

Mouse Models for Studies of Retinal Degeneration and Diseases

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Abstract

Mouse models, with their well-developed genetics and similarity to human physiology and anatomy, serve as powerful tools with which to investigate the etiology of human retinal degeneration. Mutant mice also provide reproducible, experimental systems for elucidating pathways of normal development and function. Here, I describe the tools used in the discoveries of many retinal degeneration models, including indirect ophthalmoscopy (to look at the fundus appearance), fundus photography and fluorescein angiography (to document the fundus appearance), electroretinography (to check retinal function), as well as the heritability test (for genetic characterization).

Key words: Mouse models, Retinal degeneration, Indirect ophthalmoscopy, Fundus, Electroretinography

1. Introduction

The number of known serious or disabling eye diseases in humans is large and affects millions of individuals worldwide. Yet research on these diseases frequently is limited by the obvious restrictions on studying pathophysiologic processes in the human eye. Mouse models of inherited ocular disease provide powerful tools for genetic analysis and characterization and intervention assessment. Studies of mouse models of human retinal degeneration are important to understanding the pathophysiology, as well as the etiology, of these diseases. Using these mouse models much progress has been made in elucidating gene defects underlying retinal disease, understanding mechanisms leading to disease, and designing molecules for translational research and gene-based therapy to interfere with the progression of disease.

Discovery of human retinal degenerations is not particularly difficult when patients visit their ophthalmologist for eye examinations,

but research on human retinal degenerations is impeded by the lack of availability of human eye tissues and the impossibility of doing genetic manipulation for research. Human eye tissue (including biopsies) for most human ocular diseases is seldom available because it is difficult to obtain tissue samples from the eye without the risk of damage to the patient's vision. Compared with diagnosis in humans, animal models of human retinal degeneration are not easy to find, but animal models make research advances feasible not only through developmental and invasive studies but also through rapid genetic analysis. By screening mice using indirect ophthalmoscopy and electroretinography at The Jackson Laboratory (TJL), many mouse models of retinal degeneration and diseases have been discovered (1, 2). A major advantage in using the mouse as a model system is the depth of well-developed techniques available for manipulating the genome. The ability to target and alter a specific gene(s) is an important and necessary tool to produce mouse models with mutations in genes of choice. Inducing mutations in genes of choice (known as knockout or transgenic) is termed "reverse genetics," as it is the opposite of "forward genetics" approaches whereby spontaneous/induced mutations are discovered as a result of the overt phenotypes and the underlying mutation is subsequently identified. Through the "forward" and "reverse" genetic approaches, mouse models in 100 genes that underlie human retinal diseases have been studied (3). In some cases there are multiple models available for the same mutated gene. For example, of the mouse models for human Leber Congenital Amaurosis 2 (LCA2) caused by mutation in the retinal pigment epithelium 65 (*Rpe65*) gene, there is a knockout model *Rpe65^{tm1Tmr}* (4), a transgenic (knockin) model *Rpe65^{tm1Lrcb}* (5), an induced model *Rpe65^{tvrm148}* (2), as well as a spontaneous model *Rpe65^{rd12}* (6, 7). The mouse eye is remarkably similar in structure to the human eye, and both species have many similar ocular disorders. Not only are developmental and invasive studies possible in mice, but also the mouse's accelerated life span and generation time (one mouse year = about 30 human years) make it possible to follow the natural progression of eye diseases in a relatively brief length of time. Because mouse mutations can be maintained on controlled genetic backgrounds, mutant and control mice can differ only by the mutated gene being studied. Thus, it is possible to analyze the effects of a mutant gene in same-sex, same-age littermates that differ only by whether they carry a specific mutation.

Models of retinal degeneration in mice have been known for many years. The first retinal degeneration, discovered by Dr. Clyde E. Keeler more than 80 years ago, is *Pde6b^{rd1}* (formerly *rd1*, *rd*, identical with Keeler rodless retina, *r*) (8–10). Fifty years later, the second retinal degeneration was discovered and it was named retinal degeneration-slow (*Rds*) (11). The third retinal degeneration was discovered in 1993 and it was named *rd3* in sequence allowing *rd* to be equivalent to *rd1* and *Rds* to be equivalent to *Rd2* (12).

