Bioinformatic Analysis of Experimentally Verified Functional Disease Associations with Disease

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Kingston University London

Schedule

Day 1
Bioinformatics tools for the assessment of genetic variants
Bioinformatic analysis of experimentally verified functional SNP associations with disease
Bioinformatic tools for the investigation of tissue specificity of variant effects
Online tools: Standard operating procedures for gene and variant analysis
Applications and practice on participant projects

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Outline

Examples of SNP annotations:

rs9343369 & vascular disorders
rs4917014 & SLE
rs2395185 & multiple cancers and autoimmune disorders

(also exemplifying "using genetic epidemiology as a probe for disease biology")

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eQTL effect

SNCA rs356168

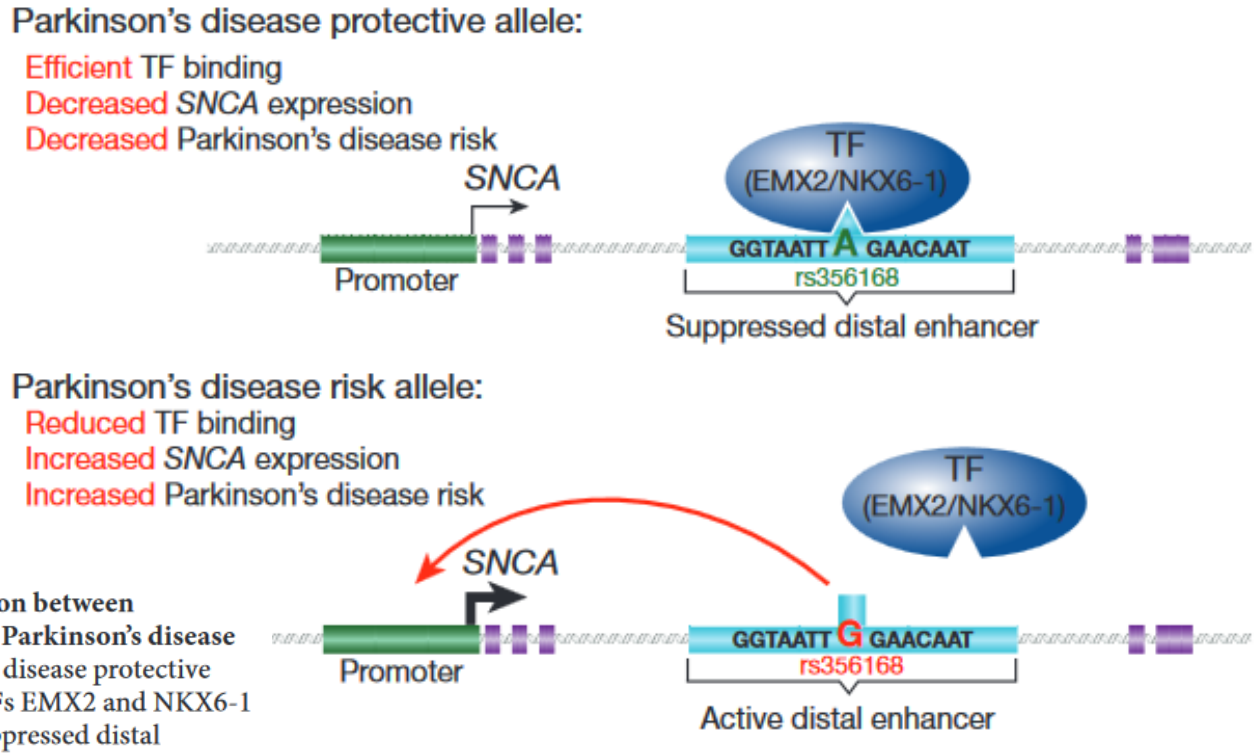

Figure 4 | Proposed model describing the correlation between SNP-dependent TF binding, *SNCA* expression and Parkinson's disease risk. Carriers of the A allele at rs356168 (Parkinson's disease protective allele) show efficient binding of the brain-specific TFs EMX2 and NKX6-1 at the distal intron-4 enhancer, which results in a suppressed distal enhancer and consequently lower expression of *SNCA* associated with a reduced risk to develop Parkinson's disease. In contrast, carriers of the G allele at rs356168 (Parkinson's disease risk allele) show reduced TF binding, which results in an active distal enhancer leading to increased expression of *SNCA* and increased risk of developing Parkinson's disease.

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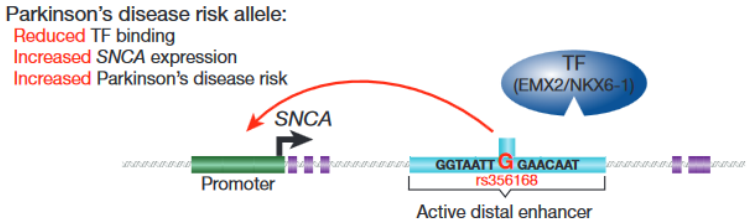
Parkinson-associated risk variant in distal enhancer of α-synuclein modulates target gene expression

Frank Soldner[1], Yonatan Stelzer[1], Chikdu S. Shivalila[1,2], Brian J. Abraham[1], Jeanne C. Latourelle[3], M. Inmaculada Barrasa[1], Johanna Goldmann[1], Richard H. Myers[3], Richard A. Young[1,2] & Rudolf Jaenisch[1,2]

eQTL effect

SNCA rs356168



eQTL studies showing correlation of SNP with cis expression

Study ID	Paper Title	PMID	Tissue	Correlated gene
Fairfax2014	Innate immune activity conditions the effect of regulatory variants upon monocyte gene expression	24604202	Monocytes_Naive	SNCA
Zou2012	Brain expression genome-wide association study (eGWAS) identifies human disease-associated variants	22685416	Cerebellum	SNCA
Zou2012	Brain expression genome-wide association study (eGWAS) identifies human disease-associated variants	22685416	Temporal_Cortex	SNCA

Regulatory motifs altered

Position Weight Matrix ID (Library from Kheradpour and Kellis, 2013)	Strand	Ref	Alt	Match on: Ref: CAAACGCTTCTGTTTTGATTGTGGTAATTGGAACAATCAGGGCACAAACTGCAAGGTCA Alt: CAAACGCTTCTGTTTTGATTGTGGTAATTAGAACAATCAGGGCACAAACTGCAAGGTCA
CHX10	-	7.6	13.9	NVBTAATTAGCBHD
DMRT2	-	10.9	-1.1	WMAWTGTAWCAWWWTV
Dlx2	+	11	12.3	VVDRYAATTRBHHHAN
En-1_1	+	8.6	6.3	RWDDTBB
GR_known10	-	-0.7	11.3	NNMHHHAGAACANMHHGTNMYHNNNHN
Hoxa3_2	+	9.6	14.3	NBSHRBTAATTAVY
Hoxa5_3	+	10.4	13.8	AMRBTAATTAVYHHDD
Hoxb3	+	9.8	12.8	HHBHRSTMATKASBKYW
Hoxb6	+	10.5	12.4	NHNGYAATTRCNHHWW
Ncx_1	+	11.1	9.5	BBKTAAKKKB
Pou2f2_known3	+	8.6	10.6	NNNRTAATNRBDD
Sox_15	+	10.5	13.1	NWWNANAACAATDR
Vax2	+	9.4	12.4	SBVBTAATTARYNNHV

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HaploReg v4

BROAD INSTITUTE

rs9349379

A Genetic Variant Associated with Five Vascular Diseases Is a Distal Regulator of Endothelin-1 Gene Expression

Rajat M. Gupta,[1,2,3,8,*] Joseph Hadaya,[1] Aditi Trehan,[1] Seyedeh M. Zekavat,[1] Carolina Roselli,[1] Derek Klarin,[1] Connor A. Emdin,[1] Catharina R.E. Hilvering,[4] Valerio Bianchi,[4] Christian Mueller,[6] Amit V. Khera,[1,2,3] Russell J.H. Ryan,[1,5] Jesse M. Engreitz,[1] Robbyn Issner,[1] Noam Shoresh,[1] Charles B. Epstein,[1] Wouter de Laat,[4] Jonathan D. Brown,[7] Renate B. Schnabel,[6] Bradley E. Bernstein,[1,5] and Sekar Kathiresan[1,2,3,*]

SUMMARY

Genome-wide association studies (GWASs) implicate the *PHACTR1* locus (6p24) in risk for five vascular diseases, including coronary artery disease, migraine headache, cervical artery dissection, fibromuscular dysplasia, and hypertension. Through genetic fine mapping, we prioritized rs9349379, a common SNP in the third intron of the *PHACTR1* gene, as the putative causal variant. Epigenomic data from human tissue revealed an enhancer signature at rs9349379 exclusively in aorta, suggesting a regulatory function for this SNP in the vasculature. CRISPR-edited stem cell-derived endothelial cells demonstrate rs9349379 regulates expression of endothelin 1 (*EDN1*), a gene located 600 kb upstream of *PHACTR1*. The known physiologic effects of *EDN1* on the vasculature may explain the pattern of risk for the five associated diseases. Overall, these data illustrate the integration of genetic, phenotypic, and epigenetic analysis to identify the biologic mechanism by which a common, non-coding variant can distally regulate a gene and contribute to the pathogenesis of multiple vascular diseases.

Trait annotations

Variant association

trait	p-value	source DB	source entry/link
Myocardial infarction	$<9.00\times10^{-35}$	GWAS Catalog	26343387
Coronary Artery Disease	$<2.00\times10^{-42}$	GWAS Catalog	26343387
Cervical artery dissection	$<1.00\times10^{-11}$	GWAS Catalog	25420145
Migraine - clinic-based	$<2.00\times10^{-6}$	GWAS Catalog	23793025
Migraine	$<5.00\times10^{-8}$	GWAS Catalog	23793025
Migraine without aura	$<3.00\times10^{-10}$	GWAS Catalog	23793025
Coronary heart disease	$<2.00\times10^{-9}$	GWAS Catalog	22751097
Coronary heart disease	$<8.00\times10^{-10}$	GWAS Catalog	22745674
Migraine	$<3.00\times10^{-8}$	GWAS Catalog	22683712
Coronary artery calcification	$<4.00\times10^{-22}$	GWAS Catalog	22144573
Coronary heart disease	$<9.00\times10^{-26}$	GWAS Catalog	21846871
Coronary heart disease	$<9.00\times10^{-26}$	GWAS Catalog	21378988
Coronary disease	3.33×10^{-5}	dbGaP	pha003056
Coronary artery disease	7.66×10^{-10}	dbGaP	pha003031
Coronary artery disease	5.28×10^{-8}	dbGaP	pha003030

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rs9349379

SNiPA
single nucleotide polymorphisms annotator

HelmholtzZentrum münchen
German Research Center for Environmental Health

Weill Cornell Medical College in Qatar

سنيبا

Home

Browse
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- Association Maps

Annotation
- Variant Annotation
- Block Annotation

Plots
- Regional Association Plot
- Linkage Disequilibrium Plot

Linkage Disequilibrium
- Proxy Search
- Pairwise LD

Variant Annotation

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

Variant annotations | Report

rs9349379 — show static URL | add to clipboard | save as PDF | delete

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

rs9349379 (alias rs58957411, rs17679549)

position / outlink		allele info	
physical position	chr6: 12,903,957	alleles	A/G
genetic position [cM]	28.89	frequencies	0.599/0.401
outlink	e!	VEP effect allele	A

Basic features

Conservation/deleteriousness		Linked genes	
phyloP	1.761	gene(s) hit or close-by	PHACTR1 e!
phastCons	0.682	eQTL gene(s)	PHACTR1 e!, RP1-257A7.5 e!
GERP++	0.0476	pQTL gene(s)	–
CADD score	5.511	potentially regulated gene(s)	–
SnpEff effect impact	modifier	disease gene(s)	–

