Community Blood Center

Saint Luke's

Scianna Blood Group System and Case Study

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Objectives

- Discuss Scianna blood group history.
- Discuss Scianna in Transfusion Medicine by reviewing a recent case study at Community Blood Center and St. Luke's Hospital.
- Describe structure and function of the Scianna protein and associated genomics.

Objective 1

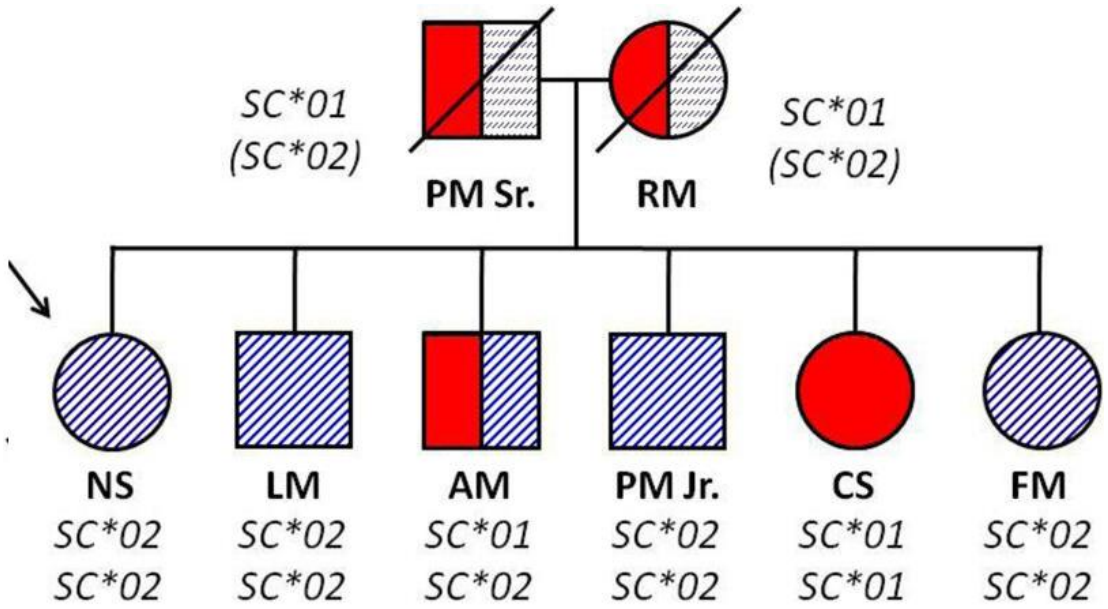
Discuss Scianna Blood Group History

Scianna System History

- 1962 first identified antigens.
  - Antibody to high prevalence antigen, first named anti-Sm, found with a coexisting anti-D.
    - Some siblings were found to be antigen negative.
    - No antigen negative D- specimens found in unrelated population.
    - Clinical significance was uncertain due to coexisting antibody.
  - Low prevalence antigen first named anti-Bu^{a}.
    - Locus determined to be separate from other known blood groups.

Scianna System History

- 1964 Sm and Bu^a found to be antithetical.
  - Anti-Bu^a was used to type the family members of the anti-Sm patient
  - Parents of anti-Sm patient were found to be heterozygous (Sm/Bu^a)
- Mennonite population discovered to have a higher prevalence of the Bu^a antigen compared to other Caucasians.

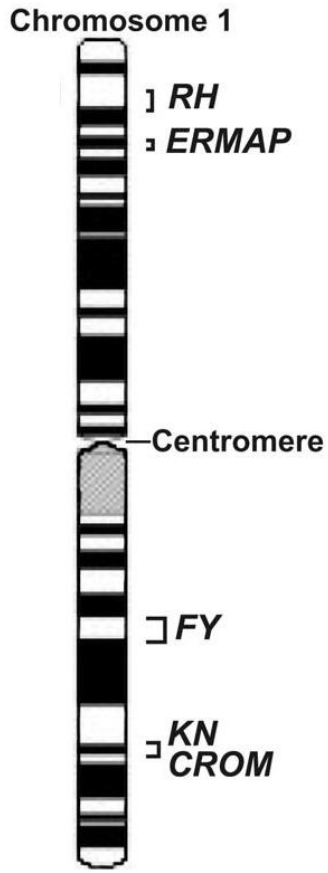


Brunker PA, Flegel WA

Scianna System History

- In 1974 group renamed Scianna
  - Sm was renamed Sc1, Bu^a was renamed Sc2.
  - Established as the 13th ISBT blood group system
  - Last previously serologically defined, protein based blood group system

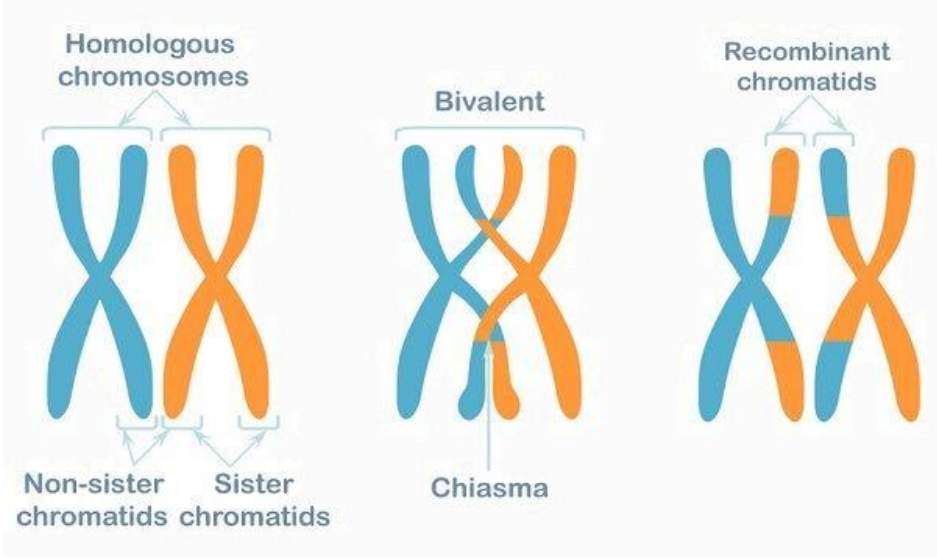
- 1976-1978
  - Locus identified on chromosome 1
  - Linkage between *RH* and *SC* established.



The Blood Group Antigen FactsBook.

Linkage Review

- Physical association between two genes on the same chromosome.
- Gene are located close together and are inherited together.
- Genes that are far apart on the chromosome are dispersed by crossing over and termed syntenic.
- Crossing over, also called recombination, occurs during meiosis when homologous pairs of chromosomes break and recombine with the partner chromosome.



