<http://www.uniprot.org/uniprot/P30926>

**Neuronal acetylcholine receptor subunit beta-4**

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.

**Sites**

* [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) http://www.uniprot.org/citations/18387948
* [acetylcholine receptor activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015464) http://www.uniprot.org/citations/8906617
* [ligand-gated ion channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015276) http://www.uniprot.org/citations/20438829
* [protein heterodimerization activity](https://www.ebi.ac.uk/QuickGO/term/GO:0046982) Source: Ensembl

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=P30926)

#### GO - Biological processi

* [action potential](https://www.ebi.ac.uk/QuickGO/term/GO:0001508) Source: Ensembl
* [behavioral response to nicotine](https://www.ebi.ac.uk/QuickGO/term/GO:0035095) Source: Ensembl
* [ion transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006811) http://www.uniprot.org/citations/8906617
* [locomotory behavior](https://www.ebi.ac.uk/QuickGO/term/GO:0007626) Source: Ensembl
* [neutrophil degranulation](https://www.ebi.ac.uk/QuickGO/term/GO:0043312) Source: Reactome
* [positive regulation of transmission of nerve impulse](https://www.ebi.ac.uk/QuickGO/term/GO:0051971) Source: Ensembl
* [protein heterooligomerization](https://www.ebi.ac.uk/QuickGO/term/GO:0051291) Source: Ensembl
* [regulation of neurotransmitter secretion](https://www.ebi.ac.uk/QuickGO/term/GO:0046928) Source: UniProtKB
* [regulation of smooth muscle contraction](https://www.ebi.ac.uk/QuickGO/term/GO:0006940) 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
* [smooth muscle contraction](https://www.ebi.ac.uk/QuickGO/term/GO:0006939) Source: Ensembl
* [synaptic transmission, cholinergic](https://www.ebi.ac.uk/QuickGO/term/GO:0007271) Source: ProtInc
* [synaptic transmission involved in micturition](https://www.ebi.ac.uk/QuickGO/term/GO:0060084) Source: UniProtKB

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=P30926)

[DB00514](https://www.drugbank.ca/drugs/DB00514) Dextromethorphan https://www.drugbank.ca/drugs/DB00514  
[DB00898](https://www.drugbank.ca/drugs/DB00898) Ethanol https://www.drugbank.ca/drugs/DB00898  
[DB00674](https://www.drugbank.ca/drugs/DB00674) Galantamine https://www.drugbank.ca/drugs/DB00674  
[DB01227](https://www.drugbank.ca/drugs/DB01227) Levomethadyl Acetate https://www.drugbank.ca/drugs/DB01227  
[DB00184](https://www.drugbank.ca/drugs/DB00184) Nicotine https://www.drugbank.ca/drugs/DB00184  
[DB01090](https://www.drugbank.ca/drugs/DB01090) Pentolinium <https://www.drugbank.ca/drugs/DB01090>

[Cell junction](http://www.uniprot.org/keywords/KW-0965), [Cell membrane](http://www.uniprot.org/keywords/KW-1003), [Membrane](http://www.uniprot.org/keywords/KW-0472), [Postsynaptic cell membrane](http://www.uniprot.org/keywords/KW-0628), [Synapse](http://www.uniprot.org/keywords/KW-0770)

<https://www.ncbi.nlm.nih.gov/gene/1143>

This gene is found within a conserved gene cluster and encodes one of the beta subunits of the nicotinic acetylcholine receptor (nAChRs) superfamily which form ligand-gated ion channels with a central pore that forms a cation channel. Neuronal nAChRs are pentameric structures that can be either homomeric or heteromeric, with heteromeric structures containing both alpha and beta subunits. Each subunit contains an extracellular amino terminus and four transmembrane domains. Nicotine is one of the agonists that binds to the receptor. Variants in this gene have been associated with nicotine dependence and lung cancer. Alternative splicing results in multiple transcript variants encoding different isoforms. [provided by RefSeq, Sep 2017]

Biased expression in testis (RPKM 1.1), adrenal (RPKM 0.6)

<https://www.omim.org/entry/118509>

### **CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, BETA POLYPEPTIDE 4; CHRNB4**

Alternative titles; symbols

#### ACETYLCHOLINE RECEPTOR, NEURONAL NICOTINIC, BETA-4 SUBUNIT

**HGNC Approved Gene Symbol:**[***CHRNB4***](https://www.genenames.org/cgi-bin/gene_symbol_report?match=CHRNB4)

**Cytogenetic location:**[***15q25.1***](https://www.omim.org/geneMap/15/382?start=-3&limit=10&highlight=382)**Genomic coordinates (GRCh38):**[***15:78,623,281-78,655,585***](https://genome.ucsc.edu/cgi-bin/hgTracks?db=hg38&position=chr15:78623281-78655585&dgv=pack&knownGene=pack&omimGene=pack)[(from NCBI)](https://www.ncbi.nlm.nih.gov/)

#### ****TEXT****

#### ▼ ****Cloning and Expression****

The nicotinic acetylcholine receptors (nAChRs) are members of a superfamily of ligand-gated ion channels that mediate fast signal transmission at synapses. The nAChRs are thought to be (hetero)pentamers composed of homologous subunits. See [118508](https://www.omim.org/entry/118508) for additional background information on AChRs.

