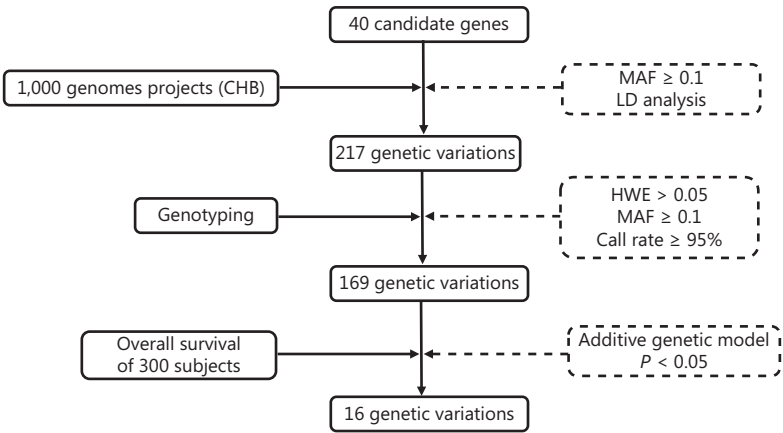
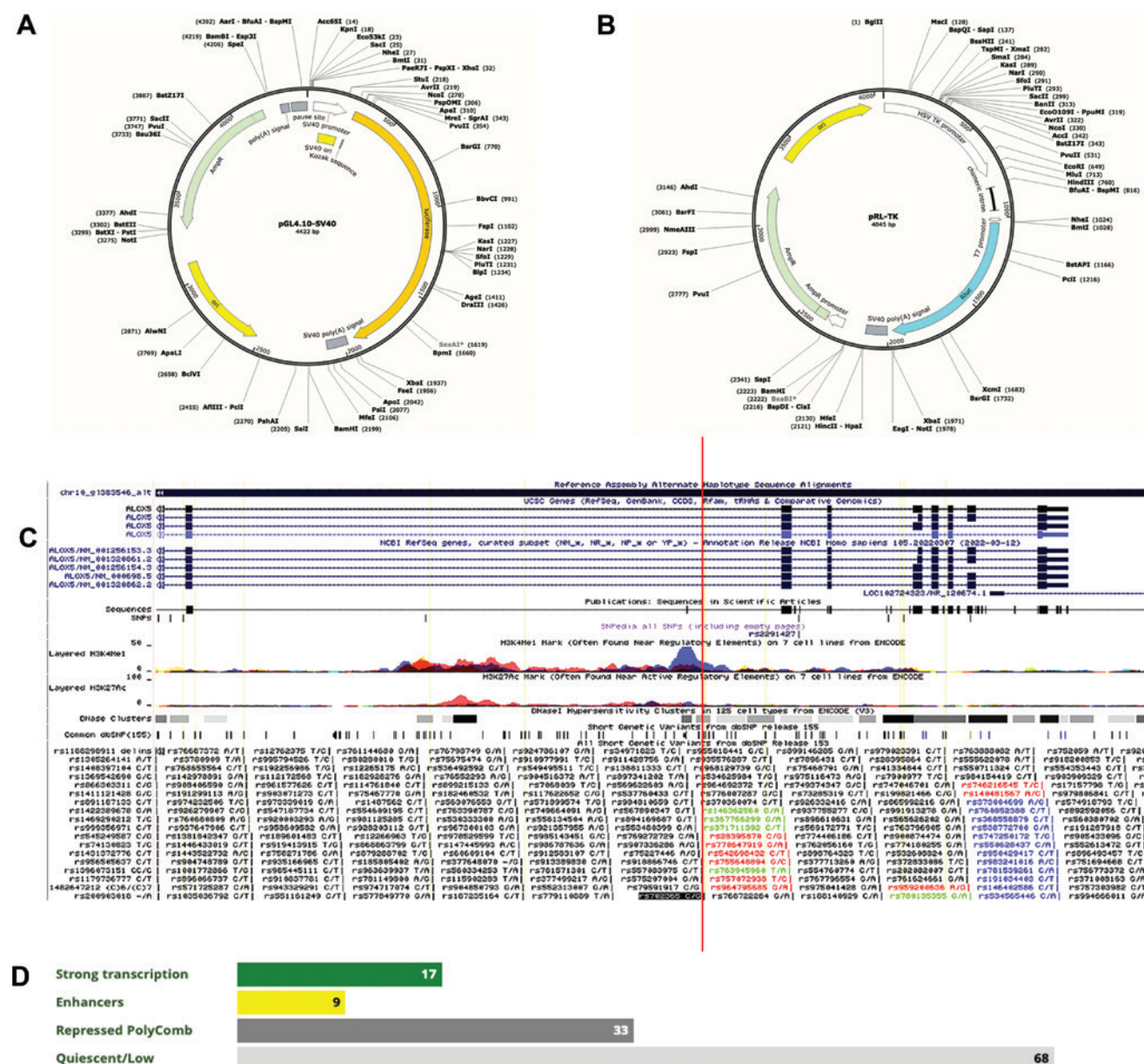


