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
東　範行	眼疾病学	丸尾敏夫・栗屋忍	視能矯正学改訂第2版増補	金原出版	東京	2008	125-137
東　範行	未熟児網膜症	山本　節	視能訓練士用語解説辞典	メディカル葵	東京	2009	印刷中
東　範行	網膜裂孔	山本　節	視能訓練士用語解説辞典	メディカル葵	東京	2009	印刷中

雑　誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Yokoi T, Nishina S, Azuma N.	Glial extrusion from the regressed retinoblastoma afterconservative treatment.	Acta Ophthalmol Scand	86	462-464	2008
Hiraoka M, Nishina S, Nakagawa A, Matsuoka K, Azuma N.	Case of aggressive posterior retinopathy of prematurity with atypical neovascular growth.	Jpn J Ophthalmol	52	417-419	2008
Nishina S, Suzuki Y, Azuma N.	Exudative retinal detachment following cataract surgery in Hallermenn-Steiff syndrome.	Jpn J Ophthalmol	246	453-455	2008
Seko Y, Azuma N, Takahashi Y, Makino H, Morito T, Muneta T, Matsumoto K, Saito H, Sekiya I, Umezawa A.	Human sclera maintains common characteristics with cartilage throughout evolution.. 2008 2008 Nov 12	PLoS ONE	3 (11)	e3709. Epub	2008
Iso M, Fukami M, Horikawa R, Azuma N, Kawashiro N, Ogata T.	SOX10 mutation in Warrdenburg syndrome type II. .	Am J Med Genet	146A	2162-2163	2008
Azuma N, Hida T, Kohsaka S.	Hypovascular glial overgrowth from the optic nerve head in fetuses of 16 weeks gestation	Acta Ophthalmol Scand	86	Epub	2008

Yokoi T, Nakagawa A, Matsuoka K, Koide R, Azuma N.	Analysis of pathology in type I Stickler syndrome.	Acta Ophthalmol Scand	86	Epub	2008
Suzuki Y, Yokoi T, Hiraoka M, Nishina S, Azuma N.	Congenital rotated macula with relatively good vision and binocularity.	Jpn J Ophthalmol		In press	2009
Yokoi T, Nakagawa A, Matsuoka K, Koide R, Azuma N.	Analysis of pathology in type I Stickler syndrome.	Acta Ophthalmol Scand		In press	2009
Kobayashi Y, Suzuki K, Oba S, Nishina S, Azuma N, Okuyama M.	Ocular manifestations and prognosis of shaken baby syndrome in Japanese children's hospitals.	Jpn J Ophthalmol		In press	2009
Yokoi T, Hiraoka M, Miyamoto M, Yokoi T, Kobayashi Y, Nishina S, Azuma N.	Vascular abnormalities of aggressive posterior retinopathy of prematurity by fluorescein angiography findings.	Ophthalmology		In press	2009
Nishina S, Yokoi T, Yokoi T, Kobayashi Y, Hiraoka M, Azuma N.	Effect of early vitreous surgery for aggressive posterior retinopathy of prematurity detected by fluorescein angiography.	Ophthalmology		In press	2009
Shimizu N, Watanabe H, Kubota J, Wu J, Saito R, Yokoi T, Era T, Iwatsubo T, Watanabe T, Nishina S, Azuma N, Katada T, Nishina H..	Pax6-5a promotes neuronal differentiation of murine embryonic stem cells.	Biol Pharm Bull		In press	2009
東　範行	黄斑を形成する遺伝子システムと再生医療への応用.	医学のあゆみ	226	965-972	2008
東　範行	熟児網膜症の最新の医療.	医療	63	In press	2009
東　範行	未熟児網膜症の診断と治療.	日本眼科医会		In press	2009
Zako M, Kataoka T, Ohno-Jinno A, Inoue Y, Kondo M, Iwaki M	Analysis of progressive ophthalmic lesion in a patient with subacute [illegible]	European Journal of Ophthalmology	15	155-158	2008
Hood DC, Bach M, Keating D, Kondo M, Lyons JS, Palmowski-Wolfe AM	Standard for multifocal electroretinography.	Documenta Ophthalmologica	116	1-11	2008

Koyasu T, Kondo M, Miyata K, Ueno S, Nishizawa Y, Miyake Y, Terasaki H	Photopic electroretinograms of mGluR6-deficient mice.	Current Eye Research	33	91-99	2008
Kondo M, Ueno S, Piao CH, Miyake Y. Terasaki H	Focal macular cone ERG in complete type CSNB: A comparison with APB-treated monkeys.	Vision Research	48	273-280	2008
Kurimoto T, Kondo M, Nishimura M, Oono S, Tagami Y, Okamoto N, Mimura O.	Acute bilateral peripheral cone system dysfunction.	Retinal Cases & Brief Reports	2	193-195	2008
Miyata K, Ueno S, Kondo M, Koyasu T, Terasaki H	Comparison of photopic negative response elicited by red and white xenon flashes in monkeys.	Japanese Journal of Ophthalmology	52	327-330	2008
Nishihara H, Kondo M, Ishikawa K, Sugita T, Piao CH, Nakamura Y, Terasaki H.	Focal macular electroretinograms in eyes with wet type age-related macular degeneration.	Investigative Ophthalmology & Visual Science	49	3121-3125	2008
Kondo M, Kurimoto Y, Sakai T, Koyasu T, Miyata K, Ueno S, Terasaki H.	Recording focal macular photopic negative response (PhNR) from monkeys.	Investigative Ophthalmology & Visual Science	49	3544-3550	2008
Sato S, Omori Y, Katoh K , Kondo M , Kanagawa M , Miyata K, Funabiki K, Koyasu T, Kajimura N, Miyoshi T, Sawai H, Kobayashi K, Tani A, Toda T, Usukura J, Tano Y , Fujikado T, Furukawa T	An essential role of pikachurin, a novel dystroglycan-binding protein, in bipolar dendrite apposition to photoreceptor ribbon synapse in the retina.	Nature Neuroscience	11	923-931	2008
Sugita T, Kondo M, Piao CH, Ito Y, Terasaki H.	Correlation between macular volume and focal macular electroretinogram in patients with retinitis pigmentosa.	Investigative Ophthalmology & Visual Science	49	3551-3558	2008
Kurimoto Y, Kondo M, Ueno S, Sakai T, Machida S, Terasaki H	Asymmetry of focal macular photopic negative responses (PhNRs) in monkeys.	Experimental Eye Research	88	92-98	2009

Kondo M, Sakai T, Komeima K, Kurimoto Y, Ueno S, Nishizawa Y, Usukura J, Tano Y, Terasaki H.	Generation of a transgenic rabbit model of retinal degeneration.	Investigative Ophthalmology & Visual Science	50	in press	2009
Nakazawa T, Shimura M, Mourin R, Kondo M, Yokokura S, Saido C Takaomi, Nishida K, EndoS.	Calpain-mediated degradation of G-substrate plays a critical role in retinal excitotoxicity for amacrine cells.	Journal of Neuroscience Research	87	in press	2009
Tanaka-Kitajima N, Iwata N, Ando Y, Sakurai H, Iwami M, Tsuzuki K, Kondo M, Ito Y, Kimura H.	Acute retinal necrosis caused by herpes simplex virus type 2 in a 3-year-old Japanese boy.	European Journal of Pediatrics	168	in press	2009
Ishikawa K, Nishihara H, Ozawa S, Piao CH, Ito T, Kondo M, Terasaki H.	Focal macular electroretinograms after photodynamic therapy combined with posterior juxtascleral triamcinolone acetonide.	Retina	29	in press	2009
Ito N, Kachi S, Kondo M, Takai Y, Terasaki H.	Concentration of vascular endothelial growth factor in aqueous humor of eyes with advanced retinopathy of prematurity before and after injection of bevacizumab.	Retina	29	in press	2009
Nakamura Y, Kondo M, Asami T, Terasaki H.	Comparison of macular hole surgery without internal limiting membrane peeling to eyes with internal limiting membrane peeling with and without indocyanine green staining: Three year follow-up.	Ophthalmic Research	41	in press	2009
浅野麻衣、正木勢津子、稲垣理佐子、彦谷明子、堀田喜裕、佐藤美保	液晶視力表　システムチャートSC-2000の臨床評価	眼臨紀	1	60-63	2008
佐藤美保	間欠性外斜視　小児の両外直筋後転術.	眼臨紀	1	47-50	2008

