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Original Article

ORIGINAL ARTICLE

Re-recognition of *BMPR1A*-related polyposis: beyond juvenile polyposis and hereditary mixed polyposis syndrome

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Abstract

Background Bone morphogenetic protein receptor type 1A (*BMPR1A*) is responsible for two individual Mendelian diseases: juvenile polyposis syndrome and hereditary mixed polyposis syndrome 2, which have overlapping phenotypes. This study aimed to elucidate whether these two syndromes are just two subtypes of a single syndrome rather than two isolated syndromes.
Methods We sequenced the *BMPR1A* gene in 186 patients with polyposis and colorectal cancer, and evaluated the clinicopathological features and phenotypes of the probands and their available relatives with *BMPR1A* mutations.
Results *BMPR1A* germline mutations were found in six probands and their three available relatives. The numbers of frameshift, nonsense, splice-site, and missense mutations were one, one, two, and two, respectively; two of the six mutations were novel. Typical juvenile polyps were found in only three patients. Two patients had colorectal cancer rather than any polyps.
Conclusions Diseases in *BMPR1A* germline mutation carriers vary from mixed polyposis to sole colorectal cancer, and typical juvenile polyps do not always occur in these carriers. The variety of phenotypes reflected the features of *BMPR1A*-mutation carriers, which should be recognized as a spectrum of one syndrome. Genetic testing may be a good approach to identifying *BMPR1A*-related syndromes.

Key words: *BMPR1A* gene; juvenile polyposis syndrome; hereditary mixed polyposis syndrome; hamartoma; polyposis

Introduction

During the last two decades, our understanding of hereditary colorectal cancer (CRC) syndrome has progressed considerably, especially gastrointestinal (GI) polyposis. Researchers have gained awareness of more polyposis categories and have studied their clinical presentations, pathological features, treatment strategies, and prognoses. Seven polyposis types have been independently described in the American College of

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Gastroenterology (ACG) guidelines, with specific management recommendations including familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), *MUTYH*-associated polyposis (MAP), Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), Cowden syndrome, and serrated polyposis syndrome [1]. With the development of molecular diagnostic techniques, classifying polyposis syndromes by genetic alterations is a tendency to facilitate disease management in genetic counseling and risk assessment. For example, adenomatous polyposis syndromes can be classified as *APC*-associated polyposis (AAP), MAP, *AXIN2*-associated colorectal adenomatous polyposis, polymerase proofreading-associated polyposis, and Constitutional mismatch repair deficiency (CMMRD) syndromes [2].

Generally, mutations in a gene cause a hereditary disease. According to Online Mendelian Inheritance in Man (https://omim.org/), bone morphogenetic protein receptor type 1A (*BMPR1A*) mutations can cause two syndromes: JPS (OMIM 174900) and hereditary mixed polyposis syndrome 2 (HMPS-2; OMIM 610069). JPS is an autosomal dominant GI polyposis syndrome that was first reported by McColl in 1964 [3]. In addition to *BMPR1A* mutations, JPS can also be caused by *SMAD4* mutations [4]. Although these two genes play significant roles in the transforming growth factor (TGF-beta-) pathway, the two JPS types are phenotypically different. Patients with *SMAD4* mutations tend to develop upper GI diseases and hereditary hemorrhagic telangiectasia (HHT) [5]. There are diverse diagnostic criteria for JPS and the argument lies in the number of polyps. HMPS-2 is characterized by the presence of polyps with mixed pathological components. HMPS can also be caused by heterozygous duplication on chromosome 15q13–q14 that causes increased and ectopic expression of the *GREM1* gene (HMPS-1; OMIM 601228). Whitelaw *et al.* [6] first described St. Mark's family 96 (SM96) as "to have a dominantly inherited predisposition to a mixed polyposis syndrome and early onset CRC," which was the origin of the HMPS designation. Since then, diverse diagnostic criteria for HMPS have been utilized in several studies [7–9]. Cao *et al.* [8] verified that *BMPR1A* mutations account for HMPS. Here, we discuss only HMPS-2 caused by *BMPR1A* mutations.

With a lower incidence (1:100,000 to 1:16,000) [5] and sometimes inconspicuous and diverse phenotypes, JPS reports are fewer than those of FAP. HMPS is rarely reported and is difficult to distinguish from other polyposis syndromes. Furthermore, there are no clear quantitative criteria for the diagnosis or strategies recommended for HMPS in the mainstream consensus. According to previous studies, these two syndromes have a significant overlap or similarity in phenotype, mode of inheritance, and genetic alterations [5, 8–11].

