Journées du Collège d'Hématologie des Hôpitaux
8 décembre 2025

La découverte des nouveaux groupes sanguins : enjeux en médecine transfusionnelle et physio-pathologie humaine

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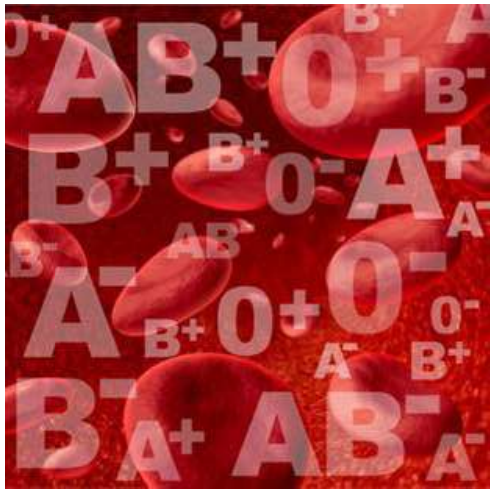
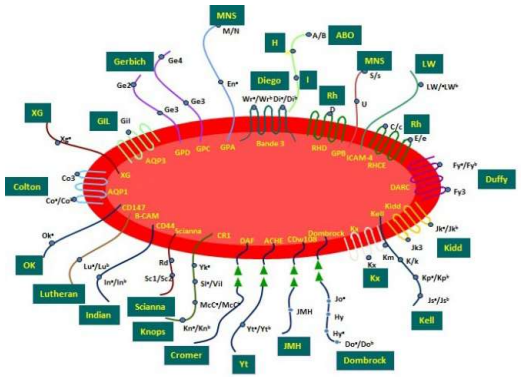
LES GROUPES SANGUINS





1ère détermination le 14/05/2019

A Rh Positif D+C+E-c+e+, K- (RH:1,2,-3,4,5; KEL:-1)

2ème détermination le 15/05/2019

A Rh Positif D+C+E-c+e+, K- (RH:1,2,-3,4,5; KEL:-1)

Phénotypage de routine (ABO/Rh/K)
8 antigènes testés A, B, D, C, E, c, e, K,
répartis dans 3 systèmes
(ABO, Rh, Kell)

Phénotypage étendu : 6 antigènes supplémentaires chez les patients transfusés chroniques et/ou allo-immunisés
Fy^a/Fy^b, Jk^a/Jk^b, S/s, répartis dans 3 systèmes
(Duffy, Kidd, MNS)

LES ANTIGÈNES ET SYSTÈMES DE GROUPES SANGUINS

ISBT (Société Internationale de Transfusion Sanguine) 2025

- **48 systèmes de groupes sanguins**
  - **371 antigènes**
  - **53 gènes (plus 2 gènes associés : *GATA1, KLF1)***
- **Autres familles d'antigènes**
  - **Collections : 9 antigènes**
  - **Série 700 : 16 antigènes**
  - **Série 901 : 2 antigènes**

=>Total de 398 antigènes érythrocytaires chez l'Homme

N°	Nom du système	Symbole	Gène(s)	Chromosome	Nombre total d'antigènes	Nombre d'antigènes de prévalence > 99%	Nombre d'antigènes de prévalence < 1%	Nombre d'antigènes de prévalence 1 à 99%
001	**ABO**	ABO	*ABO*	9q34.2	4	0	0	4
002	**MNS**	MNS	*GYPA, GYPB, GYPE*	4q31.21	50	10	36	4
003	**P1PK**	P1PK	*A4GALT*	22q11.2–qter	3	1	1	1
004	**Rh**	RH	*RHD, RHCE*	1p36.11	56	14	27	15
005	**Lutheran**	LU	*LU*	19q13.32	29	24	1	4
006	**Kell**	KEL	*KEL*	7q34	38	25	11	2
007	**Lewis**	LE	*FUT3*	19p13.3	6	0	0	6
008	**Duffy**	FY	*ACKR1*	1q23.2	5	3	0	2
009	**Kidd**	JK	*SLC14A1*	18q12.3	3	1	0	2
010	**Diego**	DI	*SLC4A1*	17q21.31	23	3	20	0
011	**Yt**	YT	*ACHE*	7q22.1	6	5	0	1

N°	Nom du système	Symbole	Gène(s)	Chromosome	Nombre total d'antigènes	Nombre d'antigènes de prévalence > 99%	Nombre d'antigènes de prévalence < 1%	Nombre d'antigènes de prévalence 1 à 99%
012	**Xg**	XG	*XG, CD99*	Xp22.33	2	1	0	1
013	**Scianna**	SC	*ERMAP*	1p34.2	11	7	4	0
014	**Dombrock**	DO	*ART4*	12p12.3	10	8	0	2
015	**Colton**	CO	*AQP1*	7p14.3	4	3	0	1
016	**Landsteiner-Wiener**	LW	*ICAM4*	19p13.2	4	3	1	0
017	**Chido/ Rodgers**	CH/RG	*C4B, C4A*	6p21.3	9	3	0	6
018	**H**	H	*FUT1*	19q13.33	1	1	0	0
019	**Kx**	XK	*XK*	Xp21.1	1	1	0	0
020	**Gerbich**	GE	*GYPC*	2q14.3	13	8	5	0
021	**Cromer**	CROM	*CD55*	1q32.2	21	18	3	0
022	**Knops**	KN	*CR1*	1q32.2	14	3	2	9
023	**Indian**	IN	*CD44*	11p13	6	5	1	0
024	**Ok**	OK	*BSG*	19p13.3	3	3	0	0

N°	Nom du système	Symbole	Gène(s)	Chromosome	Nombre total d'antigènes	Nombre d'antigènes de prévalence > 99%	Nombre d'antigènes de prévalence < 1%	Nombre d'antigènes de prévalence 1 à 99%
025	**Raph**	RAPH	*CD151*	11p15.5	1	0	0	1
026	**John Milton Hagen**	JMH	*SEMA7A*	15q24.1	8	8	0	0
027	**I**	I	*GCNT2*	6p24.2	1	1	0	0
028	**Globoside**	GLOB	*B3GALT3*	3q26.1	3	2	0	1
029	**Gill**	GIL	*AQP3*	9p13.3	1	1	0	0
030	**Rh-associated glycoprotein**	RHAG	*RHAG*	6p21-qter	6	2	4	0
031	**Forssman**	FORS	*GBGT1*	9q34.2	1	0	1	0
032	**Jr**	JR	*ABCG2*	4q22.1	1	1	0	0
033	**Langereis**	LAN	*ABCB6*	2q36	1	1	0	0
034	**Vel**	VEL	*SMIM1*	1p36	1	1	0	0
035	**CD59**	CD59	*CD59*	11p13	1	1	0	0
036	**Augustine**	AUG	*SLC29A1*	6p21.1	4	3	1	0
037	**Kanno**	KANNO	*PRNP*	20p13	1	1	0	0
038	**Sid**	SID	*B4GALNT2*	17q21.32	1	0	0	1

N°	Nom du système	Symbole	Gène(s)	Chromosome	Nombre total d'antigènes	Nombre d'antigènes de prévalence > 99%	Nombre d'antigènes de prévalence < 1%	Nombre d'antigènes de prévalence 1 à 99%
039	**CTL2**	CTL2	*SLC44A2*	19p13.2	5	3	0	2
040	**Pel**	PEL	*ABCC4*	13q32.1	1	1	0	0
041	**Mam**	MAM	*EMP3*	19q13.3	1	1	0	0
042	**Emm**	EMM	*PIGG*	4p16.3	1	1	0	0
043	**ABCC1**	ABCC1	*ABCC1*	16p13	1	1	0	0
044	**Er**	ER	*PIEZO1*	16q24.3	5	4	1	0
045	**CD36**	CD36	*CD36*	7q11.2	1	1	0	0
046	**ATP11C**	ATP11C	*ATP11C*	Xq27.1	1	1	0	0
047	**MAL**	MAL	*MAL*	2q11.1	1	1	0	0
048	**PIGZ**	PIGZ	*PIGZ*	3q29	1	1	0	0
Total	**48 systèmes**		**53 gènes**		**371**	**187**	**119**	**65**

Number	Name of the system	Symbol
025	**Raph**	RAPH
026	**John Milton Hagen**	JMH
027	**I**	I
028	**Globoside**	GLOB
029	**Gill**	GIL
030	**Rh-associated glycoprotein**	RHAG
031	**Forssman**	FORS
032	**Jr**	JR
033	**Langereis**	LAN
034	**Vel**	VEL
035	**CD59**	CD59
036	**Augustine**	AUG
037	**Kanno**	KANNO
038	**Sid**	SID

Number	Name of the system	Symbol
039	**CTL2**	CTL2
040	**Pel**	PEL
041	**Mam**	MAM
042	**Emm**	EMM
043	**ABCC1**	ABCC1
044	**Er**	ER
045	**CD36**	CD36
046	**ATP11C**	ATP11C
047	**MAL**	MAL
048	**PIGZ**	PIGZ

Sur les 17 derniers systèmes découverts depuis 2012, 10 ont été mis en évidence par les équipes de recherche de l'UMR_S1134/Université Paris Cité/EFS-CNRGS en première ligne :

JR, LAN, VEL, AUG, CTL2, PEL, EMM, ABCC1, ATP11C, PIGZ

Par ailleurs, depuis 2010, caractérisation de la base moléculaire de 15 nouveaux antigènes

LES COLLECTIONS D'ANTIGÈNES

Collections			Antigènes		
N°	Nom	Symbole	N°	Symbole	Prévalence %
207	Ii	I	207002	I (I2)	>99
210			210001 210002	Le^c Le^d	1 6
213	MN CHO	MN CHO	213001 213002 213003 213004 213005 213006	Hu M1 Tm Can Sext Sj	1 5 (24% Africains) 25 27 <1 2

LES COLLECTIONS D'ANTIGÈNES 2023

Collections			Antigènes		
N°	Nom	Symbole	N°	Symbole	Prévalence %
~~205~~	~~Cost~~	~~COST~~	~~205001~~ ~~205002~~	~~Cs^a (COST1)~~ ~~Cs^b (COST2)~~	~~>98~~ ~~34~~
207	Ii	I	207002	I (I2)	>99
208	Er	ER	208001 208002 208002	Er^a (ER1) Er^b (ER2) Er3 (ER3)	>99 <0.01 >99
210			210001 210002	Le^c Le^d	1 6
213	MN CHO	MN CHO	213001 213002 213003 213004 213005 213006	Hu M1 Tm Can Sext Sj	1 5 (24% Africains) 25 27 <1 2

