



Review

Inheritance of Monogenic Hereditary Skin Disease and Related Canine Breeds

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Simple Summary: The high prevalence of genetic diseases in dog breeds and the structure of their populations has led to detailed studies of the canine genome, which are important for understanding the origin of these pathologies. The location of certain genes involved in a few autosomal recessive monogenic diseases, including genodermatosis. The most prevalent canine genodermatosis are non-epidermolytic ichthyosis, epidermolytic ichthyosis, and junctional epidermolysis bullosa. Other genodermatoses are nasal paraqueratosis, cutaneous mucinosis, dermoid sinus, lethal acrodermatitis, palmoplantar hyperkeratosis, or exfoliative cutaneous lupus erythematosus. Most of this genodermatosis is associated with a specific and known number of mutations, which have a higher prevalence in certain canine breeds. The main objective of this review is to analyze each of these genodermatoses, the genes and mutations associated with them, and the breeds with the greatest predisposition to suffer from them.

Abstract: The plasticity of the genome is an evolutionary factor in all animal species, including canines, but it can also be the origin of diseases caused by hereditary genetic mutation. Genetic changes, or mutations, that give rise to a pathology in most cases result from recessive alleles that are normally found with minority allelic frequency. The use of genetic improvement increases the consanguinity within canine breeds and, on many occasions, also increases the frequency of these recessive alleles, increasing the prevalence of these pathologies. This prevalence has been known for a long time, but mutations differ according to the canine breed. These genetic diseases, including skin diseases, or genodermatosis, which is narrowly defined as monogenic hereditary dermatosis. In this review, we focus on genodermatosis *sensu stricto*, i.e., monogenic, and hereditary dermatosis, in addition to the clinical features, diagnosis, pathogeny, and treatment. Specifically, this review analyzes epidermolytic and non-epidermolytic ichthyosis, junctional epidermolysis bullosa, nasal parakeratosis, mucinosis, dermoid sinus, among others, in canine breeds, such as Golden Retriever, German Pointer, Australian Shepherd, American Bulldog, Great Dane, Jack Russell Terrier, Labrador Retriever, Shar-Pei, and Rhodesian Ridgeback.

Keywords: skin disorders; genodermatosis; monogenic hereditary dermatosis; ichthyosis; epidermolysis; parakeratosis; mucinosis



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1. Introduction

During recent centuries, genetic pathologies in canine breeds have increased considerably, possibly because of a reduction in the effective number of individuals in canine populations due to genetic selection. Such a focus on morphological characteristics has limited the number of alleles, thereby increased consanguinity, and reduced genetic diversity. This has mainly occurred due to inadequate crossing practices, together with insufficient selective pressure on canine well-being and health characteristics [1]. In fact, the effective number of some canine breeds has been estimated at 30–70%, and inbred dogs

after two generations have ranged from 1 to 8%, depending on mating practices [2]. Genetic selection has focused on aesthetics rather than function or health, so a small number of breeders have been crossed with closed relatives, producing significantly reduced genetic diversity and increasing the prevalence of specific deleterious alleles [3–5]. Dermatological pathologies are no exception, and some have increased considerably in certain breeds. For these, it is important to distinguish genodermatosis (dermatoses of a monogenic origin) from polygenic dermatoses with racial predisposition, the latter being more frequent than others [6]. In this review, we focused strictly on genodermatosis, i.e., monogenic, and hereditary dermatosis.

The high prevalence of genetic diseases in dog breeds and the structure of their populations has led to detailed studies of the canine genome, which are important for understanding the origin of these pathologies. For this reason, it was possible to determine that the canine genome has about 2.42 gigabases (Gb) composed of 20,000 genes distributed on 78 chromosomes, 38 pairs of acrocentric autosomes, and a pair of sex chromosomes: the X chromosome, the largest karyotype with 128 megabases (Mb), and the Y chromosome with the smallest karyotype of 27 Mb [7]. Whole canine genome mapping, sequencing, and linkage analyses has made possible the highlighting of several disease-related sources. First, the high incidence of SINE (short interspersed nuclear element), which are repeated sequences associated with many diseases [8]; the frequent occurrence of SNPs (single nucleotide polymorphisms), which are variations of a single nucleotide in the genome [9], and the location of certain genes involved in several autosomal recessive monogenic diseases, including genodermatosis, have made it possible to reveal multiple causes of disease occurrence.

