COMT: methylphenidate 6432/6433

95% CI = 95% confidence interval, COMT = catechol-O-methyltransferase, Met/Met = genotype leading to reduced COMT activity, NS = not significant, OR = odds ratio, S = significant, Val/Met = genotype leading to slightly reduced COMT activity, Val/Val = genotype leading to normal COMT activity.

Disclaimer: The Pharmacogenetics Working Group of the KNMP formulates the optimal recommendations for each phenotype group based on the available evidence. If this optimal recommendation cannot be followed due to practical restrictions, e.g. therapeutic drug monitoring or a lower dose is not available, the health care professional should consider the next best option.

Brief summary and justification of choices:
Methylphenidate is thought to exert its therapeutic effects by increasing synaptic levels of dopamine and noradrenaline through the inhibition of dopamine and noradrenaline transporters. Catechol-O-methyltransferase (COMT) inactivates catecholamines as dopamine and noradrenaline by methylation. A gene variant of COMT, named the Met-allele, results in a reduced COMT activity and thus higher basal levels of dopamine and noradrenaline. For this reason, this gene variant might influence the effect of methylphenidate.
However, of 11 studies investigating the effect of this gene variant on efficacy of methylphenidate in ADHD patients, 8 studies did not find a significant effect (Pagerols 2017 (107 patients), Unal 2016 (108 patients), Park 2014 (120 patients), Contini 2012 (164 patients), Froehlich 2011 (89 patients), McGough 2009 (82 patients), Sengupta 2008 (212 patients), and Cheon 2008 (124 patients)). In two of these studies the significance of the effect disappeared after correction for multiple testing (Park 2014 (120 patients) and Cheon 2008 (124 patients)). A study with 112 ADHD patients found a better (or faster) response for patients with the Met-allele (genotypes Val/Met and Met/Met) (Salatino-Oliveira 2011). A study with 122 ADHD patients found a worse response for patients with the Met-allele (comparing Met/Met versus Val/Met versus Val/Val) (Kereszturi 2008). A study with 514 patients receiving methylphenidate during one week found a better response for Val/Met, but not for Met/Met (Fageera 2021). A meta-analysis of 7 studies with a total of 699 patients found a worse response for Val/Met+Met/Met (Myer 2018). However, this meta-analysis overestimates the effect by using a fixed-effects model despite high heterogeneity between the studies. Thus, this meta-analysis actually provides no evidence for a statistically significant effect.
Of two studies investigating the effect on adverse events, a study with 107 ADHD patients found no effect (Pagerols 2017) and a study with 82 ADHD patients found a decrease in the adverse event irritability for (Met/Met + Val/Met) versus Val/Val (McGough 2009).
Because the results on the efficacy are mostly negative and partly contradictory and because the results on the adverse events are not confirmed, the KNMP Pharmacogenetics Working Group concludes that there is not enough evidence for a gene-drug interaction and thus for a need of adjustment of therapy in patients with a genetic variant (no/no-interactions).
You can find an overview of the effects per genotype in the background information text of the gene-drug interactions in the KNMP Kennisbank. You might also have access to this background information text via your pharmacy or physician electronic decision support system.

Source	Code	Effect	Comments
ref. 1 Fageera W et al. COMT by DRD3 epistatic interaction in modulating behaviors in children with ADHD: a pharmaco-dynamic behavioral approach. J Atten Disord 2021;25:1720-30.	3	514 ADHD patients aged 6-12 years were treated with methylphenidate 0.5 mg/kg per day for 1 week. ADHD symptoms were assessed with the Conners' Parent and Teacher Rating Scales (Conners'-P and Conners'-T). Co-medication was excluded. If necessary, the study was preceded by 1 week of medication wash out. Children having an IQ < 70 or a history of Tourette's syndrome, autism, or psychosis were excluded. However, ADHD symptoms were not scored by a physician, which is the gold standard. In addition, treatment and scoring were during a very short period of 1 week, while scoring for a period of 6-8 weeks is usual and a period of 4 weeks is considered the minimum. Genotyping:	Author's conclusion: 'Conners' teacher scores: a marginal significant difference between the Val/Val group and the Val/Met was detected under methylphenidate, where the Val/Met group has a greater improvement on methylpheni-

<table>
<tr>
<td>PMID: 32564645.

ref. 1, continuation</td>
<td>Met/Met: AA
Val/Met: A</td>
<td>- 147x Val/Val
- 261x Val/Met
- 106x Met/Met

