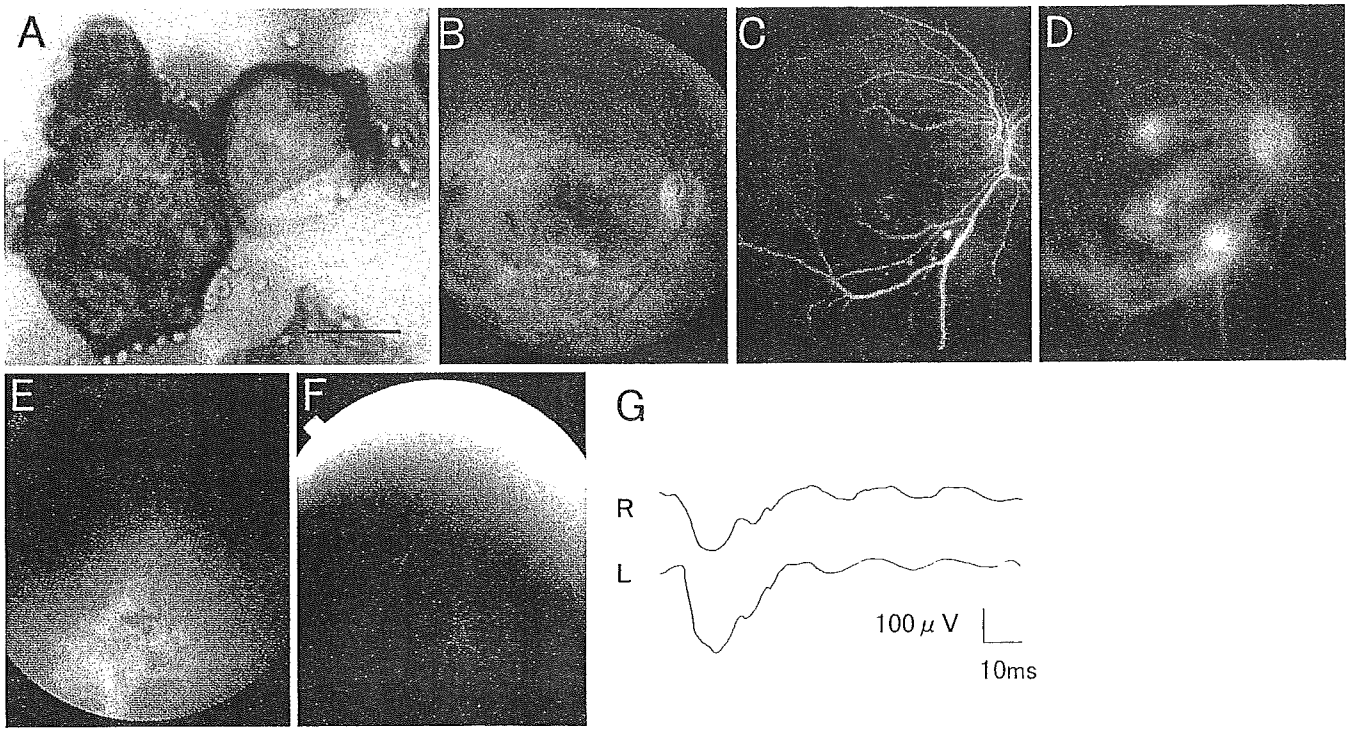

Figure 1. **A** Leukemic blasts obtained from bone marrow (May-Giemsa staining). Bar = 5μm. **B** Fundus photography of the right eye 4 months after BMT. Retinal edema, intraretinal hemorrhage, soft exudates, and lipid deposits are mainly in the central retina. **C** Early-stage fluorescein angiography of the right eye shows fluorescein dye leakage from the retinal vessels and microvascular abnormalities. **D** Late-stage fluorescein angiography of the right eye shows expansion of dye leakage indicating neovascularization. **E** Fundus photography of the left eye 4 months after BMT. The same findings as in the right eye are seen locally in the nasal periphery. **F** Fluorescein angiography of the left eye shows the same findings as in the right eye at the nasal periphery. **G** Electroretinography with a single flash stimulus of 25 J with a red filter shows normal responses from the left eye and reduced A and B wave amplitudes from the right eye. (100μV × 10ms).

