Causality Assessment of HLA Region Associations in GWAS for Autoimmune Diseases

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XIV. CONGRESS OF MEDICAL BIOLOGY AND GENETICS

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OUTLINE

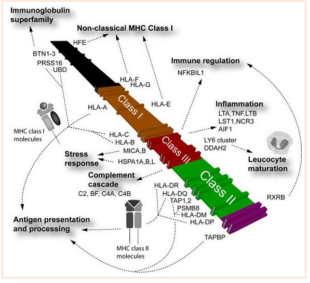
Autoimmune diseases, GWAS and HLA complex

Online tools to assess functionality of disease-associated SNPs

Disease association databases

Large biologicals datasets

An overview of the issues with causality assessment in the HLA region



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AUTOIMMUNE DISEASES and HLA COMPLEX

More than 80 autoimmune diseases (AIDs) affect 5 to 9% of the population worldwide

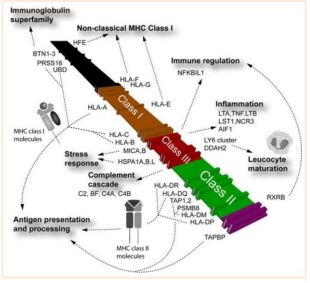
The etiology of the AIDs is still poorly understood

Autoimmune disorders result from a complex interaction of genetic and epigenetic variations, as well as triggering environmental factors

Over 130 GWAS have established AID susceptibility markers, some of which are shared among multiple AIDs

The mechanism of the gender effect is still elusive

All AIDs have some linkage to HLA region variation



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AUTOIMMUNE DISEASES: Prevalance

Table 1
Recent prevalence data for autoimmune diseases, by geographic area.

Disease[a]	Hospital-based Data, Denmark[b]	Hospital and non-Hospital-based data				
		Studies from Europe, North America, Australia, New Zealand			Studies from Asia, Middle East, Caribbean, South America	
	Rate per 100,000	Rate per 100,000	Study area	Reference	Rate per 100,000	Study area
Addison	18	11–14	UK, Italy, Norway	[4–6]		
Alopecia	21	1700	US	[7]		
Celiac disease	50	180–350	Greece, Netherlands	[8,9]	140–280	Iran, Tunisia
		740–1000	Iceland, Italy	[10,11]	470–600	Brazil, Argentina
		1900	Finland	[12]	900	Turkey
Crohn disease	225	28–53	Bosnia-Herzegovina, Hungary	[19,20]	6–53	Puerto Rico, Malaysia, Lebanon
		96–201	US, Spain, Denmark, New Zealand	[21–26]	113	Israel
Ulcerative colitis	378	143–294	US, Hungary, Denmark, New Zealand	[19,21–23,25,26]	6	Lebanon
					102	Puerto Rico
Diabetes (Type 1)						
All ages	946	118	Lithuania	[31]		
All ages		340–570	UK, Sweden, Australia	[32–34]		
Ages < 20		87–120	Spain, Germany	[35,36]	31	Bahamas
Ages < 20		227–355	US, New Zealand	[37,38]	110–270	Kuwait, Saudi Arabia
Ages < 20		70	US- American Indian	[39]		
Liver – Chronic active hepatitis	45	11–17	Spain, Sweden, Norway	[43–45]	3–8	Singapore
		36	US-Alaska Natives	[46]		
Liver – Primary biliary cirrhosis	12	15–40	Norway, Finland, Spain, UK,	[45,48–51]	4–18	Israel
		4–20	US, Australia	[52]		
Thyroid – Hyper	629	500	US	[54]	20	Iran
		626	UK	[55]		
Thyroid – Hypo	62	300	US	[54]	350	Iran
		2980	UK	[55]		
Multiple sclerosis	182	177–358	US, Canada	[57–60]	4–20	Colombia, Brazil, Argentina
		100	Canada-First Nations	[60]	13	Japan
		121–200	Italy, Greece, France, Ireland	[61–69]	11–62	Israel, Kuwait, Jordan, Iran
		46	Norway	[70]	101	Turkey
		50	Portugal, New Zealand	[71]		
Myasthenia gravis	18	8–15	Greece, Estonia, Croatia	[81–83]	3	Colombia
			Netherlands, Sweden, UK	[84–86]	7	Curacuo and Aruba
Polymyalgia rheumatica	112	739[c]	US	[89,90]		
		150–370[c]	Greece	[91]		

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Recent insights in the epidemiology of autoimmune diseases: Improved prevalence estimates and understanding of clustering of diseases

Glinda S. Cooper[a,b,*], Milele L.K. Bynum[c], Emily C. Somers[d]

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AUTOIMMUNE DISEASES: Co-occurrence

Table 2
Intra-person coexistence of autoimmune diseases.

Reference location data source; measure of association[a]	Index disease cases; control or reference population	Comorbid autoimmune disease(s)	Probands/controls *n* (%); *n* (%) or *n* observed/*n* expected	Measure of association (95% confidence interval)
Somers et al. [146] United Kingdom, General Practice Research Database (pop-based); SIR	RA ($n = 22,888$)	AIT	337/208.6	1.6 (1.5, 1.8)
	RA	MS	13/17.8	0.73 (0.39, 1.3)
	AIT ($n = 26,198$)	RA	296/224.7	1.3 (1.2, 1.5)
	AIT	MS	23/20.7	1.1 (0.70, 1.7)
	MS ($n = 4332$)	RA	30/37.6	0.80 (0.54, 1.1)
	MS	AIT	61/42.2	1.4 (1.1, 1.9)
	T1DM ($n = 6170$)	RA	72/44.9	1.6 (1.3, 2.0)
	T1DM	AIT	175/39.0	4.5 (3.9, 5.2)
	T1DM; UK general population	MS	15/12.5	1.2 (0.67, 2.0)
Nielsen et al. [148] Denmark Danish MS & Hospital Discharge Registers; RR	MS ($n = 10,596$); Danish general population	42 diseases[b]	133/153.1	0.9 (0.7, 1.0)
		Ulcerative colitis	29/14.9	2.0 (1.4, 2.8)
		Pemphigoid	12/0.8	15.4 (8.7, 27.1)
		Pemphigus	2/0.03	53.6 (13.4, 214.3)
		RA	28/53.0	0.5 (0.4, 0.8)
		Temporal arteritis	11/20.6	0.5 (0.3, 0.97)
Nielsen et al. [147] Denmark Danish MS & Hospital Discharge Registers; RR	MS ($n = 6078$); Danish general population	T1DM	11/3.38	3.3 (1.8, 5.9)
Ramagopalan et al. [149] Canada Longitudinal, pop-based MS study (19 centers); OR	MS ($n = 5031$); Spousal controls ($n = 2707$)	T1DM	19 (0.4); 24 (0.5)	0.7 (0.3, 1.6)[c]
		RA	153 (3.0); 66 (2.4)	1.3 (0.9, 1.7)[c]
		Ulcerative colitis	9 (0.2); 4 (0.2)	1.2 (0.3, 5.4)[c]
		Crohn disease	11 (0.2); 4 (0.2)	1.5 (0.4, 6.4)[c]
		Psoriasis	293 (5.8); 146 (5.4)	1.1 (0.9. 1.3)[c]
		Pernicious anemia	123 (2.4); 25 (0.9)	2.7 (1.7, 4.3)[c]
		SLE	28 (0.6); 7 (0.3)	2.2 (0.9, 5.9)[c]
		Vitiligo	35 (0.7); 12 (0.4)	1.6 (0.8, 3.3)[c]
		AITD	395 (7.9); 116 (4.3)	1.9 (1.5, 2.4)[c]
		MG	7 (0.1); 3 (0.1)	1.3 (0.3, 7.5)[c]
		≥1 of above	Not reported	1.1 (0.86–1.2)[c]

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Journal of Autoimmunity

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AUTOIMMUNE DISEASES: Gender Effect

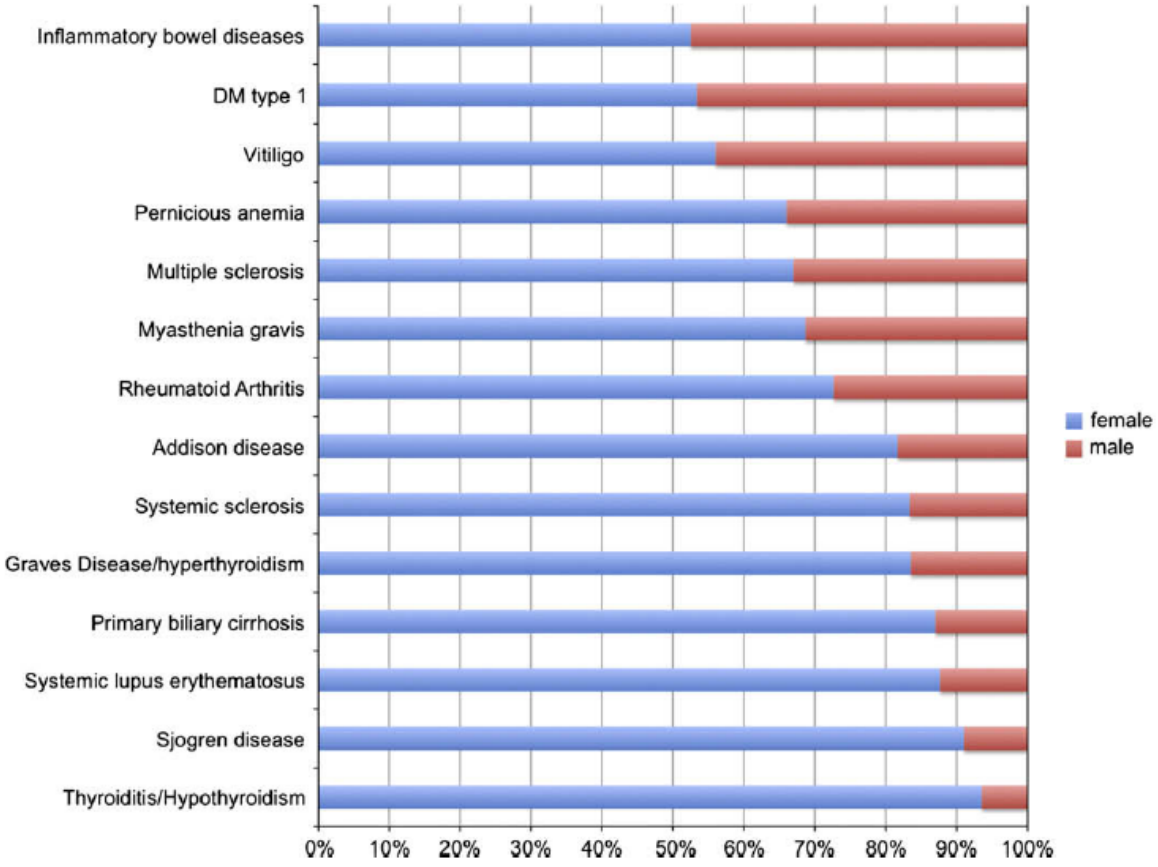

Fig. 1. Female to male ratio of selected autoimmune diseases expressed as percentage (x axis) and calculated as average based on four reviews of the literature [2,3,16,62].

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Review

Female predominance and X chromosome defects in autoimmune diseases

Pietro Invernizzi [a,c,*], Simone Pasini [a,b], Carlo Selmi [a,b,c], M. Eric Gershwin [c], Mauro Podda [a,b]

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AUTOIMMUNE DISEASES and GWAS

Table 1 Autoimmune diseases with published GWAS and respective number of associated loci

	Number of	
Autoimmune disease	*GWAS*	*loci*
Alopecia areata	1	8
Ankylosing spondylitis	3	21
Behçet's disease	4	10
Celiac disease	5	60
Crohn's disease	15	110
Graves' disease	3	13
Granulomatosis with polyangiitis	1	6
Inflammatory bowel disease	4	117
Juvenile idiopathic arthritis	3	5
Kawasaki disease	6	16
Multiple sclerosis	15	22
Myasthenia gravis	1	5
Primary biliary cirrhosis	4	25
Primary sclerosing cholangitis	1	2
Psoriasis	7	23
Psoriatic arthritis	2	4
Rheumatoid arthritis	18	117
Sarcoidosis	2	3
Sjögren's syndrome	1	4
Systemic lupus erythematosus	11	73
Systemic sclerosis	3	10
Type 1 diabetes	9	60
Ulcerative colitis	10	73
Vitiligo	7	32

Abbreviation: GWAS, genome-wide association studies.
Numbers compiled from the National Human Genome Research Institute's Catalog of Published Genome-Wide Association Studies (http://www.genome.gov/gwastudies) accessed on 27 March 2015.[94]

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REVIEW

Genetics of autoimmune diseases: insights from population genetics

Paula S Ramos[1], Andrew M Shedlock[2,3] and Carl D Langefeld[4]

AUTOIMMUNE DISEASES and GWAS

Table 2 Autoimmune disease regions with the evidence for selection and implicated agents of selection

Gene region	*Position*	*Autoimmune disease association*	*References for evidence of natural selection*	*Selective pressure*
IL23R	1p31.3	IBD, CD, UC, PS, AS and BeD	19	Protozoa
PTPN22	1p13.2	SLE, RA, CD, T1D, VT, MG, AITD and UC	21,22	Protozoa
TNFRSF18	1p36.33	IBD	19	
ARHGEF2	1q21-q22	CD	95	Protozoa
SCAMP3	1q22	CD	95	Protozoa
FCGR2B	1q23.3	SLE	77	*Plasmodium falciparum*
TNFSF18	1q24.3	IBD	19	
TNFSF4	1q25.1	SLE, MS, RA, CD, CeID and SS	21	
CR1	1q32	SLE, SA	96	*Plasmodium falciparum*
TLR5	1q41-q42	SLE	22	*Salmonella enterica* ser. Typhimurium and other exposures
TET3-DGUOK	2p13	SLE	21	
IL18RAP	2q12.1	CeID, CD and IBD	20	
IFIH1	2q24.2	PS, VT, T1D and IBD	76,97,98	Antiviral response
IL8RA, SLC11A1	2q35	IBD, UC	19	Mycobacterial infection
BTLA	3q13.2	RA	22	
ARHGAP31, CD80	3q13.33	MS, CeID, PBC, JIA, SLE and VT	23	
CD86	3q13.33	MS	23	
LEKR1	3q25.31	MS	23	
IL12A	3q25.33	CeID, BeD, MS and PBC	20,23	
IL2, IL21	4q27	CeID, RA, UC, IBD, T1D and AA	23	
PTGER4	5p13.1	CD, UC, IBD, MS and AS	95	Protozoa
SLC22A5, IRF1	5q31.1	CD, IBD	23,95	Protozoa
TNIP1	5q33.1	SLE, SScl, PS, PSA, IBD and MG	21	
PTTG1	5q33.3	SLE	21	
ITPR3	6p21.31	SLE, T1D, GD and CD	22	
UHRF1BP1	6p21.31	SLE	21,23	*Mycobacterium tuberculosis*
HLA	6p22.1-21.32	All ADs	23,99–102	Bacterial infection
POPDC3	6q21	MS	23	
IKZF1	7p12.2	SLE, CD and IBD	21	

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IMMUNE TRAITS and GWAS

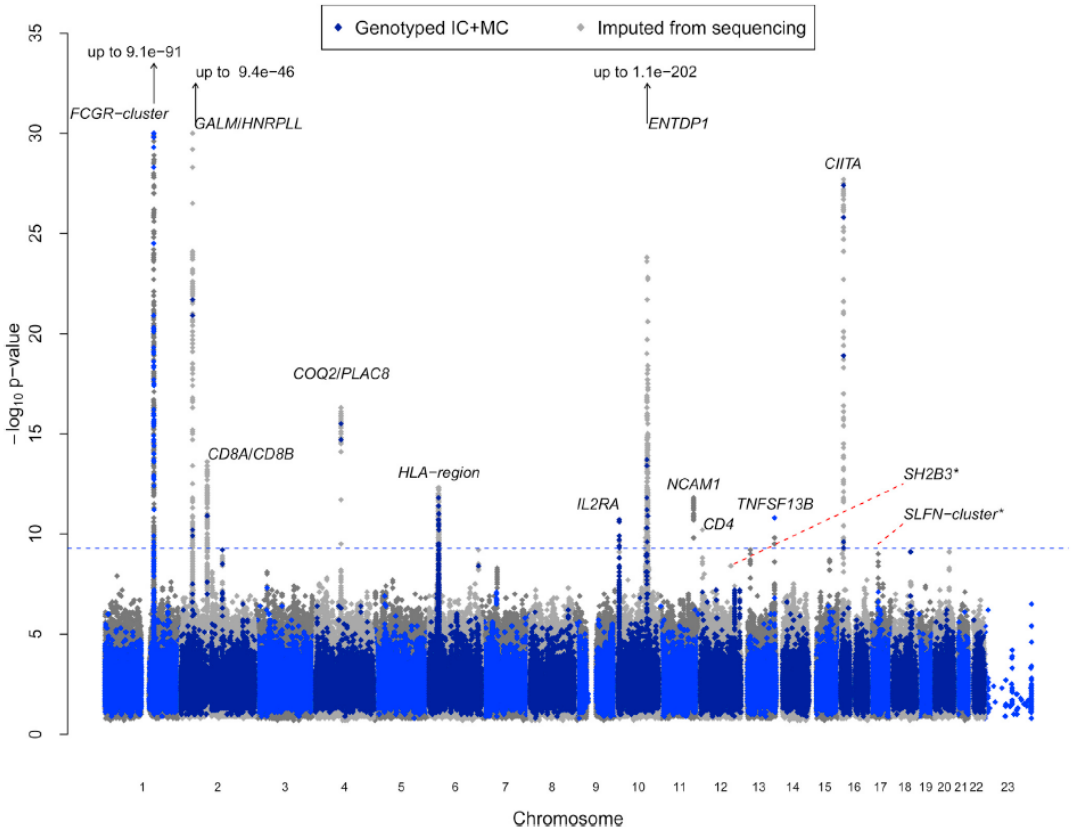

Figure 3. Manhattan Plot of Best p Values

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.

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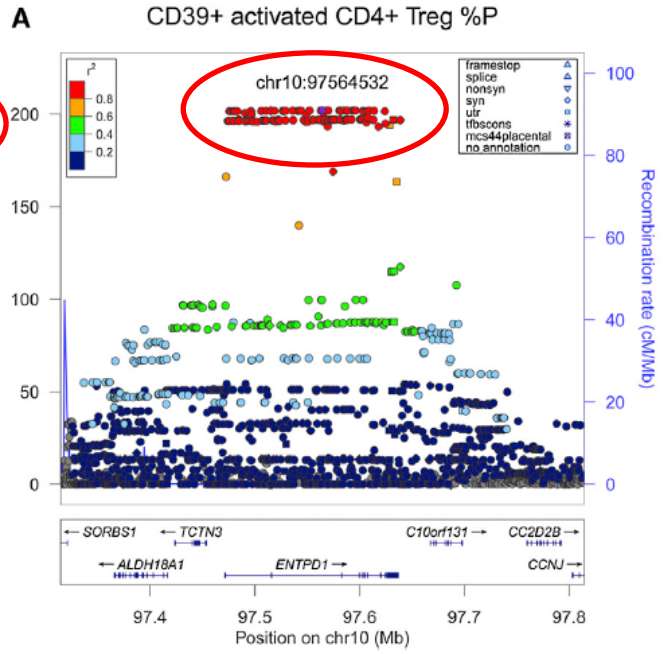
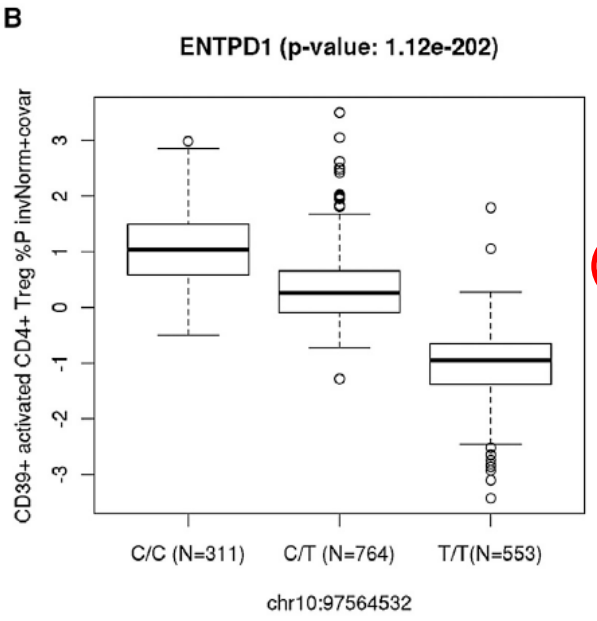
IMMUNE TRAITS and GWAS

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.

