What does acne genetics teach us about disease pathogenesis?

Common, J. E. A.; Barker, J. N.; van Steensel, Maurice A. M.

2019

Common, J. E. A., Barker, J. N., & Steensel, M. A. M. (2019). What does acne genetics teach us about disease pathogenesis? *British Journal of Dermatology*, 181(4), 665–676.
doi:10.1111/bjd.17721

<https://hdl.handle.net/10356/144457>

<https://doi.org/10.1111/bjd.17721>

This is the accepted version of the following article: Common, J. E. A., Barker, J. N., & Steensel, M. A. M. (2019). What does acne genetics teach us about disease pathogenesis? *British Journal of Dermatology*, 181(4), 665–676., which has been published in final form at doi:10.1111/bjd.17721. This article may be used for non-commercial purposes in accordance with the Wiley Self-Archiving Policy [<https://authorservices.wiley.com/authorresources/Journal-Authors/licensing/self-archiving.html>].

Downloaded on 26 Apr 2023 17:52:52 SGT

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

DRO 30.1.19
Scholarly review 19/72R1
Short title: Genetics of acne vulgaris

What does acne genetics teach us about disease pathogenesis?

J.E. Common,¹ J.N. Barker² and M. van Steensel^{1,3}

¹Skin Research Institute of Singapore, Agency for Science, Technology and Research (A*STAR), Singapore

²St John’s Institute of Dermatology, Faculty of Life Sciences and Medicine, King’s College London, London, U.K.

³LKC Medicine, NTU, Clinical Sciences Building, Novena, Singapore

Correspondence: John Common.
E-mail: john.common@sris.a-star.edu.sg

<https://orcid.org/0000-0002-3280-7365> (J.E. Common)
<https://orcid.org/0000-0002-9030-183X> (J.N. Barker)
<https://orcid.org/0000-0002-7507-2442> (M. van Steensel; URLs checked and working)

Accepted for publication
28 January 2019

Funding sources

J.E.C. is funded by the Biomedical Research Council (BMRC) A*STAR, BMRC-A*STAR-EDB IAF-PP for the Skin Research Institute of Singapore (H17/01/a0/004) and the Asian Skin Microbiome Programme (H18/01/a0/016). M.vS. is funded by the Biomedical Research Council (BMRC) A*STAR, BMRC-A*STAR-EDB IAF-PP for the Skin Research Institute of Singapore (H17/01/a0/004) and the Acne and Sebaceous Gland Program (H17/H17/01/a0/008). J.N.B. acknowledges support from the NIHR Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London.

Conflicts of interest

None to declare.

Summary

Background Acne vulgaris is a highly prevalent inflammatory skin disorder with a complex pathogenesis, characterized by comedones, papules, pustules and nodules. Familial preponderance clearly indicates a genetic basis for acne vulgaris, but until recently solid genetic associations were lacking.

Results The advent of high-resolution genotyping array technologies has allowed for large-scale studies with both family-based and cross-sectional designs. These studies have revealed genetic loci encompassing genes that could be active in biological pathways and processes underlying acne vulgaris. However, specific functional consequences of those variants remain elusive. In parallel, investigations into rare disorders and syndromes that incorporate features of acne or acne-like lesions have recently accelerated our understanding of disease pathogenesis. The genes revealed by these rare disorders highlight mechanisms cardinal for pilosebaceous biology and therefore anchor our insights from genetic association studies for acne vulgaris.

Conclusions The next phase of research will require more in-depth mechanistic investigations of loci and genes implicated in acne phenotypes to define the key molecular players driving the disorder. Concurrently, new treatments for acne vulgaris could be developed by dissecting the candidate molecular pathways to identify druggable targets.

What's already known about this topic?

- Acne vulgaris is a highly heritable trait.
- Genetic loci are associated with multiple biological processes and systems.
- Monogenic disorders with acne and acne-like manifestations identify sebaceous gland development and tissue remodelling as key mechanisms in acne pathogenesis.

What does this study add?

- We comprehensively review the available literature to catalogue the human genetic variation associated with acne vulgaris.
- We contextualize the genetic data with underlying disease mechanisms for better understanding of acne pathogenesis.

Acne vulgaris is a chronic inflammatory skin disorder, characterized by comedones, pustules and papules, nodules and cysts.^{1,2} The appearance of these lesions in highly visible regions of the skin during adolescence is associated with a severe psychological, social and, eventually, economic impact on the affected individuals. Effects have been reported to include low self-esteem, elevated rates of unemployment and depression with suicidal ideation.³⁻⁵ Irreversible facial scarring occurs in up to 20% of teenagers, with acne vulgaris resulting in a lasting, significant negative impact on emotional and mental health.^{1,6}

The incidence of acne vulgaris is high, with cross-sectional studies indicating that as many as 95% of adolescents are affected to some degree, without a significant sex bias in the teenage years.⁶⁻⁹ Most affected individuals fall in the mild-to-moderate bracket, with approximately 10% of adolescents affected with severe disease.^{6,8} Disease usually regresses by the age of 25 years, but the incidence of adult acne is significant. It is reported that at least 12% of women over 25 years of age have acne.⁹ The incidence in men of a similar age is reported as lower. The difference might, in part, be due to ascertainment bias.^{8,10} Unsurprisingly with such high prevalence rates, a recent global disease burden analysis indicated that acne vulgaris is the eighth most prevalent disease worldwide.^{10,11} Epidemiologically, there are only minor differences in the incidence, severity and types of acne in different ethnicities; however, the genetic associations appear divergent.¹²⁻¹⁴ Nonetheless, what has emerged as a common

theme among all studies is the onset of acne around puberty, the persistence of disease into early adulthood and a strong link to family history, suggestive of a prominent genetic component.

Onset of acne vulgaris during puberty coincides with androgen-induced sebaceous gland enlargement and subsequent increased sebum production, driving major changes in skin physiology during pathogenesis (reviewed by Clayton *et al.* in this issue of the *BJD*).^{15,16} As well as alterations to sebum production, pathogenic mechanisms that have been proposed include altered keratinization in the infundibulum, microbial infection and chronic inflammation as an end result.^{16–19} More recent insights from genetics implicate abnormalities in differentiation of sebaceous progenitor cells and tissue remodelling in the pathogenesis of the acne vulgaris phenotype.

In this review, we focus on genetic susceptibility loci for acne vulgaris, as well as Mendelian disorders associated with acne or acne-like phenotypes that provide insights into the biological basis of the disease. We also describe how pathways and mechanisms that have been identified from genetic studies could provide new targets for the development of novel treatments.

Family and twin-based studies

It has long been recognized from family and twin studies that acne vulgaris has a strong hereditary component.^{11,20–22} Family-based case–control studies have highlighted that affected first-degree relatives are a major risk factor for developing the disorder.^{23–25} Cross-sectional prevalence studies also indicate a similar genetic contribution, with family history strongly correlating with disease risk and severity.^{7,24,26}

Observations of familial disease clustering and twin studies show clear heritability, with estimates upwards of 78% in multiple large studies encompassing numerous ethnicities.^{24,26–28} As expected with strong heritability, concordance between monozygotic twins compared with dizygotic twins was higher for both acne occurrence and severity.^{26,29–31} The statistics for heritability are striking and highlight acne vulgaris as a genetically determined complex trait.

Genome-wide association studies

Genome-wide arrays, genomic genotyping technologies and computing power have now made it feasible, and affordable, to approach genetic associations with large case–control

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

study designs. Five genome-wide association studies (GWASs) for acne vulgaris have been completed in four distinct geographical locations covering North America, Northern Europe, China and Australia.^{12,14,29,32,33} Four studies recruited white patients and the fifth was performed with a cohort of Han Chinese patients. Each GWAS identified previously unreported susceptibility loci that did not overlap in genetic location, suggesting genetic heterogeneity between, and within, ethnicities, as well as underscoring the importance of cohort recruitment criteria and study design. Crucially, the follow-up study from the U.K. group replicated their originally identified genetic loci with the same study design (Table S1; see Supporting Information).¹⁴

Irrespective of design, these studies have revealed associations in biological pathways with overlapping functions concordant with what is known about acne pathogenesis, such as androgen metabolism, inflammation, stem cell fate and tissue remodelling. Here we summarize the main findings from the primary literature and discuss their implications.

The Han Chinese GWAS was conducted on a cohort of 1056 cases of severe acne vulgaris, compared against 1056 unaffected controls for the primary-stage identification of lead single-nucleotide polymorphisms (SNPs).¹² The authors performed a replication study where three SNPs were validated with significant genome-wide associations. These SNPs identified two significant susceptibility loci at 1q24.2 (rs7531806 and rs1060573) and one at 11p11.2 (rs7531806), containing the genes *DDB2* (DNA-binding protein 2) and *SELL* (L-selectin), respectively. In the context of acne vulgaris pathogenesis, *DDB2* has been implicated in androgen metabolism, whereas *SELL* is proposed to be involved in inflammation, wound healing and scar formation via leucocytes (Table S1; see Supporting Information).^{12,34,35}

Gene–gene interaction analysis performed with data generated by He *et al.*¹² identified nine additional genes significantly associated with acne vulgaris. Interestingly, this study highlighted an association with *TP63*, a critical regulator of epithelial stem cell fate, proliferation and stratification.^{36,37}

A second GWAS was conducted in the U.K. soon after the Han Chinese report. It identified three additional genetic loci associated with severe (hospital-based collection) acne vulgaris at chromosomal locations 11q13.1, 5q11.2 and 1q41.³² All three genetic loci contained genes from the transforming growth factor receptor (TGF)- β signalling pathway that were in linkage disequilibrium with lead SNPs (Table S1; see Supporting Information). The first was *OVOL1*, a zinc-finger transcription factor involved in hair formation and a downstream target of TGF- β . The second, *FST*, binds activin, to regulate activity of the TGF- β pathway, and

provides a putative hormonal link. The third, *TGFB2*, has myriad functions, but is strongly implicated in wound healing, scarring and tissue regeneration.³² The apparent convergence on the TGF- β pathway indicates a link to tissue remodeling.³² Intriguingly, a number of genes associated with monogenic disorders that cause acne also have major roles in tissue remodelling, as discussed later in this review (Tables 1 and 2).

