Patient with a heterozygous pathogenic variant in CSNK2A1 gene: A new case to update the Okur–Chung neurodevelopmental syndrome

Albin Blanc | Céline Bonnet | Marion Wandzel | Virginie Roth
Yannis Duffourd | Hanna Safranou | Bruno Leheup | Florence Muller
Julie D Colne | François Feillet | Emmanuelle Schmitt | Matheus Castro
Jullian Savatt | Adriano Burcheri | Christophe Nemos
Christophe Philippe | Laëtitia Lambert

1Service de génétique clinique, CHRU de Nancy, Nancy, France
2Laboratoire de génétique médicale, CHRU Nancy, Nancy, France
3Université de Lorraine, INSERM UMR_S1256, NGERE, Nancy, France
4Unité Fonctionnelle Innovation en Diagnostic génomique des maladies rares, CHU Bourgogne, Dijon, France
5Université de Bourgogne, INSERM UMR_1231 GAD, Dijon, France
6Service de Chirurgie orthopédique infantile, CHRU Nancy, Nancy, France
7Service d'Ophthalmonologie, CHRU Nancy, Nancy, France
8Centre de Référence des maladies métaboliques, CHRU Nancy, Nancy, France
9Service de Radiologie, CHRU Nancy, Nancy, France
10Mendelics Genomic Analysis, São Paulo, Brazil
11Medical Genetics Unit, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo HCFMUSP, São Paulo, Brazil
12Autism & Developmental Medicine Institute, Danville, Pennsylvania, USA
13Département de Biopathologie - Anatomie et Cytologie Pathologiques, CHRU de Nancy, Nancy, France
14Laboratoire de fœtopathologie et de placentologie, CHRU Nancy, Nancy, France
15Département d'histologie, embryologie et cytogénétique de la faculté de médecine, Université de Lorraine, Nancy, France
16Département de Génie Biologique Santé de l'IUT Nancy-Brabois, Université de Lorraine, Nancy, France
17Université de Lorraine Biofonctionnalités et Risques Neurotoxiques (Calbinotox), Nancy, France

Abstract
The autosomal dominant Okur–Chung neurodevelopmental syndrome (OCNDS: OMIM #617062) is a rare neurodevelopmental disorder first described in 2016. Features include developmental delay (DD), intellectual disability (ID), behavioral problems, hypotonia, language deficits, congenital heart abnormalities, and non-specific dysmorphic facial features. OCNDS is caused by heterozygous pathogenic variants in CSNK2A1 (OMIM *115440; NM_177559.3). To date, 160 patients have been diagnosed worldwide. The number will likely increase due to the growing use of exome sequencing (ES) and genome sequencing (GS). Here, we describe a novel OCNDS case.
patient carrying a CSNK2A1 variant (NM_177559.3:c.140G>A; NP_808227.1:p. Arg47Gln). Phenotypically, he presented with DD, ID, generalized hypotonia, speech delay, short stature, microcephaly, and dysmorphic features such as low-set ears, hypertelorism, thin upper lip, and a round face. The patient showed several signs not yet described that may extend the phenotypic spectrum of OCNDS. These include prenatal bilateral clubfeet, exotropia, and peg lateral incisors. However, unlike the majority of descriptions, he did not present sleep disturbance, seizures or gait difficulties. A literature review shows phenotypic heterogeneity for OCNDS, whether these patients have the same variant or not. This case report is an opportunity to refine the phenotype of this syndrome and raise the question of the genotype-phenotype correlation.

KEYWORDS
CK2α, CSNK2A1, genotype-phenotype correlation, Okur–Chung neurodevelopmental syndrome

