



# Interpretation of GWAS Findings in Transplant Outcome Studies

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UNDER THE AUSPICES OF EUROPEAN FEDERATION FOR IMMUNOGENETICS  
**ANNUAL EFI REGION 8 EPT MEETING**  
5<sup>TH</sup> DECEMBER 2015 BUCHAREST

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## Session I - Chairmen: Elissaveta Naumova, Amal Bishara

09.10-09.40	Interpretation of GWAS findings in transplant outcome studies Mehmet Tefvik DORAK, Liverpool, United Kingdom
09.40-9.55	Role of H&I laboratory in Cord blood transplantation – standards, accreditation and beyond Elissaveta Naumova, Sofia, Bulgaria
9.55-10.10	The role of non-HLA genes in HSCT outcome Katerina Tarassi, Athens, Greece
10.10-10.25	HLA and KIR gene analysis as a predictive tool for the HSCT outcome Svetlana Vojvodić, Novi Sad, Serbia
10.25-10.40	Unrelated Stem Cell Transplantation – novel cell therapy in the treatment of heme malignancies in Clinical Institute „Fundeni” Daniel Coriu, Bucharest, Romania
10.40-11.10	Coffee break



# OUTLINE

## What is GWAS?

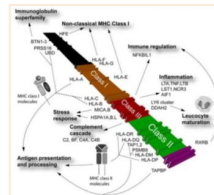
Genetic prediction of transplant outcomes

Unique features of the HLA region

Interpretation of GWAS findings

Imputation (SNPs and HLA types)

Existing GWAS results: What to do with them?





# What and What Isn't GWAS?

**Supposedly genome-wide, but, due to constraints, not 100%**

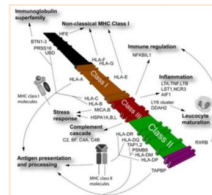
**Generally contains common polymorphisms**

**Most results (~95% in autoimmune disorders) are non-causal**

**Results need to be followed up to identify causal variants**

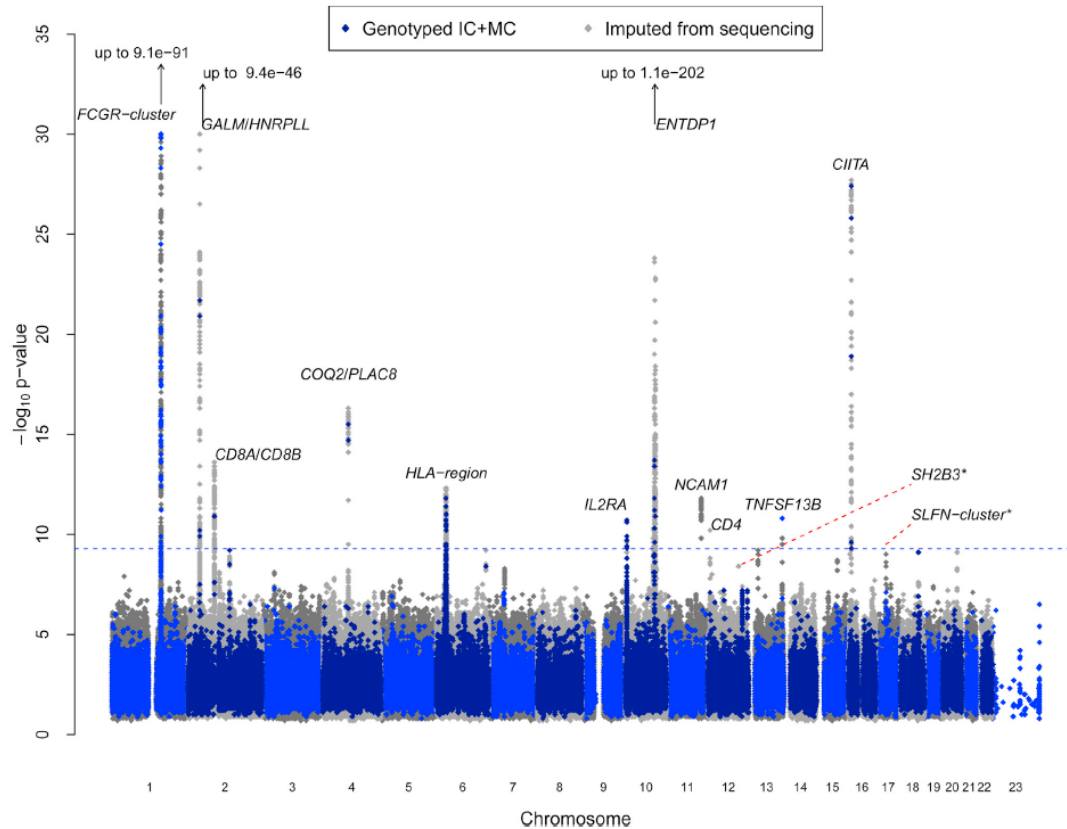
**Most causal variants correlate with expression levels of their target genes (not necessarily the nearest gene)**

**HLA region is the most difficult region to work with and requires special attention**





# GWAS Results



**Figure 3. Manhattan Plot of Best p Values**

For each SNP, the best p value observed among all assessed traits is plotted on a  $-\log_{10}$  scale (y axis), according to its genomic coordinates (x axis). SNPs are colored in blue if the corresponding best p value was directly genotyped with ImmunoChip (IC) or Cardio-MetaboChip (MC) and in gray if imputed from genomic sequencing of Sardinians. The dotted horizontal line indicates the threshold for declaring a locus genome wide to be significant ( $5.26 \times 10^{-10}$ ). The best candidate gene is indicated near the peak. Loci below the significance threshold and previously described are marked with an asterisk.

Cell

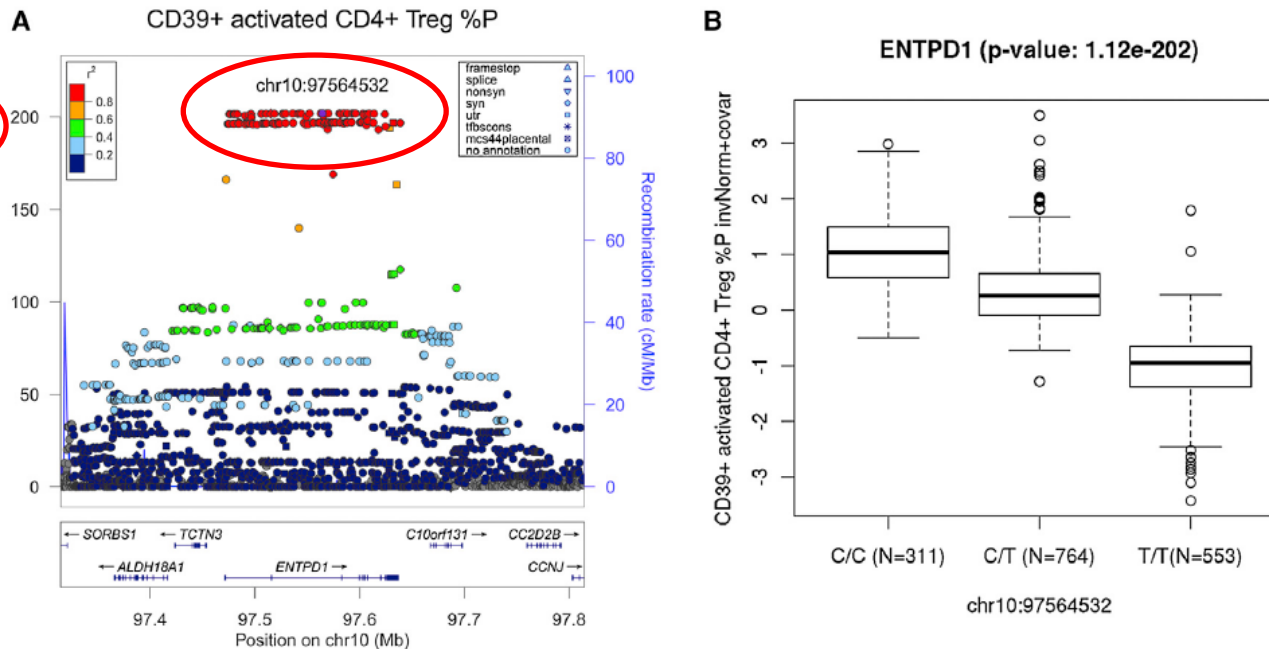
Resource

## Genetic Variants Regulating Immune Cell Levels in Health and Disease

Valeria Orrù,<sup>1,10</sup> Mariastella Sten,<sup>1,10</sup> Gabriella Sole,<sup>1</sup> Carlo Sidore,<sup>1,2,3</sup> Francesca Virdi,<sup>1</sup> Mariano Dei,<sup>1</sup> Sandra Lai,<sup>1</sup> Magdalena Zoladzewska,<sup>1</sup> Fabio Busonero,<sup>1</sup> Antonella Mulas,<sup>1,3</sup> Matteo Floris,<sup>1</sup> Wiesława I. Mentzen,<sup>1</sup> Silvana A.M. Uru,<sup>4</sup> Stefania Olla,<sup>1</sup> Michele Marongiu,<sup>1</sup> Maria G. Piras,<sup>1</sup> Monica Lobina,<sup>1,2</sup> Andrea Maschio,<sup>1,2</sup> Mariastella Pitzalis,<sup>1</sup> Maria F. Uru,<sup>4</sup> Marco Marcelli,<sup>4</sup> Roberto Cusano,<sup>1,4</sup> Francesca Deidda,<sup>1,4</sup> Valentina Serra,<sup>1,2</sup> Manuela Oppo,<sup>5</sup> Rosella Piu,<sup>1,4</sup> Frederic Renier,<sup>4</sup> Riccardo Berutti,<sup>1,4</sup> Luca Piredda,<sup>1,2</sup> Ilaria Zana,<sup>4</sup> Eleonora Porcu,<sup>1,2</sup> Alan Kwong,<sup>6</sup> Christine Brennan,<sup>11</sup> Brendan Tierney,<sup>11</sup> Robert Lyons,<sup>11</sup> Hyun M. Kang,<sup>7</sup> Sergio Uzzau,<sup>10</sup> Rossano Atzeni,<sup>4</sup> Maria Valentini,<sup>4</sup> Davide Finnu,<sup>1</sup> Lidia Leoni,<sup>4</sup> Gianluca Rotta,<sup>4</sup> Silvia Naitza,<sup>1</sup> Andrea Angius,<sup>1,4</sup> Mauro Congia,<sup>2</sup> Michael B. Whalen,<sup>8</sup> Chris M. Jones,<sup>9</sup> David Schlessinger,<sup>10</sup> Gonzalo R. Abecasis,<sup>10</sup> Edoardo Fiorillo,<sup>1,12</sup> Serena Sanna,<sup>1,12</sup> and Francesco Cucca<sup>1,2,3,10,12</sup>



# GWAS Results



**Figure 4. Regional Plot and Box Plot for the Top Signal in *ENTPD1***

(A and B) Representation of the association in the genomic context (A) and in the biological context (B) for the most strongly associated variant at the *ENTPD1* gene.