[Tarroni et al. (1992)](https://www.omim.org/entry/118509#8) cloned a partial beta-4 subunit cDNA by screening a human neuroblastoma cDNA library with a rat beta-4 subunit probe. Using Northern blots and RT-PCR, [Tarroni et al. (1992)](https://www.omim.org/entry/118509" \l "8" \o ") found that the human beta-4 subunit is expressed as a 3.1-kb mRNA in neuroblastoma and small-cell lung carcinoma cell lines. [Elliott et al. (1996)](https://www.omim.org/entry/118509#2) isolated a complete beta-4 clone from a neuroblastoma cell line cDNA library. The predicted 498-amino acid protein is 84% identical to rat beta-4 protein. They demonstrated that human beta-4 encoded a functional receptor when expressed in combination with alpha-2 ([118502](https://www.omim.org/entry/118502)), alpha-3 ([118503](https://www.omim.org/entry/118503)), or alpha-4 ([118504](https://www.omim.org/entry/118504)) subunits in Xenopus oocytes. [Groot Kormelink and Luyten (1997)](https://www.omim.org/entry/118509#3) also cloned a complete beta-4 cDNA from neuroblastoma cell line mRNA. On Northern blots of a neuroblastoma cell line, [Groot Kormelink and Luyten (1997)](https://www.omim.org/entry/118509#3)found that the human beta-4 subunit is expressed as a 2.4-kb mRNA.

#### ▼ ****Gene Function****

Transmitter-gated cation channels are detectors of excitatory chemical signals at synapses in the nervous system. [Khakh et al. (2000)](https://www.omim.org/entry/118509" \l "4" \o ") showed that structurally distinct alpha-3-beta-4 nicotinic and P2X(2) ([600844](https://www.omim.org/entry/600844)) channels influence each other when coactivated. The activation of one channel type affects distinct kinetic and conductance states of the other, and coactivation results in nonadditive responses owing to inhibition of both channel types. State-dependent inhibition of nicotinic channels was revealed most clearly with mutant P2X(2) channels, and inhibition was decreased at lower densities of channel expression. In synaptically coupled myenteric neurons, nicotinic fast excitatory postsynaptic currents were occluded during activation of endogenously coexpressed P2X channels. [Khakh et al. (2000)](https://www.omim.org/entry/118509" \l "4" \o ") concluded that their data provide a molecular basis and a synaptic context for cross-inhibition between transmitter-gated channels.

[Lou et al. (2007)](https://www.omim.org/entry/118509#5) reported a generalized MDR (GMDR) method that permitted adjustment for discrete and quantitative covariates and was applicable to both dichotomous and continuous phenotypes in population-based studies of various designs. They applied the method to a genetic study of 4 genes that were reported to be associated with nicotine dependence ([188890](https://www.omim.org/entry/188890)): CHRNA2 ([118502](https://www.omim.org/entry/118502)), CHRNB4, BDNF ([113503](https://www.omim.org/entry/113503)), and NTRK2 ([600456](https://www.omim.org/entry/600456)). They found significant joint action between CHRNB4 and NTRK2. [Lou et al. (2007)](https://www.omim.org/entry/118509#5) commented that ubiquity of joint actions appears to be a natural property of complex inherited traits and that the term 'epistasis,' coined for a specific type of gene-by-gene interaction, has evolved to have different meanings in biologic and statistical genetics.

By using a combination of pharmacologic, molecular genetic, electrophysiologic, and feeding studies, [Mineur et al. (2011)](https://www.omim.org/entry/118509" \l "6" \o ")found that activation of hypothalamic alpha-3 ([118503](https://www.omim.org/entry/118503))-beta-4 nicotinic acetylcholine receptors leads to activation of proopiomelanocortin (POMC; [176830](https://www.omim.org/entry/176830)) neurons. POMC neurons and subsequent activation of melanocortin-4 receptors (MC4R; [155541](https://www.omim.org/entry/155541)) were critical for nicotinic-induced decreases in food intake in mice. The study of [Mineur et al. (2011)](https://www.omim.org/entry/118509" \l "6" \o ")demonstrated that nicotine decreases food intake and body weight by influencing the hypothalamic melanocortin system and identified critical molecular and synaptic mechanisms involved in nicotine-induced decreases in appetite.

