Genetic Colorectal Cancer and Adenoma Risk Variants are Associated with Increasing Adenoma Counts

Supplementary Materials

**Supplemental Table 1: Comparison of CSP #380 Participants Included or Not in Biorepository**

|  |  |  |  |
| --- | --- | --- | --- |
|  | In Biorepository  (n=612) | Not in Biorepository  (n=2509) | p-value |
| Age, Mean (SD) | 64.1 (6.7) | 62.6 (7.2) | <.0001 |
| Male Sex, N (%) | 594 (97.1) | 2427 (96.7) | 0.68 |
| Race, N (%) |  |  | 0.38 |
| White, non Hisp. | 500 (81.7) | 2104 (83.9) |  |
| Black, non Hisp. | 57 (9.3) | 240 (9.6) |  |
| Hispanic | 32 (5.2) | 105 (4.2) |  |
| American Indian/Alaskan Native | 14 (2.3) | 38 (1.5) |  |
| Asian | 7 (1.1) | 19 (0.8) |  |
| Missing | 2 (0.3) | 3(0.1) |  |
| Family history, N (%) | 136 (22.2) | 298 (11.9) | <.0001 |
| Current smoker, N (%) | 136 (22.2) | 557 (22.2) | 0.99 |
| Pack years, Mean (SD) | 42.88 (29.4) | 44.19 (27.9) | 0.63 |
| Past smoker, N (%) | 328 (53.6) | 1324 (52.8) | 0.71 |
| Past pack years, Mean (SD) | 42.37 (36.1) | 39.98 (36.4) | 0.29 |
| Education, N (%) |  |  | 0.44 |
| Completed graduate training | 42 (6.9) | 222 (8.8) |  |
| College graduate | 86 (14.1) | 318 (12.7) |  |
| Some college | 189 (30.9) | 768 (30.6) |  |
| High school graduate | 156 (25.5) | 691 (27.5) |  |
| Some high school | 65 (10.6) | 247 (9.8) |  |
| Junior high school | 58 (9.5) | 211 (8.4) |  |
| Under 7 years schooling | 16 (2.6) | 48 (1.9) |  |
| Missing | 0 (0) | 4 (0.2) |  |
| Marital Status, N (%) |  |  | 0.24 |
| Married | 352 (57.5) | 1395 (55.6) |  |
| Remarried | 27 (4.4) | 77 (3.1) |  |
| Widowed | 43 (7) | 151 (6) |  |
| Separated | 16 (2.6) | 63 (2.5) |  |
| Divorced | 134 (21.9) | 614 (24.5) |  |
| Never Married | 40 (6.5) | 204 (8.1) |  |
| Missing | 0 (0) | 5 (0.2) |  |
| Screening Outcomes |  |  |  |
| Baseline cancer histology, N (%) | 20 (3.3) | 10 (0.4) | <.0001 |
| Baseline advanced neoplasia, N (%) | 172 (28.1) | 158 (6.3) | <.0001 |

