

Component-resolved diagnostics in pet allergy

Abstract

Furry mammals kept as pets are important allergen sources, and the prevalence of sensitization to dander from various animals appears to be increasing worldwide. Several mammalian allergens from diverse species and distinct protein families have been characterized, and some are available for component-resolved diagnostics (CRD). This review presents an overview of mammalian respiratory allergens with a focus on cat, dog, and horse allergens. The potential of CRD in fine-tuning the diagnostic work-up following traditional methods based on whole allergen extracts and in allergen immunotherapy are discussed. Finally, the review highlights the clinical utility of CRD, particularly as a marker/predictor of increased asthma risk and disease severity.

Background

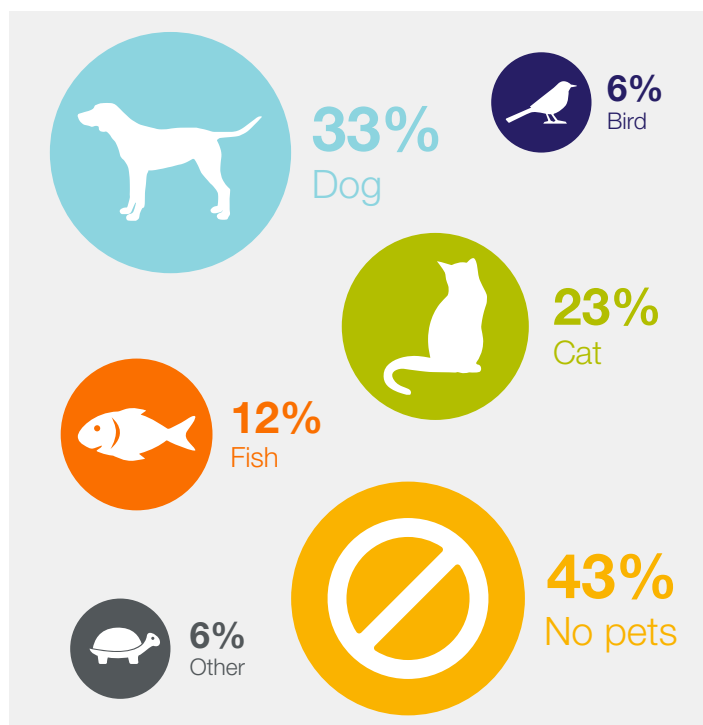
Domesticated furry animals are among the most common sources of respiratory allergens, causing development of sensitization and respiratory allergic diseases. Symptoms of pet allergy range in severity from the discomfort associated with rhinitis and conjunctivitis to potentially life-threatening asthmatic episodes.¹

An international survey of over 27,000 participants estimated that 57% of the population have at least one pet at home, most commonly dogs (33%) and cats (23%)² (Figure 1). Allergy to cat and dog is considered a major risk factor for the development of asthma and rhinitis, and sensitization to a major horse component is associated with severe childhood asthma.³

A survey of almost 13,000 German children reported a sensitization rate of 12.6% to animal danders. The prevalence increased with age from 5.7% in 3–6 year-olds to 11.5% in 7–10 year-olds, and reached 17.2% in 14–17 year-olds.⁴ A Swedish birth cohort study of over

4,000 children reported a similar increase in sensitization rates to horse, cat, and dog from 4–16 years, respectively reaching 10.6%, 19.0%, and 22.6%.^{5,6} Increased prevalence of sensitization to common airborne allergens, including from cat and dog, has also been observed in adults,⁷ although prevalence rates are lower and in at least one Swedish study monosensitization to pet allergen components is more frequent.⁸ In Brazil, sensitization to furry animals, especially to dog, increased dramatically among allergic children and adolescents between 2004 and 2016, seemingly reflecting a sedentary “indoor lifestyle”.⁹ This increase is worrying, because sensitization to cat and dog is a risk factor for the development of asthma and rhinitis, as reported in a study that showed that sensitization to key pet components was observed in young children before the development of respiratory symptoms.¹⁰

