ORIGINAL ARTICLE

A genome-wide association meta-analysis links hidradenitis suppurativa to common and rare sequence variants causing disruption of the Notch and Wnt/β-catenin signaling pathways

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Background: The contributions of genetic and environmental risk factors to hidradenitis suppurativa (HS) are both poorly understood.

Objective: To identify sequence variants that associate with HS and determine the contribution of environmental risk factors and inflammatory diseases to HS pathogenesis.

Methods: A genome-wide association meta-analysis of 4814 HS cases (Denmark: 1977; Iceland: 1266; Finland: 800; UK: 569; and US: 202) and 1.2 million controls, searching for sequence variants associated with HS.

Results: We found 8 independent sequence variants associating with HS, 6 common and 2 rare (frequency <1%). Four associations point to candidate causal genes, *NCSTN, PSENEN, WNT10A*, and *TMED10*, that all map to the Notch and Wnt/β-catenin signaling pathways, involved in epidermal keratinization.

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Limitations: Limited racial diversity may prevent identification of sequence variants of particular importance in non-Caucasian populations.

Conclusions: These findings demonstrate that genes and pathways involved in epidermal keratinization are the genetic backbone of HS pathology. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2024.11.050.)

Key words: γ-secretase; causality; genetics; genome-wide association study; GWAS; hidradenitis suppurativa; inheritance; NOTCH; Notch signaling; pathway analysis; WNT; Wnt signaling.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the intertriginous skin areas,[1,2] where hyperkeratinization of the epithelium causes pathologic hair follicle occlusion, with subsequent dilation and rupture.[2-5] The worldwide prevalence of HS is around 1%,[6-11] albeit with regional differences as high as 3.4%.[12] Obesity and tobacco smoking are the main environmental risk factors of HS, but causal relationships are debated.[13,14]

HS heritability is estimated around 80%.[15,16] Mendelian-based family studies implicated loss-of-function mutations in genes encoding the γ-secretase complex proteins and abrogated Notch signaling in HS pathology.[17-20] Those mutations are, however, rare (<0.01%) and have only small effects on HS risk at a population level,[21-25] consequently a complex genetic inheritance has been suggested.[16,26] Conversely, sequence variants involving immunomodulating pathways are believed to play an important role.[4,27,28] A recent genome-wide association study (GWAS) in 1,640 HS cases and 756,394 controls found only 2 independent sequence variants (rs10512572-A and rs17090189-A) to associate with HS.[29]

CAPSULE SUMMARY

- This study identifies common and rare sequence variants in genes in the Notch and Wnt/β-catenin signaling pathways, responsible for epidermal keratinization and hair follicle/keratinocyte proliferation and differentiation, as contributors to the risk of developing hidradenitis suppurativa.
- These findings may direct research into the treatment and prevention of hidradenitis suppurativa with modalities that alleviate hyperkeratinization rather than suppress the immune system and highlight the benefits of weight loss.

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Patient consent: The authors attest to obtaining written patient consent for the publication of recognizable patient photographs or other identifiable material, with the understanding that this information may be publicly available.

IRB approval status: DK: DDPA genetic approval: P-2019-99, and the National and Zealand Region Committees on Health Research Ethics: NVK-1700407. IS: The Icelandic study on the genetics of HS was approved by the National Bioethics Committee in Iceland (Approval no. VSN-18-080). FI: The FinnGen research project, controlled by the University of Helsinki, has provided publicly available GWAS results for numerous phenotypes through the online FinnGen database UK: This research has been conducted using the UK Biobank Resource under Application Number '56270'. US: Intermountain Healthcare Institutional Review Board approved this study (IRB# 1051071), and all participants provided written informed consent and samples for genotyping.

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Abbreviations used:

eQTL:	expression quantitative trait loci
FDR:	false discovery rate
GWAS:	genome-wide association study
HS:	hidradenitis suppurativa
LD:	linkage disequilibrium
NCSTN:	nicastrin
pQTL:	protein quantitative trait loci
PSENEN:	presenilin enhancer protein 2
TMED10:	transmembrane P24 trafficking protein 10
Wnt:	wingless/integrated

Those variants are located close to *SOX9* and *KLF5*, but neither variant was shown to affect their expression. Therefore, to search for sequence variants associating with HS we conducted a meta-GWAS of HS in cohorts from 5 countries.

MATERIALS AND METHODS

Study cohorts and ethics statements

Our combined meta-GWAS cohort consists of 4,814 HS cases and 1,216,105 controls from Denmark, Iceland, Finland, the United Kingdom, and the United States. Cases of HS were identified through International Code of Disease codes.

