

Review: Role of genetics and the environment in the pathogenesis of canine atopic dermatitis

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Background – Multiple levels of evidence support the role of genetics and the environment in the pathogenesis of canine atopic dermatitis (AD).

Objectives – This review summarizes the current evidence in genetics and the effect of environmental factors on the development and perpetuation of canine AD.

Methods – Citation databases, abstracts and proceedings from international meetings published between 2001 and 2013 were reviewed in this update. Where necessary, older articles were included for background information.

Results – Canine AD is a heritable disease, in which interaction with environmental factors influences disease risk and phenotype. A study of British guide dogs indicated that nearly 50% of the risk of developing AD was determined by an individual's genotype. Genomic studies performed so far in canine AD have uncovered numerous gene candidates likely to be involved in pathogenesis through their role in immunity, skin barrier formation, apoptosis and inflammation. In addition to genetics, there is evidence to suggest that exposure to certain environmental factors influences the prevalence and course of canine AD. For example, living in rural areas or feeding noncommercial diets was negatively associated with the development of AD in dogs, while exposure to high levels of smoke was associated with increased prevalence of allergic skin disease.

Conclusions – It is becoming clear that canine AD is genotypically complex and influenced by a variety of environmental factors. Well-designed studies with sufficient statistical power will be critical to identify the complex genetic and environmental factors involved in disease development and progression. Recognition of such factors may help to identify new targets for therapy and enable better disease prevention and management.

Introduction

Canine atopic dermatitis (AD) is an inflammatory and pruritic disease with typical clinical signs associated with an immunoglobulin E (IgE) production directed most commonly against environmental allergens.¹ Genetic predisposition has been accepted as an important com-

ponent in the pathogenesis of this disease for several decades. The recently increased availability of advanced molecular techniques such as genome-wide association and candidate gene association studies commenced investigations of the hereditary component of AD in dogs. Although the published genetic background of canine AD is still far from being completed, it is becoming clear that a complex network of potential candidate genes is likely to be involved. Moreover, the multifaceted nature of the disease supports the role of other elements, including environmental factors. The aim of this paper is to review the current evidence in the genetics of canine AD and the effect of the environment on the disease development and phenotype.

The genetics of canine atopic dermatitis

Historical perspective

At the time of the 2001 American College of Veterinary Dermatology Task Force on Canine Atopic

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Dermatitis review, a number of studies had been published to determine the heritability of atopic dermatitis in the dog.² The earliest study had attempted to identify associations between canine leucocyte antigen (DLA) genes and total IgE levels in healthy dogs and in dogs with positive intradermal allergen test results.³ No significant difference could be found in total IgE levels and DLA haplotype between healthy and atopic dogs.³ However, the combination of the haplotypes DLA-A3 and R15 was found to be present more frequently in atopic versus healthy dogs.³

Many of the later works were simple descriptive studies designed to determine breed predisposition.^{4–7} Unfortunately, interpretation of the results of many of these reports was limited by a failure to adjust the analyses for the breed prevalence of the test populations. It is notable that the lists of predisposed breeds differed considerably between these studies despite the correction for hospital populations, suggesting that other factors (such as within-breed variation between different geographical areas) may have significantly influenced results.^{4–6}

Attempts to determine heritability by prospective or retrospective pedigree or breeding analysis were generally not supportive of a simple mode of inheritance. Breeding studies performed during attempts to develop a colony of atopic dogs by breeding affected individuals demonstrated that relatively few (18%) of the offspring developed spontaneous clinical disease.⁸ Likewise, a prospective study evaluating West Highland white terriers (WHWTs) also failed to find clear evidence of heritability.⁹ In contrast, the tendency of certain beagle dogs to develop high IgE levels following early allergen sensitization appeared to follow a dominant mode of inheritance.¹⁰ However, the high IgE reactivity was dependent upon early-life exposure to allergen, indicating the critical nature of environmental–genetic interactions.¹⁰ Furthermore, only some of the high IgE responders developed clinical signs consistent with AD postchallenge, further underscoring the complex nature of the development of clinical disease.¹⁰

Update on the genetics of canine atopic dermatitis

In contrast to murine AD models, canine AD appears to have a complex genetic basis, which, together with environmental factors, predisposes individuals to develop clinical disease. The strong breed predilection for AD supports a genetic basis for the condition.^{11–14} Golden retrievers, WHWTs, German shepherd dogs, cocker spaniels, boxers and French bulldogs were the most commonly reported breeds in these studies, although the predilection for AD varied between different regions and continents. A study of British guide dogs (mostly Labrador and golden retrievers and their crosses used to guide blind and partially sighted people) showed that the heritability was estimated to be 0.47, indicating that nearly 50% of the risk of developing AD was determined by an individual's genotype.¹⁵ The same study also showed that the risk of a dog developing AD was greatest if both parents were atopic, moderate if only one was and lowest if neither parent was atopic.

