
A new autosomal recessive gene, dysgenetic lens (dyl), in the mouse is described. Homozygotes are fully viable and exhibit smaller eye, corneal opacity, adhesion of the iris, developmental failure of lens vesicle-ectoderm separation is associated with cataractous degeneration, and extrusion of the lens nucleus and persistent lens-epithelium attachment. Developmental failure of lens vesicle-ectoderm separation is recognized as the earliest expression of the genetic defect. Possible significance of this mutant in the understanding of Peter's anomaly is indicated.

Individuals with abnormalities in the eyes appeared spontaneously in the Balb/c line of our mouse colony. Histomorphological observations, developmental studies, and breeding experiments were undertaken to analyze this condition. The findings show that the condition is caused by a new mutation affecting primarily the lens and is inherited as an autosomal recessive trait. In this report, we describe the mutant phenotype, its development, and mode of inheritance. We suggest the gene be designated dysgenetic lens (dyl).

Materials and methods. Balb/cLiA mice have been maintained by sib mating under normal conditions of lighting, temperature, and feeding. When individuals with abnormal eyes were first noticed, appropriate matings were set (Table I). All individuals were screened first, at 14 days after birth, when the eyelids have just opened, and again at the time of weaning while under light ether anesthesia, with an ophthalmoscope or a stereo dissecting binocular. Histological observations were made on the normal and the affected eyes after routine procedure. Embryonic stages were obtained by sacrificing pregnant females at known intervals after mating, the day of vaginal plug being counted as day 0. The entire heads were fixed. For postnatal stages, intact eyes were removed from animals at different times after birth.

Results. On superficial examination, most of the affected mice were easily identified by the occurrence of a smaller than normal eye (Fig. 1). This varied between individuals and also sometimes between the two eyes of the same individual. In some cases, the eyes appeared to be of normal proportion, whereas in a few cases the eyelids were completely closed, resembling the condition of anophthalmia, though an eyeball was always present in the orbit.

The affected condition was readily recognized when the mice were observed with an ophthalmoscope or stereo dissecting microscope. The pupil was markedly smaller and showed a distorted outline. Pupillary reaction was usually absent. Varying degrees of corneal opacity were encountered and ranged from a few tiny spots in the pupillary area to a completely opaque central cornea. In the older animals, the cornea was often found to be vascularized.

In the sections of the whole eyes (Fig. 2), most pronounced defects were seen in the lens. These were very much reduced in size and irregular in shape. But the striking feature of this anomalous condition was the persistent connection between the lens and the corneal epithelium. The corneal

Table I. Breeding data showing segregation of the dysgenetic lens (dyl) phenotype

<table>
<thead>
<tr>
<th>Matings</th>
<th>Number of offspring</th>
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<tbody>
<tr>
<td>AFFECTED × AFFECTED</td>
<td>257 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>AFFECTED × NORMAL</td>
<td>0</td>
<td>130 (100%)</td>
</tr>
<tr>
<td>F₁ × AFFECTED</td>
<td>79 (53.4%)</td>
<td>69 (46.6%)</td>
</tr>
<tr>
<td>F₁ × F₁</td>
<td>76 (27.3%)</td>
<td>202 (72.7%)</td>
</tr>
</tbody>
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*First generation hybrids.
Fig. 1. a, Close-up photograph of the eye of a normal Balb/c mouse. b, Eye of an affected Balb/c mouse. Note small size of the eye, small pupil (arrow), and whitish appearance of the area inside and around the pupil.

Fig. 2. a, Microphotograph of section of eye from a 14-day-old Balb/c mouse. b, Section of eye from a 14-day-old affected Balb/c mouse showing small size, irregular contour, and vacuolated appearance of the lens. Note connection between the lens and the corneal epithelium and attachment with the iris.

endothelium was interrupted in this region but appeared normal in the surrounding area. Inside the lens some fibrous structures were present, but these were very much disorganized and interspersed by large irregular vacuoles. The iris showed adhesive attachment with the lens. The ciliary body appeared to be swollen. The retina was completely normal.

