Geography of house dust mite allergens

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Summary

Objective: **To consider how the different distribution of house dust mites and their species in different geographical locations affects the allergens in the environment and their use.**

Data sources: **Data were obtained from Medline, Genbank and library and web searches.**

Study selections: **A comprehensive description of the genetic variations of allergens is given. The distribution of house dust mites is illustrated with publications that either make pertinent observations or would be useful for a broad appreciation of their geographical distribution.**

Results: **The review identifies regions where glycyphagid house dust mites have been found and the distribution of the pyroglyphid *Dermatophagoides* spp. The antigenic differences the allergens of *D. pteronyssinus* and *D. farinae* are outlined and how this should affect optimal allergen usage in different regions. The allelic variations within the major allergens of *Dermatophagoides* sp. are similarly presented.**

Conclusions: **While there is a broad knowledge of the distribution of different species of house dust mites, regions that require further examination have been identified and there are examples of incorrect use of allergens for different regions. The extension of allergy research and practice into new regions will benefit from allergen formulations designed for regional use. Specific knowledge of the allergens in the environments will be required to optimally implement some of the new molecularly-defined medicaments currently being developed for effective allergy vaccination and immunotherapy. *(Asian Pac J Allergy Immunol 2010;28:211-24)***

Key words: *Dermatophagoides, pteronyssinus, farinae, Blomia, tropicalis, allergen, allergy, allergen variants, allergen polymorphism, house dust mite.*

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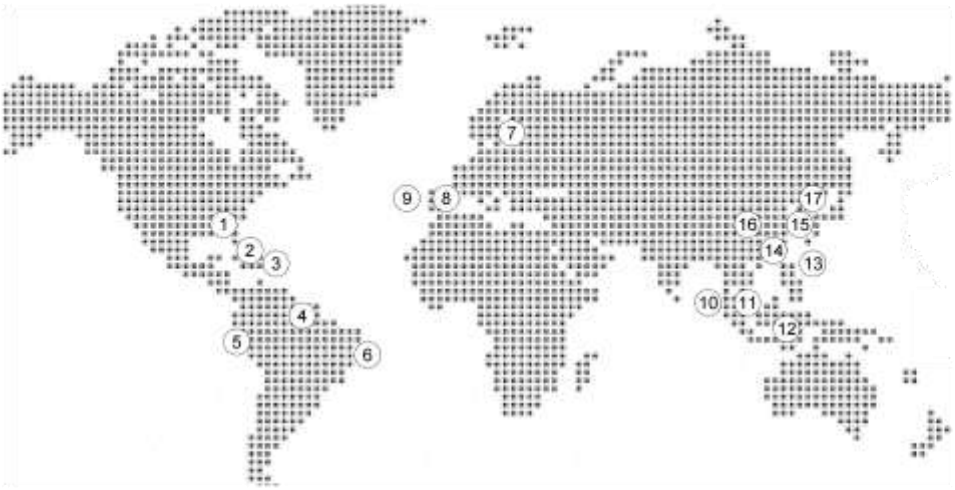
Introduction

House dust mites (HDM) are the most prevalent source of indoor allergens shown by multicentre studies across Europe,[1] USA,[2] Asia,[3,4] and South America[5] and New Zealand[6] and Australia.[7] Africa also has HDM allergy.[8,9] Regions with a few months of relative humidity below 50% have low infestations.[10] These include high altitudes in temperate regions in New Mexico,[11] the Rocky Mountain states of USA[12] and European Alps.[13] and the subarctic and cold continental climates of northern Sweden,[14] Norway,[15] Siberia,[16] Estonia,[17] the Mongolian plateau[18] and Iceland.[19] The combined effect of poor housing and cold in the inner cities of northeast USA also promotes low infestation.[20 21] The effect of relative humidity can be seen within the one province of Canada where HDM sensitisation is common in the humid coastal regions of British Columbia and rare in the semi-arid high-altitude districts.[23] High altitude by itself is not not sufficient to reduce HDM as shown by the abundant populations in the Andes.[23]Low HDM infestation is found in the deserts of Isreal,[24] Saudi Arabia,[25] and Kuwait[26] although infestation increases with humidity from air conditioning.[27] Decreased HDM with increased fungal allergy is also documented in Arizona, USA[28] and inland Australia.[29] The global distribution of glycyphagid and pyroglyphid HDM species will be considered below and then how this affects the allergens in the environment.



