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Juvenile Polyposis and Other Intestinal Polyposis Syndromes with Microdeletions of Chromosome 10q22-23

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Abstract

Juvenile Polyposis (JP) is an autosomal dominant hamartomatous polyposis syndrome that carries a significant risk for the development of colorectal cancer. Microdeletions of one of the two predisposing genes to JP, *BMPR1A*, have been associated with a severe form of JP called juvenile polyposis of infancy. Many of these deletions have also been found to contiguously include *PTEN*, which is the gene responsible for the development of Cowden syndrome. The advent of molecular techniques that localize genomic copy number variations and others that target specific genes such as multiplex-ligation probe analysis has allowed researchers to explore this area further for deletions. Here, we review the literature for microdeletions described on chromosome 10q22-23 in patients with JP and other intestinal polyposis syndromes.

Introduction

Copy number variation (CNV) is the term used to describe genomic structural variations ranging in size from kilobases (kb) to Megabases (Mb). The recent extensive utilization of genome-wide study tools such as comparative genomic hybridization (CGH) has led to the rapid expansion of these studies (1–3). Altering the copy number of dosage-sensitive regions has been well established as a mechanism leading to clinically relevant phenotypes (4), and since the early 1980s, a number microscopic deletion syndromes have been described. Microdeletion of chromosome 15q11.2q12 was identified as a cause of Prader-Willi syndrome, and reports of other disorders that contain variable deletion break-points followed, such as α-thalassemia and Duchenne muscular dystrophy (5–8). Due to the lack of accurate molecular tools that screened the whole genome for CNVs 1–50 kb in size (3, 9), investigators focused their search to previously identified regions of disease-predisposing genes, which enabled localization of smaller CNVs. This approach proved fruitful in identifying CNVs as the cause of a number of common complex traits such as Parkinson's disease, Alzheimer's disease and epilepsy (10–13).

Juvenile Polyposis (JP) is an autosomal dominant disorder characterized by the development of multiple hamartomatous polyps of the GI tract (14, 15). JP carries an increased risk of GI malignancy, with a lifetime risk of approximately 50% (16). In 1998, a JP gene was localized to chromosome 18q21 by linkage analysis and germline mutations were found in the tumor suppressor gene *SMAD4* in several families (17, 18). In 2001, another JP locus was found in four kindreds mapping to chromosome 10q22-23. Germline mutations were identified in the bone morphogenetic protein receptor type 1A (*BMPR1A*), a receptor

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involved in the BMP signaling pathway, of which SMAD4 is the intracellular mediator (19). Prior to this, mutations in the tumor suppressor gene *PTEN*, also located on 10q22-23, about 1Mb telomeric to *BMPR1A*, had been found in the germline of patients with Cowden Syndrome (CS), in which some patients also develop hamartomatous intestinal polyps (20, 21). Prior to the discovery of *BMPR1A* as a JP gene, there were 2 reports of JP patients with *PTEN* germline mutations (22, 23). However, further review of the clinical data suggested these patients might have CS rather than JP, and Eng and Ji concluded that patients with inherited hamartoma syndromes and *PTEN* mutations should be considered to have CS or Bannayan-Riley-Ruvalcaba syndrome (BRRS) (24). Beside BRRS, it later became evident that *PTEN* mutations were present in the other distinct hamartomatous syndromes Proteus syndrome and Proteus-like syndrome ((25, 26) and reviewed in (27)).

Due to the phenotypic diversity exhibited by patients with *PTEN* mutations and the fact that germline single base substitutions and small deletion/insertions in the JP genes *BMPR1A* and *SMAD4* only account for less than half of JP cases (28, 29), alternative means of gene inactivation have been explored. This was largely facilitated by the improvement and increased availability of molecular tools that identify smaller-scale CNVs. Multiplex ligation-dependent probe amplification (MLPA) is one method by which many genomic deletions/duplications have been found in target genes (30–33), and this technique has been particularly useful in the study of JP related CNVs. Here we review the literature for studies that describe chromosome 10q22-23 microdeletions in JP and other intestinal polyposis syndromes.

