TROIS NOUVEAUX SYSTEMES DE GROUPES SANGUINS :
FORS, JR ET LAN

THREE NEW BLOOD GROUP SYSTEMS:
FORS, JR AND LAN

Dr. Thierry PEYRARD

INTS/CNRGS - PARIS

Cours de formation continue en immuno-hématologie et médecine transfusionnelle de l’ASMT

Vendredi 25 Janvier 2013 - Berne
2012 : UNE ANNEE FASTE POUR LES GROUPES SANGUINS !

2012: A REMARKABLE YEAR FOR BLOOD GROUPS!
Adapted from Daniels G & Reid ME. Blood groups: the past 50 years. *Transfusion*. 2010;50:281-9
THE FORS STORY
FORSSMAN GLYCOLIPID

- α3-N-acetylgalactosamine on H substance => A antigen
- α3-N-acetylgalactosamine on P (globoside) substance => Forssman glycolipid (firstly identified in 1911)
- Primates, including humans, lack Forssman synthase activity and have naturally-occurring antibodies to Forssman in plasma
A_{pae} BLOOD TYPE: THE KEY TO THE DISCOVERY OF THE FORSSMAN BLOOD GROUP

Stamps R & al. A new variant of blood group A: A_{pae} Transfusion 1987

A_{pae} phenotype described in 3 English families

Initially thought to be a weak subgroup of A
Forssman expression on human erythrocytes: biochemical and genetic evidence of a new histo-blood group system

**A_{pae} AND FORSSMAN ANTIGEN**

- \( A_{pae} \) with a \( O/O \) genotype!

- No A antigen on RBCs but expression of the Forssman glycolipid \( \Rightarrow \) may explain the crossreactivity with some anti-A reagents
In the rare $A_{pae}$ individuals, the Forssman synthase gene $GBGT1$ encodes a Arg296Gln change.

Gln296 mutation is present in lower mammals, whereas Arg296 (wild type) is found in primates, including humans.
THE FORSSMAN ANTIGEN

• 296Gln mutation reactivates the human Forssman synthase => expression of Forssman glycolipid on human RBCs

• Antibody to Forssman glycolipid always exists in humans and Forssman substance may exceptionally be found on some human RBCs => Forssman is now considered a RBC antigen
THE FORSSMAN ANTIGEN

• Forssman (FORS) is a new blood group system (#31 ISBT), with one low-prevalence antigen, FORS1

• Exceptional human RBCs that display FORS1 antigen demonstrate the so-called “polyagglutinability” phenomenon, of inherited type (such as Tn, Cad, HEMPAS, Nor)

• RBCs carrying FORS1 are strongly agglutinated by *Helix Pomatia* lectin
Jr\textsuperscript{a} and Lan: two known antigens within the 901 series

Unknown molecular and biochemical basis
### Antigens of the 901 Series

**Prevalence > 90% / 2011**

<table>
<thead>
<tr>
<th>Nº</th>
<th>Name</th>
<th>Symbol</th>
<th>Prevalence (%)</th>
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<tr>
<td>901002</td>
<td>Langereis</td>
<td>Lan</td>
<td>&gt; 99</td>
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<tr>
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<td>August</td>
<td>At(^a)</td>
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<td>&gt; 99</td>
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<td>Sd(^a)</td>
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<td>901016</td>
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<td>&gt; 99</td>
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THE JR STORY
Jr\textsuperscript{a} ANTIGEN

Terminology
ISBT symbol \{Number\} Jr\textsuperscript{a} (901.005) 
Other names Jr\textsuperscript{a} (900.012)  
History The first five examples of anti-Jr\textsuperscript{a} were reported in 1970. Named for the first maker of anti-Jr\textsuperscript{a}

Occurrence
All populations: >99\%. Approximately half of the known Jr\textsuperscript{a} persons are Japanese. The Jr\textsuperscript{a} phenotype has also been found in persons of northern European extraction, Bedouin Arabs and in one Mexican.

Jr(a-) in Japan: 0.04-0.07\% (>50,000 people) 
Jr(a-) in France: 2-3 new subjects identified/year

Expression
Cord RBCs Expressed

Effect of enzymes/chemicals on Jr\textsuperscript{a} antigen on intact RBCs

- Ficin/papain Resistant
- Trypsin Resistant
- \(\alpha\)-Chymotrypsin Resistant
- Pronase Resistant
- Sialidase Resistant
- DTT 200 mM Resistant
- Acid Resistant
WHY STUDYING JR?

• 40 Jr(a-) in the French National Registry of People with a Rare Blood Type (most are Gypsies)

• 34/40 with anti-Jr^a

• Anti-Jr^a considered a clinically significant alloantibody, either in obstetrics and RBC transfusion

• Monoclonal antibody available
3 other severe HDFN cases followed by our reference laboratory.
HMR0921, a monoclonal antibody to Jr\textsuperscript{a} has been available since 1994.

