

Quantifying the proportion of women at risk of an FNAIT pregnancy in diverse populations in the United States

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Introduction

- Fetal and neonatal alloimmune thrombocytopenia (FNAIT) is a rare immune disorder that can occur during pregnancy and can lead to potentially catastrophic consequences in the fetus and newborn, including life-long neurological disability and loss of the baby.
- FNAIT can arise due to an immune incompatibility between a pregnant woman and her fetus in a specific platelet antigen called HPA-1. HPA-1a negative women carrying an HPA-1a positive fetus are at risk of alloimmunizing and developing FNAIT. Women who also carry the HLA-DRB3*01:01 allele are 25x more likely to alloimmunize and are therefore considered at higher risk.
- To date, the risk of FNAIT has only been well characterized in White Caucasian populations.

Objective

- The aim of this study is to quantify the number of women across racial and ethnic groups in the US who are likely to be at-risk and at higher-risk of maternal alloimmunization and FNAIT based on their HPA-1 and HLA-DRB3*01:01 genotypes.

Methodology

- Allele frequencies were obtained from gnomAD v4 for HPA-1 with an additional article¹ used to provide more granular HPA-1 frequencies in East Asian populations, and from the US National Marrow Donor Registry (NMDR) for HLA-DRB3*01:01.
- HPA-1a negative rates and HLA-DRB3*01:01 carrier frequency were both calculated from the population-specific allele frequencies assuming Hardy-Weinberg equilibrium.
- The proportion of women 'at-risk' of FNAIT in each ancestry was taken as the HPA-1a negative proportion, and the proportion of women at 'higher-risk' of FNAIT was obtained by multiplying the HPA-1a negative proportion by the population-specific HLA-DRB3*01:01 carrier frequency after mapping the gnomAD v4 ancestry groups to the NMDR populations.
- The number of women at-risk and at higher-risk of FNAIT was obtained by multiplying the proportion of women at-risk and higher-risk by the female population of the US disaggregated by self-reported ethnic group and mapped to gnomAD v4 and NMDR ancestry and population groups.
- The number of pregnancies at-risk and at higher-risk of FNAIT was obtained by multiplying the number of women at-risk and at higher-risk by the 2023 birth rate in the US.

