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Case Report

Okur-Chung Neurodevelopmental Syndrome: A Case Report in One Chinese Neonate and Review of Literature

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Abstract ***Background:*** Okur-Chung neurodevelopmental syndrome (OCNDS) is a rare mendelian disease related to the *CSNK2A1* gene variant. So far, there is no report of confirmed case in the neonatal period. ***Methods:*** The clinical characteristics and importance in early diagnosis of genetic testing in a newborn with OCNDS were retrospectively reported. ***Findings:*** A 14-day-old, female, and full-term neonate characterised by the poor response, weak low cry, congenital heart disease, and special facial features was referred to our Neonatal Intensive Care Unit. This patient was confirmed to carry one novel variant in the *CSNK2A1* gene (p.K198T) with whole-exome sequencing testing. This variant was classified as pathogenic and the cause of the presentation in this neonate. ***Conclusions:*** It is very necessary for a neonate with poor response and long-time weak low cry if routine examinations show no definite findings to make a genetic diagnosis as early as possible.

Key words *Case report; CSNK2A1; Neonate; Okur-Chung neurodevelopmental syndrome*

Introduction

Okur-Chung neurodevelopmental syndrome (OCNDS, OMIM617062) was the first reported and named by Okur et al in 2016,[1] which reinforced the link to neurodevelopmental abnormalities and dysmorphic features caused by heterozygous mutations in the casein kinase II, alpha-1 gene (CSNK2A1) located on chromosome 20p13. The main clinical features of patients with *CSNK2A1* gene variations are intellectual disability and multiple systems involved,[1-3] such as microcephalus and hypotonia–decreased muscle tone. Missense variation is the main cause, and p.K198R is the hot spot variation. To our knowledge, fewer than 30 cases of OCNDS due to *CSNK2A1* gene variation have been reported to present,[2-7] but there is no literature report of a neonatal case.

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Case Presentation

Patient and Clinical Evaluation

We report a female neonate who was born at 39 weeks of gestational age and 14-day-old when transferred to our Neonatal Intensive Care Unit because of "poor response, weak low cry". Her birth weight was 3.27 kg, head circumference was 34 cm and body length was 50 cm, which were all normal. Poor response, weak low cry was observed in the infant without cyanosis, cough, screaming, convulsions or dyspnoea. The infant was given one-week

treatment after birth and was transferred to our hospital for no treatment effect in local hospital. The infant still had poor response and weak low cry. She also had a special face (hypertelorism and flat nasal bridge) (Figure 1), right-hand transverse palm, soft cardiac murmur and hypotonia–decreased muscle tone at the limbs. Her admission weight increased to 3.48 kg and vital signs were stable without other abnormal signs. The results of the infant suggested that: echocardiography found congenital heart disease: 3 atrial septal defects (size 0.31 cm, 0.18 cm, 0.29 cm respectively) with normal cardiac function, laryngoscopy found mild laryngomalacia, MRI of the brain found mild enlargement of the lateral ventricles. The patient`s biochemical tests were normal in all except total bilirubin slightly increased. During hospitalisation, the baby was only given physical therapy such as gastric tube feeding, neonatal touch and swallowing function training without drug treatment. Her clinical situation gradually improved for treatment and she was discharged from hospital at 1 month of age.

Whole Exome Sequencing (WES) Analysis and Sanger Sequencing

After obtaining written informed consent, peripheral blood samples of 2-3 ml were collected from the patient and her parents. Then place the peripheral blood samples in an EDTA anticoagulation tube, and send it to Guangzhou Jiajian Medical Testing Company to proceed WES on this patient's blood, then Sanger sequencing was performed on her parents' blood samples to verify the variants. Use second-generation sequencing technology (average sequencing depth over 200x) for point mutation and copy number variations analysis. The genomic DNA was extracted from peripheral blood samples by using the Solpure Blood DNA Kit（Magen) according to the manufacturer's instructions. 1.0 μg genomic DNA sample was used for the preparation of sequencing libraries by ultrasonic disrupter, end repair, amplification, purification, and other operations. The specific capture probe was used to hybridise and enrich the DNA sequence of the target region. The target region included all exon regions of about 5000 target genes related to OMIM and 30bp intron regions of upstream, downstream, and known deep introns. Region mutation, and then performed second-generation sequencing on the Illumina NovaSeq 6000 platform.

