PATIENT GENOMICS EXPLAIN PRESENCE OF COMMON CHRONIC WOUND PATHOGENS USING A NOVEL ANALYTICAL APPROACH

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Introduction

•Reducing microbial load and biofilm in wounds improves healing (Wolcott et al. 2008) and is a treatment guideline (Lavery et al. 2023).

•Patient genetics associates with chronic wound microbiomes and healing (Tipton et al. 2020, Omeir et al. 2025, Gabrilska et al. 2025).

•The many combinations of species, patient genetics and their interactions complicates developing a clear multi-omic model for healing differences.

•Our recent work shows microbiomes in a structural equation modeling (SEM) framework predicts healing (Ancira et al. 2025).

•SEM facilitates complex causal models, includes interactions and multi-level design, and is a framework to unify multi-omic perspectives.

•To increase discovery power the first goal of this study was to integrate SEM into genome wide association analysis (GWAS), referred to here as latent-GWAS, by modeling patient genomic regions as latent variables predicting bacterial species occurrence in wounds.

•Next, we applied this analytical framework to identify genomic regions associated to *Staphylococcus aureus* and *Pseudomonas aeruginosa*, two important pathogens thus far unlinked to patient genetics, as well as *Anaerococcus obesiensis*, which previous work shows has strong relationship to patient genetics.

•Finally, owing to extensive prior research and known effect loci, we incorporated an independent dataset of 1286 patients with and without Alzheimer's Disease (AD) to serve as an independent validation set.

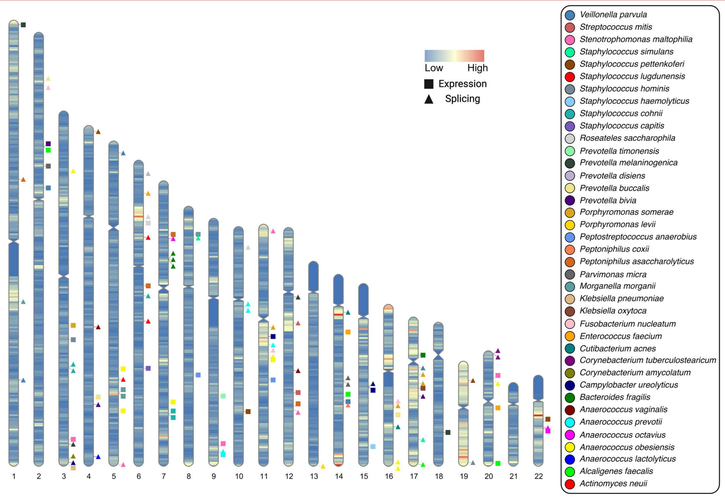

Figure 1. *Chromosomal ideogram illustrating the 109 significant genes identified through two-cohort mbTWAS analysis. Each marker represents the mid-position of a significant gene on chromosomes directly to the left. Marker colours indicate the species to which genes were associated, and shapes indicate if the association was for a gene or intron retention. Chromosomal gene density is illustrated by banding. (Omeir et al. 2025).*

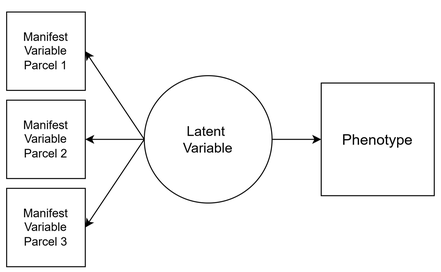

Figure 2. *Basic diagram of an SEM model serving as the foundation for how LD structure among SNPs is parceled (grouped) to estimate a latent variable summarizing a genomic region's relationship to phenotype.*

Methodology

• Wound care protocol was informed by 16s sequencing based microbial clinical reports provided by MicroGenDX (Lubbock, TX). Patient genomes were characterized at 6.2 million SNPs using genotyping arrays and imputation.

•Alzheimer's Disease validation dataset of ~600k SNPS using genotyping arrays and imputation.

•Latent-GWAS entails A) a sliding window approach identifying outlier regions with respect to a phenotype (here species presence or relative abundance), B) covariance structure of SNPs within outlier regions are modeled as latent variables using methods from Ancira et al. (2025), and C) permutational validation of significance.

•Comparator statistical methods, MAGMA and LDAK, were performed for benchmarking.

