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Original article

A de novo subterminal trisomy 10p and monosomy 18q in a girl with MCA/MR: case report and review

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Abstract

We report on a 3-year-old girl with psychomotor retardation, cardiopathy, strabismus, umbilical hernia, and facial dysmorphism in whom a de novo unbalanced submicroscopic translocation (10p;18q) was found by MLPA (Multiplex Ligation dependent Probe Amplification) and FISH analyses. Additional FISH studies with locus specific RP11 BAC probes and analyses with microsatellites revealed that the translocation resulted in a deletion estimated between 6 and 9 Mb on the maternal chromosome 18 and a subtelomeric 10p duplication of ~6.9 Mb. The proband's karyotype is 46,XX,ish der(18) t(10;18)(18pter→18q23:10p15 → 10pter). A subterminal duplication of 10p, as well as a subterminal deletion of 18q have been rarely reported so far. The clinical phenotype of this patient is reviewed and discussed.

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Keywords: Subtelomeric duplication 10p; Subtelomeric deletion 18q; Mental retardation; Cardiopathy; Facial dysmorphism; MLPA analyses

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1. Introduction

Segmental aneusomies are a common cause of mental retardation and multiple congenital anomalies. Derivative chromosomes can be characterized by conventional chromosome analyses but a number of small rearrangements cannot be observed by this technique due to the limited resolution. Subtelomeric Multiplex Ligation-Dependent Probe Amplification (MLPA), a recently developed technique based on PCR amplification of ligated probes hybridised to chromosome ends, allows to screen for these small cytogenetically invisible telomeric rearrangements. Subtelomeric deletions and/or duplications are then confirmed by FISH analyses [23]. It is believed that the high degree of sequence similarity between subtelomeric domains on different chromosomes underlies the deletions or translocations of genetic material. As subtelomeric regions are relatively gene-rich, these abnormalities usually have severe clinical implications. In this girl with psychomotor delay, multiple congenital anomalies and facial dysmorphism, MLPA allowed to detect an unbalanced submicroscopic translocation (10p;18q), causing a 10p subterminal duplication and a 18q subterminal deletion.

The 18q- syndrome, associated with a terminal deletion of the long arm of chromosome 18, is one of the more common deletion syndromes. Most deletions range in size from 18q21.1-qter to 18q22.3-qter [30]. De novo deletions are mostly paternal in origin [5]. Deletion of terminal 18q can result in a recognizable syndrome, but the phenotype of the disorder varies greatly between individuals. It generally includes developmental delay, hypotonia, growth deficiency, malformed ears, downturned corners of the mouth, midfacial hypoplasia, high/cleft palate, hearing loss, and other anomalies [7,10,30].

Patients with trisomy of the short arm of chromosome 10 reported to date have shown variable clinical manifestations. Most cases are the result of unbalanced segregations of familial translocations resulting in trisomy 10p associated with other additional segmental imbalances [4,34]. Pure partial trisomy 10p cases have been reported [8,20,24,28], as well as patients with pure complete trisomy 10p [3,11,12,14,21,27]. A subterminal trisomy 10p (p14/p15→ pter), as present in the *proposita*, has to our knowledge only been reported three times so far [2,9,29] (Table 1).

2. Materials and methods

2.1. Case report

The female proband was the second child of a healthy 30-year-old G3P3 Mauritian mother and a 39-year-old unrelated Belgian father. Her 5-year-old sister and 12-year-old halfsister were in good health. There was no family history of mental retardation, cardiopathy, or malformations except for the presence of mild learning difficulties of unknown origin in the patient's cousin.

Pregnancy was normal, but oligohydramnios was noted ~2 weeks before delivery. She was born at term with birthweight 4280 g (> 97th centile), birthlength 52 cm (90th centile) and a normal headcircumference (36 cm; between 50th and 75th centile). Delivery was difficult and the child presented congenital torticollis. She displayed feeding difficulties requiring hospitalisation at the age of 3 weeks. RSV bronchitis and gastro-oesophageal reflux were diagnosed, as well as a heart murmur. Ultrasound heart examination disclosed the presence of mild pulmonary valve stenosis. Transfontanel and abdominal ultrasound examination were normal. She was

Table 1

Clinical findings in patients with trisomy 10p and in patients with subterminal trisomy 10p (10p14/15→pter) *

