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Research Progress of Pathogenic Genes of Atopic Dermatitis

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Abstract. The genetic mechanisms underlying atopic dermatitis (AD), a complex immune-mediated skin disorder, have garnered significant research attention in recent years. This study systematically reviews key breakthroughs in pathogenic gene discovery and functional studies within the international scientific community. It reveals synergistic effect between mutations in skin barrier-related genes and variations in immune regulation genes in disease pathogenesis. Genome-wide association studies (GWAS) has significantly enhanced the identification of critical disease-associated loci. Notably, loss-of-function mutations in the FLG gene impair epidermal barrier integrity, leaving the skin vulnerable to external triggers. Meanwhile, novel candidate genes such as IL4R and IL13 have been linked to the excessive activation of type 2 immune responses, laying the foundation for precision-targeted therapies. Some discoveries have led to clinical applications, with biologic therapies targeting specific cytokine pathways showing promising efficacy. Future research should prioritize elucidating gene-environment interactions and cross-ethnic genetic variations to advance personalized diagnostic and therapeutic approaches for AD.

Keywords: Atopic dermatitis, FLG gene, IL4/IL13 signaling pathway, KIF3A gene, targeted therapy

1. Introduction

The rapid advancement of industrialization has coincided with a rising global incidence of atopic dermatitis (AD). Characterized by a chronic course and intense pruritus, AD significantly impairs patients' quality of life. The disease arises from a dual immune and barrier dysfunction, driven by genetic susceptibility and environmental factors. Consequently, investigating its genetic mechanisms has become central to understanding AD's pathogenesis.

Twin studies from the late 20th century indicated a heritability rate of up to 75%, prompting systematic efforts to identify pathogenic genes. Initial linkage analyses pinpointed susceptibility loci on chromosomes 1q21 and 3q21, though precise localization was hindered by technological constraints. Recent breakthroughs in high-throughput sequencing have shifted focus toward the interplay between skin barrier genes and immune regulatory genes. Mutations in the FLG gene, which encodes filaggrin—a crucial component of the skin barrier—are particularly significant, as loss of filaggrin function compromises epidermal hydration, increasing vulnerability to allergens. Additionally, mutations in Th2 pathway genes such as IL4R and IL13 trigger an exaggerated immune response, sustaining chronic inflammatory cascades.

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This study reviews the research progress of the pathogenesis of atopic dermatitis (AD), and explores the potential of precision-targeted therapies based on these genetic insights. This study contributes to the development of personalized diagnostic tools and targeted therapeutic strategies, enhancing patient outcomes and quality of life.

2. Progress in the methodology of gene research on atopic dermatitis

2.1. Application of genome-wide association study (GWAS) in ad research

As a key tool for investigating the genetic basis of complex diseases, genome-wide association studies (GWAS) offer distinct advantages in identifying pathogenic genes associated with AD. Twin studies by Schuler et al . authenticated that AD has a heritability of up to 80%, which provided theoretical support of the application of GWAS [1].

In the field of AD research, GWAS has confirmed the critical role of skin barrier-related genes. For instance, the FLG gene in the 1q21 chromosomal region has been identified as the strongest risk locus, where loss-of-function mutations disrupt epidermal structural proteins. These mutations are directly linked to dry skin and heightened allergen permeability in patients. Notably, GWAS has also revealed significant population heterogeneity in FLG mutations, which are far more prevalent among European AD patients than in Asian populations, underscoring the importance of cross-ethnic genetic differences research. Additionally, GWAS has uncovered several novel immune regulatory genes, including key components of the Th2 pathway such as IL4R, IL13, and STAT6. Polymorphisms at these loci alter cytokine receptor structures, functioning like a "mis-fitted key" that perpetuates type 2 immune activation. This dysregulation leads to excessive production of inflammatory cytokines, including IL-4 and IL-13.

Advances in GWAS technology have greatly enhanced theidentification of pathogenic loci. Recent studies employ a multi-stage validation strategy: initial screening of potential sites via high-throughput chips, followed by fine-mapping using targeted sequencing, and functional validation of candidate genes via experimental method. This "discovery-verification-mechanism" approach has clarified the role of the OVOL1 transcription factor in skin keratinocytes, demonstrating its involvement in barrier function remodeling through the regulation of epithelial differentiation. Notably, integrating GWAS data with epigenetic analyses has uncovered a novel mechanism by which certain risk loci modulate gene expression via DNA methylation modification.

