Strategies for finding and maintaining rare donors

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SABTC
Sun City
2017
A rare Blood type is any Blood type that is difficult to find.
What is Rare Blood?

About one person in 1,000 will inherit a rare Blood type:

• Unusual combinations of common antigens
• Negative for a high incidence antigen
  – Homozygosity for a recessive gene e.g. Kp(b-), Rh\text{null}
  – Inheritance of an "Inhibitor" gene e.g. Lu(a-b-)
• Absence of a whole protein
  – Lan, Jr^{a}, Jk3
## Rare blood types that are challenging to find

<table>
<thead>
<tr>
<th>Country</th>
<th>Challenging type to obtain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>Rare Rh Phenotypes with mixtures of antibodies</td>
</tr>
<tr>
<td>Brazil</td>
<td>McLeod, K₀, Lan⁻, U⁻, RH:⁻29, RH:⁻17</td>
</tr>
<tr>
<td>Finland</td>
<td>Vel⁻, Ge:⁻2</td>
</tr>
<tr>
<td>France</td>
<td>D⁻U⁻, hr⁵⁻, hr⁸⁻, Js(b⁻), RH:⁻46, RH_null, Jr(a⁻), Co(a⁻b⁻)</td>
</tr>
<tr>
<td>Germany</td>
<td>Fy(a⁻b⁻), In(b⁻), Ge:⁻2,⁻3,</td>
</tr>
<tr>
<td>China (Hong Kong)</td>
<td>Di(b⁻), Fy(a⁻b⁻), Jk:⁻3</td>
</tr>
<tr>
<td>Oman and India</td>
<td>D⁻⁻, In(b⁻), Co(a⁻b⁻)</td>
</tr>
<tr>
<td>Israel</td>
<td>p, Jr(a⁻), O_r, K₀, U⁻, Vel⁻ Lan⁻</td>
</tr>
<tr>
<td>Italy</td>
<td>Sc:⁻¹, LW(a⁻), K₀, Jk:⁻³, U⁻, Di(b⁻)</td>
</tr>
<tr>
<td>Japan</td>
<td>Ge⁻, En(a⁻), M⁺M⁻, Lan⁻</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>D⁻U⁻, Fy(a⁻b⁻), D⁻ Lu(a⁻b⁻), At(a⁻), Cr(a⁻)</td>
</tr>
<tr>
<td>New Zealand</td>
<td>D⁻⁻, K₀, McLeod, p, Ge:⁻2, Js(b⁻)</td>
</tr>
<tr>
<td>Spain</td>
<td>Yt(a⁻), Co(a⁻), Js(b⁻), Lan⁻, Ge⁻, L⁻, Jr(a⁻)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>Kp(b⁻), Vel⁻, Pk, Jk:⁻³, D⁻⁻, K₀, Lan⁻</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Rh_null, Sc:⁻¹. P1k, Ge:⁻²,⁻³, D⁻⁻, McLeod, U⁻</td>
</tr>
<tr>
<td>United States</td>
<td>At(a⁻), En(a⁻), Hy⁻, K₀, Cr(a⁻), Ge:⁻², In(b⁻), Lan⁻, Di(b⁻), Ge:⁻², Jk:⁻³, Lu(a⁻b⁻), hr⁵⁻ E⁻, Gy⁻, K⁻² Vel⁻, Wes(b⁻)</td>
</tr>
</tbody>
</table>

Requests for rare blood from ARDP

Fig. 2 High-incidence antigen-negative RBC requests, 2005 to 2010.
Rare types are needed all the time...

Paper 60: Ms Fikile Mosia
Identification of anti-Lan in a patient with CML and the challenges in procuring blood for rare blood types
Rare Blood and Ethnicity

• Founder effect?
  – PP1Pk– phenotype in the Amish people, Northern Sweden
  – Jr(a–) in Roma people in Slovakia, Japan

• Spontaneous mutations
  – e.g. PP1Pk– phenotype in Europe

• Genetic selection based on pathogens
  – E.g. Fy(a–b–) RBCs are resistant to infection by *Plasmodium vivax*
  – Ok(a–)? Basigin receptor for *P. falciparum* (Crosnier Nature 2011)
World Conflicts 2000-2017
Impact of migration

