

Familial chondrodysplasia in Holstein calves

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Abstract. After the release of a report from France on the occurrence of malformed calves genetically related to a Holstein sire, a study was performed to characterize the defect. Danish breeders were encouraged to submit defective progeny of the sire for laboratory examination. Four cases were submitted, whereas a fifth case was only reported. Lesions in affected calves were analogous, with disproportionate growth retardation characterized by fascial dysplasia and shortening of the vertebral column and the abaxial skeleton. Endochondral osteogenesis was disturbed with disorganization of epiphyseal plate chondrocytes, a lesion consistent with generalized chondrodysplasia. Based on morphology, the defect was grouped as a “Dexter bulldog type”. A genetic etiology was suspected as cases occurred in a familial pattern. Genealogical evaluation revealed several common ancestors belonging to widely used breeding lines of US Holstein, but because of the extensive use of these sires, their presence in the pedigrees of affected calves might be accidental. Further studies are needed to determine the mode of inheritance.

Since the first scientific report on chondrodysplasia (achondroplasia) in calves almost a 100 years ago,⁹ descriptions of different phenotypes in several cattle breeds across various geographic regions have been published.⁶ The phenotypical variation of chondrodysplasia is wide, ranging from lethal fetal disorders through semilethal cases to short-legged viable animals. Lesions may be local as well as generalized. A genetic etiology has been demonstrated in some types of chondrodysplasia, whereas it has only been indicated in others. The mode of inheritance varies between different phenotypes and cattle breeds.⁶ Chondrodysplasia is pathogenetically characterized by disturbed endochondral osteogenesis. Many genetic pathways may be involved in this process, and abnormal function in several of these may be expressed as disproportionate dwarfism.

Cases of chondrodysplasia in the Holstein–Friesian breed sharing morphological features with the Dexter bulldog calves³ have been reported from the United States,^{5,7} the Netherlands,⁴ and Great Britain.^{2,8} Unreported cases probably occur more widely. Cases in British Friesians occurred in a familial pattern and segregated in accordance with autosomal recessive inheritance.⁸ In September 1999, the French breeding association Sersia France released information on the oc-

currence of a familial lethal defect in calves that were progeny of the internationally used Holstein sire Igale Masc (French herd book No. 4493050102) (Sercia France, press release, Sep 29, 1999). Affected calves were reported to have a flat face and short legs and of being nonviable, a description consistent with chondrodysplasia. As semen of Igale Masc had been used in Denmark, a study was conducted on this anomaly.

Materials and methods

Shortly after the release of information regarding Igale Masc, Danish cattle breeders were requested to submit malformed calves for laboratory examination.

Submitted calves were necropsied, and bone specimens were radiographed using a Polydoros XL 50 X-ray apparatus,^a Fuji Medical HR-L X-ray film,^b and 3M intensifying screens (T16) without grids.^c

Samples for histopathology were taken, fixed by immersion in 10% neutral buffered formalin, processed routinely, sectioned at 2–3 μm , and stained with hematoxylin and eosin. Before processing, bones were decalcified in a 3.3% formaldehyde/17% formic acid solution. Selected bone sections were also stained by Kossa’s method for calcium, Masson’s trichrome connective tissue stain, McManus’ method for glycogen, and toluidine blue. Pedigree analysis was performed on all affected calves. Pedigrees were initially obtained from the Danish Cattle Database. Additional pedigree information was obtained from breeding associations in the United States, Canada, the Netherlands, and France.

Based on information obtained from the Danish Cattle Database, a retrospective evaluation of breeding results was performed. Cows and heifers that had received an embryo or had been inseminated with semen from Igale Masc and had had a registered calving or abortion before February 10, 2000, were selected. The breeders received a questionnaire and were requested to submit information on obtained progeny.

