**Whole-exome sequencing reveals migraine associated novel functional variants**

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**Supplementary Table 1:** List of migraine associated (*p* value <0.00001) variants identified through exome sequencing.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP** | **locus contig** | **locus position** | **alleles** | **Consequence** | **SYMBOL** | **Amino acids** | **Protein position** | **Codons** | ***p*-value** |
| rs772174 | chr2 | 96325754 | ['A', 'G'] | 5\_prime\_UTR\_variant | ITPRIPL1 | - | - | - | 5.2E-07 |
| rs9878093 | chr3 | 108755677 | ['A', 'C'] | 3\_prime\_UTR\_variant | RETNLB | - | - | - | 3.45E-06 |
| rs5851607 | chr3 | 108757146 | ['G', 'GGGGG ATTA'] | stop\_gained,frameshift\_variant | RETNLB | -/\*SX | 13-14 | -/TAAT CCCC | 3.45E-06 |
| rs3214023 | chr12 | 53289202 | ['C', 'T'] | non\_coding\_transcript\_exon\_variant | ESPL1 | - | - | - | 3.56E-06 |
| rs2230354 | chr17 | 14191992 | ['A', 'G'] | synonymous\_variant | COX10 | P | 233 | ccA/ccG | 5.32E-06 |
| rs1455774 | chr15 | 92472091 | ['T', 'G'] | non\_coding\_transcript\_exon\_variant | C15orf32 | - | - | - | 7.96E-06 |
| rs589292 | chr9 | 125055997 | ['C', 'T'] | missense\_variant | SCAI | A/T | 37 | Gct/Act | 1.17E-05 |
| rs1126671 | chr4 | 99127263 | ['T', 'C'] | missense\_variant | ADH4 | I/V | 309 | Att/Gtt | 1.58E-05 |
| rs1126673 | chr4 | 99124465 | ['C', 'T'] | missense\_variant,splice\_region\_variant | ADH4 | V/I | 393 | Gtc/Atc | 1.58E-05 |
| rs1126670 | chr4 | 99131582 | ['C', 'A'] | synonymous\_variant | ADH4 | P | 255 | ccG/ccT | 1.58E-05 |
| rs7644369 | chr3 | 134951682 | ['C', 'T'] | synonymous\_variant | EPHB1 | S | 145 | agC/agT | 1.67E-05 |
| rs12318072 | chr12 | 124314255 | ['C', 'T'] | synonymous\_variant | RFLNA | P | 127 | ccC/ccT | 2.19E-05 |
| rs6580942 | chr12 | 53268840 | ['C', 'A'] | 5\_prime\_UTR\_variant | ESPL1 | - | - | - | 3.41E-05 |
| rs2229917 | chr9 | 128218658 | ['G', 'A'] | synonymous\_variant | DNM1 | E | 104 | gaG/gaA | 3.42E-05 |
| rs1799821 | chr1 | 53210776 | ['G', 'A'] | missense\_variant | CPT2 | V/I | 368 | Gtc/Atc | 3.58E-05 |
| rs3126075 | chr1 | 152304150 | ['G', 'C'] | missense\_variant | FLG | T/R | 3579 | aCg/aGg | 4.27E-05 |
| rs329003 | chr18 | 9570322 | ['T', 'C'] | missense\_variant | PPP4R1 | I/V | 381 | Ata/Gta | 4.5E-05 |
| rs2289520 | chr18 | 63493087 | ['G', 'C'] | missense\_variant | SERPINB5 | V/L | 16 | Gtc/Ctc | 4.56E-05 |
| rs198460 | chr11 | 61757502 | ['G', 'A'] | non\_coding\_transcript\_exon\_variant | DKFZP434K028 | - | - | - | 5.23E-05 |
| rs200899890 | chr14 | 18999427 | ['A', 'G'] | 3\_prime\_UTR\_variant | POTEM | - | - | - | 5.29E-05 |
| rs62027634 | chr15 | 101744472 | ['A', 'G'] | non\_coding\_transcript\_exon\_variant | LOC100128108 | - | - | - | 5.35E-05 |
| rs913589 | chr9 | 7174773 | ['G', 'A'] | 3\_prime\_UTR\_variant | KDM4C | - | - | - | 5.4E-05 |
| rs12390 | chrX | 119470473 | ['T', 'C'] | synonymous\_variant | SLC25A5 | T | 233 | acT/acC | 5.5E-05 |
| rs56358776 | chr12 | 53288673 | ['G', 'A'] | missense\_variant | ESPL1 | R/Q | 1561 | cGg/cAg | 5.92E-05 |
| rs12452761 | chr17 | 73472128 | ['G', 'A'] | synonymous\_variant | SDK2 | T | 105 | acC/acT | 6.2E-05 |
| - | chr1 | 196788867 | ['G', 'T'] | non\_coding\_transcript\_exon\_variant | CFHR3 | - | - | - | 6.7E-05 |
| rs7251612 | chr19 | 20776362 | ['C', 'G'] | 5\_prime\_UTR\_variant | ZNF66 | - | - | - | 7.33E-05 |
