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Dog allergy: can a prevalent or exclusive sensitization to Can f 5 be considered a lucky or negative event in "real life"?

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Summary
Recent studies have shown the increasing relevance of allergic sensitization to Can f 5 (a prostatic kallicrein), which is an androgen-regulated protein expressed in the prostate and detectable only in male dogs. Can f 5 can be a prevalent or exclusive sensitizing agent in a considerable percentage of dog-allergic patients. Its specific allergenic characteristics are able to induce possible "negative" as well as "positive" clinical effects in individuals sensitized to dogs. In the present article we pointed out the possible pros or cons of sensitization to this allergen in "real life".
Further studies should be carried out to correctly assess some peculiar characteristics of Can f 5, in order to support the most of "positive" aspects and remedy at best the "negative" effects.

Dog allergens are a common cause of allergic sensitization and triggering respiratory symptoms worldwide. The impact of dog allergens is particularly relevant in geographical areas characterized by a high level of pet ownership, such as US and Northern Europe (1).
Common described dog allergens belong to lipocalins (Can f 1, Can f 2, Can f 4 and Can f 6) or albumins (Can f 3) families of proteins (2). In 2009 Mattson et al. (3) identified a new dog allergen named Can f 5, a prostatic kallicrein which is an androgen-regulated protein expressed in the prostate and detectable only in male dogs (small amounts might also be present in dog epithelia). Recent studies have highlighted the increasing importance of allergic sensitization to Can f 5, which has been found as exclusive allergen in about a third (3) up to 37% of dog-sensitized individuals (4). However, further studies should confirm the real value of Can f 5 sensitization in "real life" (5).
Considering this background, we will describe in the present article some specific aspects of Can f 5 and will try to balance possible pros or cons of being prevalently of exclusively sensitized to this allergen in "real life".

Reasons for possible "negative" events

It is well known that literature data on dog allergen immunotherapy (AIT) demonstrated poor and conflicting results on clinical efficacy, correlated with the poor-quality extracts and the inherent complex allergenic profile of dog materials. It is also likely that the concomitant sensitization to lipocalins

and/or albumins of other furry animals, especially in those patients directly exposed, could be a further aspect which determines the efficacy of dog AIT in sensitized individuals (6). Molecular-based diagnosis (CRD) can be considered a prototype of so-called "Precision Medicine", because CRD provides the possibility of a better targeted prescription of AIT, discriminating against primary and cross-sensitization to allergens (7). Considering the presence of different allergenic materials in extract of mammalian origin, it is evident that a standard dog AIT is not likely to be effective in Can f 5 mono-sensitized individuals.

Since Can f 5 is a prostatic kallicrein, similar to human prostatic antigen, some studies have shown that it can be involved in cases of human seminal plasma allergy (8,9).

Possible necessity of re-location of male dogs owned by patients with established allergic sensitization exclusively to Can f 5 and uncontrolled respiratory symptoms should be considered (see also the possible "lucky events" below).

Reasons for possible "lucky" events

We have previously shown that pet (cat or dog) ownership, or their presence in indoor environments, cannot be considered the main criterion to assess the exposure to animals. The use of this criterion represents a potential bias of underestimation in clinical practice and in large epidemiological studies (10-12). In fact, exposure to dogs and cats can happen via several direct and indirect modalities, such as through various pet allergen-contaminated items. The indirect modality of exposure may explain the common findings that dog allergens (Can f 1 and Can f 2) can be present in indoor environments where dogs cannot be kept. In developed countries, the consequence of pet allergen ubiquity is a persistent stimulation of airways, similar to that induced by dust mite, that may consequently increase the risk of allergic sensitization.

To the best of our knowledge, no studies have previously demonstrated a passive transport of Can f 5 in dog-free indoor environments. Therefore, also considering that the source of Can f 5 is dog prostate, we believe that the main way of exposure to this allergen should be the direct dog exposure for ownership or direct contact elsewhere. In a previous study on a similar topic we demonstrated that sensitization to urine allergens was exclusive of patients with rabbit at home, whereas individuals exposed indirectly to rabbit-derived materials exhibited allergic sensitization only to epithelial allergens (13).

