

# Clinical, histopathological and genetic data of ichthyosis in the golden retriever: a prospective study

**OBJECTIVES:** We described epidemiological, clinical, histopathological and ultrastructural features of ichthyosis in the golden retriever breed in a prospective study. We also investigated the mode of transmission of this disease.

**MATERIALS AND METHODS:** We examined 150 golden retrievers, 73 of which were affected by ichthyosis (35 males and 38 females). We carried out detailed clinical and histopathological examinations for 40 affected dogs. Transmission electron microscopy was performed for two of them. We used pedigree analysis with the Cyrillic software to determine the mode of transmission.

**RESULTS:** Dermatological signs included a mild to moderate or severe generalised scaling with initially small to large whitish scales and progressively blackish scales. The ventral glabrous skin was hyperpigmented and rough, similar to sandpaper. Histopathological features were characterised by moderate to severe laminated or compact orthokeratotic epidermal hyperkeratosis without significant involvement of the stratum granulosum. Ultrastructural findings revealed laminated or compact keratin layers and numerous persistent corneodesmosomes within the stratum corneum. Analysis of the pedigree suggested an autosomal recessive inheritance.

**CONCLUSION:** The histopathological and ultrastructural characteristics strongly suggest that golden retriever ichthyosis is a retention ichthyosis, caused by absence of corneodesmosomal degradation, transmitted through an autosomal recessive mode.

## INTRODUCTION

Cornification disorders form a heterogeneous group of diseases characterised by abnormal differentiation (cornification) of the epidermis. The ichthyoses, a member of this group, are distinguishable clinically by generalised scaling and histopathologically, in most cases, by a thickened stratum corneum. In human beings, the ichthyoses themselves constitute a heterogeneous group of disorders, with both inherited and acquired forms (Digiiovanna 2003). Ichthyoses were initially classified based on differences in epidermal turnover rate. These cornification defects were thereby characterised as either epidermal hyperproliferation disorders or prolonged retention of the stratum corneum disorders (Frost and Van Scott 1966, Frost 1973). More recently, a new classification system, based on the underlying genetic and molecular mechanisms of these disorders, was proposed (Bale and Digiiovanna 1997).

In veterinary medicine, ichthyosis is now commonly classified into either epidermolytic or non-epidermolytic subtypes (Gross and others 2005). Most reported cases in dogs are non-epidermolytic with heterogeneous clinical, histopathological and ultrastructural profiles (Scott and others 2001, Gross and others 2005). Epidermolytic ichthyoses have been found in Norfolk terriers and are associated to a defect in keratin 10 because of a splice site mutation (Credille and others 2005). Recently, ichthyosiform dermatitis was reported in golden retrievers (Cochet-Faivre and others 2007, Guaguère and others 2007, Mauldin and others 2007, 2008, Cadiergues and others 2008).

In dogs, the breed specificity of most hereditary diseases is because of the small numbers of founders and the breeding practices, in particular the popular sire effect and high levels of consanguinity. The high incidence of hereditary diseases in some breeds causes considerable concern for breeders and veterinary medicine. However, at the same time, it represents, an unique opportunity to elucidate the molecular and genetic

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mechanisms underlying hereditary diseases in these breeds, providing spontaneous models of the homologous human diseases. Ichthyosis in the golden retriever breed has the characteristics of a hereditary breed-specific disease: a high and increasing incidence within the breed, a familial transmission mode and specific clinical and histopathological features.

In this prospective study, we obtain detailed epidemiological, clinical, histopathological and ultrastructural data for ichthyosis in golden retrievers and undertake a genetic study of a family of 108 dogs.

## MATERIALS AND METHODS

We examined 150 affected and unaffected golden retrievers, 40 dogs diagnosed with ichthyosis were analysed in detail between January 2003 and September 2007 at two dermatological referral centres (Clinique Vétérinaire Saint-Bernard, Lomme, France and Clinique Vétérinaire, Cesson-Sévigné, France).

Diagnosis was confirmed based on clinical examination and histopathological examination of lesional skin biopsies. Epidemiological and clinical data (lesional distribution, cutaneous lesions, pruritus, otitis externa, concurrent bacterial or *Malassezia* infections) were collected by means of a questionnaire for each affected dog.

Punch biopsy skin specimens of 6 or 8 mm were collected from the affected ventral and dorsal areas of each dog in our series. Specimens were fixed in 10 per cent formaldehyde; wax sections were stained with haematoxylin and eosin and periodic acid-Schiff (PAS) for routine histopathological analysis.