Methods employed to identify the genes associated with development of canine AD include genome-wide linkage, genome-wide association and candidate gene association studies. To date, six genome-wide linkage and association studies have been published.^{16–21} In the first study, from the USA, genotyping and linkage analysis were performed on 30 WHWTs with AD, 50 healthy dogs and 28 dogs of undetermined status that belonged to three family groups based on their pedigrees.¹⁷ The authors were not able to detect any chromosomal regions that were significantly linked to AD, but they were able to exclude linkage of AD to the filaggrin (*FLG*) locus in this breed. The second study analysed WHWTs from Australia and included 35 dogs with AD, six undetermined dogs without classical signs of AD but with a history of one episode of otitis externa and/or occasional mild pruritus and 19 healthy dogs.¹⁶ Five of the undetermined and all healthy dogs belonged to one family line with a low prevalence of AD. Genome-wide single nucleotide polymorphism (SNP) analysis revealed a significant association between a projected 1.3 Mb area (53.4–54.7 Mb) on chromosome 17 and canine AD. This area was at least 10 Mb upstream from the canine *FLG* locus, further supporting the conclusion that *FLG* is not likely to be associated with AD in this breed.¹⁷ Furthermore, a candidate gene study of the *FLG* locus using haplotype sharing analysis excluded *FLG* as a major causative factor in AD in WHWTs.²² *PTPN22*, a gene among the 19 located <0.5 Mb from the interval of association on the chromosome 17, emerged as a plausible candidate gene for AD. This encodes a lymphoid tyrosine phosphatase involved in the prevention of spontaneous activation of T and B cells. Sequencing of *PTPN22* in three atopic and three healthy WHWTs revealed 18 polymorphisms possibly associated with AD, five of which were predicted to have a functional effect on the protein.²³ Another possible candidate gene located near chromosome 17 is the canine orthologue of the cytochrome P450 26B1 gene, which is involved in adipogenesis and retinoic acid pathways.¹⁶ Alteration of this enzyme could result in disruption of normal skin lipid metabolism and skin barrier function.

The third genome-wide association study looked at SNPs associated with AD in golden retriever dogs.¹⁸ The study reported two intronic SNPs to be significantly associated with AD in dogs of this breed (*PROM1* and *RAB3C*). Of these two, *RAB3C* is potentially relevant to the pathogenesis of AD, as a gene coding for a transporting protein found on lipid anchors.¹⁸ The same group performed further validation studies using the top 40 SNPs in 659 dogs from eight different dog breeds (boxer, German shepherd dog, Labrador and golden retriever, shiba inu, pit bull, shih tzu and WHWT) from the USA, UK and Japan. Thirteen SNPs were associated with AD, but only two were associated with AD in all eight breeds. These two SNPs are located on chromosomes 10 and 29 and, according to a conditional regression analysis and the odds ratios, are independent of each other, with one likely to be a protective and the other a susceptibility SNP.¹⁸ Further analysis detected an additional 11 SNPs associated with the atopic phenotype in individual breeds, suggesting that the atopic genotype is breed specific. This may explain breed-specific differences in the clinical

phenotype of AD. However, low statistical power limited the breed-specific analysis. This group further genotyped 97 SNPs in 25 candidate genes in the same 659 dogs.²⁴ The selection of these candidate genes was based on a literature search of human and canine AD and data from their previous mRNA microarray and quantitative RT-PCR studies.^{25,26} Using this approach, only one SNP within the thymic stromal lymphopoietin receptor was associated with AD in all eight dog breeds. The other five AD-associated SNPs were restricted to breeds from specific geographical locations. Interestingly, the associations were lost when the data were analysed with the focus on specific dog breeds only. The authors concluded that the small number of dogs from each breed limited the power to detect associations and that future studies should be breed and region specific.²⁴

In the fourth and fifth studies, genome-wide significant associations with high IgE levels were detected on chromosomes 5 and 35 in Labrador retriever and WHWT dogs, respectively.^{19,20} However, the Labrador dog study used allergen-specific immunoglobulin levels (IgE, IgG1 and IgG4, specific for a variety of house dust and storage mite, fungal, cat and insect allergens) as phenotypic markers for AD. Three SNPs on *Canis familiaris* chromosome 5 (CFA5; 79–82.5 Mb) were significantly associated with serum specific IgE levels; two with *Acarus siro* and one with *Tyrophagus putrescentiae*. The relevance of *Acarus*- and *Tyrophagus*-specific serum IgE in the pathogenesis of canine AD is unclear, and the use of surrogate markers does not accurately predict the AD phenotype. The West Highland white terrier dog study also included dogs with high allergen-specific IgE, with or without clinical signs of AD. Moreover, no genes involved in IgE regulation are known to reside in these areas on CFA5 and CFA35.

