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Immunogenetics of posttraumatic stress disorder (PTSD) in women veterans

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ABSTRACT

Posttraumatic stress disorder (PTSD) is a debilitating psychiatric condition that is associated with concomitant immune system dysfunction. Here we evaluated the influence of genes involved in the human immune response, Human Leukocyte Antigen (HLA), on lifetime PTSD in primarily Caucasian women veterans. High-resolution HLA genotyping was completed for 372 participants. We assessed differences in HLA makeup between Control ($n = 277$) and lifetime PTSD ($n = 95$) groups. HLA was found to have a significant overall effect on lifetime PTSD occurrence ($P < 0.00001$). Of the 192 alleles identified in this sample, the frequencies of 15 alleles significantly differed between groups. Two alleles – HLA-A*02:01 and DPB1*04:01 –occurred more frequently in controls, presumably indicating protective effects. Thirteen alleles (6 Class I, 7 Class II) occurred more frequently in the lifetime PTSD group, presumably indicating susceptibility effects. In analysis evaluating the effect of the combined presence in individual participants of a protective allele and a susceptibility allele, the presence of a protective allele neutralized the effect of the susceptibility alleles. These findings, which add to the nascent literature on immunogenetics of PTSD, are discussed in terms of the evolutionary role of HLA in host protection against foreign antigens.

1. Introduction

Posttraumatic stress disorder (PTSD) is a disabling psychiatric condition characterized by intrusive thoughts, avoidance, negative alterations in mood and cognitions, and physiological hyperarousal that can develop following exposure to events such as combat, physical or sexual assault, natural or human-made disasters, and life-threatening illness or injury (APA, 2013). Although PTSD is fairly common in the general population (Kessler et al., 2017; Kilpatrick et al., 2013), certain populations such as veterans experience substantially higher rates of PTSD (Fulton et al., 2015; Gates et al., 2012; Yaeger et al., 2006) and, for various reasons (Street et al., 2009), women veterans in particular are at exceptionally high risk for developing PTSD (Lehavot et al., 2018; Street et al., 2009; Wisco et al., 2014; Zinzow et al., 2007). PTSD is the only psychiatric condition with definitive etiology – namely, exposure to a traumatic event; yet only a subset of individuals who are exposed to trauma develop PTSD (Bonanno, 2004; Bonanno and Mancini, 2012; Bonanno et al., 2012; Donoho et al., 2017; Galatzer-Levy et al., 2018). That is particularly true for women veterans, for whom trauma exposure is nearly ubiquitous (Zinzow et al., 2007). The discordance between trauma exposure and PTSD suggests that additional factors, including genes, influence the variability in outcomes subsequent to trauma exposure. Here we focus on the influence of Human Leukocyte Antigen (HLA), genes involved in adaptive immunity, on PTSD.

Although PTSD is primarily a psychiatric disorder, substantial research points to immune system dysfunction in PTSD (Gill et al., 2009; Neigh and Ali, 2016; Sumner et al., 2020) leading some to characterize PTSD as an immunological (Wang et al., 2017) or psychoneuroimmunological (Pace and Heim, 2011) disorder. For instance, PTSD is associated with perturbations in immune cell distribution and function (Yang and Jiang, 2020; Katrinli and Smith, 2021), epigenetic changes of immune-related genes (Bam et al., 2016; Katrinli et al., 2019; Uddin et al., 2010; Zhou et al., 2014), systemic low-grade inflammation (Speer et al., 2018), and increased inflammatory markers (Passos et al., 2015; Katrinli et al., 2022), the latter of which have been shown to correspond to symptom severity (Michopoulos et al., 2015a,b; Zhou et al., 2014). Links between immune system disruption and PTSD are further supported by evidence that elevated inflammation, prior to or in the acute aftermath of trauma, increases PTSD risk (Eraly et al., 2014; Sumner et al., 2020) and by evidence of changes in inflammatory markers

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following PTSD treatment (Wang et al., 2017). PTSD-associated cognitive deficits in attention and processing speed, executive function, and memory have also been linked to inflammatory mechanisms (Quinones et al., 2020). Finally, individuals with PTSD are at elevated risk for conditions linked to immune dysfunction, including metabolic syndrome, diabetes, cardiovascular disease, and accelerated biological aging (Mellon et al., 2018; Yang et al., 2021), as well as autoimmune diseases (Boscarino, 2004; Bookwalter et al., 2020; O'Donovan et al., 2015). In light of substantial literature documenting immune dysfunction in PTSD and the role of HLA in immune system functioning, there is burgeoning interest in the role of HLA in PTSD.

