

# Novel Methylation Patterns Predict Outcome in Uveal Melanoma

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**Table S1.** Differentially methylated genes in the Pathways in Cancer KEGG pathway with a log FC  $\geq 1.5$ .

| ID    | Gene Name                                                | Species      | Differentially Methylated Probes | Log Fold Change (High vs Low Risk) | Adjusted P Value | Average Beta Value, Low | Average Beta Value, High |
|-------|----------------------------------------------------------|--------------|----------------------------------|------------------------------------|------------------|-------------------------|--------------------------|
| ABL1  | ABL proto-oncogene 1, non-receptor tyrosine kinase(ABL1) | Homo sapiens | cg13440206,                      | −1.85238                           | 1.39E−06         | 0.576589                | 0.259088                 |
|       |                                                          |              | cg02915920                       | −1.84042                           | 8.03E−06         | 0.482846                | 0.192714                 |
|       |                                                          |              | cg21195763                       | 1.685721                           | 3.13E−19         | 0.573548                | 0.83358                  |
| ADCY2 | adenylate cyclase 2(ADCY2)                               | Homo sapiens | cg14116052                       | 2.454448                           | 4.3E−24          | 0.513149                | 0.885217                 |
| ADCY6 | adenylate cyclase 6(ADCY6)                               | Homo sapiens | cg25196508                       | 3.480923                           | 2.9E−25          | 0.188362                | 0.792499                 |
| AKT1  | AKT serine/threonine kinase 1(AKT1)                      | Homo sapiens | cg14116052                       | 2.454448                           | 4.3E−24          | 0.513149                | 0.885217                 |
| BMP4  | bone morphogenetic protein 4(BMP4)                       | Homo sapiens | cg08046044                       | 1.527233                           | 3.98E−06         | 0.049923                | 0.209543                 |
|       |                                                          |              | cg01873886                       | 1.789942                           | 2.55E−05         | 0.026254                | 0.1723                   |

|               |                                                     |              |            |          |          |          |          |
|---------------|-----------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>CDKN1B</b> | cyclin dependent kinase inhibitor<br>1B(CDKN1B)     | Homo sapiens | cg06197769 | 3.78761  | 1.9E-30  | 0.187364 | 0.82662  |
| <b>CTNNA3</b> | catenin alpha 3(CTNNA3)                             | Homo sapiens | cg09538287 | 2.037243 | 5.62E-09 | 0.251955 | 0.539339 |
| <b>DAPK3</b>  | death associated protein kinase<br>3(DAPK3)         | Homo sapiens | cg22304239 | 1.939735 | 1.18E-13 |          |          |
| <b>EDNRB</b>  | endothelin receptor type<br>B(EDNRB)                | Homo sapiens | cg18210860 | 2.815506 | 1.87E-14 | 0.444524 | 0.810551 |
|               |                                                     |              | cg24785726 | 3.163564 | 2.54E-15 | 0.080629 | 0.539854 |
|               |                                                     |              | cg23326536 | 3.195834 | 6.45E-17 | 0.071876 | 0.541248 |
|               |                                                     |              | cg13866767 | 3.463542 | 1.49E-19 | 0.28389  | 0.815008 |
| <b>EPAS1</b>  | endothelial PAS domain protein<br>1(EPAS1)          | Homo sapiens | cg21276379 | 1.824026 | 5.68E-14 | 0.186755 | 0.437118 |
|               |                                                     |              | cg17091312 | 2.112437 | 2.76E-23 |          |          |
| <b>ETS1</b>   | ETS proto-oncogene 1,<br>transcription factor(ETS1) | Homo sapiens | cg25244476 | 2.507626 | 9.92E-07 | 0.25583  | 0.602367 |
| <b>FGF1</b>   | fibroblast growth factor 1(FGF1)                    | Homo sapiens | cg15371881 | 3.061708 | 4.38E-25 | 0.219393 | 0.69523  |
| <b>FZD6</b>   | frizzled class receptor 6(FZD6)                     | Homo sapiens | cg10929921 | 3.957203 | 3.22E-19 | 0.333365 | 0.912152 |
| <b>GNA11</b>  | G protein subunit alpha<br>11(GNA11)                | Homo sapiens | cg02261780 | 2.268738 | 2.51E-16 | 0.353174 | 0.732472 |
|               |                                                     |              | cg24366168 | 2.349167 | 6.69E-12 | 0.43427  | 0.894937 |
|               |                                                     |              | cg00168191 | 2.478771 | 1.2E-11  | 0.510916 | 0.876102 |
|               |                                                     |              | cg13527233 | 2.144414 | 1.19E-11 | 0.540858 | 0.863307 |
| <b>GNAI1</b>  | G protein subunit alpha i1(GNAI1)                   | Homo sapiens | cg05424060 | 1.904542 | 2.69E-07 |          |          |
| <b>GNB4</b>   | G protein subunit beta 4(GNB4)                      | Homo sapiens | cg01750654 | 1.647758 | 4.02E-11 | 0.594913 | 0.827501 |
|               |                                                     |              | cg03466124 | 1.862402 | 3.31E-08 | 0.108087 | 0.324521 |

|               |                                                           |              |            |          |          |          |          |
|---------------|-----------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>GNG11</b>  | G protein subunit gamma<br>11(GNG11)                      | Homo sapiens | cg06439941 | 2.094159 | 1.67E-09 | 0.218242 | 0.565099 |
|               |                                                           |              | cg08038054 | 2.335425 | 3.13E-11 | 0.069817 | 0.348166 |
|               |                                                           |              | cg02914800 | 3.14371  | 1.04E-14 | 0.10902  | 0.602134 |
| <b>GSTP1</b>  | glutathione S-transferase pi<br>1(GSTP1)                  | Homo sapiens | cg22224704 | 2.261199 | 1.11E-08 | 0.19543  | 0.520111 |
|               |                                                           |              | cg11566244 | 3.087685 | 6.52E-12 | 0.134838 | 0.555003 |
| <b>IGF1R</b>  | insulin like growth factor 1<br>receptor(IGF1R)           | Homo sapiens | cg11852333 | 1.967845 | 3.57E-14 | 0.258781 | 0.568105 |
| <b>ITGA3</b>  | integrin subunit alpha 3(ITGA3)                           | Homo sapiens | cg12127162 | 1.833962 | 2.92E-16 | 0.254277 | 0.538208 |
| <b>ITGAV</b>  | integrin subunit alpha V(ITGAV)                           | Homo sapiens | cg03192874 | 2.961775 | 2.21E-15 |          |          |
| <b>KRAS</b>   | KRAS proto-oncogene,<br>GTPase(KRAS)                      | Homo sapiens | cg23152216 | 2.293392 | 5.96E-27 | 0.470784 | 0.837552 |
| <b>LPAR6</b>  | lysophosphatidic acid receptor<br>6(LPAR6)                | Homo sapiens | cg03646329 | 2.221789 | 8.4E-09  | 0.105173 | 0.345011 |
| <b>MAPK8</b>  | mitogen-activated protein kinase<br>8(MAPK8)              | Homo sapiens | cg19612574 | 1.694113 | 4.14E-15 | 0.113088 | 0.332177 |
| <b>MAPK9</b>  | mitogen-activated protein kinase<br>9(MAPK9)              | Homo sapiens | cg09663237 | 2.203989 | 3.06E-06 | 0.584195 | 0.883176 |
| <b>MMP2</b>   | matrix metalloproteinase 2(MMP2)                          | Homo sapiens | cg00355286 | 1.518071 | 7.31E-10 | 0.183672 | 0.439098 |
| <b>PDGFRA</b> | platelet derived growth factor<br>receptor alpha(PDGFRA)  | Homo sapiens | cg02273436 | 1.911305 | 1.17E-06 | 0.160494 | 0.467324 |
| <b>PIK3R1</b> | phosphoinositide-3-kinase<br>regulatory subunit 1(PIK3R1) | Homo sapiens | cg01251150 | 2.237358 | 1.26E-17 | 0.060815 | 0.28225  |

