## A list linking genes to a disease, using evidence codes and literature citations:

-

-

symbol: LINC00309

function: long intergenic non-protein coding RNA 309

chromosome: 2

start: 64185078

end: 64205485

strand: -

gene\_type: lincRNA

unification\_links:

- HGNC: HGNC:25279

curators:

- rtearle

- taltman

symbol: CFL1P1

function: cofilin 1 pseudogene 1

chromosome: 10

start: 87817928

end: 87845612

strand: +

gene\_type: transcribed\_unprocessed\_pseudogene

unification\_links:

- HGNC: HGNC:28560

curators:

- rtearle

- taltman

-

symbol: TECTB

function: beta-tectorin

chromosome: 10

start: 112283735

end: 112305035

strand: +

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q96PL2

- HGNC: HGNC:11721

curators:

- rtearle

- taltman

-

symbol: OTOG

function: otogelin

chromosome: 11

start: 17547373

end: 17647150

strand: +

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q6ZRI0

- HGNC: HGNC:8516

curators:

- rtearle

- taltman

-

-

-

symbol: GRIN2B

function: glutamate receptor ionotropic, NMDA 2B

chromosome: 12

start: 13537337

end: 13981957

strand: -

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q13224

- HGNC: HGNC:4586

curators:

- rtearle

- taltman

-

symbol: PPFIBP1

function: liprin-beta-1

chromosome: 12

start: 27523431

end: 27695564

strand: +

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q86W92

- HGNC: HGNC:9249

curators:

- rtearle

- taltman

-

symbol: FLJ41278

function: long intergenic non-protein coding RNA 2389

chromosome: 12

start: 64883394

end: 64977522

strand: +

gene\_type: lincRNA

unification\_links:

- HGNC: HGNC:53316

curators:

- rtearle

- taltman

-

-

-

symbol: HS6ST3

function: heparan-sulfate 6-O-sulfotransferase 3

chromosome: 13

start: 96090839

end: 96839562

strand: +

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q8IZP7

- HGNC: HGNC:19134

curators:

- rtearle

- taltman

-

-

-

symbol: KRT33A

function: keratin, type I cuticular Ha3-I

chromosome: 17

start: 41346092

end: 41350812

strand: -

gene\_type: protein\_coding

unification\_links:

- UNIPROT: O76009

- HGNC: HGNC:6450

curators:

- rtearle

- taltman

-

-

symbol: LILRB4

function: leukocyte immunoglobulin-like receptor subfamily B member 4

chromosome: 19

start: 54643889

end: 54670359

strand: +

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q8NHJ6

- HGNC: HGNC:6608

curators:

- rtearle

- taltman

-

symbol: NLRP13

function: NACHT, LRR, and PYD domains-containing protein 13

chromosome: 19

start: 55891699

end: 55932336

strand: -

gene\_type: protein\_coding

unification\_links:

- UNIPROT: Q86W25

- HGNC: HGNC:22937

curators:

- rtearle

- taltman

-

symbol: KCNJ6

chromosome: 21

start: 37607376

end: 37916446

strand: -

gene\_type: protein\_coding

unification\_links:

- UNIPROT: P48051

- HGNC: HGNC:6267

curators:

- rtearle

- taltman

-

symbol: MAOA

function: amine oxidase [flavin-containing] A

chromosome: X

start: 43654907

end: 43746824

strand: +

gene\_type: protein\_coding

unification\_links:

- UNIPROT: P21397

- HGNC: HGNC:6833

curators:

- rtearle

- taltman

-

<https://www.ncbi.nlm.nih.gov/pubmed/21584188>

hCV245410 (on gene TPH2) and hCV7911132 (on gene SLC6A4

<http://camda.duke.edu/camda06/papers/days/thursday/presson/presentation.pot/horvath-presson-06-presentation.pdf>

<https://www.ncbi.nlm.nih.gov/pubmed/20941551>

G-allele of rs6311

The −1438G/A (rs6311) and C102T (rs6313)

Our current study examined HTR2A methylation in subjects from a population-based clinical study of CFS and identified two CpG sites, −1,224 and −1,420 that showed differential methylation between CFS and NF subjects and dependence on sequence variation at position −1,438. We recently demonstrated the first experimental evidence for the binding of GR at CpG site −1,420 (Falkenberg and Rajeevan [2010](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044825/#CR4)), whereas binding of Sp1 at CpG site −1,224 and the genotype-dependent binding of E47 at −1,438 were reported earlier (Smith et al. [2008](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044825/#CR23); Zhu et al. [1995](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3044825/#CR28)). Changes at these cis-regulatory elements, two of which are potentially heritable (methylation at −1,439 and −1,420), may have contributed to increased expression of A-allele and to the overall up-regulation of HTR2A in CFS.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2066085/>

<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** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ADRA1A | rs2322333 | 6.2e-05 | 0.059 | 0.059 | AA | 19 | 4 | 0.08 |
| AG | 40 | 48 | 0.5 |
| GG | 18 | 43 | 1 |
| TRPM1 | rs4779824 | 0.002 | 0.788 | 1 | CC | 34 | 4 | 0.02 |
| TC | 39 | 51 | 0.26 |
| TT | 4 | 20 | 1 |
| TRPM6 | rs11787707 | 0.004 | 0.788 | 1 | AA | 54 | 84 | 1 |
| AG | 22 | 11 | 0.32 |
| GG | 1 | 0 | 0 |
| TRPM1 | rs10467996 | 0.005 | 0.788 | 1 | CC | 4 | 17 | 5.72 |
| TC | 34 | 49 | 1.94 |
| TT | 39 | 29 | 1 |
| TRPM3 | rs10118380 | 0.01 | 0.788 | 1 | CC | 8 | 21 | 3.39 |
| TC | 52 | 43 | 1.07 |
| TT | 31 | 24 | 1 |
| TRPM3 | rs7022747 | 0.013 | 0.788 | 1 | AG | 8 | 1 | NA |
| GG | 69 | 94 | 10.9 |
| AA | NA | NA | NA |
| CHRNB4 | rs1316971 | 0.013 | 0.788 | 1 | AA | 10 | 0 | 0 |
| AG | 38 | 32 | 0.65 |
| GG | 46 | 60 | 0 |
| ADRA1A | rs526302 | 0.013 | 0.788 | 1 | GG | 39 | 63 | 1 |
| TG | 29 | 30 | 0.64 |
| TT | 9 | 2 | 0.14 |
| TRPM8 | rs6719311 | 0.013 | 0.788 | 1 | AA | 0 | 0 | NA |
| AG | 20 | 8 | 0.37 |
| GG | 68 | 74 | NA |
| ADRA1A | rs11782159 | 0.016 | 0.788 | 1 | AA | 29 | 21 | 1 |
| AC | 39 | 50 | 1.77 |
| CC | 9 | 24 | 3.68 |

