Adenomatous Polyposis Phenotype in *BMPR1A* and *SMAD4* Variant Carriers

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INTRODUCTION: **Variants in *SMAD4* or *BMPR1A* cause juvenile polyposis syndrome, a rare autosomal dominant condition characterized by multiple gastrointestinal hamartomatous polyps. A phenotype of attenuated adenomatous polyposis without hamartomatous polyps is rare.**

METHODS: **We describe a retrospective cohort of individuals with *SMAD4* or *BMPR1A* heterozygous germline variants, having ≥10 cumulative colorectal adenomas and/or colorectal cancer without hamartomatous polyps. All individuals had multigene panel and duplication/deletion analysis to exclude other genetic syndromes.**

RESULTS: **The study cohort included 8 individuals. The pathogenic potential of the variants was analyzed. Variants detected included 4 missense variants, 1 nonsense variant, 1 splice site variant, and 2 genomic deletions. Features of pathogenicity were present in most variants, and cosegregation of the variant with polyposis or colorectal cancer was obtained in 7 of the 8 families. Three of 8 individuals had colorectal cancer (age less than 50 years) in addition to the polyposis phenotype. Two individuals had extraintestinal neoplasms (pancreas and ampulla of Vater).**

DISCUSSION: **The clinical phenotype of *SMAD4* and *BMPR1A* variants may infrequently extend beyond the classical juvenile polyposis syndrome phenotype. Applying multigene panel analysis of hereditary cancer-related genes in individuals with unexplained polyposis can provide syndrome-based clinical surveillance for carriers and their family members.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A869, http://links.lww.com/CTG/A870

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INTRODUCTION

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant condition, affecting approximately 1:100,000 individuals (1,2). It is characterized by multiple gastrointestinal (GI) hamartomatous polyps. Individuals with JPS are at increased risk of colorectal, gastric, and small bowel cancers (3,4). JPS is clinically diagnosed in an individual with any of the following: (i) ≥5 colorectal juvenile polyps, (ii) juvenile polyps in other parts of the GI tract, or (iii) any number of juvenile polyps and ≥1 affected family member.

Up to 60% of individuals with clinically defined JPS carry variants in *SMAD4* or *BMPR1A* genes (5,6), encoding 2 members of the transforming growth factor beta (TGF-β) superfamily signaling pathway. Approximately 20%–50% of JPS cases have no family history and may harbor *de novo* variants (7–10). On the other hand, approximately 80%–90% of the individuals having multiple colorectal adenomas (20–100 cumulative colorectal adenomas) remain genetically unsolved by testing the major high predisposition genes *APC* and *MUTYH* (11,12).

Interestingly, variants in *SMAD4* and *BMPR1A* are also associated with a clinical picture of hereditary mixed polyposis syndrome characterized by adenomatous, serrated, and juvenile polyps (7,13–15). Sporadic observations suggest that individuals with *SMAD4* or *BMPR1A* variants may also have otherwise unexplained attenuated adenomatous polyposis with no juvenile polyps (16,17). We describe the clinical and molecular phenotype of a small cohort of individuals with variants in *SMAD4* or *BMPR1A* genes and adenomatous polyposis without juvenile polyps.

METHODS

This retrospective cohort study included individuals heterozygous for genetic variants in *SMAD4* or *BMPR1A*, with multiple

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(≥10) cumulative colorectal adenomas or colorectal cancer (CRC), but without juvenile polyps. Individuals were followed over a period of 13 years (2009 until 2021) in 3 tertiary academic centers in Israel. Institutional review board approval was obtained in each center.

Individuals underwent upper and lower GI endoscopy, and polypectomy was performed as indicated. Polyp histology was reviewed by experienced GI pathologists in each of the medical centers, and juvenile polyp pathology was excluded in all cases.

Genetic evaluation was performed in all individuals. Genomic DNA was extracted from whole blood using a dedicated kit (5 PRIME, Gaithersburg, MD, ArchivePure) as instructed by manufacturer guidelines. Multigene panel analysis of hereditary cancer-related genes (testing 31–123 genes including *APC*, *MUTYH*, *MSH2*, *MSH6*, *PMS2*, *MLH1*, *BMPR1A*, *SMAD4*, *STK11*, *PTEN*, *POLD1*, *POLE*, *GREM1*, *MSH3*, *NTHL1*) was performed in certified genetic laboratories. The genes included in the panels are listed in Supplementary Table 1 (see Supplementary Digital Content, http://links.lww.com/CTG/A870). Segregation analysis results were available for 7 of the 8 families.

