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Variation of the response to the optokinetic drum among various strains of mice

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1. ABSTRACT

The optokinetic drum has become an appropriate tool to examine visual properties of mice. We performed baseline measurements using mice of the inbred strains C3H, C57BL/6, BALB/c, JF1, 129 and DBA/2 at the age of 8-15 weeks. Each individual C57BL/6, 129 and JF1 mouse was reliably identified as non-affected in vision by determining head-tracking responses. C3H mice were used as negative control because of their inherited retinal degeneration; as expected, they did not respond to the moving stripe pattern. Surprisingly, BALB/c and DBA/2 mice showed the same result. Electroretinography, funduscopy and histology of BALB/c mice did not reveal any abnormality concerning the structure or function of the retina and the remaining eye. Therefore, it might be assumed that BALB/c mice suffer from disturbances of the central visual system. Preliminary results from linkage analysis of the non-responding phenotype in the BALB/c mice indicate a recessive, monogenic mode of inheritance; the causative gene is located on chromosome 7, but significantly different from the *albino* locus. In conclusion, C57BL/6, 129 and JF1 represent appropriate inbred strains for high throughput screenings with the optokinetic drum.

2. INTRODUCTION

The mouse is currently an established mammalian model for studying hereditary disorders, which have an effect on eye structure and function. In order to select and characterize mouse mutants suffering from ocular defects, a variety of test systems are well established, like slit lamp analysis for detecting lens opacities, iris and corneal abnormalities (1-3), funduscopy for abnormalities of the retinal fundus, reflecting retinal degeneration, vascular problems and optic disc alterations (4), or electroretinography for functional disorders of the retina (5), or optical low coherence interferometry for eye size variations (6, 7). However, these techniques do not allow conclusions about visual acuity or functionality of the central visual system. For this purpose, the optokinetic drum turned out to be a fast and effective test (2, 3, 8-10). If the mouse has a normal visual system, its body and head (head-tracking reflex) follow a rotating vertical stripe pattern.

The movement behavior of the mouse during this vision test can be evaluated by two different strategies: first, the investigator monitors the head-tracking reflex; this way of evaluation was shown to be appropriate for reliable

discrimination between mice with normal vision and mice with severely decreased vision even under high throughput conditions (2). As a second strategy, a computer based automated movement analysis was developed (11) in order to enable a quantitative characterization of the body movement during the measurement. In detail, movement of the body mass center as well as rotation of the snout-tail-axis is tracked by this system, which has been successfully applied in long term studies concerning grating acuity of different rod or cone lacking mutants (11) and the influence of spectacle lenses or diffusers on visual acuity (12). However, in contrast to the non-automated head-tracking monitoring, suitability of the automated movement analysis for reliable identification of visually non-affected individuals in high throughput screenings remains to be proved.

In this study, we performed baseline vision tests of the inbred strains C3H, C57BL/6, BALB/c, JF1, 129 and DBA/2 by non-automated monitoring of head-tracking response using an optokinetic drum. BALB/c and DBA/2 mice did not show a positive response to the drum movement. However, electroretinography, funduscopy and histology of BALB/c and DBA/2 mice did not point to any abnormality. Preliminary results from linkage analysis of the non-responding phenotype in the BALB/c mice indicate a recessive, monogenic mode of inheritance; the causative gene is located on chromosome 7, but significantly different from the *albino* locus.

3. MATERIALS AND METHODS

3.1. Animals

Five different mouse strains, which were considered in many laboratories as reference strains, were included in this study: C57BL/6J (n=28; 11 male / 17 female), BALB/cByJ (n=12; 9 male / 3 female), JF1 (n=21; 10 male / 11 female), 129S2/SvPasCrl (n=20; 10 male / 10 female) and DBA/2NCrl (n=16; 7 male / 9 female). Blind mice from the inbred strain C3HeB/FeJ (n=30; 14 male / 16 female) were used as an established control. At the time of analysis, mice were eight to 15 weeks old. C57BL/6, C3H and JF1 mice were obtained from the breeding colonies of the GSF-National Research Center for Environment and Health; 129, BALB/c and DBA/2 wild type mice were purchased from Charles River (Sulzfeld, Germany). The mice were housed in groups of three to five animals in the animal facilities of the GSF with a photoperiod of twelve hours lightness (start at 6 a. m.) and twelve hours darkness. Mice were fed ad libitum with Altromin 1324 breeding diet (Altromin Special animal Feed GmBH, Lage, Germany). The use of animals was in accordance with the German Law of Animal Protection, the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the tenets of the Declaration of Helsinki.