1. Florida and Texas Bt minor
2. Puerto Rico Bt most abundant
3. Barbados Bt most abundant
4. Colombia Bt abundant
5. Lima Peru Bt most abundant
6. Salvador Brazil Bt abundant
7. Gotlund Sweden Ld
8. North Spain Ca and Gd
9. Canary Island Bt found
10. Singapore Bt most abundant
11. Malaysia Bt most abundant
12. Indonesia Bt found
13. Philippines Bt predominant
14. Hong Kong Bt most abundant
15. Taiwan Bt important
16. Mainland China Bt found
17. Korea Tp found

Figure 1. Distribution of glycyphagid house dust mites Bt. *Blomia tropicalis*; Ld, Lepidoglyphus destructor; Ca, *Chortoglyphus arcuatus;* Gd, *Glycyphagus domesticus*; Tp, *Tyrophagus putrescence*

The respective distributions are summarised in Figure 1 and Figure 2.

Blomia tropicalis

Blomia tropicalis from the family glycyphagidae can be a HDM. Its allergens typically have 30-40% amino acid sequence identity with their Dermatophagoides homologues[30] but cross reactivity with allergen extracts exists.[31] The major allergens are Blo t 5[30] and possibly Blo t 21.[32] They do not cross-react with *Dermatophagoides* sp. by IgE binding[33] or by skin test[34] so they are useful for assessing the sensitisation. The tropomyosin and glutathione-S-transferase of *B. tropicalis* antigens cross-react with ascaris proteins limiting the usefulness of extracts in many regions.[35]

B. tropicalis is the most abundant HDM in Singapore[36], Hong-Kong,[37] Malaysia[38] and the Philippines.[39] It constitutes 40% of the HDM in Taiwan[40] although it is not present in all homes and sensitisation is less than in Singapore.[41] *B. tropicalis* has been reported as 17% of the HDM in Shenzhen province of China.[42] This agrees with the skin test reactivity to extracts determined in centres across China which was lower than reactivity to *Dermatophagoides* sp.[4] and rarely occurred by itself. A recent study from Chengdu province however showed that 49% of patients had antibodies to Blo t 5, a high degree of sensitisation.[43] A small study from Jakarta showed that *B. tropicalis* only constituted 14% of the HDM[44] which is interesting given its proximity to Singapore and Malaysia and a reported high prevalence of IgE antibody to Blo t 5.[45] *B. tropicalis* is not abundant in India[46,47] and sensitisation in Mumbai measured with Blo t 5 was 15%.[45] Bangkok and Chiang Mai in Thailand have been shown to have 22 and 14.5% of subjects with anti-Blo t 5[45] so some infestation can be expected. Blo t 5 however only elicited skin test reactions in 10% of atopic subjects in Chiang Mai[48] compared with over 30% to *D. pteronyssinus* confirming *Dermatophagoides* spp. as the main HDM.[49]

1. Vancouver Dp	12. Virginia DfDp	23. Sao Paulo Dp	34. Netherlands DpDf	45. Palestine Dp	56. Philippines Dp
2. Seattle Dp	13. Florida Dp	24. Chile Dp	35. Belgium DfDp	46. Saudi Ara. Dp(Df)	57. India Dp(Df)
3. Los Angeles DfDp	14. Cuba DpDs	25. Argentina DpDf	36. Switzerland Df	47. Ghana Dp	58. Thailand Dp(Df)
4. San Diego Dp	15. Puerto Rica Dp	26. Iceland NIL	37. France DpDf	48. Nigeria Dp	59. Singapore Dp
5. Nunavut NIL	16. Barbados Dp	27. Norway Dp	38. Spain Dp(Df)	49. Mauritius Dp	60. Malaysia Dp
6. Midwest DfDp	17. Mexico DpDf	28. Finland Dp	39. Italy Df	50. South Afr. Dp(Df)	61. Indonesia DfDp
7. Rockies Df	18. Colombia Dp	29. Sweden DfDp	40. Croatia Dp	51. Japan DpDf	62. Australia Dp
8. Arizona DfDp	19. Venezuela Dp	30. Denmark DfDp	41. Turkey Dp	52. Korea Df(Dp)	63. New Zealand Dp
9. Texas Dp	20. Ecuador DpDf	31. Moscow Dp	42. Kuwait Dp	53. Taiwan Dp(Df)	
10. Louisiana Dp	21. Inland Brazil DfDp	32. Germany DfDp	43. Iran Dp	54. Hong Kong Dp	
11. North east Df(Dp)	22. Salvador Dp	33. England Dp	44. Israel Dp	55. Mainl. China DpDf	