Each genetic variant was evaluated and classified according to the American College of Medical Genetics and Genomics (ACMG) guidelines (18). In addition, missense variants were introduced to the SWISS-MODEL algorithm (www.swissmodel.expasy.org/interactive), to evaluate their effect on the protein secondary structure. This effect was evaluated by comparing the predicted protein structure of the variants to those of the canonic wild types (NP_005350.1 for *SMAD4* and NP_004320.2 for *BMPR1A*).

RESULTS

Clinical characteristics

Registries from 3 medical centers of individuals with variants in *SMAD4* or *BMPR1A* revealed 8 individuals fulfilling inclusion criteria. Table 1 lists demographic data, clinical phenotypes, genetic findings, and variant classification.

Clinically, 3 individuals had early-onset (age less than 50 years) CRC; 2 were left-sided and 1 right-sided. Two of these individuals had first-degree and second-degree relatives with CRC. In the 5 individuals without a personal history of CRC, 4 had ≥1 first-degree relative with CRC. Extraintestinal neoplasms were detected in 2 individuals and included an ampulla of Vater carcinoma in a *BMPR1A* variant carrier (individual 6) and a pancreatic side-branch intraductal papillary mucinous neoplasm (SB-IPMN) in a *SMAD4* variant carrier (individual 2). The phenotypes and segregation analysis of each family are described in detail in the Supplementary File (see Supplementary Digital Content, http://links.lww.com/CTG/A869).

Genetic findings

Six individuals carried a heterozygous single-base variant: 2 in *SMAD4* (1 missense and 1 nonsense) and 4 in *BMPR1A* (3 missense variants and 1 splice site variant). Two individuals had genomic deletions encompassing *BMPR1A* exons 1–13 and exons 3–13, respectively. The 8 pedigrees are presented in Figure 1.

All detected missense variants replace a conserved nucleic acid (with positive phyloP100way scores). Seven of the 8 individuals had no genetic variant in any other hereditary cancer-related gene. One individual (pedigree 7, Supplementary File [see Supplementary Digital Content, http://links.lww.com/CTG/A869]) carried an additional genetic variant in *FANCI* (c.1856T>A, p.L619Q), which is associated with Fanconi anemia, a recessive syndrome not associated with a risk for colorectal polyps. This variant did not cosegregate with the affected individuals in the extended family, and we, therefore, considered it to be an incidental finding.

The *SMAD4* c.403C>T, p.R135* variant (individual number 1) causes a premature stop codon (PVS1 by the ACMG criteria) and, therefore, is classified as a pathogenic variant. In addition, this variant was not found among 141,456 normal adult exome and genome sequencing samples in the Genome Aggregation Database (gnomAD; https://gnomad.broadinstitute.org).

BMPR1A: c.675G>A, p.L225= (individual number 2) is a synonymous inherited variant, located in the donor canonic splice site (−1) of exon 8. Therefore, it is predicted to affect the splicing process and is accordingly classified by varSEAK (https://varseak.bio) as class 4. This tool also recognizes a potential alternative splicing site in the intron, 30 nucleotides downstream of the 5' splice site position 675 + 1. In accordance, the combined annotation-dependent depletion (https://cadd.gs.washington.edu/snv) scaled score is 22, placing this variant among the 1% most deleterious variants in the human genome. This is further supported by a Transcript-inferred Pathogenicity score of 0.998 of 1. As expected, this nucleotide location is very conserved (genetic resources and enhancement program score = 5.51). All this *in silico* evidence fulfills PP3 ACMG criteria. In addition, this variant is not found in any healthy population (gnomAD), supporting PM2 criteria. It was recently reported in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar) by just a single submitter with no linked publication. Segregation of this variant in the family fulfills PP1 ACMG criteria for pathogenicity.

Individuals 3 and 4 were carriers of inherited copy number variations in *BMPR1A*. Individual number 3 had a deletion of exons 1–13 (with no boundaries defined). Individual number 4 had a deletion of exons 3–13 as part of the 429 kb deletion, encompassing 8 additional genes, downstream to *BMPR1A*, which has previously been reported as a common founder variant occurring in 1 of 124 Israelis of Jewish Bukharan origin, with a wide spectrum of clinical features (19).

