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Short Report

Variable phenotypes associated with 10q23 microdeletions involving the *PTEN* and *BMPR1A* genes

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Infantile juvenile polyposis is a rare disease with severe gastrointestinal symptoms and a grave clinical course. Recently, 10q23 microdeletions involving the *PTEN* and *BMPR1A* genes were found in four patients with infantile juvenile polyposis. It was hypothesized that a combined and synergistic effect of the deletion of both genes would explain the condition. Subsequently, however, a patient with a larger 10q23 deletion including the same genes but with a mild clinical phenotype was identified. Here, we present four additional patients with 10q23 microdeletions involving the *PTEN* and *BMPR1A* genes. The sizes of the deletions were analyzed using single nucleotide polymorphism array analysis. All patients had macrocephaly, dysmorphic features, retardation and congenital abnormalities. One patient developed colorectal cancer. However, only one case had disease onset before 2 years of age and severe symptoms requiring colectomy. No clear correlation was found between ages at onset or severity of gastrointestinal symptoms and the sizes of the deletions. We conclude that patients with 10q23 microdeletions involving the *PTEN* and *BMPR1A* genes have variable clinical phenotypes, which cannot be explained merely by the deletion sizes. The phenotypes are not restricted to severe infantile juvenile polyposis but include childhood-onset cases with macrocephaly, retardation, mild gastrointestinal symptoms and possibly early-onset colorectal cancer.

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Juvenile polyps are defined by their microscopic appearance: they show abundant stroma composed of inflamed, often edematous granulation tissue that surrounds cystically dilated glands containing mucus (1). A single juvenile polyp in the distal colorectum is a common cause of rectal bleeding in children. In contrast, juvenile polyposis, defined by the occurrence of multiple juvenile polyps, is rare and occurs in a heterogeneous group of conditions, including 'juvenile polyposis syndrome' (JPS) and '*PTEN* hamartoma syndrome'.

JPS (OMIM 174900) is clinically defined by exclusion of syndromes with multisystem involvement. Criteria for the diagnosis are more than five juvenile polyps in the colorectum, or juvenile polyps throughout the gastrointestinal tract, or any number of juvenile polyps with a family history of juvenile polyposis (1). JPS may be due to germline mutations in the *SMAD4* (18q21.1) or *BMPR1A* (10q23.2) genes (2). The related group of syndromes characterized by juvenile polyposis and multisystem involvement is largely due to *PTEN* germline mutations (10q23). The associated clinical disorders are Cowden disease (OMIM 158350), Lhermitte–Duclos disease, Bannayan–Riley–Ruvalcaba syndrome (BRRS, OMIM 153480) and Proteus/Proteus-like syndrome, now grouped together as *PTEN*-hamartoma syndrome (3).

All forms of juvenile polyposis usually present initially in older children or young adults. However, rare patients with infantile juvenile polyposis have been described who presented in the first year of life with severe gastrointestinal symptoms, including diarrhea, intestinal bleeding, protein-losing enteropathy and intussusception. Many of these patients, in addition, had congenital abnormalities, in particular macrocephaly and generalized hypotonia. Usually, their clinical course was severe, leading to death in early childhood. An autosomal recessive inheritance pattern has been proposed for this condition (4–11).

Recently, Delnatte et al. (12) presented four patients with infantile juvenile polyposis and a 10q23 microdeletion involving both the *PTEN* and the *BMPR1A* genes. These authors hypothesized that infantile juvenile polyposis may not be due to autosomal recessive inheritance but, instead, to a combined and synergistic effect of the deletion of both the *PTEN* and the *BMPR1A* genes. Subsequently, however, Salviati et al. (13) presented a patient with a 10q23 deletion of larger size than those described by Delnatte et al. (12). The deletion again involved both genes but with a mild clinical phenotype without the severe gastrointestinal symptoms of infantile juvenile polyposis.

Here, we present four additional patients with 10q23 microdeletions encompassing both the *BMPRIA* and the *PTEN* genes. We describe the sizes of the deletions determined by single nucleotide polymorphism (SNP) array analysis. In one case with a combined *PTEN* and *BMPR1A* defect, early-onset colorectal cancer was documented.