Transmission electron microscopy of lesional skin biopsies were performed for two affected dogs and one control dog. Skin biopsies were fixed in 2.5 per cent glutaraldehyde in 0.1M cacodylate buffer at pH 7.3 and postfixed in 1 per cent osmium tetroxide in demineralised water. Samples were embedded in 2 per cent agar, cut into small pieces, block stained in 2 per cent uranyl acetate in aqua dest, dehydrated and embedded in Epon/Spurr (50/50).

Acetate tape preparations (Scotch tests) were performed for all dogs on the ventrum and rump (after clipping) and stained with a Diff Quik staining.

A three-generation pedigree was constructed using Cyrillic software v2.1 for data management and pedigree construction. This software can manage genetic data from highly inbred families, with frequent marriage loops.

## RESULTS

### Epidemiological data

Of the 150 dogs clinically examined, 73 were affected by ichthyosis; no sex bias was observed (35 males and 38 females). The age at the onset of clinical signs differed between three weeks and three years. Of the 40 dogs examined in detail (19 males and 21 females), 34 dogs (85 per cent in total) developed lesions before one year of age. The age at diagnosis differed between four weeks and eight years. Sixteen dogs belonging to three different litters (five from the first litter of nine puppies, three from the second litter of 10 and eight from the third litter of 11) were affected by ichthyosis. Some breeders detected the disease in their puppies as early as three to six weeks of age. The most common complaint was whitish or blackish scaling on the trunk (29 dogs), a dry haircoat (14 dogs) or severe hypermelanosis associated with rough and hyperpigmented skin on the ventrum (18 dogs).

### Clinical findings

General physical examination of the 40 dogs revealed no abnormalities. Dermatological

signs were typical of disease. They included a mild (eight dogs) to moderate (16 dogs) or severe generalised scaling (16 dogs). This scaling was characterised initially by small (pityriasiform) to large (psoriasiform) whitish scales, in 29 dogs and 34 dogs, respectively (Fig 1). Pityriasiform scaling (without psoriasiform scaling) was observed in only 12 cases less than eight months of age. Thirty-five dogs had greyish or blackish scaling (Figs 2 and 3). The owners and breeders indicated that these dark scales appeared rapidly, two to three months after the onset of the first clinical signs. Large ichthyosiform scales were observed in eight dogs. These scales were distributed over most areas of the body in all dogs in our series: the lateral and ventral regions of the neck, trunk, rump, dorsum and ventrum folds (inguinal areas). These scales were adherent on the skin and had a paving-stone appearance (ichthyosiform) (Fig 4), particularly visible in the lateral areas of the trunk after clipping. Lesions were noted on the face and thighs of only two and four dogs, respectively. Only one dog had lesions on the paw pad (thick, dry keratinous proliferations and fissures). None of the dogs studied had lesions in the nasal area. The ventral glabrous skin had a typical appearance, dark (hyperpigmented) and rough like sandpaper (Fig 5). These features could be detected by breeders in puppies aged between three and six weeks. They could therefore be considered as an early cutaneous sign, often visible before the occurrence of the scaling. Pruritus



FIG 1. Severe generalised scaling characterised by small to large whitish scales





FIG 2. Generalised blackish scaling over the trunk

was absent (34 dogs) or minimal (six dogs). A mild ceruminous bilateral otitis externa was observed in six dogs. Bacterial overgrowth or superficial pyoderma (epidermal collarettes, papules or rare pustules) was reported in four dogs (aged four, five, six and eight years). *Malassezia* overgrowth was demonstrated in one dog (aged eight years). No dogs exhibited clinical signs suggestive of atopic dermatitis.

### Histopathological features

We detected laminated or compact orthokeratotic epidermal hyperkeratosis composed of many keratin layers, ranging from moderate (12 of 40) to severe (28 of 40) (Fig 6). The epidermis was hyperacanthotic in a few cases (six of 40). No

or very mild involvement of the granular cell layer (37 of 40) was reported; keratohyalin granules were normal in size and number for these dogs. Diffuse epidermal melanin pigmentation was found in 37 of 40 dogs; the degree of this melanin pigmentation was mild (four of 40), moderate (three of 40) or severe (30 of 40). The epidermis seemed to have a pleated appearance in many cases (33 of 50) (Fig 7). Keratinocytes from the basal and spinous layers seemed to form agglutinated cell masses (Fig 8). Isolated vacuolated keratinocytes were regularly visible in the stratum granulosum (Fig 8). Regular pleats also appeared in the basement membrane when stained with PAS for 25 dogs (Fig 9). Bacterial colonies and *Malassezia* yeasts were

detected within the superficial layers of the stratum corneum in two of the 40 dogs.

