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Study on the Ophthalmic Diseases in ICR Mice and BALB/c Mice

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Abstract: *In pharmaceutical companies and research institutes, many toxicity tests are performed with laboratory animals. This study was performed to produce reference data for eye toxicity tests and to investigate the ophthalmic diseases of 408 ICR mice and 119 BALB/c mice, which are commonly used as subjects in toxicity tests. The experimental animals without clinical disorders were selected regardless of sex. The ophthalmic diseases were examined by using special ophthalmic instruments: direct ophthalmoscope, indirect ophthalmoscope, slit-lamp biomicroscope and focal illuminator. The most prevalent ocular variation within normal limits was hyaloid vessel remnant (ICR mice, 28.2%; BALB/c mice, 31.9%) and the incidence gradually decreased with age. The ocular diseases found in ICR mice were retinal degeneration (9.8%), corneal scar (4.2%), focal cataract (2.2%), anisocoria (1.2%), corneal ulcer (0.2%) and uveitis (0.2%). In BALB/c mice, corneal scar (9.2%), focal cataract (1.7%) and corneal ulcer (0.8%) were the ocular diseases found.*

Key words: *BALB/c, ICR, mouse, ophthalmic disease*

Introduction

In pharmaceutical companies and research institutes, many toxicity tests are performed using laboratory animals. When new medicines or new materials are developed, they are screened with several acute or chronic toxicity tests using laboratory animals. Ophthalmic examinations play an essential part in toxicological evaluation of both topical and systemic drugs [3, 6, 8, 9, 11].

The mouse, *mus musculus*, has been used as an experimental species, providing an animal model for human ocular disease and generalized toxicity studies for many years. However, the interpretation of the

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Table 1. Age and sex distributions according to breeding facility in ICR mice

Age/Sex	A (n=107)	B (n=84)	C (n=30)	D (n=187)
1–2 weeks		17		
3–4 weeks		41		22
5–6 weeks		5		54
7–8 weeks		4	30	35
9–10 weeks	107*			
over 11 weeks		17		76
Male	107	45	15	76
Female		39	15	111

*: No. of mice. A, C: IcrTacSam:ICR. B, D: KRIBB.

results of the eye toxicity test is difficult, because there are few reports about spontaneous ocular diseases of the mouse. Even within mice, differences in ocular diseases due to variations in genetic characteristics exist between different breeds, and there is little in the literature that differentiates ocular diseases of mouse according to breed.

Rubin [4] reported on selected ocular diseases of a few laboratory animals from the viewpoint of clinical pathology.

The main purpose of this study was to study and provide information on representative ocular diseases and provide basic data on eye toxicity tests on breeds of ICR and BALB/c mice that are commonly used.

Materials and Methods

Animals

Four hundred eight ICR mice and one hundred nineteen BALB/c mice were used in this study without regard to sex. The laboratory animals were obtained from a laboratory animal company, pharmaceutical companies, and research centers in Korea. Healthy mice were selected before performing ophthalmic examinations. The age and sex distributions according to breeding facility of 408 ICR mice and 119 BALB/c mice are shown in Tables 1, 2. A commercial pellet diet and water were supplied *ad libitum*. The mice were housed in a controlled environment, at a temperature of 20–25℃ and humidity of 50-70% with a 12 h light/12 h dark cycle per day. The examination adhered to the strict guidelines of the "Guide for the Care and Use of Laboratory Animals" of Seoul National University (Seoul, South Korea).

Table 2. Age and sex distributions in BALB/c mice

Age/Sex	A (n=65)	B (n=54)
3–4 weeks		54
5–6 weeks	10*	
7–8 weeks	55	
9–10 weeks		
over 11 weeks		
Male	55	27
Female	10	27

*: No. of mice.
A: KRIBB. B: BALB/cAnNTacSam.

Ophthalmic instruments

Ophthalmic instruments used in this study included a direct ophthalmoscope (EN-100®, Heine, Germany), indirect ophthalmoscope (Vantage®, Keeler, UK), slit-lamp biomicroscope (SL-14®, Kowa, Japan) and a focal illuminator.