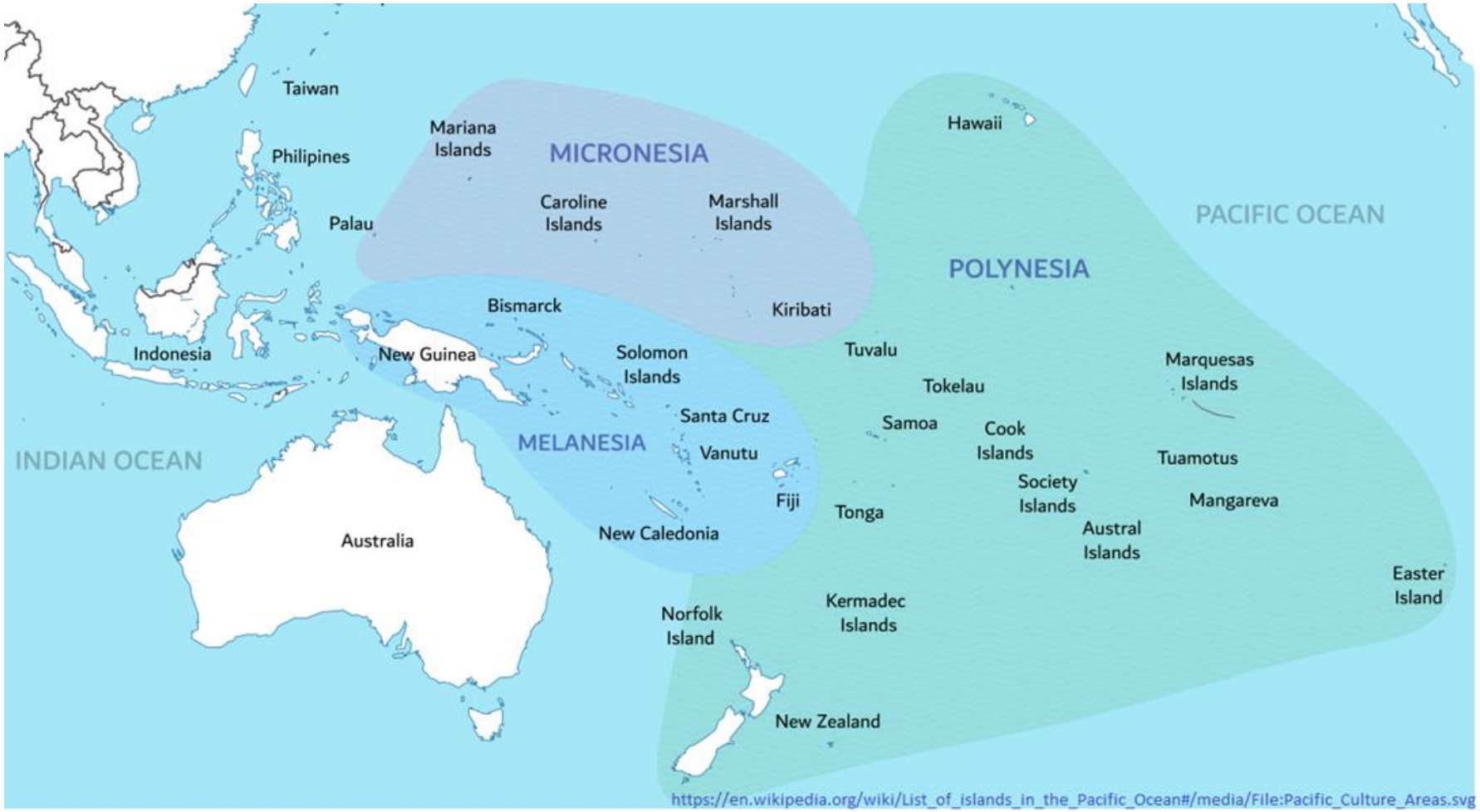
https://biologydictionary.net/prophase-2/#google_vignette

Scianna System History

- 1980
  - Although first documented in 1973
  - Antibody against a high prevalence antigen made by Marshallese individuals who typed SC:-1,-2.
  - 1980 antibody demonstrated no separable anti-Sc1 or anti-Sc2.
  - Term Sc3 created.

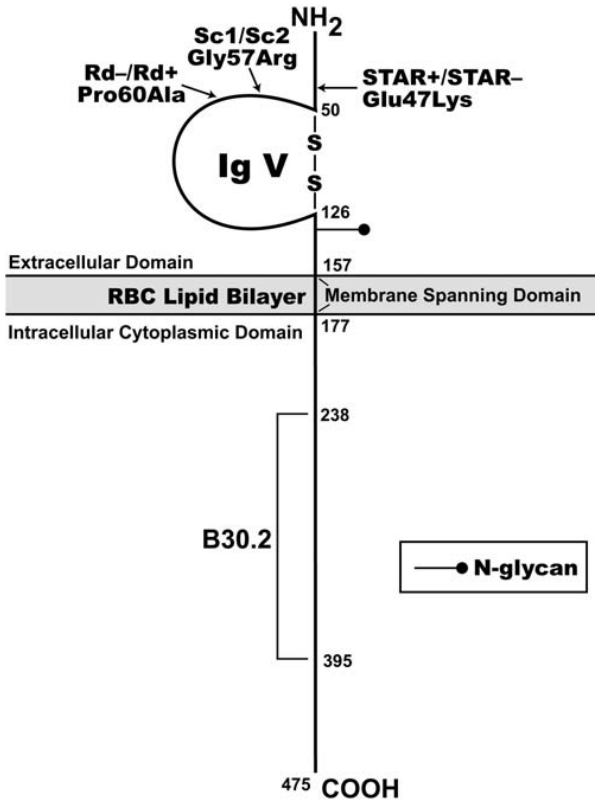
- 1986
  - Patient from Papua New Guinea demonstrated Anti-Sc3
  - 20.6% population found to phenotype as SC:-1,-2

Scianna System History



Scianna System History

- 2003 source protein and molecular variants described.
  - Antigen caused by variants in the erythroid membrane-associated protein (ERMAP).
  - Additional high prevalence antigens described:
    - STAR (SC5)
    - SCER (SC6)
    - SCAN (SC7)
- 2008-2022
  - Final two known high prevalence antigens described:
    - SCAR (SC7)
    - SCAC (SC8)
  - New null variant found in a patient from South India.
    - *SC*01N.03*



The Blood Group Antigen FactsBook.

Scianna System Antigens

- 2 low prevalence antigens
  - Sc2
  - Sc4(Rd)

- 7 High prevalence antigens
  - Sc1
  - Sc3
  - STAR
  - SCER
  - SCAN
  - SCAR
  - SCAC

Sc1 Antigen Characteristics

- Originally labeled Sm
- >99% occurrence in all populations
- Expressed on Cord Cells
- Enzyme and Chemical Effect:
  - Ficin: Resistant
  - Papain: Resistant
  - Trypsin: Resistant
  - DTT: Resistant

Sc2 Antigen Characteristics

- Originally named Bu^a.
- Occurs in 1% of people with European ancestry.
  - More common within the Mennonite community.
  - Variable expression
- Expressed on cord cells
- Enzyme and Chemical Effect:
  - Ficin: Resistant
  - Papain: Resistant
  - Trypsin: Variable
  - DTT: Variable

Sc3 Antigen Characteristics

- On all Sc1 or Sc2 positive cells
- Present in 100% of most populations.
  - Null phenotypes phenotype as SC:-1,-2,-3
  - 3 different alleles coding null variants
    - found in Saudi Arabian, Pacific Islander and South Asian populations.
- Expressed on cord cells
- Enzyme and Chemical Effect:
  - Ficin: Resistant
  - Papain: Resistant
  - Trypsin: Variable
  - DTT: Resistant

Sc4 Antigen Characteristics

- Called Rd (Radin)
  - Low prevalence, very rare (<0.01% most populations)
  - Expressed on cord cells
- Enzyme and Chemical Effect:
  - Ficin: Resistant
  - Papain: Resistant
  - Trypsin: Variable, but often Sensitive
  - DTT: Resistant

Other Scianna Antigens

- High prevalence antigens
  - SC5 (STAR), SC6(SCER), SC7(SCAN), SC8(SCAR), and SC9(SCAC)
  - Only one antigen negative proband found for each.
- Type as Sc1 positive
- Enzyme and Chemical Effect:
  - Ficin: Resistant
  - Papain: Resistant
  - Trypsin: Resistant
  - DTT: Resistant

Scianna Antibody Characteristics

- Immunoglobulin Class:
  - All: IgG
- Optimal reactions with indirect antiglobulin technique.
- Transfusion Reactions:
  - Anti-Sc1, -Sc2, -Rd : None reported.
  - Anti-Sc3: None to mild/delayed.
- Hemolytic Disease of the Fetus and Newborn:
  - Anti-Sc1: DAT+, but no clinical symptoms.
  - Anti-Sc2: DAT+, but no clinical symptoms to mild.
  - Anti-Sc3: Mild.
  - Anti-Rd: Mild to severe.
- Not enough information on other antibodies due to rarity.