Follicular units were not distended by keratin in 36 dogs and hair shafts remained normal. However, abnormal keratin forming a bridge-like structure of hair follicle ostia was frequently observed (Fig 10). Follicular dysplasia was not found in any dogs. No glandular (sebaceous and sweat glands) abnormalities were detected. Dermal lesions were minimal but were characterised by a discrete lymphoplasmacytic infiltration in some cases (five of 40).

### Transmission electron microscopic features

Ultrastructural studies demonstrated laminated or compact keratin layers associated with numerous persistent corneodesmosomes, normal in size, within the stratum corneum (Fig 11). The persistence of these corneodesmosomes may be caused by absence of their degradation and thus severe disruption of the desquamation process. Melanin granules (melanosomes) were found throughout the epidermis, suggesting an absence of degradation and elimination of the melanosomes with normal desquamation. We did not detect any abnormalities of the keratohyalin granules or tonofilaments. We did not observe structural abnormalities in the cornified envelope. Lipidic vacuoles were frequently identified within the stratum corneum. Finally, some small vacuoles were present in the scattered clear keratinocytes from the spinous layer.

### Cytology

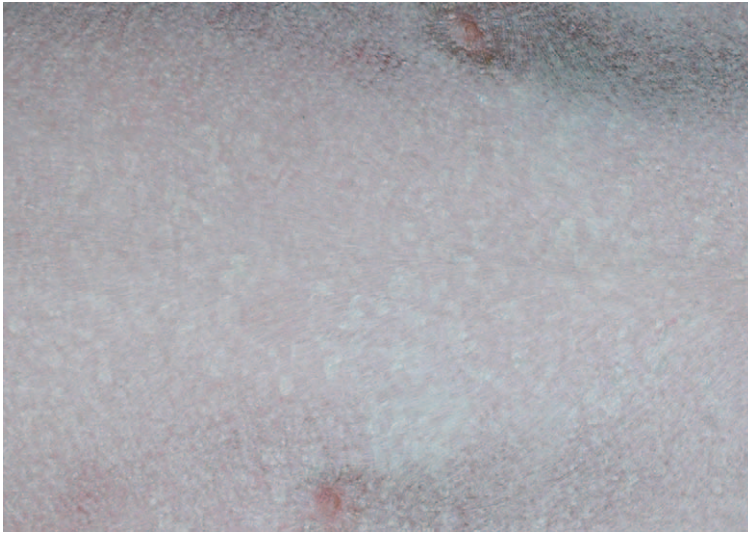
Using acetate tape preparations, we detected cocci in only four dogs and *Malassezia* yeasts in only one. Pigmented scales (with melanin granules) were systematically observed.

### Pedigree analysis

Cases and controls were firstly collected, as well as related dogs, to investigate the mode of transmission of the disease. Among these 150 dogs, 73 were affected (35 males and 38 females). Golden retrievers were recruited from France and Belgium, with no geographical bias suspected in the sampling. One pedigree of 108 individuals was constructed from the genealogical data of each dog (Fig 12). Careful analysis of this



FIG 3. Large blackish scales adherent on the skin



**FIG 4. Adherent whitish scales on the skin with a paving-stone appearance**

family showed no sex differences and demonstrated an autosomal mode of inheritance: one mating between affected dogs produced only affected puppies; and four matings between healthy dogs all produced at least one affected puppy. These observations are consistent with an autosomal recessive mode of transmission.

## DISCUSSION

Ichthyosis is a hereditary, monogenic, cornification disorder, appearing early and persisting for life (Digiovanna 2003, Hohl 2004). In human beings, the heterogeneity of the clinical, pathogenic and molecular abnormalities observed in these diseases



**FIG 5. The ventral glabrous skin has a typical appearance, dark (hyperpigmented) and rough like sandpaper**

has prompted classification of the various forms of the disorder (Frost and Van Scott 1966, Frost 1973, Bale and Digiovanna 1997): congenital ichthyosis (first lesions diagnosed at birth) and ichthyosis vulgaris (first lesions diagnosed in the first years of life); isolated ichthyosis (only skin lesions) and complete ichthyosis (association with visceral lesions); autosomal recessive or X-linked, depending on the genetic transmission of the defect; epidermolytic or non-epidermolytic ichthyosis, depending on the histopathological abnormalities; and, more recently, a classification system depending on the molecular mechanism responsible for the lesions was proposed (transglutaminase deficiency, steroid-sulphatase mutation, etc.) (Digiovanna 2003, Hohl 2004).

