<https://www.ncbi.nlm.nih.gov/pubmed/21584188>

hCV245410 (on gene TPH2) and hCV7911132 (on gene SLC6A4

<https://www.ncbi.nlm.nih.gov/pubmed/18986552>

Average absolute value of severity associations for the SNPs within eight candidate genes.

| **Gene Name** | **Gene Location** | **Average Correlation (SD)** | **Count of SNPs in candidate gene** | **Most Correlated SNP** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Name | Correlation | p-value |
| TPH2 | 12q21 | 0.23 (0.04) | 7 | rs10784941 | 0.275 | 0.010 |

TPH2 with seven SNPs had the highest average association with CFS severity.

<https://www.ncbi.nlm.nih.gov/pubmed/16610957>

The top three genes containing the SNPs accounting for the highest accumulated importances were neuronal tryptophan hydroxylase (*TPH2*), catechol-*O*-methyltransferase (*COMT*) and nuclear receptor subfamily 3, group C, member 1 glucocorticoid receptor (*NR3C1*).

<https://www.ncbi.nlm.nih.gov/pubmed/26063326>

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 111 | *TPH2* | rs1386486 | 12 | 70698487 | 0.14 | 0.41 | 0.46 | 1.07 |
| 108 | *TPH2* | rs2171363 | 12 | 70646531 | 0.17 | 0.41 | 0.42 | 1.05 |

rs10784941

<https://www.ncbi.nlm.nih.gov/pubmed/22655589>

Serotonergic transmission is considered relevant in the pathophysiology and the treatment of schizophrenia. Tryptophan hydroxylase (TPH) is the rate limiting enzyme in the biosynthesis of serotonin. While the TPH1 gene has been found to be associated with schizophrenia, studies focusing on TPH2 variants did not yield conclusive results for schizophrenia or the response to antipsychotic medication. We analyzed eleven TPH2 SNPs in two case-control samples consisting of 4453 individuals in total. Six SNPs were selected because of their potential functional relevance (rs4570625, rs11178997, rs11178998, rs7954758, rs7305115, and, rs4290270) and were supported by another 5 tagging SNPs selected based on HapMap LD information. In the discovery sample (1476 individuals), we observed a significant association with schizophrenia for rs10784941 (p = 0.009, OR minor G-allele 0.82 [0.71-0.95]) and rs4565946 (p = 0.011, OR minor T-allele 0.83 [0.71-0.96]). Association was also observed with a common rs4570625-rs4565946 haplotype (OR G-C haplotype 1.20 [1.02-1.40]; p = 0.0046). Single-marker associations could not be replicated in the replication sample consisting of 2977 individuals, but there was a strong trend regarding the rs4570625-rs4565946 G-C haplotype (OR 1.10 [0.98-1.24]; p(one-sided test) = 0.054). In smaller sub-samples, the rare rs4570625-rs4565946 T-T haplotype was associated with reduced processing speed (n = 193, p = 0.004) and sensorimotor gating (n = 68, p = 0.006) of schizophrenia patients. TPH2 variants and the rs4570625-rs4565946 G-C haplotype did not influence the beneficial response to antipsychotic drugs (n = 210) after four weeks of treatment administering the Positive and Negative Syndrome Scale of Schizophrenia (PANSS). We also investigated the association of the SNPs to treatment response, but did not get significant results. In sum, our results argue for only a minor role of TPH2 in schizophrenia.

rs1386486

https://www.ncbi.nlm.nih.gov/pubmed/19352219

Bipolar affective disorder (BPAD) is a highly inherited genetic disorder and may be caused in part by deficits in serotonergic neurotransmission. We investigated whether variants within the tryptophan hydroxylase-2 (TPH2) gene, which is required for the synthesis of serotonin (5-HT), are associated with susceptibility to developing BPAD. Thirteen single nucleotide polymorphisms (SNPs) within TPH2 were genotyped in a collection of 151 Irish BPAD type I trios and were tested for association using the transmission disequilibrium test. SNPs rs1386482 and rs1386486, which are in very strong linkage disequilibrium, were associated with BPAD (P=0.006). The association retained significance after a correction for multiple testing. The associated SNPs are in perfect linkage disequilibrium with SNPs previously associated with BPAD (rs4290270) and impulsivity (rs1386483), a core trait of BPAD. These results strongly support a role for TPH2 in the aetiology of BPAD.

https://www.ncbi.nlm.nih.gov/pubmed/25152196

Bipolar disorder (BPD) is a serious and common mental disorder with high heritability. The serotonergic system is known to be implicated in the etiology of the disorder. Tryptophan hydroxylase isoform-2 (TPH2), which controls the synthesis of serotonin in the brain, has been suggested as a candidate gene for BDP. The aim of this study was to examine the association between the polymorphisms in TPH2 and BPD.

