

Werfen 1st Transfusion Scientific Seminar
Vilnius, Lithuania – 16-17 October 2025

The Role of Molecular Biology and Genotyping in Enhancing Immunohematology Practices

Martin L. Olsson
M.D., Ph.D.

Professor of Transfusion Medicine
Wallenberg Clinical Scholar 2016-2026
President, Swedish Society of Clinical Immunology and Transfusion Medicine
Medical Director of the Nordic Reference Laboratory for Genomic Blood Group Typing

Division of Transfusion Medicine
Department of Laboratory Medicine,
Lund University, Sweden



Department of Clinical Immunology
and Transfusion Medicine,
Skåne University Hospital,
Lund, Sweden



1

Disclosures

- ◆ CEO, President and 50% co-owner of BLUsang AB, a consulting firm handling intellectual property, patents, royalties and related licensing agreements
- ◆ Member of the Scientific Advisory Committee on Transfusion Medicine for Werfen
- ◆ Have given lectures for:
 - Ortho Quidel
 - Grifols
 - Bio-Rad
 - Werfen
- ◆ Holder of patents and patent applications regarding:
 - Blood group genotyping
 - Bacterial exoglycosidases to develop ABO-universal blood



2



LUND
UNIVERSITY

Division of Transfusion Medicine
Department of Laboratory Medicine

The Blood Group @ LU

Our translational research aims to uncover new roles of the **red blood cell** surface in health and disease, with a special focus on the polymorphic molecules known as **blood groups**.



SKANE

Clinical Immunology & Transfusion Medicine
LabMedicine, Skåne University Hospital





Yan Quan Lee
Ph.D., Post-doc
LabManager



Annika Hult
Ph.D., staff
scientist



Maria Ailhorn
Ph.D.



Bakram Hossaini-Maaf
Ph.D., BMA



Anja Nylander
M.D., Ph.D.



Linn Stenfelt
Ph.D., post-doc



Jill Story
Adj. Prof. Ph.D.,
Deputy group
leader



Åsa Hellberg
Ph.D., Reference
laboratory
coordinator



Ann-Marie Lenndin
Research
administrator



Stephan Hasse
Ph.D., Post-doc



Nysa McGowan
Ph.D., Post-doc



Jennifer Ricci Hagman
Ph.D.



Mattias Möller
M.D., Ph.D.
student
Bioinformatician



Namrata Singh
Ph.D., post-doc



Magnus Jöud
M.D., Ph.D.
Consultant

During 2016-2026 our work is funded by:



novo nordisk fonden

Mats Paulssons Stiftelse
för forskning, innovation
och samhällsbyggande



OLLE ENKVISTS STIFTELSE

Crafoordska stiftelsen

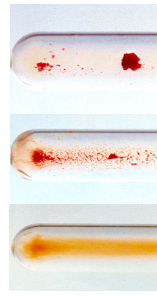
Alfred Österlunds Stiftelse

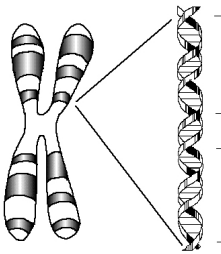


3

From Serology to Molecular Biology

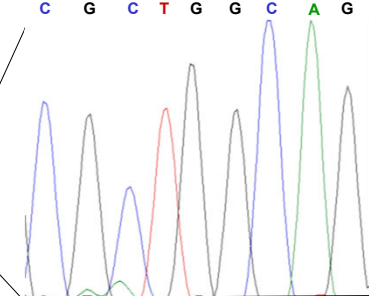
- a revolution started already in the 1980s



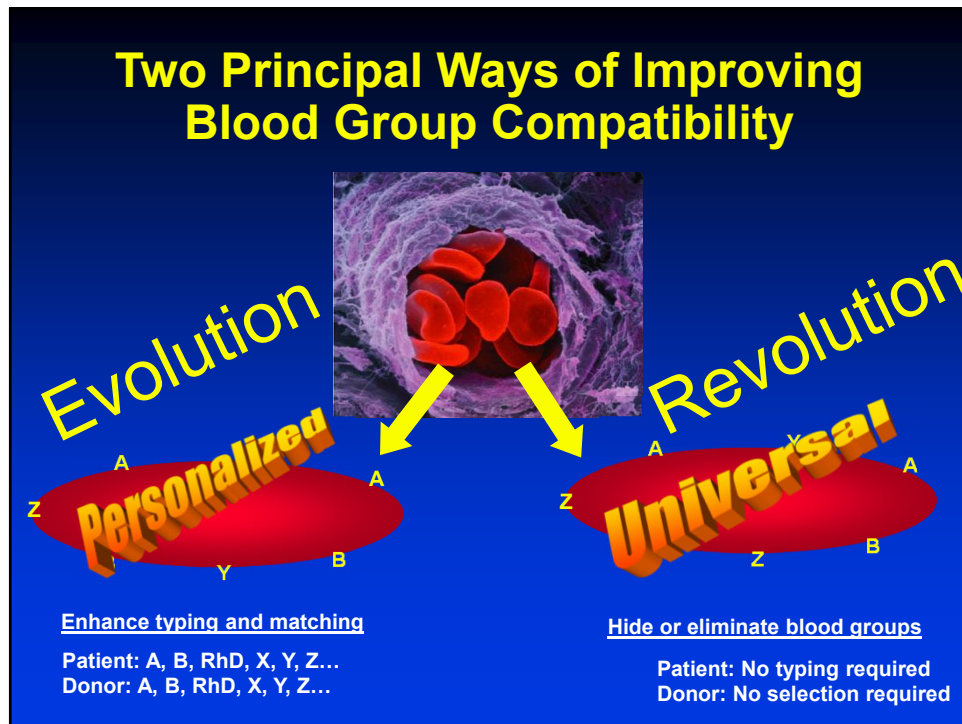


Chromosome
DNA

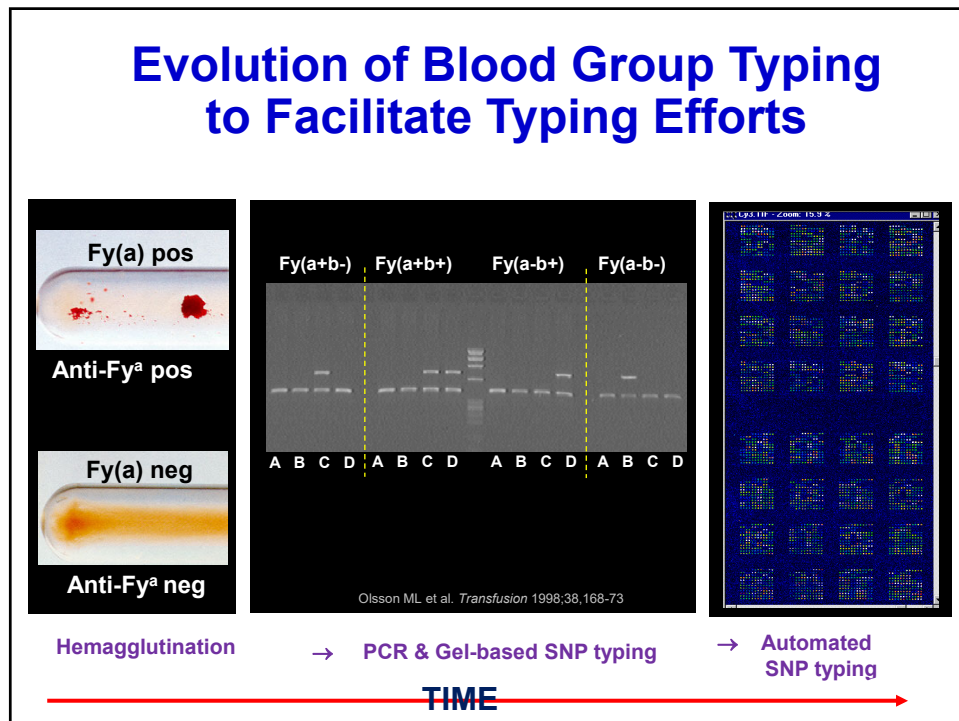
C G C T G G C A G



4

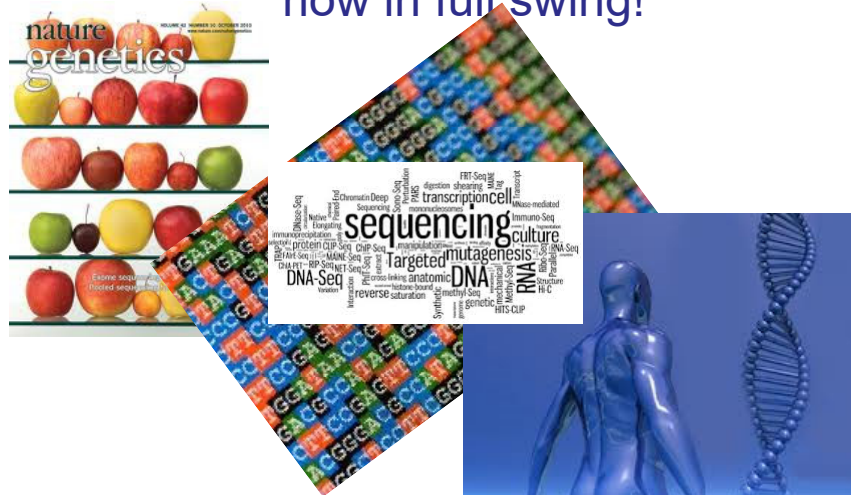


6



7

The wonderful but complicated world of molecular biology now in full swing!



