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An update on the Scianna blood group system

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Abstract

This update of the Scianna blood group system (Brunker PA, Flegel WA. Scianna: the lucky 13th blood group system. Immunohematology 2011;27:41–57) provides the recent work on the genetic variation of *ERMAP* across more world populations, the elucidation of the molecular basis of an historical serologic case, new cases of antibodies in the system, the development of new serologic reagents, and new discoveries in the biology of the erythroid membrane associated protein (ERMAP). Although genetic variation in *ERMAP* has been extensively cataloged, nonsynonymous variants associated with alloantigens have remained limited, and no new antigens have been identified. The first case of a severe hemolytic transfusion reaction to anti-Sc2 has recently been reported, highlighting the importance of pursuing the possibility of antibodies to low-prevalence antigens via indirect antiglobulin testing as a routine component of all transfusion reaction investigations. The expanding use of molecular testing in blood centers and transfusion services has uncovered a wider population distribution of Scianna antigens and heightened the awareness of this blood group system. The International Society of Blood Transfusion recognizes seven antigens in the Scianna blood group system 13.

Keywords

Scianna; *ERMAP*; Radin

New *ERMAP* Variants, Haplotypes, and Population Distributions

The International Society of Blood Transfusion recognizes seven antigens in the Scianna system,[1] each of which results from genetic variations that have rather low minor allele frequencies in all studied populations.[2,3] In recent years, several groups have mined public genetic databases and cataloged the variation in known blood group genes. Using the 1000 Genomes data, the Erythrogene project found 357 nonsynonymous mutations in extracellular regions of known blood group genes that are putative undiscovered antigens, 46 of which were in *ERMAP*.[4] Review of the 1000 Genomes data 2 years later identified another variant seemingly confined to East Asian populations that is proposed as a possible new antigen target (Trp177Ter).[5] In addition, the broader population sampling in the 2018

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analysis revealed Sc2 in South Asians for the first time and expanded detection of the rare SC:–5 and SC:–7 variants that were previously confined to isolated probands to populations.

A true *tour de force* of *ERMAP* variation included meticulous haplotype determination via long-range polymerase chain reaction of 50 blood donors of diverse ethnicity.[6] This group carefully cataloged and empirically determined *ERMAP* haplotypes, including single nucleotide polymorphisms (SNPs) in both coding and non-coding regions and found several novel variations in the non-coding regions. Consistent with prior reports, all coding region variation was present at low frequency, with the exception of the 76C>T (His26Tyr) variant, which had a minor allele frequency of 15 percent. This SNP was found at an even higher frequency in donors of Hispanic ethnicity (44%) and was in significant linkage disequilibrium with the 54C>T (Leu18Leu) synonymous variant.[7]

The Pacific Null Variant Is Definitively Resolved at the Molecular Level

The molecular basis of the Scianna null phenotype had previously been determined in two Sc_{null} individuals from California, but index cases from Pacific Islanders had only been characterized serologically. Hue-Roye and colleagues[8] unified these two patient groups in their report showing that the SC*994C>T nonsense variation was shared in all cases. They further reported that a patient with an anti-Sc3 tolerated uneventful transfusions, providing further evidence that it is usually a clinically insignificant alloantibody.

New Antibody Case Reports: The First Severe Hemolytic Reaction from Anti-Sc2 and Clinical Relevance in Pregnancy

This update provides an opportunity to include a clinical case abstract from 2005 that had been inadvertently overlooked in the initial review.[1] Hurstell and Banks[9] reported a case of clinically relevant hemolytic disease of the fetus and newborn (HDFN) attributed to anti-Sc2 that was detected on routine neonatal direct antiglobulin testing. Like the previously reported anti-Sc2 HDFN case, the maternal antibody detection test was negative, as expected for testing using a screening cell panel lacking low-prevalence antigens.

An important recent report of an acute hemolytic transfusion reaction due to anti-Sc2 provides an excellent example of the potential adverse consequences of categorizing low-prevalence antibodies as “clinically insignificant.”[10] In their patient with a previously identified anti-Sc2, electronic or immediate-spin crossmatches were performed rather than compatibility testing using an indirect antiglobulin test because of an assumption that anti-Sc2 was not clinically significant. The patient subsequently experienced fever, rigors, nausea, and abdominal pain requiring an inpatient admission when she was transfused with blood from the same donor implicated in her seroconversion with anti-Sc2. Moreover, this patient’s plasma showed a phagocytic index greater than 50 percent in a monocyte monolayer assay (the normal control with an insignificant phagocytosis is 5% or less) that correlated very well with clinical relevance.[11]

To further add to our tally of reports of clinical consequences of Scianna system alloantibodies, a case of severe fetal anemia was reported recently in which anti-Sc4 (or anti-

Rd) was implicated.[12] Clinically significant reports involving anti-Rd, including the five cases in the initial description of this antibody by Rausen et al. in 1967,[13] have all been associated with cases of HDFN. Again, strategies designed to detect antibodies to low-prevalence antigens were used in this case, including neonatal direct antiglobulin testing and paternal typing. Given the apparent association between anti-Rd and HDFN, which is now strengthened by this additional report, Scianna system low-prevalence antigens should be near the top of the list when investigating cases of fetal anemia with a negative maternal antibody detection test.

Broadened Range of Serologic Reagents for Scianna Antigens by Recombinant Proteins

Genetic testing continues to play a major role in defining Scianna variants in patients and donors, but new serologic reagents such as recombinant blood group proteins offer a complementary strategy to solving complicated immunohematologic problems. The high-prevalence Scianna system antigens Sc1, Sc3, Sc4 (STAR), Sc5 (SCER), and Sc6 (SCAN) can now be detected using CE-marked recombinant proteins.[14] Particularly in specimens containing mixtures of antibodies that include antibodies to a high-prevalence antigen, these reagents can be useful tools to remove the high-prevalence antibody and permit alloantibody identification by standard methods.[15,16]

Discoveries and Future Therapies Based on ERMAP Biology

The erythroid membrane associated protein (ERMAP) is a butyrophilin-like transmembrane protein, categorized within the immunoglobulin superfamily.[17] Although other butyrophilins have defined immunologic functions, ERMAP still remains somewhat elusive. An exciting new feature of *ERMAP* genetics that unites it with other blood group genes is the recent discovery of a binding site for the erythropoietic transcription factor KLF-1 in the two alternative *ERMAP* gene promoters.[18–20] ERMAP itself was also recently found to directly inhibit T-cell functions by decreasing cell proliferation and decreasing cytokine secretion, leading to exciting proposals to use soluble ERMAP as an immune system regulator in patients with autoimmune or neoplastic diseases.[21] The functions of the “lucky 13th” blood group in essential processes such as erythropoiesis and immunity could help explain the generally low-frequency and population-specific genetic variation seen in *ERMAP*. Mutations that interfere with such vital functions would likely be deleterious. There continues to be interest and enthusiasm for continuing work on the Scianna system antibodies and their underlying diversity, revealed through continued patient case reports and cutting-edge approaches like “big data” genetics and recombinant protein serology.

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