



INSTITUT NATIONAL DE LA TRANSFUSION SANGUINE

Characterization of a novel high-prevalence antigen in the JMH blood group system

**Cédric Vrignaud^{1,2,3}, Stéphanie Ramelet¹, Alexandre Herb¹, Alexandre Raneri¹,
Mohammed Khalloufi⁴, Guy Laiguillon¹, Jérôme Babinet¹, Slim Azouzi^{1,2,3}, Thierry Peyrard^{1,2,3}**

¹Institut National de la Transfusion Sanguine, CNRGS, Paris, France

²UMR_S1134, Inserm/Université de Paris, Paris, France

³Laboratoire d'Excellence GR-Ex, Paris, France

⁴Etablissement Français du Sang Ile de France, Bobigny, France



THE JMH BLOOD GROUP SYSTEM

- **John Milton Hagen**
- First antigen JMH described in 1978 (Sabo *et al.*)
- First anti-JMH cases identified in elderly men and later also discovered in elderly women
- As the women were often cat owners, the early nicknames of this blood group were “The Boys” and “Cat”!

THE JMH BLOOD GROUP SYSTEM

- Became a blood group system in 2000 (#26)
- GPI-linked protein
 - Semaphorin 7-A (Sema7A), encoded by *SEMA7A*
 - CD108
- RBC antibodies mostly considered clinically irrelevant
- Sema7A has both immune and neurological functions, but unknown role on RBCs

THE JMH BLOOD GROUP SYSTEM

Cell

Structural Basis of Semaphorin-Plexin Recognition and Viral Mimicry from Sema7A and A39R Complexes with PlexinC1

Heli Liu,¹ Z. Sean Juo,^{2,3,4} Ann Hye-Ryong Shim,¹ Pamela J. Focia,¹ Xiaoyan Chen,¹ K. Christopher Garcia,^{2,3,4} and Xiaolin He^{1,*}

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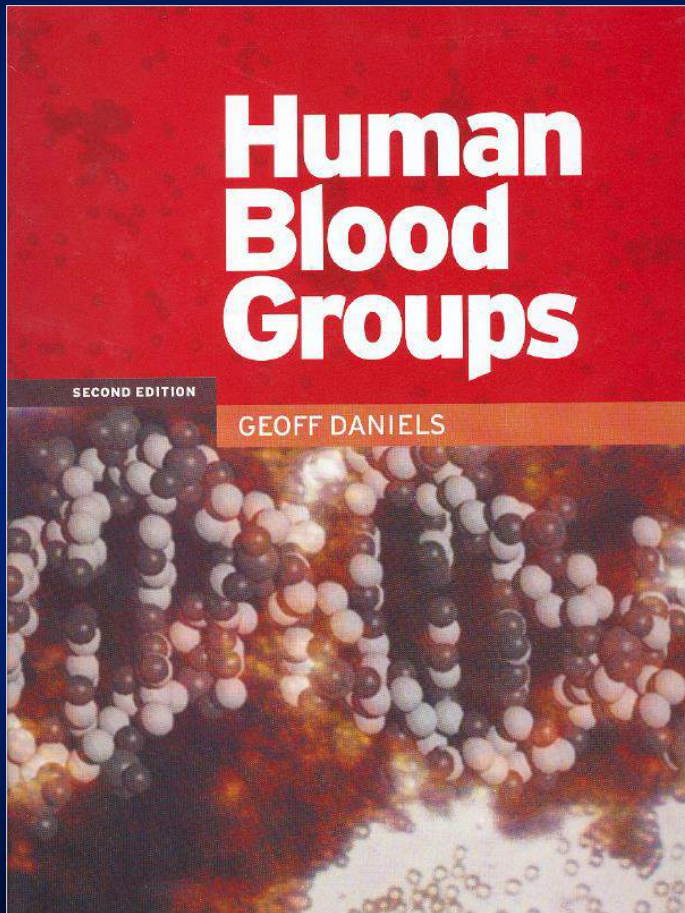
 PLOS | PATHOGENS

Semaphorin-7A Is an Erythrocyte Receptor for *P. falciparum* Merozoite-Specific TRAP Homolog, MTRAP

S. Josefin Bartholdson^{1,2}, Leyla Y. Bustamante², Cecile Crosnier^{1,2}, Steven Johnson³, Susan Lea³, Julian C. Rayner², Gavin J. Wright^{1,2*}

