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# Association between the DRD2 TaqIA gene polymorphism and Parkinson disease risk: an updated meta-analysis

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**Abstract**

**Background:** DRD2 TaqIA polymorphism may be associated with an increased risk of developing Parkinson disease (PD). However, the individual study's results are still inconsistent.

**Methods:** A meta-analysis of 4232 cases and 4774 controls from 14 separate studies were performed to explore the possible relationship between the DRD2 TaqIA gene polymorphism and PD. Pooled odds ratios (ORs) for the association and the corresponding 95% confidence intervals (CIs) were evaluated by a fixed-effect model.

**Results:** The pooled results revealed a significant association between DRD2 gene TaqIA polymorphism under recessive genetic model (OR: 0.91, 95% CI:0.83,0.99, $P=.031$) and additive genetic models (OR:0.93,95%CI:0.87,0.99, $P=.032$), but not associated with PD susceptibility under other genetic models in the whole population. Moreover, subgroups based on ethnicity and genotyping methods showed this association in the Caucasian subgroup under recessive genetic model (OR: 0.85, 95% CI:0.76,0.95, $P=.003$) and additive genetic models (OR:0.87,95%CI:0.79,0.96, $P=.004$) were existed. Besides, no significant association was detected under 6 genetic models in the Asian populations and PCR-RFLP subgroup.

**Conclusions:** The current meta-analysis suggested that a significant association between DRD2 TaqIA polymorphism and PD under the recessive genetic mode, and additive genetic models, especially in Caucasians.

**Abbreviations:** CI = confidence interval, DRD2 = dopamine D2 receptor, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa Scale, OR = odd ratio, PD = Parkinson disease.

**Keywords:** dopamine D2 receptor, meta-analysis, Parkinson disease, polymorphisms, TaqIA

## 1. Introduction

Parkinson disease (PD), also known as paralysis agitans, is commonly found in middle-aged and elderly patients. It is clinically characterized by resting tremor, bradykinesia, muscle rigidity, and posture balance disorder.[1] It is the second most common neurodegenerative disorder around the world, and with the advent of an aging society, the increase in the aging population has led to a significant increase in the global prevalence of PD.[2] It is expected that by 2030, the number of patients of PD will be between 8.7 and 9.3 million.[3] Due to the long course, high disability rate and lack of effective treatment of this disease, PD affects the quality of life of patients and causes a serious financial burden both for families and society.[4]

Although the initial triggering factors remain unknown, emerging studies suggest that PD is generally as a multifactorial disorder, which may cause by the combination and intricate interplay between genes and environmental factors.[3] Previous studies demonstrated that the degeneration of dopaminergic neurons in the substantia nigra is one of the pathogenesis of PD.[5,6] Dopamine is an important substance for control of motor and cognitive functions and plays its role through interaction with receptors that are part of the seven transmembrane domain G protein-coupled receptors family.[7–9] The animal experiments suggested that dopamine D2 receptor (DRD2) is particularly relevant to locomotor function and sensory processing for mice appearing parkinsonian-like phenotype,[10,11] and dopamine agonists with high selectivity for DRD2 have also already been used to improve symptoms.[1,12,13] Costa et al [14] demonstrated that the genetic mutation in the gene DRD2 located on chromosome 11q22-q23 is related to the occurrence of PD. Several case-control trials have been carried out to prove the correlation between DRD2 TaqIA polymorphism and PD,[15,16] while others revealed no association.[17,18] Dai et al[19] performed a meta-analysis on the DRD2 TaqIA polymorphism and showed that the DRD2 TaqIA polymorphism might not be a genetic risk factor for PD. Since several researches[20,18] on DRD2

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MY and FH contributed equally to this paper.

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polymorphism have been reported appearing different results with the one reported by Dai et al in recent years. Considering the inconsistent results in these researches, a comprehensive meta-analysis of case-control was performed to integrate results from multiple studies in an unbiased fashion, and provide a prescription for basic research and clinical diagnosis.

## 2. Methods and materials

This system review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[21] Ethical approval was unnecessary in this study because this paper was based on the previous articles.

### 2.1. Search strategy

Data were collected from the Cochrane Library, PubMed, Embase, Web of Science, China National Knowledge Infrastructure, WanFang and VIP databases, using the search terms "DRD2", "rs1800497", "Parkinson disease" and "polymorphism". The last research was performed on January 23, 2019. The search was restricted to English and Chinese language publications. Relevant publications were also identified via searched reference lists of articles identified in the initial searches.

### 2.2. Inclusion and exclusion criteria

Included criteria of eligible studies were as follows: (1) case–control or cohort studies; (2) investigating the association between DRD2 TaqIA polymorphism and Parkinson disease; (3) reported sufficient data of cases and controls to calculate an odd ratio (OR) with 95% confidence interval (CI); (4) Genotype in control group follows Hardy–Weinberg equilibrium (HWE).

Studies were excluded for the major following reasons: (1) animal trials, review, abstract, or conference literature; (2) the genotype frequency of cases and controls were not reported; (3) duplication of previous publications.

### 2.3. Data extraction and quality assessment

Included data were extracted using a standardized protocol. Two investigators independently reviewed and extracted data from all eligible studies according to the inclusion and exclusion criteria. Inconsistencies were resolved by discussion with a third researcher. The following data was extracted from included eligible studies: the first author, years of publication, country, ethnicity, genotyping method, sample size, number of genotypes, Hardy–Winberg equilibrium. The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS).[22] The NOS ranges from 0 to 9 stars, and scores equal to or higher than 7 was regarded high quality. Disagreement was resolved as through discussion.

### 2.4. Statistical analyses

Statistical analyses were performed using Stata 12.0 software (StataCorp, College Station, TX). In the present meta-analysis, six genetic models as the allelic, recessive, dominant, homozygous, heterozygous, and additive genetic models, and subgroup analyses were performed based on the ethnicities or genotyping methods. The pooled odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were used to assess the strength of association between DRD2 TaqIA polymorphism and PD risk, $P<.05$ was considered as statistically significant. The Chi-square test and $I^2$ test were used to assess heterogeneity among the studies. If $P>.10$ or $I^2<50\%$, suggesting the existence of heterogeneity and the fixed-effect model was adopted. Otherwise, the random-effect model would be used. Sensitivity analysis was performed to evaluate the stability of pooled results. Begg funnel plot and Egger linear regression test was used to estimate potential publication bias. Moreover, the Fisher exact test was used to evaluate whether genotype distribution of the control group follow HWE.

