13 Scianna Blood Group System

13.1 Introduction

The Scianna system consists of seven antigens: a pair of antithetical antigens, the high and low frequency antigens SC1 and SC2, an antigen of low frequency (SC4, previously Rd), and four antigens of very high frequency (Table 13.1). SC3 is absent only from cells of the Scianna null phenotype. Scianna antigens are located on the immunoglobulin-superfamily glycoprotein, ERMAP. The Scianna gene is linked to the Rh genes on chromosome 1p.

13.2 ERMAP, the Scianna glycoprotein, and the gene that encodes it

Spring *et al.* [1,2] demonstrated by immunoblotting of red cell membranes with alloantibodies that SC1, SC2, and Rd (SC4) are located on a glycoprotein of apparent MW between 60 and 68 kDa. No bands were present if the membranes were prepared in the presence of a thiol reducing agent, showing that one or more disulphide bonds are required for antigen integrity. Variation in sialic acid content of the *N*-glycans probably accounts for the diffuse nature of the bands representing the glycoprotein. The Scianna glycoprotein was also immunostained on protein blots by autoanti-SC1 [3].

Analysis of families with SC:2 members demonstrated linkage between *SC* and the Rh genes, located at chromosome 1p36, with a male recombination fraction of about 0.10 [4,5]. Other studies demonstrated linkage, with a similar recombination fraction, between the genes controlling SC4 and Rh [6,7].

Human cDNA encoding a protein with a high level of homology to mouse ERMAP (erythroid membrane-associated protein) [8] was cloned from human fetal liver cDNA libraries [9,10]. The encoded 475 amino acid protein belongs to the immunoglobulin superfamily (IgSF) of adhesion and receptor proteins (see Section 6.2.2). The N-terminal extracellular domain of about 156 amino acids contains a single IgSF V domain. There is a single membrane-spanning domain, and a C-terminal cytoplasmic domain of about 298 amino acids that contains a B30.2 domain, a conserved motif of 157 amino acids found in many proteins with diverse functions. Human ERMAP is highly expressed on erythroid cells and may also be expressed at low levels on other haemopoietic cells [10]. *ERMAP* mRNA was not detected in many other adult tissues. Almost nothing is known about the function of ERMAP, a member of the butyrophilin-like subset of the IgSF (reviewed in [11]).

The human *ERMAP* gene was then identified from the GenBank database with a sequence at chromosome 1p34 [10]. It consists of 11 exons spanning about 19 kb. Exon 1 is untranslated; exon 2 encodes the translation initiation methionine codon, the leader sequence, which is not part of the mature protein, and the N-terminal domain; exon 3 the IgSF domain; exon 4 the membrane-spanning domain; exons 5–10 are very small; and exon 11 encodes the B30.2 domain and the 3′ untranslated region [10].

In 2003 Wagner *et al.* [12] recognised from its chromosomal location that *ERMAP* was a good candidate for the Scianna gene. Furthermore, the MW of the Scianna glycoprotein was compatible with the predicted MW of ERMAP. By identifying nucleotide changes in *ERMAP* associated with SC:2, SC:4, and SC_{null} phenotypes, Wagner

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Table 13.1 Antigens of the Scianna blood group system.

Antigen				Molecular basis*		
No.	Name	Frequency	Antithetical antigen	Nucleotides	Exon	Amino acids
SC1	Sc1	High	SC2	169G (A)	3	Gly57 (Arg)
SC2	Sc2	Low	SC1	169G>A	3	Gly57Arg
SC3	Sc3	High		Various		Various
SC4	Rd	Low		178C>G	3	Pro60Ala
SC5	STAR	High		139G (A)	3	Glu47 (Lys)
SC6	SCER	High		242G (A)	3	Arg81 (Gln)
SC7	SCAN	High		103G (A)	2	Gly35 (Ser)

*Molecular basis of antigen-negative phenotype in parentheses.

Table 13.2 Frequency of SC2 in various populations.

