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Review

Genetics of inherited skin disorders in dogs

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ABSTRACT

Canine genodermatoses represent a broad spectrum of diseases with diverse phenotypes. Modern genetic technology including whole genome sequencing has expedited the identification of novel genes and greatly simplified the establishment of genetic diagnoses in such heterogeneous disorders. The precise genetic diagnosis of a heritable skin disorder is essential for the appropriate counselling of owners regarding the course of the disease, prognosis and implications for breeding. Understanding the underlying pathophysiology is a prerequisite to developing specific, targeted or individualized therapeutic approaches. This review aims to create a comprehensive overview of canine genodermatoses and their respective genetic aetiology known to date. Raising awareness of genodermatoses in dogs is important and this review may help clinicians to apply modern genetics in daily clinical practice, so that a precise diagnoses can be established in suspected genodermatoses.

Introduction

Currently, 6000–8000 rare diseases are known in humans, most of them inherited as monogenic traits. The causative genetic variants have been identified in more than 5600 monogenic diseases.[1,2] While each of these diseases is rare, it is currently thought that up to 10% of the human population in the United States may be affected by at least one rare disease.[3] More than 500 heritable diseases of the skin (genodermatoses) are known in humans (Leech and Moss, 2007; Feramisco et al., 2009; Lemke et al., 2014). Nonetheless, new patients with yet undescribed genodermatoses continue to be identified. Compelling arguments for the growing importance of genetic analyses in clinical practice were provided in an excellent review on human genodermatoses (Lemke et al., 2014).

In dogs, far fewer heritable skin diseases with known molecular aetiology are known. Five years ago, we compiled 19 canine genodermatoses (Leeb et al., 2017). Thanks to collaborations between private veterinarians, veterinary dermatology specialists and veterinary dermatopathologists and due to advances in genetics and sequencing technology, this number is growing rapidly. In this review, we will summarize data on 36 canine genodermatoses and their underlying causative genes. We searched OMIA[4] and PubMed[5] for the relevant information on canine genodermatoses and their respective genetic aetiology known to date.

Dogs and humans are closely related and share the vast majority of their ~20,000 protein coding genes. Not surprisingly, many genodermatoses are homologous between dogs and humans. Their comparative investigation in related species may be considered a One Health approach and is of mutual benefit to human and veterinary medicine. While the majority of newly described canine genodermatoses has already a well characterized homologous disease in humans, there are several examples, for which the causative gene was initially discovered in dogs. This suggests that more genes with important roles for the development and maintenance of a healthy skin are still likely to be discovered.

This review focuses on skin disorders with a monogenic inheritance or with clearly identified major genetic risk factors. We did not include normal hair morphology traits (e.g. long vs. short hair, curly vs. straight

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[1] See: Online Mendelian Inheritance in Man (OMIM). https://www.omim.org. (Accessed 19 November 2021).
[2] See: Orphanet. https://www.orpha.net. (Accessed 9 April 2021).
[3] See: Genetic and Rare Diseases Information Center. https://rarediseases.info.nih.gov. (Accessed 19 November 2021).
[4] See: Online Inheritance in Animals (OMIA) https://www.omia.org. (Accessed 19 November 2021).
[5] See: Pubmed https://pubmed.ncbi.nlm.nih.gov. (Accessed 19 November 2021).

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Table 1
Ichthyoses and other disorders of cornification with known causative genetic variants.

Phenotype	Gene	Variant[a]	Breed	Inheritance[b]	OMIA no.	Reference
Footpad hyperkeratosis and allergies	*DSG1*	c.2541_2545del; p.G848Wfs*2	Rottweiler	AR/ASD	002266-9615	Backel et al. (2020)
Footpad hyperkeratosis	*FAM83G*	c.155G>C; p.R52P	Irish terrier, Kromfohrländer	AR	001327-9615	Drögemüller et al. (2014)
Footpad hyperkeratosis	*KRT16*	Complex rearrangement; p.E392*	Dogue de Bordeaux	AR	002088-9615	Plassais et al. (2015)
Hyperkeratosis, epidermolytic	*KRT10*	c.1125+2G>T; r.spl	Norfolk terrier	AR	001415-9615	Credille et al. (2005)
Ichthyosis	*ABHD5*	c.1006_1019del; p.N336Sfs*6	Golden retriever	AR	002368-9615	Kiener et al. (2021)
Ichthyosis	*ASPRV1*	c.1052C>T; p.L351P	German shepherd	AD	002099-9615	Bauer et al. (2017a)
Ichthyosis	*KRT1*	c.567_569del; p.Asn190del	Shar-Pei	AD	002425-9615	Affolter et al., submitted
Ichthyosis	*PNPLA1*	c.1445_1447delinsTACTACTA; p.N482Ifs*11	Golden retriever	AR	001588-9615	Grall et al. (2012)
Ichthyosis	*NIPAL4*	c.744delC; p.I249*	American bulldog	AR	001980-9615	Casal et al. (2017)
Ichthyosis	*SLC27A4*	c.1250G>A; p.Arg417Gln/r.spl	Great Dane	AR	001973-9615	Metzger et al. (2015)
Ichthyosis	*TGM1*	1980 bp LINE-1 insertion	Jack Russell terrier	AR	000546-9615	Credille et al. (2009)
Keratoconjunctivitis sicca and ichthyosiform dermatosis	*FAM83H*	c.977delC; p.P326Hfs*258	Cavalier King Charles spaniel	AR	001683-9615	Forman et al. (2012)
Nasal parakeratosis	*SUV39H2*	c.972T>G; p.N324K	Labrador retriever	AR	001373-9615	Jagannathan et al. (2013)
		c.996+3_996+6delAAGT; r.spl	Greyhound			Bauer et al. (2018a)
Verrucous epidermal keratinocytic nevi	*NSDHL*	14.4 kb genomic deletion	Labrador retriever	XSD	002117-9615	Bauer et al. (2017b)
		c.700G>A; p.G234R	Chihuahua			Leuthard et al. (2019)
		c.718_722delGAACA; p.E240Pfs*17	Mixed breed			Christen et al. (2020)

[a] A detailed description of genetic variant nomenclature can be found at[+]. A simplified designation is given for some complex variants. [+]See: Sequence Variant Nomenclature. https://varnomen.hgvs.org (Accessed 19 November 2021).
[b] AD: autosomal dominant; AR: autosomal recessive; ASD: autosomal semi-dominant; XSD. X-chromosomal semi-dominant.