HLA codes for cell surface proteins that play an integral role in immune system surveillance and elimination of foreign (e.g., viral, bacterial) antigens via two primary pathways. Class I HLA molecules (HLA-A, B, C), which are expressed on nucleated cells, bind small peptides from proteolytically degraded cytosolic viruses and bacteria, and those bound peptides are exported to the cell surface for presentation to $CD8^+$ cytotoxic T cells, signaling cell destruction. Class II HLA molecules (HLA-DPB1, DQB1, DRB1) are expressed on lymphocytes and professional antigen presenting cells (e.g., macrophages, dendritic cells, and monocytes). Class II HLA present larger peptides derived from endocytosed exogenous antigens to $CD4^+$ T cells to facilitate B cell mediated antibody production and adaptive immunity. Variation in the HLA region, the most highly polymorphic region of the human genome (Trowsdale and Knight, 2013), has been shown to contribute to disease susceptibility (Dendrou et al., 2018), including some evidence implicating HLA in PTSD. An initial genome-wide association study (GWAS) identified the HLA-B locus as relevant to PTSD in African American males (Nievergelt et al., 2018), and DNA methylation in the HLA region has been associated with post-deployment PTSD status in male veterans of European American ancestry (Snijders et al., 2020) and in African American women (Katrinli et al., 2021). To our knowledge, only one prior study has investigated the influence of specific HLA alleles, imputed from GWAS, on PTSD. In a sample of primarily female African American individuals with PTSD and trauma-exposed controls, Katrinli and colleages (2019) reported that 5 HLA alleles were more frequent in those with PTSD (*HLA-B*58:01, HLA-C*07:01, HLA-DQA1*01:01, HLA-DQB1*05:01, HLA-DPB1*17:*01) whereas 3 HLA alleles (*HLA-A*02:01, HLA-DQA1*05:05, and HLA-DRB1*11:01)* were more frequent in controls. That study, the first to evaluate HLA alleles with regard to PTSD, demonstrated immunogenetic influence on PTSD in African American women; however, the extent to which those findings extend to other populations remains to be determined, particularly since HLA composition varies within and across geographic and ethnic groups (Buhler and Sanchez-Mazas, 2011; Buhler et al., 2012; Sanchez-Mazas et al., 2013) and is differentially associated with disease (Hill et al., 1991; Singh et al., 2007). Thus, in this study we evaluate the influence of HLA alleles on lifetime PTSD in a sample of primarily European American women.

2. Methods

2.1. Participants

A total of 372 women veterans participated in this study (mean age ± SD: 55.5 ± 16.1 y; range: 24.6–102.3 y), 277 of whom were healthy controls who had never been diagnosed with PTSD and 95 of whom met lifetime diagnostic criteria for PTSD as determined by the Clinician Administered PTSD Scale (Weathers et al., 2013). Control participants were healthy women, free of any medical or psychiatric condition affecting brain function. Participants in the PTSD group had a primary diagnosis of lifetime PTSD documented in their medical chart and confirmed as part of the present study. As part of the diagnostic assessment, trauma exposure was evaluated and documented for everyone in the PTSD group and for a subset (n = 75) of participants in the control group. Differences in HLA composition for Controls with documented trauma exposure and those for whom trauma exposure was not formally assessed were evaluated as described below. Nearly all of the participants were Caucasian (93%) and non-Hispanic (95%). The study protocol was approved by the Minneapolis VAHCS institutional review board. All participants provided informed consent prior to participating in the study and were paid for their participation.

2.2. HLA

DNA isolation was carried out from 3 ml of whole blood drawn in EDTA tubes, using a commercially available kit (ArchivePure cat. 2300730) from 5Prime (distributed by Fisher Scientific or VWR) with an expected yield of 50–150 μg of DNA. The purified DNA samples were sent to Histogenetics (http://www.histogenetics.com/) for high-resolution HLA Sequence-based Typing (SBT; details are given in https://bioinformatics.bethematchclinical.org/HLA-Resources/HLA-Typing/High-Resolution-Typing-Procedures/and https://bioinformatics.bethematchclinical.org/WorkArea/DownloadAsset.aspx?id=6482). Their sequencing DNA templates are produced by locus- and group-specific amplifications that include exon 2 and 3 for class I (A, B, C) and exon 2 for class II (DRB1, DRB3/4/5, DQB1, and DPB1) and reported as Antigen Recognition Site (ARS) alleles as per ASHI recommendation (Cano et al., 2007).

Among the 372 participants, 192 discrete HLA alleles were identified. The overall frequencies of those alleles are provided in Table 1.

2.3. Data analysis

Standard statistical methods were used to analyze the data, including descriptive statistics (mean, SD, SEM), independent samples *t*-test, chi-square statistics of two-way tables, Mantel-Haenszel statistics (odds ratio), Fisher's method for combining tests of significance (explained below), and testing of proportions (Wald H0 test). The IBM-SPSS statistical package (version 27) was used for these analyses. A P-value of $P < 0.05$ (two-sided) was used to reject the null hypothesis.

