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

Lubna Al Asoom1, Johra Khan2,3\*, Ahmad Al Sunni1, Nazish Rafique1, Rabia Latif1, Majed Alabdali4, Azhar Alhariri5, Majed Aloqaily5**,** Sayed AbdulAzeez5, J. Francis Borgio5,6\*

1Department of Physiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, 31541, Saudi Arabia.

2Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Majmaah, 11952, Saudi Arabia.

3Health and Basic Sciences Research Center, Majmaah University, Majmaah, 11952, Saudi Arabia.

4Department of Neurology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, 31952, Saudi Arabia.

5Department of Genetic Research, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam 31441, Saudi Arabia.

6Department of Epidemic Diseases Research, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, Dammam 31441, Saudi Arabia.

**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:

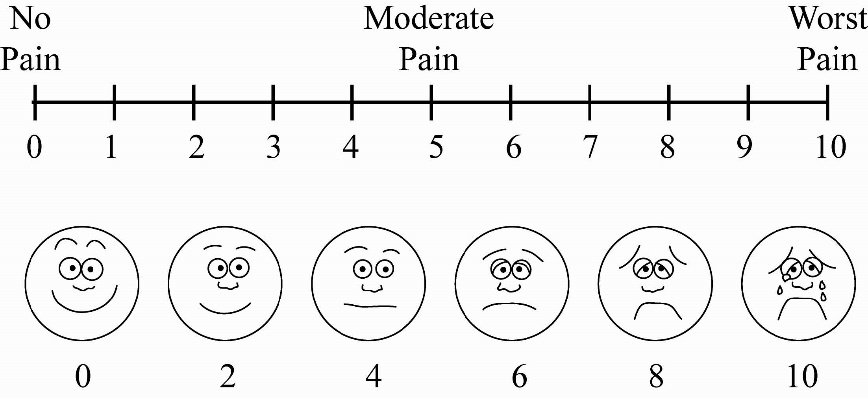
Number of attacks per month:

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