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IMMUNE TRAITS and GWAS

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)*	chr6:30466505/ rs117765619	G/T	0.516	CD45RA− CD8+ AC	−0.228 (0.037)	2.62	5.24×10^{-10}	chr6:30482993/ 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}	chr6:32383138/ 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)

Lead SNP

Perfect Proxy


Cell

Resource

Genetic Variants Regulating Immune Cell Levels in Health and Disease

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IMMUNE TRAITS and GWAS

Table 2. Overlapping Associations with Complex Diseases

Gene/Region	Immune Trait	SNP	Effect Allele/ Other	Effect (SE)	p Value	Disease	SNP Disease	Best Reported p Value	Risk Allele/ Other	r^2	Risk Allele/ Corresponding Trait Allele (Effect)	Source
HLA Class II (chr6p21.1)	CD45RA− CD28− CD8+ AC	rs6923504	G/C	−0.249 (0.037)	2.81×10^{-11}	Hodgkin's lymphoma	rs6903608	2.84×10^{-50}	G/A	0.99	G/G (decrease)	1
						Systemic sclerosis	rs3129882	1.89×10^{-27}	G/A	0.803	G/G (decrease)	1
						Ulcerative colitis	rs9268877	3.90×10^{-23}	T/C	0.83	G/G (decrease)	1
						Parkinson's disease	rs3129882	1.90×10^{-10}	G/A	0.803	G/G (decrease)	1
IL2RA (chr10p15.1)	CD25hi CD4+ %P	rs61839660	C/T	−0.484 (0.072)	2.38×10^{-11}	Type 1 diabetes	rs61839660	5.10×10^{-9}	C/T	1	C/C (decrease)	1
	CD45RA− CD25hi CD4+ not Treg AC	rs61839660	C/T	−0.484 (0.072)	1.05×10^{-10}	Type 1 diabetes	rs61839660	5.10×10^{-9}			C/C (decrease)	1
	CD45RA− CD25hi CD4+ not Treg %P	rs61839660	C/T	−0.484 (0.072)	1.85×10^{-11}	Type 1 diabetes	rs61839660	5.10×10^{-9}			C/C (decrease)	1
SH2B3/ATXN2 (chr12q24.12)	T lymphocyte AC	rs597808	G/A	−0.195 (0.035)	3.84×10^{-8}	Type 1 diabetes	rs3184504	2.80×10^{-27}	T/C	0.95	T/A (increase)	1,2
						Celiac disease	rs3184504	5.40×10^{-21}	T/C		T/A (increase)	2
						Primary hypothyroidism	rs3184504	2.60×10^{-12}	T/C		T/A (increase)	1
						Primary sclerosing cholangitis	rs3184504	5.91×10^{-11}	T/C		T/A (increase)	3
						Juvenile rheumatoid arthritis	rs3184504	2.60×10^{-9}	T/C		T/A (increase)	2
						Rheumatoid arthritis[a]	rs3184504	6.00×10^{-6}	T/C		T/A (increase)	1
						Coronary heart disease[a]	rs3184504	6.35×10^{-6}	T/C		T/A (increase)	1
						Multiple sclerosis[a]	rs3184504	6.70×10^{-5}	T/C		T/A (increase)	2
	CD4+ AC	rs597808	G/A	−0.195 (0.036)	4.66×10^{-8}	Type 1 diabetes	rs3184504	2.80×10^{-27}			T/A (increase)	1,2
						Celiac disease	rs3184504	5.40×10^{-21}			T/A (increase)	2
						Primary hypothyroidism	rs3184504	2.60×10^{-12}			T/A (increase)	1
						Primary sclerosing cholangitis	rs3184504	5.91×10^{-11}			T/A (increase)	3
						Juvenile rheumatoid arthritis	rs3184504	2.60×10^{-9}			T/A (increase)	2
						Rheumatoid arthritis[a]	rs3184504	6.00×10^{-6}			T/A (increase)	1
						Coronary heart disease[a]	rs3184504	6.35×10^{-6}			T/A (increase)	1
						Multiple sclerosis[a]	rs3184504	6.70×10^{-5}			T/A (increase)	2
	CD4+ not Treg AC	rs597808	G/A	−0.195 (0.036)	4.80×10^{-8}	Type 1 diabetes	rs3184504	2.80×10^{-27}			T/A (increase)	1,2

(Continued on next page)


Cell

Resource

Genetic Variants Regulating Immune Cell Levels in Health and Disease

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

IMMUNE TRAITS and GWAS: rs6923504

> rs6923504 and rs6903608 have shown replicated RA associations (OR ~ 0.40)

> Also associated with T1D, GD, MDS, PBC, UC and SLE (in GRASP, dbGAP; none in GWAS Catalog)

> They map to the *HLA-DRB9* gene

> They are linked to a particular HLA lineage

> They are eQTLs for *HLA-DRA*, *-DQA1*, *-DQB1*

IMMUNE TRAITS and GWAS: rs6923504

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	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

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

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HLA REGION SNPs and HLA TYPES

ASHI 2015

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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]

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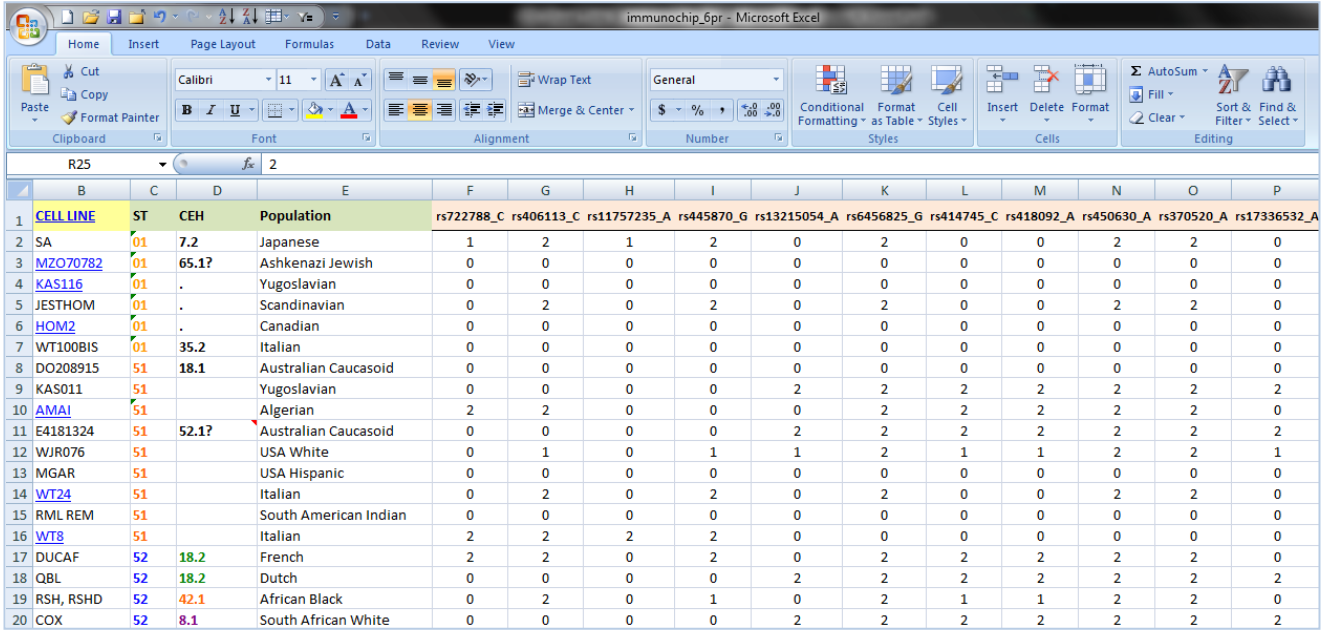

	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	CELL LINE	ST	CEH	Population	rs722788_C	rs406113_C	rs11757235_A	rs445870_G	rs13215054_A	rs6456825_G	rs414745_C	rs418092_A	rs450630_A	rs370520_A	rs17336532_A
2	SA	01	7.2	Japanese	1	2	1	2	0	2	0	0	2	2	0
3	MZO70782	01	65.1?	Ashkenazi Jewish	0	0	0	0	0	0	0	0	0	0	0
4	KAS116	01	.	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

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HLA REGION SNPs 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

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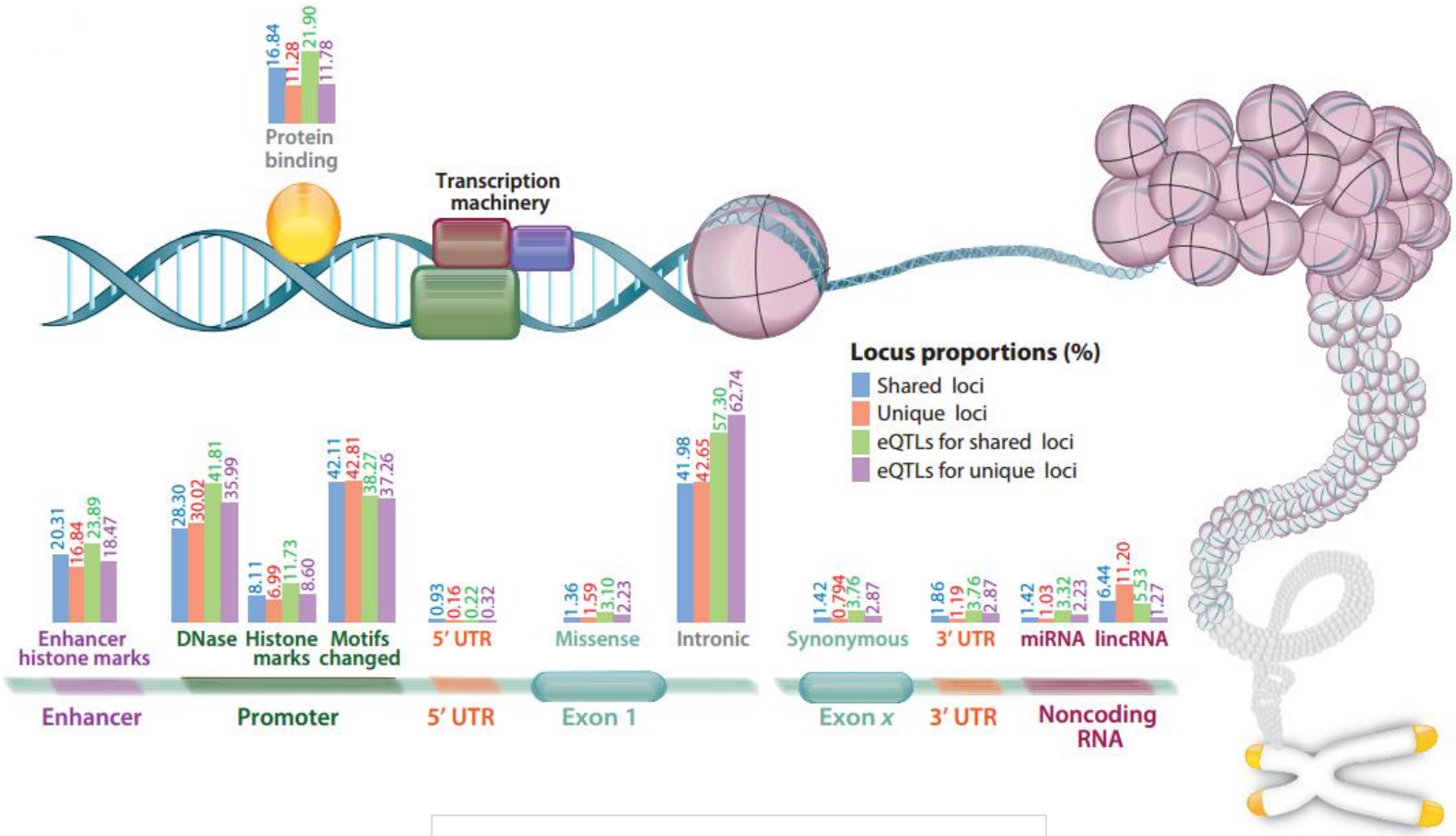
AUTOIMMUNE DISEASES and GWAS



Mapping of Immune-Mediated Disease Genes

Isis Ricaño-Ponce and Cisca Wijmenga

Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; email: c.wijmenga@umcg.nl

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AUTOIMMUNE DISEASES and GWAS

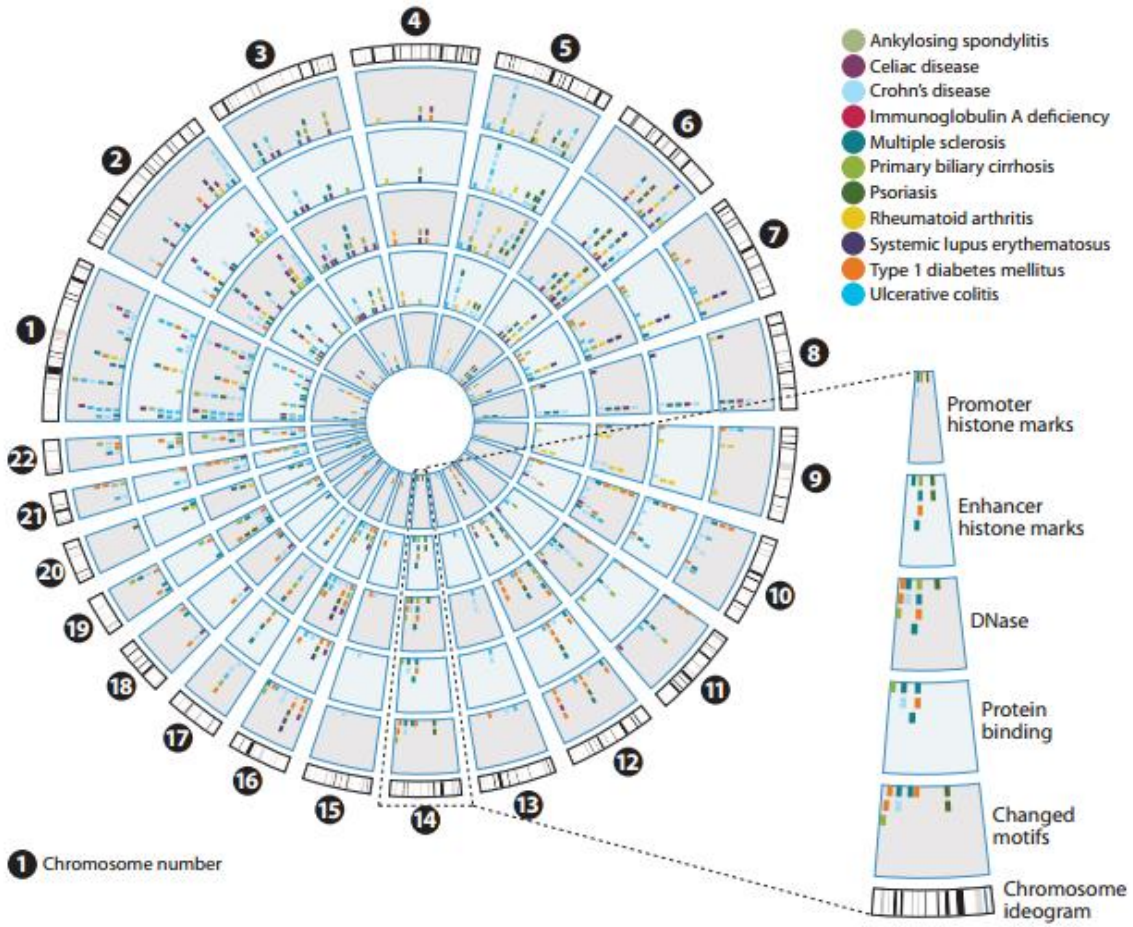

Figure 2
Characterization of variants associated with immune-mediated diseases. (*a*) Circos plot summarizing the functional annotation of the associated GWAS single-nucleotide polymorphisms (SNPs) for the GWAS loci present in Caucasian populations. From inner to outer rings: promoter histone marks,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

Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; email: c.wijmenga@umcg.nl

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AUTOIMMUNE DISEASES and GWAS

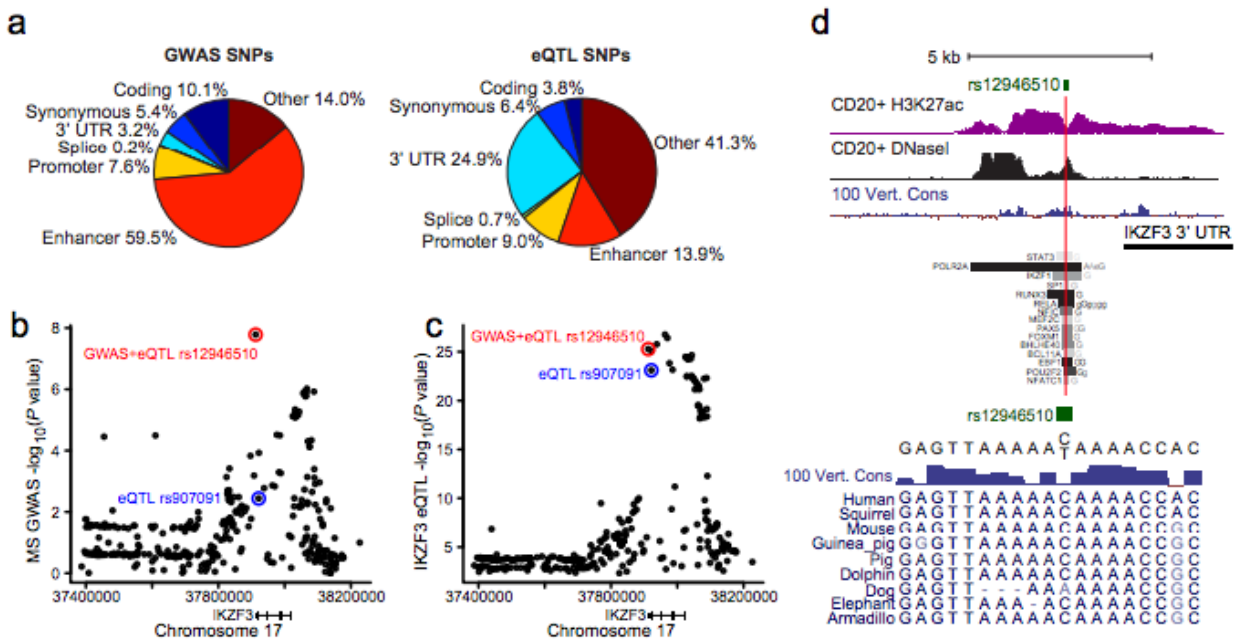

Figure 6 | Functional Effects of Disease Variants on Gene Expression. a, Pie charts show the fraction of PICS autoimmunity SNPs (left) or peripheral blood eQTLs (right) explained by the indicated genomic features. **b**, GWAS signal for MS risk at the IKZF3 locus. The minor allele of rs12946510 (red) is associated with both disease risk and eQTL effect (decreased IKZF3 expression), while the minor allele of rs907091 (blue) scored as eQTL only (increased IKZF3 expression). **c**, eQTL association signal for IKZF3 shown for the same regions as in b. **d**, H3K27ac, DNaseI and conservation signals, and selected TF binding intervals are shown in the vicinity of rs12946510, which occurs in a conserved site marked by H3K27ac in multiple cell types, including CD20+ B-cells, and bound by multiple TFs. The C/T variation at this SNP does not disrupt any clearly defined DNA motif, but coincides with a degenerate MEF2 motif.

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§]

AUTOIMMUNE DISEASES and GWAS

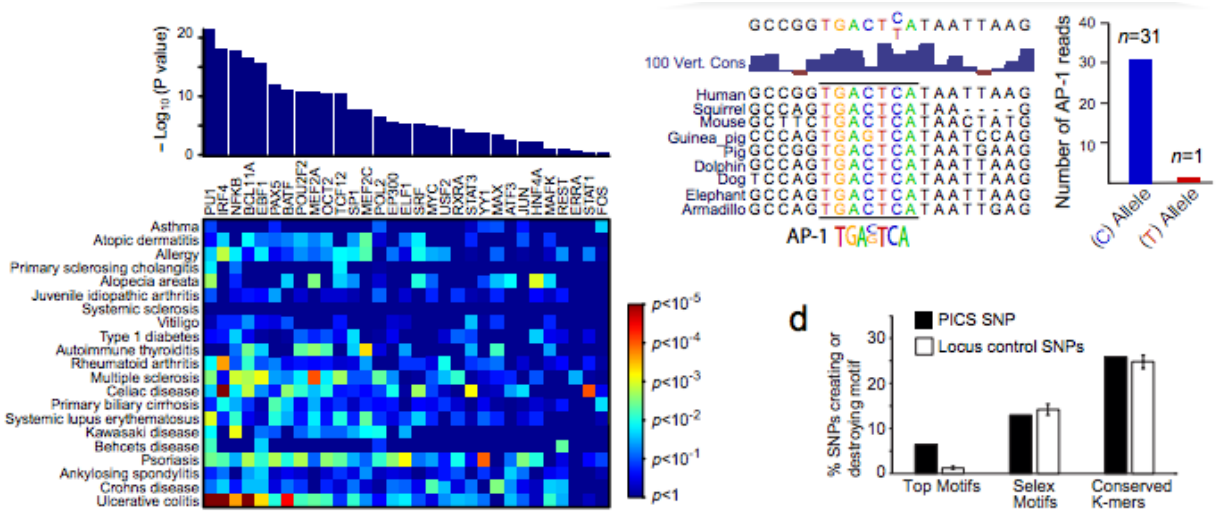

Figure 5 | Causal variants map to regions of TF binding. a, Plot depicts composite H3K27ac and DNase signals26 in immune cells over PICS autoimmunity SNPs. PICS SNPs overall coincide with nucleosome-depleted, hypersensitive sites, indicative of TF binding. **b**, Bar plot indicates TFs whose binding is enriched near PICS SNPs for all 21 autoimmune diseases26. Heatmap depicts enrichment of these TFs near variants associated with specific diseases (red:high; blue:low). **c**, H3K27ac, DNaseI26 and conservation signals, and selected TF binding intervals are shown in a SMAD3 intronic locus. rs17293632, a noncoding candidate causal SNP for Crohn's disease, disrupts a conserved AP-1 binding motif in an enhancer marked by H3K27ac in CD14+ monocytes. Summing of ChIP-seq reads overlapping the SNP in the heterozygous HeLa cell line shows that only the intact motif binds AP-1 TFs, Jun and Fos. **d**, Bar graph shows the fraction of PICS SNPs (black) versus random SNPs from the same locus (white) that create or disrupt one of the significantly enriched motifs, any Selex motif, or any conserved K-mer. Error bars indicate standard deviation from 1000 iterations using locus-matched control SNPs.

