Deletion of *PTEN* and *BMPR1A* on Chromosome 10q23 Is Not Always Associated with Juvenile Polyposis of Infancy

To the Editor: We read, with great interest, the report by Delnatte et al.[1] published in the June 2006 issue of *The American Journal of Human Genetics*. The authors describe four patients who presented with a severe form of juvenile polyposis of infancy (JPI), with interstitial deletions of chromosome 10q23 encompassing the *BMPR1A* and *PTEN* genes. The authors hypothesize that this genetic defect is specific to JPI and that such a severe phenotype reflects cooperation between these two tumor-suppressor genes.

We report a patient who had a similar interstitial deletion of chromosome 10 that was, however, associated with a significantly milder phenotype. The patient, an 8-year-old girl, was born in the 36th gestational week to nonconsanguineous parents with a family history negative for JPI. Birth weight was 2,850 g (75th percentile), length was 50 cm (75th–90th percentile), and head circumference was 34 cm (50th–75th percentile). Perinatality and early development were normal. Mild developmental delay was noticed during the 2nd year of life.

She was first seen at our clinic at age 3 years and 7 mo. Head circumference was 49 cm (−0.5 SD), weight was 14.5 kg (10th–25th percentile), and height was 97.5 cm (50th percentile). She had mildly dysmorphic features: sparse

Figure 1. Histology of resected polyps. Hematoxylin and eosin stain is shown at 50 × (*A* and *C*) and 200 × (*B* and *D*) magnification. *A,* Sessile-peduncolated lesion with features of a typical juvenile polyp, characterized by large cysts containing mucus. *B,* Area with atypical epithelium in the head of the lesion. *C,* Another polypoid lesion with features of juvenile polyp. *D,* Proliferation of gangliar cells in the lamina propria.

hair, epicanthic folds, hypoplastic nasal bone, protruding lower lip, small ears, and high-arched palate, with normal tooth development. A single 1.5 × 1.5–cm café-au-lait spot on the left thigh was present; no other cutaneous lesions were noticed.

Heart sonogram revealed a small atrial septal defect. Results from electroencephalogram, brain magnetic resonance imaging, audiometric tests, and funduscopic examination were normal. Our patient had never complained of gastrointestinal symptoms, and she did not have her first episode of mild rectal bleeding until age 5 years. Colonoscopy performed at age 6 years detected multiple (>15) polyps throughout the entire length of the colon. Histology of resected lesions was compatible with juvenile polyps, and the largest polyp also had areas of low-grade focal dysplasia in the head of the lesion (fig. 1). Upper-gastrointestinal-tract endoscopy and videoendos-

Table 1. BAC Clones Spanning the Region from 10q22 to 10q23 Used in FISH Experiments

BAC Clone	Location (Mb)	Cytogenetic Band	FISH Signals on Chromosome 10
RP11-119F19	81.0–81.2	10q22.3	+/+
RP11-773D16	81.4–81.5	10q22.3	+/+
RP11-479O17	81.6–81.8	10q22.3	+/+
RP11-40F6	81.91–81.99	10q22.3	+/+
RP11-36D19	82.0–82.15	10q22.3	Weaker signal on del(10q)
RP11-93O23	82.16–82.33	10q22.3	+/−
RP11-175M21	82.4–82.6	10q22.3	+/−
RP11-102H24	82.8–82.95	10q22.3	+/−
RP11-202D18	83.8–83.4	10q23.1	+/−
RP11-156D10	84.5–84.7	10q23.1	+/−
RP11-99I12	84.7–84.9	10q23.1	+/−
RP11-124L5	85.8–86.0	10q23.1	+/−
RP11-134O16	87.6–87.8	10q23.2	+/−
RP11-96C23	88.7–88.9	10q23.2	+/−
RP11-79A15	89.4–89.6	10q23.31	+/−
RP11-380G5	89.6–89.8	10q23.31	+/−
RP11-106M14	93.3–93.5	10q23.32	+/−
RP11-74B2	93.9–94.1	10q23.32	+/−
RP11-61K23	94.0–94.2	10q23.33	+/−
RP11-366I13	94.2–94.4	10q23.33	+/−
RP11-469M1	94.4–94.6	10q23.33	Weaker signal on del(10q)
RP11-148C9	94.6–94.8	10q23.33	+/+
RP11-280G19	94.8–95.0	10q23.33	+/+
RP11-162K11	95.7–95.9	10q23.33	+/+
RP11-30E16	95.2–95.4	10q23.33	+/+
RP11-146P21	96.0–96.2	10q23.33	+/+
RP11-208c17	96.6–96.8	10q23.33	+/+
RP11-248J23	97.6–97.8	10q24.1	+/+
RP11-34E5	98.2–98.4	10q24.1	+/+

