|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplemental Table S1: HR-HPV methylation in cases and controls by CPG site** | | | | | | | | | |
|  |  |  | **Median (IQR) (%)** | | | **Mann-Whitney U Test** | **Univariate Regression**  **T3 *versus* T1 and T2** | | |
| HPV Type | Region | CpG Site | Controls | Cases | Difference | p value | OR | 95% CI | p value |
| 16 | L2 | **4240** | 4.97 (4.15-7.9) | 7.40 (5.04-10.4) | 2.43 | 0.09 | 3.40 | 0.88-13.2 | 0.08 |
|  |  | **4249** | 3.01 (2.41-5.6) | 4.47 (2.31-6.1) | 1.46 | 0.35 | 2.71 | 0.71-10.4 | 0.15 |
|  |  | **4261** | 4.02 (3.08-6.8) | 5.72 (4.63-7.3) | 1.70 | 0.15 | 1.73 | 0.45-6.6 | 0.42 |
|  |  | **4270** | 3.42 (2.99-5.5) | 5.11 (3.97-6.2) | 1.69 | 0.22 | 2.71 | 0.71-10.4 | 0.15 |
|  |  | **4277** | 3.73 (3.31-5.4) | 4.96 (3.46-6.9) | 1.23 | 0.28 | 2.17 | 0.57-8.3 | 0.26 |
|  | L1 | **5602** | 5.84 (4.63-7.4) | 9.08 (5.95-17.3) | 3.24 | **0.013** | 4.69 | 1.20-18.4 | **0.03** |
|  |  | **5608** | 3.42 (3.05-4.2) | 4.52 (4.04-6.0) | 1.10 | **0.014** | 8.12 | 1.87-35.2 | **0.005** |
|  |  | **5611** | 4.85 (4.17-5.6) | 7.77 (5.47-13.0) | 2.92 | **0.002** | 8.12 | 1.87-35.2 | **0.005** |
|  |  | **5617** | 2.62 (2.28-3.2) | 3.67 (2.76-4.9) | 1.05 | **0.007** | 8.12 | 1.87-35.2 | **0.005** |
| 18 | L2 | **5331** | 19.53 (17.97-25.4) | 20.48 (13.44-27.8) | 0.95 | 0.95 | 1.46 | 0.26-8.1 | 0.67 |
|  |  | **5333** | 14.11 (12.08-19.4) | 14.63 (10.26-22.3) | 0.52 | 0.69 | 1.00 | 0.18-5.7 | 1.00 |
|  |  | **5367** | 11.70 (10.83-15.4) | 12.51 (10.10-18.2) | 0.81 | 0.47 | 1.46 | 0.26-8. 1 | 0.67 |
|  |  | **5406** | 13.71 (11.24-17.2) | 11.72 (10.34-15.5) | -1.96 | 0.60 | 0.66 | 0.11-4.0 | 0.65 |
|  | L1 | **7011** | 1.87 (1.60-2.0) | 4.42 (1.43-6.6) | 2.55 | 0.17 | 3.06 | 0.54-17.4 | 0.21 |
|  |  | **7038** | 4.83 (3.86-5.0) | 17.14 (4.25-22.1) | 12.31 | 0.07 | 3.06 | 0.54-17.4 | 0.21 |
|  |  | **7041** | 4.51 (4.15-5.3) | 18.33 (4.18-22.8) | 13.82 | 0.07 | 4.67 | 0.77-28.5 | 0.10 |
|  |  | **7062** | 5.80 (4.80-6.3) | 19.25 (6.23-23.6) | 13.45 | **0.015** | 7.87 | 1.10-56.1 | **0.04** |
|  |  | **7068** | 4.34 (3.45-4.6) | 17.04 (3.67-22.4) | 12.70 | 0.08 | 3.06 | 0.54-17.4 | 0.21 |
|  |  | **7090** | 3.46 (3.23-4.2) | 5.69 (4.49-16.5) | 2.23 | **0.013** | 7.87 | 1.10-56.1 | **0.04** |
|  |  | **7110** | 37.27 (26.44-38.9) | 35.19 (32.05-40.5) | -2.08 | 0.79 | 0.66 | 0.11-4.0 | 0.65 |
|  |  | **7116** | 5.56 (5.07-5.8) | 10.86 (5.08-22.3) | 5.30 | 0.10 | 3.06 | 0.54-17.4 | 0.21 |
