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# Modern vision of pathogenesis, clinical and immunological features and new methods of atopic dermatitis treatment

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## Abstract

The article provides a literature review of one of the modern medical social problems in the world — atopic dermatitis. Epidemiological data, current view on the pathogenesis of this disease, the role of genetic factors and epigenetic mechanisms in the development of dermatosis and modern treatment approaches are highlighted. Atopic dermatitis is a chronic inflammatory skin disease which common for children and adolescents, as well as for adults. Epidemiological studies conducted in different countries reveal the high prevalence and increased incidence of atopic dermatitis over the past three decades. Atopic dermatitis significantly affects the quality of patients' and their relatives' lives and also results in considerable social and economic burdens. Atopic dermatitis is a heterogeneous disease which pathogenesis is associated with mutations in genes encoding epidermal structural proteins, as well as genes that regulate innate and adaptive immune responses to environmental factors. In addition, the review reflects studies on the mechanisms of epigenetic regulation underlying the development of atopic dermatitis: Deoxyribonucleic acid (DNA) methylation, histone modification, and micro ribonucleic acid (microRNA)-mediated mechanisms of gene expression regulation. Epigenetic modifications in parents are realized in offspring in several generations, causing a wide range of clinical differences in the course of the disease in different age and gender groups. Currently available treatments for atopic dermatitis achieve remission but not a cure. The study of the disease pathogenesis, combined with the continuation of research on finding effective drugs, determines the prospects for developing prevention and treatment of atopic dermatitis.

**Keywords**: review, atopic dermatitis, epidemiology, genetics, epigenetics.

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## Background

Atopic dermatitis (AD) is a multifactorial and genetically determined inflammatory skin disease that is characterized by itching, chronic relapsing course, age-related localization aspects, and lesion morphology [1, 2].

AD is one of the most common non-infectious skin diseases, which affects up to 20% of children and 2%–8% of adults worldwide [1]. In Germany, the prevalence of AD is 10%–15% [2], whereas 10.7% in children and 7.2% in adults in the United States of America [3], and 24% among the pediatric population in Japan. Additionally, several countries have noted a steady increase in the AD frequency over the past three decades. On the territory of the Russian Federation, according to the results of the standardized epidemiological study International Study of Asthma and Allergy in Childhood, the prevalence of AD ranges from 6.2%–to 15.5% depending on the region [4]. Thus, AD is the most common chronic disease in children.

## Genetic factors of AD development

Data of existing studies indicate the polygenic nature of AD inheritance with the presence of a leading gene involved in the implementation of hereditary predisposition and skin lesions determination, as well as additional genes. Additionally, the clinical course characteristics are associated with both the interaction of genes and the influence

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of environmental factors. Moreover, >70 AD-associated genes are known [5].

The currently known AD-associated genes can be divided into the groups of genes that affect the epidermal barrier function, encode the production of biologically active substances by keratinocytes (interleukins [IL-25 and IL-33], thymic stromal lymphopoietin), and affect innate and adaptive immune response. The genes that regulate deoxyribonucleic acid (DNA) methylation (*KIF3A* gene) are also involved in AD pathogenesis. Additionally, the association of AD with genes regulates ergo- and cholecalciferol metabolism and calcitriol receptor synthesis (*CYP27A1, CYP2R1,* and *VDR* genes) [5].

## The role of mutations in the filaggrin gene in AD pathogenesis

The main genetic factor in AD development is considered a filaggrin gene mutation, which causes impaired epidermal barrier function [6, 7]. The filaggrin gene (*FLG*) is located on chromosome 1q2, and the filaggrin protein (*FLG*) serves as the main structural protein of the corneal layer [8]. Profilaggrin (*Pro-FLG*) polymers are proteolytically cleaved and dephosphorylated to *FLG* monomers, which are associated with keratin filament aggregation and corneal layer formation [9]. *FLG* null mutations impair the skin barrier function and increase the risk of AD [8, 10]. *FLG* mutations, especially homozygous ones, are associated with an increased risk of severe recurrent AD with earlier onset and skin infections [10–12].

