**Gene symbol**

COMT

**Full name of gene**

catechol-O-methyltransferase

**Overview**

The *COMT* gene creates the catechol-O-methyltransferase enzyme. The enzyme created by nerve cells helps break down and balance levels of dopamine and norepinephrine. The enzyme produced in the liver, kidneys, and blood helps control hormone levels. COMT has been associated with schizophrenia, pain tolerance, breast cancer, endometriosis, alcohol and nicotine dependence, anxiety, and depression.

This gene is located on chromosome 22. The enzyme it creates acts in your brain and nervous system.

<body highlight brain>

**What are some common variants in the gene?**

There are two well known variants in this gene: T928G (Ser310Ala) polymorphism and

[1][6][9]

This variant is a change at a specific point in the GRIK3 gene from guanine (G) to adesine (A), resulting in incorrect protein formation. This substitution of a single nucleotide is known as a missense variant.

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**What does this mean? (Homozygous variant)**

In the gene family of glutamate receptors, there is a T/G polymorphism at codon 928 in the ionotropic glutamate receptor kainite 3 gene (GRIK3) that causes a serine to alanine change at position 310 in the extracellular N terminus of the protein.[4]

**What is the effect of this variant? (Homozygous variant)**

You are at greater risk for schizophrenia, depression, and glutamate problems.  See below for more information.

**How common is this variant in the general population? (Homozygous variant)**

This variant affects 0.1% of the general population.

**How sure are we? (Homozygous variant)**

**How common is the variant in the ME/CFS community? (Homozygous variant)**

**What are the effects of variances in GRIK3?**

The variants in GRIK3 have strong associations with increased risk of schizophrenia, but for most patients this may not change treatment for CFS.  However, its variant’s association with glutamate and other neurological issues may interact with other genes, so we have included it in this disease panel.

**GRIK3 Variant Effects (no severity or efficiency)**

<Side box: T928G 0.1% population frequency>

This gene creates a protein that helps form receptors for glutamate that act as excitatory neurotransmitters in your brain and nervous system.[1]  Excitatory transmitters increase the chance that the neuron will fire, enhancing electrical flow among brain cells.[13]  Glutamate is the most important transmitter for normal brain function, but elevated levels are toxic to neurons.[11]

GRIK3 Ser310Ala polymorphism has been linked to schizophrenia and major depression.[3][5]  The Ser310Ala allele in homozygosity is associated with higher scores in harm avoidance, anticipatory worry, and shyness, with lower scores in exploratory excitability, responsibility, resourcefulness, helpfulness, compassion, self-directedness, and cooperativeness.[4] This pattern of scores is akin to that observed in depressed patients.[4]  GRIK3 rs6691840 polymorphism was found to increase the risk of schizophrenia by 30%.[3][9]  Microdeletions have also been indicated in severe developmental delays.[2]

**What should I do about this?**

CFS is linked to improper Glutamate:GABA balance, as well as exposure to extracellular glutamate caused by neuroinflammatory stimuli.  Sustained exposure to extracellular glutamate in CFS patients causes sickness behavior, neurotoxicity, stress, and peripheral nervous sensitivity. [10]

Helpful dietary supplements may include:  Omega-3 PUFAs, CoQ10, N-acetylcysteine, vitamin B12, curcumin, zinc, magnesium, L-Taurine, and L-carnitine.[10]

<symptoms depression, stress, problems with thinking or memory, brain fog, pain>

**References**

<https://www.ncbi.nlm.nih.gov/pubmed/15507517>

Cytochromes 1A1/1B1- and catechol-O-methyltransferase-derived metabolites mediate estradiol-induced antimitogenesis in human cardiac fibroblast.

PMID: 15507517

DOI: [10.1210/jc.2003-032154](https://doi.org/10.1210/jc.2003-032154)

<https://www.ncbi.nlm.nih.gov/pubmed/19647494>

Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects.

