Duplication of the Miller-Dieker Critical Region in a Patient with a Subtelomeric Unbalanced Translocation t(10;17)(p15.3;p13.3)

R. Ruiz Esparza-Garrido A.C. Velázquez-Wong M.A. Araujo-Solís
J.C. Huicochea-Montiel M.Á. Velázquez-Flores F. Salamanca-Gómez
D.J. Arenas-Aranda

Unidad de Investigación Médica en Genética Humana (UIMGH), Hospital de Pediatría, Instituto Mexicano del Seguro Social (IMSS), Mexico City, Mexico

Key Words

Miller-Dieker syndrome critical region • Partial deletion 10p • Partial duplication 17p • Subtelomeres • Unbalanced translocation

Abstract

Submicroscopic duplications in the Miller-Dieker critical region have been recently described as new genomic disorders. To date, only a few cases have been reported with overlapping 17p13.3 duplications in this region. Also, small deletions that affect chromosome region 10p14→pter are rarely described in the literature. In this study, we describe, to our knowledge for the first time, a 5-year-old female patient with intellectual disability who has an unbalanced 10;17 translocation inherited from the father. The girl was diagnosed by subtelomeric FISH and array-CGH, showing a 4.43-Mb heterozygous deletion on chromosome 10p that involved 14 genes and a 3.22-Mb single-copy gain on chromosome 17p, which includes the critical region of the Miller-Dieker syndrome and 61 genes. The patient's karyotype was established as 46,XX, arr 10p15.3p15.1(138,206–4,574,436) x1, 17p13.3(87,009–3,312,600) x3. Because our patient exhibits a combination of 2 imbalances, she has phenotypic features of both chromosome abnormalities, which have been re-

ported separately. Interestingly, the majority of patients who carry the deletion 10p have visual and auditory deficiencies that are attributed to loss of the *GATA3* gene. However, our patient also presents severe hearing and visual problems even though *GATA3* is present, suggesting the involvement of different genes that affect the development of the visual and auditory systems.

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Subtelomeres are particular chromosome regions made up of a large number of genes and a high amount of different repetitive sequences [Mefford and Trask, 2002; Riethman et al., 2005]. Due to this structural composition, these regions are involved in chromosome rearrangements [Saccone et al., 1992; De Vries, 2003; Linardopoulou et al., 2005; Ledbetter and Martin, 2007]. The development of advanced molecular cytogenetic methods has allowed for the identification of subtelomeric rearrangements as an important cause of mental retardation and/or congenital malformation [Knight and Flint, 2000]. Some of the subtelomeric chromosome regions with a relatively high proportion of disease-associated rearrangements or copy number variation are subtelomeres of chromosomes 10p and 17p

[Verri et al., 2004; Linardopoulou et al., 2005; Wu et al., 2010].

In the Miller-Dieker syndrome (MDS) critical region, 17p13.3 microdeletions and duplications have been described in different groups of patients with distinct but overlapping phenotypes. In the MDS critical region, some genes are mapped that play an important role during central nervous system development as the platelet-activating factor acetylhydrolase gene (*PAFAH1B1*), which encodes the LIS1 protein and the candidate gene tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, epsilon polypeptide (*YWHAΕ*), which encodes the 14-3-3ε protein. [Assadi et al., 2003; Toyo-oka et al., 2003] When one of these genes is lost or duplicated, patients present brain malformation [Chong et al., 1996, 1997; Cardoso et al., 2000, 2003]. Importantly, microduplications in this region are rare; to date, very few cases have been reported in detail [Ravnan et al., 2006; Lu et al., 2007; Bi et al., 2009; Roos et al., 2009; Bruno et al., 2010; Shchelochkov et al., 2010].

Terminal deletions of chromosome 10p have been published on several occasions [Bourrouillou et al., 1981; Fryns et al., 1981; Suciū and Nanulescu, 1983; Kinoshita et al., 1992; Shapira et al., 1994; Schinzel, 2001; Roos et al., 2006; Battaglia et al., 2007; Lindstrand et al., 2010]; however, only 5 cases with a small deletion that affected the chromosome region 10p14→pter have been reported [Bourrouillou et al., 1981; Fryns et al., 1981; Lindstrand et al., 2010]. In general, the majority of the pure deletions reported for chromosome 10p are associated with the DiGeorge-like phenotype (DGSII) or with the hypoparathyroidism-sensorineural deafness/renal syndrome (HDR), the latter associated with the *GATA3* gene [Schuffenhauer et al., 1995; Dasouiki et al., 1997; Van Esch et al., 2000; Fukami et al., 2011].