| rs7251614 | chr19 | 20776371 | ['C', 'G'] | 5\_prime\_UTR\_variant | ZNF66 | - | - | - | 7.33E-05 |
| - | chr19 | 20807177 | ['G', 'GACAT AAGA GAATT CATA CTGG AGAG AAAC CCTA CAAA TGTG AAGA ATGT GGCA AAGC TTTT AATC ATCC CGCA ACCC TTTT TTC'] | inframe\_insertion | ZNF66 | R/RHK RIHT GEKP YKCE ECGK AFNH PATL FS | 526 | aga/ag ACAT AAGA GAAT TCAT ACTG GAGA GAAA CCCT ACAA ATGT GAAG AATG TGGC AAAG CTTT TAAT CATC CCGC AACC CTTT TTTCa | 7.33E-05 |
| rs10413187 | chr19 | 20793848 | ['C', 'A'] | missense\_variant | ZNF66 | Q/K | 66 | Cag/Aag | 7.33E-05 |
| rs432839 | chr19 | 20806118 | ['G', 'T'] | missense\_variant | ZNF66 | C/F | 173 | tGc/tTc | 7.33E-05 |
| rs383038 | chr19 | 20806162 | ['T', 'C'] | missense\_variant | ZNF66 | F/L | 188 | Ttt/Ctt | 7.33E-05 |
| rs370551 | chr19 | 20806858 | ['A', 'G'] | missense\_variant | ZNF66 | T/A | 420 | Act/Gct | 7.33E-05 |
| rs366949 | chr19 | 20805906 | ['G', 'A'] | synonymous\_variant | ZNF66 | R | 102 | agG/agA | 7.33E-05 |
| rs77897802 | chr17 | 36212117 | ['G', 'A'] | 3\_prime\_UTR\_variant | CCL4L2 | - | - | - | 7.77E-05 |
| rs1270983160 | chr17 | 36211816 | ['C', 'T'] | synonymous\_variant | CCL4L2 | T | 39 | acC/acT | 7.77E-05 |
| rs12984041 | chr19 | 46746039 | ['G', 'C'] | 5\_prime\_UTR\_variant | FKRP | - | - | - | 8.18E-05 |
| rs2187473 | chr11 | 111513121 | ['C', 'T'] | non\_coding\_transcript\_exon\_variant | LOC728196 | - | - | - | 8.39E-05 |
| rs61740794 | chr2 | 67404699 | ['G', 'A'] | missense\_variant | ETAA1 | E/K | 673 | Gaa/Aaa | 8.51E-05 |
| rs4876458 | chr8 | 112224816 | ['C', 'T'] | synonymous\_variant | CSMD3 | A | 2159 | gcG/gcA | 8.72E-05 |
| rs735943 | chr1 | 241866849 | ['A', 'G'] | missense\_variant | EXO1 | H/R | 354 | cAt/cGt | 8.98E-05 |
| rs17343819 | chr8 | 67484680 | ['T', 'C'] | missense\_variant,splice\_region\_variant | CPA6 | N/S | 101 | aAt/aGt | 9.09E-05 |
| rs162008 | chr18 | 26865728 | ['C', 'T'] | 5\_prime\_UTR\_variant | AQP4 | - | - | - | 9.29E-05 |
| rs16907852 | chr11 | 10482209 | ['G', 'A'] | synonymous\_variant | AMPD3 | P | 32 | ccG/ccA | 9.53E-05 |
| rs72297783 | chr10 | 23014163 | ['A', 'AG'] | 3\_prime\_UTR\_variant | ARMC3 | - | - | - | 9.55E-05 |
| rs61760973 | chr11 | 34966796 | ['T', 'C'] | synonymous\_variant | PDHX | P | 251 | ccT/ccC | 9.55E-05 |
| rs3213590 | chr6 | 167915298 | ['G', 'C'] | non\_coding\_transcript\_exon\_variant | AFDN | - | - | - | 9.97E-05 |
| rs6906754 | chr6 | 167917136 | ['A', 'C'] | non\_coding\_transcript\_exon\_variant | AFDN | - | - | - | 9.97E-05 |
| rs3213590 | chr6 | 167915298 | ['G', 'C'] | synonymous\_variant | AFDN | V | 636 | gtG/gtC | 9.97E-05 |
| rs6906754 | chr6 | 167917136 | ['A', 'C'] | synonymous\_variant | AFDN | P | 697 | ccA/ccC | 9.97E-05 |
| rs3213590 | chr6 | 167915298 | ['G', 'C'] | synonymous\_variant | AFDN | V | 787 | gtG/gtC | 9.97E-05 |
| rs6906754 | chr6 | 167917136 | ['A', 'C'] | synonymous\_variant | AFDN | P | 848 | ccA/ccC | 9.97E-05 |
| rs3213590 | chr6 | 167915298 | ['G', 'C'] | synonymous\_variant | AFDN | V | 762 | gtG/gtC | 9.97E-05 |
| rs6906754 | chr6 | 167917136 | ['A', 'C'] | synonymous\_variant | AFDN | P | 864 | ccA/ccC | 9.97E-05 |
| rs3213590 | chr6 | 167915298 | ['G', 'C'] | synonymous\_variant | AFDN | V | 811 | gtG/gtC | 9.97E-05 |
| rs6906754 | chr6 | 167917136 | ['A', 'C'] | synonymous\_variant | AFDN | P | 872 | ccA/ccC | 9.97E-05 |

