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

Amanda Hayward (a), James Cook (b), Joshua Card-Gowers (b), Tim Coker (b), Róisín Armstrong (a)

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 aims of this study are to quantify:

- The number of women across racial and ethnic groups in the US 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.
- The expected number of affected pregnancies, based on the genotype counts and the US birth rate.

Assumptions and Limitations

- Hardy-Weinberg equilibrium (HWE) 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.

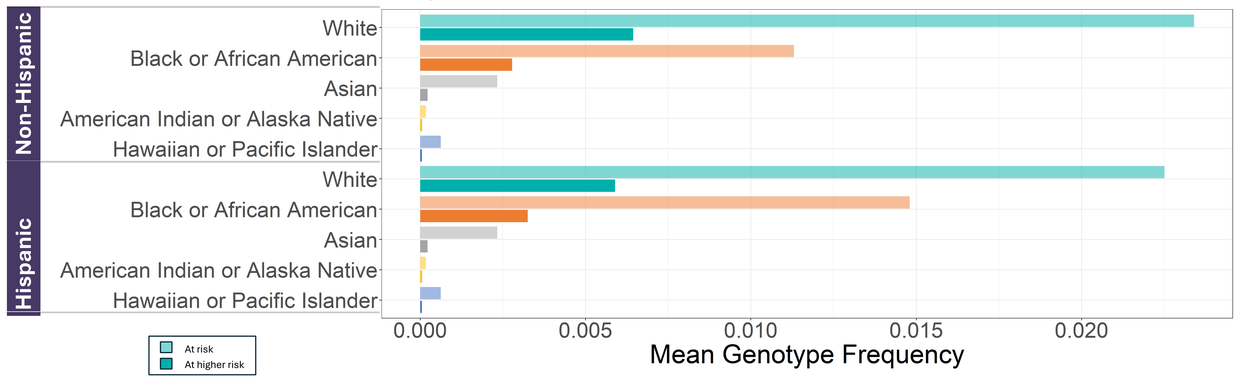
Methods

- Allele frequencies were obtained from gnomAD v4 for HPA-1 with an additional article[1] (denoted as * in Table 1) 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 HWE.
- 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 calculated by multiplying the genotype frequencies by the number of women in the US in 2023 after mapping population groups to US Census Groups.

Table 1. Carrier Frequencies by Ancestry Group

US NMDR Population	gnomAD Ancestry Group	HLA3 DRB3*01:01	HPA1b	Both
North American Amerindian	Admixed American - Amerindigenous	0.3190	1.73E-04	5.53E-05
European Caucasian	European (non-Finnish)	0.2756	2.34E-02	6.44E-03
	Ashkenazi Jewish	0.2756	2.36E-02	6.51E-03
	Middle Eastern	0.2756	2.25E-02	6.21E-03
	European (Finnish)	0.2756	2.03E-02	5.60E-03
	Amish	0.2756	2.22E-02	6.13E-03
Mexican or Chicano	Admixed American - European	0.2619	2.25E-02	5.89E-03
Caribbean Black	African / African American	0.2497	1.13E-02	2.83E-03
African American pop 2	African / African American	0.2492	1.13E-02	2.82E-03
African	African / African American	0.2363	1.13E-02	2.68E-03
Caribbean Hispanic	Admixed American - African	0.2189	1.48E-02	3.25E-03
Middle East / North Africa	Middle Eastern	0.1741	2.25E-02	3.92E-03
South Asian Indian	South Asian	0.0971	9.28E-03	9.01E-04
Korean	East Asian – Korean*	0.1410	1.44E-04	2.03E-05
Japanese	East Asian – Japanese*	0.1213	4.00E-06	4.85E-07
Southeast Asian	East Asian – Malay*	0.0861	6.25E-04	5.38E-05
Chinese	East Asian - Han Chinese*	0.0759	3.60E-05	2.73E-06
Filipino	East Asian – Indonesian*	0.0589	8.10E-05	4.77E-06

Figure 1. Carrier Frequencies by US Census Group



Results

- Genotype carrier frequencies for HLA DRB3*01:01, HPA1b and both are displayed in table 1 for the US NMDR population and gnomAD v4 ancestry groups, and in figure 1 for US Census groups.
- 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.

Poster presented at the 2024 American Society of Human Genetics Meeting, November 5-9 (Denver, CO)
References: [1] Tan JY *et al*. Blood Transfus. 10(3): 368-376.
Contact: For additional information, please contact Amanda Hayward: ahayward@rallybio.com

Affiliations: a) Rallybio, 234 Church St, New Haven, CT 06510, USA; b) HealthLumen Ltd, London, United Kingdom
Disclosures: JC, JCG and TC are employees of HealthLumen, who was contracted by Rallybio for genetic database analysis expertise. AH and RA are employees of and stockholders in Rallybio. This research was funded by Rallybio.