Association of Genetic Factors in the Occurrence of Acne Vulgaris and its Implication in the Development of Severe Acne

Héctor Zúñiga-Gazcón¹, Miguel Angel Flores Delgado¹, Diego Eduardo Saavedra Mayorga², Cindy Chavira Macias³, Massiel Alfonsina Ávila Ramírez⁴
¹Departamento de Cirugía, Unidad Médica de Alta Especialidad (UMAE), Hospital de Especialidades (HE), Centro Médico Nacional de Occidente (CMNO), IMSS, Guadalajara, Jalisco, México
²Departamento de Anestesiología, Unidad Médica de Alta Especialidad (UMAE), Hospital de Especialidades (HE), Centro Médico Nacional de Occidente (CMNO), IMSS, Guadalajara, Jalisco, México
³Universidad Xochicalco, Campus Ensenada. Ensenada, Baja California, México
⁴Hospital Regional Licenciado Adolfo López Mateos. Ciudad de México, México.

ABSTRACT
Acne is an inflammatory disease that usually affects the pilosebaceous unit. It is a very common disease worldwide and its onset during puberty is common. Multiple studies have shown that up to 95% of adolescents will be affected to some degree during their lifetime, being the female sex the most affected. It is frequently associated with monogenic diseases such as Apert syndrome; comedonal nevus; Frank-ter Haar syndrome, among others.

The pathogenesis is multifactorial, however, it has been demonstrated that there are four interrelated factors, being these the increase of sebum production, hyperkeratinization of the follicular infundibulum, inflammation and microbial infection. Some genes frequently involved in affected patients are SELL, DBB2 and TP53, whose function is the regulation of hemostasis and cutaneous inflammation; the regulation of apoptosis of damaged DNA and the formation of scars associated with severe acne, respectively. It is common to observe comedones, pustules, papules and cysts as characteristic lesions, face and thorax are the most frequent location. It has been shown that the incidence decreases between the fourth and fifth decades of life, also, generally in affected individuals the lesions resolve spontaneously leaving scars in severe cases.

INTRODUCTION
Acne is an obstructive condition that usually complicates and inflames the pilosebaceous unit. It is most frequently observed on the face and thorax and affects only human beings at some stage of their lives (1).

Acne as a chronic inflammatory skin disease is characterized by the presence of comedones, pustules, papules, nodules and cysts (2).

Incidence is high, with multiple cross-sectional cohort studies indicating that up to 95% of adolescents are affected to some degree (10). The incidence rate decreases until the fourth or fifth decades of life (2).

Most affected individuals are in the mild to moderate group (10).

The onset of acne during puberty is common; persistence of the disease into early adulthood and a strong link to family history, suggesting a genetic component (4).

Acne usually affects the pilosebaceous unit. The pathogenesis is multifactorial, however, there are four interrelated factors: increased sebum production, hyperkeratinization of the follicular infundibulum, inflammation and microbial infection (Cutibacterium acnes) (2).

Several studies have revealed the association between some biological pathways with overlapping functions consistent with what is known about acne pathogenesis, such as androgen metabolism, inflammation, stem cell fate and remodeling tissues (7).
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Cohort studies of patients diagnosed with acne and apparently unaffected patients have identified mutations in some nucleotide polymorphisms associated with pathogenesis (10). There is a relationship between a wide variability of genes and the appearance of acne, being very frequent mutations in DDB2 genes, related to the regulation of androgen metabolism and SELL, involved in inflammation, wound healing and scar formation through leukocytes (2,3).

Some monogenic diseases are related as a cause of acne, including Apert syndrome, Comedonal nevus, Frank-ter Haar syndrome, Winchester syndrome and retinal dystrophy (4).

There are some endocrine syndromes that cause phenotypes similar to acne, among them we find polycystic ovary syndrome, congenital adrenal hyperplasia and insulin resistance syndrome (2,4).

This research was carried out with the aim of determining the association of genetic factors in the appearance of acne vulgaris and the subsequent development of severe acne due to the latter entity.

