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Frequencies of *SLC44A2* alleles encoding human neutrophil antigen-3 (HNA-3) variants in the African American population

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Abstract

Background—The human neutrophil antigen-3 (HNA-3) epitopes reside on the choline transporter-like protein-2 (CTL2). A single-nucleotide substitution (461G>A; Arg154Gln) on the CTL2 gene (*SLC44A2*) defines the allele *SLC44A2*1*, which expresses HNA-3a, and *SLC44A2*2*, which expresses HNA-3b; an additional substitution (457C>T; Leu153Phe) in *SLC44A2*1:2* may impact genotyping systems. People who only express HNA-3b may develop anti-HNA-3a. These alloantibodies have been linked to severe transfusion-related acute lung injury (TRALI), which may be a reason to screen blood donors for *SLC44A2*2* homozygosity. For Caucasian and Asian populations, *SLC44A2* allele frequencies are known. Our primary objective was to determine the *SLC44A2* allele frequencies in the African American population.

Study design and methods—Purified DNA from 334 individuals (202 male, 132 female; 241 African American, 93 Caucasian) was collected. Two real-time PCR assays were developed to genotype all samples; results were confirmed by nucleotide sequencing.

Results—In 241 African American donors, the allele frequency of *SLC44A2*1* was 93% (85% to <100%; 95% confidence intervals, Poisson distribution) while *SLC44A2*2* was 7% (5% to 10%). In 93 Caucasian donors, the allele frequencies of *SLC44A2*1* was 83% (71% to 98%) and *SLC44A2*2* was 17% (11% to 24%), matching previously reported data for Caucasians but differing from African Americans ($p<0.001$, Fisher's exact test).

Conclusions—This study describes the allele frequencies of the 3 known HNA-3 variants in an African American population. We found that African Americans have a significantly lower probability of possessing the *SLC44A2*2* allele, and may thus be less likely to form the clinically relevant anti-HNA-3a.

Introduction

Transfusion-related acute lung injury (TRALI) is a major cause of transfusion-associated morbidity and mortality.[1–3] It is characterized as acute respiratory distress during or within 6 hours of transfusion, radiographic evidence of new bilateral pulmonary infiltrates, and signs of hypoxia in the absence of circulatory overload.[2,4] Hypotension is typically associated with TRALI, but not required for diagnosis.[5] Approximately 80% of reported TRALI cases

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could be linked to transfused blood products containing leukocyte-specific alloantibodies, the majority of which are against human leukocyte antigen (HLA) class I or II.[6] Although alloantibodies directed against human neutrophil antigen (HNA) were detected in only about 5% of cases, these antibodies, in particular against HNA-3, are strong.[7] Residual plasma (~20 mL) in an RBC unit can hold enough antibodies against HNA-3 to cause TRALI.[7]

In 1964, HNA-3 was first described serologically by van Leeuwen et al. as group 5a and 5b antigens.[8] HNA-3 may be expressed on granulocytes, platelets, and mononuclear white blood cells (WBCs).[3] Antibody detection and phenotyping was performed by granulocyte agglutination and granulocyte immunofluorescence assays, tests that required highly trained staff and rare polyclonal anti-sera.[9] But in 2010 the molecular basis of HNA-3 was elucidated.[10] This discovery made genotyping possible. The HNA-3 epitopes are associated with a biallelic polymorphism caused by a single-nucleotide exchange (461G>A; Arg154Gln) in the choline transporter-like protein-2 gene (*SLC44A2*).[10–13] The allele *SLC44A2*1*, which expresses the HNA-3a phenotype (formerly 5b), is caused by a 461G; *SLC44A2**2, which expresses the HNA-3b phenotype (formerly 5a), is caused by a 461A (Table 1).[14] Furthermore, an additional single-nucleotide exchange (457C>T; Leu153Phe) was recently reported that creates a variant of the *SLC44A2*1* allele (*SLC44A2*1:2*) and may yield false negative genotyping results for HNA-3a if the specific primer encompasses the mutation.[15]

HNA-3 genotyping can be used to screen for donors capable of developing anti-HNA-3a, antibodies that have a well documented association with severe TRALI.[3,16,17] Pregnant women who are homozygous for HNA-3b are the most likely to become immunized against HNA-3a. In countries applying leukodepletion to RBC units, men have been found to be usually negative for anti-leukocyte antibodies.[7,18]

Frequencies of the *SLC44A2* alleles that encode the HNA-3 variants, so far described in various populations, influence the risk of immunization and thus the risk for TRALI in transfusion patients. In a German population, the allele frequency of *SLC44A2*1* was 79.2% while *SLC44A2*2* was 20.7%.[14] The frequency of *SLC44A2*1:1* with the highly prevalent 457C was 99%; the frequency of *SLC44A2*1:2*, which encodes for the rare 457T variant, was 1%.[15] In a Chinese population, the frequency of *SLC44A2*1* was 73.8% and *SLC44A2*2* was 26.2%.[19] These *SLC44A2*2* allele frequencies are comparable with allele frequencies listed in dbSNP (cluster rs2288904) for Caucasian and Asian populations. In contrast, the *SLC44A2*2* allele frequency is only 0% to 1.9% for Sub-Saharan Africans (mainly HapMap and 1000 Genomes projects data), which indicates that a different allele frequency has to be expected also for African Americans. The aim of this study was to determine the allele frequencies for an African American population.

