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Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD

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Abstract

Stimulant medication has long been effective in treating attention-deficit/hyperactivity disorder (ADHD) and is currently the first-line pharmacological treatment for children. Both methylphenidate and amphetamine modulate extracellular catecholamine levels through interaction with dopaminergic, adrenergic and serotonergic system components; it is therefore likely that catecholaminergic molecular components influence the effects of ADHD treatment. Using meta-analysis, we sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. We identified 36 studies (3647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 *ADRA2A* (odds ratio: 1.69; confidence interval: 1.12–2.55), rs4680 *COMT* (odds ratio (OR): 1.40; confidence interval: 1.04–1.87), rs5569 *SLC6A2* (odds ratio: 1.73; confidence interval: 1.26–2.37) and rs28386840 *SLC6A2* (odds ratio: 2.93; confidence interval: 1.76–4.90), and, repeat variants variable number tandem repeat (VNTR) 4 *DRD4* (odds ratio: 1.66; confidence interval: 1.16–2.37) and VNTR 10 *SLC6A3* (odds ratio: 0.74; confidence interval: 0.60–0.90), whereas the following variants were not statistically significant: rs1947274 *LPHN3* (odds ratio: 0.95; confidence interval: 0.71–1.26), rs5661665 *LPHN3* (odds ratio: 1.07; confidence interval: 0.84–1.37) and VNTR 7 *DRD4* (odds ratio: 0.68; confidence interval: 0.47–1.00). Funnel plot asymmetry among *SLC6A3* studies was identified and attributed largely to small study effects. Egger's regression test and Duval and Tweedie's 'trim and fill' were used to examine and correct for publication bias. These findings have major implications for advancing our therapeutic approach to childhood ADHD treatment.

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CONFLICT OF INTEREST

NMM and JRB were employed by Genomind during the *research and authorship of this manuscript*. In the past year, SVF received income, potential income, travel expenses, continuing education support and/or research support from Lundbeck, KenPharm, Rhodes, Arbor, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA, Sunovion, Genomind and NeuroLifeSciences. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD.

Supplementary Information accompanies the paper on the *Molecular Psychiatry* website (http://www.nature.com/mp)

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is the most common neuropsychiatric disease treated in children today with a recent study reporting a pooled-prevalence of 5.3%.[1] There are currently five FDA-approved medications for the treatment of childhood ADHD, each falling within one of two drug classes: stimulant (methylphenidate (MPH) or amphetamine (AMP)) or non-stimulant (atomoxetine (ATX), extended-release guanfacine or extended-release clonidine).[2,3] The use of stimulant medication has long been considered safe and efficacious; prescription stimulant use continues to be the first-line psychopharmacological treatment for childhood ADHD[4–9] and is exclusively indicated—in conjunction with behavioral therapy—for preschool-aged children (4–5 years of age).[2] Many similarities exist between MPH and other psychostimulant preparations, both in terms of efficacy and side effect profile. Despite this, patient response varies greatly and some individuals preferentially respond to or tolerate one treatment over another.[10–13]

Over the past 20 years many independent studies have assessed the treatment of ADHD-diagnosed children and adolescents with MPH. Though MPH treatment proved beneficial by reducing hyperactive and inattentive behaviors,[14,15] it is important to note that rare but serious adverse reactions occurred in about 3% of children.[16,17] For example, the development of tic disorder, elongated QT durations or the onset of depression, psychosis and/or mania were identified in some MPH-treated individuals.[11,18] Furthermore, a recent comprehensive meta-analysis including 185 studies of MPH use for ADHD treatment reported a high frequency of non-serious adverse events associated with treatment, including for example, insomnia and loss of appetite.[19] Currently, no clinical guidelines exist to address these issues with a personalized approach for individualized medication.

Inter-individual variability in MPH response may be influenced by genetic factors.[20] Classification of 60 thousand single nucleotide polymorphisms (SNPs), that fell within exon coding regions, were categorized through navigation of the 1.42 million SNPs within the human genome.[21] As a means to direct ADHD treatment through use of clinical predictors, subsequent molecular genetic studies have facilitated the identification of relevant genetic markers likely responsible for interindividual drug response. The metabolic system influences plasma concentrations of MPH before it reaches the brain[22] and studies in ADHD-children report significant inter-individual variability of MPH plasma concentrations following administration of standardized doses.[23–25] Characterization and sequencing of the carboxylesterase 1A1 *(CES1A1)* gene led to the identification of variants that are associated with signficantly reduced enzyme activity.[26–28] For example, C/T (rs71647871;Gly143Glu) heterozygotes required appreciably less MPH than C/C homozygotes, suggesting reduced CES1A1 enzyme activity.[29] Furthermore, possession of the G allele (rs3815583; – 75T>G) was associated with worsening anorexia during MPH treatment in stimulant-naïve ADHD children.[30]

Moreover, polymorphisms within key monoaminergic genes have been associated with the response to stimulant medication, albeit through conflicting evidence. This is mechanistically intuitive as both MPH and AMP modulate extracellular catecholamine levels through interaction with dopaminergic, adrenergic and serotonergic system

components. AMP increases synaptic dopamine (DA) levels through three major pathways: competitive inhibition of the DA transporter (DAT), enhanced release of vesicular DA and promotion of reverse DA transport into the synaptic cleft.[31] AMP also disrupts vesicular DA storage and inhibits normal monoamine oxidase degradation.[32] More recently, it was shown that at low doses, AMP cannot reach sufficient vesicular concentrations to facilitate emanation and this may account for phasic pharmacological effects.[33] Similarly, MPH inhibits catecholamine reuptake and modulates DA and norepinephrine levels by binding to and blocking DA and norepinephrine transporters, thereby increasing extracellular concentrations.[34] Therapeutic doses of MPH cause 80% blockage of DAT and significantly enhance extracellular DA in the basal ganglia.[35] This effect is modulated by the rate of DA release, which can be influenced by age: a heightened effect can be seen in younger children.[36] Thus, it is likely that catecholaminergic molecular components influence the effects of ADHD treatment.

