The Acne Genes

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Core Messages

- As one of the most common and complex skin diseases, the inheritance of acne is unlikely to follow simple Mendelian models but rather the polygenic inheritance with phenotypes complicated by a great deal of interaction between genes and the environment especially the sex hormones.
- So far, no commanding genes have been identified in acne development. Candidate genes may include those molecules regulating keratinocyte differentiation in the hair infundibulum (retinoid metabolism and epidermal growth factor), sebocyte proliferation and differentiation (steroidogenesis, insulin signaling, peroxisome proliferator-activated receptor), and inflammation induced by *Propionibacterium acnes* (Toll-like receptors).
- Syndromes accompanied by acne may also point the way to the future research, such as polycystic ovarian syndrome, PAPA syndrome, and Apert syndrome.

47.1 Introduction

Acne is one of the most common skin diseases. Many epidemiologic studies and twin studies have provided substantial evidence about the

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genetic influence in the development of acne [1–5], at least in certain stages of acne such as neonatal acne, teenage acne [6], adult persistent acne, or in special forms of acne such as acne comedonica, acne inversa [7, 8], acne fulminans [9], or in acne severity [10] and therapeutic resistance [11]. Acne is very likely mediated by polygenic inheritance or multifactorial inheritance attributed to the interplay between multiple genes and the environment, especially the sex hormones. It is unknown if each candidate "acne gene" contributes equally or additively to the disease phenotype, or whether there exists a master gene that presides or leads the disease development. All the candidate genes may influence each other and perpetuate the disease process. The problem in many of the existing epidemiologic studies may include (1) a small sample size with single or few families examined without matched control; (2) lack of standardization in the disease definition or severity classification; (3) variability of age onset, duration, course, and psychosocial influence.

47.1.1 Acne Genes, Acne Pathogenesis and Acne-Associated Syndromes

Another approach to identify the "acne genes" is to look into the pathogenic factors contributing to acne development, including (1) hyperkeratosis of hair follicles, (2) sebum overproduction, (3) inflammation, and (4) *Propionibacterium acnes*.

Studies on "complex syndromes" manifesting with acne may also shed light on the genetic influences of acne formation. However, not much has been performed in screening the potential genes. There is so far no gene being identified to cause or contribute substantially to acne development. The following discussion proceeds on a logical way, based mostly on experimental research and clinical observation.

1. Hyperkeratosis of the hair infra-infundibulum:
   One of the earliest lesions in acne development is the microcomedone, the histology of which shows proliferation/retention hyperkeratosis in the infra-infundibulum part and sebaceous duct of sebaceous hair follicles [12]. It is conceivable that the molecules influencing epidermal proliferation and differentiation will play a role in acne formation, such as retinoic acid and epidermal growth factors. Polymorphism in the human cytochrome P-450 1A1 gene (CYP1A1), one of the most active isozymes involved in interconversion of endogenous retinoids and their natural metabolites, has been demonstrated to be associated with acne development [13]. On the other hand, CYP26A1, one of the key enzymes in inactivation of all-trans-retinoic acid, was also found to have a strong constitutive expression restricted to basal epidermal keratinocytes, eccrine sweat glands, and sebaceous glands [14], which merits further examination on its function in comedogenesis. In vitro studies and newly clinical experience in oncology lend support to the role of epidermal growth factors and their receptors in acne pathogenesis [15, 16]. Controversial results exist in terms of the effect of insulin-like growth factor [17, 18]. Apert syndrome or acrocephalosyndactyly is characterized by early development of severe inflammatory acne on the face and trunk, with extension to the upper arms and forearms [19]. Mutation in fibroblast growth factor receptor (FGFR)-2 was found to be a significant causal factor [20], and mice lacking epidermal Fgfr2b displayed striking abnormalities in hair and sebaceous gland development [21]. It would be interesting to see whether gene polymorphisms of these molecules also occur in acne patients.
2. Sebum overproduction:
   Twin studies have shown that sebum excretion rate measures alike in identical twins but significantly different in nonidentical twins [22, 23]. As sebum production is strongly influenced by androgens, potential genes regulating androgenesis and androgen action have been focus of interest. The sex-determining genes SRY, SOX-9, WT-1, SF-1, and DAX-1 were found to play a pivotal role in regulation of steroidogenesis, where SRY and SOX-9 seem to potentiate steroidogenesis, but DAX-1 antagonizes the androgen function [24]. Our previous work proved the cutaneous expression of these genes except SF-1 while the protein levels of