The canine genodermatosis are mainly non-epidermolytic ichthyosis in the Golden Retriever and the Jack Russell Terrier, epidermolytic ichthyosis in the Norfolk Terrier, junctional epidermolysis bullosa in the German Shorthaired Pointer, and Shar-Pei mucinosis, although other types of canine genodermatosis exist (Table 1).

Table 1. Genodermatosis with known causative genetic variants in dog breeds.

Phenotype	Breed	Inheritance ¹	Reference
Junctional epidermolysis bullosa	German Pointer, Australian Shepherd	AR	[10,11]
Epidermolysis bullosa dystrophic	Golden Retriever, Akita Inu	AR	[12,13]
Ichthyosis	American Bulldog, Great Dane, Jack Russell Terrier, Golden Retriever	AR	[14–18]
Nasal parakeratosis	Labrador Retriever	AR	[19]
Mucinosis	Shar-Pei	ASD	[20]
Dermoid sinus	Rhodesian Ridgeback	AR	[21]

¹ AR: autosomal recessive inheritance; ASD: autosomal semi-dominant inheritance.

Different genodermatosis has been correlated to canine breed, and the several genes seems to be the responsible for these diseases (Figure 1).

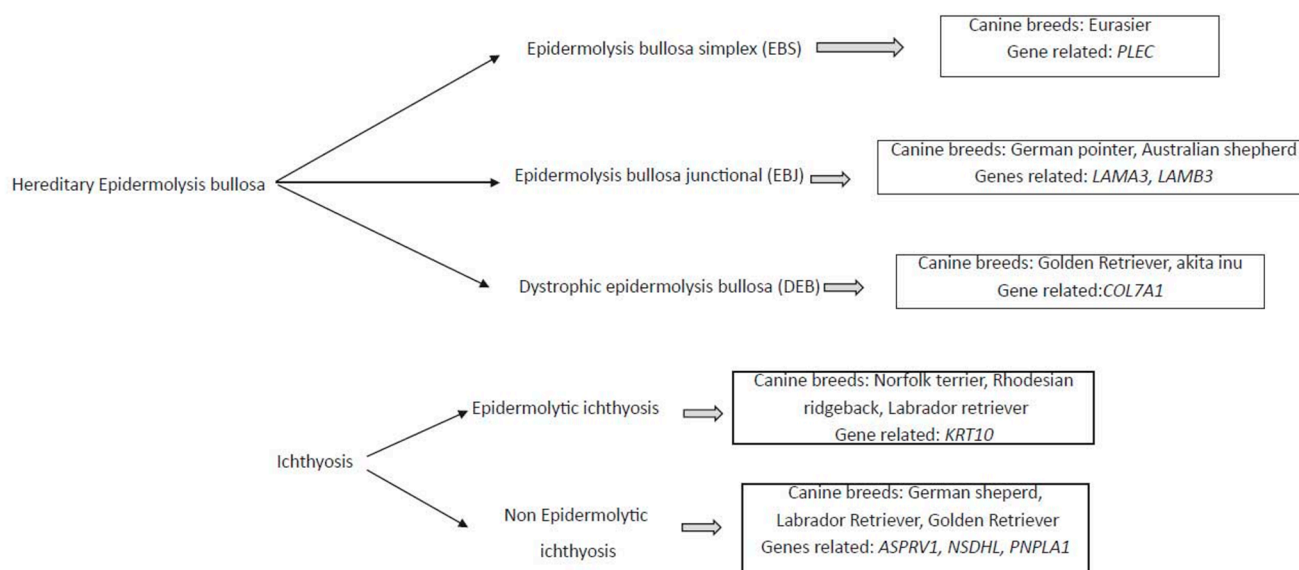


Figure 1. Diagram of mainly monogenic hereditary skin disease, the associated canine breed, and the related genes.

