TRPM3 (transient receptor potential cation channel subfamily M member 3) controls [calcium channels](<http://www.uniprot.org/uniprot/Q9HCF6#expression>). These channels help to detect temperature and pain to maintain homeostasis in the body, and incorrect function may lead to [generalized pain and central nervous system impairments](<https://link.springer.com/article/10.1007/s10067-006-0433-9>). Linked health issues include [cataracts, glaucoma](https://link.springer.com/chapter/10.1007/978-3-642-54215-2\_17), [inflammatory pain syndromes, rheumatoid arthritis, and secretion of proinflammatory cytokines](<http://jme.endocrinology-journals.org/content/50/3/R75.short>). In CFS/ME patients, [insulin and glucose dysregulation](<http://jme.endocrinology-journals.org/content/50/3/R75.short>), [multiple chemical sensitivity (MCS)](<http://journals.sagepub.com/doi/pdf/10.4137/III.S25147>), [problems maintaining body temperature](<http://pediatrics.aappublications.org/content/120/1/e129.short>), and [impaired natural killer cell (NKC) function leading to increased inflammation and illness](<https://www.ncbi.nlm.nih.gov/pubmed/27245705>) may be linked to variants.

TRPM3 channels transport calcium and zinc and incorrect function has been linked to [cataracts, glaucoma](https://link.springer.com/chapter/10.1007/978-3-642-54215-2\_17), inflammatory pain syndromes, rheumatoid arthritis, and secretion of proinflammatory cytokines as well as [insulin and glucose dysregulation in CFS patients](<http://jme.endocrinology-journals.org/content/50/3/R75.short>). These channels help detect heat and pain transmission, and dysregulation may lead to [generalized pain and central nervous system impairments without tissue damage](<https://link.springer.com/article/10.1007/s10067-006-0433-9>). [Incorrect theormoregulatory responses, including significantly more shivering, sweating, sudden change of skin color, and feeling unusually warm,](http://pediatrics.aappublications.org/content/120/1/e129.short) have been reported in CFS patients.

<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** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TRPM3 | rs10118380 | 0.01 | 0.788 | 1 | CC | 8 | 21 | 3.39 |
| TC | 52 | 43 | 1.07 |
|  |  |  |  |
| TRPM3 | rs7022747 | 0.013 | 0.788 | 1 | GG | 69 | 94 | 10.9 |

<https://www.ncbi.nlm.nih.gov/pubmed/27245705>

TRPM3 cell surface expression was identified for NK and B lymphocytes in healthy controls (CD56brightTRPM3 35.72 % ± 7.37; CD56dim 5.74 % ± 2.00; B lymphocytes 2.05 % ± 0.19, respectively). There was a significant reduction of TRPM3 surface expression on CD19+ B cells (1.56 ± 0.191) and CD56bright NK cells (17.37 % ± 5.34) in CFS/ME compared with healthy controls. Anti-CD21 and anti-IgM conjugated biotin was cross-linked with streptavidin,and subsequently treatment with thapsigargin. This showed a significant reduction in cytoplasmic calcium ion concentration in CD19+ B lymphocytes. CD56bright NK cells also had a significant decrease in cytoplasmic calcium in the presence of 2-APB and thapsigargin in CFS/ME patients.

The results from this preliminary investigation identify, for the first time, TRPM3 surface expression on both NK and B lymphocytes in healthy controls. We also report for the first time, significant reduction in TRPM3 cell surface expression in NK and B lymphocytes, as well as decreased intracellular calcium within specific conditions in CFS/ME patients. This warrants further examination of these pathways to elucidate whether TRPM3 and impaired calcium mobilisation has a role in CFS/ME.

