Case Report: Coffin-Lowry Syndrome: The First Molecularly Confirmed Report in Iran

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ABSTRACT

Coffin-Lowry syndrome (CLS) is an X-linked disorder, which affects hemizygous males more severely than females. It is characterized by mental retardation, short stature, head and facial abnormalities, skeletal anomalies and developmental delays. The signs and symptoms vary in different people. We report a 14-year-old male patient, diagnosed with CLS based on his clinical features. Genetic testing revealed a de novo mutation in ribosomal protein S6 kinase alpha-3 (*RPS6KA3*) gene (c.2185C>T; p. Arg729Trp). This is the first molecularly confirmed case report of a patient with CLS from Iran.

Highlights

- Coffin-Lowry Syndrome is caused by mutations in the ribosomal protein S6 kinase alpha-3 (RPS6KA3) gene, which encodes ribosomal S6 kinase-2 (RSK2), a growth factor-regulated protein kinase.
- In the current study, Whole Exome Sequencing (WES) revealed a de novo missense mutation (c.2185C>T; p.Arg729Trp) in exon 22 of *RPS6KA3* gene.
- Whole Exome Sequencing (WES) seems to be an efficient and sensitive method to identify possible disease-causing mutations.
- To the best of our knowledge, this is the first molecularly confirmed report of CLS in Iran.

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Plain Language Summary

Coffin-Lowry Syndrome (CLS) is a rare genetic disorder with X-linked dominant inheritance affecting multiple systems. Approximately 80% of patients have no history of this illness in their families. Signs and symptoms may include intellectual disability, delayed development, short stature, skeletal abnormalities and characteristic dysmorphism, most notably affecting the face and hands. Mutations in the RPS6KA3 gene cause this syndrome. This gene provides instructions for synthesis of a protein involved in signaling within cells. Treatment is symptomatic and supportive. Prognosis is poor and depends on the severity of the disease. Early intervention may improve the outlook for patients. Diagnosis is usually based on the clinical presentation. Early on, RPS6KA3 mutation analysis may be used for rapid diagnosis. Here, we elaborate the clinical and genetic analysis of an Iranian patient with CLS. He was the second child of non-consanguineous parents. Clinical examinations revealed signs and symptoms of CLS. His karyotype was normal. We applied Whole Exome Sequencing (WES), a genomic technique for sequencing all of the protein-coding genes in a genome, to identify the causal variant in the patient. Results from WES revealed a hemizygous missense variant in exo 22 (c.2185C>T; p.Arg729Trp) of RPS6KA3 gene. To the best of our knowledge, this is the first report of molecularly confirmed case of CLS in the Iranian population.

1. Introduction

Coffin-Lowry syndrome (CLS, OMIM 303600) is a rare X-linked intellectual disability syndrome characterized by mental retardation associated with severe developmental delays, distinctive facial features, and skeletal changes. It has an estimated prevalence of 1 in 50000 to 1 in 100000 male infants [1]. The condition was firstly described, independently, by Coffin et al. in 1966 [2] and by Lowry et al. in 1971 [3].

Some of the typical facial features of the disorder include a prominent forehead, hypertelorism, downward-slanting palpebral fissures, epicanthic folds, wide mouth, thick everted lips, broad nose with thick nasal septum and hypodontia. Affected individuals also have broad, soft, and fleshy hands with short tapering fingers. Other reported symptom is a short horizontal crease in the hypothenar region. Skeletal deformities like spinal kyphosis/scoliosis and pectus carinatum or excavatum may present in some patients [4-6]. Here, we report a case of CLS with a disease-causing mutation. To our knowledge, this is the first case report of this syndrome in Iran with a confirmed molecular diagnosis.

2. Case Report

This case study reports a 14-year-old Iranian male patient (Figure 1), who was referred to our genetic counseling center for his dysmorphic features and mental retardation. He was the second child of non-consanguineous and healthy parents. His older brother died in early infancy without diagnosis. Parameters at birth were within the normal range. His developmental progress was delayed; he started walking at age 3 and started speaking at age 4. At the age of 14, his height was 132 cm and weighted 35 kg. He had mild intellectual disability and seizure. His hearing was normal. Facial features included prominent forehead, widely spaced and downward-slanting eyes, broad and short nose, flat nasal bridge, wide mouth with full lips and hypodontia (Figure 2 A-C).