THEORETICAL FRAMEWORK

Sensing the incredible variation that existed around cases of acne in the 19th century, dermatologists Viel and Wolf began to hypothesize that a genetic factor could be the answer. However, it wasn’t until the 20th century that a German dermatologist, Dr. Hermann Werner Siemens, began research into the role of genes in various dermatological diseases, and among them was acne.

Later, due to the passing of the Second World War, medicine, like other sciences, began to become more and more relevant. At this point, Dr. Hecht published the first specific study on acne and its heritability, taking as a sample population his patients, their relatives, and even friends or acquaintances with whom they maintained a close relationship, this was through questionnaires. Surprisingly, the research yielded novel results, which could demonstrate the possibility of predicting whether a child would be affected by severe acne as an adolescent, this possibility lay in how much the child physically resembled any of his relatives, so the doctor observed that if this resembled a relative who had or still had acne, the child also developed the pathology.

These relevant data were the guideline for the beginning of the still ongoing search for the genetic factors involved, and currently most of these have been found to be related to the innate immune system and hormone metabolism.

ACNE

Acne is defined as a “chronic inflammation of the pilosebaceous unit caused by sebum retention” (1). It appears more frequently during puberty, especially in people with seborrhoeic skin and in 99% of cases it appears on the face. It tends to disappear after the age of 20-25 years and although males are more likely to suffer from more severe and prolonged symptoms, females are above them in prevalence at younger ages (8-12 years), which could be justified by the onset of puberty that occurs first in them.

The lesions that characterize acne are: comedones, papules and pustules, although there may also be abscesses, cysts and scars. These lesions can be complicated by atrophic or hypertrophic scars. Acne can develop into refractory cysts, nodules and subcutaneous fistulas resistant to treatment.

Acne most commonly appears on the face, neck, chest and upper back, where sebaceous follicles predominate. In addition to acne vulgaris, related disorders include follicular occlusive diseases such as acne conglobata, perifolliculitis capitis, and hidradenitis suppurativa.(13)

The type of inheritance is autosomal dominant. It is believed to have a polygenic basis, both familial and epidemiological data determine its etiopathogenesis. The most important factors for its development are: abnormal follicular keratinization, increased sebaceous secretion, bacterial colonization and local inflammation (12).

HERITABILITY OF ACNE

Studies of twins showed that 47% of twins with acne had a family history of acne and the risk of acne increases even more if the relative is a first-degree relative (3).

In Croatia, research was conducted to identify the correlation between family history and age of acne in relation to sex and type of acne and found the following: among patients with a history of family history, 37% were male and 63% were female. Seventy-seven percent of the men had severe acne and the most common locations were the face and trunk. In addition, it was suggested that it may be linked to the X chromosome since the most important family member to increase the risk of having severe to moderate acne is the mother (4).

In a study conducted in Ardabil, Iran(11), it was shown that both parents of the girls and adolescents studied suffered from acne vulgaris in 38.2% of the group with mild acne. This increased to 41% of the parents in the moderate acne group, and reached 50% in the parents of patients with severe acne.

GENES AND LOCI INVOLVED IN ACNE

In 2014 a series of studies were conducted where it was shown that loci 1q24.2 and 11p11.2 contain genes related to androgen metabolism, inflammation, scar formation, L-selectin and DDB2. SELL, DBB2 and TP53 play an important role in inflammation and scar formation associated with severe acne. Selectins (SELL, SELP, SELE) regulate skin homeostasis and inflammation, facilitating leukocyte migration to secondary lymphoid organs and sites of inflammation; they also accumulate leukocytes at sites of inflammation. DDB2 is responsible for inducing or inhibiting apoptosis of damaged DNA and interacts with androgen receptors and TP53 is essential for ectoderm development, maintenance of basal
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cells and terminal differentiation of the stratified epithelium (3).

There are 3 loci involved in severe acne: 11q13.1, 5q11.2 and 1q41; these are related to the genes TNFβ, OVOL1, FST and TGFβ2. TNFβ inhibits keratinocyte hyperproliferation, decreases sebaceous-producing glands, and modulates innate immune responses caused by P. acnes. OVOL1 is expressed in hair follicles and interfollicular epidermis, it also regulates keratinocyte growth and FST regulates the TGFβ superfamily (2).

