|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SLC6A4 | Loss of 5 % to 95% of serotonin uptake activity - Major Depressive Disorder, Bipolar Disorder, Depressive disorder, Mood Disorders, Autistic Disorder, Schizophrenia, Anxiety Disorders, Obsessive-Compulsive disorder, Unipolar Depression, Alcohol abuse, Personality Disorder | likely - depression, energy medication (amphetamines) https://www.ncbi.nlm.nih.gov/pubmed/26473596 | antidepressants, dopamine, doxepin, tramadol, flueoxetine, and many more | do not drink, http://www.omim.org/entry/103780 , OBSESSIVE-COMPULSIVE DISORDER; OCD, treatment for that |  | possible | likely | likely | likely |

**Fatigue, depression, stress, anxiety**

**References**

CFS patients have a significant increase in L;L variants, which may cause [concentrated extracellular serotonin and higher susceptibility to CFS.](<https://www.ncbi.nlm.nih.gov/pubmed/14592408>)

Association between serotonin transporter gene polymorphism and chronic fatigue syndrome.

PMID: 14592408

Interaction between the hypothalamo-pituitary-adrenal axis and the serotonergic system is thought to be disrupted in chronic fatigue syndrome (CFS) patients. We examined a serotonin transporter (5-HTT) gene promoter polymorphism, which affects the transcriptional efficiency of 5-HTT, in 78 CFS patients using PCR amplification of the blood genomic DNA. A significant increase of longer (L and XL) alleic variants was found in the CFS patients compared to the controls both by the genotype-wise and the allele-wise analyses (both p<0.05, by chi(2) test and Fisher's exact test). Attenuated concentration of extracellular serotonin due to longer variants may cause higher susceptibility to CFS.

[1.77 Odds ratio]( <https://www.ncbi.nlm.nih.gov/pubmed/17414739>) for adverse reactions to selective serotonin reuptake inhibitors

[2.37 Odds ratio]( <https://www.ncbi.nlm.nih.gov/pubmed/17414739>) for adverse reactions to selective serotonin reuptake inhibitors

<https://www.ncbi.nlm.nih.gov/pubmed/17414739>

Serotonin transporter polymorphisms and the occurrence of adverse events during treatment with selective serotonin reuptake inhibitors.

PMID: 17414739

DOI: [10.1097/YIC.0b013e328014822a](https://doi.org/10.1097/YIC.0b013e328014822a)

During treatment with selective serotonin reuptake inhibitors, some patients experience adverse events whereas others do not. This study evaluates the association between adverse events during selective serotonin reuptake inhibitor treatment and two polymorphisms in the serotonin transporter (5-HTTLPR) gene. Patients with the 5-HTTLPR s/s or s/l genotype appeared to have an increased risk of adverse events, especially general adverse events (dermatologic reactions, weight change and fatigue); odds ratio 1.77 (95% confidence interval 0.80-3.92) for the s/s genotype, odds ratio 2.37 (95% confidence interval 1.13-4.96) for the s/l genotype. Our findings indicate that patients with the 5-HTTLPR s/s or s/l genotype have an increased risk of developing adverse events during selective serotonin reuptake inhibitor treatment.

<https://www.ncbi.nlm.nih.gov/pubmed/18079067>

Genetic evaluation of the serotonergic system in chronic fatigue syndrome.

PMID: 18079067

DOI: [10.1016/j.psyneuen.2007.11.001](https://doi.org/10.1016/j.psyneuen.2007.11.001)

