Variable Features of Juvenile Polyposis Syndrome With Gastric Involvement Among Patients With a Large Genomic Deletion of *BMPR1A*

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OBJECTIVES: Loss-of-function mutations of *BMPR1A* cause juvenile polyposis syndrome (JPS), but large genomic deletions in *BMPR1A* are rare, reported in few families only, and data regarding the associated phenotype are limited.

METHODS: We investigated clinical features and genomic data of 7 extended seemingly unrelated families with a genomic deletion of the entire coding region of *BMPR1A*. We defined mutation size, mutation prevalence, and tumor pathogenesis using whole-genome sequencing, targeted genotyping, and haplotype analysis.

RESULTS: Patients with JPS from 7 families of Bukharin Jewish ancestry carried a deletion of 429 kb, encompassing the *BMPR1A* coding sequence and 8 downstream genes. Haplotype analysis and testing controls identified this as a common founder mutation occurring in 1/124 individuals of Bukharin origin. Tumor testing did not demonstrate loss of heterozygosity. Among carriers, JPS was almost fully penetrant, but clinical features varied widely, ranging from mild to very severe, including pan-enteric polyps, gastritis, and colorectal, esophageal, and testicular cancer, and carriers with phenotypes, which would not have raised suspicion of JPS.

DISCUSSION: The phenotype in this large cohort was extremely variable, although all carriers shared the same variant and the same genetic background. New observations include a preponderance of adenomatous rather than juvenile polyps, possible association with testicular cancer, and unexpected upper gastrointestinal involvement.

INTRODUCTION

Juvenile polyposis syndrome (JPS, OMIM 174900) is a rare autosomal dominant disorder, affecting between 1 in 100,000 and 1 in 160,000 (1), characterized by hamartomatous polyps and increased risk of gastrointestinal (GI) cancer. JPS is diagnosed clinically when a person has any one of the following: (i) more than 5 juvenile polyps of the colon or rectum; (ii) juvenile polyps in other parts of the GI tract; or (iii) any number of juvenile polyps and one or more affected family members (National Comprehensive Cancer Network [NCCN] guidelines) (2). Up to 60% of individuals with clinically defined JPS are now found to exhibit mutations in *SMAD4* or *BMPR1A* genes (3). JPS polyps are

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typically colonic with edematous, markedly inflamed lamina propria, with cystic dilation and smooth muscle proliferation. Although dysplastic polyps may appear with variable histology, one study reported "mixed polyposis syndrome" with polyps containing variable pathology of adenomatous, hyperplastic, and juvenile features caused by small base pair deletions in the *BMPR1A* gene (4); adenomas comprise less than 10% of JPS polyps (5).

JPS can involve the entire GI tract. Although colonic phenotype is similar between patients with *SMAD4* and *BMPR1A* mutations, upper GI and gastric polyposis is much more common in *SMAD4* mutation (1,6,7). As reported by Aretz et al. (6), *SMAD4* mutation carriers had a significantly higher frequency of gastric polyposis than did patients with *BMPR1A* mutations (83% vs 8%, respectively). All cases of gastric cancer occurred in families with *SMAD4* mutations (6,7).

Lifetime risk estimates of GI cancers, mostly colorectal cancer (CRC), are highly variable, ranging from 14% to 55% in different series (1,8,9). Although surveillance guidelines exist, the NCCN guidelines for surveillance recommend referral of patients with JPS to a specialized team due to the rarity of the syndrome and complexities of diagnosis and management (2).

The molecular alterations involved in polyp and tumor formation in JPS are attributed to defective BMP signaling, where aberrant BMP signaling disrupts stem cell self-renewal and differentiation, contributing to tumor formation (10). Loss of heterozygosity (LOH) was reported in half of *BMPR1A*-related polyps, compatible with *BMPR1A* acting as a tumor suppressor gene (11). However, *BMPR1A* LOH has not been documented yet in cancerous tumors.