Figure 2. Distribution of Dermatophagoides spp. Dp, *D. pteronyssinus* predominant; Df, *D. farinae* predominant; DpDf Mixed with more *D. pteronyssinus* than *D. farinae*; DfDp Mixed with more *D. farinae* than *D. pteronyssinus*; Ds *D. siboney*; Parentheses indicate low levels or specific pockets of infestation. The figure should be read in conjunction with the detail in the text

In Central and South America *B. tropicalis* are the most prevalent HDM in Barbados[50] and Puerto Rico.[51] but probably not Cuba. Skin test reactions to extracts detected there[52] are likely to be cross-reactions. It is a minor HDM in nearby Florida and Texas.[53] *B. tropicalis* abound in the tropical coastal area of Salvador, Brazil along with a high prevalence of *D. pteronyssinus*.[54,55] They constitute half the HDM in the low altitude tropical regions of Columbia[56] and are the most prevalent HDM in Peru.[57] They however constitute a small percentage of HDM in neighbouring Ecuador[58] and Venezuela.[59] The HDM in the tropical high altitude regions are *Dermatophagoides* spp. [23,60] and *B. tropicalis* is not found in the mountainous inland region of Uberaba in Brazil.[61]

B. tropicalis needs to be assessed more thoroughly in some regions. They have been observed in Uganda[62] but the details were not reported. Few *B. tropicalis* were found at Cape York at the northeastern tip of the Australia,[63] but the rest of the tropical north remains unexplored as well as Papua New Guinea where the HDM in the highlands was mostly *D. pteronyssius*.[64] Sensitisation to *Blomia kulagini* was detected by skin prick test with extracts in subtropical Canary Islands. The extracts are however antigenically indistinguishable from those of *B. tropicalis*[65] and *B. tropicalis* only constituted 10% of the HDM in homes, mainly infested with *D. pteronyssinus*.[66] The studies are significant because they suggest sensitisation to *Blomia* spp. in a non-agricultural European setting.

Glycyphagid mites besides Blomia spp.

Some storage mites can become HDM. *Lepidoglyphus destructor* in Gotland, Sweden[67] infests damp rooms and induces allergic sensitisation from domestic exposure. The predilection of storage mites for damp walls of dwellings in France was also recently reported.[68] *Chortoglyphus arcuatus* often associated with

allergy in poultry workers is abundant in homes in the northern coast of Spain.[69] People sensitised to *C. arcuatus* produced large responses to conjunctival challenge to *C. arcuatus* extract with small responses to *D. pteronyssinus* . The sera also showed low cross reactivity for IgE binding. *C. arcuatus* infestations were high but so were infestations with *D. pteronyssinus*. About 50% of allergic patients in this region also had skin test reactivity to extracts of *Glycyphagus domesticus*, which is similarly abundant. Frequent skin test reactivity to these mites was found in Colombia where they constitute 8% of the HDM.[70] *Tyrophagus putrescence* infests homes in Korea but generally at low levels,[71] and absorption studies show that the IgE antibodies to *T. putrescence* are cross reactivities to *Dermatophagoides* spp.[72]

Distribution of *Dermatophagoides* species

D. farinae grows with relative humidities of 50%[73] while *D. pteronyssinus* prefers them over 60%.[74,75] Exact predictions from climate data are difficult because of diurnal variations and high relative humidity in microenvironments such as the base of carpets. There are also variations of sensitivity of different mite strains within the one species.[76] *D. pteronyssinus* tends to be most abundant in regions with high HDM densities. This would arise from its faster growth rate[75] and that they only thrive with optimal relative humidity.

Only a few countries have either predominantly *D. pteronyssinus* or *D. farinae*. Australia,[63,77] New Zealand,[78] England[79,80] and Mauritius[81] have *D. pteronyssinus* with few other HDM. Singapore has a bias to *D. pteronyssinus* but with *B. tropicalis* infestations.[36] Most of South Korea has a bias to *D. farinae* especially in the northwest.[71] Italy also has *D. farinae*-biased infestations from Turin,[80] Pavia[80] and Milan[82] in the west to Verona[80] in the east and southern regions of Rome[83] and Naples.[84] These regions do not have low relative humidity and similar locations in Western Australia[85] and San Diego, USA[86] have *D. pteronyssinus*.