Thus, we hypothesized that these two syndromes caused by *BMPR1A* mutations may be the only diverse phenotypes of an identical disease entity instead of two separate ones. Therefore, in this study, within our registry of >500 patients, we identified six families or individuals of polyposis or CRC with exact *BMPR1A* mutations utilizing Sanger or next-generation sequencing (NGS). Herein, we present and compare diverse *BMPR1A* variants and phenotypes in patients, supporting our hypothesis.

Patients and methods

Patients and biological sample collection

We tested 166 unrelated patients who were previously diagnosed as having colorectal polyposis and were all registered in Changhai Hereditary Colorectal Cancer Registry (Shanghai, China) as of December 2020. In addition, we tested 20 patients with CRC who were <50 years old at diagnosis. Clinicopathological data and family histories of the patients were collected from the hospital information system or through interviews. During hospitalization or interviews, we recruited patients with polyposis in the Polyposis Surveillance and Research Program and collected blood or oral mucosa samples or paraffin-embedded tissue samples of these patients and their available family members. Biospecimens of CRC patients were obtained from the Changhai Hospital Biobank (Shanghai, China). All biological samples were collected after informed consent was obtained. This study was approved by the Institutional Review Board of Changhai Hospital.

DNA sequencing

Genomic DNA of the biospecimens was extracted using an animal genomic DNA kit (TSP201, TsingKe Biotech, Beijing, China) according to the manufacturer's instructions. For Sanger sequencing, all 11 coding *BMPR1A* gene exons were amplified by polymerase chain reaction (PCR) using a 2× modified DNA polymerase mix (TSE004, TsingKe Biotech, Beijing, China) and then sequenced by Map Biotech Co. Ltd (Shanghai, China). For NGS, extraction, PCR, and sequencing experiments were conducted by DiagRe Biotech Co. Ltd (Shanghai, China). The details of our approach have been reported previously [12] and the primer sequences are depicted in Table 1.

After sequencing, the patients with *BMPR1A* mutations were diagnosed with *BMPR1A*-associated polyposis/CRC. We then determined whether they met the diagnosis of JPS or HMPS according to the consensus diagnosis criteria. We utilized the same diagnostic criteria for HMPS as those used in the study by Cao *et al.* [8]: the occurrence of three or more adenomatous,

Table 1. Primers used for *BMPR1A* exon amplification and sequencing

Exon[a]	Forward primer (5′-3′)	Reverse primer (5′-3′)
3	AGTCGTAAGAAAGCAGTGGGAGT	ACAGGGATGAGTTGAAAGAACAGA
4	CGCAATACCTGGTGCAGTAAT	AGGCTTTTTGGCTTTCTGGAA
5	TGGCTCAGACATAACTTTCATTTG	AGGCATGTTTCTCCTGGGG
6 and 7	AAAGCCATTTTGCAGTCTTCA	TGGTTTCTGCAACTGGCTTTA
8	TGAGGGAAGGATAATGGTATAGAG	CATTATTGTTCCCTGATCTGCAA
9	GGTACACCATGCTTTTTGATGAG	TAGGTTTCCTTTAGCCAAATGTAT
10	GTTTTTCTCAGTATCCAGAATGAGC	TCCATTATCTTGAATACAAATAGGG
11	GAGTTGGATTAAGAGTGCTGCC	CAAAGGATAAATGTCTGAAGGGA
12 and 13	CCGTTTTAGTTCCATAGTTTAGCAA	TGAAGAAAGAGTCTGAGAACCAAGT

[a]Coding sequences begin from exon 3.

