 rs356653

**Convergent genomic studies identify association of GRIK2 and NPAS2 with chronic fatigue syndrome.**

[Smith AK](https://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20AK%5BAuthor%5D&cauthor=true&cauthor_uid=21912186)1, [Fang H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Fang%20H%5BAuthor%5D&cauthor=true&cauthor_uid=21912186), [Whistler T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Whistler%20T%5BAuthor%5D&cauthor=true&cauthor_uid=21912186), [Unger ER](https://www.ncbi.nlm.nih.gov/pubmed/?term=Unger%20ER%5BAuthor%5D&cauthor=true&cauthor_uid=21912186), [Rajeevan MS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rajeevan%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=21912186).

[**Author information**](https://www.ncbi.nlm.nih.gov/pubmed)

**Abstract**

**BACKGROUND:**

There is no consistent evidence of specific gene(s) or molecular pathways that contribute to the pathogenesis, therapeutic intervention or diagnosis of chronic fatigue syndrome (CFS). While multiple studies support a role for genetic variation in CFS, genome-wide efforts to identify associated loci remain unexplored. We employed a novel convergent functional genomics approach that incorporates the findings from single-nucleotide polymorphism (SNP) and mRNA expression studies to identify associations between CFS and novel candidate genes for further investigation.

**METHODS:**

We evaluated 116,204 SNPs in 40 CFS and 40 nonfatigued control subjects along with mRNA expression of 20,160 genes in a subset of these subjects (35 CFS subjects and 27 controls) derived from a population-based study.

**RESULTS:**

Sixty-five SNPs were nominally associated with CFS (p<0.001), and 165 genes were differentially expressed (≥4-fold; p≤0.05) in peripheral blood mononuclear cells of CFS subjects. Two genes, glutamate receptor, ionotropic, kinase 2 (GRIK2) and neuronal PAS domain protein 2 (NPAS2), were identified by both SNP and gene expression analyses. Subjects with the G allele of rs2247215 (GRIK2) were more likely to have CFS (p=0.0005), and CFS subjects showed decreased GRIK2 expression (10-fold; p=0.015). Subjects with the T allele of rs356653 (NPAS2) were more likely to have CFS (p=0.0007), and NPAS2 expression was increased (10-fold; p=0.027) in those with CFS.

**CONCLUSION:**

Using an integrated genomic strategy, this study suggests a possible role for genes involved in glutamatergic neurotransmission and circadian rhythm in CFS and supports further study of novel candidate genes in independent populations of CFS subjects.

<https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21912186/>

Finally, the T allele of rs356653, an SNP located in NPAS2, a gene implicated in circadian regulation, was more common in subjects with CFS (p = 0.0007).

inally, NPAS2 was upregulated (nearly 10-fold; p = 0.027) in CFS subjects. However, only GRIK2 and NPAS2 were associated with CFS in both the SNP association and mRNA expression experiments.

Also, a polymorphism in NPAS2 was more common in subjects with CFS, while NPAS2 expression was increased in CFS subjects. It is interesting to note that both GRIK2 and NPAS2 have been reported to be associated with impaired cognition as well as memory and sleep, 2 of the hallmark symptoms of CFS