Genetic and epigenetic fine mapping of causal autoimmune disease variants

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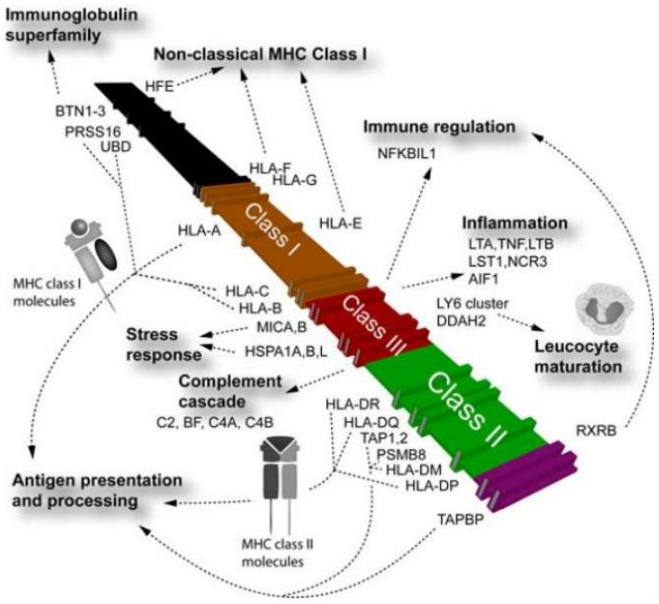
AUTOIMMUNE DISEASES and GWAS

Even though many loci have been identified by GWAS, the goal remains the discovery of "new biology"



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AUTOIMMUNE DISEASES and GWAS

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]§

Genome-wide association studies have identified loci underlying human diseases, but the causal nucleotide changes and mechanisms remain largely unknown. Here we developed a fine-mapping algorithm to identify candidate causal variants for 21 autoimmune diseases from genotyping data. We integrated these predictions with transcription and *cis*-regulatory element annotations, derived by mapping RNA and chromatin in primary immune cells, including resting and stimulated $CD4^+$ T-cell subsets, regulatory T cells, $CD8^+$ T cells, B cells, and monocytes. We find that ~90% of causal variants are non-coding, with ~60% mapping to immune-cell enhancers, many of which gain histone acetylation and transcribe enhancer-associated RNA upon immune stimulation. Causal variants tend to occur near binding sites for master regulators of immune differentiation and stimulus-dependent gene activation, but only 10–20% directly alter recognizable transcription factor binding motifs. Rather, most non-coding risk variants, including those that alter gene expression, affect non-canonical sequence determinants not well-explained by current gene regulatory models.

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AUTOIMMUNE DISEASES and GWAS

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)

The PICS algorithm described in this paper identified the causal SNP for 12% of AID risk markers

Almost all causal SNPs map to enhancers and promoters

Genetic and epigenetic fine mapping of causal autoimmune disease variants

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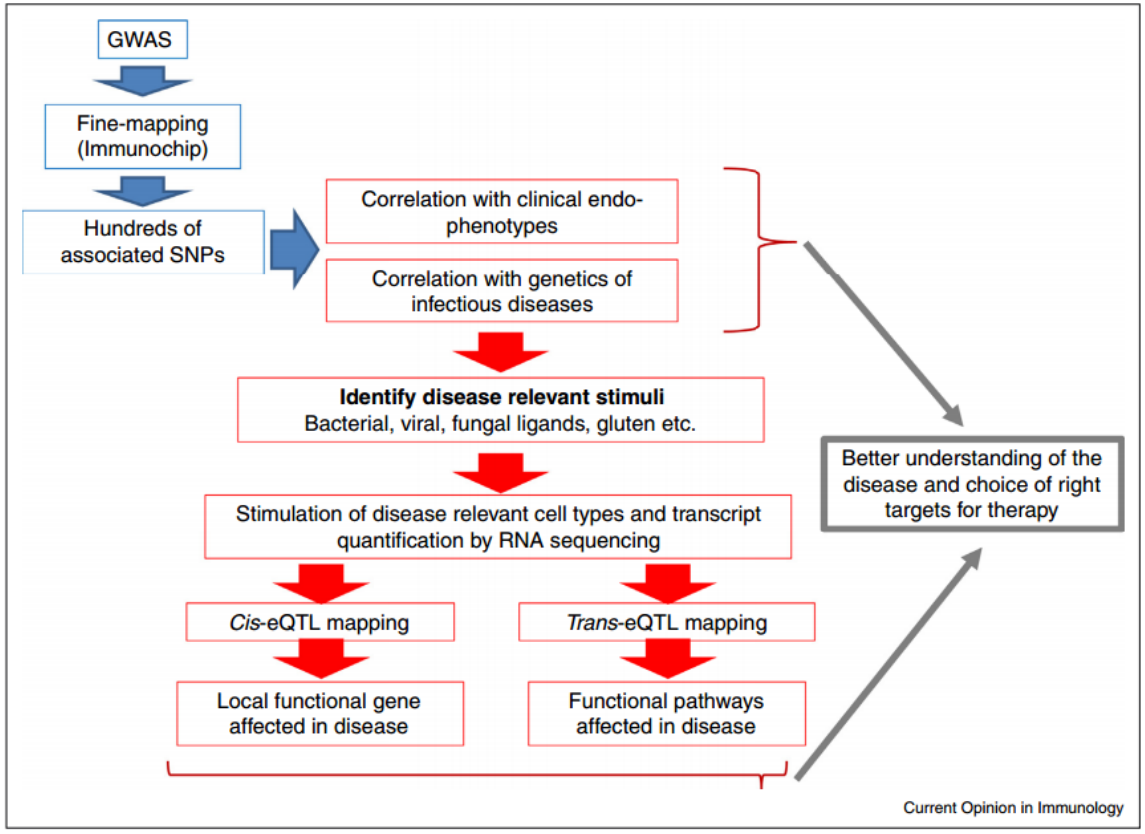
AUTOIMMUNE DISEASES and GWAS: Annotation



Shown is a flowchart outlining the steps to identify relevant triggers of autoimmunity. Analyzing the intersection between SNPs associated with immune-mediated diseases and the genetics of infectious diseases and other endophenotypes helps us to prioritize microbial and environmental triggers. These triggers can then be used as stimuli to activate immune cells to obtain transcriptional responses by RNA sequencing. *Cis*-eQTL mapping and *trans*-eQTL mapping can then identify both the causal genes and pathways. This information will yield insight into disease mechanisms and in turn inform the choice of relevant therapeutic targets.

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Current Opinion in Immunology
ELSEVIER
Genetics of immune-mediated disorders: from genome-wide association to molecular mechanism
Vinod Kumar[1], Cisca Wijmenga[1] and Ramnik J Xavier[2,3]

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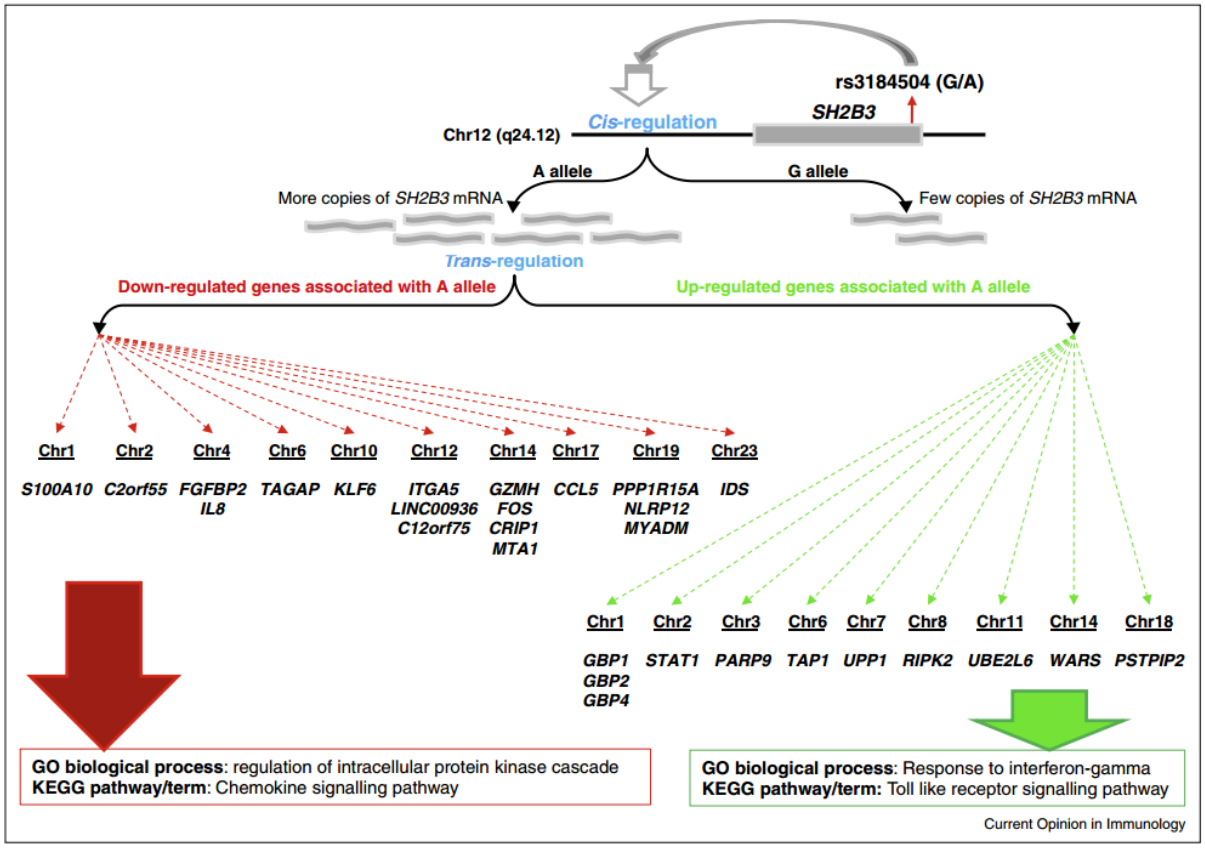
AUTOIMMUNE DISEASES and GWAS: Pathway Analysis



SNP rs3184504 on human chromosome 12 is associated with autoimmune diseases. eQTL mapping showed that the autoimmune risk allele (A allele) up-regulates *SH2B3* gene expression (*cis*-eQTL) and also affects 29 other genes on different chromosomes (*trans*-eQTL). Pathway analysis showed enrichment of genes for innate immunity among the up-regulated genes (green dotted arrows), and enrichment of genes for chemokine signalling pathway among the down-regulated genes (red dotted arrows).

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Current Opinion in Immunology
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Genetics of immune-mediated disorders: from genome-wide association to molecular mechanism

Vinod Kumar[1], Cisca Wijmenga[1] and Ramnik J Xavier[2,3]

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AUTOIMMUNE DISEASES and GWAS

What have we learned from GWAS in AID?

The most common mechanism is the regulation of gene expression (most SNPs are eQTLs)

T-cell-specific eQTLs are overrepresented among AID-associated SNPs

Most AID-associated SNPs are in non-coding regioins and within DNAse hypersensitivity regions

1.2% of AID-associated SNPs alter miRNA binding site, 8.5% map to lincRNA (expression in specific cell types)

Top three pathways appeared to be involved in AID pathogenesis are JAK-STAT, TCR signaling and cytokine-cytokine interaction pathways

AUTOIMMUNE DISEASES and GWAS

Table 1 | **Examples of genes and pathways that are associated with two or more immune-mediated diseases***

Pathway or genes	Positional candidate gene shared by ≥2 diseases (cytogenetic position)‡	Diseases associated with this pathway or ≥1 of these loci (genes)	Diseases for which the main signal is discordant or not correlated with the others (gene)
IL-23 and T_H1	*IL23R* (1p31), *IL12B* (5q33), *IL12A* (3q25), *TYK2* (19p13), *JAK2* (9p24), *STAT3* (17q21), *STAT4* (2q32), *IL27* (16p11) and *CCR6* (6q27)	Ankylosing spondylitis (*IL23R*, *IL12B*, *TYK2*, *JAK2*, and *IL27*); IBD (*IL23R*, *IL12B*, *TYK2*, *JAK2*, *STAT3*, *STAT4* and *IL27*); psoriasis (*IL23R*, *IL12B*, *TYK2* and *STAT3*); coeliac disease (*IL12A* and *STAT4*); rheumatoid arthritis (*TYK2*, *STAT4* and *CCR6*); T1D (*TYK2*); SLE (*TYK2*, *STAT4* and *IL27*); and multiple sclerosis (*IL12B*, *IL12A*, *TYK2* and *STAT3*)	Psoriasis (*IL12B*); psoriasis and rheumatoid arthritis (*TYK2*); multiple sclerosis (*STAT3* and *TYK2*); IBD and rheumatoid arthritis (*STAT4*)
NF-κB	*REL* (2p16), *TNFAIP3* (6q23), *NFKB1* (4q24) and *TNIP1* (5q32)	IBD (*REL*, *TNFAIP3* and *NFKB1*); psoriasis (*REL*, *TNFAIP3*, *NFKB1* and *TNIP1*); coeliac disease (*REL* and *TNFAIP3*); rheumatoid arthritis (*REL* and *TNFAIP3*); T1D (*TNFAIP3*); SLE (*TNFAIP3* and *TNIP1*); and multiple sclerosis (*NFKB1*)	Psoriasis (*REL* and *TNFAIP3*); rheumatoid arthritis (*REL*) and SLE (*TNFAIP3*)
Aminopeptidase	*ERAP1* (5q15) and *ERAP2* (5q15)	Ankylosing spondylitis (*ERAP1* and *ERAP2*); IBD (*ERAP2*); and psoriasis (*ERAP1* and *ERAP2*)	-
IL-2 and IL-21	*IL2*, *IL21*§ (4q26), *IL2RA* (10p15 and *IL2RB* (22q13)	IBD (*IL2*, *IL21* and *IL2RA*); coeliac disease (*IL2*, *IL21*); rheumatoid arthritis (*IL2*, *IL21*, *IL2RA* and *IL2RB*); T1D (*IL2*, *IL21*, *IL2RA* and *IL2RB*); and multiple sclerosis (*IL2RA*)	IBD (*IL2*, *IL21*) and coeliac disease (*IL2RA*)
IRF family	*IRF4* (6p25), *IRF5* (7q32), *IRF7* (11p15) and *IRF8* (16q24)	IBD (*IRF5* and *IRF8*); psoriasis (*IRF4*); coeliac disease (*IRF4*); rheumatoid arthritis (*IRF5* and *IRF8*); SLE (*IRF5*, *IRF7* and *IRF8*); and multiple sclerosis (*IRF8*)	Psoriasis (*IRF4*) and rheumatoid arthritis (*IRF8*)
T-cell co-stimulation	*CD40* (20q12), *CD28*, *CTLA4*, *ICOS*§ (2q33) and *ICOSLG* (21q22)	Ankylosing spondylitis (*ICOSLG*); IBD (*ICOSLG*); coeliac disease (*CD28*, *CTLA4* and *ICOSLG*); rheumatoid arthritis (*CD40*, *CD28* and *CTLA4*); T1D (*CD28*, *CTLA4*); and multiple sclerosis (*CD40*)	Coeliac disease (*ICOSLG*) and IBD (*CD40*)
PTPN2, *PTPN22*	*PTPN2* (18p11) and *PTPN22* (1p13)	IBD (*PTPN2* and *PTPN22*); coeliac disease (*PTPN2*); rheumatoid arthritis (*PTPN22*); T1D (*PTPN2* and *PTPN22*); and SLE (*PTPN22*)	Crohn's disease (*PTPN22*)
Ubiquitylation	*UBE2L3* (22q11)	Ankylosing spondylitis, IBD, psoriasis, coeliac disease, rheumatoid arthritis, SLE and multiple sclerosis	-
Viral response	*IFIH1* (2q24)	IBD, psoriasis, T1D and SLE	IBD
Other	*IL10* (1q32)	IBD, T1D and SLE	T1D
	IL18RAP (2q12),	IBD, coeliac disease and T1D	-
	FCGR2A (1q23),	Ankylosing spondylitis, IBD (ulcerative colitis), rheumatoid arthritis, T1D, SLE and multiple sclerosis	Ulcerative colitis
	PTGER4 (5p13)	Ankylosing spondylitis, IBD and multiple sclerosis	-
	BACH2 (6q15),	Ankylosing spondylitis, IBD, coeliac disease, T1D and multiple sclerosis	IBD
	CARD9 (9q34),	Ankylosing spondylitis and IBD	-
	ZMIZ1 (10q22),	IBD, psoriasis, coeliac disease and multiple sclerosis	-
	YDJC (22q11),	IBD, psoriasis, coeliac disease, rheumatoid arthritis and SLE	-
	TAGAP (6q25)	IBD, psoriasis, coeliac disease, rheumatoid arthritis, T1D and multiple sclerosis	Rheumatoid arthritis, T1D
	PRDM1 (6q21)	IBD, rheumatoid arthritis and SLE	Rheumatoid arthritis, SLE

No HLA region gene among the candidates!