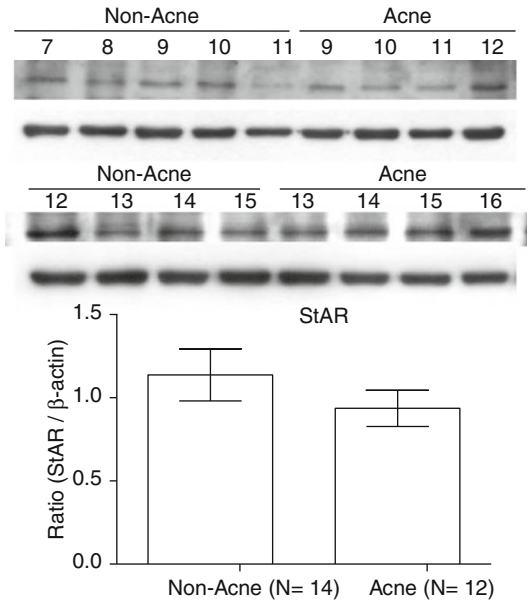

Fig. 47.1 Western blot study of the cutaneous expression of DAX-1 protein. Significantly higher expression could be seen in the facial skin from 15 non-acne (mean age 45 years, range 19–58) as compared to 16 acne-prone (mean age 37 years, range 14–58) male patients ($p<0.005$, Wilcoxon rank-sum test). Primary antibody used was rabbit antihuman DAX-1 polyclonal IgG (Santa Cruz, CA, USA) at a concentration of 1:250 [24]

DAX-1, SRY, and WT-1 were significantly higher in the bald scalp of men with androgenetic alopecia [25]. As compared to 16 acne-prone patients, the facial skin from 15 patients without acne had a higher expression of DAX-1 protein (Fig. 47.1). On the other hand, there was no difference in the protein expression of steroidogenic acute regulatory protein (StAR) and type I 3β-hydroxysteroid dehydrogenase in patients with or without acne (Fig. 47.2), although their mRNA amount was found to be higher in the bald scalp of men with androgenetic alopecia [26]. The available data failed to establish the association between androgenetic alopecia and the genes encoding steroid sulfatase (STS) and the two 5α-reductase isoenzymes (SRD5A1 versus SRD5A2) [27–29], meanwhile little is known about their relation to acne occurrence. On the other hand, people with a shorter CAG repeats in the androgen receptor gene were found to have an increased androgen sensitivity and thus higher risk for development of precocious pubarche and ovarian hyperandrogenism [30].