In Asia; Singapore, Malaysia, Hong Kong and the Phillipines have *D. pteronyssinus* as the dominant pyroglyphid HDM.[36,38,79,39] Thailand and Taiwan and have more *D. pteronyssinus* than *D. farinae* [49,87,40] while regions in mainland China[3,4] and Japan[88,89] have mixed populations. South Korea is heavily infested with *D. farinae* although south and south western cites have *D. pteronyssinus*.[71] A study in Jakarta, Indonesia reported that *D. farinae* constituted 39% of the HDM while *D. pteronyssinus* was 25%.[44] The relative humidity of Jakarta is high so *D. farinae* are unusual and the HDM in Bali are *D. pteronyssinus*.[90] *D. pteronyssinus* is the abundant HDM in Dehli[91] and Bangalor[47] but the inland mountainous region of Pune has a bias to *D. farinae*[92] and low levels of HDM. Nearby more humid regions of Kerala and Neyveli have predominantly *D. pteronyssinus*.[92]

D. pteronyssinus is abundant in South and Central America. On the west, Valdivia in Chile has infestations of *D. pteronyssinus*[93] as does Santiago but with lower infestations.[92] In Brazil *D. pteronyssinus* dominate in populous Sao Paulo,[94] and Salvador.[95] Drier regions in Sao Paulo State[96] and Belo Horizonte[97] however have a predominance of *D. farinae* and the inland areas of Uberlândia[98] and Uberaba[99] which have dry summers have both species. Argentina[100] has a mixed population while Venezuela[59] and Colombia[56] have predominantly *D. pteronyssinus*. The tropical high altitude region of Quito[101] in Ecuador have both *D. farinae* and *D. pteronyssinus*. HDM in the Barbados,[50,102] and Puerto Rico,[51] are abundant and primarily *D. pteronyssinus*. Cuba has *D. siboney*, closely related to *D. farinae*, as its most abundant HDM along with high infestations of *D. pteronyssinus*.[103] Mexico which experiences months with low relative humidity has both species.[104]

A regional pattern for HDM in North America has been described.[53, 86,105,106] *D. pteronyssinus* can predominate along the west coast as shown for San Diego[53,86,106] and Seattle[106] however Vancouver[107] and Los Angeles,[53,86] have high *D. pteronyssinus* and *D. farinae*. The Rocky Mountain States have low infestations of *D. farinae*.[12,86,106] The midwest extending to Illinios[108] and Winnipeg[109] have mixed populations. HDM become biased to *D. farinae* in the northeast including Ohio,[110] New York,[111] Baltimore,[106] Massachussets,[106] Cincinnati,[53,86] Detroit[112] and Toronto.[106] Well-insulated homes have high infestations that remain *D. farinae*. Der f 1 concentrations of 40μg/g dust are reached in Ottawa.[113] Local climate can be important; *D. pteronyssinus* predominates along the upper

Connecticut river[114] with its milder weather. HDM along the east coast from Virginia[115] to Georgia[116] and Alabama[112] are mixed. *D. pteronyssinus* predominates towards the south in Texas,[53,112] and Louisiana[53] but despite its high relative humidity the Florida gulf region has both species.[53,117] Litner *et al.* reported more *D. farinae* in the hot deserts but it was only marginally more than *D. pteronyssinus*.[105]

The bias to *D. pteronyssinus* in England[79,80] and to *D. farinae* in Italy[80,82-84] has been noted. The HDM in Turkey[118] are predominantly *D. pteronyssinus* and Croatia[119] has *D. pteronyssinus* with pockets of *D. farinae.* Most of Spain is highly infested with *D. pteronyssinus*.[80,120,121] except that the dry interior and Barcelona are biased towards *D. farinae*.[80] *D. farinae* predominate in the alpine towns of Grenoble, France[80] and Basel, Switzerland[80] but infestation is low. *D. pteronyssinus* however cannot be ignored in alpine regions since HDM in the Briançon high in the French Alps has equal, although low, infestations of both species.[122] HDM in Poland are biased to *D. farinae* but other western and central European countries including much of France[80,123] Netherlands[80,124] Belgium[80,125] and Germany[80,126] have mixed populations that tend to increase in *D. farinae* in more continental climates. As shown in the Netherlands[124] considerable species variation can exists in neighbouring cities. Moscow has more *D. pteronyssinus*.[127] HDM infestations in Scandinavia decrease with increasing latitude.[128] Denmark[129] and Sweden[80,128] have more *D. farinae* but with significant infestations of *D. pteronyssinus*. Norway[130,131] and Finland[132,133] counter-intuitively have mostly *D. pteronyssinus*.

