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A Study of Blindness in the House Mouse[1]

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Abstract. A study of blindness in mice, heterozygous for a dominant lethal mutation is reported. The eyelids may fail to fuse in the late embryo or may open at 2 or 3 days of age. The expression of the character may be an opacity of one or both eyes, reduced size of eyeball in one or both eyes, or opacity in one with reduced size in the other. Penetrance is incomplete.

The purpose of this investigation was to determine the development of blindness of mice heterozygous for a dominant lethal mutation for blindness. This mutation was first observed in the laboratory of Dr. Ernst W. Caspari, then of Wesleyan University at Middletown, Connecticut, who sent the stock to Dr. Margaret Watson.

DESCRIPTION

Homozygotes for this mutation are inviable. Death occurs at the end of the seventh day of embryonic development. The embryos are resorbed (1).

Heterozygotes are usually born with their eyelids wide open. The lids may be dry and cornified. During the first few days of life there is often hemorrhage. Fluids are secreted from the tissues, and scabs form over the eyes. These scabs may be present from the fourth to the tenth day.

There are various degrees of expressivity of the character as observed in adult animals. There may be an opacity of one or both eyes, there may be a reduced size of eyeball in one or both eyes, or opacity in one with reduced size in the other. In the case of very small eyeballs, the orbital fat can be seen directly under the closed eyelids. Most blind mice have roughened eyelids with excessive secretions that tend to solidify into masses which may adhere to the cornea.

GENETICS

The results of breeding are shown in Table 1. The blind and normal offspring were determined at the time of marking, or about one month of age.

In our opinion, the data differ from an expected ratio for a dominant lethal for three reasons: (1) the viability of the het-

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erozygote, especially during the first day of life may be lower than that of his normal sib, (2) penetrance is probably not complete, and (3) mice may become blind after marking.

Table 1. Breeding Data. Blindness determined at the time of marking (one month).

Mating	Left Eye Blind	Right Eye Blind	Both Eyes Blind	Total Blind	Total Normal	Expected Blind	Expected Normal
Blind x blind	12	1	52	65	85	100	50
Blind x normal	25	10	40	85	213	149	149
Normal x normal	1				116	0	117

Some matings produced offspring much closer to expected ratios than did others. In four selected matings of blind x normal, a ratio of 21 normals to 20 blind was secured. This is as close to expectation as possible. However, from four other matings a ratio of 84 normals to 18 blind was secured.

In this stock, as well as in a case of recessive blindness in the rat (2), the left eye is affected more often than the right. The reason for this is unknown.

The one exceptional mouse born from a normal x normal mating was probably either a new mutation or a case of lack of penetrance in one of the parent animals. The breeding behavior of this exceptional mouse seems to follow the pattern of the rest of the blind stock, but it is being tested further.

In every mating with at least one blind parent, blind offspring were produced. Mice slightly affected gave rise to offspring varying from mildly to severely affected. There was similar variation from severely affected parents. The ramifications of this diversity are being studied.

The mean litter size, as shown in Table 2 is smaller in blind x blind matings than in either blind x normal or normal x normal matings. This indicates the presence of a lethal effect. We have observed embryos in the process of being resorbed at eight days.

Table 2. Litter Size at Birth

Mating	Mean Litter Size	Standard Deviation	Mean Litter Size, from Vankin(6)
Blind x Blind	4.95	2.0	4.4
Blind x normal	6.86	2.2	5.6
Normal x normal	6.30	2.8	7.5

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Embryological Study

The investigation began as an embryological study to determine the sequence of events which leads to the birth of the mouse with open dry eyes. For this purpose, timed matings were established. The time of copulation was determined by the presence of a vaginal plug. The females were sacrificed 13 to 19 days later, and the embryos were fixed in Bouin's or Kolmer's fixative, embedded in paraffin, and stained with haematoxylin and eosin.

The only abnormalities observed in the heterozygous embryos were failure of the eyelids to grow over the eye, a protrusion of the eye, and hemorrhage between cornea and lens. Unlike the character "open eyelids", the optic nerve of these blind mice appeared to be straight and normal. Likewise there was no apparent folding of the retina.

Study Of Young Mice

Young mice were observed regularly from birth until twenty-two days of age. It was found that mice born with open eyelids may develop various expressions of blindness, from opacity to extreme diminution of eyeball. In some cases, mice are born with very thin eyelids. These lids may open after two or three days and subsequently the eyes become blind. These eyes are typically opaque. If eyelids open prematurely but as late as six days, with scabs forming over the eyes, the eyes usually become normal. Mice of this type are being studied to determine if this early opening is a very mild expression of the mutant type.

In at least three cases, mice have become blind after the time of weaning. Two cases were first noticed at three months of age, and one case at eight months. This seems to indicate that some mice, discarded as normal, might have been potentially blind animals.

Discussion

A dominant lethal mutation for blindness occurred spontaneously in a Bagg albino strain of mice. Other mutations for blindness which have been reported have been recessive in inheritance.

Grüneberg has described "eyelids open at birth" in mice homozygous for the recessive gene (3). The mice were born with various degrees of eyelids open when embryonic fusion of the eyelids failed. A slight hemorrhage occurred the first day after

birth, and a hemorrhagic exudate was formed between the lids. The exudate later dried and filled the interval between the eyelids. The exudate usually disappeared by the fifth or sixth day, but occasionally it adhered to the cornea in a staphyloma-like form.

Mackensen (4) has described "open eyelids" that were effected by a "single recessive autosomal gene (symbol oe), with complete penetrance." The mice were born with eyelids opened and with inflamed eyeballs. Hemorrhagic exudate was formed within a few hours after birth and scab formation occurred between the lids. The scabs were gone within a few days and the eyes were redder than in normal pink-eyed mice. Opacity of the lens and corneal staphylomas were present in a few mice.

Hauschka and Brown (5) have described "eyelids open" in mice that were affected by a recessive gene (oe). The manifestations were eyelids opened at birth, inflamed eyeballs, hemorrhage, and permanent corneal damage.

Quisenberry and Brown (2) have described recessive blindness in the albino rat. They observed a slight reduction or complete absence of the eye and recorded a greater effect to the left than to the right eye.

This dominant lethal mutation appears to be incompletely penetrant, with a wide range of expressivity. The onset of abnormality may be from about 14 days of embryological development up to 3 to 8 months of age. The degree of expressivity may be from slight opacity of one eye to severely reduced eyeballs, with orbits almost completely filled with fat.

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