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Genomic loci and molecular genetic mechanisms for hidradenitis suppurativa

K. Alaine Broadaway[*,1], **Quan Sun**[*,2,3], **Sharon N Edmiston**[4,5], **Kevin W Currin**[1], **Swarooparani Vadlamudi**[1], **Tyne W Miller-Fleming**[6,7], **Yue Shi**[8,9,10], **Kristen Fajgenbaum**[11], **Maria Melendez-Gonzalez**[4], **Helen Bui**[12], **Franklin R Blum**[4], **Linnea Westerkam**[4], **Rayad Shams**[13], **Teja Mallela**[4], **Brandt Levitt**[14], **Lan Lin**[4], **Honglin Hao**[4], **Aylin Memili**[13], **Peter Straub**[6,7], **Wei Zhou**[8,9,15], **Kathleen Mullan Harris**[14,16], **Alicia Martin**[8,9,10], **Nancy J Cox**[6,7], **Zhi Liu**[4,5], **Nancy E Thomas**[4,5], **Yun Li**[*,2,1], **Karen L Mohlke**[*,1], **Christopher J Sayed**[*,4]

[1]Department of Genetics, University of North Carolina, Chapel Hill, NC, USA,

[2]Department of Biostatistics, University of North Carolina, Chapel Hill, NC, USA,

[3]Center for Computational and Genomic Medicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA,

[4]Department of Dermatology, University of North Carolina, Chapel Hill, NC, USA,

[5]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA,

[6]Department of Medicine, Division of Genetic Medicine, Vanderbilt University Medical Center, Nashville, TN, USA,

[7]Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, USA,

[8]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA,

[9]Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA,

[10]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, USA,

[11]Nashville Skin Comprehensive Dermatology Center, Nashville, TN, USA,

[12]Department of Dermatology, Howard University College of Medicine, Washington, DC, USA,

[13]School of Medicine, University of North Carolina, Chapel Hill, NC, USA,

[14]Carolina Population Center, University of North Carolina, Chapel Hill, NC, USA,

Correspondence: Karen Mohlke. mohlke@med.unc.edu.

[*]K.A.B. and Q.S. contributed equally to this work; Y.L., K.L.M., and C.J.S. contributed equally to this work

Conflicts of interest

CS is an investigator for Abbvie, Novartis, Incyte, InflaRx, UCB, and Astrazeneca, a consultant for Abbvie, Novartis, Sanofi, Sandoz, Astrazeneca, Incyte, InflaRx, UCB, Navigator Medicines, Moonlake Immunotherapeutics, and Alumis, a speaker for Abbvie, Novartis, and UCB, and is the secretary of the HS Foundation.

Ethics statement

The UNC Chapel Hill Institutional Review Board approved this study.

Patient consent

Patients with HS presenting to UNC Dermatology outpatient clinics provided written informed consent.

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[15]Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA,

[16]Sociology Department, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract

Background: Hidradenitis suppurativa (HS) is a common, chronic, and debilitating inflammatory disease that most commonly affects intertriginous skin. Despite its high heritability, the genetic underpinnings of HS remain poorly understood.

Objective: To identify genetic signals associated with HS, determine genetic relationships with other diseases, and investigate potential molecular genetic mechanisms.

Methods: We performed a genome-wide association study meta-analysis of six studies, totaling 4,540 cases and over 1 million controls and identified genetic correlations with other common diseases. We integrated the HS data with expression quantitative trait loci from 10 trait-relevant tissues, epigenomic and transcriptomic data from human scalp, differential expression data from HS lesions versus adjacent skin, and mesenchymal Hi-C chromatin looping data. To identify functional noncoding variants, we performed transcriptional reporter assays for signals near *KLF5* and *SOX9*.

Results: We identified eleven significant HS signals across seven loci: four corresponded to previously reported associations, four represented novel signals within known loci, and three were signals in newly implicated loci. We identified significant genetic correlation between HS and other inflammatory conditions, particularly inflammatory bowel disease, rheumatoid arthritis, type 2 diabetes, and asthma. We prioritized candidate genes for the 11 signals. The risk allele at *KLF5* exhibited 10-fold greater transcriptional activity than the non-risk allele, while risk alleles at *SOX9* showed significantly reduced transcriptional activity.

Conclusions: Our results provide insights into potential genetic mechanisms underlying HS and suggest potential therapeutic targets for this challenging condition.

Plain Language Summary

Hidradenitis suppurativa (HS) is a chronic skin disease that causes painful, recurring nodules and inflammation, most commonly in areas where skin rubs together. Although HS runs in families, its genetic causes are not well understood. To uncover genetic risk factors, we analyzed data from six studies, including 4,540 people with HS.

We discovered 11 genetic signals linked to HS. Four of these signals had been previously reported, while seven were new. We also found genetic connections between HS and other inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis, type 2 diabetes, and asthma.

To better understand how these genetic signals might influence HS, we examined gene activity in different types of skin cells and in HS lesions. Some signals may affect how skin protects the body while others affect the body's defense system. We also performed experiments to test how HS-associated DNA variants affect genes. We found that genetic changes near *KLF5* and *SOX9*—two important genes for skin development and healing—directly affected gene activity.

These findings provide new insights into the genetic basis of HS and suggest possible biological pathways involved in the disease. By understanding these genetic mechanisms, researchers can

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explore potential targets for future treatments, offering hope for improved therapies for people with HS.

Introduction

Hidradenitis suppurativa (HS) is a highly heritable[1–3] chronic inflammatory skin disease characterized by recurrent painful nodules, abscesses, and tunnels, primarily affecting intertriginous regions[4]. HS is associated with many comorbidities, including psoriasis[5], inflammatory bowel disease (IBD)[6], and polycystic ovarian syndrome (PCOS)[7]. Due to the complexity of HS pathophysiology, the manifestations and progressions of HS phenotypes are highly heterogeneous, as observed by differences across environmental and genetic factors[8,9].

Genetic studies have begun to illuminate the HS etiology. Rare variants analyses have pointed to genes related to the γ-secretase complex and autoinflammatory pathways[3,10–14]. Two genome-wide association studies (GWAS) have identified common variants associated with HS. Our previous meta-analysis of HS Program for Research and Care Excellence (ProCARE) and two biobanks identified associations near *SOX9* and *KLF5*[15]. More recently, a meta-analysis of Nordic, UK, and US-based studies provided further support for these signals and identified four additional common-variant signals: one in *WNT10A*, one near *TMED10*, and intergenic signals on chromosomes 6 and 9[14].

