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A rare case of Coffin–Lowry syndrome accompanied by a copper-beaten skull appearance

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Abstract

Coffin-Lowry syndrome (CLS), usually a result of loss-of-function mutations in the *RPS6KA3* gene located at Xp22.2, is a very rare genetic condition. It is associated with different phenotypes, including dysmorphic facial features, neuro-developmental impairment, short stature, and skeletal deformities. Here we describe a four-year-old boy who had distinct clinical features of CLS: moderate mental and motor retardation, brachycephaly, microcephaly, hypertelorism, low-set and prominent ears, down-slanted palpebral fissures, a depressed nasal bridge with thick nasal alae and septum, a high-arched palate, widely spaced teeth, and retrognathia. Genetic analysis revealed a pathogenic variant in the *RPS6KA3* gene, NM_004586.3: exon 22: c.2186G>A: (p.Arg729Gln). His healthy mother was a heterozygous carrier of the variant. In addition to the clinical findings, the patient's X-ray revealed a very rare feature of a copper-beaten skull appearance. The link between CLS and a copper-beaten skull has never been reported before. This case demonstrates the variability in presentation of CLS and signifies the association of a rare radiographic finding of copper-beaten skull with CLS. Based on this case, we recommend screening skull radiographs at the clinic for copper-beaten skulls in patients with CLS.

Keywords: Coffin-Lowry syndrome, copper-beaten skull, radiography, whole-exome sequencing, X-linked intellectual disability.

INTRODUCTION

Coffin–Lowry syndrome (CLS) (MIM ID #303600) is a X-linked syndrome consisting of psychomotor retardation, short stature, skeletal deformities (kyphoscoliosis, pectus carinatum/excavatum), digit abnormalities, and distinctive facial features (prominent forehead, ocular hypertelorism; downward slanting palpebral fissures, epicanthus, large and prominent ears, thick lips).[1] Different phenotypes are seen in males and females with CLS. It leads to severe intellectual disability and dysmorphism in males, while females have high variability in clinical presentations.[2] This condition is very rare; the estimated prevalence is 1:50,000 to 1:100,000; about 70–80% of probands are sporadic cases.[3]

The loss-of-function mutations in the *RPS6KA3* gene, which maps to Xp22.2 and encodes the ribosomal protein S6 kinase polypeptide 3, are associated with CLS.[4] To date, there have been reports of cases with different symptoms and more than 150 distinct mutations in the *RPS6KA3* gene.[5] *RPS6KA3* gene mutations have been shown to be related to cardiomyopathy, osteosarcoma, and compression in the foramen magnum.[6-8] Here, we report a pathogenic mutation of *RPS6KA3* in a Turkish boy with an atypical radiographic finding of a copper-beaten pattern of skull bones.

CASE REPORT

The patient is a 4-year-old Turkish boy who is the single child of healthy non-consanguineous parents. He was born at 37 weeks of gestation by vaginal delivery without any complications. His birth weight was 3,100 g (25^{th}-50^{th} percentile), his birth height was 46.5 cm (10^{th}-25^{th} percentile), and his head circumference was 34.0 cm. In the family history, it was learned that his uncle (mother's brother) had severe mental retardation. The patient was referred to our clinic by pediatric neurology for facial dysmorphism, neurodevelopmental delay, and intellectual disability. His weight was

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13,7 kg (25th-50th percentile), his height was 95 cm (10th-25th percentile), and his head circumference was 47 cm. His craniofacial features exhibited a large forehead, brachycephaly, microcephaly, hypertelorism, low-set and prominent ears, downslanted palpebral fissures, a flat nasal bridge with thick nasal alae and septum, a high-arched palate, widely spaced teeth, and retrognathia (Figure 1: A, B, and C).

