Lutheran Blood Group System

Number of antigens 20

Polymorphic	Lu[a], Au[a], Au[b]
Low prevalence	Lu9, Lu14
High prevalence	Lub, Lu3, Lu4, Lu5, Lu6, Lu7, Lu8, Lu11, Lu12, Lu13, Lu16, Lu17, Lu20, Lu21, LURC

Terminology

ISBT symbol (number)	LU (005)
CD number	CD239
Other name	B-CAM (Basal-cell adhesion molecule)
History	The first Lutheran antigen was described in 1945, and should have been named Lutteran, after the first Lu(a+) donor, but the writing on the label of the blood sample was misread as Lutheran.

Expression

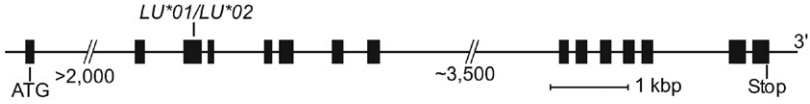
Soluble form	Not described in a natural form
Other blood cells	Not on lymphocytes, granulocytes, monocytes, platelets
Tissues	Predominantly in the basal layer of the epithelium and endothelium of blood vessels, and in a broad range of cells and tissues: brain, heart, kidney glomeruli, liver, lung, pancreas, placenta, skeletal muscle, arterial wall, tongue, trachea, skin, esophagus, cervix, ileum, colon, stomach, gall bladder[1]

Gene[2]

Chromosome	19q13.32
Name	*LU*
Organization	15 exons distributed over approximately 12 kbp of DNA

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00007-7

Product	Lutheran glycoprotein (597 amino acids) and B-CAM (557 amino acids) by alternative splicing of exon 13[1,3]



Database accession numbers

GenBank	NM_005581 (mRNA); X83425 (gene)
Entrez Gene ID	4059

Molecular basis of Lutheran phenotypes

The reference allele, *LU*02* or *LU*B* (Accession number X83425) encodes Lu^b (LU2), LU3, LU4, LU5, LU6, LU8, LU12, LU13, LU16, LU17, LU18, LU20, LU21, LURC. Nucleotide differences from this reference allele, and the amino acids affected, are given.

Allele encodes	Allele name	Exon	Nucleotide	Restriction enzyme	Amino acid	Ethnicity (prevalence)
Lu(a+) or LU:1	*LU*01* or *LU*A*	3	230G>A[†]	*Aci*I–	Arg77His	Caucasian (Many), Blacks (Several)
Lu(a+) or LU:1	*LU*01.02* or *LU*A*	3 5	230G>A 586G>A		Arg77His Val196His	
LU:–4	*LU*02.–04.1*	5	524G>A	*Hpa*II–	Arg175Gln	Caucasian (Rare)
LU:–4	*LU*02.–04.2*	5	524G>T	HpaII–	Arg175Leu	Caucasian (Rare)
LU:–5	*LU*02.–05*	3	326G>A	DraIII+	Arg109His	Caucasian (Several)
LU:–7	*LU*02.–07*	10	127A>C	*Mni*I–	Glu425Ala	Caucasian (Rare)
LU:–6,9	*LU*02.09*	7	824C>T	*Cfo*I+	Ser275Phe	Iranian Jews (Rare)
LU:–8,14	*LU*02.14*	6	611T>A	*Nla*III–	Met204Lys	Caucasian (Several)
LU:–12	*LU*02.–12.1*	2	99–104del GCGCTT	*Hsp*AI–	delArg34, Leu35	Caucasian (Rare)

(*Continued*)

(Continued)

Allele encodes	Allele name	Exon	Nucleotide	Restriction enzyme	Amino acid	Ethnicity (prevalence)
LU:–12	*LU*02.–12.2*	3	419G>A	*Bst*UI–	Arg140Gln	Caucasian (Rare)
LU:–13	*LU*02.–13*	11 13	1340C>T 1742A>T	*Msp*AI–	Ser447Leu Gln581Leu	(Rare)
LU:–16	*LU*01.–16*	6	679C>T	*Nla*IV–	Arg227Cys	Blacks (Rare)
LU:–17	*LU*02.–17*	3	340G>A	*Bbv*CI–	Glu114Lys	Italians (Rare)
Au(a–b+) or LU:18,19	*LU*02.19*	12	1615A>G		Thr539Ala	Caucasian, Blacks (Many)
LU:–20	*LU*02.–20*	7	905C>T	*Acc*I–	Thr302Met	Israeli (Rare)
LU:–21	*LU*02.–21*	3	282C>G	*Bss*SI+	Asp94Glu	Israeli (Rare)
LURC– or LU:–22^	*LU*01.–22*	2	223C>T	*Sac*I–	Arg75Cys	(Rare)

†Also associated with 586G>A in exon 5 (Val96Ile)[4].
^Expression of LURC is dependant on Arg77[5].