PMID: 19647494

PMCID: [PMC2757484](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2757484/)

DOI: [10.1016/j.jpain.2009.06.003](https://doi.org/10.1016/j.jpain.2009.06.003)

Chronic fatigue syndrome (CFS) is characterized by debilitating fatigue, often accompanied by widespread muscle pain that meets criteria for fibromyalgia syndrome (FMS). Symptoms become markedly worse after exercise. Previous studies implicated dysregulation of the sympathetic nervous system (SNS), and immune system (IS) in CFS and FMS. We recently demonstrated that acid sensing ion channel (probably ASIC3), purinergic type 2X receptors (probably P2X4 and P2X5) and the transient receptor potential vanilloid type 1 (TRPV1) are molecular receptors in mouse sensory neurons detecting metabolites that cause acute muscle pain and possibly muscle fatigue. After a sustained moderate exercise test, CFS patients showed greater increases than control subjects in gene expression in COMT lasting from 0.5 to 48 hours (P < .05). These increases were also seen in the CFS subgroup with comorbid FMS and were highly correlated with symptoms of physical fatigue, mental fatigue, and pain. These new findings suggest dysregulation of metabolite detecting receptors in CFS and CFS-FMS.

**PERSPECTIVE:**

Muscle fatigue and pain are major symptoms of CFS. After moderate exercise, CFS and CFS-FMS patients show enhanced gene expression for receptors detecting muscle metabolites and for SNS and IS, which correlate with these symptoms. These findings suggest possible new causes, points for intervention, and objective biomarkers for these disorders.

<https://www.ncbi.nlm.nih.gov/pubmed/21059181>

Polymorphisms of adrenergic cardiovascular control genes are associated with adolescent chronic fatigue syndrome.

PMID: 21059181

DOI: [10.1111/j.1651-2227.2010.02072.x](https://doi.org/10.1111/j.1651-2227.2010.02072.x)

For the COMT SNP Rs4680, patients with CFS had a higher frequency of the AA genotype and a lower frequency of the G containing genotypes (AG and GG), when compared to the reference sample (p = 0.046). Also, the AA genotype was associated with a smaller increase in LF/HF ratio (low-frequency:high-frequency heart rate variability ratio, an index of cardiac sympathovagal balance) during head-up tilt when compared to the AG/GG genotypes.

#### CONCLUSIONS:

CFS might be related to polymorphisms of COMT.

rs4680 (Val158Met) is a well studied SNP in the [COMT](https://www.snpedia.com/index.php/COMT) gene. The COMT gene codes for the COMT enzyme, which breaks down dopamine in the brain's prefrontal cortex. The wild-type allele is a (G), coding for a valine amino acid; the (A) substitution polymorphism changes the amino acid to a methionine. This alters the structure of the resultant enzyme such that its activity is only 25% of the wild type. As a result, A allele carriers have more dopamine in their prefrontal cortex, which may be responsible for many of the neuropsychological associations listed below.

[23andMe blog](http://blog.23andme.com/2009/07/31/dna-variation-may-help-us-break-free-from-our-routines/) summarizes the alleles at this SNP as

* rs4680(A) = Worrier. Met, more exploratory, lower COMT enzymatic activity, therefore higher dopamine levels; lower pain threshold, enhanced vulnerability to stress, yet also more efficient at processing information under most conditions
* rs4680(G) = Warrior. Val, less exploratory, higher COMT enzymatic activity, therefore lower dopamine levels; higher pain threshold, better stress resiliency, albeit with a modest reduction in executive cognition performance under most conditions

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| [(A;A)](https://www.snpedia.com/index.php/Rs4680(A;A)) | 2.5 | (worrier) advantage in memory and attention tasks |
| [(A;G)](https://www.snpedia.com/index.php/Rs4680(A;G)) |  | Intermediate dopamine levels, other effects |
| [(G;G)](https://www.snpedia.com/index.php/Rs4680(G;G)) | 2.5 | (warrior) multiple associations, see details |

* 0.418 472G>A
* XP\_005261286.1:p.Val158Met

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| Reference | [GRCh38](https://www.snpedia.com/index.php/GRCh38)38.1/141 |

