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GENES OF CONGENITAL DERMATOLOGIC DISORDERS IN DOGS—A REVIEW

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ABSTRACT

This article presents an overview of up-to-date identified genes responsible for congenital canine skin diseases of dogs and the characteristics of these diseases. Congenital skin diseases constitute a specific group of dermatologic disorders that plays an important role in breeding of purebred dogs. They include primary seborrhoea, ichthyosis, hereditary nasal parakeratosis, dermatomyositis, colour dilution alopecia, skin mucinosis, dermoid sinus, lethal acrodermatitis, acral mutilation syndrome, keratoconjunctivitis sicca, ichthyosiform dermatosis, bullous epidermolysis, exfoliative dermal lupus erythematosus, congenital footpad hyperkeratosis and sebaceous adenitis. In the majority of cases, their occurrence is linked to particular breeds. In more than half of these diseases a specific defective gene variant responsible for the disease has been identified. Genetic tests for identification of the relevant defective genes serve as an important tool in the diagnostics of diseases in veterinary practice and in breeding of purebred dogs.

Key words: congenital dermatologic disease; dog; gene; skin

INTRODUCTION

The group of dermatologic disorders of dogs consists of diseases of different origin (bacterial, parasitic, autoimmune, hormonal, viral, metabolic, hereditary, etc.) and, typically, they have very similar clinical signs. The differential diagnostics in veterinary dermatology is very complicated and for various reasons, incorrect diagnosis has frequently been made [20].

Congenital skin disorders constitute a specific type of skin diseases. They are not common, or sporadic, and play an important role in the breeding of purebred dogs. Many congenital diseases developed first as spontaneous mutations that by cognation, or very limited selection of individuals used for breeding, were gradually induced in the genome of many descendants. The majority of congenital skin disorders are monogenic as they are caused by one defective gene and there is still no cure for them. In the ma-

jority of cases, autosomal recessive inheritance is involved and the simple Mendelian way of inheritance is applicable [17]. Congenital canine skin diseases include: primary seborrhoea, ichthyosis, hereditary nasal parakeratosis, dermatomyositis, colour dilution alopecia, skin mucinosis, dermoid sinus, lethal acrodermatitis, acral mutilation syndrome, keratoconjunctivitis sicca, ichthyosiform dermatosis, bullous epidermolysis, exfoliative dermal lupus erythematosus, congenital footpad hyperkeratosis and sebaceous adenitis [2, 4, 14, 18, 21, 22, 27, 33, 35, 40, 42, 47, 48, 52]. The congenital skin diseases are mostly linked to specific breeds or their direct crossbreds. More than half of these diseases have been identified genetically and the variant of the gene responsible for the disease were confirmed (Tab. 1) [5, 10—14, 16, 17, 23, 25, 27, 32, 36, 38, 46, 51]. Standardized genetic tests based on PCR were developed to identify the particular defective genes. For some congenital diseases the defective genes have not yet been identified or for the time being there is available only information about their presumptive localisation in certain chromosome [4, 22, 47, 48]. The clinical picture of an individual disease may differ depending on the specific affected breed, but also within the breed, the signs may vary considerably among the individuals [17]. The introduction of genetic tests into a veterinary practice can prevent many erroneous diagnoses of skin diseases. Genetic tests may constitute an important contribution to the breeding of purebred dogs, whether in planning of parental pairs or elimination of individuals unsuitable for breeding; because not all congenital skin diseases may be confirmed by genetic tests and due to a broad range of severity of clinical signs of individual diseases, biopsies of skin and the subsequent histopathologic examination play an important role [20, 22].

The aim of this article was to present an overview of up-to-date identified genes responsible for congenital canine skin diseases of dogs and characteristics of these diseases.