Table 2
Epidermolyses and blistering disorders with known causative genetic variants.

Phenotype	Gene	Variant[a]	Breed	Inheritance[b]	OMIA No.	Reference
Ectodermal dysplasia/skin fragility syndrome	*PKP1*	c.202+1G>C; r.spl	Chesapeake Bay retriever	AR	001864-9615	Olivry et al. (2012)
Epidermolysis bullosa, dystrophic	*COL7A1*	Complex rearrangement	Basset hound	AR	000341-9615	Garcia et al. (2020)
		c.4579C>T; p.R1527*	Central Asian shepherd			Niskanen et al. (2017)
		c.5716G>A; p.G1906S	Golden retriever			Baldeschi et al. (2003)
Epidermolysis bullosa, junctional	*LAMA3*	6.5 kb insertion	German pointer	AR	001677-9615	Capt et al. (2005)
Epidermolysis bullosa, junctional	*LAMB3*	c.1174C>T; p.C392R	Australian shepherd	AR	002269-9615	Kiener et al. (2020)
Epidermolysis bullosa, simplex	*PLEC*	c.3947G>A; p.W1316*	Eurasier	AR	002080-9615	Mauldin et al. (2017)
Hyperkeratosis, epidermolytic	*KRT10*	c.1125+2G>T; r.spl	Norfolk Ttrrier	AR	001415-9615	Credille et al. (2005)

[a] A detailed description of genetic variant nomenclature can be found at https://varnomen.hgvs.org/. A simplified designation is given for some complex variants.
[b] AR: autosomal recessive.

hair) or normal coat colour variation, except in those cases where a specific coat colour is clearly associated with a skin disease (e.g. coat colour dilution alopecia). A few syndromic diseases with major skin involvement were also included (e.g. acral mutilation syndrome, a sensory neuropathy, in which the skin lesions are a secondary consequence of the primary disease). The review will not deal with multifactorial diseases such as atopic dermatitis that are probably influenced by (many) genetic risk factors with small effects. We provide lists of the currently known canine genodermatoses and their underlying causative genetic variants. The review will also briefly discuss the use of genetic analyses as a complementary approach to clinical and histopathological examinations and its potential impact for precision medicine.

Canine genodermatoses with known genetic aetiology

A total of 36 genes related to heritable skin disorders were identified. To facilitate the use for clinicians, we grouped these genes according to phenotype/disease. We classified the resulting diseases into ichthyoses and other disorders of keratinization (Table 1, Figs. 1–4), epidermolyses and blistering disorders (Table 2; Fig. 5), and all other genodermatoses (Table 3; Fig. 6). Our grouping is not mutually exclusive. For example, the epidermolytic hyperkeratosis caused by *KRT10* variants is listed in the ichthyoses and the epidermolyses groups. The vast majority of canine genodermatoses is caused by relatively young deleterious alleles, which have arisen by spontaneous mutation events during the last decades. This explains why most genodermatoses are restricted to a single dog breed or a group of closely related breeds that may have had some recent genetic exchange. Notable exceptions are the ancient *FOXI3* allele causing ectodermal dysplasia in several hairless dog breeds (Drögemüller et al., 2008) and the various *MLPH* alleles for coat colour dilution that segregate in many dog breeds and Mixed breed dogs (Drögemüller et al., 2007; Bauer et al., 2018c; Van Buren et al., 2020).

Table 3
Other skin-related disorders with known causative genetic variants.

