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REVIEW

The Genetics of Hidradenitis Suppurativa

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Abstract: Hidradenitis suppurativa (HS) is a chronic, relapsing inflammatory skin disease characterized by painful nodules, abscesses, tunnels, and scarring, with substantial clinical and psychological burden. Genetic studies have revealed that HS has a complex and heterogeneous architecture, encompassing rare monogenic mutations, intermediate-frequency variants, and polygenic risk distributed across multiple loci. Familial aggregation, twin studies, and genome-wide association studies collectively demonstrate that inherited factors contribute substantially to disease susceptibility. Different genetic profiles influence disease onset, severity, and clinical phenotype. Monogenic γ-secretase mutations are associated with early-onset, severe, and extensive disease, whereas polygenic risk shapes heterogeneous presentations and may modify disease trajectory. Genetic variants implicated in HS also intersect with systemic comorbidities including inflammatory bowel disease, spondyloarthritis, coronary artery disease, and diabetes, highlighting shared pathogenic pathways. Mechanistic insights indicate that dysregulated Notch and Wnt/β-catenin signaling; keratinization and epithelial differentiation are central drivers of genotype-informed clinical trials. Despite advances, many variants remain uncharacterized, and polygenic risk scores currently have limited predictive power. Integration of genetic findings with clinical, environmental, and longitudinal phenotypic data is therefore essential to inform risk assessment, patient stratification, and early intervention. This review synthesizes current knowledge on HS genetics, emphasizing genotype-phenotype correlations, comorbidity associations, and translated opportunities, and outlines research priorities needed to advance toward precision medicine approaches for HS.

Keywords: inflammatory skin disease, polygenic risk, γ-secretase mutations, genotype–phenotype correlation, notch signaling, precision medicine

Introduction

Hidradenitis suppurativa (HS) is a chronic, relapsing inflammatory skin disease characterized by painful nodules, abscesses, tunnels, and scarring, most commonly affecting intertriginous areas.[1] It affects approximately 1–4% of the population, though prevalence varies by region and diagnostic criteria, and is frequently underrecognized.[2,3] HS imposes a substantial clinical and psychological burden, with patients experiencing delayed diagnosis, recurrent flares, chronic pain, impaired quality of life, high rates of work disability, and an elevated risk of systemic comorbidities.[4,5] The clinical presentation is highly heterogenous, with substantial variation in severity, lesion distribution, and disease trajectory.[6,7]

Genetic factors have long been suspected to play an important role in HS. Up to one-third of patients report a family history, and heritability estimates from family-based and twin studies support a strong inherited component.[8,9] Advances in sequencing and genome-wide association studies (GWAS) have dramatically expanded the understanding of HS genetics, revealing contributions from rare high-penetrance mutations, intermediate-frequency variants, and polygenic risk distributed across multiple loci.[10,11] These insights increasingly point to dysregulation of epidermal differentiation, Notch and Wnt signaling, and keratinization pathways as central to HS pathogenesis.[11] Notch signaling plays a central role in epidermal biology, where ligand binding between adjacent cells triggers proteolytic cleavage of the Notch receptor

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and release of the Notch intracellular domain (NICD), allowing it to translocate to the nucleus and regulate transcriptional programs that control keratinocyte differentiation and hair follicle homeostasis.[12]

HS is increasingly understood as a disorder in which inherited alterations in epithelial structure and signaling predispose the follicle to dysfunction before inflammation becomes clinically evident.[13] Clarifying the genetic architecture of HS has implications for pathophysiology, diagnosis, and management. Genetic insights can inform family counseling, help identify individuals at higher risk, and highlight pathways that may inform targeted therapies or guide patient stratification in clinical trials.[14]

This review synthesizes current evidence on HS genetics, integrating monogenic and polygenic findings and emphasizing their clinical implications. By examining genotype-phenotype correlations, associations with comorbidities, and emerging translational opportunities, the review aims to clarify how genetic insights can inform patient care today while outlining key research priorities needed to advance toward personalized medicine approaches for HS.