Table 1. Congenital dermatologic disorders of dogs—genes responsible for the disease and the most frequently affected dog breeds [5, 10—14, 16, 17, 23, 25, 27, 32, 36, 38, 46, 51]

Congenital dermatologic disorders	Defective variant of the gene	The most frequently affected dog breeds
Hereditary nasal parakeratosis	*SUV39H2*	Labrador Retriever, Greyhound
Colour dilution alopecia	*MLPH*	Doberman, German Pinscher, Dachshund, Greyhound, Whippet, Great Dane, Labrador Retriever, Yorkshire Terrier, German Shepherd, Chow
Lethal acrodermatitis	*MKLN1*	Bull Terrier, Miniature Bull Terrier
Acral mutilation syndrome	*GDNF*	English Cocker Spaniel, English Pointer, English Springer Spaniel, French Spaniel, German Shorthaired Pointer
Congenital keratoconjunctivitis sicca and ichthyosiform dermatosis	*FAM83H*	Cavalier King Charles Spaniel
Junction bullous epidermolysis	*LAMA3*	German Shorthaired Pointer
Epidermolysis bullosa simplex	*PLEC*	Eurasier dog, Chesapeake Bay Retriever
Dystrophic epidermolysis bullosa	*COL7A1*	Central Asian Shepherd
Exfoliative cutaneous lupus erythematosus	*p.Pro480Thr*	German Shorthaired Pointer, Hungarian Vizsla, Braque du Bourbonnais
Hereditary footpad hyperkeratosis	*FAM83G*	Irish Terrier, Cromforland Dog, Bordeaux Dane, French Mastiff, German Jagdterrier
Non-epidermolytic ichthyosis	*PNPLA1* *SLC27A4* *NIPAL4* *TGM1*	Golden Retriever German Dane American Bulldog Jack Russell Terrier
Epidermolytic ichthyosis	*KRT10*	Norfolk Terrier

Hereditary nasal parakeratosis

Hereditary nasal parakeratosis is described as an autosomal recessive condition. It is unique to the Labrador Retriever and English Greyhound. Mutation ("N324K missense variant") in the *SUV39H2* gene has been described as the genetic cause of the development of hereditary nasal parakeratosis. This genetic variant *SUV39H2* is associated with an inactive enzyme SUV39H2 [6, 23, 49]. It has been assumed that the *SUV39H2* gene affects a great number of cell processes, such as: proliferation and differentiation of keratinocytes and the synthesis of some specific proteins. The unequivocal role of the *SUV39H2* gene in skin has not yet been completely elucidated. The proteins specific for the terminal differentiation processes include loricrin, invulocrin and filagrin. It is likely that the loricrin may play a key role in the hereditary nasal parakeratosis [1]. In the healthy dog, loricrin is the main constituent of the epidermal keratinised coat where it accounts for 70—85 % of the proteinaceous components [9], while the amount of loricrin detected in the *planum nasale* of dog suffering from hereditary nasal parakeratosis is insufficient. It has been assumed that the deficiency of loricrin seriously disturbs the final phase of differentiation and results in impaired *stratum corneum*. Besides loricrin, changes involve also keratin, involucrin and other proteins therefore it is not possible to identify clearly the ways and causes of the development of this disorder [1].

The main and exclusive sign is a non-pruritic hyperkeratosis of the *nasal planum* in otherwise healthy dogs. The first visible changes are in the muzzle and can be observed in 6 to 12 weeks old puppies, but the clinical signs do not appear until the age of 6 to 24 months. The signs may be mild, in the form of the dry crusty layer on the dorsal portion of the muzzle that cannot be detached, or they may be more serious with the occurrence of erosions and fissures [40, 44]. Only one study described intercurrent signs that affected the entire dorsal part of the nose, ears and paws [26]. Mandatory genetic testing of dogs in breeding centres may prevent the development of hereditary nasal parakeratosis and significantly reduce its incidence in the future.

