研究成果の刊行に関する一覧表

書　籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
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Ⅴ．研究成果の刊行物・別冊

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Short clinical report

Concurrent deletion of *BMP4* and *OTX2* genes, two master genes in ophthalmogenesis

Toshiki Takenouchi [a], Sachiko Nishina [b], Rika Kosaki [c], Chiharu Torii [d], Ritsuko Furukawa [e], Takao Takahashi [a], Kenjiro Kosaki [d,*]

[a] Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan
[b] Division of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan
[c] Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan
[d] Center for Medical Genetics, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
[e] Department of Pediatrics, Keiyu Hospital, Kanagawa, Japan

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ABSTRACT

BMP4 and *OTX2* are master genes in ophthalmogenesis. Mutations of *BMP4* and *OTX2* often lead to eye defects, including anophthalmia–microphthalmia. A significant degree of variable expressivity has been reported in heterozygous individuals with *BMP4* or *OTX2* mutation. Interestingly, both *BMP4* and *OTX2* reside on 14q22, being only 2.8 Mb apart. Previous studies reported that among three patients with 14q22 deletion involving *BMP4* and *OTX2*, all had severe eye defects. The minimal degree of variable expressivity among these individuals who were doubly deleted for *BMP4* and *OTX2* could be attributed to the combinatorial relationship of the two genes observed in animal models. We herein report a patient with a concurrent deletion of *BMP4* and *OTX2* who exhibited bilateral microphthalmia, more specifically, anterior segment dysgenesis with microcornea. Evolutionarily conserved physical linkage of *Bmp4* and *Otx2* loci may suggest an advantage of the proximal alignment of the two genes. Another striking feature in the propositus was the progressive white matter loss observed by serial neuroimaging. A review of twelve previously reported patients with 14q22 microdeletion revealed decreased white matter volume in half of the patients. It remains to be elucidated whether the white matter lesion is age-dependent and progressive. In conclusion, anterior segment defects of the eyes, especially when accompanied by decreased white matter volume on neuroimaging, should raise the clinical suspicion of 14q22 microdeletion.

1. Introduction

14q22 microdeletion syndrome has been proposed as a recognizable contiguous gene deletion syndrome, mainly characterized by anophthalmia–microphthalmia (AM) and developmental delay [1]. In terms of AM, it is noteworthy that the 14q22 region contains two master genes for ophthalmogenesis, *BMP4* and *OTX2*, the two genes being only 2.8 Mb apart. *Bmp4* belongs to the *Tgfb1* superfamily and plays a pivotal role in ocular development as well as in the development of the teeth, limbs and bones [2]. *Otx2* is a critical gene for tissue specification in the forebrain and its derivative, eyes [3].

Mutations of *BMP4* lead to eye defects, including AM [4]. Similarly, mutations of *OTX2* can also cause an indistinguishable phenotype [5]. In both humans and mice, with heterozygous mutation of *BMP4* [4,6], and in those with heterozygous mutations of *OTX2* [5,7], a significant degree of variable expressivity of the ocular phenotype is the rule. In mice, *Bmp4* +/− causes anterior segment dysgenesis, but the penetrance and severity of the ocular phenotype is strongly influenced by the genetic background. On the C57BL/6J background, most of *Bmp4* +/− mice exhibit a bilateral severe ocular phenotype, whereas on other genetic backgrounds, few heterozygous mice show clinically detectable ocular phenotypes [6]. Similarly, in humans, the severity of the ocular phenotype varies significantly among affected patients, and truncating mutation of *OTX2* identified in children with bilateral AM have been detected in unaffected parents, providing evidence for incomplete penetrance [5].

Among three patients with 14q22 deletion involving *BMP4* and *OTX2*, all had severe eye defects. The minimal degree of variable

Abbreviations: AM, anophthalmia–microphthalmia.

* Corresponding author. Tel.: +81 3 3353 1211x62901; fax: +81 3 5379 1978.
E-mail address: kkosaki@z3.keio.jp (K. Kosaki).

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expressivity among these individuals with doubly heterozygous mutations of *BMP4* and *OTX2* could be attributed to the functionally related roles of the two genes observed in animal models. Both *Otx2* and *Bmp4* are involved in retinal pigment epithelial differentiation and formation of the anterior structures of the eyes in vertebrates [8]. Co-expression of the two genes was observed in some species [9]. Here, we present a patient with concurrent deletion of *OTX2* and *BMP4* that lends support to the aforementioned hypothesis, and to better delineate, in further detail, the phenotypic characteristics of the 14q22 microdeletion syndrome.

2. Clinical report

The propositus is a Japanese girl born to non-consanguineous parents. Her family history was non-contributory. The pregnancy was uneventful and she was born at 37 and 5/7 weeks of gestation via cesarean section for decreased fetal movements. Her birth weight was 2335 g and head circumference was 33 cm. She had a wide open anterior fontanelle measuring approximately 3 × 3 cm. Her face was characterized by a prominent forehead, microphthalmia, thin upper lip, long palpebral fissures, and long eyelashes (Fig. 1-A). Ophthalmic slit-lamp examination revealed bilateral extreme microcornea with a corneal diameter of 4 mm in the right eye and 2 mm in the left eye, severe anterior segment dysgenesis with bilateral corneal opacities, iris coloboma in the right eye, and occluded pupil in the left eye (Fig. 1-B). No posterior segment abnormalities were identified in either eye by ultrasonography. Both eyes showed light perception, but grating visual acuity could not be measured. Involuntary upward movements of the eye were seen on both sides. There was a prominent finger pad and a small but deep sacral dimple. She also had a small atrial septal defect, which closed spontaneously. She showed delayed tooth eruption. At two weeks of age, a computed tomography of the head revealed only an extremely thin corpus callosum without significant cerebral volume changes (Fig. 1-C). A magnetic resonance imaging at the age of 21 months demonstrated significant and progressive global atrophy, most prominent in the frontal lobes. The striking volume loss predominantly involved the white matter, with relative preservation of the gray matter (Fig. 1-D). Neuroimaging did not reveal any suprasellar abnormalities. Her thyroid function test results were all within normal limits (thyroid-stimulating hormone 4.28 mU/L (reference for age: 0.7–6.4 mIU/L); free triiodothyronine 4.1 pg/mL (2.3–5.6 pg/mL); free thyroxine1.2 ng/dL (0.8–2.2 ng/dL)). Serum somatomedin C was normal for age. i.e., 93.0 ng/mL (74–202 ng/mL). Her development was profoundly delayed despite the absence of microcephaly, failure to thrive, or deafness on auditory brainstem response. Currently, she is 2 years and 10 months old and her height is 85.7 cm (−1.35SD), weight is 10.34 kg (−1.64SD), and head circumference is 48.4 cm (+0.08SD). She is only able to sit without support. She does not follow commands or