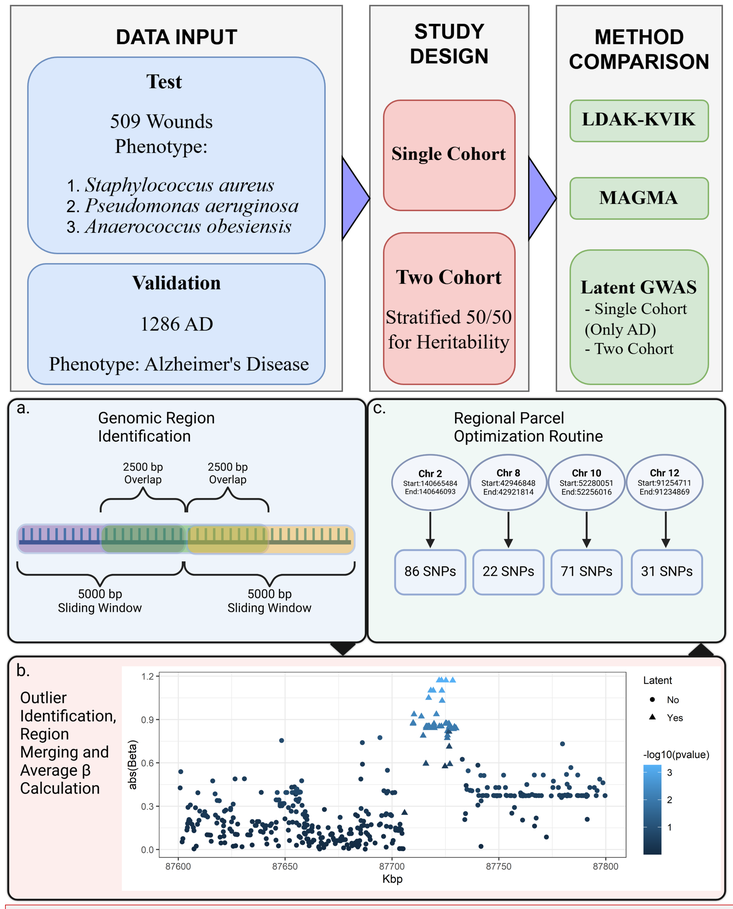

Figure 3. *Conceptual diagram of overall workflow. A test dataset and a validation dataset were used to compare method performance. AD was used as validation due to well characterized genes.*

Figure 4. *Conceptual diagram of the latent GWAS workflow. a) genomic outlier regions identified via sliding windows and merging, b) example ~40kb outlier locus modeled as a latent variable, c) example of 4 loci denoting size and inclusive SNPs.*

Results

• Latent-GWAS identified more significantly associated genomic loci than comparators. This was the case even though latent-GWAS was the only method subjected to standards of a two-cohort design.

• Here, wound pathogens *S. aureus* and *P. aeruginosa* are linked to the human genome for the first time.

• Latent-GWAS performance was particularly strong when associating loci to species presence/absence.

• Gene ontology (i.e., function type) enrichment, which serves as further validation that identified regions are non-random, was only observed for latent-GWAS.

• A cohort of AD patient genotypes serving as method validation identified 17 to 21 times more genes with a positive predictive value ranging from 85% to 88% vs 33% (LDAK-KVIK) associated with AD or neurodegeneration.

	Method	Significant Loci (Method Dependent)	Associated Genes (Method Dependent)	Gene Ontology Enrichment	
Staphylococcus aureus	Latent-GWAS	478	275	17	Presence/Absence
	MAGMA	279	279	0	
	LDAK-KVIK	2	2	0	
	Latent-GWAS	23	7	11	CLR-Relative Abundance
	MAGMA	0	0	0	
	LDAK-KVIK	0	0	0	
Pseudomonas aeruginosa	Latent-GWAS	1362	741	71	Presence/Absence
	MAGMA	25	25	0	
	LDAK-KVIK	1	1	0	
	Latent-GWAS	145	66	0	CLR-Relative Abundance
	MAGMA	1	1	0	
	LDAK-KVIK	13	13	0	
Anaerococcus obesiensis	Latent-GWAS	3320	1682	210	Presence/Absence
	MAGMA	7	7	0	
	LDAK-KVIK	0	0	0	
	Latent-GWAS	45	23	0	CLR-Relative Abundance
	MAGMA	8	8	0	
	LDAK-KVIK	51	51	0	

Table 1. *GWAS methods comparison table. Significant Loci refers to the number of regions or genes significantly associated with phenotypes, which are denoted by row groupings. Associated Genes reports how many genes were within latent-GWAS significant regions. Gene Ontology Enrichment reports total significant terms for each method and dataset.*

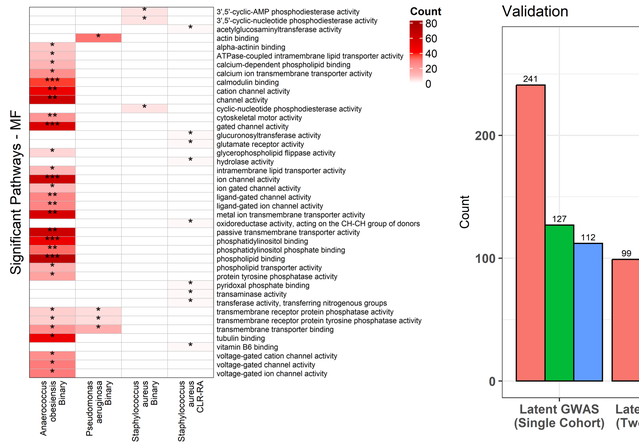

Figure 5. *Heatmap of MF level ontologies significantly enriched for all tested methods. Cells colored by count and annotated by adjusted p-value.*

Figure 6. *Bar plot of the loci, genes, and AD genes for each tested method. MAGMA was not included due to no significant loci identified.*

Conclusions

• Latent-GWAS demonstrated strong performance relative to other common methods and is agnostic to the GWAS phenotype of interest.

• Connecting human genetics to key pathogens within the chronic wound, supports further development of polygenic risk scores for infection.

• Moreover, this work is the first to suggest that peoples' genetic uniqueness may predispose them to infection by serious pathogens, including *S. aureus* and *P. aeruginosa*.

• Next steps in this project include A) multi-omic (genomic, metagenomic) integration into a unified SEM and B) distribution of latent-GWAS as an R package.

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