COVID-19 Vaccine Side Effects Are Associated With *HLA-A*03:01* Carriage and Fewer Breakthrough Infections

Weill Institute for Neurosciences | Department of Neurology

Anshika Srivastava[1], Rayo Suseno[1], Sean Lin[1], Tasneem Yusufali[1], Noah D. Peyser[2], Gregory M. Marcus[2], Jeffrey E. Olgin[2], Mark J. Pletcher[3,4], Martin Maiers[5], Jill A. Hollenbach[1,3]

1. Department of Neurology, University of California San Francisco, San Francisco, CA, USA
2. Division of Cardiology, Department of Medicine, University of California, San Francisco, CA, USA.
3. Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA
4. Division of General Internal Medicine, University of California, San Francisco, CA, USA
5. National Marrow Donor Program, Minneapolis, MN, USA

Unraveling the HLA Link to Vaccine Responses

Vaccination has proven to be the most formidable tool in mitigating the COVID-19 pandemic. However, some individuals experience side effects that cause distress and interfere with daily activities, which can limit vaccine uptake. Understanding the factors underlying individual differences in vaccine side effects thus has important public health implications.

Here, we considered the impact of HLA on propensity for side effects with COVID-19 vaccination. We analyzed *HLA-A, -B, -C, -DRB1* and *-DQB1* for association with self-reported side effects in a very large discovery cohort of U.S. Euro-ancestry vaccinated individuals (N=50,535) and confirmed results in an independent replication cohort (N=4,575).

Methods

In our discovery cohort, we examined the association of five HLA loci (HLA-A, -B, -C, -DRB1, -DQB1). We employed a generalized logistic regression model using 'glm' in the R (V 4.3) base package to consider relevant covariates, including sex, and age. For the replication cohort, we tested only the allele of interest, using the generalized logistic regression model framework as described. Forest plots were built using ggplot2 in R.

Results

In order to understand the distribution of side effects to SARS-CoV-2 vaccines in our discovery cohort, we first calculated the covariation matrix for all reported side effects (**Figure 1**).

We found that systemic side effects (SSE) like fever or chills, muscle or body fatigue, or headaches, showed substantial co-occurrence in individuals, with a median number of two SSE reported per individual. To evaluate whether HLA variation plays a role in increasing side effects in vaccination to SARS-CoV-2 and to capture cases with the greatest burden of symptoms, we considered individuals who reported greater than the median number of SSE.

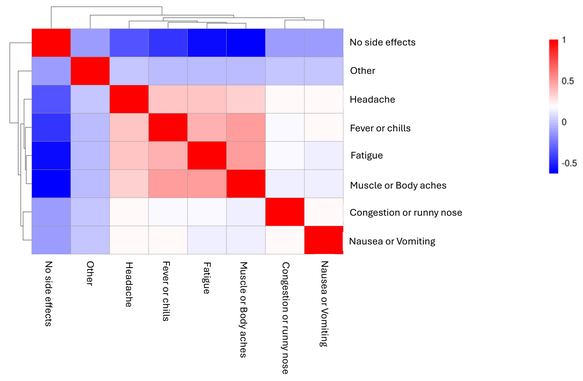

Figure 1. Heatmap of the covariation matrix for all observed side effects in the discovery cohort (N=50,535).