|                |                                                              |              |            |          |          |          |          |
|----------------|--------------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>PLEKHG5</b> | pleckstrin homology and RhoGEF domain containing G5(PLEKHG5) | Homo sapiens | cg07181374 | 1.727515 | 1.69E-17 |          |          |
| <b>PML</b>     | promyelocytic leukemia(PML)                                  | Homo sapiens | cg01947066 | 1.959361 | 1.08E-06 |          |          |
| <b>PPARD</b>   | peroxisome proliferator activated receptor delta(PPARD)      | Homo sapiens | cg26668919 | 2.934903 | 3.68E-17 |          |          |
| <b>PRKCA</b>   | protein kinase C alpha(PRKCA)                                | Homo sapiens | cg14121185 | -2.67592 | 1.62E-20 | 0.874693 | 0.429846 |
|                |                                                              |              | cg05115424 | 1.608107 | 7.51E-10 | 0.081959 | 0.220044 |
|                |                                                              |              | cg09655520 | 1.820661 | 1.39E-09 | 0.166933 | 0.419827 |
| <b>PTEN</b>    | phosphatase and tensin homolog(PTEN)                         | Homo sapiens | cg26127345 | 1.535502 | 0.001508 | 0.429051 | 0.633389 |
|                |                                                              |              | cg19358349 | 1.702888 | 0.000271 | 0.401807 | 0.644288 |
|                |                                                              |              | cg01228636 | 1.712449 | 0.000372 | 0.491384 | 0.734546 |
|                |                                                              |              | cg19634213 | 1.721931 | 0.00022  | 0.40649  | 0.663402 |
|                |                                                              |              | cg04616691 | 1.78722  | 0.000905 | 0.364272 | 0.561777 |
|                |                                                              |              | cg03236184 | 1.901193 | 7.83E-05 | 0.438936 | 0.706127 |
| <b>RARB</b>    | retinoic acid receptor beta(RARB)                            | Homo sapiens | cg21902772 | 2.206659 | 9.56E-18 | 0.291665 | 0.708268 |
|                |                                                              |              | cg23518541 | 3.4762   | 1.05E-16 | 0.096579 | 0.60235  |
| <b>RASSF1</b>  | Ras association domain family member 1(RASSF1)               | Homo sapiens | cg02930432 | 1.590468 | 2.75E-09 | 0.197452 | 0.462608 |
|                |                                                              |              | cg21418575 | 1.510304 | 9.39E-08 | 0.335072 | 0.572985 |
|                |                                                              |              | cg07130266 | 2.266083 | 3.24E-09 | 0.249514 | 0.57952  |
| <b>RB1</b>     | RB transcriptional corepressor 1(RB1)                        | Homo sapiens | cg13221796 | 1.972518 | 2.27E-20 |          |          |
| <b>RXRB</b>    | retinoid X receptor beta(RXRB)                               | Homo sapiens | cg07931652 | 1.523593 | 4.19E-17 | 0.524678 | 0.77896  |

|               |                                                        |              |            |          |          |          |          |
|---------------|--------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>SLC2A1</b> | solute carrier family 2 member<br>1(SLC2A1)            | Homo sapiens | cg22025263 | 2.001813 | 8.33E−11 | 0.510382 | 0.81735  |
| <b>SMAD3</b>  | SMAD family member 3(SMAD3)                            | Homo sapiens | cg04809597 | 1.97252  | 1.92E−23 | 0.05713  | 0.252782 |
| <b>SUFU</b>   | SUFU negative regulator of<br>hedgehog signaling(SUFU) | Homo sapiens | cg09119776 | 1.824803 | 1.59E−16 | 0.068277 | 0.233147 |
| <b>TCF7L1</b> | transcription factor 7 like<br>1(TCF7L1)               | Homo sapiens | cg20693690 | −1.5635  | 3.97E−07 | 0.533941 | 0.240248 |
|               |                                                        |              | cg22834443 | 1.837207 | 1.9E−12  | 0.548775 | 0.843847 |
|               |                                                        |              | cg20693690 | −1.5635  | 3.97E−07 | 0.533941 | 0.240248 |
| <b>TCF7L2</b> | transcription factor 7 like<br>2(TCF7L2)               | Homo sapiens | cg07168930 | 1.804367 | 1.5E−14  | 0.712649 | 0.911392 |
|               |                                                        |              | cg03339956 | 2.395134 | 3.93E−26 | 0.218402 | 0.600015 |
| <b>TGFB2</b>  | transforming growth factor beta<br>2(TGFB2)            | Homo sapiens | cg11976166 | −1.8673  | 2.93E−05 | 0.442588 | 0.167974 |
|               |                                                        |              | cg10484211 | 2.167142 | 1.63E−13 | 0.08019  | 0.33298  |
|               |                                                        |              | cg13285637 | −1.8383  | 6.64E−05 | 0.424687 | 0.162007 |
|               |                                                        |              | cg06899755 | −1.54824 | 0.000222 | 0.447125 | 0.173171 |
|               |                                                        |              | cg22021178 | −1.50285 | 0.000406 | 0.359804 | 0.125219 |

**Table S2.** Differentially methylated genes in the Tumor Suppressors KEGG pathway with a log FC ≥ 1.5.

| Gene Name | Species | Differentially<br>Methylated Probes | Log Fold Change<br>(High vs Low<br>Risk) | Adjusted P<br>Value | Average<br>Beta Value,<br>Low | Average<br>Beta Value,<br>High |
|-----------|---------|-------------------------------------|------------------------------------------|---------------------|-------------------------------|--------------------------------|
|-----------|---------|-------------------------------------|------------------------------------------|---------------------|-------------------------------|--------------------------------|

|               |                                                 |              |            |          |          |          |          |
|---------------|-------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>ATM</b>    | ATM serine/threonine kinase(ATM)                | Homo sapiens | cg14761454 | 2.171709 | 5.33E-11 | 0.113337 | 0.410785 |
| <b>CDKN1B</b> | cyclin dependent kinase inhibitor 1B(CDKN1B)    | Homo sapiens | cg06197769 | 3.78761  | 1.9E-30  | 0.187364 | 0.82662  |
| <b>CDKN1C</b> | cyclin dependent kinase inhibitor 1C(CDKN1C)    | Homo sapiens | cg17265994 | 1.60087  | 5.24E-15 | 0.098808 | 0.272309 |
|               |                                                 |              | cg03143849 | 1.697443 | 4.88E-16 | 0.380944 | 0.710675 |
| <b>CDKN2D</b> | cyclin dependent kinase inhibitor 2D(CDKN2D)    | Homo sapiens | cg25685983 | 1.766552 | 7.18E-23 | 0.110149 | 0.323895 |
| <b>DAB2</b>   | DAB2, clathrin adaptor protein(DAB2)            | Homo sapiens | cg12290311 | 3.117633 | 5.95E-21 | 0.09455  | 0.555251 |
| <b>DAPK3</b>  | death associated protein kinase 3(DAPK3)        | Homo sapiens | cg22304239 | 1.939735 | 1.18E-13 |          |          |
| <b>DIS3L2</b> | DIS3 like 3'-5' exoribonuclease 2(DIS3L2)       | Homo sapiens | cg14802771 | 2.279833 | 3.93E-17 | 0.193749 | 0.543178 |
| <b>DLC1</b>   | DLC1 Rho GTPase activating protein(DLC1)        | Homo sapiens | cg18792365 | 2.274905 | 5.82E-10 | 0.185786 | 0.565794 |
|               |                                                 |              | cg22045977 | 2.575186 | 2.44E-15 | 0.407574 | 0.828947 |
| <b>EFNA1</b>  | ephrin A1(EFNA1)                                | Homo sapiens | cg07207669 | 1.829389 | 7.93E-07 | 0.308278 | 0.606053 |
| <b>FES</b>    | FES proto-oncogene, tyrosine kinase(FES)        | Homo sapiens | cg25647583 | 1.620561 | 1.83E-12 | 0.337424 | 0.613609 |
|               |                                                 |              | cg26405020 | 1.775185 | 3.08E-16 | 0.103383 | 0.313802 |
|               |                                                 |              | cg09397246 | 1.7864   | 4.28E-11 | 0.038035 | 0.194971 |
| <b>HIF3A</b>  | hypoxia inducible factor 3 alpha subunit(HIF3A) | Homo sapiens | cg12068280 | 2.287241 | 3.28E-19 | 0.23857  | 0.656095 |