The U.K. group followed up their initial findings with a larger independent GWAS of 3823 cases of severe acne compared with 16 144 unselected population controls.¹⁴ This study was able to replicate the three genetic loci identified in their original GWAS,³² but not the ones previously identified in the Han Chinese individuals,¹² further suggesting ethnicity differences in acne genetics. Additionally, a meta-GWAS was conducted using the original U.K. GWAS genotypes together with the data from the second study. A combined total of 5602 cases of severe acne and 21 120 population controls were analysed, resulting in genome-wide significance at 15 genetic loci, of which 12 had not been previously reported (Table S1; see Supporting Information).¹⁴ The candidate genes in these loci implicated mediators of hair follicle development and morphogenesis as risk factors for acne. Specifically, *WNT10A* encodes a WNT family member that contributes to cell fate and patterning. Sequence variants in *WNT10A* have been previously associated with ectodermal dysplasias (OMIM 257980, 224750 and 150400). *LGR6*, a WNT signalling pathway mediator, was also associated with acne in this GWAS. *LGR6* marks stem cell populations within the pilosebaceous unit and is likely to have a role in the maintenance and function of the sebaceous gland stem cells.^{38,39} *SEMA4B* has been proposed to be a regulator of basophil-mediated immune responses, with deletion in mice resulting in an increase in IgE.⁴⁰ The causal variant identified in the acne GWAS study is located in intron 1 of *SEMA4B*, within a p63 transcription factor binding site, and disruption to this motif was proposed as a potential molecular event for acne risk. Additional associated genes were *LAMC2*, a major component of the basement membrane; *FGF2* (encoding fibroblast growth factor 2), which has a role in wound healing and scarring; and *SPECCIL*, a cytoskeleton cross-linking protein with a role in cell adhesion and migration.

Bioinformatics analysis was further employed to look for enrichment of genes with related biological function in the 15 statistically significant loci, and in 54 with a less stringent statistical threshold. This associated *BCL11A* at 2p16.1, a transcriptional regulator, and *GLI2* at 2q14.2, a transcription factor mediator of the sonic hedgehog pathway responsible for tissue development, as additional acne risk loci (Table S1; see Supporting Information).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Taking the data together, this study reaffirms the link to tissue remodelling and identifies additional candidate genes in biologically relevant pathways that were not previously implicated by mechanistic studies of acne vulgaris.

A much smaller GWAS with European American individuals compared 81 patients with severe acne vulgaris against 847 controls without a history of the disease. Two SNPs on 8q24 were identified but failed to reach genome-wide significance.³³ *MYC* was the closest gene to the associated SNPs. c-MYC is a proto-oncogene with a major role in sebaceous gland proliferation and differentiation, and stem cell fate decisions.⁴¹ c-MYC acts through leucine-rich repeats and immunoglobulin-like domains 1 (Lrig1) to orchestrate sebaceous gland proliferation and differentiation via a regulatory network that includes p53 and the androgen receptor (Table S1; see Supporting Information).^{41–44} Lrig1 expression labels sebaceous gland stem cells, which are proposed as the sebaceous progenitor population crucial for morphogenesis.⁴⁵

Finally, a large GWAS with 4762 individuals was completed using twins to study acne vulgaris severity.²⁹ The study did not detect any specific genetic loci that were statistically significant in their association with disease severity, although association was suggestive for three loci: rs10515088 locus 5q13.1, rs12738078 locus 1p35.5 and rs117943429 locus 18q21.2.²⁹ Three genes in linkage disequilibrium at these genetic loci, *PTPRU*, *PIK3R1* and *DCC*, are implicated in growth, differentiation and cell adhesion, respectively. Further studies are required to validate these pathways (Table S1; see Supporting Information). As expected for acne vulgaris, heritability was higher in the monozygotic twins than in the dizygotic twins.

GWAS data have thus provided a number of smoking guns pointing at biological pathways that could contribute to disease pathogenesis of acne vulgaris and provide information about potential targets for treatment development. Rational development of targets for acne vulgaris identified through genetic studies can provide new, much needed drug-development strategies. The drawback of the GWAS data is that generally, additional analysis is required to identify functional variants associated with the intriguing genetic loci that have been identified. Additionally, the acne vulgaris SNP-based polymorphic marker studies described rely on the ‘common disease, common variant’ hypothesis to assign associations to specific alleles linked with disease.⁴⁶ As technologies and computing power advance, it will be possible to perform larger exome and whole-genome sequencing studies that will reveal additional rare variants, with functional consequences and high penetrance, contributing to acne vulgaris susceptibility. This rare-variant approach has recently been successfully

employed for other inflammatory skin diseases to reveal additional genetic associations and would likely be a useful strategy for acne vulgaris.^{47,48}

Human monogenic disorders that cause acne

A number of human monogenic disorders and syndromes are associated with (severe) acne. These disorders point to molecular mechanisms underlying the pathogenesis of acne vulgaris and can inform hypotheses on underlying biological processes. Such clinical and genetic insights might result in the development of more targeted treatments for the common acne vulgaris phenotypes that we observe in the clinic.

Apert syndrome (MIM 101200)

Apert syndrome is a rare autosomal dominant disorder first described in 1906. It is characterized by craniosynostosis, facial anomalies and symmetrical syndactyly of the hands and feet.^{49,50} Apert syndrome causes a severe acne phenotype that is indistinguishable from its sporadic counterpart, responding to treatment with retinoids and oral contraceptives.⁵¹ The disorder is caused by gain-of-function mutations in *FGFR2*, which encodes the receptor tyrosine kinase fibroblast growth factor receptor 2.^{52–56} In total 98% of patients carry one of the two predominant mutations in exon 7 of *FGFR2* that were originally identified in 39 unrelated families and subsequently confirmed in a larger cohort of 260 patients.^{50,52,57} The two predominant mutations in exon 7 are in an extracellular linker region between Ig-like domains II and III.⁵⁷ Ig-like domain III is alternatively spliced to form the two reported isoforms: FGFR2IIIb, expressed in epithelial tissue encompassing exon 8, and FGFR2IIIc, the mesenchymal-expressed isoform encoded to include exon 9.^{58,59} The missense mutations in Apert syndrome result in inappropriate receptor activation due to loss of ligand specificity.⁶⁰ Molecular crosstalk with the epidermal growth factor and platelet-derived growth factor signalling pathways has also been reported for mutant *FGFR2*.⁶¹ Mosaicism has been reported with *FGFR2* sequence variants, resulting in a localized form of Apert syndrome, with somatic mutations resulting in clusters of comedones and inflammatory cysts distributed along Blaschko lines.⁵⁴ Somatic *FGFR2* sequence variants in the keratinocytes were sufficient to induce alterations in the pilosebaceous unit, resulting in severe comedonal naevi.⁶² Apert syndrome and its somatic mosaic form highlight the importance of FGFR2 signalling in comedogenesis and in the pathogenesis of acne.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Naevus comedonicus (MIM 617025)

Naevus comedonicus (NC) is another severe localized comedonal naevus disorder, with onset reported soon after birth or before the age of 10 years.⁶³ The linear configuration of NC lesions is suggestive of a mosaic disorder arising from somatic mutations acquired during embryo development. NC is caused by mutations in the serine–threonine protein kinase gene *NEK9* (encoding NIMA-related kinase 9).⁶⁴ Three gain-of-function mutations were identified in three unrelated families with NC. These mutations affect highly conserved residues in the kinase or RCC1 (regulator of chromosome condensation 1) domains, resulting in increased phosphorylation of Thr210, a hallmark of NEK9 activation.⁶⁴ NEK9 is an important regulator of cell-cycle and checkpoint control that depends on kinase activation via the Thr210 phosphorylation site in the activation loop.^{65,66} NEK9 mutations disrupt follicular differentiation, associated with loss of differentiation markers and an expansion of keratin 15-positive cells. These cells expand out of the bulge and into the sub-bulge region of the follicle and the cysts in NC.⁶⁴

Despite the reported role of NEK family members in checkpoint regulation and spindle orientation, the identification of mutations in NC suggests that NEK9 may have additional as yet unreported functions in epithelial stem cell fate decisions and directional cell division.⁶⁴ The mechanism by which NEK9 is involved with cell fate decisions will need further investigation, focusing on the interactions with signalling pathways known to be crucial for epidermal homeostasis and directional cell division.

