HLA-B As A Potential Risk Factor To Pulmonary Arterial Hypertension In Systemic Sclerosis (SSc-PAH)

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Introduction

Pulmonary Arterial Hypertension (PAH) in Systemic Sclerosis (SSc)

- SSc is a chronic **autoimmune** disorder affecting connective tissues with the **highest mortality rate** among all the rheumatic diseases, mainly due to lung complications.
- PAH affects **5-19%** of **SSc patients** (SSc-PAH).
- The **Major Histocompatibility Complex** (MHC) has the greatest genetic effect in SSc. Previous studies underscore the role of this region in SSc-PAH.

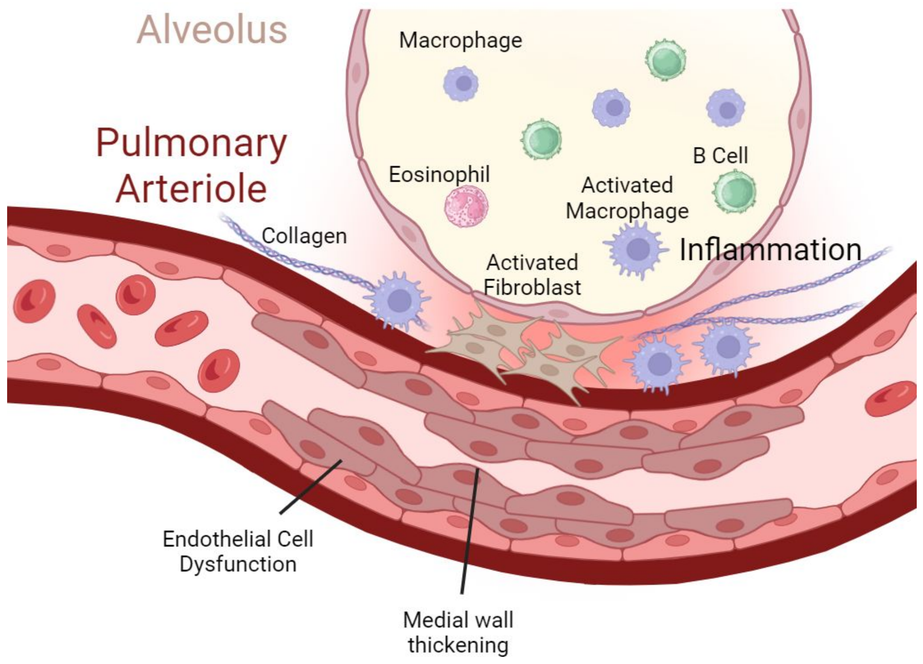

Figure 1. Pathogenesis of PAH-SSc. In the pulmonary circulation, endothelial damage might promote a proliferative vascular response that includes multiple cell types and results in medial wall thickening. Vascular fibrosis and perivascular inflammation can subsequently occur. (Done with biorender.com)

Objective

To identify **genetic risk factors** involved in **SSc-PAH** within the **MHC**, leveraging the largest Genome Wide Association Study (GWAS) conducted to date in SSc.

Methods

- 315 SSc-PAH
- 2,661 SSc-noPAH
- 17,584 controls

Genotyping → **Quality Control** (Plink software) → **Imputation** (SNP2HLA software)

Logistic Regression of **8,961 variants, amino acids and HLA alleles** (Plink software)

Comparisons

(1) SSc-PAH vs SSc-noPAH
(2) SSc-PAH vs Controls
(3) SSc-noPAH vs Controls

SSc-PAH comparisons: Nominal Significance (p-value < 0.05) → Not significant (p-value > 0.05)

Variants meeting these criteria were further prioritized

Linkage Disequilibrium (LD) Analysis → Assessed for Human Leukocyte Antigen (HLA) alleles ($r^2 > 0.8$), a subset of highly polymorphic genes within the MHC.