1 | INTRODUCTION

The autosomal dominant Okur–Chung neurodevelopmental syndrome (OCNDS, OMIM #617062) is a rare genetic disorder of dominant expression caused by heterozygous pathogenic variant in the Casein kinase II subunit alpha gene, CSNK2A1 (OMIM *115440; NM_177559.3) localized in 20p13. Approximately 160 patients have been diagnosed to date (www.csnk2a1foundation.org). This syndrome was first described in 2016 (Okur et al., 2016). A complete review of the literature reveals that there is no real consensus concerning the phenotypic spectrum of OCNDS (Akahira-Azuma et al., 2018; Jafari Khamirani et al., 2022; Nakashima et al., 2019; Owen et al., 2018). Patients with OCNDS frequently have nonspecific clinical features, including generalized hypotonia starting in infancy, feeding difficulties, speech and motor delay, mild-to-moderate range intellectual disability, and nonspecific dysmorphic facial features (Wu et al., 2020, 2021). Developmental delay affects all areas of development, but language is more impaired than gross motor skills in most individuals. Intellectual disability (ID) has been reported in about three-quarters of individuals. Less common findings may include congenital heart abnormalities, kyphoscoliosis, postnatal short stature, disrupted circadian rhythm leading to sleep disturbance, seizures, and poor motor coordination (Trinh et al., 2017; Owen et al., 2018; Zhao et al., 2023; Belnap et al., 2023). To date, genotype-phenotype correlation for OCNDS is not clearly established (Duan et al., 2019; Wu et al., 2021) and needs to be confirmed. Here, we describe a patient with the previously described 140G>A heterozygous pathogenic variant in CSNK2A1 (NM_177559.3) leading to an Arg47Gln substitution (NP_808227.1) identified by exome sequencing (ES). His phenotype differs from previous descriptions, whether these patients have the same variant or not (Chiu et al., 2018; Okur et al., 2016; Owen et al., 2018). Indeed, our patient does not report sleep disturbance, seizures or gait difficulties and does not have scoliosis, kyphosis, or hyperextensible joints. Interestingly he presents clinical signs not yet described in the OCNDS including: prenatally diagnosed clubfeet, divergent strabismus and peg lateral incisors. This case report is an opportunity to refine the phenotype of this syndrome and raise the question of the genotype-phenotype correlation.

2 | CASE REPORT

We describe a 7-year-old French Caucasian male with ID, motor and speech delay, severe growth retardation, behavioral problems, distinctive facial features, and abnormal brain MRI (Magnetic Resonance Imaging) findings. The patient is the fifth child of non-consanguineous parents. He was born after a spontaneous vaginal delivery at 39 weeks of gestational age. At conception, his father was 42 years old and his mother was 34 years old, both had learning disabilities. During pregnancy, bilateral clubfeet were highlighted by fetal ultrasound examination. In contrast to normal birth weight (2170 g, –1.3 Standard Deviation [SD] according to World Health Organization Growth Standards and Growth Reference 2007 charts), he presented with neonatal short stature (45 cm, –2.6 SD), and microcephaly (30 cm, –3 SD). His Apgar scores were 9 at 1 min and 10 at 5 min after birth. The neonatal physical examination revealed generalized hypotonia, and severe congenital talipes equinovarus feet. A hip dislocation was excluded by hip ultrasound examination. Clubfeet were treated at 1 month and 2 weeks, by the Ponseti method (by using manipulation, casting, and heel cord tenotomy). At the age of 1 year and 2 months the patient was referred for strabismus. On ophthalmological examination, he presented divergent strabismus without ophthalmoplegia, induced increased tear lake, and a scleral show. Fundus ophthalmoscopy was normal. Exotropia was treated by orthoptic rehabilitation. Due to postnatal short stature and neurodevelopmental disorder, he was referred to a clinical geneticist at 1 year and 9 months. Concerning anthropometric data, the patient’s weight, length, and head circumference were 7.38 kg (–1.06 SD), 76 cm (–2.84 SD), and 43.5 cm (–4.45 SD) corresponding to an aggravation of his microcephaly. The Body Mass Index (BMI) has been evaluated...
at 12.77 kg/m² (−2.69 SD). The physical examination revealed several
dermal features including ocular proptosis with relative
oblitration of the orbital rim, microcephaly, low set ears, small and
slightly spaced teeth, and thin vermilion of the upper lip with down-
turned corners of the mouth, smooth philtrum, hypertelorism, and
facial hypotonia responsible for amimia. (Figure 1).

Chromosomal microarray analysis was performed on patient
DNA. Parental DNA were analyzed by qPCR for variant segregation.
Chromosomal microarray analysis showed a paternally inherited het-
erozygous interstitial duplication at locus 22q13.32 of 18 kb in mini-
imum size and 31 kb in maximum size including the intron 2 of the
TAFA5 gene (arr[GRCh38] 22q13.32(48682824–48700863 in mini-
imum size and 48675294–48706607 in maximum size x3)). This dupli-
cation seems not related to the patient’s phenotype and is classified
as a variant of uncertain significance (VUS).

MRI analysis showed a ventriculomegaly (fourth ventricle too visi-
able for the age as well as spaces of Virchow Robin) with a white mat-
ter hypoplasia (Figure 2).