|               |                                                          |              |            |          |          |          |          |
|---------------|----------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>HPGD</b>   | hydroxyprostaglandin<br>dehydrogenase 15-(NAD)(HPGD)     | Homo sapiens | cg03772063 | 2.169526 | 7.27E-13 | 0.544367 | 0.843968 |
| <b>MCC</b>    | mutated in colorectal<br>cancers(MCC)                    | Homo sapiens | cg02528008 | 2.18208  | 3.41E-17 | 0.138006 | 0.447979 |
| <b>MTUS1</b>  | microtubule associated tumor<br>suppressor 1(MTUS1)      | Homo sapiens | cg00121389 | 2.338386 | 4.67E-18 | 0.289024 | 0.711872 |
|               |                                                          |              | cg01993952 | 3.183913 | 3.56E-18 | 0.331804 | 0.792952 |
|               |                                                          |              | cg23002008 | 3.231493 | 8.86E-18 | 0.394688 | 0.876206 |
|               |                                                          |              | cg12548824 | 3.485792 | 2.2E-25  | 0.250505 | 0.83362  |
|               |                                                          |              | cg18563140 | 3.558719 | 8.99E-23 |          |          |
| <b>PINX1</b>  | PIN2/TERF1 interacting,<br>telomerase inhibitor 1(PINX1) | Homo sapiens | cg26886855 | 2.717973 | 1.02E-10 |          |          |
| <b>PML</b>    | promyelocytic leukemia(PML)                              | Homo sapiens | cg01947066 | 1.959361 | 1.08E-06 |          |          |
| <b>PRKCD</b>  | protein kinase C delta(PRKCD)                            | Homo sapiens | cg08170911 | 2.447478 | 8.68E-26 | 0.173984 | 0.533695 |
| <b>PTEN</b>   | phosphatase and tensin<br>homolog(PTEN)                  | Homo sapiens | cg26127345 | 1.535502 | 0.001508 | 0.429051 | 0.633389 |
|               |                                                          |              | cg19358349 | 1.702888 | 0.000271 | 0.401807 | 0.644288 |
|               |                                                          |              | cg01228636 | 1.712449 | 0.000372 | 0.491384 | 0.734546 |
|               |                                                          |              | cg19634213 | 1.721931 | 0.00022  | 0.40649  | 0.663402 |
|               |                                                          |              | cg04616691 | 1.78722  | 0.000905 | 0.364272 | 0.561777 |
|               |                                                          |              | cg03236184 | 1.901193 | 7.83E-05 | 0.438936 | 0.706127 |
| <b>RASSF1</b> | Ras association domain family<br>member 1(RASSF1)        | Homo sapiens | cg02930432 | 1.590468 | 2.75E-09 | 0.197452 | 0.462608 |
|               |                                                          |              | cg07130266 | 2.266083 | 3.24E-09 | 0.249514 | 0.57952  |
|               |                                                          |              | cg21418575 | 1.510304 | 9.39E-08 | 0.335072 | 0.572985 |

|                |                                                           |              |            |          |          |          |          |
|----------------|-----------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
|                |                                                           |              | cg21372200 | 1.510504 | 3.36E-08 | 0.329236 | 0.588495 |
|                |                                                           |              | cg06117233 | 1.592409 | 1.03E-08 | 0.240456 | 0.475515 |
|                |                                                           |              | cg06980053 | 1.753488 | 7.45E-09 | 0.27348  | 0.555539 |
| <b>RASSF4</b>  | Ras association domain family member 4(RASSF4)            | Homo sapiens | cg11753018 | 1.574196 | 2.82E-09 | 0.522055 | 0.784378 |
|                |                                                           |              | cg24483689 | 1.967374 | 7.13E-17 | 0.475436 | 0.788271 |
| <b>RB1</b>     | RB transcriptional corepressor 1(RB1)                     | Homo sapiens | cg13221796 | 1.972518 | 2.27E-20 |          |          |
|                |                                                           |              | cg17419299 | 2.21785  | 3.31E-21 |          |          |
|                |                                                           |              | cg19473653 | 2.335442 | 1.98E-23 |          |          |
| <b>RB1CC1</b>  | RB1 inducible coiled-coil 1(RB1CC1)                       | Homo sapiens | cg15973818 | 2.328448 | 5.92E-23 | 0.35814  | 0.755258 |
| <b>SASH1</b>   | SAM and SH3 domain containing 1(SASH1)                    | Homo sapiens | cg22685901 | 2.204937 | 4.66E-14 | 0.460327 | 0.832441 |
| <b>SIK1</b>    | salt inducible kinase 1(SIK1)                             | Homo sapiens | cg19135247 | 2.488609 | 7.04E-11 | 0.100361 | 0.473306 |
| <b>STARD13</b> | StAR related lipid transfer domain containing 13(STARD13) | Homo sapiens | cg16223976 | 1.697226 | 8.07E-15 | 0.451039 | 0.743896 |
| <b>STK11</b>   | serine/threonine kinase 11(STK11)                         | Homo sapiens | cg16601904 | 2.278019 | 7.92E-13 | 0.274959 | 0.621749 |
| <b>SUFU</b>    | SUFU negative regulator of hedgehog signaling(SUFU)       | Homo sapiens | cg09119776 | 1.824803 | 1.59E-16 | 0.068277 | 0.233147 |
| <b>TSC1</b>    | tuberous sclerosis 1(TSC1)                                | Homo sapiens | cg14211075 | 1.914518 | 5.87E-18 | 0.421238 | 0.780034 |
| <b>WWOX</b>    | WW domain containing oxidoreductase(WWOX)                 | Homo sapiens | cg01623475 | -2.46666 | 5.04E-11 | 0.761141 | 0.327081 |
|                |                                                           |              | cg04254167 | 2.54376  | 3.56E-12 | 0.193268 | 0.586033 |



|               |                        |              |            |          |          |          |          |
|---------------|------------------------|--------------|------------|----------|----------|----------|----------|
| <b>ZDHHC1</b> | zinc finger DHHC-type  | Homo sapiens | cg18837713 | 2.451172 | 2.91E-24 | 0.328923 | 0.801488 |
| <b>7</b>      | containing 17(ZDHHC17) |              |            |          |          |          |          |

