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Phenotypic Heterogeneity in Hidradenitis Suppurativa (Acne Inversa): Classification Is an Essential Step Toward Personalized Therapy

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Awareness is increasing that there is phenotypic heterogeneity within the hidradenitis suppurativa (HS) disease spectrum. However, the few randomized HS trials that are available have not distinguished between the subtypes of the disease. In this issue, Canoui-Poitrine *et al.* used latent class (LC) analysis of the largest HS cohort described to date to generate three phenotypic subtypes. LC 1 correlates with "typical" European HS, mainly involving the axilla, groin, and, in women, the inframammary region. "Atypical" HS, which may be linked to γ-secretase gene mutations, was subdivided further into LC2 and LC3 subtypes.

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A model for how HS might be subdivided may be found in recent experiences of investigators in characterizing psoriasis. In fact, not all psoriasis is the same; we now recognize several distinct subtypes, based on clinical phenotype, demographics, genetic predisposition, and response to treatment. For example, guttate psoriasis is composed of multiple small plaques on the trunk of young people of the HLA Cw0602 genotype, and it commonly responds well to phototherapy. Personalized medicine projects are now in progress to match more precisely psoriasis genotypes with clinical phenotypes and treatment responses, including the pharmacogenetics of systemic therapy.

HS (also known as acne inversa) research is running to catch up, and increasing awareness indicates that there is phenotypic heterogeneity within the disease spectrum. Common to all HS patients are recurrent, painful nodules, papules, and/or abscesses of apocrine gland-bearing sites, in particular the groin and axilla. "Typical" European HS patients have lesions that are restricted largely to these sites, but "atypical" HS includes lesions that are more widespread. In this issue, Canoui-Poitrine *et al.* (2013) have provided a helpful step by meticulously phenotyping 648 patients with HS. LC analysis, with no *a priori* hypotheses, was used to subdivide the HS clinical phenotype into three groups, based on affected skin sites, lesion types, family history, and associations with (severe) acne. "Axillary-mammary" (LC1) HS corresponded to the "typical" phenotype seen in European populations. "Follicular" (LC2) HS was characterized by comedones, other follicular lesions, and severe acne, whereas the "gluteal" (LC3) HS had a predilection for the buttocks.

Utility of the proposed classification

The study by Canoui-Poitrine *et al.* (2013) has several strengths, including the large size of the patient population and very little missing data. External generalizations are probably limited to European secondary-care centers because of the recruitment of patients from specialist clinics. Reasonable face validity was confirmed by clustering of the associated demographic data such that, compared with the "axillary–mammary" class, "follicular" patients were more likely to be male, current smokers, and have more severe disease. A number of the demographic associations fit with preexisting observations, for example, males were less likely to have inframammary disease. As the authors point out, validation studies using other patient populations are now needed.

Nomenclature has been a difficult problem in HS research, exemplified by the lack of universal agreement regarding the condition's name and disease definition. Division of HS into a "typical" European "axillary–mammary" phenotype, with disease restricted to axillary, inframammary, and groin flexural sites, and an "atypical" group provides a relatively clear distinction on the basis of whether nonflexural sites are involved. There will probably be some debate regarding the subclassification of the atypical group into "follicular" and "gluteal". In particular, the conditional probability of gluteal involvement was only 54% in the "gluteal" group, meaning that half of this group did not have gluteal involvement. Furthermore, one-third of the "follicular" group did exhibit gluteal involvement. In this context, it may be prudent to consider renaming the "gluteal" phenotype. One option would be to focus on absent features. For example, the "gluteal" group lacked hypertrophic scars and epidermal cysts.

Genotype–phenotype correlation

The data provided by Canoui-Poitrine *et al.* (2013) confirm that about one-third of HS patients report a family history of the condition. An autosomal dominant pattern of inheritance was reported 25 years ago, and, in 2010, a Chinese group demonstrated underlying pathogenic mutations in *NCSTN*, one of the six genes encoding the γ-secretase transmembrane complex (Wang *et al.*, 2010). The Han Chinese HS patients concerned were members of six families with a relatively severe HS phenotype, including extensive involvement

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Table 1. Correlation between HS patient characteristics (phenotype) and γ-secretase gene mutations