At 1 year and 10 months an iron deficiency was detected, supple-
mentation was followed by metabolic tests evaluation including
plasma dosage of CPK (creatine phosphokinase), T3 (triiodothyronine),
T4 (thyroxine), TSH (thyroid stimulating hormone), and creatinine. All
of these examinations were found to be normal. Moreover, urinary
organic acid and urinary amino acid chromatographies were normal.
His neurodevelopmental trajectory, was marked by delayed language
development, and motor delay. The holding of the head, and the sit-
ting position were acquired, respectively, at 1 year and 1 year
and 4 months. He walked at 2 years, and his first words were spoken at
4 and a half years. The development of eating, sleeping and sphincter
control were present, although delayed. No disturbances were noted.
in social interaction. At the age of 4 years and 5 months during a follow-up consultation with a clinical geneticist, several diagnostic hypotheses have been put forward including myotonic dystrophy (DM1, #160900). This diagnostic hypothesis was motivated by facial hypotonia, developmental delay and bilateral equine varus clubfeet. The physical examination revealed that the weight, length, and head circumference were 10 kg (−3 SD), 91 cm (−3.25 SD), and 45 cm (−5 SD). The BMI was 12 kg/m² (−2.7 SD). We therefore noticed that the microcephaly has continued to worsen. Thus, it was prescribed a trio ES (the patient and his parents) was performed. It revealed a pathogenic variant (class 5 according to the classification of ACMG (American College of Medical Genetics and Genomics)) in the CSNK2A1 gene (Table S1). The variant NM_177559.3 (CSNK2A1:c.140G>A p. (Arg47Gln)) located in the first exon of CSNK2A1. This disease-causing variant is de novo and has been previously submitted to the ClinVar database six times (Variation ID: 224796, our patient was recorded with Accession: SCV000803834.1). This result led to the diagnosis of OCNDS.