DISEASE MECHANISMS

Genetic insights into common pathways and complex relationships among immune-mediated diseases

Miles Parkes[1], Adrian Cortes[2]*, David A. van Heel[3] and Matthew A. Brown[2]*

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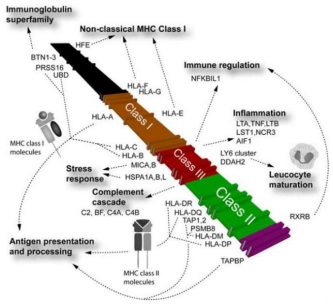
HLA REGION: UNIQUE FEATURES



- 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

An invited review paper is in preparation

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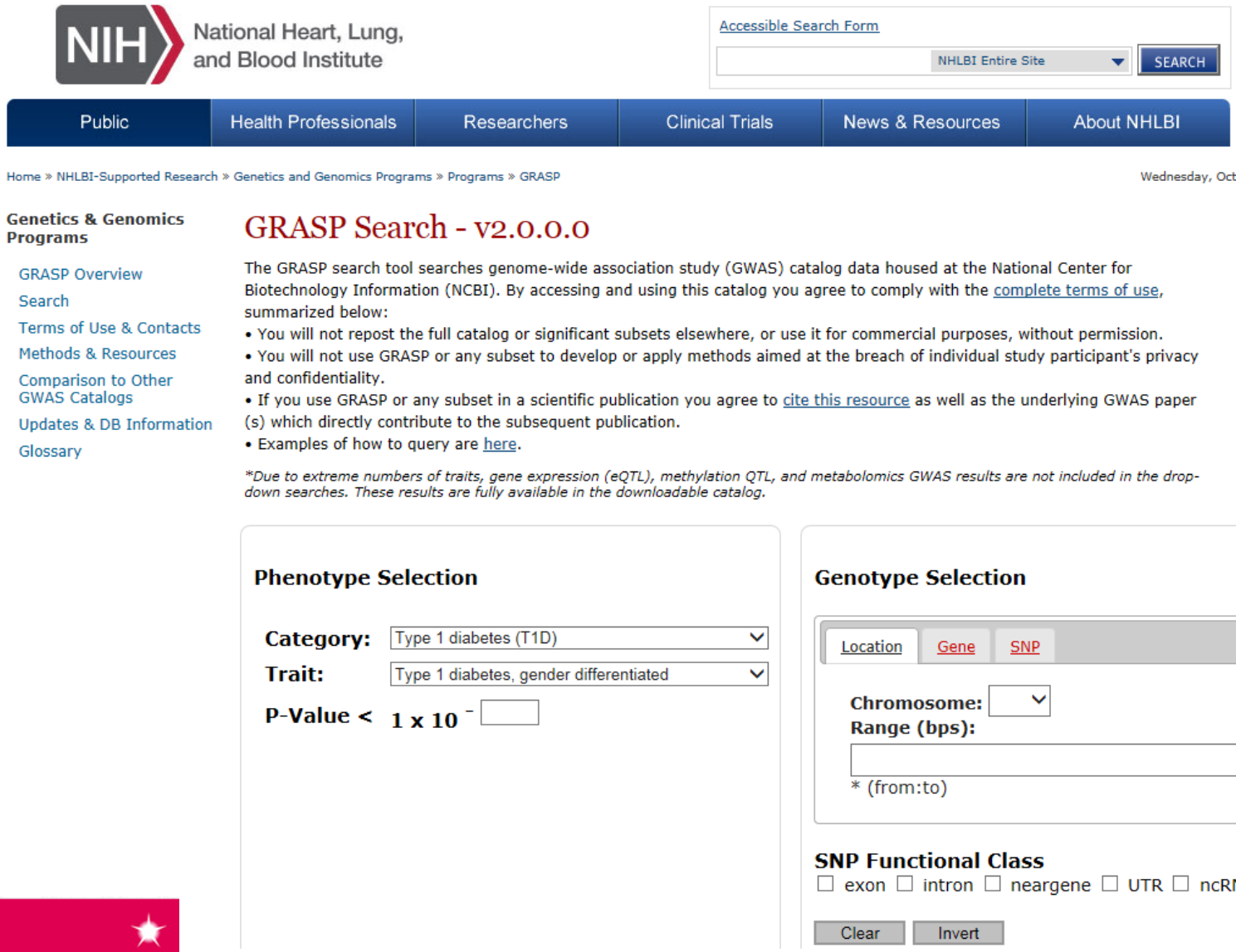
FUNCTIONAL ANNOTATION of HLA REGION SNPs



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FUNCTIONAL ANNOTATION of HLA REGION SNPs

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NHLBI key	Snp Id	Pvalue	PMID	Location	Phenotype	Phenotype Category	chr	pos	InGene	Total Samples	Platform
2045384232776...	rs6903608	1.2E-124	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32460508		41282	Affymetrix & Illumina [~2716259 (imputed)
2045384232923...	rs6923504	2.2E-86	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32460409		41282	Affymetrix & Illumina [~2716259 (imputed)
1950308832776...	rs6903608	3.1E-80	19503088	Table S2	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32460508		12408	Illumina [278502]
2103756832776...	rs6903608	2.8E-50	21037568	Table 1	Classical Hodgkin's lymphoma	Cancer,Blood-related,Blood cancer,Leukemia,Lymp	6	32460508		11261	Illumina [504374]
2115676132776...	rs6903608	9.7E-49	21156761	Table S3	Rheumatoid arthritis (ACPA-positive)	Inflammation,Arthriti... arthritis	6	32460508		9129	Illumina [1723056]
1780483632775...	rs6903608	4.5E-42	17804836	RawUna...	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32460508		6235	Illumina [297086]
2228621276144...	rs6903608	2.6E-34	22286212	Table 4	Nodular sclerosis Hodgkin lymphoma (EBV -negative)	Cancer,Blood-related,Blood cancer,Leukemia,Lymp	6	32460508		8793	Illumina [502,514]
2228621276144...	rs6903608	1.1E-31	22286212	Table 4	Classical Hodgkin lymphoma (EBV -negative)	Cancer,Blood-related,Blood cancer,Leukemia,Lymp	6	32460508		8793	Illumina [502,514]
2184178032776...	rs6903608	5.1E-24	21841780	Table1	Grave's disease	Grave's disease,Thyroid	6	32460508		10488	Illumina [486049]
1763254532775...	rs6903608	1.6E-17	17632545	TableS1	Type 1 diabetes	Type 1 diabetes (T1D),Developmental,C risk factor (CVD RF)	6	32460508		6625	Illumina [543071]
2103756832776...	rs6903608	5.3E-14	21037568	Table S7a	Classical Hodgkin's lymphoma (Epstein-Barr virus subtype)	Cancer,Blood-related,Blood cancer,Leukemia,Lymp	6	32460508		11261	Illumina [504374]
2208641732776...	rs6903608	1.2E-12	22086417	Text	Adolescent/yo... adult nodular sclerosis Hodgkin lymphoma	Cancer,Blood-related,Blood cancer,Leukemia,Lymp	6	32460508		4035	Illumina [705591]
2369663076213...	rs6923504	1.1E-11	23696630	Table S1	Joint damage severity in rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32460409		1526	Illumina [130,841]
2369663076144...	rs6903608	1.1E-11	23696630	Table S1	Joint damage severity in rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32460508		1526	Illumina [130,841]

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FUNCTIONAL ANNOTATION of HLA REGION SNPs

Type 1 Diabetes - Gender-differentiated

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NHLBI key	Snp Id	Pvalue	PMID	Location	Phenotype	Phenotype Category	chr	pos	InGene	Total Samples	Platform
175543002215269	rs3131622	4.7E-13	17554300	Webdata	Type 1 diabetes, gender differentiated	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavioral,I disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental,A arthritis,Crohn's disease	6	31452723		4806	Affymetrix [469557]
17554300270780	rs388629	6.8E-12	17554300	Webdata	Type 1 diabetes, gender differentiated	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavioral,I disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental,A arthritis,Crohn's disease	6	32137735		4806	Affymetrix [469557]
175543009744	rs6531	5.2E-06	17554300	Webdata	Type 1 diabetes, gender differentiated	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavioral,I disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental,A arthritis,Crohn's disease	6	33195674	(RXRB)	4806	Affymetrix [469557]

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FUNCTIONAL ANNOTATION of HLA REGION SNPs

Showing 1 to 21 of 21 entries

◀ Previous Next ▶

NHLBI key	Snp Id	Pvalue	PMID	Location	Phenotype	Phenotype Category	chr	pos	InGene	Total Samples	Platform
2045384227078	rs388629	5.6E-31	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	32137735		41282	Affymetrix & Illumina [~2716259 (imputed)
1755430022152	rs3131622	4.7E-13	17554300	Webdata	Type 1 diabetes, gender differentiated	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavioral, disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental,A arthritis,Crohn's disease	6	31452723		4806	Affymetrix [469557]
1755430027078	rs388629	6.8E-12	17554300	Webdata	Type 1 diabetes, gender differentiated	Cardiovascular disease (CVD),Myocardial infarction (MI),Neuro,Behavioral, disorder,Blood pressure,CVD risk factor (CVD RF),Blood-related,Type 1 diabetes (T1D),Type 2 diabetes (T2D),Developmental,A arthritis,Crohn's disease	6	32137735		4806	Affymetrix [469557]
1766053022152	rs3131622	7.7E-10	17660530	RawUna...	Multiple sclerosis	Neuro,Inflammation,... sclerosis (MS)	6	31452723		12360	Affymetrix [334923]
2045384222152	rs3131622	3.9E-09	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	31452723		41282	Affymetrix & Illumina [~2716259 (imputed)
2345563663944	rs388629	9.4E-08	23455636	FullData	Advanced age-related macular degeneration	Eye-related,Aging,Age-related macular degeneration (ARMD)	6	32137735		77255	Illumina & Affymetrix [2,442,884 (imputed)
204538429750	rs6531	1.9E-07	20453842	FullScan	Rheumatoid arthritis	Inflammation,Arthriti... arthritis	6	33195674	(RXRB)	41282	Affymetrix & Illumina [~2716259 (imputed)
2357772563944	rs388629	2.0E-07	23577725	TableS4	Age-related macular degeneration in ever smokers	Eye-related,Aging,Age-related macular degeneration (ARMD)	6	32137735		2101	Affymetrix [2,543,887 (imputed)

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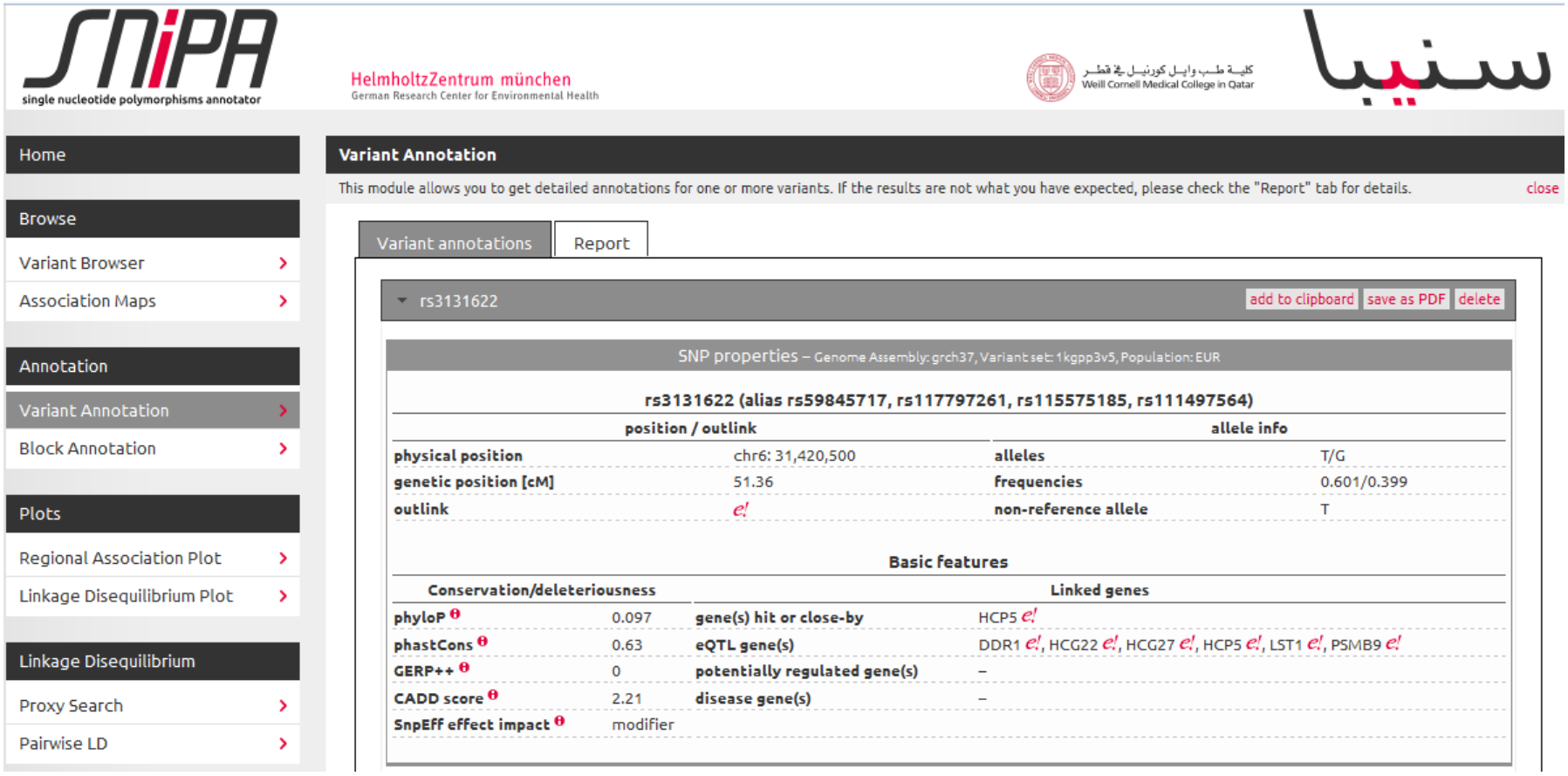
FUNCTIONAL ANNOTATION of HLA REGION SNPs



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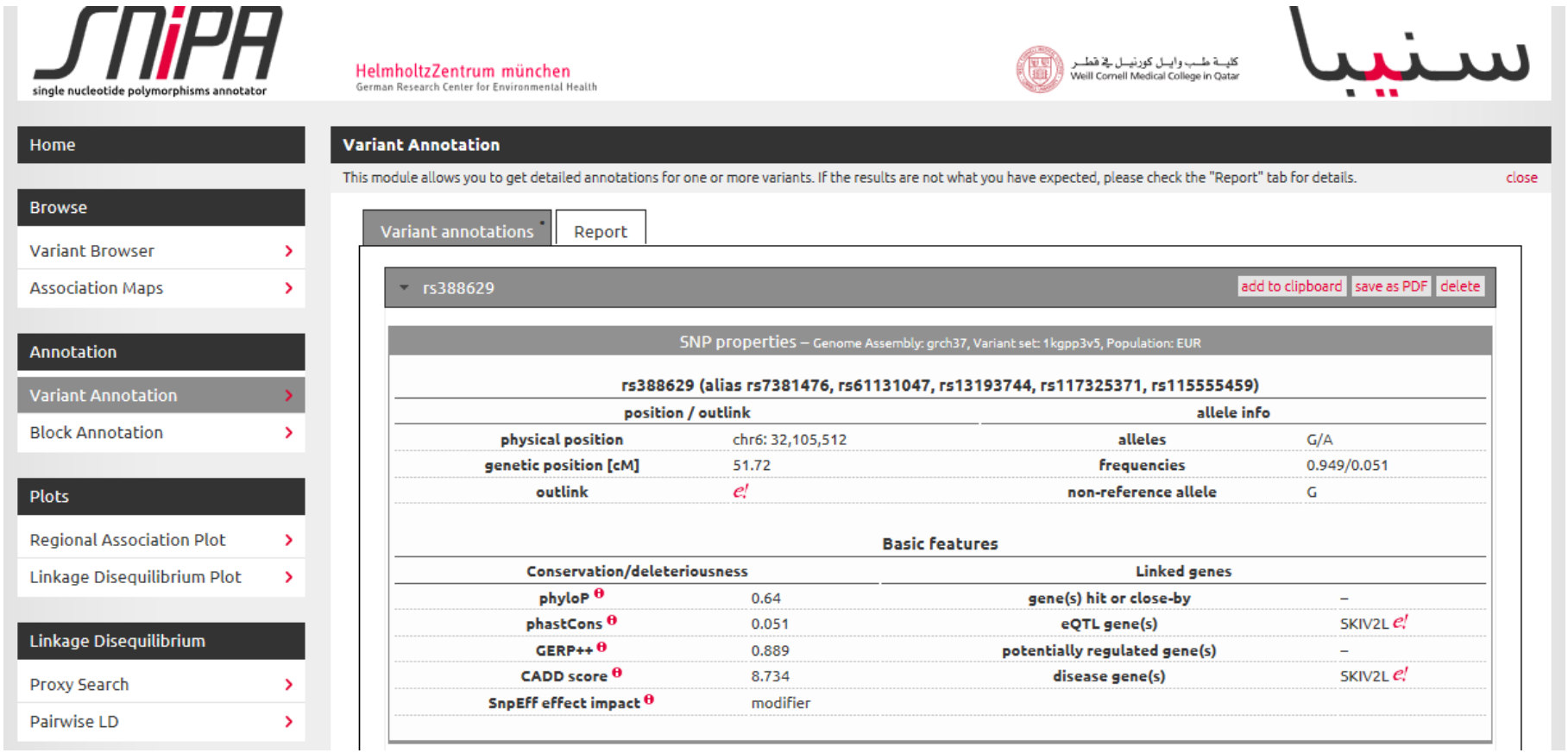
FUNCTIONAL ANNOTATION of HLA REGION SNPs



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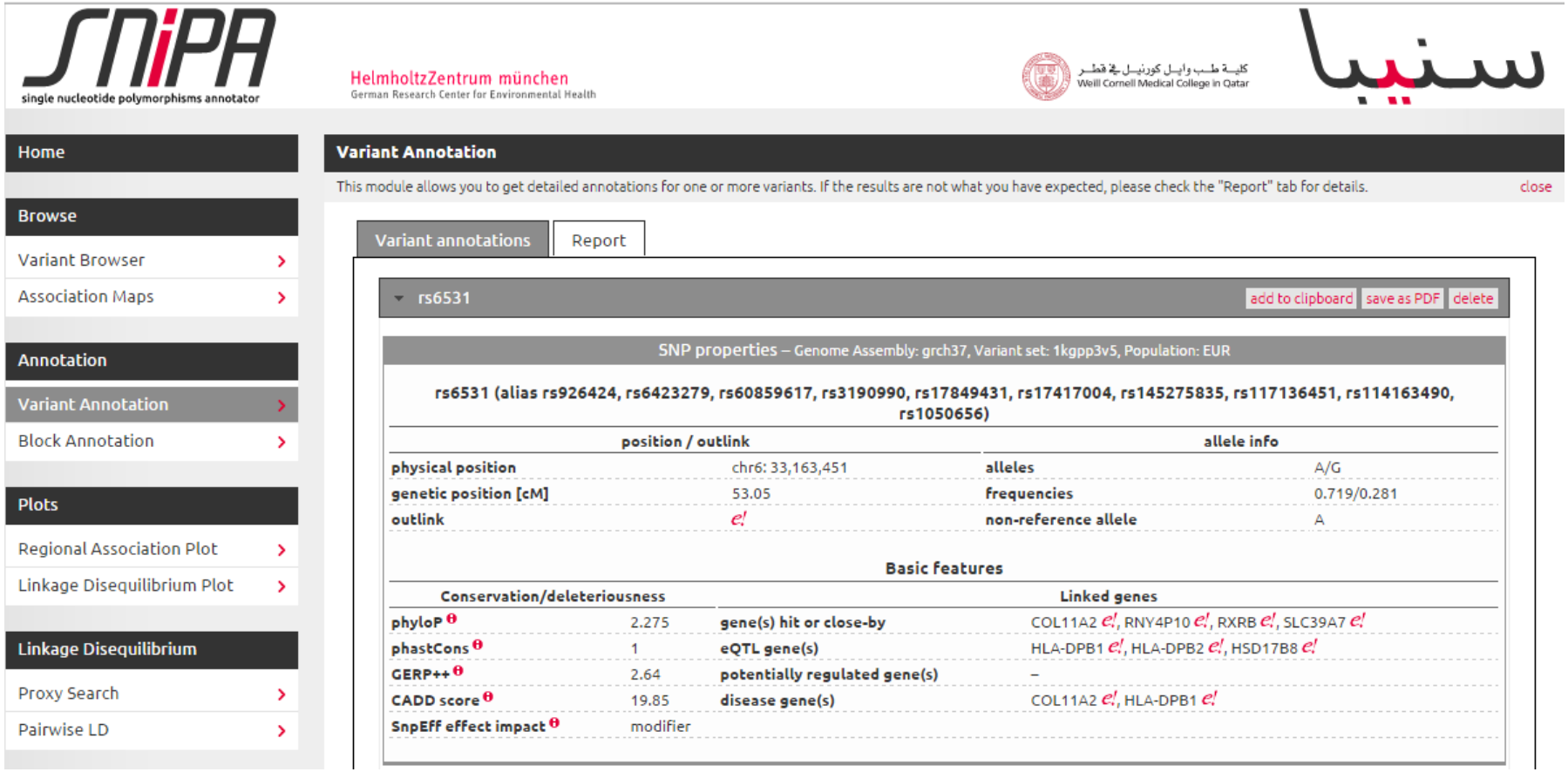
FUNCTIONAL ANNOTATION of HLA REGION SNPs



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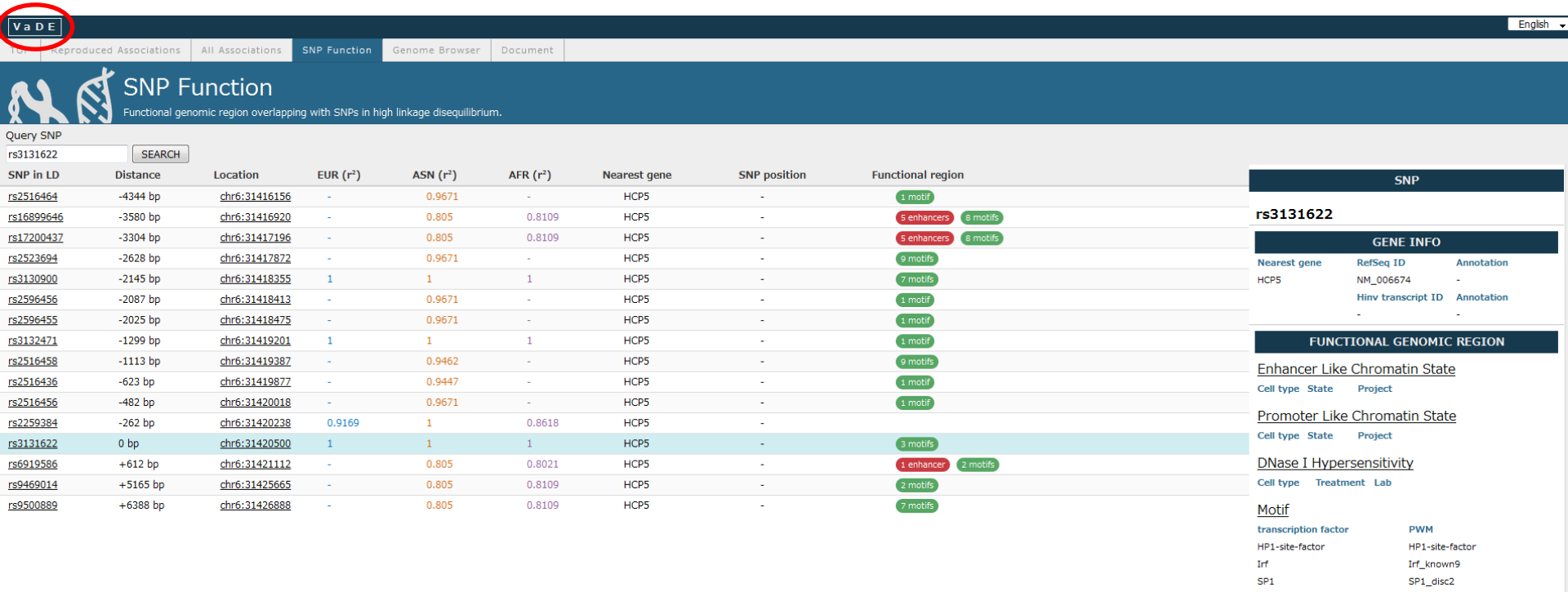
FUNCTIONAL ANNOTATION of HLA REGION SNPs