Miho Sato, Emi Amano, Yoshiko Takai, Akiko Hikoya, Yuka Koide,	Superior oblique palsy with class III tendon anomaly.	Am J Ophthalmol	146	385-394,	2008
Akiko Hikoya, Miho Sato, Kinnichi Tsuzuki, Yuka Maruyama Koide, Ryo Asaoka, Yoshihiro Hotta.	Central corneal thickness in Japanese children.	Jpn J Ophthalmol	53	7-11	2009
Emi Amano, Miho Sato, Kiyoko Ukai, Hiroko Terasaki.	Magnetic resonance imaging of extraocular muscle path before and after strabismus surgery for treating large degree of cyclotorsion induced by macular translocation surgery.	Jpn J Ophthalmol		In press	2009
Wang C-X, Nakanishi N, Ohishi K, Hikoya A, Koide K, Sato M, Nakamura M, Hotta Y, Minoshima S	Novel *RDH5* mutation in family with mother having fundus albipunctatus and three children with retinitis pigmentosa.	Ophthalmic Genetics	29	29-32	2008
平井敦子、不二門 尚他	顕微鏡下における立体視機能の検討	眼科臨床紀要	2巻2号	149-152	2009
Bessho K, Fujikado T,et al.	Photoreceptor images of normal eyes and of eyes with macular dystrophy obtained in vivo with an adaptive optics fundus camera.	Jpn J Ophthalmology	52巻	380-385	2008
Kitaguchi Y, Fujikado T, et al	Adaptive Optics Fundus Camera to Examine Localized Changes in the Photoreceptor Layer of the Fovea.	Ophthalmology	115巻10号	1171-1177	2008
Mochizuki Y, Enaida Hisatomi T, Hata Y, Miura M, Arita R, Kawahara S, Kita T, Ueno A, Ishibashi T	The internal limiting membrane peeling with brilliant blue G staining for retinal detachment due to macular hole in high myopia.	Br J Ophthalmol	92	1009	2008

Kawahara S, Hata Y, Kita T, Arita R, Miura M, Nakao S, Mochizuki Y, Enaida H, Kagimoto T, Goto Y, Hafezi-Moghadam A, Ishibashi T:	Potent inhibition of cicatricial contraction in proliferative vitreoretinal diseases by statins	Diabetes	57	2784-2793	2008
Murakami Y, Ikeda Y, Yonemitsu Y, Onimaru M, Nakagawa K, Kohno R, Miyazaki M, Hisatomi T,Nakamura M, Yabe T, Hasegawa M,Ishibashi T,Sueishi K	Inhibition of nuclear translocation of apoptosis-inducing factor is an essential mechanism of the neuroprotective activity of pigment epithelium-derived factor in a rat model of retinal	Am J Pathol	173	1326-1338	2008
Kita T, Hata Y, Arita R, Kawahara S, Miura M, Nakao S, Mochizuki Y, Enaida H, Goto Y, Shimokawa H, Hafezi-Moghadam A, Ishibashi T	Role of TGF-beta in proliferative vitreoretinal diseases and ROCK as a therapeutic target.	PNAS	45	17504-17509	2008

Case of Aggressive Posterior Retinopathy of Prematurity with Atypical Neovascular Growth

Fibrovascular proliferation in eyes with retinopathy of prematurity (ROP) usually, but not always, appears at the junction of the vascularized and nonvascularized retina.[1] Aggressive posterior ROP (AP-ROP) occurs in the posterior retina and progresses rapidly to total retinal detachment.[2] We report an atypical case of AP-ROP in which the neovascularization developed in the posterior retina around the optic disc.

Case Report

A female infant was born at 30 weeks' gestation (birth weight, 1670 g) with severe persistent pulmonary hypertension from prolonged premature rupture of the membranes and oligohydramnios. She was treated with nitric oxide (NO) inhalation for 28 days. At 33 weeks postmenstrual age, an ophthalmoscopic examination identified initial signs of zone I AP-ROP bilaterally, including marked dilation and tortuosity of the posterior pole vessels (zone I, stage 1 ROP with plus disease).

Argon laser photocoagulation was performed (duration, 300–400 ms; power, 300–400 mW; 3751 shots OD, 3658 shots OS) under intravenous sedation (fentanyl) with topical anesthesia. However, fibrovascular proliferation and retinal detachment developed bilaterally in the posterior retina around the optic disc 1 week postoperatively (Fig. 1a, b). The patient underwent vitrectomy with lensectomy as a secondary treatment at 35 weeks postmenstrual age. The retina was reattached and the ROP stabilized in the left eye, but the fibrovascular tissue regrew from the posterior retina of the right eye (Fig. 1c). A second vitrectomy stabilized the ROP in that eye (Fig. 1d).

Immunohistochemistry of the fibrovascular tissue collected during vitrectomy was strongly positive for factor VIII over a wide area and locally positive for vimentin but negative for glial fibrillary acidic protein. These findings suggested that the tissue consisted mainly of vascular endothelial cells (Fig. 2).

Comments

We report the successful surgical results of early vitrectomy for AP-ROP.[3] Our findings suggest that when neovascularization develops only at the peripheral end of the developing vessels, the retina can be reattached by removing the vitreous framework around the fibrovascular tissue and the vitreous base. These procedures reduce the tractional forces of the fibrovascular tissue and suppress neovascular growth. Residual vitreous gel did not affect the retinal reattachment, and a regrowth of neovascularization was not observed in a previous study.[3]

In our case, the neovascularization that developed in the posterior retina could have grown along the residual vitreous gel on the retinal surface and around the optic disc. This tissue could not be completely removed during the initial vitrectomy. In cases such as this, another vitrectomy to peel the residual vitreous gel can lead to retinal reattachment, which worked well in our case.

Jpn J Ophthalmol
Vol 52: 407–425, 2008

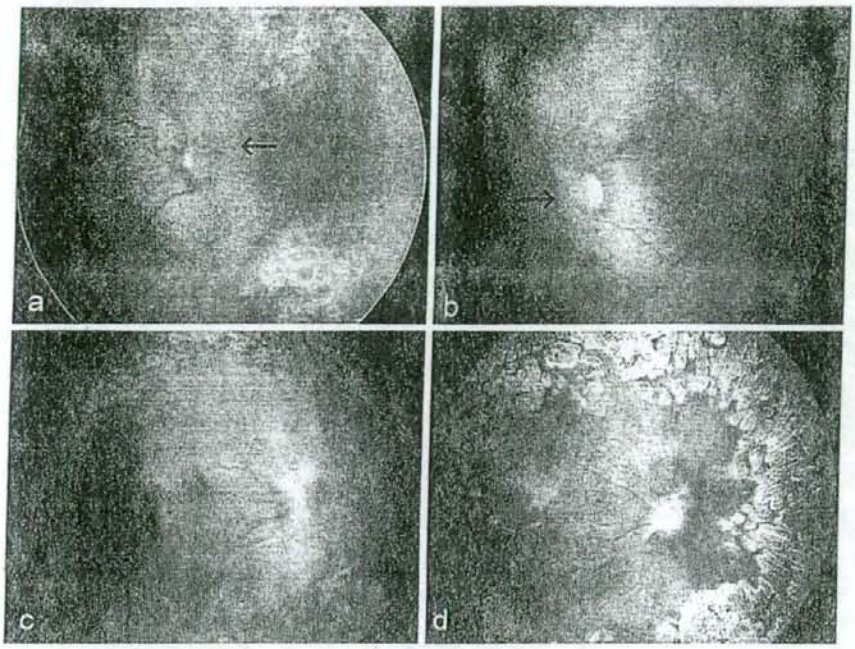

Figure 1a–d. Preoperative and postoperative fundus photographs of eyes with aggressive posterior retinopathy of prematurity (ROP). **a** Preoperative fundus image of the right eye. **b** Preoperative fundus image of the left eye. Fibrovascular proliferation and tractional retinal detachment (*arrows*) are present nasally in the posterior retina of both eyes. **c** Two weeks after the initial vitrectomy, the neovascularization has regrown and formed a fibrous membrane and tractional retinal detachment in the right eye. **d** The retina is reattached and the ROP is stabilized after additional vitrectomy of the right eye.