<https://www.ncbi.nlm.nih.gov/pubmed/26859813>

# Table 1

**Twenty-three most significant SNPs based on the GWAS and genotypic association test P-value**

| **Chrom** | **Posn** | **SNP ID** | **Gene** | **Genotype** | | | | **P-value** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  | **Ctrl** | **CFS** | **GWAS** | **Genotypic test** | **Allelic test** |
| 1 | 36983994 | rs3913434 | GRIK3 | CC | 37 | 11 | 1.26E−11 | 7.15E−10 | 1.06E−09 |
|  |  |  |  | CT | 1 | 30 |  |  |  |
|  |  |  |  | TT | 0 | 1 |  |  |  |
| 2 | 7643373 | rs270838 | LOC101929510 | AA | 30 | 3 | 3.61E−11 | 5.72E−10 | 2.84E−07 |
|  |  |  |  | AC | 8 | 38 |  |  |  |
|  |  |  |  | CC | 0 | 1 |  |  |  |
|  | 65650464 | rs6757577 | KRT18P33 | GG | 33 | 7 | 2.77E−10 | 2.74E−09 | 3.00E−08 |
|  |  |  |  | AG | 5 | 33 |  |  |  |
|  |  |  |  | AA | 0 | 2 |  |  |  |
|  | 231342446 | rs16827966 | ARMC9 | CC | 37 | 12 | 5.32E−11 | 2.84E−10 | 6.24E−09 |
|  |  |  |  | CT | 1 | 30 |  |  |  |
| 3 | 56871895 | rs6445832 | ARHGEF3 | AA | 32 | 6 | 4.36E−10 | 3.99E−10 | 2.84E−07 |
|  |  |  |  | AG | 6 | 36 |  |  |  |
|  | 97300204 | rs1523773 | EPHA6 | AA | 38 | 15 | 4.73E−11 | 1.26E−09 | 2.68E−09 |
|  |  |  |  | AT | 0 | 27 |  |  |  |
| 5 | 135086514 | rs254577 | C5orf66 | CC | 3 | 25 | 2.35E−11 | 4.42E−09 | 8.22E−12 |
|  |  |  |  | CT | 14 | 17 |  |  |  |
|  |  |  |  | TT | 21 | 0 |  |  |  |
| 6 | 22141516 | rs41378447 | CASC14 | CC | 32 | 4 | 1.06E−11 | 1.72E−10 | 2.61E−09 |
|  |  |  |  | CT | 5 | 32 |  |  |  |
|  |  |  |  | TT | 1 | 6 |  |  |  |
| 8 | 96338727 | rs7010471 | PTDSS1 | AA | 34 | 8 | 2.49E−10 | 2.99E−10 | 6.93E−08 |
|  |  |  |  | AG | 4 | 34 |  |  |  |
| 9 | 36091136 | rs12235235 | RECK | CC | 34 | 3 | 5.76E−16 | 1.84E−13 | 2.08E−08 |
|  |  |  |  | CT | 2 | 38 |  |  |  |
|  |  |  |  | TT | 2 | 1 |  |  |  |
|  | 119856753 | rs7849492 | — | TT | 28 | 3 | 9.95E−10 | 8.13E−09 | 1.78E−06 |
|  |  |  |  | CT | 9 | 36 |  |  |  |
|  |  |  |  | CC | 1 | 3 |  |  |  |
| 12 | 91754952 | rs12312259 | — | TT | 26 | 2 | 3.60E−10 | 9.30E−09 | 2.48E−07 |
|  |  |  |  | CT | 12 | 34 |  |  |  |
|  |  |  |  | CC | 0 | 6 |  |  |  |
| 13 | 99394905 | rs9585049 | UBAC2 | AA | 35 | 10 | 5.25E−10 | 6.06E−09 | 2.85E−08 |
|  |  |  |  | AT | 3 | 31 |  |  |  |
|  |  |  |  | TT | 0 | 1 |  |  |  |
| 14 | 22194962 | rs17255510 | TRA | TT | 28 | 3 | 6.61E−10 | 6.29E−09 | 6.70E−11 |
|  |  |  |  | CT | 7 | 21 |  |  |  |
|  |  |  |  | CC | 3 | 18 |  |  |  |
|  | 22420786 | rs11157573 | TRA | AA | 29 | 4 | 2.97E−10 | 2.85E−09 | 9.81E−06 |
|  |  |  |  | AG | 6 | 35 |  |  |  |
|  |  |  |  | GG | 3 | 3 |  |  |  |
|  | 22464970 | rs10144138 | TRA/TRD | CC | 36 | 6 | 6.99E−14 | 6.21E−13 | 2.91E−10 |
|  |  |  |  | CT | 2 | 36 |  |  |  |
|  | 84743518 | rs17120254 | — | AA | 11 | 42 | 5.20E−13 | 1.65E−10 | 4.70E−12 |
|  |  |  |  | AT | 24 | 0 |  |  |  |
|  |  |  |  | TT | 3 | 0 |  |  |  |
|  | 91917655 | rs2249954 | FBLN5 | AA | 32 | 5 | 5.47E−11 | 7.14E−10 | 4.86E−08 |
|  |  |  |  | AG | 6 | 35 |  |  |  |
|  |  |  |  | GG | 0 | 2 |  |  |  |
| 15 | 91945362 | rs8029503 | SLCO3A1 | CC | 31 | 4 | 5.66E−11 | 6.70E−10 | 1.28E−07 |
|  |  |  |  | CT | 6 | 35 |  |  |  |
|  |  |  |  | TT | 1 | 3 |  |  |  |
| 16 | 52532950 | rs3095598 | TOX3 | TT | 35 | 9 | 1.02E−10 | 1.73E−09 | 2.25E−09 |
|  |  |  |  | CT | 3 | 30 |  |  |  |
|  |  |  |  | CC | 0 | 3 |  |  |  |
| 18 | 37241025 | rs948440 | CELF4 | TT | 28 | 3 | 3.92E−10 | 5.76E−09 | 2.81E−07 |
|  |  |  |  | CT | 10 | 35 |  |  |  |
|  |  |  |  | CC | 0 | 4 |  |  |  |
| 20 | 52341088 | rs41493945 | — | GG | 37 | 9 | 6.25E−13 | 6.82E−12 | 4.27E−10 |
|  |  |  |  | AG | 1 | 33 |  |  |  |
| 21 | 43928298 | rs3788079 | AGPAT3 | AA | 38 | 13 | 3.42E−12 | 1.40E−10 | 4.82E−10 |
|  |  |  |  | AC | 0 | 29 |  |  |  |

