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Inherited Lethal Genes

Effects of these Genes in cattle in homozygous conditions

W. G. Venzke, D.V.M., M.S., Ph.D.*

A type of factor or gene which produces so drastic an effect as to cause the death of the individual, usually during gestation or shortly following parturition is known as a lethal factor. Such factors produce their lethal effect only in the homozygous condition. Some lethal factors produce a visible but non-lethal effect when in the heterozygous condition, in addition to their lethal effect when in a homozygous state. Other lethal factors produce no visible effect in the heterozygous condition, their only visible effect being the killing of the animal when in the homozygous state.

Types of Lethals

Several distinct types of inherited lethals are recognized; viz., recessive, dominant, and sex-linked. The difference between the results produced by the recessive and dominant factors in animals is not apparent, but there is a difference in the manner in which they are inherited.

Most animals presenting recessive defects are usually the progeny of visibly normal parents, each of which however, carries the factor not only for the defect, but also the factor for the normal. Since the factor for the normal in these animals is dominant, it predominates and hides the factor for the recessive. Since such parents carry the factor for normal, it is obvious that some of their offspring would be normal and carry no factors for recessive defects. On the other hand, some of their offspring would be like themselves and carry factors for defects. When animals have no recessive factors for defects, and are mated, their offspring are always normal. Some defective animals are the progeny of a normal parent on one side and a defective parent on the other side. Other defective animals are the progeny of parents both of which are abnormal. The offspring from such a mating are defective.

A simple diagram will prove helpful to summarize what has been presented. It is customary to designate the recessive factors by small letters, and the dominant factors by large letters. The parents of defective calves are usually normal and each carries the normal factor (N), as well as the recessive factor (n), in each body cell. An individual of this type is represented by (Nn). Each spermatozoon and each ovum carries only one of the pair of

<table>
<thead>
<tr>
<th>PARENTS</th>
<th>Nn ♂</th>
<th>Nn ♀</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAMETES</td>
<td>N n</td>
<td>N n</td>
</tr>
<tr>
<td>OFFSPRING</td>
<td>N ♀</td>
<td>n ♀</td>
</tr>
<tr>
<td></td>
<td>N ♂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N n</td>
<td>Nn</td>
</tr>
<tr>
<td></td>
<td>n ♂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nn normal</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Inheritance of a recessive factor.
factors, since reductional division occurs during their maturation. When fertilization occurs, one factor from each parent comes together in the new individual.

Figure 1 shows how a recessive defect is inherited. Both sire and dam appeared normal, yet both carried the recessive factor for the defect as well as the factor for the normal. Out of four calves born from such a mating, the ratio would be one calf (NN) without the defects or the recessive factor for it; two calves (Nn) apparently normal, yet carrying the recessive factor; and one calf (nn) showing the defect.

The homozygous (NN) individuals cannot be distinguished from the heterozygous (Nn) individuals; therefore, the ratio observed is three normal to one homozygous recessive (nn) defective. The (NN) individuals can never produce defective offspring. The (nn) individuals will always produce defective offspring if it is possible to mate them.

If two normal parents never produce defective offspring, but if two defective parents frequently produce some normal offspring, it is obvious that the defect cannot be the result of a recessive factor. It can however, be the result of a dominant factor. If a defect is the result of a dominant factor, the defective animal must always be heterozygous, since defective crossed with normal always gives a one to one ratio. This is the ratio obtained by crossing a heterozygous individual with a recessive individual.

Letting (N) represent the gene for the defective, and (n) the gene for the normal, and remembering that lethal genes produce their lethal effect only in the homozygous state, one may diagram the cross between two defective animals as shown in figure 2. The death of the homozygous defective results in the two to one ratio of defective and normal. The cross of a defective with a normal would be:

\[
\begin{array}{c|c}
\text{PARENTS} & \text{GAMETES} \\
Nn \delta & N n \\
\text{defective} & N n \\
\text{defective} & n \delta \\
\end{array}
\]

Fig. 2. Inheritance of a dominant factor.