JP, CS and BRRS

Three subtypes of JP were defined by Sachatello et al. in 1975: 1-Juvenile polyposis coli (JPC); 2-Generalized juvenile polyposis (GJP); and 3-Juvenile polyposis of infancy (JPI) (34). The first two subtypes are distinguished by the location and extent of polyps along the GI tract with JPC having polyps in the colon only and GJP in the colon and upper GI tract. These are thought to be variable manifestations of the same condition since both subtypes can be present in the same families and commonly present in the first two decades of life (35). In contrast, JPI is characterized by a very early age of onset (often before 2 years of age) and a substantially more severe clinical course due to recurrent gastrointestinal bleeding, diarrhea and exudative enteropathy. JPI has rarely been reported in the literature, and the infrequency of this condition and its high rate of mortality have limited the study of its molecular basis in the past.

CS was first described in 1963 by Lloyd et al. (36). It is autosomal dominant and is characterized by the formation of multiple disorganized benign growths (hamartomas) and an increased risk of benign and malignant tumor development. More than 90% of affected patients manifest the phenotype before 20 years of age and almost all have CS-mucocutaneous involvement (37). Of note, thyroid abnormalities occur in over 50% of cases, 38% have macrocephaly and 40% develop GI hamartomatous polyps. Clinical diagnosis is often challenging, and can be aided by genetic testing (37). BRRS is a rare disorder that also has an autosomal dominant mode of transmission, and affected members manifest with macrocephaly, lipomatosis, angiomatosis, penile abnormalities and occasional intestinal polyps (38). It is estimated that 60% of BRRS cases have germline mutations in *PTEN* and some cases even overlap with CS from a clinical perspective (25). The correlation between genotype and phenotype in these two syndromes is not fully understood, and there is overlap of mutations suggesting that the two conditions are allelic (39).

Cytogenetic Studies

The first report to describe a germline chromosomal anomaly in a patient with a hamartomatous polyposis syndrome came from Jacoby et al. in 1997 (40). The authors described a 4 year-old boy referred for a 1-year history of hematochezia who had several dozen polyps of typical juvenile histology distributed along the colon on endoscopy. This patient had multiple congenital abnormalities including dysmorphic features, as well as growth and developmental delays which suggested the presence of a chromosomal abnormality. Using a standard Giemsa-banding method, metaphase analysis of peripheral leukocytes revealed an interstitial deletion of the long arm of chromosome 10, with a karyotype of 46,XY,del(10)(q22.3.24.1). This change was *de novo,* as cytogenetic analysis did not reveal a similar abnormality in either parent. Figure 1 illustrates the locations of the different deletions reported here and in subsequent studies.

Later that year, Arch et al. reported a similar case (41). The authors described an 18-month old boy with a presumed diagnosis of BRRS who had multiple anomalies consistent with that diagnosis, such as remarkable macrosomia that was 7 SD above the age-adjusted mean, 2 lipomas, developmental delay and pseudopapilledema. On endoscopy, multiple hamartomatous polyps that extended throughout the duodenum and small intestine were found, and since polyps in BRRS are usually confined to the distal ileum and colon, the authors proposed that features of Cowden's syndrome (CS) might overlap in this patient. Standard Giemsa-banding was used for the karyotyping. which revealed a hemizygous deletion of chromosome 10q23.2-q24.1. The authors further demonstrated the absence of *PTEN* by performing FISH using a bacterial artificial chromosome (BAC) clone specific for that gene. Examination of the parental chromosomes revealed no abnormalities.

Zigman et al. reported 2 additional patients soon afterwards (42). The first patient they described was a male who presented with developmental delay, macrocephaly, a subcutaneous hamartoma and multiple juvenile polyps in the intestine, features thought to be typical of BRRS. The second patient was a girl who additionally had complex congenital cardiac anomalies, as well as clubfoot. Both patients had abnormal karyotypes by Geimsa-staining. The deletion in the first patient was part of an unbalanced translocation with the distal short arm of chromosome 9 (46,XY,der(9)t(9;10)(p24.1;q24.1),der(10)del(10)(q23.2q24.1)t(9;10)(p24.1;q23.2)), and was unbalanced in the second patient (46,XX,del(10)(q23.1q24.2)). Chromatin loss was confirmed in both patients, however the deletion was substantially larger in the second patient (11.6 cM) compared to the first (~1cM). Since the diagnosis of JP was highly suspected in the second patient, the authors concluded that genes responsible for JP and BRRS were within that chromosomal segment. In both patients, the parental karyotypes were normal.

