**ADDITIONAL SUPPORTING INFORMATION**

**Table S1.** Markers and LOD scores at chromosome 3p25.2-p22.3 linkage region (29-57 cM). The 95% confidence interval consists of one LOD drop from the maximum LOD score found under the exponential model with a peak linkage at rs2293787 (in bold). Additional markers included for fine-mapping of the region are indicated with an asterisk.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **cM** | **SNP** | **ZSCORE** | **Linear LOD** | **P-Value** | **Exponential LOD** | **P-Value** |
| 29.098 | rs1618545 | 1.865 | 1.431 | 0.005127 | 0.86 | 0.02331 |
| 29.346 | rs12629133 | 1.989 | 1.527 | 0.004008 | 0.949 | 0.01829 |
| 30.598 | rs514084 | 2.187 | 1.789 | 0.002052 | 1.232 | 0.008609 |
| 30.804 | rs13064319 | 2.251 | 1.865 | 0.00169 | 1.341 | 0.006482 |
| 31.156 | rs9843344 | 2.36 | 1.975 | 0.001281 | 1.491 | 0.004388 |
| 31.726 | rs2470353 | 2.413 | 2.02 | 0.001144 | 1.538 | 0.003888 |
| 32.831 | rs2276755 | 2.383 | 1.983 | 0.001257 | 1.435 | 0.005079 |
| 33.247 | rs17040196 | 2.447 | 2.053 | 0.001053 | 1.533 | 0.003946 |
| 33.583 | rs7636593 | 2.549 | 2.17 | 0.000786 | 1.73 | 0.00238 |
| 33.855 | rs9869512 | 2.628 | 2.24 | 0.00066 | 1.832 | 0.001839 |
| 34.327 | rs2470549 | 2.604 | 2.182 | 0.000762 | 1.672 | 0.002758 |
| 34.734 | rs15767 | 2.649 | 2.208 | 0.000714 | 1.685 | 0.002674 |
| 34.885 | rs690241 | 2.679 | 2.255 | 0.000636 | 1.726 | 0.002406 |
| 35.747 | rs17272796 | 2.742 | 2.355 | 0.000496 | 1.821 | 0.001892 |
| 36.167 | rs2060628 | 2.732 | 2.354 | 0.000496 | 1.823 | 0.001883 |
| 37.722 | rs11923699 | 2.666 | 2.239 | 0.000662 | 1.8 | 0.001993 |
| 38.137 | rs13078867\* | 2.651 | 2.149 | 0.000828 | 1.716 | 0.002471 |
| 38.178 | rs4103004 | 2.645 | 2.131 | 0.000866 | 1.698 | 0.002587 |
| 38.427 | rs17006623 | 2.655 | 2.144 | 0.000838 | 1.729 | 0.002389 |
| 40.376 | rs7636784 | 2.665 | 2.215 | 0.000702 | 1.866 | 0.001686 |
| 42.378 | rs11921580 | 2.691 | 2.236 | 0.000667 | 1.864 | 0.001695 |
| 43.436 | rs3752874 | 2.765 | 2.316 | 0.000545 | 2.046 | 0.001072 |
| 45.58 | rs7627753 | 2.807 | 2.381 | 0.000464 | 2.213 | 0.000706 |
| 46.482 | rs17016865\* | 2.831 | 2.4 | 0.000443 | 2.25 | 0.000644 |
| 46.484 | **rs2293787** | 2.831 | 2.4 | 0.000443 | 2.25 | 0.000644 |
| 46.62 | rs7634752\* | 2.823 | 2.393 | 0.000451 | 2.238 | 0.000663 |
| 46.638 | rs17017016 | 2.823 | 2.392 | 0.000452 | 2.236 | 0.000666 |
| 48.213 | rs3213930 | 2.744 | 2.278 | 0.0006 | 1.982 | 0.001258 |
| 49.484 | rs17021360 | 2.739 | 2.264 | 0.000621 | 1.971 | 0.001293 |
| 51.529 | rs3773022 | 2.746 | 2.244 | 0.000653 | 1.941 | 0.001396 |
| 51.794 | rs1371840 | 2.747 | 2.241 | 0.000659 | 1.934 | 0.00142 |
| 52.364 | rs1868491 | 2.716 | 2.211 | 0.000709 | 1.894 | 0.001573 |
| 53.544 | rs17025864 | 2.54 | 2.027 | 0.001124 | 1.624 | 0.003125 |
| 53.875 | rs1494738 | 2.492 | 1.97 | 0.001299 | 1.538 | 0.003893 |
| 54.483 | rs17027714 | 2.444 | 1.919 | 0.001474 | 1.475 | 0.004577 |
| 54.886 | rs7643025 | 2.41 | 1.886 | 0.001603 | 1.44 | 0.005016 |
| 55.427 | rs4639011 | 2.351 | 1.828 | 0.001855 | 1.385 | 0.00578 |
| 55.579 | rs13321685 | 2.334 | 1.811 | 0.00194 | 1.368 | 0.006042 |
| 56.565 | rs17029526 | 2.226 | 1.689 | 0.002646 | 1.246 | 0.008298 |
| 56.766 | rs11558687 | 2.205 | 1.662 | 0.002833 | 1.219 | 0.008912 |
| 57.216 | rs7637099 | 2.155 | 1.597 | 0.003349 | 1.153 | 0.01061 |
| 57.497 | rs2293250 | 2.101 | 1.524 | 0.00403 | 1.08 | 0.01288 |