Individuals 5–8, a were each found to carry a missense variant. The *SMAD4*: c.746A>C, p.Q249P variant (individual number 5) is classified by search engines Franklin (https://www.genoox.com) and VarSome (https://varsome.com) as a variant of unknown significance (VUS) and as a benign variant, respectively. However, this variant is rare in Ashkenazi population (0.18%) and causes a change in conserved amino acid (phyloP100way score 5.006) (https://gnomad.broadinstitute.org, https://genome.ucsc.edu). Furthermore, the SWISS-MODEL predicted an apparent difference in the protein structure between the wild type and the variant protein (Figure 2), supporting the suspected pathogenicity of this variant.

The *BMPR1A*: c.388T>C, p.C130R variant (individual number 6) is not found in the gnomAD database of healthy populations, fulfilling the PM2 criteria of ACMG. Cysteine at position 130 is located in a disulfide bond domain. Cysteine is a sulfur-containing nucleophilic amino acid, frequently involved in bonds with molecules. Thus, its replacement by arginine, which has different biologic characteristics, is predicted to affect protein function. The *BMPR1A* secondary structure is also predicted by the SWISS-MODEL to be affected (Figure 2). Indeed, the Rare Exome Variant Ensemble Learner (REVEL) is a method for predicting pathogenicity of missense variants . REVEL provides this variant with an almost maximal combined score of 0.973

Table 1. **Demographic, clinical phenotype, and genetic findings**

Patient no. (sex)	Origin	Age of onset (yr)	Clinical phenotype	Extraintestinal involvement	Surgical treatment	Genetic findings	Family history of colorectal cancer and colorectal polyposis	Familial cosegregation	Classification Verdict by: Franklin[a]; VarSome[b] Commercial laboratory
1 (female)	Ashkenazi Jewish	40–50	10 adenomas (right colon) + small gastric hyperplastic polyps	Pancreas SB-IPMN	None	*SMAD4* (NM_005359.6):c.403C>T p.R135*	No	*De novo*	Pathogenic; Pathogenic Pathogenic
2 (female)	Sephardic Jewish	40–50	Left-sided CRC + <10 adenomas	None	Left hemicolectomy	*BMPR1A* (NM_004329.3): c.675G>A p.L225=	First degree: CRC, polyposis Second degree: CRC	Yes	Likely pathogenic; Pathogenic Likely pathogenic
3 (male)	Sephardic Jewish	20–30	~40 adenomas (whole colon, advanced)	None	None	*BMPR1A* (NM_004329.3): del ex1-13 Chr10: 86875867–89041308[hg19]	First degree: CRC, polyposis Second degree: N/A	Yes	Pathogenic; Pathogenic Pathogenic
4 (female)	Sephardic Jewish	20–30	~20 adenomas (right colon)	None	None	*BMPR1A* (NM_004329.3): del ex3-13 chr10:88611882-89041308[hg19]	First degree: CRC, polyposis Second degree: CRC, polyposis	Unknown	Pathogenic; Likely pathogenic Pathogenic
5 (male)	Ashkenazi Jewish	30–40	Left-sided CRC + ~20 adenomas (whole colon, advanced)	None	Total proctocolectomy with IPAA	*SMAD4* (NM_005359.6): c.746A>C p.Q249P	Second degree: CRC, gastric carcinoma	Yes	VUS; Benign VUS
6 (female)	Ashkenazi Jewish	10–20	~20 adenomas (whole colon, advanced)	None	Total proctocolectomy with IPAA	*BMPR1A* (NM_004329.3): c.388T>C p.C130R	First degree: CRC Second degree: CRC	Yes	Likely pathogenic; VUS VUS
7 (male)	Ashkenazi Jewish	40–50	Right-sided CRC + 10 adenomas (ascending and transverse colon, advanced)	None	Subtotal colectomy	*BMPR1A* (NM_004329.3): c.760C>T p.R254C FANCI (MN_001376911.1): c.1856T>A p.L619Q	First degree: CRC Second degree: CRC	Yes No	VUS; VUS VUS VUS; VUS VUS
8 (female)	Ashkenazi Jewish	50–60	~20 adenomas (whole colon, advanced)	Papilla of Vater carcinoma	Whipple procedure	*BMPR1A* (NM_004329.3): c.676G>T p.V226F	First degree: CRC Second degree: CRC	Unknown	VUS; VUS VUS

CRC, colorectal cancer; IPAA, ileal pouch anal anastomosis; SB-IPMN, side branch intraductal papillary mucinous neoplasm; VUS, variant of unknown significance.
[a]Franklin: gene-specific artificial intelligence-based variant search engine, by Genoox.
[b]VarSome: the human genomic variant search engine.

