# Spectrum of Pathogenic Variants in the Juvenile Polyposis Genes *SMAD4* and *BMPR1A* Using a Multi-Gene Hereditary Cancer Panel

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## BACKGROUND

- Pathogenic variants (PVs) in *SMAD4* or *BMPR1A* are diagnostic of Juvenile Polyposis Syndrome (JPS), which is associated with a high risk of polyps and/or cancer in the digestive tract at a young age.
- Because JPS is rare, there is limited information available about the type and location of PVs identified in these genes.
- Here we review the PVs identified in *SMAD4* and *BMPR1A* as part of hereditary cancer testing.

## METHODS

- We assessed individuals who were tested with a 25- or 28-gene hereditary cancer panel between September 2013 and September 2017 and were found to carry a PV in *SMAD4* or *BMPR1A*.
- Individuals who were tested for a known familial mutation were not included.
- Clinical information was obtained from provider-completed test request forms, which included a check-box to indicate a history of polyps, but not specifically JPS.

## RESULTS

- In this time period, 31 different PVs in *SMAD4* and *BMPR1A* were identified in 45 individuals (Table 1).
- The age at testing was about 40 for both *SMAD4* and *BMPR1A* carriers (Figure 1).
- Colon polyps were diagnosed at an early age among *SMAD4* (25.5 years) and *BMPR1A* (29.5 years) carriers (Figure 1).
- The majority of PV carriers had a personal history of colon polyps and/or colon cancer (Table 2).

***Table 1. PVs Identified in JPS Genes***

| | *SMAD4* | *BMPR1A* | Total |
|---|---|---|---|
| **Different PVs** | 14 | 17 | 31 |
| **Novel PVs*** | 6 | 13 | 19 |
| **All Carriers** | 20 | 25 | 45 |

*Defined as PVs that have not been published.

***Figure 1. Median Age at Testing & Diagnosis***

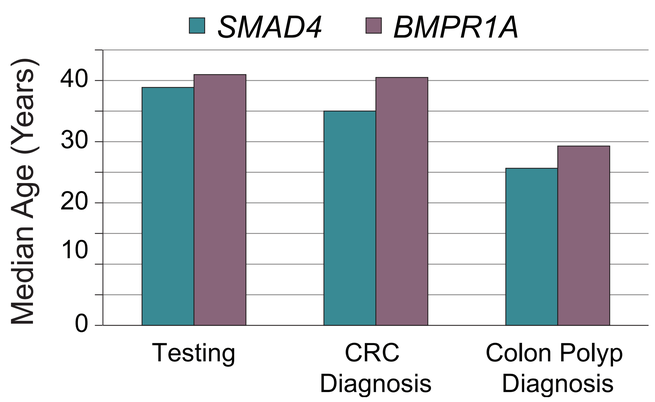
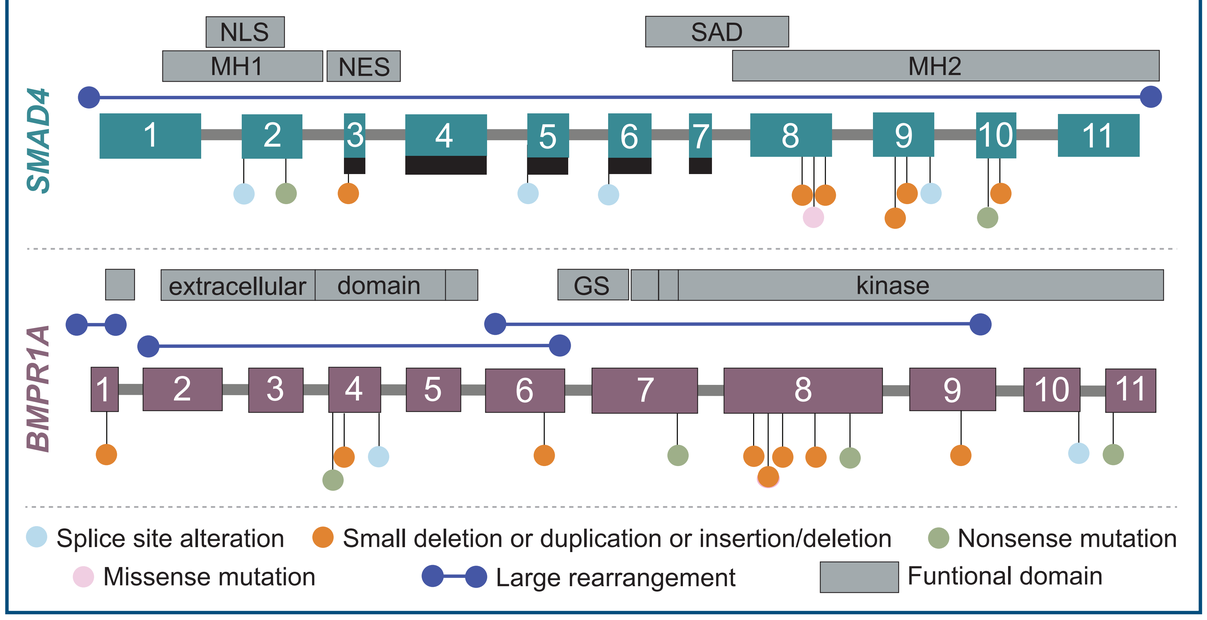



***Table 2. Personal Cancer History***

| | *SMAD4* (n=20) | *BMPR1A* (n=25) | Total (n=45) |
|---|---|---|---|
| **Personal History, N (%)** | | | |
| **Colon Polyps** | 14 (70.0%) | 16 (64.0%) | 30 (66.7%) |
| **Colon Cancer** | 9 (45.0%) | 10 (40.0%) | 19 (42.2%) |
| **Breast Cancer** | 2 (10.0%) | 3 (12.0%) | 5 (11.1%) |
| **Other Cancer** | 3 (15.0%) | 2 (8.0%) | 5 (11.1%) |
| **No Cancer** | 1 (5.0%) | 2 (8.0%) | 3 (6.7%) |

- The different PVs consisted of 14 deletions or duplications involving ≥1 nucleotide, 6 nonsense mutations, 5 splice site alterations, 4 large rearrangements, 1 missense mutation, and 1 insertion/deletion (Table 1).
- 19 novel PVs not previously reported were identified in 22 patients (Table 1).
- 8 PVs were identified in multiple unrelated individuals.
- PVs in the JPS genes were identified throughout the genes and in most important functional domains (Figure 2).

***Figure 2. Distribution of Pathogenic Variants in the JPS Genes***




## CONCLUSIONS

- The phenotype of *SMAD4* and *BMPR1A* PV carriers identified here was consistent with JPS, with the majority of carriers reporting a history of colon polyps and/or colon cancer at an early age.
- Hereditary cancer genetic testing has expanded upon the known mutation profile of PVs in the JPS genes.

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