



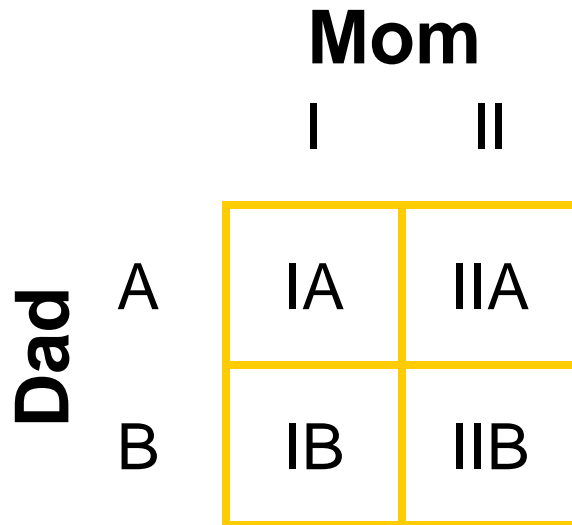
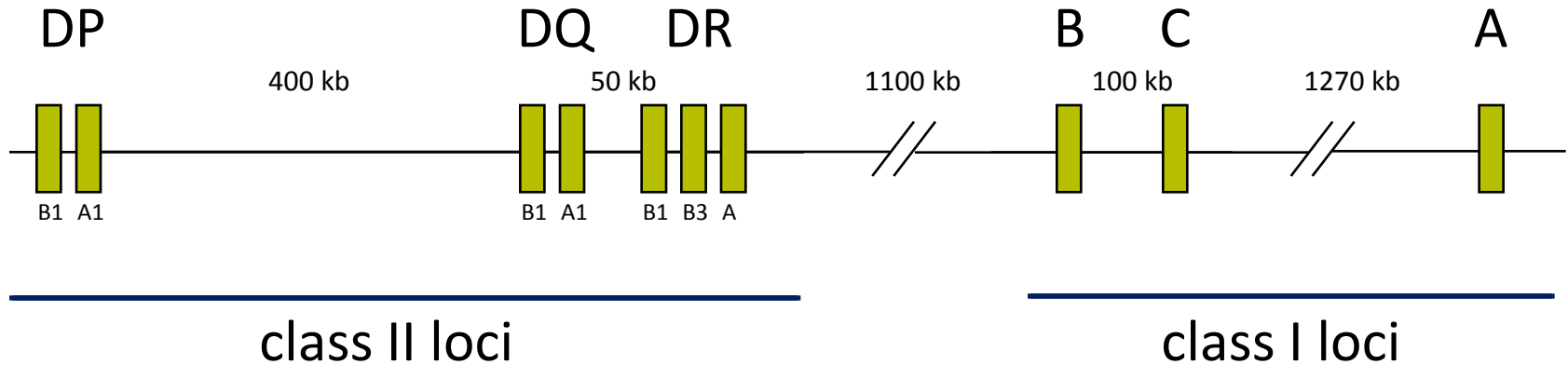
HLA Typing, Donor Selection and Donor Registries

Dennis L. Confer, MD
National Marrow Donor Program
3rd Workshop of WBMT
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General Approach to Finding a Donor

- HLA type willing family members –
 - Full siblings
 - Parents (to identify haplotypes)
- If unrelated donor is considered -
 - Search for adult donor
 - Search for umbilical cord blood unit(s)
- Consider haploidentical donors

The HLA System on Chromosome #6



Likelihood of a Sibling Match

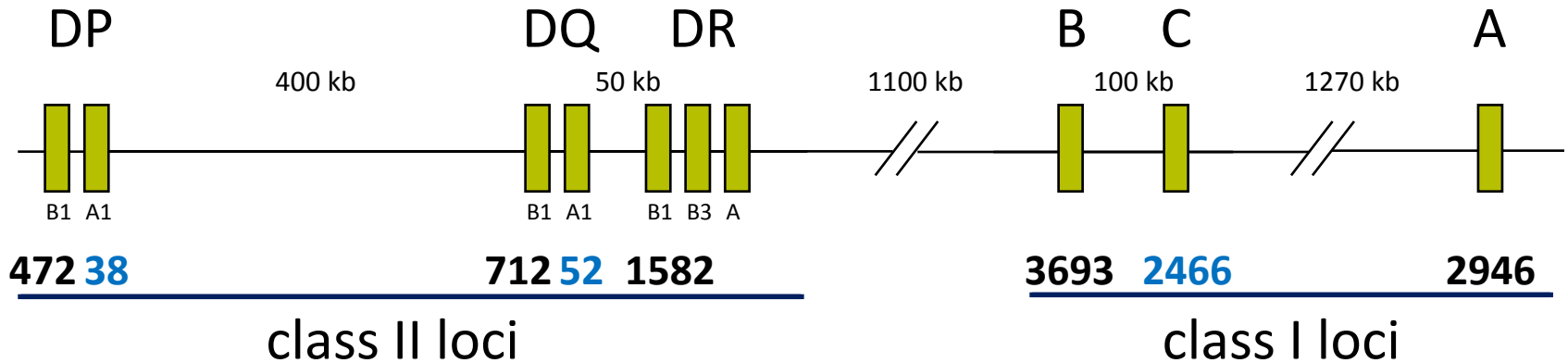
Match likelihood	1 – no match
“n” siblings	$1 - (0.75)^n$
1 sibling	$1 - (0.75)^1 = 0.25$
2 siblings	$1 - (0.75)^2 = 0.44$
4 siblings	$1 - (0.75)^4 = 0.68$
7 siblings	$1 - (0.75)^7 = 0.87$
USA:	
1.3 siblings	$1 - (0.75)^{1.3} = 0.30$

