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Clinical Presentation of 13 Patients With Subtelomeric Rearrangements and a Review of the Literature

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To re-examine the potential clinical indications for subtelomeric FISH testing and to provide additional cases to the growing literature on subtelomeric abnormalities and their genotype-phenotype correlations, we present a single center case series of 13 patients with chromosomal abnormalities detected by subtelomeric FISH testing over a 21 month period. The most common abnormality involved chromosome 1p (23%). Partial monosomy was present in 69% of the patients, complex rearrangements in 23%, and partial trisomy in 8%. The mean time from first normal karyotype to positive subtelomeric FISH result was 3.8 years (n = 11, median 3.5 years, range: 6 months–10 years). One patient had an abnormal high resolution karyotype recognized retrospectively, and two other patients had abnormal karyotypes that were fully deciphered only after subtelomeric FISH analysis. Eighty five percent of cases occurred de novo. The subtelomeric FISH results were useful for adjusting the recurrence risks and helping to focus medical screening and monitoring. The results impacted family planning and satisfied families in search of a diagnosis. Our findings support the use of subtelomeric FISH analysis as a second tier test in patients suspected of having a chromosomal abnormality with a normal karyotype. Potential benefits of subtelomeric FISH testing include faster time to diagnosis, better informed patient prognosis, and more accurate genetic counseling.

KEY WORDS: subtelomeric FISH; monosomy; trisomy; rearrangement; cryptic chromosome abnormalities

INTRODUCTION

Subtelomeric fluorescent in situ hybridization (FISH) testing is a technology seeking its place in the genetic evaluation. Despite differences in inclusion criteria, several studies have established a prevalence rate for cryptic rearrangements detectable by subtelomeric FISH of approximately 3–6% [Vorsanova et al., 1998; Knight et al., 1999; Ballif et al., 2000; De Vries et al., 2001a; Fan et al., 2001; Joyce et al., 2001; Riegel et al., 2001; Clarkson et al., 2002]. Proponents of the technology point to the inadequacy of karyotype analysis to detect these clinically significant aberrations. Others are more cautious given the tremendous labor and cost involved with subtelomeric FISH testing. Common clinical features that have been suggested as being predictive of a subtelomeric abnormality include developmental delay, mental retardation, prenatal growth deficiency, and a family history of mental retardation.

We present a case series of 13 patients referred to our Genetics Clinic who were identified as having a chromosomal rearrangement by subtelomeric FISH. We describe the most commonly observed clinical features and subtelomeric abnormalities. We evaluate the benefits of testing for the family and the physician. We also review the literature related to each rearrangement. These cases demonstrate the many different clinical presentations of children with these deletions and duplications. Given the large number of potential duplications and deletions of varying size and combination, it is unlikely that specific commonalities will be found. Rather, we provide detailed phenotype descriptions to augment the literature in a way that we hope will aid in future patient management as discrete syndrome patterns emerge with continued use of subtelomeric FISH analysis and associated phenotype reporting.

CLINICAL REPORTS AND LITERATURE REVIEWS

Patient 1 and Patient 2: Monosomy 1p36

Patient 1. A 4-year-old girl was first evaluated at age 2 for developmental delay. She had an uncomplicated gestation and delivery. The family history was significant for one maternal male first cousin with cerebral palsy thought secondary to birth trauma and one maternal female first cousin born with a congenital heart malformation requiring surgical repair.

She started rolling at 8 months, sat alone at 1 year, began crawling at 20 months, and began pulling to a stand at 22 months. She used about 12 words. She had a brain MRI that revealed stable periatrial white matter changes. At 26 months, her weight, length, and head circumference were all at the 25th centile.

On physical examination, she had a high forehead, depressed midface, deeply set eyes, epicanthal folds, broad nose with a bulbous tip, short columella, anteverted nares, broad mouth, short philtrum, and full lips (Fig. 1a,b). She also had 5th finger clinodactyly, broad halluces, a crease between the 1st and 2nd toes, proximally placed 2nd toes, syndactyly of the 2nd and 3rd toes, and hypotonia. Six months after a normal female karyotype was obtained at the 450 band level, subtelomeric FISH studies identified a subtelomeric deletion of the

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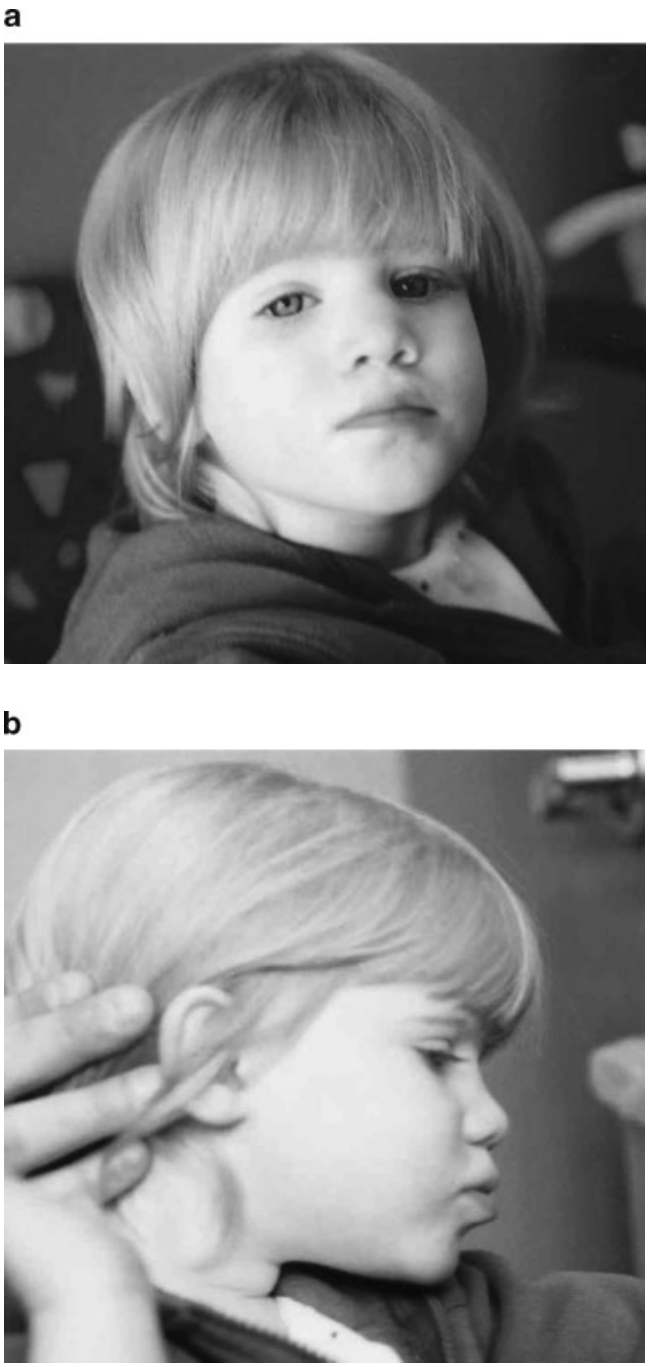

Fig. 1. **a**: AP face. **b**: Lateral face. Patient 1, age 2 years. Terminal deletion 1p: Note depressed midface, deeply set eyes, epicanthal folds, a broad nose with a bulbous tip, short columella, anteverted nares, broad mouth, short philtrum, and full lips.

terminal region of the short arm of chromosome 1, falling into the 1p36 monosomy spectrum: ish del(1)(p36.3p36.3)(pcplp−). Parental studies were normal.

Patient 2. A 15-year-old girl with developmental delay and monosomy 1p36 was referred to the Genetics Clinic for clinical evaluation and genetic counseling. She was the full-term product of a pregnancy complicated by first trimester bleeding that resolved with bed rest. Family history was significant for a brother with attention deficit disorder, and a paternal second cousin (female) with mild mental retardation whose daughter and granddaughter were similarly affected. In the first 2 weeks of life, the patient was noted to have a weak suck with poor feeding and weight gain. At 10 weeks, she was admitted to the hospital for new-onset seizures and was treated for 6 months with no recurrence. The patient had the following features: ASD; chronic respiratory infections, otitis media, and streptococcal pharyngitis; chronic constipation; unilateral conductive hearing loss; cerebral and hindbrain under development; and left eye amblyopia and myopia. At age 9, she was noted to have gained a significant amount of weight. She had global developmental delay. At age 10, she functioned at a 6 to 7-year-old level. She was treated with both Ritalin and Dexedrine for attention deficit disorder without alleviation of symptoms.

