

CASE REPORT

16p SUBTELOMERIC DUPLICATION WITH VASCULAR ANOMALIES: AN ALBANIAN CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

A patient with karyotype 46,XY,der(4) was recognized by standard cytogenetic techniques, and presented with facial features, neurological impairment and pulmonary hypertension. Multiplex ligation-dependent probe amplification (MLPA) demonstrated duplication of the subtelomeric region of chromosome 16p and deletion of the subtelomeric region of chromosome 4q, suggesting a translocation between 4q and 16p. The karyotype of his parents was normal and their MLPA analysis also indicated a *de novo* imbalance. He had microcephaly, high frontal hairline, thin blond hair, bilateral blepharophimosis and palpebral ptosis, short nose, everted upper lip, cleft palate, micrognathia, cupped anteverted ears, hypoplastic distal phalanges and bilateral inguinal hernia. He also had pulmonary hypertension with tricuspidal regurgitation; cavernous liver hemangioma anomalies have been previously described in association with dup16p. We concluded that pulmonary and other vascular anomalies can be a feature of dup16p. We believe this is the first confirmed case of a 16p

subtelomeric duplication with vascular anomalies identified in Albania.

Keywords: Duplication chromosome 16p; Multiplex ligation-dependent probe amplification (MLPA) technique; Pulmonary hypertension

INTRODUCTION

Partial trisomy 16p is a rare chromosome imbalance characterized by mental retardation, prenatal and postnatal growth deficiency, facial anomalies, cleft palate, congenital heart defect and urogenital anomalies [1-8]. The majority of the patients present chromosome duplications recognizable by standard cytogenetic techniques. Previous studies have established that the phenotypic severity could not be correlated with the size of the duplicated segment, and that region 16p13.1-p13.3 was ‘critical’ in determining this disorder. Subtelomere analysis has also identified submicroscopic duplications of the subterminal region of chromosome 16p (dup16p) [7-10].

We report on a patient with karyotype 46,XY,der(4) recognized by standard cytogenetic techniques, in whom subtelomeric analysis by the multiplex ligation-dependent probe amplification (MLPA) technique demonstrated a *de novo* duplication of the subtelomeric anomalies in chromosome 16p and chromosome 4q. We believe this is the first confirmed case of 16p subtelomeric duplication with vascular anomalies identified in Albania.

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CASE REPORT

The male patient was the first child of healthy non consanguineous parents. His mother and father were 32 and 40 years old, respectively, at the time of his birth. Family history was unremarkable. He was born by vaginal delivery at the 35th week of a normal gestation. Birth weight was 2450 g, length 49 cm, and head circumference 34 cm. He was referred to our service when he was 12 months old. Clinical evaluation demonstrated microcephaly, high frontal hairline, thin blond hair, bilateral blepharophimosis and palpebral ptosis, short nose, everted upper lip, cleft palate, micrognathia, cupped anteverted ears (Figure 1a and 1b) and bilateral inguinal hernia, hypotonia and developmental delay. A two-dimensional color Doppler echocardiography revealed pulmonary hypertension and tricuspid regurgitation. The hypertension was not related to congenital heart defects. Cardiac catheterization showed a systemic level pulmonary artery pressure, elevated pulmonary vascular resistance, and no response to administration of oxygen and nitric oxide. Cerebral magnetic resonance imaging (MRI) demonstrated corpus callosum hypoplasia. Renal ultrasonography was normal and abdominal ultrasonography showed a cavernous liver hemangioma. Ophthalmologic evaluation was normal. At 2 years old, he presented developmental delay and moderate mental retardation.