Clinical data

Case 1 is the second child of healthy, non-consanguineous Moroccan parents. He was born at term after a normal pregnancy and an uneventful delivery with a birth weight of 3850 g. Congenital abnormalities were present including macrocephaly (39 cm, +3 SD) and mild dysmorphic features: low-set ears, telecanthus, eye proptosis, and a long philtrum. There was generalized hypotonia. No abnormal penile pigmentation was observed. Perimembranous and muscular ventricular septal defect with left superior vena cava was diagnosed. An episode of cardiac failure occurred at the age of 6 months. The septal defects closed spontaneously. Gross motor and speech–language development were delayed – motor milestones included sitting at 12 months and walking without support at 28 months. The macrocephaly was progressive (55.5 cm, +5 SD at 14 months). Neurological examination at the age of 2.5 years showed poor maturation of gross and fine motor performance, delay in emotional and cognitive behavior and generalized hypotonia. There was no history of epilepsy. Magnetic resonance imaging (MRI) of the brain showed megalencephaly, dysplastic cerebral ventricles and persistent septum pellucidum and cavum vergae. No hydrocephalus or focal abnormalities of the cerebral architecture were noted. Diarrhea with bloody stools began at the age of 2 years. Colonoscopy performed at the age of 3 years showed multiple pedunculated polyps throughout the large bowel and in between hundreds of small elevations that had the appearance of developing polyps. The five largest polyps were removed. Histological examination showed juvenile characteristics. Upper gastrointestinal tract endoscopy showed several sessile polyps at the pylorus and in the proximal duodenum. Video capsule enteroscopy and MRI enteroclysis showed mild duodenal polyposis and extensive small bowel involvement (Fig. 1).

The family history was negative for any of the clinical signs found in the proband.

Case 2 is the first male child of healthy parents, the father and mother being of Turkish and Iranian origin, respectively. At the age of 5 months, he was admitted to hospital because of dehydration attributed to gastrointestinal infection. The

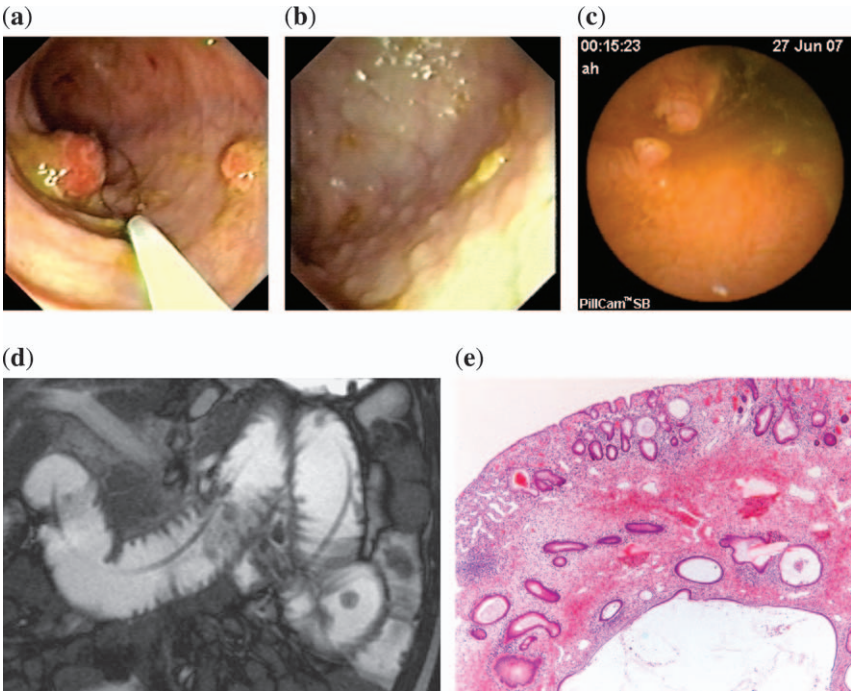

Fig. 1. Case 1. Images obtained during colonoscopy (**a** and **b**), video capsule enteroscopy (**c**) and magnetic resonance enteroclysis (**d**) and polyp histology on hematoxylin–eosin staining (**e**).

patient had macrosomia, length, weight and head circumferences being 2 SD above the mean. At follow-up, the main clinical features were a large head, mild dysmorphic features, mild mental and motor delay, and hypotonia. At the age of 18 months, watery diarrhea occurred that led to a second hospital admission. Colonoscopy revealed juvenile polyposis of the large bowel. At radiological examination, no small bowel polyps were detected. Because of persistent diarrhea, rectal blood loss, anemia and hypoalbuminemia, subtotal ileocolectomy was performed at the age of 23 months. The surgical specimen of 80-cm length showed an enormous number of polyps, with diameters varying from several millimeters to 3.3 cm. A large number of these polyps were spherical and pedunculated. The 3-cm part of the ileum resected also contained multiple polyps. Histologically, the polyps showed juvenile characteristics without features of dysplasia. Physical examination at follow-up at the age of 2 years, previously described by Hendriks et al. (14), showed a hypotonic boy with motor delay. Height and head circumference (54 cm) were above the 97th percentile. His ears were low set and posteriorly rotated. A slight downslant of the eyes was noticed. His philtrum appeared long and his mouth broad. A hemangioma was noted on the thorax. The glans penis could not be examined due to phimosis.