**Table S3.** Differentially methylated genes in the mTOR signaling KEGG pathway with a log FC ≥ 1.5

| ID            | Gene Name                                              | Species      | Differentially Methylated Probes | Log Fold Change (High vs Low Risk) | Adjusted P Value | Average beta Value, Low | Average Beta Value, High |
|---------------|--------------------------------------------------------|--------------|----------------------------------|------------------------------------|------------------|-------------------------|--------------------------|
| <b>AKT1</b>   | AKT serine/threonine kinase 1(AKT1)                    | Homo sapiens | cg14116052                       | 2.454448                           | 4.3E-24          | 0.513149                | 0.885217                 |
| <b>CAB39L</b> | calcium binding protein 39 like(CAB39L)                | Homo sapiens | cg01618923                       | 1.76264                            | 4.39E-13         | 0.616829                | 0.876456                 |
| <b>IRS1</b>   | insulin receptor substrate 1(IRS1)                     | Homo sapiens | cg05263838                       | 1.69305                            | 4.84E-07         | 0.230883                | 0.485612                 |
| <b>PTEN</b>   | phosphatase and tensin homolog(PTEN)                   | Homo sapiens | cg26127345                       | 1.535502                           | 0.001508         | 0.429051                | 0.633389                 |
|               |                                                        |              | cg19358349                       | 1.702888                           | 0.000271         | 0.401807                | 0.644288                 |
|               |                                                        |              | cg01228636                       | 1.712449                           | 0.000372         | 0.491384                | 0.734546                 |
|               |                                                        |              | cg19634213                       | 1.721931                           | 0.00022          | 0.40649                 | 0.663402                 |
|               |                                                        |              | cg04616691                       | 1.78722                            | 0.000905         | 0.364272                | 0.561777                 |
|               |                                                        |              | cg03236184                       | 1.901193                           | 7.83E-05         | 0.438936                | 0.706127                 |
| <b>PIK3R1</b> | phosphoinositide-3-kinase regulatory subunit 1(PIK3R1) | Homo sapiens | cg01251150                       | 2.237358                           | 1.26E-17         | 0.060815                | 0.28225                  |
| <b>PRKCA</b>  | protein kinase C alpha(PRKCA)                          | Homo sapiens | cg14121185                       | -2.67592                           | 1.62E-20         | 0.874693                | 0.429846                 |

|              |                               |        |              |            |          |          |          |          |
|--------------|-------------------------------|--------|--------------|------------|----------|----------|----------|----------|
| <b>STK11</b> | serine/threonine<br>11(STK11) | kinase | Homo sapiens | cg16601904 | 2.278019 | 7.92E-13 | 0.274959 | 0.621749 |
| <b>TSC1</b>  | tuberous sclerosis 1(TSC1)    |        | Homo sapiens | cg14211075 | 1.914518 | 5.87E-18 | 0.421238 | 0.780034 |
| <b>ULK3</b>  | unc-51 like kinase 3(ULK3)    |        | Homo sapiens | cg20801110 | 1.87354  | 2.79E-14 | 0.131913 | 0.501952 |

**Table S4.** Differentially methylated genes in the PI3K-Akt signaling KEGG pathway with a log FC ≥ 1.5

| ID      | Gene Name                               |               |           |   | Species      | Differentially Methylated Probes | Log Fold Change (High vs Low Risk) | Adjusted P Value | Average Beta Value, Low | Average Beta Value, High |
|---------|-----------------------------------------|---------------|-----------|---|--------------|----------------------------------|------------------------------------|------------------|-------------------------|--------------------------|
| AKT1    | AKT serine/threonine kinase 1(AKT1)     |               |           |   | Homo sapiens | cg14116052                       | 2.454448                           | 4.3E-24          | 0.513149                | 0.885217                 |
| ANGPT1  | angiopoietin 1(ANGPT1)                  |               |           |   | Homo sapiens | cg18031596                       | 1.632527                           | 2.79E-07         | 0.459754                | 0.702836                 |
| ATF6B   | activating                              | transcription | factor    | 6 | Homo sapiens | cg11580844                       | 1.503817                           | 9.54E-09         | 0.567255                | 0.798651                 |
|         | beta(ATF6B)                             |               |           |   |              | cg12273368                       | 1.507859                           | 2.01E-05         | 0.157889                | 0.347245                 |
|         |                                         |               |           |   |              | cg26037142                       | 1.73427                            | 1.27E-07         | 0.093327                | 0.302313                 |
| BCL2L11 | BCL2 like 11(BCL2L11)                   |               |           |   | Homo sapiens | cg06223562                       | 2.960699                           | 2.06E-15         | 0.427113                | 0.867355                 |
| CCND3   | cyclin D3(CCND3)                        |               |           |   | Homo sapiens | cg12151296                       | 1.692885                           | 8.55E-11         | 0.037846                | 0.113328                 |
|         |                                         |               |           |   |              | cg00374492                       | 1.772585                           | 5.58E-23         | 0.077127                | 0.287289                 |
|         |                                         |               |           |   |              | cg19297231                       | 2.509268                           | 9.23E-32         | 0.041721                | 0.283341                 |
| CDKN1B  | cyclin dependent                        | kinase        | inhibitor |   | Homo sapiens | cg06197769                       | 3.78761                            | 1.9E-30          | 0.187364                | 0.82662                  |
|         | 1B(CDKN1B)                              |               |           |   |              |                                  |                                    |                  |                         |                          |
| COL11A1 | collagen type XI alpha 1 chain(COL11A1) |               |           |   | Homo sapiens | cg03520644                       | 1.618823                           | 4.82E-08         | 0.031405                | 0.196742                 |
|         |                                         |               |           |   |              | cg00172849                       | 1.999957                           | 4.41E-09         | 0.055192                | 0.274217                 |

|                |                                                           |              |            |          |          |          |          |
|----------------|-----------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
|                |                                                           |              | cg26913669 | 2.102304 | 2.44E-13 | 0.598955 | 0.89671  |
| <b>COL11A2</b> | collagen type XI alpha 2 chain(COL11A2)                   | Homo sapiens | cg08733307 | 2.660359 | 8.15E-18 | 0.47069  | 0.943783 |
|                |                                                           |              | cg04770813 | -1.64486 | 0.000256 |          |          |
|                |                                                           |              | cg16634404 | 1.505328 | 6.48E-16 | 0.136766 | 0.339358 |
|                |                                                           |              | cg26385062 | 1.533797 | 8.69E-14 | 0.126167 | 0.302528 |
|                |                                                           |              | cg02266086 | 1.534744 | 1.18E-15 | 0.050627 | 0.183503 |
|                |                                                           |              | cg21893764 | 1.662155 | 6.59E-13 | 0.600363 | 0.84737  |
|                |                                                           |              | cg22320183 | 1.767212 | 8.55E-18 | 0.420494 | 0.728267 |
|                |                                                           |              | cg15407213 | 1.859479 | 1.05E-11 | 0.526713 | 0.812844 |
|                |                                                           |              | cg14683730 | 1.902269 | 5.28E-16 | 0.601684 | 0.877669 |
|                |                                                           |              | cg17560929 | 2.002801 | 9.49E-18 | 0.260409 | 0.597083 |
| <b>CREB3L4</b> | cAMP responsive element binding protein 3 like 4(CREB3L4) | Homo sapiens | cg09895920 | 2.307801 | 3.32E-10 | 0.30769  | 0.759773 |
| <b>CREB5</b>   | cAMP responsive element binding protein 5(CREB5)          | Homo sapiens | cg23281552 | -2.15895 | 1.45E-13 | 0.56621  | 0.166395 |
|                |                                                           |              | cg03226887 | 1.513661 | 1.5E-06  | 0.307877 | 0.535686 |
|                |                                                           |              | cg22681186 | 1.76285  | 2.16E-09 | 0.191216 | 0.455499 |
| <b>EFNA1</b>   | ephrin A1(EFNA1)                                          | Homo sapiens | cg07207669 | 1.829389 | 7.93E-07 | 0.308278 | 0.606053 |
| <b>FGF1</b>    | fibroblast growth factor 1(FGF1)                          | Homo sapiens | cg15371881 | 3.061708 | 4.38E-25 | 0.219393 | 0.69523  |
|                |                                                           |              | cg17593472 | 1.862401 | 4.58E-19 | 0.103875 | 0.337684 |
|                |                                                           |              | cg19954000 | 2.476565 | 5.38E-24 | 0.110559 | 0.444379 |
| <b>FOXO3</b>   | forkhead box O3(FOXO3)                                    | Homo sapiens | cg04855107 | 2.656668 | 6.13E-16 | 0.422016 | 0.833628 |
|                |                                                           |              | cg21184115 | 2.092368 | 6.11E-20 | 0.629905 | 0.886342 |
|                |                                                           |              | cg08792630 | 2.964245 | 3.28E-14 |          |          |

