

## SUPPLEMENTARY MATERIAL

**Table S1.** Characteristics of the 465 MMR-proficient non-polyposis unrelated CRC patients included in the study.

|                                                | n                    | Mean Age at Cancer<br>Diagnosis | Median Age at Cancer<br>Diagnosis | Age Range    |
|------------------------------------------------|----------------------|---------------------------------|-----------------------------------|--------------|
| <b>Proband affected with CRC</b>               |                      |                                 |                                   |              |
| Amsterdam [I / II]                             | 59 [43/15]           | 46.08                           | 46                                | 32-78        |
| Bethesda                                       | 378                  | 45.95                           | 47                                | 16-82        |
| No HNPCC criteria                              | 24                   | 40.35                           | 40                                | 37-44        |
| Subtotal                                       | 461                  | 45.88                           | 47                                | 16-82        |
| <b>Proband affected with other tumor types</b> |                      |                                 |                                   |              |
| Amsterdam [I / II]                             | 3 [0/3] <sup>a</sup> | 44.13                           | 44                                | 39-51        |
| Bethesda                                       | 1 <sup>b</sup>       | 47                              | 47                                | 47           |
| Subtotal                                       | 4                    | 44.81                           | 45.5                              | 39-51        |
| <b>TOTAL</b>                                   | <b>465</b>           | <b>45.87</b>                    | <b>47</b>                         | <b>16-82</b> |

<sup>a</sup>Two probands diagnosed with gastric cancer at ages 51 and 39, respectively, and one proband diagnosed with urethral cancer at age 44). <sup>b</sup>Proband diagnosed with endometrial cancer at age 47. Abbreviations: CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer.

**Table S2.** Characteristics of the 177 unrelated adenomatous polyposis patients included in the study.

| Polyp Number                                       | # Of Patients (Median Age Polyposis dx; Range) | # Of Patients with CRC (Median Age at 1 <sup>st</sup> CRC Diagnosis; Range) | # Of Patients with Synchronous or Metachronous CRC | # Of Patients with Multiple Primary Tumors (CRC and/or Extracolonic) | # Of Patients with a FDR with Polyposis | # Of Patients with a FDR with CRC |
|----------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------|-----------------------------------------|-----------------------------------|
|                                                    | 177 (56.5; 14-83)                              | 106/177 [59.9%] (59; 29-75)                                                 | 33/177 [18.6%]                                     | 42 [23.7%]                                                           | 39/176 [22.1%]                          | 66/176 [37.5%]                    |
| <b>ADENOMATOUS POLYPOSIS</b>                       |                                                |                                                                             |                                                    |                                                                      |                                         |                                   |
| >100 polyps                                        | 4 (52.5; 38-58)                                | 3/4 (50; 38-58)                                                             | 1/4                                                | 1/4                                                                  | 1/4                                     | 2/4                               |
| 51-100                                             | 19 (56.5; 29-77)                               | 9/19 (61; 29-77)                                                            | 6/19                                               | 6/19                                                                 | 5/19                                    | 4/19                              |
| 21-50                                              | 50 (59.5; 29-83)                               | 33/50 (64; 35-76)                                                           | 14/50                                              | 18/50                                                                | 10/50                                   | 25/50                             |
| 10-20                                              | 44 (59; 30-78)                                 | 29/44 (60; 30-76)                                                           | 5/44                                               | 8/44                                                                 | 11/43                                   | 15/43                             |
| <10                                                | 6 (51.5; 14-66)                                | 2/6 (64; 63-65)                                                             | 1/6                                                | 1/6                                                                  | 3/6                                     | 2/6                               |
| unknown polyp #                                    | 1 (42)                                         | 1/1 (42)                                                                    | 0/1                                                | 0/1                                                                  | 0/1                                     | 1/1                               |
| <b>SUBTOTAL</b>                                    | <b>124 (59; 14-83)</b>                         | <b>77/124 (61; 29-77)</b>                                                   | <b>27/77</b>                                       | <b>34/77</b>                                                         | <b>30/76</b>                            | <b>49/76</b>                      |
| <b>POLYPOSIS OF MULTIPLE POLYP TYPES (Ad + HP)</b> |                                                |                                                                             |                                                    |                                                                      |                                         |                                   |
| >100 polyps                                        | 2 (52; 48-56)                                  | 2/2 (52; 48-56)                                                             | 0/2                                                | 0/2                                                                  | 1/2                                     | 1/2                               |
| 51-100                                             | 8 (54; 41-61)                                  | 3/8 (54; 41-65)                                                             | 1/8                                                | 1/8                                                                  | 1/8                                     | 3/8                               |
| 21-50                                              | 22 (56; 42-75)                                 | 11/22 (56; 44-75)                                                           | 2/22                                               | 3/22                                                                 | 5/22                                    | 9/22                              |
| 10-20                                              | 13 (57; 36-63)                                 | 8/13 (51.5; 46-59)                                                          | 1/13                                               | 2/13                                                                 | 1/13                                    | 3/13                              |
| unknown polyp #                                    | 1 (49)                                         | 1/1 (49)                                                                    | 1/1                                                | 1/1                                                                  | 0/1                                     | 0/1                               |
| <b>SUBTOTAL</b>                                    | <b>46 (55; 36-75)</b>                          | <b>25/46 (54; 41-75)</b>                                                    | <b>5/46</b>                                        | <b>7/46</b>                                                          | <b>8/46</b>                             | <b>16/46</b>                      |
| <b>NON-CLASSIFIED POLYPOSIS</b>                    |                                                |                                                                             |                                                    |                                                                      |                                         |                                   |
| >100 polyps                                        | 1 (40)                                         | 0/1                                                                         | 0/1                                                | 0/1                                                                  | 1/1                                     | 1/1                               |
| 51-100                                             | 1 (49)                                         | 1/1 (49)                                                                    | 0/1                                                | 0/1                                                                  | 0/1                                     | 0/1                               |
| 21-50                                              | 2 (53.5; 53-54)                                | 2/2 (53.5; 53-54)                                                           | 0/2                                                | 0/2                                                                  | 0/2                                     | 0/2                               |
| 10-20                                              | 1 (35)                                         | 1/1 (35)                                                                    | 1/1                                                | 1/1                                                                  | 0/1                                     | 0/1                               |
| unknown polyp #                                    | 1 (36)                                         | 0/1                                                                         | 0/1                                                | 0/1                                                                  | 0/2                                     | 0/2                               |
| <b>SUBTOTAL</b>                                    | <b>6 (44.5; 35-54)</b>                         | <b>4/6 (51; 35-54)</b>                                                      | <b>1/6</b>                                         | <b>1/6</b>                                                           | <b>1/6</b>                              | <b>1/6</b>                        |
| <b>DUODENAL POLYPOSIS</b>                          |                                                |                                                                             |                                                    |                                                                      |                                         |                                   |
| <10 (2 Ad + 2 HP)                                  | <b>1 (69)</b>                                  | 0/1                                                                         | 0/1                                                | 0/1                                                                  | 1/1                                     | 0/1                               |

Abbreviations: Ad, adenoma; CRC, colorectal cancer; FDR, first degree relative; HP, hyperplastic polyp; #, number.

**Table S3.** Characteristics of the 94 serrated polyposis patients included in the study.

|                                                                 |                                            |
|-----------------------------------------------------------------|--------------------------------------------|
| Age at polyposis diagnosis                                      | Mean age: 51.8 years (range: 8-73)         |
| Total # of polyps                                               | Mean #: 39 (range: 3-195)                  |
| # of hyperplastic/serrated polyps                               | Mean #: 28.6 (range: 3-163)                |
| # of adenomas                                                   | Mean #: 3.9 (range: 0-65)                  |
| # of patients with histologic report of serrated polyps         | Total #: 45 (47.9%)                        |
| <b>Characteristics of the serrated polyposis patients</b>       |                                            |
|                                                                 | <b># cases (%)</b>                         |
| Gender                                                          | Male: 61 (64.9%)                           |
|                                                                 | Female: 33 (35.1%)                         |
| CRC diagnosis                                                   | 34 (36.2%)                                 |
| Family history of polyposis                                     | Mean age at diagnosis: 51.9 (range: 24-75) |
|                                                                 | 14 (14.9%)                                 |
| Cases with adenomas in addition to hyperplastic/serrated polyps | 66 (70.2%)                                 |
|                                                                 | Mean # of adenomas: 6 (range:1-65)         |
| APC gene tested                                                 | <sup>a</sup> 37/94 (39.4%)                 |
| MUTYH gene tested                                               | 45/94 (47.9%)                              |
| RNF43 gene tested                                               | 94/94 (100%)                               |

a. Variants of unknown significance in APC were detected in 2 individuals.