Ophthalmic examinations

All ophthalmic examinations were performed in a darkened room, and the age, sex, place of rearing, and other information were recorded. Preliminary ophthalmic examinations of blepharospasm, photophobia, orbit, structure of tissues surrounding the eye, size and position of globe, condition and position of upper and lower lid, ocular discharge, lid margin, palpebral conjunctiva, bulbar conjunctiva, fornix, cornea and each surface were done without ophthalmic instruments. Lid margin, conjunctiva, cornea (opaque, neovascularization, pig-

mentation), depth of anterior chamber, aqueous flare in anterior chamber, iris, and pupillary light reflex were examined in a darkened room using the focal illuminator and the slit-lamp biomicroscope. Lens, vitreous body, and fundus were examined using the direct ophthalmoscope, and the indirect ophthalmoscope about 10 min after applying a mydriatic agent, 1% tropicamide (Mydriacyl®, Alcon, USA). The size and color of the optic disc, papilloedema, and retinal vessels were examined during the fundic examination. After ophthalmic examination, photographs of the animals with normal appearance (Figs. 1–3, 10–12) as well as ones with ocular diseases were taken using a fundus camera (Genesis®, Kowa, Japan).

Data analysis

The distributional results of ophthalmic examinations were analyzed based on the disease, sex, age, and rearing facility.

Results

Ocular findings in ICR mice and BALB/c mice

Remnant of the hyaloid vessel was found in 113 ICR mice (28.2%) and prominence of the lens nucleus (Fig. 3) was found in 38 ICR mice (9.3%). These symptoms were variations within the normal limit. As ocular diseases, retinal degeneration (Figs. 8, 9) was found in 40 ICR mice (9.8%) and all were found to be bilateral. Corneal scar (Fig. 5) was found in 17 ICR mice (4.2%), focal cataract (Fig. 6) in 9 (2.2%), anisocoria in 5 (1.2%), corneal ulcer (Fig. 4) in 1 (0.2%), and uveitis (Fig. 7) in 1 (0.2%). Overall, 17.9% of ICR mice showed ocular disease (Table 3).

Hyaloid vessel remnant (Fig. 11) was found in 38 BALB/c mice (31.9%), and prominence of the lens nucleus (Fig. 12) was found in 18 BALB/c mice (15.1%). These symptoms were variations within the normal limit. As ocular diseases, corneal scar (Fig. 13) was found in 11 BALB/c mice (9.2%) and bilateral conditions were more common; focal cataract (Fig. 15) was found in 2 BALB/c mice (1.7%) and corneal ulcer (Fig. 14) in 1 (0.8%). Overall, 11.8% of BALB/c mice showed ocular diseases (Table 4).

Distribution of ocular diseases based on sex and age

ICR mice showed a higher distribution of hyaloid vessel remnant in females (33.9%) than in males (24.3%). Furthermore, prominence of the lens nucleus (Fig. 3) was found in 21.8% of females, which was much higher than in males, 1.2%. Among abnormalities, retinal degeneration (Figs. 15, 16) was found in 20.0% of cases in females and 2.9% of cases in males (Table 5). The distribution based on age showed 100.0% occurrence of hyaloid vessel remnant in 1–2 weeks old mice, 77.8% in 9-10 weeks old, and 27.1% in 5–6 weeks old. However, only a 14.5% occurrence was found in 7–8 weeks old, 17.8% in 9–10 weeks old and 4.3% in the 11 weeks old mice (Table 6).

The distribution of ocular diseases based on sex for BALB/c mice showed a higher distribution of variation of hyaloid vessel remnant (Fig. 10) within the normal limit in females (54.1%) than in males (22.0%). Furthermore, prominence of the lens nucleus (Fig. 11) was found in 40.5% of females which was much higher than in males, 3.7% (Table 7). Also, abnormalities were found in 18.9% of females and 8.5% of males (Table 8).

Distribution of ocular disease occurrence based on rearing facilities

ICR mice showed incidences of changes within the normal limit of 67.9% in B facility, 38.5% in D facility, 17.8% in A facility, and 16.7% in C facility. An incidence of retinal degeneration (Figs. 15, 16) of 19.8% was found for mice from D facility and the incidence of anisocoria was 4.7% for mice from A facility (Table 9).

