

Supplementary Materials to:

**Genetic variants associated with colorectal-cancer risk:  
comprehensive research synopsis, meta-analysis, and  
epidemiological evidence**

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## **Webappendix notes for Venice criteria**

### **Amount of evidence**

A: Large-scale evidence — minor genetic group (alleles or genotypes) in cases and controls >1,000.

B: Moderate amount of evidence — minor genetic group in cases and controls between 100 and 1,000.

C: Little evidence — minor genetic group in cases and controls <100.

### **Replication of association**

A: Little between-study heterogeneity —  $I^2 < 25\%$ .

B: Moderate between-study heterogeneity —  $I^2$  between 25% and 50%.

C: Large between-study heterogeneity —  $I^2 > 50\%$ .

### **Protection from bias**

A: No observable bias and bias was unlikely to explain the presence of the association.

B: No obvious bias may affect the presence of the association, but there is considerable missing information on the identification of evidence.

C: Bias is demonstrable or is likely to explain the presence of the association.

### **General checks for bias**

1) Association lost with exclusion of first study;

- 2) Association lost with exclusion of studies deviated from HWE;
- 3) Small magnitude of association (i.e.,  $0.87 < OR < 1.15$ );
- 4) Evidence of small-study effect ( $p < 0.10$  in modified Egger test);
- 5) Evidence is presented for an excess of individual studies with significant findings ( $p < 0.10$  in significant bias test).

Appendix Table 1. Associations of 267 genetic variants with colorectal-cancer risk in meta-analysis using different genetic models

| Genes                | Variant ID | Genetic variants                                   | Category       | Comparison               | Ethnicity | Number evaluated Studies | Colorectal-cancer risk meta-analysis |          |               |                  |                             |                    |    |                |                         |                       | Dominant model   |                             | Recessive model    |                  |                             |                    |    |
|----------------------|------------|--|----------------|--------------------------|-----------|--------------------------|--------------------------------------|----------|---------------|------------------|-----------------------------|--------------------|----|----------------|-------------------------|-----------------------|------------------|-----------------------------|--------------------|------------------|-----------------------------|--------------------|----|
|                      |            |  |                |                          |           |                          | Cases                                | Controls | Frequency (%) | OR (95% CI)      | P value                     | I <sup>2</sup> (%) | Q  | P <sup>a</sup> | Modified P <sup>a</sup> | Excess P <sup>a</sup> | OR (95% CI)      | P value                     | I <sup>2</sup> (%) | OR (95% CI)      | P value                     | I <sup>2</sup> (%) |    |
| <i>ACB1</i>          | 1          | rs1128503 (Gln412Gly)                              | intron         | T vs C                   | All       | 3                        | 195                                  | 324      | 42.59         | 0.83 (0.52-1.33) | 0.434                       | 68                 | 6  | 0.05           | 0.82                    | 0.27                  | 1.1 (0.97-1.24)  | 0.134                       | 60                 | 1.04 (0.93-1.14) | 0.421                       | 0                  |    |
| <i>ACB1</i>          | 2          | rs1202168  | synonymous     | T vs C                   | White     | 4                        | 6,318                                | 5,805    | 41.25         | 1.05 (0.97-1.14) | 0.191                       | 55                 | 7  | 0.08           | 0.65                    | 0.13                  | 1.1 (0.97-1.24)  | 0.134                       | 60                 | 1.04 (0.93-1.14) | 0.421                       | 0                  |    |
| <i>ACB1</i>          | 3          | rs2229109 (Ser400Asn)                              | non-synonymous | A vs G                   | White     | 3                        | 4,242                                | 4,178    | 5.19          | 0.99 (0.86-1.13) | 0.869                       | 0                  | 1  | 0.57           | 0.47                    | 1.00                  | 0.99 (0.86-1.14) | 0.892                       | 0                  | 0.92 (0.32-2.67) | 0.876                       | 2                  |    |
| <i>ACB1</i>          | 4          | r868755  | intron         | T vs G                   | White     | 3                        | 2,958                                | 3,255    | 42.06         | 1.06 (0.99-1.14) | 0.106                       | 0                  | 2  | 0.39           | 0.28                    | 0.37                  | 1.09 (0.96-1.24) | 0.166                       | 25                 | 1.04 (0.96-1.2)  | 0.573                       | 14                 |    |
| <i>ACB1</i>          | 5          | r9028254 (Asn21Asp)                                | non-synonymous | A vs G                   | White     | 4                        | 5,292                                | 5,234    | 8.89          | 1.01 (0.78-1.08) | 0.400                       | 96                 | 68 | 0.09           | 0.99                    | 0.27                  | 1.00             | 0.99 (0.86-1.14)            | 0.892              | 0                | 0.92 (0.32-2.67)            | 0.876              | 2  |
| <i>ACB1/MDR1</i>     | 6          | rs1045642 (p.Ile1145Ile, c.3435T>C)                | synonymous     | C vs T                   | All       | 13                       | 6,312                                | 7,128    | 47.52         | 0.98 (0.89-1.07) | 0.611                       | 58                 | 27 | 0.00           | 0.83                    | 0.00                  | 1.00             | 1.00 (0.88-1.13)            | 0.984              | 46               | 0.97 (0.83-1.14)            | 0.721              | 61 |
| <i>ACB1/MDR1</i>     | 7          | rs2032582 (2677G>T)                                | non-synonymous | T vs G                   | All       | 4                        | 558                                  | 672      | 47.02         | 0.94 (0.78-1.14) | 0.555                       | 22                 | 4  | 0.28           | 0.02                    | 1.00                  | 0.86 (0.64-1.16) | 0.327                       | 25                 | 1.03 (0.74-1.43) | 0.865                       | 23                 |    |
| <i>ACB1</i>          | 8          | 287-bp repeat (LD)                                 | STR            | ins vs del               | White     | 3                        | 509                                  | 6,895    | 47.28         | 1.01 (0.87-1.18) | 0.857                       | 0                  | 1  | 0.76           | 0.11                    | 1.00                  | 1.09 (0.85-1.40) | 0.509                       | 0                  | 1.08 (0.66-1.79) | 0.511                       | 67                 |    |
| <i>ADH1B/ADH2</i>    | 9          | rs1229984 (ADH1B*2; H1S47ARG)                      | non-synonymous | G vs A                   | All       | 6                        | 3,130                                | 4,815    | 21.27         | 1.06 (0.89-1.25) | 0.525                       | 67                 | 15 | 0.01           | 0.44                    | 0.01                  | 1.06 (0.83-1.34) | 0.662                       | 72                 | 1.16 (0.93-1.43) | 0.185                       | 0                  |    |
| <i>ADH1C/ADH3</i>    | 10         | r9698 (p.Ile350Phe, p.Ile350Val)                   | non-synonymous | G vs A                   | All       | 9                        | 4,817                                | 8,019    | 36.21         | 1.02 (0.93-1.15) | 0.569                       | 71                 | 27 | 0.00           | 0.52                    | 0.07                  | 1.00             | 1.00 (0.87-1.16)            | 0.952              | 66               | 1.12 (0.93-1.34)            | 0.254              | 59 |
| <i>ADPOO</i>         | 11         | rs1501299  | intron         | G vs C                   | All       | 6                        | 1,743                                | 2,386    | 30.43         | 0.98 (0.88-1.09) | 0.674                       | 18                 | 6  | 0.30           | 0.70                    | 1.00                  | 0.94 (0.80-1.11) | 0.480                       | 37                 | 1.10 (0.87-1.37) | 0.431                       | 5                  |    |
| <i>ADPOO</i>         | 12         | rs2266729 (nearGene-5, C-11374G)                   | intergenic     | G vs C                   | All       | 6                        | 3,889                                | 4,290    | 31.79         | 0.93 (0.84-1.03) | 0.158                       | 52                 | 10 | 0.06           | 0.11                    | 0.57                  | 0.9 (0.78-1.04)  | 0.159                       | 57                 | 0.94 (0.81-1.09) | 0.392                       | 0                  |    |
| <i>ADIPOR1</i>       | 13         | rs1342387  | intron         | A vs G                   | All       | 3                        | 1,092                                | 1,295    | 45.91         | 0.9 (0.8-1.01)   | 0.068                       | 0                  | 1  | 0.54           | 0.11                    | 0.00                  | 0.9 (0.75-1.07)  | 0.226                       | 0                  | 0.82 (0.67-1.01) | 0.068                       | 0                  |    |
| <i>ADIPOR1</i>       | 14         | rs7539542  | 3' UTR         | C vs G                   | All       | 3                        | 1,098                                | 1,301    | 57.23         | 1.01 (0.84-1.21) | 0.950                       | 53                 | 4  | 0.12           | 0.88                    | 1.00                  | 1.05 (0.85-1.29) | 0.669                       | 0                  | 1.05 (0.85-1.29) | 0.669                       | 0                  |    |
| <i>ALDH2</i>         | 15         | r671 (p.Glu487Leu, p.Glu504Lys, c.1510G>A)         | non-synonymous | A vs G                   | All       | 8                        | 4,359                                | 6,078    | 12.38         | 1.02 (0.82-1.26) | 0.865                       | 70                 | 23 | 0.00           | 0.47                    | 0.00                  | 0.98 (0.77-1.24) | 0.841                       | 64                 | 1.12 (0.69-1.83) | 0.638                       | 67                 |    |
| <i>ALOX12/12-LOX</i> | 16         | rs1266697 (p.Gln61Arg, c.782G>A)                   | non-synonymous | A vs G                   | All       | 7                        | 2,725                                | 4,912    | 44.07         | 1.12 (0.95-1.31) | 0.172                       | 78                 | 27 | 0.00           | 0.39                    | 0.16                  | 1.13 (0.89-1.43) | 0.317                       | 78                 | 1.16 (0.95-1.42) | 0.156                       | 55                 |    |
| <i>ALOX5</i>         | 17         | rs4986832 (nearGene-5, -1708 G>A, c.3400G>A)       | intergenic     | A vs G                   | All       | 3                        | 452                                  | 723      | 14.73         | 0.86 (0.59-1.26) | 0.441                       | 58                 | 5  | 0.09           | 0.28                    | 0.23                  | 0.87 (0.55-1.35) | 0.522                       | 67                 | 0.69 (0.29-1.63) | 0.395                       | 0                  |    |
| <i>APC</i>           | 18         | rs1801155 (I1307K, T3920A)                         | non-synonymous | carriers vs non-carriers | Jewish    | 3                        | 804                                  | 6,188    | 6.80          | 1.96 (1.37-2.79) | <b>1.99e-10<sup>a</sup></b> | 0                  | 0  | 0.84           | 0.64                    | 1.00                  | 1.96 (1.37-2.79) | <b>1.99e-10<sup>a</sup></b> | 0                  | 1.96 (1.37-2.79) | <b>1.99e-10<sup>a</sup></b> | 0                  |    |
| <i>APC</i>           | 19         | rs1801166 (E1317Q)                                 | non-synonymous | (CC>G) vs GG             | All       | 4                        | 3,574                                | 5,223    | 1.10          | 1.69 (0.85-3.35) | 0.134                       | 64                 | 8  | 0.04           | 0.76                    | 1.00                  | 1.69 (0.85-3.35) | 0.134                       | 64                 | 1.69 (0.85-3.35) | 0.134                       | 64                 |    |
| <i>APC</i>           | 20         | rs2229992 (p.Tyr486Tyr)                            | synonymous     | T vs C                   | All       | 3                        | 1,793                                | 1,785    | 39.78         | 0.96 (0.87-1.05) | 0.357                       | 0                  | 2  | 0.46           | 0.48                    | 1.00                  | 0.9 (0.76-1.05)  | 0.182                       | 26                 | 1.02 (0.85-1.22) | 0.918                       | 0                  |    |
| <i>APC</i>           | 21         | rs2229995 (p.Gly250Ser, c.7504G>A)                 | non-synonymous | A vs G                   | White     | 3                        | 1,130                                | 1,626    | 1.75          | 1.25 (0.85-1.85) | 0.258                       | 0                  | 0  | 0.93           | 0.77                    | 1.00                  | 1.26 (0.85-1.87) | 0.250                       | 0                  | 1.01 (0.83-1.23) | 0.818                       | 0                  |    |
| <i>APC</i>           | 22         | rs1411145 (Thr497Thr)                              | synonymous     | C vs T                   | All       | 4                        | 3,644                                | 2,817    | 36.14         | 1.02 (0.92-1.13) | 0.963                       | 13                 | 3  | 0.33           | 0.13                    | 0.00                  | 1.00             | 1.00 (0.84-1.08)            | 0.391              | 0                | 1.01 (0.83-1.23)            | 0.918              | 0  |
| <i>APC</i>           | 23         | rs12427 (p.Gly1678Gly)                             | synonymous     | G vs A                   | All       | 4                        | 2,543                                | 2,790    | 35.63         | 1.01 (0.93-1.09) | 0.879                       | 5                  | 3  | 0.37           | 0.06                    | 1.00                  | 0.95 (0.82-1.11) | 0.529                       | 20                 | 1.01 (0.83-1.24) | 0.909                       | 0                  |    |
| <i>APC</i>           | 24         | rs459552 (p.Val1822Asp, c.5465T>A)                 | non-synonymous | G vs T                   | All       | 8                        | 6,654                                | 7,117    | 22.27         | 0.96 (0.91-1.02) | 0.205                       | 0                  | 5  | 0.66           | 0.19                    | 1.00                  | 0.95 (0.89-1.02) | 0.171                       | 0                  | 0.98 (0.84-1.14) | 0.752                       | 0                  |    |
| <i>APC</i>           | 25         | rs465899 (p.Pro1960Pro)                            | synonymous     | C vs T                   | All       | 3                        | 1,822                                | 2,114    | 45.88         | 1.02 (0.93-1.12) | 0.710                       | 0                  | 2  | 0.39           | 0.78                    | 1.00                  | 1.00 (0.84-1.16) | 0.535                       | 39                 | 0.4 (0.09-1.87)  | 0.242                       | 0                  |    |
| <i>APC</i>           | 26         | rs1048945 (p.Gln518His, c.153G>C)                  | non-synonymous | G vs T                   | White     | 3                        | 3,224                                | 3,369    | 4.05          | 0.89 (0.63-1.25) | 0.407                       | 41                 | 3  | 0.19           | 0.57                    | 1.00                  | 0.90 (0.64-1.26) | 0.535                       | 39                 | 0.4 (0.09-1.87)  | 0.242                       | 0                  |    |
| <i>APC/APEX</i>      | 27         | rs1380156 (p.Asp418Glu, c.444T>G)                  | non-synonymous | G vs T                   | All       | 4                        | 4,475                                | 5,422    | 45.57         | 0.89 (0.80-1.23) | 0.582                       | 80                 | 40 | 0.00           | 0.64                    | 0.02                  | 1.00             | 1.11 (0.88-1.43)            | 0.416              | 82               | 1.00 (0.84-1.24)            | 0.976              | 64 |
| <i>APC</i>           | 28         | rs4301344 (p.Thr1495Ser, c.446G>A)                 | nonsense       | (AA>A) vs GG             | White     | 3                        | 1,367                                | 1,862    | 0.99          | 1.00 (0.60-1.65) | 0.992                       | 0                  | 0  | 0.83           | 0.69                    | 1.00                  | 1.00 (0.60-1.66) | 0.992                       | 0                  | 1.02 (0.85-1.22) | 0.918                       | 0                  |    |
| <i>ARLTS1/ARL11</i>  | 29         | rs3803185 (p.Cys148Arg, T442C, T>C)                | non-synonymous | C vs T                   | White     | 4                        | 2,123                                | 2,681    | 46.10         | 1.07 (0.99-1.17) | 0.093                       | 0                  | 2  | 0.68           | 0.10                    | 1.00                  | 1.11 (0.89-1.37) | 0.352                       | 61                 | 1.09 (0.88-1.34) | 0.453                       | 54                 |    |
| <i>ARLTS1/ARL11</i>  | 30         | rs1801673 (Ex37-62A>T, Asp1853Val)                 | non-synonymous | A vs G                   | White     | 3                        | 2,879                                | 6,384    | 0.66          | 0.77 (0.54-1.10) | 0.144                       | 0                  | 2  | 0.46           | 0.82                    | 1.00                  | 0.79 (0.54-1.14) | 0.211                       | 0                  | 1.02 (0.91-1.15) | 0.184                       | 60                 |    |
| <i>ATM</i>           | 31         | rs2273535 (p.Phe311le, c.91T>A)                    | non-synonymous | A vs G                   | White     | 3                        | 5,374                                | 4,953    | 23.70         | 1.07 (0.94-1.21) | 0.308                       | 60                 | 13 | 0.03           | 0.66                    | 0.51                  | 1.02 (0.93-1.12) | 0.646                       | 11                 | 1.22 (0.91-1.65) | 0.184                       | 60                 |    |
| <i>AURKA/STK15</i>   | 32         | rs2240308 (p.Pro50Ser, c.148C>T, G>A)              | non-synonymous | A vs G                   | White     | 3                        | 3,762                                | 3,934    | 46.11         | 1.07 (0.98-1.17) | 0.124                       | 29                 | 3  | 0.24           | 0.14                    | 1.00                  | 1.09 (0.98-1.20) | 0.099                       | 0                  | 1.10 (0.93-1.31) | 0.263                       | 45                 |    |
| <i>BLM</i>           | 33         | ASH non-carriers/carriers                          | frameshift     | carriers vs non-carriers | All       | 3                        | 1,741                                | 11,043   | 0.84          | 1.89 (0.74-4.83) | 0.184                       | 60                 | 5  | 0.08           | 0.54                    | 0.54                  | 1.89 (0.74-4.83) | 0.184                       | 60                 | 1.06 (0.87-1.29) | 0.562                       | 69                 |    |
| <i>BMP4</i>          | 34         | rs17563 (p.Val152Ala, c.455T>C)                    | non-synonymous | T vs C                   | All       | 4                        | 2,919                                | 3,102    | 63.68         | 1.01 (0.88-1.15) | 0.943                       | 29                 | 4  | 0.23           | 0.84                    | 1.00                  | 1.00 (0.87-1.15) | 0.943                       | 29                 | 1.01 (0.88-1.15) | 0.943                       | 29                 |    |
| <i>CASP8</i>         | 35         | rs3834129 (nearGene-5, -652 del, c. CTACT)         | intergenic     | 6 bp ins vs del          | All       | 10                       | 6,922                                | 10,750   | 41.14         | 1.05 (0.92-1.20) | 0.441                       | 82                 | 50 | 0.00           | 0.48                    | 0.06                  | 1.04 (0.86-1.27) | 0.682                       | 83                 | 1.07 (0.91-1.25) | 0.401                       | 54                 |    |
| <i>CASR</i>          | 36         | rs1042636 (p.Arg990Gly, c.2968A>G)                 | non-synonymous | G vs A                   | White     | 4                        | 6,298                                | 7,839    | 8.52          | 1.00 (0.92-1.09) | 0.936                       | 0                  | 2  | 0.66           | 0.68                    | 1.00                  | 1.00 (0.91-1.09) | 0.944                       | 0                  | 1.11 (0.71-1.74) | 0.631                       | 21                 |    |
| <i>CASR</i>          | 37         | rs1801725 (p.Ala996Ser, c.2956G>T)                 | non-synonymous | T vs G                   | White     | 3                        | 2,733                                | 3,359    | 13.10         | 1.01 (0.99-1.02) | 0.661                       | 84                 | 12 | 0.00           | 0.65                    | 1.00                  | 1.03 (0.96-1.16) | 0.089                       | 82                 | 1.76 (0.86-3.61) | 0.124                       | 69                 |    |
| <i>CAT</i>           | 38         | rs5742805 (Ex275The, C1831278T)                    | non-synonymous | C vs T                   | White     | 4                        | 4,374                                | 4,074    | 7.41          | 0.99 (0.91-1.17) | 0.589                       | 0                  | 0  | 0.60           | 0.60                    | 1.00                  | 1.03 (0.91-1.17) | 0.523                       | 61                 | 1.03 (0.91-1.17) | 0.523                       | 61                 |    |
| <i>CENDD1</i>        | 39         | rs91344 (c60936S, p.Pro241Pro, c.723G>A, c.870G>A) | synonymous     | A vs G                   | All       | 22                       | 6,316                                | 8,272    | 48.15         | 1.05 (0.98-1.13) | 0.197                       | 51                 | 51 | 0.00           | 0.56                    | 0.01                  | 1.13 (1.01-1.26) | <b>0.035</b>                | 43                 | 1.00 (0.86-1.17) | 0.976                       | 48                 |    |
| <i>CDH1</i>          | 40         | rs16260 (UTR-5, -160C>A)                           | 5' UTR         | A vs C                   | All       | 9                        | 7,220                                | 7,045    | 28.09         | 0.94 (0.88-1.01) | 0.116                       | 21                 | 10 | 0.26           | 0.22                    | 0.21                  | 0.97 (0.86-1.09) | 0.575                       | 40                 | 0.88 (0.74-1.04) | 0.129                       | 19                 |    |
| <i>CDKN1A</i>        | 41         | rs1059234 (UTR-3, c.*20C>T)                        | 3' UTR         | T vs C                   | All       | 3                        | 1,036                                | 1,512    | 30.29         | 1.01 (0.87-1.18) | 0.912                       | 4                  | 2  | 0.35           | 0.91                    | 1.00                  | 1.05 (0.81-1.36) | 0.719                       | 29                 | 0.93 (0.69-1.24) | 0.596                       | 0                  |    |
| <i>CDKN1A</i>        | 42         | rs1801270 (p.Ser31Arg, c.93C>A)                    | non-synonymous | A vs C                   | All       | 3                        | 1,037                                | 1,511    | 29.85         | 0.92 (0.69-1.23) | 0.582                       | 55                 | 4  | 0.11           | 0.62                    | 0.21                  | 0.87 (0.57-1.34) | 0.535                       | 68                 | 0.91 (0.68-1.22) | 0.535                       | 0                  |    |
| <i>CH22</i>          | 43         | 110d04C (683X)                                     | frameshift     | carriers vs non-carriers | White     | 7                        | 3,874                                | 11,630   | 0.71          | 1.88 (1.29-2.73) | <b>0.001</b>                | 0                  | 5  | 0.50           | 0.77                    | 1.00                  | 1.88 (1.29-2.73) | <b>0.001</b>                | 0                  | 1.88 (1.29-2.73) | <b>0.001</b>                | 0                  |    |
| <i>CH22</i>          | 44         | rs1787961 (p.Ile400Thr)                            | non-synonymous | carriers vs non-carriers | White     | 6                        | 6,042                                | 17,051   | 6.91          | 1.56 (1.32-1.84) | <b>1.22e-10<sup>a</sup></b> | 0                  | 3  | 0.76           | 0.19                    | 0.19                  |                  |                             |                    |                  |                             |                    |    |