Phenotype	Gene	Variant[a]	Breed	Inheritance[b]	OMIA no.	Reference
Acral mutilation syndrome	*GDNF*	Non-coding regulatory SNV	Various hunting dogs	AR	001514-9615	Plassais et al. (2016)
Acrodermatitis, lethal	*MKLN1*	c.400+3A>C; r.spl	Bull terrier, Mini BT	AR	002146-9615	Bauer et al. (2018b)
Darier disease	*ATP2A2*	Intronic SINE insertion; r.spl	Irish terrier	AD	002265-9615	Linek et al., 2020
Dermoid sinus	*FGF3, FGF4, FGF19*	133 kb genomic duplication	Rhodesian Ridgeback, Thai Ridgeback	AR (complex)	000272-9615	Salmon Hillbertz et al. (2007)
Dilute coat colour (predisposing risk factor for colour dilution alopecia)	*MLPH*	c.-22G>A; r.spl(?)	Many breeds	AR (complex)	000031-9615	Drögemüller et al. (2007)
		c.667_668insC; p.H223Pfs*41	Many breeds			Van Buren et al. (2020)
		c.705G>C; pQ253H	Many breeds			Bauer et al. (2018c)
Dilute coat colour with neurological defects	*MYO5A*	c.4973_4974insA; p.N1658Kfs*28	Dachshund	AR	001501-9615	Christen et al. (2021)
Ectodermal dysplasia	*FOXI3*	c.57_63dup7; p.A23fs*219	Chinese crested dog, Mexican hairless dog, Peruvian hairless dog	ASD	000323-9615	Drögemüller et al. (2008)
Ectodermal dysplasia, anhidrotic	*EDA*	c.842delT; p.L281Hfs*22	Dachshund	XR	000543-9615	Hadji Rasouliha et al. (2018)
		c.910-1G>A; r.spl	German shepherd			Casal et al. (2005)
		r.385_487del	Mixed breed			Waluk et al. (2016)
Ectodermal dysplasia/skin fragility syndrome	*PKP1*	c.202+1G>C; r.spl	Chesapeake Bay retriever	AR	001864-9615	Olivry et al. (2012)
Ehlers-Danlos syndrome, classic type 1	*COL5A1*	c.3038delG; p.G1013Vfs*260	Labrador retriever	AD	002165-9615	Bauer et al. (2019)
		c.4711G>A; p.G1571R	Mixed breed			Bauer et al. (2019)
Ehlers-Danlos syndrome, type VII, dermatosparaxis	*ADAMTS2*	c.769C>T ; p.R257*	Doberman Pinscher	AR	000328-9615	Jaffey et al. (2019)
Exfoliative cutaneous lupus erythemathosus	*UNC93B1*	c.1438C>A; p.P480T	Various hunting dogs	AR	001609-9615	Leeb et al. (2020)
Hyaluronanosis	*HAS2*	16.5 kb genomic duplication	Shar-Pei	ASD	001561-9615	Olsson et al. (2011)
Hypotrichosis	*SGK3*	c.137_138insT; p.E47Gfs*3	Scottish deerhound	AR	001279-9615	Hytönen and Lohi (2019)
		c.287_290delTTAG; p.V96Gfs*50	American hairless terrier			Parker et al. (2017)
Keratoconjunctivitis sicca and ichthyosiform dermatosis	*FAM83H*	c.977delC; p.P326Hfs*258	Cavalier King Charles spaniel	AR	001683-9615	Forman et al. (2012)
Ligneous membranitis	*PLG*	c.1256+2T>A, r.spl	Scottish terrier	AR	002020-9615	Ainsworth et al. (2015)
Musladin-Lueke syndrome (geleophysic dysplasia)	*ADAMTSL2*	c.661C>T; p.R221C	Beagle	AR	001509-9615	Bader et al. (2010)
Oculocutaneous albinism (predisposing risk factor for melanocytic neoplasms)	*SLC45A2*	4.1 kb deletion	Doberman Pinscher	AR	001821-9615	Winkler et al. (2014)
Renal cystadenocarcinoma and nodular dermatofibrosis	*FLCN*	c.764A>G; p.H255R	German shepherd	AD	001335-9615	Lingaas et al. (2003)

[a] A detailed description of genetic variant nomenclature can be found at https://varnomen.hgvs.org/. A simplified designation is given for some complex variants.
[b] AD: autosomal dominant; AR: autosomal recessive; ASD: autosomal semi-dominant; XR: X-chromosomal recessive.

Purebred vs. Mixed breed dogs

Mixed breed dogs have a similar population structure as most human populations. Consequently, monogenic heritable diseases in Mixed breed dogs are relatively rare overall. However, dominant diseases affect Mixed breed and purebred dogs equally likely.

Purebred dogs are bred in strictly isolated populations. This requires a certain degree of inbreeding and promotes the expression of recessive alleles. These breeding practices have enabled to create ~400 phenotypically highly diverse dog breeds with relatively little intra-breed phenotypic variability. However, the inbreeding has also negative consequences. Inbred dogs have an increased probability to inherit identical genome segments from their parents. Consequently, recessive diseases also occur more frequently in purebred than in Mixed breed dogs. This partly resembles the situation in some isolated human populations where consanguineous marriages are common. In purebred dogs, the problem is further exacerbated by the excessive use of elite breeding animals ('popular sire effect'). Every dog carries a small number of recessive deleterious alleles. As long as the effective population size is reasonably large and the breeding dogs are used with roughly equal intensity, the population will contain many deleterious alleles with very small individual frequencies. The risk that any of these deleterious alleles will come together in a homozygous state in an offspring is not negligible due to the inbreeding, but is still limited. The excessive use of very few breeding animals may rapidly shift this towards a situation, in which some of the deleterious alleles reach very high frequencies. Therefore, without proper breeding programs, monogenic recessive diseases in purebred dogs may quickly evolve from rare to common diseases.

The most striking real example of these theoretical considerations can be seen in the recessive Golden retriever ichthyosis, which is caused by a *PNPLA1* variant (Fig. 1). Due to the intensive use of a carrier as breeding sire in the 1990s, the pathogenic allele had reached the alarmingly high frequency of more than 50% in the breeding population at the time when the causative variant was finally identified (Grall et al., 2012). The corresponding genotype frequencies amounted to roughly 32% affected dogs, 49% heterozygous carriers and only 20% clear dogs (Owczarek-Lipska et al., 2011).