**Table S4.** Amplification and sequencing primers used for Sanger and targeted next generation sequencing.

| Gene                            | Exon/s | Forward Primer (5'-3')    | Reverse Primer (5'-3')          | Size (bp) |
|---------------------------------|--------|---------------------------|---------------------------------|-----------|
| <b>NSD1</b><br>(NM_022455)      | 1A     | AGGCCACTAGGCCTTGAAGT      | ATCTGCATCGTCCACACAAG            | 597       |
|                                 | 1B     | TTCCTTGAGTCCTGGTGGTC      | TTTCCCTTTAAGTGGCCTGT            | 653       |
|                                 | 2      | TGCTTTTTCAGAAGGCTAATAGG   | TCATTACAAAAATGTTCCAAGG          | 332       |
|                                 | 3      | GCAATGATGTGGCTGTTCTC      | TCCAATCTGGGAAACAGAGC            | 364       |
|                                 | 4A     | TCTGATTTTCATCTCCCTTTTCC   | GGCTCTGCACTCTTAGTACAACC         | 999       |
|                                 | 4B     | TGTCCTTGAAATTCAGATGC      | TCCGGTAAGAGACCAGGTTTT           | 830       |
|                                 | 4C     | TGGAACATCAAAGCCATCAA      | CTCCCTGCAGTACAGCATCA            | 575       |
|                                 | 4D     | ATGCTTTTTCAGCCCAAATG      | TGATTCTTCCCCGCTAGTTT            | 822       |
|                                 | 5      | GGGAGTATCAGATGGTCTCATAAAA | TTCATGAAGATAAAGTATGACAT<br>TGAA | 291       |
|                                 | 6      | GCCTTTGTGAGAATTTTCATTCC   | CCAGGACAAAAGGGGGTAGT            | 499       |
|                                 | 7      | ATGACGGGGAAAAACATCAA      | CAACTGCAAAACAGCCTTTC            | 399       |
|                                 | 8      | TGGCAGCTGACAATTCAGAC      | TGGTTAACAGACAAAGCACTTCA         | 233       |
|                                 | 9      | CCACAAAGCTGGAGAATTAATG    | TCAAGGGAAAGAGGGATGTG            | 317       |
|                                 | 10     | AGAGGGAGGGGGTCAAATG       | CCATCATAAAGAGATGGAGTGG          | 291       |
|                                 | 11     | CCCACTGACACTGGTTTACTC     | CCCAGTGTGCGCACAATAA             | 296       |
|                                 | 12     | TGGGTTTCAGACGATGTCAA      | CAGCGAGACTCTGTCTCAA             | 438       |
|                                 | 13     | TGGTCATTCTTCTATTTGTGA     | TTCCAGTGGCAATATGATGAA           | 399       |
|                                 | 14     | GCTTATGCTGTTTATACTCTGGTCA | CGTTAAGCATTGTATCTGAGAGG         | 396       |
|                                 | 15     | TGTGGACAGACAGACATTGCT     | TGGAGCATATGTGAATTCTAAAA<br>CA   | 398       |
|                                 | 16     | TCTCCAACCTAAAGGGGAAAAA    | TTGTGCTTCCGTTCTTGTC             | 298       |
|                                 | 17     | TTTGCCTTTTTCAGGACGTG      | CGGTAGAAGGATATGGCAAGA           | 490       |
|                                 | 18     | CATTATCAAATAGTTGGGGATCG   | CCTTGGGAACTGCGTTACAT            | 381       |
|                                 | 19     | CTGGTCCAGGGATCACACTT      | AAAATTATAATCTGAGGAAGCTG<br>TTTG | 394       |
|                                 | 20     | TCTGTTCTCTTGGGAGTTGG      | AAAATGTAGACTGCCCTAACACT<br>G    | 281       |
|                                 | 21     | TTTCCCAGAGAAGAGAATGAGG    | AAATGGCATGAGACCTGTG             | 374       |
|                                 | 22A    | CACACCTTCGGACTGTAGCA      | TGAGATCCATCACCAAGCA             | 998       |
|                                 | 22B    | CCTACTGACAAACCCCATGC      | GAAAGTGTTCGGGGCAGAT             | 989       |
| <b>HDAC10</b><br>(NM_001159286) | 1      | GAGCCTGCCTAGTTCTGTG       | AACCGCAGACACCTCTGTTC            | 384       |
|                                 | 2      | TGAAGTGAAGTCTCTCATCTGC    | GGCCAGGTTCTTAGGTTTC             | 233       |
|                                 | 3      | CCACCATGAATCCCAGGTC       | ACGTGCATGTGTGTCTGCAC            | 227       |