3.2. Vision test protocol

Vision tests were performed between 9 am and 4 pm with an optokinetic drum setup as described previously (11). Briefly, the tested mouse was freely moving in a transparent acrylic glass cylinder (diameter: 15 cm; height: 18 cm), which was placed in the center of the optokinetic drum (diameter: 63 cm; height: 35 cm). Movement behavior and head tracking were analyzed in ambient room light (illuminance = 18.5 fc; measured in the center of the cylinder with a LM-80 luminance meter, Amprobe, Glottertal, Germany) with a rotation speed of 10 rpm and a spatial frequency of 0.1 cyc/deg. The contrast was close to 100% (12). Prior to the analysis, the mice were allowed to adapt to the environment of the non-rotating drum for three minutes. Measurements started with the counter-clockwise rotating drum. Direction of the drum was changed 10 times, each time after 30 seconds; i.e. five 30-second intervals per direction. Occurrence of head-tracking reflexes was judged by the observer during each 30-sec period. Head tracking was defined as horizontal head movement at the same rate and the same direction as the drum for at least 15° (as described previously (2)). To check learning effects to the test setup on head tracking, these tests were repeated with the same mice under the same conditions after a retention time of at least 24 hours.

3.3. Statistical analysis

Head-tracking reflex was quantified using a head-tracking rating scale. A score was given within each 30-second interval, in which at least one head-tracking reflex was observed. Consequently, a maximum head-tracking quantity score of ten was attainable by each investigated mouse. Since no significant differences in head-tracking quantity scores were observed between males and females ($p>0.05$; calculated by Mann-Whitney U-test), data of both sexes were combined. For characterization of the score distribution functions, medians, first quartiles and third quartiles were calculated for each responding inbred strain. Scoring between these inbred strains was compared with the Mann-Whitney U-test; learning effects were statistically proofed with the Wilcoxon signed-rank test.

3.4. Funduscopy

Mice were administered 1% atropine to each eye to dilate their pupils. The fundus examination was performed with a Heine Sigma 150K indirect ophthalmoscope (Haag-Streit GmbH, Wedel, Germany) and a Volk 90D superfield lens (Haag-Streit GmbH). Digital fundus images were taken with a Heine Video Omega 2C indirect Ophthalmoscope connected to a VRmAVC Video Grabber (Dieter Mann GmbH, Mainaschaff, Germany) and a Volk 40D or 60D lens (Fronhäuser GmbH, Unterhaching, Germany). The images were imported in an image-processing program (Photoshop, ver.7.0; Adobe, Unterschleißheim, Germany).

3.5. Electroretinography

Ganzfeld ERGs were recorded simultaneously from both eyes to examine the retinal function as described (13). In brief, mice were dark-adapted for at least 12 hours and anaesthetized. After pupil dilation (1 drop Atropine 1%), individual mice were fixed on a sled and gold wires (as active electrodes) were placed on the cornea. The ground electrode was a subcutaneous needle in the tail; a reference electrode was placed subcutaneously between the eyes. The mice were introduced into an ESPION ColorBurst Handheld Ganzfeld LED stimulator (Diagnosys LLC, Littleton, MA, USA) on a rail to guide the sled