Approximately 10% of the European population is heterozygous carriers of *FLG* mutations resulting in a 50% decrease in protein expression [10]. However, AD pathophysiology goes far beyond *FLG* mutations. Japanese and Korean patients have a lower frequency of *FLG* mutations than patients from Western populations [9, 13]. Additionally, approximately 40% of patients with *FLG* null alleles do not have clinical manifestations of AD, and most patients with AD and *FLG* mutations eventually "outgrow" the disease [14].

## Immune dysfunction

Another key link in AD pathogenesis is immune dysfunction, which causes an altered inflammatory response in the affected skin. The immune response aspects of such skin are closely related to changes in the corneal layer barrier function, and these two links mutually influence each other.

An inflammatory reaction in the skin develops with the participation of T-lymphocytes in AD. The Th2 immune response predominates in the acute disease phase. Hyperproduction of immunoglobulins E (IgE) occurs due to T-helpers (Th) type 2 stimulation, and transition from Th2 to Th1 immune response occurs in the chronic disease phase [15].

Gene polymorphisms in various immune pathways are associated with an increased risk of AD due to Th-2 cell signaling pathway changes [8, 16]. The key cytokines involved in the pathophysiological mechanisms of AD are IL-4, -13, -31, and -33 and interferon-γ, which use the Janus kinase (JAK)/ Signal transducer and activator of transcription (STAT) signaling system for signal transduction, including the JAK-1 [17], implemented both in the norm and in case of secondary infection.

Increased levels of IL-4 and IL-13 reduce the *FLG* expression, which leads to skin barrier defects [18]. Increased functional polymorphisms of type 2 cytokine receptors (IL-4R and IL-13R) are also significant in AD pathogenesis [18, 19]. The regulatory genes and cytokines that promote AD development include IL-31, IL-33, STAT 6, thymic stromal lymphopoietin and its receptors (IL-7R and TSLPR), interferon regulatory factor 2 (IRF2), Toll-like receptor 2 (TLR2), and high-affinity IgE receptor gene (*FcεRI*) *α* in certain populations [8, 16, 20–23].

Single nucleotide polymorphisms in the serine protease inhibitors *SPINK5* and *SPKLK7* are known, as well as mutations in the tight junction protein claudin-1. Mutations of the IgE receptor gene *FcεRb*, as well as the receptor of genes associated with innate immunity (*NOD1, NOD2*, and *TLR2*, *-4* and *-9*) and with acquired immunity (*IL-4, -5, -9, -10, -12, -13, -18, and -31* and *TSLP*), have been described [24].

The study of the influence of mutations in various genes on the development and course of AD is actively conducted. Martin et al. revealed an association between the rs893051 mutation in the *CLDN1* gene and the early onset of AD and the rs3745367 mutation in the *RETN* gene with gender and age differences in the clinical disease presentation. Several *TSLP* gene mutations determine the sensitivity to external therapy with topical glucocorticoids and calcineurin inhibitors, and mutations in the *CARD11* gene are associated with severe AD and recurrent infection development [25].

## Gene *Klotho*

The *Klotho* genes were originally identified as aging suppressor genes, and blocking their expression induces a phenotype similar to human aging in experimental animals. Recent evidence confirms that the *Klotho* gene acts as a tumor suppressor by inhibiting Wnt signaling, which ultimately controls gene expression programs. *Klotho* gene suppression, including its DNA methylation, occurs in several cancers. A decreased gene expression is accompanied

by epigenetic rearrangements of the genome in prostate cancer cell lines [26]. Conversely, an increased gene expression induces apoptosis of atypical cells, which exert an antitumor effect [27].

Numerous gene effects, accompanied by an increased lifespan, are partly due to its ability to suppress inflammation [28]. Thus, the anti-inflammatory effect of *Klotho* is due to an increased expression of the *HSP70* gene. The latter, acts through the nuclear transcription factor-κB, thereby reducing the severity of inflammation and apoptosis [29, 30].

