https://doi.org/10.17221/70/2022-CJAS

Long-term pedigree analysis: An effective tool for managing congenital malformations in cattle

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Citation: Čítek J., Večerek L., Šlosárková S., Fleischer P., Vostrý L., Vostrá-Vydrová H., Schröffelová D., Kučera J. (2022): Long-term pedigree analysis: An effective tool for managing congenital malformations in cattle. Czech J. Anim. Sci., 67: 385–393.

Abstract: Controlling congenital defects is an important aspect of breeding for genetic health; however, whether malformations are caused by genetic or nongenetic factors may not be clear. This study aims to analyse the incidence of *aplasia genitalis*, *atresia ani et recti* and *hernia cerebralis* in the Czech cattle population, analyse the relatedness of affected calves by a relationship matrix, and assess the potential future threat. The sires fathering affected calves were born in the Czech Republic or imported from 1986 to 2001. The cases occurred on farms across the Czech Republic. The pedigree of each case was examined for common maternal and paternal ancestors (inbreeding loops) and for ancestors shared by other cases of the defect. The average relatedness coefficient of each individual was computed based on the relationship matrix. The results of the analysis of pedigrees and of the relationship matrix support the hereditary aetiology. The 13 calves affected by *aplasia genitalis* had common ancestors in 12 cases. The results indicate hereditary causation with recessive inheritance. In *atresia ani et recti*, some of the pedigrees of 25 affected calves support hereditary causation, and repeating ancestors were found for 11 calves. Our analysis of 11 *hernia cerebralis* cases also hints at the genetic background, but not as unequivocally as in other congenital defects studied. A high number of descendants fathered by sires of affected calves constitutes a risk for future. The relationship matrix and pedigree analysis could help in managing genetic health, although the final goal in terms of inherited defects must be the description of causal genes and mutations. Measures to control sires and dams with affected calves should be appropriate under the current knowledge, which include culling or prudent use of breeding with the monitoring of descendants.

Keywords: genetic health; surveillance program; *aplasia genitalis*; *atresia ani et recti*; *hernia cerebralis*

Supported by the Ministry of Agriculture (Project MZe NAZV QK1910320) and by the Grant Agency of University of South Bohemia (Project No. 005/2022/Z).

https://doi.org/10.17221/70/2022-CJAS

The ultimate goal of breeding is to produce animals with a genetic background of desirable production and sound health. Genetic health must be ensured at all levels, an ideal status is the population free of genetically caused afflictions. It concerns mutations of individual genes, chromosomal abnormalities and aneuploidies, and the health of the animals, including the animal's fertility, which is controlled by multiple minor genes, should be improved continuously as well. The intensive selection merely based on higher milk production has been the cause of prevailing health and fertility deterioration (Zavadilova et al. 2021), therefore since the last decades of the 20th century genetic selection programs have been increasingly focused on increasing resistance to diseases and improving fertility traits.

The control of congenital malformations plays an important role in the breeding process. In humans, approximately 50% of congenital anomalies cannot be linked to a specific cause. However, known cases include single gene defects, chromosomal disorders, multifactorial inheritance, environmental teratogens and micronutrient deficiencies. Genetic cases can be traced to inherited genes or mutations. The aetiology of congenital defects in farm animals is often unclear because many teratogens, including infectious agents, may be involved, and whether an anomaly is acquired or inherited can be uncertain. Some occur only rarely; therefore, thorough analyses of these defects are difficult. In some cases, the genetic background can be uncertain and whether the defect is caused by monogenic or polygenic factors or dominant or recessive inheritance can be dubious as well.

The occurrence of congenital malformations in livestock production, especially when caused by gene variants passed down by parents, hinders genetic progress. To study the genetic basis of these diseases and find strategies to eradicate them in livestock populations is an issue that breeders must overcome to avoid economic losses, as summed up by Albarella et al. (2017). Deleterious genetic conditions need to be recognized because they limit the productivity of animals expressing the trait. According to Casas and Kehrli (2016), a point of caution is that in spite of the current genetic testing being highly effective at accurately identifying carrier animals of particular traits, leukocyte chimaerism can result in erroneous test results if blood is used as a convenient DNA source; test results must always be confirmed with an independent tissue source not subject to mixed genotypes.