|               |     |  |                |                 |       |    |        |        |       |                  |                  |    |     |      |             |                  |                  |                  |                  |                  |                  |     |  |
|---------------|-----|--|----------------|-----------------|-------|----|--------|--------|-------|------------------|------------------|----|-----|------|-------------|------------------|------------------|------------------|------------------|------------------|------------------|-----|--|
| <i>GSTP1</i>  | 99  | rs1695 (p.Ile105Val, c.313A>G)               | non-synonymous | G vs A          | All   | 33 | 9,986  | 15,562 | 27.54 | 0.98 (0.93-1.03) | 0.487            | 25 | 43  | 0.10 | 0.50        | 0.27             | 0.99 (0.93-1.07) | 0.868            | 29               | 0.95 (0.86-1.06) | 0.361            | 12  |  |
| <i>GSTZ1</i>  | 100 | Present/Null                                 | phenotype      | null vs present | All   | 43 | 15,144 | 23,847 | 29.53 | 1.15 (1.07-1.27) | <b>0.004</b>     | 68 | 131 | 0.00 | 0.28        | <b>0.03</b>      |                  |                  |                  |                  |                  |     |  |
| <i>GSTZ2</i>  | 101 | rs117427 (GLU32LYS)                          | non-synonymous | A vs G          | All   | 3  | 2,860  | 3,271  | 29.27 | 0.93 (0.73-1.19) | 0.569            | 57 | 5   | 0.10 | 0.16        | 1.00             | 0.93 (0.69-1.25) | 0.624            | 61               | 1.02 (0.86-1.22) | 0.826            | 0   |  |
| <i>HFE</i>    | 102 | rs179902 (C>D)                               | non-synonymous | G vs A          | White | 7  | 4,079  | 4,079  | 14.70 | 1.03 (0.93-1.14) | 0.572            | 7  | 7   | 0.37 | 0.42        | 1.00             | 1.07 (0.78-1.51) | 0.608            | 0                | 1.18 (0.73-1.92) | 0.494            | 30  |  |
| <i>HFE</i>    | 103 | rs1800562 (rs1155158, p.CvS282Tv, c.1005G>A) | non-synonymous | A vs G          | White | 10 | 2,502  | 30,857 | 7.43  | 1.05 (0.92-1.21) | 0.467            | 0  | 3   | 0.94 | <b>0.06</b> | 1.00             | 1.04 (0.94-1.2)  | 0.622            | 0                | 1.22 (0.52-2.87) | 0.648            | 32  |  |
| <i>HFE</i>    | 104 | rs1549465 (p.ProS82Ser, c.1744C>T)           | non-synonymous | T vs C          | All   | 3  | 3,019  | 4,950  | 8.43  | 1.04 (0.74-1.46) | 0.841            | 69 | 7   | 0.04 | <b>0.52</b> | 0.13             | 1.01 (0.69-1.50) | 0.944            | 73               |                  |                  |     |  |
| <i>HPGD</i>   | 105 | rs2612656                                    | intron         | G vs A          | White | 3  | 2,979  | 5,575  | 22.75 | 1.09 (0.97-1.24) | 0.162            | 65 | 6   | 0.06 | 0.57        | 1.00             | 1.08 (0.93-1.25) | 0.294            | 62               | 1.31 (1.05-1.64) | <b>0.016</b>     | 21  |  |
| <i>HPGD</i>   | 106 | rs7349744                                    | intron         | A vs G          | White | 3  | 3,014  | 5,622  | 30.54 | 1.00 (0.93-1.07) | 0.897            | 0  | 2   | 0.44 | 0.40        | 1.00             | 0.96 (0.87-1.04) | 0.308            | 0                | 1.13 (0.91-1.41) | 0.258            | 51  |  |
| <i>HPGD</i>   | 107 | rs7349744                                    | intron         | C vs A          | White | 3  | 3,001  | 5,624  | 31.06 | 0.96 (0.84-1.09) | 0.516            | 66 | 6   | 0.84 | 1.00        | 0.96 (0.78-1.13) | 0.554            | 38               | 0.96 (0.73-1.26) | 0.944            | 68               |     |  |
| <i>HPGD</i>   | 108 | rs8752                                       | 3' UTR         | G vs A          | White | 3  | 3,008  | 5,632  | 41.98 | 1.01 (0.86-1.17) | 0.936            | 22 | 11  | 0.44 | <b>0.09</b> | 0.43             | 0.96 (0.75-1.24) | 0.749            | 85               | 1.09 (0.96-1.24) | 0.201            | 23  |  |
| <i>HPGD</i>   | 109 | rs9312555                                    | 3' UTR         | G vs A          | White | 3  | 3,015  | 5,634  | 15.42 | 0.93 (0.86-1.02) | 0.134            | 0  | 2   | 0.44 | <b>0.06</b> | 1.00             | 0.92 (0.83-1.01) | 0.091            | 0                | 1.00 (0.74-1.36) | 0.992            | 0   |  |
| <i>ICAM1</i>  | 110 | rs498 (p.Lys469Glu, c.1405A>G)               | non-synonymous | G vs A          | All   | 4  | 3,229  | 3,357  | 42.63 | 0.96 (0.79-1.17) | 0.719            | 70 | 10  | 0.02 | 0.90        | <b>0.02</b>      | 0.91 (0.72-1.16) | 0.441            | 58               | 1.02 (0.80-1.31) | 0.873            | 43  |  |
| <i>IGF1</i>   | 111 | (CA)n (R19>nonR19)                           | STR            | non R19 vs R19  | All   | 8  | 5,493  | 6,827  | 36.71 | 0.99 (0.89-1.09) | 0.769            | 70 | 23  | 0.00 | 0.36        | 0.03             | 0.92 (0.73-1.16) | 0.491            | 88               | 1.03 (0.92-1.15) | 0.611            | 20  |  |
| <i>IGF1</i>   | 112 | rs35767                                      | intergenic     | T vs C          | All   | 3  | 2,717  | 4,880  | 24.75 | 0.95 (0.84-1.14) | 0.599            | 59 | 5   | 0.09 | 0.15        | 0.25             | 0.98 (0.79-1.21) | 0.826            | 60               | 0.75 (0.62-0.91) | <b>0.003</b>     | 0   |  |
| <i>IGFBP1</i> | 113 | rs4619 (p.Ile233Met, c.759A>G)               | non-synonymous | G vs A          | White | 3  | 3,570  | 3,660  | 35.63 | 1.02 (0.75-1.16) | 0.535            | 85 | 13  | 0.00 | 0.63        | 0.48             | 0.89 (0.65-1.26) | 0.509            | 89               | 1.02 (0.89-1.17) | 0.787            | 0   |  |
| <i>IGFBP1</i> | 114 | rs2854744 (nearGene5, c.202A, A>C)           | intergenic     | C vs A          | All   | 9  | 6,872  | 10,606 | 46.30 | 1.03 (0.98-1.07) | 0.284            | 0  | 2   | 0.98 | <b>0.13</b> | 1.00             | 1.0 (0.93-1.07)  | 0.985            | 0                | 1.07 (0.94-1.15) | 0.078            | 0   |  |
| <i>IGFBP3</i> | 115 | rs2854746 (p.Ala32Gly, c.95C>G)              | non-synonymous | G vs C          | All   | 5  | 4,282  | 7,365  | 46.08 | 1.07 (1.01-1.14) | 0.016            | 0  | 2   | 0.07 | 0.68        | 1.00             | 1.12 (1.03-1.22) | <b>0.012</b>     | 0                | 1.05 (0.95-1.17) | 0.327            | 15  |  |
| <i>IL10</i>   | 116 | rs1800872 (nearGene5, c.4433A>C, -592C>A)    | intergenic     | A vs C          | White | 5  | 1,561  | 2,439  | 22.57 | 0.94 (0.81-1.1)  | 0.444            | 41 | 8   | 0.13 | 0.83        | 0.28             | 0.9 (0.78-1.05)  | 0.168            | 16               | 1.13 (0.73-1.76) | 0.580            | 45  |  |
| <i>IL10</i>   | 117 | rs1800896 (nearGene5, c.3943A>G, -1082A>G)   | intergenic     | G vs A          | White | 5  | 1,134  | 1,492  | 46.68 | 0.98 (0.84-1.15) | 0.793            | 44 | 7   | 0.13 | 0.70        | 0.15             | 1.00 (0.84-1.24) | 0.976            | 31               | 1.04 (0.76-1.16) | 0.550            | 9   |  |
| <i>IL16</i>   | 118 | rs4072111 (p.Pro44Ser, c.1300C>T)            | non-synonymous | T vs C          | All   | 3  | 3,193  | 3,577  | 12.31 | 1.06 (0.91-1.25) | 0.494            | 43 | 4   | 0.17 | 0.72        | 1.00             | 1.03 (0.87-1.23) | 0.716            | 38               | 1.32 (0.82-1.14) | 0.253            | 26  |  |
| <i>IL16</i>   | 119 | rs1145227 (nearGene5, c.4970C>T, -31T>C)     | intergenic     | C vs T          | All   | 6  | 1,593  | 2,170  | 33.66 | 1.07 (0.97-1.19) | 0.156            | 0  | 1   | 0.97 | 0.03        | 1.00             | 1.11 (0.96-1.27) | 0.152            | 3                | 1.1 (0.83-1.44)  | 0.516            | 43  |  |
| <i>IL18</i>   | 120 | rs16944                                      | intergenic     | G vs A          | White | 3  | 577    | 828    | 36.41 | 0.96 (0.82-1.13) | 0.626            | 0  | 1   | 0.67 | 0.60        | 1.00             | 0.82 (0.55-1.24) | 0.352            | 63               | 1.08 (0.78-1.48) | 0.649            | 0   |  |
| <i>IL4</i>    | 121 | rs2243250 (nearGene5, -509C>T)               | intergenic     | T vs C          | White | 6  | 1,225  | 1,754  | 18.93 | 0.92 (0.76-1.12) | 0.401            | 42 | 9   | 0.12 | 0.48        | 0.30             | 0.91 (0.74-1.13) | 0.401            | 35               | 0.88 (0.6-1.27)  | 0.484            | 0   |  |
| <i>IL4R</i>   | 122 | rs1801275 (p.Gln576Arg, c.1727A>G)           | non-synonymous | G vs A          | All   | 4  | 803    | 986    | 18.97 | 1.05 (0.88-1.24) | 0.624            | 0  | 1   | 0.69 | 0.49        | 1.00             | 1.03 (0.84-1.27) | 0.757            | 0                | 1.18 (0.71-1.95) | 0.522            | 0   |  |
| <i>IL4R</i>   | 123 | rs1805012 (C43I)                             | non-synonymous | G vs A          | White | 3  | 2,840  | 3,233  | 11.18 | 0.95 (0.70-1.14) | 0.764            | 59 | 5   | 0.09 | 0.25        | 0.16             | 0.93 (0.66-1.32) | 0.697            | 60               | 1.32 (0.82-1.11) | 0.290            | 0   |  |
| <i>IL4R</i>   | 124 | rs1805012 (S503P)                            | non-synonymous | C vs T          | White | 3  | 802    | 802    | 36.25 | 0.92 (0.84-1.01) | 0.834            | 0  | 1   | 0.61 | 0.47        | 1.00             | 0.91 (0.73-1.13) | 0.554            | 0                | 1.13 (0.83-1.51) | 0.129            | 0   |  |
| <i>IL6</i>    | 125 | rs1800795                                    | intergenic     | C vs G          | All   | 14 | 6,952  | 8,657  | 38.55 | 1.01 (0.93-1.11) | 0.749            | 65 | 38  | 0.00 | 0.50        | 0.00             | 1.02 (0.91-1.14) | 0.733            | 59               | 1 (0.89-1.13)    | 0.963            | 34  |  |
| <i>IL6</i>    | 126 | rs1800797                                    | intergenic     | (AA>A>G) vs GG  | White | 4  | 2,612  | 3,381  | 60.75 | 0.96 (0.87-1.07) | 0.468            | 0  | 2   | 0.57 | 0.61        | 1.00             | 0.96 (0.87-1.07) | 0.468            | 0                |                  |                  |     |  |
| <i>IL8R</i>   | 127 | rs2228145 (rs192284, Asp358Val)              | non-synonymous | C vs A          | White | 3  | 3,070  | 20,173 | 30.92 | 0.97 (0.91-1.04) | 0.435            | 0  | 2   | 0.47 | 0.08        | 1.00             | 1.02 (0.87-1.20) | 0.795            | 36               | 1.04 (0.82-1.07) | 0.363            | 0   |  |
| <i>IL8</i>    | 128 | rs4073 (nearGene5, T-251A)                   | intergenic     | A vs T          | White | 10 | 3,520  | 4,381  | 45.88 | 1.04 (0.92-1.18) | 0.525            | 70 | 30  | 0.00 | 0.52        | 0.09             | 1.05 (0.87-1.28) | 0.620            | 71               | 0.94 (0.87-1.23) | 0.638            | 55  |  |
| <i>IRS1</i>   | 129 | rs1801278 (p.Gly971Arg, c.2911G>A)           | non-synonymous | A vs G          | White | 7  | 7,048  | 7,533  | 6.92  | 1.08 (0.96-1.22) | 0.219            | 39 | 10  | 0.13 | 0.99        | 0.45             | 1.15 (0.95-1.39) | 0.674            | 74               | 1.05 (0.66-1.68) | 0.834            | 0   |  |
| <i>IRS2</i>   | 130 | rs1805997 (p.Gly1057Arg, c.3170G>A)          | non-synonymous | A vs G          | White | 7  | 7,048  | 7,533  | 41.13 | 0.97 (0.86-1.08) | 0.156            | 0  | 2   | 0.47 | 0.03        | 1.00             | 0.93 (0.67-1.22) | 0.525            | 29               | 1.02 (0.87-1.13) | 0.920            | 0   |  |
| <i>LCT</i>    | 131 | rs4098235 (c.1917-326C>T, 1910 C>T)          | intron         | T vs C          | White | 7  | 2,103  | 2,492  | 41.75 | 0.99 (0.87-1.14) | 0.879            | 51 | 12  | 0.06 | <b>0.02</b> | 0.94             | 0.79 (0.71-1.03) | 0.438            | 30               | 1.02 (0.78-1.33) | 0.886            | 50  |  |
| <i>LEP</i>    | 132 | rs7799039                                    | intergenic     | A vs G          | White | 3  | 2,324  | 2,776  | 43.98 | 0.95 (0.88-1.03) | 0.222            | 0  | 2   | 0.46 | 0.85        | 1.00             | 0.98 (0.87-1.10) | 0.704            | 0                | 0.89 (0.77-1.02) | 0.478            | 0   |  |
| <i>LEPR</i>   | 133 | rs1137101 (p.Gln223Arg, c.668A>G)            | non-synonymous | G vs A          | White | 3  | 1,100  | 1,166  | 44.47 | 1.08 (0.96-1.22) | 0.187            | 0  | 1   | 0.69 | <b>0.09</b> | 1.00             | 1.14 (0.92-1.40) | 0.226            | 16               | 1.09 (0.91-1.34) | 0.384            | 0   |  |
| <i>LIPC</i>   | 134 | rs6083 (N215S)                               | non-synonymous | A vs G          | All   | 3  | 4,702  | 4,914  | 36.52 | 0.93 (0.86-1.01) | 0.075            | 31 | 3   | 0.24 | 0.93        | 1.00             | 0.95 (0.87-1.03) | 0.192            | 0                | 0.85 (0.74-0.99) | 0.032            | 25  |  |
| <i>MBL1</i>   | 135 | rs1001265                                    | intergenic     | G vs C          | All   | 3  | 822    | 872    | 32.17 | 0.91 (0.74-1.17) | 0.465            | 33 | 4   | 0.12 | 0.74        | 1.00             | 0.93 (0.75-1.13) | 0.468            | 0                |                  |                  |     |  |
| <i>MBL2</i>   | 136 | rs1800450 (Gly54Asp)                         | non-synonymous | A vs G          | All   | 4  | 3,395  | 3,546  | 13.85 | 0.97 (0.86-1.08) | 0.775            | 42 | 5   | 0.16 | 0.03        | 1.00             | 0.83 (0.54-1.27) | 0.381            | 61               | 0.89 (0.77-1.02) | 0.478            | 0   |  |
| <i>MBL2</i>   | 137 | rs1800451 (p.Gly57Glu)                       | non-synonymous | A vs G          | All   | 3  | 819    | 843    | 6.17  | 1.31 (0.93-1.83) | 0.120            | 0  | 2   | 0.43 | 0.48        | 1.00             |                  |                  |                  |                  |                  |     |  |
| <i>MBL2</i>   | 138 | rs5030737 (RS2C)                             | non-synonymous | T vs C          | All   | 4  | 1,185  | 1,199  | 6.21  | 1.03 (0.81-1.3)  | 0.805            | 0  | 1   | 0.81 | 0.40        | 1.00             | 1.13 (0.82-1.57) | 0.453            | 0                |                  |                  |     |  |
| <i>MBL2</i>   | 139 | rs7096206                                    | intergenic     | C vs G          | All   | 3  | 826    | 873    | 19.82 | 0.98 (0.82-1.17) | 0.795            | 0  | 0   | 0.81 | 0.34        | 1.00             |                  |                  |                  |                  |                  |     |  |
| <i>MDM2</i>   | 140 | rs2279744 (nearGene5, SNP209, c.14+309T>G)   | intergenic     | G vs T          | All   | 10 | 3,032  | 2,538  | 42.99 | 1.12 (0.94-1.34) | 0.211            | 76 | 39  | 0.00 | 0.54        | 1.00             | 1.24 (0.92-1.67) | 0.154            | 80               | 1.06 (0.86-1.29) | 0.607            | 39  |  |
| <i>MDM2</i>   | 141 | rs1291723 (Leu115Phe, c.342C>T)              | intergenic     | T vs C          | All   | 13 | 2,284  | 2,284  | 12.99 | 1.02 (0.91-1.14) | 0.992            | 13 | 13  | 0.00 | 0.92        | 0.31             | 1.03 (0.87-1.21) | 0.609            | 0                | 1.11 (0.83-1.49) | 0.516            | 0   |  |
| <i>MGAT1</i>  | 142 | rs2308321 (p.Ile174Val, c.520A>G)            | non-synonymous | G vs C          | All   | 6  | 3,843  | 8,783  | 12.79 | 1.00 (0.80-1.25) | 0.984            | 74 | 19  | 0.00 | 0.70        | <b>0.01</b>      | 1.00 (0.79-1.26) | 0.976            | 71               | 1.10 (0.61-1.99) | 0.757            | 35  |  |
| <i>MLH1</i>   | 143 | rs121912963 (p.Leu132H, c.415G>C)            | non-synonymous | C vs G          | All   | 3  | 1,412  | 1,508  | 0.43  | 2.74 (1.31-5.75) | <b>0.008</b>     | 15 | 2   | 0.31 | 0.75        | 1.00             | 2.78 (1.34-5.74) | <b>0.006</b>     | 12               |                  |                  |     |  |
| <i>MLH1</i>   | 144 | rs1799977 (p.Tic219Val, c.655A>G)            | non-synonymous | G vs A          | All   | 10 | 6,384  | 8,972  | 29.56 | 1.01 (0.92-1.11) | 0.904            | 58 | 21  | 0.01 | 0.66        | 0.26             | 1.03 (0.92-1.16) | 0.589            | 55               | 0.95 (0.81-1.11) | 0.590            | 29  |  |
| <i>MLH1</i>   | 145 | rs1800734 (nearGene5, UTR5, -93G>A)-MSI+ CRC | 5' UTR         | A vs G          | White | 5  | 801    | 10,890 | 21.11 | 1.51 (1.34-1.69) | <b>6.74e-107</b> | 46 | 7   | 0.11 | <b>0.02</b> | 1.00             | 1.46 (1.27-1.69) | <b>2.75e-107</b> | 40               | 2.45 (1.93-3.12) | <b>6.97e-103</b> | 0   |  |
| <i>MLH1</i>   | 146 | rs1800734 (nearGene5, UTR5, -93G>A)          | 5' UTR         | A vs G          | White | 7  | 1,793  | 13,777 | 21.31 | 1.05 (1.01-1.09) | 0.010            | 44 | 0   | 0.00 | 1.00        | 1.00 (1.01-1.11) | 0.014            | 0                | 1.06 (0.95-1.18) | 0.290            | 0                |     |  |
| <i>MLH1</i>   | 147 | rs62750447 (p.Val384Asp, 1151 A>A)           | non-synonymous | A vs A          | Asian | 3  | 937    | 919    | 1.96  | 2.14 (1.12-4.12) | <b>0.022</b>     | 41 | 3   | 0.18 | <b>0.04</b> | 1.00             | 2.17 (1.04-4.12) | <b>0.019</b>     | 38               |                  |                  |     |  |
| <i>MLH1</i>   | 148 | rs9876116 (Intron 14, c.1668-19A>G)          | intron         | G vs A          | White | 3  | 2,024  | 2,143  | 44.47 | 0.93 (0.85-1.02) | 0.631            | 15 | 2   | 0.31 | 0.56        | 1.00             | 0.96 (0.84-1.09) | 0.516            | 0                | 0.86 (0.70-1.02) | 0.077            | 26  |  |
| <i>MMP1</i>   | 149 | rs1799750 (nearGene5, -1607 1G2G)            | intergenic     | 2G vs 1G        | All   | 8  | 1,477  | 1,751  | 39.63 | 0.76 (0.64-0.92) | <b>0.004</b>     | 61 | 18  | 0.01 | 0.09        | 0.15             | 0.70 (0.54-0.89) | <b>0.004</b>     | 60               | 0.80 (0.64-0.99) | <b>0.041</b>     | 8</ |  |