Most pathogenic variants in *BMPR1A* are point mutations or small deletions. Large deletions of *BMPR1A* are rare, accounting for approximately 6% of cases, many of them are contiguous with *PTEN* (6,12–14). Contiguous gene deletions may lead to more pronounced manifestations; however, the rarity and variability of *BMPR1A* deletions not including *PTEN* have made genotype-phenotype relationships of large *BMPR1A* deletions difficult to assess (14).

We identified a deletion of the entire coding region of the *BMPR1A* gene among and investigated the clinical features in over 50 individuals from 7 unrelated families. This cohort enables expanding our knowledge about this rare predisposition syndrome.

METHODS

Patients were identified at 3 medical institutions in Israel. Clinical and pathology data were retrieved from medical records. This study was approved by the institutional review boards. The series of control patients genotyped for the deletion were Bukharin individuals referred for prenatal carrier screening or for genetic counseling due to other conditions.

Genetic testing

Testing for the founder deletion was performed either by multigene panels, chromosomal microarray analysis, or directed polymerase chain reaction (PCR) analysis as detailed below. Whole-genome approach chromosomal microarray analysis was performed using single nucleotide polymorphism–based array platforms (Illumina, San Diego, CA). BROCA multigene panel was used for testing for genes known or suggested to harbor mutations leading to solid tumors (15). Sequencing was performed, and variants were evaluated as previously described (16,17). Genomic deletions and duplications were identified by analysis of BROCA

sequence read depth (18). With the exception of the *BMPR1A* deletion, no potentially damaging variants were detected in any family in any of the 65 genes sequenced. Whole-genome sequencing: DNA (1 μg) from the proband of family 2 was sequenced to an average depth of 32x on a HiSeq X instrument. The fastq files were aligned to the hg19 reference gene using iSAAC v.01.15.02.08 (19), and copy number variations were called using Control-FREEC v6.4 (20). The breakpoints of *BMPR1A* copy number variations were identified by analysis of the split reads obtained by local realignment using Burrows-Wheeler Aligner-mem v0.7.12 (21) and visualization within integrative genomics viewer.

Directed PCR

Multiplex PCR was performed on whole blood genomic DNA using 2 primer pairs. One pair of primers that amplify a 541 bp inside the deletion area was used as the control amplicon of the wild-type allele, and second pair of primers flanking the deletion breakpoints, amplifying mutation-specific 359-bp fragment. The size of the deletion was determined by Sanger sequencing of the deletion junction in 2 affected individuals from 2 families.

Haplotype analysis

Six short tandem repeat (STR) markers that span a region of approximately 2.4 Mb flanking the deletion at 10q23.2 were used. The STR markers were used for PCR amplification of whole blood genomic DNA using fluorescently end-labeled primers and analyzed by capillary electrophoresis on a 3500 or ABI3130xl Genetic Analyzer using standard methods. We examined these STR markers in 7 individuals from 4 families and built the haplotype according to the mutation status of the family members. For 2 single affected individuals, it was not possible to reconstruct the haplotype with certainty, but we did see the allele sizes we expected, and haplotypes were built according to the hypothesis of a common mutation haplotype conservation.

LOH tumor testing was performed on 2 tumor samples (CRC from patient III-1 family 1 and testicular seminoma form patient III-5 family 2). The tumor area was identified by a pathologist on an hematoxylin & eosin slide. An appropriate region was selected from the corresponding unstained slide(s). Tumor cells consisted 60% of cells analyzed. DNA was extracted from formalin-fixed paraffin-embedded tumor and normal tissues using QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). The same STR markers used for haplotyping were used for haplotype comparison between normal and tumor tissue to check for LOH.

The standardized incidence ratios were computed as a ratio of observed to expected cancers. Person-years at risk were computed from date of birth up to December 31, 2015 (last date of follow-up) or the date of death for those who died of nonmalignant causes or the date of cancer diagnosis or total proctocolectomy. The expected number of malignancies was computed by applying the appropriate age and sex according to the tables of the Israeli cancer registry for CRC.