Despite these discoveries, much of HS heritability remains unexplained, and the functional consequences of GWAS associations across populations are unclear. To address these gaps, we expanded ProCARE and conducted a GWAS meta-analysis across six studies with 4,540 cases, identifying eleven association signals. To link these signals to potential genes, we integrated them with transcriptomic and epigenomic data. Lastly, to investigate plausible causal regulatory variants, we analyzed allelic differences in transcriptional activity of variants at *KLF5* and *SOX9*, providing mechanistic evidence of variant effects.

Materials and Methods

Genetic Association and Meta-analyses

We expanded the HS ProCARE study to 986 patients and used METAL[16] to conduct a GWAS meta-analysis across six studies (Table S1, Supplementary Methods). To control for population structure, we stratified analyses by population: self-reported black/African participants (AFR) and all other participants (EUR+AMR) (Table S1). GWAS were performed separately in each cohort by population group before meta-analysis. We first performed a GWAS meta-analysis by combining all population groups from all cohorts. Next, we performed analyses stratified by population group, separating AFR participants from all other participants, and then performed analyses stratified by sex (Table S2, Supplementary Methods).

We defined a locus as a lead variant with P-value $< 5\times10^{-8}$ and all variants within 1 Mb of the lead variant, extending to 2 Mb in the HLA region due to extensive linkage disequilibrium (LD). A locus can harbor several genetic signals distinctly associated with

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HS; to identify conditionally distinct signals within a locus, we performed approximate conditional analysis using GCTA[17,18] (Supplementary Methods).

Fine-Mapping

To identify likely causal variants at each locus, we used the Bayesian fine-mapping method SuSiE[19] (susieR package 0.12.35) to identify 95% credible sets (Supplementary Methods). To match a signal to credible set, we required that the lead variant be in the credible set.

Genetic Correlation with Comorbid Traits

We applied LD score regression (LDSC)[20,21] to estimate the genetic correlation between HS and celiac disease[22], IBD[23], PCOS[24], rheumatoid arthritis (RA)[25], type 2 diabetes (T2D)[26], atopic dermatitis[27], psoriasis[28], schizophrenia[29], and asthma[30] (Supplementary Methods). We reviewed the lead HS variants in the GWAS Catalog[31] to identify reported associations with related traits.

Candidate Genes and Regulatory Elements

To prioritize potential candidate genes, we generated variant-level annotation using WGSA Annotator[32], tested for colocalization between HS signals and signals from ten sources of expression quantitative trait loci (eQTL) data in HS-relevant tissues[33–37], and we queried if genes were differentially expressed between cell types of the scalp[38] or differentially expressed in HS lesions versus unaffected skin of HS patients[39] (Supplementary Methods).

To investigate potential regulatory elements and their likely effector genes, we examined Hi-C chromatin interaction data from mesenchymal cells[40] and compared the HS-associated variants to regions of chromatin accessibility in human scalp cell types[38] (Supplementary Methods).

Transcriptional Reporter Assays

We performed transcriptional reporter assays in the HaCaT cell line to test allelic differences in transcriptional activity. DNA fragments spanning rs981625 or a 3-variant haplotype (rs17226067, rs17825774, rs17825799) were cloned into a luciferase reporter vector and transfected into HaCaT cells (Table S3). Luciferase and Renilla activities were measured 48 hours after transfection, and the differences in activity between alleles were tested using two-tailed Student's t-tests (Supplementary Methods).

Results

Identification of HS Association Signals

In a GWAS meta-analysis of all participants, we identified five genome-wide significant loci (P-value < 5×10^{-8}), including two we previously reported near *SOX9* and *KLF5*, two that others previously reported on chromosome 6 and on chromosome 9[14], and an additional locus near *SUCNR1* on chromosome 3 (Figure 1, Table 1, Table S4, Figures S1–S6).

We then performed population- and sex-stratified GWAS meta-analyses. In a EUR+AMR analysis, we found a sixth locus near *NIN* (P-value = 2.5×10^{-8}, Figure 1, Table 1, Figures

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S7–8). The lead variant, rs10146136, is rare in African populations (1000G minor allele frequency (MAF) = .005) but common in European populations (1000G MAF = 0.133). While we could detect the variant in three AFR studies, it did not meet the significance threshold in the full meta-analysis (P-value = 1.3×10^{-7}) (Figure S9). In the male-only HS analyses, we found a seventh locus near *MXRA7* (rs9901332, P-value = 3.4×10^{-8}) (Figures 1–2, Table 1, Table S4, Figure S10). The lead variant's effect size in men (beta = 0.43, SE = 0.08) is comparable to the strongest effect of any other lead variant (e.g. rs981625 near *KLF5*, beta = 0.44, SE = 0.06), but it had no observable effect in women, despite a four-fold larger sample size (beta = −0.04, SE = 0.04, P-value = 0.32). By leveraging population- and sex-stratified analyses, we reinforced the role of common genetic variants in HS pathogenesis while identifying two additional signals that may help elucidate the genetic basis of HS.

To discover additional genetic variants that influence HS risk, we performed approximate conditional analyses on all seven loci[17,18]. In the all-population meta-analysis, we identified a second signal on chromosome 9 near *KLF4* (Table 1, Table S5, Figure S11). The EUR+AMR summary data confirmed this signal and revealed three more: a second signal on chromosome 6 near the *HLA* region (Figure S12–S13) and two additional signals near *KLF5* (Figure S14–S17, Table S5). The *HLA* and *KLF5* non-primary signals narrowly missed the significance threshold in the all-population analysis (conditional P-values ≤ 1.7×10^{-7}). Across all analyses, we found 11 signals in 7 loci.

Fine-Mapping

We identified credible sets of plausibly causal variants for our HS signals. We identified nine credible sets that matched with nine of the eleven HS association signals (Table S6); the two HLA signals did not converge. The primary *KLF5* credible set consisted of a single variant (rs981625) that is in low LD with the previous lead (rs17090189 LD $r^2 = 0.24$ in EUR subset of UK Biobank). While the *NIN* signal and the non-primary *KLF5* signals narrowly missed genome-wide significance in the all-population meta-analysis ($1.7\times10^{-7} \leq$ P-values $= 1.3\times10^{-7}$), they were detected in the all-population meta-analysis using fine-mapping, suggesting that the three signals were not exclusive to the population-stratified results.

Since the extent of LD is typically shorter in AFR populations, we compared credible sets sizes from all-population versus EUR+AMR data. Five of eight credible sets were smaller in the all-population analysis, two were the same size, and only one credible set, near *NIN*, yielded a smaller credible set with the EUR+AMR data. While differences in variant representation across studies could also influence credible set size, all EUR-specific credible set variants were well represented in the full summary statistics from the all-population analysis. These results highlight the value of multi-population meta-analyses, even when under-represented populations do not yield population-specific signals.