2. Hereditary Epidermolysis Bullosa

Hereditary epidermolysis bullosa constitutes a heterogeneous group of hereditary blistering diseases of the skin and mucous membranes [22,23]. These pathologies are characterized by the spontaneous development of vesicles, erosions, and ulcers because of minimal trauma to the excessively fragile dermal–epidermal junction (DEJ) [24]. This group of dermal diseases is classified according to the level of cleavage as epidermolysis bullosa simplex (EBS), epidermolysis bullosa junctional (EBJ), and dystrophic epidermolysis bullosa (DEB). Different dog breeds have been associated with each of these diseases and have presented different types of ulcers. Some genes with recessive autosomal inheritance have been associated with them (Table 2).

Table 2. Classification of canine epidermolysis, related ulcerations, and the associated genes and canine breeds.

Classification Epidermolysis	Dog Breeds	Type of Ulceration	Gene Associated	Reference
Epidermolysis bullosa simplex (EBS)	Eurasier dog	Multifocal ulcers	<i>PLEC</i>	[25]
Epidermolysis bullosa junctional (EBJ)	German Pointer, Australian Shepherd	Skin and mucous membrane ulcers	<i>LAMA3</i> , <i>LAMB3</i>	[10,11,26,27]
Dystrophic epidermolysis bullosa (DEB)	Golden Retriever, Akita Inu	Oral cavity ulcers	<i>COL7A1</i>	[12,13]

Epidermolysis bullosa simplex (EBS) is a skin disease, in which the keratinocytes or basal and suprabasal are related [25]. This disease is not unique to dogs, so different subtypes of EBS have also been observed in humans, and different genes play a role [28–36]. However, in dogs, only two genes have been associated with it. The mutation of the *PLEC* gene has been associated so far with EBS in Eurasier dogs [25]. The product of the *PLEC* gene is plectin, a 500 kDa protein found in skin and other tissues, such as bone, muscle, and the nervous system [37]. There are likely different isoforms of plectin that are cell-type dependent and/or developmentally regulated [38]. Mauldin et al. (2017) demonstrated that in dogs with a homozygous G-to-A variant in the *PLEC* gene, a tryptophan is converted to

a premature stop codon in exon 27, resulting in this disease with autosomal recessive inheritance [39]. On the other hand, Olivry et al. (2012) showed the association between a single mutation in the first intron of *PKP1* gene. This single mutation results in a premature stop codon, and the absence of the protein plakophilin-1, a protein that stabilizes desmosomes in the skin [40,41]. The inheritance of this mutation was also autosomal recessive, and this detection occurred in dog breed Chesapeake Bay Retriever, resulting in an ectodermal dysplasia-skin fragility syndrome [40].

In epidermolysis bullosa junctional (EBJ), cleft formation occurs through the lamina lucida of the basement membrane zone. Affected individuals exhibit blisters, deep erosions, and ulcers [22]. In humans, mutations in several genes have been associated with this pathology, including genes encoding subunits of integrins (*ITGA6*, *ITGB4*, and *ITGA3*), collagen (*COL17A1*), and laminin 332 (*LAMA3*, *LAMB3*, and *LAMC2*) [42,43]. Recently, mutations in the *LAMA3* and *LAMB3* genes have been associated with EBJ in Australian shepherd dogs [11,26]. In the study by Kiener et al. (2020), a *LAMB3*:c.1174T > C mutation was reported as the cause of EBJ, suggesting an autosomal recessive inheritance of this mutation [11]. The *LAMB3* gene encodes the $\beta 3$ -polypeptide chain of laminin-1 [44] and has been associated with the progression of several human tumors [45]. The recent study by Herrmann et al. (2021) reported a *LAMA3* mutation associated with EBJ and severe upper respiratory disease in Australian Shepherd dogs [26]. This mutation (Asp2867Val) results in a missense variant in the laminin- $\alpha 3$ chain with autosomal recessive inheritance. Other mutations in the same gene have been found in the German Pointer dog breed associated with EBJ. Specifically, an insertion of repetitive satellite DNA in intron 35 of this gene has been associated with EBJ [10,27]. This insertion results in an $\alpha 3$ -pre-messenger RNA that is not well matured and a decrease in laminin 5 expression, thereby impairing adhesion and the clonogenic potential of the EBJ keratinocytes.

