Whole Exome Sequencing Identifies a Homozygous PYCR1 Missense Variant in a Patient with Autosomal Recessive Cutis Laxa Type 2B: A Case Report

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Abstract

Autosomal recessive cutis laxa type 2B (ARCL2B) is a rare genetic connective tissue disorder characterized by wrinkled inelastic skin, intellectual disability, growth retardation, developmental delay, skeletal abnormalities, and facial dysmorphism. Recently, PYCR1, encoding the pyrroline-5-carboxylate reductase 1, was reported as the first gene involved in ARCL2B. In this study, using whole exome sequencing, we identified a homozygous PYCR1 missense mutation, c.722C>A; p.Ala241Asp, in an Iranian male patient. Our report expands the clinical spectrum of PYCR1 mutations. Furthermore, this study shows that whole exome sequencing could serve as a viable diagnostic approach to identify the etiology of rare genetic diseases.

Keywords: Autosomal Recessive Cutis Laxa Type 2B, PYCR1, Whole Exome Sequencing

1. Introduction

Cutis laxa (CL) is a rare heterogeneous disorder of connective tissue characterized by loose, hypoelastic, wrinkled, sagging and redundant skin resulting in a prematurely aged appearance. It can be inherited or acquired, but inherited cases are more common. Inherited CL has considerably heterogeneous etiology and may be presented as autosomal dominant, autosomal recessive and X-linked recessive (1, 2). The autosomal recessive form of CL has most commonly been reported (3, 4). CL is separated into subtypes based on the genetic basis of the disorder. Autosomal recessive cutis laxa type 2B (ARCL2B; OMIM 612940) is caused by homozygous or compound heterozygous mutation in the pyrroline-5-carboxylate reductase 1 (PYCR1) gene, which is located on 17q25.3 (5, 6). Typical features of ARCL2B are wrinkled loose skin, progeroid appearance, developmental delay, growth retardation, and joint laxity (7). Patients may also have distinctive dysmorphic facial features including triangular face, high forehead, large ears, prognathism, hypotelorism, bulbous nose, epicanthal folds, and blue sclera. Affected individuals may also suffer from skeletal anomalies, hypotonia, and variable central nervous system involvement (6, 8, 9). Using whole exome sequencing, we identified a homozygous mutation, c.722C>A, in PYCR1 gene, and a subsequent diagnosis of ARCL2B was made.

2. Case Presentation

We reported a case on a 9-year-old boy (Figure 1) referred to our genetic counseling center due to his intellectual disability, developmental delay, and dysmorphic appearance. He was born as the first child of his consanguineous Iranian parents at 36 weeks of gestation via cesarean section. His birth weight was 2080 g (< 5th centile), length was 49 cm (25th centile), and head circumference was 30 cm (< 5th centile). No remarkable family history was reported. He could sit independently at 9 months, and was able to walk at the age of 32 months. On examination at the age of 9 years, his weight was 29.9 kg (< 5th centile), length 141 cm (90th centile), and OFC was 49.5 cm (50th centile).
Clinical findings were lax wrinkled skin, intrauterine growth retardation, joint hyperlaxity, hypotonia, facial dysmorphisms including triangular-shaped face with a prematurely-aged appearance, prognathism, large ears, bulbous nose, broad nasal bridge, down-slanting palpebral fissures, and strabismus (Figure 1B and C). The patient also suffered from intellectual disability and developmental delay. He had a learning disorder as well as a language delay. His learning difficulties required special education.

Conventional cytogenetic studies gave normal results. In addition, no pathogenic copy number variation (CNV), neither gain nor loss, was identified by array-CGH (Figure 2A). Whole exome sequencing (WES) was performed on the genomic DNA of the patient using Illumina Hiseq 4000. We found a homozygous missense mutation (c.722C>A; p.Ala241Asp) in exon six of the PYCR1 gene (NM-006907), which was confirmed by Sanger sequencing (Figure 2B). Both parents were heterozygous carriers of the causative genetic variant. The patient’s clinical phenotype, along with the PYCR1 mutation, was consistent with ARCL2B.

3. Discussion

We identified a homozygous PYCR1 missense variant (c.722C>A) in an Iranian boy with intellectual disability, developmental delay, cutis laxa, and dysmorphic facial fea-
Figure 2. A. Whole genome oligo array CGH analysis. No nonpolymorphic genomic imbalance was detected. B. Sanger sequencing of the PYCR1 mutation. The pathogenic variation, c.722C>A; p.Ala241Asp, was found in homozygous state in patient and heterozygous in his parents.

