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

5TH DECEMBER 2015 BUCHAREST

Session I - Chairmen: Elissaveta Naumova, Amal Bishara

09.10-09.40	Interpretation of GWAS findings in transplant outcome studies Mehmet Tevfik 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?

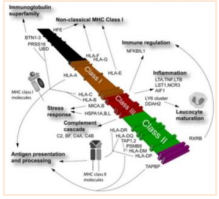
Genetic prediction of transplant outcomes

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%

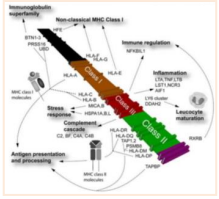
Generally contains common polymorphisms

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

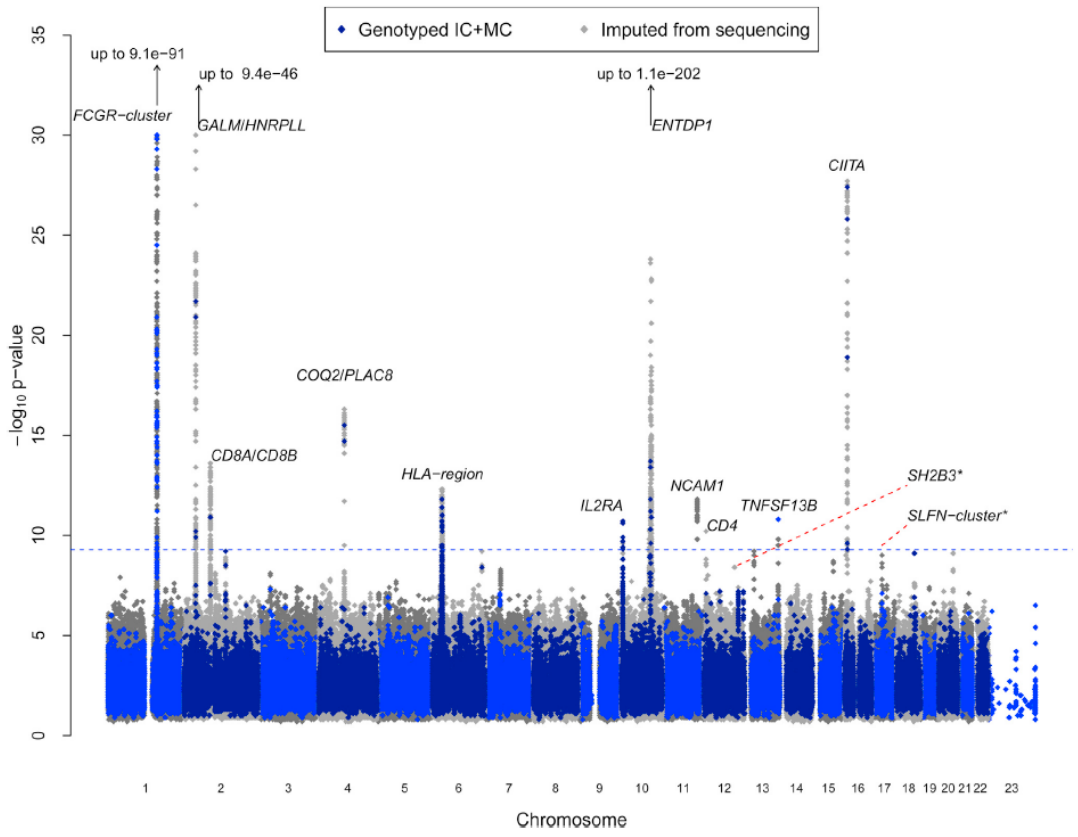


Figure 3. Manhattan Plot of Best p Values

For each SNP, the best p value observed among all assessed traits is plotted on a –log10 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 (5.26×10^{-10}). The best candidate gene is indicated near the peak. Loci below the significance threshold and previously described are marked with an asterisk.

Cell

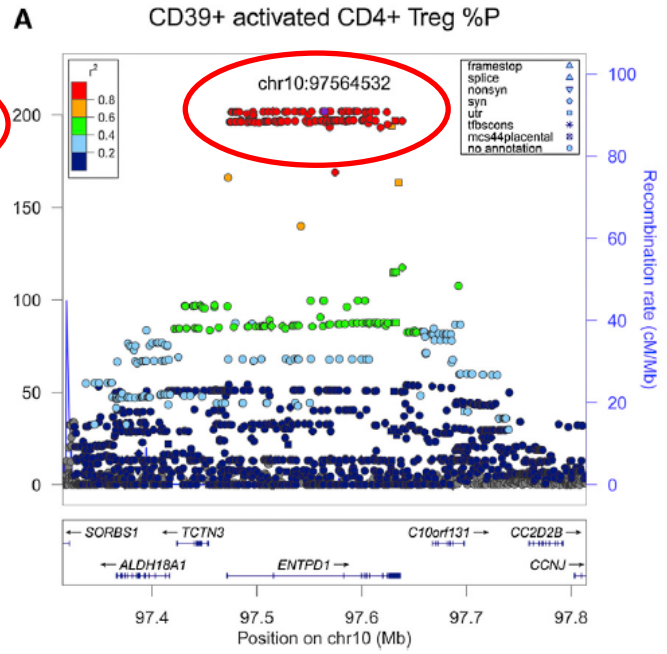
Resource

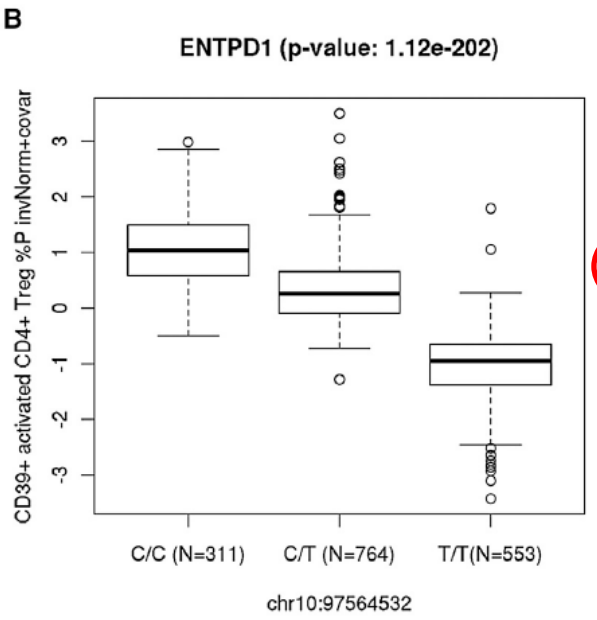
Genetic Variants Regulating Immune Cell Levels in Health and Disease

Valeria Orrú,[1,12] Maristella Steri,[1,12] Gabriella Sole,[1] Carlo Sidore,[1,2,3] Francesca Virdis,[1] Mariano Dei,[1] Sandra Lai,[1] Magdalena Zoledziewska,[1] Fabio Busonero,[1] Antonella Mulas,[1,3] Matteo Floris,[4] Wieslawa I. Mentzen,[1] Silvana A.M. Urru,[4] Stefania Olla,[1] Michele Marongiu,[1] Maria G. Piras,[1] Monia Lobina,[1,3] Andrea Maschio,[1,2] Maristella Pitzalis,[1] Maria F. Urru,[4] Marco Marcelli,[4] Roberto Cusano,[1,4] Francesca Deidda,[1,4] Valentina Serra,[1,3] Manuela Oppo,[4] Rosella Pilu,[1,4] Frederic Reinier,[5] Riccardo Berutti,[1,4] Luca Pireddu,[1,3] Ilenia Zara,[4] Eleonora Porcu,[1,3] Alan Kwong,[1] Christine Brennan,[11] Brendan Tarrier,[11] Robert Lyons,[11] Hyun M. Kang,[6] Sergio Uzzau,[3,5] Rossano Atzeni,[4] Maria Valentini,[4] Davide Firinu,[7] Lidia Leoni,[4] Gianluca Rotta,[8] Silvia Naitza,[1] Andrea Angius,[1,4] Mauro Congia,[9] Michael B. Whalen,[1] Chris M. Jones,[4] David Schlessinger,[10] Gonçalo R. Abecasis,[2] Edoardo Fiorillo,[1,12,*] Serena Sanna,[1,12,*] and Francesco Cucca[1,3,12,*]

GWAS Results

Lead SNP and perfect proxies





eQTLeffect

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 –log10 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

Lead SNP

Perfect Proxy

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^2 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^{-91}	chr1:161515326/ rs55971447	0.937	6.83×10^{-129}
2	*HNRPLL(p)*	chr2:38792045/ rs183949931	T/C	0.967	CD45RA− CD28− CD8br %P	0.778 (0.105)	4.05	1.05×10^{-13}	chr2:38792045/ rs183949931	same SNP	1.046×10^{-20}
2	*GALM(p,c,e), HNRPLL(b)*	chr2:38897074/ rs13011383	G/A	0.730	TD CD4+ %GP	−0.371 (0.042)	5.52	6.05×10^{-19}	chr2:38886041/ rs4670262	0.87	1.26×10^{-27}
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^{-46}	chr2:38932777/ rs4670265	0.9	2.82×10^{-62}
3	*CD8A(p,c,o), RMND5A(p), CD8B(b), VPS24(e)*	chr2:87014377/ rs2944254	C/T	0.810	CD4+ CD8dim AC	0.383 (0.05)	4.55	2.52×10^{-14}	chr2:87018547/ rs3810831	0.943	1.3×10^{-22}
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^{-17}	chr4:84179071/ rs7667017	0.84	3.37×10^{-23}
5	*HLA-E(p,c,e), HCG27(e), GNL1(c), ABCF1(e), C2(e), PSORS1C3(e), RPP21(e), TRIM39(e), ZKSCAN2(e)*	chr6:29466505/ rs117765619	G/T	0.516	CD45RA− CD8+ AC	−0.228 (0.037)	2.62	5.24×10^{-10}	chr6:30483993/ rs2534812	0.974	1.34×10^{-11}
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^{-12}	chr6:31327382/ rs2395476	same SNP	1.827×10^{-19}
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), HMGA1(e), RPL34(e)[a], AOAH(e)[a]*	chr6:32386433/ rs113534101	G/A	0.776	CD4+ CD8dim %P	−0.299 (0.043)	3.07	5.68×10^{-12}	chr6:32382138/ rs115615758	0.97	2.78×10^{-16}
5	*HLA-DRA(p), LOC642073(e), HLA-DOB(e), RPL34(e)[a], ARHGAP24(e)[a], AOAH(e)[a]*	chr6:32428186/ rs6923504	G/C	0.618	CD45RA− CD28− CD8+ AC	−0.249 (0.037)	3.01	2.81×10^{-11}	chr6:32428285/ rs6903608	0.99	4.3×10^{-13}
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^{-11}	chr10:6094697/ rs61839660	same SNP	5.65×10^{-23}
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^{-10}	chr10:6158412/ rs8463	same SNP	2.02×10^{-15}
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^{-25}	chr10:97331958/ rs7099430	0.969	1.32×10^{-35}
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^{-20}	chr10:97550405/ rs11188485	0.97	2.97×10^{-32}
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^{-202}	chr10:97515137/ rs3814159	0.993	7.05×10^{-327}
7	*ZNF518A(p), BLNK(p,o), ENTPD1(b)*	chr10:97932006/ rs117592294	C/T	0.955	CD39+ CD25hi CD4+ %P	0.497 (0.066)	4.33	6.26×10^{-14}	chr10:97932006/ rs117592294	same SNP	1.35×10^{-15}