RESULTS

We report a genomic deletion of 429,426 bp (chr10:88,611,882-89,041,308 [hg19]), encompassing the entire coding region (exons 3-13) of *BMPR1A*, and the complete loci of 8 downstream genes. The deletion was heterozygous members from 7 families of Bukharin Jewish origin, who originate from a highly endogamous community in Central Asia for some 2,500 years. After the collapse of the former Soviet Union in 1991, most members immigrated to

the United States and Israel. Genomic analysis among mutation carriers revealed a shared haplotype of at least 2.4 Mb flanking the *BMPR1A* region, reflecting a founder mutation. The deletion was present in 1 of 124 adult Bukharin Jewish controls.

Loss of heterozygosity

LOH was assessed in a colorectal tumor from patient 1-III-1 and in a testicular seminoma from patient 2-III-5. Both *BMPR1A* alleles were present in both tumors.

Clinical presentation

Clinical presentations among mutation carriers varied widely, both with and among families (Figure 1 and Table 1).

Family 1. The proband (III-5) was diagnosed with CRC and multiple polyps at age 19 years. Tumor pathology showed adenocarcinoma with mucinous, tubular, and villotubular patterns with high cytological grade. Sampled polyps were first diagnosed as hyperplastic and adenomatous, but reclassified as JPS with dysplasia following genetic diagnosis. Four siblings also carry the deletion. Two siblings had multiple and 2 had few colonic polyps. The polyp pathology was JP in 3 siblings (as many as 100 polyps) and variable polyps in another with adenomatous, inflammatory, sessile serrated polyps seen. All had gastritis with one having fundic gland polyps. The proband's mother is not a carrier. No information is available about the father or his family members. Three carriers had capsule endoscopy without small bowel polyps.

Family 2. The proband (III-1) had multiple polyps at age 12 years, CRC at age 23 years, and testicular seminoma at 44 years. Gastroscopy showed chronic gastritis and a hyperplastic polyp. The proband's parents are first cousins, with relatives with polyposis, CRC, and other tumors throughout the family. Only his children were tested so far. The proband's son is a carrier, with few polyps, first diagnosed at age 14 years.

Family 3. The 75-year-old proband (II-2) had multiple polyps at the age of 20 years and underwent preventive colectomy at 25 years. Multigene testing detected the large deletion in *BMPR1A*. The proband's mother and 2 of her siblings died of CRC at ages 49, 38, and 63 years, respectively. Two of her sisters had had prophylactic colectomy in their 20s, but both succumbed to GI cancer, one had CRC and the other had esophageal cancer. The proband's siblings died by the time genetic diagnosis was possible, but most members from generation III and IV underwent targeted testing. All carriers had polyps. Number and age of polyp onset varied significantly; patient III-9 had multiple polyps and CRC, patient III-10 had multiple polyps and seminoma, and others (III-1 and III-2) had only few polyps by age 50 years. Upper GI findings included esophageal carcinoma, gastritis, gastric polyps, and a prepyloric polyp at the age 14 years (IV-7).

Family 4. The deletion was revealed incidentally in the proband (IV-1) when he underwent chromosomal analysis due to developmental delay. During genetic counseling, the father reported colonic polyps since childhood in his brother. The father, his brother, and their father carry the deletion. Endoscopy revealed multiple variable colonic polyps in all adult carriers.

Family 5. The proband (IV-4) had 8 juvenile polyps by age 18 years. His maternal grandparents are first cousins, with polyposis

and CRC reported from both sides of the family. His mother (III-4) had multiple colonic adenomas by age 30 years and multiple gastric and duodenal polyps of inflammatory and hyperplastic histology. Both the proband and his mother had gastritis negative for *Helicobacter pylori* (HP).

Family 6. The proband (III-1) had multiple juvenile polyps from age 8 years. Upper endoscopy revealed multiple gastric hyperplastic and inflammatory polyps and HP-negative chronic gastritis with intestinal metaplasia and foveolar hyperplasia. The proband's sister, age 44 years, is a carrier and has not yet had colonoscopy. Multiple polyps were reported in a maternal uncle and cousins, but none had genetic testing.