**Original Paper**

Vox Sang 1994;66:51–54

\textbf{A Human Monoclonal Antibody to High-Frequency Red Cell Antigen Jr\textsuperscript{a}}

\begin{itemize}
  \item T. Miyazaki\textsuperscript{a}
  \item K. W. Kwon\textsuperscript{a}
  \item K. Yamamoto\textsuperscript{a}
  \item Y. Tone\textsuperscript{a}
  \item H. Ikara\textsuperscript{a}
  \item T. Kato\textsuperscript{a}
  \item H. Ikeda\textsuperscript{b}
  \item S. Sekiguchi\textsuperscript{a}
\end{itemize}

\textsuperscript{a} Hokkaido Red Cross Blood Center, Sapporo;
\textsuperscript{b} Asahikawa Medical College, Asahikawa, Japan

- Agglutination
- Flow cytometry (Weakly reactive on human RBCs)
- **Western blot** did not work...

Immunoprecipitation of the Jr\textsuperscript{a} carrier from human RBCs did not work...
Study of Jr\textsuperscript{a} expression extended to different mammalians

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<th>RBC</th>
<th>HMR0921 reactivity by flow cytometry analysis</th>
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<tr>
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<tr>
<td>Cow</td>
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<td>Mouse</td>
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</table>
Jra found to be highly expressed on cat RBCs!

Human RBCs  Mouse RBCs  Cat RBCs

x10/human
HMR0921 anti-Jr\textsuperscript{a} immunoprecipitates Abcg2 protein from cat RBCs

Silver-stained gel

Protein identification by mass spectrometry after trypsin digest:
Despite no mass spectrometry database was available for cat genome, 5 peptides were predicted to be from human ABCG2!
ABC2G2 is absent in the membrane of all tested Jr(a-) RBCs

Western Blot on Jr(a-) with anti-ABCG2

Jr(a-) => Jr_{null}
Null alleles of \( \text{ABCG2} \) 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\(^1\)

Received 6 May 2011; accepted 9 December 2011; published online 15 January 2012; doi:10.1038/ng.1070
ABCG2 null alleles define the Jr(a−) blood group phenotype

Teresa Zelinski1,2, Gail Coghlan1, Xiao-Qing Liu2,3 & Marion E Reid4

homozygous region in an unrelated Asian individual was 664,000 bp in length, and this subject was identically homozygous to the sister and brother of Asian descent for 397,000 bp (Supplementary Table 1, green haplotype 5, and Supplementary Methods). A fourth individual of Asian ancestry, unrelated to the other three, was uniquely homozygous (Supplementary Table 1, haplotype in blue, and Supplementary
The ATP-Binding Cassette (ABC) transporter family

'full transporters'

'half transporters'

ABCG2

Cytoplasm

ATP-binding cassette transporters actively facilitate the transmembrane movement of numerous substances.
Several null alleles of *ABCG2* are responsible for the Jr(a-)* type

*ABCG2* (4q22)  
16 exons

2 ethnic *ABCG2* stop codon mutations encode the Jr(a-) type:  
- Arg236Ter in European Gypsies  
- Gln126Ter in Asians (prevalence in Japan: 1.6-2.4%)

=> Important data for implementation in RBC genotyping devices!
WHAT WAS UNEXPECTED!

• Jr(a-) is a human « knock out » for ABCG2, whereas it is known to be an essential transporter in cell detoxification (abundant in intestine, liver, stem cells and placenta)

• ABCG2 also known as the Breast Cancer Resistance Protein (BCRP). Allows a strong efflux (in ➔ out) of a large number of anti-cancer drugs:
  ✓ Mitoxantrone
  ✓ Camptothecin derivates: Topotecan, Irinotecan
  ✓ Anthracyclins: Daunorubicin, Doxorubicin, Epirubicin
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<th>References</th>
<th>Organic Molecule</th>
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<td>4-MUS</td>
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<td>Indolocarbazole</td>
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<td>Topoisomerase I inhibitors (NB-506; I-107088)</td>
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<td>Flavopiridol</td>
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<td>ErbB1 tyrosine kinase inhibitor (CI1033)</td>
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<td>Imatinib mesylate (STI571)</td>
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<tr>
<td>Pantoprazole</td>
<td>68</td>
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</table>

* Whether these compounds are substrates of BCRP depends on the amino acid at position 482.
ABCG2 has been a largely studied molecule!