Molecular basis of silencing of *LU*

Homozygosity or compound heterozygosity leads to the recessive Lu(a–b–) phenotype. Nucleotide changes from the *LU*02* reference allele (Accession number X83425), and the amino acid affected, are given.

Allele name	Exon	Nucleotide	Restriction enzyme	Amino acid	Ethnicity (prevalence)
*LU*02N.01*	6	691C>T	*Dde*I+	Arg231Stop	Caucasian (Rare)
*LU*02N.02*	3 4	322intron2 to exon4del		Thr69-Glu168 del	Caucasian (Rare)
*LU*02N.03*	6	711C>A	*Dde*I+ and *Cfo*I–	Cys237Stop	Japanese (Rare)
*LU*02N.04*	3	361C>T		Arg121Stop	Caucasian (Rare)
*LU*02N.05*	2	Ins123GG		42Gly-Arg-Stop[6]	Caucasian (Dutch)

Molecular basis of dominant Lu(a–b–) phenotype [In(Lu)]

KLF1 encodes erythroid Krüppel-like factor (EKLF). Heterozygosity for one of several nucleotide changes in this gene are responsible for the dominant Lu(a–b–) phenotype[7,8], which is also known as the *In*(*Lu*) phenotype, and is characterized by reduced expression of antigens in the Lutheran system and for P1, In^b, and AnWj antigens. The KLF1 gene is located at 19p13.13–p13.12 and has 3 exons; the initiation codon is in exon 1 and the stop codon is in exon 3. GenBank accession numbers are U37106 (gene) and NM_006563 (mRNA); Entrez Gene ID 10661. Nucleotide changes from the *KLF1*01* reference allele (Accession number NM_006563), and the amino acid affected, are given. Heterozygosity leads to the dominant Lu(a–b–) phenotype whilst homozygosity for is not thought to be compatible with life.

Allele name	Exon (intron)	Nucleotide	Amino acid	Ethnicity (prevalence)
*KLF1*BGM01*	Promoter	−124T>C		(Rare)
*KLF1*BGM02*	2	380T>A	Leu127Stop	(Rare)
*KLF1*BGM03*	2	569delC	Pro190LeufsStop	(Rare)
*KLF1*BGM04*	2	874A>T	Lys292Stop	(Rare)
*KLF1*BGM05*	2	895C>T	His299Tyr	(Rare)
*KLF1*BGM06*	3	954dupG	Arg319GlufsStop	(Rare)
*KLF1*BGM07*	3	983G>T	Arg328Leu	(Rare)
*KLF1*BGM08*	3	983G>A	Arg328His	(Rare)
*KLF1*BGM09*	3	991C>G	Arg331Gly	(Rare)
*KLF1*BGM11*	1	90G>A	Trp30Stop	(Rare)
*KLF1*BGM12*	2	304T>C	Ser102Pro	(Rare)

Molecular basis of X-linked Lu(a–b–) phenotype (Lu_{mod} phenotype)

The X-borne transcription factor, GATA-1, is essential for erythroid and megakaryocyte development. A nucleotide change in this gene causes the X-linked Lu(a–b–) phenotype[9].

The gene (Accession number NG_008846; X17254; Entrez Gene ID 2623) is located at Xp11.23 and has 6 exons; the initiation codon is in exon 2 and the stop codon is in exon 6.
Nucleotide change from the *GATA1*01* reference allele (NM_002049), and the amino acid affected, are given.

Allele name	Exon	Nucleotide	Restriction enzyme	Amino acid	Ethnicity (prevalence)
*GATA1*BGM01*	6	1240T>C	*Bsp*HI	Stop414Arg^	Australian (Rare)

^ = The Stop codon becomes arginine, which leads to an elongated protein product.

Amino acid sequence[2]

