**SUPPLEMENTARY DATA**

**Table S1.** SNPs genotyped in this study previously associated to CRC genetic susceptibility.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **SNP ID** | **Chr.** | **Gene** | **Used OR (95%CI)** | **Reference** |
| **rs6983267** | 8q24.21 | *MYC* | 1.16 (1.14-1.18) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs719725** | 9p24 | *TPD52L3-UHRF2* | 1.14(1.05-1.15) | Zanke BW et al. Nature Genetics 2007 |
| **rs4939827** | 18q21.1 | *SMAD7* | 1.17 (1.15-1.19) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs7229639** | 18q21 | *SMAD7* | 1.22(1.15-1.29) | Zhang B, et al. Int J Cancer. 2014a |
| **rs16892766** | 8q23.3 | *EIF3H* | 1.20 (1.17-1.24) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3802842** | 11q23.1 | *COLCA2/COLCA1* | 1.12 (1.10-1.14) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs4779584** | 15q13.3 | *GREM1* | 1.26 (1.19-1.34) | Tomlinson IP, et al. Nat Genet. 2008 |
| **rs10795668** | 10p14 | *ARN5SP299/GATA3* | 1.09 (1.07-1.12) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs4444235** | 14q22.2 | *BMP4* | 1.09 (1.07-1.11) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs9929218** | 16q22.1 | *CDH1* | 1.06 (1.04-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs10411210** | 19q13 | *RHNP2* | 1.21 (1.17-1.26) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs961253** | 20p12.3 | *BMP2* | 1.10 (1.08-1.12) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs6691170** | 1q41 | *DUSP10* | 1.09 (1.07-1.12) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs7136702** | 12q13.13 | *LARP4/DIP2B* | 1.06(1.04-1.08) | Houlston et al. Nat Genet 2010 |
| **rs10936599** | 3q26.2 | *TERC* | 1.05 (1.03-1.07) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs11169552** | 12q13.3 | *DIP2B/ATF1* | 1.09 (1.07-1.11) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs4925386** | 20q13.33 | *LAMA5* | 1.12 (1.10-1.15) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs1957636** | 14q22.2 | *BMP4* | 1.06 (1.04-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs4813802** | 20p12.3 | *BMP2* | 1.07 (1.05-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs2736100** | 5p15.33 | *TERT* | 1.07 (1.04-1.10) | Kinnersley et al. Br J Cancer 2012 |
| **rs1321311** | 6p21 | *CDKN1A* | 1.06 (1.03-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3824999** | 11q13.4 | *POLD3* | 1.08 (1.07-1.10) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs5934683** | Xp22.2 | *SHROOM2* | 1.07 (1.04-1.10) | Dunlop et al. Nat Genet. 2012 |
| **rs12080929** | 1p33 | *SLC5A9* | 0.86 (0.78-0.95) | Fernandez-Rozadilla et al. BMC Genomics 2013 |
| **rs11987193** | 8p12 | *DUSP4* | 0.78 (0.70-0.87) | Fernandez-Rozadilla et al. BMC Genomics 2013 |
| **rs10774214** | 12p13.32 | *CCND2* | 1.08 (1.06-1.11) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs647161** | 5q31.1 | *PITX1* | 1.07 (1.05-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs2423279** | 20p12.3 | *HAQ1* | 1.09 (1.07-1.12) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs11903757** | 2q32.3 | *NABP1* | 1.04 (1.02-1.07) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs10911251** | 1q25.3 | *LAMC1* | 1.08 (1.06-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3217810** | 12p13.32 | *CCND2* | 1.13 (1.10-1.17) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3217901** | 12p13.32 | *CCND2* | 1.10 (1.06-1.14) | Peters et al. Gastroenterology 2013 |
