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Early Immunogenetic Markers For Predicting Food Allergy Development In Children: Clinical And Molecular Approaches

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Abstract. Food allergy (FA) is a rapidly increasing immunopathological condition in childhood, often developing during the first years of life when immune regulation, epithelial barrier integrity and microbiota composition are still maturing. Early detection is essential to prevent progression toward atopic dermatitis, asthma, and allergic rhinitis. Immunogenetic markers—including cytokine signatures, epithelial alarmins, filaggrin gene mutations and microRNA profiles—represent promising early predictors of FA.
Aim. To analyze and summarize clinical, immunological and molecular markers that predict the early development of food allergy in children, with emphasis on Th2-associated cytokines, epithelial barrier biomarkers, FLG gene mutations and microRNA expression patterns.
Methods. A comprehensive analytical review of 126 scientific publications (2015–2024) was conducted using PubMed, Scopus, Web of Science, Elsevier and EAACI/WAO guidelines. Inclusion criteria comprised pediatric studies assessing Th2 cytokines, sIgE profiles, IL-33/TSLP axis activity, epithelial barrier function, filaggrin gene variants and microRNAs. Data were synthesized narratively, comparing predictive value, sensitivity, specificity and AUC values across biomarkers.
Results. Early-onset eczema, dry skin phenotype and gastrointestinal dysregulation were identified as the strongest phenotypic indicators of early immune deviation. Elevated IL-4, IL-5, IL-13, IL-33 and TSLP levels showed high predictive value for early sensitization, while FLG loss-of-function mutations conferred a 3–5-fold increased risk of FA. MicroRNA dysregulation—particularly increased miR-21 and miR-155 with reduced miR-146a—was associated with Th2 amplification and impaired immune tolerance. Component-resolved diagnostics and basophil activation tests significantly improved early diagnostic accuracy, with combined biomarker approaches achieving AUC values of 0.82–0.93.
Conclusion. Immunogenetic markers—especially FLG mutations, IL-33/TSLP axis activation, Th2 cytokine signatures and microRNA profiles—offer highly reliable early predictors of food allergy in children. Integrating clinical, immunological and molecular indicators provides superior diagnostic accuracy compared with isolated tests, supporting the adoption of multimodal early detection strategies in pediatric allergology.

Keywords. Food allergy; children; early prediction; Th2 cytokines; IL-33; TSLP; filaggrin gene; FLG mutations; microRNA; molecular allergodiagnostics; basophil activation test; epithelial barrier dysfunction; biomarkers.

Introduction. Food allergy (FA) is one of the fastest-growing immunopathological conditions in childhood, representing a major global health challenge due to its early onset, increasing prevalence, heterogeneous manifestations and high risk of progression to other atopic diseases. According to the latest EAACI and WAO epidemiological analyses (2020–2024), FA affects 6–10% of children worldwide, with the highest incidence among infants during the first years of life when the immune system, gut barrier integrity and microbiota composition are actively developing. The early initiation of Th2-dominant immune responses, epithelial barrier immaturity and genetic predisposition significantly increase susceptibility to sensitization even at minimal allergen exposure [2,3,5,8,].

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A growing body of evidence indicates that traditional diagnostic tools — such as total IgE levels, skin prick tests and standard allergen-specific IgE assays — are insufficient for detecting early or preclinical stages of FA. Many children develop subclinical immune dysregulation, cytokine imbalance, microRNA expression changes and epithelial barrier defects long before clinical symptoms appear. Therefore, identification of early immunogenetic predictors is essential for timely diagnosis, primary prevention and interruption of the "atopic march" toward atopic dermatitis, asthma and allergic rhinitis [7,9,12,13].

Molecular allergodiagnostics has opened new horizons by enabling the assessment of allergen components, basophil activation potential and genetic/epigenetic susceptibility. Mutations of the filaggrin (FLG) gene, polymorphisms in cytokine-regulating genes (IL-4, IL-13, TSLP, IL-33), as well as expression patterns of microRNA-21, microRNA-155 and microRNA-146a**,** have emerged as promising biomarkers that reflect early immune deviation towards allergic inflammation. In parallel, clinical markers such as early-onset eczema, dry skin phenotype, gastrointestinal dysmotility, familial atopy and early antibiotic exposure can serve as phenotypic risk indicators.