(Continued on next page)

GWAS Results

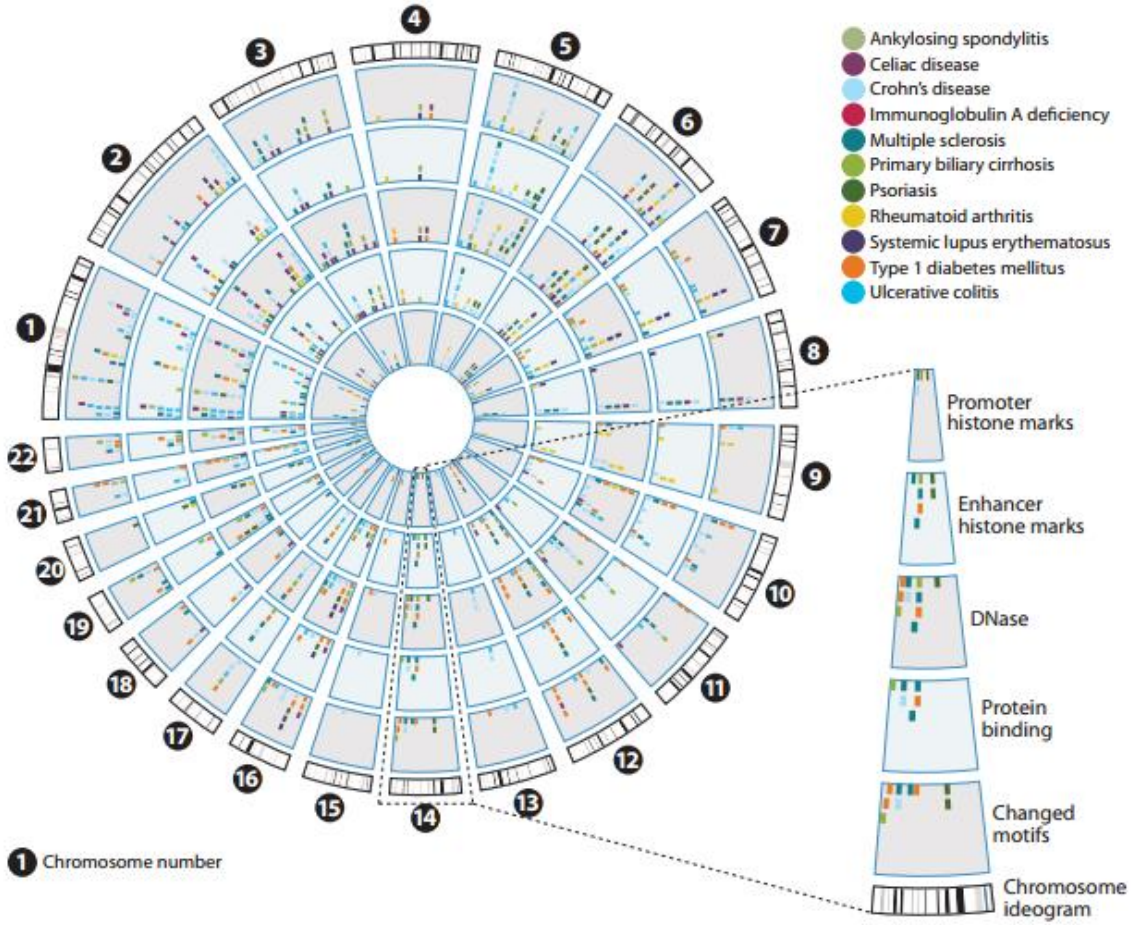


Figure 2
Characterization of variants associated with immune-mediated diseases. (*a*) Circos plot summarizing the functional annotation of the associated GWAS single-nucleotide polymorphisms (SNPs) for the GWAS loci present in Caucasian populations. From inner to outer rings: promoter histone marks, 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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Liverpool Hope University EST. 1844

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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)

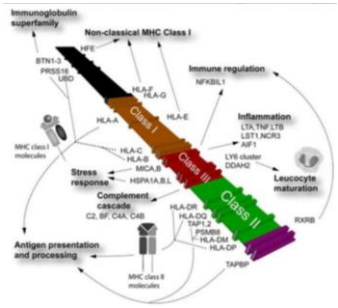
Lead SNPs and causal SNPs are not necessarily in tight LD (r^2 = 0.50 is not unusual)

Almost all causal SNPs map to enhancers and promoters

Genetic and epigenetic fine mapping of causal autoimmune disease variants

Kyle Kai-How Farh[1,2*], Alexander Marson[3*], Jiang Zhu[1,4,5,6], Markus Kleinewietfeld[1,7†], William J. Housley[7], Samantha Beik[1], Noam Shoresh[1], Holly Whitton[1], Russell J. H. Ryan[1,5], Alexander A. Shishkin[1,8], Meital Hatan[1], Marlene J. Carrasco-Alfonso[9], Dita Mayer[9], C. John Luckey[9], Nikolaos A. Patsopoulos[1,10,11], Philip L. De Jager[1,10,11], Vijay K. Kuchroo[12], Charles B. Epstein[1], Mark J. Daly[1,2], David A. Hafler[1,7§] & Bradley E. Bernstein[1,4,5,6§]

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

Science Translational Medicine AAAS

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	Donor genotype	1.72×10^{-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	Donor genotype	2.34×10^{-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	Patient genotype	7.48×10^{-5}	**CC**	1254/1909	1	
					AC	201/296	1.11 (0.94-1.31)	.23
					AA	18/19	3.47 (1.95-6.16)	2.27×10^{-5}
Disease-free survival‡	rs429916	1.2 kb centromeric of HLA-DOA	Patient genotype	4.28×10^{-5}	**CC**	1147/1708	1	
					AC	188/268	1.06 (0.88-1.26)	.56
					AA	18/19	3.75 (2.10-6.68)	7.86×10^{-6}
Relapse‡	rs2244546	2.2 kb telomeric of HCP5	Donor genotype	6.92×10^{-4}	**CC**	373/1611	1	
					CG	117/435	1.19 (0.95-1.50)	.14
					GG	16/30	2.79 (1.60-4.85)	2.87×10^{-4}
	rs986522	COL11A2, intron	Donor genotype	3.20×10^{-5}	**CG**	209/1025	1	
					CC	136/478	1.46 (1.16-1.85)	1.45×10^{-3}
					GG	161/573	1.62 (1.30-2.03)	2.14×10^{-5}
Transplant-related mortality	rs915654	1.4 kb telomeric of LTA	Patient genotype	9.93×10^{-5}	**AT**	394/964	1	
					AA	142/300	1.45 (1.16-1.80)	1.16×10^{-3}
					TT	332/718	1.39 (1.17-1.64)	1.43×10^{-4}
	rs429916	1.2 kb centromeric of HLA-DOA	Patient genotype	2.82×10^{-5}	**CC**	720/1696	1	
					AC	134/267	1.20 (0.97-1.49)	9.67×10^{-2}
					AA	14/19	4.52 (2.31-8.86)	1.11×10^{-5}
Grades II-IV acute GVHD§	rs2242656	BAG6, intron	Mismatch	3.13×10^{-4}	**Matched**	865/1535	1	
					HVG	122/214	1.00 (0.82-1.22)	1
					GVH	136/203	1.46 (1.21-1.77)	6.92×10^{-5}
Grades III-IV acute GVHD	rs209130	3 kb telomeric of TRIM27	Mismatch	6.42×10^{-5}	**Matched**	251/920	1	
					HVG	154/488	1.22 (0.99-1.50)	6.11×10^{-2}
					GVH	124/420	1.19 (0.96-1.49)	.12
					Bi	45/103	2.17 (1.56-3.01)	3.70×10^{-6}
	rs2075800	HSPA1L, Glu602Lys	Patient genotype	8.37×10^{-4}	GG	289/848	1	
					AG	214/819	0.72 (0.60-0.86)	4.01×10^{-4}
					AA	71/264	0.73 (0.56-0.95)	2.07×10^{-2}
	rs394657	NOTCH4, intron	Donor genotype	4.15×10^{-4}	**AA**	150/626	1	
					AG	301/923	1.48 (1.21-1.81)	1.16×10^{-4}

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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.[31] 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.[32] 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-α, IFN-γ, IL-4, and IL-17.[33] Alternatively, SNP rs394657 might influence GVHD through its role as a putative expression quantitative locus for HLA-DQA1,[34] the gene that encodes the DQα chain of the HLA-DQ heterodimer. Differential DQα expression may have consequences for alloantigen recognition in GVHD.