<https://www.ncbi.nlm.nih.gov/pubmed/26473596>

 5-HTT genotype i.e. the short (S) versus long (L) 5-HTTLPR allele and the SNP rs25531 A > G

Patients with the 5-HTT SS or SLG genotype also had a significantly higher FDI score than patients with the 5-HTT LALG, SLA or LALA genotype. Thus, CFS patients with the 5-HTT SS or SLG genotype had worse 30 weeks outcome than CFS patients with the 5-HTT LALG, SLA or LALA genotype. The present study suggests that the 5-HTT genotype may be a factor that contributes to maintenance of CFS

<https://www.ncbi.nlm.nih.gov/pubmed/26116897>

Four SNPs each associated with a different SF-36 subscale (rs11214105 in interleukin 18/testis expressed 12(IL18/TEX12) with body pain, p = 8.0 × 10−3 adjusted for age; rs6112 in SERPINA5with physical function, p = 1.8 × 10−2 adjusted for age; rs227680 in CXCL16 with general health, p = 2.0 × 10−3 adjusted for age; and rs1801058 in G protein-coupled receptor kinase 4 (GRK4) with social function, p = 1.2 × 10−2). Two of these same SNPs were associated with MFI physical fatigue score (rs11214105 in IL18/TEX12and rs6112 in SERPINA5; p = 3.0–6.0 × 10−3). The IL18/TEX12 SNP (rs11214105) was also associated with CDC SI score for CFS case defining symptoms (p = 6.06 × 10−5) and the number of CFS symptoms (p = 4.1 × 10−4). In each instance, homozyogisty for the minor allele A of rs11214105 in IL18/TEX12 was associated with more severity for each of the measures. rs6112 in SERPINA5 was also associated with the number of CFS symptoms (p = 8.1 × 10−4). The non-synonymous variant, rs2278831 in sialic acid binding Ig-like lectin 5 (SIGLEC5), was also associated with CDC SI score for CFS case defining symptoms (p = 4.7 × 10−3).

A 5′ UTR polymorphism (rs11214105) in IL18also associated with physical fatigue, body pain and score for CFS case defining symptoms.

<https://www.ncbi.nlm.nih.gov/pubmed/26063326>

Top 10 genetic markers associated with CFS based on weighted genetic variation (WGV) estimated by the Bayesian model

| **SNP ID** | **Proxy SNP** | **Gene symbola** | **SNP annotationa** | **WGV** | **SE of WGVb** |
| --- | --- | --- | --- | --- | --- |
| rs2288831 | rs3212227 | IL12B | Intron (UTR-3) | 3.95 | 0.0299 |
| rs2071376 |  | IL1A | Intron | 3.6 | 0.0296 |
| rs2069718 |  | IFNG | Intron | 3.34 | 0.0272 |
| rs846906 |  | HSD11B1 | Intron | 3.29 | 0.0337 |
| rs1923884 |  | HTR2A | Intron | 3.16 | 0.0324 |
| rs1799836 |  | MAOB | Intron | 2.56 | 0.0394 |
| rs363236 | rs3814230 | SLC18A2 (PDZD8) | UTR-3 (synonymous codon) | 2.31 | 0.0272 |
| rs1396862 | rs1218523 | CRHR1 (IMP5) | Intron (missense codon) | 2.31 | 0.0334 |
| rs891512 | rs743507 | NOS3 | Intron | 2.18 | 0.0287 |
| rs1124492 | rs46220755 | DRD2 | Intron | 2.02 | 0.0312 |

aGene symbol and SNP annotation in parenthesis correspond to proxy SNPs, if different from the genotyped SNPs for the model

bSE of WGV standard error of weighted genetic variation

<https://www.ncbi.nlm.nih.gov/pubmed/25240059>

| **RefSNP ID** | **Alleles** | **Gene** | **SNP allele associated with CFS/ME** | **CFS/ME** | **Normal** | **Depression** | **χ2 test, p value for distribution between CFS/ME, depression and normals** | **χ2 test, p value for distribution between CFS/ME and normals** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Allele (%)** | **Allele%** | **Allele%** |
| rs11895568 | AG | FAM126B | A | 99.1 | 100.0 | 94.1 | 0.011 | 0.011 |
| rs1860661 | AG | TCF3 | A | 77.5 | 95.5 | 79.4 | <0.0001 | <0.0001 |
| rs10787901 | AG | EIF3A | A | 56.1 | 51.1 | 54.2 | <0.0001 | <0.0001 |
| rs2071167 | AG | UBTF | A | 31.9 | 19.9 | 21.9 | 0.036 | 0.024 |
| rs3752411 | AG | METTL3 | A | 13.1 | 5.9 | 2.9 | 0.032 | 0.031 |
| rs3737529 | CT | SORL1 | C | 94.8 | 99.3 | 100.0 | 0.038 | 0.028 |
| rs7719246 | AT | IL6ST | A | 81.94 | 91.9 | 82.4 | 0.030 | NS |
| rs540516 | CT | PNPLA6 | C | 87.5 | 77.2 | 67.6 | 0.0034 | NS |
| rs12796043 | CT | SORL1 | C | 67.6 | 51.5 | 52.9 | 0.0067 | NS |
| rs3775525 | CT | BMP2K | C | 4.2 | 5.2 | 17.6 | 0.0072 | NS |
| rs3775513 | AG | BMP2K | A | 95.3 | 95.5 | 82.4 | 0.0081 | NS |
| rs3822106 | AC | BMP2K | A | 27.8 | 26.1 | 47.1 | 0.048 | NS |
| rs6850116 | GT | BMP2K | G | 95.8 | 95.5 | 79.4 | 0.00059 | NS |
| rs1426137 | AT | BMP2K | A | 96.2 | 95.5 | 84.4 | 0.016 | NS |
| rs2228431 | CT | ARSD | C | 9.3 | 5.2 | 20.6 | 0.018 | NS |
| rs306772 | CT | GSN | C | 80.7 | 84.3 | 61.8 | 0.013 | NS |
| rs11549467 | AG | HIF1A | A | 0 | 0.7 | 5.9 | 0.0017 | NS |
| rs3775516 | AG | BMP2K | A | 4.9 | 5.4 | 21.4 | 0.010 | 0.0025 |
| rs1426139 | AT | BMP2K | A | 5.6 | 5.1 | 17.6 | 0.021 | 0.0091 |
| rs1373998 | CT | IL6ST | C | 88.0 | 91.9 | 74.3 | 0.016 | 0.013 |
| rs3802758 | CT | PEX16 | C | 31.9 | 11.8 | 38.2 | <0.0001 | <0.0001 |