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Missense mutations compose the main part of mutations causing this disease. The majority of the missense mutations were located within exons four to six, which encode the most highly conserved parts of the PYCR1 protein containing many residues involved in enzymatic function (12). PYCR1 encodes pyrroline-5-carboxylate reductase 1, a housekeeping mitochondrial enzyme, that catalyzes the last step in proline biosynthesis through NAD(P)H-dependent reduction of pyrroline-5-carboxylate (PSC) to L-proline (13).

In conclusion, this study identified a homozygous missense variant (c.722C>A; p.Ala241Asp) in a patient from a consanguineous Iranian family. PYCR1 mutations at the homozygous state results in ARCL2B. Our findings confirmed the previous two reports for ARCL2B patients with similar mutation. These results expand our insight for the clinical phenotype of ARCL2B. Further reports are required to better understand the PYCR1-related phenotypes, genotype-
Table 1. Findings in the Patient of This Study Compared with Clinical Features Described in Patients with PYCR1 Mutations at the Same Position

| Author/Reference | Dimopoulou et al. (10) | Dimopoulou et al. (10) | Dimopoulou et al. (10) | Scherer et al. (11) | Our patient |
|------------------|------------------------|------------------------|------------------------|---------------------|-------------|
| Case number      | Case 1                 | Case 2                 | Case 3                 | Case 4              | Case 5      |
| Origin           | Turkey                 | Turkey                 | France                 | Brazil              | Iran        |
| Gender           | NK                     | NK                     | NK                     | Male                | Male        |
| Mutations        |                        |                        |                        |                     |             |
| Status           | hom                    | hom                    | het, het               | hom                 | hom         |
| cDNA             | c.722C>A               | c.722C>A               | c.722C>T, c.138 + 2T>C | c.722C>T            | c.722C>A    |
| Consequence      | p.Ala241Asp            | p.Ala241Asp            | p.Ala241Val, Splicing  | p.Ala241Val         | p.Ala241Asp |
| Exon             | 6                      | 6                      | 6, 2                   | 6                   | 6           |
| Signs and symptoms |                        |                        |                        |                     |             |
| Lax wrinkled skin | NK                     | +                      | +                      | +                   | +           |
| IUGR             | NK                     | +                      | +                      | +                   | +           |
| Hypotonia        | +                      | +                      | +                      | +                   | +           |
| Psychomotor retardation | + | + | + | + | + |
| Dysmorphic features | + | + | + | + | + |
| Triangular face  | +                      | +                      | +                      | +                   | +           |
| Large ears       | +                      | +                      | +                      | +                   | +           |
| Prominent chin   | +                      | +                      | +                      | +                   | +           |
| Postnatal growth delay | NK | - | - | + | - |
| Microcephaly     | NK                     | +                      | -                      | -                   | -           |
| Joint hyperlaxity| NK                     | +                      | +                      | +                   | +           |
| Thin, translucent skin | NK | + | - | NK | + |
| Hip dislocation  | NK                     | +                      | -                      | +                   | -           |
| Hernias          | NK                     | -                      | +                      | +                   | -           |
| Cataract/corneal clouding | NK | - | - | - | - |
| Strabismus       | NK                     | -                      | +                      | NK                  | +           |
| Blue sclerae     | +                      | +                      | -                      | NK                  | -           |
| Adducted thumb   | NK                     | -                      | -                      | +                   | -           |
| Osteopenia       | NK                     | +                      | NK                    | +                   | -           |
| Wormian bones    | NK                     | +                      | NK                    | NK                  | -           |
| Late fontanel closure | NK | + | + | + | - |
| Corpus callosum dysgenesis | NK | - | NK | - | - |
| Athetoid movements | NK | - | + | - | - |

Abbreviations: het, heterozygous; hom, homozygous; IUGR, intrauterine growth retardation; NK, not known.

phenotype association, pathophysiology, and epidemiology to reach a critical number of patients for prevention or therapeutic studies.

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Footnotes

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: This study was approved by the Genetics Specialized Committee of Welfare Organization of Zanjan province.

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**Patient Consent:** Informed consent was obtained from all participants.

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