3 | DISCUSSION

Patients with OCNDS frequently present with behavior problems including stereotypic movements, autism spectrum disorder, aggressiveness and tantrums, and attention-deficit/hyperactivity disorder. Nonspecific dysmorphic features are described including micrognathia, low-set ears, folded ears, hypertelorism, epicanthal folds, arched eyebrows, synophrys, ptosis, broad nasal bridge, upturned nose, high palate, thin upper lip and a round face (Wu et al., 2020, 2021). Clinical history often reveals generalized hypotonia in infancy and/or in childhood (Colavito et al., 2018; Okur et al., 2016). Brain MRI can show delayed myelination, smaller anterior pituitary gland, or thin corpus callosum (Akahira-Azuma et al., 2018; Martinez-Montesey et al., 2020; Wu et al., 2021). Congenital heart abnormalities have been also described in one-third of patients (Owen et al., 2018; Trinh et al., 2017; Zhao et al., 2023). Slow growth, failure to thrive, or difficulty gaining weight are very common (Okur et al., 2016; Seo et al., 2020). Postnatal short stature is generally between −2 and −3 SD. Microcephaly is reported in approximately 57% of patients, typically ranging between −1 and −3 SD (Akahira-Azuma et al., 2018; Chiu et al., 2018; Okur et al., 2016; Trinh et al., 2017). Here, we report a new patient with a heterozygous pathogenic variant in CSNK2A1 that partially shares common features with previously reported patients. All the reported patients have a mild-to-moderate developmental delay or intellectual disability, similar to our patient. Speech delay is the most prevalent clinical symptom. Unlike the majority of patients in the literature, this patient does not report sleep disturbance, seizures, gait difficulties, congenital heart abnormalities and he does not have scoliosis, kyphosis or hyperextensible joints. Our patient exhibits microcephaly (−5 SD) more severe than that typically described in Okur–Chung syndrome. However, since these signs are usually reported later in life, the patient may not yet be old enough. In this case, we report new clinical features that had not previously been described not only in patients with the same pathogenic variant, but also across the entire phenotypic spectrum of OCNDS. These clinical findings include prenatally diagnosed clubfeet, divergent strabismus, and peg lateral incisors. This highlights the need to extend the phenotypic description of this syndrome. We report that our patient presents a single nucleotide variant (NM_177559.3 (CSNK2A1:c.140G>A (p. Arg47Gln)) located in the first exon of CSNK2A1. CSNK2A1 gene is involved in OCNDS and encodes the alpha subunit of casein kinase 2 protein (CK2). CK2 is composed of 2 catalytic (α and α') and 2 regulatory subunits (β) (Niefind et al., 2001). In 2021, literature review by Wu et al. (2021) identified 12 studies describing 35 CSNK2A1 variants in various protein-coding regions of CK2a. CK2a contains three conserved functional domains an N-terminal ATP/GTP binding motif, a basic cluster, and a C-terminal activation domain (Niefind et al., 2001). By quantitatively analyzing data related to these CSNK2A1 variants and their phenotypes, it was showed that variants in protein-coding CK2a regions appear to influence the phenotypic spectrum of OCNDS. Mutations altering the ATP/GTP-binding loop were more likely to cause the widest range of phenotypes (Wu et al., 2021). As is the case in our present description. Interestingly the same variant has been submitted to ClinVar database six times and described three times in PubMed (Chiu et al., 2018; Okur et al., 2016; Owen et al., 2018) (Table S2). We can then attempt to identify a genotype-phenotype correlation related to this protein domain. The first description was given by Okur et al., 2016 (Patient 1, ClinVar: Variation ID224796 Accession: SCV00297877.1). The patient was a 6 years old female. She shared with our proband several clinical features (intellectual disability, developmental delay, microcephaly, post-natal short stature, and hypotonia). She had also a brain MRI abnormality but different from our patient, a global pachygyria in her case. Her facial dysmorphism overlapped with our description (hypertelorism and low set ears). However, she had several facial features not present in our patient, including a high palate, micrognathia, ptosis, and arched eyebrows. She distinguished herself at the level of the extremities by presenting a fifth finger clinodactyly, brachydactyly, and unilateral single palmar crease. Other symptoms differed from our case such as umbilical hernia at birth and cutis marmorata. In 2017, Savatt diagnosed OCNDS in an American 9 years old boy with the same disease-causing variant. (Patient 2, ClinVar: Variation ID: 224796 Accession: SCV001443592.1). The patient’s phenotype has not been published so far. The phenotypic description was provided by Savatt. It included feeding difficulties in infancy, generalized hypotonia, microcephaly, seizure precipitated by febrile infection and otitis media. Owen et al., 2018 described another patient presenting the same pathogenic variant (Patient 3, ClinVar: Variation ID: 224796, Accession: SCV002768376.1). The subject was a 6 years old male presenting with a similar phenotype as the present case, neonatal hypotonia, feeding difficulties, ID, and speech delay. Nevertheless, he had no behavior problems or seizures. The brain MRI performed was normal. Chiu et al., 2018 published, the description of a 2-year-old girl
whose phenotype is overlapping with case (Patient 4, Variation ID: 224796. Accession: SCV00212356.1). It includes global developmental delay, microcephaly short stature, and hypertelorism. Differences include dystrophic pulmonary valve, butterfly vertebrae, cholestataoma, single palmer crease, long and thin fingers, generalized joint laxity, widely spaced nipples, kyphosis, gingival hypertrophy, and febrile seizures. Interestingly her brain MRI showed vermian hypoplasia and thin non-dysplastic corpus callosum. Finally, Castro in 2019 made the diagnosis of OCNDs in a Brazilian 5 years old boy with the same pathogenic variant (Patient 5, ClinVar: Variation ID: 224796, Accession: SCV001142176.1). That description has not yet been published. The phenotypic description was shared by Castro. He presents a global developmental delay with autistic features, epilepsy, hypopigmentation and facial dysmorphism (long face, anteverted ears and open mouth with protruding tongue). A cardiac ultrasound showed membranous ventricular septal defect and a brain MRI with hypoplasia of the lower portion of the cerebellar vermis. Ultimately, the hypothesis of a genotype–phenotype correlation regarding the ATP/GTP-binding loop domain of the alpha subunit of casein kinase 2 protein (CK2) remains to be firmly established. Overall, these clinical descriptions reinforce the notion of clinical variability associated with the same CSNK2A1 genotype (Table S2). It remains uncertain whether the emerging or uncommon phenotypic characteristics observed in individuals with OCNDs (or any other disorder) can definitively be attributed to OCNDs itself, or if they are influenced by other genetic factors, familial, ethnic, or environmental variability. This case underscores the challenge of defining common phenotypes and expanding the phenotype in rare neurodevelopmental disorders.

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CONFLICT OF INTEREST STATEMENT
The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are openly available in [the repository associated with the American Journal of Medical Genetics (Journal Code: AJMG)] at [the DOI: 10.1002/ajmg.a.63642], reference number [DH_ID:17970505].

ORCID
Albin Blanc https://orcid.org/0009-0006-8769-7892
Céline Bonnet https://orcid.org/0000-0002-6799-0438

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