

Allergy to furry animals: New insights, diagnostic approaches, and challenges

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The prevalence of allergy to furry animals has been increasing, and allergy to cats, dogs, or both is considered a major risk factor for the development of asthma and rhinitis. An important step forward in the diagnosis of allergy to furry animals has been made with the introduction of molecular-based allergy diagnostics. A workshop on furry animals was convened to provide an up-to-date assessment of our understanding of (1) the exposure and immune response to the major mammalian allergens, (2) the relationship of these responses (particularly those to specific proteins or components) to symptoms, and (3) the relevance of these specific antibody responses to current or future investigation of patients presenting with allergic diseases. In this review research results discussed at the workshop are presented, including the effect of concomitant exposures from other allergens or microorganisms, the significance of the

community prevalence of furry animals, molecular-based allergy diagnostics, and a detailed discussion of cat and dog components. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: Molecular-based allergy diagnostics, allergy, allergens, furry animals, cats, dogs, allergic asthma, allergic rhinitis, pork-cat syndrome

Allergy to furry animals, cats and dogs in particular, has been recognized for many years and is considered to be a major risk factor for the development of asthma and rhinitis.¹ The prevalence of allergy to furry animals² and the prevalence of allergic airway disease³ have been increasing. Exposure to allergens from these animals is ubiquitous, and the clinician should evaluate all patients with allergic airway disease for sensitization to animal dander.⁴ Allergic sensitization to several mammalian animals is prevalent, which might reflect cosensitization or cross-reactivity.⁵ In some countries sensitization to furry animals is associated with more severe allergic disease,⁶ which poses extended diagnostic and therapeutic challenges.

An important step forward in the diagnosis of allergy to furry animals has been made with the introduction of molecular-based allergy diagnostics,^{7,8} which offer new opportunities for improved characterization. One example of novel insights gained by this approach is the differentiation of reactions to meat from patients with pork-cat syndrome.⁹⁻¹¹ Patients with this syndrome sensitized to albumins from animal dander report symptoms after the consumption of pork because of the cross-reactivity of albumins from different species.

The workshop on furry animals was convened to provide an up-to-date assessment of our understanding of (1) the exposure and immune response to the major mammalian allergens, (2) the relationship of these responses (particularly those to specific proteins or components) to symptoms, and (3) the relevance of these specific antibody responses to current or future investigation of patients presenting with allergic diseases.

DEFINITIONS

Allergic sensitization was defined as the presence of specific IgE antibodies to an allergen. *Allergy* was defined as the occurrence of reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by nonallergic persons and mediated by specific immunologic mechanisms (antibody or cell mediated). A *component* was defined as a molecule (ie, protein or glycoprotein) derived from a given allergen source that is identified by IgE antibodies. *Cross-reactivity* was defined

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Abbreviation usedAlpha-gal: Galactose- α -1,3-galactose

as the process of IgE antibodies originally developed against a given allergen binding homologous molecules originating from a different allergen source.

ALLERGEN SOURCES

Given that most persons in Western societies spend more than 90% of their lives in indoor environments, it is not surprising that indoor allergens play an important role in allergic sensitization and symptoms. In addition to residential environments, exposure to furry animal allergens can occur in schools and occupational and/or leisure environments (eg, animal facilities, stables, pet shops, and farms). The allergen quantities derived from these sources might be clinically significant at the site where the animal is kept or at another site because of passive transfer (Table I). The primary source of cat and dog allergens is thought to be dander coming off the skin,^{4,12} whereas for mice and rats, urine is thought to be a more important source.^{13,14}