3. Results

3.1. HLA and PTSD

We assessed differences in HLA makeup between Control and PTSD groups as follows. For each HLA allele, we first computed its proportion of occurrence in the Control and PTSD groups and then tested the difference in these proportions between the two groups. A higher proportion in Control (vs. PTSD) would indicate a protective effect of that allele, whereas the opposite would indicate a susceptibility effect. We then computed the Z statistic (normal deviate, Wald H0 test) and screened provisionally the results to identify alleles with $|Z| > 1.96$, a reasonable threshold of 1.96 signal-to-noise ratio; this threshold corresponds to a P value of 0.05. This screening procedure identified 15 alleles (Table 2): 2 with a protective effect and 13 with a susceptibility effect. Mantel-Haenszel statistics (estimates of common odds ratio and its logarithm) are given in Table 3. We assessed the statistical significance of the set of these differences in the proportions of occurrence of those 15 alleles in the trauma-exposed Control participants and the Control participants for whom trauma exposure was not formally assessed. There were no significant differences in the proportions between the Control subgroups for any of the 15 alleles. We then formally assessed the statistical significance of the combined effect of the 15 alleles above (Table 3) using Fisher's (1925) method and derived an estimate of the statistical significance of the overall HLA effect on PTSD. The formula is the following:

$$X^2_{2k} \sim -2\sum_{i=1}^{k} \ln(p_i) \quad (1)$$

Table 1
HLA alleles identified in study participants and their frequencies (Freq.).

Allele	Freq.	Allele	Freq.	Allele	Freq.	Allele	Freq.	Allele	Freq.
A*01:01	0.1465	B*15:24	0.0027	C*05:01	0.0659	DPB1*50:01	0.0013	DRB1*11:03	0.0108
A*02:01	0.2124	B*15:35	0.0013	C*06:02	0.0766	DPB1*92:01	0.0013	DRB1*11:04	0.0175
A*02:02	0.0054	B*18:01	0.039	C*07:01	0.1425	DQB1*0:201	0.1129	DRB1*12:01	0.0175
A*02:05	0.0081	B*27:02	0.0013	C*07:02	0.1465	DQB1*0:202	0.0726	DRB1*13:01	0.0887
A*02:06	0.0013	B*27:05	0.0511	C*07:04	0.0121	DQB1*02:10	0.0027	DRB1*13:02	0.0444
A*02:30	0.0013	B*27:07	0.0027	C*07:19	0.0013	DQB1*03:01	0.1626	DRB1*13:03	0.0094
A*02:35	0.0013	B*35:01	0.0524	C*08:02	0.0309	DQB1*03:02	0.0874	DRB1*13:04	0.0013
A*03:01	0.1546	B*35:02	0.0054	C*12:01	0.0067	DQB1*03:03	0.0403	DRB1*13:05	0.0027
A*03:02	0.0013	B*35:03	0.0081	C*12:02	0.0027	DQB1*03:05	0.0013	DRB1*14:01	0.0027
A*11:01	0.0524	B*35:08	0.004	C*12:03	0.0403	DQB1*03:19	0.0081	DRB1*14:02	0.0013
A*23:01	0.0188	B*37:01	0.0108	C*14:02	0.0148	DQB1*04:02	0.0309	DRB1*14:04	0.0013
A*24:02	0.086	B*38:01	0.0161	C*15:02	0.0255	DQB1*05:01	0.1129	DRB1*14:54	0.0242
A*24:03	0.004	B*39:01	0.0148	C*15:04	0.0013	DQB1*05:02	0.0134	DRB1*15:01	0.1317
A*25:01	0.0282	B*39:06	0.004	C*15:05	0.004	DQB1*05:03	0.0282	DRB1*15:02	0.0081
A*26:01	0.0269	B*40:01	0.0565	C*15:09	0.0013	DQB1*06:01	0.0094	DRB1*15:03	0.0054
A*26:08	0.0013	B*40:02	0.0121	C*16:01	0.0349	DQB1*06:02	0.1398	DRB1*16:01	0.0094
A*29:01	0.004	B*41:01	0.0013	C*16:02	0.0027	DQB1*06:03	0.0914	DRB1*16:02	0.0067
A*29:02	0.0269	B*41:02	0.004	C*16:04	0.0013	DQB1*06:04	0.0255		
A*30:01	0.0202	B*42:02	0.0013	C*16:50	0.0013	DQB1*06:09	0.0161		
A*30:02	0.0067	B*44:02	0.0672	C*17:01	0.0067	DQB1*06:84	0.0013		
A*31:01	0.0282	B*44:03	0.0336	DPB1*01:01	0.0457	DRB1*01:01	0.0927		
A*32:01	0.0296	B*44:04	0.0013	DPB1*02:01	0.1196	DRB1*01:02	0.0027		
A*33:01	0.004	B*44:05	0.0013	DPB1*02:02	0.0027	DRB1*01:03	0.004		
A*33:03	0.0054	B*44:27	0.004	DPB1*03:01	0.1022	DRB1*03:01	0.1062		
A*34:01	0.0013	B*45:01	0.0148	DPB1*04:01	0.336	DRB1*03:02	0.0013		
A*34:02	0.0027	B*47:01	0.0027	DPB1*04:02	0.1008	DRB1*04:01	0.0712		
A*36:01	0.0013	B*49:01	0.0134	DPB1*05:01	0.0282	DRB1*04:02	0.0054		
A*66:01	0.0013	B*50:01	0.0067	DPB1*06:01	0.0148	DRB1*04:03	0.0081		
A*68:01	0.043	B*51:01	0.0551	DPB1*09:01	0.0081	DRB1*04:04	0.039		
A*68:02	0.0054	B*52:01	0.0148	DPB1*10:01	0.0148	DRB1*04:05	0.0027		
A*74:01	0.0013	B*53:01	0.0134	DPB1*10:50	0.0054	DRB1*04:06	0.0013		
A*80:01	0.0027	B*54:01	0.0013	DPB1*11:01	0.0175	DRB1*04:07	0.0134		
B*07:02	0.1425	B*55:01	0.0081	DPB1*13:01	0.0161	DRB1*04:08	0.0067		
B*07:05	0.004	B*56:01	0.0134	DPB1*13:10	0.0013	DRB1*04:11	0.0013		
B*08:01	0.1008	B*57:01	0.0269	DPB1*14:01	0.0121	DRB1*07:01	0.1075		
B*13:02	0.0255	B*58:01	0.0081	DPB1*15:01	0.0094	DRB1*08:01	0.0242		
B*14:01	0.0067	C*01:02	0.043	DPB1*16:01	0.0054	DRB1*08:02	0.0013		
B*14:02	0.0228	C*02:01	0.0013	DPB1*17:01	0.0188	DRB1*08:03	0.0027		
B*14:03	0.0013	C*02:02	0.0511	DPB1*18:01	0.0013	DRB1*08:04	0.0027		
B*15:01	0.0659	C*02:10	0.0013	DPB1*19:01	0.0134	DRB1*08:11	0.0013		
B*15:03	0.004	C*03:02	0.0054	DPB1*20:01	0.0067	DRB1*09:01	0.0108		
B*15:16	0.0013	C*03:03	0.0551	DPB1*23:01	0.0054	DRB1*10:01	0.0094		
B*15:17	0.0013	C*03:04	0.0793	DPB1*35:01	0.0013	DRB1*11:01	0.0578		
B*15:18	0.0013	C*04:01	0.0887	DPB1*40:01	0.0013	DRB1*11:02	0.0054		