Concurrently, the *Klotho* gene itself can be subjected to epigenetic rearrangements due to stress [31], malnutrition or overnutrition [32], and pollutant exposure [33].

The study of the role of the *Klotho* gene and its expression in AD is currently of interest for scientific research since its effects have been studied only in laboratory animals and cell cultures [34, 35]. However, the control of its expression in the area of damage may be promising due to its practical application.

**Epigenetic mechanisms of AD**

At present, a large number of involved genes in AD pathogenesis have been described, which are responsible both for impaired epidermal barrier and immune response aspects and cytokine and chemokine production. However, only 30%–50% of patients (depending on gender, age, and geographic and economic living conditions) suffer from AD; the detected genetic mutations accompany the development of dermatosis [36, 37].

In recent years, when studying the mechanisms underlying AD development, much attention has been paid to epigenetic regulation analyses. This is a process that leads to a change in the gene activity without coding sequence changes, which is steadily inherited after the disappearance of the factor that caused this change. Epigenetic factors affect the expression activity of certain genes at several levels, which leads to a change in the phenotype of a cell or organism [38].

The main epigenetic mechanisms include DNA methylation, histone modification, and microRNA[1]-mediated mechanisms of gene expression regulation [39, 40]. These epigenetic mechanisms can lead to various types of pathology, including allergic conditions [39–41].

Ferreira et al., in their course of studying the relationship between DNA methylation and factors contributing to AD development, identified 36 genes, which expression significantly differed in groups of patients and healthy people due to methylation of their promoters [42]. Similarly, Boorgula et al. found a relationship in another 490 gene promoters. These included genes encoding the production of IL-4, IL-13, and other cytokines [43].

**MicroRNA-mediated mechanisms in AD**

Currently, two approaches can be distinguished, namely the study of the influence of known miRNAs on the development of dermatosis and the search for new, previously undescribed miRNAs, which are found only in patients with AD. Thus, when using the first approach, the role of *miR-124* [44] was established, as well as *miR-143* is involved in T-cell proliferation regulation [45], *miR-26* that activates hyaluronan synthase-3 [46, 47]*, 182 miRNA, hsa-miR-148b, hsa-miR-152,* and *hsa-miR-324* [48]. Additionally, when searching for microRNAs that are differentially expressed in the blood serum of patients compared with healthy people, the expression level of some microRNAs was significantly higher, such as *miR-144* [49], *miR-151a*, and *miR-409* [50], whereas the previously described *miR-146a* did not show differences in blood concentrations in patients with AD and the comparison group [51], despite the previously demonstrated role of this miRNA in regulating the immune system and signaling pathways of inflammatory responses [52, 53].

Notably, the role of epigenetic mechanisms that are implemented during pregnancy and early childhood probably cause a wide range of clinical differences in the disease course in patients of different gender and age [5].

**Clinical presentation and endotypes of AD**

The clinical presentation of AD is characterized by skin rashes, which are different in localization and prevalence, and pruritus, which is a mandatory symptom of AD. Itching increases in the evening and at night, causing anxiety and disturbing the sleep of patients. Zuberbier et al. indicated that a patient suffering from AD spends an average of 67 sleepless nights per year (with an average exacerbation duration of 136.2 days per year) [54].

Moreover, skin rashes on visible and socially significant areas of the skin, face, and neck can lead to decreased self-esteem, mood, and working ability in both children and adults. Additionally, constant itching, as well as rash and its localization in visible areas of the body, lead to increased personal and situational anxiety, decreased social activity, and distrust toward other people. Thus, both objective and subjective symptoms, as well as personality traits formed under the disease influence, drastically reduce the quality of life of patients.

[1] RNA — ribonucleic acid.

AD has a greater impact on the quality of life than epilepsy, bronchial asthma, or diabetes mellitus, which, according to subjective perception, is comparable to cerebral palsy [54–57].