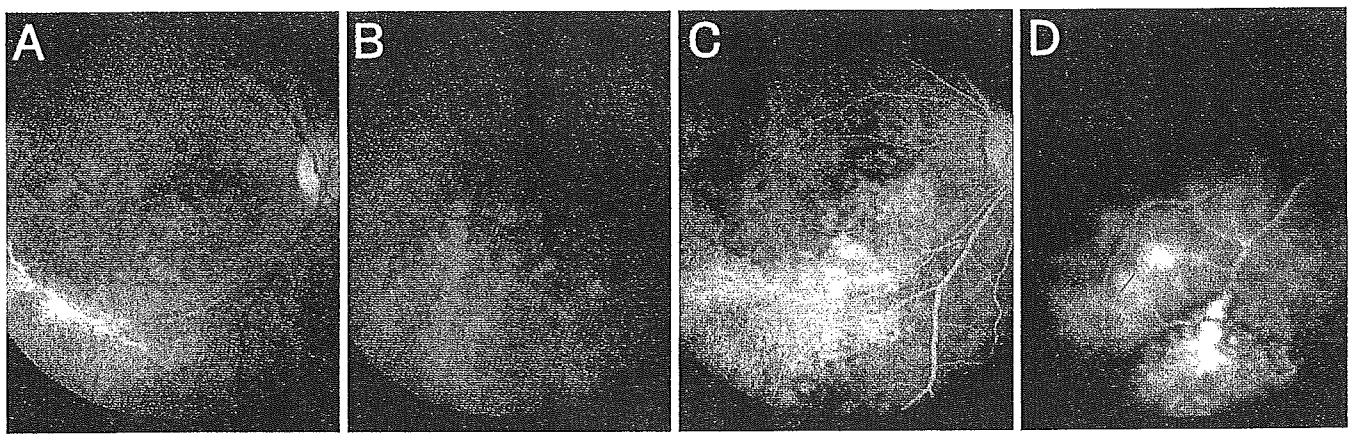

Figure 2. **A** Fundus photography of the right eye 3 months after prednisolone treatment. The chorioretinal atrophy remains in the posterior fundus and inferior branched arcade vessel sheathing. **B** Fundus photography of the left eye 3 months after prednisolone treatment shows chorioretinal atrophy is in the nasal periphery. **C** Fluorescein angiography of the right eye 3 months after treatment with oral prednisolone shows fluorescein staining in the chorioretinal atrophy area and branched vessel infarction. **D** Fluorescein angiography of the left eye 3 months after treatment with oral prednisolone shows fluorescein staining in the chorioretinal atrophy area and branched vessel infarction in the nasal periphery.

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leukemia (ALL). By bone marrow cytological analysis, the blast cells showed the rearrangement of the mixed lineage leukemia (*MLL*) gene (Fig. 1A). Immunohistochemical analysis showed that the blast cells were negative for CD10 but positive for CD19 and HLA-DR. Chromosomal analysis identified translocation of chromosomes 5 to 11 [t (5;11)(q31;q23)]. The patient initially underwent three sessions of chemotherapy with etoposide, cytosine arabinoside, and mitoxantrone, according to the protocol of the MLL98 study.[5] After pretreatment with whole-body irradiation (12 Gy) and administration of etoposide and cyclophosphamide, BMT was performed when the patient was 6 months old. Despite administration of tacrolimus and methotrexate to prevent GVHD, acute GVHD developed in the liver and skin 6 days after BMT. The GVHD gradually improved after administration of intravenous methylprednisolone. Careful examinations were performed by pediatricians, dermatologists, and ophthalmologists.

Four months after BMT, edema, hemorrhage, and soft exudates appeared widely in the posterior retina of the right eye (Fig. 1B) and locally in the periphery of the left eye (Fig. 1E); the anterior segment was normal. Fluorescein angiography showed some areas of nonperfusion of the capillary vessels and dye leakage, which indicated neovascularization of the retinal vessels (Fig. 1C, D, F). Electroretinography showed normal responses in the left eye and reduced A and B wave amplitudes in the right eye (Fig. 1G). Bone marrow aspiration indicated that the donor cells had survived and there was no recurrence of ALL; however, mild liver damage from the GVHD was still observed. Seven months after BMT, inflammation of the skin developed on the trunk, legs, arms, and face. Biopsy showed invasion of inflammatory cells into the subcutaneous tissue, suggesting chronic GVHD. Following administration of oral prednisolone (5 mg/kg per day), the retinopathy cicatrized to fibrous tissue and chorioretinal atrophy (Fig. 2A, B). The retinopathy gradually improved, and the dye leakage on fluorescein angiography stopped (Fig. 2C, D). The following fixation in the right eye was poor, and the visual evoked potential (obtained by flash stimulus of 1.2 J in a dark room) was also poor, while the responses of the right eye were normal. At 2 years of age, the patient's corrected visual acuity was 0.01 in the right eye and 0.5 in the left eye.