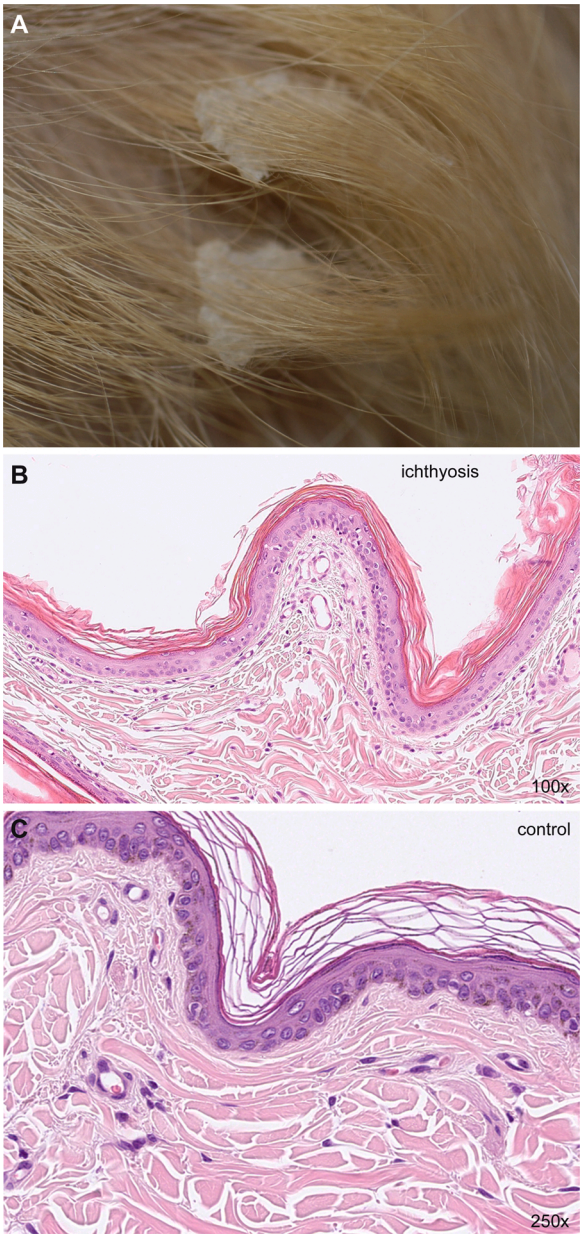

Fig. 1. *PNPLA1*-related ichthyosis in Golden retrievers. (A) Scales on an affected dog. The phenotype of this genodermatosis is quite variable and often so mild that owners do not notice any problem. The role of the *PNPLA1* gene for skin integrity was initially discovered in Golden retrievers. Only later on, human patients with a related homologous ichthyosis were identified (Grall et al., 2012). (B) Histologically, the epidermis is covered by dense laminar orthokeratotic keratin, which is exfoliating in layers. (C) Healthy control skin. Note the basket-weave orthokeratosis in the stratum corneum.

Targeted genetic testing for breeders and veterinarians

For many of the known genodermatoses, commercial genetic testing is available. Such a test will only interrogate a single genetic variant in the genome. An overview on different flavours of targeted genetic tests is provided in Supplementary Table S1 (see Appendix A: Supplementary material). These tests are very helpful, if a particular recessive disease has spread in a dog breed. When a recessive disease allele has a frequency of more than 1%–5% in a population, it is strongly recommended that breeders test their breeding animals to identify heterozygous carriers and to avoid carrier x carrier matings.

These targeted genetic tests can also be valuable for veterinarians to confirm a presumptive diagnosis, avoid unnecessary or invasive diagnostics and prevent futile therapies. A precise genetic diagnosis can be of great help in counselling a dog owner regarding the prognosis, required therapeutic management or humane euthanasia. For example, dogs with inherited footpad hyperkeratosis have a normal life expectancy but an impaired quality of life as walking is painful and their footpads require continuous lifelong management (Drögemüller et al., 2014; Plassais et al., 2015; Backel et al., 2020). Thus, having a dog with a genodermatosis can be a non-negligible financial and emotional burden for an owner (Fig. 4).

If a dog with a suspected genodermatosis tests positive, the genetic test will definitively establish the suspected diagnosis. However, a negative genetic test result must be considered inconclusive. If the tested disease allele is not present, it is still possible that an independent mutation event, perhaps in the same gene, has happened. Targeted tests interrogate only a single position in the genome, they do not comprehensively test an entire gene or the entire genome.

There are numerous laboratories providing single targeted genetic tests and panels of targeted tests. Good overviews and databases on these laboratories are provided by the WSAVA[6] and the IPFD initiative.[7]

Thus, the use of a targeted genetic test to confirm a suspected diagnosis is primarily recommended for recessive diseases and in purebred dogs of the same or at least a closely related breed, in which the causative genetic variant was originally reported. In all other constellations, it is unlikely that a targeted test will come up positive and then it may be better to consider a more comprehensive analysis, such as the sequence analysis of entire candidate genes or whole genome sequencing (WGS). Such analyses have become routine diagnostic procedures in human medicine. In veterinary medicine, they are technically feasible, but are not (yet) considered routine diagnostics and mostly undertaken in the framework of research projects.

Genetic analyses in a research context

In this chapter, we will briefly summarize the available methods to identify new pathogenic variants in dogs with suspected genodermatoses. Specific details on the methods are shown in Supplementary Table S1 (see Appendix A: Supplementary material). Gene panel sequencing and whole exome sequencing (WES), two currently popular approaches in human genetics, are not practical in dogs or any other domestic animal species due to cost considerations and a lack of commercially available reagents.

At the time of writing this review, only two approaches are routinely used in veterinary genetics. The first of these comprises PCR amplification followed by conventional Sanger sequencing of all exons of a given candidate gene. This approach has been in use for more than 20 years with little variations. It is most attractive for highly characteristic phenotypes, for which only a single candidate gene with few exons is known (e.g. verrucous epidermal keratinocytic nevi in female dogs due to heterozygous *NSDHL* variants; Leuthard et al., 2019). This approach requires a laboratory with experienced personnel and specifically adapted protocols (primers) for each disease and each individual candidate gene. It will also only detect relatively small coding variants and has little sensitivity for large structural variants. The main advantage of this method is that it requires very little data analysis and can provide results within 1–2 weeks.