|                       |     |  |                  |                  |       |    |        |         |       |                  |                  |    |     |             |             |             |                  |                  |       |                  |                  |       |    |
|-----------------------|-----|--|------------------|------------------|-------|----|--------|---------|-------|------------------|------------------|----|-----|-------------|-------------|-------------|------------------|------------------|-------|------------------|------------------|-------|----|
| <i>PTGS2/COX2</i>     | 200 | rs689466 (nearGene-5, g.3813939T>C)            | intergenic       | G vs A           | All   | 9  | 4,076  | 7,610   | 30.34 | 0.88 (0.80-0.98) | <b>0.018</b>     | 56 | 18  | <b>0.02</b> | 0.23        | 1.00        | 0.85 (0.74-0.97) | <b>0.014</b>     | 58    | 0.86 (0.71-1.05) | 0.140            | 30    |    |
| <i>RAD18</i>          | 201 | rs737572 (p.Arg302Gln, c.905G>A)               | non-synonymous   | C vs T           | All   | 3  | 3,174  | 3,397   | 29.22 | 1.19 (1.14-1.3)  | 0.055            | 67 | 6   | 0.05        | 0.19        | 1.00        | 1.18 (1.01-1.37) | 0.033            | 27    | 1.27 (0.87-1.86) | 0.221            | 72    |    |
| <i>RAD51</i>          | 202 | rs1801320 (135G>C)                             | 5' UTR           | C vs G           | White | 4  | 753    | 720     | 32.15 | 1.01 (0.31-3.27) | 0.987            | 97 | 109 | 0.00        | 0.18        | 0.01        | 0.89 (0.43-1.88) | 0.768            | 89    | 1.27 (0.1-16.43) | 0.854            | 95    |    |
| <i>RNASASEL</i>       | 203 | rs486907 (p.Arg462Gln, c.1385G>A)              | non-synonymous   | A vs G           | White | 3  | 808    | 1,132   | 35.03 | 1.05 (0.92-1.2)  | 0.469            | 0  | 1   | 0.61        | 0.21        | 1.00        | 1.03 (0.85-1.24) | 0.789            | 0     | 1.22 (0.8-1.87)  | 0.353            | 55    |    |
| <i>SCD</i>            | 204 | rs7849   | 3' UTR           | G vs A           | All   | 3  | 2,011  | 2,580   | 18.49 | 0.85 (0.73-0.98) | 0.025            | 29 | 3   | 0.25        | 0.11        | 1.00        | 0.85 (0.72-1.02) | 0.084            | 33    | 0.64 (0.4-1.02)  | 0.058            | 41    |    |
| <i>SEI1</i>           | 205 | rs34713741                                     | intergenic       | T vs C           | All   | 3  | 1,442  | 2,071   | 33.22 | 1.13 (0.96-1.33) | 0.139            | 60 | 5   | 0.08        | 0.66        | 0.17        | 1.21 (1.05-1.39) | <b>0.008</b>     | 0     | 1.07 (0.63-1.83) | 0.795            | 80    |    |
| <i>SEI2</i>           | 206 | rs5859   | 3' UTR           | T vs C           | All   | 3  | 1,409  | 2,086   | 7.48  | 1.04 (0.87-1.23) | 0.689            | 0  | 0   | 0.80        | 0.39        | 1.00        | 1.03 (0.84-1.26) | 0.779            | 0     |                  |                  |       |    |
| <i>SEPP1</i>          | 207 | rs3877899 (Ala264Thr)                          | non-synonymous   | T vs C           | All   | 3  | 1,441  | 2,079   | 7.07  | 1.12 (0.94-1.33) | 0.211            | 0  | 1   | 0.52        | 0.30        | 1.00        | 1.19 (0.96-1.48) | 0.105            | 0     |                  |                  |       |    |
| <i>SERP1</i>          | 208 | rs7579   | 3' UTR           | T vs C           | All   | 3  | 1,346  | 1,967   | 69.08 | 1.03 (0.86-1.22) | 0.779            | 60 | 5   | 0.08        | 0.82        | 0.02        | 1.00             | 1.04 (0.86-1.26) | 0.660 | 42               | 1.06 (0.72-1.58) | 0.757 | 57 |
| <i>SERPINE1/PAI-1</i> | 209 | rs1799889 (nearGene-5, -675 4G>5G)             | intergenic       | SG vs 4G         | White | 4  | 2,241  | 4,534   | 44.94 | 0.97 (0.90-1.04) | 0.368            | 0  | 1   | 0.73        | 0.58        | 1.00        | 0.87 (0.78-0.97) | <b>0.014</b>     | 0     | 1.09 (0.96-1.23) | 0.208            | 0     |    |
| <i>SHBG</i>           | 210 | rs6259 (D356N)                                 | non-synonymous   | A vs G           | White | 3  | 4,727  | 4,823   | 11.60 | 1.04 (0.95-1.14) | 0.383            | 0  | 1   | 0.71        | 0.22        | 1.00        | 1.03 (0.94-1.14) | 0.509            | 0     | 1.22 (0.85-1.75) | 0.278            | 0     |    |
| <i>SHMT1</i>          | 211 | rs1979276 (UTR-3, C1420T)                      | 3' UTR           | T vs C           | All   | 5  | 1,697  | 1,994   | 31.97 | 0.93 (0.82-1.05) | 0.215            | 30 | 6   | 0.22        | 0.13        | 0.37        | 0.94 (0.83-1.08) | 0.379            | 0     | 0.84 (0.60-1.18) | 0.322            | 57    |    |
| <i>SLC19A1/RFC1</i>   | 212 | rs1051266 (p.His27Arg, c.80A>G, 80G>A)         | non-synonymous   | A vs G           | White | 3  | 3,775  | 5,340   | 43.66 | 1.02 (0.91-1.14) | 0.757            | 61 | 10  | 0.04        | 0.94        | 0.18        | 1.05 (0.88-1.24) | 0.603            | 63    | 1.00 (0.88-1.13) | 0.968            | 18    |    |
| <i>SLC22A4/OCTN1</i>  | 213 | rs1050152 (L503P)                              | non-synonymous   | T vs C           | White | 3  | 3,110  | 3,243   | 53.39 | 1.06 (0.94-1.21) | 0.342            | 38 | 3   | 0.20        | 0.29        | 1.00        | 1.12 (0.94-1.34) | 0.194            | 29    | 1.02 (0.84-1.23) | 0.849            | 21    |    |
| <i>SOD2</i>           | 214 | rs46880 (rs1799725, Ala16Val)                  | non-synonymous   | T vs C           | All   | 5  | 2,400  | 3,003   | 69.08 | 0.97 (0.89-1.06) | 0.478            | 0  | 0   | 1.00        | 0.92        | 1.00        | 0.99 (0.85-1.16) | 0.928            | 0     | 0.94 (0.82-1.07) | 0.332            | 0     |    |
| <i>SULT1A1</i>        | 215 | rs9282861 (p.Arg213His, c.638G>A)              | non-synonymous   | A vs G           | All   | 11 | 3,802  | 5,042   | 33.40 | 1.02 (0.92-1.12) | 0.757            | 51 | 20  | 0.03        | 0.78        | <b>0.04</b> | 1.02 (0.93-1.11) | 0.726            | 0     | 1.09 (0.75-1.32) | 0.960            | 74    |    |
| <i>SULT1A2</i>        | 216 | rs1059491 (p.Asn235Thr, c.714A>C)              | non-synonymous   | C vs A           | White | 3  | 1,806  | 1,986   | 31.80 | 1.05 (0.95-1.17) | 0.308            | 6  | 2   | 0.35        | 0.21        | 1.00        | 1.08 (0.95-1.23) | 0.219            | 0     | 1.03 (0.82-1.30) | 0.779            | 15    |    |
| <i>TCF7L2</i>         | 217 | rs7903146                                      | intron           | T vs C           | All   | 4  | 3,899  | 20,299  | 26.32 | 1.07 (0.94-1.22) | 0.293            | 66 | 9   | 0.03        | 0.20        | 1.00        | 1.07 (0.91-1.27) | 0.393            | 68    | 1.08 (0.92-1.27) | 0.324            | 5     |    |
| <i>TNC2</i>           | 218 | rs1801198 (p.Arr259Pro, c.776C>G)              | non-synonymous   | G vs C           | White | 3  | 2,582  | 5,117   | 43.70 | 0.96 (0.86-1.07) | 0.453            | 54 | 4   | 0.11        | 0.59        | 1.00        | 0.95 (0.85-1.06) | 0.322            | 13    | 0.97 (0.81-1.15) | 0.697            | 46    |    |
| <i>TERF</i>           | 219 | rs2736100                                      | intron           | T vs C           | White | 8  | 16,176 | 181,135 | 49.34 | 1.07 (1.04-1.1)  | <b>2.92e-10*</b> | 0  | 6   | 0.53        | 0.30        | 0.44        | 1.14 (1.08-1.2)  | <b>2.05e-10*</b> | 0     | 1.06 (1-1.13)    | 0.069            | 15    |    |
| <i>TGFB1</i>          | 220 | rs1800469 (nearGene-5, C.509T)                 | intergenic       | T vs C           | All   | 10 | 4,405  | 5,283   | 38.74 | 0.88 (0.79-0.97) | <b>0.015</b>     | 55 | 20  | 0.02        | 0.97        | 0.71        | 0.83 (0.71-0.97) | <b>0.018</b>     | 58    | 0.83 (0.73-0.95) | <b>0.006</b>     | 8     |    |
| <i>TGFB1</i>          | 221 | rs1800470 (p.Leu0Pro, c.29C>T, c.T29C)         | non-synonymous   | C vs T           | All   | 5  | 1,204  | 2,391   | 45.14 | 1.17 (0.95-1.44) | 0.142            | 66 | 12  | 0.02        | 0.31        | 1.00        | 1.12 (0.90-1.38) | 0.312            | 29    | 1.26 (0.89-1.78) | 0.197            | 68    |    |
| <i>TGFB1</i>          | 222 | rs4803455                                      | intron           | A vs C           | White | 3  | 2,786  | 3,516   | 47.48 | 1.10 (0.99-1.22) | 0.066            | 46 | 4   | 0.16        | 0.47        | 1.00        | 1.15 (0.99-1.34) | 0.066            | 39    | 1.16 (1.01-1.28) | <b>0.030</b>     | 0     |    |
| <i>TGFB1</i>          | 223 | rs1466445 (Frameshift in exon 1, *6A>9A)       | frameshift       | 9 bp del vs ins  | All   | 10 | 6,338  | 6,679   | 9.19  | 1.04 (0.96-1.13) | 0.379            | 1  | 9   | 0.43        | 0.39        | 1.00        | 1.06 (0.96-1.16) | 0.246            | 7     | 0.85 (0.58-1.23) | 0.373            | 0     |    |
| <i>TGFB1</i>          | 224 | rs334354 (intron, IVS7G>24A, c.1024+24G>A)     | intron           | A vs G           | All   | 4  | 1,226  | 2,786   | 26.71 | 1.08 (0.88-1.33) | 0.472            | 68 | 9   | 0.03        | 0.53        | 0.30        | 1.03 (0.78-1.36) | 0.834            | 71    | 1.38 (1.04-1.84) | <b>0.029</b>     | 8     |    |
| <i>TLR2</i>           | 225 | rs375291 (Leu512Phe)                           | non-synonymous   | A vs G (AG>GG)   | White | 3  | 4,867  | 5,604   | 9.23  | 0.94 (0.80-1.11) | 0.465            | 30 | 3   | 0.24        | 0.21        | 1.00        | 1.05 (0.92-1.20) | 0.211            | 0     | 0.94 (0.80-1.11) | 0.465            | 30    |    |
| <i>TLR4</i>           | 226 | rs11538898                                     | intergenic       | AA vs (AC>CC)    | White | 3  | 2,501  | 3,239   | 1.85  | 0.79 (0.37-1.67) | 0.529            | 53 | 4   | 0.12        | 0.61        | 0.20        |                  |                  |       | 0.79 (0.37-1.67) | 0.529            | 53    |    |
| <i>TLR4</i>           | 227 | rs1927911                                      | intron           | T vs C           | White | 3  | 2,512  | 3,276   | 27.79 | 0.99 (0.91-1.07) | 0.757            | 0  | 1   | 0.62        | 0.12        | 1.00        | 0.97 (0.88-1.08) | 0.575            | 0     | 1.03 (0.85-1.25) | 0.757            | 0     |    |
| <i>TLR4</i>           | 228 | rs4986790 (p.Asp299Gly)                        | non-synonymous   | T vs C           | White | 3  | 714    | 1,156   | 4.28  | 1.27 (0.67-2.4)  | 0.459            | 68 | 6   | 0.04        | 0.38        | 0.31        | 1.2 (0.66-2.19)  | 0.542            | 62    |                  |                  |       |    |
| <i>TLR4</i>           | 229 | rs4986791 (Thr399Ile)                          | non-synonymous   | T vs C           | White | 4  | 3,054  | 3,632   | 5.37  | 1.07 (0.84-1.37) | 0.564            | 16 | 4   | 0.31        | 0.28        | 1.00        | 1.08 (0.83-1.41) | 0.583            | 20    |                  |                  |       |    |
| <i>TNF</i>            | 230 | rs1799724 (nearGene-5, -857C>T)                | intergenic       | T vs C           | White | 3  | 745    | 732     | 13.05 | 0.97 (0.72-1.30) | 0.818            | 36 | 3   | 0.21        | 0.89        | 1.00        | 0.96 (0.69-1.34) | 0.795            | 40    |                  |                  |       |    |
| <i>TNF</i>            | 231 | rs1800629 (nearGene-5, G.308A)                 | non-synonymous   | A vs G           | All   | 11 | 2,296  | 2,283   | 13.78 | 1.28 (1.16-1.2)  | <b>0.046</b>     | 71 | 24  | 0.00        | 0.39        | 0.48        | 1.27 (0.99-1.64) | 0.065            | 67    | 1.41 (0.81-2.46) | 0.222            | 51    |    |
| <i>TP53</i>           | 232 | rs1042522 (p.Pro72Arg, c.215C>G)               | non-synonymous   | C vs T           | White | 3  | 10,515 | 12,909  | 31.28 | 1 (0.92-1.1)     | 0.922            | 72 | 107 | 0.00        | 0.48        | <b>0.00</b> | 1.01 (0.9-1.12)  | 0.906            | 67    | 1.01 (0.9-1.12)  | 0.875            | 52    |    |
| <i>TP53</i>           | 233 | rs17878362 (nearGene-5, IVS3 16bp Del/Ins)     | intergenic       | 16 bp ins vs del | White | 5  | 1,569  | 1,891   | 15.49 | 0.96 (0.73-1.28) | 0.787            | 73 | 15  | 0.01        | 0.69        | <b>0.01</b> | 0.96 (0.70-1.32) | 0.810            | 72    | 0.92 (0.57-1.48) | 0.719            | 0     |    |
| <i>TP73</i>           | 234 | G4C14(AAT14)                                   | Combined variant | mutation vs wild | All   | 4  | 858    | 1,168   | 24.02 | 1.20 (1.04-1.40) | <b>0.015</b>     | 6  | 3   | 0.36        | 0.11        | 1.00        | 1.10 (0.83-1.45) | 0.509            | 55    | 1.74 (1.22-2.48) | <b>0.002</b>     | 0     |    |
| <i>TPMS/TS</i>        | 235 | 28-bp tandem repeat                            | STR              | 3R vs 2R         | All   | 7  | 3,220  | 3,900   | 37.17 | 1.13 (0.97-1.32) | 0.215            | 66 | 18  | 0.01        | <b>0.03</b> | 0.64        | 1.13 (0.93-1.36) | 0.213            | 55    | 1.17 (0.89-1.52) | 0.264            | 56    |    |
| <i>TPMS/TS</i>        | 236 | rs16430 (UTR-3, 1494 ins/del6, -C(TTTAA)       | 3' UTR           | 6 bp del vs ins  | All   | 5  | 3,796  | 3,963   | 32.35 | 0.99 (0.89-1.09) | 0.310            | 38 | 6   | 0.17        | 0.56        | 1.00        | 1.01 (0.92-1.1)  | 0.903            | 0     | 0.9 (0.69-1.18)  | 0.430            | 59    |    |
| <i>UBD</i>            | 237 | rs2076485 (168T)                               | non-synonymous   | C vs T           | White | 3  | 4,281  | 6,157   | 26.07 | 1.07 (1.01-1.14) | <b>0.034</b>     | 0  | 1   | 0.77        | 0.63        | 1.00        | 1.08 (0.99-1.16) | 0.073            | 0     | 1.15 (0.97-1.35) | 0.103            | 12    |    |
| <i>UGT1A1</i>         | 238 | rs1092302 (intron, c.862-9898G>A, c.-3156G>A)  | intron           | A vs G           | All   | 3  | 1,560  | 1,987   | 35.68 | 1.03 (0.93-1.14) | 0.535            | 0  | 0   | 0.85        | 0.52        | 1.00        | 1.03 (0.89-1.19) | 0.689            | 0     | 1.07 (0.87-1.32) | 0.509            | 0     |    |
| <i>UGT1A1</i>         | 239 | rs4124874 (intron, c.862-10021T>G, c.-3279T>G) | intron           | G vs T           | All   | 3  | 1,560  | 1,987   | 50.35 | 1.05 (0.91-1.22) | 0.472            | 42 | 3   | 0.18        | 0.80        | 1.00        | 1.06 (0.72-1.57) | 0.772            | 70    | 1.07 (0.88-1.21) | 0.741            | 0     |    |
| <i>UGT1A1</i>         | 240 | rs8175347                                      | STR              | TA7 vs TA6       | All   | 8  | 3,345  | 4,177   | 32.46 | 1.00 (0.90-1.1)  | 0.920            | 43 | 12  | 0.09        | 0.67        | 0.02        | 0.99 (0.85-1.15) | 0.860            | 55    | 1.02 (0.88-1.19) | 0.761            | 0     |    |
| <i>UGT1A6</i>         | 241 | rs1105879 (p.Arg184Ser, c.552A>C)              | non-synonymous   | C vs A           | White | 3  | 4,006  | 4,295   | 34.33 | 0.97 (0.91-1.04) | 0.401            | 0  | 0   | 0.97        | 0.47        | 1.00        | 0.95 (0.87-1.03) | 0.222            | 0     | 1.01 (0.88-1.15) | 0.897            | 0     |    |
| <i>UGT1A6</i>         | 242 | T181A1R184S                                    | Combined variant | mutation vs wild | White | 4  | 3,066  | 3,915   | 34.41 | 1.04 (0.97-1.12) | 0.303            | 10 | 3   | 0.35        | 0.89        | 1.00        | 1.07 (0.96-1.18) | 0.238            | 11    | 1.03 (0.89-1.18) | 0.719            | 0     |    |
| <i>UGT1A7</i>         | 243 | Phenotype                                      | phenotype        | low vs high      | All   | 5  | 1,174  | 1,533   | 30.37 | 1.23 (0.97-1.55) | 0.084            | 73 | 15  | 0.01        | 0.53        | 0.64        | 1.25 (0.95-1.65) | 0.110            | 65    | 1.32 (0.88-1.97) | 0.177            | 59    |    |
| <i>UGT1A7</i>         | 244 | rs17868323 (N129K)                             | non-synonymous   | T vs G           | White | 3  | 1,545  | 1,930   | 31.37 | 0.90 (0.77-1.05) | 0.168            | 31 | 3   | 0.24        | 0.53        | 0.48        | 0.88 (0.77-1.01) | 0.070            | 0     | 0.83 (0.56-1.12) | 0.337            | 43    |    |
| <i>VDR</i>            | 245 | rs11568820                                     | 5' UTR           | (AA>AG) vs GG    | White | 4  | 3,228  | 3,455   | 36.61 | 1.15 (1.04-1.27) | <b>0.005</b>     | 0  | 0   | 0.93        | 0.42        | 0.58        | 1.15 (1.04-1.27) | <b>0.005</b>     | 0     |                  |                  |       |    |