(A) Representation of the association strength (y axis shows the  $-\log_{10}$  p value) versus the genomic positions (on hg19/GRCh37 genomic build) around the most significant SNP, which is indicated with a purple circle. Other SNPs in the region are color coded to reflect their LD with the top SNP, as in the left inset (taken from pairwise  $r^2$  values calculated on Sardinian haplotypes), whereas symbols reflecting genomic functional annotation are indicated in the right inset. Genes and the position of exons, as well as the direction of transcription, are noted in lower boxes. This plot was drawn using the standalone version of the LocusZoom package (Pruim et al., 2010).

(B) The distribution of the immunophenotypic levels within each genotype class considering the normalized trait adjusted for age and gender in relation to the 1,629 initial samples, showing the additive effect that was statistically observed.



# GWAS Results

Table 1. Twenty-Three Variants at the Thirteen Associated Loci

Locus	Candidate Genes	topSNP (chr:position/rsID)	A1/A2	Freq A1	Trait	Effect (SE)	Var. Expl.	p Value (n = 1,629)	SNP for Validation (chr:position/rsID)	r <sup>2</sup> with topSNP	Validation p Value (n = 2,870)
1	FCGR3A(p,c,o), FCGR2C(p,o), FCGR2A(e,c,o), FCGR2B(e,o), HSPA6(e), HSPA7(e)	chr1:161536758/ rs58055840	T/C	0.742	CD62L— myeloidcDC AC	−0.895 (0.044)	30.26	3.73 × 10 <sup>−91</sup>	chr1:161515326/ rs55971447	0.937	6.83 × 10 <sup>−129</sup>
2	HNRPLL(p)	chr2:38792045/ rs183949931	T/C	0.967	CD45RA— CD28— CD8br %P	0.778 (0.105)	4.05	1.05 × 10 <sup>−13</sup>	chr2:38792045/ rs183949931	same SNP	1.046 × 10 <sup>−20</sup>
2	GALM(p,c,e), HNRPLL(p)	chr2:38897074/ rs13011383	G/A	0.730	TD CD4+ %GP	−0.371 (0.042)	5.52	6.05 × 10 <sup>−19</sup>	chr2:38886041/ rs4670262	0.87	1.26 × 10 <sup>−27</sup>
2	GALM(p), DHX57(e), HNRPLL(b)	chr2:38921934/ rs7583259	G/C	0.508	CD45RA— CD28— CD8br %P	−0.548 (0.039)	15.09	9.40 × 10 <sup>−46</sup>	chr2:38932777/ rs4670265	0.9	2.82 × 10 <sup>−62</sup>
3	CD8A(p,c,o), RNMDS5A(p), CD8B(b), VPS24(e)	chr2:87014377/ rs2944254	C/T	0.810	CD4+ CD8dim AC	0.383 (0.05)	4.55	2.52 × 10 <sup>−14</sup>	chr2:87018547/ rs3810831	0.943	1.3 × 10 <sup>−22</sup>
4	COQ2(e), PLAC8(e), HPSE(e)	chr4:84150313/ rs4431216	T/C	0.633	CD62L— plasmacytoidcDC %P	0.337 (0.04)	5.19	4.96 × 10 <sup>−17</sup>	chr4:84179071/ rs7667017	0.84	3.37 × 10 <sup>−23</sup>
5	HLA-E(p,c,e), HCG27(e), GNL1(c), ABCF1(e), C2(e), PSORS1C3(e), RPP21(e), TRIM39(e), ZKSCAN2(e)	chr6:32466505/ rs117765619	G/T	0.516	CD45RA— CD8+ AC	−0.228 (0.037)	2.62	5.24 × 10 <sup>−10</sup>	chr6:32462993/ rs2534812	0.974	1.34 × 10 <sup>−11</sup>
5	HLA-B(p,c), VARS2(e), IER3(e), ZFP57(e)	chr6:31327382/ rs2395476	T/G	0.858	CD45RA— CD28+ CD8+ %P	0.352 (0.051)	3.21	3.69 × 10 <sup>−12</sup>	chr6:31327382/ rs2395476	same SNP	1.827 × 10 <sup>−19</sup>
5	HLA-DRA(p,e), BTNL2(p,c), HLA- DRB1(c,e), HLA-DQA1(e), HLA- DQB1(e), HLA-DRB5(e), HLA-DOB(e), LOC642073(e), VARS2(e), LST1(e), IER3(e), GTF2H4(e), HMGAI(e), RPL34(e) <sup>9</sup> , AOAHE(e) <sup>9</sup>	chr6:32396433/ rs113534101	G/A	0.776	CD4+ CD8dim %P	−0.299 (0.043)	3.07	5.68 × 10 <sup>−12</sup>	chr6:32396433/ rs115615758	0.97	2.78 × 10 <sup>−16</sup>
5	HLA-DRA(p), LOC642073(e), HLA-DOB(e), RPL34(e) <sup>9</sup> , ARHGAP24(e) <sup>9</sup> , AOAHE(e) <sup>9</sup>	chr6:32428186/ rs6923504	G/C	0.618	CD45RA— CD28— CD8+ AC	−0.249 (0.037)	3.01	2.81 × 10 <sup>−11</sup>	chr6:32428285/ rs6903608	0.99	4.3 × 10 <sup>−13</sup>
6	IL2RA(p,o)	chr10:6094697/ rs61839660	C/T	0.934	CD45RA— CD25hi CD4+ not Treg %P	−0.49 (0.073)	2.82	1.85 × 10 <sup>−11</sup>	chr10:6094697/ rs61839660	same SNP	5.65 × 10 <sup>−23</sup>
6	RBM17(p), IL2RA(p,o)	chr10:6158412/ rs8463	A/G	0.802	CD25hi CD4+ %P	−0.294 (0.046)	2.85	1.21 × 10 <sup>−10</sup>	chr10:6158412/ rs8463	same SNP	2.02 × 10 <sup>−15</sup>
7	SORBS1(p), C10orf61(e), ALDH18A1(c), ENTPD1(e)	chr10:97331924/ rs117568941	T/C	0.955	CD39+ CD8+ %GP	−0.650 (0.062)	6.68	1.45 × 10 <sup>−25</sup>	chr10:97331958/ rs7099430	0.969	1.32 × 10 <sup>−35</sup>
7	ALDH18A1(p), ENTPD1(b)	chr10:97393678/ rs1890187	A/G	0.975	CD39+ activated CD4+ Treg %P	−0.671 (0.073)	5.97	5.72 × 10 <sup>−20</sup>	chr10:97550405/ rs11188485	0.97	2.97 × 10 <sup>−32</sup>
7	ENTPD1(p,e)	chr10:97564532/ rs11517041	T/C	0.578	CD39+ activated CD4+ Treg %P	−1.113 (0.037)	60.81	1.12 × 10 <sup>−202</sup>	chr10:97515137/ rs3814159	0.993	7.05 × 10 <sup>−327</sup>
7	ZNF518A(p), BLNK(p,o), ENTPD1(p)	chr10:97932006/ rs117592294	C/T	0.955	CD39+ CD25hi CD4+ %P	0.497 (0.066)	4.33	6.26 × 10 <sup>−14</sup>	chr10:97932006/ rs117592294	same SNP	1.35 × 10 <sup>−15</sup>

(Continued on next page)

Lead SNP

Perfect Proxy



# GWAS Results

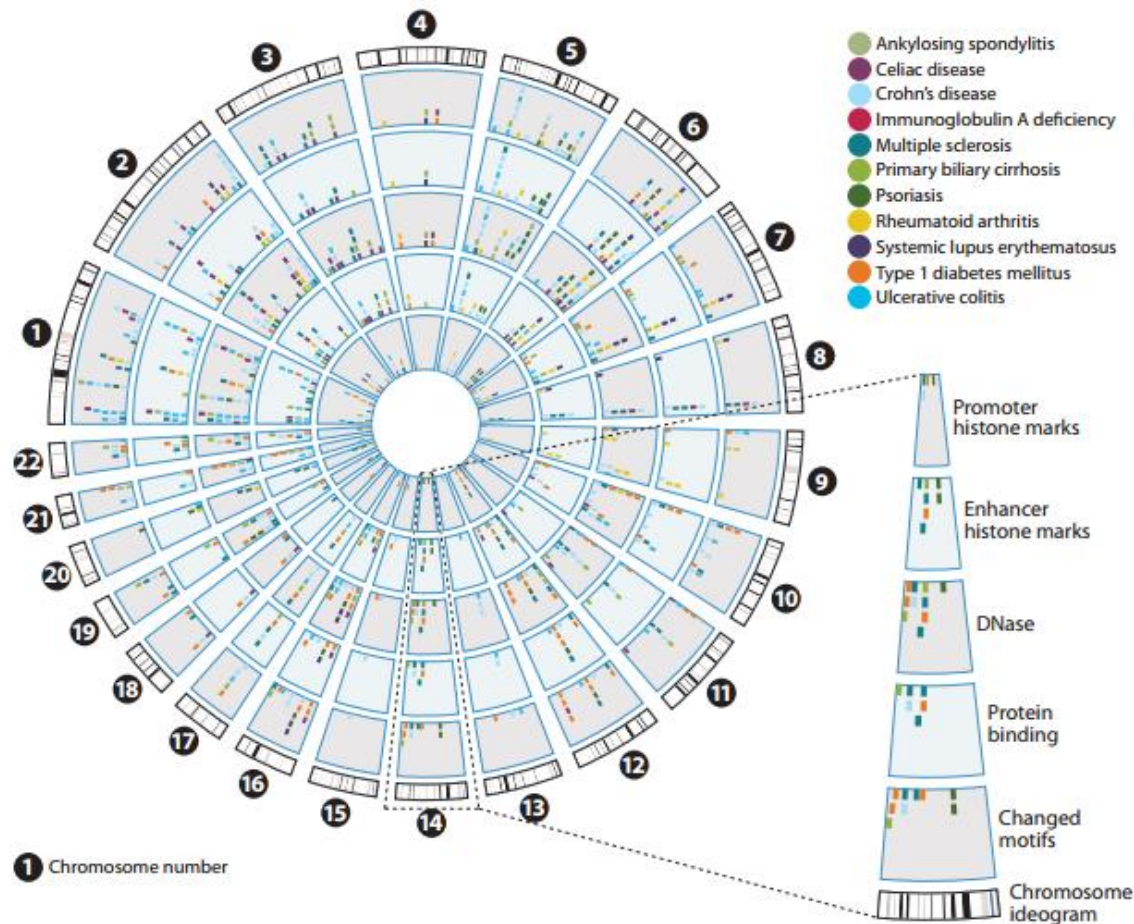


Figure 2

Characterization of variants associated with immune-mediated diseases. (a) Circos plot summarizing the functional annotation of the associated GWAS single-nucleotide polymorphisms (SNPs) for the GWAS loci present in Caucasian populations. From inner to outer rings: promoter histone marks, enhancer histone marks, DNase-hypersensitive sites, protein binding, and changed motifs, as analyzed for lead SNPs and their proxies ( $r^2 = 1$ ). Each disease is in a different color. (b) Localization of GWAS SNPs into functional elements along a chromosome for both shared and unique loci. Lead SNPs present in genome-wide significant loci from Caucasian populations and perfect proxies ( $r^2 = 1$ ) were mapped to the noncoding genome using HaploReg. Blue bars show the percentage of shared SNPs (i.e., those shared by at least two diseases), and red bars show the percentage of unique SNPs; the percentage of expression quantitative trait locus (eQTL) mapping to each functional element is shown for both the shared (green) and unique (purple) loci. Additional abbreviation: UTR, untranslated region.