He was hypotonic and walked in the middle

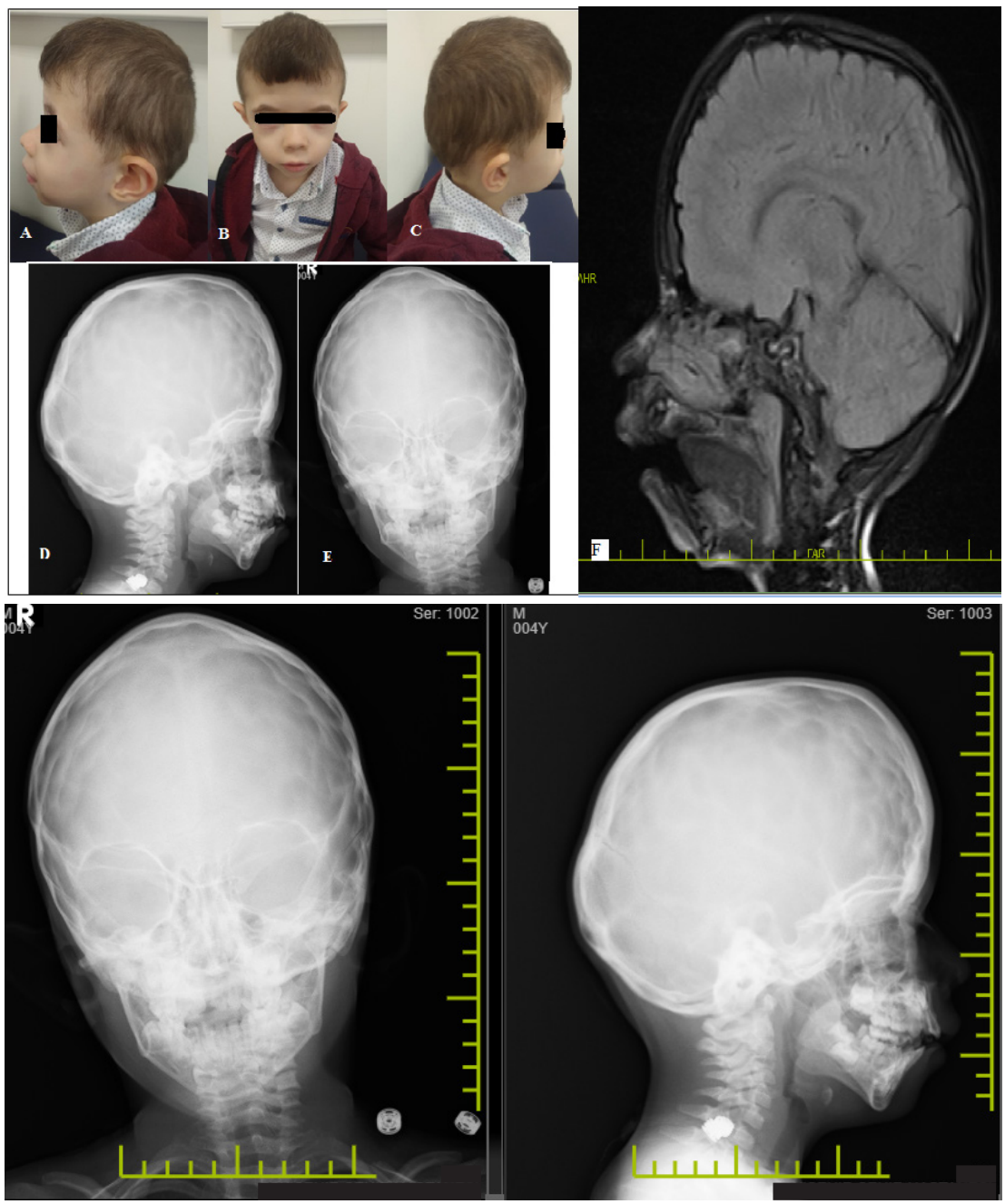

Figure 1. Patient's craniofacial manifestations. A, B and C. The patient has a large forehead, brachycephaly, microcephaly, hypertelorism, telecanthus, a depressed nasal bridge with thick nasal alae and septum, downslanted palpebral fissures, low-set and prominent ears, and retrognathia. The figures are published with the consent of the patient's parents. Skull radiographs, lateral (D) and anterior-posterior (E), views show convolutional markings appearing as a copper beaten skull.

guard position. He started sitting alone for the first time at 9-months-old, and he was unable to stand without a support until he was 12 months old. His speech development was slow, and he could only say a few short sentences. His hands were soft and fleshy, but tapered fingers were not apparent. The deep tendon reflex examination was normal in the upper and lower extremities.