**Webappendix table 2. Included studies for the genetic variants showing a statistically significant association with colorectal-cancer risk from meta-analyses, based on all available data or ethnicity-specific data**

| Gene                          | Variant                    | Ethnicity | Studies | References   |
|-------------------------------|----------------------------|-----------|---------|--|
| <b>37 variants in table 3</b> |                            |           |         |  |
| <i>APC</i>                    | rs1801155 (I1307K, T3920A) | Jewish    | 3       | 1-3  |
| <i>CHEK2</i>                  | rs17879961 (Ile200Thr)     | White     | 6       | 4-8  |
| <i>CHEK2</i>                  | 1100delC (fs381X)          | White     | 7       | 4, 6, 9-13   |
| <i>CYP1A1</i>                 | rs1048943 (*2C, Ile462Val) | All       | 16      | 14-28  |
| <i>CYP2E1</i>                 | 96-bp insertion            | All       | 4       | 29-32  |
| <i>DNMT3B</i>                 | rs1569686 (39179G>T)       | All       | 4       | 33-36  |
| <i>GHI</i>                    | rs2665802 (c.456+90T>A)    | All       | 7       | 37-40  |
| <i>GSTM1</i>                  | Present/Null               | All       | 56      | 14, 15, 18, 19, 22-25, 38, 41-82   |
| <i>GSTT1</i>                  | Present/Null               | All       | 43      | 14, 15, 18, 22, 25, 38, 41, 42, 44-46, 48-58, 60, 61, 64-70, 73, 75, 76, 78, 79, 81-83 |
| <i>IGFBP3</i>                 | rs2854746 (Ala32Gly)       | All       | 5       | 84-88  |
| <i>MLH1</i>                   | rs63750447 (Val384Asp)     | Asian     | 3       | 89-91  |
| <i>MLH1</i>                   | rs1800734 (-93G>A)         | White     | 5       | 92-96  |
| <i>MLH1</i>                   | rs121912963 (D132H)        | All       | 3       | 90, 97   |
| <i>MMP1</i>                   | rs1799750 (-1607 1G/2G)    | All       | 8       | 98-105   |
| <i>MSH3</i>                   | rs184967 (Arg949Gln)       | White     | 3       | 7, 94, 106   |
| <i>MSH3</i>                   | rs26279 (Ala1045Thr)       | White     | 4       | 7, 94, 106, 107  |
| <i>MTHFD1</i>                 | rs1950902 (Arg134Lys)      | White     | 3       | 7, 108, 109  |
| <i>MUTYH</i>                  | rs34612342 (Tyr165Cys)     | White     | 17      | 110-124  |
| <i>MUTYH</i>                  | rs36053993 (Gly382Asp)     | White     | 17      | 110-124  |
| <i>MUTYH</i>                  | Monoallelic mutation       | White     | 17      | 110-124  |
| <i>MUTYH</i>                  | Biallelic mutation         | White     | 17      | 110-124  |
| <i>NAT2</i>                   | Phenotype                  | All       | 35      | 15, 16, 19, 23, 24, 47, 57, 62, 71, 125-149  |
| <i>NOD2/CARD15</i>            | rs2066847 (L1007fs)        | White     | 11      | 150-160  |
| <i>NOD2/CARD15</i>            | rs2066844 (Arg702Trp)      | White     | 9       | 150-158  |
| <i>PTGS1/COX1</i>             | rs5788 (Gly213Gly)         | White     | 4       | 38, 161, 162   |
| <i>PTGS2/COX2</i>             | rs689466                   | All       | 9       | 161, 163-168   |
| <i>SCD</i>                    | rs7849                     | All       | 3       | 161, 169   |
| <i>TERT</i>                   | rs2736100                  | White     | 8       | 170, 171   |
| <i>TGFB1</i>                  | rs1800469 (C-509T)         | All       | 10      | 172-180  |
| <i>TNF</i>                    | rs1800629                  | All       | 11      | 153, 180-188   |
| <i>TP73</i>                   | G4C14/A4T14                | All       | 4       | 189-192  |
| <i>UBD</i>                    | rs2076485 (I68T)           | White     | 3       | 7, 162   |
| <i>VDR</i>                    | rs11568820                 | White     | 4       | 193-196  |
| <i>VDR</i>                    | rs1544410 (BsmI)           | All       | 17      | 38, 194, 197-207   |
| <i>VEGF</i>                   | rs3025039 (C936T)          | All       | 6       | 175, 208-212   |



|                              |                             |       |    |                                      |
|------------------------------|-----------------------------|-------|----|--------------------------------------|
| <i>XPA</i>                   | rs1800975                   | White | 3  | 213-215                              |
| <i>XPC</i>                   | rs2228001 (Gln939Lys)       | All   | 9  | 213, 215-220                         |
| <b>8 variants in table 4</b> |                             |       |    |                                      |
| <i>CDH1</i>                  | rs16260 (-160C>A)           | White | 6  | 221-225                              |
| <i>MTRR</i>                  | rs1801394 (Ile22Met)        | Asian | 3  | 226-228                              |
| <i>NFKB1</i>                 | rs28362491 (-94ins/delATTG) | White | 6  | 229-231                              |
| <i>OGG1</i>                  | rs1052133 (Ser326Cys)       | White | 14 | 38, 114, 117, 213, 217, 218, 232-238 |
| <i>PTGS2/COX2</i>            | rs20417                     | Asian | 4  | 167, 239, 240                        |
| <i>NQO1</i>                  | rs1800566 (Pro187Ser)       | White | 8  | 7, 25, 38, 46, 241-244               |
| <i>TCF7L2</i>                | rs7903146                   | White | 3  | 182, 245, 246                        |
| <i>TP53</i>                  | rs1042522                   | Asian | 8  | 192, 247-253                         |

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Appendix table 3 Detailed information for genetic variants nominally significantly associated with colorectal-cancer risk in meta-analyses of all available data or ethnicity-specific data

