Novel Cataract Mouse Model Using ddY Strain: Hereditary and Histological Characteristics

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ABSTRACT. A novel cataract model was identified in the ddY strain (outbred colony) reared at Osaka Prefecture University. Opacity appeared as a white pinpoint focus in the unpigmented eyes of cataract mice at 6 weeks of age. All mice, fully viable and fertile, were bilaterally affected by the time they were 10 weeks of age. There were no gender differences in the incidence of cataracts. Histologically, 5-month-old cataract mice showed vacuolation of epithelial cells, disruption of lens fibers, and dislocation of the lens nucleus to the posterior lens cortex. To elucidate the mode of inheritance, heterozygous mutant hybrids between cataract mice and wild-type ddY mice, as well as offspring between the heterozygous mutants, were analyzed. No affected mice were observed among the heterozygous mutants, and the ratio of affected to unaffected mice was 1:3 among offspring between heterozygous mutants. For linkage analysis, we produced backcross progeny [cataract mouse $\times$ (cataract mouse $\times$ MSM/Ms mouse)], and concluded that the cataracts are inherited by an autosomal recessive gene. Moreover, the locus of the cataract gene, *mct*, was mapped to the 3.91 cM region encompassed by *D2Mit467* and *D2Mit320* on mouse chromosome 2 by linkage analysis. Thus, the present cataract mice represent a novel cataract mouse model, and have been designated Morioka cataract (MCT) mice.

KEY WORDS: hereditary cataract mouse model, linkage analysis, MCT mouse.

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A cataract is one of the most common eye defects and causes of lens opacity [12]. Lens opacity may lead to blindness [10]. Causes of cataracts include congenital defects, senility, metabolic disorders and exposure to a variety of physical and chemical agents [22]. About 10 to 30 percent of childhood blindness cases are due to congenital cataracts [1], and approximately one-quarter to one-third of congenital cataract cases are hereditary [2, 4, 9]. Thus, establishment of an animal model of cataracts is an effective method to elucidate human cataractogenesis [5]. Many types of cataracts, that may be inherited and that have been evaluated developmentally, histologically and genetically, have been studied in mice [7, 11, 14, 16, 18]. In the cataract lens, various morphological features, including the posterior dislocation of the nucleus [23], vacuolation of the epithelium [15] and vacuolation of the lens [22] are observed.

In our laboratory, mice with cataracts were identified in a colony of ddY mice in 1997. The cataract mice were isolated from the colony, and bred by random mating. In the present study, we investigated the hereditary and histological characteristics of these cataract mice.

MATERIALS AND METHODS

Animals and husbandry: Cataract mice, a novel cataract strain derived from mice of the ddY strain (outbred colony),

were used. Normal ddY mice (wild-type) were purchased from Japan SLC (Hamamatsu, Japan) and were used as controls. The MSM/Ms mice were kindly donated by Dr. Moriwaki (National Institute of Genetics, Mishima, Japan) and used for linkage analysis. All the animals were maintained under regulated room temperature ($24 \pm 1^\circ\text{C}$), humidity ($55 \pm 5\%$) and lighting (from 06:00 to 20:00). Animals were given a commercial diet (CE-2; Clea, Osaka, Japan) and water *ad libitum*. The present study was performed in accordance with the Guidelines for Animal Experimentation of Osaka Prefecture University, Japan.

Observations and histological studies: Mice were observed with the naked eye under non-anesthetic conditions more than once a week after their eyes opened at approximately 2 weeks of age. For histological studies, 5-week-old and 5-month-old cataract mice were used. Under isoflurane anesthesia, the mice were infused with heparin-saline, followed by 10% neutral buffered formalin. Eyes were then removed and immersed in the same fixative for two days. Eyes were dehydrated through a graded series of ethanol, soaked in butyl alcohol and embedded in paraffin (Tissue Prep, Fisher Scientific, Fair Lawn, NJ, U.S.A.). Sections ($6 \mu\text{m}$) were cut in a plane perpendicular to the anterior-posterior axis of the eye and were stained with hematoxylin and eosin.