**Supplementary Table 2: Gene ontology pathway analysis of the top 50 genes.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **GO\_Biological\_Process\_Enrichment** |   |   |   |   |   |
| **Term** | **P-value** | **Adjusted P-value** | **Genes from top 50 list** | **total Genes** | **Genes** |
| organic hydroxy compound catabolic process (GO:1901616) | **9.12893E-05** | **0.026108731** | 2 | 6 | ADH4;CYP4F12 |
| quinone metabolic process (GO:1901661) | **0.000272123** | **0.038913602** | 2 | 10 | ADH4;AKR1C1 |
| regulation of insulin-like growth factor receptor signaling pathway (GO:0043567) | **0.000813271** | 0.077531867 | 2 | 17 | IGFBP1;CDH3 |
| renal water homeostasis (GO:0003091) | **0.002719256** | 0.172746714 | 2 | 31 | AQP4;CYP4F12 |
| adherens junction organization (GO:0034332) | **0.005418766** | 0.172746714 | 2 | 44 | AFDN;CDH3 |
| diterpenoid metabolic process (GO:0016101) | **0.010526589** | 0.172746714 | 2 | 62 | ADH4;AKR1C1 |
| cell-cell junction organization (GO:0045216) | **0.014004804** | 0.172746714 | 2 | 72 | AFDN;CDH3 |
| regulation of cell cycle checkpoint (GO:1901976) | **0.014908285** | 0.172746714 | 1 | 6 | ETAA1 |
| establishment of endothelial intestinal barrier (GO:0090557) | **0.014908285** | 0.172746714 | 1 | 6 | AFDN |
| negative regulation of transforming growth factor beta production (GO:0071635) | **0.014908285** | 0.172746714 | 1 | 6 | CDH3 |
| regulation of transforming growth factor beta2 production (GO:0032909) | **0.014908285** | 0.172746714 | 1 | 6 | CDH3 |
| renal system process involved in regulation of blood volume (GO:0001977) | **0.014908285** | 0.172746714 | 1 | 6 | CYP4F12 |
| retinoid metabolic process (GO:0001523) | **0.015132736** | 0.172746714 | 2 | 75 | ADH4;AKR1C1 |
| positive regulation of insulin-like growth factor receptor signaling pathway (GO:0043568) | **0.017371741** | 0.172746714 | 1 | 7 | CDH3 |
| positive regulation of keratinocyte proliferation (GO:0010838) | **0.017371741** | 0.172746714 | 1 | 7 | CDH3 |
| positive regulation of mitotic sister chromatid separation (GO:1901970) | **0.017371741** | 0.172746714 | 1 | 7 | ESPL1 |
| long-chain fatty acid catabolic process (GO:0042758) | **0.017371741** | 0.172746714 | 1 | 7 | CYP4F12 |
| granulocyte migration (GO:0097530) | **0.017371741** | 0.172746714 | 1 | 7 | ADGRE2 |
| positive regulation of metaphase/anaphase transition of cell cycle (GO:1902101) | **0.017371741** | 0.172746714 | 1 | 7 | ESPL1 |
| intestinal cholesterol absorption (GO:0030299) | **0.019829161** | 0.172746714 | 1 | 8 | AKR1C1 |
| positive regulation of mitotic metaphase/anaphase transition (GO:0045842) | **0.019829161** | 0.172746714 | 1 | 8 | ESPL1 |
| daunorubicin metabolic process (GO:0044597) | **0.019829161** | 0.172746714 | 1 | 8 | AKR1C1 |
| aminoglycoside antibiotic metabolic process (GO:0030647) | **0.019829161** | 0.172746714 | 1 | 8 | AKR1C1 |
| doxorubicin metabolic process (GO:0044598) | **0.019829161** | 0.172746714 | 1 | 8 | AKR1C1 |
| histone H3-K36 demethylation (GO:0070544) | **0.019829161** | 0.172746714 | 1 | 8 | KDM4C |
| intestinal lipid absorption (GO:0098856) | **0.022280559** | 0.172746714 | 1 | 9 | AKR1C1 |
| regulation of leukocyte degranulation (GO:0043300) | **0.022280559** | 0.172746714 | 1 | 9 | ADGRE2 |
| regulation of mast cell activation involved in immune response (GO:0033006) | **0.022280559** | 0.172746714 | 1 | 9 | ADGRE2 |
| regulation of hair cycle (GO:0042634) | **0.022280559** | 0.172746714 | 1 | 9 | CDH3 |
| regulation of DNA damage checkpoint (GO:2000001) | **0.024725949** | 0.172746714 | 1 | 10 | ETAA1 |
| establishment of spindle localization (GO:0051293) | **0.024725949** | 0.172746714 | 1 | 10 | ESPL1 |
| formation of extrachromosomal circular DNA (GO:0001325) | **0.027165345** | 0.172746714 | 1 | 11 | EXO1 |
| carnitine shuttle (GO:0006853) | **0.027165345** | 0.172746714 | 1 | 11 | CPT2 |
| replicative senescence (GO:0090399) | **0.027165345** | 0.172746714 | 1 | 11 | ATR |
| protein O-linked mannosylation (GO:0035269) | **0.027165345** | 0.172746714 | 1 | 11 | FKRP |
| regulation of myeloid leukocyte mediated immunity (GO:0002886) | **0.027165345** | 0.172746714 | 1 | 11 | ADGRE2 |
| fatty acid transmembrane transport (GO:1902001) | **0.027165345** | 0.172746714 | 1 | 11 | CPT2 |