The integration of clinical observations with immunological and molecular markers makes it possible to stratify children into high-risk groups, detect sensitization before overt clinical disease, and optimize preventive and therapeutic strategies. In this context, studying early immunogenetic markers provides a deeper understanding of FA pathogenesis and offers innovative opportunities for personalized pediatric allergology.

Aim of the study. The aim of this study is to identify and analyze early immunogenetic markers that can predict the development of food allergy in children by integrating clinical risk factors, immunological indicators and molecular biomarkers. The research focuses on assessing the prognostic value of Th2-associated cytokines (IL-4, IL-5, IL-13, IL-33, TSLP), allergen-specific IgE profiles, epithelial barrier dysfunction markers, filaggrin (FLG) gene mutations and microRNA expression patterns (miR-21, miR-155, miR-146a) for early detection and risk stratification of food allergy in pediatric patients.

Materials and methods. This analytical review was conducted based on a comprehensive evaluation of scientific literature published between 2015 and 2024 across leading international databases, including PubMed, Scopus, Web of Science, Elsevier, and official guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) and the World Allergy Organization (WAO). A total of 126 full-text clinical trials, prospective and retrospective cohort studies, systematic reviews, and molecular allergology research papers related to early immunological and genetic predictors of food allergy (FA) in children were analyzed.

Inclusion criteria were:

1. studies conducted in pediatric populations aged 0–14 years;
2. availability of immunological parameters such as total IgE, allergen-specific IgE, Th2-associated cytokines (IL-4, IL-5, IL-13), epithelial alarmins (IL-33, TSLP), and basophil activation markers;
3. investigations examining epithelial barrier dysfunction and filaggrin (FLG) gene mutations;
4. studies assessing expression patterns of allergy-related microRNAs (miR-21, miR-155, miR-146a);
5. research employing molecular allergodiagnostic techniques, including component-resolved diagnostics (CRD), basophil activation tests (BAT), and epigenetic/microRNA profiling.

Exclusion criteria included studies not involving children, animal-based experiments (unless mechanistically essential), publications lacking measurable immunological data, and papers without validated diagnostic outcomes.

Data extraction was focused on identifying:

- clinical early-risk phenotypes, including early-onset eczema, xerosis, gastrointestinal dysregulation, and family history of atopy;
- immunological biomarkers, such as IgE profiles, cytokine signatures, eosinophil counts, TSLP-IL-33–driven epithelial responses;
- molecular and genetic markers, including FLG loss-of-function mutations and microRNA expression related to Th2 immune activation and epithelial barrier impairment.

Each included study was evaluated for its methodological quality, diagnostic relevance, predictive performance indicators (sensitivity, specificity, predictive values), and AUC (area under the ROC curve) when available. The synthesis followed a narrative analytical approach, integrating clinical observations with

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immunogenetic mechanisms to determine the most robust early biomarkers associated with the development of food allergy in children.

Results. Analysis of the selected literature revealed that early immunogenetic markers play a decisive role in predicting the development of food allergy (FA) in children long before the onset of overt clinical symptoms. Numerous studies consistently demonstrated that infants who later developed confirmed FA exhibited distinct clinical, immunological, and molecular features during the first months of life. Among clinical markers, early-onset eczema, persistent dry skin, sebostatic phenotype, and gastrointestinal dysmotility were the strongest phenotypic predictors, especially when accompanied by a positive family history of atopy. These early clinical signs were tightly correlated with underlying immunological changes, indicating subclinical sensitization even in the absence of detectable IgE responses.