Figure 1. Percentage of people living with pets (survey of >27,000 internet users in 22 countries)²



Allergens and sensitization phenotypes

Allergy diagnosis is supported by the detection of allergen-specific IgE (sIgE) antibodies using whole extracts or individual allergenic proteins from animal dander. The use of CRD provides a tool to identify sIgE responses to specific molecular targets, which may represent species-specific or cross-reactive sensitizations.^{18,19}

Allergens from pet animals are mainly present in their fur, saliva and urine and are spread into the environment through shedding of hair and dander.¹⁷ A study reported that all of 831 homes sampled in the United States contained dog allergen and most contained cat allergen, even those that never had an animal in the house.²⁰

The World Health Organization/International Union of Immunological Societies (WHO/IUIS, available from www.allergen.org) lists 36 allergens from mammals. Major mammalian-derived respiratory allergens can be classified into the following protein families: lipocalins, secretoglobins, serum albumins, kallikreins, and latherins.^{17,21}

Lipocalins

The most important group of mammalian respiratory allergens are lipocalins. These allergens are produced in secretory glands and are present in skin, urine, saliva, sweat and sebum. At least one allergen from the lipocalin protein family has been identified in each species, such as major allergens Can f 1 in dog and Equ c 1 in horse.²²

IgE reactivity to cat allergen Fel d 4 has been observed in up to 63% of cat-allergic subjects²³ and high levels of IgE antibodies to Fel d 4 have been associated with atopic dermatitis (AD) in children with cat allergy.²⁴ IgE reactivity to Fel d 7 has been reported in 38% of subjects with cat allergy.²⁵ Fel d 7 has 62% amino acid identity with Can f 1.²²

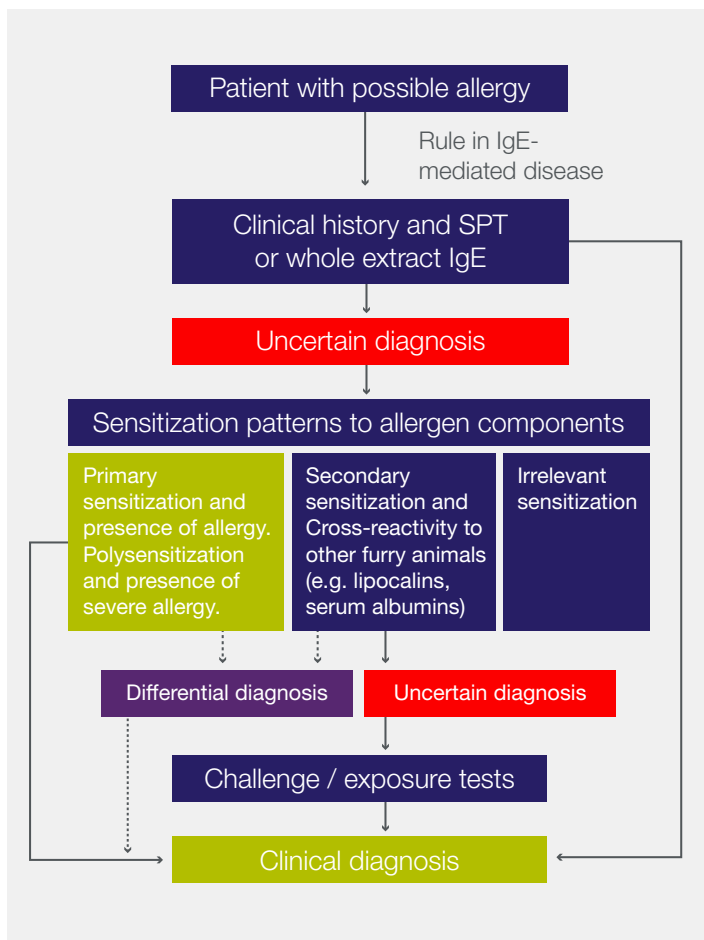
Among dog allergic patients, 50%–90% have antibodies to Can f 1, 20%–33% to Can f 2^{3,26,27} and 35% to Can f 4.²⁸ Sera from 56% (18/32) of children with dog allergy reacted with Can f 6.²⁹

