Rubinstein-Taybi syndrome with normal FISH result and CREBBP gene analysis: a case report

Sevim Balcı[1], Mehmet Ali Ergün[2], E. Berrin Yüksel-Konuk[3], Oliver Bartsch[4]

[1]Clinical Genetics Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, and [2]Department of Medical Genetics, Gazi University Faculty of Medicine, and [3]Division of Pediatric Molecular Genetics, Ankara University Faculty of Medicine, Ankara, Turkey, and [4]Institut für Humangenetik Universitaetsklinik Mainz, Germany

SUMMARY: Balcı S, Ergün MA, Yüksel-Konuk EB, Bartsch O. Rubinstein-Taybi syndrome with normal FISH result and CREBBP gene analysis: a case report. Turk J Pediatr 2008; 50: 265-268.

We report on a six-year-old boy with typical Rubinstein-Taybi syndrome (RSTS) phenotype. Clinical findings included mental and motor retardation, patent ductus arteriosus (PDA), undescended testes, hirsutism, broad thumbs with radial angulation and broad toes, and inguinal hernia. His karyotype was normal (46, XY) and fluorescence in situ hybridization (FISH) showed no deletion of the CREBBP [cAMP response element-binding (CREB) binding protein] gene on chromosome 16p13.3. CREBBP gene sequencing also revealed normal results. We wish to present this case because this patient had typical RSTS phenotype, but normal FISH and CREBBP gene sequencing results. It could be possible that genetic heterogeneity is related with novel mutations in other genes. With the publication of such cases, their significance will be brought to the attention of researchers in this field.

Key words: Rubinstein-Taybi syndrome, normal fluorescence in situ hybridization 16p13.3, cAMP response element-binding binding protein (CREBBP) gene sequencing.

Rubinstein-Taybi syndrome (RSTS) was first delineated as a recognizable syndrome in 1963, characterized by severe mental and motor retardation, typical facial appearance, and broad and deviated thumbs and toes[1]. More recent studies showed that some patients with RSTS have a deletion at chromosome 16p13.3. This region contains the gene for the human [cAMP response element-binding (CREB) binding protein (CREBBP, alias CBP)]. In different studies, using fluorescence in situ hybridization (FISH), 4-25% of patients with RSTS were found to have the CREBBP deletion on chromosome 16p13.3.[2-5]

Here we present a Turkish patient with typical RSTS phenotype and normal FISH and CREBBP gene sequencing results. The recent literature on RSTS is also reviewed.

Case Report

The presented case, a six-year-old boy, was the product of the third pregnancy of unrelated parents from Turkey. The first child was a normal boy and the second pregnancy resulted in a blighted ovum. In infancy, the patient showed severe hypotonia and feeding difficulties. At the age of 10 months, he presented with typical facial anomalies, frontal nevus flammeus, downward slanted palpebral fissures, mild hypertelorism, large beaked nose, high arched palate (Fig. 1), broad and deviated thumbs (Fig. 2a), and broad toes (Fig. 2b). He also had mild central obesity, bilaterally undescended testes, pes planus, hirsutism and patent ductus arteriosus (PDA). Height was 100 cm (<3rd percentile), weight 19 kg (22% overweight), and head circumference 47.5 cm (<3rd percentile). An X-ray of the hand (Fig. 3) showed broad thumbs with radial angulation and short terminal phalanges of thumb, triangular proximal phalanges, and retarded bone age. Panoramic mandibular X-ray (Fig. 4) demonstrated irregular and crowded teeth. Lumbar X-ray (Fig. 5) showed mild scoliosis and spina bifida occulta on the 5th lumbar vertebra.

Chromosome analysis from cultured peripheral lymphocytes showed a normal karyotype, 46, XY. On FISH analysis using cosmids RT100, RT 191, RT203, and RT166, respectively, positive

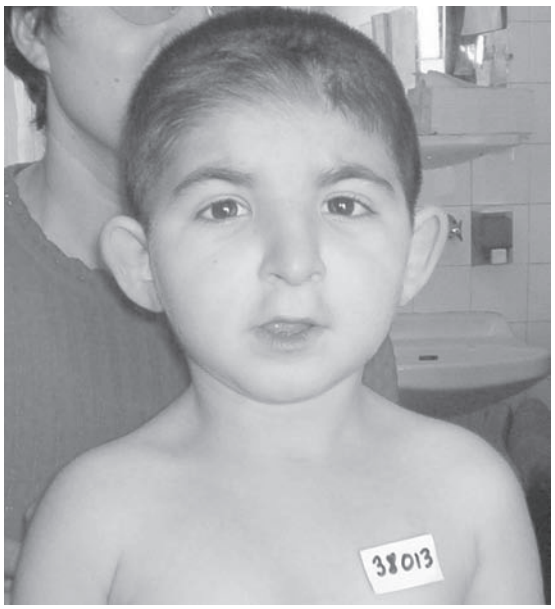

Fig. 1. Characteristic facial appearance with downward slant of palpebral fissure, mild hypertelorism, long philtrum, beaked nose, and strabismus in a six-year-old case with Rubinstein-Taybi syndrome.