Results

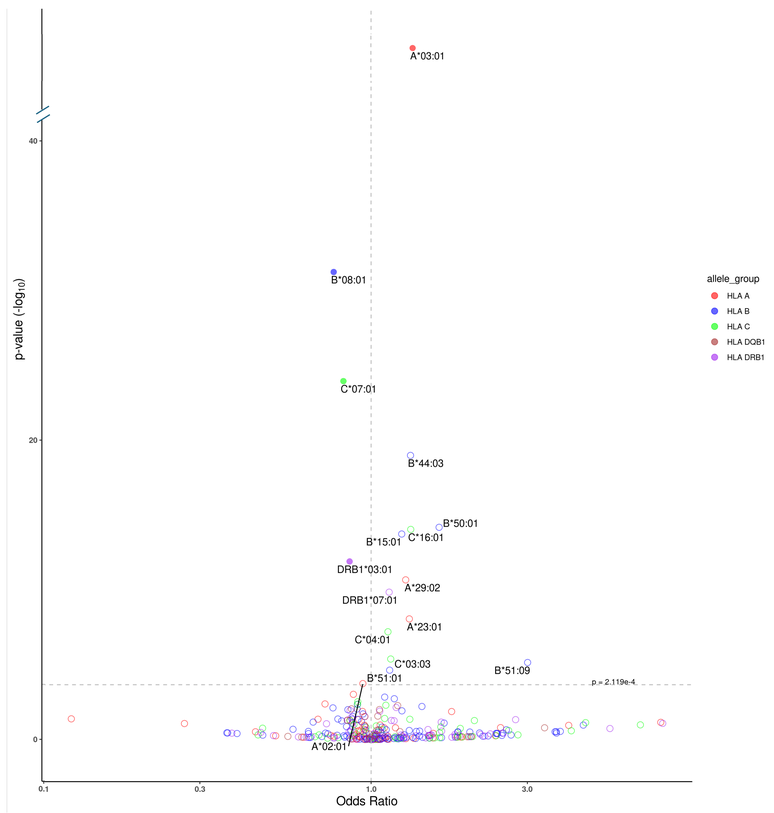

Figure 2. Association of HLA alleles with three or more systemic side effects in the discovery cohort (European ancestry, N=50,535). Odds ratio is shown on the x-axis and p-value (-ve log 10) is shown on the y-axis. Alleles that are significant in both discovery and replication cohort are highlighted in solid circles.

We observed that *HLA-A*03:01* was significantly associated with three or more systemic side effects (**Figure 2**), particularly to the Pfizer-BioNTech vaccine (OR=1.70 [1.61-1.79], p =4.5 $\times 10^{-88,}$ **Figure 3**) .

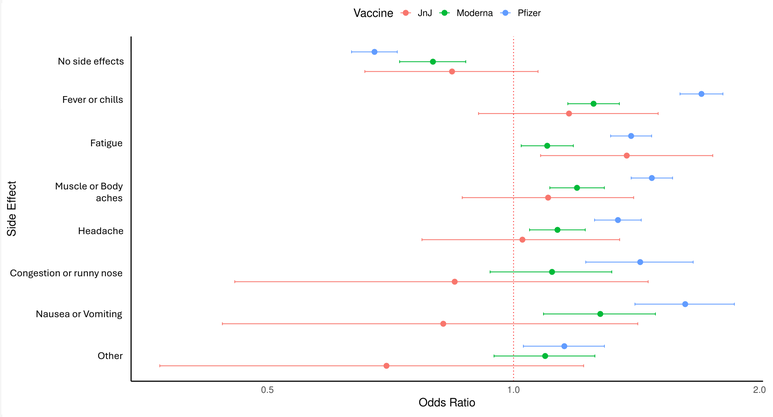

Figure 3. Forest plot showing association between *HLA-A*03:01* and vaccine side effects in all Pfizer vaccinated individuals (N=26250), Moderna vaccinated individuals (N=18307), and J&J vaccinated individuals (N=3312), in the discovery cohort.

Results

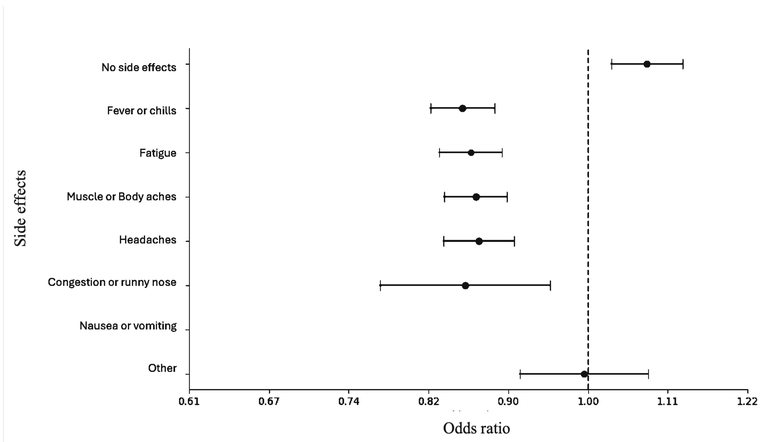

Figure 4. Forest plot showing association between vaccine side effects and breakthrough infection in discovery cohort (European ancestry, N=41657).

Notably, we did not observe any difference in effect size in individuals who went on to BTI (OR=1.37 [1.01-1.83], p=0.036) or who had experienced infection prior to vaccination (OR=1.41 [1.34-1.48], p=1.56 $\times 10^{-42}$).

Strikingly, we also found that *HLA-A*03:01* carriers were less likely to go on to BTI (OR=0.91 [0.88-0.95], p=1.6 $\times 10^{-5}$); however, we observed that overall, individuals who reported systemic side effects are significantly less likely to go on to BTI (OR=0.85 [0.82-0.89], p=1.5 $\times 10^{-14}$, **Figure 4**) regardless of *HLA-A*03:01* status, suggesting that the hyper-responsiveness itself confers a protective benefit.

Conclusion

We showed significant associations of *HLA-A*03:01* with increased side effects such as fever, chills, and muscle pain, particularly with higher effect sizes in individuals who received the Pfizer vaccine.

Additionally, the negative correlation of *HLA-A*03:01* is not a direct cause, but rather a result of a broader negative correlation with vaccination adverse effects associated with BTI.