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ENVIRONMENTAL RISK FACTORS FOR ASTHMA: ALLERGEN EXPOSURE

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- **An allergen** is defined as "***a harmless substance capable of triggering a response that starts in the immune system and results in an allergic reaction***".
- In patients with **atopic asthma**, allergen exposure often exacerbates the asthma through crosslinking of mast cell/basophil surface IgE molecules and/or activation of antigen-specific Th2 cells.
- **More than 900 types of allergens** have been reported to date, about half of which are airborne (Table 1).

TABLE 1

Major allergens associated with asthma*

Origin	Species	Allergen	MW (kDa)	Main source	Function
HDM	*Dermatophagoides farinae*	*Der f* 1	27	feces	Cysteine protease
		Der f 2	15	feces	NPC2 family
	Dermatophagoides pteronyssinus	*Der p* 1	24	feces	Cysteine protease
		Der p 2	15	feces	NPC2 family
Cockroach	*Blattella germanica*	*Bla g* 1	46	feces	Lipid-associated and/or binding protein
		Bla g 2	36	feces	Inactive aspartic protease
Mouse	*Mus musculus*	*Mus m* 1	17	urine	Lipocalin/ urinary prealbumin
Cat	*Felis domesticus*	*Fel d* 1	38	dander	Uteroglobin
Dog	*Canis familiaris*	*Can f* 1	23-25	dander	Lipocalin
Fungi	*Alternaria alternata*	*Alt a* 1	16.4 and 15.3		IL-33 inducer
	Aspergillus fumigatus	*Asp f* 1	18		Mitogillin family
		Asp f 2	37		
Ragweed	*Ambrosia artemisiifolia*	*Amb a* 1	38	pollen	Pectate lyase

HDM: house dust mite; MW: molecular weight; NPC2: Niemann-Pick type C2.

- **Six mite species**, including *Dermatophagoides pteronyssinus* and *D. farinae*, are the major sources of allergens in house dust in many countries.
- **More than 13 allergenic proteins** are reported as mite-derived allergens; *Der f*1 and *Der p*1 originate mainly from the feces of the mites.
- The **growth of mites is strongly dependent on the environment** (optimal conditions: >25°C temperature and >75% relative humidity).
- Therefore, the **amount of house dust mite** (HDM) allergens is critically influenced by climate, season, housing type, presence/absence of carpeting, pets, plants, vacuum cleaners and others (Figure 1).