The second commonly used method for genetic variant identification in canine genetics is whole genome sequencing (WGS). WGS has become increasingly popular during the last 10 years and is expected to become the primary approach for the analysis of single gene disorders in humans

[6] See: Hereditary Disease Guidelines. https://wsava.org/global-guidelines/hereditary-disease-guidelines/. (Accessed 19 November 2021).

[7] See: IPFD DogWellNet. https://dogwellnet.com/. (Accessed 19 November 2021).

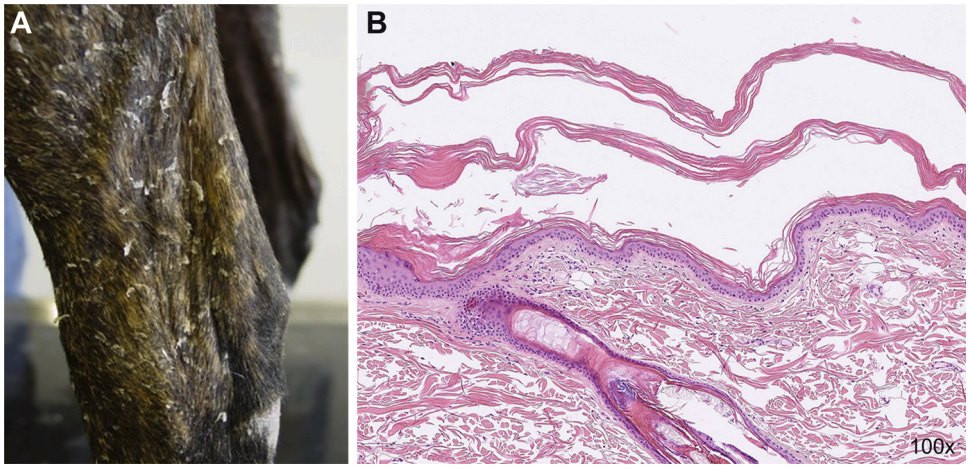

Fig. 2. *NIPAL4*-related ichthyosis in American bulldogs. (A) Severe scale formation and mutifocal moderate hypotrichosis on the hind leg. Identical findings are present all over the body. (B) Histologically, the epidermis is covered by abundant laminar orthokeratotic keratin which is exfoliating as thick layers.

(Lionel et al., 2018). The laboratory costs to sequence a dog genome are less than $ 800. Unfortunately, these costs cover only the generation of the raw sequencing data and not (yet) the data analysis, which currently constitutes the major bottleneck for this technology. WGS has many advantages: It provides a nearly complete list of all genetic variants in a given dog's genome. Thus, WGS is the method of choice, if more than one candidate gene needs to be considered or if the candidate gene has many exons. The lab work for WGS is highly standardized and can be outsourced to commercial service providers. WGS has a higher sensitivity to detect structural variants than amplicon-based approaches. The only major drawback of WGS are the large data amounts necessitating complex bioinformatic analyses. Currently, this requires highly qualified personnel and considerable computational hardware. In the environment of the authors, WGS-based variant discovery in dogs still takes a few months. It is expected that WGS based approaches will further evolve and become more automated. In the not too distant future, it seems feasible that a WGS experiment of a single dog including data analysis may be completed in two weeks for approximately $1000. In specialized centres for human newborns, WGS can already be completed in less than a week to enable rapid therapeutic intervention (Hayeems et al., 2020). A hypothetical future diagnostic WGS analysis in a dog should provide a clear and concise report that is of use to veterinary clinicians. The report will have to be limited to all pathogenic and likely pathogenic genetic variants in clinically relevant genes with known functions. With these pending developments, it is a matter of time when the genetic analysis of canine patients with known genodermatoses transitions from research to standard diagnostics, similar to what has happened in human genetics (Lemke et al., 2014; Richards et al., 2015; Hayeems et al., 2020).

However, there is always the possibility that spontaneous mutation events result in the emergence of truly new heritable diseases that have never been seen before. New heritable diseases will remain the primary domain of veterinary genetics research. For almost a third of the 36 genes listed in this review, their significance for dermatology has initially been discovered in dogs, prior to any insights from humans, mice or any other species (Figs. 1, 3, and 4). The population structures of dogs in general and purebred dogs in particular are ideally suited for the elucidation of causative genetic variants in new genodermatoses and other heritable phenotypes, when no functional candidate genes are available. In these situations, hypothesis-free unbiased approaches have proven stunningly successful in veterinary genetics (Karlsson and Lindblad-Toh, 2008; Parker et al., 2010), although it is beyond the scope of this review to explain all these techniques in detail. The advances in sequencing technology and decreases in costs enable very direct experiments, in which complete genome sequences of single or multiple cases are directly compared to hundreds or thousands of control genome sequences. It is then straightforward to identify the so-called private variants that exclusively occur in an affected dog. If sufficiently large numbers of control genomes from genetically diverse dogs are available, these lists of private variants will become very short and may allow the direct identification of likely candidate causative genetic variants.

Benefits of genetic analyses

Increasing numbers of known genodermatoses in dogs and the substantial variability of their clinical and histopathological phenotypes pose significant challenges for the clinician to reach the correct diagnosis. Genetic analyses have matured into an important part of the diagnostic portfolio (Fig. 7). Genetic analysis is ideally performed on an EDTA blood sample and does not require highly invasive sample procurement. The costs for targeted genetic tests are comparable to many routine laboratory tests. The costs for experiments to detect new genetic variation are admittedly higher, but still in the range of commonly used diagnostic tests like MRI. Moreover, if a new heritable disease is suspected, the costs for genetic analyses can often be covered by research funds. The genome sequence or any experimentally determined genotype will remain stable and need to be determined only once throughout the life of a dog.