Frank–ter Haar syndrome (MIM 249420)

Frank–ter Haar syndrome (FTHS) causes a wide range of developmental abnormalities such as brachycephaly, wide fontanel, prominent forehead, hypertelorism, prominent eyes, megalocornea with or without glaucoma, full cheeks and multiple skeletal anomalies, including osteolysis, contractures and short stature.⁶⁷ Adult patients with this syndrome have been characterized as having acne conglobata with hypertrophic scarring and thickened skin.⁶⁸ FTHS is inherited as an autosomal recessive trait and is caused by loss-of-function mutations and deletions in *SH3PXD2B* on chromosome 5q35.1.^{69–72} *SH3PXD2B* codes for TKS4, a tyrosine kinase substrate adaptor protein required for podosome maturation. Invadosomes (the collective term for podosomes and invadopodia) are large actin-rich protein complexes that mediate focal degradation of the extracellular matrix.⁷³ TKS proteins act as scaffolds for interactions between membrane and cellular components in the podosome. Upon phosphorylation by SRC, TKS4 recruits the membrane type-1 matrix metalloproteinase

(MMP14 or MT1-MMP) to the podosome, where it acts to degrade collagen and activate pro-MMP2 (see Winchester syndrome below). In the absence of TSK4, MMP14 is not recruited, inhibiting extracellular matrix (ECM) degradation and attenuating podosome function. This phospho-specific function of TSK4 is not rescued by the paralogue TKS5.⁷⁴

Disruption of TKS4 has been associated with actin remodelling and cell spreading, likely due to an interaction between the TKS4 PX domain and phosphatidylinositol (3,4,5)-trisphosphate,⁷⁵ as well as alterations to epidermal growth factor-dependent epithelial cell migration.⁷⁶ The role of TSK4 in podosome and ECM degradation is suggestive of a function specific to cell migration and tissue remodelling. The FT HS phenotype can be phenocopied with mutant or knockout mouse models.^{69,77}

During puberty, tissue remodelling around the hair follicle and the rapidly expanding sebaceous gland is likely to involve cell migration and ECM digestion, which would require the activity of TKS4 and its multiprotein interactome. This hypothesis is supported by recent observations of disorders with a phenotype similar to FT HS and caused by mutations that affect proteins depending on TKS4.

Winchester syndrome (MIM 277950)

Winchester syndrome (WS) is a rare autosomal recessive disorder that resembles FT HS and is characterized mainly by skeletal dysplasia with progressive joint destruction and osteolysis.^{78–80} We have previously reported that it can cause severe acne with hypertrophic scarring and thickened skin.⁸¹ Mutations in *MMP14* have been associated with WS via one mutation that decreases the membrane localization and another that disrupts the catalytic activity, resulting in impaired pro-MMP2 activation.^{81,82} WS is part of a continuous clinical spectrum together with multicentric osteolysis, nodulosis and arthropathy (MONA) syndrome, Torg syndrome and nodulosis–arthropathy–osteolysis (NAO) syndrome (MIM 259600).⁸¹ Based on the identification of *MMP2* gene mutations, MONA, Torg and NAO syndromes were originally thought to be distinct from WS, but they are now seen as allelic disorders due to overlapping mechanisms of action.^{79,83–85} Disease-causing *MMP14* mutations result in a lack of activated MMP2,^{81,82} explaining the phenotypic continuity and justifying their grouping into one spectrum. Interestingly, genetic variants in *MMP2* have also been reported to be associated with acne vulgaris.⁸⁶

Taken together, FT HS and WS implicate remodelling of the tissue microenvironment in the development of syndromic acne. By way of association these syndromes also highlight the important roles that the podosome-related genes *TSK4*, *MMP14* and *MMP2* play during

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

developmental enlargement of the sebaceous gland. Podosome dysfunction could also be linked to scarring in acne vulgaris. WS and FTTHS are both associated with acne scarring, but also with spontaneous fibrosis, suggesting a common basis for both acne and scars, potentially via mechanisms related to collagen digestion.⁸⁷ The mechanisms governing sebaceous gland enlargement and the role of podosome proteins in acne and scarring are still under investigation. Further in-depth studies that investigate additional podosome molecules will be important for our mechanistic understanding of sebaceous gland formation and disease.

Retinal dystrophy, iris coloboma and comedogenic acne syndrome (MIM 615147)

Retinal dystrophy, iris coloboma and comedogenic acne syndrome is a syndrome with severe comedonal acne.⁸⁸ Mutations have been reported in the *RBP4* gene, encoding retinol-binding protein 4.⁸⁹ *RBP4* loss-of-function mutations result in serum retinol deficiency. The RBP4 protein delivers circulating retinol to tissues, thus defects in or a lack of the protein are thought to result in localized tissue retinol deficiency. In the context of skin and sebaceous gland biology a serum deficiency of retinol would result in a localized defect of vitamin A. Vitamin A has long been known to be important for differentiation, and topical treatment has long been a mainstay of acne therapy.^{90,91} Retinal dystrophy is associated with approximately 150 genes; however, only mutations in *RBP4* are comorbid with comedogenesis, highlighting a mechanistic link between retinol distribution and acne.

Human disorders that cause acne-like phenotypes

There are a number of syndromic disorders with a genetic basis that cause acne-like skin changes and that can inform our understanding of acne vulgaris.⁹² Although these disorders appear with divergent pathogenesis, there are numerous overlapping mechanistic features that provide foundational knowledge for the development of acne.

Hidradenitis suppurativa (MIM 142690)

Hidradenitis suppurativa (HS) is an inflammatory disorder of the apocrine glands that is characterized by abscesses, fistulae, sinuses and scarring in the axillary, inguinal and perianal regions. The disease is also known by the misnomer acne inversa. While HS is distinct from acne vulgaris, with different responses to treatment, its genetic architecture is informative with regards to the pathogenesis of acne vulgaris. HS was first associated to chromosomal

region 1p21.1–1q25.3, and subsequently mutations were identified in multiple genes of the γ -secretase complex in subsets of patients.^{93–95} The genetic association of γ -secretase genes with HS was confirmed with mutations in *PSENEN* (MIM 607632), *PSEN1* (MIM 104311) and *NCSTN* (MIM 605254),^{95–100} making it allelic to Alzheimer disease.¹⁰¹ Reticulate hyperpigmentation similar to that observed in Dowling–Degos disease has also been reported together with HS in patients with *PSENEN* mutations (MIM 613736).^{102–104} Additional gene defects in the Notch signalling pathway could also be important for HS and Dowling–Degos disease, such as the recently reported mutations in *POFUT1* and *POGLUT1*.^{105–109}

Mutations in genes from the γ -secretase complex result in haploinsufficiency, which is predicted to decrease activity of Notch signalling in the skin.¹⁰¹ γ -Secretase is an enzyme complex of four proteins that cleaves the intracellular domain of Notch, allowing translocation to the nucleus and activation of Notch target genes.^{110,111} Functional γ -secretase is crucial for activation of Notch downstream signalling cascades.¹¹² Notch is responsible for a variety of cell fate decisions, and mutations in components of this pathway are known to be responsible for numerous human disorders.^{113,114} The role of Notch in controlling stem cell maintenance and proliferation via mediators such as Lrig1 has wide implications for tissue homeostasis and tissue remodelling during sebaceous gland maturation (reviewed by Clayton *et al.* in this issue of the *BJD*).^{15,42,115} Lrig1 is a direct target of c-MYC, genetically implicated in acne vulgarism and can act in a negative feedback loop to control stem cell progenitors.^{33,44}

Mice with loss-of-function alleles in γ -secretase were reported as having abnormal epidermal differentiation.^{116,117} Gene-targeted γ -secretase mouse models have further shown that loss of Notch signalling causes keratinocytes within the other root sheath of the hair follicle to exhibit epidermal differentiation. The affected hair follicles convert to epidermal cysts that resemble comedones, described as analogous to a human comedonal naevi phenotype.¹¹⁸ The sebaceous glands also fail to form correctly in these mice, as a result of defective Notch signalling presumably impacting on sebaceous gland progenitor cells. In corroboration, compound loss of *Notch1* and *Notch2* in mouse models phenocopies the loss of γ -secretase in the hair follicle and sebaceous gland, implicating Notch1 and Notch2 as the major mediators of γ -secretase function.¹¹⁸ The consequences of γ -secretase, *POFUT1* and *POGLUT1* mutations in human pathology are suggestive of Notch signalling having an important role in apocrine-gland-bearing regions. γ -Secretase and Notch mouse models provide mechanisms for the maintenance of hair follicles and the establishment of the sebaceous gland that lead to the development of epidermal cysts.

Pyrogenic arthritis–pyoderma gangrenosum–acne syndrome (MIM 604416)

Pyrogenic arthritis–pyoderma gangrenosum–acne (PAPA) syndrome is an autoinflammatory disorder characterized by pyogenic arthritis, pyoderma gangrenosum and cystic inflammatory lesions resembling severe acne.¹¹⁹ The genetic locus was mapped to 15q24, prior to the identification of mutations in the *PSTPIP1* gene (encoding proline-serine-threonine phosphatase-interacting protein 1).^{120,121} *PSTPIP1* encodes an actin-associated protein with a role in inflammatory processes via the binding of CD2, an effector of T-cell activation, and pyrin, an inhibitor of inflammation. Increased infiltration of neutrophils into acne lesions and increased interleukin (IL)-1 β production have been reported in patients with PAPA syndrome.¹²² Accordingly, the disease manifestations respond well to IL-1 β inhibition. However, acne vulgaris does not respond to IL-1 β inhibition, suggesting that the ‘acne’ in PAPA syndrome is a different disorder in spite of its phenotypic resemblance. Of note, PSTPIP1 has been reported as a regulator of actin cytoskeleton dynamics during cell migration via podosomes and in cell division as a potential inhibitor of cytokinesis, which bears similarities to the molecular pathways implicated by the genetics of acne vulgaris.^{123–126} Although the phenotypes and pathogenesis of HS and PAPA are distinct from those of acne vulgaris, there are overlapping molecular mechanisms that provide functional understanding, which adds to the growing literature for acne pathogenesis. The role of Notch signalling highlights the importance of the stem cell niche in the sebaceous gland, and PSTPIP1 again points to migration, podosomes and cell division.

