Lewis Blood Group System

Number of antigens 6

Polymorphic	Le^a, Le^b, Le^{bH}, ALe^b, BLe^b
High prevalence	Le^{ab}

Terminology

ISBT symbol (number)	LE (007)
History	Discovered by Mourant in 1946; named after one of the two original donors in whom anti-Le^a was identified.

Expression

Soluble form	Glycoproteins in saliva and body fluids except CSF plus glycolipids in plasma; the concerted effect of Lewis, ABH, and secretor status determines, what if any, Lewis antigens are present
Other blood cells	Lymphocytes, platelets
Tissues	For instance, pancreas, mucosa of stomach, small and large intestine (large intestine has Le^a only), renal cortex, adrenal glands

Gene

Chromosome	19p13.3
Name	*LE* (*FUT3*)
Organization	3 exons distributed over approximately 8 kbp of gDNA
Product	α(1,3/4) fucosyltransferase

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00009-0

Database accession numbers

GenBank	NM_000149; X53578 (mRNA)
Entrez Gene ID	2525

Molecular basis of Le phenotypes

Lewis determinants are carbohydrates on glycolipids and glycoproteins, and are built on type 1 precursor structures. RBC membranes acquire Lewis glycolipids from circulating lipoproteins. The synthesis of the Lewis antigens is dependent only on *FUT3* which encodes the α(1,3/4) fucosyltransferase (FUT3). However, the type of precursor FUT3 utilizes determines what type of Lewis antigen is made. In individuals **without** the *FUT2* (secretor *SE*) gene which encodes the α(1,2) fucosyltransferase (FUT2) (see H Blood Group System [**018**]) only Le^a can be made by the Lewis FUT3 enzyme. In individuals **with** both the Lewis FUT3 and secretor FUT2 the final products made are determined by their ABO type. If group O, then Le^b is made (with small amounts of Le^a remaining). If group A, then predominantly ALe^b will be made (from A antigen) followed by lesser amounts of Le^b, and trace amounts of Le^a. A similar process occurs for B and AB individuals, but with appropriate A/B antigens resulting. The Le^a antigen cannot be converted into Le^b, hence once made it will remain as Le^a. This is why Le^b positive individuals always have Le^a (which is undetectable with serologically formulated reagents), and why the Le(a+b+) phenotype exists in persons with inefficient FUT2 glycosyltransferases. In individuals not inheriting a functional FUT3, their RBCs will phenotype as Le(a–b–) regardless of the FUT2 status.
As Lewis antigens are adsorbed by RBCs from plasma (not intrinsic) the ISBT has not yet named the alleles in the Lewis system (see dbRBC).

Molecular basis of Le(a+b+) phenotype due to nucleotide changes in *FUT2*

The Le(a+b+) phenotype is caused by mutation(s) in secretor *FUT2*, which changes the generally highly efficient FUT2 enzyme to become less efficient[1]. As a consequence, the Lewis FUT3 enzyme becomes relatively more efficient, and is thus able to compete more effectively for precursor. More Le^a means less H type 1 is made, and less H type 1 results in less Le^b and ABH substances, hence the association of this phenotype with the partial/weak secretor phenotypes.

Molecular basis of Le(a–b–) phenotype due to nucleotide changes in *FUT3* and other genes

More than 30 null alleles at the *FUT3* locus are known (see dbRBC). Homozygosity or compound heterozygosity for these alleles will result in

absence of both Le^a and Le^b antigens on RBCs. In addition, FUT6 deficiency is associated with the Le(a–b–) phenotype. The *FUT6* locus which encodes a plasma fucosyltransferase is closely linked to *FUT3* at 19p13.3, so there is a high degree of genetic linkage between these loci. Another very rare reason for this phenotype is mutations in the gene encoding the GDP-fucose transporter, see the H [**018**] Blood Group System.

Amino acid sequence of α(1,3/4) fucosyltransferase (FUT3)[2]

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MDPLGAAKPQ  WPWRRCLAAL  LFQLLVAVCF  FSYLRVSRDD  ATGSPRAPSG   50
SSRQDTTPTR  PTLLILLWTW  PFHIPVALSR  CSEMVPGTAD  CHITADRKVY  100
PQADTVIVHH  WDIMSNPKSR  LPPSPRPQGQ  RWIWFNLEPP  PNCQHLEALD  150
RYFNLTMSYR  SDSDIFTPYG  WLEPWSGQPA  HPPLNLSAKT  ELVAWAVSNW  200
KPDSARVRYY  QSLQAHLKVD  VYGRSHKPLP  KGTMMETLSR  YKFYLAFENS  250
LHPDYITEKL  WRNALEAWAV  PVVLGPSRSN  YERFLPPDAF  IHVDDFQSPK  300
DLARYLQELD  KDHARYLSYF  RWRETLRPRS  FSWALDFCKA  CWKLQQESRY  350
QTVRSIAAWF  T                                            361
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Carrier molecule[3]