| retinal metabolic process (GO:0042574) | **0.027165345** | 0.172746714 | 1 | 11 | AKR1C1 |
| activation of cysteine-type endopeptidase activity involved in apoptotic signaling pathway (GO:0097296) | **0.027165345** | 0.172746714 | 1 | 11 | TNFRSF10B |
| alcohol catabolic process (GO:0046164) | **0.027165345** | 0.172746714 | 1 | 11 | ADH4 |
| telomere maintenance via telomere trimming (GO:0090737) | **0.027165345** | 0.172746714 | 1 | 11 | EXO1 |
| t-circle formation (GO:0090656) | **0.027165345** | 0.172746714 | 1 | 11 | EXO1 |
| progesterone metabolic process (GO:0042448) | **0.027165345** | 0.172746714 | 1 | 11 | AKR1C1 |
| PERK-mediated unfolded protein response (GO:0036499) | **0.029598762** | 0.172746714 | 1 | 12 | IGFBP1 |
| histone H3-K9 demethylation (GO:0033169) | **0.029598762** | 0.172746714 | 1 | 12 | KDM4C |
| prostanoid metabolic process (GO:0006692) | **0.029598762** | 0.172746714 | 1 | 12 | AKR1C1 |
| regulation of sister chromatid cohesion (GO:0007063) | **0.029598762** | 0.172746714 | 1 | 12 | ESPL1 |
| retinol metabolic process (GO:0042572) | **0.029598762** | 0.172746714 | 1 | 12 | ADH4 |
| water transport (GO:0006833) | **0.032026213** | 0.172746714 | 1 | 13 | AQP4 |
| fluid transport (GO:0042044) | **0.034447714** | 0.172746714 | 1 | 14 | AQP4 |
| glycoside metabolic process (GO:0016137) | **0.034447714** | 0.172746714 | 1 | 14 | AKR1C1 |
| positive regulation of DNA damage response, signal transduction by p53 class mediator (GO:0043517) | **0.034447714** | 0.172746714 | 1 | 14 | ATR |
| negative regulation of Rho protein signal transduction (GO:0035024) | **0.034447714** | 0.172746714 | 1 | 14 | SCAI |
| positive regulation of protein serine/threonine kinase activity (GO:0071902) | **0.035176955** | 0.172746714 | 2 | 118 | ETAA1;TNFRSF10B |
| DNA replication (GO:0006260) | **0.036270617** | 0.172746714 | 2 | 120 | EXO1;ATR |
| positive regulation of cysteine-type endopeptidase activity involved in apoptotic signaling pathway (GO:2001269) | **0.036863279** | 0.172746714 | 1 | 15 | TNFRSF10B |
| intracellular lipid transport (GO:0032365) | **0.036863279** | 0.172746714 | 1 | 15 | CPT2 |
| protein localization to chromosome, telomeric region (GO:0070198) | **0.036863279** | 0.172746714 | 1 | 15 | ATR |
| regulation of mast cell degranulation (GO:0043304) | **0.036863279** | 0.172746714 | 1 | 15 | ADGRE2 |
| regulation of mitotic metaphase/anaphase transition (GO:0030071) | **0.036863279** | 0.172746714 | 1 | 15 | ESPL1 |
| activation of NF-kappaB-inducing kinase activity (GO:0007250) | **0.039272921** | 0.172746714 | 1 | 16 | TNFRSF10B |
| regulation of water loss via skin (GO:0033561) | **0.039272921** | 0.172746714 | 1 | 16 | FLG |
| establishment of skin barrier (GO:0061436) | **0.039272921** | 0.172746714 | 1 | 16 | FLG |
| negative regulation of DNA replication (GO:0008156) | **0.039272921** | 0.172746714 | 1 | 16 | ATR |
| positive regulation of hormone secretion (GO:0046887) | **0.041676655** | 0.172746714 | 1 | 17 | GRP |
| positive regulation of G-protein coupled receptor protein signaling pathway (GO:0045745) | **0.041676655** | 0.172746714 | 1 | 17 | GRP |
| protein mannosylation (GO:0035268) | **0.041676655** | 0.172746714 | 1 | 17 | FKRP |
| positive regulation of signal transduction by p53 class mediator (GO:1901798) | **0.041676655** | 0.172746714 | 1 | 17 | ATR |
| cellular response to gamma radiation (GO:0071480) | **0.041676655** | 0.172746714 | 1 | 17 | ATR |
| regulation of keratinocyte proliferation (GO:0010837) | **0.044074495** | 0.175073688 | 1 | 18 | CDH3 |
| establishment of mitotic spindle localization (GO:0040001) | **0.044074495** | 0.175073688 | 1 | 18 | ESPL1 |
| response to organophosphorus (GO:0046683) | **0.044074495** | 0.175073688 | 1 | 18 | AKR1C1 |
| endoplasmic reticulum mannose trimming (GO:1904380) | **0.046466455** | 0.178024688 | 1 | 19 | RNF103 |
| primary alcohol metabolic process (GO:0034308) | **0.046466455** | 0.178024688 | 1 | 19 | ADH4 |
| regulation of signal transduction by p53 class mediator (GO:1901796) | **0.046684796** | 0.178024688 | 2 | 138 | EXO1;ATR |
| cellular response to DNA damage stimulus (GO:0006974) | **0.049035416** | 0.184528015 | 3 | 329 | ETAA1;EXO1;ATR |
|   |   |   |   |   |   |
| **GO\_Cellular\_Component\_Enrichment** |   |   |   |   |   |