In 1998, Tsuchiya et al. reported another case of a 6-year old boy with rectal bleeding since the age of 2(43). He was found to have multiple juvenile polyps that extended from the duodenum to the rectum. Other clinical features included developmental delay, prominent dysmorphic facies, a large head circumference (>90th percentile) and hyperpigmentation of the mouth and penis. Cytogenetic analysis of Giemsa/Trypsin/Leishman-banded chromosomes revealed a karyotype of 46,XY,del(10)(q23.2q23.33), and the estimated size of the deletion was between 11 and 15 cM by FISH. BRRS was thought to be unlikely in this patient as there was no evidence of lipomas or hemangiomas. Moreover, CS was not confirmed either due to the lack of characteristic findings such as papillomatous skin lesions, thyroid or genitourinary abnormalities. Other family members reportedly had no such signs, and the mother's karyotype was found to be normal.

In 2005, Delnatte et al. described 4 unrelated cases of JPI who had deletions of both *BMPR1A* and *PTEN* (44). All patients presented at an early age (between 1 and 18 months) and had multiple juvenile polyps extending throughout the upper and lower GI tracts. Furthermore, they all had macrocephaly, but hemangiomas were only found in 2 out of the 4. Facial dysmorphism was present in 3 patients and none showed evidence of mental retardation (other features are summarized in table 1). FISH was performed using BAC clones encompassing *PTEN* and *BMPR1A* in the first 3 patients, which confirmed loss of this region. In patient 4, quantitative PCR of all *BMPR1A* and *PTEN* exons demonstrated the complete loss of both genes. Interestingly, one patient was mosaic for this deletion, exhibiting it in only 17% of examined peripheral lymphocytes. Using CGH and serial microsatellite typings, the deletions in patients 1, 2 and 4 were further characterized and found to be between 1.2 and 2 Mb in length. In two of these patients, genetic testing revealed no abnormalities in either parent (data was not available from the other two patients).

These reports gave rise to the hypothesis that the more aggressive JPI is caused by deletion of the 2 contiguous genes known to cause JP, CS and BRRS (*BMPR1A* and *PTEN*). However, clinical and molecular data were not always consistent. Features associated with BRRS, such as macrocephaly, facial dysmorphy, speckled penis, and lipomas were not found in all subjects thought to have JPI, and furthermore, Zigman et al. did not find a deletion of *BMPR1A* in one patient (42). A later report by Salviati et al. (45) argued the notion that a more complex mechanism underlies the development of JPI, and that the phenotypic expression of contiguous *BMPR1A* and *PTEN* deletions is variable. The authors reported one patient who had a notably milder phenotype, yet was found to have an interstitial deletion of chromosome 10 that included both genes. Delnatte et al. previously suggested that this was the molecular defect underlying the severity of JPI (44). Salviati's patient was first evaluated at 3 years of age, had no macrocephaly, only mild developmental delay, mild dysmorphic features, and a small atrial septal defect. Interestingly, high-resolution karyotyping and FISH using BAC clones spanning from10q22 to 10q23 revealed that the deletion was in fact considerably larger than those that had been previously reported (12 Mb versus 2 Mb). This added another layer of complexity, as the size of the deletion did not seem to correlate with the severity of the phenotype.

The most recent study on JPI came in 2008 by Menko et al. (46) in 2008, and provided valuable insight on the phenotypic outcome of these deletions. The authors described 4 new patients with JPI who had 10q23 microdeletions that involved both *BMPR1A* and *PTEN*. All 4 cases had macrocephaly, dysmorphic features and other congenital abnormalities. This study was unique in that it combined data from MLPA with FISH and then further characterized the deletions by SNP analysis using the Affymetrix 250k *Nsp*I array. The amount of heterozygous loss of DNA ranged between 2.88 and 4.26 Mb, with larger deletions not predicting a more severe course of disease. The authors concluded that the clinical consequences of these molecular abnormalities were fairly heterogeneous.