Cs^a et Cs^b ont rejoint le système n°39 CTL2 en 2024

Correspondent aux antigènes HNA-3a et HNA-3b sur le polynucléaire neutrophile !

blood
Brief Report

TRANSFUSION MEDICINE

The neutrophil antigen 3a/b polymorphism in *SLC44A2* unexpectedly encodes the Cs^a/Cs^b red cell antigens

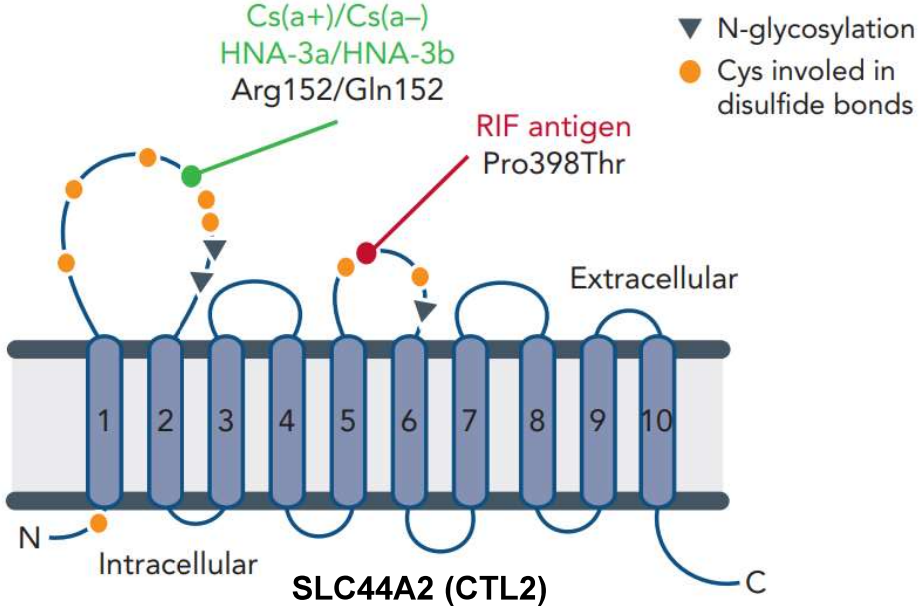
Romain Duval,[1,2,*] Alissa Soudry,[1,*] Jonathan De Oliveira Rios,[1,3] Sarah Liane Linguet,[1] Miguel Taillepierre,[1,4] Graziella Matesic,[1] Alexandre Raneri,[2] Guy Laiguillon,[2] Emilie Le Toriellec,[5] Emilie-Fleur Gautier,[6] Damien Vainqueur,[1,4] Jérôme Babinet,[2] Cécile Masson,[7] Jean Christophe Gelly,[1] Caroline Le Van Kim,[1] Marc Romana,[1] Dawei Chen,[8] Sentot Santoso,[8] Berengere Koehl,[1,9,†] Thierry Peyrard,[1,2,†] and Slim Azouzi[1,2]

[1]Université Paris Cité and Université des Antilles, INSERM, Unité Mixte de Recherche (UMR)-S1134, Laboratory of Blood Group Antigens, Hematopoiesis and Sickle Cell Disease, Paris, France; [2]Centre National de Référence pour les Groupes Sanguins, Établissement Français du Sang Ile-de-France, Paris, France; [3]Laboratory of Hemoglobins and Genetics of Hematologic Diseases, São Paulo State University, São Paulo, Brazil; [4]Établissement Français du Sang, Guadeloupe, Pointe-à-Pitre, France; [5]Laboratoire Human Leukocyte Antigen, Département d'Immunologie Leucoplaquettaire, Établissement Français du Sang Ile-de-France, Créteil, France; [6]Université Paris Cité, UMR_S1016, UMR 8104, Plateforme de Protéomique (3P5), Institut Cochin, Paris, France; [7]Bioinformatics Core Facility, Institut Imagine-Structure Fédérative de Recherche Necker, INSERM U1163 and INSERM US24/CNRS UAR3633, Université Paris Cité, Paris, France; [8]Blood Research Institute, Guangzhou, China; and [9]Sickle Cell Disease Center, Hematology Unit, Hôpital Robert Debré, Assistance Publique–Hôpitaux de Paris, Paris, France

KEY POINTS

- **The HNA-3a/b polymorphism underlies the genetic basis of the Cs^a/Cs^b red cell antigens.**
- **Anti-Cs^a and anti-HNA-3a recognize different epitopes on the SLC44A2 protein.**

The Cs^a blood group antigen was identified >50 years ago, but its genetic basis has yet to be elucidated. All our recent genomic investigation has failed to resolve the genetic basis of this enigmatic antigen. By investigating the association of the human neutrophil antigen (HNA)-3a/b polymorphism (rs2288904-G/A) in *SLC44A2* with clinical features of sickle cell disease, we incidentally discovered that rare subjects with the homozygous HNA-3b/b genotype also carry the uncommon Cs(a–) phenotype. We genotyped this single-nucleotide polymorphism in a cohort of 25 Cs(a–) subjects and found that all of them showed an HNA-3b/b genotype. This result suggests that the high-prevalence allele with rs2288904 (HNA-3a; 455G) encoding Arg152 encodes the high-prevalence Cs^a. Accordingly, anti-Cs^a does not react with solute carrier (SLC)44A2$_{null}$ red blood cells (RBCs),



SLC44A2 (CTL2)

- **L'anticorps anti-Cs^a correspond à l'anticorps anti-HNA-3a**
- **L'anticorps anti-Cs^b correspond à l'anticorps anti-HNA-3b**
- **Allèle *HNA-3b* protecteur vis-à-vis de la thrombose veineuse profonde (diminution du risque de 30%)**
- **Le phénotype Cs(a-) (5% de la population générale) correspond au génotype *HNA-3b/b***
- **Le phénotype Cs(b+) est protecteur vis-à-vis de la thrombose veineuse profonde: Cs(a-b+) et Cs(a+b+)**

Série 700

Antigènes privés, avec un nom attribué
Base moléculaire inconnue

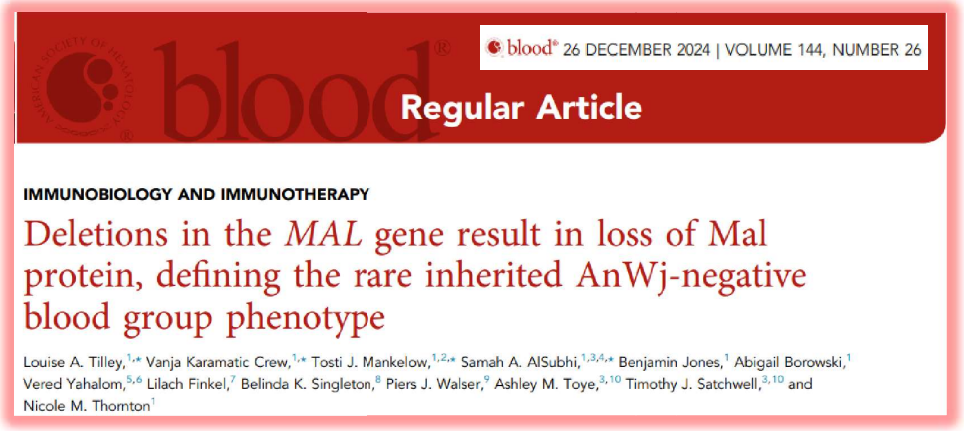
N°	Nom	Symbole
700002	Batty	By
700003	Christiansen	Chr[a]
700005	Biles	Bi
700006	Box	Bx[a]
700017	Torkildsen	To[a]
700018	Peters	Pt[a]
700019	Reid	Re[a]
700021	Jensen	Je[a]
700028	Livesay	Li[a]
700039	Milne	
700040	Rasmussen	RASM
700044		JFV
700047	Jones	JONES
700049		HJK
700050		HOFM
700054		REIT

Série 901

Antigènes publics, avec un nom attribué
Base moléculaire inconnue

N°	Nom	Symbole	Prévalence (%)
901009	Anton	**AnWj**	> 99
901015		**ABTI**	>99
901017	Luke	**LKE**	98

Est devenu fin 2024 le système #47



blood® 26 DECEMBER 2024 | VOLUME 144, NUMBER 26

Regular Article

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Deletions in the *MAL* gene result in loss of Mal protein, defining the rare inherited AnWj-negative blood group phenotype

Louise A. Tilley,[1,*] Vanja Karamatic Crew,[1,*] Tosti J. Mankelow,[1,2,*] Samah A. AlSubhi,[1,3,4,*] Benjamin Jones,[1] Abigail Borowski,[1] Vered Yahalom,[5,6] Lilach Finkel,[7] Belinda K. Singleton,[8] Piers J. Walser,[9] Ashley M. Toye,[3,10] Timothy J. Satchwell,[3,10] and Nicole M. Thornton[1]

Immunohematology
JOURNAL OF BLOOD GROUP SEROLOGY AND EDUCATION
VOLUME 17, NUMBER 1, 2001

Red blood cell antigen changes in malignancy: case report and review

J.L. Winters and D.S. Howard

Lewis	Loss of Lewis antigens	Lewis gene – *19p13* Secretor gene – *19q13*	AML CML Gastric carcinoma
Ii	Decreased I and increased i Increased i with normal I	Unknown	AML CML ALL CLL
MNSs	Loss of s	*4q28*	CML
LW	Loss of LW antigens	*19p13*	Hodgkin's disease Non-Hodgkin's lymphoma
Colton	Loss of Colton antigens	*7p14*	MDS with monosomy 7
AnWj (Anton)	Loss of AnWj	Unknown	Hodgkin's disease Non-Hodgkin's lymphoma
Cromer	Loss of Cromer antigens	*1q32*	PNH MDS
Cartwright	Loss of Cartwright antigens	*7q22*	PNH MDS
Dombrock	Loss of Dombrock antigens	*12p13*	PNH MDS
JMH (John Milton Hagen)	Loss of JMH	*15q23*	PNH MDS
Tn antigen	Expression of Tn antigen	_____	AML Myelofibrosis MDS

Phénotype rare AnWj- de type "acquis" avec apparition concomitante d'un anti-AnWj

Anticorps le plus souvent retrouvé dans hémopathies lymphoïdes (facteur de mauvais pronostic)

Exceptionnel phénotype AnWj- de type récessif (quelques familles dans le monde !)

