Component-Resolved Diagnostics in Wheat Allergy*

Introduction

Wheat (*Triticum aestivum*) is an important cereal grass and global food source, with world trade in wheat exceeding that of all other crops combined. Wheat contains more vegetable protein than corn or rice, with unprocessed wheat grains consisting of 70% carbohydrates, 12% protein, and 2% fat, plus several other nutrients. The list of foods containing wheat is extensive, including:

- cereals
- pasta
- flour
- baked goods
- bulgur
- couscous
- semolina
- spelt

Gluten-free products are not necessarily wheat-free or safe for wheat-allergic individuals. However, some people with wheat allergy may tolerate buckwheat, which isn’t related to wheat. Given the variety of wheat-containing products, allergen exposure can be through ingestion, inhalation, or topical contact. Wheat-containing foods must be labeled as such in the U.S. and European Union.

Wheat is also found hidden in unexpected foods, such as:

- batter-fried foods
- beer
- candy
- ice cream
- hydrolyzed vegetable protein (HVP)
- imitation crab meat
- hot dogs
- baking powder
- potato chips
- salad dressings and sauces
- cosmetics
- bath products
- Play-Doh

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The worldwide prevalence of wheat allergy is estimated to be between 0.5% and 9% of the population. In the U.S., wheat allergy is one of the eight most common IgE-mediated food allergies. Primary wheat allergy starts in infancy but in most cases resolves by school age. In preschool-age children the prevalence of wheat sensitization is approximately 4% and increases, primarily due to co-sensitization with grass pollen, until age 10. Yet while wheat allergy reportedly affects up to 8% of children during the first three years of life, only 2% of teens or adults suffer from the condition. Baker’s allergy affects from 1% to 10% of bakery workers exposed to respiratory or topical contact with wheat. Finally, wheat-dependent exercise-induced allergy (WDEIA) occurs mostly in adolescents and young adults.

Overview

- Component-resolved diagnostics may help identify primary wheat sensitization and exclude irrelevant cross-reactivity to grass.
- ImmunoCAP™ menu offers one whole allergen wheat extract test and three allergen component tests.
- These tests help assess risk for severe reaction and may improve patient management by facilitating tailored avoidance recommendations.

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Allergenic molecules of wheat
Wheat allergens are classified into 4 categories based on solubility (Figure 1). The albumins and globulins are water/salt soluble, whereas wheat gluten and its constituent proteins (gliadins and glutenins) are not. The gliadins and glutenins comprise 85% of wheat proteins. The gliadins are further broken down into three classes by their electrophoretic mobility as fast (alpha and beta gliadins), intermediate (gamma gliadins) or slow (omega gliadins). Omega-5 gliadin is the best characterized single component of wheat. The glutenins are grouped by their high or low molecular weights. Sensitization to all of the gliadins and glutenins is common among wheat-allergic individuals. Other potentially allergenic proteins in wheat include alpha-amylase inhibitors and wheat lipid transfer proteins.

As a grass in the Poaceae family, wheat contains proteins that cross-react with grass-pollen allergens. Using Tri a 14 may help to differentiate wheat sensitization from grass pollen allergy, though this testing has low sensitivity. Wheat is highly cross-reactive with both rye and barley.

The clinical patterns of wheat allergy
The symptoms of wheat sensitization and allergy overlap those of non-IgE-mediated food reactions and celiac disease, and may include diarrhea, nausea/vomiting, bloating, abdominal pain, weight gain or loss, and skin rash. The pathogenesis of gluten-related disorders can be autoimmune, allergic, or neither autoimmune or allergic (Figure 2).

Gluten-related disorders can have distinctly different underlying pathogenesis, although symptoms may overlap. Four distinct clinical patterns characterize IgE-mediated wheat sensitizations.

Wheat allergy: As in milk or egg allergy, infants and children develop symptoms within minutes or a few hours of ingesting or contacting stable wheat proteins. Symptoms may manifest as oral, cutaneous, respiratory, gastrointestinal, or cardiovascular. Severe cases can result in anaphylaxis. Delayed symptoms may include worsening of atopic dermatitis or gastrointestinal distress. Other cereals such as rye and barley may also elicit these symptoms. Resolution occurs before school age in many cases. Children who do not develop tolerance tend to have higher mean specific IgE (sIgE) levels than those who do—16.0 kU/L vs. 9.12 kU/L, respectively, in one study.

Young children can be challenged at intervals to test for tolerance. Sensitization to Tri a 19 in patients with a history of clinical reactivity to wheat could be an indication to avoid oral food challenge, as these patients could be at risk of anaphylaxis. Avoidance of all wheat-containing foods is recommended in cases of anaphylaxis, but individuals with delayed symptoms or IgE-negative results for wheat should be encouraged to eat wheat as long as they are symptom-free.