Evidence for Genetic Predisposition

Familial aggregation and early-onset disease were among the earliest indications that heredity contributes substantially to HS.[15] Multiple cohort and registry studies report that roughly 30–40% of patients have an affected family member, with early-onset cases showing particularly high familial clustering.[8,16] Early-onset HS is particularly suggestive of stronger genetic susceptibility, as cohorts with onset in adolescence show higher rates of positive family history and more extensive disease.[16,17] Twin studies provide stronger confirmation: narrow-sense heritability has been estimated as high as ~77%, consistent with a polygenic architecture rather than simple Mendelian inheritance.[8] Together, these findings demonstrate that inherited factors, including rare high-penetrance mutations in a minority of families alongside broader polygenic contributions, play a substantial role in HS susceptibility.

Given the strength of the genetic evidence, structured family history should be part of routine HS assessment,[18] and a positive family history or very early onset may warrant genetic counselling and, in select cases, targeted sequencing, for example when clinical features suggest γ-secretase–related familial HS.[19–21] Genetic risk information can support anticipatory guidance, help identify relatives who may benefit from earlier evaluation or risk-modifying interventions, and provides a rationale for genotype-informed research focused on early detection and prevention.

Y-Secretase Complex and Monogenic HS

A subset of HS, particularly familial and early-onset cases, is caused by mutations in genes encoding components of the γ-secretase complex (NCSTN, PSEN1, PSENEN) (Table 1).[19,22] These mutations are rare and account for only a small fraction of all HS cases,[23,24] but they provide a clear monogenic cause in affected families.[19,22] Patients with these

Table 1 Genes Implicated in Monogenic and Syndromic Forms of Hidradenitis Suppurativa

Gene	Pathway/Biological Function	HS Phenotype	Key Clinical Features	Evidence Type
NCSTN	γ-secretase complex	Familial monogenic	Early onset, severe and extensive disease, variable penetrance	Familial sequencing studies[19]
PSEN1	γ-secretase catalytic unit, Notch signaling	Familial monogenic	Early onset, aggressive disease in some families	Familial sequencing studies[19]
PSENEN	γ-secretase complex, Notch signaling	Familial monogenic	Early onset, follicular occlusion	Familial sequencing studies[19]
NOD2	Innate immune sensing, NF-κB signaling	Syndromic/ autoinflammatory	HS with inflammatory bowel disease, arthritis, systemic inflammation	Whole-exome sequencing[25]
OTULIN	Ubiquitin regulation, immune signaling	Autoinflammatory	Multisystem inflammation with cutaneous disease	Rare variant reports[25]
PSTPIP1	Inflammasome regulation, cytoskeletal signaling	PASH/ PAPASH syndromes	HS with pyoderma gangrenosum, acne and arthritis	Whole exome sequencing[25]
NLRC4	Inflammasome activation, innate immunity	Syndromic	HS with neutrophilic dermatoses and systemic inflammation	Whole-exome sequencing[25]

mutations often present with earlier disease onset, more extensive lesions, and severe disease courses, although penetrance is variable.[9]

Mutations in γ-secretase impair Notch signaling (Figure 1), as loss of γ-secretase activity prevents cleavage of the Notch receptor and reduces generation of the NICD, leading to reduced Notch-dependent transcriptional activity, which disrupts keratinocyte differentiation and follicular epithelial homeostasis,[12] and likely leads to the follicular occlusion and nodules formation characteristic of HS.[20,26,27] Recognition of familial patterns and early-onset HS could be used to guide the consideration of genetic counseling or, in some instances, sequencing of γ-secretase genes. However, routine genetic testing is not currently recommended for all HS patients, as most cases are polygenic or sporadic.

These rare γ-secretase mutations represent one category of genetic HS, illustrating how single-gene defects can cause disruptions that lead to disease.

