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Research Article

THE ROLE OF GENETIC MUTATIONS IN THE DEVELOPMENT OF ACNE

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Khamidova Farida Muinovna
Samarkand State Medical University, Department of Pathological Anatomy with a sectional course, Uzbekistan

Khusinova Firuza Azgar Kizi
Samarkand State Medical University, Department of Pathological Anatomy with a sectional course, Uzbekistan

ABSTRACT

Relevance: Understanding of the molecular and genetic mechanisms underlying acne and acne scar formation is still in its infancy. However, ongoing research in this area increases our knowledge of disease mechanisms and may contribute to the development of new preventive and treatment strategies. Research confirms the significant role of genetic factors in the development of acne, affecting its occurrence, course and effectiveness of treatment. Particular attention is paid to gene polymorphisms associated with inflammation, androgen metabolism and the immune response, such as CYP17A1 and TNF-α. These data highlight the importance of taking patients' genetic profile into account when diagnosing and choosing therapy, which can improve treatment outcomes and prevent disease relapse. Based on an analysis of literature data, in Uzbekistan there is insufficient understanding of the prognostic significance and role of the NLR and TLR2 genes in the development of acne. This highlights the complexity of the genetic component of acne and indicates the need for additional research to better understand the influence of these and other genetic factors on the pathogenesis of the disease.

Conclusion. An in-depth study of the genetic aspects of acne will not only enrich the scientific understanding of the disease, but will also open up new opportunities for its more effective treatment and prevention.

KEYWORDS

Acne, molecular genetic mechanisms, kelliod, prognosis.

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INTRODUCTION

Acne (L70, L73. 0.) is a chronic inflammatory skin disease affecting the hair sebaceous follicles and is caused by a variety of factors including genetics and androgens. Neonatal acne (acne neonatorum) occurs in the first four weeks of life, and infantile acne appears between 3 and 6 months. These conditions may be associated with high androgen levels in girls and boys (1,7).

Acne can develop at any age and is often seen in teenagers and young adults. Symptoms include comedones, pustules and inflammatory nodules. Microbial flora, in particular Cutibacterium acnes, plays a significant role in pathogenesis, causing inflammation and infection.

Treatment for acne includes topical retinoids, benzoyl peroxide, antibiotics and, in some cases, oral contraceptives or isotretinoin. It is important to consider antibiotic resistance and the potential psychological effects of the disease (2,8).

Historically, acne has been known since ancient times; its descriptions are found among the ancient Egyptians and Greeks. Current understanding of the disease emphasizes the importance of genetic and immune factors in its development.

Acne is an inflammatory skin disease that can appear at different points in life and is often associated with genetic factors (1,2,3,4).

Neonatal, nodular cystic and conglobate acne have a pronounced genetic predisposition, and acne after adolescence is associated with a family history of acne in 50% of cases.

Research has identified genetic markers associated with acne, including apolipoprotein A1 and various loci detected through genome-wide analyses. Several genetic pathways, including PI3K/AKT/mTOR, may regulate sebum production and inflammation, which play a key role in the development of acne (5).

Acne severity scoring systems vary and may include analysis of comedones, papules and pustules. Immunity research has shown that inflammation in acne can be caused by a variety of factors, including skin microbes and innate immune responses.

The following clinical and morphological forms of acne are distinguished:

L70.0- Common acne (acne vulgaris), L70.1 - Globular acne, L70.2 Smallpox acne, Necrotic miliary acne, L70.3-Tropical acne, L70.4-Children's acne, L70.5- Acne excoriée, Excoriated acne, L70.5-Other acne, L70.9-Acne, unspecified.

Acne Vulgaris is a globally common chronic inflammatory disease of the hair and sebaceous follicles. Although acne is not life-threatening, it can cause scarring, irritation and serious psychological problems, including depression. Our review examines the various causes of acne and methods of treating

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them. Major pathophysiological factors include excessive sebum production, hyperkeratinization, P. acnes colonization, and inflammation. In diagnosing acne, it is important to distinguish between inflammatory and non-inflammatory forms of lesions. Problems of antibiotic resistance require the development of new treatments (12).

Epidemiological studies show that acne affects up to 80% of adolescents and young adults. The age at which acne most often begins ranges from 14 to 16 years in girls and 16 to 17 years in boys. However, although acne affects men and women at approximately the same frequency, severe forms are more common among men (17,18,19,20,21,22).