CAT ALLERGEN EXPOSURE AND ALLERGIC SENSITIZATION

For many years, it was assumed that living in a house with a cat increased the risk of allergy. However, in 1999, Hesselmar et al¹⁵ reported that children who lived in a house with a cat were less likely to be sensitized to cat allergens. This observation has had a major effect and has been confirmed in many, but certainly not all, subsequent studies.^{1,16-19} A systematic review of recently published articles from birth cohorts and cross-sectional and case-control studies of the association between cat exposure and allergic diseases suggests that early-life cat exposure is likely to protect against allergic disease.²⁰ A recent meta-analysis of pooled results from 11 prospective European birth cohorts concluded that there is no clear evidence for a protective or "harmful" effect of cat ownership on sensitization to animal dander.²¹ These reviews confirm 2 observations: that the very high levels of cat allergens present in a house with a cat do not increase the risk of sensitization and that a large proportion of subjects who become sensitized to cat allergens do not live in a house with a cat. Furthermore, in the review of birth cohorts, the results were similar among children of parents without allergies compared with those among children of parents with allergies, indicating that selection bias did not have a major effect on the results of these studies. However, the issue of selection bias could be more complex; families with the most severe allergy could avoid owning pets, whereas families with mild allergy could be more highly represented among those who have cats at home. If this is the case, the apparent protective effect of cat ownership could be explained in part by the fact that the families with the most severe allergic constitution do not have pets at home.

CLINICAL EFFECTS OF ALLERGEN EXPOSURE IN THE SENSITIZED SUBJECT

Several studies have found a strong relationship between allergen exposure in sensitized subjects and allergic airway

disease.²² For instance, cat-sensitized children exposed to cat allergen have increased bronchial hyperreactivity compared with nonexposed children.²³ The lung function of dog-sensitized 3-year-old children who are exposed to dog allergens is reduced compared with that of sensitized children without exposure and exposed children without sensitization.²⁴ Sensitization to furry animals has been associated with increased bronchial hyperresponsiveness in adolescents.²⁵ In a population-based study IgE antibodies to 103 allergen molecules were assessed by microarray, and subjects with IgE antibodies to allergen components from furry animals had increased asthma prevalence, higher fraction of exhaled nitric oxide levels, and increased bronchial hyperresponsiveness.²⁶ Furthermore, a follow-up of children with asthma clearly showed that the probability of remission from age 7 years to age 19 years was significantly reduced if the child had been sensitized to furry animals at age 7 years.²⁷ In addition, exposure to allergens from small furry animals, such as hamsters or mice, has also been associated with symptoms of asthma in sensitized subjects.^{28,29}

FREQUENCIES OF ALLERGIC SENSITIZATION

In the United States and Europe the prevalence of sensitization to furry animals has increased over the past decades.^{2,30,31} Age- and sex-adjusted data from a pan-European study published in 2009 found that 26% and 27% of adults were sensitized to cats and dogs (by using skin prick tests), respectively,³² which could be compared with data from 1992 showing that the frequency of sensitization to cat (by using skin prick tests) was 8.8%.³³ In the United States the frequencies of cat and dog sensitization in subjects aged 6 years and older are 12.1% and 11.8%, respectively.³⁴ A population-based study from Germany (n = 17,641; age, 3-17 years) reported sensitization to dogs of 11.6% and 7.6% and to cats of 9.6% and 6.6% in boys and girls, respectively.³⁵ The prevalence of sensitization is modified by the age of the subject, with increasing prevalence throughout childhood³⁶⁻³⁸ culminating in peak prevalence during adolescence.³⁹ However, it should be emphasized that estimates of the prevalence of sensitization are based on skin tests or *in vitro* assays with extracts. If the extract's constituents or the strength of the extract changes over time, this could lead to an apparent change in prevalence.

DETERMINANTS FOR ALLERGIC SENSITIZATION

A number of determinants for allergic sensitization to furry animals in the exposed subject have been identified, including factors not directly related to the pet. In particular, the genetic constitution of the exposed subject,^{40,41} the environmental setting,^{42,43} and other environmental exposures, including concomitant exposure to other allergen sources^{1,44} and microorganisms^{45,46} have been shown to be important in this connection.⁴⁷⁻⁴⁹ Additionally, several determinants directly related to the animal have proved to be of importance, such as the biological activity of the allergen⁵⁰ and the timing,^{51,52} variability,¹³ and intensity^{16,53,54} of the allergen exposure. Of particular interest is that there seems to be a tolerance effect with increasing levels of exposure, which could be caused by a modification of the T_H2 response¹⁶ or induced by concomitant exposures.