Table 3

p Values of χ2 tests of the allele distribution between 8 CFS/ME subtypes for 27 CFS/ME subtype-associated single-nucleotide polymorphisms (SNPs) with an eight-column χ2 test, p value ≤0.05

| **RefSNP ID** | **Alleles** | **Gene** | **8-column χ2 test** | **CFS/ME gene expression subtype (no. of patients tested in each subtype)** | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
|
|
| rs11658169 | CT | AKAP10 | 0.036 |
| rs2515194 | CT | ATP6V1C1 | 0.00034 |
| rs12687359 | AT | BCOR | 0.00032 |
| rs5917933 | AG | BCOR | 0.0054 |
| rs1373998\* | CT | IL6ST | 0.0063 |
| rs3752411\* | AG | METTL3 | 0.040 |
| rs1139130 | AG | METTL3 | 0.0083 |
| rs7115 | AG | MRPS6 | 0.013 |
| rs2834384 | GT | MRPS6 | 0.013 |
| rs11621566 | AG | PAPOLA | 0.016 |  |  | |
| rs2274795 | CT | PAPOLA | 0.016 |  | |
| rs9654453 | CT | PDCD6 | 0.0083 |
| rs3802758\* | CT | PEX16 | 0.0016 |
| rs540516\* | CT | PNPLA6 | 0.029 |
| rs1904298 | CT | PPP2R5C | 0.0067 |
| rs11686919 | AG | PUM2 | 0.040 |
| rs157476 | AG | SFXN1 | 0.0061 |
| rs925197 | AG | SFXN1 | 0.013 |
| rs2662170 | CT | SFXN1 | 0.024 |
| rs937353 | CG | SFXN1 | 0.011 |
| rs2834378 | CT | SLC5A3 | 0.013 |
| rs1860661\* | AG | TCF3 | 0.0079 |
| rs1061026 | GT | TOX4 | 0.037 |
| rs13128884 | AG | USP38 | 0.014 |
| rs28470858 | AT | USP38 | 0.016 |
| rs34461753 | AG | USP38 | 0.0063 |
| rs4690779 | AG | USP38 | 0.014 |

| **SNP** | **CFS/ME- associated gene** | **Alleles** | **CFS/ME- associated allele** | **CFS/ME-associated transcription factor** | **Mutation resulting in no binding (predicted)** |
| --- | --- | --- | --- | --- | --- |
| rs3802758 | PEX16 | TC | C | NHLH1 (HEN1) | T>C |
| rs1904298 | PPP2R5C | CT | T | GABPA | C>T |
| rs11218304 | SORL1 | AG | G | REPIN1 (AP4) | A>G |
| rs1426137 | BMP2K | AT | A | ETS1 | T>A |

<https://www.ncbi.nlm.nih.gov/pubmed/21912186>

Subjects with the G allele of rs2247215 (GRIK2) were more likely to have CFS (p = 0.0005), and CFS subjects showed decreased GRIK2 expression (10-fold; p = 0.015). Subjects with the T allele of rs356653 (NPAS2) were more likely to have CFS (p = 0.0007), and NPAS2expression was increased (10-fold; p = 0.027) in those with CFS.

<https://www.ncbi.nlm.nih.gov/pubmed/21059181>

For the COMT SNP Rs4680, patients with CFS had a higher frequency of the AA genotype and a lower frequency of the G containing genotypes (AG and GG), when compared to the reference sample (p = 0.046). Also, the AA genotype was associated with a smaller increase in LF/HF ratio (low-frequency:high-frequency heart rate variability ratio, an index of cardiac sympathovagal balance) during head-up tilt when compared to the AG/GG genotypes. For the β₂ -adrenergic receptor SNP Rs1042714, patients with CFS had a lower frequency of the GG genotype and a higher frequency of the genotypes containing C (CG and CC) (p = 0.044).

<https://www.ncbi.nlm.nih.gov/pubmed/20227423>

We found that the Cys704 allele of Ser704Cys SNP was associated with an increased risk of CFS development compared with the Ser704 allele.

Disrupted-in schizophrenia 1 (DISC1)

<https://www.ncbi.nlm.nih.gov/pubmed/18986552>

Average absolute value of severity associations for the SNPs within eight candidate genes.

| **Gene Name** | **Gene Location** | **Average Correlation (SD)** | **Count of SNPs in candidate gene** | **Most Correlated SNP** | | |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Name | Correlation | p-value |
| POMC | 2p24 | 0.14 (NA) | 1 | rs12473543 | 0.135 | 0.216 |
| NR3C1 | 5q34 | 0.07 (0.06) | 7 | rs258750 | 0.198 | 0.069 |
| CRHR2 | 7p15 | 0.15 (0.08) | 3 | hCV15960586 | 0.225 | 0.036 |
| TH | 11p15 | 0.07 (0.01) | 2 | rs4074905 | 0.080 | 0.466 |
| TPH2 | 12q21 | 0.23 (0.04) | 7 | rs10784941 | 0.275 | 0.010 |
| SLC6A4 | 17q11.1 | 0.18 (0.17) | 3 | rs4325622 | 0.347 | 0.001 |
| CRHR1 | 17q21 | 0.03 (0.02) | 6 | rs242940 | 0.069 | 0.531 |
| COMT | 22q11.1 | 0.04 (0.02) | 7 | hCV11804654 | 0.077 | 0.479 |

TPH2 with seven SNPs had the highest average association with CFS severity.