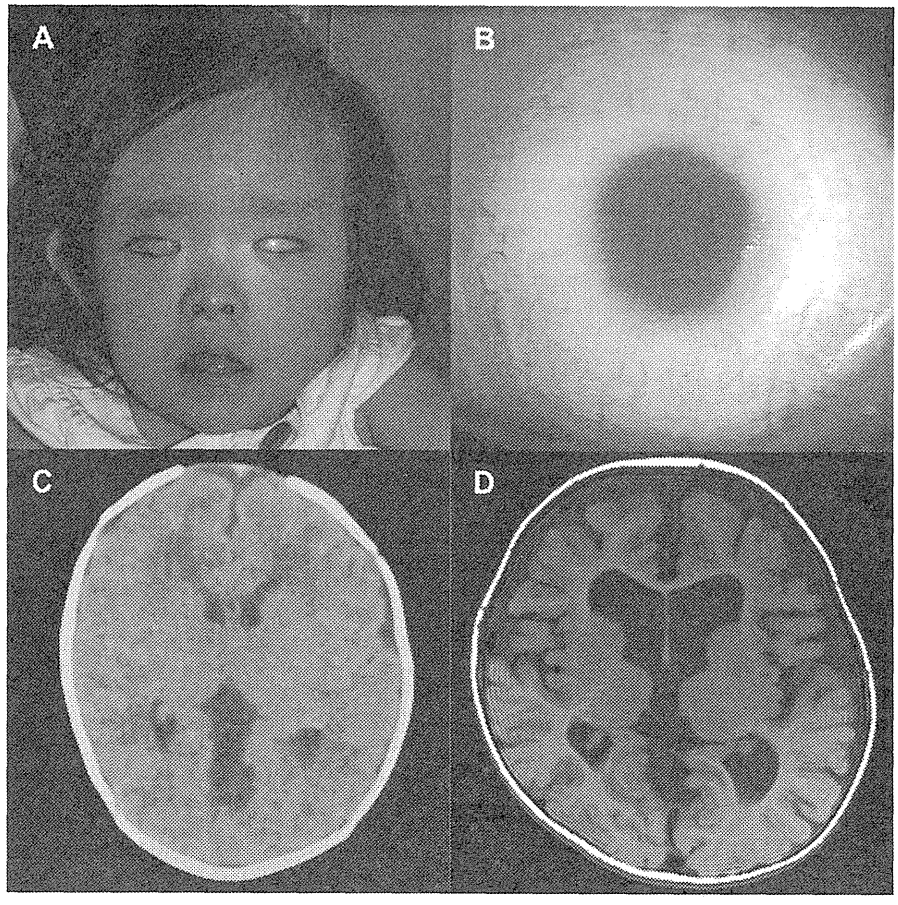


Fig. 1. Clinical and radiographic features of the propositus. A: Facial appearance of the propositus. Note the prominent forehead, microphthalmia, thin upper lip, long palpebral fissures, and long eyelashes, B: Appearance of the left eye at the age of 2 years: extreme microcornea with an occluded pupil can be seen. C: Axial computed tomography at 2 weeks of age. Note the preserved white matter volume. D: Axial magnetic resonance imaging of the brain at 21 months of age, demonstrating significant global volume loss predominantly involving white matter.

speak any meaningful words. She has never had seizures. On examination, she has bilateral microphthalmia, and diffuse hypotonia. There are no dystonic movements or diurnal fluctuations in her muscle tone. A G-band analysis was reportedly normal. A microarray analysis demonstrated a de novo 6.2-Mb deletion in 14q22.2-22.1 from position 52,830,547 to 59, 031,284 (NCBI36/hg18, March 2006), which included approximately 53 genes (Fig. 2).

3. Discussion

Here, we report a patient with severe anterior segment dysgenesis due to concurrent heterozygous deletion involving both the *OTX2* and *BMP4* loci. A review of the previously reported patients with concurrent deletion of *OTX2* and *BMP4*, i.e. [1], Case 1 and 2 in Ref. [4] reveals that the severe AM phenotype indeed showed high penetrance: all three patients with such concurrent deletion showed severe AM. Our clinical observation is compatible with the notion that BMP4 and OTX2 act via a common pathway.

It is intriguing that two functionally close genes such as *BMP4* and *OTX2* are in physical proximity to each other. Another example of functional proximity between two neighboring genes has been reported for the combination of *EVC* and *EVC2* at the Ellis-van Creveld syndrome (MIM 225500) locus: mutations in the two genes, which share no sequence homology, lead to the same syndromic phenotype [10]. It is speculated that the two genes, namely, *EVC* and *EVC2*, are under the control of the same regulatory element, and a similar explanation could apply to the combination of *BMP4* and *OTX2*. Phylogenetic analysis of the alignment of *Bmp4* and *Otx2* reveals that the proximity of the two genes is conserved down to the chicken. This genomic observation does not prove, but lends support to the idea that the alignment of the two genes in proximity may be advantageous from an evolutionary standpoint. Alternatively, *OTX2* and *BMP4* may not have any functional complementarity despite their physical proximity, since *Otx2* interacts with *Sox2*, whereas *Bmp4* interacts with *Pax6* and *Bmp7* in lens formation [11].

We confirmed that AM represents a cardinal sign of the 14q22 microdeletion syndrome. In order to define 14q22 microdeletion syndrome as a clinically recognizable entity, we further attempted to delineate the extra-ocular phenotypes in patients with 14q22 microdeletion. At least seven out of thirteen patients with microdeletion involving 14q22 showed decreased white matter volume or increased ventricular size at some point in their clinical course [1,12]:, case 1 and 2 in Ref. [4], III-5 and III-6 in Ref. [13] and the propositus.

