HLA region and Type 1 diabetes

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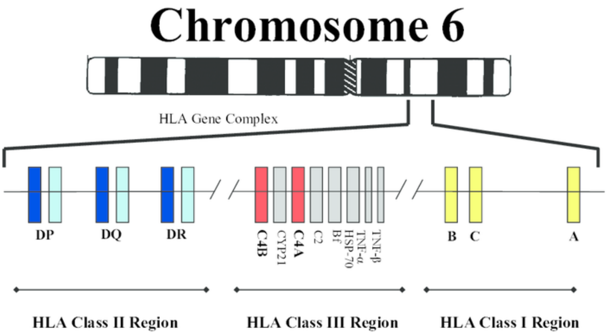
The HLA region



HLA genes

6 genes encode proteins that present foreign antigens to T cells.

- Class I proteins have $\beta 2$ subunits recognized by CD8 molecules on cytotoxic T cells
- Class II proteins have $\beta 1$ and $\beta 2$ subunits recognized by CD4 molecules on helper T cells

T cells that react to self antigens are deselected in fetal life.

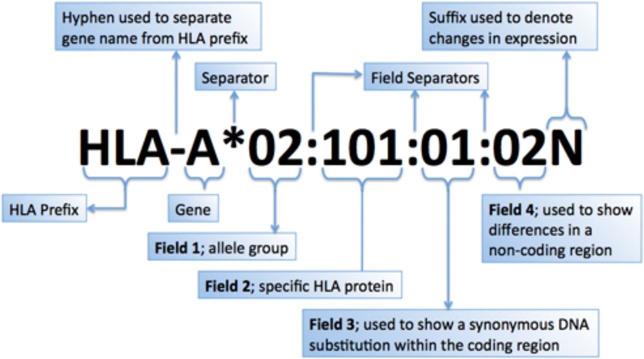
How much does HLA region contribute to risk of Type 1 DM?

- Genetic effect on a binary strait is quantified as sibling recurrence risk ratio λ_S
  - about 15 for juvenile-onset Type 1 diabetes
  - λ_S for a single locus can be estimated from affected sib-pairs as $\frac{0.25}{p_0}$ where p_0 is the proportion sharing 0 copies identical by descent
- Under a polygenic multiplicative model for genetic effects
  - Information for discrimination (bits) $\Lambda = \log_2 \lambda_S$
  - Contributions of independent loci are multiplicative on scale of λ, additive on scale of Λ
- For juvenile-onset Type 1 diabetes:-
  - HLA-specific $\lambda_S \approx 3.1$ (1.6 bits)
  - predictive performance of logistic regression model based on 6 SNPs in HLA region with main effects and interaction terms is close to this maximum value (Clayton 2010)

HLA allele naming based on antigen typing

- Before DNA genotyping, HLA variation was determined serologically (by binding of antibodies to antigens)
- nomenclature consisting of
  - letters to denote the locus: A, B, C, DR, DQ
  - number to specify the allele e.g. DR3, DQ8

HLA allele naming based on DNA sequence variants



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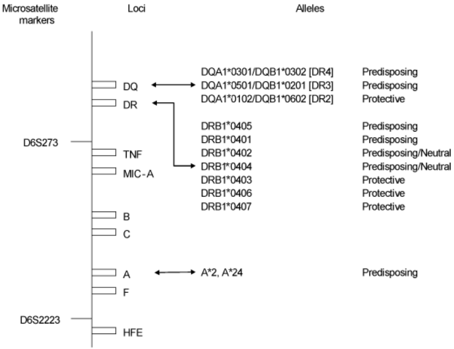
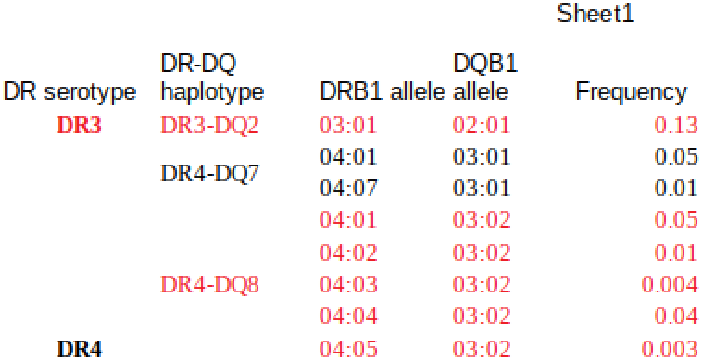
HLA loci associated with Type 1 diabetes



From Steck, et al. Type 1 diabetes mellitus in man: genetic susceptibility and resistance. In Immunology of Diabetes, electronic book available at www.barbaradaviscenter.org.

Figure 3. HLA Region and IDDM Susceptibility. Schematic representation of the HLA region on Chromosome 6 showing microsatellite markers, loci, and alleles associated with IDDM susceptibility. Distances between loci are grossly approximated (20).

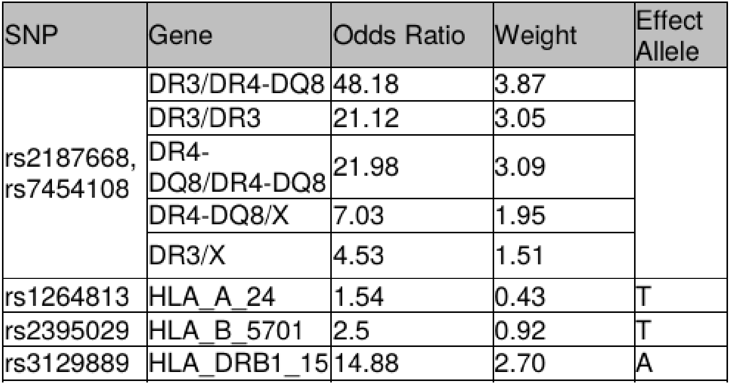
Diabetes-associated HLA alleles grouped by serotype



Sheet1

DR serotype	DR-DQ haplotype	DRB1 allele	DQB1 allele	Frequency
DR3	DR3-DQ2	03:01	02:01	0.13
DR4	DR4-DQ7	04:01	03:01	0.05
		04:07	03:01	0.01
	DR4-DQ8	04:01	03:02	0.05
		04:02	03:02	0.01
		04:03	03:02	0.004
		04:04	03:02	0.04
		04:05	03:02	0.003

Oram (2017): Type 1 diabetes score weights for HLA region



SNP	Gene	Odds Ratio	Weight	Effect Allele
rs2187668, rs7454108	DR3/DR4-DQ8	48.18	3.87	
	DR3/DR3	21.12	3.05	
	DR4-DQ8/DR4-DQ8	21.98	3.09	
	DR4-DQ8/X	7.03	1.95	
	DR3/X	4.53	1.51	
rs1264813	HLA_A_24	1.54	0.43	T
rs2395029	HLA_B_5701	2.5	0.92	T
rs3129889	HLA_DRB1_15	14.88	2.70	A

HLA imputation from SNP genotypes

- 3 programs:
  - HIBAG: R package easy to set up but can only impute one locus at a time
  - SNP2HLA: compatible only with old version of BEAGLE
  - HLA*IMP:02

1. Select SNPs that are typed in target individuals and in reference panel (1000 Genomes)
2. Train model on reference panel
3. Predict HLA alleles in target