

John Milton Hagen Blood Group System

Number of antigens 6

High prevalence **JMH, JMHK, JMHL, JMHG, JMHM, JMHQ**

Terminology

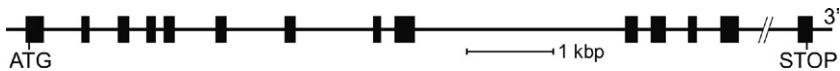
ISBT symbol (number)	JMH (026)
CD number	CD108
Obsolete names	901007; Sema7A
History	JMH became a system in 2000 after it was shown that the JMH glycoprotein is CD108 ¹ , and the gene encoding CD108 was cloned ^{2,3} .

Expression

Red blood cells	Aberrant expression on RBCs can be (transiently) acquired, and study of people with JMH– or JMH-weak phenotypes suggests a post-transcriptional or post-translational mechanism may affect RBC expression ⁴ .
Other blood cells	Weak on lymphocytes, strong on activated lymphocytes and activated macrophages ¹ .
Tissues	Neurons of central nervous system; respiratory epithelium, placenta, testes, spleen ⁵ , keratinocytes and fibroblasts in the skin ⁶ , and odontoblasts ⁷ ; low expression in brain and thymus

Gene^{2,3}

Chromosome 15q24.1
Name *JMH* (*SEMA7A*, *CD108*, *SEMA-L*)
Organization 14 exons over 9 kb of gDNA
Product Semaphorin 7A; JMH; CD108; H-Sema-L



Database accession numbers

GenBank AF069493 (mRNA); AY885237 (gene);
NM_003612
Entrez Gene ID 8482

Molecular bases of John Milton Hagen phenotypes

The reference allele, *JMH*01* (Accession number AY885237) encodes JMH (JMH1), JMH2, JMH3, JMH4, JMH5, JMH6. Nucleotide differences from this reference allele, and the amino acids affected, are given.

Allele encodes	Allele name	Exon	Nucleotide	Amino acid	Ethnicity (prevalence)
JMHK– or JMH:–2	<i>JMH*01.–02</i>	6	619C>T	Arg207Trp	Japanese (Rare)
JMHL– or JMH:–3	<i>JMH*01.–03</i>	6	620G>A	Arg207Gln	Canadian, German (Rare)
JMHG– or JMH:–4	<i>JMH*01.–04</i>	11	1379G>A	Arg460His	American (Rare)
JMHM– or JMH:–5	<i>JMH*01.–05</i>	11	1381C>T	Arg461Cys	Polish (Rare)
JMHQ– or JMH:–6	<i>JMH*01.–06</i>	9	1040G>T	Arg347Leu	Native American (Few)