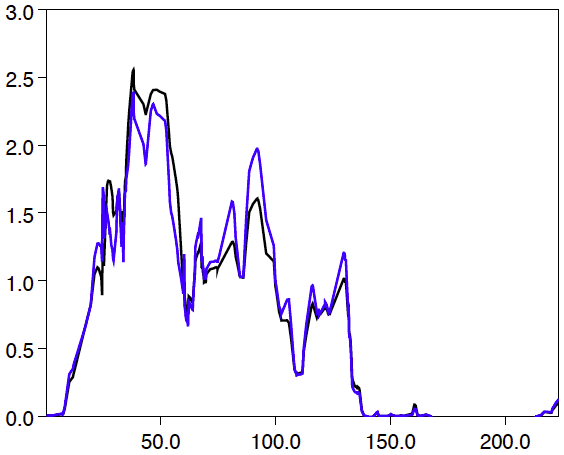
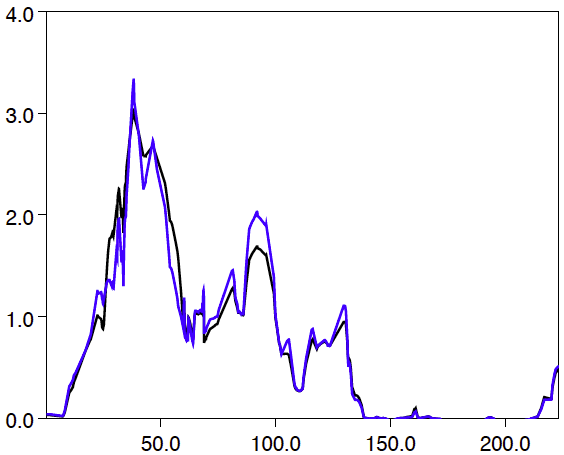
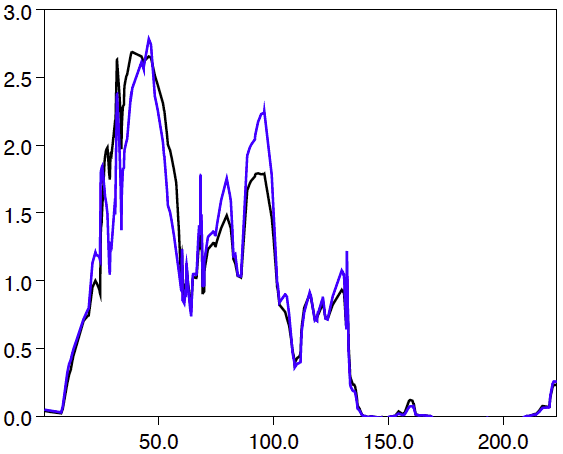
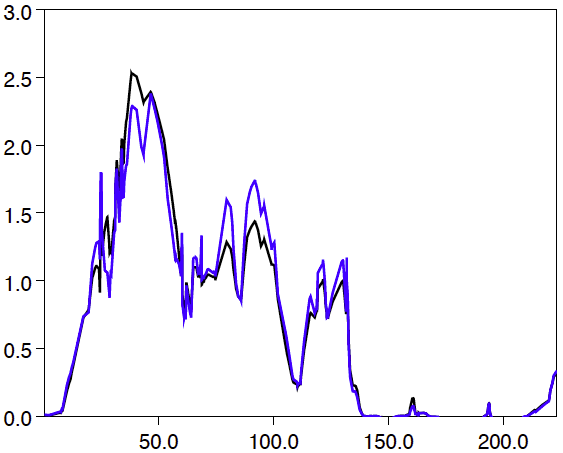
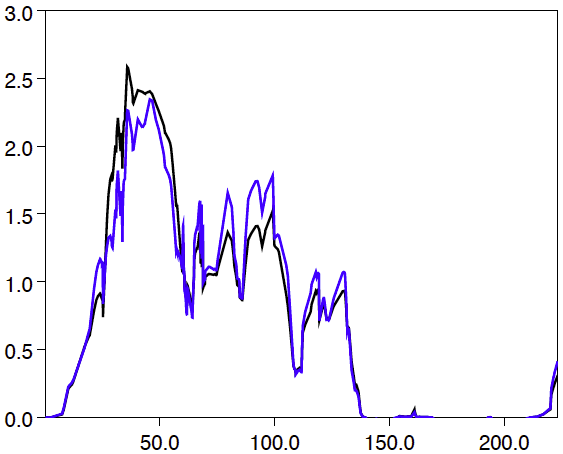
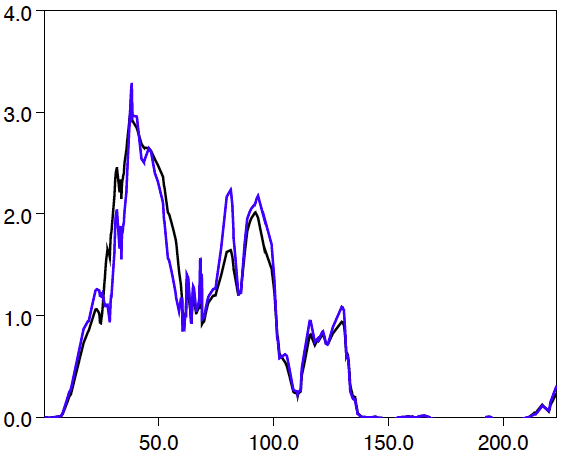
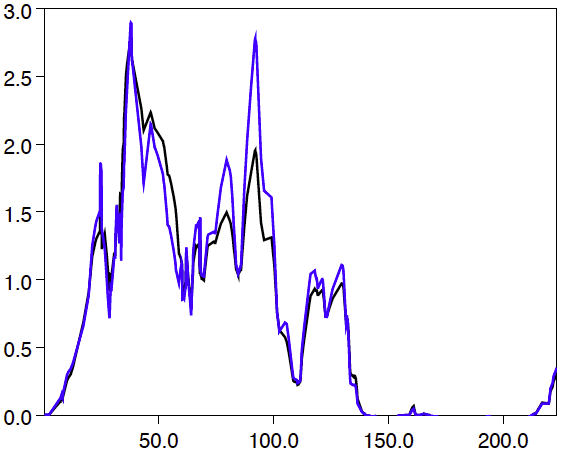
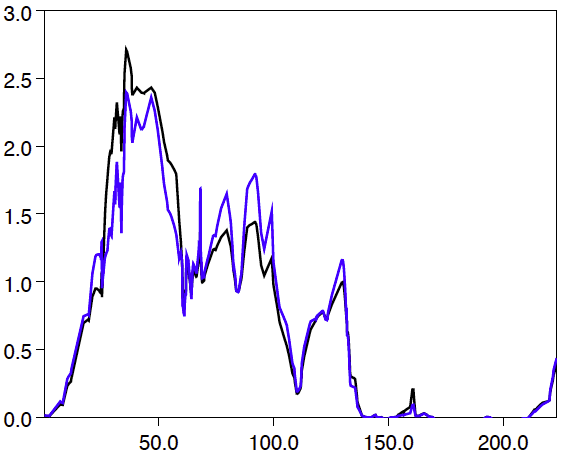
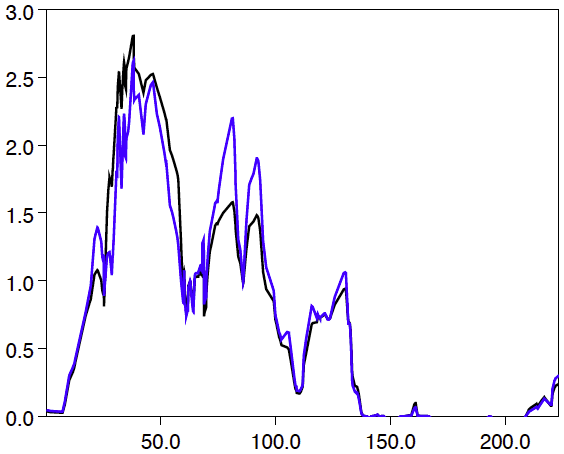
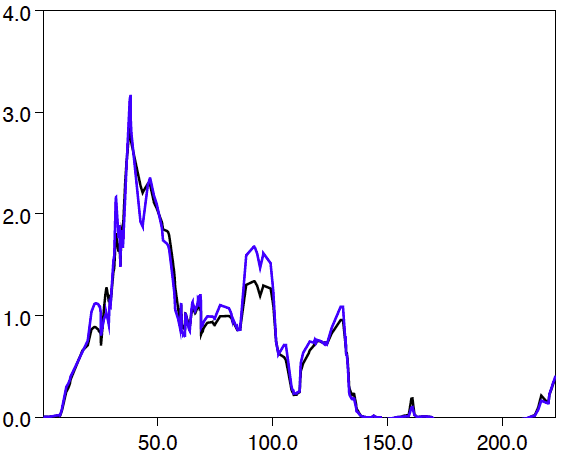
**Table S2.** Linkage contribution for each SPS family at linkage peak on chromosome 3p25.2-p22.3. The maximum LOD score is reported at marker rs2293787, using the Kong and Cox method (LOD).