| **Term** | **P-value** | **Adjusted P-value** | **Genes from top 50 list** | **Total genes** | **Genes** |
| nuclear replication fork (GO:0043596) | 0.027165345 | 0.298372914 | 1 | 11 | ETAA1 |
| NuRD complex (GO:0016581) | 0.039272921 | 0.298372914 | 1 | 16 | APLP2 |
| CHD-type complex (GO:0090545) | 0.039272921 | 0.298372914 | 1 | 16 | APLP2 |
| platelet alpha granule membrane (GO:0031092) | 0.041676655 | 0.298372914 | 1 | 17 | APLP2 |
|   |   |   |   |   |   |
|   |   |   |   |   |   |
| **GO\_Molecular\_Function\_Enrichment** |   |   |   |   |   |
| **Term** | **P-value** | **Adjusted P-value** | **Genes from top 50 list** | **Total Genes** | **Genes** |
| oxidoreductase activity, acting on NAD(P)H, quinone or similar compound as acceptor (GO:0016655) | 0.000629902 | 0.05480148 | 2 | 15 | ADH4;AKR1C1 |
| oxidoreductase activity, acting on paired donors (GO:0016709) | 0.004719495 | 0.09951002 | 2 | 41 | AKR1C1;CYP4F12 |
| small GTPase binding (GO:0031267) | 0.010854501 | 0.09951002 | 2 | 63 | AFDN;APLP2 |
| alcohol dehydrogenase activity, zinc-dependent (GO:0004024) | 0.014908285 | 0.09951002 | 1 | 6 | ADH4 |
| retinol binding (GO:0019841) | 0.014908285 | 0.09951002 | 1 | 6 | ADH4 |
| ketosteroid monooxygenase activity (GO:0047086) | 0.014908285 | 0.09951002 | 1 | 6 | AKR1C1 |
| aldehyde dehydrogenase [NAD(P)+] activity (GO:0004030) | 0.014908285 | 0.09951002 | 1 | 6 | ADH4 |
| 5'-3' exodeoxyribonuclease activity (GO:0035312) | 0.014908285 | 0.09951002 | 1 | 6 | EXO1 |
| oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen (GO:0016713) | 0.017371741 | 0.09951002 | 1 | 7 | CYP4F12 |
| insulin-like growth factor II binding (GO:0031995) | 0.017371741 | 0.09951002 | 1 | 7 | IGFBP1 |
| flap endonuclease activity (GO:0048256) | 0.017371741 | 0.09951002 | 1 | 7 | EXO1 |
| single-stranded DNA exodeoxyribonuclease activity (GO:0008297) | 0.017371741 | 0.09951002 | 1 | 7 | EXO1 |
| hormone activity (GO:0005179) | 0.018324143 | 0.09951002 | 2 | 83 | RETNLB;GRP |
| mismatch repair complex binding (GO:0032404) | 0.019829161 | 0.09951002 | 1 | 8 | ATR |
| bile acid binding (GO:0032052) | 0.019829161 | 0.09951002 | 1 | 8 | AKR1C1 |
| alcohol dehydrogenase (NAD) activity (GO:0004022) | 0.019829161 | 0.09951002 | 1 | 8 | ADH4 |
| oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor (GO:0016616) | 0.020450528 | 0.09951002 | 2 | 88 | ADH4;AKR1C1 |
| histone demethylase activity (H3-K36 specific) (GO:0051864) | 0.022280559 | 0.09951002 | 1 | 9 | KDM4C |
| exodeoxyribonuclease activity, producing 5'-phosphomonoesters (GO:0016895) | 0.024725949 | 0.09951002 | 1 | 10 | EXO1 |
| lipid phosphatase activity (GO:0042577) | 0.027165345 | 0.09951002 | 1 | 11 | PLPPR5 |
| phosphatase activity (GO:0016791) | 0.027901009 | 0.09951002 | 2 | 104 | PPP4R1;PLPPR5 |
| alditol:NADP+ 1-oxidoreductase activity (GO:0004032) | 0.029598762 | 0.09951002 | 1 | 12 | AKR1C1 |
| histone demethylase activity (H3-K9 specific) (GO:0032454) | 0.032026213 | 0.09951002 | 1 | 13 | KDM4C |
| water transmembrane transporter activity (GO:0005372) | 0.032026213 | 0.09951002 | 1 | 13 | AQP4 |
| water channel activity (GO:0015250) | 0.032026213 | 0.09951002 | 1 | 13 | AQP4 |
| phosphatidate phosphatase activity (GO:0008195) | 0.032026213 | 0.09951002 | 1 | 13 | PLPPR5 |
| ubiquitin protein ligase activity involved in ERAD pathway (GO:1904264) | 0.032026213 | 0.09951002 | 1 | 13 | RNF103 |
| insulin-like growth factor I binding (GO:0031994) | 0.032026213 | 0.09951002 | 1 | 13 | IGFBP1 |
| insulin-like growth factor binding (GO:0005520) | 0.034447714 | 0.103343143 | 1 | 14 | IGFBP1 |
| 5'-3' exonuclease activity (GO:0008409) | 0.036863279 | 0.106643205 | 1 | 15 | EXO1 |
| oxidoreductase activity, acting on the CH-CH group of donors, NAD or NADP as acceptor (GO:0016628) | 0.041676655 | 0.106643205 | 1 | 17 | AKR1C1 |
| arachidonic acid epoxygenase activity (GO:0008392) | 0.041676655 | 0.106643205 | 1 | 17 | CYP4F12 |
| arachidonic acid monooxygenase activity (GO:0008391) | 0.041676655 | 0.106643205 | 1 | 17 | CYP4F12 |
| retinol dehydrogenase activity (GO:0004745) | 0.041676655 | 0.106643205 | 1 | 17 | ADH4 |
| alcohol dehydrogenase (NADP+) activity (GO:0008106) | 0.04885255 | 0.118033817 | 1 | 20 | AKR1C1 |
| aldo-keto reductase (NADP) activity (GO:0004033) | 0.04885255 | 0.118033817 | 1 | 20 | AKR1C1 |

