

Autoantibody-Peptide and Amino-Acid Motif Signatures of HLA Genotypes in Human Health

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BACKGROUND

The Human Leukocyte Antigen (HLA) region of chromosome 6p21 is perhaps the most medically significant region of the human genome, with many distinct pathologic associations to genetic variations. Our project utilizes high-resolution genotypes of serum fm healthy donors collected from the National Marrow Donor Program and a programmable phage display human peptidome identify and characterize antibody-peptide (ab-peptide) binding and peptide amino-acid (AA) motif signatures overexpressed in healthy donors homozygous for one of four HLA genotypes: HLA-DRB1*0301, HLA-DRB1*0401, HLA-DRB1*0701, HLA-DRB1*1501.

METHODS

1. Serum collected from 106 healthy human donors homozygous for HLA genotypes above were mixed w/ phage library to assess ab-peptide binding w/ 2 replicates.
2. Candidate ab-peptides identified w/ PairSeq pipeline.
3. Each HLA genotype sequentially set as experimental against remaining three genotypes as reference.
4. Candidate ab-peptides were analyzed with SLIMFinder to identify over-represented, AA motifs of interest.
5. Motifs associated w/ peptides Titin & Obscurin excluded.
6. Ab-peptide rPKs of top AA motifs were summed across replicates and analyzed to assess for separation of motifs by HLA genotype.

RESULTS

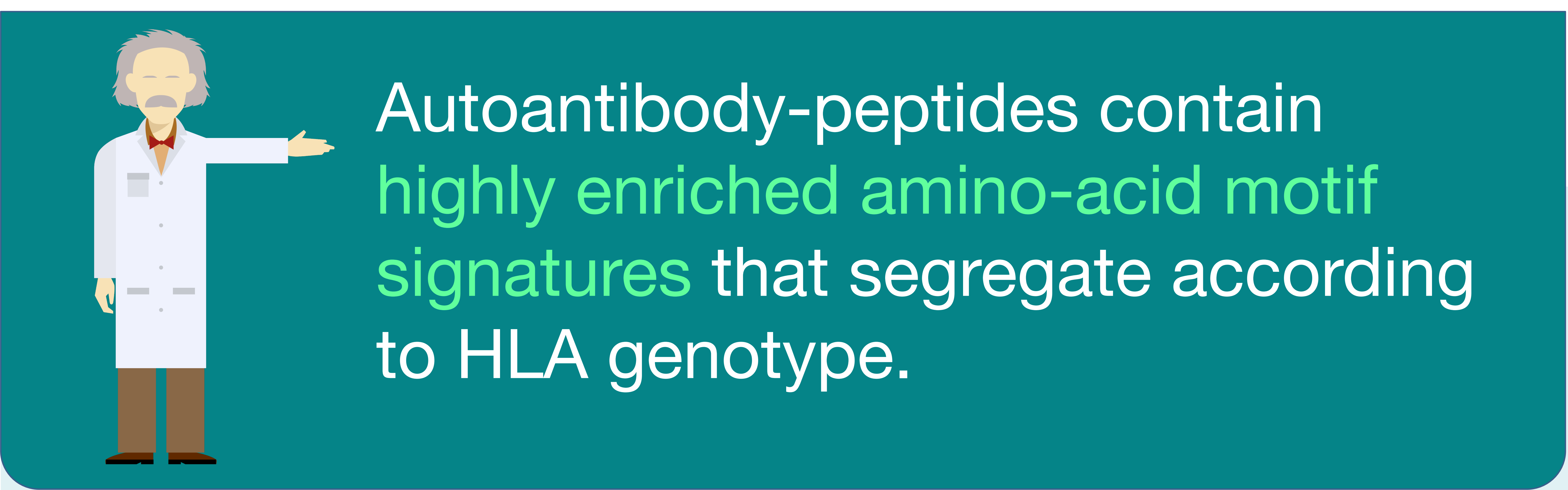
Genotype	Ab-Peptides	SLiMs	FDR
HLA-DRB1*0301	2593	162	< 1e-40
HLA-DRB1*0401	2877	860	< 1e-40
HLA-DRB1*0701	2651	317	< 1e-40
HLA-DRB1*1501	2811	692	< 1e-40