The family history was unremarkable although incomplete. A paternal brother possibly had a mental handicap.

Case 3, a girl, was born at term to unrelated parents from southern Belgium. A heart murmur was caused by a ventricular septal defect. Repeated urinary infections due to vesicoureteral reflux necessitated reimplantation of the ureters. At the age of 10 months, a cleft palate was treated surgically. No skin abnormalities were recorded. Psychomotor development was delayed; walking without assistance began at 20 months and there was no speech development at the age of 4 years. At that age, persistent anemia led to further evaluation. Colonoscopy showed numerous polyps throughout the large bowel. At colonoscopy 1 year later, a great number of polyps was observed, more than 15 at all levels. At upper gastrointestinal endoscopy, several polyps were observed in the gastric fundus, duodenum and jejunum; some had confirmed juvenile histology. At 6 years of age, lung alveolitis was diagnosed and treated with corticosteroids. The patient is presently 16 years of age and is generally doing well. She has macrocephaly and mild mental retardation. Recently, at repeat colonoscopy, several dozens of colorectal juvenile polyps were found, some of which showed features of low-grade dysplasia. The family history in this case was unremarkable.

Case 4 is a patient with mental retardation and remarkable macrocephaly. At the age of 5 years, he was described as having an exceptionally large head that continued to grow well above the 98th percentile. He was a rather short child, being on the third percentile for height with a slightly coarse facies and generalized hypotonia. The

patient's intellectual capacity was significantly delayed. No hemangiomas or other skin lesions were present. Early puberty, kyphosis and an unusual skin condition described as being akin to morphoea were recorded. At the age of 24 years, rectal cancer and liver metastases were diagnosed. The patient presented with weight loss, anorexia and rectal bleeding and was found to have a large polypoidal obstructing tumor in the rectum. Thus, the rest of the bowel was not visualized. Biopsy of the tumor confirmed a moderately differentiated adenocarcinoma. A palliative ileostoma was created but no other treatment was felt appropriate. A contrast-enhanced computed tomography (CT) confirmed a bulky and extensive circumferential thickening of rectum extending up to mid-sigmoid colon, with extensive infiltration of surrounding mesorectal fat, but the tumor did not definitely extend to involve mesorectal fascia. Local, para-aortic and aortocaval lymphadenopathy was noted and extensive hepatic metastases were identified. It was not possible to assess the remainder of the bowel with any degree of certainty due to the marked fecal loading. In conclusion, the patient had a very bulky rectosigmoid tumor, staged on CT san as T3N2M1. Thus, unfortunately, no information on the rest of the bowel was available as the patient never had a laparotomy or colonoscopy due to the obstructing and metastatic nature of his primary tumor. The patient died at the age of 25 years.

The patient had two healthy younger siblings. Both parents were healthy, of normal intelligence and not dysmorphic. No genetic testing could be performed in the parents.

The patient's family history was negative for colorectal cancer in first- and second-degree family members.

Molecular studies

Because all four patients showed developmental delay and features of *PTEN* hamartoma syndrome, routine chromosome analysis (resolution ~600 bands) and DNA sequence analysis of the *PTEN* gene were performed. Additionally, fluorescence in situ hybridization (FISH) using different probes for bands 10q23.2 to 10q23.31 and multiplex ligation-dependent probe amplification (MLPA) analysis (15) of the *PTEN* and *BMPR1A* genes were performed. For this, the SALSA MLPA Kit P158 Juvenile Polyposis (MRC-Holland, Amsterdam, the Netherlands) was used. Information regarding the number and distribution of the different gene probes is given in Fig. 2 (see also http://www.mlpa.com/pages/p158pag.html).

Genotype software allowed determination of the peak height for each polymerase chain reaction product; these data were entered into a spreadsheet developed using Microsoft™ Excel. Data were normalized by dividing each individual peak height by the average of all the autosomal peak heights for the sample. The normalized peak value thus obtained was divided by the average peak height of the same fragment of all control samples within the experiment. Probes with too high a variation between control individuals were excluded.