**Supplementary Table 3:** KEGG pathway enrichment from the 1349 genes based on the expression in brain related tissues associated in the GWAS analysis**.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Term** | **p-value** | **Adjusted p-value** | **Genes from 1349** **list** | **Total Genes** | **Genes** |
| Systemic lupus erythematosus | 8.071E-12 | 2.36479E-09 | 34 | 133 | *HIST1H2BM;C1S;HIST1H2BJ;HIST1H2BI;HIST2H4B;C7;**HIST1H3F;HIST1H2AD; HIST1H3G;HIST1H2AG;HIST1H3H;**HLA-DOA;HIST1H3B;HIST1H3D;HIST1H2AB;HIST1H3E;**HIST1H2AI;HIST1H2AH; ACTN1;HIST1H2AJ;ACTN4;HIST1H4A;**HIST2H3A;HIST1H4B;HIST4H4; HIST1H2BF;HIST1H2BE; HIST2H3D;HIST1H4D;HIST1H2BD;HIST1H4E;HLA-DRB1;**HIST1H2BC;HIST1H4F* |
| Focal adhesion | 2.6659E-11 | 3.9055E-09 | 42 | 199 | *ITGB1;GSK3B;LAMA5;TNXB;FLT1;LAMA2;SHC1;ITGB3;* *PXN;LAMC2;LAMC1; THBS2;EGFR;THBS4;IGF1R;CCND1;**AKT2;ERBB2;KDR; CAPN2;FLNB;FLNC;PDGFRB;PDGFRA;**VWF; LAMB2;ACTN1;LAMB4;FN1;ACTN4;IGF1;PARVB;VEGFA;**COL1A1;MYLPF; COL4A2;COL4A1;MYL2;COL6A2;COL4A3;**COL6A3;ITGA7* |
| ECM-receptor interaction | 4.6932E-10 | 4.58374E-08 | 24 | 82 | *ITGB1;LAMA5;TNXB;VWF;LAMA2;LAMB2;ITGB3;* *LAMB4;FN1;LAMC2;LAMC1; THBS2;HSPG2;THBS4;**COL1A1;COL4A2;COL4A1; COL6A2;COL4A3;DAG1;ITGA7;**COL6A3;CD36;AGRN* |
| Human papillomavirus infection | 3.167E-09 | 2.31985E-07 | 53 | 330 | *ITGB1;GSK3B;PATJ;IFNA7;ITGB3;LAMC2;CHD4;LAMC1;**RBPJ;IFNA8;CCND1; AKT2;CREB3L2;PDGFRB;VWF;TSC2;**TNFRSF1A;CCNE2; COL4A2;COL4A1; COL6A2;COL4A3; COL6A3;ITGA7;LLGL2;NOTCH3;LAMA5;TNXB;LAMA2;**NOTCH4;PXN;THBS2; PRKCZ;EGFR;THBS4;PPP2CB;HES1;**TCF7L1; FZD2;JAG1;FZD5;FZD4;LAMB2;LAMB4;FN1;**PPP2R3A;VEGFA;COL1A1;DLG3; APC;GNAS;KRAS;ATR* |
| Alcoholism | 1.1422E-08 | 6.69356E-07 | 35 | 180 | *HIST1H2BM;DDC;HIST1H2BJ;SHC1;HIST1H2BI;CAMKK2;**HIST2H4B; CREB3L2;HIST1H3F;HIST1H2AD;HIST1H3G;**HIST1H2AG;HIST1H3H; HIST1H3B;DRD2;HIST1H3D;**HIST1H2AB; HIST1H3E;HIST1H2AI; HIST1H2AH;HIST1H2AJ; HIST1H4A;HIST2H3A;HIST1H4B; HIST4H4;HIST1H2BF;**GNAS;HIST1H2BE;KRAS; HIST2H3D;HIST1H4D;HIST1H2BD;**HIST1H4E; HIST1H2BC;HIST1H4F* |
| Pathways in cancer | 2.1908E-08 | 1.06982E-06 | 71 | 530 | *ITGB1;GSK3B;IFNA7;IL5RA;LAMC2;LAMC1; BRCA2;IFNA8;GLI3;IGF1R;EDNRA; MECOM;CCND1;CDH1;AKT2;JAK3;PDGFRB; PDGFRA;**ARHGEF12;APAF1;IL15; DAPK2;MMP2;IL13; TGFBR2;ADCY9;COL4A2;CCNE2;MSH3;COL4A1;* *KIT;COL4A3;PPARG;IL6ST; NOTCH3;LAMA5;CTBP2;**LAMA2;CTBP1;EPAS1;NOTCH4;MGST3;LRP5; TGFA;STK4;**EGFR;LRP6;GNA11; TPR;ERBB2;CTNNA1;HES1;RXRG;**TCF7L1;FZD2;JAG1;SMAD3;FZD5; GADD45B;FZD4; LAMB2;LAMB4;FN1;IGF2;IGF1;EPOR;VEGFA;CXCL12;**APC;GNAS;KRAS* |
| PI3K-Akt signaling pathway | 9.2376E-08 | 3.86662E-06 | 52 | 354 | *ITGB1;GSK3B;IFNA7;FLT1;IRS1;ITGB3;LAMC2; LAMC1;**IFNA8;IGF1R;CCND1; AKT2;CREB3L2;KDR;JAK3;PDGFRB;**PDGFRA;VWF;TSC2;CCNE2;COL4A2; COL4A1;COL6A2;**KIT;COL4A3; COL6A3;ITGA7;LAMA5;TNXB;LAMA2;TGFA;* *FOXO3;THBS2;EGFR;THBS4; PPP2CB;ERBB2;PCK1;MCL1;ANGPT2;LAMB2;INSR;**LAMB4;IGF2;FN1;IGF1; PPP2R3A;EPOR;VEGFA;COL1A1;**PKN2;KRAS* |