|  |  |  |  |
| --- | --- | --- | --- |
| **Pedigree** | **z-score** | **DELTA** | **LOD** |
| CAR\_SPS\_1 | 0.691893 | 0.707107 | 0.172965 |
| CAR\_SPS\_2 | -0.049412 | -0.745356 | -0.015707 |
| CAR\_SPS\_3 | 1.399295 | 0.955533 | 0.368672 |
| CAR\_SPS\_4 | 1.072868 | 0.745356 | 0.255192 |
| CAR\_SPS\_6 | 1.387479 | 0.707107 | 0.296906 |
| CAR\_SPS\_7 | 1.396011 | 0.707107 | 0.298226 |
| CAR\_SPS\_8 | 0.25326 | 0.707107 | 0.071544 |
| CAR\_SPS\_9 | -0.595284 | -0.430331 | -0.099048 |
| CAR\_SPS\_12 | 1.338181 | 0.707107 | 0.289196 |
| CAR\_SPS\_13 | 0.783803 | 0.707107 | 0.191516 |
| CAR\_SPS\_16 | 1.389215 | 0.707107 | 0.297175 |
| DONOS\_SPS\_5 | 1.084914 | 0.707107 | 0.247273 |
| MOS\_SPS\_11 | -0.005402 | -0.707107 | -0.001656 |
| MOS\_SPS\_14 | 1.23476 | 0.707107 | 0.272563 |
| MOS\_SPS\_15 | -0.224347 | -0.707107 | -0.063948 |
| OUR\_SPS\_10 | 0.16558 | 0.88028 | 0.059092 |