The causes and mechanisms of acne development are not fully understood, but they are believed to be associated with a number of factors. These include hormonal imbalance and hypersecretion of sebum, changes in its chemical composition, follicular hyperkeratosis and colonization of the skin by the bacteria Propionibacterium acnes. An important role in the development of acne belongs to the immune response to the antigens of these microorganisms, which activate neutrophils and phagocytes.

These cells stimulate the complement system through Toll-like receptors (TLR2), resulting in the synthesis of pro-inflammatory interleukins such as IL-8, TNF-α, IL-1β and IL-12. These interleukins activate cyclooxygenase, which promotes the production of inflammatory mediators, such as leukotriene B4 from arachidonic acid. It has been established that leukotriene B4 activates monocytes, eosinophils, T-lymphocytes and other cells that secrete hydrolytic enzymes that destroy the wall of the sebaceous gland. This leads to the release of the contents of the gland into the surrounding tissues and causes the development of inflammation at the site of the lesion (23,24).

Immunodeficiencies such as chronic granulomatous disease (CGD) can aggravate skin conditions such as folliculitis. CGD is a rare inherited disease caused by a defect in the enzyme NADPH oxidase, which prevents white blood cells from effectively killing pathogens. Such patients may experience recurrent bacterial and fungal skin infections, including folliculitis and acne. Diagnosis of CGD involves specific tests for neutrophil function, and treatment includes infection prevention and immunomodulators (6,7,8).

Hidradenitis suppurativa, also known as acne inversus or acne inversus, is a chronic inflammatory skin disease affecting the hair follicles and is associated with acne. The disease manifests in intertriginous areas and can cause significant burden due to pain, itching, malodor, and emotional distress. Treatment may include antibiotics, antimicrobials, and surgical interventions to control symptoms and prevent disease progression (9,10,11).

A study by Ballanger et al shows a significant influence of heredity on the development and course of acne. A family history of acne (A+) is associated with earlier onset of the disease, often before puberty, and

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increases the recurrence rate after isotretinoin treatment. In addition, acne patients whose parents also suffered from acne (M+ and M+F+) are more likely to experience problems with retention lesions. This highlights the role of genetic factors as an important prognostic indicator in clinical practice in the diagnosis and selection of treatment strategies for acne (15).

Modern research focuses on the genetic aspects of acne, indicating that genetic predisposition significantly influences the occurrence, clinical presentation, course and effectiveness of acne treatment. Acne is a polygenic disease, which means that it does not follow the classical laws of Mednellian inheritance (25,26).

There are many genetic markers associated with acne, including polymorphisms in genes such as tumor necrosis factor alpha, matrix metalloproteinases (MMPs), tissue inhibitors of metalloproteinases (TIMPs), interleukin-1, CYP17A1, CYP1A1, and others. Research by Yaykasli K.O. showed that genotype frequencies for matrix metalloproteinase-2 (MMP-2) and TIMP-2 inhibitor polymorphisms were similar in a Turkish population between acne patients and controls. However, an imbalance between MMPs and TIMP-2 may increase susceptibility to acne, as shown for the TIMP-2 (-418 C/C) genotype, which was twice as common in patients compared to controls (27).

Most of the genes studied in the context of acne play key roles in innate immune function, skin lesion formation, or steroid hormone metabolism. Particular attention is paid to polymorphisms of genes involved in the biosynthesis of androgens, including testosterone, such as cytochrome P450c17α, encoded by the CYP17A1 gene (28,29,30,31,32).

A study by N. Malikova et al. in the Uzbek population showed that certain genotypic variants of the CYP17A1 gene are associated with a higher likelihood of developing acne and its severe course. For example, the heterozygous A/G genotype was typical for patients with moderate acne, while the G/G genotype was more common in patients with severe acne. The A/A variant was protective and associated with a reduced risk of acne (33,34).

In China, the CYP17-34T/C polymorphism was associated with acne, with men with the homozygous C/C variant and the C allele having a high risk of severe acne, in contrast to women with mild to moderate acne, where no such association was observed (35 ,36).

A polymerase chain reaction (PCR) study examined the effect of CYP17 gene polymorphisms on the development of acne in Chinese men. The homozygous C/C variant and the C allele were found to be significantly more common in men with severe forms of acne compared to the control group, confirming statistically significant differences. However, among women with mild and moderate forms of acne, no statistically significant differences were found with the control group, indicating a possible sex difference in the genetic predisposition to severe forms of acne. Another study among Indonesian patients showed

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that polymorphisms in the CYP17A1, CYP1A1 and TNF-α genes did not correlate with the risk of developing severe acne. However, it has been found that polymorphisms in the CYP1A1 gene may contribute to acne in general. These findings highlight the complexity of the genetic background of acne and the need for further research to determine the precise role of these and other genetic factors in the development of the disease (37).