Two horse lipocalins, Equ c 1 and Equ c 2, have been identified. Up to 76% of patients with horse allergy react to Equ c 1.³⁰ Sensitization to Equ c 1 has been associated with severe childhood asthma.¹⁶ In a population of 25

Geographic variation in the prevalence of allergic sensitization to furry animals has been attributed to cultural differences, environmental factors, and rate of pet ownership.^{11,12} A large international multicenter study in adults reported 8.8% (range, 1.2%–22.4%) sensitization to cat as measured by skin tests¹³, and the sensitization rate for dog was 20.4% among adult Korean subjects.¹⁴ Approximately 26% of European adults coming to the clinic for suspected allergy to inhalant allergens are sensitized to cat and 27% to dog, according to another large patient-based study of skin prick testing (SPT) for aeroallergens (Global Asthma and Allergy European Network [GAL2EN]).^{12,15}

A number of pet animal components, mostly produced as recombinant proteins, are now available for CRD, offering improved diagnostic work-up (Figure 2), particularly in patients with polysensitization and/or severe asthma.^{16,17}

Figure 2. Algorithm for diagnostic work-up of patients allergic to animal dander (adapted from⁷¹)



horse-allergic individuals, 13 (52%) were sensitized to Equ c 2 with an IgE level ≥ 0.1 kUA/L.³¹

The lipocalins comprise a diverse protein family with specific patterns of cross-reactivity among certain of its members, for example between Can f 6, Fel d 4 and Equ c 1³²⁻³⁴, Mus m 1 and Rat n 1³⁵, Equ c 1 and Mus m 1³⁰, and Fel d 7 and Can f 1.³⁶ Lipocalin allergens Equ c 1, Fel d 4, Can f 6, Cav p 6, Ory c 4, Rat n 1 and Mus m 1 show sequence identities between 45% and 67% (Figure 3a).⁵

Secretoglobins

Two mammalian allergens have been categorized as members of the secretoglobin protein family, namely Fel d 1 from cat and Ory c 3 from rabbit.³² Sequence identity between both allergens is very low and no IgE cross-reactivity has been observed.³⁷ Fel d 1 is mainly produced in sebaceous and salivary glands and is transferred to fur by grooming.³⁸

Fel d 1 is the most important allergen in cat allergy, shown to react with IgE from 90% of cat-sensitized individuals, and to account for up to 90% of IgE reactivity to cat dander.¹

Serum albumins

According to the WHO/IUIS allergen nomenclature database, seven mammalian serum albumin allergens have been identified, including Bos d 6 (domestic cattle), Can f 3 (dog), Cav p 4 (guinea pig), Equ c 3 (domestic horse), Fel d 2 (cat), and Sus s 1 (domestic pig).

Serum albumins, highly abundant proteins present in blood, dander, milk and other secretions, are considered minor allergens. However, high levels of IgE antibodies to Fel d 2 have been associated with AD in children with cat allergy.²⁴ Serum albumins remain relevant, because they are responsible for species cross-reactivity due to high sequence identity (up to 82%)²¹, for example, between cat and pig (Figure 3b). In a group of 39 highly sensitized cat-allergic patients, 23% had sIgE to Fel d 2 (cat) and more than half of those had sIgE to Sus s 1 (pig).³⁹

Figure 3. Amino acid sequence identity (adapted from⁵)

A. Lipocalins

	Rat n 1	Ory c 4	Mus m 1	Cav p 6	Can f 6	Can f 1	Fel d 7	Fel d 4	Equ c 1
Equ c 1	47	52	46	48	57	28	26	67	100
Fel d 4	55	63	49	53	67	26	20	100	
Fel d 7	24	25	22	24	25	62	100		
Can f 1	23	24	21	24	26	100			
Can f 6	52	58	47	53	100				
Cav p 6	50	49	45	100					
Mus m 1	64	51	100						
Ory c 4	54	100							
Rat n 1	100								