Le phénotype rare AnWj-

blood
Regular Article

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Deletions in the *MAL* gene result in loss of Mal protein, defining the rare inherited AnWj-negative blood group phenotype

Louise A. Tilley,[1,*] Vanja Karamatic Crew,[1,*] Tosti J. Mankelow,[1,2,*] Samah A. AlSubhi,[1,3,4,*] Benjamin Jones,[1] Abigail Borowski,[1] Vered Yahalom,[5,6] Lilach Finkel,[7] Belinda K. Singleton,[8] Piers J. Walser,[9] Ashley M. Toye,[3,10] Timothy J. Satchwell,[3,10] and Nicole M. Thornton[1]

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KEY POINTS

- The inherited AnWj-negative blood group phenotype is caused by homozygosity for a deletion in *MAL*, encoding Mal protein.
- Mal protein is expressed on red blood cell membranes of AnWj-positive, but not AnWj-negative, individuals.

The genetic background of the high prevalence red blood cell antigen AnWj has remained unresolved since its identification in 1972, despite reported associations with both CD44 and Smyd1 histone methyltransferase. Development of anti-AnWj, which may be clinically significant, is usually due to transient suppression of antigen expression, but a small number of individuals with persistent, autosomally recessive inherited AnWj-negative phenotype have been reported. Whole-exome sequencing of individuals with the rare inherited AnWj-negative phenotype revealed no shared mutations in *CD44H* or *SMYD1*; instead, we discovered homozygosity for the same large exonic deletion in *MAL*, which was confirmed in additional unrelated AnWj-negative individuals. *MAL* encodes an integral multipass membrane proteolipid, myelin and lymphocyte protein (Mal), which has been reported to have essential roles in cell transport and membrane stability. AnWj-positive individuals were shown to express full-length Mal on their red cell membranes, which was not present on the membranes of AnWj-negative individuals, regardless of

dependent pathway. *Nat Med.* 2009;15(2):151-158.

https://doi.org/10.1182/blood.2024026717

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Tilley et al, page 2735

An uncommon MALady: is the AnWj puzzle complete?

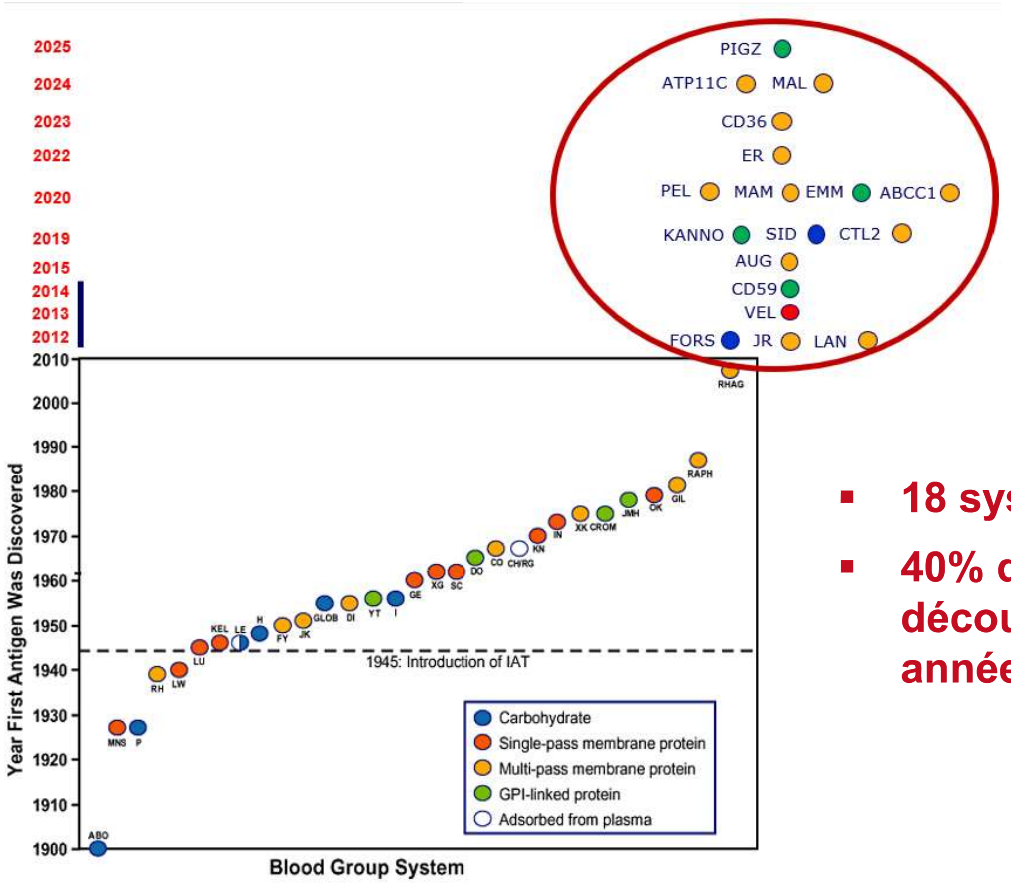
Jill R. Storry[1] and Slim Azouzi[2] | [1]Lund University and [2]INSERM Biologie Intégrée du Globule Rouge

In this issue of *Blood*, Tilley and colleagues report the discovery of the gene underlying the inherited AnWj-negative phenotype.[1] They identified a 6646-base-pair deletion at the *MAL* locus in 8 individuals with the AnWj-negative phenotype but not in family members with the AnWj-positive phenotype. Anti-Mal agglutinated AnWj-positive red blood cells (RBCs) but not AnWj-negative RBCs, which was confirmed by flow cytometric analysis. They further demonstrated that overexpression of the Mal protein resulted in expression of the AnWj antigen, which was inhibited by competitive antibody binding assays.

However, a number of unanswered questions remain in the enigmatic AnWj story. Human blood groups are currently

cases, the waning of protein expression during erythropoiesis, the WP has agreed to consider an antigen that is

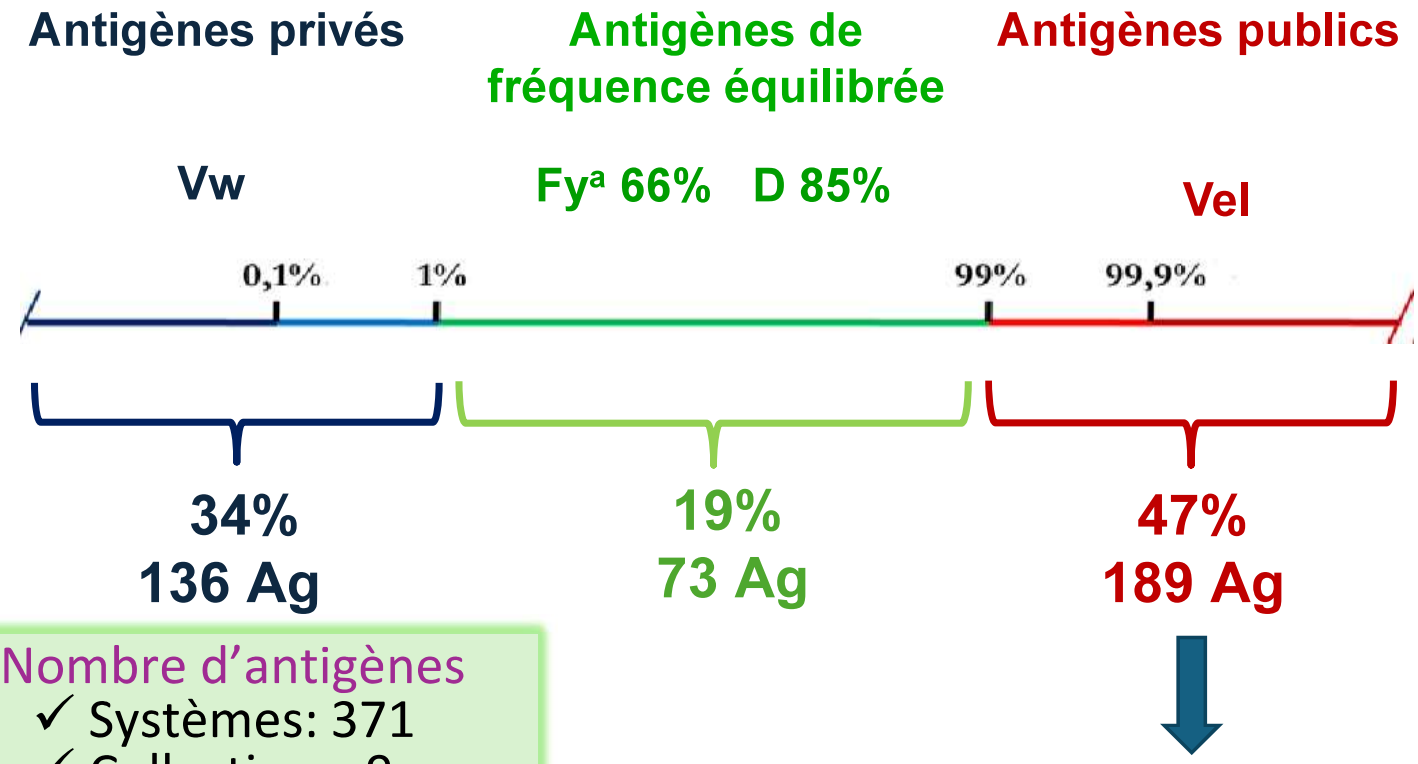
La base moléculaire du phénotype rare AnWj- acquis demeure non résolue (protéine MAL absente mais aucune mutation trouvée dans le gène *MAL*)



Adapté de Daniels G & Reid ME.
Blood groups: the past 50 years.
Transfusion. 2010;50:281-9

- ***Protéomique***
- ***Génomique (NGS)***

- **18 systèmes découverts depuis 2012 !**
- **40% du nombre total de systèmes découverts au cours des 15 dernières années !**

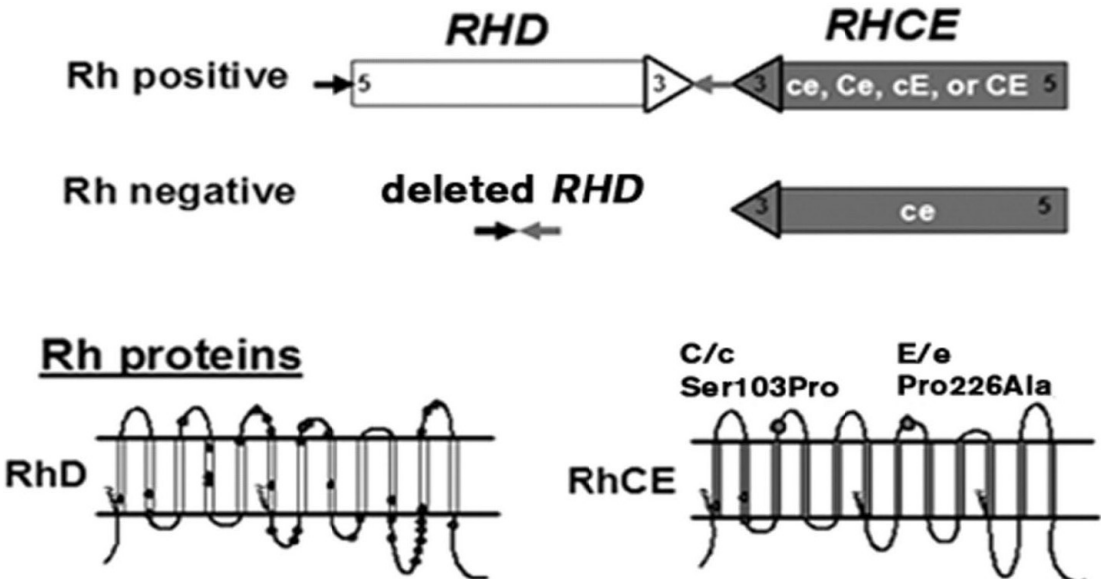


Nombre d'antigènes
- ✓ Systèmes: 371
- ✓ Collections: 9
- ✓ Série 700 : 16
- ✓ Série 901 : 2

Total: 398

189 possibilités différentes de phenotypes rares correspondant à l'absence d'un antigène public !