Physical examination was significant for weight at the 97th centile, height at the 25th centile, and head circumference at the 50−75th centile. She had deeply set eyes, a short philtrum, and a thin upper lip. She was diffusely hypotonic. Karyotype analysis at the 450 band level was normal 46,XX. Subtelomeric FISH testing was requested by her neurologist for evaluation of developmental delay, and the results revealed monosomy 1p36. Parental chromosome and FISH testing were normal.

Many of the clinical features of Patients 1 and 2 are consistent with other children with monosomy 1p36, including developmental delay, onset of obesity in late childhood, seizures, ophthalmologic problems, hearing loss, prominent forehead, deeply set eyes, midface hypoplasia, and fifth finger clinodactyly [Slavotinek et al., 1999]. Other children with monosomy 1p36 have been reported to have growth problems, developmental delay or mental retardation, hypotonia, cardiac abnormalities, and hypothyroidism. Heilstedt et al. [2003] reported detailed clinical phenotypes of 30 patients with monosomy 1p36 and found that 83% had notable visual disorders, 82% had hearing impairment, 72% had oropharyngeal dysphagia, 50% had a history of seizures, 43% had various structural cardiac abnormalities, nearly 25% had dilated hypertrophic cardiomyopathy, 20% had clinical hypothyroidism, and 17% had palatal abnormalities. As a result of this diagnosis, our patients now undergo annual hearing and thyroid screening studies. The diagnosis led to a focused and specific medical monitoring plan that would not have been possible without the subtelomeric FISH results.

Patient 3: Partial Trisomy 4p, Partial Monosomy 1p

A 6-year-old boy had been followed in the Genetics Clinic since infancy with a presumptive diagnosis of CHARGE Association. There were no pregnancy or delivery complications, and family history was noncontributory.

His features included membranous choanal atresia, patent ductus arteriosus, ventricular septal defect, ASD, profound bilateral hearing loss, poor visual acuity, hypoplastic optic nerves, left arachnoid cyst and hydrocephalus, polycystic kidney disease, hypertension, cryptorchidism, genital hypoplasia, and scoliosis. He also had a history of infantile spasms and seizure disorder, severe pharyngeal dysphagia, gastroesophageal reflux, hiatal hernia, gallstones, sleep apnea, failure to thrive, capillary fragility, and global developmental delay.

On physical examination, the patient had brachycephaly, low anterior hairline, increased body hair, high forehead, square face, flat profile, long eyelashes, downslanting palpebral fissures, telecanthus, short nose, pinched nostrils, thin upper lip, long philtrum, thick lower lip, small and widely spaced teeth, lop-shaped and low set ears, and a short neck (Fig. 2). He also had redundant neck skin, widely spaced nipples, mild scoliosis, small penis with poorly developed

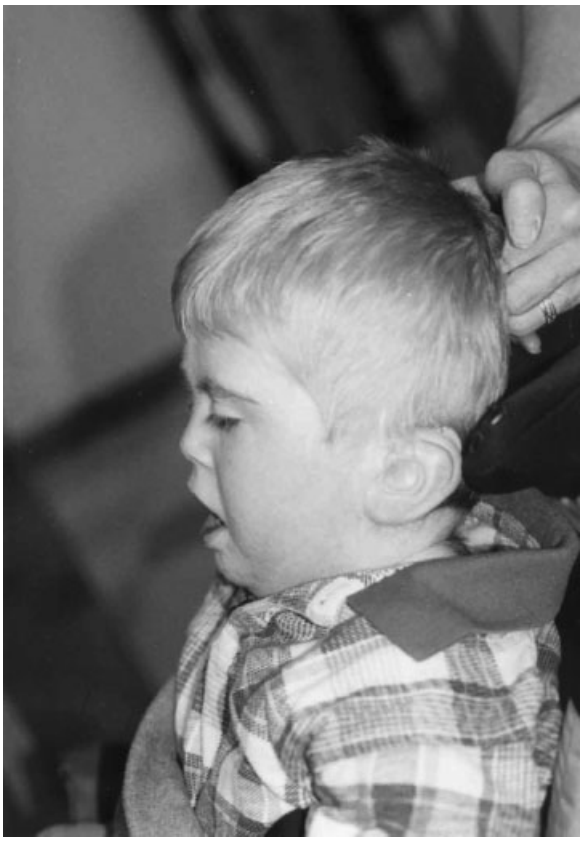

Fig. 2. Patient 3, age 6 years. Partial trisomy 4p, partial monosomy 1p: Note low anterior hairline, high forehead, long eyelashes, short nose, pinched nostril, thin upper lip, long philtrum, thick lower lip, lop shaped and low set ears, and short neck.

scrotum, thin nails, everted feet, crowded and overlapping toes, and increased tone.

Four years after a normal karyotype was obtained at the 500 band level, subtelomeric FISH studies were found to be abnormal: ish der(1)t(1;4)(p36.3;p16)(1pSUBTEL−,p58−, D1Z2−,D4S3359+, WHSC1+). His unbalanced chromosome complement resulted in partial monosomy for the tip of the short arm of chromosome 1 and partial trisomy for the tip of the short arm of chromosome 4. Parental chromosome and subtelomeric FISH analyses were normal.

There are no other reports of patients with these specific chromosome findings. Terminal deletions of the short arm of chromosome 1 are associated with hypotonia, developmental delay, microcephaly, high forehead, cardiac malformations, small genitalia, seizures, ventricular dilation, sensorineural hearing loss, severe mental retardation, growth retardation, and ophthalmologic abnormalities [Slavotinek et al., 1999]. Wyandt et al. [1993] reported a male infant with partial duplication of 4p16 who had a small head, large and low set ears, beaked nose, micrognathia, choanal stenosis, proptosis, ASD, and left inguinal hernia. Other children with duplications of the short arm of chromosome 4 have been characterized and share some features in common with our patient, including high forehead, short palpebral fissures, abnormally shaped ears, heart malformations, inguinal hernia, small penis, seizures, renal malformations, mental retardation, aspiration pneumonia, and growth retardation [Patel et al., 1995]. As a result of making this diagnosis, further diagnostic testing was discontinued. Additionally, reduction of the recurrence risk from that of a possible autosomal recessive disorder to a sporadic condition influenced the parents' family planning.

Patient 4: Partial Trisomy 16q, Partial Monosomy 18p

A 5-year-old boy was referred to the Genetic Clinic at 17 months of age for evaluation of severe hypotonia, developmental delay, failure to thrive, supraventricular tachycardia, ASD, recurrent wheezing, and pneumonia with an oxygen requirement, severe constipation, and seizures. The prenatal and family histories were unremarkable.

Radiographic examination revealed right-sided shallow acetabulum and coxa valga. Brain computed tomography showed prominent sulci and ventricles consistent with atrophic changes. The patient developed intermittent fevers of unknown origin and took only thickened liquids by mouth. At 32 months, he was rolling, belly crawling, clapping, babbling, and saying "mama" but was unable to sit without support.

His weight, length, and head circumference were all below the 5th centile. On physical examination, he had a scarred scalp defect, low anterior hairline, microcephaly, flat occiput, narrow forehead, midface hypoplasia, up-slanting palpebral fissures, broad nasal root, upturned nares, short philtrum, full lower lip, thin vermilion, mild prognathism, prominent ears, right preauricular pit, broad mouth, small widely spaced teeth, small scrotum, cryptorchidism, tapering fingers, finger like thumbs, broad halluces, hyperconvex nails, increased joint range of motion, bilateral clinodactyly and contractures of the 5th fingers, prominent toe pads, weakness, and severe hypotonia. Fifteen months after a normal karyotype analysis of at least 400 band level resolution, subtelomeric FISH testing revealed partial trisomy 16q and a question of partial monosomy 18p: add(18)t(16;18)(q24.3;p11.23) (16qSUBTEL+, D18S552+,D18Z1) mat. The 16qsubtel probe is distal to the still present 18psubtel probe. Therefore, very little 18p material is involved.