Study and country of origin	Family/ individual	Patient characteristics: Affected sites	Patient characteristics: Lesion types	Patient characteristics: Other info	Phenotype match	Mutation
Wang *et al.* (2010), China	Family 1	Not stated	Not stated	Proband had axillary SCC, FHx	—	*PSENEN* frameshift
	Family 2	Axillae, groin, gluteal, back, posterior neck	Hypertrophic scars	FHx	LC2	*PSENEN* frameshift
	Family 3	Prominent—gluteal, back, chest, face, posterior neck, waist Mild—axillary	Hypertrophic scars	FHx	LC2	*NCSTN* frameshift
	Family 4	Prominent—axillae, groin, gluteal Mild—back, face, posterior neck, waist Proband folliculitis of elbows and knees	Hypertrophic scars, folliculitis (proband)	FHx	LC2	*PSEN1* frameshift
	Family 5	Prominent—gluteal, back, chest, face, posterior neck, waist Mild—axillary	Hypertrophic scars	FHx	LC2	*NCSTN* altered splicing
	Family 6	Prominent—gluteal, back, chest, face, posterior neck, waist Mild—axillary	Hypertrophic scars	FHx	LC2	*NCSTN* nonsense
Pink *et al.* (2011), UK	Patient 1	Axillae, breast, groin	Comedones	Caucasian, female, BMI 33, never smoker, FHx	LC2[1]	*PSENEN* frameshift
	Patient 2	Axillae, breast, groin gluteal	Hypertrophic scars, sinus tracts	Caucasian, female, BMI 23, never smoker, severe disease, FHx	LC2	*PSENEN* frameshift
	Patient 3	Axillae, suprapubic, groin, gluteal, thighs, neck	Sinus tracts, probably hypertrophic scars	Caucasian, male, BMI 30, current smoker, FHx	Atypical, probably LC2	*NCSTN* altered splicing
Liu *et al.* (2011), China	Family 1	Axillae, gluteal, scalp, face, neck, trunk, groin, limbs	Hypertrophic scars	FHx	LC2	*NCSTN* altered splicing
	Family 2	Back, abdomen, breast, gluteal	Hypertrophic scars	FHx	LC2	*NCSTN* frameshift
Li *et al.* (2011), China	Patient 1	Axillae, posterior neck, groin, gluteal	Hypertrophic scars, inflamed papules	Male, 21 year duration, onset age 26, FHx	LC2	*NCSTN* nonsense
	Patient 2	Posterior neck, axillae, gluteal	Inflamed papules, open comedones	Female, 3 year duration, onset age 15, FHx	LC2	*NCSTN* nonsense
	Patient 3	Axillae, groin, chest, back, gluteal, posterior neck	Hypertrophic scars	Male, 10 year duration, onset age 38, no FHx	LC2	*NCSTN* missense
Zhang *et al.* (2012), China	Family 1	Axillae, posterior neck, groin, gluteal	Hypertrophic scars, inflamed papules	FHx	LC2	*NCSTN* missense
	Family 2	Face, posterior neck, genital	Hypertrophic scars, inflamed papules, cysts	FHx	LC2	*NCSTN* missense
Pink *et al.* (2012), UK	Patient 1	Axillae, breast, groin, gluteal	Hypertrophic scars, sinus tracts	Caucasian, female, BMI 38, current smoker, no FHx, T2DM	LC2	*NCSTN* missense
	Patient 2	Axillae, groin, gluteal	Hypertrophic scars, sinus tracts	Caucasian, female, BMI 37, current smoker, no FHx, T2DM	LC2	*NCSTN* altered splicing
Miskinyte *et al.* (2012), France	Family 1	Axillae, groin, perianal	Hypertrophic scars, fistulae	FHx, severe disease, associated acne conglobata	LC2	*NCSTN* nonsense
	Family 2	Axillae, groin, perianal, gluteal	Hypertrophic scars, fistulae	FHx, associated acne conglobata	LC2	*NCSTN* frameshift
	Family 3	Axillae, groin, perianal	Hypertrophic scars	FHx, sacroiliitis in two individuals and Crohn's disease in one	LC2	*NCSTN* altered splicing
Nomura *et al.* (2012), Japan	Patient 1	Posterior neck, groin, genital, back	Hypertrophic scars, fistulae	Female, FHx	LC2	*NCSTN* altered splicing
	Patient 2	Posterior neck, (also lesions in typical flexural sites)	Comedones	Male, FHx, mild disease	LC2	*NCSTN* altered splicing

Abbreviations: BMI, body mass index; FHx, family history of hidradenitis suppurativa; SCC, squamous cell carcinoma; T2DM, type 2 diabetes mellitus.
Phenotypic data are reproduced from descriptions and photographs included in genetic studies of individuals or families with hidradenitis suppurativa.
[1]The presence of comedones suggests LC2 rather than LC1 phenotype.

