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Significance of IL4 rs2243250 and FCER1A rs2251746 Gene Polymorphisms in the Molecular Genetic Diagnosis of Allergic Rhinitis

Abstract

Allergic rhinitis is one of the most prevalent chronic immunoglobulin E (IgE)-mediated inflammatory disorders worldwide, imposing a substantial clinical and socioeconomic burden due to impaired quality of life, reduced productivity, and increasing healthcare costs. Although environmental allergens are major triggers, accumulating evidence indicates that genetic susceptibility plays a crucial role in disease onset, severity, and therapeutic response. Among the numerous candidate genes, the IL4 rs2243250 and FCER1A rs2251746 polymorphisms have attracted considerable attention because of their involvement in T-helper 2 (Th2)-mediated immune responses, IgE synthesis, and high-affinity IgE receptor regulation. The present study aimed to investigate the significance of these two genetic polymorphisms in the molecular genetic diagnosis of allergic rhinitis and to evaluate their potential as biomarkers for precision diagnostic strategies. A case–control study was conducted involving clinically confirmed allergic rhinitis patients and healthy controls. Genomic DNA was isolated from peripheral blood samples, followed by polymerase chain reaction-based single nucleotide polymorphism genotyping. Serum total IgE concentrations, eosinophil counts, and clinical severity according to the Allergic Rhinitis and its Impact on Asthma (ARIA) classification were assessed. Multivariate statistical analyses, logistic regression models, receiver operating characteristic (ROC) analysis, and integrated molecular risk prediction models were applied to determine the diagnostic performance of individual and combined biomarkers. The findings demonstrated significant associations between specific IL4 rs2243250 and FCER1A rs2251746 genotypes and increased susceptibility to allergic rhinitis, elevated serum IgE concentrations, enhanced eosinophilic inflammation, and greater clinical severity. The combined molecular diagnostic model incorporating both polymorphisms with immunological biomarkers exhibited superior diagnostic accuracy compared with conventional clinical assessment alone. The originality of this study lies in the development of an integrated molecular genetic framework that combines genetic polymorphisms, immunological indicators, and clinical characteristics to improve individualized diagnosis of allergic rhinitis. These findings support the implementation of molecular biomarkers in precision allergy medicine and may facilitate earlier diagnosis, improved risk stratification, and personalized therapeutic decision-making for patients with allergic rhinitis.

Introduction

Allergic rhinitis (AR) is one of the most common chronic inflammatory disorders of the upper respiratory tract and represents a major global public health concern due to its increasing prevalence, socioeconomic burden, and substantial impact on patients' quality of life. Characterized by nasal congestion, rhinorrhea, sneezing, nasal itching, and varying degrees of ocular symptoms, AR affects both children and adults and frequently persists throughout life. According to recent epidemiological estimates, allergic rhinitis affects approximately 20–30% of the global population, with prevalence continuing to rise in both developed and developing countries. Urbanization, environmental pollution, climate change, altered microbial exposure, and lifestyle modifications have all been implicated in this increasing disease burden (Bousquet et al., 2023; World Allergy Organization, 2024).

Beyond its direct clinical manifestations, allergic rhinitis is increasingly recognized as a systemic immune-mediated disorder associated with asthma, chronic rhinosinusitis, atopic dermatitis, food allergy, and allergic conjunctivitis. The concept of "one airway, one disease" emphasizes the close relationship between upper and lower airway inflammation, explaining why uncontrolled allergic rhinitis significantly increases the risk of asthma development and poor asthma control. Consequently, international guidelines recommend early diagnosis and effective management not only to alleviate symptoms but also to prevent disease progression and improve long-term respiratory health (Brożek et al., 2022).

The socioeconomic consequences of allergic rhinitis extend beyond healthcare expenditures. Patients frequently experience impaired sleep quality, daytime fatigue, reduced academic and occupational performance, diminished cognitive function, and psychological distress. Indirect costs related to reduced productivity often exceed direct medical expenses, making allergic rhinitis one of the most economically important chronic allergic diseases worldwide. Despite the availability of effective pharmacological therapies, considerable heterogeneity exists in disease severity, treatment response, and clinical progression, suggesting that individual genetic susceptibility plays an essential role in disease pathogenesis (Greiner et al., 2023).

The immunopathogenesis of allergic rhinitis is primarily mediated through **immunoglobulin E (IgE)-dependent hypersensitivity reactions**. Initial exposure to environmental allergens—including pollens, house dust mites, animal dander, molds, and occupational allergens—induces antigen presentation by dendritic cells to naïve CD4+ T lymphocytes. Under the influence of specific cytokines, these cells differentiate predominantly into T-helper 2 (Th2) lymphocytes, initiating a cascade of allergic inflammation. Activated Th2 cells secrete characteristic cytokines, including interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-9 (IL-9), and interleukin-13 (IL-13), which collectively stimulate B-cell class switching to IgE production, eosinophil recruitment, mast-cell activation, and mucus hypersecretion (Lambrecht & Hammad, 2022).

Among these cytokines, **IL-4 occupies a central position** in allergic immune regulation. IL-4 promotes differentiation of naïve T cells toward the Th2 phenotype, enhances IgE synthesis by activated B lymphocytes, suppresses Th1-mediated immune responses, and amplifies allergic inflammation through multiple downstream signaling pathways. IL-4 exerts its biological effects through binding to the IL-4 receptor complex, activating Janus kinase (JAK) and signal transducer and activator of transcription 6 (STAT6), thereby inducing transcription of genes involved in allergic inflammation. Dysregulation of IL-4 signaling has consistently been associated with increased susceptibility to atopic diseases, including allergic rhinitis, asthma, and atopic dermatitis (Gandhi et al., 2023).

An equally important component of allergic inflammation is the **high-affinity IgE receptor (FcεRI)**. FcεRI is expressed primarily on mast cells, basophils, dendritic cells, and other antigen-presenting cells. Binding of allergen-specific IgE to FcεRI sensitizes these immune cells, allowing rapid activation upon subsequent allergen exposure. Cross-linking of receptor-bound IgE triggers cellular degranulation and release of histamine, leukotrienes, prostaglandins, proteases, and numerous inflammatory mediators responsible for the immediate allergic response. Continued activation also stimulates production of cytokines and chemokines that maintain chronic inflammation and tissue remodeling. Consequently, FcεRI represents one of the most important molecular regulators of IgE-mediated allergic disease and an attractive target for both diagnostic and therapeutic strategies (Galli et al., 2022).

Recent advances in molecular immunology have demonstrated that allergic rhinitis results not only from environmental allergen exposure but also from complex interactions between genetic predisposition and immune regulation. Twin studies, family aggregation analyses, and genome-wide association studies consistently demonstrate substantial heritability of allergic diseases. However, allergic rhinitis is considered a polygenic disorder in which numerous genetic variants individually exert modest effects while collectively determining disease susceptibility. Candidate genes involved in cytokine signaling, IgE regulation, epithelial barrier integrity, innate immunity, and inflammatory pathways have therefore become important targets for molecular investigation (Ferreira et al., 2024).

The rapid development of molecular genetics has substantially improved understanding of allergic disease mechanisms. Single nucleotide polymorphisms (SNPs) have emerged as valuable genetic biomarkers because they may influence gene transcription, protein expression, cytokine production, receptor function, and downstream immune responses. Identification of clinically relevant

polymorphisms offers opportunities for early disease prediction, individualized risk assessment, and precision medicine. Polymerase chain reaction (PCR)-based genotyping technologies, including real-time PCR and allele-specific assays, now enable rapid, accurate, and cost-effective detection of disease-associated genetic variants, making molecular diagnostics increasingly accessible for clinical practice (Goodwin et al., 2023).

These developments have shifted allergy research from conventional symptom-based diagnosis toward biomarker-driven precision medicine. Rather than relying solely on clinical manifestations and allergen testing, contemporary approaches increasingly integrate immunological, molecular, and genetic information to improve diagnostic accuracy and personalize therapeutic decision-making. Such strategies are particularly important for heterogeneous disorders such as allergic rhinitis, in which patients with similar clinical symptoms often exhibit markedly different immunological profiles and treatment responses.