Subsequent testing of his parents demonstrated the same chromosomal imbalance in the patient's mother. Review of her medical history revealed that she had significant problems with constipation and reading problems in school. Whether the mother's condition represents a milder manifestation of the chromosomal rearrangement is unclear. Given the severity of the patient's phenotype, we cannot exclude the possibility that the rearrangement is benign and unrelated.

Hahm et al. [1987] reviewed reported cases of partial duplication 16q. Infants with the largest duplications died early in infancy. Features common to these children and our patient include microcephaly, postnatal failure to thrive, hypotonia, developmental delay, congenital heart disease, and genital hypoplasia. An autistic male with mental retardation, large ears and nose, hyperextensible joints, and duplication (16)(q24→ter) was reported by Maher et al. [1991].

Chromosome 18p− is a well-characterized syndrome [Jones, 1997]. Like our patient, children with 18p− have mild to moderate growth deficiency, hypotonia, microcephaly, prominent ears, broad mouth, and fifth finger clinodactyly. Although less common, genital anomalies and cardiac defects have been described. Because these other cases had complete monosomy 18p, our patient might not be expected to have all of the described features.

Many of this patient's clinical features are not typical of either partial duplication 16q or monosomy 18p. These include his facial appearance (low anterior hairline, flat occiput, narrow forehead, up-slanting palpebral fissures, upturned nares, full lower lip, preauricular pit), increased joint range of motion, extremity abnormalities (5th finger contracture, finger-like thumbs, broad halluces, prominent toe pads, and

hyperconvex nails), and history of constipation and seizures. This discrepancy, coupled with his mother having the same apparent chromosomal abnormality, make it even more likely that the rearrangement does not explain the patient's developmental and medical problems. This case highlights the importance of obtaining parental studies to aid in the interpretation of diagnostic test results.

Patient 5: Terminal Deletion 1q

A 9-year-old girl had been followed in the Genetic Clinic since infancy. She was the product of a full-term pregnancy complicated by a second trimester viral infection and elevated alpha-fetoprotein on maternal serum screen. She had a normal karyotype on amniocentesis. Prenatal ultrasound revealed intrauterine growth retardation, microcephaly, and possible agenesis of the corpus callosum. The patient's mother had one 1st trimester miscarriage; otherwise, the family history was unremarkable.

In early infancy, the patient had a weak suck and was slow to gain weight. She had surgery for a blocked tear duct, right ptosis, and entropion. She had recurrent otitis media, mild hearing loss, febrile seizures, a non-febrile seizure, and chronic constipation. A brain MRI performed at age 5 revealed partial agenesis of the corpus callosum and colpocephaly. At age 8, she used six words and knew some signs. She ambulated with support.

On physical examination, her weight, height, and head circumference were all below the 3rd centile. She had an asymmetric and long face, flattened midface, bitemporal hollowing, prominent metopic sutures, up-slanting palpebral fissures, bilateral ptosis, hypotelorism, arched eyebrows, broad nasal root, anteverted nares, short columella, large ears, smooth and long philtrum, and a bowed upper lip (Fig. 3a,b). She also had inverted nipples, sacral dimple, increased range of motion of the upper extremities, diffuse hypotonia, and frequent laughing. After birth, a karyotype at the 500 band level was normal. Eight years after her initial karyotype, a repeat chromosome analysis and FISH studies revealed a de novo deletion of chromosome 1q44: 46,XX,del(1)(q44)de novo.ish del(1)(wcpl+,D1S3738−). The parents had normal karyotypes with no evidence of a rearrangement using FISH 1 probes.

Patients reported with a deletion of this general region have had a pattern of findings that includes microcephaly, prominent forehead/metopic suture, up-slanting palpebral fissures, broad nasal bridge, growth retardation, global developmental delay/mental retardation, hypotonia, feeding problems, and agenesis or hypoplasia of the corpus callosum, all of which were noted in our patient. Some patients also have had cardiac anomalies, and some have had seizures [Villa et al., 2000; De Vries et al., 2001b]. Review of the literature led Gentile et al. [2003] to conclude that hand and foot anomalies and many of the major malformations described in 1q deletions are uncommon in de novo cases with a breakpoint distal to 1q42. Villa reported a patient with monosomy 1q44-qter who presented with acute lymphoblastic leukemia at age 3. After many years without a diagnosis, the family greatly appreciated knowing the specific reason for their daughter's medical and developmental problems.

Patient 6: Interstitial Deletion 2q

A 20-year-old young woman was first evaluated at age 13 for learning problems, hyperextensible joints and skin, brachydactyly, myopia, and Crohn's disease. Her prenatal and family histories were unremarkable. Early on she had a history of lens dislocation, mitral valve prolapse, mitral valve regurgitation, and dilation of the aortic root, but subsequent ophthalmologic and echocardiographic evaluations found no further evidence of these problems.

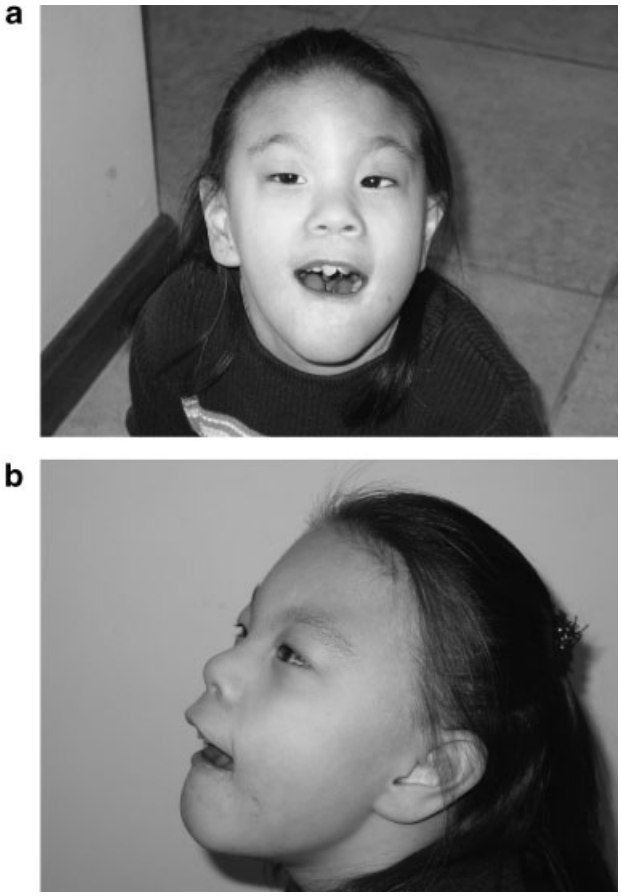

Fig. 3. **a**: AP face. **b**: Lateral face. Patient 5, age 9 years. Terminal deletion 1q: Note asymmetric and long face, flattened midface, bitemporal hollowing, upslanting palpebral fissures, bilateral ptosis, hypotelorism, arched eyebrows, broad nasal root, anteverted nares, short columella, large ears, smooth and long philtrum, and bowed upper lip.

On physical examination at age 15, she was found to have slightly hyperextensible and soft skin, full cheeks, bitemporal narrowing, up-slanting palpebral fissures, midface hypoplasia, deeply set eyes, long face, square forehead, high palate, short nose, smooth philtrum, thin lips, broad thumbs and short fingers (Fig. 4a), and broad halluces, and small nails (Fig. 4b). Hand X-rays showed shortening of the 3rd and 4th metacarpals and short distal phalanges of both thumbs. Foot X-rays showed brachydactyly with shortening of the proximal phalanges of the 2nd and 3rd toes. A 450 band resolution karyotype was normal. Four years after her initial karyotype analysis, subtelomeric FISH testing revealed an interstitial subtelomeric deletion on the long arm of chromosome 2: 46,XX.ish del(2)(q37.1q37.3)(WCP2+, AHT+, D2S447−). Parental studies were normal.

