

# Molecular Allergology:

THE FUTURE OF ALLERGY DIAGNOSTICS

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Allergies are a major health and socioeconomic burden worldwide, but especially in industrialised nations. For example, more than 40% of the population in Europe now suffers from at least one form of allergy. About 70% of these allergic patients are polysensitised. Children are frequently affected by atopic dermatitis, allergic rhinitis and allergic asthma. Precise in vitro diagnostics complement conventional diagnostics and are essential for optimal patient management and efficient treatment. Multiplex systems streamline the procedure by delivering a comprehensive and detailed patient profile in a single test. In particular, immunoblots containing optimised combinations of relevant allergens provide efficient multiparameter detection of specific IgE antibodies in different indications

### Molecular Allergology: From Extracts to Components

Molecular allergology is a state-of-the-art approach to allergy diagnostics, whereby defined single allergen components are used for detection of specific IgE in place of traditionally used allergen extracts (Figure 1). The molecular components are highly purified proteins, which are either isolated directly from the allergen source or produced recombinantly. They provide a higher level of standardisation than allergen extracts and enable highly differentiated diagnostics. Molecular allergology systems are a powerful diagnostic tool as they can pinpoint the precise trigger of the allergy, thus facilitating risk assessment and therapy decisions.

### Identification of Cross Reactions

Before embarking on therapy it is critical to establish the exact trigger of the allergy. However, it is common for patients to show multiple reactions in clinical tests such as skin prick tests and in extract-based antibody assays. These may be due to an actual polysensitisation or a monosensitisation with cross reactions. The latter involves an initial reaction against a single source, but the IgE antibodies can also bind to structurally related allergens from other sources, potentially inducing an immune response and a positive in vitro test result. Analysis of the individual components of the allergen sources and the most important panallergens enables the precise trigger

of the allergy symptoms to be determined quickly and accurately.

For example, a pollen-allergic patient who has a confirmed sensitisation to Bet v1 from birch pollen will probably also react to the homologue Cor a1 from hazel pollen. But a Bet v1-induced cross reaction with grasses is unlikely, since there is no Bet v1 homologue in grass pollens. If a birch-pollen allergic patient nevertheless reacts to grasses, this could in turn be because birch and grass pollens also contain ubiquitous allergens (panallergens) which can also lead to cross reactions, for example Bet v4 from birch and Phl p7 from timothy grass (Figure 2). Bet v1 homologues are, moreover, found not just in tree pollen but also in foods. Thus, Bet v1-specific antibodies can also cross react with Ara h8 from peanut. If this causes symptoms it is known as a birch pollen-associated food allergy.

### Selection of Suitable Therapy

Depending on the trigger, allergies can be treated by avoidance of the allergen, if possible, or by specific immunotherapy (SIT). SIT has a high chance of success when the patient is primarily sensitised to the major components of the allergen extract, so called if more than 50% of patients sensitised to the allergen source react to these components. Only molecular allergy diagnostics can deliver this in-depth information. The optimal treatment can then be selected, and the patient is spared the stress of unnecessary allergen avoidance or ineffective SIT.

### Risk Assessment and Risk Management

Components from different protein families elicit symptoms of varying severity. Thus, molecular profiling can establish if a patient has a low or high risk of severe systemic reactions such as anaphylactic shock. Patients at risk of life-threatening reactions can then be advised on avoidance of the allergen and on appropriate measures to take in an emergency situation. For example, if a patient is sensitised to allergens from the family of profilins, then mild symptoms are generally to be expected. While, patients who are sensitised to allergens belonging to the family of storage proteins have a high risk of life-threatening systemic reactions.

Furthermore, families of proteins differ in their heat stability, which plays an important role in food allergies. Heat-labile allergen

components (profilins, PR10 proteins) in foods are usually denatured by cooking processes, thus reducing the risk of a reaction.