**METHODS:**

We conducted a case-control study by genotyping six SNPs (rs10784941, rs1386494, rs2171363, rs4760816, rs1386486, and rs1872824) in 506 bipolar patients and 507 controls of Chinese Han origin.

**RESULTS:**

rs10784941 was not in the Hardy-Weinberg equilibrium and therefore excluded from further analysis. rs1386486 and rs1872824 showed statistically significant differences between cases and controls in genotype frequencies (rs1386486: p=0.043351; rs1872824: p=0.016563), but no association in allele frequencies. Strong LD was found among rs1386494, rs2171363 and rs4760816, but no positive association with BPD was found for haplotypes.

Rs2171363

https://www.ncbi.nlm.nih.gov/pubmed/27521242

Variation in genes implicated in monoamine neurotransmission may interact with environmental factors to influence antidepressant response. We aimed to determine how a range of single nucleotide polymorphisms in monoaminergic genes influence this response to treatment and how they interact with childhood trauma and recent life stress in a Chinese sample. An initial study of monoaminergic coding region single nucleotide polymorphisms identified significant associations of TPH2 and HTR1B single nucleotide polymorphisms with treatment response that showed interactions with childhood and recent life stress, respectively (Xu et al., 2012).

#### METHODS:

A total of 47 further single nucleotide polymorphisms in 17 candidate monoaminergic genes were genotyped in 281 Chinese Han patients with major depressive disorder. Response to 6 weeks' antidepressant treatment was determined by change in the 17-item Hamilton Depression Rating Scale score, and previous stressful events were evaluated by the Life Events Scale and Childhood Trauma Questionnaire-Short Form.

#### RESULTS:

Three TPH2 single nucleotide polymorphisms (rs11178998, rs7963717, and rs2171363) were significantly associated with antidepressant response in this Chinese sample, as was a haplotype in TPH2 (rs2171363 and rs1487278). One of these, rs2171363, showed a significant interaction with childhood adversity in its association with antidepressant response.

#### CONCLUSIONS:

These findings provide further evidence that variation in TPH2 is associated with antidepressant response and may also interact with childhood trauma to influence outcome of antidepressant treatment.

<https://www.ncbi.nlm.nih.gov/pubmed/19272410>

Tryptophan hydroxylase-2 (TPH2) is the rate-limiting biosynthetic isoenzyme for serotonin that is preferentially expressed in the brain and has been implicated in the pathogenesis of major depressive disorder (MDD) and in the mechanism of antidepressant action. This study aimed to investigate whether common genetic variation in the TPH2 gene is associated with MDD and therapeutic response to antidepressants in a Chinese population. A total of 508 MDD patients and 463 unrelated controls were recruited. Among the MDD patients, 187 accepted selective serotonin reuptake inhibitor (fluoxetine or citalopram) antidepressant treatment for 8 weeks with therapeutic evaluation before and after treatment. Five TPH2 polymorphisms were genotyped and their association with MDD or treatment response was assessed by haplotype and single-marker analysis. In single-marker-based analysis, the rs17110747-G homozygote polymorphism was found to be more frequent in the MDD patients than in the controls (P=0.002). Genotype analysis in responders (defined as those with a 50% reduction in baseline Hamilton score) and non-responders after 8 weeks of antidepressant treatment showed that the proportion of rs2171363 heterozygote carriers was higher in the responders than the non-responders (P=0.009). No significant association with MDD or antidepressant therapeutic response was discovered in haplotype analyses. Our findings show that TPH2 genetic variants may play a role in MDD susceptibility and in acute therapeutic response to selective serotonin reuptake inhibitors.

rs4760816

# Association study of TPH2 polymorphisms and bipolar disorder in the Han Chinese population.

[Chen S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chen%20S%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Huang X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Huang%20X%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Yu T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yu%20T%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Li X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20X%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Cao Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cao%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Li X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20X%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Xu F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xu%20F%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Yang F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Yang%20F%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Jesse FF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jesse%20FF%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Xu M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Xu%20M%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [Li W](https://www.ncbi.nlm.nih.gov/pubmed/?term=Li%20W%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)1, [He L](https://www.ncbi.nlm.nih.gov/pubmed/?term=He%20L%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)2, [He G](https://www.ncbi.nlm.nih.gov/pubmed/?term=He%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25152196)3.