Finally, in dystrophic epidermolysis bullosa (DEB), blistering occurs in the sublamina densa, and the skin and mucosa are extremely sensitive. The blisters heal with scarring, and end with progressive disability and the deformation of the fingers [46]. This disease, which affects dogs, sheep, cattle, cats, and humans, is caused by mutations in the *COL7A1* gene, which encodes collagen type VII [47]. A total of 500 mutations of this gene have been associated with DEB, and the severity of the phenotype depends on the type of mutations and their location [48]. Most of these mutations were observed in the golden retriever, although Nagata et al. (1995) reported a case of DEB in Akita Inu dog breed [12]. The authors did not perform a genetic study on the animal, and the results they observed when analyzing the bladders by electronic microscopy and immunohistochemistry were comparable to those in humans and other dogs suffering with this disease [12]. Several studies reported new therapies to control and eradicate this disease. In one study, canine keratinocytes were used to generate autologous epidermal layers in dogs with homozygous missense mutation in the *COL7A1* gene, which expressed an aberrant protein, with good results [49]. Other authors attempted gene therapy with retroviral vectors [50]. Recently, Gretzmeier et al. (2021) published good results when recombinant protein collagen VII (C7) was administered to mice and dogs [51].

3. Ichthyosis

The term ichthyosis describes rare congenital or hereditary pathologies caused by primary defects in the formation of the stratum corneum [52]. This ichthyosis could be epidermolytic or non-epidermolytic, depending on whether they are vacuoles and lysis of keratinocytes within the spinous and granular cell layers [53]. Epidermolytic ichthyosis has been described in the Norfolk Terrier concerning a mutation to the epidermal keratin gene (*KRT10*) with autosomal recessive inheritance [54], although the same pathology has been described in the Rhodesian Ridgeback and Labrador Retriever.

However, the most common ichthyosis is non-epidermolytic and presents autosomal recessive inheritance. In humans, there are X-linked dominant forms [55], but in dogs these forms are yet to be documented [52], with two exceptions. The first is the autosomal domi-

nant inheritance of mutation c.1052C > T in the *ASPRV1* gene in the German Shepherd [56]; the second is the deletion identified in the *NSDHL* gene of two female Labrador Retrievers, which encoded an NAD(P)-dependent steroid dehydrogenase-like protein related to cholesterol biosynthesis and with monogenic X-chromosomal semidominant inheritance [57]. Different mutations in several genes have been related (Table 3).

Table 3. Ichthyosis with known gene associated in canine breed.

Dog Breeds	Gene Associated	Inheritance ¹	Reference
Golden Retriever	<i>ABHD5</i>	AR	[58]
	<i>PNPLA1</i>	AR	[17]
German Shepherd	<i>ASPRV1</i>	AD	[56]
American Bulldog	<i>NIPAL4</i>	AR	[59]
Great Dane	<i>SLC27A4</i>	AR	[15]
Jack Russell Terrier	<i>TGM1</i>	AR	[16]

¹ AR: autosomal recessive inheritance; AD: autosomal dominant inheritance.