### Molecular Allergy Diagnostics of Childhood Allergies

Sensitisations to peanut, milk and egg are the most common allergies in childhood. Peanut allergy in particular can have serious consequences, often triggering anaphylaxis. Accurate diagnosis of allergies in infants and children is important for assessing the risk of systemic reactions, evaluating the chances of tolerance induction and establishing the necessity of dietary restriction. A paediatric profile (defined partial allergen diagnostics, DPA-Dx, Figure 3) containing the most important allergen components from these three sources provides fast and efficient screening of these sensitisations and is the optimal diagnostic tool to supplement the results from anamnesis and skin testing.

The characteristics and impact of the allergen components of the paediatric profile are explained briefly in the following sections:

**Egg:** In egg allergy, Gal d1 (ovomucoid) is the main allergen and serves as an indicator for the severity of the allergic reaction. Sensitisations to the heat-sensitive components Gal d2 (ovalbumin), Gal d3 (conalbumin) and Gal d4 (lysozyme) are associated with symptoms only with consumption of raw or slightly cooked eggs. Ovalbumin is used in vaccines and lysozyme is used as a preserving agent, so patients with these sensitisations may exhibit reactions to pharmaceutical or food products containing the corresponding component.

**Milk:** A reaction to Bos d8 (casein) indicates a strong allergy to milk and milk products. Casein is frequently used as an additive, thus a sensitisation can also cause intolerance to a wide variety of foods such as chocolates or potato chips. The components Bos d (lactoferrin), Bos d4, Bos d5 and Bos d6 are heat sensitive, and sensitisations to them are mainly associated with reactions to fresh milk. Antibodies against Bos d6 (bovine serum albumin) may in addition cause a reaction to beef.

**Peanut:** The peanut section of the profile can distinguish a primary peanut sensitisation from a cross reaction with birch pollen and establish the risk for the patient. IgE antibodies against the seed storage proteins Ara h1, Ara h2 and Ara h3 and the lipid transfer protein Ara h9 carry ▶

a high risk of a systemic reaction. The severity of the allergy is, moreover, greater when multiple high-risk components are involved. A reaction with Bet v1 on the other hand indicates a cross reaction from a birch pollen allergy.

### Case Report Peanut Allergy: The Same, But Different

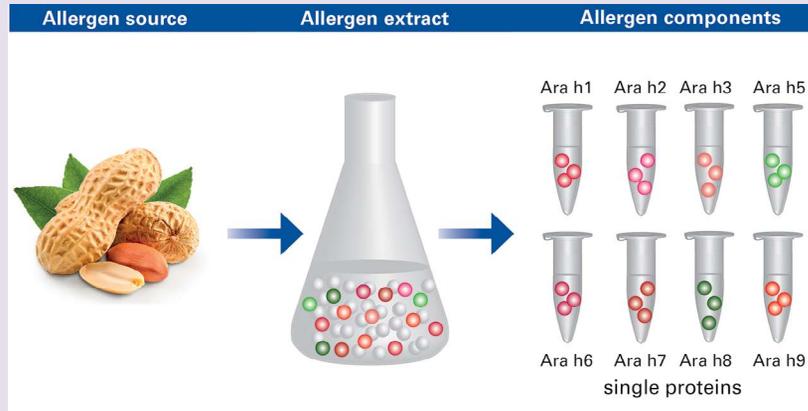
Two patients individually attend an allergologist with unspecific symptoms, namely prickling in the mouth, eczema, nausea and rhinoconjunctivitis. After detailed anamnesis the allergologist performs a screening test for IgE antibodies against food allergens. A sensitisation to peanut is diagnosed in both patients. In order to assess the risk of a severe systemic reaction and anaphylactic shock, molecular allergy diagnostics are used for the next step, for example using the paediatrics profile (Figure 4).