Need for double-competent staff – a new challenge for blood establishments and reference laboratories

8

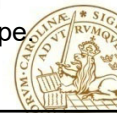
Brief look-back at blood groups and genotyping

- ◆ The first blood group gene was cloned in the mid-1980s. Genes underlying ABO and Rh followed in early 1990s.
- ◆ Since 2018, all blood group systems can be genetically predicted (the P1PK and XG systems were the last existing systems to be resolved).
- ◆ Now 48 blood group systems acknowledged by ISBT. But still, the genetic bases for a number of antigens remain unresolved.
- ◆ The majority of blood group antigens depend on single nucleotide variants (SNVs) in our genome
- ◆ Deletions, insertions, gene conversions and other rearrangements can also cause changes in blood group phenotype
- ◆ Simple and straight-forward for most but complex for a few systems
 - e.g. ABO hybrids and subgroups, weak and category RhD, MNS hybrids
 - Also, null alleles causing loss of all antigens in a system constitute a challenge because there are many ways to "kill a gene"

9

Some well-known examples (reminder)

- ♦ **Group O** depends on homozygosity for c.261delG in >97% of cases
- ♦ **RhD neg** depends on homozygosity for deletion of *RHD* gene in most cases but ethnic variation is challenging
- ♦ The **Kell antigen** depends on a SNP causing an amino acid change in the *KEL* gene (c.578C>T) resulting in p.Thr193Met.
- ♦ Whilst **Fy^a vs. Fy^b** is due to a simple SNP in *ACKR1* (*FY*) gene, c.125G/A, the common Fy(a-b-) phenotype is caused by loss of GATA1-binding site in the proximal promoter (c.-67T>C) regulating transcription in RBCs.
- ♦ **Genotyping** is about detecting these and other genetic bases of blood groups in a safe way to predict the resulting RBC phenotype



10

Some of the reasons for performing a blood group genotyping test today

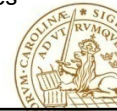
- ♦ Cell-free plasma DNA to predict fetal RBC phenotype
- ♦ Prediction of common RBC phenotype in multi-transfused or DAT positive patients but also in blood donors
- ♦ Resolution of serological discrepancies in both patients and donors
 - e.g. weak/category D, ABO subgroups
- ♦ Screening for, or resolution of, rare variants, e.g. in patients with “difficult” antibody specificities or mixtures
 - includes donor typing for the corresponding antigens
 - screening for rare donors
- ♦ Quality assurance of test RBC phenotype
 - donor zygosity, weak antigen expression, confirm rare phenotypes



11

Some of the reasons for performing a blood group genotyping test today

- 🔥 Cell-free plasma DNA to predict fetal RBC phenotype
- 🔥 Prediction of common RBC phenotype in multi-transfused or DAT positive patients but also in blood **donors**
- 🔥 Resolution of serological discrepancies in both patients and **donors**
 - e.g. weak/category D, ABO subgroups
- 🔥 Screening for, or resolution of, rare variants, e.g. in patients with “difficult” antibody specificities or mixtures
 - includes **donor** typing for the corresponding antigens
 - screening for rare **donors**
- 🔥 Quality assurance of test RBC phenotype
 - **donor** zygosity, weak antigen expression, confirm rare phenotypes



12

DNA-based blood group typing - a major global trend

- ★ Based on the discovery of molecular genetic basis of blood groups
 - Ongoing since late 1980s
 - Still continuing: orphan and emerging blood groups remain
- ★ Driven by technological progress in high-throughput molecular biology
- ★ Needed to address the growing concern that blood group incompatibility is an important and not improving reason for:
 - Serious adverse events following transfusion
 - High degree of immunization and too short transfusion intervals in chronically transfused patients (e.g. sickle cell disease, thalassemia)
- ★ Trend in many countries
 - EU
 - North America: USA, Canada
 - South America: Brazil
 - Middle East: Kuwait, Saudi Arabia, UAE etc
 - Asia and beyond: Japan, China, Malaysia, Singapore, Australia, New Zealand etc.
- ★ Interesting trend in some countries that serological expansion is skipped in favour of DNA-based progress!
 - Mainly Middle East, some Indian centres, Malaysia, China etc

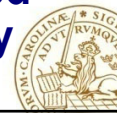


13

We started offering the first clinical routine tests to customers in 1996...

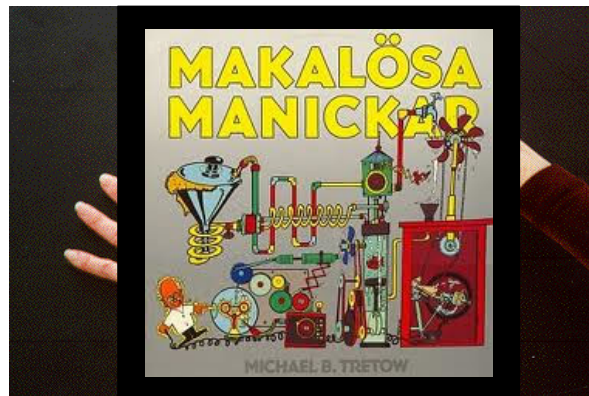


In 2001, Lund was formally appointed as the Nordic Reference Laboratory for Blood Group Genomics



14

**Manual techniques
- a limitation for routine large-scale use**



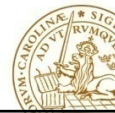
**Luckily, company-driven development
has happened in parallel...**



15

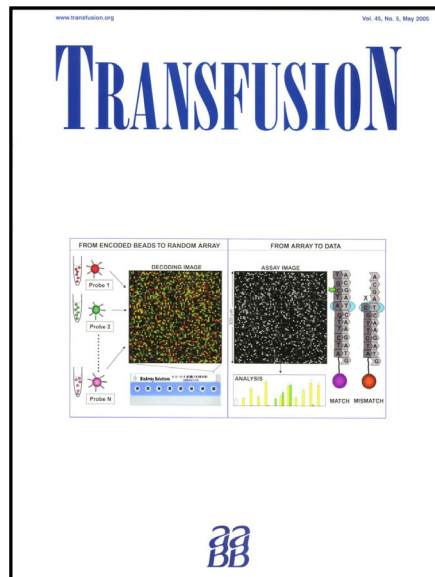
Some of all the companies that have been or are involved in developing systems (equipment and/or kits) for DNA-based blood group typing

- ★ Inno-Train Diagnostik GmbH, Germany
- ★ BAG Diagnostics, Germany
- ★ Axo Science, France
- ★ Immucor/BioArray Systems, USA
- ★ Grifols/Progenika, Spain
- ★ Agena/Sequenom, USA/Germany
- ★ Life Technologies Open Array, USA
- ★ Beckman Coulter/GenomeLab SNP stream, USA
- ★ Thermo Fisher Scientific, USA
- ★ HaploGNX, USA
- ★ Devyser, Sweden
- ★ And so on...



16

Goodbye to agglutination and all that?*



*Anstee DJ.
Transfusion
2005; 45: 652-3



17

Microarrays and Blood Grouping – 20 years ago!