During the last 20 years, many mouse models of retinal degeneration have been found because common methods used in human clinical eye examinations have been adapted for use with mouse eyes to screen for mouse retinal degeneration (1, 2, 12–14). These methods, including indirect ophthalmoscopy, fundus photography, fluorescein angiography, electroretinography, as well as histology, are broadly used in identifying and characterizing mouse models of retinal degeneration and diseases.

2. Materials

TJL, having the world's largest collection of mouse mutant stocks and genetically diverse inbred strains (<http://jaxmice.jax.org/index.html>), is an ideal place to discover and characterize genetically determined retinal disorders.

2.1. Mice

The mice were bred and maintained in standardized conditions in the Research Animal Facility at TJL. They were maintained on NIH31 6% fat chow and acidified water, with a 14-h light/10-h dark cycle in conventional facilities that were monitored regularly to maintain a pathogen-free environment. All experiments were approved by the Institutional Animal Care and Use Committee and conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

2.2. Drugs and Chemicals

1. 1% Atropine Sulfate Ophthalmic Solution (sterile), Alcon Laboratories, INC. Fort Worth, TX 76134, USA.
2. 1% Cyclopentolate Hydrochloride Ophthalmic Solution USP (sterile), Bausch & Lomb Incorporated Tampa, FL 33637, USA.
3. Cyclomydril® (0.2% cyclopentolate hydrochloride, 1% phenylephrine hydrochloride ophthalmic solution, sterile), Alcon Laboratories, INC. Fort Worth, TX 76134, USA.
4. 2.5% Gonioscopic Prism Solution (Hypromellose Ophthalmic Demulcent Solution, sterile), Wilson Ophthalmic, Mustang, OK 73064, USA.
5. 25% Fluorescein Sodium Injection (250 mg/ml, for intravenous injection only), Altaire Pharmaceuticals, Inc., Aquebogue, NY 11931, USA.
6. Ketathesia (ketamine HCL injection USP, 100 mg/ml), Dublin, OH 43017, USA.
7. AnaSed® Injection (Xylazine sterile solution, 20 mg/ml), Shenandoah, IA, 51601, USA.
8. 0.9% Sodium Chloride, Injection, USP (for use as sterile diluents), Hospira, INC., Lake Forest, IL 60045, USA.

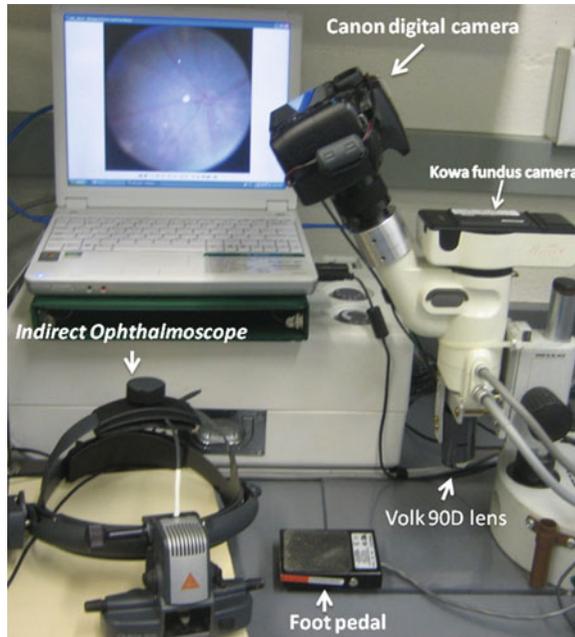


Fig. 1. Ophthalmic instruments used for mouse fundus examination.

2.3. Ophthalmic Instruments and Equipment

1. Heine Omega 500® Binocular Indirect Ophthalmoscope (Fig. 1), Heine USA Ltd., 10 Innovation Way, Dover, NH 03820.
2. Classic 78D, Classic 90D, SuperField NC Volk Optical Lenses, Volk Optical, Inc., 7893 Enterprise Drive, Mentor, OH 44060, USA.
3. Kowa Genesis small animal fundus camera (Fig. 1) (Tokyo, Japan) (15).
4. Canon digital camera (Canon EOS Rebel Xsi) (Fig. 1) (Canon USA., Inc., headquartered in Lake Success, New York, USA).
5. Electroretinogram (ERG) system (Fig. 2) (16).

