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ORIGINAL ARTICLE

Endoscopy and Procedures

Juvenile polyposis syndrome in children: The impact of *SMAD4* and *BMPR1A* mutations on clinical phenotype and polyp burden

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Abstract

Objective: A constitutional disease-causing variant (DCV) in the *SMAD4* or *BMPR1A* genes is present in 40%–60% of patients with juvenile polyposis syndrome (JPS). The aim of this study was to characterize the clinical course and polyp burden in children with DCV-positive JPS compared to DCV-negative JPS.

Methods: Demographic, clinical, genetic, and endoscopic data of children with JPS were compiled from eight international centers in the ESPHGAN/NASPGHAN polyposis working group.

Results: A total of 124 children with JPS were included: 69 (56%) DCV-negative and 55 (44%) DCV-positive (53% *SMAD4* and 47% *BMPR1A*) with a median (interquartile range [IQR]) follow-up of 4 (2.8–6.4) years. DCV-positive children were diagnosed at an older age compared to DCV-negative children [12 (8–15.7) years vs. 5 (4–7) years, respectively, $p < 0.001$], had a higher frequency of family

Abbreviations: DCV, disease-causing variants; EIM, extra-intestinal manifestations; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; GI, gastrointestinal; HHT, hereditary hemorrhagic telangiectasia; IQR, interquartile range; IRR, incidence rate ratio; JP, juvenile polyps; JPS, Juvenile polyposis syndrome; NASPGHAN, North American Society for Pediatric Gastroenterology, Hepatology and Nutrition; NCCN, National Comprehensive Cancer Network; VCE, video-capsule endoscopy.

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history of polyposis syndromes (50.9% vs. 1.4%, $p < 0.001$), experienced a greater frequency of extraintestinal manifestations (27.3% vs. 5.8%, $p < 0.001$), and underwent more gastrointestinal surgeries (16.4% vs. 1.4%, $p = 0.002$). The incidence rate ratio for the development of new colonic polyps was 6.15 (95% confidence interval 3.93–9.63, $p < 0.001$) in the DCV-positive group compared to the DCV-negative group, with an average of 12.2 versus 2 new polyps for every year of follow-up. There was no difference in the burden of polyps between patients with *SMAD4* and *BMPR1A* mutations.

Conclusions: This largest international cohort of pediatric JPS revealed that DCV-positive and DCV-negative children exhibit distinct clinical phenotype. These findings suggest a potential need of differentiated surveillance strategies based upon mutation status.

KEYWORDS

hamartomatous-polyp, JPS, pediatric

1 | INTRODUCTION

Juvenile polyposis syndrome (JPS) is a rare precancerous polyposis syndrome, characterized by the presence of multiple juvenile type hamartomatous polyps in the gastrointestinal (GI) tract. Disease-causing variants (DCV) in the *SMAD4* or *BMPR1A* genes, can be identified in up to 40%–60% of patients with JPS; approximately 25% of these are de novo.[1] The percentage of DCV-positive may rise to 95% when using wide polyposis panel and whole genome sequencing analyses (REF).

Such DCVs are inherited in an autosomal dominant manner. In the remainder, there is no clear genetic cause identified, even in those where there is a family history of JPS. In the absence of a DCV, JPS can be diagnosed on clinical grounds.[2]

In JPS, the polyps are located predominantly in the large bowel. They also commonly develop in the stomach, particularly in those who carry a *SMAD4* DCV.[3]

De novo JPS typically presents during childhood, with rectal bleeding or iron deficiency anemia.[2,4,5] Patients with JPS are at increased risk for GI malignancy, with an estimated cumulative lifetime risk of colorectal cancer of 38%–68%,[2,4] which can largely be mitigated by endoscopic surveillance.[6]

There are limited data on a genotype-phenotype correlation in JPS.[7] Patients with a *SMAD4* DCV are at a greater risk of severe gastric polyposis, gastric malignancy, and hereditary hemorrhagic telangiectasia (HHT).[3,8] Data on clinical and endoscopic differences between DCV-positive and DCV-negative patients with JPS are limited. Even though a recent cohort of adults and children with JPS demonstrated distinct phenotypic differences between DCV-positive and DCV-negative patients,[9] current surveillance guidelines are not personalized according to DCV status.[10,11]

Surveillance in polyposis syndromes aims to alleviate syndrome-related symptoms and to mitigate risk of malignancy and associated complications. While the current surveillance guidelines for JPS in children fail to differentiate between DCV-positive and DCV-negative patients,[12,13] the National Comprehensive Cancer Network (NCCN) has incorporated these differences in phenotypic presentation between DCV-positive and DCV-negative adult patients.[14] The current NCCN guidelines recommend considering increasing the interval of endoscopic surveillance of children with DCV-negative JPS to 5 years if no polyps are identified, whereas endoscopic surveillance of children with DCV-positive JPS is recommended every 1–3 years.

