Classical HLA alleles

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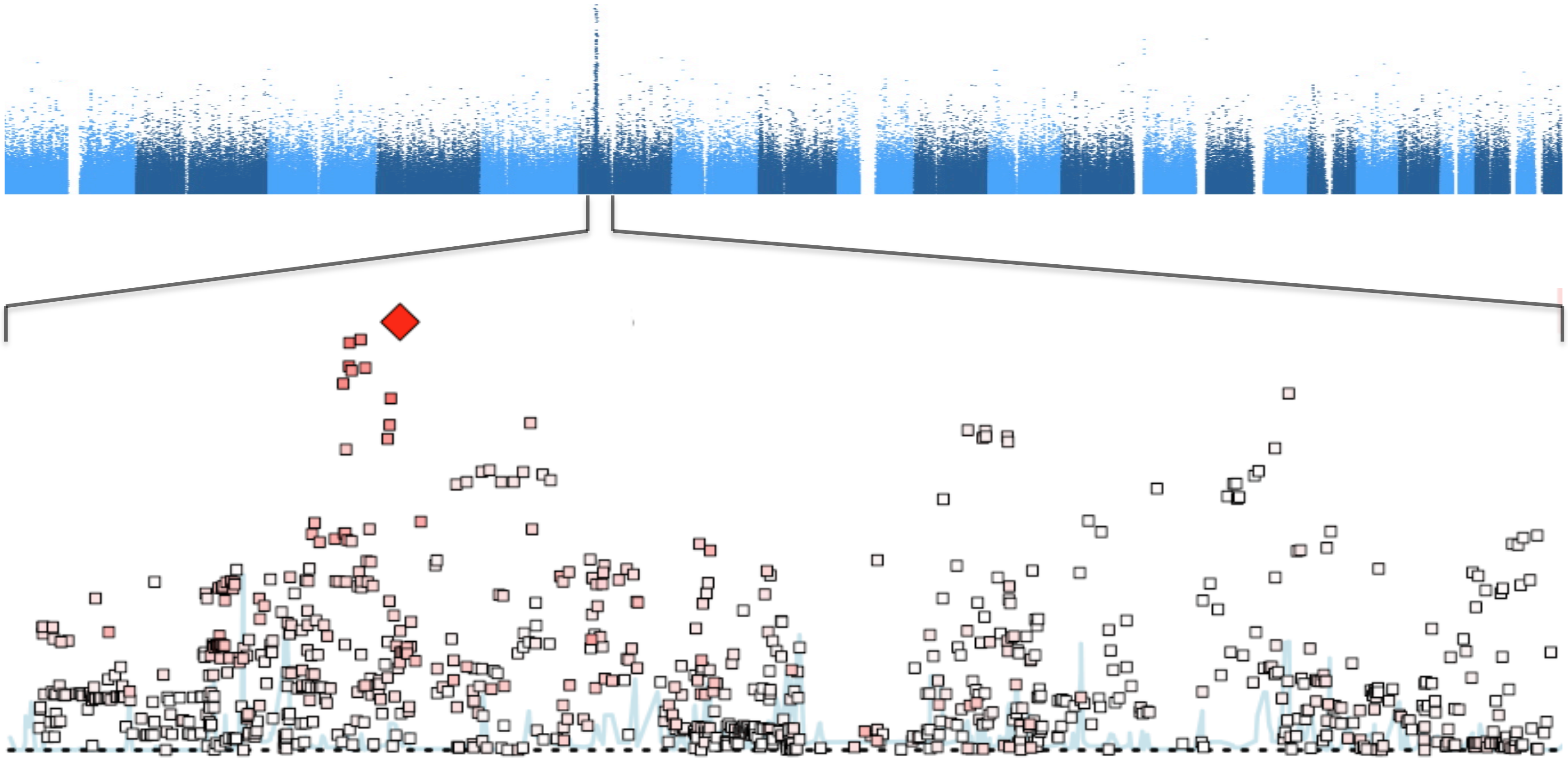
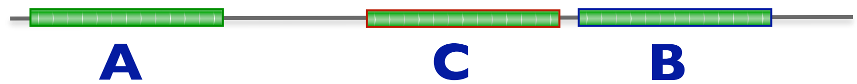
Motivation: many associations reported at MHC for various traits



