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

Sevim Balcı¹, Mehmet Ali Ergün², E. Berrin Yüksel-Konuk³, Oliver Bartsch⁴

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


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 toes¹. 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.
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. 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 heterogeneity13.

REFERENCES