Fig. 2a. Broad and radially deviated bilateral thumbs.

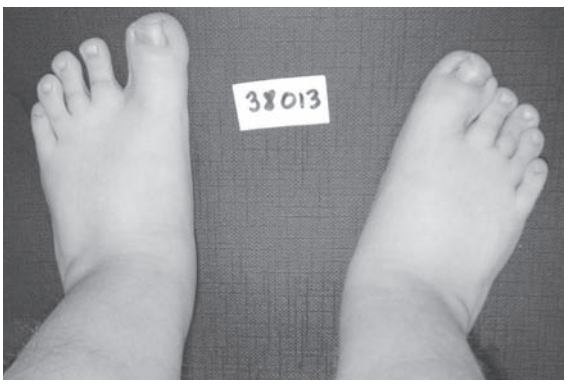

Fig. 2b. Broad great toes, with hypoplastic nails and in-grown toenails.

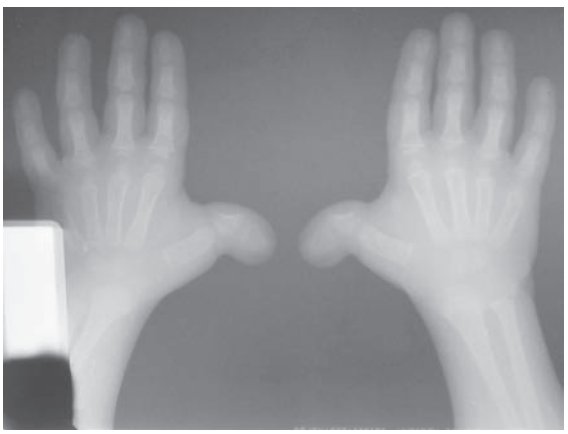

Fig. 3. Hand X-ray showed broad and short terminal phalanges and triangular proximal phalanges of thumb.

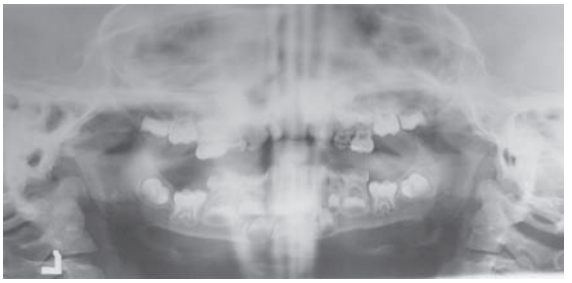

Fig. 4. Panoramic mandibular X-ray demonstrated irregular and crowded teeth.

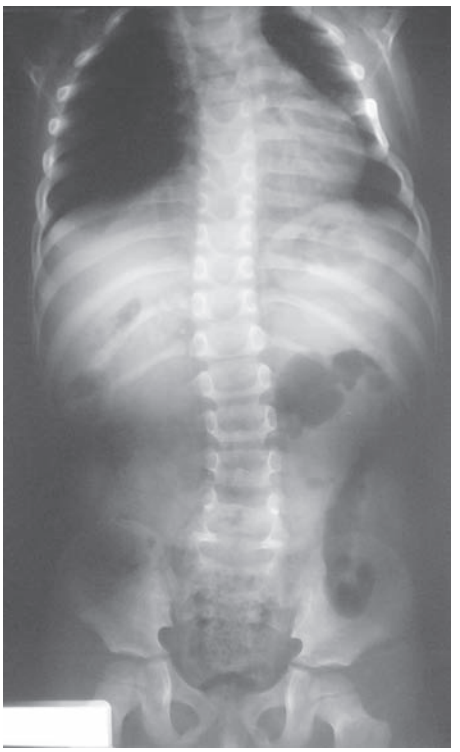

Fig. 5. Lumbar X-ray showed mild scoliosis spina bifida occulta on the 5th lumbar vertebra.

hybridization was seen at both homologues of chromosome 16, indicating no deletion at chromosome 16p13.3 (CBP/e31-e17x2, CBP/e13-e3x2, CBP/e3x2, CBP/e2-e1x2). CREBBP gene sequencing results were also normal.

Discussion

Rubinstein-Taybi syndrome (RSTS) is a multiple congenital anomalies/mental retardation syndrome with potential multi-organic involvement including heart, kidney, genitalia, eye, and brain malformations. This syndrome can also be regarded as a microdeletion syndrome with a low rate of microdeletions[6].

The prevalence of RSTS has been estimated to be 1 in 100,000 to 125,000 live births in the Netherlands. The recurrence risk for offspring of affected individuals could be as high as 50%, particularly in individuals with deletions[7].