DISCUSSION

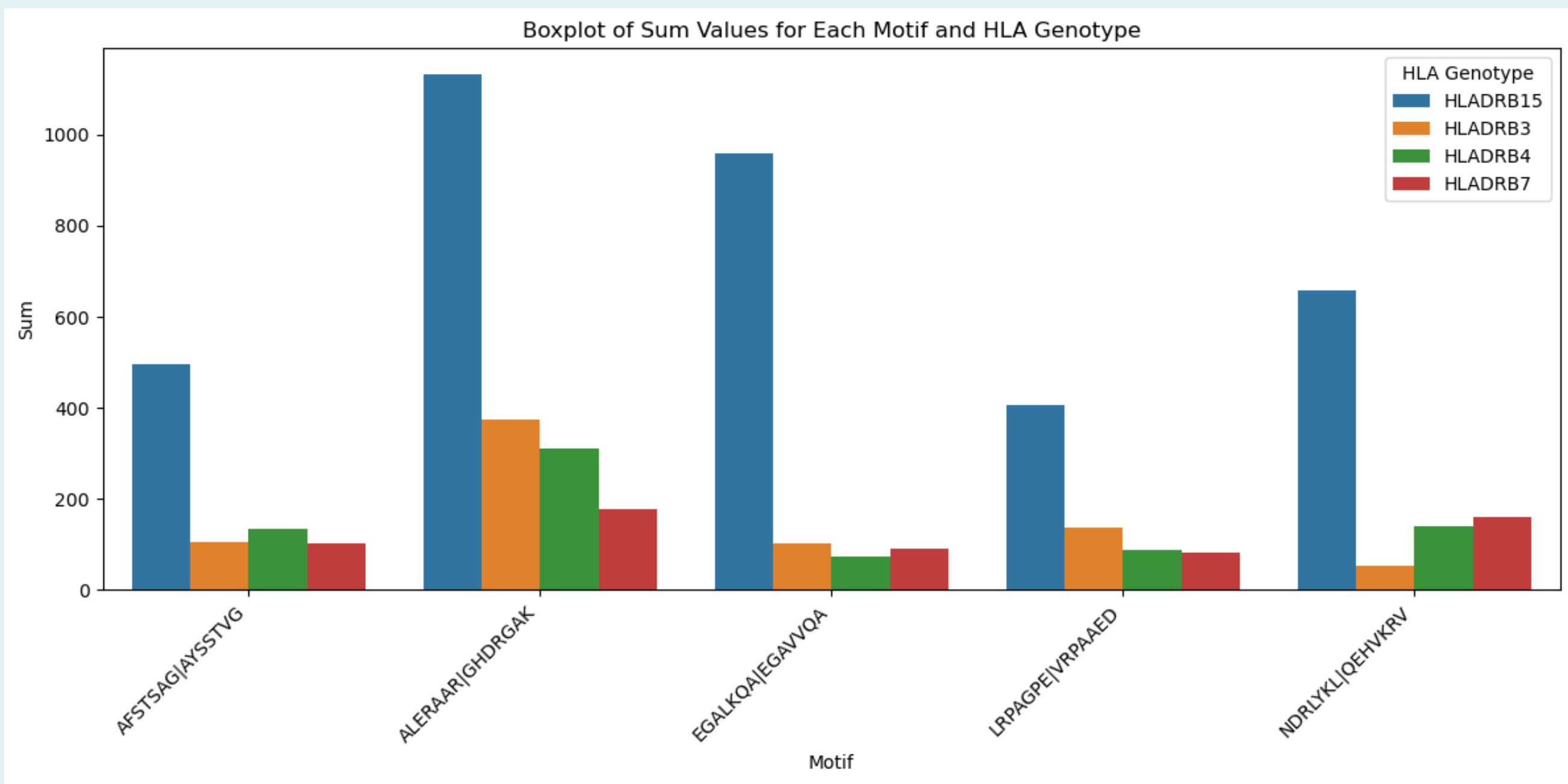
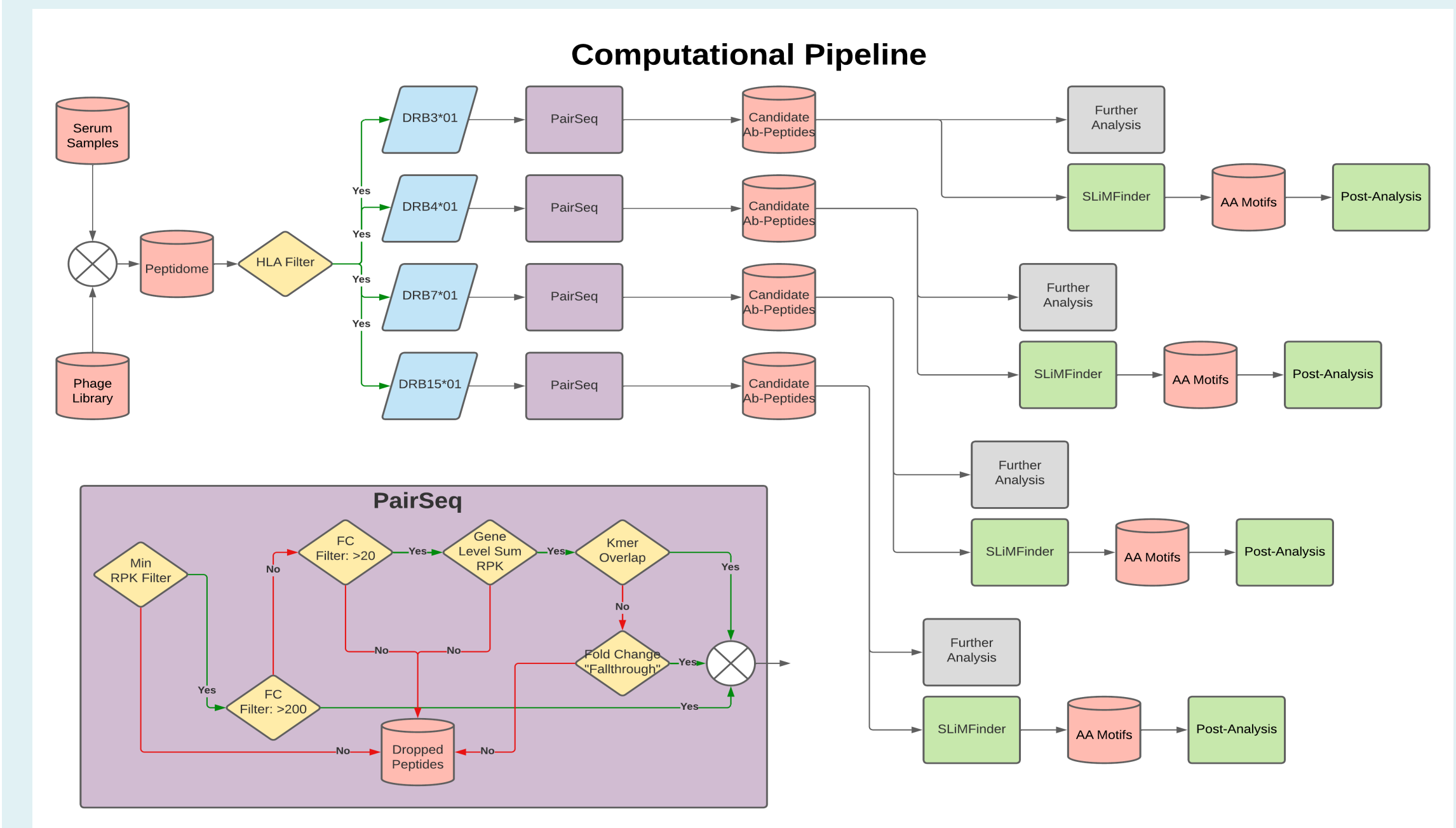
Our analysis yielded large numbers of Ab-peptide targets and distinct overrepresented AA motifs associated with each HLA genotype. The summation of the Ab-peptide binding for top AA motifs had significant enrichment compared with the control HLA genotypes. The next steps in our investigation involve using motif and Ab-peptide data to build a logistic regression model and exploring the utility of unsupervised machine learning to create a predictive model for HLA genotype based on Ab-peptide expression signature and AA motifs. We will integrate this model into a broader computational pipeline, along with additional Ab-peptide data for additional HLA genotypes currently in process, towards a comprehensive characterization of Ab-peptides and AA motifs for all known HLA haplotypes.