| Cholesterol metabolism | 5.9868E-07 | 2.19268E-05 | 15 | 50 | *ABCA1;SCARB1;LRPAP1;LRP1;APOA2;APOC3;LRP2;NPC2;**APOH;LIPG; CD36;LDLRAP1;LPA;APOB;LDLR* |
| Tight junction | 9.7627E-06 | 0.000317831 | 28 | 170 | *ITGB1;PATJ;PRKAG2;F11R;PRKCZ;EPB41L4B;PPP2CB;**CCND1;ERBB2; MYH14;SYNPO;MPDZ;ACTN1;ACTN4;**MYH2;DLG3; CLDN9;MYL2;CLDN7;RAB13;MYH8;RAPGEF2;**NF2; EZR;MYH4;CFTR;LLGL2;TJP2*  |
| AMPK signaling pathway | 1.5463E-05 | 0.000453074 | 22 | 120 | *IRS1;INSR;ADIPOQ;TSC2;PRKAG2;IGF1;PPP2R3A;FOXO3;CPT1B;**ACACB; IGF1R;CAMKK2;PPP2CB;CCND1;AKT2;HNF4A;CREB3L2;**PPARG;CD36;PCK1; PPARGC1A;CFTR* |
| PPAR signaling pathway | 2.7079E-05 | 0.000721279 | 16 | 74 | *GK;ADIPOQ;APOA2;UCP1;NR1H3;APOC3;CPT1B;SCP2;**ACOX2;EHHADH; PPARG;ACSBG1;CD36;ACAA1;PCK1;RXRG* |
| Amoebiasis | 6.5888E-05 | 0.001608753 | 18 | 96 | *LAMA5;RAB5C;SERPINB13;LAMA2;IL1R1;LAMB2;ACTN1; LAMB4;FN1;LAMC2;LAMC1;ACTN4;COL1A1; COL4A2;COL4A1; GNA11;COL4A3; GNAS* |
| Adherens junction | 7.5485E-05 | 0.00170131 | 15 | 72 | *TCF7L1;SMAD3;ACTN1;INSR;PTPRM;ACTN4;BAIAP2; PTPRF;EGFR;IGF1R;TGFBR2;CDH1;ERBB2;CTNNA1;NECTIN3* |
| Viral carcinogenesis | 8.5655E-05 | 0.00179263 | 29 | 201 | *HIST1H2BM;SP100;HIST1H2BJ;HIST1H2BI;HPN;PXN;**CHD4;RBPJ;HIST2H4B; CCND1;CREB3L2;JAK3;GSN;ACTN1;**ACTN4;HIST1H4A;**HIST1H4B;CCNE2; HIST4H4;HIST1H2BF; HIST1H2BE;KRAS;LTBR;IL6ST;HIST1H4D;HIST1H4E;**HIST1H2BD; HIST1H4F; HIST1H2BC* |
| Insulin resistance | 0.00010269 | 0.001881295 | 19 | 108 | *MLXIP;GSK3B;IRS1;INSR;PRKAG2;NR1H3;PYGM;CPT1B;**PRKCZ;ACACB;PTPRF; TNFRSF1A;TBC1D4;AKT2;CREB3L2;CD36;SLC27A3;PCK1;**PPARGC1A* |
| Thyroid hormone synthesis | 0.00010494 | 0.001881295 | 15 | 74 | *HSPA5;GPX3;ITPR1;GPX7;ITPR3;LRP2;TTF1;ATP1B1; ADCY9;TG;CREB3L2;CANX;GNAS;SLC26A4;DUOX2* |
| Dilated cardiomyopathy (DCM) | 0.00010915 | 0.001881295 | 17 | 91 | *ITGB1;RYR2;LAMA2;ITGB3;TNNC1;TPM1;IGF1;TTN; ADCY9;MYL2;TNNT2;LMNA;DAG1;GNAS;ITGA7;**CACNA1S;MYH6* |
| Breast cancer | 0.00013204 | 0.002149267 | 23 | 147 | *NOTCH3;GSK3B;TCF7L1;FZD2;JAG1;FZD5; GADD45B;SHC1;FZD4;NOTCH4;LRP5; IGF1;BRCA2;EGFR;IGF1R;LRP6;CCND1;APC; AKT2;KIT;**ERBB2;HES1;KRAS* |
| Small cell lung cancer | 0.00014419 | 0.002223522 | 17 | 93 | *ITGB1;LAMA5;APAF1;LAMA2;GADD45B;LAMB2;LAMB4; FN1;LAMC2;LAMC1;CCND1;CCNE2;COL4A2; COL4A1;**AKT2;COL4A3;RXRG* |
| Hypertrophic cardiomyopathy (HCM) | 0.00015702 | 0.002300345 | 16 | 85 | *ITGB1;RYR2;LAMA2;ITGB3;TNNC1;TPM1;PRKAG2;IGF1; TTN;MYL2;TNNT2;LMNA;DAG1;ITGA7;CACNA1S;MYH6* |
| MAPK signaling pathway | 0.00019985 | 0.002788423 | 37 | 295 | *FLT1;TGFA;CACNA1A;STK4;EGFR;IGF1R;STK3;PPP3CC; MECOM;AKT2;ERBB2;KDR; FLNB;FLNC;CACNA1S;MAP3K6;MAP2K5;DUSP4;PDGFRB;PDGFRA; ANGPT2;GADD45B;IL1R1;INSR;PLA2G4B;IGF2; NFATC3;IGF1;VEGFA;TNFRSF1A; TGFBR2;JMJD7-PLA2G4B;KIT;TAOK2;NF1;RAPGEF2;KRAS* |