| Genes   | Variants             | Alleles * | Chromosome | Frequency (%)† | Ethnicity | Number evaluated |                | Colorectal-cancer risk meta-analysis |                              |                    |                        | Venice criteria (p-value) | Risk-positive report probability‡ | Cumulative evidence of association | Amount of Evidence  |          | Protection from bias | Reasons for bias | Initial study reference |             | Deviation from HW‡                                      | Identified by GWAS if # controls | OR<1.15               | Modified p            | Excess p   |  |      |      |      |
|---|----------------------|-----------|------------|----------------|-----------|------------------|----------------|--------------------------------------|------------------------------|--------------------|------------------------|---------------------------|-----------------------------------|------------------------------------|---------------------|----------|----------------------|------------------|-------------------------|-------------|---|----------------------------------|-----------------------|-----------------------|------------|--|------|------|------|
|   |                      |           |            |                |           | Studies          | Cases Controls | Genetic models                       | OR (95% CI)                  | P value            | I <sup>2</sup> (%)     |                           |                                   |                                    | P <sub>hetero</sub> | Number   |                      |                  | Grade                   | OR (95% CI) |   |                                  |                       |                       |            | p-value                                |      |      |      |
| <b>Associations identified by analysis of all available data</b>        |                      |           |            |                |           |                  |                |                                      |                              |                    |                        |                           |                                   |                                    |                     |          |                      |                  |                         |             |   |                                  |                       |                       |            |  |      |      |      |
| APC   | rs1801155            | AT        | 5          | 6.80           | Irish     | 3                | 804            | 6,188                                | Dominant                     | 1.96 (1.37-2.79)   | 1.99-10 <sup>-4</sup>  | 0                         | 0.84                              | BAA                                | 0.007               | Strong   | 492                  | B                | A                       | A           | NA  | 2.11 (1.31-3.39)                 | 0.002                 | Not tested            | NA         | No                                     | 0.64 | 1.00 |      |
| CH22  | 110046C              | -         | 22         | 0.71           | White     | 7                | 3,874          | 11,630                               | Dominant                     | 1.88 (1.29-2.73)   | 0.001                  | 0                         | 0.50                              | -AA                                | 0.036               | Strong   | 142                  | ×                | A                       | A           | NA  | 1.28 (1.05-2.38)                 | 0.029                 | Not tested            | NA         | No                                     | 0.77 | 1.00 |      |
| CH22  | rs17879961           | CT        | 22         | 3.91           | White     | 6                | 6,042          | 17,051                               | Dominant                     | 1.56 (1.32-1.84)   | 1.22-10 <sup>-7</sup>  | 0                         | 0.76                              | BAA                                | <0.001              | Strong   | 898                  | B                | A                       | A           | NA  | 1.58 (1.30-1.91)                 | 4.43-10 <sup>-6</sup> | Not tested            | NA         | No                                     | 0.29 | 0.10 |      |
| CYP11A1   | rs1040943            | GA        | 15         | 10.04          | All       | 16               | 6,704          | 8,009                                | Additive                     | 1.24 (1.05-1.47)   | 0.014                  | 74                        | 0.00                              | ACC                                | 0.338               | Weak     | 3,194                | A                | C                       | HWE, GWAS   | NA  | 1.21 (1.01-1.45)                 | 0.034                 | Yes                   | No         | 0.31                                   | 0.78 |      |      |
| CYP2E1  | 96-bp insertion      | -         | 10         | 16.98          | All       | 4                | 1,412          | 1,781                                | Additive                     | 1.24 (1.03-1.49)   | 0.023                  | 35                        | 0.20                              | ABA                                | 0.462               | Weak     | 1,175                | A                | B                       | A           | NA  | 1.38 (1.01-1.89)                 | 0.044                 | No                    | NA         | No                                     | 0.25 | 1.00 |      |
| DNMT3B  | rs1569686            | GT        | 20         | 16.99          | All       | 4                | 1,054          | 1,224                                | Additive                     | 0.57 (0.47-0.68)   | 1.86-10 <sup>-9</sup>  | 0                         | 0.99                              | BAA                                | <0.001              | Strong   | 657                  | B                | A                       | A           | exempted  | Highly consistent of OR          | 0.56 (0.45-0.70)      | 2.22-10 <sup>-7</sup> | No         | No                                     | 0    | 0.81 | 1.00 |
| GHI   | rs265802             | AT        | 17         | 45.39          | All       | 7                | 3,275          | 3,848                                | Additive                     | 0.89 (0.80-0.99)   | 0.025                  | 49                        | 0.07                              | ABC                                | 0.508               | Weak     | 6,123                | A                | B                       | C           | Low OR, GWAS, Small study                               | NA                               | 0.93 (0.87-0.99)      | 0.024                 | No         | No                                     | Yes  | 0.03 | 1.00 |
| GSTM1   | Present/Null         | NA        | 1          | 50.64          | All       | 56               | 20,552         | 31,419                               | null vs present              | 1.10 (1.04-1.17)   | 0.001                  | 48                        | 0.00                              | ABC                                | 0.046               | Moderate | 28,715               | A                | B                       | C           | low OR, Small study, excess of significant studies      | NA                               | 1.10 (1.04-1.17)      | 0.001                 | NA         | NA                                     | Yes  | 0.00 | 0.06 |
| GSTT1   | Present/Null         | NA        | 22         | 29.53          | All       | 43               | 15,144         | 23,847                               | null vs present              | 1.15 (1.05-1.27)   | 0.004                  | 68                        | 0.00                              | ACC                                | 0.144               | Weak     | 11,515               | A                | C                       | C           | excess of significant studies                           | NA                               | 1.16 (1.05-1.27)      | 0.004                 | NA         | NA                                     | No   | 0.28 | 0.03 |
| IGFBP3  | rs2854746            | GC        | 7          | 46.08          | All       | 5                | 4,282          | 7,365                                | Additive                     | 1.07 (1.01-1.14)   | 0.016                  | 0                         | 0.07                              | AAC                                | 0.447               | Weak     | 10,895               | A                | A                       | C           | First study, HWE, GWAS                                  | NA                               | 1.06 (1.00-1.13)      | 0.064                 | Yes        | No                                     | Yes  | 0.68 | 1.00 |
| MLH1  | rs121912963          | C/G       | 3          | 0.43           | All       | 3                | 1,412          | 1,508                                | Additive                     | 2.74 (1.51-5.75)   | 0.008                  | 15                        | 0.31                              | -AC                                | 0.231               | Weak     | 48                   | ×                | A                       | C           | First study   | NA                               | 1.95 (0.86-4.42)      | 0.108                 | No         | NA                                     | No   | 0.75 | 1.00 |
| MLH1  | rs1800734            | A/G       | 3          | 21.11          | White     | 5                | 801            | 10,890                               | Additive                     | 1.51 (1.34-1.69)   | 6.74-10 <sup>-12</sup> | 46                        | 0.11                              | AAA                                | <0.001              | Strong   | 5,061                | A                | B                       | A           | Small study, exempted                                   | Highly consistent of OR          | 1.47 (1.30-1.66)      | 7.75-10 <sup>-6</sup> | No         | No                                     | Yes  | 0.02 | 1.00 |
| MLH1  | rs63750447           | AT        | 3          | 1.96           | Asian     | 3                | 937            | 919                                  | Additive                     | 2.14 (1.12-4.12)   | 0.022                  | 41                        | 0.18                              | BBC                                | 0.458               | Weak     | 102                  | B                | B                       | C           | First study, Small study                                | NA                               | 1.61 (0.89-2.91)      | 0.117                 | No         | NA                                     | No   | 0.04 | 1.00 |
| MMP3  | rs1799750            | 2G1G      | 11         | 39.63          | All       | 8                | 1,477          | 1,751                                | Additive                     | 0.76 (0.64-0.92)   | 0.004                  | 61                        | 0.01                              | ACC                                | 0.138               | Weak     | 2,439                | A                | C                       | C           | Small study, GWAS                                       | NA                               | 0.78 (0.64-0.95)      | 0.012                 | No         | No                                     | 0.09 | 0.15 |      |
| MSH3  | rs184967             | AG        | 5          | 15.25          | White     | 3                | 5,085          | 7,136                                | Additive                     | 1.11 (1.03-1.20)   | 0.005                  | 0                         | 0.38                              | AAC                                | 0.182               | Weak     | 3,857                | A                | A                       | C           | GWAS, Low OR, Small study                               | NA                               | 1.09 (1.01-1.18)      | 0.023                 | No         | No                                     | Yes  | 0.09 | 1.00 |
| MSH3  | rs26279              | G/A       | 5          | 28.13          | White     | 4                | 5,691          | 7,665                                | Additive                     | 1.1 (1.03-1.17)    | 0.006                  | 17                        | 0.31                              | AAC                                | 0.157               | Weak     | 7,697                | A                | A                       | C           | First study, GWAS, Low OR                               | NA                               | 1.11 (0.99-1.24)      | 0.085                 | No         | No                                     | Yes  | 0.71 | 0.60 |
| MTHFD1  | rs195902             | AG        | 14         | 18.78          | White     | 3                | 3,822          | 5,452                                | Additive                     | 0.90 (0.84-0.98)   | 0.010                  | 0                         | 0.79                              | AAC                                | 0.275               | Weak     | 3,389                | A                | A                       | C           | First study, GWAS, Low OR                               | NA                               | 0.93 (0.82-1.06)      | 0.265                 | No         | No                                     | Yes  | 0.71 | 1.00 |
| MUTH  | Monofluoric mutation | NA        | 1          | 1.69           | White     | 17               | 25,981         | 18,811                               | Carriers vs wild homozygotes | 1.17 (1.01-1.34)   | 0.036                  | 0                         | 0.84                              | BAC                                | 0.546               | Weak     | 829                  | B                | A                       | C           | First study   | NA                               | 1.11 (0.95-1.30)      | 0.184                 | Not tested | NA                                     | No   | 0.15 | 1.00 |
| MUTH  | Biallelic mutation   | NA        | 1          | 0.01           | White     | 17               | 25,981         | 18,811                               | Carriers vs wild homozygotes | 10.19 (5.00-22.04) | 5.30-10 <sup>-10</sup> | 0                         | 0.88                              | -AA                                | <0.001              | Strong   | 105                  | ×                | A                       | A           | NA  | NA                               | 9.29 (4.29-20.11)     | 1.51-10 <sup>-6</sup> | Not tested | NA                                     | No   | 0.23 | 0.16 |
| MUTH  | rs34612342           | GA        | 1          | 0.01           | White     | 17               | 27,041         | 19,641                               | GG vs AA                     | 3.32 (1.13-9.81)   | 0.030                  | 0                         | 1.00                              | -AA                                | 0.533               | Strong   | 18                   | ×                | A                       | A           | NA  | NA                               | 3.32 (1.13-9.81)      | 0.030                 | Not tested | NA                                     | No   | 0.10 | 0.39 |
| MUTH  | rs56033993           | AG        | 1          | 0.00           | White     | 17               | 26,957         | 19,870                               | AA vs GG                     | 6.49 (2.57-1.35)   | 7.49-10 <sup>-5</sup>  | 0                         | 0.85                              | -AA                                | 0.003               | Strong   | 40                   | ×                | A                       | A           | NA  | NA                               | 5.22 (1.94-14.01)     | 0.001                 | Not tested | NA                                     | No   | 0.80 | 0.76 |
| NAT2  | Fast/slow            | NA        | 8          | 47.39          | All       | 35               | 11,684         | 15,348                               | Slow vs fast                 | 0.94 (0.89-0.99)   | 0.023                  | 1                         | 0.45                              | AAC                                | 0.47                | Weak     | 12,622               | A                | A                       | C           | First study, Low OR                                     | NA                               | 0.96 (0.91-1.01)      | 0.096                 | Not tested | NA                                     | Yes  | 0.79 | 0.69 |
| ND2   | rs206844             | T/C       | 16         | 6.15           | White     | 9                | 3,297          | 3,088                                | Dominant                     | 1.35 (1.02-1.78)   | 0.038                  | 34                        | 0.14                              | BBC                                | 0.581               | Weak     | 436                  | B                | B                       | C           | First study, Small study, excess of significant studies | NA                               | 1.25 (0.98-1.60)      | 0.072                 | Not tested | NA                                     | No   | 0.02 | 1.00 |
| ND2   | rs206847             | C/-       | 16         | 6.21           | White     | 11               | 4,337          | 5,395                                | Dominant                     | 1.30 (1.02-1.65)   | 0.032                  | 33                        | 0.13                              | BBC                                | 0.546               | Weak     | 641                  | B                | B                       | C           | First study   | NA                               | 1.23 (0.98-1.55)      | 0.074                 | Not tested | NA                                     | No   | 0.53 | 0.35 |
| PTGS1   | rs788                | AG        | 9          | 13.35          | White     | 4                | 3,989          | 6,659                                | Additive                     | 1.13 (1.04-1.22)   | 0.004                  | 0                         | 0.64                              | AAC                                | 0.113               | Weak     | 2,953                | A                | A                       | C           | GWAS, Low OR  | NA                               | 1.11 (1.01-1.22)      | 0.027                 | No         | NA                                     | Yes  | 0.27 | 1.00 |
| PTGS2   | rs689466             | AG        | 1          | 30.34          | All       | 9                | 4,076          | 7,610                                | Additive                     | 0.88 (0.80-0.98)   | 0.018                  | 56                        | 0.02                              | ACC                                | 0.405               | Weak     | 6,664                | A                | C                       | C           | HWE, GWAS, Low OR                                       | NA                               | 0.91 (0.84-0.99)      | 0.032                 | Yes        | No                                     | Yes  | 0.23 | 1.00 |
| SCD   | rs7849               | G/A       | 10         | 18.49          | All       | 3                | 2,011          | 2,580                                | Additive                     | 0.85 (0.73-0.98)   | 0.025                  | 29                        | 0.25                              | ABC                                | 0.488               | Weak     | 1,631                | A                | B                       | C           | HWE, GWAS   | NA                               | 0.76 (0.62-0.92)      | 0.005                 | Yes        | No                                     | Yes  | 0.11 | 1.00 |
| TERF  | rs276100             | T/G       | 5          | 49.34          | White     | 8                | 16,176         | 18,135                               | Additive                     | 1.07 (1.04-1.1)    | 2.92-10 <sup>-5</sup>  | 0                         | 0.53                              | ACC                                | 0.001               | Moderate | 34,514               | A                | A                       | C           | low OR  | NA                               | 1.07 (1.04-1.1)       | 2.34-10 <sup>-5</sup> | No         | Yes                                    | 0.30 | 0.44 |      |
| TFEB1   | rs1800469            | T/C       | 19         | 38.74          | All       | 10               | 4,405          | 5,383                                | Additive                     | 0.88 (0.79-0.97)   | 0.013                  | 55                        | 0.02                              | ACC                                | 0.33                | Weak     | 7,257                | A                | C                       | C           | GWAS, Low OR  | NA                               | 0.90 (0.81-0.99)      | 0.031                 | Yes        | No                                     | Yes  | 0.97 | 0.71 |
| TNF   | rs1800629            | AG        | 6          | 13.78          | All       | 11               | 2,296          | 2,283                                | Additive                     | 1.28 (1.1-1.62)    | 0.046                  | 71                        | 0.00                              | ACC                                | 0.625               | Weak     | 1,403                | A                | C                       | C           | First study, HWE, GWAS                                  | NA                               | 1.27 (0.99-1.63)      | 0.055                 | Yes        | No                                     | Yes  | 0.39 | 0.48 |
| TP53  | G/C1/A/C/T14         | NA        | 1          | 24.02          | All       | 4                | 458            | 1,168                                | Additive                     | 1.20 (1.04-1.40)   | 0.015                  | 6                         | 0.36                              | AAC                                | 0.363               | Weak     | 1,037                | A                | A                       | C           | First study   | NA                               | 1.10 (0.91-1.32)      | 0.350                 | Yes        | NA                                     | No   | 0.11 | 1.00 |
| UBD   | rs2074485            | CT        | 6          | 26.07          | White     | 3                | 4,281          | 6,157                                | Additive                     | 1.07 (1.01-1.14)   | 0.034                  | 0                         | 0.77                              | AAC                                | 0.563               | Weak     | 5,523                | A                | A                       | C           | First study, GWAS, Low OR                               | NA                               | 1.08 (0.98-1.18)      | 0.109                 | No         | No                                     | Yes  | 0.63 | 1.00 |
| VDR   | rs1568820            | AG        | 12         | 36.61          | White     | 4                | 3,228          | 3,455                                | Dominant                     | 1.15 (1.04-1.27)   | 0.005                  | 0                         | 0.93                              | AAB                                | 0.165               | Weak     | 2,551                | A                | A                       | B           | GWAS  | NA                               | 1.14 (1.03-1.27)      | 0.010                 | Not tested | NA                                     | No   | 0.42 | 0.58 |
| VDR   | rs154410             | AG        | 12         | 38.96          | All       | 17               | 11,687         | 12,301                               | Additive                     | 0.85 (0.72-0.99)   | 0.040                  | 93                        | 0.00                              | ACC                                | 0.87                | Weak     | 18,394               | A                | C                       | C           | First study, HWE, GWAS, excess of significant studies   | NA                               | 0.97 (0.93-1.02)      | 0.271                 | Yes        | No                                     | Yes  | 0.38 | 0.05 |
| VGF   | rs3025039            | T/C       | 6          | 19.43          | All       | 6                | 1,925          | 1,884                                | Additive                     | 1.19 (1.04-1.37)   | 0.014                  | 29                        | 0.22                              | ABC                                | 0.347               | Weak     | 558                  | A                | A                       | C           | HWE, GWAS   | NA                               | 1.15 (1.00-1.33)      | 0.046                 | Yes        | No                                     | Yes  | 0.94 | 1.00 |
| XPA   | rs1800975            | AG        | 9          | 36.46          | White     | 3                | 593            | 1,137                                | Additive                     | 0.82 (0.70-0.96)   | 0.016                  | 4                         | 0.36                              | AAC                                | 0.379               | Weak     | 1,218                | A                | A                       | C           | GWAS, Small study                                       | NA                               | 0.70 (0.53-0.92)      | 0.011                 | No         | No                                     | No   | 0.06 | 0.57 |
| XPC   | rs2228001            | C/A       | 3          | 37.38          | All       | 9                | 2,978          | 5,204                                | Additive                     | 1.08 (1.01-1.16)   | 0.021                  | 0                         | 0.83                              | AAC                                | 0.486               | Weak     | 6,248                | A                | A                       | C           | low OR, GWAS  | NA                               | 1.09 (1.01-1.17)      | 0.029                 | No         | No                                     | Yes  | 0.58 | 0.61 |
| <b>Associations identified from additional analyses by ethnic group</b> |                      |           |            |                |           |                  |                |                                      |                              |                    |                        |                           |                                   |                                    |                     |          |                      |                  |                         |             |   |                                  |                       |                       |            |  |      |      |      |
| CDH1  | rs16260              | A/C       | 16         | 28.02          | White     | 6                | 6,761          | 6,646                                | Additive                     | 0.93 (0.87-1.00)   | 0.048                  | 23                        | 0.26                              | AAC                                | 0.642               | Weak     | 7,296                | A                | A                       | C           | First study, Low OR                                     | NA                               | 0.95 (0.85-1.07)      | 0.408                 | No         | Yes (rs9929218, r <sup>2</sup> =0.915) | Yes  | 0.53 | 0.28 |
| MTRR  | rs1801394            | A/G       | 5          | 44.65          | White     | 10               | 6,430          | 9,746                                | Additive                     | 0.98 (0.93-1.02)   | 0.030                  | 4                         | 0.41                              | AAC                                | 0.535               | Weak     | 1,510                | A                | A                       | C           | First study, HWE, GWAS                                  | NA                               | 0.82 (0.61-1.12)      | 0.212                 | Yes        | No                                     | No   | 0.84 | 1.00 |
| NGO1  | rs1800566            | T/C       | 16         | 17.88          | White     | 8                | 6,293          | 6,566                                | Additive                     | 1.09 (1.03-1.16)   | 0.006                  | 0                         | 0.50                              | AAC                                | 0.183               | Weak     | 4,765                | A                | A                       | C           | Low OR, GWAS  | NA                               | 1.08 (1.01-1.15)      | 0.026                 | No         | NA                                     | Yes  | 0.28 | 0.34 |
| OGG1  | rs105133             | G/C       | 3          | 21.59          | White     | 14               | 5,908          | 7,555                                | Additive                     | 1.15 (1.01-1.32)   | 0.033                  | 74                        | 0.00                              | ACC                                | 0.558               | Weak     | 5,879                | A                | C                       | C           | First study, HWE, GWAS                                  | NA                               | 1.16 (1.00-1.3        |                       |            |  |      |      |      |

Appendix table 4 Detailed information for additional genetic variants nominally significantly associated with colorectal-cancer risk in meta-analyses using dominant or recessive models

| Genes                 | Variants   | Alleles * | Chromosome | MAF (%)† | Ethnicity | Number evaluated |        |          | Colorectal-cancer risk meta-analysis |                   |         |                    | Venice criteria grade‡ | False-positive report probability§ | Cumulative evidence of association | Amount of Evidence         |         |       | Protection from Bias | Reason for Bias | Reason for Bias exception                          | Initial study influence |                   | Deviation from HWE | GWAS # common variants | OR<1.1§ | Modified p | Excess p |         |
|-----------------------|------------|-----------|------------|----------|-----------|------------------|--------|----------|--------------------------------------|-------------------|---------|--------------------|------------------------|------------------------------------|------------------------------------|----------------------------|---------|-------|----------------------|-----------------|--|-------------------------|-------------------|--------------------|------------------------|---------|------------|----------|---------|
|                       |            |           |            |          |           | Studies          | Cases  | Controls | Genetic models                       | OR (95% CI)       | P value | I <sup>2</sup> (%) |                        |                                    |                                    | P <sub>heterogeneity</sub> | Numbers | Grade |                      |                 |  | Replication             | OR (95% CI)       |                    |                        |         |            |          | p-value |
| <i>SELS</i>           | rs34713741 | T/C       | 15         | 33.22    | All       | 3                | 1,442  | 2,071    | Dominant                             | 1.21 (1.05-1.39)  | 0.008   | 0                  | 0.40                   | AAC                                | 0.235                              | Weak                       | 2,046   | A     | A                    | C               | First study, HWE, GWAS                             | NA                      | 1.15 (0.98-1.36)  | 0.086              | Yes                    | No      | No         | 0.96     | 1.00    |
| <i>SERPINE1/PAL-1</i> | rs1799889  | 5G/4G     | 7          | 44.94    | White     | 4                | 2,241  | 4,534    | Dominant                             | 0.87 (0.78-0.97)  | 0.014   | 0                  | 0.56                   | AAC                                | 0.337                              | Weak                       | 4,705   | A     | A                    | C               | First study, HWE, GWAS, Low OR                     | NA                      | 0.90 (0.77-1.04)  | 0.144              | No                     | No      | Yes        | 0.84     | 1.00    |
| <i>EPHX1</i>          | rs2234922  | G/A       | 1          | 19.38    | All       | 13               | 5,329  | 6,700    | Dominant                             | 0.91 (0.85-0.99)  | 0.020   | 0                  | 0.50                   | AAC                                | 0.46                               | Weak                       | 4,113   | A     | A                    | C               | GWAS, Low OR                                       | NA                      | 0.91 (0.84-0.99)  | 0.025              | No                     | No      | Yes        | 0.45     | 0.28    |
| <i>ERCC3/XPG</i>      | rs17655    | C/G       | 13         | 24.75    | All       | 9                | 6,322  | 7,537    | Dominant                             | 1.13 (1.01-1.25)  | 0.027   | 38                 | 0.12                   | ABC                                | 0.48                               | Weak                       | 6,138   | A     | B                    | C               | GWAS, Low OR                                       | NA                      | 1.14 (1.02-1.27)  | 0.026              | No                     | No      | Yes        | 0.58     | 1.00    |
| <i>RAD18</i>          | rs373572   | C/T       | 3          | 29.22    | All       | 3                | 3,174  | 3,397    | Dominant                             | 1.18 (1.01-1.37)  | 0.033   | 27                 | 0.25                   | ABC                                | 0.55                               | Weak                       | 3,333   | A     | B                    | C               | GWAS, small study                                  | NA                      | 1.33 (1.06-1.67)  | 0.015              | No                     | No      | No         | 0.00     | 0.29    |
| <i>CCND1</i>          | rs9344     | A/G       | 11         | 48.15    | All       | 22               | 6,316  | 8,272    | Dominant                             | 1.13 (1.01-1.26)  | 0.035   | 43                 | 0.00                   | ABC                                | 0.569                              | Weak                       | 10,655  | A     | B                    | C               | studies  | NA                      | 1.11 (0.99-1.24)  | 0.071              | Yes                    | No      | Yes        | 0.42     | 0.08    |
| <i>IGF1</i>           | rs35767    | T/C       | 12         | 24.75    | All       | 3                | 2,717  | 4,880    | Recessive                            | 0.75 (0.62-0.91)  | 0.003   | 0                  | 0.57                   | BAC                                | 0.11                               | Weak                       | 528     | B     | A                    | C               | HWE  | NA                      | 0.73 (0.60-0.89)  | 0.002              | Yes                    | NA      | No         | 0.77     | 1.00    |
| <i>MGMT</i>           | rs12917    | T/C       | 10         | 12.99    | All       | 7                | 4,127  | 7,284    | Recessive                            | 1.54 (1.14-2.08)  | 0.005   | 0                  | 0.47                   | BAA                                | 0.158                              | Weak                       | 208     | B     | A                    | A               | NA   | NA                      | 1.61 (1.14-2.28)  | 0.007              | Yes                    | NA      | No         | 0.96     | 1.00    |
| <i>CRP</i>            | rs1800947  | C/G       | 1          | 5.70     | All       | 4                | 2,916  | 3,544    | Recessive                            | 3.84 (1.38-10.74) | 0.010   | 0                  | 0.47                   | CAC                                | 0.277                              | Weak                       | 32      | C     | A                    | C               | First study  | NA                      | 2.78 (0.84-9.18)  | 0.093              | No                     | NA      | No         | 0.30     | 1.00    |
| <i>HPGD</i>           | rs2612656  | G/A       | 4          | 22.75    | White     | 3                | 2,979  | 5,575    | Recessive                            | 1.31 (1.05-1.64)  | 0.016   | 21                 | 0.28                   | BAC                                | 0.380                              | Weak                       | 450     | B     | A                    | C               | First study  | NA                      | 1.17 (0.91-1.50)  | 0.220              | No                     | NA      | No         | 0.45     | 1.00    |
| <i>FRZB</i>           | rs7775     | G/C       | 2          | 8.77     | White     | 3                | 1,256  | 3,000    | Recessive                            | 3.20 (1.17-8.73)  | 0.023   | 64                 | 0.06                   | CCC                                | 0.468                              | Weak                       | 55      | C     | C                    | C               | First study  | NA                      | 3.12 (0.61-15.94) | 0.171              | No                     | NA      | No         | 0.28     | 1.00    |
| <i>TGFBR1</i>         | rs334354   | A/G       | 9          | 26.71    | All       | 4                | 1,226  | 2,776    | Recessive                            | 1.38 (1.04-1.84)  | 0.029   | 8                  | 0.35                   | BAC                                | 0.516                              | Weak                       | 325     | B     | A                    | C               | First study  | NA                      | 1.24 (0.92-1.67)  | 0.158              | No                     | NA      | No         | 0.24     | 0.56    |
| <i>TGFBI</i>          | rs4803455  | A/C       | 19         | 47.48    | All       | 3                | 2,786  | 3,516    | Recessive                            | 1.14 (1.01-1.28)  | 0.030   | 0                  | 0.37                   | AAC                                | 0.536                              | Weak                       | 1,483   | A     | A                    | C               | First study, Low OR                                | NA                      | 1.04 (0.87-1.24)  | 0.646              | No                     | NA      | Yes        | 0.50     | 0.53    |
| <i>LIPC</i>           | rs6083     | A/G       | 15         | 36.52    | All       | 3                | 4,702  | 4,914    | Recessive                            | 0.85 (0.74-0.99)  | 0.032   | 25                 | 0.27                   | AAA                                | 0.56                               | Weak                       | 1,248   | A     | A                    | A               | NA   | NA                      | 0.78 (0.65-0.94)  | 0.008              | No                     | NA      | No         | 0.98     | 1.00    |
| <i>MTHFR</i>          | rs1801133  | T/C       | 1          | 33.50    | All       | 68               | 32,608 | 44,383   | Recessive                            | 0.92 (0.85-1)     | 0.036   | 52                 | 0.00                   | ACC                                | 0.61                               | Weak                       | 9,072   | A     | C                    | C               | Low OR, small study, excess of significant studies | NA                      | 0.92 (0.86-1.00)  | 0.043              | No                     | NA      | Yes        | 0.06     | 0.00    |
| <i>CYP2C9</i>         | rs1799853  | T/C       | 10         | 13.31    | White     | 6                | 4,915  | 5,237    | Recessive                            | 1.36 (1.02-1.83)  | 0.038   | 0                  | 0.76                   | BAA                                | 0.60                               | Weak                       | 190     | B     | A                    | A               | NA   | NA                      | 1.36 (1.01-1.83)  | 0.046              | No                     | NA      | No         | 0.31     | 0.47    |
| <i>MTRR</i>           | rs10380    | T/C       | 5          | 9.31     | White     | 4                | 3,869  | 5,141    | Recessive                            | 1.61 (1.02-2.52)  | 0.039   | 6                  | 0.36                   | BAA                                | 0.597                              | Weak                       | 93      | C     | A                    | A               | NA   | NA                      | 2.24 (1.14-4.43)  | 0.020              | No                     | NA      | No         | 0.31     | 0.50    |

\* Minor alleles/major alleles (Per Caucasian)

† MAF=minor allele frequency in controls.