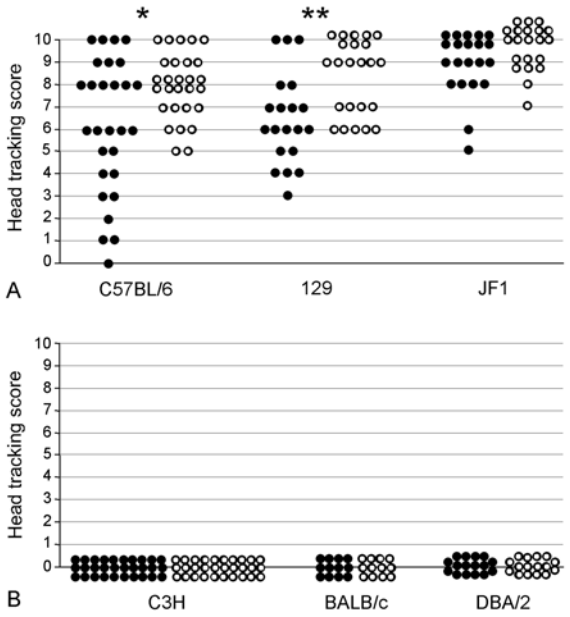

Figure 1. Head-tracking score distribution of (a) the responding inbred strains C57BL/6, 129 and JF1 and (b) the non-responding inbred strains C3H, BALB/c and DBA/2 obtained in the first (naive) (●) and second (adapted) (○) vision test. Each spot represents the head-tracking score of one tested mouse. Asterisks represent significant differences between the distribution of both vision tests (Wilcoxon signed-rank test); *: $p<0.02$; **: $p<0.01$. There was no head tracking observed for BALB/c, C3H or DBA/2 mice.

(High-Throughput Mouse-ERG, STZ for Biomedical Optics and Function Testing, Tübingen, Germany). 10 ms light pulses were delivered at a frequency of 0.48 Hz in two steps at 500 and 12,500 cd/m^2. Responses were recorded with an ESPION Console (Diagnosys LLC, Littleton, MA, USA) and stored.

3.6. Histology

Eyes were fixed 24 hours in Davidson solution, dehydrated and embedded in plastic medium (JB4-Plus; Polysciences, Inc. Eppelheim, Germany). Transverse 2 µm sections were cut with an ultramicrotome (Ultratom OMU3; Reichert, Walldorf, Germany) and stained with methylene blue and basic fuchsin. Sections were evaluated with a light microscope (Axioplan; Carl Zeiss Jena GmbH, Göttingen, Germany) for the presence and appearance of the retinal layers. Images were taken with a scanning camera (Axiocam; Carl Zeiss) equipped with a screen-capture program (KS100; Carl Zeiss Vision, Hallbergmoos, Germany) and imported in an image-processing program (Photoshop, ver.7.0; Adobe, Unterschleissheim, Germany).

4. RESULTS

4.1. Head-tracking behavior

Under naive test conditions (no learning), head-tracking behavior was observed for C57BL/6, 129 and JF1, but not for BALB/c, DBA/2 and C3H mice. Because of the test protocol (ten 30-second intervals), a maximum score of 10 could be obtained for one single mouse. Mice of the C57BL/6 inbred strain exhibited a head-tracking quantity score with a median of $x_{0.50}=6$ (25% quantile $x_{0.25}=4$; 75% quantile $x_{0.75}=8.25$). About half of the investigated C57BL/6 individuals (13 out of 28) scored in more than seven 30-second intervals. However, there were also eight individuals exhibiting a poor quantity score of less than five (Figure 1a). A median of $x_{0.50}=6$ was also detected for non-adapted 129 mice ($x_{0.25}=5$; $x_{0.75}=7.25$). However, only a quarter of the tested mice (five out of 20) scored regularly in more than seven observation intervals, while eleven mice exhibited a final score of five to seven. The remaining four individuals reacted only rarely to the moving stripe pattern (quantity score of less than five; Figure 1a).

The significantly best response ($p<0.001$) was observed for JF1. Mice of this strain revealed a score median of $x_{0.50}=9$ under naive test conditions ($x_{0.25}=8$; $x_{0.75}=10$). Moreover, nearly all of the tested JF1 mice (19 out of 21) scored frequently in more than seven observation intervals, while two JF1 mice exhibited during at least five intervals one or more head-tracking reflexes (Figure 1a).

No head-tracking activity could be observed in the negative C3H control during the observation intervals. Surprisingly, we made the same observation for all BALB/c and DBA/2 mice (Figure 1b), even under modified conditions like broader stripe pattern (0.05 cyc/deg), reduced rotation speed (down to 4 rpm) or dimmed room light (data not shown).

For all mice the test was repeated at least 24 hours later. For C57BL/6 and 129 mice, positive learning effects were observed. In particular, C57BL/6J mice exhibited after learning an elevated median of $x_{0.50}=8$ ($x_{0.25}=7$; $x_{0.75}=9$). Minimum response among the C57BL/6 individuals after learning was a head-tracking quantity score of five (Figure 1a). Altogether, this is a significantly elevated score distribution ($p<0.02$) in comparison to the result obtained under conditions without learning.