Wheat-dependent exercise-induced anaphylaxis: Symptoms such as urticaria or anaphylaxis occur in adults or adolescents after wheat ingestion that is followed by physical exercise. Onset is rapid and may be enhanced by co-factors such as alcohol consumption, aspirin, or non-steroidal anti-inflammatory drug (NSAID) use. Sensitization to omega-5-gliadin (Tri a 19) is a specific marker for this condition, but affected individuals are often sensitized to other wheat allergens, such as other gliadins and the lipid transfer protein Tri a 14. Treatment relies on avoiding exercise for 4-6 hours after eating wheat, not running alone or in pollen season, and carrying emergency medication.

Figure 2. Spectrum of gluten-related adverse food reactions
Baker’s allergy: Inhalation or topical contact with wheat flour and dust can cause rhinoconjunctivitis and asthma symptoms in sensitized individuals within a few hours of exposure. The specificity of whole-wheat flour testing can be improved using component-resolved diagnostics (CRD). Recombinant Tri a 14 is a useful tool for assessing baker’s allergy diagnosis, based on its physicochemical and immunological similarity with its natural counterpart. Wheat Tri a 14 shows a high thermal stability and resistance to gastrointestinal digestion, which is important for long-term management of this condition. Exposure avoidance or mitigation is the main treatment when diagnosed.

Contact urticaria: Topical contact with hydrolyzed wheat protein in cosmetics can cause urticaria or possibly anaphylaxis in individuals allergic to gluten-containing foods. Avoidance of products containing hydrolyzed vegetable protein (HVP) is the treatment of choice.

Allergen component naming conventions

Allergen components are named using the first three letters of their genus and first letter of their species names, and a number based on their order of discovery. Thus, wheat designations start with “Tri a” for Triticum aestivum, followed by a number (e.g., Tri a 14 or Tri a 19 [omega-5-gliadin]). The prefix “n” is added to native-sourced proteins and an “r” to recombinant proteins that are used for CRD testing. n-Gliadin is a natural, non-recombinant component mix of 4 gliadins (alpha, beta, gamma and omega) made from purified wheat extract and purified to 99%. rTri a 14 and rTri a 19 (omega-gliadin) are single recombinant proteins.

Wheat cross-reactivity

The value of component resolved diagnostics in wheat allergy

Wheat allergy produces symptoms that can range from mild to life-threatening. Whole allergen wheat extracts used for skin prick testing or serum assays have low specificity. Component-resolved diagnostics can help:

- Identify primary wheat sensitization and exclude irrelevant cross-reactivity to grass
- Assess risk for severe reactions, which are more likely with positive results for Tri a 19 and n-Gliadin
- Improve patient management by facilitating tailored avoidance recommendations

sIgE testing should be conducted in the context of the patient’s history, clinical symptoms, physical examination, and possible allergen exposure. If wheat sensitization or allergy is suspected:

- Test for whole wheat extract through skin prick testing or through sIgE testing (f4)
- In addition to whole wheat extract, add n-Gliadin (f98) to the initial assessment of suspected wheat allergy, since it is not adequately represented in the f4 Wheat whole extract test
- Reflex positive whole allergen wheat extract (f4) to Tri a 14 (f433), cross-reactive carbohydrate determinants (CCD), and grass profilin Phl p 12 (g212)
- Reflex positive n-Gliadin (f98) to Tri a 19 (f416)

1 Surrogate markers for profilin Phl p 12, Bet v 2 or Pru p 4.
2 Gliadin is purified from a wheat extract and consists of 4 native, highly purified (99%) gliadins: α-, β-, γ- and ω-gladiins (including ω-5 gliadin)
Wheat protein characteristics

n-Gliadin is associated with acute wheat allergy and a risk for severe reactions. Gliadins are resistant to heat and digestion, so baked wheat may cause symptoms. WDEIA is also possible with sensitized patients and should be considered.

Tri a 14 is important in food allergy, baker’s allergy and WDEIA. Because this non-specific lipid transfer protein is stable to heat and digestion, baked or unbaked wheat may cause symptoms. Tri a 14 is unlikely to cross-react with grass pollen.

Omega-5-gliadin (Tri a 19), a wheat seed storage protein, has poor aqueous solubility and is not well represented in wheat extracts. Fifty to 70 percent of wheat-allergic patients are sensitized to this protein. Using Tri a 19 can dramatically increase both sensitivity and specificity compared to testing with whole wheat extracts. Tri a 19 is usually associated with acute food reactions and indicates an elevated risk for childhood food allergies that are unlikely to be outgrown. Stable to heat and digestion, Tri a 19 can cause symptoms whether raw or baked. IgE antibodies to Tri a 19 are detectable in a majority of WDEIA patients and are a marker for severe reactions, particularly in adults. The addition of n-Gliadin (alpha, beta and gamma gliadin) adds diagnostic value in WDEIA, specifically for Tri a 19-negative patients.

