

## Get to know a gene: ADRA2A

**Summary:** The ADRA2A -1291 G>C polymorphism has been studied extensively with methylphenidate treatment outcomes in ADHD. While certain studies have produced inconclusive results, evidence suggests that individuals with the C/C genotype may have a moderately reduced response to methylphenidate compared to G allele carriers.

### What is ADRA2A?

ADRA2A encodes the  $\alpha$ -2A adrenergic receptor, which is a norepinephrine receptor. The  $\alpha$ -2A adrenergic receptor is predominantly found in the brain and is concentrated in the prefrontal cortex (PFC).<sup>1</sup> This receptor is thought to mediate the effects of norepinephrine in the PFC and regulate symptoms of attention-deficit/hyperactivity disorder (ADHD).<sup>2</sup> Certain ADHD-indicated medications directly stimulate the  $\alpha$ -2A adrenergic receptor, while others mediate changes in circulating norepinephrine levels, which may indirectly impact the activity of this receptor.<sup>3</sup>

A few polymorphisms have been identified in this gene. The most studied is a single G>C substitution at position -1291 (rs1800544) in the promotor region of ADRA2A.<sup>4</sup> While the functional effect of this polymorphism is not well understood, studies have shown that this polymorphism may result in altered outcomes with methylphenidate when utilized for the treatment of ADHD.

### Is there a connection between ADRA2A genotype and methylphenidate treatment outcomes?

Fourteen studies and two meta-analyses have assessed the effect of the ADRA2A -1291G>C polymorphism on methylphenidate (MPH) treatment outcomes in ADHD.<sup>5-19</sup> Three studies (n=279) showed that the -1291G>C polymorphism was associated with reduced MPH treatment response.<sup>5-7</sup> Two of these studies (n=165) found that the presence of the G allele improved inattentive symptoms for adolescent patients taking MPH compared to those with the C/C genotype (p=0.01 and p=0.016, respectively).<sup>5,6</sup> Similarly, the third study by Cheon et al. (n=114) found that adolescents with the G/G genotype who were taking MPH had greater improvement of inattentive and total ADHD symptoms compared to C allele carriers (p=0.029).<sup>7</sup> Another study showed an association with the -1291G>C polymorphism and increased side effects with MPH treatment. This study (n=101) found that G allele carriers had lower diastolic blood pressure changes during MPH treatment in comparison to those with the C/C genotype (p=0.009).<sup>8</sup>

In contrast, one study (n=108) found that the G/G genotype was associated with reduced treatment response in an adolescent sample (p=0.045).<sup>9</sup> Additionally, nine studies found inconclusive results when evaluating the -1291G>C polymorphism on MPH treatment outcomes in ADHD.<sup>10-18</sup> Differences in study results may be due to the different methods of study design, sample demographics, and outcome measures utilized.

Myer et al. conducted a meta-analysis on pharmacogenetic predictors of MPH efficacy in childhood ADHD, which included the ADRA2A -1291G>C polymorphism.<sup>19</sup> Four ADRA2A studies<sup>5,6,11,13</sup> were included in this meta-analysis, and results showed a significant association between the G allele and improved MPH treatment response in comparison to C allele carriers (OR=1.69, p=0.01).<sup>19</sup> However, it is important to note that significant heterogeneity between studies was found alongside these results, further supporting differences in study designs and outcome measurements utilized between studies. Therefore, Myriad Neuroscience conducted an internal meta-analysis to assess the association between the -1291 G>C polymorphism and MPH treatment outcomes in ADHD utilizing methods to assess individual studies with varying study designs and outcome measurement types. Results showed a significant association of improved MPH treatment outcomes in G allele carriers vs. the C/C genotype, though the effect size of this finding was small.<sup>20</sup>

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## Is there a connection between ADRA2A genotype and other ADHD medications?

There is a lack of evidence surrounding the association of the -1291 G>C polymorphism and treatment outcomes with other ADHD medications besides MPH. There are currently no studies that have evaluated the potential effect of ADRA2A genotype on clonidine and guanfacine in ADHD patients. Similarly, there are currently no studies between the -1291 G>C polymorphism and amphetamine salts. One study (n=111) has been conducted between atomoxetine efficacy and the -1291 G>C polymorphism in ADHD patients, but the results were not significant.<sup>21</sup>

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