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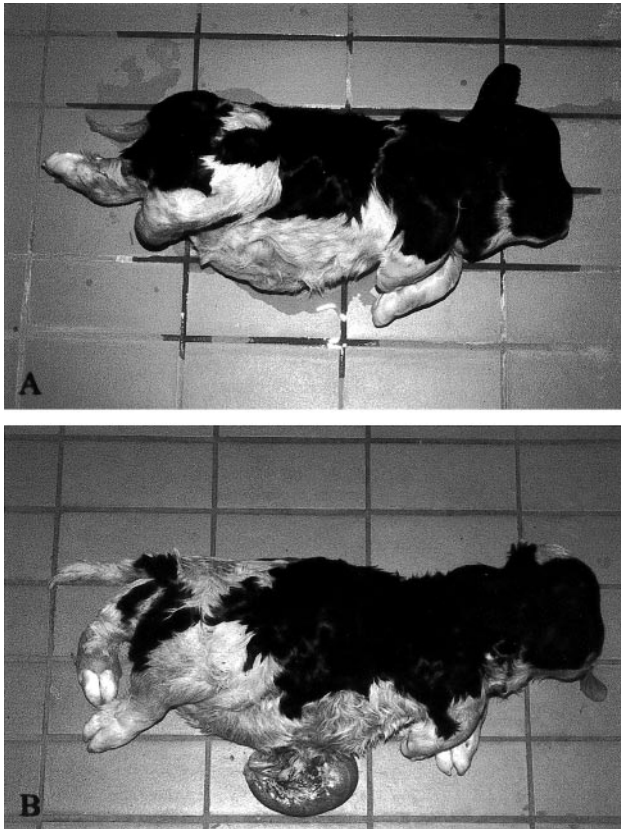


Figure 1. External appearance of 2 cases of bovine chondrodysplasia.

Results

A total of 167 cows and heifers were registered in the database as fulfilling the inclusion criteria. The calvings resulted in 175 calves, including 8 pairs of twins. Three fetuses were aborted, of which 1 was lost on pasture, whereas 2 fetuses were reported as unaffected. Four calves were reported as chondrodysplastic. Three of these calves and a further case delivered after February 10, 2000, were available for laboratory examination.

Three cases were the result of embryo transfer, of which 1 embryo had been imported from the Netherlands. The other 2 cases were obtained by insemination. The gestation period varied from 260 to 283 days (mean 272.8 days), and the body weights varied from 19 to 22 kg (mean 20.5 kg). Three calves were males, and 2 were females. One was born as a twin to a holocardius amorphus. The cases originated from different herds.

Necropsy findings. The calves were almost similar in appearance, being characterized by prominent disproportionate dwarfism. The body was short and compressed because of decreased length of the axial skeleton, with a mean crown-rump length of approximately 55 cm. Limbs exhibited a bilateral symmetric



Figure 2. Longitudinal section through the head of a chondrodysplastic calf demonstrating a ventrally rotated and dysplastic splanchnocranium. Frozen specimen.

malformation with a compact appearance and severely reduced length. Digits were of almost normal size (Fig. 1). One calf had an umbilical eventration of the abomasum (Fig. 1B). Severe dysplasia of the splanchnocranium with broadening of the neurocranium, bilateral exophthalmus, caudal displacement of the ears, and a wide palatoschisis was evident in all cases. The neurocranium had increased hardness. The splanchnocranium was rotated ventrally with an angle of approximately 70° to the brainstem (Fig. 2).

Longitudinal sections of bones revealed small irregular diaphyses with marked cortical bone formation and centrally located spongy bone. The epiphyses were prominent, with a light red color, pale streaks, and a rubber-like texture (Fig. 3). In the vertebrae, the epiphyses were extremely prominent, causing spinal cord compression (Fig. 4).

The trachea was stenotic at the cranial thoracic aperture. The ribs were reduced, causing narrowing of the thorax and compression and hypoplasia of the lungs. The heart was rounded with bilateral ventricular hypertrophy and reduced ventricular volume. The lungs were not aerated.

