<http://www.uniprot.org/uniprot/Q9UBN4>

**Short transient receptor potential channel 4**

Form a receptor-activated non-selective calcium permeant cation channel. Acts as a cell-cell contact-dependent endothelial calcium entry channel. Probably operated by a phosphatidylinositol second messenger system activated by receptor tyrosine kinases or G-protein coupled receptors. Mediates cation entry, with an enhanced permeability to barium over calcium. May also be activated by intracellular calcium store depletion.2 Publications

#### Miscellaneous

The interaction with spectrin is important in controlling the translocation of TRPC4 channels to the plasma membrane following EGF stimulation.

The cell membrane presentation, the calcium entry function and the interaction with junctional proteins (CTNNB1 and CDH5) are controlled by endothelial cell-cell contacts.

#### GO - Molecular functioni

* [beta-catenin binding](https://www.ebi.ac.uk/QuickGO/term/GO:0008013) Source: BHF-UCL
* [cadherin binding](https://www.ebi.ac.uk/QuickGO/term/GO:0045296) Source: BHF-UCL
* [calcium channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0005262) Source: Reactome
* [inositol 1,4,5 trisphosphate binding](https://www.ebi.ac.uk/QuickGO/term/GO:0070679) Source: Ensembl
* [store-operated calcium channel activity](https://www.ebi.ac.uk/QuickGO/term/GO:0015279) Source: UniProtKB

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q9UBN4)

#### GO - Biological processi

* [calcium ion import](https://www.ebi.ac.uk/QuickGO/term/GO:0070509) Source: BHF-UCL
* [calcium ion transmembrane transport](https://www.ebi.ac.uk/QuickGO/term/GO:0070588) Source: Reactome
* [calcium ion transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006816) Source: ProtInc
* [gamma-aminobutyric acid secretion](https://www.ebi.ac.uk/QuickGO/term/GO:0014051) Source: Ensembl
* [manganese ion transport](https://www.ebi.ac.uk/QuickGO/term/GO:0006828) Source: GO\_Central
* [oligodendrocyte differentiation](https://www.ebi.ac.uk/QuickGO/term/GO:0048709) Source: Ensembl
* [regulation of cytosolic calcium ion concentration](https://www.ebi.ac.uk/QuickGO/term/GO:0051480) Source: GO\_Central

[View the complete GO annotation on QuickGO ...](http://www.ebi.ac.uk/QuickGO/annotations?geneProductId=Q9UBN4)

#### Keywordsi

|  |  |
| --- | --- |
| Molecular function | [Calcium channel](http://www.uniprot.org/keywords/KW-0107), [Ion channel](http://www.uniprot.org/keywords/KW-0407) |
| Biological process | [Calcium transport](http://www.uniprot.org/keywords/KW-0109), [Ion transport](http://www.uniprot.org/keywords/KW-0406), [Transport](http://www.uniprot.org/keywords/KW-0813) |
| Ligand | [Calcium](http://www.uniprot.org/keywords/KW-0106) |

<https://www.ncbi.nlm.nih.gov/gene/7223>

This gene encodes a member of the canonical subfamily of transient receptor potential cation channels. The encoded protein forms a non-selective calcium-permeable cation channel that is activated by Gq-coupled receptors and tyrosine kinases, and plays a role in multiple processes including endothelial permeability, vasodilation, neurotransmitter release and cell proliferation. Single nucleotide polymorphisms in this gene may be associated with generalized epilepsy with photosensitivity. Alternatively spliced transcript variants encoding multiple isoforms have been observed for this gene. [provided by RefSeq, Aug 2011]

<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** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TRPC4 | 13 | rs2985167 | AA | 20 (76.9) | 6 (23.1) | 7.07 | 4.21 | 0.008 |
| TRPC4 | 13 | rs1570612 | GG | 30 (68.2) | 14 (31.8) | 6.72 | 3.81 | 0.01 |
| TRPC4 | 13 | rs655207 | GG | 12 (85.7) | 2 (14.3) | 6.09 | 6.22 | 0.014 |