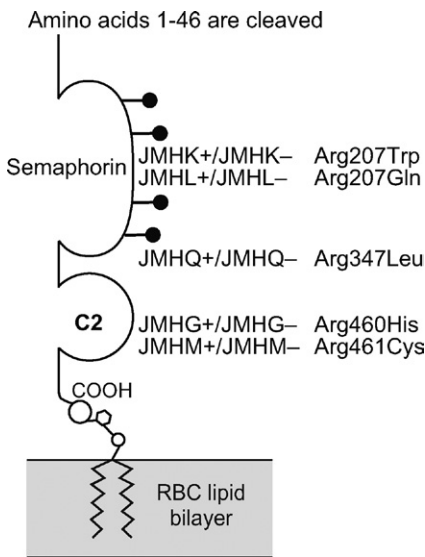
Amino acid sequence²

MTPPPPGRAA	PSAPRARVPG	PPARLGLPLR	LRLLLLLWAA	AASAQGHLSR	50
GPRIFAVWKG	HVGQDRVDFG	QTEPHTVLFH	EPGSSSVWVG	GRGKVYLFDF	100
PEGKNASVRT	VNIGSTKGSC	LDKRDCENYI	TLLERRSEGL	LACGTNARHP	150
SCWNLVNGTV	VPLGEMRGYA	PFSPDENSLV	LFEGDEVYST	IRKQEYNGKI	200
PRFRRIRGES	ELYTSDTVMQ	NPQFIKATIV	HQDQAYDDKI	YFFRFREDNPD	250
KNPEAPLNVS	RVAQLCRGDQ	GGESSLSVSK	WNTFLKAMLV	CSDAATNKNF	300
NRLQDVFLLP	DPSGQWRDTR	VYGVFSNPWN	YSAVCVYSLG	DIDKVFTSS	350
LKGYHSSLPN	PRPGKCLPDQ	QPIPTETFQV	ADRHPEVAQR	VEPMGPLKTP	400
LFHSKYHYQK	VAVHRMQASH	GETFHVLYLT	TDRGTIHKVV	EPGEQEHSFA	450
FNIMEIQPFR	RAAAIQTMSL	DAERRKLYVS	SQWEVSQVPL	DLCEVYGGGC	500
HGCLMSRDPY	CGWDQGRGIS	IYSSERSVLQ	SINPAEPHKE	CPNPKPKAP	550
LQKVS LAPNS	RYYLSCP MES	RHATYSWRHK	ENVEQSCPEP	HQSPNCILFI	600
ENLTAQQYGH	YFCEAQEGSY	FREAQHWQLL	PEDGIMAEHL	LGHACALAAS	650
LWLGVLPTLT	LGLLVH				666

A signal peptide of 46 amino acids is cleaved after membrane attachment.
A GPI anchor motif of 19 amino acids is cleaved.

Carrier molecule¹

A GPI-linked glycoprotein.



<i>M_r</i> (SDS-PAGE)	68,000 to 76,000
CHO: N-glycan	5 potential; 4 likely
Cysteine residues	19

Function

Secreted and membrane-bound Sema7A function as signals which guide axons in developing nervous tissue⁸. Sema7A is also involved in immune responses, particularly in the effector phase of cellular immunity⁹. It has been described to stimulate human monocytes, and be an effector molecule in T cell-mediated inflammation, and may have an important role in limiting autoimmune response¹⁰. CD108 contains an Arg-Gly-Asp (267-269) cell attachment motif, which is common in adhesion molecules. The main receptors for Sema7A identified so far are $\alpha_1\beta_1$ integrin^{5,6}, and plexin C1¹¹. Function of Sema7A on RBCs is not known.

References

- ¹ Mudad, R., et al., 1995. Evidence of CDw108 membrane protein bears the JMH blood group antigen. *Transfusion* 35, 566–570.
- ² Lange, C., et al., 1998. New eukaryotic semaphorins with close homology to semaphorins of DNA viruses. *Genomics* 51, 340–350.
- ³ Yamada, A., et al., 1999. Molecular cloning of a glycosylphosphatidylinositol-anchored molecule CDw108. *J Immunol* 162, 4094–4100.
- ⁴ Seltsam, A., et al., 2007. The molecular diversity of Sema7A, the semaphorin that carries the JMH blood group antigens. *Transfusion* 47, 133–146.
- ⁵ Bobolis, K.A., et al., 1992. Isolation of the JMH antigen on a novel phosphatidylinositol-linked human membrane protein. *Blood* 79, 1574–1581.
- ⁶ Scott, G.A., et al., 2008. Semaphorin 7a promotes spreading and dendricity in human melanocytes through beta1-integrins. *J Invest Dermatol* 128, 151–161.
- ⁷ Maurin, J.C., et al., 2005. Odontoblast expression of semaphorin 7A during innervation of human dentin. *Matrix Biol* 24, 232–238.
- ⁸ Pasterkamp, R.J., et al., 2003. Semaphorin 7A promotes axon outgrowth through integrins and MAPKs. *Nature* 424, 398–405.
- ⁹ Suzuki, K., et al., 2007. Semaphorin 7A initiates T-cell-mediated inflammatory responses through alpha1beta1 integrin. *Nature* 446, 680–684.
- ¹⁰ Czopik, A.K., et al., 2006. Semaphorin 7A is a negative regulator of T cell responses. *Immunity* 24, 591–600.
- ¹¹ Tamagnone, L., et al., 1999. Plexins are a large family of receptors for transmembrane, secreted, and GPI-anchored semaphorins in vertebrates. *Cell* 99, 71–80.

JMH Antigen

Terminology

ISBT symbol (number)	JMH1 (026001 or 26.1)
Obsolete names	John Milton Hagen; “Old Boys”; 900018
History	Named after the first antibody producer, John <u>M</u> ilton <u>H</u> agen.