Immunological markers showed high predictive value. Elevated Th2-associated cytokines—particularly IL-4, IL-5, IL-13—and epithelial alarmins IL-33 and TSLP were consistently identified as key drivers of early sensitization. Infants with increased IL-33/TSLP levels during the first year of life exhibited a 2–4-fold higher risk of developing FA, according to several cohort studies. Total IgE was less sensitive in early detection, while allergen-specific IgE (especially to egg white, cow's milk proteins, peanut Ara h components) demonstrated moderate predictive accuracy. Importantly, basophil activation tests (BAT) showed superior sensitivity and specificity for early detection compared to conventional IgE testing, particularly in children with ambiguous serological profiles.

Molecular markers provided deeper insights into FA predisposition. Loss-of-function mutations in the filaggrin (FLG) gene were identified as one of the strongest genetic predictors, conferring a 3–5-fold increased risk of FA, especially when combined with early eczema. FLG mutations were associated not only with impaired skin barrier formation but also with increased systemic Th2 activity, promoting sensitization through cutaneous and gastrointestinal pathways. Furthermore, microRNA profiling revealed characteristic upregulation of miR-21 and miR-155 and downregulation of miR-146a in children predisposed to FA. These microRNA signatures correlated with cytokine dysregulation, epithelial barrier damage, and enhanced allergen presentation, indicating their potential use as early molecular biomarkers.

Evidence from molecular allergodiagnostics confirmed that component-resolved diagnostics (CRD), including assessment of PR-10 proteins, Ara h components, ovomucoid, and casein fractions, significantly improved early diagnostic precision. Combining CRD with immunological markers and clinical phenotypes yielded higher predictive accuracy (AUC 0.82–0.93) compared to traditional diagnostic methods alone. Importantly, early integration of immunogenetic and clinical markers allowed the identification of high-risk infants even before sensitization was confirmed serologically, underscoring the need for early monitoring and preventive strategies.

Discussion. The findings of this analytical review confirm that early immunogenetic markers serve as essential predictors of food allergy (FA) development in children, aligning with recent global research trends. Numerous studies underscore that FA pathogenesis begins months or even years before the first clinical manifestation, and this preclinical phase is strongly influenced by a combination of epithelial barrier dysfunction, Th2-driven immune deviation, and genetic predisposition [6]. According to Spergel et al. (2021) and Kimura et al. (2022), early-onset eczema and xerosis are not merely dermatological findings but represent key external indicators of underlying immunological dysregulation. This supports the concept of the "outside-in" mechanism, where skin barrier impairment precedes allergen sensitization and systemic Th2 activation. Similarly, Brown et al. (2020) demonstrated that infants with persistent dry skin during the first six months of life exhibited significantly higher IL-33 and TSLP levels, placing these alarmins at the center of early sensitization pathways.

The role of Th2 cytokines in early immune deviation is consistently emphasized across multiple studies. Research by Nowak-Wegrzyn et al. (2019) and Narisety et al. (2020) confirmed that elevated IL-4, IL-5, and IL-13 levels are detectable in high-risk infants well before the onset of detectable allergen-specific IgE. This highlights the limited sensitivity of traditional IgE testing in early FA detection. Moreover, the longitudinal cohort study by Martin et al. (2023) revealed that infants with high IL-33 concentrations at 3–6 months had a 3.4-fold increased risk of developing clinically confirmed FA by age two, supporting the significance of epithelial-derived cytokines as early biomarkers.

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Genetic predisposition, particularly filaggrin (FLG) mutations, continues to be one of the most widely studied and reliable predictors of FA. The work of Keet & Wood (2019) and Palmer et al. (2021) demonstrated that FLG loss-of-function variants significantly increase the risk of sensitization to egg, milk, peanut, and tree nuts, even in the absence of early eczema. This suggests that FLG dysfunction may lead to systemic immune consequences beyond the cutaneous barrier. Furthermore, a meta-analysis by van der Merwe et al. (2022) confirmed a strong association between FLG mutations and persistent FA phenotypes, highlighting their prognostic significance.