	Stone et al., 1996 [29]	Stone et al., 1996 [29]	Fryns et al., 1997 [9]	Benzacken et al., 1998 [2]	Present patient	Total	In patients with partial terminal trisomy 10p syndrome**	In patients with total pure trisomy 10p***
	<i>Proband</i>	<i>Affected sister</i>						
Described duplicated region of 10p	p14/15→pter (> 9 Mb)	p14/15→pter (idem as proband)	p15 (or p13?)→pter	p14→pter	p15→pter (6.9 Mb)	5 patients	Different re- gions	10p10 (or cen)→pter
Associated anomalies	Der(9)	Idem as pro- band	1p deficiency (1p36→pter)	– Der(6)	18q subterm- inal deletion	5/5	Different chromosome anomalies	
	9pter deficiency?			6pter defi- ciency? – twin preg- nancy				
De novo	– (segmental 10p trisomy in the father****)	Idem as pro- band	– Paternal translocation	+	+	2/5		
Sex	F	F	M	F	F	1 M/4 F		
Age at examination	13 years	N.R.	Foetus (141/2 w)	15 days; 8 months	3 years 5 months	foetus –13 years		
Birthweight	8 pounds 11 ounces	8 pounds 8 ounces	N.R.	2630 g (P10–50)	4280 g (> P97)	Normal to high in 4/4		
Birthlength (cm)	N.R.	N.R.	N.R.	46 (P10–50)	52 (P90)	Normal to high in 4/4		
OFC (cm)	N.R.	N.R.	N.R.	34 (P90)	36 (P50–75)	Normal to high in 4/4		
Gestational age	at term	at term	151/2 w	37 w	41 w			
IUGR	–	–	N.R.	–	–	0/4		
Weight (kg)	N.R.	N.R.	Mors in utero	6100 (< P3)	15 (P50)			
Length (cm)	N.R.	N.R.		63 (< P3)	104.5 (P97)			
OFC (cm)	N.R.	N.R.		44.5 (P25–50)	50.5 (P90)			
At age	13 years			8 m	3 years 5 months			

(continued on next page)

Table 1 (continued)

	Stone et al., 1996 [29]	Stone et al., 1996 [29]	Fryns et al., 1997 [9]	Benzacken et al., 1998 [2]	Present patient	Total	In patients with partial terminal trisomy 10p syndrome**	In patients with total pure trisomy 10p***
	<i>Proband</i>	<i>Affected sister</i>						
Postnatal growth retardation	N.R.	N.R.	N.R.	+	–	1/2	63%	100%
Developmental delay /mental retardation	+ Learning difficulties with normal IQ	+; learning dif- ficulties milder than proband	N.R.	+	+	4/4	63% (severe to profound)	100%
Seizures	–	–	N.R.	–	–	0/4	21%	100%
Hypotonia	N.R.	N.R.	N.R.	+	+	2/4	53%	44%
Renal/urinary tract abnormal- ities	N.R.	N.R.	+	–	+	2/5	18–26%	33%
Cardiac/vascular abnormalities	N.R.	N.R.	N.R.	–	+	1/5	28–33%	22%
Ocular anomalies	+	– (except for a minor vessel anomaly at the right optic nerve)	N.R.	–	+	2/4	20–21%	
	– Surgery for strabismus and ptosis							
	– Optic neuropathy							
	– Partially tilted disk in her right eye with a probable optic nerve coloboma							
	– legally blind							
	– Limited upward eyemovement							

(continued on next page)

Table 1 (continued)

	Stone et al., 1996 [29]	Stone et al., 1996 [29]	Fryns et al., 1997 [9]	Benzacken et al., 1998 [2]	Present patient	Total	In patients with partial terminal trisomy 10p syndrome**	In patients with total pure trisomy 10p***
	<i>Proband</i>	<i>Affected sister</i>						
Gastro-oesophageal reflux	N.R.	N.R.	N.R.	+	+	2/4	9%	
High forehead	+	+	N.R.	–	+	3/4	52–70%	77%
Abnormal palpebral fissures	–	–	N.R.	+	–	1/4	28–33%	77%
Ear abnormalities	+ (earlobe pits)	–	N.R.	+	–	2/4	70–81%	77%
Micro-/retrognathia	–	–	N.R.	–	–	0/4	37%	55%
Hypertelorism	– (hypotelorism)	– (hypotelorism)	N.R.	+	+	2/4	30–46%	55%
Microcephaly	N.R.	N.R.	N.R.	–	–	0/4	42%	55%
Other	– Recurrent infections attributed to decreased IgG levels – Midface hypoplasia – Epicanthal folds	– Metatarsus adductus – Decreased IgG levels	– Megacystis – Early urethra obstruction sequence	– Corpus callosum agenesis – Glottic stenosis – Pigmentation deficiency				