Aplasia genitalis is the lack of development of female genitalia. The most extreme abnormality of Müllerian ducts is congenital absence of the uterus and vagina, and the aetiology is still unclear (Zhang et al. 2017). Congenital atresia of the vagina in the region of the hymen sometimes occurs in heifers.

White heifer disease or Müllerian duct hypoplasia 1 show phenotypic similarity to the abovementioned defects. The affected females are sterile, the aetiology is hereditary, and defects occur mainly in Belgian blue and Shorthorn white heifers (Millar et al. 2000). The differentiation and development of genitals are suppressed, but the ovarian function and periodicity are maintained. The defect is caused by the Roan gene on BTA5 (Seitz et al. 1999).

Studies based on targeted mutagenesis in mice have identified genes participating in the development of Müllerian ducts (Guerrier et al. 2006). Online Mendelian Inheritance in Animals (OMIA 2020) classified genital hypoplasia as an inherited defect without published evidence for single-locus inheritance (OMIA 2020; number 000406-9913).

Additional defects with different aetiologies are hypoplasia bisexualis and freemartinism. The signs are larger clitoris, small blind vagina, hypoplasia or aplasia of the uterus. The syndrome is triggered by placental anastomoses between foetal membranes of heterosexual twins, and androgenic hormones suppress the normal development of female gonads (Kochneva et al. 2016). However, in a comprehensive publication on the genetics of cattle (Garrick and Ruvinski 2015), freemartinism is listed as an inherited disorder for which there is insufficient published evidence for single-locus inheritance (OMIA 2020; number 000393-9913).

Intestinal atresias are inborn defects of mammals, including humans. As reported by van der Gaag and Tibboel (1980), atretics can occur in the gut from the duodenum to the anus. Thus far, the causation has not been definitively elucidated. Although genetic and nongenetic reasons remain possible, the prevailing assumption is that the defect is hereditary and caused by an autosomal recessive allele (Martens et al. 1995; OMIA 2020).

In cattle, atresia of the large intestine and anus is the most common form (van der Gaag and Tibboel 1980). The latter is easily diagnosed by breeders a few days after delivery, and surgical treatment

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has a good prognosis. The frequency in male and female calves is reported to be even (Azizi et al. 2010).

Hernia cerebralis or encephalocele is the herniation of the brain into a sac covered with a membrane. According to Rolo et al. (2019), the defect does not likely occur because of faulty closing of the neural tube; rather, it is likely caused by later damage to superficial ectodermal structures of the already closed neural tube. As reported by Kisipan et al. (2016), such congenital defects of the skull also occur in other mammals, including horses, pigs and humans.

Cranial meningocele (containing only the meninx) has been well documented in the Ayrshire calf, and cranioschisis with meningocele has been well documented in the Shorthorn calf and is associated with additional anomalies, including tibial hemimelia and abdominal hernia. The Shorthorn calf is a member of a group of related calves that present tibial hemimelia and other defects (Lapointe et al. 2000; Kisipan et al. 2016).

In humans, as reviewed by Zaganjor et al. (2016), the aetiology of these defects seems to be multifactorial, polygenic, and epigenetic under the influence of external factors. Namely, occipital encephalocele usually occurs with a monogenic hereditary syndrome, and some causal genes have already been identified. The defect can also be a consequence of trisomy 13 or 18 (Logan et al. 2011).

This study aims to perform and analyze the pedigree of calves in the Czech Republic affected by one of the three congenital defects: *aplasia genitalis* (AG), *atresia ani et recti* (AAR) and *hernia cerebralis* (HC), and the incidence of the defects in the Czech cattle population.