Results:
<table>
<tr><td colspan="5">Score for ADHD symptoms on the Conner’s rating scale (rated by either teachers or parents) compared to Val/Val:</td></tr>
<tr><td></td><td></td><td>Met/Met</td><td>Val/Met</td><td>value for Val/ Val</td></tr>
<tr><td rowspan="2">teacher</td><td>pre-treatment</td><td>x 0.96 (NS)</td><td>x 1.02 (NS)</td><td>68.9</td></tr>
<tr><td>after treatment</td><td>x 0.97 (NS)</td><td>x 0.98 (S)</td><td>56.6</td></tr>
<tr><td rowspan="2">parent</td><td>pre-treatment</td><td>x 1.00 (NS)</td><td>x 1.00 (NS)</td><td>73.1</td></tr>
<tr><td>after treatment</td><td>x 0.99 (NS)</td><td>x 1.00 (NS)</td><td>57.3</td></tr>
<tr><td colspan="5">Note: The only significant result would not be significant after Bonferroni correction for the three genotype groups (p = 0.05/3 = 0.017) (NS). Neither would this result be significant after Bonferroni correction for the two rater groups (p = 0.05/2 = 0.025) (NS).</td></tr>
<tr><td colspan="5">Methylphenidate treatment significantly reduced the ADHD symptom score.</td></tr>
</table>
Note: This study found significantly lower pre-treatment teacher rated ADHD symptom scores for Met/Met than for Val/Met.</td>
<td>date.’</td>
</tr>
<tr>
<td>ref. 2
Myer NM et al. Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD. Mol Psychiatry 2018;23:1929-36.
PMID: 29230023.</td>
<td>3

Val/Met+ Met/Met: B</td>
<td>Meta-analyses of 7 studies, with a total of 699 patients, investigating methylphenidate response in childhood ADHD. All studies were prospective.
6 of the 7 studies in the meta-analysis have also been included in this risk analysis separately (Park 2014, Froehlich 2011, Salatino-Oliveira 2011, McGough 2009, Cheon 2008, Kereszturi 2008).
Prospective registration of the protocol was not mentioned. In addition, the analysis protocol chosen was incorrect. A fixed-effects model was used for the analyses, but because heterogeneity cannot be a priori excluded in studies in humans, a random-effects model should have been chosen. A fixed-effects model overestimates the effect in case of heterogeneity between the studies. The search and selection strategy was transparent and data exaction was standardised.
Quality of the included studies (binned into ‘strong’, ‘moderate’ or ‘weak’ categories) was analysed with the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative Studies, but only published in a figure without reference to the separate studies. Most included studies were strong quality studies.
Publication bias was assessed with funnel plot. Results of Egger’s regression test were not reported for the COMT-variant.

Results:
<table>
<tr><td>Response for Val/Met+Met/Met compared to Val/Val:</td></tr>
<tr><td>OR = 0.71 (95% CI: 0.53-0.96) (S)</td></tr>
<tr><td>Heterogeneity between the studies was high.
Meta-regression analysis using a fixed-effect model showed association of the gene variant with methylphenidate response to be weaker in studies that included a higher proportion of male participants (S). Differences in mean age of the study participants and study quality did not explain heterogeneity.</td></tr>
<tr><td>Note: In case of heterogeneity between the studies, the fixed-effects model used for this meta-analysis overestimates the effect. Thus, this meta-analysis actually provides no evidence for a statistically significant effect.</td></tr>
<tr><td>Funnel plot showed no indications for publication bias.</td></tr>
</table></td>
<td>Author’s conclusion:
‘Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 ADRA-2A, rs4680 COMT, rs5569 SLC6A2 and rs28386840 SLC6A2, and, repeat variants variable number tandem repeat (VNTR) 4 DRD4 and VNTR 10 SLC6A3. These findings have major implications for advancing our therapeutic approach to childhood ADHD treatment.’</td>
</tr>
<tr>
<td>ref. 3
Pagerols M et al. Pharmacogene-</td>
<td>3</td>
<td>107 methylphenidate naive ADHD patients aged 5-16 years were treated with methylphenidate for 8 weeks. The mean dose of methylphenidate was 1.07 mg/kg per day. Treatment was</td>
<td>Author’s conclusion:</td>
</tr>
</table>