~4 Mb region on chromosome 6 with >400 genes

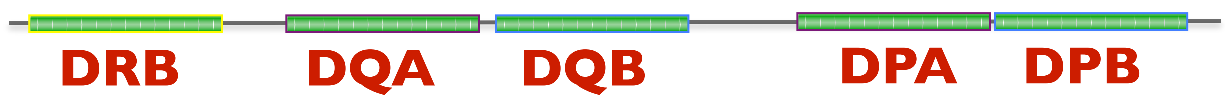
Disease associations with classical HLA alleles

- Class I



  - Ankylosing spondylitis B*27
  - Abacavir hypersensitivity B*57

- Class II



  - Type I diabetes DRB*03, DRB*04
  - Rheumatoid Arthritis DRB*04, DQA*03 …
  - Celiac disease DQB*02, DRB*03 …
  - Multiple sclerosis DRB*15, DQB1*06 …

Challenges

- Interpretation of these associations remains difficult
  - Broad linkage disequilibrium across many genes
  - Difficult to pinpoint causal genes/variants

- Complete sequence data across MHC is ideal
  - But difficult to acquire
  - Extremely polymorphic: difficult to capture, amplify, sequence, and align

Human Leukocyte Antigen (HLA)

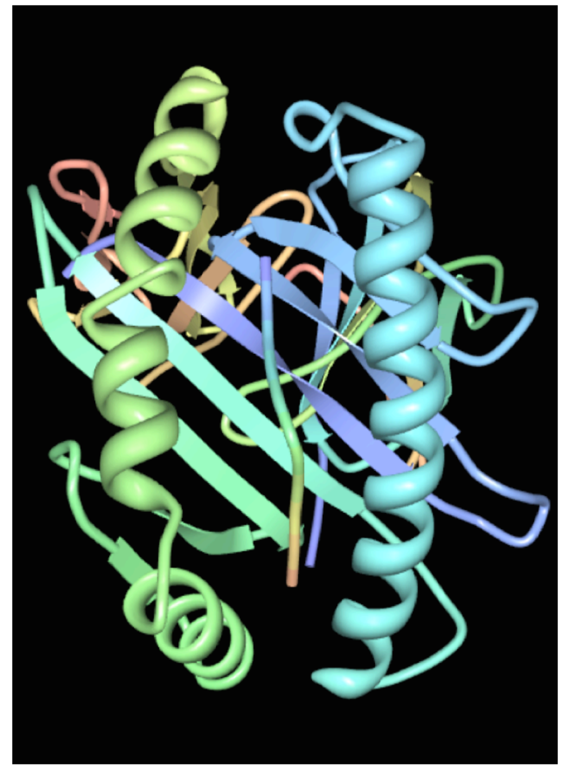
- Encode cell surface proteins for antigen presentation