Details on recruitment, sample collection, genotyping, and sequencing as well as quality control are described in Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1.

Association analysis

We used logistic regression analysis assuming a multiplicative model to test for association[30] between HS and sequence variants in each of the 5 cohorts adjusting for relevant potential confounders. We used linkage disequilibrium (LD) score regression intercepts[31] to adjust for inflation of *P* values due to cryptic relatedness and stratification.

The meta-analyses combined GWASs from the respective cohorts using a fixed effects inverse-variance method assuming a common odds ratio but allowing different population frequencies for alleles and genotypes. The threshold for genome-wide significance was corrected by weighted Bonferroni adjustment using as weights the enrichment of variant classes with predicted functional impact among association signals.[32] For full information on confounder adjustments, significance threshold, and conditional analyses, see the Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1.

Variant to gene mapping and functional analyses

To predict the most likely causal gene for each association signal, variants to gene mapping were conducted for all variants in high LD with the top variant ($r^2 > 0.8$). Expression quantitative trait loci (eQTL) were determined in multiple tissues using RNA sequencing data sets from deCODE, GTEx (https://www.gtexportal.org/home/), and other available public data sets.[33,34] Effects of top associating variants and variants in high LD on plasma protein levels (protein quantitative trait loci [pQTL]) were determined in available measurements from deCODE (SomaScan)[35] and UK Biobank (Olink).[36]

Any consequences of the coding variants on protein structure and function were assessed by AlphaFold[37] and Polyphen-2 v2.2.3.[38]

We performed functional enrichment analysis (cellular components, cellular pathways, tissue localization, and known diseases) of the candidate causative genes supported by coding and/or eQTL effects and genes encoding proteins which plasma levels were affected by trans-pQTLs, using STRING v11 in combination with Cytoscape 3.9.1 and the functional enrichment tool in the stringApp add-on.[39-42]

Figures

Figures in this article were created using a combination of STRING v11 and Cytoscape 3.9.1,[39-41] the Chimera software[43] or https://BioRender.com.

RESULTS

GWAS meta-analysis

In a meta-analysis, we combined HS GWAS results using 4,814 cases and 1,216,105 controls from 5 data sets (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1). Assuming additive effect and applying a fixed effects inverse variance model, we found 8 independent signals that associate with HS (Table I, Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1, and Fig 1). Two were rare loss-of-function variants in nicastrin (*NCSTN*) (Icelandic variant), encoding nicastrin, an integral component of the multimeric γ-secretase and presenilin enhancer protein 2 (*PSENEN*) (Danish variant), encoding presenilin enhancer 2, a subunit of the γ-secretase complex, both previously reported in family studies[20,22] and 4 were common variants not reported previously. The remaining 2 signals were reported in a recent GWAS[29] and we replicated the association of the lead variant rs17090189-G while the other lead

Table I. Information on the 6 common and 2 rare independent variants found during the HS meta-analysis

Locus	Chr	PosB38	rsID	OA	EA	EAF (%)	Candidate gene	Variant type	OR	*P*	P_{bonf}	P_{het}	I^2
1q23.2	chr1	160354223	rs771414318*	C	T	0.0052	*NCSTN*	Stop gained	112.3	2.4E-15	9.1E-10	-	-
2q35	chr2	218890289	rs121908120	T	A	2.13	*WNT10A*	Missense‡	0.580	1.4E-10	0.00028	.78	0
6p21.32	chr6	32433162	rs3129859	G	C	34.2	.	Intergenic	0.843	4.4E-14	5.60E-06	.36	8.8
9q31.3	chr9	108703801	rs10816701	T	C	50.9	.	Intergenic	0.859	4.3E-13	1.8E-05	.18	35.8
13q22.1	chr13	73432270	rs17090189	A	G	15.9	.	Intergenic	0.792	1.8E-14	7.6E-07	.22	29.7
14q24.3	chr14	75,230,213	rs17103088	A	G	23.2	*TMED10*	TF binding site	1.208	1.1E-14	4.7E-07	.15	40.1
17q24.3	chr17	71519473	rs17226067	A	G	10.3	.	Regulatory region	1.279	1.3E-13	5.6E-06	.080	52.1
19q13.12	chr19	35746829	.†	AC	A	0.0076	*PSENEN*	Frameshift	58.3	1.3E-11	5.0E-06	-	-

Association results for the 8 lead variants that associate with HS. The table shows for each variant, the loci (cytogenetic band), chromosome, its position in NCBI Hg38 build, the rs-ID, other allele (OA), effect allele (EA), effect allele frequency (EAF) as simple average over frequencies in the 5 data sets included, the likely candidate gene (see next section), the effect (odds ratio [OR]) and *P* values from a fixed effect inverse variance weighted meta-analysis of association results from logistic regression of HS on genotype count in individual data set. P_{bonf} is the Bonferroni adjusted *P* value, adjusted according to variant class, and P_{het} and I^2 correspond to a test of heterogeneity in effect estimates between data sets.