Rare Variants and Syndromic Forms

Although most HS cases are sporadic or polygenic,[28] a minority occur in the context of rare syndromic or autoinflammatory conditions for which genetic factors beyond γ-secretase genes have been implicated.[29] Recognizing these forms is clinically important because they may present with additional systemic features (eg., arthritis, gastrointestinal inflammation, neutrophilic dermatoses)[29,30] and may require tailored diagnostic and management strategies.

A subset of HS occurs as part of autoinflammatory syndromes characterized by dysregulated innate immunity, including pyoderma gangrenosum, acne and suppurative hidradenitis (PASH); pyogenic arthritis, pyoderma gangrenosum, acne and suppurative hidradenitis (PAPASH); and synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO).[29] These syndromes share overlapping cutaneous and musculoskeletal inflammatory manifestations, and HS may represent one component of broader systemic disease involving arthritis, osteitis, pustulosis, and neutrophilic dermatoses.[31,32] Recognition of these presentations may prompt evaluation for extra-cutaneous involvement and influence therapeutic decisions.

Genetic studies of syndromic HS and related conditions have begun to elucidate variants outside the classical γ-secretase components.[9] Whole-exome sequencing in small cohorts has identified variants in genes involved in innate immune signaling and autoinflammation, including NOD2, OTULIN, PSTPIP1, and NLRC4, in individuals with combined features of HS, pyoderma gangrenosum, arthritis, and gut inflammation.[25] These findings support the concept that syndromic HS represents a polygenic autoinflammatory subset with contributions from multiple immune-regulatory loci.