|                             |       |                                 |                               |     |
|-----------------------------|-------|---------------------------------|-------------------------------|-----|
|                             | 4     | GTGGGTATGGCCTGCAAAG             | GAGTAGGATTTGGGTCACGTC         | 250 |
|                             | 5     | GTGAGAGCTGCCCCCTCC              | GTGCTGGCTGGGTTCTCTC           | 287 |
|                             | 6     | GAGAGAACCCAGCCAGCAC             | ATCTCACCCCTGGATTTTCC          | 245 |
|                             | 7     | CTCAGGGGTCAGCGTTCTAC            | GGGCTTGAGGGTGAACCTGT          | 293 |
|                             | 8     | CTCGGCTTCACTGTCAACCT            | CTCCTCCTGCCTTCACTGG           | 341 |
|                             | 9     | AAGGCAGGAGGAGGGTTATG            | AACCAGAGCCATGTGTGATG          | 277 |
|                             | 10    | GAGGGCTTCTGGGGTCCT              | GCTCCCATGCTCCTGACC            | 213 |
|                             | 11-14 | GTGACATCCCATCCCAGTG             | CAAGGCAATGTTACATCCA           | 968 |
|                             | 15-16 | TGGATCTGTTTACCTGGCTTG           | TGAGGAAGGCTCCATTCACT          | 479 |
|                             | 17    | CTCTTCCACCTCTGCCTCTG            | ATCATGACAATGCCAGCAAA          | 240 |
|                             | 18    | TTCCTGTCTCCCTGCTCCTA            | CACTGGTCCTTTCCCTCGT           | 343 |
|                             | 19-20 | ACGAGGGAAAGGACCAGTG             | GTTCCGTGCCCCAGAGTC            | 480 |
| <b>KRT24</b><br>(NM_019016) | 1     | GGCAGCCTTGAATACACTCTTC          | CATCAGGTCCCACCTTTGCAT         | 822 |
|                             | 2     | AACACAGGCAACAGCTACCC            | TCTCCCGTAACACTTGTTTTCA        | 212 |
|                             | 3     | AAACACGGCCAGGTGAGC              | CGTGCCAGGCCTATTTTACT          | 461 |
|                             | 4-5   | GGCACATTTTCGGAAGTCAT            | TGTGCCTAGTGAACCTCTTGG         | 537 |
|                             | 6     | GGCGAAGGTGCACTTCTAGT            | AGCCCTGAGTCCCATTTTG           | 395 |
|                             | 7-8   | GAGGCTTTCTCCTGCCTTTG            | GATGCCATTTCTTCGCTTGT          | 546 |
| <b>ACACA</b><br>(NM_198837) | 1     | AGAGGGTGCGTTTCAATCAG            | CTGCTTTGTGCAATGTCTGG          | 245 |
|                             | 2     | GCTGAGCAAAAACAGGAATTGA          | TGTGGAAGTCAACTTTTAACACA<br>AA | 228 |
|                             | 3     | TCTCAAATTGCCTTGCTTCC            | TGACATAGGAAAAGGCCAAAGC        | 486 |
|                             | 4     | CACAGGATGCAGTTGTGAAAG           | TAGGATGCTAGGGAGGCAGA          | 389 |
|                             | 5     | TTGGGGAAGCCAGTTTCTAA            | TCCCCCTAAGTTAACATTCTCC        | 395 |
|                             | 6     | TCCCTGACCTTTACGTAGTTTT          | CGAAAATGATGCTTTACAAAAAT<br>G  | 299 |
|                             | 7     | GGCCAGCCTGGATAGAGAC             | AAGAGAGAGAGAGCCCAGCA          | 276 |
|                             | 8     | GGCAACTACATGTGCCAGAA            | TTTCAAAAAGAGGTAAGTCCCAAA      | 245 |
|                             | 9     | AGAATGCAGAGCAGAAAATTGA          | CATCCCTAACACCACCTTGG          | 289 |
|                             | 10    | CATGTGTGGGTGTATGAATGC           | TTTTTCTCTGCTAATATGCAGGT       | 591 |
|                             | 11    | TTCTGGACATCTGCTTGTGA            | TGCCATTGTTCTCAGATTGG          | 395 |
|                             | 12    | TGTGCTCTCATGTGGCTAAAA           | AGGAGGTGCTTTTCTCTTATCA        | 397 |
|                             | 13-14 | TTAGGGAGTGGCTCCAAAAA            | CCATGCTCACACCTTCACTT          | 850 |
|                             | 15    | TTTGTGCTGAAACAGATTGG            | AAAACCCAATCCCAGCATCT          | 227 |
|                             | 16    | TCACAACAAATTTGAGCCTGAT          | TGCAGTTGACTCCCCAAAT           | 386 |
|                             | 17-18 | TCTAGGAAATGCTACAATCAATAAT<br>GT | TGGGAAAATCCCAAGAGCTA          | 834 |
|                             | 19    | TGCAGTGAATATGTCTGTGTGTG         | CCCAGCCTCCTTTCTGTAAC          | 385 |
|                             | 20-21 | GGTGTGGTCCAACTTAGATGC           | GCCAAACAGCTTTCTTTTCC          | 841 |
|                             | 22    | TGGAACCAATTTCCACGTA             | GGAGGATCCAAATAGGAAGGA         | 373 |
|                             | 23    | GAAGATTCTACTGGTCGTGCT           | TTTCCAATTTCTTGAAGTCAAATC      | 300 |
|                             | 24    | TGGAGGTAAATTTGGCCTTT            | CCTATAGGGATAGTTTGGGTTGG       | 246 |
|                             | 25    | TTCTTCTCACTGCTCGTCTCA           | AGCCCCATTATCCCATAAAT          | 357 |
|                             | 26    | TCCAGCTGGGTTTACTTTGTTT          | TGTTCTGAGGAAAACGTGACA         | 358 |
|                             | 27    | TTTATCTGTGATGCCTGCACTT          | GGCAGGCCTATTTGATTTTT          | 463 |
|                             | 28    | TCAAATGCCAAATAGTGCCA            | TGACATGGCAGCCAAATAGA          | 244 |
|                             | 29    | CTTCTCTCCCCACAGAGCAC            | AAAGAAGTGGGCACCAAAAG          | 400 |
|                             | 30    | TGGAGCTCCTCATGACTGGT            | GCTCAGGACTCCCTAGCAGA          | 246 |
|                             | 31    | GCTCTGCAACCTGACCCTAC            | ATGGCTATTCTGGGAGACCTT         | 364 |
|                             | 32    | GCCACTGGTGATTCTGTTC             | TTCCAGAAAATACTTTGGTGAGG       | 393 |
|                             | 33    | TCTCTTTTTCAGGTATTCTACCAAA       | GACATAGCCATAAACTAGCAACT<br>GA | 300 |
|                             | 34    | AGCCTTACAAGGGCCGAAT             | AAGTTGTAGCAGCAGCATAAGAA<br>A  | 195 |
|                             | 35    | GGATTTATGCAGAGAAATAACCA         | CTCCCAAAGTGCTGGGATTA          | 364 |
|                             | 36    | GTGATGGTTATGCGGAGGAT            | CCAAACCAAACCTTTTCAGA          | 397 |

|                        |       |                         |                          |      |
|------------------------|-------|-------------------------|--------------------------|------|
|                        | 37    | TGTAGCTCATTTTTGTTGCTCA  | AGAACAAGAACCTTGATTCAAAA  | 499  |
|                        | 38    | TCTCTTCACCAAGTGCCTTATG  | TAAGGGCTCAACAGCCTGAA     | 391  |
|                        | 39    | TTGTCCCTGACTTGTTCCAA    | TGAACCAATGGGATTTGTGA     | 495  |
|                        | 40    | GGCATATCTCAGCTACTCAACC  | ATTCTTGCCCTTTGGAGTG      | 397  |
|                        | 41    | TGGAAAAGAAGGCAAAACCA    | CCCAACAAGACTACCATGCTC    | 353  |
|                        | 42    | TTTGGCTCTTTAGCAATGTGT   | TGGTGATTTTGAACCTTAAACCTC | 500  |
|                        |       |                         | T                        |      |
|                        | 43    | GCTGTGGAACAAGCTTCATTA   | CATCTTCAATGTTCTTCAAGGTT  | 300  |
|                        | 44    | GGCACCAAGCTAAGAAGGAA    | TGCTCTCATTTGGGACTGAA     | 398  |
|                        | 45    | GCCTGAATTTTGCATCATTGT   | CTGCTTCCTTCCAATCAGGA     | 397  |
|                        | 46-47 | CCCATTTTAGTGCGACTTGTG   | TGATTGAAAAGAACGCTAAAAGC  | 1000 |
|                        | 48    | CAGCTGCCTAATGCTTCCAT    | CTTGGGCATGGCTATAATCC     | 390  |
|                        | 49    | GGATTGGAACAAATGGCTA     | GCAATGTTCTGATGTATTAC     | 250  |
|                        | 50    | GACAAGGTCAAAGATCGAGGA   | GATGTCTCAGAGAGGGCAGAA    | 463  |
|                        | 51    | TATAGGGTGGCCAAACAGGA    | CATTCTCCAGGAGGAAACCA     | 379  |
|                        | 52    | GGCCTCATTCTGTTGTCTCC    | TTTTAGGGCTCACTTTCCTA     | 379  |
|                        | 53    | GTTGAGCTTCCCGTGATTGT    | GCTTATGAGCCTGTGTGCAA     | 323  |
|                        | 54    | TACAGCCAGCTCTTGGGTCT    | GACTCTTGCTGGCGAGACT      | 381  |
|                        | 55    | ACGGAGCACACTTTTGGAGT    | CCATATCTGTACCTGTGGGTCA   | 400  |
|                        | 56    | GGGCAGTTCTTTAGCTGTCT    | GGTCTCCTGTGCCTTCTCAT     | 296  |
| TP63<br>(NM_001114978) | 1     | TTTGACCCTATTGCTTTTAGCC  | CAAGGCACTTCAATTAAGTTTGA  | 225  |
|                        | 2     | CCTGCATGGTTTATAGATTCATT | GAACAAAGAGATGGCATTGGA    | 393  |
|                        | 3     | ACCAATGAGCCTTGCTGACT    | CCTGCCTTTTCACACATGAC     | 336  |
|                        | 4     | GAAGTGCTTCCGACGTGAG     | TCCACCATGAACATGGAATC     | 486  |
|                        | 5     | GCAGCATGCAGCTCTAAAAA    | TGAATCAGGTAGGTGGGTCTC    | 389  |
|                        | 6     | CACCAACATCCTGTTTCATGC   | GAAACATCCCTGTTGCTGAAA    | 292  |
|                        | 7     | TTGCCCTTTTAGGAGGAAGC    | GCAAGGATTTAGAGCACAAAGG   | 369  |
|                        | 8-9   | TGGTAGATCTTCAGGGGACTTT  | TCCTTTCCCATTGTACAGA      | 1000 |
|                        | 10    | TTGCAATTACGGAATCCTCA    | GAAAGAGGGTTGCCATACCA     | 384  |
|                        | 11    | GTTTGGTTTGAGGCCATGTT    | CCAAGCCACTCCACTTTGAT     | 398  |
|                        | 12    | GCTGGTAGTTTAGGCCCTTG    | AACTCCAACCACAGGACTGC     | 374  |
|                        | 13    | TTTCCCTTATCTCGCCAATG    | CTACAAGGCGTTGTTCATCA     | 244  |
|                        | 14    | CCAGAGCATCAGGGAATGAT    | AGACAAGAGGAAGGGGAGGA     | 498  |

Table S5. Reasons for exclusion for the other 44 genes identified by Park et al. [1].