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MEPPDAPAQA  RGAPRLLLLA  VLLAAHPDAQ  AEVRLSVPPL  VEVMRGKSVI   50
LDCTPTGTHD  HYMLEWFLTD  RSGARPRLAS  AEMQGSELQV  TMHDTRGRSP  100
PYQLDSQGRL  VLAEAQVGDE  RDYVCVVRAG  AAGTAEATAR  LNVFAKPEAT  150
EVSPNKGTLS  VMEDSAQEIA  TCNSRNGNPA  PKITWYRNGQ  RLEVPVEMNP  200
EGYMTSRTVR  EASGLLSLTS  TLYLRLRKDD  RDASFHCAAH  YSLPEGRHGR  250
LDSPTFHLTL  HYPTEHVQFW  VGSPSTPAGW  VREGDTVQLL  CRGDGSPSPE  300
YTLFRLQDEQ  EEVLNVNLEG  NLTLEGVTRG  QSGTYGCRVE  DYDAADDVQL  350
SKTLELRVAY  LDPLELSEGK  VLSLPLNSSA  VVNCSVHGLP  TPALRWTKDS  400
TPLGDGPMLS  LSSITFDSNG  TYVCEASLPT  VPVLSRTQNF  TLLVQGSPEL  450
KTAEIEPKAD  GSWREGDEVT  LICSARGHPD  PKLSWSQLGG  SPAEPIPGRQ  500
GWVSSSLTLK  VTSALSRDGI  SCEASNPHGN  KRHVFHFGAV  SPQTSQAGVA  550
VMAVAVSVGL  LLLVVAVFYC  VRRKGGPCCR  QRREKGAPPP  GEPGLSHSGS  600
EQPEQTGLLM  GGASGGARGG  SGGFGDEC                           628
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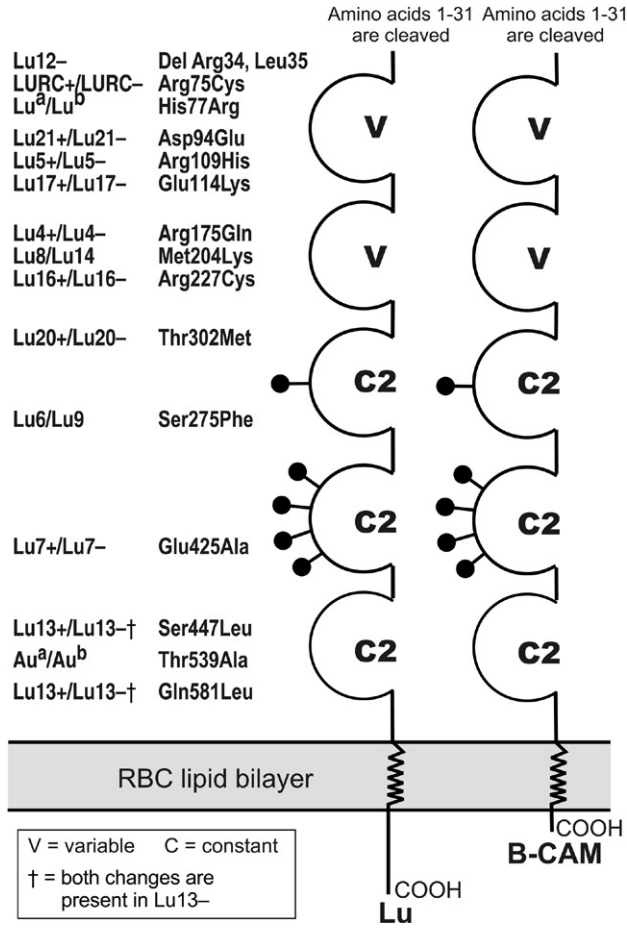
LU encodes a signal peptide of 31 amino acids which is cleaved off to form the mature protein found in the red cell membrane.

Carrier molecule

The predicted mature protein has five disulfide-bonded, extracellular, immunoglobulin superfamily (IgSF) domains (two variable-region (V) sets and three constant region (C) sets)[1].



M_r (SDS-PAGE)	Lu: 85,000 (has a cytoplasmic tail) B-CAM: 78,000 (has no cytoplasmic tail)
CHO: N-glycan	5 potential sites (residues 290, 346, 352, 388, 408)
CHO: O-glycan	Present
Cysteine residues	10 extracellular
Copies per RBC	1,500 to 4,000

Function

Possibly has adhesion properties and may mediate intracellular signaling. The extracellular domains and the cytoplasmic domain contain consensus motifs for the binding of integrin and Src homology 3 domains, respectively, suggesting possible receptor and signal-transduction function[1]. Lutheran glycoprotein binds to laminin (particularly to isoforms that contain α5 chains), strongly suggesting

that it is a membrane constituent that is involved in cell–cell and cell–matrix binding events, and may function as a laminin receptor during erythropoiesis[10]. IgSF domains 1 to 3, and possibly domain 5, are involved in laminin binding[11–13]. Lu-glycoproteins may be involved in facilitating movement of maturing erythroid cells from erythroblastic islands of the bone marrow to the peripheral circulation, and may play a role in the migration of erythroid progenitors from fetal liver to the bone marrow.

Disease association

Expression of B-CAM is increased in certain malignant tumors and cells. May mediate adhesion of sickle cells to vascular endothelium, and contribute to blockage of the vessels and painful episodes of vaso-occlusion. In polycythemia vera, the Lu-glycoproteins are phosphorylated which increases RBC adhesion, and may promote thrombosis in polycythemia vera.