| **rs59336** | 12q24.21 | *TBX3* | 1.09 (1.06-1.13) | Peters et al. Gastroenterology 2013 |
| **rs704017** | 10q22.3 | *ZMIZ1-AS1* | 1.08 (1.06-1.10) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs11196172** | 10q25.2 | *TCF7L2* | 1.06 (1.03-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs174537** | 11q12.2 | *MYRF* | 1.07 (1.05-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs4246215** | 11q12.2 | *FEN1* | 1.15(1.12–1.19) | Zhang et al. Nat Genet. 2014b |
| **rs174550** | 11q12.2 | *FADS1* | 1.15(1.12–1.19) | Zhang et al. Nat Genet. 2014b |
| **rs1535** | 11q12.2 | *FADS2* | 1.15(1.12–1.19) | Zhang et al. Nat Genet. 2014b |
| **rs10849432** | 12p13.31 | *CD9* | 1.07 (1.04-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs12603526** | 17p13.3 | *NXN* | 1.07 (1.05-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs1800469** | 19q13.2 | *TGFB1* | 1.05 (1.03-1.06) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs2241714** | 19q13.2 | *B9D2* | 1.09(1.06–1.12) | Zhang et al. Nat Genet. 2014b |
| **rs812481** | 3p14.1 | *LRIG1* | 1.06 (1.04-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs35360328** | 3p22.1 | *CTNNB1* | 1.10 (1.08-1.13) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3184504** | 12q24.12 | *SH2B3* | 1.08 (1.06-1.10) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs73208120** | 12q24.22 | *NOS1* | 1.07 (1.04-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs6066825** | 20q13.13 | *PREX1* | 1.07 (1.06-1.09) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs11190164** | 10q24.2 | *SLC25A28* | 1.08 (1.06-1.10) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs1035209** | 10q24.2 | *ABCC2/MRP2* | 1.08 (1.06-1.10) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3987** | 4q26 | *NDST3* | 1.36 | Real LM et al Plos One 2014 |
| **rs72647484** | 1p36.2 | *CDC42/WNT4* | 1.05 (1.02-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs16941835** | 16q24.1 | *RP11-58A18.1/FOXL1* | 1.05 (1.03-1.07) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs10904849** | 10p13 | *CUBN* | 1.13(1.08-1.19) | Al-Tassan et al. Scientific Reports 2015 |
| **rs17094983** | 14q23.1 | *RTN1* | 1,09 (1,06-1,12) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs12241008** | 10q25.2 | *VTI1A* | 1.19(1.12-1.26) | Wang H et al. Nat Commun. 2014 |
| **rs12970291** | 18q22.3 | *TSHZ1* | 1.27(1.16-1.38) | Cheng TH et al Scientific Reports 2015 |
| **rs4711689** | 6p21.1 | *TFEB* | 1.03 (1.01-1.05) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs6469656** | 8q23.3 | *EIF3H* | 1.12(1.07-1.16) | Zeng et al, Gastroenterology 2016 |
| **rs11064437** | 12p13.3 | *SPSB2* | 1.24 (1.02-1.51) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs6061231** | 20q13.3 | *RPS21* | 1.19(1.12-1.27) | Zeng et al, Gastroenterology 2016 |
| **rs11676348** | 2q35 | *CXCR2* | 0.93 (0.89-0.99) | Khalili et al Carcinogenesis 2015 |
| **rs2238126** | 12p13.2 | *ETV6* | 1.01 (0.99-1.04) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs992157** | 2q35 | *PNKD/TMBIM1* | 1.06 (1.04-1.08) | Huyghe JR, et al. Nat Genet. 2019 |
| **rs3764482** | 18q21.1 | *SMAD7* | 1.48 (1.29-1.70) | Li J et al, Mol Carcinog 2017 |