|  |  | **7122** | 3.90 (3.28-4.3) | 13.51 (3.60-16.6) | 9.61 | 0.06 | 3.06 | 0.54-17.4 | 0.21 |
| 31 | L2 | **5518** | 2.33 (1.85-2.5) | 6.23 (4.00-9.5) | 3.90 | **0.000** | 28.00 | 2.82-278 | **0.004** |
|  |  | **5521** | 2.86 (2.23-3.1) | 4.25 (3.06- 5.8) | 1.39 | **0.002** | 8.00 | 1.52-42.0 | **0.01** |
|  |  | **5524** | 8.59 (7.11-17.6) | 11.69 (9.75-16.0) | 3.10 | 0.14 | 1.75 | 0.40-7.7 | 0.46 |
|  |  | **5530** | 4.67 (3.65-7.3) | 6.77 (5.25-8.0) | 2.10 | 0.17 | 2.29 | 0.52-10.0 | 0.27 |
|  |  | **5564** | 9.06 (7.64-19.0) | 14.15 (12.19-22.2) | 5.09 | **0.04** | 5.50 | 1.15-26.4 | **0.03** |
|  |  | **5572** | 11.10 (8.91-21.3) | 18.31 (15.46-29.6) | 7.21 | **0.02** | 13.00 | 2.07-81.5 | **0.006** |
|  |  | **5622** | 19.31 (15.62-33.6) | 19.39 (17.39-29.4) | 0.07 | 0.90 | 0.73 | 0.15-3.5 | 0.69 |
|  |  | **5639** | 13.50 (11.82-16.6) | 20.11 (15.40-31.1) | 6.61 | **0.01** | 5.50 | 1.15-26.4 | **0.03** |
|  |  | **5659** | 21.57 (16.07-35.9) | 28.12 (22.58-38.2) | 6.55 | 0.08 | 4.00 | 0.88-18.3 | 0.07 |
|  | L1 | **6283** | 14.80 (7.49-22.3) | 15.35 (12.16-23.2) | 0.55 | 0.40 | 1.11 | 0.24-5.1 | 0.89 |
|  |  | **6305** | 9.42 (6.78-21.3) | 15.98 (9.62-17.5) | 6.56 | 0.45 | 2.00 | 0.45-9.0 | 0.37 |
|  |  | **6351** | 13.84 (9.24-20.6) | 14.28 (10.83-24.0) | 0.44 | 0.50 | 1.11 | 0.24-5.1 | 0.89 |
|  |  | **6363** | 11.54 (6.01-19.2) | 12.64 (9.33-17.8) | 1.10 | 0.45 | 0.80 | 0.16-3.9 | 0.78 |
| 33 | L2 | **4222** | 2.20 (1.97-2.4) | 11.76 (3.19-18.3) | 9.56 | 0.15 | n/a | n/a | n/a |
|  |  | **4234** | 13.71 (7.03-20.4) | 13.86 (8.97-20.7) | 0.15 | 0.90 | n/a | n/a | n/a |
|  |  | **4240** | 7.91 (3.96-11.9) | 13.95 (7.73-20.4) | 6.04 | 0.51 | n/a | n/a | n/a |
|  |  | **4293** | 2.71 (2.13-3.3) | 5.46 (3.02-13.0) | 2.75 | 0.24 | n/a | n/a | n/a |
|  | L1 | **6986** | 14.33 (8.33-20.3) | 9.10 (8.31-11.5) | -5.23 | 0.70 | n/a | n/a | n/a |
|  |  | **7034** | 1.84 (1.60-2.1) | 2.54 (1.78-3.2) | 0.70 | 0.51 | n/a | n/a | n/a |
|  |  | **7055** | 1.90 (1.87-1.9) | 2.61 (1.75-3.5) | 0.71 | 0.36 | n/a | n/a | n/a |
|  |  | **7062** | 1.79 (1.71-1.9) | 2.36 (2.03-2.8) | 0.57 | 0.24 | n/a | n/a | n/a |
|  |  | **7073** | 2.46 (2.36-2.6) | 3.83 (2.88-4. 6) | 1.37 | 0.24 | n/a | n/a | n/a |
| 35 | L2 | **4214** | 0.94 (0.73-1.8) | 2.81 (1.97-3.6) | 1.87 | **0.03** | 22.00 | 1.54-314 | **0.02** |
|  |  | **4235** | 1.38 (0.74-2.8) | 2.32 (1.84-7.4) | 0.94 | 0.10 | 4.00 | 0.50-32.0 | 0.19 |
|  |  | **4244** | 0.92 (0.57-1.6) | 2.34 (1.95-5.3) | 1.42 | **0.03** | 10.00 | 1.03-97.5 | **0.04** |