3. Methods

Retinal vessel attenuation and retinal pigment epithelial disturbance are easily detected signs that are often associated with retinal degenerations and diseases. However if the retina looks normal (normal fundus), it is still possible that retinal functional abnormalities exist. A quick screening ERG test is needed to detect any retinal functional defects, such as retinal cone photoreceptor function loss (achromatopsia) (17, 18) and no *b*-wave (*nob*) mutations (19, 20). Heritability is subsequently established by genetic characterization (1, 2).

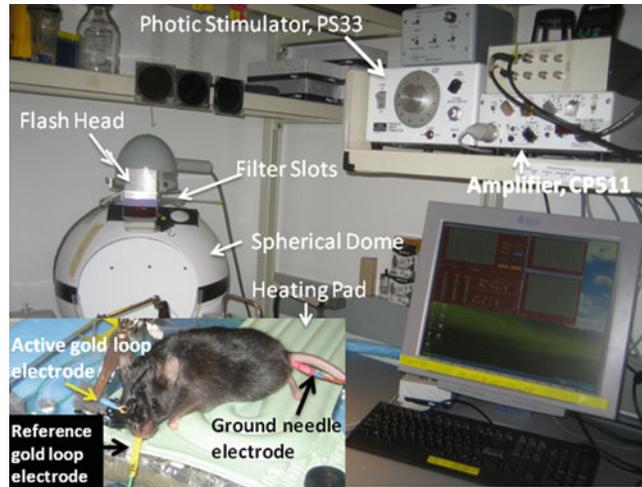


Fig. 2. The major components of the electroretinogram system used in our laboratory.

3.1. Mouse Fundus Examination

For indirect ophthalmoscopy the examiner wears a light attached to a headband and uses a small handheld lens to see inside the fundus of the mouse eye. The fundus of a mouse eye is the interior surface of the eye and includes the retina and optic disc. The color of the mouse fundus varies between pigmented (black) and albino (red). Dilated fundus examination is a diagnostic procedure that employs the use of mydriatic eye drops (such as 1% atropine) to dilate or enlarge the pupil in order to obtain a better view of the fundus of the eye. Once the pupil is dilated, examiners often use specialized equipment such as an indirect ophthalmoscope or fundus camera to view the inner surfaces of the eye. Abnormal signs that can be detected from observation of mouse fundus include hemorrhages, exudates, cotton wool spots, blood vessel abnormalities (tortuosity, pulsation, and new vessels), and pigmentation. Mouse fundus examination is a more effective method for the evaluation of internal ocular health and is routinely used to screen whether a mouse presents with abnormalities of the fundus such as retinal degeneration, optic disc coloboma, or vascular problems (see Note 1).

3.1.1. Routine Fundus Examination

1. Pupil dilation: Remove the screw top from the vial containing the mydriatic (1% atropine). Restrain and hold the mouse firmly in one hand, pick up the vial containing the mydriatic, and squeeze directly above an eye of the mouse allowing a drop to cover the surface of the eye. Repeat the procedure for the second eye. Return the mouse to its cage and allow at least 5 min for the effect of the mydriatic to take place.
2. Fundus examination 1: Place the Heine Omega 500® Binocular Indirect Ophthalmoscope onto your head and adjust the binoculars accordingly. Adjust the light being emitted from the ophthalmoscope. Hold and restrain the mouse firmly in one