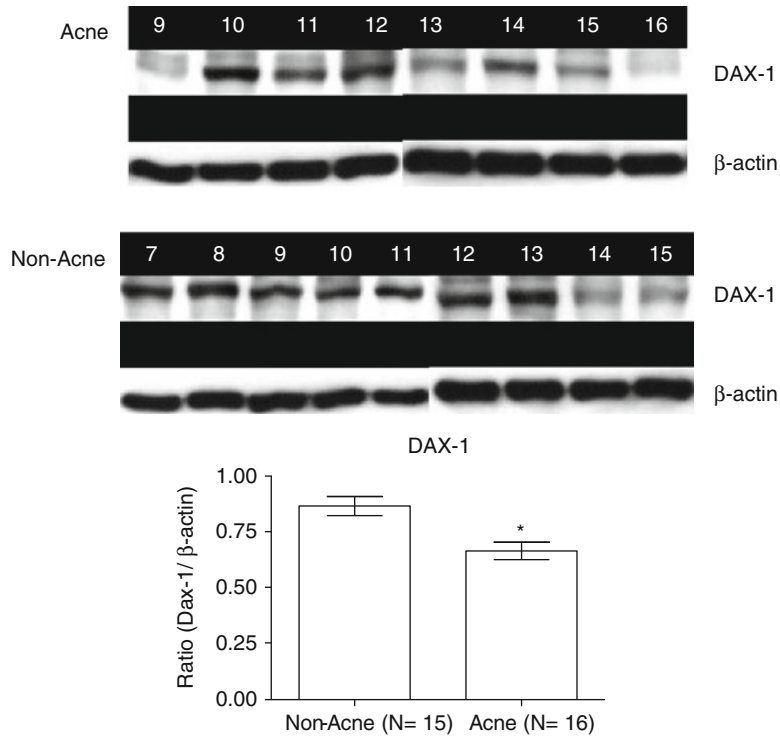

Fig. 47.2 Western blot study of the cutaneous expression of steroidogenic acuter regulatory protein (StAR). No difference of protein expression could be detected in the facial skin from 14 non-acne (mean age 36years, average 17–55) as compared to 12 acne-prone (mean age 29 years, average 18–55) male patients ($p=0.320$, Wilcoxon rank-sum test). Primary antibody used was rabbit anti-human StAR polyclonal IgG (Santa Cruz, CA, USA) at a concentration of 1:100

Some syndromes and their candidate genes may also pose a research target:

(a) Polycystic ovarian syndrome: under investigation are genes related to steroidogenesis (e.g., CYP11A), insulin resistance (e.g., insulin gene VNTR; variable number of tandem repeats), gonadotropin function, obesity, sex hormone binding genes, fetal programming, and X-chromosome inactivation [31, 32];

(b) Nonclassical congenital adrenal hyperplasia and steroid 21-hydroxylase deficiency: The functional significance of the mutations of CYP21A2 in acne pathogenesis is ambiguous [33–35];

(c) HAIR-AN syndrome (hyperandrogenism, insulin resistance, acanthosis nigricans): The possible genes remain elusive and mutations in the tyrosine kinase domain of the insulin receptor gene was found to be rather irrelevant [36]. In addition, although the involvement of cortcotropin releasing hormone/alpha-melanocyte-stimulating hormone/melanocortin receptor system in sebocyte biology was implied by many in vitro and in vivo studies, more concrete evidence is needed to confirm its clinical significance [37, 38].

3. Inflammation:
PAPA syndrome (pyogenic arthritis, pyoderma gangrenosum, and cystic acne), a multisystemic autoinflammatory syndrome, has been described in a three-generation kindred with autosomal-dominant transmission. The culprit gene was mapped to chromosome 15q [39], where mutations in proline serine threonine phosphatase-interacting protein (PSTPIP), or CD2-binding protein 1 (CD2BP1), a tyrosine-phosphorylated protein involved in cytoskeletal organization, were suspected to be a causative element [40]. Familial cases of SAPHO syndrome with synovitis, acne, pustulosis, hyperostosis, and osteitis have been published [41], but the corresponding gene is not yet identified.

4. *Propionibacterium acnes*:
Toll-like receptors (TLR) have been recognized to be fundamental molecules in mediating innate immunity [42]. In vivo expression of TLR-2 and TLR-4 was enhanced in the epidermis of acne lesions; moreover, in vitro incubation of the human keratinocytes with bacterial fractions induced a rapid increased expression of TLR-2 and TLR-4 as well as matrix metallo-proteinase 9 (MMP-9) [43], indicating that *Propionibacterium acnes* can trigger inflammatory cytokine responses in acne by activation of TLR2 [44]. However, gene polymorphisms in TLR2 and TLR4 were not associated with acne vulgaris [45].

Many molecules affect not only one pathogenic pathway; androgens and cytokines may also act upon the infundibular hyper-/dyskeratosis [15, 46]. The peroxisome proliferator-activated receptor (PPAR) family can regulate the sebocyte differentiation [47, 48] as well as keratinocyte proliferation/differentiation [49] and even inflammation [50].

In the future, strict and uniform diagnostic criteria, improved application of the candidate gene approach using haplotype-based analyses, replication of positive results in large cohorts, more family-based studies, gene selection from expression studies, and whole-genome approaches will enhance identification and determination of acne genes [51].

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