|  |  | **4268** | 1.23 (1.00-1.9) | 2.80 (2.16-3.5) | 1.57 | **0.04** | 22.00 | 1.54-314 | **0.03** |
|  |  | **4848** | 1.26 (0.94-2.5) | 3.73 (1.57-6.3) | 2.47 | 0.07 | 4.00 | 0.50-32.0 | 0.19 |
|  |  | **4865** | 1.28 (1.01-3.3) | 3.98 (1.55-8.8) | 2.70 | 0.07 | 4.00 | 0.50-32.0 | 0.19 |
|  |  | **4872** | 1.08 (0.89-1.4) | 4.25 (2.03-9.0) | 3.17 | **0.01** | 22.00 | 1.54-314 | **0.03** |
|  |  | **4877** | 1.00 (0.89-2.4) | 5.00 (2.32-8.6) | 4.00 | **0.01** | 10.00 | 1.03-97.5 | **0.04** |
|  | L2L1 | **5567** | 1.07 (0.50-1.2) | 2.26 (1.71-3.4) | 1.19 | **0.01** | 22.00 | 1.54-314 | **0.03** |
|  |  | **5570** | 0.95 (0.63-1.1) | 1.90 (1.28-2.3) | 0.95 | **0.03** | 6.00 | 0.70-51.1 | 0.10 |
|  |  | **5573** | 1.43 (0.79-1.5) | 2.97 (1.83-5.1) | 1.54 | **0.04** | 6.00 | 0.70-51.1 | 0.10 |
|  |  | **5579** | 0.70 (0.57-1.4) | 2.05 (1.26-2.9) | 1.35 | **0.04** | 10.00 | 1.03-97.5 | **0.04** |
|  |  | **5613** | 5.31 (5.01-6.5) | 8.92 (6.89-13.1) | 3.61 | 0.10 | 10.00 | 1.03-97.5 | **0.04** |
|  |  | **5621** | 3.20 (1.44-3.6) | 5.99 (3.99-8.4) | 2.79 | **0.04** | 6.00 | 0.70-51.1 | 0.10 |
|  |  | **5688** | 5.24 (3.97-6.1) | 12.53 (8.60-19.0) | 7.29 | **0.01** | 10.00 | 1.03-97.5 | **0.04** |
| **Continued next page** | | | | | | | | | |
| 39 | L2L1 | **5615** | 3.40 (2.09-5.7) | 3.00 (1.97-4.9) | -0.40 | 0.71 | 0.56 | 0.06-4.8 | 0.59 |
|  |  | **5621** | 2.45 (2.04-3.5) | 4.80 (2.75-12.0) | 2.35 | 0.07 | 5.00 | 0.58-42.8 | 0.14 |
|  |  | **5655** | 18.98 (14.15-24.4) | 27.94 (15.09-40.4) | 8.96 | 0.27 | 2.78 | 0.37-21.0 | 0.32 |
|  |  | **5698** | 26.13 (21.72-28.9) | 31.63 (21.35-36.7) | 5.50 | 0.37 | 2.78 | 0.37-21.0 | 0.32 |
|  |  | **5731** | 12.07 (8.91-14.2) | 19.82 (17.59-23.5) | 7.75 | **0.01** | 11.66 | 0.92-147 | 0.06 |
| 45 | L2 | **4588** | 22.02 (20.08-26.0) | 26.81 (22.26-36.8) | 4.79 | 0.31 | 3.00 | 0.15-59.9 | 0.47 |
|  |  | **4604** | 30.50 (26.85-42.1) | 32.60 (28.95-42.1) | 2.10 | 0.31 | 3.00 | 0.15-59.9 | 0.47 |
|  |  | **4627** | 14.90 (12.24-17.9) | 15.55 (13.26-22.0) | 0.65 | 1.00 | 1.00 | 0.04-24.6 | 1.00 |
|  |  | **4673** | 10.56 (8.93-11.9) | 11.91 (9.84-15.9) | 1.35 | 0.47 | 3.00 | 0.15-59.9 | 0.47 |
|  |  | **4693** | 10.06 (8.99-11.0) | 11.38 (9.31-14.7) | 1.32 | 0.31 | 9.00 | 0.37-220 | 0.18 |