Knowing the causative genetic defect of a genodermatosis enables reliable predictions about the mode of inheritance, which is an essential prerequisite for rational breeding decisions. For example, the discovery that a new ichthyosis in a young German shepherd was due to a spontaneously arisen dominant allele was very good news for the breed as only the affected dog and its parents had to be excluded from breeding in order to reliably eradicate this specific disorder (Bauer et al., 2017a). Knowledge on the molecular pathogenesis furthermore directed the therapeutic management.

In some instances, the genetic diagnosis sheds light onto different aspects of a heritable disease that are not immediately obvious from the clinical presentation. A Rottweiler with pronounced footpad hyperkeratosis developed severe allergies at a few months of age (Backel et al., 2020). While the allergies were initially considered as a separate disease, the genetic analysis revealed a genetic variant in the *DSG1* gene, which leads to a barrier defect and causes a syndromic genodermatosis that is characterized by a combination of footpad hyperkeratosis and multiple allergies (Samuelov et al., 2013; Has et al., 2015; Backel et al., 2020).

In very rare instances, a precise diagnosis may even open options for a targeted therapy. Female dogs with heterozygous *NSDHL* loss-of-function variants develop verrucous epidermal keratinocytic nevi that

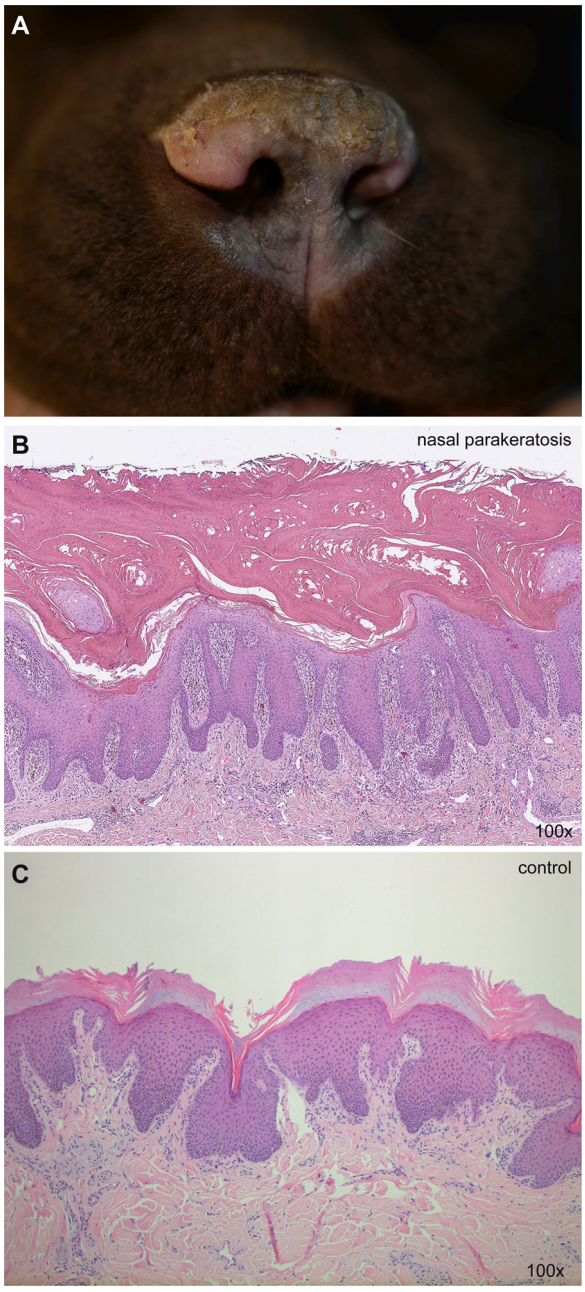

Fig. 3. *SUV39H2*-related hereditary nasal parakeratosis in Labrador retrievers. (A) Clinical phenotype. (B) Histopathology of affected nasal skin demonstrates pronounced parakeratotic hyperkeratosis. (C) Healthy control nasal skin (panel C from Jagannathan et al. (2013)). The *SUV39H2* gene encodes a histone 3 lysine 9 methyltransferase, which mediates transcriptional silencing of chromatin. Research into this disease helped to better understand the role of epigenetic processes during differentiation of keratinocytes (Balmer et al., 2021).

