A rare case of 2q37 microdeletion with Albright hereditary osteodystrophy-like phenotype

Pelin Özlem Şimşek-Kiper[1], Gülen Eda Ütine[1], Yasemin Alanay[1], Dilek Aktaş[2], Mehmet Alikaşifoğlu[2], Koray Boduroğlu[1]

[1]Pediatric Genetics Unit, Department of Pediatrics, and [2]Department of Medical Genetics, Hacettepe University Faculty of Medicine, Ankara, Turkey.

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Chromosome 2q37 microdeletion syndrome is a rare disorder characterized by mild-moderate psychomotor and growth retardation, autistic-like behavior, Albright hereditary osteodystrophy-like metacarpal/metatarsal shortening, and facial characteristics. We here report on a patient with 2q37 microdeletion presenting with learning difficulty, hyperactivity and attention deficit. Physical examination revealed psychomotor and growth retardation, facial dysmorphism and brachydactyly, suggestive of Albright hereditary osteodystrophy-like phenotype. Laboratory evaluation revealed 46, XX.ish subtel(2q)(D2S447-) confirming 2q37 microdeletion. Chromosome 2q37 microdeletion syndrome should be considered in the differential diagnosis of patients presenting with psychomotor and growth retardation and an Albright hereditary osteodystrophy-like phenotype, especially in the presence of brachydactyly, even if the characteristic facial features are missing.

Key words: chromosome 2q37 microdeletion, brachydactyly, psychomotor and growth retardation, Albright hereditary osteodystrophy-like phenotype.

Chromosome deletions involving the 2q37 region result in brachydactyly mental retardation syndrome (BDMR [MIM 600430]), also known as Albright hereditary osteodystrophy-like (AHO-like) syndrome. The patients may present with a spectrum of clinical features including developmental delay, obesity, autism spectrum disorder, and craniofacial and skeletal abnormalities[1-3]. There are essentially two distinctively different phenotypes[3]. The majority of patients are associated with moderate-severe psychomotor and growth retardation without characteristic dysmorphic features, whereas the minority are characterized by milder mental retardation and an AHO-like phenotype[1]. Characteristic facial features of chromosome 2q37 microdeletion are thin, arched eye brows with deeply set eyes, hypoplastic nares, prominent columella, thin vermilion border, and minor ear dysmorphism with or without round face[2]. Brachymetacarpia and brachymetaphalangia typical of AHO are well described in 2q37 microdeletion syndrome[1]. Major malformations such as esophageal atresia, malrotation, duodenal atresia, small intestine atresia, horseshoe kidney, hypospadias, holoprosencephaly, hydrocephalus, dilated ventricles, corpus callosum agenesis, and situs abnormalities may occur in about 30% of patients with 2q37 microdeletion, and congenital heart malformations, among which septal defects are the most common, have been noted in up to 20% of patients[1]. Hypotonia has been reported in about half of the patients. Conventional karyotype is normal in 15-20% of cases where higher resolution molecular cytogenetic techniques are necessary[4]. Here, we report on a patient with 2q37 microdeletion presenting with mild psychomotor and growth retardation and brachydactyly without typical facial features. While characteristic facial features may show variation, recognition of brachydactyly may lead to the diagnosis.

Case Report

A seven-year-old female patient was referred because of learning difficulty and hyperactivity.

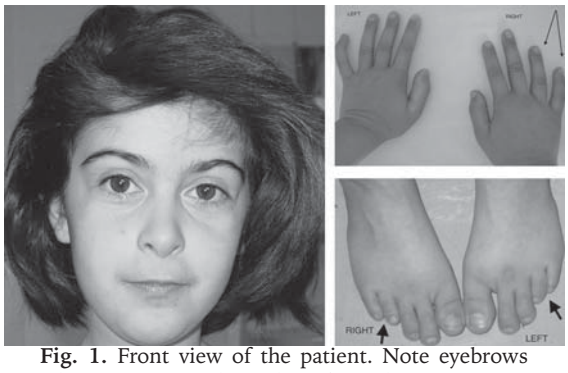

Fig. 1. Front view of the patient. Note eyebrows with prominent arch, V-shaped nasal tip, prominent columella, poorly formed cupid's bow, thin upper lip, and brachymesophalangy of 4-5 involving both hands and feet.

She was the first child of nonconsanguineous parents. The family and prenatal histories were unremarkable. The patient was born at term with a birth weight of 3500 g (75-90th centile). She had head control at eight months of age, was able to sit with support at one year of age, without support at 18 months of age, and walk unaided at 24 months of age. She started speaking single words at 12 months of age and simple sentences at six years of age. Language and social skills were both markedly delayed. On physical examination, she weighed 22.5 kg (50th centile), and her height and head circumference were 121 cm (50-75th centile) and 50 cm (50th centile), respectively. Facial features such as eyebrows with prominent arch, V-shaped nasal tip, prominent columella, poorly formed cupid's bow and thin upper lip, and brachymesophalangy of 4-5 involving both hands and feet, suggestive of an AHO-like phenotype, were noticed (Fig. 1). Psychometric evaluation with Stanford-Binet Intelligence Scale revealed a score of 45-55. There was no evidence of congenital heart defect. Abdominal and renal ultrasonographies were normal. Audiological and ophthalmological assessments including fundus examination were both normal. Radiological evaluation confirmed brachymesophalangy of 4-5 involving both hands and feet. Osteopenia was not evident. Chromosome analysis revealed 46,XX (Fig. 2). Subtelomeric fluorescence in situ hybridization (FISH) analysis using ToTelVysion Multicolor FISH Probe Panel that applied the probe VIJyRM2112 (D2S447-) flanking 60 kb lying between 242.88-243.2 Mb on chromosome 2q37.3 revealed 46, XX.ish subtel(2q)(D2S447-) (Fig. 3). Maternal and paternal FISH analyses were normal (*de novo* deletion).