Transfusion
May 2005
Vol 45

Rapid genotyping of blood group antigens by multiplex polymerase chain reaction and DNA microarray hybridization

Sigrid H.W. Beiboer, Tinka Wieringa-Jelsma, Petra A. Maaskant-Van Wijk, C. Ellen van der Schoot, Rob van Zuijlen, Dirk Roos, Johan T. den Dunnen, and Masja de Haas

Microarray-based genotyping for blood groups: comparison of gene array and 5'-nuclease assay techniques with human platelet antigen as a model

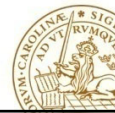
Peter Bugert, Simon McBride,* Graham Smith, Alex Dugrillon, Harald Klüter, Willem H. Ouwehand, and Paul Metcalfe*

High-throughput multiplex single-nucleotide polymorphism analysis for red cell and platelet antigen genotypes

G.A. Denomme and M. Van Oene

A flexible array format for large-scale, rapid blood group DNA typing

Ghazala Hashmi, Tasmia Shariff, Michael Seul, Prabhakar Vissavajhala, Kim Hue-Roye, Dalisay Charles-Pierre, Christine Lomas-Francis, Asok Chaudhuri, and Marion E. Reid



18

Microarrays Come in Different Flavours

♦ Expression (cDNA) arrays most widely used

- ✓ High or low density chips depending on spotting device etc

♦ SNP arrays (those used for blood group genotyping)

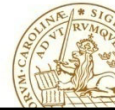
- ✓ Oligonucleotides include polymorphic position of interest

♦ Protein arrays

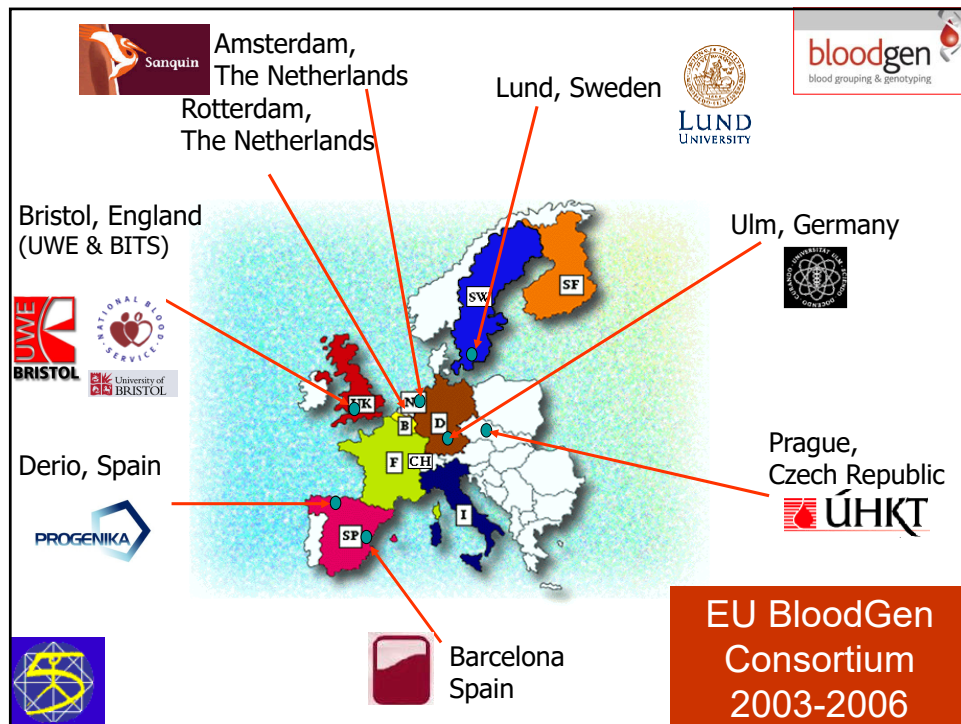
- ✓ Target protein on chip
- ✓ Catch antibodies on chip

♦ Glycan arrays

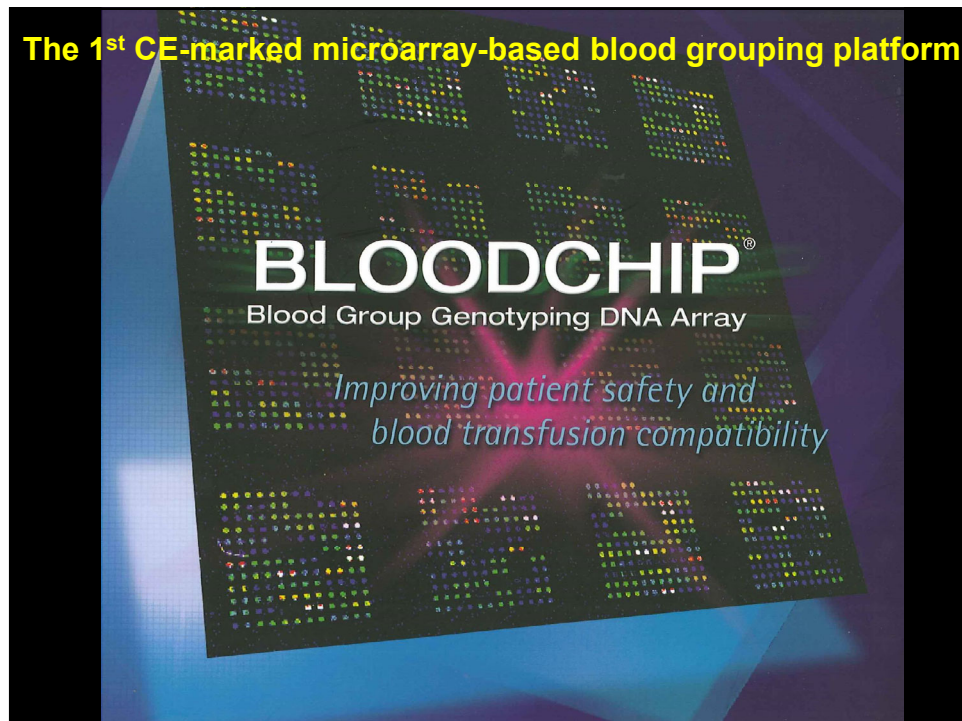
- ✓ Target oligosaccharides
- ✓ Glycoproteins (targeting combined epitopes)



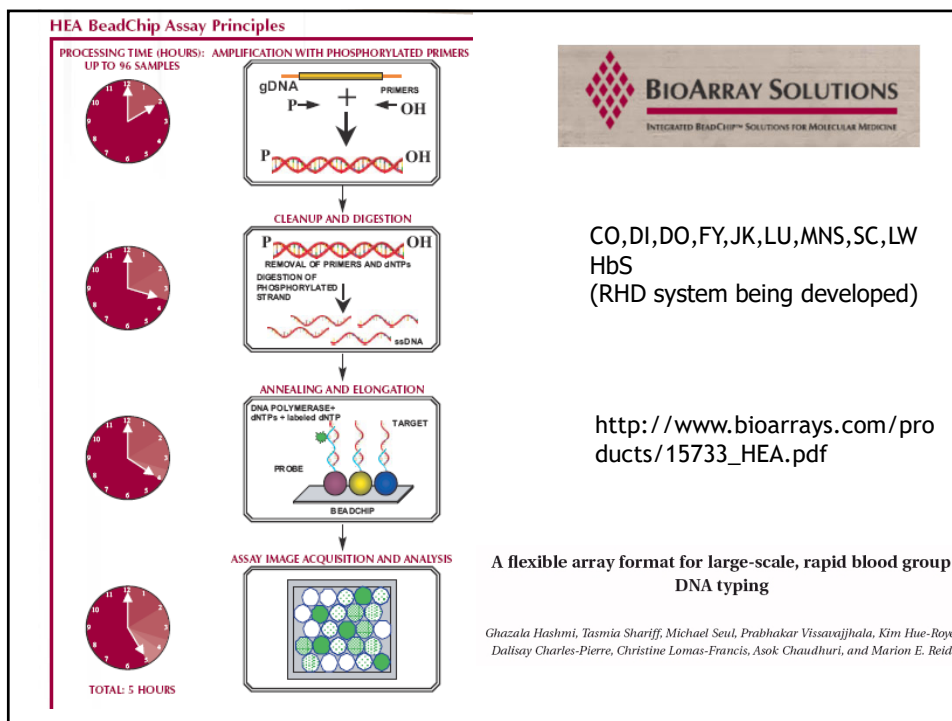
19



20



21



22

NEWSFOCUS

MEDICINE

Blood-Matching Goes Genetic

Hoping to prevent adverse transfusion reactions and save lives, European researchers are lobbying to replace serology-based blood typing with matching based on DNA tests

Two decades ago, a 20-year-old man entered Duke University hospital for a hip replacement. He had sickle cell disease and because he was anemic, he needed a blood transfusion before the operation. As with most sickle cell patients, he had received transfusions before. But on this occasion, his body rejected the blood.

The doctors tried again and again with different blood, but the man's immune system rebelled against every new transfusion, generating antibodies that killed the new blood

with rare blood types that are hard to find in emergency situations.

"The argument that we will have 100% perfect blood for every patient will never be the case," says Neil Ament of the University of the West of England (UWE) in Bristol, who has led a European research consortium exploring blood genotyping. "But when you have all the information available, you can find the best blood."