Objective 2

Discuss Scianna in Transfusion Medicine by Reviewing a Recent Case Study at Community Blood Center and St. Luke's Hospital

2010 Sample

- 38-year-old, Caucasian male
- Diagnosis: Chronic Renal Insufficiency
- Transfused: 6 months ago
- Hospital orders
  - Antibody identification
  - 2 units RBCs

Sample Workup

- History of warm autoantibody from prior sample in 2009
- ABO/Rh
  - Group O, Rh Positive
- DAT
  - Negative (Poly, IgG and C)

Antibody Panel

	Rh					Kell		Duffy		Kidd		Lewis		MNS				Plasma
	D	C	E	c	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	M	N	S	s	PEG IAT
1	+	+	0	0	+	+	0	+	W	+	+	0	0	+	0	0	+	1+
2	+	0	+	+	0	0	+	+	+	+	0	0	+	0	+	+	+	1+
3	+	0	0	+	+	0	+	0	+	+	+	0	+	0	+	0	+	1+
4	0	+	0	+	+	0	+	+	0	+	+	+	0	+	0	+	0	1+
5	0	0	0	+	+	0	+	+	+	+	0	0	+	+	0	+	0	1+
6	+	0	0	+	+	0	+	0	0	0	+	0	+	+	+	0	+	1+
7	+	+	0	0	+	+	+	+	0	+	+	+	0	+	+	0	+	1+
8	+	0	+	+	0	0	+	+	+	0	+	0	+	+	+	0	+	1+
9	0	+	0	+	+	0	+	+	0	0	+	0	+	+	0	+	0	1+
10	0	0	0	+	+	+	+	0	+	+	0	0	+	0	+	+	+	1+
11	+	0	0	+	+	0	+	0	0	+	0	0	+	+	+	0	+	1+
AC																		0 √

Recap

- DAT is negative
- Antibody panel is all weakly positive
- Autocontrol is negative
  - Probable alloantibody to high prevalence antigen?

Additional Testing

- Ficin Treated Reagent RBCs
  - Positive

- Dithiothreitol (DTT) treated RBCs
  - Positive

- Serologic typing:
  - C+, E+, c+, e+; K-; Fy(a+b-); Jk(a+b+); S-s+
    - Patient can make an anti-f, -K, -Fy^b and/or -S

Blood Group Antigens FactsBook

- Helps give guidance as to what the antibody reactivity may be

Ficin/ Papain	Trypsin	α-Chymo-trypsin	200 mM DTT/AET	Possible specificity
Negative	Negative	Negative	Positive	Bp^a; Ch/Rg; XG
Negative	Negative	Negative	Negative	IN; JMH
Negative	Negative	Positive	Positive	M, N, En^aTS; Ge2, Ge4
Negative	Positive	Negative	Positive	'N'; Fy^a, Fy^b
Variable	Positive	Negative	Positive	S, s
Variable	Positive	Negative	Weak or negative	YT
Negative	Positive	Positive	Positive	En^aFS
Positive	Negative	Negative	Weak or negative	LU, MER2
Positive – Papain Weak or negative – Ficin	Negative	Negative	Negative	KN
Positive	Negative	Weak	Negative	DO
Positive	Positive	Negative	Weak	CROM
Positive	Positive	Negative	Positive	Some DI (3^{rd} loop)
Positive	Positive	Positive/weak	Negative	LW
Positive	Positive/weak	Positive/weak	Positive	SC
Positive	Positive^	Positive^	Negative	KEL^ (except KALT, which is trypsin sensitive)
Positive	Positive	Positive	Positive	ABO; En^aFR, U; P1PK; RH; LE; Fy3; JK; most DI; CO; H; Ge3; OK; I/i; P, FORS; JR; LAN, Cs^a; ER; LKE, PX2; Vel,$^+$ ABTI; At^a; Emm; AnWj; Sd^a; PEL; MAM
Positive	Positive	Positive	Enhanced	Kx

Blood Group Antigen FactsBook

- Focus on section that matches our reactivity
- Ficin-positive
- DTT-positive

Ficin/ Papain	Trypsin	α-Chymo-trypsin	200 mM DTT/AET	Possible specificity
Positive	Positive	Negative	Positive	Some DI (3rd loop)
Positive	Positive	Positive/weak	Negative	LW
Positive	Positive/weak	Positive/weak	Positive	SC
Positive	Positive^	Positive^	Negative	KEL^ (except KALT, which is trypsin sensitive)
Positive	Positive	Positive	Positive	ABO; En^{a}FR, U; P1PK; RH; LE; Fy3; JK; most DI; CO; H; Ge3; OK; I/i; P, FORS; JR; LAN, Cs^a; ER; LKE, PX2; Vel,$^+$ ABTI; At^a; Emm; AnWj; Sd^a; PEL; MAM
Positive	Positive	Positive	Enhanced	Kx

Plasma Against Rare Cells

Rare Cell	Reactivity PEG IAT
Hy- Gy(a-)	2+
McLeod	2+
Jr(a-)	2+
Co(a-b-)	2+
K_o	2+
EMM	2+
Cr(a-)	2+
TC (a-b-c+)	2+
Rh null	2+
SC:-1,2	2+

Rare Cell	Reactivity PEG IAT
Er(a-)	2+
O_h Bombay	2+
Lu:-3	2+
Lu(a-b-)	2+
U-	2+
AnWj-	2+
Lan-	2+
Yt(a-)	2+
In(b-)	2+
Vel -	2+

Next Steps?

- Alloadsorption with a phenotypically matched RBC
  - See if we can remove the antibody to a high prevalence antigen and leave any alloantibodies behind in the plasma.

- Need an adsorbing cell that is f-; K-; Fy(b-); S-
  - We selected an E-, c-, K- Fy(b-) S- unit.
    - Could enzyme treat the adsorbing RBCs if not able to match for Fy^b and S antigens
    - The f antigen status may be determined by the Rh phenotype (R_1R_1 or R_2R_2). Typing for the f antigen is not necessary.

Adsorption/Elution

- Alloadsorbed plasma
  - 2x alloadsorption, reactivity still present
  - 3x, reactivity still present
  - 4x, reactivity still present (microscopic reactivity)

- Elution of Adsorbing Cells.
  - Prepared from 1st set of RBCs used for adsorption
  - No anti-A or anti-B, can test against all blood groups.
  - Tested against rare cells again

Eluate from Adsorbing Cell Against Rare Cells

Previously tested with plasma

Rare Cell	Reactivity PEG IAT
AnWj-	2+
Lan-	2+
Lu(a-b-)	2+
Yt(a-)	2+
In(b-)	2+
Co(a-b-)	2+
SC:-1,2	2+

Not tested prior with plasma

Rare Cell	Reactivity PEG IAT
Pelletier-	2+
In(Lu) Lu(a-b-)	2+
SC:-1,-2	0 √
SC:-1	2+
SC:-1	2+
SC:-1,2	2+

Possible anti-Sc3?

Anti-Sc3 Confirmation

- Only one SC:-1,-2 rare red cell available.
- Tested with patient plasma.
- Repeated with eluate from adsorbing cell.

		Rh					Kell		Duffy		Kidd		MNS				Plasma	Eluate from Adsorbing Cell
		D	C	E	c	e	K	k	Fy^a	Fy^b	Jk^a	Jk^b	M	N	S	s	PEG IAT	PEG IAT
1	SC:-1,-2	+	+	0	0	+	0	+	+	0	+	+	+	+	+	+	0 √	0 √
2	SC:-1,2	+	+	+	+	+	0	+	0	+	+	+	+	+	0	+	2+	2+
3	SC:-1	+	+	0	0	+	0	+	0	+	+	+	+	0	0	+	2+	2+

Anti-Sc3 Confirmation

- Our patient is listed as Caucasian.
  - Anti-Sc3 not expected in this population.

- Verify the patient's race/ethnicity:
  - Hospital reports their records say Caucasian.
  - Requested they check with the patient.

- **Patient reports Native Hawaiian/Pacific Islander**
  - Helps to confirm suspected Anti-Sc3
  - SC:-1-2 mostly found in Marshallese/Pacific Islanders

Final Steps

- No other SC:-1,-2 rare cells available.
  - Unable to exclude presence of additional alloantibodies the patient can make

- Send for HEA Phenotyping by DNA Analysis

HEA Results

Blood Group	Antigen	Result	Notes
Rh	c	+	
	C	+	
	e	+	
	E	+	
Kell	K	0	
	k	+	
	Kpa	0	
	Kpb	+	
	Jsa	0	
	Jsb	+	
Kidd	Jka	+	
	Jkb	+	
Duffy	Fya	+	
	Fyb	0	
MNS	M	+	
	N	+	
	S	0	
	s	+	
Lutheran	Lua	0	
	Lub	+	
Diego	Dia	0	
	Dib	+	
Colton	Coa	+	
	Cob	0	
Dombrock	Doa	0	
	Dob	+	
	Joa	+	
	Hy	+	
Landsteiner-Wiener	LWa	+	
	LWb	0	
Scianna	Sc1	+	
	Sc2	0	
Hemoglobin S	HbS	0	

Scianna	Sc1	+
	Sc2	0

2010 Report

- **ABORH:** Group O, Rh Positive
- **DAT:** Negative
- **Antibody:**
  - Probable anti-Sc3
  - Unable to exclude common alloantibodies
- **Transfusion Recommendation:**
  - Give phenotype matched (f-, K-, Fy(b-), S-) RBCs
  - Significance of anti-Sc3 varies from no significance to mild/delayed transfusion reactions.