Genetic Correlation with Other Complex Traits

To better understand the genetic relationships between HS and other complex traits, we tested for genetic correlation. We established a significant genetic correlation between HS and IBD (rg = 0.53, P-value = 6.0×10^{-4})[23], RA (rg = 0.31, P-value = 6.0×10^{-4})[25], T2D (rg =

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0.37, P-value = 1.1×10^{-7})[26], and asthma (rg = 0.28, P-value = 4.0×10^{-4})[30] (Figure 3, Table S7). As a negative control, schizophrenia showed no evidence of correlation (rg = −0.002, P-value = 0.97). We also found that the lead variant for the primary *KLF5* signal, rs981625, is also the lead variant for related traits including eczema, asthma, hay fever, and allergic rhinitis[30,41,42] (UK Biobank traits, see web resources).

Candidate Genes and Regulatory Elements

To prioritize candidate genes and to identify potential regulatory elements affected by HS risk variants, we integrated GWAS findings with variant annotations and transcriptomic, eQTL, chromatin accessibility, and Hi-C data (Tables S8–S14). We strengthened evidence for *KLF5* and *SOX9* as candidate genes. *KLF5* was less expressed in HS lesions vs unaffected skin ($\log_2$FC = −0.6, P-value = 2.9×10^{-9}) and exhibited high gene activity in scalp keratinocyte clusters ($\log_2$ fold-change ($\log_2$FC) 0.6 – 2.6, P-values ≤ 4.0×10^{-166}) but no other cell type (Figure 4, Tables S10). The *KLF5* primary signal lead variant was in a regulatory element that appears to be only accessible in keratinocytes (Figure 5, Table S13). *SOX9* was highly expressed in hair-follicle, spinous, and basal keratinocyte cell clusters ($\log_2$FC 0.3 – 5.2, P-values ≤ 5×10^{-86}), but no other scalp cell type (Figure 4, Table S10). The *SOX9* lead and LD proxies were also in a regulatory region showing chromatin accessibility in keratinocytes but not seen in other profiled cell types (Figure 5, Table S13). These findings add support that *KLF5* and *SOX9* signals could act through a keratinocyte-accessible regulatory element not observed in other cell types examined to influence *KLF5* and *SOX9* expression levels in keratinocytes.

The two chromosome 6 signals were near *HLA-DRA* and *HLA-DRB5*. Both genes were highly expressed in immune-relevant cell type clusters, including dendritic cells and macrophages, and were more highly expressed in HS lesion than non-lesion tissue (Figure 4, Table S10). In addition, all proxies for the second HLA signal were in one a regulatory element that appears to be only accessible in lymphoids (Table S13), consistent with the known role of HLA genes in immunity.

Mesenchymal Hi-C chromatin interaction data[40] suggested long-range regulatory effects for lead variants on chromosomes 14 and 9. rs10146136 on chromosome 14 interacted with *NIN* (Figure S18), suggesting a regulatory link to *NIN* (107 kb from TSS). *NIN* showed increased expression in HS lesions (Figure 4, Table S10). Similarly, both lead variants on chromosome 9 (rs1994799 and rs1535620) interacted with the promoter of *KLF4* (Figure 6, Figure S19), despite 900 kb between the leads and the *KLF4* TSS. *KLF4* demonstrated decreased expression in HS lesions ($\log_2$FC = −0.96, P-value = 1.0×10^{-10}, Figure 4, Table S10). Hi-C links were not observed in mesenchymal for the closer *ACTL7B* gene (185 kb from TSS), and *ACTL7B* showed no change in lesion versus non-lesion tissue ($\log_2$FC = 0.93, P-value = 0.71) (Figure 4). These findings suggested potential regulatory links between the identified variants and target genes, although further investigation is needed.

Web resources
GTEx summary results: https://console.cloud.google.com/storage/browser/gtex-resources
Neale lab, GWAS summary statistics of UK Biobank: http://www.nealelab.is/uk-biobank/

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For nine of the eleven signals, at least one lead or high-LD proxy variant in the signal's credible set was located within a scalp regulatory element (Table S13). These data suggest that causal variants reside within these elements, refining the set of most plausible causal variants (Table S6).

Variant Function

To investigate allelic effects of two signals with clear lead variants, we examined regulatory function in transcriptional reporter assays in epidermal HaCaT cells. The *KLF5* rs981625-C HS risk allele showed 10-fold greater transcriptional activity than the reference allele (P-value < 2.9×10^{-7}) (Figure 5, Figure S20). At *SOX9*, a three-variant haplotype that included the lead HS risk variant rs17226067-G as well as rs17825774-A and rs17825799-A, showed >2-fold lower transcriptional activity than the reference haplotype (P-value = 0.001) (Figure 5, Figure S20). These data suggest that rs981625 and at least one variant in the haplotype are plausible functional regulatory variants responsible for HS risk at the *SOX9* and *KLF5* signals.

Discussion

We performed a meta-analysis of HS on 4,540 cases, identifying 11 HS signals in 7 loci. We identified five loci in the all-population meta-analysis, an additional locus in a EUR+AMR analysis and a locus in the male-only analysis. Four loci overlapped known regions (*SOX9*, *KLF5*, *KLF4*, and *HLA*), while three were novel: *SUCNR1*, *NIN* (EUR+AMR-only locus), and *MXRA7* (male-only locus). Collectively, these results highlight the complexity of HS genetics, the importance of considering population structure, and the potential of sex differences in HS etiology.

We established a genetic correlation between HS and four common inflammatory and metabolic conditions: IBD[23], RA[25], T2D[26], and asthma[30]. The correlation with IBD was the strongest; patients with IBD were nine times more likely to develop HS compared to the general population[43], suggesting that overlapping immune and inflammatory mechanisms may contribute to both conditions. Rare variants in *NOD2*, a gene that has been widely implicated in Crohn's disease[44], have been associated with HS[45]. While many of these variants have been classified as benign or likely benign in silico[46], one variant (rs104895452) has a high probability of being deleterious silico[45,47]. Both HS and IBD are often successfully treated with TNF-alpha inhibitors[48,49], highlighting how shared genetic architecture can inform therapeutic strategies. Further, rs981625, the lead variant at *KLF5*, was also the lead variant for eczema, asthma, hay fever, and allergic rhinitis[30,41,42]. Understanding these shared genetic bases could offer insights into common pathophysiological mechanisms and potentially guide future research toward more integrated therapeutic strategies.