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| Chromosome | 22 |

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| Position | 19963748 |

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| Gene | [COMT](https://www.snpedia.com/index.php/COMT), [MIR4761](https://www.snpedia.com/index.php/MIR4761) |

| **Geno** | [**Mag**](https://www.snpedia.com/index.php/Magnitude) | **Summary** |
| --- | --- | --- |
| [(C;C)](https://www.snpedia.com/index.php/Rs165631(C;C)) | 0 | common/normal |
| [(C;T)](https://www.snpedia.com/index.php/Rs165631(C;T)) | 1 | Perhaps slightly lower risk for breast cancer in BRCA1/2 mutation carriers? |

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| Make [rs165631(T;T)](https://www.snpedia.com/index.php/Special:FormEdit/Genotype/rs165631(T;T)) |

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| Reference | [GRCh38.p7](https://www.snpedia.com/index.php?title=GRCh38.p7&action=edit&redlink=1)38.3/150 |

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| Chromosome | 22 |

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| Position | 19964293 |

.021 609C>T

rs165631, also known as p.L203, represents a synonymous variant in the [COMT](https://www.snpedia.com/index.php/COMT) gene; the minor rs165631(T) allele has a population allele frequency of 1% (based on exome sequencing of 60,000 individuals).

Admittedly based on only a handful of cases, a preliminary report hunting for variants that might delay or prevent [breast cancer](https://www.snpedia.com/index.php/Breast_cancer) in women carrying either disease-causing [BRCA1](https://www.snpedia.com/index.php/BRCA1) or [BRCA2](https://www.snpedia.com/index.php/BRCA2) mutations observed that the rs165631(T) allele was present in 5 of 15 women with BRCA1/2 mutations (but not breast cancer), while it was not present in any of 25 women with breast cancer (in a different group of women). The authors believe their study "suggests an intriguing genetic correlation", i.e. that rs165631(T) carriers who harbor BRCA1 or BRCA2 mutations might be at lower risk for breast cancer than non-carriers (of this COMT allele).[[PMID 28538113](https://www.ncbi.nlm.nih.gov/pubmed/28538113?dopt=Abstract)[OA-icon.png](https://www.snpedia.com/index.php/File:OA-icon.png)]

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| --- | --- | --- |
| [(A;A)](https://www.snpedia.com/index.php/Rs165599(A;A)) | 0 |  |
| [(A;G)](https://www.snpedia.com/index.php/Rs165599(A;G)) | 1 |  |
| [(G;G)](https://www.snpedia.com/index.php/Rs165599(G;G)) | 1.5 | May indicate increased susceptibility to schizophrenia |

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| Reference | [GRCh38](https://www.snpedia.com/index.php/GRCh38)38.1/141 |

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| Chromosome | 22 |

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| --- | --- |
| Position | 19969258 |

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| Gene | [ARVCF](https://www.snpedia.com/index.php/Special:FormEdit/Gene/ARVCF), [COMT](https://www.snpedia.com/index.php/COMT) |

[anxiety](https://www.snpedia.com/index.php/Anxiety)-related personality traits, [ADHD](https://www.snpedia.com/index.php/ADHD), [schizophrenia](https://www.snpedia.com/index.php/Schizophrenia)

part of a three marker haplotype [rs737865](https://www.snpedia.com/index.php/Rs737865)-[rs4680](https://www.snpedia.com/index.php/Rs4680)-rs165599

epistasis between SNPs in COMT ([rs2097603](https://www.snpedia.com/index.php/Rs2097603), Val158Met ([rs4680](https://www.snpedia.com/index.php/Rs4680)), rs165599) and polymorphisms in other [schizophrenia](https://www.snpedia.com/index.php/Schizophrenia) susceptibility genes

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| [(C;C)](https://www.snpedia.com/index.php/Rs4633(C;C)) | 0 | Normal |
| [(C;T)](https://www.snpedia.com/index.php/Rs4633(C;T)) | 2 | higher risk for endometrial cancer |
| [(T;T)](https://www.snpedia.com/index.php/Rs4633(T;T)) | 2 | higher risk for endometrial cancer |

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| Reference | [GRCh38](https://www.snpedia.com/index.php/GRCh38)38.1/141 |

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| --- | --- |
| Chromosome | 22 |

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| Position | 19962712 |

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| Gene | [COMT](https://www.snpedia.com/index.php/COMT), [MIR4761](https://www.snpedia.com/index.php/MIR4761) |
| 0.498 186C>T |  |

rs4633 is a variant at codon 62 of the [COMT](https://www.snpedia.com/index.php/COMT) gene, however, it does not change the amino acid sequence of the COMT protein.

