# A *de novo* 11q23 deletion in a patient presenting with severe ophthalmologic findings, psychomotor retardation and facial dysmorphism

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**SUMMARY: Şimşek-Kiper PÖ, Bayram Y, Ütine GE, Alanay Y, Boduroğlu K. A *de novo* 11q23 deletion in a patient presenting with severe ophthalmologic findings, psychomotor retardation and facial dysmorphism. Turk J Pediatr 2014; 56: 80-84.**

**Distal 11q deletion, previously known as Jacobsen syndrome, is caused by segmental aneusomy for the distal end of the long arm of chromosome 11. Typical clinical features include facial dysmorphism, mild-to-moderate psychomotor retardation, trigonocephaly, cardiac defects, and thrombocytopenia. There is a significant variability in the range of clinical features. We report herein a five-year-old girl with severe ophthalmological findings, facial dysmorphism, and psychomotor retardation with normal platelet function, in whom a *de novo* 11q23 deletion was detected, suggesting that distal 11q monosomy should be kept in mind in patients presenting with dysmorphic facial features and psychomotor retardation even in the absence of hematological findings.**

***Key words: distal 11q monosomy, facial dysmorphism, psychomotor retardation, trigonocephaly, ophthalmological findings.***

Distal 11q monosomy, previously known as Jacobsen syndrome (MIM 147791), is a contiguous gene syndrome caused by partial deletion of the long arm of chromosome 11. This condition was first described by Jacobsen in a family with multiple members that inherited an unbalanced t(11;12) derived from a balanced translocation carrier parent[1]. The incidence is difficult to estimate, but is probably <1 in 100,000[2-4]. The chromosome aberration is usually a *de novo* pure terminal deletion (85%); however, in 15% of patients, it results from an unbalanced segregation of a familial balanced translocation, as in the original report by Jacobsen[1]. Other chromosomal rearrangements such as ring 11, may also be possible[5,6]. The deletion is classically described as del(11)(q23qter), but heterogeneity in the size of deletions, along with a significant variability in the range of clinical findings, is observed. The most common clinical features include pre- and postnatal physical growth retardation, psychomotor retardation, characteristic facial dysmorphism, and thrombocytopenia or pancytopenia. Some patients may have malformations of the heart, kidney, gastrointestinal tract, genitalia, central nervous system, and/or skeleton. Ocular, hearing, immunological, and hormonal problems may also be present[2,3]. Clinical features of patients with 11q deletion, including the present patient, are shown in Table I.

The clinical manifestations usually depend on the extent of the deletion. The deletion size ranges from 7 to 20 Mb[2,3]. Although patients with the largest deletions usually show the most severe phenotype, some of the phenotypes demonstrate incomplete penetrance and are highly variable between patients[7]. We report herein the case of a five-year-old girl presenting with severe ophthalmological findings and facial dysmorphism along with psychomotor retardation and normal platelet function, in whom a *de novo* 11q23qter deletion was detected.

## Case Report

A two-year-old female patient was referred to

our clinic with atypical facial features. She was the second child of nonconsanguineous parents (mother 29, father 35 years old). The younger child was healthy, and the family history was negative for intellectual disability, autism or any other known chromosomal abnormalities. Prenatal history was unremarkable. The patient was born at term by normal delivery with a birth weight of 3650 g (90$^{th}$ centile). Her birth length and head circumference were not noted. She did not require admission to neonatal intensive care unit. She had head control at three months, was able to sit with support at 12 months, and without support at 18 months of age. She was still not able to walk at 24 months of age. She started speaking single words after 12 months and was able to speak with simple sentences after two years of age. She underwent surgery for trigonocephaly correction at 10 months of age. She was then referred to our center for further evaluation. Her physical examination at two years of age revealed body weight 8.3 kg (<3$^{rd}$ centile), body height 77 cm (-2.6 SD), and head circumference 45 cm (<3$^{rd}$ centile). She had prominent forehead, trigonocephaly, hypertelorism, arched eyebrows, wide base to nose, blepharophimosis, narrow palpebral fissure, telecanthus, low-set ears, preauricular skin tag, hypoplasia of the glabella, long and flat philtrum, and thin upper lip (Fig. 1). She also had webbed and short neck, narrow shoulders, mild scoliosis, broad hallux, and slender fingers. There was no evidence of abdominal organ malformations, and abdominal ultrasonography was normal. Radiographic examination revealed mild scoliosis (Fig. 2). Cervical vertebrae were normal Echocardiography revealed secundum atrial septal defect. Cranial magnetic resonance imaging was normal. Ophthalmologic examination revealed strabismus and error of refraction in both eyes. She also had hypoplasia of the right optic nerve and iris in addition to choroid colobomas in both eyes. She had a vision loss of 70% in her right eye. Chromosomal analysis of the patient was performed using GTG-banding techniques on stimulated blood lymphocytes. Cytogenetics revealed a deletion of the long arm of chromosome 11 in the band q23 (Fig. 3A). Fluorescence in situ hybridization (FISH) using a commercially available subtelomeric probe (ToTelVysion Multicolor FISH Probe Panel) for 11qter confirmed the suggested deletion (Fig. 3B). The parental karyotypes were normal, suggesting a *de novo* occurrence of the deletion.

