29 Low Frequency Antigens

29.1 Antigens

Many red cell antigens occur only very rarely in most populations and have not been shown to belong to any of the existing blood group systems or collections. Some have only been found in a solitary family. In the numerical notation, low frequency antigens (LFAs) make up the 700 series. The criteria for joining this series of antigens are as follows:

1 the antigen must have a frequency of less than 1%;
2 it must be an inherited character;
3 it must not be part of an existing blood group system or be related closely enough to another antigen to merit collection status;
4 it must have been shown to be serologically distinct from all other antigens of low frequency;
5 antibody and red cells carrying the antigen must be available, so that further examples can be identified.

LFAs of the 700 series are listed in Table 29.1. Many numbers have become obsolete, either because the corresponding antigens have been elevated to blood group systems or collections, or because they have become extinct because antibody or antigen-positive red cells are unavailable. Frequencies of LFAs are shown in Table 29.2.

When recombination is demonstrated between the gene controlling an LFA and that for a blood group system, the LFA is considered not to be part of that system. None of the 700 series antigens has been shown to be independent of all blood group systems and none of the genes encoding those antigens has been identified.

29.2 Antibodies

Frequency of occurrence and some characteristics of antibodies to LFAs are shown in Table 29.3. Like most other blood group antibodies, antibodies to some LFAs arise from immunisation caused by pregnancy or transfusion; a few have been responsible for HDFN (Section 29.3.4). In most cases, however, the antibodies arise as a result of no known stimulus and are often found together with other antibodies to LFAs. Some sera contain numerous antibodies to LFAs. Serum samples from the same donor taken at different times may contain different specificities and the antibodies often react by different methods. Occasionally, sera containing an 'immune' antibody to an LFA also contain apparently 'naturally occurring' antibodies to other LFAs. As an example, the serum of a healthy blood donor, Mrs Tillett, contained the following antibodies to red cell antigens of low frequency: anti-Pt^a, -M^g (MNS11), -Vw (MNS12), -Ri^a (MNS16), -Hut (MNS19), -Dantu (MNS25), -Or (MNS31), -Go^a (RH30), -Rh32, -Evans (RH37), -Wr^a (DI3), -Wd^a (DI5), -Rb^a (DI6), -ELO (DI8), -Bp^a (DI10), -Mo^a (DI11), -Vg^a (DI13), -BOW (DI15), -NFLD (DI16), -Jn^a (DI17), -Tr^a (DI19), -Ls^a (GE6), and eight unpublished specificities.

Antibodies to LFAs usually come to light for one of the following reasons:

1 the antibody causes HDFN;
2 a single red cell sample reacts with a patient's serum during compatibility testing;
3 a serum blood grouping reagent contains a contaminating antibody to an LFA that gives an unexpected reaction during red cell phenotyping;

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Table 29.1 Low frequency antigens: the 700 series.

Number	Name	Symbol	References
700002	Batty	By	[1]
700003	Christiansen	Chr^a	[2]
700005	Biles	Bi	[3]
700006	Box	Bx^a	[4,5]
700017	Torkildsen	To^a	[6]
700018	Peters	Pt^a	[7]
700019	Reid	Re^a	[8]
700021	Jensen	Je^a	[9]
700028	Livesay	Li^a	[10]
700039	Milne		[11]
700040	Rasmussen	RASM	[12]
700044		JFV	[13]
700045	Katagiri	Kg	[14]
700047	Jones	JONES	[15]
700049		HJK	[16]
700050		HOFM	[17]
700052		SARA	[18]
700054		REIT	[19]
		SHIN	[20]

4 an antibody is detected when sera are screened with antigen-positive red cells;
5 an additional specificity is found in a serum known to contain one or more antibodies to LFAs when it is tested against cells of rare phenotype.

When red cells react with a serum known to contain a certain antibody to an LFA, the assumption cannot be made that those red cells carry that LFA, because the serum may contain more antibodies than those previously known to be present. Consequently, cross-adsorption/elution tests must be carried out for confirmation. The cross-adsorption method is not infallible, however, as antibodies of related, but different, specificities might be removed together from a serum by adsorption with red cells apparently expressing only one of the antigens.

29.3 Additional information on some of the antigens and antibodies

29.3.1 Pt^a (700018)

Many examples of anti-Pt^a have been found, all in sera containing other 'naturally occurring' antibodies to LFAs

Table 29.2 Frequencies of low frequency antigens.