The variation within the normal limit for BALB/c mice was 10.8% for mice from A facility and 90.7% for mice from B facility. Abnormal ocular diseases showed a 22.2% occurrence for B facility (Table 10).

Discussion

This study examined 408 ICR mice and 119 BALB/c mice to investigate spontaneous ocular diseases. In this study, ocular findings were classified into variations within normal limits and disease conditions not within normal limits.

In the present study, normal eye variations found in ICR and BALB/c mice were hyaloid vessel remnant and prominence of the lens nucleus. It was considered that these variations related to the eye development af-

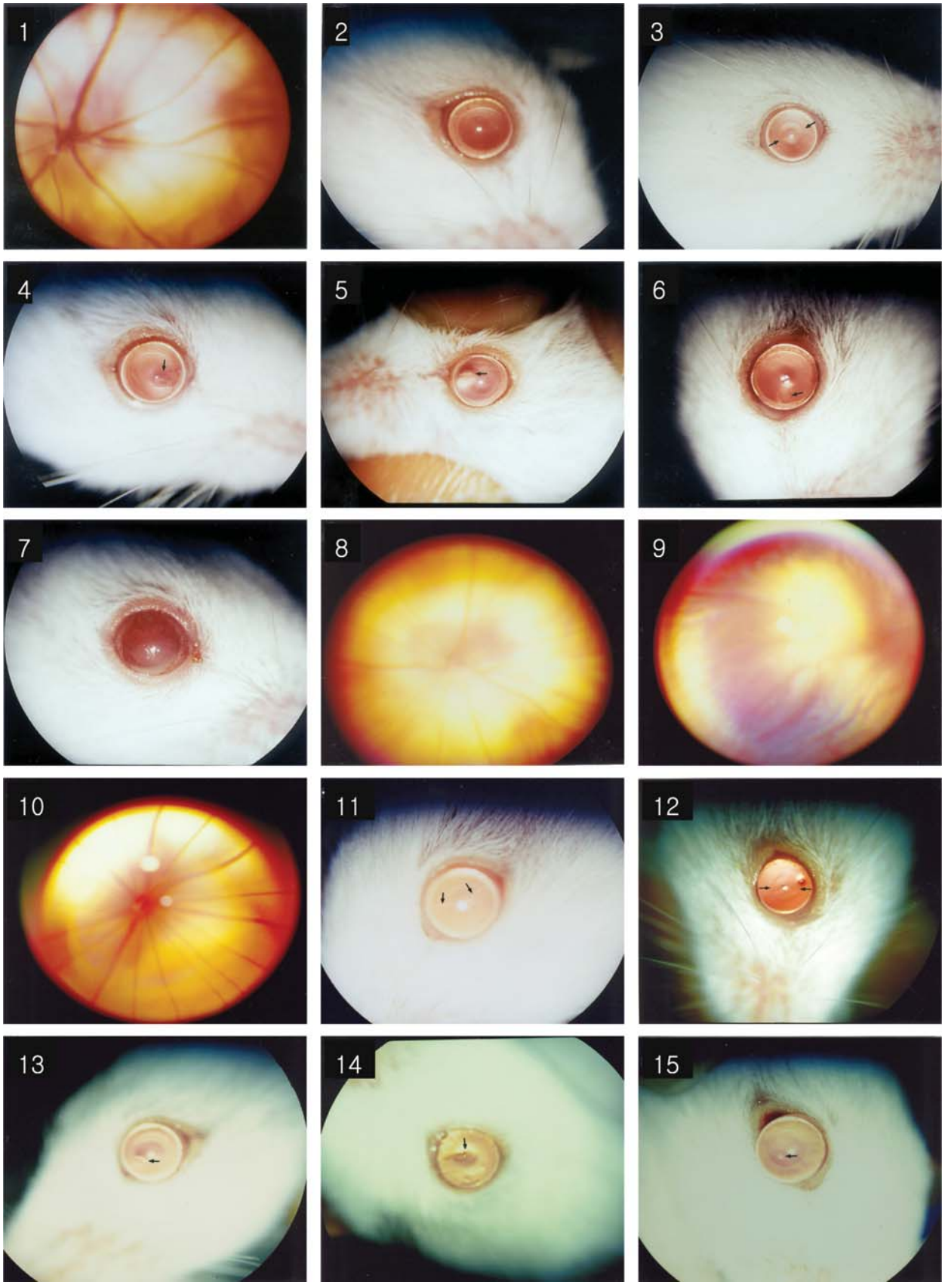
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Table 3. Ocular findings in 408 ICR mice