¹ Cell Surface Signalling Laboratory, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom, ² Malaria Programme, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom, ³ Sir William Dunn School of Pathology, University of Oxford, Oxford, United Kingdom

JMH ANTIGENS



2002

JMH blood group system

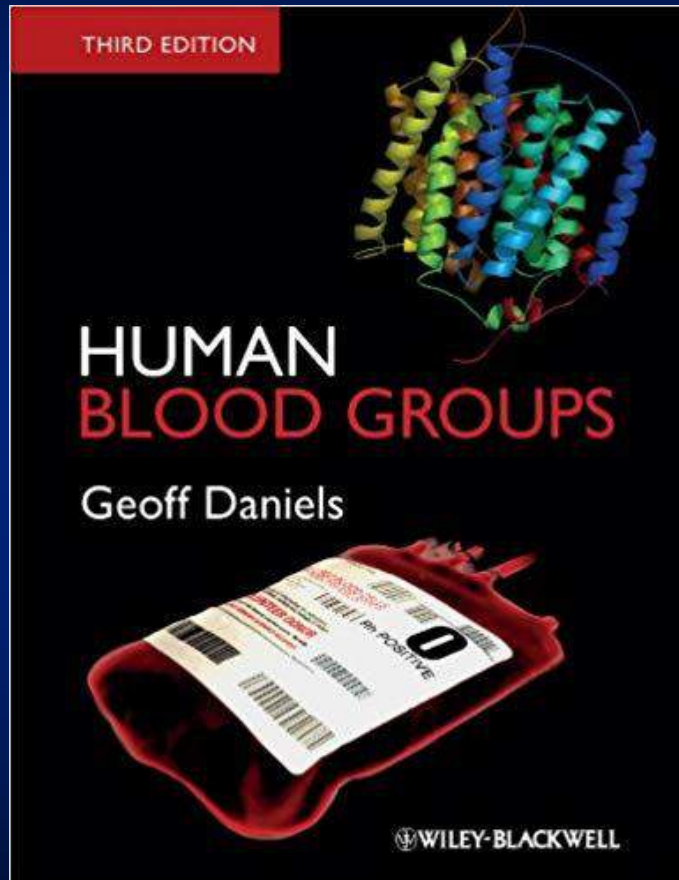
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-

24.1 Introduction

The very high frequency antigen JMH (JMH1) is the only antigen of the John Milton Hagen (JMH) system.

One single antigen

JMH ANTIGENS



2013

JMH Blood Group System

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24.1 Introduction

The original John Milton Hagen (JMH1) antigen represents determinants on the signalling protein semaphorin 7A (Sema7A, CD108). JMH:-1 is usually an acquired phenotype most often found in people over 50 years old. Inherited variants of JMH lacking antigens **JMH2 to JMH6** represent amino acid substitutions in Sema7A resulting from homozygosity for missense mutations in *SEMA7A*.

Five additional antigens

6 ANTIGENS AND 6 RARE BLOOD TYPES

Phenotype	Alternate name	Allele name	Molecular basis	Exon	Amino acid change	Comments
JMH:–1	JMH–		Unknown		Protein deficiency	<ul style="list-style-type: none"> ✓ Acquired ✓ May be transient ✓ Mostly in elderly people
JMH:–2	JMHK–	<i>JMH*01.–02</i>	c.619C>T	6	p.Arg207Trp	Japanese
JMH:–3	JMHL–	<i>JMH*01.–03</i>	c.620G>A	6	p.Arg207Gln	Canadian German French
JMH:–4	JMHG–	<i>JMH*01.–04</i>	c.1379G>A	11	p.Arg460His	American
JMH:–5	JMHM–	<i>JMH*01.–05</i>	c.1381C>T	11	p.Arg461Cys	Polish
JMH:–6	JMHQ–	<i>JMH*01.–06</i>	c.1040G>T	9	p.Arg347Leu	Native Americans

IS THE LIST OF JMH ANTIGENS TO BE CONTINUED?