2. Literature Review

2.1 Allergic Rhinitis

Allergic rhinitis (AR) is a chronic inflammatory disease of the nasal mucosa mediated by immunoglobulin E (IgE) following exposure to environmental allergens. It is characterized by sneezing, nasal congestion, rhinorrhea, and nasal itching, frequently accompanied by conjunctival symptoms. Current epidemiological evidence indicates that AR affects approximately one-quarter of the global population, making it one of the most prevalent chronic allergic disorders. Its prevalence continues to increase because of urbanization, air pollution, climate change, altered microbial exposure, and genetic susceptibility. In addition to impairing quality of life, AR is strongly associated with asthma, chronic rhinosinusitis, sleep disturbances, reduced school and work performance, and increased healthcare utilization. Consequently, AR is now regarded as a systemic inflammatory disorder rather than an isolated disease of the upper airways.

Although environmental allergen exposure remains essential for disease initiation, numerous studies demonstrate that only a proportion of exposed individuals develop clinically significant disease. This observation highlights the importance of inherited genetic susceptibility and immune regulation in determining individual risk.

2.2 Molecular Immunopathogenesis

The molecular pathogenesis of allergic rhinitis is driven by a complex interaction between environmental allergens, epithelial barrier dysfunction, innate immunity, and adaptive immune responses. Allergens penetrate the nasal epithelial barrier and are captured by dendritic cells, which present antigenic peptides to naïve CD4+ T lymphocytes. Under cytokine stimulation, these cells preferentially differentiate into T-helper 2 (Th2) lymphocytes, producing IL-4, IL-5, IL-9, and IL-13. These cytokines promote IgE synthesis, eosinophil recruitment, mast-cell activation, mucus hypersecretion, and chronic allergic inflammation.

Recent molecular investigations have also emphasized the importance of epithelial-derived cytokines, including thymic stromal lymphopoietin (TSLP), IL-25, and IL-33, which amplify type-2 immune responses before adaptive immunity becomes fully activated. Therefore, allergic rhinitis should be viewed as a disease involving multiple interacting immune pathways rather than a simple IgE-mediated reaction.

2.3 IL-4 Biology

Among the cytokines involved in allergic inflammation, **interleukin-4 (IL-4)** occupies a central regulatory position. IL-4 promotes differentiation of naïve T cells toward the Th2 phenotype, induces immunoglobulin class switching in B lymphocytes from IgM to IgE, suppresses Th1-mediated immunity, and enhances eosinophilic inflammation. Activation of the IL-4 receptor initiates the JAK–STAT6 signaling pathway, resulting in transcription of numerous genes associated with allergic inflammation.

Experimental studies consistently demonstrate that increased IL-4 expression is associated with elevated serum IgE concentrations, greater eosinophilic infiltration, and more severe allergic symptoms. However, considerable variability exists among patients, suggesting that genetic polymorphisms within the *IL4* gene may partially explain differences in cytokine production and disease susceptibility.

2.4 FcεRI Receptor Function

The high-affinity IgE receptor (**FcεRI**) represents another critical component of allergic immune responses. FcεRI is expressed predominantly on mast cells, basophils, dendritic cells, and antigen-presenting cells. Following allergen exposure, allergen-specific IgE binds FcεRI, sensitizing immune cells for rapid activation during subsequent allergen encounters.

Cross-linking of receptor-bound IgE induces immediate degranulation with release of histamine, leukotrienes, prostaglandins, tryptase, and numerous inflammatory mediators responsible for acute allergic symptoms. Continued activation also stimulates cytokine production, eosinophil recruitment, and chronic mucosal inflammation. Because FcεRI directly regulates IgE-mediated hypersensitivity, genetic variation affecting receptor expression may substantially influence allergic disease severity.

2.5 IL4 rs2243250 Polymorphism

The promoter polymorphism **IL4 rs2243250 (C-590T/C-589T)** has become one of the most extensively

investigated genetic variants in allergic diseases. Located within the promoter region of the *IL4* gene, this polymorphism influences transcriptional activity and cytokine production. Several studies have reported that the T allele is associated with increased IL-4 expression, enhanced IgE synthesis, and greater susceptibility to allergic rhinitis. Nevertheless, the magnitude of this association varies considerably among ethnic populations.

A comprehensive meta-analysis demonstrated a significant overall association between rs2243250 and allergic rhinitis susceptibility, although subgroup analyses indicated stronger associations in Asian populations than in European cohorts. These findings suggest that ethnic background, gene–gene interactions, and environmental exposures may modify the biological effect of this polymorphism.

Despite encouraging evidence, contradictory findings remain. Several case–control studies have failed to identify statistically significant associations after adjustment for age, sex, and environmental factors. Such inconsistencies may reflect differences in sample size, diagnostic criteria, Hardy–Weinberg equilibrium, genotyping methodology, or population structure. Consequently, additional multicenter investigations remain necessary.

2.6 FCER1A rs2251746 Polymorphism

The **FCER1A rs2251746** polymorphism has attracted increasing attention because it influences expression of the α-chain of the high-affinity IgE receptor. Functional studies suggest that promoter variants affecting FCER1A transcription may modify receptor density on mast cells and basophils, thereby influencing IgE-mediated immune activation.

Several genome-wide association studies have demonstrated significant associations between FCER1A variants and circulating serum IgE concentrations. However, evidence linking rs2251746 specifically with allergic rhinitis remains less consistent than for IL4 polymorphisms. Some investigations report increased disease susceptibility among carriers of the risk allele, whereas others identify associations only with serum IgE levels rather than clinical disease.

This inconsistency indicates that FCER1A polymorphisms may function primarily as modifiers of allergic immune responses instead of independent determinants of disease occurrence.

2.7 Molecular Genetic Diagnosis

Conventional diagnosis of allergic rhinitis primarily relies on clinical history, physical examination, allergen sensitization testing, and serum IgE measurement. Although these approaches provide valuable clinical information, they do not explain interindividual variation in disease susceptibility, progression, or therapeutic response.

Advances in molecular genetics have therefore introduced **single nucleotide polymorphisms (SNPs)** as potential diagnostic biomarkers. Identification of disease-associated polymorphisms enables estimation of inherited genetic susceptibility before clinical manifestations become fully established. Integrating genetic markers with immunological biomarkers may therefore improve diagnostic accuracy and support individualized patient management.

Current evidence suggests that combining IL4 and FCER1A polymorphisms with serum IgE concentrations and eosinophil counts provides greater diagnostic discrimination than conventional clinical assessment alone.

2.8 PCR-Based Genotyping

Polymerase chain reaction (PCR)-based technologies remain the standard laboratory approach for SNP detection. Conventional PCR, real-time PCR, allele-specific PCR, TaqMan assays, and high-resolution melting analysis provide rapid, sensitive, and highly reproducible identification of genetic variants.

Compared with earlier sequencing methods, PCR-based genotyping offers lower cost, shorter turnaround time, and greater suitability for routine clinical laboratories. Nevertheless, technical standardization, quality control, and validation remain essential because inaccurate genotyping may substantially influence association analyses. Appropriate Hardy–Weinberg equilibrium testing, duplicate quality-control samples, and blinded laboratory procedures are therefore recommended for molecular epidemiological studies.

2.9 Precision Allergy Medicine

Recent developments in **precision medicine** have transformed allergy research from population-based treatment toward individualized clinical management. Precision allergy medicine integrates clinical symptoms, molecular biomarkers, genomic information, immunological profiles, and environmental exposures to optimize diagnosis and treatment.

For allergic rhinitis, this approach enables identification of genetically susceptible individuals, prediction of disease severity, estimation of treatment response, and selection of targeted biological therapies. Molecular biomarkers including IL4, FCER1A, IL13, TSLP, and related immune genes may therefore contribute to personalized risk prediction models. Digital health technologies, artificial intelligence, and machine-learning algorithms further enhance precision medicine by integrating multiple biological variables into individualized diagnostic frameworks.

2.10 Research Gap

Despite considerable advances in molecular allergy research, several important knowledge gaps remain. Most previous investigations have evaluated **IL4 rs2243250** or **FCER1A rs2251746** independently, whereas relatively few studies have assessed their combined diagnostic performance within an integrated molecular model. Moreover, many published studies focused primarily on genotype frequencies without simultaneously evaluating serum IgE, eosinophil counts, clinical severity according to ARIA classification, and molecular biomarkers.

Another limitation concerns population diversity. Existing association studies have been conducted predominantly in Asian or European populations, while evidence from Central Asian populations remains scarce. Differences in ethnicity, environmental allergen exposure, and genetic background may substantially influence polymorphism–disease associations.

To address these limitations, the present study proposes the **Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)**, which combines *IL4* rs2243250 and *FCER1A* rs2251746 polymorphisms with serum IgE, eosinophil counts, ARIA clinical classification, PCR-based genotyping, and molecular biomarker assessment within a unified precision diagnostic model. This framework aims to improve early diagnosis, individualized risk stratification, and personalized clinical management of allergic rhinitis while providing new insights into the molecular mechanisms underlying disease susceptibility.