Previously, we described how dysregulation of *KLF5* and *SOX9* could be linked to the perturbations in follicular and epidermal differentiation, inflammation and wound healing that are characteristic of HS. Here, we identified likely causal variants driving these non-coding signals. The *KLF5* rs981625-C allele was associated with greater transcriptional activity and higher HS risk, aligning with mouse studies where *Klf5* overexpression led

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to hyperkeratosis and follicular occlusions[50]. Similarly, a *SOX9* haplotype including the rs17226067-G allele was associated with reduced transcriptional activity and increased risk of HS, consistent with the observation that mice deficient in *Sox9* exhibit follicular degeneration, epidermal hyperplasia, and dermal scarring[51].

Chromatin interaction data[40] implicated *KLF4* as a target gene for two chromosome 9 signals. A transcription factor linked to psoriasis,[52] KLF4 regulates wound healing, skin barrier function, proliferation, and follicular/epidermal differentiation[53]. It is both regulated by and regulates *NOTCH1* signaling and is induced by inflammatory cytokines[54,55]. KLF4 stimulates production of IL-36 and IL-8, both potent inducers of neutrophil-mediated inflammation, IL-6, and IL-10. In human keratinocyte knockdown models of *NCST*, a γ-secretase family member that is mutated in some familial HS cases, *KLF4* was upregulated, particularly in the presence of *S. aureus*, consistent with the role of bacteria in potentiating inflammation in HS[56]. Overexpression of K*lf4* in mice led to impaired differentiation of follicular epithelium with impaired hair growth[57]. Given its similarities to SOX9 and KLF5 in follicular/epidermal differentiation, wound healing, and inflammation, KLF4 may also influence HS pathogenesis.

We also identified plausible candidate genes at our other loci. *HLA-DRA*, which is upregulated in HS lesions, regulates antigen presentation and may contribute to inflammation via dysregulated host-microbiome interactions. NIN, a microtubule regulator, is crucial for immune function, barrier function[58] and neutrophil extracellular trap regulation[59]. In sepsis, IL-6 downregulation reduced NIN in monocytes, which allowed for persistence of pathogens and potentiation of other inflammatory bacterial responses[60]. A similar process could contribute to dysbiosis, biofilm formation, and chronic inflammation in HS tissue[61]. SUCNR1, the succinate receptor, regulates inflammasome priming and glucose homeostasis. Deficiency in *Sucnr1* is linked to obesity, glucose intolerance and enhanced inflammatory signaling[62], but also with reduced inflammasome activation in mouse colitis models, suggesting it may also play a pro-inflammatory role in some settings[63]. In macrophages, *KLF4* knockdown has been associated with reduced expression of *SUCNR1*[64], potentially linking these risk loci together in HS pathogenesis. Finally, MXRA7 may protect against pro-psoriasis cytokines[65], as mouse models deficient in *Mxra7* develop more severe disease. Loss of *MXRA7* resulted in epidermal proliferation increases, expression of TNF-α, IL-6, and IL-1, and impaired wound healing[66], all of which are linked to HS pathogenesis. However, many genes near *MXRA7* could contribute to risk. Further studies are needed to investigate these and/or other nearby genes in their roles in HS pathogenesis.

This GWAS meta-analysis has limitations. First, due to sample size constraints, we examined at most two population groups per cohort and analyzed people together from European and admixed American populations. The results cannot be interpreted to infer racial or ethnic differences. Most signals were not significant in the AFR GWAS ($0.005 \leq$ P-value $\leq .78$), highlighting the need for larger AFR HS cohorts to identify additional HS GWAS signals and improve fine-mapping. Allele frequency differences affect association detection; all but one lead variant (*SOX9* lead variant rs17226067) was less common in the AFR versus EUR+AMR populations. New signals, especially those with different effects

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across populations, should be validated. Second, since individuals with HS suffer an average of 7–10 years between manifestation of first symptoms until a formal diagnosis is made[67,68], some controls may be affected with HS, biasing results towards the null. Third, we found only one colocalization between HS signals and eQTLs; as eQTL studies expand, we expect to uncover further HS-eQTL colocalizations that could enhance understanding of HS pathogenesis. Fourth, this study focused on common variants (MAF ≥ 1%); HS is known to be associated with rare variants[45], and integrating rare variant analyses with future common genetic association studies would enhance our understanding of its genetic basis.

Overall, we identified potential mechanisms and candidate genes for HS by stratifying analyses by population and sex, conducting conditional analyses, and integrating HS signals with complementary GWAS traits, expression and regulatory data, and studies of variant function. This work represents one of the largest HS meta-analyses to date (effective sample size: 17,244) and the largest meta-analysis in AFR participants (effective sample size: 4,212). While further research with larger and more diverse cohorts is needed to fully elucidate the genetic contributors to HS, our findings provide valuable insights into disease pathology and may inform the development of novel therapeutics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this topic?

- HS is a chronic inflammatory skin disease with a strong genetic component. Prior common-variant GWAS studies identified six genetic loci associated with HS, but the underlying biological mechanisms remain poorly understood.

What does this study add?

- We identified 11 genetic signals, including seven novel signals.
- Integrative analyses found genetic links between HS and other inflammatory diseases
- Our study prioritized potential causal genes and functional follow-up identified variants near *SOX9* and *KLF5* that likely drive two non-coding signals.

What is the translational message?

- Our findings reveal biological pathways involving keratinocyte function and inflammation, suggesting potential therapeutic targets for HS. Identifying causal genes could inform precision medicine approaches for treatment.