The Frequency of Large Deletions in JP

The first study to address the frequency of CNV in the causative genes for JP was performed by Aretz et al. in 2007 (29). The authors examined 80 unrelated cases of JP where patient DNA was first subjected to direct sequencing of *BMPR1A, SMAD4, PTEN* and *CDH1*. For MLPA analysis, 60 patients were examined (50 did not have any point mutations and another 10 had missense mutations or unspecified variants). DNA from these 60 probands was analyzed by MLPA kit P158 (MRC Holland, Amsterdam, the Netherlands). A total of 6/80 (7.5%) were found to have deletions in *SMAD4* and 3/80 (3.8%) had deletions in *BMPR1A*. One of these latter patients had decreased amplification in the probes for the two

first noncoding exons and first exon and another only had the first exon deleted. The third patient had a deletion of the entire genes of *BMPR1A* and *PTEN*. Further review of this patient's history revealed the age at diagnosis was 3, (possibly consistent with JPI), but additional information regarding the patient's phenotype was not reported.

A similar study by van Hattem et al. examined a well-documented group of 27 JP patients and utilized the same MLPA kit as Aretz et al. (47). To check first for point mutations and small deletions/insertions, direct sequencing was performed and mutations in *SMAD4* and *BMPR1A* were only found in 9 (33.3%) patients. MLPA was subsequently used on the remaining 18 patients, and 4 large hemizygous deletions were found (one including all exons of *SMAD4*, one in exons 10 and 11 of *BMPR1A*, and 2 involving all exons of *PTEN* and *BMPR1A*). Both patients that had the contiguous deletion of *BMPR1A* and *PTEN* at 10q22-23 had typical multiple juvenile polyps, however one of them was reported to have thyroid carcinoma making CS also a potential diagnosis. Other pertinent features and age of onset were not mentioned.

The most recent study searching for large deletions in JP probands came from our lab in 2009 (48). A total of 102 subjects were analyzed, all meeting the clinical criteria set by Jass et al.(49). Direct sequencing identified *SMAD4* and *BMPR1A* mutations in (42/102) 41.2% of patients. The remaining 60 patients were examined by MLPA, and two patients were found to have deletions involving parts or all of *SMAD4*. Two patients were found to have large deletions involving *BMPR1A*. One involved the promoter and 1st non-coding exon (50) and the other a contiguous deletion of *BMPR1A* and *PTEN*. This patient did not appear to have JPI based on age of diagnosis (20 years), but had intriguing manifestations suggestive of BRRS such as macrocephaly (95th percentile head circumference), a dermatofibroma, trichoepithelioma and recurrent hernias (48). A summary of the deletions found by MLPA in these studies is shown in Figure 2.

Contiguous Deletions Must Include *PTEN*

In this review, we found that all patients with chromosome 10 microdeletions who presented with signs of polyposis were found to have a hemizygous deletion which included both *BMPR1A* and *PTEN*. Further insight on that could be derived by examining two individual studies by Balciuniene (51) and Alliman (52). Balciuniene et al. reported three unrelated probands who had deletions in the 10q22.3-23.3 region. The first two probands had a deletion ~7.2Mb in size that included *BMPR1A*, but not *PTEN*. Both patients manifested with developmental delay and macrocephaly, and had no evidence of polyposis. The third proband was the same patient described by Arch et al. (41) in 1997. The authors confirmed the loss of both *BMPR1A* and *PTEN* in this patient and again confirmed the presence of hamartomatous polyps at that age. Alliman et al. reported an additional 6 patients with deletions similar to the first two probands reported by Balciuniene et al. (52). Likewise, none had any signs of polyposis, which suggested the requirement of a contiguous deletion of both genes for polyposis to take place. Nevertheless, due to the rarity of this condition, and the fact that point mutations and smaller deletions (detected by MLPA) in *BMPR1A* cause JP, the risk of polyposis in these patients with microdeletions cannot be ruled out entirely.

Summary

Mutations in *BMPR1A* have been found in patients with JP, whereas *PTEN* mutations have been described in CS and BRRS. These two genes map to chromosome 10q22-23 and contiguous deletions of both genes have been reported. We reviewed the literature for studies that describe large deletions in JP-predisposing genes and further focused on the phenotype of patients with contiguous deletions of *BMR1A* and *PTEN*.