Direct effect on regulation

***cis*-eQTL**

gene	transcript	probe	tissue	statistic (type)	source
PHACTR1 e!	?	ENSG00000112137 e!	coronary artery	8.60×10^{-7} (p-value)	GTEx Portal V6
RP1-257A7.5 e!	?	ENSG00000272379 e!	coronary artery	5.35×10^{-9} (p-value)	GTEx Portal V6
PHACTR1 e!	?	ENSG00000112137 e!	aorta	4.26×10^{-12} (p-value)	GTEx Portal V6
RP1-257A7.5 e!	?	ENSG00000272379 e!	aorta	2.44×10^{-10} (p-value)	GTEx Portal V6
PHACTR1 e!	?	ENSG00000112137 e!	tibial artery	7.21×10^{-16} (p-value)	GTEx Portal V6
RP1-257A7.5 e!	?	ENSG00000272379 e!	tibial artery	3.01×10^{-15} (p-value)	GTEx Portal V6

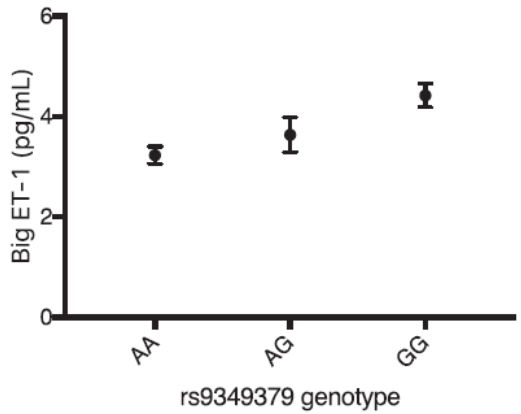

Figure 6. Minor Allele at rs9349379 Increases Plasma Levels of Big ET-1 in Healthy Subjects

Association between circulating levels of ET-1 precursor protein and genotype at rs9349379 in human plasma samples. Each copy of G allele results in higher Big ET-1 expression (n=33 for each rs9349379 genotype; p = 0.00136, additive model of regression).

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rs9349379

Chromatin state | Related regulatory elements | Target genes | Other information

Chromatin state (count:11 , 50 per page) page: 1

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No.	Chromosome Location	Chromatin state	Cell line	Tissue
1	chr6:12885600-12908800	Weak transcription	iPS DF 19.11 Cell Line	embryonic stem cell
2	chr6:12894000-12908800	Weak transcription	Fetal Brain Female	brain
3	chr6:12896600-12904800	Weak transcription	Brain Anterior Caudate	brain
4	chr6:12896600-12911000	Weak transcription	Brain Dorsolateral Prefrontal Cortex	brain
5	chr6:12898000-12907000	Weak transcription	Primary hematopoietic stem cells short term culture	blood
6	chr6:12900200-12905400	Weak transcription	Aorta	Aorta
7	chr6:12901400-12908800	Weak transcription	Brain Germinal Matrix	brain
8	chr6:12903000-12904000	Enhancers	Primary monocytes fromperipheralblood	blood
9	chr6:12903000-12904000	Enhancers	Monocytes-CD14+_RO01746	blood
10	chr6:12903200-12904000	Enhancers	Skeletal Muscle Male	skeletal muscle
11	chr6:12903200-12904000	Enhancers	Stomach Smooth Muscle	stomach

rs9349379

A Genetic Variant Associated with Five Vascular Diseases Is a Distal Regulator of Endothelin-1 Gene Expression

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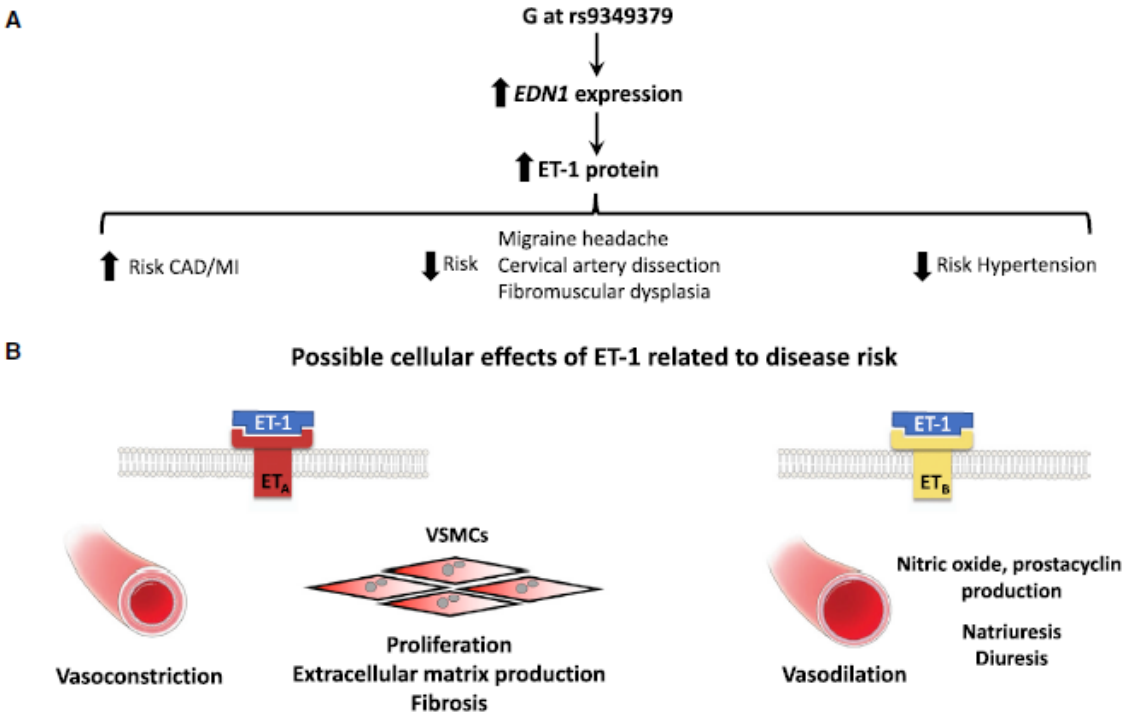

Figure 7. The Relationship between rs9349379 Genotype, Endothelin-1, and Risk of Five Vascular Diseases

(A) The *cis*-regulatory effect of the G allele at rs9349379 is associated with higher *EDN1* expression and higher ET-1 secreted protein. The G allele at rs9349379 is associated with increased risk of CAD/MI and lower risk of migraine headache, cervical artery dissection, fibromuscular dysplasia, and hypertension.

(B) Proposed model for ET-1 function and risk of five vascular diseases. Activation of ET_A receptor results in vasoconstriction, VSMC proliferation, ECM production, and fibrosis. These downstream effects of ET-1 result in increased risk of CAD/MI and decreased risk of migraine headache, cervical artery dissection, and fibromuscular dysplasia. ET_B receptors are predominantly in large arteries and the renal collecting system. Higher ET-1 levels may result in hypotension via ET_B-induced nitric oxide and prostacyclin production, resultant vasodilation, diuresis, and natriuresis.

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rs4917014

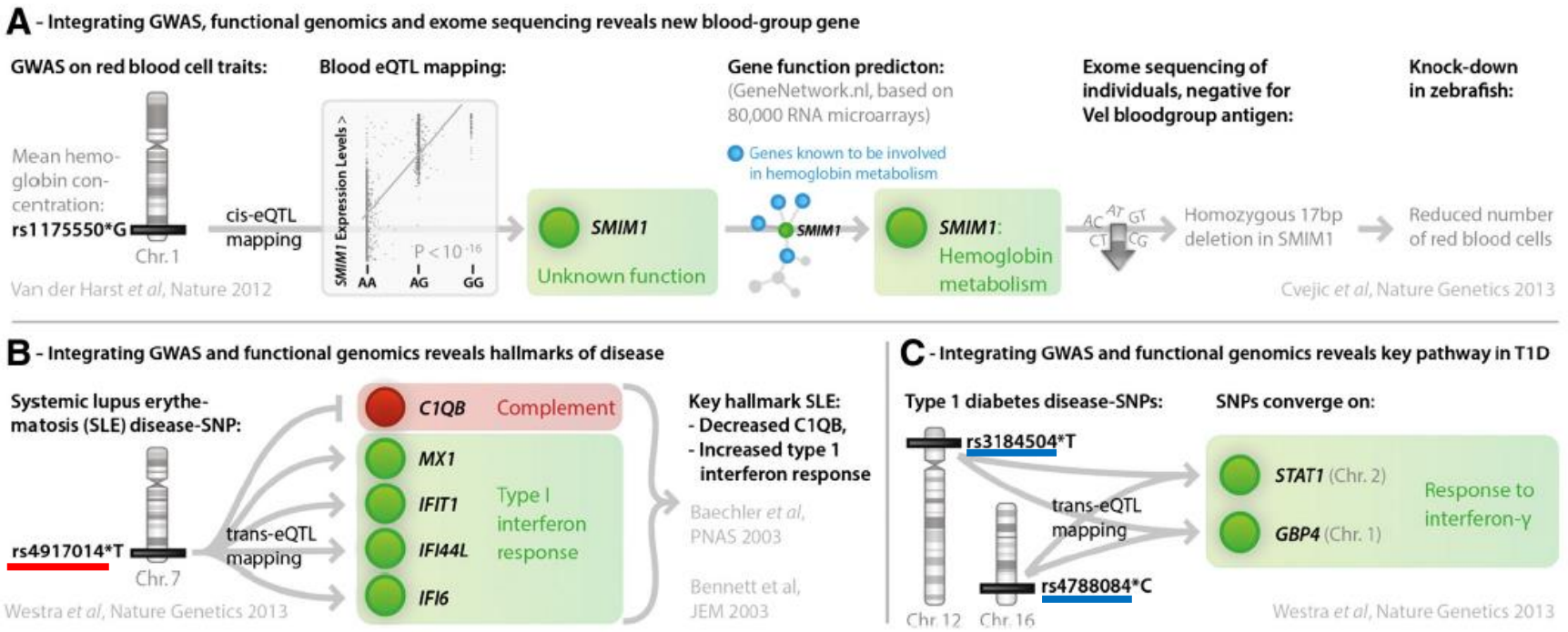

Fig. 2. Functional genomic studies translate GWAS findings into clear biological insight. (A) A recent GWAS conducted on red blood cell traits identified a locus on chromosome 1 associated with mean hemoglobin concentration. Through subsequent *cis*-eQTL mapping and gene function prediction (using a compendium of 80,000 microarrays), *SMIM1* was identified as the possibly causal gene in the locus on chromosome 1 that was predicted to be involved in hemoglobin metabolism. Subsequent exome-sequencing revealed this gene underlies the rare Vel blood group, and knock-down of Vel1 in zebrafish resulted in a reduced number of red blood cells. (B) Through *trans*-eQTL mapping in healthy individuals the downstream effects for the systemic lupus erythematosis (SLE) SNP rs4917014 were identified. These effects are identical to the key hallmarks of SLE: decreased complement 1q levels and an increased type 1 interferon response. (C) SNPs that increase risk for the same disease 'converge' on the same downstream genes: two unlinked type 1 diabetes SNPs affect exactly the same down-stream genes in *trans* (*STAT1* and *GBP4*, both involved in the interferon-γ response).