In this study, we report, to our knowledge for the first time, the identification of a patient with a cryptic unbalanced 10;17 translocation identified by subtelomeric FISH and array-CGH. Our results also demonstrate that the unbalanced translocation in the patient was inherited from the father, which has not been reported to date. Likewise, the visual and auditory abnormalities present in our patient are not related to the *GATA3* gene.

Clinical Report

The patient is the second child of healthy, nonconsanguineous Mexican-mestizo parents without a familial history of mental retardation or genetic conditions. Her parents and sister were healthy. She was born at term (38 weeks of gestation) by cesarean

Fig. 1. Patient aged 2 years. **a** Note some dysmorphic features present in the patient, such as pointed chin, ears with an absent superior fork of the antihelix and frontal hemangioma. **b** Image shows hypertelorism, sparse eyebrows, palpebral fissures slanted upward, and bilateral epicanthus. Note the small nose with rounded tip and broad nasal root. **c** Lateral photo showing cupped ears and flat facial profile.

section due to fetal distress. Her weight at birth was 3,000 g (25th percentile). The patient measured 51 cm in length (50–75th percentile) and had an Apgar score of 8/9 at 1 and 5 min, respectively. At 5 months of age, clinical examination showed medial frontal hemangioma, microcephaly with a head circumference of 37 cm (<3rd percentile) and sagittal synostosis, which did not require surgical intervention. She showed other dysmorphic features, including sloping forehead, flat facial profile, hypertelorism, and sparse eyebrows. The patient presented palpebral fissures, slanted upward, and bilateral epicanthus. The nose was small with rounded tip and a broad nasal root. The ears were cup-shaped, with an absent superior fork of the antihelix. Additionally, the patient showed a short philtrum, high-arched palate and short neck (fig. 1, 2). She has abnormalities in hands and feet, showing long fingers on both hands, bilateral equinovagis, clinodactyly of the 4th toe on each foot, dysplastic concave toenails, and reduced extension of the upper and lower extremities. In addition, hyperpigmented skin in the genital area was observed. X-ray studies revealed left scoliosis, vertebral bodies with lateral outgrowths and a dysrhythmic bone age. Brain MRI showed cortical atrophy and hypoplasia of corpus callosum (image not shown), whereas evoked potentials indicated severe bilateral visual dysfunction and immaturity of auditory brainstem-evoked responses. Furthermore, the patient has developmental delay and exhibits no verbal language at 5 years of age.

Fig. 2. Patient aged 5 years. **a, b** Note facial dysmorphic features that are more noticeable, such as pointed chin, ears with and absent superior fork of the antihelix, palpebral fissures, bilateral epicanthus, strabismus, and broad nasal root.

Fig. 3. Partial monosomy 10p and partial trisomy 17p detected with simultaneous FISH for subtelomeric regions in the patient. **a** The specific probe shows only 1 signal for chromosome 10, which is involved in the rearrangement. **b** Three signals for the specific region 17p were detected; the extra signal was found on chromosome 10p, which lost the subtelomeric region.

Materials and Methods

Peripheral blood samples were taken from the patient and from her parents to culture peripheral blood lymphocytes. Chromosome analysis was performed by conventional GTG-banding (550 bands). FISH analysis for all 41 subtelomeric regions was also performed using the ToTelVysion Multi-color DNA probe mixture (Vysis, Inc., USA). A minimum of 50 metaphases were analyzed under an Axio Images (Carl Zeiss) fluorescence microscope equipped with the appropriate filters. The images were captured with specific ISIS (Meta Systems) software. Finally, aiming to delimit and to analyze the involved segments, we performed a 60,000 oligonucleotide array-CGH, sourced from the University of California, Santa Cruz (UCSC), Calif., USA, hg18 (NCBI Build 36), March 2006, probe spacing: 41 KB overall median probe spacing (33 KB in Refseq genes) (Agilent Technologies; Santa Clara, Calif., USA). The research was prospectively reviewed and approved by a duly constituted ethics committee.

Results and Discussion

Standard cytogenetic GTG-banding analysis (550 bands) revealed a normal karyotype of the patient and her parents. However, due to the dysmorphic features present

in the girl, we performed a subtelomeric FISH analysis on the patient and her parents. Analysis showed the absence of 1 subtelomeric signal of chromosome 10p (partial monosomy) and 1 extra signal for chromosome 17p (partial trisomy), resulting in an unbalanced 10p;17p translocation in the girl (fig. 3). Array-CGH analysis showed a heterozygous deletion of 4.43 Mb on chromosome 10p and a single-copy gain of 3.22 Mb on chromosome 17p (fig. 4): 46,XX, arr 10p15.3p15.1(138,206–4,574,436)x1, 17p13.3(87,009–3,312,600)x3 in the patient. Additionally, subtelomeric FISH analysis revealed a balanced 10p;17p translocation in her father, indicating that he is the carrier of the alteration (fig. 5). The father's karyotype was established as: ish t(10;17)(p15.3–,p13.3±; p13.3–,p15.3±) (Z96139–,282M16/SP6±; Z96139–,282M16/SP6±).