Genetic variation may lead to differential symptom changes and side effect profiles. Often, discontinuation of treatment due to side effects or the administration of sub-optimal treatment regimens limits the effectiveness of stimulant treatment. This leaves children impaired and exposes them to undue consequences from untreated ADHD.[14] There is currently no way to predict this preferential response in treatment naïve patients, nor to direct a personalized treatment regimen. Pharmacogenetics testing has the potential to reduce discontinuation due to adverse events and improve time to efficacy. Here we report a meta-analysis evaluating the aggregate body of literature in an effort to identify clinically significant predictors of MPH response in children. We report five genes—*SLC6A2, SLC6A3, COMT, DRD4* and *ADRA2A*—that may cumulatively act as reliable predictors to MPH response.

METHODS

Search strategy

To identify eligible studies, a systematic review of the National Center for Biotechnology Information (NCBI) PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) was performed using the broad search terms ‘ADHD’, ‘Attention-Deficit/Hyperactivity Disorder’, ‘pharmacogenetics’, ‘stimulant medication’, ‘methylphenidate’, ‘medication response AND genetic’, ‘methylphenidate AND gene’, ‘methylphenidate AND genetic’. Further specification of literature relevant to clinical care and research was obtained through use of MeSH headings and filters, and by tailoring search terms using Boolean logic: methylphenidate OR MPH AND (Attention-Deficit/Hyperactivity Disorder OR ADHD) AND pharmacogenetic OR pharmacogenomic; amphetamine AND (Attention-Deficit/Hyperactivity Disorder OR ADHD) AND pharmacogenetic OR pharmacogenomic; stimulant AND (Attention-Deficit/Hyperactivity Disorder OR ADHD) AND pharmacogenetic OR pharmacogenomics. Searches were limited to articles available in English and included publications up to April 2017. Additionally, relevant citations were followed after initial searches. Of the available literature, only articles addressing pharmacogenetics, treatment efficacy and childhood ADHD were considered.

Inclusion criteria

To minimize heterogeneity among studies we initially assessed literature for violation of inclusion criteria and included only studies that met set criteria in further analyses. Articles were included if the patient cohort comprised children and/or adolescents under 18 years of age. Review articles, meta-analyses and case studies with a sample size of nine or less were excluded; original research articles with a sample size of at least 10 subjects were required. Within studies ADHD diagnosis must have been determined by use of DSM criteria (third, fourth or fifth edition) or a comparable diagnostic method. Results from studies that were further stratified by comorbidity or ADHD subtype were not included in this analysis. Likewise, studies were excluded if their reported results did not include quantitative measures transformable into ORs (for example, Cohen's *d*, Cohen's f^2, F-test, etc.). Upon completion of a robust search, further stratification of results was performed. Research articles correlating specific genetic variants to MPH efficacy in childhood ADHD were considered eligible. Few studies reported tolerability results and were therefore not analyzable. Furthermore, studies with overlapping patient samples were excluded to only include the study with the larger number of patients. Research articles were further categorized by gene and then genetic variant. Results from genetic variants reported in three or more independent research articles were combined and meta-analyzed.

Outcome measures

Pre- and post-treatment outcome measures and/or effect size changes were analyzed to evaluate differential treatment response. Publications were included regardless of measurement scale used to evaluate the treatment effect of MPH. Therefore, both categorical and dimensional measurements were extracted for analysis. For studies that employed a quantitative scale or instrument to gauge ADHD symptoms, only those studies using validated ADHD rating scales were used.

Study selection

Article abstracts were initially assessed to determine if they met overall inclusion criteria. Subsequently, full version articles were blindly reviewed by three independent researchers and evaluated for methodological soundness. Candidate genes were selected for review if evaluated by two or more studies and entered into meta-analysis if data for the same genetic variant was available from at least three studies.

Data extraction

Demographic information, including mean age, sex ratios and cohort ethnicity, were extracted. Relevant aspects of study design, including study type, sample size, drug choice and dosage, were compiled. Appropriate transformations were used to estimate effect sizes of MPH efficacy—expressed as odds ratios (ORs)—and those values were evaluated using Review Manager (RevMan) version 5.3, an open-source software publicly available from the Cochrane Collaboration (http://community.cochrane.org/tools/review-production-tools/revman-5). As mentioned previously, few studies reported tolerability data and we were therefore unable to obtain a MPH tolerability effect size. If more than one source of data was

available in a publication (that is, CPT and CGI-I), we preferentially pooled data from a clinician-administered scale over those scales administered by a parent or teacher.

Statistical analysis

Individual OR and standard error (s.e.) values were calculated for each study. In several studies ORs for differential treatment response by genotype were reported. For cases in which ORs were not reported additional calculations were required. Any valid measure of differential treatment response among alleles was extracted or statistically derived. Transformations from these measures, including alternative metrics of effect size (r, Cohen's d, η^2, and Cohen's f^2) and measures of mean difference (ANOVA and χ^2), were performed following the methods of Borenstein *et al.*[37] Heterogeneity among studies was assessed in RevMan 5 with the χ^2-test and calculation of I^2. The overall effect for each SNP was calculated using a fixed effect model.