Discussion

Posterior segment complications have rarely been reported in pediatric patients after BMT. Suh et al.[4] surveyed ocular findings in 104 pediatric patients after BMT. In 14 of the 104 patients, the posterior segment had radiation retinopathy, disc edema, cytomegalovirus retinitis, and nocardia retinitis. Microvascular occlusive retinopathy developed in only four patients, aged 10 to 18 years, and there were no infants. In the 14 patients, telangiectasia, hemorrhages, cotton-wool spots, lipid exudates in the retina, macular edema, papillitis, and optic atrophy were seen, as is common in adults, but neovascularization, capillary nonperfusion, vitreous hemorrhage, tractional retinal detachment, and neovascular glaucoma did not develop.

Microvascular retinopathy after BMT occurs as the result of various mechanisms, including GVHD, total-body irradiation, immunosuppression, and administration of high-dose anticancer agents.[3] Our patient underwent total-body irradiation, received immunosuppressant and high-dose anticancer agents, and developed GVHD. Because the GVHD and occlusive microvascular retinopathy occurred simultaneously, the retinopathy in our patient was inferred to be mainly caused by the GVHD. Cyclosporine may worsen occlusive microvascular retinopathy because of its toxic effects, and total-body irradiation may modify the retinopathy, but it takes about 1 year for these changes to occur.[3] Thus, early occurrence of retinopathy in our patient also supports the theory that the retinopathy originated from the GVHD.

As a mechanism of chronic GVHD, the endothelia of the retinal vessels can be damaged by a lymphocyte-mediated immunologic attack that results in capillary occlusive retinopathy.[2,3] In our patient, occlusive microvascular retinopathy after BMT might have resulted from injury of the immature vessels in the neonatal and infantile eyes. Neovascularization was minimized not by the use of photocoagulation but by administration of oral prednisolone, because the occlusion of the capillary vessels occurred in a small area.

The visual prognosis after occlusive microvascular retinopathy after BMT is usually excellent, because lesions in the posterior retina are small and the fovea is rarely affected. However, the development of extensive neovascularization that covers the posterior retina is serious and vision threatening. As BMT has become an increasingly successful treatment and its indication is expanding in infantile patients, ophthalmologic evaluation followed by careful management is important for improving the visual prognosis after retinopathy.

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CASE REPORT

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Two patients with different features of congenital optic disc anomalies in the two eyes

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Abstract *Purpose:* Description of two patients, each with different features of congenital optic disc anomalies in the two eyes. *Methods:* Case report *Results:* Patient 1, a 3-month-old girl, showed retinochoroidal coloboma involving the optic nerve in the right eye and optic nerve hypoplasia in the left eye. Patient 2, a 5-month-old boy, showed retinal fold extending inferiorly in the right eye and optic disc coloboma in the left eye. *Conclusions:* Since in both cases coloboma was seen in one eye, the optic nerve hypoplasia or retinal fold in the fellow eye of these two patients may have been related to the timing of embryonic fissure opening or closing.

Keywords Congenital optic disc anomalies · Coloboma · Optic nerve hypoplasia · Retinal fold

Introduction

Numerous developmental events contribute to optic disc/nerve formation, including transient formation of embryonic fissure, hyaloid artery, and Bergmeister's papilla, and projection of nerve fibers. Thus, optic disc/nerve malformations occur when these developmental events transiently or spatially arrest and may present a variety of fundus features. Bilateral anomalies usually show the same phenotype, because of the same genetic background, intrauterine circumstances, or timing of a causative intervention. We report two patients with bilateral optic disc/nerve anomalies that were different clinical entities in the two eyes.

Case report

Patient 1, a 3-month-old girl, presented with nystagmus in both eyes. Ocular examinations showed normal anterior segments, large retinochoroidal coloboma involving the optic nerve in the right eye, and hypoplasia of the optic nerve with a small optic disc and surrounding depigmented ring (double-ring sign) in the left eye. Computed tomography (CT) identified hypoplasia of the cerebellar vermis, a callosal defect, ventricular enlargement, and extrusion of the posterior portion of the eyeball in the right eye and a thin optic nerve in the left eye (Fig. 1). The patient, now 3 years old and mentally challenged, has normal growth and no systemic abnormalities.

