

HLA and Minorities

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HLA and Minorities

- Human Populations & Evolving HLA
- Informativeness of HLA
- Partitioning minorities in a sample
- Registry design implications

Human *Population* History

- The 6,000 human languages reflect more or less discrete human populations and attest to human population level diversity.
- 90% of these languages are spoken increasingly less with many nearing extinction.
- Along with other forces of assimilation, this loss of cultural identity has promoted genetic mixing (admixture) among populations.
- At least some degree of admixture among human populations is now nearly universal, and "minorities" are present virtually everywhere.

HLA* as a genetic system

- Enormous stability of allelic classes
- New alleles from point mutations and gene conversion (at a rate of $\sim 1/10,000$ per generation)
- Balancing selection \sim a few % per generation
- Recombination of haplotypes $\sim 2-3\%$ per generation
- Founder and demographic effects
- Polymorphism (# of alleles per locus) is most meaningful on a population basis

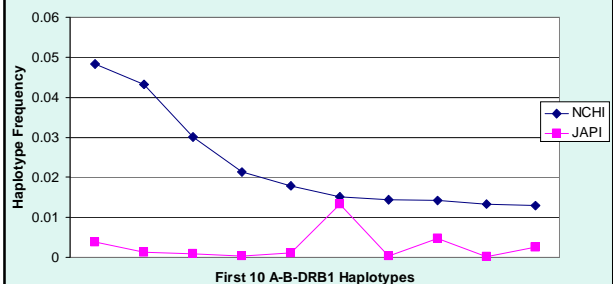
* KIR system variation should be included.

Informativeness of HLA

Examples for three levels of discrimination

- Between continents
Africa : Asia : Europe
- Within continents
Chinese : Japanese : Filipino
- Recently diverged
Ashkenazi Jewish Populations

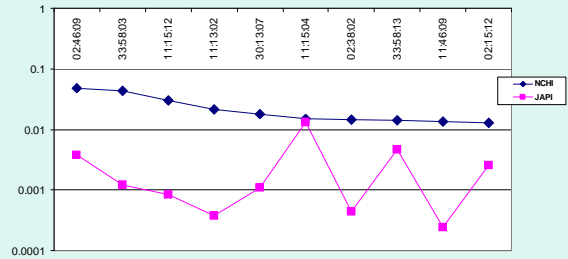
Chinese vs Japanese A-B-DRB1 Haplotypes



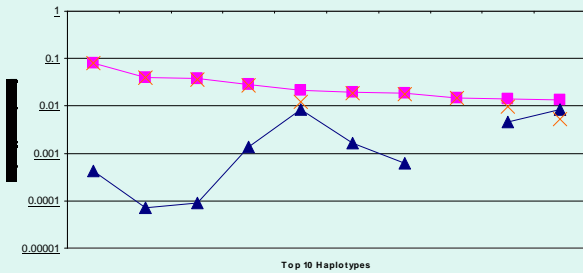
Chinese vs Japanese A-B-DRB1 Haplotypes

A:B:DRB1	NCHI	JAPI
02:46:09	0.04838	0.00382
33:58:03	0.04324	0.0012
11:15:12	0.03015	0.00085
11:13:02	0.0213	0.00038
30:13:07	0.01789	0.00108
11:15:04	0.01514	0.01325
02:38:02	0.01447	0.00044
33:58:13	0.01424	0.00466
11:46:09	0.01334	0.00024
02:15:12	0.01294	0.00255

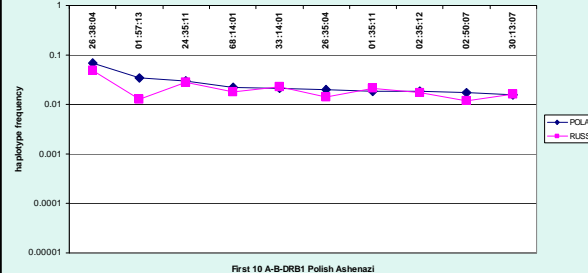
Chinese vs Japanese A-B-DRB1 Haplotypes



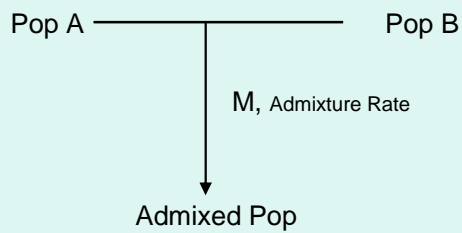
10 most common Japanese vs Filipino A-B-DRB1 haplotypes