TABLE I. Furry animals: characteristics of allergen exposures in residential and nonresidential environments*

Animals	Present in the home	Contribution to the microbiome	Passive transfer to homes without an animal
Domestic	Dust	Airborne	
Cats (dander)	++ to +++	+ to ++	± to ++†
Dogs (dander)	++ to +++	+ to ++	± to ++
Pets			
Guinea pig	?	?	?
Hamsters (dander)	?	?	Not known
Rabbits	++ to +++	?	Likely
Mice (urine)	Rare	++	Not known
Rats (urine)	Rare	+	Not known
Pests			
Mice (urine)	+ to +++	+++	Likely
Rats (urine)	Yes	–	Not known
Laboratories	In the laboratory		
Mice (urine)	++	+ to +++	?
Rats (urine)	++	+ to +++	?
Farms and stables	In stable	At home	
Horses	+++	Yes	?
Cows	+++	+ to ++	?

+, Measurable levels but contribution to sensitization or symptoms is less clear; ++, levels consistent with sensitization and symptoms; +++, levels consistently higher than those known to cause sensitization.

*Data were derived from discussions at the workshop and published data.

†Airborne cat allergen has been measured in homes without a cat.

Concomitant exposures

Prediction of the effects of concomitant exposures to other allergen sources is not straightforward. In one study from northern Sweden, where there are no house dust mites, having a cat at home was associated with a reduced frequency of sensitization to other allergens.¹ However, in a study from New Zealand, where children have high exposure to both cat and mite allergens, there appears to be little or no effect of cat ownership on sensitization to dust mite allergens.¹⁷

With respect to concomitant exposure to microorganisms, it has been shown that in addition to proteins derived from the animal itself, animals can carry significant quantities of endotoxin, pollens, or fungal spores. Although it is possible to measure endotoxin in both cat and dog hair, interpretation of the data on the effects of animals on airborne endotoxin levels is not simple. Cat ownership does not seem to increase endotoxin levels in the home,^{55,56} but cats can act as a vector for *Staphylococcus aureus*.⁵⁷ The presence of a dog in the house does increase airborne endotoxin levels.⁵⁵ In addition, the microbiome of the dust and the fecal microbiome of children can be altered by the presence of a dog in the house.^{45,46} If this has an effect on the development of allergic sensitization in the infant, we assume this would be comparable with the effect of bacterial exposure on children living on a farm and would not be allergen specific.⁵⁸ Whether comparable effects can occur with other pets requires further investigation. Clearly, there is a need for more studies directly documenting the effects of pet ownership on the microbiome of homes and their occupants.

Effect of the community prevalence of pets

The percentage of homes that report the presence of an animal varies from approximately 5% in Spain to approximately 20% in Sweden and 65% or greater in New Zealand.^{59,60} In a population-based study on 3400 children in Sweden, at least three quarters of the children who had IgE antibodies to cat had never lived in a house with a cat.¹ The quantity of cat allergen in schools is

directly related to the number of children in the class who have a cat at home.⁶¹ Sensitization to cat allergens would only occur in houses without a cat if there were sufficient houses in the community with a cat.⁴⁹ If animals are present in a small proportion of homes (eg, <10%), the exposure in homes without a cat might be inadequate to result in a high prevalence of sensitization; by contrast, if animals are present in the majority of homes, the allergen levels in schools or homes without an animal might actually be supraoptimal or sufficient to induce tolerance.⁶² At present, there is not sufficient information to predict these effects, and there are very few comparative data between countries about the quantities of cat or dog allergens (dust or airborne) in homes without an animal or in schools.

Small furry pets, such as rabbits, guinea pigs, and hamsters, have also become increasingly popular over the last 20 years.⁶³ Up to 5% of US and European households have a small furry animal, but data on allergen quantities in house dust are lacking.

IMMUNE RESPONSES TO FURRY ANIMAL ALLERGENS IN ADDITION TO IgE

The immune response to domestic animal allergens includes T cells and IgE antibodies, as well as different isotypes of antibodies. At present, both the significance of IgE antibodies and the techniques for measuring IgE antibody levels are better established than the techniques for describing any other aspect of the immune response.