**Supplemental Table 2: Prespecified CRC-risk SNPs with effects on CRC susceptibility13,17**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CRC-Risk SNP (n=43) | Locus | Published Risk Allele | Published Risk Allele Frequency | Minor (Risk) Allele CRC OR | Closest Gene |
| rs1035209 | 10q24.2 | T | 0.2 | 1.12 | SLC25A28, NKX2-3 |
| rs10411210 | 19q13.1 | C | 0.9 | 0.87 (1.15) | RHPN2 |
| rs10505477 | 8q24 | A | 0.58 | 0.85 (1.18) | MYC |
| rs10795668 | 10p14 | G | 0.67 | 0.89 (1.12) |  |
| rs10849432 | 12p13.31 | T | 0.91 | 1.07 | CD9 |
| rs10936599 | 3q26.2 | C | 0.75 | 0.93 (1.08) | TERC, MYNN |
| rs11169552 | 12q13.13 | C | 0.75 | 0.92 (1.09) | DIP2B, ATF1 |
| rs11190164 | 10q24.2 | G | 0.16 | 1.10 | SLC25A28, ENTPD7, COX15, CUTC, ABCC2 |
| rs11196172 | 10q25.2 | A | 0.11 | 1.06 | TCF7L2 |
| rs11213809 | 11q23.1 | A | 0.2 | 1.20 | POU2AF1 |
| rs11632715 | 15q13 | A | 0.55 | 0.89 (1.12) | CRAC1/HMPS/GREM1 |
| rs11986063 | 8q23 | T | 0.13 | 1.29 | EIF3H |
| rs12241008 | 10q25.2 | C | 0.09 | 1.12 | VTI1A |
| rs12603526 | 17p13.3 | C | 0.26 | 1.07 | NXN |
| rs12953717 | 18q21 | T | 0.3 | 1.17 | SMAD7 |
| rs1321311 | 6p21.31 | A | 0.2 | 1.10 | CDKN1A |
| rs1535 | 11q12.2 | A | 0.64 | 1.20 | FADS2 |
| rs16892766 | 8q23.3 | C | 0.09 | 1.25 | EIF3H |
| rs16969681 | 15q13 | T | 0.2 | 1.18 | CRAC1/HMPS/GREM1 |
| rs17094983 | 14q23.1 | G | 0.9 | 0.87 (1.15) |  |
| rs17879961 | 22q12 | C | 0.04 | 1.56 | CHEK2 |
| rs1800469 | 19q13.2 | G | 0.69 | 1.16 | TGFB1 |
| rs1800734 | 3p22.2 | A | 0.26 | 1.51 | MLH1 |
| rs1957636 | 14q22.2 | A | 0.41 | 0.93 (1.08) | BMP4 |
| rs2423279 | 20p12.3 | C | 0.26 | 1.07 | HAO1 |
| rs3184504 | 12q24.12 | C | 0.53 | 0.92 (1.09) | SH2B3 |
| rs3217901 | 12p13.32 | G | 0.39 | 1.10 | CCND2 |
| rs3802842 | 11q23 | C | 0.27 | 1.12 |  |
| rs4444235 | 14q22.2 | C | 0.48 | 1.11 | BMP4 |
| rs4464148 | 18q21 | C | 0.16 | 1.15 | SMAD7 |
| rs4813802 | 20p12.3 | G | 0.34 | 1.09 | BMP2 |
| rs4925386 | 20q13.33 | C | 0.68 | 0.93 (1.08) | LAMA5 |
| rs4939827 | 18q21.1 | T | 0.53 | 1.18 | SMAD7 |
| rs6687758 | 1q41 | G | 0.22 | 1.09 |  |
| rs6983267 | 8q24.21 | G | 0.48 | 0.83 (1.20) | MYC |
| rs7014346 | 8q24 | A | 0.34 | 1.19 | MYC |
| rs704017 | 10q22.3 | G | 0.58 | 1.07 | ZMIZ1/AS1 |
| rs7136702 | 12q13.13 | T | 0.33 | 1.06 |  |
| rs7229639 | 18q21.1 | A | 0.16 | 1.02 | SMAD7 |
| rs7259371 | 19q13.1 | A | 0.51 | 0.89 (1.12) | RHPN2 |
| rs73208120 | 12q24.22 | G | 0.11 | 1.16 | NOS1 |
| rs7758229 | 6q25.3 | T | 0.32 | 1.04 | SLC22A3 |
| rs961253 | 20p12.3 | A | 0.37 | 1.12 | BMP2 |

