Longevity-associated HLA Class II Region Variants Map to the B-cell-specific Super-enhancer XL9

Sandeep K. SINGH, Mehmet Tevfik DORAK

GenTox (Research and Development), Lucknow, India;

School of Life Sciences, Pharmacy & Chemistry, Kingston University London, UK

Kingston University London

Outline

The Super-enhancer XL9 in the HLA Class II Region

Polymorphic Content of XL9

Longevity Associations with HLA Region Variants

Functional Annotations

Conclusions

Kingston University London

Background

The Super-enhancer XL9 in the HLA Class II Region

One of the regulatory elements called X box-like (XL) sequences, XL9, is located between *HLA-DRB1* and -*DQA1*. Multiple enhancers regulating the expression of HLA class II genes map to XL9. XL9 is involved in the formation of long-distance chromatin loops with the promoters of the *DRB1* and *DQA1* genes.

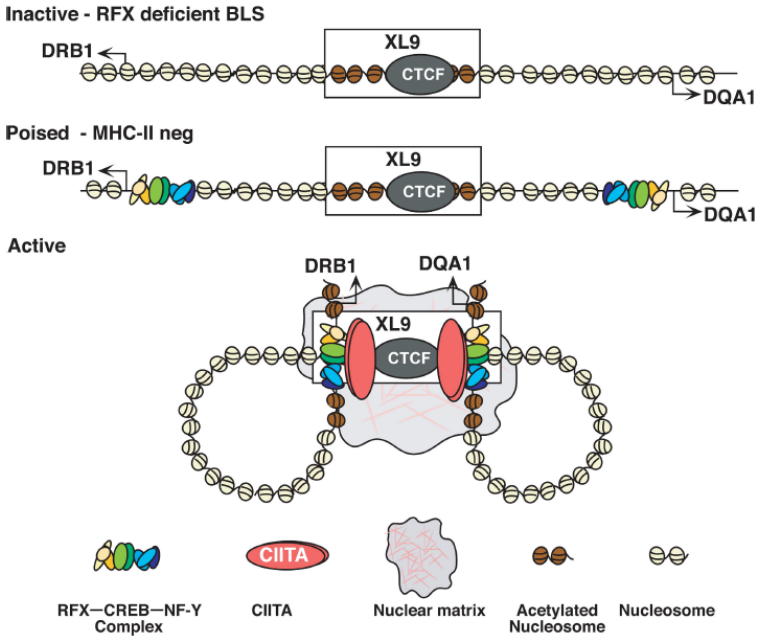


Figure 9. Models of interactions between *HLA-DRB1* and *HLA-DQA1* and the *XL9* region. Three potential states are shown. The inactive state represents RFX-deficient cell types as in SJO cells from bare lymphocyte syndrome patients with no factors bound to the MHC-II proximal regulatory regions. In the inactive state, no interactions with *XL9* occur and the proximal regulatory regions of MHC-II genes display background chromatin marks associated with the gene activation. A poised state is suggested for normal MHC-II–nonexpressing cells. In such cells, RFX–CREB–NF-Y but not CIITA are assembled at the MHC-II proximal regulatory regions. No interactions with *XL9* occur in the poised state, but chromatin marks associated with genes that can be activated are present. In MHC-II–expressing cells, CIITA is expressed and an "active state" is proposed with the proximal promoter regions of the *HLA-DRB1* and/or *HLA-DQA1* genes interacting directly with *XL9*. The potential for both genes to interact with *XL9* is depicted, but it is possible that only one gene interacts or is transcribed at a time.

The insulator factor CTCF controls MHC class II gene expression and is required for the formation of long-distance chromatin interactions