Phenotypes (% occurrence)

Phenotype	Most populations
Lu(a+b–)	0.2
Lu(a–b+)	92.4
Lu(a+b+)	7.4
Lu(a–b–)	Rare
Null: Lu(a–b–) recessive type	
Unusual: Lu(a–b–) dominant type and X-linked type	

Comparison of three types of Lu(a–b–) phenotypes

Lu(a–b–) phenotype	Lutheran antigens	Make anti-Lu3	CD44	CD75	I/i antigen
Recessive	Absent	Yes	Normal	Normal	Normal/normal
Dominant	Weak	No, except in one case[1]	Weak (25–39% of normal)	Strong	Normal/weak
X-linked	Weak	No	Normal	Absent	Weak/strong

Comments

Lu(a–b–) dominant type RBCs have reduced expression of Lutheran, P1, AnWj, Indian, Knops, Cs^a, and MER2 blood group antigens. The X-linked type (*XS2*) of Lu(a–b–) has only been found in one family.
Lutheran, along with *Secretor*, provided the first example of autosomal linkage in humans. Some Lu(a–b–) RBCs are acanthocytic[14].

References

1 Parsons, S.F., et al., 1995. The Lutheran blood group glycoprotein, another member of the immunoglobulin superfamily, is widely expressed in human tissues and is developmentally regulated in human liver. Proc Natl Acad Sci USA 92, 5496–5500.

2 El Nemer, W., et al., 1997. Organization of the human LU gene and molecular basis of the Lu^a/Lu^b blood group polymorphism. Blood 89, 4608–4616.

3 Rahuel, C., et al., 1996. A unique gene encodes spliceoforms of the B-cell adhesion molecule cell surface glycoprotein of epithelial cancer and of the Lutheran blood group glycoprotein. Blood 88, 1865–1872.

4 Gowland, P., et al., 2005. A new polymorphism within the Lua/Lub blood group [abstract]. Transf Med Hemother 32 (Suppl. 1), 54–55.

5 Karamatic Crew, V., et al., 2009a. Two heterozygous mutations in an individual result in the loss of a novel high incidence Lutheran antigen Lurc [abstract]. Transfus Med 19 (Suppl. 1), 10.

6 Karamatic Crew, V., et al., 2009b. A novel LU mutation giving rise to a new example of the recessive type Lutheran-null phenotype [abstract]. Transfus Med 19 (Suppl. 1), 24.

7 Crowley, J., et al., 2010. Novel mutations in *EKLF/KLF1* encoding In(Lu) phenotype [abstract]. Transfusion 50 (Suppl. 47A).

8 Singleton, B.K., et al., 2008. Mutations in EKLF/KLF1 form the molecular basis of the rare blood group In(Lu) phenotype. Blood 112, 2081–2088.

9 Singleton, B.K., et al., 2009. A novel GATA-1 mutation (Ter414Arg) in a family with the rare X-linked blood group Lu(a–b–) phenotype [abstract]. Blood 114, 783.

10 El Nemer, W., et al., 1998. The Lutheran blood group glycoproteins, the erythroid receptors for laminin, are adhesion molecules. J Biol Chem 273, 16686–16693.

11 El Nemer, W., et al., 2001. Characterization of the laminin binding domains of the Lutheran blood group glycoprotein. J Biol Chem 276, 23757–23762.

12 Udani, M., et al., 1998. Basal cell adhesion molecule Lutheran protein: The receptor critical for sickle cell adhesion to laminin. J Clin Invest 101, 2550–2558.

13 Zen, Q., et al., 1999. Critical factors in basal cell adhesion molecule/Lutheran-mediated adhesion to laminin. J Biol Chem 274, 728–734.

14 Udden, M.M., et al., 1987. New abnormalities in the morphology, cell surface receptors, and electrolyte metabolism of In(Lu) erythrocytes. Blood 69, 52–57.

Lu^a Antigen

Terminology

ISBT symbol (number)	LU1 (005001 or 5.1)
History	Identified in 1945; named after the donor whose blood stimulated the production of anti-Lu^a in a patient with SLE who had received multiple transfusions.

Occurrence

Caucasians	8%
Blacks	5%

Antithetical antigen

Lu^b (**LU2**)

Expression

Cord RBCs	Weak

There is considerable variation in the strength of Lu^a expression on RBCs. This variation is inherited.

Molecular basis associated with Lu^a antigen[1,2]

Amino acid	His77 in IgSF domain 1
Nucleotide	A at bp 230 in exon 3

*LU*A* also encodes Val196Ile in IgSF domain 2 (586G>A in exon 5)[3].