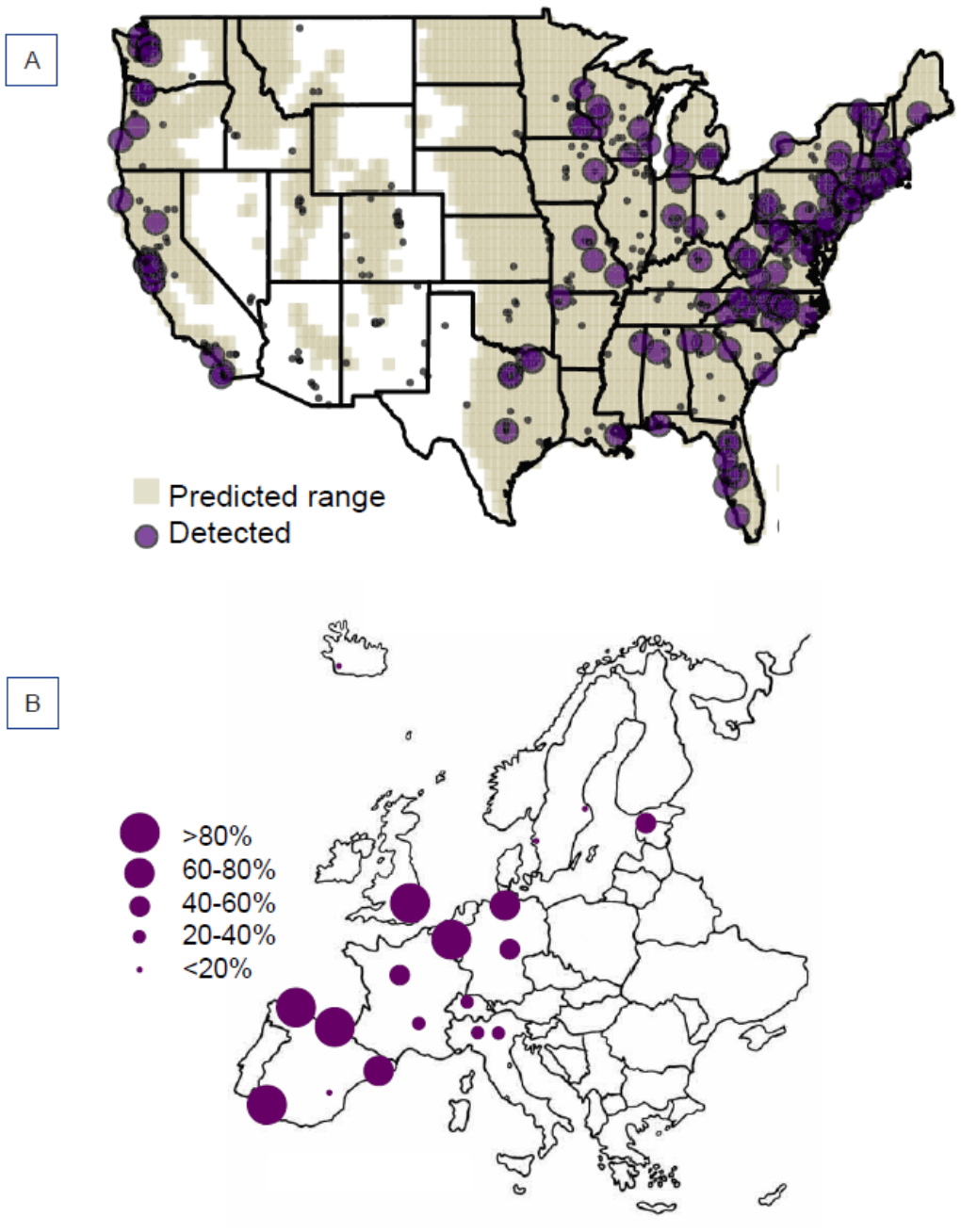

Figure 1 A. Distributions of house dust mite (Dermatophagoides spp.) range vs. detected range. B. Detection rates of house dust mite antigen (Der p1 > 0.1 µg/g dust) in different cities in Europe.

- A previous birth cohort study reported that **exposure to *Der p*1 >2 µg/g of dust during infancy** was associated with increased prevalence of sensitization to mites by age 5 years, and **levels above 10 µg/g** were associated with a 4.8-fold relative risk for development of asthma by age 11 years.

- Several intervention trials showed that **HDM avoidance** improved asthma control in sensitised patients.
- However, such avoidance showed controversial results **for primary prevention of sensitization in high-risk children.**
- In addition, a couple of preliminary studies that tried **to induce oral tolerance to HDM allergens for primary prevention of sensitization** were **ineffective**, indicating that new approaches are needed in this regard.

- **Cockroaches** infest homes and buildings in many countries.
- **The major allergen of the German cockroach** (*Blattella germanica*), *Bla g*1, is contained in their feces, and it causes asthma exacerbation, especially in patients living in urban areas and inner cities.
- A combination of integrated pest management strategies, such as dust formulations, bait and paint insecticide formulations, improve asthma control.

- **Mice, cats, dogs and other domestic animals** are also sources of allergens for sensitized patients with atopic asthma.
- The **dander, saliva and urine of these animals** contain allergenic proteins (Table 1).
- Interestingly, according to several observation studies, **the presence of dogs in early life** reduced the risk of asthma later in life.

- **Various fungi**, including *Aspergillus fumigatus*, *Alternaria alternata* and *Penicillium* species, are well known to induce IgE-sensitization and mast cell/basophil activation, leading to asthma upon exposure.
- In addition, **non-IgE-mediated mechanisms for airway inflammation** have also been elucidated: *A. fumigatus*-specific IgG/precipitating antibodies play critical roles in the pathogenesis of **allergic bronchopulmonary aspergillosis.**
- Similarly, ***Alternaria*** is known to induce IL-33-mediated severe asthma exacerbation.

- **Some pollens**, such as those from **ragweed** (*Ambrosia artemisiifolia*), are well-known to sensitize and often cause asthma with severe rhinitis.
- Interestingly, however, some other pollens, such as those from **Bermuda grass** (*Cynodon dactylon*) and **Japanese cedar** (*Cryptomeria japonica*), also sensitize and frequently cause rhinoconjunctivitis, *but* rarely cause asthma.

- The **primary mechanism of involvement of allergen exposure in the pathogenesis of asthma** is sensitization to the allergens followed by IgE-driven eosinophilic inflammation.
- **Many of the indoor allergens**, such as *Der f*1, *Der p*1 and *A. alternata*, have protease activity.
- Protease activity itself induces allergic airway inflammation in mice through epithelial-derived cytokine IL-33, independent of acquired immunity via T cells and IgE antibodies.
- In addition, such **epithelial-derived cytokines as IL-33 and thymic stromal lymphopoietin** can prime antigen-presenting cells to induce T-cell development towards Th2.

- **Allergen proteases** reportedly induce bronchial epithelial barrier dysfunction by degrading tight junction proteins and intercellular adhesion molecules such as zona occludens (ZO)-1 and E-cadherin.
- Accumulating evidence suggests that the **pathogenesis of asthma is not limited to IgE-mediated mechanisms** (acquired immunity), **but also involves activation/damage of bronchial epithelial cells**, leading to release of epithelial-derived cytokines and activation of innate lymphoid cells that then release type 2 cytokines (innate immunity).
- **Some allergens can activate both acquired and innate immunity**, which further highlights the importance of allergen avoidance.

- Finally, **global and regional climate changes** that may be influencing the distribution and amounts of airborne allergens and thus may facilitate/exacerbate allergic diseases worldwide.

KEY MESSAGES

- Allergen exposure causes exacerbation in patients with atopic asthma through crosslinking of mast cell/basophil surface IgE molecules and/or activation of antigen-specific Th2 cells
- Exposure to high amounts of house dust mite during infancy is a risk for sensitization and development of asthma later in life
- Some allergens can activate both acquired (IgE-mediated) and innate (epithelial-derived cytokine-mediated) immunity, which further highlights the importance of allergen avoidance
- Recent global and regional climate changes may be influencing the distribution and amounts of airborne allergens