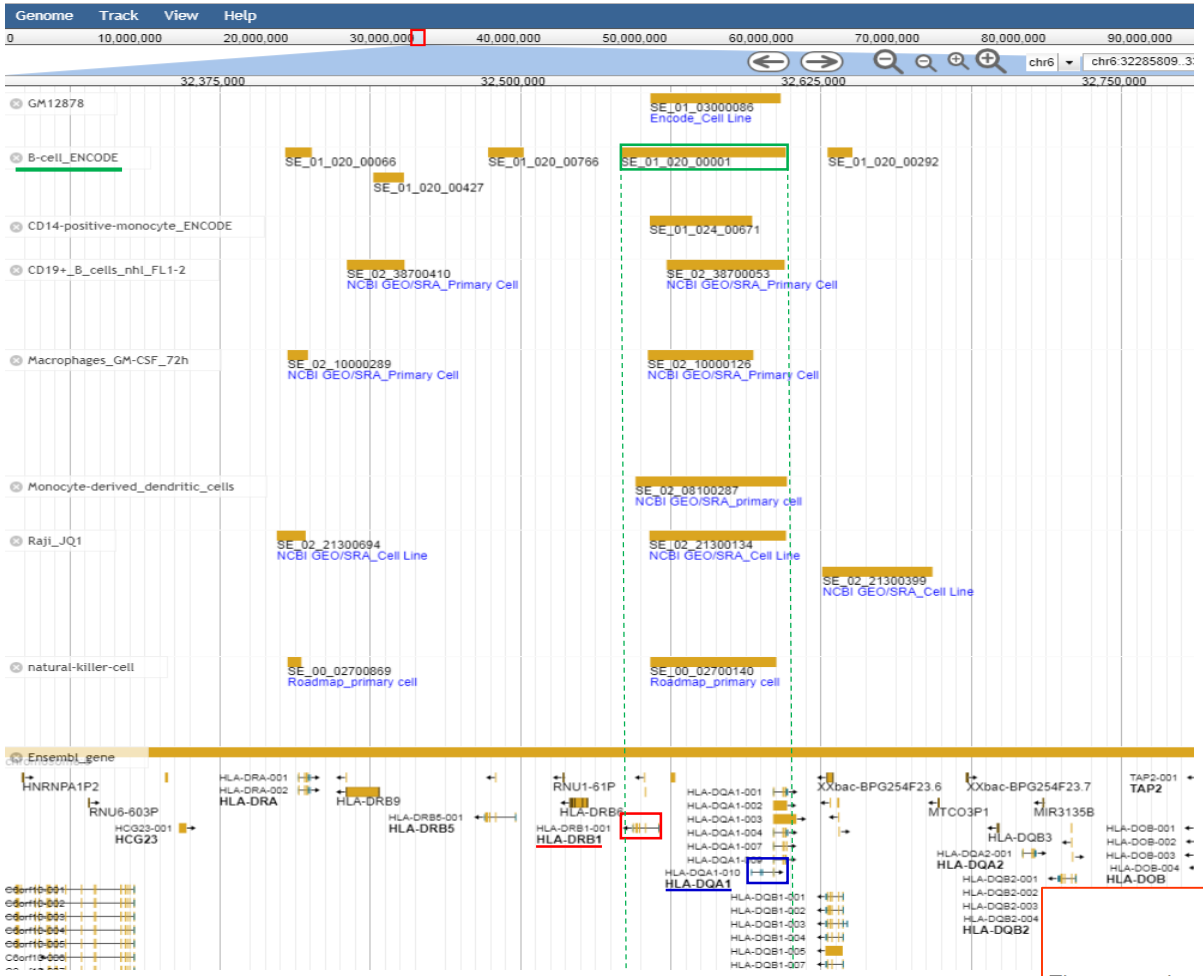
Parimal Majumder,[1] Jorge A. Gomez,[1] Brian P. Chadwick,[2] and Jeremy M. Boss[1]

Kingston University London

Background

Super-enhancer XL9

The XL9 super-enhancer maps to chr6:32,541,785..32,610,513 (hg19) in the SuperEnhancer Database (SEdb) in the ENCODE primary B cell line. XL9 covers the whole intergenic region between the *DRB1* to *DQA1* genes and partially overlaps with them.