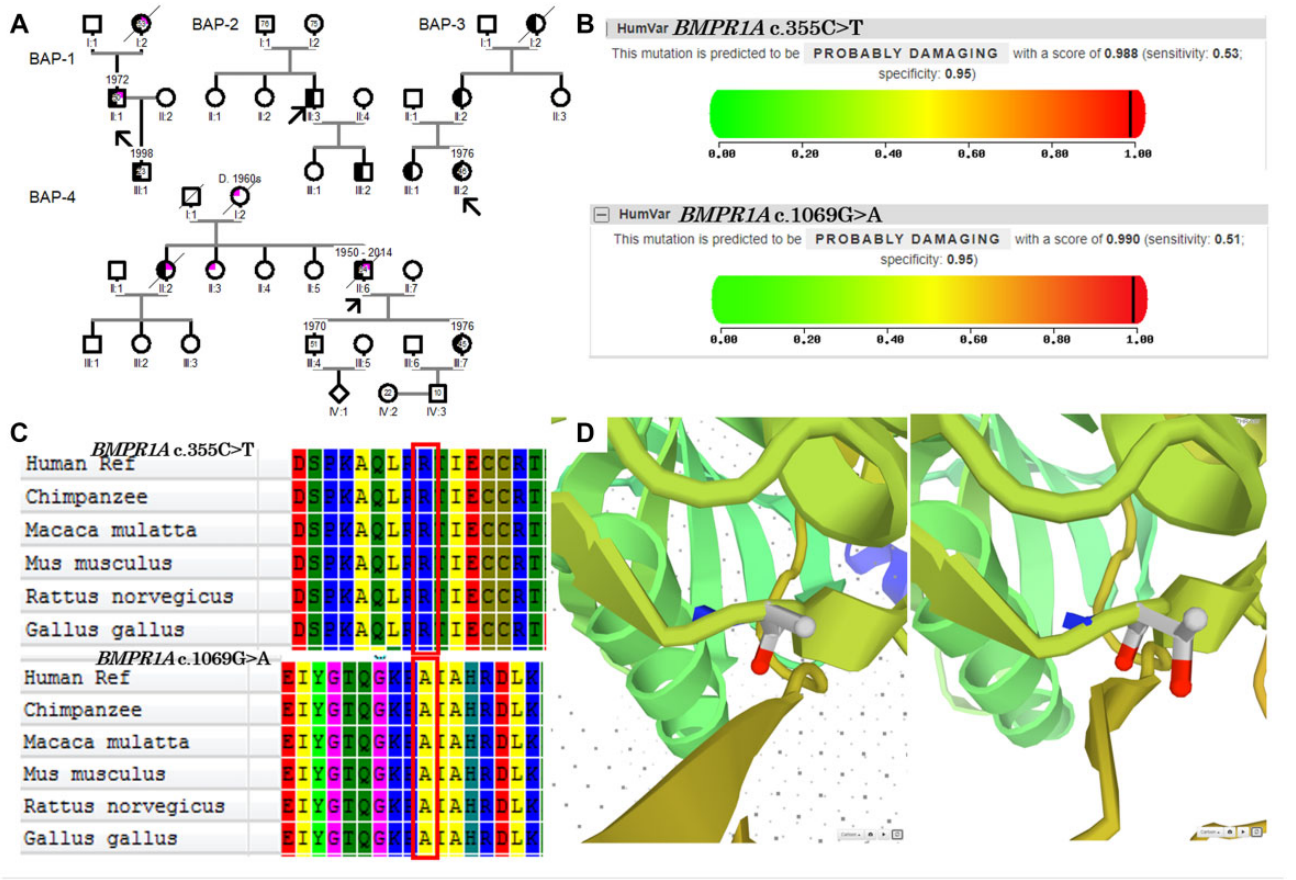

Figure 1. Pedigrees and genetic information on the BAP families. (A) Genograms (squares = males and circles = females; left half black symbols = colorectal polyp, quart-pink = cancer; an oblique line indicates a deceased individual; the index patient is indicated by an arrow). (B) PolyPhen-2 score indicates the damaging effect of the mutations. (C) The amino-acid residues altered by the mutations are evolutionarily conserved across diverse species. (D) The local structures around the mutation site of the wild-type (left) and mutant (right) BMPR1A proteins generated by Swiss-model online software depict obvious differences.

Table 2. BMPR1A mutation detected in the probands

Family	Method	Exon	Nucleotide	Amino-acid change/effect	Documented	Interpretation
BAP-1	NGS	8	949_952delCTCT	L317Mfs*4	PMID 32487124	Pathologic
BAP-2	Sanger	4	355C>T	R119C	PMID 17873119	Likely pathogenic
BAP-3	NGS	4	68-1G>A	Splice error	VCV000482869.3	Pathogenic
BAP-4	NGS	8	567C>G	Y189*	No	Pathologic
BAP-5	NGS	8	1069G>A	A357T	VCV000411619.6	Likely pathogenic
BAP-6	NGS	6	675 + 1G>T	Splice error	No	Pathogenic

NGS, next-generation sequencing; Sanger, Sanger sequencing.

hyperplastic, or juvenile polyps or polyps of mixed histology of these three types. The diagnosis of JPS was based on the National Comprehensive Cancer Network (NCCN) guidelines criteria: more than five juvenile polyps in the colorectum, several juvenile polyps in the GI tract, or a family history of JPS and any number of juvenile polyps (NCCN guidelines, https://www.nccn.org/professionals/physician_gls/default.aspx).

