Human Leucocyte Antigen variation is associated with Cytomegalovirus serostatus

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Introduction

Cytomegalovirus (CMV) is a β-herpes virus common worldwide with prevalence of seropositivity reaching 80% in some parts of the USA. Primary infection is relatively benign for most infected individuals, after which the virus will persist lifelong in a latent state. However, CMV can cause severe effects in newborns in whom it is acquired congenitally, as well as immunocompromised individuals, including transplant recipients. CMV reactivation after allogeneic hematopoietic stem cell transplantation has been associated with increased transplant-related mortality and increased risk for graft-versus-host disease. Thus, understanding the role of immunogenetic variation in risk for CMV infection can provide insight into the immune control of this ubiquitous pathogen.

Here, we evaluated the association of *HLA* (Human Leukocyte Antigen) variation with CMV seropositivity in two cohorts: 366,481 individuals registered with Be The Match/NMDP (discovery) and 152,335 individuals registered with DKMS (replication).

Methods

We examined 5 *HLA* loci (*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DRB1*, *HLA-DQB1*) for association with CMV serostatus, while adjusting for sex, age, ancestry and socioeconomic status.

The protein structure modeling prediction included the α (*HLA-DRA*) and β (*HLA-DRB1*) chains and the stronger binder CMV pp65 peptide. Modeling prediction was performed on AlphaFold 3, parameters set as default. The electrostatic potential for contacts between α and β chains with the CMV peptide was performed using USCF ChimeraX.

Table 1. Significant *HLA* alleles associated with CMV that replicate in at least two population subgroups in both cohorts

	NMDP			DKMS			NDMP (homozygous)		
***HLA* Allele**	**OR**	**CI97.5%**	**p-value***	**OR**	**CI97.5%**	**p-value****	**OR**	**CI97.5%**	**p-value***
*DRB1*01:03*									
European descent	0.618	(0.581-0.657)	2.81E-52	0.669	(0.618-0.725)	5.80E-23	0.259	(0.076-0.661)	1.18E-02
Hispanic or Latino	0.491	(0.412-0.583)	7.26E-16	0.602	(0.419-0.862)	5.60E-03			
*DRB1*04:03*									
European descent	1.2	(1.129-1.275)	3.67E-09	1.292	(1.189-1.404)	1.55E-09	3.083	(1.642-5.874)	4.85E-04
Hispanic or Latino	1.306	(1.182-1.443)	1.61E-07	1.316	(1.063-1.636)	1.24E-02			

Logistic regression; OR: odds ratio; CI: confidence interval. *α = 8.62E-04; **α = 5.0E-02.

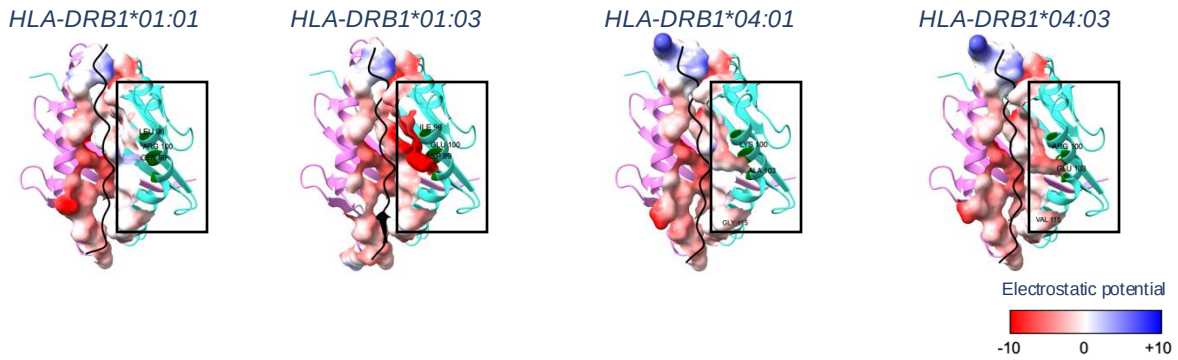

Figure 2. *HLA-DRB1* binding groove and CMV peptide

HLA-DRB1 binding groove and CMV pp65 DTPVLPHETRLLQTG peptide for *HLA-DRB1*01:01* and *HLA-DRB1*01:03* (A and B); and pp65 VSQYTPDSTPCHRGD peptide for *HLA-DRB1*04:01* and *HLA-DRB1*04:03* (C and D). A) *HLA-DRB1*01:01*. B) *HLA-DRB1*01:03*. C) *HLA-DRB1*04:01*. D) *HLA-DRB1*04:03*. α-chain: violet. β-chain: turquoise. CMV pp65 peptides: black. Blue: positive charges. White: neutral charges. Red: negative charges. Variant peptides between *HLA-DRB1*01:01* and *HLA-DRB1*01:03* as well as *HLA-DRB1*04:01* and *HLA-DRB1*04:03* are highlighted in green and labeled.

Results

A substantial number of alleles with frequency >1% were found to be associated with CMV serostatus in both cohorts. Of these, four alleles were significantly associated with CMV serostatus in at least two different population subgroups (*HLA-C*04:01* and *HLA-DRB1*04:03* with risk effect; *HLA-DRB1*01:03* and *HLA-DRB1*07:01* with protective effect) (Figure 1). A transpopulation meta-analysis showed statistically significant associations for all four alleles tested ($p < 0.001$). Further, we observed a strong dose effect for these alleles. Of note, the risk associated with two copies of *HLA-DRB1*04:03* was almost three times higher in European descent subgroup (OR = 3.083; CI = 1.642 – 5.874; p = 4.85E-04) relative to a single copy. Likewise, *HLA-DRB1*01:03* homozygotes showed a protective effect almost three times higher than heterozygotes in European descent subgroup (OR = 0.259; CI = 0.076 – 0.661; p = 1.18E-02) (Table 1).

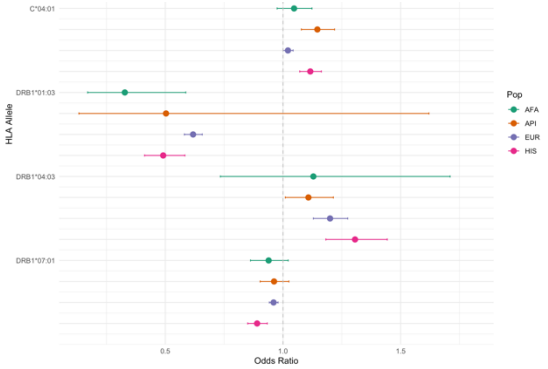

Figure 1. Significant HLA alleles associated with CMV

Conclusion

Our results provide population-scale evidence of the role of *HLA* in mediating infection with this common and important virus, and may provide a framework for understanding immunological conditions for efficient viral control.