Further characterization of the deletions was achieved by SNP analysis using the Affymetrix 250k *Nsp*I array, which contains 25-mer oligonucleotides representing a total of 262,264 SNPs. The SNP array experiment was performed according to protocols provided by the manufacturer (Affymetrix, Inc., Santa Clara, CA). Copy number estimates were determined using the updated version 2.0 of the CNAG (Copy Number Analyzer for Affymetrix GeneChip mapping) software package (16). The normalized ratios were subsequently analyzed for genomic imbalances by a standard hidden Markov model, essentially as described by de Vries et al. (17). The SNP array data obtained from patient DNA were compared with SNP array data from multiple healthy sex-matched individuals.

Results

In all four patients, routine chromosome analysis and DNA sequence analysis of the *PTEN* gene did not reveal any abnormalities.

In Case 1, the loss in 10q23 initially identified by FISH (data not shown) was confirmed by region-specific MLPA analysis (Fig. 2) and further characterized by SNP array analysis (Fig. 3). The deletion was *de novo* and appeared to be 2.88 Mb in size (260 SNPs). The deleted region involves 31 known genes, including *BMPR1A* and *PTEN*, with the proximal breakpoint at 88.30 Mb in front of *LDB3* (10q23.2) and the distal breakpoint at 91.18 Mb in SLC16A12 (10q23.31).

The loss in 10q23 in Case 2 was identified by MLPA analysis. Upon SNP array analysis (Fig. 3), it appeared to be 4.26 Mb in size (434 SNPs). This deleted region harbors 38 known genes, including *PTEN* and *BMPR1A*, with the proximal breakpoint between 88.46 and 88.49 Mb in *LDB3* (10q23.2) and the distal breakpoint at 92.72 Mb close to *ANKRD1* (10q23.31). Genetic testing in the parents could not be performed.

The 10q23 microdeletion in Case 3 was observed upon MLPA and appeared to be 3.55 Mb in size (317 SNPs), with the proximal breakpoint at

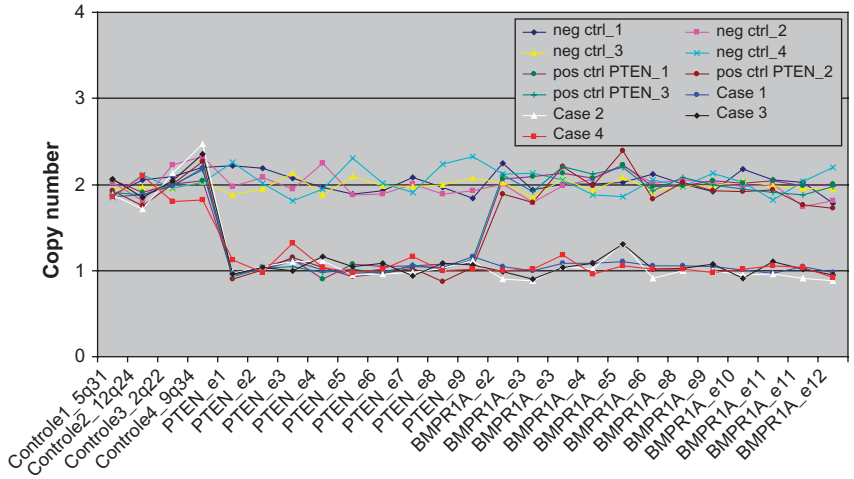

Fig. 2. Copy numbers of the *PTEN* and *BMPR1A* genes. Copy numbers of the *PTEN* and *BMPR1A* genes in patients with a *PTEN* deletion (*pos ctrl PTEN_1-3*) or a combined deletion of *PTEN* and *BMPR1A* (Cases 1–4) and that of control individuals (*neg ctrl*) were determined using multiplex ligation-dependent probe amplification (MLPA) analysis. For this, probes complementary to the indicated chromosomal regions and (parts) of the indicated gene exons (e) within the SALSA MLPA Kit P158 (MRC Holland) have been used. MLPA signals were quantified and normalized to the probes in the control chromosomal regions and control individuals.

86.52 Mb (10q23.2) and the distal breakpoint at 90.07 Mb in BC005364 (10q23.31). The *de novo* deleted region in this patient contains *PTEN* and *BMPR1A* and 15 other known genes.

In Case 4, a combined *PTEN* and *BMPR1A* deletion was detected upon MLPA analysis. The deletion was subsequently confirmed by SNP array analysis and appeared to be 4.01 Mb in size (390 SNPs). The proximal and distal breakpoints are at 86.83 Mb (10q23.1) and 90.84 Mb (10q23.31), respectively.