Patient 2, a 5-month-old boy, presented with nystagmus in both eyes. A retinal fold was seen extending from the optic disc and connected to fibrous tissue on the inferior portion of the posterior lens surface in the right eye. The left anterior segment was normal, although the fundus had a classic optic disc coloboma (Fig. 2). CT was normal, except for the retinal fold in the right eye and eye wall ectasia of the optic nerve region in the left eye. The patient, now 7 years old and mentally challenged, has normal growth and no systemic abnormalities. Other family members of each patient were apparently normal, thus indicating sporadic onset. Each patient was the product of a full-term pregnancy, and careful pediatric examination failed to identify any history of infectious disease.

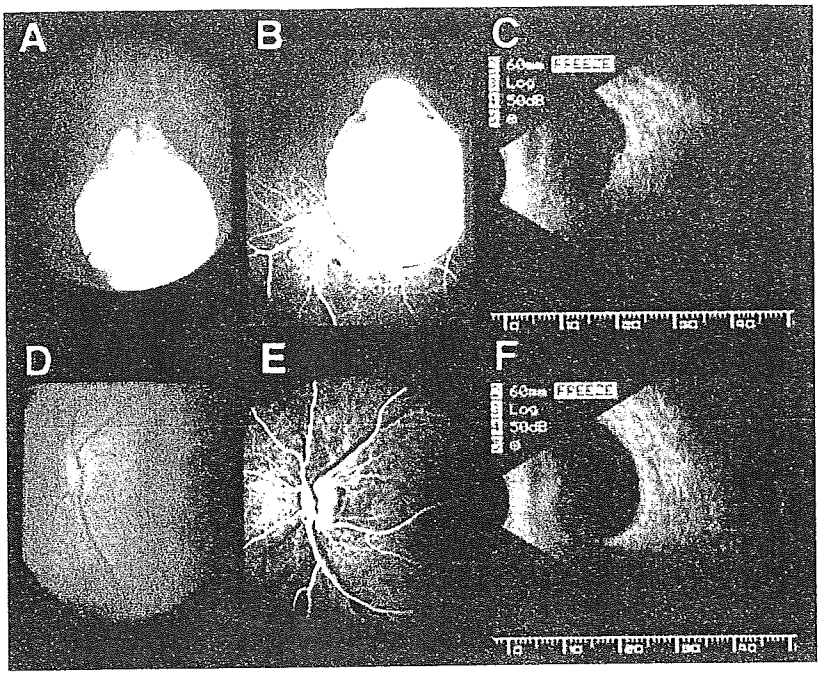

Fig. 1 Fundus photography (**a**, **d**), fluorescein angiography (**b**, **e**), and echography (**c**, **f**) of patient 1 show large retinochoroidal coloboma that involves the optic disc OD (**a**–**c**) and optic hypoplasia OS (**d**–**f**)

Discussion

Among events related to optic disc/nerve formation, opening and closing of the embryonic fissure at 5–6 weeks gestation, when transiently arrested, are the most common pathogenetic factors for malformations associated with peripapillary excavation, including coloboma, peripapillary staphyloma, and morning glory disc anomaly. Slightly different manifestations of optic disc/nerve anomalies (coloboma, optic disc pit) were reported bilaterally in the affected members of a pedigree showing inherited defects, suggesting that the difference depended on the degree of peripapillary excavation and that both anomalies are in the same spectrum [9].

In contrast, the fundus features in the two eyes of each of our patients markedly differed. Optic nerve hypoplasia is

