Short Report

Clinical and molecular characterization of individuals with recurrent genomic disorder at 10q22.3q23.2


The identification of genomic imbalances in young patients can affect medical management by allowing early intervention for developmental delay and by identifying patients at risk for unexpected medical complications. Using a 105K-feature oligonucleotide array, we identified a 7.25 Mb deletion at 10q22.3q23.2 in six unrelated patients. Deletions of this region have been described in individuals with cognitive and behavioral abnormalities, including autistic features, and may represent a recurring genetic syndrome. All four patients in this study for whom clinical information was available had mild dysmorphic features and three had developmental delay. Of note is the emerging clinical phenotype in these individuals with similar dysmorphic features such as macrocephaly, hypertelorism, and arachnodactyly, and neurodevelopmental delay that includes failure to thrive, hypotonia, and feeding difficulties in the neonatal period, and receptive and expressive language delay with global neurodevelopmental delay after the neonatal period. However, there is no pattern of abnormalities, craniofacial, behavioral, or otherwise, that would have aroused clinical suspicion of a specific syndrome. Finally, the patients’ deletions encompass BMPR1A but not PTEN, and these patients may be at risk for colon cancer and should be referred for appropriate prophylactic care and surveillance. Of the two patients in this study who had colonoscopy following the array results, neither had polyps. Therefore, the magnitude of the increased risk for colon cancer is currently unknown.

Deletions of 10q22.3q23.2 were recently described in three unrelated patients as a recurrent genomic disorder associated with cognitive and neurobehavioral abnormalities including autism and mild developmental delay (1). One patient had a 5.73 Mb deletion (genomic coordinates [UCSC 2006 assembly]: approximately 84.147 Mb to approximately 89.875 Mb), whereas two patients had similar approximately 7.2 Mb deletions (genomic coordinates: approximately 81.625 Mb to approximately
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89.140 Mb). Both of these patients presented with neurobehavioral abnormalities and dysmorphic features including macrocephaly. Analysis of the architecture of 10q22.3q23.2 identified low-copy repeats (LCRs), highly homologous segmental duplications, flanking the deletion breakpoints. LCRs are known to mediate rearrangement through non-allelic homologous recombination and likely caused the genomic deletions seen in these patients (2, 3).

The 10q22.3q23.2 region is of clinical interest because point mutations in bone morphogenesis protein receptor protein 1A (BMPR1A; genomic coordinates: 88.507 Mb–88.674 Mb) are known to cause juvenile polyposis syndrome (JPS), a rare autosomal dominant condition that is characterized by multiple gastrointestinal juvenile polyps and an increased risk of colorectal cancer ('juvenile' referring to the histological type of polyp, not the age at onset of the polyps nor of cancer) (4, 5). BMPR1A is a gene involved in the BMP superfamily that downregulates cell proliferation in the gastrointestinal track (6). Direct sequencing of the BMPR1A gene has identified point mutations in 21.6% of patients diagnosed with JPS (4). Analysis by multiplex ligation-dependent probe amplification (MLPA) identified larger deletions in two of 60 patients (3.3%) (4). One of these deletions included only the promoter and the first non-coding exon of BMPR1A, whereas the second was a contiguous gene deletion that included BMPR1A and the phosphatase and tensin homolog (PTEN- genomic coordinates: ~89.614 Mb to ~89.714 Mb) (4). Although deletions that encompass one or a few exons of BMPR1A have been described in patients with JPS, no deletions that remove the entire BMPR1A gene but no additional genes have been identified in patients presenting with JPS (5, 7). Thus, it is unclear whether deletion of BMPR1A without PTEN is a risk factor for JPS.

Recent publications (8–10) suggest the combined effects of PTEN and BMPR1A cause variability in one subtype of JPS called juvenile polyposis of infancy (JPI). The deletions of both of these genes together seemingly cause juvenile polyposis, although there is variability in age of onset. The tumor suppressor role of PTEN has long been recognized (11). PTEN hamartoma tumor syndrome includes several distinct syndromes caused by point mutations in or whole-gene deletions of the PTEN gene – Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome (BRRS), and Proteus syndrome (12).

Here, we report the molecular and clinical findings in four additional individuals with deletions of 10q22.3q23.2 that delete BMPR1A but not PTEN. The common clinical features among this cohort further refine the phenotype of the 10q23 microdeletion syndrome.

Materials and methods

Study subjects

Individuals in this study were identified among 9647 samples with clinical indications of mental retardation, developmental delay, and multiple congenital anomalies tested by microarray-based comparative genomic hybridization (aCGH) between November 2007 and December 2008. For the individuals with deletions of 10q22.3q23.2 presented here, consent to review medical records was obtained using forms approved by the Institutional Review Board of Spokane.