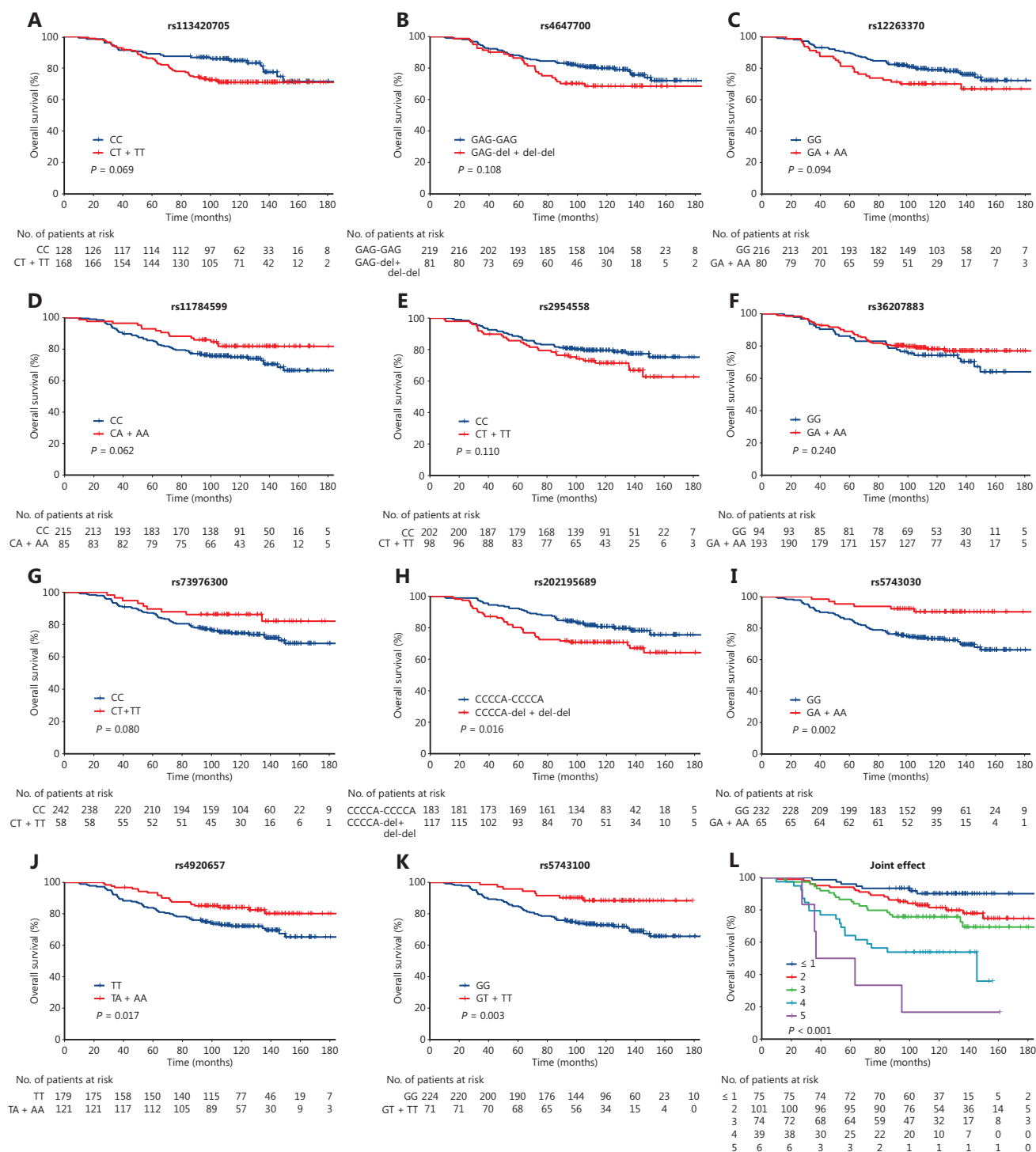
# Supplementary materials



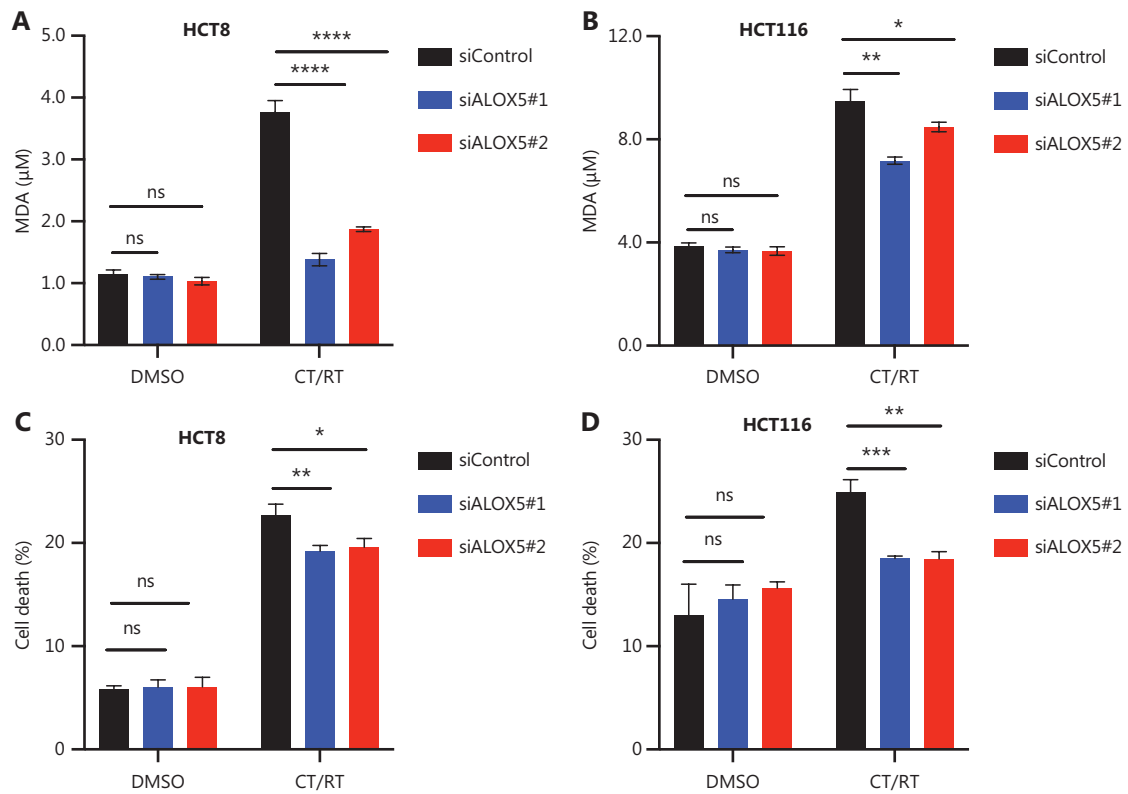
**Figure S1** Flow chart for selecting genetic variations in the apoptosis, pyroptosis, and ferroptosis pathway genes. CHB, Chinese Han Beijing population; MAF, minor allele frequency; LD, linkage disequilibrium; HWE, Hardy-Weinberg equilibrium.



**Figure S2** The maps of pGL4.10-SV40 vector and pRL-TK plasmid and functional annotation of region around rs702365. (A) The pGL4.10-SV40 vector map. (B) The pRL-TK plasmid map. (C) Annotation of intronic regions containing rs702365 using the ENCODE database. Colored histograms denote histone modification markers (H3K4Me1 and H3K27ac) in 7 human cell types. The darkness of DNase hypersensitive peaks represents the maximum signal strength observed in 125 cell lines. The red line indicates the location of rs702365. (D) Chromatin state data surrounding rs702365 in RegulomeDB.



**Figure S3** The Kaplan-Meier survival curves of rectal cancer patients treated with postoperative chemoradiotherapy by genotypes. (A) rs113420705 (log-rank test,  $P = 0.069$ ); (B) rs4647700 (log-rank test,  $P = 0.108$ ); (C) rs12263370 (log-rank test,  $P = 0.094$ ); (D) rs11784599 (log-rank test,  $P = 0.062$ ); (E) rs2954558 (log-rank test,  $P = 0.110$ ); (F) rs36207883 (log-rank test,  $P = 0.240$ ); (G) rs73976300 (log-rank test,  $P = 0.080$ ); (H) rs202195689 (log-rank test,  $P = 0.016$ ); (I) rs5743030 (log-rank test,  $P = 0.002$ ); (J) rs4920657 (log-rank test,  $P = 0.017$ ); (K) rs5743100 (log-rank test,  $P = 0.003$ ); (L) Five risk groups (log-rank test,  $P < 0.001$ ) of the joint effect of unfavorable genotypes (*CASP4* rs571407 TT, *ALOX5* rs2242332 CC, *HO-1* rs17883419 CT + TT, *hsa-miR-4274* rs202195689 CCCC-del + del-del, and *PMS1* rs5743030 GG).



**Figure S4** ALOX5-mediated lipid peroxidation and cell death. (A, B) HCT8 (A) and HCT116 (B) cells transfected with siControl or ALOX5 siRNA were treated with DMSO or CT/RT, followed by detecting the concentration of MDA. (C, D) HCT8 (C) and HCT116 (D) cells transfected with siControl or ALOX5 siRNA were cultured with DMSO or CT/RT, followed by analyzing of cell death. Data are presented as the mean  $\pm$  SD. These assays were performed three times. DMSO: dimethyl sulfoxide; CT/RT: 5-fluorouracil (dissolved in DMSO) and irradiation treatment; \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.001$ , \*\*\*\* $P < 0.0001$ .