Point mutations and small insertions/deletions in *SMAD4* and *BMPR1A* have been identified through direct sequencing in 21.6% and 18.5% of JP cases, respectively. That suggested CNV as an alternative mechanism of inactivation of these genes. Three major independent studies utilizing MLPA have been conducted to date to screen for CNVs in patients with JP (29, 47, 48). These collectively reported a total of 6.3% of JP patients to have large germline deletions of one of the two causative genes (*BMPR1A* and *SMAD4*). Despite thorough evaluation of these two genes, a significant portion of patients with the clinical diagnosis of JP remain genetically unaccounted for, which suggests that other genes might be involved in the pathogenesis of JP.

JP usually presents in older children or young adults, but when it presents at a very early age, it is associated with a more severe clinical course and more pronounced extraintestinal manifestations, often leading to a significantly reduced life expectancy. Recently, 2 studies attempted to correlate the extent of DNA loss with the severity of the symptoms (suggesting that the hemizygous deletion of more genes could potentially lead to more pronounced manifestations), and found no clear association (45, 46). However, it is plausible that large deletions involving both *BMPR1A* and *PTEN* lead to a clinical picture that is more severe than JP. Additionally, part of the controversy may be due to the lack of a unified diagnostic definition for JPI. Salviati et al. argued that since their patient did not present prior to 2 years of age with GI bleeding, diarrhea and rectal prolapse, JPI was a questionable diagnosis (45) (referring to the criteria proposed by Sachatello in 1974 (53)). In response, Sanalville et al. argued that an age of diagnosis at 6 years points towards an onset of the disease process in infancy and that the diagnosis of JPI appropriate (54). The rarity and variability of these deletions has made the correlation between phenotype and genotype difficult. Nevertheless, the accumulation of these data can point researchers to study this area more closely and perhaps examine other genes in 10q22-23 in patients with features of these disorders. Finally, while the range of phenotypes is variable, we conclude that JPI is a unique entity that often combines features of both CS and BRRS with JP, and requires the loss of both *BMPR1A* and *PTEN*.

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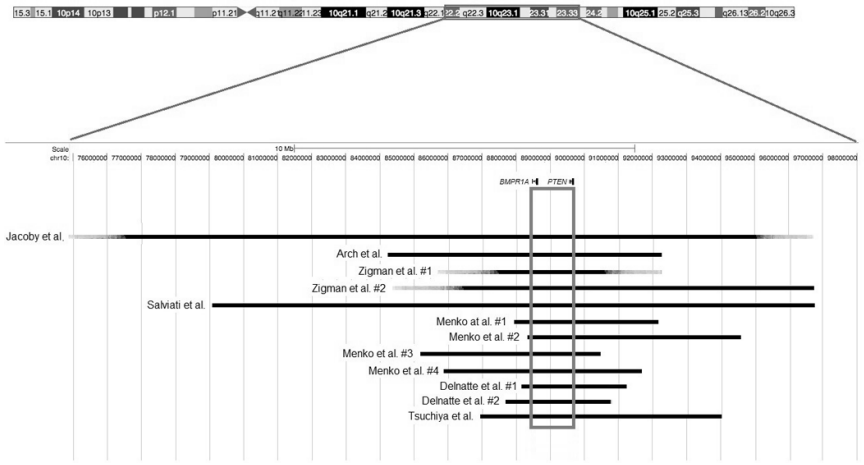

Figure 1.

Deletions in chromosome 10q22-23 are associated with a severe form of JP. Deletions are shown in black. Deletions described by Jacoby et al. (40) and Zigman et al. (42) were studied by Giemsa banding only and the exact positions of the breakpoints were therefore not determined. *BMPR1A* and *PTEN* are within red boxes with the common area lost in all patients outlined in blue. Numbers next to the author names refer to the individual cases in the order that they were listed in their corresponding primary publications.

