Systematic Review and Meta-Analysis

Medicine®

OPEN

# Noradrenergic genes polymorphisms and response to methylphenidate in children with ADHD

## A systematic review and meta-analysis

Danfeng Yuan, MD[a], Manxue Zhang, PhD[a], Yan Huang, MD[a], Xinwei Wang, MS[d], Jian Jiao, PhD[a], Yi Huang, MD, PhD[a,b,c,*]

**Abstract**

**Background:** Attention-deficit hyperactivity disorder (ADHD) is the most common childhood-onset neurodevelopmental disorder, and methylphenidate (MPH) is considered one of the first-line medicine for ADHD. Unfortunately, this medication is only effective for some children with ADHD. This meta-analysis was conducted to evaluate whether noradrenergic gene polymorphisms impact the efficacy of MPH in children with ADHD.

**Methods:** Candidate gene studies published in English until March 1, 2020, were identified through literature searches on PubMed, Web of Science, and Embase. Data were pooled from individual clinical trials considering MPH pharmacogenomics. According to the heterogeneity, the odds ratio and mean differences were calculated by applying fixed-effects or random-effects models.

**Results:** This meta-analysis includes 15 studies and 1382 patients. Four polymorphisms of the *NET* gene (rs5569, rs28386840, rs2242446, rs3785143) and 2 polymorphisms of the α2A-adrenergic receptor gene (*ADRA2A*) gene (MspI and DraI) were selected for the analysis. In the pooled data from all studies, T allele carriers of the rs28386840 polymorphism were significantly more likely to respond to MPH ($P < .001$, $OR_{Tcarriers} = 2.051$, 95% confidence interval [CI]:1.316, 3.197) and showed a relationship with significantly greater hyperactive-impulsive symptoms improvement ($P < .001$, mean difference:1.70, 95% CI:0.24, 3.16). None of the *ADRA2A* polymorphisms correlated significantly with MPH response as a whole. However, G allele carriers of the MspI polymorphism showed a relationship with significantly inattention symptoms improvement ($P < .001$, mean difference:0.31, 95% CI: 0.15, 0.47).

**Conclusion:** Our meta-analysis results indicate that the noradrenergic gene polymorphisms may impact MPH response. *The NET* rs28386840 is linked to improved MPH response in ADHD children. And the *ADRA2A* MspI is associated with inattention symptom improvements. Further investigations with larger samples will be needed to confirm these results.

Registration: PROSPERO (no. CRD42021265830).

**Abbreviations:** ADHD = attention-deficit/hyperactivity disorder, ADRA2A = α2A-adrenergic receptor gene, ARS = ADHD rating scale, CGI = clinical global impression scale, CI = confidence interval, FPRP = false positive reporting probability, MD = mean difference, MPH = methylphenidate, NET = norepinephrine transporter gene, ODD/CD = oppositional defiant disorder/conduct disorder, OR = odds ratio.

**Keywords:** adolescent, Attention-deficit hyperactivity disorder, child, methylphenidate, noradrenergic gene polymorphism

*Editor: Shreedhar Kulkarni.*

*This work is supported by the National Natural Science Foundation of China (NO.2018HXFH045), the National Key Research & Development Program of China (NO.2016YFC1306100) and the Virtual Reality Based Child Attention Assessment and Training Platform (NO.2018HXFH045).*

*The authors have no conflicts of interest to disclose.*

*All data generated or analyzed during this study are included in this published article [and its supplementary information files].*

*Supplemental Digital Content is available for this article.*

*[a] Mental Health Center, West China Hospital of Sichuan University, Chengdu, China, [b] Psychiatric Laboratory, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China, [c] Brain Research Center, West China Hospital of Sichuan University, Chengdu, China, [d] Crestwood Preparatory College, Toronto, Canada.*

*[*] Correspondence: Yi Huang, Mental Health Center, West China Hospital of Sichuan University, Chengdu, 610000 China (e-mail: huangyu@scu.edu.cn).*



*How to cite this article: Yuan D, Zhang M, Huang Y, Wang X, Jiao J, Huang Y. Noradrenergic genes polymorphisms and response to methylphenidate in children with ADHD: A systematic review and meta-analysis. Medicine 2021;100:46(e27858).*

*Received: 25 July 2021 / Received in final form: 14 October 2021 / Accepted: 3 November 2021*

*http://dx.doi.org/10.1097/MD.0000000000027858*

## 1. Introduction

Attention-deficit hyperactivity disorder (ADHD) is a common childhood behavioral disorder. Systematic reviews indicated that the global community prevalence is between 2% and 7%, with an average of around 5%.[1] Pharmacologic studies proved that catecholamines dopamine (DA) and norepinephrine (NE) are involved in the disorder.

Methylphenidate (MPH) is the most commonly used drug among psychostimulants for the treatment of ADHD. It blocks the DA and NE transporter and causes the synaptic concentration of these neurotransmitters to increase.[2] Unfortunately, the clinical response varies significantly between patients. A considerable proportion of patients (approximately one-third) do not respond adequately to stimulant treatment or poor tolerance.[3,4] The main reason is that genetic factors may contribute to individual differences of the efficacy of drug therapy.[5] Several studies have been conducted to examine the association between genetic factors and MPH treatment response. Drug target-related pharmacodynamic genes, especially the dopamine system genes and noradrenergic system genes, have been proved to be associated with the efficacy of MPH medication. Among them, noradrenergic genes like norepinephrine transporter gene (*NET/SLC2A6*) and $\alpha_{2A}$-adrenergic receptor gene (*ADRA2A*) are pivotal factors that affect the treatment effect of MPH.[6]

Norepinephrine transporter protein (NET) is encoded by *NET* and is responsible for NE and DA reuptake and maintains the norepinephrine-dopamine balance in the frontal lobe.[7] The sensitivity of NET to MPH was similar to that of DA transporter.[8,9] Evidence suggests that *NET* gene polymorphism is a candidate gene for MPH treatment response, among which the silent polymorphism rs5569(A>G) and functional promoter variant rs28386840(T>A) are examined most frequently.[10–13] In addition, other promoter SNPs such as rs2242446(C>T) and rs3785143(C>T), which regulate the expression of NET, have also been reported to be associated with ADHD in candidate gene studies and have been investigated in pharmacogenetic studies.[14,15]

*ADRA2A* encodes the $\alpha_{2A}$-adrenergic receptor. The activation of this receptor enhances the function of the prefrontal cortex, which is a crucial area of deficits in ADHD, including working memory, focused attention, and response control.[16] Besides, stimulation of the $\alpha_2$ receptor mediates the increase in intrinsic excitability induced by MPH.[17,18] Therefore, the *ADRA2A* gene is also regarded as one of the candidate pharmacogenomics genes of MPH response, with rs1800544(G>A,C) in the MspI site and rs553668(A>G,T) in the DraI site, located in the 5'-promoter region and the 3'-non-coding region, respectively, becoming genetic polymorphisms of interest.[19–21] In addition to the *NET* and *ADRA2A* genes, other noradrenergic system genes such as the Monoamine Oxidase A gene (*MAOA*) and dopamine β-hydroxylase (*DBH*) also play an essential role in the etiology of the disease, but the pharmacological research of MPH is still lacking.[22,23]

However, results from limited studies on the role of *NET* and *ADRA2A* genes in MPH response have been inconsistent.[12,24–29] A genome-wide association study (GWAS) of response to MPH in ADHD children found that the rs17841329 and rs192303 polymorphisms of the *NET* gene were found to be associated with treatment outcomes.[30] Nevertheless, in a recent genome-wide association study, no associations were reported.[31] Recently, a meta-analysis of the relationship between MPH response and 6 candidate genes was conducted on the pharmacogenomics study of children with ADHD. It was found that MspI in the *ADRA2A* gene, rs5569 and rs28386840 in the *NET* gene were associated with improved MPH response,[27] although it was not replicated.[32]

Taking into account the importance of norepinephrine in the activation of MPH medication as well as the inconsistent findings of the noradrenergic gene polymorphisms in terms of treatment effects. This meta-analysis involved the latest studies and added 3 SNPs (DraI, rs2242446, and rs3785143) of noradrenergic genes that were not investigated in the previous meta-analysis. In order to comprehensively and accurately evaluate the effects of noradrenergic genes on the treatment outcome, we further included quantitative measures like changes in behavioral symptoms and neurocognitive function as outcome variables. As the outcomes may vary due to the use of different assessment tools and various aspects of the evaluator and duration of treatment, a subgroup analysis was conducted to assess this influence. Therefore, the aims of this study are to identify the association between noradrenergic genes (*NET* and *ADRA2A*) and MPH response in children with ADHD by using outcome variables of dichotomous measures and quantitative measures, including behavioral symptoms and neurocognitive functions; add polymorphisms rs2242446 and rs3785143 in *NET* and DraI polymorphism in *ADRA2A*; examine the effects of other factors that may influence the relationship between noradrenergic gene and MPH response in children with ADHD, such as drug dosage, treatment duration, comorbidity, gender, ADHD subtype, treatment duration, and evaluation tools.