|  | L1 | **6990** | 2.54 (1.80-2.7) | 4.61 (2.76-6.0) | 2.07 | 0.19 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7015** | 2.31 (1.92-3.0) | 6.93 (2.82-10.1) | 4.62 | 0.31 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7042** | 2.78 (2.42-3.0) | 7.26 (3.20-10.7) | 4.48 | 0.19 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7045** | 1.91 (1.69-2.6) | 6.95 (2.53-10.3) | 5.04 | 0.31 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7066** | 5.17 (4.04-6.6) | 10.24 (6.81-13.2) | 5.07 | 0.11 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7072** | 3.85 (3.05-4.2) | 10.22 (5.99-14.8) | 6.37 | **0.03** | n/a | n/a | n/a |
|  |  | **7088** | 4.12 (3.29-4.7) | 9.21 (4.42-12.2) | 5.09 | 0.31 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7123** | 3.77 (2.74-5.2) | 8.45 (4.23-11.5) | 4.68 | 0.31 | 9.00 | 0.37-220 | 0.18 |
|  |  | **7129** | 7.44 (4.66-9.2) | 10.89 (7.21-12.7) | 3.45 | 0.31 | 3.00 | 0.15-59.9 | 0.47 |
|  |  | **7135** | 5.41 (3.74-7.0) | 9.05 (7.15-9.4) | 3.64 | 0.11 | 9.00 | 0.37-220 | 0.18 |
| 51 | L2L1 | **5484** | 2.02 (1.33-3.9) | 4.11 (2.46-29.3) | 2.09 | 0.23 | 3.00 | 0.15-59.9 | 0.47 |
|  |  | **5490** | 1.49 (0.67-1.5) | 2.58 (1.99-7.4) | 1.09 | 0.14 | n/a | n/a | n/a |
|  |  | **5493** | 3.65 (2.18-6.0) | 4.17 (2.69-26.3) | 0.52 | 0.55 | 0.75 | 0.04-15.0 | 0.85 |
|  |  | **5499** | 1.47 (1.01-1.6) | 3.17 (2.25-22.0) | 1.70 | 0.07 | n/a | n/a | n/a |
|  |  | **5533** | 3.72 (1.78-5.1) | 6.18 (4.33-31.6) | 2.46 | 0.14 | 3.00 | 0.15-59.9 | 0.47 |
| 52 | L2 | **4258** | 9.76 (8.65-11.1) | 11.44 (9.01-12.8) | 1.68 | 0.54 | 4.50 | 0.25-80.6 | 0.31 |
|  |  | **4274** | 2.73 (2.56-2.9) | 3.45 (2.72-3.7) | 0.72 | 0.39 | 4.50 | 0.25-80.6 | 0.31 |
|  |  | **4283** | 3.96 (3.58-4.3) | 6.25 (4.33-7.7) | 2.29 | 0.11 | 12.00 | 0.51-280 | 0.12 |
|  |  | **4292** | 2.05 (2.03-2.3) | 3.73 (2.70-5.6) | 1.68 | 0.18 | 12.00 | 0.51-280 | 0.12 |
|  |  | **4348** | 1.42 (1.28-1.7) | 3.36 (1.91-4.1) | 1.94 | 0.18 | 12.00 | 0.51-280 | 0.12 |
|  | L1 | **7098** | 1.09 (0.75-1.3) | 1.59 (1.41-2.4) | 0.50 | 0.11 | 12.00 | 0.51-280 | 0.12 |
|  |  | **7111** | 1.35 (0.88-1.7) | 1.29 (1.07-1.5) | -0.06 | 1.00 | 0.75 | 0.03-17.5 | 0.86 |
|  |  | **7119** | 0.77 (0.73-1.2) | 1.41 (1.05-2.0) | 0.64 | 0.11 | 4.50 | 0.25-80.6 | 0.31 |
| 58 | E2E4 | **3397** | 0.86 (0.65-8.7) | 20.99 (7.76-27.5) | 20.13 | **0.03** | 9.00 | 0.56-143 | 0.12 |
|  |  | **3412** | 3.29 (1.38-6. 7) | 17.68 (12.50-38.8) | 14.39 | **0.02** | 21.00 | 0.96-458 | 0.05 |
|  |  | **3434** | 2.63 (1.80-9.5) | 22.32 (17.05-50.4) | 19.69 | **0.01** | 21.00 | 0.96-458 | 0.05 |
|  |  | **3437** | 2.61 (1.17-8.3) | 23.91 (13.11-42.8) | 21.30 | **0.02** | 21.00 | 0.96-458 | 0.05 |