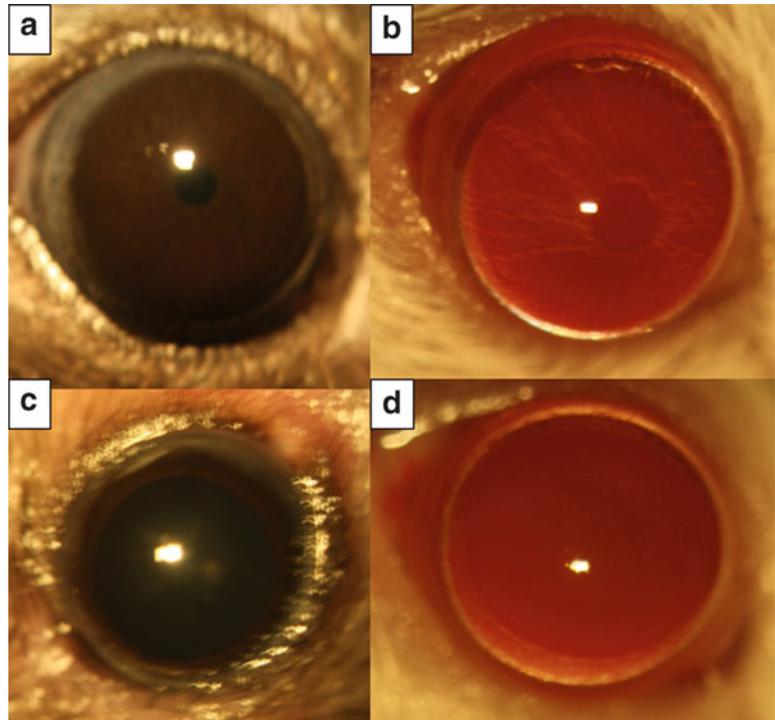


Fig. 3. An eye prior to dilation in pigmented mice (a) and albino mice (b) and the pupil of the same eye in its dilated state (c, d).

hand and shine the light into the mouse eye to see if the pupil has fully dilated (Fig. 3).

3. Fundus examination 2: Pick up the Volk 90D or 78D lens and place it between the mouse eye and the beam of light. Pass (or focus) the beam of light through the Volk lens and you should see the mouse eye through the lens. Adjust the lens in and out until the back of the retina can be visualized. Orientate the field of view by visualizing the optic disc and then moving the lens around the eye (or twist the mouse head) to alter the view so that the whole fundus can be examined.
4. Repeat the above for the second eye examination.
5. Record the fundus appearance, such as retinal spots, retinal pigment patch, or retinal vessel changes. If any fundus abnormalities are observed, fundus photography is taken. If no fundus abnormalities are observed, this mouse will go through the simple screening ERG test.

3.1.2. Fundus Photography and Fluorescein Angiography

Mouse fundus photography and fluorescein angiography are used to document the new phenotypes discovered by fundus examination. In the past, we used the Kowa Genesis small animal fundus camera fitted to a dissection microscope base (15) to take fundus pictures with special films, but have improved the efficiency and

reduced the cost of this system by adapting a digital camera (Canon EOS Rebel Xsi) to focus through the eyepiece view (Fig. 1). This Canon digital camera can be directly connected to a personal computer (through the USB port) and the fundus view is displayed on the computer monitor. Fundus pictures are then captured and saved on the computer by using the Canon EOS utility software.

1. Pupil dilation, same as in step 1 in Subheading 3.1.1 above.
2. Plug the Canon camera USB cable to the computer's USB port and turn on the computer (the Canon EOS utility software should be installed first).
3. Switch the Canon camera power on and wait for the Canon EOS utility software to start. Once the Canon EOS utility software is running, select the "Camera Setting/Remote Shooting," and then select "Remote Live View Shooting" from the software menu.
4. Turn on the power (light) from the powerpack and the "Remote Live View Shooting" window lights up on the computer monitor.
5. Hold and restrain the mouse firmly in one hand and place the mouse eye under the light beneath the Volk lens to see on the computer monitor if the pupil has fully dilated (Fig. 3). Retract the mouse eyelids with two fingers from your other hand, orientate the field of view by visualizing the optic disc, and then move the mouse eye around until you get the best fundus view (the most focused).
6. Capture the fundus images by a foot pedal (to operate the shutter) when the best fundus view occurs on the computer monitor. Figure 4 shows the normal mouse fundus in pigmented mice (C57BL/6J) as well as albino mice (BALB/cJ) and abnormal fundus in pigmented mice (C3H/HeJ) as well as albino mice (FVB/NJ) (see Note 2).
7. For retinal angiography the same general fundus photography procedure is used except one must push a button on the powerpack to select the fluorescein filter for angiography.
8. Intraperitoneally inject the mouse with 25% sodium fluorescein at a dose of 0.01 ml per 5–6 g body weight. The retinal vessels began filling about 30 s after fluorescein administration. Single photographs are then taken at appropriate intervals. Although timing varies due to variable rates of intraperitoneal absorption, capillary washout usually occurs 5 min after dye administration. Figure 5 shows the mouse fundus as well as fluorescein angiogram.