Lewis antigens are not a primary gene product, but are instead the result of action of the FUT3 enzyme on different precursors. Lewis antigens can exist on both glycoproteins and glycolipids, and have different carrier chains, although only those based on the type 1 precursors (Galβ1-3GlcNAc) are considered as Lewis antigens. Antigens (e.g., Le^x and Le^y) also formed by the FUT3 enzyme but on type 2 precursors (Galβ1-4GlcNAc) are not considered red cell antigens, although they may be present. Glycoprotein forms of the Lewis antigen are found primarily in bodily secretions such as saliva and milk, while only the glycolipid forms are adsorbed onto red cells from the plasma.

Function

There are no apparent pathological consequences in Le(a–b–) people.
Sialylated forms of Le^a and Le^b may serve as ligands for E-selectins, although their type 2 cousins, Le^x and Le^y, are more likely to be the antigens of biological significance.

Disease association

The Le^b antigen in the gastric mucosal epithelium is the receptor for *Helicobacter pylori*, a major causative agent of gastric ulcers[4,5].
Lewis antigens may be lost from RBCs as a result of infectious mononucleosis complicated with hemolysis, severe alcoholic cirrhosis, alcoholic pancreatitis, and pregnancy.

Patients with fucosidosis may have increased expression of Lewis antigens in their saliva and on their RBCs.
RBCs from patients with leukocyte adhesion deficiency (LADII) syndrome are Le(a–b–), and are Bombay phenotype, due to a mutation in the GDP-fucose transporter[6,7].

Phenotypes (% occurrence)

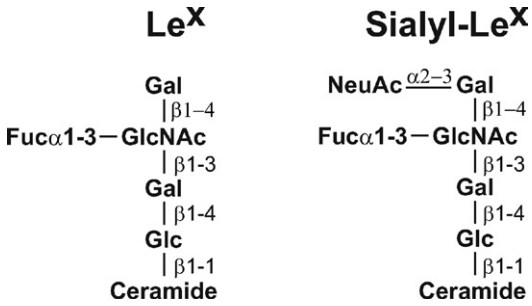
	Caucasians	Blacks	Japanese
Le(a+b–)	22	23	0.2
Le(a–b+)	72	55	73
Le(a+b+)	Rare	Rare	16.8
Le(a–b–)	6	22	10

Null: Le(a–b–)
Unusual: Le(a+b+), rare in European populations, is found in most Australasian populations (e.g., Australian Aborigines, Chinese in Taiwan, Japanese, and Polynesians) with an incidence of 10% to 40%. The phenotype is the result of a mutation in the *FUT2* (*SE*) gene: 385A>T; Ile129Phe. (See H [**018**] System)

Comments

Saliva is a good source of soluble Lewis antigens, and should be made isotonic (if not already) before use in hemagglutination tests. Monoclonal Lewis reagents should never be used in determining the presence of Lewis antigens in saliva. It is well-established that quality anti-Le^b serological reagents are always neutralized by Le^a saliva.
During pregnancy, expression of Lewis antigens on RBCs is often greatly reduced, although the level of antigen in plasma remains normal[8].
Le^x (SSEA-1; CD15) and Le^y, products of *FUT3* on type 2 precursor chains, are only found in trace amounts on the RBC surface, and are not part of the Lewis blood group system[9]. Le^x and Le^y are isomers of, respectively, Le^a and Le^b, and often occur in sialylated forms. Sialyl-Le^x is a major neutrophil ligand for E-selectin[10]. Le^a, Le^x, their sialyl derivates, and also Le^b and Le^y, accumulate in tumor tissues. Evidence indicates that adhesion of tumor cells to endothelial cells is mediated between the sialylated Le^a and Le^x antigens and

E-selectin, and represents an important factor in hematogenous metastasis of tumor cells.



References

1 Henry, S., et al., 1996. Molecular basis for erythrocyte Le(a+b+) and salivary ABH partial-secretor phenotypes: expression of a FUT2 secretor allele with an A-->T mutation at nucleotide 385 correlates with reduced α(1,2)fucosyltransferase activity. Glycoconj J 13, 985–993.