3. Research Novelty and Original Contribution

The present study introduces an original conceptual framework entitled the **Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)**, designed to improve the molecular diagnosis of allergic rhinitis by integrating genetic susceptibility markers, immunological biomarkers, molecular laboratory techniques, and standardized clinical assessment into a unified precision medicine model. Although considerable progress has been achieved in understanding the immunopathogenesis of allergic rhinitis, contemporary diagnostic practice continues to rely predominantly on clinical symptoms, allergen sensitization testing, serum immunoglobulin E (IgE) determination, and skin prick testing. These approaches effectively identify allergic sensitization but provide limited information regarding inherited disease susceptibility, molecular heterogeneity, or individual differences in disease severity and treatment response. Consequently, there remains a significant need for comprehensive molecular diagnostic models capable of integrating genomic and immunological information into routine clinical decision-making.

The principal novelty of the proposed framework lies in the simultaneous evaluation of **IL4 rs2243250** and **FCER1A rs2251746** polymorphisms within a comprehensive diagnostic algorithm. Previous investigations have generally examined these genetic variants independently, focusing either on cytokine regulation or IgE receptor biology. However, allergic rhinitis is a multifactorial immune disorder in which multiple genetic pathways interact simultaneously to determine disease susceptibility and clinical phenotype. The IMGARDF therefore recognizes that isolated genetic markers have limited predictive value, whereas their combined interpretation alongside immunological and clinical variables substantially enhances diagnostic precision.

The first innovative component of IMGARDF is the incorporation of the **IL4 rs2243250 polymorphism** as a primary molecular susceptibility marker. Located within the promoter region of the *IL4* gene, this polymorphism influences transcriptional activity and cytokine production, thereby regulating T-helper 2 (Th2) differentiation and immunoglobulin E synthesis. Numerous association studies suggest that carriers of the risk allele exhibit increased IL-4 expression, enhanced IgE production, and greater predisposition to allergic diseases. Nevertheless, considerable heterogeneity exists among different ethnic populations, indicating that IL4 polymorphisms should be interpreted within broader molecular and immunological contexts rather than as independent diagnostic markers (Yang et al., 2021).

The second major innovation involves integration of the **FCER1A rs2251746 polymorphism**, which regulates expression of the α-chain of the high-affinity IgE receptor (FcεRI). FcεRI plays a central role in allergic inflammation by mediating IgE-dependent activation of mast cells and basophils. Genetic variation affecting receptor expression may therefore influence both the magnitude of allergic responses and clinical disease severity. While previous investigations have primarily examined associations between FCER1A variants and serum IgE concentrations, the present framework incorporates receptor-related genetic information into individualized clinical risk assessment. This integrated interpretation provides a more comprehensive understanding of IgE-mediated immune activation than evaluation of serum IgE alone.

A further innovative aspect of IMGARDF is the incorporation of **serum total IgE concentration** as a dynamic immunological biomarker. Although elevated IgE levels remain one of the most widely used laboratory indicators of allergic sensitization, substantial interindividual variability limits their diagnostic specificity. Some genetically susceptible individuals exhibit relatively modest IgE elevations, whereas others demonstrate persistently increased concentrations without clinically significant allergic disease. Accordingly, the proposed framework interprets serum IgE together with genetic polymorphisms, cytokine activity, eosinophilic inflammation, and clinical phenotype rather than as an isolated laboratory parameter.

The framework further incorporates **peripheral blood eosinophil count** as an indicator of ongoing allergic inflammation. Eosinophils represent major effector cells during chronic allergic responses and contribute to tissue injury through release of cytotoxic proteins, inflammatory mediators, and cytokines. Increased eosinophil counts have consistently been associated with disease severity and persistent nasal inflammation. However, eosinophilia alone cannot distinguish between different allergic phenotypes. By integrating eosinophil counts with genetic biomarkers and cytokine profiles, IMGARDF improves characterization of inflammatory activity and disease heterogeneity.

Another original contribution is the inclusion of a comprehensive **cytokine profile**, particularly biomarkers reflecting **Th2 immune responses**. Contemporary evidence demonstrates that allergic rhinitis results from coordinated activity of multiple cytokines, including IL-4, IL-5, IL-13, IL-33, thymic stromal lymphopoietin (TSLP), and related inflammatory mediators. Within the proposed framework, cytokine activity is interpreted as a functional reflection of underlying genetic susceptibility rather than an isolated laboratory finding. This integrated biological perspective strengthens mechanistic understanding of allergic inflammation and improves interpretation of molecular diagnostic results.

The **expression of the high-affinity IgE receptor (FcεRI)** constitutes another important innovation within IMGARDF. Instead of considering receptor biology solely at the genetic level, the framework recognizes receptor expression as a functional immunological indicator reflecting both inherited genetic variation and immune activation. Integrating FCER1A genotype with receptor function provides a more biologically meaningful assessment of allergic susceptibility and may improve prediction of disease severity and therapeutic response.

A further distinguishing feature of the proposed framework is the incorporation of **polymerase chain reaction (PCR)-based genotyping** as the principal molecular diagnostic platform. Real-time PCR and allele-specific amplification provide highly sensitive, specific, reproducible, and clinically applicable methods for detecting single nucleotide polymorphisms. By incorporating standardized molecular laboratory procedures into routine diagnostic evaluation, IMGARDF bridges the gap between genomic research and clinical allergy practice. This translational approach facilitates implementation of molecular biomarkers in everyday diagnostic workflows.

The framework additionally integrates multiple **molecular biomarkers** rather than relying upon individual genetic variants. Recent advances in precision medicine emphasize that complex multifactorial diseases cannot be explained by single biomarkers alone. Instead, combinations of genomic, immunological, biochemical, and clinical indicators provide substantially greater diagnostic accuracy. Accordingly, IMGARDF simultaneously evaluates IL4 and FCER1A polymorphisms, serum IgE, eosinophil count, cytokine profile, FcεRI-related immune activation, and molecular laboratory findings to generate individualized diagnostic profiles.

One of the most clinically important innovations involves combining molecular findings with **clinical symptoms** and the **Allergic Rhinitis and its Impact on Asthma (ARIA)** classification. Existing molecular studies frequently focus exclusively on laboratory biomarkers without considering symptom severity or disease phenotype. In contrast, IMGARDF interprets genetic and immunological findings within established clinical classifications, thereby enhancing clinical applicability and facilitating translation of molecular discoveries into patient-centered healthcare. This integration enables clinicians to associate molecular risk profiles with symptom burden, disease persistence, and treatment planning.

The ultimate objective of IMGARDF is to support **personalized diagnosis** within the framework of precision allergy medicine. Rather than applying identical diagnostic strategies to all patients with suspected allergic rhinitis, the framework classifies individuals according to their integrated molecular, immunological, and clinical characteristics. Patients demonstrating high-risk genetic profiles together with elevated IgE concentrations, eosinophilia, increased Th2 activity, and severe ARIA classification may benefit from earlier intervention, intensified monitoring, and individualized therapeutic strategies. Conversely, patients with lower molecular risk may avoid unnecessary investigations and overtreatment.

From a scientific perspective, the proposed framework contributes to molecular allergy research by integrating genomic susceptibility, immune regulation, biomarker assessment, and standardized clinical evaluation within a single conceptual model. Unlike previous studies that examined isolated genetic polymorphisms, IMGARDF provides a systems-oriented interpretation of allergic rhinitis as the result of dynamic interactions among inherited susceptibility, immune activation, and clinical expression. This multidimensional approach represents a significant advancement toward precision diagnostics in allergic diseases.

Overall, the **Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)** constitutes an original scientific contribution by combining **IL4 rs2243250**, **FCER1A rs2251746**, serum IgE, eosinophil count, cytokine profiling, Th2 immune responses, FcεRI expression, PCR-based genotyping, molecular biomarkers, ARIA clinical classification, and individualized diagnostic algorithms within a unified precision medicine framework. By improving diagnostic accuracy, facilitating personalized risk stratification, and strengthening the integration of molecular genetics with clinical allergy practice, the framework provides a robust theoretical and translational foundation for future research and individualized management of allergic rhinitis.

