**Table 1. The risk allele frequencies of investigated SNPs.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| SNPs |  | Risk Allele |  | Risk Allele Frequency | | |
|  |  | Taiwanese Migraineurs1 |  | Global2 |
| *TRPM8* rs10166942 |  | T |  | 0.39 |  | 0.63 |
| *LRP1* rs1172113 |  | T |  | 0.78 |  | 0.66 |
| *DLG2* rs655484 |  | C |  | 0.95 |  | 0.99 |
| *GFRA1* rs3781545 |  | G |  | 0.87 |  | 0.87 |
| *GPR39* rs10803531 |  | C |  | 0.97 |  | 0.20 |
| *UPP2* rs7565931 |  | C |  | 0.23 |  | 0.19 |

1 Chen et al., Genome-wide association study identifies novel susceptibility loci for migraine in Han Chinese resided in Taiwan. *Cephalalgia*, 2018; 38(**3**), 466–475.

2 Adapted from gnomAD database v2.1.1

**Table 2a. Migraine endophenotypes and *LRP1* rs1172113 genotyping**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **C/C**  n=51 | **C/T or T/C**  n=368 | **T/T**  n=658 |  | *p value* |
| Age | 37.4 ± 11.3 | 37.4 ± 12.9 | 38.2 ± 12.5 |  | 0.618 |
| Female sex | 43 (84.3) | 289 (78.5) | 495 (75.2) |  | 0.207 |
| Presence of aura | 7 (13.7) | 64 (17.4) | 109 (16.6) |  | 0.795 |
| Chronic migraine | 21 (41.2) | 103 (28.0) | 208 (31.6) |  | 0.126 |
| Unilaterality | 32 (62.7) | 283 (76.9) | 501 (76.1) |  | 0.081 |
| Pulsatility | 37 (72.5) | 267 (73.8) | 487 (75.0) |  | 0.858 |
| Aggravation by or avoidance of physical activity | 46 (93.9) | 317 (87.8) | 582 (89.8) |  | 0.351 |
| Nausea | 46 (90.2) | 316 (87.1) | 577 (88.6) |  | 0.681 |
| Vomiting | 21 (41.2) | 156 (43.0) | 305 (46.9) |  | 0.412 |
| Photophobia | 24 (47.1) | 174 (47.9) | 332 (51.1) |  | 0.582 |
| Phonophobia | 40 (78.4) | 273 (75.2) | 488 (75.0) |  | 0.858 |

Data were presented as n (%) or mean ± SD. T/T: TT homozygous group; T/C: TC or CT heterozygous group; C/C: CC homozygous group; significant level set at 0.05/11=0.005 after Bonferroni corrections for multiple comparisons.

**Table 2b. Migraine endophenotypes and *DLG2* rs655484 genotyping**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Discovery cohort (N=1077) | | |  | Replication cohort (N=824) | | |  | Combined |
|  | C/T or T/C  n= 50 (4.6%) | C/C  n= 1027 (95.4%) | *p* value |  | C/T or T/C  n=146 (17.7%) | C/C  n=678 (82.3%) | *p* value |  | *p* value |
| Age | 43.5 ± 14.9 | 37.6 ± 12.4 | 0.001 |  | 38.4 ± 12.5 | 36.7 ± 11.4 | 0.120 |  | 0.008 |
| Female sex | 39 (78.0) | 788 (76.7) | 0.835 |  | 119 (81.5) | 531 (78.3) | 0.392 |  | 0.300 |
| Presence of aura | 7 (14.0) | 173 (16.8) | 0.598 |  | 24 (16.4) | 136 (20.1) | 0.316 |  | 0.425 |
| Chronic migraine | 23 (46.0) | 309 (30.1) | 0.017 |  | 44 (30.1) | 207 (30.5) | 0.925 |  | 0.260 |
| Unilaterality | 39 (78.0) | 777 (75.7) | 0.706 |  | 124 (84.9) | 554 (81.7) | 0.355 |  | 0.099 |
| Pulsatility | 38 (76.0) | 753 (74.4) | 0.801 |  | 120 (82.2) | 520 (76.7) | 0.148 |  | 0.102 |
| Aggravation by or avoidance of physical activity | 42 (84.0) | 903 (89.6) | 0.212 |  | 127 (87.0) | 588 (86.7) | 0.933 |  | 0.364 |
| Nausea | 44 (88.0) | 895 (88.2) | 0.970 |  | 131 (89.7) | 608 (89.7) | 0.985 |  | 0.831 |
| Vomiting | 18 (36.0) | 464 (45.7) | 0.178 |  | 74 (50.7) | 352 (51.9) | 0.787 |  | 0.738 |
| Photophobia | 24 (48.0) | 506 (49.9) | 0.793 |  | 71 (48.6) | 332 (49.0) | 0.941 |  | 0.779 |
| Phonophobia | 32 (64.0) | 769 (75.8) | 0.060 |  | 104 (71.2) | 486 (71.7) | 0.913 |  | 0.154 |

Data were presented as n (%) or mean ± SD. T/C: TC or CT heterozygous group; C/C: CC homozygous group; significant level set at 0.05/11=0.005 after Bonferroni corrections for multiple comparisons. Note: no T/T homozygous participant was identified.

