

# Deletion within *SMAD4* Gene Cause JPS Resulting in Total Abdominal Colectomy with Ileorectal Anastomosis

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**Abstract:** *Juvenile polyposis syndrome (JPS) is an autosomal dominant disorder characterised by developed frequent benign gastrointestinal polyps from normal tissue that may transformed to malignancy. Here, we describe a patient with frequent bloody mucous diarrhea associated with lower abdominal pain and multiple variable sized polyps all over different segments of the colon. Molecular DNA sequencing revealed presence of a de novo heterozygous c.1245\_1248CAGA mutation that located within the highly conserved MH2 domain of the SMAD4 gene. Familial molecular analysis showed that both parents are not carrier for any mutation. Therefore, such molecular study is important in confirming the diagnosis of JPS and identifying patient who harboring SMAD4 mutation and at high risk in developing malignancy. Thus, appropriate surveillance management care may provide.*

**Keywords:** SMAD4, juvenile polyposis syndrome, *BMPRI1A*, autosomal

## 1. Introduction

Juvenile Polyposis Syndrome (JPS) (OMIM 174900) is a rare autosomal dominant disorder that is characterized by recurrent multiple hamartomatous polyps in the gastrointestinal tract associated with severe diarrhea resulting into protein-losing enteropathy that leads to failure to thrive. JPS may be present with rectal bleeding, anemia or rectal prolapses. The patients with JPS are at high risk of developing cancer [1],[2]. In fact, males and females are equally affected with an estimated prevalence of 1 in 100,000 live births [3], [4]. Genetic studies have demonstrated that mutation within Mothers against decapentaplegic protein homolog 4 (*SMAD4*) [1] and bone morphogenetic protein receptor, type 1A (*BMPRI1A*) [5] genes are responsible for JPS. *SMAD4* and *BMPRI1A* genes were mapped on to the long arm of chromosome 18 (18q21.1) [1] and chromosome 10 (10q22.3) [6] respectively and both are required essentially for the normal signaling pathway of the transforming growth factor beta (TGF- $\beta$ ) superfamily [7].

## 2. Case Report

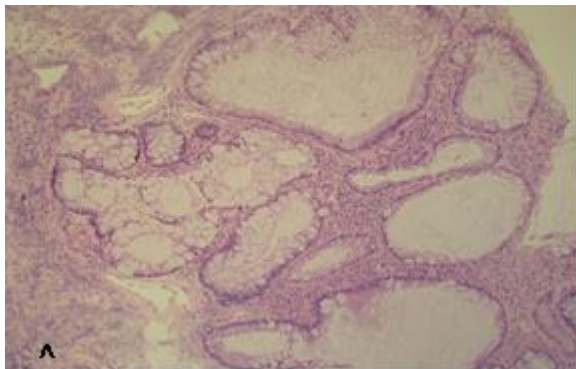
This boy was delivered via normal spontaneous vaginal delivery at term without any complication and with no history of any medication during pregnancy. His systemic examination was within normal. The birth weight was 2kg, below the 5<sup>th</sup> percentile; the length was 49cm, in the 5<sup>th</sup> percentile; and the head circumference was 33cm, at the 10<sup>th</sup> percentile. The baby had normal examination with no dysmorphic features noted.

At the age of three, he started to have bloody stool associated with lower abdominal pain but there was no diarrhea or vomiting. There was no known consanguinity among the parents and no family history of a similar presentation in his siblings. His vaccination was up-to-date. Colonoscopy was performed and four polyps were identified and removed.

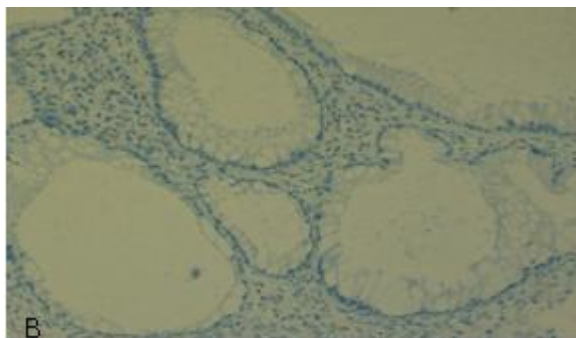
Three months later, two polyps were removed after repeated colonoscopy. At the age of four, he developed loose stools up to seven times per day. Later when his lower abdominal pain recurs, he went for colonoscopy and four polyps were removed. At the age of seven, he developed more frequent diarrhea with mucous and blood where then was referred to our tertiary health institute for further investigation.