In this study, we observed an association between CFS and a polymorphism (rs356653) in NPAS2, a member of the basic helix-loop-helix PAS family of transcription factors that is a central component of the molecular circadian oscillator. NPAS2 heterodimerizes with BMAL1 and functions as a positive element of the circadian system to drive the transcription of clock-controlled genes [[39](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B39), https://www.ncbi.nlm.nih.gov/pubmed/17417633]. NPAS2 may function primarily as part of a molecular clock operating in the forebrain, but being a paralog of CLOCK,it can also substitute for CLOCK in the master clock in the hypothalamic suprachiasmatic nuclei to regulate circadian rhythmicity [[41](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B41), https://www.ncbi.nlm.nih.gov/pubmed/11441147]. NPAS2 has been associated with cued and contextual memory [https://www.ncbi.nlm.nih.gov/pubmed/10864874] and may function as a transcriptional regulator of non-rapid eye movement sleep in mice [[44](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B44),[45](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3701888/#B45)]. Polymorphisms in NPAS2 have been associated with multiple psychiatric disorders. For example, variants have been associated with autism (rs1811399) [https://www.ncbi.nlm.nih.gov/pubmed/17264841], winter depression (rs11541353) [https://www.ncbi.nlm.nih.gov/pubmed/17457720], mood disorders and schizophrenia (rs13025524 and rs11123857) [https://www.ncbi.nlm.nih.gov/pubmed/19839995, https://www.ncbi.nlm.nih.gov/pubmed/20072116] as well as breast cancer and non-Hodgkin's lymphoma (NHL) [https://www.ncbi.nlm.nih.gov/pubmed/18819933]. The associations between NPAS2 variants and CFS and NHL are interesting in the context of anecdotal reports suggesting that CFS may predispose subjects to NHL [https://www.ncbi.nlm.nih.gov/pubmed/1394166]. While none of these studies report an association with a common NPAS2 polymorphism, these associations suggest an overlapping role for NPAS2 in CFS and psychiatric disorders, potentially via common symptomatology such as sleep architecture or metabolic imbalances [https://www.ncbi.nlm.nih.gov/pubmed/21127246].

<https://www.ncbi.nlm.nih.gov/gene/4862>

The protein encoded by this gene is a member of the basic helix-loop-helix (bHLH)-PAS family of transcription factors. A similar mouse protein may play a regulatory role in the acquisition of specific types of memory. It also may function as a part of a molecular clock operative in the mammalian forebrain. [provided by RefSeq, Jul 2008]

Depression D003866; insomnia D007319; ME/CFS D015673; metabolic syndrome D024821; cardiovascular disease D002318; cancer D009369; Seasonal Affective Disorder D016574;

fatigue D005221; depression D003863; sleep disorder D012893; memory problems D008569;

NPAS2 ([Neuronal PAS domain-containing protein 2](http://www.uniprot.org/uniprot/Q99743)) encodes a protein that helps bind RNA to DNA to begin transcription, or expression, of the gene. This protein is a core component of the 24-hour circadian clock in the brain, which may be controlled through light, neurological, and hormonal cues. NPAS2 synchronizes hunger with food availability, maintains sleep/wake cycles due to light interactions in the retina, and helps regulate cell cycles in the liver that repair DNA. Disruptions in the circadian rhythm may contribute to [cardiovascular disease, cancer, metabolic syndrome, and aging](http://www.uniprot.org/uniprot/Q99743). Variants in NPAS2 are associated with [major depressive disorder](https://www.omim.org/entry/608516), [seasonal affective disorder](http://www.uniprot.org/uniprot/Q99743), and ME/CFS.

NPAS2 variants may be linked to [sleep problems, metabolic imbalances, and mood disorders](https://www.ncbi.nlm.nih.gov/pubmed/21127246) in ME/CFS patients due to disrupted circadian rhythms. Your T allele is [1.9X more common](https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21912186/) in ME/CFS patients compared to the normal population, and it causes a [10-fold increase](https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21912186/) in NPAS2 gene expression. This may disrupt hunger cues and sleep cycles, causing impaired [cued and contextual memory](https://www.ncbi.nlm.nih.gov/pubmed/10864874), [depression](https://www.omim.org/entry/608516), or [seasonal affective disorder](https://www.ncbi.nlm.nih.gov/pubmed/17457720).

# What should I do about this?

Patients should monitor their dietary intake and hunger cues to maintain weight.