## 2. Methods

The study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses protocols (PRISMA-P) statement.[33] The protocol of the systematic review has been registered in PROSPERO (registration number CRD42021265830).

### 2.1. Search strategy

We conducted a literature search using PubMed, Web of Science, and Embase to identify articles in English published before March 1, 2020. The search queries used were combinations of the following phrases: "Attention-deficit hyperactivity disorder or ADHD", "*NET* or *SLC6A2* or Norepinephrine Transporter", "*ADRA2A* or Alpha-2A adrenergic receptor or α2 receptor", "noradrenergic or norepinephrine", "methylphenidate or MPH", "response or efficacy", "gene or polymorphism". (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/G489 for detailed search strategy).

### 2.2. Inclusion criteria, data extraction, and outcome

The following inclusion criteria were applied to select studies that can be included: if the patient cohort included children and/or adolescents under 18 years of age; articles on the relationship between *NET* or *ADRA2A* polymorphisms and MPH clinical efficacy; the diagnosis of ADHD must be determined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R, DSM-IV, and DSM-IV-TR) or the International Classification

of Diseases (ICD-10); genotype distribution was in Hardy-Weinberg equilibrium; studies adopted the candidate gene approach; studies was published in a peer-reviewed journal in English.

Studies were excluded if their results did not include quantitative or dichotomous measures that can be transformed into odds ratio (OR) or mean difference (MD). Two authors (D-F.Y. and M-X.Z.) independently extracted and checked the data. Any disagreement was resolved through discussion until a consensus was reached with the third reviewer (Y.H.). The efficacy of MPH was evaluated from dichotomous outcomes and continuous outcomes. The MPH response was regarded as an indicator of the dichotomous outcomes and evaluated by ADHD rating scale (ARS) or clinical global impression-improvement scale (CGI-I). If multiple data sources existed for categorical analysis (ARS and CGI-I), we preferred to pool data from ADHD-RS and CGI-I or CGI-I. The changes in behavioral symptoms of ADHD and neurocognitive function were considered as the continuous outcomes and pooled from ARS-subscore, Swanson, Nolan, and Pelham-IV (SNAP-IV) rating scale, and Continuous Performance Test (CPT). All conducted tests were 2-tailed, and *P* values less than.05 were considered significant.

### 2.3. Quality assessment

The selected studies' quality was assessed using the Methodological Index of Non-randomized Studies (MINOR).[34] The outcomes of the MINOR ratings are shown in Table 1. The global ideal score is 16 for non-comparative studies and 24 for comparative studies. The items are scored: 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The quality of each study was independently evaluated by 2 authors (D-F.Y. and M-X.Z.), and dispute cases were resolved through consensus with the third reviewer (Y.H.).

### 2.4. Ethical approval

All data in this meta-analysis were extracted from the previous published studies, no ethical approval or patient consent was required.

### 2.5. Data analysis

The heterogeneity between studies was examined by Cochran Q and $I^2$ tests.[35] Data were analyzed using a random-effects model (if $I^2 \geqq 50\%$) or a fixed-effects model (if $I^2 \leqq 50\%$).[36] For *P* values less than.05, the heterogeneity was considered statistically significant. The MD and its 95% confidence interval (CI) were calculated for continuous outcomes. The OR and its 95% CI were calculated for dichotomous outcomes. The results may vary due to the use of different evaluation tools and the aspects of the evaluators. And the intervention time may also influence the effects of gene polymorphisms. We performed a subgroup analysis based on the length of treatment duration and different evaluation tools. Furthermore, in order to assess the influence of potential confounding variables, we performed a meta-regression using age, sex (%), subtype (% inattentive/hyperactive/combined subtype), comorbidity (% oppositional defiant disorder and conduct disorder), treatment duration (weeks), the dose of MPH, study quality, and baseline severity of ADHD. Publication bias was visually assessed by conducting funnel plots of symmetry. Data were analyzed using Comprehensive Meta-Analysis 2.0 (Biostat Inc., Englewood, NJ). And Stata/IC 12.0 (Stata Corporation, College Station, TX) was used to perform the meta-regression and sensitivity analyses. Publication bias analysis was performed if there were more than 5 studies.[37]

For each statistically significant association identified, we estimated the false-positive report probability (FPRP).[38] The FPRP value was determined by the *P* value, the prior probability for the association, and statistical power. We calculated FPRP

**Table 1**

**Description of included studies.**

| Study | Sample size | Country | Age | Male (%) | ARS baseline | Subtype (I/H/C%) | Comorbidity (%) | Diagnostic criteria | Duration (wk) | Drug dose | Outcome measure | SNP | Quality score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kim 2010 | 112 | Korea | 9.2 | 88.5 | 26.9 | 7.8 | ODD:13.4 anxiety:1.07 | DSM-IV | 8 | 29.2 mg/d | CGI-I | rs28386840 rs5569 | 11 |
| Hong 2012 | 103 | Korea | 9.1 | NA | 26.9 | 26.9 | ODD:14.6, anxiety:11.7 | DSM-IV | 8 | 29.1 mg/d | CGI-I and ARS | rs28386840 rs5569, MspI,DraI | 11 |
| Song 2011 | 114 | Korea | 9.08 | 83.3 | 32.2 | 9 | NA | DSM-IV | 8 | 29.47 mg/d | CGI-S or ARS | rs5569 | 9 |
| Gough 2009 | 82 | America | 9.82 | 77 | NA | 14.8 | ODD/OD:41.5 anxiety:5 | DSM-IV | 4–5 | 0.3-2.4 mg/kg/d | ARS | rs5569 | 9 |
| Yang 2004 | 45 | China | 10.08 | 77.8 | 48.8 | NA | NA | DSM-IV | NA | 0.45-0.6 mg/kg/d | ARS | rs5569 | 8 |
| Lee 2011 | 112 | Korea | 10.2 | 83 | 31.1 | 23 | ODD/OD:31.25 anxiety:7.14 | DSM-IV | 8 | 0.85 mg/kg/d | CGI-I and ARS | rs5569,rs2242446 | 10 |
| Park 2012 | 53 | Korea | 9.06 | 84.9 | 28.3 | 13 | ODD/OD:10.8, anxiety:5.4 | DSM-IV | 8 | 0.86 mg/kg/d | ARS and CPT | rs5569,rs28386840 | 11 |
| Unal 2016 | 108 | Turkey | 9.9 | 72.7 | NA | 0 | ODD/OD:42.9 | DSM-IV | 4–6 | 0.7-1.1 mg/kg/d | CGI-S,CPRS/CTRS, GAS | MspI | 10 |
| Huang 2017 | 59 | China | 11.47 | 89.9 | NA | NA | NA | DSM-IV | 4 | 0.9 mg/kg/d | SNAP-IV | MspI | 9 |
| Park 2013 | 115 | Korea | 9.1 | 81.7 | NA | 16.4 | ODD:16, anxiety:8 | DSM-IV | 8 | 0.81-0.83 mg/kg/d | CGI-I and CPT | MspI,DraI | 9 |
| Cheon 2009 | 114 | Korea | 9.08 | 83.3 | 32.2 | 9 | ODD/OD:3.5 anxiety:10.5 | DSM-IV | 8 | 29.5 mg/d | CGI-I and ARS | MspI | 11 |
| Angyal 2018 | 122 | Korea | 9.3 | 88.5 | 32.9 | NA | NA | DSM-IV | 20-24 | 0.55 mg/kg/d | CGI-S and ARS | rs28386840,rs5569 rs2242446 | 10 |
| Polancyk 2007 | 106 | Brazil | 10 | 77.4 | NA | 7.5 | ODD/OD:67.9, anxiety:23.6 | DSM-IV | 4 | 0.65 mg/kg/d | SNAP-IV | MspI | 11 |
| da Silva 2008 | 59 | Brazil | 12 | 76.3 | NA | NA | ODD/OD:40.7, anxiety:44 | DSM-IV | 4 | 0.63 mg/kg/d | SNAP-IV | MspI | 10 |
| Kim 2015 | 78 | Korea | 9.6 | 79.5 | 25.9 | 77.5 | ODD:5.5 | DSM-IV | 8 | 0.67 mg/kg/d | CGI-I | rs28386840,rs5569 MspI, DraI | 11 |