Inclusion mapping among patients with 14q22 microdeletion suggests that the shortest region of overlap for decreased white matter volume is located between the centromeric end of the deletion interval of the propositus and the telomeric end of the deletion interval reported by Hayashi et al. (Fig. 3) [12]. Exclusion mapping with Case 1 described in the report by Wyatt et al., who had no abnormal findings on computed tomography findings, indicated *BMP4* as the only candidate gene for the white matter lesion [14]. However, intragenic loss-of-function mutations in *BMP4* have been reported to cause ophthalmic lesions without exerting any effect on the white matter [15]. Lumaka et al. described a family with microscopic deletions involving *BMP4*, and only half of affected members had brain lesions [13]. A possible explanation for this inconsistency in the mappings is that decreased white matter volume associated with 14q22 microdeletion could be an age-dependent lesion. Indeed, serial neuroimaging in the propositus showed normal white matter volume at 2 weeks of age, but a striking progressive white matter loss at 21 months of age. We suggest that serial neuroimaging be performed in other patients with 14q22 microdeletion to confirm whether the decreased white matter volume associated with 14q22 microdeletion might be age-dependent and progressive. If so, the above mapping data require some modification.

From the genetic counseling standpoint, it is critical to investigate the exact etiology of AM. 14q22 microdeletion syndrome, which is essentially a de novo condition, carries a low risk of recurrence, whereas the risk can be as high as 25% in other autosomal recessive conditions [16]. In conclusion, 14q22 microdeletion should be included in the differential diagnosis of patients presenting with anterior segment dysgenesis of the eyes, and decreased white matter volume on brain imaging may be helpful for the clinical diagnosis.

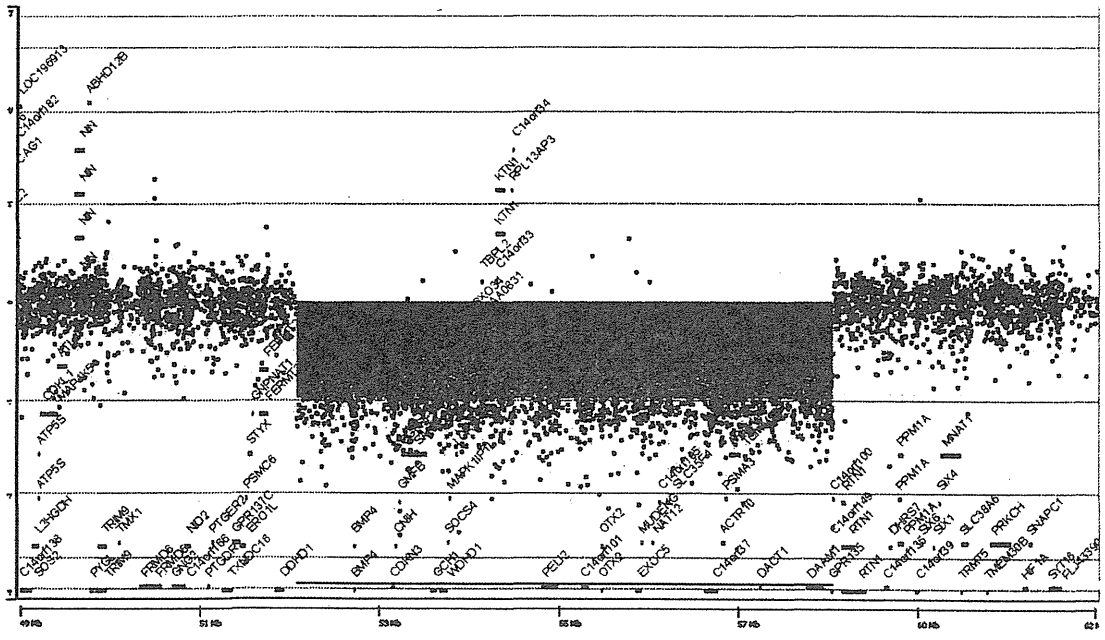
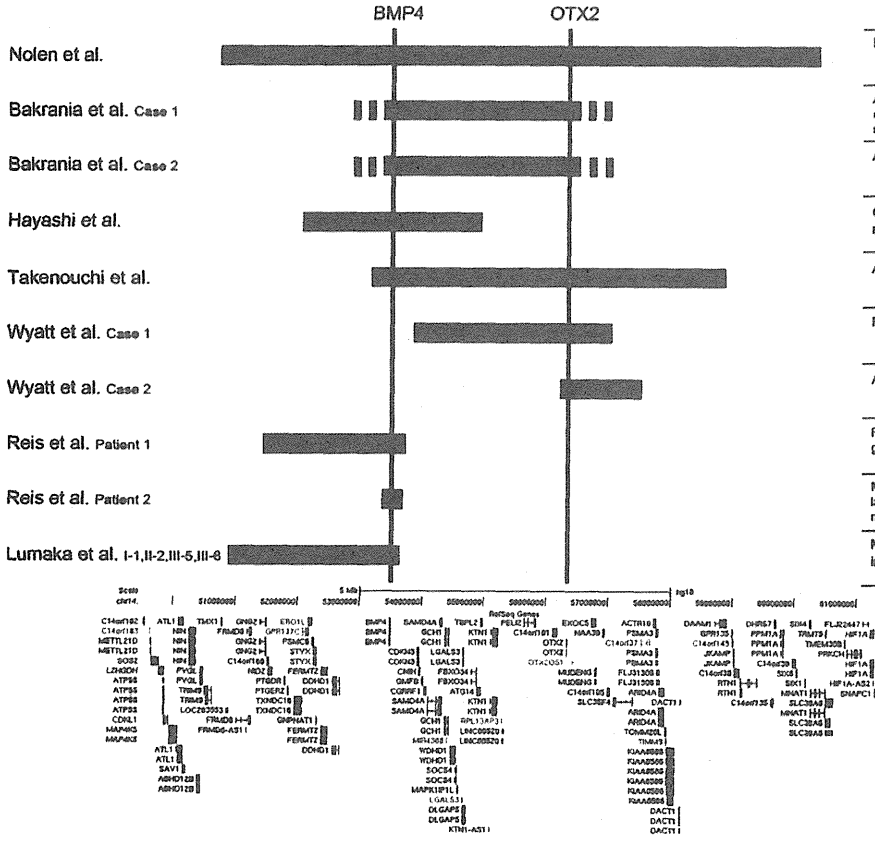


Fig. 2. Result of the microarray analysis. Note the deleted region highlighted in green.