Interpreting test results

Patients who have positive results for wheat whole allergen extract and negative results for Tri a 14 have a low likelihood of primary wheat sensitization (Figure 3). Positive results for both n-Gliadin and Tri a 19 indicate a high probability of primary wheat sensitization and severe events.

Available ImmunoCAP Specific IgE Wheat Allergen Component Tests

<table>
<thead>
<tr>
<th>Component</th>
<th>Composition</th>
<th>Code</th>
<th>Product Name</th>
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<tbody>
<tr>
<td>Wheat</td>
<td>Whole allergen</td>
<td>f4</td>
<td>ImmunoCAP Allergen f4, Wheat</td>
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<tr>
<td>Gliadin</td>
<td>Alpha, beta, gamma and omega gliadins</td>
<td>f98</td>
<td>ImmunoCAP Allergen component f98 Gliadin, Wheat*</td>
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<tr>
<td>Tri a 14</td>
<td>Lipid transfer protein</td>
<td>f433</td>
<td>ImmunoCAP Allergen component rTri a 14, Wheat*</td>
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<tr>
<td>Tri a 19</td>
<td>Omega-5-gliadin</td>
<td>f416</td>
<td>ImmunoCAP Allergen component rTri a 19, Wheat*</td>
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</table>

Figure 3. Wheat test algorithm

Testing with allergen components can help distinguish patients who have a low probability of primary wheat sensitization from those who have a high probability and are at risk for severe allergic reactions.

Note: Results should be interpreted in the context of a patient’s clinical symptoms and history. Patients may be sensitized to more than one component.
## Diagnostic Considerations

### Wheat  |  Gliadin  |  Tri a 14  |  Tri a 19

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<tr>
<td><strong>If clinical symptoms are present with exposure to wheat</strong>, consider immediate type wheat allergy. Patient at high risk of severe, systemic reactions. Consider the following:</td>
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<td>• Wheat-dependent exercise induced anaphylaxis (WDEIA) likely in Tri a 19-negative patients</td>
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<td>• Patient likely to react to oral food challenge (OFC)(^{1,5,11})</td>
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<tr>
<td><strong>If clinical symptoms are present with exposure to wheat</strong>, consider immediate type wheat allergy. Patient at high risk of severe, systemic reactions and WDEIA with co-factors present. Consider the following:</td>
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<td>• Patient likely to react to OFC(^{1,5,11})</td>
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<td>• Usually associated with elevated risk for childhood food allergies, atopic eczema. Allergy is unlikely to be outgrown.(^{11})</td>
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<td><strong>If clinical symptoms are present with exposure to wheat</strong>, consider the following:</td>
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<tr>
<td>• Systemic and local symptoms such as oral allergy syndrome (OAS) are possible(^1)</td>
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<tr>
<td>• Patient may be sensitized to other LTPs contained in other plant foods/pollens due to cross-reactions which can cause systemic symptoms(^1)</td>
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<tr>
<td>• Consider bakers allergy and WDEIA with Tri a 14-positive patients(^5)</td>
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<td><strong>If clinical symptoms are present with exposure to wheat</strong>, consider the following:</td>
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<td>• Further investigation to identify primary allergen by investigating what other allergens patient is exposed to(^{5,14})</td>
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<tr>
<td>• Testing for CCD, Profilin (Phl p 12), and regional grasses(^{1,5,14})</td>
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<td>• OFC with a specialist may be recommended</td>
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<tr>
<td><strong>If no clinical symptoms are present with exposure to wheat and no detection of sIgE</strong>, clinical wheat allergy and severe reactions unlikely. Consider the following:</td>
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<tr>
<td>• OFC with a specialist may be recommended</td>
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**Note:** As in all diagnostic testing, any diagnosis or treatment plan must be made by the clinician based on test results, individual patient history, the clinician’s knowledge of the patient, as well as their clinical judgment. Patients can be sensitized to more than one allergen component.

\(^{1}\)Official product names mentioned within this document: ImmunoCAP Allergen f4, Wheat; ImmunoCAP Allergen f98, Gliadin; ImmunoCAP Allergen f433, Allergen Component rTri a 14 Wheat, ImmunoCAP Allergen f419, ImmunoCAP Allergen f416, Allergen component rTri a 19 Omega-5 Gliadin, Wheat

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### References


Learn more at [thermofisher.com/allergy](https://www.thermofisher.com/allergy)