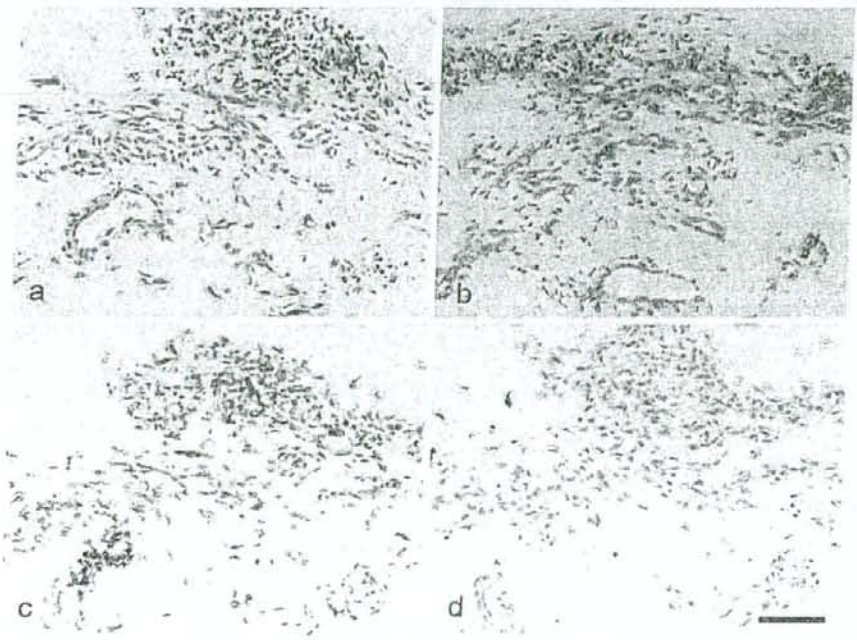

Figure 2a–d. Pathology and immunohistochemistry of the fibrovascular tissue obtained during the second vitrectomy. H&E staining (**a**) and immunohistochemistry with antibodies against factor VIII (**b**), vimentin (**c**), and glial fibrillary acidic protein (**d**). Immunohistochemistry showed that the fibrovascular tissue was strongly positive for factor VIII over a wide area (**b**), and was locally positive for vimentin (**c**) but negative for glial fibrillary acidic protein (**d**). These findings suggest that the tissue was composed of vascular endothelial cells (scale bar = 50 μm).

In eyes with AP-ROP, a flat network of neovascularization arises from the peripheral terminals of the developing vessels as in classical ROP, even though vascular shunts occur in the vascularized retina. However, in our patient, the fibrovascular proliferation developed atypically in the posterior retina around the optic disc. Except for the prolonged NO inhalation, systemic therapies including oxygen administration and laser application might not contribute

to the atypical growth of the neovascularization. While NO is known to derive vasodilatation and up-regulates regional basal blood flow,[4] it also activates angiogenic cell migration and proliferation-inducing factors, including fibroblast growth factor 2 and vascular endothelial growth factor.[5] Because retinal angiogenesis is ongoing in premature infants, NO might have contributed to the atypical neovascularization near the optic disc in our patient.

In animal models of oxygen-induced retinopathy, neovascularization induced by obliteration of the immature capillaries also develops from the optic disc and posterior retina.[6] Because AP-ROP develops in the posterior retinal area, including zone I, this suggests that immature capillaries may be widely present, and neovascularization arises from the retina near the optic disc. Capillary nonperfusion in vascularized retinas has been identified in eyes with threshold ROP.[7] Thus, there might be a much wider area of nonperfusion in the posterior retina in eyes with AP-ROP, which should be studied using fluorescein angiography.

Acknowledgments: This work was supported by grants for research on sensory disorders from the Ministry of Health, Labour and Welfare, Japan.

Key Words: aggressive posterior retinopathy of prematurity, fibrovascular proliferation, photocoagulation, regrowth, vitrectomy

Miina Hiraoka, Sachiko Nishina, Atsuko Nakagawa, Kentaro Matsuoka, and Noriyuki Azuma
Department of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan

Received: December 11, 2007 / Accepted: April 23, 2008
Correspondence to: Noriyuki Azuma, Department of Ophthalmology, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan
e-mail: azuma-n@ncchd.go.jp

DOI 10.1007/s10384-008-0557-3

References

1. Foos RY. Retinopathy of prematurity. Pathologic correlation of clinical stages. Retina 1987;7:260–276.
2. International Committee for the Classification of Retinopathy of Prematurity. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol 2005;123:991–999.
3. Azuma N, Ishikawa K, Hama Y, Hiraoka M, Suzuki Y, Nishina S. Early vitreous surgery for aggressive posterior retinopathy of prematurity. Am J Ophthalmol 2006;142:636–643.
4. Gross SS, Wolin MS. Nitric oxide: pathophysiological mechanisms. Annu Rev Physiol 1995;57:737–769.
5. Ziche M, Morbidelli L. Nitric oxide and angiogenesis. J Neurooncol 2000;50:139–148.
6. McLeod DS, D'Anna SA, Lutty GA. Clinical and histopathological features of canine oxygen-induced proliferative retinopathy. Invest Ophthalmol Vis Sci 1998;39:1918–1932.
7. Schulenburg WE, Tsanaktsidis G. Variations in the morphology of retinopathy of prematurity in extremely low birthweight infants. Br J Ophthalmol 2004;88:1500–1503.

Graefes Arch Clin Exp Ophthalmol (2008) 246:453–455
DOI 10.1007/s00417-007-0741-z

CASE REPORT

Exudative retinal detachment following cataract surgery in Hallermann-Streiff syndrome

Sachiko Nishina · Yumi Suzuki · Noriyuki Azuma

Received: 7 September 2007 / Revised: 17 November 2007 / Accepted: 27 November 2007 / Published online: 12 January 2008

Abstract
Purpose To report two cases of Hallermann-Streiff syndrome with exudative retinal detachment after cataract surgery.
Methods Case report.
Results Four eyes of two patients with Hallermann-Streiff syndrome developed exudative retinal detachments after lensectomy and anterior vitrectomy at 2 and 4 months of age. Both patients had extreme microphthalmia. The exudative retinal detachment regressed spontaneously in three of the four eyes; however, one eye required subscleral sclerectomy. In one patient, the best-corrected visual acuity was 20/200 at 3 years of age; the other patient had good fixation and following behavior in each eye at 1 year of age.
Conclusions Early surgery to treat congenital cataracts in extremely microphthalmic eyes associated with the Hallermann-Streiff syndrome may induce exudative retinal detachment. However, the retinal detachments tend to regress and may not cause severe visual impairment.

Keywords Hallermann-Streiff syndrome · Exudative retinal detachment · Cataract surgery · Microphthalmos

Introduction

The Hallermann-Streiff syndrome is a rare complex of developmental abnormalities characterized by dyscephaly with bird face, beak nose and micrognathia, dental anomalies, hypotrichosis, skin atrophy, microphthalmia, congenital cataracts, and proportionate dwarfism [1]. Most cases are sporadic, and the etiology is unknown. Various ocular findings and fundus anomalies have been reported, including vitreous degeneration, retinal folds, coloboma, and Coats' disease; however, a few reports have described detailed fundus changes after cataract surgery [2–4]. To our knowledge, this is the first report on the development of exudative retinal detachments after cataract surgery in four microphthalmic eyes of two patients with the Hallermann-Streiff syndrome.

Case report

Patient 1, a 1-month-old Japanese male infant, referred with a diagnosis of bilateral congenital cataracts and microphthalmia. He had the typical features of the Hallermann-Streiff syndrome, including dyscephaly with beak nose and micrognathia, dental anomalies, hypotrichosis, skin atrophy, and proportionate dwarfism (Fig. 1a). A slit-lamp examination revealed total cataracts, a microcornea (corneal diameter, 7×7.5 mm OD and 8×8.5 mm OS), a shallow anterior chamber, posterior synechiae, and poor pupil dilation in both eyes. Ultrasonography showed bilateral microphthalmia (axial length, 13 mm OD and 14 mm OS) but no other posterior segment anomalies. Lensectomy and anterior vitrectomy via the limbal approach using a 25-gauge surgical system was performed in both eyes at 2 months of age. No intraoperative or postoperative complications developed except for transient corneal edema. Ophthalmoscopy identified small retinal folds between the disc and fovea in both eyes. The aphakic eyes were corrected with glasses, and both eyes developed fixation and following behavior.

The authors have no proprietary interest in any aspect of this report.