In Fig. 4, the fully characterized deletions in 10q23 of Cases 1–4 identified in this study and four patients identified in previous studies are depicted schematically. The overlapping region deleted in all eight patients is further delineated proximally by Case C and distally by Case 3, making *PTEN* the most distal deleted gene. This region is 1.47 Mb in size and contains a total number of 10 genes, including *PTEN* and *BMPR1A* as well as *MMRN2*, *SNCG*, *C10orf116*, *GLUD1*, *FAM35A*, *MINPP1*, *PAPSS2* and *ATAD1*.

Discussion

Juvenile polyposis, the occurrence of multiple polyps with juvenile histology, is a rare group of conditions, heterogeneous with regard to clinical picture and underlying cause. Sachatello et al. (9) proposed 'infantile juvenile polyposis' to be a separate clinical entity based on the patient they reported and six cases described previously. These authors defined infantile juvenile polyposis as being characterized by gastrointestinal bleeding, diarrhea, recurrent rectal prolapse, inanition, and intussusception in infants. The authors emphasized that 'six of seven infants with extensive juvenile polyposis died before age 2 years'. The data of the patients described by Sachatello et al. (9), five previous cases (4–8) and two subsequent cases (10, 11) are summarized in Table 1. In all these patients, the family history for polyposis was negative.

The more recently described cases with infantile and childhood-onset juvenile polyposis were subjected to detailed chromosomal and molecular analysis, summarized in Table 2, and now, adding the case histories of four such patients in this report, we can compare the eight patients in whom the sizes of the 10q23 deletions were analyzed in detail, schematically depicted in Fig. 4.

Among these patients, the clinically severe group as defined by requiring colectomy are patients B, C and Case 2. Apparently, there is no clear correlation between deletion size and phenotype in these eight patients.

In recent literature, there has been renewed discussion on the definition of juvenile polyposis of infancy. Salviati et al. (13) stated that 'our patient did not have any of the features of juvenile polyposis of infancy, i.e. onset before age 2 years, severe bleeding, diarrhea, protein-losing enteropathy, inanition, and rectal prolapse'. For this definition, the authors refer to Sachatello et al. (9). Sanlaville et al. (18) state that 'by operational definition, juvenile polyposis in patients younger than 6 years may be classified as "juvenile polyposis of infancy"'. Apparently, two different