Deux grands types de situations pour les phénotypes : Polymorphisme simple (SNP) Phénotype nul (*null phenotype*)



Chou ST & Westhoff CM *Hematology* 2009;2009:178-184

E/e : ***c.676C>G (SNP)***
p.Pro226Ala

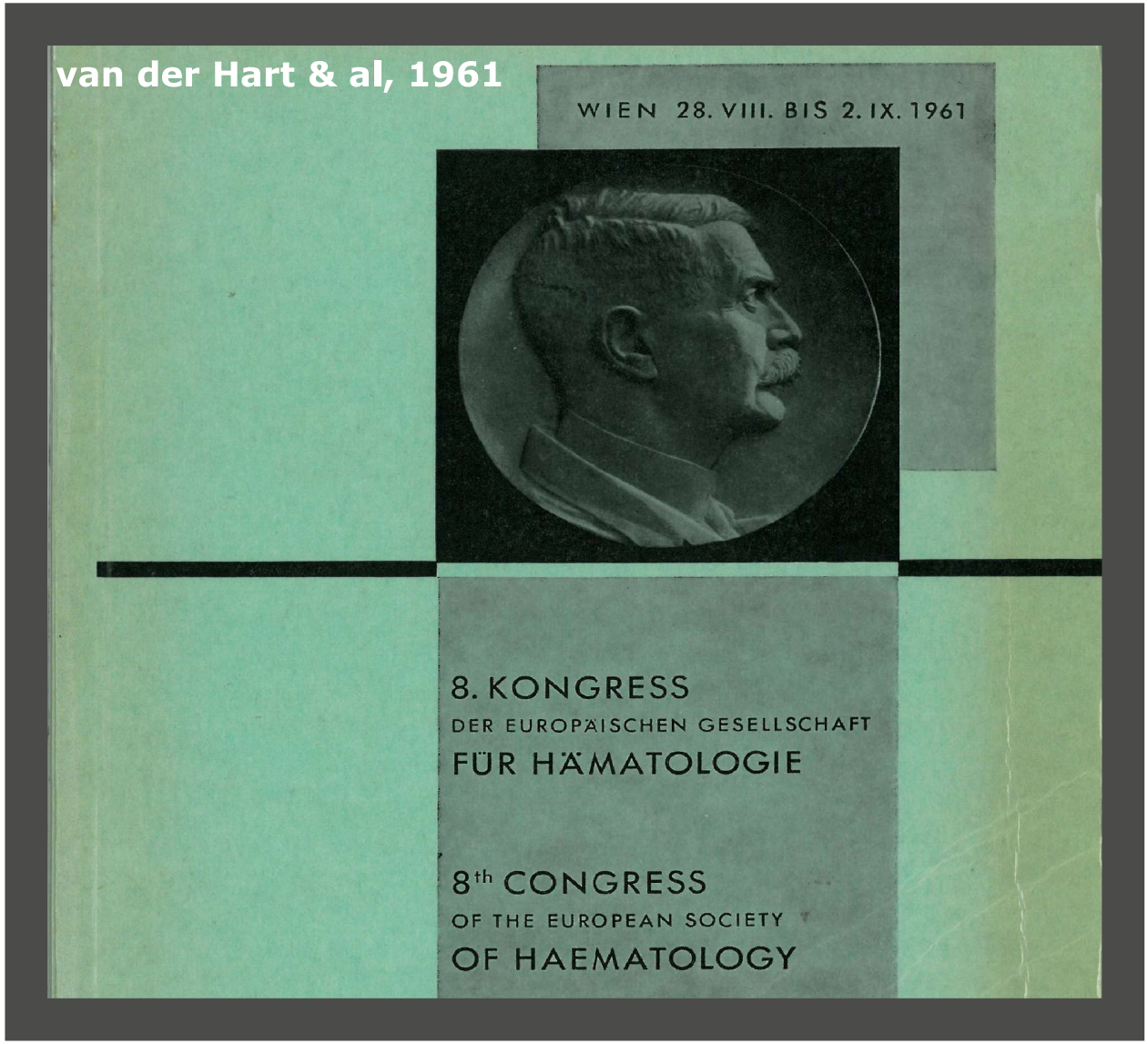
D- : absence de protéine RhD

Rh_{null} : absence de protéine RhD et RhCE

QUELQUES EXEMPLES DE SYSTÈMES DE GROUPES SANGUINS DÉCOUVERTS DEPUIS 2012

LE SYSTÈME DE GROUPE SANGUIN LAN

L’antigène Lan, un mystère de plus de 50 ans !



L'ANTIGÈNE LAN

The 901 series of high incidence antigens

Lan ANTIGEN

Terminology

ISBT symbol (Number)	Lan (901.002)
Other names	Langereis; Gn^a; Gonsowski; So; 900.003
History	Reported in 1961; named after the first antigen-negative proband to make anti-Lan

Occurrence

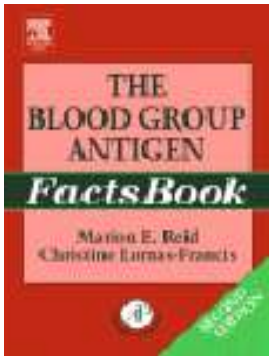
All populations: >99%.
The Lan– phenotype occurs in about 1 in 20000 people; found in Blacks,[1,2] Caucasians and Japanese.

Effect of enzymes/chemicals on Lan antigen on intact RBCs

Ficin/papain	Resistant
Trypsin	Resistant
α-Chymotrypsin	Resistant
Pronase	Resistant
Sialidase	Resistant
DTT 200 mM	Resistant
Acid	Resistant

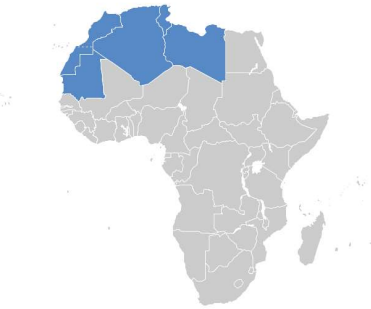
Série 901 avant juillet 2012

N°	Name	Symbol	Prevalence (%)
901002	Langereis	**Lan**	**> 99**
901003	August	**At^a**	> 99
901005		**Jr^a**	> 99
901008		**Emm**	> 99
901009	Anton	**AnWj**	> 99
901011	Sid	**Sd^a**	90
901014		**PEL**	> 99
901016		**MAM**	> 99



LE PHÉNOTYPE RARE LAN-

- 30 sujets Lan- dans le registre national français, la plupart étant originaires d'Afrique du Nord
- 25 avec anti-Lan (32 aujourd'hui)
- Anti-Lan considéré comme cliniquement significatif



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1. Hemolytic disease of the newborn caused by anti-Lan, anti-Jka, and anti-c.
   Shertz WT, Carty L, Wolford F.
   Transfusion. 1987 Jan-Feb;27(1):117. No abstract available.
   PMID: 3101246 [PubMed - indexed for MEDLINE]
   Related citations Remove from clipboard

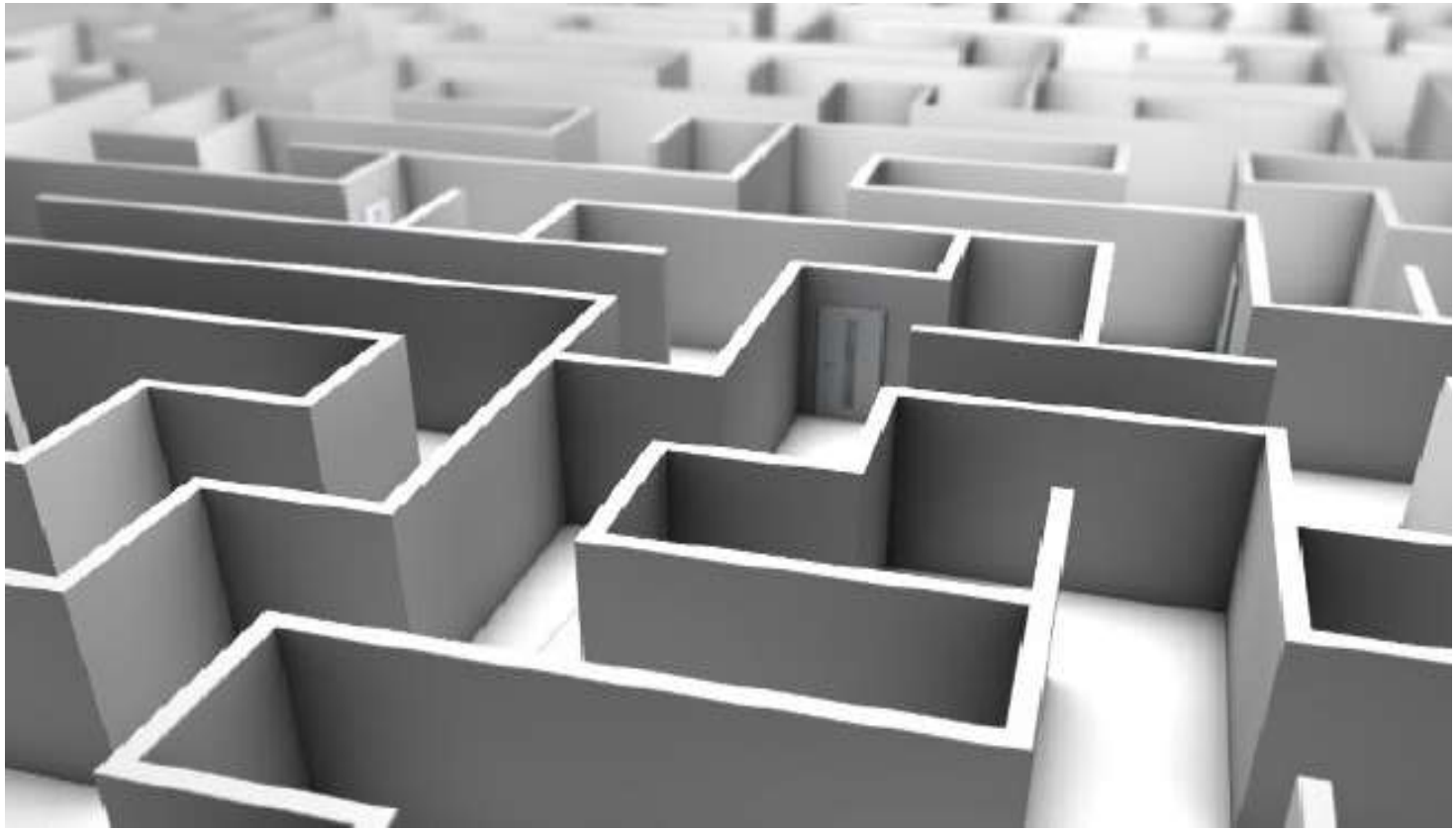
2. Clinical significance of anti-Lan.
   Judd WJ, Oberman HA, Silenieks A, Steiner EA.
   Transfusion. 1984 Mar-Apr;24(2):181. No abstract available.
   PMID: 6585080 [PubMed - indexed for MEDLINE]
   Related citations Remove from clipboard