Ocular findings	Unilateral	Bilateral	Total
Within normal limits			
Hyaloid vessel remnant	9 (2.2)*	106 (26.0)	115 (28.2)
Prominence of lens nucleus		38 (9.3)	38 (9.3)
Subtotal	9 (2.2)	144 (35.3)	153 (37.5)
Not within normal limits			
Anisocoria	5 (1.2)		5 (1.2)
Corneal ulcer	1 (0.2)		1 (0.2)
Corneal scar	14 (3.4)	3 (0.7)	17 (4.2)
Focal cataract	7 (1.7)	2 (0.5)	9 (2.2)
Retinal degeneration		40 (9.8)	40 (9.8)
Uveitis	1 (0.2)		1 (0.2)
Subtotal	28 (6.9)	45 (11.0)	73 (17.9)

*: No. of mice (%).

Table 4. Ocular findings in 119 BALB/c mice

Ocular findings	Unilateral	Bilateral	Total
Within normal limits			
Hyaloid vessel remnant	2 (1.7)*	36 (30.3)	38 (31.9)
Prominence of lens nucleus		18 (15.1)	18 (15.1)
Subtotal	2 (1.7)	54 (45.4)	56 (47.1)
Not within normal limits			
Corneal scar	4 (3.4)	7 (5.9)	11 (9.2)
Corneal ulcer	1 (0.8)		1 (0.8)
Focal cataract	1 (0.8)	1 (0.8)	2 (1.7)
Subtotal	6 (5.0)	8 (6.7)	14 (11.8)

*: No. of mice (%).

ter birth. Hyaloid vessel remnant appeared as a white, irregular strand extending from the posterior pole of the lens. Williams [12] described that persistence of the hyaloid vasculature is common in rats 5 to 6 weeks of age and that the regression of these vessels occurred in the next few months. In this study, hyaloid vessel remnant was commonly observed in mice under 5 to 6 weeks of age. The distribution based on age in ICR mice showed 100% occurrence of hyaloid vessel remnant in 1–2 weeks old mice. However, its occurrence decreased with age and it was only 4.3% in 11 week old mice. Also, its dramatic decrease at the age of 7–8 weeks in ICR and BALB/c mice indicated that the eye of mice was developing until this age. It was reported that vitreal hemorrhage is found during this period [12]. However in this study, vitreal hemorrhage was not found in ICR and BALB/c mice.

Prominence of the lens nucleus was found in 3-6 weeks old ICR mice and 3-4 weeks old BALB/c mice with most showing a bilateral condition. It was seen at a much higher incidence than that reported in 4-5 week old young Swiss mice by Hubert [2].

Fig. 1. Normal fundus of ICR mouse.
Fig. 2. Normal eye of ICR mouse.
Fig. 3. Prominence of lens nucleus (arrows) of ICR mouse.
Fig. 4. Corneal ulcer (arrow) of ICR mouse.
Fig. 5. Corneal scar (arrow) of ICR mouse.
Fig. 6. Focal cataract (arrow) of ICR mouse.
Fig. 7. Uveitis of ICR mouse.
Fig. 8. Retinal degeneration of ICR mouse. Diffuse attenuation of retinal vessel is shown.
Fig. 9. Severe retinal degeneration of ICR mouse.
Fig. 10. Normal fundus of BALB/c mouse.
Fig. 11. Hyaloid vessel remnants (arrows) of BALB/c mouse.
Fig. 12. Prominence of lens nucleus (arrows) of BALB/c mouse.
Fig. 13. Corneal scar (arrow) of BALB/c mouse.
Fig. 14. Corneal ulcer (arrow) of BALB/c mouse.
Fig. 15. Focal cataract (arrow) of BALB/c mouse.