<https://www.ncbi.nlm.nih.gov/pubmed/27834303>

### Table 3.

| **Gene** | **CHR** | **Ref SNP** | **Genotype** | **CFS (%)** | **Non-fatigued controls (%)** | **χ2** | **OR** | P**-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TRPM3 | 9 | rs7038646 | AG | 9 (81.8%) | 4 (36%) | 4.70 | 7.88 (1.11 – 56.12) | 0.030 |

<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 (%)** | χ**2** | **OR** | P**-value** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TRPM3 | 9 | rs6560200 | CC | 15 (83.3) | 3 (16.7) | 7.12 | 5.63 | 0.008 |
| TRPM3 | 9 | rs11142822 | GG | 36 (63.2) | 21 (36.8) | 5.87 | 5.14 | 0.015 |
| TRPM3 | 9 | rs1106948 | TT | 15 (78.9) | 4 (21.1) | 5.37 | 4.06 | 0.021 |
| TRPM3 | 9 | rs1891301 | TT | 14 (77.8) | 4 (22.2) | 4.48 | 3.64 | 0.034 |
| TRPM3 | 9 | rs12350232 | TT | 15 (75) | 5 (25) | 3.91 | 3.13 | 0.048 |

<http://journals.sagepub.com/doi/pdf/10.4137/III.S37042>

Table 1. Genotype frequencies of TRPM3 and mAChM3 gene polymorphisms in CFS/ME patients and nonfatigued controls.

GENE CHROMOSOME REF SNP ID GENOTYPE CFS (%) NONFATIGUED CONTROLS (%) χ2 P-VALUE OR

TRPM3 9 rs12682832 AA 24 (75%) 8 (25%) 5.501 0.019 2.703

TRPM3 9 rs11142508 CC 25 (73.5%) 9 (26.5%) 5.029 0.025 2.500

TRPM3 9 rs3763619 AA 25 (71.4%) 10 (28.6%) 4.028 0.045 2.222

Notes: Data are presented for genes TRPM3 (100 CFS/ME patients and 90 controls) and mAChM3 (91 CFS patients and 76 controls), chromosome location (CHR), reference SNP identification (Ref SNP ID), genotype, and number and percentage of CFS patients and nonfatigued controls with a genotype; Pearson’s chi-square test was used for genotype frequency (1 df), and P-value for this test was set at a significance of P , 0.05, odds ratio (OR).

https://www.ncbi.nlm.nih.gov/pubmed/23993353

Most therapeutic approaches have focused upon the susceptibility to Herpesviruses and the application of prophylactic antiviral drugs. Anecdotal cases have described perceived success, with the most common being the use of acyclovir, gancyclovir and related agents.[22](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917661/#R22),[27](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917661/#R27),[47](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917661/#R47),[50](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917661/#R50) Breakthrough infections may require treatment with higher doses or parenteral forms. Therapies for papillomaviruses have also been described with more limited success, including topical agents, physical approaches and immunostimulants. Given the susceptibility to HPV, all patients diagnosed with NKD should be considered for HPV vaccination.

Systemic administration of cytokine therapies have also been described, either for antiviral effect or even for some potential effect upon the NK cells themselves. A recently reported example is that of IFN-α in CNKD1,[33](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917661/#R33) which potentially induced some NK cell cytotoxic function. It has also been used for this purpose in FNKD.[53](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3917661/#R53) Theoretically, any therapeutic NK cell stimulatory cytokine has the potential to be of value, but this topic requires more specific evaluation.

https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet

[White blood cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000045993&version=Patient&language=English) are the primary players in immune system responses. Some white blood cells, including [macrophages](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044054&version=Patient&language=English) and [natural killer cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044062&version=Patient&language=English), patrol the body, seeking out foreign invaders and diseased, damaged, or dead cells. These white blood cells provide a general—or nonspecific—level of immune protection.

Researchers have found that one type of INF, INF-alfa, can enhance a patient’s immune response to cancer cells by activating certain white blood cells, such as [natural killer cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044062&version=Patient&language=English)and [dendritic cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044948&version=Patient&language=English) ([3](https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet#r3)). INF-alfa may also inhibit the growth of cancer cells or promote their death ([4](https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet#r4),[5](https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet#r5)). INF-alfa has been approved for the treatment of [melanoma](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000045135&version=Patient&language=English), [Kaposi sarcoma](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000045134&version=Patient&language=English), and several [hematologic cancers](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000045708&version=Patient&language=English).