| Gene   | Reason(s) for Exclusion                                                                                                                                                                                    |
|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BRCA1  | Known hereditary cancer gene                                                                                                                                                                               |
| BRCA2  | Known hereditary cancer gene                                                                                                                                                                               |
| ATM    | Known hereditary cancer gene                                                                                                                                                                               |
| MYH1   | Known hereditary cancer gene                                                                                                                                                                               |
| MNT    | Not a cancer driver gene <sup>a</sup> , no disruptive or predicted pathogenic variants in 1006 familial/early-onset CRC patients (Chubb et al.) <sup>b</sup>                                               |
| KCNG4  | Low expression in normal colon mucosa, not a cancer driver gene, high observed vs. expected ratio of LoF variants in controls, disruptive variants in cases << controls (Chubb et al.)                     |
| NOP56  | Not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                                                                                          |
| TPCN2  | Not a cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                                          |
| KCNH5  | Low expression in normal colon mucosa, not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                                                   |
| NIPAL3 | Not a cancer driver gene, no disruptive or predicted pathogenic variants in 1006 familial/early-onset CRC patients (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms |
| PRPF8  | Not a cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                                          |
| ANK2   | Not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms                              |
| INO80  | Predicted pathogenic missense variants in cases << controls (Chubb et al.)                                                                                                                                 |
| MYH3   | Low expression in normal colon mucosa, not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.)                                                                |

|                |                                                                                                                                                                                        |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PATE2</b>   | Low expression in normal colon mucosa, not a cancer driver gene, no disruptive or predicted pathogenic variants in 1006 familial/early-onset CRC patients (Chubb et al.)               |
| <b>ABCF3</b>   | Not a cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                      |
| <b>GANC</b>    | Not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                                                                      |
| <b>MLH1</b>    | Known hereditary cancer gene                                                                                                                                                           |
| <b>GUCY1A3</b> | Predicted pathogenic missense variants in cases << controls (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                    |
| <b>COL7A1</b>  | Not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                                                                      |
| <b>BEST1</b>   | Low expression in normal colon mucosa, not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                               |
| <b>GLDC</b>    | Low expression in normal colon mucosa, not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                               |
| <b>COLQ</b>    | Low expression in normal colon mucosa, not a cancer driver gene, no disruptive or predicted pathogenic variants in 1006 familial/early-onset CRC patients (Chubb et al.)               |
| <b>TULP4</b>   | Not a cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                      |
| <b>RPH3AL</b>  | Not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms          |
| <b>ALDH9A1</b> | Not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms          |
| <b>ECEL1</b>   | Low expression in normal colon mucosa, not a cancer driver gene                                                                                                                        |
| <b>RCL1</b>    | Not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.)                                                                                   |
| <b>ABCC4</b>   | Not cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                        |
| <b>MUC17</b>   | Not a cancer driver gene, high observed vs. expected ratio of LoF variants in controls, disruptive variants in cases << controls (Chubb et al.)                                        |
| <b>ALOX12B</b> | Low expression in normal colon mucosa, not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                               |
| <b>HOGA1</b>   | Low expression in normal colon mucosa, not a cancer driver gene, high observed vs. expected ratio of LoF variants in controls                                                          |
| <b>KRT36</b>   | Low expression in normal colon mucosa, not a cancer driver gene                                                                                                                        |
| <b>BBS1</b>    | Not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                                                                      |
| <b>SCN10A</b>  | Low expression in normal colon mucosa, not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                               |
| <b>THBS3</b>   | Not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms          |
| <b>RYR1</b>    | Low expression in normal colon mucosa, not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                               |
| <b>USH2A</b>   | Low expression in normal colon mucosa, not a cancer driver gene                                                                                                                        |
| <b>HK3</b>     | Not a cancer driver gene, disruptive variants in cases << controls (Chubb et al.)                                                                                                      |
| <b>ALK</b>     | Low expression in normal colon mucosa, predicted pathogenic missense variants in cases << controls (Chubb et al.)                                                                      |
| <b>CTSB</b>    | Not a cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                      |
| <b>ABCC12</b>  | Low expression in normal colon mucosa, not a cancer driver gene, high observed vs. expected ratio of LoF variants in controls, disruptive variants in cases << controls (Chubb et al.) |
| <b>SLC7A8</b>  | Not a cancer driver gene, predicted pathogenic missense variants in cases << controls (Chubb et al.), not involved in colorectal cancer or hereditary CRC pathways/mechanisms          |
| <b>SLC12A4</b> | Not a cancer driver gene, not involved in colorectal cancer or hereditary CRC pathways/mechanisms                                                                                      |

<sup>a</sup> Source: <https://www.intogen.org>, <sup>b</sup> Data source: Rare disruptive mutations and their contribution to the heritable risk of colorectal cancer. Chubb et al. [2].

**Table S6.** Clinical characteristics, co-segregation data and 2<sup>nd</sup> hit results of the carriers of the rare, predicted damaging variants identified among the 736 patients included in the study.

| Family ID | Variant | Proband's Phenotype<br>(age at diagnosis) | Family History <sup>a</sup>                                       | Family History <sup>a</sup>                                      | Co-Segregation Information | 2 <sup>nd</sup> Hit Analysis <sup>b</sup> |
|-----------|---------|-------------------------------------------|-------------------------------------------------------------------|------------------------------------------------------------------|----------------------------|-------------------------------------------|
|           |         |                                           | – 1 <sup>st</sup> Degree Affected Relatives<br>(age at diagnosis) | – 2 <sup>nd</sup> Degree Affected Relatives – (age at diagnosis) |                            |                                           |

|            |                                         |                                               |                                                                      |                                        |                                                                                                  |                                               |
|------------|-----------------------------------------|-----------------------------------------------|----------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------|
| <b>F1</b>  | <i>NSD1</i><br>c.3056G>A;<br>p.(R1019H) | 10-20 Ad (50), BC (50)                        |                                                                      |                                        |                                                                                                  | Not performed                                 |
| <b>F2</b>  | <i>NSD1</i><br>c.3089T>C;<br>p.(L1030S) | 2 CRC (52, 59), <10 Ad,                       |                                                                      | BC (46); Lym (9)                       |                                                                                                  | CRC: no somatic <i>NSD1</i> mutations         |
| <b>F3</b>  | <i>NSD1</i><br>c.3151G>A;<br>p.(E1051K) | >70 H/SP (55), CRC (55)                       | 13 H/SP (61), 1 Ad (61); 2 polyps (36); CRC (79); BIC (72), LiC (76) | Sto (60)                               | Carriers: sister, 13 H/SP (61), 1 Ad (61) and son, 2 polyps (36)<br>Non carrier: son, unaffected | CRC: no somatic <i>NSD1</i> mutations         |
| <b>F4</b>  | <i>HDAC10</i><br>c.308C>T;<br>p.(A103V) | BC (26), CRC (35), polyps (35)                |                                                                      |                                        |                                                                                                  | Not performed                                 |
| <b>F5</b>  | <i>HDAC10</i><br>c.308C>T;<br>p.(A103V) | 11 H/SP (63), 11 Ad (63)                      | LC (79)                                                              |                                        |                                                                                                  | Not performed                                 |
| <b>F6</b>  | <i>HDAC10</i><br>c.827G>A;<br>p.(R276G) | 2 CRC (37, 43), 26 H/SP (37), 1 Ad (37)       | Polyps (43); Polyps (62)                                             | CRC (60); PaC (70); PC                 |                                                                                                  | Not performed                                 |
| <b>F7</b>  | <i>KRT24</i> c.130C>T;<br>p.(R44X)      | CRC (47)                                      | Lym                                                                  | Lym; LC; Polyps; BIC; CRC (39); LC     |                                                                                                  | CRC: no somatic <i>KRT24</i> mutations        |
| <b>F8</b>  | <i>KRT24</i><br>c.449G>A;<br>p.(R150H)  | OvC (34), <30 H/SP (40), 10 Ad (40), CRC (50) | Polyps (35)                                                          | BC (70)                                |                                                                                                  | CRC: no somatic <i>KRT24</i> mutations in CRC |
| <b>F9</b>  | <i>KRT24</i><br>c.1096C>T;<br>p.(R366C) | CRC (40)                                      |                                                                      | CRC (72); EsC                          |                                                                                                  | CRC: no somatic <i>KRT24</i> mutations        |
| <b>F10</b> | <i>KRT24</i><br>c.1096C>T;<br>p.(R366C) | CRC (44)                                      | PC (78); LiC                                                         |                                        |                                                                                                  | Not performed                                 |
| <b>F11</b> | <i>KRT24</i><br>c.1096C>T;<br>p.(R366C) | CRC (44)                                      |                                                                      | Leu (1)                                |                                                                                                  | CRC: no somatic <i>KRT24</i> mutations        |
| <b>F12</b> | <i>KRT24</i><br>c.1096C>T;<br>p.(R366C) | CRC (69)                                      | CRC (45)                                                             | CRC (80), Sto                          | Carriers: son, CRC (45)                                                                          | CRC: no somatic <i>KRT24</i> mutations        |
| <b>F13</b> | <i>KRT24</i><br>c.1096C>T;<br>p.(R366C) | EC (55), CRC (77)                             | ThC (4), PC (63), HNC; CRC (48); EC (54)                             | CRC; LC; PC; BC                        |                                                                                                  | Not performed                                 |
| <b>F14</b> | <i>KRT24</i><br>c.1143G>A;<br>p.(M381I) | CRC (35)                                      |                                                                      | Lym                                    |                                                                                                  | CRC: no somatic <i>KRT24</i> mutations        |
| <b>F15</b> | <i>TP63</i> c.84T>G;<br>p.(H28Q)        | CRC (50)                                      | Sto (71)                                                             | Sto (43); CRC (70); LiC (50); Sto (40) |                                                                                                  | Not performed                                 |
| <b>F16</b> | <i>TP63</i> c.84T>G;<br>p.(H28Q)        | EC (46), CRC (49)                             | BIC (60), LC (71); OvC (55)                                          | PaC (86), LC (58)                      |                                                                                                  | Not performed                                 |