ARS = ADHD rating scale, CD = conduct disorder, CGI-I = clinical global impression of improvement, CGI-S = clinical global impression of severity, CPT = continuous performance test, DSM-IV = diagnostic criteria of mental disorder IV, I/H/C = inattentive/hyperactive/combined subtype, MPH = methylphenidate, NA = not available, ODD = oppositional defiant disorder, SD = standard deviation, SNAP-IV = Swanson, Nolan, and Pelham Scale version IV, SNP = single nucleotide polymorphism.

assuming a prior probability of.1 proposed for candidate gene analyses.[39] The statistical power was based on the ability to detect an OR of 1.50, with α equalled to the observed *P* value.[38] To assess whether the association was noteworthy, we set the FPRP cut-off value to.2 and advocated for summary analyses. Hence, an FPRP value < . 2 was considered to indicate a robust association.[38]

## 3. Results

### 3.1. Included studies

The flow chart of study selection and inclusion is shown in Figure 1. The characteristics of the included studies are listed in Table 1. Tables 2 and 3 show the analysis of dichotomous data and continuous data, respectively. In all studies, the authors mentioned that the genotype distributions of *NET* and *ADRA2A* polymorphisms are in Hardy-Weinberg equilibrium (HWE).

### 3.2. Relationship between NET rs28386840 polymorphism and MPH response

Figure 2 demonstrates the forest plot of the relationship between the *NET* rs28386840 polymorphism and MPH response using different genetic contrasted models. The pooled analysis from 5 studies[12,24,32,40] showed that T allele carriers were significantly associated with a better MPH response ($P < .001$, $OR_{Tcarriers} = 2.051$, 95% CI:1.316, 3.197). Two studies[24,32] further evaluated the behavioral symptom reduction of ADHD and observed a correlation was between the rs28386840 polymorphism and the hyperactive-impulsive score (Table 3). Using the ARS, we found that the T allele carriers were associated with

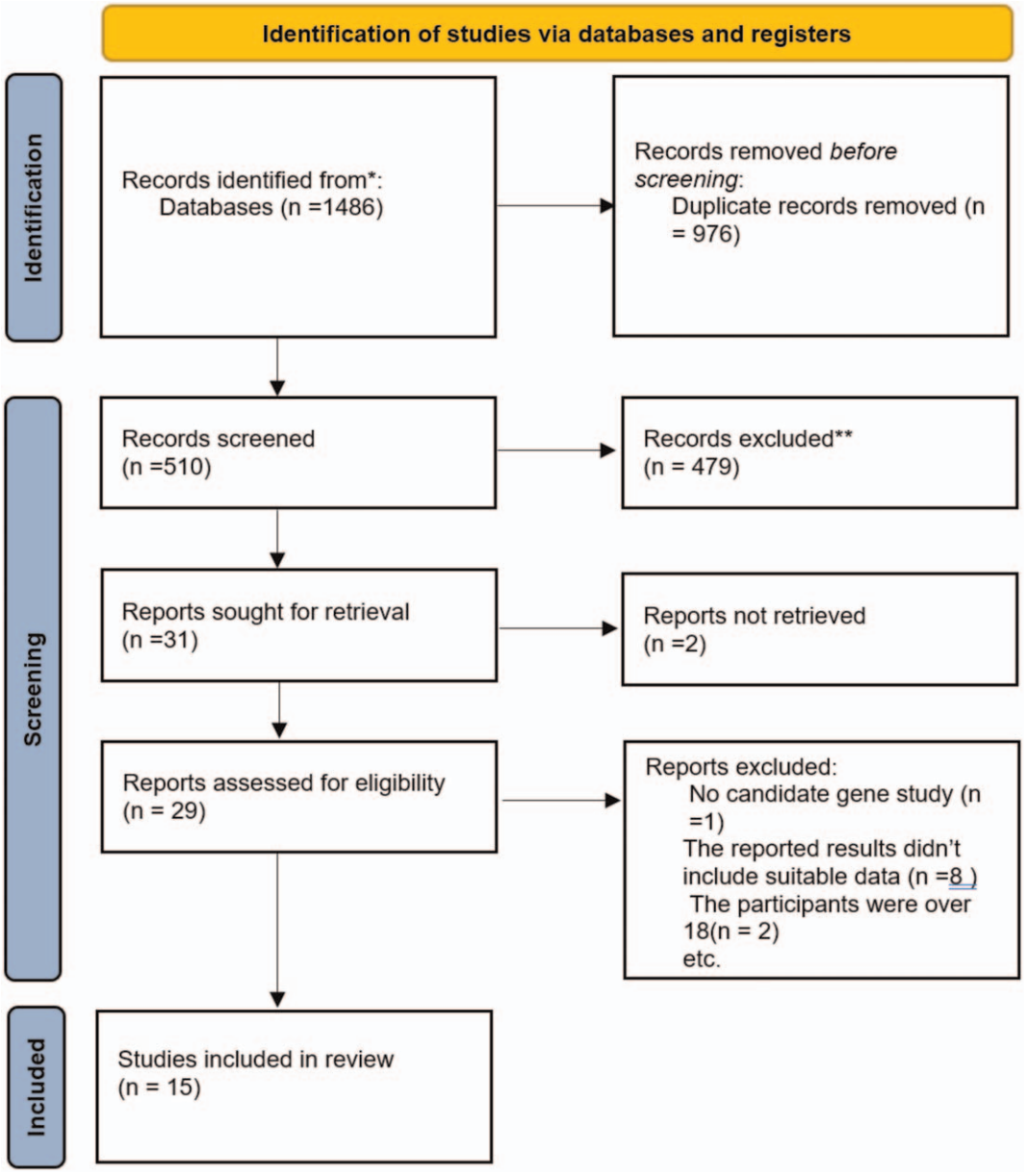


**Figure 1.** Flowchart of the study's inclusion and exclusion criteria.

**Table 2**

**Association between the NET and ADRA2A gene polymorphisms and methylphenidate response (Dichotomized).**

| | | Test for overall effect | | | | Heterogeneity | | |
|---|---|---|---|---|---|---|---|---|
| Polymorphism | N | OR | 95% CI | *P* | FPRP | Z | *P* | $I^2$ (%) |
| rs5569 | | | | | | | | |
| GG vs A carriers | 9 | 1.716 | 1.049, 2.806 | .03* | 0.488 | 2.152 | .09 | 60.569 |
| G carriers vs AA | 5 | 1.448 | 0.740, 2.834 | .28 | 0.823 | 1.081 | .176 | 36.811 |
| GG vs AA | 4 | 0.921 | –0.208, 0.835 | .84 | 0.908 | –0.208 | .712 | 0.000 |
| GG vs GA | 4 | 1.280 | 0.563, 2.909 | .56 | 0.885 | 0.589 | .008 | 74.679 |
| Assessed by CGI | 7 | 1.501 | 1.087, 2.071 | .12 | 0.378 | 2.470 | .009 | 65.106 |
| Assessed by ARS | 3 | 2.919 | 1.628, 5.235 | .00 | 0.321 | 3.594 | .607 | 0.000 |
| rs28386840 | | | | | | | | |
| T carriers vs AA | 5 | 2.051 | 1.316, 3.197 | .002** | 0.140 | 3.172 | .566 | 0.000 |
| TT vs A carriers | 2 | 1.120 | 0.530, 2.340 | .77 | 0.898 | 0.290 | .180 | 43.000 |
| MspI | | | | | | | | |
| GG vs C carriers | 6 | 0.865 | 0.393, 1.904 | .72 | 0.897 | –0.361 | .001 | 74.762 |
| GG vs CC | 3 | 0.693 | 0.072, 6.709 | .76 | 0.929 | –0.317 | .009 | 78.917 |
| GC vs CC | 3 | 1.098 | 0.543, 2.220 | .80 | 0.899 | 0.259 | .726 | 0.000 |
| G carriers vs CC | 3 | 1.095 | 0.568, 2.109 | .79 | 0.895 | 0.271 | .262 | 25.263 |
| >7 wk | 4 | 1.297 | 0.562, 2.990 | .54 | 0.885 | 0.609 | .009 | 74.311 |
| ≤4 wk | 2 | 0.303 | 0.118, 0.778 | .01 | 0.699 | –2.484 | .841 | 0.000 |
| DraI | | | | | | | | |
| CC vs T carriers | 2 | 1.34 | 0.770, 2.340 | .30 | 0.865 | 1.040 | .750 | 0.000 |
| rs2242446 | | | | | | | | |
| TT vs C carriers | 2 | 0.730 | 0.410, 1.290 | .28 | 0.801 | 1.090 | .340 | 0.000 |
| rs3785143 | | | | | | | | |
| CC vs T carriers | 2 | 1.280 | 0.710, 2.310 | .41 | 0.841 | 0.820 | .550 | 0.000 |