The MYC proto-oncogene has many functions, including regulating androgenic effect and AR mRNA expression in prostate. This is why patients with a history of severe acne during adolescence have a 17% higher risk of breast cancer and a 70% higher risk of prostate cancer (3).

TNF-α has a proinflammatory effect on acne lesions and is associated with acne vulgaris. P. acnes causes monocytes to secrete proinflammatory cytokines: TNF-α, IL-1β, IL-8. TLR2 polymorphisms cause inflammation and acne. Uplifting IL1A and IL6 are highly implicated in the initial development of lesions, mainly comedogenic lesions, as a result of hyperproliferation and abnormal differentiation in sebaceous glands (3).

CYP1A1, CYP17A1 and CYP21A2 are involved in severe acne as they influence the efficacy of retinoids and hyperandrogenism, which increases sebum production and follicular keratosis (3).

Three loci have also been identified in the genome that harbor alleles that are associated with acne in the European population and two in the Chinese population. These loci have provided information on the biological mechanisms related to the pathogenesis of the disease, including the important role of some components of the TGF β pathway, as well as loci that increase susceptibility to severe acne have been identified by studying the genetic variation in 15 genomic loci that contribute to the risk of disease, the associated alleles in these indicate that the contribution to susceptibility to acne may be mediated by variation in the structure and maintenance of the pilosebaceous unit in the skin.

WNT10A encodes a member of the Wnt family of secreted signaling proteins that contribute to the regulation of cell fate and patterning. Wnt-10a itself is strongly expressed in the dermal papilla within the pilosebaceous unit during the anagen phase of hair growth and is expressed in the dermal condensate and adjacent follicular epithelium. On the other hand, refinement of the phenotypic effects of the p.F228I allele revealed that both dry skin and sparse hair are recurrently observed in homozygous individuals, but also often in heterozygous carriers.

Cutibacterium acnes contributes to the inflammatory nature of acne by inducing monocytes to secrete proinflammatory cytokines. Human β-defensins are found primarily in epithelial cells and at numerous sites throughout the body DEFB1 generally transcribes them at a low level in epithelial cells. However, this transcription is induced by a variety of factors, including proinflammatory cytokines and bacterial lipopolysaccharides. The DEFB1 gene is one of the major antimicrobial peptides that play a central role in the pathogenesis of acne. A study included 104 patients with acne vulgaris and 126 healthy participants to analyze the association between acne vulgaris and polymorphisms in the DEFB1 gene G-52A, C-44 G and G-20A, then analyzed the relationship between the different genotypes and susceptibility to acne vulgaris. The positive regulation of DEFB1 in acne vulgaris lesions suggested that DEFB1 may be involved in the pathogenesis of acne vulgaris by protecting the pilosebaceous unit from microbial invasion and its genetic variation results in the altered expression of the peptide may influence susceptibility to inflammation. There are three respective polymorphic gene types of DEFB1 G-52A, C-44G and G-20A. The allelic variant could influence the actions of DEFB1, which may be closely related to the occurrence of acne. The -44G or -20A allele was low expression in acne vulgaris, which has already been shown to correlate with low risk of acne vulgaris, here we hypothesize that the DEFB1 -44G or G-20A allele is associated with increased constitutive expression of DEFB1 mRNA, increased antimicrobial activity in acne vulgaris and increased reporter protein expression in transfected cells. Based on the test results, effective treatments can be employed in the early stage of acne to avoid damaging the physical appearance of patients or reduce the possibility of acne scarring by creating a clinical formulation of personalized treatment programs and the development of defensin-related drugs.

DISCUSSION

Acne is a dermatological pathology of high incidence, predominantly in young adults and adolescents, is described as chronic inflammation of the pilosebaceous unit produced by sebum retention. This disease disappears between the ages of 20-25 years, it appears in both sexes, although in men it is usually more severe and prolonged. The most affected areas are: face, back and thorax. The lesions that characterize acne are: comedones, papules and pustules; there may also be abscesses, cysts and scars. It is considered a disease with genetic predisposition, with autosomal dominant inheritance. And the pathogenic factors of acne vulgaris are: local inflammation, abnormal follicular keratinization, bacterial colonization and sebum production.

