Indian Blood Group System

Number of antigens 4

Low prevalence	In[a]
High prevalence	In[b], INFI, INJA

Terminology

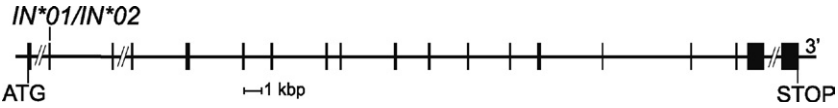
ISBT symbol (number)	IN (023)
CD number	CD44
Obsolete name	ISBT Collection 203
History	Named because the first In(a+) people were from India.

Expression

Other blood cells	Neutrophils, lymphocytes, monocytes
Tissues	Brain, breast, colon epithelium, gastric, heart, kidney, liver, lung, placenta, skin, spleen, thymus, fibroblasts

Gene

Chromosome	11p13
Name	*IN* (*CD44*)
Organization	At least 19 exons distributed over 50 kbp of gDNA (10 exons are variable). The hemopoietic isoform uses exons 1 to 5, 15 to 17, and 19
Product	CD44, Indian glycoprotein, Hermes antigen



Database accession numbers

GenBank	M59040 (mRNA); NG_008937 (gene)
Entrez Gene ID	960

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00025-9

Molecular basis of Indian phenotypes

The reference allele, *IN*02* or *IN*B* (Accession number M59040) encodes In^{b} (IN2), IN3, IN4. Nucleotide differences from this reference allele, and the amino acids affected, are given.

Allele encodes	Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
In(a+b–) or IN:1,–2	*IN*01* or *IN*A*	2 3 6	137G>C 326A>C 716G>A	Arg46Pro Tyr109Ser Gly239Glu	Arabs, Iranians, South Asian Indians (Several), Asians, Blacks, Caucasians (Rare)
INFI– or IN:–3	*IN*02.–03*	3	255C>G	His85Gln	Moroccan (Rare)
INJA– or IN:–4	*IN*02.–04*	5	488C>A	Thr163Lys^	Pakistani (Rare)

^= Originally reported, incorrectly, as Thr163Arg[1].

Molecular basis of IN:–1,–2 phenotype (suppression)

KLF1 encodes erythroid Krüppel-like factor (EKLF). Several nucleotide changes in this gene are responsible for the dominant Lu(a–b–) phenotype, which is also known as the In(lu) phenotype (see Lutheran blood group system). The *KLF1* gene, which is located at 19p13.1–p13.12, 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). Differences from the *KLF1*01* reference allele (Accession number NM_006563), and amino acid affected, are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (Prevalence)
*KLF1*BGM10*	3	973G>A^	Glu325Lys	Rare

^= This change caused dyserythropoietic anemia and suppression of CO, IN, and LW antigens[1,2].

Amino acid sequence[2]

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MDKFWWHAAW  GLCLVPLSLA  QIDLNITCRF  AGVFHVEKNG  RYSISRTEAA    50
DLCKAFNSTL  PTMAQMEKAL  SIGFETCRYG  FIEGHVVIPR  IHPNSICAAN   100
NTGVYILTYN  TSQYDTYCFN  ASAPPEEDCT  SVTDLPNAFD  GPITITIVNR   150
DGTRYVQKGE  YRTNPEDIYP  SNPTDDDVSS  GSSSERSSTS  GGYIFYTFST   200
VHPIPDEDSP  WITDSTDRIP  ATRDQDTFHP  SGGSHTTHES  ESDGHSHGSQ   250
EGGANTTSGP  IRTPQIPEWL  IILASLLALA  LILAVCIAVN  SRRRCGQKKK   300
LVINSGNGAV  EDRKPSGLNG  EASKSQEMVH  LVNKESSETP  DQFMTADETR   350
NLQNVDMKIG  V                                              361
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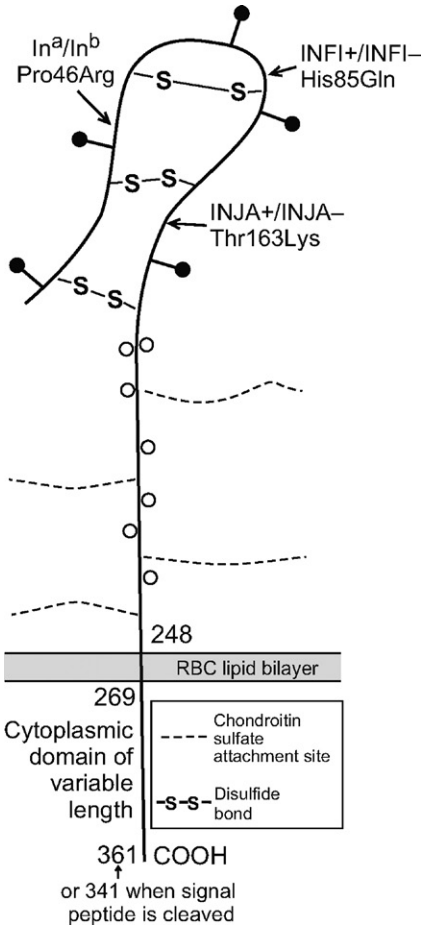
Signal peptide: 20 amino acid residues; which are sometimes cleaved.

