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## Genetics of ichthyosiform disorders in domestic animals: A mini review

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### Abstract

“Ichthyosis” refers to several cutaneous keratinization disorders which affect both man and animals and mostly have a genetic origin. In animals, this disease has been reported in cattle, swine, dogs, chicken, mice, llamas, kudu, sheep and goat. It poses economic and animal welfare issues. Two forms of the disease are described in cattle: ichthyosis fetalis (severe and fatal form) and ichthyosis congenita (mild form). Earlier, the diagnosis was mostly based on clinical examination findings and histopathology. At present genetic heterogeneity of inherited ichthyosiform disorders can be analyzed using whole-genome sequencing (WGS)-based precision diagnostics. In humans ichthyotic disorders are associated with variants in more than 50 genes with varied functions. In animals, specific allelic variants have been identified only in a few populations as of now mainly in cattle. This review presents the genetic basis of ichthyotic disorders in animals.

**Keywords:** Ichthyosiform disorders, domestic animals, ichthyosis

### Introduction

“Ichthyosis” refers to several cutaneous keratinization disorders which affect both man and animals and mostly have a genetic origin (Molteni *et al.*, 2006) [13]. In veterinary medicine, the term ichthyosis describes generalized scaling that arises from congenital and/or hereditary defects in the formation of stratum corneum (Mouldin and Peters-Kennedy, 2016) [11]. In animals, this disease has been reported in cattle, swine, dogs, chicken, mice, llamas, kudu, sheep and goat (Jones *et al.*, 1997; Belknap and Dustan, 1990; Chittick *et al.*, 2002; Camara *et al.*, 2017; Edginton *et al.*, 2014) [7]. The condition has been recorded most frequently in cattle, mainly calves (Baker and Ward, 1985) [2]. Ichthyosis fetalis is a genetic disorder in animals which is similar to Harlequin ichthyosis in humans. It is an autosomal recessive genetic disorder, caused due to a mutation in the gene ABCA12 which is also the cause for Harlequin ichthyosis in humans. Congenital ichthyosis is a rare disease involving the hair loss and presence of horny plates in the epidermis, covering the entire surface of the skin. It includes keratinization disorders in the skin and changes in lipid metabolism. It is exhibited by skin fissures deeply penetrating the skin and creating ulcers. Seborrhea is also seen in the area, and the skin loses its flexibility (Moghaddam *et al.*, 2021) [12].

In human medicine, “ichthyosis” is used for both hereditary and acquired conditions. “Inherited ichthyosis” is the term used for Mendelian disorders of cornification (MeDOC). For classification of various ichthyotic diseases in humans one can refer to the seminal paper written by Oji *et al.* (2009) [15]. In animals there is no such classification system as of now and two congenital forms of ichthyosis are recognized in cattle (Scott, 1988; Mauldin *et al.*, 2016; Gentile and Testoni, 2006; Raoofi *et al.*, 2001; Molteni *et al.*, 2006; Cho *et al.*, 2007) [18, 11, 19, 8, 17, 13, 6]. The most severe form is ichthyosis fetalis (IF), also known as bovine Harlequin fetus or Harlequin-like ichthyosis (OMIA 002238-9913) has been reported in Chianina, Holstein Friesian, brown Swiss, Norwegian red poll, Belgian white and red, HanWoo, Scottish Highland and Shorthorn cattle (Scott, 1988; Mauldin and Peters-Kennedy, 2016; Gentile and Testoni, 2006; Molteni *et al.*, 2006; Cho *et al.*, 2007; Radostits *et al.*, 2007; Woolley *et al.*, 2019) [18, 11, 19, 8, 13, 6, 16, 22]. This form is incompatible with life and affected calves either are dead at birth or die within a few days. The skin is thick and scaly, and is divided into plates by deep fissures. The tight, inelastic skin can be everted at the mucocutaneous junctions, especially the lips (eclabium) and eyes (ectropion) (Scott, 1988; Mauldin and Peters-Kennedy, 2016; Gentile and Testoni, 2006; Raoofi *et al.*, 2001; Molteni *et al.*, 2006; Cho *et al.*, 2007)

[18, 11, 19, 8, 17, 13, 6]. Ichthyosis congenita (IC) is a milder clinical form with hyper-keratosis and hypotrichosis, reported in Jersey, Pinzgauer, Holstein–Friesian and Chianina breeds (Scott, 1988; Mauldin and Peters-Kennedy, 2016; Raoofi *et al.*, 2001; Molteni *et al.*, 2006; Radostits *et al.*, 2007; Moghaddam *et al.*, 2021) [11, 17, 13, 12, 16]. The form of ichthyosis described for the goat was likely IC (Edginton *et al.*, 2014) [18, 7].

### Genetic basis of ichthyosiform disorders in animals: review of literature

Ichthyotic diseases in humans are associated with variants in at least 50 genes encoding structural proteins and enzymes affecting several cellular functions which include DNA repair, lipid biosynthesis, adhesion, desquamation and other pathways. Various forms of non-syndromic, mostly inherited forms of ichthyosis have been identified in domestic animals. In older reports, the diagnosis was based only on the clinical and/or histopathological findings (Baker and Ward, 1985; Julian, 1960; Raoofi *et al.*, 2001; Molteni *et al.*, 2006; Cho *et al.*, 2007; Testoni *et al.*, 2006) [2, 17, 13, 6, 19]. The underlying genetic causes for ichthyosis are mostly unknown in cattle, except for an ABCA12-related harlequin-like form (OMIA 002238-9913) and a homozygous frameshift 1 bp insertion in the FA2H gene associated with ichthyosis congenita. At present, the obvious genetic heterogeneity of inherited ichthyosiform disorders can be analyzed using whole-genome sequencing (WGS)-based precision diagnostics (Bourneuf *et al.*, 2017) [13].