- Variation nomenclature based on haplotypes across HLA gene

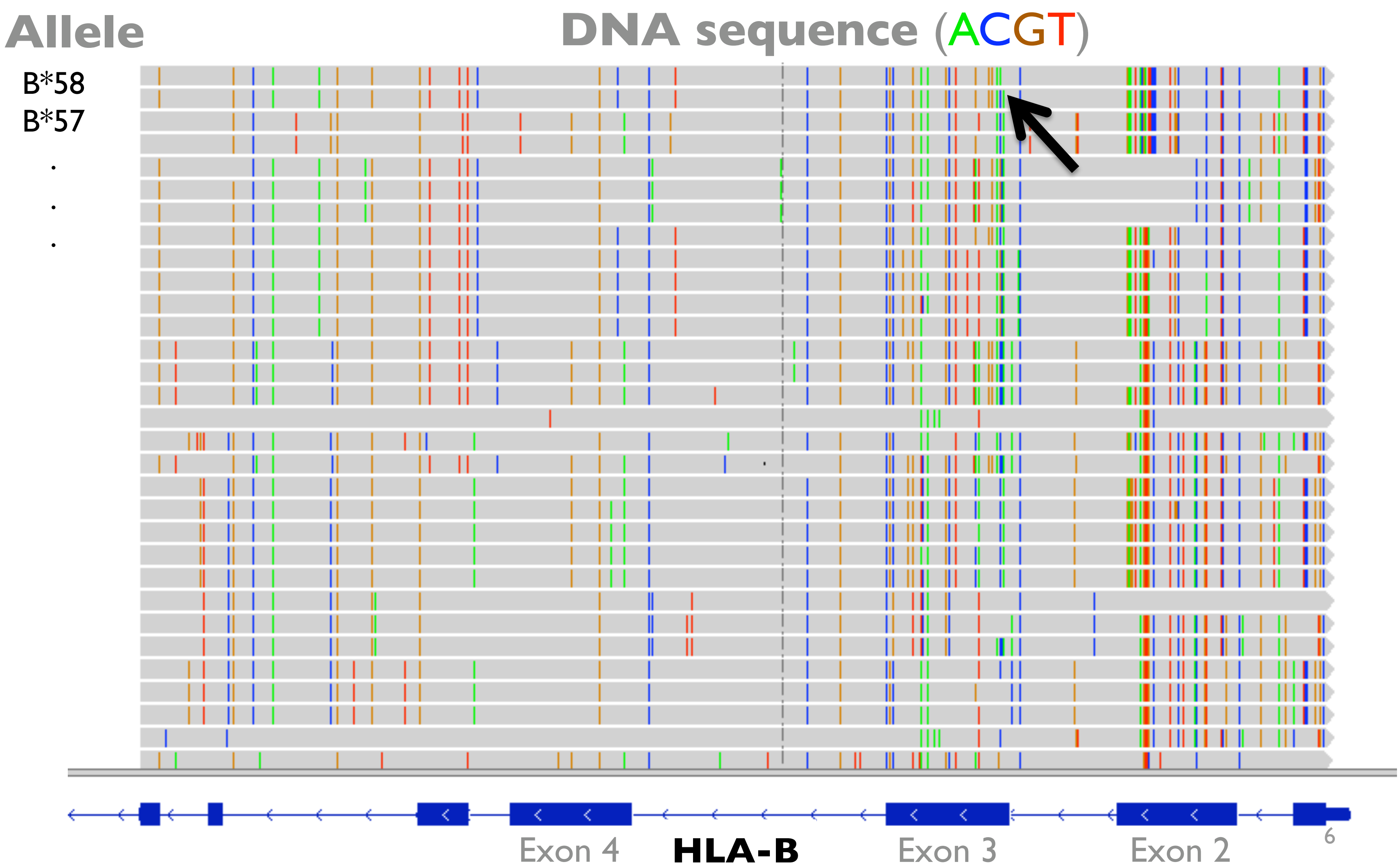
  [locus]*[allele]