SEdb

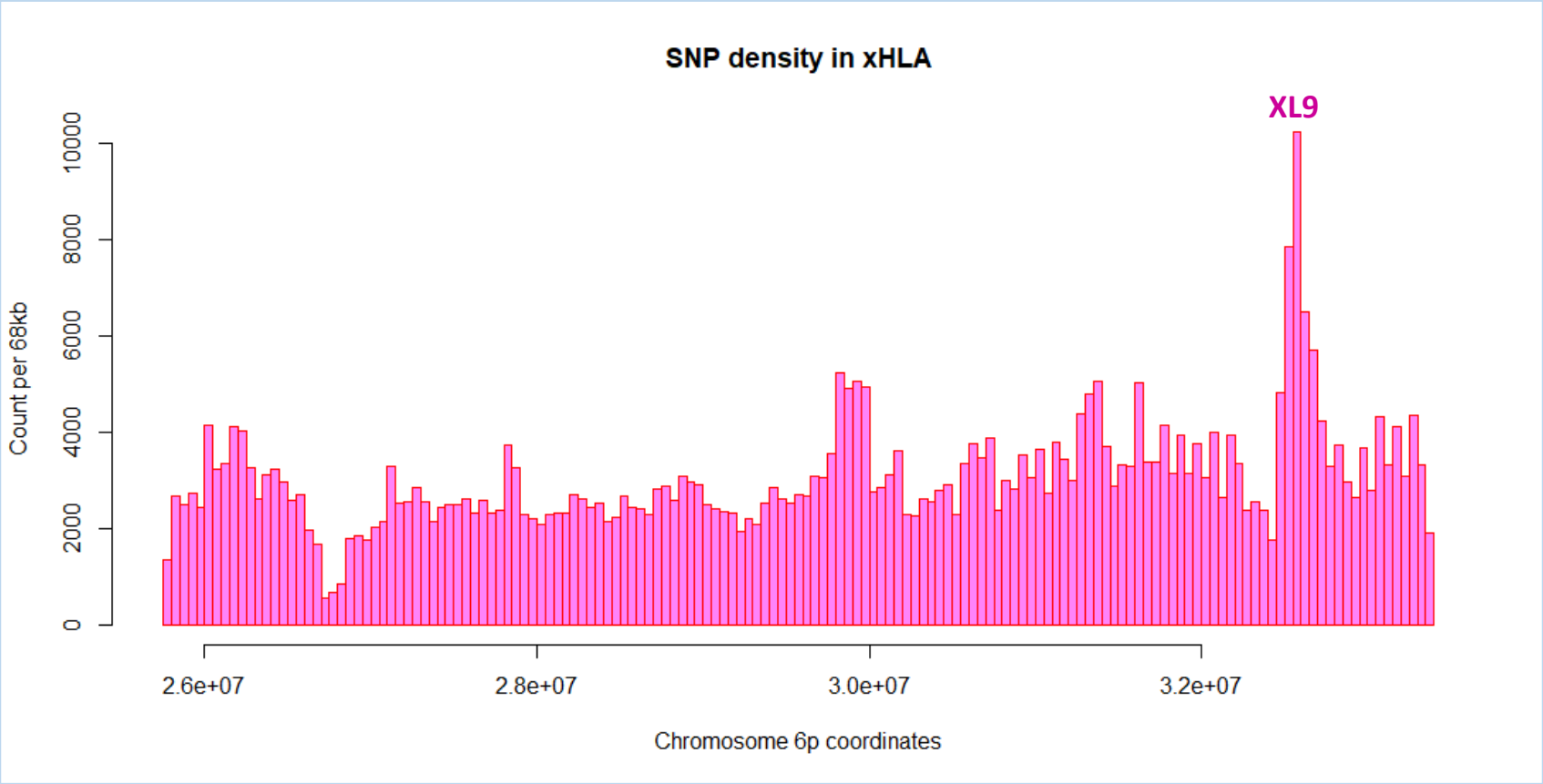
The comprehensive human **S**uper-**E**nhancer **d**ata**b**ase

Kingston University London

Background

Super-enhancer XL9 SNPs

There are 11,193 SNPs within the XL9 (68kb) some of which are missense coding region or splicing site SNPs



The Immunochip v.1 contains only 90 of those variants

Kingston University London

Aim

To assess the extent of the involvement of XL9 SNPs in disease associations, and explore potential mechanisms using *in silico* methods

Specifically, to examine longevity associations with HLA region SNPs and explore their mechanistic aspects

Kingston University London

Material & Methods

We have used publicly available data on GWAS results, genomic features of the region and a number of bioinformatics tools.

BIOINFORMATICS TOOLS

(for Genetic Epidemiologists)

Mehmet Tevfik DORAK, MD, PhD

http://www.dorak.info/mtd/bioinf.html

We used the Immunochip genotyping data on 95 IHWG cell lines and 1KG Project data genotypes downloaded using Ferret (Limou S *et al*, *Bioinformatics* 2016) and HLA typings of 1KG Project participants (Gourraud PA *et al*, *PLoS ONE* 2014) for correlations of SNPs with HLA types.