Like INFs, ILs play important roles in the body’s normal immune response and in the immune system’s ability to respond to cancer. Researchers have identified more than a dozen distinct ILs, including [IL-2](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044367&version=Patient&language=English), which is also called [T-cell](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044928&version=Patient&language=English) growth factor. IL-2 is naturally produced by activated T cells. It increases the proliferation of white blood cells, including cytotoxic T cells and natural killer cells, leading to an enhanced anticancer immune response ([6](https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet#r6)). IL-2 also facilitates the production of [antibodies](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000044918&version=Patient&language=English) by [B cells](https://www.cancer.gov/Common/PopUps/popDefinition.aspx?id=CDR0000045611&version=Patient&language=English) to further target cancer cells. Aldesleukin, IL-2 that is made in a laboratory, has been approved for the treatment of metastatic kidney cancer and metastatic melanoma. Researchers are currently investigating whether combining aldesleukin treatment with other types of biological therapies may enhance its anticancer effects.

https://www.cdc.gov/me-cfs/about/possible-causes.html

It is possible that ME/CFS is caused by a change in the person’s immune system and the way it responds to infection or stress. ME/CFS shares some features of autoimmune illnesses (diseases in which the immune system attacks healthy tissues in own body, like in rheumatoid arthritis). For example, both ME/CFS and most autoimmune diseases are more common in women and both are characterized by increased inflammation. However, other signs of autoimmune disease, like tissue damage, are not found in patients with ME/CFS.

Scientists think that the immune system might be contributing to ME/CFS in other ways, including:

* **Chronic production of cytokines** (cytokines are proteins that are produced by the immune system and regulate behavior of other cells). Higher levels of cytokines for a prolonged period can lead to changes in the body’s ability to respond to stress and might lead to the development of health conditions, including ME/CFS.
* **Low-functioning natural killer (NK) cells**. NK cells are cells of the immune system that help the body fight infections. Many patients with ME/CFS have NK cells with lower functional ability to fight infections. Studies have found that the poorer the function of NK cells in ME/CFS patients, the worse the severity of the illness. NK cell function tests are hard to do and their results are not reliable outside of research studies. Because of this problem, NK cell function testing is not yet useful for healthcare providers. Also, low NK cell function can occur in other illnesses and thus cannot be used to diagnose ME/CFS.

https://www.ncbi.nlm.nih.gov/pubmed/25541298

Arabinoxylan rice bran (MGN-3/Biobran Our data show that MGN-3/Biobran upregulates NK cell activation markers, stimulates NK cell cytotoxic activity against neuroblastoma in vitro and in vivo and selectively augments the expansion of NK cells. These results may be useful for future NK celltherapeutic strategies of the treatment of neuroblastoma.

https://www.ncbi.nlm.nih.gov/pubmed/24755139

The data obtained in this study indicate that RBEP supplementation increases IFN-γ secretion without causing significant adverse effects, and thus may be beneficial to healthy individuals. This new rice bran-derived product may therefore be potentially useful to include in the formulation of solid and liquid foods designed for treatment and prevention of pathological states associated with defective immune responses.

<https://www.ncbi.nlm.nih.gov/pubmed/11366552>

Inositol hexaphosphate (IP6) inhibit cancer development in laboratory animals. Studies show IP6 can help fight bacterial and fungal infections. The substance is found in the germ or branportions of whole grains; the highest concentration is found in whole-kernel corn.

<https://www.ncbi.nlm.nih.gov/pubmed/27021581>

 A disrupted zinc homeostasis affects these cells, leading to impaired formation, activation, and maturation of lymphocytes, disturbed intercellular communication via cytokines, and weakened innate host defense via phagocytosis and oxidative burst. This review outlines the connection between zinc and immunity by giving a survey on the major roles of zinc in immune cell function, and their potential consequences in vivo.

<https://www.ncbi.nlm.nih.gov/pubmed/26686726>

Oral administration of the EPS or yogurt fermented with OLL1073R-1 and Streptococcus thermophilus OLS3059 (OLL1073R-1 yogurt) augmented natural killer (NK) cell activity and induced IFN-γ production in spleen cellsin mice, whereas 2 other yogurts fermented with other strains had no effect on NK cell activity. Cellular preparations of the OLL1073R-1 strain also slightly augmented NK cell activity, but were less effective than EPS itself.  Bulgarian yogurt could exert immunostimulatory effects by selecting starter strains and part of the mechanisms depend on IFN-γ inducible EPS produced from L. delbrueckii ssp. bulgaricus. Further investigations on processes of fermentation to increase of the EPS may lead to the development of new functional foods that keep our immune functions stable.