3.2. Simple Screening Electroretinography

The basic method of recording the electrical response, known as the global or full-field ERG, is to stimulate the eye with a bright light source such as a flash produced by LEDs or a strobe lamp.

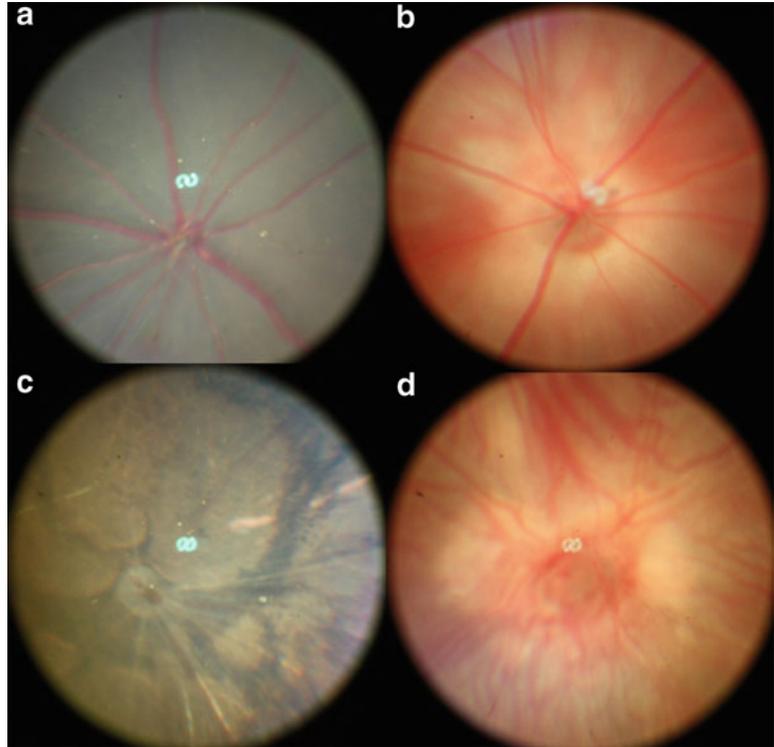


Fig. 4. Normal mouse fundus in pigmented mice (a) and albino mice (b) as well as retinal degeneration fundus in pigmented mice (c) and albino mice (d).

The flash of light elicits a biphasic waveform recordable at the cornea. The two components that are most often measured are the a - and b -waves. The a -wave is the first large negative component, followed by the b -wave which is corneal positive and usually larger in amplitude. Two principal measures of the ERG waveform are taken: (1) the amplitude (a) from the baseline to the negative trough of the a -wave, and the amplitude of the b -wave measured from the trough of the a -wave to the following peak of the b -wave, and (2) the time (t) from flash onset to the trough of the a -wave and the time (t) from flash onset to the peak of the b -wave. These times, reflecting peak latency, are referred to as “implicit times” in the jargon of electroretinography. Scotopic ERGs (also called dark-adapted) are used to evaluate responses starting from rod photoreceptors exposed to flush light in darkness, and photopic ERGs (also called light-adapted) are used to evaluate responses starting from cone photoreceptors exposed to flush light under constant light exposure. Because regular ERG testing is time consuming (about 30–60 min per mouse without the time used for dark adaptation), we have developed a simple screening ERG test. Our simple screening ERG testing does not need dark or light adaptation and one simple ERG test takes less than 10 min (see Note 3). Most of the simple screening ERGs are normal and only a few of them are