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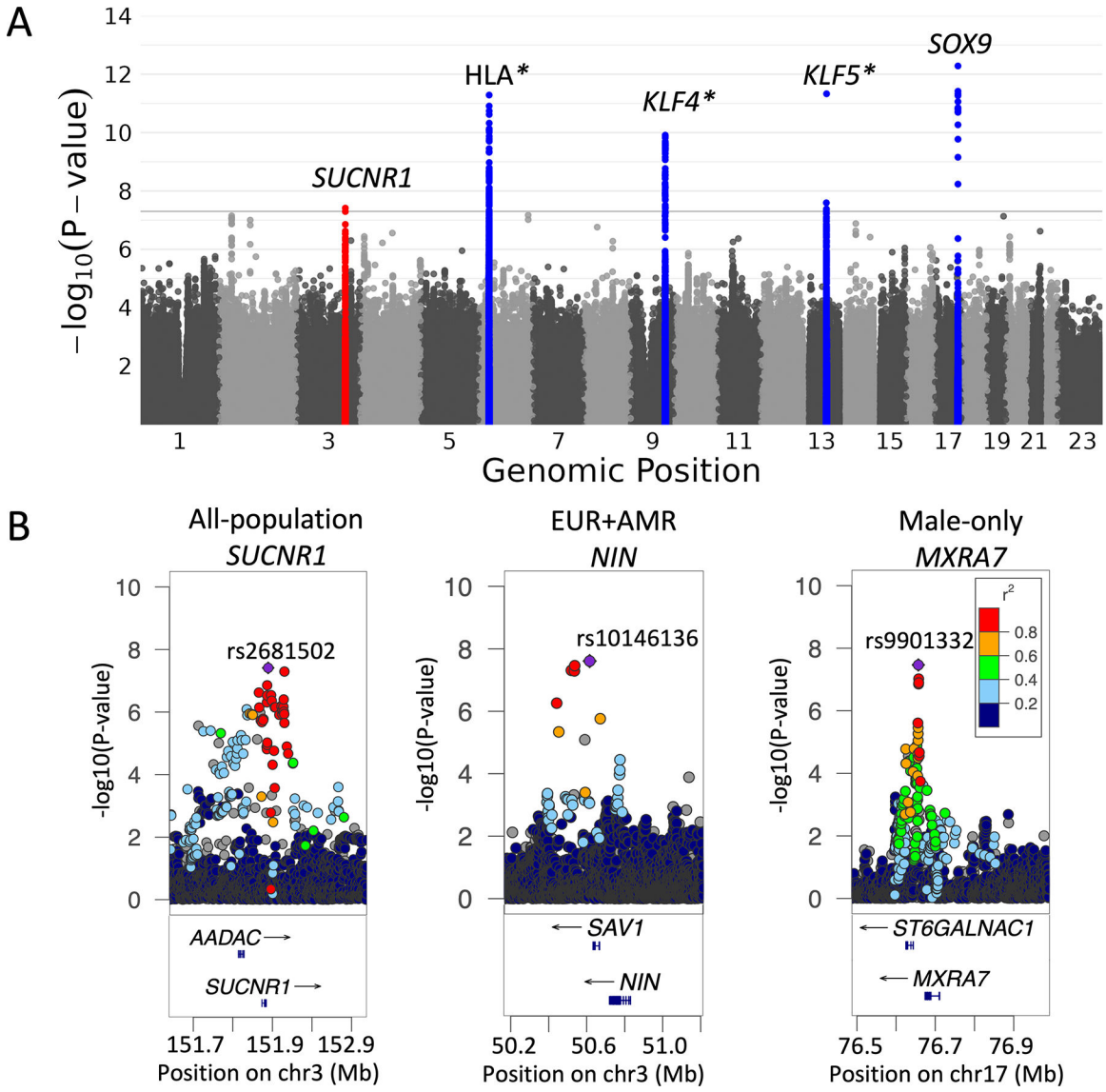


Figure 1:

HS genetic association signals. **A:** Manhattan plot of the associations between variants and HS in all populations. Variants within 1 Mb of a previously known HS locus are colored in blue; variants within 1 Mb of a new HS locus (P-value ≤ 5×10^{-8}) are colored in red. Loci with asterisks represent multi-signal loci. **B:** Variant associations for new HS loci. **Left**: a signal near *SUNCR1* was significantly associated with HS in the all-population analysis; **Middle**: a signal near *NIN* was significantly associated with HS in the EUR+AMR stratified analysis; **Right**: a signal near *MXRA7* was significantly associated with HS in males.

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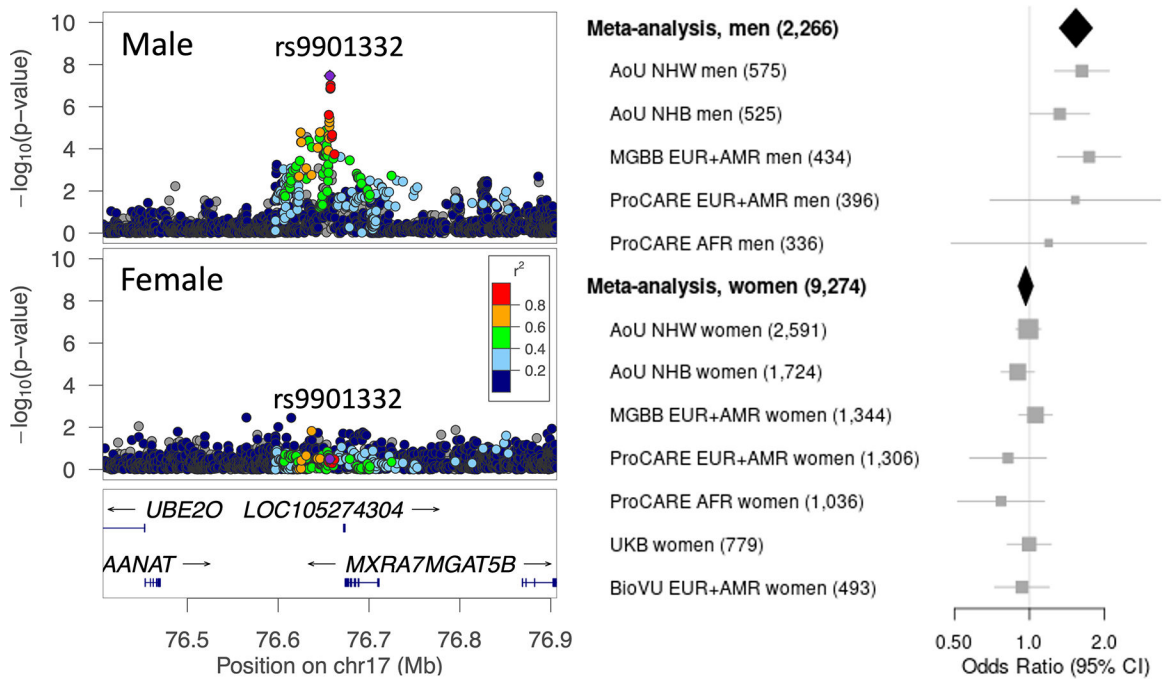


Figure 2: HS locus detected in male-only GWAS.

Left: Variants associated with HS in men (top) versus women (bottom). **Right:** Forest plot of male-only and female-only GWAS results. The *MXRA7* locus is strong in men and shows consistent direction and strength of effect across all contributing studies. An effect is not detected in any female-only or sex-combined GWAS results. Studies noted with an asterisk (*) were not included in the meta-analysis due to small sample size.