Endocrine system syndromes

Another group of syndromes relates to the endocrine system and highlights the sebaceous gland as an endocrine responsive organ. This group of syndromes encompasses synovitis–acne–pustulosis–hyperostosis–osteitis (SAPHO) syndrome, polycystic ovary syndrome (PCOS, MIM 184700), hyperandrogenism–insulin resistance–acanthosis nigricans (HAIR-AN) syndrome, congenital adrenal hyperplasia (CAH) and seborrhoea–acne–hirsutism–androgenetic alopecia (SAHA) syndrome. HAIR-AN syndrome is considered a subset of PCOS and the genetic basis is unclear. SAHA and SAPHO syndromes have unclear genetics and will not be discussed further here.⁹² PCOS and CAH have been associated with a number of genetic loci. PCOS presents with acne symptoms together with polycystic ovaries, oligo-anovulation and

hyperandrogenism.^{127,128} Hyperandrogenism likely drives acne in PCOS, although as it is a proinflammatory disease, immune genes and cytokines could likewise predispose to acne symptoms.^{129–133} A number of GWASs have been performed for PCOS.^{134–138} Hormonal therapies are a well-tolerated and effective way to control acne with and without endocrine disorders.^{139,140} CAH is linked to endocrine abnormalities with deficiency in the synthesis of cortisol from the adrenal cortex.^{92,141} The majority of patients with classical or nonclassical CAH presentation have mutations in *CYP21A2*.¹⁴¹ The excess androgens in afflicted patients enhance sebum production, which can in turn trigger acne.¹⁴³

Conclusions

The genetic analysis of acne has provided a wealth of data that expand our understanding of sebaceous gland biology. The varied genetic approaches to studying acne phenotypes with large cohorts, family clusters, twins and monogenetic disorders have provided overlapping functional insights to anchor the underlying biological pathogenesis. We can now begin to connect the biological data related to stem cell compartment size, cell fate decisions, cell migration, tissue architecture and matrix remodelling and apply these to mechanisms of disease state.

The role of pilosebaceous unit development and maturation in the pathogenesis of acne vulgaris has been implicated by multiple studies identifying the TGF- β , TP63, WNT, FGF and phosphoinositol-3-kinase pathways in GWASs, and familial studies associated with the FGF pathway, NEK9, podosome-related genes and Notch signalling (Fig. 1). Specifically, Notch and c-MYC are important in sebaceous gland maturation and homeostasis from the perspective of stem cell maintenance and proliferation. TGF- β -related genes were associated with acne in GWASs and have mechanistic functions related to epidermal cell proliferation, follicular obstruction, lipid production and innate immunity. Podosome-related genes, FGF signalling and retinol–vitamin A play a role in tissue remodelling that is likely necessary for sebaceous gland enlargement and differentiation, and cell migration of sebaceous progenitors into the gland. Sebaceous gland dysfunction, as highlighted by genetic studies (inability to migrate, abnormal cell division and lack of differentiation), will result in epithelial cells remaining in the junctional zone, causing junctional zone expansion, which then gives rise to comedones (Fig. 2).

Notably absent from current genetic associations is a strong link to inflammation, perhaps with the exception of *SELL*, encoding an adhesion molecule with a role in controlling

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

inflammation, and *SEMA4B*, encoding a mediator of basophil function. The genetic studies to date indicate a strong link to the tissue microenvironment and the tissue remodelling that occurs during development of the mature sebaceous gland, and not to inflammation, which therefore may be considered a secondary event.

The outlook for the identification and development of new targeted treatments is encouraging, with key pathogenic pathways identified and mechanistic understanding starting to emerge. Of note, the majority of genetic studies to date have focused on severe acne, which makes up 10% of cases. It will therefore be important to replicate and expand studies to include the more prevalent mild-to-moderate acne vulgaris phenotype to confirm that the mechanisms hold true. Murine models of acne vulgaris are not faithful to the human phenotype and thus it will be vital to develop informative, cell-based models with sebocytes or, preferably, sebaceous gland organoids to accelerate discovery. It is hoped that the use of mechanistic data generated from the genes and pathways identified from genetic studies will lead to the development of novel, more specific classes of therapeutics to treat acne.

Acknowledgments

The authors would like to thank Jia Shee Hee (SRIS, A*STAR) for proofreading of the final manuscript.

References

1 Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet* 2012; **379**:361–72.
2 Kligman AM. An overview of acne. *J Invest Dermatol* 1974; **62**:268–87.
3 Cunliffe WJ. Acne and unemployment. *Br J Dermatol* 1986; **115**:386.
4 Bhate K, Williams HC. Epidemiology of acne vulgaris. *Br J Dermatol* 2013; **168**:474–85.
5 Smithard A, Glazebrook C, Williams HC. Acne prevalence, knowledge about acne and psychological morbidity in mid-adolescence: a community-based study. *Br J Dermatol* 2001; **145**:274–9.
6 Cunliffe WJ, Gould DJ. Prevalence of facial acne vulgaris in late adolescence and in adults. *Br Med J* 1979; **1**:1109–10.
7 Tan HH, Tan AW, Barkham T *et al.* Community-based study of acne vulgaris in adolescents in Singapore. *Br J Dermatol* 2007; **157**:547–51.

- 8 Shen Y, Wang T, Zhou C *et al*. Prevalence of acne vulgaris in Chinese adolescents and adults: a community-based study of 17,345 subjects in six cities. *Acta Derm Venereol* 2012; **92**:40–4.
- 9 Goulden V, Stables GI, Cunliffe WJ. Prevalence of facial acne in adults. *J Am Acad Dermatol* 1999; **41**:577–80.
- 10 Hay RJ, Johns NE, Williams HC *et al*. The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *J Invest Dermatol* 2014; **134**:1527–34.
- 11 Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol* 2015; **172** (Suppl. 1):3–12.
- 12 He L, Wu WJ, Yang JK *et al*. Two new susceptibility loci 1q24.2 and 11p11.2 confer risk to severe acne. *Nat Commun* 2014; **5**:2870.
- 13 Perkins AC, Cheng CE, Hillebrand GG *et al*. Comparison of the epidemiology of acne vulgaris among Caucasian, Asian, Continental Indian and African American women. *J Eur Acad Dermatol Venereol* 2011; **25**:1054–60.
- 14 Petridis C, Navarini AA, Dand N *et al*. Genome-wide meta-analysis implicates mediators of hair follicle development and morphogenesis in risk for severe acne. *Nat Commun* 2018; **9**:5075.
- 15 Clayton RW, Göbel K, Niessen CM *et al*. Homeostasis of the sebaceous gland and mechanisms of acne pathogenesis. *Br J Dermatol* 2019; in press.
- 16 Zouboulis CC, Eady A, Philpott M *et al*. What is the pathogenesis of acne? *Exp Dermatol* 2005; **14**:143–52.
- 17 Koreck A, Pivarsci A, Dobozy A *et al*. The role of innate immunity in the pathogenesis of acne. *Dermatology* 2003; **206**:96–105.
- 18 Gollnick HP. From new findings in acne pathogenesis to new approaches in treatment. *J Eur Acad Dermatol Venereol* 2015; **29** (Suppl. 5):1–7.
- 19 Dreno B, Gollnick HP, Kang S *et al*. Understanding innate immunity and inflammation in acne: implications for management. *J Eur Acad Dermatol Venereol* 2015; **29** (Suppl. 4):3–11.
- 20 Lichtenberger R, Simpson MA, Smith C *et al*. Genetic architecture of acne vulgaris. *J Eur Acad Dermatol Venereol* 2017; **31**:1978–90.
- 21 Hecht H. Hereditary trends in acne vulgaris. Prevention of acne. *Dermatologica* 1960; **121**:297–307.
- 22 Friedman GD. Twin studies of disease heritability based on medical records: application to acne vulgaris. *Acta Genet Med Gemellol (Roma)* 1984; **33**:487–95.

- 23 Di Landro A, Cazzaniga S, Parazzini F *et al.* Family history, body mass index, selected dietary factors, menstrual history, and risk of moderate to severe acne in adolescents and young adults. *J Am Acad Dermatol* 2012; **67**:1129–35.
- 24 Ghodsi SZ, Orawa H, Zouboulis CC. Prevalence, severity, and severity risk factors of acne in high school pupils: a community-based study. *J Invest Dermatol* 2009; **129**:2136–41.
- 25 Xu SX, Wang HL, Fan X *et al.* The familial risk of acne vulgaris in Chinese Hans – a case–control study. *J Eur Acad Dermatol Venereol* 2007; **21**:602–5.
- 26 Evans DM, Kirk KM, Nyholt DR *et al.* Teenage acne is influenced by genetic factors. *Br J Dermatol* 2005; **152**:579–81.
- 27 Bataille V, Snieder H, MacGregor AJ *et al.* The influence of genetics and environmental factors in the pathogenesis of acne: a twin study of acne in women. *J Invest Dermatol* 2002; **119**:1317–22.
- 28 Wei B, Pang Y, Zhu H *et al.* The epidemiology of adolescent acne in North East China. *J Eur Acad Dermatol Venereol* 2010; **24**:953–7.
- 29 Mina-Vargas A, Colodro-Conde L, Grasby K *et al.* Heritability and GWAS analyses of acne in Australian adolescent twins. *Twin Res Hum Genet* 2017; **20**:541–9.
- 30 Walton S, Wyatt EH, Cunliffe WJ. Genetic control of sebum excretion and acne – a twin study. *Br J Dermatol* 1988; **118**:393–6.
- 31 Suggs A, Loesch M, Ezaldein H *et al.* An acne survey from the world’s largest annual gathering of twins. *J Drugs Dermatol* 2018; **17**:380–2.
- 32 Navarini AA, Simpson MA, Weale M *et al.* Genome-wide association study identifies three novel susceptibility loci for severe acne vulgaris. *Nat Commun* 2014; **5**:4020.
- 33 Zhang M, Qureshi AA, Hunter DJ *et al.* A genome-wide association study of severe teenage acne in European Americans. *Hum Genet* 2014; **133**:259–64.
- 34 Trivedi NR, Gilliland KL, Zhao W *et al.* Gene array expression profiling in acne lesions reveals marked upregulation of genes involved in inflammation and matrix remodeling. *J Invest Dermatol* 2006; **126**:1071–9.
- 35 Nagaoka T, Kaburagi Y, Hamaguchi Y *et al.* Delayed wound healing in the absence of intercellular adhesion molecule-1 or L-selectin expression. *Am J Pathol* 2000; **157**:237–47.
- 36 Koster MI, Kim S, Mills AA *et al.* p63 is the molecular switch for initiation of an epithelial stratification program. *Genes Dev* 2004; **18**:126–31.
- 37 Honeycutt KA, Koster MI, Roop DR. Genes involved in stem cell fate decisions and commitment to differentiation play a role in skin disease. *J Invest Dermatol Symp Proc* 2004; **9**:261–8.