|                |                                                           |              |            |          |          |          |          |
|----------------|-----------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>G6PC3</b>   | glucose-6-phosphatase catalytic subunit 3(G6PC3)          | Homo sapiens | cg26534477 | 1.86973  | 2.34E-11 | 0.31365  | 0.618814 |
|                |                                                           |              | cg18426551 | 1.894664 | 8.07E-10 | 0.154885 | 0.405578 |
|                |                                                           |              | cg22243039 | 2.547672 | 4.45E-15 | 0.179281 | 0.560702 |
| <b>GNB4</b>    | G protein subunit beta 4(GNB4)                            | Homo sapiens | cg01750654 | 1.647758 | 4.02E-11 | 0.594913 | 0.827501 |
|                |                                                           |              | cg03466124 | 1.862402 | 3.31E-08 | 0.108087 | 0.324521 |
| <b>GNG11</b>   | G protein subunit gamma 11(GNG11)                         | Homo sapiens | cg06439941 | 2.094159 | 1.67E-09 | 0.218242 | 0.565099 |
|                |                                                           |              | cg02914800 | 3.14371  | 1.04E-14 | 0.10902  | 0.602134 |
|                |                                                           |              | cg08038054 | 2.335425 | 3.13E-11 | 0.069817 | 0.348166 |
| <b>IGF1R</b>   | insulin like growth factor 1 receptor(IGF1R)              | Homo sapiens | cg11852333 | 1.967845 | 3.57E-14 | 0.258781 | 0.568105 |
| <b>IRS1</b>    | insulin receptor substrate 1(IRS1)                        | Homo sapiens | cg05263838 | 1.69305  | 4.84E-07 | 0.230883 | 0.485612 |
| <b>ITGA3</b>   | integrin subunit alpha 3(ITGA3)                           | Homo sapiens | cg12127162 | 1.833962 | 2.92E-16 | 0.254277 | 0.538208 |
| <b>ITGAV</b>   | integrin subunit alpha V(ITGAV)                           | Homo sapiens | cg03192874 | 2.961775 | 2.21E-15 |          |          |
| <b>ITGB4</b>   | integrin subunit beta 4(ITGB4)                            | Homo sapiens | cg07436562 | 2.221927 | 1.07E-25 | 0.274514 | 0.657516 |
| <b>KRAS</b>    | KRAS proto-oncogene, GTPase(KRAS)                         | Homo sapiens | cg23152216 | 2.293392 | 5.96E-27 | 0.470784 | 0.837552 |
| <b>LPAR6</b>   | lysophosphatidic acid receptor 6(LPAR6)                   | Homo sapiens | cg03646329 | 2.221789 | 8.4E-09  | 0.105173 | 0.345011 |
| <b>PDGFRA</b>  | platelet derived growth factor receptor alpha(PDGFRA)     | Homo sapiens | cg02273436 | 1.911305 | 1.17E-06 | 0.160494 | 0.467324 |
| <b>PIK3R1</b>  | phosphoinositide-3-kinase regulatory subunit 1(PIK3R1)    | Homo sapiens | cg01251150 | 2.237358 | 1.26E-17 | 0.060815 | 0.28225  |
| <b>PKN1</b>    | protein kinase N1(PKN1)                                   | Homo sapiens | cg03626511 | 1.795673 | 9.46E-12 | 0.412789 | 0.70717  |
| <b>PPP2R3A</b> | protein phosphatase 2 regulatory subunit B"alpha(PPP2R3A) | Homo sapiens | cg23194766 | 3.347877 | 2.96E-27 | 0.155295 | 0.722266 |
| <b>PRKCA</b>   | protein kinase C alpha(PRKCA)                             | Homo sapiens | cg14121185 | -2.67592 | 1.62E-20 | 0.874693 | 0.429846 |

|              |                                                                                     |              |            |          |          |          |          |
|--------------|-------------------------------------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>PTEN</b>  | phosphatase and tensin homolog(PTEN)                                                | Homo sapiens | cg26127345 | 1.535502 | 0.001508 | 0.429051 | 0.633389 |
|              |                                                                                     |              | cg19358349 | 1.702888 | 0.000271 | 0.401807 | 0.644288 |
|              |                                                                                     |              | cg01228636 | 1.712449 | 0.000372 | 0.491384 | 0.734546 |
|              |                                                                                     |              | cg19634213 | 1.721931 | 0.00022  | 0.40649  | 0.663402 |
|              |                                                                                     |              | cg04616691 | 1.78722  | 0.000905 | 0.364272 | 0.561777 |
|              |                                                                                     |              | cg03236184 | 1.901193 | 7.83E-05 | 0.438936 | 0.706127 |
| <b>SPP1</b>  | secreted phosphoprotein 1(SPP1)                                                     | Homo sapiens | cg15460348 | 2.747597 | 1.08E-11 | 0.418663 | 0.838071 |
|              |                                                                                     |              | cg20261167 | 2.937721 | 1.39E-12 | 0.460194 | 0.885425 |
| <b>STK11</b> | serine/threonine kinase 11(STK11)                                                   | Homo sapiens | cg16601904 | 2.278019 | 7.92E-13 | 0.274959 | 0.621749 |
| <b>THEM4</b> | thioesterase superfamily member 4(THEM4)                                            | Homo sapiens | cg09063149 | 1.639568 | 4.13E-10 |          |          |
|              |                                                                                     |              | cg26347189 | 1.92722  | 5.09E-12 |          |          |
| <b>TNXB</b>  | tenascin XB(TNXB)                                                                   | Homo sapiens | cg09114581 | -1.77386 | 1.03E-06 | 0.331392 | 0.102144 |
|              |                                                                                     |              | cg13823701 | -1.72872 | 1.04E-10 | 0.783831 | 0.471462 |
|              |                                                                                     |              | cg19268434 | -1.70504 | 8.14E-06 | 0.466698 | 0.212354 |
|              |                                                                                     |              | cg18417373 | -1.59536 | 6.52E-09 | 0.212665 | 0.063564 |
|              |                                                                                     |              | cg15540749 | -1.53238 | 3.03E-09 |          |          |
|              |                                                                                     |              | cg21337909 | 1.516293 | 1.25E-06 | 0.420422 | 0.668582 |
|              |                                                                                     |              | cg01337207 | 1.525985 | 2.84E-06 | 0.091661 | 0.219728 |
| <b>TSC1</b>  | tuberous sclerosis 1(TSC1)                                                          | Homo sapiens | cg10365886 | 1.813212 | 1.56E-06 | 0.081412 | 0.199427 |
|              |                                                                                     |              | cg14211075 | 1.914518 | 5.87E-18 | 0.421238 | 0.780034 |
| <b>YWHAQ</b> | tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein theta(YWHAQ) | Homo sapiens | cg15748006 | 1.764721 | 2.69E-10 | 0.120031 | 0.339017 |