Publication bias analyses

To detect publication bias, funnel plot—ORs against s.e.(log[OR])—dispersion patterns were visually assessed for symmetry. Symmetry is based on a weighted linear regression of standard normal deviation of the OR (standardized effect) on the inverse of the s.e. of the OR (precision) (that is, the larger the deviation of each study from the funnel curve, the more pronounced the asymmetry). Publication bias was quantitatively measured using Egger's Regression Tests, where a P-value of < 0.05 indicated statistically significant publication bias. For those genetic variants with significant publication bias Duval and Tweedie's 'Trim and Fill' was used to generate an adjusted best estimate of the unbiased effect size.

Meta-regression

To assess the relationship between covariates (moderators)—mean age, gender ratio (% male), ethnicity (% white) or study quality—and ORs we performed individual meta-regressions for each genetic variant. Ethnicity regressions were incomplete as many studies did not include usable ethnicity data. For study quality analyses, studies were binned into 'strong', 'moderate' or 'weak' categories according to the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies. The regression coefficient was then assessed for statistical significance. A Welch's unequal variances t-test comparing randomized controlled trials to all other study designs was also performed.

RESULTS

The study selection procedure is illustrated in Figure 1. A total of 161 eligible studies were identified both manually (n = 41 studies) and through systematic PubMed review (n = 120 studies). Several studies were excluded based on our *a priori* eligibility criteria: 15 included adult participants over the age of 18, 19 reported data that was not transformable into a binary effect size, 54 were not primary research articles (for example, review articles), 13 employed non-MPH drugs (that is, atomoxetine or amphetamine), 1 included a repeat patient cohort, 17 addressed unrelated topics (for example, autism disorder and MPH response), and 6 included genetic variants whose total study cohort did not exceed three. After filtering by

these criteria, 36 total studies (n = 3647 children) remained and were used to assess MPH efficacy for childhood ADHD treatment.

From the pooled childhood cohort (mean age = 9.5 years; age range = 4.3–12.8 years; % male = 83%), we report results from nine allelic variants distributed among six genes (Supplementary Table 1). Of these, we meta-analyzed data from three publications for rs28386840 (*SLC6A2*), seven for rs5569 (*SLC6A2*), four for rs1800544 (*ADRA2A*), seven for rs4680 (*COMT*), four for rs6551665 (*LPHN3*), three for rs1947274 (*LPHN3*), six for the 4-repeat VNTR of *DRD4*, five for the 7-repeat VNTR of *DRD4*, and 16 for the 10-repeat VNTR of *SLC6A3*. All but two studies used DSM-IV criteria to diagnose ADHD; DSM-III and ICD-10 codes were used by Winsberg *et al*[38] and Seeger *et al.*,[39] respectively. Most of the studies analyzed were of high quality—58.9% of studies were rated ‘strong’, 35.7% were rated ‘moderate’ and 3.6% were rated ‘weak’ using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies (QA). All but two studies (Tharoor *et al.*,[40] and Kirley et al,[41]) utilized a prospective study design.

Association of MPH and variants

Using a fixed-effect model for analysis, we identified a significant association between MPH efficacy and DNA variants tagging the genes. Five studies reported data on adverse events in addition to efficacy; however, there was not enough data to support statistical analysis. Several genes significantly affected the response to MPH: *SLC6A2, ADRA2A, COMT, DRD4* and *SLC6A3* (Figures 2, 3). Odds ratios were used as a measure of effect size and ranged from 0.95 to 2.9. When correlating MPH efficacy to polymorphisms, four SNPs reached statistical significance: rs28386840 (*SLC6A2*), rs5569 (*SLC6A2*), rs1800544 (*ADRA2A*) and rs4680 (*COMT*) (Figures 2a–d). For rs28386840 (*SLC6A2*), the T allele was associated with an improved response to MPH treatment when compared to the A/A genotype (OR: 2.93, CI: 1.76–4.90, $P < 0.0001$) (Figure 2a). The G/G genotype of rs5569 (*SLC6A2*) was associated with an improved MPH response compared to A allele carriers (OR: 1.73, CI: 1.26–2.37, $P = 0.0007$) (Figure 2b). Furthermore, the G allele of rs1800544 (*ADRA2A*) was associated with improved MPH response compared to C allele carriers (OR: 1.69, CI: 1.12–2.55, $P = 0.01$) (Figure 2c). Meta-analysis of the rs4680 variant in *COMT* revealed that the Val/Val genotype was associated with improved treatment response compared with Met allele carriers (OR: 1.40, CI: 1.04–1.87, $P = 0.02$) (Figure 2d). Two variants within the *LPHN3* gene were not significantly associated with MPH response: rs5661665 (OR: 1.07, CI: 0.84–1.37, $P = 0.59$) and rs1947274 (OR: 0.95, CI: 0.71–1.26, $P = 0.70$) (Figures 2e and f).

Two classifications of the *DRD4* 48bp VNTR polymorphism have been reported in the literature, the 4-repeat allele versus others and the 7-repeat allele versus others. The homozygous 4-repeat genotype demonstrated an association with improved MPH response when compared to other genotypes (OR: 1.66, CI: 1.16–2.37, $P = 0.005$) (Figure 3a). In contrast, meta-analysis of the 7-repeat allele versus others did not reach statistical significance (OR: 0.68, CI: 0.47–1.00, $P = 0.05$) (Figure 3b). Lastly, the homozygous 10-repeat genotype of the 40bp VNTR in the *SLC6A3* gene was significantly associated with reduced efficacy (OR: 0.74, CI: 0.60–0.90, $P = 0.004$) (Figure 3c).