There was a short horizontal hypothenar crease on the palmar surface of the hands (Figure 2D). The hands were broad with short puffy tapered fingers, which were wide at the base and narrow distally (Figure 2E). His karyotype was normal and pedigree analysis showed that none of the other family members had the same anomalies.

To explore the genetic basis of the disease, we collected peripheral blood samples of the patient and his parents,

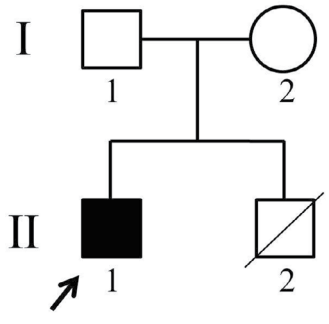

Figure 1. Pedigree of the family Iranian Rehabilitation Journal

Symbols are as follows: Circle: Female; Squares: Males; Filled: Affected individual; Empty: Healthy; Slash: Deceased; An arrow indicates the proband.

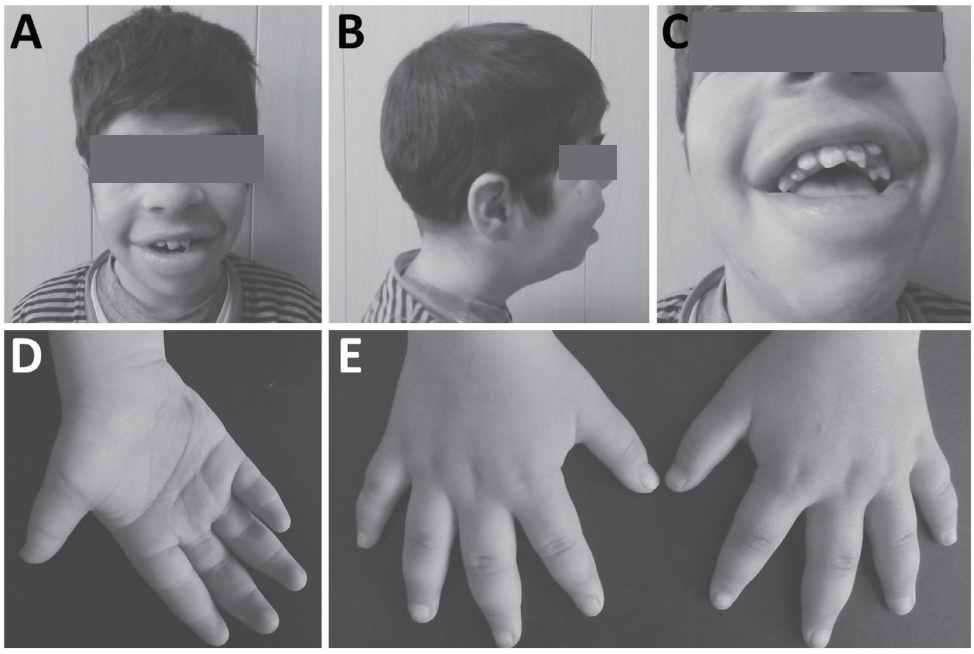

Figure 2. Clinical photographs of the patient

(A-C): Facial views of the patient: Note the prominent forehead, hypertelorism, downward-slanting eyes, broad and short nose, flat nasal bridge, wide mouth, thick lips and hypodontia. (D): Palmar view of the hand showing a hypothenar crease. (E) Dorsal view of the hands showing short, broad and tapering fingers.

after obtaining written informed consent. Genomic DNA was extracted from whole blood by standard methods. By whole exome sequencing, we identified a hemizygous missense variant in exon 22 (c.2185C>T; p. Arg729Trp) of *RPS6KA3* gene in the patient (Figure 3). The mutation detection was validated by PCR-Sanger sequencing. Segregation analysis showed that both asymptomatic parents do not have this mutation. These findings confirmed the de novo nature of detected mutation in the patient.