SNP ID, single nucleotide polymorphism identification. Chr: Chromosome; OR, odds ratio.

**Association tests for individual SNPs**

**Table S2.** Case-control association results obtained by logistic regression analyses. Association results for 1,200 cases and 1,629 controls. Results are based on the reported risk allele from previous CRC GWAS.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **SNP ID\*** | **Region** | **Relevant gene** | **Variant type** | **Risk**  **allele** | **RAF**  **cases/controls** | **OR** | **95%CI** | **P-value** |
| **rs12080929** | 1p33 | *SLC5A9* | intronic variant | T | 0.73/0.73 | 1 | (0.89-1.13) | 0.9984 |
| **rs10911251** | 1q25.3 | *CDC42/WNT* | intergenic variant | A | 0.59/0.59 | 1 | (0.9-1.12) | 0.9507 |
| **rs72647484** | 1p36.12 | *LAMC1* | intronic variant | C | 0.07/0.07 | 0.97 | (0.78-1.19) | 0.7494 |
| **rs6691170** | 1q41 | *DUSP10* | intergenic variant | T | 0.37/0.36 | 1.05 | (0.94-1.17) | 0.3685 |
| **rs992157** | 2q35 | *NABP1* | intergenic variant | A | 0.51/0.52 | 0.98 | (0.88-1.09) | 0.7308 |
| **rs11676348** | 2q35 | *PNKD/TMBIM1* | intronic variant | T | 0.52/0.52 | 1 | (0.9-1.11) | 0.9823 |
| **rs11903757** | 2q32.3 | *CXCR2* | intergenic variant | C | 0.14/0.15 | 0.92 | (0.8-1.07) | 0.2917 |
| **rs10936599** | 3q26.2 | *LRIG1* | intronic variant | C | 0.79/0.76 | 1.16 | (1.02-1.31) | 0.0232 |
| **rs35360328** | 3p22.1 | *CTNNB1* | intergenic variant | A | 0.16/0.14 | 1.12 | (0.97-1.3) | 0.1154 |
| **rs812481** | 3p14.1 | *TERC* | synonymous variant | G | 0.54/0.52 | 1.08 | (0.97-1.2) | 0.1577 |
| **rs7136702** | 4q13.2 | *LARP4/DIP2B* | intergenic variant | T | 0.38/0.36 | 1.07 | (0.96-1.2) | 0.1928 |
| **rs3987** | 4q26 | *NDST3* | intergenic variant | G | 0.45/0.44 | 1.01 | (0.91-1.12) | 0.8651 |
| **rs2736100** | 5p15.33 | *TERT* | intronic variant | A | 0.49/0.5 | 0.94 | (0.84-1.04) | 0.2461 |
| **rs647161** | 5q31.1 | *PITX1* | intronic variant | A | 0.71/0.7 | 1.05 | (0.94-1.17) | 0.3977 |
| **rs4711689** | 6p21.1 | *CDKN1A* | intergenic variant | A | 0.56/0.55 | 1.03 | (0.93-1.15) | 0.5442 |
| **rs1321311** | 6p1.2 | *TFEB* | intronic variant | A | 0.26/0.25 | 1.04 | (0.92-1.17) | 0.537 |
| **rs719725** | 8q23.3 | *DUSP4* | intergenic variant | A | 0.58/0.58 | 0.97 | (0.87-1.08) | 0.5939 |
| **rs16892766** | 8q23.3 | *EIF3H* | intergenic variant | C | 0.06/0.06 | 1.03 | (0.83-1.27) | 0.8119 |
| **rs6983267** | 8q24.21 | *EIF3H* | intargenic variant | G | 0.54/0.53 | 1.05 | (0.94-1.17) | 0.3843 |
| **rs6469656** | 8q23.3 | *MYC* | non coding transcript variant / intronic variant | A | 0.88/0.88 | 1.04 | (0.88-1.23) | 0.627 |
| **rs11987193** | 8p12 | *TPD52L3/UHRF2* | intronic variant | C | 0.73/0.74 | 0.94 | (0.84-1.06) | 0.3477 |
| **rs10795668** | 10p14 | *ARN5SP299/GATA3* | intronic variant | A | 0.3/0.32 | 0.9 | (0.8-1) | 0.0597 |
| **rs704017** | 10q22.3 | *ZMIZ1-AS1* | intronic variant | G | 0.56/0.52 | 1.2 | (1.08-1.34) | 6,00E-04 |
| **rs11196172** | 10q25.2 | *ABCC2/MRP2* | intergenic variant | A | 0.14/0.16 | 0.88 | (0.75-1.02) | 0.0836 |
| **rs1035209** | 10q24.2 | *SLC25A28* | intergenic variant | T | 0.2/0.17 | 1.2 | (1.05-1.38) | 0.0074 |
| **rs12241008** | 10q25.2 | *TCF7L2* | intronic variant | C | 0.09/0.09 | 0.95 | (0.79-1.15) | 0.6137 |
| **rs11190164** | 10q24.2 | *VTI1A* | intronic variant | G | 0.25/0.23 | 1.12 | (0.99-1.26) | 0.0806 |
| **rs4246215** | 11q12.2 | *FEN1* | 3'-UTR variant | T | 0.3/0.34 | 0.84 | (0.75-0.95) | 0.0039 |