tics of methylphenidate response and tolerability in attention-deficit/ hyperactivity disorder. Pharmacogenomics J 2017;17:98-104. PubMed PMID: 26810137. **ref. 3, continuation**		started with low-to-moderate doses and doses were subsequently increased until no further clinical improvement or limiting adverse effects were observed. 21.5% of patients failed to show a response to methylphenidate and 65.1% had some treatment-related side effect (mainly insomnia (34.3%) and appetite reduction (25%)). The 7 point Clinical Global Impression - Improvement Subscale (CGI-I) was used to assess treatment success. Response was defined as a rating of 'very much improved' or 'very improved' by the parents and non-response as one of the other ratings, ranging from 'minimally or less improved' to 'very much worse'. In addition, treatment success was rated by clinicians using the 7 point Clinical Global Impression - Severity Scale (CGI-S). Response was defined as a decrease of at least two points on the CGI-S. Comedication with other psychotropic medications was not excluded. Comorbid oppositional defiant disorder, conduct disorder, depression and anxiety disorders were only excluded if they were the primary cause of ADHD symptomatology. For a gene variant with a minor allele frequency of 0.15, the study had a power of 76% and 90% to detect OR values > 2.5 for treatment failure and adverse events respectively, assuming a prevalence of 0.30 and 0.39. Because also other genes were investigated, the significance threshold was $p \leq 0.00022$ (0.05/228) according to Bonferroni correction for multiple comparisons. Genotyping: Genotyping was for 10 single nucleotide polymorphisms in the COMT gene, including the one resulting in the 158 Val → Met substitution. The genotyping results were not reported. Results: No effect of COMT gene variants on: - response (NS) - adverse events (NS)	'Pharmacogenetic research has focused on genes presumably related to the mechanism of action of methylphenidate, namely DAT1, DRD4 or COMT. … However, none of the SNPs located in these genes displayed significant associations with either methylphenidate response or side effects.'
	Met/Met: AA Val/Met: AA		
ref. 4 Unal D et al. Genetic variations in attention deficit hyperactivity disorder subtypes and treatment resistant cases. Psychiatry Investig 2016;13:427-33. PubMed PMID: 27482244.	3	108 stimulant naive ADHD patients aged 6-18 years were treated with methylphenidate for 4-6 weeks. The dose range of methylphenidate was 0.7-1.1 mg/kg per day. Doses were increased during follow-up until no further clinical improvement or limiting adverse effects were observed. 13 patients that did not comply with treatment and withdrew from the study prior to treatment response assessment were excluded. 9% of patients with the Val/Val genotype, 7% of patients with the Val/Met genotype and 19% of patients with the Met/Met genotype withdrew from the study prior to response assessment (significance not determined). The 7 point Clinical Global Impression - Severity Scale (CGI-S) was used to assess the severity of symptoms. The 100 point Global Assessment of Functioning Scale (GAS) was used to assess functionality. A score below 60 on this scale was considered to represent low functionality. ADHD symptoms were assessed with the Conners' Parent and Teacher Rating Scales (CPRS and CTRS). The Continuous Performance (CPT) and Trail Making tests (TMT-A and B) were used to assess neuropsychological deficits. Treatment response was defined as 2 points or greater improvement on the CGI-S and a total GAS score of 60 points or greater, a minimum of 50% improvement on any of the subscales of CPRS/CTRS, or improvement in one of the neuropsychological tests. Co-medication with other psychotropic medications was excluded. Psychiatric comorbidities other than oppositional defiant disorder, conduct disorder, and learning disorder were excluded. Genotyping:	Author's conclusion: 'COMT polymorphism was not associated with treatment response in the univariate analysis, similar to prior studies. However, the valine allele for rs4680 (COMT) was more frequent among treatment responders relative to prior reports.'

<table>
<tr>
<td>ref. 4, continuation</td>
<td>Met/Met: AA
Val/Met: AA</td>
<td>- 29x Val/Val
- 54x Val/Met
- 25x Met/Met

Results:
<table>
<tr><td colspan="4">Met/Met versus Val/Met versus Val/Val:</td></tr>
<tr><td></td><td>Met/Met</td><td>Val/Met</td><td>value for Val/Val</td></tr>
<tr><td rowspan="2">% of responders</td><td colspan="2">NS for Met/Met versus Val/Met versus Val/Val</td><td>76%</td></tr>
<tr><td colspan="3">Multiple regression analysis confirmed the absence of an effect of the COMT genotype on treatment response (NS).</td></tr>
</table>

Note: This study also did not find an association between COMT genotypes and ADHD (risk for ADHD, ADHD subtypes, symptom severity, global functioning, any of the CPRS/CTRS subscales and psychiatric comorbidities).</td>
<td></td>
</tr>
<tr>
<td>ref. 5
Park S et al. Catechol-O-methyltransferase Val158-Met polymorphism and a response of hyperactive-impulsive symptoms to methylphenidate: a replication study from South Korea.
J Psychopharmacol 2014;28:671-6.
PubMed PMID: 24763183.</td>
<td>4</td>
<td>120 stimulant naive ADHD patients aged 6-15 years were treated with methylphenidate for 8 weeks. The dose of methylphenidate was adjusted after 2 and 4 weeks based on symptoms and adverse effects.
The 7 point Clinical Global Impression - Severity Scale (CGI-S) was used to assess the severity of symptoms. The Continuous Performance Test (CPT, completed by the patients), the parent version of the ADHD Rating Scale-IV (ADHD-RS) and the investigator-rated 7 point Clinical Global Impressions-Improvement Scale (CGI-I) were used to measure response. In the CPT patients get stimuli on a computer screen for an extended period of time and should respond to part of these stimuli. Response was defined as a 10% decrease in missed responses, incorrect responses, response time or response-time variability in the CPT, a 50% decrease in the total, inattentive or hyperactive-impulsive scores on the ADHD-RS or a rating of ‘very much improved’ or ‘very improved’ on the CGI-I.
Psychiatric comorbidities, other than oppositional defiant disorder or anxiety disorder for which no medication was required, were excluded. Patients who missed medication more than three times were excluded.
Patient with the Val/Val genotype were older, had more often the inattentive and less often the hyperactive-impulsive or not otherwise specified ADHD subtype, and had a longer CPT response time before start of methylphenidate. However, odds ratios were corrected for age, ADHD subtype and final dose of methylphenidate.

