Persistent Hyperplastic Primary Vitreous with Microphthalmia and Coloboma in a Patient with Okur-Chung Neurodevelopmental Syndrome

Hiroaki Murakami\textsuperscript{a} Tomoko Uehara\textsuperscript{b} Yumi Enomoto\textsuperscript{c} Naoto Nishimura\textsuperscript{a} Tatsuro Kumaki\textsuperscript{a} Yukiko Kuroda\textsuperscript{a} Mizuki Asano\textsuperscript{d} Noriko Aida\textsuperscript{e} Kenjiro Kosaki\textsuperscript{b} Kenji Kurosawa\textsuperscript{a}

\textsuperscript{a}Division of Medical Genetics, Kanagawa Children’s Medical Center, Yokohama, Japan; \textsuperscript{b}Center for Medical Genetics, Keio University School of Medicine, Tokyo, Japan; \textsuperscript{c}Clinical Research Institute, Kanagawa Children’s Medical Center, Yokohama, Japan; \textsuperscript{d}Department of Ophthalmology, Kanagawa Children’s Medical Center, Yokohama, Japan; \textsuperscript{e}Department of Radiology, Kanagawa Children’s Medical Center, Yokohama, Japan

Established Facts

- Okur-Chung neurodevelopmental syndrome is a rare autosomal dominant disorder caused by pathogenic variants in \textit{CSNK2A1}, which encodes the alpha 1 catalytic subunit of casein kinase II.
- This syndrome is characterized by intellectual disability, developmental delay, and multisystemic abnormalities including those of the brain, extremities, and skin as well as cardiovascular, gastrointestinal, and immune systems.

Novel Insights

- We describe a 5-year-old boy with a de novo novel nonsense variant in \textit{CSNK2A1}, who showed novel eye abnormalities of bilateral persistent hyperplastic primary vitreous (PHPV) with microphthalmia, lens dysplasia, and coloboma.
- This is the first report to show an association between the \textit{CSNK2A1} variant and PHPV, and expands the spectrum of clinical presentations associated with Okur-Chung neurodevelopmental syndrome.

Keywords

Okur-Chung neurodevelopmental syndrome · \textit{CSNK2A1} · Microphthalmia · Persistent hyperplastic primary vitreous · Coloboma

Abstract

Okur-Chung neurodevelopmental syndrome is a rare autosomal dominant disorder caused by pathogenic variants in \textit{CSNK2A1}, which encodes the alpha 1 catalytic subunit of casein kinase II. This syndrome is characterized by intellec-
Intellectual disability, developmental delay, and multisystemic abnormalities including those of the brain, extremities, and skin as well as cardiovascular, gastrointestinal, and immune systems. In this study, we describe a 5-year-old boy with a de novo novel nonsense variant in CSNK2A1, NM_001895.3:c.319C>T (p.Arg107*). He showed bilateral persistent hyperplastic primary vitreous with microphthalmia, lens dysplasia, and coloboma. Ocular manifestations are very rare in this syndrome, and this study expands the spectrum of the clinical presentations of this syndrome.

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Introduction

Okur-Chung neurodevelopmental syndrome (OCNDS; OMIM #617062) is a rare autosomal dominant disorder caused by pathogenic variants in CSNK2A1, which encodes the alpha 1 catalytic subunit of casein kinase II (CK2) [Okur et al., 2016]. OCNDS is characterized by intellectual disability, developmental delay, hypotonia, and multisystemic abnormalities including those of the brain, extremities, and skin as well as cardiovascular, gastrointestinal, and immune systems, but there are few reports of patients with ocular abnormalities. To date, 30 cases with de novo variants in CSNK2A1 have been reported, but only one patient has shown ophthalmologic complications [Okur et al., 2016; Trinh et al., 2017; Akahira-Azuma et al., 2018; Chiu et al., 2018; Colavito et al., 2018; Owen et al., 2018; Nakashima et al., 2019; Martinez-Monseny et al., 2020]. We present a 5-year-old Japanese boy with a de novo novel nonsense variant in CSNK2A1, c.319C>T (p.Arg107*). He showed novel ocular findings of bilateral persistent hyperplastic primary vitreous (PHPV) with microphthalmia, lens dysplasia, and coloboma.