| **rs3802842** | 11q23.1 | *MYRF* | intronic variant | C | 0.28/0.28 | 1.03 | (0.92-1.16) | 0.607 |
| **rs174537** | 11q12.2 | *FADS2* | intronic variant | G | 0.7/0.66 | 1.18 | (1.05-1.32) | 0.0043 |
| **rs1535** | 11q12.2 | *FADS1* | intronic variant | A | 0.69/0.65 | 1.17 | (1.05-1.31) | 0.0061 |
| **rs174550** | 11q12.2 | *POLD3* | intronic variant | T | 0.7/0.66 | 1.2 | (1.07-1.34) | 0.0016 |
| **rs3824999** | 11q13.4 | *COLCA1/COLCA2* | intronic variant | G | 0.5/0.5 | 1.04 | (0.93-1.15) | 0.4936 |
| **rs73208120** | 12q24.22 | *ETV6* | intronic variant | G | 0.06/0.06 | 1.02 | (0.81-1.27) | 0.8886 |
| **rs3217901** | 12.13.32 | *CD9* | intronic variant | G | 0.36/0.36 | 0.99 | (0.88-1.1) | 0.8354 |
| **rs11169552** | 12q13.12 | *SPSB2* | splice acceptor variant | C | 0.77/0.76 | 1.04 | (0.92-1.18) | 0.5512 |
| **rs59336** | 12q24.21 | *CCND2* | intronic variant | T | 0.53/0.51 | 1.07 | (0.96-1.19) | 0.1996 |
| **rs10849432** | 12p13.31 | *CCND2* | intronic variant | T | 0.87/0.86 | 1.04 | (0.89-1.21) | 0.6366 |
| **rs3184504** | 12q24.12 | *CCND2* | intronic variant | C | 0.55/0.56 | 0.97 | (0.87-1.07) | 0.5241 |
| **rs11064437** | 12p13.31 | *DIP2B/ATF1* | intergenic variant | C | 0.99/0.98 | 1.49 | (0.95-2.35) | 0.0859 |
| **rs10774214** | 12p13.32 | *SH2B3* | missense variant | T | 0.37/0.36 | 1.08 | (0.97-1.2) | 0.1823 |
| **rs2238126** | 12p13.2 | *TBX3* | intronic variant | G | 0.17/0.17 | 1 | (0.87-1.14) | 0.9638 |
| **rs3217810** | 12p13.32 | *NOS1* | intronic variant | T | 0.1/0.08 | 1.21 | (1.01-1.46) | 0.0425 |
| **rs4444235** | 14q22.2 | *BMP4* | intergenic variant | C | 0.55/0.55 | 1.01 | (0.91-1.13) | 0.8243 |
| **rs17094983** | 14q23.1 | *BMP4* | intronic variant | G | 0.86/0.85 | 1.08 | (0.93-1.25) | 0.3255 |
| **rs1957636** | 14q22.2 | *RTN1* | intergenic variant | T | 0.42/0.41 | 1.06 | (0.95-1.18) | 0.291 |
| **rs4779584** | 15q13.3 | *GREM1* | intergenic variant | T | 0.19/0.18 | 1.06 | (0.93-1.22) | 0.3726 |
| **rs9929218** | 16q22.1 | *CDH1* | intronic variant | G | 0.71/0.69 | 1.12 | (0.99-1.25) | 0.0619 |
| **rs16941835** | 16q24.1 | *FOXL1* | intergenic variant | C | 0.17/0.18 | 0.95 | (0.83-1.09) | 0.4603 |
| **rs12603526** | 17q13.3 | *NXN* | intron variant | C | 0.01/0.01 | 1.22 | (0.77-1.93) | 0.3991 |
| **rs4939827** | 18q21.1 | *SMAD7* | intronic variant | T | 0.57/0.53 | 1.17 | (1.05-1.31) | 0.0031 |
| **rs12970291** | 18q22.3 | *TSHZ1* | intergenic variant | A | 0.03/0.04 | 0.89 | (0.67-1.18) | 0.4007 |
| **rs10411210** | 19q13.11 | *RHPN2* | intronic variant | C | 0.88/0.88 | 1.04 | (0.88-1.22) | 0.6621 |
| **rs2241714** | 19q13.2 | *B9D2* | missense variant / 2 kb upstream variant | C | 0.67/0.64 | 1.12 | (1-1.25) | 0.0443 |
| **rs1800469** | 19q13.2 | *TGFB1* | 2 kb upstream variant / 0.5 kb downstream variant | G | 0.67/0.64 | 1.13 | (1.01-1.27) | 0.0272 |
| **rs2423279** | 20p12.3 | *HAQ1* | intergenic variant | C | 0.32/0.3 | 1.06 | (0.94-1.18) | 0.3389 |
| **rs961253** | 20p12.3 | *BMP2* | intergenic variant | A | 0.36/0.32 | 1.16 | (1.04-1.3) | 0.0093 |
| **rs6066825** | 20q13.13 | *BMP2* | intergenic variant | A | 0.6/0.57 | 1.1 | (0.99-1.23) | 0.0717 |
| **rs6061231** | 20q13.33 | *PREX1* | intronic variant | C | 0.75/0.72 | 1.19 | (1.06-1.34) | 0.0035 |
| **rs4925386** | 20q13.33 | *LAMA5* | intergenic variant | C | 0.71/0.67 | 1.18 | (1.05-1.32) | 0.0039 |
| **rs4813802** | 20p12.3 | *LAMA5* | intronic variant | G | 0.31/0.31 | 1.03 | (0.92-1.16) | 0.5898 |
| **rs5934683** | Xp22.2 | *SHROOM2* | intronic variant | C | 0.61/0.62 | 0.94 | (0.83-1.06) | 0.3191 |