Histologic findings. The epiphyses consisted of a homogenous hyaline cartilage without ossification. Large fibrous septae with arteries and dilated veins transversed the cartilage. Numerous chondrocytes located in lacunae and separated by a homogenous ground substance were scattered throughout the epiphysis. Most chondrocytes were hypertrophied and located in variably sized lacunae (Fig. 5). The epiphyseal chondroid matrix had abnormal staining abilities characterized by weak PAS and metachromatic stainings, which became stronger in the metaphyses. The articular surfaces appeared smooth and regular, with small chondrocytes located in elliptical-shaped lacunae in the periarticular cartilage. Similar minor chondrocytes were present in the subperichondrial areas.

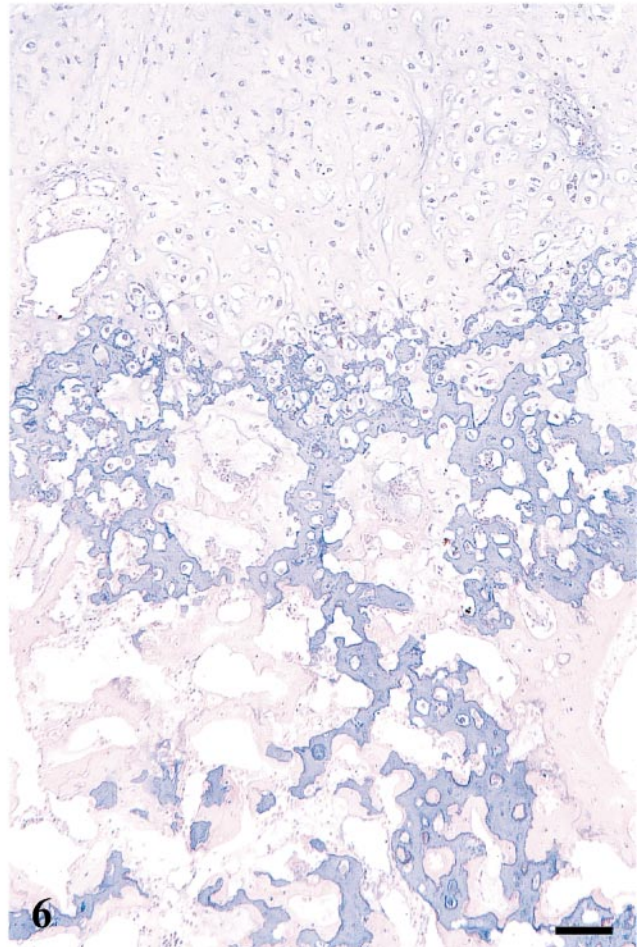
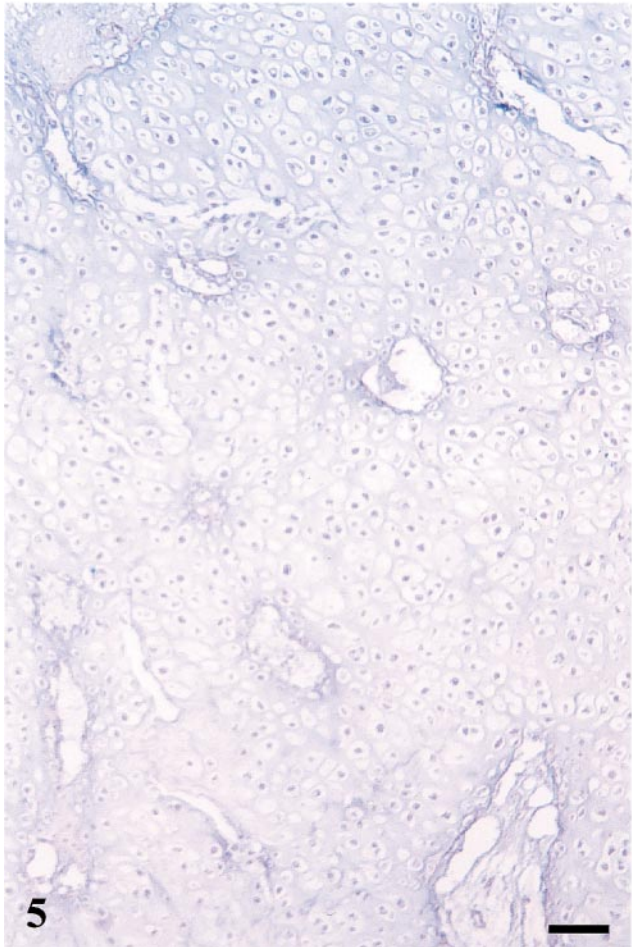
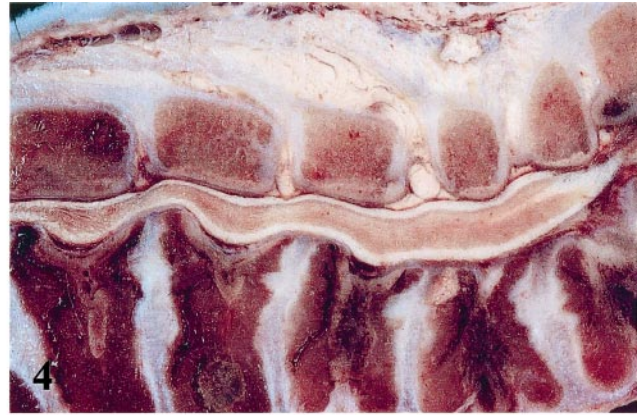