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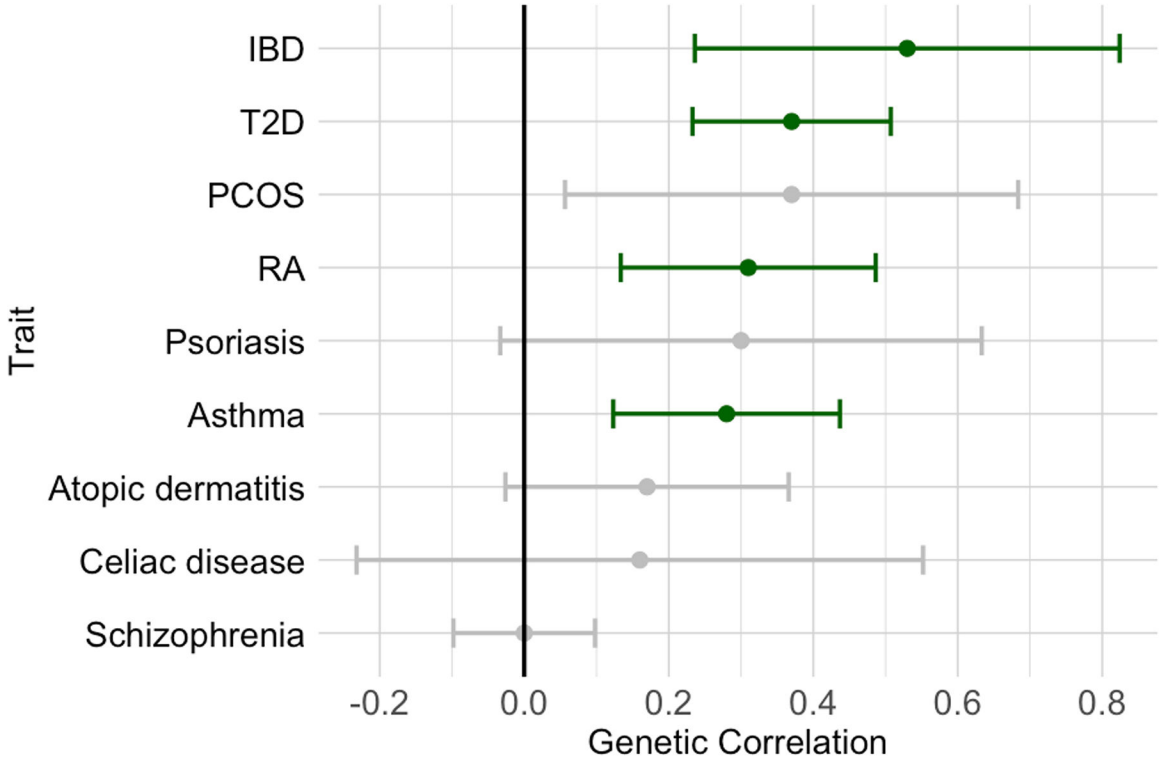


Figure 3: Genetic correlation between HS and other complex traits.

Green indicates Bonferroni-significant correlations. IBD: inflammatory bowel disease; T2D: type 2 diabetes; PCOS: polycystic ovarian syndrome; RA: rheumatoid arthritis.

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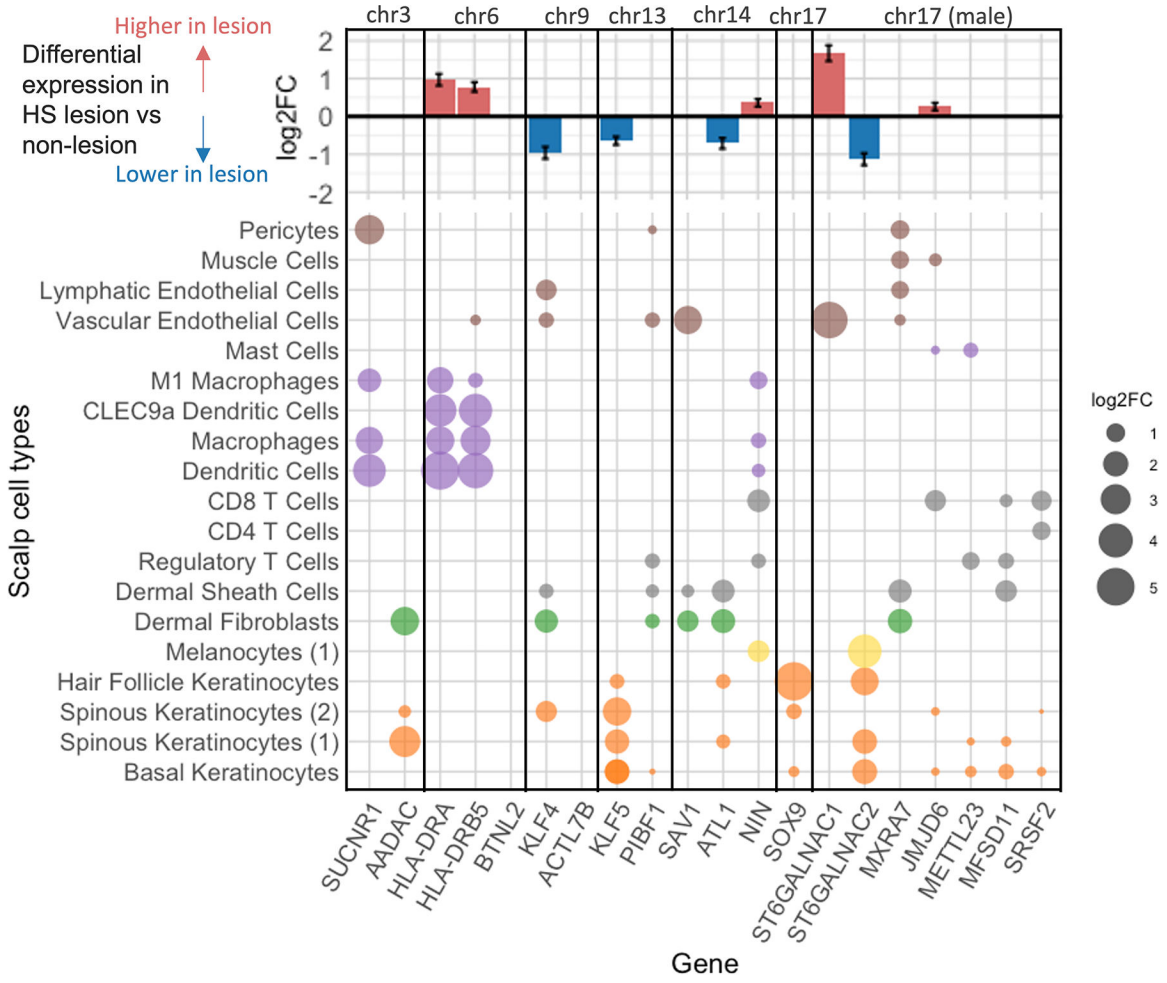


Figure 4: Differential expression of prioritized candidate genes in lesion vs non-lesion tissue and in scalp cell types.