The primary objective of this study was to assess and compare the clinical phenotypes of children diagnosed with DCV-positive and DCV-negative JPS.

What is Known

- Juvenile polyposis syndrome (JPS) can be diagnosed based upon identification of a disease-causing variant (DCV) in the *SMAD4* or *BMPR1A* genes.
- These variants are identified in up to 40%–60% of the patients and inherited in an autosomal dominant manner.
- There are limited data regarding phenotypic differences based on the presence or absence of a DCV.
- Surveillance guidelines for JPS in children fail to differentiate between DCV-positive and DCV-negative patients.

What is New

- DCV-positive and DCV-negative children exhibit distinct clinical phenotypes.
- DCV-positive children have a higher burden of colonic polyps than DCV-negative children, suggesting the need for surveillance strategies based upon mutation status.

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A secondary objective was to characterize the burden of new colonic polyps in both groups throughout the follow-up period.

2 | METHODS

2.1 | Study design

This retrospective, multicenter cohort study was conducted at eight medical centers between 01/01/2021 and 31/10/2023. The study was approved by the Ethics Committee of the Tel Aviv Sourasky Medical Center (TLV-0804-20) and equivalent committees of all contributing centers. Informed consent was waived based upon its retrospective and anonymous design.

2.2 | Study population

Children and adolescents (<21 years of age) with a clinical or genetic diagnosis of JPS were included in this study. Retrospective data were collected from medical centers affiliated with the polyposis working group of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) or the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), anonymized and collated centrally for analysis. The clinical diagnosis of JPS was based upon the following criteria: five or more juvenile polyps (JP) of the colon or rectum or JP in other parts of the GI tract, or any number of JP and a positive family history.[2] Patients with the clinical diagnosis of JPS were included if genetic testing was available for presence of DCV mutations (DCV-positive) or absence of DCV mutations (DCV-negative) in the *SMAD4* and *BMPR1A* genes. Genetic analysis was performed according to the recommendation of the genetic counseling in each polyposis center. Patients without documented genetic testing and those with positive genetic findings of others polyposis syndromes were excluded, as were patients with extra-intestinal manifestations (EIM) consistent with *PTEN* hamartoma tumor syndrome.

2.3 | Data collection

The data collected included age at diagnosis, sex, family history of polyposis, mutation status, GI symptoms and EIM at presentation, laboratory measurements, past and present malignancy, findings of small bowel imaging by video-capsule endoscopy (VCE), use of chemoprevention (e.g., sirolimus), and need of polyposis-related surgery. Endoscopic data included the number and location of polyps at each endoscopic evaluation, polypectomies, number of polyps remaining after each colonoscopy, and the histological findings of resected polyps. Polyp burden was calculated as the number of new polyps (from first to last colonoscopy) divided by the number of years of follow-up.

2.4 | Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR). Categorical variables were presented as frequency and percentage and compared between patients with positive and negative mutations, and between patients with a mutation in the *SMAD4* gene compared to the *BMPR1A* gene by means of the χ^2 test or the Fisher's Exact test, as appropriate. Continuous variables were compared with the Mann–Whitney test. A negative binomial regression model was used to compare the number of new polyps during the follow-up and the total number of polyps between patients with positive and negative mutation, and between patients with a mutation in the *SMAD4* gene compared to the *BMPR1A* gene. The natural logarithm of the patients' ages at the last follow-up was used as the offset variable. All of the statistical tests were two-tailed. A $p < 0.05$ was considered statistically significant. SPSS (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) was used for all statistical analyses.

3 | RESULTS

3.1 | DCV-positive versus DCV-negative JPS

In total 135 children and adolescents with JPS were assessed. Eleven patients were excluded from the study: four due to incomplete genetic testing, four due to incomplete endoscopic data, and three due to a microdeletion which involved both *BMPR1A* and *PTEN*. The remaining 124 patients comprised the study cohort, and included 55 (44%) who were DCV-positive and 69 (56%) who were DCV-negative. The median (IQR) follow-up was 4 (2.8–6.4) years. Patients who were DCV-positive were older at presentation, were more frequently females, had a higher frequency of family history of polyposis syndromes, and a higher rate of EIM compared to those who were DCV-negative (Table 1). The clinical symptoms were comparable between the two groups with the exception of rectal bleeding, which was significantly more frequent in DCV-negative patients (92.8% vs. 56.4% in DCV-positive patients, $p < 0.001$). Failure to thrive was more frequent in DCV-positive patients (14.5% vs. 2.9% in DCV-negative patients, $p = 0.022$).