Effect of enzymes and chemicals on Lu^a antigen on intact RBCs

Ficin/Papain	Resistant (may be weakened)
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)
Acid	Resistant

In vitro characteristics of alloanti-Lu^a

Immunoglobulin class	IgM; IgG
Optimal technique	RT or IAT with characteristic "loose" agglutinates surrounded by unagglutinated RBCs; capillary
Complement binding	Rare

Clinical significance of alloanti-Lu^a

Transfusion reaction	No
HDFN	No to mild (rare). The presence of fetal Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens.

Comments

Anti-Lu^a is not infrequently found in serum from patients following transfusion, and also may be naturally-occurring. Sera containing anti-Lu^a often also contain HLA antibodies.

References

[1] El Nemer, W., et al., 1997. Organization of the human LU gene and molecular basis of the Lu^a/Lu^b blood group polymorphism. Blood 89, 4608–4616.

[2] Parsons, S.F., et al., 1997. Use of domain-deletion mutants to locate Lutheran blood group antigens to each of the five immunoglobulin superfamily domains of the Lutheran glycoprotein: Elucidation of the molecular basis of the Lu^a/Lu^b and the Au^a/Au^b polymorphisms. Blood 89, 4219–4225.

[3] Gowland, P., et al., 2005. A new polymorphism within the Lu^a/Lu^b blood group [abstract]. Transf Med Hemother 32 (Suppl. 1), 54–55.

Lu^b Antigen

Terminology

ISBT symbol (number)	LU2 (005002 or 5.2)
History	Named because of its antithetical relationship to Lu^a; anti-Lu^b was identified in 1956.

Occurrence

All populations	99.8%

Antithetical antigen

Lu^a (**LU1**)

Expression

Cord RBCs	Weak
Altered	Weak on RBCs of the dominant type of Lu(a–b–)

There is considerable variation in the strength of Lu^b expression on RBCs. This variation is inherited.

Molecular basis associated with Lu^b antigen[1,2]

Amino acid	Arg77 in IgSF domain 1
Nucleotide	G at bp 230 in exon 3

Effect of enzymes and chemicals on Lu^b antigen on intact RBCs

Ficin/Papain	Resistant (may be weakened)
Trypsin	Sensitive
α-Chymotrypsin	Sensitive

Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)
Acid	Resistant

In vitro characteristics of alloanti-Lu^b

Immunoglobulin class	IgG; IgM
Optimal technique	RT; IAT; capillary
Complement binding	Rare

Clinical significance of alloanti-Lu^b

Transfusion reaction	Mild to moderate
HDFN	Mild; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Weak expression of Lu^b on dominant type Lu(a–b–) RBCs is detectable by absorption/elution.

Siblings of patients with anti-Lu^b should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

References

[1] El Nemer, W., et al., 1997. Organization of the human LU gene and molecular basis of the Lu^a/Lu^b blood group polymorphism. Blood 89, 4608–4616.

[2] Parsons, S.F., et al., 1997. Use of domain-deletion mutants to locate Lutheran blood group antigens to each of the five immunoglobulin superfamily domains of the Lutheran glycoprotein: elucidation of the molecular basis of the Lu^a/Lu^b and the Au^a/Au^b polymorphisms. Blood 89, 4219–4225.

Lu3 Antigen

Terminology

ISBT symbol (number)	LU3 (005003 or 5.3)
Obsolete names	Lu^{ab}; Lu^{a}Lu^b
History	Reported in 1963; renamed Lu3 to be computer-friendly after Lu(a–b–) RBCs were shown to lack other high prevalence antigens in the Lutheran system. Dr. Crawford, a blood banker, found her own RBCs to be of the dominant type of Lu(a–b–).

Occurrence

All populations	100%

Expression

Cord RBCs	Weak
Altered	Weak or non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with the LU:–3 phenotype

See System pages for molecular basis of LU:–3 phenotype.

Effect of enzymes and chemicals on Lu3 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)
Acid	Resistant

In vitro characteristics of alloanti-Lu3

Immunoglobulin class	IgG
Optimal technique	IAT
Complement binding	Rare

Clinical significance of alloanti-Lu3

No data are available because anti-Lu3 is rare.

Comments

Anti-Lu3 is only made by immunized individuals of the rare recessive type Lu(a–b–). In these cases, Lu(a–b–) blood of the recessive or dominant type can be used for transfusion. One person with the dominant type Lu(a–b–) has made anti-Lu3[1].

Siblings of patients with anti-Lu3 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

Reference

[1] Crowley, J., et al., 2010. Novel mutations in *EKLF/KLF1* encoding In(Lu) phenotype [abstract]. Transfusion 50 (Suppl. 47A).

Lu4 Antigen

Terminology

ISBT symbol (number)	LU4 (005004 or 5.4)
Obsolete name	Barnes
History	The first of a series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs. Described in 1971.

Occurrence

Only one family with the LU:–4 phenotype has been reported.