Results

Mutation detection and pathogenicity analysis

Among the 186 subjects, six probands were identified to carry heterozygous germline mutations of *BMPR1A* gene but no mutations of other CRC-related genes (Figure 1A and Table 2). Two of these mutations (c.675 + 1G>T and c.567C>G) have not been reported in the literature or recorded in databases (dbSNP, ClinVar, ExAC, and the Human Gene Mutation Database).

Among the six mutations, c.949_952delCTCT and c.567C>G are frameshift and nonsense, respectively. They resulted in the BMPR1A protein truncation, and thus were defined as pathological variants. c.68-1G>A and c.675 + 1G>T are splice-site mutations. Using splice-site score calculation (http://rulai.cshl.edu/new_alt_exon_db2/HTML/score.html), we discovered that c.68-1G>A induced a decrease in the splicing score from 10.6 to −0.4, and c.675 + 1G>T caused a decrease from 9.2 to −1.5. Since the results indicated that they caused a dramatic decrease in splicing function, we also defined them as pathologic variants.

Table 3. Classification of evidence of missense *BMPR1A* mutations

Evidence	c.R119C	c.A357T
(1) Population data	Absent in databases (PM2)	Absent in databases (PM2)
(2) Computational and predictive data	Same amino-acid change as an established pathogenic variant (PS1)	Multiple lines of computational evidence support a deleterious effect on the gene (PP3)
(3) Functional data	Not applicable	Not applicable
(4) Segregation data	Co-segregation with BAP (PP1)	Co-segregation with BAP (PP1)
(5) De novo data	De novo (without paternity and maternity verified) (PM6)	De novo (without paternity and maternity verified) (PM6)
(6) Other data	Patient's phenotype and Familiy History highly specific for gene	Patient's phenotype highly specific for gene (PP4)
Conclusion	Likely pathogenic (1 PS +2PM +2PP)	Likely pathogenic (2PM +3PP)

Table 4. Phenotypes of *BMPR1A* mutation carriers

Family	No.	Phenotype		Pathology	Intervention	Age		Syndrome
		CRC	Polyp			Onset	Diagnosis	
BAP-1	II : 1	Yes	Polyposis	Adenocarcinoma + adenoma	TPC+IPAA	42	42	AFAP
	III : 1	No	Polyposis	Juvenile polyp	Subtotal colectomy	19	21	JPS
BAP-2	II : 3	No	Multiple	Adenoma + hyperplastic polyps	Colectomy	45	45	AFAP
	III : 2	No	Polyposis	Juvenile polyp	Colonoscopy	6	15	JPS
BAP-3	III : 2	No	Polyposis	Adenoma with HIGN	TPC+IPAA	26	33	AFAP
BAP-4	II : 6	Yes	Multiple	Mucous adenocarcinoma	Radical sigmoid colectomy	62	63	NA
	III : 7	No	Multiple	MHA + retention polyp	Colectomy	14	14	HMPS
BAP-5	1	Yes	Single	Adenocarcinoma	Anterior resection	42	42	NA
BAP-6	1	No	Multiple	Juvenile + hyperplastic polyps	Colonoscopy	NR	22	JPS

AFAP, attenuated familial adenomatous polyposis; CRC, colorectal cancer; HMPS, hereditary mixed polyposis syndrome; MHA, mixed hyperplastic adenoma; MP, multiple polyps; NA, not available; NR, not recorded; Po, polyposis.

The missense mutations c.1069G>A and c.355C>T resulted in one amino-acid-residue substitution (p.A357T and p. R119C, respectively). The PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) scores were 0.988 and 0.990, respectively (Figure 1B), indicating that they were probably damaging. Additionally, evolutionary conservation analysis of amino-acid residues demonstrated that these two proteins were conserved among species (Figure 1C). Protein structure prediction using SWISS-MODEL (http://swissmodel.expasy.org) demonstrated that the amino-acid-residue substitution caused an obvious change in the local structure (Figure 1D). Altogether, the variants were defined as likely pathological according to The American College of Medical Genetics and Genomics (ACMG) standard (Table 3) [13].