All children in the cohort underwent colonoscopies, and 61 of 124 (49%) children with available data

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TABLE 1 Demographic and clinical characteristics of the study cohort.

	DCV-negative, *N* = 69 (56%)	DCV-positive, *N* = 55 (44%)	*p*
Age at presentation, years (median, IQR)	5 (4–7)	12 (8–15.7)	<0.001
Males	49 (71%)	28 (50.9%)	0.022
Ethnicity			0.627
Caucasian	54 (78.3%)	41 (74.5%)	
Non-Caucasian	15 (21.7%)	14 (25.5%)	
Family history of polyposis syndromes			<0.001
JPS	0	28 (50.9%)	
Lynch syndrome	1 (1.4%)	0	
Clinical symptoms			
Abdominal pain	20 (29%)	20 (36.4%)	0.383
Rectal bleeding	64 (92.8%)	31 (56.4%)	<0.001
Diarrhea	6 (8.7%)	7 (12.7%)	0.467
Constipation	6 (8.7%)	3 (5.5%)	0.730
Vomiting	2 (2.9%)	3 (5.5%)	0.654
Failure to thrive	2 (2.9%)	8 (14.5%)	0.022
Growth retardation	1 (1.4%)	4 (7.3%)	0.170
Extra-intestinal manifestations	4 (5.8%)	15 (27.3%)	<0.001
Dermal	0	2 (3.6%)	0.195
Cardiac	2 (2.9%)	7 (12.7%)	0.036
HHT	0	6 (10.9%)	0.006
Skeletal	1 (1.4%)	3 (5.5%)	0.321
Neurological	1 (1.4%)	5 (9.1%)	0.087
Anemia (Hb <10 g/dL)	11 (15.9%)	16 (29.1%)	0.078
Hypoalbuminemia (albumin <34 g/L)	8 (11.6%)	9 (16.4%)	0.443
Presence of colonic polyps at presentation	69 (100%)	43 (78.2%)	<0.001
Total colonic polyps at presentation, *n*			<0.001
0	0	12 (21.8%)	
1–10	58 (84.1%)	29 (52.7%)	
11–25	11 (15.9%)	9 (16.4%)	
>25	0	5 (9.1%)	
Presence of polyps by location at presentation			
Right colon	32 (76.2%)	21 (67.7%)	0.424
Transverse colon	22 (52.4%)	16 (51.6%)	0.948
Left colon	36 (85.7%)	23 (74.2%)	0.217
Number of polyps by location at presentation			
Right colon	3 (2–5)	5 (2–9)	0.132
Transverse colon	2 (1–3)	4 (2–9)	0.110
Left colon	4 (3–6)	5 (3–10)	0.625
Follow-up duration, years (median, IQR)	4 (2.9–6.5)	3.7 (2.8–6)	0.697

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; JPS, juvenile polyposis syndrome.

underwent gastroscopies. Greater numbers of colonic polyps at presentation were more frequent in the DCV-positive group compared with the DCV-negative group ($p < 0.001$) (Table 1). The distribution of polyps within the colon was similar between the two groups (Table 1). While gastric polyps were detected in 34.6% of the DCV-positive patients, none were identified in the DCV-negative group ($p < 0.001$).

EIM were more commonly present in the DCV-positive group. The frequencies of the dermal, cardiac, skeletal and neurological EIM of the patients, as well as HHT, are presented in Table 1. Brain magnetic resonance imaging was performed in nine patients in the DCV-positive group, all without pathological findings.

None of the patients had small bowel polyps detected by endoscopy. Eighteen patients underwent small bowel assessment by VCE, 8 (11.6%) from the DCV-negative group and 10 (18.2%) from the DCV-positive group ($p = 0.301$). Small bowel polyps were detected by VCE in one DCV-negative patient and in five DCV-positive patients ($p = 0.094$). Small bowel enteroscopy was performed in one patient and showed no pathological findings.

3.2 | *SMAD4* versus *BMPR1A* Mutations

Among the 55 DCV-positive patients, 29 (53%) had a mutation in *SMAD4* and 26 (47%) had a mutation in *BMPR1A* (Table 2). While most of the demographic and clinical characteristics were comparable between the two study groups, anemia was more frequent in the patients with the *SMAD4* mutation (55.2% vs. 0% for the patients with *BMPR1A* mutation, $p < 0.001$) as well as the frequency of HHT (20.7% vs. 0% for the patients with *BMPR1A* mutation, $p = 0.024$). A higher frequency of gastric polyps was observed in the *SMAD4* group (55.3% vs. 9.1% for the patients in the *BMPR1A* group, $p = 0.004$).

