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

**RESULTS:**

ME/CFS patients had a significant reduction in NK percentage lysis of target cells (17%±4.68%) compared with the unfatigued control group (31%±6.78%). Of the 678 SNPs examined, eleven SNPs for TRP ion channel genes (TRPC4, TRPC2, TRPM3, and TRPM8) were identified in the ME/CFS group. Five of these SNPs were associated with TRPM3, while the remainder were associated with TRPM8, TRPC2, and TRPC4 (P<0.05). Fourteen SNPs were associated with nicotinic and muscarinic AChR genes: six with CHRNA3, while the remainder were associated with CHRNA2, CHRNB4, CHRNA5, and CHRNE (P<0.05). There were sixteen genotypes identified from SNPs in TRP ion channels and AChRs for TRPM3(n=5), TRPM8 (n=2), TRPC4 (n=3), TRPC2 (n=1), CHRNE (n=1), CHRNA2 (n=2), CHRNA3 (n=1), and CHRNB4 (n=1) (P<0.05).

**CONCLUSION:**

We identified a number of SNPs and genotypes for TRP ion channels and AChRs from isolated NK cells in patients with ME/CFS, suggesting these SNPs and genotypes may be involved in changes in NK cell function and the development of ME/CFS pathology. These anomalies suggest a role for dysregulation of Ca(2+) in AChR and TRP ion channel signaling in the pathomechanism of ME/CFS.

PMID:

27099524

Natural killer (NK) cells are granular lymphocytes found in peripheral blood, bone marrow, spleen, and lymph nodes.[1](https://www.dovepress.com/natural-killer-cells-and-single-nucleotide-polymorphisms-of-specific-i-peer-reviewed-fulltext-article-TACG#ref1)–[4](https://www.dovepress.com/natural-killer-cells-and-single-nucleotide-polymorphisms-of-specific-i-peer-reviewed-fulltext-article-TACG#ref4) Importantly, NK cell dysfunction, in particular reduced NK cell cytotoxic activity, is a common finding in ME/CFS patients.

There was a significant difference for NK cytotoxic activity between groups at the E:T ratio of 25:1. ME/CFS patients had a significant reduction in NK percentage lysis of target cells (17%±4.68%) compared with the control group (31%±6.78%)

  Interestingly, this SNP is located in the 3’-untranslated region, which is a binding site for regulatory proteins as well as microRNAs (miRNAs).[65](https://www.dovepress.com/natural-killer-cells-and-single-nucleotide-polymorphisms-of-specific-i-peer-reviewed-fulltext-article-TACG#ref65) Binding to specific sites within the 3’-untranslated region, miRNAs can decrease gene expression of various messenger RNAs by either inhibiting translation or directly causing degradation of the transcript. Our previous research has found significant differences in NK cytotoxic activity, as well as in miRNAs from isolated NK cells from ME/CFS patients.[32](https://www.dovepress.com/natural-killer-cells-and-single-nucleotide-polymorphisms-of-specific-i-peer-reviewed-fulltext-article-TACG#ref32)

<https://www.ncbi.nlm.nih.gov/pubmed/27779167>

Congenital myasthenic syndromes are a group of rare disorders that are clinically and genetically heterogeneous and caused by mutations in the genes encoding proteins of the neuromuscular junction. Here, we described a Chinese family that presented with phenotypes of classic slow-channel congenital myasthenic syndrome (SCCMS).

However, weakness, scoliosis, and repetitive-compound muscle action potential were found in all affected members in the family. A heterozygous C>T missense mutation at nucleotide 865 in acetylcholine receptor epsilon-subunit (CHRNE) gene that causes a leucine-to-phenylalanine substitution at position 289 (L289F) was found.

PMID: 27779167

<https://www.ncbi.nlm.nih.gov/pubmed/23108489>

Our study argues in favor of frequent clinical worsening of symptoms during pregnancy in patients with CMS. These patients should be closely followed by neurologists during the course of pregnancy. However, the overall clinical prognosis is good since the vast majority of patients recovered their pre-pregnancy clinical status six months after the delivery.

PMID:

23108489

<https://www.ncbi.nlm.nih.gov/pubmed/21150643>

We describe the clinical characteristics of 3 siblings from 1 family with congenital myasthenic syndrome due to homozygous mutations of the gene coding for the epsilon subunit of the acetylcholine receptor (CHRNE). Onset of symptoms occurred in the first few months of life with ptosis, restricted ocular motility, mild proximal weakness, and difficulty swallowing. Multiple hospital admissions were required due to recurrent pulmonary infections. There was no decremental conduction on repetitive nerve stimulation, but jitter was increased on single fiber electromyographic. Since early childhood, our patients have done well without pulmonary or bulbar symptoms and with partial improvement on pyridostigmine therapy. Response of ptosis to diagnostic ice pack test was striking. Although these siblings have a clinical history and examination findings typical of homozygous CHRNE mutations, the clinical presentation of congenital myasthenia subtypes is variable, and accurate genotyping is essential in choosing the appropriate treatment.