Jeddah in Saudi Arabia with its arid climate has infestations of *D. farinae* while Riyadh in the central desert has few HDM.[134] The southern mountains with their more humid climate have *D. pteronyssinus*.[134] The humid areas in Iran have abundant *D. pteronyssinus*[135] and *D. pteronyssinus* is main infestation throughout Israel[24] and Palestine.[136] *D. pteronyssinus* predominance has been reported for Ghana[9] and Nigeria[137] and most of South Africa.[138] The inland highlands have few HDM but *D. farinae* can heavily infest well-insulated homes.[139] Mauritius,1000 km off the coast, has *D. pteronyssinus*.[81]

The dominance of *D. pteronyssinus* in Australia has been documented in New South Wales, Cape York, the south of Western Australia and the central desert centre where few homes had HDM.[63] 14% of the HDM in Cape York and 6% in Alice Springs were *D. farinae*. Other studies have shown that *D. pteronyssinus* predominates in south Western Australia[85] and Melbourne.[140] In Tasmania with a cold wet climate 2/72 homes were found with predominantly *D. farinae.*[141] In all however only 6/72 of the homes had detectable *D. farinae*. New Zealand has high infestations of *D. pteronyssinus* without *D. farinae*.[78,142]

D. pteronyssinus and *D. farinae* extracts for cross-species diagnosis and immunotherapy

Allergen extracts cannot be used to attribute sensitisation to different *Dermatophagoides* sp. The allergens are cross-reactive and their allergen content varies.[143,144] The Australian experience is instructive. Different studies have reported either more skin test reactivity to *D. farinae* than *D. pteronyssinus,*[145] the same reactivity,[146] or less reactivity to *D. farinae*.[147] Not only is *D. farinae* rare but low reactivity was reported from Tasmania, where at least a few homes have a predominance of this species. Sensitisation in New Zealand, which also lacks *D. farinae*, can be measured equally well with extracts of both species.[148] Qualified credence can be given to studies that compare anti-*Dermatophagoides* spp. reactivity with a single extract. The low skin test reactivity in inland compared to coastal regions of Australia,[29] the low sensitisation found at altitude,[11]in the Swedish arctic[14] and Mongolia[18] are examples. In Iceland however the sensitisation reflects cross reactivities with storage mites.[149]

A key question is whether or not immunotherapy should be tailored to the sensitising species. There are no direct comparisons but the benefits reported for the immunotherapy conducted with *D. pteronyssinus* in Italy[150,151] in regions where the sensitising species is *D. farinae* do not differ markedly from those conducted in England with *D. pteronyssinus* for *D. pteronyssinus* sensitisation[152] or those conducted in South Korea with *D. farinae* for *D. farinae* sensitisation.[153] The results in Italy also do not differ from those conducted with a mixture of extracts.[154] These comparison are however made for a treatment which delivers a highly variable

and incomplete benefit . T cell recognition of peptides representing Der p 1 and Der f 1 is different[155] so possibly new molecularly defined medicaments will need to consider the species.

Cross reactivity of D. pteronyssinus and *D. farinae* allergens

About 50-60% of the IgE binding activity to *D. pteronyssinus* extracts can be accounted for by the binding of the Der p 1 and Der p 2.[156,157] Collectively most of the remaining binding is to the group 4, 5, 7 and 21 allergens[157,158, 159] Similar conclusions have been drawn from skin prick testing.[160] With few exceptions there is a good correlation between the IgE binding to Der p 1 and Der p 2[161,162] and HDM extract.[156,157] The inter-species cross reactivity of these allergens is therefore paramount.

A good correlation of IgE binding to Der p 1 and Der f 1 was found in a Japanese population exposed to both species.[163] The titres to Der p 1 were however over twice those to Der f 1 in a third of the subjects and the ability to absorb IgE binding to Der p 1 with Der f 1 varied from 15% to almost 100%. A good correlation was also found in Virginia, USA where the patients would be exposed to both species, biased to *D. farinae*.[164] There were however 10 fold differences for some individuals. Using a small sample of sera from England and the USA it was found that *D. pteronyssinus* could absorb out over 80% of the anti-Der f 1 reactivity of subjects mainly exposed to *D. farinae* and all of the reactivity of subjects exposed to *D. pteronyssinus*. Absorption studies with a saturating dose of allergen found that about 50% of the IgE binding, of atopic dogs from Tokyo, was species specific.[165] A study of sera from Belgium, where *D. pteronyssinus* predominates, used competitive inhibition. For most sera over 100 fold more Der f 1 was required for 50% inhibition[166] with the inhibitory concentrations of Der f 1 approaching those found for denatured Der p 1. Thus using an assay that might reflect affinity a large effect was found.