B. Serum albumins

	Sus s 1	HSA*	Fel d 2	Equ c 3	Cav p 4	Can f 3	Bos d 6
Bos d 6	79	76	78	74	70	76	100
Can f 3	78	80	87	76	73	100	
Cav p 4	72	72	76	72	100		
Equ c 3	76	76	78	100			
Fel d 2	79	82	100				
HSA*	75	100					
Sus s 1	100						

*Human serum albumin

Monosensitization to serum albumins seems rare. Sensitization to serum albumins is in the vast majority of cases observed in combination with sIgE directed against major allergens.³² Serum albumins may play a significant role as cross-reacting allergens in individuals sensitized to dander of multiple animal species, in association with lipocalins.⁴⁰ Indeed, because of cross-reactivity, children with persistent milk allergy and bovine serum albumin sensitization show an increased risk of allergy to animal dander with symptoms of rhinoconjunctivitis and asthma.⁴¹

Kallikrein

Can f 5 is so far the only identified allergen from the kallikrein protein family. The protein was isolated from the urine of a male dog, and was shown to be present in dog dander.⁴² Among patients allergic to dogs, 31–70% showed IgE reactivity to Can f 5, and 19.5%–37% of these patients were monosensitized to Can f 5 alone.^{42–46} Can f 5 has also been reported as the most common dog component sensitization in a Swedish adult population.⁸

The Can f 5 amino acid sequence shows no significant similarity to any known animal dander or urinary allergen.¹⁷ Therefore, monosensitization to Can f 5 could be a highly specific marker for allergy to male dogs.⁴⁷ Of note, Can f 5 cross-reacts with prostate-specific antigen of human seminal plasma (HSP), as suggested by several reports worldwide.^{48–50} A study in women sensitized to Can f 5 found that 8/27 patients reported allergic symptoms to HSP during intercourse.⁵¹

Latherins

Two allergens belonging to the latherin protein family, namely Equ c 4 and Fel d 8, have been identified. Equ c 4 is an abundant protein constituent in sweat, saliva and dander of horse.⁵² An IgE binding frequency to Equ c 4 of 77% (17/22 sera from horse-sensitized subjects) has been reported.⁵³

Fel d 8 has been characterized from the salivary glands of cats. However, with an IgE binding frequency of 19% among cat allergic individuals, it is not considered a major cat allergen.²⁵

Clinical utility of component-resolved diagnostics

Component-based IgE testing can distinguish a primary sensitization from a cross-sensitization to a higher extent than whole allergen extracts.⁵ While the possibility of using single components to replace whole extracts in daily diagnostic practice has been widely debated,^{54,55} a dominating view is that extracts are still needed as first line testing to ensure the detection of patients sensitized to components other than those available for CRD.

The availability of allergen component tests has driven new epidemiological studies to analyze the prevalence and clinical relevance of sIgE directed against individual allergens. Thus, CRD may be useful in detecting atypical sensitization profiles that involve minor allergen components, and in describing patient-specific IgE profiles to establish predictive risk markers and to develop strategies for therapeutic intervention.^{1,32} When clinical history and investigations are inconclusive, molecular allergology can add valuable clinical information in the diagnostic work-up (Figure 2).⁵⁶

Improved clinical sensitivity and specificity

Component-resolved diagnostics may prove useful in terms of improved clinical sensitivity in cases where a relevant allergen is scarcely represented in the natural allergens extract, as is the case of PR-10 allergens in certain plant foods such as fruits and nuts. Superior clinical specificity of component IgE testing compared to whole extract testing has been demonstrated for allergies to several foods, including peanut,⁵⁷ hazelnut,^{58,59} and cashew nut.^{60,61}

Markers of increased asthma risk and disease severity

Component-resolved diagnostics could provide markers of increased asthma risk, since asthmatic children with cat allergy have been shown to have higher Fel d 1-specific IgE levels than children with rhinitis only.⁶² A study of 696 cat-allergic Swedish children found that asthma symptoms upon contact with cat were significantly associated with sIgE to cat allergens Fel d 1 and Fel d 4 in cat-allergic children.⁴⁵ Among dog-sensitized children, the majority were sensitized to more than one dog component, and co-sensitization to Can f 5, Can f 1, and Can f 2 conferred the greatest risk for asthma.⁴⁵ The study further confirmed

that asthma was associated with higher levels of component sensitization.

