

The WHO/IUIS Allergen Nomenclature

The number of proteins which induce allergic symptoms by binding to specific IgE antibodies and thus activate mast cells and basophils has been rapidly growing over the past 35 years. The WHO/IUIS Allergen Nomenclature Sub-Committee (<http://www.allergen.org/>), an international body of experts, has developed the much needed allergen nomenclature system¹ to provide a common language for unambiguous communications between researchers, clinicians, pharmaceutical companies, and regulatory authorities regarding specific allergenic proteins. The nomenclature is periodically refined and updated.² This Editorial highlights the necessary steps to obtain an official allergen name and the high importance of having an official and binding allergen nomenclature.

Most allergens are proteins or glycoproteins from organisms that are classified taxonomically by genus and species names. Allergen names are based on this binominal nomenclature and are composed of the first three or four letters of the genus followed by one or two letters of the species name. The numbers after the allergen designa-

tions are often associated with the time of discovery of the allergen within the species. When possible, similar numbers for the same type of protein are used within a taxonomic group of species such as the 2S albumins of walnut (Jug r 1) and pecan (Car i 1), both members of the taxonomic Juglandaceae family, or the tropomyosins of various shrimp species (eg, Pen a 1, Cra c 1, Lit v 1, Met e 1, Pan b 1). The identification of individual allergens in allergen sources is essential as clinicians are increasingly using in vitro diagnostic systems based on purified allergens to determine to which individual proteins patients have developed a specific IgE response. These data provide indications regarding the risks of developing allergic reactions or cross-reactions with homologous proteins.³ These data may also offer guidance to clinicians for patient management or immunotherapy.⁴

Official allergen names are assigned by the WHO/IUIS Nomenclature Sub-Committee (<http://www.allergen.org/>). In order to obtain the official designation of a new allergen, specific information

TABLE 1 Prerequisites for submitting a new allergen to the WHO/IUIS Allergen Nomenclature Sub-Committee (<http://www.allergen.org/>)

Category	Required information for submission	Additional helpful information for submission
Allergen source	- Description of the allergen source (eg, pollen, nut, seed, root, milk, saliva, venom) - Correct taxonomic name of the species	For plants, information on particular cultivar and source tissue and whether the allergic reactions occurred to the processed or heated material
Allergen, natural	- Description of purification methods and proof of purity - Determination of amino acid sequence (N-terminal sequencing, LC-MSMS) - Determination of glycosylation - Determination of IgE-binding (eg, IgE-immunoblot, ELISA, ImmunoCAP) - Determination of ability to inhibit IgE-binding to extract from allergens source	- Basophil activation test with description of cell type (autologous or donor) - SPT with extract or with pure protein
Allergen, recombinant	- Description of source of nucleic acid (mRNA, genomic DNA) - Complete nucleotide sequence - Acquirement of database sequence accession number - Description of expression system (eg, <i>E. coli</i>, <i>P. pastoris</i>, baculovirus) - Determination of IgE-binding (eg, IgE-immunoblot, ELISA, ImmunoCAP)	- Basophil activation test with description of cell type (autologous or donor) - Determination of ability of protein to inhibit IgE-binding to extract or purified natural allergen from allergen source
Patients	- Description of donor patients or subjects (eg, number of subjects, age, gender, geographical origin, symptoms on natural exposure to source) - Route of sensitization (inhalation, ingestion, dermal, injection) - Clinical evidence of allergy to the allergen source - Inclusion of preferably more than 5 allergic subjects and 3 or more controls not allergic to the allergen's source	Ethical approval of donors or subjects based on Institutional Review Board or Governmental agencies with protection of the identity of the subjects

(Table 1) needs to be provided by submitting a completed application form (<http://www.allergen.org/submission.php>) describing the source, the protein, the type of exposure (airway, ingestion, contact, or injection), the characteristics of the protein and its amino acid sequence, and the IgE-binding results using sera from relevant subjects.⁵ The complete submission, evaluation, and publication process is summarized in Table 2. Some researchers use IUIS-like names in DNA and protein sequence databases or in research papers without previous application and approval by the Allergen Nomenclature Sub-Committee, but these names are illegitimate and create confusion in the allergy community worldwide.

In order to qualify as an allergen, a protein must be carefully characterized including its amino acid sequence and its binding to serum IgE from appropriate donors along with a description of the source of the protein and its taxonomic name. IgE-binding assays should be performed with serum samples from well-characterized individual subjects allergic to the source and control subjects who are not allergic to this source but to unrelated allergen sources that do not contain homologous allergens; for example as controls for a pollen allergen, sera from cat allergic individuals could be used. A brief description of the subject's clinical characteristics (eg, dermatitis, gastrointestinal, or respiratory symptoms) should be provided. For allergen sources that are recognized by larger patient numbers, sera from 10 or more subjects allergic to this source should be used. For less frequently recognized allergen sources, smaller numbers of subjects may be used. Test samples should include extracts of the natural source and highly purified natural or recombinant protein. As cross-reactivity can be anticipated for evolutionarily conserved proteins, it is useful to demonstrate IgE-binding to the candidate protein and related proteins to demonstrate the specificity of binding.