T-cell responses

After the cloning of Fel d 1,⁶⁴ a wide range of studies have been carried out on T-cell responses to cat allergens using both the protein Fel d 1 and overlapping peptides derived from Fel d 1.⁶⁵⁻⁶⁷ These studies demonstrated that responses to Fel d 1 are, broadly speaking, of a T_H2 type. Furthermore, several groups have identified specific peptides of Fel d 1, which are significant to the response and led to the testing of peptide vaccines based on Fel

TABLE II. Purified and characterized animal allergens*

Animal	Major allergen†	Other allergens
Cat	Fel d 1 (uterglobin) 14 + 4 kDa	Fel d 2 (albumin)‡ Fel d 4 (lipocalin) Fel d 7 (VEGP)§ Fel d 3 (cystatin) Fel d 5w (cat IgA) Fel d 8 (latherin-like)
Dog	Can f 1 (lipocalin) 23-25 kDa	Can f 2 (lipocalin) Can f 4 (lipocalin) Can f 6 (lipocalin) Can f 3 (albumin)‡ Can f 5 (arginine esterase)¶
Guinea pig	Cav p 1 (lipocalin) 20 kDa Cav p 2 (lipocalin) 17 kDa	Cav p 3 (lipocalin) Cav p 4 (albumin)
Horse	Equ c 1 (lipocalin) 25 kDa	Equ c 2 (lipocalin) Equ c 4 (latherin) Equ c 3 (albumin)‡
Mouse	Mus m 1 (lipocalin; urinary prealbumin) 17 kDa	
Rat	Rat n 1 (lipocalin; alpha-2u-globulin) 17 kDa	
Rabbit	Ory c 1 (lipocalin) 17-18 kDa	Ory c 3 (lipophilin) 19-21 kDa

*Component-specific IgE levels can be measured with component-specific IgE assays or by using the Immuno Solid-phase Allergen Chip (ISAC Thermo Fisher Scientific, Uppsala Sweden).

†Airborne measurements of each allergen source have been based on the major allergen.

‡Albumins have molecular weights of 67 to 69 kDa and can cross-react extensively.

§von Ebner gland protein.

||The main epitope on cat IgA and also on cat IgM is the oligosaccharide alpha-gal.

¶This molecule is a kallikrein.

d 1.^{65,68} Evaluation of T-cell responses to animal (or other) allergens is not part of the routine assessment of patients presenting with symptoms, and all studies on T-cell responses to Fel d 1 have focused on subjects with positive skin test results. Although it is possible that there are patients who have symptoms related to cat or dog allergen exposure on the basis of a T-cell response without an associated IgE antibody response, this has not been demonstrated.

IgG antibody responses, including IgG₁ and IgG₄

In 1935, it was demonstrated that there are 2 types of antibodies in the sera of patients with hay fever and that the “blocking antibodies” increased with immunotherapy.⁶⁹ Almost all studies have recognized that IgE levels decrease and IgG₄ levels increase during subcutaneous immunotherapy.⁷⁰ Currently, there are mixed data about the isotypes other than IgE and IgG₄, and the data on IgG₁ and IgA have to be considered with caution.^{71,72} Many publications report detectable IgG₄ antibodies in most allergic and nonallergic subjects in contrast to extensive earlier data. Although the results might not be relevant to the clinical evaluation of patients, they are important to understanding the immune response to cat allergens in those atopic children who live in a house with a cat but do not become symptomatic on exposure to cat allergens.¹⁹ Recently, an interesting dissociation of

allergen-specific IgE and IgG responses to cat, dog, and horse was reported, indicating that nonsequential class-switch mechanisms are operative in patients with animal allergy and might explain why naturally occurring allergen-specific IgG is not always protective.⁷³ Measurement of IgG antibodies might also be relevant to understanding why some subjects experience increased symptoms on entering a house with an animal after a period of decreased exposure.

CLINICAL CONSIDERATIONS IN THE DIAGNOSIS AND MANAGEMENT OF ALLERGY TO FURRY ANIMALS

The management of patients with allergic disease with sensitization to furry animals includes a judgment about (1) exposure to relevant allergens, (2) the effect of that exposure on symptoms, and (3) sound advice about controlling exposure. This includes advice about whether to keep a domestic animal and judgment about whether one allergen in the home is more relevant than another. A good example of this is the common problem of a patient who is sensitized to both mite and cat and is exposed to both allergens. Extract-based diagnosis of sensitization can only provide information about the source in general. Our question here is as follows: How much can identification of sensitization to specific proteins in these extracts contribute to the diagnosis or management of allergic patients?