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplemental Table 3. Prespecified CRC-risk SNPs and Risk for Higher Cumulative Adenomas** | | | | | | | | | | | |
|  | | | | | **Cumulative Adenoma Counts** | | | **≥10 Cumulative Adenomas** | | |  |
| **CRC risk-SNP (n=41)** | **CHR** | **CSP# 380 Minor Allele** | **CSP# 380 Minor Allele Frequency** | **CSP# 380 Risk Allele** | **CSP# 380 Minor Allele RR for Multiple Adenomas (Risk RR)** | **95% CI** | **p-value** | **CSP# 380 Minor Allele OR for ≥10 Cumulative Adenomas**  **(Risk OR)** | **95% CI** | **p-value** | **Closest Gene13** |
| rs6687758 | 1 | G | 0.19 | G | 1.10 | 0.89-1.35 | 0.38 | 0.61 (1.65) | 0.22-1.67 | 0.33 |  |
| rs10936599 | 3 | A | 0.24 | G | 0.99 (1.01) | 0.78-1.25 | 0.93 | 0.83 (1.20) | 0.39-1.79 | 0.64 | TERC, MYNN |
| rs1800734 | 3 | A | 0.21 | A | 1.01 | 0.82-1.23 | 0.95 | 1.04 | 0.49-2.22 | 0.92 | MLH1 |
| rs1321311 | 6 | A | 0.25 | G | 0.93 (1.08) | 0.76-1.13 | 0.45 | 0.65 (1.54) | 0.28-1.49 | 0.31 | CDKN1A |
| rs7758229 | 6 | A | 0.33 | G | 0.89 (1.13) | 0.75-1.06 | 0.18 | 0.70 (1.44) | 0.35-1.41 | 0.31 | SLC22A3 |
| rs10505477 | 8 | G | 0.47 | A | 0.92 (1.08) | 0.78-1.09 | 0.35 | 0.68 (1.47) | 0.35-1.34 | 0.26 | MYC |
| rs11986063 | 8 | A | 0.09 | A | 1.14 | 0.85-1.55 | 0.39 | 1.63 | 0.61-4.31 | 0.33 | EIF3H |
| rs16892766 | 8 | C | 0.08 | C | 1.21 | 0.88-1.67 | 0.23 | 1.75 | 0.58-5.25 | 0.32 | EIF3H |
| rs6983267 | 8 | A | 0.46 | G | 0.92 (1.09) | 0.78-1.08 | 0.30 | 0.71 (1.42) | 0.35-1.41 | 0.32 | MYC |
| rs7014346 | 8 | A | 0.36 | A | 1.00 | 0.82-1.21 | 0.96 | 1.17 | 0.59-2.34 | 0.65 | MYC |
| rs1035209 | 10 | A | 0.17 | G | 0.93 (1.08) | 0.74-1.17 | 0.52 | 0.61 (1.65) | 0.22-1.70 | 0.34 | SLC25A28, NKX2-3 |
| rs10795668 | 10 | A | 0.29 | G | 0.98 (1.02) | 0.81-1.18 | 0.80 | 0.83 (1.20) | 0.43-1.61 | 0.59 |  |
| rs11190164 | 10 | G | 0.24 | G | 0.99 (1.01) | 0.82-1.21 | 0.95 | 1.06 | 0.52-2.18 | 0.87 | SLC25A28, ENTPD7, COX15, CUTC, ABCC2 |
| rs11196172 | 10 | A | 0.13 | G | 0.97 (1.04) | 0.76-1.23 | 0.77 | 0.62 (1.61) | 0.18-2.15 | 0.45 | TCF7L2 |
| ***rs12241008*** | ***10*** | ***G*** | ***0.10*** | ***G*** | ***1.31*** | 1.00-1.71 | ***0.05*** | **1.82** | 0.77-4.31 | **0.18** | **VTI1A** |
| rs704017 | 10 | A | 0.44 | G | 0.92 (1.08) | 0.79-1.09 | 0.34 | 1.38 | 0.74-2.57 | 0.32 | ZMIZ1/AS1 |
| rs11213809 | 11 | A | 0.30 | A | 1.06 | 0.88-1.27 | 0.54 | 1.42 | 0.77-2.65 | 0.26 | POU2AF1 |
| rs1535 | 11 | G | 0.35 | G | 1.01 | 0.84-1.12 | 0.95 | 0.94 (1.07) | 0.47-1.87 | 0.86 | FADS2 |
| rs3802842 | 11 | C | 0.30 | C | 1.08 | 0.91-1.28 | 0.39 | 1.41 | 0.75-2.66 | 0.29 |  |
| rs10849432 | 12 | G | 0.13 | G | 1.19 | 0.93-1.50 | 0.16 | 1.45 | 0.58-3.64 | 0.42 | CD9 |
| rs11169552 | 12 | A | 0.26 | G | 0.94 (1.07) | 0.78-1.13 | 0.50 | 0.62 (1.61) | 0.28-1.37 | 0.24 | DIP2B, ATF1 |
| ***rs3184504*** | ***12*** | ***A*** | ***0.42*** | ***G*** | ***0.81 (1.24)*** | 0.69-0.96 | ***0.01*** | **0.48 (2.09)** | 0.24-0.96 | **0.04** | **SH2B3** |
| **rs3217901** | **12** | **G** | **0.42** | **G** | ***1.12*** | 0.95-1.33 | ***0.17*** | **1.94** | 1.02-3.67 | **0.04** | **CCND2** |
| rs7136702 | 12 | A | 0.39 | G | 0.96 (1.04) | 0.81-1.14 | 0.65 | 0.83 (1.20) | 0.42-1.64 | 0.59 |  |
| rs73208120 | 12 | C | 0.09 | C | 1.16 | 0.89-1.51 | 0.28 | 1.46 | 0.53-4.01 | 0.47 | NOS1 |
| rs17094983 | 14 | A | 0.11 | A | 1.03 | 0.79-1.35 | 0.83 | 0.49 (2.02) | 0.15-1.66 | 0.25 |  |
| rs1957636 | 14 | A | 0.44 | G | 0.91 (1.10) | 0.76-1.08 | 0.27 | 0.96 (1.04) | 0.49-1.90 | 0.92 | BMP4 |
| rs4444235 | 14 | G | 0.46 | A | 0.94 (1.06) | 0.80-1.11 | 0.46 | 0.82 (1.22) | 0.44-1.52 | 0.53 | BMP4 |
| rs11632715 | 15 | A | 0.46 | A | 1.01 | 0.86-1.20 | 0.86 | 1.42 | 0.75-2.71 | 0.28 | CRAC1/HMPS/GREM1 |
| rs16969681 | 15 | A | 0.09 | G | 0.86 (1.17) | 0.62-1.18 | 0.34 | 0.76 (1.32) | 0.22-2.60 | 0.66 | CRAC1/HMPS/GREM1 |
| rs12953717 | 18 | A | 0.43 | A | 1.11 | 0.94-1.32 | 0.21 | 1.29 | 0.67-2.47 | 0.45 | SMAD7 |
| rs4464148 | 18 | G | 0.29 | G | 1.13 | 0.95-1.36 | 0.17 | 1.45 | 0.75-2.78 | 0.27 | SMAD7 |
| rs4939827 | 18 | A | 0.50 | A | 1.12 | 0.95-1.32 | 0.17 | 1.09 | 0.58-2.04 | 0.79 | SMAD7 |
| rs7229639 | 18 | A | 0.11 | A | 1.00 | 0.75-1.33 | 0.99 | 0.43 (2.32) | 0.10-1.88 | 0.26 | SMAD7 |
| rs10411210 | 19 | A | 0.14 | A | 1.07 | 0.82-1.39 | 0.62 | 1.62 | 0.59-4.44 | 0.35 | RHPN2 |
| rs1800469 | 19 | A | 0.29 |  | 0.98 (1.02) | 0.80-1.20 | 0.83 | 0.79 (1.27) | 0.39-1.58 | 0.50 | TGFB1 |
| rs7259371 | 19 | A | 0.26 | A | 1.02 | 0.82-1.26 | 0.87 | 1.12 | 0.50-2.48 | 0.78 | RHPN2 |
| ***rs2423279*** | ***20*** | ***G*** | ***0.27*** | ***G*** | ***1.29*** | 1.07-1.55 | ***0.01*** | **1.62** | 0.81-3.22 | **0.17** | **HAO1** |
| rs4813802 | 20 | C | 0.32 | T | 0.90 (1.11) | 0.76-1.07 | 0.25 | 0.82 (1.22) | 0.42-1.58 | 0.55 | BMP2 |
| rs4925386 | 20 | A | 0.33 | A | 1.00 | 0.82-1.21 | 0.97 | 0.90 (1.11) | 0.44-1.86 | 0.79 | LAMA5 |
| ***rs961253*** | ***20*** | ***A*** | ***0.33*** | ***A*** | ***1.23*** | 1.04-1.47 | ***0.02*** | **2.30** | 1.17-4.49 | **0.02** | **BMP2** |