Kingston University London

Results: Associations

www.aging-us.com AGING 2017, Vol. 9, No. 12

Research Paper

Human longevity: 25 genetic loci associated in 389,166 UK biobank participants

Luke C. Pilling[1], Chia-Ling Kuo[2], Kamil Sicinski[3], Jone Tamosauskaite[1], George A. Kuchel[4], Lorna W. Harries[5], Pamela Herd[6], Robert Wallace[7], Luigi Ferrucci[8], David Melzer[1,4]

rs28383322-C	5 x 10^{-11}		0.783	-	0.0182 unit increase	[0.013-0.024]	HLA-DQA1, HLA-DRB1	Parental longevity (combined parental attained age, Martingale residuals)	parental longevity	GCST006697	6:32625019
rs34831921-A	4 x 10^{-8}	(EA)	0.09	-	0.6 years increase	-	HLA-DRB1, HLA-DQA1	Parental lifespan	parental longevity	GCST004983	6:32622991

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-00934-5 OPEN

Genome-wide meta-analysis associates *HLA-DQA1/DRB1* and *LPA* and lifestyle factors with human longevity

Peter K. Joshi et al.#

Kingston University London

Results: Associations

eLIFE Research Communication Genetics and Genomics

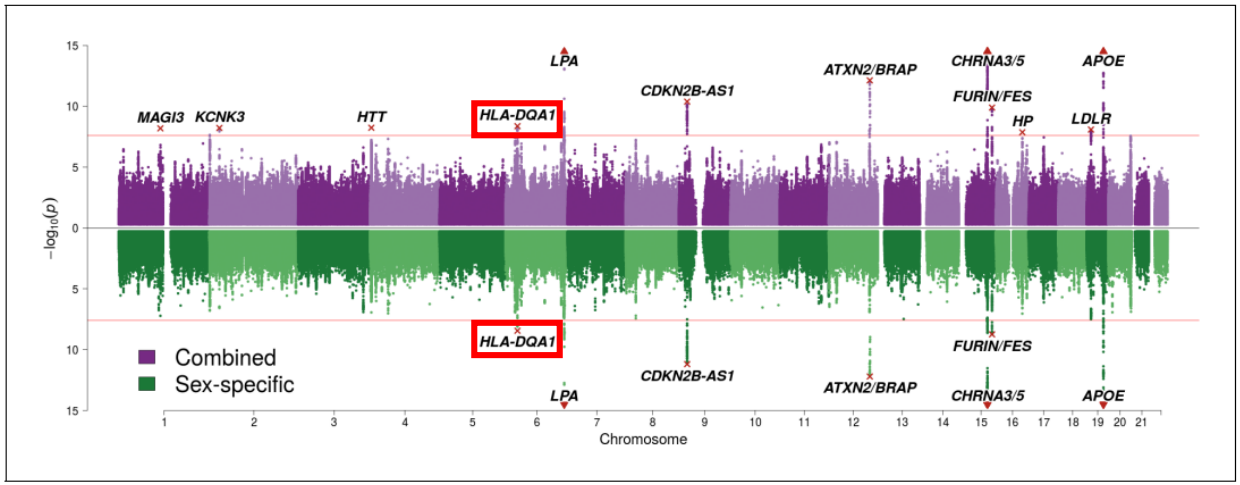


Figure 1. SNP associations with lifespan across both parents under the assumption of common and sex-specific effect sizes. Miami plot of genetic associations with joint parental survival. In purple are the associations under the assumption of common SNP effect sizes across sexes (CES); in green are the associations under the assumption of sex-specific effect sizes (SSE). P refers to the two-sided P values for association of allelic dosage on survival under the residualised Cox model. The red line represents our multiple testing-adjusted genome-wide significance threshold ($p = 2.5 \times 10^{-8}$). Annotated are the gene, set of genes, or cytogenetic band near the index SNP, marked in red. P values have been capped at $-\log_{10}(p) = 15$ to better visualise associations close to genome-wide significance. SNPs with P values beyond this cap (near *APOE*, *CHRNA3/5* and *LPA*) are represented by triangles.