Chromosome analysis carried out on peripheral lymphocytes using standard techniques by R banding revealed the karyotype 46,XY,der(4) (Figure 2). Subtelomeric regions were analyzed using the multiplex ligation-dependent probe amplification (MLPA) technique (with probes for testing subtelomeric imbalances in the SALSA P070 and P036B

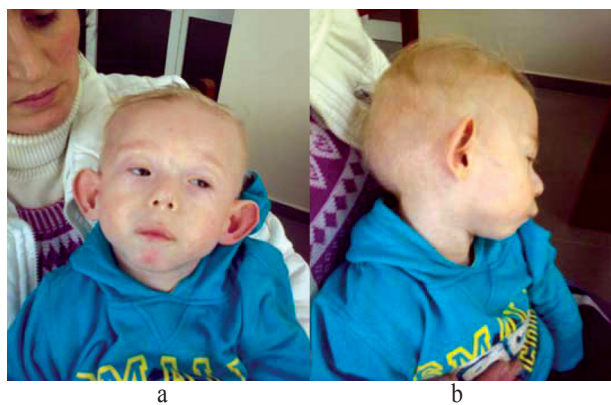


Figure 1. a) Front view of the patient. b) Side view of the patient.

human telomere test kits; MRC-Holland, Amsterdam, The Netherlands). This revealed a duplication of the subtelomeric region of chromosome 16p and a deletion of the subtelomeric region of chromosome 4q, suggesting a translocation between 4q and 16p. Cytogenetic analysis of the parents revealed normal karyotypes and no duplication of the subtelomeric region of 16p by MLPA technique. This indicates that the imbalance was a *de novo* event.

DISCUSSION

The distinguishing clinical features of dup16p syndrome, determined by the terminal 16p13.1-p13.3 critical region, include specific facial anomalies, mental retardation, congenital cardiac and vascular defects, urinary malformations, and hypoplastic distal phalanges of hands [6-11]. Our case demonstrated a duplication of the subtelomeric region of chromosome 16p representing a chromosome 16p duplication, encompassing the critical region of 16p13.1-p13.3. Facial anomalies in our patient such as thin blond thin hair, blepharophimosis with palpebral ptosis, short nose, open mouth with everted upper lip, high-arched palate, wide-spaced teeth and cupped everted ears, are similar to those reported previously by Sommer *et al.* [6] and De Ravel *et al.* [9].

Patients with large 16p duplications detected using standard techniques have also suffered from tetralogy of Fallot or ventricular septal defect [3-12] and early onset of pulmonary vascular disease has also been reported [3]. In our patient, the pulmonary hypertension was not related to congenital heart defects, which suggests that pulmonary vascular disease can be a feature of this syndrome. Thus, a cardiologic evaluation and a continuous monitoring for the onset of pulmonary hypertension is recommended.

The association of partial trisomy 16p (16p13.1-p13.3) with pulmonary vascular disease, pulmonary hypertension, portal cavernoma, vascular ring and vascular disruption has been reported, suggesting that this critical region is related to vascular abnormalities [13]. The presence of a cavernous liver hemangioma with pulmonary vascular disease in our case suggests a possible association between this imbalance and vascular anomalies. Terminal hypoplasia of the hands and manifestation of vascular disruption, has also been reported in association with dup16p [7]. Pre- and post-natal growth and mental retardation

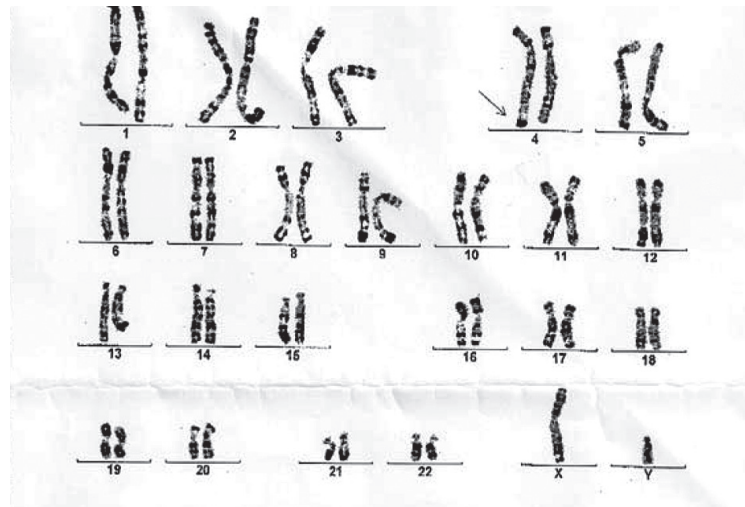


Figure 2. Karyotype of the patient; the arrow shows the abnormal chromosome 4.

were present in all patients described in the literature [5-12]. The urinary abnormalities described in the literature [7] were not found in our case.