Carrier molecule[2,3]

A single pass (type 1) membrane glycoprotein.



M_r (SDS-PAGE)	Reduced 80,000
CHO: N-glycan	6 sites
CHO: O-glycan	Depends on isoform
Chondroitin sulfate	4 sites
Cysteine residues	Depends on isoform
Copies per RBC	2,000 to 5,000 on mature RBCs

Two amino acid domains have been identified as being important in hyaluronate binding: residues 18 to 26, and 130 to 142.

Function

CD44 is an adhesion molecule in lymphocytes, monocytes, and other tumor cells, binds to hyaluronate and other components of the extracellular matrix, and is also involved in immune stimulation and signaling between cells. Its function in RBCs is not known.

Disease association

In(a–b–) individuals with CDA may also be Co(a–b–)[4], and have weak expression of LW antigens.

Joint fluid from patients with inflammatory synovitis has higher than normal levels of soluble CD44[3]. Serum CD44 is elevated in some patients with lymphoma.

Phenotypes (% occurrence)

Phenotype	Caucasians & Blacks	Indians (South Asians)	Iranians & Arabs
In(a+b–)	Rare	Rare	Rare
In(a–b+)	99.9	96	90
In(a+b+)	<0.1	4	10

Comments

CD44 is present in reduced (variable) amounts in dominant type Lu(a–b–) RBCs, but is expressed normally in other cells from these people.

Ser-Gly is a potential chondroitin sulfate linkage site. After Thr202, various sequences can be generated by alternative splicing of at least 10 exons. Different splicing events occur during different stages of hemopoiesis. In mature RBCs, nine exons are usually encoded. A protein of 361 amino acids is the predominant type in the RBC membrane.

References

[1] Poole, J., et al., 2007. Correction to "Two missense mutations in the *CD44* gene encode two new antigens of the Indian blood group system". Transfusion 47, 1306–1311. Transfusion 47, 1741.
[2] Spring, F.A., et al., 1988. The In^a and In^b blood group antigens are located on a glycoprotein of 80,000 MW (the CDw44 glycoprotein) whose expression is influenced by the *In*(*Lu*) gene. Immunology 64, 37–43.
[3] Moulds, J.M., 1994. Association of blood group antigens with immunologically important proteins. In: Garratty, G. (Ed.), Immunobiology of Transfusion Medicine. Marcel Dekker, Inc., New York, NY, pp. 273–297.
[4] Parsons, S.F., et al., 1994. A novel form of congenital dyserythropoietic anemia associated with deficiency of erythroid CD44 and a unique blood group phenotype [In(a−b−), Co(a−b−)]. Blood 83, 860–868.

In^a Antigen

Terminology

ISBT symbol (number)	IN1 (023001 or 23.1)
Obsolete name	203001
History	"In" is an abbreviation of Indian, in honor of the ethnic group in which this antigen was first found.

Occurrence

Caucasians	0.1%
Asians and Blacks	0.1%
Indians (South Asians)	4%
Iranians	10.6%
Arabs	11.8%

Antithetical antigen

In^b (**IN2**)

Expression

Cord RBCs	Weak
Altered	Weak on RBCs from pregnant women

Molecular basis associated with In^a antigen[1]

Amino acid	Pro46
Nucleotide	C at bp 137 in exon 2

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

Ficin/Papain	Sensitive
Trypsin	Sensitive

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

In vitro characteristics of alloanti-In^a

Immunoglobulin class	IgG; IgM
Optimal technique	IAT; RT

Clinical significance of alloanti-In^a

Transfusion reaction	Decreased cell survival
HDFN	Positive DAT; no clinical HDFN

Comments

Anti-In^a can be naturally-occurring.