Figure 3. Longitudinal section through femur of a chondrodysplastic calf demonstrating centrally located bone and peripheral development of chondroid tissue.

Figure 4. Longitudinal section through column, pars lumbo-sacralis of a chondrodysplastic calf showing multiple areas of marked spinal cord compression due to abnormal epiphyseal development.

Figure 5. Central area of metacarpal distal epiphysis dominated by hypertrophic chondrocytes and large veins. HE. Bar = 100 μ m.

Figure 6. Disorganized epiphyseal plate dominated by hypertrophied chondrocytes. Distinct zones of chondrocyte alignment are absent, and cartilage penetrates into the metaphysis, leaving cores of partly calcified cartilage in the spongiosa. Metacarpus, proximal epiphyseal plate. HE. Bar = 100 μ m

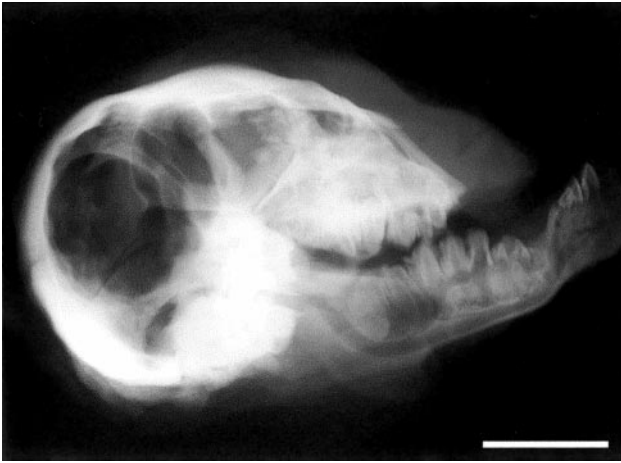


Figure 7. Radiograph of the head of a chondrodysplastic calf after sagittal sawing. Notice a prominent dysplasia of the splanchnocranium. Bar = 5 cm.

The epiphyseal plates were irregular, disorganized, and dominated by hypertrophied chondrocytes. Distinct zones of chondrocyte alignment were nearly absent; when present, only few columns of chondrocytes had developed. Toward the metaphysis, the cartilage was bordered by a broad irregular zone of interstitial calcification and chondrocyte degeneration. Focal protrusions of cartilage penetrated into the metaphysis. Ossification was incomplete, leaving large cores of partly calcified cartilage in the bony spicules (Fig. 6). Cartilagenous cores were found in both the metaphysis and the diaphyseal trabeculae. The intertrabecular spaces were occupied by bone marrow.

Diaphyseal cortical bone was well developed and morphologically normal. Metaphyseal and epiphyseal cortex had nests or irregular trabeculae of calcified cartilage.