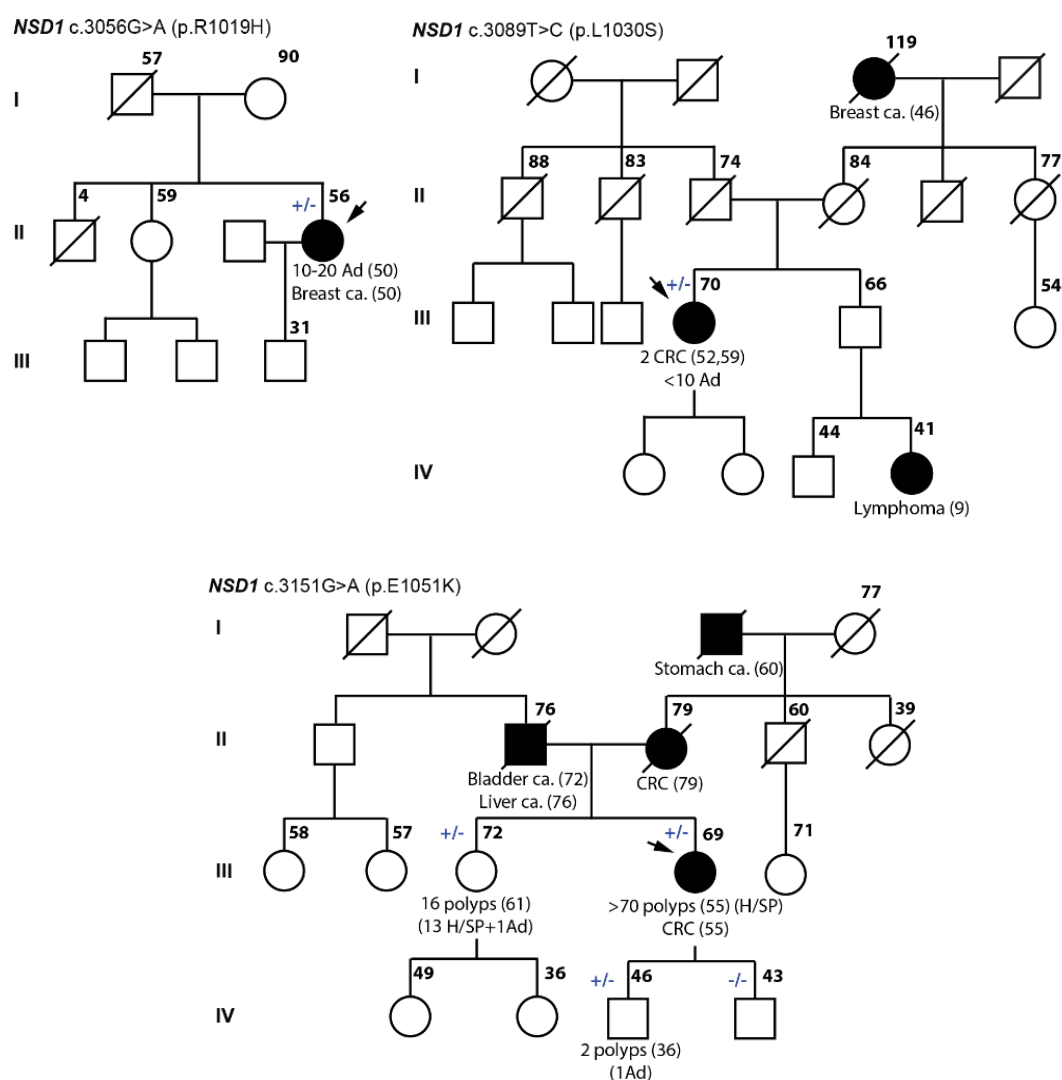
|            |                                     |                              |                                      |                                                 |               |
|------------|-------------------------------------|------------------------------|--------------------------------------|-------------------------------------------------|---------------|
| <b>F17</b> | <i>TP63</i> c.1127G>A;<br>p.(R376H) | CRC (56), BC (59)            | CRC (56); 2 BC (46,<br>49); HNC (53) | BC (31); CRC<br>(75); CRC (86);<br>CRC (56); BC | Not performed |
| <b>F18</b> | <i>TP63</i> c.1459C>T;<br>p.(R487C) | 5 CRC (39), 11-20<br>Ad (39) |                                      |                                                 | Not performed |

<sup>a</sup> Individual cancer-affected family relatives are separated by semicolons. <sup>b</sup> Mutational analysis of the corresponding gene in the tumor was performed by Sanger Sequencing. Chromatograms did not show evidence of LOH in any of the tested tumors for the corresponding gene, when assessing the allele peak height corresponding to the germline variant in tumor DNA compared to blood DNA. Abbreviations: Ad., adenoma; BC, breast cancer; BIC, bladder cancer; BrC, brain cancer; CRC, colorectal cancer; DCy, desmoid cyst; EC, endometrial cancer; EsC, esophageal cancer; GC, gastric cancer; HNC, head and neck cancer; H/SP, hyperplastic/serrated polyps; OC, oral cancer; OvC, ovarian cancer; LarC, laryngeal cancer; LC, lung cancer; Leu, leukemia; LiC, liver cancer; Lym, lymphoma; PaC, pancreatic cancer; PC, prostate cancer; Sto, stomach cancer; ThC, thyroid cancer.

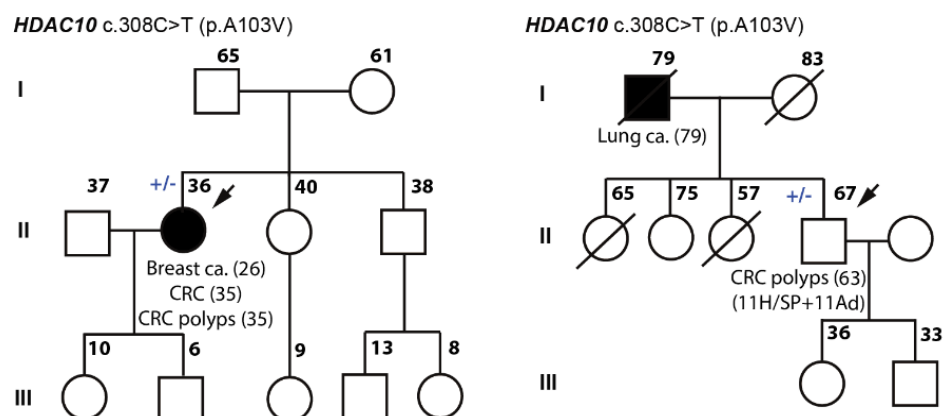
**Table S7.** Case-control analysis of the germline variants identified in the five selected candidate genes, considering the gnomAD non-Finnish European (NFE), non-cancer subpopulation as controls.