Reference

[1] Telen, M.J., et al., 1996. A blood group-related polymorphism of CD44 abolishes a hyaluronan-binding consensus sequence without preventing hyaluronan binding. J Biol Chem 271, 7147–7153.

In^b Antigen

Terminology

ISBT symbol (number)	IN2 (023002 or 23.2)
Obsolete names	203002; Salis
History	Named when its antithetical relationship to In^a was identified.

Occurrence

Caucasians	99%
Indians (South Asians)	96%

Antithetical antigen

In^a (**IN1**)

Expression

Cord RBCs	Weak
Altered	Weak on dominant Lu(a–b–) RBCs Weak on RBCs from pregnant women

Molecular basis associated with In^b antigen[1]

Amino acid	Arg46
Nucleotide	G at bp 137 in exon 2

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

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

In vitro characteristics of alloanti-In^b

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-In^b

Transfusion reaction	No to severe/delayed and hemolytic[2]
HDFN	Positive DAT, but no clinical HDFN[3]

References

[1] Telen, M.J., et al., 1996. A blood group-related polymorphism of CD44 abolishes a hyaluronan-binding consensus sequence without preventing hyaluronan binding. J Biol Chem 271, 7147–7153.

[2] Joshi, S.R., 1992. Immediate haemolytic transfusion reaction due to anti-In^b. Vox Sang 63, 232–233.

[3] Longster, G.H., et al., 1981. Four further examples of anti-In^b detected during pregnancy. Clin Lab Haemat 3, 351–356.

INFI Antigen

Terminology

ISBT symbol (number)	IN3 (023003 or 23.3)
History	Reported and named in 2006, "IN" from the Indian system and "FI" from the INFI– proband's name.

Occurrence

The three INFI– probands (found as a result of anti-INFI in pregnancy) were from Morocco.

Expression

Cord RBCs	Weak
Altered	Weak on dominant Lu(a–b–) RBCs
	Weak on RBCs from pregnant women

Molecular basis associated with INFI antigen[1,2]

Amino acid	His85
Nucleotide	C at bp 255 in exon 3
INFI–	Gln85 and G at bp 255

Effect of enzymes and chemicals on INFI antigen on intact RBCs

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

In vitro characteristics of alloanti-INFI

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-INFI

Transfusion reaction	No data because anti-INFI is rare[1,2]
HDFN	The baby of a woman with anti-INFI had mild HDFN

Comments

INFI– RBCs have a weaker than normal expression of In^b.

References

[1] Poole, J., et al., 2007. Two missense mutations in the CD44 gene encode two new antigens of the Indian blood group system. Transfusion 47, 1306–1311.

[2] Poole, J., et al., 2007. Correction to Two missense mutations in the *CD44* gene encode two new antigens of the Indian blood group system. Transfusion 47, 1306–1311. Transfusion 47, 1741.

INJA Antigen

Terminology

ISBT symbol (number)	IN4 (023004 or 23.4)
History	Reported and named in 2006, "IN" from the Indian system and "JA" from the INJA– proband's name.

Occurrence

The two INJA– probands (both found as a result of anti-INJA in pregnancy) were from Pakistan.

Expression

Cord RBCs	Weak
Altered	Weak on dominant Lu(a–b–) RBCs Weak on RBCs from pregnant women

Molecular basis associated with INJA antigen[1,2]

Amino acid	Thr163
Nucleotide	C at bp 488 in exon 5
INJA–	Lys163 (not Arg as originally reported) and A at bp 488

Effect of enzymes and chemicals on INJA antigen on intact RBCs

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

In vitro characteristics of alloanti-INJA

Immunoglobulin class	IgG
Optimal technique	IAT

Clinical significance of alloanti-INJA

No data because only two examples of anti-INJA have been described.

References

[1] Poole, J., et al., 2007. Two missense mutations in the CD44 gene encode two new antigens of the Indian blood group system. Transfusion 47, 1306–1311.

[2] Poole, J., et al., 2007. Correction to "Two missense mutations in the *CD44* gene encode two new antigens of the Indian blood group system". Transfusion 47, 1306–1311. Transfusion 47, 1741.