Landsteiner-Wiener Blood Group System

Number of antigens 3

High prevalence	LW^a, LW^{ab}
Low prevalence	LW^b

Terminology

ISBT symbol (number)	LW (016)
CD number	CD242
History	Anti-LW, or "anti-Rh" as it was called, was produced in 1940. However, the phenotypic relationship between LW and the RhD antigen delayed recognition that LW was an independent blood group system until 1963, when it was named to honor Landsteiner and Wiener who made anti-LW in rabbits and guinea pigs after immunizing them with blood from *Macacus rhesus*. In 1982, it became a three-antigen system. The LW_1, LW_2, LW_3, and LW_4 terminology was changed when it was realized that anti-Ne^a (now called anti-LW^b) detects an antigen antithetical to that recognized by anti-LW made by LW_3 people (now called anti-LW^a)[1].

Expression

Tissues	May be found in placenta

Gene[2]

Chromosome	19p13.2
Name	*LW (ICAM4, CD242)*
Organization	3 exons distributed over 2.6 kbp of gDNA
Product	LW glycoprotein, ICAM-4

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00018-1

Database accession numbers

GenBank	X93093 (gene), NM_001544 (mRNA), S78852
Entrez Gene ID	3386

Molecular basis of Landsteiner-Wiener phenotypes

The reference allele, *LW*05* or *LW*A* (Accession number S78852), encodes LW^a (LW5), LW6. Nucleotide differences from this reference allele, and amino acids affected, are given.

Allele encodes	Allele name	Exon	Nucleotide	Restriction enzyme	Amino acid†	Ethnicity (prevalence)
LW(a–b+) or LW:–5,7	*LW*07* or *LW*B*	1	299A>G	*Pvu*II –	Gln100 Arg	Estonians> Finns> Latvians> Lithuanians> Poles> Russians (Several), Others (Rare)

†Change from historical counting of #1 as Ala of the mature membrane-bound protein to #1, as Met results in all amino acid numbers being increased by 30. Thus, the LW5/LW7 polymorphism used to be amino acid number 70 and is now 100.

Molecular basis of silencing of *LW*

Homozygosity leads to LW_{null} [LW:–5,–6,–7; LW(a–b–)] phenotype. Nucleotide changes from *LW*05* reference allele (Accession number S78852), and amino acids affected, are given.

Allele name	Exon	Nucleotide	Amino acid†	Ethnicity (prevalence)
*LW*05N.01*	1	346–355del	116del;fs,118Stop	Canadian (Rare)

†Change from historical counting of #1 as Ala of the mature (membrane-bound protein) results in all amino acid numbers increasing by 30.

Molecular basis of weak LW antigens

KLF1 encodes erythroid Krüppel-like factor (EKLF). Several nucleotide changes in this gene are responsible for the dominant Lu(a–b–) phenotype encoded by *In*(*Lu*) (see Lutheran blood group system)[3,4]. *KLF1* 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).
Nucleotide difference 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)

^ = Heterozygosity for this change caused dyserythropoietic anemia and suppression of CO, IN, and LW antigens[5,6].

Amino acid sequence

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MGSLFPLSLL  FFLAAAYPGV  GSALGRRTKR  AQSPKGSPLA  PSGTSVPFWV   50
RMSPEFVAVQ  PGKSVQLNCS  NSCPQPQNSS  LRTPLRQGKT  LRGPGWVSYQ  100
LLDVRAWSSL  AHCLVTCAGK  TRWATSRITA  YKPPHSVILE  PPVLKGRKYT  150
LRCHVTQVFP  VGYLVVTLRH  GSRVIYSESL  ERFTGLDLAN  VTLTYEFAAG  200
PRDFWQPVIC  HARLNLDGLV  VRNSSAPITL  MLAWSPAPTA  LASGSIAALV  250
GILLTVGAAY  LCKCLAMKSQ  A                                  271
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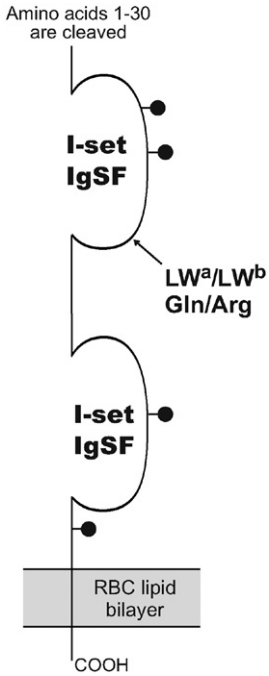
LW encodes a signal peptide of 30 amino acids.

Carrier molecule[7]

A single pass type I membrane glycoprotein with two IgSF domains. A secreted form also has been described[8].