VoxSanguinis

The International Journal of Transfusion Medicine

ISBT International Society
of Blood Transfusion

Vox Sanguinis (2011) 100, 322–326

ORIGINAL PAPER

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DOI: 10.1111/j.1423-0410.2010.01413.x

A new *SEMA7A* variant found in Native Americans with alloantibody

M. Richard,¹ J. St-Laurent,¹ J. Perreault,¹ A. Long² & M. St-Louis¹

¹Research and Development, Héma-Québec, Quebec City, QC, Canada

²Medical Affairs Haematology, Héma-Quebec, Quebec City, QC, Canada

**No novel JMH antigen since 2011
=> Others to be discovered?**

STUDY BACKGROUND

Proband

- 32-year-old female patient
- Moroccan origin
- Pregnant
- Antibody to a high-prevalence RBC antigen

ANTIBODY IDENTIFICATION

	RH						KEL				FY		JK		LE		MNS				P1PK	LU		IAT	IAT Papain	IAT Trypsin
	D	C	E	c	e	C ^w	K	k	Kp ^a	Kp ^b	Fy ^a	Fy ^b	Jk ^a	Jk ^b	Le ^a	Le ^b	M	N	S	s	P1	Lu ^a	Lu ^b			
1	0	+	0	0	+	0	0	+	0	+	+	+	+	+	0	0	+	0	+	0	+	0	+	1+	0	0
2	0	0	+	+	+	0	0	+	0	+	+	+	+	0	0	+	0	+	0	+	+	0	+	1+	0	0
3	0	0	0	+	+	0	+	+	0	+	+	0	0	+	0	+	+	0	+	+	+	+	+	1+	0	0
4	0	0	0	+	+	0	0	+	0	+	0	+	+	+	+	0	+	+	+	+	+	+	+	1+	0	0
5	0	0	0	+	+	0	0	+	0	+	0	+	+	+	0	0	+	0	+	0	+	0	+	1+	0	0
6	0	0	0	+	+	0	0	+	0	+	0	+	+	0	0	+	+	+	0	+	0	+	+	1+	0	0
7	+	0	+	+	0	0	0	+	0	+	0	+	0	+	0	+	0	+	0	+	+	0	+	1+	0	0
8	+	+	0	0	+	+	0	+	0	+	+	0	0	+	0	+	+	+	+	0	+	+	+	1+	0	0
9	+	+	0	0	+	0	+	+	0	+	+	+	+	0	0	+	0	+	+	+	0	0	+	1+	0	0
10	+	+	0	0	+	0	0	+	0	+	+	0	+	+	0	+	0	+	0	+	+	0	+	1+	0	0
11	+	0	0	+	+	0	0	+	0	+	+	+	+	0	+	0	+	0	+	0	0	0	+	1+	0	0
12	+	+	+	0	+	0	0	+	0	+	+	+	+	0	0	+	+	+	0	+	+	0	+	1+	0	0
13	+	+	0	0	+	0	0	+	+	+	+	+	+	0	0	+	+	+	0	+	0	0	+	1+	0	0
14	+	+	0	0	+	0	+	+	0	+	+	+	+	0	+	+	0	+	0	+	+	0	+	1+	0	0
15	0	0	0	+	+	0	0	+	0	+	+	0	+	0	0	+	0	+	0	+	+	0	+	1+	0	0
																						Autocontrols	0	0	0	

First hypothesis was anti-Ge2 due to the pattern of reactivity and ethnic background

SEROLOGICAL WORKUP

- Anti-Ge2 could be ruled out
 - The serum was nonreactive with two JMH:–1 samples but the patient was found to be JMH:1
 - JMH:–3 RBCs were positive with the patient's serum => not an anti-JMH3
 - Antibody was found to be an **IgG4**, consistent with a JMH-related antibody
- ⇒ **Antibody to a high-prevalence antigen other than JMH1 and JMH3?**

SEROLOGICAL WORKUP

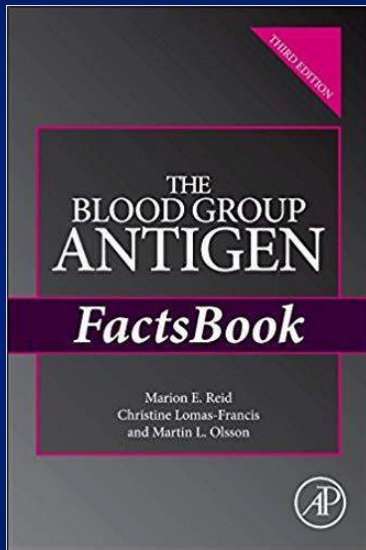
- A **soluble recombinant JMH protein** (JMH Imusyn/Inno-train) **fully abolished the reactivity of the antibody** => confirms the antibody to be related to the JMH blood group system
 - No JMH:–2, JMH:–4, JMH:–5, JMH:–6 rare cells in our inventory to be tested with the patient's serum
- => Genomic DNA sequencing of *SEMA7A***