3. Hemolytic disease of the newborn due to anti-Lan.
   Page PL.
   Transfusion. 1983 May-Jun;23(3):256-7. No abstract available.
   PMID: 6679383 [PubMed - indexed for MEDLINE]
   Related citations Remove from clipboard

4. Haemolytic disease of the newborn caused by anti-Lan antibody.
   Smith DS, Stratton F, Johnson T, Brown R, Howell P, Riches R.
   Br Med J. 1969 Jul 12;3(5662):90-2.
   PMID: 5790273 [PubMed - indexed for MEDLINE] **Free PMC Article**
   Related citations Remove from clipboard

5. [Lan antigen of erythrocytes and clinical significance of anti-Lan antibody].
   Kuśnierz-Alejska G, Wiecek B.
   Acta Haematol Pol. 1993;24(2):169-75. Polish.
   PMID: 8372617 [PubMed - indexed for MEDLINE]
   Related citations Remove from clipboard

Comment découvrir la base moléculaire de l'antigène Lan ?



XVIIIth Regional Congress Asia - ISBT, Hanoi, Vietnam, 2007 P-071

ESTABLISHMENT AND CHARACTERIZATION OF HUMAN MONOCLONAL ANTI-LAN

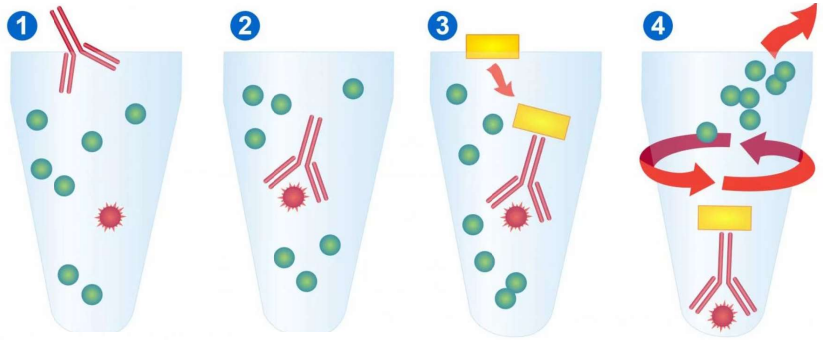
Tani *et al.*

Japanese Red Cross Osaka Blood Center, Osaka, Japan.

Anti-Lan monoclonal humain clone OSK43 (IgG1κ)

↓

Immunoprécipitation d'un lysat d'hématies standards (Lan+)

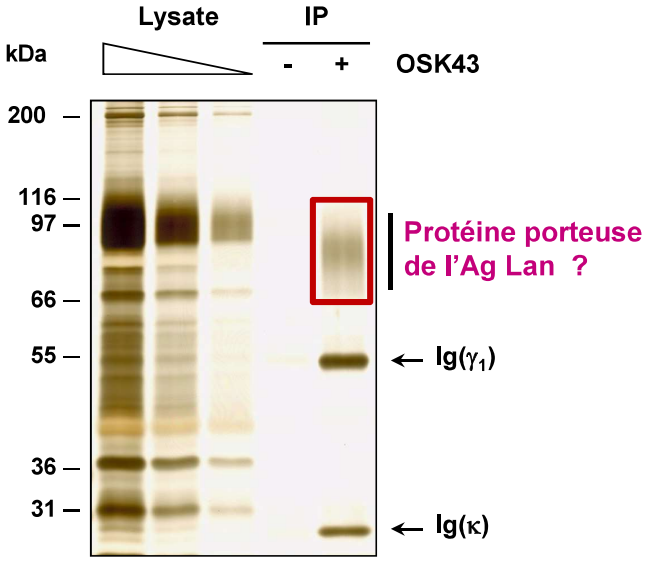


1. Suitable antibody is added.
2. Antibody binds to protein of interest.
3. Protein A or G added to make antibody-protein complexes insoluble.
4. Centrifugation of solution pellets antibody-protein complex. Removal cf supernatant and washing.

→ **Produit d'immunoprécipitation sujet à une électrophorèse et coloration des protéines à l'argent**

↓

Analyse des bandes obtenues après électrophorèse

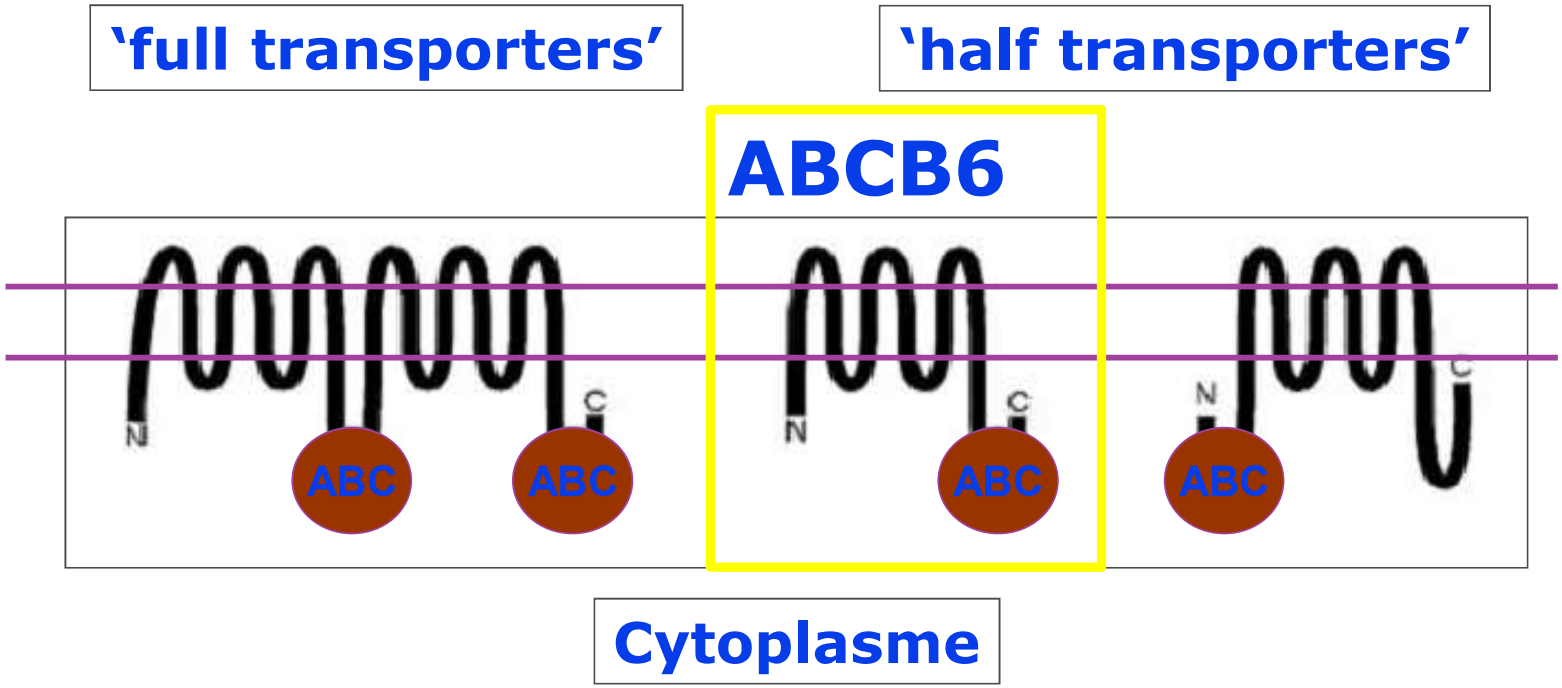


ABCB6

MVTVGNYCEAEGPVGPAWMQDGLSPCFFFTLVPSTRMALGTLALVLALPCRRRERPAG
ADSLSWGAGPRISPYVLQLLLATLQAALPLAGLAGRVGTARGAPLPSYLLLASVLESL
AGACGLWLLVVERSQARQRLAMGIWIKFRHSPGLLLLWTVAFAAENLALVSWNSPQWW
WARADLGQQVQFSLWVLRYVVSGGLFVLGLWAPGLRPQSYTLQVHEEDQDVERSQVRS
AAQQSTWRDFGRKLRLLSGYLWPRGSPALQLVVLICLGLMGLERALNVLVPIFYRNIV
NLLTEKAPWNSLAWTVTSYVFLKFLQGGGTGSTGFVSNLRTFLWIRVQQFTSRRVELL
IFSHLHELSLRWHLGRRTGEVLRIADRGTSSVTGLLSYLVFNVIPTLADIIIGIIYFS
MFFNAWFGLIVFLCMSLYLTLTIVVTEWRTKFRRAMNTQENATRARAVDSLLNFETVK
YYNAESYEVERYREAIIKYQGLEWKSSASLVLLNQTQNLVIGLGLLAGSLLCAYFVTE
QKLQVGDYVLFGTYIIQLYMPLNWFGTYYRMIQTNFIDMENMFDLLKEETEVKDLPGA
GPLRFQKGRIEFENVHFSYADGRETLQDVSFTVMPGQTLALVGPSGAGKSTILRLLFR
FYDISSGCIRIDGQDISQVTQASLRSHIGVVPQDTVLFNDTIADNIRYGRVTAGNDEV
EAAAQAAGIHDAIMAFPEGYRTQVGERGLKLSGGEKQRVAIARTILKAPGIILLDEAT
SALDTSNERAIQASLAKVCANRTTIVVAHRLSTVVNADQILVIKDGCIVERGRHEALL
SRGGVYADMWQLQQGQEETSEDTKPQTMER

Spectrométrie de masse après digestion à la trypsine
Haut degré de confiance : 17 peptides!