Lead SNP and proxy SNPs (statistically similar SNP set) with functional annotation



SNP in LD	Distance	Location	EUR (r^2)	ASN (r^2)	AFR (r^2)	Nearest gene	SNP position	Functional region
rs2516464	-4344 bp	chr6:31416156	-	0.9671	-	HCP5	-	1 motif
rs16899646	-3580 bp	chr6:31416920	-	0.805	0.8109	HCP5	-	5 enhancers 8 motifs
rs17200437	-3304 bp	chr6:31417196	-	0.805	0.8109	HCP5	-	5 enhancers 8 motifs
rs2523694	-2628 bp	chr6:31417872	-	0.9671	-	HCP5	-	9 motifs
rs3130900	-2145 bp	chr6:31418355	1	1	1	HCP5	-	7 motifs
rs2596456	-2087 bp	chr6:31418413	-	0.9671	-	HCP5	-	1 motif
rs2596455	-2025 bp	chr6:31418475	-	0.9671	-	HCP5	-	1 motif
rs3132471	-1299 bp	chr6:31419201	1	1	1	HCP5	-	1 motif
rs2516458	-1113 bp	chr6:31419387	-	0.9462	-	HCP5	-	9 motifs
rs2516436	-623 bp	chr6:31419877	-	0.9447	-	HCP5	-	1 motif
rs2516456	-482 bp	chr6:31420018	-	0.9671	-	HCP5	-	1 motif
rs2259384	-262 bp	chr6:31420238	0.9169	1	0.8618	HCP5	-	
rs3131622	0 bp	chr6:31420500	1	1	1	HCP5	-	3 motifs
rs6919586	+612 bp	chr6:31421112	-	0.805	0.8021	HCP5	-	1 enhancer 2 motifs
rs9469014	+5165 bp	chr6:31425665	-	0.805	0.8109	HCP5	-	2 motifs
rs9500889	+6388 bp	chr6:31426888	-	0.805	0.8109	HCP5	-	7 motifs

SNP

rs3131622

GENE INFO

Nearest gene	RefSeq ID	Annotation
HCP5	NM_006674	-
	Hinv transcript ID	Annotation
	-	-

FUNCTIONAL GENOMIC REGION

Enhancer Like Chromatin State

Cell type State Project

Promoter Like Chromatin State

Cell type State Project

DNase I Hypersensitivity

Cell type Treatment Lab

Motif

transcription factor	PWM
HP1-site-factor	HP1-site-factor
Irf	Irf_known9
SP1	SP1_disc2

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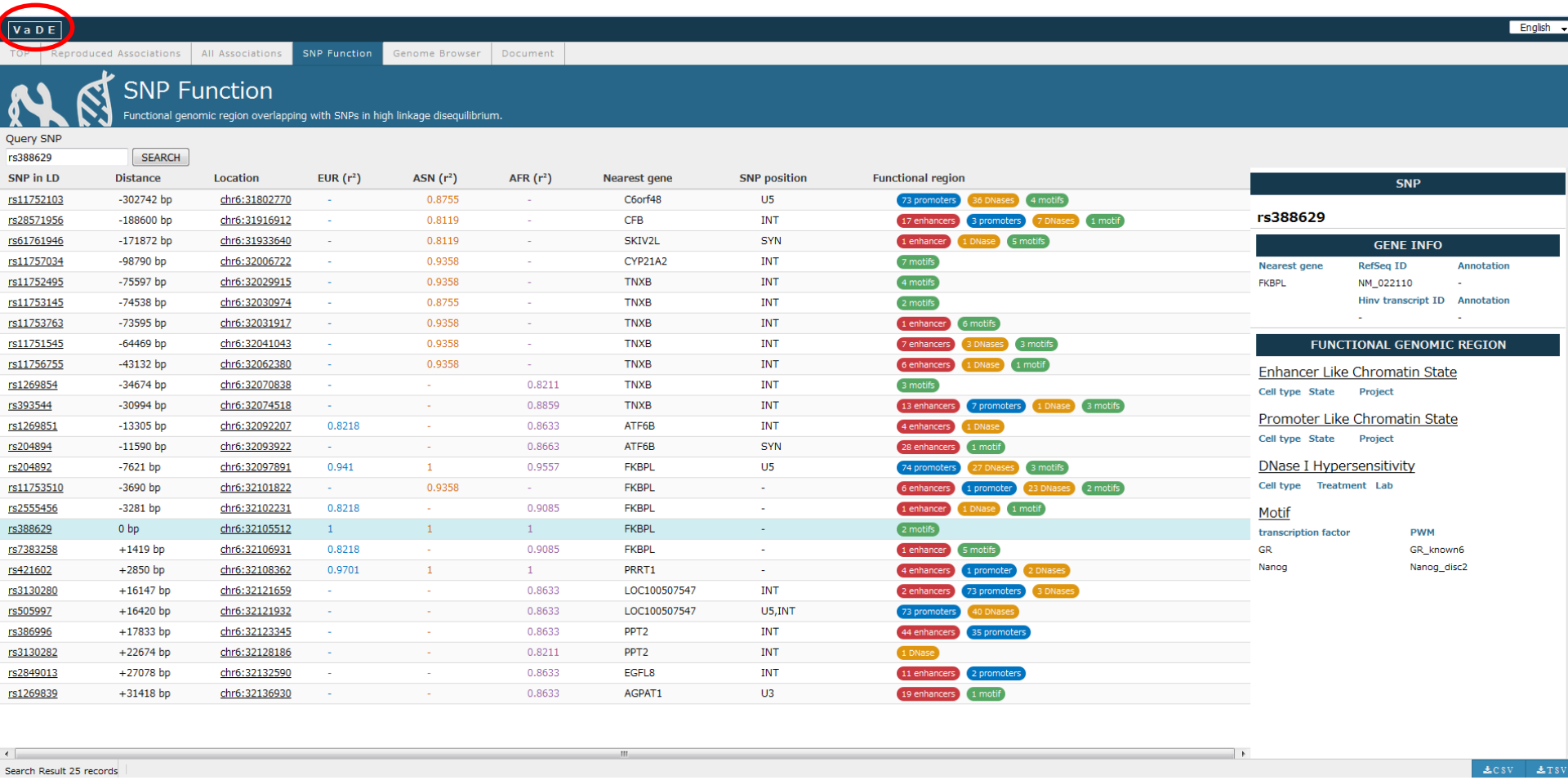
FUNCTIONAL ANNOTATION of HLA REGION SNPs

Lead SNP and proxy SNPs (statistically similar SNP set) with functional annotation



SNP in LD	Distance	Location	EUR (r^2)	ASN (r^2)	AFR (r^2)	Nearest gene	SNP position	Functional region
rs11752103	-302742 bp	chr6:31802770	-	0.8755	-	C6orf48	U5	73 promoters, 36 DNases, 4 motifs
rs28571956	-188600 bp	chr6:31916912	-	0.8119	-	CFB	INT	17 enhancers, 3 promoters, 7 DNases, 1 motif
rs61761946	-171872 bp	chr6:31933640	-	0.8119	-	SKIV2L	SYN	1 enhancer, 1 DNase, 5 motifs
rs11757034	-98790 bp	chr6:32006722	-	0.9358	-	CYP21A2	INT	7 motifs
rs11752495	-75597 bp	chr6:32029915	-	0.9358	-	TNXB	INT	4 motifs
rs11753145	-74538 bp	chr6:32030974	-	0.8755	-	TNXB	INT	2 motifs
rs11753763	-73595 bp	chr6:32031917	-	0.9358	-	TNXB	INT	1 enhancer, 6 motifs
rs11751545	-64469 bp	chr6:32041043	-	0.9358	-	TNXB	INT	7 enhancers, 3 DNases, 3 motifs
rs11756755	-43132 bp	chr6:32062380	-	0.9358	-	TNXB	INT	6 enhancers, 1 DNase, 1 motif
rs1269854	-34674 bp	chr6:32070838	-	-	0.8211	TNXB	INT	3 motifs
rs393544	-30994 bp	chr6:32074518	-	-	0.8859	TNXB	INT	13 enhancers, 7 promoters, 1 DNase, 3 motifs
rs1269851	-13305 bp	chr6:32092207	0.8218	-	0.8633	ATF6B	INT	4 enhancers, 1 DNase
rs204894	-11590 bp	chr6:32093922	-	-	0.8663	ATF6B	SYN	28 enhancers, 1 motif
rs204892	-7621 bp	chr6:32097891	0.941	1	0.9557	FKBPL	U5	74 promoters, 27 DNases, 3 motifs
rs11753510	-3690 bp	chr6:32101822	-	0.9358	-	FKBPL	-	6 enhancers, 1 promoter, 23 DNases, 2 motifs
rs2555456	-3281 bp	chr6:32102231	0.8218	-	0.9085	FKBPL	-	1 enhancer, 1 DNase, 1 motif
rs388629	0 bp	chr6:32105512	1	1	1	FKBPL	-	2 motifs
rs7383258	+1419 bp	chr6:32106931	0.8218	-	0.9085	FKBPL	-	1 enhancer, 5 motifs
rs421602	+2850 bp	chr6:32108362	0.9701	1	1	PRRT1	-	4 enhancers, 1 promoter, 2 DNases
rs3130280	+16147 bp	chr6:32121659	-	-	0.8633	LOC100507547	INT	2 enhancers, 73 promoters, 3 DNases
rs505997	+16420 bp	chr6:32121932	-	-	0.8633	LOC100507547	U5,INT	73 promoters, 40 DNases
rs386996	+17833 bp	chr6:32123345	-	-	0.8633	PPT2	INT	44 enhancers, 35 promoters
rs3130282	+22674 bp	chr6:32128186	-	-	0.8211	PPT2	INT	1 DNase
rs2849013	+27078 bp	chr6:32132590	-	-	0.8633	EGFL8	INT	11 enhancers, 2 promoters
rs1269839	+31418 bp	chr6:32136930	-	-	0.8633	AGPAT1	U3	19 enhancers, 1 motif

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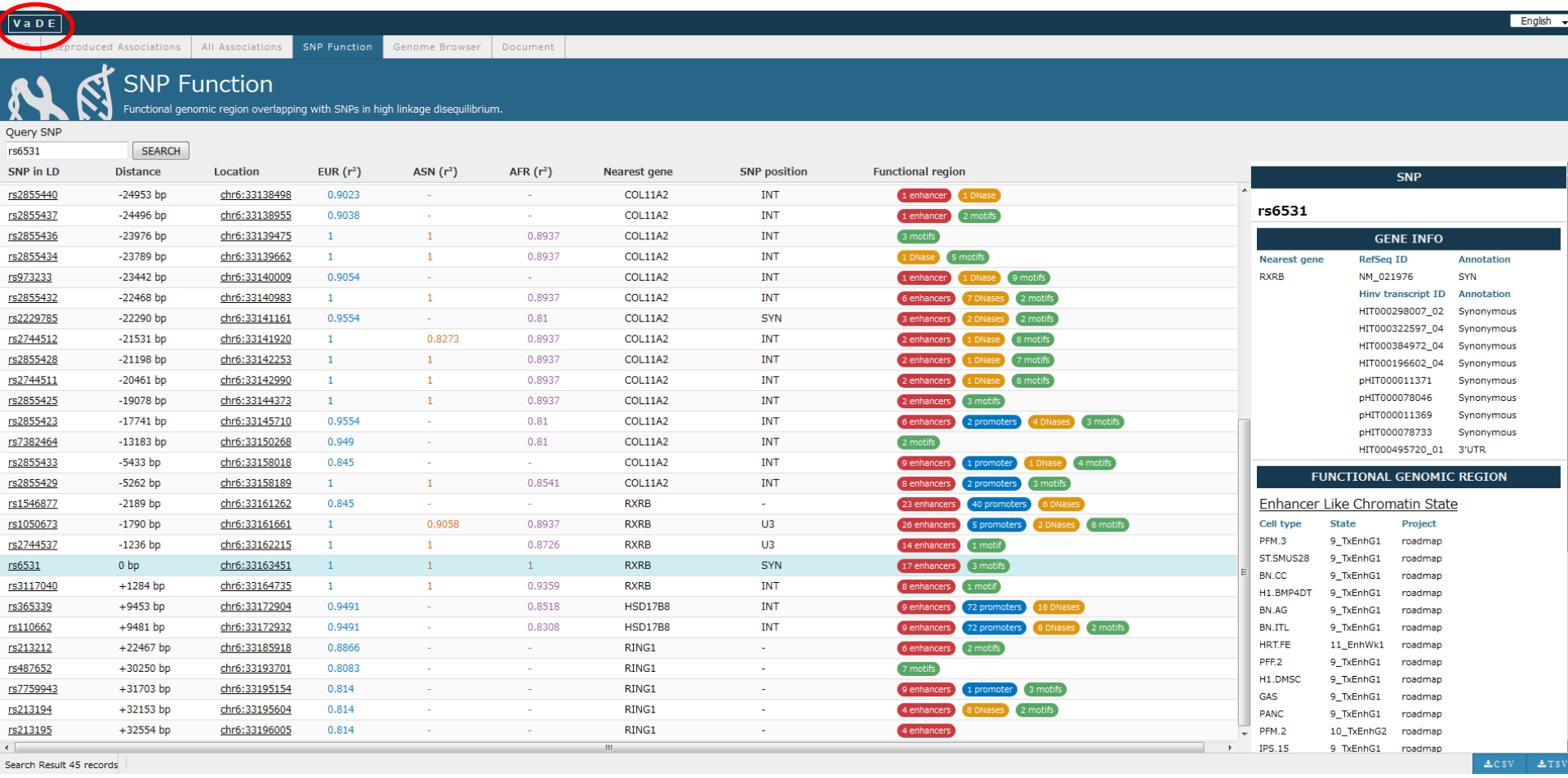
FUNCTIONAL ANNOTATION of HLA REGION SNPs

Lead SNP and proxy SNPs (statistically similar SNP set) with functional annotation



SNP in LD	Distance	Location	EUR (r^2)	ASN (r^2)	AFR (r^2)	Nearest gene	SNP position	Functional region
rs2855440	-24953 bp	chr6:33138498	0.9023	-	-	COL11A2	INT	1 enhancer, 1 DNase
rs2855437	-24496 bp	chr6:33138955	0.9038	-	-	COL11A2	INT	1 enhancer, 2 motifs
rs2855436	-23976 bp	chr6:33139475	1	1	0.8937	COL11A2	INT	3 motifs
rs2855434	-23789 bp	chr6:33139662	1	1	0.8937	COL11A2	INT	1 DNase, 5 motifs
rs973233	-23442 bp	chr6:33140009	0.9054	-	-	COL11A2	INT	1 enhancer, 1 DNase, 9 motifs
rs2855432	-22468 bp	chr6:33140983	1	1	0.8937	COL11A2	INT	6 enhancers, 7 DNases, 2 motifs
rs2229785	-22290 bp	chr6:33141161	0.9554	-	0.81	COL11A2	SYN	3 enhancers, 2 DNases, 2 motifs
rs2744512	-21531 bp	chr6:33141920	1	0.8273	0.8937	COL11A2	INT	2 enhancers, 1 DNase, 8 motifs
rs2855428	-21198 bp	chr6:33142253	1	1	0.8937	COL11A2	INT	2 enhancers, 1 DNase, 7 motifs
rs2744511	-20461 bp	chr6:33142990	1	1	0.8937	COL11A2	INT	2 enhancers, 1 DNase, 8 motifs
rs2855425	-19078 bp	chr6:33144373	1	1	0.8937	COL11A2	INT	2 enhancers, 3 motifs
rs2855423	-17741 bp	chr6:33145710	0.9554	-	0.81	COL11A2	INT	6 enhancers, 2 promoters, 4 DNases, 3 motifs
rs7382464	-13183 bp	chr6:33150268	0.949	-	0.81	COL11A2	INT	2 motifs
rs2855433	-5433 bp	chr6:33158018	0.845	-	-	COL11A2	INT	9 enhancers, 1 promoter, 1 DNase, 4 motifs
rs2855429	-5262 bp	chr6:33158189	1	1	0.8541	COL11A2	INT	8 enhancers, 2 promoters, 3 motifs
rs1546877	-2189 bp	chr6:33161262	0.845	-	-	RXRB	-	23 enhancers, 40 promoters, 6 DNases
rs1050673	-1790 bp	chr6:33161661	1	0.9058	0.8937	RXRB	U3	26 enhancers, 5 promoters, 2 DNases, 8 motifs
rs2744537	-1236 bp	chr6:33162215	1	1	0.8726	RXRB	U3	14 enhancers, 1 motif
rs6531	0 bp	chr6:33163451	1	1	1	RXRB	SYN	17 enhancers, 3 motifs
rs3117040	+1284 bp	chr6:33164735	1	1	0.9359	RXRB	INT	8 enhancers, 1 motif
rs365339	+9453 bp	chr6:33172904	0.9491	-	0.8518	HSD17B8	INT	9 enhancers, 72 promoters, 16 DNases
rs110662	+9481 bp	chr6:33172932	0.9491	-	0.8308	HSD17B8	INT	9 enhancers, 72 promoters, 8 DNases, 2 motifs
rs213212	+22467 bp	chr6:33185918	0.8866	-	-	RING1	-	6 enhancers, 2 motifs
rs487652	+30250 bp	chr6:33193701	0.8083	-	-	RING1	-	7 motifs
rs7759943	+31703 bp	chr6:33195154	0.814	-	-	RING1	-	9 enhancers, 1 promoter, 3 motifs
rs213194	+32153 bp	chr6:33195604	0.814	-	-	RING1	-	4 enhancers, 8 DNases, 2 motifs
rs213195	+32554 bp	chr6:33196005	0.814	-	-	RING1	-	4 enhancers

Search Result 45 records

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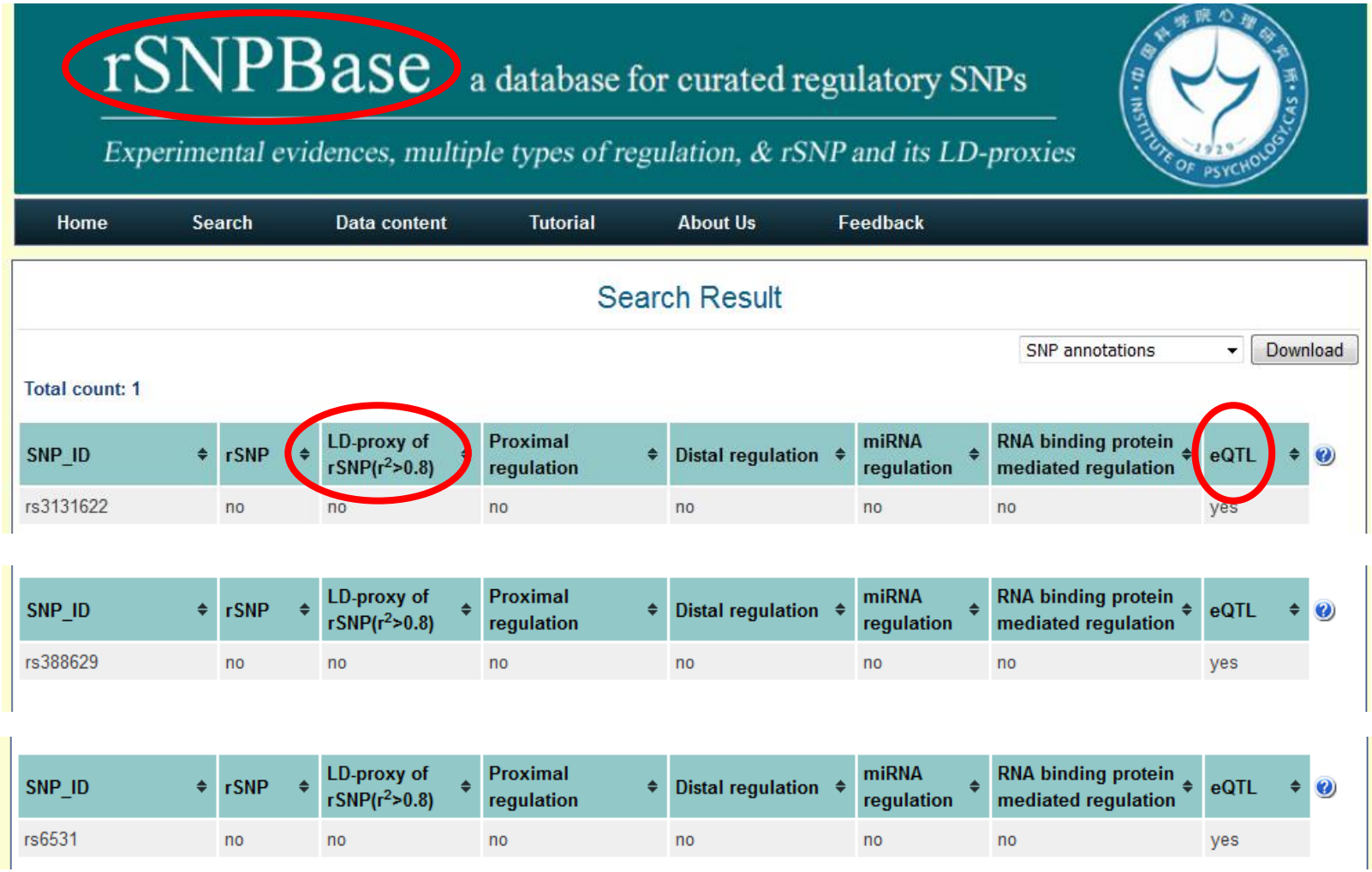
Average number of perfect proxies for AID-associated lead SNPs = 7.6

FUNCTIONAL ANNOTATION of HLA REGION SNPs



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

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FUNCTIONAL ANNOTATION of HLA REGION SNPs

RegulomeDB provides a score for regulatory function

RegulomeDB

Download About Help

The search has evaluated **3** input line(s) and found **3** SNP(s).