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Expression vector construction | Primer sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| pGL4.10-rs702365[C]            | Forward: CTAGCTAGCTGGGGACATGTCAGAAAGTGTCTCA<br>Reverse: GATCGATCGACATGAAACCAATCTAAACTATTA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| ALOX5 promoter                 | Forward: CTCGAGATAGCACTGCGGTAATCAAG<br>Reverse: AAGCTTGGACCAGACTGAAG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Promoter                       | Sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| ALOX5 promoter                 | ATAGCACTGCGGTAATCAAGCAGTGTGGCACTGTATAGCATGTACATTACAGATCAGTGGACTAGAATCA<br>ATGTCCAGAAATAAACCGTTATGTTTATAATGAATTACTTTTTAATAAGGTGTCAAGACAACGCAATGGGA<br>AAAGAATAATGAATTCAACAAATGATGCATGGACAACCGGACATGCACATGCAACACAATGAATTTGAAT<br>TCTTCTATCGCTCCATGCATAAAATACTCAAAATGGGTCACGGATGTAAATGAAAAGCTAAAACTATA<br>ATAATCCTAGAGGAAAACCTAGGAGTAAATCTTTAAGATGTTATTGTAGGCAGTGGTTTCTCAGATAGGA<br>CCCCAAAATCACAAGCGACAAAAGAAATTGGACTTAAAGTTAAATACTTTTGTGCTTCAAACATCATCAA<br>GAAAGTGAAAACACAACCCGAGAGCAATAAAATGTCTGTAAGTCATGTATCCGATTAGAGACTTCTA<br>TCCAGGATATATAAATAATGCAATTCAATGATAAAAAAGATAAATAGCCAGTTTTCCAAAGAGTCAAGCA<br>TCTGAATATACATCTCTCCAAAAATATACAGATATCCAACAAGCATGTGAAAAGATGTTCAAAGCCATTTGC<br>CAGGTGCACAAACCAAGACAGTATGAGGAGATGCTACAGGGACTCTGCTGCTTCACAGACATGAAGCG<br>TTGGTGAGAATGTAGGCAGCCGCTTTGGGGACTTCACATCCCCGCCGCCACGCACGGTGAGCTAGT<br>GTTTAAACTTAGCCGAGATCAATACACGCGACTGTGTGCCGTCAGACCTGCGCTGCCGGCGGGGCTG<br>GGAGAGGCGGGCGCCAGGAGTGGGCGGGAACCTGGGGGTGAGGCCCCAGCCGCGGAAGCCGCC<br>AGGAGCGCGGAAACCTTCTCCACACCTTCCAGGCATTTGCCCCGCCGCGATTAGAGAGCCGACCCGT<br>GACCCCTGGCCTCCCTAGACAGCCCCGATGTCCAGATGTGCCGTCCGCTGCTCCCGCAGCCACTG<br>GCCATCTCTGGGCTGGGCGCGGTCTCGGCGCCCGCTGCCCCGCCAGGAGCCGAGGTCCAGCCAG<br>TGAAGAAGCCCGCGTGAAGGAGCCTCTGTGCTCCAGAATCCATCTCAGTATCAGCGTGGGGTGGCC<br>TCCTCCAGGAAGCCCTTCTGATTCTCTCATGGGTGCTCTTCTCTGCAGACTCCCGAGCACCCCTGCTC<br>CAAGTACCGCAAGTGGCACTGAGAACTGGGGAGAGCAGAGGCTGTGCCTAGATTGTAGGGAGTCCC<br>CGCAGCTCCACCCAGGGCCTACAGGAGCCTGGCCTTGGGCGAAGCCGAGGCAGGCAGGCAGGGCAA<br>AGGGTGGAAGCAATTCAGGAGAGAACGAGTGAACGAATGGATGAGGGGTGGCAGCCGAGGTTGCCCC<br>AGTCCCCTGGCTGCAGGAACAGACACCTCGCTGAGGAGAGACCCAGGAGCGAGGCCCTGCCCCGCC<br>GAGGCGAGGTCCCGCCAGTCGGCGCCGCTGAAGAGTGGGAGAGAAGTACTGCGGGGGCGGGGGC<br>GGGGGCGGGGGCGGGGGCGGGGGCAGCCGGGAGCCTGGAGCCAGACCGGGGCGGGGGCGGGGACC<br>GGGGCCAGGGACCACTGGTGGGAGGAGGCTGCGGCGCTAGATGCGGACACCTGGACCGCCGCGCCG<br>AGGCTCCCGGCGCTCGTCTGCTCCCGGGCCCGGCCATGCCCTCTACACGGTCACCGTGGCCACTGGC<br>AGCCAGTGGTTCGCCGGCACTGACGACTACATCTACCTCAGCCTCGTGGGCTCGGCGGGCTGCAGCGA<br>GAAGCACCTGCTGGACAAGCCCTTCTACAACGACTTCGAGCGTGGCGCGGTGAGCGCGGGCGGGGCA<br>CGGGTGAGCGCGGGCTGAGGTGCGTCCGGGACCCGTTTGGACGGCAGAGGCTGGGCGGGGGCG<br>CCGAGGGCCCGTGGGGCGGCCCGGACAGGACTGGGGGTGTCAGGACCCTGTCAGGAGGGGCAGA |

Table S1 Continued

|                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Expression vector construction         | Primer sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|                                        | ACTGCGGTGGGGCGTGCCCTGGGCTCCAGTGGCCGGTGGGTACCTGGTGGGCAAGCGTCCAGGACC<br>CCTCGCGGGCGCCGCGACCCCTGTCGAAACGGAGACTTCCGCGTGCCGCTGCAAGGCGTCTCCCT<br>GGGAGGAGAAGGCCCAAGGTTCCCTCCACTTCAAGATCTGGGCTCCGAGGCTCCGGAGCCCCCTCA<br>CTGGGCCGCGTTTCTTGCCACCTTCTCTTAGGCTCCTTCTGCAGGTCGCACAGGGAGGGAGAGGCAG<br>ATGAGTCATGCTCACAGAACTCTGAGGGCACCTCGGAGCAGCCAGCTGTGAGCCGTGGGGAAGGGTGCA<br>CGTCAGCGGGTCCAGAGGCCTGAGTTCTGTCCAGACATGACCACCAGCTCACTCTACCGTCTGTCTGGGC<br>CTCAGTTTCCCCAGCTGAAAATGGAGGGTTGGCTTCAGTCTGGTCC |
| Site-direct mutant vector construction | Primer sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| pGL4.10-rs702365[G]                    | Forward: CTGCTCTCCCTCCTGCCTCCCCCTCCTT<br>Reverse: AAGGAGGGGGGAGGCAGGAGGGAGAGCAG                                                                                                                                                                                                                                                                                                                                                                                                           |
| EMSA                                   | Probe sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| EMSA-rs702365[C]                       | Forward: Biotin-GCTCTCCCTCCTCCCTCCCCCTCC<br>Reverse: Biotin-GGAGGGGGGAGGGAGGAGGGAGAGC                                                                                                                                                                                                                                                                                                                                                                                                     |
| EMSA-rs702365[G]                       | Forward: Biotin-GCTCTCCCTCCTGCCTCCCCCTCC<br>Reverse: Biotin-GGAGGGGGGAGGCAGGAGGGAGAGC                                                                                                                                                                                                                                                                                                                                                                                                     |
| Quantitative real-time PCR             | Primer sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <i>ALOX5</i>                           | Forward: GGAGAACCTGTTTCATCAACCGC<br>Reverse: CAGGTCTTCCTGCCAGTGATTC                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <i>GAPDH</i>                           | Forward: AACGGATTGGTCGTATTGGG<br>Reverse: TGATTTTGAGGGATCTCGC                                                                                                                                                                                                                                                                                                                                                                                                                             |
| siRNA transduction                     | Sense sequence (5'→3')                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| siControl                              | GCGACGAUCUGCCUAAGAUTT                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| siALOX5#1                              | GCAGGAAGACCUGAUGUUUTT                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| siALOX5#2                              | CUGAGCGCAACAAGAAGAATT                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