In our patient, duplication in chromosome 16p was associated with deletion in chromosome 4q. That facial dysmorphisms and vascular anomalies are not usually found in deletion of the subtelomeric region of chromosome 4q, suggests that these features of dup16p syndrome result from duplication of the gene dosage of the subterminal region of chromosome 16.

In conclusion, we have confirmed the clinical features of patients with dup16p, involving the terminal 16p13.1-p13.3 region. Facial anomalies, developmental delay and terminal hypoplasia of fingers are clinical features that should suggest this rare syndrome, which can be confirmed by molecular-cytogenetic analysis. The pulmonary hypertension and other vascular anomalies in our patient and in other published cases [13], can be a feature of dup16p, and suggests that this subtelomeric region can be associated with vascular anomalies.

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REFERENCES

- O'Connor TA, Higgins RR. Trisomy 16p in a liveborn infant and review of trisomy 16p. *Am J Med Genet.* 1992; 42(3): 316-319.
- Juan JLC, Cigudosa JC, Gomez AO, Almeida MTA, Miranda LG. *De novo* trisomy 16p. *Am J Med Genet.* 1997; 68(2): 219-221.
- Movahhedian HR, Kashani DS, Bull D, Jones KL, Rothman A. Pulmonary hypertension and trisomy 16. *Pediatr Cardiol.* 1998; 19(2): 187-189.
- Kokalj-Vokac N, Medica I, Zagorac A, Zagradisnik B, Erjavec A, Gregoric A: A case insertional translocation resulting in partial trisomy 16p. *Ann Genet.* 2000; 43(3-4): 131-135.
- Tschernigg M, Petek E, Leonhardtsberger A, Wagner K, Kroisel PM. Terminal tandem duplication of 16p: a case with 'pure' partial trisomy (16)(pter p13). *Genet Couns.* 2002; 13(3): 303-307.
- Sommer A, Pastore M, Wenger G. Trisomy 16p: a longitudinal profile and photo essay. *Am J Med Genet.* 2006; 140(2): 174-179.
- Martin CL, Waggoner DJ, Wong A, Uhrig S, Roseberry JA, Hedrick JF, Pack SD, Russell K, Zackai E, Dobyns WB, Ledbetter DH. 'Molecular rulers' for calibrating phenotypic effects of telomere imbalance. *J Med Genet.* 2002; 39(10): 734-740.
- Leonard C, Huret JL, Imbert MC, Lebouc Y, Selva J, Bouley AM. Trisomy 16p in a liveborn offspring due to maternal translocation t(16;21)(q11;p11) and review of the literature. *Am J Med Genet.* 1992; 43(3): 621-625.
- De Ravel T, Aerssens P, Vermeesch JR, Fryns JP. Trisomy of chromosome 16p13.3 e to an unbalanced insertional translocation into chromosome 22q13. *Eur J Med Genet.* 2005; 48(3): 355-359.

10. Ruiters EM, Koolen DA, Kleefstra T, Nillesen WM, Pfundt R, De Leuw N, Hamel BCJ, Brunner HG, Siskens EA, De Vries BBA. Pure subtelomeric microduplications as a cause of mental retardation. *Clin Genet.* 2007; 72(4): 362-368.
11. Rochat MK, Riegel M, Schinzel AA. Long-term follow-up of a 26-year-old male with duplication of 16p: clinical report and review. *Am J Med Genet.* 2007; 143(4): 399-408.
12. Leschot NJ, Deneff JJ, Geraedts JPM, Becker-Bloemkolk MJ, Talma A, Bijlsma JB, Vejaal M. Five familial cases with a trisomy 16p syndrome due to translocation. *Clin Genet.* 1979; 16(3): 205-214.
13. Digilio CM, Bernardini L, Capalbo A, Capolino R, Gagliardi GM, Marino B, Novelli A, Dallapiccola B. 16p Subtelomeric duplication: a clinically recognizable syndrome. *Eur J Hum Genet.* 2009; 17(9): 1135-1140.