Functional Annotation

- OpenTargets Genetics
- FORGEdb Functional SNP
- SNPnexus Annotation tool

Results

87 variants were prioritized, 3 of which were in high LD with HLA alleles, which also met the criteria.

	rs2308488		rs17881210		rs16868789	
	p-value	OR (CI95)	p-value	OR (CI95)	p-value	OR (CI95)
SSc-PAH vs SSc-noPAH	0.046	7.66 (1.0-56.6)	0.049	0.66 (0.4-1.0)	0.028	1.70 (1.1-2.7)
SSc-PAH vs Controls	0.009	10.24 (1.8-59.2)	0.020	0.62 (0.4-0.9)	0.032	1.66 (1.0-2.6)
SSc-noPAH vs Controls	0.676	1.46 (0.2-8.7)	0.060	0.88 (0.8-1.0)	0.841	1.02 (0.8-1.3)
HLA in LD (r^2)	***HLA-B***48:01* (0.92)		***HLA-B***15:01* (0.92)		*HLA-DPB1*17:01* (0.87)	

- **Missense variant in HLA-B Protein** Coding Sequence
  - Substitution in position 269: Ala → Thr
- PolyPhen Database:
  - Evaluation: **Damaging consequences**
  - Score: 0.986/1

- FORGEdb: **Regulatory variant** (Score: 10/10)
- eQTL in LUNGS, ARTERIES, BLOOD and SKIN:
  - ***MICA*** (MHC Class I Polypeptide-Related Sequence A)
  - ***PSORS1C1*** (Psoriasis Susceptibility 1 Candidate 1)
  - *PSORS1C1* has been previously reported in SSc, but not *MICA*

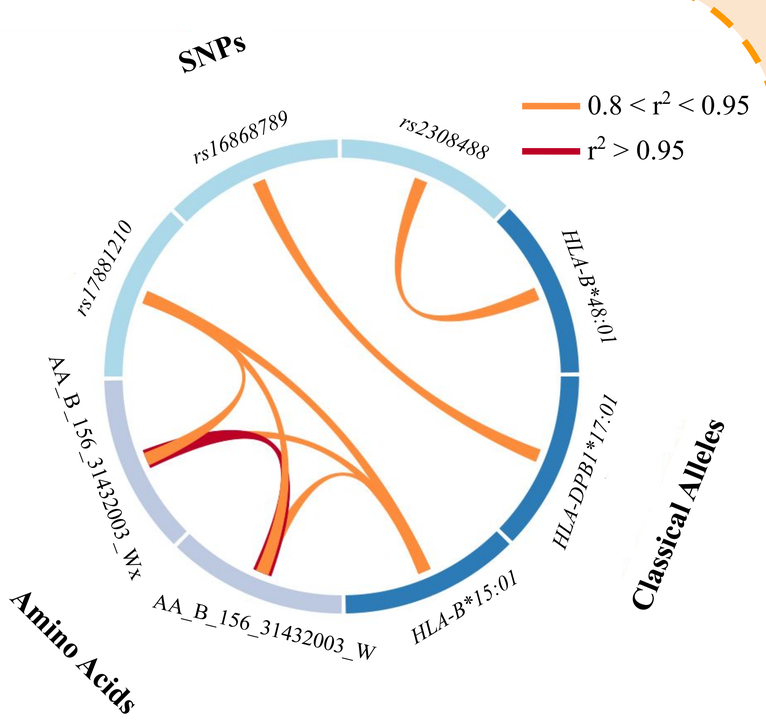

Figure 2. Linkage Disequilibrium (LD) among the variants. Circos plot depicting the LD relationship among the SNPs, classical HLA alleles and HLA amino acid residues ($r^2 > 0.8$). All variants, except for the amino acids, met the significance criteria. HLA, human leucocyte antigen; LD, linkage disequilibrium; SNP, single-nucleotide polymorphism.

Conclusion

Our preliminary results suggest the **importance** of **HLA-B alleles** in **SSc-PAH** and its **potential use as disease biomarkers**. However, further validation studies in an independent cohort are necessary to confirm our findings.

References:

1. Volkmann ER et al. Systemic sclerosis. Lancet. 2023;401(10373):304-318. doi:10.1016/S0140-6736(22)01692-0
2. Denton CP et al. Major lung complications of systemic sclerosis. Nat Rev Rheumatol. 2018;14(9):511-527. doi:10.1038/s41584-018-0062-0
3. Lenna S et al. The HLA-B*35 allele modulates ER stress, inflammation and proliferation in PBMCs from Limited Cutaneous Systemic Sclerosis patients. Arthritis Res Ther. 2015;17:363. Published 2015 Dec 16. doi:10.1186/s13075-015-0881-1

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