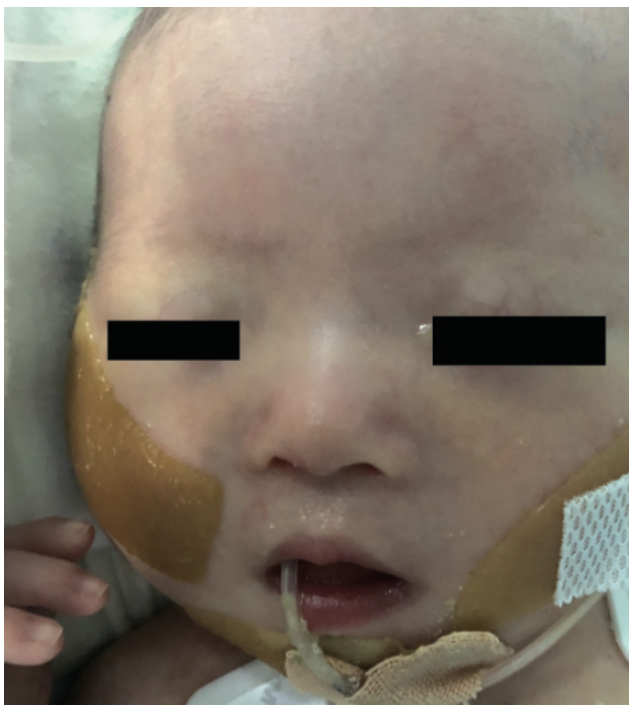

Figure 1 The face picture of infant.

The raw sequencing data were converted into fastq files by using Illumina bcl2fastq software, and the data was processed. NextGENe software aligned the sequencing reads with the human reference genome (GRCh37/hg19) sequence to generate a mutation list. Filter high-frequency mutations were through the population frequency database of mutations (dbSNP, ExAC, gnomAD, etc.). Prediction software was used to predict the conservativeness and pathogenicity of mutations. According to the American College of Medical Genetics and Genomics/The Association for Molecular Pathology (ACMG/AMP) variant interpretation guidelines,[8] the variation was classified. Following these filtering steps, potential variants were considered to cause disease and were subsequently validated by Sanger sequencing. The mean coverage depth of this patient against RefSeq protein-coding regions is 281+/-192X with 99.7% being covered by over 10x, and 99.6% was covered by over 20x.

We identified a CSNK2A1 variant (NM_001895: c.593A>C, p. K198T) which was a novel variant (Figure 2). The variant c.593A>C (p. K198T) on the CSNK2A1 gene has not previously been reported in the medical literature, but other pathogenic mutation at the same amino acid position, p.K198R, has been reported in clinical cases (PMID: 27048600). The region where the mutation is located is an important part of this protein, and computer-aided analysis predicts that this mutation is more likely to affect protein structure/function. Combined with the clinical manifestations and family analysis of the submitter, according to the ACMG/AMP guidelines