Patient 1 has no reaction to the peanut-specific allergen components Ara h1, h2, h3 and h9, but is positive for Bet v1 of birch pollen (Figure 4 A). This patient has a primary sensitisation to Bet v1 from birch, and therefore most likely has a birch pollen-associated food allergy due to a cross reaction. Since the patient does not have a true peanut allergy, the risk of life-threatening reactions is low and a strict peanut-free diet is not absolutely necessary. If the birch pollen allergy is a burden for the patient, the recommended therapy would be SIT against birch pollen, which has a high probability of success since the patient is sensitised to the major allergen Bet v1. Since the peanut symptoms are due to a cross reaction, it is likely that the pollen-associated food allergy will also be alleviated by the SIT.

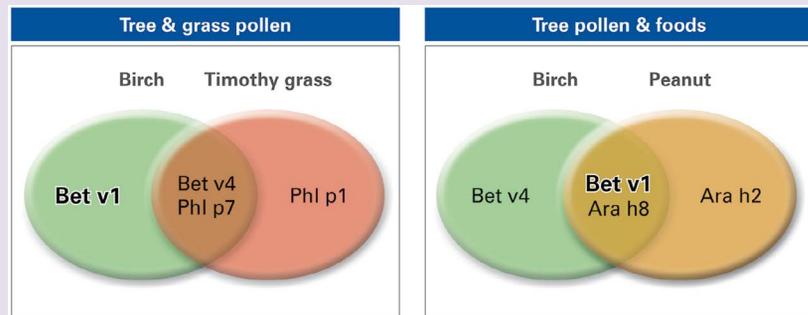
Patient 2 has positive reactions to the peanut-specific allergen components Ara h1, h2, h3 and h9, but is negative for Bet v1 of birch pollen (Figure 4 B). The patient thus has a true peanut-associated food allergy with a high risk of a systemic reaction, since the sensitisation is directed against several storage proteins. Even traces of peanut could trigger a severe systemic reaction. The patient must therefore strictly avoid the allergen source and should always carry an emergency set.

For patients such as these, only molecular allergy diagnostics are able to pinpoint the exact trigger of the allergic symptoms and clarify the associated risk.

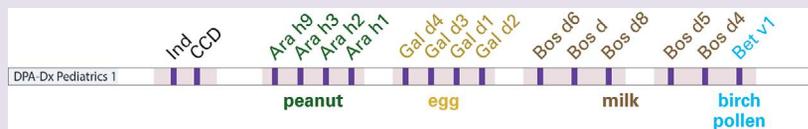
▼ FIGURE 1. Single allergen components



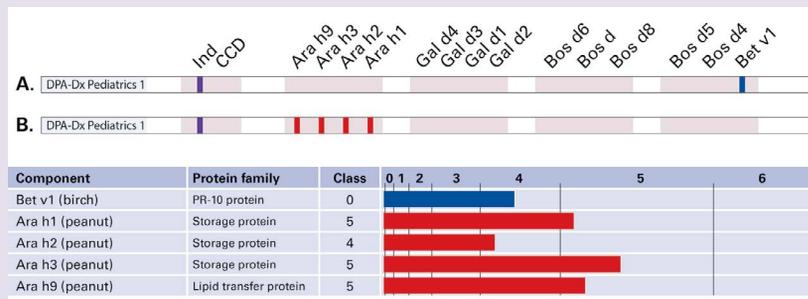
▼ FIGURE 2. Potential cross reactions in pollen allergies



▼ FIGURE 3. Paediatric profile for molecular allergy diagnostics



▼ FIGURE 4. Profiles of patients with A. birch pollen-associated food allergy (patient 1) and B. true peanut allergy (patient 2)



### Optimal Strategy

Multiplex molecular allergy tests are an indispensable tool for deciding on the optimal strategy for patient management. The tests allow differentiation between cross reactions and multiple sensitisations, which is particularly important for advising patients on the risk of severe allergic reactions. Precise identification of the allergy trigger,

moreover, allows selection of patients for SIT who are most likely to benefit from it, thus improving prognosis. Targeted therapy can spare patients the burden of multiple therapies or unnecessary lifestyle changes involved in allergen avoidance. Thus, molecular allergology provides the bedrock for improved patient care and a better quality of life for allergy sufferers. **ML**