American journal of medical genetics*. Feb 21 1997;74(1):40-43. 22. Barlas IO, Cetin M, Erdal ME, et al. Lack of association between DRD3 gene polymorphism and response to clozapine in Turkish schizophrenia patients. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. Jan 05 2009;150B(1):56-60. 23. Yao J, Pan YQ, Ding M, Pang H, Wang BJ. Association between DRD2 (rs1799732 and rs1801028) and ANKK1 (rs1800497) polymorphisms and schizophrenia: a meta-analysis. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. Jan 2015;168B(1):1-13. 24. Lanara Z, Giannopoulou E, Fullen M, et al. Comparative study and meta-analysis of meta-analysis studies for the correlation of genomic markers with early cancer detection. *Human genomics*. Jun 5 2013;7:14. 25. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. *Journal of epidemiology and community health*. Nov 1 2013;67(11):974-978. 26. Williams J, Spurlock G, Holmans P, et al. A meta-analysis and transmission disequilibrium study of association between the dopamine D3 receptor gene and schizophrenia. *Molecular psychiatry*. Mar 1998;3(2):141-149. 27. Dubertret C, Gorwood P, Ades J, Feingold J, Schwartz JC, Sokoloff P. Meta-analysis of DRD3 gene and schizophrenia: ethnic heterogeneity and significant association in Caucasians. *American journal of medical genetics*. Jul 10 1998;81(4):318-322. 28. Jonsson EG, Flyckt L, Burgert E, et al. Dopamine D3 receptor gene Ser9Gly variant and schizophrenia: association study and meta-analysis. *Psychiatric genetics*. Mar 2003;13(1):1-12. 29. Jonsson EG, Kaiser R, Brockmoller J, Nimgaonkar VL, Crocq MA. Meta-analysis of the dopamine D3 receptor gene (DRD3) Ser9Gly variant and schizophrenia. *Psychiatric genetics*. Mar 2004;14(1):9-12. 30. Utsunomiya K, Shinkai T, De Luca V, et al. Genetic association between the dopamine D3 gene polymorphism (Ser9Gly) and schizophrenia in Japanese populations: evidence from a case-control study and meta-analysis. *Neuroscience letters*. Oct 24 2008;444(2):161-165. 31. Nunokawa A, Watanabe Y, Kaneko N, et al. The dopamine D3 receptor (DRD3) gene and risk of schizophrenia: case-control studies and an updated meta-analysis. *Schizophrenia research*. Jan 2010;116(1):61-67. 32. Qi XL, Xuan JF, Xing JX, Wang BJ, Yao J. No association between dopamine D3 receptor gene Ser9Gly polymorphism (rs6280) and risk of schizophrenia: an updated meta-analysis. *Neuropsychiatric disease and treatment*. 2017;13:2855-2865. 33. Yang Z, Thomas DC. Two-stage family-based designs for sequencing studies. *BMC proceedings*. 2014;8(Suppl 1):S32. 34. Yang B, Chan RC, Jing J, Li T, Sham P, Chen RY. A meta-analysis of association studies between the 10-repeat allele of a VNTR polymorphism in the 3'-UTR of dopamine transporter gene and attention deficit hyperactivity disorder. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. Jun 5 2007;144B(4):541-550. 35. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Bmj*. Sep 6 2003;327(7414):557-560. 36. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. *Genetic epidemiology*. Feb 2005;28(2):123-137. 37. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*. Jun 15 2002;21(11):1539-1558. 38. Macciardi F, Verga M, Kennedy JL, et al. An association study between schizophrenia and the dopamine receptor genes DRD3 and DRD4 using haplotype relative risk. *Human heredity*. Nov-Dec 1994;44(6):328-336. 39. Rothschild LG, Badner J, Cravchik A, Gershon ES, Gejman PV.