Microarray analysis

aCGH was initially performed with a bacterial artificial chromosome (BAC)-based microarray (the SignatureChip Whole Genome™; Signature Genomics, Spokane, WA) (13) or with an oligonucleotide microarray using a 105K-feature whole-genome microarray (SignatureChipOS™, made for Signature Genomic Laboratories by Agilent Technologies, Santa Clara, CA) as previously described (14, 15). All cases run on a BAC platform were re-run on the oligonucleotide microarray platform. Results were visualized using Signature Genomics’ laboratory-developed computer software program Genoglyphix (http://www.signaturegenomics.com/genoglyphix.html).

Fluorescence in situ hybridization

Deletions of 10q22.3q23.2 were confirmed and visualized by metaphase fluorescence in situ hybridization (FISH) using BAC clone RP11-1005L9 from 10q23.2 as previously described (16).

Results

Molecular characterization of deletions

We identified six individuals with deletion of 10q22.3q23.2 among our patient population. In all six individuals, high-density 105K oligonucleotide microarray analysis detected a single-copy loss of 181 probes spanning 7.25 Mb of 10q22.3q23.2 (chr10: 81,682,644-88,931,994, based on the UCSC 2006 hg18 assembly) (Fig. 1a). Both the proximal and distal breakpoints are flanked by LCRs. The LCR encompassing the proximal breakpoint contains two large (>300 kb),
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Table 1. Clinical features of individuals with deletion of 10q22.3q23.2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>2 years 7 months</td>
<td>17 years 1 month</td>
<td>8 days</td>
<td>1 year 8 months</td>
</tr>
<tr>
<td>Indication for study</td>
<td>Dysmorphic features, congenital heart defect (PDA, requiring surgery) del(10)(q22.3q23.2)dn</td>
<td>Developmental delay, dysmorphic features, mild hypotonia, del(10)(q23.1q23.3)dn</td>
<td>Dysmorphic features, bilateral hearing loss, club feet</td>
<td>Developmental delay, FTT, macrocephaly</td>
</tr>
<tr>
<td>Craniofacial</td>
<td>mild, sparse blond-gray hair</td>
<td>Normal brown hair, mild facial asymmetry</td>
<td>Nomocephalic with mild plagiocephaly</td>
<td>Macrocephaly, frontal bossing, fine, sparse straight blond hair</td>
</tr>
<tr>
<td>Mouth and jaw</td>
<td>Micrognathia, high-arched palate, thin upper lip</td>
<td>High palate, prognathic mandible</td>
<td>Intact palate</td>
<td>Narrow philtrum, retroglossa, small mouth</td>
</tr>
<tr>
<td>Eyes</td>
<td>Upslanting palpebral fissures, mild hypertelorism</td>
<td>Downsllanting palpebral fissures</td>
<td>Hypertelorism, mild epicanthal folds</td>
<td>Downsllanting palpebral fissures, hypertelorism</td>
</tr>
<tr>
<td>Ears</td>
<td>Overfolding of lateral pinna, earlobe creases</td>
<td>Borderline position</td>
<td>Low-set, posteriorly rotated ears, narrow ear canals</td>
<td>Small (&lt; 2 SD) swept-back ears, bilateral notch mid helix</td>
</tr>
<tr>
<td>Marfan features</td>
<td>Arachnodactyly, joint hyperextensibility</td>
<td>Mild arachnodactyly, joint hyperextensibility, history of myopia, malar flattening, high-arched palate, proagnathism</td>
<td>No; height at 52%, weight at 90%, hands and feet at 97%</td>
<td></td>
</tr>
<tr>
<td>Feeding issues</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>None noted</td>
<td>Hypotonia</td>
<td>Mild hypotonia</td>
<td>Mild hypotonia</td>
</tr>
<tr>
<td>Behavioral abnormalities</td>
<td>Severe tantrums, poking at eyes, laughing, repetitive gulping sounds, fascination with lights</td>
<td>None of note</td>
<td>None of note</td>
<td>None of note</td>
</tr>
<tr>
<td>Development</td>
<td>Significant delay</td>
<td>Borderline to low cognitive ability, ADHD</td>
<td>Delayed</td>
<td>Delayed</td>
</tr>
<tr>
<td>Language</td>
<td>Delayed receptive language</td>
<td>Delayed receptive, expressive, auditory language processing, speech impairment, mild oral motor deficits</td>
<td>Delayed receptive and expressive language</td>
<td></td>
</tr>
<tr>
<td>JPS symptoms</td>
<td>Rectal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADHD, attention deficit/hyperactive disorder; FTT, failure to thrive; JPS, juvenile polyposis.