Finally, the last study performed a genome-wide association analysis in a Swedish population of German shepherd dogs.²¹ Owing to the strong positive correlation between AD and low IgA, IgA levels were included in the analysis. A significant association was identified on chromosome 27. The associated region contained eight genes, from which 11 smaller haplotype blocks were identified by targeted resequencing and additional genotyping. Two of these blocks showed the strongest association with AD, both being localized in the plakophilin 2 (*PKP2*) gene region. The authors hypothesized that plakophilin 2, a structural protein involved in desmosome and corneodesmosome formations, is likely to play an important role in skin barrier formation and thus represents a relevant candidate gene for AD.²¹ Indeed, a previous study in dogs showed statistically significant alteration of mRNA expression of *PKP2* in atopic dogs compared with that of healthy control dogs.²⁶

In summary, canine AD is a heritable disease, in which the interaction with environmental factors influences the disease risk and phenotype. New techniques, such as genome-wide association studies, will allow us greatly to improve our knowledge about this disease and help us to identify relevant gene polymorphisms. Previous experience suggests that genome-wide association and candidate gene approach studies should focus on specific

breeds and regions to increase the chance of finding such associations. It is also critical to design studies with a sufficient statistical power to allow for identification of polymorphisms with a relatively small effect on risk of disease.

Environmental contributions to atopic dermatitis

Historical perspective

Early studies on the role of the environment in the pathogenesis of canine AD focused on identification of allergens commonly associated with allergic disease. The original Task Force report reviewed studies reporting allergens identified by intradermal and serum testing, as well as putative allergens identified by response to immunotherapy and those presumed by inference from human studies.²⁷ That review identified a number of commonly reported allergens, including house dust, house dust mites (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*), storage mites (*Acarus siro* and *Tyrophagus putrescentiae*) and epidermal allergens (human, horse, cat and dog).²⁷ Other potential allergens (pollens, moulds) were more variable, as might be expected based upon varying geographical locations of the researchers and test subjects.²⁷ Nonetheless, the review found that individual studies often reported very different findings, even for allergens that would be expected to be relatively consistent over wide variations in geographical location, such as cat allergen.^{6,27,28} The authors proposed several reasons for these disparities, including the following: there was little to no consistency between studies with regard to the allergen types or concentrations tested; the allergen sources tested differed by manufacturer (and thus were likely to differ in precise content and biological potency); and *in vitro* assays may have varied with respect to specificity for canine IgE.²⁷ Simple extrapolation of allergens from studies in humans also proved likely to be of limited benefit, because preliminary attempts at more specific allergen identification in dogs (usually via western blotting methods) often found significant differences in reactivity between dogs and humans.^{27,29,30}

As a result, although these studies collectively provided large amounts of information regarding the identification of potential allergens in canine AD, they also identified several factors that needed to be addressed in future allergy-related research. These factors included the need for standardization of allergen testing methods, standardization of allergen extract preparation and identification of major allergens relevant to the dog.²⁷

In contrast to these descriptive studies, very little work had been performed specifically to identify environmental factors that might actively contribute to (or protect from) the development of AD in dogs. One study failed to demonstrate a clear association between housing status (research colony versus privately owned) and serum total IgE and total IgA levels.³¹ However, the animals evaluated in this study were all healthy, so no determination of the effect of housing upon the prevalence of atopic disease was possible.

Update on environmental contributions to atopic dermatitis

The 'hygiene hypothesis'

In 1989, David Strachan published the results of an epidemiological study of British children that demonstrated an inverse relationship between the number of children in a household and the incidence of both allergic respiratory disease and eczema.³² This effect was most pronounced for the younger children, i.e. each successive child became less likely to develop allergic disease. These findings suggested that early-life exposure to 'normal' childhood infections could protect against the development of allergic disease later in life. This phenomenon was named the 'hygiene hypothesis'. Support for this hypothesis was found in subsequent birth cohort studies demonstrating a lower prevalence of allergic disease in children raised in farm environments compared with their cohorts raised in the cities.^{33–36} Although several factors could be responsible for this apparent discrepancy (e.g. higher pollution levels in cities), the adoption of this hypothesis raised the possibility that the environment itself may play an active role in the development of hypersensitivity.