One of the canine breeds most affected by non-epidermolytic ichthyosis is the golden retriever. In this breed, the clinical signs include a generalized scaling and hyperpigmented and rough ventral glabrous skin. The histopathology shows a laminated orthokeratosis and an epidermal hyperkeratosis without significant involvement of the stratum granulosum [39,60]. The *PNPLA1* variant that produces this pathology reached more than 50% frequency in the breeding population now of identification [17]. The frequencies of genotypes are estimated around 32% in affected dogs (homozygous recessives), 49% heterozygous, and 20% homozygous dominant, thus clean of defective variants [61]. More recently, these frequencies have been estimated at 21% in wild-type, 48% in heterozygous, and 31% in recessive homozygous [18]. The PNPLA protein family has nine patatin-like phospholipases (PNPLA1–PNPLA9) with lipolytic and acyltransferase activities and are related to lipid metabolism [62,63]. In humans, five mutations of *PNPLA1* caused autosomal recessive congenital ichthyosis, which affects the composition and organization of epidermal lipids. All five mutations provoke a *PNPLA1* amino acid change [64]. In dogs, specifically Golden Retrievers with this mutation, an indel in exon 8 is reported to cause non-epidermolytic ichthyosis by GWAS analysis [17]. To evaluate the efficacy of treatment with shampoo and lotion containing gluconolactone and other hydroxylated acids, a prospective study was carried out, and the results were encouraging: the extension and size of the scales was reduced between 60 and 75% after 14 and 30 days of treatment, respectively [65]. Recently, Kiener et al. (2021) reported a *ABHD5* gene frameshift deletion in Golden Retrievers with non-epidermolytic ichthyosis [59]. The mutation is a 14 bp deletion that provokes a frameshift that alters the last 14 codons. The *ABHD5* gene encodes an acyltransferase related to lipid metabolism, and defects in this gene are related to Chanarin–Dorfman syndrome, a neutral lipid storage disease with ichthyosis [66,67]. To date, these mutations have not been reported in other breeds; however, they have presented mutations related to non-epidermolytic ichthyosis. For example, a variant of *ASPRV1* gene has been found in German Shepherds [56]. This gene encodes a retroviral-like protease involved in profilaggrin-to-filaggrin processing and plays a relevant role in skin barrier formation [68]. The missense variant of c.1052T < C has found in this breed, which affects a conserved residue and produces the amino acid change Leu351Pro. This change provokes a deficient *ASPRV1* protein, which produces a lower level of stratum corneum hydration [69]. In the American Bulldog, mutations in the *NIPAL4* gene are related to non-epidermolytic ichthyosis [14,70] and in humans to autosomal recessive congenital ichthyosis [71]. In dogs, the frameshift deletion of the *NIPAL4* gene produces a premature stop codon that results in a truncated and defective *NIPAL4* protein [59]. This protein seems to have a relevant role in lipid metabolism, and it is associated with keratins and desmosomes in the epidermis [72]. Therefore, animals with deficient *NIPAL4* protein fail to form normal lamellar bilayers, leading to the appearance of the typical clinical signs of non-epidermolytic ichthyosis [73].

In Great Danes, a mutant transcript of the *SLC27A4* gene has been correlated to the ichthyosis phenotype by sequence analysis [15]. The mutation provokes an in-frame loss of 54 bp in exon 8, that probably affects protein expression. The mutant dogs presented a truncated protein levels elevated. The *SLC27A4* protein has acyl-CoA synthetase activity, which is related to fatty-acid and phospholipid synthesis and, consequently, to lipid metabolism [74] and fatty-acid transport in the cell membrane [75]. Some mutations in the *SLC27A4* gene have been associated with ichthyosis in human patients [76–78], so it is probable that the mutation in Great Danes is not the only one in this gene related to the disease in dogs. In Jack Russell Terriers, [16] related the lamellar ichthyosis to a LINE-1 insertion in the transglutaminase 1 (*TGM1*) gene, which encodes an enzyme with a role in cornified envelope formation, and 30–40% of humans with non-epidermolytic (lamellar) ichthyosis present mutations in this gene [79]. The authors identified a LINE-1 insertion in this gene related to non-epidermolytic ichthyosis phenotype as found in humans.

Finally, mutations in *CERS3* have been related to autosomal recessive congenital ichthyosis in humans [80]. Even though these mutations have not yet been found in dogs, it would be interesting to analyze the prevalence of these mutations to see if the phenotype they produce is like that of humans. This gene encodes a protein with a relevant role in sphingolipid metabolism and is essential for the maintenance of epidermal lipid homeostasis. In fact, mutations found in other human genes related to ichthyosis have been related to different types of canine genodermatosis. For example, Caroppo et al. (2020) recently reported a novel keratin 1 (*KRT1*) c.1433A > G mutation related to human epidermolytic ichthyosis [81]. Other mutations in the same gene [82] or others of the same family [83] have been related to human ichthyosis and to different canine skin pathologies: epidermolytic ichthyosis, epidermolytic hyperkeratosis, and nasal parakeratosis [54,84,85].