Very little veterinary dermatological information is available on these diseases. Most studies have been case reports or have involved series of limited size. Breeds at risk are cavalier King Charles spaniels (Alhaidari and others 1994, Barnett 2006), Norfolk terriers (Barnhart and others 2004, Credille and others 2005), Jack Russell terriers (Lewis and others 1998) and soft-coated wheaten terriers (Helman and others 1997), but many other breeds can be affected (Scott and others 2001, Gross and others 2005).

In dogs, ichthyoses have long been considered as a single disease. However, similarly to human beings, they comprise different dermatoses caused by different genetic defects of the cornification process (Digiovanna 2003, Hohl 2004). The clinical characteristics (in particular the type of squamosis), prognostic criteria and histology (Gross and others 2005) are also highly variable. Some of these diseases may serve as good models for human hereditary skin diseases (Credille and others 2005).

Ichthyosis subtypes in dogs have thus not been extensively classified. One previous study classified this disease based on the histopathological morphology of the lesions, distinguishing between epidermolytic and non-epidermolytic ichthyosis (Credille and others 1998). Epidermolytic ichthyosis is characterised by hydropic degeneration of keratinocytes (Gross and others 2005). Further classification differentiating hyperproliferative ichthyoses from retention ichthyoses may be helpful.



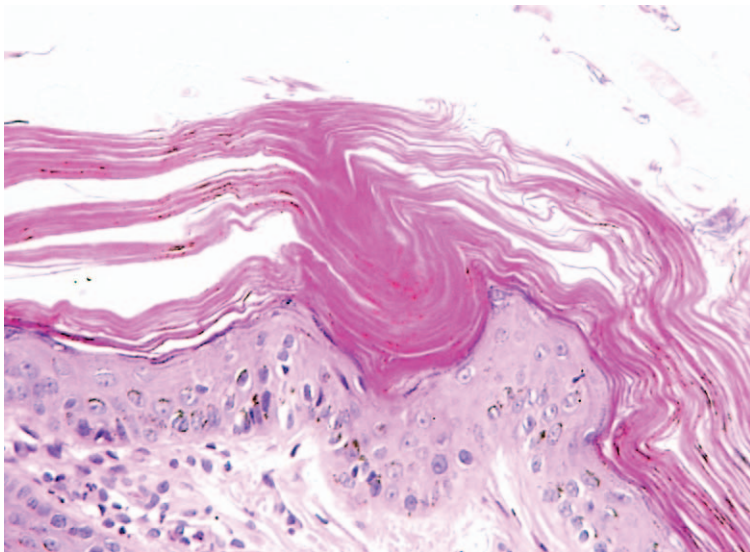


FIG 6. Severe laminated or compact orthokeratotic epidermal hyperkeratosis (H&E  $\times 250$ )

Retention ichthyoses are distinguished by the absence of desquamation or hyperproliferation of epidermal cells.

The molecular characteristics of ichthyoses are beginning to be elucidated (Credille and others 2001, Barnhart and others 2004, Credille and others 2005). Ichthyosis in Norfolk terriers is epidermolytic and associated to a defect in keratin 10 because of a splice site mutation (Barnhart and others 2004, Credille and others 2005); this type of ichthyosis may also exist in other breeds, such as cavalier King Charles spaniels, despite ultrastructural features of the disease in this particular breed being similar to the human

form, ichthyosis hystrix of Curth and Macklin (Alhaidari and others 1994). Certain breeds, such as crossed Labradors (Mecklenburg and others 2000) or Rhodesian ridgebacks, may be associated with sporadic cases of epidermolytic ichthyosis (Hargis, A. M., unpublished observations cited by Gross and others 2005).

Non-epidermolytic ichthyoses are more frequent. They have similar clinical characteristics to the human lamellar ichthyosis, caused by a defect in transglutaminase 1 (TGM1), an enzyme involved in the formation of the corneous envelope in the stratum corneum. A decreased quantity and activity of TGM1 and a diminished corneous enve-