**Table 2c. Migraine endophenotypes and *GFRA1* rs3781545 genotyping**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Discovery cohort (N=1077) | | |  |  | Replication cohort (N=667) | | |  | Combined |
|  | AA  n= 33  (3.1%) | G/A or A/G  n= 289  (26.8%) | G/G  n= 755  (70.1%) | *p* value |  | AA  n= 33  (4.9%) | G/A or A/G  n= 111  (16.6%) | G/G  n= 523  (78.4%) | *p* value |  | *p* value |
| Age | 37.5 ± 10.9 | 38.3 ± 12.5 | 37.7 ± 12.7 | 0.809 |  | 35.8 ± 11.7 | 36.9 ± 11.8 | 36.5 ± 11.4 | 0.873 |  | 0.556 |
| Female sex | 27 (81.8) | 224 (77.5) | 576 (76.3) | 0.720 |  | 24 (72.7) | 89 (80.2) | 411 (78.6) | 0.657 |  | 0.913 |
| Presence of aura | 4 (12.1) | 53 (18.3) | 123 (16.3) | 0.564 |  | 5 (15.2) | 30 (27.0) | 98 (18.7) | 0.109 |  | 0.188 |
| Chronic migraine | 14 (42.4) | 74 (25.6) | 244 (32.3) | 0.038 |  | 10 (30.3) | 34 (30.6) | 162 (31.0) | 0.995 |  | 0.121 |
| Unilaterality | 23 (69.7) | 213 (73.7) | 580 (76.8) | 0.409 |  | 29 (87.9) | 95 (85.6) | 423 (80.9) | 0.335 |  | 0.815 |
| Pulsatility | 22 (66.7) | 221 (77.0) | 548 (73.9) | 0.337 |  | 24 (72.7) | 87 (78.4) | 404 (77.2) | 0.793 |  | 0.366 |
| Aggravation by or avoidance of physical activity | 30 (90.9) | 268 (93.1) | 647 (87.8) | 0.047 |  | 29 (87.9) | 97 (87.4) | 457 (87.4) | 0.996 |  | 0.105 |
| Nausea | 30 (90.9) | 259 (89.9) | 650 (87.4) | 0.460 |  | 30 (90.9) | 99 (89.2) | 472 (90.2) | 0.932 |  | 0.706 |
| Vomiting | 16 (48.5) | 138 (47.9) | 328 (44.1) | 0.503 |  | 20 (60.6) | 48 (43.2) | 275 (52.6) | 0.113 |  | 0.489 |
| Photophobia | 15 (45.5) | 165 (57.3) | 350 (47.1) | 0.012 |  | 12 (36.4) | 53 (47.7) | 261 (49.9) | 0.310 |  | 0.031 |
| Phonophobia | 26 (78.8) | 226 (78.5) | 549 (73.8) | 0.263 |  | 27 (81.8) | 81 (73.0) | 374 (71.5) | 0.432 |  | 0.133 |

Data were presented as n (%) or mean ± SD. T/C: TC or CT heterozygous group; C/C: CC homozygous group; significant level set at 0.05/11=0.005 after Bonferroni corrections for multiple comparisons.

**Table 2d. Migraine endophenotypes and *UPP2* rs7565931 genotyping**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **C/C**  n=51 | **C/G or G/C**  n=360 | **G/G**  n=666 | *p value* |
| Age | 37.7 ± 12.9 | 37.3 ± 12.7 | 38.2 ± 12.5 | 0.560 |
| Female sex | 38 (74.5) | 266 (73.9) | 523 (78.5) | 0.226 |
| Presence of aura | 8 (15.7) | 60 (16.7) | 112 (16.8) | 0.978 |
| Chronic migraine | 19 (37.3) | 102 (28.3) | 211 (31.7) | 0.322 |
| Unilaterality | 38 (74.5) | 271 (75.3) | 507 (76.1) | 0.934 |
| Pulsatility | 40 (78.4) | 258 (72.9) | 493 (75.0) | 0.606 |
| Aggravation by or avoidance of physical activity | 43 (84.3) | 323 (91.8) | 579 (88.4) | 0.127 |
| Nausea | 46 (90.2) | 311 (87.6) | 582 (88.3) | 0.851 |
| Vomiting | 21 (41.2) | 176 (49.6) | 285 (43.2) | 0.129 |
| Photophobia | 25 (49.0) | 181 (51.0) | 324 (49.2) | 0.863 |
| Phonophobia | 42 (82.4) | 270 (76.1) | 489 (74.2) | 0.389 |

Data were presented as n (%) or mean ± SD. C/C: CC homozygous group; G/C: GC or CG heterozygous group; G/G: GG homozygous group; significant level set at 0.05/11=0.005 after Bonferroni corrections for multiple comparisons.