| Protein digestion and absorption | 0.00031166 | 0.004150776 | 16 | 90 | *COL18A1;COL14A1;ELN;KCNJ13;PRCP;ATP1B1;COL1A1; SLC7A8;COL4A2;COL5A1;COL4A1;COL6A2; COL5A3;COL4A3;COL5A2;COL6A3* |
| Endometrial cancer | 0.00041372 | 0.005270461 | 12 | 58 | *GSK3B;TCF7L1;CCND1;GADD45B;APC;CDH1;AKT2;ERBB2; CTNNA1;KRAS;FOXO3;EGFR* |
| Hippo signaling pathway | 0.00046752 | 0.005524396 | 23 | 160 | *GSK3B;PATJ;TCF7L1;SMAD3;FZD2;FZD5;FZD4;WWC1;* *BMP8A; PRKCZ;STK3;BMP5; TGFBR2;PPP2CB;CCND1;DLG3;**APC;CDH1;CTNNA1; FAT4;NF2;LLGL2;TEAD3* |
| Proteoglycans in cancer | 0.00047741 | 0.005524396 | 27 | 201 | *ITGB1;CD63;ITGB3;PXN;ITPR1;ITPR3;EGFR; IGF1R; CCND1;AKT2;ERBB2;KDR; FLNB;FLNC;FZD2;ARHGEF12;**FZD5;FZD4; MMP2; IGF2;FN1;ANK3;IGF1;HSPG2;* *VEGFA;KRAS;EZR* |
| Mineral absorption | 0.00049022 | 0.005524396 | 11 | 51 | *MT2A;TF;VDR;MT1M;MT1G;CYBRD1;MT1X;MT1H;**ATP1B1;SLC39A4;FTL* |
| Adipocytokine signaling pathway | 0.00062715 | 0.006805764 | 13 | 69 | *IRS1;ADIPOQ;PRKAG2;CPT1B;ACACB;TNFRSF1A; CAMKK2;AKT2;ACSBG1;CD36; PCK1;RXRG;PPARGC1A* |
| Prostate cancer | 0.0007383 | 0.007601937 | 16 | 97 | *PDGFRB;PDGFRA;GSK3B;TCF7L1;TGFA;IGF1;EGFR; IGF1R;ZEB1;CCND1;SPINT1;CCNE2;AKT2;CREB3L2;**ERBB2;KRAS* |
| Transcriptional misregulation in cancer | 0.00075241 | 0.007601937 | 25 | 186 | *FLT1;MLLT3;AFF1;IGF1R;HHEX;HIST1H3F;HIST1H3G;**HIST1H3H; HIST1H3B;RXRG;HIST1H3D;SSX1;HIST1H3E;**TAF15;GADD45B; PBX3;IGF1;TGFBR2;MAF;HIST2H3A;ZEB1;**SPINT1;BMP2K;PPARG;HIST2H3D* |
| Insulin signaling pathway | 0.00087481 | 0.008543939 | 20 | 137 | *GSK3B;IRS1;SHC1;INSR;TSC2;PRKAG2;PYGM;PHKA2;PRKCZ; ACACB;PTPRF;HK1;SOCS1;PRKAR1B;AKT2; PHKG2;FLOT1;KRAS;PCK1;PPARGC1A* |
| Gastric cancer | 0.00104697 | 0.009895575 | 21 | 149 | *GSK3B;TCF7L1;SMAD3;FZD2;FZD5;GADD45B;SHC1;FZD4;LRP5; EGFR;TGFBR2;LRP6;CCND1;CCNE2;APC;CDH1; AKT2;ERBB2;CTNNA1;KRAS;RXRG* |

**Supplementary Material 1:** Migraine data collection sheet

Patient ID:

Age:

Marital status

Menstrual history: Menarche: Duration of the period: regularity:

Use of oral contraceptives: Yes No

Migraine history:

Onset of the disease:

Type of migraine:

1. With aura
2. Without aura

Frequency of the headache:

Number of attacks per month:

1. 1
2. 2
3. 4
4. 8
5. 16
6. 28

Duration of the attack:

1. 4 hours
2. 8hours
3. 12 hours
4. 24 hours
5. 48 hours
6. 72 hours
7. >72 hours

Severity of the attack:



Use of medications:

1. No medication
2. Pain killer only
3. Prophylactic treatment only
4. Both pain killer and prophylactic.

Associated symptoms:

1. Nausea
2. Vomiting
3. Visual (blurring of vision, tunnel vision, streaks, flash light)
4. Auditory
5. Cutaneous.

Triggering factors:

1. Stress
2. Sleep disturbances
3. Weather changes
4. Skipped meal
5. Certain type of food
6. Coffee
7. Bright lights
8. Excessive noise
9. Strong smell
10. Physical exertion