129 mice revealed a score median of $x_{0.50}=9$ in the second vision test ($x_{0.25}=7$; $x_{0.75}=10$). Regarding the head-tracking behavior in detail, 14 out of 20 adapted 129 mice attained a head-tracking quantity score of more than seven, while the remaining seven individuals scored at least five times (Figure 1a). This improvement is also statistically significant ($p<0.01$). Similar to C57BL/6 and 129, JF1 mice exhibited after learning an improved score median of $x_{0.50}=10$ ($x_{0.25}=9$; $x_{0.75}=10$). However, because of the high response level under naive test conditions, the improvement after learning was not statistically significant ($p>0.1$) among JF1 individuals. Similar to the observation under naive conditions, for mice of the C3H, BALB/c and DBA/2 strains no head-tracking response could be observed under conditions after learning (Figure 1b).

4.2. Electroretinography, funduscopy and histology of DBA/2 and BALB/c mice

To get a first idea of the reason for the missing head-tracking response in the BALB/c and DBA/2 mice, they were examined for eye abnormalities by funduscopy,

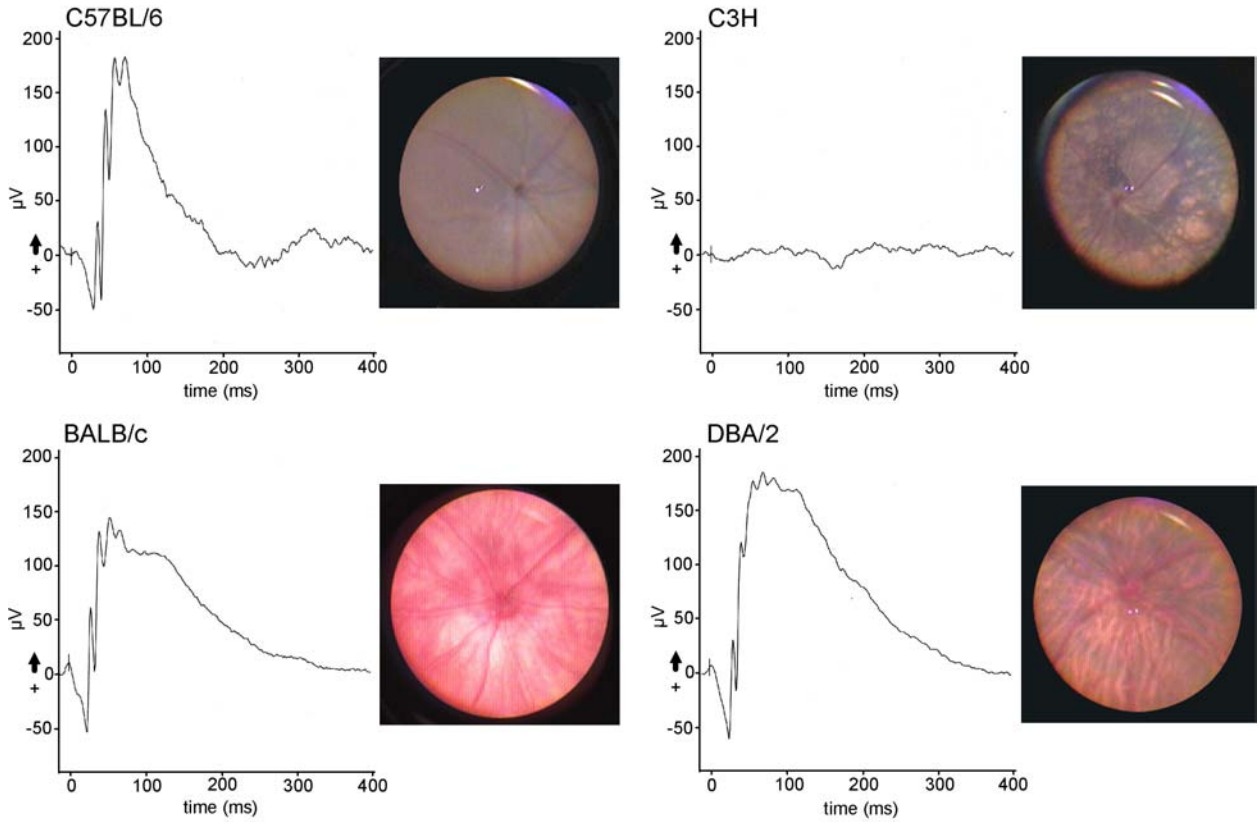

Figure 2. Electroretinography and funduscopy of C57BL/6J, C3H, BALB/c and DBA/2 at the age of 11 weeks. The ERG response of a mouse eye is given together with the corresponding fundus image. The data are typical for mice of these strains.