Worldwide Unrelated Donor Pool

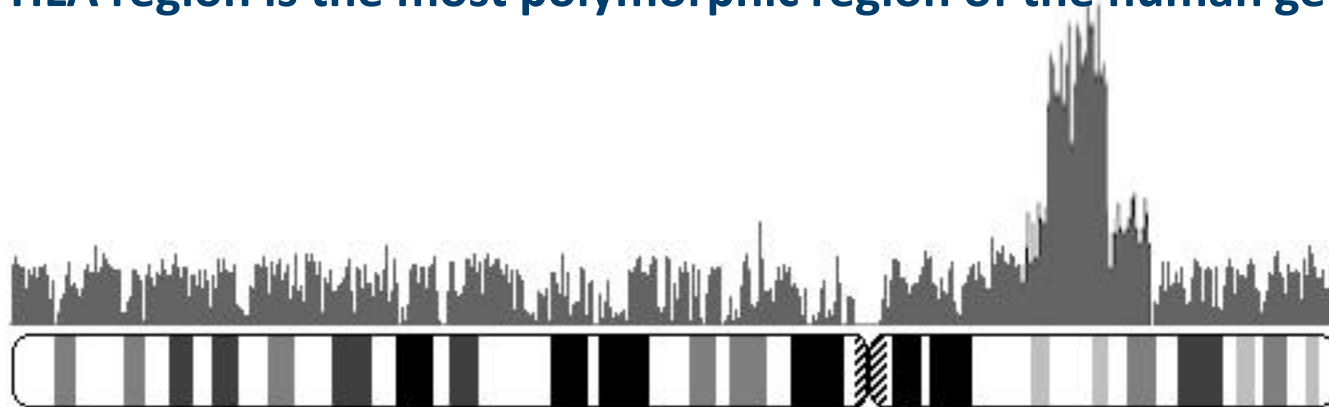
- World Marrow Donor Association (WMDA) surveyed 77 registries and 154 cord blood banks in 2013
 - 22 million HLA-A, B and DR-typed adults
 - 731,000 umbilical cord blood units
- Most are accessible through the Bone Marrow Donors Worldwide (BMDW)
 - www.bmdw.org

Huge Numbers of HLA Alleles

Most human genes have only a few (5-10) variants (alleles)



The HLA region is the most polymorphic region of the human genome



Nov 2014



What Does “Availability” Mean?

- A “matching” HLA type
- Is in the correct age range –
 - Related donors: 6 mos – 75+ years
 - Unrelated donors: Birth or 18 – 60 years
- Can be located: “contactable”
- Is willing to donate: “interested”
- Is healthy enough to donate: “suitable”
- Has no disease that will be transmitted – infectious or genetic
- Is not pregnant or “temporarily” unable

What are the Challenges for Registries?

- Data management
- Regulatory issues
- Quality and consistency
- Donor attrition and retention
- Emerging registries

Data Management

- HLA Data: Managing serology, low resolution DNA-based, high-resolution and next generation sequencing
- Emerging loci of interest with unclear importance: NIMA, KIR, HLA-DP, SNPs
- Multiple matching algorithms
- No “single solution”: www.bmdw.org consolidates much of the donor data, but there is no workflow
- EMDIS supports search and workflow, but is variably available and variably implemented