- Genetic blood disorders that require transfusion
  - SCD, thalassemia
- Different blood group antigen profiles
- Common W. African RBC profile:
  - D+C-E-c+e+, K-k+, S-s+, Fy(a-b-), Jk(a+b-)
  - 30-40% of African American donors
  - 1:1000 Caucasian donors?
  - Screen D− units?
Rare blood is not just absence of a high prevalence antigen – Case 1

• 51 year old man - Swedish
• Transfusion-dependent, terminally ill
• Plasma contained anti-c, -E, -K, -Jk^a, -s
• Incidence of the phenotype:
  – 0.15 x 0.98 x 0.24 x 0.13 = 0.00459
  – That is 4.59 donors/1000
• To find one unit, need to screen 218 donors (ABO-compatible!!)
Rare blood – multiple alloantibodies

• Supported by blood transfusions every week from all over Sweden
• Enormous stress on screening resources
  – Very expensive
  – Very time-consuming
• Is there a better way?
Characterisation of rare blood groups – Serological methods

- Often dependent on limited supplies of antisera from patients
  - No QA
  - Limited infectious-disease testing
- Monoclonal antibodies available for some antigens
  - Ask for antibodies: often, the lab will send them out free of charge
Screening at the Japanese RC


<table>
<thead>
<tr>
<th>Monoclonal antibody</th>
<th>Number of tested</th>
<th>Rare blood</th>
<th>Number of detected</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>anti-U+N</td>
<td>2,062,873</td>
<td>U−</td>
<td>3</td>
<td>0.00015%</td>
</tr>
<tr>
<td>anti-En³</td>
<td>1,369,681</td>
<td>En(a−)</td>
<td>2</td>
<td>0.00002%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M⁰M⁺</td>
<td>1</td>
<td>0.00001%</td>
</tr>
<tr>
<td>anti-Hro</td>
<td>2,285,766</td>
<td>−D−</td>
<td>183</td>
<td>0.00082%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rhnull</td>
<td>10</td>
<td>0.00005%</td>
</tr>
<tr>
<td>anti-CD44</td>
<td>6,730,998</td>
<td>Lu(a−b−)</td>
<td>607</td>
<td>0.00902%</td>
</tr>
<tr>
<td>anti-K2, Anti-K5,</td>
<td>16,290,609</td>
<td>Ko</td>
<td>286</td>
<td>0.00176%</td>
</tr>
<tr>
<td>Anti-K14</td>
<td></td>
<td>McLeod or Kmod</td>
<td>83</td>
<td>0.00112%</td>
</tr>
<tr>
<td>anti-Fy3</td>
<td>795,239</td>
<td>Fy(a−b−)</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>anti-Ge</td>
<td>6,648,374</td>
<td>Ge−</td>
<td>17</td>
<td>0.00027%</td>
</tr>
<tr>
<td>anti-IFC</td>
<td>237,459</td>
<td>IFC−</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>anti-I</td>
<td>1,086,228</td>
<td>i</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>anti-Jr²</td>
<td>10,708,646</td>
<td>Jr(a−)</td>
<td>4,454</td>
<td>0.04159%</td>
</tr>
<tr>
<td>anti-Lan</td>
<td>713,523</td>
<td>Lan−</td>
<td>14</td>
<td>0.00196%</td>
</tr>
</tbody>
</table>

*Including repeat donors.
Characterisation of rare blood groups – Genotyping methods

Genotyping programs

• Molecular basis for (almost) all rare blood group phenotypes known
  – Majority are single nucleotide polymorphisms

• Various commercial kits and platforms available for genotyping
## Genotype-derived phenotypes by BioArray