Occurrence

All populations 100%

Expression

Cord RBCs	Weak (some variation)
Altered	JMH variants
Absent	PNH III RBCs

Molecular basis associated with JMH antigen

The original JMH– phenotype was the acquired type.
For Molecular basis of JMH phenotypes see table in System pages.

Effect of enzymes and chemicals on JMH antigen on intact RBCs¹

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

In vitro characteristics of alloanti-JMH

Immunoglobulin class	IgG (predominantly IgG4 in people with the acquired JMH-negative phenotype)
Optimal technique	IAT

Clinical significance of alloanti-JMH

Transfusion reaction	No
HDFN	No

Autoanti-JMH

Autoanti-JMH is often found in elderly persons with an acquired absent or weak expression of JMH; the DAT may be positive.

Comments

One family has shown dominant inheritance of the JMH-negative phenotype in three generations².
Alloanti-JMH, present in JMH-positive individuals are due to variant forms of CD108; see JMHK, JMHL, JMHG, JMHM, and JMHQ below.

References

- ¹ Mudad, R., et al., 1995. JMH variants: serologic, clinical, and biochemical analyses in two cases. *Transfusion* 35, 925–930.
- ² Kollmar, M., et al., 1981. Evidence of a genetic mechanism for the production of the JMH negative phenotype [abstract]. *Transfusion* 21, 612.

JMHK Antigen

Terminology

ISBT symbol (number)	JMH2 (026002 or 26.2)
History	Found in 1984, and named in 2006 from “JMH” for the system, and “K” from the first initial of the family name of the JMHK– proband ¹ .

Occurrence

Only one Japanese JMHK– proband has been reported.

Antithetical antigen

JMHL (JMH3)

Expression

Cord RBCs	Presumed expressed (may be some variation)
Absent	PNH III RBCs

Molecular basis associated with JMHK antigen²

Amino acid	Arg207
Nucleotide	C at bp 619 in exon 6
JMHK–	Trp207 and T at bp 619

Effect of enzymes and chemicals on JMHK antigen on intact RBCs³

Ficin/Papain	Sensitive
Trypsin	Sensitive
α-Chymotrypsin	Presumed sensitive
DTT 200 mM/50 mM	Presumed sensitive

In vitro characteristics of alloanti-JMHK

Immunoglobulin class	IgG (IgG1, IgG2, and/or IgG3)
Optimal technique	IAT

Clinical significance of alloanti-JMHK

Transfusion reaction	Decreased RBC survival ¹
HDFN	No data

Comments

Cross-testing showed that the JMHK and JMHL variants are mutually compatible².

References

¹ Moulds, J.J. 2011. Personal Communication.

² Seltsam, A., et al., 2007. The molecular diversity of Sema7A, the semaphorin that carries the JMH blood group antigens. Transfusion 47, 133–146.

³ Mudad, R., et al., 1995. JMH variants: serologic, clinical, and biochemical analyses in two cases. Transfusion 35, 925–930.

JMHL Antigen

Terminology

ISBT symbol (number)	JMH3 (026003 or 26.3)
History	Found in 1984, and named in 2006 from “JMH” for the system and “L” from the first initial of the family name of the JMHL– proband ¹ .

Occurrence

Two JMHL– probands, one from Canada and one from Germany.

Antithetical antigen

JMHK (JMH2)

Expression

Cord RBCs	Presumed expressed (may be some variation)
Absent	PNH III RBCs

Molecular basis associated with JMHL antigen²

Amino acid	Arg207
Nucleotide	G at bp 620 in exon 6
JMHL–	Gln207 and A at bp 620

Effect of enzymes and chemicals on JMHL antigen on intact RBCs³

Ficin/Papain	Sensitive
Trypsin	Sensitive
α-Chymotrypsin	Presumed sensitive
DTT 200 mM/50 mM	Presumed sensitive

In vitro characteristics of alloanti-JMHL

Immunoglobulin class	IgG (IgG1, IgG2, and/or IgG3)
Optimal technique	IAT

Clinical significance of alloanti-JMHL

Transfusion reaction	Decreased RBC survival ¹
HDFN	No data

Comment

Cross-testing showed that the JMHL and JMHL variants are mutually compatible².

References

¹ Moulds J.J. 2011. Personal Communication.