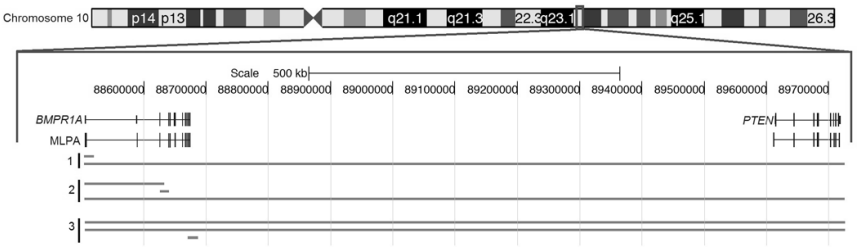

Figure 2.

Three studies used MLPA to localize deletions in JP patients. Top: Chromosome 10 with area expanded within the red square. Reference genes are shown in the middle, with MLPA probes corresponding to different coding and non-coding exons below them. (1) Calva et al. (48); (2) Aretz et al. (29); (3) Van Hattem et al. (47).

Table 1

10q deletions in patients with childhood-onset JP. A summary of the studies that describe patients presenting in childhood with JP.

Author (year)	Onset	Juvenile Polyps U/L	Macrocephaly	Additional abnormalities	Mental/ Developmental retardation	Karyotype	Further characterization
(40) Jacoby et al. (1997)	3 years	?/+	No (2nd percentile, proportionate to size)	Club foot, Tricuspid insufficiency	Yes	46,XY,del(10)(q22.3q24.1)	
(41) Arch et al. (1997)	18 months	+/+	Yes (+7 SD)	Lipoma, hemangioma,	Yes	46,XY,del(10)(q23.2q24.1)	5.73 Mb, confirmed by Balciuniene et al. (51)
(42) Zigman et al. (1997)	Not reported	?/+	Yes	Subcutaneous hamartomas	Yes	46,XY,del(10)(q23.2q24.1)	1 cM, part of an unbalanced translocation
	Not reported	?/+	Not reported	ASD, VSD, club feet	Yes	46,XX,del(10)(q23.1q24.2)	11.6 cM
(43) Tsuchiya et al. (1998)	2 years	+/+	Yes (>90th percentile)	Hyperpigmentation multiple areas	Yes	46,XY,del(10)(q23.2q23.33)	10–15 cM
(44) Delnatte et al. (2006)	1 month	+/+	Yes (+2 SD)	Lipoma, hemangioma	No	46,XX.ish del(10)(q23.2q23.3)	2Mb by CGH and PCR
	2.5 months	+/+	Yes (+2 SD)	None reported	No	46,XX.ish del(10)(q23.2q23.3)	2Mb by CGH and PCR
	3 months	+/+	Yes (+2.5 SD)	Hemangioma, speckled penis	No	46,XY.ish del(10)(q23.2q23.3)	Detected in 17% of lymphocytes
	18 months	+/+	Yes (+4 SD)	ASD VSD	No	46,XX,t(2;10)(q31;p15)	1.2 Mb by microsatellite typings and PCR
(45) Salviati et al. (2006)	5 years	−/+	No	Hemangioma, ASD, café-au-lait	Yes	46,XX,del(10)(q22.3q23.33)dn	12.3 Mb by FISH
(46) Menko et al. (2008)	2 years	+/+	Yes (+3 SD)	Cleft palate, VSD	Yes	46,XY.ish del(10)(q23.2q23.31)	2.88 Mb (SNP array)
	18 months	+/+	Yes (+2 SD)	Kyphosis	Yes	46,XY.ish del(10)(q23.2q24.31)	4.26 Mb (SNP array)
	4 years	+/+	Yes (+2 SD)	VSD	Yes	46,XX.ish del(10)(q23.2q23.31)	3.55 Mb (SNP array)
	Not reported		Yes (98th percentile)	Kyphosis	Yes	46,XY.ish del(10)(q23.2q23.31)	4.01 Mb (SNP array)

(ASD: Atrial Septal Defect; CGH: Comparative Genomic Hybridization; cM: centimorgan; dn: *de novo; ish*: in situ hybridization; Mb: Mega-base; SD: Standard deviation; STRP: Single tandem repeat polymorphism; U/L: upper/lower GI tract; VSD: Ventricular Septal Defect.)