Case Presentation

The proband was a 5-year-old male. He was born as the second child of healthy and nonconsanguineous parents after an uneventful pregnancy with a birth weight of 3.076 g (−0.2 standard deviation (SD)), height of 50.0 cm (±0.6 SD), and occipital frontal circumference (OFC) of 33.5 cm (±0.2 SD) at 39 weeks of gestation. He was referred to our hospital at the age of 1 month because he had never opened his eyes. Magnetic resonance imaging (MRI) of his eyes showed bilateral microphthalmia with several structural abnormalities (Fig. 1a, b). Both eyeballs were small, and each had an irregular shape. Dysplastic lens

Fig. 1. MRI images of the eyes and a photograph of the patient. a, b MRI of the patient’s eyes at the age of 1 month show bilateral PHPV with microphthalmia and colobomatous cysts. Axial view of T2-weighted image focused on the right (a) and left eye (b). Both eyeballs are small and irregularly shaped. Dysplastic lenses (arrows) are located in the center of vitreous chambers and funicular structures (arrow heads) extend to the posterior wall of eyeballs. Multiple cystic structures (asterisks) were found behind eyeballs. c Photograph of the patient at the age of 3 years and 4 months showing straight eyebrows, epicanthal folds, strabismus, and a prominent philtrum.
lenses were located in the center of vitreous chambers, and f�
unicular structures behind the lenses elongated to the posterior 
wall of eyeballs. There were multiple cystic structures behind 
the eyeballs with similar signal intensities as the eyeball. His 
ophthalmic diagnosis was bilateral PHPV with microphthalmia, 
len$\text{s dysplasia, and colobomatous}$ cysts. Brain MRI showed no 
abnormalities. By the second year of life, his developmental de-
lay was evident. He began to control his head at 6 months, crawl 
at 16 months, walk independently at 17 months, and speak 
meaningful words at 24 months. He had distinctive facial fea-
tures including straight eyebrows, epicanthal folds, strabismus, 
and a prominent philtrum (Fig. 1c). He had autistic behavioral 
problems including restlessness and hyperactivity. His karyo-
type was normal (46,XY). At age 5 years, his weight was 16.9 kg 
(−0.6 SD), height 105.3 cm (−0.8 SD), and OFC 51.0 cm (+0.1 SD). Written informed consent was obtained from his parents 
in accordance with the Kanagawa Children's Medical Center 
Review Board and Ethics Committee, and we performed trio 
whole-exome sequencing as described below. Exome sequenc-
ing data were analyzed as described previously [Uehara et al., 
2018]. The mean depth of coverage for the RefSeq coding genes 
was 150, 148, and 155, and 99.5%, 99.4%, and 99.6% of the total 
coding sequence was covered by ≥10 reads in the patient, father, 
and mother, respectively. Whole-exome sequencing revealed a 
novel nonsense variant of $\text{CSNK2A1, NM_001895.3:c.319C>T}$ 
(p.Arg107*). This variant was confirmed to be de novo by 
trio Sanger sequencing and was absent from the database of the 
control healthy populations including gnomAD (https://gnom-
ad.broadinstitute.org) and jMorp (https://jmorpe.megabank. 
tohoku.ac.jp/202001/variants). Considering that the probabili-
ty score for the loss-of-function intolerant (pLI) of $\text{CSNK2A1}$ 
was high (0.99) (https://gnomad.broadinstitute.org/gene/
ENSG00000101266?dataset=gnomad_r2_1), we concluded that 
this variant was pathogenic.