Discussion

The clinical features of terminal microdeletions of 2q37 were first described in 1989 by Gorski et al.[5] The incidence is unknown, but more than 100 patients carrying isolated, primarily terminal deletions with breakpoint at or within chromosome 2q37 have been reported previously[1]. A minority of patients like the present patient show milder psychomotor and growth retardation and an AHO-like phenotype. Typical facial characteristics of AHO such as round face, prominent forehead, depressed nasal bridge, deficient nasal alar flare, deep-set eyes, upslanting palpebral fissures, and pinna anomalies were not present in this patient. However, it is well known and documented that patients with chromosome 2q37 microdeletion may have quite a variation in phenotype[1], and the present patient does not appear to have the typical facial features. On the other hand, the key skeletal feature in this patient was brachymesophalangy. It is a variable but characteristic feature, which is reported in almost half of the patients with 2q37 microdeletion[1]. Defects in social interaction, hyperactivity, attention deficit, and sleep disturbances have all been described in 2q37microdeletion. Our patient had a short span of attention, hyperactivity and some repetitive behaviors. Patients with 2q37 microdeletions have milder cognitive deficits and are less likely to have major congenital abnormalities compared to patients with cytogenetically visible deletions. The present patient had mild

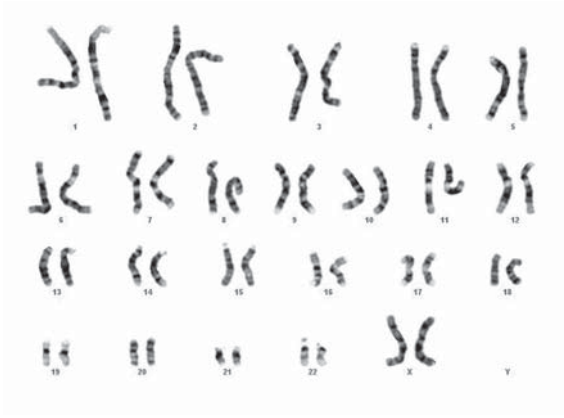

Fig. 2. Chromosomal analysis of the patient demonstrating 46,XX.

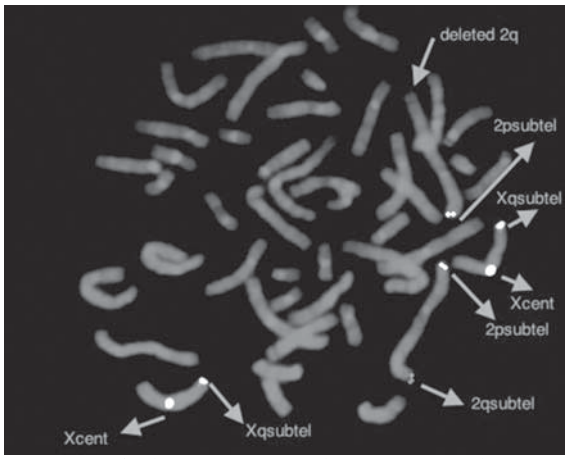

Fig. 3. Subtelomeric FISH analysis using ToTelVysion Multicolor FISH Probe Panel on chromosome 2q37.3 revealing 46, XX .ish subtel(2q)(D2S447-).

intellectual disability, developmental delay and brachymesophalangy but no major congenital malformations, suggesting the possibility of 2q37 microdeletion syndrome.

Since 1995, there has been a great effort toward finding the genes responsible for the AHO-like phenotype. Glypican 1 (GPC1), G protein-coupled receptor 35 and serine/threonine protein kinase 25 are included among the candidate genes for brachymeta phalangism[1,6,7]. A study of 20 patients with 2q37 microdeletion allowed assignment of the critical interval to the 3 Mb region from *HDAC4* to the telomere[2]. Recently, another study concluded that haploinsufficiency of *HDAC4* may result in an AHO-like phenotype in 2q37 microdeletion[8]. Variable expressivity and reduced penetrance for most major features in 2q37 microdeletion syndrome complicate genotype-phenotype correlations and further impair diagnosis.

In conclusion, chromosome 2q37 microdeletion should be considered in the differential diagnosis of psychomotor retardation and an AHO-like phenotype, especially in the presence of brachydactyly. Reporting clinical and molecular characteristics of patients with 2q37 microdeletion will not only provide pediatricians and clinical geneticists a combined clinical and genetic approach to the child with psychomotor retardation and characteristic facial features but also aid in the establishment of genotype-phenotype correlations in this syndrome.

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