Table 5. Sex distribution of ocular findings in 408 ICR mice

Ocular findings	Male (n=243)	Female (n=165)
Within normal limits		
Hyaloid vessel remnant	59 (24.3)*	56 (33.9)
Prominence of lens nucleus	2 (0.8)	36 (21.8)
Subtotal	61 (25.1)	92 (55.8)
Not within normal limits		
Anisocoria	5 (2.1)	
Corneal ulcer	1 (0.4)	
Corneal scar	1 (0.4)	16 (9.7)
Focal cataract	2 (0.8)	7 (4.2)
Retinal degeneration	7 (2.9)	33 (20.0)
Uveitis		1 (0.6)
Subtotal	16 (6.6)	57 (34.5)

*: No. of mice (%).

Table 6. Age distribution of ocular findings in 408 ICR mice (weeks)

Ocular findings	1–2 (n=17)	3–4 (n=63)	5–6 (n=59)	7–8 (n=69)	9–10 (n=107)	>11 (n=93)
Within normal limits						
Hyaloid vessel remnant	17 (100.0)*	49 (77.8)	16 (27.1)	10 (14.5)	19 (17.8)	4 (4.3)
Prominence of lens nucleus		19 (30.2)	19 (32.2)			
Subtotal	17 (100.0)	68 (107.9)	35 (59.3)	10 (14.5)	19 (17.8)	4 (4.3)
Not within normal limits						
Anisocoria					5 (4.7)	
Corneal ulcer				1 (1.4)		
Corneal scar		2 (3.2)	9 (15.3)	3 (4.3)	1 (0.9)	2 (2.2)
Focal cataract		2 (3.2)	4 (6.8)	1 (1.4)	2 (1.9)	
Retinal degeneration		10 (15.9)	11 (18.6)	11 (15.9)	3 (2.8)	4 (4.3)
Uveitis						1 (1.1)
Subtotal		14 (22.2)	24 (40.7)	15 (21.7)	11 (10.3)	7 (7.5)

*: No. of mice (%).

Table 7. Sex distribution of ocular findings in 119 BALB/c mice

Ocular findings	Male (n=82)	Female (n=37)
Within normal limits		
Hyaloid vessel remnant	18 (22.0)*	20 (54.1)
Prominence of lens nucleus	3 (3.7)	15 (40.5)
Subtotal	21 (25.6)	35 (94.6)
Not within normal limits		
Corneal scar	6 (7.3)	5 (13.5)
Corneal ulcer	1 (1.2)	
Focal cataract		2 (5.4)
Subtotal	7 (8.5)	7 (18.9)

*: No. of mice (%).

In this study, retinal degeneration was the most prevalent ocular diseases not within normal limits and all showed a bilateral condition in ICR mice. Ophthalmoscopically diffuse attenuation of vessels and hyperreflectivity were found. It might have been caused by inbreeding because it was found predominantly in one facility. Inherited retinal degeneration was reported to be a widespread abnormality in mice by Drager and Hubel [1]. It has been documented in various mouse breeds including ICR Swiss mice [5]. It is characterized by total absence of retinal photoreceptors and is inherited in an autosomal recessive manner [5].

Traumatic or inflammatory eye diseases such as corneal scar, corneal ulcer and uveitis were found in ICR and BALB/c mice. In BALB/c mice, the most pre-

Table 8. Age distribution of ocular findings in 119 BALB/c mice (weeks)

Ocular findings	3–4 (n=54)	5–6 (n=10)	7–8 (n=55)
Within normal limits			
Hyaloid vessel remnant	33 (61.1)*	3 (30.0)	2 (3.6)
Prominence of lens nucleus	16 (29.6)		2 (3.6)
Subtotal	49 (90.7)	3 (30.0)	4 (7.3)
Not within normal limits			
Corneal scar	9 (16.7)		2 (3.6)
Corneal ulcer	1 (1.9)		
Focal cataract	2 (3.7)		
Subtotal	12 (22.2)	0 (0.0)	2 (3.6)

*: No. of mice (%).