**Table S2** Associations of 169 genetic variations and OS of rectal cancer patients based on the additive model

| Gene                | Chr.      | Genetic variations             | Allele              | MAF in CHB  | Crude                   |              | Adjusted <sup>†</sup>   |              |
|---------------------|-----------|--------------------------------|---------------------|-------------|-------------------------|--------------|-------------------------|--------------|
|                     |           |                                |                     |             | HR (95% CI)             | P-value      | HR (95% CI)             | P-value      |
| <i>APAF1</i>        | 12        | rs10860361                     | G > A               | 0.48        | 1.04 (0.76–1.43)        | 0.802        | 1.04 (0.76–1.41)        | 0.822        |
| <i>APAF1</i>        | 12        | rs11296996                     | A > del             | 0.37        | 1.03 (0.75–1.43)        | 0.848        | 1.06 (0.76–1.47)        | 0.725        |
| <i>APAF1</i>        | 12        | rs12581708                     | A > G               | 0.29        | 1.02 (0.71–1.45)        | 0.924        | 1.13 (0.78–1.63)        | 0.514        |
| <i>APAF1</i>        | 12        | rs2118851 <sup>‡</sup>         | C > G               | 0.21        | 0.98 (0.66–1.45)        | 0.918        | 1.15 (0.78–1.71)        | 0.481        |
| <i>APAF1</i>        | 12        | rs74619561                     | G > A               | 0.15        | 0.96 (0.58–1.59)        | 0.887        | 0.80 (0.48–1.34)        | 0.398        |
| <i>BAK</i>          | 6         | rs5745568                      | G > T               | 0.25        | 0.85 (0.59–1.22)        | 0.380        | 0.77 (0.53–1.12)        | 0.164        |
| <i>BAK</i>          | 6         | rs74499662                     | GTAA > del          | 0.41        | 0.90 (0.64–1.25)        | 0.520        | 0.96 (0.68–1.35)        | 0.798        |
| <i>BAX</i>          | 19        | rs4645904                      | G > A               | 0.49        | 1.22 (0.87–1.71)        | 0.246        | 1.21 (0.86–1.70)        | 0.266        |
| <i>BAX</i>          | 19        | rs905238                       | A > G               | 0.37        | 0.79 (0.56–1.13)        | 0.197        | 0.82 (0.57–1.18)        | 0.285        |
| <i>BCL2</i>         | 18        | rs1944423 <sup>‡</sup>         | A > G               | 0.41        | 0.82 (0.58–1.17)        | 0.279        | 0.82 (0.57–1.18)        | 0.283        |
| <i>BID</i>          | 22        | rs366542                       | T > C               | 0.47        | 1.05 (0.76–1.45)        | 0.787        | 1.05 (0.75–1.47)        | 0.757        |
| <i>BID</i>          | 22        | rs148719901 <sup>‡</sup>       | del > ins           | 0.50        | 1.12 (0.81–1.54)        | 0.491        | 1.08 (0.78–1.50)        | 0.632        |
| <i>BID</i>          | 22        | rs8190256 <sup>‡</sup>         | T > G               | 0.11        | 1.13 (0.71–1.81)        | 0.602        | 1.17 (0.73–1.89)        | 0.520        |
| <b><i>CASP3</i></b> | <b>4</b>  | <b>rs113420705<sup>‡</sup></b> | <b>C &gt; T</b>     | <b>0.32</b> | <b>1.45 (1.05–2.00)</b> | <b>0.026</b> | <b>1.54 (1.09–2.16)</b> | <b>0.013</b> |
| <b><i>CASP3</i></b> | <b>4</b>  | <b>rs4647700</b>               | <b>GAG &gt; del</b> | <b>0.12</b> | <b>1.60 (1.07–2.39)</b> | <b>0.022</b> | <b>1.52 (1.01–2.29)</b> | <b>0.045</b> |
| <i>CASP3</i>        | 4         | rs1049216                      | G > A               | 0.21        | 0.93 (0.62–1.38)        | 0.704        | 0.96 (0.64–1.45)        | 0.859        |
| <i>CASP3</i>        | 4         | rs4647602                      | T > G               | 0.38        | 1.25 (0.92–1.70)        | 0.154        | 1.28 (0.93–1.77)        | 0.126        |
| <i>CASP6</i>        | 4         | rs1042891                      | G > A               | 0.47        | 1.12 (0.81–1.56)        | 0.477        | 1.30 (0.94–1.81)        | 0.116        |
| <i>CASP6</i>        | 4         | rs71595508                     | del > ins           | 0.18        | 1.04 (0.71–1.52)        | 0.841        | 0.96 (0.65–1.43)        | 0.854        |
| <i>CASP6</i>        | 4         | rs7682236 <sup>‡</sup>         | A > G               | 0.40        | 1.00 (0.72–1.40)        | 0.986        | 1.09 (0.77–1.53)        | 0.641        |
| <i>CASP6</i>        | 4         | rs7660005 <sup>‡</sup>         | T > C               | 0.49        | 0.88 (0.63–1.23)        | 0.455        | 0.84 (0.60–1.18)        | 0.308        |
| <i>CASP7</i>        | 10        | rs10787498                     | T > G               | 0.19        | 1.21 (0.85–1.73)        | 0.292        | 1.26 (0.86–1.84)        | 0.231        |
| <i>CASP7</i>        | 10        | rs1127687                      | G > A               | 0.20        | 0.87 (0.58–1.32)        | 0.518        | 0.95 (0.61–1.46)        | 0.804        |
| <i>CASP7</i>        | 10        | rs12415607                     | C > A               | 0.42        | 1.04 (0.75–1.44)        | 0.825        | 0.98 (0.70–1.38)        | 0.910        |
| <i>CASP7</i>        | 10        | rs7921977 <sup>‡</sup>         | T > C               | 0.19        | 0.74 (0.47–1.16)        | 0.186        | 0.70 (0.45–1.09)        | 0.118        |
| <i>CASP7</i>        | 10        | rs10553596                     | TT > del            | 0.21        | 1.13 (0.78–1.62)        | 0.519        | 1.27 (0.86–1.86)        | 0.225        |
| <b><i>CASP7</i></b> | <b>10</b> | <b>rs12263370<sup>‡</sup></b>  | <b>G &gt; A</b>     | <b>0.14</b> | <b>1.75 (1.18–2.58)</b> | <b>0.005</b> | <b>1.81 (1.23–2.66)</b> | <b>0.003</b> |
| <i>CASP7</i>        | 10        | rs2227310                      | C > G               | 0.43        | 1.03 (0.74–1.44)        | 0.869        | 0.98 (0.69–1.39)        | 0.918        |
| <i>CASP7</i>        | 10        | rs12247479                     | G > A               | 0.11        | 1.51 (0.97–2.35)        | 0.066        | 1.47 (0.93–2.33)        | 0.101        |
| <i>CASP8</i>        | 2         | rs13113 <sup>‡</sup>           | T > A               | 0.48        | 1.12 (0.80–1.57)        | 0.503        | 1.13 (0.80–1.59)        | 0.501        |
| <i>CASP8</i>        | 2         | rs3729647                      | G > C               | 0.19        | 1.06 (0.71–1.57)        | 0.783        | 1.09 (0.73–1.61)        | 0.673        |
| <i>CASP8</i>        | 2         | rs3769823                      | G > A               | 0.31        | 0.96 (0.68–1.36)        | 0.831        | 0.95 (0.67–1.36)        | 0.796        |
| <i>CASP9</i>        | 1         | rs1052576 <sup>‡</sup>         | C > T               | 0.38        | 1.11 (0.80–1.56)        | 0.526        | 1.14 (0.81–1.60)        | 0.446        |
| <i>CASP9</i>        | 1         | rs12741552 <sup>‡</sup>        | C > T               | 0.45        | 0.96 (0.70–1.33)        | 0.820        | 0.94 (0.68–1.31)        | 0.729        |