MOLECULAR-BASED ALLERGY DIAGNOSTICS

The purification and characterization of allergens started with work on rye grass and ragweed pollen.^{74,75} This was followed by the purification of Fel d 1 by Ohman et al⁷⁶ in 1974 and has now been extended to hundreds of proteins. The definitions and correct nomenclature for these allergens are by agreement of the International Union of Immunological Societies subcommittee on allergen nomenclature (Table II).⁷⁷ Characterization of allergens has made many different developments possible. These include measurement of class-specific antibodies, production of peptides to test T-cell responses, and development of the mAbs used to measure environmental exposure.

Allergen components can be classified into separate protein families, and allergens within the same protein family often display cross-reactivity between them. This is particularly clear for the albumins⁷⁸ and some lipocalins⁷⁹ from furry animals.

Assessment of allergen components can be done either by measuring antibodies to individual components or by using an allergen microarray chip.^{8,80} The former approach provides quantitative results on a single allergen component, whereas the latter approach allows semiquantitative measurement of IgE antibodies to a large number of components simultaneously. Some allergens are recognized as specific markers of an allergen source,^{8,81} and by identifying these allergens, it is possible to determine which are the sensitizing and which are the cross-reactive allergen sources. Questions regarding the clinical utility of molecular-based allergy diagnostics are summarized in Box 1.

Secretoglobulin Fel d 1: The major cat allergen

Fel d 1 is the major cat allergen because up to 95% of all patients with cat allergy react to Fel d 1.⁸¹⁻⁸³ This protein accounts for 60% to 90% of all IgE reactivity to cat dander^{82,84,85} and does

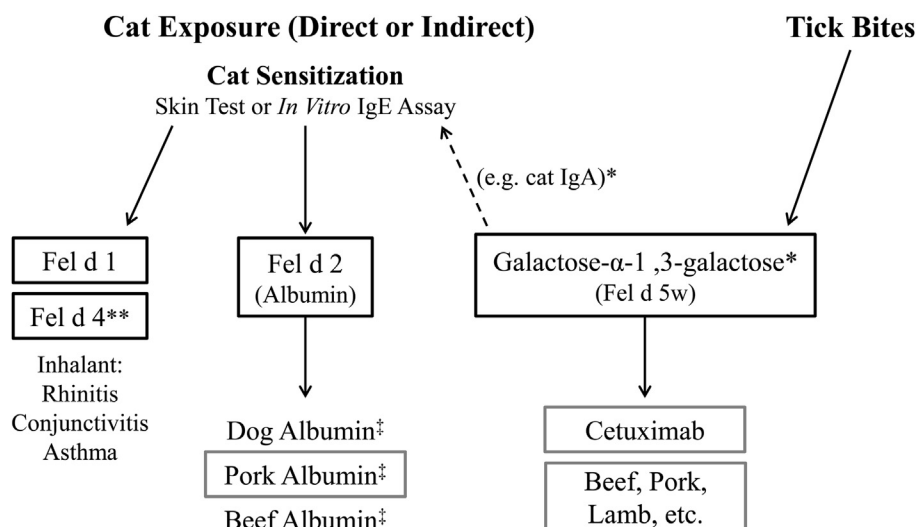


FIG 1. IgE responses to different cat components can be induced through different routes of exposure and are associated with either inhalant symptoms or 2 forms of food allergy. *Cat IgA and other cat proteins carrying alpha-gal are present as minor constituents of cat dander extracts but are better represented in epithelial extracts. **Fel d 4 is a lipocalin that cross-reacts with Can f 6 and Equ c 1. ‡The albumins all cross-react, but the reactivity between cat and pork albumin is the most consistent.

not display significant cross-reactivity with other mammalian sources. Fel d 1 is a secretoglobulin that is primarily produced in sebaceous, anal, and salivary glands and is mainly present in the epidermis and fur. Fel d 1 is spread to the environment predominantly through airborne dander,^{12,86} which can be detected both in homes with and those without a cat.⁸⁷ The biological role of secretoglobulin is unknown. The allergenicity of inhaled Fel d 1 can be increased by its binding to the mannose receptor on dendritic cells, thereby initiating the process of internalization and the production of Fel d 1–specific IgE and IgG₁.⁵⁰ Asthmatic children with cat allergy have higher Fel d 1–specific IgE levels compared with those in children with rhinitis,⁸¹ which suggests that high IgE levels to Fel d 1 could be a marker of increased asthma risk.