Population	No. tested	No. SC:2	SC2 frequency	References
Canadian donors	1000	1	0.0010	[14]
White Canadians	348	5*	0.0144	[15]
White Canadians	1000	17	0.0170	[18]
Londoners	1039	7	0.0067	[21]
Oxford donors	5306	41	0.0077	[5]
Warsaw donors	1025	9	0.0088	[21]
Berlin donors	2015	15	0.0074	[22]
Czech donors	2100	7	0.0033	[23]
Black Canadians	212	0		[24]
Japanese	4900	5	0.0005	[25]

*Includes three Mennonites.

et al. [12] confirmed that the Scianna antigens are located on ERMAP. Soluble recombinant ERMAP, produced in human embryonic kidney cells, inhibited haemagglutination reactions with anti-SC1 and -SC5 [13].

13.3 Scianna antigens

13.3.1 SC1 and SC2

In 1962, Schmidt *et al.* [14] identified an antibody in a Caucasian woman (Mrs N.S.) defining a new, inherited antigen of very high frequency. They named the antigen Sm. The following year, Anderson *et al.* [15] described a new low incidence antigen, Bu^a. Lewis *et al.* [16] were quick to notice that the original Sm– cells were Bu(a+). Sm and Bu^a were renamed SC1 and SC2, respectively, following confirmation through family studies that they were the products of alleles [17,18].

Expression of SC2 and concomitant loss of SC1 results from a Gly57Arg substitution in the IgSF domain of ERMAP (Table 13.1) [12]. The mutation destroys an *Sma*I site.

Testing of 269 000 South London blood donors with anti-SC1 revealed one SC:–1 individual [19], suggesting the following gene frequencies: *SC*01* 0.9981; *SC*02* 0.0019. No SC:–1 person was found as a result of testing red cells from 1600 North Americans [14,18] and 29 737 Welsh donors [20]. Frequency studies with anti-SC2 are shown in Table 13.2. In Canada the frequency of SC2 is high amongst the Mennonite community, which may be

responsible for the high SC2 frequency in some Canadian studies.

Treatment of SC:1 red cells with the proteases papain, trypsin, and chymotrypsin does not affect their reactions with anti-SC1 in haemagglutination tests; pronase and a mixture of trypsin and chymotrypsin reduces their reactivity. As expected for antigens located within an IgSF domain, SC1 and SC2 are substantially weakened by the disulphide bond reducing agent 6% 2-aminoethylisothiouronium bromide (AET) [1]. In contrast, SC2 is sensitive or markedly weakened by trypsin or chymotrypsin, possibly as a result of Arg57, not present on the SC1 protein [26]. SC1 is fully developed at birth [15]. Fluorescent flow cytometry demonstrated that SC1 is not present on lymphocytes, granulocytes, or monocytes [27].

13.3.1.1 Anti-SC1 and -SC2

Scianna system antibodies are very uncommon. They react best by an antiglobulin test and do not fix complement. Directly agglutinating anti-SC1 is known. No 'naturally occurring' Scianna alloantibody has been described.

The original anti-SC2 was found in a transfused man; three of the donors were traced and red cells from one reacted with the antibody [15]. Four examples of anti-SC2 were found among 14 anti-D sera produced by immunising D– volunteers with D+ red cell samples, one of which was also SC:2 [21].

Neither anti-SC1 nor -SC2 been incriminated in an HTR. One anti-SC1 gave a high score in a monocyte monolayer assay, suggesting potential clinical significance [28]. IgG3 anti-SC1 was responsible for a positive DAT on a baby's red cells, but no treatment was required [19]. There are two reports of anti-SC2 causing HDFN: one case was very mild [29]; the other required neonatal transfusion [30].

Several examples of autoanti-SC1 have been described, some of which have been responsible for AIHA [3,31–34]; two of them were in individuals whose red cells had weakened expression of SC1 [32,34]. Two of the antibodies were only detectable in serum, not in plasma [31,33]. Some autoantibodies in patients with depressed SC1 and SC3 reacted strongly with SC:1,–2 cells, weakly with SC:–1,2 cells, and did not react with SC_{null} cells [35,36].