Mating experiment: To elucidate the mode of inheritance, cataract mice were mated with wild-type ddY mice in order to obtain heterozygous mutants. Heterozygous mutants were then mated in order to obtain the segregation ratio of affected and unaffected mice. The incidence of lens opacity was determined with the naked eye by visual examination more than once a week from 2 weeks until 5 months of age.

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Linkage analysis: Genomic DNA was extracted from the tail of affected backcrossed progeny [cataract mouse $\times$ (cataract mouse $\times$ MSM/Ms mouse)]. For linkage analysis, 54 polymorphic microsatellite markers (Sigma Aldrich Japan, Tokyo, Japan) were selected. These markers had typed polymorphisms between the cataract and MSM/Ms mice. Markers and their approximate centimorgan (cM) distances from the centromeric telomere are shown in Table 3. For the primary examination, 20 to 60 DNA samples from affected mice were used. For further mapping, 23 microsatellite markers on chromosome 2 (Chr 2) were added. For the secondary check, 135 to 332 DNA samples from affected mice were used. PCR was performed in a 10- μ l reaction mixture containing 50 ng of template DNA, 1 mM dNTPs, 0.5 U Taq polymerase (Takara Bio Co., Otsu, Japan), and each primer at 6.6 μ M. PCR amplification was carried out with an initial denaturation at 94°C for 3 min, annealing for 45 sec and extension at 72°C for 45 sec, followed by a final extension step at 72°C for 10 min. Annealing temperatures varied with the markers. Each PCR product was mixed with 3 μ l of loading buffer and electrophoresed on 8% polyacrylamide gels for 3 hr at 120 V. Gels were stained with ethidium bromide or with a silver staining kit (Daiichi Pure Chemical Co., Tokyo, Japan). Significance of linkages was evaluated by a χ^2 test of independence (degree of freedom=1) of frequencies of hetero- and homozygotes in the affected backcross mice.

RESULTS

Incidence of cataract: Both wild-type ddY (Fig. 1a) and

cataract (Fig. 1b) mice are shown in Fig. 1, and the incidence of opacity with age is listed in Table 1. Opacity appeared as a white pinpoint focus in the pink eyes of mice at 6 weeks of age. The rate of progression of opacity in each eye was almost equal, and the size of the opacity in the eyes increased with age. All mice were completely affected by 10 weeks of age and manifestation was bilateral. There were no gender differences in the incidence of cataracts. All mice were fully viable and fertile. The mean litter size was 9.6, and the weaning rate was 82.1% at the first parity (data not shown). It was impossible to distinguish affected and unaffected mice by shape, size or any other bodily feature, except lens opacity. Opacities were very similar in shape in each affected mouse.

Histological findings: In the lens of 5-month-old cataract mice, the lens nucleus was abnormally eosinophilic and was moved to the posterior region of the lens, while the lens nucleus was almost normal in the lens of 5-week-old cataract mice (Fig. 2). In the anterior region of the lens of 5-week-old cataract mice, some of the lens fibers were swollen, while in that of wild-type ddY mouse, lens fibers were normal (Figs. 3a and 3b). In the anterior region of the lens of 5-month-old cataract mice, epithelial cells were vacuolated, some of the lens fibers were swollen, and numerous pyknotic nuclei were observed, while in the wild-type ddY mouse, epithelial cells and lens fibers were normal, with no pyknotic nuclei observed (Figs. 3c and 3d).

Mode of inheritance: The results of the mating experiments are presented in Table 2. Heterozygous mutants between the cataract and wild-type ddY mice were phenotypically normal. The ratio of affected to unaffected mice

Fig. 1. Wild-type ddY and cataract mice. Wild-type ddY mouse (1a) has pink eyes with no opacity, whereas cataract mouse (1b) has pink eyes with opacity.

Table 1. Incidence of cataract in the cataract mouse with age

	Age (weeks)				
	6	7	8	9	10
Normal	198 (99, 99) ^{a)}	51 (27, 24)	3 (3, 0)	1 (1, 0)	0 (0, 0)
Unilateral cataract	7 (3, 4)	12 (4, 8)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Bilateral cataract	21 (9, 12)	163 (80, 83)	223 (108, 115)	225 (110, 115)	226 (111, 115)

n=226 (female:111, male: 115), a) female, male.