Chronic fatigue syndrome (CFS) is a debilitating disorder of unknown etiology with no known lesions, diagnostic markers or therapeutic intervention. The pathophysiology of CFS remains elusive, although abnormalities in the central nervous system (CNS) have been implicated, particularly hyperactivity of the serotonergic (5-hydroxytryptamine; 5-HT) system and hypoactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Since alterations in 5-HT signaling can lead to physiologic and behavioral changes, a genetic evaluation of the 5-HT system was undertaken to identify serotonergic markers associated with CFS and potential mechanisms for CNS abnormality. A total of 77 polymorphisms in genes related to serotonin synthesis (TPH2), signaling (HTR1A, HTR1E, HTR2A, HTR2B, HTR2C, HTR3A, HTR3B, HTR4, HTR5A, HTR6, and HTR7), transport (SLC6A4), and catabolism (MAOA) were examined in 137 clinically evaluated subjects (40 CFS, 55 with insufficient fatigue, and 42 non-fatigued, NF, controls) derived from a population-based CFS surveillance study in Wichita, Kansas. Of the polymorphisms examined, three markers (-1438G/A, C102T, and rs1923884) all located in the 5-HT receptor subtype HTR2A were associated with CFS when compared to NF controls. Additionally, consistent associations were observed between HTR2A variants and quantitative measures of disability and fatigue in all subjects. The most compelling of these associations was with the A allele of -1438G/A (rs6311) which is suggested to have increased promoter activity in functional studies. Further, in silico analysis revealed that the -1438 A allele creates a consensus binding site for Th1/E47, a transcription factor implicated in the development of the nervous system. Electrophoretic mobility shift assay supports allele-specific binding of E47 to the A allele but not the G allele at this locus. These data indicate that sequence variation in HTR2A, potentially resulting in its enhanced activity, may be involved in the pathophysiology of CFS.

<https://www.ncbi.nlm.nih.gov/pubmed/19704949>

Gender effects on association of serotonin transporter gene polymorphism with symptoms of central fatigue.

PMID: 19704949

In order to test the "serotonin" hypothesis of the genesis of central fatigue, we studied association between genotype and fatigue (3-hour mental workload consisting of information processing and logical task solution) using analysis of variance for different indices (well-being, activity, mood, mental fatigue index). It was concluded that young men with serotonin deficit (LL genotype) and girls with serotonin excess (S genotype) were less tolerant to long-lasting mental workload. Thus, we confirmed that the degree of central fatigue depends on the function of the serotonin system and revealed gender differences in adaptive capacities of carriers of different variants of serotonin transporter.

<https://www.ncbi.nlm.nih.gov/pubmed/25040499>

Induction of interleukin-1β by activated microglia is a prerequisite for immunologically induced fatigue.

PMID: 25040499

DOI: [10.1111/ejn.12668](https://doi.org/10.1111/ejn.12668)

The poly-I:C-induced fatigue was associated with serotonin transporter (5-HTT) overexpression in the prefrontal cortex (PFC), a brain region that has been suggested to be critical for fatigue sensation. We therefore propose that poly-I:C-induced microglial activation, which may be at least partly caused by a direct action of poly-I:C, enhances IL-1β expression. Then, IL-1β induces 5-HTT expression in astrocytes, resulting in the immunologically induced fatigue.

<https://www.ncbi.nlm.nih.gov/pubmed/26473596>

Maintenance of Chronic Fatigue Syndrome (CFS) in Young CFS Patients Is Associated with the 5-HTTLPR and SNP rs25531 A > G Genotype.

PMID: 26473596

PMCID: [PMC4608737](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4608737/)

DOI: [10.1371/journal.pone.0140883](https://doi.org/10.1371/journal.pone.0140883)

Earlier studies have shown that genetic variability in the SLC6A4 gene encoding the serotonin transporter (5-HTT) may be important for the re-uptake of serotonin (5-HT) in the central nervous system. In the present study we investigated how the 5-HTT genotype i.e. the short (S) versus long (L) 5-HTTLPR allele and the SNP rs25531 A > G affect the physical and psychosocial functioning in patients with chronic fatigue syndrome (CFS). Patients with the 5-HTT SS or SLG genotype had a significantly lower number of steps per day than patients with the 5-HTT LALG, SLA or LALA genotype. Patients with the 5-HTT SS or SLG genotype also had a significantly higher FDI score than patients with the 5-HTT LALG, SLA or LALA genotype. Thus, CFS patients with the 5-HTT SS or SLG genotype had worse 30 weeks outcome than CFS patients with the 5-HTT LALG, SLA or LALA genotype. The present study suggests that the 5-HTT genotype may be a factor that contributes to maintenance of CFS.