Genotyping:
- 70x Val/Val
- 43x Val/Met
- 7x Met/Met

Results:
<table>
<tr><td colspan="3">Percentage of patients with treatment response for (Val/Met + Met/Met) versus Val/Val:</td></tr>
<tr><td>Test or subscale used</td><td>Val/Met + Met/Met</td><td>value for Val/Val</td></tr>
<tr><td>CGI-I</td><td>NS</td><td>64.3%</td></tr>
<tr><td>ADHD-RS, total score</td><td>NS</td><td>65.7%</td></tr>
<tr><td>ADHD-RS, inattention score</td><td>NS</td><td>57.1%</td></tr>
<tr><td rowspan="2">ADHD-RS, hyperactive-impulsive score</td><td>OR = 0.38 (95% CI: 0.15-0.97) (S)</td><td>74.3%</td></tr>
<tr><td colspan="2">p was 0.044. Thus, the result did not stay significant after correction for multiple testing (significance for</td></tr>
</table>
</td>
<td>Author’s conclusion:
‘Although the reported nominally significant associations did not stay significant after correcting for multiple testing, our results support previous findings about the possible involvement of the COMT (Val^{158}-Met) polymorphism in the treatment response to methylphenidate in children with ADHD.’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 5, continuation</td>
<td>Val/Met + Met/Met: AA</td>
<td>
<table>
<tr><td></td><td colspan="2">p < 0.05/7 (= 0.007)) (NS).</td></tr>
<tr><td>CPT, missed responses</td><td>NS</td><td>57.1%</td></tr>
<tr><td>CPT, incorrect responses</td><td>NS</td><td>48.6%</td></tr>
<tr><td>CPT, response time</td><td>NS</td><td>27.1%</td></tr>
<tr><td rowspan="2">CPT, response time variability</td><td>OR = 0.38 (95% CI: 0.16-0.90) (S)</td><td>67.1%</td></tr>
<tr><td colspan="2">p was 0.028. Thus, the result did not stay significant after correction for multiple testing (significance for p < 0.05/7 (= 0.007)) (NS).</td></tr>
</table>

Note: Patients with the Val/Val genotype had more often the inattentive and less often the hyperactive-impulsive or not otherwise specified ADHD subtype. In addition, these patients had a significantly longer response time in the CPT before start of methylphenidate than patients with the Val/Met or Met/Met genotype. However, the p-values for these results were 0.042 and 0.010 respectively, so the results did not stay significant after correction for multiple testing.
</td>
<td></td>
</tr>
<tr>
<td>ref. 6
Contini V et al. No significant association between genetic variants in 7 candidate genes and response to methylphenidate treatment in adult patients with ADHD. J Clin Psychopharmacol 2012;32:820-3. PubMed PMID: 23131881.</td>
<td>4

Val/Met + Met/Met: AA</td>
<td>164 adult ADHD patients were treated with immediate release methylphenidate for 30 days. The dose of methylphenidate was increased weekly until symptom control or occurrence of limiting adverse effects. The minimum dose was 0.3 mg/kg per day and the mean final dose was 0.52 mg/kg per day.
Response was defined as a 30% symptom reduction on the Swanson, Nolan and Pelham Rating Scale version IV (SNAP-IV) and a score of 2 points or less on the 7 point Clinical Global Impression-Severity scale (CGI-S).
Relevant co-medication was not excluded, but p was > 0.20 for the association between co-medication and response.
Associations were analysed by logistic regression analysis. Correction was for covariates with an association with both the study factor and outcome with p ≤ 0.20. For COMT, these were sex and baseline CGI-S score.

