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.