## Mapping of Immune-Mediated Disease Genes

Isis Ricaño-Ponce and Cisca Wijmenga

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# GWAS Results

## ***What have we learned from GWAS in AID?***

**The lead SNP reported in GWAS has only 5% chance of being the causal SNP**

**Lead SNPs are typically some distance from the causal SNPs (median~ 14kb)**

**Lead SNPs and causal SNPs are not necessarily in tight LD ( $r^2 = 0.50$  is not unusual)**

**Almost all causal SNPs map to enhancers and promoters**

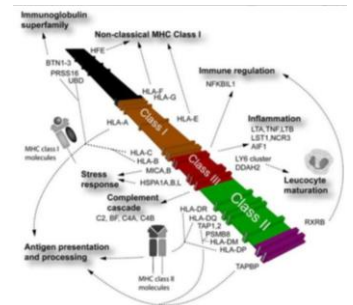
## **Genetic and epigenetic fine mapping of causal autoimmune disease variants**

Kyle Kai-How Farh<sup>1,2\*</sup>, Alexander Marson<sup>3\*</sup>, Jiang Zhu<sup>1,4,5,6</sup>, Markus Klei<sup>newietfeld<sup>1,7</sup></sup>, William J. Housley<sup>7</sup>, Samantha Beil<sup>1</sup>, Noam Shores<sup>1</sup>, Holly Whitton<sup>1</sup>, Russell J. H. Ryan<sup>1,5</sup>, Alexander A. Shishkin<sup>1,8</sup>, Meital Hatan<sup>1</sup>, Marlene J. Carrasco-Alfonso<sup>9</sup>, Dita Mayer<sup>9</sup>, C. John Luckey<sup>9</sup>, Nikolaos A. Patzopoulos<sup>1,10,11</sup>, Philip L. De Jager<sup>1,10,11</sup>, Vijay K. Kuchroo<sup>12</sup>, Charles B. Epstein<sup>1</sup>, Mark J. Daly<sup>1,2</sup>, David A. Hafler<sup>1,2</sup> & Bradley E. Bernstein<sup>1,4,5,6</sup>



## HLA Region: Unique Features

- Most gene dense
- Extremely polymorphic
- Paralog regions and genes
- CNV and structural variation
- Very high linkage disequilibrium over very long range resulting from conserved extended haplotypes (CEH)
- Greatest trans-eQTL density
- Very strong selective pressures
- Extreme geographical, racial and ethnic differential in allele frequencies
- So many lineages and groupings of alleles & haplotypes
- So many functional dimorphisms or supertypes with no single corresponding SNPs





# Transplant Outcomes: Markers

**HLA mismatching**

**mH mismatching**

**Donor or recipient genotype**



# Genetic Prediction of Transplant Outcomes



## MHC-Resident Variation Affects Risks After Unrelated Donor Hematopoietic Cell Transplantation

Effie W. Petersdorf *et al.*

*Sci Transl Med* 4, 144ra101 (2012);

Blood malignancies can be cured with hematopoietic cell transplantation from human leukocyte antigen (HLA)-matched unrelated donors; however, acute graft-versus-host disease (GVHD) affects up to 80% of patients and contributes to increased mortality. To test the hypothesis that undetected patient-donor differences for non-HLA genetic variation within the major histocompatibility complex (MHC) could confer risks after HLA-matched transplantation, we conducted a discovery-validation study of 4205 transplants for 1120 MHC region single-nucleotide polymorphisms (SNPs). Two SNPs were identified as markers for disease-free survival and acute GVHD. Among patients with two or more HLA-matched unrelated donors identified on their search, SNP genotyping of patients and their potential donors demonstrated that most patients have a choice of SNP-matched donors. In conclusion, the success of HLA-matched unrelated donor hematopoietic cell transplantation depends on non-HLA MHC region genetic variation. Prospective SNP screening and matching provides an approach for lowering risks to patients.

Grade III to IV acute GVHD	rs3132486	HLA-C/ flanking 5'UTR	<u>Donor genotype</u>	$1.72 \times 10^{-4}$	AA	174/620	1.00
					AG	215/1093	0.66 (0.54–0.81)
					GG	129/527	0.87 (0.69–1.10)
	rs2859091	HLA-DQA2/ flanking 5'UTR	<u>Donor genotype</u>	$2.34 \times 10^{-6}$	TT	252/897	1.00
					AT	195/1013	0.62 (0.51–0.75)
					AA	71/330	0.68 (0.52–0.89)



# Genetic Prediction of Transplant Outcomes



**blood**

2013 121: 1896-1905  
doi:10.1182/blood-2012-11-465161 originally published  
online January 10, 2013

## Mapping MHC haplotype effects in unrelated donor hematopoietic cell transplantation

Effie W. Petersdorf, Mari Malkki, Mary M. Horowitz, Stephen R. Spellman, Michael D. Haagenson and Tao Wang

### Key Points

- HLA haplotypes encode single nucleotide polymorphisms (SNPs) that are associated with risks after HLA-mismatched unrelated donor HCT.
- SNPs associated with graft-versus-host disease (GVHD) are independent of those associated with relapse.

Outcome	SNP	Gene/location*	Model	Overall P	Genotype or mismatch group	Number of events	HR (95% CI)	P
Survival	rs429916	1.2 kb centromeric of HLA-DOA	<u>Patient genotype</u>	$7.48 \times 10^{-5}$	CC	1254/1909	1	
					AC	201/296	1.11 (0.94-1.31)	.23
					AA	18/19	3.47 (1.95-6.16)	$2.27 \times 10^{-5}$
Disease-free survival†	rs429916	1.2 kb centromeric of HLA-DOA	<u>Patient genotype</u>	$4.28 \times 10^{-5}$	CC	1147/1708	1	
					AC	188/268	1.06 (0.88-1.26)	.56
					AA	18/19	3.75 (2.10-6.68)	$7.86 \times 10^{-6}$
Relapse‡	rs2244546	2.2 kb telomeric of HCP5	<u>Donor genotype</u>	$6.92 \times 10^{-4}$	CC	373/1611	1	
					CG	117/435	1.19 (0.95-1.50)	.14
					GG	16/30	2.79 (1.60-4.85)	$2.87 \times 10^{-4}$
	rs986522	COL11A2, intron	<u>Donor genotype</u>	$3.20 \times 10^{-5}$	CG	209/1025	1	
					CC	136/478	1.46 (1.16-1.85)	$1.45 \times 10^{-3}$
					GG	161/573	1.62 (1.30-2.03)	$2.14 \times 10^{-5}$
Transplant-related mortality	rs915654	1.4 kb telomeric of LTA	<u>Patient genotype</u>	$9.93 \times 10^{-5}$	AT	394/964	1	
					AA	142/300	1.45 (1.16-1.80)	$1.16 \times 10^{-3}$
					TT	332/718	1.39 (1.17-1.64)	$1.43 \times 10^{-4}$
	rs429916	1.2 kb centromeric of HLA-DOA	<u>Patient genotype</u>	$2.82 \times 10^{-5}$	CC	720/1696	1	
					AC	134/267	1.20 (0.97-1.49)	$9.67 \times 10^{-2}$
					AA	14/19	4.52 (2.31-8.86)	$1.11 \times 10^{-5}$
Grades II-IV acute GVHD§	rs2242656	BAG6, intron	Mismatch	$3.13 \times 10^{-4}$	Matched	865/1535	1	
					HVG	122/214	1.00 (0.82-1.22)	1
					GVH	136/203	1.46 (1.21-1.77)	$6.92 \times 10^{-5}$
Grades III-IV acute GVHD	rs209130	3 kb telomeric of TRIM27	Mismatch	$6.42 \times 10^{-5}$	Matched	251/920	1	
					HVG	154/488	1.22 (0.99-1.50)	$6.11 \times 10^{-2}$
					GVH	124/420	1.19 (0.96-1.49)	.12
	rs2075800	HSPA1L, Glu602Lys	<u>Patient genotype</u>	$8.37 \times 10^{-4}$	Bi	45/103	2.17 (1.56-3.01)	$3.70 \times 10^{-6}$
					GG	289/848	1	
					AG	214/819	0.72 (0.60-0.86)	$4.01 \times 10^{-4}$
	rs394657	NOTCH4, intron	<u>Donor genotype</u>	$4.15 \times 10^{-4}$	AA	71/264	0.73 (0.56-0.95)	$2.07 \times 10^{-2}$
					AG	150/626	1	
						301/923	1.48 (1.21-1.81)	$1.16 \times 10^{-4}$



# Genetic Prediction of Transplant Outcomes



blood

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## Mapping MHC haplotype effects in unrelated donor hematopoietic cell transplantation

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### Key Points

- HLA haplotypes encode single nucleotide polymorphisms (SNPs) that are associated with risks after HLA-mismatched unrelated donor HCT.
- SNPs associated with graft-versus-host disease (GVHD) are independent of those associated with relapse.

SNPs provide clues to the candidate genes and mechanisms involved in transplant-associated complications. The identification of 2 SNPs within the HLA-DOA and -DOB genes provides strong evidence for a role for antigen processing and presentation in immune responses in HLA-mismatched transplantation.<sup>31</sup> The rs2075800G/A SNP defines a glutamic acid/lysine substitution at residue 602 of the heat shock protein-70 A1L molecule. We hypothesize a possible role for the differential binding of peptides by heat shock protein-A1L molecules and/or stimulation of cytokines in GVHD.<sup>32</sup> The second SNP marker for grades III-IV acute GVHD, rs394657, resides within the NOTCH4 gene intron and is in positive linkage disequilibrium with nonsynonymous substitutions. Sequence polymorphism of NOTCH4 receptors could influence the inflammatory nature of acute GVHD through altered ligand-receptor binding and production of TNF- $\alpha$ , IFN- $\gamma$ , IL-4, and IL-17.<sup>33</sup> Alternatively, SNP rs394657 might influence GVHD through its role as a putative expression quantitative locus for HLA-DQA1,<sup>34</sup> the gene that encodes the DQ $\alpha$  chain of the HLA-DQ heterodimer. Differential DQ $\alpha$  expression may have consequences for alloantigen recognition in GVHD.