**Supplemental Table 4: Association between Unweighted and Weighted Polygenic Risk Scores (PRS) and Cumulative Adenoma Counts, Stratified by Sex, Race, or Age at Last Colonoscopy\***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Risk Group | Unweighted PRS RR for Multiple Adenomas (95% CI) | p-value | Weighted PRS RR for Multiple Adenomas (95% CI) | p-value |
| Sex |  |  |  |  |
| Male (n=594) | 1.06 (1.00-1.13) | 0.05 | 1.62 (1.07-2.45) | 0.02 |
| Female (n=18) | 1.20 (0.75-2.04) | 0.52 | 2.48 (0.10-86.53) | 0.64 |
| Race |  |  |  |  |
| European (n=500) | 1.06 (0.99-1.13) | 0.08 | 1.51 (0.98-2.32) | 0.06 |
| NonEuropean (n=112) | 1.11 (0.93-1.33) | 0.23 | 0.916 (0.82-7.98) | 0.08 |
| Age |  |  |  |  |
| Age 50-64 (n=153) | 1.17 (1.00-1.37) | 0.05 | 2.48 (1.03-7.78) | 0.04 |
| Age 65-75+ (n=459) | 1.04 (0.97-1.11) | 0.25 | 1.39 (0.90-2.14) | 0.14 |

\* In the each stratified analysis, the respective covariate was not included as an adjustment in the multivariate model (E.G., an adjustment was not made for age in the age stratified analysis, although adjustments for ancestry and sex remained).