In the affected mice, the initial events in the development of the optic cup and the lens placode were indistinguishable from those observed in normal mice. The first recognizable deviation was the failure of the lens vesicle to separate from the ectoderm, which, in control Balb/c mice, occurred at day 10 of gestation. At day 13, elongation of lens fibers had resulted in the development of the rudimentary lens nucleus. Although configuration and orientation of the fibers were similar in the two types, the lenses in the affected mice were markedly smaller in size (Fig. 3). By late day 14 or day 15, vacuolar structures had appeared in the lens concomitantly with disorganization of the fiber orientation. At day 16, the lens appeared cataractous in all affected animals. Around this time, part of the lens protruded to the exterior through the persistent ectodermal connection, and eventually materials from the lens interior were expelled (Fig. 3, d). This resulted in the greatly reduced and distorted appearance of the lens seen in the young animals.

The breeding data are summarized in Table I. No sex difference was observed in the frequency of
Fig. 3. a, Microphotograph showing the frontal region of the eye from a day 13 embryo of normal Balb/c mouse. b, Frontal region of the eye from a day 13 embryo of affected Balb/c mouse. The lens is smaller in size and attached to the ectoderm. c, Section of eye from a day 16 embryo of affected mouse showing cataractous lens and extrusion of lens material. d, Magnified view of the lens-cornea area from a newborn affected mouse. Note, that masses of lens tissue including nuclei are expelled through the cornea from the lens.
the affected phenotype, and therefore the individuals of the two sexes were considered together. Occurrence of 100% affected offspring was noted when both parents were affected. Except for the condition of the eyes, the affected individuals, so far as can be seen, did not show any overt difference from the normal Balb/c mice in behavior, breeding, and longevity. All F, heterozygotes obtained from matings of affected and normal parents were found to be phenotypically normal and indistinguishable from normal Balb/c mice. Ratio of segregation of the normal and the affected mice in the offspring from the parental backcross was close to 1:1. In the F, generation, the segregation ratio was close to 3:1.

**Discussion.** The genetic data are fully consistent with the conclusion that the affected condition is caused by a single mutant gene which is autosomal, recessive, and fully viable. Although the manifestation of the genetic defect is seen in several tissues in the adult eye, observed developmental sequence of these anomalies strongly suggests that the mutation primarily affects the lens. This mutant shows some superficial resemblance to the phenotype of the dominat mutation *small eye* (*Sey*) and *eye lens obsolence* (*Elo*) and to the vacuolated lens and degenerated fibers encountered in some of the hereditary cataracts. But the persistence of the lens-ectoderm connection, which is the most consistent feature of the pathogenesis, was not observed in any of these mutants. However, persistent lens-ectoderm connection was observed in mice bearing the mutation *aphakia* (*ak*), along with complete failure of histological differentiation of lens; in mice bearing the semidominant gene *Dickie’s small eye* (*Dey*), along with abnormalities in the optic vesicle and stalk; and in sporadic instances of corneal opacity and microphthalmia occurring among the inbred mice of C57BL strain. In contrast, the anomalies encountered in this mutant appear to be preceded by and result from this specific developmental failure, namely the lens-ectoderm separation. We therefore propose to call this mutation *dysgenetic lens* (*dyl*). It is not clear how this defect is directly related to the cataractous development that immediately follows. Persistent ectodermal connection can facilitate expulsion of lens tissue and can thereby reduce intraocular pressure, which in turn may result in smaller eyes because optimum pressure is known to be necessary for the normal growth of the eyeball. Attachment of the iris and central corneal opacity may also conceivably result from the altered topography of the anterior chamber caused by this initial defect.

Anomalies observed in this mutant resemble many of the features reported in the clinical findings of anterior chamber defects. Of particular interest are the cases classified under Peter’s anomaly which are characterized by keratolenticular adhesion and central leukoma and are often associated with microphthalmia and adhesion of the iris. Developmental defect in the separation of lens and surface ectoderm, as opposed to inflammatory changes, has been proposed as the cause of keratolenticular adhesion. In a limited sense, these mice can be of value as an experimental animal model for a better understanding of the etiology of pathogenesis in the human eye.

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**REFERENCES**