4. Other Genodermatosis

Other genodermatosis have been described in different canine breeds and the genes candidates have been studied (Figure 2).

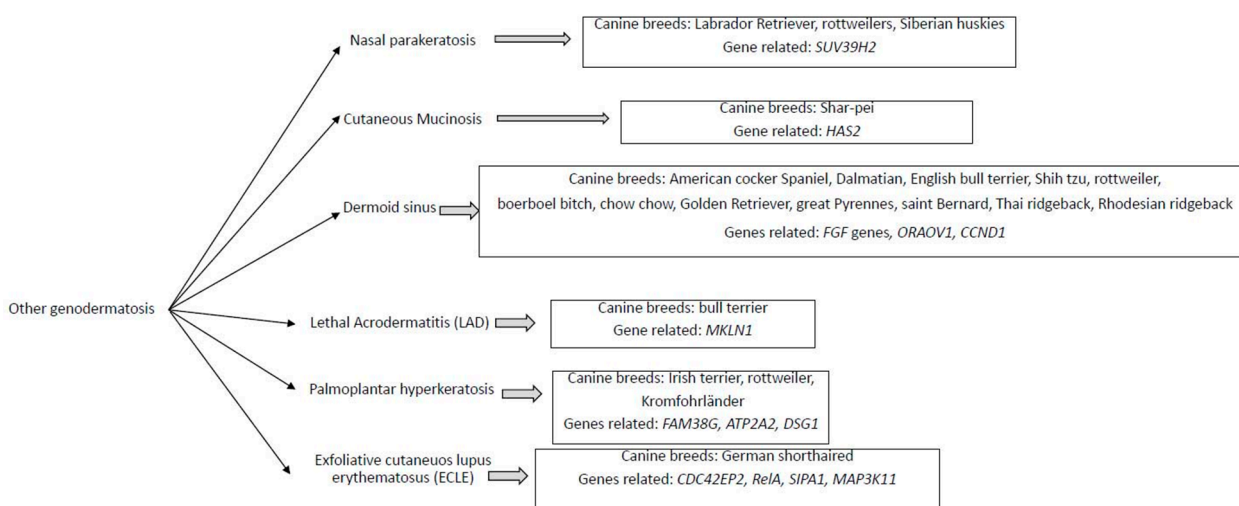


Figure 2. Diagram of other genodermatosis found the associated canine breed and the genes candidates to be responsible.

Nasal parakeratosis is a variety of genodermatosis characterized by a thick, slightly verrucous, brown scale on the nasal planum with variable depigmentation [86]. Detected in Labrador Retrievers, Rottweilers and Siberian Huskies, this pathology is characterized by the accumulation of serum in the nasal epidermis and numerous intracorneal vacuoles [87,88]. Afterwards, several studies connected a mutation in the *SUV39H2* gene with this pathology in Labrador Retrievers [19] and Greyhounds [39]. The gene encoded histone 3 methyltransferase, which helps regulate protein stability and activity, protein–protein

interactions, and epigenetic silencing [89,90]. Jagannathan et al. (2013) detected a missense variant c.972T > G, with the amino acid change Asn324Lys in Labrador Retrievers affected by nasal parakeratosis [19]. Later, the same group related nasal parakeratosis in Greyhounds with a 4 bp deletion at the 5'-splice site of intron 4 [39]. These data suggest that mutations in the *SUV39H2* gene could be related to nasal parakeratosis in different breeds. More recently, Bannoehr et al. (2020) analyzed Labrador Retrievers affected by nasal parakeratosis and the c.972T > G mutation in the *SUV39H2* gene [85]. The results showed an up-regulation of genes that encode keratins 1, 10, and 14, although their expression did not cause changes in the nasal planum, suggesting that the *SUV39H2* enzyme affected several genes or pathways related to epidermal differentiation.