Investigations in hematology, blood chemistry tests, and urine analysis were normal. Diagnostic studies to localize other abnormalities in the urinary tract and cardiovascular system were normal. His skull radiograph showed prominent convolutional markings described as having a copper-beaten skull appearance (Figure 1, D, and E). A postero-anterior chest X-ray revealed no kyphoscoliosis. G-banding chromosomal analysis revealed a normal 46,XY male karyotype. An agilent oligonucleotide microarray with an 8X60K probe was used to investigate copy number variants. When the agilent cytogenomic 5.0.0.38 (GRCh 37/hg 19) analysis program was used, there was no detection of any deletion or duplication. Whole-exome sequencing of a DNA sample from the patient and the parents was performed by MGI (DNBSEQ-G400) (Figure 2). The data analysis using the genemaster analysis program revealed a heterozygous mutation in the *RPS6KA3* gene (c.2186G>A: p.Arg729Gln), which was predicted to be pathogenic according to the SIFT, PolyPhen-2, and Mutation Taster tools. His mother was a heterozygous carrier of the variant. It was predicted that the uncle and grandmother of the proband would have the same variant; however, a genetic analysis could not be performed. Informed consent was obtained from the patient's parents for the publication of this report and the use of the patient's photographs.

DISCUSSION

Loss-of-function mutations of the *RPS6KA3* gene, which encodes the RSK2 (ribosomal S6 kinase) protein, cause CLS, a rare X-linked disorder.[9,10] RSK2 is dominantly expressed in the cerebellum, hippocampus, Purkinje cells, and neocortex.[10] More than 150 inactivating mutations of the *RPS6KA3* gene have been reported. Previous reported mutations include missense, nonsense, splice-site errors, short deletions or duplications, and large intragenic deletions.[3,5] CLS is characterized by craniofacial and skeletal abnormalities, moderate to severe intellectual disability, hypotonia, and short stature.[4] Our patient has the classical characteristics of CLS, including intellectual disability, global developmental delay, speech delay, and craniofacial dysmorphisms such as brachycephaly, microcephaly, hypertelorism, low-set and prominent ears, downslanted palpebral fissures, a depressed nasal bridge, a high-arched palate, widely spaced teeth, and retrognathia.

The radiological findings of the CLS patients may include variable enlargement or hypoplasia of the skull and frontal sinuses, and sclerosis localized to the frontal bones. The anterior fontanel is generally broad and has delayed closure. Hypotonia and increased joint laxity contribute to the development of kyphoscoliosis.[3,11] However, in our case, an atypical radiographic finding of a copper-beaten pattern appearance was identified on the X-ray of the skull. The 'Copper-beaten