Three additional genetic variants—within the Glutamate Ionotropic Receptor NMDA Type Subunit 2B (*GRIN2B*), Brain-derived Neurotrophic Factor (*BDNF*) and Synaptosomal-associated Protein 25 (*SNAP-25*) genes—were found in our systematic search, but did not meet our inclusion criteria because the total study cohort for these variants did not exceed three.[42–46] The C/C genotype of rs2284411 (*GRIN2B*) was associated with improved MPH treatment response (OR: 9.03, CI: 1.02–79.99, $P = 0.05$). The Val/Val genotype of rs6265 *(BDNF)* was not significantly associated with MPH response, despite having a substantial effect size (OR: 6.67, CI: 0.84–52.89, $P = 0.07$). Finally, the T/T genotype of rs3746544 (*SNAP25*) was not significantly associated with treatment response in two studies (OR:1.12, CI: 0.55–2.25, $P = 0.86$;OR: 1.66, CI: 0.51–5.39, $P = 0.41$).

Evidence for publication bias

We tested for publication bias by first assessing funnel plots for symmetry. Funnel plots present the relationship between effect size (odds ratio) and s.e. of log(OR) (Supplementary Figure 1). An asymmetrical distribution was visually identified in funnel plots for rs6551665 (*LPHN3*) and the 10-repeat VNTR (*SLC6A3*) (Supplementary Figures 1F and 1I, respectively). Egger's regression tests detected significant publication bias (asymmetry) for both DNA variants ($P = 0.01$). To adjust for this publication bias, we recomputed the effect sizes for both DNA variants using Duval and Tweedie's trim and fill method, which removes the most extreme small studies from the positive side of the funnel plot, provides an estimate of the number of studies that were not published, imputes the effect sizes of those missing studies, and calculates an adjusted overall effect.[47,48] The adjusted effect size for the G allele of rs6551665 (*LPHN3*), as compared to the A allele, was not significant after imputing two studies (OR: 0.84, CI: 0.68–1.04, $P < 0.1$) (Supplementary Figure 2A). In contrast, the adjusted effect size for the 10-repeat homozygous VNTR (*SLC6A3*), compared with other repeat variants, remained significant after imputing four studies (OR: 0.82, CI: 0.67–1.00, $P < 0.05$) (Supplementary Figures 2A,B).

Accounting for heterogeneity

Heterogeneity and inconsistency statistics (χ^2 and I^2) were computed for all genetic variants meta-analyzed: rs28386840 (*SLC6A2*) ($\chi^2 = 2.18$, $P = 0.34$; $I^2 = 8\%$), rs5569 (*SLC6A2*) ($\chi^2 = 5.92$, $P = 0.43$; $I^2 = 0\%$), rs1800544 (*ADRA2A*) ($\chi^2 = 14.73$, $P = 0.002$; $I^2 = 80\%$), rs4680 (*COMT*) ($\chi^2 = 19.96$, $P = 0.003$; $I^2 = 70\%$), rs5661665 (*LPHN3*) ($\chi^2 = 12.96$, $P = 0.005$; $I^2 = 77\%$), rs1947274 (*LPHN3*) ($\chi^2 = 10.44$, $P = 0.005$; $I^2 = 81\%$), 4-repeat VNTR (*DRD4*) ($\chi^2 = 8.23$, $P = 0.14$; $I^2 = 39\%$), 7-repeat VNTR (*DRD4*) ($\chi^2 = 11.36$, $P = 0.02$; $I^2 = 65\%$), 10-repeat VNTR (*SLC6A3*) ($\chi^2 = 47.37$, $P < 0.0001$; $I^2 = 68\%$). The *ADRA2A, COMT, SLC6A3* and *LPHN3* genes had high heterogeneity (> 65%) while *DRD4* had moderate (30–64%) and *SLC6A2* had no to low (< 29%) heterogeneity. As many of the meta-analyzed variants had moderate to high heterogeneity, we performed meta-regressions using a fixed-effect model to assess the relationship between covariates (mean age, gender and study quality) and effect size.

The majority of effect sizes were not significantly associated with the mean age of the study participants; however, the association between the G allele of rs1800544 (*ADRA2A*) and MPH response was stronger in studies of older cohorts ((k) = 4 (number of studies), $b =$

0.3662, $P = 0.01$). The opposite was true when examining the association between the G/G genotype of rs5569 (*SLC6A2*) and MPH efficacy—the association was stronger in studies with a relatively younger cohort ($k = 7$, $b = -0.7139$, $P = 0.04$). Effect sizes of several genetic variants were moderated by study participant gender ratios. The association of MPH response and both the Val/Val genotype of rs4680 (*COMT*) and the 7-repeat VNTR (*DRD4*) was weaker in studies that included a higher proportion of male participants ($k = 7$, $b = -0.0490$, $P = 0.004$ and $k = 2$, $b = -0.1952$, $P = 0.005$, respectively). The opposite was true for the associations of the G allele of rs1800544 (*ADRA2A*), the A allele of rs1947274 (*LPHN3*), and the G allele of rs6551665 (*LPHN3*); a larger proportion of male participants yielded a stronger association ($k = 4$, $b = 0.2226$, $P = 0.002$; $k = 2$, $b = 0.0865$, $P = 0.004$; $k = 2$, $b = 12.4$, $P = 0.03$, respectively). Study quality was significantly associated with the effect size of rs1800544 (*ADRA2A*) such that studies of higher quality revealed stronger associations between the G allele and MPH efficacy ($k = 4$, $b = 1.0876$, $P = 0.01$). Finally, genetic variants that reached statistical significance in the meta-analysis and showed no evidence of publication bias were combined in a meta-regression analysis to determine whether study quality predicted effect size. This analysis found no significant effect size associations with MPH response ($k = 55$, $b = 0.0626$, $P = 0.4885$) (Supplementary Figure 3). Finally, a Welch's unequal variances *t*-test comparing randomized controlled trials to all other study designs was not significant ($P = 0.35$).