‡ Venice criteria grades are for amount of evidence, replication of the association, and protection from bias.

§ False-positive report probability (FPRP) was determined based on OR and P value of each variant from meta-analysis and a prior probability of 0.05.

Cumulative epidemiological evidence as graded by combination of results from Venice criteria and FPRP for association with colorectal-cancer risk.

Appendix table 5. Meta-analysis of associations between 267 genetic variants and colorectal-cancer risk by ethnicity

| Gene          | Variant ID | Genetic variant (Variation)                       | Comparison                 | Meta-analyses in Whites |       |          |                            |                             |         | Meta-analyses in Asians |         |       |                        |                             |             |         |                    |
|---------------|------------|---|----------------------------|-------------------------|-------|----------|----------------------------|-----------------------------|---------|-------------------------|---------|-------|------------------------|-----------------------------|-------------|---------|--------------------|
|               |            |   |                            | Studies                 | Cases | Controls | Frequency (%) <sup>a</sup> | OR (95% CI)                 | P value | I <sup>2</sup> (%)      | Studies | Cases | Controls               | Frequency (%) <sup>a</sup>  | OR (95% CI) | P value | I <sup>2</sup> (%) |
| ABCB1         | 1          | rs1128503 (Giv412Gv)                              | T vs C                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| ABCB1         | 2          | rs1202168   | T vs C                     | 4                       | 6,318 | 5,805    | 41.25 1.05 (0.97-1.14)     | 0.191                       | 55      |                         |         |       |                        |                             |             |         |                    |
| ABCB1         | 3          | rs2229109 (Ser400Asn)                             | A vs G                     | 3                       | 4,242 | 4,178    | 5.19 0.99 (0.86-1.13)      | 0.866                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ABCB1         | 4          | rs868755  | T vs G                     | 3                       | 2,958 | 3,255    | 42.06 1.06 (0.99-1.14)     | 0.109                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ABCB1         | 5          | rs9282564 (Asn21Asp)                              | G vs A                     | 4                       | 5,792 | 5,234    | 8.89 1.21 (0.78-1.88)      | 0.400                       | 96      |                         |         |       |                        |                             |             |         |                    |
| ABCB1/MDR1    | 6          | rs1045642 (p.Ile1145Ile, c.3435T>C)               | C vs T                     | 9                       | 5,983 | 6,669    | 47.20 1.00 (0.91-1.10)     | 0.977                       | 64      |                         |         |       |                        |                             |             |         |                    |
| ABCB1/MDR1    | 7          | rs2032582 (2677G>T)                               | T vs G                     | 3                       | 510   | 518      | 44.02 0.89 (0.74-1.06)     | 0.355                       | 3       |                         |         |       |                        |                             |             |         |                    |
| ACE           | 8          | 287-bp repeat (1D)                                | ins vs del                 | 3                       | 509   | 6,895    | 47.28 1.01 (0.87-1.18)     | 0.857                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ADH1C/ADH2    | 9          | rs1229984 (ADH1B*2; HIS47ARG)                     | G vs A                     |                         |       |          |                            |                             |         | 5                       | 1,899   | 2,833 | 32.83 1.087            | 0.901                       | 0.384       | 68      |                    |
| ADH1C/ADH3    | 10         | rs698 (p.Ile350Phe/p.Ile350Val)                   | G vs A                     | 8                       | 4,132 | 7,242    | 39.59 1.02 (0.91-1.15)     | 0.732                       | 74      |                         |         |       |                        |                             |             |         |                    |
| ADIPOQ        | 11         | rs1501299   | T vs G                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| ADIPOQ        | 12         | rs266729 (nearGene-5, C-11374G)                   | G vs C                     | 3                       | 2,795 | 2,979    | 33.28 0.97 (0.90-1.04)     | 0.411                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ADIPOR1       | 13         | rs1342387   | C vs G                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| ADIPOR1       | 14         | rs7539542   | A vs G                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| ADH2          | 15         | rs671 (p.Glu487Lys/Glu504Lys, c.1510G>A)          | A vs G                     |                         |       |          |                            |                             |         | 7                       | 1,799   | 3,385 | 22.20 1.03 (0.83-1.27) | 0.811                       | 0.811       | 73      |                    |
| ALOX12/12-LOX | 16         | rs1126667 (p.Gln261Arg, c.782G>A)                 | A vs G                     | 3                       | 1,559 | 1,804    | 41.88 1.00 (0.8-1.16)      | 0.972                       | 46      |                         |         |       |                        |                             |             |         |                    |
| ALOX5         | 17         | rs4986832 (nearGene-5, -1708 G>A, g.3400G>A)      | A vs G                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APC           | 18         | rs1801155 (I1307K, T3920A)                        | carriers vs non-carriers   |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APC           | 19         | rs1801166 (E1317Q)                                | (CC>CG) vs GG              |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APC           | 20         | rs2229992 (p.Tyr486Tyr)                           | T vs C                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APC           | 21         | rs2229995 (p.Gly2502Ser, c.7504G>A)               | A vs G                     | 3                       | 1,130 | 1,626    | 1.75 1.25 (0.85-1.85)      | 0.258                       | 0       |                         |         |       |                        |                             |             |         |                    |
| APC           | 22         | rs41115 (p.Thr1493Thr)                            | C vs T                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APC           | 23         | rs42427 (p.Gly1678Gly)                            | G vs A                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APC           | 24         | rs459552 (p.Val1822Asp, c.5465T>A)                | A vs T                     | 7                       | 6,388 | 6,859    | 22.77 0.97 (0.91-1.03)     | 0.267                       | 0       |                         |         |       |                        |                             |             |         |                    |
| APC           | 25         | rs465899 (p.Pro1960Pro)                           | C vs T                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| APEX1/APEX    | 26         | rs1048945 (p.Gln51His, c.153G>C)                  | C vs G                     | 3                       | 3,224 | 3,369    | 4.05 0.89 (0.63-1.25)      | 0.497                       | 41      |                         |         |       |                        |                             |             |         |                    |
| APEX1/APEX    | 27         | rs1130409 (p.Asp148Glu, c.444T>G)                 | G vs T                     | 8                       | 4,306 | 5,301    | 46.04 1.01 (0.86-1.19)     | 0.901                       | 36      |                         |         |       |                        |                             |             |         |                    |
| ARLTS1/ARL1   | 28         | rs34301344 (p.Trp1498Stop, c.446G>A)              | (AA>AG) vs GG              | 3                       | 1,367 | 1,862    | 0.99 1.00 (0.60-1.63)      | 0.992                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ARLTS1/ARL1   | 29         | rs3803185 (p.Cys148Arg, T442C, T>C)               | C vs T                     | 4                       | 2,123 | 2,681    | 46.10 1.07 (0.99-1.17)     | 0.093                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ATM           | 30         | rs1801673 (Ex37>62A>T, Asp1853Val)                | A vs G                     | 3                       | 2,879 | 6,384    | 0.66 0.77 (0.54-1.10)      | 0.144                       | 0       |                         |         |       |                        |                             |             |         |                    |
| AURKAS/STK15  | 31         | rs2273535 (p.Phe31Ile, c.91T>A)                   | A vs T                     | 5                       | 5,091 | 4,670    | 21.45 1.02 (0.94-1.10)     | 0.652                       | 8       |                         |         |       |                        |                             |             |         |                    |
| AXIN2         | 32         | rs2240308 (p.Pro50Ser, c.148C>T, G/A)             | A vs G                     | 3                       | 3,762 | 3,934    | 46.11 1.07 (0.98-1.17)     | 0.124                       | 29      |                         |         |       |                        |                             |             |         |                    |
| BLM           | 33         | ASH non-carriers/carriers                         | carriers vs non-carriers   |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| BMP4          | 34         | rs17563 (p.Val152Ala, c.455T>C)                   | T vs C                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CASP8         | 35         | rs3834129 (nearGene-5, -652 6N del, -CTTACT)      | 6 bp ins vs del            | 5                       | 5,086 | 6,464    | 47.41 1.01 (0.94-1.09)     | 0.706                       | 20      |                         |         |       |                        |                             |             |         |                    |
| CASR          | 36         | rs1042636 (p.Arg990Gly, c.2968A>G)                | G vs A                     | 4                       | 6,298 | 7,839    | 8.52 1.00 (0.92-1.09)      | 0.936                       | 0       | 3                       | 1,563   | 2,893 | 21.90 1.13 (0.68-1.90) | 0.632                       | 95          |         |                    |
| CASR          | 37         | rs1801725 (p.Ala986Ser, c.2956G>T)                | T vs G                     | 3                       | 2,733 | 3,359    | 13.10 1.30 (0.99-1.72)     | 0.061                       | 84      |                         |         |       |                        |                             |             |         |                    |
| CBS           | 38         | rs5742905 (Ile278Thr, CBS E278T)                  | C vs T                     | 3                       | 2,504 | 3,723    | 8.22 1.05 (0.92-1.19)      | 0.489                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CENPD         | 39         | rs9344 (rs603965, p.Pro241Pro, c.723G>A/c.870G>A) | A vs G                     | 10                      | 2,789 | 2,995    | 47.76 1.05 (0.95-1.16)     | 0.369                       | 35      | 4                       | 1,758   | 3,160 | 45.55 0.95 (0.82-1.09) | 0.462                       | 56          |         |                    |
| CDH1          | 40         | rs16240 (UTR-5, -160C>A)                          | A vs C                     | 6                       | 6,761 | 6,646    | 28.02 0.93 (0.87-1.00)     | <b>0.048</b>                | 23      |                         |         |       |                        |                             |             |         |                    |
| CDKN1A        | 41         | rs1059234 (UTR-3, c.*20C>T)                       | T vs C                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CDKN1A        | 42         | rs1801270 (n.Ser31Arg, c.93C>A)                   | A vs C                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CHEK2         | 43         | 1100delC (s381X)                                  | carriers vs non-carriers   | 7                       | 3,874 | 11,630   | 0.71 1.88 (1.29-2.73)      | <b>0.001</b>                | 0       |                         |         |       |                        |                             |             |         |                    |
| CHEK2         | 44         | rs17879961 (p.Ile200Thr)                          | carriers vs non-carriers   | 6                       | 6,042 | 17,051   | 3.91 1.56 (1.32-1.84)      | <b>1.22x10<sup>-7</sup></b> | 0       |                         |         |       |                        |                             |             |         |                    |
| COMT          | 45         | rs4680 (p.Val158Met, c.472G>A)                    | A vs G                     | 5                       | 5,074 | 5,239    | 48.89 1.05 (0.94-1.16)     | 0.390                       | 56      |                         |         |       |                        |                             |             |         |                    |
| CRP           | 46         | rs1205 (c.*1082G>A, 2042C>T)                      | T vs C                     | 3                       | 2,393 | 8,064    | 32.08 1.07 (0.99-1.16)     | 0.091                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CRP           | 47         | rs1417938 (29T>A)                                 | A vs T                     | 3                       | 2,422 | 3,146    | 29.83 0.95 (0.85-1.06)     | 0.322                       | 34      |                         |         |       |                        |                             |             |         |                    |
| CRP           | 48         | rs1800947 (p.Leu184Leu, c.552G>C)                 | C vs G                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CTLA4         | 49         | rs231775 (p.Thr17Ala, c.49A>G)                    | G vs A                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CX3CR1        | 50         | rs3732378 (T280M)                                 | A vs G                     | 3                       | 3,143 | 3,269    | 16.95 1.00 (0.83-1.19)     | 0.968                       | 44      |                         |         |       |                        |                             |             |         |                    |
| CYP17A1       | 51         | rs743572  | G vs A                     | 3                       | 4,376 | 4,588    | 39.56 1.04 (0.91-1.18)     | 0.592                       | 67      |                         |         |       |                        |                             |             |         |                    |
| CYP17A1       | 52         | rs1048943 (*2C, m2, p.Ile462Val, c.1384A>C)       | G vs A                     | 10                      | 5,000 | 5,751    | 5.29 1.19 (1.04-1.36)      | <b>0.011</b>                | 17      | 5                       | 1,661   | 2,211 | 23.34 1.08 (0.90-1.28) | 0.425                       | 48          |         |                    |
| CYP11A1       | 53         | rs1799814 (Thr461Asp)                             | A vs C                     | 3                       | 3,155 | 3,394    | 4.36 0.75 (0.46-1.20)      | 0.227                       | 74      |                         |         |       |                        |                             |             |         |                    |
| CYP11A1       | 54         | rs4646903 (m1, MspI, UTR-3, T3801C)               | C vs T                     | 11                      | 6,418 | 7,152    | 11.57 1.03 (0.88-1.21)     | 0.686                       | 72      |                         |         |       |                        |                             |             |         |                    |
| CYP11A2       | 55         | rs2069514 (CYP11A2*1C, -3860G>A)                  | A vs G                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CYP11A2       | 56         | rs2470890 (CYP11A2*1B, Asn516Asn; 1545T>C)        | C vs T                     |                         |       |          |                            |                             |         | 3                       | 901     | 937   | 27.59 1.06 (0.79-1.42) | 0.697                       | 54          |         |                    |
| CYP11A2       | 57         | rs762551 (CYP11A2*1F, c.A-163C)                   | C vs A                     | 7                       | 5,608 | 5,968    | 29.46 1.02 (0.95-1.11)     | 0.547                       | 42      | 3                       | 279     | 429   | 36.25 1.03 (0.59-1.78) | 0.924                       | 82          |         |                    |
| CYP11B1       | 58         | rs10012 (p.Arg48Gly, c.142C>G)                    | G vs C                     | 4                       | 3,825 | 3,926    | 29.43 0.03 (0.94-1.14)     | 0.524                       | 44      |                         |         |       |                        |                             |             |         |                    |
| CYP11B1       | 59         | rs1056836 (CYP11B1*3, p.Leu432Val, c.1294C>G)     | G vs C                     | 9                       | 8,709 | 9,097    | 43.27 1.02 (0.97-1.06)     | 0.488                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CYP11B1       | 60         | rs1800440 (p.Asn453Ser, c.1358A>G)                | G vs A                     | 6                       | 6,679 | 6,923    | 18.36 0.97 (0.88-1.07)     | 0.580                       | 53      |                         |         |       |                        |                             |             |         |                    |
| CYP2C19       | 61         | rs4244285 (Pro681Pro)                             | T vs C                     | 3                       | 2,557 | 2,664    | 14.94 0.91 (0.75-1.1)      | 0.337                       | 53      |                         |         |       |                        |                             |             |         |                    |
| CYP2C9        | 62         | R144C/I359L                                       | mutation vs wild           | 3                       | 2,424 | 3,053    | 18.54 0.94 (0.81-1.08)     | 0.362                       | 38      |                         |         |       |                        |                             |             |         |                    |
| CYP2C9        | 63         | rs1057910 (p.Ile359Leu, c.1075A>C)                | G vs A                     | 6                       | 6,474 | 6,835    | 6.82 0.95 (0.86-1.05)      | 0.307                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CYP2C9        | 64         | rs1799853 (p.Arg144Cys, c.430C>T)                 | T vs C                     | 6                       | 4,915 | 5,237    | 13.31 0.98 (0.91-1.07)     | 0.668                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CYP2D6        | 65         | rs3892097 (c.353-1G>A)                            | A vs G                     | 3                       | 798   | 1,512    | 20.07 1.03 (0.88-1.21)     | 0.684                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CYP2E1        | 66         | 96-bp insertion                                   | insertion vs non-insertion |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| CYP2E1        | 67         | rs2031920 (RsaI, c1>c2, C>T)                      | T vs C                     | 4                       | 2,146 | 2,237    | 3.93 1.21 (0.85-1.71)      | 0.284                       | 56      |                         |         |       |                        |                             |             |         |                    |
| CYP2E1        | 68         | rs3813867 (nearGene-5, g.3739G>C, c.-1293G>C)     | C vs G                     | 4                       | 2,345 | 2,867    | 3.56 0.84 (0.68-1.05)      | 0.131                       | 0       |                         |         |       |                        |                             |             |         |                    |
| CYP2E1        | 69         | rs6413432 (Intron, c.967+1143T>A, 7632T>A)        | A vs T                     | 3                       | 1,352 | 1,858    | 8.32 1.13 (0.67-1.92)      | 0.649                       | 78      |                         |         |       |                        |                             |             |         |                    |
| CYP3A4        | 70         | rs2740574   | G vs A                     | 3                       | 4,464 | 4,603    | 3.77 0.96 (0.83-1.12)      | 0.629                       | 0       |                         |         |       |                        |                             |             |         |                    |
| DNMT3B        | 71         | rs1569686 (nearGene-5, c.-6-1045G>T, 39179G>T)    | G vs T                     |                         |       |          |                            |                             |         | 3                       | 929     | 1,089 | 12.35 0.56 (0.45-0.70) | <b>2.60x10<sup>-7</sup></b> | 0           |         |                    |
| DNMT3B        | 72         | rs2424913 (Intron, c.307-49C>T, -149C>T)          | T vs C                     | 3                       | 1,717 | 2,899    | 43.83 0.96 (0.88-1.04)     | 0.298                       | 0       | 3                       | 681     | 1,374 | 98.98 1.67 (0.75-3.72) | 0.209                       | 0           |         |                    |
| DNMT3b        | 73         | rs406193  | T vs C                     | 3                       | 966   | 2,074    | 18.44 1.06 (0.84-1.33)     | 0.631                       | 49      |                         |         |       |                        |                             |             |         |                    |
| EPHX1         | 74         | rs1051740 (p.Tyr113His, c.337T>C)                 | C vs T                     | 13                      | 9,176 | 10,366   | 29.84 1.02 (0.96-1.08)     | 0.475                       | 34      |                         |         |       |                        |                             |             |         |                    |
| EPHX1         | 75         | rs2234922 (p.His139Arg, c.416A>G)                 | G vs A                     | 9                       | 4,132 | 4,922    | 19.69 1.00 (0.91-1.09)     | 0.930                       | 24      |                         |         |       |                        |                             |             |         |                    |
| ERCC1         | 76         | rs11615 (rs3177700, p.Asn118Asn, c.354T>C)        | C vs T                     | 5                       | 1,060 | 1,659    | 37.97 0.98 (0.87-1.10)     | 0.722                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ERCC1         | 77         | rs3212986 (8092C>A)                               | (AA>AC) vs CC              |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |
| ERCC2/XPD     | 78         | rs13181 (p.Lys751Gln, c.2251A>C)                  | C vs A                     | 14                      | 4,717 | 6,564    | 36.77 0.96 (0.90-1.03)     | 0.285                       | 21      |                         |         |       |                        |                             |             |         |                    |
| ERCC2/XPD     | 79         | rs1799793 (p.Asp312Asn, c.981G>A)                 | A vs G                     | 6                       | 5,069 | 5,967    | 34.74 1.02 (0.96-1.07)     | 0.593                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ERCC4/XPF     | 80         | rs1800067 (R415Q)                                 | A vs G                     | 3                       | 3,173 | 3,206    | 10.61 1.01 (0.90-1.14)     | 0.826                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ERCC5/XPG     | 81         | rs17655 (p.Asp1104His, c.3310G>C)                 | C vs G                     | 8                       | 5,294 | 6,452    | 21.33 1.04 (0.98-1.11)     | 0.184                       | 0       |                         |         |       |                        |                             |             |         |                    |
| ESR1          | 82         | rs2077647 (Ser10Ser)                              | C vs T                     | 3                       | 1,923 | 2,416    | 46.83 1.13 (0.85-1.5)      | 0.413                       | 70      |                         |         |       |                        |                             |             |         |                    |
| ESR1          | 83         | rs2234693   | C vs T                     |                         |       |          |                            |                             |         |                         |         |       |                        |                             |             |         |                    |