Despite these advances, key limitations persist. Most GWAS findings are derived from European populations, potentially overlooking population-specific risk loci. Additionally, common variants identified in GWAS often explain only a fraction of heritability risk, underscoring the importance of rare variants and gene-environment interactions. Further study by combining single-cell sequencing and spatial transcriptomics is needed to analyze the functional heterogeneity across cell subpopulations. Such approaches may provide a more comprehensive genetic foundation for developing precise therapeutic targets.

2.2. Precise localization of pathogenic genes by next generation sequencing

The breakthrough development of next-generation sequencing (NGS) provides a new perspective for precise localization of the pathogenic genes of AD. Unlike traditional methods, NGS offers superior resolution and throughput, enabling the simultaneous detection of single nucleotide variants, copy number variations, and structural rearrangements across the genome. This advancement has ushered AD genetics into the precision medicine era.

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Whole-exome sequencing (WES), a core NGS technology, has proven particularly valuable in identifying rare AD-associated variants. By sequencing all coding regions, WES has uncovered novel loss-of-function mutations in the FLG gene, compromising epidermal barrier integrity, akin to "missing bricks" in a wall. Additionally, it has revealed compound heterozygous mutations in the SPINK5 gene, where defective LEKTI can disrupt the cutaneous protease-antiprotease balance [2]. Targeted sequencing further enhanced identification efficiency by customizing skin barrier-related gene panels, reducing analysis time from weeks to hours.

Long-read sequencing has overcome the challenge of deciphering complex genomic regions. For instance, the FLG gene, located within the epidermal differentiation complex (EDC), is often confounded by repetitive sequences in short-read sequencing. However, third-gereneration sequencing accurately maps these regions, identifying large EDC deletions in some AD patients, suggesting structural variations may cause synergistic defects in multiple barrier proteins.

The NGS and functional genomics has established a multidimensional research framework. Combining sequencing data with chromatin accessibility analysis has revealed population-specific variations in the enhancer region of the IL13 locus, which regulates Th2 cytokine overexpression. The CRISPR-guided approachby Bhat et al. demonstrates that editing these regulatory elements significantly reduces IL-13 secretion, offering novel insights for targeted therapy. Furthermore, microneedle-assisted delivery systems enable localized skin gene editing, showing promising therapeutic potential in AD animal models [3].

Future research should address the clinical translation bottleneck of NGS. While numerous candidate genes have been identified, the functional relevance of most variants remains unclear. Systematic validation of pathogenic mechanisms, using humanized mouse models and 3D skin organ cultures, is underway. Additionally, integrated multi-omics analyses are becoming increasingly critical. Recent studies reveal significant differences in genetic risk loci across populations, underscoring the need for ethnicity-specific genetic screening criteria [4]. As sequencing costs decline and bioinformatics tools improve, NGS is poised to become a standard technique for personalized AD diagnosis and treatment.

3. Functional analysis of key pathogenic genes

Firstly, the silk polyprotein encoded by filaggrin (FLG) gene plays a critical role in maintaining skin barrier integrity, and loss-of-function mutations are key drivers of AD development. Located within the epidermal differentiation complex, FLG is expressed in keratinocytes and hydrolyzed during terminal differentiation into free amino acids, forming a major component of the skin’s natural moisturizing factor. A longitudinal birth cohort study by Schuler et al. demonstrated that children carrying FLG deletion variants exhibited persistent AD symptoms into adolescence, highlighting the long-term impact of this genetic defect on skin barrier function [1]. When FLG is functionally impaired, the stratum corneum’s "brick-and-mortar" structure becomes compromised. This barrier dysfunction resembles a "broken wall," facilitating the penetration of allergens and microbes. Additionally, FLG-deficient keratinocytes exhibit abnormally high expression of thymic stromal lymphopoietin (TSLP), a pro-inflammatory cytokine that acts as an alarmin, activating dendritic cells and triggering a Th2-type immune response [5]. A bidirectional relationship exists between FLG mutations and immune dysregulation. On one hand, barrier disruption leads to chronic immune activation by external stimuli, driving excessive production of Th2 cytokines (e.g., IL-4, IL-13). Conversely, these cytokines further suppress FLG expression, creating a vicious cycle. This is particularly evident in chronic AD lesions, where patients exhibit reduced epidermal differentiation markers and inflammatory cell infiltration [6].