- 38 Fullgrabe A, Joost S, Are A *et al.* Dynamics of Lgr6⁺ progenitor cells in the hair follicle, sebaceous gland, and interfollicular epidermis. *Stem Cell Reports* 2015; **5**:843–55.
- 39 Snippert HJ, Haegebarth A, Kasper M *et al.* Lgr6 marks stem cells in the hair follicle that generate all cell lineages of the skin. *Science* 2010; **327**:1385–9.
- 40 Nakagawa Y, Takamatsu H, Okuno T *et al.* Identification of semaphorin 4B as a negative regulator of basophil-mediated immune responses. *J Immunol* 2011; **186**:2881–8.
- 41 Arnold I, Watt FM. c-Myc activation in transgenic mouse epidermis results in mobilization of stem cells and differentiation of their progeny. *Curr Biol* 2001; **11**:558–68.
- 42 Jensen KB, Collins CA, Nascimento E *et al.* Lrig1 expression defines a distinct multipotent stem cell population in mammalian epidermis. *Cell Stem Cell* 2009; **4**:427–39.
- 43 Ordonez-Moran P, Huelsken J. Lrig1: a new master regulator of epithelial stem cells. *EMBO J* 2012; **31**:2064–6.
- 44 Cottle DL, Kretzschmar K, Schweiger PJ *et al.* c-MYC-induced sebaceous gland differentiation is controlled by an androgen receptor/p53 axis. *Cell Rep* 2013; **3**:427–41.
- 45 Frances D, Niemann C. Stem cell dynamics in sebaceous gland morphogenesis in mouse skin. *Dev Biol* 2012; **363**:138–46.
- 46 Schork NJ, Murray SS, Frazer KA *et al.* Common vs. rare allele hypotheses for complex diseases. *Curr Opin Genet Dev* 2009; **19**:212–19.
- 47 Zuo X, Sun L, Yin X *et al.* Whole-exome SNP array identifies 15 new susceptibility loci for psoriasis. *Nat Commun* 2015; **6**:6793.
- 48 Pigors M, Common JEA, Wong X *et al.* Exome sequencing and rare variant analysis reveals multiple filaggrin mutations in Bangladeshi families with atopic eczema and additional risk genes. *J Invest Dermatol* 2018; **138**:2674–7.
- 49 Apert ME. [Acrocephalosyndactyly]. *Bull Memoires Soc Med Hosp Paris* 1908; **23**:1310–13 (in French).
- 50 Park WJ, Theda C, Maestri NE *et al.* Analysis of phenotypic features and *FGFR2* mutations in Apert syndrome. *Am J Hum Genet* 1995; **57**:321–8.
- 51 Cohen MM Jr, Kreiborg S. Cutaneous manifestations of Apert syndrome. *Am J Med Genet* 1995; **58**:94–6.
- 52 Wilkie AO, Slaney SF, Oldridge M *et al.* Apert syndrome results from localized mutations of *FGFR2* and is allelic with Crouzon syndrome. *Nat Genet* 1995; **9**:165–72.
- 53 Higgins R, Pink A, Hunger R *et al.* Generalized comedones, acne, and hidradenitis suppurativa in a patient with an *FGFR2* missense mutation. *Front Med (Lausanne)* 2017; **4**:16.

- 54 Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: somatic mutation in *FGFR2*. *Lancet* 1998; **352**:704–5.
- 55 Fenwick AL, Bowdin SC, Klatt RE *et al*. A deletion of *FGFR2* creating a chimeric IIIb/IIIc exon in a child with Apert syndrome. *BMC Med Genet* 2011; **12**:122.
- 56 Wilkie AO. Bad bones, absent smell, selfish testes: the pleiotropic consequences of human FGF receptor mutations. *Cytokine Growth Factor Rev* 2005; **16**:187–203.
- 57 Oldridge M, Zackai EH, McDonald-McGinn DM *et al*. *De novo* alu-element insertions in *FGFR2* identify a distinct pathological basis for Apert syndrome. *Am J Hum Genet* 1999; **64**:446–61.
- 58 Bonano VI, Oltean S, Brazas RM *et al*. Imaging the alternative silencing of *FGFR2* exon IIIb *in vivo*. *RNA* 2006; **12**:2073–9.
- 59 Orr-Urtreger A, Bedford MT, Burakova T *et al*. Developmental localization of the splicing alternatives of fibroblast growth factor receptor-2 (FGFR2). *Dev Biol* 1993; **158**:475–86.
- 60 Yu K, Herr AB, Waksman G *et al*. Loss of fibroblast growth factor receptor 2 ligand-binding specificity in Apert syndrome. *Proc Natl Acad Sci U S A* 2000; **97**:14536–41.
- 61 Miraoui H, Ringe J, Haupl T *et al*. Increased EFG- and PDGF α -receptor signaling by mutant FGF-receptor 2 contributes to osteoblast dysfunction in Apert craniosynostosis. *Hum Mol Genet* 2010; **19**:1678–89.
- 62 Kiritsi D, Lorente AI, Happle R *et al*. Blaschko line acne on pre-existent hypomelanosis reflecting a mosaic *FGFR2* mutation. *Br J Dermatol* 2015; **172**:1125–7.
- 63 Tchernev G, Ananiev J, Semkova K *et al*. Nevus comedonicus: an updated review. *Dermatol Ther (Heidelb)* 2013; **3**:33–40.
- 64 Levinsohn JL, Sugarman JL, McNiff JM *et al*. Somatic mutations in *NEK9* cause nevus comedonicus. *Am J Hum Genet* 2016; **98**:1030–7.
- 65 Roig J, Mikhailov A, Belham C *et al*. Nercc1, a mammalian NIMA-family kinase, binds the Ran GTPase and regulates mitotic progression. *Genes Dev* 2002; **16**:1640–58.
- 66 Bertran MT, Sdelci S, Regue L *et al*. Nek9 is a Plk1-activated kinase that controls early centrosome separation through Nek6/7 and Eg5. *EMBO J* 2011; **30**:2634–47.
- 67 ter Haar B, Hamel B, Hendriks J *et al*. Melnick–Needles syndrome: indication for an autosomal recessive form. *Am J Med Genet* 1982; **13**:469–77.
- 68 Borrone C, Di Rocco M, Crovato F *et al*. New multisystemic disorder involving heart valves, skin, bones, and joints in two brothers. *Am J Med Genet* 1993; **46**:228–34.

- 69 Iqbal Z, Cejudo-Martin P, de Brouwer A *et al*. Disruption of the podosome adaptor protein TKS4 (SH3PXD2B) causes the skeletal dysplasia, eye, and cardiac abnormalities of Frank–Ter Haar syndrome. *Am J Hum Genet* 2010; **86**:254–61.
- 70 Wilson GR, Sunley J, Smith KR *et al*. Mutations in *SH3PXD2B* cause Borrone dermatocardio-skeletal syndrome. *Eur J Hum Genet* 2014; **22**:741–7.
- 71 Zrhidri A, Jaouad IC, Lyahyai J *et al*. Identification of two novel *SH3PXD2B* gene mutations in Frank–Ter Haar syndrome by exome sequencing: case report and review of the literature. *Gene* 2017; **628**:190–3.
- 72 Bendon CL, Fenwick AL, Hurst JA *et al*. Frank–ter Haar syndrome associated with sagittal craniosynostosis and raised intracranial pressure. *BMC Med Genet* 2012; **13**:104.
- 73 Saini P, Courtneidge SA. Tks adaptor proteins at a glance. *J Cell Sci* 2018; **131**:jcs203661.
- 74 Buschman MD, Bromann PA, Cejudo-Martin P *et al*. The novel adaptor protein Tks4 (SH3PXD2B) is required for functional podosome formation. *Mol Biol Cell* 2009; **20**:1302–11.
- 75 Lanyi A, Barath M, Peterfi Z *et al*. The homolog of the five SH3-domain protein (HOF1/SH3PXD2B) regulates lamellipodia formation and cell spreading. *PLOS ONE* 2011; **6**:e23653.
- 76 Bogel G, Gujdar A, Geiszt M *et al*. Frank–ter Haar syndrome protein Tks4 regulates epidermal growth factor-dependent cell migration. *J Biol Chem* 2012; **287**:31321–9.
- 77 Mao M, Hedberg-Buenz A, Koehn D *et al*. Anterior segment dysgenesis and early-onset glaucoma in nee mice with mutation of *Sh3pxd2b*. *Invest Ophthalmol Vis Sci* 2011; **52**:2679–88.
- 78 Winchester P, Grossman H, Lim WN *et al*. A new acid mucopolysaccharidosis with skeletal deformities simulating rheumatoid arthritis. *Am J Roentgenol Radium Ther Nucl Med* 1969; **106**:121–8.
- 79 Zankl A, Pachman L, Poznanski A *et al*. Torg syndrome is caused by inactivating mutations in *MMP2* and is allelic to NAO and Winchester syndrome. *J Bone Miner Res* 2007; **22**:329–33.
- 80 Brown SI, Kuwabara T. Peripheral corneal opacification and skeletal deformities. A newly recognized acid mucopolysaccharidosis simulating rheumatoid arthritis. *Arch Ophthalmol* 1970; **83**:667–77.
- 81 de Vos I, Tao EY, Ong SLM *et al*. Functional analysis of a hypomorphic allele shows that MMP14 catalytic activity is the prime determinant of the Winchester syndrome phenotype. *Hum Mol Genet* 2018; **27**:2775–88.