Table 2
HLA alleles (in alphabetical order) with a statistically significant difference in allele proportions between Control and PTSD groups. ASE, asymptotic standard error of the difference; Z, normal deviate. Blue, protective; Red, susceptibility alleles.

Allele	Control Proportion	PTSD Proportion	Control – PTSD	ASE	Z	P value (2-sided)
A*02:01	0.455	0.337	0.118	0.057	2.008	0.045
B*13:02	0.036	0.095	-0.059	0.032	-2.240	0.025
B*15:24	0.000	0.021	-0.021	0.015	-2.421	0.015
B*38:01	0.022	0.063	-0.041	0.026	-1.975	0.048
B*47:01	0.000	0.021	-0.021	0.015	-2.421	0.015
C*06:02	0.130	0.221	-0.091	0.047	-2.127	0.033
C*16:02	0.000	0.021	-0.021	0.015	-2.421	0.015
DPB1*04:01	0.700	0.589	0.111	0.057	1.987	0.047
DPB1*05:01	0.036	0.116	-0.080	0.035	-2.904	0.004
DPB1*17:01	0.025	0.074	-0.049	0.028	-2.140	0.032
DPB1*23:01	0.004	0.032	-0.028	0.018	-2.281	0.023
DQB1*06:03	0.152	0.274	-0.122	0.051	-2.656	0.008
DRB1*01:02	0.000	0.021	-0.021	0.015	-2.421	0.015
DRB1*13:01	0.144	0.274	-0.130	0.05	-2.846	0.004
DRB1*14:01	0.000	0.0021	-0.002	0.015	-2.421	0.015

Table 3
Mantel-Haenszel Common Odds Ratio Estimates. Values of $\widehat{\omega} < 1$ indicate higher prevalence of the allele in the Control group and, hence, protection from PTSD; and, conversely, alleles with $\widehat{\omega} > 1$ indicate a higher proportion of the allele in the PTSD group and. Hence, susceptibility to PTSD. Allele frequencies are from Table 1. PTSD Risk was calculated as the product of $\ln(\widehat{\omega})$ x Allele Frequency.