DOI: https://doi.org/10.7554/eLife.39856.007

Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances

Paul RHJ Timmers[1], Ninon Mounier[2,3], Kristi Lall[4,5], Krista Fischer[4,5], Zheng Ning[6], Xiao Feng[7], Andrew D Bretherick[8], David W Clark[1], eQTLGen Consortium, Xia Shen[1,6,7], Tõnu Esko[4,9], Zoltán Kutalik[2,3], James F Wilson[1,8], Peter K Joshi[1,2]*

Kingston University London

Results: Associations

eLIFE Research Communication Genetics and Genomics

Table 1. Twelve genome-wide significant associations with lifespan using UK Biobank and LifeGen.
Parental phenotypes from UK Biobank and LifeGen meta-analysis, described in ***Table 1—source data 1***, were tested for association with subject genotype. See ***Table 1—source data 2*** for LD Score regression intercept of each cohort separately and combined. Displayed here are loci associating with lifespan at genome-wide significance ($p < 2.5 \times 10^{-8}$). At or near – Gene, set of genes, or cytogenetic band nearest to the index SNP; rsID – The index SNP with the lowest P value in the standard or sex-specific effect (SSE) analysis. Chr – Chromosome; Position – Base-pair position on chromosome (GRCh37); A1 – the effect allele, increasing lifespan; Freq1 – Frequency of the A1 allele; Years1 – Years of life gained for carrying one copy of the A1 allele; SE – Standard Error; P – the P value for the Wald test of association between imputed dosage and cox model residual; Disease – Category of disease for known associations with SNP or close proxies ($r^2 > 0.6$), see ***Table 1—source data 3*** for details and references. Despite the well-known function of the *HTT* gene in Huntington's disease, SNPs within the identified locus near this gene have not been associated with the disease at genome-wide significance.

At or near	rsID	Chr	Position	A1	Freq1	Years1	SE	P	SSE P	Disease
MAGI3	rs1230666	1	114173410	G	0.85	0.3224	0.0555	6.4E-09	6.1E-08	Autoimmune
KCNK3	rs1275922	2	26932887	G	0.74	0.2579	0.0443	6.0E-09	2.7E-07	Cardiometabolic
HTT	rs61348208	4	3089564	T	0.39	0.2299	0.0395	5.8E-09	1.2E-07	-
HLA-DQA1	rs34967069	6	32591248	T	0.07	0.5613	0.0956	4.3E-09	3.6E-09	Autoimmune
LPA	rs10455872	6	161010118	A	0.92	0.7639	0.0743	8.5E-25	3.1E-24	Cardiometabolic
CDKN2B-AS1	rs1556516	9	22100176	G	0.50	0.2510	0.0386	7.5E-11	6.4E-12	Cardiometabolic
ATXN2/BRAP	rs11065979	12	112059557	C	0.56	0.2798	0.0393	1.0E-12	6.2E-13	Autoimmune/ Cardiometabolic
CHRNA3/5	rs8042849	15	78817929	T	0.65	0.4368	0.0410	1.6E-26	1.9E-30	Smoking-related
FURIN/FES	rs6224	15	91423543	G	0.52	0.2507	0.0390	1.3E-10	1.8E-09	Cardiometabolic
HP	rs12924886	16	72075593	A	0.80	0.2798	0.0493	1.4E-08	9.1E-08	Cardiometabolic
LDLR	rs142158911	19	11190534	A	0.12	0.3550	0.0616	8.1E-09	3.3E-08	Cardiometabolic
APOE	rs429358	19	45411941	T	0.85	1.0561	0.0546	3.1E-83	1.8E-85	Cardiometabolic/ Neuropsychiatric