Matchmaking
Finding the best blood seems simple. Two antigens on red blood cells determine the major blood group—A, B, AB, or O. A person with type A naturally harbors antibodies to B antigens and vice versa. Give type-B blood to a patient with type A, and antibody reactions will cause blood cells to clump together, sometimes with fatal results. AB people don't have antibodies to either antigen, making it easier to find blood for them. But O people have antibodies to both A and B, as their blood cells have neither antigen, so they can only receive O blood.

But there's more to blood than A and B antigens. Physicians also routinely test for D, an antigen in the Rhesus (Rh) blood group that can evoke a strong immune response. They try never to give RhD+ blood to an RhD- person.

The possibilities get even more complicated. Ament, who also directs UWE's Centre for Research in Biomedicine, says there are 29 known blood groups, which are determined by about 200 antigens. A person's full blood type might read: AB, D+, M+, N+, K-, Leav, and so on.

A simple antibody test can identify a donor's or patient's ABO blood type, and in

another genotyping product that tests for 11 blood groups

pletely abandon serology. "We would never throw out our old toolbox," she says.

Moving forward
A few countries are already forging ahead with blood genotyping on a large scale. Canada is among the leaders. In December, for example, Quebec announced plans to genotype 22,000 blood donors. Currently, when a patient with a rare blood group needs a transfusion, practitioners have to blindly order blood from banks based on ABO and D grouping alone and then test it with more detailed serology on site. This trial-and-error approach wastes time and money. The screening should make the process faster by narrowing initial blood selection, but serological testing will still serve as a follow-up.

Chipping away. Two new gene chips (BioArray above) can test for many blood groups beyond ABO.

Blood Type	ABOchip	BeadChip
RHCE and RHDF		
RHCE	4	
KEL	7	2
JK	3	2
FY	3	2
MNS	6	4
DI	2	2
DO	2	4
CO	2	2
SC	2	
LU	2	
LW	2	
ABO	4	

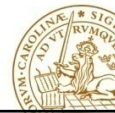
A bloody debate
Ament is adamant that genotyping will replace serology for most blood groups within the decade and in some cases sooner. He predicts European hospitals will demand blood genotyping of patients expecting to receive a transfusion. "For transfused patients, I expect a change in policy this year," Ament says. "Then I would expect other vulnerable groups [such as pregnant women to be] tested. Then I would like

Quill E. Blood-Matching Goes Genetic.
Science 2008; 319: 1478-9

23

Many other technologies available, e.g. ...

- 🔥 Luminex xMAP
- 🔥 MALDI-TOF
- 🔥 TaqMan open array
- 🔥 Nextgen sequencing
- 🔥 Long-read, single-molecule sequencing



25

Many other technologies available, e.g. ...

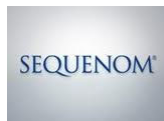
ID|CORE

ID|CORE+

BLOODchip
REFERENCE



🔥 Luminex xMAP



🔥 MALDI-TOF



HEMOCARTA



26

Many other technologies have been used over the years, e.g. ...

🔥 TaqMan open array

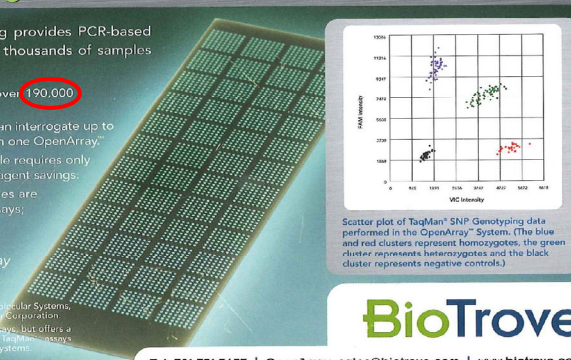
OpenArray™ SNP Genotyping System

OpenArray™ SNP Genotyping provides PCR-based SNP analysis of hundreds to thousands of samples and candidate SNPs.

- **High Throughput.** Generate over **190,000** genotypes per day.
- **Flexible Format.** Researchers can interrogate up to 48 samples against 64 assays on one OpenArray™.
- **Low Volume.** Each through-hole requires only **33 nL**, resulting in significant reagent savings.
- **Easy to Use.** OpenArray™ plates are loaded with your TaqMan™ assays; researchers only need to add sample, cycle, and image.

Coming soon: The OpenArray Real Time System.

TaqMan is a registered trademark of Roche Molecular Systems, Inc. MC is a registered trademark of Applied Biosystems. BioTrove does not make or sell TaqMan assays, but offers a liquid dispensing service using customers' TaqMan assays which may be purchased from Applied Biosystems. © BioTrove, Inc. 2006



Scatter plot of TaqMan® SNP Genotyping data performed in the OpenArray™ System. (The blue and red clusters represent homozygotes, the green cluster represents heterozygotes and the black cluster represents negative controls.)

BioTrove

Tel: 781 721 3657 | OpenArray_sales@biotrove.com | www.biotrove.com

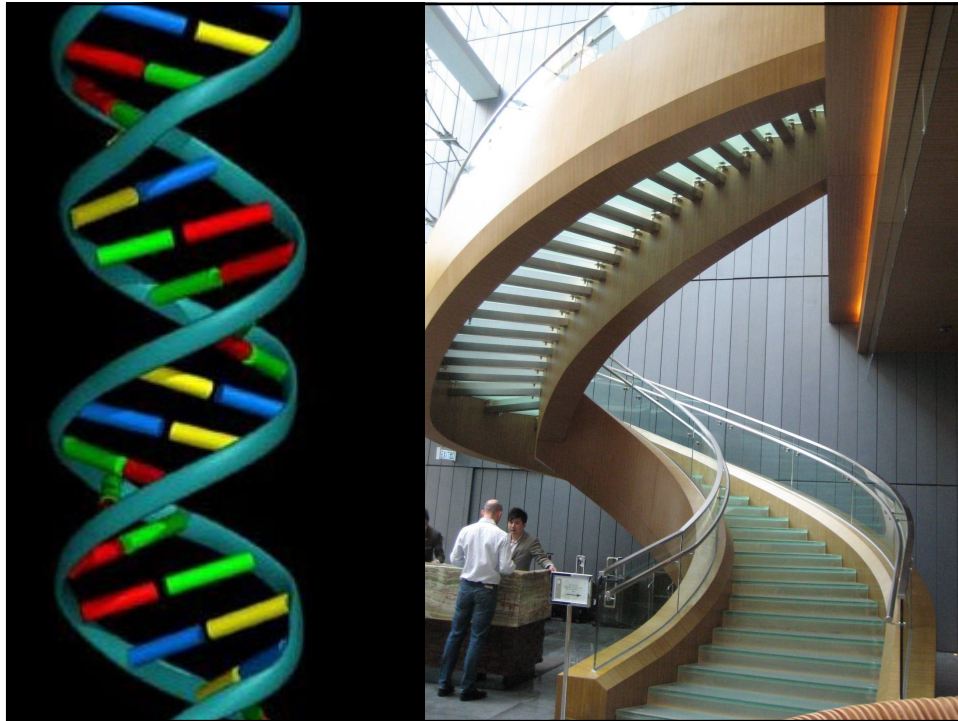
27

DNA-based blood group typing - fast pick-up in the Nordic countries

- ★ **National RHD screening on maternal plasma started in Denmark in 2010**
 - Netherlands, England, Finland and other countries followed
 - Sweden in national phase soon thereafter (Stockholm, Lund, others)
 - Antenatal Rh prophylaxis
 - Clinical benefit and cost-efficiency
 - Centralization or not?
- ★ **Many Nordic centers have tried kits/platforms or equipment for DNA-based blood group typing and most (if not all) have started routine use**
- ★ **ABO (and advanced RHD markers) are poorly represented on many of the commercially available platforms**
 - As a substitute, some centres have developed in-house methods
 - Many of these published, and some even proven better, but not CE-marked
- ★ **Some centers consider prices still prohibitive**
 - Several new platforms will soon be launched and (hopefully) CE-marked/FDA-approved
 - Prices are expected to come down as competition hardens
 - Continuous upgrades constitute challenge for CE/IVDR/FDA approvals (e.g. BloodChip=>ID-Core => ID-Core+ => ID-Core XT etc)



28

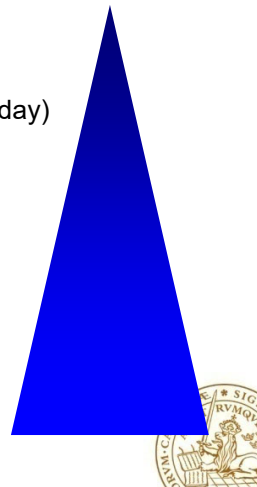


29

At what level should genotyping be implemented? National, regional, local? Blood centres and/or hospitals?