Natural killer cells (NKC) are a type of white blood cells found in the blood, bone marrow, spleen, and lymph nodes.  They kill viral infected cells and tumorous cells.  Many patients with ME/CFS have NK cells with lower functional ability to fight infections, where [the level of impairment of NKC function is associated with illness severity](https://www.cdc.gov/me-cfs/about/possible-causes.html). Compared with the general population, CFS patients have half the cellular efficiency with a [17% cellular death rate](https://www.ncbi.nlm.nih.gov/pubmed/27099524).  The G3264+2567A variant decreases gene expression in both the DNA and RNA, causing significant reduction in NKC activity.  This variant was 2X as common in [CFS patients at 73.3% with an odds ratio of 3.56](https://www.ncbi.nlm.nih.gov/pubmed/27099524). The G3264+630A variant also decreases gene expression in both the DNA and RNA, causing significant reduction in NKC activity.  This variant was 2X as common in [CFS patients at 82.1% with an odds ratio of 7.19.](<https://www.ncbi.nlm.nih.gov/pubmed/27099524>)

Some pharmaceuticals may increase or decrease natural killer cell function.

- [Histone deacetylase inhibitors (HDACi), including suberoylanilide hydroxamic acid and valproic acid,](https://www.ncbi.nlm.nih.gov/pubmed/17349632/) impair NKC function and should be avoided.

- [Acyclovir, ganciclovir, and related prophylactic antiviral drugs](<https://www.ncbi.nlm.nih.gov/pubmed/23993353>) may improve cellular function.

- [Therapies for papillomaviruses, topical agents, physical approaches and immunostimulants,](<https://www.ncbi.nlm.nih.gov/pubmed/23993353>) may activate NK cells.

- [Cytokine therapies](<https://www.ncbi.nlm.nih.gov/pubmed/23993353>), such as [IFN-α](https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet) in CNKD1, may induce higher levels of NKC cytotoxic activity by [activating white blood cells](https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/bio-therapies-fact-sheet).

- Consider the [HPV vaccine](<https://www.ncbi.nlm.nih.gov/pubmed/23993353>) as issues with natural killer cells cause higher susceptibility.

- [CFS patients show muscarinic antibody positivity and reduced symptom presentation following anti-CD20 intervention.](<https://www.ncbi.nlm.nih.gov/pubmed/27834303>)

Many dietary supplements have been found to increase natural killer cell function.

- [Resveratrol](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855330/) stimulates the immune system by increasing NKC activity, but sufficient body concentration can only be achieved through supplementation.

- [Myricetin](https://www.ncbi.nlm.nih.gov/pubmed/25075019), a flavonoid found in food and red wine, can increase NKC activity.

- [Quercetin](https://www.ncbi.nlm.nih.gov/pubmed/19449452), a flavonoid in onions and fruits, may improve NKC and T cell function.

- [Bulgarian yogurt fermented with L. delbrueckii ssp. Bulgaricus augments NKC activity.](<https://www.ncbi.nlm.nih.gov/pubmed/26686726>)

- [Zinc](<https://www.ncbi.nlm.nih.gov/pubmed/27021581>) helps to improve immune system activity and response.

- [Inositol hexaphosphate (IP6), found in germ, bran, and whole kernel corn](<https://www.ncbi.nlm.nih.gov/pubmed/11366552>) may activate the immune system and help fight bacterial and fungal infections.

- [Arabinoxylan rice bran (MGN-3/Biobran](<https://www.ncbi.nlm.nih.gov/pubmed/25541298>) increases activation and stimulates cell killing activity.