Clinical presentations

We re-diagnosed the patient with *BMPR1A* mutations. Seven patients from four families and two patients without family history were screened for analysis, with an average diagnosis age of 33.0 years (Table 4). Typical juvenile polyps were detected in only three of the nine patients (BMPR1A-associated polyposis [BAP]-1 III : 1, BAP-2 III : 2, and BAP-6 : 1; average age, 19.3 years; Figure 2A and B). Two patients (BAP-1 II : 1 and BAP-4 II : 6) had CRC with multiple adenomas, and one patient (BAP-5 : 1) had solitary rectal cancer (Figure 2C), all of whom were treated with radical resection. One patient (BAP-4 III : 7) had mixed hyperplastic adenoma. One patient (BAP-2 II : 3) had a "mixed polyp" detected but the treatment was conducted in another hospital so that the original pathological data were inaccessible to us. One patient (BAP-6 : 1) had polyps that were pathologically diagnosed as hyperplastic and juvenile. Three patients (BAP-1 II : 1, BAP-2 II : 3, and BAP-3 III : 2) had multiple adenomas.

Of the nine patients, three (33.3%) underwent radical surgery, four (44.4%) underwent prophylactic colectomy (Figure 2D), and only two younger patients (22.2%) had polyps removed by regular colonoscopy. At the time of writing, one patient (BAP-4 II : 6) had died 16 months post-surgery due to metastasis, while the others were still being followed up or receiving intensive treatment at our center.

Members of the same family exhibit diverse phenotypes. In the BAP-1 family, the proband was diagnosed with FAP based on the presence of adenocarcinoma with multiple adenomas. However, his son presented with the typical JPS (Figure 2E) phenotypic features. In the BAP-2 family, the pathological results of proband demonstrated adenomas with moderate dysplasia and hyperplastic polyps, whereas his son had juvenile polyps and one mixed polyp. The original pathological diagnoses of patients BAP-4 III : 7 and BAP-6 polyps were retention and hyperplastic polyps, respectively (Figure 2F and G).

Discussion

In this study, we identified nine patients with *BMPR1A* mutations from six families. The phenotypes of these patients were diverse, including JPS, HMPS, and attenuated FAP. Moreover, the