Progression of allergic sensitization over time has been shown to involve IgE recognition of an increasing number of components from the sensitizing allergen source, forming the basis for the concept of molecular spreading, in which sensitization to a greater number of components from the same allergen source correlates with disease severity.⁶³ A recent study reported that asthmatic pediatric patients with IgE to Fel d 2 serum albumin, Fel d 4 and Fel d 7 lipocalins were more likely to have persistent type-2 inflammation.⁶⁴ A cross-sectional cohort study in 269 children found that asthma was significantly associated with sensitization to members of the lipocalin protein family.⁶⁵ The relationship between sensitization to specific allergen components and disease has been investigated by Simpson et al., who identified patterns of response to allergen component groups and investigated associations with asthma in children. Sensitization to a group that included 27 components of plant, animal, and fungal origin from 12 protein families was most strongly associated with asthma and decreased lung function (lower FEV1, $p < 0.001$).⁶⁶ Similar results have been reported in several subsequent studies.^{67,68} In another study, multisensitization to three or more animal-derived components (lipocalins, kallikrein, and secretoglobin) was associated with severe asthma, increased bronchial inflammation, and a trend towards more courses of oral corticosteroid treatment.⁶⁹ Similar findings were recently reported in a study of dog sensitized children.⁵⁶

A small early study comparing children with severe asthma vs. controlled asthmatic children demonstrated that those with severe asthma had higher levels of IgE antibodies towards cat, dog, and horse components.¹⁶ The use of allergen components compared with whole extracts as predictors of disease severity was evaluated by Asaranoj et al. in a large cross-sectional and longitudinal population-based pediatric study. Sensitization to Fel d 1 and Can f 1 at 4 years of age and molecular polysensitization to cat or dog components predicted allergy to cat and dog at 16 years of age significantly better than did IgE to whole cat or dog extracts.⁶⁸ In comparing allergen extract vs. component sensitization, Patelis et al. showed that adults sensitized to both cat extract and one or more of cat components Fel d 1, Fel d 2 and Fel d 4 had higher exhaled nitric oxide (FeNO) ($p=0.008$) and more bronchial responsiveness ($p=0.002$) than subjects sensitized to the extract but not to any of

the cat components tested.⁵⁴ Further, subjects who were sensitized to the tested cat components were more likely to develop asthma ($p=0.005$) and rhinitis ($p=0.007$) over a 12-year period than those who were not, highlighting the value of CRD in predicting disease severity.⁵⁴ Another adult study identified sensitization to furry animal allergen components, sensitization patterns and clusters as associated with a substantially increased risk of asthma, rhinitis, and concomitant asthma/rhinitis. Sensitization to Fel d 1, Can f 1, Can f 2, and Can f 3, polysensitization, and multisensitized cluster were further associated with increased FeNO and eosinophil levels. Thus, sensitization to furry animal allergen components is an important predictor of asthma outcome and an indicator of severity.⁷⁰

Taken together, available data indicate that measuring component-specific IgE offers insights into the progression and severity of allergy.

Allergen components in allergen immunotherapy

Treatment options for individuals who are allergic to furry animals include allergen avoidance, medications, and allergen immunotherapy (AIT).⁵ The ability of components to distinguish primary sensitization from cross-sensitization is important when immunotherapy is envisaged, in order to choose the primary sensitizing allergen source for therapy. The availability of CRD has raised the possibility of better targeted AIT, which is the only treatment able to change the natural course of allergic disease.

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