Interpretation of GWAS Findings: Individual SNPs

U.S. Department of Health & Human Services

NIH National Heart, Lung, and Blood Institute

GRASP Search - v2.0.0.0

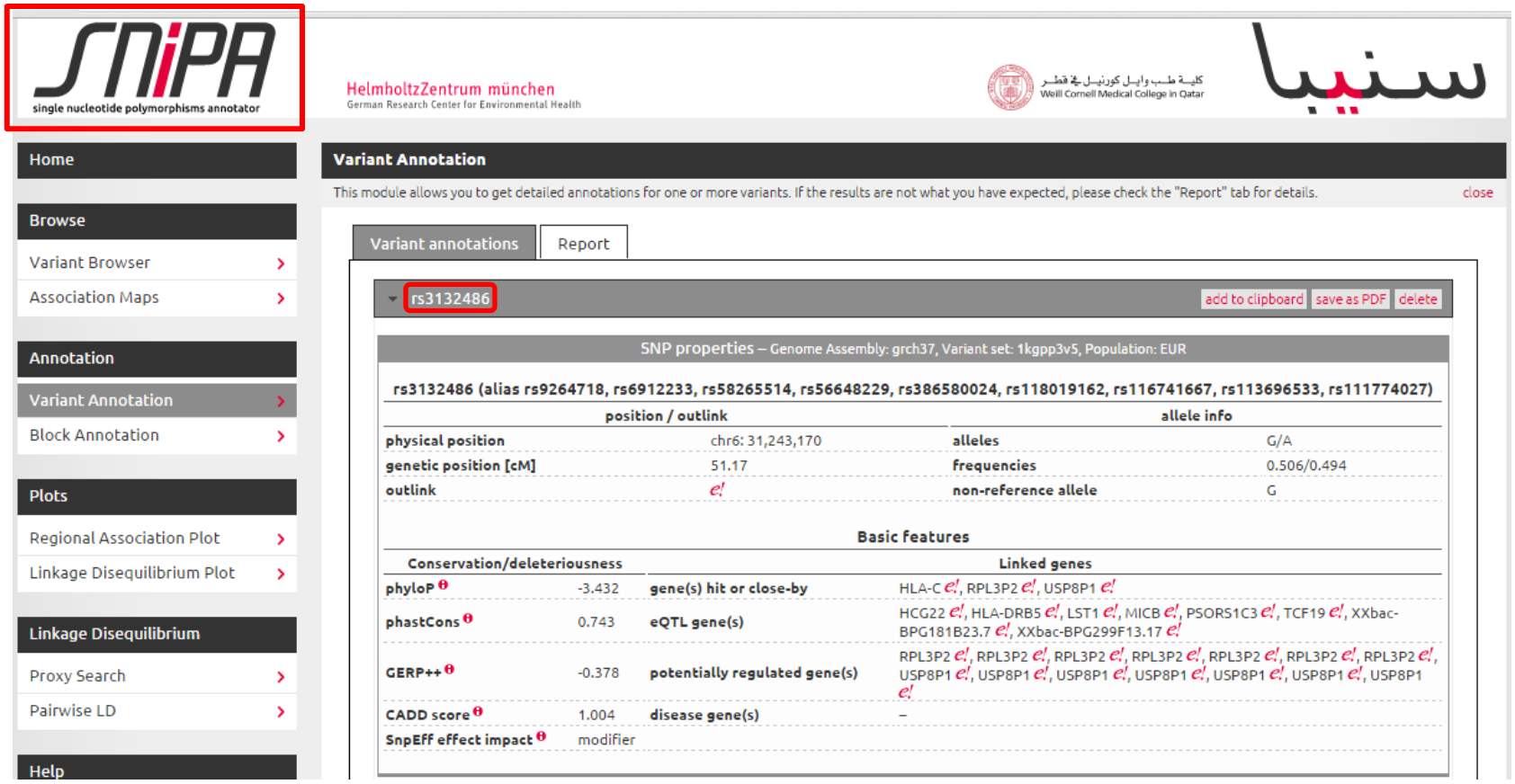
NHLBI key	Snp Id	Pvalue	PMID	Location	Phenotype	Phenotype Category	chr	pos	InGene
204538421544740	rs2075800	2.4E-100	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
175543002216079	rs3132486	3.3E-63	17554300	Webdata	Type 1 diabetes, combined control dataset	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	17554300	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	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31275393	
195030881544734	rs2075800	8.3E-36	19503088	Table S2	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
211567611544753	rs2075800	1.3E-31	21156761	Table S3	Rheumatoid arthritis (ACPA-positive)	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
178048361544730	rs2075800	2.0E-29	17804836	RawUna...	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31810169	(HSPA1L)
21323541273999	rs394657	8.2E-17	21323541	Table S6	Idiopathic membranous nephropathy	Renal	6	32219246	(NOTCH4)
176325452216080	rs3132486	1.1E-16	17632545	TableS1	Type 1 diabetes	Type 1 diabetes (T1D),Developmental... risk factor (CVD RF)	6	31275393	
204538422097312	rs2859100	1.7E-16	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32731702	
234556366395722	rs394657	9.5E-11	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration (ARMD)	6	32219246	(NOTCH4)
20453842273995	rs394657	1.2E-09	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32219246	(NOTCH4)
176605302216081	rs3132486	2.9E-09	17660530	RawUna...	Multiple sclerosis	Neuro,Inflammation,... sclerosis (MS)	6	31275393	
19503088273993	rs394657	8.1E-08	19503088	Table S2	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32219246	(NOTCH4)
203831471544739	rs2075800	1.6E-07	20383147	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)

Liverpool Hope University EST. 1844

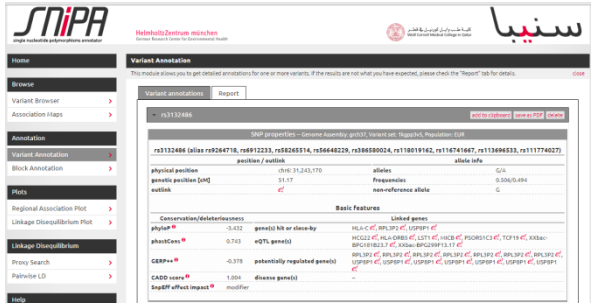
UNDER THE AUSPICES OF EUROPEAN FEDERATION FOR IMMUNOGENETICS
ANNUAL EFI REGION 8 EPT MEETING
5TH DECEMBER 2015 BUCHAREST

Interpretation of GWAS Findings: Individual SNPs



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

Interpretation of GWAS Findings: Individual SNPs



Your query: rs3132486

Trans-eQTLs

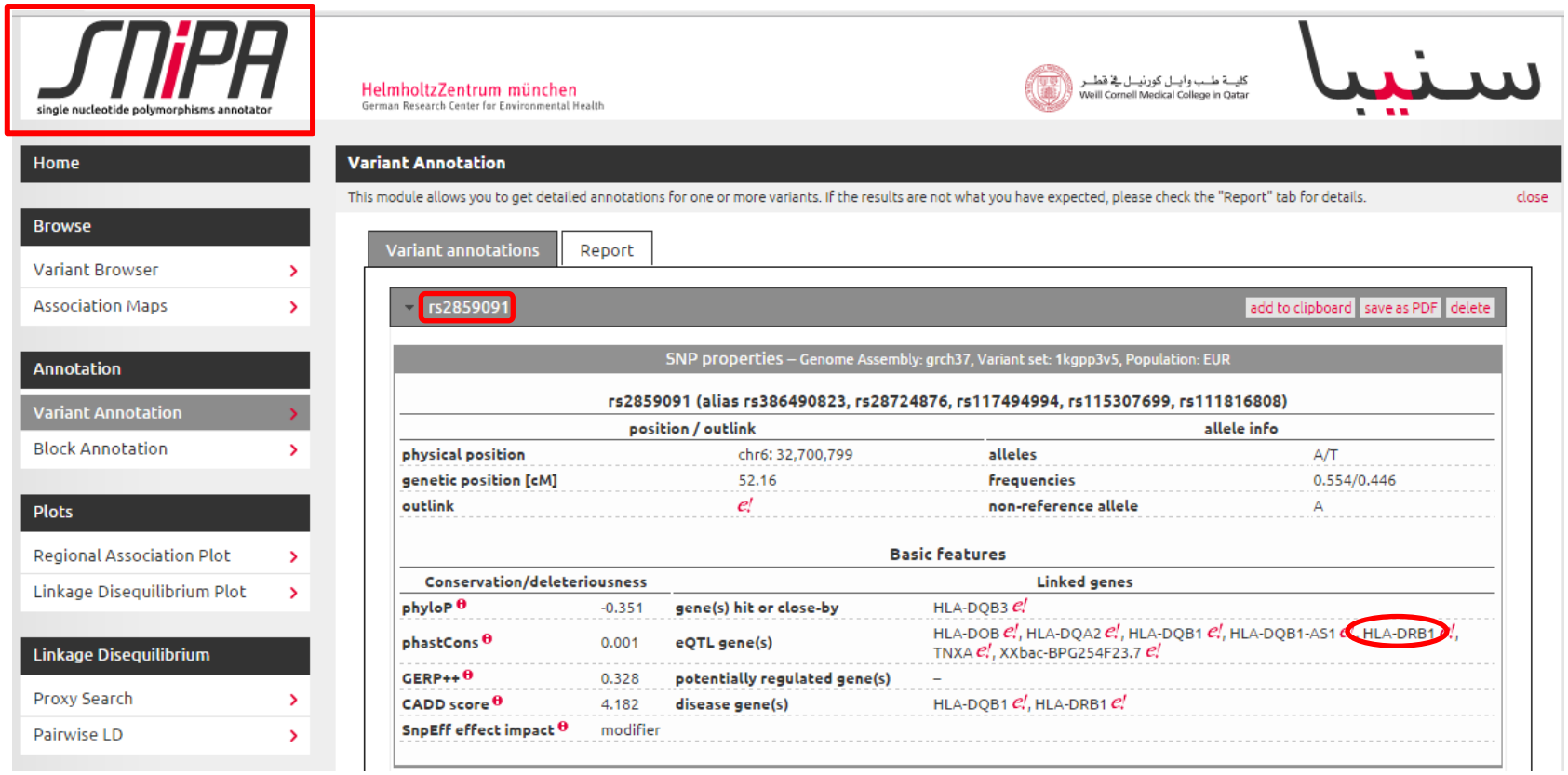
P-value SNP SNP Chr. SNP Chr. position Probe Probe Chr. Probe Chr. position SNP Alleles Minor Allele Z-score Gene name FDR

No records found.