ARS = ADHD rating scale, CGI-I = clinical global impression, CI = confidence interval, FPRP = false positive reporting probability, N = number, OR = odds ratio.
* $P < .05$.
** $P < .01$.

more hyperactive-impulsive improvement ($P = .02$, $MD_{Tcarriers} = 1.70$, 95% CI:0.24, 3.16).

### 3.3. Relationship between NET rs5569 polymorphism and MPH response

Figure 3 shows the forest plot for the relationship between the *NET* rs*5569* polymorphism and MPH response using different genetic contrasted models. The pooled OR from 9 studies showed that the GG genotype of rs5569 was associated with a better response to MPH in children than A allele carriers ($P = .03$, $OR_{GG} = 1.716$, 95% CI:1.049, 2.806). As for outcome measures, 3 of the selected studies[11,13,26] used the ADHD Symptom Rating Scales (ARS), and 7 of the studies[12,13,24,25,32,40,41] used the CGI-I. Subgroup analysis indicated that the differences in outcome measurement tools (ARS and CGI-I) contributed to the effect of heterogeneity on MPH response (Table 2). A meta-regression analysis to study the effect of covariates on heterogeneity showed

**Table 3**

**Association between the NET and ADRA2A gene polymorphisms and symptom improvement (Continuous).**

| | | Test for overall effect | | | Heterogeneity | | |
|---|---|---|---|---|---|---|---|
| Polymorphism | N | MD | 95% CI | *P* | Z | *P* | $I^2$ (%) |
| rs28386840 T carriers VS AA | | | | | | | |
| IA | 2 | 0.84 | 0.44, 2.18 | .19 | 1.3 | .75 | 0 |
| Hy/Imp | 2 | 1.70 | 0.24, 3.16 | .02** | 2.34 | .48 | 0 |
| CE | 1 | –19.48 | –32.09, –6.88 | .003** | | | |
| rs5569 GG vs A carriers | | | | | | | |
| Hy/Imp | 2 | 2.80 | –2.18, 7.78 | .27 | 1.1 | .11 | 60 |
| OE | 1 | –15.19 | –25.81, –4.57 | .006** | | | |
| MspI G carriers vs CC | | | | | | | |
| IA | 3 | 0.31 | 0.15, 0.47 | .0002** | 3.79 | .77 | 0 |
| MspI GG vs C carriers | | | | | | | |
| RTSD | 2 | –6.38 | –7.8, –4.96 | <.00001** | 8.82 | .56 | 0 |
| RT | 2 | –7.91 | –9.50, –6.31 | <.00001** | 9.7 | .65 | 0 |
| DraI | | | | | | | |
| CE | 2 | –10.83 | –12.69, –8.97 | <.00001** | 11.39 | .36 | 0 |
| RTSD | 2 | –5.62 | –12.81, 1.57 | .13 | 1.53 | .04 | 76 |

CE = commission errors, Hy/Imp = hyperactive/impulsive, IA = inattention, OE = omission errors, RT = response time, RTSD = response time variability.
* $P < .05$.
** $P < .01$.

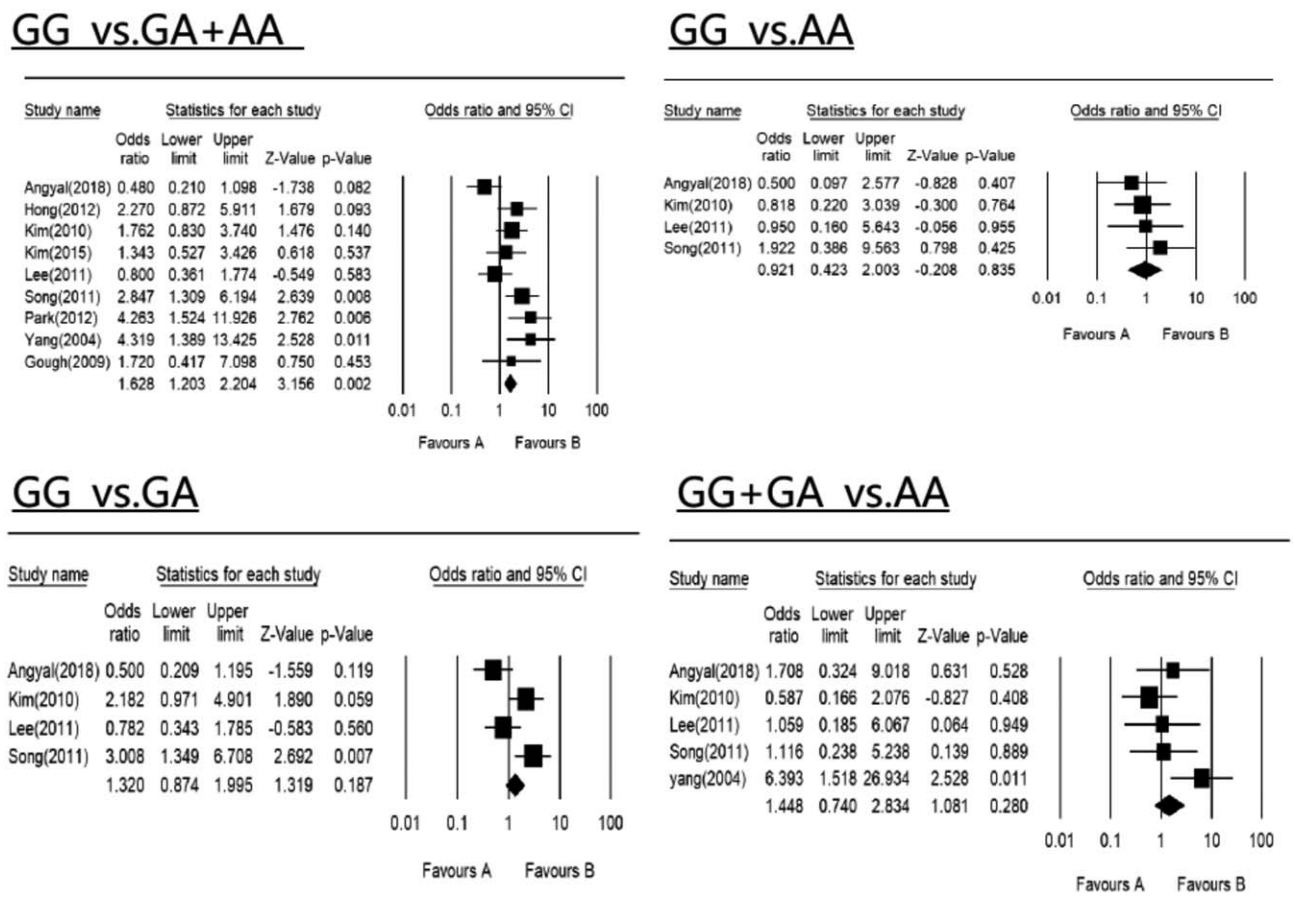


**Figure 2.** The forest plot for the association between NET rs5569 polymorphism and MPH response using different genetic contrasted models.