Recently, another secretoglobulin has been isolated from rabbits. The molecule, despite a high structural similarity with Fel d 1, does not display IgE cross-reactivity, probably because of low sequence identity. This protein, Ory c 3, is present on rabbit fur and can be detected in settled airborne dust from houses with a pet rabbit.⁸⁸

Lipocalins

More than 50% of the allergens that have been identified from furry animals are lipocalins.⁸⁹ These allergens are found in dander, saliva, and urine; the particles they are carried on are sticky; and they easily become airborne, disperse effectively, and are widely present in indoor environments.⁹⁰ In general, they share sequence identities of only 20% to 30%, but their tertiary structures are highly similar, and several inhibition studies have shown cross-reactivity between lipocalins in conditions of excess inhibitor.^{79,91,92} Some lipocalins display much higher sequence identities (about 60%) and cross-react at low doses in a patient-dependent manner. These include Can f 6, Equ c 1, and Fel d 4,^{93,94} as well as Can f 1 and human tear lipocalin.⁷⁹ Lipocalins are a group of proteins involved as ligand transport proteins with enzymatic activity, participating in cell homeostasis,

or both. Lipocalins do not seem to activate dendritic cells,⁹⁵ and the existence of endogenous human lipocalins could be responsible for the generally low T-cell reactivity to lipocalins.⁹⁰

Cat lipocalin allergens

Two lipocalin allergens have been identified from cats: Fel d 4⁹⁶ and Fel d 7.⁹⁷ Fel d 4 is found primarily in cat saliva and cross-reacts with lipocalin allergens from other animals, mainly Can f 6 and Equ c 1.^{6,93,94} IgE reactivity to Fel d 4 has been found in up to 63% of cat-sensitized subjects.⁹⁶ High levels of IgE antibodies to Fel d 4 have been associated with atopic dermatitis in children with cat allergy.⁹⁸ Fel d 7 is not yet widely available for IgE testing but has been reported to bind IgE in 38% of all subjects with cat allergy.⁹⁷ Fel d 7 and Can f 1 share a high sequence identity (62%), and cross-reactivity between these proteins seems probable.

Dog lipocalin allergens

Four of 6 currently identified dog allergens, Can f 1, Can f 2,⁹⁹ Can f 4,⁹¹ and Can f 6,^{93,94} are lipocalins. Can f 1 is secreted from canine sebaceous glands and is found in dog hair, dander, and saliva. Airborne levels and particle size distribution of Can f 1 are similar to those of cat allergen¹⁰⁰; it becomes airborne with minimal disturbance, remains airborne for a long time, and can be inhaled into the smaller airways more easily than larger particles, such as mite feces or pollen grains, because of the small size of the particles. Can f 1 is detectable in all homes with a dog and in one third of homes without dogs.¹⁰¹ Fifty percent to 90% of patients sensitized to dog have antibodies to Can f 1. Twenty percent to 33% of dog-sensitized subjects have IgE antibodies to Can f 2; however, all reported patients with antibodies specific for Can f 2 also reacted to Can f 1. The structure of the Can f 2 calyx is very similar to that of Equ c 1 from the horse, but no cross-reactivity was detected between these molecules. Can f 2 shows limited, patient-dependent cross-reactivity with Fel d 4, although only

22% of the sequence is identical.⁹² Can f 4 was reported to bind IgE in around 30% of dog-sensitized subjects.⁹¹ Can f 6 has a very similar structure to Fel d 4⁹⁴; it cross-reacts with Fel d 4 and Equ c 1. IgE to Can f 6 have been found in 38% of subjects sensitized to dog.⁹³ In a selected group of patients with combined sensitization to cats and dogs, IgE to Can f 6 was found in 61%.⁹⁴ These patterns of cross-reactions probably explain in part the frequently observed pattern of cosensitization between dog, cat, and horse.