Researchers in Germany found that having the GG genotype of the CYP1A1 gene may increase the risk of developing acne. This genotype is thought to contribute to a deficiency of natural retinoids leading to follicular hyperkeratosis and acne vulgaris. This may also explain the high effectiveness of retinoids in the treatment of severe acne in patients with this polymorphism, since they show a better therapeutic response than patients without this polymorphism (38).

Studies have shown that the -308 G/A and -238 G/A polymorphisms in the TNF gene are significantly more common in patients with acne vulgaris, especially those suffering from severe forms of acne, than in healthy individuals. This is confirmed by the increased risk of developing acne in the European population compared to the Asian population. In addition, high levels of the proinflammatory cytokine IL-8 and a significant frequency of the IL-8-251T>A polymorphism are found in Pakistani patients with acne, highlighting a genetic predisposition to the development and severity of acne (39,40,41,42).

In addition, analysis of the rs4646421 polymorphism of the CYP1A1 gene showed that although the activity of the cytochrome CYP1A1 enzyme is important for the metabolism of sex hormones and vitamin A, a direct connection of this polymorphism with the development of acne was not found. However, this genetic marker has been shown to have significant prognostic value for predicting severe acne, as patients with severe acne are more than twice as likely to have an unfavorable allelic variant as controls (43).

An increase in the level of TSPO in the skin of patients with acne, along with other enzymes that metabolize steroids - 3βHSD, CYP11A1, may indicate an intensification of the synthesis of steroids in the skin during this period. Pathology, as well as their contribution to the development of chronic inflammation in acne (50).

A study from Western Iran found that the PPARγ Pro12Ala and C161T polymorphisms do not directly influence the risk of developing acne vulgaris (AV), but the PPARγ Pro allele is associated with increased susceptibility to AV in adults over 20 years of age. In addition, polymorphisms influence the lipid profile of patients, indicating significantly higher levels of total cholesterol and triglycerides in carriers of the variant CG genotype compared to the CC genotype. The study also found that CT and TT genotypes were associated with lower serum cholesterol and LDL-C levels. These

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data highlight the importance of genetic factors in the pathogenesis and clinical presentation of acne, as well as their possible influence on the lipid profile, which may have implications for the choice of acne treatment strategy (16).

A study conducted among Turkish patients with acne vulgaris found significant differences in the frequency of the IGF-I (CA)19 genotype between affected and healthy subjects, supporting its possible influence on the development of acne (P=0.0002). This genotype was also found to be associated with acne severity (P=0.015), suggesting a role in disease progression in this ethnic group (44,45).

Studies have also shown that tumor necrosis factor alpha (TNF-α), a powerful pro-inflammatory cytokine, plays a key role in triggering and regulating the cytokine cascade in inflammation and the immune response. One of the functional polymorphic loci, G-308A, has a significant effect on the synthesis and level of TNF-α in the body, which emphasizes its potential importance in the pathogenesis of acne and its clinical course (46,47).

The authors concluded that elevated levels of interleukin-8 and its genetic polymorphism IL-8-251T>A may contribute to the development of acne in the population. Genetic markers play a key role in the development and progression of acne. A detailed study of the genetic and immunogenetic factors associated with acne may lead to a better understanding of the molecular and genetic mechanisms of this condition. This knowledge will help in the development of new methods to predict the course of the disease and effective therapeutic approaches to treat acne, taking into account genetic polymorphisms (48,49).

The formation of scar tissue includes three phases that follow in a certain time sequence: inflammatory, proliferative and remodeling phase (51).

The main structural units active in the inflammatory and proliferative phase are fibroblasts, capillary endothelium, transform-transient growth factor (TGF) β1 and β2, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-1) and epidermal growth factor (EGF). Vascular endothelial growth factor (VEGF), which is produced by epidermal cells, acts as a positive regulator of angiogenesis. Tissue inhibitors of metalloproteinases (TIMPs) are endogenous inhibitors of matrix metalloproteinases (MMPs). Thus, increased levels of TIMP are presumably associated with hypertrophic scar formation. Tumor necrosis factor α (TNF-α) is an inflammatory cytokine produced by monocytes and macrophages during the inflammatory phase. This cytokine is known to cause collagen degradation and help minimize excessive scarring (52). During the remodeling phase, excess extracellular matrix is degraded and type III collagen, the immature form of collagen, is replaced by mature type I collagen. TGF-β3 is believed to play a leading role in this process. Also, members of the MMP family have a significant effect on the degradation and remodeling of the ECM and mediate the degradation of collagen types I and III,

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reducing inflammation and neutralizing the effects of chemokines (53).