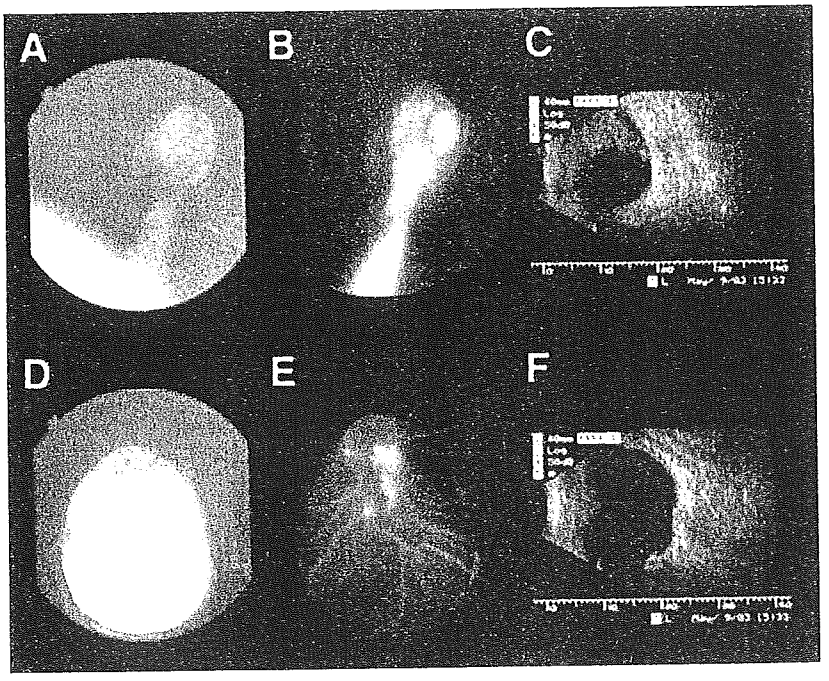

Fig. 2 Fundus photography (**a**, **d**), fluorescein angiography (**b**, **e**), and echography (**c**, **f**) of patient 2 show fibrous tissue on the inferior retinal periphery and retinal fold OD (**a**–**c**) and coloboma that involves the optic disc OS (**d**–**f**)

rarely associated with coloboma in the same patient [1, 3]. The case of a patient with hemifacial microsomia showing optic nerve hypoplasia in the ipsilateral eye and optic nerve coloboma in the contralateral eye has been reported [5]. Optic disc/nerve hypoplasia arises from insufficient growth of retinal ganglion cells and nerve fibers [4], or retrograde nerve fiber degeneration secondary to central nervous system abnormalities [6], while excessive closure of the embryonic fissure may disturb nerve fiber projections in the optic nerve, resulting in optic disc/nerve hypoplasia [3]. Retinal folds and tractional retinal detachments caused by vascular or mesenchymal proliferation in the developing vitreous and retina occur in eyes with persistent fetal vasculature (PFV), familial exudative vitreoretinopathy, and retinopathy of prematurity. Because fibrous proliferations in patient 2 were in the inferior peripheral vitreous cavity, which coincides with part of the embryonic fissure, the tissue may be PFV with excessive migration of mesenchymal cells through the fissure. Thus, each anomaly might result from abnormalities in closing of the embryonic fissure.

Mutations of the *PAX2* or *PAX6* gene have been identified in a variety of optic disc/nerve anomalies [2, 7]. *PAX2* plays a crucial role in the development of the optic stalk, and *PAX6* in that of the optic cup [8]. The affected members of a pedigree showed a variety of phenotypes when these genes were mutated, while there was not much difference in the phenotypes between the two eyes in each affected member, suggesting that downstream *PAX2* or *PAX6* genes modify phenotypic expression. However, differences in phenotypes between the two eyes also occurred, albeit in few cases [2]. Although no mutation of these genes was identified in our patients, stochastic effects on developmental events may modify ocular cell growth and differentiation, resulting in different phenotypic manifestations.

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Small Eye Phenotypes Observed in a Human *tau* Gene Transgenic Rat

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ABSTRACT We developed a rat line showing small eye from transgenic rats that were obtained by microinjection of a DNA segment containing the human (h)*tau* cDNA (GenBank: BC000558: 31-677,774-1180) expressed under control of CAG promoter, which is related to Alzheimer disease, into the pronuclei rat embryos. The rat line was established by selective brother-sister mating of rats showing small eyes. Of 11 offspring in the 11th generation, there were eight animals with microphthalmia and the transgene. The remaining three rats without transgene did not show the small eyes phenotype. The globes of affected rats were 1.2 mm in length compared with normal globes (3.5 mm), and all other ocular structures were normal. The expression of hTau protein was evident immunohistochemically in the ciliary body, extraocular muscle, lens epithelium, and pigment epithelium. Cytogenetic analysis suggested that the chromosome location of the transgene was chromosome 1 (1p12). This region may include genes related to lens development, such as *Cat5*.

KEYWORDS *Cat5*; cataract; rat; small eye; Tau

INTRODUCTION

It is reported that Parkinson disease is inherited as an autosomal dominant gene, and the gene is linked to chromosome 17q21-22.[1] Human (h)*tau* gene was located on the locus, and mutation of the gene was found in frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17). The neurofibrillary tangles composed of microtubule-associated protein Tau are related to not only the FTDP-17 but also to Alzheimer disease. The gene encoding microtubule-associated protein has been reported in rats as well, and the gene (Map1a) was linked to chromosome 3q36.[2] Many transgenic mouse lines that express hTau protein have been established to investigate the relationship between the hTau protein and tauopathy.[3] Recently, we generated three transgenic rats (founder) carrying the h*tau* gene, and they showed small eyes.