**Table 5.** Differentially methylated genes in the RAS signaling KEGG pathway with a log FC  $\geq 1.5$ .

| ID     | Gene Name                                                | Species      | Differentially Methylated Probes | Log Fold Change (High vs Low Risk) | Adjusted P Value | Average beta Value, Low | Average Beta Value, High |
|--------|----------------------------------------------------------|--------------|----------------------------------|------------------------------------|------------------|-------------------------|--------------------------|
| ABL1   | ABL proto-oncogene 1, non-receptor tyrosine kinase(ABL1) | Homo sapiens | cg13440206,                      | −1.85238                           | 1.39E−06         | 0.576589                | 0.259088                 |
|        |                                                          |              | cg02915920                       | −1.84042                           | 8.03E−06         | 0.482846                | 0.192714                 |
| AKT1   | AKT serine/threonine kinase 1(AKT1)                      | Homo sapiens | cg14116052                       | 2.454448                           | 4.3E−24          | 0.513149                | 0.885217                 |
| ANGPT1 | angiopoietin 1(ANGPT1)                                   | Homo sapiens | cg03245734                       | 1.885287                           | 3.19E−07         | 0.300807                | 0.572671                 |
|        |                                                          |              | cg18031596                       | 1.632527                           | 2.79E−07         | 0.459754                | 0.702836                 |
| EFNA1  | ephrin A1(EFNA1)                                         | Homo sapiens | cg07207669                       | 1.829389                           | 7.93E−07         | 0.308278                | 0.606053                 |
| ETS1   | ETS proto-oncogene 1, transcription factor(ETS1)         | Homo sapiens | cg25244476                       | 2.507626                           | 9.92E−07         | 0.25583                 | 0.602367                 |
|        |                                                          |              | cg03295554                       | 1.542659                           | 2.23E−09         | 0.40522                 | 0.685169                 |
| ETS2   | ETS proto-oncogene 2, transcription factor(ETS2)         | Homo sapiens |                                  |                                    |                  |                         |                          |
| EXOC2  | exocyst complex component 2(EXOC2)                       | Homo sapiens | cg14219317                       | −2.4566                            | 8.53E−13         | 0.791947                | 0.35102                  |
|        |                                                          |              | cg26889659                       | −2.06602                           | 4.46E−08         | 0.942684                | 0.736261                 |
|        |                                                          |              | cg09607658                       | 2.586518                           | 5.1E−21          |                         |                          |
| FGF1   | fibroblast growth factor 1(FGF1)                         | Homo sapiens | cg15371881                       | 3.061708                           | 4.38E−25         | 0.219393                | 0.69523                  |

|               |                                                        |              |            |          |          |          |          |
|---------------|--------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>GNB4</b>   | G protein subunit beta 4(GNB4)                         | Homo sapiens | cg01750654 | 1.647758 | 4.02E-11 | 0.594913 | 0.827501 |
|               |                                                        |              | cg03466124 | 1.862402 | 3.31E-08 | 0.108087 | 0.324521 |
| <b>GNG11</b>  | G protein subunit gamma 11(GNG11)                      | Homo sapiens | cg06439941 | 2.094159 | 1.67E-09 | 0.218242 | 0.565099 |
|               |                                                        |              | cg02914800 | 3.14371  | 1.04E-14 | 0.10902  | 0.602134 |
|               |                                                        |              | cg08038054 | 2.335425 | 3.13E-11 | 0.069817 | 0.348166 |
| <b>IGF1R</b>  | insulin like growth factor 1 receptor(IGF1R)           | Homo sapiens | cg11852333 | 1.967845 | 3.57E-14 | 0.258781 | 0.568105 |
| <b>KRAS</b>   | KRAS proto-oncogene, GTPase(KRAS)                      | Homo sapiens | cg23152216 | 2.293392 | 5.96E-27 | 0.470784 | 0.837552 |
| <b>MAPK8</b>  | mitogen-activated protein kinase 8(MAPK8)              | Homo sapiens | cg19612574 | 1.694113 | 4.14E-15 | 0.113088 | 0.332177 |
| <b>MAPK9</b>  | mitogen-activated protein kinase 9(MAPK9)              | Homo sapiens | cg09663237 | 2.203989 | 3.06E-06 | 0.584195 | 0.883176 |
| <b>PAK1</b>   | p21 (RAC1) activated kinase 1(PAK1)                    | Homo sapiens | cg14076258 | 2.244198 | 9.31E-17 | 0.249832 | 0.669792 |
| <b>PDGFRA</b> | platelet derived growth factor receptor alpha(PDGFA)   | Homo sapiens | cg02273436 | 1.911305 | 1.17E-06 | 0.160494 | 0.467324 |
| <b>PIK3R1</b> | phosphoinositide-3-kinase regulatory subunit 1(PIK3R1) | Homo sapiens | cg01251150 | 2.237358 | 1.26E-17 | 0.060815 | 0.28225  |
| <b>PLA1A</b>  | phospholipase A1 member A(PLA1A)                       | Homo sapiens | cg06068392 | 3.589907 | 6.18E-20 | 0.282764 | 0.853068 |
| <b>PRKCA</b>  | protein kinase C alpha(PRKCA)                          | Homo sapiens | cg14121185 | -2.67592 | 1.62E-20 | 0.874693 | 0.429846 |

|                |                                                   |              |              |  |            |          |          |          |          |
|----------------|---------------------------------------------------|--------------|--------------|--|------------|----------|----------|----------|----------|
|                |                                                   |              |              |  | cg05115424 | 1.608107 | 7.51E-10 | 0.081959 | 0.220044 |
|                |                                                   |              |              |  | cg09655520 | 1.820661 | 1.39E-09 | 0.166933 | 0.419827 |
| <b>RAB5C</b>   | RAB5C, member family(RAB5C)                       | RAS oncogene | Homo sapiens |  | cg00435173 | 1.705061 | 8.56E-12 | 0.055333 | 0.200904 |
| <b>RAPGEF5</b> | Rap guanine nucleotide exchange factor 5(RAPGEF5) |              | Homo sapiens |  | cg12894814 | 2.365007 | 7.45E-13 | 0.578418 | 0.915151 |
| <b>RASSF1</b>  | Ras association domain family member 1(RASSF1)    |              | Homo sapiens |  | cg02930432 | 1.590468 | 2.75E-09 | 0.197452 | 0.462608 |
|                |                                                   |              |              |  | cg07130266 | 2.266083 | 3.24E-09 | 0.249514 | 0.57952  |
|                |                                                   |              |              |  | cg21418575 | 1.510304 | 9.39E-08 | 0.335072 | 0.572985 |
|                |                                                   |              |              |  | cg21372200 | 1.510504 | 3.36E-08 | 0.329236 | 0.588495 |
|                |                                                   |              |              |  | cg06117233 | 1.592409 | 1.03E-08 | 0.240456 | 0.475515 |
|                |                                                   |              |              |  | cg06980053 | 1.753488 | 7.45E-09 | 0.27348  | 0.555539 |
| <b>SHC4</b>    | SHC adaptor protein 4(SHC4)                       |              | Homo sapiens |  | cg26337669 | 1.812095 | 7.98E-19 | 0.527409 | 0.896985 |
|                |                                                   |              |              |  | cg26814712 | 2.746152 | 9.7E-19  | 0.085799 | 0.427092 |

