FORS Blood Group System

Number of antigens 1

Low prevalence	FORS1

Terminology

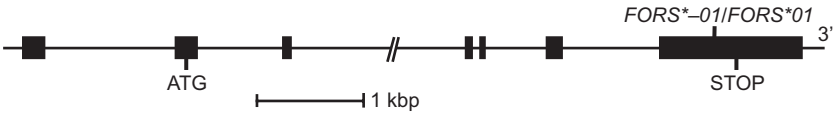
ISBT symbol (number)	FORS (031)
History	A_{pae} was reported in 1987 as a subgroup of A in three English families[1]. In 2011, it was shown to be independent of ABO, and was indeed the Forssman antigen[2]. Thus, A_{pae} was renamed in honor of John Forssman who first discovered this antigen that bears his name. At the time of printing, Forssman had been provisionally assigned the ISBT System number 031 and the name "FORS".

Expression

Other blood cells	Not normally expressed on blood cells
Tissues	Reports about Forssman glycolipid expression in normal human gastric and colonic mucosa, lung, and kidney

Gene

Chromosome	9q34.2
Name	*FORS* (*GBGT1, A3GALNT*)
Organization	7 exons spread over approximately 11 kbp of gDNA
Product	Globoside 3-α-*N*-acetylgalactosaminyltransferase 1 (Forssman glycolipid synthetase)



The Blood Group Antigen (3/e). DOI: http://dx.doi.org/10.1016/B978-0-12-415849-8.00033-8

Database accession numbers

GenBank	NM_021996 (mRNA); NC_000009.11
EMBL	HE583597
Entrez Gene ID	26301

Molecular bases of the FORS1+ RBC phenotype[2]

*GBGT1*01.01* (EMBL accession number HE583597) encodes FORS1 on RBCs. The nucleotide difference from the reference allele (NM_021996, *GBGT1*01N.01* below), and amino acid affected, are given.

Allele encodes	Allele name^	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
FORS:1 (FORS1+)	*GBGT1*01.01*[a]	7	887G>A	Arg296Gln	British (Rare)
FORS:1 (FORS1+)	*GBGT1*01.02*[b]	2 7	58C>T 887G>A	Leu20Phe Arg296Gln	British (Rare)

^The sequences encoding these alleles have been deposited in the EMBL database under the following accession numbers: HE583597[a] and HE583598[b].

Molecular bases of the FORS1– RBC phenotype[2,4]

*GBGT1*01.01* (EMBL accession number HE583597) encodes FORS1 on RBCs. The reference allele (NM_021996, *GBGT1*01N.01*) is a null allele and is compared with other null alleles in the table below. Nucleotides of importance and amino acids affected are given.

Allele encodes	Allele name^	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
FORS:–1 (FORS1–)	*GBGT1*01N.01*[a]	7	887G	Arg296	(Common)
FORS:–1 (FORS1–)	*GBGT1*01N.02*[b]	2 7	58C>T 887G	Leu20Phe Arg296	(Common)
FORS:–1 (FORS1–)	*GBGT1*01N.03*[c]	7	363C>A	Tyr121Stop	(Several)

^The sequences encoding these alleles have been deposited in the EMBL database under the following accession numbers: HE583599[a] (consensus), HE583600[b], HE583596[c].

Amino acid sequence for globoside 3-α-*N*-acetylgalactosaminyltransferase 1

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MHRRRLALGL  GFCLLAGTSL  SVLWVYLENW  LPVSYVPYYL  PCPEIFNMKL   50
HYKREKPLQP  VVWSQYPQPK  LLEHRPTQLL  TLTPWLAPIV  SEGTFNPELL  100
QHIYQPLNLT  IGVTVFAVGK  YTHFIQSFLE  SAEEFFMRGY  RVHYYIFTDN  150
PAAVPGVPLG  PHRLLSSIPI  QGHSHWEETS  MRRMETISQH  IAKRAHREVD  200
YLFCLDVDMV  FRNPWGPETL  GDLVAAIHPS  YYAVPRQQFP  YERRRVSTAF  250
VADSEGDFYY  GGAVFGGQVA  RVYEFTRGCH  MAILADKANG  IMAAWREESH  300
LNRHFISNKP  SKVLSPEYLW  DDRKPQPPSL  KLIRFSTLDK  DISCLRS     347
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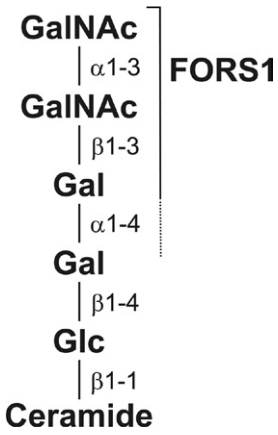
Carrier molecule

The *GBGT1* gene product adds α1-3GalNAc to globoside (the P antigen).