We prioritized 20 genes that were within 100 kb of a lead variant, or the nearest protein-coding gene if none were within 100 kb, and genes with external evidence of relevance to HS. **Top:** the $\log_2$ fold change of gene expression in HS lesion versus matched non-lesion tissue. **Bottom**: the $\log_2$ fold change of gene expression in scalp cell types. Only increased expression in a cell type is shown. To be included, the cell type must be more highly expressed in at least one prioritized gene. Circles show the size of the fold change. Orange: keratinocytes; yellow: melanocytes; green: fibroblasts; purple: immune cells; brown: muscle or endothelial cells.

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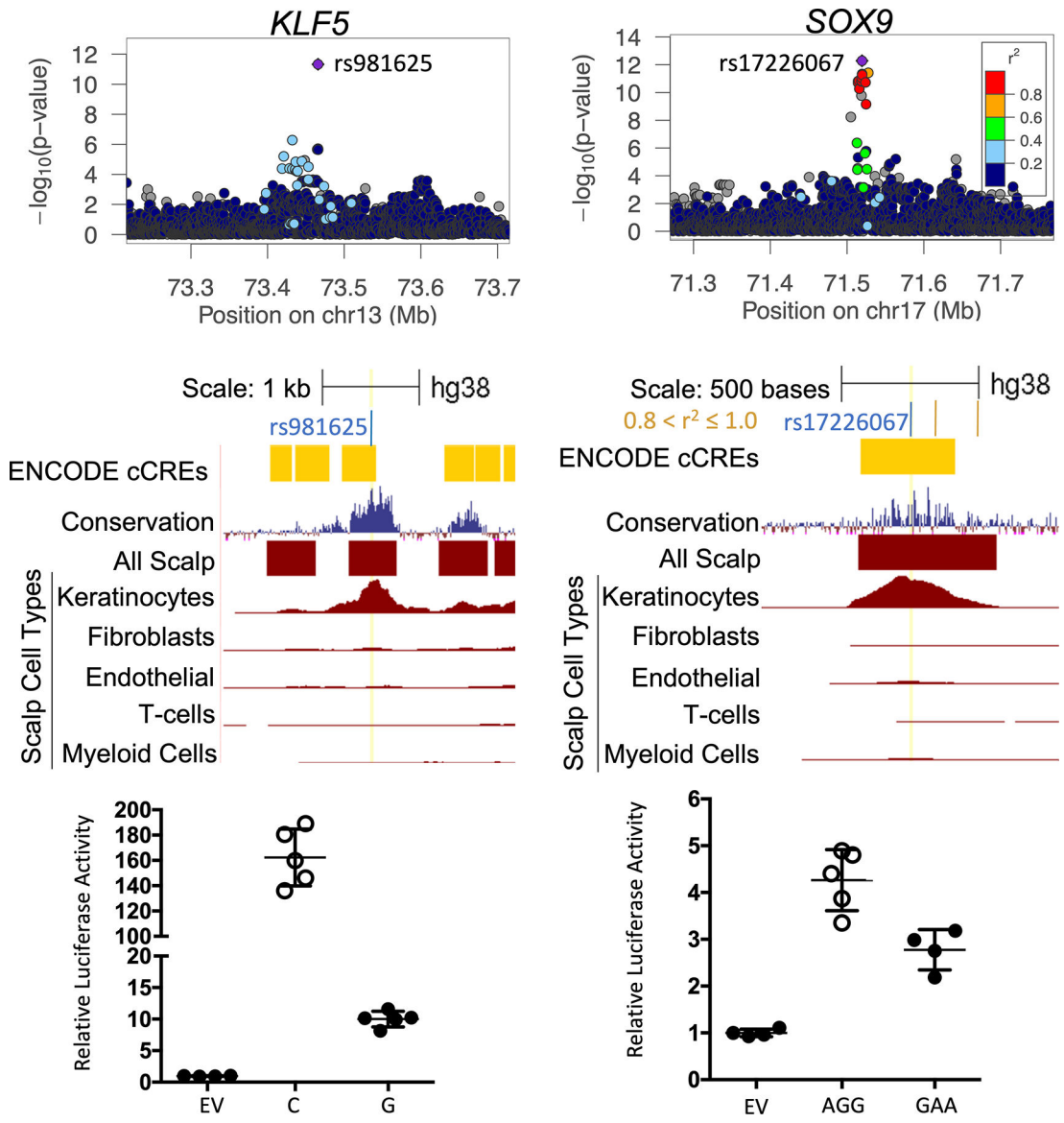


Figure 5: HS loci *KLF5* (left) and *SOX9* (right) may influence expression levels of their target genes in keratinocytes via a regulatory element that appears to be only accessible in keratinocytes.

Top row: Variant associations with HS for the two signals. **Middle left:** Genome browser plots showing scalp chromatin accessibility by cell type. The lead variant of *KLF5* (rs981625) is located within a keratinocyte-accessible regulatory element that was not observed in other examined cell types (chr13_73465564_73466065) and is strongly conserved across vertebrates. No other LD proxies of the lead variant are located within accessible chromatin. *KLF5* was much more strongly expressed in keratinocytes than any other cell type ($\log_2$fold change = 0.56 – 1.93 for keratinocyte cell clusters, P-values $\leq 4\times10^{-166}$). **Bottom left**: the rs981625-C allele, which was associated with higher HS risk, showed a 10-fold greater transcriptional activity than the rs981625-G reference allele (P-value = 2.9×10^{-7}). **Middle right**: the *SOX9* lead variant rs17226067, and its LD proxies rs17825774 and rs17825799 ($r^2 = 1$, shown in gold) are located within a

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region of open chromatin detected in keratinocytes but not in other surveyed cell types (chr17_71519287_71519788); no other LD proxies are located within accessible chromatin. *SOX9* was also more highly expressed in hair-follicle (HF) keratinocyte clusters than other scalp cell types ($\log_2$ fold-change = 0.28 – 5.19, P-values ≤ 5×10^{-86}). **Bottom right:** the 3-variant risk haplotype of rs17226067-G, rs17825774-A, and rs17825799-A alleles showed >2-fold reduced transcriptional activity versus the reference haplotype AGG haplotype (P-value = 0.001).