### [Author information](https://www.ncbi.nlm.nih.gov/pubmed/?term=rs4760816)

### Abstract

#### OBJECTIVE:

Bipolar disorder (BPD) is a serious and common mental disorder with high heritability. The serotonergic system is known to be implicated in the etiology of the disorder. Tryptophan hydroxylase isoform-2 (TPH2), which controls the synthesis of serotonin in the brain, has been suggested as a candidate gene for BDP. The aim of this study was to examine the association between the polymorphisms in TPH2 and BPD.

#### METHODS:

We conducted a case-control study by genotyping six SNPs (rs10784941, rs1386494, rs2171363, rs4760816, rs1386486, and rs1872824) in 506 bipolar patients and 507 controls of Chinese Han origin.

#### RESULTS:

rs10784941 was not in the Hardy-Weinberg equilibrium and therefore excluded from further analysis. rs1386486 and rs1872824 showed statistically significant differences between cases and controls in genotype frequencies (rs1386486: p=0.043351; rs1872824: p=0.016563), but no association in allele frequencies. Strong LD was found among rs1386494, rs2171363 and rs4760816, but no positive association with BPD was found for haplotypes.

#### CONCLUSION:

Our results indicate that in the Han Chinese population TPH2 may be a potential susceptibility gene for bipolar disorder. Further studies are needed to validate this association.

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Bipolar

<https://www.mayoclinic.org/diseases-conditions/bipolar-disorder/symptoms-causes/syc-20355955?p=1>

* **Pay attention to warning signs.** Addressing symptoms early on can prevent episodes from getting worse. You may have identified a pattern to your bipolar episodes and what triggers them. Call your doctor if you feel you're falling into an episode of depression or mania. Involve family members or friends in watching for warning signs.
* **Avoid drugs and alcohol.** Using alcohol or recreational drugs can worsen your symptoms and make them more likely to come back.
* **Take your medications exactly as directed.** You may be tempted to stop treatment — but don't. Stopping your medication or reducing your dose on your own may cause withdrawal effects or your symptoms may worsen or return.

However, there are effective treatments to control symptoms: medicine and talk therapy. A combination usually works best.

Depression  including [antidepressants](https://medlineplus.gov/antidepressants.html), talk therapy, or both.

Schizophrenia https://medlineplus.gov/schizophrenia.html

Medicine can help control many of the symptoms. You may need to try different medicines to see which works best. You should stay on your medicine for as long as your doctor recommends. Additional treatments can help you deal with your illness from day to day. These include therapy, family education, rehabilitation, and skills training.

* [Brain Stimulation Therapies](https://www.nimh.nih.gov/health/topics/brain-stimulation-therapies/brain-stimulation-therapies.shtml) From the National Institutes of Health (National Institute of Mental Health)
* [Mental Health Medications](https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtml) From the National Institutes of Health (National Institute of Mental Health)
* [Psychotherapies](https://www.nimh.nih.gov/health/topics/psychotherapies/index.shtml) From the National Institutes of Health (National Institute of Mental Health)

<http://www.uniprot.org/uniprot/Q8IWU9>

**Tryptophan 5-hydroxylase 2**

This protein is involved in step **1** of the subpathway that synthesizes serotonin from L-tryptophan.  
Proteins known to be involved in the 2 steps of the subpathway in this organism are:

1. Tryptophan 5-hydroxylase 2 (**TPH2**), [Tryptophan 5-hydroxylase 1 (**TPH1**)](http://www.uniprot.org/uniprot/P17752)
2. no protein annotated in this organism

This subpathway is part of the pathway serotonin biosynthesis, which is itself part of Aromatic compound metabolism.  
View all proteins of this organism that are known to be involved in the subpathway that synthesizes [serotonin from L-tryptophan](http://www.uniprot.org/uniprot/?query=organism:9606+pathway:433.846.398), the pathway [serotonin biosynthesis](http://www.uniprot.org/uniprot/?query=organism:9606+pathway:433.846) and in [Aromatic compound metabolism](http://www.uniprot.org/uniprot/?query=organism:9606+pathway:433).