Array-CGH analysis did not demonstrate deletions or duplications in the patient's parents. The region deleted on chromosome 10p involved 14 genes, while the gain in chromosome 17 resulted in the duplication of 61 genes (online supplementary fig. 1 and 2, www.karger.com/doi/10.1159/000339639). Interestingly, this duplication involves the complete MDS region, and, to date, only 6 cases have been reported with this type of

Fig. 4. Graphic representation of the involved regions of chromosomes 10 and 17. **a** Monoallelic deletion of 4.43 Mb on chromosome 10p detected in the patient. **b** Single-copy gain of 3.22 Mb on chromosome 17p found in the girl.

Fig. 5. Translocation 10p;17p detected in the father with FISH for subtelomeric regions. The image shows one normal chromosome 10 and one chromosome 10 involved in a balanced translocation with chromosome 17.

Table 1. Comparison of clinical features of the 7 patients with duplication of the 17p13.3 from the literature and contrasted with our patient

	Bi et al., [2009] Patient 7	Roos et al., [2009] Patient 1	Roos et al., [2009] Patient 2	Roos et al., [2009] Patient 3	Bruno et al., [2010] Patient 10	Hyon et al., [2011] Patient 1	Our patient
Size of duplication, Mb	3.6	1.8	3.0	4.0	2.0	4.22	3.22
Inheritance	de novo	de novo	de novo	de novo	de novo	?	from the father
Age at diagnosis, years	10	14	1	1	6.5	13	0.5
Gender	F	M	F	M	M	F	F
Birth height, cm	53	53	N/A	50	normal	normal	51
Birth weight, g	3,060	3,350	4,200	3,380	normal	normal	3,000
Current height	+1 SD	+3.5 SD	normal	+1 SD	normal	+1 SD	50–75th percentile
Current weight	+2 SD	+1 SD	–2 SD	+1 SD	normal	+1 SD	25th percentile
Brain imaging results	reduced brain size, corpus callosum hypoplasia, cerebellar agenesis	no apparent brain alterations	N/A	dilated lateral ventricles, corpus callosum agenesis, abnormal signal intensities of white matter	N/A	no apparent brain alterations	cortical atrophy and hypoplasia of corpus callosum

SD = Standard deviation; N/A = Not available.

Table 2. Phenotype of the 7 patients with duplication of Miller-Dieker completed region

	Cases from the literature	Our patient
Craniofacial features		
Hypotonic face	4/6	–
Broad midface	3/6	–
Low-set ears	2/6	–
Frontal bossing	3/6	–
Triangular chin	3/6	+
Down-slanting palpebral fissures	4/6	–
Upward palpebral fissures	1/6	+
Hypertelorism	4/6	+
Broad nasal root	4/6	+
Strabismus	1/6	+
Small mouth	3/6	–
Short neck	2/6	+
Cleft lip and palate	1/6	–
Neurological features		
Hypotonia	5/6	–
Speech delay	4/6	+
Delay in mental development	5/6	+
Abnormal behavior	6/6	+
Reduced sensitivity to pain	2/6	–
Other features		
Clinodactyly	2/6	+
Hip luxation	1/6	–
Equinovalgus, both feet	1/6	+
Recurrent infections	5/6	+

Bi et al., [2009]; Roos et al., [2009] Bruno et al., [2010]; Hyon et al., [2011].