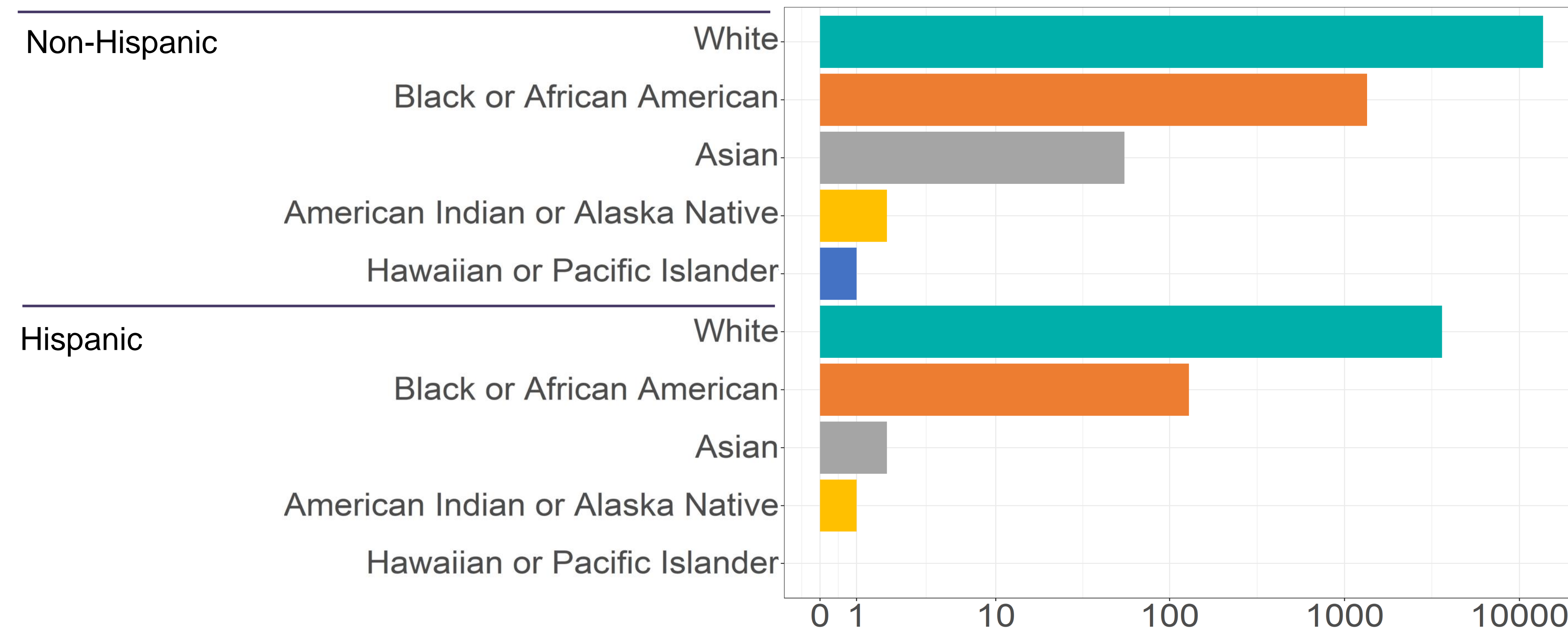
Results

- Risk of alloimmunization and FNAIT was highest in White Caucasian populations, with the highest proportions in the Ashkenazi Jewish population (2.36% and 0.65% of women at-risk and at higher-risk, respectively), followed by non-Finnish Europeans (2.34% and 0.64%), Middle Eastern (2.25% and 0.62%), Amish (2.25% and 0.62%), White Hispanic (2.25% and 0.59%) and Finnish (2.03% and 0.56%).
- Women in non-White population groups were also found to carry higher FNAIT risk, with the highest proportions in the Caribbean Hispanic population (1.48% and 0.33%), followed by African / African American (1.13% and 0.28%) and women of South Asian, East Asian, and Amerindigenous ancestries (<1% and <0.1%).
- A total of 908,602 women are estimated to carry both risk alleles (HPA-1a negative, HLA-DRB3*01:01 positive). A further 2,475,107 (or 3,383,709 in total) women carry the HPA-1a negative risk genotype.
- Multiplying these figures by the 2023 US birth rate gives estimated totals of 70,095 at-risk of FNAIT and 18,822 pregnancies at higher-risk of FNAIT in the US in 2023.

Conclusions

- This study is the first to report FNAIT risk across diverse ancestries using data from genetic databases to calculate the expected number of women carrying the underlying causal genetic variants.
- Estimations of the FNAIT at-risk and at higher-risk populations in White Caucasian groups were broadly in line with previously reported estimates of allelic frequencies.
- With the identification of non-White populations also carrying higher FNAIT risk, this study suggests that nearly 20,000 pregnancies in the US are at higher FNAIT risk each year, a significantly greater number than previously estimated.
- These data support the case for screening all pregnant women for potential FNAIT risk, regardless of race and ethnicity.

Number of Higher-Risk FNAIT Pregnancies by Ethnicity (log scale)



Assumptions and Limitations

- Hardy-Weinberg equilibrium was considered applicable in calculating the carrier frequencies of both HPA-1 and HLA-DRB3*01:01 from the allele frequencies.
- All women in the US were considered equally likely to become pregnant; this study did not account for differences in the ancestral composition of the population of women overall vs. the population of women of child-bearing age.
- The 2023 US birth rate was calculated using the reported number of births in the US and the number of women in the US population, and assumed to be the same in all ancestry groups in the US.
- Only maternal genotypes were considered in this study.

US Census Group		At Higher-Risk of FNAIT		At-Risk of FNAIT	
		Women	Pregnancies	Women	Pregnancies
Non-Hispanic	White	660,035	13,673	2,394,653	49,606
	Black or African American	65,078	1,348	265,562	5,501
	Asian	2,669	55	27,666	573
	American Indian or Alaska Native	99	2	311	6
	Hawaiian or Pacific Islander	26	1	300	6
Hispanic	White	174,284	3,610	665,340	13,783
	Black or African American	6,234	129	28,480	590
	Asian	107	2	1,103	23
	American Indian or Alaska Native	62	1	195	4
	Hawaiian or Pacific Islander	8	0	97	2
Total		908,602	18,822	3,383,707	70,095