Highly homologous (99.8% identity) segmental duplications which are composed of smaller modules with different orientations that are dispersed elsewhere on chromosome 10 and on other chromosomes. The LCR spanning the distal break-point contains approximately 170 kb of sequence homologous to the proximal LCR and >100 kb of sequence homologous to LCRs located near the chromosome 10 centromere (1). Metaphase FISH analysis with BAC probe RP11-100S5L9 to 10q23 confirmed a deletion in all subjects (Fig. 1b). FISH performed on both parents for Patients 3 and 4 was normal, indicating the patients’ deletions are apparently de novo. Two of the patients studied were known to have a 10q22.3q23.2 deletion. One (Patient 1) was referred to elucidate the breakpoints of the 10q deletion seen by karyotyping, and a second patient’s (Patient 2) sample was referred after oligonucleotide aCGH at another institution identified a 4.5-Mb deletion at 10q23.1q23.2, with a 5.8 Mb proximal gap and a 1.1 Mb distal gap in coverage. By report, parental FISH analyses did not identify any deletion or rearrangement, indicating that these too were apparently de novo events.

Clinical characterization of subjects with 10q deletions

The clinical features for the four individuals with deletion of 10q22.3q23.2 for whom records were available are summarized in Table 1.
Recurrent microdeletion at 10q22.3q23.2

Fig. 1. Analysis of individuals with microdeletions of 10q22.3q23.2. (a) Representative microarray plot showing single-copy loss of 181 oligonucleotide probes spanning approximately 7.25 Mb at 10q22.3-10q23.2 (chr10:81,682,644-88,931,994). Clones are ordered on the x-axis according to physical mapping positions with distal 10p to the left and distal 10q to the right. (b) Metaphase fluorescence in situ hybridization (FISH) analysis showing deletion of 10q23.2. BAC clone RP11-1005L9 from the deleted region on the microarray is labeled in red, and the chromosome 10 centromere 10 probe is labeled in green as a control. One red signal is present, indicating a deletion. (c–f) Facial features of patients (c) 1, (d,e) 2, and (f) 4. Note the prominent forehead, apparent macrocephaly, relative mild midface hypoplasia (Patients 1 and 2), and thin upper lip (Patients 1, 2 and 4). (g) Schematic of the 10q22.3-q23.31 region. Deletion sizes of individuals in this and previous studies (Balciuniene et al. 2007) are represented by green bars. The genes BMPRIA and PTEN are represented by blue boxes.

Patient 1 is a 2-year 7-month-old male who was born at 33 weeks’ gestation to a 21-year-old G1P0 mother as a result of an emergency C-section due to maternal bleeding and fetal distress. Patient was 4 lbs, 7 oz at birth (less than fifth percentile) and was 22 inches in length (>95th percentile). The genetics service was consulted for mild dysmorphic features noted at birth. Assessment showed a long, flat head; micrognathia; a high-arched palate; tongue tie; a thin upper lip; mild hypertelorism and upslanting palpebral fissures, earlobe creases, overfolding of the lateral pinna, sparse and pale hair, tapering of the fingers distally, long fingers and toes giving the impression of arachnodactyly, mild bilateral hyperextensibility, and prominent bilateral fingerpads. Karyotype analysis revealed a deletion at 10q22.3q23.2. Subsequent FISH analysis of the PTEN locus using a commercially available probe showed hybridization signals on both chromosome 10 homologs, indicating that the PTEN locus was not deleted.

This patient is significantly delayed in both development and communication. Assessment at 2 years showed that his functional skill level was less than the first percentile for cognition, language, and motor skills. He is not hypotonic. He walked at 14 months. A speech assessment at age 2-½ years showed that he was functioning at the level of a 10- to 12-month-old. At that time, his fine motor skills were noted to be delayed to the level of a 12- to 14-month-old. He could not feed himself nor is he toilet trained. He has significant temper tantrums and is in the high-risk range.
for autism because of several peculiar behaviors. Figure 1c shows the facial features of Patient 1.