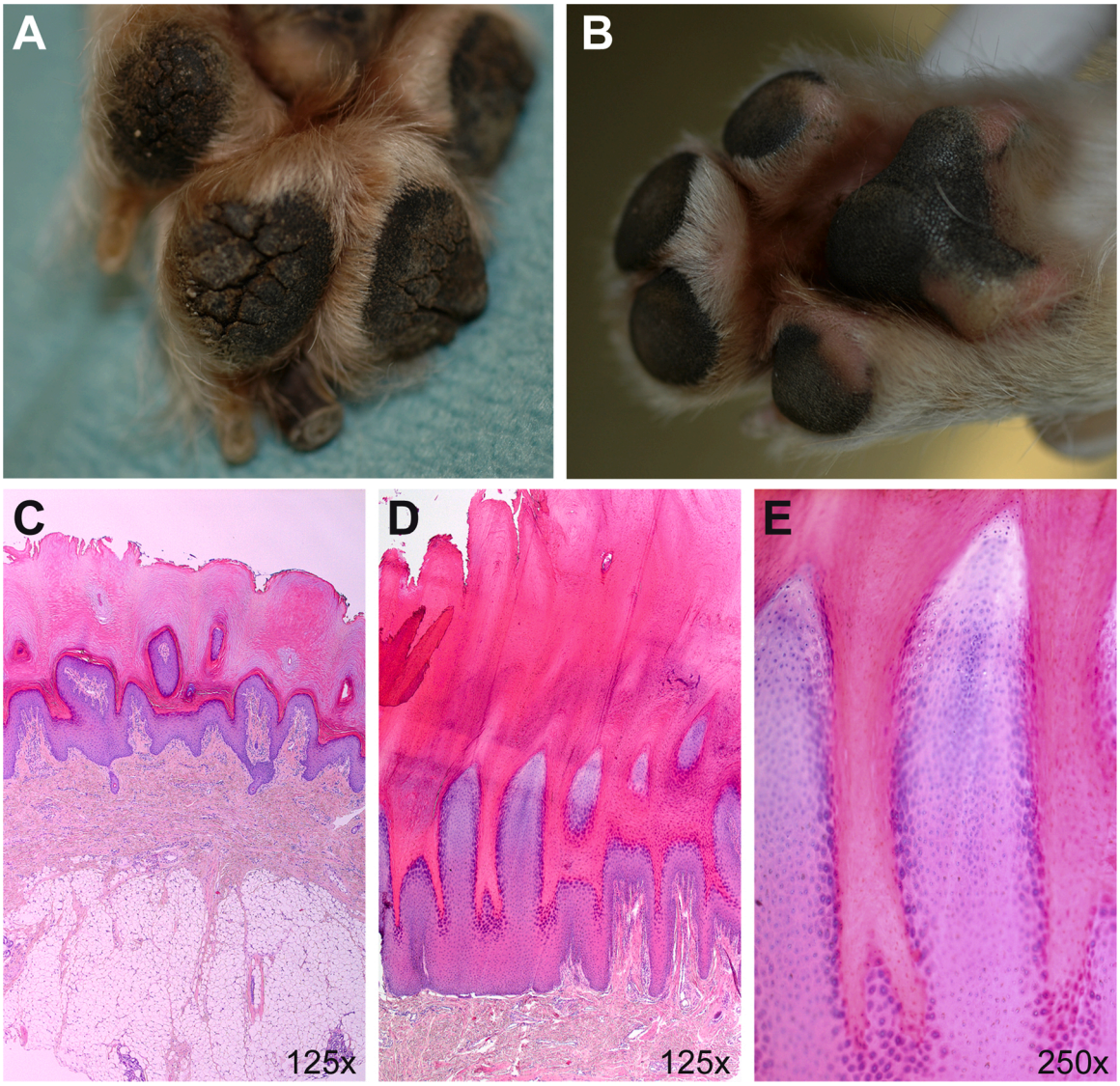

Fig. 4. *FAM83G*-related footpad hyperkeratosis in a Kromfohrländer (Drögemüller et al., 2014). (A) Footpad of an affected dog with deep fissures that require lifelong management and are prone to painful secondary infections. (B) Normal footpad from a control dog. (C) Control footpad skin biopsy. (D, E) Biopsy from an affected footpad showing the markedly thickened epidermis. The important role of FAM83G for the integrity of palmoplantar epidermis was initially discovered in dogs.