(and if so How and for Whom?)

- ♦ No, not cost-effective or practically possible
- ♦ Yes, but for rare cases only (similar to genotyping today)
- ♦ Yes, on a partial basis (e.g. chronically transfused)
- ♦ Yes, for all group O repeat donors
- ♦ Yes, for all repeat donors
- ♦ Yes, for all donors and non-emergency patients
(to allow for computerized selection of the best unit)



30

Large-scale blood group genotyping of donors

ORIGINAL PAPER

Set-up and routine use of a database of 10 555 genotyped blood donors to facilitate the screening of compatible blood components for alloimmunized patients

J. Perreault,¹ J. Lavoie,¹ P. Painschaud,² M. Côté,³ J. Constanzo-Yametz,⁴ R. Côté,⁵ G. R. Lemieux,¹ & M. St-Louis¹

¹Héma-Québec, Research and Development, Québec City, Québec, Canada
²Héma-Québec, Information Technology, Montréal, Québec, Canada
³Héma-Québec, Medical Affairs, Québec City, Québec, Canada
⁴Héma-Québec, Medical Affairs, Montréal, Québec, Canada
⁵Héma-Québec, Information Technology, Québec City, Québec, Canada
⁶Héma-Québec, Finance and Administration, Montréal, Québec, Canada

Vox Sanguinis

Background and Objectives Large-scale genotyping of red cell and platelet antigens has been predictive of compatible blood components. Several genotyping platforms have been developed to perform genotyping efficiently and accurately. **Materials and Methods** Here we describe the set-up and routine use of a database of 10 555 genotyped blood donors to facilitate the screening of compatible blood components for alloimmunized patients. **Results** Preliminary cost-benefit analysis showed that the database is a valuable tool. A computer application was developed to manage the database. **Conclusion** Since October 2007, 10 555 blood donors have been genotyped. The database is used on a regular basis to find compatible blood components with a genotype-phenotype concordance of 99.99%. **Key words:** automated platform, blood group antigens, compatible blood, database, donor genotyping.

Received: 22 December 2008
revised: 16 February 2009
accepted: 17 February 2009
published online 16 March 2009

Transfusion Clinique et Biologique

Volume 17, Issue 4, October 2010, Pages 242–248

Article original

Génotypage de 21 000 donneurs de sang au Québec et analyse du RHD

Genotyping of 21,000 blood donors in Quebec and RHD analysis

M. St-Louis¹, J. Perreault¹, J. Lavoie¹, P. Painschaud², M. Côté³, J. Constanzo-Yametz⁴, R. Côté⁵, G. R. Lemieux¹ & M. St-Louis¹

¹ Recherche et développement, Héma-Québec, 1070, avenue des Sciences-de-la-Vie, Québec, Q1V 5C3 Canada
² Affaires médicales hématologie, Héma-Québec, Québec, Canada

31

BLOOD GROUP GENOMICS

Implementing mass-scale red cell genotyping at a blood center

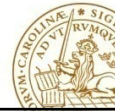
Willy A. Flegel,¹ Jerome L. Gottschall,^{2,3} and Gregory A. Denomme³

- ♦ Genotyped >43,000 donors over 4 years
 - 32 polymorphisms predicting 42 common and rare blood group antigens
- ♦ 0.52% of tests showed geno/pheno discrepancy
- ♦ By the 4th year, 29% of the RBC inventory had been genotyped

32

Genotyping to match donor and patient

- ♦ Has the introduction of phenotype prediction by genotyping reduced alloimmunisation?
 - Likely, but still too early to tell for sure
 - Many blood centers have adopted a policy for genotyping
 - Cost/benefit is a hot topic
 - Sickle-cell disease patients prioritized (more on this later)
- ♦ What are the benefits of genotyping strategies?
 - **More accurate** than phenotyping, e.g. *RHD/RHCE* typing
 - Some patients who appear RhD positive make allo-anti-D
 - Same goes for Rhc and Rhe categories
 - **More** extensively typed blood readily available on the shelf
 - **Reduced delays** in getting blood to the patient



33

Potential to save by decreasing...

- ♦ ...manual serology workload in the phenotyping lab
- ♦ ...emergency phenotyping to find typed or even rare blood units (incl. day, night, weekend shifts)
- ♦ ...import/transportation of typed/rare blood
- ♦ ...frequency of transfusion-induced blood group immunization by transfusing more compatible units
 - ✓ Either by chronically transfused patients only
 - ✓ According to responder gene markers (not yet available)
 - ✓ All nonacute transfusions
- ♦ ...the number of cases requiring antibody ID workups or referral to other lab



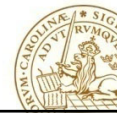
34

Genotyping can also open new possibilities to do something we couldn't do before

Before 2013, Vel-negative donors were very hard to find (1 in 4000-5000 in Europe).

No approved anti-Vel reagents were commercially available for serological screening.

What to do for Vel-immunized patients? (anti-Vel is very hemolytic)



35

Homozygosity for a null allele of *SMIM1* defines the Vel-negative blood group phenotype

Received 14 November 2012; accepted 6 March 2013; published online 7 April 2013

Jill R Storry^{1,2,6}, Magnus Jöud^{1,2,6}, Mikael Kronborg Christophersen¹, Britt Thuresson^{1,2}, Bo Åkerström³, Birgitta Nilsson Sojka⁴, Björn Nilsson^{1,2,5,7} & Martin L Olsson^{1,2,7}

nature
genetics

SMIM1 underlies the Vel blood group and influences red blood cell traits

Received 19 December 2012; accepted 8 March 2013; published online 7 April 2013

Ana Cvejic^{1,2,21}, Lonneke Haer-Wigman^{3,4,21}, Jonathan C Stephens^{1,5,6,21}, Myrto Kostadima⁷, Peter A Smethurst^{1,5,6}, Mattia Frontini^{1,5,6}, Emile van den Akker^{4,8}, Paul Bertone⁷, Ewa Bielczyk-Maczyńska^{1,2,5,6}, Samantha Farrow^{1,5,6}, Rudolf S N Fehrmann⁹, Alan Gray¹⁰, Masja de Haas^{3,4}, Vincent G Haver¹¹, Gregory Jordan¹², Juha Karjalainen⁹, Hindrik H D Kerstens¹³, Graham Kiddle^{1,5,6}, Heather Lloyd-Jones^{1,5,6}, Malcolm Needs¹⁰, Joyce Poole¹⁴, Aicha Ait Soussan^{3,4}, Augusto Rendon^{1,5,6,15}, Klaus Rieneck¹⁶, Jennifer G Sambrook^{1,5,6}, Hein Schepers^{17,18}, Herman H W Silljé¹¹, Botond Sipos⁷, Dorine Swinkels¹⁹, Asif U Tamuri⁷, Niek Verweij¹¹, Nicholas A Watkins⁶, Harm-Jan Westra⁹, Derek Stemple², Lude Franke⁹, Nicole Soranzo², Hendrik G Stunnenberg¹³, Nick Goldman⁷, Pim van der Harst^{9,11,22}, C Ellen van der Schoot^{3,4,22}, Willem H Ouwehand^{1,2,5,6,22} & Cornelis A Albers^{1,2,5,6,20,22}

nature
genetics

Disruption of *SMIM1* causes the Vel— blood type

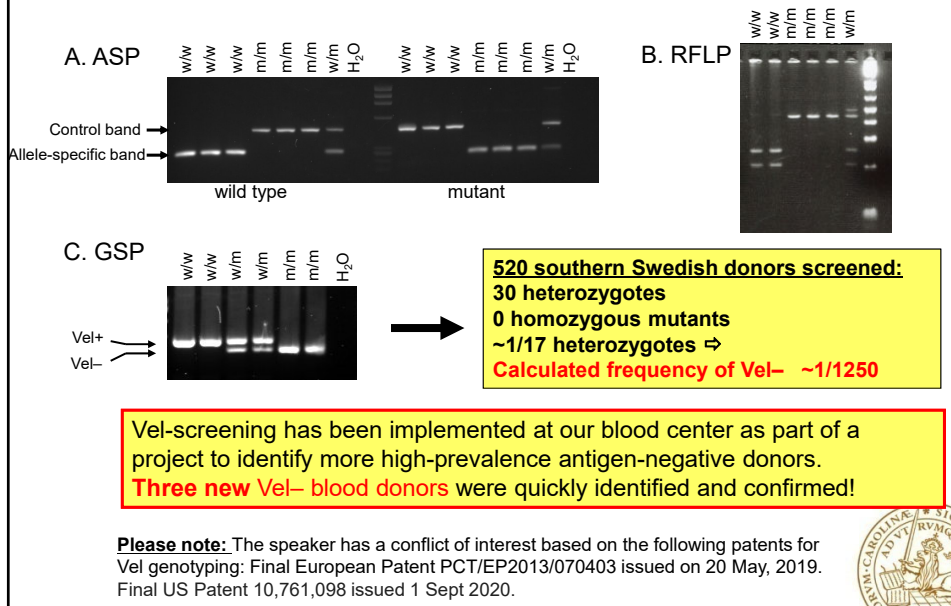
Received January 07, 2013
Revised March 05, 2013
Accepted March 10, 2013