Endotoxin and other bacterial and fungal components

A possible explanation for the apparent decrease in allergic disease prevalence in adults and children in 'dirty' environments was proposed.³⁷ This study demonstrated that the response to endotoxin (lipopolysaccharide) was dose dependent; mice treated with aerosolized ovalbumin developed T helper 2 inflammatory responses in the presence of co-administered low-dose endotoxin, whereas the inflammatory response following exposure to high doses of endotoxin was predominantly T helper 1 in nature.³⁷ Further papers demonstrated an inverse correlation between the development of allergic diseases (including AD) in humans and environmental endotoxin exposure in children. One study showed that high endotoxin levels in the mother's mattress decreased the risk of AD in her children.³⁸ A meta-analysis demonstrated that people living in homes with high endotoxin levels were at a modestly reduced risk of developing allergic symptoms.³⁹ An even greater degree of protection was found in children living on farms with livestock in comparison to similar rural homes without livestock, suggesting that the protective effect of farm living was likely to involve more than endotoxin alone.³⁹ Other studies have demonstrated similar protective effects of livestock and rural living on the development of allergy in children and young adults.^{33,34} However, these findings are not universal, as other studies have failed to find a beneficial effect of early-life exposure to endotoxin or fungal components (β -glucans, ergosterol) on the development of allergic sensitization or asthma.^{40,41} Environmental microbial products other than endotoxin may also influence the development of sensitization. Proteases derived from *Aspergillus oryzae* can induce maturation of human dendritic cells (DCs), which subsequently enhanced the production of interleukin (IL)-4, IL-5 and IL-13 by co-cultured allogenic T cells.⁴²

In contrast to the human literature, there are very few reports specifically investigating the role of environmental

microbial components in the development or clinical course of canine AD. One study demonstrated a significant inverse association between canine hair coat endotoxin levels and atopic status, although this effect was no longer significant once the values were adjusted for age and sex.⁴³ The reason for this decrease is uncertain, although the authors state that they were unable to relate the decrease to bathing frequency (F. A. Loozingh van Beeck, 2011, unpublished data). In the same study, no significant association was seen between atopic status and the levels of exposure to fungal glucans in the hair coat and environment (floor, bedding) or to environmental endotoxin levels.⁴³

Although not directly related to evaluation of microbial exposure, three studies have investigated the role of geographical and environmental risk factors in the development of canine AD. One study demonstrated a reduced risk for developing AD in dogs living in a rural environment, with other animals or walking in forests. In contrast, living in a shed during puppyhood and adoption at an older age were associated with an increased risk of AD.⁴⁴ A second study found a significant negative association between feeding a noncommercial (and possibly microbe-rich) diet during lactation and the subsequent development of AD in the pups.⁴⁵ Finally, a study of insured Swedish dogs demonstrated an increased prevalence of AD in cities, areas with higher human density, higher rainfall, southern geographical locations and having a veterinary dermatologist in the county.⁴⁶ It is important to remember that these studies can only evaluate correlations, not causation. While some of the risk factors identified in these studies may indeed be related to an increased or decreased likelihood of developing AD in dogs, others are more likely to be artifactual (e.g. the increased prevalence of AD in counties with veterinary dermatologists may simply reflect an increased rate of diagnosis). Some effects, moreover, may be breed dependent. For example, there were no environmental triggers associated with AD in WHWTs, suggesting that the genotype is more critical in this breed.⁴⁵

Parasites

Helminth parasitism has been described to have varying effects on the development of atopic disease in humans, with both increased and decreased predisposition reported.⁴⁷ Dogs were administered helminth eggs as a means of treatment for AD in two studies. In the initial study, dogs with AD were administered *Trichuris vulpis* eggs.⁴⁸ This was associated with an improvement in pruritus and Canine Atopic Dermatitis Extent and Severity Index scores, but histological inflammation was not changed. However, in a follow-up placebo-controlled study, no significant difference was demonstrated between dogs receiving placebo or *T. vulpis* eggs.⁴⁹ The reasons for this discrepancy remain unclear, but the authors noted a distinct trend for a better response in dogs with more severe clinical signs.

House dust mites and storage mites

Several articles have reported that many mite components may be able to induce inflammatory responses directly in cells and tissues from nonsensitized individu-

als.^{50–59} This may result in an inflammatory milieu capable of driving overt sensitization in predisposed individuals.

Proteases. Group 1 mite allergens (Der f 1 and Der p 1) are potent cysteine proteases. They are active at relatively acid pH, similar to that found on the surface of mammalian skin. They have been documented to increase epithelial permeability in several *in vitro* culture systems through a variety of mechanisms, including the degradation of occludin, claudin and the tight junction protein zona occludens 1.^{60,61} Evidence suggests that they may increase epithelial permeability *in vivo* as well, because Der f 1 was found to enter the dermis and co-localize with CD1c⁺ dermal DCs after application of a crude slurry of *D. farinae* mites to intact canine skin.⁵⁰ This could increase the penetration of mite (and possibly nonmite) allergens through grossly intact skin, facilitating sensitization and exacerbating inflammation. Mite cysteine allergens also facilitate the actions of serine proteases by degrading α_1 -antitrypsin, providing another means of proteolytic degradation of epithelial surfaces.⁶²