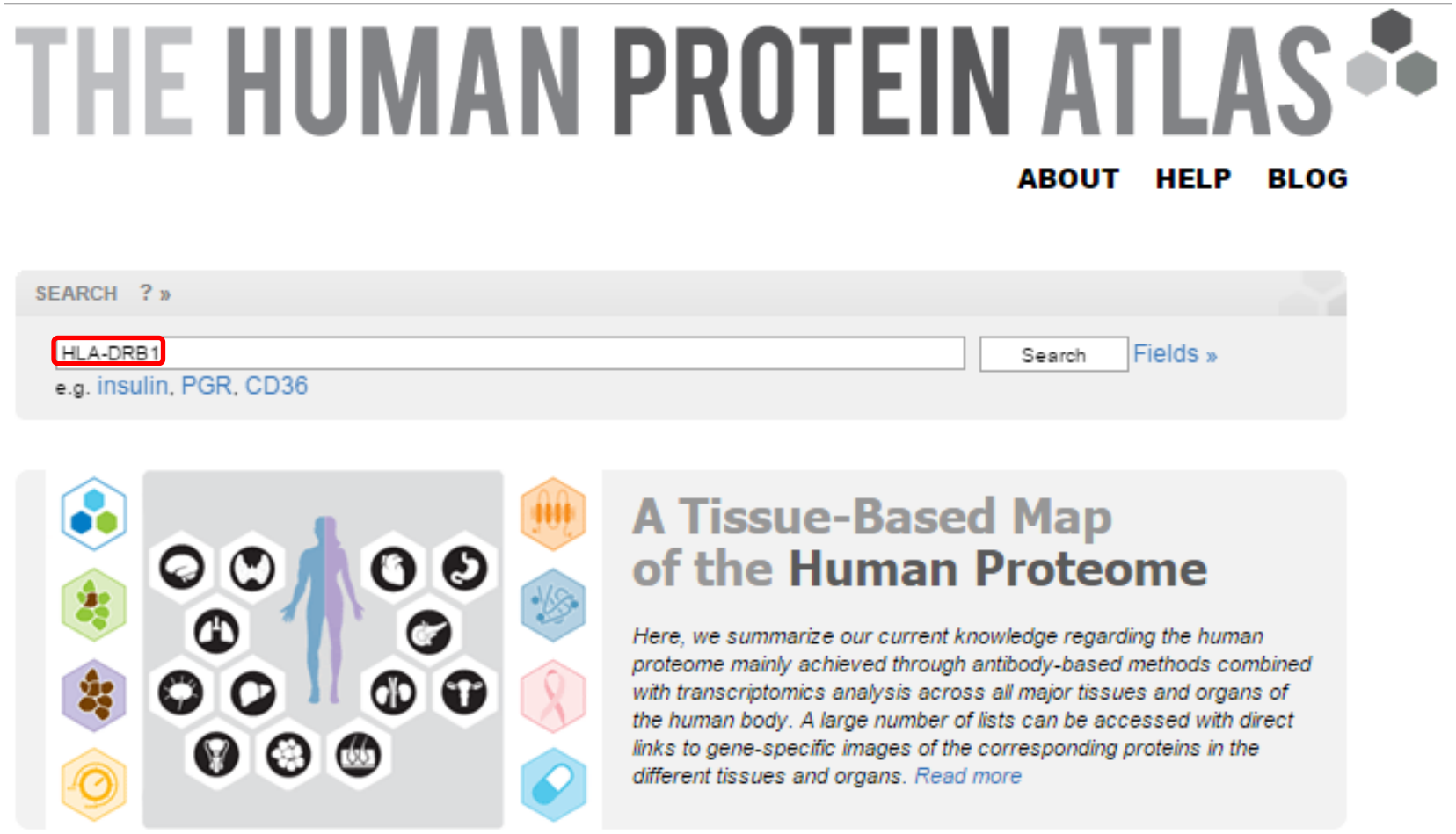
Cis-eQTLs

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	rs3132486	6	31351149	580452	6	31558934	G/A	A	12.71	-	0.00
8.8792092502963E-26	rs3132486	6	31351149	1440603	6	31556059	G/A	A	-10.50	-	0.00
2.617756407729722E-5	rs3132486	6	31351149	3890097	6	31239621	G/A	A	-4.20	TCF19	0.01
1.8212601781875332E-4	rs3132486	6	31351149	3170064	6	31586789	G/A	A	3.74	MICB	0.07
0.0026436099021629866	rs3132486	6	31351149	780600	6	31541393	G/A	A	-3.01	HCP5	0.43

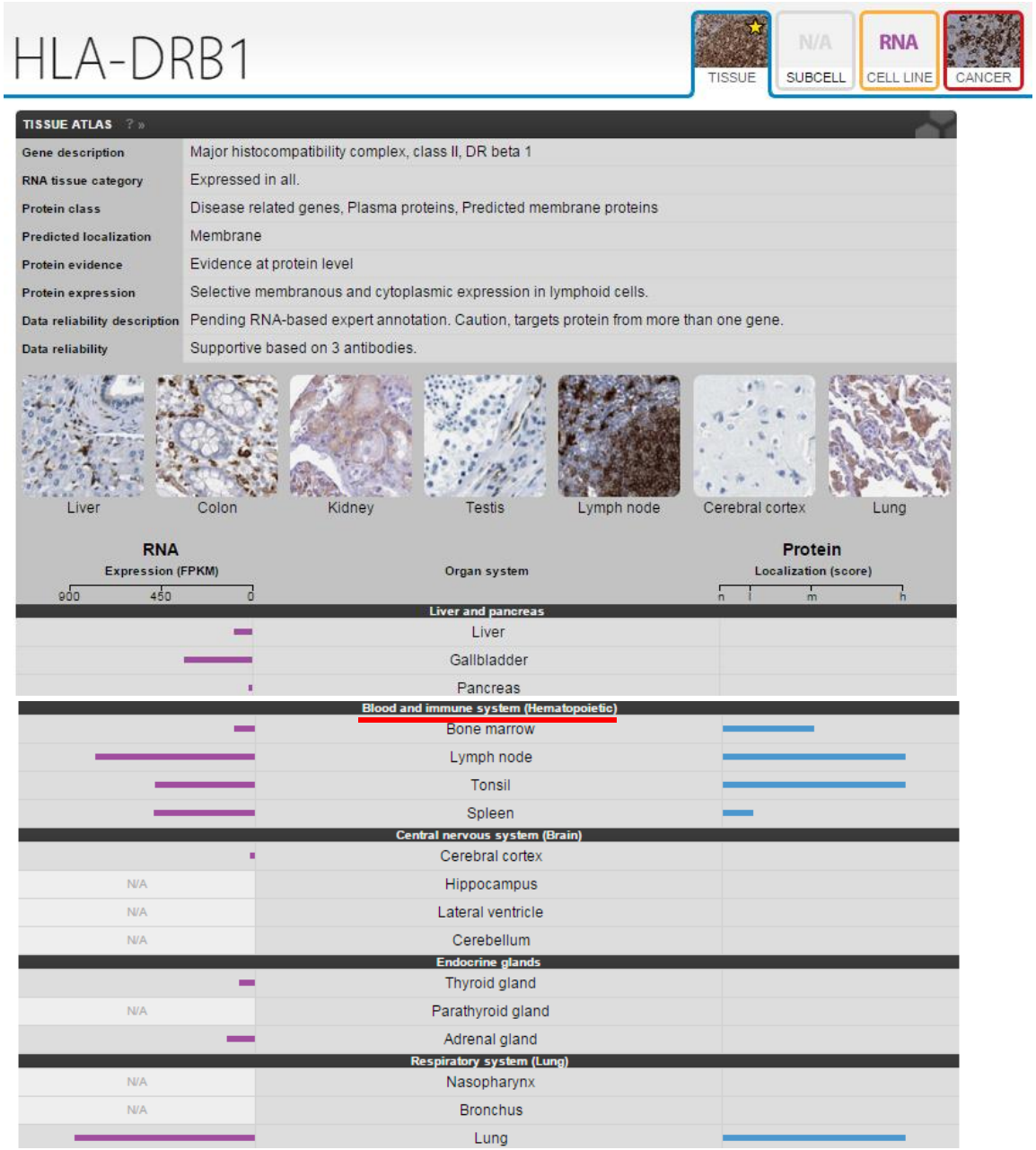
Interpretation of GWAS Findings: Individual SNPs