Cutaneous mucinosis was described for the first time in seven Shar-Peis that presented asymptomatic nodules, papules, or plaques on the skin or oral mucosa and an excess accumulation of mucin within the dermis or submucosa [91]. Immunohistochemical techniques revealed the sulphated acid glycosaminoglycans in mast cell granules and other mast cell subtypes [92,93]. An analysis of those with mucinosis revealed a high serum concentration of hyaluronic acid, the main component of mucin [94]. In fact, there was a higher transcription of hyaluronan synthase 2 and protein expression in fibroblasts [95,96], indicating a relationship between cutaneous mucinosis and the genetic cause related to this enzyme. In humans, the *HAS2* gene expresses a protein that correlates with malignant transformation [97]. Its activity is regulated by the phosphorylation of protein kinase C [98] and adenosine monophosphate-activated protein kinase [99], which can induce *HAS2* transcript accumulation in dermal fibroblasts [100]. HAS proteins facilitated the extrusion of hyaluronan to the extracellular space [101], and this could explain the relationship between mucinosis in the Shar-Peis and high levels of *HAS2* protein expression and hyaluronan accumulation. However, more study is necessary to determine the causal mutation related to this genodermatosis.

Dermoid sinus is caused by incomplete separation of the skin and neural tube during embryonic development [102]. This congenital malformation has been found in different species, including humans [103,104] and dogs. Up to now, the canine breeds where it has been reported are the American Cocker Spaniel [105], Dalmatian [106], English Bull Terrier [107], Shih Tzu [108], Rottweiler [109], Boerboel Bitch [110], Chow Chow [111], Golden Retriever [112], Great Pyrenees [113], Saint Bernard [114], Thai Ridgeback [21] and Rhodesian Ridgeback [115–118]. In the last one, several authors concluded that the Ridgeback has an autosomal dominant mutation related to dermoid sinus emergence [21,119]. This mutation is a 133 Kb duplication of three fibroblast growth factor (FGF) genes (*FGF3*, *FGF4*, *FGF19*), the oral cancer overexpressed gene (*ORAOV1*), and the *CCND1* gene, which encodes cyclin D1 [21]. The FGF family comprises 17 members with mitogenic or metabolic activity (*FGF19*, *FGF21* and *FGF23*). The FGFs with mitogenic activity play a critical role in metabolic development, while those with metabolic activity play a role in its regulation [120]. On the other hand, the *ORAOV1* gene is associated with different types of cancer in human patients [121–124] because it is a regulator of the cell cycle and apoptosis [125]. Furthermore, the expression of cyclin D1 (encoded by *CCND1* gene) is reduced in *ORAOV1*-silenced cells [126], which could indicate dysregulation of the cell cycle mediated by this gene and cyclin D1 in animals with this mutation. However, few studies have been carried out in this regard.

Lethal acrodermatitis (LAD) is a genetically determined metabolic disease of Bull Terriers that was found in the U.S. in the 1980s [125]. This disease is not exclusively a pathology of the skin, so different characteristics are also reported: stunting, splayed digits, eating difficulties, and increased susceptibility to microbial infections [125,127]. After analyzing the liver-soluble proteome, 13 differentially expressed proteins, including chaperones, for calcium binding, energy metabolism, and inflammatory response were identified [128]. In a genome-wide association study and haplotype analysis, Bauer et al. (2018) showed a splice-region variant in the *MKLN1* gene associated with the presence of disease [129].