There have been no reports in the literature of patients with the same subtelomeric deletion. Reddy et al. [1999] reviewed 33 cases of deletion of chromosome band 2q37 as the sole abnormality. These patients were noted to have developmental problems, joint hyperlaxity, hearing loss, short fingers, congenital heart defect, and facial characteristics similar to that seen in our patient. Crohns disease has not previously been reported. Two patients with microdeletion of sub-band 2q37.3 were noted to have abnormal situs viscerum [Reddy et al., 1999]. Abdominal ultrasonography confirmed normal situs in

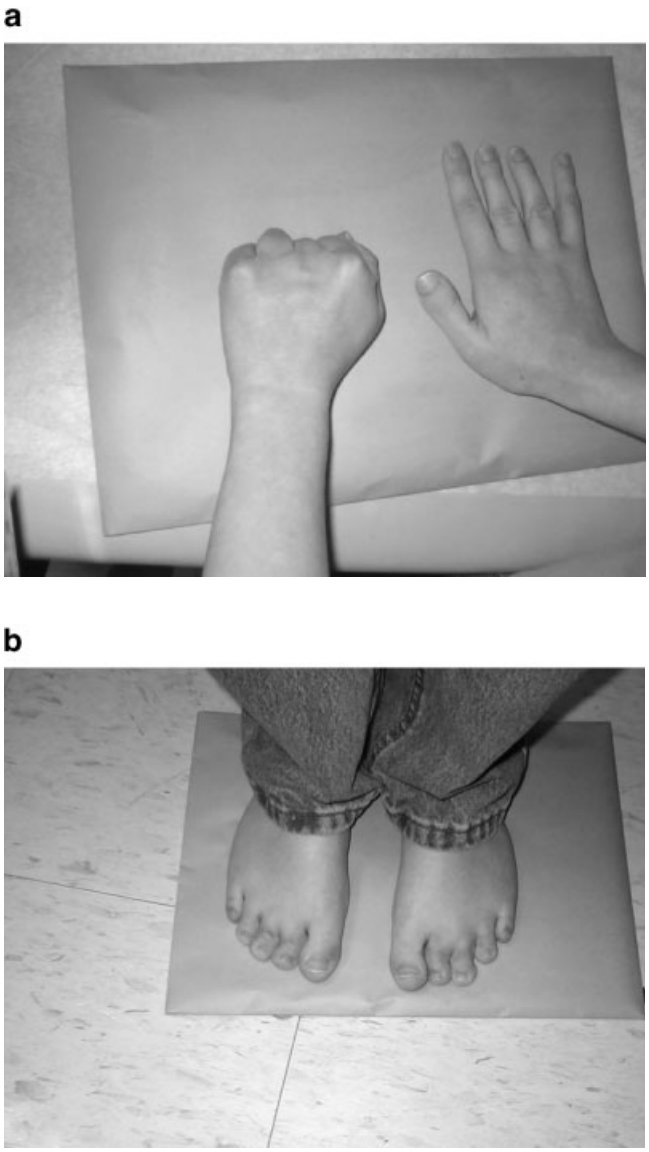

Fig. 4. **a**: Patient 6 AP hands. Interstitial deletion 2q: Note broad thumbs, brachydactyly, shortening of the third and fourth metacarpals. **b**: Patient 6. AP feet. Interstitial deletion 2q: Note broad halluces, small nails, brachydactyly.

our patient. The subtelomeric FISH results were helpful in eliminating a known connective tissue disorder and in establishing a long sought after diagnosis.

Patient 7: Terminal Deletion 6q

A 5-year-old girl with multiple congenital anomalies was first evaluated in the Genetics Clinic at age 18 months. Hydrocephalus was noted by prenatal ultrasound. Family history was noncontributory. Soon after birth, the hydrocephalus was confirmed and she was found to have sacral dysgenesis with a tethered cord, imperforate anus, and an ASD. She was initially given a diagnosis of VACTERL Association. When she was assessed developmentally by her school at age 3, no areas of concern were identified. She was judged to be an intelligent girl.

Physical examination was notable for weight, length, and head circumference all measuring below the 5th centile, fine hair, prominent cheeks, up-slanting palpebral fissures, epicanthal folds, broad nasal root, upturned nares, prominent nasal tip, hypoplastic nasal alae, long philtrum, thin lips, simple helices, and small chin (Fig. 5a,b). She also had hallux varus, overlapping 2nd upon 3rd right toe, bilateral 4th and 5th digit clinodactyly of the feet, and variable muscle tone. Karyotype analysis performed at greater than the 400 band level revealed 46,XX with a derivative chromosome 6. The cytogeneticist was unable to differentiate a deletion from a translocation. One year after her initial karyotype analysis, subtelomeric FISH studies confirmed a subtelomeric deletion of 6q using the TEL6Q probe. Parental studies were normal.

There is one other case in the literature of a patient with a similar deletion [46,XX,inv(6)(q22.1q27).ish del (6)(q27)(RM2158−) de novo]. This patient had minor craniofacial anomalies: depressed nasal root, epicanthal folds, hypertelorism, wide nasal tip, cupid's bow upper lip, and protruding tongue; mild hypoplasia of the corpus callosum on head MRI; microcephaly; and developmental delay [Lorda-Sanchez et al., 2000]. Kumar et al. [1999] described a girl with a small 6q interstitial deletion (q23.3-q24.2) who was developmentally normal with very mild phenotypic abnormalities. Other children with larger deletions of 6q had low birth weight, hypotonia, congenital heart defects, genital anomalies, mental retardation, hydrocephalus, seizures, and retinal pits on ophthalmologic examination [Hopkin et al., 1997; Sukumar et al., 1999]. None of these reports describe VATER or VACTERL-like presentations. Until additional similar cases are reported, we cannot exclude the possibility that our patient's small deletion is a benign variant and unrelated to her multiple congenital anomalies. However, it is possible that her rearrangement at least contributed to, if it was not entirely causal of, her VACTERL phenotype.

Patient 8: Partial Monosomy 7q, Partial Trisomy 11p

A 12-year-old boy was first referred to the Genetics Clinic at age 5 for evaluation of multiple congenital anomalies, growth retardation, and severe mental retardation. He was the product of a full term pregnancy that was complicated by intrauterine growth retardation and breech presentation. The maternal history was notable for three 1st trimester miscarriages. A maternal uncle died soon after birth of unknown causes. The patient's anomalies included cleft lip and palate, sacral agenesis with a tethered cord, and hypospadius with chordee. As a neonate, poor feeding and failure to thrive led to fundoplication and gastric tube placement. He had chronic otitis media, mild bilateral hearing loss, and chronic upper respiratory tract infections with oxygen dependence. Development and growth were severely delayed. At 3.5 years of age, he suffered head trauma that resulted in a seizure disorder. A subsequent brain MRI showed moderate ventriculomegaly with evidence of hypoxic ischemic injury and hypoplasia of the cerebellar vermis. Ophthalmology evaluation revealed cortical visual impairment, blepharophimosis, and microphthalmia. He had hypothyroidism and precocious puberty thought to be of central etiology that was briefly treated with Lupron and then resolved. He had both bowel and bladder incontinence. At age 10, he was nonverbal and nonambulatory with minimal social interactions. He could roll from side to side and sit briefly with support.