MATERIAL AND METHODS

Cases of AG, AAR and HC, among other congenital disorders, were diagnosed and reported by veterinarians to the mandatory Czech surveillance program for bovine genetic disorders. No experiments were performed on living animals. Field veterinarians noted the diagnosis of the affected calves and identified the sires and dams. The study was limited to calves fathered by sires born between January 1986 and December 2001. The sires were born in the Czech Republic or included in the herd book due to semen import (Citek et al. 2009). The study period is based on the non-mandatory reporting of congenital disorders after 2001. In total, 6 047 sires were newly recorded into pedigree books in the period from 1986 to 2001, and 2 740 were Holsteins and 3 307 were Czech Simmentals. Seventy-eight percent of Holstein sires and 15% of Simmental sires were imported, mainly as frozen semen. Of the recorded sires, 474 (7.8%) fathered offspring with different congenital disorders. The latest data are not available because the supervising program has ended. The cases occurred on farms throughout the Czech Republic.

There were 13 reported cases of *aplasia genitalis* in female calves. In 12 cases, both parents were known, and in one case, the mother could not be traced back. Twenty-five calves presented *atresia ani et recti*. In 21 cases, the sex was not recorded, including two affected males and females. In 21 calves, both parents were known, and in four calves, the mother was not reported. For *hernia cerebralis*, 11 cases were reported. In nine cases, both parents were known, and in two cases, the mother was not reported. The sex of affected calves was not reported. The overview of sires fathering affected calves is in Table S1 in electronic supplementary material (ESM, for the supplementary material see the electronic version).

The pedigree of each case was examined for common maternal and paternal ancestors (inbreeding loops) and for ancestors shared by other cases. The total offspring for the sires of affected calves was found in the documented breeding materials.

The pedigree data were used to estimate the classical inbreeding coefficient (F_X). The classical inbreeding coefficient of each individual was estimated using a tabular method (Falconer and Mackay 1996):

$$F_X = 1 - a_{ii} \quad (1)$$

where:

F_X – inbreeding coefficient of individual i;

a_{ii} – additive genetic relationship between individual i and itself.

The average relatedness coefficient of each individual was computed as the average coefficient integrating the row from the individual in the numerator relationship matrix **A**. This coefficient indicates the probability that a randomly selected allele in the population occurs in a selected indi-

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vidual or among a group of individuals (Falconer and Mackay 1996).

RESULTS AND DISCUSSION

The results of the analysis of the incidence of *aplasia genitalis* are shown in Figures 1–3. Of the thirteen females affected by *aplasia genitalis*, three were from heterosexual twins, i.e., nongenetic causation and freemartinism. These cases were fathered by ten sires, i.e., two percent of 474 sires with affected offspring. The pedigrees consisted of three to eight generations, and unfortunately, they were not complete in all branches, which was similar to the other two congenital malformations studied.

Considering the ten affected calves without freemartinism as a cause, common ancestors were found in all cases. In Figure 1, sire I/2 fathered two affected daughters from different mothers. Figure 2

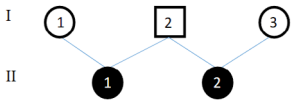

Figure 1. Pedigree of two female calves affected by *aplasia genitalis*

○/● = unaffected/affected female; □ = unaffected male

The common father I/2 is crossbred Simmental (78%) and Ayrshire (22%)

Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

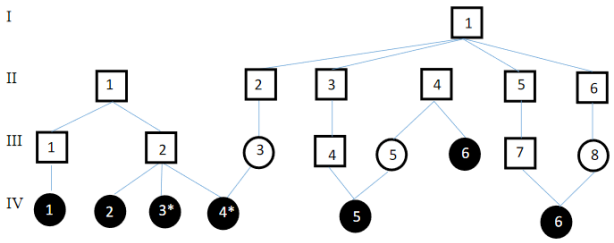

Figure 2. Pedigree of six female calves affected by *aplasia genitalis*

○/● = unaffected/affected female; □ = unaffected male

*Heifer had a twin brother, and the causation is probably freemartinism

The common father I/1 is Holstein (100%) and other fathers are Holsteins (100%)

Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

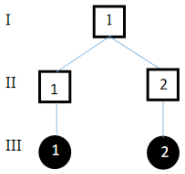

Figure 3. Pedigree of two female calves affected by *aplasia genitalis*

○/● = unaffected/affected female; □ = unaffected male

The common father I/1 is Holstein (100%). Sires II/1,2 are Holsteins (100%)

Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

shows a slightly more complicated pedigree. Sire III/2 fathered three calves with AG, and calves IV/3,4 were from heterosexual twins and thus probably affected by freemartinism. The half-brother III/1 also fathered one calf with AG. The affected calves IV/5,6 had common ancestor I/1. Sire II/4 was the father of one affected calf III/6 and the grandfather of IV/5. Moreover, calf IV/6 was a product of close inbreeding. Additionally, the affected calves in Figure 3 had a common ancestor. For the breed of fathers, seven Holsteins prevailed in three crosses of Czech Simmental with Holsteins and Ayrshire.

Of ten sires fathering AG, nine were inbred, the average F_X was 0.029. Two affected calves were inbred as well, F_X = 0.020 and 0.031, respectively. Of 13 affected calves incl. freemartin, 12 were related, i.e. they had common ancestors in their pedigrees. The average grade of relationship was 0.097 as determined by the relationship matrix, when the individual is related to himself by 1. In ten pedigrees of affected nonfreemartin calves with common ancestors, there was no pedigree without a shared ancestor with another pedigree. Such results indicate a hereditary background of *aplasia genitalis*. Low inbreeding in the population is laudable because the degree of inbreeding significantly influences production and reproductive parameters (Gutierrez-Reinoso et al. 2020). Studies of multiple closely related cases by molecular techniques, such as SNP-based association mapping, would probably be most helpful in demonstrating a genetic aetiology (Charlier et al. 2008). To ensure accurate diagnosis, a uniform collection of cases for molecular examination is needed. Previously described genes with roles in sexual development should be a focus

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(Guerrier et al. 2006). Moreover, different mutations may be associated with an AG phenotype.

The analysis hints at the recessive inheritance of AG; thus, a count of respective genes should be established. When widely used elite sires, producing large numbers of calves, turn out in retrospect to have been carriers of a defective gene, the consequences are serious. In the last major occurrence of the genetic defects, bovine leukocyte adhesion deficiency (BLAD) and complex vertebral malformation (CVM), the bull responsible almost completely for the spread of BLAD throughout the Holstein breed was Carlin-M Ivanhoe Bell. The same bull was also a carrier of CVM. The diseases did not start to reveal themselves until years later when male descendants of Bell were bred to his female descendants (Citek et al. 2008). Surely to prevent the spread of the disease is more beneficial than its eradication from the population. Dominant inheritance of AG is not involved when sires that father daughters with defects also sire many healthy daughters. Moreover, the X-linkage is questionable. The infectious aetiology seems to be implausible, and other nongenetic factors are unlikely for cases reported as isolated events spread in different regions.

The ten sires with calves affected by *aplasia genitalis* have fathered over sixty-four thousand descendants of both sexes as well as eleven sires (Table S1 in ESM). This information is a cause for concern with respect to genetic health in the Czech cattle population, which numbers 360 thousand dairy cows. Moreover, some of the sires were imported, so they could father descendants also in other countries. Besides, two sires fathering AG were also found in pedigrees of aborted or stillborn calves, and this defect was characterized at the DNA level on BTA18 (OMIA 2020). Similarly, three sires in pedigrees of AG calves that were slightly more distant from the affected descendants were also found in pedigrees of stillborn calves and calves with *schistosoma reflexus*.

The 25 calves with *atresia ani et recti* were fathered by 23 sires, with one siring three affected descendants and the others siring one affected descendant. Sixteen sires were Holsteins, one was Simmental, and six were crosses of Simmental, Holstein, and Ayrshire. The F_X of 19 inbred sires was 0.027 on average. The pedigrees consisted of three to ten generations, but in many cases they were uncomplete, mainly in the maternal branch.