- 82 Evans BR, Mosig RA, Lobl M *et al.* Mutation of membrane type-1 metalloproteinase, MT1-MMP, causes the multicentric osteolysis and arthritis disease Winchester syndrome. *Am J Hum Genet* 2012; **91**:572–6.
- 83 Zankl A, Bonafe L, Calcaterra V *et al.* Winchester syndrome caused by a homozygous mutation affecting the active site of matrix metalloproteinase 2. *Clin Genet* 2005; **67**:261–6.
- 84 Rouzier C, Vanatka R, Bannwarth S *et al.* A novel homozygous *MMP2* mutation in a family with Winchester syndrome. *Clin Genet* 2006; **69**:271–6.
- 85 Jeong SY, Kim BY, Kim HJ *et al.* A novel homozygous *MMP2* mutation in a patient with Torg–Winchester syndrome. *J Hum Genet* 2010; **55**:764–6.
- 86 Yaykasli KO, Turan H, Kaya E *et al.* Polymorphisms in the promoters of MMP-2 and TIMP-2 genes in patients with acne vulgaris. *Int J Clin Exp Med* 2013; **6**:967–72.
- 87 Marshall CD, Hu MS, Leavitt T *et al.* Cutaneous scarring: basic science, current treatments, and future directions. *Adv Wound Care (New Rochelle)* 2018; **7**:29–45.
- 88 Seeliger MW, Biesalski HK, Wissinger B *et al.* Phenotype in retinol deficiency due to a hereditary defect in retinol binding protein synthesis. *Invest Ophthalmol Vis Sci* 1999; **40**:3–11.
- 89 Cukras C, Gaasterland T, Lee P *et al.* Exome analysis identified a novel mutation in the *RBP4* gene in a consanguineous pedigree with retinal dystrophy and developmental abnormalities. *PLOS ONE* 2012; **7**:e50205.
- 90 Kligman AM. The treatment of acne with topical retinoids: one man’s opinions. *J Am Acad Dermatol* 1997; **36**:S92–5.
- 91 Anderson JA, Stokoe IH. Vitamin A in acne vulgaris. *Br Med J* 1963; **2**:294–6.
- 92 Chen W, Obermayer-Pietsch B, Hong JB *et al.* Acne-associated syndromes: models for better understanding of acne pathogenesis. *J Eur Acad Dermatol Venereol* 2011; **25**:637–46.
- 93 Gao M, Wang PG, Cui Y *et al.* Inversa acne (hidradenitis suppurativa): a case report and identification of the locus at chromosome 1p21.1–1q25.3. *J Invest Dermatol* 2006; **126**:1302–6.
- 94 Al-Ali FM, Ratnamala U, Mehta TY *et al.* Hidradenitis suppurativa (or acne inversa) with autosomal dominant inheritance is not linked to chromosome 1p21.1–1q25.3 region. *Exp Dermatol* 2010; **19**:851–3.
- 95 Wang B, Yang W, Wen W *et al.* Gamma-secretase gene mutations in familial acne inversa. *Science* 2010; **330**:1065.

- 96 Ratnamala U, Jhala D, Jain NK *et al.* Expanding the spectrum of gamma-secretase gene mutation-associated phenotypes: two novel mutations segregating with familial hidradenitis suppurativa (acne inversa) and acne conglobata. *Exp Dermatol* 2016; **25**:314–16.
- 97 Liu Y, Gao M, Lv YM *et al.* Confirmation by exome sequencing of the pathogenic role of *NCSTN* mutations in acne inversa (hidradenitis suppurativa). *J Invest Dermatol* 2011; **131**:1570–2.
- 98 Li CR, Jiang MJ, Shen DB *et al.* Two novel mutations of the nicastrin gene in Chinese patients with acne inversa. *Br J Dermatol* 2011; **165**:415–18.
- 99 Zhang C, Wang L, Chen L *et al.* Two novel mutations of the *NCSTN* gene in Chinese familial acne inverse. *J Eur Acad Dermatol Venereol* 2013; **27**:1571–4.
- 100 Pink AE, Simpson MA, Brice GW *et al.* *PSENEN* and *NCSTN* mutations in familial hidradenitis suppurativa (acne inversa). *J Invest Dermatol* 2011; **131**:1568–70.
- 101 Kelleher RJ 3rd, Shen J. Genetics. Gamma-secretase and human disease. *Science* 2010; **330**:1055–6.
- 102 Zhou C, Wen GD, Soe LM *et al.* Novel mutations in *PSENEN* gene in two Chinese acne inversa families manifested as familial multiple comedones and Dowling–Degos disease. *Chin Med J (Engl)* 2016; **129**:2834–9.
- 103 Pavlovsky M, Sarig O, Eskin-Schwartz M *et al.* A phenotype combining hidradenitis suppurativa with Dowling–Degos disease caused by a founder mutation in *PSENEN*. *Br J Dermatol* 2018; **178**:502–8.
- 104 Ralser DJ, Basmanav FB, Tafazzoli A *et al.* Mutations in gamma-secretase subunit-encoding *PSENEN* underlie Dowling–Degos disease associated with acne inversa. *J Clin Invest* 2017; **127**:1485–90.
- 105 Gonzalez-Villanueva I, Gutierrez M, Hispan P *et al.* Novel *POFUT1* mutation associated with hidradenitis suppurativa–Dowling–Degos disease firm up a role for Notch signalling in the pathogenesis of this disorder. *Br J Dermatol* 2018; **178**:984–6.
- 106 Pavlovsky M, Sarig O, Eskin-Schwartz M *et al.* Novel *POFUT1* mutation associated with hidradenitis suppurativa–Dowling–Degos disease firm up a role for Notch signalling in the pathogenesis of this disorder: reply from the authors. *Br J Dermatol* 2018; **178**:986.
- 107 Ralser DJ, Takeuchi H, Fritz G *et al.* Altered Notch signaling in Dowling–Degos disease: additional mutations in *POGLUT1* and further insights into disease pathogenesis. *J Invest Dermatol* 2019; in press.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

108 Li A, Peng Y, Taiclet LM *et al.* Analysis of hidradenitis suppurativa-linked mutations in four genes and the effects of PSEN1-P242LfsX11 on cytokine and chemokine expression in macrophages. *Hum Mol Genet* 2019; in press.

109 Li C, Li W, Xu H *et al.* PSENEN mutation carriers with co-manifestation of acne inversa (AI) and Dowling–Degos disease (DDD): is AI or DDD the subphenotype? *J Invest Dermatol* 2017; **137**:2234–6.

110 Fortini ME. Gamma-secretase-mediated proteolysis in cell-surface-receptor signalling. *Nat Rev Mol Cell Biol* 2002; **3**:673–84.

111 Mumm JS, Kopan R. Notch signaling: from the outside in. *Dev Biol* 2000; **228**:151–65.

112 Nichols AM, Pan Y, Herreman A *et al.* Notch pathway is dispensable for adipocyte specification. *Genesis* 2004; **40**:40–4.

113 Nowell C, Radtke F. Cutaneous Notch signaling in health and disease. *Cold Spring Harb Perspect Med* 2013; **3**:a017772.

114 Gridley T. Notch signaling and inherited disease syndromes. *Hum Mol Genet* 2003; **12** (Spec No. 1):R9–13.

115 Wong VW, Stange DE, Page ME *et al.* Lrig1 controls intestinal stem-cell homeostasis by negative regulation of ErbB signalling. *Nat Cell Biol* 2012; **14**:401–8.

116 Xia X, Qian S, Soriano S *et al.* Loss of presenilin 1 is associated with enhanced beta-catenin signaling and skin tumorigenesis. *Proc Natl Acad Sci U S A* 2001; **98**:10863–8.

117 Li T, Wen H, Brayton C *et al.* Epidermal growth factor receptor and notch pathways participate in the tumor suppressor function of γ -secretase. *J Biol Chem* 2007; **282**:32264–73.

118 Pan Y, Lin MH, Tian X *et al.* γ -Secretase functions through Notch signaling to maintain skin appendages but is not required for their patterning or initial morphogenesis. *Dev Cell* 2004; **7**:731–43.

119 Lindor NM, Arsenault TM, Solomon H *et al.* A new autosomal dominant disorder of pyogenic sterile arthritis, pyoderma gangrenosum, and acne: PAPA syndrome. *Mayo Clin Proc* 1997; **72**:611–15.

120 Yeon HB, Lindor NM, Seidman JG *et al.* Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome maps to chromosome 15q. *Am J Hum Genet* 2000; **66**:1443–8.

121 Wise CA, Gillum JD, Seidman CE *et al.* Mutations in CD2BP1 disrupt binding to PTP PEST and are responsible for PAPA syndrome, an autoinflammatory disorder. *Hum Mol Genet* 2002; **11**:961–9.