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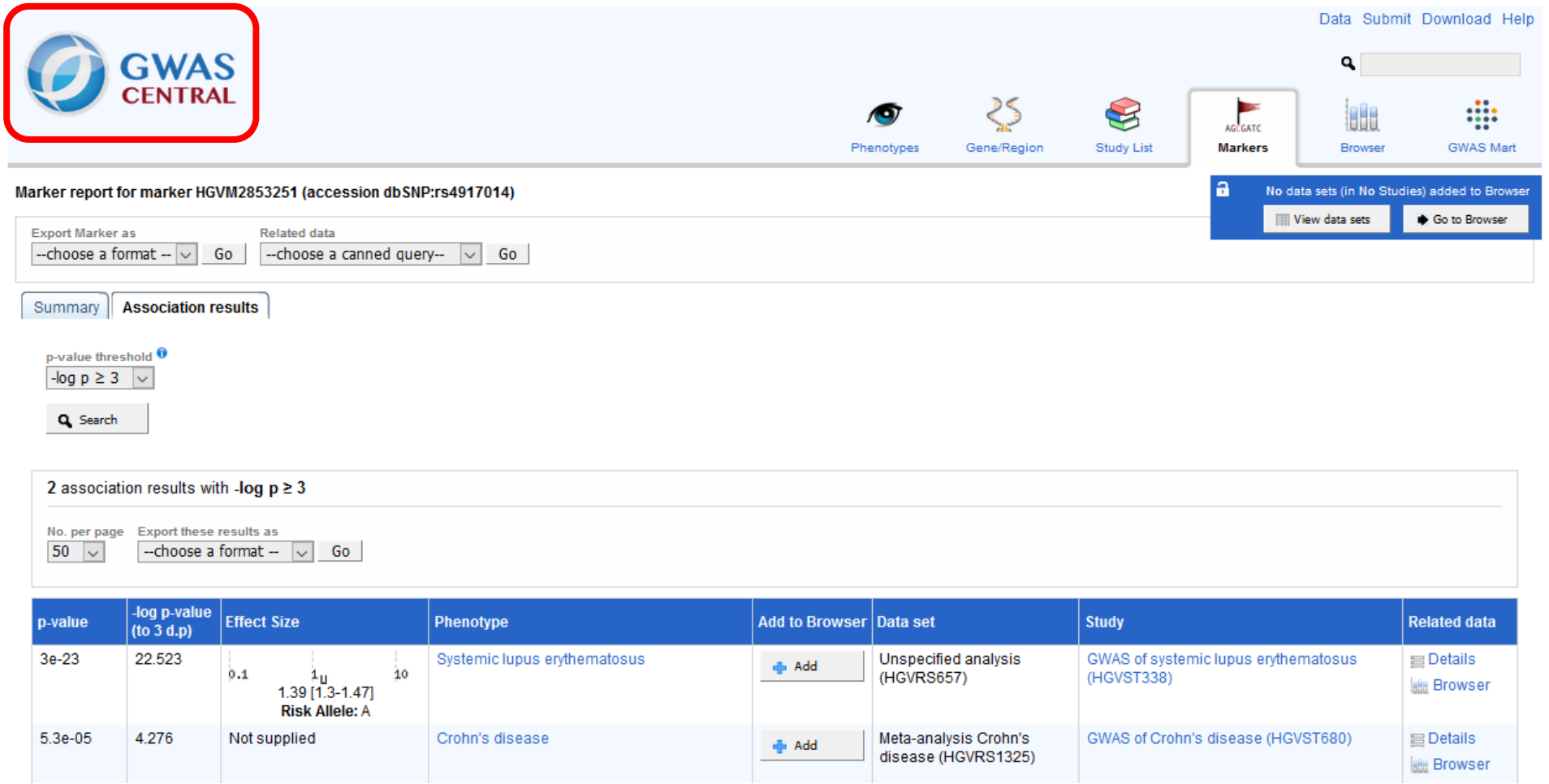
From genome to function by studying eQTLs ☆

Harm-Jan Westra, Lude Franke *

rs4917014



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rs4917014

UNIVERSITY OF CAMBRIDGE Cardiovascular Epidemiology Unit

PhenoScanner | Information | Team

Top 10 results by *p*-value
(Download all results below)

SNP	Proxy rsID	Proxy Pos (hg19)	r2	Trait	Study	PMID	Ancestry	Association Alleles	Beta	SE	P	N	Unit
rs4917014	rs4917014	chr7:50305863	1	Systemic lupus erythematosus SLE	Han JW	19838193	Asian	NA	NA	NA	2.75e-23	12454	NA
rs4917014	rs4917014	chr7:50305863	1	Selective immunoglobulin A deficiency IgAD	Ferreira RC	20694011	European	NA	NA	NA	2.80e-23	2748	NA
rs4917014	rs4917014	chr7:50305863	1	Lupus Erythematosus Systemic	Han JW	19838193	Asian	NA	NA	NA	3.00e-23	NA	NA
rs4917014	rs4917014	chr7:50305863	1	Systemic lupus erythematosus	Han JW	19838193	Asian	G/T	-0.3293	0.03315	3.00e-23	NA	log(OR)
rs4917014	rs4917014	chr7:50305863	1	Gene expression of CLEC4C in Peripheral blood monocytes	Zeller	20502693	European	NA	NA	NA	1.28e-12	2362	NA
rs4917014	rs4917014	chr7:50305863	1	Cold medicine related Stevens Johnson syndrometoxic epidermal necrolysis SJS TEN with severe mucosal involvement	Ueta M	25672763	Mixed	NA	NA	NA	8.00e-11	NA	NA
rs4917014	rs4917014	chr7:50305863	1	Gene expression of PACSIN1 in Peripheral blood monocytes	Zeller	20502693	European	NA	NA	NA	1.47e-10	2362	NA
rs4917014	rs4917014	chr7:50305863	1	Gene expression of MCOLN2 in Peripheral blood monocytes	Zeller	20502693	European	NA	NA	NA	6.60e-10	2362	NA
rs4917014	rs4917014	chr7:50305863	1	Gene expression of SPIB in Peripheral blood monocytes	Zeller	20502693	European	NA	NA	NA	5.81e-09	2362	NA
rs4917014	rs4917014	chr7:50305863	1	HDL cholesterol	GLGC	24097068	European	G/T	0.022	0.003839	1.00e-08	NA	unit increase

Download SNP information here.
Download phenotype GWAS association results here.
Download eQTL association results here.
Download metabolite association results here.

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rs4917014

rVarBase:an updated database for regulatory features of human variants

Chromatin states, regulatory elements and target genes

The 2.0 version of rSNPBase

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Variant report

Variant	rs4917014
Chromosome Location	chr7:50305863-50305864
allele	G/T
Outlinks	Ensembl UCSC

Chromatin state | Related regulatory elements | Target genes | Other information

Chromatin state (count:39 , 50 per page) page: 1 ▲To Top

No.	Chromosome Location	Chromatin state	Cell line	Tissue
1	chr7:50298000-50306200	Enhancers	Primary T killer naive cells fromperipheralblood	blood
2	chr7:50299000-50306000	Enhancers	Primary T cells effector/memory enriched fromperipheralblood	blood
3	chr7:50300000-50306000	Enhancers	Primary hematopoietic stem cells short term culture	blood
4	chr7:50300200-50306000	Enhancers	Primary hematopoietic stem cells G-CSF-mobilized Female	--
5	chr7:50300800-50306400	Enhancers	Primary hematopoietic stem cells	blood
6	chr7:50301000-50306400	Enhancers	Primary Natural Killer cells fromperipheralblood	blood
7	chr7:50301200-50306200	Enhancers	K562	blood
8	chr7:50301800-50306200	Enhancers	Primary B cells from cord blood	blood
9	chr7:50301800-50306200	Enhancers	Primary B cells from peripheral blood	blood

Quick Search:

Search here... Search

Input of quick search could be:

- dbSNP/dbVar ID: rs12345 /nsv7879
- a single nucleotide as 0-based coordinates: chr1:12345
- chromosomal regions: chr1:12345-34567

what's new

- New variant types
- New dimension of annotation
- New regulatory manner
- More detailed annotation on variant overlapped TFBS
- More extended data
- New search manner

Quick links

rSNPBase a database for curated regulatory SNPs

Experimental evidences, multiple types of regulation, & rSNP and its LD-proxies

ENCODE: Encyclopedia of DNA Elements

ROADMAP epigenomics PROJECT

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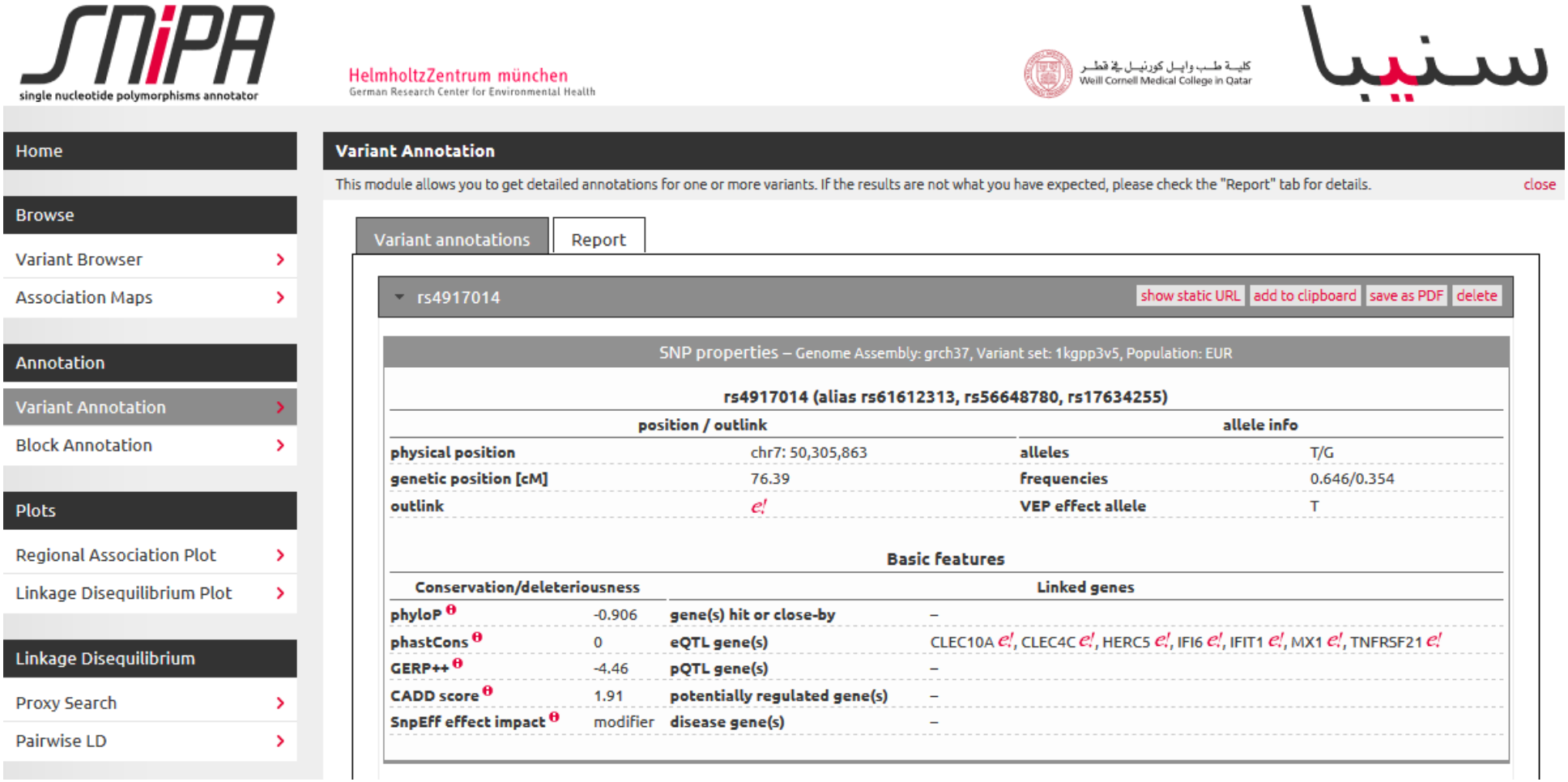
rs4917014



