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|  |  |  |  |
| --- | --- | --- | --- |
| Supplementary Table 1. Population and design of each contributed study | | | |
| Cancer | Study | Locations | Design |
| Initial analytical data in GAME-ON | | | |
| Colon & Rectum | MECC | US | Cohort |
| (CORECT) | CFR | US | Cohort |
|  | Kentucky | US | Pop. CC |
|  | CPS-II/ACS | US | Cohort |
|  | Melbourne | Australia | Cohort |
|  | Newfoundland | Canada | Pop. CC |
|  |  |  |  |
| Lung | MDACC | US | Hospital CC |
| (TRICL) | ICR | UK | Hospital CC |
|  | Toronto | Canada | Clinic CC |
|  | IARC | Europe | Hospital CC |
|  | GLC | German | Pop. CC |
|  | NCI | US | Pop. CC and nested CC |
|  |  |  |  |
| Ovary | UKGWAS | UK | CC |
| (FOCI) | USGWAS | US, Canada, Poland | CC |
|  | U19 | US | CC |
|  |  |  |  |
| Prostate | BPC3 | US | CC, nested CC |
| (ELLIPSE) | CRUK1 | UK | CC |
|  | CRUK2 | UK | CC |
|  | CAPS1 | Sweden | CC |
|  | CAPS2 | Sweden | CC |
|  |  |  |  |
| Replication data |  |  |  |
| Prostate (PLCO) | PLCO | US | Nested CC |
|  |  |  |  |
| Colon & Rectum |  |  |  |
| (GECCO) | ASTERISK | France | Hospital CC |
|  | COLO23 | US | Pop. CC |
|  | DACHS1 | Germany | Pop. CC |
|  | DACHS2 | Germany | Pop. CC |
|  | DALS1 | US | Pop. CC |
|  | DALS2 | US | Pop. CC |
|  | HPFS1 | US | Nested CC |
|  | HPFS2 | US | Nested CC |
|  | HPFSad | US | Nested CC |
|  | MEC | US | Nested CC |
|  | NHS1 | US | Nested CC |
|  | NHS2 | US | Nested CC |
|  | NHSad | US | Nested CC |
|  | OFCCR | Canada | Pop.CC |
|  | PHS1P2 | US | Nested CC |
|  | PLCO1 | US | Nested CC |
|  | PLCO2 | US | Nested CC |
|  | PMH | US | Pop. CC |
|  | VITAL | US | Nested CC |
|  | WHI1 | US | Nested CC |
|  | WHI2 | US | Nested CC |

CC: case-control

Supplementary table 2. Gene- and pathway-based p-values for overall and aggressive prostate cancer

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Combined results | |  | Aggressive prostate | |
|  |  | (14818 cases, 14227 controls) | |  | (up to 4446 cases, 12724 controls) | |
| Gene | Chr | N.SNPs | P-value |  | N.SNPs | P-value |
| Circadian rhythm pathway | | |  |  |  |  |
| ARNTL | 11 | 80 | 0.29 |  | 80 | 0.54 |
| CK1E | 22 | 48 | 0.30 |  | 48 | 0.58 |
| CLOCK | 4 | 24 | **0.021** |  | 24 | 0.093 |
| CRYI | 12 | 35 | 0.55 |  | 35 | 0.87 |
| CRY2 | 11 | 20 | **0.043** |  | 20 | 0.57 |
| NPAS2 | 2 | 167 | **0.0062** |  | 167 | 0.18 |
| PER1 | 17 | 30 | 0.063 |  | 30 | 0.70 |
| PER2 | 2 | 50 | 0.060 |  | 50 | 0.23 |
| PER3 | 1 | 67 | 0.24 |  | 67 | **0.030** |
| Pathway-level | | 521 | **0.0016\*** |  | 521 | 0.29 |
|  |  |  |  |  |  |  |
| Melanotin pathway | |  |  |  |  |  |
| AANAT | 17 | 38 | **0.00078\*** |  | 38 | 0.47 |
| DDC | 7 | 84 | **0.050** |  | 84 | 0.49 |
| MTNR1A | 4 | 35 | 0.35 |  | 35 | 0.22 |
| MTNR1B | 11 | 23 | 0.96 |  | 23 | 0.32 |
| TPH1 | 11 | 18 | 0.15 |  | 18 | 0.96 |
| TPH2 | 12 | 65 | 0.21 |  | 65 | 0.35 |
| Pathway-level | | 263 | **0.0060\*** |  | 263 | 0.66 |

\*Statistically significant after Bonferroni correction (p < 0.05/8=0.00625 at pathway level; p < 0.05/60=0.00083 at gene level)

P<0.05 in bold

Supplementary Table 3. Comparison of SNP-based results between overall and aggressive prostate cancer\*

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Allele | | Overall | | | Aggressive | | | | |
| Gene | SNP\* | Ref\*\* | Eff\*\* | log(OR) | SE | P-value | | log(OR) | SE | | P-value |
| Circadian rhythm pathway | | | | | | | | | |
| CLOCK | rs62309758 | T | C | -0.09 | 0.03 | 1.45E-03 | | -0.09 | 0.04 | | 7.57E-03 |
| CRY2 | rs7108730 | T | C | 0.08 | 0.03 | 3.66E-03 | | 0.06 | 0.04 | | 1.05E-01 |
| NPAS2 | rs2305160 | A | G | 0.08 | 0.02 | 3.47E-05 | | 0.06 | 0.03 | | 3.00E-02 |
| Melatonin pathway | | | | | | | | | |
| AANAT | rs150316415 | G | A | 0.28 | 0.07 | 3.41E-05 | | 0.16 | 0.08 | | 6.49E-02 |
| DDC | rs12718611 | G | A | -0.11 | 0.04 | 1.72E-03 | | -0.07 | 0.05 | | 1.12E-01 |

\*SNPs with the smallest p-value in the genes with Pgene≤0.05, based on association with overall prostate cancer.