Summary of SNP analysis

Show 10 entries

Coordinate (0-based)	dbSNP ID	? Regulome DB Score	Other Resources
chr6:31420499	rs3131622	1f	UCSC | ENSEMBL | dbSNP
chr6:33163450	rs6531	1f	UCSC | ENSEMBL | dbSNP
chr6:32105511	rs388629	6	UCSC | ENSEMBL | dbSNP

Showing 1 to 3 of 3 entries

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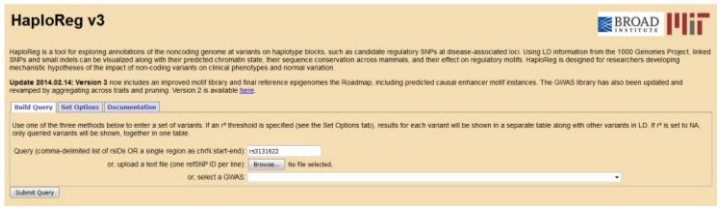
A project of the Center for Genomics and Personalized Medicine at Stanford University.

FUNCTIONAL ANNOTATION of HLA REGION SNPs

Lead SNP and proxy SNPs (statistically similar SNP set) with functional annotation



Query SNP: rs3131622 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
chr6:31414580	chr6:31446803	0.65	1	rs2596462	T	C	0.63	0.54	0.27	0.51			STRM, LNG				4 altered motifs		XXbac-BPG181B23.4	
chr6:31416156	chr6:31448379	0.74	1	rs2516464	A	G	0.60	0.54	0.20	0.48							Foxj1		HCP5	
chr6:31416639	chr6:31448862	0.65	1	rs2516462	A	G	0.63	0.54	0.27	0.51			ESC, IPSC				AIRE		HCP5	
chr6:31417872	chr6:31450095	0.74	1	rs2523694	G	A	0.60	0.53	0.20	0.48							8 altered motifs		HCP5	
chr6:31418124	chr6:31450347	0.65	1	rs2523693	C	T	0.63	0.54	0.27	0.51							CEBPB,CEBPD,STAT		HCP5	
chr6:31418355	chr6:31450578	1	1	rs3130900	G	T	0.36	0.43	0.19	0.41							5 altered motifs		HCP5	
chr6:31418413	chr6:31450636	0.7	0.95	rs2596456	A	G	0.60	0.53	0.20	0.47							p53		HCP5	
chr6:31418475	chr6:31450698	0.74	1	rs2596455	A	G	0.60	0.54	0.20	0.48							Foxp3		HCP5	
chr6:31418700	chr6:31450923	0.65	1	rs2516460	T	G	0.63	0.54	0.27	0.51				BLD,BLD			Pax-3		HCP5	
chr6:31419042	chr6:31451265	0.65	1	rs2516459	A	G	0.63	0.54	0.27	0.51							Pax-4		HCP5	
chr6:31419201	chr6:31451424	1	1	rs3132471	G	A	0.36	0.43	0.19	0.41							Mef2		HCP5	
chr6:31419387	chr6:31451610	0.74	1	rs2516458	T	C	0.60	0.54	0.20	0.48							28 altered motifs		HCP5	
chr6:31419800	chr6:31452023	0.65	1	rs2516457	A	G	0.63	0.54	0.27	0.51							5 altered motifs		HCP5	
chr6:31419877	chr6:31452100	0.74	0.99	rs2516436	C	G	0.60	0.53	0.19	0.48							Nkx2		HCP5	
chr6:31420018	chr6:31452241	0.74	1	rs2516456	T	C	0.60	0.54	0.20	0.48							Evi-1		HCP5	
chr6:31420238	chr6:31452461	0.92	1	rs2259384	G	C,T	0.39	0.47	0.19	0.43									HCP5	
chr6:31420500	chr6:31452723	1	1	rs3131622	T	G	0.36	0.43	0.19	0.41							HP1-site-factor,Irf,SP1		HCP5	
chr6:31424917	chr6:31457140	0.64	0.99	rs2516453	A	T	0.63	0.54	0.27	0.51							GR,Pax-2		HCP5	
chr6:31425033	chr6:31457256	0.64	0.99	rs2254386	T	C	0.63	0.54	0.27	0.51							AP-1,Pax-4		HCP5	

Motifs changed

4 altered motifs
Foxj1
AIRE
8 altered motifs
CEBPB,CEBPD,STAT
5 altered motifs
p53
Foxp3
Pax-3
Pax-4
Mef2
28 altered motifs
5 altered motifs
Nkx2
Evi-1

HP1-site-factor,Irf,SP1
GR,Pax-2
AP-1,Pax-4

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FUNCTIONAL ANNOTATION of HLA REGION SNPs

Lead SNP and proxy SNPs (statistically similar SNP set) with functional annotation

Query SNP: rs388629 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
chr6:31870873	chr6:31903096	0.71	0.93	rs6939227	C	A	0.09	0.05	0.00	0.04		9 organs	21 organs	6 organs			ATF3,STAT		C2	intronic
chr6:31878006	chr6:31910229	0.71	0.93	rs115067530	A	G	0.08	0.05	0.00	0.04			9 organs	5 organs			7 altered motifs		C2	intronic
chr6:31908224	chr6:31940447	0.71	0.93	rs638383	C	T	0.08	0.06	0.00	0.04		CRVX	12 organs	12 organs	6 bound proteins		LUN-1		C2	intronic
chr6:31910456	chr6:31942679	0.71	0.93	rs542654	G	T	0.08	0.06	0.00	0.04		SKIN, CRVX	5 organs				7 altered motifs		C2	intronic
chr6:31916062	chr6:31948285	0.71	0.93	rs512559	A	G	0.08	0.06	0.00	0.04		SKIN, CRVX	6 organs				BDP1,Ets		CFB	intronic
chr6:31937037	chr6:31969260	0.71	0.93	rs449283	C	T	0.09	0.06	0.00	0.04			6 organs				EWSR1-FLI1,HDAC2		SKIV2L	intronic
chr6:31938635	chr6:31970858	0.68	0.9	rs416002	G	C	0.09	0.06	0.00	0.04		14 organs	16 organs	BLD,OVRY,MUS			9 altered motifs		DOM3Z	intronic
chr6:31941390	chr6:31973613	0.71	0.93	rs374780	A	G	0.08	0.06	0.00	0.04		17 organs	13 organs				Foxl1,Pax-4		STK19	intronic
chr6:32017545	chr6:32049766	0.65	0.89	rs11331391	T	TG	0.09	0.06	0.00	0.04		SKIN	FAT, ADRL, MUS	ADRL,MUS			7 altered motifs		TNXB	intronic
chr6:32023903	chr6:32056126	0.65	0.89	rs440160	G	C	0.09	0.06	0.00	0.04							4 altered motifs		TNXB	missense
chr6:32045226	chr6:32077449	0.65	0.89	rs204878	T	A	0.09	0.06	0.00	0.04			9 organs				11 altered motifs		TNXB	intronic
chr6:32059400	chr6:32091623	0.71	0.93	rs204898	C	T	0.09	0.06	0.00	0.04			PLCNT, OVRY						TNXB	intronic
chr6:32066220	chr6:32098443	0.62	0.96	rs204895	C	T	0.01	0.04	0.00	0.03							GR		TNXB	intronic
chr6:32070838	chr6:32103061	0.79	1	rs1269854	T	C	0.09	0.06	0.00	0.04				CRVX			Pou2f2,TFIIA		TNXB	intronic
chr6:32073913	chr6:32106136	0.68	0.9	rs1269853	G	C	0.07	0.06	0.00	0.04		FAT, GI	5 organs				24 altered motifs		TNXB	intronic
chr6:32074518	chr6:32106741	0.79	1	rs393544	C	G	0.09	0.06	0.00	0.04		5 organs	10 organs				BDP1,SP1,STAT		TNXB	intronic
chr6:32085598	chr6:32117821	0.7	0.96	rs204890	C	T	0.08	0.06	0.00	0.04			SKIN, MUS				THAP1		ATF6B	intronic
chr6:32086092	chr6:32118315	0.7	1	rs204889	G	A	0.03	0.05	0.00	0.03			FAT, SKIN				9 altered motifs		ATF6B	intronic
chr6:32092207	chr6:32124430	0.82	1	rs1269851	T	C	0.09	0.06	0.00	0.04			BLD						ATF6B	intronic
chr6:32093922	chr6:32126145	0.77	0.93	rs204894	G	A	0.10	0.06	0.00	0.04			8 organs	BLD			CDP		ATF6B	synonymous
chr6:32097891	chr6:32130114	0.94	0.97	rs204892	A	G	0.10	0.07	0.03	0.05		24 organs	BLD	46 organs	8 bound proteins		SP1,TCF12,TLX1::NFIC		FKBPL	5'-UTR
chr6:32102231	chr6:32134454	0.82	1	rs2555456	C	T	0.09	0.06	0.00	0.04			BLD				Irf		4.2kb 5' of FKBPL	
chr6:32102605	chr6:32134828	0.97	1	rs145902171	GCTCT	G	0.10	0.07	0.03	0.04			BLD				CEBPB,Hdx,STAT		4.5kb 5' of FKBPL	
chr6:32105512	chr6:32137735	1	1	rs388629	G	A	0.10	0.07	0.03	0.05		SKIN	OVRY, LIV				GR,Nanog		7.4kb 5' of FKBPL	
chr6:32106931	chr6:32139154	0.82	1	rs7383258	C	T	0.09	0.06	0.00	0.04			OVRY, LIV				4 altered motifs		8.9kb 5' of FKBPL	
chr6:32108362	chr6:32140585	0.97	1	rs421602	C	G	0.10	0.07	0.03	0.04		LIV	7 organs	ADRL,OVRY,BLD	GATA2,TAL1,GATA1				7.8kb 3' of PRRT1	
chr6:32108367	chr6:32140590	0.68	1	rs439343	A	G	0.01	0.04	0.00	0.03		LIV	7 organs	ADRL,OVRY,BLD	GATA2,TAL1,GATA1		Pou3f2		7.8kb 3' of PRRT1	
chr6:32121659	chr6:32153882	0.76	0.96	rs3130280	T	C	0.09	0.06	0.00	0.04		24 organs	4 organs	44 organs	11 bound proteins				PRRT1	intronic
chr6:32121932	chr6:32154155	0.79	1	rs505997	C	T	0.09	0.06	0.00	0.04		24 organs	BLD, SKIN, THYM	52 organs	26 bound proteins				PRRT1	5'-UTR
chr6:32123345	chr6:32155568	0.79	1	rs386996	G	A	0.09	0.06	0.00	0.04		10 organs	19 organs		POL2				PPT2	intronic
chr6:32128186	chr6:32160409	0.73	0.96	rs3130282	G	T	0.09	0.06	0.00	0.04									PPT2	intronic
chr6:32132590	chr6:32164813	0.73	0.96	rs2849013	A	G	0.09	0.06	0.00	0.04		SKIN	ESDR, BRN, MUS						EGFL8	intronic
chr6:32136930	chr6:32169153	0.73	0.96	rs1269839	G	T	0.09	0.06	0.00	0.04			8 organs	BLD	CTCF,POL2,YY1		CEBPB		XXbac-BPG300A18.12	3'-UTR
chr6:32140003	chr6:32172226	0.73	0.96	rs417035	C	T	0.10	0.06	0.00	0.04			BLD						AGPAT1	intronic
chr6:32149883	chr6:32182106	0.61	0.83	rs204996	C	T	0.11	0.07	0.08	0.04			9 organs	GI	POL2,GATA2,GATA1		15 altered motifs		RNF5	intronic
chr6:32174755	chr6:32206978	0.68	0.96	rs2515891	T	C	0.08	0.07	0.00	0.03							Mtf1,RFX5,Zfx		NOTCH4	intronic
chr6:32184139	chr6:32216362	0.62	0.96	rs477785	G	A	0.06	0.06	0.00	0.03			BLD		YY1		5 altered motifs		NOTCH4	intronic

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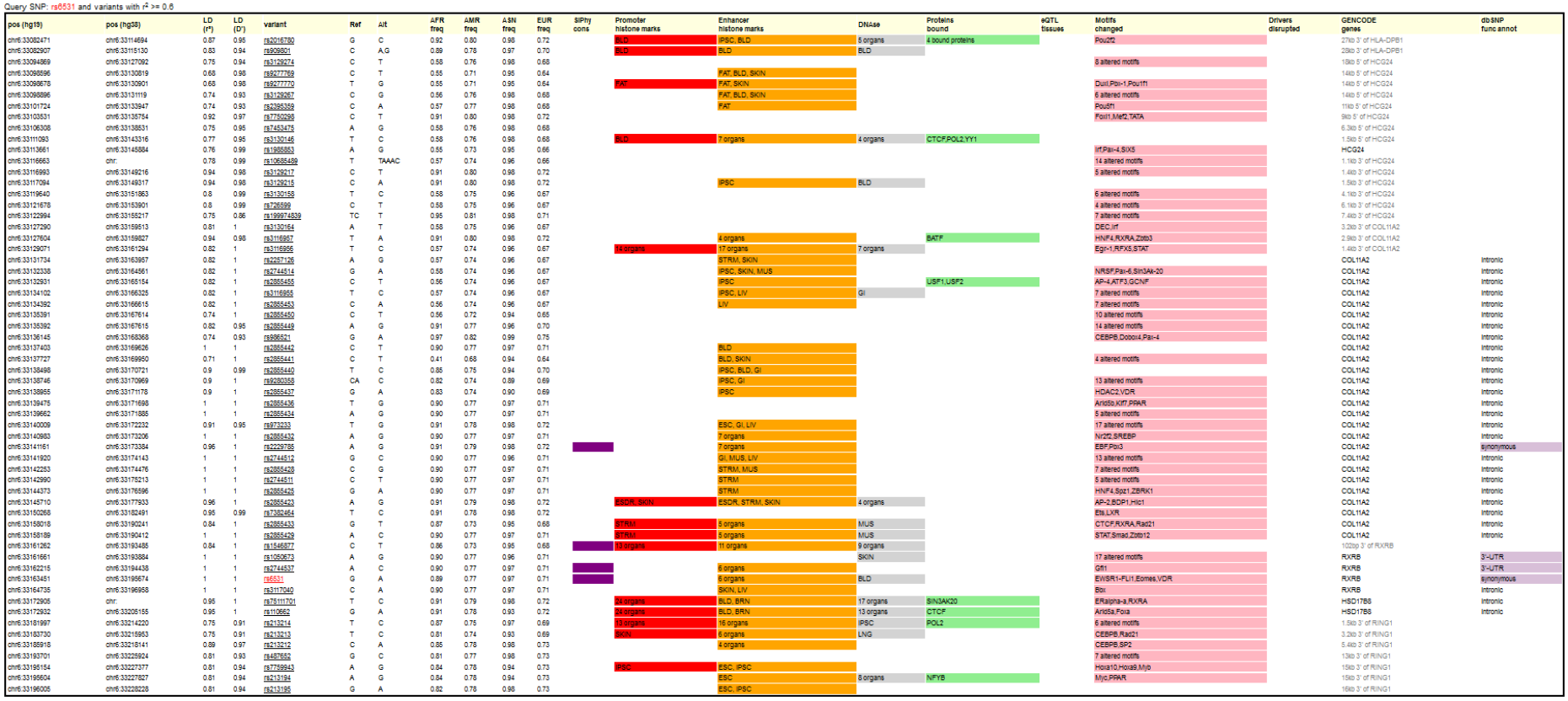
FUNCTIONAL ANNOTATION of HLA REGION SNPs

Lead SNP and proxy SNPs (statistically similar SNP set) with functional annotation



