**Supplementary Material - Case Descriptions:**

**Family A** (Figure 1, Pedigree 1)**:** The proband is an Ashkenazi-Jewish female, diagnosed at age 40-50 years with eight 1-2cm adenomatous polyps in the cecum. Colonoscopy performed two years later detected 25mm and 35mm adenomas, one with a villous component. Subsequent endoscopy revealed gastric hyperplastic polyps. In addition, 22mm pancreatic head side-branch intrapapillary mucinous neoplasm (SB-IPMN) was detected on abdominal MRI. Family history (first and second-degree relatives) was negative for polyposis or gastrointestinal (GI) cancer. Multigene panel analysis of 72 hereditary cancer-related genes (GGA Genetic Center, Israel, see supplementary table 1) detected a *SMAD4* heterozygous stop codon in exon 2: c.403C>T, p.R135\*. This pathogenic variant was excluded in the proband's three children, brother and sister, and given no family history of GI cancers, it could have occurred de-novo.

**Family B** (Figure 1, Pedigree 2): The proband is a Sephardic-Jewish female, diagnosed at age of 40-50 years with left-sided CRC, and few years later she had a 3mm adenoma in the left colon. Multigene panel analysis of 30 hereditary cancer genes (Color Genomics, California, supplementary table 1) detected a heterozygous silent variant of BMPR1A: c. 675G>A, p.L225=. The proband's sister, who carry the same genetic variant had two small colorectal adenomas between at age < 50 years. The probands' other sister, her brother, and her children tested negative for this variant and did not have any colonic polyps on colonoscopy. The proband's deceased mother, maternal aunt, and maternal cousin were diagnosed with CRC at ages 50-70 years but were not tested genetically.

 **Family C** (Figure 1, Pedigree 3): The proband is a Sephardic-Jewish male (of Moroccan ancestry) with >40 cumulative adenomas and dozens of hyperplastic polyps throughout the colon, diagnosed since at age 20-30 years. He undergoes colonoscopy at intervals of every 6 months. No polyps were detected in his upper GI endoscopies. The probands' mother had colon cancer at age 33 years and his brother at age 28 years. The probands' daughter had juvenile polyps at the age of 22 years. Genetic analysis in the proband (and in his daughter) detected the genomic deletion of exons 1-13 of the *BMPR1A* gene (Trusight multigene panel). The probands' son had normal colonoscopy at the age of 41 years, yet appeared to be a carrier of the familial *BMPR1A* genetic variant.

**Family D** (Figure 1, Pedigree 4): The proband is a Sephardic-Jewish female (of Bukharian ancestry) who had >30 colorectal adenomas at age 20-30 years. Upper GI endoscopies did not detect any gastric polyps. Multigene panel analysis of 54 hereditary cancer-related genes detected a deletion of exons 3-13 in the *BMPR1A* gene. The probands' sister, who is in her thirties, appeared not to carry the *BMPR1A* genetic variant and had a normal colonoscopy. Other family members who had multiple colorectal adenomas, were not yet tested for this familial *BMPR1A* pathogenic copy number variation.

**Family E** (Figure 1, Pedigree 5)**:** The proband is an Ashkenazi-Jewish male, diagnosed with rectal adenocarcinoma at age 30-40 years and concomitant dozens of 0.5-10mm sessile polyps throughout the colon. Polyps' histology showed multiple tubular adenomas with low grade dysplasia. The patient underwent total proctocolectomy with ileal pouch anastomosis with no recurrent polyps in six subsequent annual colonoscopies and three upper endoscopies. Following his diagnosis, all his first degree relatives underwent colonoscopies with no findings of colonic polyposis or malignancies in neither of them. Multigene panel analysis of 72 hereditary cancer-related genes, including *APC*, *MUTYH, MSH2, MSH6, PMS2, MLH1, BMPR1A* and *SMAD4*, *POLD1, POLE, GREM1, MSH3, NTHL1* did not reveal any variant of known clinical significance (GGA Genetic Center, Israel, supplementary table 1). Re-analysis of raw sequencing results (VCF format) by bioinformatic software (Geneyx) revealed an heterozygote variant of unknown significance (VUS) in *SMAD4*: c.746A>C, p.Q249P. Segregation analysis showed that this variant was inherited from the proband's mother. The proband's maternal grandmother and grandfather had colon cancer at age 60 years and gastric cancer (age unknown) respectively. The maternal aunt died at her twenties from cancer of unknown origin**.**

**Family F** (Figure 1, Pedigree 6)**:** The proband is an Ashkenazi-Jewish female, having dozens of adenomatous polyps since age 10-20 years and underwent total proctocolectomy with ileal pouch anal anastomosis before age 20 years. Her paternal grandfather, father, brother, and sister died from colorectal cancer (CRC) at ages 20-40 years. Multigene panel analysis of 36 hereditary cancer-related genes (Ambry Genetics, California, supplementary table 1), detected a missense variant in exon 4 of the *BMPR1A* gene: c.388T>C, p.R130C (Heterozygote). This variant was detected in the proband's deceased sister who had CRC and in one of her children (the proband's nephew) who had colorectal adenomatous polyps at age 12 years. The proband had preimplantation genetic diagnosis, with the birth of two healthy noncarrier children.

**Family G** (Figure 1, Pedigree 7): The proband is an Ashkenazi-Jewish male. At age 40-50 years, he was diagnosed with right-sided CRC and ~10 concomitant right-sided adenomatous polyps. He underwent subtotal colectomy with no recurrence of polyps in follow-up colonoscopies and upper GI endoscopies. The probands' father, identical twin brother, and sister who had also CRC, and his nephew all had colonic polyposis, detected before age 40 years. Multigene panel analysis of 72 hereditary cancer-related genes (GGA Genetic Center, Israel, supplementary table 1), found two heterozygous variants of unknown significance: *BMPR1A*: c.760C>T, p.R254C, and FANCl: c.1856T>A, p.L619Q. Only the *BMPR1A* variant co-segregated with all of the aforementioned family members. Two younger nephews (ages less than 30 years) also carry the *BMPR1A* variant, but currently show no colorectal polyps.

**Family H** (Figure 1, Pedigree 8): The proband is an Ashkenazi-Jewish female diagnosed with >50 adenomatous polyps throughout the colon, at age of 50-60 years. At age 63 years she was diagnosed with ampullary carcinoma and underwent a successful pancreaticoduodenectomy. Her father and paternal grandfather had CRC at age 60-70 years. Whole exome sequencing detected a heterozygous missense variant in the *BMPR1A* gene: c.676G>T, p.V226F. Segregation analysis was not available in this family.