² Seltsam, A., et al., 2007. The molecular diversity of Sema7A, the semaphorin that carries the JMHL blood group antigens. Transfusion 47, 133–146.

³ Mudad, R., et al., 1995. JMHL variants: serologic, clinical, and biochemical analyses in two cases. Transfusion 35, 925–930.

JMHG Antigen

Terminology

ISBT symbol (number)	JMH4 (026004 or 26.4)
History	Found in 1981, and named in 2006 from “JMH” for the system and “G” from the first initial of the family name of the JMHG– proband ¹ .

Occurrence

One JMHG– proband from Florida, USA.

Expression

Cord RBCs	Presumed expressed (may be some variation)
Absent	PNH III RBCs

Molecular basis associated with JMHG antigen²

Amino acid	Arg460
Nucleotide	G at bp 1379 in exon 11
JMHG–	His460 and A at bp 1379

Effect of enzymes and chemicals on JMHG antigen on intact RBCs

Ficin/Papain	Sensitive
Trypsin	Sensitive
α-Chymotrypsin	Presumed sensitive
DTT 200 mM/50 mM	Presumed sensitive

In vitro characteristics of alloanti-JMHG

Immunoglobulin class	IgG (IgG1, IgG2, and/or IgG3)
Optimal technique	IAT

Clinical significance of alloanti-JMHG

No data because only one anti-JMHG has been described.

Comment

The anti-JMHG was compatible with JMHM– RBCs, but anti-JMHM reacted with JMHG– RBCs².

References

¹ Moulds, J.J. 2011. Personal Communication.
² Seltsam, A., et al., 2007. The molecular diversity of Sema7A, the semaphorin that carries the JMH blood group antigens. Transfusion 47, 133–146.

JMHH Antigen

Terminology

ISBT symbol (number)	JMH5 (026005 or 26.5)
History	Found in 1980, and named in 2006 from “JMH” for the system and “M” from the first initial of the family name of the JMHH– proband ¹ .

Occurrence

One JMHH– proband from Israel; of Polish descent.

Expression

Cord RBCs	Presumed expressed (may be some variation)
Absent	PNH III RBCs

Molecular basis associated with JMHM antigen²

Amino acid	Arg461
Nucleotide	C at bp 1381 in exon 11
JMHM–	461Cys and T at bp 1381

Effect of enzymes and chemicals on JMHM antigen on intact RBCs

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

In vitro characteristics of alloanti-JMHM

Immunoglobulin class	IgG (IgG1, IgG2, and/or IgG3)
Optimal technique	IAT

Clinical significance of alloanti-JMHM

No data because only one anti-JMHM has been described.

Comment

The anti-JMHG was compatible with JMHM– RBCs, but anti-JMHM reacted with JMHG– RBCs².

References

- ¹ Moulds, J.J. 2011. Personal Communication.
- ² Seltsam, A., et al., 2007. The molecular diversity of Sema7A, the semaphorin that carries the JMH blood group antigens. *Transfusion* 47, 133–146.

JMHQ Antigen

Terminology

ISBT symbol (number)	JMH6 (026006 or 26.6)
History	Found and named in 2010 from “JMH” for the system and “Q” for Quebec when four JMHQ– probands were found.

Occurrence

All populations 100%
Five JMHQ– probands were Native Americans from a reservation northwest of Quebec City.

Expression

Cord RBCs Presumed expressed (may be some variation)
Absent PNH III RBCs

Molecular basis associated with JMHQ antigen¹

Amino acid Arg347
Nucleotide G at bp 1040 in exon 9
JMHQ– Leu347 and T at bp 1040

Effect of enzymes and chemicals on JMHQ antigen on intact RBCs

Ficin/Papain Sensitive
Trypsin Sensitive
α-Chymotrypsin Presumed sensitive
DTT 200 mM/50 mM Presumed sensitive

In vitro characteristics of alloanti-JMHQ

Immunoglobulin class IgG
Optimal technique IAT

Clinical significance of alloanti-JMHQ

No data because anti-JMHQ is rare.

Comments

The alloanti-JMHQ is compatible with JMH1– RBCs. JMHQ– RBCs are JMH1+¹.

Reference

¹ Richard, M., et al., 2011. A new *SEMA7A* variant found in Native Americans with alloantibody. Vox Sang 100, 322–326.