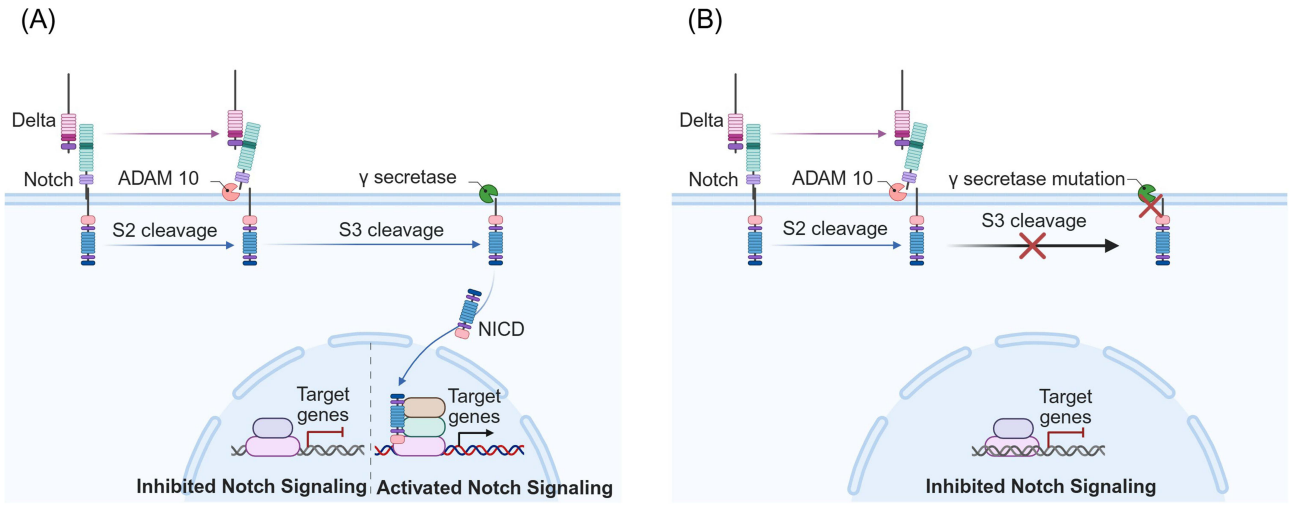

Figure 1 Disrupted Notch signaling in hidradenitis suppurativa (HS). (**A**) The Notch receptor is activated when Delta binds, triggering sequential proteolytic cleavages at sites S2 by ADAM10 and S3 by γ-secretase. This releases the NICD, which translocates to the nucleus to regulate transcription programs. (**B**) Mutations in γ-secretase components impair S3 cleavage of the Notch receptor, preventing NICD translocation and inhibiting Notch-dependent transcription.
Notes: ADAM10 – ADAM metallopeptidase domain 10; Delta – Delta like canonical Notch ligand; Notch – Notch receptor; S2 – Site 2; S3 – Site 3; X–indicates that an activity is not happening.

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These findings highlight the genetic heterogeneity of HS, with implicated genes spanning multiple biological pathways (Table 1). While monogenic forms are primarily driven by mutations in components of the γ-secretase complex, leading to impaired Notch signaling and disrupted follicular epithelial differentiation,[19,22] genes associated with syndromic and autoinflammatory HS, including *NOD2, OTULIN, PSTPIP1*, and *NLRC4*, are involved in innate immune sensing, ubiquitin regulation, and inflammasome activation.[25,33,34] This distribution of genetic risk across epithelial and immune-regulatory pathways supports a model in which both follicular structural defects and dysregulated inflammation contribute to disease pathogenesis.

In addition, HS may co-occur with other genetically mediated disorders of keratinization or follicular occlusion, such as Dowling-Degos disease[35] and the follicular occlusion tetrad,[36] reinforcing the intersection of epidermal differentiation and innate immune pathways in a subset of HS presentations. An increased prevalence of HS has also been reported in individuals with chromosomal abnormalities, most notably trisomy 21 (Down syndrome), likely reflecting altered keratinocyte proliferation and follicular occlusion rather than single-gene effects.[37,38] Although uncommon, these syndromic presentations are documented in case series and reports and, in selected patients, consideration of targeted genetic evaluation and multidisciplinary management may be warranted.[39–41]

Polygenic Risk and Common Variants

Accumulating evidence indicates that the majority of HS susceptibility is driven by the combined effects of multiple common genetic variants with modest individual effect sizes, consistent with a polygenic disease architecture.[11,42,43] GWAS and large-scale sequencing efforts have identified several risk loci associated with HS, implicating genes involved in epidermal differentiation, follicular development, and epithelial stem cell regulation.[11,43] Notably, variants mapping to pathways regulating keratinization, cell–cell adhesion, and follicular integrity have emerged across studies, reinforcing the central role of epithelial dysfunction in HS pathogenesis.[11,43]

A recent GWAS has highlighted enrichment of risk loci within or near genes involved in Notch and Wnt/β-catenin signaling,[11] pathways already implicated by rare γ-secretase mutations in familial HS.[44] These broader trends are further exemplified by a large meta-analysis of 4540 HS cases, which identified multiple genome-wide significant loci, including SOX9, KLF5, KLF4, and the HLA region, emphasizing the genetic complexity of HS and the influence of population structure and sex-specific effects on disease susceptibility.[10] Functional annotation of associated variants implicated regulatory effects on transcription factors central to follicular and epidermal biology, with risk alleles at KLF5 and SOX9 altering transcriptional activity in directions consistent with follicular hyperkeratosis and impaired differentiation.[10] Chromatin interaction analyses further highlighted KLF4 as a candidate target gene, linking common variant risk to epidermal differentiation, wound repair, and pro-inflammatory signaling pathways.[10]

These findings suggest that disruption of follicular signaling and differentiation represents a shared pathogenic mechanism across both monogenic and polygenic forms of disease.[11] Additional associated loci point to immune-related pathways, supporting a model in which genetically primed epithelial dysfunction precedes and secondary inflammation.[10,45]

Despite these advances, the translation of polygenic findings into clinical practice remains limited. Individual variants confer small increments in risk, and current polygenic risk scores lack sufficient predictive power for diagnosis or prognosis.[46,47] Moreover, most GWAS have been conducted in populations of European ancestry, limiting generalizability and underscoring the need for more diverse cohorts.[11] Nevertheless, polygenic analyses provide important mechanistic insight and may ultimately contribute to patient stratification, identification of high-risk subgroups, and the design of genotype-informed clinical trials as datasets expand and functional annotation improves.