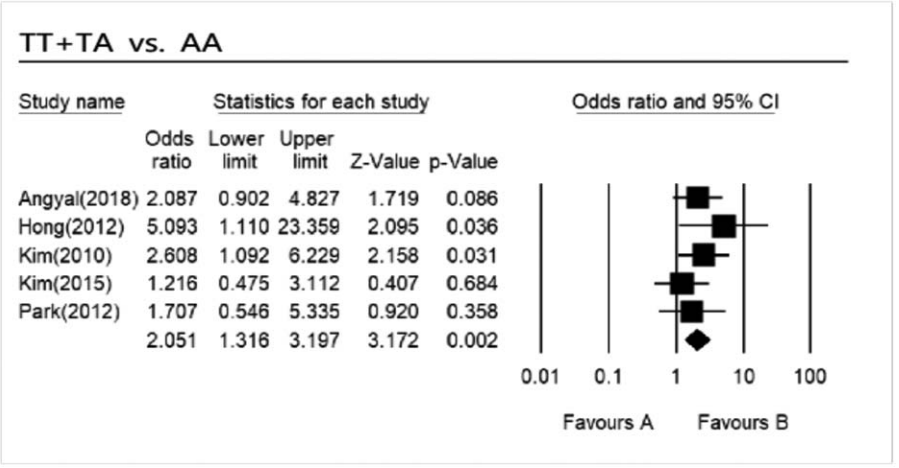


**Figure 3.** The forest plot for the association between NET rs28386840 polymorphism and MPH response using different genetic contrasted models.

that age and MPH dose might contribute to heterogeneous effects of MPH response (Table 4).

### *3.4. Relationship of ADRA2A MspI and DraI polymorphism to MPH response*

Figure 4 illustrates the main results of the meta-analysis of the association between *ADRA2A* variants and MPH response. Our pooled analysis revealed no significant association between *ADRA2A* MspI and and MPH response under different inheritance patterns. However, based on evidence from 3 studies,[19,21,42] a correlation was observed between the MspI site and the reduction in the inattentive score. The presence of the G allele was associated with elevated inattentive symptom improvement to MPH in ADHD children ($P < .001$, MDG carriers: 0.31, 95% CI: 0.15, 0.47). Two studies[40,43] further

**Table 4**

**Results of meta-regression analysis.**

| | | Fixed effect regression | | |
|---|---|---|---|---|
| | Polymorphism | Point estimate lower limit | Upper limit | *P* value |
| rs5569 GG vs C carriers | | | | |
| Age | –1.002 | –1.652 | –0.351 | .003** |
| Gender | –0.069 | –0.152 | 0.014 | .103 |
| Subtype | –0.008 | –0.024 | 0.007 | .290 |
| Drug dose | 1.400 | –0.040 | 2.860 | |
| ARS baseline | 0.023 | –0.031 | 0.077 | .411 |
| ODD/CD | –0.024 | –0.059 | 0.011 | .176 |
| Anxiety | –0.005 | –0.116 | 0.107 | .935 |
| rs28386840 T carriers vs AA | | | | |
| Age | –1.443 | –3.827 | 0.741 | .236 |
| Subtype | –0.01 | –0.027 | 0.007 | .255 |
| Drug dose | 0.690 | –3.730 | 5.120 | |
| Gender | 0.072 | –0.051 | 0.196 | .251 |
| ODD/CD | 0.001 | –0.016 | 0.019 | .883 |
| ARS baseline | 0.013 | –0.146 | 0.171 | .877 |
| MspI G carriers vs CC | | | | |
| Age | –0.82 | –1.361 | –0.286 | .002** |
| Drug dose | 2.170 | –3.460 | 8.600 | |
| Gender | 0.045 | –0.059 | 0.150 | .396 |
| Subtype | –0.017 | –0.032 | –0.0008 | .040* |
| ODD/CD | –0.048 | –0.088 | –0.008 | .019* |

ARS = ADHD rating scale, CD = conduct disorder, ODD = oppositional defiant disorder.
* $P < .05$.
** $P < .01$.

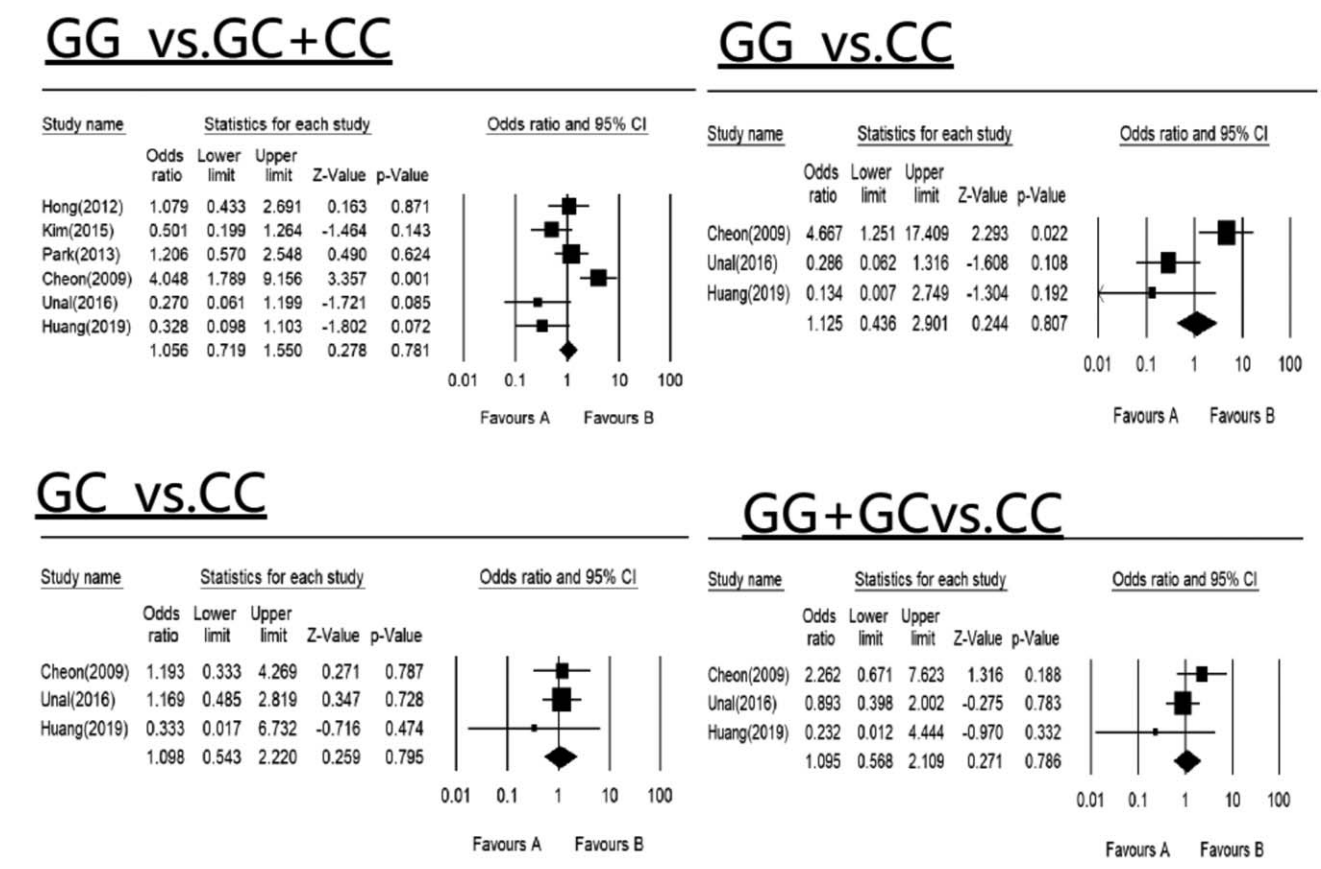


**Figure 4.** The forest plot for the association between ADRA2A MspI polymorphism and MPH response using different genetic contrasted models.

investigated the changes in neurocognitive function and found that GG genotype was related to more improvement in the response time variability ($P < .001$ $MD_{GG}$: –7.91, 95% CI: –9.50, –6.31) (Table 3). As for the duration of treatment, 2 selected studies[29,44] used MPH for 4 weeks, and 4 studied[12,21,28,41] in 8 weeks. Subgroup analysis showed that the treatment duration could not explain the heterogeneity of effect on MPH response (Table 2). In the meta-regression analysis, age, comorbidity of oppositional defiant disorder/conduct disorder (ODD/CD), and subtype in ADHD might contribute to the heterogeneity in the effect estimates (Table 4). Three of the selected studies[12,28,41] investigated the relationship between *ADRA2A* DraI SNP and MPH response. Our results showed no significant association for MPH response with *ADRA2A* DraI polymorphism ($P = .30$, $OR_{CC} = 1.34$, 95% CI:0.77, 2.34) (Table 2).