No association detected between a D3 receptor gene-expressed variant and schizophrenia. *American journal of medical genetics*. Apr 9 1996;67(2):232-234. 40. Malhotra AK, Goldman D, Buchanan RW, et al. The dopamine D3 receptor (DRD3) Ser9Gly polymorphism and schizophrenia: a haplotype relative risk study and association with clozapine response. *Molecular psychiatry*. Jan 1998;3(1):72-75. 41. Kalsi G, Curtis D, Brynjolfsson J, et al. Tests of linkage, allelic and genotypic association between schizophrenia and the gene for the D3 dopamine receptor, DRD3. *Psychiatric genetics*. Autumn 1998;8(3):187-189. 42. Ambrosio AM, Kennedy JL, Macciardi F, et al. Family association study between DRD2 and DRD3 gene polymorphisms and schizophrenia in a Portuguese population. *Psychiatry research*. Mar 15 2004;125(3):185-191. 43. Luxian Lu HZ, Suqin Guo, Yuzhong Shi. Association between DRD3 gene Ser9Gly polymorphism and schizophrenia in center families. *Journal of Fourth Military Medical University*. 2005;26(24):2261-2264. 44. Yuhong Wang YS, Luixan Lu, et al. Association of dopamine D3 receptor Ser9Gly polymorphism with schizophrenia. *Journal of Clinical Psychology Medicine*. 2006;16(1):38-39. 45. Talkowski ME, Mansour H, Chowdari KV, et al. Novel, replicated associations between dopamine D3 receptor gene polymorphisms and schizophrenia in two independent samples. *Biological psychiatry*. Sep 15 2006;60(6):570-577. 46. Pawel K, Hauser J, Skibinska M, et al. [Family based association study of DRD1, DRD2, DRD3, DRD4, DAT, COMT gene polymorphism in schizophrenia]. *Psychiatria polska*. May-Jun 2010;44(3):405-413. 47. Prasad S, Deshpande SN, Bhatia T, Wood J, Nimgaonkar VL, Thelma BK. Association study of schizophrenia among Indian families. *American journal of medical genetics*. Aug 20 1999;88(4):298-300. 48. Kremer I, Rietschel M, Dobrusin M, et al. No association between the dopamine D3 receptor Bal I polymorphism and schizophrenia in a family-based study of a Palestinian Arab population. *American journal of medical genetics*. Dec 4 2000;96(6):778-780. 49. Zai CC, Manchia M, De Luca V, et al. Association study of BDNF and DRD3 genes in schizophrenia diagnosis using matched case-control and family based study designs. *Progress in neuro-psychopharmacology & biological psychiatry*. Dec 1 2010;34(8):1412-1418. 50. Ma G, He Z, Fang W, et al. The Ser9Gly polymorphism of the dopamine D3 receptor gene and risk of schizophrenia: an association study and a large meta-analysis. *Schizophrenia research*. Apr 2008;101(1-3):26-35.

Tables

Due to technical limitations, tables are only available as a download in the supplemental files section.