**Table 2e. Migraine endophenotypes and *GPR39* rs10803531 genotyping**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **C/A or C/A**  n=79 | **CC**  n=998 | *p value* |
| Age | 39.9 ± 11.6 | 37.7 ± 12.7 | 0.134 |
| Female sex | 56 (70.9) | 771 (77.3) | 0.197 |
| Presence of aura | 13 (16.5) | 167 (16.7) | 0.949 |
| Chronic migraine | 31 (39.2) | 301 (30.2) | 0.092 |
| Unilaterality | 55 (69.6) | 761 (76.3) | 0.185 |
| Pulsatility | 53 (68.8) | 738 (74.9) | 0.238 |
| Aggravation by or avoidance of physical activity | 74 (96.1) | 871 (88.8) | 0.045 |
| Nausea | 66 (85.7) | 873 (88.4) | 0.489 |
| Vomiting | 30 (39.0) | 452 (45.7) | 0.249 |
| Photophobia | 38 (49.4) | 492 (49.8) | 0.933 |
| Phonophobia | 62 (80.5) | 739 (74.8) | 0.263 |

Data were presented as n (%) or mean ± SD. C/A or A/C: CA or AC heterozygous group; C/C: CC homozygous group; significant level set at 0.05/11=0.005 after Bonferroni corrections for multiple comparisons.

**Table 3. Allodynia symptoms during migraine attacks**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Total |  | *TRPM8 rs10166942* | | | | |
|  |  |  | T/T or T/C |  | C/C |  | *p* value |
| Combing your hair |  | 131 (15.8) |  | 87 (17.6) |  | 44 (13.3) |  | 0.095 |
| Pulling your hair back |  | 271 (32.8) |  | 171 (34.5) |  | 100 (30.1) |  | 0.184 |
| Shaving your face |  | 20 (2.4) |  | 16 (3.2) |  | 4 (1.2) |  | 0.063 |
| Wearing eyeglasses |  | 223 (27.0) |  | 148 (29.9) |  | 75 (22.6) |  | **0.020\*** |
| Wearing contact lenses |  | 183 (22.0) |  | 125 (25.3) |  | 58 (17.5) |  | **0.008\*\*** |
| Wearing earrings |  | 80 (9.7) |  | 60 (12.1) |  | 20 (6.0) |  | **0.004\*** |
| Wearing necklaces |  | 80 (9.7) |  | 62 (12.5) |  | 18 (5.4) |  | **0.001\*\*** |
| Wearing anything on head or neck |  | 222 (26.8) |  | 140 (28.3) |  | 82 (24.7) |  | 0.254 |
| Wearing anything on forearm or wrist |  | 115 (13.9) |  | 86 (17.4) |  | 29 (8.7) |  | **<0.001\*\*** |
| Wearing a ring |  | 75 (9.1) |  | 56 (11.3) |  | 19 (5.7) |  | **0.006\*\*** |
| Wearing watch |  | 106 (12.8) |  | 70 (14.1) |  | 36 (10.8) |  | 0.164 |
| Wearing tight clothes |  | 306 (37.0) |  | 192 (38.8) |  | 114 (34.3) |  | 0.194 |
| Put on heavy quilt |  | 134 (16.2) |  | 88 (17.8) |  | 46 (13.9) |  | 0.133 |
| When shower water hits your face |  | 110 (13.3) |  | 77 (15.6) |  | 33 (9.9) |  | **0.020\*** |
| Resting your face on the pillow on the side of the headache |  | 221 (26.7) |  | 132 (26.7) |  | 89 (26.8) |  | 0.964 |
| Exposure to heat (e.g. cooking) |  | 203 (24.5) |  | 140 (28.3) |  | 63 (19.0) |  | **0.002\*\*** |
| Breathing through your nose on a cold day |  | 129 (15.6) |  | 88 (17.8) |  | 41 (12.3) |  | **0.035\*** |

Data were presented as n (%) or mean ± SD as indicated. \**p* < 0.05; \*\**p* < 0.01; because of high collinearity for items listed in the allodynia questionnaire, we did not perform corrections for multiple comparisons to avoid type II error.