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CCDC47 gene and trichohepatoneurodevelopmental syndrome: report of the fifth and sixth cases from Saudi Arabia

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Abstract

Trichohepatoneurodevelopmental syndrome (THNS) is an ultra-rare and complex disorder affecting multiple organ systems. It is characterized by liver dysfunction, hypotonia, global developmental delay, coarse hair, and dysmorphic features. We describe two cases of THNS of Saudi origin, the fifth and sixth cases in the medical literature. Both cases presented with multiple dysmorphic features, generalized hypotonia, global developmental delay, and high liver enzyme level. Exome sequencing of Case 1 identified a pathogenic homozygous variant within the *CCDC47*: NM_020198.2:c.567_570del, p.(Glu190Profs*7). Genome sequencing of Case 2 identified two likely pathogenic heterozygous variants within the *CCDC47*: NM_020198.2:c.1327C>T, p.(Arg443*) and NM_020198.2:c.422dup, p.(Leu141Phefs*19). The trans phase of the detected variants has been confirmed by the parental testing. Furthermore, we evaluated the gene–disease association as per ClinGen guidelines and reached a strong level of association after inclusion of the new patients/variants. The findings from these cases will help to delineate the clinical phenotype and the mutational spectrum of this complex disorder.

KEYWORDS: *CCDC47*, dysmorphic features, trichohepatoneurodevelopmental syndrome

1 INTRODUCTION

The major calcium store in muscle cells is in the sarcoplasmic reticulum (Somlyo et al., 1985). Dysregulation of cellular calcium-ion concentration is known to contribute to many genetic disorders (Böhm et al., 2013; Endo et al., 2015; Misceo et al., 2014; Odermatt et al., 1996; Picard et al., 2009; Sakuntabhai et al., 1999; Shen et al., 2009; Zhang et al., 1993). Coiled-coil domain-containing protein 47 (*CCDC47*), also known as calumin, is present in several organ tissues (Zhang et al., 2007), is involved in calcium-ion homeostasis in the endoplasmic reticulum and contributes to embryonic development (Yamamoto et al., 2014; Zhang et al., 2007).

Trichohepatoneurodevelopmental syndrome (THNS) is an exceedingly rare autosomal recessive disorder, documented in only four cases worldwide and extensively detailed by Morimoto in a single scientific publication. It manifests across multiple organ systems, featuring liver dysfunction, hypotonia, global developmental delay, and distinctive dysmorphic characteristics. Morimoto et al. (2018) delineated this complex multisystem disorder in four unrelated children, all displaying dysmorphic facial features such as coarse facies, ptosis, downturned mouth, and simple ears, along with aberrant hair texture including coarseness, woolliness, or curliness. Common features among all cases encompassed microcephaly, brachycephaly, severe global developmental delay, liver dysfunction, pruritus, hypotonia, joint laxity or distal arthrogryposis, nipple hypoplasia, and overlapping toes. Additionally, midface hypoplasia, hypertelorism, dental abnormalities, plagiocephaly, narrow chest, hip dysplasia, and bilateral clubfoot were prevalent in most cases. Furthermore, patients exhibited severe developmental delay, being nonverbal with generalized hypotonia between the ages of 5 and 8, with neuroimaging revealing cerebral atrophy in all cases and abnormal ventricular morphology in three. Immunodeficiency with recurrent infections was noted in two patients. Morimoto et al.'s comprehensive analysis underscored the diverse clinical presentations within affected individuals, elucidating the intricate nature of THNS (Morimoto et al., 2018).

Here, we report the fifth and sixth cases of THNS in the medical literature, with a view to establishing the core clinical features of this phenotypically variable complex multisystem disorder and expand the mutational spectrum of *CCDC47*.

2 CASE PRESENTATION

2.1 Case 1

The case is a 32-month-old female, born at 39 weeks of gestation via normal spontaneous vaginal delivery (NSVD), with a birth weight of 1.5 kg. She was considered small for the gestational age. At birth, she was admitted to the neonatal intensive care unit for 20 days due to congenital heart disease associated with episodes of oxygen desaturation. She was born to parents who are first-degree cousins of Saudi origin. They have two healthy children. The patient's paternal uncle, who died aged 6 years, exhibited developmental delay, hypotonia, and brain atrophy, but was not assessed.