According to his mother, he got easily tired and was losing weight. He also had occasional vomiting. Examination showed pale child, fingers clubbing but no edema or lymphadenopathy. His vital signs and growth were normal. Abdominal exam was soft non-distended with normal bowel sounds and no organomegaly. The rest of the examination was unremarkable. Upon presentation to our center, his laboratory investigation showed: hemoglobin 101, MCV 73, RBC 3.9 and platelet 625. Serum albumin was low at 21g/l.

In addition, serum electrolytes, liver enzymes and coagulation markers were normal. Stool was high for alpha 1-antitrypsin. Double contrast barium enema study revealed multiple variable sized polyps all over the different segments of the colon; some are pedunculated without bowel obstruction or stricture. Upper endoscopy was normal, however; lower colonoscopy showed >20 multiple polyps of different sizes (4mm-15mm) distributed along the colon. Histopathological studies on the resected polyps tissue were composed of varying degree of inflammatory and hyperplastic glandular changes (Figure 1).



**Figure 1(a):** Micrographs of juvenile polyp showing dilated crypts lined by benign epithelium with prominent goblet cells. The lamina propria shows inflammatory cells (H&E stain x100).



**Figure 1(b):** Micrographs showing negative immunostain for SMAD4 expression (IHC x100).

Furthermore, no adenomatous changes were seen in any of the resected polyps. These finding was consistent with retention juvenile polyposis and no evidence of metaplasia or malignancy.

Based on these constellations of data, for better management our patient went for laparoscopic assisted total abdominal colectomy with ileorectal anastomosis. He was discharged after recovery and he tolerated regular diet. As rectal

polyposis surveillances, he recommended for regular follow-up and lower endoscopy examination.

Blood samples were obtained from the patient with informed consent from her parents and healthy controls. Genomic DNA was extracted from peripheral blood leukocytes using standard techniques. The *SMAD4* gene was amplified by PCR and bidirectionally sequenced using an ABI Prism BigDye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) in an ABI 3130 Genetic Analyzer sequencer (Applied Biosystems). Mutations were identified by comparison to a reference sequence (GenBank Accession No. NM\_005359.5; <http://www.ncbi.nlm.nih.gov>) using CLC Genomics Workbench v4.0 (CLC bio, Aarhus, Denmark) and were checked against the updated SNP database (dSNPs; <http://www.ncbi.nlm.nih.gov>). *SMAD4* molecular mutation analysis of the patient revealed the presence of de nova heterozygous 4 base pair deletion mutation, (c.1245\_1248delCAGA) in exon 9 and causes a frame shift that creates a new stop codon at codon 435 (p.Asp415GlufsX20). This mutation was first reported in a patient with JPS which has been previously reported<sup>1</sup> as a common hotspot mutation<sup>[8]</sup> and up to our knowledge; this is the first report of such mutation in our community. Both parents are not carrier for this mutation.

### 3. Discussion

JPS is inherited via autosomal dominance due to loss-of-function mutations of the *SMAD4* gene, which belongs to a tumor suppressor gene and involves in the signal transduction on the (TGF- $\beta$ ) pathway and its ligands<sup>[7]</sup>. Therefore, *SMAD4* is required to regulate cell proliferation and the activity of certain genes. Studies have shown that mutation of *SMAD4* lead to production of abnormal protein (non-functional) where unregulated cell growth that resulting in polyps formation were associated with juvenile polyposis/hereditary hemorrhagic telangiectasia syndrome.

There are more than 80 mutations in the *SMAD4* gene reported within the Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff (<http://www.hgmd.cf.ac.uk/ac/index.php>). Molecular analysis revealed the presence of heterozygous (c.1245\_1248delCAGA) deletion mutation within the highly conserved MH2 domain of the *SMAD4* gene.

### 4. Conclusion

We conclude that this is the first report illustrating a de nova mutation in the *SMAD4* gene causing JPS in a Saudi patient and represents a majority of the spectrum of clinical signs shared with JPS cases. Such finding is important in providing insight into the underlining pathology of JPS where annual follow-up surveillance management care is recommended.

### 5. Acknowledgement

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## 6. Competing Interest

The authors declare no competing interests.

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## Author Profile

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