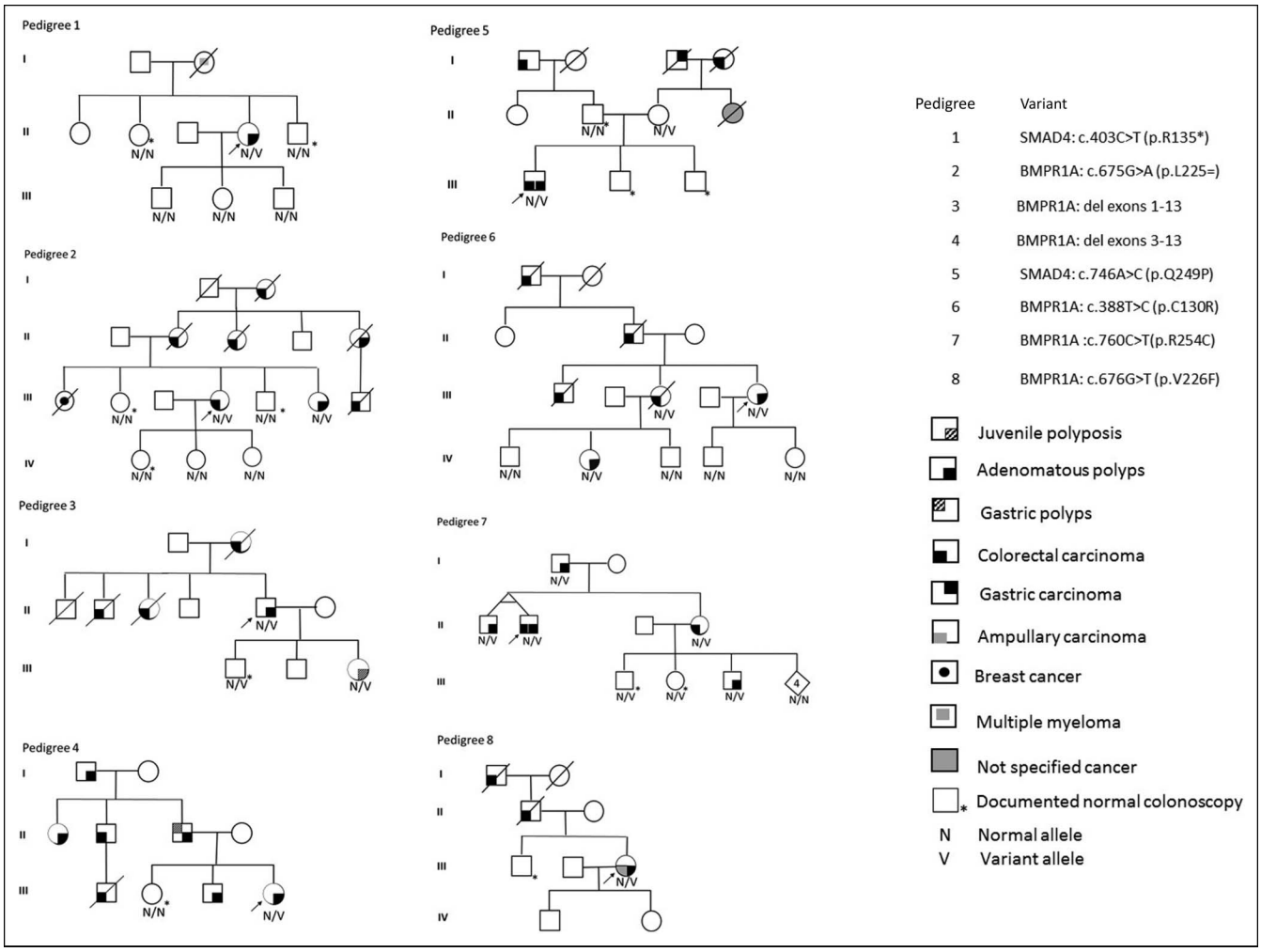

Figure 1. Pedigrees.