Query SNP: rs6531 and variants with r² >= 0.6

pos (hg19)	pos (hg38)	LD (r²)	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
chr6:33082471	chr6:33114694	0.87	0.95	rs2016780	G	C	0.92	0.80	0.98	0.72		BLD	IPSC, BLD	8 organs	4 bound proteins		Pou2f2		27kb 3' of HLA-DPB1	
chr6:33082907	chr6:33115130	0.83	0.94	rs909801	C	A,G	0.89	0.78	0.97	0.70		BLD	BLD	BLD					23kb 3' of HLA-DPB1	
chr6:33094969	chr6:33127092	0.75	0.94	rs3129274	C	T	0.58	0.76	0.98	0.68							8 altered motifs		19kb 5' of HCG24	
chr6:33098596	chr6:33130819	0.68	0.98	rs9277769	C	T	0.55	0.71	0.95	0.64			FAT, BLD, SKIN						14kb 5' of HCG24	
chr6:33098678	chr6:33130901	0.68	0.98	rs9277770	T	G	0.55	0.71	0.95	0.64		FAT	FAT, SKIN				Dux1,Pbx-1,Pou1f1		14kb 5' of HCG24	
chr6:33098896	chr6:3313119	0.74	0.93	rs3129267	C	G	0.56	0.76	0.98	0.68			FAT, BLD, SKIN				6 altered motifs		14kb 5' of HCG24	
chr6:33101724	chr6:33133947	0.74	0.93	rs2395359	C	A	0.57	0.77	0.98	0.68			FAT				Pou5f1		11kb 5' of HCG24	
chr6:33103531	chr6:33135754	0.92	0.97	rs7750296	C	T	0.91	0.80	0.98	0.72							Foxl1,Mef2,TATA		9kb 5' of HCG24	
chr6:33106308	chr6:33138531	0.75	0.95	rs7453475	A	G	0.58	0.76	0.98	0.68									6.3kb 5' of HCG24	
chr6:33111093	chr6:33143316	0.77	0.95	rs3130146	T	C	0.58	0.76	0.98	0.68		BLD	7 organs	4 organs	CTCF,POL2,YY1				1.5kb 5' of HCG24	
chr6:33113661	chr6:33145884	0.76	0.99	rs1986863	A	G	0.55	0.73	0.95	0.66							Irf,Pax-4,SIX5		HCG24	
chr6:33116663	chr:	0.78	0.99	rs10685489	T	TAAAC	0.57	0.74	0.96	0.66							14 altered motifs		1.1kb 3' of HCG24	
chr6:33116993	chr6:33149216	0.94	0.98	rs3129217	C	T	0.91	0.80	0.98	0.72							8 altered motifs		1.4kb 3' of HCG24	
chr6:33117094	chr6:33149317	0.94	0.98	rs3129218	C	A	0.91	0.80	0.98	0.72			IPSC	BLD					1.5kb 3' of HCG24	
chr6:33119640	chr6:33151863	0.8	0.99	rs3130156	T	C	0.58	0.75	0.96	0.67							6 altered motifs		4.1kb 3' of HCG24	
chr6:33121678	chr6:33153901	0.8	0.99	rs726599	C	T	0.58	0.75	0.96	0.67							4 altered motifs		6.1kb 3' of HCG24	
chr6:33122994	chr6:33155217	0.75	0.86	rs199974839	TC	T	0.95	0.81	0.98	0.71							7 altered motifs		7.4kb 3' of HCG24	
chr6:33127290	chr6:33159513	0.81	1	rs3130164	A	T	0.58	0.75	0.96	0.67							DEC,Irf		3.2kb 3' of COL11A2	
chr6:33127604	chr6:33159827	0.94	0.98	rs3116967	T	A	0.91	0.80	0.98	0.72			4 organs		BATF		HNF4,RXRA,Zbtb3		2.9kb 3' of COL11A2	
chr6:33129071	chr6:33161294	0.82	1	rs3116956	T	C	0.57	0.74	0.96	0.67		14 organs	17 organs	7 organs			Egr-1,RFX5,STAT		1.4kb 3' of COL11A2	
chr6:33131734	chr6:33163957	0.82	1	rs2257126	A	G	0.57	0.74	0.96	0.67			STRM, SKIN						COL11A2	Intronic
chr6:33132338	chr6:33164561	0.82	1	rs2744514	G	A	0.58	0.74	0.96	0.67			IPSC, SKIN, MUS				NRSF,Pax-6,Sin3Ak-20		COL11A2	Intronic
chr6:33132931	chr6:33165154	0.82	1	rs2855455	C	T	0.56	0.74	0.96	0.67			IPSC		USF1,USF2		AP-4,ATF3,GCNF		COL11A2	Intronic
chr6:33134102	chr6:33166325	0.82	1	rs3116955	T	C	0.57	0.74	0.96	0.67			IPSC, LIV	GI			7 altered motifs		COL11A2	Intronic
chr6:33134392	chr6:33166615	0.82	1	rs2855453	C	A	0.56	0.74	0.96	0.67			LIV				7 altered motifs		COL11A2	Intronic
chr6:33135391	chr6:33167614	0.74	1	rs2855450	C	T	0.56	0.72	0.94	0.65							10 altered motifs		COL11A2	Intronic
chr6:33135392	chr6:33167615	0.82	0.95	rs2855449	A	G	0.91	0.77	0.96	0.70							14 altered motifs		COL11A2	Intronic
chr6:33136145	chr6:33168368	0.74	0.93	rs996521	G	A	0.97	0.82	0.99	0.75							CEBPB,Dobox4,Pax-4		COL11A2	Intronic
chr6:33137403	chr6:33169626	1	1	rs2855442	C	T	0.90	0.77	0.97	0.71			BLD						COL11A2	Intronic
chr6:33137727	chr6:33169950	0.71	1	rs2855441	C	T	0.41	0.68	0.94	0.64			BLD, SKIN				4 altered motifs		COL11A2	Intronic
chr6:33138498	chr6:33170721	0.9	0.99	rs2855440	T	C	0.85	0.75	0.94	0.70			IPSC, BLD, GI						COL11A2	Intronic
chr6:33138746	chr6:33170969	0.9	1	rs9280358	CA	C	0.82	0.74	0.89	0.69			IPSC, GI				13 altered motifs		COL11A2	Intronic
chr6:33138955	chr6:33171178	0.9	1	rs2855437	G	A	0.83	0.74	0.90	0.69			IPSC				HDAC2,VDR		COL11A2	Intronic
chr6:33139475	chr6:33171698	1	1	rs2855436	T	G	0.90	0.77	0.97	0.71							Arid5b,Klf7,PPAR		COL11A2	Intronic
chr6:33139662	chr6:33171885	1	1	rs2855434	A	G	0.90	0.77	0.97	0.71							5 altered motifs		COL11A2	Intronic
chr6:33140009	chr6:33172232	0.91	0.95	rs973233	T	G	0.91	0.78	0.98	0.72			ESC, GI, LIV				17 altered motifs		COL11A2	Intronic
chr6:33140983	chr6:33173206	1	1	rs2855432	A	G	0.90	0.77	0.97	0.71			7 organs				Nr2f2,SREBP		COL11A2	Intronic
chr6:33141161	chr6:33173384	0.96	1	rs2229785	A	G	0.91	0.79	0.98	0.72			7 organs				EBF,Pax3		COL11A2	synonymous
chr6:33141920	chr6:33174143	1	1	rs2744512	G	C	0.90	0.77	0.96	0.71			GI, MUS, LIV				13 altered motifs		COL11A2	Intronic
chr6:33142253	chr6:33174476	1	1	rs2855426	C	G	0.90	0.77	0.97	0.71			STRM, MUS				7 altered motifs		COL11A2	Intronic
chr6:33142990	chr6:33175213	1	1	rs2744511	C	T	0.90	0.77	0.97	0.71			STRM				5 altered motifs		COL11A2	Intronic
chr6:33144373	chr6:33176696	1	1	rs2855425	G	A	0.90	0.77	0.97	0.71			STRM				HNF4,Sp21,ZBRK1		COL11A2	Intronic
chr6:33145710	chr6:33177933	0.96	1	rs2855423	A	G	0.91	0.79	0.98	0.72		ESDR, SKIN	ESDR, STRM, SKIN	4 organs			AP-2,EDP1,Hic1		COL11A2	Intronic
chr6:33150268	chr6:33182491	0.95	0.99	rs7382464	T	C	0.91	0.78	0.98	0.72							Ets,LXR		COL11A2	Intronic
chr6:33158018	chr6:33190241	0.84	1	rs2855433	G	T	0.87	0.73	0.95	0.68		STRM	5 organs	MUS			CTCF,RXRA,Rad21		COL11A2	Intronic
chr6:33158189	chr6:33190412	1	1	rs2855429	A	C	0.90	0.77	0.97	0.71		STRM	5 organs	MUS			STAT,Smad,Zbtb12		COL11A2	Intronic
chr6:33161262	chr6:33193485	0.84	1	rs1546877	C	T	0.86	0.73	0.95	0.68		13 organs	11 organs	9 organs					102bp 3' of RXRB	
chr6:33161661	chr6:33193884	1	1	rs1050573	A	G	0.90	0.77	0.96	0.71				SKIN			17 altered motifs		RXRB	3'-UTR
chr6:33162215	chr6:33194438	1	1	rs2744537	A	C	0.90	0.77	0.97	0.71			6 organs				Gfi1		RXRB	3'-UTR
chr6:33163451	chr6:33195674	1	1	rs6531	G	A	0.89	0.77	0.97	0.71			6 organs	BLD			EWSR1-FLI1,Eomes,VDR		RXRB	synonymous
chr6:33164735	chr6:33196958	1	1	rs3117040	C	A	0.90	0.77	0.97	0.71			SKIN, LIV				Box		RXRB	Intronic
chr6:33172905	chr:	0.95	1	rs75111701	T	C	0.91	0.79	0.98	0.72		24 organs	BLD, BRN	17 organs	SIN3AK20		ERalpha-a,RXRA		HSD17B8	Intronic
chr6:33172932	chr6:33205155	0.95	1	rs110662	G	A	0.91	0.78	0.93	0.72		24 organs	BLD, BRN	13 organs	CTCF		Arid5a,Foxa		HSD17B8	Intronic
chr6:33181997	chr6:33214220	0.75	0.91	rs213214	T	C	0.87	0.75	0.97	0.69		13 organs	16 organs	iPSC	POL2		6 altered motifs		1.5kb 3' of RING1	
chr6:33183730	chr6:33216963	0.75	0.91	rs213213	T	C	0.81	0.74	0.93	0.69		SKIN	6 organs	LNG			CEBPB,Rad21		3.2kb 3' of RING1	
chr6:33185918	chr6:33218141	0.89	0.97	rs213212	C	A	0.85	0.76	0.98	0.73			4 organs				CEBPB,SP2		5.4kb 3' of RING1	
chr6:33193701	chr6:33225924	0.81	0.93	rs487652	G	C	0.81	0.77	0.98	0.73							7 altered motifs		13kb 3' of RING1	
chr6:33195154	chr6:33227377	0.81	0.94	rs7759943	A	G	0.84	0.78	0.94	0.73		IPSC	ESC, IPSC				Hoxa10,Hoxd9,Myb		15kb 3' of RING1	
chr6:33195604	chr6:33227827	0.81	0.94	rs213194	A	G	0.84	0.78	0.94	0.73			ESC	8 organs	NFYB		Myc,PPAR		15kb 3' of RING1	
chr6:33196005	chr6:33228228	0.81	0.94	rs213195	G	A	0.82	0.78	0.98	0.73			ESC, IPSC						16kb 3' of RING1	

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FUNCTIONAL ANNOTATION of HLA REGION SNPs

Detailed HaploReg results can be saved as a text file and viewed on Excel

T	U
Proteins	**Motifs**
GM12878,MEF2A,HudsonAlpha,None;GM12878,OCT2,HudsonAlpha,None;GM12878,POU2F2,H	Pou2f2_known9
.	.
.	AP-1_known3;ATF3_known10;ATF6;GATA_disc6;Mef2_disc3;Myc_disc6;RXRA_disc3;XBP-1_1
.	.
.	Duxl;Pbx-1_2;Pbx-1_3;Pou1f1_2
.	AP-2rep;Foxd1_1;Foxf1;Foxj1_2;Foxl1_1;Foxo_1
.	Pou5f1_known2
.	Foxl1_2;Mef2_known1;TATA_known1
.	.
GM06990,CTCF,UW,None;GM12864,CTCF,UW,None;GM12873,CTCF,UW,None;GM12875,CTCF,U	.
.	Irf_known2;Pax-4_5;SIX5_disc4
.	Bbx;Dbx1;Foxa_known2;Foxc1_1;Foxj1_1;Foxj1_2;Hmx_2;Hoxd8;Irx;Ncx_2;Nkx6-1_1;Pou3f2_2;Pou3f4;Prrx2_1;Sox_1;S
.	Bbx;GR_known8;Hoxa10;Ncx_2;PLZF
.	.
.	Arid5a;CAC-binding-protein;CACD_2;Klf7;RXRA_known5;RXRA_known7;Zfp740
.	Foxo_2;Foxo_3;Foxo_4;Hsf_known2;RFX5_known2;SETDB1_disc1
.	Evi-1_4;Foxp1;HDAC2_disc6;Irf_disc3;Pax-5_disc3;RXRA_disc4;Zfp105
.	DEC;Irf_known4
GM12878,BATF,HudsonAlpha,None	HNF4_disc1;HNF4_known1;HNF4_known3;HNF4_known4;RXRA_known1;Zbtb3
.	Egr-1_disc4;RFX5_known2;STAT_known1;STAT_known2
.	.
.	NRSF_known1;Pax-6_2;Sin3Ak-20_disc5
HepG2,USF1,HudsonAlpha,None;HepG2,USF2,Stanford,None;K562,USF1,HudsonAlpha,None	AP-4_1;ATF3_disc2;GCNF
.	BCL_disc6;EBF_known3;Ik-2_1;Ik-3;RBP-Jkappa_2;SETDB1_disc1;Smad_1
.	Ascl2;BDP1_disc3;E2A_2;GCM;GR_disc5;Myf_3;Spz1_1
.	Myc_disc10;NF-E2_disc4;PU.1_disc3;Pax-5_known3;Pou2f2_disc2;Rad21_disc10;SMC3_disc3;SP1_disc3;TFII-I;ZNF263_d
.	AP-1_disc10;BDP1_disc1;E2F_disc3;EWSR1-FLI1;Myc_disc10;NF-E2_disc4;PU.1_disc3;Pax-5_known3;Pou2f2_disc2;Rad2
.	CEBPB_known4;Dobox4;Pax-4_5
.	.
.	GATA_known8;MZF1::1-4_2;Pou2f2_known11;p300_disc5

Results suggest a cumulative effect on POU2F2 binding site alteration by the statistically similar SNP set (gender-specific type 1 diabetes risk market)

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Candidate Gene: POU2F2

NCBI Resources How To

Gene Gene Advanced

Full Report Send to:

POU2F2 POU class 2 homeobox 2 [*Homo sapiens* (human)]

Gene ID: 5452, updated on 4-Oct-2015

Summary

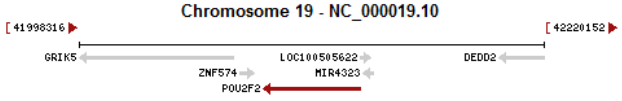
Official Symbol	POU2F2 provided by HGNC
Official Full Name	POU class 2 homeobox 2 provided by HGNC
Primary source	HGNC:HGNC:9213
See related	Ensembl:ENSG00000028277; HPRD:01251; MIM:164176; Vega:OTTHUMG00000165991
Gene type	protein coding
RefSeq status	REVIEWED
Organism	Homo sapiens
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Also known as	OCT2; OTF2; Oct-2
Summary	The protein encoded by this gene is a homeobox-containing transcription factor of the POU domain family. The encoded protein binds the octamer sequence 5'-ATTTGCAT-3', a common transcription factor binding site in immunoglobulin gene promoters. Several transcript variants encoding different isoforms have been found for this gene. [provided by RefSeq, Oct 2011]
Orthologs	mouse all

Genomic context

Location: 19q13.2 See POU2F2 in Epigenomics, MapViewer

Exon count: 15

Annotation release	Status	Assembly	Chr	Location
107	current	GRCh38.p2 (GCF_000001405.28)	19	NC_000019.10 (42086110..42132473, complement)
105	previous assembly	GRCh37.p13 (GCF_000001405.25)	19	NC_000019.9 (42590262..42636625, complement)



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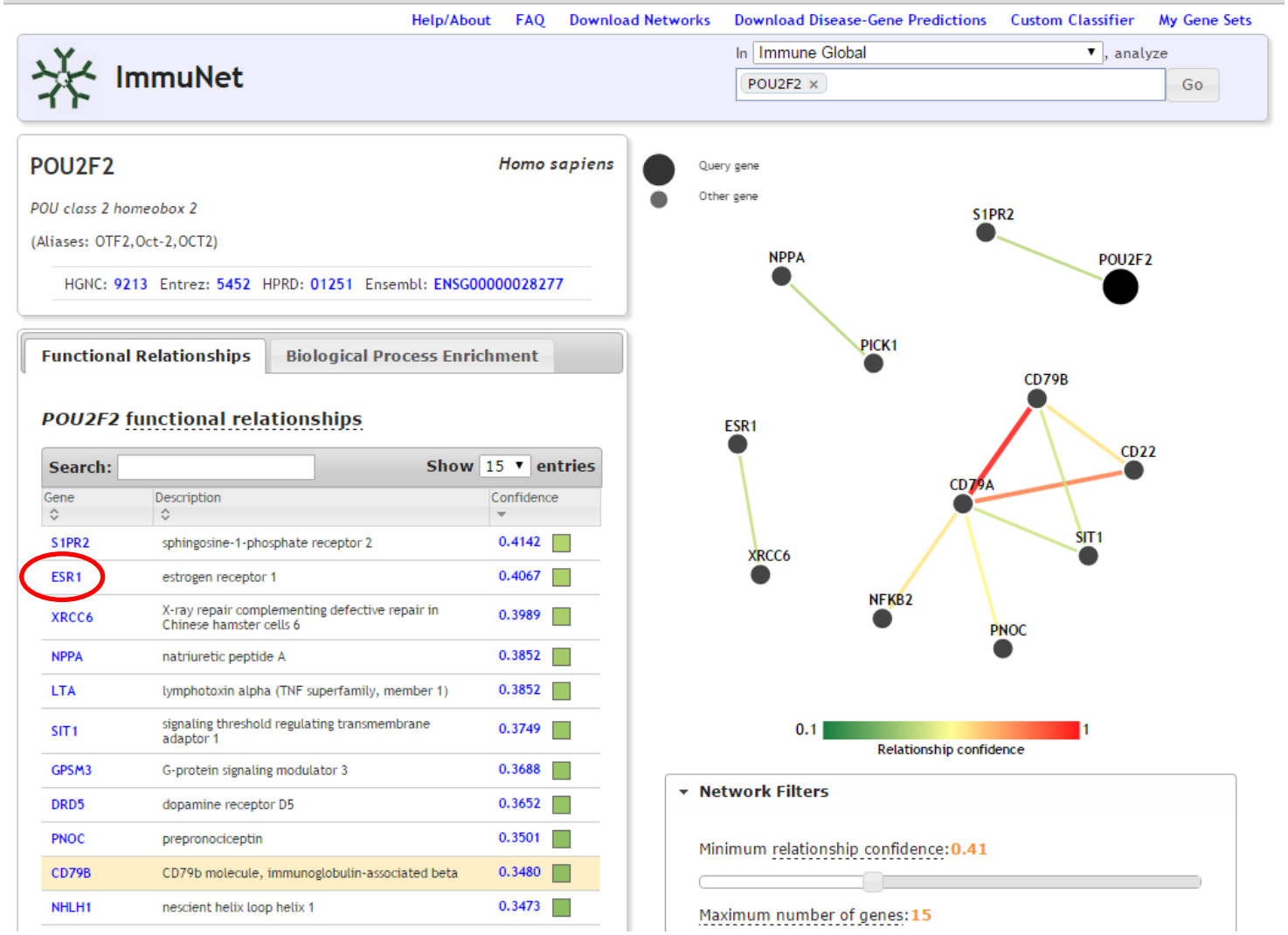
Candidate Gene: POU2F2



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RESOURCES

IDAWG
GCTAATGCACTGTACAGTATATCA
IMMUNOGENOMICS DATA ANALYSIS WORKING GROUP

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01000100011000010111010001100001
IMMUNOGENOMICS DATA
ANALYSIS WORKING GROUP
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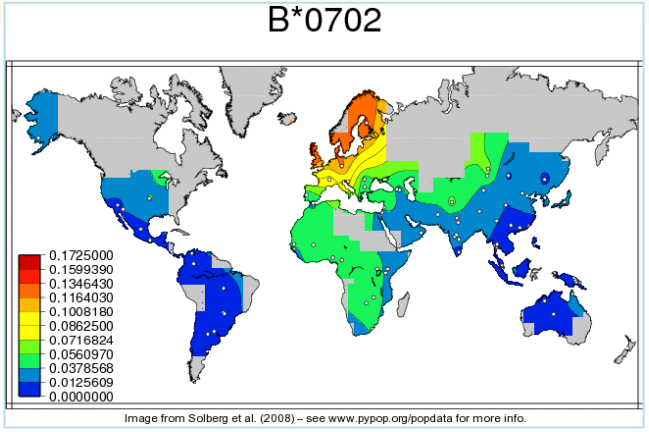
The immunogenomics data analysis working group (IDAWG) is an international collaboration of histocompatibility and immunogenetics investigators who share the goal of facilitating the sharing of immunogenomic data (HLA, KIR, etc.) and fostering the consistent analysis and interpretation of those data by the immunogenomics community and the larger genomics communities.

SOFTWARE

The immunogenomics data analysis working group is developing software intended to make the analysis of immunogenomic data simpler, faster, and more consistent across studies. Currently, the ANTT and UNCL allele name translation applications, the BIGDAWG R package and web-app for case-control analysis and the Global Frequency Map Browser are available for download or use over the internet.