ACKNOWLEDGEMENTS

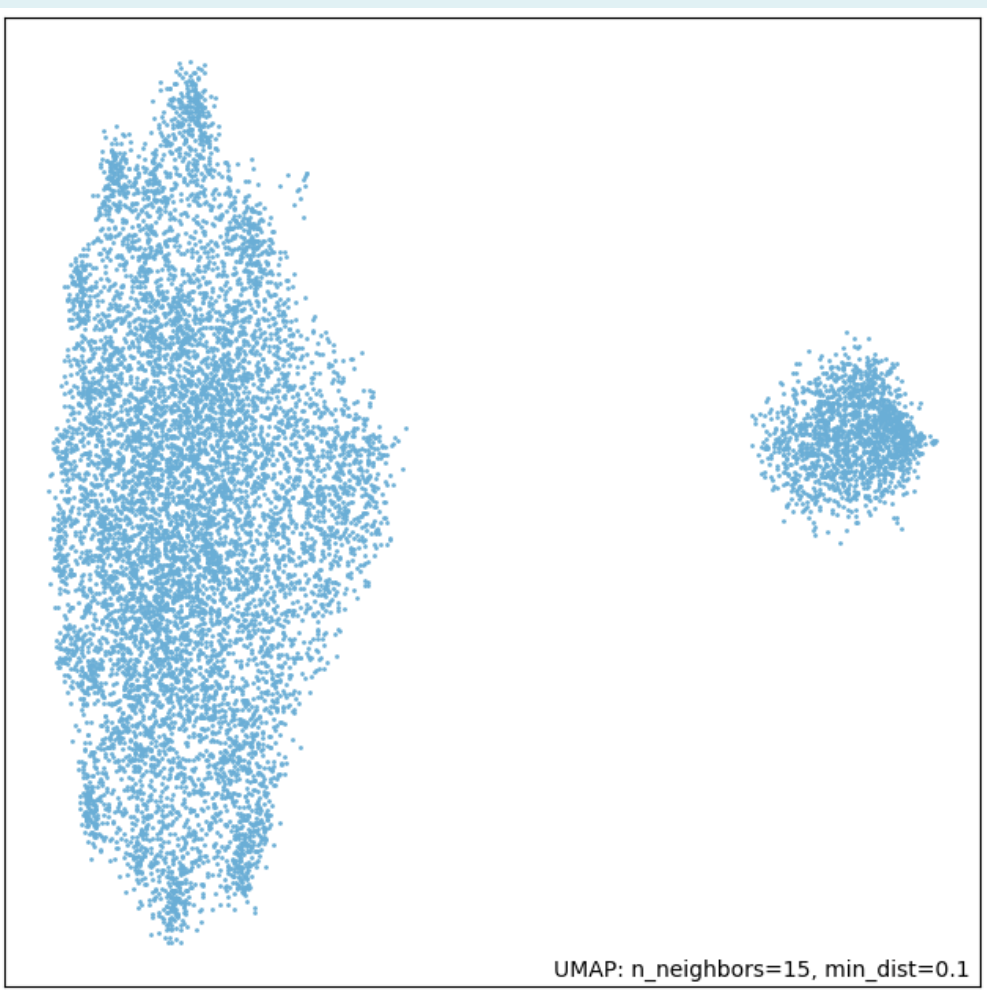
Immense thanks to Dr. Michael Wilson and the Wilson Lab, Dr. Jill Hollenbach and the Hollenbach Lab, Dr. Joe DeRisi and the DeRisi Lab, and the UCSF SOM.