Decorin is a proteoglycan component of cutaneous connective tissue that binds to type I collagen fibrils and influences TGF-β. By binding and neutralizing TGF-β, decorin reduces the stimulating effect of TGF-β on the synthesis of collagen, fibronectin and glycosaminoglycan. Decorin levels are reduced in keloids and hypertrophic scars, and its antifibrotic properties have attracted attention as a possible therapeutic agent (54,55).

The role of periosteum (extracellular matrix protein), the level of which is sharply increased in hypertrophic scars and keloids compared to normal tissues, is also actively discussed (56,57).

Proinflammatory factors such as interleukins IL-1α, IL-1β, IL-6, and tumor necrosis factor alpha are upregulated in keloid tissues, suggesting that patients with keloids have increased expression of proinflammatory genes in the skin. This may contribute to chronic inflammation, which, in turn, can cause invasive growth of keloids, although according to the results of a study that was conducted in Turkey (90 people in the study group and 30 in the control group), polymorphic variants

Ants TNF-α (-308 G/A) and IL-1β (-511 C/T) were not associated with acne susceptibility, acne scarring, or acne severity (58).

Increased expression of pro-inflammatory factors means that keloids and hypertrophic scars are a consequence of inflammatory processes in the reticular layer of the dermis. Various external and internal stimuli (local, systemic and genetic) after injury can contribute to inflammation. The nature of these irritants most likely determines the characteristics, number, and development of keloids and hypertrophic scars. In England, when studying a small group of patients with keloid scars (including acne), they found that the presence of HLADRB5 and HLA-DRB1*15 was associated with keloid disease (59).

A meta-analysis of the association of the Arg72Pro polymorphism of the P53 gene with keloid scars in the Chinese population included the results of 6 studies, which included 359 patients with keloid scars and 493 people. as a control. It was determined that the Pro allele of the Arg72Pro polymorphism of the P53 gene is a risk factor for the development of keloids in the Chinese population compared to the Arg allele (OR = 2.29, 95% CI = 1.45–3.60) (60).

A study was conducted in China in which the first stage analyzed 1056 patients with acne and 1056 controls using high-density chips. At the second stage of the study, in an independent cohort (1860 patients and 3660 people in the control group), 101 single nucleotide polymorphisms were tested, of which 3 showed an association: rs747650 of the DDB2 gene and rs1060573 (11p11.2), rs7531806 of the SELL gene (1q24.2), which are involved in androgen metabolism, inflammation, and scar formation in severe acne (61).

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Keloids develop in fibroproliferative disorders against the background of chronic inflammatory processes in the skin. A genome-wide association study showed an association with rs8032158 in the NEDD4 gene. This gene is expressed by neural progenitor cells and has six different transcripts. Carriage of the rs8032158 risk allele C in patients with keloids is associated with selectively higher expression of type 3 transcript (TV3 NEDD4) and activation of the NF-κB pathway. The analysis revealed that NEDD4 TV3 is involved in NF-κB activation through its association with the adapter protein RIP. These results suggest that NEDD4 TV3 is a potential diagnostic marker and therapeutic target for chronic skin diseases, including keloid (62).

A genome-wide association study of 478 African Americans (122 cases, 356 controls) was conducted in the USA in 2014. An association was found with the q21.2-22.3 locus on chromosome 15, which includes the NEDD4 gene. This gene has previously been shown to be associated with keloid scars in Japanese and Chinese populations. But in African Americans, a more significant association was found with the MYO1E gene. In addition, an association was established with the q13.5 locus on chromosome 11 (MYO7A gene, rs35641839, OR = 4.71, 95% CI 2.38–9.32, p = 8.34 × 10–6). The authors suggest that the identification of polymorphisms associated with the formation of keloid scars in two myosin genes indicates that the altered cytoskeleton contributes to enhanced migratory and invasive properties of keloid fibroblasts (63).