S. Nishina (✉) · Y. Suzuki · N. Azuma
Department of Ophthalmology,
National Center for Child Health and Development,
2-10-1 Ohkura, Setagaya-ku,
Tokyo 157-8535, Japan
e-mail: nishina-s@ncchd.go.jp

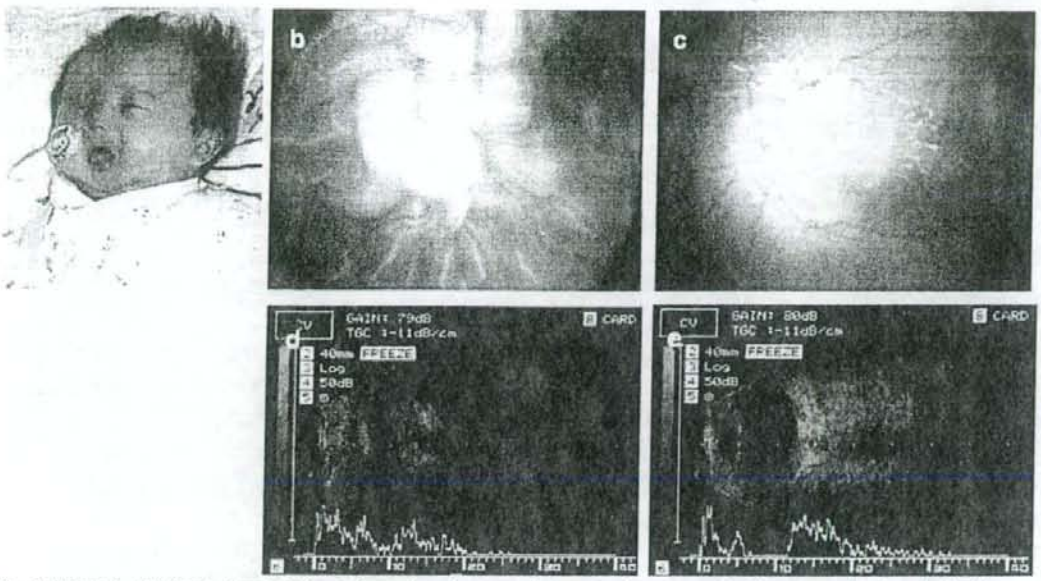

Fig. 1 Patient 1. (**a**) Facial characteristics at 2 months of age. Bilateral exudative retinal detachments at 7 months of age. The right eye (**b**) has the more severe retinal detachment and requires subscleral sclerectomy. The left eye (**c**) also has an exudative retinal detachment that regressed spontaneously. Ultrasonography shows both right eye (**d**) and left eye (**e**) have exudative retinal detachments with choroidal thickening

We examined the patient every month and then at 5 months after cataract surgery (7 months of age) when exudative retinal detachment developed in both eyes (Fig. 1b,c). Ultrasonography also showed bilateral exudative retinal detachment with choroidal thickening (Fig. 1d,e). The retinal detachment spontaneously regressed in the left eye, but progressed and did not regress in the right eye. Following behavior in the right eye deteriorated, and we performed a subscleral sclerectomy twice in that eye using 0.02% mitomycin C at 1 year 9 months and 2 years 4 months of age. The retinal detachment regressed, and at 3 years 5 months of age did not recur in either eye. The best-corrected visual acuity (BCVA) was 2/100 in the right eye and 20/200 in the left eye.

Patient 2, a 5-month-old Japanese female infant, referred with a diagnosis of bilateral retinal detachments after cataract surgery. She had undergone lensectomy and anterior vitrectomy at 4 months of age in another hospital. She exhibited the characteristic features of the Hallermann-Streiff syndrome, including dyscephaly with beak nose and micrognathia, dental anomalies, hypotrichosis, and proportionate dwarfism. A slit-lamp examination showed bilateral aphakia and a microcornea (corneal diameter, 7×7.5 mm OD and 8×8.5 mm OS). Ophthalmoscopy of both eyes showed exudative retinal detachments (Fig. 2). Ultrasonography showed bilateral microphthalmia (axial length, 13 mm OD and 14 mm OS) and retinal detachments with choroidal thickening. The retinal detachments spontaneous-

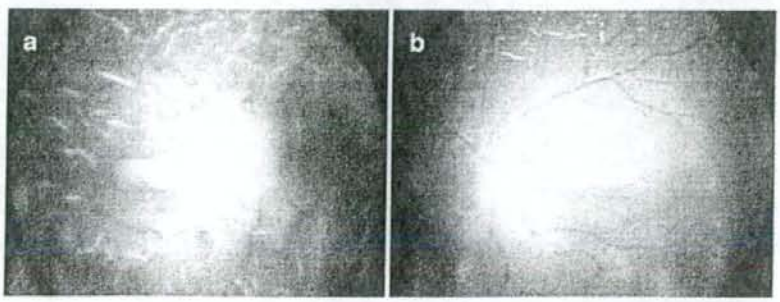

Fig. 2 Patient 2. Bilateral exudative retinal detachments at 1 years of age. The exudative retinal detachments regressed spontaneously in the right eye (**a**) and the left eye (**b**)

ly regressed in both eyes, and the patient had good fixation and following behavior with each eye at 1 year of age.

Discussion

These four eyes of two patients had severe microphthalmos and developed exudative retinal detachments after early surgery for congenital cataracts at 2 and 4 months of age. One of the four eyes required surgery; however, the retinal detachment regressed in three eyes, and the visual acuity was not severely impaired. This suggests that the extreme microphthalmic eye in the Hallermann-Streiff syndrome may have considerable scleral abnormalities that impede transscleral intraocular fluid outflow and result in congestion of the choroidal vein [5]. Early cataract surgery is supposed to induce hypotony, marked intraocular inflammation and transiently accelerate production of a protein-rich exudate. Intraocular fluid outflow may severely be resisted postoperatively and accumulated in choroid without venous drainage. It may possibly cause early onset of exudative retinal detachment in these eyes.

In this syndrome, spontaneous cataract absorption sometimes occurs, but results in deprivation amblyopia, iridocyclitis, and glaucoma [4, 6]. Although exudative retinal detachment tends to occur, it is preferable to perform early cataract surgery using less invasive procedures.

References

1. François J (1958) A new syndrome: Dyscephalia with bird face and dental anomalies, nanism, hypotrichosis, cutaneous atrophy, microphthalmia, and congenital cataract. Arch Ophthalmol 60:842–862
2. Cohen MM Jr (1991) Hallermann-Streiff syndrome: a review. Am J Med Genet 41:488–499
3. Newell SW, Hall BD, Anderson CW, Lim ES (1994) Hallermann-Streiff syndrome with Coats disease. J Pediatr Ophthalmol Strab 31:123–125
4. Hopkins DJ, Horan EC (1970) Glaucoma in the Hallermann-Streiff syndrome. Br J Ophthalmol 54:416–422
5. Ryan EA, Zwaan J, Chylack LT (1982) Nanophthalmos with uveal effusion. Clinical and embryologic considerations. Ophthalmology 89:1013–1017
6. Wolter JR, Jones DH (1965) Spontaneous cataract absorption in Hallermann-Streiff syndrome. Ophthalmologica 150:401–408

American Journal of Medical Genetics Part A 146A:2162–2163 (2008)

Research Letter

SOX10 Mutation in Waardenburg Syndrome Type II

Manami Iso,[1] Maki Fukami,[1] Reiko Horikawa,[2] Noriyuki Azuma,[3] Nobuko Kawashiro,[4] and Tsutomu Ogata[1]*

[1]Department of Endocrinology and Metabolism, National Research Institute for Child Health and Development, Tokyo, Japan
[2]Division of Endocrinology and Metabolism, National Center for Child Health and Development, Tokyo, Japan
[3]Division of Ophthalmology, National Center for Child Health and Development, Tokyo, Japan
[4]Division of Otorhinolaryngology, National Center for Child Health and Development, Tokyo, Japan

Received 20 February 2008; Accepted 3 May 2008

How to cite this article: Iso M, Fukami M, Horikawa R, Azuma N, Kawashiro N, Ogata T. 2008. *SOX10* mutation in Waardenburg syndrome type II. Am J Med Genet Part A 146A:2162–2163.