\*SNPs with genotyping success rate below 90% were removed from subsequent analyses (including rs7229639, rs3764482). We also removed a monomorphic SNP (rs10904849). SNP, single nucleotide polymorphism; RAF, risk allele frequency; OR, odds ratio; 95%CI, 95% confidence interval; UTR, untranslated region; kb, kilobase.

**Table S3.** Discriminative capacity of predictive models after 10-fold cross-validation using an unweighted PRS and comparing the total number of cases and controls.

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive model** | **AUROC (95%CI)** | **AUROC improvement** | **P-value** |
| **Sex-age-based** | 0.594 (0.573-0.615) |  |  |
| **PRS-based** | 0.611 (0.590-0.632) | 0.017\* | 0.006 |
| **FIT-based** | 0.623 (0.602-0.644) | 0.028\* | 0.0001 |
| **FIT and PRS-based** | 0.635 (0.615-0.656) | 0.012\*\* | 0.008 |

AUROC, Area Under de Curve; CI, confidence interval. \*Compared to Sex-age-based. \*\*Compared to FIT-based.

**Table S4.** Discriminative capacity of predictive models comparing extreme phenotypes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive model** | **AUROC (95%CI)** | **AUROC improvement** | **P-value** |
| **Sex-age-based** | 0.638 (0.611-0.666) |  |  |
| **PRS-based** | 0.665 (0.637-0.693) | 0.027\* | 0.00025 |
| **FIT-based** | 0.678 (0.652-0.706) | 0.040\* | 0.000014 |
| **FIT and PRS-based** | 0.698 (0.672-0.725) | 0.019\*\* | 0.0016 |

AUROC, Area Under de Curve; CI, confidence interval. \*Compared to Sex-age-based. \*\*Compared to FIT-based.