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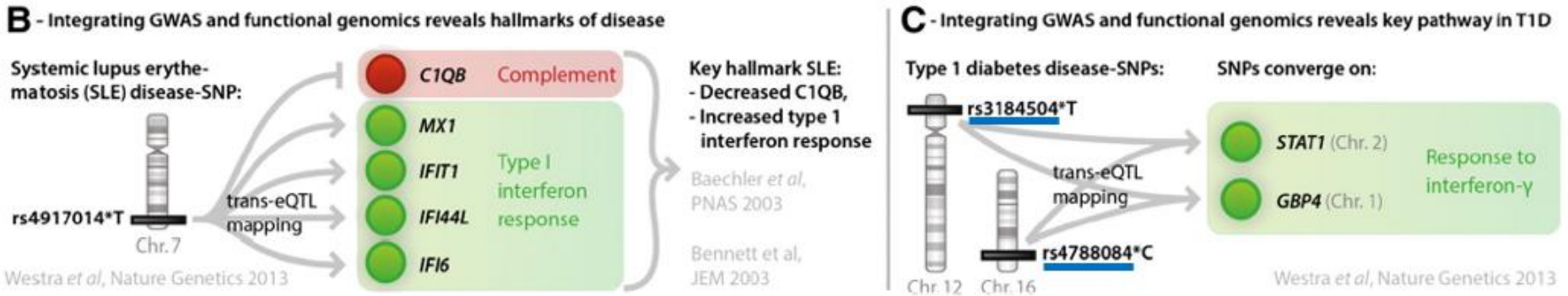
rs3184504 & rs4788084



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From genome to function by studying eQTLs ☆

Harm-Jan Westra, Lude Franke *

rs3184504 & rs4788084

Blood eQTL browser

This web page accompanies the manuscript titled *'Systematic identification of trans-eQTLs as putative drivers of known disease associations'*, by *Westra et al*, which has been published in Nature Genetics. If you want to use any of the *cis*- or *trans*-eQTL results displayed on this page in your publication, please cite this paper as indicated below. For further questions, contact the corresponding author: lude@ludesign.nl

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
6.135451079896497E-11	rs3184504	12	110368991	4810187	2	191542243	T/C	T	6.54	STAT1	0.00
5.251460604320952E-10	rs3184504	12	110368991	520470	19	58989104	T/C	T	-6.21	NALP12	0.00
1.982920070359625E-9	rs3184504	12	110368991	1980524	1	89420374	T/C	T	6.00	GBP4	0.00
4.868664101669589E-9	rs3184504	12	110368991	6650035	12	88628338	T/C	T	-5.85	-	0.00
5.934255341909855E-9	rs3184504	12	110368991	2570079	2	191548649	T/C	T	5.82	STAT1	0.00
6.823980922085895E-9	rs3184504	12	110368991	4280017	14	74818138	T/C	T	-5.80	FOS	0.00
6.856586333920168E-9	rs3184504	12	110368991	540681	1	150222229	T/C	T	-5.79	S100A10	0.00
1.282351689188786E-8	rs3184504	12	110368991	3610162	23	148385824	T/C	T	-5.69	IDS	0.00
1.365976739564349 8E-8	rs3184504	12	110368991	2070170	11	57075756	T/C	T	5.68	UBE2L6	0.00
1.720365090023578E-8	rs3184504	12	110368991	1940162	1	89346400	T/C	T	5.64	GBP2	0.00
5.547657540193922E-8	rs3184504	12	110368991	5890739	6	159380091	T/C	T	-5.43	TAGAP	0.01
6.115184179896167E-8	rs3184504	12	110368991	5810743	12	104288801	T/C	T	-5.42	-	0.01
1.0150990604763958E-7	rs3184504	12	110368991	1570553	4	74827536	T/C	T	-5.32	IL8	0.01
2.0036352580495783E-7	rs3184504	12	110368991	7570673	7	48114477	T/C	T	5.20	UPP1	0.02
2.984867135367768E-7	rs3184504	12	110368991	2190148	1	89291061	T/C	T	5.12	GBP1	0.03
4.219030840196723E-7	rs3184504	12	110368991	1340600	19	54071038	T/C	T	-5.06	PPP1R15A	0.04

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rs3184504 & rs4788084

Blood eQTL browser

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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
6.086411475032961E-11	rs4788084	16	28447349	4810187	2	191542243	T/C	T	-6.54	STAT1	0.00
1.4899267065875971E-7	rs4788084	16	28447349	1980524	1	89420374	T/C	T	-5.25	GBP4	0.02
1.6285448649605778E-7	rs4788084	16	28447349	2570079	2	191548649	T/C	T	-5.24	STAT1	0.02
1.6479791942187817E-6	rs4788084	16	28447349	150095	1	222034765	T/C	T	4.79	TP53BP2	0.13

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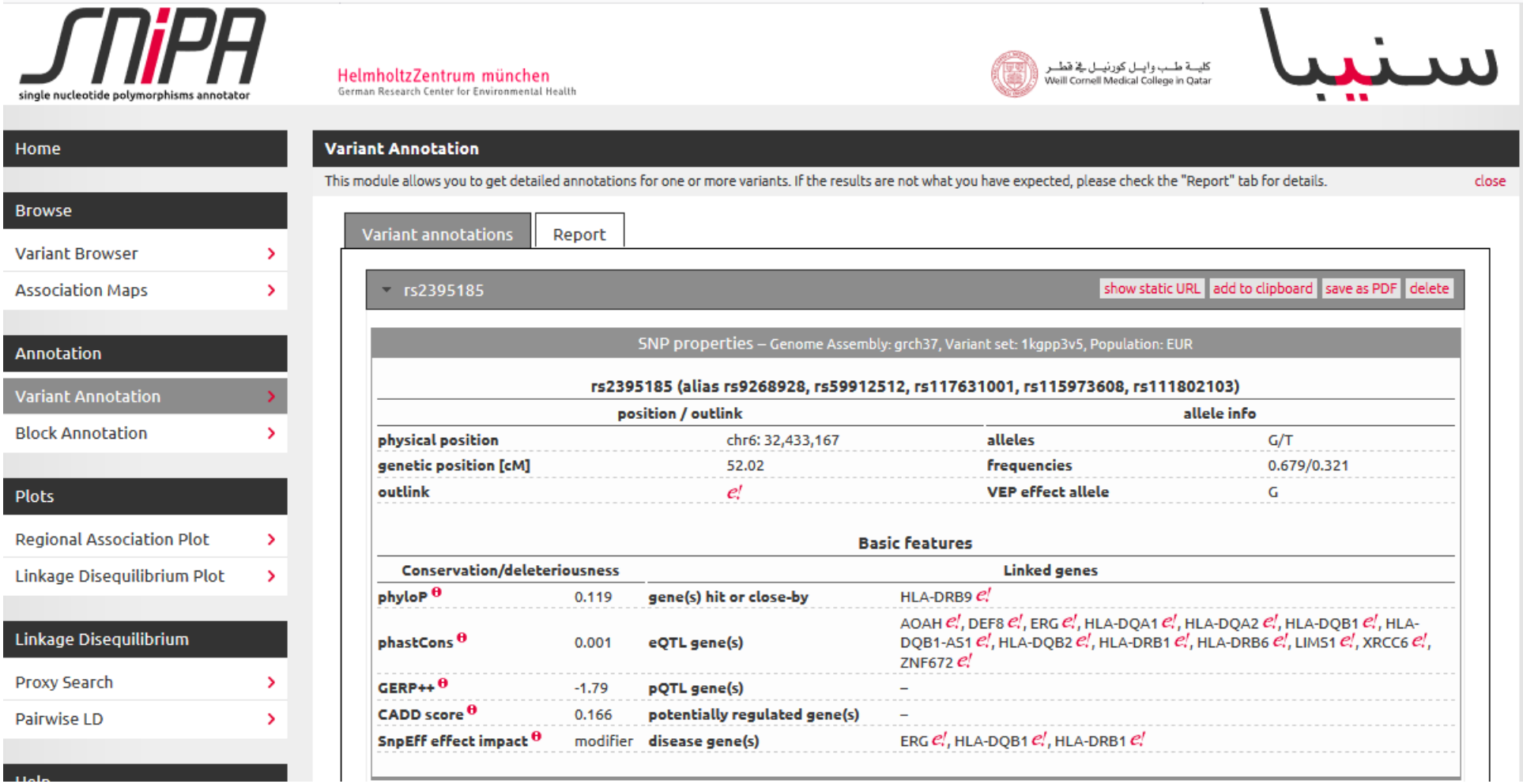
rs2395185



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rs2395185

SNiPA
single nucleotide polymorphisms annotator

HelmholtzZentrum münchen
German Research Center for Environmental Health

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Weill Cornell Medical College in Qatar

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Home

Variant Annotation

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

Trait annotations

Variant association

trait	p-value	source DB	source entry/link
Antinuclear antibody levels	$<1.00\times10^{-11}$	GWAS Catalog	25186300
LUNG CANCER	$<1.00\times10^{-8}$	GWAS Catalog	23143601
Hodgkin's lymphoma	$<4.00\times10^{-31}$	GWAS Catalog	22286212
Ulcerative colitis	$<9.00\times10^{-23}$	GWAS Catalog	20228799
Ulcerative colitis	$<5.00\times10^{-22}$	GWAS Catalog	19915573
Ulcerative colitis	$<1.00\times10^{-16}$	GWAS Catalog	19122664

Putative effect on transcript

Intron variant

gene	affected transcript	RefSeq id	protein
HLA-DRB9	ENST00000449413	?	?

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Variant Annotation

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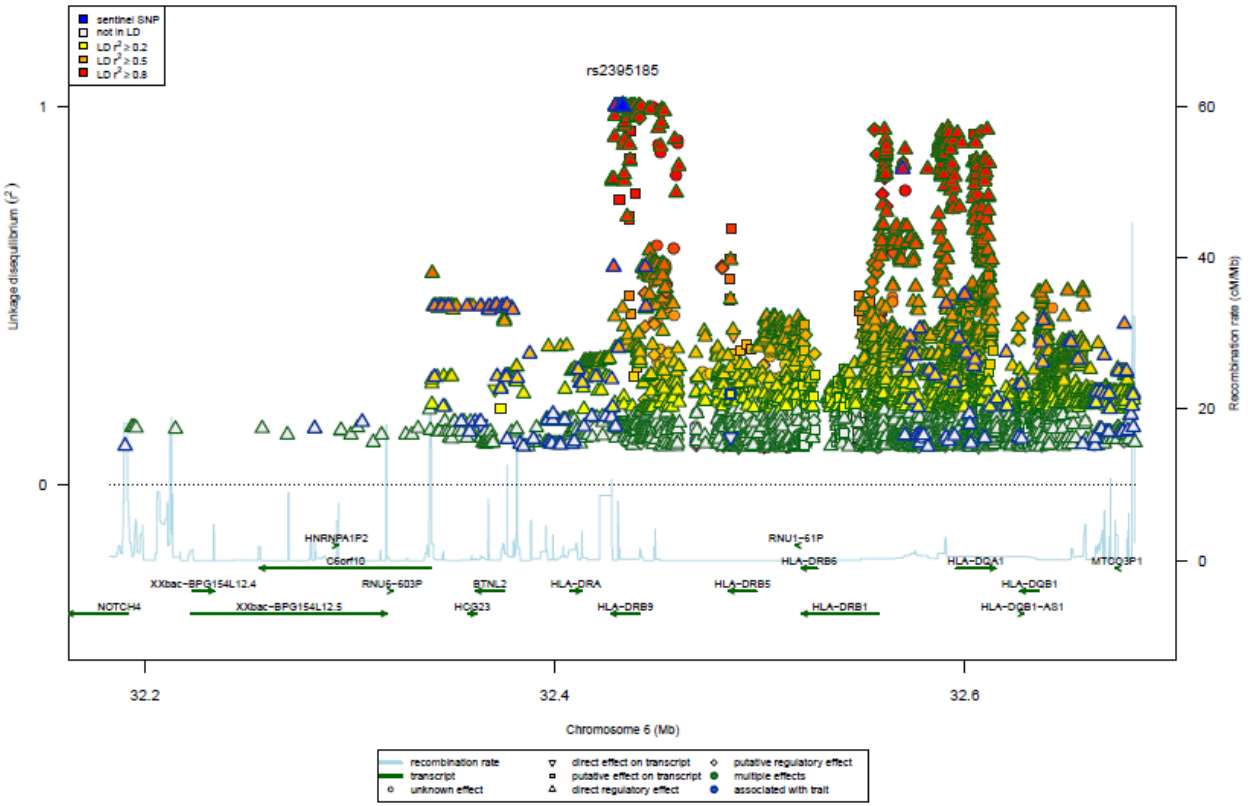