Table S2 Continued

| Gene                  | Chr.      | Genetic variations          | Allele          | MAF in CHB  | Crude                   |              | Adjusted <sup>†</sup>   |              |
|-----------------------|-----------|-----------------------------|-----------------|-------------|-------------------------|--------------|-------------------------|--------------|
|                       |           |                             |                 |             | HR (95% CI)             | P-value      | HR (95% CI)             | P-value      |
| <i>CASP10</i>         | 2         | rs13006529                  | T > A           | 0.18        | 0.98 (0.65–1.47)        | 0.919        | 1.02 (0.69–1.52)        | 0.909        |
| <i>FAS</i>            | 10        | rs1468063                   | C > T           | 0.39        | 1.22 (0.88–1.70)        | 0.233        | 1.14 (0.81–1.59)        | 0.453        |
| <i>FAS</i>            | 10        | rs4934431                   | C > T           | 0.39        | 1.11 (0.81–1.53)        | 0.504        | 1.04 (0.75–1.45)        | 0.805        |
| <i>FAS</i>            | 10        | rs1800682 <sup>‡</sup>      | A > G           | 0.38        | 0.97 (0.70–1.36)        | 0.873        | 0.97 (0.69–1.35)        | 0.835        |
| <i>FASL</i>           | 1         | rs763110                    | C > T           | 0.22        | 0.95 (0.66–1.36)        | 0.759        | 1.05 (0.71–1.55)        | 0.803        |
| <i>TNFR</i>           | 12        | rs4149570                   | C > A           | 0.47        | 1.02 (0.75–1.40)        | 0.883        | 0.97 (0.71–1.32)        | 0.834        |
| <i>TNFR</i>           | 12        | rs4149588 <sup>‡</sup>      | del > ins       | 0.27        | 0.77 (0.53–1.12)        | 0.172        | 0.84 (0.58–1.22)        | 0.356        |
| <i>TNFR</i>           | 12        | rs767455                    | T > C           | 0.12        | 1.34 (0.86–2.09)        | 0.195        | 1.53 (0.96–2.44)        | 0.073        |
| <i>TRAIL</i>          | 3         | rs112822654 <sup>‡</sup>    | GTGA > del      | 0.40        | 0.94 (0.68–1.30)        | 0.714        | 0.97 (0.70–1.35)        | 0.870        |
| <i>TRAIL</i>          | 3         | rs388515 <sup>‡</sup>       | A > G           | 0.35        | 1.00 (0.72–1.39)        | 0.982        | 0.99 (0.69–1.41)        | 0.954        |
| <i>TRAIL</i>          | 3         | rs12488654                  | A > G           | 0.50        | 1.13 (0.81–1.57)        | 0.467        | 1.20 (0.84–1.72)        | 0.323        |
| <i>TRAIL</i>          | 3         | rs1131532                   | G > A           | 0.43        | 0.92 (0.68–1.27)        | 0.627        | 0.94 (0.68–1.29)        | 0.687        |
| <i>TRAIL</i>          | 3         | rs9859259 <sup>‡</sup>      | C > A           | 0.50        | 0.89 (0.64–1.23)        | 0.475        | 0.84 (0.60–1.18)        | 0.316        |
| <i>TRAILR1</i>        | 8         | rs13255394                  | T > C           | 0.28        | 0.82 (0.57–1.19)        | 0.305        | 0.89 (0.61–1.30)        | 0.535        |
| <i>TRAILR2</i>        | 8         | rs1047266                   | G > A           | 0.26        | 1.00 (0.69–1.46)        | 0.984        | 1.00 (0.70–1.44)        | 0.988        |
| <i>TRAILR2</i>        | 8         | rs1047275                   | C > G           | 0.46        | 1.14 (0.84–1.55)        | 0.408        | 1.06 (0.78–1.44)        | 0.722        |
| <i>TRAILR2</i>        | 8         | rs2889                      | G > A           | 0.49        | 0.95 (0.69–1.31)        | 0.750        | 0.99 (0.72–1.37)        | 0.949        |
| <b><i>TRAILR2</i></b> | <b>8</b>  | <b>rs11784599</b>           | <b>C &gt; A</b> | <b>0.12</b> | <b>0.69 (0.43–1.11)</b> | <b>0.127</b> | <b>0.61 (0.37–0.98)</b> | <b>0.042</b> |
| <i>AIM2</i>           | 1         | rs2298803                   | T > C           | 0.29        | 0.93 (0.65–1.34)        | 0.708        | 0.91 (0.62–1.33)        | 0.627        |
| <i>CASP1</i>          | 11        | rs1977989 <sup>‡</sup>      | A > G           | 0.27        | 1.12 (0.75–1.67)        | 0.567        | 1.27 (0.84–1.92)        | 0.256        |
| <i>CASP11</i>         | 12        | rs10880867 <sup>‡</sup>     | A > G           | 0.33        | 1.14 (0.81–1.60)        | 0.452        | 1.22 (0.85–1.74)        | 0.284        |
| <i>CASP11</i>         | 12        | rs148361648 <sup>‡</sup>    | TA > del        | 0.17        | 0.85 (0.55–1.31)        | 0.459        | 0.94 (0.60–1.45)        | 0.774        |
| <i>CASP11</i>         | 12        | rs10880868 <sup>‡</sup>     | C > T           | 0.12        | 1.11 (0.71–1.75)        | 0.643        | 1.12 (0.70–1.79)        | 0.645        |
| <i>CASP11</i>         | 12        | rs7315731                   | T > A           | 0.43        | 1.04 (0.74–1.45)        | 0.823        | 1.06 (0.75–1.48)        | 0.749        |
| <i>CASP11</i>         | 12        | rs11574952 <sup>‡</sup>     | C > T           | 0.45        | 0.97 (0.70–1.36)        | 0.880        | 0.97 (0.70–1.34)        | 0.853        |
| <i>CASP11</i>         | 12        | rs138471442 <sup>‡</sup>    | ins > del       | 0.33        | 0.98 (0.69–1.40)        | 0.919        | 0.97 (0.68–1.38)        | 0.862        |
| <b><i>CASP4</i></b>   | <b>11</b> | <b>rs571407</b>             | <b>T &gt; C</b> | <b>0.41</b> | <b>0.61 (0.43–0.86)</b> | <b>0.005</b> | <b>0.57 (0.40–0.81)</b> | <b>0.002</b> |
| <b><i>CASP4</i></b>   | <b>11</b> | <b>rs612987</b>             | <b>T &gt; C</b> | <b>0.48</b> | <b>0.67 (0.48–0.94)</b> | <b>0.019</b> | <b>0.65 (0.46–0.93)</b> | <b>0.017</b> |
| <i>CASP4</i>          | 11        | rs11226565                  | A > G           | 0.10        | 0.48 (0.25–0.93)        | 0.030        | 0.57 (0.29–1.11)        | 0.099        |
| <b><i>CASP4</i></b>   | <b>11</b> | <b>rs623114</b>             | <b>A &gt; G</b> | <b>0.41</b> | <b>0.70 (0.50–0.98)</b> | <b>0.039</b> | <b>0.64 (0.45–0.92)</b> | <b>0.014</b> |
| <b><i>CASP4</i></b>   | <b>11</b> | <b>rs543923<sup>‡</sup></b> | <b>C &gt; T</b> | <b>0.19</b> | <b>0.66 (0.43–1.02)</b> | <b>0.063</b> | <b>0.61 (0.39–0.95)</b> | <b>0.030</b> |
| <i>CASP4</i>          | 11        | rs579408 <sup>‡</sup>       | T > A           | 0.27        | 0.68 (0.44–1.05)        | 0.080        | 0.68 (0.44–1.05)        | 0.083        |
| <i>CASP5</i>          | 11        | rs540819                    | T > A           | 0.41        | 0.75 (0.54–1.06)        | 0.104        | 0.72 (0.51–1.02)        | 0.066        |
| <i>CASP5</i>          | 11        | rs507879                    | T > C           | 0.23        | 0.84 (0.53–1.33)        | 0.462        | 0.97 (0.61–1.56)        | 0.905        |