Thus the cross of a defective with a normal always results in the one to one ratio.

**Sex-linked**

When the lethal is sex-linked, it may be easily discovered even though it kills early and has no visible effect in the heterozygous form. This lethal will result in marked alteration of the sex ratio. This results because a male, having but one X-chromosome, can never be heterozygous for the lethal factor. As a result, all males which inherit this factor will die. The factor can only be transmitted from one generation to another by heterzygous females. Such females appear perfectly normal and can only be discovered by the fact that they will produce one-half as many male offspring as female offspring. Letting (N) represent the factor for nor-

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mal, and (n) the sex-linked lethal factor, such a cross may be illustrated as follows:

| PARENTS | NY
male | Nn
"carrier"
female |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>GAMETES</td>
<td>NY</td>
<td>Nn</td>
</tr>
<tr>
<td>OFFSPRING</td>
<td>Nδ</td>
<td>Yδ</td>
</tr>
</tbody>
</table>
| N♀ | NN
normal
female | NY
normal
male |
| n♀ | Nn
normal
female | nY
dies |

Fig. 4. Inheritance of a sex-linked lethal.

One-half of the males from this cross will die, and a marked disturbance of this sort in the sex ratio is a good indication that a sex-linked recessive lethal factor is operating. No sex-linked lethal factors have been reported in cattle.

Knowledge Is Not Complete

In the present summary of lethal factors in cattle, a brief description of their phenotypic effects and mode of inheritance is presented. Some of the factors reported as distinct types should no doubt be classified with other similar defects, but insufficient knowledge at the present time makes proper classification impossible in many cases. The exact mode of inheritance cannot be stated in some cases because of lack of sufficient evidence. It is also possible that in some cases the mode of inheritance will prove, on further analysis, to be more complex than is indicated at the present time.

Summary Of Lethal Characters Observed In Cattle

Achondroplasia1 (Bull-dog calves): Crew1 and later Seligman, Wilson, and Crew2 pointed out that in the Dexter breed abnormal calves occur frequently. This abnormal calf is called "Bull-dog" because of its resemblance to that breed. The skull is vaulted and much rounder than normal, the nose flattened, upper lip split, the lower jaw protruding, and the swollen tongue thrust out. The presence of excessive subcutaneous fat gives the body an abnormal developmental appearance. These animals also have short legs. This condition is produced by a dominant lethal factor, but is not lethal in the heterozygous state.

In 1933, Carmichael3 reported the appearance of “Bull-dog” calves in African cattle. The Bull-dog type calf referred to is aborted about the fourth month of gestation. Death is produced by the dominant lethal factor in the homozygous state.

Achondroplasia2 (Bull-dog calves): Mohr and Wriedt4 investigated a similar case of heredity in the Norwegian Telemark cattle. This lethal character has also been reported in Holstein cattle. These calves are born at full-term, usually alive, but do not live more than two weeks. They have a markedly shortened head and a short upper jaw. The legs are greatly shortened and so bent that they cannot support the animal. Investigation shows that the thyroid gland is abnormal. Death is attributed to a respiratory paralysis, since the diaphragm is over worked because the calves cannot stand. The condition is inherited as a single recessive factor.

Ankylosis: Mohr5 described a character in which the lower jaw is greatly shortened and ankylosed. The condition is produced by a recessive factor and appears in Norwegian Lyngdal cattle.

Short-limbs: Ljutikow7 described a lethal in a Swiss breed of cattle which is characterized by short legs and underdeveloped phalanges. There is little indication of two separate digits. The char-
acter is not achondroplasia. Many of these calves are aborted. The evidence presented shows that the character is a simple recessive.

Acroteriasis congenita: Wriedt and Mohr\(^9\) reported a recessive lethal in the Swedish breed of Holstein-Friesian cattle (Svensk Laaglandsboskap) which in the homozygous condition produces a series of malformations and can be described under the general term acroteriasis congenita; i.e., amputation of the prominent parts. The gene produces a pronounced atrophia maxillae which is accompanied by palatum fissum, the mandible being reduced to a vestige. The fore legs are amputated to the cubital joint, and the hind legs to the hock joint. Autopsy reveals a pronounced hydrocephalus. These monsters are usually full-term and normal size, but die immediately after parturition or within two days. The factor is inherited as a single recessive.