EMBO
Molecular Medicine

Bryan A. Ballif^{2†}, Virginie Helias^{2†}, Thierry Peyrard^{2,3†}, Cécile Menanteau^{2,3}, Carole Saison², Nicole Lucien², Sébastien Bourgoin^{2,3}, Maude Le Gall⁴, Jean-Pierre Cartron², Lionel Arnaud^{2*}

36

DNA-based screening now widely available

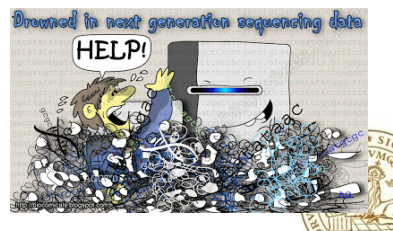


37

Next-generation sequencing or Massively parallel sequencing

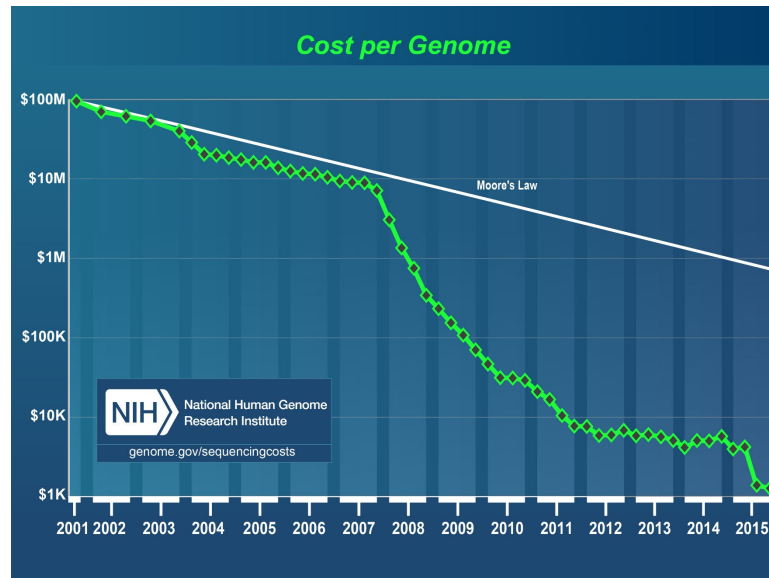


The amount of data is phenomenal and requires new strategies for storage and handling



38

Affordability of NGS is improving fast

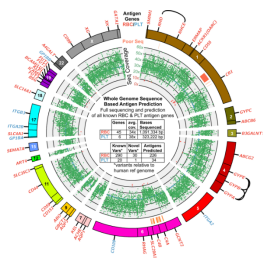


39

BLOOD GROUP GENOMICS

Comprehensive red blood cell and platelet antigen prediction from whole genome sequencing: proof of principle

William J. Lane,^{1,2} Connie M. Westhoff,³ Jon Michael Uy,¹ Maria Aguad,¹ Robin Smeland-Wagman,¹ Richard M. Kaufman,¹ Heidi L. Rehm,^{1,2,4,5} Robert C. Green,^{2,5,6} and Leslie E. Silberstein⁷ for the MedSeq Project*



NGS-based, comprehensive genotyping for all blood group antigens
(for which genetic background is known):

- ✓ Investigated 45 RBC and 6 HPA genes
- ✓ One individual
- ✓ Proof of principle

Lane et al. Transfusion 2016; 56: 743-54

40



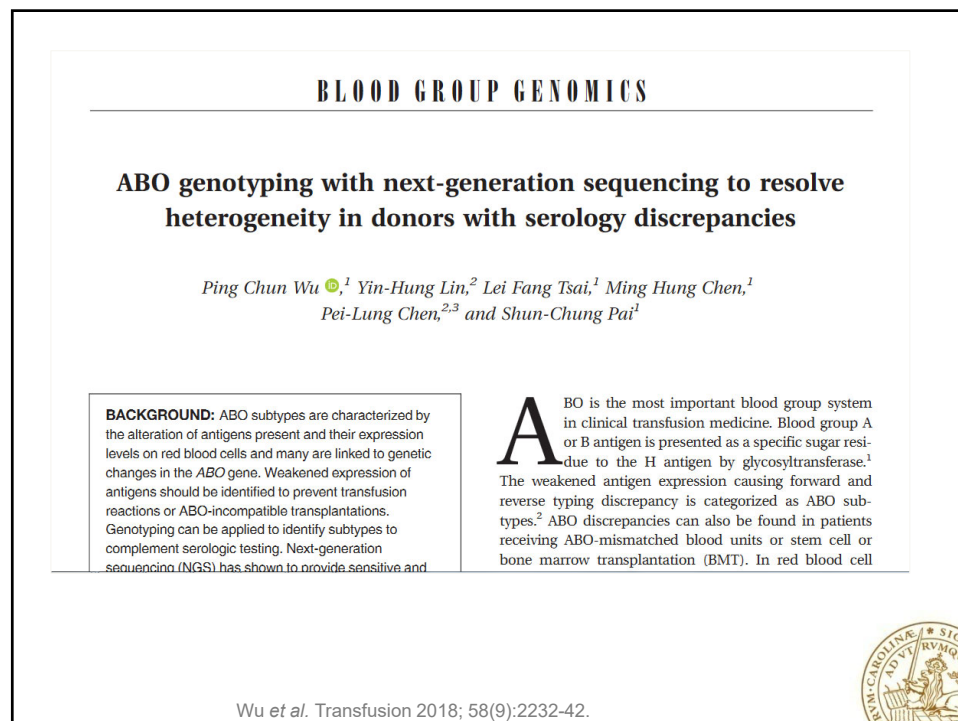
Automated whole-genome study

- ✓ 38 RBC antigens in 12 blood-group systems and 22 platelet antigens
- ✓ 110+200 individuals included: serology vs. NGS
- ✓ 99.5% =>99.8%=>99.2%(=>99.9%) concordance

Lane *et al.* Lancet Haematology, 2018;Jun;5(6):e241-e251



41



Wu *et al.* Transfusion 2018; 58(9):2232-42.



42

A targeted Next-Generation Sequencing approach can include all blood group genes (but no regulatory approval yet)

HaploGNX

Home Products Contact Us

Products

HemoSelect V3

Next Generation Blood Group Genotyping

Blood group antigen genotyping is a transformative alternative to classical serology and is gaining rapid acceptance in immunohematology laboratories. HemoSelect V3 is a modular assay that targets 40 blood group systems between 3 component panels:

- **CORE:** 19 blood group systems
- **EXPANDED:** 20 blood group systems
- **PLUS:** ABO, platelets, neutrophils, HBA1, HBA2 and HBB

These include all markers commonly used for testing donor DNA samples to identify rare donors. Each component panel (eg CORE) is a single well, two step assay that allows the user to analyze as many as 384 samples in a single run (Illumina MiniSeq System Mid Output K80).

For more information please [download the HemoSelect product information sheet](#) or [contact us](#).



43

A targeted Next-Generation Sequencing approach can include some blood group genes (but again, no regulatory approval yet)

Press release

Devysr launches Genomic Blood Typing assay: All blood groups, one simple test

Dvysr

Devysr – a new level of certainty

News | June 30, 2025

Devysr today announced the global launch of **Devysr Genomic Blood Typing**, a next-generation sequencing (NGS)-based solution that redefines molecular blood group research. Developed exclusively, this all-in-one assay enables comprehensive genetic blood typing—covering red blood cell (RBC), human platelet antigen (HPA), and human neutrophil antigen (HNA) systems—in a single, streamlined test.

Designed to address the complexities of blood group analysis in transfusion and transplantation research, Devysr Genomic Blood Typing offers high-resolution results with unprecedented workflow simplicity and software-guided interpretation.