electroretinography (ERG) and finally by histology of their eyes and compared to C3H and C57BL/6 mice. Among the different strains, a large diversity was observed in the ocular fundus (Figure 2). Particularly, albino mice, like BALB/c, displayed a much lighter, red shining fundus, due to the lacking pigmentation. However, black-eyed mice showed strain specific differences in the fundus as well. C57BL/6 mice had a uniform, grey shining retinal fundus, whereas DBA/2 mice showed a pattern of red stripes. Moreover, retinal disorders can be reflected in the retinal fundus, like the retinal degeneration (*Pde6b*^{rd1}) of C3H mice resulting in pigment patches and vessel attenuation (Figure 2).

The retinal function was tested by ERG, recorded at two different illumination intensities (5 and 125 cd-s/m²). Mice of the negative-control strain C3H showed no response to the given flash light stimuli, whereas for C57BL/6, BALB/c and DBA/2 mice well developed a- and b-waves were recorded indicating a normal retinal function (Figure 2). Histological evaluation corresponded to the ERG response. C3H mice, homozygous for *Pde6b*^{rd1}, showed the typical degeneration of the photoreceptor cell layers, while C57BL/6, BALB/c and DBA/2 were characterized by well-ordered retinal layers at the age of 11 weeks (Figure 3).

4.3. Linkage analysis of BALB/c

In order to investigate whether the mutation in the *albino* locus is responsible for the lack of head tracking response by the BALB/c mice, we initiated a linkage analysis by outcrossing BALB/c mice to JF1. Since the F1-hybrids fully reacted in the optokinetic drum, the way of inheritance was considered to be recessive. Therefore, the F1-mice were backcrossed to BALB/c (F2-generation). Among the F2-offspring, a coat color distribution of about 1:2:1 was detectable (113 brown : 200 white : 100 beige). Vision tests revealed that each of the brown and most of the beige mice was visually non-affected (drum-positive, at least one head tracking response in the clockwise and counterclockwise rotating drum, respectively), while most of the albino F2-offspring did not respond to the rotating stripe pattern (drum-negative, no head tracking response at all in three vision tests; Table 1). However, 5 % of the albino F2-offspring clearly showed the head tracking behavior indicating a functional visual pathway in these cases. These data might point to a recombination between the *albino* locus and a not yet identified additionally mutated locus on chromosome 7. The theoretical distance between this vision affecting locus and the *albino* locus is 5.00 ± 1.54 cM.

Table 1. Distribution of visual properties in the F2-generation of the BALB/c linkage-analysis

Coat color	**Number of animals**	
	Drum-negative	Drum-positive
brown	0	113
beige	3[1]	97
white (albino)	190	10

[1] were only observed in the first litter tested with the drum

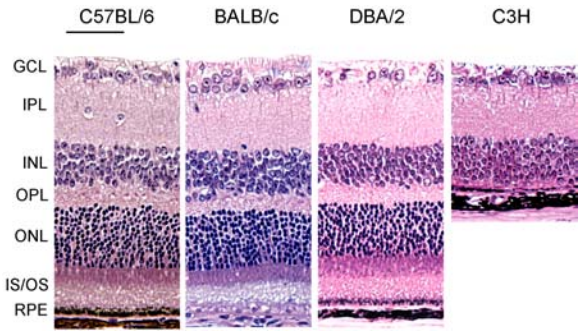

Figure 3. Histology of the retinas from C57BL/6, C3H, BALB/c and DBA/2 mice at the age of 6 weeks. There are no major differences between the mice from C57BL/6, BALB/c and DBA/2 strains; in the C3H mice the photoreceptor cells are missing and the density in the ganglion cell layer of DBA/2 seems to be lowered. GCL, ganglion cell layer; IPL, inner plexiform layer; INL, inner nuclear layer; OPL, outer plexiform layer; ONL, outer nuclear layer; IS/OS, inner/outer segments; RPE, retinal pigment epithelium. Bar = 50 μm.