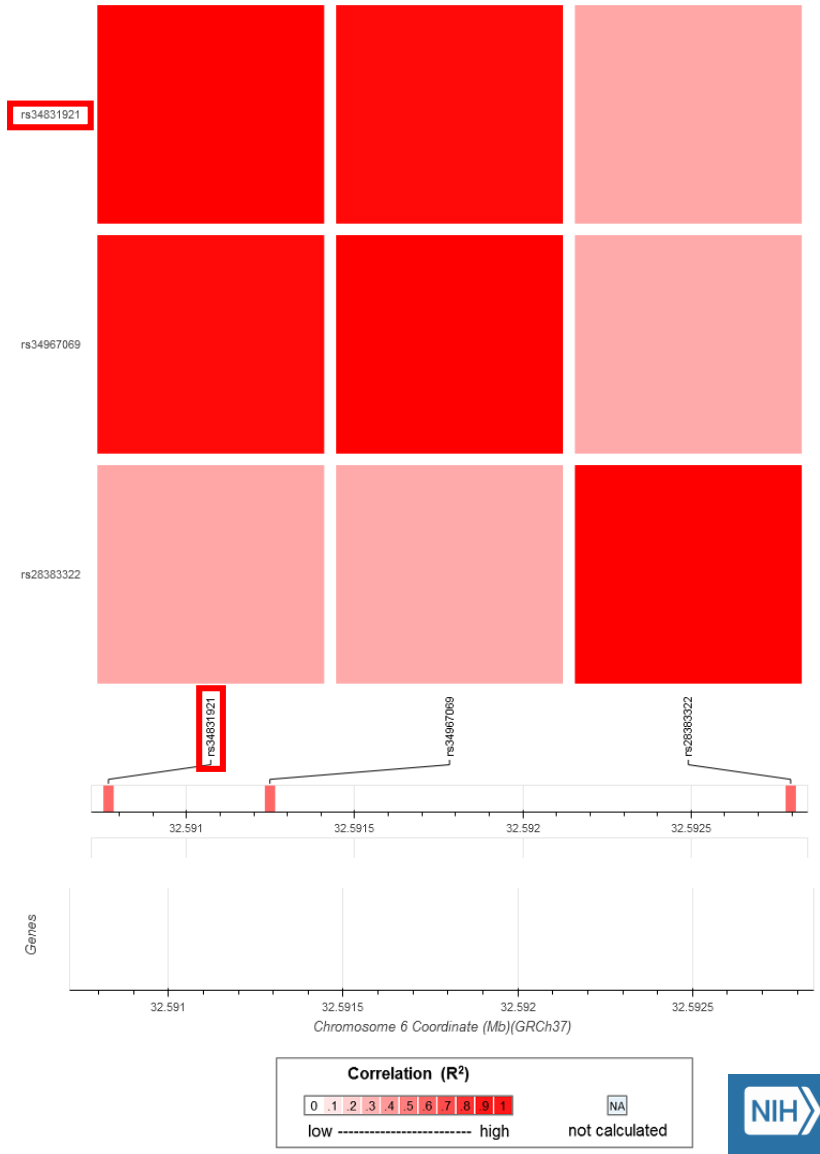
In XL9 (and in LD with the two other longevity-associated XL9 SNPs

Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances

Paul RHJ Timmers[1], Ninon Mounier[2,3], Kristi Lall[4,5], Krista Fischer[4,5], Zheng Ning[6], Xiao Feng[7], Andrew D Bretherick[8], David W Clark[1], eQTLGen Consortium, Xia Shen[1,6,7], Tõnu Esko[4,9], Zoltán Kutalik[2,3], James F Wilson[1,8], Peter K Joshi[1,2]*