13 Years Later..

December 2023 Hospital Admission

- 51-year-old, Pacific Islander
- Diagnosis:
  - CKD 3 secondary to rejection
  - Hypertension
  - Type 2 Diabetes
  - Acute kidney injury
  - End Stage Renal Disease
- Transplant: 7 Years ago (2016)

- Physician orders
  - Antibody identification

December 2023 Hospital Admission

- Medication History: patient given IVIG and Prednisone for antibody rejection

- Transfusion history: patient receiving plasma products and dialysis
  - No further transfusion history since 2010
  - Negative ABSC reported August of 2020

- Physician Orders
  - Type and Screen
    - Positive antibody screen and DAT
    - Send out to CBC IRL

IRL Sample Workup

- **ABORh:** Group O, Rh Positive
- **DAT:** Positive (Poly and IgG only)
  - Eluate nonreactive
  - Patient on known medications that can cause positive DAT
    - IVIG and insulin
- **Antibody identification:**
  - Anti-Sc3
    - Still only have 1 rare cell that is SC:-1,-2 that is nonreactive with the plasma.
    - Alloadsorbed with papain treated phenosimilar cell to exclude all other common alloantibodies
  - No new alloantibodies

HEA Repeat

- Sent for another HEA on this patient
- Platform is now licensed
- Wanted to see if the patient still results as SC:1,-2

Blood Group	Antigen	Result	Comments
Rh	c	+	
	C	+	
	e	+	
	E	+	
	V	0	
	VS	0	
Kell	K	0	
	k	+	
	Kp^a	0	
	Kp^b	+	
	Js^a	0	
	Js^b	+	
Duffy	Fy^a	+	
	Fy^b	0	
Kidd	Jk^a	+	
	Jk^b	+	
MNS	M	+	
	N	+	
	S	0	
	s	+	
	U	+	
Lutheran	Lu^a	0	
	Lu^b	+	
Diego	Di^a	0	
	Di^b	+	
Colton	Co^a	+	
	Co^b	0	
Dombrock	Do^a	0	
	Do^b	+	
	Hy	+	
	Jo^a	+	
Landsteiner-Wiener	LW^a	+	
	LW^b	0	
Scianna	Sc1	+	
	Sc2	0	

Scianna	Sc1	+	
	Sc2	0	

Sequencing

- Sent sample to New York Blood Center Genomics Laboratory

CASE HISTORY:

Kidney transplant with possible rejection. Customer indicated: warm autoantibody, probable anti-Sc3.

Service requested: Genotype for Scianna

Test(s) performed: Sanger sequencing of *SC* exons 3-12 and flanking intron regions

RESULTS:

Detected variants: c.994C>T-hxm [p.332Ter].

Inferred genotype: *SC*01N.02 / 01N.02*

Predict. phenotype: SC:–1–2–3

Reference: GRCh38.p12; het: heterozygous; hxm: homo/hemizygous; alt exp: altered expression; alt spl: altered splicing.

COMMENTS:

The patient is predicted to have Scianna null phenotype, which places him at risk for alloanti-Sc1, -Sc2, -Sc3.

Transfusion Management

- We now know the patient is Scianna null and has an anti-Sc3
  - No SC:-3 units available
    - Clinical significance is none to mild/delayed transfusion reactions

- Recommend to hospital to transfuse phenosimilar cells that are mismatched for Sc3 antigen:
  - Sent 3 E-c-(f-negative), K-, Fy(b-) S- units

Patient Status

- Patient receiving albumin during apheresis procedures and remains on dialysis
  - Transfused 3 units of FFP
  - Transfused 2 units of cryoprecipitate
- Hemoglobin is low throughout hospital stay
  - Hgb remained between 7.6 – 8.5 g/dL
  - No blood is ordered
- Patient is discharged in stable condition

January 2024 Hospital Admission

- Patient returned to the hospital with shortness of breath
  - Found to have multifocal pneumonia and started on broad spectrum antibiotics
- Patient's anemia has worsened
  - Most likely due to End Stage Renal Disease (ESRD) and the acute infection
- Patient remains on dialysis
- Physician Orders
  - Type and Screen
    - Positive antibody screen and DAT
    - Send out to CBC IRL

Patient Status

- Ordered 3 phenotype matched E-negative, c-negative (f-negative), K-negative, Fy(b-), S-negative units
  - Given prior CBC IRL antibody identification completion
  - Units are compatible on Immucor Echo
- Hemoglobin does not increase as high as expected with the first unit (5.9 g/dL)
  - Physician orders 2nd unit, bumps patient Hgb to 6.8 g/dL
  - Patient started on Erythropoietin
- With treatment and RBC transfusion the patient's hemoglobin stabilizes
  - No active signs of hemolysis

		HEMOGLOBIN
Ref. Range & Units		13,0 - 17,0 g/dL
01/23/24	09:30	7.7 ▼
01/19/24	08:06	7.7 ▼
01/18/24	02:47	7.3 ▼
01/17/24	14:05	7.7 ▼
01/17/24	08:46	7.1 ▼
01/16/24	12:47	7.2 ▼
01/16/24	02:36	6.8 ▼
01/15/24	16:55	5.9 !!
01/15/24	09:45	5.3 !!
01/14/24	20:25	6.6 ▼

January IRL Sample Workup

- **Initial sample submitted was insufficient for antibody identification.**

- **ABO/Rh:** Group O, Rh Positive

- **DAT:** Positive (Poly, IgG and C)
  - Mixed field reactivity noted

IRL Workup Continued

- **Eluate and Plasma testing were performed on samples collected after transfusion of 2 units.**
  - **Samples collected after transfusion did not look hemolyzed nor icteric**

- **Antibody Identification:**
  - Anti-Sc3 in plasma and eluate
    - Alloadsorption performed on both eluate and plasma to rule out underlying antibodies.
  - No new alloantibodies with alloadsorbed eluate or plasma

Future Transfusions

- Most recent sample indicates anti-Sc3 in eluate and plasma
  - Patient may be having mild/delayed transfusion reactions
    - Anemia
    - Positive DAT
    - Anti-Sc3 in eluate

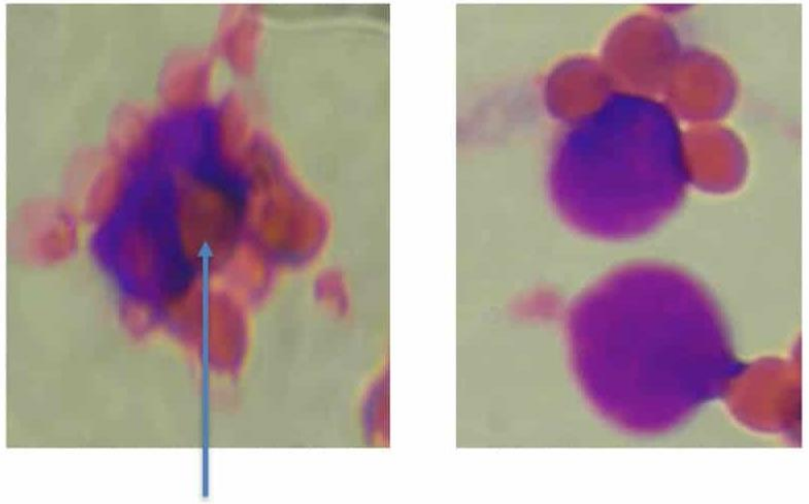
- Recommend send for Monocyte Monolayer Assay (MMA)
  - Assesses the clinical significance of the antibody

Patient Status

- Collected samples to be sent out for MMA testing
  - Sent to CBC IRL
- As no Sc:-3 units available
  - Patient's siblings requested to come to be tested
    - No matches were found
- No further transfusion were given
- Patient discharged 1/19/2024