Group 1 mite allergens can also induce inflammation by activation of human basophils and mast cells in an IgE-independent manner, inducing the release of the T helper 2 cytokine IL-4.⁵¹ They have been reported to inhibit negative feedback from IgE by cleaving the low-affinity IgE receptor (FcεRII, CD23) from the surface of human B cells.⁵² Furthermore, they inhibit the development of an effective T helper 1 cytokine response both by direct effects on human T cells (removal of the α -chain of the IL-2 receptor, CD25) and by impairing IL-12 secretion by human DCs [via removal of CD40 and dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN)].^{53,54,63} Finally, they have the potential to activate a variety of cell types via cleavage of protease-activated receptor 2 (PAR-2).⁵⁵

These pro-inflammatory properties may favour the development of allergic sensitization. For example, proteolytically active Der p 1 was found to enhance sensitization to a co-administered allergen (ovalbumin) in a mouse model.⁶⁴ Furthermore, Der f 1 has been found to enhance production of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-8/CXCL8 and tumour necrosis factor α from a canine keratinocyte cell line.⁵⁶ A second study using this cell line confirmed that production of GM-CSF was dependent upon the cysteine protease activity of Der f 1.⁵⁹ The hypersensitivity-enhancing properties of the group 1 mite allergens are not necessarily associated with their allergenicity *per se*, as although these are major allergens in humans, dogs are rarely sensitized to them.^{65,66}

Group 3, 6 and 9 allergens are serine proteases (trypsin like, chymotrypsin like and collagenase like, respectively). Serine proteases represent ~80% of the total protease activity demonstrable in dust mite extracts.⁶⁷ Like the group 1 allergens, mite serine proteases have been demonstrated to interfere with epithelial integrity by the disruption of tight junctions in multiple cell lines.⁶⁸ They are potent activators of PAR-2 in human keratinocytes and lung epithelial cells, and may directly induce mast cell and eosinophil degranulation.^{57,58} Mite serine proteases have been demonstrated to reduce epithelial localization of

E-cadherin in human bronchial epithelial cells.⁶⁹ This calcium-dependent adhesion molecule plays an important role in epidermal retention of Langerhans cells, and its decrease may be associated with increased migration of Langerhans cells to local lymph nodes, which may, in turn, facilitate sensitization.⁷⁰

Toll-like receptor interactions. The group 2 allergens Der f 2 and Der p 2 can act as molecular mimics of MD-2, which is part of the extracellular portion of Toll-like receptor 4 (TLR4; a bacterial endotoxin receptor).^{71,72} This may enhance the effects of endotoxin on TLR4-bearing immune cells or activate the receptor directly. The relevance of this was demonstrated in a study in which Der p 2 complexed with endotoxin induced T helper 2 immune responses in wild-type but not TLR4 knock-out mice.⁷² Der p 2 was also shown to induce direct activation of human B cells.⁷³

Group 2 proteins are major allergens in humans, but their relevance to canine AD is somewhat controversial. Studies seeking to define the major allergens of *D. farinae* and *D. pteronyssinus* found evidence of IgE reactivity to the group 2 allergens in only a small minority of atopic dogs in Europe and the USA.^{29,30,65} In contrast, another study reported that a 15 kDa *Dermatophagoides* antigen appeared to be a major allergen in Japanese dogs with AD.⁶⁶ This antigen was consistent with a group 2 allergen; it was recognized by an anti-Der f 2 antibody, and serum binding to purified Der f 2 could be demonstrated. These results suggest that group 2 mite allergens may play both adjuvant and allergen roles in canine AD.

The group 7 allergens may also interact with TLRs. Der p 7 has not been demonstrated to bind endotoxin, but it did bind polymixin B, a bacterial lipopeptide.⁷⁴ This allergen may serve to present other lipid structures to TLR2, resulting in its activation.

Other environmental and allergen sources

There have been fewer studies on the role of nonmite environmental agents on the development of AD. Nonmite-derived proteases from a variety of sources can induce inflammation in both cutaneous and noncutaneous models of hypersensitivity. A whole-body crude allergen extract from German cockroaches (*Blattella germanica*) activated and induced calcium mobilization in cells of the human airway cell line A549 via PAR-2 in a protease-dependent manner.⁷⁵ Both fungal (*Aspergillus oryzae* and *Penicillium citrinum*) and pollen extracts (Japanese cedar, Japanese cypress, ragweed and birch) have proteolytic activity.^{42,76–78} These proteases can degrade tight junction proteins *in vitro* in a manner similar to mite group 1 proteases and enhance the T helper 2-promoting effects of human DCs.^{42,78}