Clinical Implications

- Recognition that hidradenitis suppurativa (HS) is heterogeneous allows more accurate genotype–phenotype correlation studies, and it may help investigators to stratify clinical trials.
- Latent class (LC) analysis of a European patient population was used to differentiate HS restricted to "typical" sites from "atypical" HS, which includes additional skin sites.
- Atypical HS was subdivided further into two categories, based on the nature and location of lesions, which now requires further validation.

of nonflexural skin regions. Since then, loss-of-function γ-secretase mutations have been identified in British, French, Japanese, and other Chinese HS patients (Li *et al.*, 2011; Liu *et al.*, 2011; Pink *et al.*, 2011, 2012; Miskinyte *et al.*, 2012; Nomura *et al.*, 2012; Zhang *et al.*, 2012). However, none of the 20 consecutive HS patients seen in a tertiary UK setting were found to have pathogenic γ-secretase mutations, including 12 patients who reported a family history of HS (Ingram *et al.*, 2012). It is possible that unrecognized mutations in genes further down the γ-secretase-Notch signaling pathway may be responsible (Melnik and Plewig, 2012).

One of the potential applications of the phenotypic HS subtypes generated by Canoui-Poitrine *et al.* (2013) is in the field of genotype–phenotype correlation. It is difficult to correlate individual γ-secretase mutations with the corresponding phenotypic subtype because of a lack of complete phenotypic data in many reports. Nevertheless, Table 1 summarizes the available phenotypic information, in some cases relying in part on interpretations from clinical photographs, and it details the corresponding γ-secretase mutation. All of the mutations appear to correlate with atypical HS, and most are probably best placed in the LC2 "follicular" subgroup, because of the involvement of atypical body sites and the presence of hypertrophic scarring. Of the 20 HS patients without pathogenic γ-secretase mutations, the majority had a "typical" HS phenotype, and probably only three exhibited features of the "follicular" subgroup (Ingram *et al.*, 2012).

Minimum HS phenotype data set?

Difficulties encountered when trying to determine the phenotypic subgroups of HS patients in genetic studies reinforce the need for a minimum HS phenotype data set for future studies. This would be best determined through formal "consensus" methods, but one suggestion can be found in Table 2. Nearly all of these elements were included in the study by Canoui-Poitrine *et al.* (2013), except for a patient-reported disease severity measure in the form of quality of life scores.

Table 2. Suggested minimum HS phenotype data set

Domain	Data
Demographics	Age, gender, BMI, family history of HS/dementia
Smoking status	Never/ex/current
Disease history	Age at onset, disease duration
Associated conditions	Acne (vulgaris/conglobata), dissecting cellulitis of scalp, inflammatory bowel disease, pyoderma gangrenosum, polycystic ovary syndrome
Affected regions	Axillae, groin, gluteal, inframammary, posterior neck/ears, trunk, limbs, other
Lesion types	Hypertrophic scars, comedones, epidermal cysts, follicular papules/folliculitis, sinus tracts, flexural pigmentation
Disease severity	Physician reported—Hurley/modified Hidradenitis Suppurativa Score[1] Patient reported—validated quality of life measure
Response to treatment	Topical/systemic/surgical/other

Abbreviations: BMI, body mass index; HS, hidradenitis suppurativa.
[1]From Sartorius *et al.* (2009).

Translational value for clinical practice

For patients, perhaps the most important element of a classification system would be its predictive validity. Obviously, it is not yet known whether using the proposed system to stratify clinical trials would help to distinguish responders from nonresponders to a specific treatment modality. Another important unanswered question would be whether there are phenotypic predictors of severe disease that might justify early treatment to arrest disease progression and to prevent subsequent scarring and reduced quality of life.