Radiologic findings. The neurocranium was of nearly normal size, whereas the splanchnocranium was dysplastic with severe superior brachygnathism (Fig. 7). The mandibles had mild inferior brachygnathism. The neurocranium and mandibular bones had an almost normal trabecular structure, and the teeth anlagen appeared normal.

The vertebral spinal processes and the ribs had a normal trabecular structure and were of nearly normal size and form, although the ribs were shortened. The vertebral corpora were irregularly shaped and structured and of unequal size. The diaphyses were irregularly structured with dark lines and amorph structure, whereas the epiphyses appeared homogenous and unmineralized with soft-tissue density. The epiphyses were larger than the vertebral corpora. The number of vertebrae and ribs were normal (Fig. 8). The pelvis was irregular.

Individual bones of the limbs were severely mal-

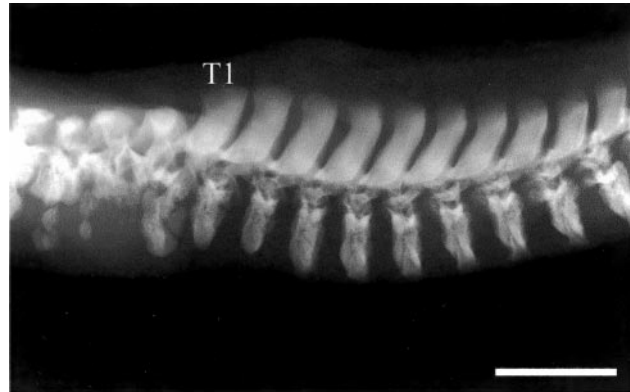


Figure 8. Radiograph of the vertebral column of a chondrodysplastic calf. T1, Processus spinosus of the first thoracic vertebra. Bar = 5 cm.

formed and only identifiable by their location. The bones, especially proximal to the phalanges, were abnormally short. The diaphyses were the only calcified bone portions and appeared short and highly irregular but with nearly normal diameter (Fig. 9). The diaphyses of individual bones were separated by large unmineralized homogenous epiphyses with soft-tissue

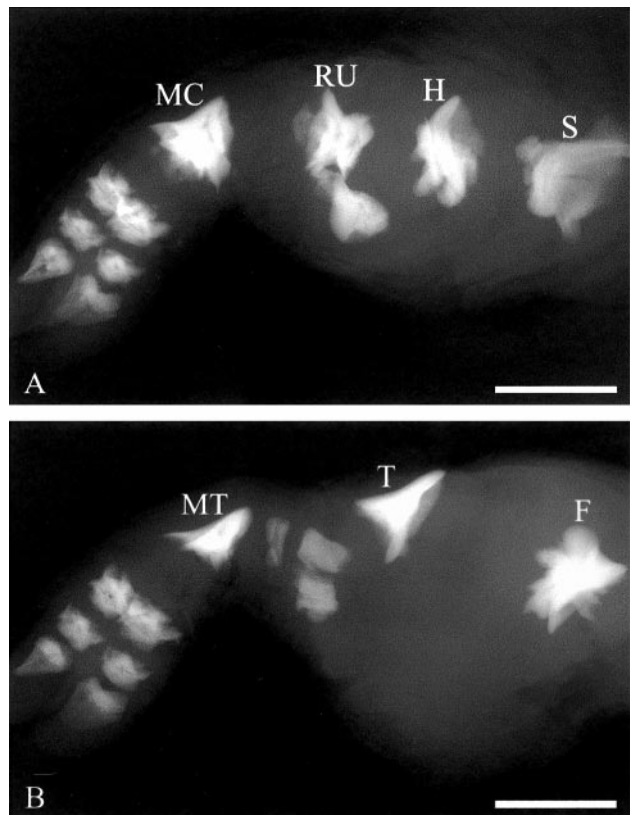


Figure 9. Radiographs of the right anterior (A) and posterior (B) limbs of a chondrodysplastic calf. The diaphyses of individual bones as indicated by letters: S, scapula; H, humerus; RU, radius/ulna; MC, metacarpus; F, femur; T, tibia; MT, metatarsus. Bar = 5 cm.