**Table 6.** Differentially methylated genes in the Negative Regulation of ERK1/2 signaling KEGG pathway with a log FC  $\geq 1.5$ .

| ID             | Gene Name                     | Species      | Differentially Methylated Probes | Log Fold Change (High vs Low Risk) | Adjusted P Value | Average beta Value, Low | Average Beta Value, High |
|----------------|-------------------------------|--------------|----------------------------------|------------------------------------|------------------|-------------------------|--------------------------|
| <b>CNKS R3</b> | CNKS family member 3(CNKS R3) | Homo sapiens | cg08927844                       | -2.27644                           | 2.97E-14         | 0.876441                | 0.497476                 |
|                |                               |              | cg16175941                       | 2.252762                           | 4.73E-16         | 0.501376                | 0.853069                 |
| <b>CSK</b>     | c-src tyrosine kinase(CSK)    | Homo sapiens | cg13578134                       | 1.70682                            | 1.71E-10         | 0.060061                | 0.34615                  |



|                 |                                                      |              |            |          |          |          |          |
|-----------------|------------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>DLG1</b>     | discs large MAGUK scaffold protein 1(DLG1)           | Homo sapiens | cg17696750 | 1.827729 | 1.99E−10 | 0.500693 | 0.829287 |
| <b>GSTP1</b>    | glutathione S-transferase pi 1(GSTP1)                | Homo sapiens | cg22224704 | 2.261199 | 1.11E−08 | 0.19543  | 0.520111 |
|                 |                                                      |              | cg09038676 | 2.666525 | 9.53E−13 | 0.029387 | 0.289375 |
| <b>ITGB1BP1</b> | integrin subunit beta 1 binding protein 1(ITGB1BP1)  | Homo sapiens | cg09734418 | −1.51915 | 0.000166 | 0.808651 | 0.578962 |
|                 |                                                      |              | cg09761705 | 1.733371 | 2.04E−06 | 0.693193 | 0.930472 |
| <b>LYN</b>      | LYN proto-oncogene, Src family tyrosine kinase(LYN)  | Homo sapiens | cg06818377 | 1.645783 | 1.02E−12 | 0.157167 | 0.390638 |
|                 |                                                      |              | cg11982546 | 2.602661 | 4.44E−21 | 0.122589 | 0.522136 |
| <b>PTEN</b>     | phosphatase and tensin homolog(PTEN)                 | Homo sapiens | cg26127345 | 1.535502 | 0.001508 | 0.429051 | 0.633389 |
|                 |                                                      |              | cg19358349 | 1.702888 | 0.000271 | 0.401807 | 0.644288 |
|                 |                                                      |              | cg01228636 | 1.712449 | 0.000372 | 0.491384 | 0.734546 |
|                 |                                                      |              | cg19634213 | 1.721931 | 0.00022  | 0.40649  | 0.663402 |
|                 |                                                      |              | cg04616691 | 1.78722  | 0.000905 | 0.364272 | 0.561777 |
|                 |                                                      |              | cg03236184 | 1.901193 | 7.83E−05 | 0.438936 | 0.706127 |
| <b>PTPRR</b>    | protein tyrosine phosphatase, receptor type R(PTPRR) | Homo sapiens | cg01432552 | 1.861903 | 4.44E−15 | 0.495372 | 0.805973 |
| <b>SPRY1</b>    | sprouty RTK signaling antagonist 1(SPRY1)            | Homo sapiens | cg15206981 | 2.101061 | 3.68E−08 | 0.21633  | 0.553251 |
|                 |                                                      |              | cg08251025 | 2.421152 | 9.1E−10  | 0.227702 | 0.613871 |
|                 |                                                      |              | cg21353144 | 2.543733 | 1.01E−09 | 0.338308 | 0.71798  |
|                 |                                                      |              | cg26449178 | 1.634087 | 4.19E−06 | 0.687759 | 0.883531 |

|              |                                                |              |            |          |          |          |          |
|--------------|------------------------------------------------|--------------|------------|----------|----------|----------|----------|
| <b>SPRY2</b> | sprouty RTK signaling antagonist<br>2(SPRY2)   | Homo sapiens | cg22369786 | 1.795045 | 1.47E-08 | 0.080262 | 0.293171 |
|              |                                                |              | cg15374435 | 1.880112 | 8.11E-08 | 0.182656 | 0.447754 |
| <b>TNIP1</b> | TNFAIP3 interacting protein<br>1(TNIP1)        | Homo sapiens | cg12642815 | 2.204535 | 6.58E-17 |          |          |
|              |                                                |              | cg22480558 | 2.571383 | 7.84E-23 |          |          |
| <b>WNK2</b>  | WNK lysine deficient protein<br>kinase 2(WNK2) | Homo sapiens | cg20616414 | -2.46363 | 2.2E-08  | 0.292862 | 0.037877 |
|              |                                                |              | cg10272601 | -1.86566 | 2.66E-05 | 0.170371 | 0.013493 |
|              |                                                |              | cg21194517 | 1.849301 | 3.85E-11 |          |          |

**Table S7.** Log Fold Change for all differentially methylated probes associated with the PTEN gene

| Name       | Relation_to_Island | UCSC_RefGene_Name | LogFC    |
|------------|--------------------|-------------------|----------|
| cg03236184 | Island             | PTEN;KILLIN       | 1.901193 |
| cg04616691 | Island             | PTEN;KILLIN       | 1.78722  |
| cg19634213 | Island             | PTEN;KILLIN       | 1.721931 |
| cg01228636 | Island             | PTEN;KILLIN       | 1.712449 |
| cg19358349 | Island             | PTEN;KILLIN       | 1.702888 |
| cg26127345 | Island             | PTEN;KILLIN       | 1.535502 |
| cg04824711 | N_Shore            | PTEN;KILLIN       | 1.444914 |
| cg25452974 | Island             | PTEN;KILLIN       | 1.436399 |
| cg08995089 | Island             | PTEN;KILLIN       | 1.393284 |
| cg27084903 | Island             | PTEN;KILLIN       | 1.357835 |

**Table S8.** Log Fold Change for all differentially methylated probes associated with the IL12RB2 gene

| Name       | Relation_to_Island | UCSC_RefGene_Name | LogFC    |
|------------|--------------------|-------------------|----------|
| cg00318756 | N_Shore            | IL12RB2           | 4.074567 |
| cg19745415 | N_Shore            | IL12RB2           | 4.035874 |
| cg06952660 | N_Shore            | IL12RB2           | 3.993203 |
| cg01356829 | N_Shore            | IL12RB2           | 3.974715 |
| cg11132246 | N_Shore            | IL12RB2           | 3.111831 |
| cg12633410 | OpenSea            | IL12RB2           | 2.705041 |
| cg03975876 | N_Shore            | IL12RB2;IL12RB2   | 2.656201 |
| cg00993824 | N_Shore            | IL12RB2;IL12RB2   | 1.361834 |
| cg27416067 | N_Shore            | IL12RB2;IL12RB2   | 1.31938  |
| cg02566391 | OpenSea            | IL12RB2           | -1.15142 |