It has been reported that RSTS patients with a deletion were presented at younger ages (mean age 0.96 years), while the mean ages of the RSTS patients with no deletion was reported as 11.1 years. Also, large deletions are characterized by visceral abnormalities (hypoplastic left heart, abnormal pulmonary lobulation, polysplenia) and early death[4].

The phenotype of RSTS patients with a deletion does not appear to differ significantly from the phenotype of non-deletion patients. In part, this can be explained by haploinsufficiency of CREBBP, which rather than having a dominant-negative effect, causes RSTS[8].

The diagnosis of RSTS continues to be made primarily by clinical examination[7]. A deletion-positive FISH study can be confirmatory, but since FISH studies show only 4-25% of CREBBP mutations, a negative FISH result clearly does not rule out the diagnosis of RSTS.

Here, we found no deletion of the CREBBP gene with sequencing. However, based in part on the fact that RSTS is a syndrome with a highly variable phenotype, it has been argued that possibly further factors, not only the loss of one functional copy of CREBBP, may play a role in the etiology of RSTS. Possibly, mutations in other genes, such as the CREBBP homologue p300 or genes encoding for proteins that interact with CREBBP in various signal transduction pathways, could contribute to or even cause the clinical signs of RSTS. Therefore, additional diagnostic methods (such as the protein truncation test, DNA sequencing, or single strand conformation polymorphism analysis) have been introduced[6,8-10]. However, these additional studies are very laborious and do not always reveal a mutation, as in our case, so that even today, careful clinical examination is the gold standard for the diagnosis of RSTS.

Recently, it has been reported that a cytogenetic or molecular abnormality can be detected in only 55% of RSTS patients[11].

Bartsch et al.[12] suggested that severe RSTS differs from mild form of RSTS and represents a novel true contiguous gene syndrome

(chromosome 16p13.3 deletion syndrome). They also indicated that the patients with severe RSTS all had deletions comprising telomeric neighbor genes of CREBBP, including DNASE1, a dominant gene encoding a nuclease that has been associated with systemic lupus erythematosus.

Finally, we stress the importance of reporting RSTS with typical phenotype but normal FISH and no mutation of CREBBP gene, as it may be associated with genetic heterogeneity[13].

REFERENCES

1. Rubinstein JH, Taybi H. Broad thumbs and toes and facial abnormalities. A possible mental retardation syndrome. Am J Dis Child 1963; 105: 588-608.
2. Breuning MH, Dauwerse HG, Fugazza G, et al. Rubinstein-Taybi syndrome caused by submicroscopic deletions within 16p13.3. Am J Hum Genet 1993; 52: 249-254.
3. Petrij F, Giles RH, Dauwerse HG, et al. Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 1995; 376: 348-351.
4. Bartsch O, Wagner A, Hinkel GK, et al. FISH studies in 45 patients with Rubinstein-Taybi syndrome: deletions associated with polysplenia, hypoplastic left heart and death in infancy. Eur J Hum Genet 1999; 7: 748-756.
5. Balci S, Bostanci S, Ekmekci P, et al. A 15-year-old boy with Rubinstein-Taybi syndrome associated with severe congenital malalignment of the toenails. Pediatr Dermatol 2004; 21: 44-47.
6. Taine L, Goizet C, Wen ZQ, et al. Submicroscopic deletion of chromosome 16p13.3 in patients with Rubinstein-Taybi syndrome. Am J Med Genet 1998; 78: 267-270.
7. Wiley S, Swayne S, Rubinstein JH, Lanphear NE, Stevens CA. Rubinstein-Taybi syndrome medical guidelines. Am J Med Genet 2003; 119A: 101-110.
8. Blough RI, Petrij F, Dauwerse JG, et al. Variation in microdeletions of the cyclic AMP-responsive element-binding protein gene at chromosome band 16p13.3 in the Rubinstein-Taybi syndrome. Am J Med Genet 2000; 90: 29-34.
9. Petrij F, Dauwerse HG, Blough RI, et al. Diagnostic analysis of the Rubinstein-Taybi syndrome: five cosmids should be used for microdeletion detection and low number of protein truncating mutations. J Med Genet 2000; 37: 168-176.
10. Coupry I, Roudaut C, Stef M, et al. Molecular analysis of the CBP gene in 60 patients with Rubinstein-Taybi syndrome. J Med Genet 2002; 39: 415-421.
11. Hennekam RC. Rubinstein-Taybi syndrome. Eur J Hum Genet 2006; 14: 981-985.
12. Bartsch O, Rasi S, Delicado A, et al. Evidence for a new contiguous gene syndrome, the chromosome 16p13.3 deletion syndrome alias severe Rubinstein-Taybi syndrome. Hum Genet 2006; 120: 179-186.
13. Roelfsema JH, White SJ, Ariyurek Y, et al. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. Am J Hum Genet 2005; 76: 572-580.