Genotyping (partly calculated with the Met allele frequency):
- 47x Val/Val
- 83x Val/Met
- 34x Met/Met

Results:
<table>
<tr><td colspan="2">Percentage of patients with treatment response compared to Val/Val (85%):</td></tr>
<tr><td>Val/Met + Met/Met</td><td>NS</td></tr>
</table>
</td>
<td>Author’s conclusion:
‘This study investigates the role of genetic variants (SLC6A4, HTR1B, TPH2, DBH, DRD4, COMT, and SNAP25) in the response to methylphenidate in a sample of 164 adults. No significant differences in allele or genotype frequencies between responders and nonresponders were detected. In conclusion, our findings do not support an effect of these genes in the pharmacogenetics of methylphenidate among adults with ADHD.’</td>
</tr>
<tr>
<td>ref. 7
Froehlich TE et al. Pharmacogenetic predictors of methylphenidate dose-response in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2011;50:1129-1139. PubMed PMID: 22024001.</td>
<td>4</td>
<td>89 stimulant naive ADHD patients aged 7-11 years received placebo and three doses of controlled release methylphenidate for 1 week each in a double blind crossover trial. Doses were 18, 27 or 36 mg per day for children ≤ 25 kg and 18, 36 or 54 mg per day for children > 25 kg. Only patients with the inattentive and combined ADHD subtype were included (in approximately equal numbers). The mean maximum dose was 1.57 mg/kg per day.
Psychiatric comorbidities were excluded with the exception of oppositional defiant disorder, conduct disorder, depression and anxiety disorders, which were not the primary cause of ADHD symptoms and did not require different treatment.
The Vanderbilt ADHD Parent Rating Scale (VADPRS) and Vanderbilt ADHD Teacher Rating Scale (VADTRS) were completed at baseline and after each week of the trial. An inattentive domain score was generated by totalling scores from the nine inattention symptoms, a hyperactive-impulsive domain by totalling score from the nine hyperactive-impulsive symptoms. Gene-</td>
<td>Author’s conclusion:
‘COMT was not significantly associated with methylphenidate response, although our pattern of results suggest that Val homozygotes experienced greater improvements in hyperactive-impulsive symptoms with increasing doses compared to other groups (p=0.09).’</td>
</tr>
</table>

<table>
<tr>
<td>ref. 7, continuation</td>
<td>Met/Met: AA
Val/Met: AA</td>
<td>dose effects were the primary outcome, because these reflect the effect of the gene on methylphenidate treatment.
Associations were analysed by linear mixed models. Bonferroni correction was for the two investigated domains ($p < 0.025$).
The study had 80% power to detect COMT-dose effect sizes of 1.03.

Genotyping:
- 30x Val/Val
- 40x Val/Met
- 19x Met/Met

Results:
<table>
<tr><td colspan="2">Methylphenidate response for Met/Met versus Val/Met versus Val/Val:</td></tr>
<tr><td>inattentive domain score</td><td>NS</td></tr>
<tr><td>hyperactive-impulsive domain score</td><td>NS</td></tr>
<tr><td colspan="2">Methylphenidate treatment significantly reduced the scores in both domains.</td></tr>
<tr><td colspan="2">The COMT genotype also did not have a treatment independent effect on the scores in both domains.</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>ref. 8
Salatino-Oliveira A et al.
Catechol-O-methyltransferase Valine158-Methionine polymorphism moderates methylphenidate effects on oppositional symptoms in boys with attention-deficit/hyperactivity disorder.
Biol Psychiatry 2011;70:216-21.
PubMed PMID: 21550019.</td>
<td>4

Val/Met + Met/Met: AA#
Val/Val: B</td>
<td>112 methylphenidate naive boys with ADHD aged 4-17 years were treated with immediate release methylphenidate for 3 months. The dose of methylphenidate was increased until no further clinical improvement was detected or until occurrence of significant side effects. The minimum dose was 0.3 mg/kg per day in 2 or 3 doses (mean starting dose 0.5 mg/kg per day and mean dose after 1 month of 0.65 mg/kg per day).
The parent-rated oppositional subscale of the Swanson, Nolan and Pelham Rating Scale version IV (SNAP-IV) was used.
Included patients had a baseline score > 1.
Relevant co-medication and concomitant psychosocial treatment were not excluded, but did not differ significantly between the genotype groups.

Genotyping (partly calculated with the Met allele frequency):
- 35x Val/Val
- 55x Val/Met
- 22x Met/Met

Results:
<table>
<tr><td colspan="2">Methylphenidate response for (Val/Met + Met/Met) versus Val/Val:</td></tr>
<tr><td rowspan="2">SNAP-IV oppositional scores</td><td>increased response (S for both the trajectory of response as for the score reduction after 1 and 3 months)</td></tr>
<tr><td>The difference in score reduction was larger after 1 month (x 1.99) than after 3 months (x 1.08), which might indicate a faster instead of a better response.</td></tr>
</table>
Note: Before start of treatment, genotype groups did not differ significantly in SNAP-IV oppositional, total, inattentive, or hyperactivity/impulsivity scores or in the rate of oppositional defiant or conduct disorder.</td>
<td>Author’s conclusion:
‘These results suggest an effect of the COMT genotype on the trajectory of oppositional defiant disorder symptoms improvement with methylphenidate treatment in boys with ADHD.’</td>
</tr>
<tr>
<td>ref. 9
McGough JJ et al.
A candidate gene analysis of methylphenidate response in attention-deficit/hyperactivity disorder.
J Am Acad Child</td>
<td>4</td>
<td>82 ADHD patients aged 6-17 years received placebo and three to four doses of immediate-release methylphenidate for 1 week each in a double blind crossover trial. Doses were 5, 10 or 15 mg per day for children < 25 kg and 5, 10, 15 or 20 mg per day for children ≥ 25 kg.
An age-appropriate math test sensitive to stimulant dose effect (the Permanent Product Measure of Performance (PERMP)) was applied 45 minutes after the first dose in each period. The number of problems attempted and correct were scored. The ADHD Rating Scale-IV (ADHD-RS) based on the investigator’s interview with parent and subject and the 7-point parent rated</td>
<td>Author’s conclusion:
‘ADHD symptom response was predicted by polymorphisms at the serotonin transporter (SLC6A4) intron 2 VNTR, with a suggested trend for catechol-</td>
</tr>
</table>

