Correspondence

Two cases of KIF11-related retinopathy with microcephaly

Dongyoung Lee¹, Sungsoon Hwang ¹,², Sang Jin Kim¹

¹Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
²Department of Clinical Research Design and Evaluation, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea.

Corresponding Author: Sang Jin Kim
Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
Tel: +82-2-3410-3568, Fax: +82-2-2410-0074
E-mail: sangjin.kim.md@gmail.com
Dear Editor,

The kinesin family member 11 (KIF11) gene which is located on 10q23.33, encodes mitotic kinesin known as Eg5 which plays a role in formation and maintenance of the bipolar mitotic spindle during cell division [1, 2]. Mutations in KIF11 gene were known to be associated with rare autosomal dominant disease called microcephaly with or without chorioretinopathy, lymphedema, or mental retardation (MCLMR) [3]. It is known to cause microcephaly due to impaired spindle development, but the mechanism of lymphatic dysfunction is unknown. [4] Mutations in this gene are also reported to be associated with familial exudative vitreoretinopathy (FEVR). FEVR is a rare genetic disorder characterized by an incomplete retinal vascularization associated with genetic mutations such as Wnt signaling pathway [3]. It is commonly diagnosed in childhood with no history of prematurity or oxygen supplementation which is differentiated from retinopathy of prematurity, and with a positive family history [5]. Herein, we report two pediatric Korean patients with FEVR and microcephaly by KIF11 gene mutation. This study was approved by the Institutional Review Board at Samsung Medical Center (IRB No. 2013-11-138-001). Written informed consent for publication was obtained from the patient’s parents.

A 4-year-old female child was referred for decreased visual acuity to the Retina Clinic at Samsung Medical Center. The child was born at full term and had no family history of visual impairment. Her best-corrected visual acuity was 20/200 in the right eye and finger count in the left eye, with spherical equivalent -4.0 diopters (D) for the right eye, +6.5 D for the left eye. She had 45 prism diopters (PD) of esotropia and 12 PD of left hypertropia by Krimsky test and right-beating nystagmus was present. Fundus examination revealed bilateral peripheral avascular retina with multiple chorioretinal atrophy in the right eye and retinal fold with temporal tractional retinal detachment in the left eye (Fig. A-C). Other than ocular findings, her head circumference was 46 cm at the age of 4 years, which was clinically suspected microcephaly, and had mild delay in language development but no significant cognitive dysfunction. Exome sequencing revealed that the patient had de novo pathogenic variant c.2220_2221del:p.(Cys740*) in exon 17 of the KIF11 gene (NM_004523.3) which is presumed to cause premature termination. This mutation is a novel variant that has not been reported before. Her parents had no corresponding variants detected by Sanger sequencing.

A 3-year-old male child visited Retina Clinic complaining of congenital nystagmus. He was born at full term and had negative family history of ocular diseases. His spherical equivalent was +7.5 D for the right eye, +3.25 D for the left eye. Orthoptic evaluation showed 20 PD of exotropia by Krimsky test with right-beating nystagmus. Fundus examination showed extensive chorioretinal degeneration with pigmentary changes in both eyes. Fundus fluorescein angiography showed peripheral avascular retina without neovascularization (Fig. D-F). Optical
coherence tomography showed retinal thinning of both eyes, but images were low-quality due to poor cooperation. In addition to ophthalmologic findings, he had developmental delay in language, and head circumference was 46 cm at the age of 9 years which was classified as microcephaly. Targeted next generation sequencing (NGS)-based gene panel sequencing for vitreoretinopathy revealed heterozygous pathogenic variant (NM_004523.3) KIF11 c.2304_2305del: p.(His768Glnfs*7) which is presumed to caused frameshift with subsequent premature termination.

Although, the primary finding of FEVR is abnormal retinal vasculature, mutations of KIF11 gene can lead to clinical overlap of MCLMR with FEVR by accompanying other ocular findings such as retinal fold, retinal detachment and microphthalmia [3, 4]. Both of the patients presented with peripheral avascular vessels and chorioretinopathy as ocular findings along with microcephaly and developmental delay as extraocular findings, but history of lymphedema or mental retardation was unclear.

In conclusion, we report two Korean patients with autosomal dominant KIF11-related retinopathy which is characterized by incomplete retinal vascularization with multiple chorioretinal atrophic lesion and extraocular abnormalities including microcephaly and developmental delay. To our best knowledge, this is the first report of KIF11 gene-related retinopathy with microcephaly in Korean patients.

Authors’ Disclosures of Potential Conflicts of Interests

No potential conflicts of interest relevant to this article were reported.

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Fig. 1. Clinical manifestations of patients with KIF11 mutations. (A,B) Fundus photographs of 4-year-old female child showing multiple choioretinal atrophy in the right eye and retinal fold in the left eye. (C) Fundus fluorescein angiography showing bilateral peripheral avascular retina. (D,E) Fundus photographs of 3-year-old male child showing extensive chorioretinal degeneration with pigmentary changes in both eyes. (F) Fundus fluorescein angiography showing bilateral avascular retina without neovascularization.