Short spine: Mohr and Wriedt\(^9\) reported a recessive lethal factor, occurring within the Oplandske mountain breed in Norway. In a homozygous condition this gene produces a shortening of the vertebral column and of the thorax. The short neck and thorax, a pucker-like prominence of the proximal thoracic processus spinosi, and the high insertion of the short tail combine, with the normal skull and the normal legs, to give the homozygous calves an elk-like appearance. The calves are full-term and, except for the shortening of the neck and thorax, are of normal size. Parturition in these cases is difficult owing to the frequent posterior presentation. Except for topographical changes in relations, the viscera seem to be normal. The malformed calves die either during or immediately after parturition.

The shortening of the vertebral column is the result of aplasia with irregular fusion and amalgamation of adjacent vertebral rudiments during development. This results in a reduced number of malformed compound vertebrae in which traces of fused or intercalated vertebral rudiments can be identified. Together with the vertebral column changes, the ribs and sternum undergo analogous changes. Instead of the normal thirteen ribs, only seven costal bones are present on the left, and six on the right side.

The skeletal abnormalities in the amputated calves are analogous to those present in the short-spine calves; viz., aplasia with amalgamation and fusion of adjacent osseous rudiments. Note that in these cases the changes effect the maxillary, mandibular, and hyoid regions of the skull together with the scapulae, the coxae, and the free extremities of the appendicular skeleton, while the spinal column, ribs and sternum present normal conditions.

Skull-defect: Shaw\(^8\) reported a skull-defect which is probably hereditary and is characterized by an opening involving the frontal and parietal bones. Anatomically this defect would be classified as meningoencephalocele and proencephalus of cranioschisis.

Impacted molars: The condition of impacted molars in calves born alive at full-term was observed in a herd of closely inbred Milking Shorthorn cattle by Heizer and Hervey\(^11\). These are of normal size, and produce no visible abnormal conditions during the gestation period. Calves showing the defect die within the first week following parturition.

The principal abnormality observed in the affected calves is the impaction of the premolar teeth in the mandible which is greatly reduced in length and width giving a "parrot-mouth" appearance. The lethal factor appears to be the result of a single simple recessive gene.

Annett\(^12\) described a similar recessive lethal in Shorthorn calves which is characterized by a deformity of the lower jaw. The mandible is only one-half the normal length. The teeth are normal and the tongue, having no support, hangs down outside the mouth. The affected calves do not survive since it is impossible for them to suckle.

Hypotrichosis congenita (Hairless): A recessive lethal gene, occurring within the Swedish breed of Holstein-Friesians, has been described by Mohr and Wriedt\(^13\). The gene produces an almost complete hair-
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lessness (hypotrichosis congenita) in the homozygous condition. When present, hairs are confined to sharply circumscribed areas. The homozygous full-term, normal-size calves die a few minutes after parturition.

A microscopic examination of the hairless skin shows that the development of the hair follicles and their appendages is delayed, since the details encountered correspond to those typical of a very early embryological stage in the normal development of the skin. The skin of the hairy areas is normal in appearance.

Wipprecht and Horlacher reported an inherited lethal condition, which is called hairless, in Jersey cattle. This hairless lethal defect appears to be caused by a single gene which is a simple recessive. There is no definite time of expulsion of the hairless fetus by the various dams. The hairless defect appears to be closely associated with the condition known as wry tail.

Muscle contracture: Hutt presented evidence that muscle contracture is a simple recessive lethal character. The newborn calves are afflicted with extreme rigidity of the neck and all legs. The long bones of the legs are bent and in some cases the legs seem to be wrapped around the body. The condition is considered to be caused by extreme contractures of the muscles of the neck and legs. The calves are alive at full-term, but die during or after parturition. Many of the feti must be dismembered to overcome dystocia.