EXAMPLE		DPB1*05:01		
		Absent	Present	Total
PTSD	Absent (Control)	267	10	277
	Present	84	11	95
Total		351	21	372

Allele	Common Odds Ratio ($\widehat{\omega}$)	$\ln(\widehat{\omega})$	Allele Frequency	PTSD Risk
A*02:01	0.609	−0.496	0.2124	−0.1054
B*13:02	2.794	1.028	0.0255	0.0262
B*15:24	14.840[a]	2.697[a]	0.0027	0.0073
B*38:01	3.045	1.113	0.0161	0.0179
B*47:01	14.840[a]	2.697[a]	0.0027	0.0073
C*06:02	1.900	0.642	0.0766	0.0492
C*16:02	14.840[a]	2.697[a]	0.0027	0.0073
DPB1*04:01	0.614	−0.487	0.3360	−0.1636
DPB1*05:01	3.496	1.252	0.0282	0.0353
DPB1*17:01	3.068	1.121	0.0188	0.0211
DPB1*23:01	9.000	2.197	0.0054	0.0119
DQB1*06:03	2.108	0.746	0.0914	0.0682
DRB1*01:02	14.840[a]	2.697[a]	0.0027	0.0073
DRB1*13:01	2.233	0.893	0.0887	0.0792
DRB1*14:01	14.840[a]	2.697[a]	0.0027	0.0073

Pearson Chi-Square = 8.434, P = 0.004.
Odds ratio $\widehat{\omega} = (267 \times 11)/(84 \times 10) = 3.496$, $\ln(\widehat{\omega}) = 1.252$.
[a] Calculated after adding 0.5 to all 4 values of the 2 × 2 table because the proportion of the allele in the Control group was zero.

where k is the number of combined tests ($k = 15$ alleles), i denotes an individual test ($i = 1$ to k), ln is the natural logarithm (base e), p is the P-value of the test (last column in Table 2), and X^2_{2k} is the chi-square statistic with $2k$ degrees of freedom. Application of this formula yielded the following result:

$$X^2_{30} = 120.76, \mathrm{P} = 7.61\mathrm{x}10^{-13} \quad (2)$$

This result documents a highly statistically significant overall effect of HLA on PTSD occurrence.

3.2. HLA-related risk for PTSD

The $\ln(\widehat{\omega})$ (Table 3) can be regarded as an estimate of PTSD risk (positive) or protection (negative) rendered by a given allele. Given the frequency of the allele (Table 1), the estimated contribution of that allele to the risk (or protection) for PTSD in this sample was estimated by computing the product of $\ln(\widehat{\omega})$ x the allele's frequency. This estimate is given in Table 3. It can be seen that protective alleles A*02:01 and DPB1*04:01 have the highest (protective) contributions, due to their high frequencies. Overall, the mean (±SEM) contribution was 0.0051 ± 0.062, a value that did not differ significantly from zero (P = 0.755, one-sample t-test), indicating that there is no HLA-related net risk for PTSD. However, the PTSD susceptibility of a particular individual will depend on the specific HLA of 12 alleles (2 per gene) carried by that individual: the sum of their $\ln(\widehat{\omega})$ would give the estimated magnitude of PTSD susceptibility, potentially useful information to the individual.

3.3. Combined effect of protective and susceptibility alleles

In this analysis we evaluated the effect of the combined presence in individual participants of one of the two protective alleles (A*02:01 and DPB1*04:01) *and* any of the susceptibility alleles listed in Table 3. Of the 2 × 13 = 26 such allele combinations, 14 could be evaluated (Table 4).

Table 4
Mantel-Haenszel Common Odds Ratio Estimates for combinations of the two protective alleles (A*02:01 and DPB1:04:01) and individual susceptibility alleles. N/A, not available for allele combinations which were not present in both groups.

Protective Allele	Odds Ratio ($\widehat{\omega}$)	P value
A*02:01 + B*13:02	2.076	0.242
A*02:01 + B*15:24	N/A	
A*02:01 + B*38:01	0.642	0.695
A*02:01 + B*47:01	N/A	
A*02:01 + C*06:02	1.304	0.547
A*02:01 + C*16:02	N/A	
A*02:01 + DPB1*05:01	0.551	0.590
A*02:01 + DPB1*17:01	1.690	0.571
A*02:01 + DPB1*23:01	N/A	
A*02:01 + DQB1*06:03	1.450	0.405
A*02:01 + DRB1*01:02	N/A	
A*02:01 + DRB1*13:01	1.473	0.385
A*02:01 + DRB1*14:01	N/A	
DPB1*04:01 + B*13:02	2.229	0.218
DPB1*04:01 + B*15:24	N/A	
DPB1*04:01 + B*38:01	2.128	0.215
DPB1*04:01 + B*47:01	N/A	
DPB1*04:01 + C*06:02	1.065	0.891
DPB1*04:01 + C*16:02	N/A	
DPB1*04:01 + DPB1*05:01	N/A	
DPB1*04:01 + DPB1*17:01	6.600	0.103
DPB1*04:01 + DPB1*23:01	2.243	0.572
DPB1*04:01 + DQB1*06:03	1.422	0.324
DPB1*04:01 + DRB1*01:02	N/A	
DPB1*04:01 + DRB1*13:01	1.583	0.244
DPB1*04:01 + DPB1*14:01	N/A	

In all cases, the susceptibility effect of all these alleles was converted to a nonsignificant, neutral effect in the presence of a protective allele, indicating the preponderance of the protective HLA effect. On the whole, since an individual carries 12 classical HLA alleles, it is possible one carries a number of protective/susceptibility alleles. Of the individuals who carried at least one of the two protective alleles (Table 2), 60.3% in the PTSD group carried at least one susceptibility allele, as compared to 29.6% in the control group; the difference between these two proportions was highly statistically significant (P = 0.000006, Wald H0 test of two proportions).