Patient 2 is a 17-year-old 10-month-old female with a history of learning delay and mild dysmorphic features. The patient was born at full-term after an uncomplicated pregnancy and normal spontaneous vaginal delivery to a 29-year-old G2P1. As a neonate, the patient had difficulty feeding because of irritability and refusal, resulting in failure to thrive. At this time, the patient had an upper endoscopy and was diagnosed with gastritis. A colonoscopy at that time showed mild chronic inflammation of the cecum. A repeated colonoscopy at 4 months revealed a large polypoid mass containing lymphoid tissue at the junction between the ascending colon and the cecum. Biopsies showed no dysplasia or hypoplasia. At 7 months of age, a colonoscopy showed a cecal mass. Biopsy showed lymphoid hypoplasia.

Concerns about developmental delays were first noted at age 24 months. At age 28 months, the patient was evaluated for speech and language delays. Evaluation revealed speech impairment in articulation and verbal expression with an oral motor component contributing to poor feeding and speech skills. Because of learning difficulties persistent at age 7 years 2 months, additional evaluation showed delayed speech and language development with borderline to low average cognition, characterized by delays in expression, and receptive and auditory language processing. The patient was also diagnosed with attention deficit hyperactive disorder.

Mild dysmorphisms include downslanting palpebral fissures, high-vaulted palate, and a possibly prognathic mandible (Fig. 1d,e). Several of this patient’s features were suggestive of Marfan syndrome, including mild arachnodactyly, history of myopia, malar flattening, high-arched palate and prognathism. However, there are no other skeletal features that are otherwise consistent with this diagnosis. Karyotype analysis performed at age 7 years 1 month was normal as was Fragile X testing. At age 16 years 11 months, aCGH analysis at another institution identified a 10q23.1q23.2 deletion of at least 4.5 Mb. Analysis of the patient’s parents by FISH revealed no similar deletion or rearrangement indicating that the deletion was likely de novo. A colonoscopy at age 17 years 10 months revealed no polyps.

Patient 3 is a 4-month-old male who was born at 38 weeks’ gestation to a 39-year-old G2P2 woman after a pregnancy complicated by visualization of clubfoot on ultrasound. The geneticist was consulted due to bilateral club feet, ear anomalies, and possible hearing loss when the patient failed the newborn hearing test (left ear only). Dysmorphic features included mild plagiocephaly, hypertelorism, mild epicanthal folds, low-set and posteriorly rotated ears with thin helices, wide nasal bridge, somewhat short neck, and mild micrognathia. Mild hypotonia was also noted. An esophagastroduodenoscopy performed at age 4 months was normal. Patient has since been lost to follow-up.

Patient 4 is a 20-month-old male born by planned C-section at 38 weeks’ gestation after an uncomplicated pregnancy to a 34-year-old G2P2. This patient’s birth weight was 8 lbs 1 oz (50th percentile) and birth length was 20 inches (50th percentile). Neonatally, the patient had difficulties feeding which resulted in failure to thrive. He passed his newborn hearing screen on the second evaluation. Feeding difficulties continued for the first 4 months of life and may have been caused by a high-arched palate. The patient sat at 7 months and at 18 months began taking independent steps. Speech evaluation at 17 months noted severe receptive and expressive delays. He was enrolled in both speech and physical therapy. Mild developmental delay was formally noted at age 20 months.

Upon physical examination at 18 months, the patient’s head was above the 98th percentile. Weight was at the 90th percentile. Height was at the 50th percentile at the most recent measurement (16 months). Dysmorphic features included apparent macrocephaly, frontal bossing, fine and straight blond hair, slight downward-slanting palpebral fissures, posteriorly rotated and ‘swept-back’ ears, well-grooved but narrow philtrum, and a small mouth (Fig. 1f). Also noted were hand and finger lengths measuring in the 97th percentile in length. The patient was mildly hypotonic. A magnetic resonance imaging (MRI) scan at 20 months was normal and parental examination suggests that the macrocephaly may be familial.

**Discussion**

The identification of genomic imbalances in young patients can affect medical management by allowing early intervention for developmental delay and by identifying patients at risk for unexpected medical complications. In this study, we report six additional unrelated patients with deletions of a 7.25 Mb region of 10q22.3q23.2 identified by aCGH and present the clinical findings in four of these cases.

Figure 1g compares the size and location of the deletion in these patients to the deletions in the patients presented by Balciuniene et al. (1). Two patients in that study have deletions comparable...
to the four presented here: a 7.25 Mb deletion of 10q22.3q23.2 that deletes BMPR1A but not PTEN. Including our study, there have been clinical reports on six patients with a 7.25 Mb deletion of 10q22.3q23.2. Only three of the individuals, one of whom is in this study, have behavioral abnormalities; however, three of four individuals in this study are likely too young to have manifested any behavior problems. All patients have global developmental delay of varying severity, usually specific to language reception and expression. Several common features in the patients presented in this study include failure to thrive and/or hypotonia, Marfan-like body habitus, and feeding difficulties in infancy.