Loje also found Red Danish calves born alive, normal in all respects, except that they were unable to stand on their hind legs. All such calves must be slaughtered, since they cannot survive without much assistance. The evidence presented indicates that the condition is a simple recessive character.

Epitheliogenesis imperfecta: Hadley described a lethal recessive gene whose appearance in the new born calf is characterized by defective formation of the skin below the carpal and tarsal joints, one or more undeveloped claws, deformed ears, defects in the integument of the muzzle, and in the mucous membrane of the nostrils, tongue, hard palate, and cheeks. The calves die shortly after parturition, since they are not able to survive the infection which is acquired through the denuded areas. A recessive, sub-lethal epithelial defect was reported in Jersey cattle by Regan et al. The defect was uncovered in the course of an inbreeding experiment. The description shows the defect to be identical with the one reported by Hadley in Holsteins.

Fetal resorption: Turner reported various stages of fetal resorption from decomposed masses to only bones or dried mummies. The mode of inheritance is not definitely known.

Mummification: Loje reported a high incidence of mummified fetuses in Red Danish dairy cattle. Most of the calves die during the eighth month of gestation, but are carried to term. Those aborted earlier show little evidence of mummification. The fetuses present short necks, stiff legs, and prominent joints. Hydrops amnii is always associated with the condition. Many cases result in dystocia.

Congenital dropsy: Larsson described a condition characterized by accumulation of fluid in the subcutaneous tissues, in the thoracic and abdominal cavities, and in the head and neck region. The calves are born at term or one to two months prematurely. The character is inherited as a single recessive, and is reported in black and white Swedish Lowland cattle.

Congenital ichthyosis: Lesser reported a lethal which produces various abnormal scaly and cracked conditions of the skin. This condition is probably allied with epitheliogenesis imperfecta. The condition is produced by a recessive factor.

Congenital cataract: Detlefson and Yapp observed well-defined congenital cataracts of the stellate type in Holstein-Friesian cattle. They conclude the condition is produced by a simple recessive Mendelian character. The histological pic-
ture of this condition has been reported by Small[23].

**Lethality**

It is a fundamental fact of genetics that mutants with rather large somatic effects tend to be lethal. This would mean that the change in the developmental processes produced by the mutant gene is so great that the proper coordination and integration of the different processes during development are impaired. The action of the gene comes into effect very early in development so that a group of cells is affected that still has a rather unrestricted prospective potency, which would be segregated later in development. The action of the gene controlled process therefore influences a large group of differentiating processes instead of only one in case of an effect at a later stage at which the cellular material is already subdivided as far as determination is concerned. Lethal gene actions may also occur if some physiological process of vital importance is damaged or inhibited.

**BIBLIOGRAPHY**


**FOX FARMING**

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at least every three weeks if the lungworm is to be controlled.

**Infectious Diseases**

Of the infectious diseases, the most dreaded is encephalitis. This disease occurs in the fall when all the foxes to be pelted are put together in the run, a large pasture. In 1935, the Kjar Fur Farm witnessed an outbreak of epizootic encephalitis in the fox range where two hundred foxes were together. No advancing symptoms were seen. One morning eight foxes were found dead. The following morning, ten more were dead. When rounding up foxes, we would notice that some foxes, acting in a perfectly normal manner, would be running only to suddenly fall over and go into violent convulsions with death following within fifteen minutes. A similar outbreak occurred the following year. The disease is caused by a filterable virus and causes 15 to 20 per cent mortality in adult foxes and 80 per cent in fox pups. Because these outbreaks occurred at about the time of pelting, we were able to save the pelts of the dead foxes with little loss of price. During the summer of 1937 an autogenous bacterin was made up against the virus. Three treatments of this bacterin were given during the summer and fall. That fall our ranch was not the host of epizootic fox encephalitis, nor has it been since. Whether or not the bacterin should be given all of the credit is not known, but its use will be continued until it has been proved false.

As a summary pertaining to diseases, it is our belief that it is much easier to