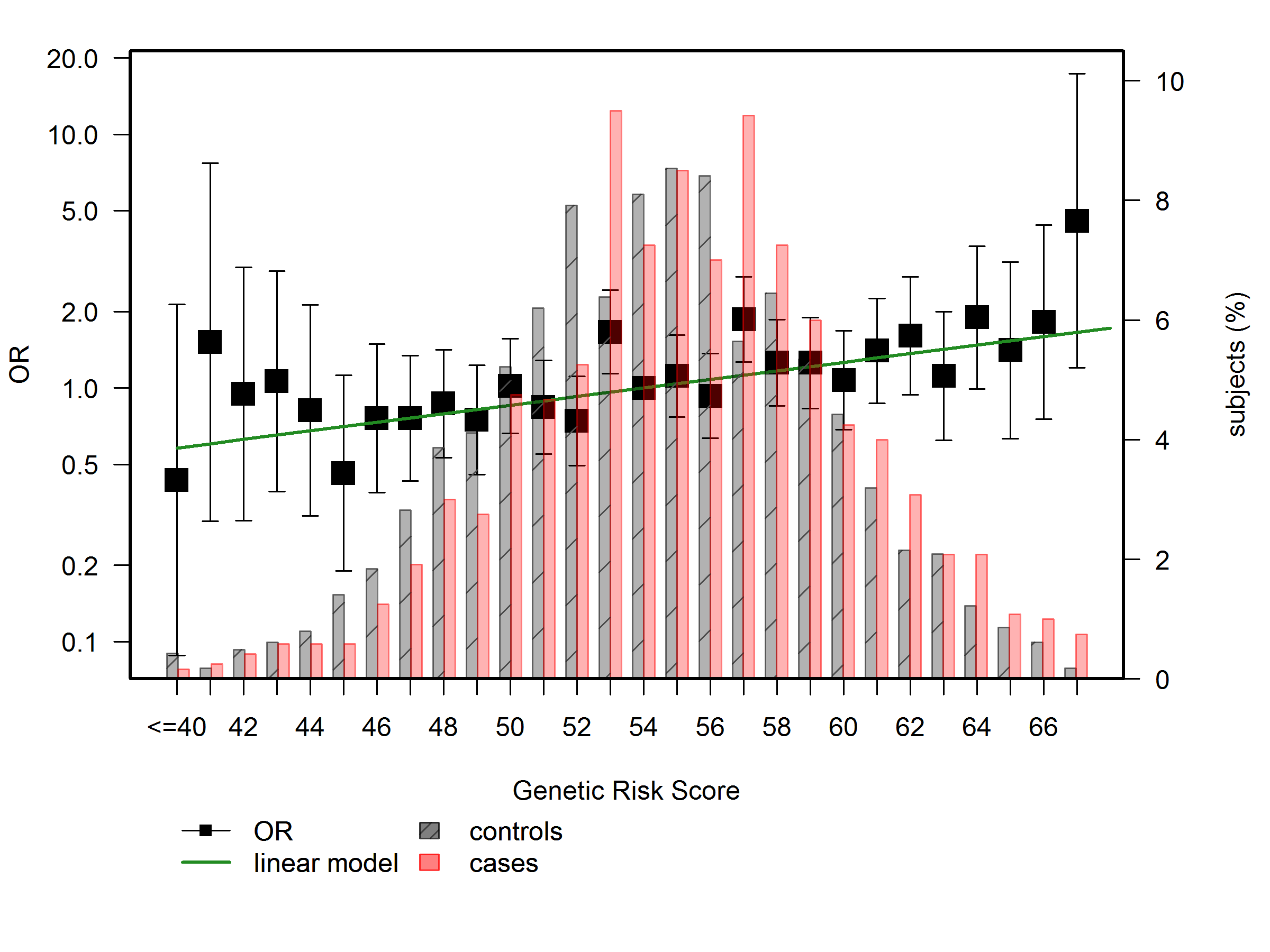
**Table S5.** Discriminative capacity of predictive models after 10-fold cross-validation comparing extreme phenotypes.

|  |  |  |  |
| --- | --- | --- | --- |
| **Predictive model** | **AUROC (95%CI)** | **AUROC improvement** | **P-value** |
| **Sex-age-based** | 0.625 (0.596-0.653) |  |  |
| **PRS-based** | 0.660 (0.632-0.688) | 0.035\* | 0.000018 |
| **FIT-based** | 0.670 (0.642-0.697) | 0.045\* | 0.0000048 |
| **FIT and PRS-based** | 0.693 (0.666-0.720) | 0.023\*\* | 0.00030 |

AUROC, Area Under de Curve; CI, confidence interval. \*Compared to Sex-age-based. \*\*Compared to FIT-based.