Oxidative stress is another possible mechanism by which environmental substances could promote the development of hypersensitivity. Ragweed pollen grains have been shown to induce intracellular markers of oxidative stress in human bone marrow-derived DCs. This is associated with the release of IL-8, IL-6 and tumour necrosis factor α and upregulation of surface markers of maturity (CD80, CD86, CD83 and HLA-DR).⁷⁹ Evidence suggests that oxidative stress may be a factor in the

pathogenesis of AD. In humans, increased levels of oxidized proteins were detected in biopsies of skin obtained from atopic compared with healthy patients.⁸⁰ A recent study evaluating oxidative stress markers in dogs reported increased serum levels of malondialdehyde, which is formed during lipid peroxidation, in dogs with AD compared with healthy dogs.⁸¹ Further evidence comes from a gene expression microarray that demonstrated decreased expression of methionine sulfoxide reductase A, which plays a key role in repairing oxidative tissue damage.⁸² Although far from definitive, these results support an association between oxidative stress and canine AD and suggest that at least some of this may be related to environmental exposure.

Environmental exposure to particulate matter (PM; such as diesel exhaust particles) or tobacco smoke may also play a role in the development of AD. The relationship between PM or tobacco smoke and the development and exacerbation of allergic and nonallergic airway disease has been well established in both human epidemiological and *in vivo* animal studies.^{83–86} Fewer studies have investigated the relationship between smoke or PM exposure and the development of AD, and most have been retrospective. One study demonstrated a decreased prevalence of AD in children of mothers who smoked during pregnancy.⁸⁴ In contrast, other studies have found strong evidence of an association between AD and environmental exposure to tobacco smoke, especially when combined with maternal PM exposure.^{87–90} One study in dogs reported an increased rate of allergic skin disease in dogs with very high levels of environmental smoke exposure compared with unexposed dogs.⁹¹

Conclusions

The advent of advanced tools for genetic analysis has enabled veterinary researchers to investigate the roles of heritability and genetic polymorphism in the development of AD in dogs. Historically, studies have been limited to observations of breed predispositions, heritability and linkage studies, but new technologies, such as genome-wide association studies, have permitted the identification of chromosomal regions with an association with atopic status in far greater detail.^{16–18} These regions can be evaluated further to identify 'candidate genes' with possible linkages to clinical disease. Although these studies are yet in their infancy, the information obtained so far has highlighted the incredible complexity of these genetic interactions. Atopic dermatitis-associated genotypes, moreover, appear to vary with breed and geographical location.²⁴ This complexity means that a screening and breeding programme to eliminate the condition is unlikely to succeed. Despite this, these techniques will allow identification of target molecules for novel treatments. In addition, we may be able to genotype atopic dogs and relate this to their phenotype. Understanding the genotype will enable better targeting of treatment options; for example, some dogs may respond well to skin barrier therapy, whereas others would benefit more from allergen-specific immunotherapy. We also may be able to identify dogs that may have a poor response or an increased risk of adverse effects to certain

anti-inflammatory drugs. Finally, it may be possible to discover atopic genotypes in young dogs and manage environmental and other factors to minimize their risk of developing clinical AD.⁹²

One key discovery in the last 10 years was the critical role of interactions between the innate immune system and the epidermis with environmental substances during the induction phase of atopic inflammation. Exposure to these agents can both protect against and trigger or exacerbate atopic inflammation through modulation of the response of innate immune 'sentinel' cells.^{37–39} Showing that keratinocytes are active cells in innate immunity with intimate relationships to epidermal Langerhans cells has been a key advance. The net effects are likely to depend on the level and timing of exposure and activation as well as the presence of concomitant factors. In turn, these cells can activate and influence the type and course of the response of the cells of the adaptive immune system. Environmental-innate immune system interactions have the potential to shape the entire future course of the immune response to any given agent. Thus, it appears that the innate immune system and the epidermis play very active roles not only during the effector phase of atopic inflammation but during induction and sensitization as well. To date, most studies have been performed in humans. However, more recent studies have specifically investigated the impact of environmental factors on the immune response in dogs.^{43,56,59,91} Further studies investigating the potential of environmental interactions with the innate immune system to influence and modulate canine AD will be important. This may identify new therapeutic targets or early-life interventions that could decrease the risk of developing the condition.

In conclusion, canine AD is a heritable disease, in which interaction with environmental factors influences the disease risk and phenotype. In genetically predisposed individuals, exposure to certain environmental substances modulates the development of concurrent and possibly future hypersensitivities. These host-environmental interactions appear to be highly complex and difficult to predict, with their effects dependent on many factors, including dose and time of exposure. New techniques, such as genome-wide association studies, will allow us greatly to improve our knowledge about this disease and help us to identify relevant gene polymorphisms. Future genome-wide association and candidate gene approach studies should focus on specific breeds and regions to increase the chance of finding such associations. It is also critical to design studies with a sufficient statistical power to allow for identification of polymorphisms with a relatively small effect on risk of disease.