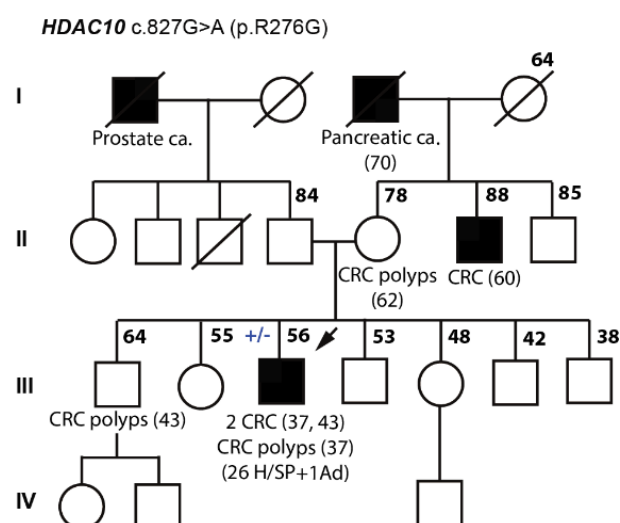
| Gene          | Cohort or Study                  | Disruptive Alleles    |                                      | Disruptive, Splice-Site, Start-Loss, Predicted Pathogenic Missense (REVEL>0.4) |                                   |
|---------------|----------------------------------|-----------------------|--------------------------------------|--------------------------------------------------------------------------------|-----------------------------------|
|               |                                  | n/ Total Alleles (%)  | OR (95%CI); p-value                  | n/ Total Alleles (%)                                                           | OR (95%CI); p-value               |
| <b>NSD1</b>   | Controls (gnomAD NFE non-cancer) | 7/118190 (0.01%)      |                                      | 281/118190 (0.24%)                                                             |                                   |
|               | Familial/EOCRC                   |                       |                                      |                                                                                |                                   |
|               | Zhunosova et al [3]              | 0/250 (0.00%)         |                                      | 1/250 (0.4%)                                                                   |                                   |
|               | Chubb et al [4]                  | 1/2012 (0.05%)        |                                      | 8/2012 (0.40%)                                                                 |                                   |
|               | Current study                    | 0/930 (0.00%)         |                                      | 0/930 (0.00%)                                                                  |                                   |
|               | Subtotal                         | 1/3192 (0.03%)        | 5.29 (0.12-41.21);<br>p=0.19         | 9/3192 (0.28%)                                                                 | 1.19 (0.54-2.29); p=0.58          |
|               | Polyposis (current study)        | 0/542 (0.00%)         | 0 (0.00-151.78); p=1                 | 1/542 (0.18%)                                                                  | 0.78 (0.02-4.38); p=1             |
|               | TCGA CRC patients                | 0/1086 (0.00%)        | 0.00 (0.00-75.56); p=1               | 2/1086 (0.18%)                                                                 | 0.77 (0.09-2.83); p=1             |
|               | <b>TOTAL</b>                     | <b>1/4820 (0.02%)</b> | <b>3.50 (0.08-27.28);<br/>p=0.27</b> | <b>12/4820 (0.25%)</b>                                                         | <b>1.05 (0.53-1.86); p=0.88</b>   |
| <b>HDAC10</b> | Controls (gnomAD NFE non-cancer) | 138/118190 (0.12%)    |                                      | 432/118190 (0.37%)                                                             |                                   |
|               | Familial/EOCRC                   |                       |                                      |                                                                                |                                   |
|               | Chubb et al [4]                  | 3/2012 (0.15%)        |                                      | 6/2012 (0.30%)                                                                 |                                   |
|               | Current study                    | 0/930 (0.00%)         |                                      | 0/930 (0.00%)                                                                  |                                   |
|               | Subtotal                         | 3/2942 (0.10%)        | 0.87 (0.18-2.61); p=1                | 6/2942 (0.20%)                                                                 | 0.56 (0.20-1.22); p=0.21          |
|               | Polyposis (current study)        | 0/542 (0.00%)         | 0 (0.00-5.92); p=1                   | 3/542 (0.55%)                                                                  | 1.52 (0.31-4.49); p=0.46          |
|               | TCGA CRC patients                | 0/1086 (0.00%)        | 0.00 (0.00-2.95);<br>p=0.64          | 3/1086 (0.28%)                                                                 | 0.76 (0.15-2.23); p=1             |
|               | <b>TOTAL</b>                     | <b>3/4570 (0.07%)</b> | <b>0.56 (0.11-1.68);<br/>p=0.50</b>  | <b>12/4570 (0.26%)</b>                                                         | <b>0.72 (0.37-1.27); p=0.31</b>   |
| <b>KRT24</b>  | Controls (gnomAD NFE non-cancer) | 92/118190 (0.08%)     |                                      | 555/118190 (0.47%)                                                             |                                   |
|               | Familial/EOCRC                   |                       |                                      |                                                                                |                                   |
|               | Chubb et al [4]                  | 2/2012 (0.10%)        |                                      | 6/2012 (0.30%)                                                                 |                                   |
|               | Current study                    | 1/930 (0.11%)         |                                      | 7/930 (0.75%)                                                                  |                                   |
|               | Subtotal                         | 3/2942 (0.10%)        | 1.31 (0.27-3.95);<br>p=0.50          | 13/2942 (0.44%)                                                                | 0.94 (0.50-1.62); p=1             |
|               | Polyposis (current study)        | 0/542 (0.00%)         | 0.00 (0.00-8.94); p=1                | 1/542 (0.18%)                                                                  | 0.39 (0.01-2.20); p=0.53          |
|               | TCGA CRC patients                | 2/1086 (0.18%)        | 2.37 (0.28-8.82);<br>p=0.21          | <b>13/1086 (1.20%)</b>                                                         | <b>2.57 (1.35-4.45); p= 0.002</b> |

|       |                                  |                   |                              |                    |                          |
|-------|----------------------------------|-------------------|------------------------------|--------------------|--------------------------|
| ACACA | TOTAL                            | 5/4570 (0.11%)    | 1.41 (0.45-3.40);<br>p=0.41  | 27/4570 (0.59%)    | 1.26 (0.82-1.86); p=0.23 |
|       | Controls (gnomAD NFE non-cancer) | 19/118190 (0.02%) |                              | 334/118190 (0.28%) |                          |
|       | Familial/EOCRC                   |                   |                              |                    |                          |
|       | Thutkawkorapin et al [5]         | 0/102 (0.00%)     |                              | 1/102 (0.98%)      |                          |
|       | Chubb et al [4]                  | 1/2012 (0.05%)    |                              | 4/2012 (0.20%)     |                          |
|       | Current study                    | 0/930 (0.00%)     |                              | 0/930 (0.00%)      |                          |
|       | Subtotal                         | 1/3044 (0.03%)    | 2.04 (0.05-12.86);<br>p=0.40 | 5/3044 (0.16%)     | 0.58 (0.19-1.37); p=0.29 |
|       | Polyposis (current study)        | 0/542 (0.00%)     | 0.00 (0.00-46.89); p=1       | 0/542 (0.00%)      | 0.00 (0.00-2.42); p=0.41 |
|       | TCGA CRC patients                | 1/1086 (0.09%)    | 5.73 (0.14-36.16);<br>p=0.17 | 5/1086 (0.46%)     | 1.63 (0.53-3.86); p=0.24 |
|       | TOTAL                            | 2/4672 (0.04%)    | 2.66 (0.30-11.05);<br>p=0.19 | 10/4672 (0.21%)    | 0.76 (0.36-1.41); p=0.48 |
| TP63  | Controls (gnomAD NFE non-cancer) | 1/118190 (0.001%) |                              | 352/118190 (0.30%) |                          |
|       | Familial/EOCRC                   |                   |                              |                    |                          |
|       | Chubb et al [4]                  | 0/2012 (0.00%)    |                              | 4/2012 (0.20%)     |                          |
|       | Current study                    | 0/930 (0.00%)     |                              | 3/930 (0.32%)      |                          |
|       | Subtotal                         | 0/2942 (0.00%)    | 0.00 (0.00-1529.34);<br>p=1  | 7/2942 (0.24%)     | 0.80 (0.32-1.66); p=0.73 |
|       | Polyposis (current study)        | 0/542 (0.00%)     | 0.00 (0.00-7507.02);<br>p=1  | 1/542 (0.18%)      | 0.62 (0.02-3.48); p=1    |
|       | TCGA CRC patients                | 0/1086 (0.00%)    | 0.00 (0.00-3980.48);<br>p=1  | 0/1086 (0.00%)     | 0.00 (0.00-1.15); p=0.08 |
|       | TOTAL                            | 0/4570 (0.00%)    | 0.00 (0.00-992.99);<br>p=1   | 8/4570 (0.18%)     | 0.59 (0.25-1.17); p=0.16 |