<table>
<tr>
<td>Adolesc Psychiatry 2009;48:1155-64.
PubMed PMID: 19858760.

ref. 9, continuation</td>
<td>Val/Met + Met/Met: AA#
Val/Val: B</td>
<td>Strength and Weaknesses of ADHD-symptoms and Normal Behaviour scale (SWAN) were used after each period to measure the ADHD symptoms. Potential side effects were evaluated with the parent rated Side Effects Scales, consisting of 4-point ratings of 11 adverse events that commonly occur with stimulants. Composite outcomes with the largest effects on variance were determined by principal components analyses. For efficacy these were ADHD symptoms, comprised of equally weighted standardized values from the ADHD-RS and SWAN total scores, and Math Problems Correct. For side effects these were Irritability, comprised of picking, worried/anxious, crabby/irritable, and tearful/sad/depressed; Vegetative Symptoms, comprised of dull/tired/listless, sleep problems, and appetite loss; Abnormal Movements, comprised of motor tics and buccal-lingual movements; and Somatic Symptoms, comprised of head-ache and stomach ache. Because side effects were absent or mild in most cases, each composite outcome for side effects was scored as absent or present.
Clinical need for other medication with central nervous system effects and current conditions that might require ongoing concomitant medication were excluded.
Bonferroni correction was for the two investigated efficacy outcomes ($p < 0.025$), but not for the four investigated side effect outcomes ($p < 0.05$).
The sample was sufficiently powered to detect small gene and gene x dose effects at $p < 0.025$ and medium effects at $p < 0.0005$.

Genotyping:
- 24x Val/Val
- 39x Val/Met
- 19x Met/Met

Results:
<table>
<tr><td colspan="2">Methylphenidate response for (Val/Met + Met/Met) versus Val/Val:</td></tr>
<tr><td>ADHD symptoms</td><td>NS</td></tr>
<tr><td>math problems correct</td><td>NS</td></tr>
<tr><td>irritability</td><td>decrease (S)</td></tr>
<tr><td>vegetative symptoms</td><td>NS</td></tr>
<tr><td>abnormal symptoms</td><td>NS</td></tr>
<tr><td>somatic symptoms</td><td>trend for an increase (NS, p = 0.07)</td></tr>
</table>

Note: There was a trend for a treatment independent effect of the COMT Val158Met polymorphism on ADHD symptoms ($p = 0.04$).</td>
<td>O-methyltransferase (COMT) (p=.04). ….. Irritability was predicted by COMT.’</td>
</tr>
<tr>
<td>ref. 10
Kereszturi E et al.
Catechol-O-methyltransferase Val158Met polymorphism is associated with methylphenidate response in ADHD children.
Am J Med Genet B Neuropsychiatr Genet 2008;147B:1431-5.
PubMed PMID: 18214865.</td>
<td>4</td>
<td>122 paediatric ADHD patients were treated for 6 months with methylphenidate 10-30 mg per day in two doses according to their body weight. The average daily dose was 0.22-0.95 mg/kg (mean 0.55 mg/kg).
The ADHD Rating Scale (ADHD-RS) and the 7 point Clinical Global Impression - Severity scale (CGI-S) were used to assess the severity of symptoms. Response was defined as a 25% decrease in ADHD-RS total score and a CGI-S score ≤ 2 points (no or minimal symptoms) after 6 months. Non-response was defined as less than 10% decrease in the ADHD-RS total score after 3 months. 90 patients were responders, 32 were non-responders.
Concomitant use of antipsychotics and antidepressants was excluded.
ADHD type differed significantly between the genotype groups with all Met/Met having the combined ADHD type and the hyperactive and inattentive types only occurring in Val/Met and Val/Val. However, the frequency of the ADHD type did not differ significantly between responders and non-responders.</td>
<td>Author’s conclusion:
‘The categorical analysis of 90 responders versus 32 non-responders showed an association between the Val-allele or Val/Val genotype and good methylphenidate response. Analyzing symptom severity as a continuous trait, significant interaction of COMT genotype and methylphenidate was found on</td>
</tr>
</table>