On physical examination, his height and weight were less than the 5th centile and head circumference was less than the 2nd percentile. He had blepharophimosis with horizontal palpebral fissures, distachiasis, absent nasal bridge, depressed nasal tip, cupped and protruding ears, depressed premaxillary

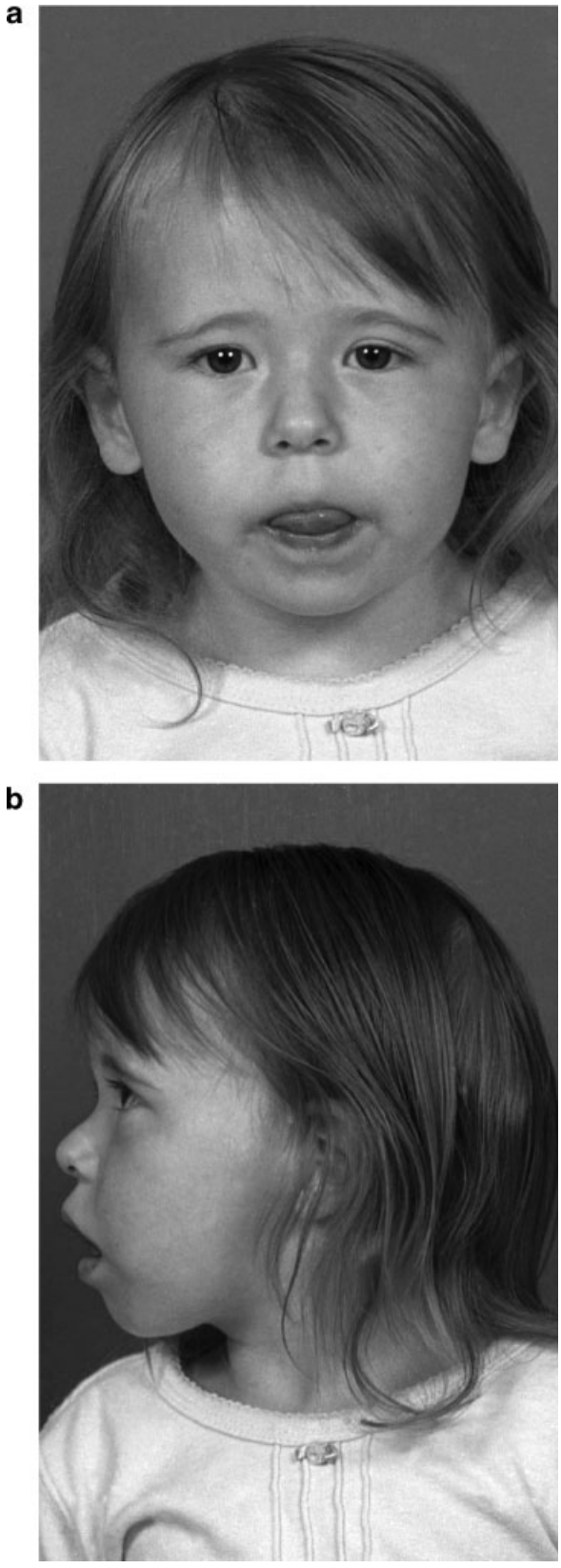

Fig. 5. **a**: AP face. **b**: Lateral face. Patient 7, age 2 years. Terminal deletion 6q: Note prominent cheeks, upslanting palpebral fissures, epicanthal folds, broad nasal root, upturned nares, prominent nasal tip, hypoplastic nasal alae, long philtrum, thin lips.

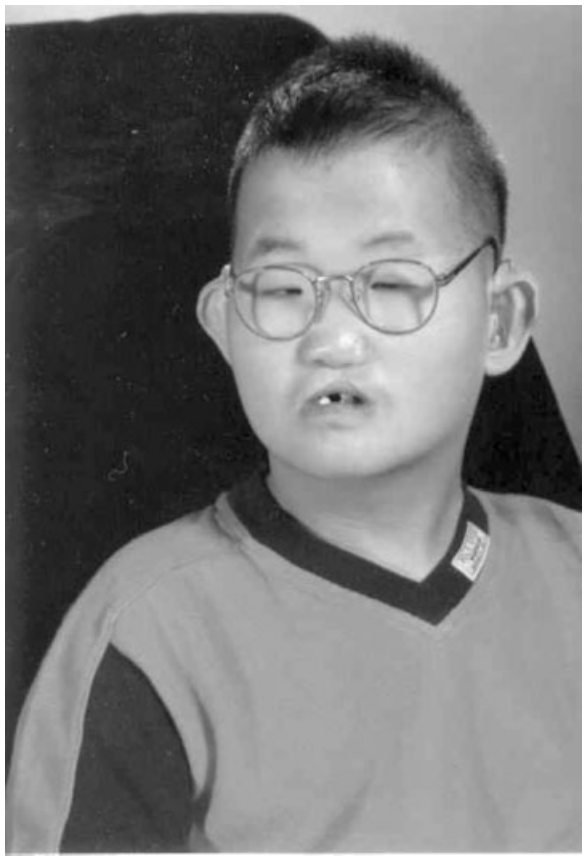

Fig. 6. Patient 8, age 12 years. Partial monosomy 7q, partial trisomy 11p: Note blepharophimosis, horizontal palpebral fissures, absent nasal bridge, depressed nasal tip, cupped and protruding ears, and depressed premaxillary region.

region, malaligned teeth, and a flattened occiput (Fig. 6). He also had one inferiorlaterally displaced nipple, partial syndactyly of the hands, single transverse palmer creases, tapering fingers, distal finger contractures with decreased flexion creases, adducted thumbs, short palms, diffuse hypotonia and absent deep tendon reflexes. He had two normal chromosome analyses at the 400 band or more level completed on leukocytes. Subtelomeric FISH testing performed 5 years after his initial karyotype analysis revealed distal monoomy 7q and distal trisomy 11p as follows: ish der(7)t(7;11)(q36;p15.5)(7pSUBTEL−,D11S2071+). Parental chromosome and subtelomeric FISH analysis revealed the mother to have a balanced 7:11 telomere translocation and an apparently unrelated Robertsonian 13;14 translocation. The latter abnormality was also present in her healthy and developmentally normal daughter who also had cupped and protruding ears.

There are no reported cases in the literature with this combination of 7q subtelomeric deletion and 11p subtelomeric duplication. Krajewska-Walasek et al. [1996] and Drut and Drut [1996] reported patients with Beckwith–Wiedemann syndrome who had trisomy 11p15 derived from a paternal balanced translocation. Case 8 does not have features of Beckwith–Wiedemann syndrome, which is consistent with the inheritance of this chromosomal region from the patient's mother. On the other hand, trisomy for maternal genes in this region may have contributed to his intrauterine and postnatal growth restriction. In three cases of maternally inherited 11p15 duplication, all had growth retardation, short palpebral fissures, prominent nasal tip, short philtrum, and 5th finger clinodactyly [Fisher et al., 2002].

Genes for autosomal dominant sacral agenesis [Lynch et al., 1995; Savage et al., 1997] and holoprosencephaly [Muenke et al., 1994] have been mapped to 7q36. Monosomy 7q36 likely explains our patient's sacral agenesis, tethered cord, and possibly his chronic constipation. Currarino triad (congenital anorectal stenosis, a sacral defect, and a presacral mass) has been associated with deletion 7q36.1→qter [Masuno et al., 1996]. Schinzel [2001] reported additional patients with 7q36→qter deletions who had short stature, upslanting palpebral fissures, a small nose with a bulbous tip, large dysplastic ears, and a small mandible. Cleft palate and micropthalmia have been reported in individual patients with 7q36→qter deletions. Thus, these results were helpful in explaining the maternal history of multiple miscarriages and allowed for more accurate counseling of recurrence risks for his parents and his sister.

Patient 9: Microdeletion 9q

A 6-year-old boy was evaluated at 22 months of age in the Genetics Clinic for developmental delay and distinctive facial features. The pregnancy and delivery were uncomplicated with birth weight, length, and head circumference at the 50th centile. He had a paternal uncle with mental retardation.

He was noted to be a slow feeder and sleepy infant. A brain MRI showed inferior displacement of the floor of the sella turcica with tethering of the pituitary stalk in the floor of the third ventricle. Hand X-rays showed shortened distal phalanges. Developmental assessment at 8 months placed him at the 3–5 month level. Repeat developmental evaluation at 20 months placed him at the 10–12 month level.

His weight was at the 50th centile, height at the 10th centile, and head circumference at the 25th centile. The physical examination was remarkable for low posterior hairline, broad forehead, epicanthal folds, upslanting palpebral fissures, hypertelorism, creases beneath the eyes, broad nasal root, short nose, anteverted nares, low set small ears, and over-folded helices (Fig. 7a,b). He also had square distal phalanges, broad great toes, deeply set nails, and diffuse hypotonia. A karyotype completed at least at the 450 band level prior to his initial Genetics Clinic evaluation was normal. Subtelomeric FISH studies performed 32 months later were abnormal: ish del(9)(q34.3)(D9S325–) de novo, consistent with a subtelomeric deletion of 9q.