+, feature present; –, feature not present; N.R., not reported; * the case reported by Grosse et al. [13] is not included because the localization of the breakpoint seems more proximal than 10p14; **as reviewed by [4,19] (in > 60 patients); ***as reviewed by [12] (in 9 patients); ****the father also had the derivative 9 chromosome; had mild learning difficulties and had asymptomatic ophthalmologic anomalies including a tilted disc in one eye and abnormal optic nerves; no colobomas were noted; he was not available for clinical examination.

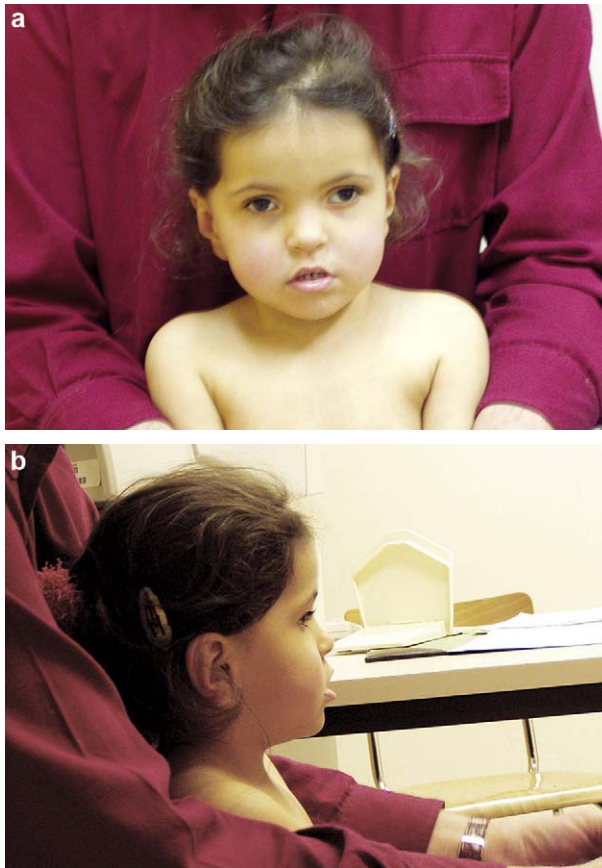


Fig. 1. a,b: clinical photograph of the patient at the age of 3 years 4 months, showing broad nasal bridge, hypertelorism, and flat facial profile.

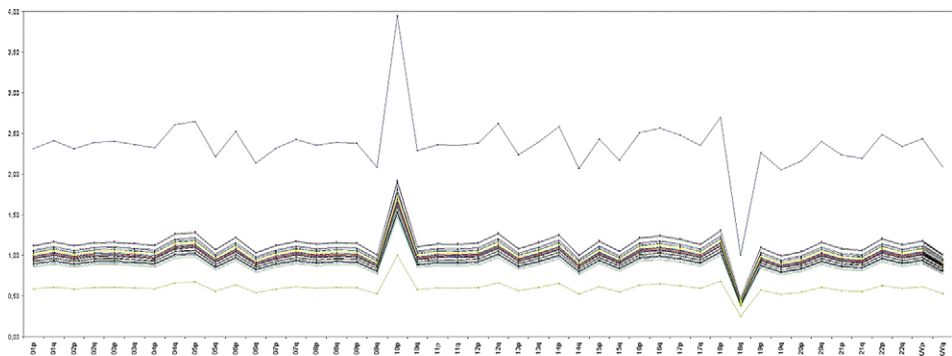


Fig. 2. MLPA (Multiplex Ligation dependent Probe Amplification) analyses established the diagnosis: it showed a diminished (1/2) intensity at telomere 18qter (Salsa probe 1758-L1292, FLJ21172 gene) and an increased intensity corresponding with telomere 10pter (Salsa probe 2277-L1768, IAA0934 gene).