  e.g. B*5701, DRB1*1501

- To date: 1,185 alleles for *HLA-B*



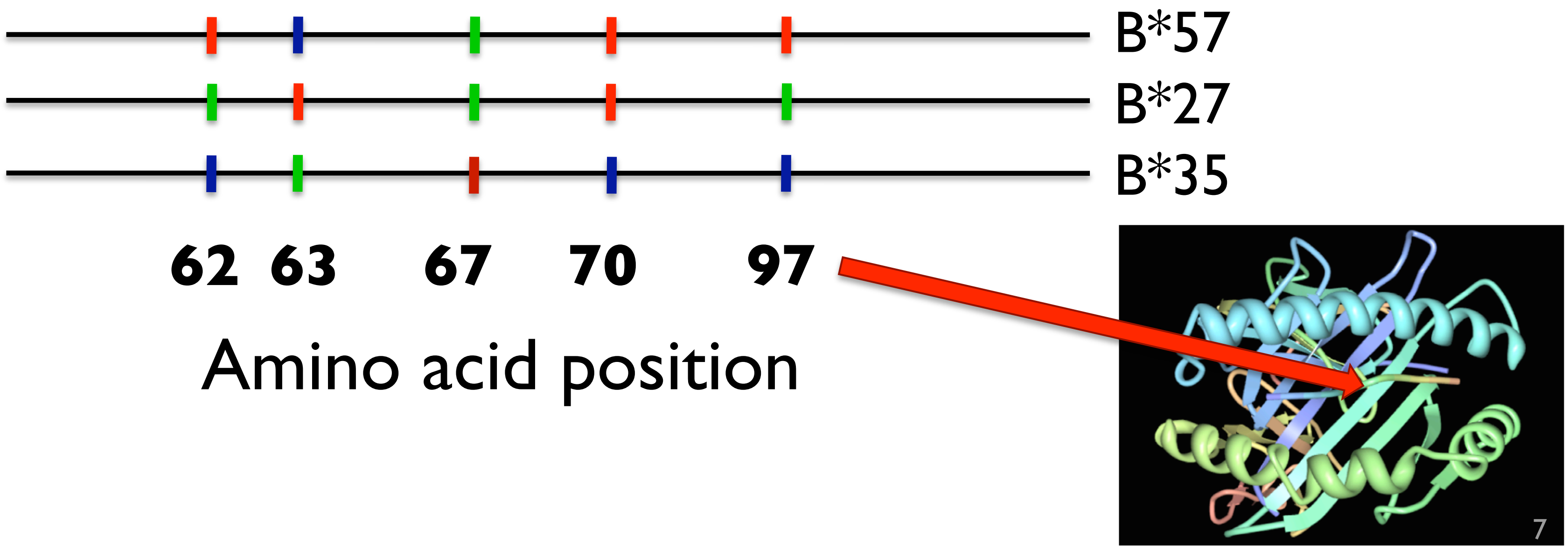
DNA sequence variation at *HLA-B*



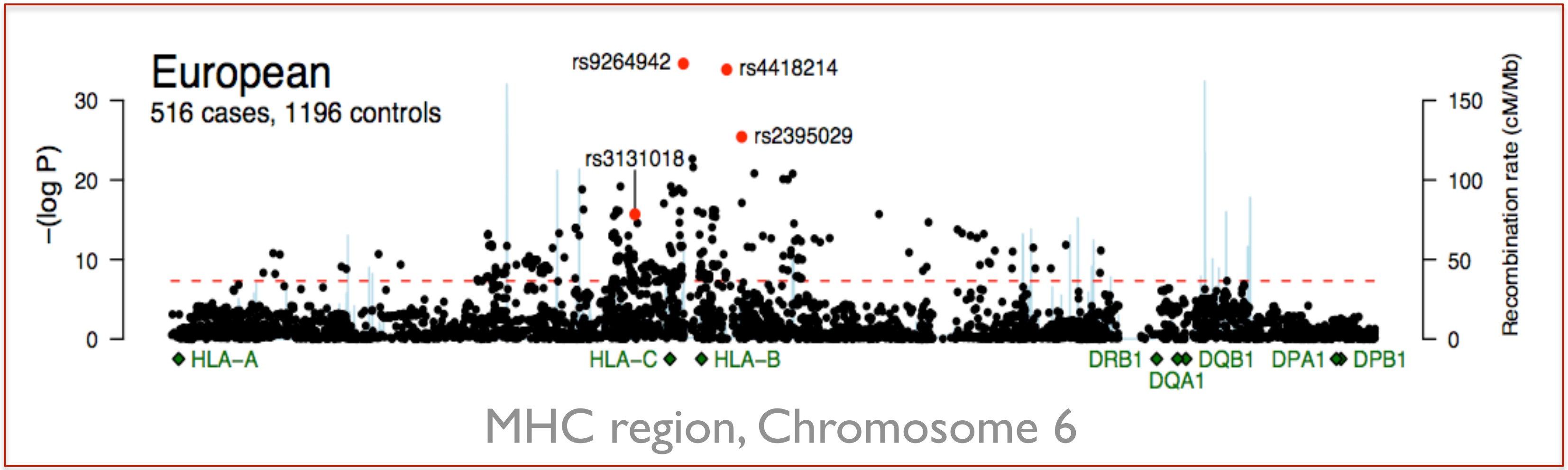
Which association test to perform?