### 3.5. Relationship of NET rs2242446 and rs3785143 polymorphism and MPH response

Two studies[32,41] investigated the rs2242446 polymorphism and found no significant association ($P = .28$, $OR_{TT} = 0.73$, 95% CI:0.41, 1.29). Another 2 studies[32,45] investigated the rs3785143 polymorphism and observed no significant association between the rs3785143 genotype and MPH response ($P = .41$, $OR_{CC} = 1.28$, 95% CI:0.71, 2.31) (Table 2).

### 3.6. Sensitivity analysis and publication bias

Sensitivity analysis was performed by sequentially omitting individual studies. The pooled results were stable in the studies of rs28386840 and MspI polymorphisms, indicating that the significance of pooled OR was not excessively influenced by any single study. However, when the study of rs5569 polymorphism was removed, the pooled result was not significant anymore (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G489). We assessed the publication bias by visually inspecting the funnel chart. The funnel chart was symmetrical, indicating that the publication bias was acceptable (Fig. 5).

### 3.7. FPRP analyses

Table 2 represents the calculated FPRP values for the main significant findings in this meta-analysis. Assuming that the prior

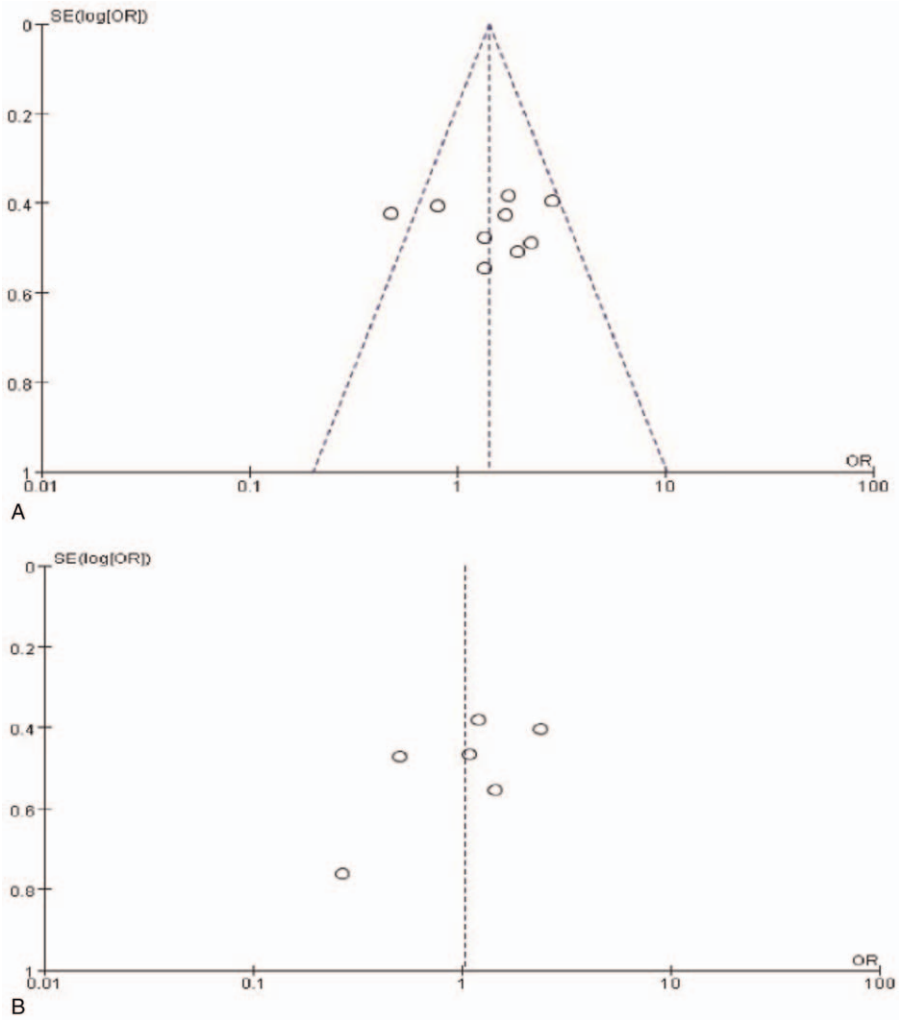


**Figure 5.** A, Funnel plot indicating publication bias of included studies comparing MPH efficacy of rs5569 polymorphism. B, Funnel plot indicating publication bias of included studies comparing MPH efficacy of MspI.

probability was.1, the FPRP value of TT+AT on rs28386840 compared with the AA genotype was less than.2, indicating a significant association.

## 4. Discussion

In this meta-analysis, 15 studies and 1382 patients were evaluated to assess the effect of noradrenergic genes on the treatment response of MPH in children with ADHD. The meta-analysis found that the T allele of rs28386840 in the *NET* gene was associated with improved treatment effects in both MPH response and hyperactive symptom change, and the G carriers at MspI locus might be associated with greater improvement in the inattention symptoms. Through meta-regression analysis, we further found that the comorbidity of ODD/CD, age, medicine dosage, and subtype may influence the study results. To the best of our knowledge, this study is the latest and comprehensive meta-analysis to investigate the relationship between noradrenergic gene polymorphism and methylphenidate response.

The analysis of the rs28386840 of *NET* indicated that the T allele carriers might have a better response to MPH. Our findings confirmed the results of a previous meta-analysis of pharmacogenetic predictors of methylphenidate efficacy in children with ADHD and found a link between the T allele and improved MPH response.[27,32] Due to the sequence alteration of the repressor binding site, the rs28386840 in the upstream promoter region has a major influence on the expression level of *NET*.[46] The T allele is associated with a significantly down-regulated promoter function, which will result in a decrease in the NET expression.[46] As the NET blocking efficiency of MPH may be more significant when the transporter level is low, the T carriers of this SNP might induce a good response of the stimulants. On the contrary, the A allele is associated with up-regulated promoter function. Thus homozygous carriers of the A allele are associated with a higher rate of ADHD.[29] Furthermore, our results suggested that AT or TT genotypes displayed more reduction in hyperactive-impulsive symptoms after the treatment with MPH. This was supported by the results of the neuropsychological study that the AT+TT genotype showed more improvement in the mean commission error scores (a measure of impulsivity).[23] Together with our results, rs28386840 of *NET* might be an important genetic marker for predicting MPH efficacy.

Rs5569 in the exon region of the NET gene has not been proven to be associated with ADHD in previous studies. However, this SNP is located in a haplotype block associated with atomoxetine, which is another drug treatment of ADHD and a specific selective norepinephrine reuptake inhibitor. Since MPH is a selective norepinephrine and dopamine reuptake inhibitor, it may also play a role in the pharmacogenetic effect of MPH.[47,48] In Oh Young's study, the establishment of rs5569 seems to indicate that the G allele may have a protective effect on the development of ADHD symptoms.[14] In this study, we found that GG individuals of rs5569 were more likely to have better responses to MPH than the C carriers, which is consistent with the previous study.[27] Nevertheless, Angyal et al[32] has provided the opposite result on the role of rs5569 in MPH response. Moreover, after conducting the sensitivity analysis, we discovered that the association between rs5569 and MPH response was primarily influenced by the result of Song et al,[13] which means that this association result with MPH response was relatively unstable. Whether this polymorphism has effects on MPH response needs to be further investigated in the future with a larger sample.