13.3.2 SC3 and the SC_{null} phenotype

The first three propositi with the SC:–1,–2 phenotype, now called SC_{null}, all had an antibody reactive with all red cells save those of the SC:–1,–2 phenotype [37–39]. Adsorption studies with SC:1,–2 and SC:–1,2 cells demonstrated that the antibody was not a mixture of anti-SC1 and -SC2, so the antibody was numbered anti-SC3 [38].The first propositus, who had been transfused seven months previously, was from the Marshall Islands in the South Pacific (Micronesia) [37]. Her cousin was also SC:–1,–2, but did not have anti-SC3 despite four pregnancies. The second propositus was a previously transfused white man [38]. The third SC:–1,–2 propositus with anti-SC3, a previously transfused four-year-old girl, was found in Papua New Guinea (Melanesia) [39]. Her mother and six other family members and villagers in her home area were also SC:–1,–2.

Two *ERMAP* mutations responsible for the Sc_{null} phenotype have been reported.

1 An SC_{null} individual from Saudi Arabia was apparently homozygous for a 2-bp deletion in exon 3 (307del2), causing a frameshift that would result in a truncated protein of 113 amino acids (*SC*01N.01*) [12].

2 Two SC_{null} individuals from California and three, plus two SC_{null} relatives, from Pacific Islands, were homozygous for 994C>T in exon 11 introducing a stop codon at the codon for Arg332 within the B30.2 domain (*SC*01N.02*) [40,41].

Survival studies with radiolabelled SC:1,–2 cells suggested that the original anti-SC3 may be clinically significant [37]. This antibody disappeared soon after its identification and was not restimulated by injection of SC:1,–2 red cells. Anti-SC3 in a Melanesian child could not be detected after splenectomy, even following transfusion of SC:1,–2 blood [39].

13.3.3 SC4, the Radin antigen (Rd)

Before Rd was assigned to the Scianna system and became SC4, it was 700015. The first five anti-SC4 were apparently stimulated through pregnancy. In the five families the gene for SC4 could be traced to Russian Jews, black people, Northern Europeans, and a Native American [42]. Rd frequencies are shown in Table 13.3. SC4 is inherited as an autosomal dominant character [42,43]. A person with the very rare SC:1,2,4 phenotype has been found [7].

Two SC:4 individuals had a SNP encoding Pro60Ala in the IgSF domain of ERMAP (*SC*01.04*) (Table 13.1) [12].

SC4 is resistant to papain, ficin, and sialidase treatment, and substantially weakened by AET. Variable results were obtained with anti-SC4 and red cells treated with trypsin or chymotrypsin [26].

Anti-SC4 has been stimulated by pregnancy and transfusion [42,43]. One example of apparently 'naturally occurring' anti-SC4 was found in an untransfused man

Table 13.3 Frequency of SC4 in various populations.

Population	No. tested	No. SC:4	SC4 frequency	References
Various ethnic groups	6773	0		[42]
New York Jews	562	3	0.0053	[42]
Danes	4933	24	0.0049	[43]
Canadians	770	3	0.0039	[6]
Winnipeg donors	2864	9	0.0031	[6]

[43]. Of 30 000 sera tested in Denmark, none contained anti-SC4 [43]. The first five anti-SC4 were all reported to have caused mild to moderate HDFN, but only one baby required exchange transfusion [42].

13.3.4 SC5 (STAR), SC6 (SCER), and SC7 (SCAN)

Three antibodies to high frequency antigens found in previously transfused Caucasian men with SC:1,–2 red cells failed to react with SC_{null} cells [44]. None of the antibodies reacted with autologous cells, but all three antibodies reacted with the red cells of the other two antibody makers and, therefore, have different specificities. The antigens they define joined the Scianna system when the antibody makers were found to be homozygous for mutations in *ERMAP* (Table 13.1) [40,45].

The only SC:–5 propositus was a previously transfused white man of Irish and English descent. He and his SC:–5 bother were homozygous for 139G>A encoding Glu46Lys in the IgSF domain of ERMAP (*SC*01.–05*); their seven children were all heterozygous 139G/A [45]. Anti-SC5 reacted with all of 8000 random donor samples [44].

The only SC:–6 propositus was a previously transfused white man of German descent homozygous for a mutation encoding Arg81Gln in the IgSF domain of ERMAP (*SC*01.–06*) [44].

The only SC:–7 propositus was a previously transfused white man of German, English, and native American descent homozygous for a mutation encoding Gly35Ser in the N-terminal domain of ERMAP (*SC*01.–07*) [45]. Anti-SC7 was reported to have caused a delayed HTR, but then disappeared over the next few months [44].

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