Eye(s)	Neuroimaging
Bilateral fused eyelids	Thin corpus callosum, global reduction of white matter at 6months, absence of the anterior pituitary gland at 2 years
Anophthalmia, sclerocornea (right), coloboma (left), optic nerve hypoplasia, no light perception	Partial agenesis of corpus callosum and hypoplasia of inferior cerebellar vermis, lateral ventricles mildly prominent
Anophthalmia	Partial cerebellar vermis hypoplasia, generalized lack of white matter
Congenital glaucoma, sclerocornea	Decreased white matter, lateral ventricle dilatation
Anterior segment dysgenesis	Progressive white matter loss at 21months
Microphthalmia	Normal
Anophthalmia	(Skull fracture and subdural hematoma)
Rieger anomaly, congenital glaucoma, microcornea, nystagmus	Normal
Microphthalmia, persistence of pupillary membrane, high myopia, strabismus, nystagmus, corectopia (right)	Not performed
Microphthalmia and sclerocornea in III-6	Mild bilateral white matter lesions in III-6 and ventricular dilatation in III-5

Fig. 3. Schematic mapping of patients with 14q22 microdeletion. The black vertical lines represent the extent of deletion on the UCSC genome browser (http://genome.ucsc.edu/) (NCBI36/hg18, March 2006) in each patient, whose ocular and neuroimaging characteristics are listed on the right.

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sue in concentric layers, and (5) external loose connective tissue with fibroadipose elements, muscle, and blood vessels. Our patient had each of these elements.

Conservative treatment includes observation with aspiration as needed. In recalcitrant cases not amenable to aspiration or if considerable facial dysmorphism exists, excision is conventionally undertaken.

In summary, congenital cystic eye is exceedingly rare. Diagnosis historically was based on physical and histopathological findings. However, newer imaging modalities are revealing characteristic findings of the condition at or even prior to birth, as in our case. Given the frequent association with intracranial abnormalities, including the possibility of septo-optic dysplasia, neuroimaging is warranted to screen for such aberrations. Finally, although not always required, treatment conventionally involves excision.

James R. Singer, DO
Patrick J. Droste, MS, MD
Adam S. Hassan, MD

Author Affiliations: Metro Health Hospital, Wyoming, Michigan (Singer); Department of Neurology and Ophthalmology, Michigan State University, East Lansing (Singer, Droste, Hassan); Helen DeVos Children's Hospital, Grand Rapids, Michigan (Droste, Hassan).

Corresponding Author: Dr Singer, Metro Health Hospital, 2221 Health Dr SW, Ste 1100, Wyoming, MI 49519 (james-singer@hotmail.com).

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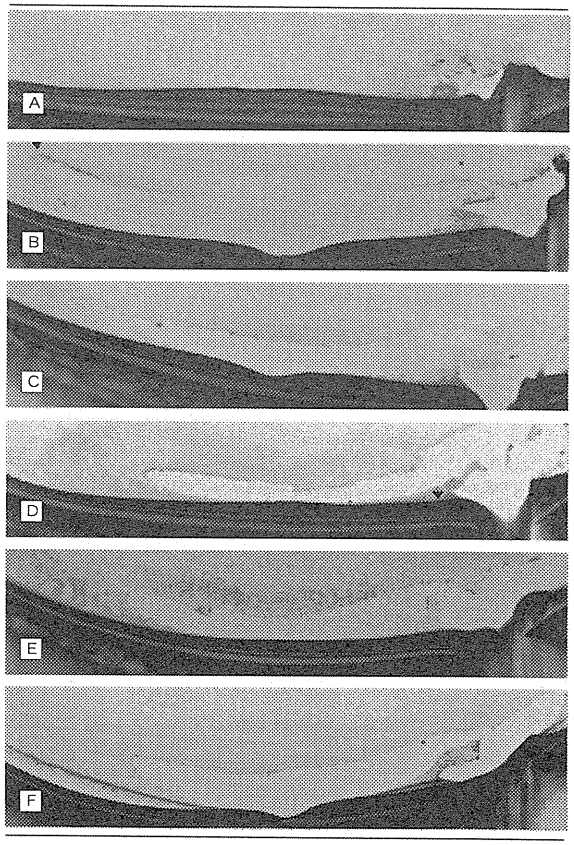
Figure 1. Age-Dependent Changes in Premacular Vitreous Pockets



A, No premacular vitreous pocket is seen in the eye of a 2-year-old boy. B, A premacular crack in the formed vitreous (arrowheads) is seen in the eye of a 3-year-old girl, and the Cloquet canal is connected to the crack. Premacular vitreous pockets are seen in the eyes of an 8-year-old boy (C), a 13-year-old boy (D), a 30-year-old man (E), and a 54-year-old woman (F), and they are all connected to the Cloquet canal. F, A partial posterior vitreous detachment is seen in the eye of a 54-year-old woman.

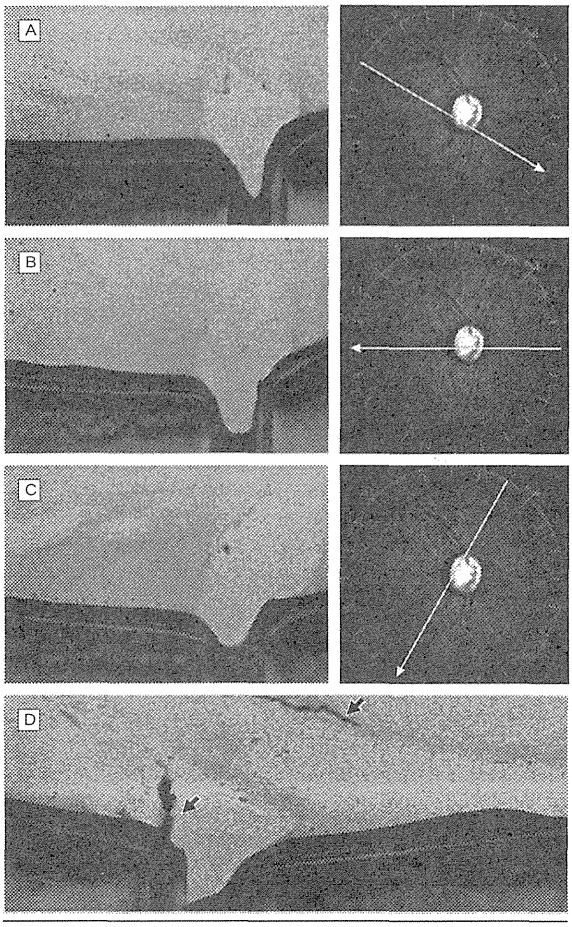
Development of a Premacular Vitreous Pocket

The premacular vitreous pocket (PVP), or vitreoschisis cavity, is a liquefied vitreous cavity in front of the posterior retina that is characteristic of various macular diseases, including macular holes and diabetic maculopathy.[1] The reason for the development of PVPs is unknown because of the difficulty observing the formed vitreous in vivo. India ink and the fluorescein staining technique have delineated the structure of the PVP in the vitreous cavity in human eyes at autopsy[2]; however, the technique is limited because of the presence of artifacts during fixation of the fragile and mobile vitreous and postmortem changes. Optical coherence tomography has facilitated observation of the vitreous structures in vivo. Herein, we describe the development and fine details of PVPs in real time.