MOLECULAR TESTING

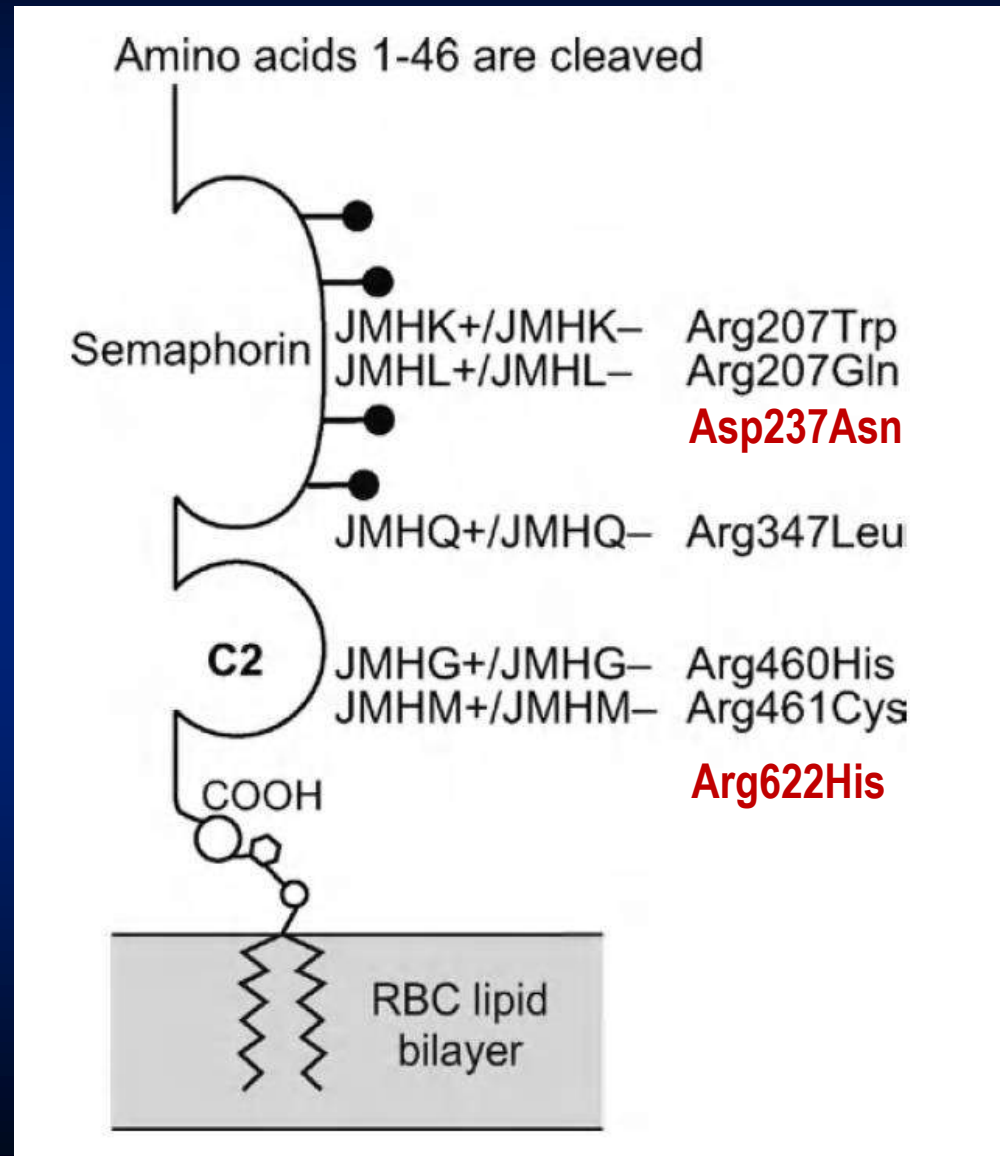
Three nucleotide changes, in homozygous state
(NM_003612.4, SEMA7A transcript variant 1)

- **A common synonymous change in exon 12,**
c.1545A>G p.Gln515Gln, rs741761, MAF=0.5 (1000G)
- **A rare non-synonymous change in exon 7, c.709G>A**
p.Asp237Asn, rs140707085, MAF<0.001, SIFT score 1
(tolerated)
- **A rare non-synonymous change in exon 14,**
c.1865G>A p.Arg622His, rs140128092, MAF<0.001,
SIFT score 0.36