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Résumé

Contexte – Plusieurs niveaux de preuve supportent le rôle de la génétique et de l'environnement dans la pathogénie de la dermatite atopique canine (AD).

Objectifs – Cette revue résume les preuves actuelles des facteurs génétiques et environnementaux sur le développement et la perpétuation de la dermatite atopique canine (AD).

Méthodes – Les bases de données, les résumés et les proceedings des congrès internationaux publiés entre 2001 et 2013 ont été revus pour cette mise à jour. Lorsque nécessaire, des articles plus anciens étaient inclus pour plus d'information.

Résultats – L'AD canine est une maladie héréditaire dans laquelle les interactions avec des facteurs environnementaux influencent les risques de la maladie et son phénotype. Une étude anglaise sur les chiens guide d'aveugle indique que près de 50% des risques de développer la maladie étaient déterminés par le génotype individuel. Les études génomiques réalisées jusqu'à présent ont déterminé de nombreux gènes candidats pouvant être impliqués dans la pathogénie via leur rôle dans l'immunité, la formation de la barrière cutanée, l'apoptose ou l'inflammation. En plus de la génétique, il y a des preuves suggérant que l'exposition à certains facteurs environnementaux influence la prévalence et l'évolution de l'AD canine. Par exemple, vivre en milieu rural ou être nourri avec une alimentation non-commerciale était négativement associé au développement de l'AD canine tandis que l'exposition à des niveaux de fumée de tabac élevés était associée avec une prévalence augmentée de dermatite allergique.

Conclusions – Il apparaît clairement que l'AD canine est génotypiquement complexe et influencée par divers facteurs environnementaux. Des études bien conçues, avec une puissance statistique suffisante, seront essentielles afin de définir le complexe génétique et les facteurs environnementaux impliqués dans le développement et l'évolution de cette maladie. La reconnaissance de ces facteurs pourrait aider à identifier de nouvelles cibles thérapeutiques et de permettre une meilleure gestion et prévention de la maladie.

Resumen

Introducción – hay evidencias a múltiples niveles indicando el papel de la genética y del ambiente en la patogenia de la dermatitis atópica canine (AD).

Objetivos – esta revisión resume las evidencias actuales en genética y el efecto de los factores ambientales en el desarrollo y perpetuación de la AD canine.

Métodos – se revisaron citaciones en bases de datos, resúmenes y extractos de reuniones internacionales publicados entre 2001 y 2013. Cuando fue necesario se incluyeron artículos más antiguos como información de soporte.

Resultados – la AD canine es una enfermedad hereditaria en la cual la interacción con los factores ambientales afecta el riesgo de enfermedad y el fenotipo. Un estudio en perros guía británicos indicaba que casi un 50% del riesgo de desarrollar AD estaba determinado por el genotipo del individuo. Estudios genómicos desarrollados hasta ahora en AD canine han descubierto numerosos genes candidatos posiblemente implicados en la patogenia debido a su papel inmunitario, formación de la barrera de la piel, apoptosis e inflamación. Además de la genética, hay evidencia que sugiere que la exposición a ciertos factores ambientales influye en la prevalencia y el curso de AD canine. Por ejemplo, vivir en áreas rurales o la alimentación con dietas no comerciales estaban negativamente asociados con el desarrollo de AD en perros, mientras que la exposición a altos niveles de contaminación atmosférica se asoció con mayor prevalencia de alergias de la piel.

Conclusiones e importancia clínica – se empieza a clarificar que la AD canine es una enfermedad genotípicamente compleja e influida por una variedad de factores ambientales. Es crítico realizar estudios bien diseñados y con buena capacidad estadística para identificar los factores genéticos y ambientales implicados en el desarrollo y progresión de la enfermedad. El reconocimiento de tales factores puede ayudar a identificar nuevas dianas y nuevas terapias para una mejor prevención de la enfermedad y para su manejo.

Zusammenfassung

Hintergrund – Eine vielschichtige Evidenz unterstützt die Rolle der Genetik und der Umwelt in Bezug auf die Pathogenese der atopischen Dermatitis des Hundes (AD).

Ziele – Diese Review fasst die aktuelle Evidenz in Bezug auf die Genetik zusammen, sowie die Auswirkungen von Umweltfaktoren auf die Entwicklung und die Aufrechterhaltung der caninen AD.

Methoden – Datenbanken, Abstracts und Preceedings von internationalen Meetings, die zwischen 2001 und 2013 publiziert worden waren, wurden für dieses Update reviewed. Wenn es nötig war, wurden ältere Artikel für mehr Hintergrundinformation inkludiert.