Methods | We retrospectively analyzed the posterior vitreous, retinas, and optic discs of 56 healthy eyes (39 patients; age range, 1-54 years) using swept-source optical coherence tomography (Topcon), which provides detailed images of the fine ocular structures. The scanning protocol used in this study was a single-line scan with 96 overlapping images and a radial scan with 32 overlapping images. Each line has a 12-mm transverse scanning length with 1024-pixel resolution. Eyes that appeared healthy were excluded if the patient had a family history of a hereditary vitreoretinal disease.

Results | A PVP (**Figure 1**C-F) was detected in all eyes of patients older than 10 years and in no eyes of patients younger than 2 years (Figure 1A). A crack in the formed vitreous (Figure 1B), considered to be a primitive structure of the PVP, developed first in eyes around age 2 years. Between ages 3 and

Figure 2. Multifocal Premacular Vitreous Pockets (PVPs) and Temporal Remnants of Regressed Hyaloid Vessels With a PVP



A-C, Sequential radial sections of the temporal premacular vitreous centered on the optic disc in the eye of a 6-year-old boy. Primitive PVPs are seen superotemporally (A) and inferotemporally (C) but no PVPs are seen temporally (B), indicating that these PVPs are multifocal in origin. D, A regressed hyaloid vessel within both the Cloquet canal and a PVP (arrows) is seen by swept-source optical coherence tomography in the eye of a 5-year-old boy.

9 years, a PVP was present in 16 eyes (49%) and a crack in 20 eyes (61%). Nine eyes (56%) with a PVP also had a crack. Among eyes with both a PVP and a crack, 16 eyes (86%) had cracks connected to the PVP. Twenty-eight eyes (80%) with PVPs had a liquefied connection between the PVP and the Cloquet canal (Figure 1C-F). The connection to the Cloquet canal was identified in both the PVP and the crack (Figure 1B). In younger eyes, the PVP was wider horizontally than vertically, and all detectable cracks were wider horizontally than vertically. During the early phase of PVP development, several eyes had multifocal PVPs and cracks (**Figure 2**A-C) in the premacular vitreous. A high-density structure, which appeared to be a remnant of regressed hyaloid vessels and was connected to the Bergmeister papilla, was present temporally along the crack and wall of the PVP in several eyes (Figure 2D).

Discussion | Kishi and Shimizu[3] originally identified PVPs in eyes at autopsy and implied that development began with slight separation of the vitreous at about age 2 years, although the PVPs might include postmortem changes. The current in vivo study showed that a PVP is often absent at birth and is often present by about age 3 years. Interestingly, the crack in the formed vitreous also was observed as an initial change around age 2 years.

The PVP and posterior Cloquet canal, which are separated by a dishlike wall of vitreous,[4] were connected in most eyes of the current patients, even in eyes with a crack at an initial stage. Aqueous humor from the posterior Cloquet canal[5] may play a role in formation of the crack and PVP.

Almost all primary PVPs and cracks that occasionally developed multifocally and coexisted with remnants of hyaloid vessels were wider horizontally than vertically. Because ocular movement is usually dominant horizontally, horizontal shear stress might generate cracks in horizontally layered premacular vitreous,[6] in which remnants of hyaloid vessels may be related to the friability of the premacular vitreous. The vitreous and hyaloid vessels are symmetric along the anteroposterior axis during early development and become asymmetric after dominant growth of the temporoposterior region. Since the remnant, cracks, and PVPs were observed only temporally in the premacular vitreous, the asymmetric vitreous growth may contribute to the asymmetric location of these structures. Further study is needed to confirm our preliminary findings.

Tadashi Yokoi, MD, PhD
Naoki Toriyama, MD
Takahiro Yamane, MD, PhD
Yuri Nakayama, MD
Sachiko Nishina, MD, PhD
Noriyuki Azuma, MD, PhD

Author Affiliations: Department of Ophthalmology and Cell Biology, National Center for Child Health and Development, Tokyo, Japan (Yokoi, Toriyama, Yamane, Nakayama, Nishina, Azuma).

Corresponding Author: Dr Azuma, Department of Ophthalmology and Cell Biology, National Center for Child Health and Development, 2-10-1, Okura, Setagaya-ku, Tokyo 157-8535, Japan (azuma-n@ncchd.go.jp).

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Electroretinography combined with spectral domain optical coherence tomography to detect retinal damage in shaken baby syndrome

Yuri Nakayama, MD, Tadashi Yokoi, MD, PhD, Nishina Sachiko, MD, PhD, Makiko Okuyama, MD, PhD, and Noriyuki Azuma, MD, PhD

In order to correlate anatomical changes with visual function in shaken baby syndrome, we performed electroretinography and spectral domain optical coherence tomography on a 2-month-old girl and a 9-month-old girl after the retinal hemorrhages absorbed. Both patients had significant abnormalities in spectral domain optical coherence tomography images of the macular area. The amplitudes of the focal macular electroretinograms were more severely decreased than those of the full-field electroretinograms. Combining spectral domain coherence tomography with focal macular electroretinograms might better estimate the functional damage to the macula in patients with shaken baby syndrome.

Case 1

A 2-month-old otherwise healthy girl with convulsions and epileptic seizures was transferred to the Pediatric Intensive Care Unit at the National Center for Child's Health and Development, Tokyo, for evaluation. Computed tomography scan showed massive subdural hemorrhages from the anterior skull base to the parietal lobe, with diffuse brain edema and multiple brain contusions around the sylvian fissure. Fourteen hours after admission, an ophthalmologic examination showed bilateral multilayered retinal hemorrhages (Figure 1A). The diffuse and dense preretinal, intraretinal, and subhyaloidal hemorrhages were predominantly in the posterior pole but were obscured bilaterally by the vitreous hemorrhages. The intraretinal hemorrhages also extended to the peripheral area. The Suspected Child Abuse and Neglect team diagnosed the patient with shaken baby syndrome (SBS).