Expression

Cord RBCs	Weak
Altered	Weak or non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu4 antigen[1]

Amino acid	Arg175 in IgSF domain 2
Nucleotide	G at bp 524 in exon 5
Lu4−	Gln175 and A at bp 524

Effect of enzymes and chemicals on Lu4 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu4

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu4

Transfusion reaction	No data are available because only one anti-Lu4 has been described
HDFN	No in two infants born to one LU:–4 female. The presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens.

Comments

Siblings of patients with anti-Lu4 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu5 Antigen

Terminology

ISBT symbol (number)	LU5 (005005 or 5.5)
Obsolete names	Beal; Fox
History	Identified in 1972; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

All populations	100%

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu5 antigen[1]

Amino acid	Arg109 in IgSF domain 1
Nucleotide	G at bp 326 in exon 3
Lu5–	His109 and A at bp 326

Effect of enzymes and chemicals on Lu5 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu5

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu5

Transfusion reaction	No (potentially significant by a chemiluminescent assay)
HDFN	No; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Several examples of immune anti-Lu5 have been reported.
Siblings of patients with anti-Lu5 should be tested for compatibility and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu6 Antigen

Terminology

ISBT symbol (number)	LU6 (005006 or 5.6)
Obsolete names	Jan; Jankowski
History	Identified in 1972; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

All populations	100%

Three LU:–6 were Iranian Jews[1].

Antithetical antigen

Lu9 (**LU9**)

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu6 antigen[2]

Amino acid	Ser275 in IgSF domain 3
Nucleotide	C at bp 824 in exon 7

Effect of enzymes and chemicals on Lu6 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/Resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu6

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu6

Transfusion reaction	No to moderate
HDFN	No; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Siblings of patients with anti-Lu6 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

References

[1] Yahalom, V., et al., 2002. The rare Lu:–6 phenotype in Israel and the clinical significance of anti-Lu6. Transfusion 42, 247–250.

[2] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu7 Antigen

Terminology

ISBT symbol (number)	LU7 (005007 or 5.7)
Obsolete name	Gary
History	Identified in 1972; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

Only two Lu7– probands have been reported.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu7 antigen

Amino acid	Glu425 in IgSF domain 4
Nucleotide	A at bp 1274 in exon 10
Lu7–	Ala425 and C at bp 1274

Effect of enzymes and chemicals on Lu7 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200mM/50mM	Presumed sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu7

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu7

Transfusion reaction	No to mild
HDFN	No; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Only two examples of anti-Lu7 have been described.
Siblings of patients with anti-Lu7 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Lu8 Antigen

Terminology

ISBT symbol (number)	LU8 (005008 or 5.8)
Obsolete names	Taylor; MT
History	Identified in 1972; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

All populations	100%

Several Lu8– probands have been described.

Antithetical antigen

Lu14 (**LU14**)

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu8 antigen[1]

Amino acid	Met204 in IgSF domain 2
Nucleotide	T at bp 611 in exon 6

Effect of enzymes and chemicals on Lu8 antigen on intact RBCs

Ficin/Papain	Variable
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu8

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu8

Transfusion reaction	No to mild
HDFN	No; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Siblings of patients with anti-Lu8 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu9 Antigen

Terminology

ISBT symbol (number)	LU9 (005009 or 5.9)
Obsolete name	Mull
History	Reported in 1973; given the next available number when its antithetical relationship to Lu6 was recognized.

Occurrence

Reported as 1 to 2%, but probably lower because the original anti-Lu9 contained anti-Bg^{a}.

Antithetical antigen

Lu6 (**LU6**)

Expression

Cord RBCs	Weak

Molecular basis associated with Lu9 antigen[1]

Amino acid	Phe275 in IgSF domain 3
Nucleotide	T at bp 824 in exon 7

Effect of enzymes and chemicals on Lu9 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Presumed sensitive/resistant (thus sensitive to WARM™ and ZZAP)
Acid	Resistant

In vitro characteristics of alloanti-Lu9

Immunoglobulin class	IgG
Optimal technique	IAT, capillary

Clinical significance of alloanti-Lu9

Transfusion reaction	No data; the second example was probably stimulated by transfusion[2]
HDFN	Positive DAT, but no clinical HDFN in the only case; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

References

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

[2] Champagne, K., et al., 1999. Anti-Lu9: the finding of the second example after 25 years. Immunohematology 15, 113–116.

Lu11 Antigen

Terminology

ISBT symbol (number)	LU11 (005011 or 5.11)
Obsolete name	Reynolds
History	Identified in 1974; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

All populations	100%

Several Lu11– probands have been described.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Effect of enzymes and chemicals on Lu11 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Presumed sensitive
α-Chymotrypsin	Presumed sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Presumed sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu11

Immunoglobulin class	IgM and IgG
Optimal technique	RT and IAT

Clinical significance of alloanti-Lu11

Transfusion reaction	No to mild (not much data)
HDFN	No (not much data)

Comments

Few anti-Lu11 have been reported and are typically very weakly reactive. There is no evidence that Lu11 is inherited or carried on the Lutheran glycoprotein.