**Weighted polygenic risk score**

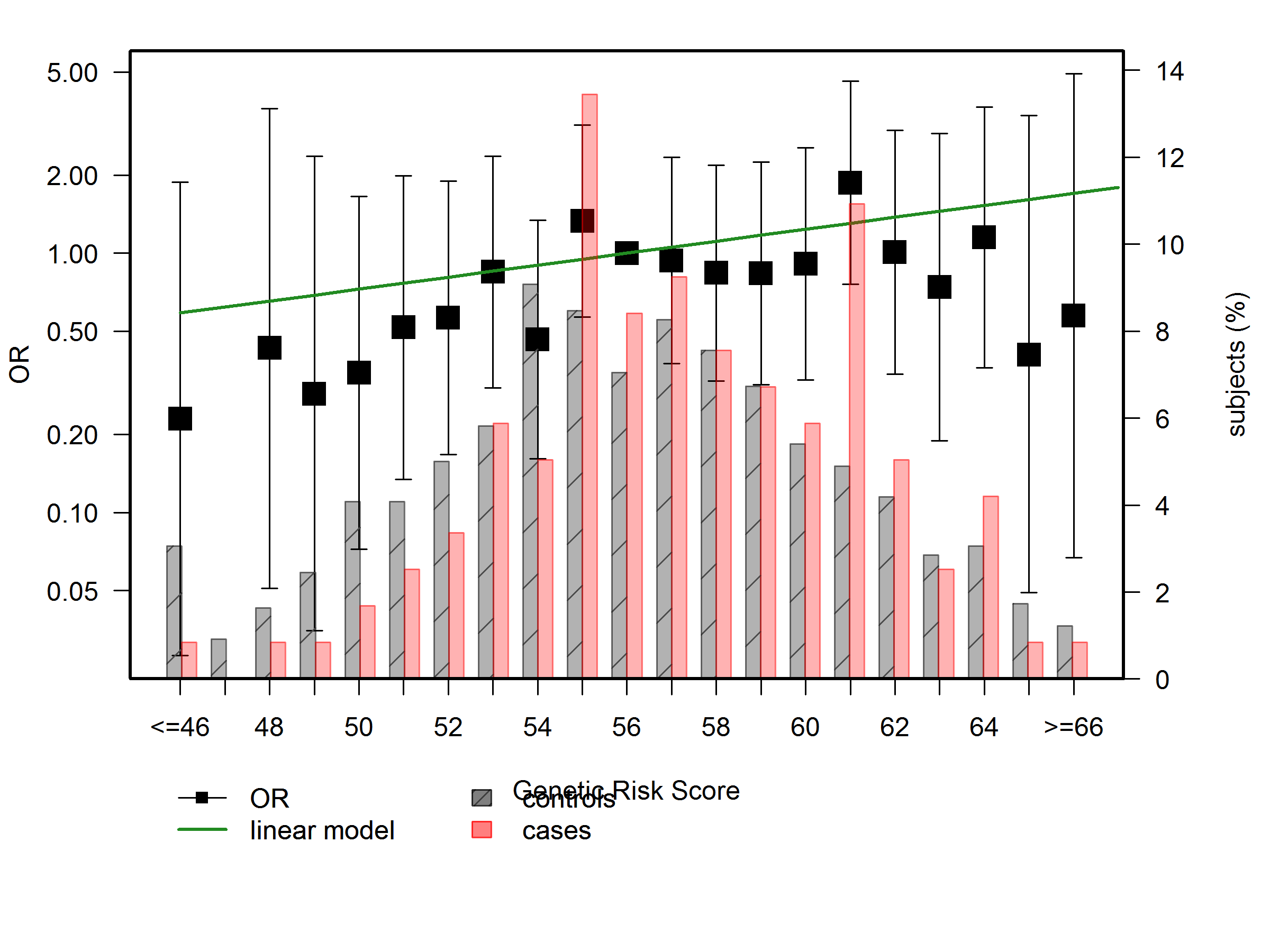
The median number of risk alleles in controls, 54, was considered as reference. Cases and controls were grouped considering subjects carrying ≤ 40 risk alleles and ≥ 68 alleles, because of the small number of subjects at these extremes. We detected that the risk score was higher in the cases group compared to the control cohort (OR=1.04; 95%CI 1.02-1.05; P-value= 0.0000). We also observed that there was a 2-fold increase in CRC risk was detected for subjects in the highest decile of risk alleles (≥ 62), compared to those in the first decile (≤ 52)(OR=2.00, 95%CI 1.42-2.81, P-value=0.0001). As shown in Figure S1, the increase in risk per allele was linear, indicating the independent additive contribution of each allele to have a HRL. We also calculated if there was an association between age and sex and PRS but there was none.