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TABLE 2 Demographic and clinical characteristics of pediatric patients with a positive JPS mutations.

	SMAD4 mutations, *N* = 29 (53%)	BMPR1A mutations, *N* = 26 (47%)	*p*
Age at presentation, years (median, IQR)	13 (9–15.6)	9.3 (7.3–16.2)	0.489
Males	14 (48.3%)	14 (53.8%)	0.680
Ethnicity			0.316
Caucasian	20 (69%)	21 (80.8%)	
Non-Caucasian	9 (31%)	5 (19.2%)	
Family history of JPS	18 (62.1%)	10 (38.5%)	0.080
Clinical symptoms			
Abdominal pain	11 (37.9%)	9 (34.6%)	0.799
Rectal bleeding	18 (62.1%)	13 (50%)	0.368
Diarrhea	5 (17.2%)	2 (7.7%)	0.426
Constipation	1 (3.4%)	2 (7.7%)	0.598
Vomiting	3 (10.3%)	0	0.238
Failure to thrive	6 (20.7%)	2 (7.7%)	0.257
Growth retardation	2 (6.9%)	2 (7.7%)	>0.999
Extra-intestinal manifestations	10 (34.5%)	5 (19.2%)	0.205
Dermal	2 (6.9%)	0	0.492
Cardiac	5 (17.2%)	2 (7.7%)	0.426
HHT	6 (20.7%)	0	0.024
Skeletal	2 (6.9%)	1 (3.8%)	>0.999
Neurological	1 (3.4%)	4 (15.4%)	0.178
Anemia (Hb < 10 g/dL)	16 (55.2%)	0	<0.001
Hypoalbuminemia (albumin < 34 g/L)	7 (24.1%)	2 (7.7%)	0.149
Presence of colonic polyps at presentation	24 (82.8%)	19 (73.1%)	0.385
Total polyps at presentation, *n*			0.363
0	5 (17.2%)	7 (26.9%)	
1–10	14 (48.3%)	15 (57.7%)	
11–25	7 (24.1%)	2 (7.7%)	
>25	3 (10.3%)	2 (7.7%)	
Follow-up duration, years (median, IQR)	3.5 (3–6.3)	4.5 (2–5.8)	0.697

Abbreviations: HHT, hereditary hemorrhagic telangiectasia; JPS, juvenile polyposis syndrome.

3.3 | Outcomes

The incidence rate ratio (IRR) of the total number of colonic polyps for age was 1.657 (95% confidence interval [CI]: 1.135–2.420) in the DCV-positive group compared to the DCV-negative group ($p = 0.009$), with an average number of polyps of 2.7 versus 1.6 for every year of age, respectively. The IRR of new polyps detected during the follow-up was 6.149 (95% CI: 3.927–9.628) in the DCV-positive group compared to the DCV-negative group ($p < 0.001$), with an average number of polyps of 12.2 versus 2, respectively, for every year of follow-up. There was no difference in the IRR of the total or new polyps between patients with the *SMAD4* and those with the *BMPR1A* mutations.

One DCV-negative patient underwent surgery (1.4%) as did 9 (16.4%) DCV-positive patients ($p = 0.002$), at a median [IQR] age of 14.5 [8–15.8] years. Those operations included four total colectomies, three right hemicolectomies, one segmental colectomy due to high burden of polyps and uncontrolled bleeding and two appendectomies due to appendicular polyps caused severe right abdominal pain mimicking appendicitis. The surgical rate per year was 0.045 in the DCV-positive and 0.004 in the DCV-negative group. The median number of colonic polyps for age in patients that underwent surgery was 3.4 (0.9–3.9) compared to 1.5 (0.5–5.7) in patients that did not underwent surgery ($p = 0.389$). All nine operations in patients from the DCV-positive group were performed in the *SMAD4* group (31% vs. 0% for the patients with a *BMPR1A* mutations, $p = 0.002$).

None of the patients in this cohort were treated with sirolimus, and no malignancies or death were reported. Therefore, the carcinogenic risk was not assessed. A tubular adenoma with low-grade dysplasia was detected in one patient with a *SMAD4* mutation at the last follow-up.