The retinal hemorrhages were absorbed completely after 6 months. During this period, we did not perform vitrectomy because the patient was comatose for 3 months as a result of the extensive cerebral injury. We confirmed that the retinal hemorrhages were symmetric and the posterior pole of the retina was observed clearly 4 months after the injury when she gradually recovered consciousness.

Two years after the first examination, the patient had mild mental retardation and cerebral palsy affected the lower legs. Right esotropia with latent nystagmus was confirmed when the left eye was covered. Fixation in the right eye was not confirmed. An aversion response was obvious in the right eye when the left eye was covered. The visual acuity based on a Teller Acuity Card examination showed 0.31 cycles per degree in the left eye.

The complete ocular examination under general anesthesia showed wide chorioretinal degeneration and epiretinal membrane around the arcade vessels in both eyes. The optic disk was pale and fundus examination did not confirm the macular ring reflex in the right eye (Figure 1B). Fluorescein angiography showed a diffuse window defect, particularly along the arcade vessels. Some foveal vascular structures disappeared and the avascular area was wider than normal bilaterally (Figure 1C). There was a relatively wide avascular area from the midperiphery to the anterior nasally and temporally in both eyes (Figure 1D). Spectral domain optical coherence tomography (SD-OCT) images showed focal posterior vitreous separation and marked disruption of the retinal layers in the macula bilaterally. All electroretinography (ERG) components were smaller bilaterally in this case than in the age-matched normal control, and the ERG responses in the right eye were lower than in the left eye (Figure 2). The bright flash response was smaller, but a negative b-wave was seen and the a-wave was preserved bilaterally. A 30 Hz flicker response was significantly reduced in the right eye. The focal macular electroretinogram (fmERG) responses in the right eye were almost flat and nonrecordable, but the responses in the left eye showed an adequate waveform, although with a lower amplitude compared with the control.

Case 2

A 9-month-old girl was referred to the National Center for Child's Health and Development for evaluation of the ocular sequelae of SBS. She had sustained bilateral vitreous and subhyaloid hemorrhages 1 month before. A magnetic resonance imaging scan showed a left frontal subdural hemorrhage and a left palpebral subdural hemorrhage. The latter was assumed to be relatively old because the magnetic resonance imaging signal was lower

Author affiliation: National Center for Child's Health and Development, Tokyo, Japan
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Correspondence: Yuri Nakayama, MD, 2-10-1 Okura, Setagaya-ku, Tokyo, Japan (email: nakayama-y@ncchd.go.jp).
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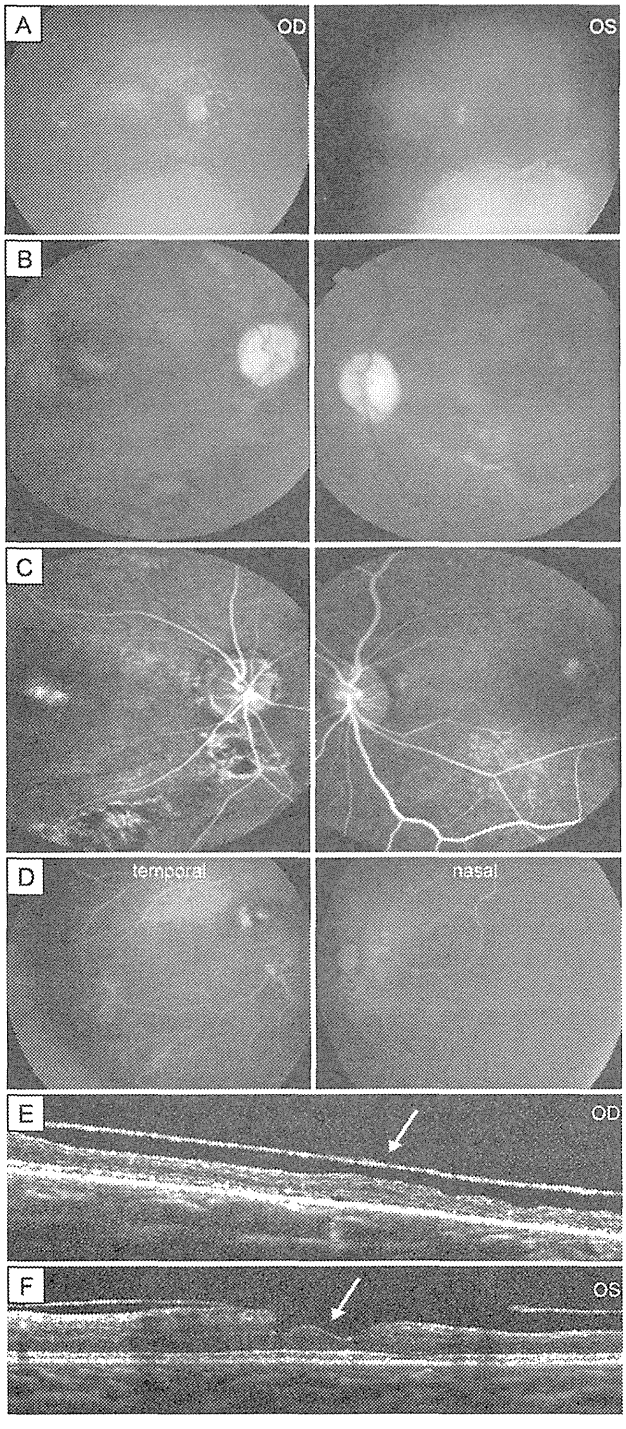

FIG 1. A, A RetCam photograph of an infant (Case 1) with shaken baby syndrome showing dense preretinal, intraretinal, and subhyaloidal hemorrhages predominantly in the posterior pole, obscured bilaterally by vitreous hemorrhages. B, Two years after the injury, marked chorioretinal degeneration with an epiretinal membrane in the posterior pole is seen bilaterally; the optic nerve is pale, and no macular reflux is seen in the right eye. C, Fluorescein angiography (FA) showing a diffuse window defect in the posterior pole bilaterally; loss of the vascular structures is confirmed in the fovea. D, A RetCam FA image showing an area of nonperfusion in the peripheral area nasally and temporally. E-F, SD-OCT images of the right eye and the left eye showing a focal posterior vitreous separation and a markedly disrupted retinal layer in the fovea bilaterally (arrows), especially in the right eye. *OD*, right eye; *OS*, left eye.