3. Discussion

We reported a 14-year-old Iranian boy with clinical CLS phenotypes. Genetic testing revealed a hemizygous mutation in the *RPS6KA3* gene, leading to the substitution of C-to-T at nucleotide 2185 in exon 22, resulting in an Arg-729 to Trp substitution. To the best of our knowledge, this is the first report of molecularly confirmed case of CLS in the Iranian population.

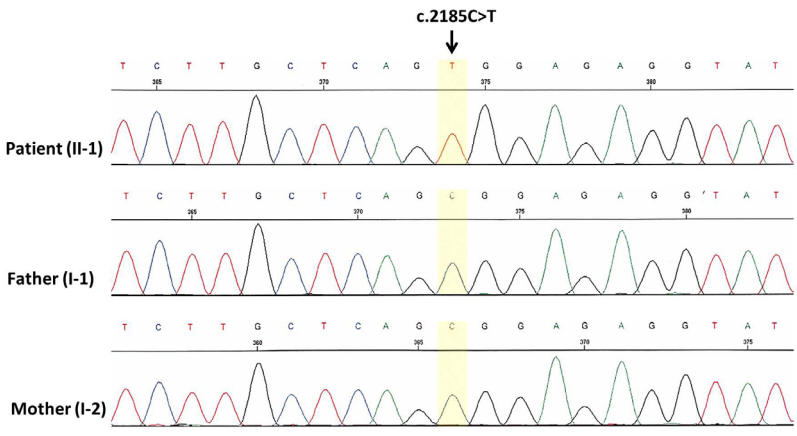

Figure 3. Sanger sequencing chromatogram revealing the pathogenic *RPS6KA3* mutation (c.2185C>T; p. Arg729Trp)

The parents are normal.

RPS6KA3 gene (OMIM 300075), which encodes ribosomal S6 kinase-2 (RSK2) is located on the short arm of chromosome X (Xp22.2) and contains 22 exons [7, 8]. RSK2 protein belongs to a highly conserved family of growth factor-activated serine/threonine kinases known as RSK family, which acts at the distal end of the Ras-MAPK signaling pathway [9]. The RSK family consists of 4 members (RSK1-4) and regulates several important cellular processes, such as cellular proliferation, differentiation, survival, stress response and apoptosis [10].

RSKs are composed of 2 non-identical functional kinase catalytic domains, linked together by a 100-amino acid linker region. Carboxyl (C)-terminal kinase domain is necessary for enzymatic activation of the amino (N)-terminal kinase domain through autophosphorylation. The activated N-terminal domain phosphorylates substrates [11].

Mutations in the *RPS6KA3* gene are extremely heterogeneous and have been detected in approximately 50% of CLS patients. Over 140 distinct inactivating mutations have been reported so far. Identified mutations are distributed over the entire gene and include missense, nonsense, splicing errors, short deletions and insertions, large intragenic deletions, and large duplications [12-15]. About 80% of the mutations are de novo and sporadic [1, 4].

The identified mutation in our patient was previously reported as a pathogenic variant by Delaunoy et al. [12], who described a moderately mentally retarded CLS patient that suffered from deafness and scoliosis, whereas our patient was a mild mentally retarded child, with neither of these symptoms. In contrast, seizure characteristic of the current patient were not found in the previous case. Altogether, further studies are necessary in order to elucidate the phenotypic heterogeneity of CLS with *RPS6KA3* mutations.

4. Conclusion

In conclusion, we described the clinical and molecular features of a male Iranian child with CLS due to a de novo missense mutation (c.2185C>T; p.Arg729Trp) in exon 22 of *RPS6KA3* gene, displaying a mild mental retardation, seizure and typical facial features, also compared the case with a previous report of similar substitution. This comparison showed that some of the symptoms were different in each case. In addition to *RPS6KA3* mutations, other factors seem to affect the disease severity and may need to be explored in a larger study on patients with CLS.

Ethical Considerations

Compliance with ethical guidelines

The authors have completely considered the ethical issues including informed consent, plagiarism, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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