On follow-up at the age of three years, significant postnatal growth retardation was observed, with body weight of 10 kg (<3$^{rd}$ centile), body height of 84 cm (-2.7 SD), and head circumference of 47 cm (3$^{rd}$-10$^{th}$ centile). She was able to walk independently and could speak using simple words.

At the age of four years, her body weight was 13 kg (3$^{rd}$-10$^{th}$ centile), body height 89 cm (-2.9 SD) and head circumference 47 cm (3$^{rd}$-10$^{th}$ centile). Her complete blood count with differential was normal. Her bleeding time was normal (5 minutes). Peripheral smear revealed normal platelet morphology. Her scoliosis was stable and required no surgical intervention. Psychomotor testing revealed a developmental age of 30 months, with delays in language and gross and fine motor skills. She is now five years old and currently attending a special education institute.

**Discussion**

The 11q terminal deletion is a well-recognized pattern of malformation caused by terminal deletion of the long arm of chromosome 11. We report herein the case of a five-year-old girl with 11q23 deletion presenting with facial dysmorphism, psychomotor retardation and severe ophthalmologic findings, with normal platelet function. The clinical findings of the present patient are in general concordance with the clinical features of the patients with 11q deletion. However, the present patient does not have the finding of chronic thrombocytopenia, which is reported in almost 94% of patients with 11q terminal deletion[3].

Most patients with 11q deletion are born with either thrombocytopenia or pancytopenia[7]. More recently, a definite platelet disorder, the Paris-Trousseau syndrome, has been reported in these patients[8,9]. This platelet abnormality is reported in almost 88.5% of patients with 11q deletion syndrome. However, it has been suggested recently that the platelet abnormality and the Paris-Trousseau syndrome are the same condition[9,10]. The megakaryocytic defects in patients with 11q deletion were mapped to a minimal region in 11q that includes the *FLI1*

gene, thus suggesting that dysmegakaryopoiesis in these patients may be caused by hemizygous loss of *FLI1*[11].

It is known that in 11q deletion syndrome, patients usually have thrombocytopenia, with counts as low as 10–20,000 at birth. Over time, the number of platelets increases to normal or near-normal levels[3]. However, prolonged bleeding time might be the case despite normal platelet counts. Recently, several adolescent patients with 11q deletion with normal platelet counts were found to have markedly prolonged bleeding times, indicating persistence of abnormal platelet function despite resolution of the thrombocytopenia[3]. The present patient had normal platelet counts and normal bleeding time. The platelet counts were obtained by the hospital laboratory automated platelet counter, and platelet morphology was analyzed independently by two pediatric hematologists with significant experience. Although we could not perform immunocytochemical or ultrastructural studies to evaluate platelet granules, peripheral smear revealed normal platelet morphology. She has not had any hematological manifestations thus far; nevertheless, we cannot rule out the possibility that thrombocytopenia was present at birth and resolved over time, before her admission to our center at the age of two years. In addition, the genetic background of the patient might have had an influence on the expression of this feature.

Trigonocephaly, resulting from premature closure of the metopic suture, is reported in almost 30% of patients with 11q deletion[7]. The presence of trigonocephaly gives a very characteristic facial appearance that usually raises the possibility of this diagnosis, which was also the case in the present patient.

Orthopedic abnormalities such as hip dislocation, scoliosis, flat feet, or club foot are reported in 19% of patients with 11q deletion[7]. The present patient had mild scoliosis, which was stable and required no intervention. In addition, skeletal findings such as short neck, broad and long hallux, and slender fingers are also reported

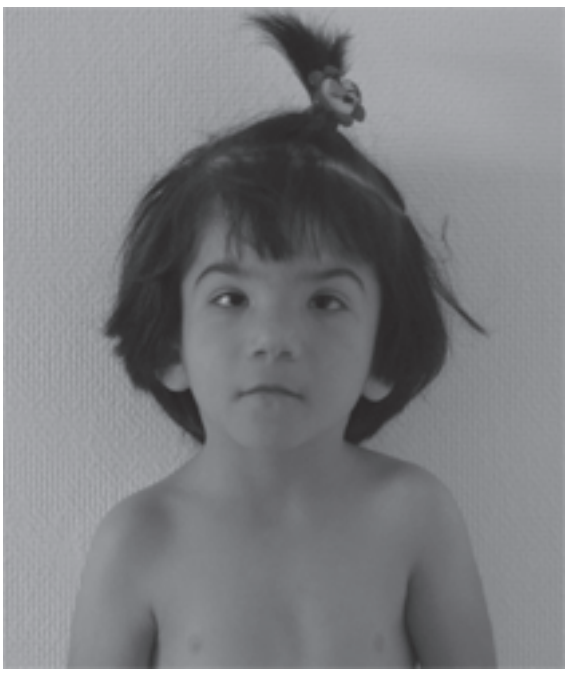

**Fig. 1.** Note prominent forehead, trigonocephaly, hypertelorism, arched eyebrows, wide base to nose, blepharophimosis, narrow palpebral fissure, telecanthus, low-set ears, preauricular skin tag, hypoplasia of the glabella, long and flat philtrum, and thin upper lip. Note also short neck and narrow shoulders.