## 3. Results

### 3.1. Characteristics of the included studies

After a preliminary online search, 633 studies were identified for further detailed evaluation. Among which 74 studies were removed due to duplication, and 534 articles were excluded because they failed to meet the inclusion criteria. Ultimately, 14 articles[14,17,20,18,23–32] were included in the analysis (Fig. 1). Of all the studies, 7 were Caucasians and 7 were Asian population and involved 4232 cases and 4774 controls. Because the same controls were used by the two researches written by lee in 2009 and 2011, we combined these two studies into one for analysis. These studies were published between 1999 and 2016. All the studies included in the meta-analysis were conformed to HWE in the control groups (Table 1).

### 3.2. Pooled analyses

There was a significant association between DRD2 TaqIA polymorphism and PD susceptibility in the whole population under recessive genetic mode (OR: 0.91, 95% CI:0.83,0.99, $P=.031$), and additive genetic models (OR:0.93,95% CI:0.87,0.99, $P=0.032$).Rather, DRD2 TaqIA polymorphism was not associated with PD susceptibility in the whole population under allelic (OR: 0.98, 95% CI: 0.93,1.03, $P=.372$), dominant (OR: 1.08, 95% CI: 0.94,1.25, $P=.280$), homozygous (OR: 0.91, 95% CI: 0.78,1.06, P=.185), heterozygous (OR: 0.96, 95% CI:0.83,1.10, $P=.544$). Meanwhile, no significant heterogeneity was detected under all 6 genetic models ($P>.05$) (Figs. 2–7, Table 2).

Subgroups based on ethnicity and genotyping methods were performed to further analyze the relationship of polymorphism with PD. In the Caucasian subgroup, a significant association between them was also detected under the recessive genetic model and additive genetic models ($P<.05$) (Table 3). Rather, we did not observe any correlation of DRD2 TaqIA polymorphism with PD susceptibility in all the 6 genetic models in the Asian populations ($P>.05$) (Table 3).

In the TaqMan subgroup, a marginally significant effect between them was also detected under the additive genetic model (OR: 0.92, 95% CI: 0.85,1.00, $P=.051$) (Table 4). In addition, no significant association was detected under 6 genetic model in PCR-RFLP subgroup ($P>.05$) (Table 4).

### 3.3. Sensitivity analysis

Sensitivity analysis was performed by excluding one study to assess the influence of any single study and found that no

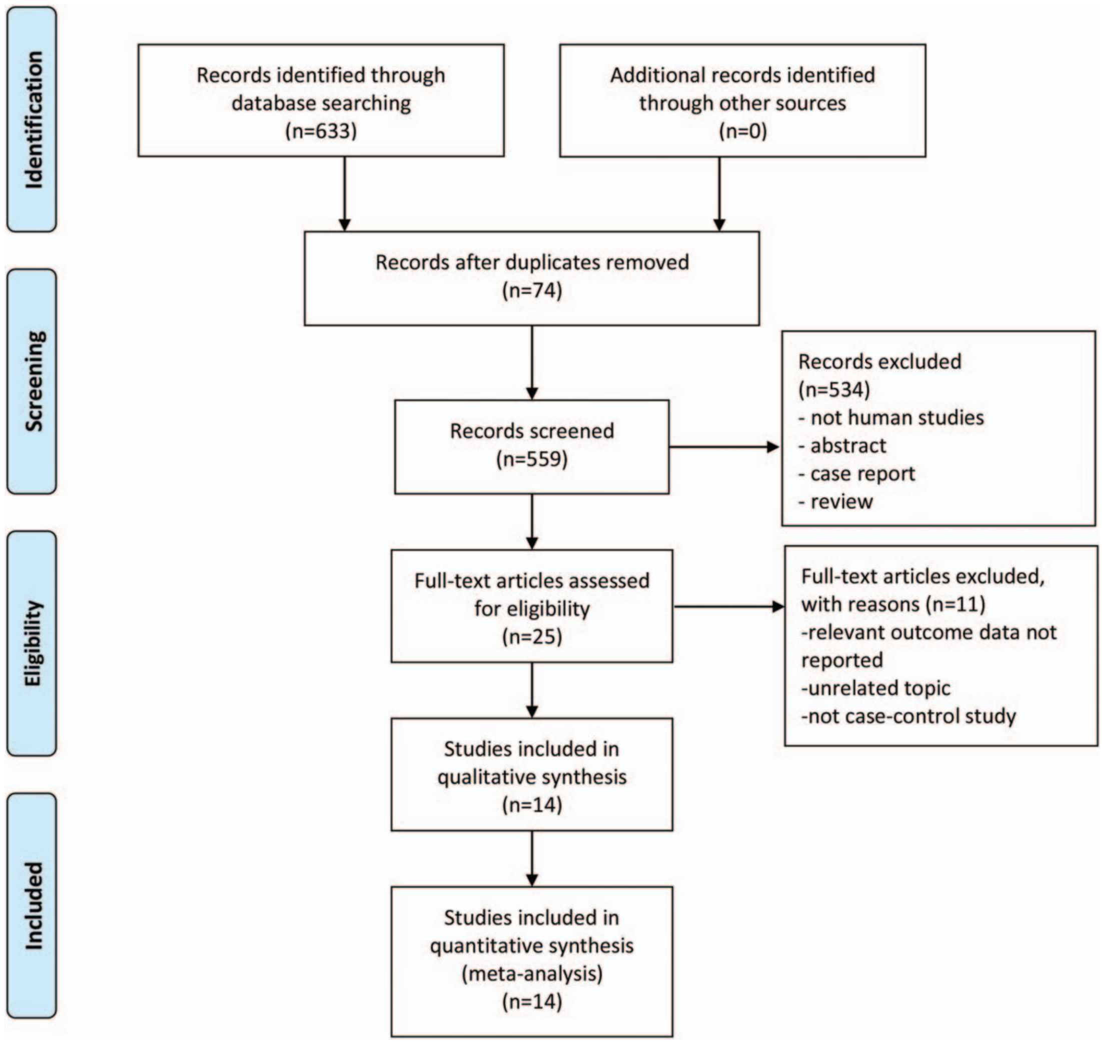


**Figure 1.** Flow diagram of study selection process.

**Table 1**

**Characteristics of the investigated studies of the association between the DRD2 TaqIA polymorphism and Parkinson disease.**