Simplifying complexity in blood group research

Traditional serological methods often struggle with weak antigen expression, rare



44

Less costly but more able microarrays are being introduced – regulatory approval is here or near

REGULAR ARTICLE **blood advances**

Development and validation of a universal blood donor genotyping platform: a multinational prospective study

Nicholas S. Gleadall,^{1,2,*} Barbara Veldhuisen,^{3,4,*} Jeremy Gollub,^{5,*} Adam S. Butterworth,^{6,8} John Ord,^{1,2} Christopher J. Penkett,^{1,9} Tiffany C. Timmer,^{10,11} Carolin M. Sauer,¹² Niek van der Bolt,² Colin Brown,¹³ Kim Brugger,¹⁴ Alexander T. Ditley,^{15,16} Daniel Duarte,^{1,8} Shane Grimsley,¹⁷ Katja van den Hurk,¹⁰ John M. Jongerius,¹⁸ Jessie Luken,¹⁹ Karyn Megy,^{1,9} Gail Milfin,¹⁹ Christopher S. Nelson,² Femmeke J. Prinsze,¹⁰ Jennifer Sambrook,^{1,9} Ilania Simeoni,¹⁸ Michael Sweeting,^{6,7,20} Nicole Thornton,¹⁷ Sara Trompeter,^{19,21} Salih Tuna,¹⁹ Ram Varma,² Matthew R. Walker,^{6,7} NIHR BioResource,² John Danesh,^{6,8,22} David J. Roberts,^{7,23,24} Willem H. Ouweland,^{1,2,7,22} Kathleen E. Stirrup,^{1,9} Augusto Rendon,²⁵ Connie M. Westhoff,²⁶ Emanuele Di Angelantonio,^{6,8} C. Ellen van der Schoot,² William J. Astle,^{7,7,27} Nicholas A. Watkins,² and William J. Lane,^{28,29} on behalf of the Blood Transfusion Genomics Consortium

"This DNA-based test is capable of simultaneously typing most clinically relevant red blood cell (RBC), human platelet (HPA), and human leukocyte (HLA) antigens.

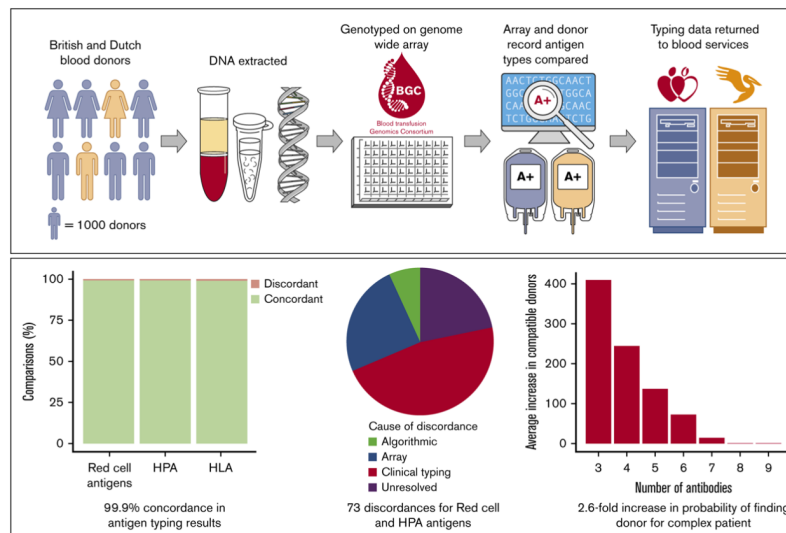
Validation was performed, using samples from 7927 European, 27 South Asian, 21 East Asian, and 9 African blood donors enrolled in 2 national biobanks."

Gleadall *et al.* Blood Adv 2020; 4(15):3495-3506

Downloaded from https://www.bloodadvances.org/

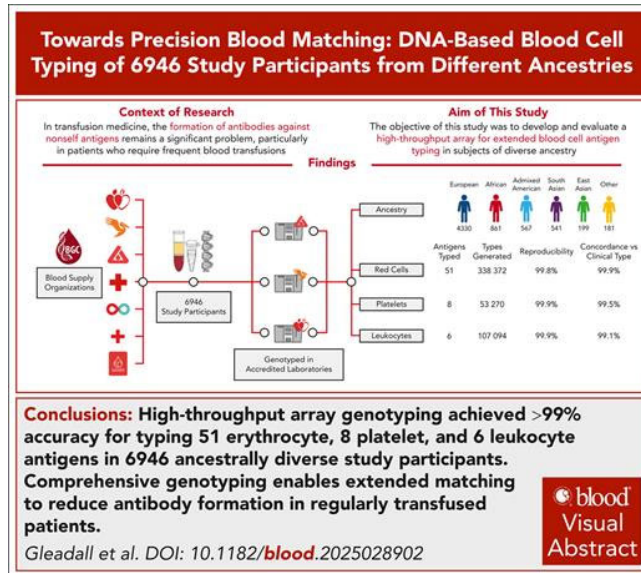
45

Genome-wide array tool at 99.9% concordance with clinical typing



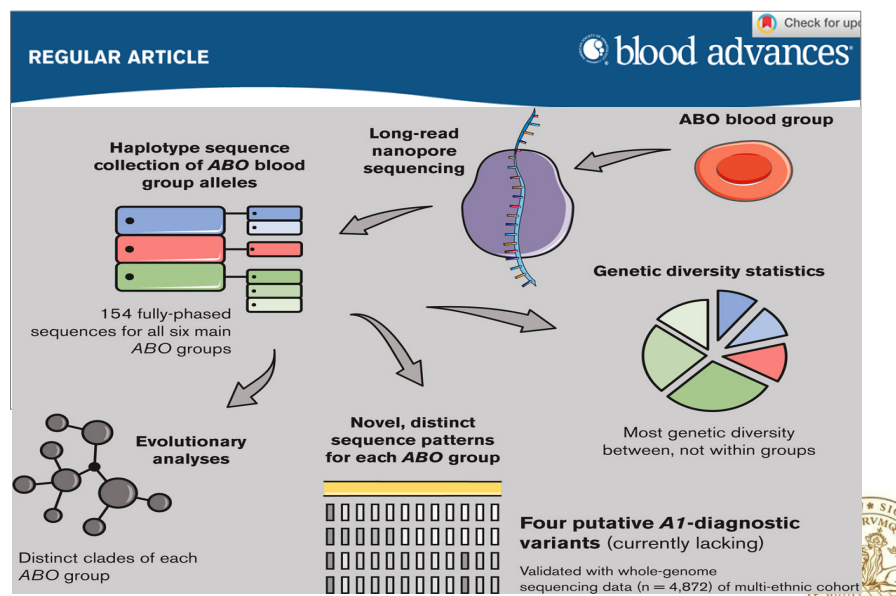
46

18 Sept 2025 (ePub): The latest paper on large-scale DNA-based genotyping



47

Long-read sequencing as a tool to resolve blood group problems



48

Can AI and machine learning help?

Received: 17 November 2023 | Revised: 17 July 2024 | Accepted: 27 August 2024
DOI: 10.1111/inf.18013

ORIGINAL RESEARCH
Blood Group Genomics

A deep learning approach for predicting blood group antigens from genomic data

Camous Moslemi^{1,2} | Thorsten Brodersen¹ | Kaspar R. Nielsen⁴ | Christina Mikkelsen³ | Jukka Partanen⁷ | Heide Sisse R. Ostrowski^{3,10}

¹Department of Clinical Immunology, Zealand University Hospital, Roskilde, Denmark; ²Institute of Science and Environment, Roskilde University, Roskilde, Denmark; ³Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; ⁴Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark; ⁵Department of Clinical Immunology, Odense University Hospital, Odense, Denmark; ⁶Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark; ⁷Finnish Red Cross Blood Service, Helsinki, Finland; ⁸Statens Serum Institut, Copenhagen, Denmark; ⁹Department of Clinical Immunology, Zealand University Hospital, Roskilde, Denmark; ¹⁰Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark

Check for updates

OPEN ACCESS

Citation: Hyvärinen K, Haimila K, Moslemi C, Ostrowski SR, et al. (2024) A machine-learning method for biobank-scale genetic prediction of blood group antigens. *PLoS Comput Biol* 20(3): e1011977. <https://doi.org/10.1371/journal.pcbi.1011977>

TRANSFUSION

PLOS COMPUTATIONAL BIOLOGY

METHODS

A machine-learning method for biobank-scale genetic prediction of blood group antigens

Kati Hyvärinen^{1*}, Katri Haimila², Camous Moslemi^{3,4}, Blood Service Biobank⁵, Martin L. Otsen^{6,7}, Sisse R. Ostrowski^{8,9}, Ole B. Pedersen¹⁰, Christian Erikstrup¹⁰, Jukka Partanen¹, Jarmo Riihari¹

