A GENETIC ANALYSIS AND MORPHOLOGICAL DESCRIPTION OF A LINE OF MICE SHOWING THE MUTATION SHORT-LEG

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As examples of certain hereditary anomalies, the mutant lines of mice luxate, luxoid, and grey-lethal are interesting; in them the skeletal anomaly of the limbs is transmitted as a recessive characteristic. In the homozygote animals (lx/lx) the mutant line luxate shows a more or less marked reduction of the femur. In many cases the bones of the pelvis are affected, and there is a reduction of the lumbar vertebrae and of the lumber groups of muscles [2, 3, 6]. Mice of the mutant line luxoid having the homozygote condition (lu/lu) resemble phenotypically mice of the

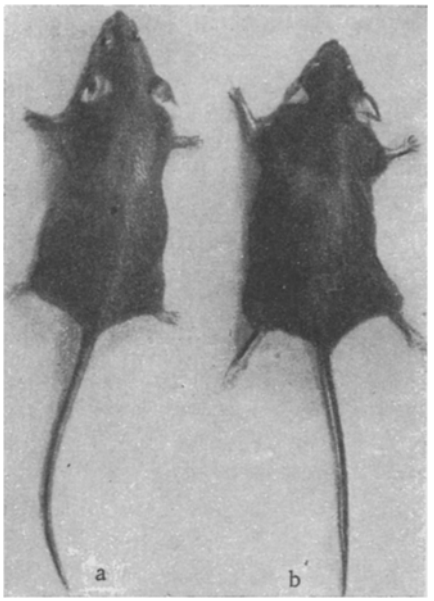


Fig. 1. Mice of the mutant line short-leg. a) With damaged limbs (sl/sl); b) with normal limbs (+/+).

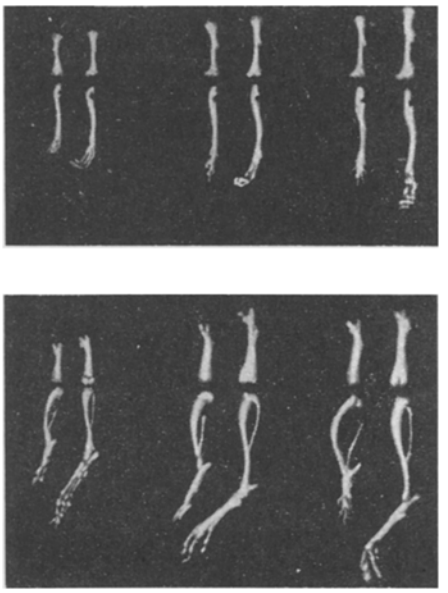
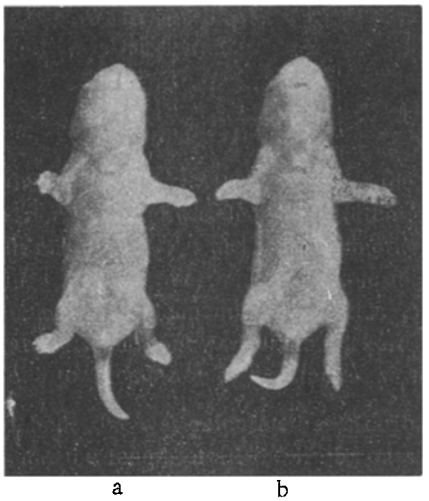


Fig. 2. Skeletons of the fore- and hind-limbs of mice aged 15 days, and 1 and 2 months. On the left – skeletons of the limbs of sl/sl mice, on the right of +/+ mice.

line luxate, but unlike them they show the anomaly only in the forelimbs [4, 6]. One of the principal developmental disturbances of the homozygote mice of the mutant line grey-lethal is the absence of reabsorption of bone, which leads to changes in the shape of all the bones [1, 5].

In 1959 in the laboratory of the Institute of Experimental and Clinical Oncology, AMN SSSR, E. E. Pogosyants discovered a new recessive mutation in which the skeleton of the limbs showed anomalies developing spontaneously

in the inbred line of mice C57BL. This new mutant line, known as short-leg (symbol sl) was very generously made available to us for study*. In the present communication we give a genetical analysis and morphological description of this mutant line.



a b

Fig. 3. Newborn mice with (a) affected and (b) normal limbs.

In the homozygote condition (sl/sl), mice of the mutant line short-leg have shortened fore- and hindlimbs, and the hindlimbs are the most strongly affected; in the heterozygous condition (+/sl) the limbs are of normal length (Fig. 1, a and b). The damage to the limbs does not seriously interfere with movement.

We studied the skeletal damage in newborn mice and in mice aged 15 days, and 1, 2, and 3 months. Altogether we examined 38 skeletons: 19 from mice with damage to the limbs, and 19 from mice with normal limbs (controls). As a control we used mice of the inbred line C57BL. The skeletons were separated by the method described by Bateman [1].