Antigen 700		Population	No. tested	No. positive	Antigen frequency	References
002	By	English	31 522	2	0.0001	[21]
003	Chr^a	Danish	500	1	0.0020	[2]
005	Bi	American	1110	0		[3]
006	Bx^a	English	24 106	2	<0.0001	[4,5,22]
017	To^a	Norwegian	6461	1	0.0002	[6]
018	Pt^a	New Zealand	14 500	0	<0.0001	[7]
		Norwegian	21 825	0	<0.0001	[7,23]
		English	10 200	1	0.0001	[24]
019	Re^a	Canadian	>10 000	0	<0.0001	[8]
		English	6635	1	0.0002	[25]
		Welsh	4770	0		[25]
021	Je^a	Danish	>1000	0		[9]
039	Milne	New Zealand	2643	0		[11]
040	RASM	North American	9541	0		[12]
044	JFV	German	1014	0		[13]
045	Kg	Japanese	68 395	131	0.0019	[26]
047	JONES	Caucasian	16 746	1	<0.0001	[15]
050	HOFM	Dutch	926	0		[17]
054	REIT	Canadian	4086	0		[19]
	SHIN	Japanese	3000	1	0.0003	[20]

Table 29.3 Frequencies and characteristics of antibodies to low frequency antigens.

Antibody Anti-700	Antibody frequency[1]	Immune	Present in multispecific sera[2]	References
002 By	1/7987 0/2000	Yes[3]	Yes	[1,22,27]
003 Chr[a]			No	[2]
005 Bi		Yes[3]	No	[3]
006 Bx[a]	0/8000 1/23 081	[4]	Yes	[4,5,22]
017 To[a]	66/5704 ~48/300		No	[6,28,29]
018 Pt[a]			Yes	[7,24,30]
019 Re[a]	0/2358	Yes[3]	No	[8,25]
021 Je[a]	1/>100 000		No	[9]
028 Li[a]		Yes	No	[10]
039 Milne	58/1242	[5]	Yes	[11]
040 RASM	0/543	Yes[3]	No	[12]
044 JFV	0/534	Yes[3]	No	[13]
045 Kg	0/57 147	Yes[3] [6]	No	[14,26]
047 JONES	0/2000	Yes[3]	Yes	[15]
049 HJK		Yes[3]	No	[16]
050 HOFM		Yes[3]	No	[17]
052 SARA	1/3150	Yes[3]	Yes	[18,31]
054 REIT		Yes[3]		[19]
SHIN	0/19 380[7]	[8]	Yes	[20]

[1]The number of sera found to contain the antibody in the total number of sera from random blood donors tested. Where more than one survey is reported, the results are shown separately.
[2]Sera containing several or many antibodies to LFAs.
[3]See Section 27.3.5 for notes on clinical significance.
[4]No anti-Bx[a] in three Bx(a–) mothers of Bx(a+) children [5].
[5]No anti-Milne in two Milne– mothers of Milne+ children [11].
[6]Human monoclonal anti-Kg produced [26].
[7]One anti-SHIN found in sera from 1662 Japanese hospital patients [20].
[8]No anti-SHIN in two SHIN– mothers of SHIN+ children [20].

[7,24,30]. Anti-Pt[a] revealed a membrane component of apparent MW 31.6 kDa by immunoblotting with red cell membranes prepared under non-reducing conditions [32]. This structure might be associated with the membrane skeleton.

29.3.2 Li[a] (700028)

There is a suggestion in one family of linkage between the gene controlling Li[a] and the *LU* locus. If an untested husband is assumed to be Lu(a–), then the lod score is 2.709 at a recombination fraction of 0.0, very close to statistical significance; if the father were Lu(a+) the score is 1.204 [10]. Immunoblotting of Li(a+) cells in order to determine whether Li[a] is on the Lutheran glycoproteins revealed no bands.

29.3.3 HOFM (700050) is associated with Rh

HOFM is associated with depressed C antigen in the only family in which it has been detected [17], but family studies do not provide statistically significant evidence that HOFM belongs to the Rh system (see Section 5.17.1).

29.3.4 Clinical significance of antibodies to LFAs

Most antibodies to LFAs of the 700 series do not appear to be clinically significant. Severe HDFN in the HJK+ baby of a mother with anti-HJK (700049) was treated by three intrauterine transfusions [16]. Anti-Kg (700045) [14,26], anti-REIT (700054) [19], and anti-SARA (700052) [31] were also responsible for HDFN requiring exchange transfusion; HDFN caused by anti-JFV (700044) [13] and by anti-JONES (700047) [15] was treated by phototherapy and blood transfusion. Antibody to the Rh-associated antigens HOFM (700050) caused mild HDFN [17]. Anti-Bi (700005) may also have been responsible for HDFN [3]. Anti-By (700002), -Re^a (700019), and -RASM (700040) caused a positive DAT on cord red cells, but no other signs of HDFN [1,8,12,25].

LFAs do not create a major transfusion problem from the aspect of finding compatible donors, but a potentially dangerous antibody to an LFA could remain undetected if a full crossmatch were not performed. Presence of an unrecognised anti-LFA in a blood-grouping reagent can also prove hazardous.

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