Ayyash et al. [1997] reported a 5-month-old male with deletion (9)(q34.3) who had multiple minor anomalies, a cardiac conduction defect, intestinal malrotation, hypospadius, clubfeet, microcephaly, growth, and developmental delay. Stewart et al. [2002] published an abstract that reported three cases of 9q telomere deletions, all of whom had features of hypertelorism, eyebrow and ear anomalies, highly arched palate, and tented upper lip. Two had severe cardiac malformations. Cormier-Daire et al. [2002] published an abstract which reported two unrelated boys with severe mental retardation, hypospadius and cryptorchidism, flat face, high forehead, synophris, anteverted nostrils, long philtrum, thin upper lip, protruding tongue, short extremities, and terminal deletion of 9q34. They also developed progressive obesity with food seeking behavior, sleep disturbance, and had absent speech. Establishment of this diagnosis resulted in a focused medical screen based upon findings identified in a cohort of patients with chromosome 9q– followed at the Children's Hospital of Philadelphia. The patient was referred for an echocardiogram which was normal.

Patient 10: 18q Terminal Deletion

A 5-year-old girl was evaluated in the Genetics Clinic for cleft palate, external auditory canal stenosis, external auditory canal atresia, bilateral conductive hearing loss, ASD, mild pulmonary valve stenosis, kyphoscoliosis, hemivertebrae, and foot deformities. The pregnancy and delivery were unremarkable. Family history was remarkable for two paternal male second cousins born with clubfeet. After birth, she was noted to have a cleft involving the hard and soft palate. At 20 months, she started walking, spoke two words, and used some hand signs.

On physical examination, her weight was at the 5th centile, length less than the 5th centile, and head circumference at the 50th centile. She had fine hair, round face, gray sclera, short, up-slanting palpebral fissures, vascular pattern circles under the eyes, broad nasal root, small nares, a long, deeply grooved philtrum, downturned corners of the mouth, prominent ear

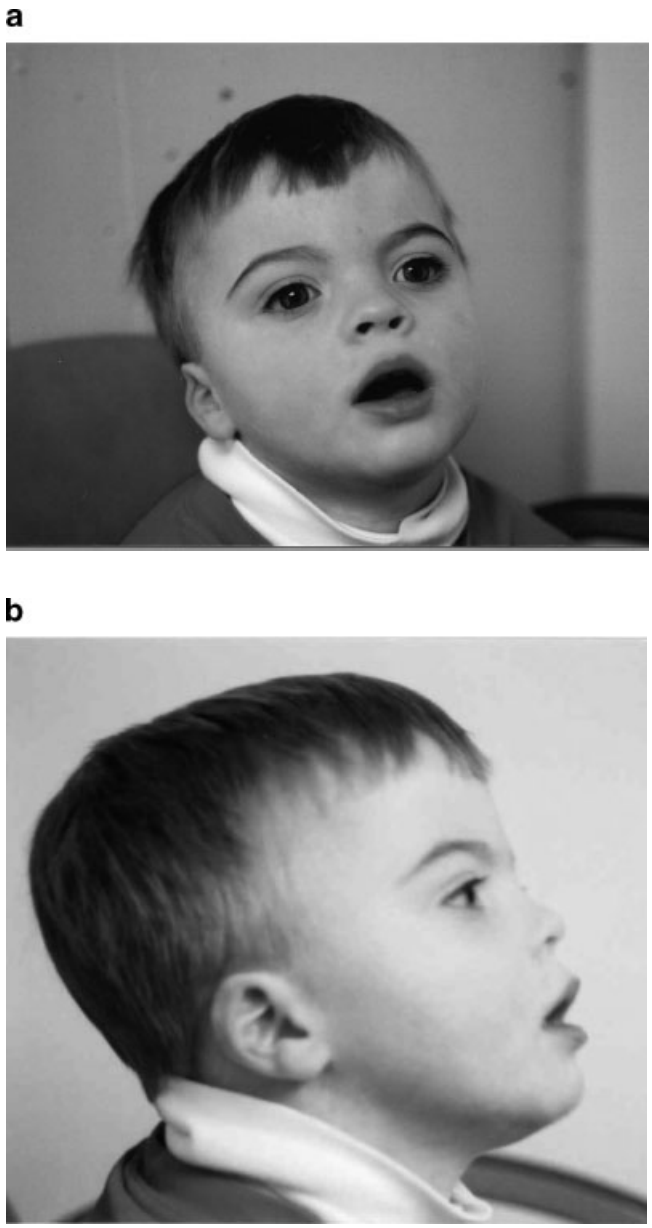

Fig. 7. **a**: AP face. **b**: Lateral face. Patient 9, age 4 years. Microdeletion 9q: Note broad forehead, epicanthal folds, upslanting palpebral fissures, hypertelorism, creases beneath the eyes, broad nasal root, short nose, anteverted nares, low set small ears, and over-folded helices.

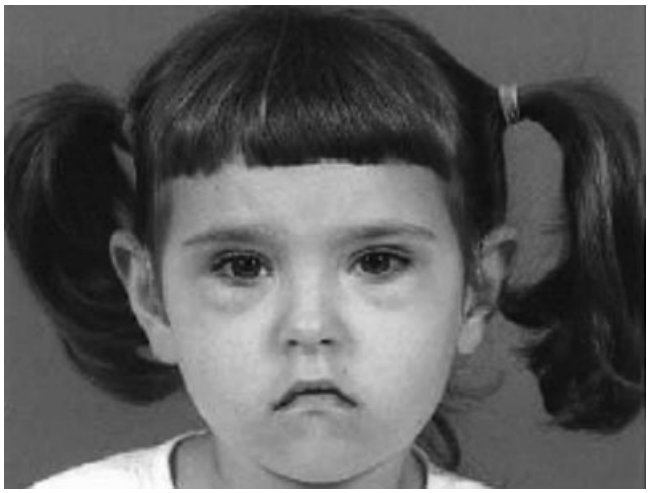

Fig. 8. Patient 10, age 3 years. 18q terminal deletion: Note round face, short upslanting palpebral fissures, vascular pattern circles beneath eyes, broad nasal root, small nares, long deeply grooved philtrum, downturned corners of mouth, and small pointed chin.

Fig. 9. Patient 11, age 4 years. 20p13→ter deletion: Note prominent forehead and large ear lobes.

antihelices, and a small pointed chin (Fig. 8). She also had a short neck, long tapering fingers, increased space between first and second toe, toe three and five clinodactyly, overlapping 2nd upon 3rd toes, decreased hip abduction, and hypotonia. Subtelomeric FISH studies performed 3.5 years after her initial normal 550 band level karyotype revealed a terminal deletion of the long arm of chromosome 18: ish del(18)(q22)(MBP−,18qSUBTEL−) de novo. A repeat blood karyotype was sent and, in retrospect, a small deletion at the end of the long arm of chromosome 18 was noted.

Our patient has many features in common with other children with deletions of chromosome 18q, including short stature, microcephaly, prominent antihelix, carp-shaped mouth, narrow ear canals, congenital heart disease, long and tapering fingers, epicanthal folds, cleft palate, hypertelorism, broad nasal bridge, thin hair, fleshy finger tips, up-slanting palpebral fissures, umbilical hernia, eczema, a gap between the 1st and 2nd toes, feeding issues early on, developmental delay, and vertical talus [Jones, 1997]. Some patients have been found to have low IgA levels and some have had growth hormone deficiency. The patient's subtelomeric FISH results were very helpful both to her family and her medical management. She underwent an endocrinologic evaluation and has started growth hormone therapy. Her family has become very involved with a chromosome 18q− parent support group, and she has been enrolled in a research study.

Patient 11: 20p13→ter Deletion

A 3-year-old boy was referred at age 20 months to the Genetics Clinic for evaluation of developmental delay and macrocrania. He was born by cesarean section delivery at term to a 30-year-old mother after an uncomplicated pregnancy. Family history was unremarkable.

Early on, he was hypotonic and gross motor milestones were delayed. He rolled at 8 months, sat without support at 12 months, belly crawled at 15 months, and crawled at 18 months. First steps were taken at 19 months. At 24 months, his social/emotional skills were judged to be at the 12 month level with little improvement from 18 to 24 months. He was prone to diarrhea. He had an abnormal BEAM FMAER study that showed absence of early cortical auditory function thought to be consistent with a diagnosis of Landau–Kleffner "syndrome."

