GWAS META-ANALYSIS IDENTIFIES SUSCEPTIBILITY LOCI FOR KELOIDS IN EUROPEANS

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Running Title
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BACKGROUND
Keloids are benign dermal fibroproliferative tumours caused by an abnormal wound healing response. Pathobiology is partially understood but current treatments remain sub-optimal. Genetic studies have identified four susceptibility loci that contribute to keloid pathogenesis in Asian and African American populations. Here, we report the first genome-wide association study (GWAS) meta-analysis for susceptibility to keloids in people of European ancestry.

METHODS
We performed a GWAS of UK Biobank participants of white British ancestry. Keloids/hypertrophic scar cases were identified based on electronic health record diagnoses encompassing primary care (read codes, v2 and CTv3) and secondary care (International Classification of Disease, version 9 and 10), for a total of 843 cases and 187,812 controls. We further obtained GWAS summary statistics from Finnish individuals from the FinnGen cohort (1,126 cases and 291,889 controls) and combined the two GWAS datasets in a fixed-effect meta-analysis. To highlight likely causal biology, we subsequently performed Bayesian fine-mapping and expression quantitative trait loci (eQTL) lookup and co-localisation.

RESULTS
We replicated three of the previously four associated loci, two at genome-wide significance (1q32.1: rs35383942, odds ratio [OR] 1.46, P-value 7.0×10^{-11}; 1q41: rs10863683, OR 0.69, P-value 3.0×10^{-25}) and one just short thereof (15q21.3: rs60890210, OR 1.24, P-value 6.7×10^{-8}). We found no evidence for association in either British or Finnish individuals for the fourth previously reported susceptibility locus (3q22.3), suggesting that this may be an ancestry-specific association. Bayesian fine-mapping using meta-analysis summary statistics within the three European loci offered strong evidence for causality of the lead SNP at 1q32.1 (posterior probability [PP] 0.79) and 1q41 (PP 1.0) but was inconclusive at 15q21.3. We identified known eQTLs within the 1q32.1 and 15q21.3 loci for *CSRP1* (P-value $1.89\text{x}10^{-47}$), *NAV1* (P-value $8.6\text{x}10^{-11}$), *RP11-134G8* (P-value $6.1\text{x}10^{-8}$) and *NEDD4* (P-value $9.29\text{x}10^{-17}$) but subsequent colocalization analysis failed to support the hypothesis that these eQTLs shared a causal variant with keloid susceptibility. No clinically significant trait associations were identified at genome-wide significance, but on relaxing our search criteria, we found a known association with Dupuytren's contracture at the 15q21.3

locus, notable also as a fibrotic disorder and hinting at a shared pathogenic mechanism.

CONCLUSION

Our findings support a shared genetic basis of keloids across populations including Europeans. Future transethnic analyses will boost study power and enable a finer dissection of keloid genetic architecture in understanding disease aetiology