Mice and rats with ocular phenotypes, such as aniridia,[4] cataract,[5] microphthalmia,[6] and small eyes,[7] were reported, and a number of genes, including *Bld*,[8] *Cat*,[9] *Maf*,[10] and *Pax*,[11] related to these abnormalities have been reported as well. In this study, we characterized the phenotype of transgenic rats with small eyes, and the candidate gene causing the phenotype was predicted.

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MATERIALS AND METHODS

Transgenic Constructs and Animals

h*tau* cDNA (GenBank: BC000558: 31-677,774-1180) and rabbit β-globin polyA provided by Dr. Oyama (Department of Neuropathology, University of Tokyo)[12] were microinjected into the pronuclei of fertilized Jcl:SD rat (CLEA Japan Inc., Tokyo, Japan) embryos, and the embryos were transferred to the oviducts of pseudopregnant SD rats. Testing for the transgene in offspring was performed by polymerase chain reaction (PCR). The primers and conditions for the PCR are described below. In histopathological, immunochemical, and fluorescent *in situ* hybridization (FISH) analysis, four out of the 8 rats, aged 8 weeks, with small eyes were used. The rats were maintained in accordance with the Animal Care Guidelines of the Central Institute for Experimental Animals (Kanagawa, Japan).

PCR Analysis

To select rats carrying the h*tau* gene, PCR analysis was performed using the oligonucleotides, t1 (5′-AAG CTC GCA TGG TCA GTA AA-3′) and t2 (5′-GAC TTG ACA TTC TTC AGG TC-3′), and *Taq* polymerase (Takara Shuzo, Co., Ltd., Shiga, Japan) according to the manufacturer's protocol.

Histopathology

The formalin-fixed materials were embedded in paraffin, and 5-μm sections were stained by a standard method with hematoxylin and eosin (HE). The sections were examined under a light microscope to evaluate morphologic characteristics and pathologic changes. For detection of hTau protein in the tissues, all sections were stained by the dextran polymer–immunoperoxidase complex method (ENVISION kit, DakoCytomation, Kyoto, Japan) using anti-bovine Tau (mouse) serum (EMB Biosciences, Inc., San Diego, CA, USA) at 1:5000 dilution as the primary antibody and then counterstained with hematoxylin.

FISH Analysis

Determination of the chromosomal location of the h*tau* gene in the transgenic rats was undertaken by FISH analysis, and closely linked genes associated with ophthalmopathy were screened using the rat genome database (http://rgd.mcw.edu/). The chromosome samples were prepared from mitogen-stimulated splenocytes of transgenic rats. The biotin-16-dUTP-labelled *tau* cDNA clone in the pCXN2 vector[13] was used for hybridization. FISH analysis was performed essentially as described by Matsuda et al.[14] Observations were carried out with a Leica Q550 system (Leica Microsystems K.K., Tokyo, Japan), and chromosomes with fluorescent signals were identified according to G-banding standards.

RESULTS

Forty-five rats in total were obtained from the founder male rat carrying the h*tau* gene. Twenty-three out of the 45 rats had the h*tau* gene, and 3 of 23 (2 males and one female) rats showed small eyes. F2 rats were obtained by mating between a rat with small eyes and a Jcl:SD rat, and the animals were maintained by selective breeding of a small-eye line and brother-sister mating. At the 11th generation, 11 offspring were obtained, and 8 of the 11 offspring showed small eyes.

Histopathological Analysis

The globes of affected rats were 1.2 mm in length compared with normal globes (3.5 mm), and all other ocular structures were normal (Figs. 1 and 2A). Vacuolation was observed in lens of the rats, but no lesions were observed in other tissues such as the cornea and iris. These abnormalities were observed only in rats of this line bearing the h*tau* gene. On the other hand,

