HHS Public Access

Author manuscript

J Hum Genet. Author manuscript; available in PMC 2022 September 25.

Published in final edited form as:

J Hum Genet. 2022 September ; 67(9): 553–556. doi:10.1038/s10038-022-01032-1.

Biallelic *BICD2* Variant is a Novel Candidate for Cohen-Like Syndrome

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Abstract

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 tappering 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*.

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Conflict of interest: The authors declare that they have no conflict of interest.

Keywords

BICD2 ; Cohen Syndrome; Genetic Counseling; Whole Exome Sequencing

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 and colleagues 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 (Figure 1A). Her prenatal history was unremarkable. Her birth weight was 3200g; head circumference and length at birth was 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 45kg (+2.4SDS), height 126cm (−0.86SDS), and head circumference 50cm (−1.5SDS). 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 (Figure 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 (Figure 1B). Patient’s some of the clinical findings, including developmental delay, speech delay, happy facial expression, truncal obesity with tappering 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)(Figure 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 (Figure 1C) and expected to be disease associated [8]. Applying American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria for *BICD2*:c.731T>C, variant is detected as PM1, PM2, PP2, and PP3, leading to a likely pathogenic classification [9]. The variant is rare and predicted to be pathogenic by most of the in silico prediction tools (Supplementary Table 1), [10, 11]. No other disease-causing variants in previously reported genes, associated with her phenotypic spectrum, were identified. The patient's exome data were further analyzed for large-scale CNV events, and no disease-causing large duplications or deletions within coding regions were identified. These results further support our claim that the identified mutation in the *BICD2* is disease-causing in our index patient. Sanger sequencing of the fourth exon of *BICD2* on the patient's parents revealed that his mother and father were heterozygous for identified mutation (Figure 1A). Given the heterozygous state of the parents for the disease-causing variant, we reexamined them for neurometabolic findings reported in the literature in other patients with heterozygous *BICD2* variants. However, they were both healthy and had no evidence of abnormal neurometabolic functioning. *BICD2* is ubiquitouslly expressed in most human tissues. Using the Human Brain Transcriptome database [12], we investigated the spatial and temporal changes in the *BICD2* expression during human cortical development. *BICD2* mRNA is expressed throughout the brain with marked expression in the fetal cerebellum. This expression remains robust in the adult brain (Supplementary Figure 1)[8, 12].

Discussion

Neomorphic mutations in *BICD2* were previously associated with dominant congenital spinal muscular atrophy [13–15], while a rare (GnomAD allele frequency 6.94×10^{-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] (Figure 1D)(Supplementary Table 1).

Previously proposed by Kolehmainen et al. [17], patients with six out of the eight clinical criteteria 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank the reported family for participating in this study

Funding

This work was supported by the Yale Center for Mendelian Genomics. The Yale Center for Mendelian Genomics (UM1HG006504) is funded by the National Human Genome Research Institute. The GSP Coordinating Center (U24HG008956) contributed to cross-program scientific initiatives and provided logistical and general study coordination. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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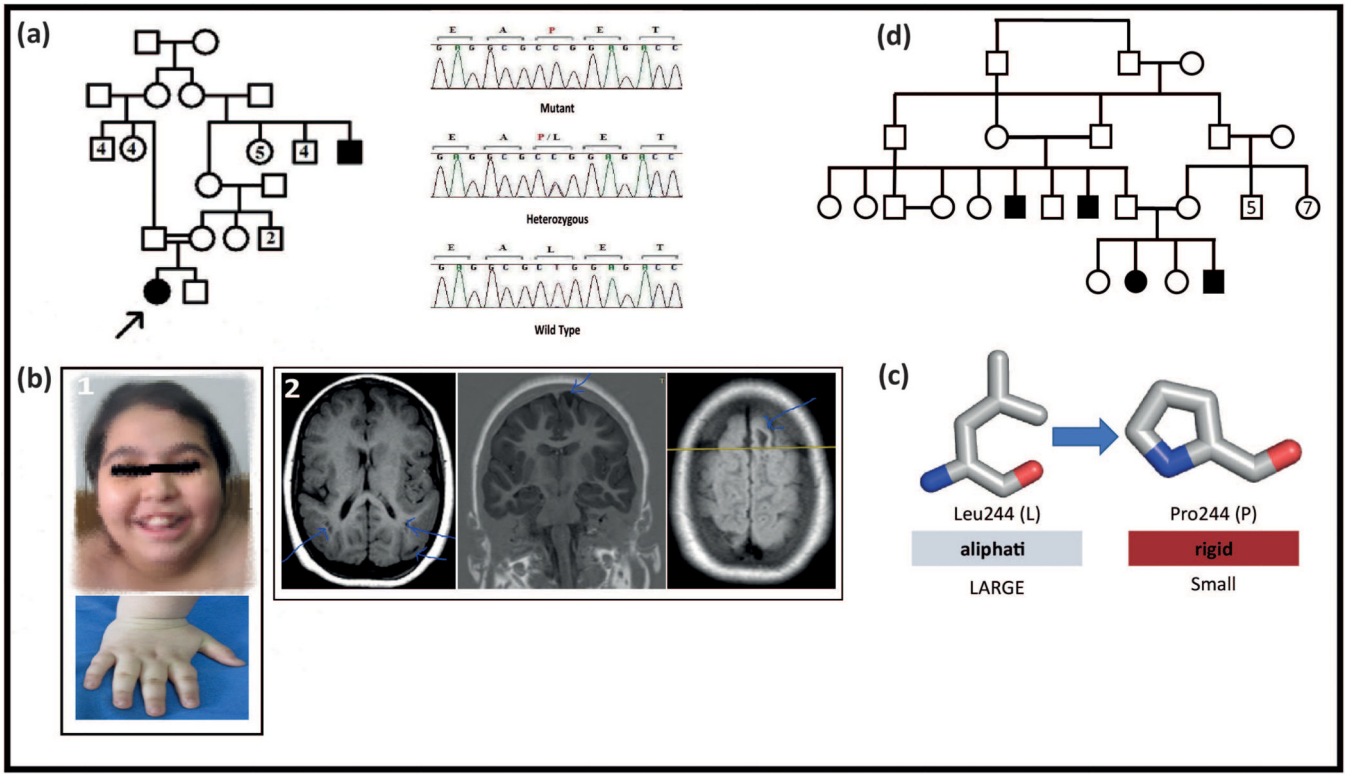