<table>
<tr>
<td>ref. 10, continuation</td>
<td>Val/Met: B
Met/Met: B</td>
<td>Genotyping:
- 39x Val/Val
- 59x Val/Met
- 24x Met/Met

Results:
<table>
<tr><td colspan="4">Methylphenidate response for Met/Met versus Val/Met versus Val/Val:</td></tr>
<tr><td></td><td>Met/Met</td><td>Val/Met</td><td>value for Val/Val</td></tr>
<tr><td rowspan="3">% responders</td><td>x 0.67</td><td>x 0.82</td><td>87%</td></tr>
<tr><td colspan="3">S for Met/Met versus Val/Met versus Val/Val</td></tr>
<tr><td colspan="3">S for the Val-allele versus the Met-allele</td></tr>
<tr><td rowspan="2">ADHD-RS inattention score after the first treatment month</td><td colspan="3">NS for Met/Met versus Val/Met ver-sus Val/Val</td></tr>
<tr><td colspan="3">trend for the multivariate interaction between methylphenidate and genotype (p = 0.097)</td></tr>
<tr><td rowspan="4">ADHD-RS hyperactivity/ impulsivity score after the first treatment month</td><td>x 1.37</td><td>x 1.16</td><td>10.97</td></tr>
<tr><td colspan="3">S for Met/Met versus Val/Met versus Val/Val</td></tr>
<tr><td colspan="3">S for the multivariate interaction between methylphenidate and genotype</td></tr>
<tr><td colspan="3">S for the extent of decrease from baseline</td></tr>
<tr><td rowspan="2">CGI-S score</td><td colspan="3">NS for Met/Met versus Val/Met versus Val/Val</td></tr>
<tr><td colspan="3">NS for the multivariate interaction between methylphenidate and genotype</td></tr>
<tr><td colspan="4">Similar results were obtained in the subgroup with the combined ADHD type.</td></tr>
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Note: Comparison of 173 paediatric ADHD patients with 284 controls, demonstrated a higher frequency of the Val-allele and the Val/Val genotype in the ADHD patients (S for both, with the significance for the Val-allele remaining after False Discovery Rate adjustment for multiple testing). Transmission Disequilibrium Test analysis showed a tendency of over-transmission of the Val-allele from the parent to the ADHD child (p = 0.087). So, the Val-allele might play a role in development of ADHD. However, the Val-allele had no effect on ADHD symptoms before start of treatment (neither on the ADHD-RS inattention subscale, the ADHD-RS hyperactivity/impulsivity subscale nor on the CGI-S) (NS).</td>
<td>the Hyperactivity-Impulsivity scale. Symptom severity scores of all three genotype groups decreased following methylphenidate administration, however Val/Val homozygote children had significantly less severe symptoms than those with Met/Met genotype after treatment.’</td>
</tr>
<tr>
<td>ref. 11
Sengupta S et al. COMT Val108/158Met polymorphism and the modulation of task-oriented behavior in children with ADHD. Neuropsychopharmacology 2008;33:3069-77.
PubMed PMID: 18580877.</td>
<td>3</td>
<td>212 ADHD patients aged 6-12 years received placebo and methylphenidate 0.5 mg/kg per day in two doses for 1 week each in a double blind crossover trial. Behaviour was measured before and after the treatment week. In addition, acute treatment effects were assessed on day 3 by comparing behaviour before and 1 hour after dosing.
Behaviour was measured with the Restricted Academic Situation Scale (RASS). After being allowed to play for 5 minutes in a clinic playroom, children were instructed to sit at a table and complete as many math problems as possible. Behavioural events were recorded at 30-seconds intervals according to five categories: off-task (looking away from the task sheet), playing with objects (touching any object not directly used in the task), out of seat (lifting buttocks off chair or moving chair), vocalizing (any vocal noise, whether task related or not), and fidgeting (repetitive, purposeless movements). The RASS score is the total number of behavioural events in a 15-minute period.
Overall motor activity of the non-dominant hand was estimated</td>
<td>Author’s conclusion:
‘These results suggest that the COMT Val108/158Met polymorphism modulates task-oriented behaviour, but it does not modulate the response of this behaviour to methylphenidate treatment.’</td>
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<td>ref. 11, continuation</td>
<td>Met/Met: AA
Val/Met: AA</td>
<td>using actiwatch® actigraphy. The total number of 30-seconds intervals with at least one movement was recorded.
Tourette syndrome, pervasive development disorder, and psychosis were excluded. Co-medication with effect on the central nervous system was not excluded.