Transporteurs de type ATP-Binding Cassette (ABC)



Les transporteurs de type ATP-binding cassette facilitent de manière active l'efflux transmembranaire de nombreuses substances

Exemples d'allèles silencieux d'*ABCB6* décrits chez les sujets Lan-

ABCB6 (2q36) 19 exons

Lan–	*ABCB6*01N.01*	197_198insG	Exon 1	Ala66fsX
Lan–	*ABCB6*01N.02*	717G>A	Exon 3	Gln239X
Lan–	*ABCB6*01N.03*	953_956delGTGG	Exon 4	Gly318fsX
Lan–	*ABCB6*01N.04*	1533_1543dupCGGCTCCCTGC	Exon 9	Leu515fsX
Lan–	*ABCB6*01N.05*	1709_1710delAG	Exon 11	Glu570fsX
Lan–	*ABCB6*01N.06*	1690_1691delAT	Exon 11	Met564fsX
Lan–	*ABCB6*01N.07*	1867delinsAACAGGTGA	Exon 14	Gly623fsX
Lan–	*ABCB6*01N.08*	1942C>T	Exon 14	Arg648X
Lan–	*ABCB6*01N.09*	1985_1986delTC	Exon 15	Leu662fsX
Lan–	*ABCB6*01N.10*	2256+2t>g	Intron 16	Splicing defect
Lan–	*ABCB6*01N.11*	1236G>A	Exon 6	Trp412X

Les sujets Lan- sont en fait « Lan null » et peuvent être considérés comme des « *knock-out* » humains pour le gène *ABCB6*

CE QUI ÉTAIT INATTENDU !

- **ABCB6 jamais décrit sur le globule rouge (membrane mitochondriale externe)**

- **ABCB6 rapporté comme absolument essentiel pour l'érythropoïèse! (biosynthèse de l'hème)**

  => Personnes Lan- ("human knock out" pour *ABCB6*) en bonne santé apparente et sans anomalies biologiques particulières !

LETTERS

nature genetics

ABCB6 is dispensable for erythropoiesis and specifies the new blood group system Langereis

Virginie Helias[1], Carole Saison[1], Bryan A Ballif[2], Thierry Peyrard[1,3], Junko Takahashi[4], Hideo Takahashi[4], Mitsunobu Tanaka[4], Jean-Charles Deybach[5], Hervé Puy[5], Maude Le Gall[6], Camille Sureau[1], Bach-Nga Pham[1,3], Pierre-Yves Le Pennec[1,3], Yoshihiko Tani[4], Jean-Pierre Cartron[1] & Lionel Arnaud[1]

VOLUME 44 | NUMBER 2 | FEBRUARY 2012 NATURE GENETICS

Lan accepté comme le
33ème système de groupe sanguin (LAN) par la
ISBT *Working Party on Red Cell*
Immunogenetics and Blood Group Terminology
en juillet 2012 (ISBT, Cancun, Mexique)

ARTICLE

ABCB6 Mutations Cause Ocular Coloboma

Mutation Leu811Val dans ABCB6

Lejing Wang,[1,14,*] Fei He,[2,3,14] Juan Bu,[1,14] Xiaqi Liu,[2,3] Wei Du,[1,13] Jiamei Dong,[1,4] Jeffrey D. Cooney,[5,6] Sushil Kumar Dubey,[7] Yi Shi,[2,3] Bo Gong,[2,3] Jing Li,[1] Paul F. McBride,[5,6] Yanlei Jia,[8] Fang Lu,[2,3] Kathleen A. Soltis,[5,6] Ying Lin,[2,3] Prasanthi Namburi,[7] Chen Liang,[1] Periasamy Sundaresan,[7] Barry H. Paw,[5,6] Dean Y. Li,[9,10,11] John D. Phillips,[12] and Zhenglin Yang[2,3,*]

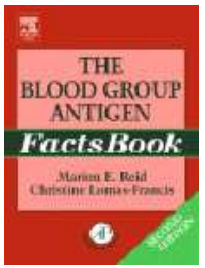
Ocular coloboma is a developmental defect of the eye and is due to abnormal or incomplete closure of the optic fissure. This disorder displays genetic and clinical heterogeneity. Using a positional cloning approach, we identified a mutation in the ATP-binding cassette (ABC) transporter *ABCB6* in a Chinese family affected by autosomal-dominant coloboma. The Leu811Val mutation was identified in seven affected members of the family and was absent in six unaffected members from three generations. A LOD score of 3.2 at $\theta = 0$ was calculated for the mutation identified in this family. Sequence analysis was performed on the *ABCB6* exons from 116 sporadic cases of microphthalmia with coloboma (MAC), isolated coloboma, and aniridia, and an additional mutation (A57T) was identified in three patients with MAC. These two mutations were not present in the ethnically matched control populations. Immunostaining of transiently transfected, Myc-tagged *ABCB6* in retinal pigment epithelial (RPE) cells showed that it localized to the endoplasmic reticulum and Golgi apparatus of RPE cells. RT-PCR of *ABCB6* mRNA in human cell lines and tissue indicated that ABCB6 is expressed in the retinae and RPE cells. Using zebrafish, we show that *abcb6* is expressed in the eye and CNS. Morpholino knockdown of *abcb6* in zebrafish produces a phenotype characteristic of coloboma and replicates the clinical phenotype observed in our index cases. The knockdown phenotype can be corrected with coinjection of the wild-type, but not mutant, *ABCB6* mRNA, suggesting that the phenotypes observed in zebrafish are due to insufficient *abcb6* function. Our results demonstrate that *ABCB6* mutations cause ocular coloboma.

The American Journal of Human Genetics *90*, 40–48, January 13, 2012

LE SYSTÈME DE GROUPE SANGUIN JR

Jr^a ANTIGEN

Jr^a découvert en 1970
Par Stroup M. & McIlroy M.
23rd AABB Meeting



Jr pour Mrs. Jacobs Rose, un des premiers sujets avec anti-Jr^a

Terminology

ISBT symbol (Number)	Jr^a (901.005)
Other names	Junior; 900.012
History	The first five examples of anti-Jr^a were reported in 1970. Named for the first maker of anti-Jr^a

Occurrence

All populations: >99%.

Approximately half of the known Jr(a−) persons are Japanese. The Jr(a−) phenotype has also been found in persons of northern European extraction, Bedouin Arabs and in one Mexican.

Jr(a-) Japon: ~ 100 000 personnes
Jr(a-) France: ~3 nouveaux cas par an

Expression

Cord RBCs	Expressed

Effect of enzymes/chemicals on Jra antigen on intact RBCs

Ficin/papain	Resistant (↑)
Trypsin	Resistant
α-Chymotrypsin	Resistant
Pronase	Resistant
Sialidase	Resistant
DTT 200 mM	Resistant
Acid	Resistant

N°	Name	Symbol	Prevalence (%)
901002	Langereis	Lan	> 99
901003	August	At^a	> 99
901005		**Jr^a**	**> 99**
901008		**Emm**	> 99
901009	Anton	**AnWj**	> 99
901011	Sid	**Sd^a**	90
901014		**PEL**	> 99
901016		**MAM**	> 99

Le phénotype rare Jr(a-)

- 46 sujets Jr(a-) répertoriés en France (la plupart dans la communauté des gens du voyage)
- 39 avec anti-Jr^{a} (92 aujourd'hui !)
- Anti-Jr^{a} considéré comme cliniquement significatif en transfusion et parfois très dangereux en obstétrique

1. Fetal and neonatal anemia associated with anti-Jr(a) : a case report showing a poorly hemolytic mechanism.
Sasamoto N, Tomimatsu T, Nagamine K, Oshida M, Kashiwagi H, Koyama S, Kanagawa T, Arahori H, Tomiyama Y, Kimura T.
J Obstet Gynaecol Res. 2011 Aug;37(8):1132-6. doi: 10.1111/j.1447-0756.2010.01477.x. Epub 2011 Apr 12.
PMID: 21481087 [PubMed - indexed for MEDLINE]
Related citations Remove from clipboard

2. Hemolytic disease of the newborn associated with anti-Jra alloimmunization in a twin pregnancy: the first case report in Korea.
Kim H, Park MJ, Sung TJ, Choi JS, Hyun J, Park KU, Han KS.
Korean J Lab Med. 2010 Oct;30(5):511-5.
PMID: 20890084 [PubMed - indexed for MEDLINE] Free Article
Related citations Remove from clipboard

3. Fatal hemolytic disease of the fetus and newborn possibly due to anti-Jr.
Arriaga F, Gomez I, Linares MD, Gascon A, Carpio N, Perales A.
Transfusion. 2009 Apr;49(4):813. No abstract available.
PMID: 19335378 [PubMed - indexed for MEDLINE]
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4. Fatal hemolytic disease of the fetus and newborn associated with anti-Jr.
Peyrard T, Pham BN, Arnaud L, Fleutiaux S, Brossard Y, Guerin B, Desmoulins I, Rouger P, Le Pennec PY.
Transfusion. 2008 Sep;48(9):1906-11. Epub 2008 Jun 2.
PMID: 18522708 [PubMed - indexed for MEDLINE]
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4 autres cas très sévères au CNRGS