HS, Hidradenitis suppurativa; *NCSTN*, nicastrin; *PSENEN*, presenilin enhancer protein 2; *TMED10*, transmembrane P24 trafficking protein 10; *WNT10A*, wingless/integrated 10A.

*Variant only found in the Icelandic data set.

†Variant only found in the Danish data set.

‡rs121908120-A showed trans-pQTL effects on plasma levels of: galanin, uridylate-specific endoribonuclease, protein cystatin M, Kallikrein-8, protein proactivator polypeptide-like 1, Kallikrein-7, serine protease inhibitor Kazal-type 5, peptidase M20 domain-containing protein 1, coiled-coil glutamate rich protein 2, interleukin-22, DNA topoisomerase I and Kallikrein-15 (see Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1).

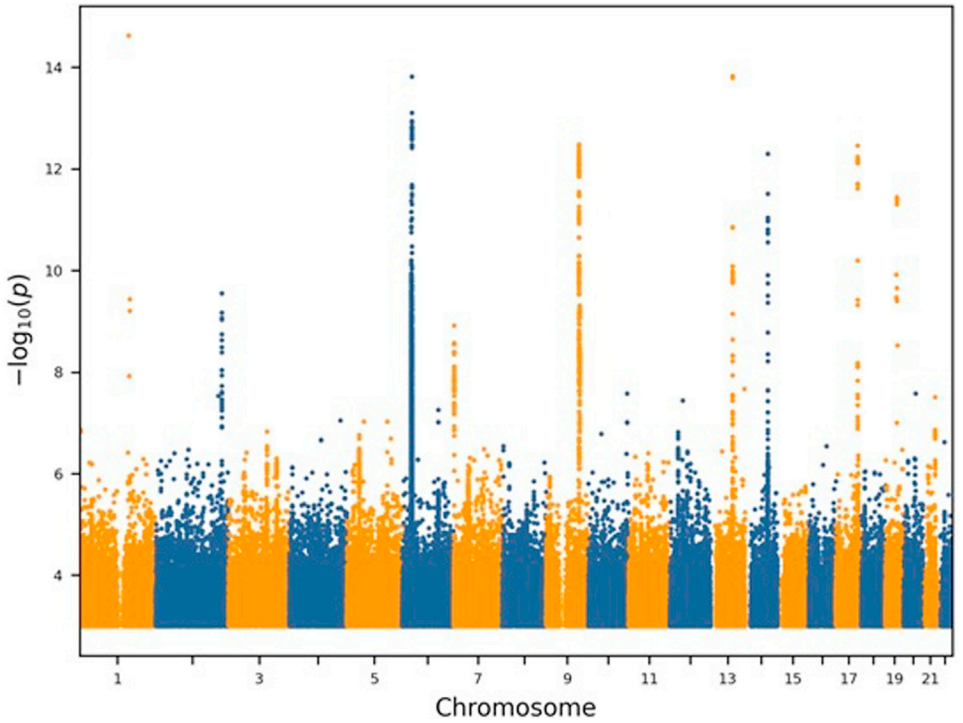

Fig 1. Manhattan plot of sequence variants associated with hidradenitis suppurativa. Manhatten plot for the association between sequence variants and the clinical phenotype hidradenitis suppurativa. No significance threshold is shown as adjusted Bonferroni procedure weighted for variant classes and predicted functional impact were used (Sveinbjornsson et al[32]).

variant rs17226067-G in our study is in strong LD with the reported variant rs10512572-A ($r^2 > 0.99$).

Functional analyses

We searched for effects of the associating variants on amino acid sequence and/or mRNA expression (eQTLs), pointing to a candidate causal gene at the locus, and effects on plasma protein levels (pQTLs). We found 3 coding variants: rs121908120-A, a missense variant in wingless/integrated (*WNT*)*10A*; rs771414318-T a stop-gain variant in *NCSTN* leading to truncation; chr19:35746829-AC:A, a frameshift mutation in *PSENEN*, and one eQTL variant: rs17103088-G, affecting expression of transmembrane P24 trafficking protein 10 (*TMED10*) in blood. We also found that rs121908120-A in *WNT10A* was a trans-pQTL that associated with levels of several plasma proteins.