# Interpretation of GWAS Findings: Individual SNPs

U.S. Department of Health & Human Services



GRASP Search - v2.0.0.0


NHLBI key	SnP Id	Pvalue	PMID	Location	Phenotype	Phenotype Category	chr	pos	InGene
204538421544740	rs2075800	2.4E-100	<a href="#">20453842</a>	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
175543002216079	rs3132486	3.3E-63	<a href="#">17554300</a>	Webdata	Type 1 diabetes, combined control dataset	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavior... disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental... arthritis,Crohn's disease	6	31275393	
175543001544729	rs2075800	9.5E-42	<a href="#">17554300</a>	Webdata	Rheumatoid arthritis, combined control dataset	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavior... disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental... arthritis,Crohn's disease	6	31810169	(HSPA1L)
204538422216107	rs3132486	1.7E-37	<a href="#">20453842</a>	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31275393	
195030881544734	rs2075800	8.3E-36	<a href="#">19503088</a>	Table S2	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
211567611544753	rs2075800	1.3E-31	<a href="#">21156761</a>	Table S3	Rheumatoid arthritis (ACPA-positive)	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)

178048361544730	rs2075800	2.0E-29	<a href="#">17804836</a>	RawUna...	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
21323541273999	rs394657	8.2E-17	<a href="#">21323541</a>	Table S6	Idiopathic membranous nephropathy	Renal	6	32219246	(NOTCH4)
176325452216080	rs3132486	1.1E-16	<a href="#">17632545</a>	TableS1	Type 1 diabetes	Type 1 diabetes (T1D),Developmental... risk factor (CVD RF)	6	31275393	
204538422097312	rs2859100	1.7E-16	<a href="#">20453842</a>	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32731702	
234556366395722	rs394657	9.5E-11	<a href="#">23455636</a>	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration (ARMD)	6	32219246	(NOTCH4)
20453842273995	rs394657	1.2E-09	<a href="#">20453842</a>	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32219246	(NOTCH4)
176605302216081	rs3132486	2.9E-09	<a href="#">17660530</a>	RawUna...	Multiple sclerosis	Neuro,Inflammation,... sclerosis (MS)	6	31275393	
19503088273993	rs394657	8.1E-08	<a href="#">19503088</a>	Table S2	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32219246	(NOTCH4)
203831471544739	rs2075800	1.6E-07	<a href="#">20383147</a>	Table S2	Systemic sclerosis	Skin-related,Muscle-related	6	31810169	(HSPA1L)

The GVHD risk markers are also associated with RA, T1D, MS, PSS and idiopathic membranous nephropathy (rs2075800, rs394657, rs3132486, rs2859091/rs2859100)




# Interpretation of GWAS Findings: Individual SNPs




**SNiPA**  
single nucleotide polymorphisms annotator

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German Research Center for Environmental Health



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## Variant Annotation

This module allows you to get detailed annotations for one or more variants. If the results are not what you have expected, please check the "Report" tab for details. close

rs3132486

[add to clipboard](#)
[save as PDF](#)
[delete](#)

SNP properties — Genome Assembly: grch37, Variant set: 1kgpp3v5, Population: EUR

**rs3132486 (alias rs9264718, rs6912233, rs58265514, rs56648229, rs386580024, rs118019162, rs116741667, rs113696533, rs111774027)**

position / outlink		allele info	
physical position	chr6: 31,243,170	alleles	G/A
genetic position [cM]	51.17	frequencies	0.506/0.494
outlink	<i>e!</i>	non-reference allele	G

Basic Features

Conservation/deleteriousness		Linked genes	
phyloP <sup>†</sup>	-3.432	gene(s) hit or close-by	HLA-C <i>e!</i> , RPL3P2 <i>e!</i> , USP8P1 <i>e!</i>
phastCons <sup>†</sup>	0.743	eQTL gene(s)	HCG22 <i>e!</i> , HLA-DRB5 <i>e!</i> , LST1 <i>e!</i> , MICB <i>e!</i> , PSORS1C3 <i>e!</i> , TCF19 <i>e!</i> , XXbac-BPG181B23.7 <i>e!</i> , XXbac-BPG299F13.17 <i>e!</i>
GERP++ <sup>†</sup>	-0.378	potentially regulated gene(s)	RPL3P2 <i>e!</i> , RPL3P2 <i>e!</i> , RPL3P2 <i>e!</i> , RPL3P2 <i>e!</i> , RPL3P2 <i>e!</i> , RPL3P2 <i>e!</i> , RPL3P2 <i>e!</i> , USP8P1 <i>e!</i> , USP8P1 <i>e!</i> , USP8P1 <i>e!</i> , USP8P1 <i>e!</i> , USP8P1 <i>e!</i> , USP8P1 <i>e!</i>
CADD score <sup>†</sup>	1.004	disease gene(s)	—
SnpEff effect impact <sup>†</sup>	modifier		

A large number of non-coding genes are eQTL targets, but not the nearest gene *HLA-C*!



**SNIPRA**  
High Performance Protein Annotation

Helmholtz Zentrum münchen  
Heinrich Heine Universität München

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---

**Variant Annotation**

This interface allows you to get detailed annotations for one or more variants. If the results are not what you have expected, please check the "Display" tab for details.

Variant annotation Report

rs13123466 [info](#) [topview](#) [detailed](#) [download](#)

chr17:g13123466 (HBB; HBB-AS1; HBB-AS2; HBB-AS3; HBB-AS4; HBB-AS5; HBB-AS6)

physical position	refseq	aliases	G/A
pos: chr17:31,425,000	A/G	frequency	0.000000000
genetic position [cM]	18.1 cM	non-reference allele	
synonymous / nontoxic			

**Basic Features**

Conservation/deletions	Linked genes
phastP = 3.432	gene(s) hit or close-by
phastC = 6.743	enigL gene(s)
GERAC = -0.378	potentially regulated gene(s)
CADD score = 1.004	disease gene(s)
SIFT effect impact = modifier	-

## Trans-eQTLs

## Cis-eQTLs

P-value	SNP	SNP Chr.	SNP Chr. Position	Probe	Probe Chr.	Probe Chr. position	SNP Alleles	Minor Allele	Z-score	Gene name	FDR
5.4069191854449905E-37	rs31324866		31351149	580452	6	31558934	G/A	A	12.71	-	0.00
8.8792092502963E-26	rs31324866		31351149	1440603	6	31556059	G/A	A	-10.50	-	0.00
2.617756407729722E-5	rs31324866		31351149	3890097	6	31239621	G/A	A	-4.20	TCF19	0.01
1.8212601781875332E-4	rs31324866		31351149	3170064	6	31586789	G/A	A	3.74	MICB	0.07
0.0026436099021629866	rs31324866		31351149	780600	6	31541393	G/A	A	-3.01	HCP5	0.43



# Interpretation of GWAS Findings: Individual SNPs



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## Variant Annotation

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Variant annotations

Report

rs2859091

[add to clipboard](#)

[save as PDF](#)

[delete](#)

SNP properties – Genome Assembly: grch37, Variant set: 1kgpp3v5, Population: EUR

rs2859091 (alias rs386490823, rs28724876, rs117494994, rs115307699, rs111816808)

position / outlink		allele info	
physical position	chr6: 32,700,799	alleles	A/T
genetic position [cM]	52.16	frequencies	0.554/0.446
outlink	<a href="#">e!</a>	non-reference allele	A

### Basic features

Conservation/deleteriousness		Linked genes	
phyloP <sup>†</sup>	-0.351	gene(s) hit or close-by	HLA-DQB3 <a href="#">e!</a>
phastCons <sup>†</sup>	0.001	eQTL gene(s)	HLA-DQB1 <a href="#">e!</a> , HLA-DQA2 <a href="#">e!</a> , HLA-DQB1 <a href="#">e!</a> , HLA-DQB1-AS1 <a href="#">e!</a> , HLA-DRB1 <a href="#">e!</a> , TNXA <a href="#">e!</a> , XXbac-BPG254F23.7 <a href="#">e!</a>
GERP++ <sup>†</sup>	0.328	potentially regulated gene(s)	–
CADD score <sup>†</sup>	4.182	disease gene(s)	HLA-DQB1 <a href="#">e!</a> , HLA-DRB1 <a href="#">e!</a>
SnpEff effect impact <sup>†</sup>	modifier		



# Interpretation of GWAS Findings: eQTLs

## THE HUMAN PROTEIN ATLAS

[ABOUT](#) [HELP](#) [BLOG](#)

SEARCH ? »

HLA-DRB1

Search

[Fields »](#)

e.g. [insulin](#), [PGR](#), [CD36](#)



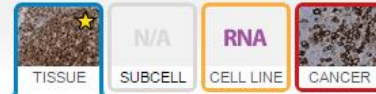
### A Tissue-Based Map of the Human Proteome

*Here, we summarize our current knowledge regarding the human proteome mainly achieved through antibody-based methods combined with transcriptomics analysis across all major tissues and organs of the human body. A large number of lists can be accessed with direct links to gene-specific images of the corresponding proteins in the different tissues and organs. [Read more](#)*



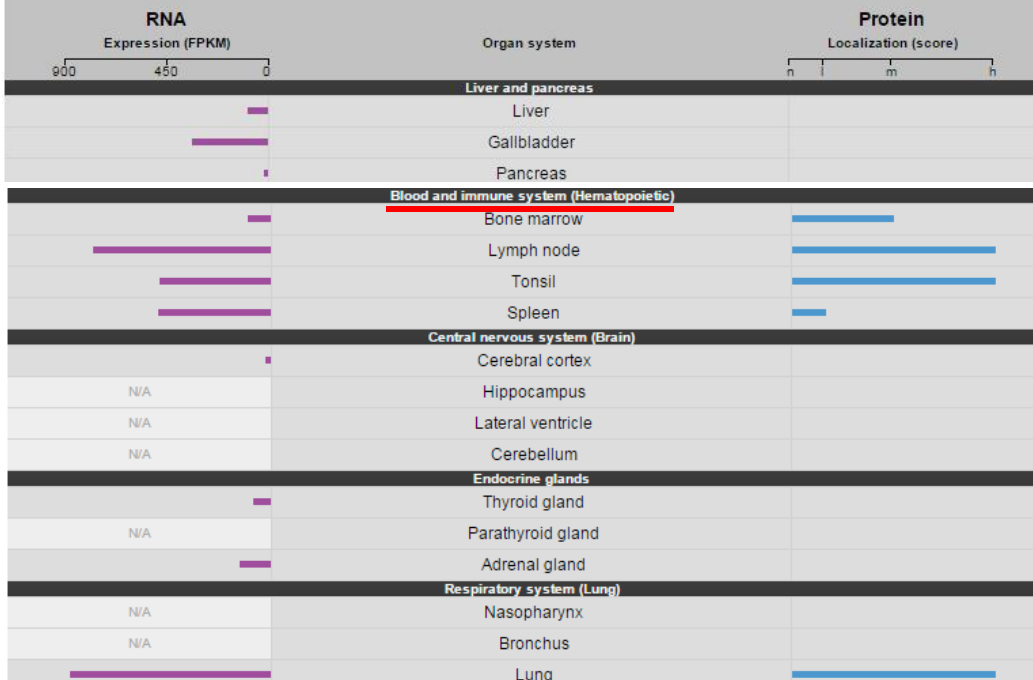
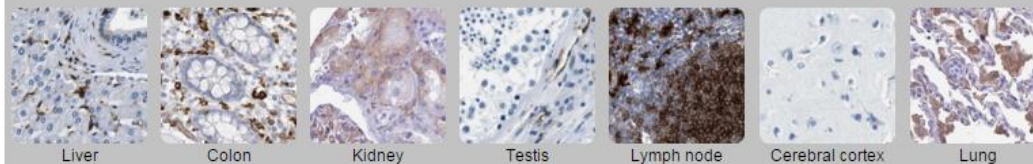
# Interpretation of GWAS Findings: eQTLs

## HLA-DRB1



### TISSUE ATLAS ? »

Gene description	Major histocompatibility complex, class II, DR beta 1
RNA tissue category	Expressed in all.
Protein class	Disease related genes, Plasma proteins, Predicted membrane proteins
Predicted localization	Membrane
Protein evidence	Evidence at protein level
Protein expression	Selective membranous and cytoplasmic expression in lymphoid cells.
Data reliability description	Pending RNA-based expert annotation. Caution, targets protein from more than one gene.
Data reliability	Supportive based on 3 antibodies.