To the Editor:

Waardenburg syndrome (WS) is a congenital developmental disorder characterized by sensorineural hearing loss and abnormal pigmentation of the eye, hair, and skin [Jones, 2006]. This condition is divided into four types [reviewed in Jones, 2006; Bondurand et al., 2007]. Type I WS (WS1) consists of dystopia canthorum and broad nasal root, and is almost exclusively caused by heterozygous mutations of *PAX3*. Type II WS (WS2) lacks the dystopia canthorum and results from heterozygous mutations of *MITF* (WS2A) in ~15% of patients and homozygous deletions of *SNAI2* (WS2D) in two patients. Type III WS (WS3) (Klein–Waardenburg syndrome), a severe form of WS1, is associated with upper limb defects, and is ascribed to heterozygous or homozygous mutations of *PAX3*. Type IV WS (WS4) (Shah–Waardenburg syndrome) is characterized by Hirschsprung disease, and is caused by heterozygous or homozygous mutations of *EDNRB* or its ligand *EDN3*, or by heterozygous mutations of *SOX10*.

Thus, the underlying causes remain to be clarified in most of the WS2 patients. While a WS2 locus is mapped to chromosome 1p (WS2B) [Lalwani et al., 1994] and chromosome 8q23 (WS2C) [Selicorni et al., 2002], a causative gene(s) has not been identified from these regions. In this regard, Bondurand et al. [2007] have recently identified *SOX10* deletions in patients with WS2, implying that *SOX10* abnormalities can cause WS2 (WS2E) as well as WS4. Here, we describe another case of WS2E caused by heterozygous *SOX10* mutation.

This Japanese girl was born to nonconsanguineous healthy parents at 41 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, her length was 49.6 cm (+0.6 SD), and her weight 3.4 kg (+0.1 SD). She was found to have light blue eyes, and referred to us at 12 days of age. She manifested hypopigmented irides and a piece of white forelock, but lacked dystopia canthorum, broad nasal root, and Hirschsprung disease. Ophthalmologic examinations revealed bilateral ocular albinism with hypopigmented fundus and hypochromic iris. At 3.5 months of age, auditory brainstem response was performed because of poor responses to sounds, showing bilateral severe sensorineural deafness (hearing level, 90 dB bilaterally). Brain computed tomography showed no abnormal finding. On the basis of the above findings, she was diagnosed as having WS2.

After obtaining written informed consent, direct sequencing was performed for leukocyte genomic DNA of this patient, detecting no abnormality in the coding sequences of *PAX3*, *MITF*, and *SNAI2*. However, we identified a heterozygous *SOX10* frameshift mutation (c.506delC) on exon 4 that is predicted to result in a premature termination at the 284th amino acid (p.Pro169fsX284) (Fig. 1A). The primer sequences and the annealing temperature used were: exon 3, GTTGGACTCTTTGCGAGGAC and ATCCACCCGAAGCTAGAGG (58°C); exon 4, AGCCCCTCTGCTGTCCTCT and CACCCTCAGCTCTGTCATCA (60°C); and exon 5, CTAACCTGCTTCCCCCTTG and CAAGGAACAGGGCACACAG (58°C). This frameshift mutation located within the high mobility group (HMG) DNA-binding domain, and removed the C-terminal part of the HMG domain and the whole transactivation domain. This mutation is predicted to destroy an *Nci*I restriction site, and

*Correspondence to: Tsutomu Ogata, M.D., Department of Endocrinology and Metabolism, National Research Institute for Child Health and Development, Tokyo 157-8535, Japan. E-mail: tomogata@nch.go.jp

Published online 14 July 2008 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/ajmg.a.32403

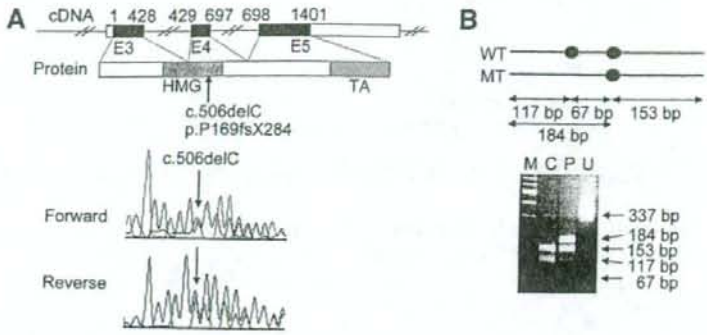

FIG. 1. Mutational analysis of *SOX10*. **A**: Direct sequencing of exon 4. Shown on the upper part is a schematic representation indicating the coding exons 3–5 (E3–E5) and the functional domains. For the *SOX10* cDNA, the black and white areas denote the coding regions and the untranslated regions, respectively, and the Arabic numbers indicate the cDNA sequence encoded by each exon. For the SOX10 protein, the gray and striped squares represent the high mobility group (HMG) DNA-binding domain and the transactivating (TA) domain. Electrochromatograms (forward and reverse) indicate a heterozygous c.506delC mutation on exon 4. **B**: Restriction enzyme analysis. The black circles represent *NciI* restriction sites. PCR products contain naturally occurring two *NciI* sites on the wild-type (WT) exon 4, and one of the two *NciI* sites is predicted to be destroyed on the mutant (MT) exon 4. After *NciI* digestion, WT sequence specific 117 and 67 bp bands only are found for a control subject (C), whereas WT specific 117 bp and 67 bp bands and a MT specific 184 bp band are shown for the patient (P). M: size marker; and U: undigested PCR product (337 bp).

this was confirmed by the *NciI* digestion of the corresponding PCR products (Fig. 1B). While the parents postponed the decision to have the genetic testing, this mutation was absent in 100 control subjects.

The results provide further support for the notion that WS2 can be caused by heterozygous abnormalities of *SOX10* (WS2E). In this regard, a *SOX10* frameshift mutation (c.1076–1077delGA, p.Thr360fsX399) has been identified not only in a patient with a typical WS4 but also in the mother with an apparently WS2-compatible deafness and white forelock only phenotype [Pingault et al., 1998]. In addition, another *SOX10* missense mutation (p.Ser135Thr) has also been detected in a patient with "Yemenite deaf-blind hypopigmentation syndrome" mimicking WS2 [Bondurand et al., 1999]. These findings, together with *SOX10* deletions in patients with WS2 [Bondurand et al., 2007], imply that heterozygous *SOX10* abnormalities lead to not only WS4 but also to the WS2 phenotype. Such phenotypic variability would not be unexpected, because it is known that heterozygous mutations of developmental genes are usually associated with wide range of expressivity and penetrance [Fisher and Scambler, 1994]. In addition, the position of the frameshift mutation on exon 4 may also be relevant to the lack of associated features, because *SOX10* mutations residing on the last exon frequently lead to more severe phenotypes such as chronic intestinal pseudo-obstruction and/or neurological features, probably due to escape from the nonsense mediated mRNA decay [Pingault et al., 2000, 2002; Inoue et al., 2004].

REFERENCES

Bondurand N, Kuhlbrodt K, Pingault V, Enderich J, Sajus M, Tommerup N, Warburg M, Hennekam RC, Read AP, Wegner M, Goossens M. 1999. A molecular analysis of the yemenite deaf-blind hypopigmentation syndrome: SOX10 dysfunction causes different neurocristopathies. Hum Mol Genet 8:1785–1789.

Bondurand N, Dastot-Le Moal F, Stanchina L, Collot N, Baral V, Marlin S, Attie-Bitach T, Giurgea I, Skopinski L, Reardon W, Toutain A, Sarda P, Echaieb A, Lackmy-Port-Lis M, Touraine R, Amiel J, Goossens M, Pingault V. 2007. Deletions at the SOX10 gene locus cause Waardenburg syndrome types 2 and 4. Am J Hum Genet 8:1169–1185.

Fisher E, Scambler P. 1994. Human haploinsufficiency—One for sorrow, two for joy. Nat Genet 7:5–7.

Inoue K, Khajavi M, Ohyama T, Hirabayashi S, Wilson J, Reggin JD, Mancias P, Butler IJ, Wilkinson MF, Wegner M, Lupski JR. 2004. Molecular mechanism for distinct neurological phenotypes conveyed by allelic truncating mutations. Nat Genet 36:361–369.

Jones KL. 2006. Waardenburg syndrome, types I and II. In: Jones KL, editor. Smith's recognizable patterns of human malformation. Philadelphia: Elseview Saunders. p 278–279.

Lalwani AK, Baldwin CT, Morell R, Friedman TB, San Agustin TB, Milunsky A, Adair R, Asher JH, Wilcox ER, Farrer LA. 1994. A locus for Waardenburg syndrome type II maps to chromosome 1p13.3–2.1. Am J Hum Genet 55:A14.