Interpretation of GWAS Findings: eQTLs



Interpretation of GWAS Findings: eQTLs



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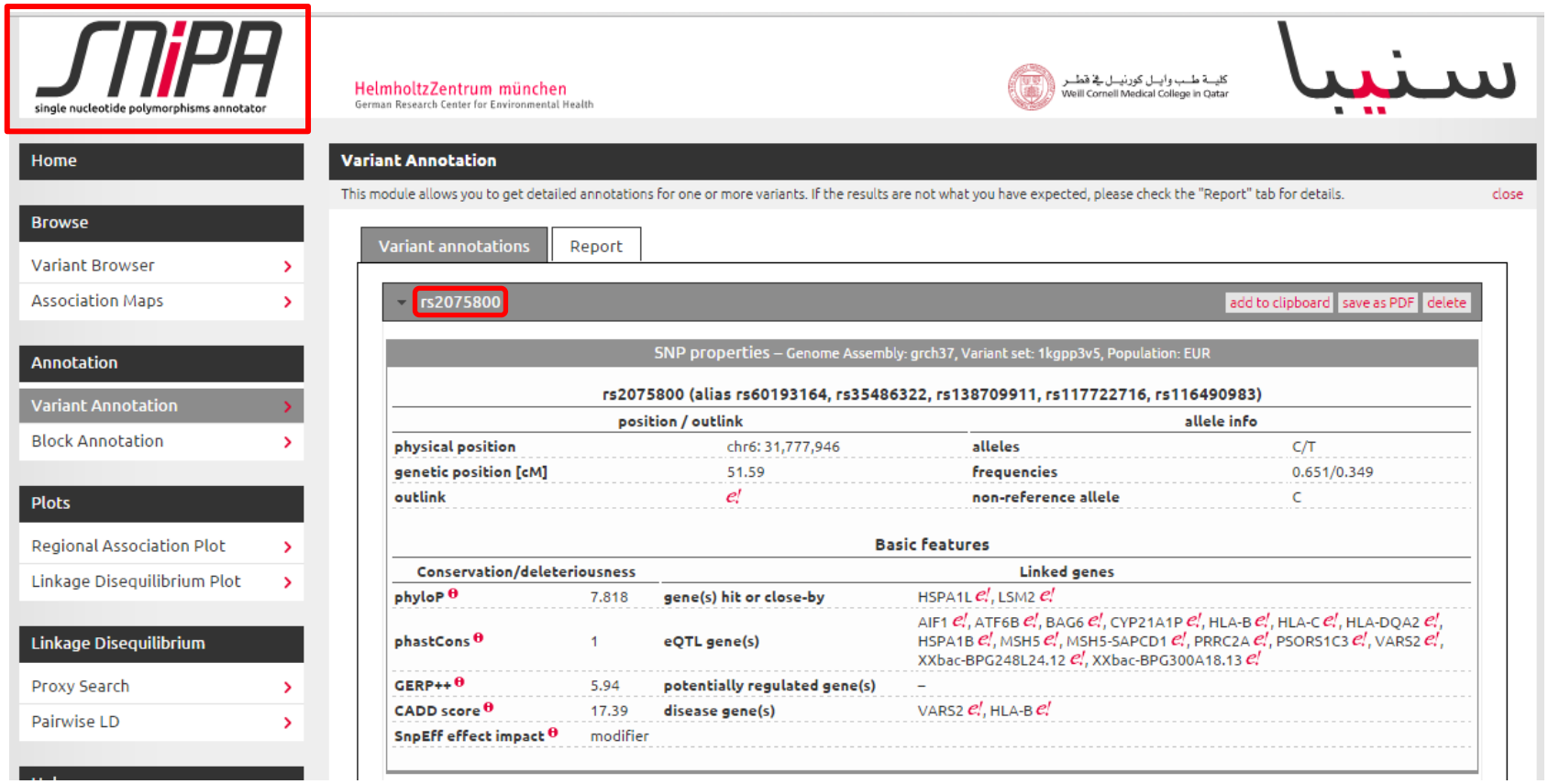
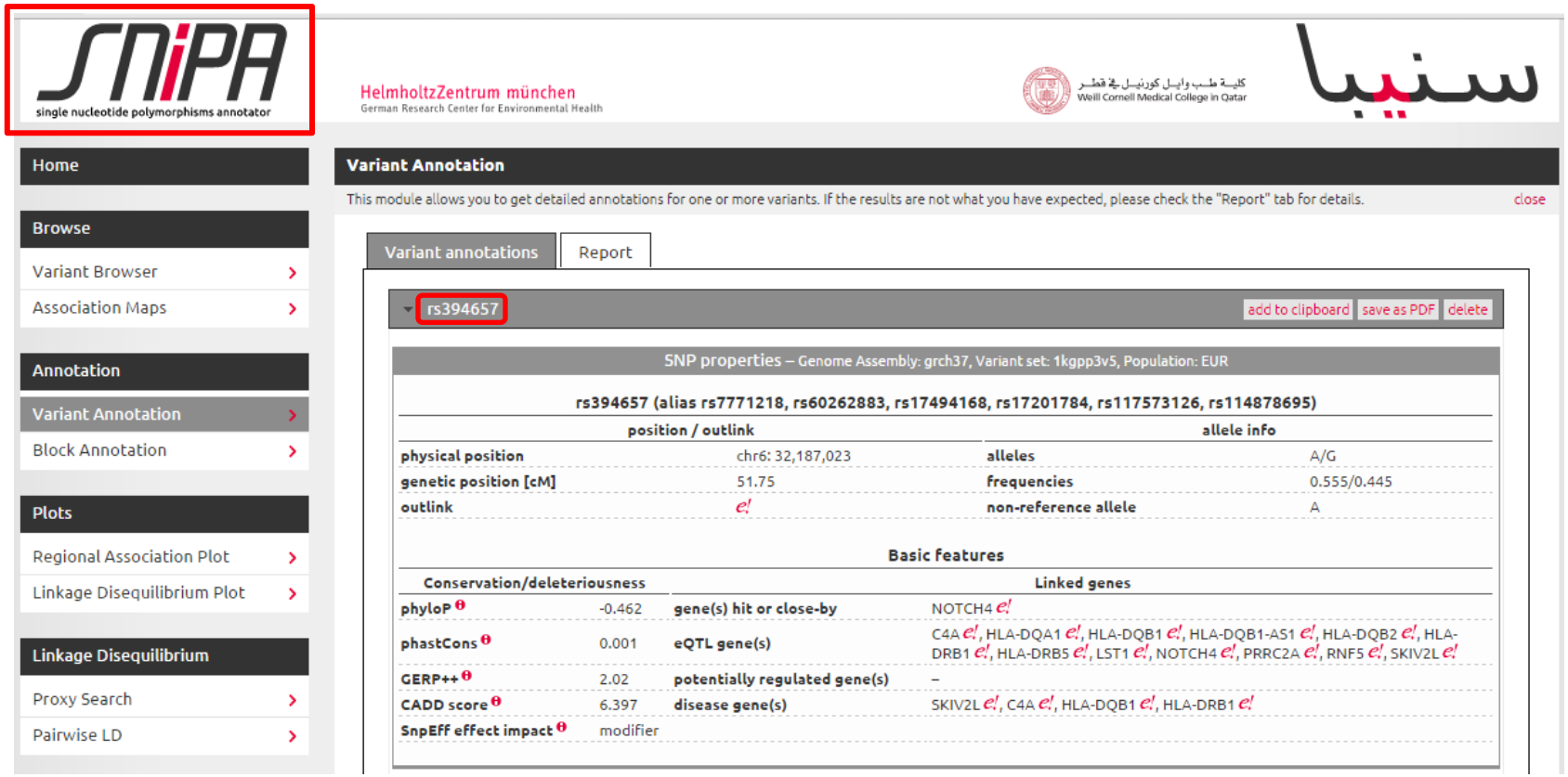
Interpretation of GWAS Findings: Individual SNPs



Interpretation of GWAS Findings: Individual SNPs



Interpretation of GWAS Findings: Individual SNPs

SNiPA single nucleotide polymorphisms annotator

HelmholtzZentrum münchen
German Research Center for Environmental Health

كلية طب وايل كورنيل في قطر
Weill Cornell Medical College in Qatar

سنيبا

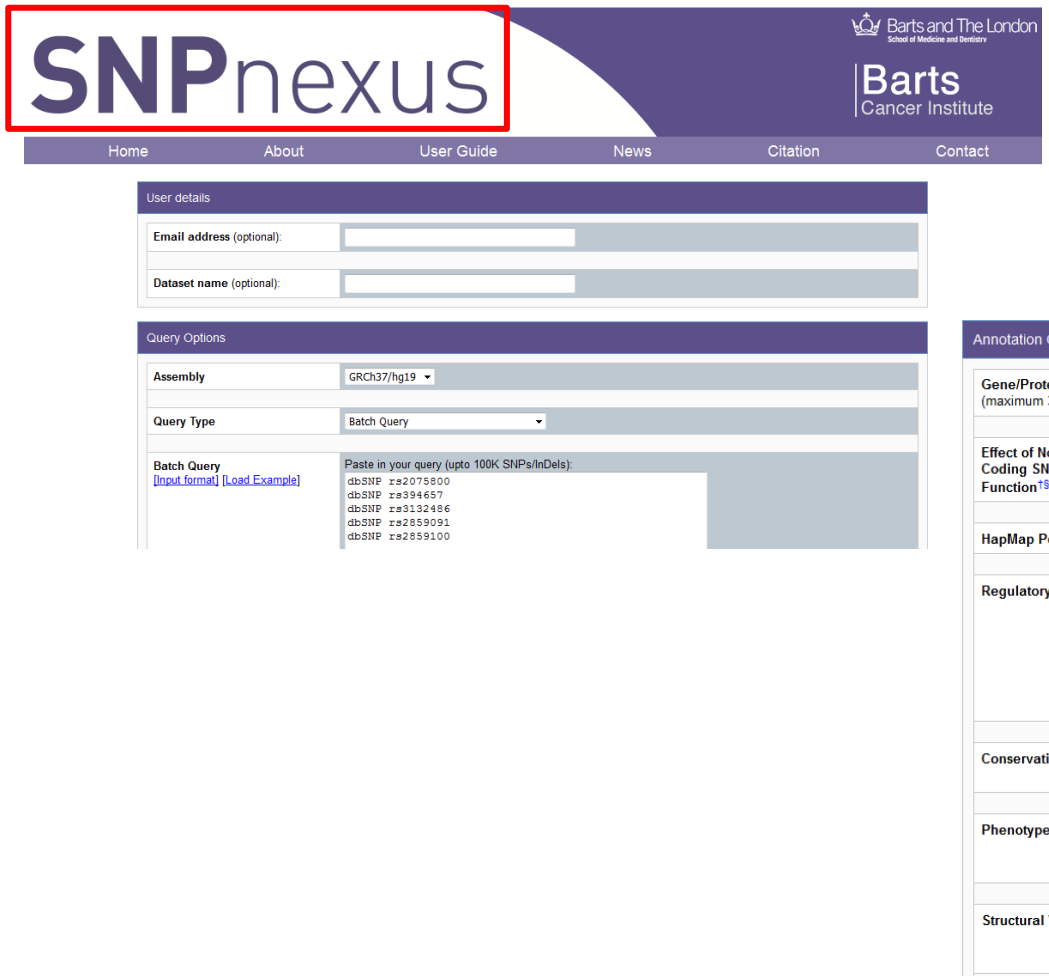
The GVHD risk markers are mainly acting as eQTLs

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



Interpretation of GWAS Findings: Individual SNPs

Number of SNPs in query: 5

Use the links below to navigate through your search results:

- Genomic Coordinates and External Links
  - Genomic Coordinates and External Links
- Gene/Protein Consequences
  - 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

Descriptive data, including HapMap frequencies, provided

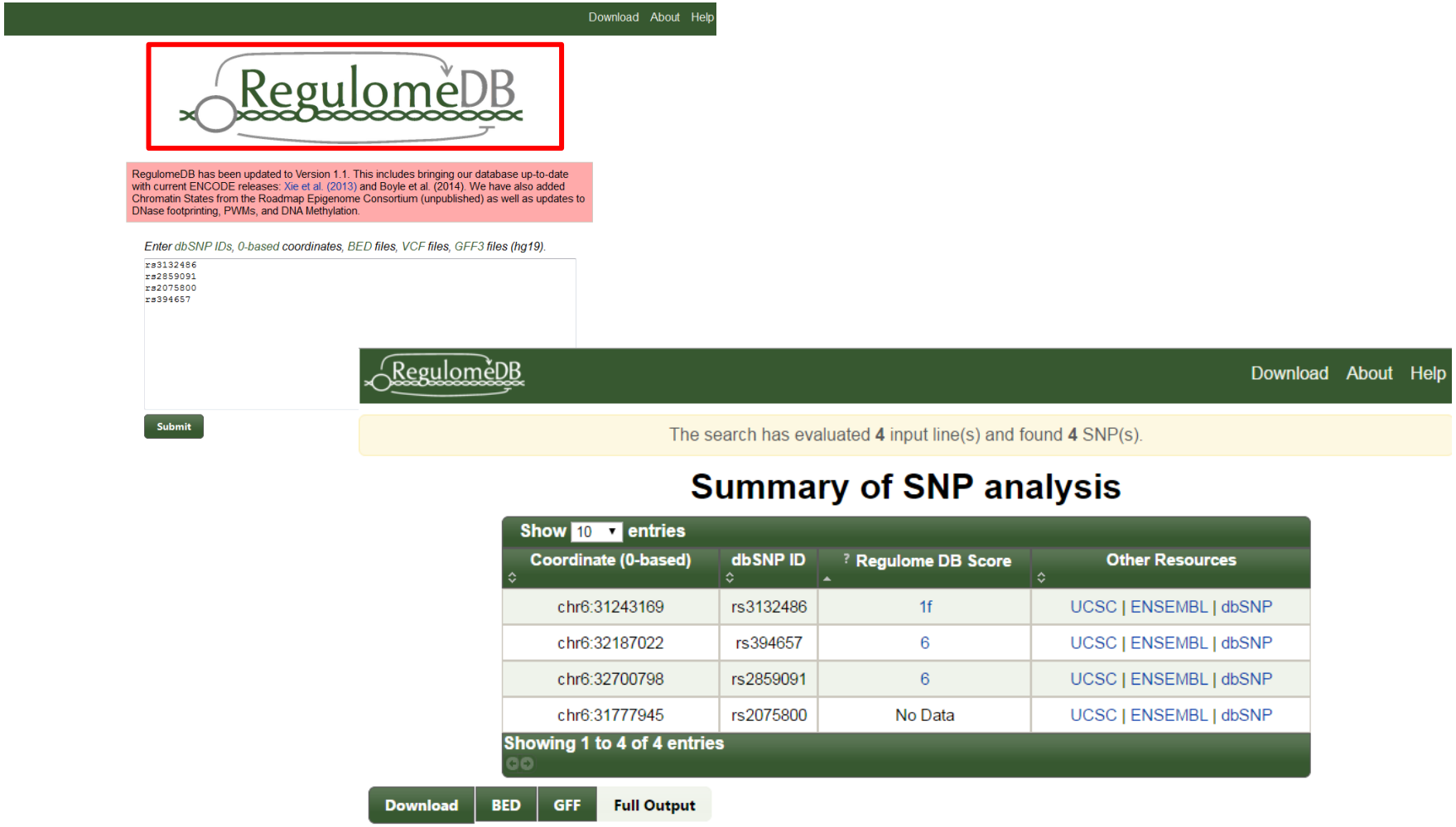
Polyphen score for the *HSPA1L* nsSNP is 0.001 (benign)

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



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

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

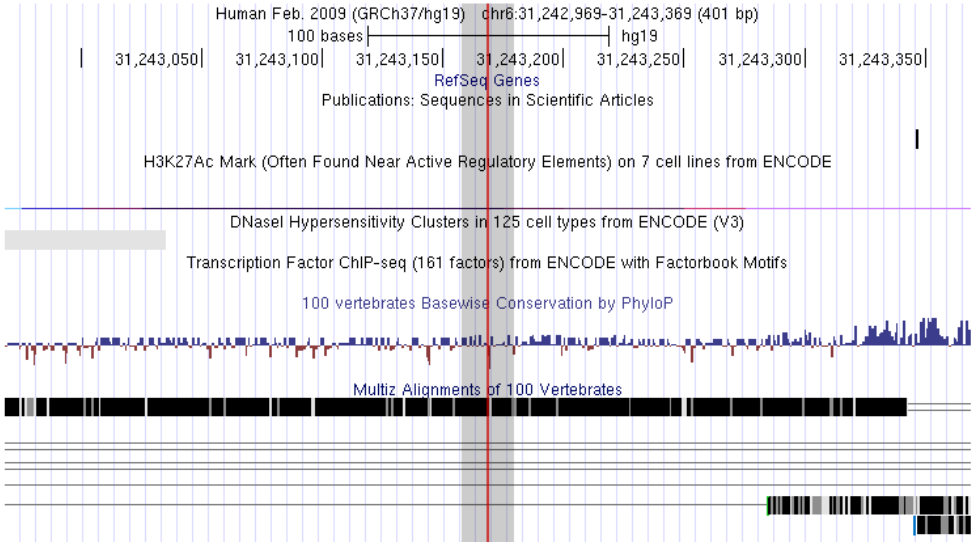
Download BED GFF Full Output

RegulomeDB Download About Help

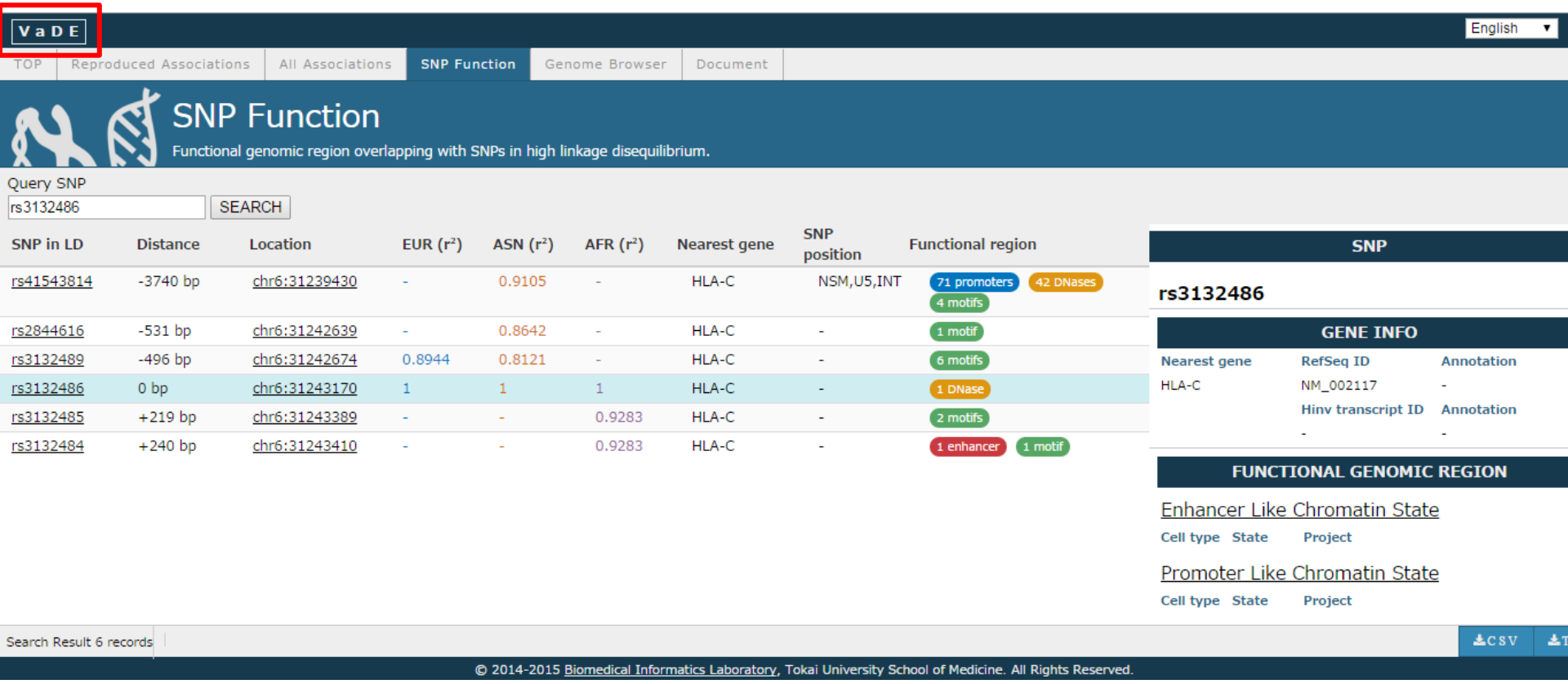
Data supporting chr6:31243169 (rs3132486)

Score: 1f

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



Interpretation of GWAS Findings: ssSNP Sets



Interpretation of GWAS Findings: ssSNP Sets

HaploReg v3

BROAD INSTITUTE

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

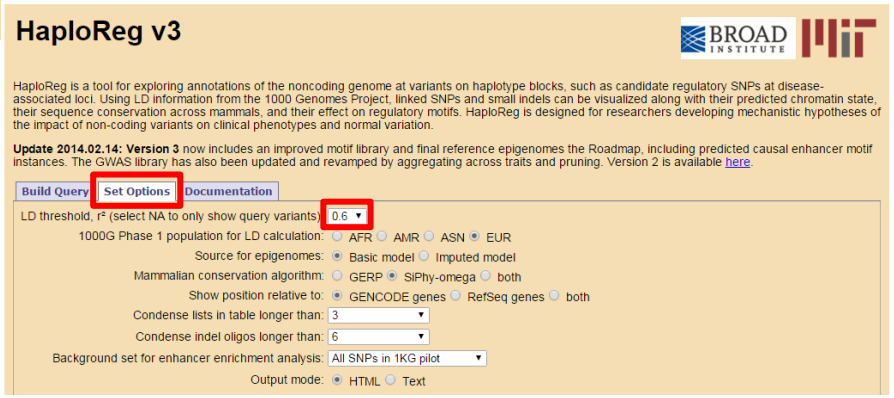
Use one of the three methods below to enter a set of variants. If an r^2 threshold is specified (see the Set Options tab), results for each variant will be shown in a separate table along with other variants in LD. If r^2 is set to NA, only queried variants will be shown, together in one table.