# Interpretation of GWAS Findings: Individual SNPs



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Variant Annotation

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Variant annotations

Report

rs2075800

[add to clipboard](#)

[save as PDF](#)

[delete](#)

SNP properties – Genome Assembly: grch37, Variant set: 1kgpp3v5, Population: EUR

rs2075800 (alias rs60193164, rs35486322, rs138709911, rs117722716, rs116490983)

position / outlink		allele info	
physical position	chr6: 31,777,946	alleles	C/T
genetic position [cM]	51.59	frequencies	0.651/0.349
outlink	e!	non-reference allele	C

Basic features

Conservation/deleteriousness		Linked genes	
phyloP <sup>⊕</sup>	7.818	gene(s) hit or close-by	HSPA1L e!, LSM2 e!
phastCons <sup>⊕</sup>	1	eQTL gene(s)	AIF1 e!, ATF6B e!, BAG6 e!, CYP21A1P e!, HLA-B e!, HLA-C e!, HLA-DQA2 e!, HSPA1B e!, MSH5 e!, MSH5-SAPCD1 e!, PRRC2A e!, PSORS1C3 e!, VARS2 e!, XXbac-BPG248L24.12 e!, XXbac-BPG300A18.13 e!
GERP++ <sup>⊕</sup>	5.94	potentially regulated gene(s)	–
CADD score <sup>⊕</sup>	17.39	disease gene(s)	VARS2 e!, HLA-B e!
SnpEff effect impact <sup>⊕</sup>	modifier		



# Interpretation of GWAS Findings: Individual SNPs



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Variant Annotation

This module allows you to get detailed annotations for one or more variants. If the results are not what you have expected, please check the "Report" tab for details. [close](#)

Variant annotations

Report

rs394657

[add to clipboard](#) [save as PDF](#) [delete](#)

SNP properties – Genome Assembly: grch37, Variant set: 1kgpp3v5, Population: EUR

rs394657 (alias rs7771218, rs60262883, rs17494168, rs17201784, rs117573126, rs114878695)

position / outlink		allele info	
physical position	chr6: 32,187,023	alleles	A/G
genetic position [cM]	51.75	frequencies	0.555/0.445
outlink	e!	non-reference allele	A

Basic features

Conservation/deleteriousness		Linked genes	
phyloP <sup>†</sup>	-0.462	gene(s) hit or close-by	NOTCH4 e!
phastCons <sup>†</sup>	0.001	eQTL gene(s)	C4A e!, HLA-DQA1 e!, HLA-DQB1 e!, HLA-DQB1-AS1 e!, HLA-DQB2 e!, HLA-DRB1 e!, HLA-DRB5 e!, LST1 e!, NOTCH4 e!, PRR2A e!, RNF5 e!, SKIV2L e!
GERP++ <sup>†</sup>	2.02	potentially regulated gene(s)	–
CADD score <sup>†</sup>	6.397	disease gene(s)	SKIV2L e!, C4A e!, HLA-DQB1 e!, HLA-DRB1 e!
SnpEff effect impact <sup>†</sup>	modifier		



# Interpretation of GWAS Findings: Individual SNPs



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**The GVHD risk markers are mainly acting as eQTLs**

**Their target genes are more commonly the genes other than the nearest gene**

**The target genes include pseudogenes and ncRNA genes**

**(rs2075800, rs394657, rs3132486, rs2859091)**



# Interpretation of GWAS Findings: Individual SNPs

**SNP**nexus

  
**Barts**  
Cancer Institute

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User details

Email address (optional):

Dataset name (optional):

Query Options

Assembly

GRCh37/hg19

Query Type

Batch Query

Batch Query

[\[Input format\]](#) [\[Load Example\]](#)

Paste in your query (upto 100K SNPs/InDels):

dbSNP rs2075500  
dbSNP rs394657  
dbSNP rs3132486  
dbSNP rs2859091  
dbSNP rs2859100

Annotation Categories

Gene/Protein Consequences  
(maximum 3 at a time)

☒ RefSeq ☐ Ensembl ☐ AceView ☐ VEGA ☐ UCSC ☐ CCDS ☐ H-inv 7.0<sup>†</sup>

Effect of Non-synonymous  
Coding SNPs on Protein  
Function<sup>†§</sup>

☒ SIFT  
☒ PolyPhen

HapMap Population Data

☒ CEU ☐ YRI ☐ CHB ☐ JPT ☐ ASW ☐ CHD ☐ GIH ☐ LWK ☐ MEX ☐ MKK ☐ TSI

Regulatory Elements

☒ Conserved Transcription Factor Binding Sites (TFBS)  
☐ First-Exon and Promoter Prediction (FirstEF)<sup>†</sup>  
☒ miRBASE 20.0  
☒ Vista HMR-Conserved Non-coding Human Enhancers  
☒ CpG Islands  
☒ TargetScan miRNA Regulatory Sites  
☒ microRNAs (miRNA Registry) / snoRNAs and scaRNAs (snoRNA-LBME-DB)

Conservation

☐ Vertebrate Alignment and Conservation (PHAST)  
☐ Genomic Evolutionary Rate Profiling (GERP++)

Phenotype & Disease Association

☐ Genetic Association of Complex Diseases and Disorders (GAD)  
☐ Catalogue of Somatic Mutations in Cancer (COSMIC)  
☒ NHGRI Catalogue of Published Genome-Wide Association Studies

Structural Variations

☐ Copy Number Variations (CNV)  
☐ Inversion  
☐ Complex



# Interpretation of GWAS Findings: Individual SNPs

# SNPnexus

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Number of SNPs in query:

5



Use the links below to navigate through your search results:

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  -  [Genomic Coordinates and External Links](#)
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  -   [Refseq](#)
  -   [Ensembl](#)
- Effect of Non-synonymous Coding SNPs on Protein Function
  -  [SIFT](#)
  -  [PolyPhen](#)
- HapMap Population Data
  -  [CEU](#)
- Regulatory Elements
  -  [Conserved Transcription Factor Binding Sites \(TFBS\)](#)
  -  [miRBASE 18.0](#)
  -  [Vista HMR-Conserved Non-coding Human Enhancers](#)
  -  [CpG Islands](#)
  -  [TargetScan miRNA Regulatory Sites](#)
  -  [miRNAs \(miRNA Registry\) / snoRNAs and scaRNAs \(snoRNA-LBME-DB\)](#)
- Phenotype & Disease Association
  -  [Catalogue of Published Genome-Wide Association Studies](#)



# Interpretation of GWAS Findings: Individual SNPs

**SNP**nexus

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**Descriptive data, including HapMap frequencies, provided**

**Polyphen score for the *HSPA1L* nsSNP is 0.001 (benign)**

**None of the SNPs are in conserved transcription factor binding sites nor in miRNA sequences/miRNA binding sites**

**None of the SNPs are in CpG islands**

**None of the SNPs are in enhancers**



# Interpretation of GWAS Findings: Individual SNPs



RegulomeDB has been updated to Version 1.1. This includes bringing our database up-to-date with current ENCODE releases: [Xie et al. \(2013\)](#) and [Boyle et al. \(2014\)](#). We have also added Chromatin States from the Roadmap Epigenome Consortium (unpublished) as well as updates to DNase footprinting, PWMs, and DNA Methylation.

Enter dbSNP IDs, 0-based coordinates, BED files, VCF files, GFF3 files (hg19).

rs3132486  
rs2859091  
rs2075800  
rs394657

Submit



Download About Help

The search has evaluated 4 input line(s) and found 4 SNP(s).

## Summary of SNP analysis

Show 10 entries			
Coordinate (0-based)	dbSNP ID	? Regulome DB Score	Other Resources
chr6:31243169	rs3132486	1f	UCSC   ENSEMBL   dbSNP
chr6:32187022	rs394657	6	UCSC   ENSEMBL   dbSNP
chr6:32700798	rs2859091	6	UCSC   ENSEMBL   dbSNP
chr6:31777945	rs2075800	No Data	UCSC   ENSEMBL   dbSNP
Showing 1 to 4 of 4 entries			

Download

BED

GFF

Full Output



# Interpretation of GWAS Findings: Individual SNPs

RegulomeDB [Download](#) [About](#) [Help](#)

The search has evaluated 4 input line(s) and found 4 SNP(s).

### Summary of SNP analysis

Coordinate (0-based)	dbSNP ID	Regulome DB Score	Other Resources
chr6:31243169	rs3132486	1f	UCSC   ENSEMBL   dbSNP
chr6:32187022	rs394657	6	UCSC   ENSEMBL   dbSNP
chr6:32700798	rs2859091	6	UCSC   ENSEMBL   dbSNP
chr6:31777945	rs2075800	No Data	UCSC   ENSEMBL   dbSNP

Showing 1 to 4 of 4 entries

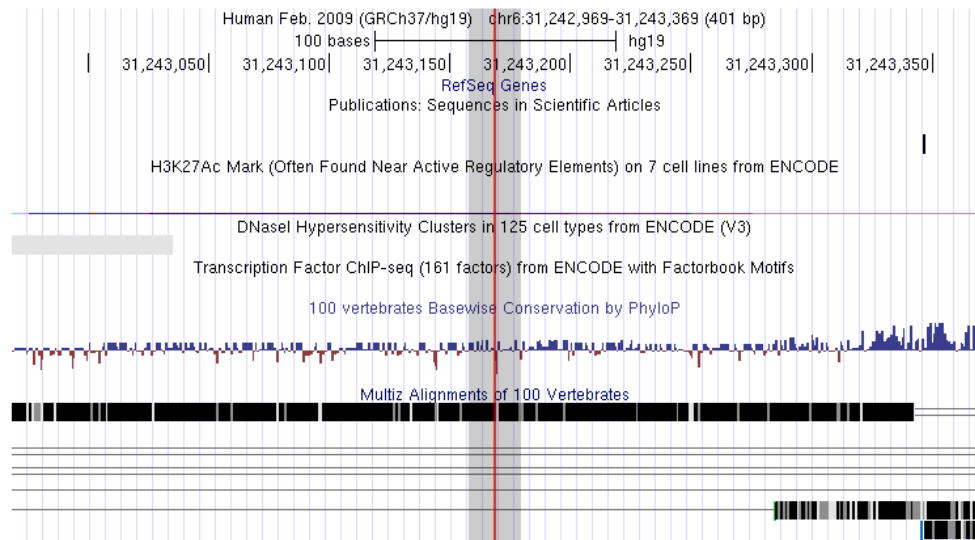
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## Data supporting chr6:31243169 (rs3132486)

Score: 1f

Likely to affect binding and linked to expression of a gene target






# Interpretation of GWAS Findings: ssSNP Sets

**VaDE**

English

TOPReproduced AssociationsAll AssociationsSNP FunctionGenome BrowserDocument



## SNP Function

Functional genomic region overlapping with SNPs in high linkage disequilibrium.