- 122 Shoham NG, Centola M, Mansfield E *et al*. Pyrin binds the PSTPIP1/CD2BP1 protein, defining familial Mediterranean fever and PAPA syndrome as disorders in the same pathway. *Proc Natl Acad Sci U S A* 2003; **100**:13501–6.
- 123 Spencer S, Dowbenko D, Cheng J *et al*. PSTPIP: a tyrosine phosphorylated cleavage furrow-associated protein that is a substrate for a PEST tyrosine phosphatase. *J Cell Biol* 1997; **138**:845–60.
- 124 Cortesio CL, Wernimont SA, Kastner DL *et al*. Impaired podosome formation and invasive migration of macrophages from patients with a *PSTPIP1* mutation and PAPA syndrome. *Arthritis Rheum* 2010; **62**:2556–8.
- 125 Maridonneau-Parini I. Podosomes are disrupted in PAPA syndrome. *Blood* 2014; **123**:2597–9.
- 126 Starnes TW, Bennin DA, Bing X *et al*. The F-BAR protein PSTPIP1 controls extracellular matrix degradation and filopodia formation in macrophages. *Blood* 2014; **123**:2703–14.
- 127 Lause M, Kamboj A, Fernandez Faith E. Dermatologic manifestations of endocrine disorders. *Transl Pediatr* 2017; **6**:300–12.
- 128 Azziz R, Woods KS, Reyna R *et al*. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004; **89**:2745–9.
- 129 Guo R, Zheng Y, Yang J *et al*. Association of TNF- α , IL-6 and IL-1 β gene polymorphisms with polycystic ovary syndrome: a meta-analysis. *BMC Genet* 2015; **16**:5.
- 130 Kolbus A, Walch K, Nagele F *et al*. Interleukin-1 α but not interleukin-1 β gene polymorphism is associated with polycystic ovary syndrome. *J Reprod Immunol* 2007; **73**:188–93.
- 131 Kucuk M, Altinkaya SO, Nergiz S *et al*. Interleukin-6 levels in relation with hormonal and metabolic profile in patients with polycystic ovary syndrome. *Gynecol Endocrinol* 2014; **30**:423–7.
- 132 Wu H, Yu K, Yang Z. Associations between TNF- α and interleukin gene polymorphisms with polycystic ovary syndrome risk: a systematic review and meta-analysis. *J Assist Reprod Genet* 2015; **32**:625–34.
- 133 Younis A, Hawkins K, Mahini H *et al*. Serum tumor necrosis factor- α , interleukin-6, monocyte chemotactic protein-1 and paraoxonase-1 profiles in women with endometriosis, PCOS, or unexplained infertility. *J Assist Reprod Genet* 2014; **31**:1445–51.

- 134 Chen ZJ, Zhao H, He L *et al.* Genome-wide association study identifies susceptibility loci for polycystic ovary syndrome on chromosome 2p16.3, 2p21 and 9q33.3. *Nat Genet* 2011; **43**:55–9.
- 135 Shi Y, Zhao H, Shi Y *et al.* Genome-wide association study identifies eight new risk loci for polycystic ovary syndrome. *Nat Genet* 2012; **44**:1020–5.
- 136 Hayes MG, Urbanek M, Ehrmann DA *et al.* Genome-wide association of polycystic ovary syndrome implicates alterations in gonadotropin secretion in European ancestry populations. *Nat Commun* 2015; **6**:7502.
- 137 Lee H, Oh JY, Sung YA *et al.* Genome-wide association study identified new susceptibility loci for polycystic ovary syndrome. *Hum Reprod* 2015; **30**:723–31.
- 138 Day FR, Hinds DA, Tung JY *et al.* Causal mechanisms and balancing selection inferred from genetic associations with polycystic ovary syndrome. *Nat Commun* 2015; **6**:8464.
- 139 Nguyen HL, Tollefson MM. Endocrine disorders and hormonal therapy for adolescent acne. *Curr Opin Pediatr* 2017; **29**:455–65.
- 140 Kamboj MK, Bonny AE. Polycystic ovary syndrome in adolescence: diagnostic and therapeutic strategies. *Transl Pediatr* 2017; **6**:248–55.
- 141 Speiser PW, White PC. Congenital adrenal hyperplasia. *N Engl J Med* 2003; **349**:776–88.
- 142 Rodrigues NR, Dunham I, Yu CY *et al.* Molecular characterization of the HLA-linked steroid 21-hydroxylase B gene from an individual with congenital adrenal hyperplasia. *EMBO J* 1987; **6**:1653–61.
- 143 Degitz K, Placzek M, Arnold B *et al.* Congenital adrenal hyperplasia and acne in male patients. *Br J Dermatol* 2003; **148**:1263–6.
- 144 Baz K, Emin Erdal M, Yazici AC *et al.* Association between tumor necrosis factor- α gene promoter polymorphism at position –308 and acne in Turkish patients. *Arch Dermatol Res* 2008; **300**:371–6.
- 145 Sobjanek M, Zablotna M, Nedoszytko B *et al.* Lack of association between the promoter polymorphisms at positions –238 and –308 of the tumour necrosis factor alpha gene and acne vulgaris in Polish patients. *J Eur Acad Dermatol Venereol* 2009; **23**:331–2.
- 146 Szabo K, Tax G, Teodorescu-Brinzeu D *et al.* TNF α gene polymorphisms in the pathogenesis of acne vulgaris. *Arch Dermatol Res* 2011; **303**:19–27.

- 147 Al-Shobaili HA, Salem TA, Alzolibani AA *et al.* Tumor necrosis factor- α -308 G/A and interleukin 10 -1082 A/G gene polymorphisms in patients with acne vulgaris. *J Dermatol Sci* 2012; **68**:52–5.
- 148 Grech I, Giatrakos S, Damoraki G *et al.* Impact of TNF haplotypes in the physical course of acne vulgaris. *Dermatology* 2014; **228**:152–7.
- 149 Yang JK, Wu WJ, Qi J *et al.* TNF-308 G/A polymorphism and risk of acne vulgaris: a meta-analysis. *PLOS ONE* 2014; **9**:e87806.
- 150 Tian L, Xie H, Yang T *et al.* TNFR 2 M196R polymorphism and acne vulgaris in Han Chinese: a case–control study. *J Huazhong Univ Sci Technol Med Sci* 2010; **30**:408–11.
- 151 Tian LM, Xie HF, Yang T *et al.* Association study of tumor necrosis factor receptor type 2 M196R and toll-like receptor 2 Arg753Gln polymorphisms with acne vulgaris in a Chinese Han ethnic group. *Dermatology* 2010; **221**:276–84.
- 152 Szabo K, Tax G, Kis K *et al.* Interleukin-1A +4845(G> T) polymorphism is a factor predisposing to acne vulgaris. *Tissue Antigens* 2010; **76**:411–15.
- 153 Younis S, Javed Q. The interleukin-6 and interleukin-1A gene promoter polymorphism is associated with the pathogenesis of acne vulgaris. *Arch Dermatol Res* 2015; **307**:365–70.
- 154 Al Robaee AA, AlZolibani A, Al Shobaili H *et al.* Association of interleukin 4 (–590 T/C) and interleukin 4 receptor (Q551R A/G) gene polymorphisms with acne vulgaris. *Ann Saudi Med* 2012; **32**:349–54.
- 155 Paraskevaidis A, Drakoulis N, Roots I *et al.* Polymorphisms in the human cytochrome P-450 1A1 gene (*CYP1A1*) as a factor for developing acne. *Dermatology* 1998; **196**:171–5.
- 156 He L, Yang Z, Yu H *et al.* The relationship between CYP17 –34T/C polymorphism and acne in Chinese subjects revealed by sequencing. *Dermatology* 2006; **212**:338–42.
- 157 Chamaie-Nejad F, Saeidi S, Najafi F *et al.* Association of the CYP17 MSP AI (T-34C) and CYP19 codon 39 (Trp/Arg) polymorphisms with susceptibility to acne vulgaris. *Clin Exp Dermatol* 2018; **43**:183–6.
- 158 Sawaya ME, Shalita AR. Androgen receptor polymorphisms (CAG repeat lengths) in androgenetic alopecia, hirsutism, and acne. *J Cutan Med Surg* 1998; **3**:9–15.
- 159 Ribero S, Sanna M, Visconti A *et al.* Acne and telomere length: a new spectrum between senescence and apoptosis pathways. *J Invest Dermatol* 2017; **137**:513–15.
- 160 Amr K, Abdel-Hameed M, Sayed K *et al.* The Pro12Ala polymorphism of the gene for peroxisome proliferator activated receptor- γ is associated with a lower Global Acne Grading System score in patients with acne vulgaris. *Clin Exp Dermatol* 2014; **39**:741–5.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

161 Martignetti JA, Aqeel AA, Sewairi WA *et al.* Mutation of the matrix metalloproteinase 2
gene (*MMP2*) causes a multicentric osteolysis and arthritis syndrome. *Nat Genet* 2001;
28:261–5.

162 Wang H, Guo M, Shen S *et al.* Variants in *SELL*, *MRPS36P2*, *TP63*, *DDB2*, *CACNA1H*,
ADAM19, *GNAI1*, *CDH13* and *GABRG2* interact to confer risk of acne in Chinese
population. *J Dermatol* 2015; **42**:378–81.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the
publisher’s website:

Table S1 Genome-wide association studies have highlighted associated loci and candidate
genes.

Figure legends

Fig 1. Acne vulgaris has a complex pathogenesis with multiple functional processes (blue
bubbles), genes and pathways implicated in the genetics of acne. Genes and biological
pathways can impact on functional processes as indicated (arrows). Based on genetics, stem
cell dynamics and tissue remodelling are the main processes implicated in acne vulgaris.
FGF, fibroblast growth factor; PSTPIP, proline-serine-threonine phosphatase-interacting
protein; TGF, transforming growth factor.

