Raph Blood Group System

Number of antigens 1

High prevalence	MER2

Terminology

ISBT symbol (number)	RAPH (025)
CD number	CD151
History	This system was established in 1998, and named RAPH after the first producer of alloanti-MER2. The antigen had been previously recognized by the monoclonal antibody, MER2, and the only antigen in the system retains this name. MER2 was shown to be expressed by tetraspanin (CD151) in 2004.

Expression

Other blood cells	CD34+ cells; there is a rapid decrease in expression during *ex vivo* erythropoiesis
Tissues	Epithelium, endothelium, muscle, renal glomeruli, and tubules, Schwann and dendritic cells, fibroblasts

Gene

Chromosome	11p15.5
Name	*CD151* (*RAPH*)
Organization	8 exons over 4.3 kbp of gDNA
Product	Raph, CD151, tetraspanin, TM4SF

The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00027-2

Database accession numbers

GenBank	BT007397 (mRNA); D29963 (mRNA); NM_004357 (mRNA)
Entrez Gene ID	977

Molecular basis of MER− phenotype[1]

The reference allele, *RAPH*01* (Accession number BT007397) encodes MER2 (RAPH1). Nucleotide differences from this reference allele, and the amino acids affected, are given.

Allele encodes	Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
MER2– or RAPH:–1	*RAPH*–01.01*	6	511C>T^	Arg171Cys	Israeli, Pakistani, Turkish (Rare)
MER2– or RAPH:–1	*RAPH*–01.02*	6	533G>A	Arg178His	Turkish (Rare)

^May be *in cis* with 579 A>G in exon 6 (Gly193Gly).

Molecular basis of silencing *RAPH* ($RAPH_{null}$ phenotype)[1]

Nucleotide difference from *RAPH*01* reference allele (Accession number BT007397), and amino acids affected, are given.

Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
*RAPH*01N.01*	5	383insG	Lys127fs → Glu140Stop	Indian Jew (Rare)

Amino acid sequence

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MGEFNEKKTT  CGTVCLKYLL  FTYNCCFWLA  GLAVMAVGIW  TLALKSDYIS   50
LLASGTYLAT  AYILVVAGTV  VMVTGVLGCC  ATFKERRNLL  RLYFILLLII  100
FLLEIIAGIL  AYAYYQQLNT  ELKENLKDTM  TKRYHQPGHE  AVTSAVDQLQ  150
QEFHCCGSNN  SQDWRDSEWI  RSQEAGGRVV  PDSCCKTVVA  LCGQRDHASN  200
IYKVEGGCIT  KLETFIQEHL  RVIGAVGIGI  ACVQVFGMIF  TCCLYRSLKL  250
EHY                                                        253
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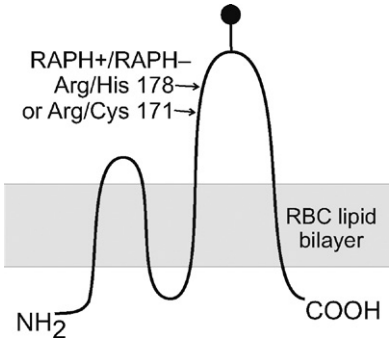
Carrier molecule

A glycoprotein with four membrane passes.



M_r (SDS-PAGE)	40,000
CHO: N-glycan	1
Cysteine residues	15

Function

CD151 interacts with α-β integrins and laminin participating in cell adhesion, proliferation, and differentiation. CD151 may be involved in the structure and development of glomerular basement membranes. In cancer cells, enhances cell motility, invasion, and metastasis.
The function of CD151 in the RBC membrane is unknown.

Disease association

An absence of CD151 has been associated with glomerulonephritis and renal failure in three people (two probands); also associated with pretibial epidermolysis bullosa and sensorineural deafness[2].

Comments

The 178His and 171Cys are spacially distinct from the ^{194}Gln-Arg-Asp^{196} motif that is likely the integrin-binding site on CD151. This is consistent with the Arg178His, and the Arg171Cys changes producing a protein lacking the MER2 epitope but retaining the integrin-binding function[3].

References

[1] Crew, V.K., et al., 2004. CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly of human basement membranes in kidney and skin. Blood 104, 2217–2223.

[2] Kagan, A., et al., 1988. Occurrence of hereditary nephritis, pretibial epidermolysis bullosa and beta-thalassemia minor in two siblings with end-stage renal disease. Nephron 49, 331–332.
[3] Kazarov, A.R., et al., 2002. An extracellular site on tetraspanin CD151 determines α3 and α6 integrin-dependent cellular morphology. J Cell Biol 158, 1299–1309.

MER2 Antigen

Terminology

ISBT symbol	RAPH1 (025001 or 25.1)
Obsolete names	Raph; Raf; 901011
History	The first red cell surface polymorphism to be defined by a monoclonal antibody (MER2) was described in 1987[1]. The alloantibody was described over a decade later, but the antigen retained the MER2 name.

Occurrence

All populations	92% (see Comments)

Expression

Cord RBCs	Not expressed or weakly expressed
Altered	Weakened (slightly) on RBCs with the dominant type of Lu(a–b–)

Effect of enzymes and chemicals on MER2 antigen on intact RBCs

Ficin/Papain	Resistant
Trypsin	Sensitive
α-Chymotrypsin	Sensitive
DTT 200 mM	Variable

In vitro characteristics of alloanti-MER2

Immunoglobulin class	IgG
Optimal technique	IAT
Complement binding	Yes; in three of four human anti-MER2

Clinical significance of alloanti-MER2

Transfusion reaction	No to moderate (chills and rigor)[2]
HDFN	No information

Comments

The 8% of people whose RBCs type MER2–, express MER2 on their erythroid precursors, and on their platelets. It is likely that MER2 is expressed on their RBCs, but is too weak to be detected by hemagglutination. These people have not made anti-MER2, nor have nucleotide changes been found in their *CD151*. Antigen strength varies on RBC samples from different people.

Three individuals (two probands) with anti-MER2 had renal failure requiring dialysis; two had made the antibody before receiving transfusion. All were Indian (South Asian) Jews. A fourth example of alloanti-MER2 was in a healthy Turkish blood donor (the 3rd proband), who had never been transfused but had been pregnant twice. A 4th proband was a Pakistani with two pregnancies and no transfusions, and the 5th proband was a Turk who had been pregnant and transfused[2]. The three Jews originating from India who made alloanti-MER2 had a silenced *CD151* ($RAPH_{null}$). The anti-MER2 made by the Turkish blood donor (*CD151*533G>A*, Arg178His) and the Pakistani and Turkish patients (*CD151*511C>T*, or Arg171Cys) likely have more precise specificities. However, limited cross-testing indicated all examples of alloanti-MER2 had the same specificity[2].

References

[1] Daniels, G.L., et al., 1988. Human alloantibodies detecting a red cell antigen apparently identical to MER2. Vox Sang 55, 161–164.

[2] Karamatic Crew, V., et al., 2008. Two MER2-negative individuals with the same novel CD151 mutation and evidence for clinical significance of anti-MER2. Transfusion 48, 1912–1916.