Query SNP  
rs3132486SEARCH

SNP in LD	Distance	Location	EUR ( $r^2$ )	ASN ( $r^2$ )	AFR ( $r^2$ )	Nearest gene	SNP position	Functional region
<a href="#">rs41543814</a>	-3740 bp	<a href="#">chr6:31239430</a>	-	0.9105	-	HLA-C	NSM,U5,INT	71 promoters 4 motifs 42 DNases
<a href="#">rs2844616</a>	-531 bp	<a href="#">chr6:31242639</a>	-	0.8642	-	HLA-C	-	1 motif
<a href="#">rs3132489</a>	-496 bp	<a href="#">chr6:31242674</a>	0.8944	0.8121	-	HLA-C	-	6 motifs
<a href="#">rs3132486</a>	0 bp	<a href="#">chr6:31243170</a>	1	1	1	HLA-C	-	1 DNase
<a href="#">rs3132485</a>	+219 bp	<a href="#">chr6:31243389</a>	-	-	0.9283	HLA-C	-	2 motifs
<a href="#">rs3132484</a>	+240 bp	<a href="#">chr6:31243410</a>	-	-	0.9283	HLA-C	-	1 enhancer 1 motif

### SNP

**rs3132486**

### GENE INFO

Nearest gene	RefSeq ID	Annotation
HLA-C	NM_002117	-
	Hinv transcript ID	Annotation
	-	-

### FUNCTIONAL GENOMIC REGION

[Enhancer Like Chromatin State](#)

Cell type   State   Project

[Promoter Like Chromatin State](#)

Cell type   State   Project

Search Result 6 records |

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CSV



# Interpretation of GWAS Findings: ssSNP Sets

## HaploReg v3



HaploReg is a tool for exploring annotations of the noncoding genome at variants on haplotype blocks, such as candidate regulatory SNPs at disease-associated loci. Using LD information from the 1000 Genomes Project, linked SNPs and small indels can be visualized along with their predicted chromatin state, their sequence conservation across mammals, and their effect on regulatory motifs. HaploReg is designed for researchers developing mechanistic hypotheses of the impact of non-coding variants on clinical phenotypes and normal variation.

**Update 2014.02.14: Version 3** now includes an improved motif library and final reference epigenomes the Roadmap, including predicted causal enhancer motif instances. The GWAS library has also been updated and revamped by aggregating across traits and pruning. Version 2 is available [here](#).

[Build Query](#) [Set Options](#) [Documentation](#)

Use one of the three methods below to enter a set of variants. If an  $r^2$  threshold is specified (see the Set Options tab), results for each variant will be shown in a separate table along with other variants in LD. If  $r^2$  is set to NA, only queried variants will be shown, together in one table.

Query (comma-delimited list of  
rsIDs OR a single region as  
chrN:start-end):

rs3132486

or, upload a text file (one  
refSNP ID per line):

[Choose File](#)

No file chosen

or, select a GWAS:

[Submit](#)

## HaploReg v3



HaploReg is a tool for exploring annotations of the noncoding genome at variants on haplotype blocks, such as candidate regulatory SNPs at disease-associated loci. Using LD information from the 1000 Genomes Project, linked SNPs and small indels can be visualized along with their predicted chromatin state, their sequence conservation across mammals, and their effect on regulatory motifs. HaploReg is designed for researchers developing mechanistic hypotheses of the impact of non-coding variants on clinical phenotypes and normal variation.

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[Build Query](#) [Set Options](#) [Documentation](#)

LD threshold,  $r^2$  (select NA to only show query variants): 0.6

1000G Phase 1 population for LD calculation: ☒ AFR ☐ AMR ☐ ASN ☐ EUR

Source for epigenomes: ☒ Basic model ☐ Imputed model

Mammalian conservation algorithm: ☐ GERP ☒ SiPhy-omega ☐ both

Show position relative to: ☒ GENCODE genes ☐ RefSeq genes ☐ both

Condense lists in table longer than: 3

Condense indel oligos longer than: 6

Background set for enhancer enrichment analysis: All SNPs in 1KG pilot

Output mode: ☒ HTML ☐ Text



# Interpretation of GWAS Findings: ssSNP Sets

Query SNP: **rs3132486** and variants with  $r^2 \geq 0.6$

pos (hg19)	pos (hg38)	LD (r <sup>2</sup> )	LD (D')	variant	Ref	Alt	AFR freq	AMR freq	ASN freq	EUR freq	SiPhy cons	Promoter histone marks	Enhancer histone marks	DNase	Proteins bound	eQTL tissues	Motifs changed	Drivers disrupted	GENCODE genes	dbSNP func annot
chr6:31242674	chr6:31274897	0.89	0.99	<a href="#">rs3132489</a>	C	T	0.33	0.49	0.60	0.47							4 altered motifs		2.8kb 5' of HLA-C	
chr6:31242817	chr6:31275040	0.77	0.99	<a href="#">rs6930376</a>	A	T	0.33	0.41	0.40	0.43							Nrf1,STAT,TCF4		2.9kb 5' of HLA-C	
chr6:31242859	chr6:31275082	0.73	0.98	<a href="#">rs3130693</a>	T	C	0.33	0.40	0.38	0.42							AP-1,Mef2,PPAR		3kb 5' of HLA-C	
chr6:31243170	chr6:31275393	1	1	<b>rs3132486</b>	G	A,C,T	0.45	0.52	0.65	0.49									3.3kb 5' of HLA-C	
chr6:31243389	chr6:31275612	0.8	0.99	<a href="#">rs3132485</a>	C	A	0.43	0.42	0.40	0.44							Gfi1b,p300		3.5kb 5' of HLA-C	
chr6:31243410	chr6:31275633	0.79	0.99	<a href="#">rs3132484</a>	G	T	0.43	0.42	0.40	0.44			BLD				Osr		3.5kb 5' of HLA-C	



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The search has evaluated 6 input line(s) and found 6 SNP(s).

## Summary of SNP analysis

Show 10 entries			
Coordinate (0-based)	dbSNP ID	? Regulome DB Score	Other Resources
chr6:31243169	rs3132486	1f	<a href="#">UCSC</a>   <a href="#">ENSEMBL</a>   <a href="#">dbSNP</a>
chr6:31242673	rs3132489	5	<a href="#">UCSC</a>   <a href="#">ENSEMBL</a>   <a href="#">dbSNP</a>
chr6:31242858	rs3130693	5	<a href="#">UCSC</a>   <a href="#">ENSEMBL</a>   <a href="#">dbSNP</a>
chr6:31242816	rs6930376	6	<a href="#">UCSC</a>   <a href="#">ENSEMBL</a>   <a href="#">dbSNP</a>
chr6:31243388	rs3132485	No Data	<a href="#">UCSC</a>   <a href="#">ENSEMBL</a>   <a href="#">dbSNP</a>
chr6:31243409	rs3132484	No Data	<a href="#">UCSC</a>   <a href="#">ENSEMBL</a>   <a href="#">dbSNP</a>

Showing 1 to 6 of 6 entries

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... can be very large and may span a very large distance.


[illegible]

**Average number of perfect proxies for AID-associated lead SNPs = 7.6**



# Interpretation of GWAS Findings: ssSNP Sets

 a database for curated regulatory SNPs  
*Experimental evidences, multiple types of regulation, & rSNP and its LD-proxies*



Home Search Data content Tutorial About Us Feedback

Search Result

SNP annotations

Total count: 1

SNP_ID	rSNP	LD-proxy of rSNP( $r^2 > 0.8$ )	Proximal regulation	Distal regulation	miRNA regulation	RNA binding protein mediated regulation	eQTL
rs3131622	no	no	no	no	no	no	yes

SNP_ID	rSNP	LD-proxy of rSNP( $r^2 > 0.8$ )	Proximal regulation	Distal regulation	miRNA regulation	RNA binding protein mediated regulation	eQTL
rs388629	no	no	no	no	no	no	yes

SNP_ID	rSNP	LD-proxy of rSNP( $r^2 > 0.8$ )	Proximal regulation	Distal regulation	miRNA regulation	RNA binding protein mediated regulation	eQTL
rs6531	no	no	no	no	no	no	yes

rSNPBase informs about the presence of a regulatory SNP among the statistically similar SNP set.



# GWAS Results and HLA Types

IHWG-ID	CELL LINE	ST	CEH	Population	ST53_012	rs2395185_A	rs722788_C	rs406113_C
9026	YAR	53	38.1	Ashkenazi Jewish	2	2	0	0
9027	PF97387	53	44.2+44.X	French	2	2	0	0
9028	PE117	53	60.1+XX.X	Amerindian	2	2	0	2
9031	BOLETH BO	53	62.1	Scandinavian	2	2	0	0
9047	PLH	53	47.1	Scandinavian	2	2	1	2
9048	LBUF	53	13.1	English	2	2	0	0
9050	MOU-MANN	53	44.3	Scandinavian	2	2	0	0
9051	PITOUT	53	44.2	South African White	2	2	0	0
9052	DBB	53	57.1	USA White	2	2	0	0
9090	AWELLS	53	44.1	Australian Caucasoid	2	2	0	0
9092	BM92	53	51.1	Italian	2	2	0	0
9093	BER	53	13.1	German	2	2	0	0
9094	CF996	53	64.1	French	2	2	1	1
9098	MT14B	53	60.1	Australian Caucasoid	2	2	1	1
9106	MANIKA	53	50.1 (H)	Tamil Asian Indian	2	2	.	2
9107	KT3, LKT3	53	54.1	Japanese	2	2	0	0
9139	WHONP439	53	46.1	Asian	2	2	0	0
9140	WHO-NP192	53	54.1+46.1	Asian	2	2	0	0
9145	FUR, RE	52,53	57.1+60.3	White	1	1	1	1
9146	COL, E	53	62.2	Unknown	2	2	0	0
9150	BOW, MF	53,53	44.1+50.1	Unknown	2	2	1	1
9151	EAV, AC	53,10	37.1+50.1	Unknown	1	1	0	0

rs2395185 is a marker for the HLA-DR53 lineage, which has unique immunological characteristics.

## CORRESPONDENCE



Re: Genome-Wide Association Study of Classical Hodgkin Lymphoma and Epstein-Barr Virus Status-Defined Subgroups