Horse lipocalin allergens

Two lipocalin allergens, Equ c 1 and Equ c 2, have been identified in the horse.^{79,102-105} Equ c 1, the major horse allergen, is present in horse dander, the sublingual and submaxillary salivary glands, and urine,¹⁰⁶ and up to 76% of patients with horse allergy react to Equ c 1.⁷⁹ There is a close structural relationship between Equ c 1 and both Can f 6 and Fel d 4. Among 100 dog-sensitized subjects, Equ c 1 was more frequently recognized than Can f 2, Can f 3, and Can f 6.⁹³ Sensitization to Equ c 1 has been associated with severe childhood asthma.¹⁰⁷ The role of Equ c 2 in horse allergy remains to be explored.

KALLIKREIN

Can f 5 is similar to prostatic kallikrein. Antibodies to this allergen have been found in up to 70% of patients with dog allergy, and 38% of these patients did not have antibodies to Can f 1, Can f 2, or Can f 3.¹⁰⁸ Can f 5 is detected in the urine of male animals. No patterns of cross-reactivity to allergens from other furry animals have been identified. However, cross-reactivity to human prostate-specific antigen, the major allergen in seminal plasma, has been reported,¹⁰⁹ which suggests that sensitization to Can f 5 could be relevant to seminal fluid allergy.

ALBUMINS AND CROSS-REACTIVITY OF CERTAIN CAT ALLERGENS AND RELATED CLINICAL SYNDROMES

The serum albumins from furry animals are Fel d 2, Can f 3, and Equ c 3 from cat, dog, and horse, respectively. Albumins are minor allergens; around 15% to 35% of patients with cat and dog allergy are sensitized to Fel d 2 and Can f 3, and around 15% to 20% of patients with horse allergy appear to be sensitized to Equ c 3.^{78,82,93,110} High levels of IgE antibodies to Fel d 2 have been associated with atopic dermatitis in children with cat allergy.⁹⁸ In patients with pork-cat syndrome, sensitization to cat was found in patients presenting with food-related or idiopathic urticarial or anaphylactic symptoms.^{10,11} Although most of these patients report reactions to pork, a small number, 10% to 20%, report reactions to beef as well; no cases with reactions to cow's milk have been reported. First there were reports of patients presenting with rapid-onset reactions to eating pork who were also sensitized to cat by using serum assays.^{11,111,112} Second were reports of patients with urticaria or anaphylaxis developing 3 to 6 hours after eating beef, pork, or lamb.^{10,113,114} Detailed investigation of these groups of patients demonstrated that the allergens involved were cat albumin in the first case and the oligosaccharide epitope on cat IgA (Fel d 5w) in the second.^{11,115,116} In patients with pork-cat syndrome, sensitization is thought to be through exposure to a cat, but in the second case bites of several species of ticks have

been implicated.^{114,117,118} The oligosaccharide epitope galactose- α -1,3-galactose (alpha-gal) is present on a variety of proteins from nonprimate mammals (Fig 1). The important observation is that sensitization detected with cat extract can be associated with 2 distinct forms of food allergy, as well as with inhalant allergy. These syndromes can only be identified reliably by measuring IgE antibodies to the specific components of the extract. In addition, it is important to realize that cat extracts made in different ways can have very different compositions (Fig 1). The finding that the primary exposure causing sensitization to alpha-gal is from tick bites is an excellent example of the complexity that can occur between the route of exposure (the skin in this case) and associated symptoms (food allergy). Allergy to gelatin can also present clinically as meat allergy. Gelatin is a protein that is most commonly derived from mammals (cow, horse, or pig) and is prepared by cooking skin or connective tissue. Patients occasionally have IgE to the protein, but in addition, some forms of gelatin also carry alpha-gal.¹¹⁹ This can present as delayed reactions after eating gelatin-containing sweets or marshmallows.

MOLECULAR-BASED ALLERGEN EXPOSURE MEASUREMENTS

Currently, all measurements of exposure to mammalian dander allergens are based on the "major allergen" of each species. Thus levels of Fel d 1, Can f 1, and Mus m 1 (from the mouse) have been extensively measured both in floor dust and airborne samples. In addition, measurements of airborne Equ c 1 have been carried out in barns, but very few data are available on homes. The case for measuring other specific proteins in airborne samples is either to further understand the relationship of specific components to allergic disease or to explain why certain allergens do not appear to be related to rhinitis or asthma.¹²⁰ There are some specific allergens that have not been adequately investigated. Two obvious cat allergens are Fel d 2 (cat serum albumin), which is associated with allergic symptoms on eating pork but might not be an inhalant allergen, and Fel d 4 (a lipocalin), which has an uncertain clinical relevance and has not had its presence in airborne samples addressed.^{94,96}