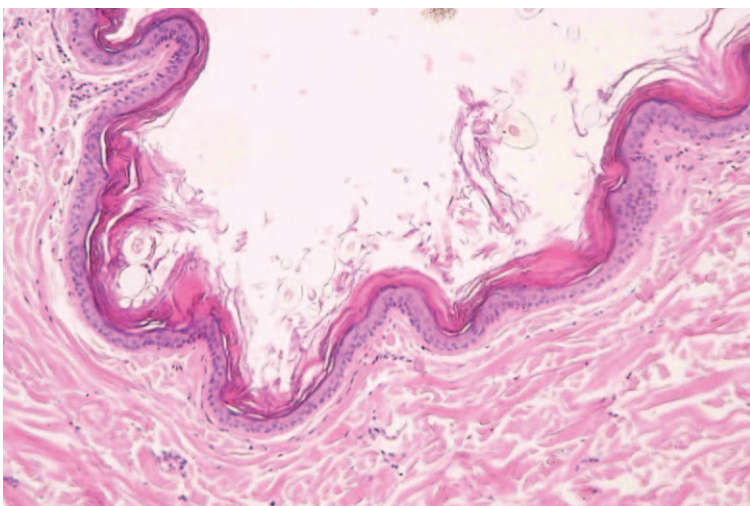


FIG 7. Pleated appearance of the epidermis (H&E  $\times 100$ )

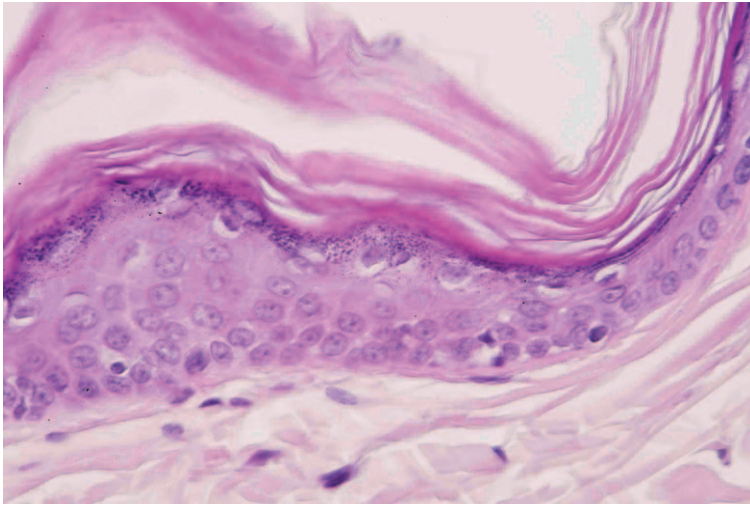
lope have been recently reported in Jack Russell terriers (Credille and others 2001, Gross and others 2005). However, the term lamellar ichthyosis is often wrongly used, based solely on the clinical and histopathological features of the skin lesions, rather than demonstrating reduced TGM1 levels and activity.

Non-epidermolytic ichthyosis has been identified in several breeds, including golden retrievers (Cochet-Faivre and others 2007, Guaguère and others 2007, Mauldin and others 2007, Cadiergues and others 2008), Jack Russell terriers (Lewis and others 1998) and American bulldogs. These breeds may be at risk. Other sporadic cases have been reported in the soft-coated wheaten terrier (Helman and others 1997), American Staffordshire terrier (Scott 1989), dobermann (Muller 1976), Rottweiler (Guaguère, E., unpublished observations), collie (Guaguère 1988), Australian terrier (August and others 1988), Manchester terrier, Boston terrier, West Highland white terrier and crossed breeds cited by Scott and others (2001).

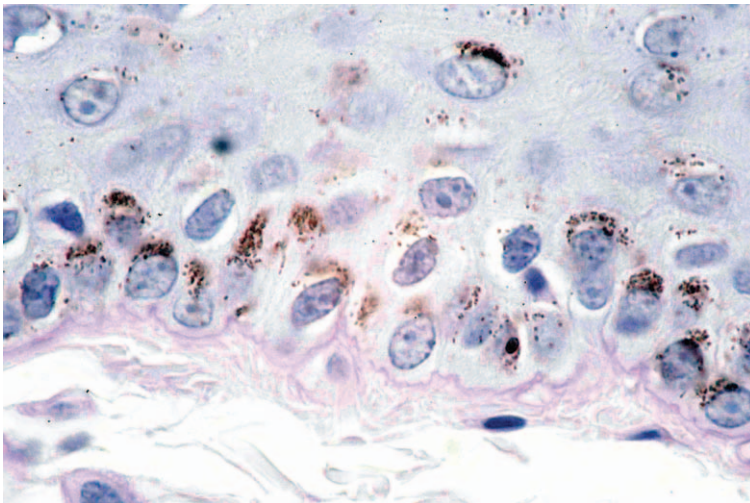
Age at the onset of first signs is variable depending on the breed affected. Very young golden retrievers may be diagnosed with the disease as early as three weeks of age. However, this seems to vary between three weeks and up to three years. In this study, 85 per cent of cases are detected before one year of age. It is likely that an improved understanding of this disease will enable earlier diagnosis in the future.

