<https://www.ncbi.nlm.nih.gov/pubmed/27099524>

Analysis of genotype, ORs, and significance of SNPs in genes for TRP ion channels and AChRs in ME/CFS patients and unfatigued controls in rank order of significance

| **Gene** | **CL** | **SNP** | **Genotype** | **ME/CFS, n %)** | **Unfatigued controls, n (%)** | **χ2** | **OR** | **P-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CHRNA2 | 8 | rs891398 | CC | 11 (91.7) | 1 (8.3) | 7.31 | 11.39 | 0.007 |
| CHRNA2 | 8 | rs2741343 | CC | 11 (91.7) | 1 (8.3) | 7.3 | 11.39 | 0.007 |

rs2472553

https://www.ncbi.nlm.nih.gov/pubmed/24253422

 these, associations of SNPs rs3735757 with FTND (P = 0.0068) and rs2472553 with both ND measures (with a P value of 0.0043 and 0.00086 for SQ and FTND, respectively) continued to be significant in the EA sample even after correction for multiple tests.

<https://www.ncbi.nlm.nih.gov/pubmed/24467848>

A cytosine to thymidine (C → T) missense mutation in the signal peptide (SP) sequence (rs2472553) of the nicotinic acetylcholine receptor (nAChR) α2 subunit produces a threonine-to-isoleucine substitution (T22I) often associated with nicotine dependence (ND). We assessed effects on function of α2\*-nAChR ('\*'indicates presence of additional subunits) of this mutation, which could alter SP cleavage, RNA/protein secondary structure, and/or efficiency of transcription, translation, subunit assembly, receptor trafficking or cell surface expression. Two-electrode voltage clamp analyses indicate peak current responses to ACh or nicotine are decreased 2.8-5.8-fold for putative low sensitivity (LS; 10:1 ratio of α:β subunit cRNAs injected) α2β2- or α2β4-nAChR and increased for putative high sensitivity (HS; 1:10 α:β subunit ratio) α2β2- (5.7-15-fold) or α2β4- (1.9-2.2-fold) nAChR as a result of the mutation. Agonist potencies are decreased 1.6-4-fold for putative LS or HS α2(T22I)β2-nAChR or for either α2\*-nAChR subtype formed in the presence of equal amounts of subunit cRNA, slightly decreased for LS α2(T22I)β4-nAChR, but increased 1.4-2.4-fold for HS α2(T22I)β4-nAChR relative to receptors containing wild-type α2 subunits. These effects suggest that the α2 subunit SP mutation generally favors formation of LS receptor isoforms. We hypothesize that lower sensitivity of human α2\*-nAChR to nicotine could contribute to increased susceptibility to ND. To our knowledge this is the first report of a SP mutation having a functional effect in a member of cys-loop family of ligand-gated ion channels.

<http://www.uniprot.org/uniprot/Q15822>

After binding acetylcholine, the AChR responds by an extensive change in conformation that affects all subunits and leads to opening of an ion-conducting channel across the plasma membrane.

#### Caution

With the use of epibatidine as high affinity ligand, an alpha-2 homopentamer has been purified and crystallized. Its physiological relevance has not been proven.1 Publication

#### GO - Molecular functioni

* [acetylcholine binding](https://www.ebi.ac.uk/QuickGO/term/GO:0042166) Source: Ensembl
* [acetylcholine-gated cation-selective channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0022848) Source: UniProtKB
* [acetylcholine receptor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015464) Source: UniProtKB
* [ligand-gated ion channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015276) Source: Reactome

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q15822)

#### GO - Biological processi

* [ion transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006811) Source: UniProtKB
* [neuromuscular synaptic transmission](https://www.ebi.ac.uk/QuickGO/term/GO:0007274) Source: GO\_Central
* [protein heterooligomerization](https://www.ebi.ac.uk/QuickGO/term/GO:0051291) Source: Ensembl
* [response to nicotine](https://www.ebi.ac.uk/QuickGO/term/GO:0035094) Source: GO\_Central
* [signal transduction](https://www.ebi.ac.uk/QuickGO/term/GO:0007165) Source: UniProtKB
* [synaptic transmission, cholinergic](https://www.ebi.ac.uk/QuickGO/term/GO:0007271) Source: GO\_Central

###### [**https://www.omim.org/entry/610353**](https://www.omim.org/entry/610353)

Nocturnal frontal lobe epilepsy is a childhood-onset focal epilepsy that displays clusters of sleep-related hypermotor seizures (summary by [Aridon et al., 2006](https://www.omim.org/entry/610353" \l "1" \o ")). Some patients with CHRNA2 mutations may have a slightly different phenotype that is more consistent with a clinical diagnosis of benign familial infantile seizures (BFIS6) ([Trivisano et al., 2015](https://www.omim.org/entry/610353" \l "3" \o ")).