MspI polymorphism in the promoter region is one of the most important polymorphisms among *ADRA2A* gene and plays a major role in gene expression and regulating the neurotransmitter release. In this study, we did not find any significant association of this polymorphism with MPH response as a whole. This is inconsistent with the previous meta-analysis of *ADRA2A* polymorphisms and MPH responses, indicating that the G allele of MspI is associated with improved responses.[27] Although some previous studies reported that the presence of the G allele in the *ADRA2A* MspI polymorphism was associated with the improvement of MPH response, more recent studies have reported that no significant association of MspI polymorphism with MPH response have been found. In addition, some studies have found a correlation between the MspI polymorphism and the treatment effects of MPH in inattention symptoms or the inattention subtype, suggesting that this polymorphism may specifically influence MPH on inattention symptoms. In fact, after we further utilized quantitative outcome measures, we did find that G allele carriers of the MspI polymorphism of *ADRA2A* were related to significant inattention symptoms improvement but had nothing to do with MPH response as a whole. One of the reasons is that, compared with quantitative measures, dichotomous measures of MPH outcome may be less capable of detecting effects.[49] Our results indicate that after MPH treatment, patients with the G allele showed a greater reduction in inattention symptoms.

This analysis could not find any relationship between MPH response and DraI, which is another important genetic polymorphism in the promoter region of the *ADRA2A* gene besides MspI. Similarly, the rs2242446 polymorphism, which is in high linkage disequilibrium (LD) with *r*s28386840 and rs3785143 that might impact the transcriptional activity and expression of *NET* has not been found to have a significant association with MPH response.[28,45] The potential reason for the negative outcomes was that the sample size and the number of studies were relatively small. Future research should be conducted in larger samples to elucidate the role of these SNPs and the treatment effects of MPH.

The present meta-regression analysis suggested that MPH dosage is an important covariate leading to the heterogeneity of the treatment efficacy. The previous study has reported that MPH dose might influence the efficacy outcome.[50] Our results show that the association between noradrenergic genes and MPH response is stronger in studies with relatively large drug doses. In the future, more studies are needed to clarify the gene × dose interactive effects. Besides, the association between genetic variants and MPH response is relatively strong in younger patients, which is consistent with the previous meta-analysis that assessed the association between rs5569 of *NET* and MPH response.[27] In addition, the comorbidity of ODD/CD in ADHD might contribute to the heterogeneity of MPH response. The higher ODD/CD comorbidity rate may reduce MPH response and increase disease severity, which is in line with the previous studies that coexisting behavioral problems were negative predictors of treatment response.[51] Furthermore, we found that the ADHD subtype is a covariate that contributes to the heterogeneity of the treatment efficacy. This can be proved by previous trials that noradrenergic gene polymorphisms may have different effects on different dimensions of ADHD symptoms during MPH treatment.

**Table 5**

**Association of noradrenergic genes polymorphisms and side effects of methylphenidate.**

| Gene | Polymorphism (s) | Authors | Sample | Findings |
|---|---|---|---|---|
| ADRA2A | DraI | Yoo et al 2020 | N = 83 | Sleep side effects |
| | MspI | Cho et al 2012 | N = 101 | More change in diastolic blood pressure (DBP) associated with MspI G allele |
| NET | A-3081T | Yoo et al 2020 | N = 83 | Sleep side effects |
| | A-3081T | Cho et al 2012 | N = 101 | More increase in heart rate associated with TT genotype at rs28386840 |
| | rs192303 | Song et al 2014 | N = 83 | Increased frequency of irritability associated with rs28386840 G allele increased severity of talk less and disinterest symptom associated with CC genotype at rs192303 |
| | rs3785143 | Song et al 2014 | N = 83 | Increased frequency of irritability associated with CC genotype at rs3785143 increased severity of talk less and disinterest symptom associated with rs192303 T allele |

The subgroup analysis revealed that variation among outcome measures tools (ARS or CGI-I) might impact the therapeutic response of MPH. However, no effect was found on the duration of treatment (4 weeks or 8 weeks). Future studies should consider these factors to facilitate the evaluation of the impacts of MPH response.

Although many studies predicted the therapeutic response of MPH, little work has been done to test the predictors of MPH side effects. According to the pharmacodynamic gene study of MPH on the side effects of ADHD, the *ADRA2A* gene polymorphisms are associated with the increase of diastolic blood pressure (DBP) after therapy. The *NET* gene polymorphisms are associated with increased heart rate changes, increased frequency of irritability, increased severity of talking less, and disinterest symptoms (Table 5).

This meta-analysis has several limitations. First, the drug response includes not only efficiency but also side effects. Most pharmacogenetic studies only focused on efficiency, and few studies focused on the potential adverse events of the noradrenergic genes, such as cardiovascular side effects, irritability, and disinterest.[52] Due to limited research on pharmacogenetic side effects of MPH, more research should be conducted to assess the potential role of noradrenergic genes in side effects. Secondly, the studies included in our analysis are varied in terms of outcome measures and thresholds for significant improvement, especially the inconsistent standard in ADHD rating scale (ARS) and CGI-I for assessing the treatment response. However, we conducted subgroup analysis to reduce the potential impact of the different outcome measures contributing to the heterogeneity. Finally, the included studies and sample size of this analysis were relatively small and the observing treatment time was relatively short. Therefore, more studies especially the genome-wide association study should be enrolled in to improve the effect size.

## 5. Conclusion

In conclusion, this meta-analysis indicates that T carriers of rs28386840 in the *NET* gene are associated with improved MPH treatment. Patients with G carriers of MspI may have a greater improvement in inattention symptoms. The results of this meta-analysis may provide additional pharmacogenetic evidence for the treatment response of MPH in children with ADHD and further develop a personalized treatment plan for ADHD patients. Larger sample size and longer treatment duration should be needed to clarify the role of noradrenergic gene polymorphisms and MPH response of children with ADHD.

## Acknowledgments

We wish to express our great appreciation to all the authors of the studies included in the current meta-analysis.

## Author contributions

Y.H. designed the study. D-F.Y. and M-X.Z. were responsible for the collection of data and performing the statistical analysis and manuscript preparation. X-W.W. and J.J. were responsible for checking the data. All authors were responsible for drafting the manuscript, read and approved the final version.
**Conceptualization:** Danfeng Yuan.
**Data curation:** Danfeng Yuan, Jian Jiao.
**Investigation:** Manxue Zhang, Jian Jiao.
**Methodology:** Manxue Zhang, Yan Huang.
**Project administration:** Manxue Zhang.
**Resources:** Yan Huang.
**Software:** Yan Huang, Xinwei Wang.
**Supervision:** Xinwei Wang, Yi Huang.
**Validation:** Yi Huang.
**Visualization:** Yan Huang.
**Writing – original draft:** Danfeng Yuan.
**Writing – review & editing:** Yi Huang.

## References

[1] Sayal K, Prasad V, Daley D, Ford T, Coghill D. ADHD in children and young people: prevalence, care pathways, and service provision. Lancet Psychiatry 2018;5:175–86.
[2] Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry 2012;200:97–106.
[3] Su Y, Li H, Chen Y, et al. Remission rate and functional outcomes during a 6-month treatment with osmotic-release oral-system methylphenidate in children with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 2015;35:525–34.
[4] Chou WJ, Chen SJ, Chen YS, et al. Remission in children and adolescents diagnosed with attention-deficit/hyperactivity disorder via an effective and tolerable titration scheme for osmotic release oral system methylphenidate. J Child Adolesc Psychopharmacol 2012;22:215–25.
[5] Shim SH, Yoon HJ, Bak J, Hahn SW, Kim YK. Clinical and neurobiological factors in the management of treatment refractory attention-deficit hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry 2016;70:237–44.