Another emerging field is epigenetic regulation, particularly through microRNAs. Studies by Liang et al. (2020) [7] and Singh et al. (2022) [12] found that microRNA-21 and microRNA-155 are consistently elevated in children predisposed to FA, contributing to amplified Th2 responses and impaired immune tolerance. Conversely, downregulation of microRNA-146a—reported by Harada et al. (2021)—correlates with increased inflammation and inadequate regulatory T-cell activity, suggesting a potential mechanistic pathway from epigenetic dysregulation to early sensitization. These findings collectively demonstrate the promising role of microRNAs as non-invasive biomarkers with high diagnostic and prognostic value.

Molecular allergodiagnostics has further strengthened early FA detection strategies. According to Beyer & Poulsen (2020) and Muraro et al. (2021), component-resolved diagnostics (CRD) allow for the differentiation between primary sensitization and cross-reactivity, significantly improving diagnostic precision. For example, ovomucoid (Gal d 1) and Ara h 2 have been shown to possess superior predictive value compared to whole-extract IgE, particularly in early-onset FA [1]. Moreover, the study by Ebisawa et al. (2023) revealed that combining CRD with basophil activation testing (BAT) achieved an AUC >0.90, emphasizing the high diagnostic performance of integrated molecular tools during early childhood [3].

Gut microbiota composition also plays a critical role. Research conducted by Yu et al. (2022) demonstrated that infants with reduced diversity of Bifidobacterium spp. and increased Enterobacteriaceae abundance were at significantly higher risk of developing FA, suggesting that microbial imbalance contributes to disrupted oral tolerance [14]. This aligns with findings from the LEAP and EAT studies (2019–2022), which illustrate how microbiome-immune interactions shape early sensitization patterns and immune tolerance development.

Overall, the integration of clinical phenotypes, immunological indicators, genetic predisposition, and molecular diagnostics offers a highly accurate model for early prediction of FA. The reviewed literature consistently shows that the most powerful predictive value lies in combining biomarkers—FLG mutations, Th2 cytokines, IL-33/TSLP axis activity, microRNA profiles, and component-resolved diagnostics—rather than relying on a single test. Such a multimodal approach enhances diagnostic sensitivity, allows timely identification of high-risk infants, and opens new opportunities for targeted early intervention, potentially preventing the progression of FA and interrupting the atopic march.

Conclusion. The results of this analytical review indicate that early immunogenetic markers provide a powerful and scientifically grounded basis for predicting the development of food allergy in children before the onset of clinical symptoms. Evidence from multiple high-quality studies demonstrates that the interplay between epithelial barrier dysfunction, Th2-mediated immune activation, and genetic predisposition defines the earliest stages of allergic sensitization. Among all evaluated indicators, filaggrin (FLG) loss-of-function mutations, elevated IL-33 and TSLP levels, Th2 cytokine signatures (IL-4, IL-5, IL-13), and characteristic microRNA expression profiles (miR-21, miR-155, miR-146a) emerged as the most reliable and consistent early biomarkers with strong prognostic value. Furthermore, component-resolved diagnostics and basophil activation tests significantly improved early diagnostic accuracy compared with traditional IgE-based methods, underscoring the importance of molecular allergodiagnostics in pediatric practice.

The accumulated evidence confirms that no single marker is sufficient on its own. Instead, the most effective predictive strategy involves integrating clinical phenotypes—such as early eczema, xerosis, and gastrointestinal dysregulation—with immunological, genetic, and molecular biomarkers. Such a multimodal approach enhances sensitivity and specificity, enabling early identification of high-risk infants and facilitating timely preventive interventions. Early detection and risk stratification based on immunogenetic markers can help clinicians initiate targeted monitoring, guide dietary strategies, prevent unnecessary food restrictions, and potentially interrupt the progression of the atopic march toward atopic dermatitis, asthma, and allergic rhinitis.

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Overall, the use of early immunogenetic markers represents a promising direction for personalized pediatric allergology. Incorporating these biomarkers into clinical practice will improve diagnostic precision, optimize early interventions, and contribute to better long-term health outcomes in children at risk of food allergy.

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