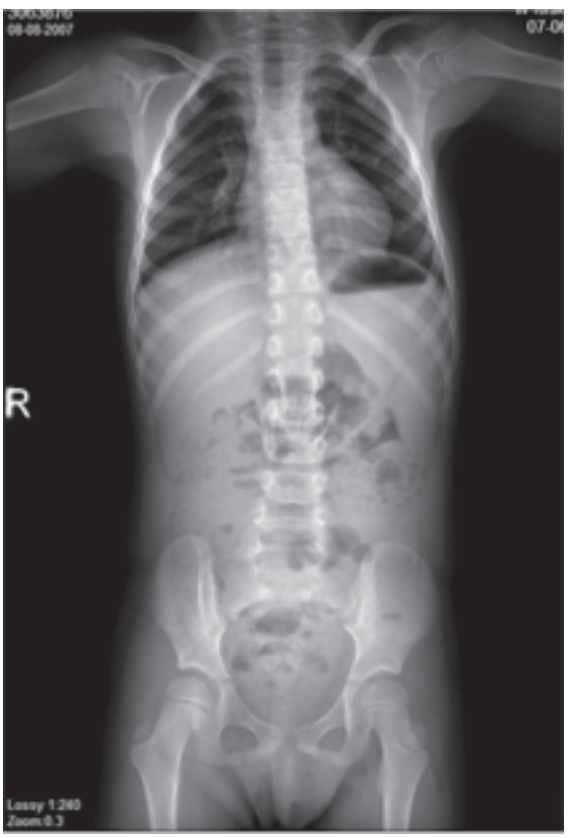


**Fig. 2.** Mild lumbar scoliosis was evident on X-ray.

**Fig. 3a.** GTG-banding analysis including high-resolution karyotyping from peripheral blood revealed 11q23 deletion.

**Fig. 3b.** A peripheral blood sample was obtained from the proband. Qbiogene PTEL11Q Tel 11qDNA probe was used, and the analysis gave the result of 46,XX,del(11)(q23).ish tel 11q(D11S4437-) karyotype.

**Table I.** Clinical Findings in Patients with 11q Deletion Syndrome[3] and the Present Patient

| Clinical findings | In patients with 11q terminal deletion[3] | Present patient |
|---|---|---|
| Number of patients | 110 | 1 |
| Sex | 38 Male; 72 Female | Female |
| *De novo* | 66 families | + |
| Age | 5 months-31 years | 5 years |
| Intrauterine growth retardation | Not recorded | - |
| Short stature (<5$^{th}$ centile) | 68% | + |
| Macrocephaly | Not recorded | - |
| Microcephaly | Not recorded | + |
| Renal/urinary tract abnormality | 8% | - |
| Cryptorchidism | 58% | Not applicable |
| Developmental delay/intellectual disability | 85% | + |
| Congenital heart disease | 56% | + |
| Seizure | Not recorded | - |
| Chronic thrombocytopenia | 94% | - |
| Hearing loss | Not recorded | - |
| Recurrent infections | 54% | - |
| Trigonocephaly | 29% | + |
| Hypertelorism | 92% | + |
| Ear anomalies (malformed/low-set) | 81% | + |
| High prominent forehead | 62% | + |
| Flat/broad nasal bridge | 47% | + |
| Short nose | 69% | + |
| Microretrognathia | 36% | + |
| Ptosis | 58% | + |
| Strabismus | 67% | + |
| Optic nerve hypoplasia | - | + |
| Short neck/webbed neck | 50%/Not recorded | +/+ |

[3]Grossfeld PD, Mattina T, Lai Z, et al. The 11q terminal deletion disorder: a prospective study of 110 cases. Am J Med Genet 2004; 129A: 51-61.

among frequent (>40%) findings[7]. The present patient demonstrated not only these skeletal findings but also the finding of webbed neck, which is a less frequent finding in patients with 11q deletion[7].

Regarding ophthalmological findings, the region distal to 11q23.3 was found to be related to ocular findings such as exotropia, coloboma and cataract[3]. The findings of hypertelorism, downslanting palpebral fissures, divergent or convergent strabismus, palpebral ptosis, sparse eyebrows, and epicanthal folds are frequently (>40% of patients) reported, whereas eyelid coloboma, ectropion, iris coloboma, cataract, and tortuosity of retinal vessels are reported less frequently[7]. The present patient demonstrated not only strabismus, blepharophimosis and error of refraction, but also hypoplasia of the right optic nerve and iris and choroid colobomas in both eyes. She had a decrease in vision of 70% in her right eye. To our knowledge, the ocular findings in the present patient represent some of the most severe ocular findings reported so far in patients with 11q deletion.

In conclusion, the symptoms and clinical findings of 11q deletion are relatively non-specific, and incomplete penetrance for specific phenotypes might be possible. This syndrome should be kept in mind as a well-described phenotype, especially in patients presenting with facial dysmorphism and psychomotor retardation even in the absence of hematological findings.

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