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Predicted phenotype</th>
<th>Donors</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPB S-s-</td>
<td>S-s-U-</td>
<td>2</td>
</tr>
<tr>
<td>FY265 AB</td>
<td>Fy(a+b\text{weak})</td>
<td>1</td>
</tr>
<tr>
<td>FYB265 BB</td>
<td>Fy(a-b\text{weak})</td>
<td>1</td>
</tr>
<tr>
<td>LU AA</td>
<td>Lu(a+b-)</td>
<td>3</td>
</tr>
<tr>
<td>LU AB</td>
<td>Lu(a+b+)</td>
<td>5</td>
</tr>
<tr>
<td>SC AB</td>
<td>Sc 1,2</td>
<td>2</td>
</tr>
<tr>
<td>DO323</td>
<td>Hy-</td>
<td>1</td>
</tr>
<tr>
<td>DO350</td>
<td>Jo(a-)</td>
<td>2</td>
</tr>
<tr>
<td>DI AA</td>
<td>Di(a+b-)</td>
<td>1</td>
</tr>
<tr>
<td>DI AB</td>
<td>Di(a+b+)</td>
<td>3</td>
</tr>
<tr>
<td>KEL AB</td>
<td>K1/K2</td>
<td>2</td>
</tr>
</tbody>
</table>

Data generously shared by Lilian Castilho, Hemo-Centro
Wagner FF et al. Transfusion 2008;48:1169-75

- Identified high incidence antigens with an antigen-negative frequency of ~1:500
  - Yt\textsuperscript{a}, Co\textsuperscript{a}, Lu\textsuperscript{b}, Kp\textsuperscript{b}

- Designed a multiplex (4 amplicons) to detect the negative phenotype
  - Different amplicon sizes

- Used a "quick and dirty" DNA prep method: Extract-N-Amp
  - PCR directly on blood
Medium throughput screening

- In normal samples, PCR showed 4 bands
- Where a specific band was missing, confirmatory serology performed on the sample to confirm absence of the antigen
- Tested 3422 group O, RhD-negative donors:
  - 1 Kp(b-); 6 Co(a-); 10 Yt(a-); 5 Lu(b-)
Medium throughput screening

• Time and cost analysis:
  – Hands-on time – 91 tests/102 minutes
  – Cost €1.52/test

• Effective method for medium throughput screening

• Can add SNPs of interest, e.g. HPA-1A
Medium-throughput screening in Skåne

MSc Project:
1799 donors screened
31 HPA-1(a-) donors
3 Co(a-) donors
2 Vel- donors

Image of DNA ladder with bands at 493, 352, 303, 266, 164, and 138 bp, indicating the presence of different alleles and variants.
Multiplex screening for rare donors

HPA-1a-negative

Confirmation by serology or DNA sequencing
Medium throughput screening


- 35 blood group antigen SNPs in 6 multiplex reactions/sample
- Screened 6000 donors:
  - Lu(b-) 9
  - k- 5
  - Kp(b-) 1
  - Yt(a-) 24
  - Co(a-) 11
Medium throughput screening


• 35 blood group antigen SNPs in 6 multiplex reactions/sample

• Costs:
  • Serology – 35-39€
  • Genotyping – 15€

• Repeat donors selected
Challenges finding rare blood

• How can Rare Donors be identified?
• High incidence antigen-negative patient?
• Always test relatives where possible
  – Siblings 1:4 chance of inheriting a rare blood group
  – Small communities have a higher incidence of rare types
Maintaining a donor base

• Consequent screening program
• Donor appreciation
  – Letters
  – Cards
  – Special events
  – SMS when blood is used
• ISBT WP :
  – International Rare Donor card launched at meeting in June 2017
  – Working on letters for rare donors and patients with rare groups
• Rare Donor WP: 29 members in 23 countries
  – South Africa has always been represented. Currently no official member but Ruwadya Soeker (WPBTS), Lavendri Govender and Latoya van Niekerk (SANBS) attended the last meeting

• Works to create and distribute material for recruitment of blood donors
• Be a resource for Transfusion Medicine community on issues related to rare blood
• Collaborate with the WHO International Rare Donor Panel (IRDP) to maintain a database of donors with rare blood types
• Increase IRDP donors by promoting the growth of rare donor programmes world-wide
• Develop and provide educational material to promote and facilitate education of blood providers, donors and patients
• Develop, maintain and revise recommendations to standardize listing, shipping, testing and reimbursement for rare blood
Local program

Paper 91 Miss Lavendri Govender
The current status of the South African Rare Donor File (April 2016 – March 2017)
Rare Donor Panels

• Several large Rare Donor Panels:
  – DGTI
  – WHO (Bristol, UK)
  – ARDP (USA)
  – CBS
  – Regional and National

• ISBT Working Party lists 118 facilities working with the various Rare Donor programs
Thank you!