Heterozygous mutations in Bicaudal D2 Drosophila homolog 2 (BICD2) gene, encodes a vesicle transport protein involved in dynein-mediated movement along microtubules, are responsible for an exceedingly rare autosomal dominant spinal muscular atrophy type 2A which starts in the childhood and predominantly effects lower extremities. Recently, a more severe form, type 2B, has also been described. Here, we present a patient born to a consanguineous union and who suffered from intellectual disability, speech delay, epilepsy, happy facial expression, truncal obesity with tapering fingers, and joint hypermobility. Whole-exome sequencing analysis revealed a rare, homozygous missense mutation (c.731T>C; p.Leu244Pro) in BICD2 gene. This finding presents the first report in the literature for homozygous BICD2 mutations and its association with a Cohen-Like syndrome. Patients presenting with Cohen-Like phenotypes should be further interrogated for mutations in BICD2.

INTRODUCTION

Cohen syndrome (CHS1; MIM#216550) is a rare, autosomal recessive dysmorphic syndrome marked by microcephaly and developmental delay [1]. After the initial description by Cohen et al. in 1973 [2], additional panethnic features [3] and diagnostic criteria were established [4, 5]. Homozygous or compound heterozygous mutations in the vesicle-sorting protein, encoded by VPS13B, have been identified in most patients with the CHS1 [6, 7]. However, some patients diagnosed with “Cohen-Like” syndrome have no mutations in VPS13 gene and genetic heterogeneity was suggested [6].

Here we describe a patient with Cohen-Like syndrome harboring a homozygous, rare variant located at a conserved site in the CC1-binding domain of the Protein bicaudal D homolog 2 in a patient who lacks mutations in VPS13B and discuss under the light of relevant literature.

CLINICAL REPORT

NG1468-1 was the first child of a third-degree consanguineous union, born at 38 gestational weeks with normal spontaneous vaginal delivery (Fig. 1a). Her prenatal history was unremarkable. Her birth weight was 3200 g; head circumference and length at birth were not documented. When she was 8 years and 9 months old, she was referred to our clinic due to epilepsy, intellectual disability, and language development disorder. She could sit without support at 8 months, and began to walk after 18 months and could use 5–10 words since she was 4 years old. At the time of admission, her weight was 45 kg (+2.4 SDS), height 126 cm (−0.86 SDS), and head circumference 50 cm (−1.5 SDS). She was unable to speak fluently. She had a happy facial expression, round-shaped face, almond-shaped eyes, maxillary hypoplasia, short filtrum, open mouth, prominent incisors, narrow and high arched palate, hypermobility in her hands, and truncal obesity (Fig. 1b). Her eye consultation demonstrated astigmatism. Electroencephalography showed bilateral sharp and slow waves complex. Hearing test, routine biochemical tests, brain electric response audiometry test, electrocardiography, abdominal ultrasound, and chromosome analysis were all within normal limits. The Stanford–Binet intelligence score demonstrated moderate intellectual disability (IQ:41). Brain magnetic resonance imaging revealed cortical dysplasia, especially in fronto-temporo-parietal brain areas bilaterally (Fig. 1b). Patient’s some of the clinical findings, including developmental delay, speech delay, happy facial expression, truncal obesity with tapering fingers, and joint hypermobility were consistent with Cohen Syndrome (Table 1).

Subsequently, we performed whole-exome sequencing analysis and identified a novel homozygous, rare, missense alteration (c.731T>C) within the fourth exon of BICD2-coding sequence at position 95,482,913 on chromosome 9 (Hg19) (NM_001003800.2 (BICD2_v001):c.731T>C p.Leu244Pro) (Fig. 1a). The Leu residue at position 244 is fully conserved across vertebrates and Leu to Pro substitution is highly unfavored in terms of conserved amino acid properties (Fig. 1c) and expected to be disease associated [8]. Applying American College of Medical Genetics and...
DISCUSSION
Neomorphic mutations in BICD2 were previously associated with dominant congenital spinal muscular atrophy [13-15], while a rare (GnomAD allele frequency $6.94 \times 10^{-5}$), homozygous loss-of-function mutation (NM_015250.4:c.1823C>T (p.Ser608Leu), (rs150861652) has been previously reported by our group in a large consanguineous family [16] (Fig. 1d) (Supplementary Table 1).

Previously proposed by Kolehmainen et al. [17], patients with six out of the eight clinical criteria can be diagnosed with CHS1 with 100% sensitivity and 77% specificity [17, 18]. For patients with five or fewer criteria, suggested diagnosis is “Cohen-like syndrome” and there are no previous reports of pathogenic VPS13B mutations in this patient group [19]. Although clinical and genetic heterogeneity was reported with CHS1, to the best of our knowledge, this is the first report linking biallelic BICD2 mutations to CHS1 which led us to further evaluate previously reported four patients from a family [16].

The known clinical findings in these four reported patients were increased deep tendon reflexes and positive clonus in four, amiotropy in two, and pes equinovarus in one (Table 1). None of these findings were present in our patient may indicate pleiotropic status of biallelic BICD2 mutations.

Since BICD2 variants disrupt Golgi integrity [20], which is also a hallmark of cells with impaired cytoplasmic dynein function [21], it is interesting that both BICD2 and VPS13B are involved in vesicle trafficking, suggesting the possibility of a common pathogenic mechanism for these mutations. The happy facial expression present in this patient is also seen in AP4M1 and AP4B1 related disorders, which are genes involved in vesicular traffic, as well as CHS1 [22].

In conclusion, we suggested that the patients with a Cohen-like syndrome should be evaluated by BICD2 screening. Future therapeutic interventions in patients with Cohen syndrome...
would benefit from identification of the underlying pathophysiologic mechanisms which can be further delineated through identification of common pathways both BICD2 and VPS13B are involved in.

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COMPETING INTERESTS
The authors declare no competing interests.

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