Table S2 Continued

| Gene                | Chr.      | Genetic variations          | Allele          | MAF in CHB  | Crude                   |              | Adjusted <sup>†</sup>   |              |
|---------------------|-----------|-----------------------------|-----------------|-------------|-------------------------|--------------|-------------------------|--------------|
|                     |           |                             |                 |             | HR (95% CI)             | P-value      | HR (95% CI)             | P-value      |
| <i>GSDMD</i>        | 8         | rs10099546 <sup>‡</sup>     | A > G           | 0.43        | 1.19 (0.85–1.66)        | 0.303        | 1.26 (0.89–1.78)        | 0.193        |
| <i>GSDMD</i>        | 8         | rs13266821 <sup>‡</sup>     | C > T           | 0.33        | 1.17 (0.82–1.65)        | 0.382        | 1.21 (0.85–1.72)        | 0.302        |
| <i>GSDMD</i>        | 8         | rs11782753                  | C > T           | 0.18        | 0.97 (0.63–1.49)        | 0.876        | 0.80 (0.51–1.26)        | 0.336        |
| <b><i>GSDME</i></b> | <b>7</b>  | <b>rs2954558</b>            | <b>C &gt; T</b> | <b>0.19</b> | <b>1.41 (0.99–2.03)</b> | <b>0.059</b> | <b>1.52 (1.06–2.19)</b> | <b>0.023</b> |
| <i>GSDME</i>        | 7         | rs12540919                  | C > T           | 0.16        | 1.32 (0.88–1.98)        | 0.179        | 1.37 (0.90–2.07)        | 0.140        |
| <i>GSDME</i>        | 7         | rs4719777 <sup>‡</sup>      | C > G           | 0.33        | 0.81 (0.56–1.17)        | 0.255        | 0.79 (0.54–1.15)        | 0.213        |
| <i>GSDME</i>        | 7         | rs2074142 <sup>‡</sup>      | T > C           | 0.30        | 0.80 (0.54–1.18)        | 0.263        | 0.84 (0.55–1.27)        | 0.404        |
| <i>GSDME</i>        | 7         | rs2237314                   | T > C           | 0.10        | 1.27 (0.82–1.97)        | 0.284        | 1.27 (0.81–1.98)        | 0.291        |
| <i>GSDME</i>        | 7         | rs2237323 <sup>‡</sup>      | G > A           | 0.16        | 1.21 (0.81–1.82)        | 0.350        | 1.23 (0.83–1.82)        | 0.309        |
| <i>GSDME</i>        | 7         | rs17149888                  | G > A           | 0.19        | 0.83 (0.54–1.26)        | 0.373        | 0.77 (0.51–1.18)        | 0.238        |
| <i>GSDME</i>        | 7         | rs2257061                   | C > T           | 0.17        | 1.16 (0.80–1.70)        | 0.433        | 1.28 (0.86–1.91)        | 0.225        |
| <i>GSDME</i>        | 7         | rs12700545                  | G > C           | 0.50        | 0.88 (0.63–1.23)        | 0.455        | 0.80 (0.58–1.12)        | 0.199        |
| <i>GSDME</i>        | 7         | rs2237311                   | G > A           | 0.33        | 0.89 (0.63–1.27)        | 0.519        | 0.89 (0.62–1.27)        | 0.515        |
| <i>GSDME</i>        | 7         | rs1476521                   | A > G           | 0.32        | 1.10 (0.79–1.54)        | 0.563        | 1.23 (0.88–1.71)        | 0.228        |
| <i>GSDME</i>        | 7         | rs2521769                   | A > G           | 0.16        | 0.90 (0.54–1.48)        | 0.673        | 0.98 (0.59–1.64)        | 0.948        |
| <i>GSDME</i>        | 7         | rs2237317                   | C > T           | 0.23        | 0.94 (0.65–1.36)        | 0.757        | 0.90 (0.62–1.31)        | 0.574        |
| <i>GSDME</i>        | 7         | rs754554                    | G > T           | 0.50        | 1.00 (0.72–1.39)        | 0.978        | 0.98 (0.70–1.36)        | 0.897        |
| <i>GSDME</i>        | 7         | rs2521772 <sup>‡</sup>      | T > A           | 0.19        | 1.00 (0.65–1.52)        | 0.991        | 0.97 (0.63–1.49)        | 0.891        |
| <i>NLRP3</i>        | 1         | rs12239046 <sup>‡</sup>     | C > T           | 0.38        | 1.36 (0.99–1.88)        | 0.059        | 1.33 (0.95–1.85)        | 0.095        |
| <i>NLRP3</i>        | 1         | rs12143966 <sup>‡</sup>     | A > G           | 0.48        | 1.35 (0.97–1.88)        | 0.071        | 1.34 (0.95–1.89)        | 0.091        |
| <i>NLRP3</i>        | 1         | rs36021952 <sup>‡</sup>     | G > A           | 0.10        | 0.66 (0.39–1.13)        | 0.132        | 0.61 (0.35–1.07)        | 0.084        |
| <i>NLRP3</i>        | 1         | rs34691535 <sup>‡</sup>     | del > ins       | 0.42        | 1.14 (0.82–1.58)        | 0.448        | 1.15 (0.82–1.61)        | 0.421        |
| <i>NLRP3</i>        | 1         | rs10925017                  | G > A           | 0.33        | 1.12 (0.79–1.58)        | 0.521        | 1.04 (0.74–1.45)        | 0.835        |
| <i>NLRP3</i>        | 1         | rs10754557                  | A > G           | 0.35        | 0.93 (0.65–1.32)        | 0.684        | 0.91 (0.63–1.31)        | 0.605        |
| <i>NLRP3</i>        | 1         | rs12048215 <sup>‡</sup>     | A > G           | 0.30        | 0.96 (0.65–1.43)        | 0.859        | 1.06 (0.70–1.60)        | 0.788        |
| <i>NLRP3</i>        | 1         | rs3806268 <sup>‡</sup>      | A > G           | 0.49        | 1.01 (0.73–1.39)        | 0.945        | 1.09 (0.79–1.52)        | 0.586        |
| <i>NLRP3</i>        | 1         | rs7525979                   | C > T           | 0.16        | 0.99 (0.66–1.48)        | 0.947        | 1.09 (0.72–1.65)        | 0.693        |
| <i>ALOX15</i>       | 17        | rs11078528 <sup>‡</sup>     | G > A           | 0.34        | 0.84 (0.59–1.22)        | 0.362        | 0.84 (0.57–1.23)        | 0.370        |
| <i>ALOX15</i>       | 17        | rs916055                    | A > G           | 0.43        | 0.86 (0.61–1.21)        | 0.383        | 0.89 (0.62–1.29)        | 0.548        |
| <i>ALOX15</i>       | 17        | rs1965923 <sup>‡</sup>      | C > G           | 0.45        | 0.98 (0.69–1.39)        | 0.912        | 1.07 (0.74–1.55)        | 0.717        |
| <i>ALOX15</i>       | 17        | rs2619117                   | G > A           | 0.47        | 1.13 (0.82–1.57)        | 0.453        | 1.06 (0.75–1.50)        | 0.733        |
| <i>ALOX15</i>       | 17        | rs2619112                   | G > A           | 0.45        | 0.87 (0.62–1.23)        | 0.429        | 1.00 (0.70–1.43)        | 0.998        |
| <b><i>ALOX5</i></b> | <b>10</b> | <b>rs702365<sup>‡</sup></b> | <b>G &gt; C</b> | <b>0.33</b> | <b>0.66 (0.47–0.93)</b> | <b>0.019</b> | <b>0.67 (0.47–0.96)</b> | <b>0.028</b> |
| <b><i>ALOX5</i></b> | <b>10</b> | <b>rs2242332</b>            | <b>C &gt; T</b> | <b>0.22</b> | <b>0.59 (0.39–0.89)</b> | <b>0.013</b> | <b>0.57 (0.38–0.87)</b> | <b>0.010</b> |

Table S2 Continued

| Gene         | Chr.      | Genetic variations            | Allele          | MAF in CHB  | Crude                   |              | Adjusted <sup>†</sup>   |              |
|--------------|-----------|-------------------------------|-----------------|-------------|-------------------------|--------------|-------------------------|--------------|
|              |           |                               |                 |             | HR (95% CI)             | P-value      | HR (95% CI)             | P-value      |
| <b>ALOX5</b> | <b>10</b> | <b>rs4948673<sup>‡</sup></b>  | <b>T &gt; A</b> | <b>0.18</b> | <b>0.56 (0.35–0.90)</b> | <b>0.017</b> | <b>0.55 (0.34–0.89)</b> | <b>0.015</b> |
| ALOX5        | 10        | rs10900213                    | T > G           | 0.41        | 0.86 (0.62–1.20)        | 0.376        | 0.86 (0.62–1.20)        | 0.367        |
| ALOX5        | 10        | rs78334475                    | C > G           | 0.15        | 0.90 (0.52–1.57)        | 0.721        | 0.79 (0.45–1.38)        | 0.404        |
| ALOX5        | 10        | rs12264801 <sup>‡</sup>       | G > A           | 0.40        | 0.80 (0.57–1.12)        | 0.186        | 0.90 (0.64–1.28)        | 0.568        |
| ALOX5        | 10        | rs3780905                     | C > T           | 0.49        | 1.08 (0.78–1.49)        | 0.642        | 1.10 (0.79–1.53)        | 0.581        |
| ALOX5        | 10        | rs11439622                    | C > CT          | 0.16        | 0.97 (0.63–1.51)        | 0.906        | 0.90 (0.57–1.42)        | 0.658        |
| ALOX5        | 10        | rs4949001 <sup>‡</sup>        | G > A           | 0.46        | 0.96 (0.69–1.32)        | 0.791        | 0.96 (0.69–1.33)        | 0.801        |
| ALOX5        | 10        | rs4948672 <sup>‡</sup>        | G > C           | 0.14        | 1.09 (0.71–1.68)        | 0.682        | 1.05 (0.68–1.61)        | 0.841        |
| BECN1        | 17        | rs11552192                    | A > T           | 0.16        | 1.00 (0.67–1.49)        | 0.998        | 1.00 (0.67–1.49)        | 0.997        |
| DMT1         | 12        | rs224446 <sup>‡</sup>         | C > T           | 0.45        | 0.85 (0.62–1.16)        | 0.300        | 0.86 (0.62–1.18)        | 0.339        |
| DMT1         | 12        | rs224575 <sup>‡</sup>         | T > C           | 0.42        | 0.96 (0.69–1.34)        | 0.820        | 0.89 (0.63–1.25)        | 0.496        |
| DMT1         | 12        | rs3809320 <sup>‡</sup>        | T > A           | 0.33        | 1.00 (0.70–1.43)        | 0.994        | 0.88 (0.62–1.27)        | 0.500        |
| EIF2S1       | 14        | rs33969193 <sup>‡</sup>       | C > CT          | 0.41        | 1.00 (0.73–1.37)        | 0.983        | 0.96 (0.68–1.34)        | 0.788        |
| EIF2S1       | 14        | rs8016024 <sup>‡</sup>        | T > C           | 0.43        | 1.04 (0.76–1.43)        | 0.789        | 0.97 (0.69–1.36)        | 0.857        |
| FADS2        | 11        | rs526126 <sup>‡</sup>         | C > G           | 0.11        | 0.83 (0.47–1.46)        | 0.515        | 0.76 (0.41–1.38)        | 0.366        |
| FADS2        | 11        | rs35622765                    | A > ACT         | 0.24        | 0.95 (0.63–1.44)        | 0.808        | 0.92 (0.60–1.40)        | 0.682        |
| FADS2        | 11        | rs74771917 <sup>‡</sup>       | C > T           | 0.16        | 0.91 (0.55–1.50)        | 0.705        | 0.93 (0.56–1.56)        | 0.793        |
| FADS2        | 11        | rs174602                      | T > C           | 0.26        | 1.00 (0.68–1.46)        | 0.986        | 0.98 (0.67–1.43)        | 0.909        |
| FADS2        | 11        | rs174561                      | T > C           | 0.34        | 0.98 (0.68–1.41)        | 0.919        | 1.02 (0.71–1.47)        | 0.921        |
| FTH1         | 11        | rs1800009                     | C > T           | 0.15        | 0.92 (0.56–1.51)        | 0.737        | 0.87 (0.52–1.46)        | 0.608        |
| FTH1         | 11        | rs17156609                    | G > A           | 0.17        | 1.08 (0.71–1.65)        | 0.712        | 1.03 (0.67–1.59)        | 0.896        |
| <b>GPX4</b>  | <b>19</b> | <b>rs36207883<sup>‡</sup></b> | <b>G &gt; A</b> | <b>0.26</b> | <b>0.73 (0.51–1.04)</b> | <b>0.081</b> | <b>0.64 (0.44–0.93)</b> | <b>0.019</b> |
| GPX4         | 19        | rs146333943                   | TGGGGTG > T     | 0.23        | 0.78 (0.50–1.20)        | 0.260        | 0.75 (0.48–1.19)        | 0.228        |
| GPX4         | 19        | rs2075711 <sup>‡</sup>        | A > G           | 0.48        | 1.20 (0.86–1.67)        | 0.288        | 1.12 (0.80–1.58)        | 0.504        |
| GPX4         | 19        | rs2074452 <sup>‡</sup>        | C > T           | 0.36        | 1.13 (0.81–1.57)        | 0.479        | 1.08 (0.77–1.52)        | 0.656        |
| GPX4         | 19        | rs713041 <sup>‡</sup>         | C > T           | 0.45        | 0.91 (0.66–1.25)        | 0.556        | 0.98 (0.70–1.37)        | 0.901        |
| <b>HO-1</b>  | <b>22</b> | <b>rs17883419<sup>‡</sup></b> | <b>C &gt; T</b> | <b>0.17</b> | <b>1.78 (1.23–2.57)</b> | <b>0.002</b> | <b>1.79 (1.24–2.58)</b> | <b>0.002</b> |
| <b>HO-1</b>  | <b>22</b> | <b>rs2071749</b>              | <b>G &gt; A</b> | <b>0.25</b> | <b>0.57 (0.37–0.88)</b> | <b>0.010</b> | <b>0.55 (0.36–0.86)</b> | <b>0.008</b> |
| HO-1         | 22        | rs2071746 <sup>‡</sup>        | T > A           | 0.45        | 0.82 (0.59–1.14)        | 0.229        | 0.78 (0.56–1.09)        | 0.150        |
| HO-1         | 22        | rs9607267                     | T > C           | 0.47        | 1.13 (0.83–1.56)        | 0.438        | 1.16 (0.84–1.59)        | 0.381        |
| NQO1         | 16        | rs2917670                     | T > C           | 0.15        | 0.70 (0.43–1.15)        | 0.163        | 0.78 (0.47–1.27)        | 0.311        |
| NQO1         | 16        | rs1800566 <sup>‡</sup>        | G > A           | 0.50        | 0.99 (0.73–1.35)        | 0.974        | 1.06 (0.78–1.44)        | 0.718        |
| NQO1         | 16        | rs2917669                     | G > A           | 0.35        | 1.19 (0.86–1.65)        | 0.282        | 1.06 (0.76–1.48)        | 0.722        |
| <b>NRF2</b>  | <b>2</b>  | <b>rs73976300</b>             | <b>C &gt; T</b> | <b>0.13</b> | <b>0.60 (0.32–1.15)</b> | <b>0.127</b> | <b>0.50 (0.25–0.99)</b> | <b>0.046</b> |