NOTE.—BAC clones spanning the region from 10q22 to 10q23 used in FISH experiments were selected from the human library RPCI-11, according to the UCSC Genome Browser (May 2004). *BMPR1A* is located between 88.5 and 88.6 Mb, *PTEN* is located between 89.6 and 89.7 Mb, and *FAS* is located at 90.4 Mb.
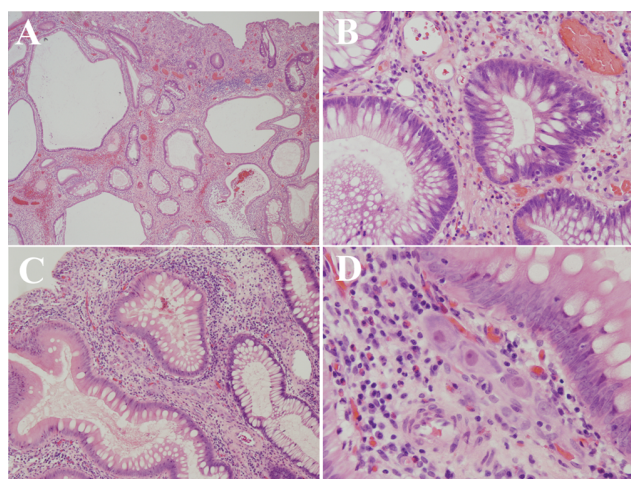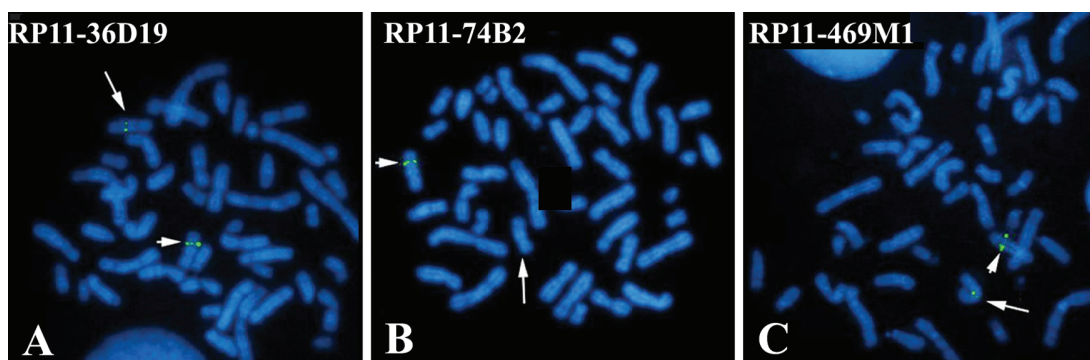
Figure 2. FISH analysis. Probes RP11-36D19 (*A*), RP11-74B2 (*B*), and RP11-469M1 (*C*) show weaker signals at the breakpoints (*A* and *C*) and absence of signal on del(10) (*B*). Short arrow = normal chromosome 10; long arrow = del(10).

copic examination of the small intestine were normal. She never experienced major bleeding, iron-deficient anemia, or diarrhea.

A high-resolution karyotype detected an interstitial deletion of chromosome 10q23. To define the deletion at the molecular level, we proceeded with FISH experiments, using BAC clones spanning the region from 10q22 to 10q23 (table 1 and fig. 2). The final interpretation of the rearrangement was a 12-Mb deletion from 10q22.3 (BAC clone RP11-36D19, at 82.1 Mb) to 10q23.3 (BAC clone RP11-469M1, at 94.4 Mb). We genotyped eight STS loci in the 10q region of the patient and of her parents. Results are summarized in table 2. The deletion was de novo and involved the paternal chromosome. Analysis of the deleted region revealed that it contains 87 genes, many still uncharacterized. *BMPR1A, PTEN,* and *FAS* are the most notable genes involved.

Juvenile polyposis syndrome (MIM 174900) is composed of three main subtypes: JPI, juvenile polyposis coli, and generalized juvenile polyposis.[2] It is still debated whether these three subtypes represent different clinical entities or are variants of the same clinical form.[3]

Delnatte et al.[1] suggest that JPI is a contiguous-gene syndrome and that the deletion of both *PTEN* and *BMPR1A* is the specific genetic defect of this form. They propose that these two genes have a synergistic effect on the development of this severe phenotype.