DISCUSSION

Here, we report the plausibility of *SLC6A2, COMT, ADRA2A, SLC6A3* and *DRD4* as genetic candidates to predict MPH efficacy in children. Several polymorphic variants tagging these genes significantly affected MPH treatment efficacy in ADHD-children: rs28386840 and rs5569 (*SLC6A2*), rs4680 (*COMT*), rs1800544 (*ADRA2A*) (Figure 2). We also report a significant association between MPH efficacy and DNA repeat variants, 10-repeat VNTR (*SLC6A3*) and 4-repeat VNTR (*DRD4*) (Figure 3). Both rs5661665 and rs1947274 (*LPHN3*) failed to reach statistical significance, as did the 7-repeat VNTR(*DRD4*); all three of these non-significant variants had moderate-to-high heterogeneity. Among the significant associations identified, *SLC6A2* variants showed no to low heterogeneity, whereas *DRD4, SLC6A3, COMT* and *ADRA2A* variants showed moderate to high heterogeneity. Finally, an Egger's Regression Test identified publication bias for the *SLC6A3* DNA variant; however, the association remained significant after correction with Duval and Tweedie's Trim and Fill (Supplementary Figure 2B).

Nineteen studies were not included in the meta-analyses because an odds ratio could not be calculated from the published data. In studies where an effect size could not be computed, relevant results were reviewed qualitatively. Three studies investigated the effect of rs1800544 (*ADRA2A*) and MPH response by measuring differential treatment outcomes in the GG genotype and C allele carriers. Each found no significant association between the SNP and an improved response to MPH.[49–51] Sengupta *et al.*[52] examined the association between *COMT* rs4680 and MPH response by rating task-oriented behavior, but found no significant genotype by treatment interaction effect. Two studies showed that there was no significant association between the 10-repeat VNTR in *SLC6A3* and response to MPH.[53,54]

Another study that examined the *SLC6A3* VNTR showed an association between the 10R/10R genotype and an improved neurocognitive response.[55]

SLC6A2 is a sensible biological candidate for predicting MPH efficacy. Encoding the norepinephrine transporter, it plays a vital role in the adrenergic system and is the main target of atomoxetine, a non-stimulant with ADHD efficacy. In addition, previous studies have shown that MPH is a potent inhibitor of the norepinephrine transporter, providing evidence of its mechanism of action. Here we report two SNPs, both of which have shown compelling associations with ADHD risk in previous studies.[56–58] Firstly, rs28386840 is at position – 3081 upstream of the transcription initiation site. The T allele significantly reduces promoter function relative to the A allele and our analyses show it to be associated with a 193% increased risk of poor MPH efficacy[59] (Figure 2a). Also, the A allele of rs5569, located at position 1287 in exon 9, was associated with a 73% increased risk for poor MPH efficacy (Figure 2b). Among the DNA variants examined in our meta-analysis, variants within the *SLC6A2* gene showed the strongest correlation to MPH efficacy in ADHD-children. Statistical results from these analyses have little to no heterogeneity and both exceeded our *a priori* standards for significance.

A similarly pivotal component of the noradrenergic system is the alpha-2-adrenergic receptor, encoded by the *ADRA2A* gene. This receptor is the main target of guanfacine and clonidine, both of which are non-stimulants. Evidence supporting *ADRA2A* involvement in the etiology of ADHD comes from studies suggesting that prefrontal cortex alpha 2a-adrenoreceptors influence executive functions like attention and inhibitory control.[60] Here, it is important to note that, generally speaking, the biology of treatment response and ADHD etiology are distinct. The two do not have to be linked and are often not (for example, in the case of narcolepsy). Further, our findings are consistent with prior evidence that MPH has been shown to increase stimulation of alpha-2A-adrenergic receptors.[61] Owing to its implication in the mode of action of MPH, it is not surprising that our meta-analysis reports a significant association between possession of a G allele and enhanced MPH efficacy for the promoter region SNP that creates a Msp1 restriction site (rs1800544). The C allele was associated with a 69% increased risk for poor MPH response (Figure 2c). In addition to the Msp1 polymorphism, Hha1 (rs1800545) and Dra1 (rs553668) restriction polymorphisms have been studied in relation to ADHD, though, they were not meta-analyzed here as they did not meet our criteria for inclusion (that is, three or more independent research articles per SNP were not identified).

Catechol-o-methyltransferase is an enzyme responsible for the degradation of catecholamines and plays an especially important role in regulating extracellular DA levels.[62] Encoded by the *COMT* gene, a SNP in exon 4 leads to a valine (Val) to methionine (Met) amino acid switch that ultimately causes reduced enzyme activity; homozygosity for the Val amino acid has been linked to 3–4 times reduced enzyme activity.[63] Owing to its function in the dopaminergic pathway, this gene was initially implicated in ADHD risk and is likely highly relevant to stimulant medication response.[56,64] We demonstrate here that Val/Val homozygotes demonstrate a 40% increased chance for efficacious MPH response (Figure 2d).