4. Theoretical Framework (Part 1)

4.1 Conceptual Foundation of the Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)

Allergic rhinitis (AR) is a multifactorial immune-mediated disorder resulting from complex interactions among inherited genetic susceptibility, environmental allergen exposure, immune regulation, epithelial barrier integrity, and inflammatory signaling pathways. Conventional diagnostic approaches rely primarily on clinical symptoms, allergen sensitization testing, serum immunoglobulin E (IgE) concentrations, and skin prick tests. Although these methods remain clinically valuable, they provide limited information regarding inherited susceptibility, molecular heterogeneity, and interindividual variability in disease progression or treatment response. Advances in molecular genetics and precision medicine have therefore created opportunities to develop integrated diagnostic models capable of combining genomic, immunological, and clinical information into individualized decision-making.

The present study introduces the **Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)** as an original conceptual model that combines **IL4 rs2243250**, **FCER1A rs2251746**, serum IgE, eosinophilic inflammation, cytokine activity, FcεRI biology, polymerase chain reaction (PCR)-based genotyping, molecular biomarkers, ARIA clinical classification, and personalized diagnostic strategies within one precision medicine framework. Rather than interpreting each biomarker independently, IMGARDF conceptualizes allergic rhinitis as the consequence of dynamic interactions among genetic regulation, immune activation, molecular signaling, and clinical phenotype.

4.2 Allergic Inflammation Theory

The first theoretical pillar of IMGARDF is **Allergic Inflammation Theory**, which explains allergic rhinitis as a chronic inflammatory disorder initiated by inappropriate immune responses to otherwise harmless environmental allergens. According to this theory, allergens penetrate the nasal epithelial barrier and activate antigen-presenting cells, resulting in recruitment of inflammatory cells and production of multiple cytokines, chemokines, lipid mediators, and inflammatory proteins.

Inflammatory activation occurs in both the early and late phases of allergic responses. Immediate mast-cell degranulation releases histamine, prostaglandins, leukotrienes, and proteases responsible for acute nasal symptoms, whereas subsequent recruitment of eosinophils, basophils, Th2 lymphocytes, and innate lymphoid cells maintains chronic inflammation and tissue remodeling.

Within IMGARDF, allergic inflammation provides the biological environment through which inherited genetic susceptibility is translated into clinical disease. Consequently, inflammatory biomarkers are interpreted as functional manifestations of underlying molecular regulation rather than isolated laboratory findings.

4.3 Th1/Th2 Balance Theory

The second theoretical foundation is **Th1/Th2 Balance Theory**. Under physiological conditions, immune homeostasis depends upon balanced interactions between Th1 and Th2 lymphocytes. Th1 responses predominantly support cellular immunity against intracellular pathogens, whereas Th2 responses regulate humoral immunity, IgE production, eosinophilic inflammation, and allergic reactions.

Allergic rhinitis is characterized by excessive Th2 polarization accompanied by relative suppression of Th1-mediated immunity. Increased production of IL-4, IL-5, and IL-13 promotes B-cell class switching toward IgE synthesis while simultaneously amplifying eosinophilic inflammation and mast-cell activation.

The proposed framework therefore interprets **IL4 rs2243250** as a molecular regulator capable of modifying Th2 differentiation and cytokine production. Individual genetic variation may therefore influence both immune polarization and allergic susceptibility.

4.4 IgE-Mediated Hypersensitivity Theory

IgE-Mediated Hypersensitivity Theory constitutes another central element of the framework.

According to this theory, allergen exposure induces production of allergen-specific IgE antibodies. These antibodies bind with extremely high affinity to FcεRI receptors expressed on mast cells and basophils.

During subsequent allergen exposure, receptor-bound IgE molecules undergo cross-linking, initiating rapid intracellular signaling and degranulation.

Release of histamine, leukotrienes, prostaglandins, tryptase, platelet-activating factor, and inflammatory cytokines produces the characteristic symptoms of allergic rhinitis.

Within IMGARDF, serum total IgE concentration and FcεRI biology represent complementary biomarkers reflecting both immunological activation and inherited susceptibility.

4.5 Molecular Genetics Theory

Modern **Molecular Genetics Theory** recognizes allergic rhinitis as a polygenic disorder resulting from cumulative effects of multiple genetic variants rather than single-gene mutations.

Single nucleotide polymorphisms (SNPs) located within regulatory regions may modify:

- cytokine expression;
- receptor synthesis;
- intracellular signaling;
- immune-cell differentiation;
- inflammatory mediator production.

The framework therefore emphasizes **IL4 rs2243250** and **FCER1A rs2251746** because both variants influence essential biological pathways regulating allergic inflammation.

Rather than evaluating these polymorphisms independently, IMGARDF proposes integrated interpretation of multiple genetic biomarkers to improve molecular diagnosis.

4.6 Precision Medicine

Precision Medicine provides the clinical philosophy underlying IMGARDF.

Traditional medical practice frequently applies identical diagnostic and therapeutic strategies to clinically similar patients despite considerable biological heterogeneity.

Precision medicine instead recognizes that genetic background, molecular biomarkers, immune responses, environmental exposure, and clinical phenotype collectively determine disease expression and treatment response.

Within allergic rhinitis, patients exhibiting similar symptoms often possess markedly different genetic susceptibility profiles.

Accordingly, IMGARDF integrates genomic information with immunological and clinical biomarkers to support individualized diagnostic decision-making rather than population-based assessment.

4.7 Biomarker Theory

Biomarker Theory proposes that objective biological indicators provide measurable evidence of physiological and pathological processes.

Within allergic rhinitis, numerous biomarkers have been investigated, including:

- serum IgE;
- eosinophil count;
- IL-4;
- IL-5;
- IL-13;
- periostin;
- eosinophil cationic protein;
- FcεRI expression.

However, no single biomarker demonstrates sufficient diagnostic accuracy when interpreted independently.

The IMGARDF therefore combines genetic polymorphisms, immunological biomarkers, inflammatory mediators, and clinical findings into one multidimensional biomarker profile, substantially improving diagnostic performance.

4.8 Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)

The proposed conceptual framework consists of six interacting domains.

Domain 1. Genetic Susceptibility

- IL4 rs2243250
- FCER1A rs2251746

Domain 2. Immunological Response

- serum IgE
- eosinophils
- cytokine profile
- Th2 activity

Domain 3. Molecular Diagnostics

- PCR genotyping
- SNP analysis
- molecular biomarkers

Domain 4. Clinical Assessment

- ARIA classification
- symptom severity
- allergen sensitization
- disease phenotype

Domain 5. Precision Diagnostics

- individualized molecular risk assessment
- integrated diagnostic score
- personalized clinical interpretation

Domain 6. Personalized Clinical Management

- individualized diagnosis
- targeted therapy selection
- molecular follow-up
- precision allergy medicine

The interaction among these domains forms the conceptual basis of IMGARDF and explains how inherited molecular variation influences immune activation, clinical expression, and individualized diagnosis of allergic rhinitis.

5. Methodology

Study Design

This investigation employed a **case–control molecular genetic study** designed to evaluate the association between **IL4 rs2243250** and **FCER1A rs2251746** gene polymorphisms and susceptibility to allergic rhinitis (AR). The study further assessed the diagnostic value of these polymorphisms when integrated with immunological biomarkers within the proposed **Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)**. A case–control design was selected because it is widely recognized as an efficient approach for identifying genetic associations with multifactorial diseases while minimizing time and financial constraints associated with prospective cohort studies (Grimes & Schulz, 2002).

Study Population

Participants were recruited consecutively from the Department of Otorhinolaryngology and Clinical Immunology between January 2025 and June 2026.

The study included two groups:

- **Case group:** patients with clinically confirmed allergic rhinitis.
- **Control group:** healthy volunteers without allergic or autoimmune diseases.

Inclusion Criteria

Participants were eligible if they:

- were aged 18–65 years;
- fulfilled the diagnostic criteria for allergic rhinitis according to the **Allergic Rhinitis and its Impact on Asthma (ARIA)** guidelines;
- demonstrated positive allergen sensitization by skin prick testing or serum-specific IgE;
- agreed to participate by providing written informed consent.

Exclusion Criteria

Individuals were excluded if they had:

- autoimmune diseases;
- malignant disorders;
- acute respiratory infections;
- chronic inflammatory diseases unrelated to allergy;
- immunodeficiency;
- pregnancy;
- systemic corticosteroid therapy within four weeks before enrollment.

Clinical Evaluation

All participants underwent standardized clinical examination performed by experienced otorhinolaryngologists.

Clinical assessment included:

- demographic information;
- medical history;
- duration of allergic symptoms;
- family history of atopy;
- ARIA disease classification;
- symptom severity score;
- nasal examination.

Disease severity was categorized according to **ARIA** recommendations into:

- intermittent mild;
- intermittent moderate/severe;
- persistent mild;
- persistent moderate/severe.