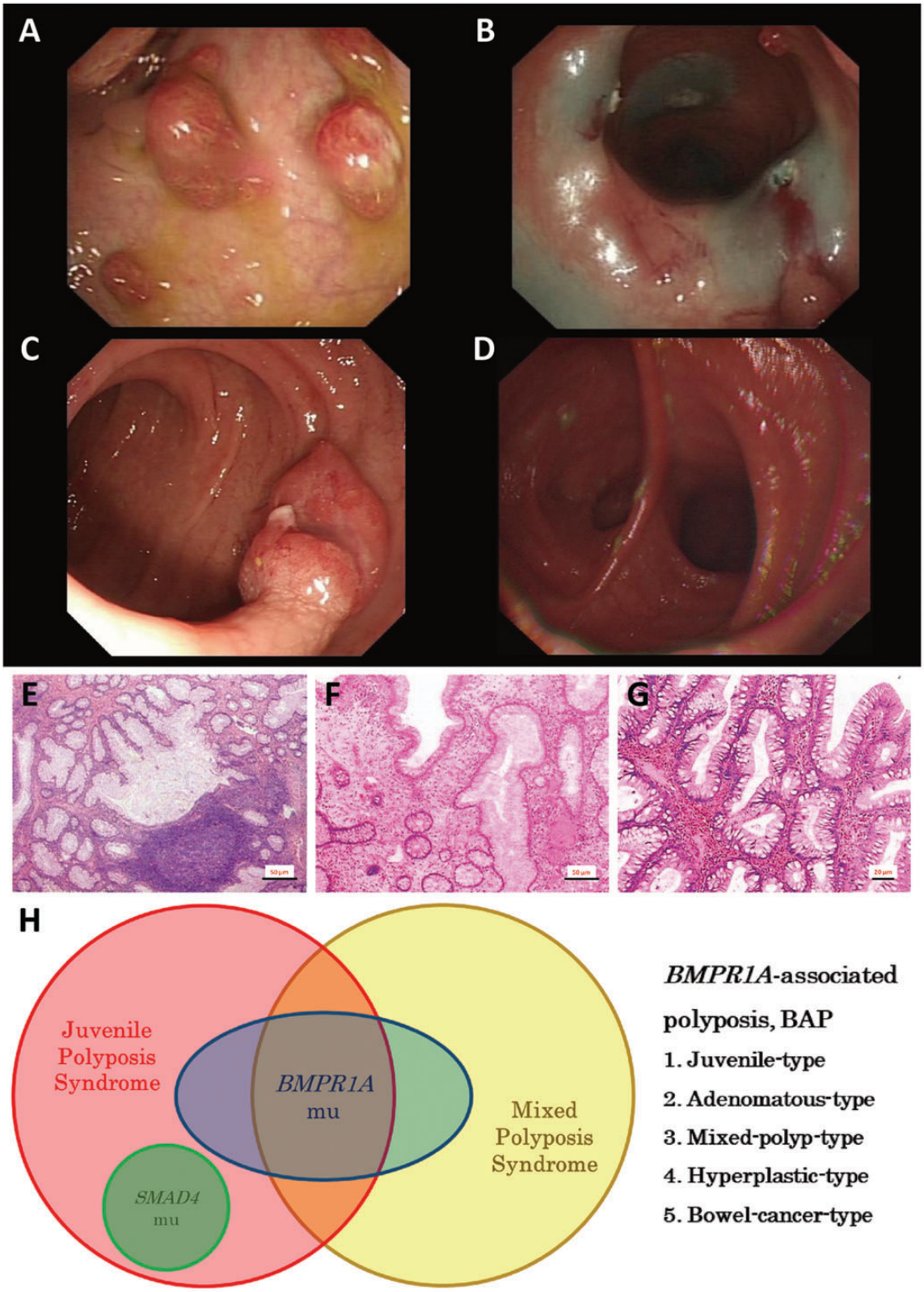

Figure 2. Clinicopathological feature of BAP patients. (A) and (B) Endoscopic view of multiple juvenile polyps before (A) and after (B) polypectomy in patient BAP-2 III : 2 who received continuous colonoscopic surveillance. (C) Endoscopic view of the ulcerative tumor proven to be a rectal cancer in patient BAP-5. (D) Endoscopic view of the ileum pouch after a restorative total proctocolectomy in patient BAP-3 II : 2. (E)–(G) Hematoxylin-eosin-stained tissue slices of the polyp specimens in patient BAP-1 III : 1 (×100 magnification), BAP-4 III : 7 (×100 magnification), and BAP-6 (×200 magnification) verified juvenile polyps. (H) Schematic diagram of relationship between juvenile polyposis syndrome, mixed polyposis, and their pathogenic genes.

phenotypes of patients within the same family were different. Additionally, we identified two unreported pathogenic *BMPR1A* mutations in Exons 6 and 8.

Owing to the low incidence and awareness of JPS and HMPS, the diagnostic criteria for both syndromes are somewhat controversial. The currently accepted NCCN guidelines recommended diagnostic criteria for JPS were based on the experience of studies of St Mark's Hospital [14], which has been mentioned in the 'Patients and methods' section. However, van Hattem *et al.* [15] used diagnostic criteria for more than three juvenile polyps. Similarly, researchers have utilized diverse diagnostic criteria for HMPS in their respective studies [8, 9]. That is a solitary mixed pathological polyp or multiple polyps with diverse pathological characteristics, both of which support HMPS diagnosis. Furthermore, there are no clear quantitative criteria for the diagnosis or strategies recommended for HMPS in several mainstream guidelines.

Acknowledging these diagnostic criteria for the two syndromes, we notice some interesting phenomena in previous studies. In the diagnosis of affected families, the two syndromes sometimes overlap. Families of both patients with HMPS and JPS could carry *BMPR1A* mutations. In this manner, once the order in which patients are discovered as the proband changes, the diagnosis of the entire family is completely overturned. O'Riordan *et al.* [16] reported an Irish family with HMPS, among which Patient II1 developed more than five juvenile polyps and met the criteria for JPS. In our study, if we defined patient II1 as the proband, this family would also meet the diagnostic criteria for JPS because he provided a family history of JPS for other family members with fewer than five juvenile polyps. Similar situations have been reported for families in other studies [10, 11]. Chow *et al.* [10] noted the similarity of the family phenotype to that of HMPS in their JPS case. Interestingly, all the patients in these families harbored *BMPR1A* mutations. In our study, there were three families, wherein we tested two patients each, but the patients in each family were phenotypically distinct. These results indicate that the phenotypes resulting from *BMPR1A* mutations may be diverse, even within the same family, which can cause difficulty and confusion in the diagnosis.