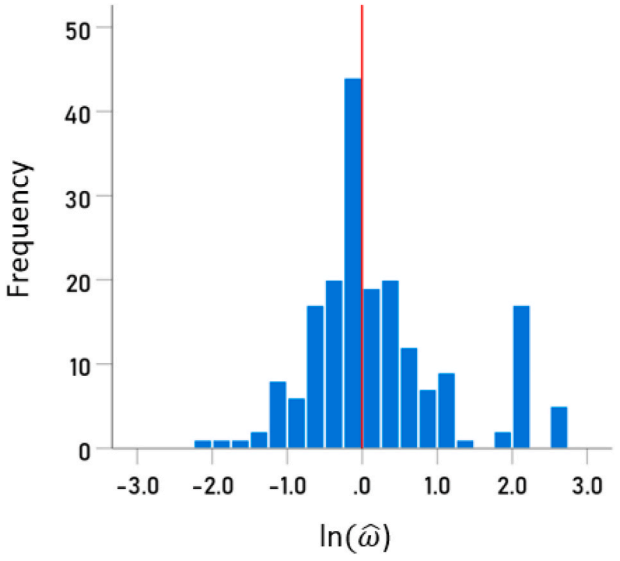

Fig. 1. Frequency distribution of the log-odds ratio, $\ln(\widehat{\omega})$. N = 192 alleles.

3.4. Association between effect on PTSD and allele frequency

For this analysis we computed the log-odds ratio, ln $(\widehat{\omega})$, for all 192 alleles (Fig. 1) and evaluated its association with allele frequency. As previously indicated, the ln$(\widehat{\omega})$ can be regarded as an estimate of PTSD risk (positive) or protection (negative) associated with a given allele. It can be seen (Fig. 1) that there is a slight preponderance of protective (negative) effects. Next, we assessed the association between ln $(\widehat{\omega})$ and allele frequency. For that purpose, we log-transformed the allele frequency to normalize its distribution (Fig. 2), and then computed the Pearson correlation between ln $(\widehat{\omega})$ and ln(allele frequency). We found a highly statistically significant, negative association between the two measures, such that lower PTSD odds ratios were associated with higher allele frequencies (Fig. 3) ($r = -0.326$, $P = 0.000004$, $N = 192$). This association was the same for both HLA Class I ($r = -0.326$, $P = 0.00057$, $N = 108$ alleles) and Class II ($r = -0.326$, $P = 0.002$, $N = 84$ alleles). Taken together, this suggests that HLA protection against PTSD is conferred from common alleles.

4. Discussion

Here we evaluated differences in HLA makeup for women with lifetime PTSD and controls, and assessed the overall influence of HLA on PTSD in this sample. We found a highly significant overall effect of HLA on PTSD occurrence and documented specific alleles in both classes of HLA that differed significantly with regard to the frequency of their occurrence in women with lifetime PTSD and controls. These findings add to the nascent literature on immunogenetics of PTSD and identify specific alleles that may influence PTSD in European American women.

In this sample, 15 out of 193 HLA alleles significantly differed between women with lifetime diagnoses of PTSD and healthy controls. Of those, 13 HLA alleles were more frequent in women with PTSD, suggesting genetic susceptibility to PTSD, whereas 2 alleles were more frequent in controls, suggesting protective effects against PTSD. Notably, two of the 15 alleles above were similarly identified in a previous study on HLA in African American women with PTSD (Katrinli et al., 2019). In both that study and ours, HLA-A*02:01 was significantly more frequent in healthy controls and HLA-DPB1*17:01 was significantly more frequent in women with PTSD, indicating associations of those alleles with PTSD extend across ethnic groups. In addition to the protective effect of HLA-A*02:01, we also documented protective effects of DPB1*04:01 on lifetime PTSD. Although ours is the first study to document an association of this specific allele with PTSD to our knowledge, one study found that PTSD is associated with increased DPB1 methylation in African Americans, and decreased DPB1 methylation in Caucasians (Katrinli et al., 2021), and DPB1*04:01 has been shown to exert protective effects against autoimmune disorders and conditions affecting the brain (Hadley et al., 2015; Kasai et al., 2022; Ollila et al., 2015; Watanabe et al., 2021). In addition to confirming previously identified risk of DPB1*17:01 on PTSD, we documented other alleles with even more robust evidence of susceptibility to PTSD (Table 2). Remarkably, the combined presence of a protective and a susceptibility allele ameliorated the susceptibility effect, converting it to a nonsignificant, neutral effect in all cases that could be tested (Table 3). The strongest effects were observed for HLA-DPB1*05:01 and DRB1*13:01. Although these alleles have not previously been associated with PTSD, both have been associated with risk and/or protection for other immune-related conditions ranging from dementia and Parkinson's disease to rheumatoid arthritis and narcolepsy (Aureli et al., 2014; Furukawa et al., 2017; James et al., 2018; Ollila et al., 2015; van der Woude et al., 2010).