No link with blood groups ever reported!
Common Defects of ABCG2, a High-Capacity Urate Exporter, Cause Gout: A Function-Based Genetic Analysis in a Japanese Population


(Published 4 November 2009; Volume 1 Issue 5 Sra11)

Gout based on hyperuricemia is a common disease with a genetic predisposition, which causes acute arthritis. The ABCG2/BCRP gene, located in a gout-susceptibility locus on chromosome 4q, has been identified by recent genome-wide association studies of serum uric acid concentrations and gout. Urate transport assays demonstrated that ABCG2 is a high-capacity urate secretion transporter. Sequencing of the ABCG2 gene in 90 hyperuricemia patients revealed several nonfunctional ABCG2 mutations, including Q126X. Quantitative trait locus analysis of 739 individuals showed that a common dysfunctional variant of ABCG2, Q141K, increases serum uric acid. Q126X is assigned to the different disease haplotype from Q141K and increases gout risk, conferring an odds ratio of 5.97. Furthermore, 10% of gout patients (16 out of 159 cases) had genotype combinations resulting in more than 75% reduction of ABCG2 function (odds ratio, 25.8). Our findings indicate that nonfunctional variants of ABCG2 essentially block gut and renal urate excretion and cause gout.

Q126X: Jr(a-) Asians

Sir Isaac Newton, Charles Darwin, and Leonardo da Vinci (6) were all affected by gout. The prevalence of gout and hyperuricemia is about 1 to 2% and 10 to 25% in males, respectively, in Japan (7) and other countries (8, 9). In men over the age of 65 years, gout prevalence is approaching 7% (9). The prevalence of gout and hyperuricemia is now increasing.

INTRODUCTION

Gout is a common disease resulting from tissue deposition of monosodium urate crystals as a consequence of hyperuricemia, which shows elevated serum uric acid (SUA) concentrations (1, 2) and has long been known to have a heritable component (3). Since Hippocrates first
Biological data in Jr(a-) people

9 Jr(a-) subjects tested for uric acid levels in plasma

220 ± 50 µmol/l

214 ± 76 µmol/l in 9 random controls tested in the same conditions

=> No significant statistical difference
Functional Validation of the Genetic Polymorphisms of Human ATP-Binding Cassette (ABC) Transporter ABCG2: Identification of Alleles That Are Defective in Porphyrin Transport

Ai Tamura, Masato Watanabe, Hikaru Saito, Hiroshi Nakagawa, Toshiaki Kamachi, Ichiro Okura, and Toshihisa Ishikawa

Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, Yokohama, Japan

Received February 15, 2006; accepted April 11, 2006
Biological data in Jr(a-) people

3 Jr(a-) subjects tested for porphyrin

- RBCs: $3.3 \pm 1.7 \, \mu\text{mol/l}$   N: 0.1 – 1.9
- Plasma: <5 µmol/l   N: 6.5 – 20.0
- Slight increase in RBCs but values not comparable at all to porphyria
- No clinical sign of porphyria or light/UV hypersensitivity

⇒ Probable compensatory mechanism
JR was elevated to the status of 32\textsuperscript{nd} human blood group system by the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology in July 2012 (ISBT, Cancun, Mexico)
PERSPECTIVES

• Since Jr(a-) patients are not able to efflux some anticancer drugs and are at risk for severe overdosage, should we not recommend a systematic Jr\textsuperscript{a} typing in Japanese and Gypsy population with breast cancer?

=> Pharmacogenetics

• Jr(a-) people do not seem to show any clinical disorders => opens the door to the use of potent ABCG2 inhibitors in breast cancer
THE LAN STORY
The Lan antigen, a 50-year-old mystery

van der Hart & al
1961
THE LAN ANTIGEN

Terminology
ISBT symbol (Number)
Lan (901.002)
Langereis; Gn⁺; Gonsowski; So; 900.003
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 20,000 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

Lan⁻ is a very rare blood type worldwide.
WHY STUDYING LAN?

- 29 Lan- in the French National Registry of People with a Rare Blood Type
- 24/29 with anti-Lan
- Anti-Lan considered a clinically significant alloantibody
- Monoclonal antibody available
   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

   Judd WJ, Oberman HA, Silenieks A, Steiner EA.
   PMID: 6585080 [PubMed - indexed for MEDLINE]
   Related citations  Remove from clipboard

3. Hemolytic disease of the newborn due to anti-Lan.
   Page PL.
   PMID: 6679383 [PubMed - indexed for MEDLINE]
   Related citations  Remove from clipboard

   PMID: 5790273 [PubMed - indexed for MEDLINE]
   Related citations  Remove from clipboard
   Free PMC Article

5. Lan antigen of erythrocytes and clinical significance of anti-Lan antibody.
   Kuśnierz-Alojsa G, Wioczek B.
   PMID: 8372617 [PubMed - indexed for MEDLINE]
   Related citations  Remove from clipboard
How to find out the molecular basis of Lan?
OSK43 monoclonal anti-Lan: The key to elucidate the Lan mystery?