Colour-dilution alopecia

Colour-dilution alopecia is associated with a generally called dd phenotype (colour-dilution genes) that changes the hair colour from black or brown to blue, fawn or taupe. A characteristic feature of this colour-dilution phenotype is the defective transport of melanosomes leading to large clumps of pigment in melanocytes. This syndrome is most common in Dobermans (Blue Doberman Syndrome) in which the blue-grey colour may develop due to inhibition of full pigmentation. Dilution of hair colour is caused by mutations in *MLPH* (the melanophilin gene). In dogs, the *MLPH* gene is associated with the D locus and three variants, c.-22G > A (d^1), c.705G > C (d^2), and c.667_668insC) (d^3) [51]. This colour-dilution alopecia affects also other breeds that possess the colour-dilution genes, for example, German Pinschers, Italian Greyhounds, Greyhounds, Whippets, Yorkshire terriers, German Shepherds, Chow Chows, Silver Labrador terriers and many other breeds [8, 26, 37, 42, 45].

Puppies with defective genes are born without signs of this disease. The first loss of hair usually occurs between 6 months to three years of age, but some even later. The signs such as dry split hair, scales, folliculitis, hypotrichosis development of comedones and alopecia are observed in the areas of blue coloured hair or hair with other colour dilution. Histopathologically, the epidermis is relatively normal but may be hyperplastic. Hair follicles are atrophied and deformed. Melanin clumps are observed in follicles, epidermis and dermis. The disease is not accompanied with pruritus, but the loss of hair cannot be affected or treated. The treatment by supportive preparations can improve only the skin status. This syndrome is undesirable but the dog can lead a normal life in the household of his owner [26, 37].

Lethal acrodermatitis

Lethal acrodermatitis is an autosomal recessive hereditary disease which affects Bull Terriers and Miniature Bull Terriers. The examination of the genome of affected dogs identified a variant in the *MKLN1* gene that encodes the intracellular protein muskelin 1. The various cellular functions that have been postulated for muskelin 1 include roles in intracellular transport processes, cell morphology, cell spreading, and cell adhesion. However, the exact pathogenesis of acrodermatitis is still unclear [5].

The clinical signs of this disease appear in puppies shortly after birth. The principal sign is the progressive acrodermatitis with typical lesions at the marginal parts of the body. The characteristic skin lesions such as erythema, scales, erosions and scabby ulcerations appear mostly on the extremities and the muzzle. Later, the disease

progresses to hyperkeratosis on paws, onychogryposis, paronychia and pyoderma. The growth of the affected animals is retarded and they often suffer from diarrhoea and bronchopneumonia. The clinical signs may include diluted hair colour in the pigmented skin areas [33, 34]. An abnormally arched hard palate in the mouth and the presence of foul smelling residues of food in the mouth may serve as a marker for the diagnosis of this disease. Lower plasma zinc levels (supplementation of zinc did not result in improvement) were detected in the pups and lymphocytes in the T-lymphocyte region of the lymphoid tissue were significantly reduced [50]. The mean age of survival is 7 months and the maximal 2 years, or even more, and the animals die mostly due to health complications related to infections or must be euthanized due to serious lesions at the extremities that do not allow them to live normally. If they live up to the age of one year, their body weight usually reaches only one half of that of the dog of a similar age. The decrease in the incidence of lethal acrodermatitis can be achieved only by identification of carriers of this disease by genetic testing and their elimination from breeding [5, 24].

Acral mutilation syndrome

Acral mutilation syndrome (AMS) is caused by one variant—mutation within the regulatory region of the gene for the Glial Cell-derived Neurotrophic Factor (GDNF), located 90 kb upstream of the *GDNF* gene. GDNF is the factor that strongly promotes development of new neurons, growth of axons and the survival of adult neurons. AMS causative mutation disturbs the expression of *GDNF* gene causing a decrease in the level of GDNF which leads to progressive degeneration and abnormal development of sensory neurons in the spinal cord and peripheral nerves. This disorder causes insensitivity to pain in the distal extremities. The pathological process affects only primary sensory neurons. This disorder affects most commonly: English Cocker Spaniels, English Pointers, English Springer Spaniels, French Spaniels and German Shorthaired Pointers [2, 41, 46].