The SLC6A4 gene encodes the serotonin transporter, a membrane protein that takes up serotonin in pre-synaptic neurons. SLC6A4 is also known as SERT or 5-HTT, since serotonin is known chemically as 5-hydroxytryptamine. The serotonin system has been studied in many behavioural and physiological conditions.

A wide range of psychiatric disorders or conditions may involve serotonin processing. The main variants of the SLC6A4 gene that have been studied, however, are not SNPs - they are short tandem repeats, also known as VNTRs (variable number tandem repeats). A review of the two VNTR polymorphisms and their potential links to human behaviour is available. [[PMID 17168841](https://www.ncbi.nlm.nih.gov/pubmed/17168841?dopt=Abstract)]

One such polymorphism is known as the 5-HTTLPR variant, where the L allele consists of a 44bp insertion as compared to the S (short or deletion) allele. Another polymorphism is the STin2 (intron 2) VNTR, which involves different alleles that correspond to 12-, 10-, 9-, or 7-repeat units of 17bp. Both of these polymorphisms have been associated in some cases (but not others) with obsessive-compulsive disorder (OCD). Most recently, the STin2.12 carriers were reported to be at over 3x risk of OCD based on a study of ~100 OCD patients.[[PMID 18191318](https://www.ncbi.nlm.nih.gov/pubmed/18191318?dopt=Abstract)]

The efficacy of commonly prescribed antidepressant drugs, such as [paroxetine](https://www.snpedia.com/index.php/Paroxetine), has also been linked to SLC6A4 VNTR variants.[10.1038/sj.tpj.6500491](http://dx.doi.org/10.1038/sj.tpj.6500491)

A few SNPs have been studied; these include:

* [rs25531](https://www.snpedia.com/index.php/Rs25531)
* C=0.1376/689
* 3609A>G
* The 16-repeat promoter VNTR allele was originally called the long allele (L) and the 14-repeat allele the short allele(S) and these are further divided into six and four kinds of allelic variants respectively as per the naming convention in Nakamura et al. (14-A, 14-B, 14-C, 14-D,16-A, 16-B, 16-C, 16-D, 16-E, 16-F) Various other repeat alleles were observed in this study. More detailed explanation regarding the methods used and the allele naming convention can be found in the supplemental section of Murdoch et al (reference given below).
* [rs1042173](https://www.snpedia.com/index.php/Rs1042173), implicated in heavier drinking alcoholics

0.379 463T>G

|  |  |  |
| --- | --- | --- |
| [(G;G)](https://www.snpedia.com/index.php/Rs1042173(G;G)) |  | Normal |
| [(G;T)](https://www.snpedia.com/index.php/Rs1042173(G;T)) |  | Normal |
| [(T;T)](https://www.snpedia.com/index.php/Rs1042173(T;T)) | 0 | among alcoholics, likely to be heavier drinkers |

* rs1042173 is a SNP in the solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 [SLC6A4](https://www.snpedia.com/index.php/SLC6A4) gene.
* A study of 275 patients seeking treatment for [alcoholism](https://www.snpedia.com/index.php/Alcoholism) concluded that Caucasians of with the rs1042173(T;T) genotype consumed an average of 11.17 drinks per drinking day, compared with an average of 8.58 for carriers of a rs1042173(G) allele (p = 0.0034). While this held true for both men and women, this association was not seen in Hispanics. [[PMID 19032574](https://www.ncbi.nlm.nih.gov/pubmed/19032574?dopt=Abstract)[OA-icon.png](https://www.snpedia.com/index.php/File:OA-icon.png)]

[AVPR1a and SLC6A4 Gene Polymorphisms Are Associated with Creative Dance Performance](http://www.plosgenetics.org/article/info:doi%2F10.1371%2Fjournal.pgen.0010042)

the T allele of rs1042173 was associated with lower mRNA and protein levels. In subsequent analyses, the TT genotype was found to be associated with higher drinking intensity in alcohol-dependent (AD) individuals T genotype was associated with higher urge to drink (p = 0.002) and crave for a drink