The natural history of *BMPR1A*-associated polyposis (BAP) is not well documented. As seen in the reported studies [10, 11, 16] and our study, patients with BAP presented with a variety of polyps during long-term colonoscopic follow-up. With no clear pattern, the order in which various types of polyps occur is irregular. Thus, the established diagnostic criteria were less significant. Diagnosis based on clinical phenotypes may be less accurate than genetic diagnosis.

Before significant advances in molecular diagnostic techniques, diverse AAP phenotypes were considered heterogeneous diseases including Gardner and Turner syndrome. However, it has been revealed that these syndromes caused by *APC* mutations may have common features. They should be considered a "homogeneous" disease entity and managed despite their different intestinal and extra-intestinal manifestations [1]. A similar situation exists in *PTEN* hamartoma tumor syndromes [17]. As mentioned above, syndromes caused by *BMPR1A* demonstrate similar features. Shen *et al.* [18] defined HMPS as the most common extra-JPS phenotype in addition to unexplained multiple polyposis, early-onset CRC, and other rare extra-intestinal syndromes attributed to pathogenic or likely pathogenic *BMPR1A* variants. Thus, we suggest that this group of diseases be more appropriately named *BMPR1A*-associated polyposis. Based on available observations, we classified BAP into the following subtypes: mixed-polyp-, juvenile-, adenomatous-, hyperplastic-, and CRC-type (Figure 2H).

Our results were obtained from patients who were misdiagnosed. None of the patients had an initial JPS or HMPS diagnosis; however, all were diagnosed with FAP or multiple polyps. We speculate that there are several situations in which such mixed polyps could be misdiagnosed: undergoing colonoscopy quite early, polyps removed several times, or no family history presented. Experience of pathologist is important and fundamental, as a correct clinical diagnosis is impeded by compromised pathological results. In another possible situation, even if a patient has a polyp with mixed pathology, the diagnosis would still be incorrect when a complete pathological examination cannot be conducted or only a portion of the tissue is obtained endoscopically. Likewise, in pathological examinations, the diagnosis of a mixed polyp could be made based on some local features of the polyp, concluding a single pathological-type polyposis. To make a correct diagnosis, a complete polyp pathology or biopsy of all polyps is more appropriate; otherwise, BAP may be misdiagnosed as FAP [11].

However, the situation in our clinical practice is another reason for the high misdiagnosis rate from a real clinical perspective, namely that a less fatal phenotype than FAP leads to a lack of attention from patients and doctors. During our study, family history was difficult to obtain due to the lack of patient cooperation. Most relatives of the probands refused to undergo colonoscopy, even though we elucidated the necessity to them. Specimens of polyps from family members who were not treated at our center were also difficult to acquire. All these obstacles led to a small sample size, which is the major limitation of this study. Fortunately, we detected *BMPR1A* variants in all these families and then made a correct diagnosis. Therefore, genetic testing is essential for this group of polyposis syndromes.

Conclusions

The results of this study highlight the significant overlap or similarity in JPS and HMPS. After reclassification, BAP should be managed as a homogeneous disease. Clinicians should be aware of the BAP characteristics, including low recognition, phenotypic diversity, high potential for CRC, high misdiagnosis rates, and inadequate genetic counseling. The concept of BAP emphasizes the significance of molecular diagnosis and genetic counseling, which will help clinicians to be more sensitive and thus reduce the misdiagnosis rate and mistreatment of the disease. Additionally, further research and exploration of polyposis, such as BAP, require the collaboration of endoscopists, pathologists, molecular diagnosticians, and clinicians.

Authors' Contributions

Z.Y.Z. and Z.M.W. collected and evaluated the patient data regarding the clinical process. Y.L. and Z.Y.Z. oversaw data presentation, analysis, and manuscript writing. Y.L. helped with the clinical examination. X.X.D., J.J.X., X.H.G., and W.Z. conducted colonoscopy and surgery. H.H. was responsible for pathological analysis. E.Y. provided advice and reviewed the manuscript. E.D.Y. and Z.Y.Z. provided research resources and supervised the study. All authors have read and approved the final manuscript.

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Conflict of Interest

None declared.

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