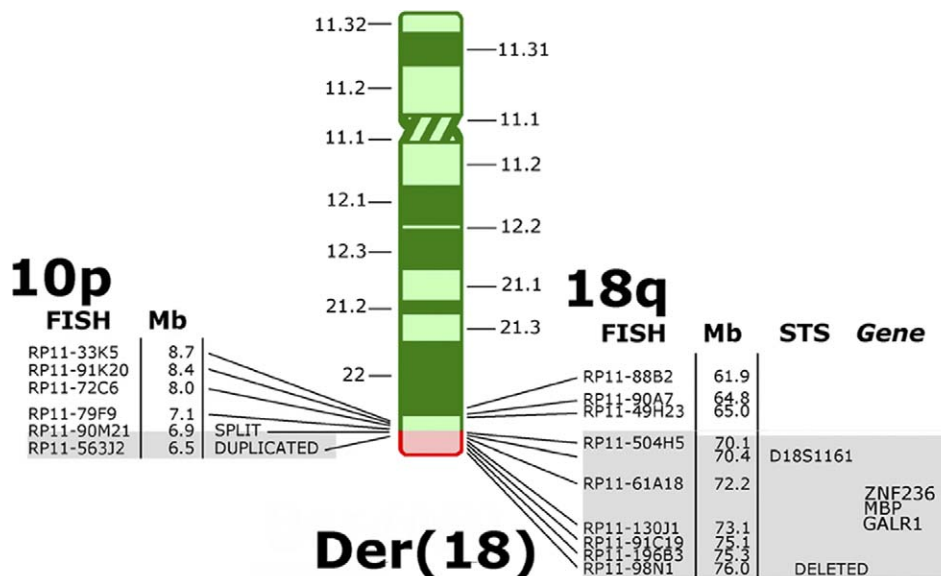


Fig. 3. Schematic presentation of the derivative chromosome 18 showing the deleted region on 18q and the duplicated region on 10p, according to the molecular and FISH analyses.

operated on for an umbilical hernia at age 3 years. Psychomotor development was delayed. She could sit unsupported at the age of 8 months; retardation in gross motor skills was diagnosed at age 14 months, and she received special training to improve her motor skills from the age of 15 months on. She was able to walk independently at the age of 24 months and said her first words at age 21/2 years. She was described as shy and anxious from early age on but this gradually improved. There were no sleeping difficulties.

We first saw the child at the age of 3^{5/12} years for delayed psychomotor development, cardiopathy, strabismus and facial dysmorphism (Fig. 1). Her weight was 15 kg (50th centile), length 104.5 cm (97th centile) and OFC 50.5 cm (90th centile). Her facial dysmorphism consisted of hypertelorism, divergent strabismus, telecanthus, flat broad nasal bridge, short nose, tendency to open mouth, highly arched palate, a deeply grooved philtrum, everted lower lip, and flat facial profile. She had a known systolic heart murmur, had an ataxic gait, and a sandal gap. Psychomotor testing (Bayley-II scales of Infant Development) performed at age 31/2 years evaluated her at the level of a 24-month-old child for cognitive skills; speech, language, gross and fine motor skills were evaluated at < 2 years, 2.3–2.6 years, 26 and 25 months, respectively. Brain magnetic resonance performed at age 2 years was normal. Electroencephalogram showed an aspecific generalized slow pattern. Urinary organic and amino acids were normal. Renal ultrasounds disclosed a duplication of the left ureteral system. Ophthalmologic examination showed an intermittent divergent strabismus at the left eye and normal eyefundi. Cardiologic follow-up only confirmed a very mild pulmonary stenosis. Skeletal X-rays disclosed a lumbar scoliosis, 11 pair of ribs, valgus deformity of both hips, hypoplastic appearance of both iliac wings, and a slight lateral bowing of both tibiae and fibulae. Bone age was normal. Fragile X syndrome could be excluded by DNA analyses and also no mutations in MECP gene were found. A standard karyotype, FISH 22q11, and FISH 7q11.2 (Williams syndrome) were normal.

2.2. Methods

Cytogenetic and fluorescence in situ hybridisation (FISH) analyses

GTG-banding analysis was performed on metaphases obtained from PHA-stimulated lymphocytes from the patient and her parents, according to standard procedures.