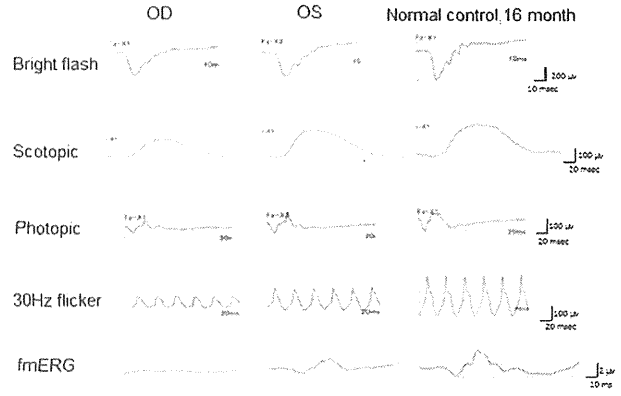

FIG 2. Full-field electroretinograms (ERGs) and focal macular electroretinograms (fmERGs) recorded from Case 1 and a normal control. All ERG components are smaller bilaterally in Case 1 than in the normal control, especially the 30 Hz flicker and fmERG responses. The fmERG shows a nonrecordable wave in the right eye and mildly reduced amplitude in the left eye. *OD*, right eye; *OS*, left eye.

than that of the hemorrhages in the frontal lobe. During our first examination, the vitreous and subhyaloid hemorrhages had almost resolved bilaterally. She could fix and follow, and was orthophoric; there was no nystagmus. Complete ophthalmologic examinations were performed subsequently.

Bilateral indirect fundus examination identified white, elevated rings outside the major vascular arcades around the macula that were consistent with perimacular folds (Figure 3A). Fluorescein angiography showed no distinct abnormal findings in the architecture of the foveal vessels using a fundus camera, and imaging showed no obvious avascular areas bilaterally.

SD-OCT images showed a wide perimacular focal posterior vitreous separation (Figure 3C, D). The foveal structures were mostly spared and the inner segment/outer segment line was seen clearly bilaterally. All full-field ERGs were smaller bilaterally in this case than in the normal control and a negative b-wave was nonrecordable (Figure 4). The waves in the right eye generally were slightly lower than those in the left eye, which was particularly obvious for the 30 Hz flicker response. However, while the fmERGs were recorded, the amplitude in the right eye decreased markedly. We did not perform vitrectomy, because we did not confirm retinal traction and the retinal hemorrhages mostly absorbed spontaneously.

After 4 months, at 10 month of age, her visual acuity measured using the Teller Acuity Cards in the right eye was 0.84 cycles per degree and in the left eye was 1.6 cycles per degree. No strabismus, nystagmus, or developmental delays were observed.

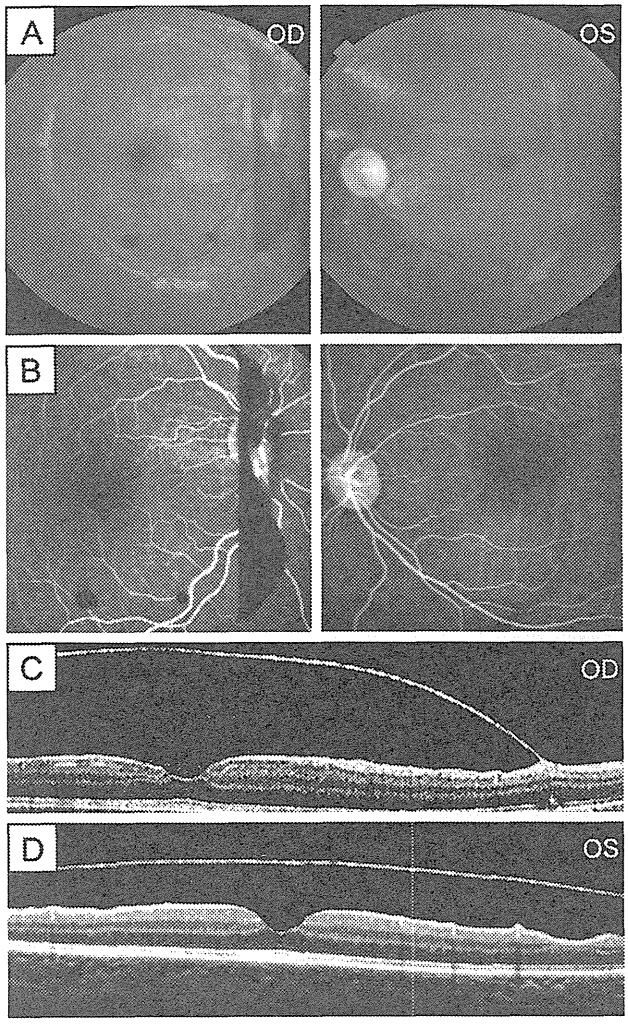

FIG 3. Fundus photograph and FA of an infant (Case 2) with bilateral SBS. A-B, Residual subhyaloid and retinal hemorrhages are confirmed in the right eye; the macula appears normal in both eyes. C-D, The foveal structures are mostly unaffected, as seen on SD-OCT images, although wide perimacular focal posterior vitreous separations are seen bilaterally. *OD*, right eye; *OS*, left eye.

Discussion

The present study investigated the correlation between the morphologic changes and fmERGs in 2 cases of SBS to predict the visual prognosis. We found that severe disruption of the retinal layers on SD-OCT might be better correlated with lower amplitude of the fmERGs than the amplitudes of the full-field ERGs; however, this study was too small to be certain that this is a true association. Previous ERG studies in patients with SBS have suggested that the inner retinal layer was primarily responsible for visual loss because a reduced b-wave and a relatively well-preserved a-wave were reported on full-field ERG.[1,2] fmERG is a noninvasive technique to objectively assess the neural activities of the macular area.[3] The correlation between the fmERG amplitude and macular volume by optical coherence tomography in retinitis pigmentosa[4] and visual acuity in age-related macular degeneration[5] has been previously reported. Performing fmERGs might facilitate further understanding of the macular functional damage in SBS.

