Germline SMAD4 or BMPR1A Mutations and Phenotype of Juvenile Polyposis

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Background: Juvenile polyposis (JP) is an inherited condition predisposing to upper gastrointestinal (UGI) polyps and colorectal cancer. Two genes are known to predispose to JP, SMAD4 and bone morphogenetic protein receptor type 1A (BMPR1A). The object of this study was to determine the differences in phenotype of patients with SMAD4 or BMPR1A mutations (MUT+) compared with those without (MUT–).

Methods: DNA was extracted from 54 JP probands and used for polymerase chain reaction of all exons of SMAD4 and BMPR1A. Products were then sequenced and analyzed for mutations. Medical record data were used to create a JP database, and statistical analysis was performed using Fisher’s exact and unpaired t-tests.

Results: Nine of 54 patients had germline SMAD4 mutations, 13 had BMPR1A mutations, and 32 had neither. There were no significant differences between SMAD4+ and BMPR1A+ cases in terms of clinical factors examined, except for a family history of UGI involvement (P < .01). There was a higher prevalence of familial cases in MUT+ patients (P = .09), >10 lower gastrointestinal polyps (P = .06), and frequency of family history of gastrointestinal cancer compared with MUT– patients (P = .01).

Conclusions: Patients with germline SMAD4 or BMPR1A mutations have a more prominent JP phenotype than those without, and SMAD4 mutations predispose to UGI polyposis.

Key Words: Intestinal polyps—Hamartomatous polyps—Polyposis syndromes—Juvenile polyposis.
candidategenes revealed that germline mutations of SMAD4 were present in a proportion of JP patients.11 This finding was confirmed in additional studies,12-15 with the largest revealing a 20% rate of germline mutations in a series of 41 patients.16 SMAD4, also known as MADH4 and DPC4 (deleted in pancreatic cancer 4), is the common intracellular mediator of the transforming growth factor β (TGF-β) superfamily signaling pathways.17 A genome screen in four JP families without SMAD4 mutations revealed linkage of a second JP locus with markers on chromosome 10q22-23. Truncating mutations were uncovered in the bone morphogenetic protein receptor 1A gene (BMPR1A; also known as ALK3) from this region in all four families.18 This encodes for a type I serine/threonine kinase receptor that is also a member of the TGF-β superfamily. In addition, the bone morphogenetic protein (BMP) pathway mediates intracellular signaling through SMAD4. Presently, the influence of SMAD4 and BMPR1A mutations on the phenotype of JP patients is unknown, and the objective of this study was to examine the association of different germline mutations with the clinical features of JP.

METHODS

Study Population

After informed consent was obtained, peripheral blood samples were drawn from each patient, and genomic DNA was extracted from lymphocytes by using a salting-out procedure.19 Medical record data, including endoscopic, surgical, and pathology reports, were reviewed and entered into a database. This was supplemented by information from JP questionnaires completed by each patient, containing data regarding symptoms, medical history, and family history. Histopathologic slides were also reviewed where available to confirm the diagnosis of JP. The clinical and pathologic fields in the database included age at onset of symptoms, age at diagnosis, presence of multiple (>10) lower GI (LGI) juvenile polyps, whether cases were familial or sporadic, family history of upper GI (UGI) juvenile polyps, or family history of GI cancer. The mean age of onset of symptoms and diagnosis was 10.8 and 16.3 years, respectively. A family history of UGI juvenile polyps was present in 12 (31%) of 39 cases, multiple (>10) LGI polyps were found in 29 (73%) of 40 cases, and a family history of GI cancer was present in 30 (68%) of 44 patients, where data were available. Clinical factors according to mutation status are listed in Table 1.

Germline mutations in either SMAD4 or BMPR1A (MUT+) were found in 22 cases (41%), and no mutation of these genes was found in 32 patients (59%; MUT-). SMAD4 mutations were found in 9 (16.7%) of 54 cases (designated as SMAD4+). Six of these mutations were microdeletions, and three were substitutions (two missense, one nonsense; Table 2). Thirteen (24%) of 54 cases had BMPR1A mutations identified (BMPR1A+), where 5 were microdeletions and 8 were substitutions (4 missense, 4 nonsense; Table 3).

The results of statistical analyses are listed in Table 4. There were no statistically significant differences in clinical factors between BMPR1A+ and MUT- cases, whereas the age of LGI polyposis diagnosis, family history of UGI polyps, and family history of cancer were significantly different between SMAD4+ and MUT- cases. The only significant difference between SMAD4+ and BMPR1A+ cases was the prevalence of family history of UGI polyps, which was 86% for SMAD4+ and 10% for BMPR1A+ cases (P < .01). Because of the similarities between SMAD4+ and BMPR1A+ cases, these groups were combined to make comparisons to MUT- cases to reduce the effect of low numbers of