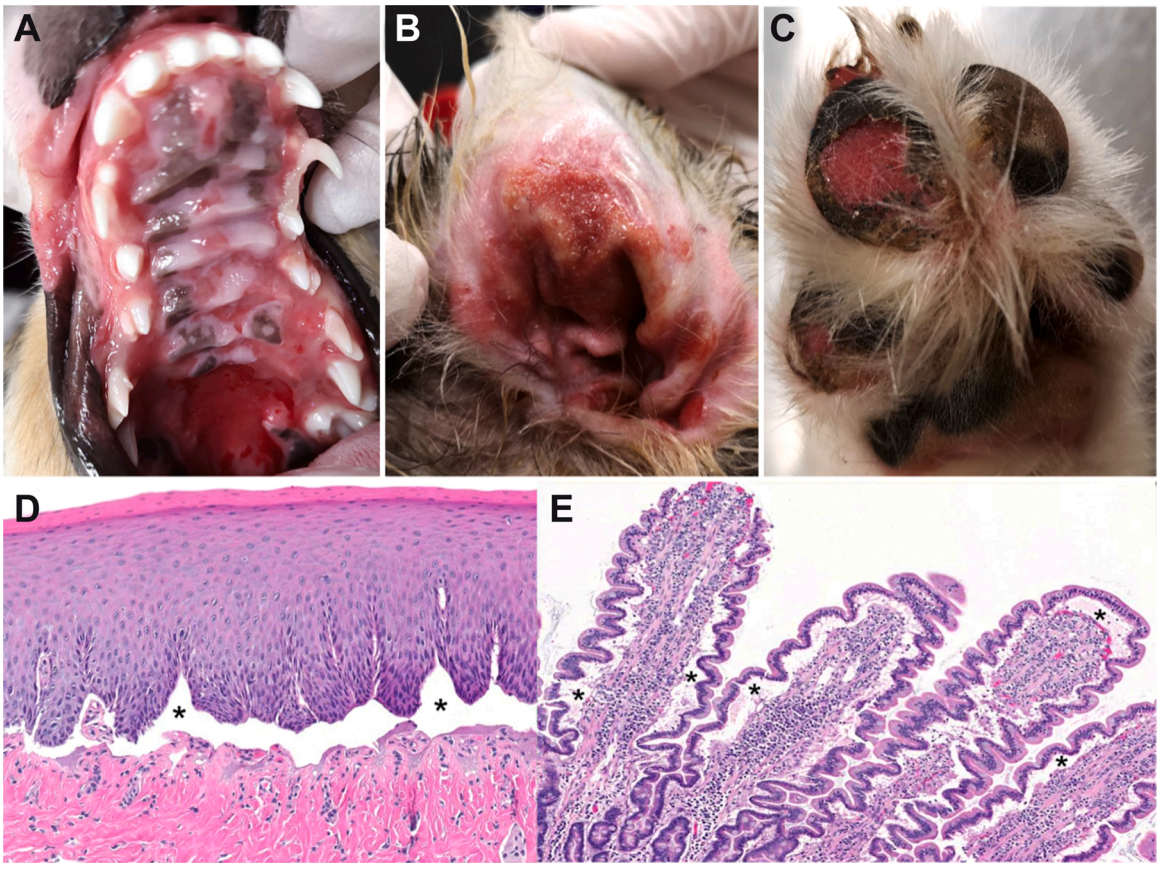

Fig. 5. *LAMB3*-related junctional epidermolysis bullosa in an Australian shepherd (Kiener et al., 2020). (A) Severe coalescing ulcers on the gingiva and hard and soft palate, (B) concave pinna and (C) footpads. Biopsy samples collected from the (D) oral cavity and (E) duodenum revealed widespread separation of the epithelium from the underlying connective tissue (asterisks).

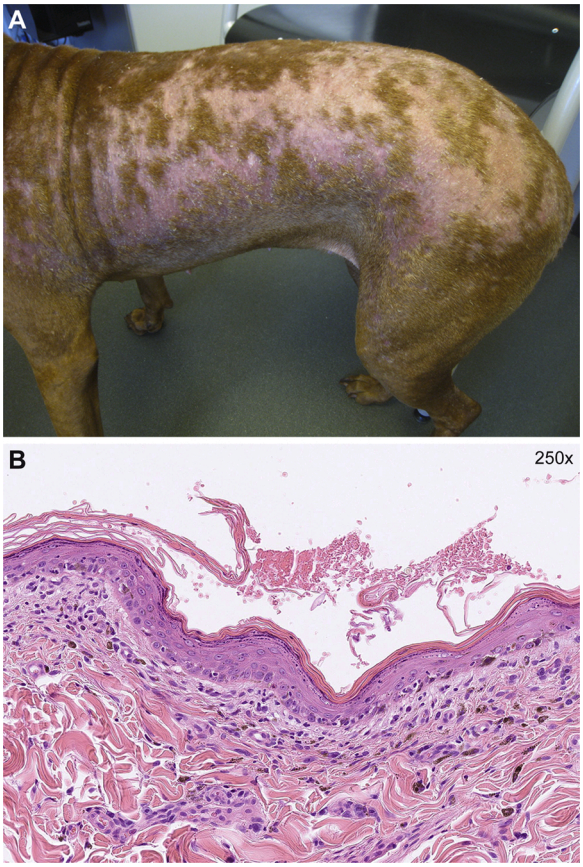

Fig. 6. *UNC93B1*-related exfoliative cutaneous lupus erythematosus (ECLE) in hunting dogs. (A) An affected Vizsla presents with severe multifocal to coalescing alopecia over the back and the lateral aspects of the trunk. The skin is erythematous and covered with large scale. (B) The histological findings are characterized by a diffuse interface dermatitis with hydropic degeneration of the basal cell layer and multifocal apoptotic cells in the basal cell layer. Subepidermally, there is a bandlike mostly lymphocytic infiltrate and severe pigmentary incontinence. The mildly hyperplastic epidermis is covered by moderate amounts of lamellar orthokeratotic keratin.

follow Blaschko's lines and are often arranged in linear patterns (Bauer et al., 2017b; Leuthard et al., 2019; Christen et al., 2020). The *NSDHL* gene encodes NAD(P) dependent steroid dehydrogenase-like, an enyzme required for cholesterol biosynthesis. The striking pattern of the skin lesions is due to the random X-chromosome inactivation in females. Cholesterol biosynthesis is blocked in skin areas, in which the X-chromosome with the defective *NSDHL* allele is expressed. In these skin areas, the lack of cholesterol and the accumulation of toxic metabolic intermediates cause the skin lesions. If the *NSDHL* defect is diagnosed in time, a topical therapy containing cholesterol and lovostatin to prevent the further production of toxic metabolites may lead to a marked improvement of the lesions (Leuthard et al., 2019).

Conclusions

Genetic analyses provide a valuable complement to clinical and histopathological examinations. They often represent the fastest and least invasive approach to enable a precise diagnosis. Knowledge on the causative genetic defect in a genodermatosis is essential to give rational breeding recommendations and may even open up options for targeted therapy. The investigation of new genodermatoses has the potential to inform human medicine and to unravel new gene functions that are required for the development and maintenance of healthy skin und thus contribute to our mechanistic understanding of skin homeostasis.

Checklist for clinical genetics

1) Clinical presentation, presumptive and differential diagnoses
   a. General and dermatological examination
   b. Skin lesions may be associated with systemic signs (or vice versa)
   c. High quality photos of the clinical lesions
2) Histopathology of skin biopsies, when indicated
   a. Correct biopsy sites, correct sampling technique
   b. Evaluation by a veterinary pathologist with special interest in dermatology
3) Family history
   a. Phenotype of dam and sire?
   b. Phenotype of littermates?
   c. Similar cases in the same breed?
4) Pedigree records of canine patient
5) EDTA blood sample from canine patient
6) Optional: EDTA blood samples from dam, sire and littermates

Fig. 7. Key requirements for the genetic analysis of a suspected new genodermatosis. If an inherited disease is suspected, it is essential to document a family history and to take appropriate samples suitable for DNA isolation. Obtaining additional samples from the parents (first priority) and/or littermates (second priority) increases the chances of success.

Interested clinicians and pathologists are encouraged to consult with veterinary geneticists if they suspect a new genodermatosis.

Conflict of interest statement

The University of Bern holds a patent on genetic testing for hereditary nasal parakeratosis in Labrador retrievers. Royalties from this patent are paid to the University of Bern and Tosso Leeb.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.tvjl.2021.105782.

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