The clinical picture of our patient, who harbors a similar deletion, is remarkably different from those of the four patients described by Delnatte et al.[1] and from that of the patient described by Tsuchiya et al.,[4] all of whom have a proven deletion of both genes. Our patient did not have any of the features of JPI (i.e., onset before age 2 years, severe bleeding, diarrhea, protein-losing enteropathy, inanition, and rectal prolapse[5]), and polyps were found only in the colon. Three of the four patients reported by Delnatte et al.[1] underwent colectomy at ages 10 mo, 17 mo, and 8 years because of the severity of symptoms, such as diarrhea and bleeding. Although our patient is still oligosymptomatic, we are now considering prophylactic co-

Table 2. Results of Genotyping of STS Loci in the 10q Region

Locus	Location (Mb)	Size of PCR Product[a] (bp)			Result
		Proband	Mother	Father	
D10S1730	78.60	234/236	236/250	234/240	Not deleted
D10S219	80.52	86/92	86/92	86/92	Not deleted
D10S1686	85.55	196	182/196	184/194	Paternal allele deleted
D10S1765	89.59	168	168/182	172	Paternal allele deleted
D10S583	94.35	203	203	212	Paternal allele deleted
D10S1709	99.37	158/166	152/166	156/158	Paternal allele deleted
D10S1266	102.31	158.11	158/160	156/158	Uninformative
D10S1741	109.11	250/252	250	248/252	Not deleted

NOTE.—Genotyping of polymorphic loci was performed by amplification with primers labeled with fluorescent probes, followed by analysis on an ABI 310 Genetic Analyzer (Applied Biosystems). Nonpolymorphic loci were assayed by electrophoresis on agarose gels (not shown).

ᵃ Some cells have two values because the individual is heterozygous for that particular STS, whereas others have just one value because the individual is either homozygous or hemizygous at that locus. The comparison with the parents allows one to distinguish between these last two cases.
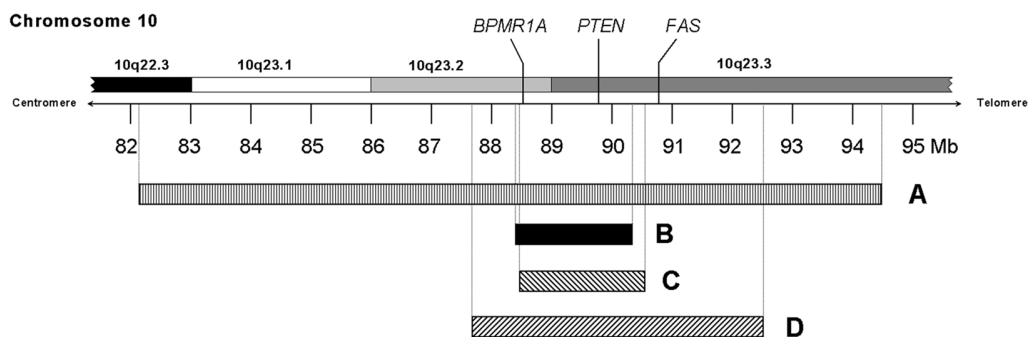
Figure 3. Schematic representation of the 10q22-10q23 deletion in our patient (*A*), in patients 1 (*B*) and 2 (*C*) reported by Delnatte et al.,[1] and in the patient (*D*) reported by Tsuchiya et al.[4]

lectomy, because of the foci of dysplasia found in one polyp. Furthermore, our patient did not display any of the clinical signs typical of Cowden syndrome (CS [MIM 158350]) or Bannayan-Riley-Ruvalcaba syndrome (MIM 153480)—in particular, she did not have macrocephaly, cutaneous lesions, or lipomas,[6] and only mild and aspecific dysmorphic signs were present. Even though some of the features of CS, as well as extracolonic polyps, may appear at a later age, the clinical picture of our patient underscores the phenotypic variability of 10q23 deletions. There are several possible explanations for this phenomenon. It may reflect the ample phenotypic variability of *PTEN* mutations (also intrafamilial), which is well documented.[6] Conversely, a rare haplotype at either the nondeleted *PTEN* or *BMPR1A* locus in our patient might be associated with a high level of expression of the remaining allele. Other genetic modifier loci may also play an important role in determining the phenotype. Our patient harbored a deletion that extended from 82.1 to 94.4 Mb, which was larger than those of the patients reported elsewhere (fig. 3). The two deletions fully characterized by Delnatte et al.[1] extended from 88.4 to 90.4 Mb (patient 1) and from 88.5 to 90.6 Mb (patient 2), whereas the deletion in the patient reported by Tsuchiya et al.[4] ranged from 87.8 to 92.5 Mb. One can speculate that deletion of one or more genes in the 82.1–87.8-Mb and 92.5–94.4-Mb regions might contribute to the milder phenotype in our patient; however, this hypothesis seems unlikely, and we could not identify any obvious gene with such a role within these regions. The size of the deletion, however, may be related to the presence of mild mental retardation. This feature was present in our patient and in the patient who harbored larger deletions, reported by Tsuchiya et al.,[4] whereas patients 1 and 2 with smaller deletions, reported by Delnatte et al.,[1] had normal intelligence. To clarify these issues, a larger number of patients must be characterized at the molecular level. Finally, the parental origin of the deletion does not seem to contribute to the clinical presentation, since Delnatte et al.[1] report both paternal and maternal deletions in their series of patients with a severe phenotype.