The mother first noticed poor feeding, hypotonia, and developmental delay 6 months after the patient's birth. The patient is currently developmentally delayed, has no head control, sits with support, cannot grasp objects, and is nonverbal. She is below the third percentile for all growth parameters. Specifically, her head circumference measures 44 cm (placing her below the first percentile with a deviation of -2.8 standard deviations), her weight is 7.88 kg (also below the first percentile with a deviation of -4.3 standard deviations), and her height is 79.5 cm (falling below the first percentile with a deviation of -3.4 standard deviations).

Her dysmorphic facial features include microcephaly, coarse hair, telecanthus, long eyelashes, ptosis, haziness and redness of the eyes, low-set ears, bulbous nasal tip, smooth philtrum, downturned mouth, and dental abnormalities (Figure 1). The ophthalmologic evaluation showed conjunctivitis and glaucoma in the left eye. Neurologically, she exhibits supine frog-leg position, hyporeflexia, and generalized hypotonia.

Magnetic resonance imaging of the brain showed mild generalized brain volume loss in the form of prominent intra- and extra-axial cerebrospinal fluid space. An echocardiogram showed a dysplastic pulmonary valve with moderate to severe pulmonary stenosis and moderate pulmonary insufficiency. Moreover, it showed mild mitral and tricuspid regurgitation. Abdominal ultrasound revealed cholelithiasis with no sign of inflammation and grade II right hydronephrosis. A skeletal survey demonstrated dextroscoliosis of the thoracic spine and diffuse rib expansion. Laboratory findings showed normal basic metabolic workup, including plasma amino acid, urine organic acid, ammonia, lactic acid, and tandem mass spectrometry. In the evaluation of liver function, notable abnormalities were observed. The direct bilirubin level was measured at $39.3 \mu\text{mol/L}$, surpassing the upper limit of the reference range ($\sim 8.6 \mu\text{mol/L}$). Similarly, the total bilirubin level was notably elevated at $52.8 \mu\text{mol/L}$, exceeding the upper reference value of $20.5 \mu\text{mol/L}$. Alkaline phosphatase activity was significantly elevated at 359 U/L , compared to the upper reference limit of 369 U/L . Gamma-glutamyl transferase was notably elevated at 182 U/L , above the upper reference limit of 36 U/L . Furthermore, alanine aminotransferase and aspartate aminotransferase (AST) levels were elevated at 108 and 96 U/L , respectively, surpassing their respective upper reference limits of 55 and 34 U/L . These findings suggest substantial hepatic dysfunction. The phenotypic characteristics of this case are summarized in Table 1.

With respect to genetic analysis, karyotype and fluorescence in situ hybridization findings were negative. However, exome sequencing of the case, performed at CENTOGENE (Trujillano et al., 2017), identified a likely pathogenic homozygous frameshift variant within the *CCDC47*: NM_020198.2:c.567_570del, p.(Glu190Profs*7), class 1. We did not detect any other clinically relevant variants in this patient. These findings are consistent with the genetic diagnosis of autosomal recessive THNS. The case's unaffected parents were heterozygous for the frameshift variant, confirming the homozygosity of the variant in the index case.

2.2 Case 2

The case is a 14-month-old female, born at 37 weeks of gestation via NSVD, with no history of admission to the neonatal intensive care unit or any neonatal complication. She was born to nonconsanguineous parents of Saudi origin. The parents first noticed hypotonia and developmental delay at 1 month of life. The patient is currently developmentally delayed, sits with support, cannot pull to stand, can transfer object from hand to hand, but still exhibits no premature pincer grasp, and is nonverbal. Her growth parameters are notable, with a head circumference measuring 50.50 cm (>99th percentile with a standard deviation of +3.4), weight of 13 kg (>99th percentile with a standard deviation of +2.5), and height of 96 cm (>99th percentile with a standard deviation of +6.8). Her dysmorphic facial features include macrocephaly, frontal bossing, synophrys, telecanthus, long eyelashes, broad nasal bridge and bulbous nasal tip, smooth philtrum, thin upper lip, tented mouth, brittle teeth, and low-set ears (Figure 2). The ophthalmologic evaluation showed pseudo-strabismus. Neurologically, she exhibits hyporeflexia and generalized hypotonia.