#### ▼ ****Mapping****

[Raimondi et al. (1992)](https://www.omim.org/entry/118509#7) mapped the CHRNA3 ([118503](https://www.omim.org/entry/118503)), CHRNA5 ([118505](https://www.omim.org/entry/118505)), and CHRNB4 genes to 15q24 by in situ hybridization and demonstrated that the 3 genes are physically linked.

[Amos et al. (2008)](https://www.omim.org/entry/118509#1) placed the CHRNA3, CHRNA5, CHRNB4, and PSMA4 ([176846](https://www.omim.org/entry/176846)) genes within a 100-kb region on chromosome 15q25.1.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| CHRNB4 | rs17487223 |  |  | NC\_000015.10:g.[78631645C>T] | CT TT | Cancer | 18385738 |
| CHRNB4 | rs17487223 |  |  | NC\_000015.10:g.[78631645C>T] | CT TT | Nicotine Dependence | 18385738 |
| CHRNB4 | rs12441088 |  |  | NC\_000015.10:g.[78635922G>T] | TT | ME/CFS | 27099524, 28219892, 20387064, PMC3042523 |
| CHRNB4 | rs1316971 |  |  | NC\_000015.10:g.[78638168A>G] | AG | ME/CFS | 27835969 |

#### <https://www.ncbi.nlm.nih.gov/pubmed/19443489?dopt=Abstract>

#### Single variant analysis

To examine whether the polymorphisms associated with nicotine dependence

| **Variant** | **Gene** | **Chromosome position** | **Allele 1 (Minor)** | **Allele 2 (Major)** | **Minor allele frequency** | ***n*** | **Regression coefficient** | **95% confidence interval** | ***P*-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **rs17487223** |  | 76711042 | T | C | 0.34 | 93 | −0.21 | −0.40, −0.02 | 3.64E−02 |

https://www.ncbi.nlm.nih.gov/pubmed/19259974?dopt=Abstract

Tobacco smoking continues to be a leading cause of preventable death. Recent research has underscored the important role of specific cholinergic nicotinic receptor subunit (CHRN) genes in risk for nicotine dependence and smoking. To detect and characterize the influence of genetic variation on vulnerability to nicotine dependence

https://www.ncbi.nlm.nih.gov/pubmed/19029397?dopt=Abstract

Characteristics, minor allele frequencies, and associations with nicotine dependence for the *CHRNA5-CHRNA3-CHRNB4* SNPs

| **#/SNP** | | **Position** | **Gene** | **SNP Region** | **Minor Allele** | **Minor Allele Frequency** | | ***P*\*** | **Excluded LCa *p*†** | **OR‡(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Cases** | **Controls** |
| 20 | rs17487223 | 76711042 | *CHRNB4* | Intron 2 | T | 1151 (39.8%) | 936 (33.9%) | 8.07E-07 | 1.68E-06 | 1.33 (1.18, 1.48) |

The risks of heavy smoking associated with each genotype of the significant SNPs in the A5A3B4 gene cluster are shown. Associations are adjusted for age and gender

| **SNP** | **Position** | **Genotype** | **#Cases** | **#Controls** | **OR (95% CI)** |
| --- | --- | --- | --- | --- | --- |
| rs17487223 | 76711042 |  |  |  |  |
|  |  | CT | 729 | 616 | 1.45 (1.23, 1.71) |
|  |  | TT | 211 | 160 | 1.64 (1.29, 2.09) |
|  |  |  |  |  | p-trend = 8.07E-07 |

https://www.ncbi.nlm.nih.gov/pubmed/18519524?dopt=Abstract

Habitual smoking caucasians

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| rs17487223 | CHRNB4 | C/T | T | 0.35 | 0.001 | -- |
|  |  |  |  |  |  |

<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** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CHRNB4 | 15 | rs12441088 | TT | 25 (71.4) | 10 (28.6) | 6.42 | 3.57 | 0.011 |

<https://www.ncbi.nlm.nih.gov/pubmed/27835969>

The study included 172 participants, consisting of 95 Fukuda defined CFS/ME patients (45.8 ± 8.9; 69 % female) and 77 healthy controls (42.3 ± 10.3; 63 % female). A total of 950 SNPs were included for analysis. 60 significant SNPs were associated with CFS/ME compared with healthy controls. After applying FDR and Bonferroni corrections, SNP rs2322333 in adrenergic receptor α1 (ADRA1A) was higher in CFS/ME compared with healthy controls (45.3 % vs. 23.4 %; p = 0.059). The genotype class that was homozygous minor (AA) was substantially lower in CFS/ME compared with healthy controls (4.2 % vs. 24.7 %).

Results of Fisher’s exact test for top 10 SNPs

| **Gene** | **SNP name** | **raw p-value** | **padj FDR** | **padj Bonferroni** | **Genotype** | **Controls allele frequency (%)** | **Cases allele frequency (%)** | **Odds ratios** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CHRNB4 | rs1316971 | 0.013 | 0.788 | 1 | AG | 38 | 32 | 0.65 |
|
|