What is an MMA

- Only available method for assessing clinical significance of an antibody
- Predicts *in vivo* survival of transfused cells
- Monocytes are isolated and placed on a slide in a monolayer
- Donor cells and patient plasma are mixed and incubated with the monolayer
- The slide is then stained and read
- The number of adhered or engulfed red cells are counted and a percentage is calculated
- Reported as monocyte index (MI) percent adhered, ingested, and total



MMA Report Interpretation

- Monocyte Index (MI) total:
  - ‘Zero’ or 0 = no adhered or phagocytized red cells
  - < 5 = incompatible blood can be given without risk of an overt hemolytic transfusion reaction
  - 5-20 = reduced risk of clinical significance, but signs and symptoms of transfusion reaction may occur
  - >20 = antibody has clinical significance, which may range from abnormal RBC survival to clinically obvious reactions

MMA Results

Antibody Source	RBC Source	AHG (IgG)	AHG (C3b/C3d)	MI Adhered RBCs (%)	MI Ingested RBCs (%)	MI Total (%)
MMA Pos Control A-D20231116	Screen Cell I & II Lot V268049	3+	NA	6.50	57.50	64.00
Patient Autocontrol		Mi+	Mi+	0.50	0.00	0.50
Patient plasma	W036523085720	0	Mi+	1.00	0.00	1.00
	W036523085718	0	Mi+	0.50	0.25	0.75
	W036523105374	0	Mi+	1.25	1.50	2.75
	W036523111272	0	Mi+	1.50	0.50	2.00
	W036523082239	Mi+	Mi+	3.50	1.25	4.75
	W036523108186	0	Mi+	0.75	0.25	1.00

Control

Patient plasma tested against various donor RBCs

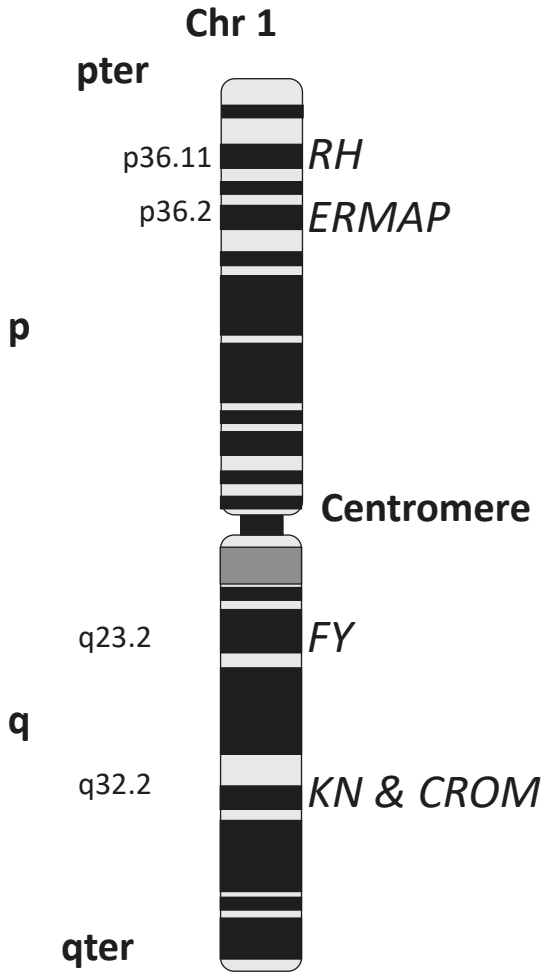
Our Anti-Sc3 Patient

- MI total (%) values ranged from 0.75-4.75
- Indicating the antibody is not currently considered clinically significant
- Patient should be able to receive Scianna positive RBCs without risk of an overt transfusion reaction
- Still administer with caution and monitor patient

Objective 3

Describe Structure and Function of the Scianna Protein and Associated Genomics

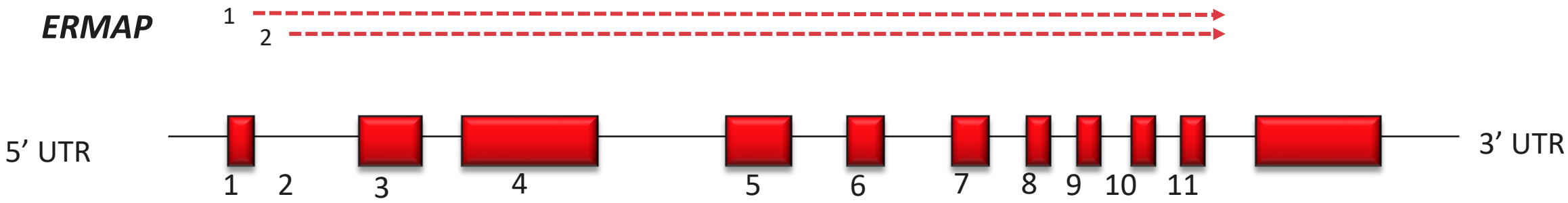
Scianna is encoded by *ERMAP*



- In the late 1970's Lewis and Kaita described distinct linkage of Radin/Scianna (*ERMAP*) and *RH* on chromosome 1p.

- In 2003, Flegel lab mapped the Scianna antigens to the *ERMAP* gene through sequencing probands with known Scianna and Radin (Rd) phenotypes.

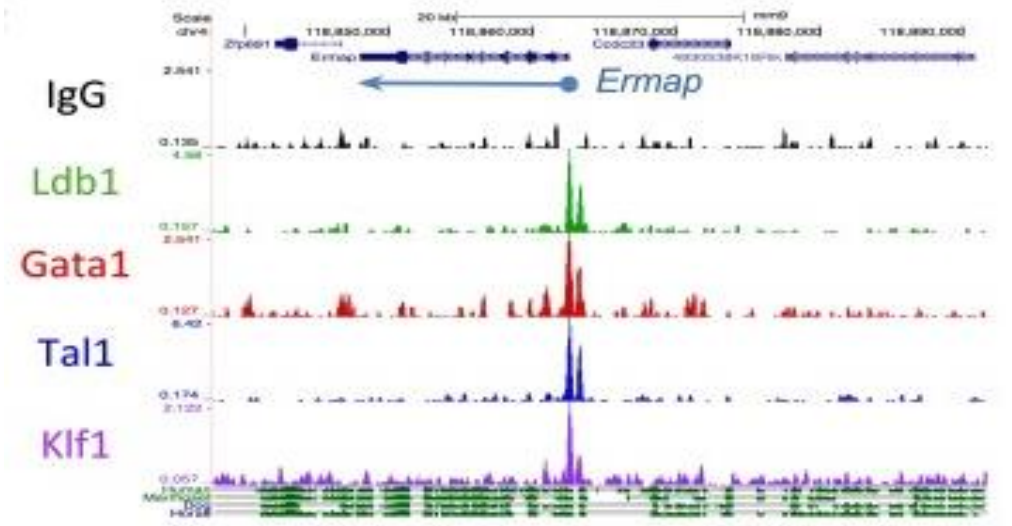
ERMAP: Molecular Basis of Scianna



- *ERMAP* is composed of 12 exons across 28kb of DNA, with exons 3-12 coding for the erythroid membrane-associated protein.