Magnetic resonance imaging of the brain and whole spine was unremarkable. Abdominal ultrasound revealed bilateral prominent ovarian follicles; otherwise, unremarkable abdominal ultrasound. A skeletal survey was unremarkable. Laboratory findings showed that liver function appears normal, with the exception of a mildly elevated level of AST, which is 42 U/L. The phenotypic characteristics of this case are summarized in Figure 2 and Table 1.

Genome sequencing of the case at CENTOGENE (Bertoli-Avella et al., 2021) identified two likely pathogenic heterozygous variants within the *CCDC47*, class 2. The first variant creates a premature stop codon and the second variant is a frameshift in exon 12 out of 13 in a position distal to previously reported variants but predicted to result in nonsense mediated messenger ribonucleic acid (mRNA) decay, both variants are absent from gnomAD, NM_020198.2:c.1237C>T, p.(Arg443*) and NM_020198.2:c.422dup, p.(Leu141Phefs*19).

The trans phase of the detected variants was confirmed by parental testing; the first variant was identified in the father in a heterozygous state and the second in the mother in a heterozygous state.

Only four variants have been described as causative for THNS in the literature: c.811C>T, p.(Arg271*); c.1145delT, p.(Leu382Argfs*2); c.1165delT, p.(Ser389Leufs*25); and c.1189C>T, p.(Arg397*) (Morimoto et al., 2018). An additional pathogenic variant has been reported in ClinVar/Decipher, c.563del, p.(Asn188fs). Therefore, we evaluated the gene–disease association evidence following the ClinGen Clinical Validity Framework guidelines used to standardize the annotation of genes to new diseases. According to the guidelines, the strength of evidence for gene–disease association can be categorized as definitive, strong, moderate, limited, or no known disease relationship (DiStefano et al., 2022; Strande et al., 2017). A total number of needed points for definitive and strong association according to the framework is 12–18, for moderate association 7–11, and for limited gene-validity 1–6 points. So far, for *CCDC47*, a moderate level of association was reached (nine points), considering the genetic evidence (Morimoto et al., 2018) and ClinVar/Decipher, and experimental data (Morimoto et al., 2018; Yamamoto et al., 2014). We then analyzed the patients in our Biodatabank and reached a total of 13 points which corresponds to a strong level of gene–disease association for *CCDC47*. The new variants/patients reported in this work: c.567_570del, p.(Glu190Profs*7); c.1327C>T, p.(Arg443*); and c.422dup, p.(Leu141Phefs*19), and additional variants c.661C>T, p.(Gln221*); c.1234C>T, p.(Arg412*) were identified in patients with overlapping phenotypes.

3 DISCUSSION AND CONCLUSION

The calumin protein encoded by *CCDC47* is present in multiple organs and systems and plays an important physiological role during embryogenesis and development. It is important for the maintenance of Ca^{2+} homeostasis and signaling in the endoplasmic reticulum. Ca^{2+} signaling regulates a number of cellular processes including synaptic vesicle exocytosis, muscle contraction, transcription, regulation of secretions, and cellular proliferation. Since Ca^{2+} signaling is a multipurpose intracellular signaling system that regulates a number of cellular processes, dysregulation of Ca^{2+} signaling due to *CCDC47* dysfunction may contribute to significant neurological, cardiac, and hepatic abnormalities. In mice, homozygous knockout of *Ccdc47* results in midgestation lethality with embryos displaying developmental delay and cardiovascular abnormalities resulting from yolk sac dysfunction (Yamamoto et al., 2014).

Morimoto et al. reported four cases of THNS caused by biallelic variants in the *CCDC47* (Morimoto et al., 2018). Morimoto et al. reported that loss of *CCDC47* expression leads to impaired endoplasmic reticulum Ca^{2+} storage and signaling, which in turn culminates in THNS (Morimoto et al., 2018). The current cases and the additional variants reported here support the notion that loss of *CCDC47* leads to THNS. Furthermore, our cases help to determine the core clinical features of this disorder.