| | | | | | | Case | | | Controls | | | HWE | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First author | Year | Country | Ethnicity | Genotyping method | Sample size (cases/controls) | A1A1 | A1A2 | A2A2 | A1A1 | A1A2 | A2A2 | Cases | Control | Quality score |
| Chen | 2006 | China | Asian | PCR-RFLP | 180/387 | 36 | 80 | 64 | 62 | 184 | 141 | 0.232 | 0.879 | 7 |
| Wang | 1999 | China | Asian | PCR-RFLP | 140/141 | 23 | 73 | 44 | 27 | 80 | 34 | 0.429 | 0.102 | 7 |
| Li | 2009 | China | Asian | PCR-RFLP | 166/170 | 31 | 75 | 60 | 31 | 81 | 58 | 0.381 | 0.770 | 7 |
| Costa-Mallen | 2000 | USA | Caucasian | PCR-RFLP | 125/202 | 4 | 37 | 84 | 8 | 59 | 135 | 0.976 | 0.629 | 8 |
| Singh | 2008 | India | Caucasian | PCR-RFLP | 70/100 | 4 | 28 | 38 | 14 | 37 | 49 | 0.694 | 0.117 | 8 |
| Oliveri | 2000 | Italy | Caucasian | PCR-RFLP | 135/202 | 4 | 48 | 83 | 5 | 49 | 148 | 0.344 | 0.696 | 8 |
| Lee[a] | 2011 | Korea | Asian | TaqMan | 912/559 | 155 | 453 | 295 | 91 | 272 | 196 | 0.386 | 0.836 | 8 |
| Grevle | 2000 | Norway | Caucasian | PCR-RFLP | 72/81 | 1 | 28 | 43 | 1 | 18 | 62 | 0.129 | 0.810 | 8 |
| Kumudini | 2013 | India | Caucasian | PCR-RFLP | 150/186 | 15 | 75 | 60 | 21 | 74 | 91 | 0.226 | 0.319 | 7 |
| Kiyohara | 2011 | Japan | Asian | TaqMan | 238/369 | 29 | 117 | 92 | 52 | 192 | 125 | 0.377 | 0.111 | 7 |
| McGuire | 2011 | USA | Caucasian | TaqMan | 1176/1443 | 69 | 378 | 729 | 66 | 461 | 916 | 0.035 | 0.413 | 7 |
| Hassan | 2016 | USA | Caucasian | TaqMan | 664/718 | 34 | 225 | 405 | 25 | 212 | 481 | 0.705 | 0.783 | 8 |
| Tan | 2003 | Singapore | Asian | PCR-RFLP | 204/216 | 36 | 94 | 74 | 35 | 100 | 81 | 0.518 | 0.658 | 8 |

HWE = Hardy–Weinberg equilibrium; a, case group represents Lee 2009 plus Lee 2011.

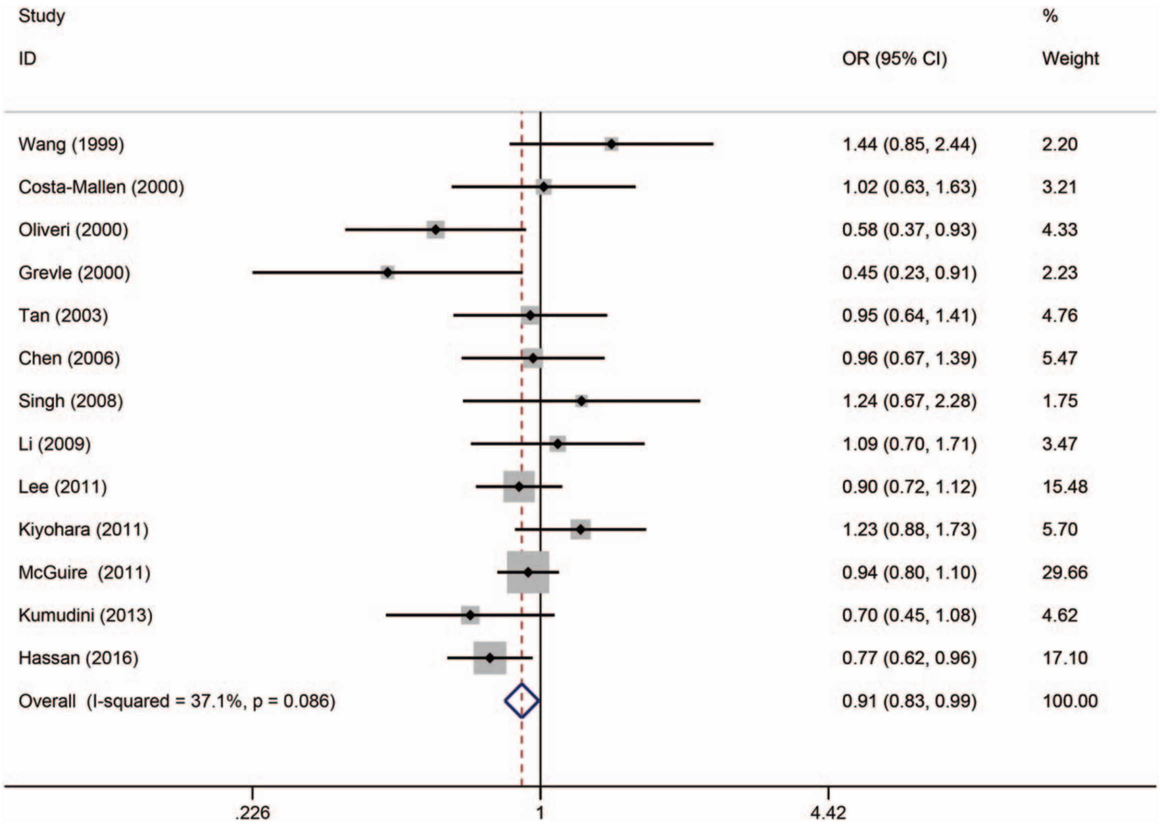


**Figure 2.** Forest plots for the association between DRD2 TaqIA polymorphism and PD risk under recessive genetic model (A2A2 vs A1A1 + A1A2).