Discussion

In this report, we described an OCNDS patient with a 
novel $\text{CSNK2A1}$ nonsense variant who presented with 
multiple congenital ocular anomalies and neurodevelop-
mental delay. MRI imaging of the patient's eyes was very 
characteristic and showed bilateral PHPV, microphthalmia 
with lens dysplasia, and coloboma. To the best of our 
knowledge, this is the second case of a patient with ocular 
manifestations among the 30 OCNDS cases reported so 
far. Another case presented previously with a de novo 
splicing variant in $\text{CSNK2A1}$ (c.1061–1G>C) was in con-
trast to our case in that he showed only retinal dystrophy 
without any morphological eye abnormalities [Colavito 
et al., 2018]. As mentioned previously, in this syndrome, 
multisystemic symptoms other than neurodevelopmental 
delay show a large phenotypic variability [Nakashima 
et al., 2019], which may also occur with ophthalmic symp-
toms.

PHPV is a congenital ocular disorder in which there is a 
failure of normal regression of the primary vasculature 
within the vitreous and a proliferation of fibrous tissue 
from the persistence of the primary vitreous. PHPV is 
known to be associated with cataracts, nystagmus, mi-
crophthalmia, retinal detachment, and glaucoma. So far, 
$\text{NDP, FZD4, and ATOH7}$ have been reported as the genes 
responsive for hereditary PHPV [Shastry, 2009; Prasov 
et al., 2012]. In addition, it has been shown that deletion 
of the tumor suppressor genes $\text{Tgfβ2 and Arf}$ in mice

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**Fig. 2.** Variant distribution reported in previous studies and the present study on the schematic representation 
of the $\text{CSNK2A1}$ protein. $\text{CSNK2A1}$ has a large kinase domain with functional segments including an ATP/GTP-
binding loop, basic cluster, active site, and activation segment.
causes blindness in the similar pathogenic process to PHPV [Freeman-Anderson et al., 2009]. However, at present, the molecular mechanism of PHPV is not fully understood. In the present study, no pathogenic mutations were detected in the above genes. However, we could not rule out the possibility that this patient had a pathogenic mutation other than CSNK2A1, which causes PHPV.

Studies in Drosophila and mice have suggested that the pathway of CK2 plays an important role in ocular development during embryogenesis. In Drosophila, it has been suggested that CK2 is required for activation of the E(spl)-M8 receptor, which regulates normal eye morphogenesis [Karandikar et al., 2004; Bandyopadhyay et al., 2016]. The inhibition of CK2 activity in mice has been shown to inhibit hypoxia-inducible factor-1 activity and, consequently, prevent the induction of vascular endothelial growth factor in the eyes [Morooka et al., 2015]. The findings in our case suggest that CK2 plays an important role in eye development in humans as well.

Although 21 de novo CSNK2A1 variants have been described in recent years, none have shown a genotype-phenotype correlation (Fig. 2). Most are missense variants and are accumulated in the functional segments within the kinase domain of CSNK2A1. Including our case, only 3 cases with truncating variants in CSNK2A1 have been reported, and 2 of them presented with ocular manifestations. However, it is difficult to conclude that there is a correlation between CSNK2A1 haploinsufficiency and ocular phenotypes. The accumulation of future cases may clarify the role of CSNK2A1 in human eye development.

Conclusion

We present a male patient with OCNDS caused by a de novo novel nonsense variant in CSNK2A1, who showed novel ocular anomalies including bilateral PHPV. This study contributes to a better understanding of the clinical spectrum of OCNDS.

References


Acknowledgments

We thank the patient and his family for participating in this work.

Statement of Ethics

This study was approved by the Review Board and Ethics Committee of the Kanagawa Children’s Medical Center (approval No. 2018-1). Written informed consent was obtained from the patient’s parents, which included consent for the pictures appearing in the manuscript.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.M., and K.Kurosawa provided clinical data, molecular genetic data, and wrote the manuscript. T.U., Y.E., and K.Kosaki provided molecular data. N.N., T.K., Y.K., M.A., and N.A. provided clinical data. All authors analyzed and interpreted the data and approved the manuscript in its final form.

Data Availability Statement

The data that support the findings of this study are openly available in figshare at http://doi.org/10.6084/m9.figshare.14731404.