The study in Japan showed that cross reactivity of the group 2 allergens was higher than that found for the group 1 allergens.[163] with cross-absorption removing all IgE binding. A close correlation of IgE binding to Der f 2 and Der p 2 was also found in Virginia.[167] Absorption was not performed but it is unlikely that the IgE binding would be with antibodies to an unrelated antigen. Jin *et al.* showed that the IgE from a pool of sera from Seoul, Korea bound recombinant Der p 2 better than a recombinant Der f 2[168] indicating high cross reactivity since subjects in Korea are exposed primarily to Der f 2. A comparison of IgE reactivity of sera from England with natural Der p 2 and recombinant Eur m 2 from the pyroglyphid mite *Euroglyphus maynei* found less correlation than that between recombinant Der p 2 variants and natural Der p 2.[169] The sera frequently had a two-fold difference in IgE binding. Since Eur m 2 has the same sequence disparity from Der p 2 as Der f 2, 20%, this shows a larger difference than the earlier studies. Similarly the sera from atopic dogs in Tokyo showed a higher inter-species disparity of IgE binding to the group 2 allergens than the group 1 allergens.[165]

The cross reactivity of Der f 7 and Der p 7 can be inferred from Shen *et al.* who showed that the IgE binding to Der f 7 were about 30-40% of the titres to Der p 7.[170] This concurs with the low *D. farinae* levels found in the study area of Taipei. The cross reactivity of the group 4, 5 and 21 pyroglyphid allergens has not been published.

The probability of children developing asthma has been shown to double from 0.25 to 0.5 for a 100-fold change in the titre of IgE.[171] Accordingly it is unlikely that species-specific differences allergens would affect any assessment of the prognosis of patients. Disease is associated with much smaller amounts of IgE than those typically produced by HDM allergic patients so if residual allergic sensitivity is left by immunotherapy with the wrong species, or if the incorrect specificity of blocking antibody is induced, then treatment could be compromised.

T-cell cross reactivity

Inter-species T-cell cross reactivity of the group 1 and group 7 allergens has been measured in Western Australians who are exposed to *D. pteronyssinus*. *In vitro* responses showed equal proliferative to *D. pteronyssinus* and *D. farinae* allergens and the same Th1 and Th2 cytokine release.[172] The allergen preparations had not been depleted of endotoxin so it is possible a difference could be found with ultra purified allergen. Th2 cytokine release was however not induced in cells of subjects sensitised to non-HDM allergens so allergen specificity was required. When synthetic peptides were used to induce *in vitro* proliferation, cross reactive responses were found Der p 1 and

Der f 1 peptides and indeed some of the stimulatory epitopes had the same sequence.[155] Fewer peptides of Der f 1 were however stimulatory showing that the species may be important especially for peptide immunotherapy. The early studies of Th2 responses in HDM allergy were conducted with Der p 1 in Rome using patients that would have mostly been sensitised to *D. farinae*.[173]

Cross reactive allergens

There is awareness of the cross-reactivity of the Der p 10 and Der f 10 tropomyosin allergens. Their amino acid sequences are 98% identical so cross reactivity is likely to be complete and almost complete with tropomyosins from glycyphagid mites, which are 96% identical. The indistinguishable binding of IgE from cockroach-allergic subjects to HDM and cockroach tropomyosin demonstrates the high cross reactivity.[174] It however needs to be appreciated that IgE binding to the group 10 allergens is rare in Europe[175] and Australia[157] and, from the study of Satinover,[174] in US subjects allergic to both HDM and cockroach. The HDM allergic subjects with IgE to Der p 10 belong to a group with higher IgE immunoglobulin levels and multisensitisation to food and pollen allergens.[175] They appear to be a distinctive clinical group but are not more prone to asthma. High IgE binding has been reported to Der f 10 in Japan[176] and Der p 10 in Zimbabwe.[177] It was not just cross reactivity to an unidentified antigen because the positive subject also had IgE antibody to a HDM major allergen. This is an area to follow up especially since the single report from Japan indicated a large response. Cross reactivity of HDM tropomyosin and shrimp tropomyosin has also been of interest although it should be noted that western blotting show cross reactivity with several allergens and tropomyosin concentrations are low in HDM extracts.[178]