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



Interpretation of GWAS Findings: ssSNP Sets

Query SNP: rs3132486 and variants with r^2 >= 0.6

pos (hg19)	pos (hg38)	LD (r^2)	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	rs3132489	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	rs6930376	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	rs3130693	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	rs3132486	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	rs3132485	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	rs3132484	G	T	0.43	0.42	0.40	0.44			BLD				Osr		3.5kb 5' of HLA-C	

RegulomeDB Download About Help

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	UCSC | ENSEMBL | dbSNP
chr6:31242673	rs3132489	5	UCSC | ENSEMBL | dbSNP
chr6:31242858	rs3130693	5	UCSC | ENSEMBL | dbSNP
chr6:31242816	rs6930376	6	UCSC | ENSEMBL | dbSNP
chr6:31243388	rs3132485	No Data	UCSC | ENSEMBL | dbSNP
chr6:31243409	rs3132484	No Data	UCSC | ENSEMBL | dbSNP

Showing 1 to 6 of 6 entries

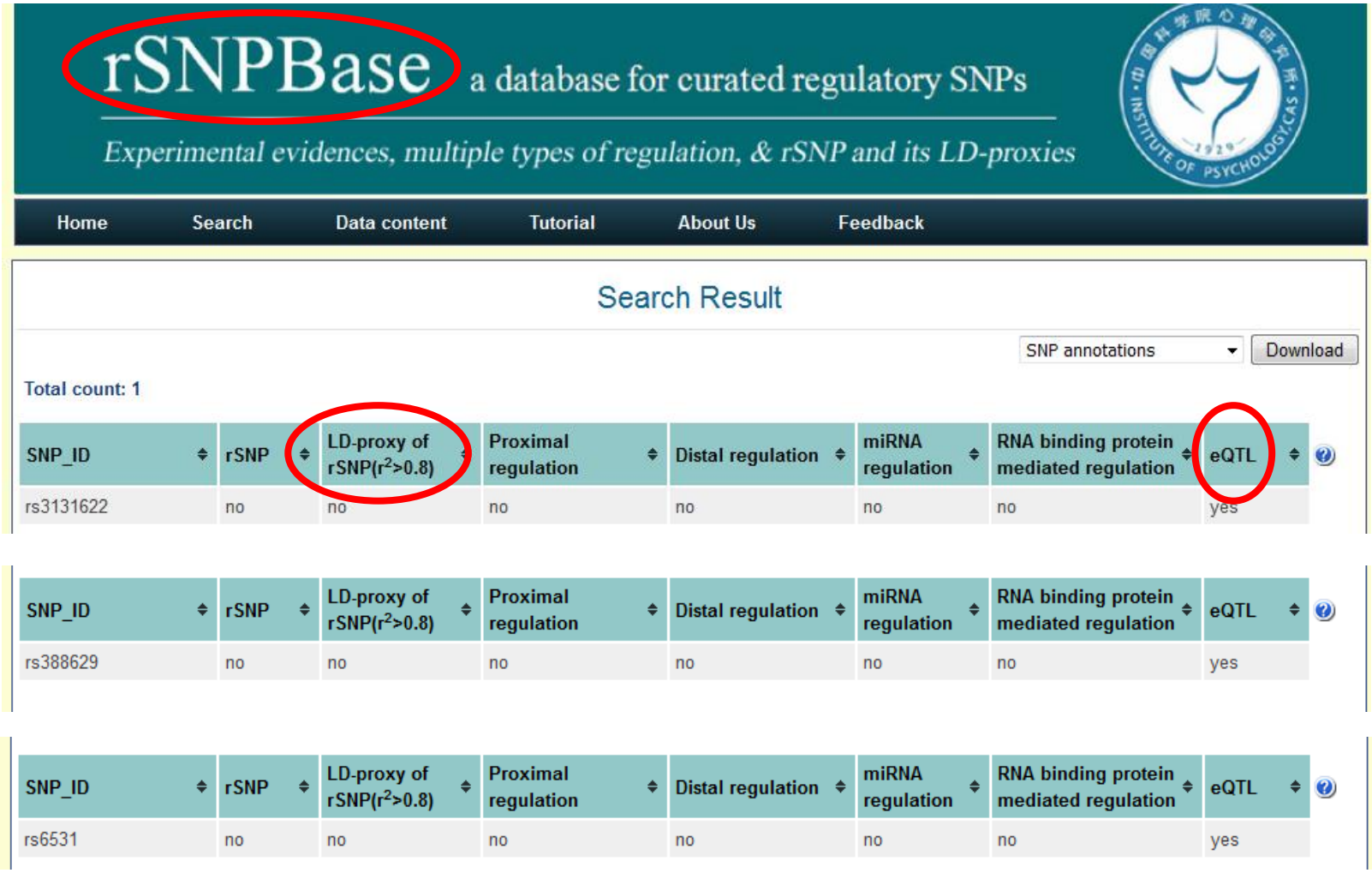
Download BED GFF Full Output

Interpretation of GWAS Findings: ssSNP Sets

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

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

Interpretation of GWAS Findings: ssSNP Sets



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

Liverpool Hope University EST. 1844

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

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	DQB1*060301
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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	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	DQB1*03:01:0
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	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	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	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	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	DQB1*06:03:0

rs6923504

IHWG #	CELL LINE	ST	CEH	Population
9008	DO208915	51	18.1	Australian Caucasoid
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 Caucasoid
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 FPF F	52	35.5?	Ashkenazi Jewish
9157	HAU, ML	52	58.1	Asian
9291	APD	52	.	Dutch

Liverpool Hope University EST. 1844

HLA Region SNPs and HLA Types

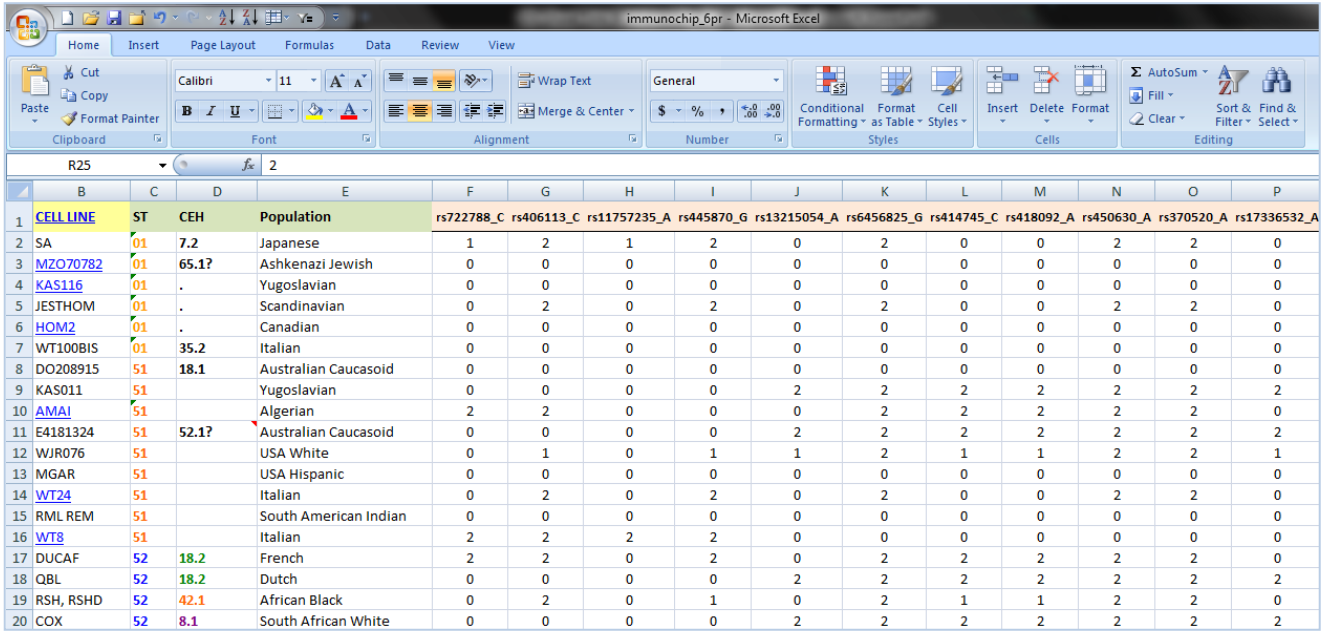
ASHI 2015

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

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

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

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



	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	CELL LINE	ST	CEH	Population	rs722788_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