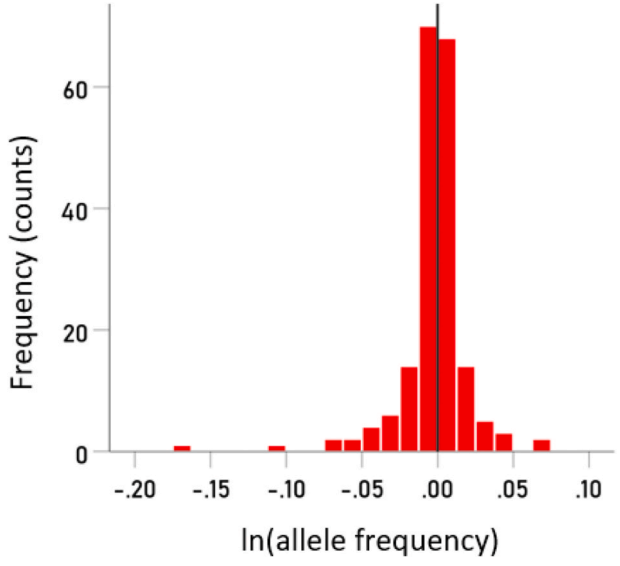

Fig. 2. Frequency distribution of the log-allele frequency. N = 192 alleles.

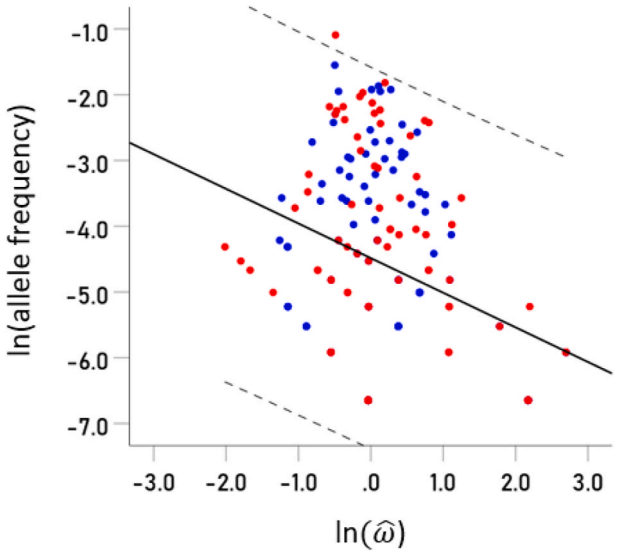

Fig. 3. The ln(allele frequency) is plotted against ln$(\widehat{\omega})$. N = 192 alleles. Red, HLA Class I (N = 108), blue, Class II (N = 84 alleles). Dotted lines are 95% individual confidence intervals on the fitted line. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

We also estimated HLA-associated risk of lifetime PTSD which takes into account both the odds ratio and the frequency of a given allele. Notably, the two alleles that were identified to be protective against PTSD in this sample – HLA-A*02:01 and HLA-DPB1*04:01 – were the most frequent alleles overall suggesting that the relatively low population prevalence of PTSD compared to high rates of trauma exposure may be partially related to protective effects exerted by these two commonly occurring genes. In contrast, HLA alleles that conferred risk for PTSD were relatively infrequent; therefore, the population risk for PTSD associated with those alleles is relatively lower. It is worth mentioning that while the current analyses focused primarily on the 15 alleles that significantly differed between the PTSD and control groups that does not mean that PTSD risk or protection is limited to those 15 alleles. Indeed, when considering all 192 HLA alleles, there is substantial variability in terms of their estimated risk or protection with the 15 alleles associated with the greatest risk and protection represented in the tails of the distribution (Fig. 1). Furthermore, with regard to all 192 HLA alleles, it is notable that there was a slight preponderance of protective (negative) effects (Fig. 1) and a highly significant negative correlation between the frequency of the alleles and the PTSD odds ratio (Fig. 3), suggesting evolutionary pressure that protects against development of PTSD.