The submissions of allergens to the WHO/IUIS Allergen Nomenclature Sub-Committee are evaluated by experts in the allergen field and comments are communicated to the authors. This process is not unlike the review of a manuscript by a journal and represents a valuable review of the data prior to submission to a journal.

The identification of individual allergenic proteins has led to new diagnostic *in vitro* tests using purified recombinant molecules including Thermo Scientific's ImmunoCAP ISAC, INDOOR Biotechnologies' MARIA, Centri Associati de Allergologia Molecolare's FABER, and Macro Array Diagnostics' ALEX. Reports on results of such tests are increasingly presented at scientific and clinical meetings and in publications.⁶⁻⁸ A number of studies presented at the EAACI Food Allergy and Anaphylaxis Meeting 2018 described IgE-binding to purified non-specific lipid transfer proteins (nsLTP) from foods and aeroallergen sources using microarray chip presentation of pure proteins. However, questions remain about the primary sensitizing source, the primary route of sensitization, and the actual ability of the nsLTPs to cause cross-reactions. Sequence identities of these proteins range from 38% to 90% as can be calculated by FASTA or BLASTP comparisons available in the public AllergenOnline database (<http://www.allergenonline.org/>) which also includes references to describe the allergens' characterization and testing.⁹ It needs to be emphasized that developers of diagnostic tests, clinicians, and clinical laboratories rely on the published data and sequences from public databases including the WHO/IUIS Allergen Nomenclature database to identify and provide data on the characterization of the proteins and their IgE-binding.

Allergenic proteins are members of protein families, such as nsLTPs, 2S albumins, profilins, or tropomyosins, based on sequence and structural conservation.¹⁰ Cross-reactivity or the capacity to induce IgE between members of a protein family and manifestations of clinical symptoms can be quite diverse. This emphasizes the need to carefully characterize each novel allergen. The 2S albumins of peanut, tree nuts, and other legumes are sequentially divergent and show little overall shared IgE-binding. The nsLTPs are more highly conserved in sequence across divergent taxa, yet allergenic responses to specific nsLTPs appear to be divergent. Profilins share highly conserved amino acid sequences, hence their cross-reactivity on the level of IgE-binding is high.

In summary, the WHO/IUIS Nomenclature Sub-Committee encourages researchers to consider previous published findings and

TABLE 2 Essential steps in the submission, evaluation, and publication of novel allergens

Steps	Tasks and processes
1. Submission	(a) Download the submission form at http://www.allergen.org/submission.php (b) Provide the required information and complete the form with as many details as possible (c) E-mail the completed form to the Chair of the WHO/IUIS Allergen Nomenclature Sub-Committee (e-mail address provided on website)
2. Evaluation	(a) Assignment of 2-3 members of the Executive Committee to review the submission by the Chair (b) Evaluation of the biochemical and molecular characterization of the submitted protein (c) Evaluation of the immunological characterization of the submitted protein
3. Decision	(a) Feedback from the reviewers (b) Communication with the corresponding author of the submission to obtain additional information when required by the reviewers (c) Final decision and—when positive—assignment of an official allergen designation
4. Publication	(a) Publication on the WHO/IUIS Allergen Nomenclature website (http://www.allergen.org/) (b) Allergen name to be used in scientific publications (c) Official allergen name should be used in other databases (eg, AllFam, AllergenOnline, Allergome, GenBank Protein, UniProt)

to provide detailed and comprehensive data for the identification and evaluation of new allergens to facilitate the communication within the worldwide allergy community.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ORCID

Richard E. Goodman  <https://orcid.org/0000-0001-8243-2285>

Heimo Breiteneder  <https://orcid.org/0000-0003-2022-8689>

Richard E. Goodman^{1,2} 

Heimo Breiteneder^{3,4} 

¹Food Allergy Research and Resource Program, University of Nebraska,
Lincoln, Nebraska

²Chair of the WHO/IUIS Allergen Nomenclature Sub-Committee,
Lincoln, Nebraska

³Institute of Pathophysiology and Allergy Research, Medical University
of Vienna, Vienna, Austria

⁴Member of the WHO/IUIS Allergen Nomenclature Sub-Committee,
Vienna, Austria

Correspondence

Richard E. Goodman, Food Allergy Research and Resource Program,
University of Nebraska, Lincoln, NE.

Email: rgoodman2@unl.edu

and

Heimo Breiteneder, Institute of Pathophysiology and Allergy Research,
Medical University of Vienna, Vienna, Austria.

Email: heimo.breiteneder@muv.ac.at

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