* [iron ion binding](https://www.ebi.ac.uk/QuickGO/term/GO:0005506) Source: InterPro
* [tryptophan 5-monooxygenase activity](https://www.ebi.ac.uk/QuickGO/term/GO:0004510) Source: UniProtKB-EC

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q8IWU9)

#### GO - Biological processi

* [aromatic amino acid family metabolic process](https://www.ebi.ac.uk/QuickGO/term/GO:0009072) Source: InterPro
* [cellular response to lithium ion](https://www.ebi.ac.uk/QuickGO/term/GO:0071285) Source: Ensembl
* [circadian rhythm](https://www.ebi.ac.uk/QuickGO/term/GO:0007623) Source: Ensembl
* [indolalkylamine biosynthetic process](https://www.ebi.ac.uk/QuickGO/term/GO:0046219) Source: Reactome
* [response to activity](https://www.ebi.ac.uk/QuickGO/term/GO:0014823) Source: Ensembl
* [response to calcium ion](https://www.ebi.ac.uk/QuickGO/term/GO:0051592) Source: Ensembl
* [response to estrogen](https://www.ebi.ac.uk/QuickGO/term/GO:0043627) Source: Ensembl
* [response to glucocorticoid](https://www.ebi.ac.uk/QuickGO/term/GO:0051384) Source: Ensembl
* [response to nutrient levels](https://www.ebi.ac.uk/QuickGO/term/GO:0031667) Source: Ensembl
* [serotonin biosynthetic process](https://www.ebi.ac.uk/QuickGO/term/GO:0042427) Source: UniProtKB-UniPathway

###### [**Major depressive disorder (MDD)**](http://www.uniprot.org/diseases/DI-00697)**1 Publication**

Disease susceptibility is associated with variations affecting the gene represented in this entry.

Disease descriptionA common psychiatric disorder. It is a complex trait characterized by one or more major depressive episodes without a history of manic, mixed, or hypomanic episodes. A major depressive episode is characterized by at least 2 weeks during which there is a new onset or clear worsening of either depressed mood or loss of interest or pleasure in nearly all activities. Four additional symptoms must also be present including changes in appetite, weight, sleep, and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. The episode must be accompanied by distress or impairment in social, occupational, or other important areas of functioning.

[See also OMIM:608516](http://www.omim.org/entry/608516)

###### [**Attention deficit-hyperactivity disorder 7 (ADHD7)**](http://www.uniprot.org/diseases/DI-02574)**1 Publication**

Disease susceptibility is associated with variations affecting the gene represented in this entry. Naturally occurring variants of TPH2 with impaired enzyme activity could cause deficiency of serotonin production and result in an increased risk of developing behavioral disorders.

Disease descriptionA neurobehavioral developmental disorder primarily characterized by the coexistence of attentional problems and hyperactivity, with each behavior occurring infrequently alone.

[DB00150](https://www.drugbank.ca/drugs/DB00150) L-Tryptophan  
[DB12095](https://www.drugbank.ca/drugs/DB12095) Telotristat

<https://www.ncbi.nlm.nih.gov/gene/121278>

This gene encodes a member of the pterin-dependent aromatic acid hydroxylase family. The encoded protein catalyzes the first and rate limiting step in the biosynthesis of serotonin, an important hormone and neurotransmitter. Mutations in this gene may be associated with psychiatric diseases such as bipolar affective disorder and major depression. [provided by RefSeq, Feb 2016]

Tryptophan hydroxylase (TPH; EC 1.14.16.4) is the rate-limiting enzyme in the synthesis of serotonin (5-hydroxytryptamine, or 5HT). 5HT is causally involved in numerous central nervous activities, and it has several functions in peripheral tissues, including the maintenance of vascular tone and gut motility.[supplied by OMIM][[7]](https://en.wikipedia.org/wiki/TPH2#cite_note-entrez-7)

**Tryptophan hydroxylase** (**TPH**) is an [enzyme](https://en.wikipedia.org/wiki/Enzyme) ([EC](https://en.wikipedia.org/wiki/Enzyme_Commission_number) [1.14.16.4](https://enzyme.expasy.org/EC/1.14.16.4)) involved in the synthesis of the neurotransmitter [serotonin](https://en.wikipedia.org/wiki/Serotonin). [Tyrosine hydroxylase](https://en.wikipedia.org/wiki/Tyrosine_hydroxylase), [phenylalanine hydroxylase](https://en.wikipedia.org/wiki/Phenylalanine_hydroxylase), and tryptophan hydroxylase together constitute the family of biopterin-dependent [aromatic amino acid hydroxylases](https://en.wikipedia.org/wiki/Aromatic_amino_acid_hydroxylase). TPH catalyzes the following chemical reaction

n humans, the stimulation of serotonin production by administration of tryptophan has an antidepressant effect[[*citation needed*](https://en.wikipedia.org/wiki/Wikipedia:Citation_needed)] and inhibition of tryptophan hydroxylase (e.g. by [p-Chlorophenylalanine](https://en.wikipedia.org/wiki/P-Chlorophenylalanine)) may precipitate depression.[[3]](https://en.wikipedia.org/wiki/Tryptophan_hydroxylase#cite_note-pmid12379098-3)