Traditional approach: test each haplotype

Alternative: test SNPs or amino acids individually



An example



GWAS of durable host control of HIV-1

>300 SNPs at $p < 5 \times 10^{-8}$, all in the MHC

Imputation of SNPs/amino acids

Reference panel (SNPs, HLA alleles, and amino acids)

	SNPs	HLA alleles	Amino acids
ID1	A/C C/G A/G C/T	B*57 / B*08	B57: / B08:
ID2	A/T C/G A/G C/C	B*27 / B*08	B27: / B08:
…			
(n = 2,700)			

Impute with Beagle

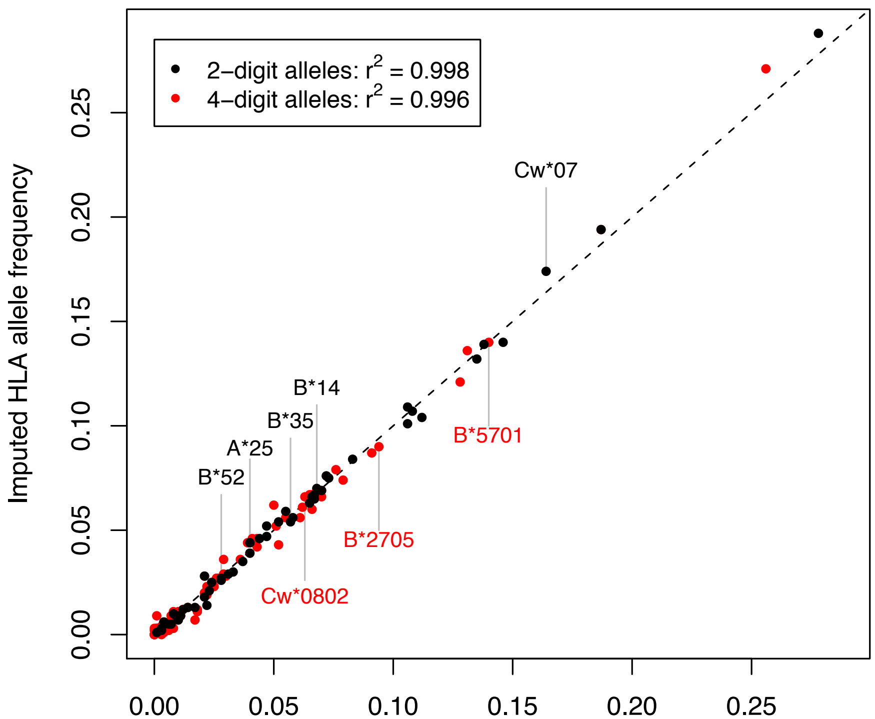
GWAS

	SNPs
ID1	A/A G/G
ID2	A/C C/G
…	

HLA alleles			Amino acids
B57	B27	B08	HLA-B
0,0	0,0	1,1	B08: / B08:
1,0	1,0	0,1	B57: / B08:

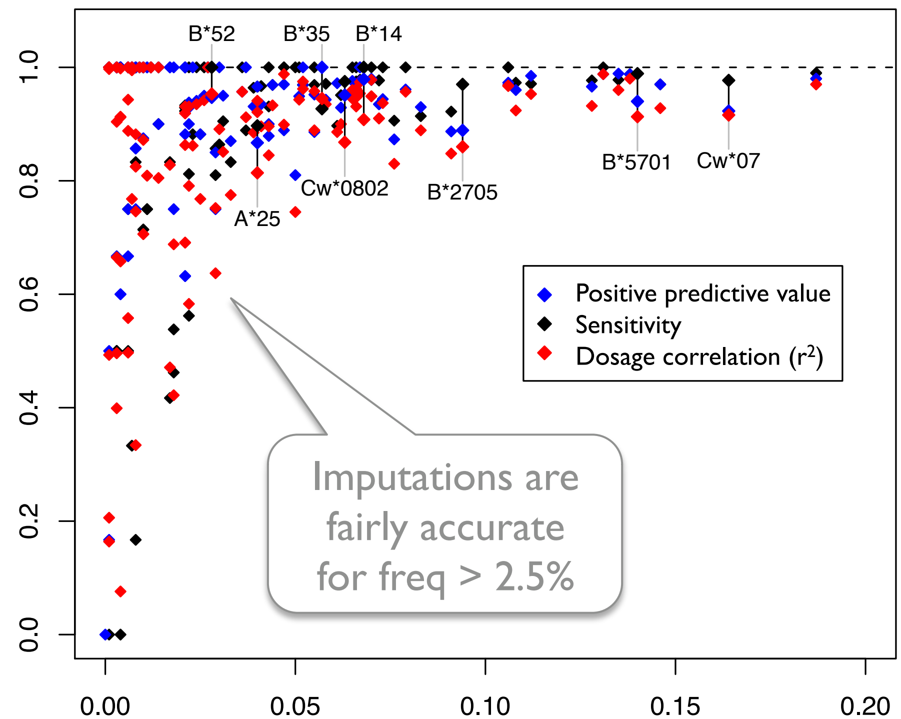
HLA imputation validation

372 cases with known HLA types



Typed HLA allele frequency

4-digit frequency R^2= .996

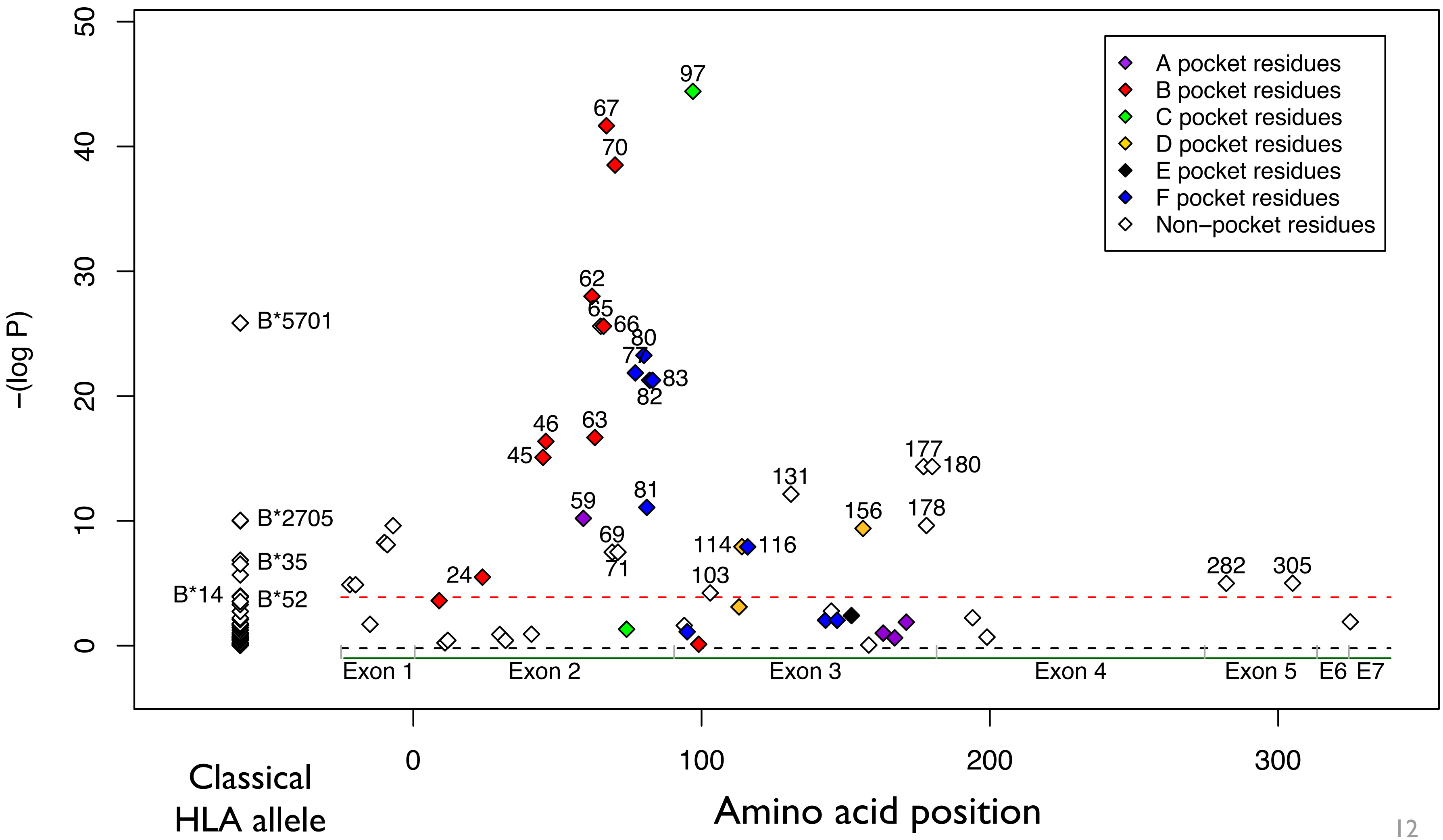


Typed HLA allele frequency

HLA allele associations

	Frequency		Univariate		Multivariate	
HLA allele	**Cases**	**Controls**	**OR**	**P-value**	**OR**	**P-value**
			Protective alleles			
B*5701	14.0%	3.2%	5.5	1.4×10^{-26}	6.0	2.3×10^{-26}
B*2705	8.4%	3.4%	3.3	9.1×10^{-11}	3.6	4.7×10^{-10}
B*14	6.9%	3.3%	2.0	1.0×10^{-4}	2.2	4.4×10^{-5}
B*52	2.5%	5.6%	3.7	3.0×10^{-4}	4.8	3.5×10^{-5}
			Risk alleles			
B*35	4.5%	9.0%	0.4	2.9×10^{-7}	0.5	5.7×10^{-5}