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The IL4/IL13 signaling pathway also plays a central role in the pathogenesis of AD, where dysregulation of its associated genes drives excessive type 2 immune responses. The core components of this pathway include the IL-4 receptor alpha subunit (IL4Rα) and the IL-13 receptor α1 (IL13Rα1), which form a heterodimeric receptor complex on the cell surface. IL-4 and IL-13 binding activates the JAK-STAT signaling cascade, leading to STAT6 phosphorylation and nuclear translocation, where it regulates the transcription of pro-inflammatory genes [7]. At the signaling level, aberrant activation of JAK1 and JAK3 is critical in pathway dysregulation. JAK1 expression is notably upregulated in AD lesional keratinocytes, where it phosphorylates IL4Rα, facilitating STAT6 recruitment. Research by Emma Guttman-Yassky's team confirmed that JAK inhibitors effectively suppress IL-4/IL-13 signaling and reduce Th2 cytokine release, supporting their therapeutic potential [7]. Additionally, STAT6 polymorphisms may impair DNA-binding affinity, leading to uncontrolled expression of downstream chemokines like TSLP and CCL26.

The abnormal activation of this pathway also disrupts epidermal barrier function. There is a two-way regulatory relationship between the two. IL-13 suppresses keratinocyte differentiation genes (e.g., FLG, LOR), compromising skin integrity. In turn, barrier dysfunction triggers Langerhans cells to release thymic stromal lymphopoietin (TSLP), further amplifying IL-4/IL-13 signaling activation and creating a vicious cycle of inflammation and barrier damage [8]. Chronic AD lesions exhibit both reduced differentiation markers and heightened STAT6 activation, underscoring this interplay. Future research should explore how genetic variations influence treatment responses, paving the way for personalized therapeutic strategies.

Lastly, the KIF3A gene contributes to the pathogenesis through epigenetic mechanisms. The encoded protein functions as a molecular motor, primarily facilitating intracellular transport and signal transduction. KIF3A plays a dual role in maintaining epidermal homeostasis. At the epigenetic level, KIF3A regulates chromatin accessibility of key inflammatory genes by interacting with histone-modifying complexes. For instance, KIF3A deficiency increases histone H3K27 acetylation in the promoter region of the IL-4 receptor gene, an epigenetic modification that acts as an "on" switch, hyperactivating the Th2 cytokine signaling pathway [9]. KIF3A may also influence AD pathogenesis through RNA editing regulation. Recent studies indicate that reduced KIF3A expression correlates with defects in the epidermal double-stranded RNA surveillance system in AD patients. Impaired KIF3A function compromises RNA editing efficiency, leading to the accumulation of incorrectly edited double-stranded RNA. These aberrant RNAs activate pattern recognition receptors, triggering sustained interferon pathway activation and a false alarm-like inflammatory response. This mechanism is particularly prominent in AD patients carrying KIF3A risk alleles. Cross-ethnic genetic studies highlight functional differences in KIF3A across populations. Multi-cohort genome-wide association analyses reveal distinct KIF3A variant loci in European and Asian populations, explaining ethnic variations in AD clinical manifestations [4].

4. Clinical transformation of gene research achievements

4.1. Application of gene detection in individualized diagnosis

The rapid advancement of gene detection technology has become a crucial tool for the individualized diagnosis of AD. By analyzing mutations in key pathogenic genes, clinicians can more accurately identify disease subtypes, predict progression, and develop targeted treatment strategies. Screening for FLG gene mutations has become a key component of clinical practice, particularly in assessing skin barrier dysfunction. Patients with loss-of-function mutations exhibit a compromised epidermal barrier—akin to a "leaky roof"—making them more susceptible to external

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irritants. These patients often benefit from early, intensive moisturizing therapy. Studies show that ceramide-based repair agents significantly improve dry skin symptoms and reduce flare-ups in FLG mutation carriers [10].

Genetic analysis of immune-related genes, such as analysis on IL4R and IL13 polymorphisms, provides a scientific basis for selecting biologic therapies. For instance, patients with specific mutation loci show enhanced responses to targeted agents like Dupilumab. This "gene-matching" strategy minimizes ineffective treatments and reduces healthcare costs. The Bhat team's CRISPR-based research demonstrates that editing the IL13 regulatory region can precisely modulate gene expression [3]. While not yet in clinical trials, this technology highlights the potential for future individualized gene therapies.

Gene detection also shows unique value in disease prediction. Polygenic risk score models help predict AD susceptibility in infants and children. For example, children carrying both FLG mutations and IL4R risk alleles have a several-fold higher likelihood of developing AD before three compared to the general population. Early environmental interventions, such as avoiding specific allergens, can significantly delay disease onset in these high-risk groups. Commercial testing facilities now offer rapid (48-hour) targeted sequencing panels covering 20 AD-associated genes.