[Lifestyle changes](https://medlineplus.gov/ency/patientinstructions/000757.htm) to help with circadian rhythm disruption sleep problems may include:

* Go to bed the same time every night.
* Do not nap in the daytime or spend time in bed during the day.
* Minimize light and sound in your bedroom, including television, computers, and cell phones.
* Work fewer night and evening shifts.
* [Walk or exercise 30 minutes most days](https://medlineplus.gov/ency/patientinstructions/000757.htm).
* Minimize alcohol, tobacco, caffeine, and cold medications.
* Properly treat any bipolar, depression, anxiety, or other mood disorders.

[Medications](https://medlineplus.gov/ency/patientinstructions/000758.htm) to aid sleep include Zolpidem (Ambien), Zaleplon (Sonata), Eszoicolone (Lunesta), Ramelteon (Rozerem), and antihistamines. Consult your doctor.

<http://www.uniprot.org/uniprot/Q99743>

**Neuronal PAS domain-containing protein 2**

Transcriptional activator which forms a core component of the circadian clock. The circadian clock, an internal time-keeping system, regulates various physiological processes through the generation of approximately 24 hour circadian rhythms in gene expression, which are translated into rhythms in metabolism and behavior. It is derived from the Latin roots 'circa' (about) and 'diem' (day) and acts as an important regulator of a wide array of physiological functions including metabolism, sleep, body temperature, blood pressure, endocrine, immune, cardiovascular, and renal function. Consists of two major components: the central clock, residing in the suprachiasmatic nucleus (SCN) of the brain, and the peripheral clocks that are present in nearly every tissue and organ system. Both the central and peripheral clocks can be reset by environmental cues, also known as Zeitgebers (German for 'timegivers'). The predominant Zeitgeber for the central clock is light, which is sensed by retina and signals directly to the SCN. The central clock entrains the peripheral clocks through neuronal and hormonal signals, body temperature and feeding-related cues, aligning all clocks with the external light/dark cycle. Circadian rhythms allow an organism to achieve temporal homeostasis with its environment at the molecular level by regulating gene expression to create a peak of protein expression once every 24 hours to control when a particular physiological process is most active with respect to the solar day. Transcription and translation of core clock components (CLOCK, NPAS2, ARNTL/BMAL1, ARNTL2/BMAL2, PER1, PER2, PER3, CRY1 and CRY2) plays a critical role in rhythm generation, whereas delays imposed by post-translational modifications (PTMs) are important for determining the period (tau) of the rhythms (tau refers to the period of a rhythm and is the length, in time, of one complete cycle). A diurnal rhythm is synchronized with the day/night cycle, while the ultradian and infradian rhythms have a period shorter and longer than 24 hours, respectively. Disruptions in the circadian rhythms contribute to the pathology of cardiovascular diseases, cancer, metabolic syndromes and aging. A transcription/translation feedback loop (TTFL) forms the core of the molecular circadian clock mechanism. Transcription factors, CLOCK or NPAS2 and ARNTL/BMAL1 or ARNTL2/BMAL2, form the positive limb of the feedback loop, act in the form of a heterodimer and activate the transcription of core clock genes and clock-controlled genes (involved in key metabolic processes), harboring E-box elements (5'-CACGTG-3') within their promoters. The core clock genes: PER1/2/3 and CRY1/2 which are transcriptional repressors form the negative limb of the feedback loop and interact with the CLOCK|NPAS2-ARNTL/BMAL1|ARNTL2/BMAL2 heterodimer inhibiting its activity and thereby negatively regulating their own expression. This heterodimer also activates nuclear receptors NR1D1/2 and RORA/B/G, which form a second feedback loop and which activate and repress ARNTL/BMAL1 transcription, respectively. The NPAS2-ARNTL/BMAL1 heterodimer positively regulates the expression of MAOA, F7 and LDHA and modulates the circadian rhythm of daytime contrast sensitivity by regulating the rhythmic expression of adenylate cyclase type 1 (ADCY1) in the retina. NPAS2 plays an important role in sleep homeostasis and in maintaining circadian behaviors in normal light/dark and feeding conditions and in the effective synchronization of feeding behavior with scheduled food availability. Regulates the gene transcription of key metabolic pathways in the liver and is involved in DNA damage response by regulating several cell cycle and DNA repair genes.5 Publications