Family 7. The proband (IV-2) had multiple juvenile polyps diagnosed at age 16 years. His father, paternal aunt, and grandmother report multiple colonic polyps. No polyps on endoscopy or small bowel capsule. Two other relatives had CRC at young ages (Figure 1). None of them had genetic testing yet.

DISCUSSION

Describing multiple individuals (up to 50 individuals with polyposis) harboring the same *BMPR1A* mutation allows the delineation of features associated with a large *BMPR1A* deletion and assessment of phenotypic variability in carriers of the same mutation.

Clinical features were variable, with polyp burden differing by both age at diagnosis and histology. Several carriers had adenomatous and sessile serrated polyps, rather than classic juvenile polyps, allowing conclusive diagnosis of JPS only after genetic testing (3). CRC was diagnosed in 6/27 (22.0%) carriers; 3 carriers had undergone prophylactic colectomy. The youngest patient with CRC, at 19 years, had a severe phenotype, with multiple polyps, including high-grade dysplastic adenomatous polyps. The mean age at CRC diagnosis was 42.1 years ($\pm$14.0 years, range 19–63 years), with standardized incidence ratio 1.16 for males and 1.43 for females, comparable with previous reports (6). We were surprised by the finding of upper GI involvement, with polyps found in 7/18 patients (39%), including 2 at ages 12 and 18 years. One patient died of esophageal cancer. Gastritis was noted in 9/18 carriers whose stomachs were biopsied, with 3 of the 7 of the available HP test results being negative, and 1 patient was initially tested positive, then tested negative twice, but still had gastritis. The clinical significance in terms of gastric cancer risk and screening recommendations is unclear because cancer in JPS has been reported primarily among *SMAD4* carriers (1,5). Testicular tumors were reported in 2/17 male carriers (12%) from 2 different families. This could be incidental, but should be further explored, especially since sex-cord tumors have been reported in Peutz-Jeghers syndrome.