In a study of 150 (Caucasian) cases of [endometrial cancer](https://www.snpedia.com/index.php/Endometrial_cancer), a significant increase in rs4633(T;T) genotype was observed in patients compared to controls (OR = 2.39, CI: 1.31-4.37, p = 0.004). Furthemore, the frequency of the C-G haplotype of rs4633-[rs4680](https://www.snpedia.com/index.php/Rs4680)was significantly higher in controls (p < 0.0001) than in patients. This correlated with lower expression levels of the COMT protein in carriers of these alleles.[[PMID 18324659](https://www.ncbi.nlm.nih.gov/pubmed/18324659?dopt=Abstract)]

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| [(C;C)](https://www.snpedia.com/index.php/Rs4818(C;C)) | 0 | common in clinvar |
| [(C;G)](https://www.snpedia.com/index.php/Rs4818(C;G)) |  |  |

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| Make [rs4818(G;G)](https://www.snpedia.com/index.php/Special:FormEdit/Genotype/rs4818(G;G)) |

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| --- | --- |
| Reference | [GRCh38](https://www.snpedia.com/index.php/GRCh38)38.1/141 |

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| Chromosome | 22 |

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| Position | 19963684 |

# **rs4818**

0.364 408C>G

| **Geno** | [**Mag**](https://www.snpedia.com/index.php/Magnitude) | **Summary** |
| --- | --- | --- |
| [(C;C)](https://www.snpedia.com/index.php/Rs4633(C;C)) | 0 | normal |
| [(C;T)](https://www.snpedia.com/index.php/Rs4633(C;T)) | 2 | higher risk for endometrial cancer |
| [(T;T)](https://www.snpedia.com/index.php/Rs4633(T;T)) | 2 | higher risk for endometrial cancer |

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| Reference | [GRCh38](https://www.snpedia.com/index.php/GRCh38)38.1/141 |

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| --- | --- |
| Chromosome | 22 |

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| --- | --- |
| Position | 19962712 |

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| Gene | [COMT](https://www.snpedia.com/index.php/COMT), [MIR4761](https://www.snpedia.com/index.php/MIR4761) |

186C>T 0.426

rs4633 is a variant at codon 62 of the [COMT](https://www.snpedia.com/index.php/COMT) gene, however, it does not change the amino acid sequence of the COMT protein.

In a study of 150 (Caucasian) cases of [endometrial cancer](https://www.snpedia.com/index.php/Endometrial_cancer), a significant increase in rs4633(T;T) genotype was observed in patients compared to controls (OR = 2.39, CI: 1.31-4.37, p = 0.004). Furthemore, the frequency of the C-G haplotype of rs4633-[rs4680](https://www.snpedia.com/index.php/Rs4680)was significantly higher in controls (p < 0.0001) than in patients. This correlated with lower expression levels of the COMT protein in carriers of these alleles.[[PMID 18324659](https://www.ncbi.nlm.nih.gov/pubmed/18324659?dopt=Abstract)]

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| Make [rs6269(A;A)](https://www.snpedia.com/index.php/Special:FormEdit/Genotype/rs6269(A;A)) |
| Make [rs6269(A;G)](https://www.snpedia.com/index.php/Special:FormEdit/Genotype/rs6269(A;G)) |
| Make [rs6269(G;G)](https://www.snpedia.com/index.php/Special:FormEdit/Genotype/rs6269(G;G)) |

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| Reference | [GRCh38](https://www.snpedia.com/index.php/GRCh38)38.1/141 |

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| Chromosome | 22 |

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| Position | 19962429 |

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| Gene | [COMT](https://www.snpedia.com/index.php/COMT), [MIR4761](https://www.snpedia.com/index.php/MIR4761) |

Schizo

# **rs6269** 0.376 het .624 norm 1-98A>G

<https://www.ncbi.nlm.nih.gov/pubmed/18324659?dopt=Abstract>

COMT polymorphisms affecting protein expression are risk factors for endometrial cancer.