**Table S3.** List of the rare variants (SNVs) used for the family-based association analysis. All variants were found in heterozygosity. The variants were selected based on their pathogenicity in at least 3 out of the 6 predictor tools (0.25 score was added in case the prediction was not available) in case of missense changes or included because they were truncating variants (stop, indels in coding regions, and variants in canonical splice sites).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chr:position** | **Ref/Alt** | **Gene** | **MAF (ExAC)** | **Heterozygous individuals** | **Pathogenic tools** | **Change** |
| chr3:12957206 | C/T | IQSEC1 | 3.16E-05 | AA3521 | 6 | missense |
| chr3:13672888 | C/G | FBLN2 | 0.000838 | AA3571,AA3572 | 4.25 | missense |
| chr3:14174081 | C/T | TMEM43 | 3.95E-05 | AA3531,AA3532 | 4 | missense |
| chr3:14555171 | A/C | GRIP2 | 0.0003189 | AA3522,AA3524,AA3540,AA3565 |  | splice donor |
| chr3:14958775 | A/G | FGD5 | 0.000128 | AA3528 | 6 | missense |
| chr3:15283704 | G/A | CAPN7 | NA | AA3569,AA3570 | 4 | missense |
| chr3:21552514 | C/G | ZNF385D | NA | AA3528 | 5 | missense |
| chr3:25781126 | C/T | NGLY1 | 3.95E-05 | AA3571 | 6 | missense |
| chr3:25824841 | G/A | NGLY1 | 8.13E-06 | AA3531,AA3532 | 6 | missense |
| chr3:29476277 | C/T | RBMS3 | 6.32E-05 | AA3534 | 5.25 | missense |
| chr3:32758667 | C/T | CNOT10 | NA | AA3572 |  | stop\_gained |