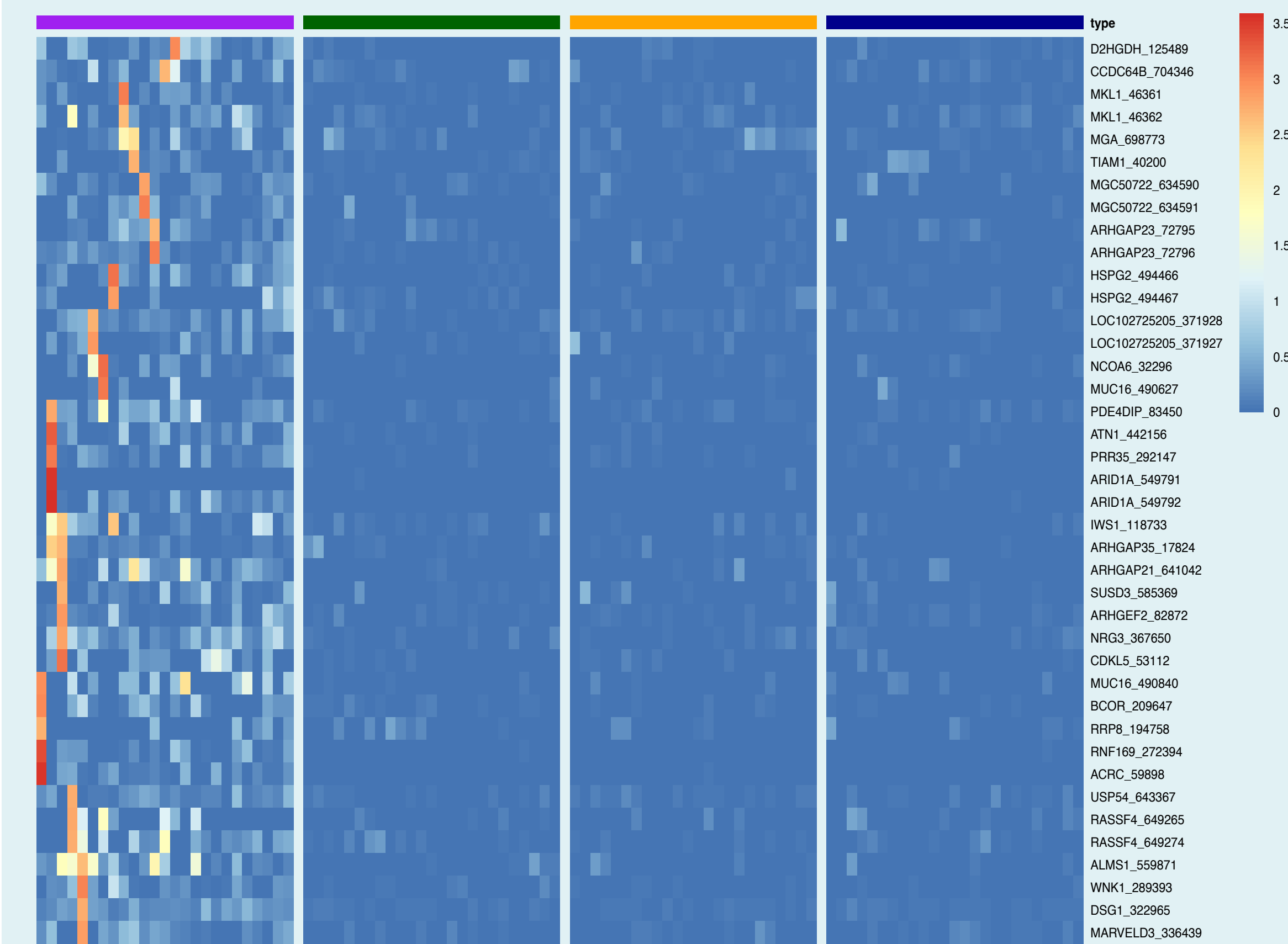
Autoantibody-peptides contain highly enriched amino-acid motif signatures that segregate according to HLA genotype.