PMID: 18324659

DOI: [10.1002/mc.20432](https://doi.org/10.1002/mc.20432)

In estrogen metabolic pathways, the COMT enzyme is related to detoxification. COMT gene polymorphisms have been shown to effect enzyme function. A significant increase in the T/T genotype of codon 62 (C/T) was observed in patients compared to controls (OR = 2.39, 95% CI: 1.31-4.37, P = 0.004). The frequency of the C-G haplotype of codon 62 C/T and codon 158 G/A was significantly higher in controls (P < 0.0001) than in patients. The expression level of COMT protein in EC tissues was significantly lower in COMT codon 62 variant TT and codon 158 variant AA genotype carriers. Therefore, the EC samples with polymorphic variants of COMT lead to lower expression of COMT protein whereas EC samples with wild-type codon 62 C/C and codon 158 G/G have higher expression of COMT protein. This is the first study demonstrating that polymorphisms in COMT codon 62 and codon 158 altered protein expression levels in EC, suggesting that they may be risk factors for EC in Caucasians.

<https://www.ncbi.nlm.nih.gov/pubmed/24448899?dopt=Abstract>

Metabolic syndrome in patients taking clozapine: prevalence and influence of catechol-O-methyltransferase genotype.

PMID: 24448899

DOI: [10.1007/s00213-013-3410-4](https://doi.org/10.1007/s00213-013-3410-4)

#### RATIONALE:

Metabolic syndrome (MetS) has consistently been identified as an adverse effect of long-term treatment with atypical antipsychotics (AAPs) such as clozapine. Elevated serum homocysteine concentration has been found to act as an independent risk factor for MetS, and catechol-O-methyltransferase (COMT) catalyzes the homocysteine metabolism. We accordingly hypothesized that COMT dysregulation may confer the susceptibility to MetS induced by AAPs, potentially in a gender-specific manner, because the interaction effects of COMT and gender have been consistently reported.

#### RESULTS:

MetS was found in 202/468 (43.2 %) of all the patients, with 40.2 % prevalence (138/343) in males and 51.2 % (64/125) in females. Patients with MetS had notably higher metabolic parameters than those without MetS. The mean levels of homocysteine in patients with MetS were significantly higher than those without MetS. We found a positive association between the rs4680 polymorphism and the serum triglyceride levels (corrected P = 0.024). Further analysis revealed that the rs4680 Met allele was significantly associated with increased triglyceride levels among female patients (P = 0.009), but not among males (P = 0.07).

#### CONCLUSIONS:

Our findings suggest a potential association between rs4680 in COMT and elevated TG levels, particularly among female patients.

<https://www.ncbi.nlm.nih.gov/pubmed/23728717?dopt=Abstract>

# Common functional polymorphisms in SLC6A4 and COMT genes are associated with circadian phenotypes in a South American sample.

PMID: 23728717

 DOI: [10.1007/s10072-013-1466-x](https://doi.org/10.1007/s10072-013-1466-x)

The aim of this study is to analyze the possible and novel associations of the functional polymorphisms in COMT and SLC6A4 genes (Val158Met and 5-HTTLPR) and circadian phenotypes in healthy Colombian subjects. 191 university students were genotyped for two functional polymorphisms in COMT and SLC6A4 genes (rs4680 and rs4795541). We found a significant association between 5-HTTLPR polymorphism and morning preference score (CSM) (p = 0.027) using an overdominant genotypic model and association of COMT Val158Met with daytime sleepiness (ESS scores) (p = 0.038) in a genotypic recessive model. These results were supported by differences in genotype frequencies between circadian typologies for SLC6A4 gene (p = 0.007) and categories of diurnal sleepiness for COMT gene (p = 0.032). Our results suggest, for the first time, a significant relationship between functional SLC6A4 and COMT polymorphisms with specific human circadian phenotypes: morning preference and diurnal sleepiness.

