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The Polygenic Architecture of Hidradenitis Suppurativa revealed by a first meta-analysis GWAS

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INTRODUCTION

The Hidradenitis Suppurativa Genetics Consortium (HSGC) was founded in 2021. Our mission is to use human genetic studies as a starting point to discover hidradenitis suppurativa (HS) disease mechanisms, to identify and prioritize drug targets, and to improve the accuracy and utility of an HS diagnosis. Here, we present the first results of this large collaborative model, in which we perform the first meta-analysis of HS GWAS.

METHODS

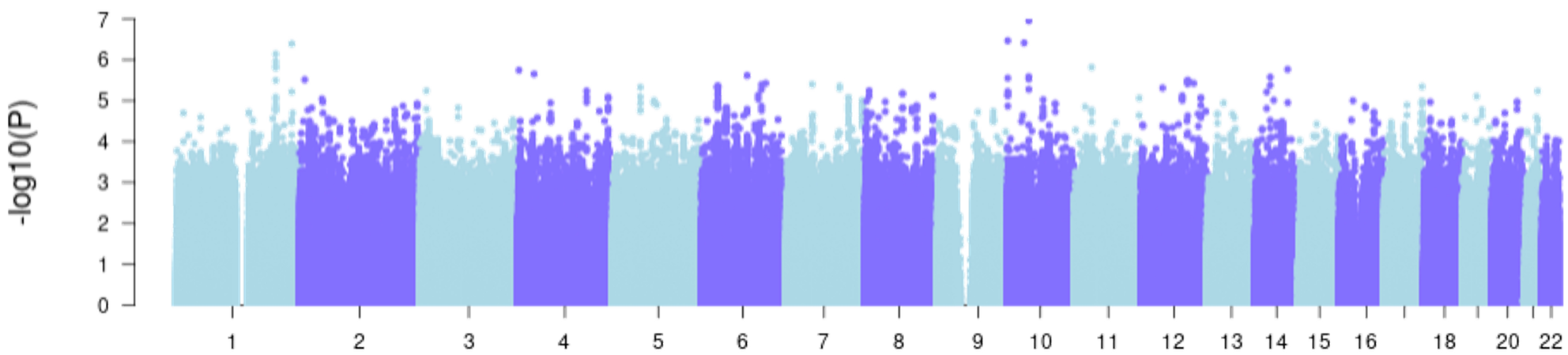
HSGC members with genome-wide genotype data on research participants performed GWAS, using research participants with one or more HS ICD diagnosis codes as cases and those without as controls. Each center performed their own GWAS, as briefly described here. First, each sample was assigned to a continental super population[1] to subdivide cohorts into groups by major continental ancestry for downstream analyses. First, imputation was performed with the Haplotype Reference Consortium panel[2]. Association tests were run adjusting for significant PCs, age, and sex[3,4]. Summary statistics were submitted to the coordinating center and combined across cohorts using an inverse variance–weighted fixed effects meta-analysis with METAL[5].

COHORT RESULTS

	All		EUR		AMR		AFR	
Source	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**
E-MERGE-III	585	84681	302	66522	41	4358	242	14801
KCL, UCD	223	7072	223	7072				
CHOP	188	42808	41	22811			147	19997
Michigan	396	47980	290	44964			106	3016
Penn	275	32492	67	25055			208	7437
TOTAL	**1667**	**215033**						

Data was contributed by five collaborators representing a total of 1,667 HS cases and 215,033 controls from three continental ancestries. EUR; European, AMR; Ad Mixed American, AFR; African.

GWAS RESULTS



No locus exceeded our stringent threshold for genome-wide significance ($p<5x10^{-8}$), indicating that the polygenic architecture of HS lacks large-effect risk polymorphisms. No associations are identified with SNPs in the HLA, a region on chromosome 6 that is a hallmark of autoimmunity.

CONCLUSIONS

The results of the first HS meta-analysis confirms our initial findings, presented at the 9th Conference of the EHSF, in which an HS GWAS of 600 cases and 80,000 controls failed to detect statistically significant associations, indicating that HS is likely to be driven risk polymorphisms with small effect estimates[6]. Our findings empirically demonstrate that resolving the polygenic architecture of HS will require samples sizes of at least 2000 to 4000 cases. Ultimately, tens of thousands of participants from diverse genetic ancestries will be needed to generate clinically meaningful genetic evidence and polygenic risks scores, which will require cooperation and coordination among many diverse stakeholders[7].

Therefore, the HSGC is committed to respectful engagement of all stakeholders, easy and streamlined collaboration requiring only summary statistics generated with standardized protocols, and open sharing and widespread dissemination of results. We have already on-boarded additional collaborators and our next meta-analysis is expected to exceed our immediate goal of 4000 cases.

REFERENCES

[1] Altshuler DM, et al. Nature. 2015. [2] McCarthy S, et al. Nat Genet. 2016. [3] Mbatchou J, et al. Nat Genet. 2021. [4] Zhou W, et al. Nat Genet. 2018. [5] Willer CJ, et al. Bioinformatics. 2010. [6] Khan A, et al. Exp. Dermatol. 2020. [7] Jabbour A, et al. Br. J. Dermatol. 2022.

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