5. Successful treatment of extremely severe fetal anemia due to anti-Jra alloimmunization.
Ishihara Y, Miyata S, Chiba Y, Kawai T.
Fetal Diagn Ther. 2006;21(3):269-71.
PMID: 16601336 [PubMed - indexed for MEDLINE]
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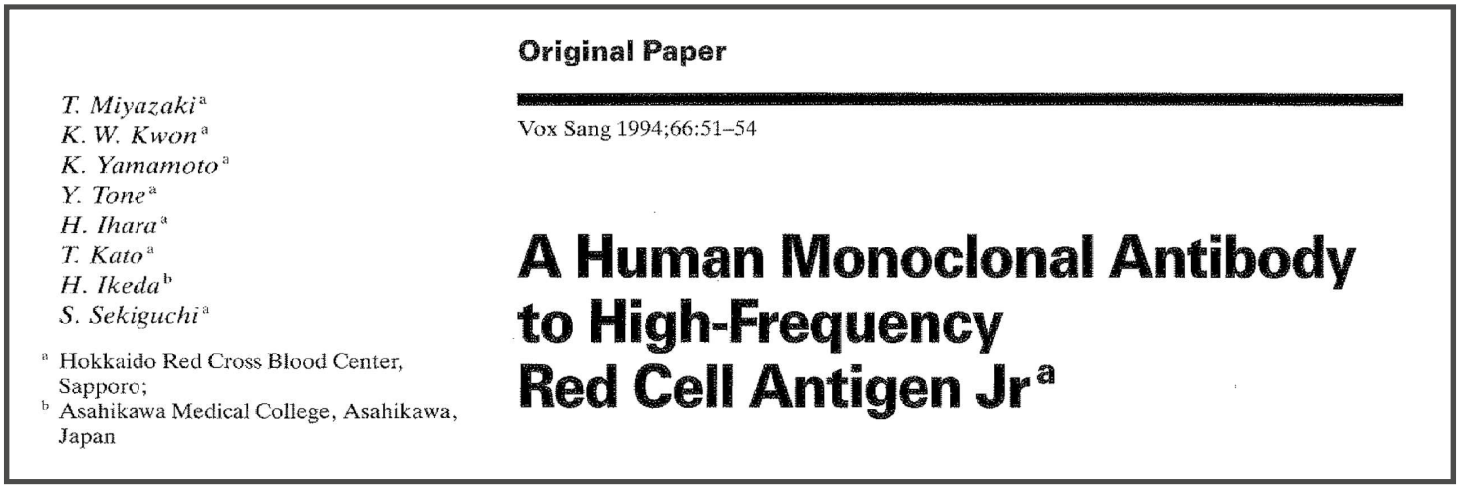
HMR0921, anticorps monoclonal anti-Jr^a (IgG3λ)



Original Paper

T. Miyazaki[a]
K. W. Kwon[a]
K. Yamamoto[a]
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H. Ihara[a]
T. Kato[a]
H. Ikeda[b]
S. Sekiguchi[a]

[a] Hokkaido Red Cross Blood Center, Sapporo;
[b] Asahikawa Medical College, Asahikawa, Japan

Vox Sang 1994;66:51–54

A Human Monoclonal Antibody to High-Frequency Red Cell Antigen Jr^a

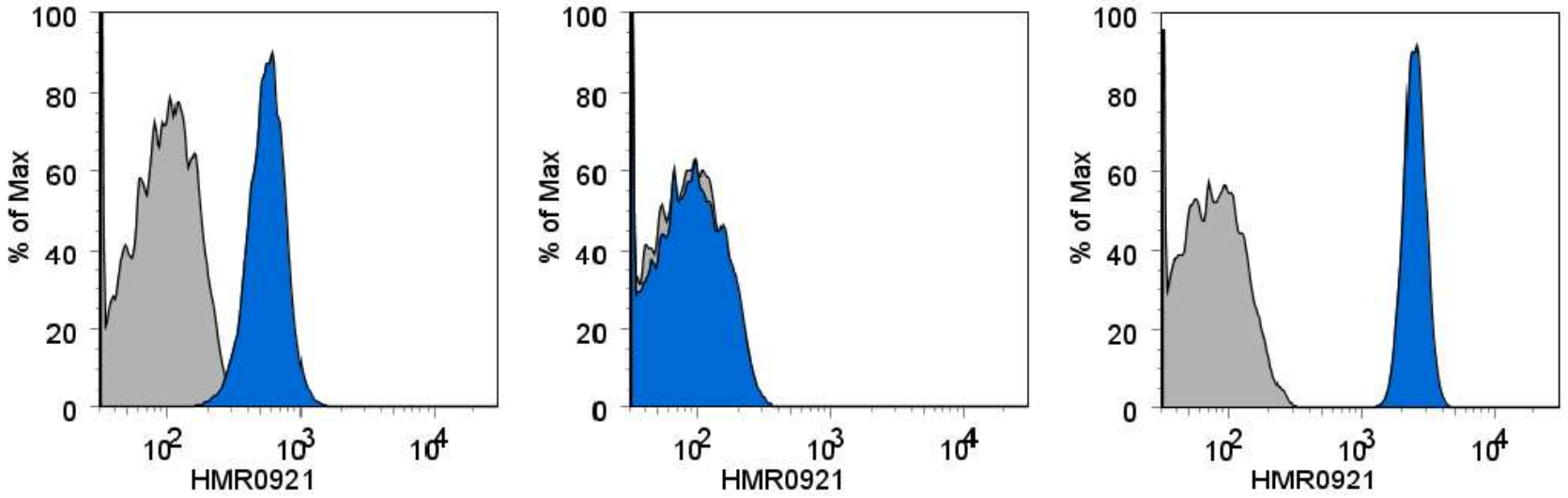
Immunoprécipitation ne fonctionne pas ☹

Etude de l'expression de Jr^a dans d'autres espèces

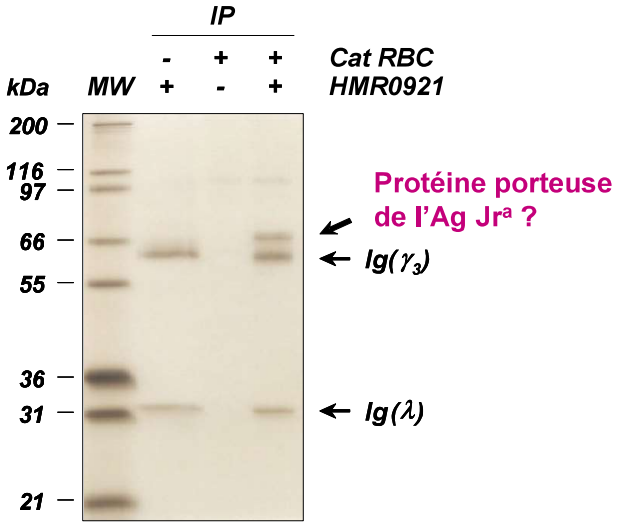
RBC	*HMR0921 reactivity by flow cytometry analysis*
Human	+
Cow	-
Horse	-
Pig	-
Goat	-
Sheep	(+)
Dog	+
Cat	+++
Rabbit	(+)
Rat	-
Mouse	-

Jr^a hautement exprimé sur les globules rouges de chat (10 fois plus que chez l'Homme !)

Hématies chat



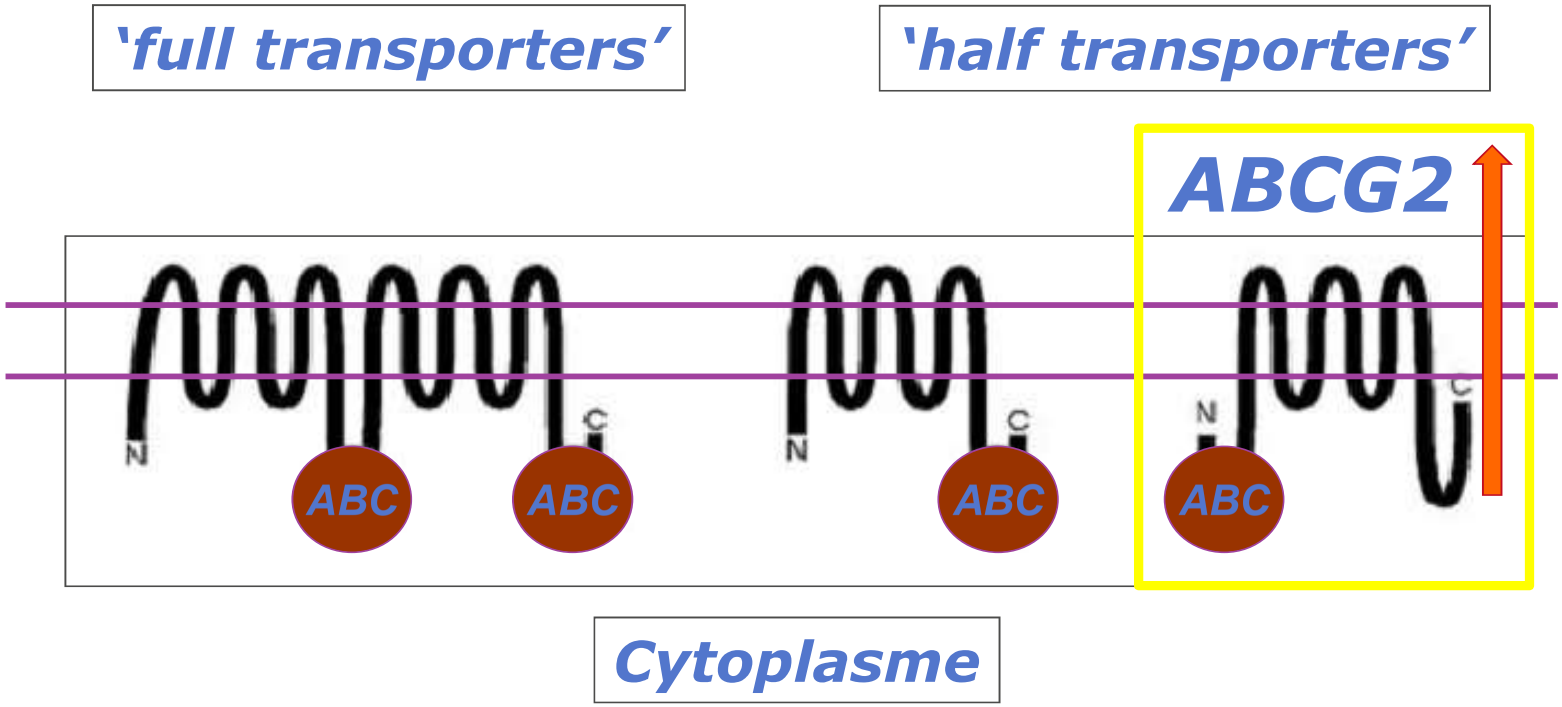
Clone anti-Jr^a HMR0921 immunoprécipite Abcg2 des hématies du chat




```
KEILSNINGIMKPGLNAILGPTGGGKSSLLDVLAARKDPSGLSGDVLINGAPRPANFKCN  Human ABCG2
XXXXXXXXGIMRPGLNAILGPTGGGKSSLLDVLAARKDPHGLSGDVLINGAPRPANFKCN  Cat Abcg2
        ***:*************************** ********************

SGYVVQDDVVMGTLTVRENLQFSAALRLATTMTNHEKNERINRVIQELGLDKVADSKVGT  Human ABCG2
SGYVVQDDVVMGTLTVRENLQFSAALRLPTTMTTNEKNMRINRVIQELGLDKVADSKVGT  Cat Abcg2
*****************************.****.:*** ********************

QFIRGVSGGERKRTSIGMELITDPSILFLDEPTTGLDSSTANAVLLLLKRMSKQGRTIIF  Human ABCG2
QFIRGVSGGERKRTSIGMELITDPAILFLDEPTTGLDSSTANAVLLLLKRMSEQGRTIIF  Cat Abcg2
************************:***************************:*******

SIHQPRYSIFKLFDSLTLLASGRLMFHGPAQEALGYFESAGYHCEAYNNPADFFLDIING  Human ABCG2
SIHQPRYSIFKLFDSLTLLASGRLMFHGPAQEALGYFALMXXXXXXXXXXXXXXXXXXXX  Cat Abcg2
************************************
```

Anticorps monoclonal anti-Jr^a reconnait la protéine Abcg2 du chat
=> Est-ce aussi le cas chez l'Homme ?
Confirmation que oui !
Sujets Jr(a-) n'expriment pas ABCG2 !

