

Rubinstein-Taybi Syndrome and Familial Mediterranean Fever in a Single Patient: Two Distinct Genetic Diseases Located on Chromosome 16p13.3

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Rubinstein-Taybi syndrome (RTS) is characterized by typical facies, short stature, mental retardation, broad thumbs and broad great toes. The syndrome is at least in part caused by microdeletions at chromosome 16p13.3 or by mutations in the gene for the CREB binding protein (CBP), which is located at 16p13.3. Familial Mediterranean fever (FMF) is an autosomal recessive disease, caused by mutations in the FMF-gene [Mediterranean fever (MEFV)] and characterized by recurrent attacks of fever and peritonitis, arthritis and pleuritis. The FMF gene (*MEFV*) has recently been cloned by two consortia and 30 point mutations, causing the disease have been identified. *MEFV* maps to chromosome 16p and encodes a 781-amino-acid protein called pyrin or marenostin, which is expressed mainly in neutrophils and myeloid bone marrow precursors. Herein, we report a case with RTS and FMF.

Key words: Rubinstein-Taybi syndrome ■ familial Mediterranean fever ■ chromosome 16p13.3

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INTRODUCTION

Rubinstein-Taybi syndrome (RTS) was first described in 1957 but was well delineated by Rubinstein and Taybi in 1963.¹ The incidence has been estimated to be one in every 100,000 newborns.² Reports of >1,000 patients have been published worldwide.² RTS is characterized by typical facies, short stature, mental retardation, broad thumbs and broad great toes.³ The syndrome is at least in part caused by microdeletions at chromosome 16p13.3 or by mutations in the gene for the CREB binding protein (CBP), which is located at 16p13.3.²

Familial Mediterranean fever (FMF) is an autosomal

recessive disease, caused by mutations in the FMF gene [Mediterranean fever (MEFV)] and characterized by recurrent attacks of fever and peritonitis, arthritis and pleuritis. Although FMF primarily affects populations living around the Mediterranean basin (Jewish, Armenian, North African, Arab and Turkish populations), it is also a worldwide disease. The prevalence reaches a high of one in 200 individuals; one in 256 to one in 500 in non-Ashkenazi Jews and one in 1,073 in the Turkish population. In a recent study, the carrier rate in Turkey to be one in five. *MEFV* has recently been cloned by two consortia and 30-point mutations, causing the disease have been identified. *MEFV* maps to chromosome 16p, and encodes a 781-amino-acid protein, called pyrin or marenostin, which is expressed mainly in neutrophils and myeloid bone marrow precursors.⁴ Herein, we report a case with RTS and FMF.

CASE REPORT

An 18-year-old Turkish male admitted for persisting right ankle arthritis for a duration of 15 days. Laboratory values of the patient upon admission were as follows; ESR 52 mm/hr, C-reactive protein (CRP) 1.97 mg/dl (0-0.5), leukocyte 16,100 and fibrinogen 462 (133-430) mg/dL. He was diagnosed with RTS when he was 16 months of age based on phenotypic findings of short stature, down-slanting palpebral fissures, mild hypertelorism, high plate, broad thumbs and toes, small penis and mental retardation. Fluorescent in situ hybridization (FISH) used with 4,6-diamidino-2-phenylindole (DAPI) staining and cosmid DNA probes RT 100, RT 191, RT 203 and RT 166 did not disclose any detectable deletion of chromosome 16p13.3. His mother said that he had been experiencing recurrent bouts of abdominal pain accompanied by fever, which had been occurring in an average of 2-5 times per year. Checked acute-phase reactant during these episodes was found to be elevated. He had also experienced left knee arthritis two months previously, which had subsided spontaneously in 10 days. His family history was positive for FMF in his cousin,

who suffers from amyloidosis. With these findings, we thought that patient may have FMF, and therefore colchicine 1.5 mg/day was prescribed. After colchicine treatment, arthritic symptoms and laboratory values (ESR 20 mm/hr, CRP 0.61 mg/dl and fibrinogen 371 mg/dL) improved. Because of the discontinued colchicines, one FMF attack was observed in following six months. MEFV mutation analysis performed with sequence analysis revealed M694V heterozygote.

DISCUSSION

This is the first case in the literature of RTS with FMF. RTS is a rare genetic disease but prevalence of FMF is relatively high in Turkey. Although, RTS with FMF can be coincidence, mutation on chromosome 16p13.3 in these diseases is noticeable.

Chromosomal microdeletions and point mutations in the CBP gene (cyclic AMP-response element binding protein or CREB) are shown to be associated with RTS. It has been demonstrated that CBP gene is located on chromosome 16p13.3 between 3,716,570–3,870,712 base pairs.⁵ CBP has histone acetyltransferase activity and “opens” the chromatin structure; thereby, transcription factors can enter and regulate gene expression. CBP is involved in different signaling pathways and in certain cellular functions, such as DNA repair, cell growth, differentiation, apoptosis and tumor suppression. Chromosomal aberrations involving CBP may cause RTS, leukemia, myelodysplastic syndrome, neurodegenerative diseases and Huntington disease.⁶

MEFV gene has been identified on chromosome 16p13.3 between 3,232,029–3,246,628 base pairs.⁷ MEFV encodes for a protein termed pyrin, which is expressed mainly in myeloid/monocytic cells. Although exact function of pyrin unknown, it has been proposed that it has modulatory effects on IL-1 β processing, NK- κ B activation and apoptosis.⁸

Except for rare cases, no phenotype-genotype correlation was observed between RTS patients with or without deletion, and negative genetic investigation results do not rule out diagnosis of RTS. FMF and RTS both are genetically determined disorders involving a region of band 16p13.3. Coexistence of RTS and FMF in this case can be explained by mutations occurring separately (or independently) in each specific gene. However, because responsible genes for these diseases are located closely to each other, other explanations can be an exposure to a possible mutagen to 16p13.3 or, alternatively, the dysfunction of another distinct gene affecting function of both specific genes.

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