Materials and Methods

Donor population recruitment

After obtaining written informed consent, EDTA blood samples from 334 individuals (202 male, 132 female) were collected and DNA extracted (EZ1 DNA blood kit on the BioRobot EZ1 Workstation; Qiagen, Valencia, CA). These donors, who were mainly African American, represented all active platelet donors, 95% of active African American whole blood donors, and all of African American research donors at our institution.

HNA-3 genotyping by real-time PCR

A real-time PCR assay was developed to genotype the DNA samples. DNA was amplified in two parallel reactions by previously described *SLC44A2*1* (AGTGGCTGAGGTGCTTCG; Eurofins MWG Operon, Huntsville, AL) or *SLC44A2*2* (GAGTGGCTGAGGTGCTTCA)

allele-specific sense primers[14] coupled with a new antisense primer (cagaggatggcaccagtcag) which produced an amplicon of 140 bp.

Real-time PCR was performed with 0.2 μL of DNA (10 to 100 ng/μL), 1 μL of 10 μM of primer, 7.8 μL of H_2O (Molecular Biology Grade Water; Crystalgen, Long Island, NY), and 10 μL of EvaGreen (SsoFast EvaGreen Supermix; Bio-Rad, Hercules, CA) for a total volume of 20 μL per reaction by a thermal cycler (Bio-Rad CFX96) with an initiation step at 95°C for 30 seconds, followed by 40 cycles at 95°C for 5 seconds and then 72°C for 4 seconds with plate read out at the end of the annealing/extension step. Each reaction was run in duplicates. Positive and negative DNA controls for *SLC44A2*1* and *SLC44A2*2* were verified with sequence analysis and used on each 96 well plate running 22 samples.

The genotype of the samples was determined by relative comparison of the quantification cycle (Cq) of both assays, where A corresponds to *SLC44A2*1:1* and B corresponds to *SLC44A2*2*.

$$\text{A:B ratio} = 2^{C_{q_b} - C_{q_a}} \quad (1)$$

The following cut-off values were used: an A:B ratio > 50 for homozygous *SLC44A2*1:1*, a ratio < 0.1 for homozygous *SLC44A2*2*, and a ratio between > 0.2 and < 25 for heterozygous *SLC44A2*1:1* and *SLC44A2*2*; ratios outside of our criteria were labeled indeterminate. Because all reactions were run in duplicates, two ratios were calculated for each sample. If a sample's genotype could not be determined unequivocally, then it was repeated (39 samples, 11.6%). All repetitions were done with 1:10 diluted DNA to overcome the presence of inhibitors[20] in the samples that were initially ruled indeterminate. The distribution of the A:B ratios were analyzed for quality control (Table S1).

HNA-3 nucleotide sequencing

DNA was sequenced similar to a previously published method for *RHD*.[21] One amplification reaction covering the HNA-3 SNP region was run for each sample (total volume 25 μl): 19.6 dH_2O, 2.5 μl 10x buffer, 0.5 μl dNTP (10 mM), 0.25 μl each of NA3f1 (CTCCCGGGACTTTGAGTACT) and NA3r1 (gtgcgccaatatcctcacTTG) primers (10 μM), 0.125 μl Taq enzyme (FastStart High Fidelity PCR System, dNTPack; Roche Applied Science, Indianapolis, IN), and 1 μl DNA (~100 ng/μl). Thermal cycler (Bio-Rad C1000) conditions were 95°C for 3 min; 45 cycles with 95°C for 30 sec, 58°C for 30 sec, 72°C for 5 min. 2.5 μl of amplified DNA was purified with 1 μL of PCR clean-up kit (ExoSAP-IT; Affymetrix, Santa Clara, CA). Sequencing reactions were run for each sample by adding 1.25 μl primer, 1.8 μl BigDye v3.1 Terminatory Mix (Applied Biosystems, Carlsbad, CA), 14 μl dH_2O. Thermocycler conditions were 25 cycles of 96°C for 15 sec, 58°C for 10 sec, 60° for 4 min. Unincorporated dye was removed (DyeEx 96 well plates; Qiagen), the sequences dehydrated (Savant SPD 2010 SpeedVac Concentrator; ThermoScientific, Wilmington, DE) and resuspended in 10 μl formamide (Hi-Di formamide; Applied Biosystems) before chromatography analysis on an AB 3730 DNA analyzer (Applied Biosystems). Sequencing results were aligned to NCBI RefSeq NC_000019.9 (range 10713121..10755235) and analyzed with CodonCode Aligner software (CodonCode, Dedham, MA).