Phenotypic variability for JPS has been reported in the past; however, this is the largest cohort describing a single mutation with a similar genetic background, showing full penetrance but intra- and inter-familial nonallelic variability. The variability in cancer occurrence and age at onset could stem from differences in surveillance, but variation applies also for age and burden of polyps, with polyps detected in 5 children younger than 15 years. Possible explanations include modifying effects of other genes, differences in environmental exposures, and chance. Our finding of nonjuvenile polyposis both of the stomach and the colon may be important in understanding the molecular pathway of polyp
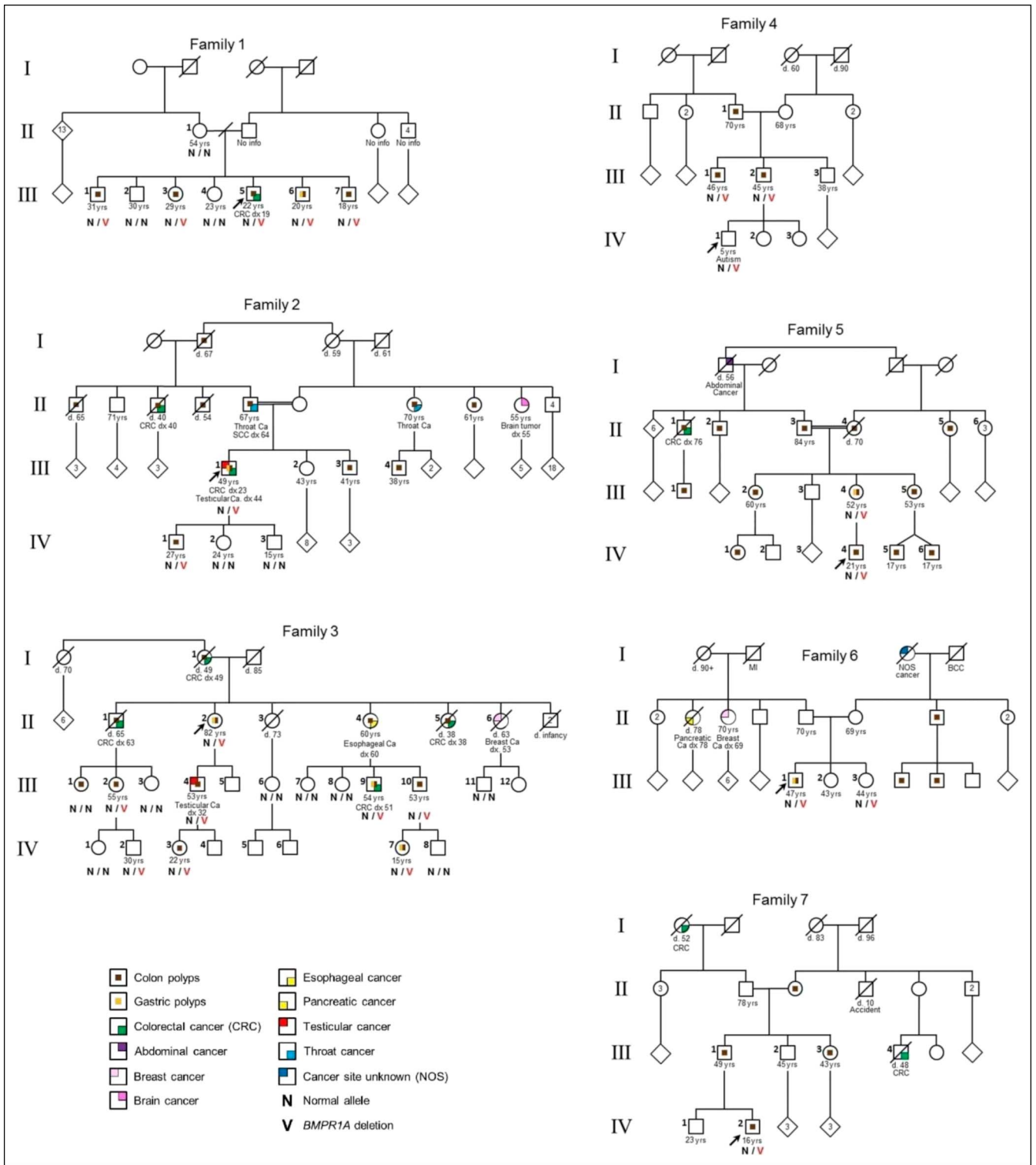
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Figure 1. Pedigrees of the 7 index individuals with the 429-kb deletion of BMPR1A germline mutation. The index persons are indicated by arrows (see main text and Table 1 for details). Circles represent females, and squares represent males. The age in years is at last contact, dx is age at cancer diagnosis, and d is age at death.

progression, as well as a clinical challenge in diagnosing carriers with JPS with predominance of polyps with nonjuvenile features.

Large gene deletions in cancer predisposition syndromes may be associated with more severe or earlier phenotypic onset, such

as MSH2-associated Lynch syndrome (22) and neurofibromatosis type 1 (23). For *BMPR1A* deletions, it has been suggested that the contiguous deletion involving *PTEN* is responsible for a more sever phenotype (14). The phenotypic variability shown in

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Table 1. Clinical features of carriers of the *BMPR1A* deletion