http://journals.sagepub.com/doi/pdf/10.4137/III.S25147

Transient receptor potential (TRP) ion channels are cation channels with putative roles in many physiological signaling pathways. Mammalian TRPs are comprised of six main groups: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin), and TRPV (vanilloid).[1](http://journals.sagepub.com/doi/10.4137/III.S25147),[2](http://journals.sagepub.com/doi/10.4137/III.S25147) Generally, the TRPC channels are nonselective cation channels; only two are highly permeable Ca2+ channels and two are impermeable for Ca2+. Importantly, several TRPs are permeable for Mg2+ and Zn2+.[3](http://journals.sagepub.com/doi/10.4137/III.S25147) TRPs are extensively expressed on almost all cells and therefore are likely to have significant effects on physiological functions.[3](http://journals.sagepub.com/doi/10.4137/III.S25147)Dysregulation in TRPs has been associated with pathological conditions and diseases including chronic pain, overactive bladder, diabetes, chronic obstructive pulmonary disease, cardiac hypertrophy, familial Alzheimer's disease, skin diseases, skeletal dysplasias, motor neuropathies, neurosensory neuropathies including Charcot–Marie–Tooth disease (type 2C), and cancer.[4](http://journals.sagepub.com/doi/10.4137/III.S25147)–[8](http://journals.sagepub.com/doi/10.4137/III.S25147) TRP ion channels are activated following fluctuations or deviations in the cellular environment. Factors that may influence these changes are stressors including pathogens, temperature, pressure, chemicals, oxidation/reduction, toxins, osmolarity, and pH.[9](http://journals.sagepub.com/doi/10.4137/III.S25147),[10](http://journals.sagepub.com/doi/10.4137/III.S25147)

Chronic fatigue syndrome (CFS) is an unexplained disorder with multiple physiological impairments. Research to date suggests significant immune impairment; however, the mechanism of this disorder remains to be determined. CFS patients may have reactions to a number of environmental and biological factors.[11](http://journals.sagepub.com/doi/10.4137/III.S25147)–[13](http://journals.sagepub.com/doi/10.4137/III.S25147) Moreover, there is evidence to suggest that CFS may have an allergic component.[14](http://journals.sagepub.com/doi/10.4137/III.S25147)–[16](http://journals.sagepub.com/doi/10.4137/III.S25147) Atypical TRP expression has been reported in CFS, particularly upregulation in the expression of *TRPV1.*[17](http://journals.sagepub.com/doi/10.4137/III.S25147) As TRPs regulate a plethora of physiological signaling pathways, they may have a role in CFS. A number of channelopathies have been associated with TRP genes and these have consequences for cellular function.[4](http://journals.sagepub.com/doi/10.4137/III.S25147),[18](http://journals.sagepub.com/doi/10.4137/III.S25147),[19](http://journals.sagepub.com/doi/10.4137/III.S25147) Additionally, TRP channels may be targeted during inflammatory reactions, as they are easily activated in the presence of irritants, inflammatory products, and xenobiotic toxins. Incidentally, CFS patients report significant sensitivity to environmental toxins and irritants, but the causes of these sensitivities remain to be fully investigated. The purpose of this pilot study was to determine whether polymorphisms in SNPs associated with TRP ion channel genes are a contributory factor in the pathogenesis of CFS.

TRPM channels are mostly permeable to magnesium and calcium. Only TRPM4 and TRPM5 are impermeable for divalent cations. TRPM3 is permeable for cations including Ca2+ and Zn2+. However, the permeation profile highly depends on the expressed spliced variant.[55](http://journals.sagepub.com/doi/10.4137/III.S25147) No hereditary TRPM3 channelopathy has been described to date. TRPM3 has been implicated in inflammatory pain syndromes, rheumatoid arthritis, and secretion of proinflammatory cytokines. As pancreatic β cells also have a high proportion of TRPM3 channels,[56](http://journals.sagepub.com/doi/10.4137/III.S25147)–[58](http://journals.sagepub.com/doi/10.4137/III.S25147) there is the likelihood of perturbations in insulin/glucose regulation in CFS patients. Metabolic disturbance has also long been identified as a cardinal feature of CFS. The most characterized TRPM3 in humans is in the central nervous system (CNS) and eye[55](http://journals.sagepub.com/doi/10.4137/III.S25147) where missense mutation of the TRPM3 gene has also been found to underlie the development of cataract and glaucoma.[59](http://journals.sagepub.com/doi/10.4137/III.S25147) TRPM3 is involved in the detection of heat and in pain transmission. TRPM3-deficient mice exhibit clear deficits in their avoidance responses to noxious heat and in the development of inflammatory heat hyperalgesia.[55](http://journals.sagepub.com/doi/10.4137/III.S25147) Dysregulation in thermoregulatory responses has been reported in CFS patients.[60](http://journals.sagepub.com/doi/10.4137/III.S25147) Generalized pain is a characteristic of CFS and occurs in the absence of tissue damage, and this is suggestive of potential CNS impairments.[61](http://journals.sagepub.com/doi/10.4137/III.S25147) As TRPM3 has a role in nociception and thermoregulation, it may have a role in the pathomechansim of CFS. Additionally, TRPM3 is activated by pregnenolone sulfate, suggesting that it has neuroendocrine effects[62](http://journals.sagepub.com/doi/10.4137/III.S25147),[63](http://journals.sagepub.com/doi/10.4137/III.S25147) and might also be involved in the regulation of glutamatergic signaling in the brain.[64](http://journals.sagepub.com/doi/10.4137/III.S25147)