| Variant |Population % | Odds Ratio |

| :-------------: |:-------------:| :-------------:|

| G71427327T (T;T) | 58.6% | 5.14 |

| T70790948C (T;C) | 49.7% | 3.39 |

| T70790948C (C;C) | 16.3% | 1.07 |

| C71402258T (T;T) | 13.3% | 4.06 |

| C70616746T (C;C) | 18.6% | 2.5 |

| T71417232G (T;T) | 17.8% | 3.13 |

| A70605775G (A;A) | 17.4% | 2.703 |

| C71403580T (T;T) | 19.6% | 3.64 |

| T70610886A (A;A) | 13.2% | 2.222 |

| T71365306C (C;C) | 12.3% | 5.63 |

| G70820112A (G;G) | 76.4% | 10.9 |

| A70822908G (A;G) | 44.8% | 7.88 |

Natural killer cells (NKC) are a type of white blood cells found in the blood, bone marrow, spleen, and lymph nodes.  They kill viral infected cells and tumorous cells.  Many patients with ME/CFS have NK cells with lower functional ability to fight infections, where [the level of impairment of NKC function is associated with illness severity](https://www.cdc.gov/me-cfs/about/possible-causes.html). Compared with the general population, CFS patients have half the cellular efficiency with a [17% cellular death rate](https://www.ncbi.nlm.nih.gov/pubmed/27099524).

The following variants decrease gene expression in both the DNA and RNA, causing significant reduction in NKC activity.

- [T71365306C (C;C)](<https://www.ncbi.nlm.nih.gov/pubmed/27099524>) is [2.2X] more common in CFS patients.

- [G71427327T (T;T)](<https://www.ncbi.nlm.nih.gov/pubmed/27099524>) is [1.7X] more common in CFS patients.

- [C71402258T (T;T)](<https://www.ncbi.nlm.nih.gov/pubmed/27099524>) is [3.7X] more common in CFS patients.

- [C71403580T (T;T)](<https://www.ncbi.nlm.nih.gov/pubmed/27099524>) is [3.5X] more common in CFS patients.

- [T71417232G (T;T)](<https://www.ncbi.nlm.nih.gov/pubmed/27099524>) is [3X] more common in CFS patients.

- [T70790948C (T;C)]<https://www.ncbi.nlm.nih.gov/pubmed/27835969>) is [2.6X] more common in CFS patients.

Calcium mobilization into white blood cells is reduced by the A70822908G (A;G) variant, which may cause increased immune system disfunction, such as improper development of antibodies, and increased symptom severity. This variant is [2.2X](<https://www.ncbi.nlm.nih.gov/pubmed/27834303>) as common in CFS patients as compared to the general population.

The following variants are more common in CFS patients.

- [T70790948C (C;C)](<https://www.ncbi.nlm.nih.gov/pubmed/27835969>) is [1.2X] more common in CFS patients.

- [G70820112A (G;G)](<https://www.ncbi.nlm.nih.gov/pubmed/27835969>) is [1.4X] more common in CFS patients.

- [C70616746T (C;C)](<http://journals.sagepub.com/doi/pdf/10.4137/III.S37042>) is [2.5X] more common in CFS patients.

- [A70605775G (A;A)](<http://journals.sagepub.com/doi/pdf/10.4137/III.S37042>) is [2.7X] more common in CFS patients.

- [T70610886A (A;A)](<http://journals.sagepub.com/doi/pdf/10.4137/III.S37042>) is [2.2X] more common in CFS patients.

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

his study further expands our previous investigations into Transient receptor potential TRPs, AChRs, and ADRs in CFS/ME. In particular, it is the first genome association study on adrenergic receptors conducted on an Australian cohort with CFS/ME. A particular strength of this study was the considerable association with ADRA1A gene found among a preliminary cohort of patients, when strict statistical considerations were applied. Further validation of this and previous preliminary findings in TRPs and AChRs, will be required in a replication study in a larger cohort of patients. However, the present findings provide supporting evidence for investigation into the role of adrenergic receptors in CFS/ME.

Biological processes responsible for the varied symptoms reported for CFS/ME may involve several ion channels and receptors that are located on cells throughout the body. Transient receptor potential (TRP) ion channels are widely expressed on tissues and cells and are activated and regulated by various stimuli in the cellular environment such as pain, temperature, taste, pressure, and vision [[5](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105265/#CR5)]. There are six TRP subfamilies: ankyrin, canonical, melastatin, mucolipin, polycystin, and TRPV [[6](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105265/#CR6)]. Most consist of non-selective channels permeable to cations such as calcium (Ca2+), sodium, and magnesium. This cation permeability has an important role in maintaining homeostasis for a number of physiological requirements. Accordingly, dysregulation of these channels are found to have a role in pathological conditions such as chronic pain, overactive bladder, diabetes, chronic obstructive pulmonary disease, cardiac hypertrophy, familial Alzheimer’s disease, skin diseases, skeletal dysplasias, neuropathy, and cancer [[7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105265/#CR7)–[12](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5105265/#CR12)].