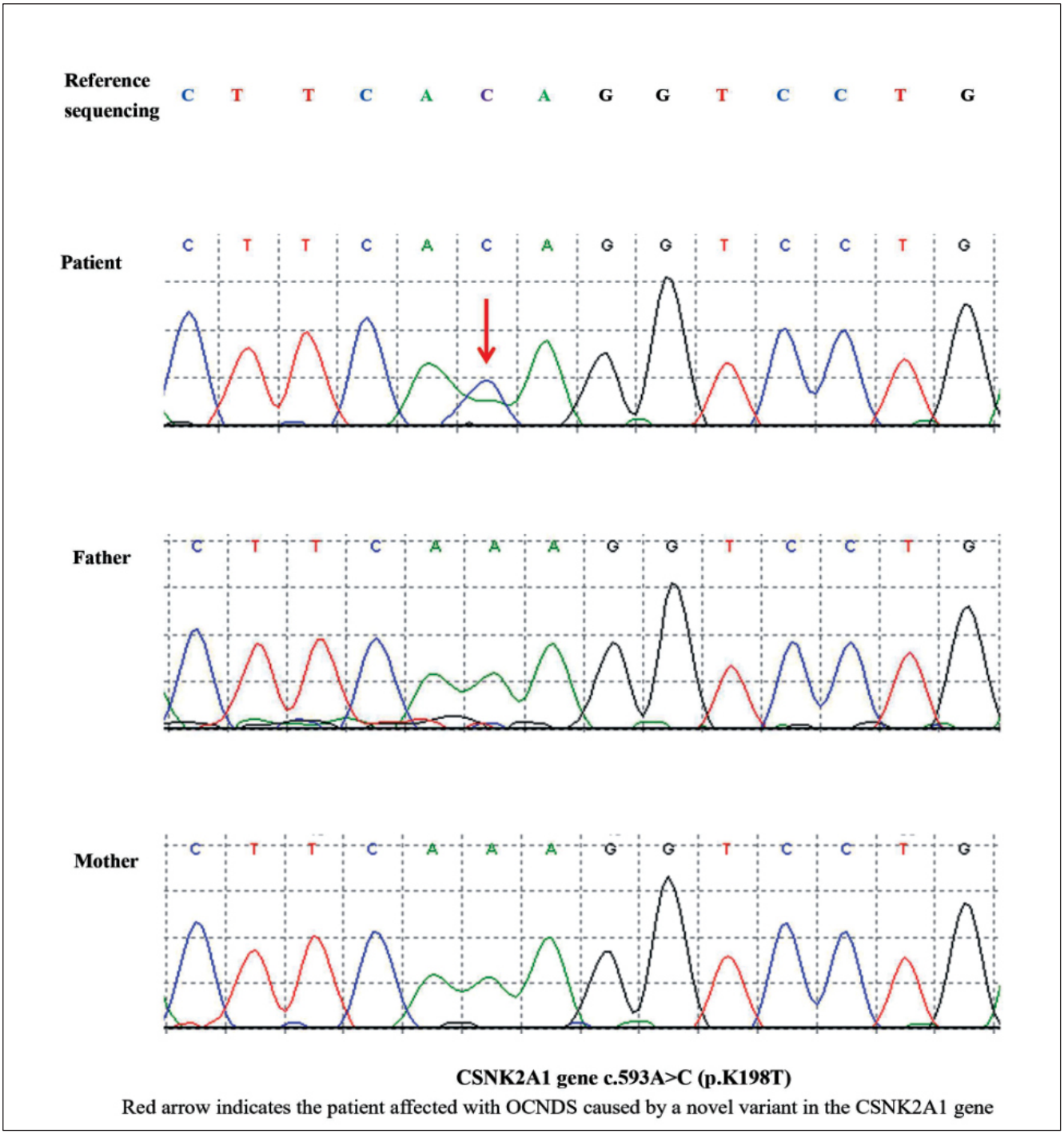

Figure 2 Validation by sanger sequencing of *CSNK2A1* gene in this family.

(PMID: 25741868),[8] this variant is classified as pathogenic.

Follow-up Results

We suggested the patients for regular follow-up for 1 time in 2-4 weeks at an outpatient clinic in the department of neonatology and rehabilitation. We also taught the parents how to continue neonatal touch at home. The family agreed to this option and continued family physical training well. At 2-month - 4-day of age, the weight of infant increased to 4.23 kg. Her muscular tone and Test of Infant Motor Performance were both normal. She could eat milk 90 ml per 3 hours by herself without other discomfort, but remained weak low cry.

Literature Retrieval

A PubMed search (MEDLINE) and Omim search were all carried out using the following terms [(CSNK2A1) AND (Okur-Chung syndrome)] (both built to November 2020). An EMBASE search (built to November 2020) was carried out using a best sensitivity-combination strategy. There were 55 individuals with *CSNK2A1* gene variation but only 28 individuals who diagnosed OCNDS according to the clinical manifestations and got clinical data reported in detail in the literature materials.[1-7] Two authors performed the database search, the manual search through references of relevant publications, and extracted the relevant data from the case-reports. The clinical features of the subjects in this cohort together with subjects in other cohorts were summarised (Table 1).

