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Research Article

First Turkish Patient Diagnosed with BCL11A-Related Intellectual Disability with A De Novo Pathogenic Variant

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Abstract

Background: BCL11A-associated intellectual disability (BCL11A-ID) is a syndrome that can cause developmental delay or intellectual disability, neonatal hypotonia, microcephaly, behavioral problems, and the persistence of fetal hemoglobin without any symptoms.

Case presentation: Here, we report a 9-year-old patient with microcephaly, developmental delay/intellectual disability, behavior problems, and asymptomatic persistence of Fetal Hemoglobin (HbF). We detected a previously unreported heterozygous c.142T>C (p.Cys48Arg) variant in the BCL11A gene through exome sequencing, which leads to BCL11A-related intellectual disability. We used Sanger sequencing to confirm this genetic variant and performed a pathogenicity assessment according to ACMG.

Conclusion: We present the first Turkish patient with the rare syndrome BCL11A-ID, identified with this variant.

Keywords: BCL11A gene; BCL11A-ID; Dias-Logan Syndrome

Introduction

BCL11A-related intellectual disability (BCL11A-ID) is known as Intellectual Developmental Disorder with the Persistence of Fetal Hemoglobin or Dias-Logan Syndrome. BCL11A-ID (OMIM: 617101) is a syndrome characterized by autosomal dominant inheritance, particularly delayed psychomotor development and intellectual disability. Other clinical features include behavioral problems, language delays, microcephaly, downward-curving palpebral fissures, strabismus, external ear abnormalities, and hereditary persistence of fetal hemoglobin (HPFH) [1,2]. BCL11A-ID was identified by Dias et al., [1] revealing BCL11A gene heterozygous mutations in chromosome 2p16 region.

The BCL11A (B-cell lymphoma/leukemia 11A) gene (OMIM: 606557) plays a role in silencing fetal hemoglobin after birth by providing C2H2 zinc-finger transcription factor expression [3-5]. It is thought that BCL11A variants are the cause of neurological deficits seen in the structural and functional infrastructure of the brain as a result of their effect on C2H2 zinc-finger transcription factor expression [6]. Identification of patients with neurodevelopmental disorders diagnosed with heterozygous mutation or copy number loss of BCL11A proves the vital role of BCL11A gene function in human brain development [7-12].

Peron et al., [7] in their review of patients to date, reported 60 unique variants including 30 frameshifts, 7 missenses, 6 splicing sites, 17 stop-gains, and 8 unique CNVs (microdeletions containing only BCL11A), in 75 patients diagnosed with BCL11A-IDD [7]. Exome sequencing revealed a previously unreported heterozygous c.142T>C (p.Cys48Arg) variant in the BCL11A gene, which led to BCL11A-related intellectual disability. We present the first clinical report of these variants with the BCL11A gene mutation in the literature.

Case Presentation

A 9-year-old male patient was referred to our clinic with a language delay and ID. He was born by normal vaginal delivery with a birth weight of 3000 g at term as the third child of nonconsanguineous parents. The 9-year-old patient had microcephaly, developmental delay/intellectual disability, hypermetropia, strabismus, scoliosis, and behavioral problems. The patient's first intelligible word pronunciation was at the age of 2. The patient, who has been receiving speech therapy for five years, can pronounce simple 3-word sentences. Moreover, he had aggressive behavior, complaints of difficulty walking, and frequent falls.

The hemoglobin electrophoresis showed that the patient's HbF value was high; however, the results of the parents were normal (Figure 1). The patient's medical history includes an operation for an inguinal hernia. Additionally, cranial MRI imaging of the patient revealed hypoplasia in the lower cerebellar vermis (Figure 2).

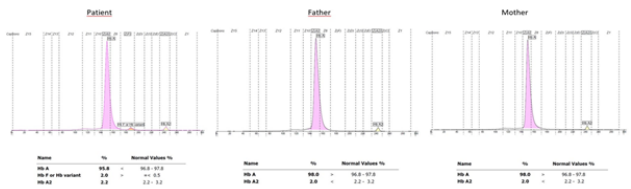

Figure 1: The hemoglobin electrophoresis showed that the patient's HbF value was high; however, the results of the parents were normal.

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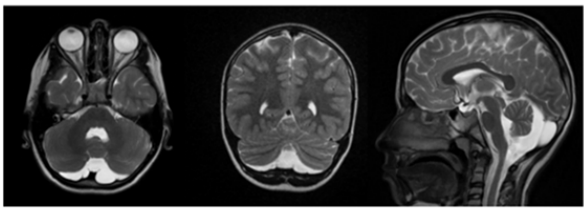

Figure 2: The patient's medical history includes an operation for an inguinal hernia. Additionally, cranial MRI imaging of the patient revealed hypoplasia in the lower cerebellar vermis.