Pingault V, Bondurand N, Kuhlbrodt K, Goerich DE, Préhu MO, Puliti A, Herbarth B, Hermans-Borgmeyer I, Legius E, Matthijs G, Amiel J, Lyonnet S, Ceccherini I, Romeo G, Smith JC, Read AP, Wegner M, Goossens M. 1998. SOX10 mutations in patients with Waardenburg-Hirschsprung disease. Nat Genet 18:171–173.

Pingault V, Guiochon-Mantel A, Bondurand N, Faure C, Lacroix C, Lyonnet S, Goossens M, Landrieu P. 2000. Peripheral neuropathy with hypomyelination, chronic intestinal pseudo-obstruction and deafness: A developmental "neural crest syndrome" related to a SOX10 mutation. Ann Neurol 48:671–676.

Pingault V, Girard M, Bondurand N, Dorkins H, Van Maldergem L, Mowat D, Shimotake T, Verma I, Baumann C, Goossens M. 2002. SOX10 mutations in chronic intestinal pseudo-obstruction suggest a complex physiopathological mechanism. Hum Genet 111:198–206.

Selicorni A, Guerneri S, Ratti A, Pizzuti A. 2002. Cytogenetic mapping of a novel locus for type II Waardenburg syndrome. Hum Genet 110:64–67.

黄斑を形成する遺伝子システムと再生医療への応用

Gene mechanism that relates to formation of the fovea and its contribution to reproducing medicine

東　範行
Noriyuki Azuma
国立成育医療センター眼科

◎黄斑は中心視力を得るための高度な網膜構造である．Pax6 はすべての動物における眼形成の master control 遺伝子であるが，ヒトの黄斑低形成で Pax6 遺伝子の変異が発見されたことから，黄斑の形成に関与していると思われる．Pax6 は選択的スプライスのエクソン 5a を含むアイソフォーム Pax6(+5a)と含まない Pax6(−5a)があり，異なる転写因子の働きをもつが，黄斑の形成には Pax6(+5a)がかかわっていることが示唆された．このような黄斑の形成にかかわる遺伝子システムを応用すれば，網膜の再生において高度な視覚を獲得できることが期待される．

Key word：黄斑，形態形成遺伝子，Pax6，選択的スプライス

黄斑は網膜において高度な視覚である中心視力をつかさどるために細胞が密に集中する特殊な部位である．この形成機構には何らかの遺伝子が働いているはずであるが，これまでほとんど検討されていなかった．先天性の黄斑低形成において眼の形成遺伝子 Pax6 の変異がみつかったことが発端になって，この遺伝子の働きが *in vitro*，*in vivo* で検討され，網膜の高度構造をつくるシステムが明らかになりつつある．

眼形成のmaster control遺伝子Pax6

Pax 遺伝子群は paired box と homeobox を共通モチーフとしてもつ遺伝子ファミリーで，422 のアミノ酸をコードする．Pax 蛋白では paired box から翻訳される paired domain がおもに標的遺伝子に結合する(図 1)．この遺伝子群は最初にショウジョウバエで発見され，脊椎動物では 9 種みつかっており，Pax6 はその 6 番目にあたる．ヒトの Pax6 遺伝子は最初に先天無虹彩の原因遺伝子として染色体 11p13 領域の欠失部位から positional cloning によって発見された[1]．

その後，この遺伝子がマウスやラットで変異があると小眼球を起こす small eye(Sey)や，ショウジョウバエで複眼が形成されない eyeless と相同であることが判明した．さらに，ショウジョウバエ初期胚のさまざまな部位にこの遺伝子を導入すると(target expression)，触覚や翅，肢などに異所性に複眼が発生したことから，眼の器官全体をつくる強力な形態形成遺伝子であることが明らかになった[2]．器官の形態形成には全体的に支配する master control 遺伝子があると予測されていたが，下等動物とはいえ，眼というもっとも複雑な器官でその遺伝子がいきなりみつかったのである(図 2)．

その後，さまざまな動物で Pax6 遺伝子がみつかり，脊椎動物，軟体動物の眼や昆虫の複眼だけでなく，プラナリアの原始眼や線虫の光感受性細胞にも存在しており，塩基配列が高度に保存されていたことから，眼の起源に関する考えに大きな転換をもたらした．動物には，種によって複眼，鏡眼，カメラ眼などさまざまな形態の眼があり，従来は 40〜60 系統が別々に発生した(収斂進化)と考えられていた．しかし，Pax6 がすべての動物

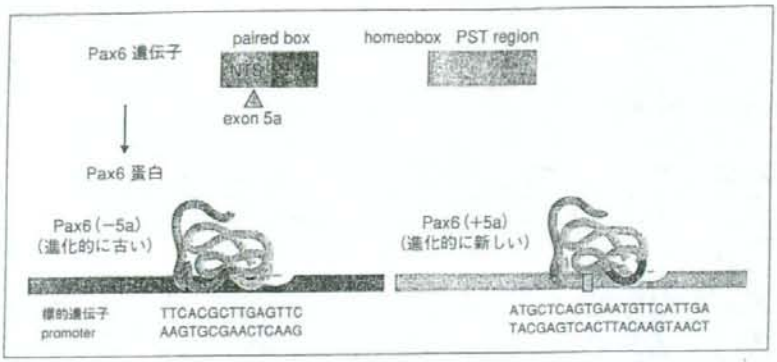

図 1　Pax6遺伝子と蛋白の構造

主要構造として，paired domain(標的 DNA に接触する部位．ここに相当する遺伝子配列を paired box という)，homeodomain(標的 DNA に接触するとともに形態形成遺伝子に特徴的な配列，遺伝子では homeobox)，末尾にプロリン，セリン，スレオニンを多く含む activating domain をもつ．エクソン 5 とエクソン 6 の間に 14 のアミノ酸をコードする選択的スプライスのエクソン 5a があり，2 種類のアイソフォームがつくられる．Paired domain はさらに N-terminal subdomain(NTS)と C-treminal subdomain(CTS)の 2 つに分かれ，標的 DNA が異なる．エクソン 5a による 14 アミノ酸が入れば CTS が，入らなければ NTS が働く．

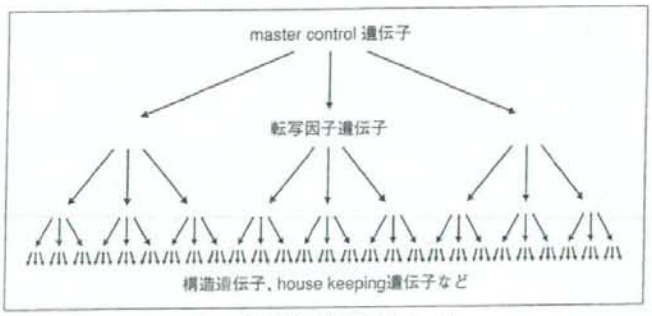

図 2　転写因子遺伝子カスケード

発生において組織ごとに上流遺伝子が下流を支配し，その頂点に器官形成全体を統合する master control 遺伝子が存在する．

の眼に存在することから，眼が原始の祖先動物で光を感じる細胞としてただ一度だけ出現し，進化とともに多彩な形態をとるようになったという単一起源説が支持されるようになった[2]．

Pax6遺伝子の変異によって起こるヒト眼形成異常

In situ hybridization や免疫染色によって Pax6 の発現を検討すると，発生初期は中枢神経や眼原基，中枢神経では前脳，後脳，神経管脳室復側，下垂体，嗅脳，眼ではまず視溝，ついで眼胞，表面外胚葉と水晶体板，網膜，角膜の順で，眼球ほぼ全体を網羅している(図 3)[3]．以上から，この遺伝子に変異が起こればきわめて多くの先天異常を起こすと推察された．

先天無虹彩では多くの変異が見出されてきたが，そのほかにも Peters 奇形のような前眼部形成不全，角膜ジストロフィー，瞳孔形成異常，先天白内障，黄斑低形成，視神経形成不全で変異がみつかり(図 4)[4-6]，Pax6 がヒトでも前眼部から眼底まで広い範囲で眼の形成を担っていることが分子遺伝学からも証明された．太古に光を感じる細胞

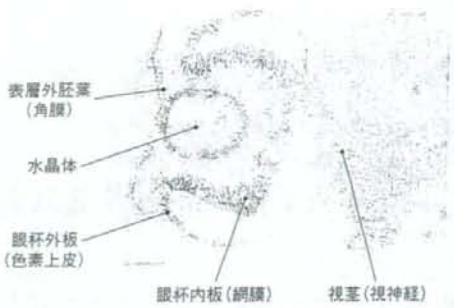

図 3 Pax6のモノクローナル抗体による発生ヒト眼(胎齢5週)の免疫染色[3]
発生初期では眼球のほぼ全体が染まる.