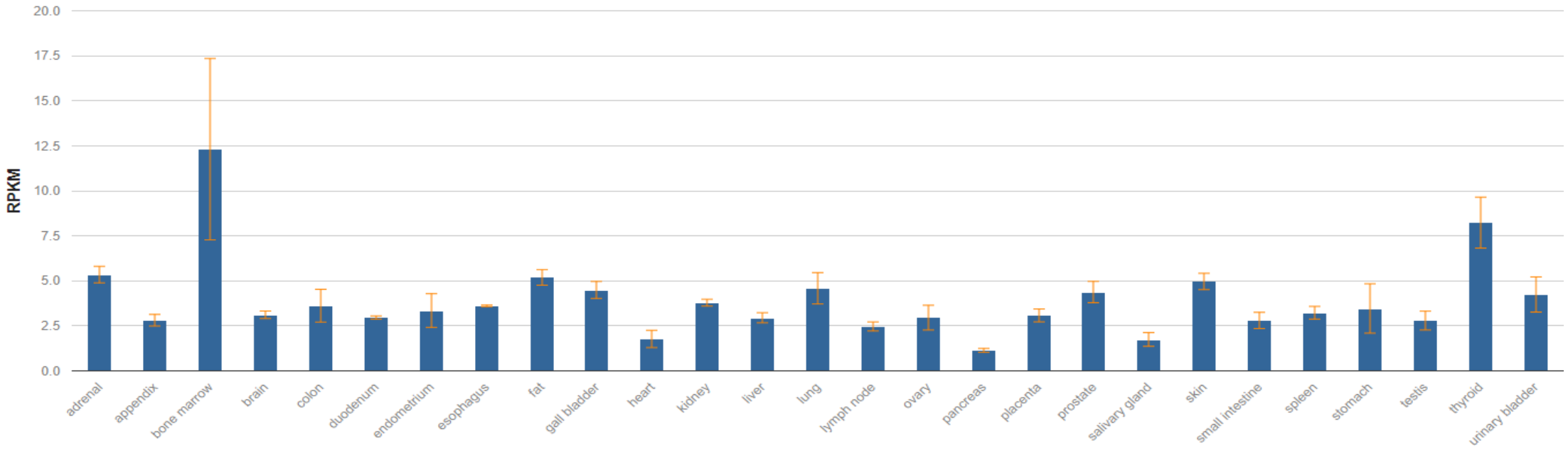
- Two transcript variants of *ERMAP* have been described
  - Transcript #1 is 3424 bp and includes exon 1, Transcript #2 excludes exon 1
  - Both share same ATG start codon, but any functional differences between the two transcripts are currently unknown.

The Gang Regulates ERMAP Expression



- Erythropoiesis transcriptional regulators Klf1, Tal1, Gata1, and Ldb1 bind to *ERMAP* promoter and activate expression.
- Knockdown of Ldb1 leads to significant decrease in *ERMAP* expression in MEL cells.
- Do In(Lu) (Δ*Klf1*) individuals also have decreased *ERMAP/SC* expression?

ERMAP Tissue Specific Expression



Faberberg, L et al. (2014)

- RNA-seq performed on 27 tissue samples from 95 human individuals
- Increased expression in bone marrow and thyroid

Potential Biological Roles of ERMAP

- Mononuclear cells isolated from umbilical cords
- treated with SCF, EPO, IL-3 to induce erythroid lineage show increased ERMAP expression

[Expression of human ermap gene in umbilical cord blood mononuclear cells during differentiation and development towards erythroid lineage]

[Article in Chinese]

Li-Dan Lin [1], Xin-Rong He, Tie-Zhen Ye, Ying-Yi He, Jing-Ming Guan, Ying Chen, Jie-Fang Liang

- ERMAP knockdown shows inhibition of erythroid differentiation of K526 cells

[Effects of human ERMAP-siRNA on erythroid differentiation of K562 cells induced by Ara-C]

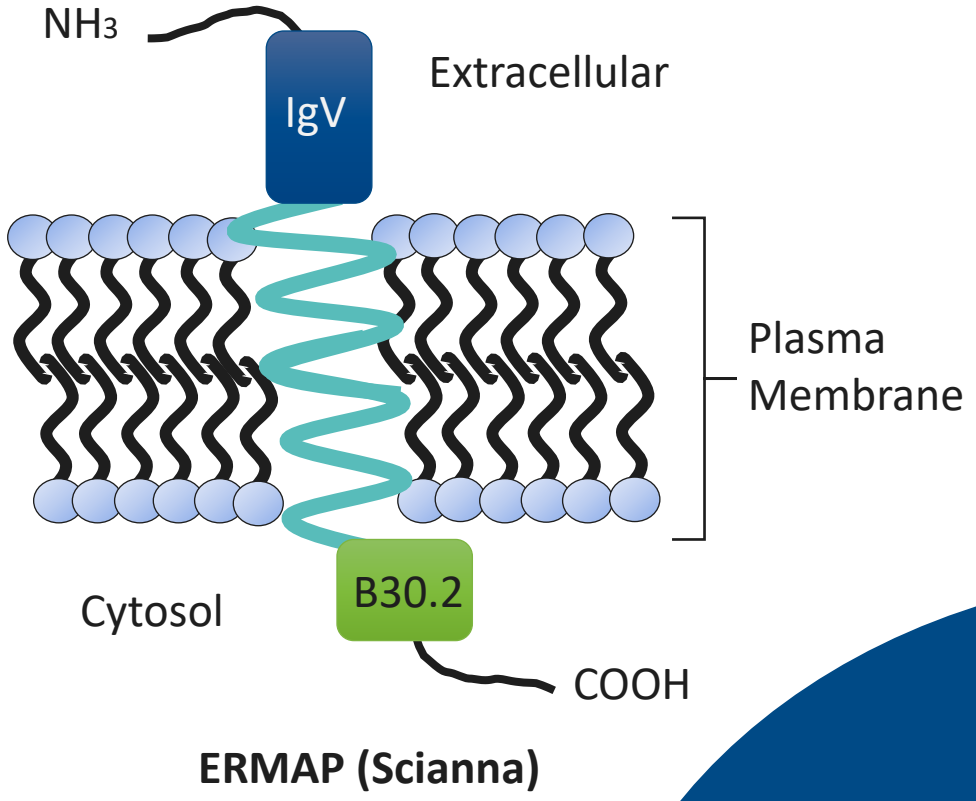
[Article in Chinese]

Jie-Fang Liang [1], Ying Chen, Tie-Zhen Ye, Ying-Yi He, Xin-Rong He, Li-Dan Lin, Sai-Jun Gao

- ERMAP likely involved in RBC developmental pathway, but exact mechanism unknown.

Properties of the Scianna Glycoprotein

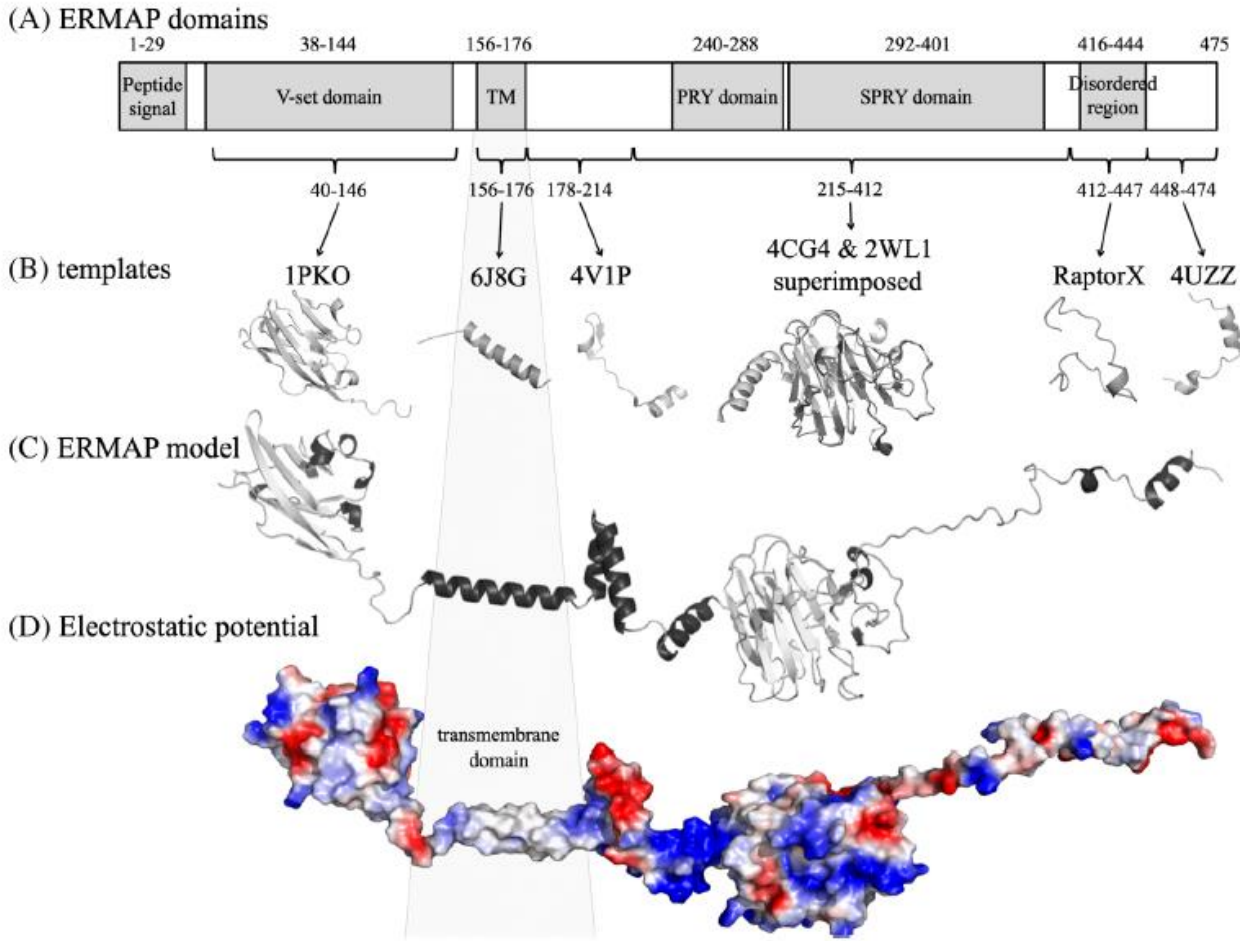
- ERMAP is a single pass transmembrane protein
  - **Extracellular IgG V-set domain:** Ig-like domains that resemble antibody variable domain. Found in diverse protein families including T-cell receptors, Cluster of Differentiation (CD) proteins, myelin membrane adhesion molecules, RTKs, and PD-1.
  - **Cytoplasmic B30.2/SPRY domain:** based on the sequence repeat discovered in the splA kinase and ryanodine receptors. Facilitates activation of many different signaling cascades.