Kingston University London

Results: LD Matrix



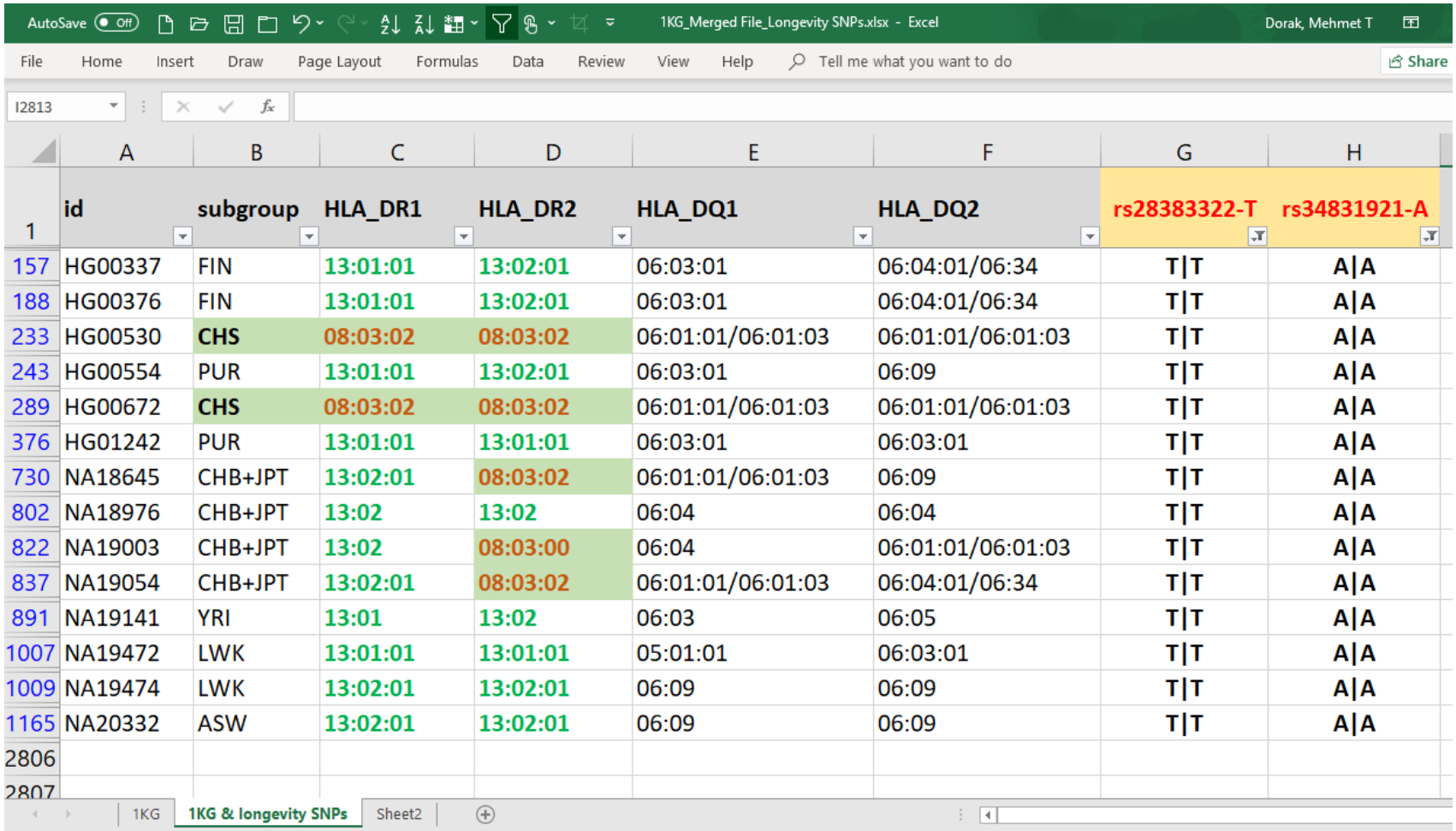
Kingston University London

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Epidemiology & Genetics

Home LDassoc LDhap LDmatrix LDpair LDpop LDproxy SNPchip SNPclip

Results: HLA linkage

Longevity associations in HLA point towards HLA-DR6 (*DRB1*13*)



	A	B	C	D	E	F	G	H
1	id	subgroup	HLA_DR1	HLA_DR2	HLA_DQ1	HLA_DQ2	rs28383322-T	rs34831921-A
157	HG00337	FIN	13:01:01	13:02:01	06:03:01	06:04:01/06:34	T|T	A|A
188	HG00376	FIN	13:01:01	13:02:01	06:03:01	06:04:01/06:34	T|T	A|A
233	HG00530	CHS	08:03:02	08:03:02	06:01:01/06:01:03	06:01:01/06:01:03	T|T	A|A
243	HG00554	PUR	13:01:01	13:02:01	06:03:01	06:09	T|T	A|A
289	HG00672	CHS	08:03:02	08:03:02	06:01:01/06:01:03	06:01:01/06:01:03	T|T	A|A
376	HG01242	PUR	13:01:01	13:01:01	06:03:01	06:03:01	T|T	A|A
730	NA18645	CHB+JPT	13:02:01	08:03:02	06:01:01/06:01:03	06:09	T|T	A|A
802	NA18976	CHB+JPT	13:02	13:02	06:04	06:04	T|T	A|A
822	NA19003	CHB+JPT	13:02	08:03:00	06:04	06:01:01/06:01:03	T|T	A|A
837	NA19054	CHB+JPT	13:02:01	08:03:02	06:01:01/06:01:03	06:04:01/06:34	T|T	A|A
891	NA19141	YRI	13:01	13:02	06:03	06:05	T|T	A|A
1007	NA19472	LWK	13:01:01	13:01:01	05:01:01	06:03:01	T|T	A|A
1009	NA19474	LWK	13:02:01	13:02:01	06:09	06:09	T|T	A|A
1165	NA20332	ASW	13:02:01	13:02:01	06:09	06:09	T|T	A|A
2806								
2807								

Kingston University London

Results: HLA-DR13

Longevity associations in HLA point towards HLA-DR6 (*DRB1*13*)

Human Molecular Genetics, 1998, Vol. 7, No. 2 187–194

HLA-DR alleles display sex-dependent effects on survival and discriminate between individual and familial longevity

Rayna Ivanova[1], Nicolas Hénon[2], Virginia Lepage[1], Dominique Charron[1], Eric Vicaut[3] and François Schächter[2,*]