The focus on accurate HS phenotyping provided by Canoui-Poitrine *et al.* (2013) is an essential step in determining potential genotype–phenotype correlations within the HS disease spectrum, and it permits a better understanding of HS etiology. For patients, ultimately, it may allow a more personalized approach to therapy.

CONFLICT OF INTEREST
Vincent Piguet has received symposium expenses from Abbott and Pfizer. The Cardiff University Department of Dermatology & Wound Healing benefits financially from the Dermatology Life Quality Index and has received unrestricted educational grants from Abbott, Janssen, MSD, Pfizer, and Galderma.

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Cutaneous Human Papillomavirus Infection and Basal Cell Carcinoma of the Skin

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Human papillomavirus (HPV) is ubiquitous in skin and has been associated with nonmelanoma skin cancer. Iannacone *et al.* investigate the role of HPV in basal cell carcinoma (BCC) by assessing the presence of HPV antibodies, HPV DNA in tumors, and the relationship between these two markers and BCC. In contrast to squamous cell carcinoma (SCC), there is no association between HPV and BCC.

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UV radiation is the most important risk factor for nonmelanoma skin cancers (NMSCs). However, in the past decade, evidence has implicated human papillomavirus (HPV) as a possible risk factor in their development. Ascertaining the role of cutaneous HPV infection in NMSCs is important, especially as certain genera of HPV are believed to augment UV radiation–induced DNA damage (Arron *et al.*, 2011).

HPV is a DNA virus that replicates exclusively in keratinocytes and relies on the differentiation of keratinocytes to complete its life cycle (Aldabagh *et al.*, 2012). There are over 180 types of HPV, which have specific tropism for cutaneous or mucosal epithelium, and belong to one of five genera: alpha, beta, gamma, mu, or nu. The association between high-risk alpha-HPV and cervical cancer and the mechanism for viral transformation have been well established, but associations reported between HPV and NMSC are inconsistent.

In this issue, Iannacone *et al.* (2013) address the question of whether HPV is associated with the development of basal cell carcinoma (BCC). They evaluated circulating antiviral antibodies and lesional HPV DNA, and determined that there is no association between this virus and BCC.

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HPV and NMSC

Several groups have reported the presence of HPV DNA in lesional tissue and antibody seropositivity to cutaneous HPV, especially beta types, in patients with squamous cell carcinoma (SCC; Bouwes Bavinck *et al.*, 2010; Aldabagh *et al.*, 2012). Both HPV carriage and SCC, but not BCC, are increased in immunosuppressed individuals, suggesting an etiological role for this virus in SCC. At present, there are only a few conflicting studies on the role of HPV in BCC.

No study to date has found a significant association between seropositivity to any genus-beta type and BCC (Feltkamp *et al.*, 2003; Andersson *et al.*, 2008; Karagas *et al.*, 2010); two studies failed to show an association with genus-alpha seropositivity as well (Andersson *et al.*, 2008, 2012). One report found that patients with BCC had lower seroprevalence than controls with benign skin diagnoses, which was postulated to be due to the inability of patients with BCC to mount an adequate HPV antibody response (Andersson *et al.*, 2008). To date, only two studies have reported findings on the association between BCC and seroreactivity to cutaneous HPV in genera other than the beta-genus (Andersson *et al.*, 2008, 2012).

In this issue, Iannacone *et al.* (2013) investigate the association between BCC and HPV in a US population, using a clinic-based case–control study of 224 immunocompetent patients with BCC and 300 controls. They report the seroprevalence of antibodies to cutaneous papillomaviridae from all five genera of HPV and the presence of lesional viral DNA in a subset of tumors. However, there was no analysis of viral DNA from tissue in control subjects for comparison. Serum antibodies investigated by Iannacone *et al.* (2013) include those against cutaneous alpha types 2, 3, 7, 10, 27, 57, and 77; beta types 5, 8, 9, 15, 17, 20, 23, 24, 36, 38, 49, 75, 76, 92, 96, and 107; gamma types 4, 48, 50, 65, 88, 95, 101, and 103; mu type 1; and nu type 41. The authors detected viral DNA in lesional tissue from of beta types 5, 8, 9, 12, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25, 36, 37, 38, 47, 49, 75, 76, 80, 92, 93, and 96; gamma types 4,