MOLECULAR TESTING



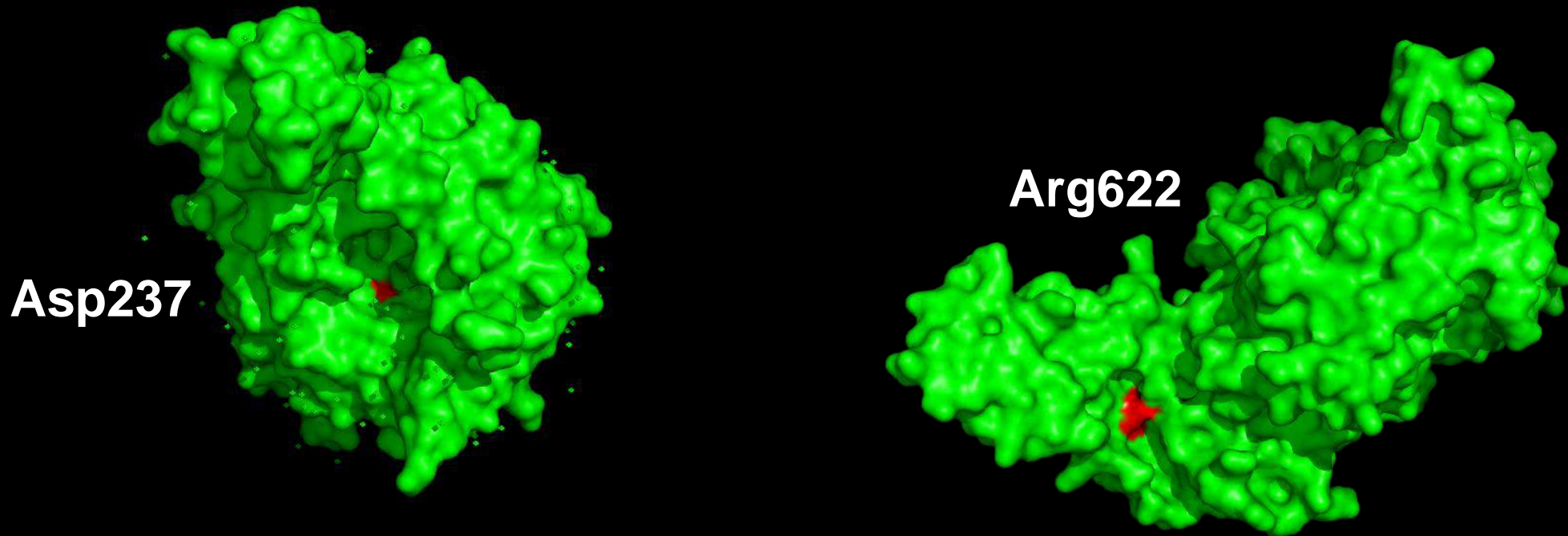
Adapted from



3D-STRUCTURE STUDY OF SEMA7A

Analysis of surface accessibility of Asp237 and Arg622 using the 3D structure of Sema7A (*PDB ID 3NVQ*)

Arg622 is predicted to be the most exposed-epitope and to be the likely critical amino acid change in Sema7A



Needs to be confirmed by other studies (site-directed mutagenesis)

A NOVEL HIGH-PREVALENCE JMH ANTIGEN

- Another case later found in a pregnant woman of Algerian ancestry, with the same 3 changes in homozygous state
- **Novel JMH antigen** acknowledged last Saturday by the *ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology* => **JMH7**
- **JMHN** for “North Africa” was proposed and accepted as the conventional alternate name

7 ANTIGENS AND 7 RARE BLOOD TYPES

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JMH:–7	JMHN–	<i>JMH*01.–07</i>	c.709G>A c.1865G>A	7 14	p.Asp237Asn p.Arg622His	North Africans

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ACKNOWLEDGEMENTS

**All the staff of the French National Immunohematology Reference Laboratory
Collaborators Specialists in Laboratory Medicine**

- Dr. Jérôme Babinet
- Dr. Marie Cuingnet
- Dr. Vincent Thonier

**Research and development team
National IRL and UMR_S1134
Inserm/University of Paris**



Dr. Slim Azouzi



Cédric Vrignaud