<https://www.ncbi.nlm.nih.gov/pubmed/21895373?dopt=Abstract>

# Psychological distress in fibromyalgia patients: a role for catechol-O-methyl-transferase Val158met polymorphism.

PMID: 21895373

DOI: [10.1037/a0025223](https://doi.org/10.1037/a0025223)

#### RESULTS:

The distribution of the COMT Val158Met polymorphism was similar in FM and controls. Out of 198 patients, 137 were able to stop medication before evaluation. In these patients, the COMT Val158Met genotype was associated with specific psychological profiles. The Met/Met subgroup scored systematically worse on all psychological and functional variables. These results suggest a possible role of COMT Val158Met polymorphism in the psychological distress observed in FM.

<https://www.ncbi.nlm.nih.gov/pubmed/19520435?dopt=Abstract>

# Acute antidepressant response to sleep deprivation combined with light therapy is influenced by the catechol-O-methyltransferase Val(108/158)Met polymorphism.

PMID: 19520435

 DOI: [10.1016/j.jad.2009.05.017](https://doi.org/10.1016/j.jad.2009.05.017)

Catechol-O-methyltransferase (COMT) inactivates norepinephrine and dopamine via methyl conjugation, and a G-A transition in the COMT gene (rs4680) influences the enzyme activity. It is a current area of debate whether rs4680 can influence antidepressant response in major depressive disorder, and whether this influence extends to bipolar depression. Chronotherapeutic interventions, such as sleep deprivation and light therapy, are multi-target in nature and are effective in bipolar depression. Here we studied the effect of rs4680 on response to sleep deprivation combined with light therapy (36 h awake followed by a night of undisturbed sleep, with 10,000 lx light administered for 30 min during the night awake and upon awakening) in 87 bipolar depressed inpatients. Patients who were homozygotic for the Val/Val variant showed a significantly less efficient antidepressant effect after the night awake than those who were heterozygotic and homozygotic for the Met variant. This effect of rs4680 is similar to its observed influence on response to serotonergic and noradrenergic drug treatments in major depressive disorder.

<https://www.ncbi.nlm.nih.gov/pubmed/19074205?dopt=Abstract>

# Drinking green tea modestly reduces breast cancer risk.

PMID: 19074205

 PMCID: [PMC2646205](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2646205/)

 DOI: [10.3945/jn.108.098699](https://doi.org/10.3945/jn.108.098699)

Green tea is a commonly consumed beverage in China. Catechol-O-methyltransferase (COMT) catalyzes catechol estrogens and tea polyphenols. The COMT rs4680 AA genotype leads to lower COMT activity, which may affect the relationship between green tea consumption and breast cancer risk. Compared with nondrinkers, regular drinking of green tea was associated with a slightly decreased risk for breast cancer (OR, 0.88; 95% CI, 0.79-0.98). Among premenopausal women, reduced risk was observed for years of green tea drinking (P-trend = 0.02) and a dose-response relationship with the amount of tea consumed per month was also observed (P-trend = 0.046). COMT rs4680 genotypes did not have a modifying effect on the association of green tea intake with breast cancer risk. Drinking green tea may be weakly associated with a decreased risk of breast cancer.

<https://www.ncbi.nlm.nih.gov/pubmed/16395295?dopt=Abstract>

# Significant association of catechol-O-methyltransferase (COMT) haplotypes with nicotine dependence in male and female smokers of two ethnic populations.

PMID: 16395295

 DOI: [10.1038/sj.npp.1300997](https://doi.org/10.1038/sj.npp.1300997)

The catechol-O-methyltransferase (COMT) gene plays a prominent role in dopaminergic circuits central to drug reward. nicotine dependence (ND). We analyzed five single nucleotide polymorphisms (SNPs), including the Val/Met variant (rs4680), which results in a three- to four-fold difference in enzyme activity within COMT. rs740603-rs4680-rs174699 high-risk C-A-T haplotype (frequency 16.9%;) in the AA sample for rs933271-rs4680-rs174699. Moreover, we found a major high-risk T-A-T haplotype (frequency 56.7%) east asian males. Further examination of two protective haplotypes, frequency 23.6% A-G-T in African American females and frequency 15.2% T-G-T in east Asian males, indicated that the low COMT enzyme activity Met allele is protective to become nicotine dependent.