The 48-bp VNTR is the most widely studied *DRD4* gene polymorphism and has been associated with ADHD susceptibility in a number of case-controlled studies and meta-analyses.[56] The dopamine D4 receptor is a G-protein-coupled receptor that modulates signal transduction by altering intracellular cyclic AMP levels. Though there is ethnic variability, the most common alleles of this DNA variant have 2-, 4-, and 7-repeats.[65] While non-significant results were obtained when comparing the 7R variant to other repeat variants, children with a 4R/4R genotype showed a 66% increased chance for efficacious MPH response (Figures 3a and b). This is consistent with reports that the 4-repeat VNTR leads to higher receptor expression and increased sensitivity to dopamine, as compared to the 7-repeat variant.[66,67] From this and our results, we postulate that 7-repeat variant carriers have reduced dopamine 4 receptor expression and hence comparatively poor MPH efficacy, whereas 4-repeat carriers likely have ‘baseline’ dopamine 4 receptor expression.

SLC6A3 encodes the transmembrane DAT. Much research on this gene has focused on the 40-base pair VNTR polymorphism located in the 3′-untranslated region (3′UTR), which plays a regulatory role during transcription. The two common alleles, 9- and 10-repeats (9R and 10R), have shown mixed associations with stimulant efficacy during ADHD treatment.[64] In a recent meta-analysis, the 40-bp VNTR polymorphism of DAT was shown to regulate striatal DA levels and the amount of DAT expression in the striatum.[68] While this gene has been implicated in the underlying pathophysiology of ADHD,[14,58] it is also a key pharmacological target of stimulant ADHD medications approved for use in treating childhood ADHD.[69] As stimulant medications block the DAT, thereby increasing the concentration of DA in the synaptic cleft, it is intuitive to associate polymorphisms within *SLC6A3* with variable stimulant efficacy. Despite having identified publication bias among the body of *SLC6A3* studies meta-analyzed, after correction, the association between *SLC6A3* and MPH efficacy in children was significant with 10R/10R homozygotes demonstrating a 26% decreased risk for improved MPH efficacy (Figure 3c).

With regard to clinical implications, our results suggest that interventions accounting for individual genetic variability may improve outcomes of childhood-ADHD treatment. Although not all children will experience a poor response to MPH, it is unclear how to identify those who will respond and what alternative clinical interventions would remediate the liability in this ‘poor response’ subgroup. While there are not enough pharmacogenetic studies of MPH response, there are even fewer examining genetic variability and AMP, atomoxetine, guanfacine or clonidine response in children. Additionally, of the 36 studies meta-analyzed here, only five reported tolerability data. Linking genetic profiles to serious tolerability concerns (for example, tic disorder) that plague some MPH recipients would truly yield clinically valuable data. Even predicting minor adverse events could be useful when choosing an initial medication. Future research should focus on replicating these pooled-findings, assessing their specificity under various environmental conditions and combining multiple variants.

A number of genetic variants associated with MPH efficacy displayed high heterogeneity (I^2 values). This heterogeneity was not accounted for by study quality (Supplementary Figure 2) and other covariates were not available for analysis. Where publication bias was identified, effect sizes were adjusted using Duval and Tweedie’s trim and fill method. Simulation

studies have found that the trim and fill methods detects missing studies even in the absence of bias. This method may therefore give conservative estimates of the true effect size.[70]

In addition to methodological limitations, results are further confounded by small sample sizes and a low number of included studies. Specifically, *LPHN3* variants rs5661665 and rs1947274 show some potential for predicting MPH response, although we obtained non-significant results (Figures 2e and f). Such results should be viewed as intriguing pilot data. *LPHN3* encodes a member of the latrophilin subfamily of G-protein-coupled receptors in GABA-ergic neurotransmission and has been associated with ADHD susceptibility.[71] Furthermore, genetic—as well as cultural—diversity is correlated to ethnicity. Patients from different ethnic groups likely possess unique risk/protective factors that influence ADHD treatment efficacy.

Individual response to stimulant medication is complex and heterogeneous. In gene-by-environment analyses, prenatal and perinatal risk factors like prenatal smoking—in conjunction with functional polymorphisms—have been identified as potential predictors of MPH efficacy and tolerability.[72] Furthermore, ancestral informative markers are missing from our analysis. Comorbid disorders and ADHD sub-type were not accounted for in this analysis and may contribute additional heterogeneity to pooled-studies.

Currently, there is no reliable biological predictor for pharmacological ADHD treatment choice. Leveraging individual genetic variants within *SLC6A2, COMT, ADRA2A, SLC6A3* and *DRD4* present a plausible multivariate to assess risk for poor MPH efficacy. Although the odd ratios for each variant are low, it is possible that a multivariate predictor would be sufficiently accurate for clinical use. Clinically controlling ADHD symptomology is especially important in preschool- and adolescent-aged children as they face adversities and an increased assumption of risk from uncontrolled ADHD. ADHD-diagnosed preschool-aged children are more likely to become socially or academically deficient whereas adolescents are at greater risk for substance abuse and more likely to engage in promiscuous behavior.[73] Only half of children with ADHD followed pharmacological treatment regimens consistently over the course of a 5-year prospective study, and many reported adverse effects.[74] Perceived tolerability may also be an impediment to adherence to pharmacological treatment regimens.[75] Thus, it is not surprising that patients receiving personalized treatment were found to be more medication adherent.[76]