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Top 10 results by *p*-value

(Download all results below)

SNP	Proxy rsID	Proxy Pos (hg19)	r2	Trait	Study	PMID	Ancestry	Association Alleles	Beta	SE	P	N	Unit
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Okada Y	24390342	European	G/T	-0.7467	0.01693	1.00e-250	58284	log(OR)
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Okada Y	24390342	Mixed	G/T	-0.6981	0.01393	1.00e-250	80799	log(OR)
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Stahl E	20453842	European	G/T	-0.802	0.02399	1.43e-235	25692	log(OR)
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Stahl E	20453842	European	NA	NA	NA	1.43e-235	41282	NA
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Gregersen PK	19503088	European	NA	NA	NA	4.42e-125	12408	NA
rs2395185	rs9268838	chr6:32428715	0.807	Vogt Koyanagi Harada syndrome	Hou S	25108386	Asian	G/A	-1.105	0.04751	1.00e-119	NA	log(OR)
rs2395185	rs9268853	chr6:32429643	1	Arthritis Rheumatoid	Eleftherohorinou	21653640	European	NA	NA	NA	5.00e-109	NA	NA
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Okada Y	24390342	Asian	G/T	-0.5822	0.02567	1.10e-107	22515	log(OR)
rs2395185	rs2395185	chr6:32433167	1	Rheumatoid arthritis	Plenge RM	17804836	European	NA	NA	NA	1.15e-83	6235	NA
rs2395185	rs9268858	chr6:32429758	1	Rheumatoid arthritis combined control dataset	WTCCC	17554300	European	NA	NA	NA	2.48e-74	4806	NA

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	A	B	C	D	E	F	G	H	I	J	K	L
1	rsID	Pos (hg	Proxy r	r2	Dprim	oxy Indi	P	Trait	Study	PMID	Beta	SE
2	rs2395185	r6:324331	rs9271605	0.906	0.972	1	0	Rheumatoid arthritis	Stahl E	20453842	-1.151	0.02662
306	rs2395185	r6:324331	rs9268838	0.807	1	1	1.00E-119	Vogt Koyanagi Harada syndrome	Hou S	25108386	-1.105	0.04751
463	rs2395185	r6:324331	rs9268853	1	1	1	1.00E-55	Colitis Ulcerative	Anderson	21297633	NA	NA
769	rs2395185	r6:324331	rs2395185	1	1	0	4.00E-31	Hodgkin Disease	Urayama H	22286212	NA	NA
788	rs2395185	r6:324331	rs9272514	0.689	0.868	1	1.59E-29	Inflammatory bowel disease	IBDGC	26192919	0.2347	0.0208
1101	rs2395185	r6:324331	rs2395185	1	1	0	1.00E-16	Type 1 diabetes	Hakonarsc	17632545	NA	NA
1121	rs2395185	r6:324331	rs2516049	0.682	0.94	1	3.24E-16	Generalized vitiligo	Jin Y	20410501	NA	NA
1133	rs2395185	r6:324331	rs2516049	0.682	0.94	1	2.90E-15	Antibody titer to hepatitis B vaccination	Png E	21764829	NA	NA
1154	rs2395185	r6:324331	rs9272775	0.778	0.894	1	6.70E-14	Height	GIANT	25282103	0.024	0.0032
1164	rs2395185	r6:324331	rs9268853	1	1	1	8.87E-13	Psoriasis	CASP	19680446	NA	NA
1173	rs2395185	r6:324331	rs9268853	1	1	1	2.00E-10	Lymphoma	Vijai J	23349640	-0.4447	0.0699
1177	rs2395185	r6:324331	rs28383312	0.715	0.932	1	5.94E-10	Sarcoidosis	Adrianto	22952805	NA	NA
1178	rs2395185	r6:324331	rs9268853	1	1	1	7.40E-10	Multiple sclerosis	IMSGC	17660530	NA	NA
1180	rs2395185	r6:324331	rs2395185	1	1	0	9.47E-10	Lung cancer adenocarcinoma in never smoking wom	Lan Q	23143601	NA	NA
1446												
1447												
1448												
1449												
1450												
1451												
1452												

rs2395185_08794_PhenoScanner_GW

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rs2395185

Blood eQTL browser

This web page accompanies the manuscript titled *'Systematic identification of trans-eQTLs as putative drivers of known disease associations'*, by *Westra et al*, which has been published in Nature Genetics. If you want to use any of the *cis*- or *trans*-eQTL results displayed on this page in your publication, please cite this paper as indicated below. For further questions, contact the corresponding author: lude@ludesign.nl

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
4.998360519267759E-45	rs2395185	6	32541145	2940424	7	36519337	G/T	T	-14.08	AOAH	0.00
1.6602738233192535E-15	rs2395185	6	32541145	2120746	7	142004891	G/T	T	7.96	U66060.1-23	0.00
7.532716768353073E-13	rs2395185	6	32541145	1090739	2	108658795	G/T	T	7.17	LIMS1	0.00
2.2266549503590302E-8	rs2395185	6	32541145	5820768	16	88561805	G/T	T	-5.59	DEF8	0.00
2.4354319375644347E-7	rs2395185	6	32541145	6380347	22	40389758	G/T	T	5.16	XRCC6	0.03
3.4109200349170565E-7	rs2395185	6	32541145	6330646	1	247110194	G/T	T	5.10	ZNF672	0.03
4.140112373455338E-7	rs2395185	6	32541145	2570703	21	38869500	G/T	T	-5.06	ERG	0.04
2.03215563753922E-6	rs2395185	6	32541145	3930537	7	142128152	G/T	T	-4.75	U66061.1-11	0.15
2.307957482677188E-6	rs2395185	6	32541145	3990435	7	141982009	G/T	T	-4.72	U66060.1-21	0.17
3.2022788317185925E-6	rs2395185	6	32541145	2650524	4	109761291	G/T	T	4.66	RPL34	0.21
4.632006484657384E-6	rs2395185	6	32541145	5270731	19	5619289	G/T	T	4.58	SAFB	0.26
1.316166001066651E-5	rs2395185	6	32541145	6560369	14	39929284	G/T	T	-4.36	-	0.46
1.4938042607888654E-5	rs2395185	6	32541145	6650639	12	6441842	G/T	T	-4.33	VAMP1	0.49

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rs2395185

Haplotype-Specific DNA Methylation | rs2395185 | Search | Random | Selected Hits | About | Downloads

rs2395185

SNP at: chr6:32433166-32433167

LD Block: chr6:32384800-32681631

External Links

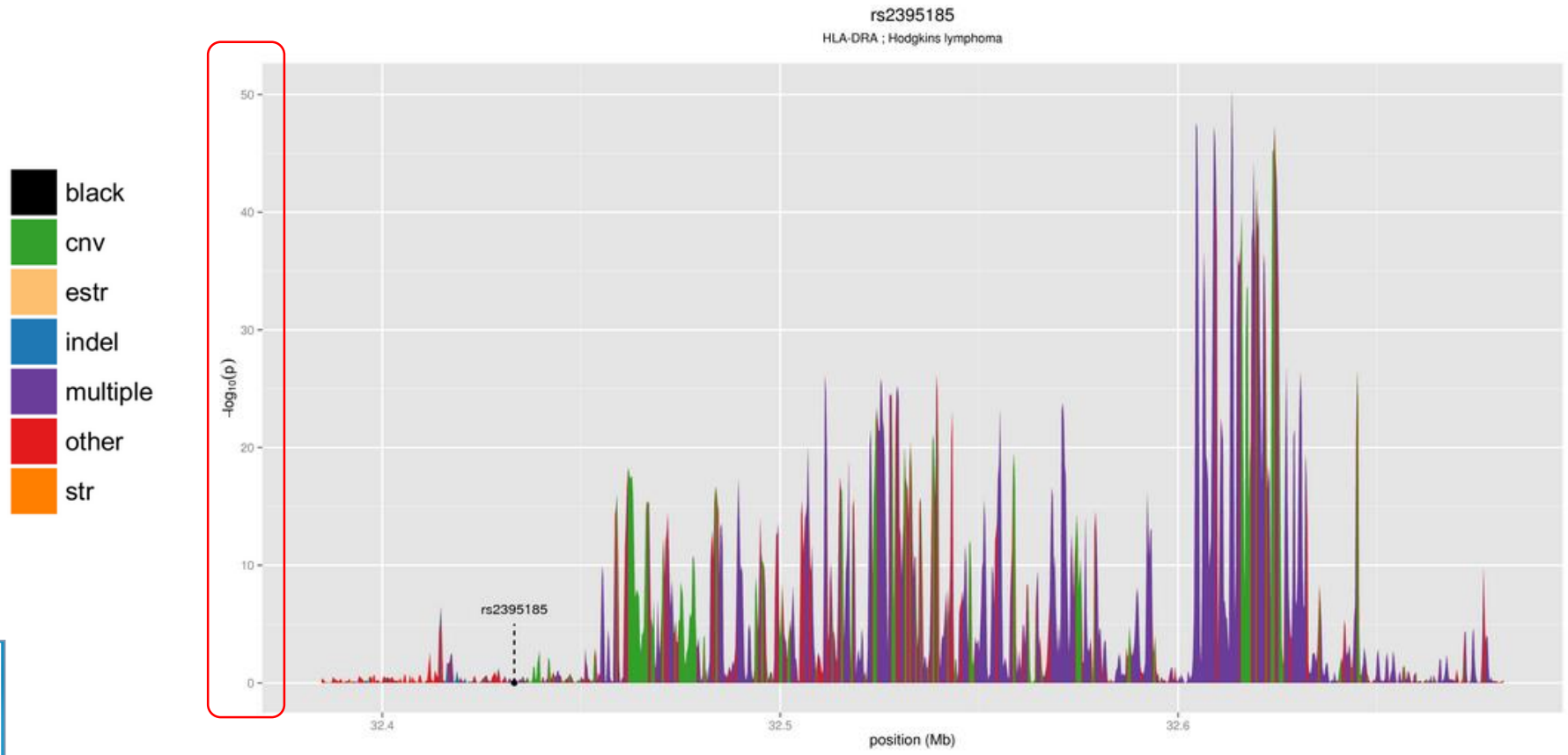
GWAS catalog | dbSNP | UCSC Genome Browser

Datasets

Download data as .txt.gz or image (png or pdf)

Download | View

View Dataset (see About for details)



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rs2395185

Haplotype-specific DNA methylation identifies significant regional DNA methylation variation between risk and non-risk GWAS SNP haplotypes for those associated human diseases.

rs2395185 is in a large linkage disequilibrium block (app. 300kb) and correlates with haplotype-specific DNA methylation variation (*P* up to 1E-50).