Lu12 Antigen

Terminology

ISBT symbol (number)	LU12 (005012 or 5.12)
Obsolete names	Muchowski; Much
History	Identified in 1973; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

Only two Lu12– probands have been reported.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with absence of Lu12 antigen[1]

Amino acid	Deletion of Arg34 and Leu35 in IgSF domain 1
Nucleotide	99_104delGCGCTT in exon 2

Effect of enzymes and chemicals on Lu12 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu12

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu12

No data are available because only two examples of anti-Lu12 have been reported.

Comments

Siblings of patients with anti-Lu12 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu13 Antigen

Terminology

ISBT symbol (number)	LU13 (005013 or 5.13)
Obsolete name	Hughes
History	Reported in 1983; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

All populations	100%

Only a few probands have been reported.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu13 antigen[1]

Amino acid	Ser447 in IgSF domain 5 and Gln581 in transmembrane domain
Nucleotide	C at bp 1340 in exon 11 and A at bp 1742 in exon 13
Lu13–	Leu447; Leu581, and T at bp 1340; T at bp 1742

Effect of enzymes and chemicals on Lu13 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu13

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu13

No data are available because only four examples of anti-Lu13 are known.

Comments

Siblings of patients with anti-Lu13 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu14 Antigen

Terminology

ISBT symbol (number)	LU14 (005014 or 5.14)
Obsolete name	Hofanesian
History	Reported in 1977; given the next available number when its antithetical relationship to Lu8 was recognized.

Occurrence

English	1.8%
Danes	1.5%

Antithetical antigen

Lu8 (**LU8**)

Expression

Cord RBCs	Presumed weak

Molecular basis associated with Lu14 antigen[1]

Amino acid	Lys204 in IgSF domain 2
Nucleotide	T at bp 611 in exon 6

Effect of enzymes and chemicals on Lu14 antigen on intact RBCs

Ficin/Papain	Variable
Trypsin	Presumed sensitive
α-Chymotrypsin	Presumed sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu14

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu14

Transfusion reaction	No data
HDFN	Positive DAT; HDFN in one case; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu16 Antigen

Terminology

ISBT symbol (number)	LU16 (005016 or 5.16)
History	Reported in 1980 when three Lu(a+b–) black women were found to have an antibody to a high prevalence antigen in addition to anti-Lu^b.

Occurrence

Only four Lu16– probands have been reported, all were of African-American heritage.

Molecular basis associated with Lu16 antigen[1]

Amino acid	Arg227 in IgSF domain 2
Nucleotide	C at bp 679 in exon 6
Lu16–	Cys227 and T at bp 679

In vitro characteristics of alloanti-Lu16

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu16

Transfusion reaction	No data
HDFN	No

Comments

Siblings of patients with anti-Lu16 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu17 Antigen

Terminology

ISBT symbol (number)	LU17 (005017 or 5.17)
Obsolete names	Delcol, nee: Pataracchia
History	Reported in 1979; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

Only one Lu17– proband, Italian, has been reported.

Expression

Cord RBCs	Expressed
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu17 antigen[1]

Amino acid	Glu114 in IgSF domain 1
Nucleotide	G at bp 340 in exon 3
Lu17–	Lys114 and A at bp 340

Effect of enzymes and chemicals on Lu17 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu17

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Lu17

Transfusion reaction	*In vivo* RBC survival study suggested that anti-Lu17 might cause modest destruction of transfused RBCs
HDFN	The only anti-Lu17 was made by a woman with four uneventful pregnancies; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Siblings of patients with anti-Lu17 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.

Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Au^a Antigen

Terminology

ISBT symbol (number)	LU18 (005018 or 5.18)
Obsolete names	Auberger; 204001

History	Named in 1961 after the first producer of anti-Au^a, a multi-transfused woman; placed into the Lutheran blood group system in 1990.

Occurrence

All populations	90% (originally the prevalence was reported as 82%)

Antithetical antigen

Au^b (**LU19**)

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

There is considerable variation in the strength of Au^a expression on RBCs. This variation is inherited.

Molecular basis associated with Au^a antigen[1]

Amino acid	Thr539 in IgSF domain 5
Nucleotide	A at bp 1615 in exon 12

Effect of enzymes and chemicals on Au^a antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Au^a

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Au^a

Transfusion reaction	No to mild
HDFN	No; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Only three examples of anti-Au^a have been reported, all in sera containing other antibodies[2].

Due to the scarcity of anti-Au^a, DNA analysis may be used to predict the antigen status.