Statistical analysis

Data are shown as mean and 95% confidence interval (CI) based on Poisson distribution. Data analysis was done with Excel (Microsoft, Redmond, WA) and MedCalc (MedCalc Software, Mariakerke, Belgium).

Results

DNA from 334 donors was collected and genotyped with real-time PCR. 241 individuals self-reported as African American and 93 as Caucasian.

Real-time PCR analysis

In the African American population (n=241), one individual was homozygous for *SLC44A2*2* (Table 2), and thus is expected to express only HNA-3b. In the Caucasian population (n=93), two individuals were homozygous for *SLC44A2*2*. The allele frequencies of *SLC44A2*1* and *SLC44A*2* differed significantly between African Americans and Caucasians (Table 3). Overall, three donors were expected to express only HNA-3b. This amounts to 0.9% of all tested donors.

Sequence analysis

Based on the publication of additional mutations in the primer region of the HNA-3a specific primer,[12] sequence analysis of the involved nucleotide region was performed for all samples. All sequences confirmed the results obtained by our real-time PCR in respect to the HNA-3a and HNA-3b polymorphism. This corresponds to a sensitivity and specificity of 100% of the real-time analysis system for 334 samples. We detected 3 samples that were heterozygous for the newly described *SLC44A2*1:2* (457C>T, also expressing HNA-3a) and the more prevalent *SLC44A2*1:1*, thus not influencing the real-time PCR assay in the tested population. We calculated the distribution of the HNA-3a expressing alleles *SLC44A2*1:1* (457C) to be 99.5% (91.7% to <100%; 95% CI, Poisson distribution) and *SLC44A2*1:2* (457T) to be 0.5% (0.1% to 1.5%).

457C>T polymorphism

To further assess the validity of our real-time PCR assay, we tested two samples that were heterozygous for *SLC44A2*1:2* and *SLC44A2*2* alleles (kindly provided by Priv.-Doz. Dr. rer. nat. Brigitte K. Flesch, Bad Kreuznach, Germany). The average A:B ratios of the samples were 0.02 and 0.01 respectively, indicating a genotype based on our algorithm that is homozygous for *SLC44A2*2*.

Discussion

The aim of this study was to determine the allele frequencies of *SLC44A2*, which encodes for the HNA-3 epitopes, in the African American population. We found that the allele frequency of *SLC44A2*2* in African Americans was 7%, which is lower than previously reported in Caucasians and Asians (21% and 26%, respectively)[14,19] but higher than known frequencies for Sub-Saharan Africans (0% to 1.9%; dbSNP cluster rs2288904). Therefore, African Americans may have a lower probability than Caucasians and Asians of being homozygous for *SLC44A2*2*, expressing only HNA-3b, and then potentially forming anti-HNA-3a, the clinically relevant antibody linked to TRALI.

The higher *SLC44A2*2* allele frequency of African Americans compared to Sub-Saharan Africans may simply be explained by admixture among populations. So far, there is no selective pressure known – as *P. vivax* malaria for the Fy(a-b-) phenotype[22] – that could explain the different allele frequencies found in Asians and Caucasians compared to Africans. Natural selection due to potentially fatal transfusion reactions caused by alloantibodies cannot explain the differences, but the impact of a tropical infectious disease agent might.

Implementing a screening strategy involves first recognizing which blood products can harbor anti-HNA-3a. Typically, it is thought that anti-HNA-3a is found in plasma-rich components like platelet concentrates. But components other than platelet concentrates can cause TRALI. A recent report from the French Hemovigilance Network reminds us that many TRALI cases are not related to plasma-rich components but rather plasma components in red blood cell (RBC) units.[23] They calculated the TRALI risk per component of single-donor fresh-frozen plasma and apheresis platelet concentrates to be 1:31,000, and the risk per component of RBCs to be 1:173,000. But when they analyzed the causes of 62 TRALI cases and 23 possible TRALI cases, they found that the approximately half of the TRALI cases were associated with RBC units. This finding may be attributed to the fact that there are many more RBC transfusions than plasma or platelet transfusions.