Despite its promise, genetic testing faces challenges in clinical challenges. Test interpretation must integrate clinical presentation and environmental factors, as individual gene variants alone cannot fully predict disease phenotype. Additionally, variability in gene panels across testing sites may compromise result comparability. Moving forward, standardized testing protocols, clear interpretation guidelines, and expanded genetic counseling services are essential to help patients understand their results. With advances in CRISPR-based gene editing technology, genetic testing may eventually extend beyond diagnosis to provide precise therapeutic intervention targets.

4.2. Progress in clinical trials of targeted gene therapy

Targeted gene therapy for atopic dermatitis (AD) has achieved significant breakthroughs in clinical applications, with multiple therapeutic strategies targeting pathogenic genes currently under evaluation in clinical trials. Among these, drug development centered on IL4R and IL13 inhibition is the most advanced. Dupilumab, the first approved biologic for AD, effectively suppresses overactivation of the Th2 immune pathway by blocking the shared receptor alpha subunit of IL-4 and IL-13. Phase III clinical trials demonstrated its strong safety and efficacy, with marked improvements in skin inflammation and pruritus in moderate-to-severe AD patients.

Another key therapeutic approach involves targeting the JAK-STAT signaling pathway. Research by Guttman-Yassky et al. showed that oral JAK inhibitors not only regulate abnormal keratinocyte differentiation but also suppress multiple cytokine signals [7]. This "broad-spectrum inhibition" mechanism offers distinct advantages for AD patients with comorbidities such as asthma or food allergies. Second-generation selective JAK inhibitors, now in multicenter trials, feature local topical formulations that minimize systemic side effects, making them particularly suitable for pediatric and elderly populations.

Gene editing technologies have also made strides toward clinical translation. CRISPR-Cas9-based precision therapies, such as microneedle-mediated local IL13 knockout, are currently in animal testing [2]. This transdermal delivery system functions like a "precision missile," enabling targeted gene modulation at lesion sites without affecting the entire genome. Notably, a novel combination therapy targeting NLRP3 inflammasomes—integrating gene editing with glucocorticoids—shows promise for treating refractory lesions.

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Despite these advances, challenges remain. Viral vector immunogenicity risk requires more rigorous assessment, and the efficiency of topical delivery systems needs further optimization. Future research should focus on developing smart, responsive gene-editing tools capable of autonomously adjusting activity based on skin microenvironmental factors (e.g., pH or inflammatory markers) to achieve spatiotemporal precision. As individualized genetic testing becomes more accessible, patient-tailored therapies based on specific genetic backgrounds may soon become a clinical reality.

5. Conclusion

This paper reveals that the interplay between skin barrier dysfunction and immune dysregulation constitutes the core pathogenic mechanism. Loss-of-function mutations in the FLG gene compromise epidermal barrier integrity, akin to a weakened wall without protection, facilitating allergen penetration and subsequent immune activation. Concurrently, mutations in immune regulatory genes such as IL4R and IL13 drive sustained overactivation of the Th2-type immune response via altered cytokine signaling. These findings provide critical theoretical foundations for understanding AD pathogenesis.

Recent research has yielded significant breakthroughs. Advances in genome-wide association studies (GWAS) and next-generation sequencing (NGS) have markedly enhanced the identification of disease-associated genes. Genetic screening of key variants (e.g., FLG, IL4R) mutation now supports personalized diagnostic and therapeutic approaches. Clinically, biologics targeting the IL-4/IL-13 pathway have demonstrated promising efficacy, validating the translational potential of genetic discoveries. Notably, epigenetic research has further elucidated how environmental factors—mediated through mechanisms such as DNA methylation—modulate gene expression, offering new insights into the rising global prevalence of AD.

However, this study also has some limitations. The findings are primarily based on existing literature, which may not fully capture the most recent advancements in the field. Additionally, the review may be subject to publication bias, as studies with negative or inconclusive results may not have been as widely reported.

Future investigations should prioritize breakthroughs in below key areas. Firstly, current data are predominantly derived from European populations; systematic studies are needed to characterize genetic variations in Asian and African cohorts. Secondly, research should explore how environmental triggers (e.g., air pollution, microbial exposure) influence expression of susceptible genes via epigenetic modifications. Besides, integrating single-cell sequencing and spatial transcriptomics could delineate dynamic gene regulation mechanism across distinct skin cell populations.

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