<https://www.ncbi.nlm.nih.gov/pubmed/16610957>

The top three genes containing the SNPs accounting for the highest accumulated importances were neuronal tryptophan hydroxylase (*TPH2*), catechol-*O*-methyltransferase (*COMT*) and nuclear receptor subfamily 3, group C, member 1 glucocorticoid receptor (*NR3C1*).

<https://www.ncbi.nlm.nih.gov/pubmed/25878398>

Oxidative stress and inflammation play a pathogenetic role in idiopathic environmental intolerances (IEI), namely, multiple chemical sensitivity (MCS), fibromyalgia (FM), and chronic fatigue syndrome (CFS). Given the reported association of nitric oxide synthase (NOS) gene polymorphisms with inflammatory disorders, we aimed to investigate the distribution of NOS2A −2.5 kb (CCTTT)n as well as Ser608Leu and NOS3 −786T>C variants and their correlation with nitrite/nitrate levels, in a study cohort including 170 MCS, 108 suspected MCS (SMCS), 89 FM/CFS, and 196 healthy subjects. Patients and controls had similar distributions of NOS2A Ser608Leu and NOS3 −786T>C polymorphisms. Interestingly, the NOS3 −786TT genotype was associated with increased nitrite/nitrate levels only in IEI patients. We also found that the NOS2A −2.5 kb (CCTTT)11 allele represents a genetic determinant for FM/CFS, and the (CCTTT)16 allele discriminates MCS from SMCS patients. Instead, the (CCTTT)8 allele reduces by three-, six-, and tenfold, respectively, the risk for MCS, SMCS, and FM/CFS. Moreover, a short number of (CCTTT) repeats is associated with higher concentrations of nitrites/nitrates. Here, we first demonstrate that NOS3 −786T>C variant affects nitrite/nitrate levels in IEI patients and that screening for NOS2A −2.5 kb (CCTTT)n polymorphism may be useful for differential diagnosis of various IEI.

Our results demonstrated for the first time that the NOS2A promoter pentanucleotide microsatellite −2.5 kb (CCTTT)n is associated with FM/CFS and may be feasible for the diagnostic assessment of this type of IEI. Moreover, the screening for the presence of some NOS2A −2.5 kb (CCTTT) variants, that is, the 8- and 16-repeat alleles, may be useful, respectively, to exclude the diagnosis of IEI and discriminate between MCS and SMCS.

### Table 1

Allele and genotype frequencies of NOS2A and NOS3 SNPs in IEI patients and healthy subjects.

| **Genotype** | **MCS  (N = 170)** | **SMCS  (N = 108)** | **FM/CFS  (N = 89)** | **Controls (N = 196)** |
| --- | --- | --- | --- | --- |
| **NOS2A C2087T Ser608Leu)** |  |  |  |  |
| CC (Ser/Ser) | 60.6% | 52.8% | 65.2% | 60.2% |
| CT (Ser/Leu) | 34.7% | 41.7% | 30.3% | 36.2% |
| TT (Leu/Leu) | 4.7% | 5.6% | 4.5% | 3.6% |
| C allele frequency | 0.78 | 0.74 | 0.80 | 0.78 |
| T allele frequency | 0.22 | 0.26 | 0.20 | 0.22 |
| −**786T>C NOS3** |  |  |  |  |
| TT | 32.9% | 34.3% | 33.7% | 33.2% |
| TC | 45.9% | 46.3% | 49.4% | 44.5% |
| CC | 21.2% | 19.4% | 16.9% | 22.3% |
| T allele frequency | 0.56 | 0.56 | 0.58 | 0.55 |
| C allele frequency | 0.44 | 0.44 | 0.42 | 0.45 |

<https://www.ncbi.nlm.nih.gov/pubmed/22110941>

CFS only significantly greater than controls for P2X4, P2X5, TRPV1, α-2A, β-1, β-2 adrenergic receptors, COMT, and IL10 assessed as area under the curve across all 4 postexercise sampling times (P < 0.05).

<https://www.ncbi.nlm.nih.gov/pubmed/27457818>

Patients homozygous for rs4680 high-activity allele randomized to clonidine took 2,500 fewer steps compared to placebo (pinteraction=0.04). There were no differences between clonidine and placebo amongst patients with COMT low-activity alleles. Similar gene-drug interactions were observed for sleep (pint=0.003) and quality of life (pint=0.018). Detrimental effects of clonidine in the subset of CFS patients homozygous for COMT high-activity allele warrant investigation of potential clonidine-COMT interaction effects in other conditions.

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

fter 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 %).

<https://www.ncbi.nlm.nih.gov/pubmed/26272340>

In patients with the Met/Met variant of COMT rs4680 we observed enhanced cortisol levels providing evidence for its functional relevance. Both enhanced IgE and diminished IgG3 levels and an increased susceptibility to RRTI were observed in CFS patients with the Met/Met variant. Such an association was not observed in 68 non-CFS patients with RRTI.