2 Kukowska-Latallo, J.F., et al., 1990. A cloned human cDNA determines expression of a mouse state-specific embryonic antigen and the Lewis blood group α(1,3/1,4)fucosyltransferase. Genes & Devel 4, 1288–1303.

3 Hauser, R., 1995. Le^a and Le^b tissue glycosphingolipids. Transfusion 35, 577–581.

4 Boren, T., et al., 1993. Attachment of *Helicobacter pylori* to human gastric epithelium mediated by blood group antigens. Science 262, 1892–1895.

5 Boren, T., et al., 1994. *Helicobacter pylori*: molecular basis for host recognition and bacterial adherence [review]. Trends Microbiol 2, 221–228.

6 Hirschberg, C.B., 2001. Golgi nucleotide sugar transport and leukocyte adhesion deficiency II. J Clin Invest 108, 3–6.

7 Luhn, K., et al., 2001. The gene defective in leukocyte adhesion deficiency II encodes a putative GDP-fucose transporter. Nat Genet 28, 69–72.

8 Henry, S., et al., 1996. A second nonsecretor allele of the blood group α(1, 2)fucosyltransferase gene (FUT2). Vox Sang 70, 21–25.

9 Lowe, J.B., 1995. Biochemistry and biosynthesis of ABH and Lewis antigens: characterization of blood group-specific glycosyltransferases. In: Cartron, J.-P., Rouger, P. (Eds.), Molecular Basis of Human Blood Group Antigens. Plenum Press, New York, NY, pp. 75–115.

10 Walz, G., et al., 1990. Recognition by ELAM-1 of the sialyl-Le^x determinant on myeloid and tumor cells. Science 250, 1132–1135.

Le^a Antigen

Terminology

ISBT symbol (number)	LE1 (007001 or 7.1)
History	Identified in 1946; named Lewis after one of the two original producers of anti-Le^a.

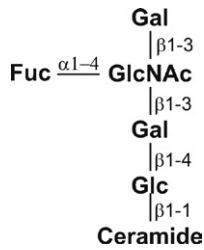
Occurrence

Caucasians	22%
Blacks	23%

Expression

Cord RBCs	Not expressed; although RBCs from some cord bloods will react with anti-Le^a by IAT
Reduced	Weak in Le(a+b+); often weakened during pregnancy and certain diseases

Molecular basis associated with Le^a antigen[1]



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

Ficin/Papain	Resistant (markedly enhanced)
Trypsin	Resistant (markedly enhanced)
α-Chymotrypsin	Resistant (markedly enhanced)
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Le^a

Immunoglobulin class	IgM more frequent than IgG
Optimal technique	RT; 37°C; IAT; enzymes
Neutralization	Plasma and isotonic saliva
Complement binding	Yes; some hemolytic

Clinical significance of alloanti-Le^a

Transfusion reaction	No (rare cases of hemolytic reactions)
HDFN	No (one mild case)

Comments

Anti-Le^a (in conjunction with anti-Le^b [see **LE2**]) is a frequent naturally-occurring antibody made by Le(a–b–) people, especially during pregnancy.

There are rare reports about Le(a–b+) individuals making anti-Le^a, but it is unclear if this only applies to a subgroup of individuals with this phenotype[2].

References

[1] Henry, S., et al., 1995. Lewis histo-blood group system and associated secretory phenotypes. Vox Sang 69, 166–182.

[2] Chan, Y.S., Lin, M., 2011. Anti-Lea in Le(a–b+) individuals [abstract]. Vox Sang 101 (Suppl. 2), 97–98.

Le^b Antigen

Terminology

ISBT symbol (number)	LE2 (007002 or 7.2)
History	Anti-Le^b was identified in 1948; initially appeared to detect an antigen antithetical to Le^a.

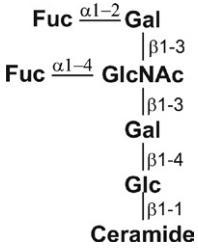
Occurrence

Caucasians	72%
Blacks	55%

Expression

Cord RBCs	Not expressed
Reduced	Weak in Le(a+b+); often weakened during pregnancy and certain diseases

Molecular basis associated with Le^b antigen[1]



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

Ficin/Papain	Resistant (markedly enhanced)
Trypsin	Resistant (markedly enhanced)
α-Chymotrypsin	Resistant (markedly enhanced)
DTT 200 mM	Resistant
Acid	Resistant

In vitro characteristics of alloanti-Le^b

Immunoglobulin class	IgM more frequent than IgG
Optimal technique	RT; 37°C; IAT; enzymes
Neutralization	Plasma and isotonic saliva from secretors
Complement binding	Yes; some hemolytic

