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LETTER TO THE EDITOR

Coffin-Lowry syndrome: two novel variants in RPS6KA3 gene

Coffin-Lowry sendromu: RPS6KA3 geninde iki yeni varyant

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To the Editor,

Coffin-Lowry syndrome (CLS) (MIM#303600) is an X-linked mental retardation disorder that was first described by Coffin et al. and Lowry et al.[1,2]. The characteristic features of this syndrome are craniofacial findings such as prominent ears, prominent chin, hypertelorism, down-slanting palpebral fissures, thick nasal alae, broad nose, high and narrow palate, thick- everted lower lip vermillion, large-open mouth and hypodontia. The most frequent skeletal abnormalities are delayed bone age, spinal scoliosis, kyphosis, soft hands, short metacarpals, short phalanges, and drumstick terminal phalanges. CLS is a very rare syndrome, with approximately 70-80% of patients being sporadic cases, with an estimated incidence between 1: 50,000 and 1:100,000[3]. In the differential diagnosis of Coffin-Lowry syndrome, conditions such as Alpha-thalassemia X-linked intellectual disability syndrome (OMIM# 301900), FG syndrome type1 (OMIM #305450), Williams syndrome, Pitt-Hopkins syndrome (OMIM #610954), and Borjeson-Forssman-Lehmann syndrome (BFLS) (OMIM #301900) should be considered, each with its own clinical features and genetic basis[4]. The underlying genetic cause of CLS is heterogeneous loss of function mutations in the RPS6KA3 gene. This gene with 22 exons is localized at Xp22.2. The RPS6KA3 gene encodes a member of the ribosomal S6 kinase (RSK) family of serine/threonine kinases, also known as p90 (rsk). Mutations in the RPS6KA3 gene are detected in approximately 40% of patients with CLS 5. Of these mutations, approximately 30% are missense mutations, 30% are short insertion or deletion, 20% are splicing errors, and 15% are nonsense mutations[3,6,7]. Until today, more than 128 different mutations with different symptoms have been reported in the RPS6KA3 gene[3,8,9]. We present two novel mutations of RPS6KA3 in two Turkish boys with CLS. As reported in previous publications, growth and developmental delay and phenotypic appearance were typical in our cases.

Our first patient was the product of the fourth pregnancy of unrelated parents. His other three siblings were healthy. He started sitting without support when he was seven months old and walking at the age of 2. He had a speech delay and could only speak 10 words. He had a happy personality. He was referred to our department at the age of 2.5 due to dysmorphic findings and motor delay. His height was 87 cm (10th p) and his weight was 13 kg (3th-10th p). In the clinical examination of the patient, facial findings such as hypertelorism, epicanthus, prominent ears, thick nasal alae and septum wide mouth and thick lips with everted lower vermilion were present (Fig.1a-1b). The hands were short, soft, and fleshy. There was skin and joint laxity, as well as tapering fingers.

The second patient was the second child of healthy, non-consanguineous parents. He achieved head control at the age of 1 and could sit without support at the age of 3. At 4 years of age, he was referred to our department due to developmental delay, intellectual disability and an atypical face. His height was 88 cm (<3th p), and his weight was 12 kg (3th p) and his occipitofrontal circumference was 52 cm (75th p). A facial examination showed hypertelorism, frontal bossing, epicanthus, prominent ears, thick nasal alae and septum, prominent philtrum, wide

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mouth, thick lips with everted lower vermilion, and hypodontia. He also had prominent xiphoid process (Fig.2). The hands were short, soft, and fleshy. There was skin and joint laxity, as well as tapering fingers.

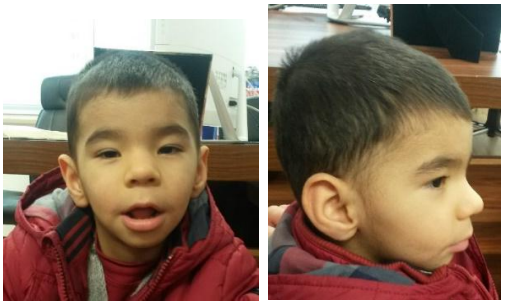

Figure 1a-1b. Facial examination of Case 1 showed hypertelorism, epicanthus, wide mouth, thick lips with everted lower vermilion, prominent ears, thick nasal alae and septum.

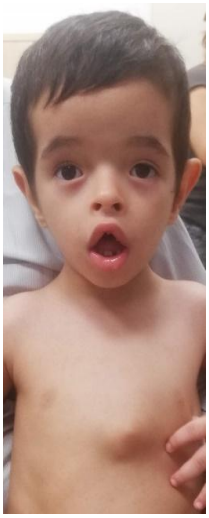

Figure 2. The facial appearance of Case 2 showed hypertelorism, frontal bossing, epicanthus, wide mouth, thick lips with everted lower vermilion, prominent ears, thick nasal alae and septum, prominent philtrum, and hypodontia. Also seen prominent xiphoid process.

CLS was considered clinically in both patients. After obtaining written informed consent from the legal guardians of both cases, peripheral blood was collected from the patients and their mothers for genomic DNA. DNA samples were extracted using the "Maxwell RSC" DNA isolation kit (Promega/USA). RPS6KA3 whole gene sequencing was performed on DNA samples. The 22 exons of the RPS6KA3 gene and their flanking intron sequences were amplified by polymerase chain reaction and sequenced with the Illumina MiSeq system. The resulting sequences were aligned to the hg19 genome using Illumina MiSeq Reporter software. Identified variants were checked against those present in 1,000 Genomes, HGMD, ClinVar, and dbSNP. ACMG (American Standards and Guidelines for Medical Genetics and Genomics) criteria were used for the detection of variant pathogenicity.

As a result of whole gene sequencing, we found two new variants in the RPS6KA3 gene. In case 1, hemizygous in exon 13 of RPS6KA3, c.1108C>G (p. P370A), and in case 2, a hemizygous variant c.325+2dupT in intron 4. We could not detect any mutations in the mothers of either patient. The absence of these mutations in the mothers suggests a potential de novo origin or germline mosaicism. This emphasizes the need for further genetic research and counseling to understand the pattern of inheritance and assess the risks of recurrence for future offspring.

HOPE (Have (y)Our Protein Explained) analysis of the hemizygous de novo novel variant [c.1108C>G (p. P370A)] that we identified in our first patient showed that the sizes of the mutant amino acids and the wild type were different. The wild-type residue is bigger, which might lead to a loss of interactions. The wild-type residue is a proline. Since prolines are very rigid, they induce a special backbone conformation that may be necessary in this position. The current mutation can disrupt this conformation[10]. According to the criteria published by the ACMG, the variant c.1108C>G (p. P370A) in case 1 was rated as "pathogenic" because it meets PS1, PM1, PM2, PP2, and PP3 criteria[11]. In the second patient, the de novo hemizygous variant c.325+2dupT was detected in intron 4. This variant was "likely pathogenic" because it met the criteria of PS1, PP3, and PM2 [10]. This variant is in the splice site in the intron and it is likely to cause a splicing error.

In conclusion, we identified two novel RPS6KA3 variations in two Turkish boys with CLS. The variants were evaluated as likely pathogenic and pathogenic according to ACMG criteria. The two variants found are presented because they have not been reported before in the literature.

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