In clinical practice, AD diagnosis is established based on clinical symptoms; however, in some cases, AD must be differentiated from allergic contact dermatitis, ichthyosis, microbial eczema, seborrheic dermatitis, scabies, psoriasis, cutaneous T-cell lymphoma, and various immune system disorders such as Wiskott-Aldrich syndrome, hyperimmunoglobulinemia E syndrome, Gianotti-Crosti syndrome, etc. [2, 8, 58].

The clinical presentation of AD is influenced by many exogenous and endogenous factors. In the range of endogenous factors, researchers note the age, gender, race of patients, whereas exogenous factors include exposure to infectious agents, allergens, and irritants. To date, most studies indicate the paramount importance of genetic and epigenetic mechanisms in AD development under the influence of exogenous factors [8, 21, 23, 25].

The individual clinical presentation of AD in a patient consists of the genotype, endotype, and clinical phenotype, which is considered as an "external" reflection of skin pathological processes. Researchers have identified several AD phenotypes with similar clinical manifestations as follows:

– AD with an onset in early childhood, spontaneously resolving before the age of 5 years;

– AD with an onset in early childhood with a persistent severe course in adolescence and adulthood;

– AD with an onset in adolescence or adults of mild or moderate severity;

– AD with an onset in adolescence or adulthood with a severe persistent course.

In addition to the characteristics in the formation of phenotypes, the authors consider the dependence on developmental mechanisms, namely exogenous (IgE-mediated AD) and endogenous (non-IgE-mediated AD), as well as the presence of complications in AD accompanied by skin colonization by *S. aureus*, with signs of secondary infection, AD accompanied by a common viral infection, such infection caused by the herpes simplex virus, with the development of a severe complication, namely Kaposi's varicelliform eruption [59, 60].

The disease endotype is determined by the molecular mechanisms underlying the phenotype. The European, American, Asian, African American, and childhood AD endotypes are distinguished, which differ in the activity of immunocompetent cells and the composition of secreted cytokines, the state of the epidermal barrier, thereby having their clinical characteristics [61].

The study of the relationship of genetic and epigenetic mechanisms with various AD endotypes, as well as their influence on phenotypic diversity, is a promising scientific direction, ultimately aimed at developing personalized approaches in AD therapy [61, 62].

## Modern AD therapy

Modern AD therapy is aimed at controlling inflammation and prolonging remission. The choice of therapeutic approach depends on the age of the patient and the clinical characteristics of AD. The first step of AD therapy is emollients, of which regular use significantly reduces the risk of disease exacerbations and the need for topical glucocorticoid therapy. A significant factor in disease control is patients' education and rejection of significant allergens in the presence of sensitization [63, 64].

During AD exacerbation, topical glucocorticoids and calcineurin inhibitors are used as the next step. Additionally, therapy with topical calcineurin inhibitors in an intermittent regimen (1–2 times a week), helps prevent exacerbations and control AD [65].

In severe disease cases, drugs with a systemic immunosuppressive or cytostatic effect are used [61, 62]. In recent years, in dermatosis that is severe and resistant to standard therapy, genetically engineered biological preparations (dupilumab and ustekinumab) are used, which are human monoclonal antibodies that selectively block the key Th-2 cytokines that cause inflammation in AD [66].

Drugs used in clinical practice for topical and systemic therapy of AD are not always effective and have several side effects that restrict their use. To date, data is unavailable on drugs that affect the epigenetic processes in AD. Glucocorticoids can reduce the activity of histone acetylase, one of the key enzymes involved in implementing epigenetic mechanisms [5]. Concurrently, attempts are made to treat AD using the latest advances in molecular biology and cytology. Thus, the use of stem cells has a therapeutic effect; however, it turned out to be temporary [67–69].

Thus, AD represents a complex multifactorial disease, which course is determined by both genetic predisposition and the impact of environmental factors, which are implemented through epigenetic mechanisms. Further study of genetic and epigenetic aspects will contribute to a deeper understanding of the pathogenetic mechanisms of this dermatosis, the complex relationship between skin cells, and the functioning of the innate and adaptive immune systems, which ultimately form the basis for the development of new effective treat-

ment methods, AD exacerbation prevention, and quality of life improvement of patients.

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