(range 0–1). In addition, the individual's family exhibited cosegregation of this variant with colonic polyposis/carcinomas. Therefore, based on this bioinformatic analysis, we predict the *BMPR1A*: c.388T>C, p.C130R variant as a likely pathogenic variant.

The *BMPR1A*: c.760C>T, p.R254C variant (individual number 7) is classified as VUS by both VarSome and Franklin engines. However, it is a rare alteration (0.086% in Ashkenazi Jews) that qualifies for ACMG PS4 criteria. Moreover, the variant is in the protein kinase domain, and its REVEL score is 0.721, which predicts pathogenicity. The SWISS-MODEL algorithm (included in the REVEL score ensemble) demonstrates an effect of this variant on the *BMPR1A* protein structure (Figure 2). These *in silico* tools fulfill the PP3 ACMG criteria. In addition, we found it to cosegregate with the polyposis and colorectal carcinoma phenotype in the family, thus fulfilling the PP1-supporting ACMG criteria for pathogenicity. Based on the combination of all these criteria, we predict this variant to be a likely pathogenic variant.

The *BMPR1A*: c.676G>T, p.V226F missense variant (individual number 8) did not affect the *BMPR1A* protein structure according to the SWISS-MODEL (Figure 2). There up-to-date 6 submissions of this variant to ClinVar, are all classified as VUS. However, 676 guanine is the first nucleotide in exon 9 and is highly conserved (Genetic Resources and Enhancement Program score 5.63). Its location within the acceptor splice site (+1) suggests a potential interruption of the splicing process by facilitating skipping of exon 9, which is highly expressed (proportion expressed across transcript score 0.80). Moreover, the distal 3' nucleic acid in exon 9 is included in the codon of the proximal 5' amino acid of exon 10; therefore, skipping exon 9 is expected to cause a frameshift in exon 10 (PM4 criteria). Accordingly, the varSEAK score of this variant is 4, indicating a likely splicing effect. In addition, this variant is extremely rare (8.36e-6 by gnomAD), supporting the PS4 criteria. Based on this interpretation, this variant is considered to be likely pathogenic.

DISCUSSION

Juvenile polyposis is characterized by colorectal hamartomas with or without adenomatous polyps. The small cohort presented here, with an atypical phenotype of multiple colorectal adenomas without juvenile polyps, further broadens the known clinical spectrum of *SMAD4* and *BMPR1A* variations. This phenotype is unique and dictates a thorough genetic workup to exclude other etiologies such as familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis. Bioinformatic analysis of the genetic variations in this cohort, some of which were novel, raises a