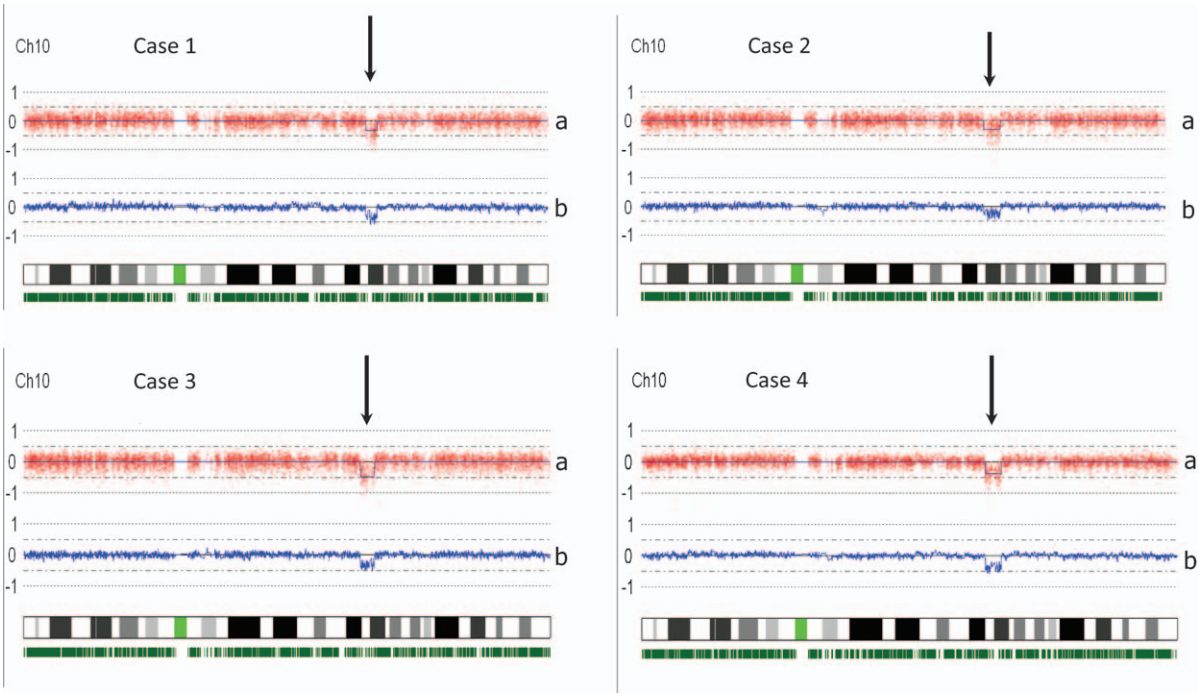

Fig. 3. Plot of chromosome 10 after single nucleotide polymorphism (SNP) analysis on DNA from patients 1, 2, 3 and 4. In the upper panel (a), the $\log_2$ test over reference ratio is plotted on the y-axis *vs* the genomic position on chromosome 10 represented by the idiogram on the x-axis in the lower part of the figure. Each dot represents the value for a certain SNP. The normal ratio with value 0 is indicated by the solid, horizontal blue line. Values for normal ratios range between −0.38 and +0.3. Values outside this range are considered abnormal. In panel (b), each measure point represents the average value of 10 neighboring SNPs. The loss in 10q23 is detected by the significantly lowered ratios shown in panels a and b (black arrow).

aspects are considered: the age of onset and the type and severity of clinical signs and symptoms. We conclude that within the group of early-onset juvenile polyposis, 'infantile juvenile polyposis' seems to stand out as a separate entity not only by its very early onset (before the age of 2 years) but also by the above-described severe clinical signs. Some cases with *PTEN* plus *BMPR1A* deletions have this clinical picture, while others do not.

Previous authors (13, 18) have proposed several possible mechanisms to explain the clinical differences between patients with 10q23 microdeletions. Because in patients with a severe phenotype, the deletions occurred both on paternal and on maternal chromosomes, the paternal origin of the deletion apparently did not play an important role.

We now have identified the proximal and distal breakpoints for each patient using SNP array analysis. The proximal breakpoints of the milder group lie between 82.1 and 88.3 Mb, whereas the severe group has proximal breakpoints between 88.42 and 88.62 Mb. Therefore, at least in theory, the presence of the region between 88.30 and 88.42 Mb may be associated with a more severe clinical phenotype. However, the possible role of the promoter of *LDB3* and the eye-specific *OPN4* gene, which are located in this region, remains elusive. There seems to be no relationship between the position of the distal breakpoints and the severity of the disease.

The overlapping region deleted in all eight patients subjected to SNP analysis is 1.47 Mb wide and includes a total number of 10 genes, including *PTEN* and *BMPR1A* as well as *MMRN2*, *SNCG*, *C10orf116*, *GLUD1*, *FAM35A*, *MINPP1*, *PAPSS2* and *ATAD1*.

Little is known about the function of these genes and their possible role in human disease. *MINPP1*, which presumably plays a role in cell differentiation and apoptosis, was studied in patients with Cowden and BRRS without germline *PTEN* mutations. No *MINPP1* germline mutations were found (19).

An important question is the risk for gastrointestinal malignancies in these patients with 10q23 microdeletions. Both *PTEN* and *BMPR1A* mutations have been associated with juvenile polyposis, whereas *BMPR1A* mutations also have been found in patients with a histologically mixed form of polyposis (20). Two of the patients described by Delnatte et al. (12) had adenomatous polyps, while in one of these patients, an adenocarcinoma in a polyp was found. Therefore, the authors considered the cancer risk for this group of patients to