The patient was consulted by a child psychiatrist. As a result of the psychiatric examination and psychometric examination, Kent EGY, and Porteus Mazes intelligence tests results, there was thought to be a mild delay in cognitive development.

Whole-exome sequencing (WES) revealed a previously unreported heterozygous c.142T>C (p.Cys48Arg) variant detected in exon 2 of the BCL11A gene which, led to BCL11A-related intellectual disability. Exome sequencing was performed using the Roche Kapa HyperExom Kit and the Illumina Novaseq 6000 platform. The variants were evaluated according to the American College of Medical Genetics and Genomics (ACMG) [13]. In silico tools, the REVEL score of the variant was determined as 0.943 (PP3) and the ExAC value was determined as 3.62 (PP2). No variant was detected in either parent in the segregation analysis(PM6) (Figure 3). As a result of all these evaluations; heterozygous variant c.142T>C (p.Cys48Arg) in the BCL11A gene was reported a likely pathogenic (PP3+PM6+PP2+PM2) heterozygous variant. Sanger sequencing was conducted for the patient and his parents to confirm this genetic variant and a pathogenicity assessment was performed according to ACMG.

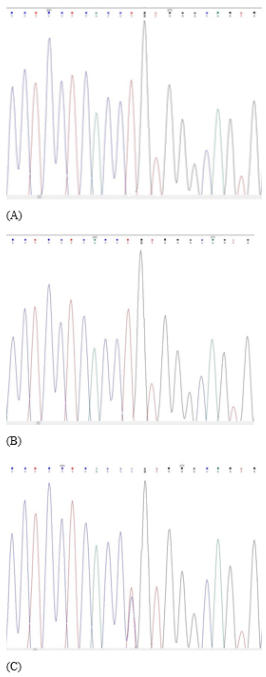

Figure 3: No variant was detected in either parent in the segregation analysis(PM6).

The patient underwent karyotype analysis, microarray, and fragile X examinations, all of which returned normal. Our patient's family history was unremarkable.

Informed consent for publication was obtained from the parents of our patient to participate in this study.

Discussion

BCL11A-ID is inherited as an autosomal dominant and occurs as a result of heterozygous variants in the BCL11A gene. BCL11A plays an important role in neurodevelopmental processes in the human brain. Moreover, BCL11A internal zinc finger domains selectively bind to g-globin promoter motifs, thus acting as a transcriptional repressor of fetal hemoglobin. Most patients may also develop ID, global delay in developmental milestones, Childhood Apraxia Of Speech (CAS), microcephaly, strabismus, flat midface, joint laxity, and persistence of HbF (OMIM: 617101) [14]. Our case involves delayed psychomotor development, ID, behavioral issues, CAS, microcephaly, strabismus, and the Hereditary Persistence of Fetal Hemoglobin (HPFH).

Of all previously reported individuals with BCL11A-ID, 73 of the 75 previous patients had a diagnosis of developmental delay and/or ID; this is the most common manifestation of the disease. The degree of ID in patients is usually moderate but varies from mild to severe/profound. The most common craniofacial findings in patients are external ear anomalies, malar flattening, thick or everted vermillion of the lower lip and thin vermillion of the upper lip, wide nose, full cheeks, and epicanthus [15-17]. Congenital anomalies such as polydactyly, cleft palate, stenosis of the pulmonary artery branches, craniosynostosis, and umbilical hernia are rarely seen. However, our patient had a congenital inguinal hernia.

BCL11A again reduces the HbF value after birth with its transcriptional repressive effect. In all patients diagnosed with BCL-11A-ID, HbF values were determined to be above the maximum reference for age in hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) results [4,7]. In light of this information, hemoglobin electrophoresis showed that our patient's HbF was high (Figure 2).

Findings such as a thin upper lip and/or an everted lower lip, microcephaly, intellectual disability, speech impairment, and behavior abnormalities have been reported in patients diagnosed with the BCL-11A-ID [1,2]. Our patient has been diagnosed with microcephaly, developmental delay/intellectual disability, hypermetropia, strabismus, and behavioral problems.

So far, Loss-of-Function (LoF) mutations in the BCL11A gene have mostly been reported, although fewer missense variants have been reported in the patients [14,18].

In conclusion, we detected a de novo heterozygous missense mutation c.142T>C (p.Cys48Arg) in the BCL11A gene in a male patient affected by ID and language delay. This case is the first Turkish patient diagnosed with BCL11A-ID with a previously unreported heterozygous variant.

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All authors have contributed significantly. All authors have revised and approved the final manuscript.

Conflict of Interest Statement

There is no conflict of interest.

Fundıng

There is no funding.

Consent

Informed patient consent was obtained.

Ethıcs Approval and Consent to Partıcıpate

Not required.

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