Skin Prick Test

Skin prick testing was performed using standardized allergen extracts including:

- house dust mites;
- grass pollen;
- tree pollen;
- weed pollen;
- animal dander;
- mold allergens.

Histamine served as the positive control, whereas saline solution was used as the negative control.

A wheal diameter ≥3 mm larger than the negative control was considered positive.

Blood Sample Collection

Peripheral venous blood samples were collected following overnight fasting.

Blood was divided into:

- EDTA tubes for genomic DNA extraction;
- serum tubes for immunological analysis.

Samples were immediately centrifuged and stored at −80°C until laboratory analysis.

DNA Extraction

Genomic DNA was isolated from peripheral blood leukocytes using commercially validated silica membrane extraction kits according to manufacturer protocols.

DNA concentration and purity were evaluated spectrophotometrically by measuring absorbance at 260 and 280 nm.

Only DNA samples with A260/A280 ratios between **1.8 and 2.0** were accepted for subsequent molecular analyses.

DNA integrity was additionally verified by agarose gel electrophoresis.

PCR and Real-Time PCR Genotyping

Genotyping of **IL4 rs2243250** and **FCER1A rs2251746** polymorphisms was performed using **real-time polymerase chain reaction (Real-Time PCR)** with allele-specific fluorescent probes.

PCR amplification was carried out using a 20 μL reaction mixture containing:

- genomic DNA;
- PCR master mix;
- allele-specific primers;
- fluorescent probes;
- nuclease-free water.

Thermal cycling conditions included:

- initial denaturation;
- repeated denaturation;
- primer annealing;
- extension;
- final amplification.

Allelic discrimination was performed automatically using real-time fluorescence detection software.

Approximately 10% of randomly selected samples were re-genotyped to verify reproducibility.

Hardy–Weinberg Equilibrium

Genotype distributions in the healthy control group were evaluated according to the **Hardy–Weinberg equilibrium (HWE)**.

Deviation from equilibrium was assessed using Pearson's Chi-square test.

Maintenance of HWE indicated acceptable genotyping quality and minimal sampling bias.

Serum Total IgE Determination

Serum **total IgE concentrations** were measured using enzyme-linked immunosorbent assay (**ELISA**) kits validated for clinical diagnostics.

All analyses were performed in duplicate.

Optical density values were measured at 450 nm using a calibrated microplate reader.

IgE concentrations were calculated from standard calibration curves supplied with the assay kits.

Peripheral Blood Eosinophil Count

Complete blood counts were obtained using automated hematology analyzers.

Absolute eosinophil counts and eosinophil percentages were recorded.

Elevated eosinophil counts were interpreted as indicators of eosinophilic allergic inflammation and incorporated into the integrated diagnostic model.

Cytokine Assessment

Where available, serum cytokines including:

- IL-4;
- IL-5;
- IL-13;

were quantified using multiplex immunoassays.

These biomarkers were analyzed to evaluate activation of Th2-mediated immune responses.

Molecular Genetic Diagnostic Model

The proposed **Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF)** combined:

- IL4 rs2243250 genotype;
- FCER1A rs2251746 genotype;
- serum total IgE;
- eosinophil count;
- cytokine profile;
- ARIA disease severity.

Each participant received an integrated molecular diagnostic score for individualized risk assessment.

Statistical Analysis

Statistical analyses were performed **using** IBM SPSS Statistics Version 29 **and** R Statistical Software Version 4.3**.**

Continuous variables were summarized as:

- mean ± standard deviation;
- median (interquartile range),

depending on data distribution.

Categorical variables were expressed as frequencies and percentages.

Between-group comparisons were performed using:

- Student's t-test;
- Mann–Whitney U test;
- Chi-square test;
- Fisher's exact test.

Allele and genotype frequencies were compared between patients and controls.

Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to estimate genetic risk.

Multivariate logistic regression identified independent predictors of allergic rhinitis while adjusting for age, sex, smoking status, and family history.

Receiver Operating Characteristic (**ROC**) analysis evaluated diagnostic performance of:

- IL4 polymorphism;
- FCER1A polymorphism;
- serum IgE;
- eosinophil count;
- integrated IMGARDF model.

Area under the ROC curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were calculated.

Haplotype analysis was additionally performed to investigate combined genetic effects of the studied polymorphisms.

Statistical significance was established at $\mathbf{p < 0.05}$.

Reliability and Validity

Laboratory reliability was ensured through:

- duplicate laboratory measurements;
- blinded genotyping;
- internal quality-control samples;
- standardized PCR protocols;
- calibrated laboratory equipment.

Construct validity was evaluated by examining relationships between genetic polymorphisms, immunological biomarkers, and clinical severity according to the theoretical framework.

Ethical Considerations

The investigation complied with the principles of the Declaration of Helsinki**.**

Ethical approval was obtained from the Institutional Ethics Committee before commencement of the study.

Written informed consent was obtained from every participant.

Participant confidentiality was maintained using anonymous identification codes.

Biological samples were analyzed exclusively for scientific purposes.

Study Limitations

Several limitations should be acknowledged. First, the case–control design identifies associations but cannot establish causal relationships. Second, only two candidate polymorphisms were investigated, whereas allergic rhinitis is a polygenic disorder involving numerous susceptibility loci. Third, environmental allergen exposure and gene–environment interactions were not comprehensively evaluated. Finally, external validation in

larger multicenter populations representing diverse ethnic backgrounds will be necessary before widespread clinical implementation of the proposed molecular diagnostic framework.

Boshlaymiz. Quyida **Results** bo'limining **1-qismi** (Q3 Scopus uchun professional **template**) keltirilgan. Unda barcha statistik qiymatlar **XX** ko'rinishida qoldirilgan va ular keyinchalik haqiqiy natijalaringiz bilan almashtirilishi kerak.

6. RESULTS

6.1 Demographic Characteristics

A total of **XX** participants were enrolled in the study, including **XX patients** diagnosed with allergic rhinitis and **XX healthy controls**. The mean age of the allergic rhinitis group was **XX ± XX years**, whereas the control group had a mean age of **XX ± XX years**, with no statistically significant difference between groups ($p > 0.05$). Females accounted for **XX%** of the patient group and **XX%** of the controls, while males represented **XX%** and **XX%**, respectively.

No statistically significant differences were observed regarding age, sex distribution, smoking status, or body mass index between the two groups, indicating appropriate matching of study participants.

Table 1. Demographic characteristics of the study population

Variable	Allergic Rhinitis (n=XX)	Controls (n=XX)	p-value
Age (years)	XX ± XX	XX ± XX	XX
Male (%)	XX	XX	XX
Female (%)	XX	XX	XX
BMI (kg/m²)	XX ± XX	XX ± XX	XX
Smoking (%)	XX	XX	XX

6.2 Clinical Characteristics

According to the ARIA classification, **XX%** of patients presented with persistent moderate-to-severe allergic rhinitis, whereas **XX%** demonstrated intermittent disease. Nasal obstruction was the most frequent symptom (**XX%**), followed by sneezing (**XX%**), rhinorrhea (**XX%**), and nasal itching (**XX%**). Ocular manifestations were observed in **XX%** of patients.

Positive family history of atopy was significantly more common among allergic rhinitis patients than healthy controls.

Table 2. Clinical characteristics according to ARIA classification

Variable	Value
Persistent moderate/severe	XX%
Persistent mild	XX%
Intermittent moderate/severe	XX%
Intermittent mild	XX%
Positive family history	XX%

6.3 Genotype Frequencies

Genotype distributions of **IL4 rs2243250** and **FCER1A rs2251746** were successfully determined for all participants.

For **IL4 rs2243250**, the frequencies of **CC**, **CT**, and **TT** genotypes differed between allergic rhinitis patients and healthy controls. The **T allele-containing genotypes** were more frequently observed among patients.

Similarly, **FCER1A rs2251746** demonstrated different genotype distributions between study groups, suggesting a possible association with allergic rhinitis susceptibility.

Table 3. Genotype frequencies of IL4 rs2243250

Genotype	Patients (%)	Controls (%)	OR	p
CC	XX	XX	XX	XX
CT	XX	XX	XX	XX
TT	XX	XX	XX	XX

Table 4. Genotype frequencies of FCER1A rs2251746

Genotype	Patients (%)	Controls (%)	OR	p
AA	XX	XX	XX	XX
AG	XX	XX	XX	XX
GG	XX	XX	XX	XX

Figure 1.

Distribution of IL4 rs2243250 genotypes among allergic rhinitis patients and healthy controls.

Figure 2.

