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

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Established Facts

- Okur-Chung neurodevelopmental syndrome is a rare autosomal dominant disorder caused by pathogenic variants in *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 *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 *CSNK2A1* variant and PHPV, and expands the spectrum of clinical presentations associated with Okur-Chung neurodevelopmental syndrome.

Keywords
Okur-Chung neurodevelopmental syndrome · *CSNK2A1* · Microphthalmia · Persistent hyperplastic primary vitreous · Coloboma

Abstract
Okur-Chung neurodevelopmental syndrome is a rare autosomal dominant disorder caused by pathogenic variants in *CSNK2A1*, which encodes the alpha 1 catalytic subunit of casein kinase II. This syndrome is characterized by intellec-

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tual 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.

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

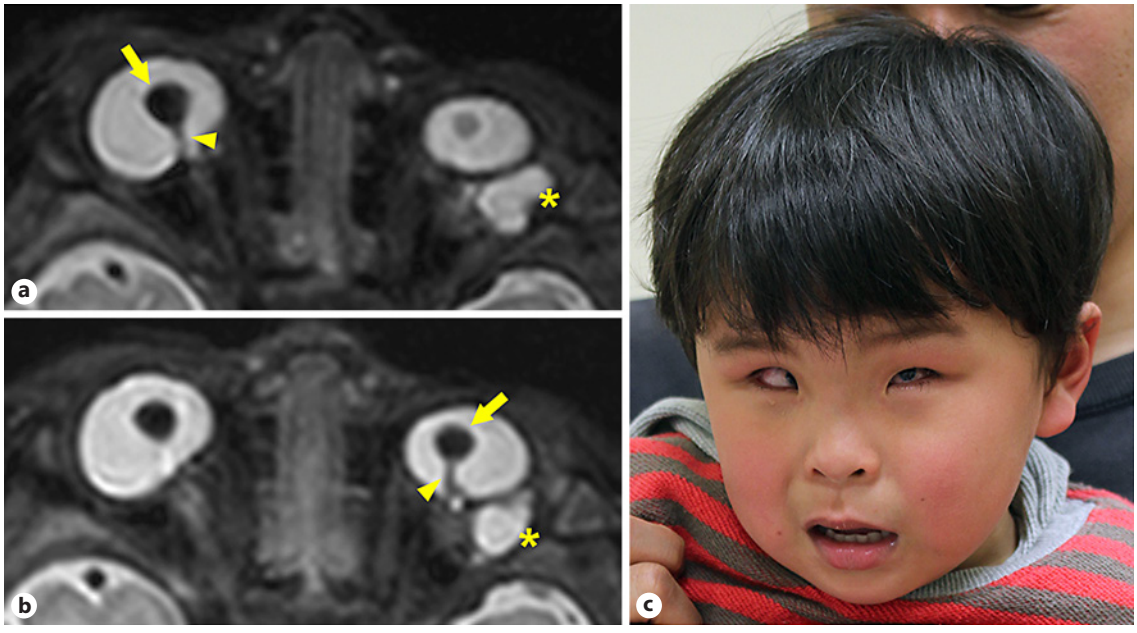

Fig. 1. MRI images of the eyes and a photograph of the patient. **a**, **b** MRI of the patient's eyes at the age of 1 month show bilateral PHPV with microphthalmia and colobomatous cysts. Axial view of T2-weighted image focused on the right (**a**) and left eye (**b**). Both eyeballs are small and irregularly 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 funicular 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, lens dysplasia, and colobomatous cysts. Brain MRI showed no abnormalities. By the second year of life, his developmental delay 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 features including straight eyebrows, epicanthal folds, strabismus, and a prominent philtrum (Fig. 1c). He had autistic behavioral problems including restlessness and hyperactivity. His karyotype 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 sequencing 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 *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://gnomad.broadinstitute.org) and jMorp (https://jmorp.megabank.tohoku.ac.jp/202001/variants). Considering that the probability score for the loss-of-function intolerant (pLI) of *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 *CSNK2A1* nonsense variant who presented with multiple congenital ocular anomalies and neurodevelopmental 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 *CSNK2A1* (c.1061–1G>C) was in contrast 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 symptoms.

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, microphthalmia, retinal detachment, and glaucoma. So far, *NDP*, *FZD4*, and *ATOH7* have been reported as the genes responsible for hereditary PHPV [Shastry, 2009; Prasov et al., 2012]. In addition, it has been shown that deletion of the tumor suppressor genes *Tgfβ2* and *Arf* in mice

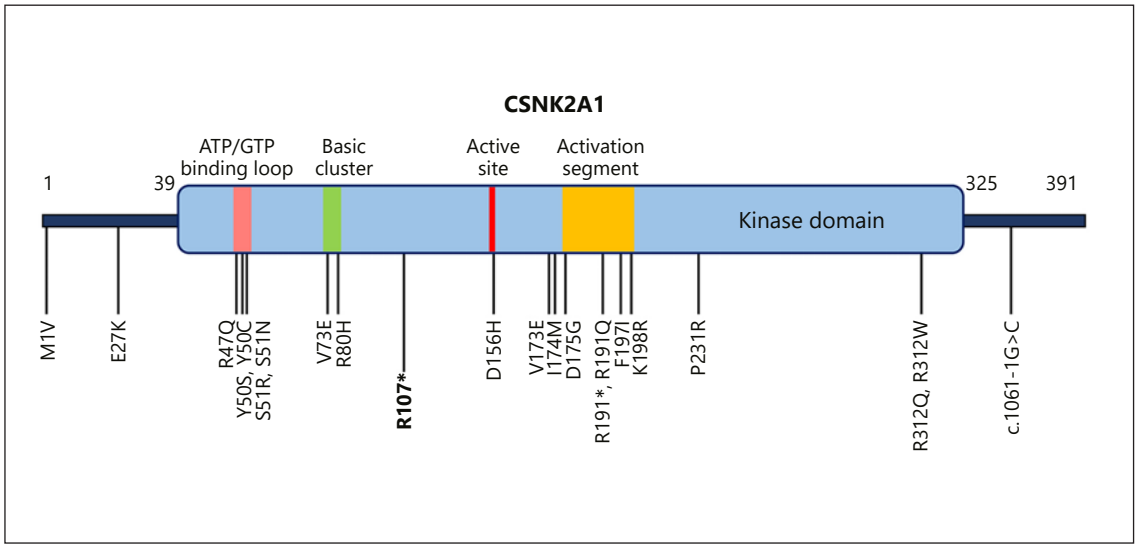

Fig. 2. Variant distribution reported in previous studies and the present study on the schematic representation of the CSNK2A1 protein. CSNK2A1 has a large kinase domain with functional segments including an ATP/GTP-binding loop, basic cluster, active site, and activation segment.

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.

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.

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