Mitotic chromosomes were visualised with conventional staining and RBA-banding from non-synchronised cultures of peripheral blood lymphocytes of the affected calves and their relatives by Molteni *et al.* (2006) [13]. No abnormality was detected in either the structure or the number of chromosomes.

Molteni *et al.* (2006) [13] established genealogical relationship between affected progeny and sires which are assumed to be carriers of ichthyosis in Chianina cattle. The authors have also suggested that inbreeding may have contributed to the manifestation of the disease and they strongly suggest the presence of autosomal recessive transmission of the trait. In another investigation, by Testoni *et al.* (2006) [19], in two Chianina calves, one affected with ichthyosis fetalis and the other with ichthyosis congenita as per clinical examination and histopathology, authors strongly suspected an underlying genetic defect on the basis of common ancestor for two sires of affected calves. Further molecular investigation was not carried out owing to lack of scientific knowledge at that time.

The most severe form in cattle, ichthyosis fetalis has been mainly associated with mutations in the ATP binding cassette subfamily A member 12 (ABCA12) (Oji *et al.*, 2010; Thomas *et al.*, 2006) [15, 20]. Mutations within ABCA12 have been observed in humans, cattle and pig (OMIM 242500, OMIA 002193-9913 and OMIA 002188-9823, respectively) (Akiyama *et al.*, 2005; Kelsell *et al.*, 2005; Charlier *et al.*, 2008; Woolley *et al.*, 2019; Wang *et al.*, 2019) [1, 10, 5, 22, 21].

In a study by O'Rourke *et al.* (2017) [14] authors investigated a Polled Hereford calf and a Shorthorn calf affected with ichthyosis fetalis. In both the affected animals, hard white plaques on the skin with excessive keratinization were observed. Histopathological evaluation revealed severe diffuse epidermal and follicular orthokeratotic hyperkeratosis. The mutation (H1935R) in ABCA12 gene, which is shown to be responsible for ichthyosis fetalis in Chianina cattle, was

found to be absent in both affected calves and their parents. These molecular genetic findings suggest the existence of allelic heterogeneity for this condition in cattle.

Studied a purebred Scottish Highland calf with a condition similar to congenital ichthyosis. Based on clinical examination, post-mortem examination and histopathological evaluation, the authors confirmed the case as congenital ichthyosis. They performed whole-genome sequencing of the affected calf and compared the sequence data with the control genomes. Upon searching for private variants in known candidate genes for skin phenotypes including genes related with erosive and hyperkeratotic lesions, they found a single homozygous protein-changing variant, DSP: c.6893 C>A, or p.Ala2298Asp. The prediction is that the variant is responsible to change a highly conserved residue in the C-terminal plakin domain of the desmoplakin protein, which one of the prominent intracellular components of desmosomes and important intercellular adhesion molecules in various tissues including epidermis. Using Sanger sequencing it was confirmed that the variant was homozygous in the affected calf and heterozygous in both parents. Additionally, upon genotyping of 257 Scottish Highland cattle from Switzerland, they found estimated allele frequency of 1.2% and the mutant allele was found to be absent in more than 4800 control animals belonging to different cattle breeds.

In a similar study by Woolley *et al.* (2019) [22] a Shorthorn calf with ichthyosis fetalis was investigated and a possible causal missense mutation in the ABCA12 gene (NM\_001191294.2:c.6776T>C) located on chromosome 2 was identified by WGS. Mutations in the ABCA12 gene are known to cause ichthyosis fetalis in cattle and Harlequin ichthyosis in humans. By using Sanger sequencing, authors confirmed that the variant was homozygous in the affected calf and heterozygous in the dam. Further 130 Shorthorn animals from the same herd were genotyped and the estimated gene frequency was found to be 3.8%.

In a study to identify the genetic etiology of a syndromic form of ichthyosis congenita observed in Italian Chianina cattle, nine affected cattle with congenital xerosis, hyperkeratosis and scaling of the skin as well as urolithiasis and cystitis associated with retarded growth were examined. Using homozygosity mapping and whole-genome sequencing, authors identified a homozygous frameshift 1 bp insertion in the FA2H gene (c.9dupC; p.Ala4ArgfsTer142) located in a 1.92 Mb shared identical-by-descent region on chromosome 18. It was present in all cases and the parents were found to be heterozygous as per expectation as obligate carriers. Estimated allelic frequency in Italian Chianina top sires was found to be around 7.5%. The findings of this study enable the selection against this sub-lethal allele (Jacinto *et al.*, 2021).

### Conclusions

Rare diseases in animals are generally not well diagnosed. Ichthyosiform diseases in animals cause economic losses and welfare issues. The presented findings in the above studies enable genetic testing for breeding and diagnostics. Molecular or genetic testing if available must be used to screen the breeding individuals especially sires for carrier state of the disease to avoid unintentional occurrence of the ichthyosis affected animals. More studies must be taken up to identify other allelic variants and to identify breed or population specific variants.

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