Regulatory Issues

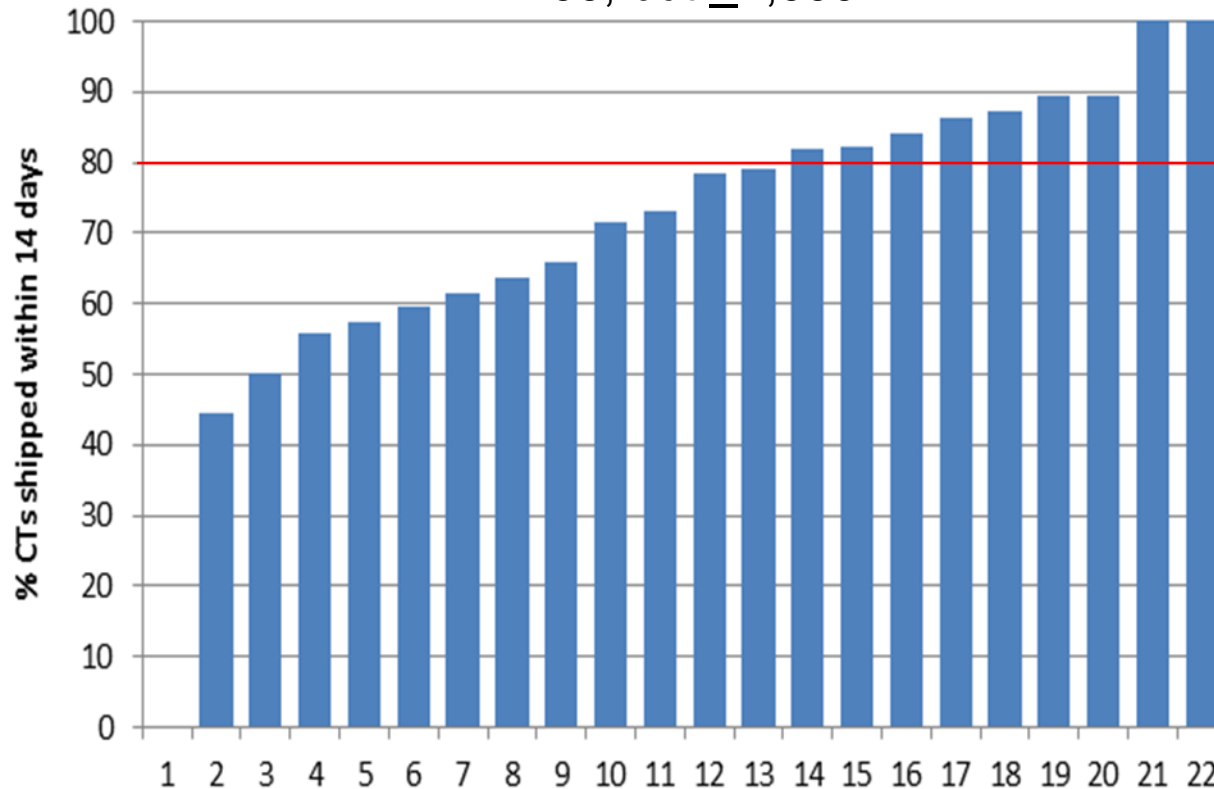
- Regulatory requirements continue to emerge without consistency or international reciprocity
 - E.g., US regulations apply to registries outside the US
- Import/export regulations, which are also inconsistent, threaten to increase complexity and cost
- Vigilance and surveillance is a global concern actively being pursued

Quality and Consistency

- WMDA promotes Standards for registry operations
- WMDA has established a registry accreditation program with on-site inspections
- WMDA is introducing a new program for “Key Performance Indicators”

Quality and Consistency

Confirmatory Testing Samples Shipped
within 14 days
>100, but $\leq 1,000$



Quality and Consistency

- WMDA promotes Standards for registry operations
- WMDA has established a registry accreditation program with on-site inspections
- WMDA is introducing a new program for “Key Performance Indicators”
- All positive steps, but –
Few standards for product manufacture or product quality exist

Donor Attrition: “Unavailable Donors”

- Attrition is a major challenge for all registries
 - Donor cannot be located
 - Is no longer interested in donation
 - Is medically unable to donate
 - Has a temporary issue, e.g., schedule conflicts
- Loss of interest is a complex problem
 - Absent commitment at recruitment
 - Incomplete education at recruitment
 - Cultural influences
 - Influence from family and friends

Retention: Reducing “Unavailable Donors”

- Recruitment without coercion or inducements
- Clear and appropriate education at recruitment
- “Two-step” recruitment: register, then activate
- Continuing engagement of registry members
- Competent reengagement during search process
- Active assessments of ambivalence, gaps in donor understanding, extent of family/friend pressure, etc.

Emerging Registries

New registries are needed to meet the diversity of HLA in worldwide populations

- Starting a new registry is expensive
 - Usually lack adequate financial support
 - Low volume HLA typing is expensive
- Must be a “comprehensive” build to succeed
 - Donor recruitment is not enough
- Success is also dependent upon medical need
 - The medical community needs to recognize and support

What are the Solutions?

- Professional Societies: WMDA and WBMT
- Collaborating and sharing information
- Establishing best practices and benchmarks
- Research to advance understanding
- Recognizing and accepting limitations