**Table S9.** Log Fold Change for all differentially methylated probes associated with the NFIA gene

| Name       | Relation_to_Island | UCSC_RefGene_Name   | LogFC    |
|------------|--------------------|---------------------|----------|
| cg18946602 | S_Shore            | NFIA;NFIA;NFIA;NFIA | 4.173637 |
| cg16001865 | OpenSea            | NFIA;NFIA;NFIA;NFIA | 3.492806 |
| cg12262372 | N_Shore            | NFIA                | 3.188973 |
| cg12126901 | OpenSea            | NFIA;NFIA;NFIA;NFIA | 2.355875 |
| cg19097500 | N_Shore            | NFIA                | 1.588947 |
| cg10628205 | N_Shore            | NFIA;NFIA;NFIA;NFIA | 1.487113 |
| cg19899972 | OpenSea            | NFIA;NFIA;NFIA;NFIA | 1.128364 |
| cg15546227 | N_Shelf            | NFIA;NFIA           | -1.58506 |
| cg14093103 | N_Shelf            | NFIA;NFIA           | -2.20013 |

**Table S10.** Log Fold Change for all differentially methylated probes associated with the RASSF1 gene

| Name       | Relation_to_Island | UCSC_RefGene_Name                  | LogFC    |
|------------|--------------------|------------------------------------|----------|
| cg07130266 | Island             | RASSF1;RASSF1;RASSF1;RASSF1;RASSF1 | 2.266083 |
| cg06980053 | S_Shore            | RASSF1;RASSF1;RASSF1;RASSF1        | 1.753488 |

|            |         |                                    |          |
|------------|---------|------------------------------------|----------|
| cg06117233 | Island  | RASSF1;RASSF1;RASSF1;RASSF1;RASSF1 | 1.592409 |
| cg02930432 | Island  | RASSF1;RASSF1;RASSF1;RASSF1        | 1.590468 |
| cg21372200 | S_Shore | RASSF1;RASSF1;RASSF1;RASSF1        | 1.510504 |
| cg21418575 | Island  | RASSF1;RASSF1;RASSF1;RASSF1        | 1.510304 |
| cg06821120 | Island  | RASSF1;RASSF1;RASSF1;RASSF1        | 1.470988 |
| cg09386807 | Island  | RASSF1;RASSF1;RASSF1;RASSF1        | 1.354297 |
| cg20826201 | Island  | RASSF1;RASSF1;RASSF1;RASSF1        | 1.283362 |
| cg25486143 | Island  | RASSF1;RASSF1                      | 1.008904 |

**Table S11.** Log Fold Change for all differentially methylated probes associated with the ZNF358 gene.

| Name       | Relation_to_Island | UCSC_RefGene_Name | LogFC    |
|------------|--------------------|-------------------|----------|
| cg00351537 | N_Shore            | ZNF358            | 4.366471 |
| cg02026535 | N_Shore            | ZNF358            | 4.199227 |
| cg19921377 | N_Shore            | ZNF358            | 3.489339 |

**Table S12.** Log Fold Change for all differentially methylated probes associated with the ZNF532 gene.

| Name       | Relation_to_Island | UCSC_RefGene_Name | LogFC    |
|------------|--------------------|-------------------|----------|
| cg06487082 | N_Shore            | ZNF532;ZNF532     | 4.044402 |
| cg12406559 | N_Shore            | ZNF532;ZNF532     | 3.646373 |
| cg12737497 | Island             | ZNF532            | 3.240236 |
| cg03096126 | Island             | ZNF532            | 2.879877 |
| cg26172016 | N_Shore            | ZNF532            | 2.635631 |
| cg24243629 | S_Shore            | ZNF532            | 2.479404 |
| cg04212150 | Island             | ZNF532            | 2.378976 |
| cg24049621 | N_Shore            | ZNF532            | 1.967654 |
| cg14269096 | S_Shore            | ZNF532            | 1.636641 |

**Table S13.** Log Fold Change for all differentially methylated probes associated with the HDAC4 gene.

| Name       | Relation_to_Island | UCSC_RefGene_Name | cFC      |
|------------|--------------------|-------------------|----------|
| cg19955928 | N_Shore            | HDAC4             | 1.046703 |
| cg26876664 | OpenSea            | HDAC4             | -1.02396 |
| cg23971806 | OpenSea            | HDAC4             | -1.03939 |

|            |         |                |          |
|------------|---------|----------------|----------|
| cg13781718 | N_Shore | HDAC4          | -1.03996 |
| cg19449565 | OpenSea | HDAC4          | -1.07381 |
| cg21996813 | N_Shelf | HDAC4          | -1.07961 |
| cg21827163 | OpenSea | HDAC4          | -1.11055 |
| cg21963406 | OpenSea | HDAC4          | -1.12288 |
| cg07618780 | OpenSea | HDAC4          | -1.13964 |
| cg06915343 | N_Shore | HDAC4          | -1.14881 |
| cg02381790 | OpenSea | HDAC4          | -1.16423 |
| cg25103905 | OpenSea | HDAC4          | -1.19481 |
| cg03886681 | N_Shore | HDAC4          | -1.20492 |
| cg14758976 | OpenSea | HDAC4;MGC16025 | -1.20535 |
| cg03475776 | S_Shore | HDAC4          | -1.20543 |
| cg20924425 | OpenSea | HDAC4          | -1.22822 |
| cg01771737 | S_Shelf | HDAC4          | -1.27317 |
| cg00630775 | N_Shore | HDAC4          | -1.27928 |
| cg12595293 | OpenSea | HDAC4          | -1.29593 |
| cg27074582 | S_Shore | HDAC4          | -1.30743 |
| cg05903736 | S_Shore | HDAC4          | -1.31141 |
| cg07609703 | N_Shore | HDAC4          | -1.3183  |
| cg21656251 | N_Shore | HDAC4          | -1.417   |
| cg19125791 | OpenSea | HDAC4          | -1.46509 |
| cg23870168 | OpenSea | HDAC4          | -1.49104 |
| cg11534215 | S_Shelf | HDAC4          | -1.54146 |
| cg01942751 | N_Shore | HDAC4          | -1.54933 |
| cg11122767 | OpenSea | HDAC4          | -1.56615 |
| cg08177681 | OpenSea | HDAC4          | -1.58758 |
| cg06533788 | OpenSea | HDAC4          | -1.61493 |
| cg01647308 | OpenSea | HDAC4          | -1.62883 |
| cg27144223 | S_Shelf | HDAC4          | -1.68685 |
| cg20149840 | OpenSea | HDAC4          | -1.699   |
| cg23949574 | OpenSea | HDAC4          | -1.73597 |

|            |         |       |          |
|------------|---------|-------|----------|
| cg16360836 | OpenSea | HDAC4 | -1.8192  |
| cg05114739 | OpenSea | HDAC4 | -1.82017 |
| cg18479711 | N_Shore | HDAC4 | -1.83972 |
| cg19246018 | N_Shore | HDAC4 | -1.84819 |
| cg27587095 | S_Shore | HDAC4 | -1.86322 |
| cg11707035 | OpenSea | HDAC4 | -2.03859 |
| cg18736431 | OpenSea | HDAC4 | -2.12299 |
| cg25828346 | S_Shore | HDAC4 | -2.15728 |
| cg26641275 | N_Shelf | HDAC4 | -2.60834 |
| cg20706597 | S_Shore | HDAC4 | -2.65649 |
| cg10515232 | S_Shore | HDAC4 | -2.67711 |
| cg21190228 | OpenSea | HDAC4 | -2.92946 |
| cg26627327 | OpenSea | HDAC4 | -3.04717 |
| cg17410431 | OpenSea | HDAC4 | -3.21471 |
| cg10071550 | OpenSea | HDAC4 | -4.08402 |