Some breeds at risk for ichthyosis, notably golden retrievers, are also predisposed to atopic dermatitis. Thus, a defect in filaggrin may be linked with atopic disease in these dogs, as recently demonstrated in human beings (Palmer and others 2006, Morar and others 2007, Weidinger and others 2007). However, the dogs included in our case series did not demonstrate signs of atopic dermatitis.

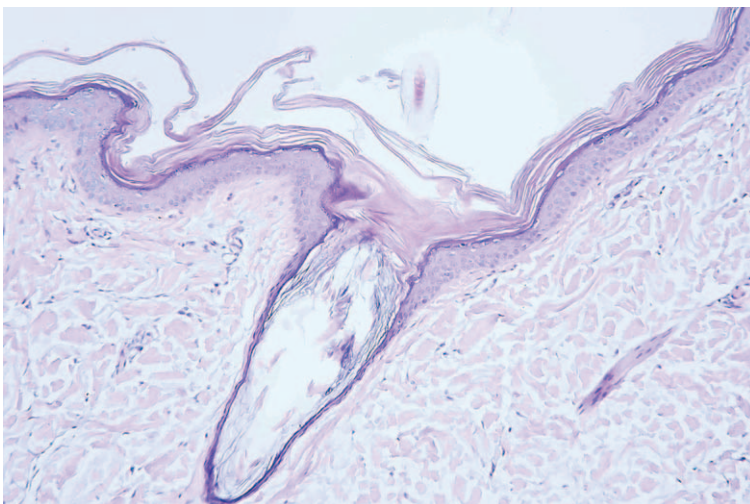
Clinical signs of ichthyosis depend on the type of the cornification defect and on the breed. This dermatosis has a very typical appearance in golden retrievers: white or grey scales, pityriasisiform, psoriasisiform or ichthyosiform, on the body surface, not including the head and the extremities. Clipping the hair allows visualisation of large adherent, fine, polygonal scales (Guaguère and others 2007, Mauldin



**FIG 8.** Keratinocytes from the basal and spinous layers seemed to form agglutinated cell masses. Isolated vacuolated keratinocytes are regularly visible in the stratum granulosum (H&E  $\times 250$ )



**FIG 9.** Regular pleated in the basement membrane like a garland (periodic acid-Schiff  $\times 400$ )



**FIG 10.** Abnormal keratin forming a bridge-like structure of hair follicle ostia (H&E  $\times 100$ )

and others 2007). These scales become pigmented and give the hair and skin a “dirty” appearance after a few weeks to months. This pigmentation may be linked to decreased degradation of melanosomes between melanocytes and keratinocytes, possibly because of the absence of desquamation. Glabrous areas of the skin (abdomen) are pigmented and rough, with a typical sandpaper-like appearance. These lesions have a similar appearance to those observed in human ichthyosis vulgaris and lamellar ichthyosis (Digiovanna 2003, Hohl 2004).

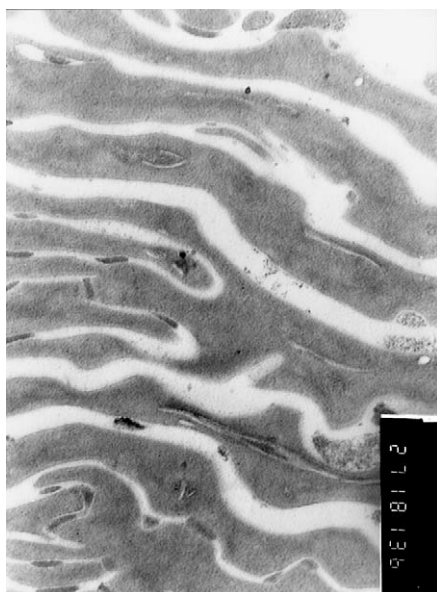
Foot pads were rarely affected (only one of 40 dogs in our study) and the nasal planum was not affected in any of the dogs. By contrast, in other types of ichthyosis, such as those found in cavalier King Charles spaniels (Alhaidari and others 1994, Barnett 2006), Jack Russell terriers (Lewis and others 1998) or a crossed Labrador retriever (Mecklenburg and others 2000), the nasal planum is frequently affected. Pruritus was absent or very mild in nearly all cases described in our study. Bacterial or yeast overgrowth also seemed to be rare.