A comparative study of the skeletons of the animals with damaged (sl/sl) and normal (+/+) limbs showed that in the sl/sl mice the length of the bones of both the fore- and hindlimbs were greatly reduced (Fig. 2). The femur and tibia were severely affected. In addition to being short, the tibia was strongly bent. It should be noted that of all the bones of the skeleton of the limbs, the most severely damaged was the fibula. This bone was greatly reduced, being thinner and of two-thirds the normal length, and the distal part was abnormal in not being applied closely to the tibia, and not being fused with it. The articulations of the fibula with the tibia were also altered. At the proximal end the junction of the tibia and fibula was displaced laterally, and at the distal end the fibula articulated directly

TABLE 1. Distribution of sl in the Offspring through Different Crosses

Cross ♀♀		♂♂	Number of pairs	Number of litters	Generation	Offspring: total mice	Offspring: with normal limbs	Offspring: with damaged limbs	χ^2
sl/sl	×	sl/sl	7	12		172		172	
sl/sl	×	+/+ . . .	2	5	F_1	28	28	—	
+/+	×	sl/sl . . .	3	5	F_1	28	28	—	
+/sl	×	+/sl . . .	22	45	F_2	361	284	77	2,58

with the talus of the heel. All the bones of the hand and foot in mice type sl/sl were greatly reduced. The small size of the foot and hand was due to a shortening of the phalanges and of the metacarpals and metatarsals. In comparison with mice type +/+, the bones of the wrist were also reduced, but not to such a great extent. In the heel, it was the talus which was most reduced. Like the other bones of the heel it was reduced in size, and the surfaces of articulation with the calcaneum, accessorius, and central bones were altered. As a result of this kind of articulation of the metatarsals, the foot was turned outwards (see Fig. 1a). Probably this alteration of the articulation of the ankle bones was due to a reduction of the fibula and the strong bending of the tibia.

When bone size was calculated as a ratio of the length of individual bones to the length of a vertebra, it was also found that the length of all the limb bones in sl/sl mice was less than normal. There were no noticeable abnormalities of the other bones of the skeleton. Neither was there any deviation from normal in the structure of the viscera. A histological study revealed no failure of resorption in the affected limbs. Mice of the mutant line short-leg showed no defects of vitality or fertility in comparison with mice of the line C57BL. However, it should be noted

*We are grateful to E. E. Pogosyants for letting us have mice of this mutant line.

that the weight of the newborn sl/sl mice was 8-9 % less than normal. These differences in weight levelled out after 3-4 weeks. The reduction in the length of the limb bones and the bending of the tibia were observed even in the newborn sl/sl animals (Fig. 3a, b). Therefore, developmental disturbances in the limbs of sl/sl mice occur in the embryonic period. Crossing affected animals with each other always resulted in offspring having affected limbs (Table 1). With reciprocal crossing of mice with abnormal limbs (sl/sl) and mice of the inbred line C57BL (+/+) no abnormal limbs were found in the offspring (F_1). On crossing F_1 mice with each other (+/sl × +/sl), two phenotypes could be distinguished: those with normal and those with abnormal limbs. The ratio of the two was 3.7 : 1, i.e., it did not differ significantly from the theoretically expected monohybrid cross. Thus, the results shown in Table 1 indicate that damage to the limbs in mice of the mutant line short-leg are inherited as a recessive characteristic.

TABLE 2. Segregation of sl in the Offspring with Dihybrid Crossing

Cross	Number of pairs	Number of litters	Generation	Total mice	Phenotype*							
					Pigmented				Albinos			
					With normal limbs		With abnormal limbs		With normal limbs		With abnormal limbs	
+/+ c/c × sl/slC/C	3	5	F_1	28	28		—		—		—	
+/slC/c × +/slC/c	10	20	F_2	169	91		32		37		9	
					♀♀	♂♂	♀♀	♂♂	♀♀	♂♂	♀♀	♂♂
					48	43	15	17	17	20	4	5

*$\chi^2 = 1.297$; N = 3; P = 0.7-0.8.

This conclusion was confirmed also by results of the dihybrid cross of pigmented (black) mice type sl/sl and +/+ albinos.

In the first generation (F_1) 28 mice were obtained, all pigmented, and all having normal limbs (Table 2). Crossing F_1 animals with each other caused four phenotypic groups to emerge: pigmented with normal limbs, pigmented with damaged limbs, albinos with normal limbs, and albinos with damaged limbs. Quantitatively, the numbers were close to the theoretically expected values for a dihybrid cross (9 : 3 : 3 : 1).

The results shown in Table 2 indicate that limb anomaly is inherited independently of albinism and is not sex-linked.

Mice of the mutant line short-leg do not differ in the inheritance pattern of limb anomaly from the previously described lines luxate, luxoid, and grey-lethal. There are however important differences in the type of limb defect.

It should be noted that by now a large number of hereditary limb anomalies affecting the human skeleton are known. The skeletal damage to limbs of mice of the mutant line short-leg resemble certain hereditary human anomalies affecting the limbs, in particular achondroplasia and brachydactyly. Therefore these researches on mice of the mutant line short-leg may help to reveal the mechanisms of development and transmission of certain human skeletal anomalies of the limbs.

SUMMARY

In mice of the new mutation known as short-leg (symbol sl) there are skeletal anomalies of the limbs, and the bones both the fore- and hindlimbs, especially the fibula, are reduced, the tibia is strongly curved, there is a disturbance of the ankle joint, and a distinct brachydactyly. There are no visible bone anomalies in the rest of the skeleton, no disturbances of the viscera, and viability and fertility are normal. The anomaly is inherited as an autosomal recessive with complete penetrance, and is not linked with albinism.

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