\*\*reference and effect alleles

Supplementary table 4. Gene- and pathway-based p-values for colorectal cancer in GAME-ON and replication samples

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Game-ON (CORECT) | |  | GECCO |  |  | Combined results | |
|  |  | (5100 cases, 4831 controls) | |  | (10738 cases, 13328 controls) | |  | (15838 cases, 18159 controls) | |
| Gene | Chr | N.SNPs | P-value |  | N.SNPs | P-value |  | N.SNPs | P-value |
| Circadian rhythm pathway | | |  |  |  |  |  |  |  |
| ARNTL | 11 | 114 | **0.0044** |  | 113 | 0.78 |  | 140 | **0.028** |
| CK1E | 22 | 38 | 0.14 |  | 55 | 0.18 |  | 68 | 0.24 |
| CLOCK | 4 | 47 | 0.18 |  | 35 | 0.34 |  | 53 | 0.11 |
| CRYI | 12 | 56 | 0.81 |  | 47 | 0.83 |  | 73 | 0.95 |
| CRY2 | 11 | 35 | 0.64 |  | 32 | 0.85 |  | 41 | 0.91 |
| NPAS2 | 2 | 202 | **0.011** |  | 212 | 0.82 |  | 245 | 0.51 |
| PER1 | 17 | 47 | 0.60 |  | 38 | 0.44 |  | 53 | 0.55 |
| PER2 | 2 | 54 | 0.63 |  | 54 | 0.40 |  | 68 | 0.59 |
| PER3 | 1 | 60 | 0.68 |  | 84 | 0.15 |  | 101 | **0.047** |
| Pathway-level |  | 653 | **0.021** |  | 670 | 0.76 |  | 842 | 0.17 |
|  |  |  |  |  |  |  |  |  |  |
| Melatonin pathway | |  |  |  |  |  |  |  |  |
| AANAT | 17 | 53 | 0.59 |  | 52 | 0.85 |  | 61 | 0.91 |
| DDC | 7 | 119 | 0.89 |  | 115 | 0.58 |  | 147 | 0.74 |
| MTNR1A | 4 | 60 | 0.18 |  | 61 | 0.86 |  | 72 | 0.30 |
| MTNR1B | 11 | 33 | 0.92 |  | 34 | 0.87 |  | 45 | 0.96 |
| TPH1 | 11 | 20 | **0.029** |  | 22 | 0.27 |  | 27 | 0.068 |
| TPH2 | 12 | 67 | 0.77 |  | 92 | **0.0064** |  | 107 | **0.013** |
| Pathway-level | | 352 | 0.24 |  | 376 | 0.066 |  | 459 | 0.091 |

P<0.05 in bold. None of gene based or pathway based p values reached Bonferroni corrected significance

Supplementary table 5. Gene- and pathway-based p-values for lung and ovarian cancers in GAME-ON

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Lung cancer  (12537 cases, 17285 controls) | |  | Ovarian cancer  (4369 cases, 9123 controls) | |
| Gene | Chr |  | N.SNP\* | P-value |  | N.SNP\* | P-value |
| Circadian rhythm pathway | | | | | | | |
| ARNTL | 11 |  | 78 | 0.18 |  | 80 | 0.58 |
| CK1E | 22 |  | 47 | 0.35 |  | 48 | **0.024** |
| CLOCK | 4 |  | 24 | 0.19 |  | 24 | 0.20 |
| CRYI | 12 |  | 33 | 0.40 |  | 35 | 0.29 |
| CRY2 | 11 |  | 18 | 0.52 |  | 20 | 0.13 |
| NPAS2 | 2 |  | 165 | 0.56 |  | 167 | **0.046** |
| PER1 | 17 |  | 29 | 0.35 |  | 30 | 0.87 |
| PER2 | 2 |  | 50 | 0.87 |  | 50 | 0.54 |
| PER3 | 1 |  | 66 | 0.90 |  | 67 | 0.68 |
| Pathway-level | |  | 510 | 0.71 |  | 521 | 0.14 |
| Melatonin pathway | |  |  |  |  |  |  |
| AANAT | 17 |  | 30 | 0.63 |  | 38 | 0.14 |
| DDC | 7 |  | 82 | 0.089 |  | 84 | 0.10 |
| MTNR1A | 4 |  | 35 | 0.93 |  | 35 | 0.20 |
| MTNR1B | 11 |  | 21 | 0.85 |  | 23 | 0.64 |
| TPH1 | 11 |  | 17 | 0.23 |  | 18 | 0.21 |
| TPH2 | 12 |  | 58 | **0.048** |  | 65 | 0.75 |
| Pathway-level | |  | 243 | 0.22 |  | 263 | 0.26 |

\*SNP numbers after the LD pruning, using r2>0.95

P<0.05 in bold. None of gene- or pathway-level p-values reached the Bonferroni correction threshold of significance.