In considering the influence of HLA on PTSD it is pertinent to acknowledge that the primary goal of HLA is immune surveillance and facilitation of antigen elimination, the success of which requires a match between foreign antigen epitopes and the HLA receptor binding groove. In the absence of an HLA-antigen match with sufficient affinity and immunogenicity, the antigen may persist resulting in disease via direct damage to cells or via chronic inflammation and autoimmunity, particularly in the presence of susceptibility alleles (James and Georgopoulos, 2021). With regard to PTSD specifically, we have proposed a two-hit model in which persistent antigens create neuroimmune disruption that, when coupled with a traumatic event and resultant intense glutamatergic neurotransmission, results in PTSD via the influence of intercellular cell adhesion molecules, notably ICAM-5 (Georgopoulos et al., 2018). Indeed, consistent with a potential influence of persistent antigens, some evidence supports links between infections and PTSD. For instance, compromised immune response to cytomegalovirus (CMV), a human herpes virus (HHV), has been documented in individuals with PTSD (Uddin et al., 2010), and reduced neutralization of herpes simplex virus-1 (HSV-1) has been documented in women who experienced intimate partner violence (Garcia-Linares et al., 2004). Of note, HSV-1 has been shown to bind with high affinity to HLA-A*02:01 molecules (Srivastava et al., 2017), one of the alleles that was found to be protective against PTSD in the present study. These findings suggest that HLA binding and elimination of HHV may protect against PTSD and, conversely, alleles that are unable to bind to HHV may predispose to PTSD. In addition to potential associations with HHV, other viruses including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the ongoing pandemic, human immunodeficiency virus, and Ebola have been associated with PTSD at rates greater than 30%, purportedly due to direct effects of pathogens on brain microvasculature and/or on brain areas associated with stress-processing such as the hypothalamic-pituitary-adrenal axis and autonomic nervous system (Sfera et al., 2021), systems widely implicated in PTSD (Neigh and Ali, 2016). Finally, as discussed elsewhere (Katrinli and Smith, 2021), HLA may also influence PTSD via non-immune functions including effects on brain plasticity, learning, memory, stress-response, and behavior (Boulanger, 2009; Huh et al., 2000; Sankar et al., 2012; Yirmiya and Goshen, 2011).

4.1. Limitations

The findings of this study must be considered within the context of study limitations. A major limitation of this study is that trauma exposure was not formally assessed in a majority of control participants. Previous studies have documented that up to 93% of women veterans have been exposed to potentially traumatic lifetime events within and outside of the military (Zinzow et al., 2007). Indeed, of the 25% of control participants for whom trauma exposure was formally assessed in the present study, all reported trauma exposure; however, in the absence of formal assessment of trauma exposure, it is uncertain whether the remaining control participants were exposed to potentially traumatic events. This distinction (trauma-exposed controls vs non-exposed/uncertain exposure) has implications for the interpretation of the present findings with regard to HLA risk and protection. We presume that the group differences in HLA frequencies observed here reflect true differences in HLA-related protection/susceptibility to PTSD, particularly since our findings overlap with that of previous studies; however, in light of uncertain trauma exposure in the control group, this interpretation much be considered with some degree of caution, especially with regard to HLA protection. Two alleles were presumed to be protective in this study based on their greater frequency in the control group and their neutralizing effects when combined with a susceptibility allele (Table 4); however, since those alleles were the most frequently occurring HLA alleles in the sample as a whole, the importance of the control group composition with regard to trauma exposure becomes even more relevant to the interpretation of the study findings. Future studies specifically evaluating HLA composition in trauma-exposed controls compared to individuals with PTSD will be useful for clarifying these issues. Future similar studies would also benefit from thorough assessment of trauma exposure in order to evaluate HLA with regard to levels and types of trauma exposure. It would also be informative to evaluate differences in clinical signs and symptoms among those with PTSD with regard to the presence/absence of HLA alleles; however, such studies would require very large samples due to the highly polymorphic nature of HLA. Additional qualifications of the present findings involving HLA are worth noting. For instance, here we evaluated the effects of 192 discrete HLA alleles; however, since HLA is the most highly polymorphic region of the human genome other alleles not identified in this sample may also be associated with PTSD protection or susceptibility. Also, since HLA varies by geography, ethnicity, and ancestry, the HLA susceptibility and protective effects documented here may mot generalize to other study populations. Finally, the present study focused solely on the influence of HLA on lifetime PTSD. Several genetic, biological, and psychosocial factors influence outcomes following exposure to potentially traumatic events (Horn and Feder, 2018); it is uncertain how those factors interact with HLA to influence PTSD risk and resilience.

Summary

The present study which used high-resolution genotyping in a sample of women with and without lifetime PTSD confirms and extends preliminary evidence of an immunogenetic influence on PTSD. As a whole, this line of research suggests a potential benefit of treatment with immunologic agents aimed at rebalancing the pro-inflammatory immune state though the effectiveness of immune-centered approaches largely remains to be investigated (Wang et al., 2017).

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Declaration of competing interest

The authors declare no conflicts of interest.

Data availability

Data will be made available on request.

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