Palmoplantar hyperkeratosis in Irish Terriers was associated with autosomal recessive inheritance in a retrospective analysis by Binder et al. (2000) and it was associated with a complex mutation in the *KRT16* gene, corresponding to an insertion/deletion of four nucleotides downstream in exon 6 [130]. The last one is a good model for human focal non-epidermolytic palmoplantar keratoderma (FNEPPK) [131]. This disease is characterized by the abnormal development of the footpad epidermis, and the affected dogs developed smooth parchment-like footpads at the age of six months. The pad epidermis hardened and grew lateral cone-like protrusions of up to 5 mm in diameter and developed fissures and cracks, which predisposed the affected dogs to secondary infections [132]. Several mutations in different genes have been associated with this disease, including mutations in the genes encoding keratin 2 and 9, and desmoglein 1 [132], and a variant is the missense c.155G > C in the *FAM83G* gene, which encodes a protein that has a largely unknown function [133]. In this same breed, the heterozygous SINE insertion into the *ATP2A2* gene is associated with Darier canine disease, a rare form of genodermatosis that affects different breeds [134,135]. Concretely, Linek et al. (2020) showed a demarcated ulcerative and crusting lesion in the ear canal in one Irish Terrier, related to canine Darier disease [135]. The dog presented a splicing defect and marker allelic imbalance in *ATP2A2* mRNA from skin. In the Kromfhländer canine breed, a variant *FAM83G:c155G > C* has been related to palmoplantar hyperkeratosis [136], and Backel et al. (2020) found recently a *DSG1* gene variant in a single male rottweiler [137]. This gene encoding desmoglein 1 and variants of this gene have been related to palmoplantar keratoderma in humans [138]. Therefore, future studies about the relationship between this gene and this disease in different dog breeds would be interesting.

Exfoliative cutaneous lupus erythematosus (ECL) has been described in German Short-haired Pointer dogs with monogenic autosomal recessive inheritance [139]. The treatment with ciclosporin, hydroxychloroquine, and adalimumab does not seem to have good long-term results [140], whereas the treatment with mycophenolate mofetil seems to achieve a complete remission of the disease [141]. This disease seemed to be related to a SNP allele on canine chromosome 18 [139]. These authors concluded that different candidate genes could be related to ECL, including genes *CDC42EP2* (a Rho GPase regulates downstream effector proteins for the assembly of the actin cytoskeleton [142]), *RelA* (part of the KfB complex, involved in immune processes [143]), *SIPA1* (involved cell cycle progression [144]), and *MAP3K11*, which is required for the activation of JNK, p38, and ERK [145]. Leeb et al. (2020) realized a genome-wide association study and they concluded that the p. Pro480Thr mutation in the *UNC93B1* gene is causing ECL in dogs [146].

Finally, hereditary sensory and autonomic neuropathies (HSAN) should be noted in this review, as lesions (gross or microscopical) are only detected in the skin. These diseases are characterized by progressive sensory loss, chronic skin ulcerations, and nail dystrophic changes [147]. Several mutations have been correlated with these HSAN in canine breeds. In Border Collies, the inversion disrupting *FAM134B* and the missense variant in the *RETREG1* (reticulophagy regulator 1) gene and are associated with HSAN has been detected in Border Collies, Spaniels, and Pointers [148–150]. The last one variant has also been associated with these diseases in other canine breeds, such as Spaniels and Pointers [150]. In Siberian Huskies, the polyneuropathy has been related to five different mutations in *NDRG1*, *ARHGEF10*, and *RAB3GAP1* genes [151], and a point mutation in a lincRNA of *GDNF* gene has been associated with HSAN in French Spaniels by genome-wide association study (GWAS) [152].

5. Conclusions

Hereditary diseases affect a great number of canine breeds. These diseases include genodermatosis, narrowly defined as monogenic hereditary dermatoses, and could be epidermolysis, ichthyosis, nasal parakeratosis, mucinosis, or dermoid sinus. All these present with a genetic inheritance in certain canine breeds and the specific canine genodermatosis of a dog is life-threatening and the animal welfare is markedly reduced, which could be

treated with reducing the skin problems. In some, the causal mutation and its type of inheritance is well known for certain breeds, while for others, only the breed with the highest prevalence of the pathology is known. Several studies are necessary to elucidate the causal mutations and their prevalence in different breeds to incorporate the studies of genetic selection programs of the different breeds to minimize or eradicate this type of dermatologic disease for which there is still no definitive cure.

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