It is understood that the genetic relationship that exists for the development of acne vulgaris, are, the alteration of transcription genes of antimicrobial peptides, hyperreactivity of pro-inflammatory cytokines present in the dermis by error in transcription genes, chromosomal alteration of genetic congenital diseases that generate acne vulgaris as a clinical picture, among other things. This is because they are involved in initiating the pathological factors of acne vulgaris. The
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Colonization of pathogens by defective antimicrobial peptides. Pro-inflammatory cytokines caused damage within the pilosebaceous unit by their defective regulation and activity in the same way.

Currently, it has been demonstrated that with the genetic information within our DNA, in addition to determining whether we are carriers of developing a disease described as "very annoying", such as acne, at an age as susceptible as adolescence, we can also know if it will be a severe case. The loci 1q13.1, 5q11.2 and 1q41 have been reflected in severe cases of acne, these are related to the genes TNFβ, OVOL1, FST and TGFβ2, which are involved in the process of inflammation, differentiation of cells (keratinocytes) and tissue scarring and hormonal metabolism (androgens). The loci or locus are the fixed position within a chromosome where a gene is located, the presence of these indicates that these genes have altered functions.

CYP1A1, CYP17A1 and CYP21A2, which are genes encoding cholesterol, steroid and lipid metabolism enzymes, are involved in acne as they influence the efficacy of retinoids, cause hyperandrogenism, which increases sebum production and follicular keratosis, predisposing factors of acne.

These are just a small sample of all the genes that are involved in acne, as seen in the development of the theoretical framework.

What we must emphasize from this research, is that we must stop stigmatizing and generalizing that patients suffering from acne, are people with bad eating habits, poor hygiene, low socioeconomic status among other myths that are behind this pathology. It should be recognized that there is a large percentage of heritability directly proportional to the parents, as with the race to which each patient belongs. It is clarified that if you have a genetic predisposition the sum of bad habits, exacerbates the picture, but from the beginning make it clear that not all patients who suffer from severe acne pictures have them, this is mentioned because patients may become distressed with themselves, develop low self-esteem, limit certain things in your life, for all the "myths" behind acne or even develop exaggerated or obsessive habits of dermal cleansing, which come to hurt your skin, without knowing that the etiologic and pathogenesis of acne is systemic and genetic.

We must also comment on the importance of taking into account the presence of acne in patients or as a history of importance, since the development of this dermal pathology may be due to other diseases, as mentioned above, some genes found in patients with acne are associated with tumor development, alteration in tumor suppressor genes such as the famous TP53, which is the main watchman of our genome. So it should be taken into account in patients with a history of severe acne with possible carcinogenic activity (breast cancer, prostate, colon), by alterations in the metabolism of hormones and cholesterol. And to take acne into account, to associate it as part of the clinical picture of different pathologies and not only to put it aside. Beginnings of polycystic ovary syndrome, cushing's syndrome, endometriosis, even genetic diseases such as Ehlers Danlos, can generate the presence of acne within their clinical picture. For all this is that acne should be treated as a systemic disease and not localized, and if necessary be handled by several specialists, to find its cause. Also limit the excessive use of cosmetological or commercial treatments that only damage the superficial layers of the skin. Acne should be treated by medical specialists.

CONCLUSIONS

The development of this research reflects the different genes involved in the pathology of acne. The genetic relationship behind acne and the different types of clinical pictures it can generate is immense and has not yet been fully discovered. However, current discoveries about our human genome indicate that acne is a systematic alteration of the autoinflammatory type. We can call it multifactorial at the genetic level, in a colloquial way, because there are many types of combinations of alterations of genetic information that can produce acne. Depending on the pathogenic factors of acne we could classify the genetic alterations that can produce it.

With the knowledge of genetics focused on clinical medicine and the pathophysiology of acne, both general practitioners and specialists should take it into account for the comprehensive management of their patients and refer to interconsultations with other colleagues if necessary.

With this we can also disprove many myths that exist about acne and stop discriminating or making less to patients who suffer from it and see it for what it really is, a disease that should be treated objectively and comprehensively.

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