Table 9. Breeding facility distribution of ocular findings in 408 ICR mice

Ocular findings	A (n=107)	B (n=84)	C (n=30)	D (n=187)
Within normal limits				
Hyaloid vessel remnant	19 (17.8)*	55 (65.5)	5 (16.7)	36 (19.3)
Prominence of lens nucleus		2 (2.4)		36 (19.3)
Subtotal	19 (17.8)	57 (67.9)	5 (16.7)	72 (38.5)
Not within normal limits				
Anisocoria	5 (4.7)			
Corneal ulcer		1 (1.2)		
Corneal scar	1 (0.9)	3 (3.6)		13 (7.0)
Focal cataract	2 (1.9)			7 (3.7)
Retinal degeneration	3 (2.8)			37 (19.8)
Uveitis		1 (1.2)		
Subtotal	11 (10.3)	5 (6.0)	0 (0.0)	57 (30.5)

*: No. of mice (%). A, C: IcrTacSam:ICR. B, D: KRIBB.

dominant eye disorder in this study was corneal scar. Corneal scar is fibroplasia that occurs with stromal injury or chronic corneal diseases [7]. In this study it was considered that corneal scars were usually the result of trauma. They should be differentiated from corneal degenerations.

Focal cataracts were found in ICR and BALB/c mice. Cataracts have been documented as both spontaneous and induced lesions in experimental animals [11]. Inherited cataracts have been documented in mice. Cataracts arising from infection with a helical spirochete, termed the *suckling mouse cataract agent* in mice, have also been reported [10]. Prevalence of cataract in our survey is lower than that of a previous study [2].

The distribution of ocular diseases based on sex for ICR and BALB/c mice showed that a higher occurrence of variations within normal limit was found in

Table 10. Breeding facility distribution of ocular findings in 119 BALB/c mice

Ocular findings	A (n=65)	B (n=54)
Within normal limits		
Hyaloid vessel remnant	5 (7.7)*	33 (61.1)
Prominence of lens nucleus	2 (3.1)	16 (29.6)
Subtotal	7 (10.8)	49 (90.7)
Not within normal limits		
Corneal scar	2 (3.1)	9 (16.7)
Corneal ulcer		1 (1.9)
Focal cataract		2 (3.7)
Subtotal	2 (3.1)	12 (22.2)

*: No. of mice (%). A: KRIBB. B: BALB/cAnNTacSam.

females compared with males. Furthermore, the ocular diseases not within normal limit, especially conditions that resulted from trauma or inflammation, were also found in females more often than in males. Further study will be needed to elucidate the cause of this gender difference.

The distribution of ocular disease occurrence based on ICR mice breeding facilities showed higher incidences of changes within the normal limit in B and D facilities than in A and C facilities. This discrepancy was assumed to be the result of the fact that young mice were a high percentage of animals from B and D facilities, while only mice older than 7–8 weeks were obtained from A and C facilities. In ocular diseases, corneal ulcer, corneal scar, focal cataract, retinal degeneration, and uveitis were found more frequently in mice from A, B, and D facilities. In addition, a high incidence of retinal degeneration of 19.8% was found in D facility, and anisocoria was found only in A facility. These results might indicate the involvement of genetic factors resulting from inbreeding.

The variation within the normal limit for BALB/c mice was 10.8% in A facility, whereas it showed a very high value of 90.7% in B facility. This result is assumed to be due to the fact that all mice were 3–4 weeks old from B facility. The comparison of breeding facilities based on abnormal ocular diseases showed 22.2% occurrence for B facility even though overall the mice from B facility were younger than those from A facility. It was supposed that these diseases were also related to the hygiene and management of the breeding facility. This indicates that breeding management and periodic eye examination are important for producing good-quality experimental animals without eye diseases.

The results of this study are intended for use as reference data in ophthalmologic toxicity tests done by pharmaceutical companies and research centers for discriminating eye diseases from normal variations. This data should also be helpful for distinguishing between spontaneous eye diseases and drug induced eye diseases.

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