The effects of the coding variants on protein function were estimated based on predictive structural models using AlphaFold and Polyphen-2 software.[37,38] Rs771414318-T encodes a p.Arg429Ter mutation in *NCSTN* causing a truncation at a luminal α-helix located close to the transmembrane border of nicastrin (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1). Chr19:35746829-AC:A encodes a p.Leu98TrpfsTer47 frameshift mutation in *PSENEN* causing a 42 amino acid elongation (40% protein elongation) at the C-terminus and signaling part of presenilin enhancer 2.[37] Rs121908120-A encodes a p.Phe228Ile missense mutation in *WNT10A* located at one of the α-helices of Wnt-10a's signaling domain,[37] leading to reduced pathway signaling and thinning of intertriginous skin which is supported in clinical findings from Mendelian-based family studies where many individuals with *WNT10A* mutations suffer from soft and thin skin.[44] The effects of such large alterations cannot be accurately predicted, but they are expected to affect both secondary and tertiary protein structures, if they do not cause post-transcriptional degradation. This is supported by Polyphen-2 as the posterior probability of each of these mutations having a deleterious effect on protein function are 100%, 99.9%, and 99%, respectively.[38]

Rs17103088-G is reported the strongest regional cis-eQTL decreasing the expression of *TMED10* in blood (Z-score = −9.433, $P = 4.0 \times 10^{-21}$),[34] a finding replicated in the deCODE RNA-seq data set ($\beta = -0.103$sd, $P = 4.5 \times 10^{-15}$) and is in high LD ($r^2 = 0.68$) with the strongest cis-eQTL of *TMED10* in

blood (rs6574213, $\beta = -0.108$sd, $P = 1.4 \times 10^{-19}$). TMED10 is a transmembrane protein that decreases the activity of γ-secretase.[45] Trans-pQTL analyses showed that rs121908120-A associated with reduced plasma levels of the proteins galanin, uridylate-specific endoribonuclease, protein cystatin M, Kallikrein-8, protein proactivator polypeptide-like 1, Kallikrein-7, serine protease inhibitor Kazal-type 5, peptidase M20 domain-containing protein 1, coiled-coil glutamate-rich protein 2, interleukin-22, DNA topoisomerase I, and Kallikrein-15 (see Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1 for β-values, *P* values, and for r^2 between rs121908120 and variants with the strongest association with the protein levels). The majority of these proteins are either implicated in hair follicle/keratinocyte proliferation/differentiation or are substantially enriched in the epidermis[46-65] (see Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1). Although there was no effect on the plasma levels of Wnt-10a itself (cis-pQTL), these many trans-pQTL effects are likely mediated through Wnt-10a, since the p.Phe228Ile missense mutation in *WNT10A* has been shown to affect Wnt-10a function.[37,38]

We performed functional enrichment analysis[40-42] of the candidate causal genes supported by coding and/or eQTL effects and genes encoding proteins which plasma levels were affected by trans-pQTLs colocalizing with HS association signals and found enrichment for the γ-secretase pathway (compartment, false discovery rate [FDR] = 4.6×10^{-4}) (Fig 2), epithelial cells of the anterior pharynx (tissue, FDR = 0.0418), signaling (reactome pathways, FDR = 3.88×10^{-7}), secreted (signal, FDR = 3.88×10^{-7}), and skin diseases (diseases, FDR = 3.9×10^{-4}).

DISCUSSION

In this meta-GWAS of 4,814 HS cases and 1,216,105 controls, we identify 8 independent association signals conferring risk of HS, of which 4 point to genes of the Notch and Wnt/β-catenin signaling pathways. Furthermore, we replicate the finding of 2 previously reported HS-associated common sequence variants.[29]

The Notch and Wnt/β-catenin signaling pathways are vital for the formation of the epidermis and subsequently for epithelial hyperkeratinization and hair follicle proliferation[3,22-24,45,50,66-71] (explained in Supplementary Material, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1 and shown in Supplementary Fig 2, available via Mendeley at https://data.mendeley.com/datasets/jvpgmxs3n6/1). A shared feature of the 2 pathways is that while embryonic abrogation causes severe reactive epidermal hyperproliferation,[3,23,68,69] postnatal inhibition results in decreased production of keratins and decreased keratinocyte proliferation.[66,69] The aforementioned changes in protein structure of *NCSTN*, *PSENEN*, and *WNT10A* can therefore be expected to affect the epithelial integrity, its level of keratinization and subsequently the thickness of the skin.