Ergebnisse – Die AD des Hundes ist eine erbliche Erkrankung, bei der die Interaktion von Umweltfaktoren das Krankheitsrisiko und den Phänotyp beeinflusst. Eine Studie der britischen Blindenführhunde zeigte, dass fast 50% des Risiko's AD zu entwickeln, durch den Genotyp des Individuums bestimmt wurde. Genomstudien, die bisher bei der caninen AD durchgeführt worden waren, haben zahlreiche Genkandidaten aufgedeckt, die wahrscheinlich in der Pathogenese durch ihre Rolle in Bezug auf Immunität, Hautbarrierenbildung, Apoptose und Entzündung eine Rolle spielen. Zusätzlich zum genetischen Hintergrund besteht Evidenz, die darauf hinweist, dass der Kontakt mit gewissen Umweltfaktoren die Prävalenz und den Verlauf der caninen AD beeinflusst. Zum Beispiel wurde das Leben in ländlichen Gebieten und das Füttern von nichtkommerziellen Diäten negativ assoziiert mit der Entwicklung von AD bei Hunden, während der Kontakt mit viel Rauch mit einer zunehmenden Prävalenz der allergischen Hauterkrankung in Zusammenhang gebracht wurde.

Schlussfolgerungen – Es wird zunehmend klar, dass die AD des Hundes genotypisch komplex ist und von einer ganzen Anzahl von Umweltfaktoren beeinflusst wird. Gut angelegte Studien mit ausreichender statistischer Aussagekraft werden wichtig sein, um die komplexen genetischen und umweltbedingten Faktoren, die bei der Entstehung und dem Fortschreiten der Krankheit eine Rolle spielen, zu identifizieren. Das Erkennen dieser Faktoren könnte dabei helfen, neue Angriffsziele für die Therapie zu identifizieren und eine bessere Krankheitsvorbeuge und ein besseres Krankheitsmanagement zu erreichen.

要約

背景 – 様々なレベルのエビデンスにより、イヌアトピー性皮膚炎(AD)の病因における遺伝と環境の役割が裏付けられている。

目的 – この総説はイヌADの発生と持続における遺伝および環境因子の効果についての最近のエビデンスを要約している。

方法 – 文献引用データベース、2001年から2013年の間に発表された国際会議での要約や抄録をこの最新情報で再検討した。必要な場合は、背景にある情報のための古い論文を含んでいる。

結果 – イヌADは環境因子の相互作用が疾患のリスクや表現型に影響する遺伝性疾患である。イギリスの盲導犬の研究でAD発生のリスクの50%近くは個々の遺伝型により決まることが示された。今までに行われたイヌADのゲノム研究は、それらの免疫、皮膚バリア形成、アポトーシスならびに炎症におけるそれらの役割を通して、病因に関わっている可能性のある複数の候補遺伝子を明らかにした。遺伝に加えて、特定の環境因子への曝露がイヌADの有病率と経過に影響することを示唆するエビデンスが存在する。例として、田舎の地域で生活することや市販ではないフードを与えることがイヌにおいてADの発生と負の相関を示す一方、煙への高いレベルの曝露はアレルギー性皮膚炎の有病率の上昇と関係する。

結論 – イヌADは遺伝子型的に複雑で、様々な環境因子に影響を受けることが明らかになってきている。十分な統計的検出率を伴った、よく設計された研究は、疾患の発生と進行に関連する複雑な遺伝的および環境要因の特定するために重要となるであろう。それらの因子の認識は新たな治療のための標的を特定するのを助けたり、よりよい疾患の予防や管理を可能にするかもしれない。

摘要

这 – 页的内容将只用作网页图形摘要的一部分。不会作为主要部分发表。

背景 – 多个级别的证据支持遗传学和环境在犬异位性皮炎(AD)发病机理中的作用。

目的 – 本次研究总述目前遗传学和环境因素的作用的证据,证明犬AD的发生和终生存在。

方法 – 本次研究回顾了2001至2013年间国际会议的引文数据库、摘要和会议记录。必要时,较早的文章会被引作背景信息。

结果 – 犬AD是种遗传性疾病,与环境因素的互作影响疾病的发病风险和表型。一项英国导盲犬的研究表示,近50% AD发生的风险取决于个体的基因型。到目前为止,犬AD基因组研究发现,有多个候选基因可能通过免疫、皮肤屏障的形成、细胞凋亡和炎症参与发病机理。另外基因学有证据支持,暴露在某些环境因素中,会影响犬AD的流行及病程。例如,生活农村地区或喂食非商业日粮的犬患AD的很少,而在大量烟雾中过敏性皮肤病发病率增加。

总结与临床意义 – 明确了犬AD 是复合基因型,并受多种环境因素影响。为了标识参与疾病发展和进程的复合基因以及环境因素,足够的统计能力、设计精良的实验是关键。识别这些因素可帮助确定新的治疗靶向,以及更好的预防和管理疾病。