Function

The *GBGT1*-encoded glycosyltransferase catalyzes the formation of Forssman glycolipids via the addition of *N*-acetylgalactosamine (GalNAc) in α-1,3-linkage to its acceptor substrate globoside, the P antigen.

Disease association

Glycolipids serve as involuntary receptors for the adherence of selected pathogens. P-fimbriated strains (expressing the PrsG adhesin that binds to terminal α3GalNAc) of *E. coli* attach to non-primate mammal cells expressing FORS1 antigen[3]. A_{pae} RBCs bind nephritogenic PrsG+ *E. coli* strains *in vitro*[4]. It is possible that FORS1 expression on human cells may increase the

susceptibility for infections with *E. coli* that normally prefer non-primate mammal hosts such as dogs and sheep. Cells expressing Forssman glycolipids are less susceptible to the effects of Shiga toxin[5].
Several studies have shown appearance of Forssman glycolipid in human cancer cells, such as lung, colon, and stomach malignancies.

Comments

Forssman glycolipid is widely considered an animal structure with unequal distribution (for instance present in mouse, sheep, dog, cat, and horse, but not in rat, rabbit, and primates). The amino acid sequence of Forssman synthetase in humans differs from that of the canine enzyme by substitution of 58 residues, one of which is amino acid 296 that is altered to the canine version in A_{pae} individuals resulting in FORS1+ RBCs.

References

[1] Stamps, R., et al., 1987. A new variant of blood group A. Apae. Transfusion 27, 315–318.
[2] Hult, A.K., et al., 2011. Forssman expression on human red cells: biochemical and genetic basis of a novel histo-blood group system candidate [abstract]. Transfusion 51 (Suppl. 3), 1A.
[3] Xu, H., et al., 1999. Characterization of the human Forssman synthetase gene. an evolving association between glycolipid synthesis and host–microbial interactions. J Biol Chem 274, 29390–29398.
[4] Hult, A.K., et al., 2011. Genetic basis of Forssman antigen expression on human red cell blood cells [abstract]. Vox Sang 101 (Suppl. 2), 33.
[5] Elliott, S.P., et al., 2003. Forssman synthetase expression results in diminished shiga toxin susceptibility: a role for glycolipids in determining host-microbe interactions. Infect Immun 71, 6543–6552.

FORS1 Antigen

Terminology

ISBT symbol (number)	FORS1 (031001 or 31.1)
Obsolete names	A_{pae}
History	Forssman antigen has been known since 1911, following Prof. Forssman's experiments in which extracts of guinea pig kidney were injected into rabbits[1]. The resulting immune sera hemolyzed sheep erythrocytes. A century later, the supposed ABO subgroup A_{pae} was shown to be independent of the ABO system, but dependent on expression of Forssman glycolipids on RBCs, and the phenotype was renamed FORS1+.

Occurrence

Caucasians	<0.1%

Molecular basis associated with expression of FORS1 antigen on RBCs[2]

Amino acid	Gln296
Nucleotide	A at bp 887 in exon 7
FORS– (wild type)	Arg296 and G at bp 887

Effect of enzymes and chemicals on FORS1 antigen on intact RBCs

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

In vitro characteristics of anti-FORS1

Immunoglobulin class	IgM (some IgG)
Optimal technique	RT or 4°C; enzymes

Clinical significance of anti-FORS1

Not known.

Comments

Group O RBCs expressing FORS1 antigen are agglutinated strongly by *Helix pomatia*, but not by *Dolichos biflorus*, and weakly by some polyclonal anti-A and anti-A,B reagents, but not by monoclonal anti-A. The terminal α3GalNAc attached to the H carbohydrate structure confers the A antigen, but when attached to the P carbohydrate structure confers the FORS1 antigen. This provides an explanation of the cross-reactivity with some anti-A.

FORS1+ donor RBCs may result in a weakly or strongly positive cross-match reaction due to naturally-occurring anti-FORS1 in the plasma of ABO-compatible FORS1– individuals.

References

[1] Forssman, J., 1911. Die Herstellung hochwertiger spezifisher Schafhämolysine ohne Verwendung von Schafblut: Ein Beitrag Zur Lehre von heterologer Antikörperbildung. Biochemische Zeitung 37, 78–115.

[2] Hult, A.K., et al., 2011. Forssman expression on human red cells: biochemical and genetic basis of a novel histo-blood group system candidate [abstract]. Transfusion 51 (Suppl. 3), 1A.