The disease can affect only one limb or more and the involvement of the pelvic limbs are more serious. Dogs lick, chew and bite distal parts of their limbs which results in various erosions and damage and in the worse cases even auto-amputation of parts of them (claws, digits, footpads). Paws are swollen and bleeding, present are skin abscesses, ulcerations, infections, hyperpigmentation and fibrosis. Insensitivity to pain in the extremities is a typical symptom of this disorder. Dogs walk normally on mutilated limbs without feeling the pain or limping. Puppies affected by AMS appear smaller than healthy pups in the litter. The first signs of limb biting are observed when they are 3.5 to 12 months old. There is no cure for this disease. It is necessary to limit the access of animals to their limbs by various bandages, protective sleeves or collars, or limit the mutilation by application of preparations with unpleasant taste. The disease is not life threatening but requires much patience and care from the owner and the outcome is not always successful. Even after all the efforts, the disease sometimes ends by euthanasia. Affected animals must not be used for breeding. Genetic tests for the identification of carriers and their elimination from breeding is recommended [2, 41].

Congenital keratoconjunctivitis sicca and ichthyosiform dermatosis

Congenital keratoconjunctivitis sicca (KCS) and ichthyosiform dermatosis present as one disease that affects only the Cavalier King Charles Spaniel breed. Dog breeders refer to this disease as "dry eye curly coat syndrome". In 2012 it was revealed that this condition is caused by deletion of one base pair in gene *FAM83H* [16].

The signs of this disorder appear at an early age and the affected individuals are smaller than their healthy siblings, they have rough curly coat on their back and after eyelid opening they suffer from KCS. Reduced production of tears and qualitative abnormality of tear film led to serious cases of sticky mucoid or mucopurulent eye discharge and ulceration of the cornea. In addition to a curly coat of poor quality along the dorsal spine, scales and alopecia appear in this region. Footpads are hyperkeratinized with nail growth abnormalities and intermitted sloughing is observed, leading to pain and limping. Dogs suffering from this disease show increase in dental diseases, extensive production of dental calculus and serious gingivitis which often results in teeth extraction. Symptomatic treatment has been used to relieve the symptoms but due to early diagnosis in puppies and unfavourable prognosis the breeders frequently decide to euthanize the affected individuals. Congenital keratoconjunctivitis sicca and ichthyosiform dermatosis is inherited by an autosomal recessive mode and can be confirmed by genetic testing [3, 16, 21].

Epidermolysis bullosa

Epidermolysis bullosa is a rare autosomal recessive dermal disease characterised by the loss of epidermal-dermal integrity, extreme fragility of skin and mucous membranes, development of blisters and erosions as a response to the smallest mechanical trauma. This disease is caused by gene mutations and frequently ends in death or euthanasia of the affected dog. The phenotypic changes are due to abnormalities in specific structural proteins within the epidermis and basement membrane zone. According to localisation of the subcellular defect, three main types of epidermolysis have been recognised in veterinary medicine: simplex, junctional and dystrophic [35].

The German Shorthair Pointer is affected by junctional bullous epidermolysis caused by a variant of the *LAMA3* gene and is typical by the development of defects in *lamina lucida*. These defects are caused by mutations affecting either extracellular matrix protein laminin 5 (essential for keratinocytes), its cellular receptor integrin α6β4, or collagen type XVII. Signs appear shortly after birth and the animal may die soon. The skin and mucous membranes are very fragile, susceptible to tearing and massive non-healing erosions, blisters, ulcers and deep wounds develop. The condition is very painful. The most frequently affected regions include: muzzle, footpads, elbows, knees, flanks, genitals and ears, but any other region can respond by damage at a small touch. Erosions can appear also in the oral cavity, nasopharynx, pharynx and other parts of the digestive and respiratory systems which causes considerable problems with accepting food or breathing. There is no cure for this disease [25, 39, 43]. Currently, the reduction in the number of affected individuals, the carriers, can be achieved by not using them for breeding which is feasible as they can be identified by commonly available genetic tests. Recently, the disease was confirmed in an Australian Shepherd litter where there was identified a single protein-changing variant, *LAMB3*: c.1174T> C. This is a "human variant" that was confirmed in the animal kingdom for the first time [25].