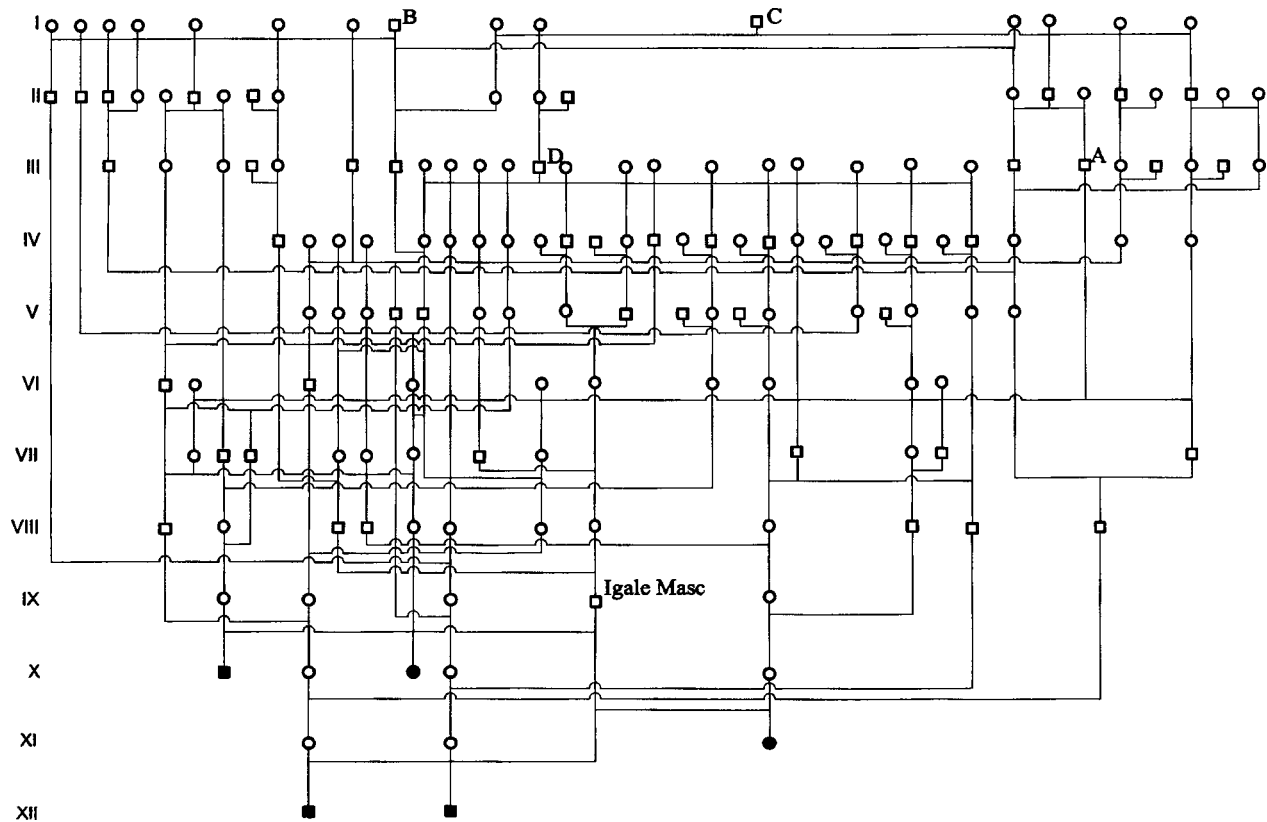


Figure 10. Genealogic diagram of calves with chondrodysplasia ($n = 5$) in reference to 2 common ancestors (sires B and C). Only the most relevant individuals are shown. ■ = affected male calf; ● = affected female calf; □ = phenotypically normal sire; ○ = phenotypically normal cow.

density. The carpal and tarsal bones were calcified with a nearly normal trabecular pattern in some cases. The third phalanx appeared normal, whereas the other phalanges were short.