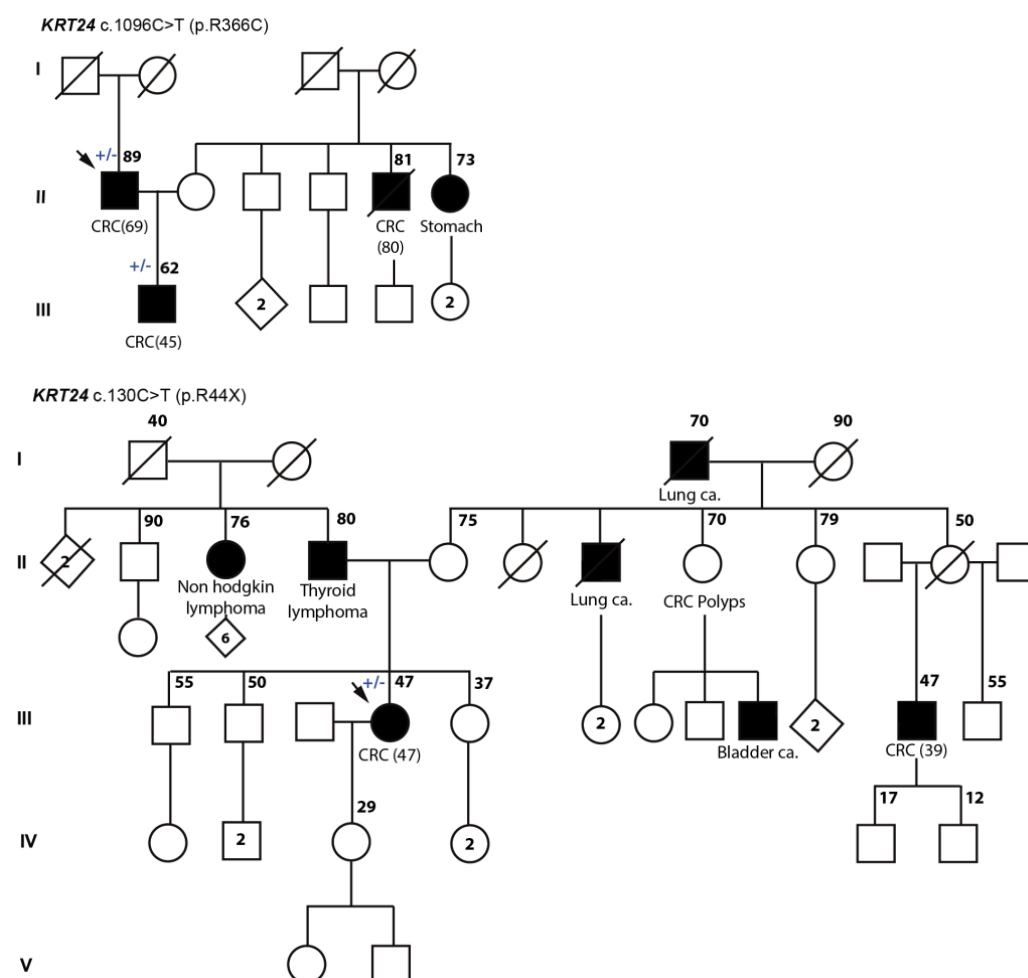


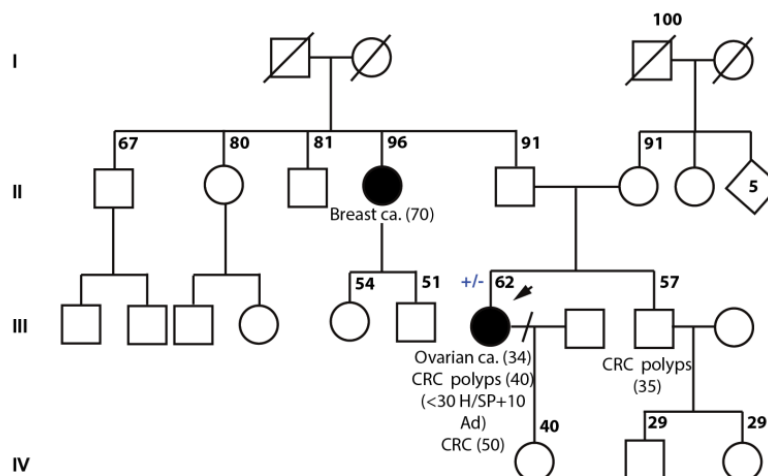
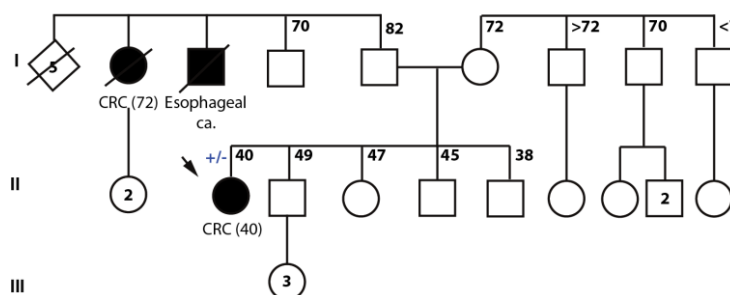
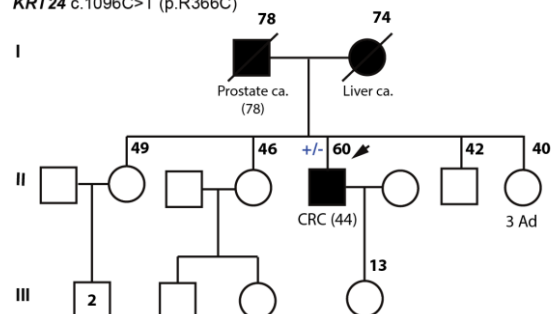
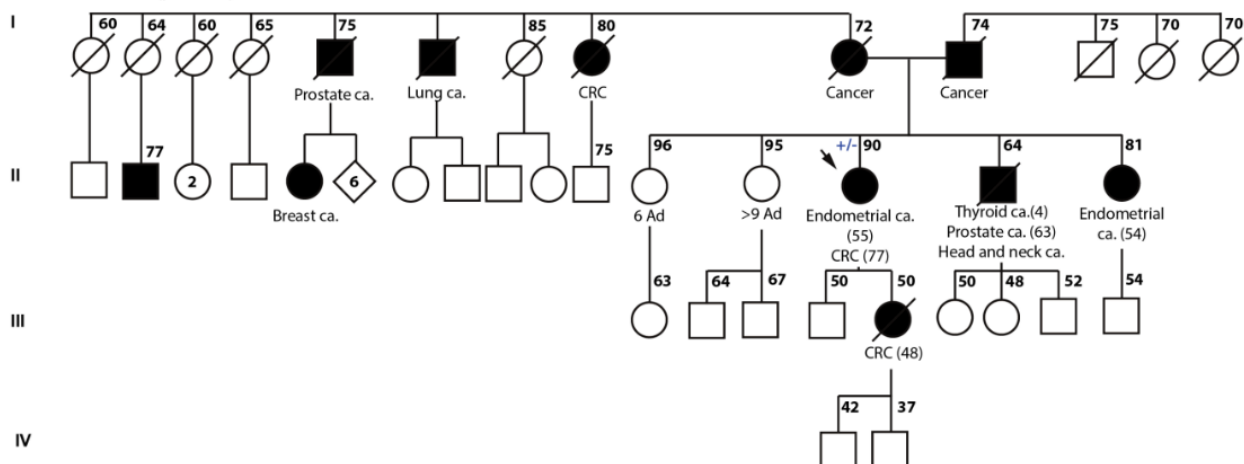
**Figure S1.** Pedigrees of the families carrying *NSD1* rare germline (predicted) damaging variants. Filled black symbol, affected with cancer; black arrow, index case. Ages at information gathering or at death, when available, are indicated on the top-right corner, and ages at cancer diagnosis, after tumor type. +/- depicts heterozygous carrier status, and -/- non carrier of the corresponding *NSD1* variant.