Discussion

According to the characteristics of cases of OCNDS reported in the past,[1-7] the most important clinical features include developmental disorders or delays, abnormal recognisable facial features, failure to thrive or short stature and hypotonia-decreased muscle tone. We found three new differences in this case for OCNDS: (1) This patient was confirmed to carry one novel variant in the CSNK2A1 gene (p.K 198T), whose parents didn't have a genetic abnormality. This one variant is classified as pathogenic and the cause of the presentation in this neonate.[8] (2) Her clinical manifestations were some different from other cases: (i) She had poor response and hypotonia–decreased muscle tone within half a month of birth. However, her response and muscular tone were gradually improved with age increasing and undergoing physical therapy, which nearly became a normal level, may even return to fully normal when growing up. (ii) The patient had no obvious signs of nervous system damage,

Table 1 Information of 29 OCNDS cases

Information	Current cohort (n=1)	Other cohorts* (n=28)
Age at examination (days or years)	14 days	1 year-18 years
Male (n,%)	No	14 (50.0)
Clinical features (n,%)		
Sleep disturbances	No	9 (32.1)
Developmental disorders or delays	No	28 (100.0)
Abnormal recognisable facial features	Yes	20 (71.4)
Failure to thrive or short stature	No	16 (57.1)
Hypotonia–decreased muscle tone	Yes	19 (67.9)
Feeding difficulties or constipation	No	13 (46.4)
Abnormal immunoglobulin or repeated infections	No	5 (17.9)
Cardiac malformation	Yes	7 (25.0)
Abnormal head MRI	Yes	10 (35.7)
Weak low cry	Yes	0 (0.0)
Poor response	Yes	Not mentioned

*Other cohorts (n=28) include: Duan et al[7] (2019, n=1), Martinez-Monseny et al[5] (2020, n=1), Chiu et al[2] (2018, n=8), Owen et al[3] (2018, n=11), Akahira-Azuma et al[4] (2018, n=1), Trinh et al[6] (2017, n=1), Okur et al[1] (2016, n=5).

compared to previous cases.[1-7] Her growth and development were improved to the nearly normal level. The possible reasons for this case with the slightest clinical manifestations may be as follows: The protein dysfunction secondary to the gene change caused by the novel spot mutation of this case may have less impact than other mutations, but it has not yet been confirmed and needs to be followed up. On the other hand, the age of this case is very young and each system is not yet mature, so clinical manifestations are often atypical. Meanwhile, the case had always accepted effective physical treatment as early as possible, but the manifestations and outcomes of the case still need longer observe and follow-up for long-term prognosis. (iii) The infant had long-time weak low cry, but there was no organic abnormal evidence in the vocal organs or heart or brain that can cause this. We speculate that it may be caused by genetic change, but follow-up is required to exclude small and imperceptible neuromuscular lesions in the local vocal organs of the case. Therefore, for infants with a long-term weak low cry of unknown causes, if there is no obvious effect of routine examination and treatment, it is suggested to further improve relevant gene testing to understand the possibility of OCNDS if necessary. (3) Our case was diagnosed OCNDS timely in neonatal period, whose genetic examination was taken very early. Although the disease of OCNDS is caused by genetic mutations without special effective treatments, if we can diagnose OCNDS as early as possible and give the patients corresponding intervention, maybe the prognosis of infants can be improved much better in the future.

Conclusions

The present report expanded the genotype and phenotype spectrum of *CSN2A1* gene associated with OCNDS by increasing the number of affected individuals from 14 days to 18 years. In order to exclude OCNDS, it is necessary for a neonate with poor response and long-time weak low cry if routine examinations showed no definite findings to make a genetic diagnosis as early as possible.

Conflict of Interest

Authors report no conflict of interest for this publication.

Funding/Support

No funding was secured for this study.

Ethics Approval

This study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University (CHCMU).

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