CONCLUSIONS AND RECOMMENDATIONS

Although there is clear evidence for the clinical importance of analyzing cat components in relation to both alpha-gal and pork-cat syndrome, we believe that future studies will clarify the clinical utility of molecular-based allergy diagnostics in the management of other patients sensitized to furry animals. The workshop identified 6 areas for future research related to the specific allergens derived from furry animals that could contribute to understanding and managing relevant allergic disease.

1. *Continued comparison of different techniques to detect or measure IgE antibodies to components:* By using both microchip and specific component assays, further studies need to be carried out on cohorts that include patients with exposure to different mammals. A major objective of these studies is to identify whether allergens other than the major allergens are relevant to the prevalence or severity of asthma and allergic disease. In addition, these studies will help to confirm the existing syndromes and search for other unexpected syndromes (Table III).

TABLE III. The arguments for assessing sensitization and exposure to single (components) allergens

I. Better specificity of the diagnosis of allergy to individual species
A. For example, cat-specific (Fel d 1) or dog-specific single allergens (or combinations); <i>goal</i> : species-specific allergens for the diagnosis of furry animal allergy
II. Identification of component-specific sensitivity related to different allergic syndromes:
A. Albumins: Fel d 2 and nSus s (swine serum albumin) in patients with pork-cat syndrome; also cross-reacts with Can f 3 and Bos d 6
B. Cat IgA (Fel d 5w): epitope is the glycosylation alpha-gal, which is associated with delayed anaphylaxis to red meat. IgE to alpha-gal is not associated with rhinitis or asthma.
III. Identification of specific allergens associated with severity of asthma as judged by symptoms or medication use
IV. Identification of allergens that are important causes of sensitization but present in small quantities in normal extracts (eg, Fel d 7)
V. Identification of cross-reactive molecules that are clinically significant (eg, Can f 6 and Fel d 4)

Box 1. Questions to be resolved regarding the clinical utility of molecular-based allergy diagnostics in patients with allergy to furry animals

- In which clinical setting? Patients with severe disease only? In multisensitized patients?
- Are there allergen components that are more specific than extract-based methods for a diagnosis of clinically relevant allergy?
- Is multisensitization to panallergens, such as lipocalins and albumins, of clinical relevance?
- Are some allergenic molecules markers of severe (or mild) disease?
- Is the number of sensitized allergenic molecules relevant for the clinical presentation of the disease?
- Could patients who are most likely to respond to immunotherapy be identified by using molecular-based allergy diagnostics?
- Is development of clinical tolerance associated with sensitization to specific allergenic molecules?

- II. *Establishment of criteria for diagnosing food-related syndromes related to cat and/or dog sensitization:* In particular, these studies will aim to establish panels of allergens that will consistently distinguish the 3 syndromes associated with cat sensitization (Fig 1).
- III. *Measurement of airborne cat, dog, or rodent allergens, other than the major allergens, in homes with or without an animal:* Although there are obvious allergens that we need to know more about, such as cat albumin (Fel d 2), Fel d 4, Fel d 7, and alpha-gal, there is also room for further evidence about the established major allergens.
- IV. *Investigation of the effects of the community prevalence of pets on quantities of cat or dog allergens found in homes or schools without pets:* These studies might need to address both levels of airborne allergen and levels in reservoir dust samples. In addition, it would be important to answer whether allergens other than Fel d 1 or Can f 1 can be “passively” transferred. This might also be an area in which multiplex assays for specific allergen components would make testing possible for a large number of samples.¹²¹
- V. *Multicenter study to compare different techniques for measuring isotype-specific antibodies, focusing on IgG₁ and IgG₄, as well as IgE:* This proposal will require establishing protocols for several different techniques and agreeing on the relevant components to be tested, as well as identifying panels of sera with high-titer antibodies and sera that are negative for the relevant antibodies.
- VI. *Further definition of T-cell responses associated with different forms of tolerance to cat or dog allergens:* These studies will have to address both specific allergens and selected relevant peptides.

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