Physical examination was notable for height at the 10th centile, weight at the 50–75th centile, and head circumference above the 95th centile. He had a prominent forehead and large earlobes (Fig. 9). He also had a single left palmar crease, partial syndactyly of the 2nd and 3rd toes, hirsutism of the upper back, and hypotonia. Subtelomeric FISH testing was completed 10 months after a normal 525 band level karyotype analysis and revealed a deletion of 20p13 to the terminus: 46,XY.ish del(20)(p13)(D20S1157−). Both parents had normal subtelomeric FISH studies.

There have been several reported cases of chromosome 20p12.2 terminal deletions with the critical region thought to be 20p13 [Garcia-Cruz et al., 1985]. Four cases were compared and a distinct syndrome was delineated that includes low birth weight, flat face, low nasal bridge, long philtrum, short neck, small overfolded ears, chest deformity, kyphoscoliosis, congenital heart defect, hypoplastic or absent ribs, and butterfly-shaped vertebral bodies. Silengo et al. [1988] reported a fifth case of a 10-month-old female with chromosome del(20)(p11) mosaicism, multiple congenital anomalies, developmental retardation, and failure to thrive. Our patient, whose deletion is smaller than those involved in these cases, does not have many of these features. Baker et al. [2002] reported a 10-year-old male with a cryptic chromosome 20pter deletion who had moderate intellectual disability, microcephaly, long face, deep-set eyes, upslanting palpebral fissures, short philtrum, small mouth, and pes planus. He also had epilepsy and a delay in the eruption of his secondary dentition. The subtelomeric FISH results were helpful in establishing a diagnosis and in greatly modifying the recurrence risk given to the parents.

Patient 12: 20q Terminal Deletion

A 9-year-old boy with global developmental delay was referred for a consultation in the Genetics Clinic.

He was born at full term after a pregnancy complicated by preterm labor. The family history was noncontributory. There were no problems in the neonatal period. He had global developmental delay, chronic constipation, and eczema. He sat at 8 months, walked at 15 months, had his first words at age 3, and began using short sentences at age 5. At age 7 cognitive testing placed him in the mentally retarded range.

On physical examination, his height was at the 25th centile, weight at the 75th centile, and head circumference at the 50th

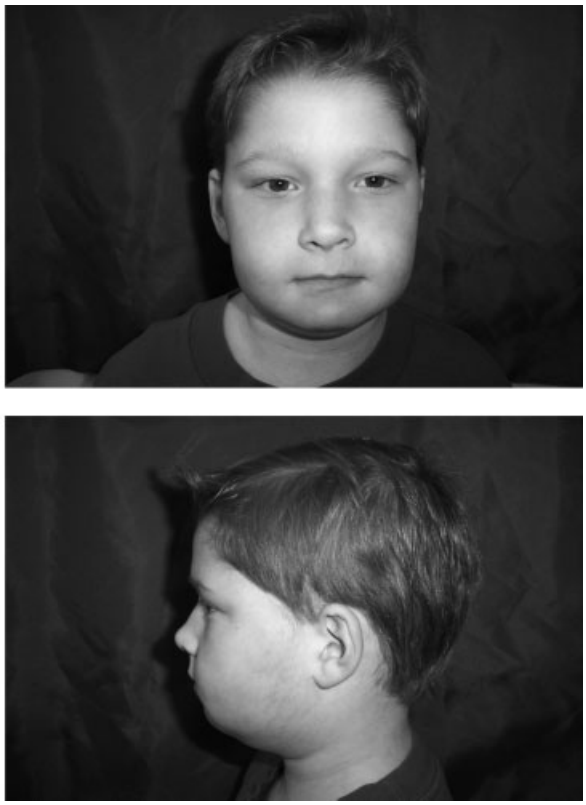

Fig. 10. **a**: AP face. Patient 12, age 9 years. 20q terminal deletion: Note frontal upsweep of hair, upslanting palpebral fissures, slightly arched eyebrows, bulbous nose, smooth short philtrum, and thin upper lip with slight cupid's bow. **b**: Lateral face. Patient 12, age 9 years. 20q terminal deletion: Note crumpled ear helices.

centile. He had a single café au lait spot, a frontal upsweep of the hair, up-slanting palpebral fissures, slightly arched eyebrows, bulbous nose, smooth short philtrum, and a thin upper lip with a slight Cupid's bow (Fig. 10a). He also had subtle bilateral crumpled ear helices (Fig. 10b), high palate, bilateral 5th finger clinodactyly, subtle syndactyly of the 2nd and 3rd toes, and a normal neurologic examination. He had a normal 500 band level karyotype but subtelomeric FISH analysis revealed a deletion on the long arm of chromosome 20: ish del(20)(qter)(20qSUBTEL−). Parental subtelomeric FISH studies were normal.

No other individuals in the literature have been reported to have this particular deletion. A much larger deletion (20q→ter) was reported in an infant who had only a few facial features in common with our patient. This infant had severe mental deficiency, epilepsy, upward slanting palpebral fissures, hypoplastic nasal bridge, bulbous nose, long philtrum, microretrognathia, and aplasia of the middle phalanx of the fingers and toes [Fraisse et al., 1982]. Two cases have been reported of patients with deletion 20q and features of Albright hereditary osteodystrophy including short stature, obesity, developmental delay, and shortening of the metacarpals [Aldred et al., 2002]. Shabtai et al. [1993] reported del 20(q13→13.33) mosaicism in a 68-year-old man with mild mental retardation and severe limb malformations. The subtelomeric FISH results were used to reduce the recurrence risk for the family.

Patient 13: Partial Trisomy 22q

A 15-year-old boy had been followed since birth for multiple congenital anomalies, moderate to severe mental retardation, dysmorphic features, and severe growth retardation. The family history was noncontributory. His medical problems included a diaphragmatic hernia, hypospadius, bilateral inguinal hernia, anal stenosis, chronic constipation, reactive airway disease, swallowing problems, moderate to severe sensorineural hearing loss, attention deficit hyperactivity disorder, migraine headache, pica, and Raynaud's phenomenon. He is able to feed and undress himself, and he communicates using pictures and signs. He is not toilet trained.

His weight, height, and head circumference are all significantly below the 5th centile. He has wiry hair, synophrys, upslanting palpebral fissures, a prominent columella, and a wide mouth (Fig. 11a,b). He also has broad fingers with distal digital hypoplasia and ruddy hands with thickened skin. A hand X-ray showed cone-shaped and ivory epiphyses. Prior karyotypes completed at least at the 400 band level on blood and skin fibroblasts revealed a normal 46,XY male. At 12.5 years of age, subtelomeric FISH studies revealed trisomy for distal 22q as follows: ish der(22)t(22;22)(q13.3;p12)
(D22S39++,ARSA++,22qSUBTEL++). Parental subtelomeric FISH and chromosome studies were normal.

Schinzel [1981] described two brothers with 22q13→ter trisomy who presented with IUGR, congenital hydrocephalus, cerebral palsy, genital hypoplasia with cryptorchidism and hypospadius, up-slanting palpebral fissures, hypertelorism, small nose with a prominent bridge, prominent upper lip, and a small mandible. The second sibling additionally had renal hypoplasia, arhinencephaly, and pentalogy of Fallot. Although there is some overlap (up-slanting palpebral fissures, microcephaly, and hypospadius), our patient's facial features and congenital abnormalities are distinctly different. Biesecker et al. [1995] reported a child with duplication of 22q13.2-qter who presented at age eight with growth retardation, hypotonia, hypertelorism, unilateral cleft lip with bilateral cleft palate, fused mandibular premolars, mixed deafness, exotropia, delayed bone age, markedly delayed development and a seizure disorder. Similarly to our case, trisomy 22q has been associated with a Fryns-like phenotype in a 32-week-old fetus with diaphragmatic hernia, facial defects, and nail hypoplasia with short distal 5th phalanges [Ladonne et al., 1996]. Wieczorek et al. [1998] reported a 9-month-old female with growth retardation, hypertelorism, bilateral cleft lip and palate, and peripheral pulmonary stenosis with de novo partial trisomy 22q13p-qter. Petek et al. [2000] reported a 9-year-old boy with 22q13→qter duplication with microphthalmia, hypoplastic and supernumerary kidneys, hypogenitalism, growth delay, and psychomotor retardation. This patient's family elected not to have more children during his early childhood when a specific diagnosis could not be found. If the subtelomeric FISH results had been available at that time, it is possible that their family planning may have been different.