Fluorescence in situ hybridisation (FISH) was performed with subtelomeric probes of chromosomes 10 (probe GS-23-B11) and 18 (probe GS-964-M9) (Flint second generation), and with their centromeric probes (chromosome 10: probe α 10RP8, chromosome 18: probe L1-84). Further FISH analyses with 18q and 10p locus specific RP11-BAC probes (Fig. 3) obtained through screening of the human genome project (<http://genome.ucsc.edu>).

2.3. Molecular analyses

DNA was extracted from peripheral blood lymphocytes from the proband and both parents according to standard procedures.

MLPA (Multiplex Ligation dependent Probe Amplification) analyses was performed using a human subtelomeric probe-set for all chromosomes (Salsa PO36, MRC-Holland b.v., Amsterdam, The Netherlands). The analysis was performed according to the manufacturer's recommendations.

Microsatellite markers D18S1161 and D18S1390 were studied. Primers and conditions for amplification of these markers were obtained from the Genome Database and forward primers were modified with a M13 sequence preceding the locus specific sequence. Physical and genetic positions were obtained from the NCBI genome database (http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi). PCR was performed according to standard procedures with both locus specific primers and FAM-fluorescent labelled M13 primers. PCR products were analysed on an ABI3100 genetic analyser.

3. Results

3.1. Cytogenetic studies

GTG-banded chromosomes obtained from the lymphocytes of the proband and her parents were normal.

3.2. MLPA analyses

MLPA showed a diminished (1/2) intensity at telomere 18qter (Salsa probe 1758-L1292, FLJ21172 gene), and an increased intensity corresponding with telomere 10pter (Salsa probe 2277-L1768, IAA0934 gene) (Fig. 2).

3.3. Fluorescence in situ hybridisation studies

FISH analysis of the proband with subtelomeric probes confirmed the presence of only one 18qter signal (probe GS-964-M9) and three 10pter signals (probe GS-23-B11). FISH analyses in both parents with those subtelomeric probes for chromosomes 10 and 18 were normal indicating a de novo anomaly in the child.

Further FISH analyses on 18q showed a deletion of the following 18q probes: from RP11-504H5 till RP11-89N1 (Fig. 3). The following probes were not deleted and were thus localised

proximal of the breakpoint, RP11-866E20 (18q21-q22), RP11-91H13 (18q22), RP11-793J2 (18q22), RP11-88B2, RP11-90A7, and RP11-49H23 (Fig. 3). The deletion occurred thus between the probes RP11-49H23 (65.0 Mb) and RP11-504H5 (70.1 Mb), localized at 18q22.2-23 according to the NCBI genome database.

The following 10p probes were not duplicated: RP11-79F9 (10p15), RP11-72C6 (10p14), RP11-91K20 (10p14), RP11-33K5 (10p14-15), and RP11-1051H14 (10p15). Probe RP11-563J2 (10p15) was duplicated, and probe RP11-90M21 (11p15) showed a split signal, indicating that the breakpoint on 10p occurred in this region (Fig. 3).

3.4. Further molecular studies

PCR analysis of polymorphic markers from this region was performed in order to determine the parental origin of the deletion. Only the paternal copy was present for the marker D18S1161 (70.4 Mb), indicating that the deletion occurred on the maternal chromosome 18.

In summary, we estimated the size of the 10p duplication 6.9 Mb and the 18q deletion between 6 and 9 Mb, based upon the physical location of the deleted probes and markers in the human DNA sequence (Fig. 3). The proband's karyotype is 46,XX,ish der(18) t(10;18) (18pter→18q23::10p15 → 10pter).