から出発した遺伝子が進化とともに眼形態形成の中心にいつづけて,角膜,虹彩,水晶体,網膜をつくるようになり,ついには視覚進化の頂点である黄斑を形成するに至ったことになる.

これまでにみつかった Pax6 の変異型と表現型には,遺伝子の変異が重篤なほど表現型も重症であるという法則がある.これは Pax6 に,①一対の対立遺伝子の両方が揃っていないと正常に機能しない(haploinsufficiency),②遺伝子障害の程度と表現型が相関する(dose dependent),という特徴があるためである.変異形式がストップコドン,フレームシフト,スプライシングエラーといったナンセンス変異では無虹彩のような眼球全体の形成不全を起こし,1 アミノ酸が置換した軽度なミスセンス変異では角膜,水晶体,網膜などで限局した形成不全を起こす.黄斑のみの形成不全がある孤立性黄斑低形成でみつかった変異はいずれもミスセンス変異である[4-6].

Pax6の選択的スプライスの働きと黄斑低形成の遺伝子変異

Pax6 遺伝子には,エクソン 5 とエクソン 6 の間に,14 のアミノ酸をコードする選択的スプライスのエクソン 5a が存在する.そして,これが読まれるか読まれないかによって,Pax6 蛋白は 14 アミノ酸が入るもの〔Pax6(+5a)〕と入らないもの〔Pax6(−5a)〕,2 種類のアイソフォームがつくられる[5].Pax6 蛋白では,転写因子として標的 DNA に接着する部位の paired domain があるが,14 アミノ酸はこのなかに存在する.paired domain はさらに N-terminal subdomain と C-terminal subdomain の 2 つに分かれ,異なるタイプの binding consensus をもつ標的 DNA を支配する.しかも生化学的検討によれば両 subdomain はたがいの働きを抑制しあっている.そして,エクソン 5a による 14 アミノ酸が入れば C-terminal が,入らなければ N-terminal が働くので,エクソン 5a は molecular switch の働きをもっている(図 1)[5].Pax6 の進化からみると,N-terminal subdomain は原始的動物にある基本的なもので,標的 DNA もいくつか判明している.一方,エクソン 5a は無脊椎動物では存在せず,脊椎動物に至って出現したので,C-terminal subdomain が働きはじめたのは進化的に比較的新しい.しかも,その機能はまったく不明で,標的遺伝子もみつかっていない.

これまでに発見された孤立性黄斑低形成の Pax6 ミスセンス変異はことごとく C-terminal subdomain あるいはエクソン 5a のなかに存在する[4,5].したがって,黄斑の形成にはこの C-terminal subdomain が関与していると推測された.

黄斑発生領域におけるPax6アイソフォームの発現

発生期の動物で時期別,眼組織別に mRNA を採取して cDNA を作成し,Pax6 の 2 つのアイソフォームを RT-PCR で検討すると,Pax6(−5a)は発生期全般にわたって広範な組織に発現する.しかし,Pax6(+5a)は発生期後半に後方網膜に強く発現することが示された.さらに免疫染色では,Pax6(−5a)に対する抗体では網膜は後方から前方まで均一に染まるのに対して,エクソン 5a がコードする 14 アミノ酸に対する抗体では黄斑領域を中心とする後極のみに染色がみられ,Pax6(+5a)は黄斑領域に限局して発現することが判明した(図 5)[7].

Pax6アイソフォームの網膜形成・分化に関する機能

Pax6 が黄斑形成に関与するならば,発生期の網膜に Pax6 を過剰に導入すると網膜の形成が進むはずである.しかし,過去の研究報告は逆の結果

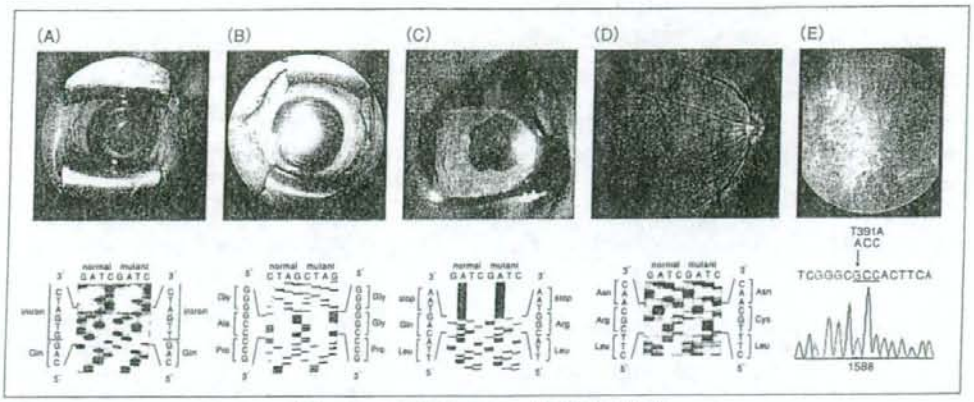

図 4　Pax6の変異がみつかった眼先天異常[4~6]
A：無虹彩，B：前眼部形成不全，C：瞳孔形成異常，D：黄斑低形成，E：視神経低形成．

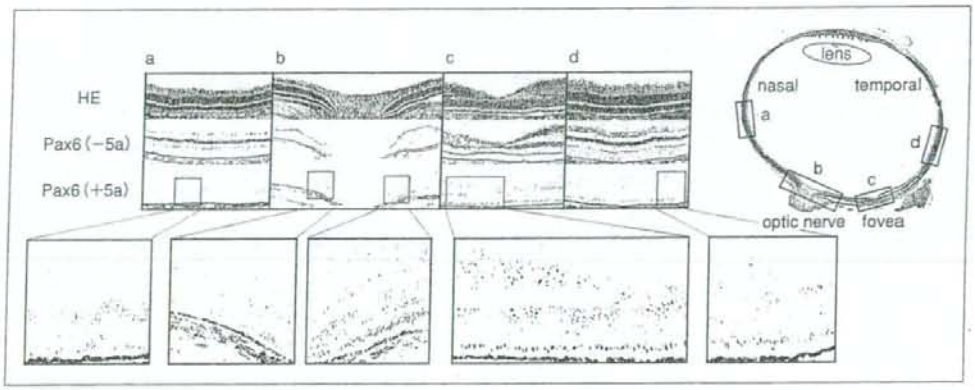

図 5　Pax6アイソフォームの発生期網膜における発現[7]
出生直後のマーモセット Pax6(−5a)に対する抗体では，網膜は後方から周辺部まで均一に染まるのに対して，エクソン 5a がコードする 14 アミノ酸に対する抗体では黄斑領域を中心とする後極のみに染色がみられる．Pax6(+5a)は黄斑領域に限局して発現することが示唆される．

を示していた．Pax6 の変異をもつマウスは小眼球になるが，一方で，Pax6 を過剰に導入したトランスジェニックマウスをつくっても小眼球が生ずる[8]．ここから Pax6 の発現量は少なくても多過ぎても正常に機能しないという考えが定着した．しかし，トランスジェニックマウスでは，導入した Pax6 が眼球だけでなく，中枢や視神経など多くの組織に発現する．小眼球は発生のわずかな均衡がくずれれば容易に起こるので，多くの組織に Pax6 が異常量発現すれば，組織間相互作用が障害され，結果として小眼球になることも考えられる．網膜への Pax6 の影響を知るためには網膜だけに遺伝子を導入しなければならない．そこでニワトリの発生期網膜に electroporation で Pax6 を直接導入した．Electroporation で導入した遺伝子は細胞質内で短期間発現するので，発生のような一時期に働く遺伝子の機能を観察する点では都合がよい．

発生初期(stage 12~16)の網膜に，エクソン 5a を含まない Pax6 のアイソフォーム Pax6(−5a)を導入すると網膜が厚くなり，神経節細胞が増加し(図 6-B)，神経線維が硝子体腔に向かって増加した(図 6-C)．導入直後では神経芽細胞の分裂が亢