Figure 1.

A Left Panel I Pedigree of the patient reported in this study. **Right Panel I** Sanger Electropherograms of mutant, hetezygous and wild type genotypes. **B 1-Upper picture shows facial findings of the patient I** A happy facial expression, round-shaped face, maxillary hypoplasia, short filtrum, open mouth, prominent incisors are noted. Lower hand picture depicts tapering fingers. **2-Patient's MRI Findings I** Increased thickness of the cerebral cortex. Arrows depict dysplasic and cystic brain areas in the axial, coronal and flair T1-weighted planes from left to right, respectively. **C** Figure depicts the residue at sequence position 244 in BICD2 protein is a leucine which has an aliphatic side chain, which is hydrophobic. The variant residue is a proline which has a rigid side chain restricting the conformation of the protein at this point. **D** Pedigree of the previously reported Family 1370.

Table 1.

Comparison of clinical findings of the previously reported family and present patient.

Features		Previous Report (Family 1370)	Present Report (NG1468)
Number of patients		4	1
Age at last examination (years)		21/16/7/2	12yrs 7mos
Sex		3M/1F	F
Neurological Findings	**Mental and Motor Retardation**	0/4	+
	Microcephaly	Not reported	None
	Dysarthria	0/4	severe speech delay, only 5–6 words, no sentence
	Cerebellar signs	0/4	None
	Seizures	Not reported	+
	Spasticity	0/4	None
	Truncal obesity developing in mid-childhood	Not reported	+
	Reflexes (Lower Limbs)	Increased deep tendon reflexes, positive clonus (4/4)	Normal
	Amyotrophy	2/4	None
Facial Findings	**Short philtrum**	1/3	+
	Round facies	0/3	+
	Mild micrognathia	1/3	+
	Dimple of chin	0/3	+
	High, narrow palate	NA	+
	Open mouth appearance	0/3	+
	Prominent upper central incisors	NA	+
Laboratory findings	**White blood cell (N:4.8–10.8)**	Not reported	14.1
	Neutrophil (N:2.2–4.8)	Not reported	8.4
	Glucose (fasting)mg/dl	Not reported	75/80/83
	Insulin (fasting) (micU/ml; N:2.6-24.9)	Not reported	33.9/18.3
	HOMA-IR (N < 2.5)	Not reported	6.7/3.75
	HbA1c (%,N;4.8–6)	Not reported	5
	Cortisol (micg/dl; N morning:5–23)	Not reported	6.5
	TSH (micIU/L;N:0.7–5.7)	Not reported	3.45
	Free T4 (ng/Dl;N:0.7–1.9)	Not reported	1.16
	Free T3 (pg/ml;N:1.8–4.2)	Not reported	3.58
Imaging findings	**Brain MRI**	Normal (0/2)	Increased thickness of the cerebral cortex. Dysplasic and cystic brain areas.

Features		Previous Report (Family 1370)	Present Report (NG1468)
	EEG	Not reported	Bilateral sharp and slow waves complex
Musculo-Skeletal deformities		1/4 (Pes equinovarus)	Joint hyperextensibility
Miscellaneous		1/1 (short stature)	Cheerfull disposition
Variant		BICD2(NM_001003800.2): c.1823C>T (p.Ser608Leu)	BICD2(ENST00000356884.11):c.731T>C (p.Leu244Pro)