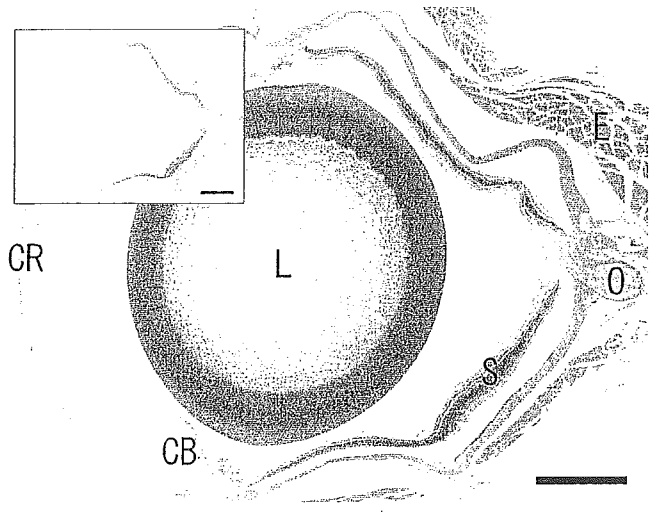
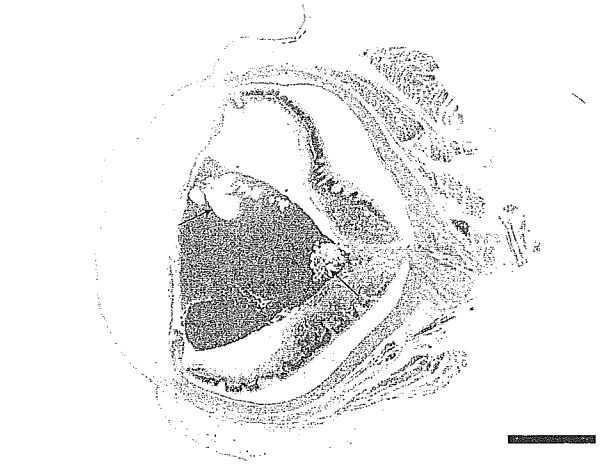
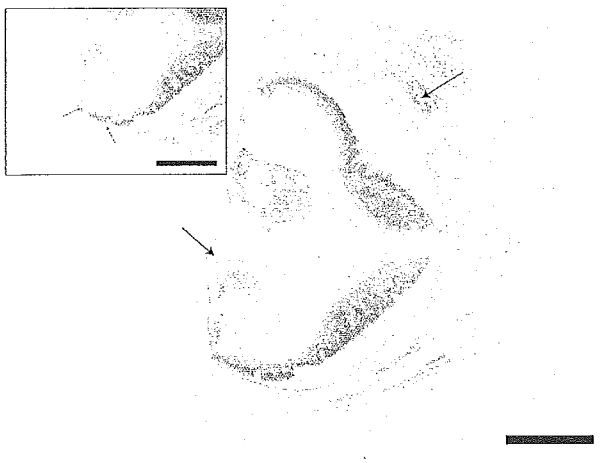


FIGURE 1 Ciliary body (CB), cornea (CR), extraocular muscle (E), lens (L), optic nerve (O), and sclera (S) from a rat not bearing the *tau* gene (H&E). Inset shows immunohistochemical stain, hematoxylin counterstain. Expression of *Tau* protein in the normal eye from a rat not bearing the *tau* gene. Bar = 1 mm.



(A)



(B)

FIGURE 2 (A) Small lens observed in human *tau* gene transgenic rats. Vacuolation is present in the lens (arrows) (H&E). Bar = 1 mm (B). Immunohistochemical stain, hematoxylin counterstain. Tau protein expression evident immunohistochemically in the ciliary body, extraocular muscle, lens epithelium, and pigment epithelium (arrow). Bar = 1 mm. Inset shows detail of ciliary body and pigment epithelium. Bar = 1 mm.

ophthalmic lesions were not observed in wild-type rats and rats from other rat lines carrying the gene (data not shown). Tau protein expression was evident immunohistochemically in the ciliary body, extraocular muscle, lens epithelium, and pigment epithelium (Fig. 2B).

Location of the h*tau* gene was analyzed by the FISH method, and the gene was found to be located on chromosome 1p12 (Figs. 3 and 4).

DISCUSSION

Tau protein is a microtubule-associated protein. In Alzheimer disease, Pick disease, and corticobasal degeneration, typical mutations were found in the gene.