4 | DISCUSSION

The results of this study including the largest, multicenter, international pediatric cohort to date revealed that the mutation status has a significant effect on the clinical phenotype of children and adolescents with JPS. Those who were DCV-positive exhibited distinct clinical features at presentation and follow-up compared to those who were DCV-negative. Notably, the burden of polyps was higher in patients from the DCV-positive group, as were EIM and the need for colonic surgery.

Our data demonstrated that DCV-positive patients presented at a significantly older age compared to DCV-negative (12 vs. 5 years, respectively). These differences are consistent with studies published by Sayed et al. (15 vs. 9 years), MacFarland et al. (18 vs. 5 years), and Papadopulos et al (21 vs. 13 years).[5,9,15] These findings are consistent even though 50% of the DCV-positive children had a family history of a polyposis syndrome, potentially increasing the awareness of JPS within this group. One feasible explanation is that unknown mutations in the DCV-negative group

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may predispose the patients to develop polyps earlier in life, possibly during the first decade of life.

We also demonstrated that rectal bleeding was a more frequent presenting symptom in the DCV-negative group. This observation aligns with our findings that all DCV-negative children presented with colonic polyps, compared to 78% of those in the DCV-positive group. This correlates with the higher frequency of positive family history in the DCV-positive group, reflecting the presymptomatic surveillance in this group. Another presenting symptom, failure to thrive, was more prevalent in the DCV-positive group. This observation could be attributed to either the delayed diagnosis within this group, the higher frequency of anemia, or to a potential systemic effect of these mutations on growth.

Children and adolescents within the DCV-positive group exhibited a significantly higher prevalence of EIM compared to those who were DCV-negative. This observation suggests that specific mutations in the *SMAD4* and *BMPR1A* genes may not only impact the GI tract, but also affect other organs. Consistent with our findings, and as noted by Latchford et al.,[6] vascular abnormalities were exclusively observed in children with *SMAD4* DCV-positive.

Gastric polyps were more predominantly observed in the DCV-positive group, also noted by MacFarland et al,[9] emphasizing the importance of comprehensive evaluation of the upper GI tract in DCV-positive patients.

The burden of colonic polyps during our follow-up period was significantly higher in DCV-positive patients compared to DCV-negative, with an average number of new polyps of 12.2 vs. 2, respectively, for every year of follow-up (IRR 6.149, 95% CI: 3.927–9.628, $p < 0.001$). This higher polyp burden suggests a more aggressive disease phenotype associated with known genetic mutations. This observation is consistent with those of previous studies, highlighting the association between specific gene mutations and disease severity in JPS.[9]

We also compared the phenotype of JPS between patients with *SMAD4* and *BMPR1A* mutations. While most of the demographic and clinical characteristics were similar between the two groups, anemia was more frequent in patients with the *SMAD4* mutations, suggesting potential variations in disease presentation, such as higher frequency of gastric polyps in patients with *SMAD4* mutations compared to those with *BMPR1A* mutations. HHT was observed only in the *SMAD4* mutations group (20.7% vs. 0 in the *BMPR1A* group. $p = 0.024$) consistent with previous reports.[6]

The need for surgical intervention was markedly elevated among the DCV-positive patients compared to DCV-negative (16% vs. 1.4%, respectively, $p = 0.002$) with higher surgical rate per year in the DCV-positive compared to the DCV-negative group. Although the need for surgery is generally very low among children with JPS, this exemplifies the more aggressive nature of the disease in this DCV-positive population, as was also noted by MacFarland et al. (33% vs. 3.1%, respectively, $p = 0.03$).[9] Notably, all operations in our DCV-positive group were performed in patients with *SMAD4* mutations, which may accentuate the potential impact of specific gene mutations on the long-term outcomes of JPS, particularly in the *SMAD4* subgroup.

While our study provides what we consider to be valuable insights into the clinical and genetic heterogeneity of JPS, several limitations should be acknowledged. Its retrospective design prevented standardized data documentation and collection. Data on the specific method of the genetic analysis was lacking. Following the report that higher percentage of DCV-positive, was detected when using whole genome sequencing (WGS), our study represents "real-life" where WGS in not performed as a standard of care (ref). Additionally, the lack of long-term follow-up data into adulthood precludes our ability to assess the natural history of JPS.

In conclusion, our study highlights the complex interplay between genetic mutations and clinical phenotypes in children with JPS, emphasizing the importance of including genetic factors in risk stratification and management decisions. The significantly higher burden of polyps that was detected in the DCV-positive group suggests the need for surveillance strategies based upon mutation status rather than employ a uniform strategy for all patients, with the ultimate target of improving diagnostic accuracy, therapeutic efficacy, and outcomes of children and adolescents with JPS.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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