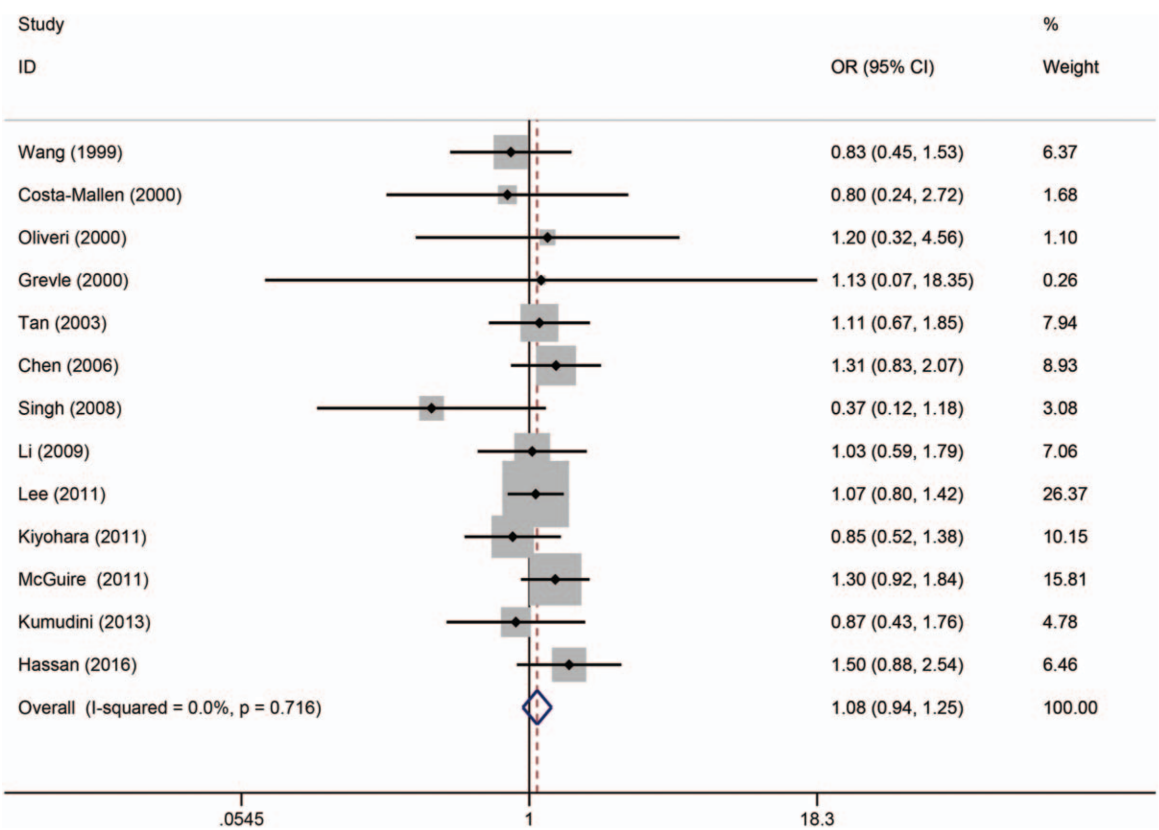


**Figure 3.** Forest plots for the association between DRD2 TaqIA polymorphism and PD risk under dominant genetic model (A1A1 vs A1A2 + A2A2).

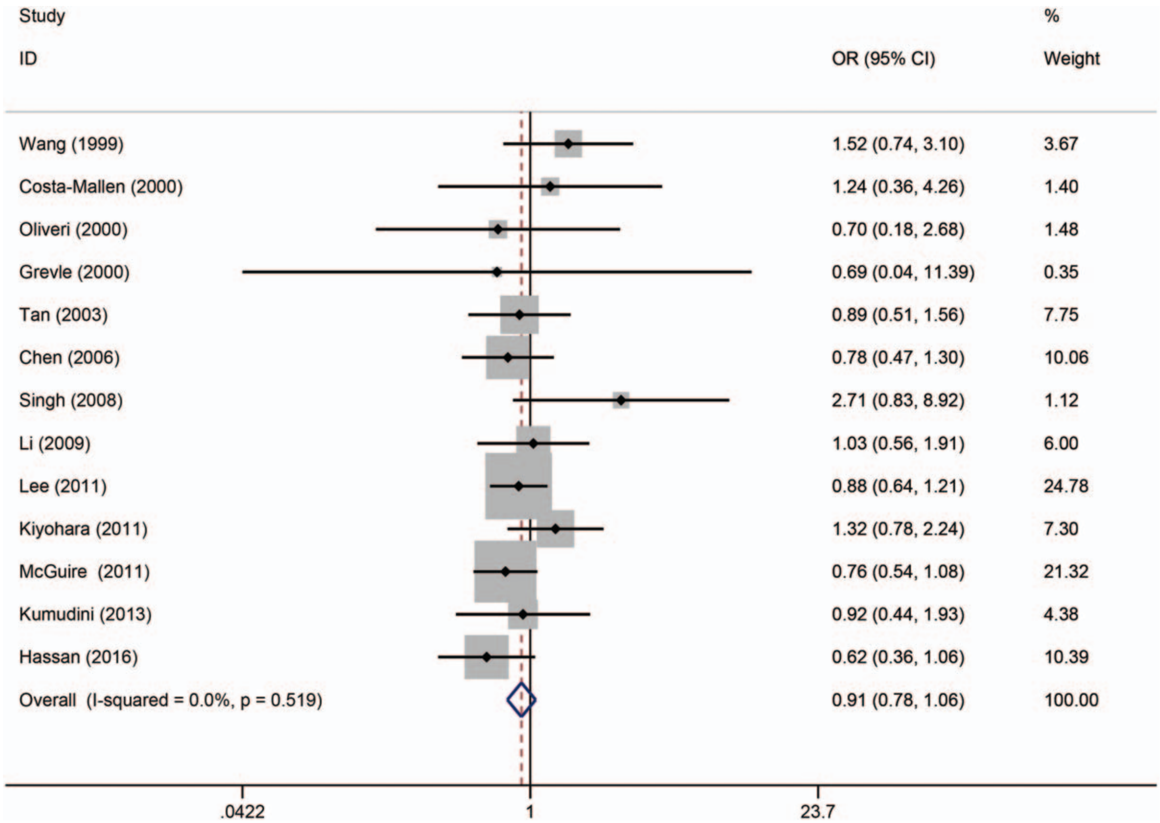


**Figure 4.** Forest plots for the association between DRD2 TaqIA polymorphism and PD risk under homozygous model (A2A2 vs A1A1).