The pedigrees of some affected calves support the hereditary causation of atresia. Repeating ancestors to the 5th generation were found for almost half of the calves, i.e., in 11 cases (Figures 4–7).

Figure 4 shows an example of inbreeding. The affected calf IV/1 had a common great grandfather – ancestor I/1 in the maternal and paternal branches of the pedigree. In Figure 5, defective calves III/1 and 2 had a common grandfather I/1. A similar case is shown in Figure 6, with calf IV/1 presenting an extra generation.

A more interesting case of the pedigree of six calves affected by AAR is given in Figure 7. Forefather I/2 had five affected descendants, V/2–6. His grandson IV/3 fathered three defective calves from three cows. Calf V/4 was a product of close inbreeding, and sire I/2 was an ancestor in both the sire and dam parts of the pedigree. Additionally, calf V/5

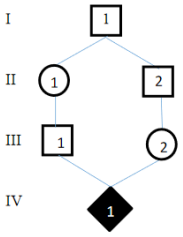

Figure 4. Pedigree of calf affected by *atresia ani et recti*
○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex
The common father I/1 is Holstein (100%). Fathers II/2 and III/1 are Holsteins (100%)
Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

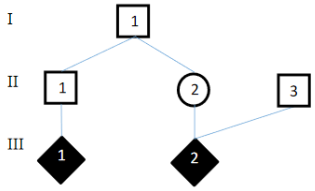

Figure 5. Pedigree of two calves affected by *atresia ani et recti*
○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex
The common father I/1 is crossbred Simmental (75%) and Ayrshire (25%). Father II/1 is crossbred Simmental (76%), Ayrshire (12%) and Holstein (12%). Father II/3 is Simmental (100%)
Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

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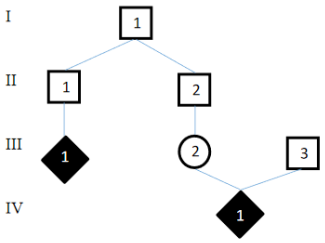

Figure 6. Pedigree of two calves affected by *atresia ani et recti*

○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex

The common father I/1 is Holstein (100%). Fathers II/1,2 and III/3 are Holsteins (100%)

Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

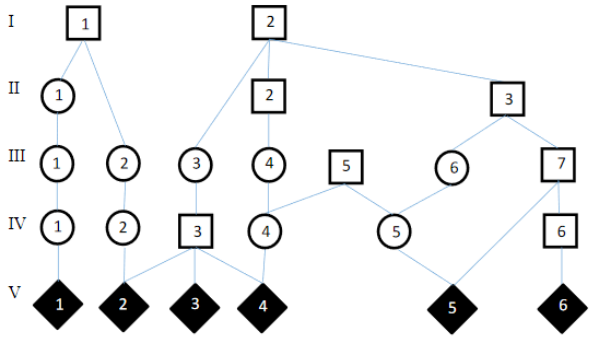

Figure 7. Pedigree of calves affected by *atresia ani et recti*

○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex

The common father I/1 is crossbred Simmental (75%) and Ayrshire (25%), father I/2 is crossbred Simmental (50%) and Holstein (50%). Father II/2 is crossbred Simmental (63%) and Holstein (37%), father II/3 is crossbred Simmental (63%), Holstein (25%) and Ayrshire (12%). Father III/5 is crossbred Simmental (85%) and Ayrshire (15%), father III/7 is crossbred Simmental (71%), Ayrshire (17%) and Holstein (12%). Father IV/3 is crossbred Holstein (65%) and Simmental (35%), father IV/6 is crossbred Simmental (70%), Ayrshire (18%) and Holstein (12%)

Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

was a product of inbreeding, with sire II/3 being a grandfather and great grandfather in the dam branch of the pedigree. Sire III/5 was a grandfather of two defective calves V/4,5. In other affected calves, no such inbreeding was found.