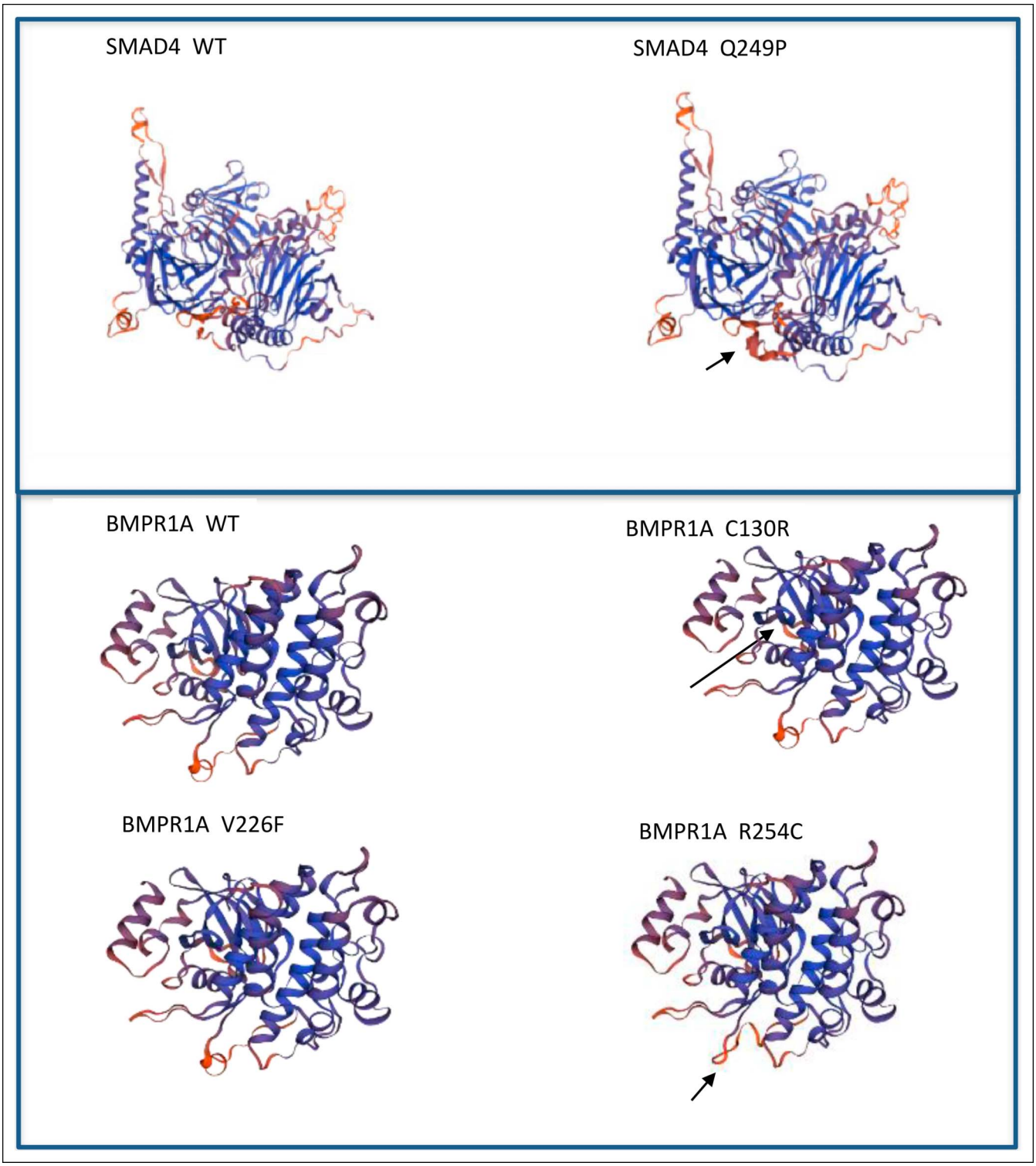

Figure 2. Comparison between local structure around the missense variant site and wild type protein, generated by Swiss-model repository online software.

suspicion for their pathogenicity based on their conservation, rarity, alteration of the protein structure or the splicing process, along with familial polyposis/CRC segregation analysis.

A review of the literature revealed rare reports of *SMAD4* or *BMPR1A* variant carriers presenting with multiple colorectal adenomas without evidence of juvenile polyps (14,16). Rohlin et al. (16) described 4 cases of FAP-like phenotype lacking an *APC* variant but with *BMPR1A* variants (3 cases) and a *SMAD4* variant (1 case). A retrospective cohort study of 221 patients with JPS from 10 European centers described adenomas or serrated polyps, in addition to multiple juvenile polyps, in 42%–50% of the cases (20). O'Riordan et al. (13) found that ~7%–14% of JPS

polyps harbored adenomatous changes; however, adenomas as the sole histology of multiple colorectal polyps were not mentioned in any of these patients. Gao et al. (8) reported a family with the *BMPR1A* variant and multiple juvenile polyps misdiagnosed as multiple adenomas. In our study, polyp histology in all 8 patients, initially reported to be adenomas, was revised by GI pathologists, and the diagnosis of adenoma was confirmed in all cases.

A retrospective study on a large European JPS cohort reported that 15.4% of the patients were diagnosed with cancer at a median age of 41 years (20). In our cohort of 8 individuals, there were 3 cases of CRC (ages 39 years in a *SMAD4* variant carrier and 43 years and 47 years in *BMPR1A* variant carriers). Interestingly, we report 1 *BMPR1A* variant carrier with an ampulla of Vater carcinoma at age 55 years. Whether the *BMPR1A* variant served as a driver variant or whether the cancer occurred sporadically is unclear because we were unable to perform somatic tumor genetic testing in this case. We also report a *SMAD4* variant carrier with pancreatic side-branch intraductal papillary mucinous neoplasm in addition to multiple right-sided colorectal adenomas. Because of these observations, we reviewed the medical history of additional patients in the JPS registry who did not fulfill the inclusion criteria for this study (57 patients). These patients did not have any pancreatic and/or ampullary abnormalities. In the European JPS cohort (20), a single case of pancreatic cancer was reported. A retrospective review of JPS from Japan reported extracolonic tumors in the stomach, jejunum/ileum, breast, and thyroid (21), and a prospective JPS study in the United States reported extracolonic tumors in the stomach, upper GI tract, and testicles (22). These studies (21,22) did not report pancreatic or ampullary cancers.