PMID:

21150643

<https://www.ncbi.nlm.nih.gov/pubmed/16156017>

# Gene symbol: CHRNE. Disease: Endplate acetylcholine receptor deficiency.

[Ohno K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ohno%20K%5BAuthor%5D&cauthor=true&cauthor_uid=16156017)1, [Engel AG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Engel%20AG%5BAuthor%5D&cauthor=true&cauthor_uid=16156017).

### [Author information](https://www.ncbi.nlm.nih.gov/pubmed/16156017)

PMID:

16156017

**Acetylcholine receptor subunit epsilon** is a [protein](https://en.wikipedia.org/wiki/Protein) that in humans is encoded by the *CHRNE* [gene](https://en.wikipedia.org/wiki/Gene).[[5]](https://en.wikipedia.org/wiki/CHRNE#cite_note-pmid7688301-5)[[6]](https://en.wikipedia.org/wiki/CHRNE#cite_note-entrez-6)

Acetylcholine receptors at mature mammalian neuromuscular junctions are [pentameric protein](https://en.wikipedia.org/wiki/Pentameric_protein)complexes composed of four subunits in the ratio of two alpha subunits to one beta, one epsilon, and one delta subunit. The achetylcholine receptor changes subunit composition shortly after birth when the epsilon subunit replaces the gamma subunit seen in embryonic receptors. Mutations in the epsilon subunit are associated with [congenital myasthenic syndrome](https://en.wikipedia.org/wiki/Congenital_myasthenic_syndrome).[[6]](https://en.wikipedia.org/wiki/CHRNE#cite_note-entrez-6)

[Congenital myasthenic syndrome](https://en.wikipedia.org/wiki/Congenital_myasthenic_syndrome)(CMS) is associated with genetic defects that affect proteins of the [neuromuscular junction](https://en.wikipedia.org/wiki/Neuromuscular_junction). Postsynaptic defects are the most frequent cause of CMS and often result in abnormalities in the [acetylcholine receptor](https://en.wikipedia.org/wiki/Acetylcholine_receptor) (AChR). The majority of mutations causing CMS are found in the AChR subunits genes.[[7]](https://en.wikipedia.org/wiki/CHRNE#cite_note-Cossins-7)

Out of all mutations associated with CMS, more than half are mutations in one of the four genes encoding the adult AChR subunits. Mutations of the AChR often result in endplate deficiency. The most common AChR gene mutation that underlies CMS is the mutation of the CHRNE gene. The CHRNE gene codes for the epsilon subunit of the AChR. Most mutations are autosomal recessive loss-of-function mutations and as a result there is endplate AChR deficiency. CHRNE is associated with changing the kinetic properties of the AChR.[[8]](https://en.wikipedia.org/wiki/CHRNE#cite_note-8) One type of mutation of the epsilon subunit of the AChR introduces an [Arginine](https://en.wikipedia.org/wiki/Arginine) (Arg) into the binding site at the α/ε subunit interface of the receptor. The addition of a cationic Arg into the anionic environment of the AChR binding site greatly reduces the kinetic properties of the receptor. The result of the newly introduced ARG is a 30-fold reduction of agonist affinity, 75-fold reduction of gating efficiency, and an extremely weakened channel opening probability. This type of mutation results in an extremely fatal form of CMS.[[9]](https://en.wikipedia.org/wiki/CHRNE#cite_note-9)

<http://www.uniprot.org/uniprot/Q04844>

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.

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.1 Publication

#### GO - Molecular functioni

* [acetylcholine-gated cation-selective channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0022848) Source: ProtInc
* [acetylcholine receptor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015464) Source: ProtInc
* [cation transmembrane transporter activity](https://www.ebi.ac.uk/QuickGO/term/GO:0008324) Source: ProtInc
* [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=Q04844)

#### GO - Biological processi

* [muscle contraction](https://www.ebi.ac.uk/QuickGO/term/GO:0006936) Source: ProtInc
* [neuromuscular synaptic transmission](https://www.ebi.ac.uk/QuickGO/term/GO:0007274) Source: GO\_Central
* [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: ProtInc
* [synaptic transmission, cholinergic](https://www.ebi.ac.uk/QuickGO/term/GO:0007271) Source: ProtInc
* [transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006810) Source: ProtInc

#### Involvement in diseasei

The muscle AChR is the major target antigen in the autoimmune disease myasthenia gravis. Myasthenia gravis is characterized by sporadic muscular fatigability and weakness, occurring chiefly in muscles innervated by cranial nerves, and characteristically improved by cholinesterase-inhibiting drugs.

###### [**Myasthenic syndrome, congenital, 4A, slow-channel (CMS4A)**](http://www.uniprot.org/diseases/DI-04397)**5 Publications**

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

Disease descriptionA form of congenital myasthenic syndrome, a group of disorders characterized by failure of neuromuscular transmission, including pre-synaptic, synaptic, and post-synaptic disorders that are not of autoimmune origin. Clinical features are easy fatigability and muscle weakness affecting the axial and limb muscles (with hypotonia in early-onset forms), the ocular muscles (leading to ptosis and ophthalmoplegia), and the facial and bulbar musculature (affecting sucking and swallowing, and leading to dysphonia). The symptoms fluctuate and worsen with physical effort. CMS4A is a slow-channel myasthenic syndrome. It is caused by kinetic abnormalities of the AChR, resulting in prolonged AChR channel opening episodes, prolonged endplate currents, and depolarization block. This is associated with calcium overload, which may contribute to subsequent degeneration of the endplate and postsynaptic membrane.