Six affected calves were inbred. Of the 25 affected calves, 23 were related to another calf. As counted in the relationship matrix, the average relationship was 0.045.

Notably, some sires with AAR affected calves fathered numerous descendants. Therefore, sire III/7 in Figure 7 sired 57 645 calves, of which 10 sires and 19 899 cows were included in the milk recording program. Sire IV/3 had 12 798 descendants, with 14 sires and 4 231 cows. In addition, other sires with breeding male descendants were found. In all, the sires with AAR calves fathered over one hundred and ten thousand calves, of it forty-three sires (Table S1 in ESM). Moreover, other congenital defects were recorded in descendants of sires fathering calves with *atresia ani et recti*, with abortions observed in the descendants of eight sires, cleft observed in one calf, AAR with polypodia observed in two calves, and AAR with acaudia observed in one calf. These alarming results are similar to the case of *aplasia genitalis*.

The aetiology can be definitively resolved by identifying causal genes and mutations. Hereditary causation is commonly considered highly likely. *Atresia ani* is classified as a defect with monogenic inheritance but no known causal mutation; and *atresia coli*, *atresia ilei* and intestinal *atresia* are considered hereditary defects without evidence for monogenic inheritance (Garrick and Ruvinski 2015; OMIA 2020). Additionally, our cases of *atresia ani et recti* were recorded in different regions across the Czech Republic.

Compared with the two previous defects, the pedigree analysis of *hernia cerebralis* did not considerably demonstrate a hereditary background. The pedigrees consisted of five to eight generations, again with gaps. Eleven HC cases were evaluated, and five admitted a possibility of genetic aetiology (Figures 8–10). The eleven calves with HC were fathered by ten sires, with one presenting two affected descendants (Figure 10) and the remaining calves presenting one affected descendant.

In Figure 8, Simmental mother IV/1 of the affected calf was a product of close inbreeding. Sire IV/2 was Charolais, his F_X was 0.063, and the number of descendants was 375.

In Figure 9, mothers III/1 and IV/2 of affected calves have a common ancestor I/1. In Figure 10, the two affected calves have a common father II/2 (F_X 0.034), with more than 13 000 descendants. The remaining six affected calves did not demonstrate such close repeating ancestors.

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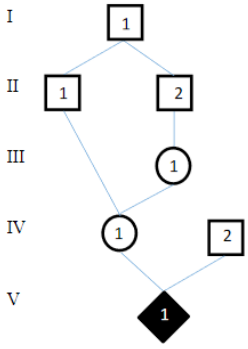

Figure 8. Pedigree of calf affected by *hernia cerebralis*
○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex
The common father I/1 is Montbeliarde (100%). Father II/1 is Montbeliarde (50%), father II/2 is Montbeliarde (100%). Father IV/2 is Charolais (100%)
Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

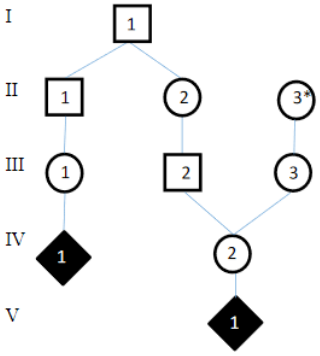

Figure 9. Pedigree of calf affected by *hernia cerebralis*
○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex
*Cow mothered another calf with an unspecified defect
The common father II/2 is Holstein (100%)
Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

In *hernia cerebralis* cases, animals rarely repeat within the pedigrees of affected calves in more distant parts of the pedigrees. Furthermore, the pedigrees were not as interconnected by common animals as in *aplasia genitalis* or *atresia ani et recti*. Of 11 affected calves, 10 were related, the average grade evaluated in the relationship matrix was 0.096. Two affected calves and one mother were inbred.

