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Clinical syndromes and molecular allergens: a clarification on the proposed “defensin-related allergy syndrome”

Comment on “Clinical terminology and biological mediators in allergology: why biomarkers do not define a syndrome” – doi: 10.23822/EurAnnACI.1764-1489.438

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We read with great interest the Letter to the Editor by Prof. Di Lorenzo addressing the methodological relationship between clinical terminology and molecular mediators in allergology (1). We fully concur with the central argument that biomarkers and biological mediators should not, per se, define clinical syndromes, and that terminological precision remains essential for maintaining coherence in clinical reasoning.

Within this conceptual framework, we would like to offer a complementary clarification regarding the proposed notion of “defensin-related allergy syndrome”. While we agree that the designation of a syndrome should be grounded in a consistent constellation of clinical signs and symptoms, it is also important to recognize that, in contemporary allergology, certain clinical entities are increasingly defined by the identification of specific allergenic molecules that drive distinct patterns of sensitization and clinical reactivity.

In this context, the so-called “defensin-related allergy syndrome” should not be interpreted as an independent clinical syndrome in the classical nosological sense, but rather as a form of food allergy characterized by sensitization to a specific family of allergenic proteins, namely defensin-like molecules. From this perspective, it may be more appropriately framed as a molecularly defined subtype within the broader spectrum of food allergy, rather than as a novel clinical syndrome.

This conceptual approach is consistent with other well-recognized entities in molecular allergology. For example, the lipid transfer protein (LTP) syndrome and the alpha-Gal syndrome are not

merely defined by clinical phenotype, but by sensitization to specific allergenic molecules (plant LTPs and galactose- α -1,3-galactose, respectively), which confer distinctive clinical and immunological characteristics. These entities illustrate how molecular specificity can meaningfully contribute to the definition of clinically relevant subgroups within broader disease categories, without necessarily replacing the primacy of clinical observation. Analogously, sensitization to defensin-like proteins may identify a subgroup of patients within the spectrum of plant-derived food allergy, potentially associated with particular patterns of cross-reactivity and clinical expression. However, this molecular characterization should be understood as complementary to, rather than substitutive of, established clinical classifications such as pollen-food syndrome.

In conclusion, while we agree that biomarkers alone do not define a syndrome, we would emphasize that allergen-specific sensitization can, in certain contexts, delineate clinically meaningful entities within broader diagnostic frameworks. A balanced integration of clinical phenotyping and molecular characterization, rather than a strict dichotomy between the two, may best reflect the current evolution of precision medicine in allergology.

References

1. Di Lorenzo G. Clinical terminology and biological mediators in allergology: why biomarkers do not define a syndrome. *Eur Annals Allergy Clin Immunol.* 2026;58(4):184-185. doi: 10.23822/EurAnnACI.1764-1489.438.