There are 19 OMIM genes in the common 7.25 Mb deletion region at 10q22.3q23.2. Of interest are two, BMPR1A and LDB3, that may affect the medical management of patients with deletions of these genes.

Although point mutations and exon-spanning deletions in BMPR1A are associated with JPS (4, 5), none of the six patients with 7.25 Mb deletions at 10q22.3q23.2 has polyps or symptoms of JPS, with the exception of rectal bleeding (Patient 2). Colonoscopy did not reveal any polyps in this 17 year old. Patient 3 had a colonoscopy because of refusal to eat, dysphagia, and the abnormal aCGH results. No polyps were reported at age 4 months. In studies of contiguous gene deletions in patients with JPS, both BMPR1A and PTEN are deleted. For example, Delnatte et al. (8), Savliati et al. (9), and Menko et al. (10) describe patients with deletions ranging in size from 1.2 to 12 Mb that include both PTEN and BMPR1A. These individuals had polyps throughout the gastrointestinal tract of varying age of onset, including under 2 years (JPI) and over 2 years (JPS). Therefore, deletion of PTEN in addition to BMPR1A may be necessary for the formation of polyps or for the severe JPI phenotype but not JPS. The absence of polyps in the patients presented here may also be because the patients are younger than the expected age of JPS presentation. JPI presents with gastrointestinal bleeding, diarrhea, protein-losing enteropathy, macrocephaly, and hypotonia in patients under 2 years (10). Symptoms of JPS usually present in older children and young adults, rarely before the age of 6 (8). Colorectal cancer as a result of the transformation of these polyps usually does not occur until the fourth decade and does not occur in all patients with JPS (17). The age at diagnosis by aCGH of our study participants ranges from 8 days to 17 years 1 month, and thus it is not expected that patients this young would have developed symptoms of JPS. Therefore, individuals with a deletion at 10q22.3q23.2 may have a predisposition to developing symptoms of JPS including rectal bleeding which could be the result of hamartomatous polyps and which if unchecked could develop into cancerous lesions. Cancer predisposition has not been excluded in patients with a deletion of BMPR1A, and so appropriate follow-up with GI specialists is of particular importance for patients with deletions of 10q22.3q23.2 involving either the BMPR1A or PTEN gene. These recommendations include esophagogastroduodenoscopy, colonoscopy, and hemogram by age 15 repeated every 3 years if no colonic juvenile polyps are found. If polyps are discovered, these should be removed endoscopically (17). Recent studies (18) have shown the benefit of early diagnosis of pediatric genetic syndromes with a predisposition to cancer. Individuals who receive an early diagnosis of a deletion of 10q22.3q23.2 may benefit from increased surveillance for the development of polyps and symptoms that suggest the development of cancer.

Mutations in the gene LDB3, which encodes an LIM binding domain 3 protein that functions in cytoskeletal assembly, have been found in patients with dilated cardiomyopathy (19, 20). The impact of this protein in the function or structure of the heart remains under evaluation. One patient in this study (Patient 1) had a cardiac abnormality, a patent ductus arteriosus (PDA) that required surgery. None of the other patients in this study had noted cardiac abnormalities, but the extent of their cardiac evaluations is not clear. Interestingly, Menko et al. (10), Delnatte et al. (8), and Salvati et al. (9) each noted a patient with a structural cardiac abnormality. Delnatte et al. (8) suggest an additional cytogenetic abnormality seen in their patient, a t(2;10)(q31;p15) may be responsible for the cardiac finding. Until the role of LDB3 is understood, a cardiac evaluation may also be appropriate for patients with 10q22.3q23.2.

In our four patients with 10q22.3q23.2 deletions for whom clinical information was available, there was no pattern of abnormalities, craniofacial, behavioral, or otherwise, that would lead to a recognizable syndrome phenotype. Three of the patients in this study and all patients reported by Balciuniene et al. (1) have developmental delay. Early identification of a chromosome abnormality that predisposes a child to developmental delay and learning disabilities means that individual education plans can be implemented to help the child reach his or her fullest intellectual capabilities. Therefore, aCGH testing on a neonate with non-specific findings, such as hypotonia and failure to
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thrive, may uncover a chromosome abnormality. Although it is unclear whether individuals with a 10q22.3q23.2 deletion encompassing BMPR1A are at increased risk for symptoms of JPS, appropriate prophylactic care and surveillance may be warranted in these patients. Specialists can now follow these patients with a certain awareness of the potential risks for JPS and for behavioral abnormalities and learning delay.

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References