While much work has been done to unravel the genetic predictors of ADHD, there is a call in the literature for ‘a more practical clinical application surrounding prediction of side effect risk and medication tolerability’ and to ‘compile a portfolio of biomarker [genetic] information that would guide pharmacological treatment in order to quickly adopt an efficient regimen’.[77] This would likely prove helpful in treatment resistant or treatment intolerant patients. Collectively evaluating genetic variability among plausible biological markers for treatment success would eliminate trial-and-error treatment used today.[64] This approach has proven to be practical during a pharmacogenetics trial linking genetic predictors of irritability, social withdrawal and abnormal movements to treatment with MPH in preschool-aged children.[42] Through multidisciplinary research, future work should aim to actualize accurate environmental and genetic predictors that confer perilous or protective

factors in order to provide a comprehensive understanding of individualized risks during ADHD treatment with MPH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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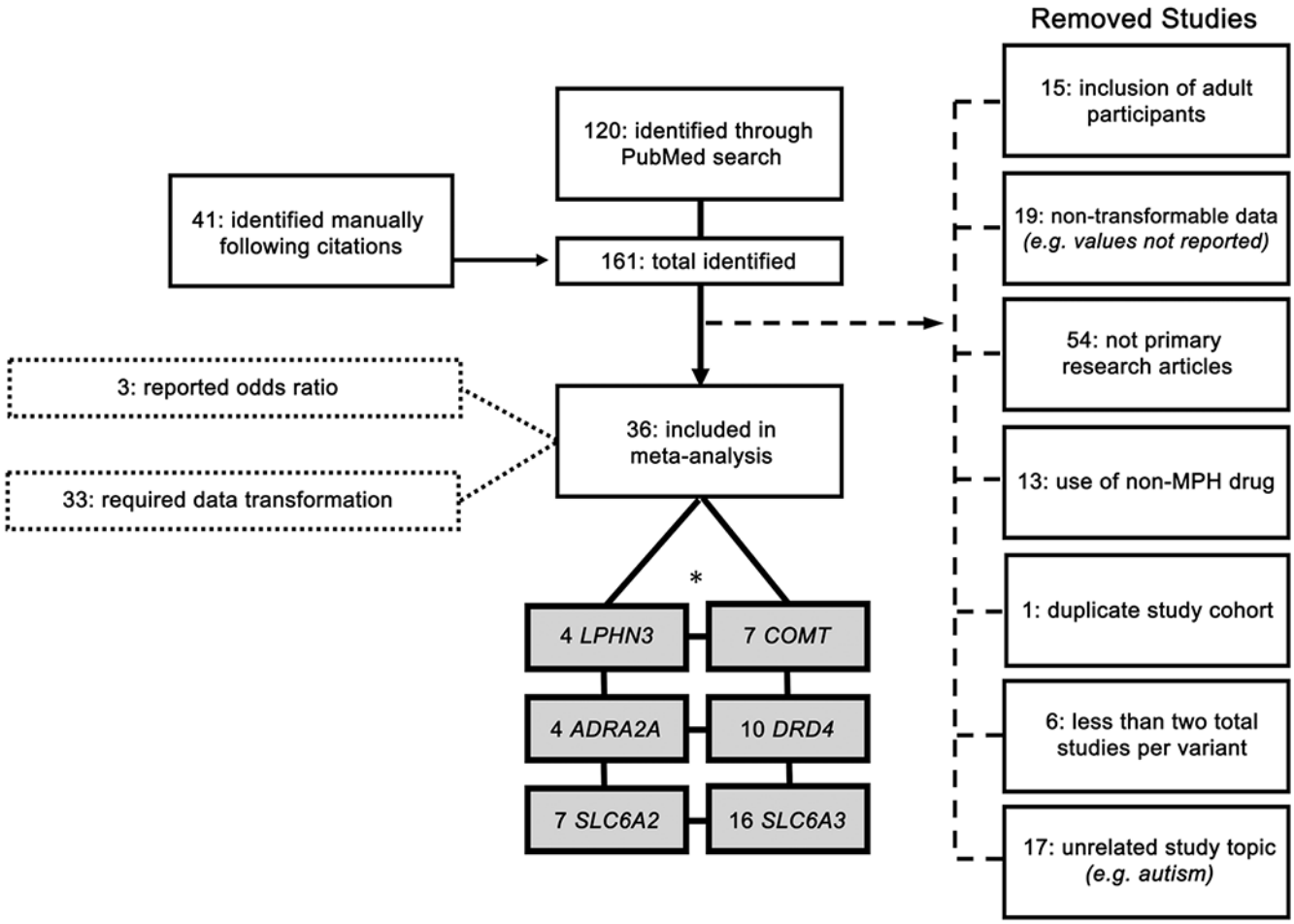

Figure 1.

Flow chart of study inclusion. Diagram depicts the systematic search progression used in this study. Boxes attached to the body of the diagram by a dashed line represent removed studies. Boxes attached to the body of the diagram by dotted lines represent data-input methods. Grayed boxes indicate included studies. *The six genes chosen for further meta-analysis exceed 36 (represented in diagram as ‘36 included in further analysis’) because some studies included more than one gene and/or genetic variant.