Normal appearing, lesion-free HS skin is characterized by hyperkeratinization of the follicular border.[72] Thus, disturbance of the Notch and Wnt/β-catenin pathways is in line with current understanding of HS pathology.[1,3,4,44,66,67] It explains why predilection sites of ectopic HS are sites of frequent pressure, friction, and hyperkeratinization.[13,73,74] Fig 3 depicts how our genetic findings could play a role in HS pathology.

All potential causal variants that map to genes in the Notch signaling pathway increase the risk of HS. The rare loss-of-function variants, rs771414318-T and chr19:35746829-A inhibit the γ-secretase complex,[20,22] but the common variant rs17103088-G decreases the expression of *TMED10* whose function is to inhibit the γ-secretase complex.

The reason for this disparity may be timing. The rare loss-of-function variants likely inhibit embryonic Notch-signaling, thus negating proper epidermal formation and causing a reactive hyperproliferation, whereas rs17103088-G may act postnatally increasing keratinization (because of an increased function of the γ-secretase complex, please see Fig 3 for visualization). This would explain the 48-93-fold difference in risk conferred by the rare and the common variants, as the embryonic deactivation will have a stronger effect on the epidermal architecture.

Rs121908120-A represents both a missense mutation in *WNT10A* and trans-pQTL effects reducing the levels of several plasma proteins, for example, serine protease inhibitor Kazal-type 5 ($\beta = -0.144$) and Kallikrein-8 ($\beta = -0.165$). While the role of the Wnt/β-catenin pathway in HS is poorly understood, chronic Wnt activity has been found throughout HS-damaged skin,[75,76] potentially playing a role in the divergence from regeneration to fibroneogenesis leading to fibrotic scar tissue formation.[75] The protective effect of rs121908120-A on the risk of developing HS may therefore be mediated through reduced Wnt signaling. The effect of reduced serine protease inhibitor Kazal-type 5 levels associated with rs121908120-A is ambiguous as it inhibits degradation of the β-catenin destruction complex[70] (ie,