**Supplemental Table 5: Comparison of Mean Unweighted and Weighted Polygenic Risk Scores (PRS) between those With and Without ≥10 Cumulative Adenomas, Stratified by Sex, Race, or Age at Last Colonoscopy**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Risk Group | Mean Unweighted PRS for ≥10 Cumulative Adenomas | Mean Unweighted PRS for 0 Cumulative Adenomas | p-value | Mean Weighted PRS for ≥10 Cumulative Adenomas | Mean Weighted PRS for 0 Cumulative Adenomas | p-value |
| Sex |  |  |  |  |  |  |
| Male | 8.43 | 7.82 | 0.13 | 1.24 | 1.13 | 0.09 |
| Female | NA | 7.67 | NA | NA | 1.11 | NA |
| Race |  |  |  |  |  |  |
| European | 8.36 | 7.65 | 0.09 | 1.23 | 1.11 | 0.08 |
| NonEuropean | 10.0 | 8.44 | 0.38 | 1.48 | 1.20 | 0.38 |
| Age |  |  |  |  |  |  |
| Age 50-64 | 9.25 | 7.87 | 0.13 | 1.37 | 1.14 | 0.10 |
| Age 65-75+ | 8.26 | 7.79 | 0.32 | 1.21 | 1.12 | 0.25 |

**Supplemental Table 6: Summary of All SNPs Found to be Associated with Multiple Adenomas**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| SNP | Closest Gene or Putative Target | Published OR | Published p-value | Associated Finding |
| rs10936599 | TERC | 0.888 | 0.007 | Multiple Adenomas18 |
| rs6983267 | MYC | 0.832 | 2.68×10−6 | Multiple Adenomas18 |
| rs10795668 | None | 0.884 | 0.004 | Multiple Adenomas18 |
| rs3802842 | POU2AF1 | 1.223 | 1.74×10−6 | Multiple Adenomas18 |
| rs4444235 | BMP4 | 1.147 | 0.001 | Multiple Adenomas18 |
| rs1957636 | BMP4 | 1.104 | 0.012 | Multiple Adenomas18 |
| rs4939827 | SMAD7 | 0.843 | 1.17×10−5 | Multiple Adenomas18 |
| rs961253 | BMP2 | 1.177 | 4.42×10−5 | Multiple Adenomas18 |
| rs3802842 | C11orf93 | 1.6 | 0.00002 | >10 Adenomas19 |
| rs4779584 | SCG5, GREM1, FMN1, CRAC1 | 1.5 | 0.001 | >10 Adenomas19 |
| rs6983267 | MYC | 1.29 | 5.6 × 10−6 | Multiple Adenomas22 |
| rs10808555 | MYC | 1.19 | 0.005 | Multiple Adenomas22 |
| rs7837328 | MYC | 1.24 | 0.0002 | Multiple Adenomas22 |
| rs10505477 | MYC | 1.14 | 0.05 | Multiple Adenomas22 |
| rs4925386 | LAMA5 | 0.75 | 0.001 | Multiple Adenomas23 |
| rs4779584 | GREM1 | 1.26 | 0.009 | Multiple Adenomas23 |
| rs10505477 | MYC | 1.28 | 0.001 | Multiple Adenomas23 |
| rs6983267 | MYC | 1.26 | 0.002 | Multiple Adenomas23 |
| rs7014346 | MYC | 1.20 | 0.017 | Multiple Adenomas23 |
| rs7837328 | MYC | 1.22 | 0.007 | Multiple Adenomas23 |
| rs6983267 | MYC | 1.54 | 3.74x10-4 | Multiple Adenomas20 |
| rs10795668 | None | 0.64 | 0.00148 | Multiple Adenomas20 |
| rs3802842 | POU2AF1 | 1.31 | 0.0278 | Multiple Adenomas20 |