30 High Frequency Antigens, including Vel

30.1 Introduction

High frequency antigens (HFAs) were originally classified together in the 900 series, but when the collections were introduced into the blood group terminology in 1990, the 900 series was decimated and was consequently abandoned and replaced by the 901 series. A red cell antigen may belong to the 901 series if it fits the following criteria:

1 it must have a frequency greater than 90% (though all antigens discussed in this chapter have frequencies in excess of 99% in most populations);
2 it must be inherited;
3 it must not be eligible to join a blood group system, form a new system, or be so closely related to another antigen as to merit collection status;
4 it must have been shown to be serologically distinct from all other antigens of high frequency.

The 901 series currently contains six antigens (Table 30.1). These include Sd^a, which has a frequency of about 91% and is described in Chapter 31. Results of some frequency studies are shown in Table 30.2.

Vel (previously 901001) and ABTI (previously 901015) are serologically related (Section 30.3) and so formed the Vel collection: Vel became VEL1 (212001) and ABTI became VEL2 (212002). The Vel antigens are described in this chapter.

None of the antigens described in this chapter are destroyed by the proteases papain, trypsin, or α-chymotrypsin, by sialidase, or the disulphide bond reducing agents AET and DTT, except that some anti-Vel react only weakly with DTT-treated red cells.

None of the genes responsible for the antigens in this chapter have been identified.

Antibodies to HFAs are a transfusion hazard as compatible blood is often very difficult to obtain. Anti-Vel and -Lan have both caused severe HTRs; anti-MAM has caused severe HDFN.

30.2 Vel (VEL1)

When Sussman and Miller [1] described anti-Vel in 1952, Vel became the first reported public antigen that was not part of an established blood group system. Anti-Vel is a dangerous antibody that has been responsible for HTRs (Section 30.2.3).

30.2.1 Frequency and inheritance

Some of the largest studies of testing random donors with anti-Vel are shown in Table 30.2. The Vel– phenotype was found to have an incidence of about one in 3000 in predominantly white English blood donors [4–6]. There are no reports of studies on large numbers of donors from other ethnic groups. Vel might be polymorphic in some populations: four of 328 Thais [14] and two of 160 Chilcotin Indians from Canada [15] were Vel–.

In the families of 11 Vel– propositi the sibling count, excluding propositi, approached very closely 3:1 Vel+:Vel–, the ratio expected if the Vel– phenotype results from

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homozygosity for a recessive allele [4]. In six families that demonstrate that Vel does not belong to the P1PK system an excess of Vel-negatives were P_2, with a probability of significance of about 1:70. This supports earlier speculations of an association between Vel and P1 [5].

30.2.2 Vel antigen

The strength of Vel shows substantial individual variation and in some people expression is very weak. It is advisable to use a two-stage complement-addition antiglobulin test to confirm a negative result with anti-Vel on red cells of individuals who have not produced anti-Vel. In population studies where apparent negatives were not checked in this way it is likely that donors with very weak Vel antigens have been mistyped as Vel–.

Table 30.1 High frequency antigens.

Number	Name	Symbol
212001	Vel	VEL1
212002	ABTI	VEL2
901003	August	At^a
901008		Emm
901009	Anton	AnWj
901012	Sid	Sd^a
901014		PEL
901016		MAM

Obsolete: 901001 Vel is now VEL1; 901002 Lan is LAN1; 901004 Jo^a is DO5; 901005 Jr^a is JR1; 901006 Ok^a is OK1; 901007 JMH is JMH1; 901010 Wr^b is DI4; 901011 is RAPH1; 901013 Duclos is RHAG1; 901015 ABTI is VEL2.

Vel is generally expressed less strongly on cord red cells than on those of adults [3,16]. Vel has been detected on fetal red cells as early as 12 weeks' gestation [17]. A patient who was Vel– when first tested developed a Vel antigen of normal strength during pregnancy; this Vel antigen persisted for at least 6 months after delivery [5].

Three of 14 anti-Vel failed to react with four Ge:–2,–3,4 samples, but did react with single examples of Ge:–2,3,4 and Ge:–2,–3,–4 cells [18]. This serological association between Vel and Gerbich suggests that the structure expressing Vel could be part of the junctional membrane-protein complex containing glycophorin C (see Section 18.7 and Figure 10.2).