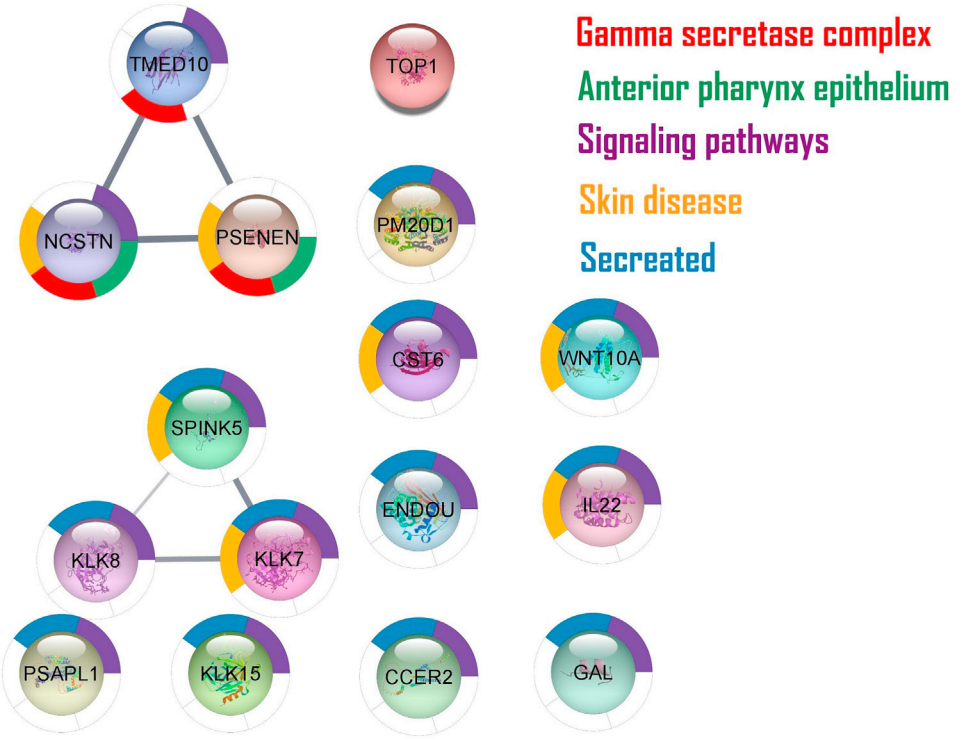

Fig 2. Functional enrichment analyses for the gene products associated with the HS phenotype. Functional enrichment analysis performed on candidate causative genes at the locus, in combination with protein quantitative trait loci affected at the locus as determined after variant to gene mapping. The enrichment was performed via STRING v11 and the Cytoscape 3.9.1 software in combination with the functional enrichment tool in the stringApp. Depictured are the 11 gene products found to be associated with the HS phenotype and color coded for the cellular components, cellular pathways, tissue localization, or known diseases enriched for within these gene products. The multicolored circle surrounding the individual products represents the areas for which the network achieved functional enrichment within the areas of cellular components, cellular pathways, tissue localization, and known diseases. The interconnecting lines indicate association between the genes in medical literature, with the bold lines indicating direct association as validated through pull-down analyses (in this figure representing, eg, the γ-secretase complex). It should be noted that while KLK8 did not appear as part of the enrichment for "skin diseases" both KLK8 and SPINK5 were statistically significantly enriched for "Netherton syndrome" (FDR = 0.0119)—a rare but well-known skin disease. *CCER2*, Coiled-coil glutamate rich protein 2; *CST6*, cystatin M; *ENDOU*, uridylate-specific endoribonuclease; *GAL*, galanin; *HS*, hidradenitis suppurativa; *IL22*, interleukin-22; *KLK7*, serine protease Kallikrein-7; *KLK8*, serine protease Kallikrein-8; *KLK15*, serine protease Kallikrein-15; *NCSTN*, nicastrin; *PM20D1*, peptidase M20 domain-containing protein 1; *PSENEN*, presenilin enhancer protein 2; *PSAPL1*, proactivator polypeptide-like 1; *SPINK5*, serine protease inhibitor Kazal-type 5; *TMED10*, transmembrane P24 trafficking protein 10; *TOP1*, DNA topoisomerase I; *WNT10A*, wingless/integrated 10A.

reduced serine protease inhibitor Kazal-type 5 will increase Wnt/β-catenin signaling and keratinization) but also inhibits Kallikrein-8 activity, that acts as an initiator of desquamation[49,50,71] (ie, reduced levels will increase desquamation and reduce hyperkeratinazation). Ultimately, the interplay between reduced levels of Kallikrein-8, serine protease inhibitor Kazal-type 5, and Wnt-10a and reduced HS risk warrant further investigation into the potential roles of these proteins in HS.

Surprisingly, while the protective variant rs121908120-A associates with reduced plasma level of IL-22 (β = −0.122) and reduced levels of IL-22 have been suggested to play a role in HS pathogenesis,[60] we did not uncover enrichment of sequence variants pointing to genes involved in inflammatory pathways. Notch signaling may have wider implications through its effect on innate immunity and defensin-mediated regulation of the epithelial microbiome.[77]

