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# The human platelet antigen-21bw is relatively common among Asians and is a potential trigger for neonatal alloimmune thrombocytopenia

**Julie A. Peterson, PhD**,
Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI

**Shannon M. Pechauer**,
Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI

**Maria L. Gitter**,
Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI

**Aniko Szabo, PhD**,
Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI

**Brian R. Curtis, PhD**, and
Platelet and Neutrophil Immunology Laboratory, BloodCenter of Wisconsin, Milwaukee, WI

**Richard H. Aster, MD**
Blood Research Institute, BloodCenter of Wisconsin, Milwaukee, WI. Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

Julie A. Peterson: Julie.Peterson@bcw.edu

We and others have identified more than 20 low-frequency human platelet (PLT) antigens (HPAs) that can induce antibodies capable of causing neonatal alloimmune thrombocytopenia (NAIT).[1–4] Like HPA-1a and HPA-4b, the antigens that most often trigger NAIT in Caucasian and Asian populations, respectively, the incidence of low-frequency antigens is likely to vary significantly in different ethnic and racial populations.

We recently described HPA-21bw, a low-frequency antigen, responsible for a single case of severe NAIT in a presumed Caucasian family.[1] The HPA-21bw antigen results from a G>A1960 mutation (RS70940817), in ITGB3, encoding PLT glycoprotein (GP) β3 subunit (GPIIIa) and creates a Glu>Lys substitution at Residue 628 in mature β3. No examples of HPA-21bw were identified in 100 unrelated Caucasian individuals.[1] We recently encountered a second case of NAIT apparently caused by HPA-21bw in an Asian family (unpublished). The mutation encoding HPA-21bw was also identified in two of 38 Asian individuals tested in a hypertension and insulin resistance study according to the human SNP database (http://www.ncbi.nlm.nih.gov/projects/SNP; ss95216694).

**CONFLICT OF INTEREST**
There are no conflicts of interest.

These observations suggested that HPA-21bw, like HPA-4b, might be more prevalent in Asian than in Caucasian populations and therefore a more common trigger for NAIT. To examine this possibility, we determined the gene frequency of the mutation encoding HPA-21bw in anonymized DNA samples identified by age, sex, and self-declared race/ethnicity obtained from the Retrovirus Epidemiology Donor Study (REDS) General Serum Repository of the National Heart, Lung, and Blood Institute (NHLBI) made available by the NHLBI Biologic Specimen and Data Repository guardian (BioLINCC). These specimens were collected from blood donors at five locations in the United States (Baltimore, Detroit, Los Angeles, Oklahoma City, and San Francisco) between December 1994 and December 1995. Anonymized samples were also obtained from Caucasian blood donors at BloodCenter of Wisconsin. Genotyping for HPA-21bw was performed with an allelic discrimination assay using PerfeCTa qPCR SuperMix, UNG, Low ROX (Quanta Biosciences, Gaithersburg, MD).[2]

Results are summarized in Table 1. No examples of HPA-21bw were found in 1110 unrelated Caucasians, 611 African Americans, or 252 Hispanic blood donors. However, 6 of 531 Asians donors were HPA-21a/bw (prevalence, 1.1%; gene frequency, 0.0056).

We used the exact binomial methods for statistical inference: Clopper-Pearson confidence intervals (CIs) and Fisher's exact test. The prevalence of HPA-21bw among Asians, estimated as 1.1% (95% CI, 0.4%–2.4%) is significantly greater than in Caucasians ($p = 0.001$) and African Americans ($p = 0.01$). The comparison with Hispanics is not significant ($p = 0.18$); however, the sample size is too small for this comparison. Based on one-sided CIs we are 95% confident that the prevalence of HPA-21bw among Caucasians is less than 0.3%, among African Americans less than 0.5%, and among Hispanics less than 1.2%.

To date the HPA-4b (Penb) polymorphism in GPIIIa is the most common trigger for antibodies that cause NAIT in the Asian population. Having an allelic frequency of 0.0045, HPA-4b is expressed in approximately 1% of the Asian population.[5] In contrast HPA-6bw in GPIIIa, though found in 2.7% of the Asian population,[5] is not a common trigger of NAIT. Taking into consideration that HPA-21bw is known to initiate severe NAIT,[1] has already been implicated as the trigger for NAIT in one Asian family (unpublished), and has an allelic frequency of 0.2% to 2.2% (95% confidence limits) in the Asian population, routine typing for this antigen in cases of suspected NAIT involving Asian families appears indicated.

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**TABLE 1**

Frequency analysis of HPA-21bw in various populations

| Population | HPA-21+/total | Allelic frequency of HPA-21bw |
|---|---|---|
| African American* | 0/611 | 0 |
| Asian* | 6/531 | 0.0056 |
| Caucasian* | 0/1010 | 0 |
| Caucasian† | 0/100 | 0 |
| Hispanic* | 0/252 | 0 |

*Collected at four blood centers in the United States.

†Collected at BloodCenter of Wisconsin.