duplication [Ravana et al., 2006; Kirchhoff et al., 2007; Bi et al., 2009; Roos et al., 2009; Bruno et al., 2010; Hyon et al., 2011]. All 17p13.3 duplications reported to date are the products of no-recurring rearrangements, with different breakpoints (3–4 Mb) distal to 17p3.3 [Bi et al., 2009; Bruno et al., 2010; Hyon et al., 2011]; therefore, the regions involved vary from patient to patient. Of the different genes located in the MDS region, the *PAFAH1B1* and *YWAHE* genes are those that are most frequently studied. Patients with duplication or triplication of the *PAFAH1B1* gene have dysgenesis of the corpus callosum and cerebellar atrophy, resulting in smaller brains, mainly in terms of the occipital cortex [Bi et al., 2009]. Related with this, mice with overexpression of the *Pafah1b1* gene show severe alterations during brain development that result in animals with small brains [Chong et al., 1996, 1997; Cardoso et al., 2000, 2003; Lindardopoulou et al., 2005]. Because duplication of 17p13.3 varies in size, Bruno et al. [2010] proposed 2 different groups of patients with distinct types of microduplication and distinct phenotypic features. Meanwhile, a third group of patients has been proposed who possess duplication of the complete MDS region [Hyon et al., 2011]. Interestingly, our patient possesses complete duplication of this region, sharing features described for this type of patient (tables 1 and 2). However, because the patient exhibits a combination of 2 imbalances, which are the result of malsegregation of a parental balanced translocation, many features might be attributed to genes that are lost in chromosome 10p (table 3).

Table 3. Clinical features reported in literature for patients with partial 10p14→pter monosomies in contrast with clinical features present in our patient

Clinical features reported for partial 10p→pter monosomies	Features in our patient
Mental retardation (psychomotor delay)	+
Microcephaly	+
Micrognathia	–
Small nose with rounded tip and broad nasal root	+
Triangular face	–
Retrognathia	–
Hypoplastic midface	+
Frontal bossing	–
Small palpebral fissures	–
Upward palpebral fissures	+
Dysmorphic ears (cup-shaped, with an absent-superior fork of the antihelix)	+
Hand and foot dysplasias	+
Cardiac defects	–
Urogenital anomalies	–
Brain anomalies	+
Seizures	–

Fryns et al., [1981]; Shapira et al. [1994]; Roos et al., [2006]; Battaglia et al., [2007]; Bruno et al., [2010]; Lindstrand et al., [2010]; Faletra et al., [2011]; Hyon et al. [2011].

The majority of patients with a duplicated MSD region have been reported with a relative increase of body weight and height and recurrent middle ear infections, features that are absent in our patient. Also, our patient presents abnormalities in hands and feet, showing long fingers, bilateral equinovagis and clinodactyly of the 4th toes, with dysplastic concave toenails, features described for some patients with duplication of 17p13.3 [Bi et al., 2009; Bruno et al., 2010; Armour et al., 2011; Hyon et al., 2011]. In addition, our patient has severe visual dysfunction and immaturity of auditory brainstem-evoked responses, which might be associated with the reduction of the visual cortex found in the 17p13.3 duplication. However, visual and auditory dysfunctions are highly conserved among all patients with partial monosomy 10p [Bourrouillou et al., 1981; Fryns et al., 1981; Battaglia et al., 2007; Lindstrand et al., 2010].

Two different critical regions of chromosome 10p have been proposed. Loss of chromosome region 10p13–14 has been described in patients with DGSII, characterized by the presentation of heart defects and T-cell deficiency [Schuffenhauer et al., 1995; Daw et al., 1996; Dasoiuki et al., 1997; Lichtner et al., 2000]. Similarly, haploinsufficiency of the region 10p14→pter, distal to DGCR2, results in

hypoparathyroidism, sensorineural deafness and renal anomaly, features that determine the HDR syndrome [Van Esch et al., 2000; Fukami et al., 2011]. In this region, it has been described that the *GATA3* gene, which is involved in the embryonic development of the parathyroids, auditory system and kidneys, plays a critical role in the development of different neural populations within the mammalian central nervous system [Van Esch et al., 2000; Karunaratne et al., 2002; Lindstrand et al., 2010]. In the embryonic midbrain, *GATA3* expression correlates with the development of the optic tectum [Kornhauser et al., 1994], while in the developing hindbrain, loss of *GATA3* affects differentiation of the vestibuloacoustic efferent neurons and migration of the facial branchiomotor neurons [Pata et al., 1999]. Interestingly, although we did not detect *GATA3* gene deletion with array-CGH in our patient, she does exhibit hearing and visual alterations. In this respect, in both *Drosophila melanogaster* and mice, it has been demonstrated that during specific development stages, the disco-interacting protein 2 gene (*DIP2C*) is highly expressed in distinct brain regions, including the optic and otic vesicles. Therefore, deletion of the 10p15.3 region, which includes the *DIP2C* gene, in our patient might be associated with the severe visual dysfunction and immaturity of the auditory brainstem-evoked responses observed [Mukhopadhyay et al., 2002]. Description of the clinical and molecular characteristics of our patient contributes to confirming and further defining the characteristics associated with the duplication of the entire MDS region and the partial monosomy of chromosome 10p15.3.

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