**Figure S1.** Weighted polygenic risk score. Distribution of risk by allele number for the 62 SNPs genotyped. The presence of multiple CRC risk alleles is displayed for SPS cases (bold bars) and controls (stripped bars). OR, odds ratio.

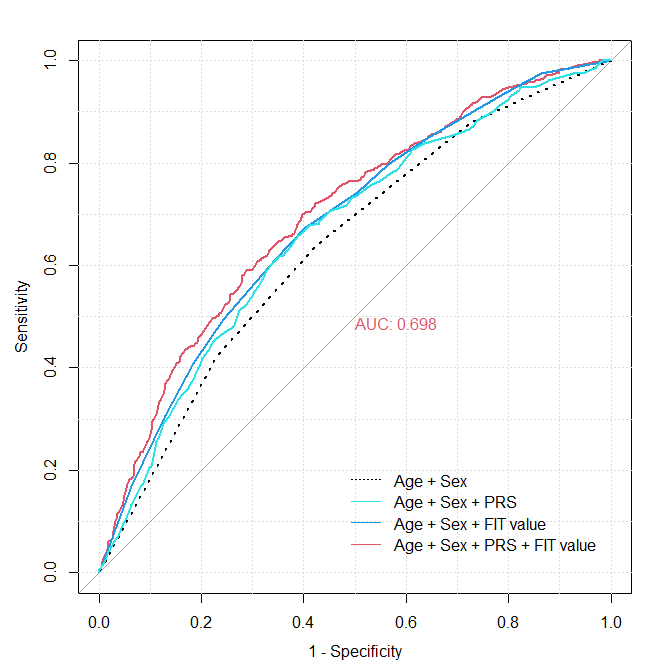
**Polygenic risk score comparing extreme phenotypes**

The median number of risk alleles in controls, 56, was considered as reference. Cases and controls were grouped considering subjects carrying ≤ 46 risk alleles and ≥ 67 alleles, because of the small number of subjects at these extremes. We detected that the risk score was higher in the cases group compared to the control cohort (OR=1.05; 95%CI 1.01-1.08; P-value= 0.0146). We also observed that there was a 3-fold increase in CRC risk was detected for subjects in the highest decile of risk alleles (≥ 64), compared to those in the first decile (≤ 51)(OR=3.15, 95%CI 1.06 -9.41, P-value=0.0395). As shown in Figure S2, the increase in risk per allele was linear, indicating the independent additive contribution of each allele to have a HRL. We also calculated if there was an association between age and sex and PRS but there was none.

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**Figure S2.** Genetic risk score. Distribution of risk by allele number for the 62 SNPs genotyped comparing extreme phenotypes (negative colonoscopy vs. CRC/HRL). The presence of multiple CRC risk alleles is displayed for SPS cases (bold bars) and controls (stripped bars). OR, odds ratio.

**Development and validation of a predictive model for colorectal cancer screening**

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**Figure S3.** Area under the curve (AUROC) of the different predictive models comparing extreme phenotypes. AUROC, Area Under de Curve; CI, confidence interval.