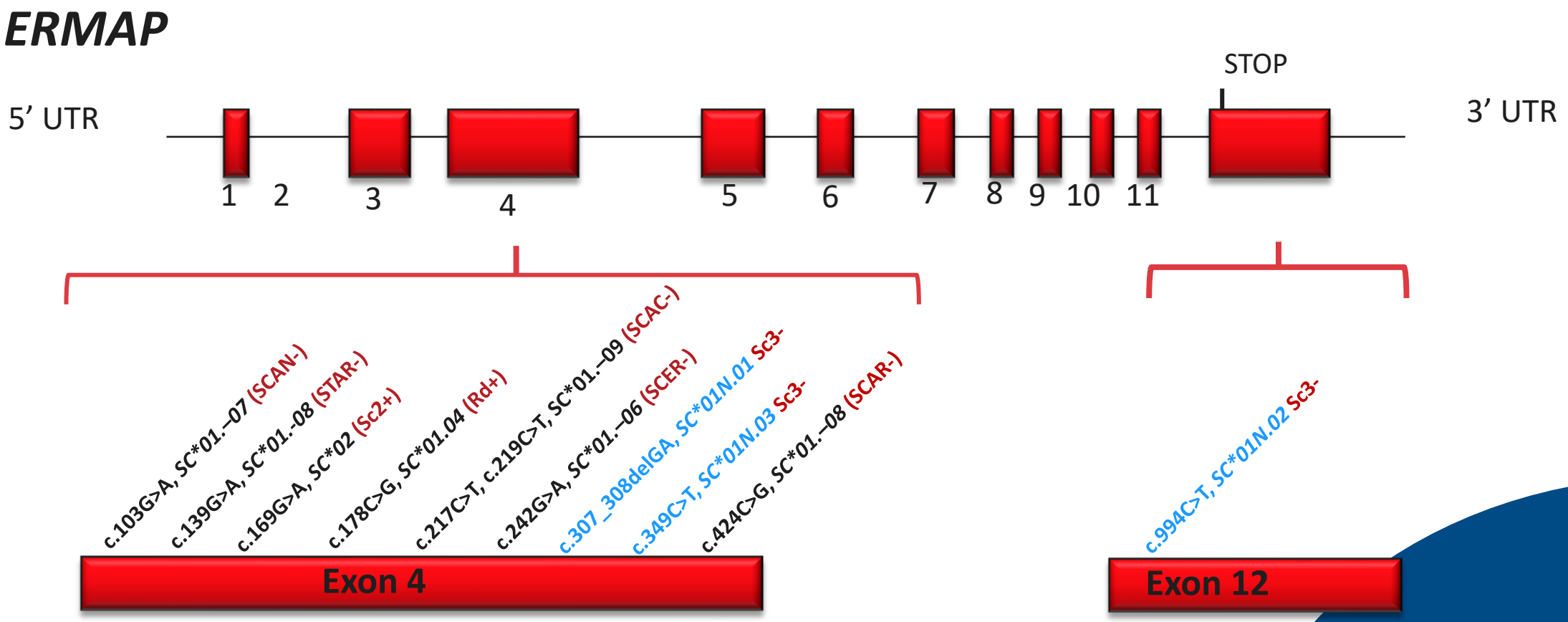
ERMAP Structural Domains Visualized

- Crystalized proteins with high homology were used as structural templates for each portion of ERMAP.
- Using multiple different models (in house, RaptorX, TrRosetta) NYBC was able to build a structural model (C&D)
- Really interesting model, but where are the Sc antigens?

Floch, A et al. (2023)



Genetic Basis of SC Polymorphisms

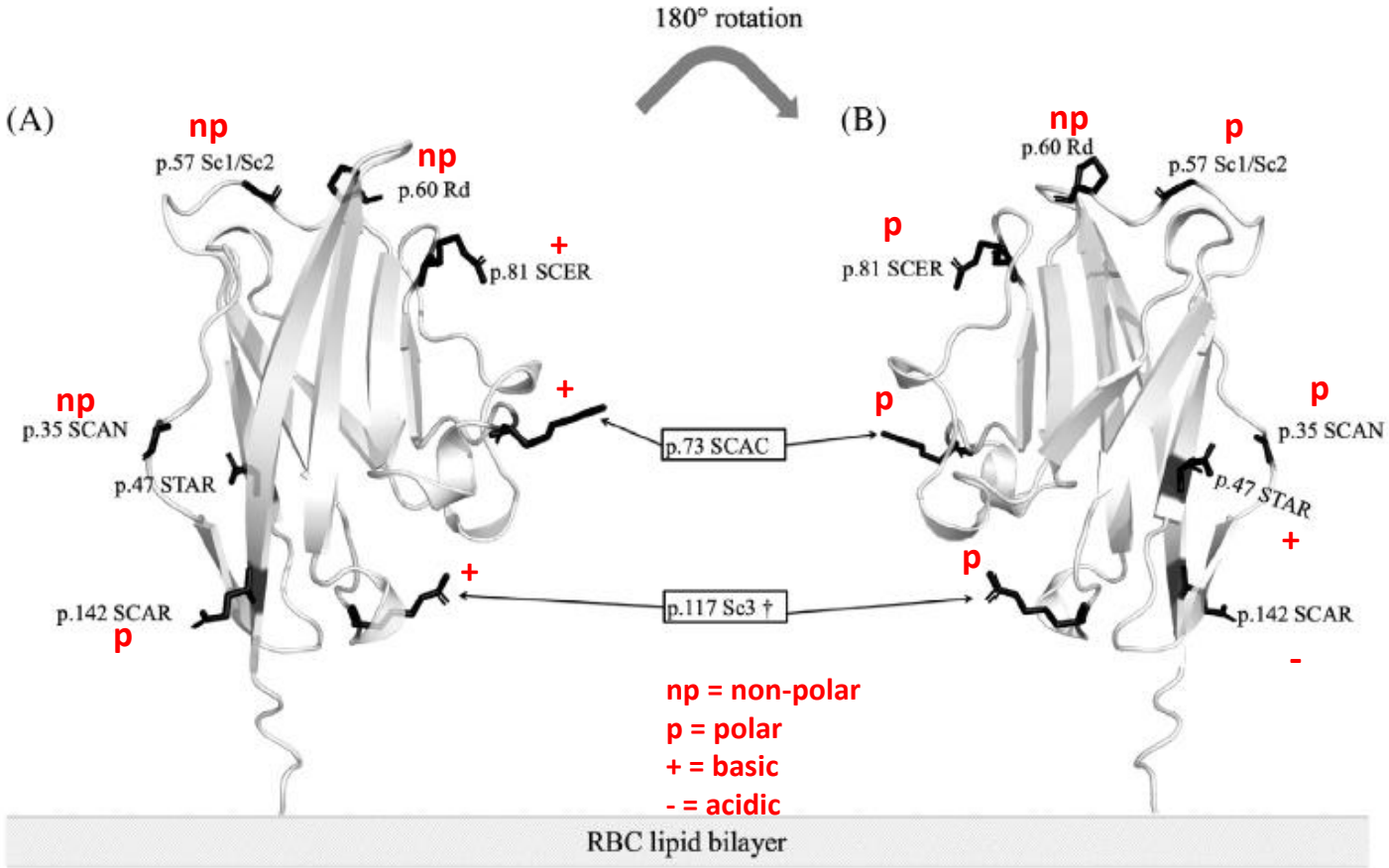


Where are these SNVs located on the ERMAP protein?