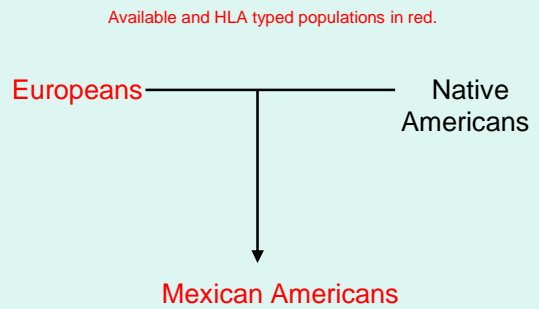
10 most common Polish Ashkenazi vs Russian Ashkenazi A-B-DRB1 haplotypes



Uncovering parental source populations at HLA Model of population admixture



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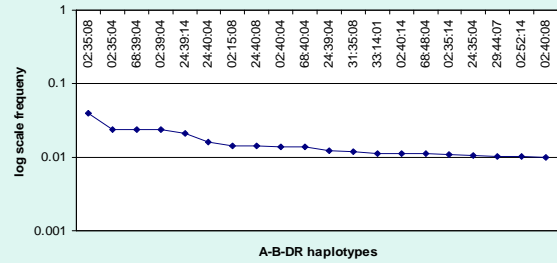


Uncovering parental source populations at HLA

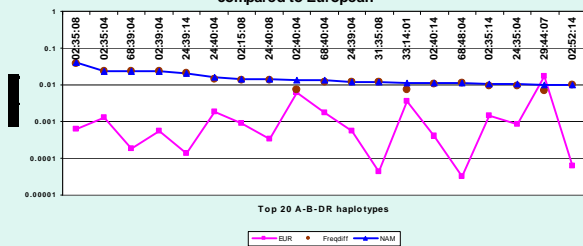
Derived Mexican Native Haplotypes

- 2-digit resolution A-B-DR haplotypes
- $2N = 80,856$
- Number of distinct haplotypes = 1,894

Native American HLA haplotypes—the top 20



Derived Native American (of Mexico) HLA haplotype frequencies compared to European



Size requirements for statistically complete sampling of an ethnic group

Observations...

A-B-DR HLA Haplotype Diversity (Using the just-derived populations as examples)

	2N	K (# distinct haplotypes)	Sum of 1st 100	Frequency at 100th
Native Americans (Mexican American Source)	80,856	1,894	64.3%	0.002%
West Africans (African American Source)	165,340	3,619	35.4%	0.002%

Donor registry construction based on knowledge of haplotype frequency distribution in a population

Genotype combinations of HLA haplotypes by frequency	Utility for donor matching
Common / Common	Very matchable
Common / Rare	matchable
Rare / Rare	Very hard to match

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Given a desired match rate, the required registry size can be calculated.

“Minorities” in the design of donor registries
or
how to maximize matching success

- Necessity of a registry for each distinct population group.
- Awareness of sample size requirements for each group and likelihood of matching success.
- Genetic (admixed) vs population mixed (substructured) samples. If population, consider reconstructing of founder populations, if mixed then identify individuals and make into separate registry.

Nature (HLA's purpose) and nurture (transplant surgery)

The dilemma of registry design:

In evolutionary terms the HLA game is to maximize population heterozygosity--the better to bind and present pathogen derived peptides. This explains the extraordinary HLA information content and differences present among individuals and populations.

This fact flies in the face of donor-patient HLA matching, and is it what makes it so difficult!

Bone marrow registries must be savvy to the facts of HLA population diversity and differences in order to maximize the likelihood of transplant matching.

Acknowledgments

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