|  |  | **3440** | 1.36 (0.96-7.8) | 25.91 (12.13-39.3) | 24.55 | **0.02** | 21.00 | 0.96-458 | 0.05 |
|  |  | **3445** | 1.33 (0.90-2.1) | 1.72 (1.66-3.6) | 0.39 | 0.20 | 1.80 | 0.12-26.2 | 0.67 |
|  |  | **3499** | 5.31 (3.35-27.6) | 44.40 (32.92-90.0) | 39.09 | 0.05 | 21.00 | 0.96-458 | 0.05 |
|  |  | **3502** | 3.45 (2.62-10.6) | 21.72 (14.72-60.3) | 18.27 | **0.02** | 21.00 | 0.96-458 | 0.05 |
|  |  | **3518** | 2.21 (1.22-8.0) | 26.65 (11.15-41.0) | 24.44 | **0.02** | 21.00 | 0.96-458 | 0.05 |
|  | L2 | **4256** | 4.76 (4.25-6.1) | 4.96 (3.84-8.3) | 0.2 | 0.80 | 1.80 | 0.12-26.2 | 0.67 |
|  |  | **4268** | 24.29 (24.09-27.2) | 23.82 (14.49-27.7) | -0.47 | 0.67 | 1.80 | 0.12-26.2 | 0.67 |
|  |  | **4276** | 16.94 (15.92-19.2) | 18.98 (10.99-21.3) | 2.04 | 0.93 | 3.00 | 0.21-42.6 | 0.42 |
|  |  | **4379** | 5.94 (5.12-6.5) | 7.03 (5.66-10.3) | 1.09 | 0.45 | 3.00 | 0.21-42.6 | 0.42 |
|  |  | **4431** | 3.38 (2.75-3.4) | 2.89 (1.69-5.7) | -0.49 | 1.00 | 3.00 | 0.21-42.6 | 0.42 |
|  | L1 | **6396** | 8.14 (6.33-9.8) | 8.13 (4.19-13.9) | -0.01 | 0.93 | 1.80 | 0.12-26.2 | 0.67 |
|  |  | **6446** | 16.90 (13.35-17.6) | 8.91 (5.74-20.2) | -7.99 | 0.27 | 1.00 | 0.06-16.0 | 1.00 |
|  |  | **6457** | 10.68 (6.93-13.2) | 9.13 (3.82-17.6) | -1.55 | 0.93 | 1.80 | 0.12-26.2 | 0.67 |
|  |  | **6482** | 8.81 (7.63-10.6) | 4.41 (2.20-13.1) | -4.40 | 0.45 | 1.00 | 0.06-16.0 | 1.00 |
|  |  | **6585** | 8.76 (7.98-9.3) | 5.56 (5.25-9.4) | -3.20 | 0.20 | 1.00 | 0.06-16.0 | 1.00 |
| 59 | L2L1 | **5572** | 12.51 (11.73-13.3) | 11.20 (10.66-54.5) | -1.31 | 0.66 | 1.00 | 0.03-29.8 | 1.00 |
|  |  | **5578** | 6.74 (6.26-6.8) | 5.90 (5.10-54.6) | -0.84 | 0.66 | 1.00 | 0.03-29.8 | 1.00 |
|  |  | **5584** | 0.59 (0.15-3.0) | 0.61 (0.35-54.6) | 0.02 | 0.66 | 1.00 | 0.03-29.8 | 1.00 |
|  |  | **5618** | 6.44 (4.12-7.0) | 5.00 (0.76-5.9) | -1.44 | 0.38 | n/a | n/a | n/a |
| IQR, interquartile range (minimum-maximum); OR, odds ratio; CI, confidence interval.  Significant p values are highlighted in bold.  There were 19 cases and 19 controls of HPV16; 11 cases and 11 controls of HPV18; 15 cases and 15 controls of HPV31; 8 cases and 2 controls of HPV33; 12 cases and 6 controls of HPV35; 8 cases and 8 controls of HPV39; 4 cases and 4 controls of HPV45; 3 cases and 5 controls of HPV51; 5 cases and 4 controls of HPV52; 8 cases and 4 controls of HPV58; 3 cases and 3 controls of HPV59. HPV56 was excluded from the analysis because it was only detected in cases harboring multiple infections. | | | | | | | | | |