AMY E. KENNEDY  
SANDEEP K. SINGH  
M. TEVFIK DORAK

JNCI

Vol. 104, Issue 11 | June 6, 2012



# GWAS Results and HLA Types

B	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ	AK	AL	AM	AN	AO
IHWG #	rs6923504_G	HLA-A 1	HLA-A 2	HLA-B 1	HLA-B 2	HLA-C 1	HLA-C 2	HLA-DRB1 1	HLA-DRB1 2	HLA-DRB3 1	HLA-DRB3 2	HLA-DRB4 1	HLA-DRB5 1	HLA-DQA1 1	HLA-DQA1 2	HLA-DQB1 1	HLA-DQB1 2
9008	2	A*2501	A*2501	B*1801	B*1801	Cw*12030101	Cw*12030101	DRB1*1501	DRB1*1501	.	.	.	.	DRB5*0101	DQA1*010201	DQA1*010202	DQB1*0602
9009	2	A*010101	A*010101	B*370101	B*370101	Cw*06020101	Cw*06020101	DRB1*160101	DRB1*160101	.	.	.	.	DRB5*0202	DQA1*010202	DQA1*010201	DQB1*050201
9010	2	A*68020101	A*68020101	B*530101	B*530101	C*040101	C*040101	DRB1*1503	DRB1*1503	.	.	.	.	.	DQA1*010201	DQA1*010201	DQB1*0602
9012	2	A*0201	A*0201	B*5701	B*5701	Cw*0701	Cw*0701	DRB1*1601	DRB1*1601	.	.	.	.	.	DQA1*010202	DQA1*010202	DQB1*0502
9014	2	A*2601	A*2601	B*0801	B*0801	Cw*070101	Cw*070101	DRB1*150101	DRB1*150101	.	.	.	.	DRB5*010101	DQA1*010201	DQA1*010201	DQB1*0602
9015	2	A*02:01:01	A*02:01:01	B*27:05:02	B*27:05:02	C*02:02:02	C*02:02:02	DRB1*16	DRB1*16	.	.	.	.	.	.	.	.
9016	2	A*0204	A*0204	B*510101	B*510101	Cw*1502	Cw*1502	DRB1*160201	DRB1*160201	.	.	.	.	DRB5*0202	.	.	DQB1*0301
9017	2	A*0301	A*0301	B*070201	B*070201	Cw*070201	Cw*070201	DRB1*150101	DRB1*150101	.	.	.	.	DRB5*0101	DQA1*01:02:01	DQA1*01:02:01	DQB1*0602
9019	2	A*3002	A*3002	B*1801	B*1801	Cw*0501	Cw*0501	DRB1*0301	DRB1*0301	DRB3*0202	.	.	.	.	DQA1*050101	DQA1*050101	DQB1*0201
9020	2	A*2601	A*2601	B*1801	B*1801	Cw*0501	Cw*0501	DRB1*0301	DRB1*0301	DRB3*020201	.	.	.	.	DQA1*050101	DQA1*050101	DQB1*0201
9036	2	A*0201	A*0201	B*4402	B*4402	Cw*0501	Cw*0501	DRB1*1101	DRB1*1101	DRB3*0202	.	.	.	.	DQA1*010202	DQA1*010202	DQB1*0502
9039	2	A*0201	A*0201	B*1801	B*1801	Cw*0501	Cw*0501	DRB1*1102	DRB1*1102	DRB3*0202	.	.	.	.	DQA1*0505	DQA1*0505	DQB1*0301
9041	2	A*0101	A*0101	B*3502	B*3502	Cw*0401	Cw*0401	DRB1*1104	DRB1*1104	DRB3*0202	.	.	.	.	DQA1*0501	DQA1*0501	DQB1*0301
9042	2	A*24020101	A*24020101	B*350801	B*350801	Cw*0401	Cw*0401	DRB1*1103	DRB1*1103	DRB3*0202	.	.	.	.	DQA1*0505	DQA1*0505	DQB1*0301
9043	2	A*0101	A*0101	B*4101	B*4101	Cw*1701	Cw*1701	DRB1*1101	DRB1*1101	DRB3*0202	.	.	.	.	DQA1*0505	DQA1*0505	DQB1*0301
9060	2	A*0101	A*0101	B*1501	B*1501	Cw*0303	Cw*0303	DRB1*1301	DRB1*1301	DRB3*0202	.	.	.	.	DQA1*0103	DQA1*0103	DQB1*060301
9066	2	A*0207	A*0207	B*460101	B*460101	C*01:02	C*01:02	DRB1*08:03:02	DRB1*08:03:02	.	.	.	.	.	DQA1*01:03	DQA1*01:03	DQB1*06:01
9070	2	A*02:01	A*02:01	B*51:01	B*51:01	C*14:02:01	C*14:02:01	DRB1*08:03:02	DRB1*08:03:02	.	.	.	.	.	DQA1*04:01	DQA1*06:01:01	DQB1*03:01:01
9081	2	A*0301	A*0301	B*070201	B*070201	Cw*070201	Cw*070201	DRB1*1501	DRB1*1501	.	.	.	.	DRB5*0101	DQA1*01:02:01	DQA1*01:02:01	DQB1*0602
9084	2	A*0201	A*0201	B*4002	B*4002	Cw*020202	Cw*020202	DRB1*1601	DRB1*1601	.	.	.	.	.	DQA1*010202	DQA1*010202	DQB1*0502
9104	2	A*3101	A*3101	B*38:01	B*38:01	C*12:03	C*12:03	DRB1*11	DRB1*11	.	.	.	.	.	.	.	.
9105	2	A*0101	A*0101	B*3502	B*3502	Cw*0401	Cw*0401	DRB1*110401	DRB1*110401	DRB3*0202	.	.	.	.	DQA1*0103	DQA1*0103	DQB1*060301
9157	2	A*33	A*33	B*5801	B*58	Cw*0302	Cw*0302	DRB1*0301	DRB1*0301	DRB3*02	.	.	.	.	DQA1*0501	DQA1*0501	DQB1*0201
9291	2	A*01:01:01:0	A*01:01:01:0	B*40:01:01	B*40:01:01	C*06:02:01:01	C*06:02:01:01	DRB1*13:01:01	DRB1*13:01:01	.	.	.	.	.	DQA1*01:03	DQA1*01:03	DQB1*06:03:01

rs6923504

IHWG #	CELL LINE	ST	CEH	Population
9008	DO208915	51	18.1	Australian Caucoid
9009	KAS011	51		Yugoslavian
9010	AMAI	51		Algerian
9012	WJR076	51		USA White
9014	MGAR	51		USA Hispanic
9015	WT24	51		Italian
9016	RML REM	51		South American Indian
9017	WT8	51		Italian
9019	DUCAF	52	18.2	French
9020	QBL	52	18.2	Dutch
9036	SPO010	52		Italian
9039	JVM	52	18.3	Dutch
9041	J0528239	52	35.5	Italian
9042	TISI	52	35.4	French
9043	BM21	52		Italian
9060	CB6B-CGB1B	52	62.3	Australian Caucoid
9066	TAB089,TAB	08	46.2	Japanese
9070	LUY	08		Dutch
9081	EA	51	7.1	Scandinavian
9084	CALOGERO	51	.	Italian
9104	DHIF	52	.	English
9105	FPAF PPF F	52	35.5?	Ashkenazi Jewish
9157	HAU, ML	52	58.1	Asian
9291	APD	52	.	Dutch



# HLA Region SNPs and HLA Types

ASHI 2015

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UNIVERSITY OF MIAMI  
MILLER SCHOOL OF MEDICINE  
JOHN P. HUSSMAN INSTITUTE  
for HUMAN GENOMICS

## A Catalog of HLA Region SNPs with Functional Annotations, Disease Associations and Correlations with HLA Types

Amy E. Kennedy <sup>1</sup>, Sushmita Mustafi <sup>2</sup>, Sandeep K. Singh <sup>2</sup>, Ioanna Konidari <sup>3</sup>,  
Jacob L. McCauley <sup>3</sup>, Alejandro M. Barbieri <sup>2</sup>, Mehmet T. Dorak <sup>4</sup>

<sup>1</sup> National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; <sup>2</sup> Florida International University, Miami, FL, USA; <sup>3</sup> John P. Hussman Institute for Human Genomics, University of Miami, Miami, FL, USA;  
<sup>4</sup> Liverpool Hope University, Liverpool, UK



This resource is available on request and will be online in 2016

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Cut Copy			A A			Wrap Text			%		Format Cell		Sort & Find		Filter & Select	
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R25 2																
B	C	D	E	F	G	H	I	J	K	L	M	N	O	P		
1	CELL LINE	ST	CEH	Population	rs272788_C	rs406113_C	rs11757235_A	rs445870_G	rs13215054_A	rs6456825_G	rs414745_C	rs418092_A	rs450630_A	rs370520_A	rs17336532_A	
2	SA	01	7.2	Japanese	1	2	1	2	0	2	0	0	2	2	0	
3	MZO70782	01	65.1?	Ashkenazi Jewish	0	0	0	0	0	0	0	0	0	0	0	
4	KAS116	01	.	Yugoslavian	0	0	0	0	0	0	0	0	0	0	0	
5	JESTHOM	01	.	Scandinavian	0	2	0	2	0	2	0	0	2	2	0	
6	HOM2	01	.	Canadian	0	0	0	0	0	0	0	0	0	0	0	
7	WT100BIS	01	35.2	Italian	0	0	0	0	0	0	0	0	0	0	0	
8	DO208915	51	18.1	Australian Caucasoid	0	0	0	0	0	0	0	0	0	0	0	
9	KAS011	51		Yugoslavian	0	0	0	0	2	2	2	2	2	2	2	
10	AMAI	51		Algerian	2	2	0	0	0	2	2	2	2	2	0	
11	E4181324	51	52.1?	Australian Caucasoid	0	0	0	0	2	2	2	2	2	2	2	
12	WJR076	51		USA White	0	1	0	1	1	2	1	1	2	2	1	
13	MGAR	51		USA Hispanic	0	0	0	0	0	0	0	0	0	0	0	
14	WT24	51		Italian	0	2	0	2	0	2	0	0	2	2	0	
15	RML REM	51		South American Indian	0	0	0	0	0	0	0	0	0	0	0	
16	WT8	51		Italian	2	2	2	2	0	0	0	0	0	0	0	
17	DUCAF	52	18.2	French	2	2	0	2	0	2	2	2	2	2	0	
18	QBL	52	18.2	Dutch	0	0	0	0	2	2	2	2	2	2	2	
19	RSH, RSHD	52	42.1	African Black	0	2	0	1	0	2	1	1	2	2	0	
20	COX	52	8.1	South African White	0	0	0	0	2	2	2	2	2	2	2	

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# HLA Region SNPs and HLA Types