DISCUSSION

In comparing and contrasting our 13 patients, there were some common features. Four children were classified as having moderate to severe mental retardation, seven as having developmental delay, one as having a mild learning disability, and one with no identified cognitive delay. Nine patients (69%) had hypotonia noted on physical examination. Ten patients (77%) had dysmorphic facial features. Seven patients (54%) had all three features of developmental delay or mental retardation, hypotonia, and dysmorphic facial features. Five patients (38%) had multiple congenital anomalies, one of whom was previously diagnosed with CHARGE and one with VACTERL Association. Many of these features are commonly found in patients referred to a clinical geneticist and do not, in

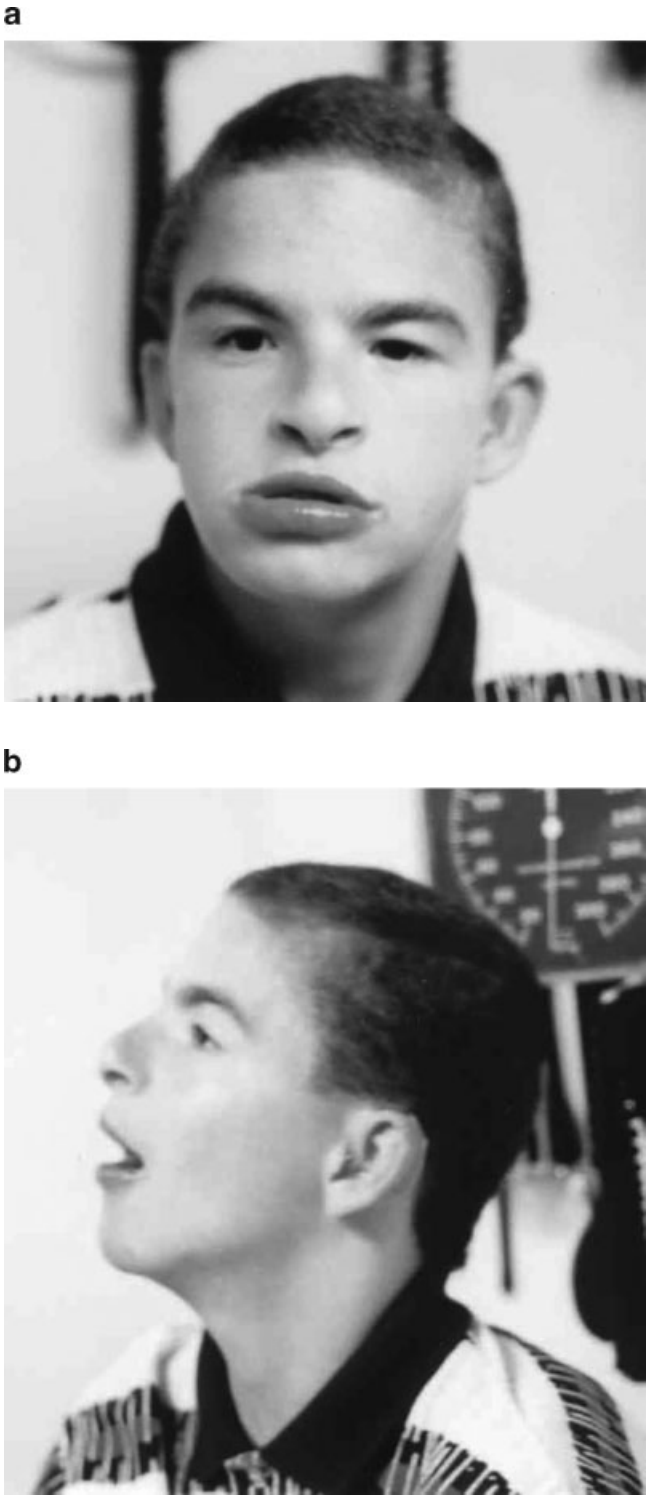

Fig. 11. **a**: AP face. **b**: Lateral face. Patient 13, age 12 years. Partial trisomy 22q: Note microcephaly, wiry hair, synophrys, upslanting palpebral fissures, prominent columella, and wide mouth.

and of themselves, identify patients likely to have a subtelomeric rearrangement.

The cytogenetic basis of the clinical syndromes was complex. Eleven cases (85%) occurred de novo, one case (8%) was derived from a maternal balanced translocation, and one case (8%) had the same abnormality as the mother. Chromosome 1p was the most commonly involved region (23%) with two cases of monosomy 1p36 and one complex rearrangement involving partial monosomy 1p. Nine cases (69%) were partial monosomies (involving 1p, 1q, 2q, 6q, 9q, 18q, 20p, and 20q), three cases (23%) were complex rearrangements (partial monosomy 7q/partial trisomy 11p, partial monosomy 1p/partial trisomy 4p, and partial monosomy 1p/partial trisomy 13q), and one case (8%) involved a partial trisomy (22q).

Subtelomeric FISH testing was used to screen for abnormalities in 11 of the cases. In two cases, the testing was used to better delineate and analyze an abnormality visible on karyotype. One patient had a chromosomal abnormality visible by karyotype only in retrospect once the subtelomeric FISH results were available. Most had duplications or deletions not specifically described in the literature making prognostication for parents challenging. The average time from first normal karyotype to diagnostic subtelomeric FISH result was 3.8 years ($n = 11$, range: 6 months–10 years, median 3.5 years). Because some of these patients were referrals and because several different labs performed the subtelomeric FISH testing, we were unable to calculate an accurate prevalence rate. These cases were collected over a 21 month period. Two cases were of questionable clinical significance. Patient 4 presented with a severe phenotype unlike his mother who carries the same rearrangement. Patient 7 presents with typical features of VACTERL association and these features have not typically been described in other patients with terminal deletion 6q. It is only after parental studies and careful literature review that a subtelomeric FISH abnormality can be causally linked to a patient's phenotype.

Our case series suggests that subtelomeric FISH analysis is indicated as a second tier test after a karyotype in children with otherwise unexplained developmental delay, hypotonia, dysmorphic facies, and/or multiple congenital anomalies. Given that a number of our patients were followed for many years without a diagnosis, subtelomeric FISH testing is warranted in patients who remain a persistent diagnostic dilemma and whose original molecular and cytogenetic evaluation was completed in the pre-subtelomeric FISH era. The addition of new diagnostic technologies provides another reason to maintain periodic follow-up in undiagnosed patients.

As described in our cases, it is helpful to families to identify subtelomeric rearrangements. Parents can be more accurately counseled regarding recurrence risk. Future pregnancies can be more closely monitored and prenatal testing can be offered. When a parent is found to be a carrier, it can lead to evaluation of the extended family. For the physician, the establishment of a cytogenetic diagnosis eliminates the need to continue to pursue metabolic, cytogenetic, or molecular testing. Additionally, as patterns become apparent for particular subtelomeric deletions or duplications, more focused medical screening and possibly periodic monitoring can be performed. Finally, families are often comforted when a reason for their child's medical and or developmental problems has been found, particularly when the diagnosis comes after a long period of evaluation.

It is no longer adequate to group children into categories based upon abnormalities visible on high resolution karyotype (for example, 18q deletion) when the cytogenetic technology of subtelomeric FISH has allowed for much more specific descriptions of partial aneuploidy (for example, del 18q22-qter). Applying the current literature based primarily on cases of duplications and deletions visible on standard karyotype to new cases of cryptic subtelomeric rearrangements is a difficult and inexact science. The continued detailed reporting of cases will help to better define the emerging subgroups of patients with subtelomeric deletions and duplications. This will lead to more specific and accurate prognostication for families and improved patient management. These cases could also help

identify regions for candidate genes through phenotypic comparisons of contiguous deletions and duplications.

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