Structural Modeling of Scianna Antigens

- Scianna antigens located on extracellular Ig-like domain:

- SCAN (p.Gly35Ser)
- STAR (p.Glu47Lys)
- Sc1/Sc2 (p.Gly57Arg)
- Rd (p.Pro60Ala)
- SCAC (p.Arg73Cys)
- SCER (p.Arg81Gln)
- p.117 Sc3 (p.Arg117Cys)
- p.142 SCAR (p.Gln142Glu)



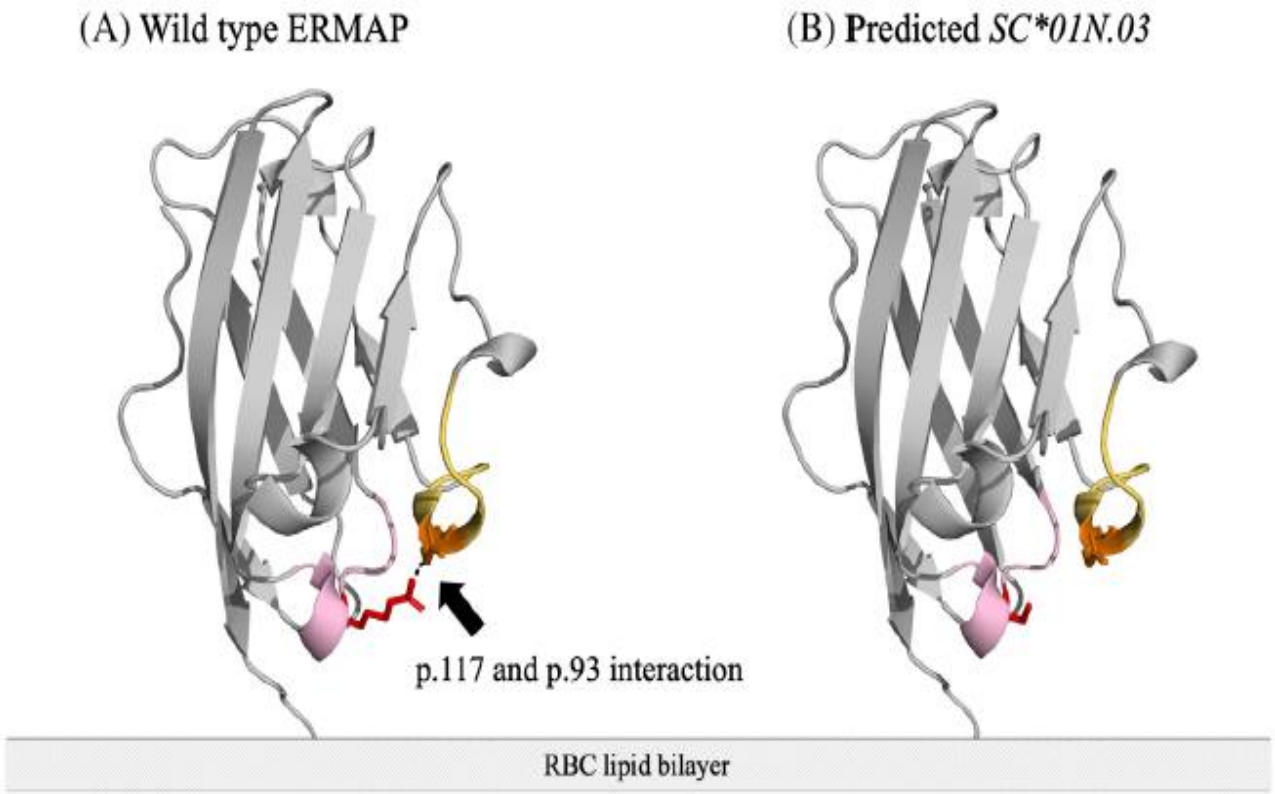
Floch, A et al. (2023)

Sc3 p.ARG117Cys Disrupts Intraprotein Interactions

- Residues 117 (red) and 93 (orange) share three interactions (arrow and dotted line) in the wild-type ERMAP, but no interactions are predicted in the variant.

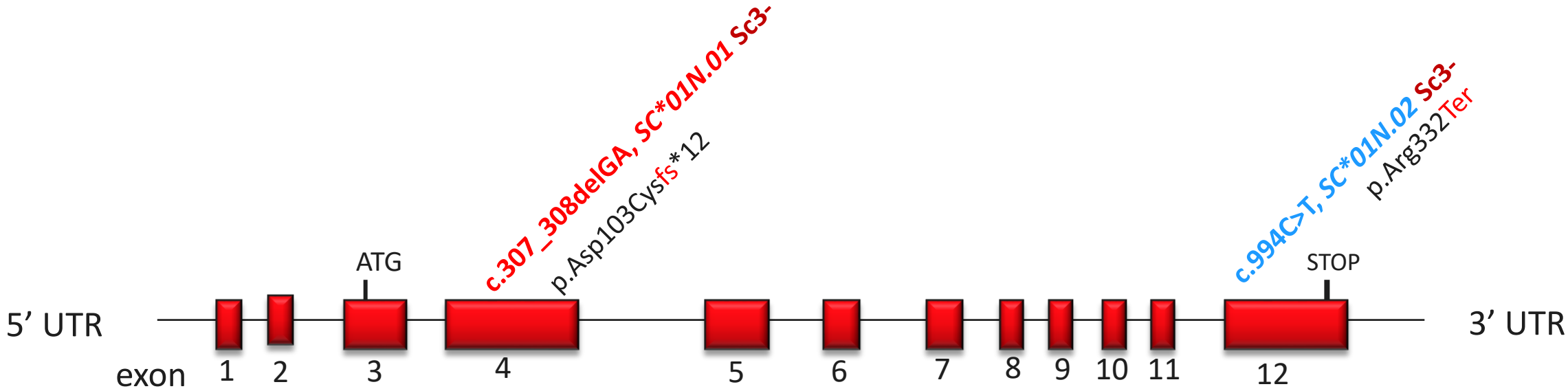
- Hypothesized that loss of intraprotein interaction prevents correct folding and/or destabilizes the domain.

What about other null antigens?
(*SC*01N.01* and *SC*01N.02*)



Floch, A et al. (2023)

Genetic Basis of SC Polymorphisms



- Unlike *SC*01N.03* reported by NY (described on previous slide):
  - *SC*01N.01* and *SC*01N.02* variants both result in a truncated non-functional protein

Call back to case study: <u>Case study patient was *SC*01N.02/ SC*01N.02*</u>

Summary: Scianna Structure and Function

- ***ERMAP*** **is located on chromosome 1 and encodes the Sc protein.**
- ***ERMAP*** **transcriptional activation is directly regulated by factors including:**
    - **Gata1, Klf1, Tal1, and Ldb1 (all known to play key roles in erythroid differentiation)**
- ***ERMAP*** **is highly expressed in both bone marrow and thyroid.**
- **ERMAP/SC protein is a single pass transmembrane protein with putative roles in erythroid development and immune signaling/modulation.**
- **Scianna antigens are mapped to SNVs occurring in the highly conserved IgV extracellular domain.**

Objectives

- Discuss Scianna blood group history.
- Discuss Scianna in Transfusion Medicine by reviewing a recent case study at Community Blood Center and St. Luke's Hospital.
- Describe structure and function of the Scianna protein and associated genomics.

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Thank You!