HLA Region SNPs and HLA Types

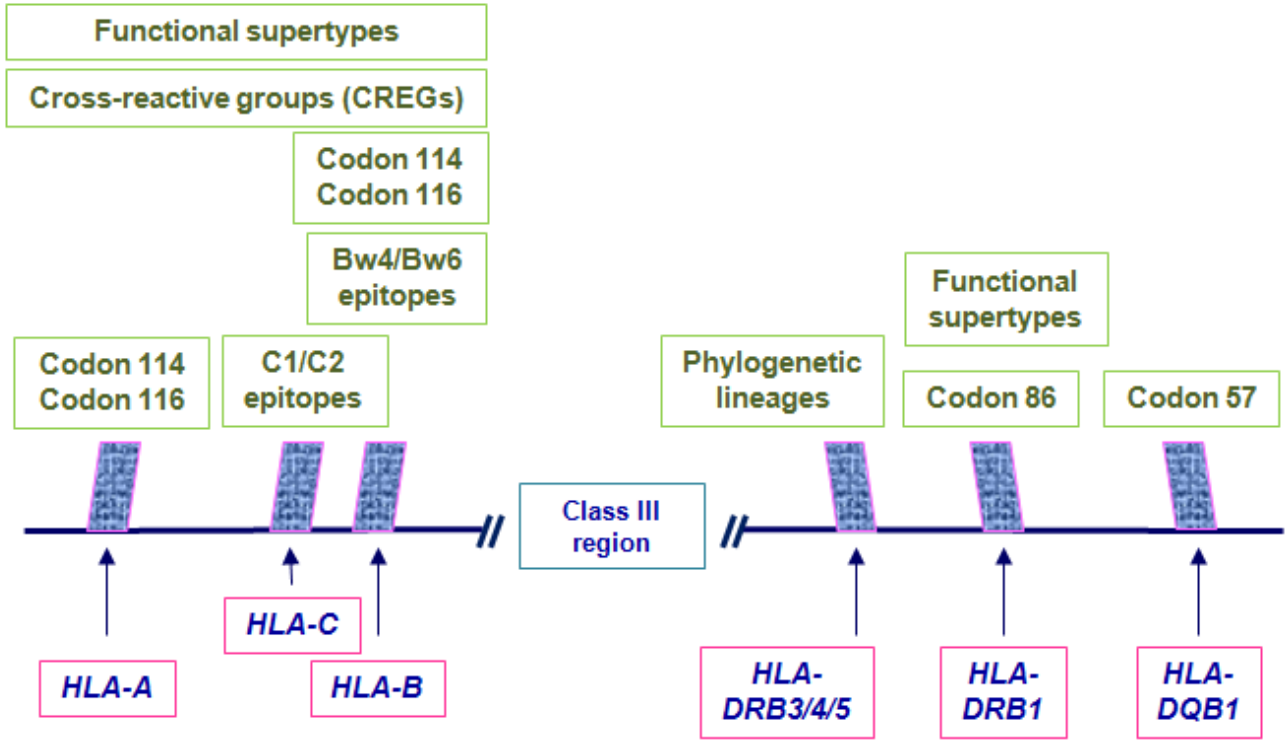
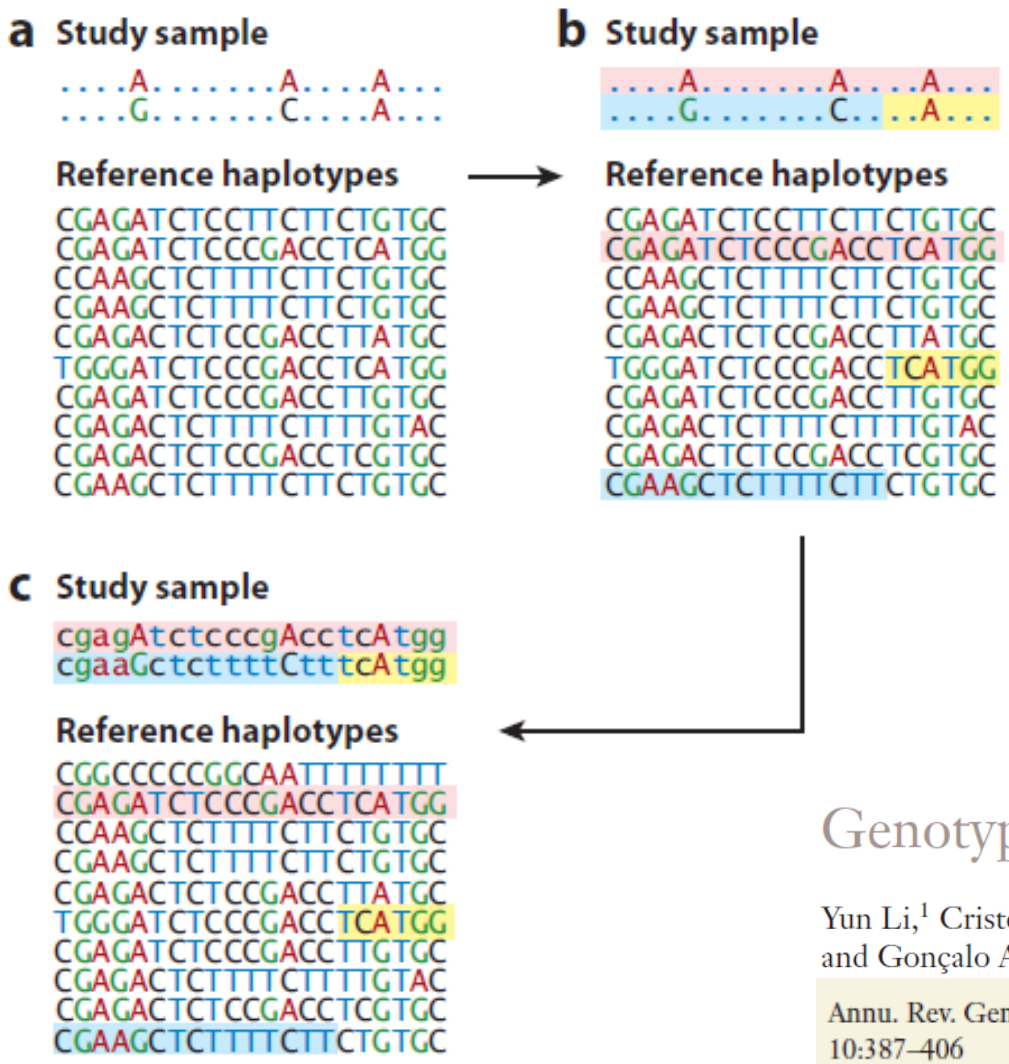


Figure 1. Functional multi-allelic HLA polymorphisms

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

Existing GWAS results: What to do with them?

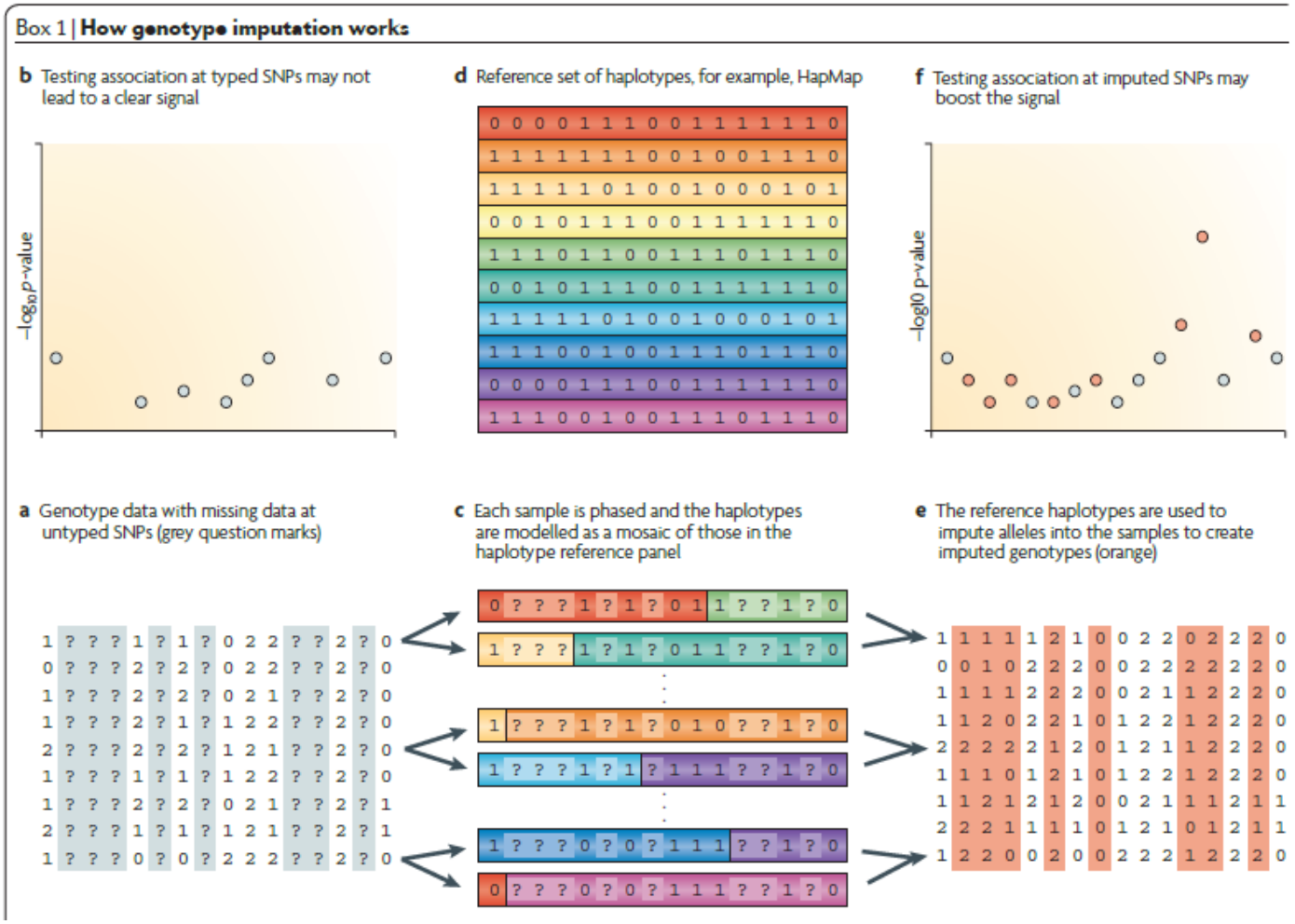


Genotype Imputation

Yun Li,[1] Cristen Willer,[1] Serena Sanna,[2] and Gonçalo Abecasis[1]

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

Existing GWAS results: What to do with them?



GENOME-WIDE ASSOCIATION STUDIES

Genotype imputation for genome-wide association studies

Jonathan Marchini and Bryan Howie‡*

NATURE REVIEWS | GENETICS
VOLUME 11 | JULY 2010 | 499

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

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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.

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

ACKNOWLEDGEMENT

Many thanks to the organizing committee of *Annual EFI Region 8 EPT Meeting* for the invitation

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