Patient	Sex	Age[a] (yrs)	Age at first polyp diagnosis (yr)	Colonic polyps at first screening (N)	Total colonic polyps (N)	Polyp histology	Upper GI	Preventive surgery	Cancers
Family 1									
Proband III5	M	22	19	Multiple[b]	Multiple	Multiple A, 2 HGD, 1H	Minimal chronic gastritis—inflammatory infiltrate and congestion. Gastroesophageal junction: moderate chronic inflammation including eosinophils. Focus of acinar pancreatic metaplasia CE: normal		Ulcerated CRC dx. 19 yrs
Proband III1	M	31	29	Multiple (~50)	Multiple	9A, 1H, 1SSA, 1I	Chronic gastritis HP positive. CE: normal		
Proband III3	F	29	27	4	4	J	NA		
Proband III6	M	20	18	Multiple (~50)	Multiple	J	Fundic gland polyps CE: normal	Prophylactic total proctocolectomy at 19 yrs: ~100 J polyps 0.4–4 cm	
Proband III7	M	18	16	7	19	J	Chronic gastritis HP negative		
Family 2									
Proband III1	M	49	12	NA	Multiple	J	2002: chronic gastritis 2005: chronic severe inflammatory infiltrate 2013: H polyp		CRC in situ dx. 23 yrs Testicular seminoma dx. 44 yrs
Proband IV1	M	27	14	3	8	4H, 1J (others NA)	NA		
Family 3									
Proband II2	F	82	20	Multiple	Multiple	A, J	Gastric H polyps	Prophylactic colectomy at 25 yrs	
Proband III2	F	55	50	2	2	A, H	NA		
Proband III4	M	53	18	Multiple	Multiple	NA	Mild chronic gastritis; HP positive		Testicular cancer dx. 32 yrs
Proband III9	M	54	49	Multiple	Multiple	A, J	1 H polyp		CRC dx. 51 yrs
Proband III10	M	53	30	Multiple	Multiple	A, J	Chronic gastritis HP positive		
Proband IV2	M	30	NA	NA	NA	NA	NA		
Proband IV3	F	22	14	1	2	J, H, I	Normal		
Proband IV7	F	15	12	2	2	J	1 Prepyloric I polyp		
Family 4									
Proband IV1	M	5	—	NP	NP	—	NP		

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Table 1. (*continued*)

Patient	Sex	Age[a] (yrs)	Age at first polyp diagnosis (yr)	Colonic polyps at first screening (N)	Total colonic polyps (N)	Polyp histology	Upper GI	Preventive surgery	Cancers
Proband II1	M	70	67	10	Multiple	J, H, I	Normal		
Proband III1	M	46	3	<10	<10	A (TVA with HGD)/H	Normal		
Proband III2	M	45	44	1	15	J, H	Normal		
Family 5									
Proband IV4	M	21	18	8	8	J	2014: chronic gastritis HP positive 2016, 2018 chronic gastritis HP negative		
Proband III4	F	52	30	Multiple	Multiple	A	Chronic active gastritis HP negative. Multiple H and I polyps; duodenal H polyps		
Family 6									
Proband III1	M	47	8	Multiple	Multiple	J with focal HGD and hamartomatous features	Chronic gastritis with intestinal metaplasia HP negative Multiple I and H polyps		
Proband III3	F	44	—	0 at 36 yrs[c]	—	—	NP		
Family 7									
Proband IV2	M	16	16	Multiple	Multiple	J, L	Normal CE normal		

A, adenomatous; CE, capsule endoscopy; CRC, colorectal cancer; F, female; GI, gastrointestinal; H, hyperplastic; HGD, high-grade dysplasia; HP, *Helicobacter pylori*; I, inflammatory; J, juvenile; L, lymphoid; M, male; NA, not available; NP, not performed; SSA, sessile serrated adenoma.
[a]Age at last follow-up or at death.
[b]Multiple ≥20 polyps.
[c]No colonoscopies after age 36 years.

here is not indicative for a more severe phenotype associated with a *BMPR1A* deletion.

Both *BMPR1A* alleles were present in the tumors tested. Blatter et al. (11) reported loss of *BMPR1A* wild-type allele in 5 of 9 juvenile polyps, but no loss in adenomas (11). Although other mechanisms of loss of function were not excluded, the presence of both *BMPR1A* alleles in the tumors suggests that, as with *SMAD4*, complete somatic loss of *BMPR1A* may not be required for *BMPR1A*-associated cancer.

In summary, among patients with genomic deletion of the *BMPR1A* gene, JPS was almost fully penetrant, but age at onset, polyp burden and histology, and cancer occurrence were highly variable, with unexpected upper GI involvement. These observations contribute to the clinical delineation of JPS. As the mutational spectrum of *BMPR1A* grows with increasingly widespread genetic testing, these observations can inform surveillance measures for carriers.

CONFLICTS OF INTEREST
Guarantor of the article: Yael Goldberg and S. Lieberman, PhD.
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