Table S2 Continued

| Gene           | Chr. | Genetic variations       | Allele    | MAF in CHB | Crude            |         | Adjusted <sup>†</sup> |         |
|----------------|------|--------------------------|-----------|------------|------------------|---------|-----------------------|---------|
|                |      |                          |           |            | HR (95% CI)      | P-value | HR (95% CI)           | P-value |
| <i>NRF2</i>    | 2    | rs147426191              | GCAAA > G | 0.42       | 0.82 (0.58–1.18) | 0.288   | 0.79 (0.55–1.13)      | 0.194   |
| <i>NRF2</i>    | 2    | rs77684420 <sup>‡</sup>  | T > C     | 0.13       | 0.92 (0.55–1.56) | 0.760   | 0.81 (0.47–1.39)      | 0.439   |
| <i>NRF2</i>    | 2    | rs36030784 <sup>‡</sup>  | A > C     | 0.10       | 1.07 (0.65–1.76) | 0.784   | 1.16 (0.70–1.93)      | 0.569   |
| <i>NRF2</i>    | 2    | rs6726395                | G > A     | 0.36       | 1.00 (0.70–1.41) | 0.987   | 1.06 (0.75–1.49)      | 0.760   |
| <i>NRF2</i>    | 2    | rs10497511               | A > G     | 0.29       | 0.97 (0.66–1.42) | 0.870   | 0.99 (0.68–1.45)      | 0.973   |
| <i>NRF2</i>    | 2    | rs1962142                | G > A     | 0.20       | 0.95 (0.64–1.43) | 0.824   | 1.01 (0.67–1.50)      | 0.976   |
| <i>NRF2</i>    | 2    | rs12471433 <sup>‡</sup>  | A > C     | 0.48       | 0.97 (0.70–1.34) | 0.856   | 1.00 (0.72–1.39)      | 0.993   |
| <i>PTGS2</i>   | 1    | rs689466 <sup>‡</sup>    | T > C     | 0.47       | 1.22 (0.87–1.71) | 0.257   | 1.22 (0.87–1.72)      | 0.256   |
| <i>SLC3A2</i>  | 11   | rs10897300 <sup>‡</sup>  | A > G     | 0.12       | 0.52 (0.27–0.99) | 0.046   | 0.57 (0.30–1.09)      | 0.090   |
| <i>SLC3A2</i>  | 11   | rs34722625 <sup>‡</sup>  | T > TG    | 0.47       | 0.83 (0.60–1.16) | 0.271   | 0.77 (0.54–1.09)      | 0.139   |
| <i>SLC3A2</i>  | 11   | rs201042920 <sup>‡</sup> | T > G     | 0.50       | 0.85 (0.61–1.18) | 0.319   | 0.78 (0.55–1.11)      | 0.170   |
| <i>SLC3A2</i>  | 11   | rs34436839 <sup>‡</sup>  | CAG > C   | 0.15       | 1.20 (0.76–1.91) | 0.432   | 1.33 (0.82–2.16)      | 0.254   |
| <i>SLC3A2</i>  | 11   | rs489381 <sup>‡</sup>    | G > A     | 0.16       | 0.76 (0.44–1.29) | 0.302   | 0.73 (0.42–1.28)      | 0.274   |
| <i>SLC3A2</i>  | 11   | rs12794763 <sup>‡</sup>  | T > G     | 0.32       | 1.08 (0.74–1.58) | 0.676   | 1.13 (0.77–1.64)      | 0.539   |
| <i>SLC3A2</i>  | 11   | rs2070870 <sup>‡</sup>   | T > C     | 0.12       | 1.10 (0.67–1.81) | 0.709   | 1.13 (0.67–1.89)      | 0.654   |
| <i>SLC3A2</i>  | 11   | rs79118350               | CG > C    | 0.30       | 1.00 (0.70–1.43) | 0.989   | 1.04 (0.71–1.51)      | 0.848   |
| <i>SLC3A2</i>  | 11   | rs2282477 <sup>‡</sup>   | T > C     | 0.23       | 0.95 (0.66–1.38) | 0.805   | 1.04 (0.72–1.50)      | 0.855   |
| <i>SLC7A11</i> | 4    | rs4330397                | C > G     | 0.36       | 0.80 (0.57–1.13) | 0.203   | 0.74 (0.52–1.04)      | 0.086   |
| <i>SLC7A11</i> | 4    | rs4353954 <sup>‡</sup>   | T > A     | 0.24       | 1.33 (0.92–1.90) | 0.125   | 1.22 (0.85–1.76)      | 0.282   |
| <i>SLC7A11</i> | 4    | rs79652067 <sup>‡</sup>  | G > A     | 0.42       | 0.85 (0.62–1.17) | 0.325   | 0.84 (0.61–1.16)      | 0.290   |
| <i>SLC7A11</i> | 4    | rs62324387               | T > C     | 0.26       | 1.09 (0.75–1.59) | 0.659   | 1.21 (0.82–1.80)      | 0.336   |
| <i>SLC7A11</i> | 4    | rs12507560               | G > T     | 0.49       | 1.18 (0.84–1.65) | 0.340   | 1.17 (0.83–1.65)      | 0.364   |
| <i>SLC7A11</i> | 4    | rs142705636              | T > TAA   | 0.10       | 1.09 (0.64–1.87) | 0.753   | 0.88 (0.50–1.54)      | 0.656   |
| <i>SLC7A11</i> | 4    | rs35372640 <sup>‡</sup>  | C > T     | 0.32       | 0.92 (0.64–1.31) | 0.639   | 0.94 (0.65–1.36)      | 0.745   |
| <i>SLC7A11</i> | 4    | rs35108180 <sup>‡</sup>  | G > A     | 0.40       | 1.12 (0.79–1.58) | 0.532   | 0.95 (0.66–1.38)      | 0.796   |
| <i>SLC7A11</i> | 4    | rs4429772 <sup>‡</sup>   | A > G     | 0.33       | 0.93 (0.66–1.33) | 0.703   | 1.05 (0.73–1.51)      | 0.801   |
| <i>SLC7A11</i> | 4    | rs4501269 <sup>‡</sup>   | G > A     | 0.36       | 1.03 (0.75–1.43) | 0.836   | 1.04 (0.75–1.44)      | 0.830   |
| <i>SLC7A11</i> | 4    | rs77293413               | TA > T    | 0.44       | 0.96 (0.69–1.34) | 0.818   | 0.97 (0.70–1.35)      | 0.860   |
| <i>SLC7A11</i> | 4    | rs4863771                | G > T     | 0.27       | 1.18 (0.83–1.69) | 0.350   | 1.02 (0.71–1.48)      | 0.898   |
| <i>SLC7A11</i> | 4    | rs7674870 <sup>‡</sup>   | A > G     | 0.32       | 1.07 (0.78–1.48) | 0.665   | 0.98 (0.70–1.38)      | 0.916   |
| <i>SLC7A11</i> | 4    | rs6832143 <sup>‡</sup>   | A > G     | 0.37       | 1.12 (0.81–1.55) | 0.479   | 0.99 (0.70–1.40)      | 0.950   |
| <i>TFRC</i>    | 3    | rs406271 <sup>‡</sup>    | T > C     | 0.17       | 1.14 (0.74–1.75) | 0.564   | 1.09 (0.68–1.72)      | 0.728   |
| <i>TFRC</i>    | 3    | rs3817672 <sup>‡</sup>   | C > T     | 0.14       | 1.04 (0.66–1.64) | 0.881   | 1.05 (0.65–1.69)      | 0.840   |