<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** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CHRNB1 | 17 | rs3829603 | CC | 8 (72.7%) | 1 (9.1%) | 9.21 | 26.67 (2.31 – 308.00) | 0.002 |
| CHRNB1 | 17 | rs4151134 | TT | 7 (63.6%) | 1 (9.1%) | 7.07 | 17.50 (1.60 – 191.89) | 0.008 |
| CHRNB1 | 17 | rs2302767 | TT | 7 (63.6%) | 1 (9.1%) | 7.07 | 17.50 (1.60 – 191.89) | 0.008 |
| CHRNA4 | 20 | rs11698563 | CC | 6 (54.5%) | 1 (9.1%) | 5.24 | 12.00 (1.12 – 128.84) | 0.022 |
| CHRNB1 | 17 | rs7210231 | CA | 7 (63.6%) | 2 (18.2%) | 4.70 | 7.88 (1.11 – 56.12) | 0.030 |
| TRPM3 | 9 | rs7038646 | AG | 9 (81.8%) | 4 (36%) | 4.70 | 7.88 (1.11 – 56.12) | 0.030 |
| TRPC6 | 11 | rs10791504 | GG | 7 (63.6%) | 2 (18.2%) | 4.70 | 7.88 (1.11 – 56.12) | 0.030 |
| CHRM3 | 1 | rs1867264 | TA | 8 (72.7%) | 3 (27.3%) | 4.55 | 7.11 (1.09 – 46.44) | 0.033 |
| CHRM3 | 1 | rs6688537 | CA | 8 (72.7%) | 3 (27.3%) | 4.55 | 7.11 (1.09 – 46.44) | 0.033 |
|  |  |  |  |  |  |  |  |  |

<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** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| TRPM8 | 2 | rs11563204 | GA | 23 (82.1) | 5 (17.9) | 12.59 | 7.19 | 0 |
| 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 |
| TRPC4 | 13 | rs2985167 | AA | 20 (76.9) | 6 (23.1) | 7.07 | 4.21 | 0.008 |
| TRPM3 | 9 | rs6560200 | CC | 15 (83.3) | 3 (16.7) | 7.12 | 5.63 | 0.008 |
| TRPC4 | 13 | rs1570612 | GG | 30 (68.2) | 14 (31.8) | 6.72 | 3.81 | 0.01 |
| CHRNB4 | 15 | rs12441088 | TT | 25 (71.4) | 10 (28.6) | 6.42 | 3.57 | 0.011 |
| TRPM8 | 2 | rs17865678 | AG | 22 (73.3) | 8 (26.7) | 6.1 | 3.56 | 0.013 |
| TRPC4 | 13 | rs655207 | GG | 12 (85.7) | 2 (14.3) | 6.09 | 6.22 | 0.014 |
| CHRNA3 | 15 | rs12914385 | TT | 12 (85.7) | 2 (14.3) | 6.09 | 6.22 | 0.014 |
| 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 |
| TRPC2 | 11 | rs7108612 | GT | 15 (78.9) | 4 (21.1) | 5.37 | 4.06 | 0.021 |
| CHRNE | 17 | rs33970119 | GG | 36 (62.1) | 22 (37.9) | 4.56 | 4.36 | 0.033 |
| 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 |

<https://www.ncbi.nlm.nih.gov/pubmed/19540336>

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | | | | | | |
| Gene | | | SNP[a](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn1) | | | Chromosome | | | Position (Mb)[b](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn2) | CFS vs. NF[c](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn3) | CFS-MDD/m vs. NF[d](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn4) |
| NR3C1[e](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn5) | | | rs2918419 | | | 5 | | | 142.641 | **0.0104** | 0.3950 |
|  | | | rs1866388 | | | 5 | | | 142.702 | **0.0010**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | **0.0472** |
|  | | | rs860458 | | | 5 | | | 142.739 | **0.0104** | 0.3950 |
|  | | | rs852977 | | | 5 | | | 146.642 | **0.0035**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | 0.1878 |
|  | | | rs6196 | | | 5 | | | 146.660 | **0.0208** | 0.6423 |
|  | | | rs6188 | | | 5 | | | 146.667 | **0.0027**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | **0.0396** |
|  | | | rs258750 | | | 5 | | | 146.674 | **0.0035**[f](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub#tblfn6) | 0.1009 |
| COMT[g](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn7) | | | rs933271 | | | 22 | | | 18.311 | 0.0649 | **0.0025** |
|  | | | rs5993882 | | | 22 | | | 18.317 | 0.4306 | **0.0114** |
| NR3C1[d](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn11) |  |  | |  |  | |  |  |  |
|  |  | |  |  | |  |  |  |
|  |  | |  |  | |  |  |  |
| **rs852977** | 0 (230) | | 0 (17,001) | 0 (2929) | | **120 (9760)** | **73 (10,139)** | **0 (261)** |
|  |  | |  |  | |  |  |  |
| **rs6188** | 0 (171) | | 7 (16,970) | 1 (3019) | | **52 (2939)** | **217 (17,074)** | **0 (147)** |
| **rs258750** | **0 (242)** | | **0 (16,279)** | **105 (3639)** | | 0 (2769) | 14 (12,590) | 0 (4801) |
| COMT[e](https://www.sciencedirect.com/science/article/pii/S0888754309001347?via%3Dihub" \l "tblfn12) | rs933271 | 0 (1943) | | 0 (15,156) | 0 (3061) | | 0 (169) | 0 (16,872) | 0 (3119) |
| rs5993882 | 0 (1022) | | 0 (14,380) | 0 (4758) | | 0 (547) | 0 (17,333) | 0 (2280) |