Genetic susceptibility in HS creates a primed environment in which environmental and lifestyle factors can trigger lesion formation.[9] Environmental and lifestyle factors such as smoking and obesity are strongly associated with increased disease risk and greater severity,[48–50] likely acting on pathways already disrupted by genetic variants. Smoking has been linked to worsening HS and may influence Notch-related follicular pathways,[48] while obesity contributes mechanical stress and systemic inflammation that exacerbate disease manifestations.[49,51] Although direct studies of genotype and environment interactions are lacking, these observations support a model in which environmental factors modulate disease expression in genetically predisposed individuals.

Environmental and Lifestyle Modifiers

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Genotype-Phenotype Correlations and Comorbidities

Emerging evidence indicates that distinct genetic architecture in HS are associated with differences in disease onset, severity, lesion distribution, and comorbidity burden.[14,28] Monogenic forms linked to γ-secretase mutations are more often characterized by early onset, extensive involvement, and severe disease, although penetrance and expressivity remain variable.[9,44] In contrast, polygenic HS appears to reflect the cumulative effects of multiple risk alleles that modulate epithelial integrity and inflammatory thresholds, contributing to heterogeneous clinical presentations.[28]

Genetic susceptibility also appears to influence the spectrum of HS-associated comorbidities. Variants affecting epithelial signaling and immune regulation overlap with pathways implicated in inflammatory bowel disease, spondyloarthritis, and other immune-mediated conditions,[10] consistent with the increased prevalence of these disorders among HS patients.[52] Syndromic and autoinflammatory forms further illustrate this overlap, as patients frequently present with musculoskeletal inflammation, neutrophilic dermatoses, and systemic inflammatory features alongside cutaneous disease.[29]

From a clinical perspective, recognizing genotype-phenotype patterns may support more individualized monitoring strategies, particularly in patients with early-onset, severe, or multisystem disease.[14] Although genetic profiling is not yet routinely used to guide management, an improved understanding of genetic contributions to disease expression and comorbidity risk may inform multidisciplinary care, anticipatory screening, and future genotype-informed therapeutic approaches.[14]

Translational Implications

Advances in understanding the genetic architecture of HS are beginning to inform therapeutic strategies and clinical trial design. Genetic evidence from GWAS implicates Notch and Wnt/β-catenin pathways, which are disrupted by rare γ-secretase mutations and by common variants near genes such as *WNT10A* and *TMED10* that influence follicular development and keratinocyte differentiation.[11,43] These findings suggest that disease mechanisms extend beyond inflammatory cascades to include epithelial signaling and follicular homeostasis defects,[11] offering rationale for exploring interventions targeting follicular biology alongside immune suppression.

Biologic therapies targeting inflammatory pathways, include TNF and IL-17/12/23 inhibitors, have shown efficacy in moderate-to-severe HS,[53,54] but responses are heterogeneous and not fully predicted by genetic or clinical features.[55] Evidence linking genetic variants to key regulatory pathways underscores the potential for novel agents that more directly modulate follicular differentiation and repair, though such approaches remain investigational and require mechanistic validation.

Several challenges limit direct clinical application of genetic findings. Most GWAS have focused on populations of European ancestry, restricting discovery of ancestry-specific risk alleles and potential therapeutic targets.[56,57] Current polygenic risk scores remain insufficient for clinical decision-making,[27,47] and functional validation of associated loci is needed to translate associations into druggable mechanisms. Addressing these gaps through multi-ancestry genomic studies, functional genomics, and integration of genetic data into clinical trials will be essential to realize precision medicine in HS, enabling improved risk stratification and pathway-guided therapy.