Clinical significance of alloanti-Le^b

Transfusion reaction	No
HDFN	No (one mild case)

Comments

Le^b is a receptor for *Helicobacter pylori* in gastric mucosal epithelium[2].
Anti-Le^b (in conjunction with anti-Le^a [see **LE1**]) is a frequent naturally-occurring antibody made by Le(a–b–) people. There are also rare reports about Le(a+b–) individuals making anti-Le^b, but it is unclear if this only applies to a subgroup of individuals with this phenotype[3].
There are two kinds of anti-Le^b: anti-Le^{bH} **(LE4)**, reacting with group O and A_2 Le(b+) RBCs, and anti-Le^{bL}, reacting with all Le(b+) RBCs. Other antibodies react specifically with the compound antigens, e.g., ALe^b **(LE5)** and BLe^b **(LE6)**.

References

[1] Henry, S., et al., 1995. Lewis histo-blood group system and associated secretory phenotypes. Vox Sang 69, 166–182.
[2] Boren, T., et al., 1994. *Helicobacter pylori*: molecular basis for host recognition and bacterial adherence [review]. Trends Microbiol 2, 221–228.
[3] Chan, Y.S., Lin, M., 2011. Anti-Lea in Le(a–b+) individuals [abstract]. Vox Sang 101 (Suppl. 2), 97–98.

Le^{ab} Antigen

Terminology

ISBT symbol (number)	LE3 (007003 or 7.3)
Obsolete names	X; Le^x; Le^{abx}
History	Described in 1949 as the antigen reacting with anti-X; referred to as Le^x from the mid-1950s; formally assigned to Lewis and renamed Le^{ab} by ISBT in 1998.

Occurrence

All populations: on Le(a+b–) and Le(a–b+) RBCs from adults and on 90% of cord samples.

Expression

Cord RBCs	Expressed

Molecular basis associated with Le^{ab} antigen[1]

The binding site for anti-Le^{ab} comprises the disaccharide Fucα1→4GlcNAc→R which is shared by the Le^a and Le^b active structures, similar to the A,B antigen being shared by A and B in the ABO system. It is of note that all serological monoclonal anti-Le^b reagents are anti-Le^{ab} reagents, but cannot detect Le^a antigen when it is present on RBCs.

In vitro characteristics of alloanti-Le^{ab}

Immunoglobulin class	IgM
Optimal technique	RT; 37°C (rare)
Effect of enzymes	Enhanced

Clinical significance of alloanti-Le^{ab}

Transfusion reaction	No
HDFN	No

Comments

Anti-Le^{ab} is a fairly common specificity, and is frequently found with anti-Le^a and/or anti-Le^b; it occurs mainly in serum from Le(a–b–) secretors of blood group A, B, or AB. Anti-Le^{ab} is inhibited by saliva that contains Le^a, and is weakly inhibited by saliva that contains Le^b. Saliva from Le(a–) non-secretors may also have a very weak inhibitory effect.
Experts recommend transfusion of Le(a–b–) blood if antibody reacts at 37°C.
The practical value of categorizing the epitope recognized by anti-Le^{ab} as a blood group antigen has been questioned by some experts, because of uncertainty about its biochemical basis and cross-reactivity issues.

Reference

[1] Schenkel-Brunner, H., 2000. In: Human Blood Groups: Chemical and Biochemical Basis of Antigen Specificity, second ed. Springer-Verlag Wien, New York, NY.

Le^{bH} Antigen

Terminology

ISBT symbol (number)	LE4 (007004 or 7.4)
History	Antigen detected by the original anti-Le^b in 1948; named Le^{bH} in 1959 upon recognition of heterogeneity of anti-Le^b; allocated ISBT number in 1998.

Occurrence

Present on group O and A_2 Le(b+) RBCs, i.e., those with strong expression of H antigen. Group A_1 or B RBCs react weakly or not at all.

Expression

Cord RBCs	Not expressed
Altered	Weak in Le(a+b+), often weakened during pregnancy and certain diseases

Molecular basis associated with Le^{bH} antigen[1]

Anti-Le^{bH} appears to require access to the fucose residue of H type 1 (see H [**018**] System) on group O RBCs, where the structure is not blocked by the immunodominant blood group A or B sugars. The determinant must also involve the L-fucose added by the *FUT3* (*LE*)-specified transferase because Le(a–b–) RBCs from secretors (which carry H type 1) do not react with anti-Le^{bH}.