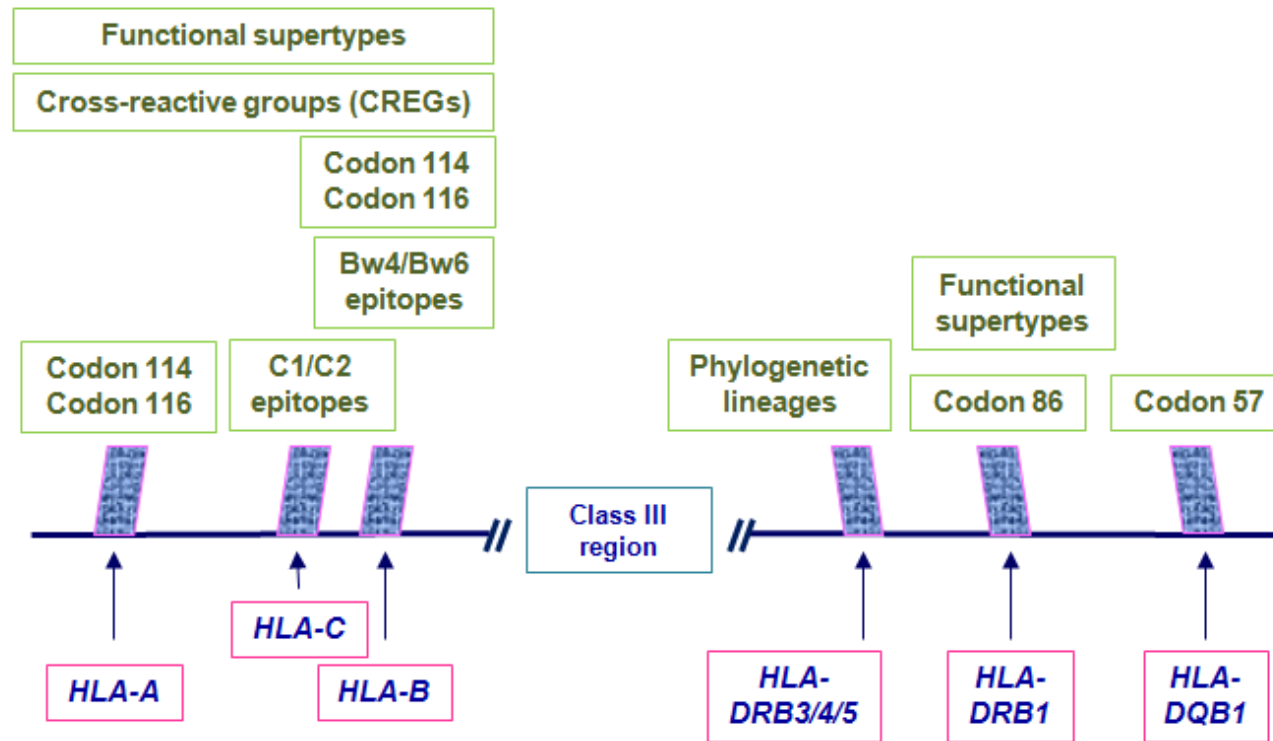
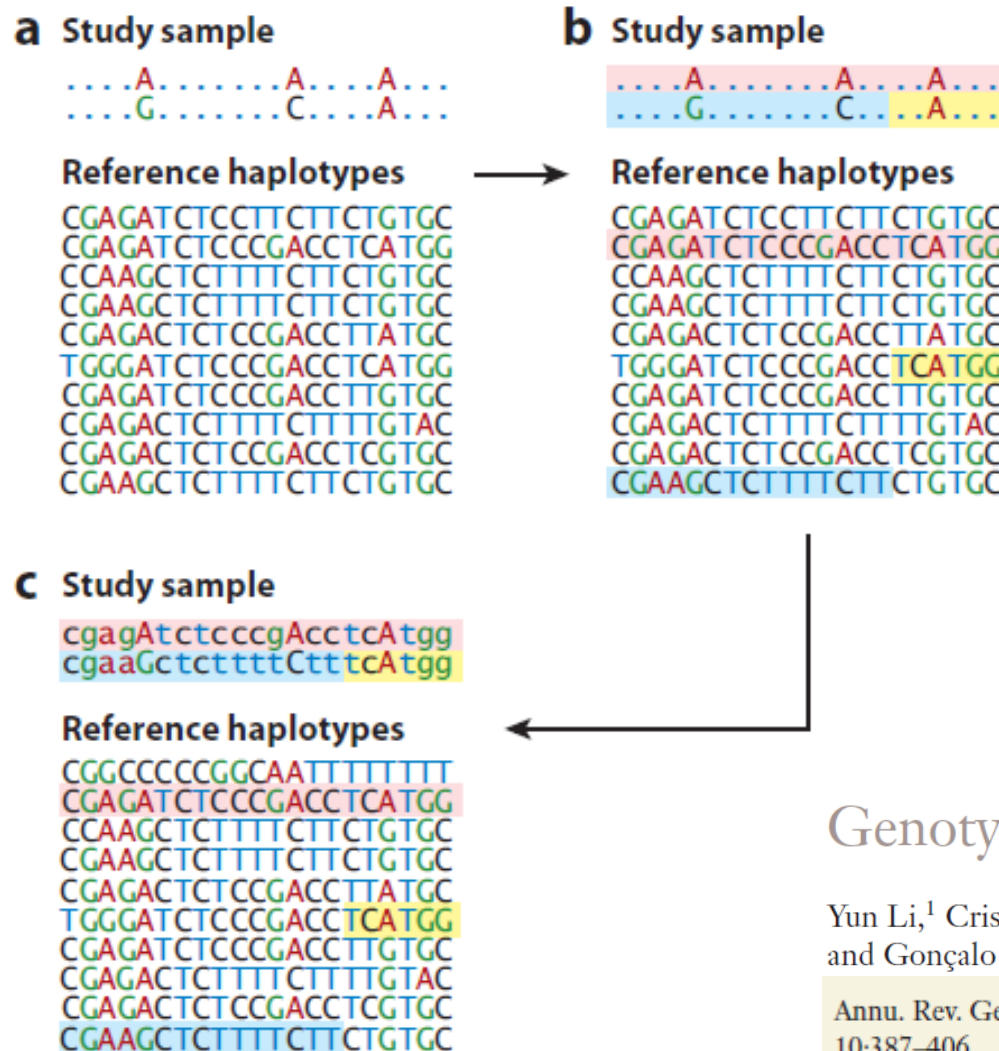


Figure 1. Functional multi-allelic HLA polymorphisms

We do not yet know the SNP equivalents of these functional groupings



# Existing GWAS results: What to do with them?



## Genotype Imputation

Yun Li,<sup>1</sup> Cristen Willer,<sup>1</sup> Serena Sanna,<sup>2</sup>  
and Gonçalo Abecasis<sup>1</sup>

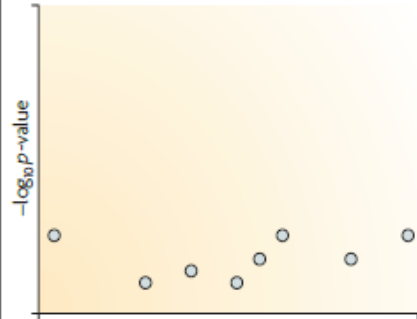
Annu. Rev. Genomics Hum. Genet. 2009.  
10:387–406



# Existing GWAS results: What to do with them?

## Box 1 | How genotype imputation works

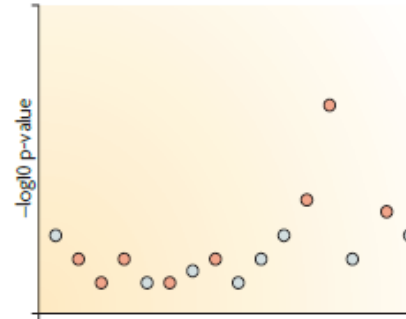
**b** Testing association at typed SNPs may not lead to a clear signal



**d** Reference set of haplotypes, for example, HapMap

0	0	0	0	1	1	1	0	0	1	1	1	1	1	0
1	1	1	1	1	1	1	0	0	1	0	0	1	1	1
1	1	1	1	1	0	1	0	0	1	0	0	0	1	0
0	0	1	0	1	1	1	0	0	1	1	1	1	1	0
1	1	1	0	1	1	0	0	1	1	1	0	1	1	0
0	0	1	0	1	1	1	0	0	1	1	1	1	1	0
1	1	1	1	1	0	1	0	0	1	0	0	0	1	0
1	1	1	0	0	1	0	0	1	1	1	0	1	1	0
0	0	0	0	1	1	1	0	0	1	1	1	1	1	0
1	1	1	0	0	1	0	0	1	1	1	0	1	1	0

**f** Testing association at imputed SNPs may boost the signal



**a** Genotype data with missing data at untyped SNPs (grey question marks)

1	?	?	?	1	?	1	?	0	2	2	?	?	?	2	?	0
0	?	?	?	2	?	2	?	0	2	2	?	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	?	2	?	0
1	?	?	?	2	?	1	?	1	2	2	?	?	?	2	?	0
2	?	?	?	2	?	2	?	1	2	1	?	?	?	2	?	0
1	?	?	?	1	?	1	?	1	2	2	?	?	?	2	?	0
1	?	?	?	2	?	2	?	0	2	1	?	?	?	2	?	1
2	?	?	?	1	?	1	?	1	2	1	?	?	?	2	?	1
1	?	?	?	0	?	0	?	2	2	2	?	?	?	2	?	0

**c** Each sample is phased and the haplotypes are modelled as a mosaic of those in the haplotype reference panel

0	?	?	?	1	?	1	?	0	1	1	?	?	1	?	0
1	?	?	?	1	?	1	?	0	1	1	?	?	1	?	0
1	?	?	?	1	?	1	?	0	1	0	?	?	1	?	0
1	?	?	?	1	?	1	?	1	1	1	?	?	1	?	0
1	?	?	?	0	?	0	?	1	1	1	?	?	1	?	0
0	?	?	?	0	?	0	?	1	1	1	?	?	1	?	0

**e** The reference haplotypes are used to impute alleles into the samples to create imputed genotypes (orange)

1	1	1	1	1	2	1	0	0	2	2	0	2	2	2	2	0
0	0	1	0	2	2	2	0	0	2	2	2	2	2	2	2	0
1	1	1	1	2	2	2	0	0	2	1	1	2	2	2	2	0
1	1	2	0	2	2	1	0	1	2	2	1	2	2	2	2	0
2	2	2	2	2	1	2	0	1	2	1	1	2	2	2	2	0
1	1	1	0	1	2	1	0	1	2	2	1	2	2	2	2	0
1	1	2	1	2	1	2	0	0	2	1	1	1	2	1	1	1
2	2	2	1	1	1	1	0	1	2	1	0	1	2	1	1	1
1	2	2	0	0	2	0	0	2	2	2	1	2	2	2	0	0

## GENOME-WIDE ASSOCIATION STUDIES

### Genotype imputation for genome-wide association studies

Jonathan Marchini\* and Bryan Howie†

NATURE REVIEWS | GENETICS

VOLUME 11 | JULY 2010 | 499



UNDER THE AUSPICES OF EUROPEAN FEDERATION FOR IMMUNOGENETICS

**ANNUAL EFI REGION 8 EPT MEETING**

5<sup>TH</sup> DECEMBER 2015 BUCHAREST



# Existing GWAS results: What to do with them?

BIOINFORMATICS

ORIGINAL PAPER

Vol. 27 no. 7 2011, pages 968–972  
doi:10.1093/bioinformatics/btr061

*Genetics and population analysis*

Advance Access publication February 7, 2011

## HLA\*IMP—an integrated framework for imputing classical HLA alleles from SNP genotypes

Alexander T. Dilthey<sup>1</sup>, Loukas Moutsianas<sup>1</sup>, Stephen Leslie<sup>1</sup> and Gil McVean<sup>1,2,\*</sup>

<sup>1</sup>Department of Statistics, University of Oxford, 1 South Parks Road, Oxford OX1 3TG and <sup>2</sup>Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Oxford OX3 7BN, UK

Associate Editor: Jeffrey Barrett

### HLA\*IMP

#### Welcome!

**Important information:** Affymetrix has exclusively licensed the HLA\*IMP algorithm from Peptide Groove and provides HLA\*IMP-based HLA type imputation for Affymetrix arrays and other platforms. For more information, please visit <http://www.affymetrix.com> or contact Affymetrix at [Bioinformatics\\_services@affymetrix.com](mailto:Bioinformatics_services@affymetrix.com).



# Existing GWAS results: What to do with them?

**Functional annotations and pathway analysis**

**\*\*\*\*\***

**Impute missing SNPs**

**Impute HLA types**

**Infer HLA functional groupings**

**Repeat association analysis for all SNPs, HLA types, supertypes, epitopes, dimorphisms and lineages**



# CONCLUSIONS

- > Besides mismatches, there are also associations of donor or recipient genotypes with transplant outcomes**
- > Reported associations should be combined with their statistically similar SNP sets (proxies) for functional annotations**
- > The nearest genes are not always the target genes for SNP effects**
- > The most common intermediate phenotype is gene expression changes (eQTL effects) between SNPs and their effect on phenotypes**
- > GVHD-associated SNPs are also associated with autoimmune disorders as previously suspected**
- > There is much more work to do with the HLA region results**



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UNDER THE AUSPICES OF EUROPEAN FEDERATION FOR IMMUNOGENETICS  
**ANNUAL EFI REGION 8 EPT MEETING**  
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