These preliminary findings implicate TRP ion channels in the etiology and pathomechanism of CFS. Dysregulation of TRPs, including the TRPM3 family, is likely pertinent in predisposing CFS patients to calcium metabolism perturbations and aligns with symptom presentation. Potentially, dysregulated influx of calcium ions into cells will impact a number of vital components of cell regulatory machinery. These components include calcium-sensitive adenylate cyclases (ACs) and hence cAMP expression and function. For example, isolated cell types that have been shown previously to have calcium-sensitive cell regulatory mechanisms in CFS patients may enable further elucidation of TRP ion channels and the likely consequences in CFS. Furthermore, population analysis of TRP SNPs for CFS susceptibility, as well as the proposed various subtypes, needs to be considered. This undertaking will likely be of considerable importance to public health and public health practitioners, as well as to researchers to assess the role of TRP ion channels in CFS symptomatology, severity, and predisposition.

The transient receptor potential (TRP) superfamily in humans comprises 27 cation channels with permeability to monovalent and divalent cations. These channels are widely expressed within humans on cells and tissues and have significant sensory and regulatory roles on most physiological functions. Chronic fatigue syndrome (CFS) is an unexplained disorder with multiple physiological impairments.

Thirteen SNPs were significantly associated with CFS patients compared with the controls.

GENE CHROMOSOME RefSNPID A1 A2 FREQUENCY\_CFS FREQUENCY\_control χ2 P-VALUE

TRPC4 13 rs6650469 T C 0.505 0.380 5.775 0.016\*

TRPC4 13 rs655207 G T 0.505 0.381 5.639 0.018\*

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/

rs2985167

The aim of this paper was to determine natural killer (NK) cytotoxic activity and if single nucleotide polymorphisms (SNPs) and genotypes in transient receptor potential (TRP) ion channels and acetylcholine receptors (AChRs) were present in isolated NK cells from previously identified myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) patients.

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 Ca2+ in AChR and TRP ion channel signaling in the pathomechanism of ME/CFS.

Transient receptor potential (TRP) ion channels are expressed on almost all cells, and have a significant effect on physiological functions.[16](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b16-tacg-9-039)Dysregulation in TRPs has been associated with pathological conditions and diseases, such as cancer, skeletal abnormalities, pain syndrome, glomerulo-sclerosis, Olmsted syndrome, mucolipidosis, and polycystic kidney disease.[17](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b17-tacg-9-039)–[21](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b21-tacg-9-039) TRP ion channels are activated in the presence of irritants, inflammatory products, and xenobiotic toxins, and have an important role in Ca2+ signaling.

Myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) has an unknown etiology, and there is no specific diagnostic test. The illness is largely characterized by significant impairment in physical activity and debilitating fatigue, and can be accompanied by impairment in memory, cognition, and concentration, enhanced experience of muscle and joint pain, headaches, sore throat, and tender lymph nodes. It is further associated with dysregulation of the gastrointestinal, cardiovascular, and immune systems.[30](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b30-tacg-9-039)–[42](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b42-tacg-9-039) Importantly, NK cell dysfunction, in particular reduced NK cell cytotoxic activity, is a common finding in ME/CFS patients.[32](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b32-tacg-9-039)–[36](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b36-tacg-9-039),[39](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b39-tacg-9-039),[43](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b43-tacg-9-039) We have previously identified single-nucleotide polymorphisms (SNPs) in TRP ion channel genes and AChR genes, namely TRPM3, TRPA1, TRPC4,[44](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b44-tacg-9-039) CHRM3, CHRNA10, CHRNA5, and CHRNA2in peripheral blood mononuclear cells from ME/CFS patients.[44](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4821384/#b44-tacg-9-039) These SNP anomalies in genes for TRP ion channels and AChRs may produce altered receptor proteins, potentially changing TRP ion channel and AChR structures and also functions.

The aim of the present study was to determine NK cytotoxic activity, as well as whether SNPs and their genotypes were present in TRP ion channel and AChR genes in isolated NK cells from ME/CFS patients.