Fig. 2. Eye of wild-type ddY and cataract mice ($\times 7.5$). Eosin staining in the lens of 5-week-old cataract mouse (2b) is similar to that in the lens of age-matched ddY mouse (2a). Eosin staining in the lens of 5-month-old cataract mouse (2d) is abnormally stronger than that in the lens of age-matched ddY mouse (2c). Lens nucleus of the 5-month-old cataract mouse is dislocated to the posterior region of the lens cortex (2d).

among the offspring between heterozygous mutants was approximately 1:3.

Linkage analysis: The results of a linkage test on each autosomal chromosome are shown in Table 3. The range of χ^2 analysis in the polymorphic 54 microsatellite loci was 0 to 60. The χ^2 values of *D2Jpk4* and *D2Nds1*, located on Chr 2, were recorded at 60 and 15, respectively. This indicates that there is a linkage between the mutant gene (*mct*) and Chr 2. Therefore, further linkage analysis was carried out with an additional 23 microsatellite markers. The results of further mapping on Chr 2 are shown in Table 4, and the distribution of haplotypes is shown in Fig. 4. Twenty recombination events among loci were observed in 332 samples. All 20 offspring arose as a result of a single crossover event. Analysis of the haplotype distribution pattern allowed the localization of the cataract gene (*mct*) to the 3.91 cM region between *D2Mit467* and *D2Mit320* (Fig. 5).

DISCUSSION

The morphology of mouse cataracts takes four major forms: nuclear, cortical, capsular-epithelial and lens extrusion [21]. In the cataracts lens, various abnormal changes have been reported; the presence of cell nuclei in the lens fibers [6], the vacuolation of epithelial cells [20], degeneration of perinuclear fibers, and progressive condensation of the nucleus [17]. A cortical cataract involves the lens cortex and is associated with the breakdown of lens fiber cells, migration of lens nuclei to the posterior lens cortex, and abnormal fiber production [21]. Singh *et al.* [20] reported that lens epithelial cells damaged by intracellular vacuole formation invariably result in cortical and posterior subcapsular cataract formation. In 5-week-old cataract mice, the eyes did not show lens opacity on observation with the naked eye. On histological observation on the lens of 5-week-old cataract mice, the lens nucleus was normal and the anterior cortical lens fibers were swollen. In the lens of 5-month-old cataract mice, the lens nucleus was abnormally stained with eosin and was dislocated to the posterior cortex. Vacuolated epithelial cells covered the anterior surface of the lens. These results suggest that abnormal lens features in cataract mice occur at least 5 weeks after birth, and they resemble those in cortical cataracts.

Aphakia cataract (*ak*) is characterized by closed eyelids, dysgenetic lens cataract (*dyl*) by cornea-lens attachment, and vacuolated lens cataract (*vl*) by spina bifida [21]. The three cataract models are cortical cataracts caused by a recessive gene. In the present study, however, the cataract mice displayed none of the features observed in these three cataract models. Therefore, the present mice represent a novel cataract model.

Congenital cataracts have been identified with all three types of Mendelian inheritance, i.e., autosomal dominant, autosomal recessive and X-linked [8, 19]. In the present study, the incidence of cataract in heterozygous mutants between the cataract and wild-type ddY mice was 0% and no difference in incidence was observed between males and females. These results indicate that the mutation in the cataract mice is autosomal recessive. In the offspring between the heterozygous mutants, 45 mice displayed cataracts and 121 mice were healthy. This segregation ratio was well in line with the expected 1:3 ratio, based on the hypothesis that the expression of cataracts in the cataract mice is controlled by an autosomal recessive gene.