Both of the cases in this study, and the four cases reported by Morimoto et al., presented with decreased body weight, unusual hair, coarse facies, ptosis, unusual nose, downturned mouth, ear abnormalities, hypotonia, and liver dysfunction suggesting these may be central features associated with calumin deficiency. Other commonly observed features associated with the six cases include hypertelorism, full or thick lips, dental abnormalities, ocular findings, and cerebral atrophy. The facial gestalt of our cases and the previous reported by Morimoto et al. is also similar. In our study, it was noted that both subjects underwent NSVD, which is a notable deviation from the cesarean deliveries exclusively reported in prior literature.

Furthermore, both cases exhibited additional ocular abnormalities, specifically glaucoma or strabismus. Additionally, while previous documented cases consistently presented with microcephaly, the second case in our study demonstrated macrocephaly.

Moreover, the first case in our article showcased various cardiac anomalies, including dysplastic pulmonary valve, pulmonary stenosis, and mitral and tricuspid regurgitation. This case also featured skeletal abnormalities, such as diffuse rib expansion.

Remarkably, neither of our cases displayed the array of associated features noted, including a high-arched palate, bilateral otitis media, and bitemporal narrowing.

Our findings substantiate the between impaired biallelic loss-of-function variants in *CCDC47* and clinical features of THNS and help to clarify which features are most frequently observed. Furthermore, formal gene–disease association evaluation reached a strong level of association confirming the causal role of *CCDC47*. Patients presenting with the above constellation of symptoms might be screened for pathogenic genetic variants within *CCDC47*.

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AUTHOR CONTRIBUTIONS

Najlaa A. Alsubeeh wrote the original manuscript. Aida Bertoli-Avella and William Davies supported in drafting the manuscript. Emir Zonic and Swathi Anikar performed the genetic analyses. Mohammed A. Almuqbil helped in taking the consent and photos for the patient and helped in drafting the manuscript. Wafaa M. Eyaid supervised the overall research, preparing the manuscript reading, and approving the final manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

AB-A, SA, and EZ are employees of CENTOGENE GmbH. All other authors declare no conflicts of interest.

Figures:

Figure 1. The patient presents with dysmorphic facial features, including coarse hair, telecanthus, long eyelashes, low-set ears, a bulbous nasal tip, a downturned mouth, and dental irregularities



Figure 2. The patient exhibits dysmorphic facial traits such as a prominent forehead, telecanthus, elongated eyelashes, a broad nasal bridge, a bulbous nasal tip, a tented mouth, fragile teeth, and low-set ears.