For a general phenotypic description and a discussion of genetic heterogeneity of nocturnal frontal lobe epilepsy, see ENFL1 ([600513](https://www.omim.org/entry/600513)).

For a general phenotypic description and a discussion of genetic heterogeneity of benign familial infantile seizures, see BFIS1 ([601764](https://www.omim.org/entry/601764)).

###### [**Epilepsy, nocturnal frontal lobe, 4 (ENFL4)**](http://www.uniprot.org/diseases/DI-00821)**1 Publication**

The disease is caused by mutations affecting the gene represented in this entry.

Disease descriptionAn autosomal dominant focal epilepsy characterized by nocturnal seizures associated with fear sensation, tongue movements, and nocturnal wandering, closely resembling nightmares and sleep walking.

An autosomal dominant focal epilepsy characterized by nocturnal seizures associated with fear sensation, tongue movements, and nocturnal wandering, closely resembling nightmares and sleep walking.

[DB00732](https://www.drugbank.ca/drugs/DB00732) Atracurium besylate  
[DB00810](https://www.drugbank.ca/drugs/DB00810) Biperiden  
[DB00411](https://www.drugbank.ca/drugs/DB00411) Carbachol  
[DB00565](https://www.drugbank.ca/drugs/DB00565) Cisatracurium besylate  
[DB01245](https://www.drugbank.ca/drugs/DB01245) Decamethonium  
[DB00514](https://www.drugbank.ca/drugs/DB00514) Dextromethorphan  
[DB01135](https://www.drugbank.ca/drugs/DB01135) Doxacurium chloride  
[DB00898](https://www.drugbank.ca/drugs/DB00898) Ethanol  
[DB00674](https://www.drugbank.ca/drugs/DB00674) Galantamine  
[DB00483](https://www.drugbank.ca/drugs/DB00483) Gallamine Triethiodide  
[DB00657](https://www.drugbank.ca/drugs/DB00657) Mecamylamine  
[DB01336](https://www.drugbank.ca/drugs/DB01336) Metocurine  
[DB00416](https://www.drugbank.ca/drugs/DB00416) Metocurine Iodide  
[DB01226](https://www.drugbank.ca/drugs/DB01226) Mivacurium  
[DB00184](https://www.drugbank.ca/drugs/DB00184) Nicotine  
[DB01337](https://www.drugbank.ca/drugs/DB01337) Pancuronium  
[DB01338](https://www.drugbank.ca/drugs/DB01338) Pipecuronium  
[DB00721](https://www.drugbank.ca/drugs/DB00721) Procaine  
[DB00728](https://www.drugbank.ca/drugs/DB00728) Rocuronium  
[DB05740](https://www.drugbank.ca/drugs/DB05740) RPI-78M  
[DB01199](https://www.drugbank.ca/drugs/DB01199) Tubocurarine  
[DB01339](https://www.drugbank.ca/drugs/DB01339) Vecuronium

<https://www.ncbi.nlm.nih.gov/gene/1135>

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels formed by a pentameric arrangement of alpha and beta subunits to create distinct muscle and neuronal receptors. Neuronal receptors are found throughout the peripheral and central nervous system where they are involved in fast synaptic transmission. This gene encodes an alpha subunit that is widely expressed in the brain. The proposed structure for nAChR subunits is a conserved N-terminal extracellular domain followed by three conserved transmembrane domains, a variable cytoplasmic loop, a fourth conserved transmembrane domain, and a short C-terminal extracellular region. Mutations in this gene cause autosomal dominant nocturnal frontal lobe epilepsy type 4. Single nucleotide polymorphisms (SNPs) in this gene have been associated with nicotine dependence.