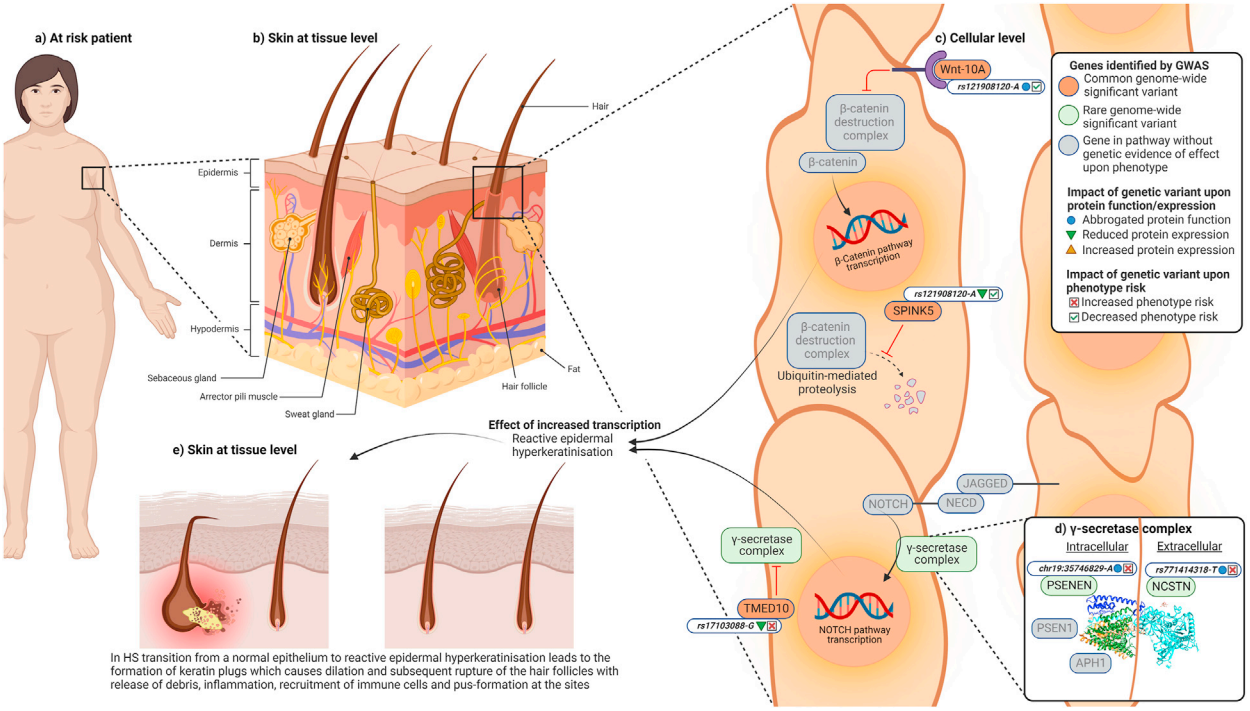

Fig 3. Overview of genetic findings in relation to disease pathology. Overview of the meta-GWAS's genetic findings in relation to known HS disease pathology. In an at-risk patient a), the normal architecture of the skin b) will be disturbed as a result of altered gene expression at a cellular level c). Here Wnt/β-catenin signaling is activated when a Wnt ligand binds to the target cell's receptor, as this lead to inhibited β-catenin degradation by the β-catenin destruction complex (referred to as the Axin-CK1α-APC-GSK-3β complex in the article's supplements). Reduced SPINK5 expression has the same effect as it functions by inhibiting the degradation of the β-catenin destruction complex, resulting in increased pathway transcription. Likewise reduced expression of TMED10 responsible for inhibition of the γ-secretase complex will lead to increased NOTCH pathway transcription. The rare variants depicted in the close-up in d) are expected to have an effect already in the embryonic stage where defects in the γ-secretase complex cause severe dysregulation of skin formation. Each of the genetic variants are therefore likely to lead to a reactive epidermal hyperkeratinization that as shown in e) transitions the skin, making in prone to formation of keratin plugs which causes dilation and subsequent rupture of the hair follicles with release of debris, inflammation, recruitment of immune cells, and pus-formation in the surrounding dermis. In the close-up of the γ-secretase complex, the Pen-2 subunit is colored blue, the presenilin-1 subunit is colored forest green, the APH-1 subunit is colored orange, and the nicastrin subunit is colored cyan. *APC*, Adenomatous polyposis coli; *CK1α*, casein kinase 1α; *GSK-3β*, glycogen synthase kinase 3β; *GWAS*, genome-wide association study; *HS*, hidradenitis suppurativa; *NCSTN*, nicastrin; *NECD*, Notch extracellular domain; *PSENEN*, presenilin enhancer protein 2; *APH-1*, anterior pharynx-defective 1; *SPINK5*, serine protease inhibitor Kazal-type 5; *TMED10*, transmembrane P24 trafficking protein 10; *Wnt*, wingless/integrated. This figure was created using Biorender (https://BioRender.com).

Our study also replicated the findings reported in a previous GWAS by Sun et al[29] Specifically, we replicated their finding of rs17090189-G and our lead variant rs17226067-G is in strong LD with their reported variant rs10512572-A ($r^2 > 0.99$). While neither we nor they could link either variants to eQTL or pQTL effects, these variants are in close proximity to the *SOX9* and *KLF5* genes both of which have important functions within the skin. *SOX9* is a central player in hair-follicle maturation and animal studies have shown that blockage of *SOX9* in mice leads to follicular epidermal thickening and dermal scarring.[78] Recently it has furthermore been shown that *SOX9* functions as a repressor of the Wnt/

β-catenin signaling pathway;[79] it thus compatible with our findings that blockage of Sox9 should increase Wnt/β-catenin signaling and keratinization.

Similarly, *KLF5* overexpression in mice has been linked to hyperkeratinization, follicular occlusion, and loss of regenerative ability,[80] which is compatible with murine intestinal studies that have shown that deletion of Klf5 in adult mice are associated with disruption of Wnt/β-catenin signaling through increased expression of Sox9.[81]

Ultimately, as our genetic findings point toward epidermal hyperkeratinization being central in disease pathology, this potentiates the role of keratinolytic agents in the treatment of HS, and dermatologists treating patients with HS should therefore consider keratinolytic agents as part of their treatment arsenal.

STRENGTHS AND LIMITATIONS

This study's greatest strength is the high-resolution sequence data for 4 of the 5 large cohorts included in the meta-analysis, allowing identification of both rare and common sequence variants associating with HS. Additionally, each cohort includes a large set of ethnically matched controls thus limiting confounding by genetic heterogeneity.