Variable expressivity is not uncommon for microdeletion syndromes. An example is DiGeorge/velocardiofacial syndrome, which is associated with deletions of the 22q11.2 region.[7] Patients display a marked clinical variability, even within the same family.[8] This variability is probably due, in part, to nongenetic factors, as demonstrated by studies of identical twins.[9] The 10q23 microdeletions probably behave in a similar fashion.

Interestingly, our patient's deletion included *FAS,* a gene with a pivotal role in regulating apoptosis. Analysis of the deletion breakpoints of the patient with severe JPI reported by Tsuchiya et al.[4] reveals that *FAS* was also deleted. Mutations in *FAS* have been associated with a fatal autosomal dominant lymphoproliferative disorder (autoimmune lymphoproliferative syndrome [MIM 601859]).[10] Our patient did not show any of the early features of this disorder (i.e., lymphadenomegaly, splenomegaly, hemolytic anemia, and hypergammaglobulinemia), and her immune function is essentially normal. No immune abnormalities were reported by Tsuchiya et al. either.[4] These data suggest that *FAS* haploinsufficiency is not associated with a specific phenotype and confirm that heterozygous mutations in *FAS* probably act through a dominant negative mechanism.[10] We are currently evaluating in depth the immune function of our patient, to unveil minor abnormalities of lymphocyte function.

In conclusion, we believe that the phenotypic spectrum of the deletion of both *PTEN* and *BMPR1A* is not restricted to JPI and that further clinical and experimental data are needed to confirm the postulated cooperative mechanism between these two genes. To avoid ascertainment bias, deletion screening should not be limited to patients with JPI but should be performed also in patients with less severe phenotypes.

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Web Resources

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for juvenile polyposis syndrome, CS, Bannayan-Riley-Ruvalcaba syndrome, and autoimmune lymphoproliferative syndrome)

UCSC Genome Browser (May 2004), http://genome.ucsc.edu/

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Reply to Salviati et al.

To the Editor: In this issue, Salviati and colleagues report the case of an 8-year-old girl whose mild developmental delay and dysmorphic features led them to perform a high-resolution karyotype.[1] A 12-Mb deletion located in 10q23 and encompassing the *PTEN* and *BMPR1A* loci was detected. The child presented with rectal bleeding at age 5 years. Colonoscopy at age 6 years uncovered >15 hamartomatous polyps throughout the entire colon, allowing the diagnosis of juvenile polyposis (JP). By operational definition, JP in patients younger than 6 years may be classified as "JP of infancy." Thus, the rectal bleeding in this child at age 5 years was almost certainly due to the juvenile polyps uncovered only the following year; therefore, this case corroborates our report.[2] However, the presentation and the disease course of the patient reported by Salviati et al.[1] were not as severe as those of the four patients reported in our recent study[2] and about which we hypothesize that the cooperation of the deletions of both tumor-suppressor genes *PTEN* and *BMPR1A* leads to severe JP and, hence, to cases of JP of infancy. The report by Salviati and colleagues[1] is very interesting, illustrating that a very large deletion (12 Mb, compared with 2 Mb in patients 1 and 2 in our report[2] and ~4.8 Mb in the patient reported by Tsuchiya et al.[3]) may be, paradoxically, associated with a less severe disease course than a small deletion or a point mutation. As proposed by Salviati and colleagues,[1] the protective effect of a modifier allele of a gene unlinked to the *PTEN* and *BMPR1A* genes may explain this phenomenon even if, at the present time, no candidate gene is suggested. Another explanation for this milder phenotype may be the increased expression level of the *PTEN* and *BMPR1A* genes by the remaining allele, which thus allows correction of the haploinsufficiency. Indeed, evidence is accumulating that allelic-specific expression is relatively common among nonimprinted autosomal genes and may be due to *cis*-acting, genetically inherited variations.[4] Because of the very large size of the 10q22.3-q23 deletion in the patient reported by Salviati and colleagues,[1] we speculate that, without the increased expression level by the remaining chromosome of some critical genes other than *PTEN* and *BMPR1A* located in the deleted region, this condition would have been lethal. Thus, we suggest that the affected child may have some *cis*-acting–specific sequences in the remaining allele that correct the haploinsufficiency in the 10q22.3-q23 region and lead, paradoxically, to an attenuated phenotype. The study by Salviati et al.[1] illustrates how meticulous analyses of cases presenting with a similar disease are useful. Together with our original publication, this study should spur the international community to cooperatively and systematically study all JP syndrome diagnoses, the frequency of deletion of either or both genes, and their pre-