M_r (SDS-PAGE)	37,000–43,000
CHO: N-glycan	4 potential sites at residue 68, 78, 190, and 223
CHO: O-glycan	Present
Cysteine residues	3 pairs at residues 69/113, 73/117, and 153/210
Copies per RBC	D+ 4,400 (Adult); 5,100 (cord)
	D– 2,800 (Adult); 3,600 (cord)

Function

The LW glycoprotein is an intercellular adhesion molecule (ICAM-4), and a ligand for integrins. LW has 30% sequence identity with other ICAMs. ICAM-4 binds to β_2 integrins including the LFA-1 and Mac-1 leukocyte integrins and VLA-4 ($\alpha_4\beta_1$) in haemopoietic tissue and also $\alpha_v\beta_1$, $\alpha_v\beta_5$, and maybe $\alpha_v\beta_3$[9,10]. Possible marker for lymphocyte maturation or differentiation. May assist in stabilizing erythroblastic islands during erythropoiesis[11]. May be involved in removal of senescent RBCs[7].

Disease association

LW antigens may be depressed during pregnancy and in some diseases, e.g., Hodgkin's disease, lymphoma, leukemia, and sarcoma[7]. Autoanti-LW is common in patients with warm AIHA.

Expression of ICAM-4 is elevated on sickle RBCs, and interaction between ICAM-4 and vascular endothelial cells may be involved in microvascular occlusions during painful crises of SCD[12].

Phenotypes (% occurrence)

Phenotype	Europeans	Finns
LW(a+b–)	97	93.9
LW(a+b+)	3	6
LW(a–b+)	Rare	0.1
Null: LW(a–b–); Rh_{null} RBCs type LW(a–b–) although *LW* is normal		

There is a phenotypic relationship between LW and D antigens: in adults, D– RBCs have lower expression of LW antigens than D+ RBCs (ratio 1:1.5). In cord RBCs, LW is strongly expressed in D– and D+ RBCs.

Obsolete compared to current phenotype names

Obsolete	Obsolete	Current
LW+, D+	LW_1	LW(a+b–) or LW(a+b+)
LW+, D–	LW_2	LW(a+b–) or LW(a+b+)
LW–, D+ or D–	LW_3	LW(a–b+)
LW–, D+ or D–	LW_4	LW(a–b–)
LW–, Rh_{null}	LW_0	LW(a–b–)

Comments

LW antigens require intramolecular disulfide bonds and the presence of divalent cations, notably Mg^{2+}, for expression[13].

References

[1] Sistonen, P., Tippett, P., 1982. A "new" allele giving further insight into the LW blood group system. Vox Sang 42, 252–255.

[2] Hermand, P., et al., 1996. Characterization of the gene encoding the human LW blood group protein in LW^+ and LW^- phenotypes. Blood 87, 2962–2967.

[3] 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.

[4] 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.

[5] Arnaud, L., et al., 2010. A dominant mutation in the gene encoding the erythroid transcription factor KLF1 causes a congenital dyserythropoietic anemia. Am J Hum Genet 87, 721–727.

[6] 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.

[7] Parsons, S.F., et al., 1999. Erythroid cell adhesion molecules Lutheran and LW in health and disease. Baillieres Clin Haematol 12, 729–745.

[8] Lee, G., et al., 2003. Novel secreted isoform of adhesion molecule ICAM-4: potential regulator of membrane-associated ICAM-4 interactions. Blood 101, 1790–1797.

[9] Bailly, P., et al., 1995. The red cell LW blood group protein is an intercellular adhesion molecule which binds to CD11/CD18 leukocyte integrins. Eur J Immunol 25, 3316–3320.

[10] Spring, F.A., et al., 2001. Intercellular adhesion molecule-4 binds $\alpha_4\beta_1$ and α_V-family integrins through novel integrin-binding mechanisms. Blood 98, 458–466.

[11] Chasis, J.A., Mohandas, N., 2008. Erythroblastic islands: Niches for erythropoiesis. Blood 112, 470–478.

[12] Zennadi, R., et al., 2004. Epinephrine acts through erythroid signaling pathways to activate sickle cell adhesion to endothelium via LW-alphavbeta3 interactions. Blood 104, 3774–3781.

[13] Bloy, C., et al., 1990. Surface orientation and antigen properties of Rh and LW polypeptides of the human erythrocyte membrane. J Biol Chem 265, 21482–21487.

LW^a Antigen

Terminology

ISBT symbol (number)	LW5 (016005 or 16.5)
Obsolete names	LW; LW_1; LW_2
History	Named LW^a in 1982 when the antithetical relationship to Ne^a (LW^b) was recognized. At that time, the antigen names LW1 to LW4 were not used, because they had been used to designate phenotypes.