#### Cofactori

[heme](https://www.ebi.ac.uk/chebi/searchId.do?chebiId=CHEBI:30413)By similarity

#### Enzyme regulationi

Carbon monoxide (CO) and the redox state of the cell can modulate the transcriptional activity of the NPAS2-ARNTL/BMAL1 heterodimer. NADH and NADPH enhance the DNA-binding activity of the heterodimer whereas CO binds the heme group in NPAS2 and inhibits the DNA-binding activity of the heterodimer.By similarity

#### Sites

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Feature key | Position(s) | DescriptionActions | Graphical view | Length |
| Metal bindingi | [119](http://www.uniprot.org/blast/?about=Q99743%5b119%5d&key=Metal%20binding) | Iron (heme B axial ligand)By similarity |  | 1 |
| Metal bindingi | [171](http://www.uniprot.org/blast/?about=Q99743%5b171%5d&key=Metal%20binding) | Iron (heme B axial ligand)By similarity |  | 1 |

#### GO - Molecular functioni

* [core promoter binding](https://www.ebi.ac.uk/QuickGO/term/GO:0001047) Source: UniProtKB
* [DNA binding](https://www.ebi.ac.uk/QuickGO/term/GO:0003677) Source: UniProtKB
* [DNA binding transcription factor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0003700) Source: ProtInc
* [Hsp90 protein binding](https://www.ebi.ac.uk/QuickGO/term/GO:0051879) Source: BHF-UCL
* [metal ion binding](https://www.ebi.ac.uk/QuickGO/term/GO:0046872) Source: UniProtKB-KW
* [protein dimerization activity](https://www.ebi.ac.uk/QuickGO/term/GO:0046983) Source: InterPro
* [RNA polymerase II transcription factor activity, sequence-specific DNA binding](https://www.ebi.ac.uk/QuickGO/term/GO:0000981) Source: NTNU\_SB

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q99743)

#### GO - Biological processi

* [cellular response to DNA damage stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:0006974) Source: UniProtKB-KW
* [central nervous system development](https://www.ebi.ac.uk/QuickGO/term/GO:0007417) Source: ProtInc
* [circadian regulation of gene expression](https://www.ebi.ac.uk/QuickGO/term/GO:0032922) Source: UniProtKB
* [circadian rhythm](https://www.ebi.ac.uk/QuickGO/term/GO:0007623) Source: Reactome
* [negative regulation of cell death](https://www.ebi.ac.uk/QuickGO/term/GO:0060548) Source: UniProtKB
* [positive regulation of DNA repair](https://www.ebi.ac.uk/QuickGO/term/GO:0045739) Source: UniProtKB
* [positive regulation of transcription, DNA-templated](https://www.ebi.ac.uk/QuickGO/term/GO:0045893) Source: UniProtKB
* [positive regulation of transcription by RNA polymerase II](https://www.ebi.ac.uk/QuickGO/term/GO:0045944) Source: MGI
* [regulation of lipid metabolic process](https://www.ebi.ac.uk/QuickGO/term/GO:0019216) Source: Reactome
* [regulation of response to DNA damage stimulus](https://www.ebi.ac.uk/QuickGO/term/GO:2001020) Source: UniProtKB
* [response to redox state](https://www.ebi.ac.uk/QuickGO/term/GO:0051775) Source: UniProtKB
* [transcription, DNA-templated](https://www.ebi.ac.uk/QuickGO/term/GO:0006351) Source: UniProtKB-KW

<https://www.omim.org/entry/608516>

### MAJOR DEPRESSIVE DISORDER; MDD

Alternative titles; symbols

#### UNIPOLAR DEPRESSION

Other entities represented in this entry:

SEASONAL AFFECTIVE DISORDER, INCLUDED; SAD, INCLUDED