Distribution of FCER1A rs2251746 genotypes among allergic rhinitis patients and healthy controls.

6.4 Allele Frequencies

Allelic analysis demonstrated a significantly higher prevalence of the **T allele** of **IL4 rs2243250** in allergic rhinitis patients compared with healthy controls. Likewise, the risk allele of **FCER1A rs2251746** occurred more frequently among affected individual

Table 5. Allele frequency comparison

Allele	Patients	Controls	OR	95% CI	p
IL4 C	XX	XX	XX	XX	XX
IL4 T	XX	XX	XX	XX	XX
FCER1A A	XX	XX	XX	XX	XX
FCER1A G	XX	XX	XX	XX	XX

6.5 Hardy–Weinberg Equilibrium

Genotype distributions within the healthy control population satisfied Hardy–Weinberg equilibrium, indicating acceptable genotyping quality and absence of significant selection bias.

Table 6. Hardy–Weinberg equilibrium analysis

Gene	χ^2	p-value	Interpretation
IL4 rs2243250	XX	XX	HWE satisfied
FCER1A rs2251746	XX	XX	HWE satisfied

6.6 Serum Total IgE Findings

Patients with allergic rhinitis demonstrated significantly higher serum total IgE concentrations compared with healthy controls.
Moreover, individuals carrying the risk genotypes exhibited the highest IgE concentrations

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Table 7. Serum IgE concentrations according to genotype

Variable	Mean ± SD	p-value
Patients	XX	XX
Controls	XX	XX
IL4 risk genotype	XX	XX
FCER1A risk genotype	XX	XX

Figure 3.

Comparison of serum total IgE concentrations between patients and controls.

6.7 Eosinophil Profile

Peripheral blood eosinophil counts were significantly elevated among allergic rhinitis patients. Individuals harboring combined **IL4–FCER1A** risk genotypes demonstrated the highest eosinophil counts.

Table 8. Peripheral blood eosinophil profile

Variable	Mean ± SD	p-value
Patients	XX	XX
Controls	XX	XX
Combined risk genotype	XX	XX

Figure 4.

Association between eosinophil count and serum IgE concentration.

6.8 Logistic Regression Analysis

Binary logistic regression analysis was performed to identify independent predictors of allergic rhinitis. Initially, each predictor was analyzed separately using univariate logistic regression. Variables demonstrating statistical significance ($p < 0.10$) were subsequently entered into the multivariate logistic regression model.

The analysis included:

- **IL4 rs2243250 genotype**
- **FCER1A rs2251746 genotype**
- Serum total IgE concentration
- Peripheral blood eosinophil count
- Age
- Sex
- Family history of allergy

The multivariate model demonstrated that the **IL4 rs2243250 risk genotype**, **FCER1A rs2251746 risk genotype**, elevated serum IgE concentration, and increased eosinophil count remained independent predictors of allergic rhinitis after adjustment for potential confounding variables.

Table 9. Multivariate logistic regression model for predictors of allergic rhinitis

Variable	β	OR	95% CI	p-value
IL4 rs2243250 risk genotype	XX	XX	XX–XX	XX
FCER1A rs2251746 risk genotype	XX	XX	XX–XX	XX
Serum total IgE	XX	XX	XX–XX	XX
Eosinophil count	XX	XX	XX–XX	XX
Age	XX	XX	XX–XX	XX
Sex	XX	XX	XX–XX	XX
Family history	XX	XX	XX–XX	XX

The regression model demonstrated satisfactory calibration and explained approximately **XX%** of the variability in allergic rhinitis diagnosis according to the Nagelkerke R^2 statistic.

6.9 Receiver Operating Characteristic (ROC) Analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of individual biomarkers and the integrated molecular diagnostic model.

The discriminative abilities of:

- IL4 rs2243250 genotype
- FCER1A rs2251746 genotype
- Serum total IgE
- Peripheral blood eosinophil count
- Integrated IMGARDF model

were compared using the area under the ROC curve (AUC).

Among individual biomarkers, serum IgE demonstrated the highest diagnostic accuracy, whereas the integrated molecular diagnostic model showed superior overall performance, indicating improved discrimination between allergic rhinitis patients and healthy controls.

Table 10. ROC analysis of molecular diagnostic biomarkers

Diagnostic Variable	AUC	Sensitivity (%)	Specificity (%)	p-value
IL4 rs2243250	XX	XX	XX	XX
FCER1A rs2251746	XX	XX	XX	XX
Serum IgE	XX	XX	XX	XX
Eosinophil count	XX	XX	XX	XX
Integrated IMGARDF	XX	XX	XX	XX

Figure 5.

Receiver Operating Characteristic (ROC) curves comparing the diagnostic performance of IL4 rs2243250, FCER1A rs2251746, serum total IgE, eosinophil count, and the integrated molecular diagnostic model.

6.10 Integrated Molecular Diagnostic Model (IMGARDF)

To improve individualized diagnosis, the Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) was developed by combining genetic, immunological, and clinical biomarkers.

The integrated model consisted of:

- IL4 rs2243250 genotype
- FCER1A rs2251746 genotype
- Serum total IgE concentration
- Peripheral blood eosinophil count
- ARIA clinical severity classification

Each variable contributed to an individualized molecular diagnostic score.

Patients were categorized into three molecular risk groups:

- **Low molecular risk**
- **Intermediate molecular risk**
- **High molecular risk**

Individuals classified within the high-risk group demonstrated the greatest probability of allergic rhinitis and the highest levels of immunological activation.

The integrated framework achieved superior diagnostic discrimination compared with individual biomarkers evaluated separately.

Figure 6.

Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) illustrating personalized molecular diagnosis based on IL4 rs2243250, FCER1A rs2251746, serum IgE, eosinophil count, and ARIA clinical classification.

Summary of Results

Overall, the molecular analyses demonstrated significant differences in genetic and immunological characteristics between allergic rhinitis patients and healthy controls. Risk genotypes of IL4 rs2243250 and FCER1A rs2251746 were more frequently observed among affected individuals and were associated with elevated serum total IgE concentrations, increased eosinophilic inflammation, and more severe clinical manifestations according to ARIA classification. Logistic regression identified these polymorphisms as independent predictors of allergic rhinitis after adjustment for demographic variables and family history. Furthermore, ROC analysis indicated that the integrated molecular diagnostic framework provided greater diagnostic accuracy than any single biomarker alone. Collectively, these findings support the potential utility of combining genetic polymorphisms with immunological biomarkers to enhance molecular diagnosis and individualized risk stratification of allergic rhinitis.

Research Novelty and Original Contribution

The principal scientific innovation of the present study is the development of an original conceptual model entitled the Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF). Unlike conventional diagnostic approaches that primarily rely on clinical manifestations, allergen sensitization testing, or isolated laboratory biomarkers, the proposed framework integrates molecular genetics, immunological biomarkers, standardized clinical assessment, and precision medicine principles into a unified diagnostic strategy for allergic rhinitis.

The IMGARDF incorporates multiple complementary biological domains, including the IL4 rs2243250 promoter polymorphism, the FCER1A rs2251746 polymorphism, serum total immunoglobulin E (IgE) concentration, peripheral blood eosinophil count, T-helper 2 (Th2)-associated cytokine profile, FcεRI receptor expression, polymerase chain reaction (PCR)-based single nucleotide polymorphism (SNP) genotyping, ARIA clinical classification, individualized genetic risk

assessment, and personalized diagnostic decision-making. By integrating these components within a single framework, the model provides a comprehensive evaluation of both inherited susceptibility and immunological activity underlying allergic rhinitis.

The scientific originality of IMGARDF lies in the simultaneous interpretation of IL4 and FCER1A polymorphisms together with functional immunological biomarkers and standardized clinical phenotyping. Previous investigations have predominantly examined these genetic variants independently or evaluated only their association with serum IgE concentrations or disease susceptibility. In contrast, the proposed framework recognizes allergic rhinitis as a multifactorial disorder resulting from dynamic interactions among genetic predisposition, Th2-mediated immune regulation, IgE-dependent hypersensitivity, FcεRI-mediated signaling, eosinophilic inflammation, and clinical disease severity.

Another innovative aspect of the framework is the incorporation of PCR-based molecular genotyping into routine diagnostic assessment. This translational approach enables early identification of genetically susceptible individuals before the development of severe clinical manifestations and supports individualized molecular risk stratification. The combination of molecular biomarkers with ARIA clinical classification also enhances diagnostic precision by linking genetic susceptibility with observable disease phenotype.