Genealogic examination. Complete 8-generation pedigrees were available in all cases. Pedigree analysis revealed the presence of common maternal and paternal ancestors (sires B, C, and D), causing inbreeding loops in the pedigree of all affected calves (Fig. 10). These sires were of US Holstein origin and belonged to important and widely used breeding lines within the Holstein breed.

In the 7-generation pedigree of Igale Masc, sire B occurred 4 times, whereas sire C and its grandson D occurred 1 and 4 times, respectively. All 3 sires occurred in both the maternal and paternal pedigree of Igale Masc. In the maternal pedigrees of the 5 malformed calves, sire B occurred 2 to 5 times in each 7-generation pedigree, sire C occurred 1 to 3 times, and sire D was present 3 to 4 times.

Discussion

The morphological changes observed in the 4 cases available for laboratory examination were similar. Gross lesions were restricted to bones having endo-

chondral osteogenesis, whereas skeletal parts with intramembranous ossification appeared normal. Morphologically aberrant organization and maturation of epiphyseal plate chondrocytes causing severe shortening of bones having endochondral osteogenesis were observed. Based on these observations, the syndrome could be categorized as a generalized chondrodysplasia (achondroplasia), often referred to as “bulldog calves.” The cases shared major features with other chondrodysplastic phenotypes, generally referred to as the “Dexter bulldog type.” This is a subgroup of chondrodysplasia in which calves have severe generalized chondrodysplasia and usually die late in the gestation period.

An apparently similar syndrome was reported in 2 US Holstein calves in 1987.⁷ As the Danish cases were of US Holstein origin, this coincidence is interesting. Unfortunately, pedigree information was not reported, so an eventual familial relationship cannot be evaluated. Chondrodysplasia has also been reported in British Friesian.^{2,8} Although these cases originally were categorized as “Dexter bulldog type”, their phenotype seems to differ from the Danish cases in several aspects, i.e., by the presence of high-grade internal hydrocephalus, normal body weight, and apparently un-

affected metacarpal and metatarsal bones. Detailed reports on the original French cases of chondrodysplasia in progeny of Igale Masc have not been published. Therefore, it is not possible to compare the Danish and French cases. However, it seems likely that they are analogous.

In this study, 5 cases of chondrodysplasia, all being progeny of 1 sire, were recorded. The occurrence of these cases in different herds without the occurrence of similar cases among other calves born on the same premises during the same period suggests a genetic etiology. The occurrence of an apparently similar syndrome in progeny of Igale Masc in France and previous reports on the etiology of chondrodysplasia in other cattle breeds support this indication.

The mode of inheritance varies between different types of chondrodysplasia.⁶ In this study, evaluation of the mode of inheritance was difficult. The occurrence of common ancestors could indicate an autosomal recessive inheritance. However, this must be evaluated with great caution because the breeding lines related to sires B and C have been used extensively. Therefore, these sires occur in the pedigrees of many Holsteins. This observation was made in another study¹ where 2 sires (A and B) occurred in the pedigrees of several calves having complex vertebral malformation (CVM). Sire A¹ is a grandson of sire C in this study (Fig. 10), whereas sire B is identical in both studies. Genotyping studies later revealed that only sire A was a carrier of CVM, whereas sire B occurred in the pedigree fortuitously. Therefore, further investigations including breeding studies or genomic analyses are needed to determine the mode of inheritance and the identity of a possible common ancestor in relation to this defect. The occurrence of chondrodysplasia in French and Danish Holstein calves in a familial pattern related to the sire Igale Masc and the report of an apparently similar syndrome in US Holstein⁷ indicate

the presence of this likely genetic disorder in the Holstein breed worldwide. Awareness of this defect is urged among breeders and veterinarians to identify further carriers, thus preventing unnoticed spread of the defect. The initial report of this defect by the breeding association Sercia France is greatly acknowledged as an important step to prevent further spread of the anomaly.

Acknowledgements

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Sources and manufacturers

- a. Siemens AG, Erlangen, Germany.
- b. Fuji Photo Film Co., Ltd., Tokyo, Japan.
- c. 3M, St. Paul, Minnesota.

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