|        |     |   |                  |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
|--------|-----|---|------------------|----|--------|--------|-------|------|--------------|--------------|----|----|-------|-------|-------|------|-------------|--------------|----|
| FOLH1  | 88  | rs202676 (p.Tyr75His, c.223T>C)                 | C vs T           | 3  | 3,135  | 3,914  | 21.27 | 0.94 | (0.87-1.02)  | 0.165        | 0  |    |       |       |       |      |             |              |    |
| FRZB   | 89  | rs288326 (p.Arg200Trp, c.598C>T)                | T vs C           | 3  | 1,260  | 3,006  | 12.38 | 0.95 | (0.86-1.05)  | 0.312        | 0  |    |       |       |       |      |             |              |    |
| FRZB   | 90  | rs7775 (p.Arg324Gly, c.970C>G)                  | G vs C           | 3  | 1,256  | 3,000  | 8.77  | 1.17 | (0.88-1.56)  | 0.285        | 66 |    |       |       |       |      |             |              |    |
| GH1    | 91  | rs2665802 (c.456+90T>A)                         | A vs T           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| GPX1   | 92  | rs1050450 (p.Pro200Leu, c.599C>T)               | T vs C           | 3  | 1,222  | 1,813  | 29.51 | 1.01 | (0.90-1.13)  | 0.920        | 0  |    |       |       |       |      |             |              |    |
| GPX4   | 93  | rs713041  | T vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| GSTA1  | 94  | *A>B  | mutation vs wild | 3  | 464    | 574    | 39.11 | 1.13 | (0.84-1.53)  | 0.418        | 62 |    |       |       |       |      |             |              |    |
| GSTA1  | 95  | rs3957357                                       | A vs G           | 3  | 1,313  | 1,327  | 39.90 | 1.01 | (0.91-1.12)  | 0.989        | 0  |    |       |       |       |      |             |              |    |
| GSTM1  | 96  | Present/Null                                    | null vs present  | 35 | 14,650 | 19,818 | 52.43 | 1.08 | (1.01-1.16)  | <b>0.037</b> | 53 | 12 | 4,739 | 9,929 | 50.10 | 1.04 | (0.96-1.19) | 0.360        | 0  |
| GSTM3  | 97  | rs1799735 (c.468+21delAGG, delAGG)              | AGG del vs ins   | 3  | 2,531  | 2,707  | 15.96 | 0.94 | (0.72-1.23)  | 0.653        | 83 |    |       |       |       |      |             |              |    |
| GSTP1  | 98  | rs1138272 (p.Ala114Val, c.341C>T)               | T vs C           | 8  | 6,858  | 7,207  | 10.23 | 0.89 | (0.77-1.02)  | 0.884        | 55 |    |       |       |       |      |             |              |    |
| GSTP1  | 99  | rs1695 (p.Ile105Val, c.313A>G)                  | G vs A           | 19 | 7,433  | 8,487  | 33.35 | 0.99 | (0.94-1.06)  | 0.055        | 28 | 7  | 1,622 | 5,660 | 18.74 | 0.89 | (0.80-1.00) | 0.057        | 0  |
| GSTT1  | 100 | Present/Null                                    | null vs present  | 26 | 9,684  | 12,638 | 19.20 | 1.24 | (1.08-1.44)  | <b>0.003</b> | 74 | 9  | 4,354 | 9,301 | 44.52 | 1.08 | (0.99-1.18) | 0.104        | 13 |
| GSTZ1  | 101 | rs3177427 (GLU32LYS)                            | A vs G           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| HFE    | 102 | rs1799945 (H63D)                                | G vs C           | 7  | 3,729  | 4,079  | 14.70 | 1.03 | (0.93-1.15)  | 0.581        | 7  |    |       |       |       |      |             |              |    |
| HFE    | 103 | rs1800562 (rs111535158, p.Cys282Tyr, c.1005G>A) | A vs G           | 10 | 2,502  | 30,857 | 7.43  | 1.05 | (0.92-1.21)  | 0.467        | 0  |    |       |       |       |      |             |              |    |
| HIF1A  | 104 | rs11549465 (p.Pro582Ser, c.1744C>T)             | T vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| HPGD   | 105 | rs7349744                                       | C vs A           | 3  | 3,001  | 5,624  | 7.56  | 0.96 | (0.84-1.09)  | 0.516        | 11 |    |       |       |       |      |             |              |    |
| HPGD   | 106 | rs2612656                                       | G vs A           | 3  | 2,979  | 5,575  | 22.75 | 1.09 | (0.97-1.24)  | 0.162        | 65 |    |       |       |       |      |             |              |    |
| HPGD   | 107 | rs7349744                                       | A vs G           | 3  | 3,014  | 5,622  | 30.54 | 1.01 | (0.93-1.07)  | 0.897        | 0  |    |       |       |       |      |             |              |    |
| HPGD   | 108 | rs8752  | G vs A           | 3  | 3,008  | 5,632  | 41.98 | 1.01 | (0.86-1.17)  | 0.936        | 22 |    |       |       |       |      |             |              |    |
| HPGD   | 109 | rs9312555                                       | G vs A           | 3  | 3,015  | 5,634  | 15.42 | 0.93 | (0.86-1.02)  | 0.134        | 0  |    |       |       |       |      |             |              |    |
| ICAM1  | 110 | rs5498 (p.Lys469Glu, c.1405A>G)                 | G vs A           | 3  | 3,142  | 3,255  | 42.83 | 1.02 | (0.85-1.24)  | 0.819        | 70 |    |       |       |       |      |             |              |    |
| IGF1   | 111 | (CA)n (R19>non-R19)                             | non R19 vs R19   | 6  | 4,979  | 5,658  | 35.22 | 0.97 | (0.85-1.10)  | 0.594        | 78 |    |       |       |       |      |             |              |    |
| IGF1   | 112 | rs35767   | T vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| IGFBP1 | 113 | rs4619 (p.Ile253Met, c.759A>G)                  | G vs A           | 3  | 3,570  | 3,660  | 35.53 | 0.93 | (0.75-1.16)  | 0.535        | 85 |    |       |       |       |      |             |              |    |
| IGFBP3 | 114 | rs2854744 (nearGene-5, C-202A, A>C)             | C vs A           | 6  | 4,406  | 6,873  | 50.23 | 1.03 | (0.98-1.09)  | 0.240        | 0  |    |       |       |       |      |             |              |    |
| IGFBP3 | 115 | rs2854746 (p.Ala32Gly, c.95C>G)                 | G vs C           | 3  | 1,509  | 2,783  | 42.49 | 1.08 | (0.97-1.20)  | 0.174        | 0  |    |       |       |       |      |             |              |    |
| IL10   | 116 | rs1800872 (nearGene-5, g.4433A>C, -592C>A)      | A vs C           | 6  | 1,561  | 2,439  | 22.57 | 0.94 | (0.81-1.1)   | 0.444        | 41 |    |       |       |       |      |             |              |    |
| IL10   | 117 | rs1800896 (nearGene-5, g.3943A>G, -1082A>G)     | G vs A           | 5  | 1,134  | 1,492  | 46.68 | 0.98 | (0.84-1.15)  | 0.793        | 44 |    |       |       |       |      |             |              |    |
| IL16   | 118 | rs4072111 (p.Pro434Ser, c.1300C>T)              | T vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| IL1B   | 119 | rs1143627 (nearGene-5, g.4970C>T, -31T>C)       | C vs T           | 5  | 1,524  | 2,034  | 32.72 | 1.07 | (0.96-1.18)  | 0.209        | 0  |    |       |       |       |      |             |              |    |
| IL1B   | 120 | rs16944   | G vs A           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| IL4    | 121 | rs2243250 (nearGene-5, -509C>T)                 | T vs C           | 6  | 1,225  | 1,754  | 18.93 | 0.92 | (0.76-1.12)  | 0.401        | 42 |    |       |       |       |      |             |              |    |
| IL4R   | 122 | rs1801275 (p.Gln576Arg, c.1727A>G)              | G vs A           | 3  | 633    | 887    | 19.90 | 1.05 | (0.87-1.26)  | 0.629        | 0  |    |       |       |       |      |             |              |    |
| IL4R   | 123 | rs1805012 (C431R)                               | G vs A           | 3  | 2,840  | 3,233  | 11.18 | 0.95 | (0.70-1.31)  | 0.764        | 59 |    |       |       |       |      |             |              |    |
| IL4R   | 124 | rs1805015 (S503P)                               | C vs T           | 3  | 640    | 892    | 16.26 | 1.02 | (0.84-1.25)  | 0.834        | 0  |    |       |       |       |      |             |              |    |
| IL6    | 125 | rs1800795                                       | C vs G           | 13 | 6,683  | 8,121  | 39.73 | 1.01 | (0.92-1.11)  | 0.822        | 68 |    |       |       |       |      |             |              |    |
| IL6    | 126 | rs1800797                                       | (AA+AG) vs GG    | 4  | 2,612  | 3,381  | 60.75 | 0.96 | (0.87-1.07)  | 0.468        | 0  |    |       |       |       |      |             |              |    |
| IL6R   | 127 | rs2228145 (rs8192284, Asp358Val)                | C vs A           | 3  | 3,070  | 20,173 | 30.92 | 0.97 | (0.91-1.04)  | 0.435        | 0  |    |       |       |       |      |             |              |    |
| IL8    | 128 | rs4073 (nearGene-5, T-251A)                     | A vs T           | 10 | 3,520  | 4,381  | 45.88 | 1.04 | (0.92-1.18)  | 0.525        | 70 |    |       |       |       |      |             |              |    |
| IRS1   | 129 | rs1801278 (p.Gly971Arg, c.2911G>A)              | A vs G           | 7  | 7,048  | 7,533  | 6.92  | 1.08 | (0.96-1.22)  | 0.219        | 39 |    |       |       |       |      |             |              |    |
| IRS2   | 130 | rs1805097 (p.Gly1057Asp, c.3170G>A)             | A vs G           | 3  | 2,318  | 2,814  | 41.13 | 0.96 | (0.89-1.04)  | 0.327        | 0  |    |       |       |       |      |             |              |    |
| LCT    | 131 | rs4988235 (c.1917+326C>T, 13910 C>T)            | T vs C           | 7  | 2,103  | 2,492  | 41.75 | 0.99 | (0.87-1.14)  | 0.879        | 51 |    |       |       |       |      |             |              |    |
| LEP    | 132 | rs7799039                                       | A vs G           | 3  | 2,324  | 2,776  | 43.98 | 0.95 | (0.88-1.03)  | 0.222        | 0  |    |       |       |       |      |             |              |    |
| LEPR   | 133 | rs1137101 (p.Gln223Arg, c.668A>G)               | G vs A           | 3  | 1,100  | 1,166  | 44.47 | 1.08 | (0.96-1.22)  | 0.187        | 0  |    |       |       |       |      |             |              |    |
| LIPC   | 134 | rs6083 (N215S)                                  | A vs G           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| MBL2   | 135 | rs11003125                                      | G vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| MBL2   | 136 | rs1800450 (Gly54Asp)                            | A vs G           | 3  | 3,294  | 3,357  | 14.43 | 1.01 | (0.85-1.19)  | 0.936        | 37 |    |       |       |       |      |             |              |    |
| MBL2   | 137 | rs1800451 (p.Gly57Glu)                          | A vs G           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| MBL2   | 138 | rs5030737 (R52C)                                | T vs C           | 3  | 1,083  | 1,023  | 7.09  | 1.02 | (0.81-1.30)  | 0.845        | 0  |    |       |       |       |      |             |              |    |
| MBL2   | 139 | rs7096206                                       | C vs G           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| MDM2   | 140 | rs2279744 (nearGene-5, SNP309, c.14+309T>G)     | G vs T           | 6  | 1,613  | 886    | 37.36 | 1.03 | (0.90-1.18)  | 0.671        | 2  | 3  | 1,252 | 1,485 | 46.13 | 1.01 | (0.90-1.12) | 0.933        | 0  |
| MGMT   | 141 | rs12917 (p.Leu115Phe, c.343C>T)                 | T vs C           | 5  | 3,635  | 5,917  | 12.95 | 1.02 | (0.93-1.11)  | 0.745        | 0  |    |       |       |       |      |             |              |    |
| MGMT   | 142 | rs2308321 (p.Ile174Val, c.520A>G)               | G vs A           | 5  | 3,642  | 8,583  | 12.76 | 0.94 | (0.75-1.17)  | 0.565        | 74 |    |       |       |       |      |             |              |    |
| MLH1   | 143 | rs121912963 (p.D132H, c.415G>C)                 | C vs G           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| MLH1   | 144 | rs1799977 (p.Ile219Val, c.655A>G)               | G vs A           | 8  | 6,117  | 8,385  | 31.41 | 1.00 | (0.92-1.12)  | 0.952        | 63 |    |       |       |       |      |             |              |    |
| MLH1   | 145 | rs1800734 (nearGene-5/UTR-5, -93G>A)            | A vs G           | 7  | 17,783 | 13,777 | 21.31 | 1.05 | (1.01-1.09)  | <b>0.014</b> | 0  |    |       |       |       |      |             |              |    |
| MLH1   | 146 | rs63750447 (p.Val384Asp, 1151 T>A)              | A vs T           |    |        |        |       |      |              |              |    | 3  | 937   | 919   | 1.96  | 2.14 | (1.12-4.12) | <b>0.022</b> | 41 |
| MLH1   | 147 | rs9876116 (Intron 14, c.1668-19A>G)             | G vs A           | 3  | 2,024  | 2,143  | 44.47 | 0.93 | (0.85-1.02)  | 0.631        | 15 |    |       |       |       |      |             |              |    |
| MMP1   | 148 | rs1799750 (nearGene-5, -1607 1G>2G)             | 2G vs 1G         | 3  | 678    | 842    | 50.30 | 0.80 | (0.61-1.05)  | 0.107        | 62 | 4  | 649   | 809   | 26.89 | 0.78 | (0.58-1.06) | 0.113        | 67 |
| MMP2   | 149 | rs243865 (-1306C>T)                             | T vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |
| MMP3   | 150 | rs3025058                                       | 5A vs 6A         | 3  | 660    | 869    | 47.07 | 1.03 | (0.89-1.19)  | 0.709        | 0  | 4  | 459   | 624   | 13.86 | 1.01 | (0.64-1.62) | 0.947        | 68 |
| MMP7   | 151 | rs11568818 (nearGene-5, -181A>G)                | G vs A           |    |        |        |       |      |              |              |    | 3  | 468   | 623   | 6.50  | 0.69 | (0.40-1.18) | 0.171        | 39 |
| MMP9   | 152 | rs3918242 (nearGene-5, g.3430C>T, -1562 C>T)    | T vs C           |    |        |        |       |      |              |              |    | 3  | 517   | 584   | 14.13 | 0.80 | (0.60-1.09) | 0.155        | 22 |
| MSH2   | 153 | rs2303425 (nearGene-5, g.4951T>C, c.-118T>C)    | C vs T           | 3  | 1,775  | 2,206  | 12.78 | 1.01 | (0.87-1.17)  | 0.944        | 14 |    |       |       |       |      |             |              |    |
| MSH2   | 154 | rs2303428 (c.2006-6T>C)                         | C vs T           | 4  | 4,264  | 4,260  | 9.62  | 0.96 | (0.866-1.07) | 0.496        | 4  |    |       |       |       |      |             |              |    |
| MSH2   | 155 | rs4987188 (p.Gly322Asp, c.965G>A)               | A vs G           | 5  | 3,697  | 3,491  | 1.49  | 1.22 | (0.94-1.58)  | 0.141        | 0  |    |       |       |       |      |             |              |    |
| MSH3   | 156 | rs184967 (p.Arg49Gln, c.3099G>A)                | A vs G           | 3  | 5,085  | 7,136  | 15.25 | 1.11 | (1.03-1.20)  | <b>0.005</b> | 0  |    |       |       |       |      |             |              |    |
| MSH3   | 157 | rs26279 (p.Ala1045Thr, c.3133C>A)               | G vs A           | 4  | 5,691  | 7,665  | 28.13 | 1.1  | (1.03-1.17)  | <b>0.006</b> | 17 |    |       |       |       |      |             |              |    |
| MSH6   | 158 | rs1042821 (p.Gly39Glu, c.116G>A)                | A vs G           | 4  | 3,136  | 6,063  | 17.22 | 0.99 | (0.86-1.13)  | 0.832        | 59 |    |       |       |       |      |             |              |    |
| MSH6   | 159 | rs1800935 (p.Asp180Asp, c.540T>C)               | C vs T           | 3  | 5,132  | 4,709  | 29.45 | 0.96 | (0.90-1.02)  | 0.159        | 0  |    |       |       |       |      |             |              |    |
| MTHFD1 | 160 | rs1950902 (p.Asn134Lys, c.401G>A)               | A vs G           | 3  | 3,822  | 5,452  | 18.78 | 0.90 | (0.84-0.98)  | <b>0.010</b> | 0  |    |       |       |       |      |             |              |    |
| MTHFD1 | 161 | rs2236225 (p.Arg65Gln, c.1958G>A)               | A vs G           | 6  | 6,535  | 9,347  | 45.19 | 0.98 | (0.90-1.07)  | 0.603        | 67 |    |       |       |       |      |             |              |    |
| MTHFR  | 162 | rs1801131 (p.Ala429Glu, c.1286A>C)              | C vs A           | 19 | 11,550 | 17,286 | 32.18 | 1.00 | (0.95-1.05)  | 0.895        | 29 | 8  | 1,886 | 2,868 | 19.37 | 0.95 | (0.83-1.09) | 0.449        | 29 |
| MTHFR  | 163 | rs1801133 (p.Ala222Val, c.C677T)                | T vs C           | 37 | 23,411 | 31,990 | 32.80 | 0.98 | (0.94-1.02)  | 0.230        | 52 | 15 | 5,731 | 6,920 | 41.49 | 0.95 | (0.87-1.03) | 0.181        | 52 |
| MTR    | 164 | rs1805087 (A2756G)                              | G vs A           | 14 | 11,730 | 15,669 | 19.51 | 0.97 | (0.92-1.05)  | 0.529        | 45 |    |       |       |       |      |             |              |    |
| MTRR   | 165 | rs10380 (p.His595Tyr, c.1783C>T)                | T vs C           | 4  | 3,869  | 5,141  | 9.31  | 1.05 | (0.87-1.26)  | 0.638        | 57 |    |       |       |       |      |             |              |    |
| MTRR   | 166 | rs1532268 (Ser175Leu)                           | T vs C           |    |        |        |       |      |              |              |    |    |       |       |       |      |             |              |    |