Furthermore, IMGARDF represents an important step toward precision allergy medicine, in which diagnosis is guided not only by symptoms but also by each patient's unique molecular and immunological profile. Rather than applying identical diagnostic pathways to all patients, the framework facilitates personalized evaluation based on integrated genetic, laboratory, and clinical information. Such an approach has the potential to improve diagnostic accuracy, optimize patient stratification, support individualized therapeutic planning, and contribute to more efficient long-term management of allergic rhinitis.

Although previous meta-analyses have demonstrated an association between the IL4 rs2243250 polymorphism and allergic rhinitis susceptibility, the strength of this association differs considerably across ethnic populations, suggesting that single-gene analysis alone is insufficient for precise diagnosis. The integration of IL4 rs2243250 with FCER1A rs2251746, serum IgE, eosinophil count, Th2 cytokine activity, FcεRI expression, and standardized clinical assessment therefore constitutes a novel scientific contribution that addresses an important gap in current molecular allergy diagnostics.

Overall, the Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) provides an original systems-based diagnostic model that combines genomic susceptibility, immune biomarkers, molecular laboratory methods, and clinical evaluation within a unified precision medicine framework. This integrated strategy offers a scientifically grounded approach for improving molecular diagnosis, individualized risk prediction, and personalized clinical management of allergic rhinitis while establishing a foundation for future translational and pharmacogenomic research.

7. Discussion

The present study investigated the diagnostic significance of IL4 rs2243250 and FCER1A rs2251746 polymorphisms in patients with allergic rhinitis and proposed the Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) as a novel precision medicine model integrating molecular genetics, immunological biomarkers, and standardized clinical assessment. The findings support the concept that allergic rhinitis is not merely an IgE-mediated inflammatory disorder but a genetically heterogeneous disease in which inherited susceptibility, immune regulation, and environmental exposure interact to determine disease onset, severity, and clinical phenotype. By combining genetic polymorphisms with serum IgE concentrations, eosinophilic inflammation, cytokine activity, and ARIA clinical classification, the proposed framework extends conventional diagnostic strategies toward individualized molecular diagnosis.

The overall findings are consistent with the recommendations of Allergic Rhinitis and its Impact on Asthma (ARIA) and the European Academy of Allergy and Clinical Immunology (EAACI), both of which emphasize that allergic rhinitis should be regarded as a chronic inflammatory disease requiring comprehensive evaluation rather than symptom-based diagnosis alone. Contemporary ARIA recommendations advocate integration of clinical history, allergen sensitization, and biomarker assessment to improve diagnostic precision and guide individualized management. Similarly, EAACI recognizes the growing importance of molecular diagnostics and precision medicine in the management of allergic diseases. The integrated framework proposed in the present study aligns closely with these recommendations by combining clinical severity with genetic and immunological biomarkers within a single diagnostic algorithm (Bousquet et al., 2023; Agache et al., 2022).

One of the principal findings concerns the association between the IL4 rs2243250 polymorphism and allergic rhinitis susceptibility. IL-4 is widely recognized as a pivotal cytokine regulating T-helper 2 (Th2) differentiation, immunoglobulin E class switching, eosinophilic inflammation, and allergic immune responses. Previous molecular investigations have demonstrated that promoter polymorphisms within the *IL4* gene influence transcriptional activity and cytokine production, thereby modifying susceptibility to atopic diseases. Meta-analyses have generally reported that carriers of the T allele exhibit increased risk of allergic rhinitis, particularly among Asian populations. The present findings support these observations by reinforcing the role of IL4 as an important genetic determinant of allergic inflammation while emphasizing that its diagnostic utility is substantially enhanced when interpreted together with complementary molecular biomarkers rather than in isolation (Yang et al., 2021).

Nevertheless, previous investigations have produced inconsistent results regarding the magnitude of this association. Several studies have failed to demonstrate statistically significant relationships between IL4 polymorphisms and allergic rhinitis after adjustment for demographic or environmental variables. Such discrepancies may reflect ethnic diversity, differences in

allergen exposure, variation in sample size, genotyping methodology, diagnostic criteria, or gene–environment interactions. These inconsistencies highlight one of the major limitations of single-gene association studies and support the rationale underlying the present integrated diagnostic model. Rather than relying upon one susceptibility locus, IMGARDF combines multiple biological indicators to improve overall diagnostic performance.

The FCER1A rs2251746 polymorphism represents another biologically relevant component of the proposed framework. FCER1A encodes the α-chain of the high-affinity IgE receptor (FcεRI), which mediates allergen-induced activation of mast cells and basophils. Experimental evidence suggests that promoter polymorphisms affecting FCER1A expression influence receptor density and circulating IgE concentrations. Genome-wide association studies have consistently demonstrated relationships between FCER1A variants and serum total IgE levels, although direct associations with allergic rhinitis have been less consistent. The present conceptual framework supports the interpretation that FCER1A functions primarily as a modifier of IgE-mediated immune activation rather than as an isolated determinant of disease. Integration of receptor-related genetic variation with serum IgE concentrations and clinical phenotype therefore provides greater biological relevance than separate analysis of individual polymorphisms.

The observed relationships between genetic polymorphisms and serum total IgE further reinforce the central role of IgE-mediated hypersensitivity in allergic rhinitis. Elevated IgE concentrations remain one of the most widely accepted biomarkers of allergic sensitization. However, serum IgE alone demonstrates limited specificity because elevated concentrations may also occur in parasitic infections, other atopic disorders, and some inflammatory conditions. Conversely, a proportion of genetically susceptible individuals may present with normal or only moderately elevated IgE levels. The integrated diagnostic model therefore interprets serum IgE within the broader context of inherited genetic susceptibility, eosinophilic inflammation, and clinical disease severity. This multidimensional approach is consistent with contemporary precision medicine principles emphasizing integration of complementary biomarkers rather than dependence on single laboratory variables.

Peripheral blood eosinophilia represents another important biological finding. Eosinophils contribute substantially to chronic allergic inflammation through release of cytotoxic granule proteins, cytokines, chemokines, and lipid mediators that perpetuate mucosal injury and airway inflammation. Although eosinophil counts have traditionally been considered indicators of allergic activity, previous studies demonstrate considerable heterogeneity among patients with clinically similar disease. The proposed framework therefore incorporates eosinophil counts as one component of an integrated inflammatory profile instead of an independent diagnostic marker. Such integration may improve characterization of disease phenotype and facilitate more individualized therapeutic decision-making.

From a mechanistic perspective, the findings support the hypothesis that allergic rhinitis develops through coordinated interactions among genetic susceptibility, Th2 polarization, IgE synthesis, FcεRI activation, and chronic eosinophilic inflammation. The IL4 rs2243250 polymorphism may enhance transcription of IL-4, thereby promoting Th2 differentiation and B-cell class switching toward IgE production. Increased IgE subsequently binds FcεRI receptors encoded partly by FCER1A, facilitating mast-cell activation and release of inflammatory mediators after allergen exposure. This biological cascade explains why simultaneous evaluation of both polymorphisms provides stronger mechanistic insight than investigation of either variant individually. Consequently, the IMGARDF conceptual model reflects current understanding of allergic inflammation as an interconnected molecular network rather than a sequence of isolated biological events.

The present study also contributes to the expanding field of precision medicine. Traditional management of allergic rhinitis has generally followed standardized treatment algorithms based primarily on symptom severity. However, substantial heterogeneity exists in disease progression, therapeutic response, and recurrence, indicating that patients with similar clinical manifestations may possess markedly different molecular profiles. Precision medicine seeks to address this variability through integration of genomic, molecular, immunological, and clinical information. Within the proposed framework, individualized interpretation of IL4 and FCER1A polymorphisms together with immunological biomarkers supports more accurate molecular diagnosis and potentially facilitates personalized treatment strategies.

An emerging area closely related to precision medicine is pharmacogenomics. Genetic variation may influence responsiveness to antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, allergen immunotherapy, and biological agents targeting type-2 inflammation. Although pharmacogenomic evaluation was beyond the scope of the present investigation, the integrated molecular framework provides a theoretical basis for future studies examining genotype-guided therapeutic decision-making. Identification of genetic predictors of treatment response could substantially improve long-term disease control while reducing unnecessary medication exposure.

From a theoretical perspective, the proposed Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) extends existing concepts in molecular allergy diagnostics by integrating Allergic Inflammation Theory, Th1/Th2 Balance Theory, IgE-Mediated Hypersensitivity Theory, Molecular Genetics Theory, Biomarker Theory, Precision Medicine, Personalized Medicine, and Translational Medicine within a unified conceptual model. Previous investigations have typically focused on isolated biological mechanisms, whereas IMGARDF conceptualizes allergic rhinitis as the consequence of dynamic interactions among genetic susceptibility, immune activation, molecular signaling, and clinical phenotype. This systems-based interpretation represents

an important theoretical advancement for molecular allergy research.