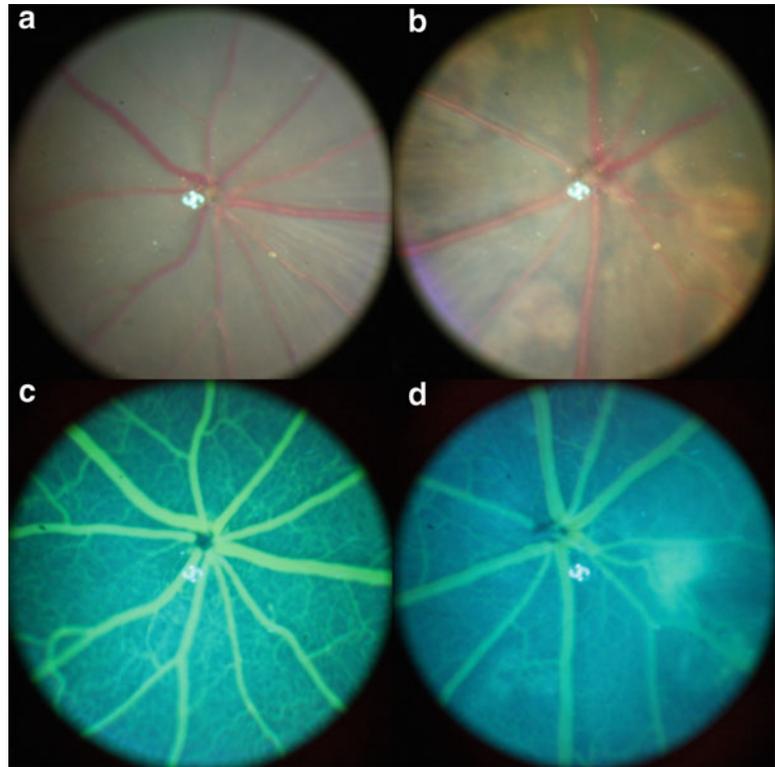


Fig. 5. Normal mouse fundus prior to the fluorescein injection (a) and the same eye after the fluorescein injection (c). Mouse fundus with neovascular depigmented spots (b) prior to the fluorescein injection and the same eye after the fluorescein injection (d).

abnormal, but once a mouse shows an abnormal ERG, it is tested again through our regular ERG test (21, 22).

1. Pupil dilation: Restrain and hold the mouse firmly in one hand, pick up the vial containing 1% Cyclopentolate (1% Cyclopentolate Hydrochloride Ophthalmic Solution), and squeeze directly above the right eye of the mouse allowing a drop to cover the surface of the eye (we test only one eye and usually the right eye). A group of 5–10 mice can be dilated in one time.
2. Anesthetize the mouse with an intraperitoneal injection. Weigh the mouse and record the weight. Restrain and hold the mouse firmly in one hand, pick up the second vial containing Cyclomydril (0.2% cyclopentolate hydrochloride, 1% phenylephrine hydrochloride ophthalmic solution, sterile), and squeeze directly above the right eye a drop to cover the surface of the eye; then inject the mouse with the anesthetic mixture solution (5 ml mixture containing 0.8 ml Katamine, 0.8 ml Xylazine, and 3.4 ml 0.9% Sodium Chloride) at a dosage of 0.1 ml per 20 g of body weight.