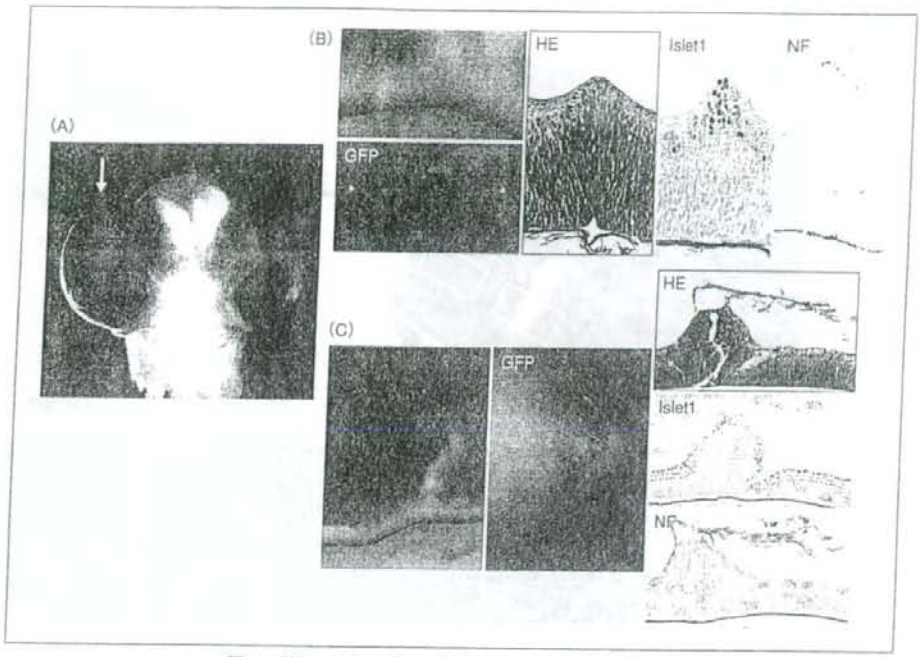

図 6　鶏胚へのPax6(−5a)導入による網膜の発育亢進[17]

2 日胚に導入，8 日胚の所見．

A：Pax6(−5a)を入れた右眼が大きくなる(矢印)．B：網膜が厚くなり，GFP で遺伝子の導入が確認され，組織所見では神経節細胞が増加している．C：網膜から硝子体腔へ線維構造が立ち上がり，組織所見では神経線維である．

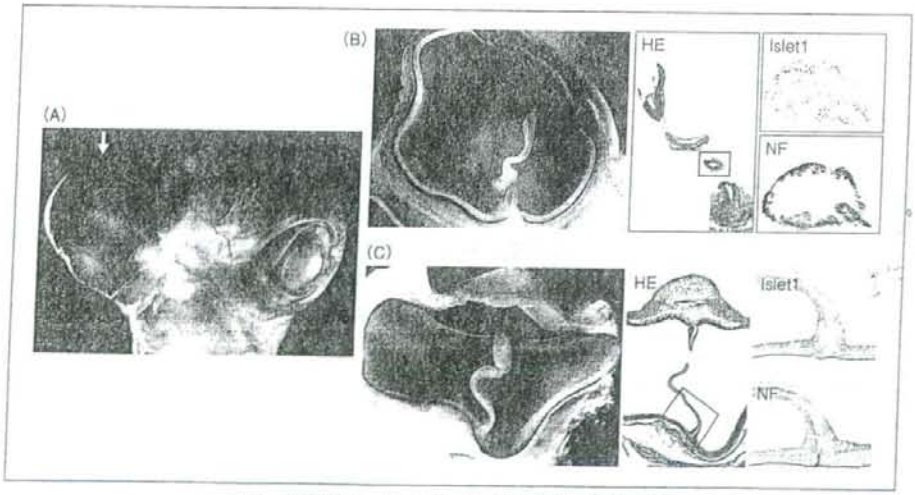

図 7　鶏胚へのPax6(+5a)導入による網膜の発育亢進[17]

2 日胚に導入，10 日胚の所見．

A：Pax6(+5a)を入れた右眼が極度に大きくなる(矢印)．B：網膜から茎状構造が立ち上がり，組織所見では管状の網膜で層構造はほぼ保たれている．C：網膜が水平に過剰発育して折りたたまれている．

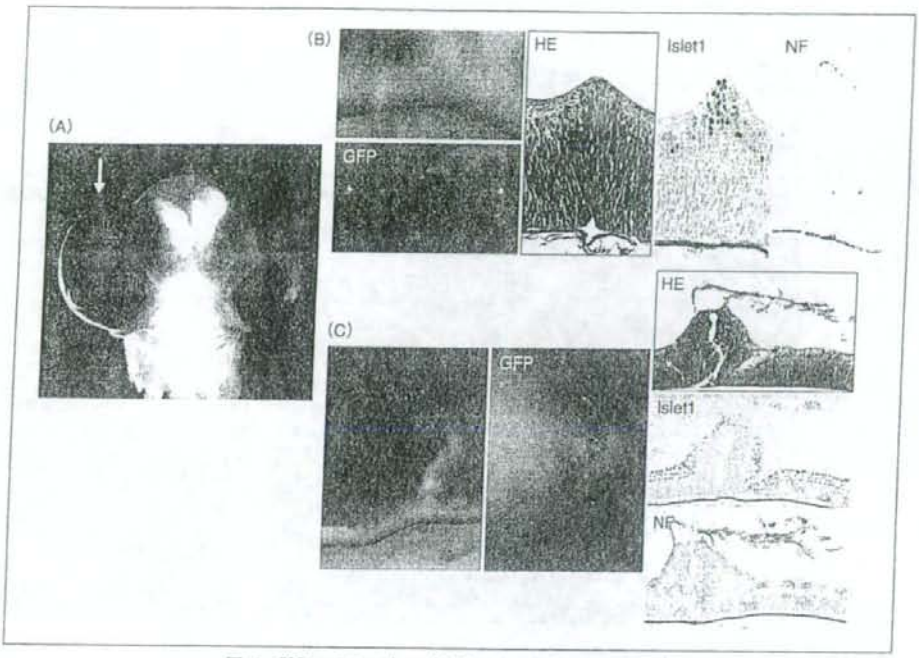

図 6　鶏胚へのPax6(−5a)導入による網膜の発育亢進[17]

2 日胚に導入，8 日胚の所見．

A：Pax6(−5a)を入れた右眼が大きくなる(矢印)．B：網膜が厚くなり，GFP で遺伝子の導入が確認され，組織所見では神経節細胞が増加している．C：網膜から硝子体腔へ線維構造が立ち上がり，組織所見では神経線維である．

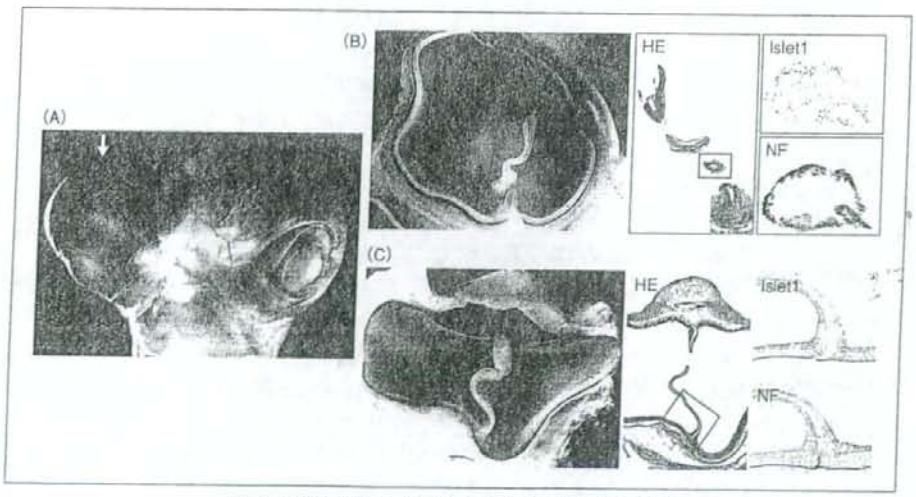

図 7　鶏胚へのPax6(+5a)導入による網膜の発育亢進[17]

2 日胚に導入，10 日胚の所見．

A：Pax6(+5a)を入れた右眼が極度に大きくなる(矢印)．B：網膜から茎状構造が立ち上がり，組織所見では管状の網膜で層構造はほぼ保たれている．C：網膜が水平に過剰発育して折りたたまれている．