Vel is not destroyed by proteases; on the contrary, treatment of cells with papain or ficin enhances detection of weak Vel antigens. Some anti-Vel react less strongly with red cells treated with DTT than with untreated cells, suggesting that some Vel epitopes are maintained by Cys–Cys bonding [19]. Vel was not detected by flow cytometry on lymphocytes, granulocytes, or monocytes [20].

30.2.3 Anti-Vel

Vel alloantibodies are never 'naturally occurring' and most producers of anti-Vel have been transfused; yet Vel antibodies are predominantly IgM and fix complement. Some anti-Vel haemolyse Vel+ cells *in vitro* and this lytic characteristic is destroyed by heating the serum to 56°C [2–4,6,21–23]. Of two IgG anti-Vel, one was IgG1, another contained IgG1 and IgG3 [24].

Anti-Vel is a dangerous antibody and patients with anti-Vel should be transfused with Vel– red cells. The first anti-Vel and other examples since have caused severe immediate HTRs [1,23,25,26]. Furthermore, anti-Vel may be missed in compatibility testing if inappropriate

Table 30.2 Frequencies of high frequency antigens in various populations.

Antigen	Population	No. tested	No. negative	Antigen frequency	References
Vel	American	21 000	8	0.9996	[[1–3]
	British	99 637	25	0.9997	[4–7]
	Swedish	91 605	52	0.9994	[5]
ABTI	Israeli Jews	509	0		[8]
	Israeli Arabs	121	0		[8]
At^a	American*	9600	0		[9,10]
	African American	14 251	1	0.9999	[11,12]
Emm	English	730	0		[13]

*Including about 2200 African Americans [9].

techniques are used [22,23]. Only 3% of radiolabelled Vel+ cells survived 1 hour after injection into a patient with IgG anti-Vel [27] and all of five anti-Vel gave strongly positive reactions in monocyte monolayer assays [24]. In some cases, however, patients with anti-Vel have been successfully transfused with Vel+ red cells despite, in one case, a strongly positive monocyte functional assay [28,29].

Anti-Vel does not usually cause HDFN, although many examples of anti-Vel have been found in pregnant women [1,16,30,31], probably because most anti-Vel are predominantly IgM and Vel antigen is usually expressed weakly on neonatal red cells, especially in babies heterozygous for the Vel gene. IgG anti-Vel has caused neonatal jaundice severe enough to require phototherapy [30,32,33], and in one case the baby also received two transfusions of the mother's red cells [32].

Two examples of autoanti-Vel were responsible AIHA [26,34], although in one case, a nine-week-old infant, the red cells gave a negative DAT [26]. Two other autoanti-Vel did not appear to destroy autologous red cells [6,35].

30.3 ABTI (VEL2)

The first three examples of anti-ABTI were present in multiparous women from an inbred Israeli Arab family [8]. There was no evidence of HDFN in any of their children. Three other members of the family were also ABTI–. Other examples of anti-ABTI were found in two unrelated German women [36]. No other example of ABTI– was found from testing Israeli blood donors (Table 30.2) or from 70 blood samples from a health clinic in the Arab village in which the Israeli propositus lived. Anti-ABTI reacted by an antiglobulin test with anti-IgG. The original anti-ABTI was IgG1 plus IgG3 [8].

Vel– red cells react weakly or give negative results with anti-ABTI [8,36]. In the one case where the results were reported, ABTI– red cells had weak Vel expression [8].

30.4 At^a (August, 901003)

The first anti-At^a was described by Applewhaite *et al.* [9] in 1967 and six more examples were reported in 1973 [37]. Another public antigen, El [10], was later shown to be the same as At^a [38].

30.4.1 Frequency and inheritance

All reported At(a–) propositi are black. Of about 16 450 African Americans tested, only one was At(a–) [11,12,39] (Table 30.2). Of the published families, nine At(a–) propositi had five At(a–) siblings and 16 At(a+) siblings, and all 11 children with an At(a–) parent were At(a+) [9,10,37,40–42]. These figures suggest that At(a–) results from homozygosity for a recessive gene.