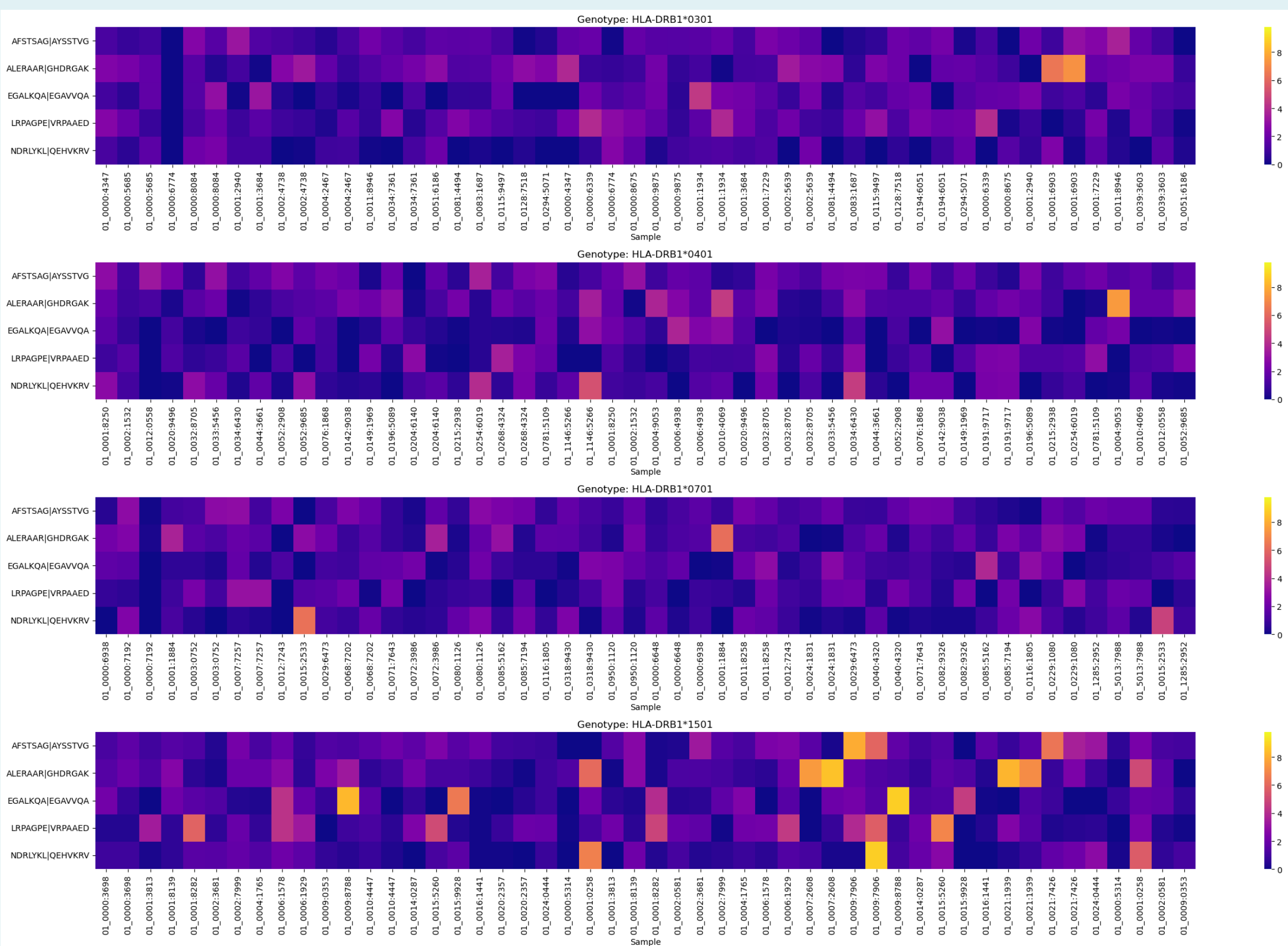
HLA-DRB1*1501 Peptide Level Ab-Peptides UMAP



Heatmap of HLA-DRB1*1501 Enriched Ab-Peptides



Heatmap of HLA-DRB1*1501 Enriched AA Motifs



HLA-DRB1*1501 Sample Level Ab-Peptides UMAP