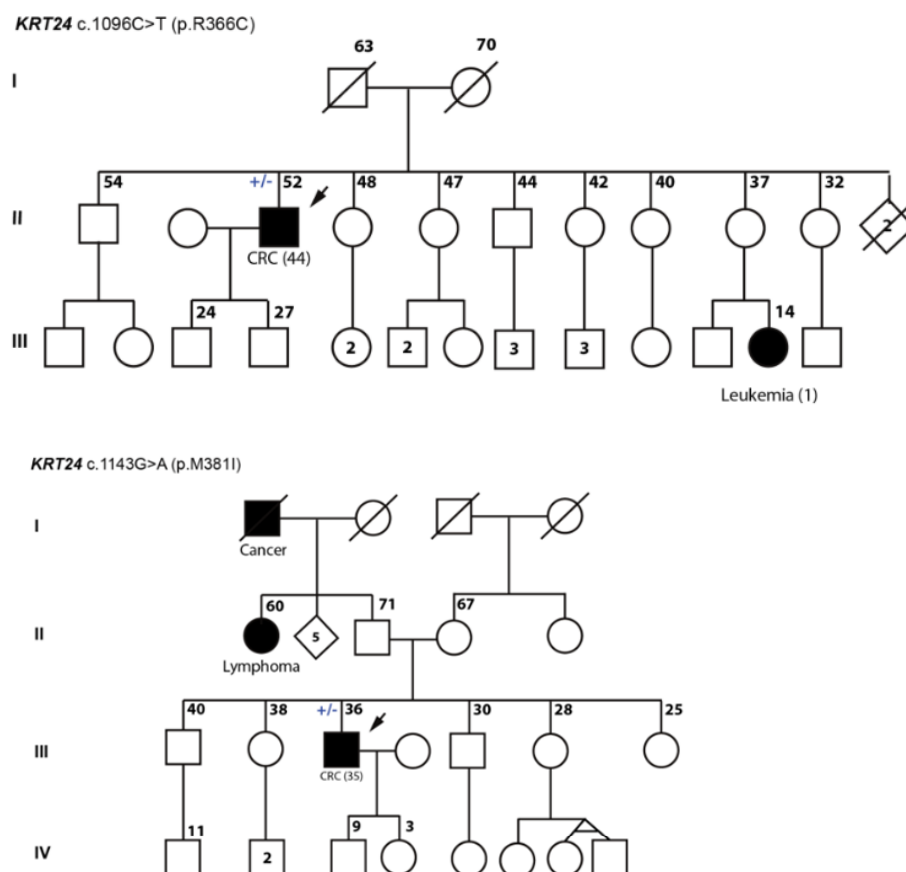




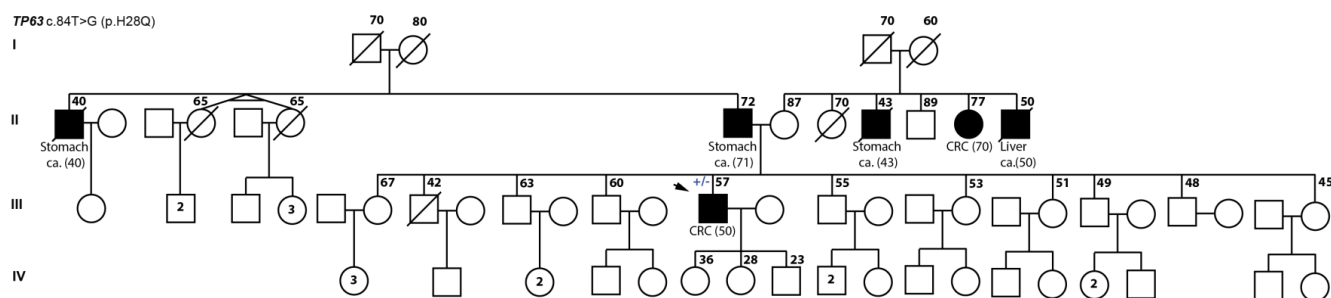
**Figure S2.** Pedigrees of the families carrying *HDAC10* rare germline variants from the cohort analyzed in the current study. Filled black symbol, affected with cancer; black arrow, index case. Ages at information gathering or at death, when available, are indicated on the top-right corner, and ages at cancer diagnosis, after tumor type. +/- depicts heterozygous carrier status of the corresponding *HDAC10* variant.

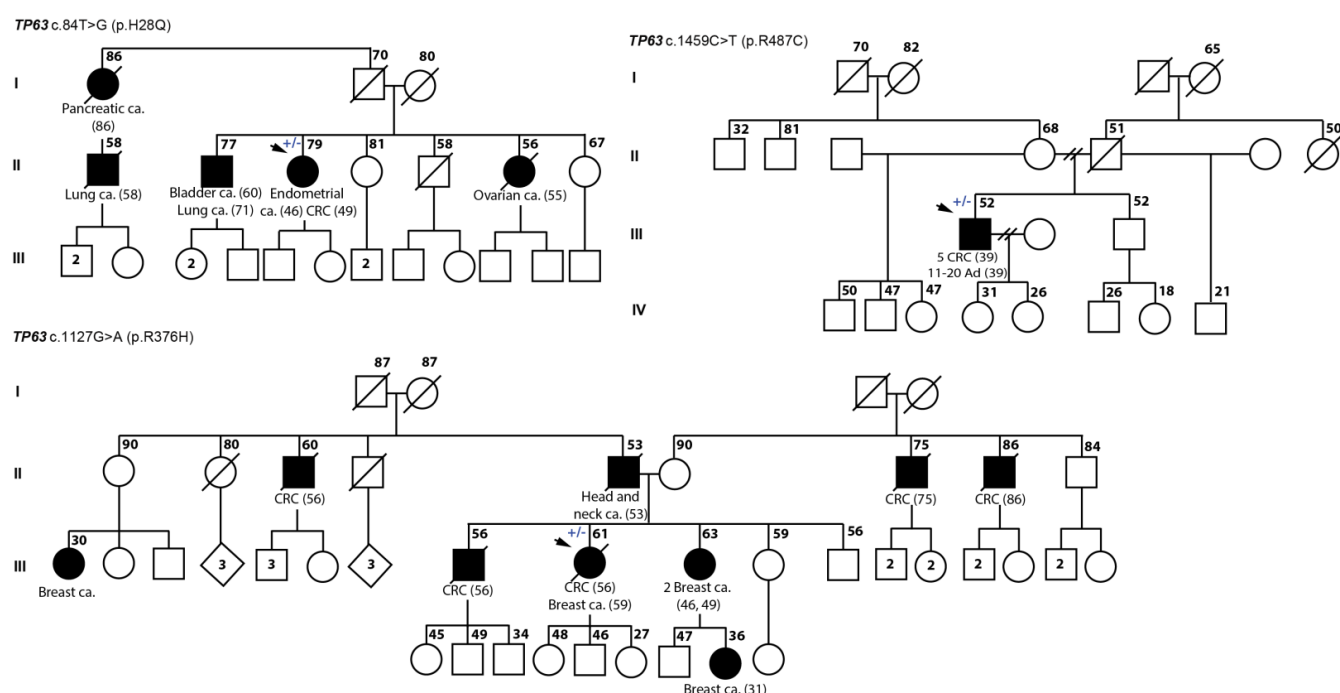


**KRT24 c.449G>A (p.R150H)****KRT24 c.1096C>T (p.R366C)****KRT24 c.1096C>T (p.R366C)****KRT24 c.1096C>T (p.R366C)**



**Figure S3.** Pedigrees of the families carrying *KRT24* rare germline variants from the cohort analyzed in the current study. Filled black symbol, affected with cancer; black arrow, index case. Ages at information gathering or at death, when available, are indicated on the top-right corner, and ages at cancer diagnosis, after tumor type. +/- depicts heterozygous carrier status of the corresponding *KRT24* variant.





**Figure S4.** Pedigrees of the families carrying *TP63* rare germline variants from the cohort analyzed in the current study. Filled black symbol, affected with cancer; black arrow, index case. Ages at information gathering or at death, when available, are indicated on the top-right corner, and ages at cancer diagnosis, after tumor type. +/- depicts heterozygous carrier status of the corresponding *TP63* variant.

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