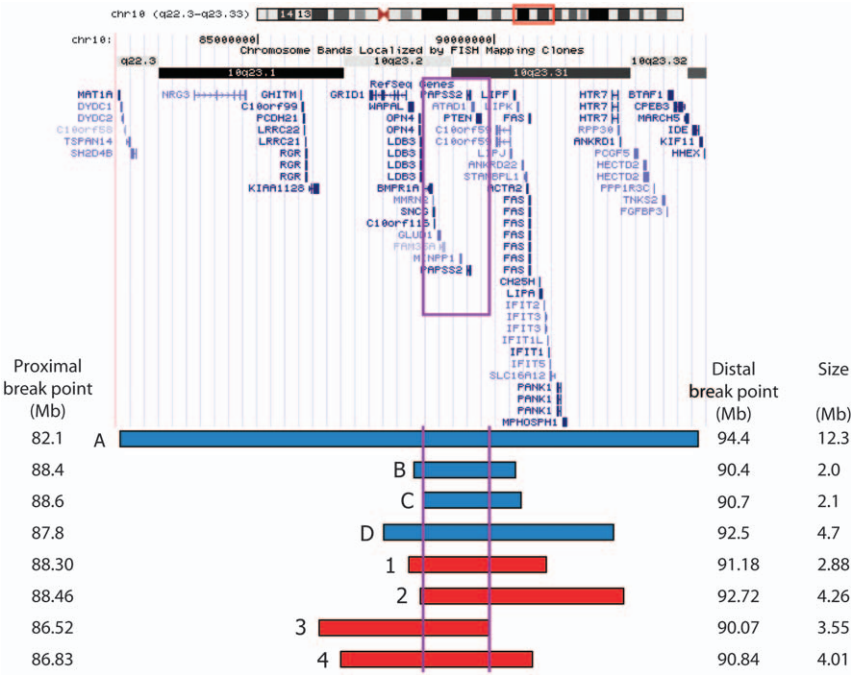

Fig. 4. Schematic representation of the deletion in chromosome 10q23 in patients described in previous studies (A–D) and this study (Cases 1–4). Patients A, B, C and D have been described by Salviati et al. (13) (A), Delnatte et al. (12) (B and C) and Tsuchiya et al. (23) (D). However, it should be noted that patients B and C are not the patients 1 and 2 reported by Delnatte et al. (12), as quoted by Salviati et al. (13); instead, B and C are patients 2 and 1, respectively. The respective deletion start and end points are 82.1–94.4 Mb (patient A), 88.4–90.4 Mb (patient B), 88.6–90.7 Mb (patient C), 87.8–92.5 Mb (patient D), 88.30–91.18 Mb (Case 1), 88.46–92.72 Mb (Case 2), 86.52–90.07 Mb (Case 3) and 86.83–90.84 Mb (Case 4). The losses in 10q23 are schematically indicated by the red rectangle in the idiogram. The overlapping deleted region is indicated by the purple rectangle and includes a total of 10 genes: *BMPR1A*, *MMRN2*, *SNCG*, *C10orf116*, *GLUD1*, *FAM35A*, *MINPP1*, *PAPSS2*, *ATAD1* and *PTEN*.

be major. Probably, the cancer risk is largely dependent on the number and type of polyps found in each individual patient. The remarkable patient whom we describe in this report (Case 4) had macrocephaly, retardation and no obvious gastrointestinal symptoms until the age of 24 years when rectal cancer with liver metastasis was noted. For this patient, a causal relationship between the chromosomal defect and the rectal cancer has not been proven. No additional data on

Table 1. Previous reports on eight patients with infantile juvenile polyposis

	Juvenile polyposis			Other clinical signs				Treatment and follow-up		
M/F	U/L	D/E	Age at onset	Macr	Dysm	Retard	Others	Surgery	Follow-up	Reference
M	+/+[a]	+	4 months					Polypectomies	Died at 6 months	(4)
M	+/+	+	9 months	+	−	+	Alopecia, clubbing, hepatosplenomegaly and hypotonia	Subtotal colectomy	Died at 16 months	(5)
M	+/+	+	6 weeks				Hepatomegaly	Laparotomies	Died at 16 months	(6)
M	+/+	+	3 months	+		+		Laparotomies	Died at 18 months	(7)
M	+/+		9 months	−				Colectomy	Polyps at 16 years	(8)
F	+/+	+	1 month			+	Clubbing, heart defect and hepatomegaly	Colectomy	Died at 22 months	(9)
M	+/+	+	6 months	+			Alopecia, clubbing, hepatomegaly and hypotonia	Ileostomy	Died at 16 months	(10)
M	−/+	+	13 months	+				Laparotomy	Recovered	(11)

D/E, (bloody) diarrhea and/or protein-losing enteropathy; Dysm, facial dysmorphism; F, female; M, male; Macr, macrocephaly; Retard, psychomotor retardation; U/L, juvenile polyposis in upper/lower gastrointestinal tract.
[a]Histological type of polyps not clearly described.

