<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 |