References

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

[2] Drachmann, O., et al., 1982. Serological characteristics of the third anti-Au^a. Vox Sang 43, 259–262.

Au^b Antigen

Terminology

ISBT symbol (number)	LU19 (005019 or 5.19)
Obsolete name	204002
History	Reported in 1989 and named because it is antithetical to Au^a.

Occurrence

Caucasians	51%
Blacks	68%

Antithetical antigen

Au^a (**LU18**)

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

There is considerable variation in the strength of Au^b expression on RBCs. This variation is inherited.

Molecular basis associated with Au^b antigen[1]

Amino acid	Ala539 in IgSF domain 5
Nucleotide	G at bp 1615 in exon 12

Effect of enzymes and chemicals on Au^b antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
Pronase	Sensitive
DTT 200 mM/50 mM	Presumed sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Au^b

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-Au^b

Transfusion reaction	No to mild
HDFN	No; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Four examples of anti-Au^b have been reported, all in sera also containing anti-Lu^a.
Due to the scarcity of anti-Au^b, DNA analysis may be used to predict the antigen status.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu20 Antigen

Terminology

ISBT symbol (number)	LU20 (005020 or 5.20)
History	Reported in 1992, antibody made by an Israeli thalassemic; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

Only one Lu20– proband, an Israeli, has been reported.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu20 antigen[1]

Amino acid	Thr302 in IgSF domain 3
Nucleotide	C at bp 905 in exon 7
Lu20–	Met302 and T at bp 905

Effect of enzymes and chemicals on Lu20 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu20

Immunoglobulin class	IgG
Optimal technique	37ºC; IAT

Clinical significance of alloanti-Lu20

Not known since only one example of anti-Lu20 has been described.

Comments

Siblings of patients with anti-Lu20 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

Lu21 Antigen

Terminology

ISBT symbol (number)	LU21 (005021 or 5.21)
History	Reported in 2002; given the next number in the series of Lu(a–b+) people who made an antibody compatible only with Lu(a–b–) RBCs.

Occurrence

Only one Lu21– proband, an Israeli, has been reported.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with Lu21 antigen[1]

Amino acid	Asp94 in IgSF domain 1
Nucleotide	C at bp 282 in exon 3
Lu21–	Glu94 and G at bp 282

Effect of enzymes and chemicals on Lu21 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-Lu21

Immunoglobulin class	IgG; IgM
Optimal technique	IAT; RT and 37°C

Clinical significance of alloanti-Lu21

Transfusion reaction	No data
HDFN	No in the proband's 2nd, 3rd, and 4th pregnancies; the presence of Lutheran glycoprotein on placental tissue may result in absorption of maternal antibodies to Lutheran antigens

Comments

Siblings of patients with anti-Lu21 should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

Reference

[1] Crew, V.K., et al., 2003. Molecular bases of the antigens of the Lutheran blood group system. Transfusion 43, 1729–1737.

LURC Antigen

Terminology

ISBT symbol (number)	LURC (005022 or 5.22)
History	Reported in 2009 and named "LU" for the system and "RC" for the amino acid change (Arg to Cys) in the antigen-negative phenotype.

Occurrence

Only one LURC– proband has been described.

Expression

Cord RBCs	Weak
Altered	Non-detectable by hemagglutination on RBCs of the dominant type of Lu(a–b–)

Molecular basis associated with LURC antigen[1]

Amino acid	Arg75 in IgSF domain 1
Nucleotide	C at bp 223 in exon 3
LURC–	Cys75 and T at bp 223

The LURC– proband was heterozygous for *LU*230A/G* (*LU*01/LU*02*) and *LU*586G/A* (a polymorphism described by Gowland, et al.[2], as well as for the *LU*223C/T* (*LU*02.22/LU*02.–22*)[1]. The presence of Lu^b (Arg77) is required for expression of LURC. LURC– RBCs have a weak expression of Lu^b and other high prevalence antigens[2].

Effect of enzymes and chemicals on LURC antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
DTT 200 mM/50 mM	Sensitive/resistant (thus sensitive to WARM™ and ZZAP)

In vitro characteristics of alloanti-LURC

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-LURC

No data as only one proband with anti-LURC has been reported.

Comments

Siblings of patients with anti-LURC should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
Experts recommend transfusing Lu(a–b–) blood (dominant or recessive type) if specific antigen-negative blood is not available.

References

[1] Karamatic Crew, V., et al., 2009. Two heterozygous mutations in an individual result in the loss of a novel high incidence Lutheran antigen Lurc [abstract]. Transfus Med 19 (Suppl. 1), 10.

[2] Gowland, P., et al., 2005. A new polymorphism within the Lu^a/Lu^b blood group [abstract]. Transf Med Hemother 32 (Suppl. 1), 54–55.