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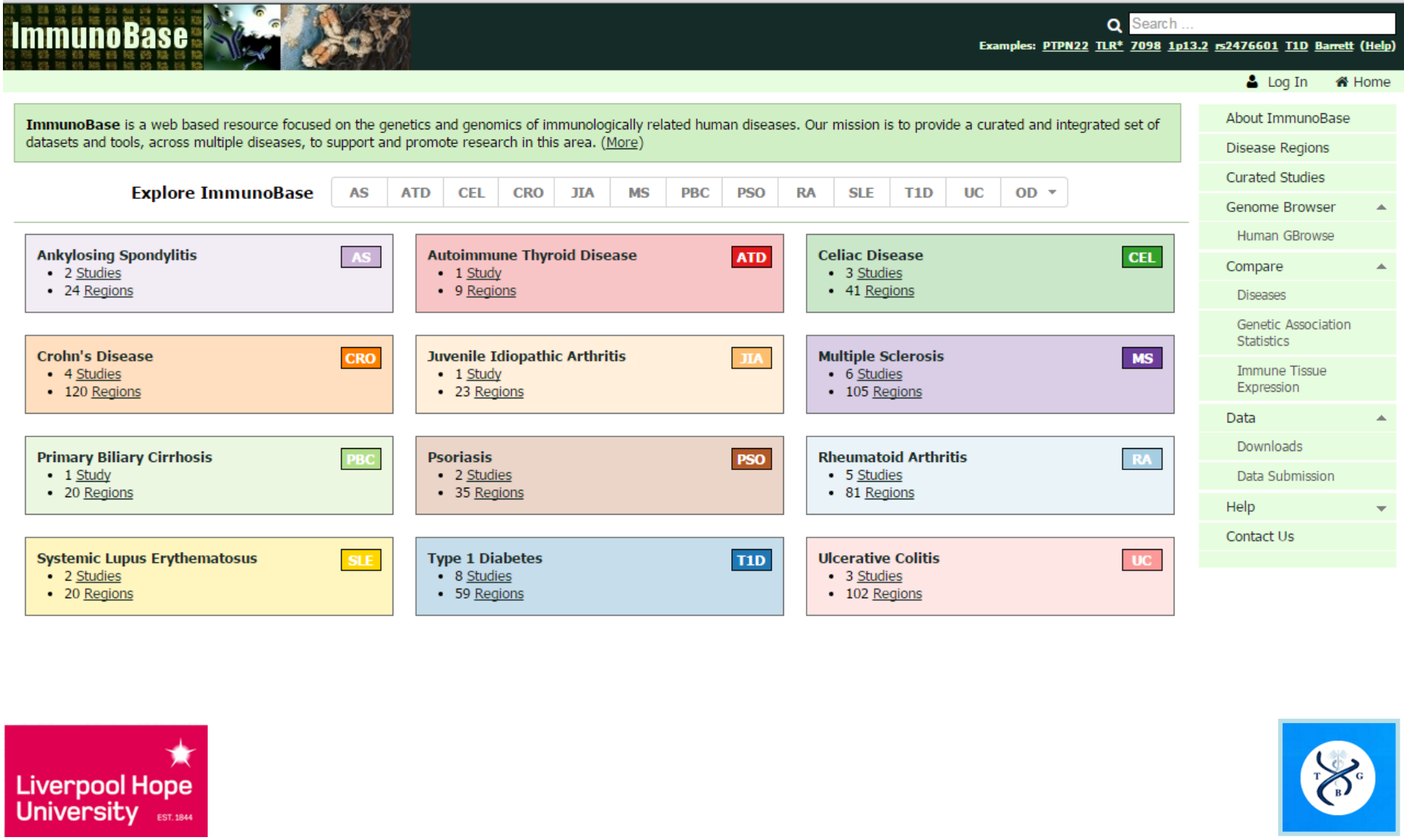

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ImmVar

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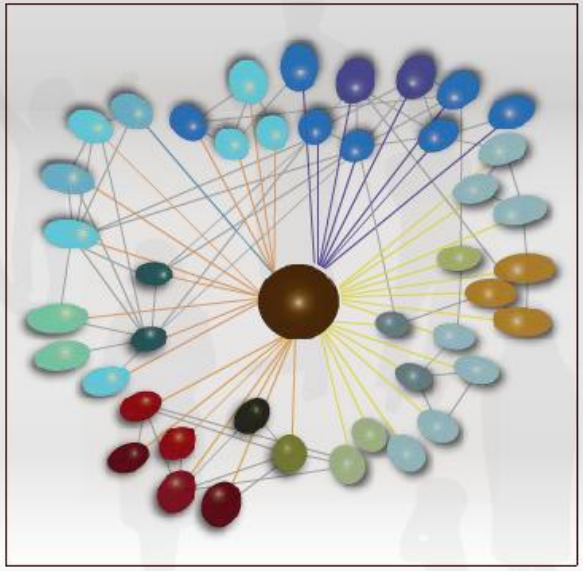
Gene expression profiling for mRNA complete



Genetic variation across human individuals impacts on the activity and function of the genes, either directly or via complex regulatory networks. In turn, these variations of gene expression condition the ability of the immune system to protect against microbes and parasites, to adapt to the environment, or to turn against self-antigens in autoimmune diseases.

ImmVar is a collaborative program which associates complementary expertise of a group of Immunologists, Geneticists and Computational Biologists. With the help of donors representing many geographical origins, we will perform a broad analysis of the variation in gene expression in cells of the innate and adaptive immune systems, and of their genetic regulatory network.

More

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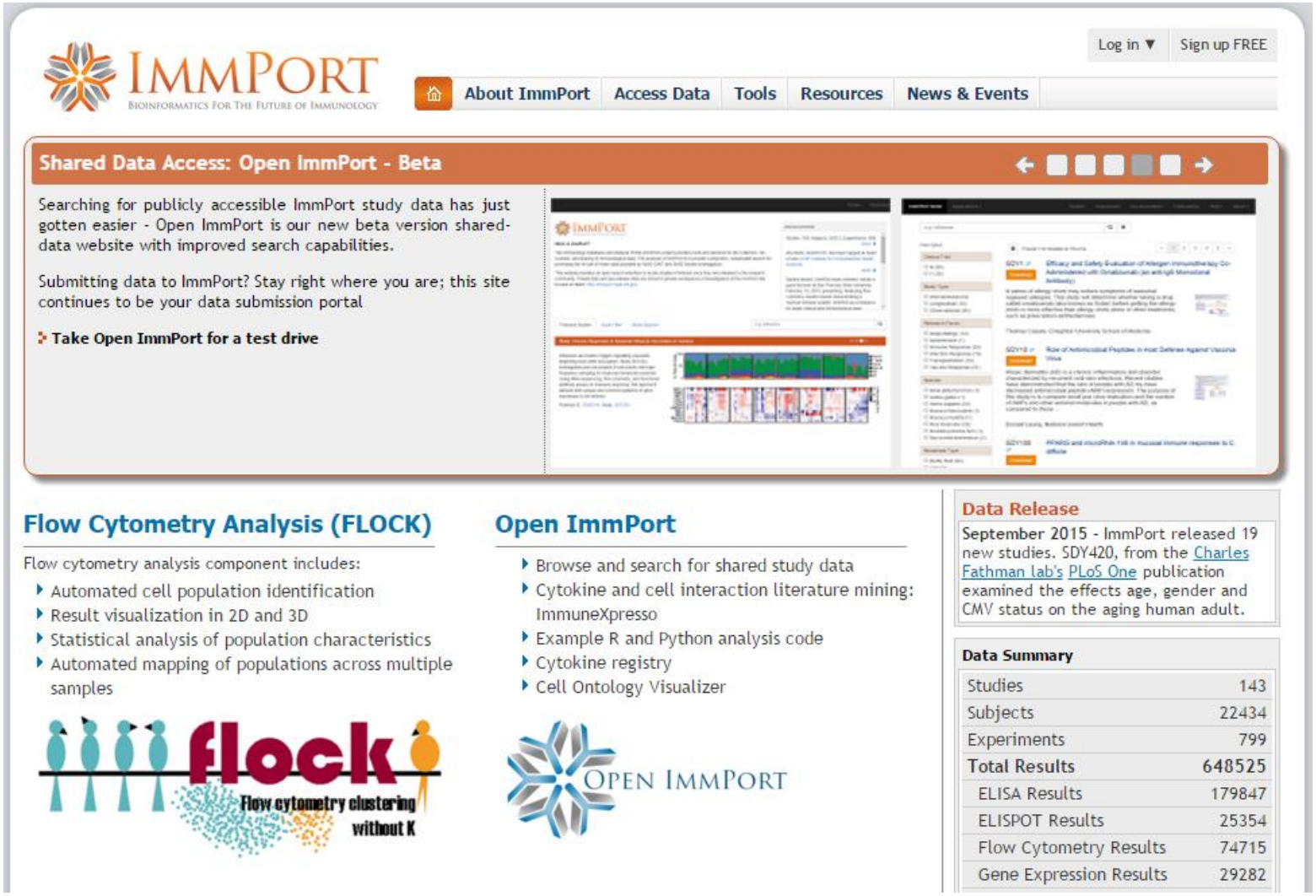

RESOURCES

Immunity

Volume 43, Issue 3, 15 September 2015, Pages 605–614

Resource

Interactive Big Data Resource to Elucidate Human Immune Pathways and Diseases

Dmitriy Gorenshteyn[1, 11], Elena Zaslavsky[2, 11], Miguel Fribourg[2, 11], Christopher Y. Park[3, 11], Aaron K. Wong[4], Alicja Tadych[1], Boris M. Hartmann[2], Randy A. Albrecht[5, 6], Adolfo García-Sastre[5, 6, 7], Steven H. Kleinstein[8, 9], Olga G. Troyanskaya[1, 4, 10, 12], Stuart C. Sealfon[2, 12]

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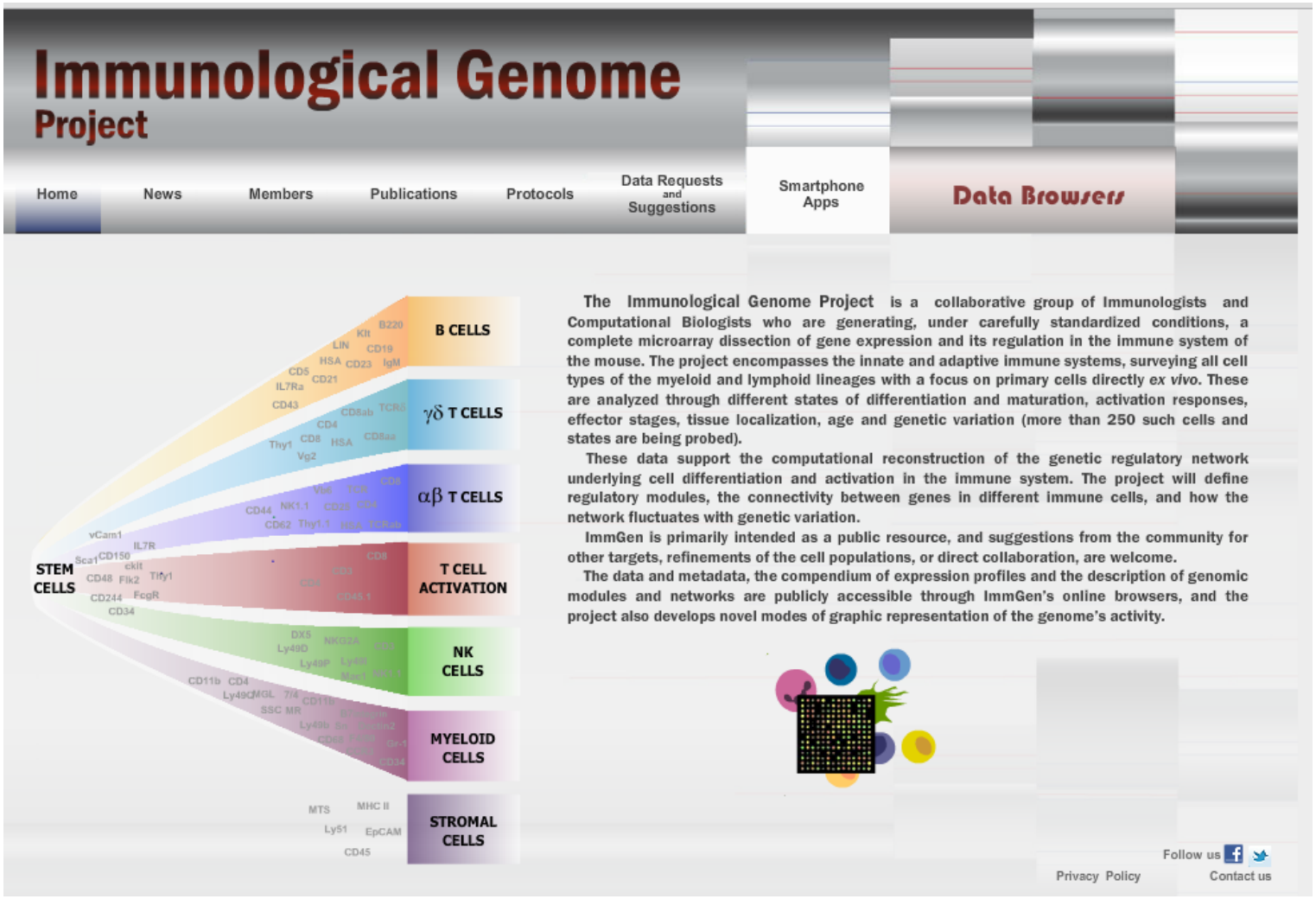

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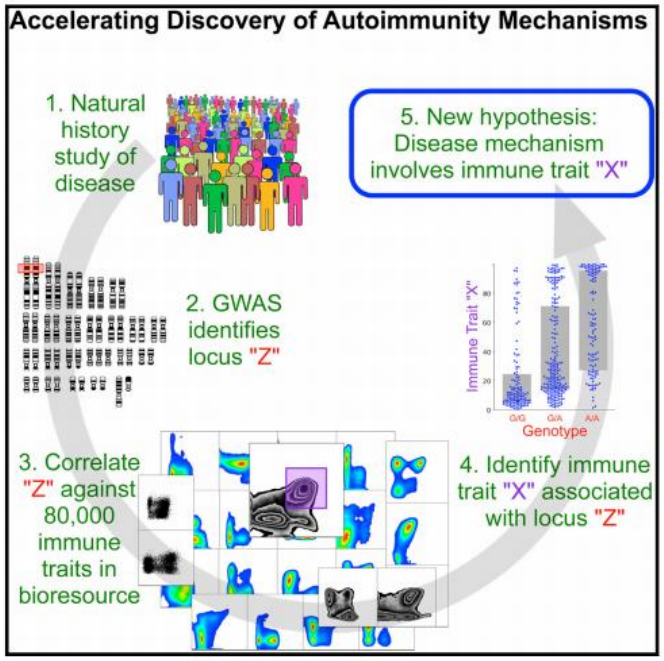


Highlights

- Resource of heritabilities and genetic associations of 80,000 immune traits in 669 twins
- Genetic associations with immune cell frequencies and surface protein expression levels
- Of the top 150 traits, 11 genetic loci explained up to 36% of variation of 19 traits
- Loci include autoimmune susceptibility genes, providing etiological hypotheses

BioData Repository

Raw and summary data is available for downloading and analysis. Genotype data is available upon request to the authors.

Flow Cytometry Data

FCS data files are deposited in the International Society for the Advancement of Cytometry public data repository. This includes 130 GB of data, comprising > 5,200 individual data files. In addition, the FlowJo workspaces used to analyze these files are also available, providing the complete gating scheme, statistical analysis, and graphical analysis for every single data file. These files are available at http://www.tinyurl.com/twinsFACSdata.

GWAS Summary

The detailed summary of all GWAS analyses performed on the 150 selected traits is provided; each trait is a separate file. These files can be downloaded from ftp://twinr-ftp.kcl.ac.uk/ImmuneCellScience, in folder "2-GWASResults."

Demographics

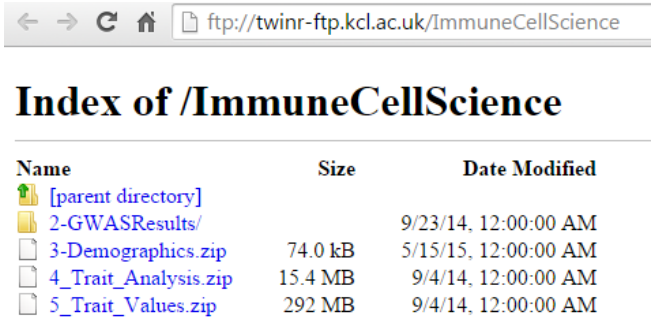
Anonymized demographic information (anonymized unique family ID, age, twin type) for subjects is provided in a single file, ftp://twinr-ftp.kcl.ac.uk/ImmuneCellScience, file name "3-Demographics.zip."

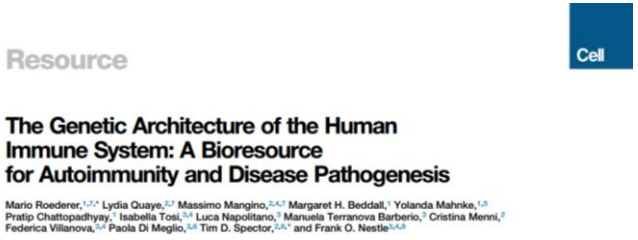
Heritability

Estimated heritability (Falconer's) for all 78,000 traits, including a detailed definition of each of the traits, suitable for sorting and analysis is available in a single file. This file can be downloaded from ftp://twinr-ftp.kcl.ac.uk/ImmuneCellScience, file name "4-Trait Analysis.zip."

Trait Values

Every measured trait value is in a single file, containing a table of 78,000 values for each individual. This file can be downloaded from ftp://twinr-ftp.kcl.ac.uk/ImmuneCellScience, file name "5-Trait Values.zip."





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Finemapping

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Genetic and Epigenetic Fine-Mapping of Causal Variants in Autoimmune Disease

Kyle Kai-How Farh, Alexander Marson, Jiang Zhu, Markus Kleinewietfeld, William J. Housley, Samantha Beik, Noam Shoresh, Holly Whitton, Russell J. H. Ryan, Alexander A. Shishkin, Meital Hatan, Marlene J. Carrasco-Alfonso, Dita Mayer, C. John Luckey, Nikolaos A. Patsopoulos, Philip L. De Jager, Vijay K. Kuchroo, Charles B. Epstein, Mark J. Daly, David A. Hafler & Bradley E. Bernstein

Nature 518, 337–343 (19 February 2015)

Summary

Genome-wide association studies have identified loci underlying human diseases, but the causal nucleotide changes and mechanisms remain largely unknown. Here we developed a fine-mapping algorithm to identify candidate causal variants for 21 autoimmune diseases from genotyping data. We integrated these predictions with transcription and cis-regulatory element annotations, derived by mapping RNA and chromatin in primary immune cells, including resting and stimulated CD4+ T-cell subsets, regulatory T-cells, CD8+ T-cells, B-cells, and monocytes. We find that ~90% of causal variants are noncoding, with ~60% mapping to immune-cell enhancers, many of which gain histone acetylation and transcribe enhancer-associated RNA upon immune stimulation. Causal variants tend to occur near binding sites for master regulators of immune differentiation and stimulus-dependent gene activation, but only 10-20% directly alter recognizable transcription factor binding motifs. Rather, most noncoding risk variants, including those that alter gene expression, affect non-canonical sequence determinants not well-explained by current gene regulatory models.

Genetic and epigenetic fine mapping of causal autoimmune disease variants

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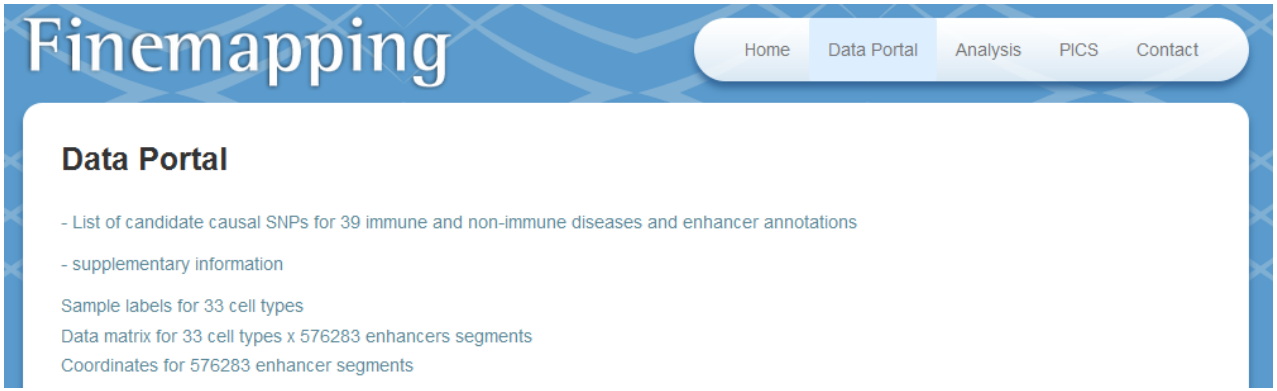
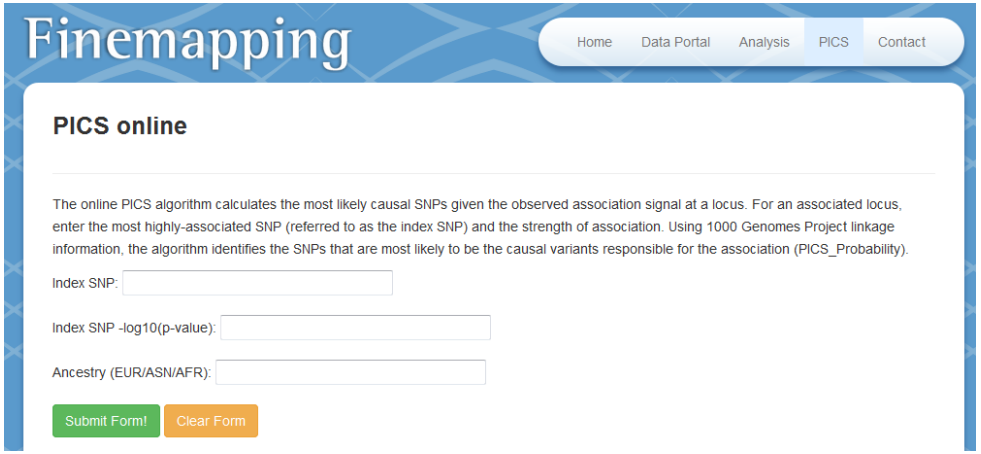
RESOURCES





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CONCLUSIONS

> GWAS have revealed plenty of risk markers for autoimmune diseases

> As in other complex diseases, molecular mechanisms of these associations and biological insights into disease pathogenesis are yet to be elucidated

> Availability of big data and user friendly bioresources should acccelerate this process

ACKNOWLEDGEMENT

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XIV. CONGRESS OF MEDICAL BIOLOGY AND GENETICS

27-30 October 2015, Oludeniz, Fethiye, Turkey

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