Future Directions

Although recent genetic studies have advanced understanding of HS, key gaps remain that must be addressed to translate findings into clinical practice. One major limitation is the lack of ancestral diversity in genetic studies, with most GWAS and meta-analyses having predominantly included individuals of European descent,[10] limiting generalizability and hampering discovery of population-specific risk alleles. This limitation is underscored by marked population differences in HS epidemiology, including sex distributions, with female predominance reported in European and North American cohorts and male predominance observed in Asian populations.[58] Larger multi-ancestry cohorts, including underrepresented groups, are essential to capture the full architecture of HS risk and enable improved risk prediction.[14]

Integration of genetic data with clinical risk factors, such as smoking, obesity, age of onset, lesion distribution, and comorbidity profiles, is critical for meaningful decision making.[49,59] Longitudinal cohort studies combining genomic, phenotypic, environmental, and health outcomes data can clarify how genetic susceptibility interacts with modifiable exposures and refine risk models. Multiomic approaches integrating whole-exome or genome sequencing with transcriptomic, proteomic, and epigenomic profiling in lesional and nonlesional tissue are needed to map causal pathways, identify biomarkers, and prioritize drug targets.[60,61]

Clinical research priorities include genotype-informed trials, where molecular subclassification may help stratify patients and tailor therapies,[14] and longitudinal studies to assess how polygenic risk specific variants influence treatment response and long-term outcomes.[27,62] Precision medicine approaches, including integrating polygenic risk scores with clinical variables and biomarker panels, hold promise for improved early intervention, targeting prevention, and personalized therapeutic decisions.[14,63] Validation in diverse populations and careful assessment of clinical utility remain critical before routine adoption.[62]

Conclusion

Over the past decade, genetic research has transformed our understanding of HS, revealing a complex interplay between rare monogenic mutations, intermediate-frequency variants, and broad polygenic architecture.[28] While rare pathogenic variants in γ-secretase components such as NCSTN, PSEN1, and PSENEN explain a small fraction of familial HS and point mechanistically to Notch pathway disruption,[20,44] most patients' genetic risk arises from numerous common alleles that cumulatively modulate epithelial integrity, follicular keratinization, and immune responses.[11,43] GWAS and meta-analyses have identified multiple loci near regulators of keratinocyte differentiation and follicular biology, including WNT10A, TMED10, SOX9, and KLF5, reinforcing that dysregulated epidermal signaling is central to disease pathology.[11,43]

Genotype-phenotype correlations illustrate that monogenic and syndromic forms often manifest with early onset, extensive lesions, and systemic inflammatory features,[30,64] whereas polygenic risk contributes to heterogenous phenotypes and overlaps with comorbid conditions such as inflammatory bowel disease, spondyloarthritis, and cardiometabolic disorders.[10,65,66] Genetic correlations between HS and coronary artery disease or diabetes further underscore shared pathways influencing inflammation and metabolism.[66]

Despite these advances, routine clinical application of genetic findings remains limited. Population diversity in genetic studies remains inadequate,[67] and polygenic risk scores are not yet predictive enough for clinical decision-making.[66] Functional validation of associated loci and integration of genetics with clinical phenotypes, environmental exposures, and longitudinal outcomes are essential next steps. As multi-ancestry cohorts, multi-omics integration, and genotype-informed clinical trials mature, genetic insights will increasingly contribute to personalized risk prediction, early intervention, and pathway-targeted therapies. Ultimately, a precision medicine framework that combines genetic profiles with clinical context holds promise for improving outcomes and reducing the substantial burden of HS.

Disclosure

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Acne and Suppurative Hidradenitis (PAPASH), Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis (SAPHO), and Rarer Forms. *Dermatol Clin*. 2024;42(2):247–265. doi:10.1016/j.det.2023.12.004
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