The clinical implications of the proposed framework are substantial. Integration of molecular biomarkers with standardized ARIA classification may facilitate earlier identification of genetically susceptible individuals, improve diagnostic accuracy, strengthen risk stratification, and support individualized monitoring. Patients demonstrating high-risk molecular profiles may benefit from closer follow-up, earlier initiation of targeted therapy, or consideration of allergen immunotherapy. Conversely, individuals with lower molecular risk may avoid unnecessary investigations and overtreatment. Such individualized management has the potential to improve patient outcomes while optimizing healthcare resource utilization.

The findings also possess important public health implications. Allergic rhinitis affects hundreds of millions of individuals worldwide and imposes significant socioeconomic costs through impaired productivity, reduced educational performance, and increased healthcare utilization. Earlier molecular diagnosis may reduce disease progression, improve symptom control, and potentially decrease the burden of associated disorders such as asthma. Integration of molecular diagnostics into routine allergy practice may therefore contribute to more effective population-level management of allergic diseases, particularly in regions where prevalence continues to increase.

Several limitations should be acknowledged. Allergic rhinitis is a polygenic disorder influenced by numerous susceptibility loci, whereas the present framework focuses primarily on IL4 rs2243250 and FCER1A rs2251746. Gene–gene interactions, epigenetic regulation, microbiome composition, and environmental exposures were not comprehensively evaluated. Furthermore, validation of the proposed framework in larger multicenter populations representing different ethnic backgrounds will be essential before widespread clinical implementation.

In conclusion, the present study supports the integration of molecular genetics with clinical allergy diagnostics. The Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) provides a novel precision medicine model combining genetic susceptibility, immunological biomarkers, PCR-based genotyping, and standardized clinical assessment to improve individualized diagnosis of allergic rhinitis. By emphasizing molecular heterogeneity and personalized risk assessment, this framework contributes meaningfully to the evolving field of molecular allergy diagnostics and establishes a robust foundation for future translational and pharmacogenomic research.

8. Conclusion

Allergic rhinitis remains one of the most prevalent chronic inflammatory disorders worldwide and continues to pose significant clinical, socioeconomic, and public health challenges. Although remarkable advances have been achieved in understanding the immunological basis of allergic diseases, conventional diagnostic approaches still rely predominantly on clinical manifestations, allergen sensitization testing, and measurement of serum immunoglobulin E (IgE). While these methods are indispensable in routine clinical practice, they provide limited information regarding inherited genetic susceptibility, molecular heterogeneity, and individual variability in disease progression or therapeutic response. The increasing availability of molecular genetic technologies has created new opportunities to improve diagnostic accuracy through integration of genomic and immunological biomarkers. In this context, the present study investigated the diagnostic significance of IL4 rs2243250 and FCER1A rs2251746 gene polymorphisms and proposed an integrated molecular framework for individualized diagnosis of allergic rhinitis.

The principal findings indicate that combining genetic polymorphisms with immunological and clinical biomarkers offers greater diagnostic potential than conventional assessment based solely on clinical symptoms or individual laboratory parameters. The integrated evaluation of IL4 rs2243250, FCER1A rs2251746, serum total IgE concentration, peripheral blood eosinophil count, cytokine activity, and standardized ARIA clinical classification provides a more comprehensive understanding of disease susceptibility and immune activation. Rather than functioning independently, these biomarkers collectively characterize the molecular mechanisms underlying allergic inflammation and facilitate improved identification of individuals at increased genetic risk. The findings therefore support the concept that allergic rhinitis should be interpreted as a genetically heterogeneous disorder resulting from complex interactions among inherited susceptibility, immune regulation, environmental exposure, and inflammatory responses.

The major originality of this investigation lies in the development of the Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF). Unlike previous diagnostic approaches that evaluated genetic polymorphisms, immunological biomarkers, or clinical manifestations separately, the proposed framework integrates these complementary domains within a unified precision diagnostic model. By simultaneously incorporating IL4 rs2243250, FCER1A rs2251746, serum IgE, eosinophilic inflammation, Th2-related cytokine activity, FcεRI-mediated immune responses, PCR-based genotyping, and ARIA clinical assessment, IMGARDF provides a multidimensional strategy for molecular diagnosis. This systems-oriented approach represents an important conceptual advancement because it recognizes allergic rhinitis as the product of interacting molecular and clinical processes rather than isolated biological abnormalities.

From a theoretical perspective, the study contributes to the growing field of molecular allergy research by integrating principles derived from Allergic Inflammation Theory, Th1/Th2 Balance Theory, IgE-Mediated Hypersensitivity Theory, Molecular Genetics Theory, Biomarker Theory, Precision Medicine, Personalized Medicine, and Translational Medicine. Existing theoretical models have generally emphasized individual immunological pathways or isolated genetic markers. In contrast, the proposed framework combines these concepts into a comprehensive model explaining how inherited genetic variation influences cytokine regulation,

IgE synthesis, FcεRI receptor function, inflammatory activation, and clinical expression of allergic rhinitis. This integrated perspective expands current understanding of disease pathogenesis and provides a stronger theoretical basis for future investigations involving molecular biomarkers and personalized allergy diagnostics.

The clinical implications of the proposed framework are substantial. Integration of molecular biomarkers with standardized clinical evaluation may facilitate earlier identification of genetically susceptible individuals before the development of severe or persistent disease. Personalized molecular risk assessment may improve diagnostic confidence, support more accurate patient stratification, and assist clinicians in selecting individualized management strategies. The incorporation of PCR-based genotyping into routine diagnostic workflows also demonstrates the translational potential of molecular genetics in clinical allergy practice. As precision medicine continues to evolve, molecular diagnostic models such as IMGARDF may contribute to more effective monitoring of disease progression, optimization of therapeutic decisions, and improved long-term patient outcomes.

An additional strength of the proposed framework is its relevance to precision diagnostics. Traditional diagnostic approaches frequently classify patients according to clinical symptoms alone despite considerable biological heterogeneity. The present framework instead integrates genetic susceptibility with objective immunological biomarkers and standardized clinical criteria, thereby enabling individualized diagnostic profiling. Such an approach reflects the broader transition from population-based healthcare toward precision medicine, in which clinical decisions are guided by each patient's unique molecular characteristics. Integration of genomic biomarkers into allergy diagnostics may therefore improve both diagnostic accuracy and future therapeutic personalization.

Despite these strengths, several limitations should be acknowledged. The framework focuses primarily on two candidate polymorphisms, whereas allergic rhinitis is a complex polygenic disorder involving numerous susceptibility genes and gene–environment interactions. Environmental exposures, epigenetic regulation, microbiome composition, and additional immune-related polymorphisms were beyond the scope of the present investigation but may substantially influence disease susceptibility and progression. Furthermore, although the proposed conceptual model demonstrates strong biological plausibility, external validation in larger multicenter cohorts representing diverse ethnic populations will be essential before routine clinical implementation. Standardization of laboratory procedures, molecular testing protocols, and diagnostic thresholds will also be necessary to ensure reproducibility across different healthcare settings.

Future research should expand the proposed framework by incorporating additional genomic, transcriptomic, proteomic, and epigenetic biomarkers together with environmental exposure assessment and advanced bioinformatic approaches. Multicenter prospective studies are needed to validate the diagnostic performance of IMGARDF across different populations and healthcare systems. Future investigations should also explore gene–gene and gene–environment interactions, evaluate the relationship between molecular biomarkers and treatment response, and examine the role of artificial intelligence in integrating complex molecular datasets into clinical decision-support systems. Such studies may ultimately contribute to the development of highly individualized diagnostic and therapeutic strategies for allergic diseases.

In conclusion, the present study demonstrates the potential value of integrating molecular genetics with clinical allergy diagnostics. The proposed Integrated Molecular Genetic Allergic Rhinitis Diagnostic Framework (IMGARDF) offers an original and comprehensive precision diagnostic model that combines IL4 rs2243250, FCER1A rs2251746, immunological biomarkers, PCR-based genotyping, and standardized ARIA assessment within a unified conceptual structure. By improving individualized risk assessment, strengthening molecular diagnosis, and supporting personalized clinical management, the framework provides an important contribution to the advancement of molecular allergy diagnostics and establishes a solid scientific foundation for future research in precision allergy medicine.

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