[6] Hoehe MR, Otterud B, Hsieh WT, et al. Genetic mapping of adrenergic receptor genes in humans. J Mol Med (Berl) 1995;73:299–306.
[7] Morón JA, Brockington A, Wise RA, Rocha BA, Hope BT. Dopamine uptake through the norepinephrine transporter in brain regions with low levels of the dopamine transporter: evidence from knock-out mouse lines. J Neurosci 2002;22:389–95.
[8] Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: a review and integration. Behav Brain Res 1998;94:127–52.
[9] Han DD, Gu HH. Comparison of the monoamine transporters from human and mouse in their sensitivities to psychostimulant drugs. BMC Pharmacol 2006;6:6. doi: 10.1186/1471-2210-6-6.
[10] Wilens TE. Effects of methylphenidate on the catecholaminergic system in attention-deficit/hyperactivity disorder. J Clin Psychopharmacol 2008;28:S46–53.
[11] Yang L, Wang YF, Li J, Faraone SV. Association of norepinephrine transporter gene with methylphenidate response. J Am Acad Child Adolesc Psychiatry 2004;43:1154–8.
[12] Hong SB, Kim JW, Cho SC, et al. Dopaminergic and noradrenergic gene polymorphisms and response to methylphenidate in Korean children with attention-deficit/hyperactivity disorder: is there an interaction? J Child Adolesc Psychopharmacol 2012;22:343–52.
[13] Song J, Song DH, Jhung K, Cheon KA. Norepinephrine transporter gene (SLC6A2) is involved with methylphenidate response in Korean children with attention deficit hyperactivity disorder. Int Clin Psychopharmacol 2011;26:107–13.
[14] Oh SY, Kim YK. Association of norepinephrine transporter gene polymorphisms in attention-deficit/hyperactivity disorder in Korean population. Prog Neuropsychopharmacol Biol Psychiatry 2017;73: 56–63.
[15] Xu X, Hawi Z, Brookes KJ, et al. Replication of a rare protective allele in the noradrenaline transporter gene and ADHD. Am J Med Genet B Neuropsychiatr Genet 2008;147B:1564–7.
[16] Nestler EJ, Hyman SE, Malenka RC. Molecular Neuropharmacology, A Foundation for Clinical Neuroscience. New York: McGraw-Hill; 2001. pp. 1–503.
[17] Andrews GD, Lavin A. Methylphenidate increases cortical excitability via activation of alpha-2 noradrenergic receptors. Neuropsychopharmacology 2006;31:594–601.
[18] Arnsten AF, Steere JC, Hunt RD. The contribution of alpha 2-noradrenergic mechanisms of prefrontal cortical cognitive function. Potential significance for attention-deficit hyperactivity disorder. Arch Gen Psychiatry 1996;53:448–55.
[19] Da Silva TL, Pianca TG, Roman T, et al. Adrenergic alpha2A receptor gene and response to methylphenidate in attention-deficit/hyperactivity disorder-predominantly inattentive type. J Neural Transm (Vienna) 2008;115:341–5.
[20] Polanczyk G, Zeni C, Genro JP, et al. Association of the adrenergic alpha2A receptor gene with methylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder. Clin Trial 2007;64:218–24.
[21] Cheon KA, Cho DY, Koo MS, Song DH, Namkoong K. Association between homozygosity of a G allele of the alpha-2a-adrenergic receptor gene and methylphenidate response in Korean children and adolescents with attention-deficit/hyperactivity disorder. Biol Psychiatry 2009;65: 564–70.
[22] Tong J, Mckinley LA, Cummins TD, et al. Identification and functional characterisation of a novel dopamine beta hydroxylase gene variant associated with attention deficit hyperactivity disorder. World J Biol Psychiatry 2015;16:610–8.
[23] Comings DE, Gade-Andavolu R, Gonzalez N, et al. Comparison of the role of dopamine, serotonin, and noradrenaline genes in ADHD, ODD and conduct disorder: multivariate regression analysis of 20 genes. Clin Genet 2000;57:178–96.
[24] Kim BN, Kim JW, Hong SB, et al. Possible association of norepinephrine transporter -3081(A/T) polymorphism with methylphenidate response in attention deficit hyperactivity disorder. Behav Brain Funct 2010;6:57. doi: 10.1186/1744-9081-6-57.
[25] Lee SH, Kim SW, Lee MG, et al. Lack of association between response of OROS-methylphenidate and norepinephrine transporter (SLC6A2) polymorphism in Korean ADHD. Psychiatry Res 2011;186:338–44.
[26] Mcgough JJ, Mccracken JT, Loo SK, et al. A candidate gene analysis of methylphenidate response in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2009;48:1155–64.
[27] Myer NM, Boland JR, Faraone SV. Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD. Mol Psychiatry 2018;23: 1929–36.
[28] Park S, Kim JW, Kim BN, et al. No significant association between the alpha-2A-adrenergic receptor gene and treatment response in combined or inattentive subtypes of attention-deficit hyperactivity disorder. Pharmacopsychiatry 2013;46:169–74.
[29] Unal D, Unal MF, Alikasifoglu M, Cetinkaya A. Genetic variations in attention deficit hyperactivity disorder subtypes and treatment resistant cases. Psychiatry Investig 2016;13:427–33.
[30] Mick E, Neale B, Middleton FA, Mcgough JJ, Faraone SV. Genome-wide association study of response to methylphenidate in 187 children with attention-deficit/hyperactivity disorder. Am J Med Genet B Neuropsychiatr Genet 2008;147B:1412–8.
[31] Pagerols M, Richarte V, Sánchez-Mora C, et al. Integrative genomic analysis of methylphenidate response in attention-deficit/hyperactivity disorder. Sci Rep 2018;8:1881. doi: 10.1038/s41598-018-20194-7.
[32] Angyal N, Horvath EZ, Tarnok Z, et al. Association analysis of norepinephrine transporter polymorphisms and methylphenidate response in ADHD patients. Prog Neuropsychopharmacol Biol Psychiatry 2018;84:122–8.
[33] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1. doi: 10.1186/2046-4053-4-1.
[34] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8:2–10.
[35] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[36] Dersimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[37] Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ 2000;320:1574–7.
[38] Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 2004;96:434–42.
[39] Thomas DC, Clayton DG. Betting odds and genetic associations. J Natl Cancer Inst 2004;96:421–3.
[40] Park S, Kim JW, Yang YH, et al. Possible effect of norepinephrine transporter polymorphisms on methylphenidate-induced changes in neuropsychological function in attention-deficit hyperactivity disorder. Behav Brain Funct 2012;8:22. doi: 10.1186/1744-9081-8-22.
[41] Kim JW, Sharma V, Ryan ND. Predicting methylphenidate response in ADHD using machine learning approaches. Int J Neuropsychopharmacol 2015;18:yv052. doi: 10.1093/ijnp/pyv052.
[42] Polanczyk G, Zeni C, Genro JP, et al. Association of the adrenergic alpha2A receptor gene with methylphenidate improvement of inattentive symptoms in children and adolescents with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 2007;64:218–24.
[43] Park S, Hong SB, Kim JW, et al. White-matter connectivity and methylphenidate-induced changes in attentional performance according to (2A-adrenergic receptor gene polymorphisms in Korean children with attention-deficit hyperactivity disorder. J Neuropsychiatry Clin Neurosci 2013;25:222–8.
[44] Huang HC, Wu LS, Yu SC, et al. The Alpha-2A adrenergic receptor gene -1291C/G single nucleotide polymorphism is associated with the efficacy of methylphenidate in treating Taiwanese children and adolescents with attention-deficit hyperactivity disorder. Psychiatry Investig 2018;15: 306–12.
[45] Song J, Kim SW, Hong HJ, et al. Association of SNAP-25, SLC6A2, and LPHN3 with OROS methylphenidate treatment response in attention-deficit/hyperactivity disorder. Clin Neuropharmacol 2014;37:136–41.
[46] Kim CH, Hahn MK, Joung Y, et al. A polymorphism in the norepinephrine transporter gene alters promoter activity and is associated with attention-deficit hyperactivity disorder. Proc Natl Acad Sci U S A 2006;103:19164–9.
[47] Yang L, Qian Q, Liu L, et al. Adrenergic neurotransmitter system transporter and receptor genes associated with atomoxetine response in attention-deficit hyperactivity disorder children. J Neural Transm (Vienna) 2013;120:1127–33.
[48] Ramoz N, Boni C, Downing AM, et al. A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical

response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). Neuropsychopharmacology 2009;34:2135–42.
[49] Yoshida K, Müller DJ. Pharmacogenetics of antipsychotic drug treatment: update and clinical implications. Mol Neuropsychiatry 2020;5:1–26.
[50] Retz W, Rösler M, Ose C, et al. Multiscale assessment of treatment efficacy in adults with ADHD: a randomized placebo-controlled, multicentre study with extended-release methylphenidate. World J Biol Psychiatry 2012;13:48–59.
[51] Oner P, Oner O, Cop E, Munir KM. Effect of ferritin on short-term treatment response in attention deficit hyperactivity disorder. Klinik Psikofarmakol Bulteni 2012;22:325–31.
[52] Cho SC, Kim BN, Cummins TD, Kim JW, Bellgrove MA. Norepinephrine transporter -3081(A/T) and alpha-2A-adrenergic receptor MspI polymorphisms are associated with cardiovascular side effects of OROS-methylphenidate treatment. J Psychopharmacol 2012;26: 380–9.