Bullous epidermolysis simplex is the most superficial form and includes damage or loss of proteins in the cytoskeleton of basal or suprabasal keratinocytes. This type was described in the Eurasier dog and is caused by the variant in the gene *PLEC*, that resulted in defective production of plectin. Plectin is a ubiquitous linker protein that acts to connect the components of the cellular cytoskeleton to proteins in the dermis, nervous system and skeletal muscles. A special form classified as suprabasal form of epidermolysis bullosa simplex is called Ectodermal Dysplasia-Skin Fragility Syndrome (ED-SFS) and affects Chesapeake Bay Retrievers known as Chesapeake. It can be confirmed by genetic testing [32].

The disorder associated with dystrophic bullous epidermolysis involves the superficial layer of the dermis. A serious form of dystrophic bullous epidermolysis was detected in a Central Asian Shepherd. It is caused by the defective gene *COL7A1*. The variant results in a premature stop codon and likely absence of the functional protein in the basement membrane of the skin in the affected dogs [38].

Exfoliative cutaneous lupus erythematosus

Exfoliative cutaneous lupus erythematosus is a serious form of a dermal disorder called lupus erythematosus. It occurs as a hereditary disease particularly in German Shorthaired Pointers but was diagnosed also in Braque du Bourbonnais. It is an autosomal recessive hereditary disease caused by a homozygous mutant variant *p.Pro480Thr* that binds to chromosome 18 and affects the C-terminal end of UNC93B1, limiting the TLR7 mediated autoimmunity by means of interaction with syndecan binding protein (adhesive role receptors). UNC93B1 is a transmembrane protein positioned in the endoplasmic reticulum and endolysosomes, necessary for correct functioning with several Toll-like receptors (TLR-transmembrane receptors play a key role in an innate immune response and constitute the primary recognition system of the body) [27].

The first skin lesions are easily visible at the age of 4 to 6 months but appear also in young adult dogs. The signs of lesions usually proceed from the face region (particularly the dorsal part of the muzzle and ears) to trunk (the neck is affected less commonly), tail, scrotum and limbs. Skin manifestations start as extensive scaling, followed by erythema with or without depigmentation, erosions, exudative ulcers, adherent crusts and gradual alopecia without growth of new hair. Secondary infections of skin and ears may appear. Over time, arthralgia develops in dogs manifested by limping, hunched posture and reluctance to move. Neither *post mortem* examination nor histological examination of joints, spinal cord and peripheral nerves shows any pathological changes that would explain the symptoms concerning the locomotory apparatus. The de-

velopment of a progressive infertility was recorded in dogs of both sexes (oligospermy, later azospermia in males and irregular or absent oestrous cycle in females), haematological abnormalities (lymphopenia, thrombocytopenia), generalised peripheral lymphadenopathy, enterocolitis and others. Treatment with immunomodulatory drugs are frequently insufficient to ensure long-term control of this disease. Dogs with progressive disease must be frequently euthanized [15, 30].

Hereditary footpad hyperkeratosis

Hereditary footpad hyperkeratosis, originally referred to as digital hyperkeratosis, causes palmoplantar hyperkeratosis in the breeds such as: Irish Terriers, Cromforland Dogs, Bordeaux Danes, French Mastiffs and German Jagdterriers. The disease is caused by a mutation in the gene expressing protein FAM83G. The family of FAM83 proteins consists of 8 known members, FAM83A to FAM83H. Another mutation in the gene *FAM83H* in dogs causes hereditary diseases: keratoconjunctivitis sicca and ichthyosiform dermatosis in the breed Cavalier King Charles Spaniels that presents with some phenotypic manifestations similar to digital hyperkeratosis [14].

The first manifestations of this disease appear from the age of 10 weeks up to one year and involves all footpads. The surface of the footpads are very hard and deep cracks often develop that open into sensitive living cell layers. Similar cracks may develop also in healthy dogs due to external factors, but they heal spontaneously in contrast to dogs with hyperkeratosis. The affected dogs have problems with walking on irregular surfaces and refuse to move due to the pain. The cracks may lead to the development of infections which intensifies the pain. The claws are very hard and it seems that they grow faster. The seriousness of the symptoms may differ between individual dogs; even between the footpads of the same dog. The available therapy is only symptomatic. In a differential diagnosis, it is necessary to eliminate idiopathic hyperkeratosis which develops for unknown reasons. Hereditary footpad hyperkeratosis can be identified by a genetic test [14].