<https://www.ncbi.nlm.nih.gov/pubmed/26063326>

| Sr. no. | Gene symbol | NCBI rsID | Chr. | Position | Homo-zygous-1 | Homo-zygous-2 | Hetero-zygous | Weighted genetic variation |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 51 | *IL12B* | rs2288831 | 5 | 158682591 | 0.10 | 0.65 | 0.25 | 3.95 |
| 9 | *IL1A* | rs2071376 | 2 | 113251866 | 0.07 | 0.60 | 0.33 | 3.60 |
| 106 | *IFNG* | rs2069718 | 12 | 66836429 | 0.12 | 0.36 | 0.52 | 3.34 |
| 6 | *HSD11B1* | rs846906 | 1 | 207954341 | 0.75 | 0.02 | 0.23 | 3.29 |
| 116 | *HTR2A* | rs1923884 | 13 | 46319837 | 0.48 | 0.07 | 0.46 | 3.16 |
| 152 | *MAOB* | rs1799836 | X | 43512943 | 0.25 | 0.32 | 0.42 | 2.56 |
| 129 | *CRHR1* | rs1396862 | 17 | 41258778 | 0.03 | 0.57 | 0.40 | 2.31 |
| 77 | *SLC18A2* | rs363236 | 10 | 119028361 | 0.02 | 0.81 | 0.17 | 2.31 |
| 59 | *NOS3* | rs891512 | 7 | 150339022 | 0.04 | 0.70 | 0.26 | 2.18 |
| 84 | *DRD2* | rs1124492 | 11 | 112787485 | 0.05 | 0.77 | 0.18 | 2.02 |
| 78 | *TH* | rs2070762 | 11 | 2142911 | 0.26 | 0.28 | 0.46 | 1.54 |
| 48 | *HTR4* | rs4289549 | 5 | 148002363 | 0.36 | 0.16 | 0.49 | 1.40 |
| 49 | *IL12B* | rs1368439 | 5 | 158674592 | 0.03 | 0.65 | 0.32 | 1.39 |
| 74 | *SLC18A2* | rs363390 | 10 | 118994069 | 0.09 | 0.59 | 0.32 | 1.37 |
| 37 | *HTR4* | rs7733410 | 5 | 147836715 | 0.15 | 0.41 | 0.45 | 1.36 |
| 131 | *ACE* | rs4978 | 17 | 58927493 | 0.33 | 0.29 | 0.39 | 1.35 |
| 117 | *HTR2A* | rs1923885 | 13 | 46321087 | 0.17 | 0.34 | 0.50 | 1.33 |
| 155 | *HTR2C* | rs12558586 | X | 113751903 | 0.76 | 0.03 | 0.21 | 1.29 |
| 17 | *HTR2B* | rs765458 | 2 | 231698911 | 0.11 | 0.43 | 0.47 | 1.24 |
| 36 | *HTR4* | rs10037493 | 5 | 147835163 | 0.39 | 0.15 | 0.47 | 1.23 |
| 103 | *TNFRSF1A* | rs1860545 | 12 | 6317038 | 0.13 | 0.41 | 0.46 | 1.22 |
| 136 | *ACE* | rs4968591 | 17 | 58951850 | 0.13 | 0.37 | 0.50 | 1.21 |
| 133 | *ACE* | rs11868324 | 17 | 58931041 | 0.19 | 0.29 | 0.52 | 1.19 |
| 45 | *HTR4* | rs980062 | 5 | 147947692 | 0.40 | 0.11 | 0.50 | 1.10 |
| 76 | *SLC18A2* | rs929493 | 10 | 119009116 | 0.05 | 0.65 | 0.30 | 1.09 |
| 111 | *TPH2* | rs1386486 | 12 | 70698487 | 0.14 | 0.41 | 0.46 | 1.07 |
| 154 | *HTR2C* | rs505971 | X | 113721064 | 0.49 | 0.17 | 0.35 | 1.07 |
| 108 | *TPH2* | rs2171363 | 12 | 70646531 | 0.17 | 0.41 | 0.42 | 1.05 |
| 19 | *SPP1* | rs11730582 | 4 | 89115445 | 0.26 | 0.22 | 0.52 | 1.04 |
| 1 | *HTR6* | rs1805054 | 1 | 19865100 | 0.80 | 0.02 | 0.18 | 1.03 |
| 57 | *NOS3* | rs1007311 | 7 | 150326941 | 0.33 | 0.24 | 0.44 | 1.02 |
| 18 | *DRD3* | rs3773678 | 3 | 115352768 | 0.02 | 0.75 | 0.23 | 1.01 |
| 42 | *HTR4* | rs2895768 | 5 | 147906430 | 0.40 | 0.12 | 0.49 | 1.01 |

| **SNP ID** | **Proxy SNP** | **Gene symbola** | **SNP annotationa** | **WGV** | **SE of WGVb** |
| --- | --- | --- | --- | --- | --- |
| rs2288831 | rs3212227 | IL12B | Intron (UTR-3) | 3.95 | 0.0299 |
| rs2071376 |  | IL1A | intron | 3.6 | 0.0296 |
| rs2069718 |  | IFNG | intron | 3.34 | 0.0272 |
| rs846906 |  | HSD11B1 | intron | 3.29 | 0.0337 |
| rs1923884 |  | HTR2A | intron | 3.16 | 0.0324 |
| rs1799836 |  | MAOB | Intron | 2.56 | 0.0394 |
| rs363236 | rs3814230 | SLC18A2 (PDZD8) | UTR-3 (synonymous codon) | 2.31 | 0.0272 |
| rs1396862 | rs1218523 | CRHR1 (IMP5) | Intron (missense codon) | 2.31 | 0.0334 |
| rs891512 | rs743507 | NOS3 | Intron | 2.18 | 0.0287 |
| rs1124492 | rs46220755 | DRD2 | Intron | 2.02 | 0.0312 |

<http://institutferran.org/documentos/estudio_genetico/JCR%20106%20140408.pdf>

Fibromyalgia (FM) and chronic fatigue syndrome or myalgic encephalomyelitis (CFS/ME) are believed to be two separate illnesses that are diagnosed using separate but overlapping clinical criteria; to date there are no biological markers for either condition. The symptoms of both disorders can differ markedly in presentation, frequency and intensity and therefore it is necessary to distinguish between the subtypes. Since recent studies have begun to determine the genetic background of these diseases, the authors suggest the use of single nucleotide polymorphism (SNP) analysis to investigate their different genetic profiles. In agreement with that study, no signifi cant associations were found in CFS/ME subtypes within the COMT gene or in rs1800795, rs7209436, rs173365 and rs2267710 (data not shown), whereas rs12473543 was considered signifi cantly associated ( p