In this study, we found that the *mct* lies 3.91 cM on Chr 2 between *D2Mit467* and *D2Mit320* (Fig. 5). At present, the

Table 2. Breeding data showing segregation in mating the cataract and wild type ddY mice

Matings	Observed (female, male)	Affected (female, male)	Incidence (%) (female, male)
heterozygous mutants (hm)	198 (99, 99)	0 (0,0)	0 (0, 0)
hm $\times$ hm	166 (74, 92)	45 (19, 26)	27.1 (25.7, 28.2)

Table 3. Linkage analysis of cataract gene (*mct*) in affected backcross progenies at selected loci

	Symbol	cM Position	Affected		χ^2 analysis	
			Homo ^{a)}	Hetero ^{b)}	χ^2 value	<i>P</i> value
Chr1	D1Mit170	19.5	7	13	1.800	0.1797
	D1Mit10	56.6	6	14	3.200	0.0736
	D1Mit15	87.9	9	11	0.200	0.6547
	D1Mit17	106.3	10	10	0.000	1.0000
Chr2	D2Jpk4	18	60	0	60.000	0.0000
	D2Nds1	53	45	15	15.000	0.0001
	D2Mit28	78.2	11	9	0.200	0.6547
	D2Mit25	102	11	9	0.200	0.6547
Chr3	D3Mit1	11.2	11	9	0.200	0.6547
	D3Mit313	49.7	13	7	1.800	0.1797
	D3Mit38	70.3	12	8	0.800	0.3711
Chr4	D4Mit1	6.3	11	9	0.200	0.6547
	D4Mit322	35.7	8	12	0.800	0.3711
	D4Mit12	57.6	10	10	0.000	1.0000
Chr5	D5Mit4	20	14	6	3.200	0.0736
	D5Mit9	54	13	7	1.800	0.1797
	D5Mit51	81	8	12	0.800	0.3711
Chr6	D6Mit158	6	12	8	0.800	0.3711
	D6Mit16	30.5	9	11	0.200	0.6547
	D6Mit12	59.6	9	11	0.200	0.6547
Chr7	D7Mit228	18	12	8	0.800	0.3711
	D7Mit62	42.6	13	7	1.800	0.1797
	D7Mit14	69	11	9	0.200	0.6547
Chr8	D8Mit155	1	26	14	3.600	0.0578
	D8Mit6	30	23	17	0.900	0.3428
	D8Mit55	62	13	7	1.800	0.1797
Chr9	D9Mit191	26	10	10	0.000	1.0000
	D9Mit10	49	11	9	0.200	0.6547
	D9Mit19	71	12	8	0.800	0.3711
Chr10	D10Mit2	16	9	11	0.200	0.6547
	D10Mit11	50	26	14	3.600	0.0578
	D10Mit103	70	5	15	5.000	0.0253
Chr11	D11Mit51	18	10	10	0.000	1.0000
	D11Nds1	43.8	11	9	0.200	0.6547
	D11Mit10	63	11	9	0.200	0.6547
Chr12	D12Mit2	19	6	14	3.200	0.0736
	D12Mit6	45	7	13	1.800	0.1797
Chr13	D13Mit117	19	25	15	2.500	0.1138
	D13Mit9	45	11	9	0.200	0.6547
	D13Mit31	71	12	8	0.800	0.3711
Chr14	D14Mit4	16.5	9	11	0.200	0.6547
	D14Mit8	48.2	12	8	0.800	0.3711
Chr15	D15Mit11	10.4	8	12	0.800	0.3711
	D15Mit123	30.6	5	15	5.000	0.0253
	D15Mit40	65	11	9	0.200	0.6547
Chr16	D16Mit34	9.6	12	8	0.800	0.3711
	D16Mit4	27.3	12	8	0.800	0.3711
	D16Mit94	57.6	24	16	1.600	0.2059
Chr17	D17Mit16	17.4	10	10	0.000	1.0000
	D17Mit20	34.3	11	9	0.200	0.6547
Chr18	D18Mit14	18	10	10	0.000	1.0000
	D18Nds1	55	5	15	5.000	0.0253
Chr19	D19Mit60	15	7	13	1.800	0.1797
	D19Mit10	47	10	10	0.000	1.0000

The location of markers and distance (cM) were cited from Mouse Genome [13].

a) Homo represent *mct/mct* allele.

b) Hetero represent *mct/MSM* allele.