¹ Research and Development, Finnish Red Cross Blood Service, Helsinki, Finland, ² Blood Group Unit, Finnish Red Cross Blood Service, Vantaa, Finland, ³ Department of Clinical Immunology, Zealand University Hospital, Koge, Denmark, ⁴ Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark, ⁵ Finnish Red Cross Blood Service, Vantaa, Finland, ⁶ Department of Laboratory Medicine, Lund University, Lund, Sweden, ⁷ Department of Clinical Immunology and Transfusion Medicine, Office for Medical Services, Region Skåne, Sweden, ⁸ Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, ⁹ Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, ¹⁰ Department of Clinical Immunology, Aarhus University Hospital, Skejby, Denmark

* kati.hyvarinen@bloodservice.fi

Abstract

A key element for successful blood transfusion is compatibility of the patient and donor red blood cell (RBC) antigens. Precise antigen matching reduces the risk for immunization and other adverse transfusion outcomes. RBC antigens are encoded by specific genes, which allows developing computational methods for determining antigens from genomic data. We describe here a classification method for determining RBC antigens from genotyping array

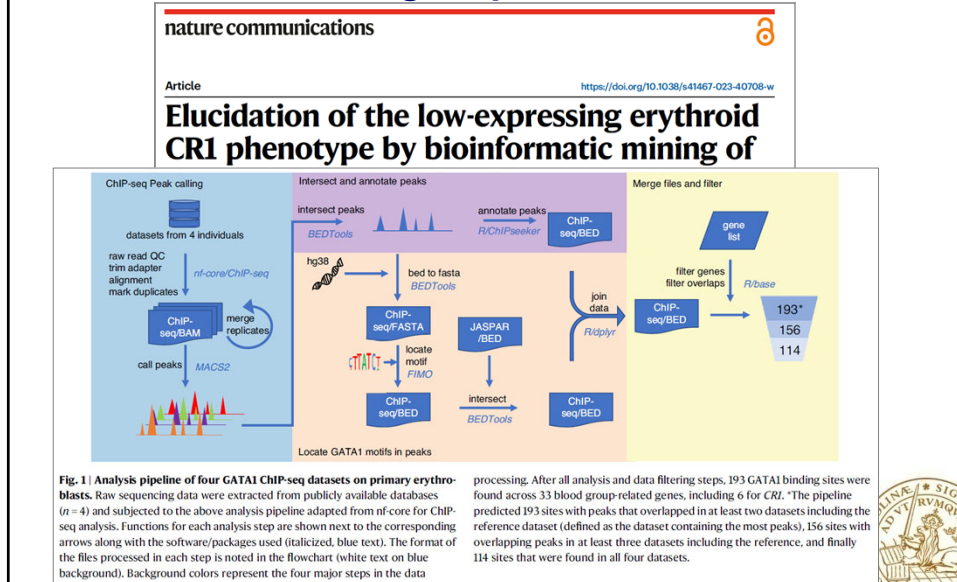
49

So far, blood group genotyping has not been able to account for weak, medium or strong expression on RBCs of a certain blood group antigen (beyond zygosity/dosage effects)

To address this, we recently started trying to understand the regulatory landscape of all blood group systems

50

The Blood Group Regulome also needs to be taken into account for prediction with higher precision!



51

ErythroGene A database of human blood group alleles

- ♦ www.erythrogene.com (Möller *et al. Blood Adv*, 2016)
- ♦ Assessment of genetic blood group variation in blood group genes

REGULAR ARTICLE

blood advances

ErythroGene: a database for in-depth analysis of the extensive variation in 36 blood group systems in the 1000 Genomes Project

Mattias Möller,¹ Magnus Jöud,^{1,2} Jill R. Story,^{1,2} and Martin L. Olsson^{1,2}

¹Hematology and Transfusion Medicine, Department of Laboratory Medicine, Lund University, Lund, Sweden; and ²Department of Clinical Immunology and Transfusion Medicine, Laboratory Medicine, Office of Medical Service, Lund, Sweden

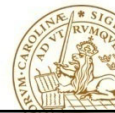
52

The Erythroгене Database

Study metadata

- ♦ ~1.75 million bp per genome were analysed
 - ✓ 2,504 individuals from 26 population groups around the globe
 - ✓ 43 blood group genes
 - ✓ Total number of nucleotides = 8,501,108,720 bp
- ♦ We identified 210,412 different blood group alleles
- ♦ 50,076 SNPs
 - ✓ 68.6% were transitions
 - ✓ 31.4% were transversions
- ♦ A total of 2,168 indels were observed

Möller *et al.* Blood Advances 2016;1(3):240-249



53

The *Erythrogene* database – a “forward genetics” approach?

Can the database predict new blood group antigens?

- ♦ Only **241** of the 1,241 non-synonymous variants identified were known blood group SNPs
- ♦ **200** of the remaining 1,000 variants occur in glycosyltransferases
 - ✓ may alter carbohydrate antigen expression by modifying enzymatic activity or specificity
- ♦ **357** of the remaining 1,000 unknown variants alter amino acids in extracellular portions of RBC proteins
 - ✓ These may constitute undiscovered or altered blood group antigens

Möller *et al.* Blood Advances 2016;1(3):240-249



54



ERYTHROGENE

The search engine for blood group genes

→

☒ All ☐ Reference ☐ 1000 Genomes



The search "ABO" returned 238 results (0.002 seconds). Showing results 1 to 20. Next

Gene	Allele	Nucleotide Change	Predicted Amino Acid Change	1000G
ABO	ABO*O.01.01	261delG	Thr88Profs*31	28.43% ▼
ABO	ABO*O.01.02	106G>T; 188G>A; 189C>T; 220C>T; 261delG; 297A>G; 646T>A; 681G>A; 771C>T; 829G>A	Val36Phe; Arg63His; Pro74Ser; Thr88Profs*31	18.55% ▼
ABO	ABO*B.01	297A>G; 526C>G; 657C>T; 703G>A; 796C>A; 803G>C; 930G>A	Arg176Gly; Gly235Ser; Leu266Met; Gly268Ala	14.16% ▼
ABO	ABO*A1.01			9.54% ▼
ABO	ABO*A1.02	467C>T	Pro156Leu	4.33% ▼
ABO	ABO*A2.01	467C>T; 1061delC	Pro156Leu; Pro354Argfs*23	4.25% ▼
ABO	ABO*O.01.09	261delG; 318C>T; 467C>T	Thr88Profs*31	4.01% ▼
ABO	ABO*O.01.35	106G>T; 188G>A; 189C>T; 220C>T; 261delG; 297A>G; 681G>A; 771C>T; 829G>A	Val36Phe; Arg63His; Pro74Ser; Thr88Profs*31	2.82% ▼
ABO	ABO*O.01.36	106G>T; 188G>A; 189C>T; 220C>T; 261delG; 297A>G; 646T>A; 681G>A; 829G>A	Val36Phe; Arg63His; Pro74Ser; Thr88Profs*31	2.48% ▼



www.erythrogene.com Möller *et al.* Blood Advances 2016;1(3):240-249



55



About Data Releases Tutorials

Release: 8 Updated: 1 Oct 2025

Sign In →

Welcome to the ISBT Blood Group Database

The official digital repository for blood group systems, antigens, and alleles, maintained by the International Society for Blood Transfusion (ISBT).

Welcome to the ISBT Blood Group Database, the authoritative source for blood group nomenclature maintained by the International Society of Blood Transfusion. This platform serves the global transfusion medicine community with comprehensive, standardized blood group information.

About

Learn about the official digital repository for ISBT blood group nomenclature, the development partnership and who to contact in case of questions.

Data

Find all allele tables and further information about each blood group system and its antigens.

Releases

Tutorials

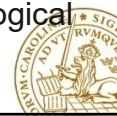


56

27

Concluding remarks

- ♦ Several medium- to high throughput platforms developed for DNA-based blood group typing in donors and patients
- ♦ Accuracy rate is now acceptable (better than serology?!)
 - So far, not all systems have been CE/IVDR/FDA-approved but many are likely to follow
- ♦ The Cost vs. Saving equation is difficult to calculate and more cost-benefit as well as implementation studies should be performed
- ♦ Some centres are using DNA-based methods to extend typing for their donor pool or improve matching for patients but many are still waiting for the "optimal tool".
- ♦ NGS/ONT platforms are not yet approved for clinical use but are widely implemented to solve immunohematological problems in the reference/research setting



57

Dont' forget:
Everybody is different – also regarding blood groups!
Thanks for listening!

GDPR-secured photo collection from Region Skåne

58