Long non-coding RNAs (lncRNAs) are believed to play a significant role in human diseases. Studies have shown that overexpression of long non-coding RNA AC067945.2 did not affect cell proliferation in hypertrophied scar tissue, but promoted early apoptosis in normal skin fibroblasts. Except Moreover, overexpression of AC067945.2 inhibited the expression of COL1A1, COL1A2, COL3A1 and α-SMA proteins. In turn, TGF-β1 can inhibit the expression of AC067945.2. In the group with overexpression of AC067945.2, 138 mRNA expression differed from the control group, of which it was increased in 14 and decreased in 124. Overexpression of AC067945.2 correlated with developmental processes, binding, extracellular region and the VEGF and Wnt signaling pathways. The study revealed the functions of the novel lncRNA AC067945.2, which may help understand the mechanisms regulated by AC067945.2 in the pathogenesis of hypertrophic scars (64).

Overexpression of long non-coding RNA ncRNA8975-1 was found in hypertrophic scars and skin fibroblasts. Overexpression of lncRNA8975-1 prevents cell proliferation and reduces the expression of COL1A2, COL1A1, COL3A1 and α-SMA in hypertrophic scar fibroblasts, whereas knockdown of lncRNA8975-1 has the opposite effect. Further studies of the mechanisms by which lncRNA8975-1 expression is regulated may

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lead to a better understanding of the pathogenesis of hypertrophic scars (65).

The study of the genetic aspects of the problem of scar formation after acne, as well as the determination of molecular genetic markers of this condition, is almost at the very initial stage. It is likely that this gap will be filled in the coming years, which will provide impetus for the development of new effective means of preventing and treating this disease (71). regulators of androgen receptors - 25-OH-VD, cytochrome p 450 (17-alpha hydroxylase), insulin-like growth factor are important in the pathogenesis of rapid non-genomic molecular cellular reactions of peripheral androgen metabolism and, in the future, may determine new algorithms for the diagnosis and treatment of acne diseases (66).

An important aspect of acne pathogenesis is the participation of keratinocytes in the inflammatory response. C. acnes activates Toll-like receptor (TLR)-2 and TLR-4 on keratinocytes, leading to activation of signaling cascades including the NF-κB pathway and the MAPK pathway. Subsequently, keratinocytes produce IL-1, IL-8, IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), TNF-α, matrix metalloproteinases (MMPs) and human β-defensin-2 (hBD-2). In addition to TLR-2 and TLR-4, the CD36 receptor expressed on keratinocytes is also involved in the recognition of C. acnes.

Once C. acnes CD36 is detected, keratinocytes begin to synthesize reactive oxygen species (ROS), especially superoxide anion, generated from the cytosolic enzymes NAD(P)H oxidases. These ROS provide an antibacterial effect and trigger an inflammatory response. Analysis of identified variants of the nucleotide sequence of keratinocyte proliferation and differentiation genes showed that severe acne is likely associated with polymorphic loci AP3B1, FERMT1, FERMT3, GBA, SUFU (67).

Data on the role of family history and possible inheritance of acne have been confirmed in a number of studies on familial cases of this dermatosis, its more frequent development in monozygotic twins, but the significance of genetic associations is not fully known. Thus, He L. et al. (2014) revealed a connection between acne and TP63, which ensures the regulation and differentiation of epithelial stem cells (68).

In another study, the authors suggested an association of acne development with LGR6, which is a mediator of the WNT signaling pathway and ensures the functioning and differentiation of sebaceous gland stem cells. Additional associated genes were LAMC2, encoding a major component of the basement membrane, and SPECC1L, encoding a cross-linking cytoskeletal protein that plays an important role in cell adhesion and migration (69).

It has been shown that the presence of the disease in first-degree relatives may be a risk factor for the development of dermatosis. A case of identification and determination of the significance of polymorphism of the NCF1, CD3E, ORAI1, IGHM, TAZ genes in patients

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with severe forms of the disease with a family history is presented. The conducted studies revealed identical allelic variants in five genes: NCF1, CD3E, ORAI1, IGHM, TAZ in two closely related patients (father and son) with severe acne. Polymorphisms of the studied genes probably influence the development of an imbalance in the oxidase system, the functioning of mitochondria, reduced proliferation of T cells, as well as the formation of an imbalance in the secretion of immunoglobulins. The data obtained may be factors in the torpid course of severe dermatosis, which determines the need for further research (70). Based on the analysis of literature data, it can be noted that in our Republic of Uzbekistan, the prognostic values, features and role of the NLR and TLR2 genes, and their relationship in the development of acne have not been fully studied.

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