<https://www.ncbi.nlm.nih.gov/pubmed/22355291?dopt=Abstract>

<https://www.ncbi.nlm.nih.gov/pubmed/28608626>

We found that male citalopram users with low functioning s/s genotype of 5HTTLPR/rs25531 were in increased risk to commit violent suicide (OR 2.50

https://www.ncbi.nlm.nih.gov/pubmed/28262188

The serotonin transporter-linked polymorphic region (5-HTTLPR) of the serotonin transporter gene (SLC6A4) has been previously associated with alcohol-related risk. Most findings point to short (S) allele carriers being at increased risk for negative alcohol outcomes relative to long allele homozygotes

Findings suggest that one mechanism by which 5-HTTLPR variation transmits alcohol-related risk is through level of response to alcohol. Furthermore, the strength and direction of this effect varied by level of parental monitoring, indicating that even in the presence of genetic and physiological vulnerability, parents can influence the likelihood of offspring developing problematic alcohol-related behaviors.

https://www.ncbi.nlm.nih.gov/pubmed/26979101

Our meta-analysis confirms that individuals with the homozygous S allele of 5HTTLPR polymorphism are at increased risks of major depressive disorder as well as alcoholdependence.

https://www.ncbi.nlm.nih.gov/pubmed/26231032

5-HTTLPR genotype moderated the effects of ecstasy on verbal memory, with L/L carriers performing worse compared to controls.

<https://www.ncbi.nlm.nih.gov/pubmed/18486105?dopt=Abstract>

The frequency of the short allele was significantly associated with alcohol dependence (OR = 1.18, <http://www.omim.org/entry/103780>

https://www.ncbi.nlm.nih.gov/pubmed/16642437

The HTTLPR L(A)L(A) genotype exerted a moderate (1.8-fold) effect on risk of OCD, thus establishing a role for the HTT gene in OCD

[Lesch et al. (1996)](http://www.omim.org/entry/182138#29) found that the short version of the 5-HTTLPR polymorphism in either homozygous or heterozygous form was associated with higher neuroticism scores and lower extraversion and openness scores (see [607834](http://www.omim.org/entry/607834)).

 The short variant of the polymorphism reduces the transcriptional efficiency of the 5-HTT gene promoter, resulting in decreased 5-HTT expression and 5-HT uptake in lymphoblasts.  5-HTT polymorphism accounts for 3 to 4 percent of total variation and 7 to 9 percent of inherited variance in anxiety-related personality traits in individuals as well as sibships.

<https://www.ncbi.nlm.nih.gov/pubmed/8929413>

reported that individuals with 1 or 2 copies of the short allele of the serotonin transporter promoter polymorphism, which has been associated with reduced serotonin expression and function and increased fear and anxiety-related behaviors, exhibited greater amygdala neuronal activity, as assessed by functional MRI, in response to fearful stimuli compared with individuals homozygous for the long allele. These results demonstrate genetically driven variation in the response of brain regions underlying human emotional behavior and suggest that differential excitability of the amygdala to emotional stimuli may contribute to the increased fear and anxiety typically associated with the short SLC6A4 allele. <https://www.ncbi.nlm.nih.gov/pubmed/12130784>

The results revealed that patients with the L/L genotype had a significantly better response to SSRI (fluoxetine) when compared to the S allele carriers on the basis of total (p = 0.013), core (p = 0.011), psychic anxiety (p = 0.005), and somatic anxiety (p = 0.002) symptoms of the Hamilton Depression Rating Scale-score percentage change.

<https://www.ncbi.nlm.nih.gov/pubmed/12476327>

The L(A) allele was 2-fold overtransmitted to the patients with OCD. The SLC6A4 L(A)L(A) genotype exerted a moderate (1.8-fold) effect on risk of OCD, thus establishing a role for the HTT gene in OCD.

https://www.ncbi.nlm.nih.gov/pubmed/16642437