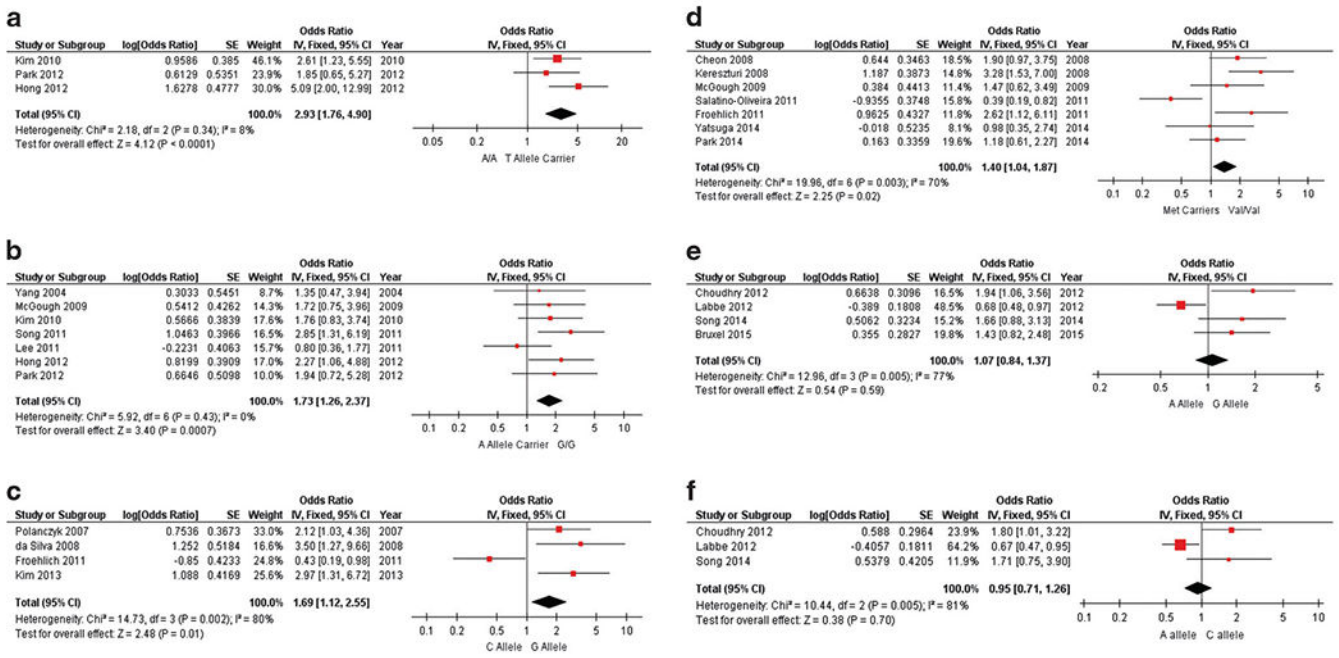

Figure 2.

Pooled results correlating MPH efficacy to SNPs. Forest plots of association between MPH efficacy and the following SNPs: (**a**) *SLC6A2* rs28386840; (**b**) *SLC6A2* rs5569; (**c**) *ADRA2A* rs1800544; (**d**) *COMT* rs4680; (**e**) *LPHN3* rs5661665; (**f**) *LPHN3 rs*1947274. Each forest plot represents one genetic variant and its computed effect size (odds ratio, measure of precision and *P*-value). Red squares are proportional to the studies' weights and horizontal black bars represent the corresponding 95% confidence interval (precision measurement) for each study. The vertical line at 1 indicates the null effect line and represents no differences between groups. The location of the black box represents the direction and magnitude of the pooled odds ratio that was generated from a fixed-effect model; its width represents the upper and lower bounds of the 95% confidence interval. Assessments of heterogeneity by χ^2 and I^2 are located on the left of each forest plot. A *P*-value is given for a test of the null. MPH, methylphenidate; SNP, single nucleotide polymorphism.

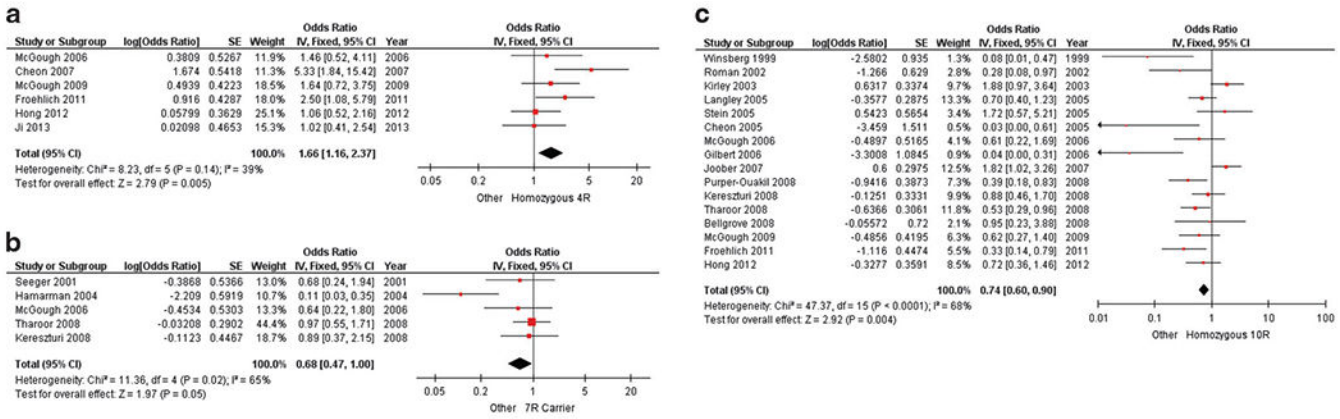

Figure 3.

Pooled results correlating MPH efficacy to VNTRs. Forest plots of association between MPH efficacy and the following DNA variants: (**a**) *DRD4* 4-repeat; (**b**) *DRD4 7*-repeat; (**c**) *SLC6A3* 10-repeat. Each forest plot represents one genetic variant and its computed effect size (odds ratio, measure of precision and *P*-value). Red squares are proportional to the studies' weights and horizontal black bars represent the corresponding 95% confidence interval (precision measurement) for each study. The vertical line at 1 indicates the null effect line and represents no differences between groups. The location of the black box represents the direction and magnitude of the pooled odds ratio that was generated from a fixed-effect model; its width represents the upper and lower bounds of the 95% confidence interval. Assessments of heterogeneity by χ^2 and I^2 are located on the left of each forest plot. A *P*-value is given for a test of the null. MPH, methylphenidate.