30.4.2 Anti-At^a

Anti-At^a may be stimulated by transfusion or pregnancy. No example of 'naturally occurring' anti-At^a is known. At^a antibodies are mostly IgG, reacting by an antiglobulin test, but one example also contained some IgM, which directly agglutinated At(a+) red cells [37]. Of two IgG anti-At^a, one was IgG1, another consisted of IgG1, IgG3, and IgG4 [24].

One anti-At^a caused an immediate HTR with chills and nausea during a red cell survival study [41] and another a severe delayed HTR after transfusion of multiple units of At(a+) red cells [42]. At^a antibodies facilitate rapid destruction of ^{51}Cr-labelled At(a+) red cells *in vivo* and give positive results in *in vitro* functional assays [24,40,41,43]. Ideally At(a–) red cells should be selected for transfusion to patients with anti-At^a, although least incompatible red cell may be suitable for patients with weak examples of the antibody. Despite numerous pregnancies involving anti-At^a, only one of the babies had moderately severe HDFN requiring phototherapy [39].

30.5 Emm (901008)

Four propositi whose red cells lacked the high frequency antigen Emm were described by Daniels *et al.* [13]: a Frenchman born in Madagascar, a Caucasian American, a Pakistani, and a French Canadian. All had anti-Emm in their sera, as did the Emm– brother of the Canadian. Four of the five examples of anti-Emm were produced by men and were apparently 'naturally occurring'; one of the antibodies was IgM, the other four were IgG. Two further examples of anti-Emm in untransfused Emm– males have been identified [44].

Emm antigen is probably a GPI-linked protein. PNHIII red cells from a paroxysmal nocturnal haemoglobinuria patient were Emm–, whilst the PNHI cells were Emm+ (see Chapter 19) [44,45].

30.6 AnWj (901009)

AnWj is an HFA that is expressed only very weakly on the red cells of individuals with an *In(Lu)* gene (Section

6.8). Evidence exists that AnWj is closely associated with CD44 glycoprotein, the membrane structure that carries antigens of the Indian system, so AnWj is described in Section 21.7.

30.7 PEL (901014)

The first two PEL– propositi with anti-PEL were French Canadian women [46]. The second PEL– propositus had three PEL– siblings. Two other examples of antibodies to HFAs that did not react with PEL– cells were found in the propositi of French Canadian families, but the red cells of these propositi and their compatible siblings reacted very weakly with anti-PEL. This weak reaction required adsorption tests for detection. The PEL-like antibodies in these two propositi were provisionally named anti-MTP [46]. Of the 18 siblings of propositi with anti-PEL (or anti-MTP), red cells of six were compatible with the serum of the propositus.

All four producers of anti-PEL (or anti-MTP) had been transfused and three had also been pregnant. Red cells of the baby of the original PEL– propositus gave a negative DAT and there was no sign of HDFN. Radiolabelled PEL+ cells survived normally in the other propositus with anti-PEL, but only 74% survived after 24 hours in one of the patients with anti-MTP [46].

30.8 MAM (901016)

Two MAM– propositi, ascertained through the presence of anti-MAM in their sera during their third pregnancies, were described by Montgomery *et al.* [47]. One propositus was of partial Irish and Cherokee descent, the other was Arabic. The second propositus had a MAM– sister, who had been pregnant once and also had anti-MAM. The parents of the MAM– sisters are cousins. Two other MAM– propositi with anti-MAM were also found during pregnancy [48,49]. None of the MAM– women had a history of transfusion.

The third baby of the second propositus with anti-MAM had severe HDFN, requiring intrauterine transfusion. Red cells of the babies of the other three propositi were DAT+, but there was no HDFN. Two of the anti-MAM contained IgG1 and IgG3, and one also had IgG2 [47]. Monocyte monolayer assays suggested that anti-MAM has the potential to shorten survival of transfused MAM+ red cells substantially [47].

Immunoblotting of red cell membranes with anti-MAM revealed a diffuse band of apparent MW 23–80 kDa, with a discrete band at 18 kDa. MAM is present on lymphocytes, granulocytes, monocytes, and probably platelets from peripheral blood and on the majority of leukaemia, fibroblast, embryonic kidney, and endothelial cell lines, but not on an epithelial cell line [47,48]. Treatment of cells with *N*-glycosidase F, which cleaves *N*-glycans, resulted in loss of reactivity with anti-MAM [50].

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