It appears that rs2395185 mediates disease susceptibility through an epigenetic mechanism.

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rs2395185

BIOS QTL browser

This web page accompanies the manuscripts titled '**Disease variants alter transcription factor levels and methylation of their binding sites**', by *Bonder et al* and '**Identification of context-dependent expression quantitative trait loci in whole blood**', by *Zhernakova et al*, both have been published to Nature Genetics.
For further questions, contact the corresponding author: lude@ludesign.nl

Trans-meQTLs

P-value	SNP	SNP Chr.	SNP Chr. position	CpG	CpG Chr.	CpG Chr. position	SNP Alleles	Assesed Allele	Z-score	Gene name	FDR
3.27167E-310	rs2395185	6	32433167	cg10154826	6	17601018	G/T	T	61.25		0.00
1.81E-31	rs2395185	6	32433167	cg07575812	5	138883534	G/T	T	11.67		0.00
2.03E-09	rs2395185	6	32433167	cg23331010	3	98512714	G/T	T	6.00		0.00
1.02E-08	rs2395185	6	32433167	cg00580354	2	179296293	G/T	T	5.73		0.00

FAM8A1
cg10154826

Trans-meQTLs

P-value	SNP	SNP Chr.	SNP Chr. position	CpG	CpG Chr.	CpG Chr. position	SNP Alleles	Assesed Allele	Z-score	Gene name	FDR
3.27167E-310	rs9268923	6	32432835	cg10154826	6	17601018	C/T	T	61.25		0.00
3.27167E-310	rs2395185	6	32433167	cg10154826	6	17601018	G/T	T	61.25		0.00
3.27167E-310	rs9268853	6	32429643	cg10154826	6	17601018	T/C	C	61.14		0.00
3.27167E-310	rs477515	6	32569691	cg10154826	6	17601018	G/A	A	58.22		0.00
3.27167E-310	rs9268516	6	32379489	cg10154826	6	17601018	C/T	T	42.12		0.00
3.27167E-310	rs9268839	6	32428772	cg10154826	6	17601018	A/G	G	41.78		0.00
3.27167E-310	rs3817963	6	32368087	cg10154826	6	17601018	T/C	C	41.15		0.00
3.27167E-310	rs9275563	6	32677912	cg10154826	6	17601018	C/T	T	39.66		0.00
3.27167E-310	rs9272105	6	32599999	cg10154826	6	17601018	G/A	G	39.13		0.00
3.27167E-310	rs9271588	6	32590953	cg10154826	6	17601018	T/C	C	38.82		0.00
3.29E-287	rs2395163	6	32387809	cg10154826	6	17601018	T/C	C	36.22		0.00
2.24E-278	rs2647045	6	32668100	cg10154826	6	17601018	G/A	A	35.65		0.00
3.81E-253	rs6927022	6	32612397	cg10154826	6	17601018	A/G	G	33.98		0.00
8.78E-234	rs9271858	6	32595223	cg10154826	6	17601018	A/G	A	32.65		0.00
5.57E-233	rs3806156	6	32373698	cg10154826	6	17601018	G/T	T	32.59		0.00
5.62E-218	rs9272346	6	32604372	cg10154826	6	17601018	G/A	G	-31.51		0.00
1.20E-212	rs9268402	6	32341353	cg10154826	6	17601018	G/A	A	31.12		0.00
3.13E-208	rs9275572	6	32678999	cg10154826	6	17601018	A/G	A	-30.79		0.00
6.65E-208	rs4273729	6	32678597	cg10154826	6	17601018	C/G	C	-30.77		0.00
1.16E-198	rs7759742	6	32381736	cg10154826	6	17601018	T/A	A	30.07		0.00
3.56E-194	rs660895	6	32577380	cg10154826	6	17601018	A/G	G	29.73		0.00
3.01E-183	rs2647012	6	32664458	cg10154826	6	17601018	T/C	T	-28.87		0.00
4.94E-176	rs9268877	6	32431147	cg10154826	6	17601018	A/G	A	-28.29		0.00
2.56E-163	rs9275596	6	32681631	cg10154826	6	17601018	C/T	C	-27.23		0.00
1.07E-154	rs2076530	6	32363816	cg10154826	6	17601018	T/C	C	26.50		0.00

The most significant meQTL effect in the genome

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rs2395185

FAM8A1
cg10154826

Also replicated in the lung tissue

mQTL Database

Timepoint	SNP	SNP Chr	SNP Pos	A1	A2	MAF	CpG	CpG Chr	CpG Pos	beta	t-stat	Effect Size	p-value	Trans
Childhood	rs116618145	6	32651254	G	C	0.256	cg10154826	6	176009940	.31417	6.71091	0.00750	3.58e-11	Y
Childhood	rs114232979	6	32651265	C	T	0.256	cg10154826	6	176009940	.31417	6.71091	0.00750	3.58e-11	Y
Adolescencers	117230773	6	32433741	A	G	0.414	cg10154826	6	176009940	.89409	30.23221	0.03491	3.33e-136	Y
Adolescencers	77377370	6	32559131	A	G	0.338	cg10154826	6	176009940	.95210	30.14475	0.03611	1.18e-135	Y
Pregnancy	rs9273440	6	32627561	T	C	0.237	cg10154826	6	176009940	-0.49097	-9.99606	0.03013	3.44e-22	Y
Adolescencers	114961538	6	32451963	A	G	0.339	cg10154826	6	176009940	.94797	29.42865	0.03611	3.69e-131	Y
Adolescencers	145110260	6	32435338	T	C	0.412	cg10154826	6	176009940	.90971	29.41115	0.03553	4.76e-131	Y
Adolescencers	116405062	6	32450580	C	T	0.389	cg10154826	6	176009940	.93030	30.33361	0.03616	7.69e-137	Y
Adolescencers	114675911	6	32451947	T	C	0.334	cg10154826	6	176009940	.95165	29.36034	0.03598	9.92e-131	Y
Adolescencers	115843682	6	32451954	C	T	0.334	cg10154826	6	176009940	.95165	29.36034	0.03598	9.92e-131	Y
Birth	rs115662287	6	32651557	T	C	0.238	cg10154826	6	176009940	.70096	14.83466	0.03019	5.72e-44	Y
Adolescencers	80294343	6	32559124	C	T	0.339	cg10154826	6	176009940	.95528	30.32510	0.03613	8.70e-137	Y
Birth	rs116271293	6	32661302	T	G	0.399	cg10154826	6	17600994	-0.58652	-14.83360	0.03029	5.79e-44	Y
Middle Age	rs115312879	6	31304395	G	A	0.327	cg10154826	6	17600994	-0.29004	-5.86265	0.02969	6.86e-09	Y
Birth	rs111371403	6	32626492	G	A	0.34	cg10154826	6	17600994	-0.61017	-14.83128	0.02973	5.95e-44	Y
Birth	rs139349160	6	31237955	T	G	0.409	cg10154826	6	17600994	-0.27256	-6.22964	0.02217	7.69e-10	Y
Childhood	rs114172383	6	32652176	G	C	0.242	cg10154826	6	176009940	.32230	6.70928	0.00755	3.61e-11	Y
Adolescencers	113705304	6	32590453	G	C	0.084	cg10154826	6	17600994	-0.43537	-5.71454	0.02874	1.53e-08	Y
Adolescencers	111955760	6	32590768	A	C	0.084	cg10154826	6	17600994	-0.43537	-5.71454	0.02874	1.53e-08	Y
Pregnancy	rs200929335	6	32652605	I	R	0.12	cg10154826	6	176009940	.62892	9.99254	0.01489	3.55e-22	Y
Adolescencers	116756682	6	32591238	G	A	0.083	cg10154826	6	17600994	-0.43650	-5.71427	0.02874	1.53e-08	Y
Adolescencers	115704361	6	32591248	T	C	0.083	cg10154826	6	17600994	-0.43650	-5.71427	0.02874	1.53e-08	Y
Adolescencers	113435978	6	32591567	A	T	0.083	cg10154826	6	17600994	-0.43650	-5.71427	0.02874	1.53e-08	Y
Childhood	rs112460460	6	32566284	A	T	0.101	cg10154826	6	17600994	-0.45163	-6.70810	0.02613	3.64e-11	Y
Adolescencers	35508382	6	32593144	G	A	0.084	cg10154826	6	17600994	-0.43650	-5.71427	0.02874	1.53e-08	Y
Adolescencers	116518618	6	32594998	T	C	0.083	cg10154826	6	17600994	-0.43650	-5.71427	0.02874	1.53e-08	Y
Pregnancy	rs116084574	6	32659112	T	C	0.116	cg10154826	6	17600994	-0.47466	-7.00947	0.02944	5.27e-12	Y
Adolescencers	114975350	6	32428062	T	C	0.333	cg10154826	6	176009940	.91182	27.58655	0.03614	1.37e-119	Y
Adolescencers	114455794	6	32428079	A	C	0.333	cg10154826	6	176009940	.91182	27.58655	0.03614	1.37e-119	Y
Adolescencers	115918645	6	32428115	A	G	0.333	cg10154826	6	176009940	.91182	27.58655	0.03614	1.37e-119	Y
Adolescencers	114800139	6	32428715	A	G	0.333	cg10154826	6	176009940	.91182	27.58655	0.03614	1.37e-119	Y
Adolescencers	115048082	6	32653018	C	T	0.383	cg10154826	6	176009940	.57721	14.84490	0.02964	2.05e-44	Y
[illegible]	[illegible]	6	32658429	C	T	0.383	cg10154826	6	176009940	.57721	14.84490	0.02964	2.05e-44	Y

a from mqtldb.org

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rs2395185: Conclusion

The meQTL target *FAM8A1* cg10154826 is a candidate to be the mediator of rs2395185 associations with disease