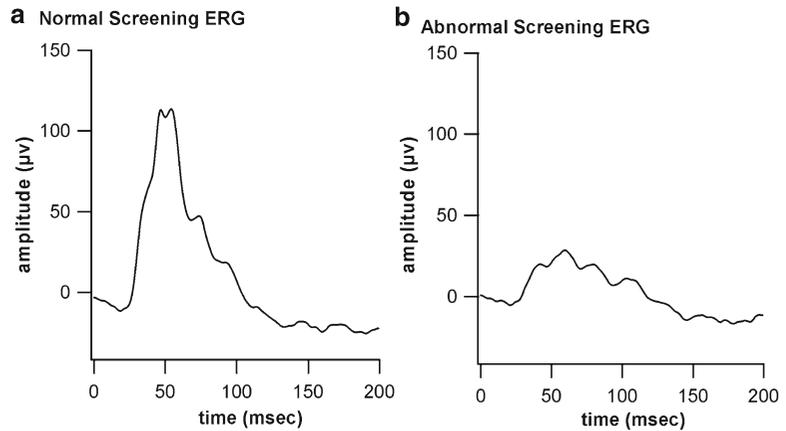


Fig. 6. Representative ERG responses to a bright flash obtained from a mouse with normal retinal function (a) and a mouse with abnormal retinal function (b).

3. Prepare the test: Place the sufficiently sedated mouse on the heated pad. Insert a needle probe just under the skin at the base of the tail, place the gold loop electrode between the gum and cheek, position the mouse near the far end of the heating pad, and place the active gold loop electrode on the cornea slightly below the middle of the eye. Pick up the third vial containing 2.5% Gonioscopic Prism Solution and squeeze directly above the cornea and electrode a drop to assure a good contact.
4. The simple ERG test: Set the photic Stimulator to 1-s flash, the flash intensity to 16 (the highest), and then set the “Sweeps” to 10 (average 10 flashes) from the ERG software menu. Click the “Aver” from the software menu, and then turn on the photic Stimulator to start the test.
5. Save the test data and analyze the results: Press the “Save” button to save the ERG data to the computer and print a copy for instant view. If a mouse has *a*, *b*-wave amplitude at or above 100 μV and the implicit times at about 50 ms, this mouse has a normal simple ERG response (Fig. 6a). If a mouse has *b*-wave amplitude at or below 50 μV and implicit times longer than 50 ms, this mouse has an abnormal simple ERG response (Fig. 6b).
6. Regular ERG test: Once we discover a mouse with an abnormal simple ERG response, we test the same mouse with our regular ERG protocol to determine if the mouse has the abnormal rod response (dark-adapted ERG), abnormal cone ERG response (light-adapted ERG), or abnormal rod and cone ERG. Then we mate this mouse to a normal mouse to produce the next generation for the heritability test.

3.3. Heritability Test

Heritability is established by outcrossing a retinal mutant mouse to a normal retinal wild-type mouse to generate F1 progeny, with

subsequent intercrossing of the resultant F1 mice to generate F2 progeny. Both F1 and F2 mice are examined by fundus examination and/or simple screening ERG depending on which phenotype occurs first. If F1 mice are affected, the pedigree is designated as a dominant mutation. If F1 mice are not affected but ~25% of F2 mice are affected, the pedigree is designated as a recessive mutation. Once heritability of the observed retinal phenotype is established, retinal mutants are bred and maintained for further characterization leading to gene identification (23, 24).

4. Notes

1. Mouse fundus examination is a very powerful, noninvasive, and high-throughput method for evaluating mouse retinal appearances. It is also very effective in screening for mouse models of human retinal degeneration and diseases, as there are many examples of mouse models of retinal degeneration that were discovered by fundus examination (see refs. 1, 2, 13) such as mouse retinal degeneration 3 (*Rd3^{rd3}*) (see refs. 12, 25) and mouse retinal degeneration 4 (*Gnb1^{Rd4}*) (see refs. 26, 27).
2. It is important for investigators evaluating eyes to be aware of *Pde6b^{rd1}* and its associated morphological findings, as it is a frequent strain background disease. Since the *Pde6b^{rd1}* mutation is common in mice, it is important to avoid mouse strains or stocks carrying the *Pde6b^{rd1}* allele, or to exclude the *Pde6b^{rd1}* allele contamination in studying new retinal disorders. Mice with the *Pde6b^{rd1}* mutation can be easily typed by fundus examination (see Fig. 4).
3. The simple screening ERG is another powerful, noninvasive, and high-throughput method to evaluate mouse retinal function. If a mouse has a normal fundus through fundus examination, it is very important to run this mouse through the simple screening ERG test because mouse retinal function loss mutants can have a normal retinal appearance (see refs. 17–20).

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