The TGF-β pathway is important in CRC progression. Bone morphogenetic proteins (BMPs) are a subgroup within the TGF-β superfamily. *BMPR1A* signals, through cell-surface serine-threonine kinase receptors, to the intracellular *SMAD4*, which accumulates in the nucleus to regulate gene expression. BMP acts as a tumor suppressor that promotes apoptosis of mature colonic epithelial cells; therefore, perturbations in BMP signaling may lead to increased tumorigenesis (23). Selective transgenic inhibition of BMP signaling in mice intestinal epithelium leads to epithelial branching and budding, crypt dilatation, and reactive inflammatory changes and the subsequent development of dysplastic foci and adenomatous change (15).

TGF-β signaling in humans plays a role in both adenoma and hamartoma formation and their progression to cancer. In the hamartoma-carcinoma sequence, BMP signaling affects the first step in the formation of dysplastic aberrant crypts (23), namely, the transition from normal epithelium to hamartomatous polyps, which is further transformed into an adenoma by a somatic *APC* variant. In the adenoma-carcinoma sequence, loss of BMP signaling correlates tightly with progression to cancer and occurs in the transition from early adenomas to advanced adenomas, with *BMPR1A* variants associated with early adenoma transformation and *SMAD4* variants associated with intermediate and advanced adenoma transformation (22). It remains unclear why most individuals with *BMPR1A* or *SMAD4* pathogenic variants exhibit a clinical phenotype of hamartomas while some develop adenomatous polyposis, even in the same family (Figure 1, Pedigree 4).

Strengths of this study are the use of multigene panel testing to rule out other unrecognized variants which might cause polyposis syndromes and the thorough clinical follow-up the individuals had at a tertiary care center. Limitations of this study are the small sample size, which is expected given the rarity of JPS and, more specifically, the unusual adenomatous polyposis phenotype in JPS. An additional limitation is the subset of individuals carrying a missense variant because pathogenicity was not entirely established. It is possible that a pathogenic variant in a gene yet to be discovered may contribute to the adenomatous polyposis phenotype and cancer described in these cases.

In conclusion, we describe an atypical clinical phenotype of *SMAD4* or *BMPR1A* variants, mimicking attenuated adenomatous polyposis syndrome. The use of multigene panel analysis of hereditary cancer-related genes in clinical practice helps achieve an accurate genetic diagnosis and allows specific syndrome-based clinical surveillance for variant carriers and their family members.

CONFLICTS OF INTEREST

Guarantor of the article: Guy Rosner, MD.

Specific author contributions: G.R. planned the study; acquired, analyzed, and interpreted study data; performed clinical follow-up of the study cohort; and wrote the manuscript. Y.P-.G. acquired, analyzed, and interpreted study data and wrote the manuscript. I.L., Z.L., R.K., H.S., and O.G. acquired study data and performed clinical follow-up of the study cohort. N.G. planned the study; acquired, analyzed, interpreted study data; and wrote the manuscript. All authors reviewed the manuscript and approved the final version.

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Data availability statement: All data analyzed during this study are included in this published article and its supplementary information files.

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Study Highlights

WHAT IS KNOWN

- ✓ Juvenile polyposis syndrome (JPS) is a rare autosomal dominant condition caused by *SMAD4* or *BMPR1A* mutations and characterized by multiple gastrointestinal hamartomatous polyps.
- ✓ A clinical phenotype of attenuated adenomatous polyposis without hamartomatous polyps is rarely described in JPS.

WHAT IS NEW HERE

- ✓ A small cohort of JPS individuals with a phenotype of attenuated familial adenomatous polyposis is described.
- ✓ Analysis of *BMPR1A* and *SMAD4* variations, including novel variants, suggests their pathogenicity based on a combination of bioinformatic and clinical tools.
- ✓ Applying multigene panel analysis of hereditary cancer-related genes provides syndrome-based clinical surveillance for the carriers and their family members.

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