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.

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

Nine of these SNPs were associated with

*TRPM3* (

rs12682832; *P* < 0.003,

rs11142508; *P* < 0.004,

rs1160742; *P* < 0.08,

rs4454352; *P* < 0.013,

rs1328153; *P* < 0.013,

rs3763619; *P* < 0.014,

rs7865858; *P* ≤ 0.021,

rs1504401; *P*≤ 0041,

rs10115622; *P* ≤ 0.050),

| Variant |Population % |

| :-------------: |:-------------:|

| A70699095G (A;G) | 50% |

| A70699095G (G;G) | 37.2% |

| T70795494C (T;C) | 35.3% |

| T70795494C (T;T) | 50.6% |

| C70801146T (C;T) | 47.6% |

| C70801146T (C;C) | 6.1% |

| A70610886C (A;C) | 49.6% |

| A70610886C (C;C) | 45.4% |

| G70589515A (G;A) | 47.6% |

| G70589515A (G;G) | 25.2% |

| C71302037T (C;T) | 31.9% |

| C71302037T (C;C) | 56.1% |

| C70691635A (C;A) | 48.3% |

| C70691635A (C;C) | 23% |

Variants in TRPM3 are more common in CFS patients versus the general population.

- [A70699095G](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) is [1.4X](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) more common

- [T70795494C](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) is [1.75X](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) more common

- [C70801146T](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) is [1.75X](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) more common

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- [G70589515A](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) is [1.4X](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) more common

- [C71302037T](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) is [1.7X](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) more common

- [C70691635A](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) is [1.3X](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147) more common

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

Biological processes responsible for the varied symptoms reported for [CFS/ME](<https://www.ncbi.nlm.nih.gov/pubmed/27835969>) may involve ion channels and receptors that are located on cells throughout the body. The channels maintain homeostasis, and incorrect function has been linked to [chronic pain, overactive bladder, diabetes, chronic obstructive pulmonary disease, cardiac hypertrophy, familial Alzheimer’s disease, skin diseases, neuropathy, and cancer](<https://www.ncbi.nlm.nih.gov/pubmed/27835969>). In CFS patients, TRP channels are targeted during inflammatory reactions, and may play a role in [multiple chemical sensitivity (MCS)](http://journals.sagepub.com/doi/pdf/10.4137/III.S25147).

TRPM3 channels transport calcium and zinc and incorrect function has been linked to [cataracts, glaucoma](https://link.springer.com/chapter/10.1007/978-3-642-54215-2\_17), inflammatory pain syndromes, rheumatoid arthritis, and secretion of proinflammatory cytokines as well as [insulin and glucose dysregulation in CFS patients](<http://jme.endocrinology-journals.org/content/50/3/R75.short>). These channels help detect heat and pain transmission, and dysregulation may lead to [generalized pain and central nervous system impairments without tissue damage](<https://link.springer.com/article/10.1007/s10067-006-0433-9>). [Incorrect theormoregulatory responses, including significantly more shivering, sweating, sudden change of skin color, and feeling unusually warm,](http://pediatrics.aappublications.org/content/120/1/e129.short) have been reported in CFS patients.

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CFS patients should be aware of their difficulty in maintaining a stable body temperature and avoid large temperature swings. Blood sugar should be checked regularly to avoid insulin and blood sugar issues.

Chronic pain relief may include:

\* [Nonsteroidal anti-inflammatory drugs](https://www.ncbi.nlm.nih.gov/pubmed/14997317/)

\* [Tricyclic antidepressants](https://www.ncbi.nlm.nih.gov/pubmed/19410099/)

\* [Gabapentin, duloxetine or pregabalin](https://www.ncbi.nlm.nih.gov/pubmed/19410099/)

\* [Multidisciplinary pain management programs](https://www.ncbi.nlm.nih.gov/pubmed/22550986), such as [cognitive behavioral therapy](https://www.ncbi.nlm.nih.gov/pubmed/11166973/)

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

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