Ichthyosis

Ichthyosis belongs to the group of genetically conditioned dermatoses that present by excessive scaling and peeling of the scales over the entire body. The scaling is caused by a defective gene that disturbs a certain phase of the formation of the *stratum corneum* [11]. The process of the *stratum corneum* formation is complicated and each step of this process is controlled by genes. In case of the presence of the defective genetic information and disturbance in one step of the process of formation of this skin layer, the formation of the healthy *stratum corneum* is impossible. The change in any step results in disturbances in the barrier function of the *stratum corneum* and in an attempt to repair them. This leads to excessive regulation of lipids in order to replenish the *stratum corneum* and as a result of this the epidermis becomes hyperplastic [18, 28].

Ichthyosis has been recognised as a disease for a long time but only in 2012 was the defective gene identified in the genome of a Golden Retriever [17]. Two basic forms of ichthyosis have been characterised in veterinary medicine, i.e., epidermolytic ichthyosis typical of Norfolk Terriers and a non-epidermolytic one that affects various breeds. It should be noted that individual breeds mostly possess mutations in different genes that result in different clinical pictures of ichthyosis in the affected breeds [17, 19, 20].

Epidermolytic ichthyosis in Golden Retrievers is caused by a mutation in the *PNPLA1* gene. It is not completely clear whether the *PNPLA1* gene is the only gene involved in the development of ichthyosis in Golden Rretrievers or other genes or environmental factors play also some role and therefore ichthyosis is sometimes classified as heterogenic disease. In Golden Retrievers ichthyosis, it is presented with adherent scales of various size (from small to large) and a wide range of colouring. Clinical signs of fully manifested disease include skin lesions, exfoliation and hyperpigmentation [17, 18]. In Great Danes, ichthyosis is caused by the mutant variant of the *SLC27A4* gene. Expression of this gene results in non-uniform distribution of lipids in the *stratum corneum* and disturbances in the formation of the dermal barrier. Ichthyosis in this breed is manifested by strong wrinkles in the head and legs area in puppies. The face of these puppies looks like that of Shar-Pei dogs. The skin on the head and legs, particularly around the nose and eyes have an oily appearance. Fine white to yellow scales begin to appear all over the body in the coat. The skin is dry, inelastic and lichenified [36]. In American Bulldogs ichthyosis is caused by a molecular defect in the *NIPAL4* gene responsible for production of non-functional shortened protein ichthyin, necessary for the formation of the healthy *stratum corneum*. It is manifested by the development of larger or smaller scales [11,

31]. Ichthyosis in Jack Russel Terriers is caused by insertion in the gene *TGM1* [13]. In German Shepherds the ichthyosis was diagnosed as *de novo* missense variant in the gene *ASPRV1*. This novel variant has arisen by mutation that must have occurred either in one of the parental germlines or during early embryonic development of this individual [7]. In English Springer Spaniels, Labrador Retrievers and West Highland White Terriers, the cases of ichthyosis were confirmed, but molecular identification has not been documented [29]. Epidermolytic ichthyosis caused by mutation in the keratin encoding gene *KRT10* occurs in Norfolk Terriers. Generalised and pigmented hyperkeratosis with epidermal fragility developed in the affected dogs [12].

CONCLUSIONS

Congenital dermatological disorders of dogs play an essential role in the breeding of purebred dogs. Individual types of these diseases are mostly associated with specific breeds although in some cases, they can develop also sporadically in any individual as a result of spontaneous mutations. Owing to the advances in genetics in the past decade, the cause of more than half of all congenital dermal diseases has been identified genetically and the relevant genetic tests for diagnosis of these diseases contributed greatly to veterinary practice and to dog breeding.

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