Fig 2. The maturation of the sebaceous gland (SG) is critical for the development of acne
vulgaris. (a) The pilosebaceous unit prior to puberty is observed with an immature SG. As the
SG develops, the stem cells in the junctional zone stem cell niche are proposed to divide and
expand due to mitotic stimulus. A number of genes, as indicated in parentheses, have been
associated with acne. (b) As the SG matures and remodels, epithelial cells exit the junctional
zone and migrate along the basement membrane to enlarge the gland. Genes and pathways
implicated in migration and tissue remodelling are shown in parentheses. (c) Failures in
biological processes that impact on the pilosebaceous unit result in the abnormal

morphogenesis of the SG with an expansion and differentiation within the junctional zone that produces a keratinized comedonal plug and the histologically observed microcomedo. (d) The comedo continues to enlarge as the junctional zone expands until the pilosebaceous unit is dominated by keratinized material. Atrophy of the SG is observed and hair follicle (HF) displacement is common. Comedones can rupture, leading to inflammation. EP, epidermis; TGF, transforming growth factor.

For Peer Review

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1 Candidate genes implicated in acne vulgaris from case–control studies in multiple ethnicities

Gene name	Chromosome location	Genetic association	Country
<i>TNF</i>	6p21.33	–308G>A	Turkey ¹⁴⁴
<i>TNF</i>	6p21.33	–308G>A	Poland ¹⁴⁵
<i>TNF</i>	6p21.33	–308G>A, –857C>T	Hungary and Romania ¹⁴⁶
<i>TNF</i>	6p21.33	–308G>A	Saudi Arabia ¹⁴⁷
<i>TNF</i>	6p21.33	–308G>A	Greece ¹⁴⁸
<i>TNF</i>	6p21.33	–308G>A	Meta-analysis ¹⁴⁹
<i>TNFRSF1B</i>	1p36.22	p.M196R	China ¹⁵⁰
<i>TLR2</i>	4q31.3	p.R753Q	China ¹⁵¹
<i>IL1A</i>	2q14.1	rs1800587 (–889C>T)	Hungary and Romania ¹⁴⁵
<i>IL1A</i>	2q14.1	rs17561 (+4845G>T)	Greece ¹⁵²
<i>IL1A</i>	2q14.1	rs1800587 (–889C>T)	Pakistan ¹⁵³
<i>IL6</i>	7p15.3	rs1800796 (–572G>C)	Pakistan ¹⁵³
<i>IL4</i>	5q31	–590 T/C	Saudi Arabia ¹⁵⁴
<i>IL4R</i>	16p12.1	p.Q551R	Saudi Arabia ¹⁵⁴
<i>IL10</i>	1q32.1	–1082 A/G	Saudi Arabia ¹⁴⁷
<i>CYP1A1</i>	15q24.1	Exon 7 –1194	Germany ¹⁵⁵
<i>CYP17A1</i>	10q24.32	–34 T/C	China ^{156, 157}
<i>CYP19A1</i>	15q21.2	p.W39R	Iran ¹⁵⁷
<i>CYP21A2</i>	6p21.33	p.L281L, p.P453S, p.P30L	Italy ¹⁵⁷
<i>AR</i>	Xq12	CAG, GGN	U.S.A. ¹⁵⁸
<i>ZNF420</i>	19q13.12	Not described	U.K. ¹⁵⁹
<i>PPARG</i>	3p25.2	p.P12A	Egypt ¹⁶⁰

Table 2 Genes identified in human syndromes that include a component of acne. These genes highlight important biological pathways in the pathogenesis of acne vulgaris

Gene identified	Chromosome location	Human genetic syndrome	OMIM	Biological function
<i>FGFR2</i> ⁵²	10q26.13	Apert, Munro acne naevus	#101200	Receptor tyrosine kinase, cell signalling, cell growth and differentiation
<i>MMP2</i> ¹⁶¹	16q12.2	MONA, Torg and NAO	#259600	Extracellular matrix remodelling
<i>MMP14</i> ⁸²	14q11.2	Winchester syndrome	#277950	Extracellular matrix remodelling
<i>NEK9</i> ⁶⁴	14q24.3	Naevus comedonicus	#617025	Cell cycle, cell fate decisions
<i>SH3PXD2B</i> ⁶⁹	5q35.1	Frank-ter Haar	#249420	Podosome function, tissue remodelling
<i>PSENEN</i> ⁹⁵	19q13.12	HS	#613736	Cleavage and activation of Notch
<i>PSEN1</i> ⁹⁵	14q24.2	HS	#613737	Cleavage and activation of Notch
<i>NCSTN</i> ⁹⁵	1q23.2	HS	#142690	Cleavage and activation of Notch
<i>POFUT1</i> ¹⁰⁵	20q11	HS	#142690	Activation of Notch
<i>POGLUT1</i> ¹⁰⁸	3q13.33	HS	#615696	Activation of Notch
<i>TNF</i> ^{129, 132}	6p21.33	PCOS	%184700	Inflammation, macrophage activation
<i>IL6</i> ¹²⁹	7p15.3	PCOS	%184700	Inflammation
<i>IL1B</i> ¹²⁹	2q14.1	PCOS	%184700	Inflammation, lymphocyte activation
<i>IL1A</i> ¹³⁰	2q14.1	PCOS	%184700	Inflammation, macrophage and neutrophil activation
<i>RBP4</i> ⁸⁸	10q23	RDCCAS	#615147	Transport of retinol (vitamin A)
<i>PSTPIP1</i> ¹²¹	15q24.3	PAPA	#604416	Cytoskeleton reorganization, inflammation
<i>CYP21A2</i> ¹⁴²	6p21.3	Congenital adrenal hyperplasia	#201910	Cortisol biosynthesis

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

HS, hidradenitis suppurativa; MONA, multicentric osteolysis, nodulosis and arthropathy;
NAO, nodulosis–arthropathy–osteolysis; PAPA, pyrogenic arthritis–pyoderma
gangrenosum–acne; PCS, polycystic ovary syndrome; RDCCAS, retinal dystrophy, iris
coloboma and comedogenic acne syndrome.

For Peer Review

A

B

C

D

Table S1 Genome-wide association studies have highlighted associated loci and candidate genes

Associated gene	Chromosome location	Genetic study design	Genetic variant association	Biological function
<i>SELL</i> ^{12, 162}	1q24.2	GWAS	rs7531806, rs7531806	Adhesion molecule, inflammation
<i>DDB2</i> ^{12, 144, 162}	11p11.2	GWAS	rs747650, rs747650	DNA binding protein, excision repair, cell fate
<i>OVOLI</i> ^{14, 32}	11q13.1	GWAS	rs478304	Cell growth, TGFβ signaling
<i>FST</i> ^{14, 32}	5q11.2	GWAS	rs38055	TGFβ signaling, epidermal hypertrophy
<i>TGFB2</i> ^{14, 32}	1q41	GWAS	rs1159268	Cell growth, TGFβ signaling
<i>MYC</i> ³³	8q24	GWAS	rs4133274, rs13248513	Stem cell fate and proliferation
<i>TP63</i> ¹⁶²	3q28	Gene-gene interaction from GWAS data	rs7631358	Stem cell fate and proliferation
<i>MRPS36P2</i> ¹⁶²	4q35.2	Gene-gene interaction from GWAS data	rs7660345	Long non-coding RNA linked to mitochondria function
<i>CACNA1H</i> ¹⁶²	16p13.3	Gene-gene interaction from GWAS data	rs2753325	Calcium signaling
<i>ADAM19</i> ¹⁶²	5q33.3	Gene-gene interaction from GWAS data	rs6896064	Metalloproteinase with functions related to cell signaling and migration
<i>GNAI1</i> ¹⁶²	7q21.11	Gene-gene interaction from GWAS data	rs1828522	Binds guanine, subunit of inhibitory complexes downstream of GPCRs
<i>CDH13</i> ¹⁶²	16q23.3	Gene-gene interaction from GWAS data	rs77502020	Cell adhesion and cell growth

<i>GABRG2</i> ¹⁶²	5q34	Gene-gene interaction from GWAS data	rs10491327	Ligand-gated chloride channel protein
<i>PTPRU</i> ²⁹	1p35.5	GWAS	rs12738078	Tyrosine kinase, cell growth and differentiation
<i>PIK3R1</i> ²⁹	5q13.1	GWAS	rs10515088	Proliferation and differentiation of
<i>DCC</i> ²⁹	18q21.2	GWAS	rs117943429	Cell adhesion molecule
<i>LAMC2</i> ¹⁴	1q32.1	Meta-GWAS	rs10911268	Basement membrane adhesion glycoprotein
<i>LGR6</i> ¹⁴	1q32.1	Meta-GWAS	rs788790	G-protein coupled receptor that mediates WNT signaling and epithelial stem cell maintenance
<i>BCL11A</i> ¹⁴	2p16.1	Meta-GWAS	rs2901000	DNA binding, gene expression, chromatin remodeling
<i>GLI2</i> ¹⁴	2q14.2	Meta-GWAS	rs1092479	Transcription factor mediating Sonic hedgehog signaling. Role in tissue development
<i>WNT10A</i> ¹⁴	2q35	Meta-GWAS	rs121908120	WNT family protein with proposed role in epidermal cell fate. Mutations result in ectodermal dysplasia (OMIM #257980, #224750, #150400)
<i>FGF2</i> ¹⁴	4q27-28.1	Meta-GWAS	rs4487353	Cell signaling, cell growth and differentiation
Not reported ¹⁴	5q11.2	Meta-GWAS	rs158639	Not applicable
Not reported ¹⁴	7p14.1	Meta-GWAS	rs7809981	Not applicable

Not reported ¹⁴	8p23.1	Meta-GWAS	rs28570522	Not applicable
Not reported ¹⁴	11p15.3-15.2	Meta-GWAS	rs2727365	Not applicable
<i>SEMA4B</i> ¹⁴	15q26.1	Meta-GWAS	rs34560261	Regulator of basophil-mediated immune responses
<i>SPECCIL</i> ¹⁴	22q11.23	Meta-GWAS	rs28360612	Cytoskeleton crosslinking protein with a role in cell adhesion and migration