The group 20 arginine kinase allergens have also been identified as potential cross-reactive allergens. Like tropomyosin they do not appear to be important allergens, at least in Australia.[157] The amino acid sequences of the arginine kinases are 84% identical between pyroglyphid HDM, which is similar to the major allergens, but 75% and 80% identical to sequences of insects and crustaceans where they are major inhalant[179] and food[180] allergens respectively. Cross-reactive IgE binding with HDM and moth arginine kinase has been demonstrated.[181]

Sequence conservation required for cross reactivity

The important allergens of *Dermatophagoides* spp. have 80-85% sequence identity. Their closest homologues are the equivalent allergens from the glycyphagid mite family, which typically have 35% identity. From overall identity the α-amylase group 4 allergen is the only one with potential cross reactivity. It shares 90% identity within *Dermatophagoides* sp.,70% with glycyphagid mites and 50% with insects and mammals.

IgE antibody binding to inhaled allergens is dependent on tertiary structure but is mediated by the interactions of the side chains of surface amino acids[182] and is therefore sequence, not fold, dependent. Studies with myoglobins from different species demonstrated that 20% disparity in sequence led to a 50% reduction in antibody binding and 30% disparity to 20%.[183] Similar findings were made for different serotypes of the influenza hemagglutinin[184] where 70% amino acid identity showed no cross reactivity and with snake venom toxins where over 60% identity was required.[185] The pollen polcalcin grass allergens Phl p 7 and Bet v 4 with only 60% identity show exceptional cross reactivity,[186] associated with a highly conserved spatial arrangement of surface amino acids.[187]

HDM extracts in unchartered waters

The use of HDM extracts can produce misleading results. Skin test reactivity of aboriginals from tropical Australia had showed a high prevalence of sensitisation to HDM in the face of a low incidence of asthma. The high titres of IgE binding were not to the major Der p 1 or 2 allergens but to the Der p 4 amylase.[188] It was restricted to subjects with positive skin test reactions but this could be attributable to the amylase allergen. The reason for the anti-amylase response has not been elucidated but there was little IgE binding to Der p 10 and Der p 20 which might have been expected from cross-reactive food or insect allergies and no reactivity to Blo t 5 which would implicate *B. tropicalis* and storage mites. Similar, but not identical, results from the Chengdu province in China showed that 25% of asthmatics had IgE binding to Blo t 4 from *B. tropicalis* but they were not classically allergic to *B. tropicalis* because of a lower reactivity the dominant Blo t 5 allergen.[43]

Allergen variants

The group 1 and 2 allergens are single gene products with frequent allelic variation. Variants in different regions could exist and be required for optimal diagnosis and immunotherapy and it is conceivable that variation contributes to allergenicity, either by increasing the diversity of epitopes, or the inherent allergenicity of particular variants. If binding to toll-like receptors (TLR) is important for the allergenicity of Der p 2, and there is evidence for this,[189,190] then variants that bind best would be more allergenic. The variants were initially found by cDNA cloning but much of the information has been derived from PCR. The calculated and observed rates of sequence error for high fidelity PCR of 300 base pairs would lead to a nucleotide error in less than 1% of the sequences.[191] For a set of 50 sequences the probability an incorrect sequence would be 0.26 and for two would be 0.08. The probability of obtaining frequent errors is according very small and finding changes in the same amino acid is most improbable. The veracity of the nature of single changes however must be established.

The sequences of Der p 1 cDNA clones from a commercial culture revealed frequent amino acid substitutions,[192] that were then shown to present in HDM in homes from Australia[193] and Thailand.[194] In all 23 variants from 44 sequences were found with substitutions found in 18 of the 221 amino acids.[192] Similar diversity has been found in China.[195] The histidine 50 in the first cDNA sequence, Der p 1.0101, was only found in commercial HDM with other sequences having tyrosine. The only frequent exchange was an alanine to valine at position 124 with multiple but infrequent substitutions at positions 19, 81 and 215. Since most substitutions are sporadic the core sequence defined by Der p 1.0102 and Der p 1.0105 which only differ at position 124 would the most abundant. The exchange at 124 is in a region that contains T-cell epitopes recognised by most HDM-allergic subjects[155] so it could be important. Unlike Der p 1, Der f 1 has little polymorphism as noted in Thailand[194] and China.[195] The nucleotide sequences were however diverse and the Der f 2 sequences from the same mites were polymorphic. The lack of polymorphism of Der f 1 suggests that polymorphism is not important for allergenicity.