Occurrence

All populations	100%

Antithetical antigen

LW^b (**LW7**)

Expression

Cord RBCs	Well expressed on D+ and D–
Altered	Weak on D– RBCs from adults Weak or absent on RBCs stored in EDTA

Molecular basis associated with LW^a antigen[1]

Amino acid	Gln100 (previously reported as 70)
Nucleotide	A at bp 299 in exon 1

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

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

In vitro characteristics of alloanti-LW^a

Immunoglobulin class	IgG (usually); IgM
Optimal technique	IAT or RT

Clinical significance of alloanti-LW^a

Transfusion reaction	No to mild/delayed [Rare; D–, LW(a+) RBCs survive well]
HDFN	No to mild (very rare)

Autoanti-LW^a

Autoanti-LW^a with suppression of LW antigens has been reported.
Sometimes observed in plasma of patients with warm AIHA.

Comments

Testing pronase or DTT treated D+ RBCs is a useful way to differentiate anti-D from anti-LW; anti-D will be reactive while anti-LW will not.
Siblings of patients with alloanti-LW^a should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits, in cases where D–, LW(a+) RBCs do not survive well.
Antigen expression requires Mg^{2+} (may be weak in EDTA samples).

Reference

[1] Hermand, P., et al., 1995. Molecular basis and expression of the LW^a/LW^b blood group polymorphism. Blood 86, 1590–1594.

LW^{ab} Antigen

Terminology

ISBT symbol (number)	LW6 (016006 or 16.6)
Obsolete names	Bigelow; Big; LW; LW_4
History	LW_4 was renamed LW^{ab} when the LW blood group system was established in 1982.

Occurrence

All populations	100%

Expression

Cord RBCs	Well expressed on D+ and D–
Altered	Weak on D– RBCs from adults Weak or absent on RBCs stored in EDTA

Molecular basis associated with LW^{ab} antigen

See System pages for molecular basis of LW(a–b–) phenotype.

Effect of enzymes and chemicals on LW^{ab} antigen on intact RBCs

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

In vitro characteristics of alloanti-LW^{ab}

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

Clinical significance of alloanti-LW^{ab}

Transfusion reaction	No data
HDFN	Mild; an autoanti-LW^{ab} has been reported to cause HDFN[1]

Autoanti-LW^{ab}

Autoanti-LW^{ab} with suppression of LW antigens occurs[2].
Sometimes observed in plasma of patients with warm AIHA.

Comments

Siblings of patients with anti-LW^{ab} should be tested for compatibility, and the patient urged to donate blood for cryogenic storage when his/her clinical state permits.
If random units have shortened survival, experts agree that D– RBCs are the component of choice.
Only one alloanti-LW^{ab} has been described in an LW(a–b–) person (Bigelow). Her brother also had the LW(a–b–) phenotype.
When LW antigens are suppressed, the anti-LW^{ab} may mimic an alloantibody and is a more common specificity than autoanti-LW^{a}.
Antigen expression requires Mg^{2+} (may be weak in EDTA samples).

References

[1] Davies, J., et al., 2009. Haemolytic disease of the foetus and newborn caused by auto anti-LW. Transfus Med 19, 218–219.
[2] Storry, J.R., 1992. Review: the LW blood group system. Immunohematology 8, 87–93.

LW^{b} Antigen

Terminology

ISBT symbol (number)	LW7 (016007 or 16.7)
Obsolete names	Ne^{a}; LW_3
History	Name changed from Ne^{a} when the antithetical relationship to LW^{a} was recognized in 1982.

Occurrence

Most populations	Rare
Estonians	8%
Finns	6%
Latvians and Lithuanians	5%
Poles and Russians	2%
Other Europeans	<1%[1]

Antithetical antigen

LW^{a} (**LW5**)

Expression

Cord RBCs	Well expressed on D+ and D–
Altered	Weak on D– RBCs from adults Weak or absent on RBCs stored in EDTA

Molecular basis associated with LW^b antigen[2]

Amino acid	Arg100 (previously reported as 70)
Nucleotide	G at bp 299 in exon 1

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

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

In vitro characteristics of alloanti-LW^b

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

Clinical significance of alloanti-LW^b

Transfusion reaction	No to mild
HDFN	No to mild

Comments

Antigen expression requires Mg^{2+} (may be weak in EDTA samples).

References

[1] Sistonen, P., et al., 1999. The LW^b blood group as a marker of prehistoric Baltic migrations and admixture. Hum Hered 49, 154–158.

[2] Hermand, P., et al., 1995. Molecular basis and expression of the LW^a/LW^b blood group polymorphism. Blood 86, 1590–1594.