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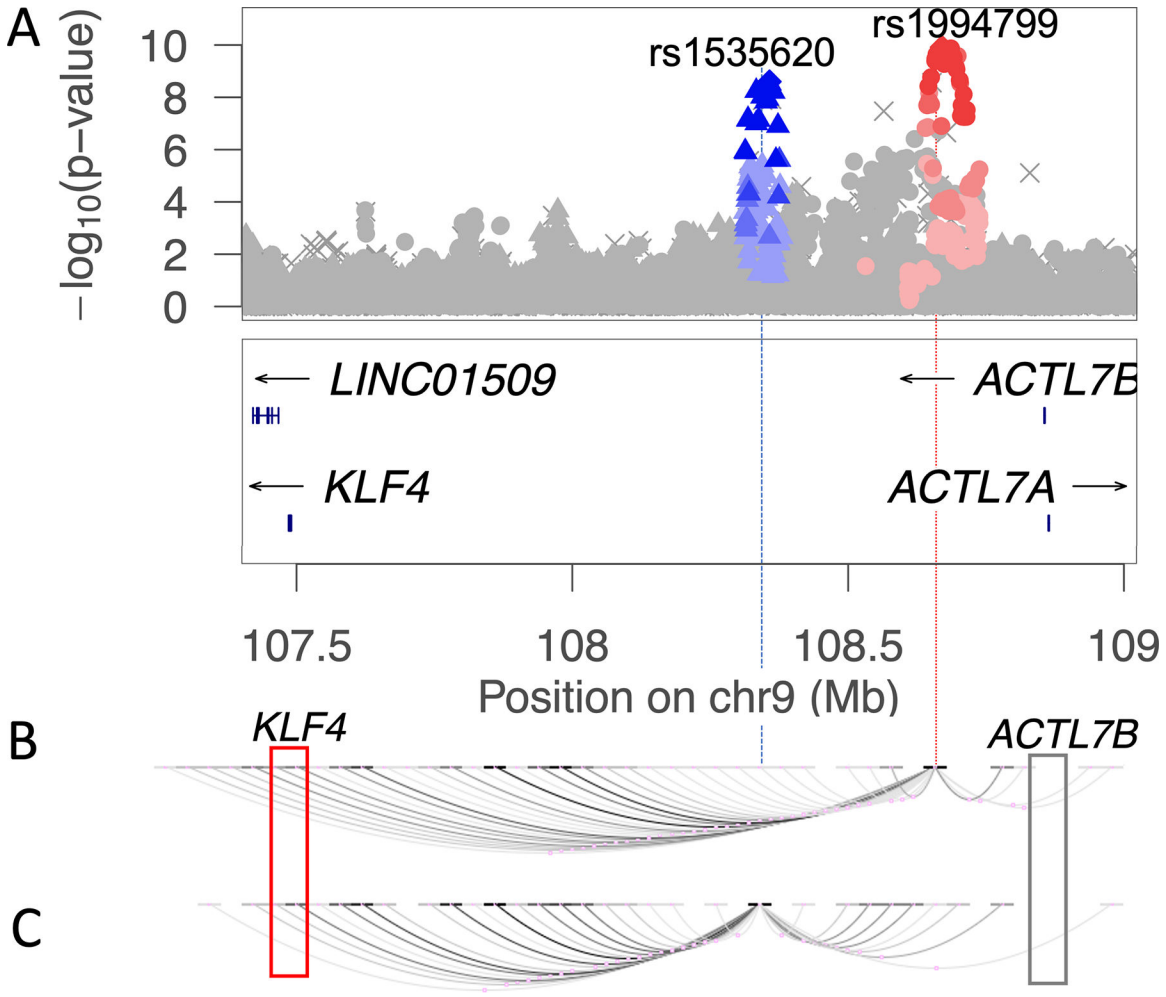


Figure 6: Both conditionally distinct signals on chromosome 9 exhibit a significant Hi-C chromatin interaction peak in mesenchymal data.

A: Variants associated with HS at two conditionally distinct signals. **B**: Mesenchymal cell Hi-C data[40] anchored around rs1994799, the lead variant for the primary HS signal. **C**: Mesenchymal cell Hi-C data anchored around rs1535620, the lead variant for the secondary HS signal. The target regions immediately flanking the anchor regions and target regions with FitHiC Q-values ≥ 0.01 are not shown. Arc colors are scaled by strength of association measured by $-\log_{10}$(P-value), with the darkest lines showing the link with the strongest P-value. Hi-C data in the red box, centered around KLF4, showed significant interactions; no significant interactions were observed around the more proximal gene *ACTL7B* (gray box).

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Table 1:

Eleven lead variants associated with HS at seven loci

Chr	Nearby Gene	Population	rsID	Alleles	EAF	OR	P-value	Neff
Previously reported signals								
17	*SOX9*	ALL	rs17226067	G/A	0.16	1.28	5.21E-13	17,274
13	*KLF5*	ALL	rs981625	C/G	0.95	1.55	4.68E-12	15,521
6	*HLA*	ALL	rs6457592	C/T	0.53	1.19	5.18E-12	17,274
9	*KLF4*	ALL	rs1994799	A/G	0.44	1.17	1.22E-10	17,274
Additional loci								
3	*SUCNR1*	ALL	rs2681502	C/T	0.06	1.35	3.87E-08	16,933
14	*NIN*	EUR+AMR	rs10146136	A/G	0.13	1.25	2.47E-08	13,062
17	*MXRA7*	Men only	rs9901332	T/C	0.61	1.54	3.42E-08	2,266
Additional signals at established loci								
9	*KLF4*	ALL	rs1535620	G/A	0.49	1.17	7.44E-10	16,933
6	*HLA*	EUR+AMR	rs9265701	A/G	0.47	1.19	9.50E-09	8,903
13	*KLF5*	EUR+AMR	rs9796066	C/T	0.37	1.18	1.42E-09	13,062
13	*KLF5*	EUR+AMR	rs12100281	A/G	0.91	1.31	1.82E-08	13,062

Population indicates samples included in the GWAS analysis. Chr: chromosome. Alleles: effect allele/noneffect allele. EAF: effect allele frequency. OR: odds ratio (exp(beta)). Neff: effective sample size. For non-primary signals, the P-values are from GCTA conditional analyses.