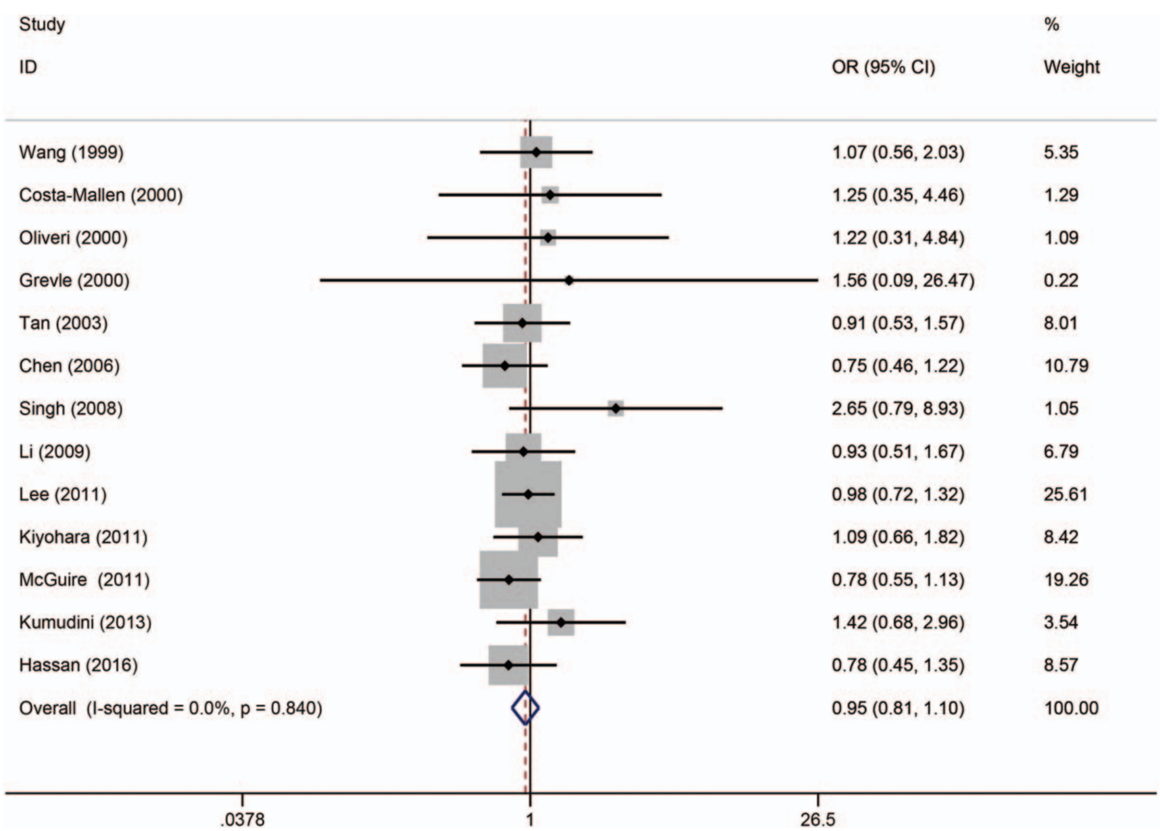


**Figure 5.** Forest plots for the association between DRD2 TaqIA polymorphism and PD risk under heterozygous model (A1A2 vs A1A1).

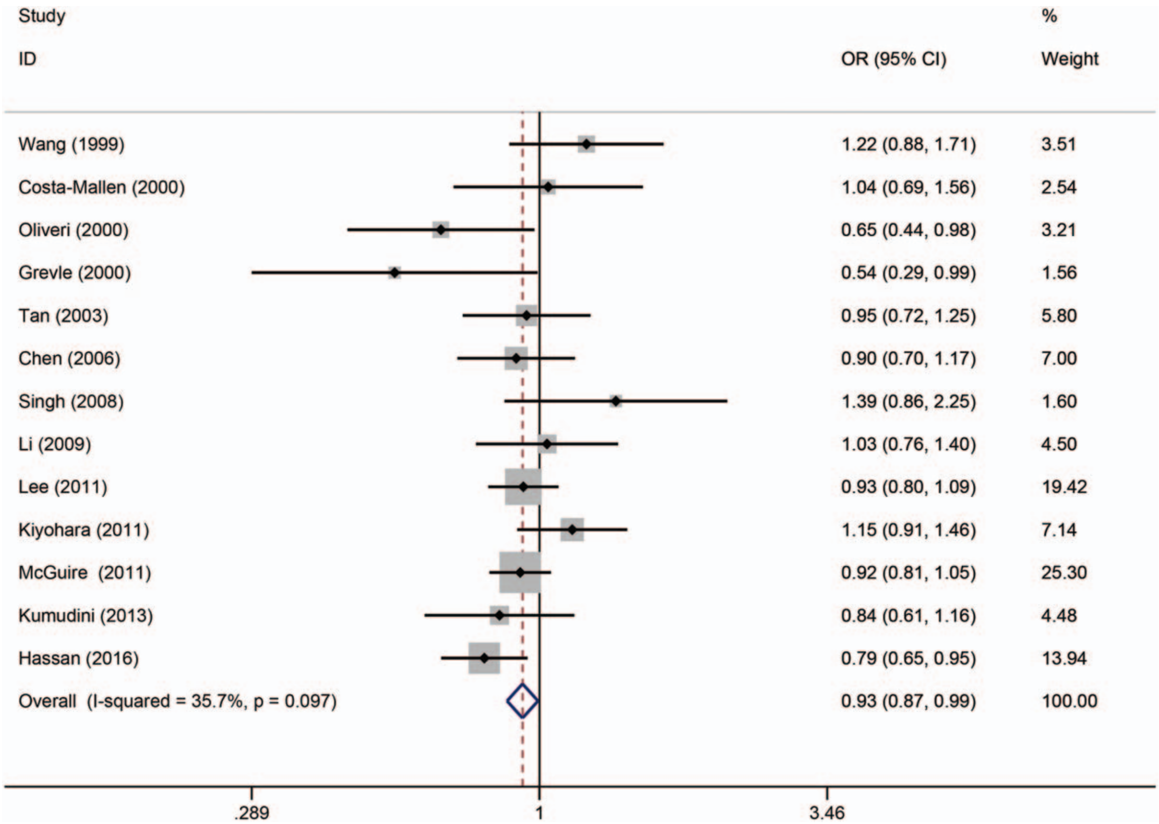


**Figure 6.** Forest plots for the association between DRD2 TaqIA polymorphism and PD risk under addictive genetic model (A2 vs A1).