It has been proposed by several experts that blood product donors should be screened for anti-HNA-3a alloantibodies.[9,10] Until recently, this was not feasible for most donor centers because sophisticated serological typing with rare anti-sera was needed. Genotyping with a PCR assay[14] – in particular a fast, sensitive, and specific real-time PCR assay, like the one described here – offers a quick and simple method for screening all donors. But both currently available genotyping assays are limited because the specific primer for the *SLC44A2*1* alleles encompasses the additional SNP that distinguishes the common *SLC44A2*1:1* allele from the rare *SLC44A2*1:2* allele. The faint bands of *SLC44A2*1:2* alleles[15] may be missed on a gel picture; an A:B ratio < 0.1 is interpreted as homozygous for *SLC44A2*2* in our very specific assay. Not detecting the *SLC44A2*1:2* allele, however, is only clinically relevant in the rare heterozygous combination with *SLC44A2*2*, a scenario that leads to a false positive denotation of a donor as *SLC44A2*2* homozygous.

Currently, *SLC44A2* genotyping assays are used to screen for donors who are homozygous for *SLC44A2*2*. Not detecting the rare *SLC44A2*1:2* variant leads to donors who are falsely labeled homozygous *SLC44A2*2* (approximately 0.07% to 0.4% of all donors, based on allele frequencies), which is a conservative and thus favorable screening approach.

While it is feasible to design an alternative PCR system with the specific primer on the alternate DNA strand, it cannot be excluded that a similar SNP can also be found in the range of this new specific primer. Thus, we preferred to use nucleotide sequencing to validate the assays and to confirm the genotype of our donors. Screening may be expanded to cover the 457 C>T polymorphism for specific detection of the *SLC44A2*1:2* allele.

It should also be noted that anti-HNA-3b may cause TRALI. While many references discuss the clinical significance of anti-HNA-3a, we have not found any report of TRALI caused by anti-HNA-3b. This may be because the circumstances leading to the development and then transfusion of anti-HNA-3b are extremely rare. Given the immunization rates of anti-HNA-3a (7%) and anti-HNA-3b (0.5%),[14] we calculated that the expected ratio of anti-HNA-3a to anti-HNA-3b TRALI cases is approximately 12:1 (assuming equal antibody potency). Furthermore, detecting anti-HNA-3b serologically is difficult due to the rare anti-sera required; this fact may contribute to underreporting of anti-HNA-3b triggered TRALI. And if anti-HNA-3b, like anti-HNA-3a, can induce TRALI, then it is a less frequent cause.

In conclusion, we developed a sensitive and specific screening assay to genotype HNA-3 in a high-throughput setting. We determined allele frequencies for African Americans, who have a lower probability of being homozygous for *SLC44A2*2* than Caucasians and Asians.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

SLC44A2 alleles associated with HNA-3 antigen expression

Allele nomenclature*	Nucleotide position†		Antigen expression	Alternatively used allele names
	457	461		
*SLC44A2*1:1*	C	G	HNA-3a	SLC44A2*461G,[10] HNA-3a,[14] CTL2-541G,[15] CTL2-537C[15]
*SLC44A2*1:2*	T	G	HNA-3a	CTL2-537T[15]
*SLC44A2*2*	C	A	HNA-3b	SLC44A2*461A,[10] HNA-3b,[14] CTL2-541A[15]

**SLC44A2*1* summarizes *SLC44A2*1:1* and *SLC44A2*1:2*

†Nucleotide positions are defined based on the reference sequence NC_000019.9 (range 10713121..10755235) with the first nucleotide of the coding sequence (CDS) of the longer splice variant designated as nucleotide position 1.

Table 2

Genotype frequencies of *SLC44A2* expressing HNA-3 variants in African Americans and Caucasians

		African American			Caucasian		
			Population frequency			Population frequency	
***SLC44A2* genotype**	**Predicted HNA-3 expression**	**Donors (n)**	**Mean**	**95% CI ***	**Donors (n)**	**Mean**	**95% CI ***
*SLC44A2*1, SLC44A2*1*	aa	209	86.7%	75% – 99%	64	68.8%	53% – 88%
*SLC44A2*1, SLC44A2*2*	ab	31	12.9%	9% – 18%	27	29.0%	19% – 42%
*SLC44A2*2, SLC44A2*2*	bb	1	0.4%	0.01% – 2%	2	2.2%	0.3% – 8%
Total		241			93		

* 95% confidence interval calculated by Poisson distribution

Table 3

Allele frequencies of *SLC44A2* in African Americans and Caucasians

	African American *			Caucasian *		
		Population frequency			Population frequency	
Allele	**n**	**Mean**	**95% CI †**	**n**	**Mean**	**95% CI †**
*SLC44A2*1*	449	93%	85% – <100%	155	83%	71% – 98%
*SLC44A2*2*	33	7%	5% – 10%	31	17%	11% – 25%
Total	482			186		

*Significant difference between African Americans and Caucasians ($p<0.0001$; Fisher's exact test)

†95% confidence interval calculated by Poisson distribution

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