Effect of enzymes and chemicals on Le^{bH} antigen on intact RBCs

Refer to Le^b antigen (**LE2**).

In vitro characteristics of alloanti-Le^{bH}

Immunoglobulin class	IgM predominates
Optimal technique	RT; 37°C; enzymes
Neutralization	Isotonic saliva (inhibited by saliva that contains H, or H and Le^b)
Complement binding	Yes; some hemolytic

Clinical significance of alloanti-Le^{bH}

Transfusion reaction	No
HDFN	No

Comments

Anti-Le^{bH} is a more common specificity than anti-Le^{bL}. Anti-Le^{bH} is unlikely to cause incompatible cross-matches if ABO-identical blood is selected. The practical value of categorizing the epitope recognized by anti-Le^{bH} as a blood group antigen has been questioned by some experts, because of uncertainty about its biochemical basis and cross-reactivity issues.

Reference

[1] Henry, S., et al., 1995. Lewis histo-blood group system and associated secretory phenotypes. Vox Sang 69, 166–182.

ALe^b Antigen

Terminology

ISBT symbol (number)	LE5 (007005 or 7.5)
Obsolete name	A_1Le^b
History	Anti-A_1Le^b was identified in 1967 during cross-matching; name derived from the unusual antibody reactivity; received an ISBT number in 1998; name amended to ALe^b.

Occurrence

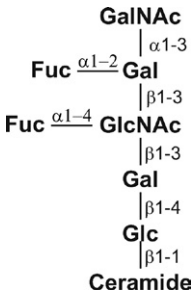
On all group A and AB RBCs which are also Le(b+), i.e., on RBCs of secretors of A who have a *FUT3* (*LE*) gene. It is of note that Le^b cannot be made into ALe^b.

All group O and group B Le(b+) RBCs and all Le(b–) people are antigen-negative.

Expression

Cord RBCs	Not expressed

Molecular basis associated with ALe^b antigen[1]



ALe^b is expressed when A type 1 is modified by the addition of *FUT3*-gene-specified L-fucose.

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

Refer to Le^b (**LE2**).

In vitro characteristics of alloanti-ALe^b

Refer to Le^b (**LE2**).

Clinical significance of alloanti-ALe^b

Few examples of anti-ALe^b have been reported; may be lymphocytotoxic.

Comments

ALe^b is adsorbed onto RBCs and lymphocytes, and is the dominant Lewis antigen on group A Le(b+) RBCs. It is also of note that the anti-Le^b does not react with ALe^b antigen, hence group A individuals may have weaker Le^b reactions than group O (and are often mistyped).
Anti-ALe^b is a single specificity that cannot be separated into anti-A and anti-Le^b. Monoclonal anti-ALe^b has been produced.

Reference

[1] Henry, S., et al., 1995. Lewis histo-blood group system and associated secretory phenotypes. Vox Sang 69, 166–182.

BLe^b Antigen

Terminology

ISBT symbol (number)	LE6 (007006 or 7.6)
History	Allocated a Lewis system number by ISBT in 1998.

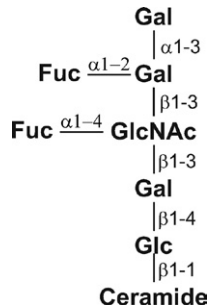
Occurrence

On all group B and AB RBCs that are also Le(b+), i.e., on RBCs of secretors of B who have a *FUT3* (*LE*). It is of note that Le^b cannot be made into BLe^b.
All group O and group A Le(b+) and all Le(b–) people are antigen-negative.

Expression

Cord RBCs	Not expressed

Molecular basis associated with BLe^b antigen[1]



BLe^b is expressed when B type 1 is modified by the addition of *FUT3*-gene-specified L-fucose.

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

Refer to Le^b antigen (**LE2**).

In vitro characteristics of alloanti-BLe^b

Refer to Le^b antigen (**LE2**).

Clinical significance of alloanti-BLe^b

Few examples of anti-BLe^b have been reported; unlikely to cause a transfusion reaction or HDFN; may be lymphocytotoxic.

Comments

BLe^b is adsorbed onto RBCs and lymphocytes, and is the dominant Lewis antigen on group B Le(b+) RBCs. It is also of note that the anti-Le^b does not react with BLe^b antigen, hence group B individuals may have weaker Le^b reactions than group O (and are often mistyped). Anti-BLe^b is a single specificity; it cannot be separated into anti-B and anti-Le^b.

Reference

[1] Henry, S., et al., 1995. Lewis histo-blood group system and associated secretory phenotypes. Vox Sang 69, 166–182.