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BMPR1A Specific Juvenile Polyposis Syndrome: A Case Series.

Nikolai Harroun[1,2], Kami Wolfe Schneider, MS, CGC[1,2], and Seth Septer, DO[1,2]
[1]Children's Hospital Colorado, Aurora, CO. [2] University of Colorado Anschutz School of Medicine, Aurora, CO.

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Introduction

Juvenile polyposis syndrome (JPS) is a rare condition affecting between 1 in 100,000 and 1 in 160,000 individuals.. It is defined by clinical criteria with any of the following: more than 5 juvenile polyps in the colorectum, multiple juvenile polyps throughout the GI tract, or any number of juvenile polyps and a family history of juvenile polyposis[1,2]. Pathogenic variants in the *SMAD4* gene are the most described molecular mechanism for JPS[3]. Pathogenic variants in other genes, such as *BMPR1A*, have also been associated with JPS but are not as well described. In a previous study, only around 60% of patients diagnosed with JPS have a confirmed pathogenic variant in *SMAD4* or *BMPR1A* identified and much of the literature on *BMPR1A* and the JPS phenotype is combined with patients with variants in the *SMAD4* gene[4].
Further evaluation of and long-term studies stratified by risks for different molecular findings may help clarify the most appropriate risks and management recommendations based on genotype. We collected the data of four patients diagnosed with JPS treated at Children's Hospital Colorado and the associated and identified pathogenic variants in *BMPR1A* via clinical evaluations. The aim of this study is to review the initial presentation and course of pediatric patients diagnosed with JPS due to pathogenic variants in *BMPR1A*.

More than 5 juvenile polyps of the colorectum
Multiple juvenile polyps throughout the GI tract
Any number of juvenile polyps and family history of juvenile polyposis

Table 1 : Jess Diagnostic criteria for Juvenile Polyposis Syndrome[1,2]

Methods

- Identified through clinical patient list at multidisciplinary polyposis program at Children's Hospital Colorado
- Chosen by clinical patient lists and identified *BMPR1A* gene variant
- Retrospective chart review completed including notes and images from procedures
- Patients following screening recommendation of surveillance every 1-3 years
- All data collected conducted under protocol approved by COMIRB

National Society of Genetic Counselors

Results

As part of their management at Children's Hospital Colorado, all patients were under continued surveillance with a gastroenterologist . All patients included in the study met a diagnosis of JPS. Below are summaries of the chart reviews of the 4 patients and their most recently updated clinical course.

	Age at First Colonoscopy	Age at First Polyp	Total # Polyps	Total Colonoscopies	Upper GI findings
Case 1	4	4	126	6	Normal
Case 2	10	10	36	3	H.pylori gastritis
Case 3	2	2	19	3	Normal
Case 4	17	17	106	4	Small intestine polyp, gastritis

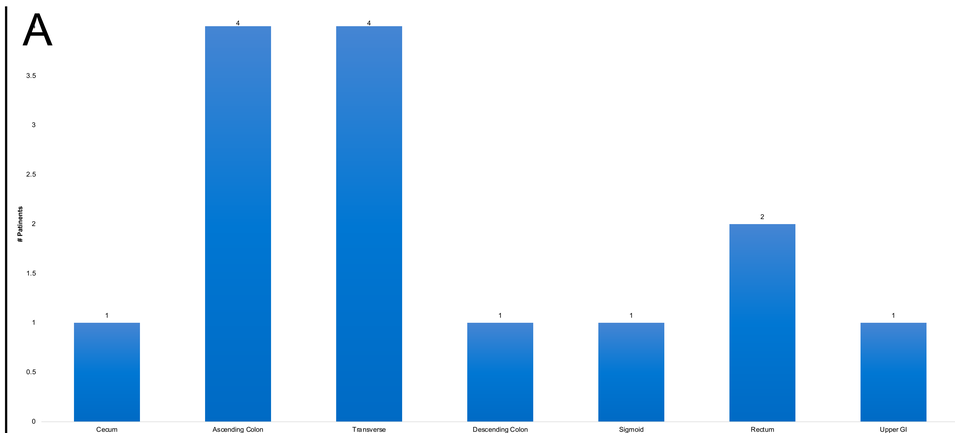
Table 2 : Overview of general information of BMPR1A mutation effected patients.

	Colon Cancer Family History	*BMPR1A* Mutation
Case 1	Positive	Splice Site Variant
Case 2	Positive, Mother = "Lynch Syndrome"	Nonsense Variant
Case 3	Positive, Maternal "FAP"	Nonsense Variant
Case 4	Negative	Frameshift Variant

Table 3 : Brief description of family history and *BMPR1A* mutations for each patient. Mutation description not further specified to protect patient identity.

Symptom	N (%)
Hematochezia	4 (100%)
Mucousy stools	1 (25%)
Diarrhea	1 (25%)
Fatigue	1 (25%)
Rectal Prolapse	1 (25%)
Cyclic vomiting	1 (25%)
Migraine	1 (25%)
Upper GI Polyps	1 (25%)

Table 4 : Symptomatic manifestations of JPS secondary to *BMPR1A* mutations.



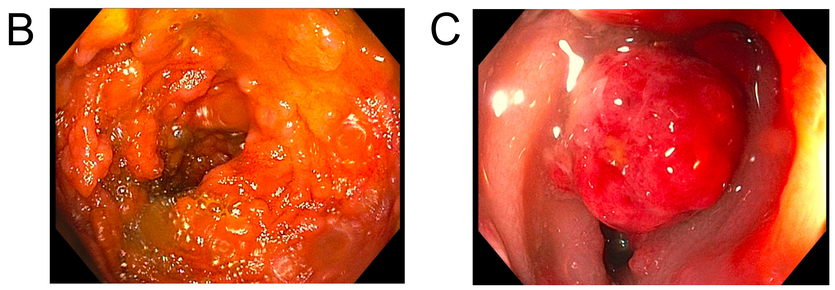


Figure 1: **A -** Location of polyps identified on various endoscopic evaluations by patient.
B - Image from Case 1 colonoscopy, sigmoid colon, identified as juvenile polyp
C - Image from Case 1 colonoscopy, sigmoid colon, identified as juvenile polyp

Discussion

Limitations :
- Small group of patients from one institution.

Conclusions :
- *BMPR1A* phenotype is different than *SMAD4* and should be better described.
- In our cases, three had family history of early colon cancer or JPS.
- Current screening protocols for those with positive family history may be too late for those with *BMPR1A* mutations.
- Earlier screening may be warranted.
- Phenotype varies in young patients.

Implications :
- Further evaluation of natural history of more patients/families with *BMPR1A* variants in indicated.
- With better understanding of *BMPR1A* related phenotypes as patients progress, surveillance recommendations can be modified.

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