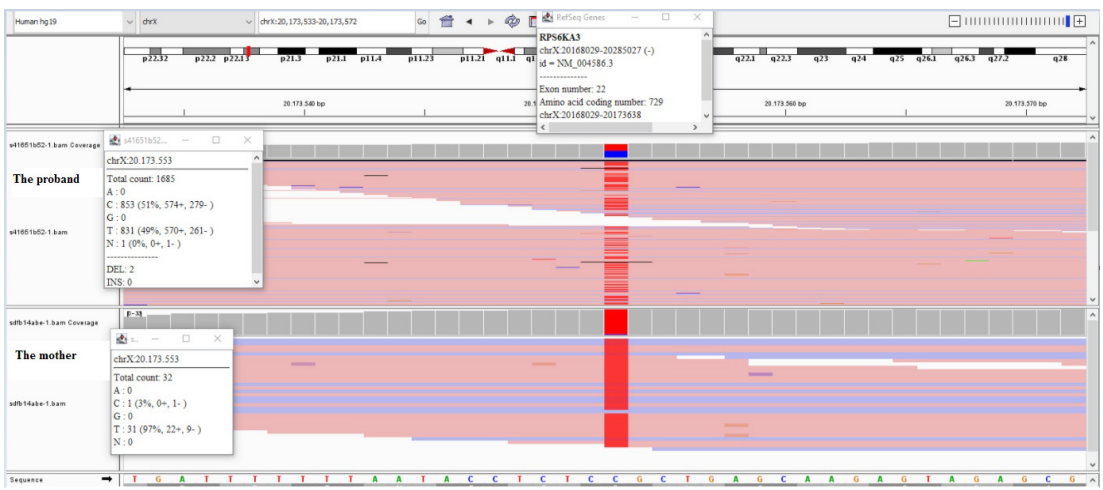

Figure 2. Whole exome sequencing showed the missense mutation (c.2186G>A:p.Arg729Gln) in the *RPS6KA3* gene. The proband and his mother were heterozygous for the variant.

skull' appearance is thought to be associated with craniosynostosis, increased intracranial pressure, obstructive hydrocephalus, and increased intracranial masses.[12,13] Copper-beaten skull is also usually associated with craniosinostosis syndromes such as Crouzon syndrome, Saethre-Chotzen syndrome, Apert syndrome and Pfeiffer syndrome.[14] This association has also been demonstrated in the literature for a few syndromes or diseases. Gupta *et al*. described an X-ray of a copper-beaten skull in a case of Treacher Collins syndrome.[15] CLS is a rare, X-linked, semi-dominantly inherited disease with typical features in affected hemizygous males.[16] As far as we know, no cases of CLS or copper-beaten skull appearance have been reported.

A pathogenic missense variant c.2186G>A:p. Arg729Gln in the *RPS6KA3* gene was detected in the proband and his mother by whole exome sequencing. The mutation leading to the substitution of G for A at nucleotide 2186 in exon 22, results in an Arg-729 to Gln substitution. Almost 70-80 percent of CLS patients are sporadic, with no family history.[3] Although not genetically confirmed, the patient's uncle (his mother's brother) had mental retardation. The proband's grandmother probably has the pathogenic variant, but testing could not be done as she passed away. The females are usually carriers with a less severe picture, or normal clinically. The phenotype in female carriers can include epilepsy, obesity, and psychiatric disorders (psychosis, depression, and schizophrenia).[17] Although the neurological and psychiatric examinations of the mother of the proband were normal, an annual follow-up was advised.

There were a few Turkish case reports with CLS in the literature. Senel *et al.* reported a novel mutation of the *RPS6KA3* (Ala180Asp) gene in a Turkish boy. This boy had spina bifida of the 4th and 5th lumbar regions, optic atrophy, and a thin corpus callosum.[18] Arslan *et al*. described stimulus-induced drop episodes in a Turkish female with a novel mutation (p.M659Dfs*55) in the *RPS6KA3* gene. Their patient exhibited the skeletal deformity of kyphosis.[19]

The mutation in our patient had been previously published as pathogenic. Their patient was moderately mentally retarded and suffered from deafness and scoliosis.[4] On the other hand, the copper-beaten skull appearance of our patient was not observed in the previous case. To date, a genotype-phenotype correlation for CLS has not been described. This case demonstrates the variability in presentation of CLS and the association of a rare radiographic finding of copper-beaten skull with CLS. Therefore, further studies are needed to illuminate the phenotypic heterogeneity of CLS with *RPS6KA3* mutations and establish the eventual genotype-phenotype correlation.

DISCLOSURE

Conflict of interest: None

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