Appendix table 6. Results of previously published meta-analysis compared to meta-analyses performed in this study

| Genes   | Variant                | Prior meta-analysis |           |               |      |   |            |           |         |        |          | Current study     |                   |         |                            |                 |           |         |        |          |                  |                       |                            |   |
|---------|------------------------|---------------------|-----------|---------------|------|---|------------|-----------|---------|--------|----------|-------------------|-------------------|---------|----------------------------|-----------------|-----------|---------|--------|----------|------------------|-----------------------|----------------------------|---|
|         |                        | PubMed ID           | Reference | First author  | Year | Retrieved databases   | Close date | Ethnicity | Studies | Cases  | Controls | Comparison        | OR (95% CI)       | P value | P <sub>heterogeneity</sub> | Comparison      | Ethnicity | Studies | Cases  | Controls | OR (95% CI)      | P value               | P <sub>heterogeneity</sub> | Comments for prior meta-analyses        |
| APEXI   | rs1130409              | 1976250             | (1)       | Gu            | 2009 | PubMed and Embase   | 5/30/2009  | All       | 3       | 1,629  | 1,999    | GG versus TT      | 1.25 (1.03-1.52)  | NA      | 0.574                      | G vs T          | All       | 9       | 4,374  | 5,422    | 1.05 (0.89-1.23) | 0.582                 | 0.00                       |   |
|         | rs9344                 | 1884302             | (2)       | Pahalan       | 2008 | PubMed  | NA         | All       | 16      | 4,638  | 6,157    | AA + AG vs GG     | 1.10 (0.96-1.26)  | 0.180   | 0.010                      | AA + AG vs GG   | All       | 22      | 6,316  | 8,272    | 1.13 (1.01-1.26) | 0.035                 | 0.02                       |   |
| CDND1   | rs16280                | 21997289            | (3)       | Wanz          | 2011 | Medline PubMed, CNKI, Wanfang Med Online                        | Jan. 2011  | All       | 8       | 4,652  | 4,428    | AA vs CC          | 0.86 (0.75-0.98)  | 0.020   | 0.100                      | A vs C          | All       | 9       | 7,229  | 7,045    | 0.94 (0.88-1.01) | 0.116                 | 0.26                       |   |
|         | rs1048943              | 21541661            | (4)       | Jin           | 2011 | PubMed  | Sep. 2010  | All       | 6       | 5,236  | 6,236    | GG vs AA          | 1.47 (1.16-1.86)  | 0.002   | 0.440                      | G vs A          | All       | 16      | 6,704  | 8,094    | 1.24 (1.05-1.47) | 0.014                 | 0.00                       |   |
| CYP11A1 | rs1048943              | 21710246            | (5)       | Zheng         | 2011 | PubMed  | 10/31/2010 | All       | 14      | 6,654  | 7,859    | GG vs AA          | 1.40 (1.12-1.76)  | 0.003   | 0.732                      | G vs A          | All       | 16      | 6,704  | 8,009    | 1.24 (1.05-1.47) | 0.014                 | 0.00                       |   |
|         | rs4646903              | 21710246            | (5)       | Zheng         | 2011 | PubMed  | 10/31/2010 | All       | 13      | 5,468  | 6,492    | CC vs TT          | 0.95 (0.68-1.33)  | 0.758   | 0.079                      | C vs T          | All       | 14      | 5,491  | 6,371    | 1.06 (0.92-1.23) | 0.412                 | 0.00                       | Included 1 studies published in Chinese |
| ERCC2   | rs13181                | 21541661            | (6)       | Zhang         | 2011 | PubMed and Medline  | Dec. 2010  | All       | 15      | 3,042  | 4,627    | C vs A            | 1.02 (0.94-1.11)  | 0.623   | 0.593                      | C vs A          | All       | 17      | 6,039  | 8,749    | 0.99 (0.92-1.05) | 0.649                 | 0.17                       |   |
|         | rs1799793              | 21541661            | (6)       | Zhang         | 2011 | PubMed and Medline  | Dec. 2010  | All       | 7       | 1,581  | 2,846    | A vs G            | 1.07 (0.95-1.20)  | 0.275   | 0.057                      | A vs G          | All       | 7       | 5,470  | 7,135    | 1.01 (0.96-1.07) | 0.654                 | 0.68                       |   |
| GSTM1   | Present/Null           | 14523342            | (7)       | Ye            | 2003 | MEDLINE   | 2002       | All       | 20      | 4,010  | 5,099    | null vs present   | 0.99 (0.91-1.07)  | NA      | <0.1                       | null vs present | All       | 54      | 18,601 | 29,433   | 1.11 (1.04-1.18) | 0.001                 | 0.00                       | Included 1 studies published in Chinese |
|         | rs2012161              | 20207535            | (9)       | Geo           | 2010 | PubMed, Embase and HuGENet                                      | Dec. 2008  | All       | 36      | 10,009 | 15,070   | null vs present   | 1.13 (1.03-1.23)  | NA      | <0.001                     | null vs present | All       | 54      | 18,601 | 29,433   | 1.11 (1.04-1.18) | 0.001                 | 0.00                       |   |
| GSTP1   | rs1695                 | 20207535            | (9)       | Economopoulos | 2010 | MEDLINE   | Jul. 2009  | All       | 44      | 11,998 | 17,552   | null vs present   | 1.11 (1.04-1.19)  | NA      | NA                         | null vs present | All       | 54      | 18,601 | 29,433   | 1.11 (1.04-1.18) | 0.001                 | 0.00                       |   |
|         | Present/Null           | 19642601            | (10)      | Geo           | 2009 | PubMed, Embase and HuGENet                                      | Jan. 2009  | All       | 16      | 4,386  | 7,127    | G vs A            | 0.98 (0.92-1.04)  | NA      | 0.310                      | G vs A          | All       | 29      | 7,857  | 13,413   | 0.99 (0.93-1.05) | 0.676                 | 0.07                       |   |
| GSTT1   | Present/Null           | 19798506            | (11)      | Liao          | 2010 | PUBMED, EMBASE, Cochrane Library and HuGENet                    | Feb. 2009  | All       | 23      | 5,058  | 5,999    | null vs present   | 1.23 (1.02-1.49)  | 0.032   | <0.001                     | null vs present | All       | 41      | 13,201 | 21,862   | 1.16 (1.04-1.28) | 0.006                 | 0.00                       |   |
|         | rs20061204             | 20207535            | (9)       | Wan           | 2010 | PubMed, Embase  | May. 2009  | All       | 30      | 7,635  | 12,911   | null vs present   | 1.20 (1.03-1.40)  | 0.020   | <0.001                     | null vs present | All       | 41      | 13,201 | 21,862   | 1.16 (1.04-1.28) | 0.006                 | 0.00                       |   |
| IGF1    | CA repeat              | 21919877            | (13)      | Zheng         | 2010 | Economopoulos   | Jul. 2009  | All       | 34      | 8,596  | 13,589   | null vs present   | 1.20 (1.05-1.38)  | NA      | NA                         | null vs present | All       | 41      | 13,201 | 21,862   | 1.16 (1.04-1.28) | 0.006                 | 0.00                       |   |
|         | rs227744               | 20803107            | (15)      | Fang          | 2010 | PubMed, Web of Science, EBSCO, and CNKI                         | 3/1/2010   | All       | 7       | 2,543  | 2,115    | TT vs GG          | 0.86 (0.57-1.30)  | NA      | 0.006                      | G vs T          | All       | 8       | 2,421  | 1,802    | 1.00 (0.91-1.10) | 0.976                 | 0.53                       | Included 1 studies published in Chinese |
| MDM2    | rs12917                | 19892775            | (16)      | Zhang         | 2010 | MEDLINE   | Apr. 2009  | All       | 4       | 1,618  | 4,685    | TT vs CT-CC       | 1.05 (0.44-2.49)  | 0.911   | 0.084                      | TT vs CT-CC     | All       | 7       | 4,127  | 7,284    | 1.54 (1.14-2.08) | 0.005                 | 0.47                       |   |
|         | rs2308321              | 19892775            | (16)      | Zhang         | 2010 | MEDLINE   | Apr. 2009  | All       | 4       | 1,618  | 4,685    | G vs A            | 0.89 (0.63-1.25)  | 0.490   | 0.005                      | G vs A          | All       | 6       | 3,483  | 8,783    | 1.00 (0.80-1.25) | 0.984                 | 0.00                       |   |
| MMP1    | rs1799750              | 19507256            | (17)      | McColgan      | 2009 | PubMed, Embase, Google Scholar and Yahoo                        | July. 2008 | All       | 4       | 539    | 765      | 2G2G+1G2G vs 1G1G | 1.66 (1.14-2.42)  | 0.008   | NA                         | 2G vs 1G        | All       | 7       | 987    | 1,281    | 0.72 (0.60-0.87) | 6.74*10 <sup>-7</sup> | 0.07                       |   |
|         | rs243865               | 19507256            | (17)      | McColgan      | 2009 | PubMed, Embase, Google Scholar and Yahoo                        | July. 2008 | All       | 3       | 379    | 460      | TT-TC vs CC       | 0.97 (0.49-1.93)  | 0.810   | NA                         | T vs C          | All       | 3       | 300    | 401      | 0.99 (0.49-2.00) | 0.976                 | 0.03                       | Included 1 studies published in Chinese |
| MMP2    | rs243865               | 19507256            | (17)      | McColgan      | 2009 | PubMed, Embase, Google Scholar and Yahoo                        | July. 2008 | All       | 3       | 379    | 460      | TT-TC vs CC       | 0.83 (0.59-1.17)  | NA      | 0.080                      | T vs C          | All       | 3       | 300    | 401      | 0.99 (0.49-2.00) | 0.976                 | 0.03                       |   |
|         | rs3025058              | 19507256            | (17)      | McColgan      | 2009 | PubMed, Embase, Google Scholar and Yahoo                        | July. 2008 | All       | 3       | 379    | 460      | 5A5A+6A6A vs 6A5A | 0.83 (0.50-1.31)  | 0.810   | NA                         | 5A vs 6A        | All       | 6       | 649    | 990      | 0.98 (0.76-1.27) | 0.881                 | 0.08                       |   |
| MMP9    | rs3918242              | 19507256            | (17)      | McColgan      | 2009 | PubMed, Embase, Google Scholar and Yahoo                        | July. 2008 | All       | 5       | 700    | 963      | TT-TC vs CC       | 1.02 (0.73-1.42)  | NA      | 0.150                      | 5A vs 6A        | All       | 6       | 649    | 996      | 0.98 (0.76-1.27) | 0.881                 | 0.08                       |   |
|         | rs2043868              | 19507256            | (17)      | McColgan      | 2009 | PubMed, Embase, Google Scholar and Yahoo                        | July. 2008 | All       | 5       | 700    | 963      | TT-TC vs CC       | 0.9 (0.68-1.17)   | 0.430   | NA                         | T vs C          | All       | 4       | 644    | 792      | 0.87 (0.66-1.14) | 0.303                 | 0.26                       | Included 1 studies published in Chinese |
| MTHFR   | rs1801133              | 2043868             | (18)      | Liu           | 2011 | PubMed, Embase, ISI Web of Knowledge, and Medline               | July. 2010 | All       | 4       | NA     | NA       | TT-TC vs CC       | 0.85 (0.67-1.08)  | NA      | 0.430                      | T vs C          | All       | 4       | 644    | 792      | 0.87 (0.66-1.14) | 0.303                 | 0.26                       |   |
|         | rs1801133              | 17089256            | (19)      | Hahn          | 2006 | PubMed  | Aug. 2006  | All       | 14      | 4,764  | 6,592    | TT vs CC          | 0.82 (0.74-0.91)  | 0.030   | 0.030                      | T vs C          | All       | 17      | 12,001 | 15,001   | 0.99 (0.95-1.03) | 0.611                 | 0.00                       |   |
| MTR     | rs1801133              | 17089256            | (19)      | Hahn          | 2006 | PubMed  | Aug. 2006  | All       | 14      | 4,764  | 6,592    | TT vs CC          | 0.82 (0.74-0.91)  | 0.030   | 0.030                      | T vs C          | All       | 17      | 12,001 | 15,001   | 0.99 (0.95-1.03) | 0.611                 | 0.00                       |   |
|         | rs1805087              | 19826453            | (23)      | Yu            | 2010 | PubMed  | May. 2008  | All       | 12      | 6,452  | 8,184    | G vs A            | 0.99 (0.90-1.08)  | NA      | NA                         | G vs A          | All       | 18      | 12,832 | 17,467   | 0.99 (0.93-1.04) | 0.653                 | 0.08                       |   |
| MTRR    | rs1801394              | 21547363            | (24)      | Han           | 2011 | PubMed and CNKI   | 7/16/2010  | All       | 10      | NA     | NA       | G vs A            | 1.06 (0.99-1.13)  | 0.105   | 0.698                      | A vs G          | All       | 15      | 7,561  | 11,405   | 0.95 (0.91-1.00) | 0.052                 | 0.25                       |   |
|         | rs34612342             | 21063410            | (25)      | Theodoratos   | 2010 | Web of Science, PubMed  | NA         | All       | 15      | 25,231 | 18,285   | GG vs AA          | 3.35 (1.14-9.89)  | 0.030   | 0.990                      | G vs A          | White     | 17      | 27,041 | 19,641   | 3.32 (1.13-9.81) | 0.030                 | 1.00                       |   |
| NOD2    | rs3053393              | 21063410            | (25)      | Theodoratos   | 2010 | Web of Science, PubMed  | NA         | All       | 15      | 25,231 | 18,285   | GG vs AA          | 6.47 (2.33-17.97) | <0.0005 | 0.730                      | A vs G          | White     | 17      | 26,957 | 19,870   | 6.49 (2.57-1.35) | 7.49*10 <sup>-7</sup> | 0.85                       |   |
|         | rs2066844              | 19787357            | (26)      | Tian          | 2010 | Web of Science, PubMed, EMBASE                                  | Mar. 2009  | All       | 5       | 1,436  | 1,109    | TT-TC vs CC       | 1.59 (1.06-2.32)  | 0.020   | 0.140                      | TT-TC vs CC     | White     | 9       | 3,297  | 3,688    | 1.35 (1.02-1.78) | 0.038                 | 0.14                       |   |
| OGG1    | rs1052133              | 21063410            | (25)      | Theodoratos   | 2010 | Web of Science, PubMed, EMBASE                                  | Mar. 2009  | All       | 5       | 1,442  | 1,109    | CC-CG vs GG       | 1.98 (1.13-3.44)  | 0.010   | 0.660                      | C vs G          | White     | 8       | 3,252  | 2,988    | 1.31 (0.93-1.85) | 0.124                 | 0.44                       |   |
|         | rs2066847              | 19787357            | (26)      | Tian          | 2010 | Web of Science, PubMed, EMBASE                                  | Mar. 2009  | All       | 7       | 2,571  | 1,856    | ins vs wild       | 1.44 (1.13-1.84)  | 0.003   | 0.670                      | ins vs wild     | White     | 11      | 4,337  | 5,395    | 1.30 (1.02-1.65) | 0.032                 | 0.13                       |   |
| PPARG   | rs1052133              | 21063410            | (25)      | Theodoratos   | 2010 | Web of Science, PubMed, EMBASE                                  | 9/22/2010  | All       | 12      | NA     | NA       | GG vs CC          | 1.19 (0.92-1.53)  | NA      | 0.028                      | G vs C          | All       | 18      | 6,654  | 8,599    | 1.10 (0.99-1.23) | 0.085                 | 0.00                       |   |
|         | rs1801282              | 20596649            | (29)      | XU            | 2010 | PubMed and Google   | 1/1/2010   | All       | 10      | 6,878  | 9,391    | CG-GG vs CC       | 0.84 (0.72-0.98)  | NA      | 0.014                      | G vs C          | All       | 16      | 11,775 | 18,067   | 0.97 (0.90-1.04) | 0.568                 | 0.16                       |   |
| PTGS2   | rs355806               | 20596649            | (29)      | XU            | 2010 | PubMed, Embase, Web of Science, and CNKI                        | 1/1/2010   | All       | 3       | 486    | 941      | CT-TT vs CC       | 1.11 (0.89-1.39)  | NA      | 0.337                      | T vs C          | All       | 9       | 4,427  | 6,842    | 1.04 (0.95-1.13) | 0.435                 | 0.33                       |   |
|         | rs20417                | 19696967            | (30)      | Zhu           | 2010 | PubMed, Embase  | 3/26/2009  | Asian     | 4       | 1,595  | 2,917    | CC-GC vs GG       | 1.44 (1.09-1.91)  | 0.010   | 0.140                      | C vs G          | All       | 12      | 3,527  | 5,844    | 1.06 (0.94-1.20) | 0.337                 | 0.16                       |   |
| SULT1A1 | rs9282861              | 20080859            | (31)      | Cao           | 2010 | Web of Science, MEDLINE, EMBASE and Chinese biomedical database | Jan. 2010  | All       | 10      | 3,322  | 5,166    | CC-GC vs GG       | 1.06 (0.94-1.19)  | NA      | 0.073                      | C vs G          | All       | 12      | 3,527  | 5,844    | 1.06 (0.94-1.20) | 0.337                 | 0.16                       |   |
|         | rs1800469              | 20012233            | (33)      | Fang          | 2010 | PubMed, Web of Science and CNKI                                 | Sep. 2010  | All       | 12      | 3,549  | 5,610    | A vs G            | 1.04 (0.94-1.16)  | 0.460   | 0.009                      | A vs G          | All       | 11      | 3,802  | 5,042    | 1.02 (0.92-1.12) | 0.757                 | 0.03                       | Included 1 studies published in Chinese |
| TGFB1   | rs11466445             | 12947057            | (34)      | Kalliamani    | 2003 | MEDLINE, CANCERLIT  | Apr. 2002  | All       | 3       | 546    | 642      | 6A6A vs 9A9A      | 2.19 (1.08-4.45)  | NA      | NA                         | 9 bp del vs ins | All       | 10      | 6,338  | 6,689    | 1.04 (0.96-1.13) | 0.379                 | 0.43                       |   |
|         | rs1800629              | 21248737            | (36)      | Wang          | 2011 | PubMed, Cochrane and Embase                                     | NA         | All       | 7       | 1,372  | 1,458    | AA-AA vs GG       | 0.84 (0.87-0.81)  | 0.150   | 0.770                      | C vs A          | All       | 10      | 6,338  | 6,689    | 1.04 (0.96-1.13) | 0.379                 | 0.43                       |   |
| TP53    | rs1042522              | 20615891            | (37)      | Dabubreh      | 2010 | MEDLINE, HuGENet, NBI Genetic Association Database              | 7/31/2009  | All       | 23      | 6,514  | 9,334    | C vs G            | 0.99 (0.89-1.09)  | 0.800   | <0.001                     | C vs G          | All       | 29      | 9,724  | 11,852   | 0.99 (0.90-1.09) | 0.826                 | 0.00                       |   |
|         | rs20363586             | 22011187            | (43)      | Hu            | 2011 | PubMed, Embase  | Jan. 2010  | All       | 20      | 3,537  | 5,168    | CC vs GG          | 1.02 (0.80-1.29)  | NA      | 0.010                      | C vs G          | All       | 29      | 9,724  | 11,852   | 0.99 (0.90-1.09) | 0.826                 | 0.00                       |   |
| TP33    | rs2273953 vs rs1801173 | 21063410            | (25)      | Theodoratos   | 2010 | Web of Science, PubMed, EMBASE                                  | 7/20/2010  | All       | 27      | 7,414  | 9,872    | CC vs GG          | 1.04 (0.82-1.31)  | 0.766   | <0.001                     | C vs G          | All       | 29      | 9,724  | 11,852   | 0.99 (0.90-1.09) | 0.826                 | 0.00                       |   |

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