significant change in the pooled ORs under the additive genetic model (Fig. 8). This result suggested that our findings are realistic and reliable.

### 3.4. Bias diagnostics

The publication bias of the individual studies was evaluated by using the funnel plot and Egger test. No visual evidence for publication bias was evident in the funnel plot under the additive genetic model (Fig. 9). No significant difference in the Egger test that implied no publication bias existed in the present meta-analysis under the additive genetic model ($T=.15$, $P=.880$). Moreover, Begg and Egger tests also revealed no publication bias in the overall analysis as well as subgroup analyses (Tables 1–4), except under the heterozygous genetic model in PCR-RFLP subgroup.

## 4. Discussion

In the current meta-analysis study, we summarized the relationship between DRD2 gene mutation and PD in 14 studies of 4232 cases and 4774 controls, and researched on different races, then obtained a relative objective conclusion.

Our study found that there is a significant association between DRD2 TaqIA polymorphism and PD susceptibility in the whole population under the recessive genetic mode, and additive genetic models, which is different from the meta-analyses reported by Dai et al.[19] Similarly, polymorphisms in DRD2 TaqIA were not associated with PD in other genetic models. The main reason for this difference may be the increase of included studies, reducing the bias of results due to the small sample size, and thus obtaining more accurate conclusions. The frequencies of gene polymorphisms are likely to differ in different ethnicities,[33] so the ethnic-based subgroup analysis can further demonstrate the relationship between DRD2 TaqIA polymorphism and PD. The difference in the effects of various genotypes on PD in the whole population is particularly pronounced among Caucasians. In the Asian population, we did not observe any correlation of DRD2 TaqIA polymorphism with PD susceptibility in all the 6 genetic models. This ethnic difference may be mainly due to the results of a multi-ethnic large-sample study[27] that is firmly demonstrated the association between homozygous TaqIA and PD risk in non-Hispanic white subjects, and non-Hispanic white who carried two TaqIA alleles had a 50% increased risk of PD.[34] Additionally, it statistically suggests that the DRD2 variant allele A2 significantly increases the risk of developing PD.[23]

Interestingly, subgroup analysis using the genotyping method also showed the difference between the 2 methods. In the TaqMan subgroup, a significant association between them was also detected under the additive genetic model. But no significant association was found under 6 genetic models in PCR-RFLP subgroup. We note several studies using TaqMan, and speculate that the reason for this difference may be the frequency of homozygous variant for Taq1 appearing more frequently than the PCR-RFLP subgroup. In other genes and disease models,[35] the 2 genotype detection methods were also compared, and the result showed no statistical significance. As to whether the 2 methods of detection have an impact on the result, more researches and larger sample size are needed to prove.

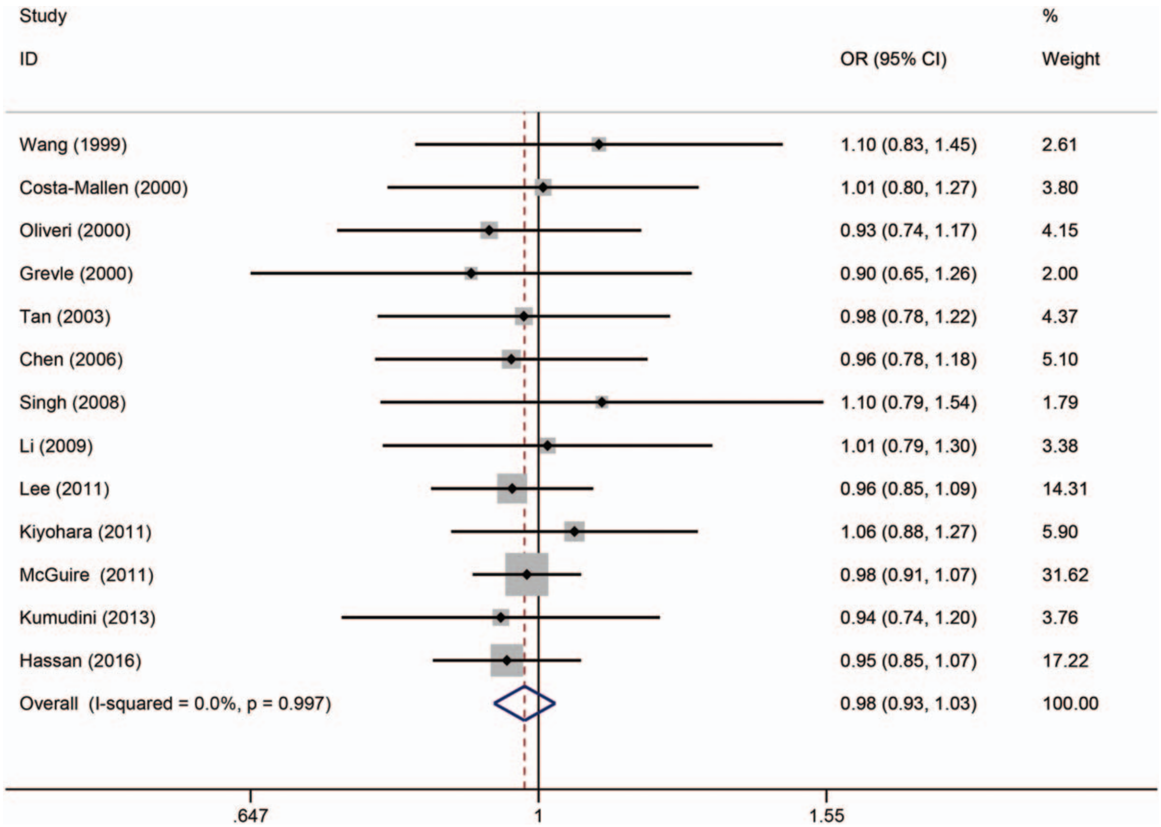


**Figure 7.** Forest plots for the association between DRD2 TaqIA polymorphism and PD risk under allelic genetic model (A2 allele distribution frequency of DRD2 TaqIA gene polymorphism).