Table 1. Summary of Clinical Features of patients with Bi-allelic Loss-of-Function CCDC47 Variants						
Clinical Features	Four cases presented by Morimoto et al ⁽¹²⁾				2 new cases presented in this paper by Alsubeeh et al	
	Case 1	Case 2	Case 3	Case 4	Case 1	Case 2
Perinatal History						
Delivery	C-section	C-section	C-section	C-section	NSVD	NSVD
Premature birth	+	term	term	term	term	term
Birth weight (%ile)	75th	NA	<3rd	10th	<3rd	<3rd
Growth Parameters						
Decreased body weight	+	+	+	+	+	+
Microcephaly	+	+	+	+	+	Macrocephaly
Physical Findings						
Coarse facies	+	+	+	+	+	+
Midface hypoplasia	+	+	+	-	-	-
Hypertelorism	+	+	+	-	+	+
Almond-shaped palpebral fissure	+	+	-	-	-	-
Epicanthal folds	-	-	+	-	-	-
Ptoisis	+	+	+	+	+	+
Long eyelashes	+	+	-	-	+	+
Synophrys	+	-	+	+	-	-
Ectropion	+	+	-	-	-	-
Unusual nose	+	+	+	+	+	+
Downturned mouth	+	+	+	+	+	+
Macrostomia	-	+	Wide mouth	-	Wide mouth	Wide mouth
Macroglossia	-	+	+	+	-	-
Full or thick lips	+	+	+	+	-	+
Dental abnormalities	+	-	+	+	+	+
High arched palate	+	+	+	+	-	-
Ear abnormalities	+	+	+	+	+	+
Bilateral otitis media	+	+	+	+	-	-
Bitemporal narrowing	-	+	+	+	-	-
Brachycephaly	+	+	+	+	-	-
Plagiocephaly	+	+	+	-	-	-
Pruritus	+	+	+	+	+	-
Unusual hair	+	+	+	+	+	+
Thoracic hypertrichosis	+	+	+	+	-	-
Fifth digit hypoplasia and/or clinodactyly	+	+	+	+	-	-
Dystrophic nails	-	-	+	-	-	-
Overlapping toes	+	+	+	+	-	-
Distal arthrogryposis / joint laxity	+	+	+	+	-	-
Hypoplastic nipples	+	+	+	+	-	-
Genital anomaly	+	+	-	-	-	-
Musculoskeletal Findings						
Hypotonia	+	+	+	+	+	+
Bilateral hip dislocation	+	+	ND	-	-	-
Hip dysplasia	+	+	+	ND	-	-
Bilateral coxa valga	+	+	ND	ND	-	-
Abnormal bone density	+	+	ND	ND	-	-
Narrow chest	+	+	-	-	-	-
Diffuse rib expansion	-	-	-	-	+	-
Fibular bowing	+	+	-	-	-	-
Genu valgum	-	-	+	-	-	-
Bilateral clubfoot	+	+	-	+	-	-
Small feet	+	+	+	+	-	-
Pectus excavatum	+	-	-	+	-	-
Scoliosis	-	+	+	-	+	-
Ocular Findings						
Hyperopia	+	NA	-	+	-	-
Astigmatism	+	NA	-	-	-	-
Cortical visual impairment	+	NA	+	+	-	-
Glaucoma	-	-	-	-	+	-
Pseudo strabismus	-	-	-	-	-	+
Immunological Findings						
Recurrent infections	-	+	+	-	-	-
Immunodeficiency	-	+	+	-	-	-

Endocrine Findings						
Hypothyroidism	-	NA	+	-	-	-
Rickets	-	+	+	-	-	-
Respiratory Findings						
Obstructive sleep apnea	+	+	+	-	-	-
Central sleep apnea	+	NA	+	-	-	-
Heart Findings						
Ventricular septal defect	-	+	-	-	-	-
Patent ductus arteriosus	+	+	-	-	-	-
Dysplastic pulmonary valve	-	-	-	-	+	-
Pulmonary stenosis	-	-	-	-	+	-
Mitral and tricuspid regurgitation.	-	-	-	-	+	-
Gastrointestinal Findings						
Hepatosplenomegaly	+	-	+	-	-	-
Liver dysfunction	+	ND	+	+	+	+
Recurrent pancreatitis	+	NA	-	-	-	-
Exocrine pancreatic insufficiency	+	NA	-	-	-	-
Gastroesophageal reflux	+	NA	+	+	+	-
Steatorrhea	+	+	-	-	-	-
Chronic diarrhea	-	+	-	+	-	-
Gallstone	+	-	-	+	+	-
Gastrostomy tube	+	-	+	+	-	-
Elevated bile acids	+	NA	+	+	-	-
Renal Findings						
Renal abnormalities	+	+	-	-	+	-
Neurological Findings						
developmental delay in the milestones	+	+	+	+	+	+
Hyperreflexia	-	-	+	+	-	-
Reduced tendon reflexes	+	+	-	-	+	+
Absent Achilles reflex	+	+	-	-	-	-
Behavioral issues	-	-	+	+	-	-
Seizures	-	NA	+	-	-	-
EEG abnormalities					-	-
Neuroimaging Findings						
Abnormal ventricle morphology	+	+	-	+	-	-
Abnormal corpus callosum	+	--		+	-	-
Cerebral atrophy	+	+	+	+	+	-
White matter abnormalities	-	-	-	+	-	-
Cerebellar hypoplasia	-	-	-	+	-	-
Abbreviations: + present; – absent; C-section, Caesarean section; NA, not available; ND, not done; NSVD, normal spontaneous vaginal delivery						