4. Discussion

A subterminal duplication 10p and subterminal deletion 18q, resulting from a de novo sub-microscopic unbalanced translocation (10p;18q) was discovered in this 3-year-old girl. Her clinical findings, including psychomotor retardation, mild pulmonary valve stenosis, strabismus, umbilical hernia, abnormal renal ultrasounds, feeding problems, increased space between first and second toe, and facial dysmorphism, are all compatible with a distal monosomy 18qter syndrome [7]. Our patient did not present growth deficiency although the GH deficiency critical region at 18q23 is included in the deletion [6]. The presence of this deletion is however not sufficient in itself to cause growth insufficiency/deficiency, since patients have been described with deletion including this region and no evidence of growth failure [6]. Our patient did also not present hearing loss, seizures nor microcephaly, findings frequently found in 18q terminal deletion syndrome [7,10,30], but it is known that patients with the 18q-syndrome have a variable phenotype, and that microcephaly has been mapped proximal to 18q22.3, a region not deleted in the present patient [30]. No apparent explanation has so far been provided for the wide clinical variation of the 18q-syndrome phenotype. Correlation between deletion size, parental origin, and severity of the clinical findings could not be established [7]. The critical region for the 18q-syndrome is presumed to be 18q23. Also patients with a small terminal deletion (18q23-qter) showed high clinical variability and demonstrated that such deletion does not always lead to the clinical features associated with this syndrome [31]. A subterminal deletion of 18q however is rare and has mostly been reported as the result of an unbalanced familial cryptic translocation. It has been described in association with a subterminal trisomy 21q [1,15,17,33], 5qter [32], and chromosomal material of unknown origin [26]. All these cases presented with MCA/MR syndrome, were often familial with variable clinical findings, and were sometimes associated with miscarriages. Features present in all these cases are postnatal growth deficiency, severe developmental delay, hypotonia, and dysmorphism. Other findings present in the probanda and also described in one or more of these patients are high arched/cleft palate, hypertelorism, divergent strabismus, early feeding pro-

blems, ASD, and umbilical hernia. Their facial dysmorphism was, however, variable and partly caused by the simultaneous presence of the concomitant partial trisomy, especially in the cases with associated trisomy of the Down syndrome critical region [1,15,33].

To our knowledge, only 3 patients with a pure subterminal deletion 18q, all de novo cases, have been reported so far [18,22,25]. One of them, a 5-year-old girl, presented with a quite similar phenotype as our patient, with mild pulmonary stenosis, umbilical hernia, developmental delay and a comparable facial dysmorphism [22]. This patient had however, in addition, cleft palate, external auditory canal stenosis, bilateral conductive hearing loss, ASD, kyphoscoliosis, hemivertebrae, foot deformities, and short stature. Unfortunately, the size of the deletion in that patient was not described. In the other 2 patients with pure subterminal 18q deletion, further molecular characterization of the deletion was described, but clinical photographs were unavailable [18,25]. One of them had a deletion comparable to our patient (9 Mb) and presented with mental retardation, abnormal genitalia, proximally implanted thumbs, tapering fingers, abnormal feet, ocular abnormalities, sacral dimple, carp-mouth, midface hypoplasia, and umbilical hernia [25]. The other patient had a 5 Mb deletion and displayed only few of the clinical features associated with the 18q- syndrome, such as hypotonia, congenital heart defect and some minor problems with attention span, but had no mental delay [18]. A variable level of developmental delay is present in most, but not in all 18q deletion patients. Previously it has been suggested that severe mental delay was associated with the larger deletions [16], but a correlation between size of deletion and IQ was not found [30]. Since mental retardation is present in our patient with a 18q deletion of 6–9 Mb, we could suggest a role of possible MR genes in the telomeric region 18q between 5 and 6–9 Mb. The MR in the present patient could of course also be caused by the subtelomeric trisomy 10p.

The contribution of the subtelomeric trisomy 10p to the clinical phenotype of the present patient is not clear. Some of the clinical features present in the proposita, were also reported in patients with trisomy 10p, including mental retardation, hypotonia, cardiac, renal and ocular anomalies, and some dysmorphic symptoms (Table 1). Pre- and postnatal growth retardation, seizures, cleft lip/palate, microcephaly and micrognathia were not present in our patient, possibly because of the very small size of the 10p duplication. However, association of the clinical findings of our case with subtelomeric trisomy 10p by comparison with other described cases is not possible because it has only been reported in 4 patients so far, all in association with another chromosomal anomaly (Table 1). Prenatal growth deficiency seems however not a feature in subtelomeric 10p duplication (Table 1). Additional patients are needed to further delineate the clinical phenotype in subtelomeric 10p trisomy.

The clinical findings in the present patient are probably mostly due to the 18q subterminal deletion although this girl did not present the typical findings of a 18q- syndrome. This case emphasize the importance to exclude subtelomeric anomalies in a child with aspecific mental retardation and multiple congenital anomalies (MR/MCA) in order to exclude a cryptic unbalanced translocation, allowing a better genetic counselling.

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