Get to know a gene: COMT

Summary: The Val158Met polymorphism (rs4680) in the COMT gene can affect baseline levels of synaptic catecholamines. Several studies have assessed the impact of this polymorphism on treatment outcomes with psychotropic medications. However, studies have not shown that it is a reliable marker of outcomes with antidepressants, antipsychotics, or stimulants. Therefore, the COMT Val158Met polymorphism is not currently a reliable pharmacogenetic marker that can inform treatment decisions for psychotropic medications.

What is COMT?

The COMT gene encodes catechol-O-methyltransferase, an enzyme that breaks down synaptic dopamine (DA) and norepinephrine (NE). The best studied polymorphism of the COMT gene is a single G>A substitution at codon 158 (rs4680), resulting in a valine (Val) to methionine (Met) amino acid change. This Val158Met polymorphism results in a decrease in COMT enzymatic activity, which can be described in a trimodal pattern for three genotypes: high in Val/Val, intermediate in Val/Met, and low in Met/Met.[1,2] Reduced COMT activity results in less catecholamine degradation and can lead to increased baseline levels of synaptic DA/NE.

Is there a connection between COMT Val158Met genotype and antidepressant treatment outcomes?

Thirty-one studies and two meta-analyses assessed the relationship between the COMT Val158Met polymorphism and treatment outcomes with antidepressant therapy (Table 1). Four studies (n=624) found better outcomes with the Val allele[3-6], and five studies (n=734) found better outcomes with the Met allele[7-11]. However, twenty-two studies (n=6325) found no relationship between COMT genotype and outcomes with various antidepressants.[12-33] A meta-analysis of 4 studies and data from the STAR*D trial (n=2510) demonstrated the lack of association between the COMT Val158Met polymorphism and the likelihood of response/remission with antidepressant therapy ($OR_{response}$=0.88, p=0.40; $OR_{remission}$=1.01, p=0.96).[34] Similarly, a more recent meta-analysis of 8 studies (n=2564) did not find a significant effect of the Val158Met polymorphism on outcomes with antidepressant pharmacotherapy across the three possible genotypes in different genetic models ($OR_{dominant}$=0.72, p=0.09; $OR_{recessive}$=0.90, p=0.70).[35] Both meta-analyses noted heterogeneity between studies in factors such as patient populations, assessment scales, treatment modalities, etc.

What does the literature say about COMT Val158Met genotype and the response to antipsychotic therapy?

Thirty-four studies and two meta-analyses assessed the relationship between the COMT Val158Met polymorphism and the likelihood of response with antipsychotic therapy (Table 1). Four studies (n=465) found better outcomes with the Val allele[36-39], and five studies (n=938) found better outcomes with the Met allele[40-44]. However, twenty-five studies (n=5343) found no association between COMT genotype and outcomes with antipsychotic therapy.[45-69] Interestingly, despite this distribution of data, two meta-analyses demonstrated improved outcomes with the Met allele.[70,71] The first meta-analysis combined data from 10 studies and 5 independent samples (n=1416).[70] In this cohort of primarily European patients, those with the Met/Met genotype were significantly more likely to be responders than Val-allele carriers (OR=1.37, p=0.039). However, the authors noted that this association would not be significant after Bonferroni correction for multiple testing. The second meta-analysis combined data from 30 articles (n=6291), which included a mixed cohort of mostly Caucasian and Asian patients, and found improved response with the Met allele compared to the Val allele (OR: not reported, p<0.001). However, this meta-analysis collected data from non-peer reviewed sources including poster sessions and 'Letters to the Editor'. Therefore, the results of this second meta-analysis should be approached with caution.

How does the COMT Val158Met genotype impact the risk of side effects with antipsychotic therapy?

Twenty-one studies and two meta-analyses assessed the relationship between the COMT Val158Met polymorphism and the risk of antipsychotic-induced side effects (Table 1). One study (n=335) found improved outcomes with the Val allele[72], and two studies (n=297) found improved outcomes with the Met allele[68,73]. Eighteen studies (n=4208) found no association between COMT Val158Met genotype and the risk of adverse events with antipsychotic therapy.[74-91] One of these studies combined the results from their trial with data from 6 other studies (n=1520) and found no differential risk (OR=1.38, p=0.10) for developing side effects based on the COMT Val158Met polymorphism[81]. However, one meta-analysis of five studies (n=1089) found a significantly lower risk of tardive dyskinesia (TD) for Met carriers compared to Val/Val patients in the fixed effects model (OR=0.66, p=0.005).[92] Interestingly, further analysis demonstrated significant differences in the risk of developing TD between Val/Val and Val/Met patients (OR=0.63, p=0.004), but not between Val/Val and Met/Met patients (OR=0.73, p=0.157). In contrast, a later meta-analysis of 11 studies (n=2886) did not find an association between COMT Val158Met polymorphism and the risk of side effects with antipsychotic therapy across the three genotypes in different genetic models ($OR_{dominant}$=0.98, p=0.87; $OR_{recessive}$=1.15, p=0.21).[93]

Is there a connection between COMT Val158Met genotype and response to methylphenidate (MPH)?

Thirteen studies and a meta-analysis assessed the relationship between the COMT Val158Met polymorphism and the efficacy of MPH for treating ADHD (Table 1). Three studies (n=366) found that the Val allele had an improved response to MPH.[94-96] Only 1 study (n=126) found that the Met allele was associated with an improved response to MPH.[97] In contrast, nine studies (n=1076) found that COMT genotype was not associated with differential outcomes after MPH therapy.[98-106] While the meta-analysis (n=699) found that Val/Val patients tended to have improved outcomes compared to Met carriers (OR=1.40, p=0.02), effect sizes were estimated from seven different studies despite the use of different subject assessment scales and high heterogeneity between samples.[107]

Is there a connection between COMT Val158Met genotype and treatment outcomes with amphetamines (AMP)?

There are currently no pharmacogenetic studies that have investigated the effect of the COMT Val158Met polymorphism on amphetamine therapy in ADHD patients. However, five studies assessed the relationship between the COMT Val158Met polymorphism and AMP response in healthy adults (Table 1). The first two studies (n=187) found better outcomes in patients with the Val allele.[108,109] However, three subsequent studies (n=627) found no association between the Val158Met polymorphism and response to amphetamines.[110-112] Two of these studies (n=581)[110,111] attempted to replicate the results of the two earlier studies (n=187)[108,109] with larger sample sizes, but were not to find a significant association between COMT Val158Met genotype and treatment outcomes with amphetamines.

Table 1. Summary of literature assessing the effect of the COMT Val158Met polymorphism on treatment outcomes with psychotropic medications. α: This number includes 1 meta-analysis. ß: This number includes 2 meta-analyses.

Treatment	No Association	Better with Val	Better with Met
Antidepressants	24ß	4	5
Antipsychotics: Response	25	4	7ß
Antipsychotics: Side Effects	19α	1	3α
ADHD: Methylphenidates	9	4α	1
ADHD: Amphetamines	3	2	0

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