MAF, minor allele frequency; CHB, Chinese Han Beijing population; HR, hazard ratio; CI, confidence interval. <sup>†</sup>Adjusted for gender, age, clinical stage, tumor grade, KPS, surgical procedure, and tumor location. <sup>‡</sup>Some samples were not successfully genotyped. The bold parts mean that the genetic variations are significantly associated with OS in Cox regression models after adjusted.

**Table S3** Relationships between four genetic variations in our previous study and OS of rectal cancer patients in co-dominant and dominant models

| Genotype                     | Alive (%)  | Death (%) | Crude            |         | Adjusted <sup>†</sup> |         |
|------------------------------|------------|-----------|------------------|---------|-----------------------|---------|
|                              |            |           | HR (95% CI)      | P-value | HR (95% CI)           | P-value |
| <b>rs202195689</b>           |            |           |                  |         |                       |         |
| CCCCA-CCCCA                  | 146 (64.6) | 37 (50.0) | 1.00 (reference) | -       | 1.00 (reference)      | -       |
| CCCCA-del                    | 72 (31.9)  | 33 (44.6) | 1.74 (1.09–2.78) | 0.021   | 1.85 (1.13–3.04)      | 0.014   |
| del-del                      | 8 (3.5)    | 4 (5.4)   | 1.73 (0.62–4.85) | 0.298   | 1.34 (0.47–3.83)      | 0.579   |
| CCCCA-del + del-del          | 80 (35.4)  | 37 (50.0) | 1.74 (1.10–2.74) | 0.017   | 1.77 (1.10–2.84)      | 0.018   |
| <b>rs5743030<sup>‡</sup></b> |            |           |                  |         |                       |         |
| GG                           | 165 (73.7) | 67 (91.8) | 1.00 (reference) | -       | 1.00 (reference)      | -       |
| GA                           | 54 (24.1)  | 6 (8.2)   | 0.32 (0.14–0.73) | 0.007   | 0.29 (0.12–0.67)      | 0.004   |
| AA                           | 5 (2.2)    | 0 (0.0)   | -                | 0.959   | -                     | 0.961   |
| GA + AA                      | 59 (26.3)  | 6 (8.2)   | 0.29 (0.13–0.67) | 0.004   | 0.26 (0.11–0.62)      | 0.002   |
| <b>rs4920657</b>             |            |           |                  |         |                       |         |
| TT                           | 126 (55.8) | 53 (71.6) | 1.00 (reference) | -       | 1.00 (reference)      | -       |
| TA                           | 81 (35.8)  | 18 (24.3) | 0.57 (0.33–0.97) | 0.039   | 0.51 (0.29–0.88)      | 0.016   |
| AA                           | 19 (8.4)   | 3 (4.1)   | 0.44 (0.14–1.41) | 0.166   | 0.38 (0.12–1.23)      | 0.105   |
| TA + AA                      | 100 (44.2) | 21 (28.4) | 0.55 (0.33–0.91) | 0.019   | 0.48 (0.29–0.81)      | 0.006   |
| <b>rs5743100<sup>‡</sup></b> |            |           |                  |         |                       |         |
| GG                           | 158 (71.5) | 66 (89.2) | 1.00 (reference) | -       | 1.00 (reference)      | -       |
| GT                           | 59 (26.7)  | 8 (10.8)  | 0.37 (0.18–0.78) | 0.008   | 0.35 (0.16–0.73)      | 0.005   |
| TT                           | 4 (1.8)    | 0 (0.0)   | -                | 0.962   | -                     | 0.965   |
| GT + TT                      | 63 (28.5)  | 8 (10.8)  | 0.35 (0.17–0.73) | 0.005   | 0.32 (0.15–0.67)      | 0.003   |

HR, hazard ratio; CI, confidence interval. <sup>†</sup>Adjusted for gender, age, clinical stage, tumor grade, KPS, surgical procedure, and tumor location.<sup>‡</sup>Some samples were not successfully genotyped.

**Table S4** Associations between different number of risk genotypes and OS in patients with rectal cancer receiving postoperative CRT for joint analysis of *CASP4* rs571407, *ALOX5* rs2242332 and *HO-1* rs17883419, hsa-miR-4274 rs202195689, and *PMS1* rs5743030

| Number of risk genotypes <sup>‡</sup> | Alive (%) | Death (%) | Crude              |         | Adjusted <sup>†</sup> |         |
|---------------------------------------|-----------|-----------|--------------------|---------|-----------------------|---------|
|                                       |           |           | HR (95% CI)        | P-value | HR (95% CI)           | P-value |
| ≤ 1                                   | 68 (30.5) | 7 (9.7)   | 1.00 (reference)   | -       | 1.00 (reference)      | -       |
| 2                                     | 80 (35.9) | 21 (29.2) | 2.21 (0.94–5.21)   | 0.069   | 2.58 (1.08–6.13)      | 0.033   |
| 3                                     | 54 (24.2) | 20 (27.8) | 3.17 (1.34–7.49)   | 0.009   | 3.88 (1.63–9.22)      | 0.002   |
| 4                                     | 20 (9.0)  | 19 (26.4) | 7.27 (3.05–17.3)   | < 0.001 | 9.07 (3.66–22.47)     | < 0.001 |
| 5                                     | 1 (0.4)   | 5 (6.9)   | 16.20 (5.12–51.25) | < 0.001 | 11.91 (3.6–39.35)     | < 0.001 |
| P-value for trend                     |           |           |                    | < 0.001 |                       | < 0.001 |
| ≥ 4 of risk genotypes                 | 21 (9.4)  | 24 (33.3) | 8.20 (3.53–19.05)  | < 0.001 | 9.68 (4.08–22.97)     | < 0.001 |

HR, hazard ratio; CI, confidence interval. <sup>†</sup>Adjusted for gender, age, clinical stage, tumor grade, KPS, surgical procedure, and tumor location. <sup>‡</sup>Risk genotypes were *CASP4* rs571407 TT, *ALOX5* rs2242332 CC and *HO-1* rs17883419 CT + TT, hsa-miR-4274 rs202195689 CCCC-del + del-del and *PMS1* rs5743030 GG.