rs104894063

Epilepsy, nocturnal frontal lobe, type 4

<https://www.ncbi.nlm.nih.gov/pubmed/16826524>

Sleep has traditionally been recognized as a precipitating factor for some forms of epilepsy, although differential diagnosis between some seizure types and parasomnias may be difficult. Autosomal dominant frontal lobe epilepsy is characterized by nocturnal seizures with hyperkinetic automatisms and poorly organized stereotyped movements and has been associated with mutations of the alpha 4 and beta 2 subunits of the neuronal nicotinic acetylcholine receptor. We performed a clinical and molecular genetic study of a large pedigree segregating sleep-related epilepsy in which seizures are associated with fear sensation, tongue movements, and nocturnal wandering, closely resembling nightmares and sleep walking. We identified a new genetic locus for familial sleep-related focal epilepsy on chromosome 8p12.3-8q12.3. By sequencing the positional candidate neuronal cholinergic receptor alpha 2 subunit gene (CHRNA2), we detected a heterozygous missense mutation, I279N, in the first transmembrane domain that is crucial for receptor function. Whole-cell recordings of transiently transfected HEK293 cells expressing either the mutant or the wild-type receptor showed that the new CHRNA2 mutation markedly increases the receptor sensitivity to acetylcholine, therefore indicating that the nicotinic alpha 2 subunit alteration is the underlying cause. CHRNA2 is the third neuronal cholinergic receptor gene to be associated with familial sleep-related epilepsies. Compared with the CHRNA4 and CHRNB2 mutations reported elsewhere, CHRNA2 mutations cause a more complex and finalized ictal behavior.

rs522582

<https://www.ncbi.nlm.nih.gov/clinvar/variation/522582/>

<https://www.ncbi.nlm.nih.gov/pubmed/25770198>

We found a c.889A>T (p.Ile297Phe) mutation in the proband (≈0.6% of the whole cohort) of a large ADNFLE family (1.2% of familial cases) and confirmed its segregation in all 6 living affected individuals. Video-EEG studies demonstrated sleep-related paroxysmal epileptic arousals in all mutation carriers. Oxcarbazepine treatment was effective in all. Whole-cell current density was reduced to about 40% in heterozygosity and to 0% in homozygosity, with minor effects on channel permeability and sensitivity to nicotine.

#### CONCLUSION:

ADNFLE had previously been associated with CHRNA2 dysfunction in one family, in which a gain of function mutation was demonstrated. We confirm the causative role of CHRNA2 mutations in ADNFLE and demonstrate that also loss of function of α2 nAChRs may have pathogenic effects. CHRNA2 mutations are a rare cause of ADNFLE but this gene should be included in mutation screening.

<https://medlineplus.gov/epilepsy.html>

Epilepsy is a brain disorder that causes people to have recurring [seizures](https://medlineplus.gov/seizures.html). The seizures happen when clusters of nerve cells, or neurons, in the brain send out the wrong signals. People may have strange sensations and emotions or behave strangely. They may have violent muscle spasms or lose consciousness.

Epilepsy has many possible causes, including illness, brain injury, and abnormal brain development. In many cases, the cause is unknown.

Doctors use brain scans and other tests to diagnose epilepsy. It is important to start treatment right away. There is no cure for epilepsy, but medicines can control seizures for most people. When medicines are not working well, surgery or implanted devices such as vagus nerve stimulators may help. Special diets can help some children with epilepsy.

* [Epilepsy Surgery](https://www.mayoclinic.org/tests-procedures/epilepsy-surgery/about/pac-20393981?p=1) (Mayo Foundation for Medical Education and Research)
* [Seizure First Aid](https://www.cdc.gov/epilepsy/basics/first_aid.htm) (Centers for Disease Control and Prevention)Also in [Spanish](https://www.cdc.gov/epilepsy/spanish/primeros-auxilios.html)
* [Vagus Nerve Stimulation for Treating Epilepsy](https://www.aan.com/Guidelines/Home/GetGuidelineContent/619) (American Academy of Neurology) – **PDF**

<https://www.cdc.gov/epilepsy/managing-epilepsy/index.htm>

Take your medicine as prescribed.

Talk with your healthcare provider when you have questions.

Recognize seizure triggers (such as stress).

Keep a record of your seizures.

Get enough sleep.

Exercise safely.

Lower stress.

Keep in touch with friends and family members that can help you.

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|  | A | a |
| A | AA Wildtype | Aa variant |
| a | Aa variant | Aa variant |