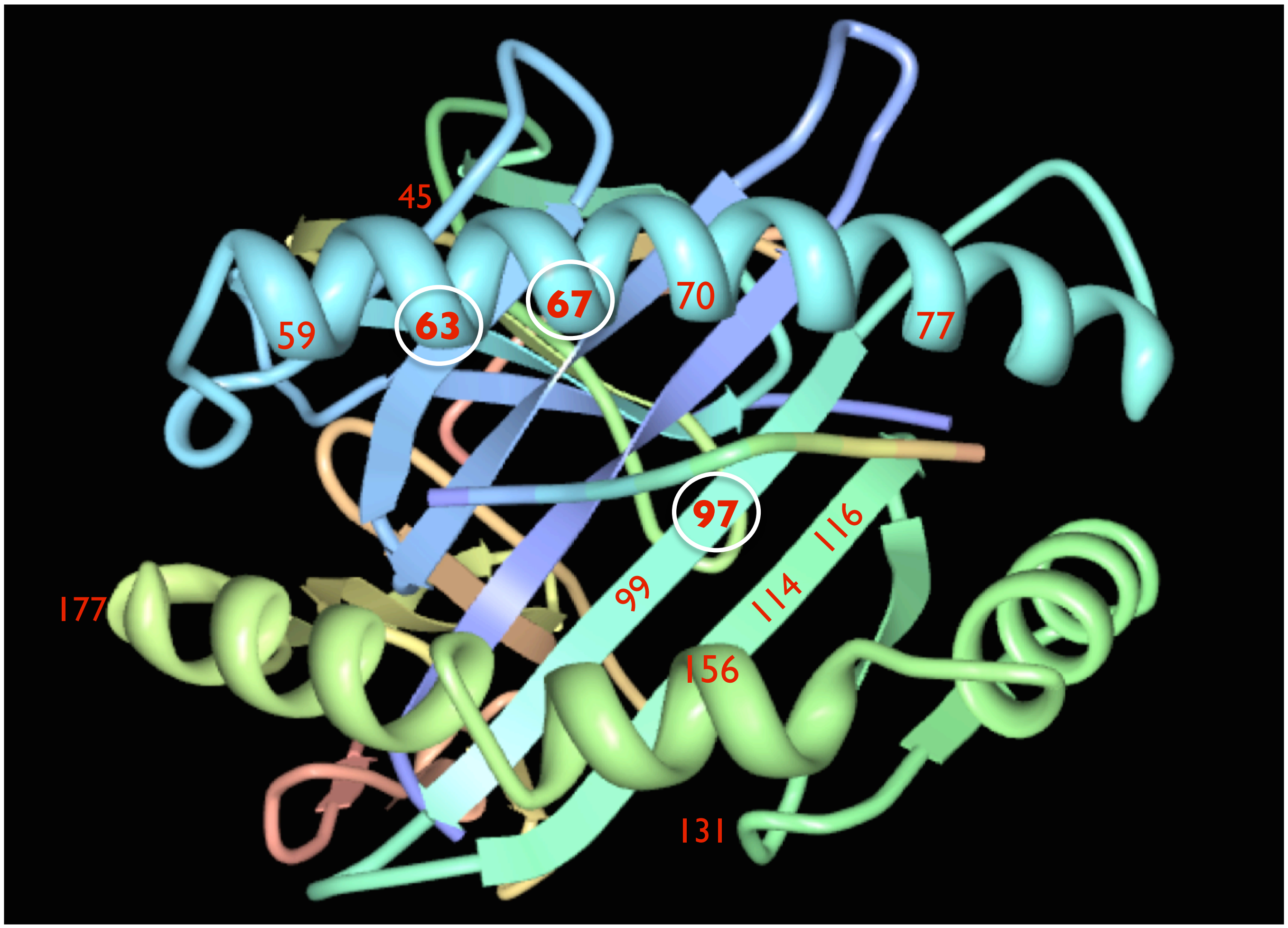
Amino acid residue associations at HLA-B

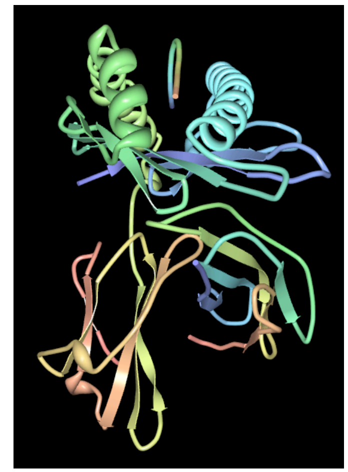


At HLA-B position 97, there are 6 possible alleles (amino acids)

Amino Acid	HLA alleles	Freq in cases	Freq in controls	P value	Odds Ratio
V (Val)	B*57	14%	3.3%	1E-27	5.6
N (Asn)	B*27	10%	4%	9E-11	2.8
W (Trp)	B*14	7%	3.5%	2E-4	1.9
T (Thr)	B*52	13.2%	11%	.17	1.2
R (Arg)	B*35	40%	51%	1E-9	0.6
S (Ser)	B*07	15%	27%	9E-11	0.5

HLA-B: significant amino acids line the peptide-binding pocket (top view)





Classical HLA alleles: Summary

- For GWA studies with strong associations in the MHC, **HLA imputation** is a useful method for evaluating signals at the HLA loci.

- HLA analysis at the resolution of **amino acid residues** may provide more insight into biological mechanism compared to analysis at the level of entire haplotypes.

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ACTG
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