**Figure S1.** Significant peak regions identified on chromosome 3 across all the ten sets of linkage analysis (from 1 to 10) using random SNPs from a selection of 2,487 WES-derived markers. A linkage peak greater than 2 was identified in all 10 replicates in both linear (black line) and exponential models (blue line).



LOD Score

LOD Score

LOD Score

LOD Score

LOD Score

**1.**

**2.**

**3.**

**4.**

**5.**

**6.**

**7.**

**8.**

**9.**

**10.**

cM

cM

cM

cM

cM

**Figure S2.** Pathway analysis for statistically-significant candidate genes arising from the family-based association analysis. The only produced network containing *FBLN2* as well as some hereditary CRC or cancer predisposition genes is depicted. Continuous lines represent direct interactions and dashed lines correspond to indirect interactions. Shaded nodes represented genes from our input set and empty nodes are those that IPA automatically includes because biologically linked to our genes based on evidence in the literature. Symbols correspondence is as follows: square, cytokine; dashed square, growth factor; vertical diamond, enzyme; vertical rectangle, G-protein coupled receptor; dashed vertical rectangle, ion channel; inverted triangle, kinase; flat rectangle, ligand-dependent nuclear receptor; flat diamond, peptidase; flat triangle, phosphatase; flat oval, transcription regulator; vertical oval, transmembrane receptor; double circle, complex/group; circle, other.

#### Network 2 (FBLN2)



Top Diseases and Functions

Cancer, Hereditary Disorder, Organismal Injury and Abnormalities

Molecules in Network

*14-3-3*, *CD3*, *CDKN1B*, *Cofilin*, *Cyclin* *A*, *ELANE*, *ERCC2*, *ERCC4*, *ERCC5*, *ERK1/2*, *F-Actin*, *FBLN2*, *GBA*, *Gsk3*, *Hsp27*, *ITK*, *LDL*, *MAP2K1/2*, *Mmp*, *NF1*, *PARP*, *PI3K (complex)*, *Pka*, *POLE*, *PRKAR1A*, *SERPINA1*, *Smad2/3*, *SRY*, *TGFBR1*, *TSC1*, *TSC2*, *Vegf*, *VHL*, *WT1*, *XPA*.

* 35 total molecules
* 18 genes hereditary cancer & CRC: *CDKN1B*, *ELANE*, *ERCC2*, *ERCC4*, *ERCC5*, *GBA*, *ITK*, *NF1*, *POLE*, *PRKAR1A*, *SERPINA1*, *SRY*, *TGFBR1*, *TSC1*, *TSC2*, *VHL*, *WT1*, *XPA*
* 1 candidate gene: ***FBLN2***