These clinical phenotypes of golden retriever ichthyosis are relatively straightforward and are notably different from other cutaneous lesions described in other breeds suffering from cornification defects. In our study, we did not observe any hair shaft abnormalities. This is in contrast to certain ichthyosiform syndromes in human beings (Digiovanna 2003, Hohl 2004) and in cavalier King Charles spaniels (Barnett 2006, Guaguère, E., personal observations), in which woolly and curly hairs are frequently observed.

Similarly, we did not detect any general abnormalities (teeth malpositioning, delay of growth and bilateral keratoconjunctivitis sicca) frequently seen in certain forms of human and cavalier King Charles spaniel ichthyosis (Barnett 2006, Guaguère, E., personal observations).

Histopathological lesions observed in golden retrievers are very typical. The absence of vacuolisation or lysis of epidermal cells is not consistent with epidermolytic ichthyosis (Barnhart and others 2004, Credille and others 2005). The granular layer is normal or slightly thickened. Keratohyalin granules are normal in shape, size and number, in contrast to those seen in

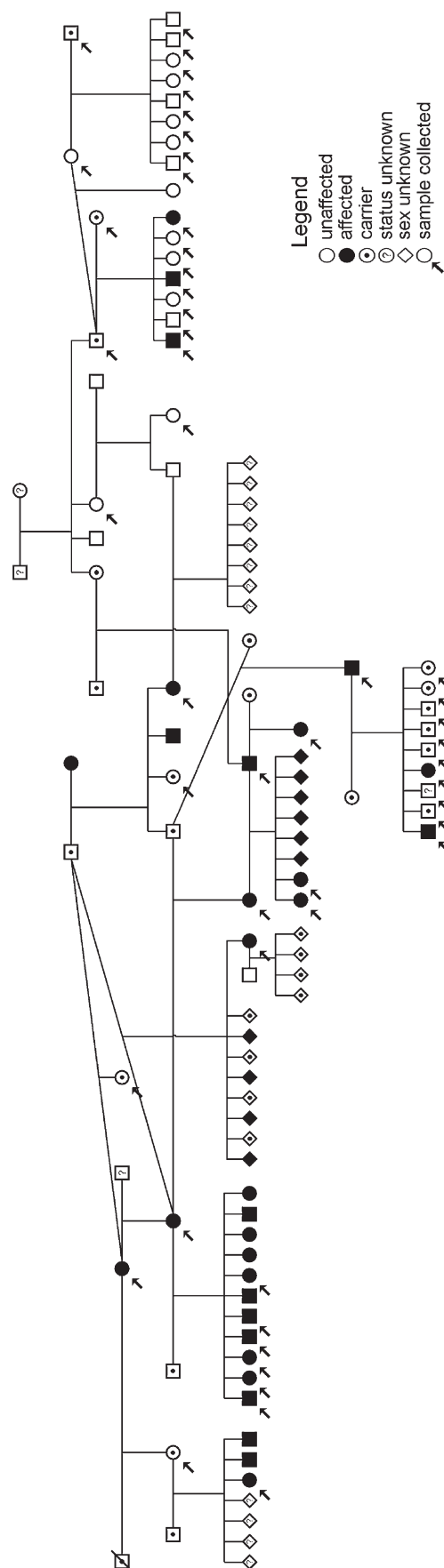




**FIG 11. Stratum corneum (ichthyotic golden retriever): persistence of numerous corneodesmosomes, normal in size within the stratum corneum**

some other types of ichthyoses (Gross and others 2005).

In our study, epidermal acanthosis was mild or absent. The significance of scattered vacuolated single keratinocytes in the spinous and granular layers is unclear. This lesion is maybe artefactual and is regularly noted by one of the authors (F. D.-R.) in dogs with severe epidermal hyperkeratosis. Keratinocytes were “agglutinated”. We observed rete ridges of the epidermis, without depolarisation of keratinocytes and with a “pleated” appearance, resembling that of a garland. The basal membrane was also undulated. The regular pleating of the epidermis explains the rough appearance of the skin. Marked melanic pigmentation was also frequently observed. We also observed laminated or compact orthokeratotic hyperkeratosis in all cases. These histopathological lesions were suggestive of retention ichthyosis, associated with the absence of desquamation. However, the hair follicles were not hyperkeratotic in contrast to other forms of ichthyosis (Gross and others 2005). Bridge-like structures formed by abnormal compact keratin were frequently detected in hair follicle ostia. Very similar histopathological findings were described in a recent study (Cadiergues and others 2008), even if some lesions were not reported: sometimes laminated orthokeratotic hyperkeratosis,