###### [**Myasthenic syndrome, congenital, 4B, fast-channel (CMS4B)**](http://www.uniprot.org/diseases/DI-04396)**3 Publications**

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

Disease descriptionA form of congenital myasthenic syndrome, a group of disorders characterized by failure of neuromuscular transmission, including pre-synaptic, synaptic, and post-synaptic disorders that are not of autoimmune origin. Clinical features are easy fatigability and muscle weakness affecting the axial and limb muscles (with hypotonia in early-onset forms), the ocular muscles (leading to ptosis and ophthalmoplegia), and the facial and bulbar musculature (affecting sucking and swallowing, and leading to dysphonia). The symptoms fluctuate and worsen with physical effort. CMS4B is a fast-channel myasthenic syndrome. It is caused by kinetic abnormalities of the AChR, resulting in brief opening and activity of the channel, with a rapid decay in endplate current, failure to achieve threshold depolarization of the endplate and consequent failure to fire an action potential.

[See also OMIM:616324](http://www.omim.org/entry/616324)

###### [**Myasthenic syndrome, congenital, 4C, associated with acetylcholine receptor deficiency (CMS4C)**](http://www.uniprot.org/diseases/DI-00369)**1 Publication**

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

Disease descriptionA form of congenital myasthenic syndrome, a group of disorders characterized by failure of neuromuscular transmission, including pre-synaptic, synaptic, and post-synaptic disorders that are not of autoimmune origin. Clinical features are easy fatigability and muscle weakness affecting the axial and limb muscles (with hypotonia in early-onset forms), the ocular muscles (leading to ptosis and ophthalmoplegia), and the facial and bulbar musculature (affecting sucking and swallowing, and leading to dysphonia). The symptoms fluctuate and worsen with physical effort. CMS4C is an autosomal recessive disorder of postsynaptic neuromuscular transmission, due to deficiency of AChR at the endplate that results in low amplitude of the miniature endplate potential and current.

[See also OMIM:608931](http://www.omim.org/entry/608931)

|  |  |
| --- | --- |
| DrugBanki | [DB00674.](https://www.drugbank.ca/drugs/DB00674) Galantamine. |

http://www.uniprot.org/keywords/KW-1004

### Definition

Protein which, if defective, causes congenital myasthenic syndrome. Congenital myasthenic syndromes constitute a group of inherited diseases characterized by a congenital defect in neuromuscular transmission at the neuromuscular junction, including pre-synaptic, synaptic, and post-synaptic disorders that are not of autoimmune origin. Congenital myasthenic syndromes are characterized by muscle weakness affecting the axial and limb muscles (with hypotonia in early-onset forms), the ocular muscles (leading to ptosis and ophthalmoplegia), and the facial and bulbar musculature (affecting sucking and swallowing, and leading to dysphonia). The symptoms fluctuate and worsen with physical effort.

<https://www.ncbi.nlm.nih.gov/pubmed/25792100>

PMID:

25792100

 Slow-channel congenital myasthenic syndrome (SCCMS) is a disorder of the postsynaptic neuromuscular junction (NMJ) characterized by early-onset progressive muscle weakness. The disorder results from kinetic abnormalities of the acetylcholine receptor channel, specifically from prolonged opening and activity of the channel, which causes prolonged synaptic currents resulting in a depolarization block. This is associated with calcium overload, which may contribute to subsequent degeneration of the endplate and postsynaptic membrane. Treatment with quinine, quinidine, or fluoxetine may be helpful; acetylcholinesterase inhibitors and amifampridine should be avoided

<https://www.omim.org/entry/254200>

### **MYASTHENIA GRAVIS; MG**

<https://www.omim.org/entry/605809>

### **MYASTHENIC SYNDROME, CONGENITAL, 4A, SLOW-CHANNEL; CMS4A**

<https://www.omim.org/entry/608931>

### **MYASTHENIC SYNDROME, CONGENITAL, 4C, ASSOCIATED WITH ACETYLCHOLINE RECEPTOR DEFICIENCY; CMS4C**

<https://www.omim.org/entry/616324>

### **MYASTHENIC SYNDROME, CONGENITAL, 4B, FAST-CHANNEL; CMS4B**

<http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=590>

Congenital myasthenic syndrome (CMS) is a group of genetic disorders of impaired neuromuscular transmission at the motor endplate characterized by fatigable muscle weakness.

* [AA epsilon1267delG deletion variant](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=244116)
* [1033-1G>C: splice acceptor variant](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=410057)

[971delT deletion variant](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=33387)

[130dupG duplication variant](https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=244117)

T865C SNV (Gravis)

G1074A