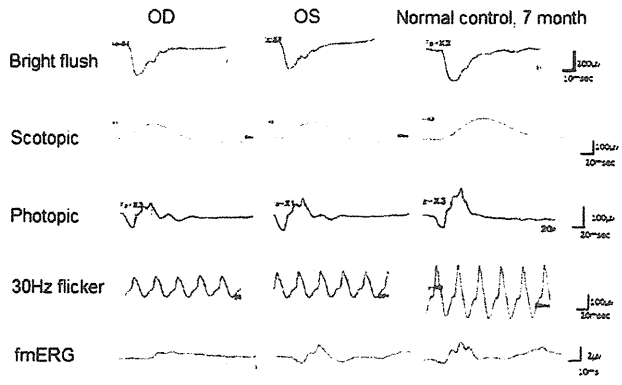

FIG 4. Full-field ERGs and fmERGs recorded from Case 2 and a normal control. All ERG components are smaller bilaterally in Case 2 than in the normal control, especially the 30 Hz flicker and fmERG responses. The fmERGs show waves with markedly lower amplitudes in the right eye and mildly reduced amplitudes in the left eye.

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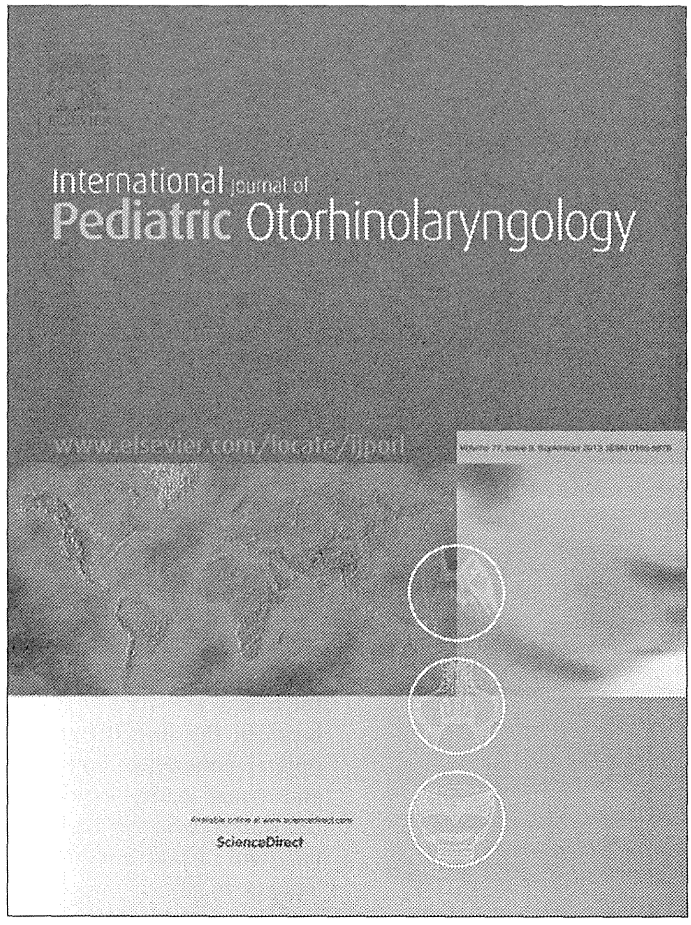

CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Identification of a Novel Missense Mutation of *MAF* in a Japanese Family With Congenital Cataract by Whole Exome Sequencing: A Clinical Report and Review of Literature

Yoko Narumi,[1,2]* Sachiko Nishina,[3] Motoharu Tokimitsu,[4] Yoko Aoki,[5] Rika Kosaki,[6] Keiko Wakui,[1] Noriyuki Azuma,[3] Toshinori Murata,[4] Fumio Takada,[2] Yoshimitsu Fukushima,[1] and Tomoki Kosho[1]

[1]Department of Medical Genetics, Shinshu University School of Medicine, Matsumoto, Japan

[2]Department of Medical Genetics, Kitasato University Graduate School of Medical Sciences, Sagamihara, Japan

[3]Division of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan

[4]Department of Ophthalmology, Shinshu University School of Medicine, Matsumoto, Japan

[5]Department of Medical Genetics, Tohoku University School of Medicine, Sendai, Japan

[6]Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan

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Congenital cataracts are the most important cause of severe visual impairment in infants. Genetic factors contribute to the disease development and 29 genes are known to cause congenital cataracts. Identifying the genetic cause of congenital cataracts can be difficult because of genetic heterogeneity. V-maf avian musculoaponeurotic fibrosarcoma oncogene homolog (*MAF*) encodes a basic region/leucine zipper transcription factor that plays a key role as a regulator of embryonic lens fiber cell development. *MAF* mutations have been reported to cause juvenile-onset pulverulent cataract, microcornea, iris coloboma, and other anterior segment dysgenesis. We report on six patients in a family who have congenital cataracts were identified *MAF* mutation by whole exome sequencing (WES). The heterozygous *MAF* mutation Q303L detected in the present family occurs in a well conserved glutamine residue at the basic region of the DNA-binding domain. All affected members showed congenital cataracts. Three of the six members showed microcornea and one showed iris coloboma. Congenital cataracts with *MAF* mutation exhibited phenotypically variable cataracts within the family. Review of the patients with *MAF* mutations supports the notion that congenital cataracts caused by *MAF* mutations could be accompanied by microcornea and/or iris coloboma. WES is a useful tool for detecting disease-causing mutations in patients with genetically heterogeneous conditions. © 2014 Wiley Periodicals, Inc.

Key words: congenital cataract; *MAF*; iris coloboma; microcornea; whole exome sequencing

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INTRODUCTION

Congenital cataracts are an ocular abnormality causing crystalline lens opacification and are the most important cause of severe visual impairment in infants. [Huang and He, 2010]. The estimated prevalence of congenital cataracts are 1–15 cases per 100,000 live births in the world [Santana and Waiswol, 2011]. Congenital cataracts are considered to occur during embryonic development. Between 8.3% and 25% of congenital cataracts are considered to be inherited as autosomal dominant, autosomal recessive, or X-linked

Conflict of interest: none.
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*Correspondence to:
Yoko Narumi, M.D., Ph.D., Department of Medical Genetics, Kitasato University Graduate School of Medical Sciences, 1-15-1, Kitasato, Sagamihara, Kanagawa 252-0373 Japan.
E-mail: ynrmk@kitasato-u.ac.jp
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