**Table 2**

**Summary of meta-analysis of association of DRD2 TaqIA polymorphism and Parkinson disease in the whole population.**

| | | Overall effect | | | Heterogeneity | | Publication bias | |
|---|---|---|---|---|---|---|---|---|
| Comparison | Studies | OR (95% CI) | *Z* score | *P* value | $I^2$ (%) | *P* value | Begg test | Egger test |
| Recessive genetic mode | 13 | 0.91 (0.83,0.99) | 2.16 | .031 | 37.1 | .086 | 1.000 | 0.975 |
| Dominant genetic model | 13 | 1.08 (0.94,1.25) | 1.08 | .280 | 0 | .716 | 0.393 | 0.182 |
| Homozygous genetic model | 13 | 0.91 (0.78,1.06) | 1.33 | .185 | 0 | .519 | 0.329 | 0.211 |
| Heterozygous genetic model | 13 | 0.95 (0.81,1.10) | 0.61 | .544 | 0 | .840 | 0.067 | 0.052 |
| Additive genetic model | 13 | 0.93 (0.87,0.99) | 2.15 | .032 | 35.7 | .097 | 0.903 | 0.880 |
| Allelic genetic | 13 | 0.98 (0.93,1.03) | 0.89 | .372 | 0 | .997 | 0.329 | 0.396 |

CI = confidence interval, OR = odds ratio.

**Table 3**

**Results of the association between DRD2 Taq1A polymorphism and Parkinson disease risk by different ethnicities.**

| | | Overall effect | | | Heterogeneity | | Publication bias | |
|---|---|---|---|---|---|---|---|---|
| Comparison | Studies | OR (95% CI) | *Z* score | *P* value | $I^2$ (%) | *P* value | Begg test | Egger test |
| Asian | | | | | | | | |
| Recessive genetic mode | 6 | 1.01 (0.88,1.17) | 0.20 | .838 | 0 | .484 | 0.188 | 0.111 |
| Dominant genetic model | 6 | 1.04 (0.87,1.25) | 0.48 | .634 | 0 | .807 | 0.348 | 0.546 |
| Homozygous genetic model | 6 | 0.97 (0.80,1.19) | 0.26 | .791 | 0 | .547 | 0.091 | 0.232 |
| Heterozygous genetic model | 6 | 0.95 (0.79,1.15) | 0.54 | .588 | 0 | .924 | 0.573 | 0.922 |
| Additive genetic model | 6 | 0.99 (0.90,1.09) | 0.11 | .909 | 0 | .496 | 0.188 | 0.261 |
| Allelic genetic | 6 | 0.99 (0.92,1.07) | 0.17 | .866 | 0 | .933 | 0.091 | 0.187 |
| Caucasian | | | | | | | | |
| Recessive genetic mode | 7 | 0.85 (0.76,0.95) | 2.93 | .003 | 43.7 | .100 | 0.453 | 0.360 |
| Dominant genetic model | 7 | 1.16 (0.91,1.49) | 1.19 | .235 | 0.1 | .423 | 0.652 | 0.192 |
| Homozygous genetic model | 7 | 0.81 (0.63,1.04) | 1.64 | .101 | 0 | .456 | 0.453 | 0.293 |
| Heterozygous genetic model | 7 | 0.94 (0.73,1.22) | 0.48 | .635 | 0 | .440 | 0.652 | 0.061 |
| Additive genetic model | 7 | 0.87 (0.79,0.96) | 2.90 | .004 | 42.8 | .105 | 0.652 | 0.755 |
| Allelic genetic | 7 | 0.97 (0.94,1.02) | 0.99 | .321 | 0 | .977 | 0.881 | 0.929 |

CI = confidence interval, OR = odds ratio.

Table 4

**Results of the association between DRD2 Taq1A polymorphism and Parkinson disease risk by different genotyping methods.**

| | | Overall effect | | | Heterogeneity | | Publication bias | |
|---|---|---|---|---|---|---|---|---|
| Comparison | Studies | OR (95% CI) | *Z* score | *P* value | $I^2$ (%) | *P* value | Begg test | Egger test |
| PCR-RFLP | | | | | | | | |
| Recessive genetic mode | 9 | 0.90 (0.77,1.05) | 1.30 | .195 | 41.5 | .091 | 0.835 | 0.719 |
| Dominant genetic model | 9 | 1.00 (0.80,1.26) | 0.03 | .977 | 0 | .755 | 0.404 | 0.206 |
| Homozygous genetic model | 9 | 1.01 (0.79,1.30) | 0.09 | .927 | 0 | .689 | 0.532 | 0.423 |
| Heterozygous genetic model | 9 | 1.01 (0.79,1.29) | 0.08 | .935 | 0 | .735 | 0.037 | 0.048 |
| Additive genetic model | 9 | 0.95 (0.84,1.06) | 0.97 | .333 | 35.6 | .133 | 1.000 | 0.612 |
| Allelic genetic | 9 | 0.98 (0.91,1.07) | 0.38 | .701 | 0 | .987 | 0.211 | 0.346 |
| TaqMan | | | | | | | | |
| Recessive genetic mode | 4 | 0.91 (0.82,1.01) | 1.73 | .084 | 44.5 | .145 | 0.327 | 0.638 |
| Dominant genetic model | 4 | 1.14 (0.95,1.37) | 1.37 | .172 | 7 | .358 | 0.497 | 0.884 |
| Homozygous genetic model | 4 | 0.85 (0.70,1.03) | 1.63 | .104 | 32.6 | .217 | 0.497 | 0.865 |
| Heterozygous genetic model | 4 | 0.91 (0.74,1.10) | 0.99 | .323 | 0 | .647 | 1.000 | 0.869 |
| Additive genetic model | 4 | 0.92 (0.85,1.00) | 1.95 | .051 | 50.8 | .106 | 0.497 | 0.643 |
| Allelic genetic | 4 | 0.98 (0.92,1.03) | 0.82 | .412 | 0 | .816 | 0.497 | 0.515 |

CI = confidence interval, OR = odds ratio.