ESTABLISHMENT AND CHARACTERIZATION OF HUMAN MONOCLONAL ANTI-LAN
Tani et al.
Japanese Red Cross Osaka Blood Center, Osaka, Japan.

Monoclonal anti-Lan OSK43 (human IgG1κ)
Agglutination  Flow cytometry  Western blot
1) Immunoprecipitation of Lan carrier with OSK43 from a RBC lysate

2) Analysis of immunoprecipitate by electrophoresis/silver staining

3) Band cutting on the gel => identification of candidate carriers by mass spectrometry after trypsin digest
OSK43 anti-Lan immunoprecipitates the ABCB6 membrane transporter of human RBCs

Silver-stained gel

Mass spectrometry analysis

High confidence level: 17 peptides!
ABC6 is dispensable for erythropoiesis and specifies the new blood group system Langereis

Virginie Helias¹, Carole Saison¹, Bryan A Ballif², Thierry Peyrand¹,³, Junko Takahashi⁴, Hideo Takahashi⁴, Mitsunobu Tanaka⁴, Jean-Charles Deybach⁵, Hervé Puy⁵, Maude Le Gall⁶, Camille Sureau¹, Bach-Nga Pham¹,³, Pierre-Yves Le Pennec¹,³, Yoshihiko Tani⁴, Jean-Pierre Cartron¹ & Lionel Arnaud¹
The **ATP-Binding Cassette (ABC)** transporter family

- **'full transporters'**
- **'half transporters'**

**Cytoplasm**
ABCB6 is absent in the membrane of all tested Lan- RBCs

 WB anti-ABCB6

 WB anti-ABCG2

 Multimer?

 Lan- => Lan$_{null}$
Up to 10 null alleles of $ABCB6$ were identified by sequencing 12 unrelated Lan- subjects.

$ABCB6$ (2q36) 19 exons

Frameshift

Nonsense mutations (stop codons)

Essential splice-site mutations
Missense mutations in \textit{ABCB6} can also be responsible for the Lan- phenotype!

\textbf{\textit{ABCB6} (2q36)}

Accelerated degradation of \textit{ABCB6}? Occurred in several ethnic backgrounds (France, Africa, Poland, Italy...).
The $ABCB6$ mutation p.Arg192Trp is a recessive mutation causing the Lan– blood type

C. Saison,¹,†, V. Helias,¹,† T. Peyraud,¹,² L. Merad,³ J.-P. Cartron¹ & L. Arnaud¹

¹National Institute of Blood Transfusion (INTS), Paris, France
²National Reference Center for Blood Groups (CNRGS), Paris, France
³Centre Europe Le Palatin, Hyères, France
WHAT WAS UNEXPECTED!

- ABCB6 not considered to be present on RBCs (described on outer mitochondrial membrane)

- ABCB6 reported to be essential in erythropoiesis through mitochondrial porphyrin uptake

However, Lan- people, who are human “knock outs” for ABCB6, appear to be healthy!
Biological data in Lan- people

- 4 Lan- subjects were tested for porphyrin levels:
  - RBCs: 2.1 µmol ± 0.2  N: 0.1 – 1.9
  - Plasma: < 5 nmol/l  N: 6.5 – 20.0

⇒ Slight increase in RBCs but not comparable at all to porphyria
⇒ Probable compensatory mechanism

- 4 Lan- subjects were tested for blood count since Lan is supposed to be essential for erythropoiesis: nothing abnormal
LAN was elevated to the status of 33rd human blood group system by the ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology in July 2012 (ISBT, Cancun, Mexico)
ISBT Working Party on Red Cell Immunogenetics and Blood Group Terminology

Chairperson: Jill Storry

Members:

L. Castilho  G. Daniels  M. de Haas
G. Denomme  W. Flegel  C. Lomas-Francis
G. Garratty  C. Gassner  C. Hyland
J. Moulds   N. Nogues  M. Olsson
T. Peyrard   J. Poole  P. Rouger
M. Scott   J. Storry  Y. Tani
E. van der Shoot  F. Wagner  S. Wendel
C. Westhoff  V. Yahalom  LC. Yu
BLOOD GROUPS IN 2013

- 33 blood group systems
- 11 new antigens accepted in July 2012 by the ISBT Working Party

=> 339 antigens
<table>
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<th>SYSTEM</th>
<th>ISBT NAME</th>
<th>NAME</th>
<th>PREVALENCE</th>
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</tr>
</tbody>
</table>

*RHCE*ceMO/RHCE*ceMO people (Africans) are RH:-61

Peyrard T & al. *Transfusion* 2010;50(Suppl):144A
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