<https://www.ncbi.nlm.nih.gov/pubmed/16232322?dopt=Abstract>

# COMT genetic variation confers risk for psychotic and affective disorders: a case control study.

PMID: 16232322

 PMCID: [PMC1282571](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1282571/)

 DOI: [10.1186/1744-9081-1-19](https://doi.org/10.1186/1744-9081-1-19)

#### BACKGROUND:

Variation in the COMT gene has been implicated in a number of psychiatric disorders, including psychotic, affective and anxiety disorders.

#### RESULTS:

SNP rs2097603, the Val/Met variant and SNP rs165599 were significantly associated (p = 0.004; p = 0.05; p = 0.035) with a broad "all affected" diagnosis. Haplotype analysis revealed a potentially protective G-A-A-A haplotype haplotype (-278A/G; rs737865; Val108/158Met; rs165599). The protective haplotype remained significantly underrepresented in most of these subgroups.

#### CONCLUSION:

Our results support the view that COMT variation provides a weak general predisposition to neuropsychiatric disease including psychotic and affective disorders.

<https://www.ncbi.nlm.nih.gov/pubmed/22208661?dopt=Abstract>

# A novel SNP in COMT is associated with alcohol dependence but not opiate or nicotine dependence: a case control study.

PMID: 22208661

 PMCID: [PMC3268714](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3268714/)

 DOI: [10.1186/1744-9081-7-51](https://doi.org/10.1186/1744-9081-7-51)

#### BACKGROUND:

It is well established that COMT is a strong candidate gene for substance use disorder and schizophrenia. Recently we identified two SNPs in COMT (rs4680 and rs165774) that are associated with schizophrenia in an Australian cohort. Individuals with schizophrenia were more than twice as likely to carry the GG genotype compared to the AA genotype for both the rs165774 and rs4680 SNPs.

#### RESULTS:

Analysis of rs165774/rs4680 haplotypes also revealed association with alcohol dependence with the G/G haplotype being almost 1.5 times more common in alcohol-dependent cases.

<https://www.ncbi.nlm.nih.gov/pubmed/22528689?dopt=Abstract>

# Pain sensitivity in fibromyalgia is associated with catechol-O-methyltransferase (COMT) gene.

PMID: 22528689

 DOI: [10.1002/j.1532-2149.2012.00153.x](https://doi.org/10.1002/j.1532-2149.2012.00153.x)

The frequency of genetic variations associated with low COMT enzyme activity was significantly higher in FM patients than in healthy volunteers. FM patients were more sensitive to experimental pain than healthy volunteers and, in particular, FM individuals with the met/met genotype (Val158Met SNP) or the HPS-APS haplotypes showing higher sensitivity to thermal and pressure pain stimuli than patients carrying the LPS haplotype or val alleles (Val158Met SNP). No differences due to genotype or haplotypes were found on non-painful touch thresholds.

<https://www.ncbi.nlm.nih.gov/pubmed/21120493?dopt=Abstract>

# Influence of catechol-O-methyltransferase (COMT) gene polymorphisms in pain sensibility of Brazilian fibromialgia patients.

PMID: 21120493

 DOI: [10.1007/s00296-010-1659-z](https://doi.org/10.1007/s00296-010-1659-z)

he frequency of mutant genotype AA of SNP rs6860 was 77.67% in patients with FS and 28.18% for the control group. For the SNP rs4818, the frequency of mutant genotype CC was 73.21 and 39.09% for patients with FS and controls, respectively. Moreover, the FIQ score was higher in patients with the homozygous mutant genotype for SNPs rs4680 (87.92 points) and rs4818 (86.14 points). These results suggest that SNPs rs4680 and rs4818 of the COMT gene may be associated with fibromyalgia and pain sensitivity

<https://www.ncbi.nlm.nih.gov/pubmed/21130573?dopt=Abstract>

# COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia.

PMID: 21130573

 PMCID: [PMC3053137](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3053137/)

 DOI: [10.1016/j.pain.2010.10.024](https://doi.org/10.1016/j.pain.2010.10.024)