For ten sires of HC affected calves in the Czech cattle population, they sired over twenty-two thou-

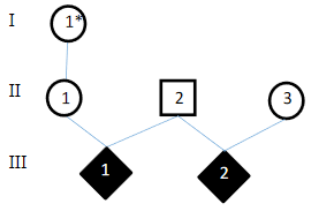

Figure 10. Pedigree of calves affected by *hernia cerebralis*
○ = unaffected female; □ = unaffected male; ◆ = affected individual of unknown sex
*Cow mothered another calf with an unspecified defect
The common father I/1 is Holstein (100%). Fathers II/1 and III/2 are Holsteins (100%)
Generations are numbered from the top of the pedigree in uppercase Roman numerals. Individuals in each generation are numbered from the left in Arabic numerals

sand descendants, with sire II/2 in Figure 10 siring more than 13 000. Again, some sires were of foreign origin and could produce calves also in other countries (Table S1 in ESM). The F_X of sires fathering *hernia cerebralis* was 0.031. When the average inbreeding coefficient was 0.025 for animals born in the Czech Republic in 2001 (Hofmanova et al. 2019), the inbred sires have a slightly higher level of F_X than the average Czech populations.

Thus, our results indicate the hereditary background of the studied cases of *hernia cerebralis*, even though not as massive as for *aplasia genitalis* and *atresia ani et recti*. In general, congenital defects can arise as developmental disorders without impaired genetic material. However, a few previous results identified the hereditary causation of HC in humans and zebrafish (Hofmeister et al. 2018). In the general survey The genetics of cattle, the brain hernia is mentioned as a genetic defect without evidence for single-locus inheritance (Garrick and Ruvinski 2015). According to OMIA (number 0457-9913), the defect was listed in cattle as a definite single-locus disorder, although the evidence for such a claim is insufficient because the only evidence is a brief and old report of a single case by Shaw (1938), who also mentioned that a still-born full sister also had the defect. Therefore, it is doubtful whether *hernia cerebralis* should be listed as a definitely genetic defect in cattle, and the defect should be studied intensively.

Finally, the health status was studied from different points of view such as heat stress, metabolic status, semen quality etc. (Bezdicek et al. 2021;

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Pytlik et al. 2022; Stadnik et al. 2022). But beyond all doubt the first task is breeding for health. In the context, applications of pedigree analyses in studies of congenital defects are not common. However, such work could be beneficial for preliminary research of afflictions without known aetiology. The advantage is that pedigree analyses could be performed even if biological samples were not available, thus preventing an examination at the gene level; moreover, old cases could be involved when pedigree information is conscientiously documented. Consecutively, the new technologies as microarrays and GWAS could be used to identify the disease-causing genes (Kyselova et al. 2021), but for such analyses the phenotypic data of high quality are needed.

CONCLUSION

The results presented herein support the hereditary causation of *aplasia genitalis* and *atresia ani et recti*, and also of *hernia cerebralis*. The relationship matrix allows the exact and reliable evaluation of relatedness of affected animals. The interconnections of affected calves revealed by the matrix are the important results obtained in this paper, they give further evidence for the genetic aetiology of the analyzed defects. The contribution of pedigree analyses to the study of congenital malformations is important, but the final goal must be the identification of causal genes and mutations. In any case, breeding for genetic health requires the systematic recording of congenital defects and strict evaluation of their occurrence in descendants of every sire. Measures against sires fathering affected calves should follow the current state of knowledge. When the causation is hereditary, the sire must be culled. If the aetiology is not obvious, then the sire could be used prudently in breeding but not for the fertilization of elite females, i.e., mothers of sires, and the descendants must be monitored conscientiously. Unfortunately, the analyses of congenital defects are not performed systematically in the Czech Republic. With regard to recessive inheritance, a high number of descendants of sires fathering affected calves documented in this paper and to possible future negative impacts, the resumption of the control of bovine health inheritance should be assessed.

Conflict of interest

The authors declare no conflict of interest.

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Received: April 7, 2022
Accepted: September 26, 2022
Published online: October 20, 2022