**FIG 12. Ichthyosis segregating in the golden retriever pedigree, constructed by the Cyrillic 2.1 software. A total of 108 dogs are represented; 49 had samples taken for further analysis, 20 of which were from affected dogs (12 females and eight males)**

**Table 1. Genetic, clinical and histopathological comparison between golden retriever ichthyosis and human vulgaris ichthyosis and lamellar ichthyosis**

	Golden retriever ichthyosis	Ichthyosis vulgaris	Lamellar ichthyosis
Mode of inheritance	Autosomal recessive	Autosomal dominant	Frequent autosomal recessive forms; Rare autosomal dominant
Age at the onset of clinical signs	Three weeks (generally before one year of age)	First or second year of age	Congenital (often collodion baby)
Associated clinical signs	None; no apparent predisposition for atopic dermatitis	Atopic dermatitis (35%)	Ectropion
Cutaneous signs	Large, polygonal, whitish to blackish scales, adherent on the skin and having a paving-stone appearance, Paw pad unaffected	Fine scales, affected palms	Large, lamellar and brownish scales
Type of ichthyosis	Retention ichthyosis	Retention ichthyosis	Hyperproliferative ichthyosis

bridge-like structures in follicular ostia, pleated epidermis, agglutinated keratinocytes and garland-like basal membrane. However, we have not noticed a marked hyper eosinophilic keratin in contrast to Cadiergues and others.

Electron microscopy of skin lesions can also be used to characterise ichthyosis subtype. Among non-epidermolytic cases in dogs, lamellar bodies may be numerous with irregular tonofilaments (Lewis and others 1998), or curvilinear structures may be observed (Credille and others 1998). In epidermolytic ichthyoses, cytolysis and fewer tonofilaments (Credille and others 2005) with aggregation at the periphery of nucleus, are observed (Mecklenburg and others 2000). In our study, we carried out ultrastructural studies for only two cases. Electron microscopy showed the persistence of numerous, but phenotypically normal, corneodesmosomes. This observation is also consistent with diagnosis of retention hyperkeratosis in these dogs.

The analysis of our series suggests that this autosomal form of ichthyosis may have appeared recently in golden retrievers. However, the repeated use of carrier, or even affected, champion sires and dams, is likely to have caused the disease to spread extremely rapidly in this breed. The identification of a potential causative gene will allow future development of a predictive genetic test. The sex ratio is not indicative of X-linked ichthyosis, in which males would be clearly over-represented. Little is known about the genetics of ichthyosis in dogs. A recessive autosomal mode of transmission has been demonstrated ex-

clusively in Jack Russell terriers (Lewis and others 1998) and Norfolk terriers (Barnhart and others 2004).

We are now continuing to collect samples, with a view to carrying out a candidate gene approach: microsatellites linked to human candidate genes will be genotyped on affected and unaffected members of the family, to screen for potential linkage. If none of the human candidate genes analysed is linked to ichthyosis in the golden retriever breed, a whole genome case-control genetic analysis using the recently available canine 27,000 single nucleotide polymorphism chips will be performed on a larger collection of cases and control dogs.

### Conclusion

This prospective study, based on 150 examined dogs, involving the detailed analysis of 40 golden retrievers with ichthyosis, confirms that this primary cornification disorder is non-epidermolytic. It is associated with retention and displays an absence of, or delay in, desquamation, which may be caused by a lack of degradation of corneodesmosomes. Yet, the definitive classification of the disease in Bale's new system (Bale and Digiovanna 1997) would require molecular elements, which could be provided by genetic studies. Analysis of the pedigree presented here strongly suggests that transmission of this disease is autosomal recessive. Further genetic studies focused on this pedigree, and using a homozygosity mapping approach, are underway to identify the gene involved. As presented in Table 1, it seems obvious that ichthyosis in golden retriever shares clinical and histopathological features with human ichthyosis vulgaris

and lamellar ichthyosis, but differences exist. These discrepancies in clinical features do not exclude the possibility that these disorders have molecular homology, given that mutations of the same gene can lead to different phenotypes. For example, mutations of the human gene *ABCA12* can cause either type 2 lamellar ichthyosis or harlequin ichthyosis (Lefevre and others 2003, Kelsell and others 2005). The recessive mode of inheritance observed for ichthyosis in golden retrievers, together with the improvement of lesions with food rich in unsaturated lipids noticed by some breeders (personal observation), suggest a likely homology with the human lamellar forms of ichthyosis. Overall, these findings suggest that the gene causing this disease in golden retrievers may be involved in lipid metabolism and may belong to the leucotriene branch of the arachidonic acid pathway.

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