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ORAL ABSTRACTS

401.BLOOD TRANSFUSION

The Cs [a] and Cs [b] Red Cell Antigens of the Cost Blood Group Collection Correspond to the HNA-3a and HNA-3b Neutrophil Antigens: Unexpected Twins with Implications for Sickle Cell Anemia

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Recent genome-wide association and murine studies identified the human neutrophil antigen 3a/b polymorphism (HNA-3a/b) in *SLC44A2* (rs2288904-G/A) as a risk factor in venous thromboembolism (VTE). We tested whether this polymorphism associates with clinical features in SCA patients in whose VTE and stroke are frequently encountered complications. Incidentally, we discovered that rare subjects with the homozygous HNA-3b/b genotype (genotype frequency < 2%) also carry the uncommon Cs(a-) red cell phenotype. Despite its discovery more than 50 years ago, the molecular basis of this red cell phenotype and the presumptive protein carrier for the antigens of the COST blood group collection (Cs [a] and Cs [b]) has remained unknown. Inspired by this fortuitous discovery, we hypothesized that rs2288904 and COST antigens are closely associated. Thus, we genotyped this SNP in a cohort of 35 Cs(a-) subjects and found that all of them showed a HNA-3b/b genotype, indicating that the high-frequency allele of rs2288904 (HNA-3a; 461G) encoding Arg154 might encode the Cs [a] antigen (COST1). Interestingly, anti-Cs [a] does not react with SLC44A2 $_{null}$ RBCs (exceptional VER- blood type) and *SLC44A2* knockout K562 cell line, confirming that the COST antigens are carried on this protein. In addition, using a panel of K562 cells expressing HNA-3a or 3b antigens developed by CRISPR/Cas9 genome editing, we confirmed that anti-Cs [a] recognizes the HNA-3a antigen. Overall, our results confirmed that HNA-3 and COST antigens have the same molecular basis. As a result, the Cs [a] and Cs [b] red cell antigens can now be included in the CTL2 blood group system, encoded by the *SLC44A2* gene. This new finding could be of medical and biological value because anti-HNA-3a may be responsible for severe cases of neonatal neutropenia and transfusion-related acute lung injury (TRALI). Current testing for HNA-3a antibodies includes the granulocyte agglutination test and granulocyteindirect immunofluorescence test, as recommended by the ISBT Working Party on Granulocyte Immunobiology. These classical methods, however, are cumbersome because they require fresh granulocytes that have to be prepared daily and used immediately. Consequently, screening for HNA-3a antibodies is restricted to a few expert laboratories. Therefore, we propose to use the simple indirect antiglobulin red cell agglutination test (IAT) and Cs(a-) RBCs to

screen for this antibody in the plasma of donors and patients. Finally, given that the starting point for this project was the study of a potential association of the HNA-3 polymorphism with clinical and biological features in SCA patients, we found that the HNA-3b allele was significantly associated with a higher monocyte and platelet count ($p<0.02$) and the occurrence of leg ulcer ($p=0.01$), suggesting an important role of the SLC44A2 protein in the SCD physiopathology.

Disclosures De Montalembert: *Vertex:* Other: Steering committee; *Novartis:* Consultancy; *Addmedica:* Consultancy, Membership on an entity's Board of Directors or advisory committees.

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