rs2395185 is also a trans-eQTL for a number of genes

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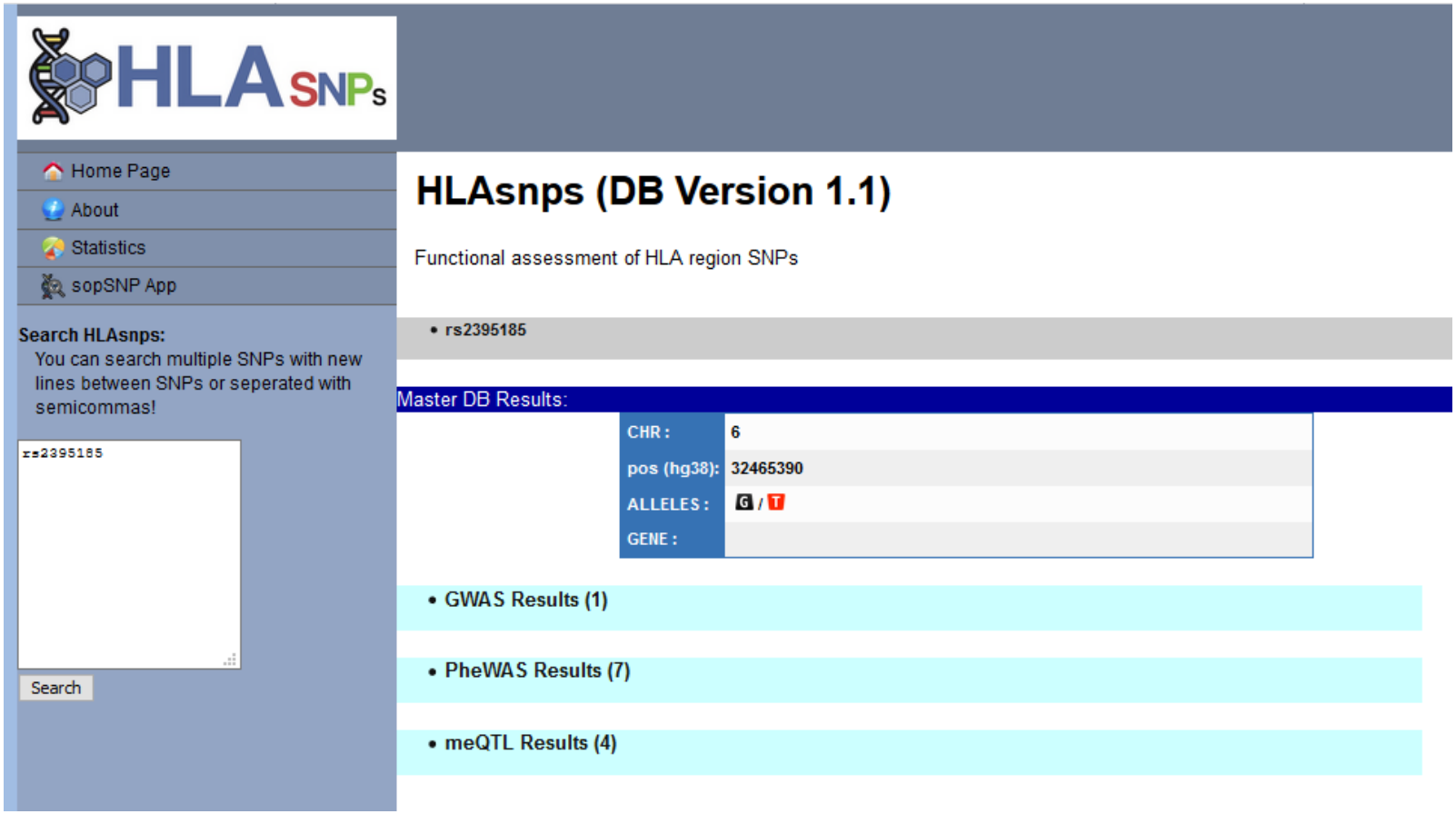
HLASNPs (beta)



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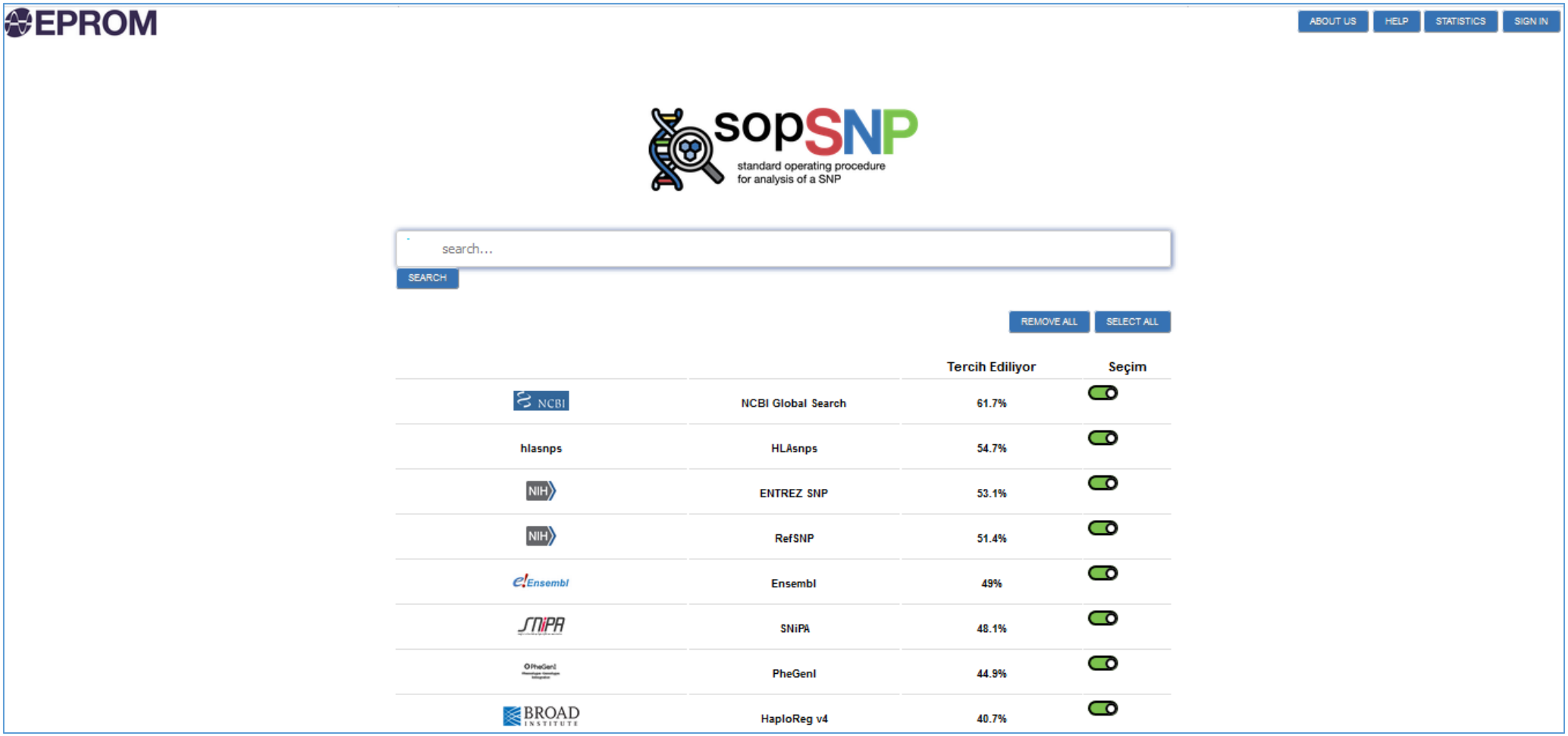
sopSNP (beta)



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3D Genome: Chromatin Interactions

An intronic polymorphism of IRF4 gene influences gene transcription *in vitro* and shows a risk association with childhood acute lymphoblastic leukemia in males

Thuy N. Do, Esma Ucisik-Akkaya, Charronne F. Davis, Brittany A. Morrison, M. Tevfik Dorak *

Genomic Immunoepidemiology Laboratory, HUMIGEN LLC, The Institute for Genetic Immunology, 2439 Kuser Road, Hamilton, NJ 08690-3303, USA

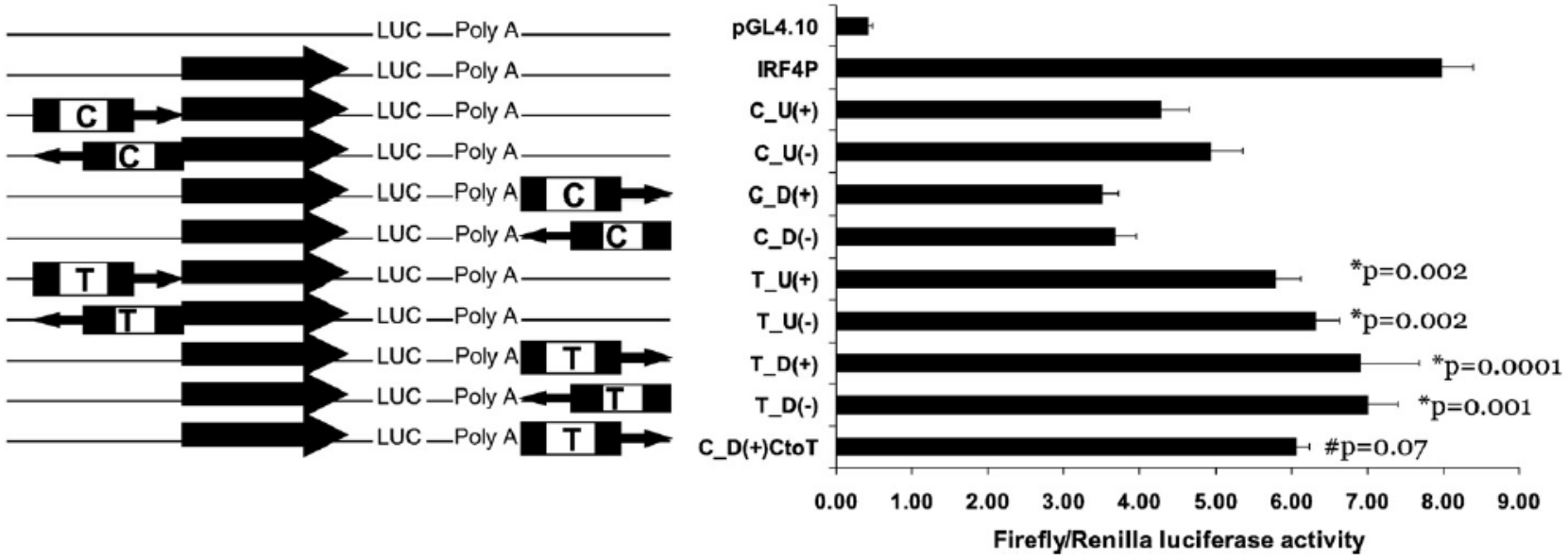

Fig. 1. IRF4 intron 4 with wild type allele C at SNP rs12203592 represses IRF4 promoter activity while IRF4 intron 4 with variant allele T significantly alleviates this repressive effect. Both work in an orientation- and position-independent manner. The full 1.2-kb fragment of intron 4 of the human IRF4 gene (contains either a wild type C or variant allele T at SNP rs12203592) was subcloned into the luciferase-reporter plasmid driven by a 2.4-kb IRF4 promoter (the big black arrow right before luciferase gene (LUC)). In all of the constructs, the LUC is used as a reporter gene whose mRNA is stabilized by a polyadenylation/splice signal from the simian virus 40 (Poly A). Raji cells were co-nucleofected with these constructs and with the internal control plasmid pGL4.13[hRenilla/SV40] and then assayed for both firefly and *Renilla* luciferases after 24 h. To adjust for differences in transfection efficiencies, firefly luciferase values were standardized to *Renilla* luciferase values. The results are from three independent experiments. The error bars represent standard errors. *Comparison between intron 4 with the variant allele T and intron 4 with the wild type allele C; #comparison between CD(+)CtoT with TD(+).