Participants were genotyped for the val(158)met single nucleotide polymorphism (rs4680) in the catechol-O-methyltransferase (COMT) gene. COMT genotype moderated the daily relations of both maladaptive coping processes and pain. FM women with the homozygous met/met genotype evidenced more pain on days when pain catastrophizing was elevated relative to heterozygous and homozygous val(158) carriers. FM women with the homozygous met/met genotype evidenced more pain on days when pain attention was elevated relative to those with the homozygous val/val genotype. genetic variation in the val(158)met polymorphism may affect FM pain through pathways of pain-related cognition. This study examined 2 forms of maladaptive coping: pain catastrophizing and pain attention. The findings provide multimeasure and multimethod support for genetic moderation of a maladaptive coping and pain process and suggest that genetic variation in the val(158)met polymorphism may affect fibromyalgia pain through pathways of pain-related cognition.

https://www.ncbi.nlm.nih.gov/pubmed/12595695?dopt=Abstract

# COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor.

PMID: 12595695

 DOI: [10.1126/science.1078546](https://doi.org/10.1126/science.1078546)

Individuals homozygous for the met158 allele of the catechol-O-methyltransferase (COMT) polymorphism (val158met) showed diminished regional mu-opioid system responses to pain compared with heterozygotes. These effects were accompanied by higher sensory and affective ratings of pain and a more negative internal affective state. Opposite effects were observed in val158 homozygotes.

<https://www.ncbi.nlm.nih.gov/pubmed/18989660?dopt=Abstract>

# The catechol-O-methyltransferase Val(108/158)Met polymorphism affects antidepressant response to paroxetine in a naturalistic setting.

PMID: 18989660

 DOI: [10.1007/s00213-008-1381-7](https://doi.org/10.1007/s00213-008-1381-7)

rs4680 significantly interacted with time in affecting antidepressant response to paroxetine, with outcome being inversely proportional to the enzyme activity: better effects in Met/Met homozygotes, worse effects in Val/Val homozygotes and intermediate effects in heterozygotes. The effect became significant at the third week of treatment.

https://www.ncbi.nlm.nih.gov/pubmed/18704099?dopt=Abstract

# Association between the catechol-O-methyltransferase Val158Met polymorphism and cocaine dependence.

PMID: 18704099

 PMCID: [PMC2583214](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2583214/)

 DOI: [10.1038/npp.2008.126](https://doi.org/10.1038/npp.2008.126)

The low enzyme activity 158Met allele or haplotypes containing this variant might have functional effects on dopamine-derived reward processes and cortical functions resulting in increased susceptibility for cocaine dependence

<https://www.ncbi.nlm.nih.gov/pubmed/18194538?dopt=Abstract>

# Combined effect of CCND1 and COMT polymorphisms and increased breast cancer risk.

PMID: 18194538

 PMCID: [PMC2254632](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2254632/)

 DOI: [10.1186/1471-2407-8-6](https://doi.org/10.1186/1471-2407-8-6)

The heterozygous COMTMedium (MetVal) 1.3x and the high enzymatic activity of COMTHigh (ValVal) 1.4x genotype was also associated with breast cancer risk

<https://www.ncbi.nlm.nih.gov/pubmed/15866551?dopt=Abstract>

# Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction.

PMID: 15866551

 DOI: [10.1016/j.biopsych.2005.01.026](https://doi.org/10.1016/j.biopsych.2005.01.026)

Carriers of the COMT valine158 allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis use had no such adverse influence on individuals with two copies of the methionine allele

<https://www.ncbi.nlm.nih.gov/pubmed/18064318?dopt=Abstract>

# Catechol-O-methyltransferase genotype is associated with plasma total homocysteine levels and may increase venous thrombosis risk.

PMID: 18064318

OMT dysfunction has been related to schizophrenia and breast cancer.  rs4680 variant, resulting in an increase in Homocysteine of 10.4% (95% CI 0.01 to 0.21, p = 0.03) for 324AA compared with 324GG subjects. Interestingly, we found that the 324AA genotype was more common in venous thrombosis patients (OR 1.61 [95% CI 0.97 to 2.65], p = 0.06) compared to control subjects. We show that the COMT rs4680 variant modulates tHcy, and might be associated with venous thrombosis risk as well.