Table 4. Further linkage analysis of cataract gene on chr 2 of the cataract mice

Symbol	cM Position	Affected		χ^2 analysis χ^2 value
		Homo ^{a)}	Hetero ^{b)}	
D2Mit318	14.0	127	8	104.90
D2Mit521	15.3	127	8	104.90
D2Mit33	17.0	133	2	127.12
D2Mit120	17.0	130	5	115.74
D2Mit217	17.0	133	2	127.12
D2Mit234	17.0	133	2	127.12
D2Jpk4	18.0	173	2	167.09
D2Mit84	18.0	324	8	300.77
D2Mit235	22.5	325	7	304.59
D2Mit515	25.7	331	1	328.01
D2Mit367	26.2	329	3	320.11
D2Mit239	28.0	329	3	320.11
D2Mit204	28.0	330	2	324.05
D2Mit467	27.3	331	1	328.01
D2Mit320	27.3	320	12	285.73
D2Mit368	27.3	320	12	285.73
D2Mit370	27.3	166	9	140.85
D2Mit466	27.3	166	9	140.85
D2Mit203	28.0	329	3	320.11
D2Mit237	28.0	166	9	140.85
D2Mit88	30.0	164	11	133.77
D2Mit155	30.0	123	12	91.27
D2Mit269	30.0	125	10	97.96
D2Mit327	40.4	113	22	61.34
D2Nds1	53	101	34	33.25

The location of markers and distance (cM) were cited from Mouse Genome [13].

a) Homo represent *mct/mct* allele.

b) Hetero represent *mct/MSM* allele.

bs (blind-sterile) and the *Lop4* (lens opacity 4) genes are mapped on Chr 2, and it is reported that the genes are causative of mouse cataracts. The *bs* gene is 83 cM from the centromere of Chr 2, and it causes both cataracts and male sterility [25]. The *Lop4* gene is mapped 96 cM from the centromere of Chr 2. This gene acts through semidominant inheritance [26]. The *Pax6* gene is mapped on 65 cM from the centromere of Chr 2. Artificial mutation of the *Pax6* gene is reported to lead to the development of cataracts [3]. As determined by linkage analysis, the *bs*, *Lop4* and *Pax6* genes, as well as the *mct* gene, all map to locations on Chr 2. The *mct* gene, however, lies in a location distinct from the three known cataract genes; therefore, the *mct* gene is distinct from these three cataract genes.

One gene in the region between *D2Mit467* and *D2Mit320* that causes eye malfunction is the *Icst* (iris-corneal strands) gene. The position of the *Icst* gene has been widely mapped, within a 7 cM region on both sides of *D2Mit365* (21.9 cM); thus, the physical-location of the *Icst* gene is uncertain. Mutations in *Icst* cause various eye diseases, but there have been no reports on a potential role in cataract development [24]. As the gene that causes cataracts is not reportedly localized to the area where the causative genes for cataracts are known to exist, we believe that the *mct* is a novel cata-

Fig. 3. Anterior region of the lens cortex of wild-type ddY and cataract mice ($\times 340$). In the 5-week-old wild-type ddY mouse, no marked changes are seen in the lens cortex (3a). In the 5-week-old cataract mouse, swollen fibers are seen in the lens cortex (3b). The anterior surface of the lens in the 5-month-old wild-type mouse is covered with a simple cuboidal epithelium (3c). In the 5-month-old cataract mouse, however, vacuolated epithelial cells (arrows) are seen in the simple cuboidal epithelium (3d). Furthermore, pyknotic nuclei (arrowheads) and disrupted arrangement of the lens fibers are seen in the anterior region (3d).

ract gene.

The present cataract mice are fully viable and fertile, and a spontaneous cataract model derived from ddY mice has not yet been reported. This cataract mouse is thus a novel

Fig. 4. Distribution of haplotypes in a set of 332 affected offspring from the backcross [cataract mouse × (cataract mouse × MSM/Ms mouse)]. Typed loci are listed on the left. Columns denote specific chromosomes identified in affected backcross progenies. Black squares represent the *mct*/MSM allele; White squares represent the *mct*/*mct* allele.

Fig. 5. Genetic linkage map of Chr 2. The map shows the chromosomal location of *mct* and other loci typed in the interspecific backcross with distances between loci given by recombination value. Typed loci are listed on the left of the chromosome and values to the right are distances between loci.

model that will be a good tool for genetic analysis and for the study of the molecular biology of cataractogenesis. We have designated the present cataract mouse as the Morioka (MCT) mouse.

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