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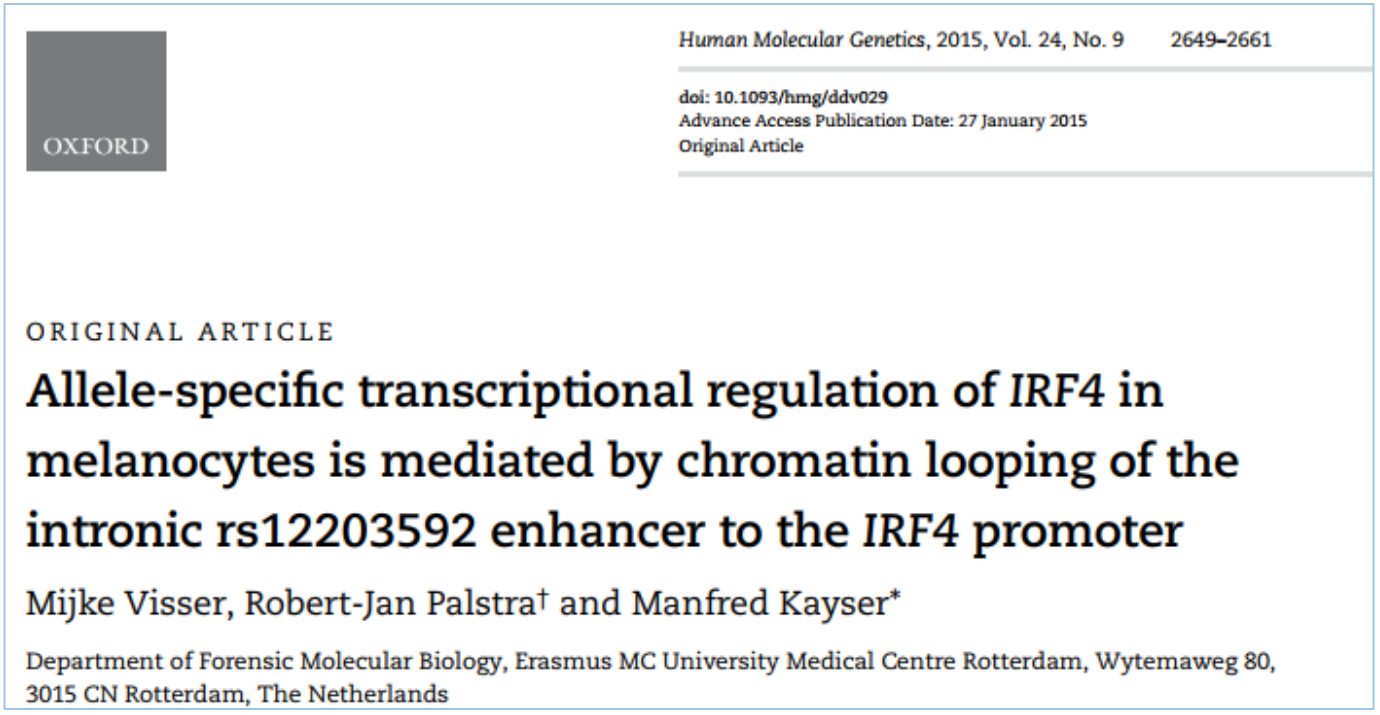
3D Genome: Chromatin Interactions



OXFORD

Human Molecular Genetics, 2015, Vol. 24, No. 9 2649–2661

doi: 10.1093/hmg/ddv029
Advance Access Publication Date: 27 January 2015
Original Article

ORIGINAL ARTICLE

Allele-specific transcriptional regulation of *IRF4* in melanocytes is mediated by chromatin looping of the intronic rs12203592 enhancer to the *IRF4* promoter

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The rs12203592 enhancer physically interacts with the *IRF4* promoter through an allele-dependent chromatin loop

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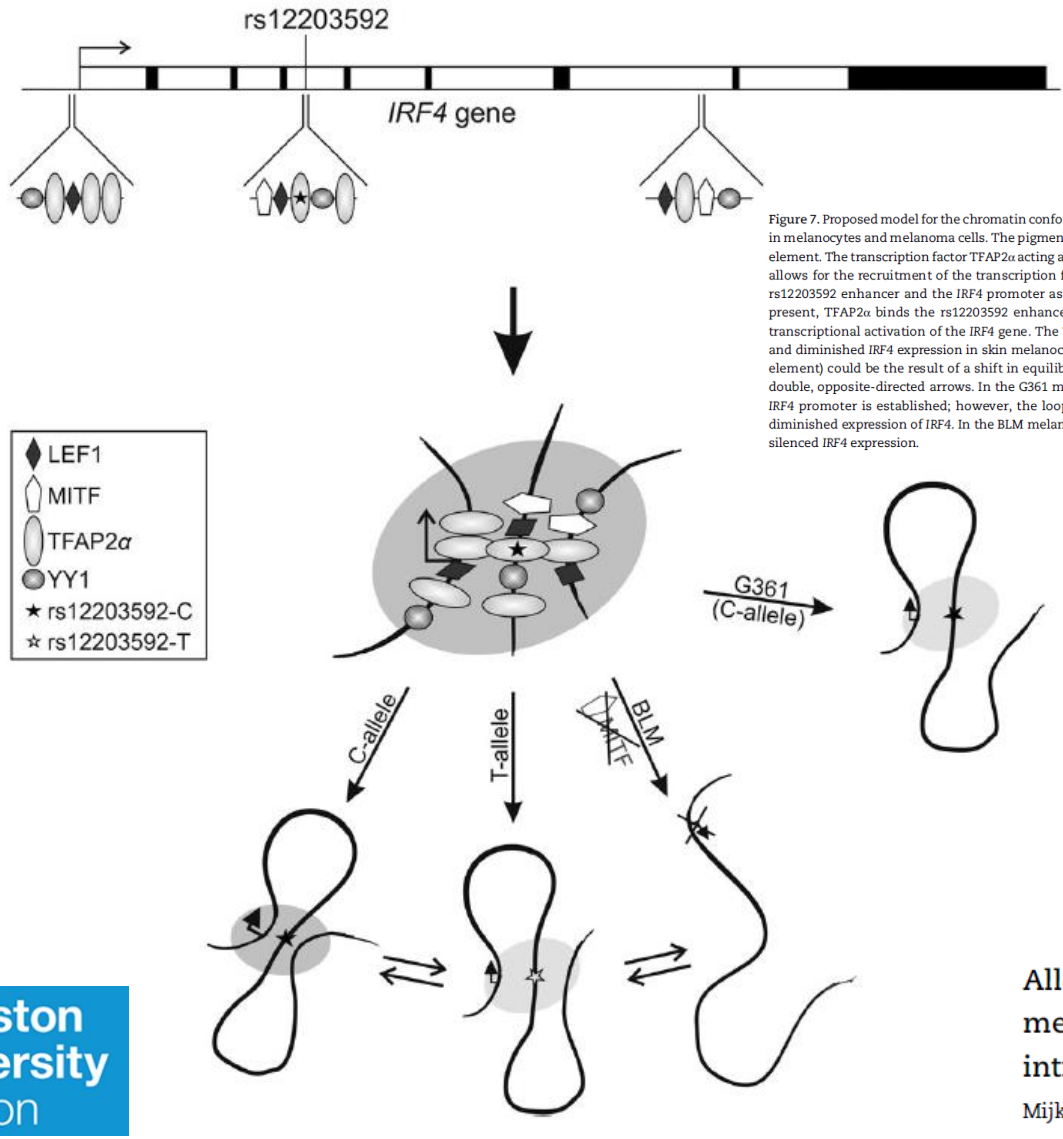

Figure 7. Proposed model for the chromatin conformation of the *IRF4* locus and subsequent transcriptional regulation of IRF4, depending on the allelic status of rs12203592 in melanocytes and melanoma cells. The pigmentation-associated SNP rs12203592 is located in intron 4 of *IRF4* and the region around this SNP functions as an enhancer element. The transcription factor TFAP2α acting as sequence specific DNA binding factor recognizes the rs12203592 enhancer in an allele-dependent manner, which then allows for the recruitment of the transcription factors MITF, YY1 and potential additional transcription factors like LEF1. Chromatin loops are formed between the rs12203592 enhancer and the *IRF4* promoter as well as the intron-7 YY1-element, both interactions depend on the allelic status of rs12203592. With the C-allele present, TFAP2α binds the rs12203592 enhancer, followed by recruitment of additional factors like MITF, YY1 and potentially LEF1, loop formation and proper transcriptional activation of the *IRF4* gene. The T-allele is unable to bind TFAP2α, which leads to reduced recruitment of additional factors, reduced loop formation and diminished *IRF4* expression in skin melanocytes. The different interactions between the rs12203592 enhancer and the *IRF4* promoter (as well as the intron-7 YY1-element) could be the result of a shift in equilibrium between the unfolded and interacting state that depends on the rs12203592 alleles, which is indicated by the double, opposite-directed arrows. In the G361 melanoma cell line, the TFAP2α factor presumably still binds the rs12203592 enhancer and loop formation toward the *IRF4* promoter is established; however, the loop toward the intron-7 YY1 element is disrupted, resulting in a less stable chromatin structure and consequently, diminished expression of *IRF4*. In the BLM melanoma cell line, MITF is absent and no chromatin loops are formed, resulting into a linear chromatin conformation and silenced *IRF4* expression.

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Allele-specific transcriptional regulation of *IRF4* in melanocytes is mediated by chromatin looping of the intronic rs12203592 enhancer to the *IRF4* promoter

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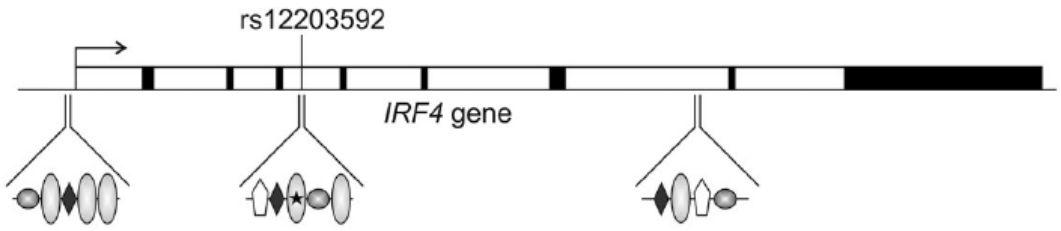
3D Genome: Chromatin Interactions

The rs12203592 enhancer physically interacts with the *IRF4* promoter through an allele-dependent chromatin loop.



Sample	Bin	Distance	Bias-removed Interaction frequency	Distance normalized Interaction frequency	Enhancer	GWAS SNP ID
Spleen	chr6:415000-420000	20000	3.00	0.17	None	rs9378805
Spleen	chr6:465000-470000	70000	13.79	1.61	None	rs1540771
Spleen	chr6:475000-480000	80000	17.26	2.47	None	rs12210050
Spleen	chr6:295000-300000	100000	11.40	2.32	Enhancer	-

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3D-genome Interaction Viewer and database

More Functional SNPs

Genetic Study of Complex Diseases in the Post-GWAS Era

Qingyang Huang*

Table 2
Successfully characterized GWAS functional SNPs

Disease or phenotype	SNP	Function[a]	Target gene of SNP	Reference
Prostate cancer	rs11986220	FOXA1		Jia et al., 2009
Prostate cancer	rs8072254/ rs1859961	AR FOXA1/AP-1	*SOX9* *SOX9*	Zhang et al., 2012
Prostate cancer	rs12653946		*IRX4*	Nguyen et al., 2012
Colorectal cancer	rs6983267	TCF7L2	*MYC*	Wasserman et al, 2010
Colorectal cancer	rs6983267	TCF4	*MYC*	Wright et al, 2010
Colorectal cancer	rs16888589	STAT	*EIF3H*	Pittman et al., 2010
Breast cancer	rs10069690	Splicing	*TRET*	Bojesen et al., 2013
Breast cancer	rs4784227	FOXA1	*TOX3*	Cowper-Sal lari et al., 2012
Breast cancer	rs4442975	FOXA1	*IGFBP5*	Ghoussaini et al. 2014
Breast cancer	rs554219	ELK4	*CCND1*	French et al., 2013
Breast cancer	rs7895676	Oct-1/Runx2	*FGFR2*	Meyer et al., 2008
Breast cancer	rs2981578	C/EBPβ	*FGFR2*	Meyer et al., 2008
Breast cancer	rs2981578	FOXA1	*FGFR2*	Meyer et al., 2013
Breast cancer	rs35054928	E2F1	*FGFR2*	Meyer et al., 2013
Renal cancer	11q13.3	HIF-2	*CCND1*	Schödel et al, 2012
Prostate cancer	rs339331	HOXB13	*RFX6*	Huang et al., 2014
T2D	rs10946398	Splicing	*CDKAL1*	Zhou et al., 2014
T2D/BMI	rs4684847	PRRX1	*PPARG2*	Claussnitzer et al, 2014

… Looking forward

Day 1
Bioinformatics tools for the assessment of genetic variants
Bioinformatic analysis of experimentally verified functional SNP associations with disease
Bioinformatic tools for the investigation of tissue specificity of variant effects
Online tools: Standard operating procedures for gene and variant analysis
Applications and practice on participant projects

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