Discriminating SNPs for CFS/ME AA AB BB

rs2168631 5 DRD1 5Upstream 4 20 77 aa

rs1800797 7 IL6 Intron 13 39 48 Aa aa

rs2770296 13 HTR2A Intron 15 40 45 Aa aa

rs2020942 17 SLC6A4 Intron 26 45 29 Aa

rs3794808 17 SLC6A4 Intron 19 53 29 Aa

rs2297518 17 NOS2A Coding 3 30 68 aa

rs5746847 22 TXNRD2 Intron 23 42 36 Aa aa

rs165815 22 ARVCF Coding 2 15 83 aa

rs165774 22 COMT Intron 5 43 52 Aa aa

rs324029 3 DRD3 Intron 6 43 51 Aa aa

rs7224199 17 SLC6A4 3Downstream 29 56 15 Aa

rs3794808 17 SLC6A4 Intron 9 54 37 Aa aa

rs10488682 11 TPH1 5Upstream 17 40 43 Aa aa

rs2020942 17 SLC6A4 Intron 61 32 8 AA

rs1474347 7 IL6 Intron 22 46 32 Aa

rs489736 X HTR2C Intron 29 48 23 Aa

rs12473543\*

<https://www.ncbi.nlm.nih.gov/pubmed/25240059>

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  | **CFS/ME gene expression subtype**  (no. patients tested in each subtype) | | | | | | | |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| RefSNP ID | Alleles | Gene | 8-column χ2 test | **A** | **B** | **C** | **D** | **E** | **F** | **G** | **H** |
|  |  |  |  | 22 | 6 | 19 | 5 | 20 | 13 | 19 | 4 |
|  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| rs2515194 | CT | ATP6V1C1 | 0.00034 | T:0.038 |  | T:0.042 |  | C:0.013 |  | C:0.0003 |  |
| rs12687359 | AT | BCOR | 0.00032 |  |  |  |  | T:0.031 |  |  | T:< 0.0001 |
| rs5917933 | AG | BCOR | 0.0054 |  |  |  | A:< 0.0001 |  |  |  |  |
| rs1373998\* | CT | IL6ST | 0.0063 |  |  | C:0.023 |  | T:0.00087 |  |  |  |
| rs7115 | AG | MRPS6 | 0.013 |  | A:0.018 |  |  | G:0.00084 |  |  |  |
| rs9654453 | CT | PDCD6 | 0.0083 |  |  |  | C:< 0.0001 |  |  |  |  |
| rs1904298 | CT | PPP2R5C | 0.0067 |  |  | T:0.034 |  |  |  |  | T:0.0004 |
| rs2256998 | AC | SHPRH |  |  |  |  |  |  |  | C:0.0095 |  |
| rs2834378 | CT | SLC5A3 | 0.013 |  | C:0.018 |  |  | G:0.00084 |  |  |  |
| rs34461753 | AG | USP38 | 0.0063 |  | G:0.00093 |  |  |  |  | G:0.013 |  |
|  |  |  |  |  |  |  |  |  |  |  |  |

\* SNP also included in Table 1.

FAM126B rs11895568 NA  
TCF3 rs1860661 (A)   
EIF3A rs10787901 NA  
UBTF rs2071167 ("A")   
METTL3 rs3752411 (A)   
SORL1 rs3737529 NA  
BMP2K rs3775516 NA  
BMP2K rs1426139 NA  
IL6ST rs1373998 NA  
PEX16 rs3802758 NA

<https://www.ncbi.nlm.nih.gov/pubmed/19955554>

<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

mAChM3 1 rs589962 TT 52 (65%) 28 (35%) 6.839 0.009 2.286

mAChM3 1 rs1072320 AG 47 (66.2%) 24 (33.8%) 6.825 0.009 2.314

mAChM3 1 rs7543259 AG 46 (65.7%) 24 (34.3%) 6.122 0.013 2.215

mAChM3 1 rs7520974 AA 30 (68.2%) 14 (31.8%) 4.515 0.034 2.178

mAChM3 1 rs726169 AA 49 (67.1%) 24 (32.9%) 8.345 0.004 2.528

mAChM3 1 rs6669810 CC 29 (67.4%) 14 (32.6%) 3.917 0.048 2.071

mAChM3 1 rs6429157 GG 25 (71.4%) 10 (28.6%) 5.123 0.024 2.500

mAChM3 1 rs12036141 AA 15 (75%) 5 (25%) 3.854 0.050 2.803

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/16740143>

**Table 2.**Association of *NR3C1*polymorphisms with CFS

| **Marker**[**\***](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-183X.2006.00244.x#t2n1) | **SNP ID** | **Alleles** | **NF** | **CFS** | | **ISF** | | **CFS + ISF** | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Allele frequency** | **Allele frequency** | ***P*‐value**[**\*\***](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-183X.2006.00244.x#t2n2) | **Allele frequency** | ***P*‐value** | **Allele frequency** | ***P*‐value**[**\*\***](https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-183X.2006.00244.x#t2n2) |
| A | rs1866388 | A/G | 0.57/0.43 | 0.74/0.26 | **0.0233** | 0.67/0.33 | 0.1300 | 0.71/0.29 | **0.0335** |
| B | rs2918419 | T/C | 0.73/0.27 | 0.88/0.12 | **0.0410** | 0.84/0.16 | 0.0744 | 0.85/0.15 | **0.0164** |
| C | rs860458 | G/A | 0.73/0.27 | 0.88/0.12 | **0.0375** | 0.84/0.16 | 0.0766 | 0.85/0.15 | **0.0180** |
| E | rs6188 | C/A | 0.57/0.43 | 0.73/0.27 | **0.0466** | 0.69/0.31 | 0.1319 | 0.70/0.30 | **0.0383** |

<https://www.ncbi.nlm.nih.gov/pubmed/25902009>

| **Genotypes of MTHFR** | | | **Prevalence** | **Activity** |
| --- | --- | --- | --- | --- |
| **677** | **1298** | **Name of combined genotype** | **%** | **%** |
| CC | AA | Original genotype | 16 | 100 |
| CC | AC | 1298C heterozygote | 23 | 60 |
| CC | CC | 1298C homozygote | 9 | 52 |
| CT | AA | 677T heterozygote | 21 | 51 |
| CT | AC | Compound heterozygote | 20 | 36 |
| TT | AA | 677T homozygote | 11 | 22 |

<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.

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

TRPM3 9 rs12682832 A G 0.444 0.293 8.808 0.003\*

TRPM3 9 rs11142508 C T 0.445 0.298 8.438 0.004\*

TRPM3 9 rs1160742 A G 0.470 0.333 7.063 0.008\*

TRPM3 9 rs4454352 C T 0.240 0.137 6.232 0.013\*

TRPM3 9 rs1328153 C T 0.240 0.137 6.232 0.013\*

TRPM3 9 rs3763619 A C 0.440 0.316 5.990 0.014\*

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\*

TRPA1 8 rs4738202 A G 0.369 0.253 5.591 0.018\*

TRPM3 9 rs7865858 A G 0.450 0.331 5.340 0.021\*

TRPA1 8 rs2383844 G A 0.505 0.398 4.218 0.040\*

TRPM3 9 rs1504401 T C 0.100 0.173 4.172 0.041\*

TRPM3 9 rs10115622 A C 0.335 0.435 3.837 0.050\*

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