While low genetic heterogeneity constitutes a methodological strength, the limited racial diversity is a weakness given the discrepancies in HS prevalence across continents[6-12,82,83] that may reflect differences in genetic risk variants. Unfortunately, when this study was initiated back in 2015, HS was still considered an orphan disease,[84] and we therefore did not have access to cohorts containing a diversity in patients of skin of color, rather we primarily had access to Scandinavian cohorts that due to low rates of migration are mostly of Caucasian origin.[85]

Our results therefore most accurately infer information on the source populations of Caucasian origin.

Another relevant limitation is that the majority of the 5 cohorts did not include severity estimates such as Hurley staging[86] or HISCR50.[87] Due to a loss of power, it was therefore not possible to accurately investigate if the 8 sequence variants also affected disease severity.

CONCLUSION

Through our meta-GWAS of 4814 HS cases and 1,216,105 controls, we found 6 common and 2 rare sequence variants that associate with risk of HS and identified 4 candidate causal genes, *PSENEN, NCSTN, TMED10*, and *WNT10A*. These variants confirm the role of γ-secretase-related Notch signaling and link the Wnt/β-catenin signaling pathway to HS pathology strongly suggesting that errant hyperkeratinization of the hair follicle constitutes at least in part the backbone of HS pathology.

DATA SHARING STATEMENT

Data sharing of individual level data is not possible for this study as they are protected by national regulations, for example, the Danish Act on Processing of Personal Data and the permit of the National Bioethics Committee in Iceland (Approval no. VSN-18-080) and conditions issued by the Data Protection Authority in Iceland (PV-2017060950ÞS), etc. Full summary statistics from the meta-analysis will be made available at URL: https://www.decode.com/summarydata/ upon publication.

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Conflicts of interest

Dr Andersen reports that his attendance at the Nordic Congress of DermatoVenerology hosted in Copenhagen in 2022 was funded by Eli Lilly. Drs Stefansdottir, Halldorsson, Ferkingstad, Oddsson, Walters, Olafsdottir, Rutsdottir, Saemundsdottir, Melsted, Norddahl, Sulem, Stefansson, Holm, Gudbjartsson, Thorleifsson, Jonsdottir, and Stefansson are employees of deCODE Genetics/Amgen, Inc. Dr Zachariae has been a speaker/consultant for Jansen Cilag, Novartis, Almirall, UCB, Leo Pharma, Galderma, with no relation to the present manuscript. Dr Thomsen has received research support from Abbvie, Janssen, LEO Pharma, Novartis, Sanofi, and UCB; and has been a speaker/consultant for Abbvie, Eli Lilly, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, Symphogen, UCB, and UNION therapeutics, with no relation to the present manuscript. Dr Brodersen's spouse is a principal level employee at LEO Pharma, part of stock incentive program, and currently hold incentive stock options to a value of approx. 7300USD (January 17 2024). Dr Brunak declares that he has ownerships in Intomics A/S, Hoba Therapeutics Aps, Novo Nordisk A/S, Lundbeck A/S, ALK abello A/S, and managing board memberships in Proscion A/S and Intomics A/S. Dr Erikstrup reports unrestricted departmental grants from Novo Nordisk and Abbott Diagnostics, no personal fees. Dr Eidsmo has received speaker honoraria from Novartis, Lilly, Leo Pharma, and Janssen; and has been a consultant for advisory boards and received research grants from Novartis. Dr Saunte has over the past 3 years received honoraria as a consultant for

advisory board meetings by AbbVie, Janssen, Sanofi, Leo Pharma, and Novartis and as a speaker and/or received grants from the following companies: AbbVie, Janssen, Novartis, Sanofi, Jamjoom Pharma, UCB, Pfizer, and Leo Pharma. Dr Jemec has received honoraria from AbbVie, Chemocentryx, Coloplast, Incyte, Inflarx, Novartis, Pierre Fabre, and UCB for participation on advisory boards, and grants from AbbVie, AstraZeneca, Inflarx, Janssen-Cilag, Leo Pharma, Novartis, Regeneron, and Sanofi, for participation as an investigator, and received speaker honoraria from AbbVie, Boehringer Ingelheim, Galderma, and MSD. He has also received unrestricted departmental grants from AbbVie, Leo Pharma, and Novartis. Drs Riis, Dinh, Knowlton, Knight, Nadauld, Banasik, Hansen, Hjalgrim, Sørensen, Mikkelsen, Ullum, Nyegaard, Bruun, Ostrowski, Sigurgeirsson, Orvar, and Pedersen have no conflicts of interest to declare.

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