Figures

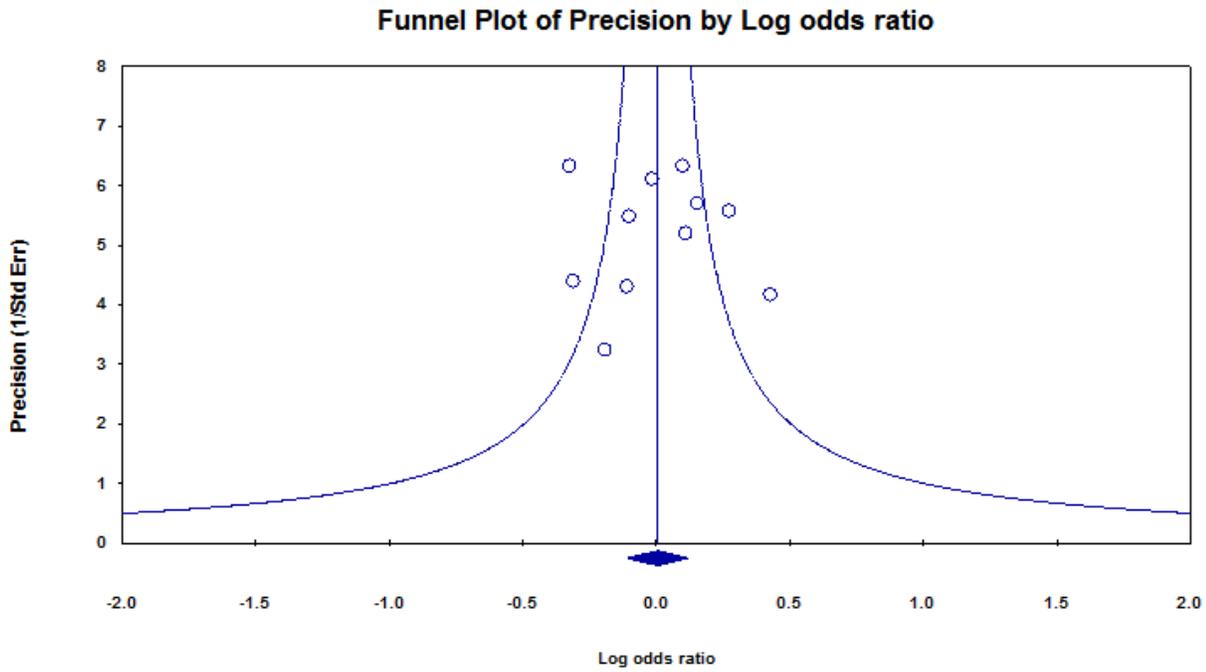


Figure 1

Funnel plot of study precision by log odds ratio for TDT studies.

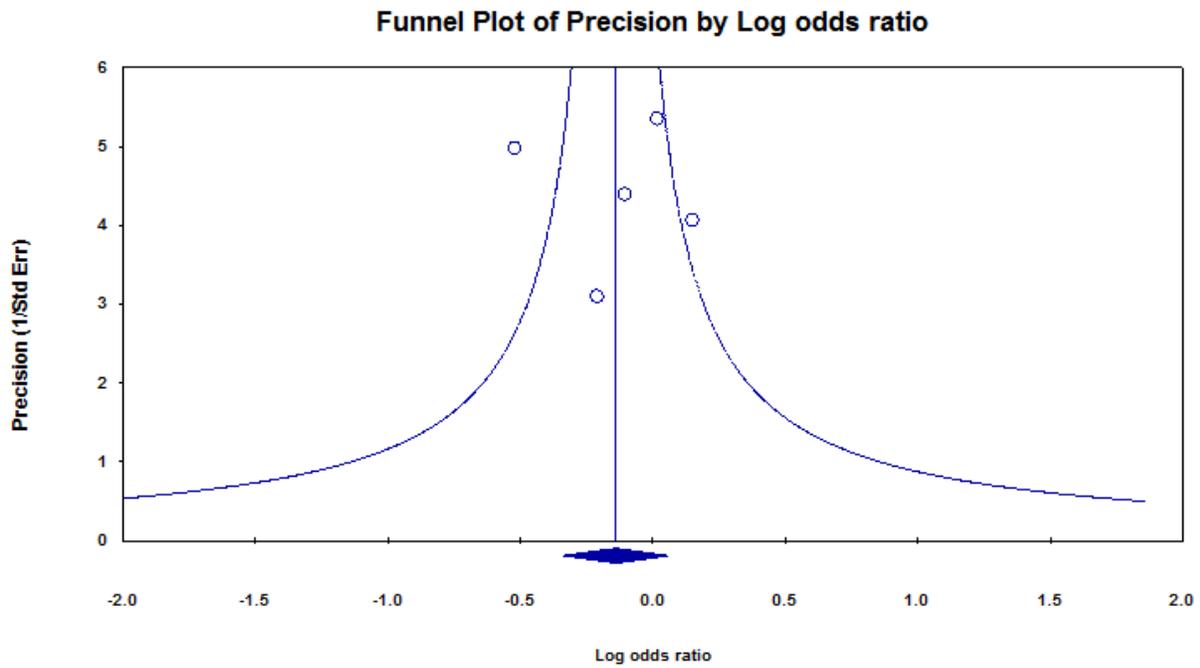


Figure 2

Funnel plot of study precision by log odds ratio for HHRR studies.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.pdf](#)
- [supplement1.pdf](#)
- [supplement3.pdf](#)