5. DISCUSSION

Head-tracking reflex behavior was determined in the optokinetic drum using mice of different inbred strains, particularly in C3H, 129, JF1, C57BL/6, DBA/2 and BALB/c. The manual head-tracking monitoring approach used in this study revealed to be a suitable method to distinguish between normally sighted mice and mice with decreased vision. This is in accordance to the result of previous investigations (2). At least C57BL/6, 129 and JF1 mice were shown to respond to the rotating stripe pattern. While all JF1 animals showed the head-tracking response frequently even under naive conditions, C57BL/6 and 129 individuals responded regularly only, when the vision test was repeated. Comparable learning effects have also been reported for C3H-BALB/c hybrids (2).

These data clearly demonstrate that the optokinetic drum represents an accurate tool for identifying visually affected individuals under high-throughput conditions when C57BL/6, 129 or JF1 are used as host strain. As a great advantage compared to alternative vision tests, untrained mice can be measured within a very short time period until the first head tracking response occurs (or five minutes at maximum for non-responders) in order to analyse vision in a qualitative manner ("blind" or "not blind"). Quantitative investigations of visual properties, as for example visual acuity, are not feasible under these conditions. However, since this is not the goal of a primary high throughput screen, visual properties of non-responders might be further investigated in more time-consuming secondary screens. For this purpose, non-responding mice should be analysed in alternative vision tests, such as the virtual optomotor system (14) or the two-alternative swim task (15).

As a consequence of the observed positive learning effect, manual head-tracking monitoring of C57BL/6 or 129 mice should be performed at least twice to exclude false selection of non-responding unaffected animals. C57BL/6, 129 or JF1 individuals completely lacking head-tracking response even in a second or third vision test are most likely visually impaired and therefore represent putative models for studies on hereditary vision defects.

In contrast to C57BL/6, 129 and JF1 mice, mice of the inbred strains C3H, DBA/2 and BALB/c did not show any response to the rotating drum and therefore do not represent suitable host strains for high throughput screenings, at least with the drum setup used in this study. This lack of head-tracking reflexes was expected for the negative control C3H, since individuals of this inbred strain are homozygous carriers of the *Pde6b*^{rd1} allele (16) leading to blindness due to a degeneration of the outer retina and loss of rods by 35 days (17, 18). Consequently, the lack of responses in C3H mice reported here confirms previous data (2).

Concerning DBA/2 and BALB/c, there is no report in the literature about hereditary, early-onset eye disorders (at least earlier than three months of age). The DBA/2 mice were described to develop progressive eye abnormalities including iris pigment dispersion, iris atrophy, anterior synechia and elevated intraocular pressure beginning after three months of age (19). Consequences on the optic nerve structure and ganglion cell apoptosis were demonstrated to be first apparent between 8 and 9 months and between 8 and 10.5 months of age, respectively (20). For this reason it is surprising that the young DBA/2 mice used in this study (15 weeks of age or younger) seem to be already affected in the ganglion cell layer density, which might be an explanation for the observed drum-negative phenotype of DBA/2. Another explanation could be performance deficits due to the generally observed high basic activity of the DBA/2 mice during the vision test, which rather explored the plastic cylinder than concentrating on the stripe pattern (even under learning conditions). This could be optimized constructing a small platform in the center of the drum, as proposed previously (14).

The effect of albinism on the processing of visual stimuli has already been described in different species including mouse, rat, rabbit and ferret (8, 21-23). A broad variety of previous studies on albino laboratory animals (based upon the fundamental findings by Lund (24)) suggests that albinos show abnormally small uncrossed retinotectal pathways (for a review see reference (25)). However, subsequent studies demonstrated that this previous generalization might not hold true, because two-

alternative swim tasks identified albino AKR mice as not affected in visual detection, pattern discrimination and visual acuity (26). Accordingly, the preliminary linkage studies with the BALB/c mice point to an additional mutation, which is linked to, but significantly different from the *albino* locus.

In conclusion, the results of this study confirm the optokinetic drum setup as an appropriate vision test for high throughput screening. To exclude false negative results, non-responders should be tested at least twice with a rest period of 24 hours between the vision tests. C57BL/6, 129 and JF1 respond regularly to the rotating drum and therefore represent suitable inbred strains in terms of selection of visually affected variants in mutagenesis programs. DBA/2 and BALB/c mice did not show a positive response due to putative degenerations of retinal ganglion cells and putative abnormalities of the visual pathway beyond the eye, respectively. For BALB/c, preliminary mapping results point to an additional, not yet characterized mutation as the causative event, which is located on chromosome 7 outside of the *albino* locus.

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