The substitutions in Der p 2 and Der f 2 showed an evolutionary pattern of polymorphism.[169,193,194,196-200] The variable amino acids in each species were however not in the same structural regions. The important polymorphisms of Der p 2 were in amino acids 40, 47, 111 and 114 that cluster together in and near a loop region.[193,194] Der p 2.0101 has valine, threonine, methionine and aspartate in these positions while Der p 2 .0104 has leucine, serine, leucine and asparagine. Other variants have different combinations of these amino acids. The dominant allergen in Western Australia was Der p 2 0101 found in 50% of cDNA clones with most other clones showing incomplete substitution towards the Der p 2.0104 type. About half the clones of Der p 2 from Korea were Der p 2.0104-like[198] and the HDM in Bangkok showed an even stronger bias to Der p 2.0104. The canonical Der p 2.0101 was not even found. Single sequences published from Germany (ncbi: CAK22338) and Denmark[199] show Der p 0104 like sequences. A sequence reported from China (ABY53034) is very interesting because it shows substitutions in positions 40 and 47 to charged aspartate and arginine amino acids and not the typical leucine and serine. Recombinant Der p 2.0101 binds less IgE than recombinant Der p 2.0104-like variants[198, 201] and correlates less with the IgE binding to natural Der p 2[169] even with sera from an environment where Der p 2.0101 is common.[201] The substitution in residue 114 is well known to determine the binding of monoclonal antibodies ID8 and 4G7 which require asparagine at that position.[169,202] It is unlikely that the 50% difference in the IgE binding between Der p 2. 0101 and 0104-like sequences would affect IgE mediated allergy because the titres are still large and this has been demonstrated by basophil degranulation.[199] Combinations of human IgE monoclonal antibodies however had a 100-fold difference in their ability to produce degranulation with different variants.[199] It is therefore possible that the variants contribute to the allergenicity by increasing the diversity of the antibody responses. They could be critical if recombinant allergens were used for immunotherapy. If blocking antibodies were important, then those produced against a recombinant Der p 2.0101 might not be sufficient to block effector responses to Der p 2.0104. To date the variants have not been isolated as natural proteins and, if they are important, this would be a research priority since structural differences between recombinant and natural Der p 2 have been demonstrated.[203] Of immediate significance is that the monoclonal

antibodies that are used to measure environmental Der p 2 do not bind to all variants.

Der f 2 from *D. farinae* in Asia[194,196,204,205] and Europe[200] fall into 2 groups.[194] Der f 2. 0101-like sequences show conservative uncharged substitutions in residues 88, 11 and 125. Another group that can be described as Der f 2.0107-like have characteristic changes in amino acids 57,58 and 59 including substitution of the surface accessible aspartate 59. In the one letter code the Der f 2.0107-like variants change SLD to NIN in amino acids 57-59. About 30% of the sequences described from Germany were of the Der f 2.0101 type and 70% the 0107 type while the proportion was reversed in Bangkok. Like Der p 2 the variants vary in different locations. Four sequences from Japan[196] and those from Korea[204] were of the Der f 20101-type and sequences from China showed both groups.[205]

Conclusions

Since allergy and allergic disease has been associated with economic development[206,207] it is anticipated that there will be an increased need to combat HDM allergy in new geographical regions. The need to diagnose allergy in new circumstances will require allergen preparation appropriate for the HDM in the regions and to take into account cross reactivities that are not encountered in the regions where the allergen extracts are used today. It has already been shown in tropical Australia[188] that diagnosis with a standard extract was not suitable for a new environment. Also, like infectious disease, there would be an enormous benefit in preventing or effectively treating allergic disease with new types of vaccination and immunotherapy. There are many new innovations that could profoundly improve immunologically based treatments and as summarised elsewhere they are being developed.[208] Many however will depend on new technologies with molecularly defined medicaments. Their optimal formulation with respect to the allergens is becoming apparent[190] and as described here they can be further tailored for the allergens in environment where they will be used. In the absence of further information this should include the variants of the major allergens since, as discussed, it is plausible that variant-specific responses could be an impediment to effective immunotherapy. These considerations do not just apply to new environments since as documented here it is not uncommon for investigations, therapy and diagnosis to be conducted without correct regard to or knowledge of the HDM allergens in the patient's environment.

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