In PD, impaired reuptake of dopamine due to presynaptic neuronal degeneration, or postsynaptic dopamine receptor stimulation by a dopamine agonist may lead to a loss of the normal physiologic response.[36] Dopamine receptor D2 which is involved in working memory, response inhibition and cognitive flexibility, mainly distributed in the striatum,[37] is a protein that is encoded by the DRD2 gene in humans. This gene encodes the D2 subtype of the dopamine receptor, which is coupled to the Gi subtype of the G protein coupled receptor that inhibits adenylate cyclase activity.[38] Recently, a lot of attention has been paid to the relationships DRD2 polymorphisms with PD susceptibility. Wiemerslage et al have found that activation of the D2 autoreceptor protected dopamine neurons from cell death induced by $MPP^+$ in flies.[39] The DRD2 gene has a TaqI A restriction fragment length polymorphism (RFLP) which has been widely studied for its association with PD.[23] Though located in the untranslated region, approximately 10 kilobases from the 3' end of the gene, the polymorphism TaqIA (rs1800497) is related to the DRD2 gene.[40] The A2 allele of DRD2 Taq1A is proved to be relevant to decreased receptor density in the striatum.[41] Wang et al have discovered DRD2 TaqIA polymorphism has been reported to be associated with an increased risk for developing motor fluctuations in PD.[42]

However, still some limitations exist in our meta-analysis. First, although some studies that met the inclusion criteria but had a small sample size, these can enhance statistical power, but it may also lead to bias and heterogeneity. Second, because of the limited sample size, we failed to accurately assess the specific relationship between DRD2 variation and PD. Due to the natural instincts of population genotype frequencies in ethnics was uneven, the association of DRD2 TaqIA polymorphism and the risk of developing PD needs further verification. Finally, our results are summarized by the complete data presented in the documents and lacks sufficient data to assess underlying influence

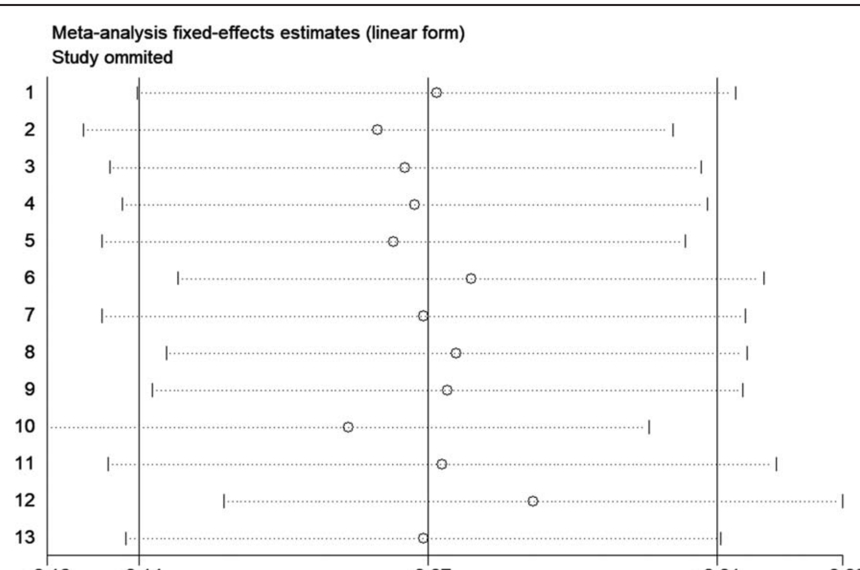


**Figure 8.** Sensitivity analysis for the association between DRD2 TaqIA polymorphism and PD risk under addictive genetic model (A2 vs A1).

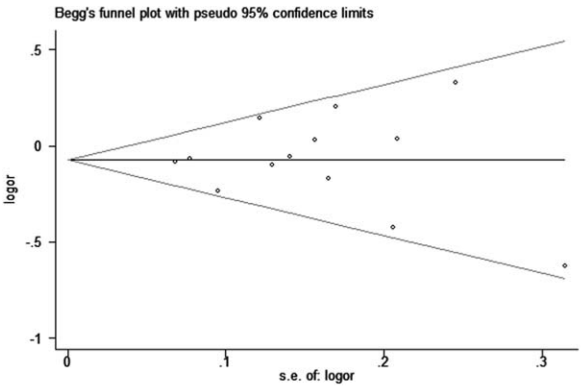


**Figure 9.** Funnel plots for the association between DRD2 TaqIA polymorphism and PD risk under addictive genetic model (A2 vs A1).

factors (such as gender, age and different sources of controls) that may influence the result. This suggests that clinicians may pay more attention to these factors when conducting clinical trials.

In summary, the current mate-analysis is the most comprehensive and objective one at present. It illustrates a significant association between DRD2 TaqIA polymorphism and PD under the recessive genetic mode, and additive genetic models, especially in Caucasians. DRD2 mutant allele increases the risk of developing PD. The conclusion of this study provides a certain guide for individualized treatment of PD. However, in view of the above limitations, more researches on DRD2 TaqIA polymorphism and PD are needed in the future to confirm this conclusion.

## Author contributions

**Conceptualization:** Ming Yu, Feiran Huang, Wei Wang
**Data curation:** Feiran Huang, Wei Wang
**Formal analysis:** Feiran Huang, Wei Wang
**Funding acquisition:** Ming Yu
**Investigation:** Ming Yu, Feiran Huang, Wei Wang
**Methodology:** Feiran Huang, Wei Wang
**Supervision:** Feiran Huang, Wei Wang
**Validation:** Ming Yu, Feiran Huang, Wei Wang, Chen Zhao
**Visualization:** Ming Yu, Feiran Huang, Wei Wang, Chen Zhao
**Writing – original draft:** Feiran Huang, Wei Wang
**Writing – review and editing:** Feiran Huang, Wei Wang

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