Transporteurs de type ATP-Binding Cassette (ABC)



Les transporteurs de type ATP-binding cassette facilitent de manière active l'efflux transmembranaire de nombreuses susbtances

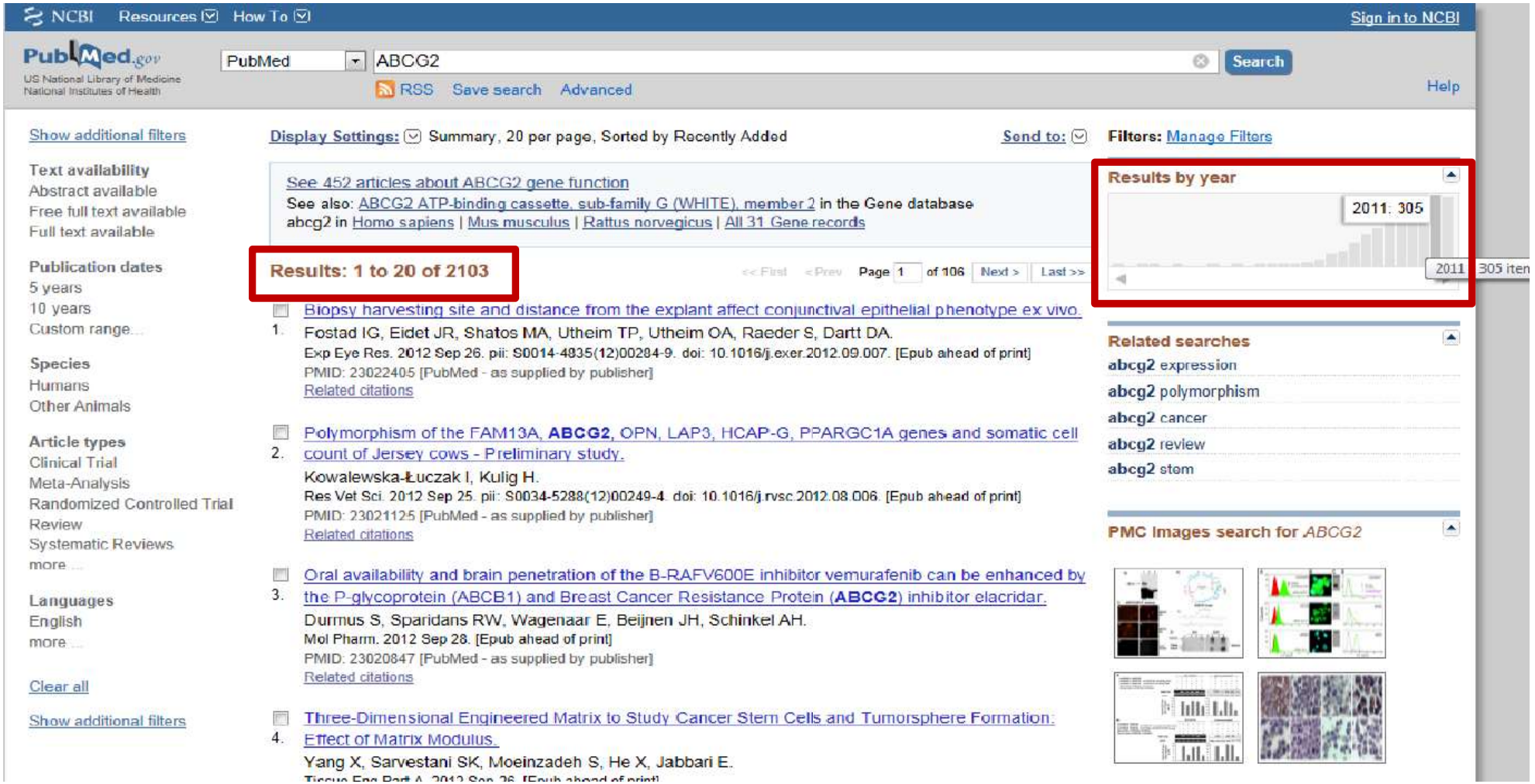
Exemples d'allèles silencieux d'*ABCG2* responsables du phénotype Jr(a-)

Jr(a−)	*ABCG2*01N.01*	376C>T	Exon 4	Gln126X
Jr(a−)	*ABCG2*01N.02.01*	706C>T	Exon 7	Arg236X
Jr(a−)	*ABCG2*01N.02.02*	34G>A 706C>T	Exon 2 Exon 7	Val12Met Arg236X
Jr(a−)	*ABCG2*01N.03*	736C>T	Exon 7	Arg246X
Jr(a−)	*ABCG2*01N.04*	337C>T	Exon 4	Arg113X
Jr(a−)	*ABCG2*01N.05*	784G>T	Exon 7	Gly262X
Jr(a−)	*ABCG2*01N.06*	34G>A 1591C>T	Exon 2 Exon 13	Val12Met Gln531X
Jr(a−)	*ABCG2*01N.07*	187_197delATATTATCGAA	Exon 2	Ile63TyrfsX
Jr(a−)	*ABCG2*01N.08*	542_543insA	Exon 6	Phe182ValfsX
Jr(a−)	*ABCG2*01N.09*	730C>T	Exon 7	Gln244X

2 mutations ABCG2 « ethniques » de type codon stop

- **Gln126Stop en Asie**
- **Arg236Stop chez les « Gens du voyage »**

ABCG2 : molécule très largement étudiée

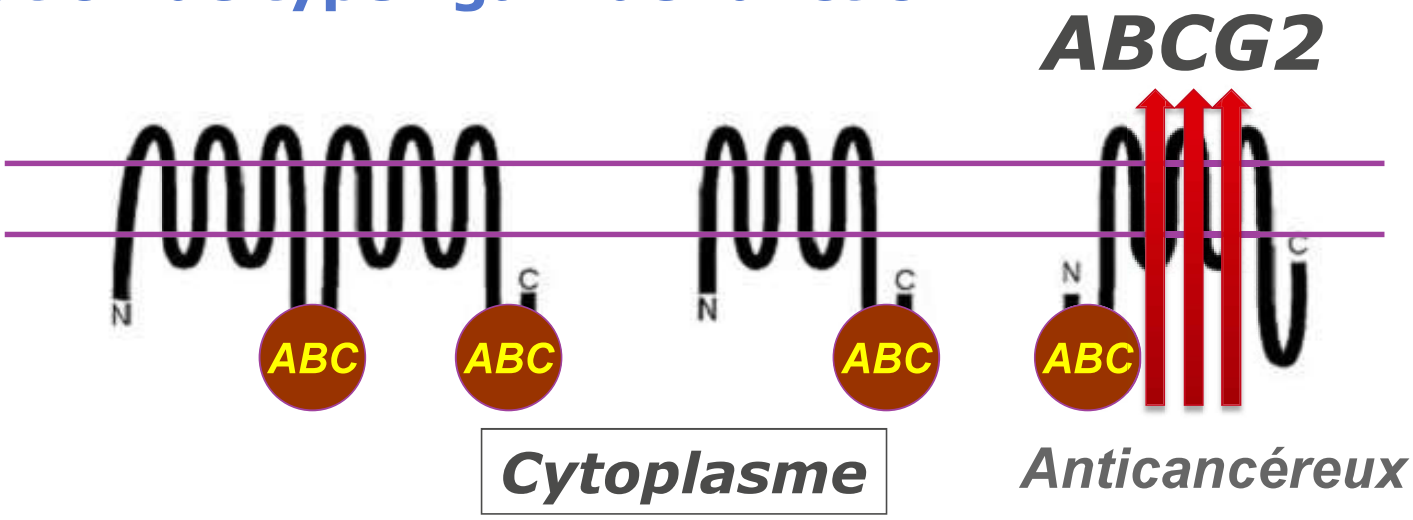


Aucun lien auparavant rapporté avec les groupes sanguins !

CE QUI ÉTAIT INATTENDU !

- **ABCG2 connu comme transporteur essentiel voire vital dans la détoxification cellulaire (intestin, foie, cellules souches et placenta)**
- **ABCG2 plus connu sous le nom de *Breast Cancer Resistance Protein* (BCRP)**

  Permet un efflux +++ (pompe in → out) d'un grand nombre d'anti-cancéreux => Risque de résistance si mutation de type "gain de function"



SYSTÈME DE GROUPE JR

- **Sujets Jr(a-) dépourvus de protéine BCRP et donc supposés incapables d'éliminer normalement certains anti-cancéreux => risque de surdosage sévère**

  => typage Jr^a systématique chez femmes japonaises et gens du voyage avec cancer du sein ? Autres cancers ?

  => Pharmacogénétique

nature genetics

Null alleles of *ABCG2* encoding the breast cancer resistance protein define the new blood group system Junior

Carole Saison[1], Virginie Helias[1], Bryan A Ballif[2], Thierry Peyrard[1,3], Hervé Puy[4], Toru Miyazaki[5], Sébastien Perrot[6], Muriel Vayssier-Taussat[7], Mauro Waldner[8], Pierre-Yves Le Pennec[1,3], Jean-Pierre Cartron[1] & Lionel Arnaud[1]

VOLUME 44 | NUMBER 2 | FEBRUARY 2012 NATURE GENETICS

Received 6 May 2011; accepted 9 December 2011; published online 15 January 2012; doi:10.1038/ng.1070

Les sujets Jr(a-) sont en fait « Jr null » et n'expriment pas la protéine ABCG2. Ils sont considérés comme des « *knock-out* » humains pour le gène *ABCG2*

Jr accepté comme le
32ème système de groupe sanguin (JR) par la
ISBT Working Party on Red Cell
Immunogenetics and Blood Group Terminology
en juillet 2012 (ISBT, Cancun, Mexique)

CTL2

LE 39ÈME SYSTÈME DE GROUPE SANGUIN