Genotyping:
- 55x Val/Val
- 115x Val/Met
- 42x Met/Met

Results:
<table>
<tr><td colspan="2">Methylphenidate response for Met/Met versus Val/Met versus Val/Val:</td></tr>
<tr><td>total RASS score</td><td>NS</td></tr>
<tr><td>motor activity</td><td>NS</td></tr>
<tr><td colspan="2">Methylphenidate treatment significantly reduced both scores.</td></tr>
</table>
Note: The COMT genotype had a treatment independent effect on the total RASS score with the Val/Val genotype resulting in more behavioural events and less engagement in the math task (S). There was no difference between Met/Met and Val/Met (NS). This treatment independent effect of the COMT genotype was also observed for the subscales off task and playing with objects (S). There was a trend for the subscale out of seat (p = 0.07) and no association for vocalizing and fidgeting (NS). Results were similar when the analysis was restricted to White children .
The COMT genotype had no effect on motor activity (NS).</td>
<td></td>
</tr>
<tr>
<td>ref. 12
Cheon KA et al. Association of the catechol-O-methyltransferase polymorphism with methylphenidate response in a classroom setting in children with attention-deficit hyperactivity disorder. Int Clin Psychopharmacol 2008;23:291-8. PubMed PMID: 18703939.</td>
<td>3

Val/Met: AA
Met/Met:</td>
<td>124 stimulant naive ADHD patients aged 6-12 years were treated for 8 weeks with methylphenidate. Doses were increased up to a dose sufficient for therapeutic effects, based on the parents' reports of symptom improvement and side effects.
The ADHD Rating Scale-IV (ADHD-RS) completed by parents and teachers was used to assess the severity of symptoms before and after treatment. For ADHD-RS, 9 items relating to inattention and 9 items relating to hyperactivity and impulsivity are scored on a 4-point scale. Response was defined as a reduction of the ADHD-RS score with 50% or more.
Comorbidity and concomitant use of other drugs with effects on the central nervous system were not excluded. However, comorbidity did not have a significant effect on treatment response.

Genotyping:
- 68x Val/Val
- 48x Val/Met
- 8x Met/Met

Results:
<table>
<tr><td colspan="4">Results for Met/Met versus Val/Met versus Val/Val:</td></tr>
<tr><td></td><td>Met/Met</td><td>Val/Met</td><td>value for Val/Val</td></tr>
<tr><td>% responders, parent rated</td><td colspan="2">NS for Met/Met versus Val/Met versus Val/Val</td><td>57%</td></tr>
<tr><td rowspan="4">% responders, teacher rated</td><td>x 0.21</td><td>x 0.81</td><td>59%</td></tr>
<tr><td colspan="3">S for Met/Met versus Val/Met versus Val/Val</td></tr>
<tr><td colspan="3">S for the Met/Met frequency in responders versus non-responders, trend for the Val/Val frequency in responders versus non-responders (NS; p = 0.077).</td></tr>
<tr><td colspan="3">None of the above results would be significant after Bonferroni correction for the three genotype</td></tr>
</table>
</td>
<td>Author's conclusion:
'Our findings provide evidence of an association between the COMT genotype and methylphenidate response as assessed by the teachers of children with ADHD. … No significant association, however, was found between the genotype of COMT and the response to treatment with methylphenidate as assessed by their parents.'</td>
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</table>

ref. 12, continuation	AA		groups (p = 0.05/3 = 0.017) (NS). Neither would any of the results be significant after Bonferroni correction for the two rater groups (p = 0.05/2 = 0.025) (NS).		
			Note: There was a large numerical difference in the response rating of the Met/Met group by parents and teachers. This genotype had numerically the best response as rated by the parents (75% responders) and the worst response as rated by the teachers (13% responders).		
		final methylphenidate dose (mg/day)	NS for Met/Met versus Val/Met versus Val/Val	34.07	
		mean methylphenidate dose (mg/day)	NS for Met/Met versus Val/Met versus Val/Val	25.86	
		Note: There was no correlation between the COMT-genotype and either the ADHD-subtype or the comorbidity.			

Risk group	-

Comments:

- Only studies with more than 75 patients were included in the risk analysis. Other articles did not contribute enough to the evidence to be included.
  Fageera 2021 J Psychiatr Res (Fageera W et al. Association between COMT methylation and response to treatment in children with ADHD. J Psychiatr Res 2021;135:86-93. PMID: 33453563) was not included in the risk analysis, because this study concerns a subset of the patients in Fageera 2021 J Atten Disord.

Date of the literature search: 14 December 2021.

	Genotype	**Code**	**Gene-drug interaction**	**Action**	**Date**
KNMP Pharmacogenetics Working Group decision	Val/Met	4 B	no	no	31 January 2022
	Met/Met	4 B	no	no	

Mechanism:

Methylphenidate is thought to exert its therapeutic effects by increasing synaptic levels of dopamine and noradrenaline through the inhibition of dopamine and noradrenaline transporters. Catechol-O-methyltransferase (COMT) inactivates catecholamines as dopamine and noradrenaline by methylation.