The possible lack of passive transport of Can f 5 could decrease the risk of allergic sensitization through indirect modalities linked to ubiquity of dog allergens, so reducing the risk due to domestic exposure. However, further studies should be planned to evaluate the presence of Can f 5 in dog-free indoor environments as consequence of a possible passive transport through various items (e.g. clothes of dog owners). This modality of exposure has been demonstrated with the main dog allergens Can f 1 and Can f 2. Moreover, further studies should be planned on the possible reduction of Can f 5 production after castration of male dog.

With the exclusion of the similarity with the human prostatic antigen, Can f 5 should not cross-react to other mammalian "pan-allergens" belonging to albumins or lipocalins family. Thus, further investigations should evaluate a possible "cross reactivity" with prostatic antigen of other pets or domestic mammals. In fact, we have previously shown, by using an *in vivo* (skin prick test) and *in vitro* model (the micro-array technique ImmunoCAP ISAC), that exposure and allergic sensitization to common pets (including dogs) may increase the risk of developing sensitization to other furry animals (14,15). These findings are likely the consequence of cross–reaction mechanisms involving lipocalins and albumins.

The peculiarity of Can f 5 of being produced only by male dogs may lead to pros or cons consequences on dog ownership. In fact, Schoos et al. (16) have recently suggested that dog-allergic patients mono-sensitized to Can f 5 seem to tolerate female dogs, since a 54-year-old female patient reported that respiratory symptoms occurred only after exposure to male dogs. Diagnostic procedures (*in vitro* and *in vivo* tests including ocular provocation test) confirmed the absence of reaction to allergenic materials extracted from a female dog but not to those from a male dog (16). If other studies will confirm this first case-report, it would open up the possibility of trying to own a female dog, with lower risks, to fulfill the wish to get a dog in the house (this is a crucial aspect in "dog-lover patients", especially children).

Conclusions

Recent studies have highlighted the role of Can f 5 as sensitizing agent of airways that can be prevalent in a considerable percentage of dog-sensitized patients. Its particular antigenic profile is likely to determine positive or negative situations in "real life" (**figure 1**).

For this reasons, further studies should be performed to evaluate some essential aspects of Can f 5 in order to make the most of "positive" characteristics and to remedy at best the "negative" effects.

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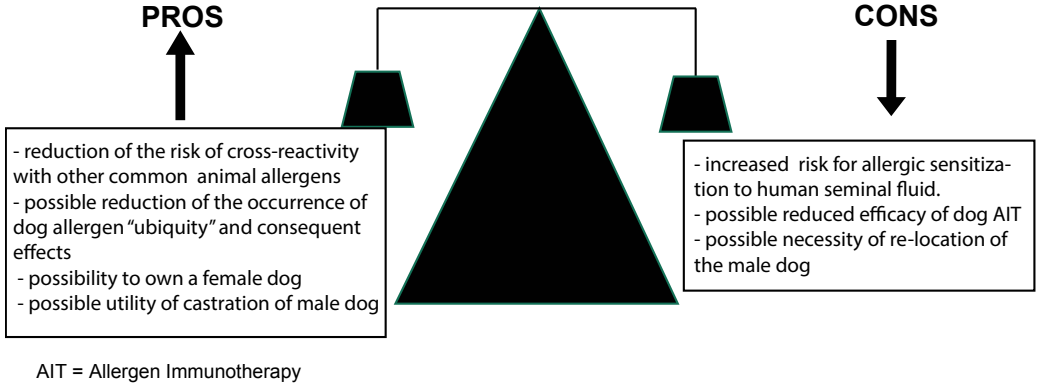
Figure 1 *- Possible Pros or Cons of being exclusively or prevalently sensitized to dog allergen Can f 5.*



Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Heinzerling LM, Burbach GJ, Edenharten G, Bachert C, Bindslev-jensen C, Bonini S. et al. GA2LE harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. Allergy 2009; 64:1498-1506.
2. Liccardi G, Asero R, D'Amato M, D'Amato G. Role of sensitization to mammalian serum albumin in allergic disease. Curr Allergy Asthma Rep 2011; 11:421-426.
3. Mattsson L, Lundgren T, Everberg H, Larsson H, Lidholm J. Prostatic kallikrein: a new major dog allergen. J Allergy Clin Immunol 2009; 123:362-368.
4. Basagaña M, Luengo O, Labrador M, Garriga T, Mattsson L, Lidholm J, et al. Component-Resolved Diagnosis of dog allergy. J Investig Allergol Clin Immunol 2017; 27:185-187.
5. Liccardi G, Calzetta L, Salzillo A, Apicella G, Di Maro E, Rogliani P. What could be the role of Can f 5 allergen in dog-sensitized patients in "real life"? J Investig Allergol Clin Immunol 2017; 27:397-398.
6. Liccardi G, Salzillo A, Calzetta L, Ora J, Rogliani P. Dog allergen immunotherapy and allergy to furry animals. Ann Allergy Asthma Immunol 2016; 116:590.
7. 7. Liccardi G, Bilò MB, Manzi F, Piccolo A, Di Maro E, Salzillo A. What could be the role of molecular-based allergy diagnostics in detecting the risk of developing allergic sensitization to furry animals? Eur Ann Allergy Clin Immunol 2015; 47:163-137.
8. Kofler L, Kofler H, Mattsson L, Lidholm J. A case of dog-related human seminal plasma allergy. Eur Ann Allergy Clin Immunol 2012; 44: 89-92.
9. Liccardi G, Caminati M, Senna GE, Calzetta L, Rogliani P. Anaphylaxis and intimate behaviour. Curr Opin Allergy Clin Immunol 2017; 17:350-355.
10. Liccardi G, Salzillo A, Cecchi L, D'Amato M, D'Amato G. Is cat keeping the main determinant of new-onset adulthood cat sensitization? J Allergy Clin Immunol 2012; 129:1689-1690.
11. Liccardi G, Salzillo A, Calzetta L, Piccolo A, Rogliani P. Assessment of pet exposure by questionnaires in epidemiological studies (but also in clinical practice!): why the questions should be simplified? J Asthma 2016; 53:879-881.
12. Liccardi G, Salzillo A, Calzetta L, Piccolo A, Menna G, Rogliani P. Can the presence of cat/dog at home be considered the only criterion of exposure to cat/dog allergens? A likely underestimated bias in clinical practice and in large epidemiological studies. Eur Ann Allergy Clin Immunol 2016; 48:61-64.
13. Liccardi G, Piccolo A, Dente B, Salzillo A, Gilder JA, Russo M, D'Amato G. Rabbit allergens: a significant risk for allergic sensitization in subjects without occupational exposure. Respir Med 2007; 101:333-339.
14. Liccardi G, Passalacqua G, Salzillo A, Piccolo A, Falagiani P, Russo M, D'Amato G. Is sensitization to furry animals an independent allergic phenotype in non-occupationally exposed individuals? J Investig Allergol Clin Immunol 2011; 21:137-141.
15. Liccardi G, Meriggi A, Russo M, Croce S, Salzillo A, Pignatti P. The risk of sensitization to furry animals in patients already sensitized to cat/dog: A in vitro evaluation using molecular-based allergy diagnostics. J Allergy Clin Immunol 2015; 135:1664-1666.
16. Schoos AM, Bønnelykke K, Chawes BL, Stokholm J, Bisgaard H, Kristensen B. Precision allergy: Separate allergies to male and female dogs. J Allergy Clin Immunol Pract 2017;9. 5: 1754-1756.