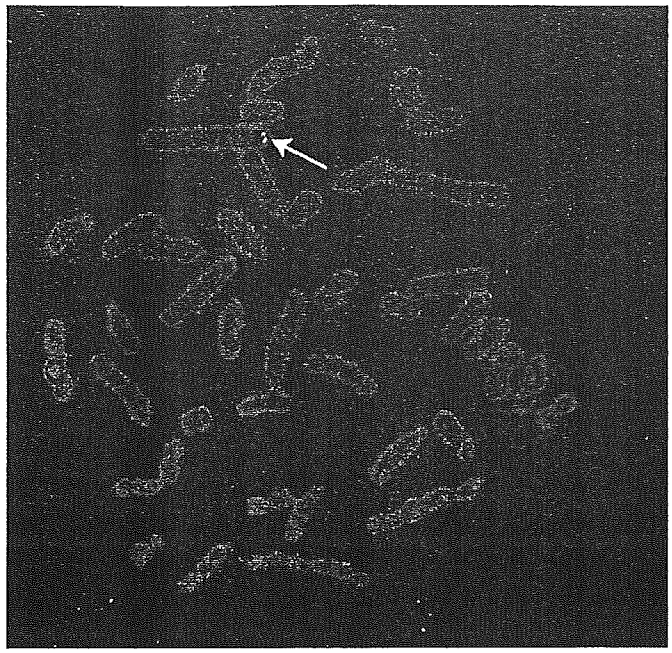


FIGURE 3 Chromosomal location of the human *tau* gene in a transgenic rat. The signal was visualized indirectly with FITC (arrow).

Mutations that affect exon 10 splicing cause frontotemporal dementia with parkinsonism.

In this study, we obtained 23 transgenic rats carrying the h*tau* gene from one founder transgenic rat, and in three out of the 23 rats small eyes appeared. Histopathologically, the lens of the rats was small in size with vacuolation. Lens development is regulated by a variety of genes, such as L-*Maf*, *Pax6*, and *Sox2*. Microphthalmic rats and mice caused by mutation of these genes were reported previously,[15,16] but all of them were not caused by the *tau* gene. Lewis et al. reported eye irritations in mice expressing mutant Tau protein but microphthalmia was not observed.[17] Only three (2 males and one female) of these 23 transgenic rats showed small eyes, suggesting that small eyes observed in this study were not caused by h*tau* gene. The human *Pax6* gene was first reported as a candidate gene for evolution of morphogenesis of the eye.[18,19] In rats, the *Pax6* gene is located on chromosome 3q32-3q36. Because the transgene in the rats with small eyes was mapped to chromosomal 1p12, it was suggested that the *Pax6* gene was not related to abnormalities in this study. Based on the database analysis of the transgene locus (1p12) in rats, several genes have been mapped in the locus. In the locus, *Cat5* was mapped as a cataract-related gene.

In conclusion, we established a rat line, that shows small eyes from transgenic rats carrying h*tau* gene.

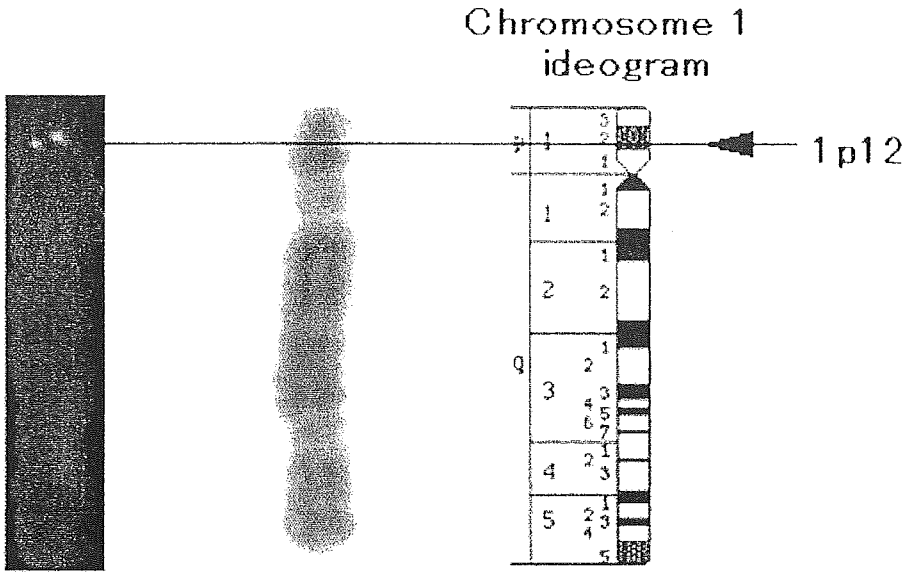


FIGURE 4 Ideogram showing the cytogenetic location of *tau* in 1p12.

Typical phenotypes were characterized by a small lens with vacuolations observed in the lens. The map location of the transgene suggested that the candidate gene causing small eye is located in 1p12.

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