Table 2. Patients with childhood-onset juvenile polyposis and a 10q aberration

		Juvenile polyposis			Other clinical signs				Treatment and follow-up			
Patient id	M/F	U/L	D/E	Age at onset	Macr	Dysm	Ret	Others	Colectomy	Follow-up	Karyotype	Reference
1	M			3 years	−	+	+	Heart defect and clubbing			46,XY,del(10)(q22.3q24.1)	(24)
2	M			18 months	+	+	+	Lipoma	+	11 years	46,XY,del(10)(q23.2q24.1)	(25–27)
3	M				+	+	+		+		46,XY,del(10)(q23.2q24.1) 1.0 cM D10S541-D10S1735	(28)
4	F							Heart defect and clubbing			46,XX,del(10)(q23.1q24.2) 11.6 cM D10S1687-D10S1736	
5[a] D	M	+/+	−	2 years	+	+	+	Digital clubbing and hyperpigmentated penile macula		6 years	46,XY.ish del(10)(q23.2q23.3)	(23)
6[a]	F	+/+	+	1 month	+	+	−	Lipoma and hemangioma	+10 months	Died at 3 years	46,XX.ish del(10)(q23.2q23.3)	(12, 29)
7[a]	F	+/+	+	2.5 months	+	+	−		+17 months	4 years	46,XX.ish del(10)(q23.2q23.3)	
8[a]	M	+/+		3 months	+	−	−	Hemangioma and speckled penis	+8 years	14 years	46,XY.ish del(10)(q23.2q23.3)	
9[a,b]	F	+/+		18 months	+	+	−	Heart defect	−	18 months	46,XX,t(2;10)(q31;p15)	
10[a] A	F	−/+	−	5 years	−	+	+	Heart defect	−	Favorable	46,XX,del(10)(q22.3q23.33)dn 12.3 Mb loss (FISH)	(13)
11 Case 1	M	+	−	2 years	+	+	+	Heart defect and hypotonia	−		46,XY.ish del(10)(q23.2q23.31) 2.88 Mb loss (SNP array)	This study
12[c] Case 2	M	+	+	18 months	+	+	+	Hypotonia and hemangioma	+23 months		46,XY.ish del(10)(q23.2q24.31) 4.26 Mb loss (SNP array)	
13 Case 3	F	/+	−	4 years	+	+	+	Cleft palate and heart defect	−		46,XX.ish del(10)(q23.2q23.31) 3.55 Mb loss (SNP array)	
14 Case 4	M		−		+	+	+	Course facies and kyphosis		Died at 25 years	46,XY.ish del(10)(q23.2q23.31) 4.01 Mb loss (SNP array)	

D/E, bloody diarrhea and/or protein-losing enteropathy; Dysm, facial dysmorphism; F, female; M, male; Macr, macrocephaly; Ret, psychomotor retardation; U/L, juvenile polyposis in upper/lower gastrointestinal tract.

[a]Patient 5 is quoted by Salviati et al. (13) as patient D in Fig. 4; patients 6–9 are patients 1–4 in Delnatte et al. (12), respectively; patients 1 and 2 in Delnatte et al. (12) are quoted by Salviati et al. (12); see also Fig. 4. Patient 10 described by Salviati et al. (12) is patient A in Fig. 4.

[b]Also described by Sweet et al. (29).

[c]Also described by Hendriks et al. (14).

gastrointestinal pathology (the presence or absence of polyposis) are available. Molecular analysis of the tumor did not indicate a mismatch repair defect. In the context of the other data, the malignancy may well be due to the 10q23 microdeletion.

Recently, additional patients with combined *PTEN* and *BMPR1A* deletions identified by MLPA analysis have been reported (21, 22). One of these cases had thyroid cancer, underlining the variability of clinical phenotypes for this group of patients.

As indicated in Tables 1 and 2, several patients with 10q23 deletions have had heart defects. These defects were mostly atrial and/or ventricular septal defects but also included left superior vena cava, tricuspid insufficiency, dysplasia of the pulmonary valve, and atresia of the portal vein. These defects may well be associated with the complex genetic alterations involved in chromosomal microdeletions and not be due to a single gene defect.

The current possibilities of DNA-based diagnosis have led to new classifications of many syndromes and may now shed new light upon infantile and childhood-onset forms of juvenile polyposis. Deletion analysis seems to be warranted in patients with clinical pictures associated with *PTEN* and *BMPR1A* mutations, in particular juvenile polyposis, histologically mixed forms of polyposis and macrocephaly. For diagnostic purposes, gene-specific deletion analyses, such as MLPA, would be adequate. However, if a detailed analysis of breakpoint boundaries is required, array CGH would be the method of choice.

We conclude that patients with 10q23 microdeletions involving the *PTEN* and *BMPR1A* genes have variable clinical phenotypes, which are largely independent of the deletion size. Moreover, the phenotypes are not restricted to severe infantile juvenile polyposis but include childhood-onset cases with macrocephaly, retardation and mild gastrointestinal symptoms and possibly early-onset colorectal cancer and other malignancies.

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