In an effort to reassess the contribution of HLA-DRB1 polymorphisms to inter-individual variations of human longevity, we have compared their genotypic distributions between longevous and adult control groups in the French population. The longevous groups included two independent cohorts totalling 533 centenarians, and 163 nonagenarian siblings. Allelic distributions were significantly different between controls and longevous groups. Three individual alleles were mostly responsible for these differences: DR7, DR11 and DR13. Multivariate logistic analyses were performed in order to sort out interactions between gender- and age-specific genetic effects. DR7 frequency was elevated in longevous men, in centenarians as well as nonagenarian siblings [OR = 1.72 (1.2–2.5)]. DR11's influence on longevity displayed a significant interaction with sex, with an increase in women from longevous sibships [OR = 2.03 (1.4–3.0)]. DR13's frequency was increased in centenarians of both genders [OR = 1.46 (1.2–1.75)]. These results are discussed in the context of other pathophysiological effects of the implicated alleles. Our data support the direct involvement of three HLA-DR alleles in survival at very old ages. Two allele-specific effects on longevity appear to depend on gender and one on familial status for aggregation of this trait. The latter is an original finding for humans.

Kingston University London

Results: Functional Annotation

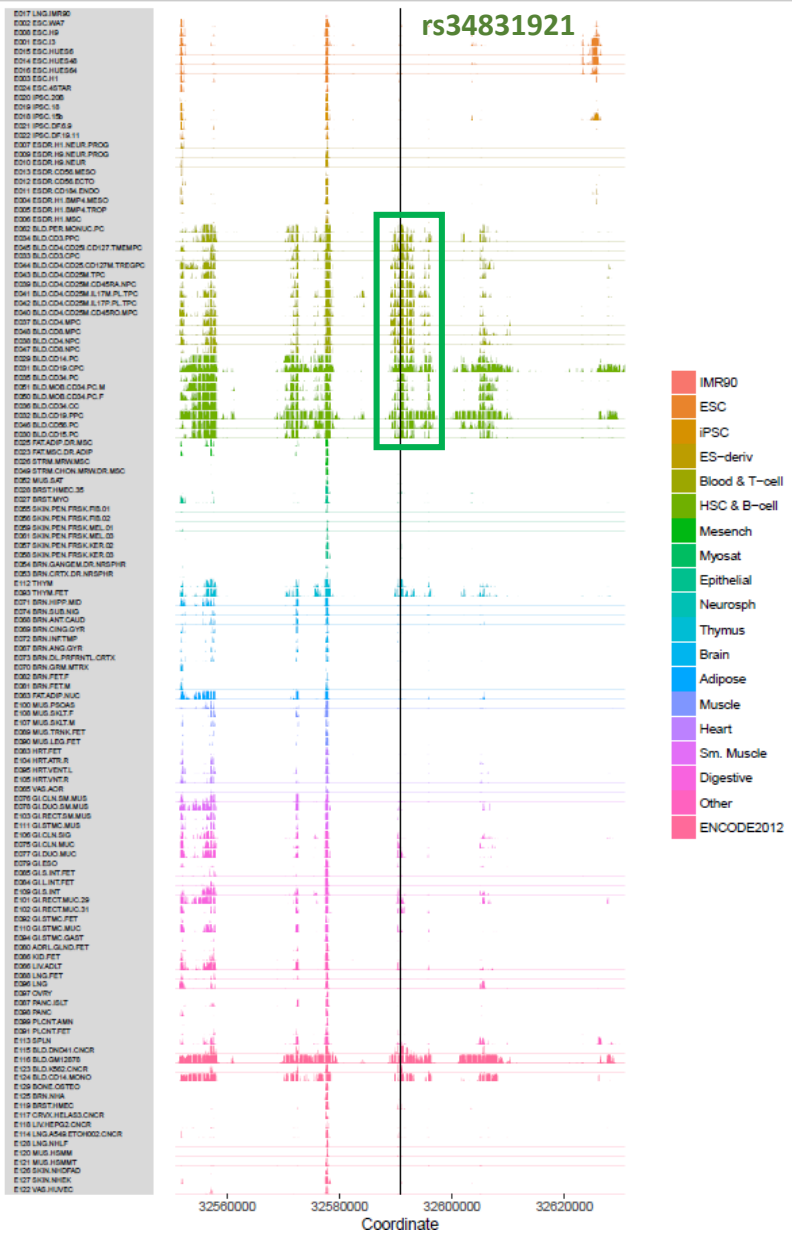
Longevity-associated SNPs show eQTL and meQTL effects

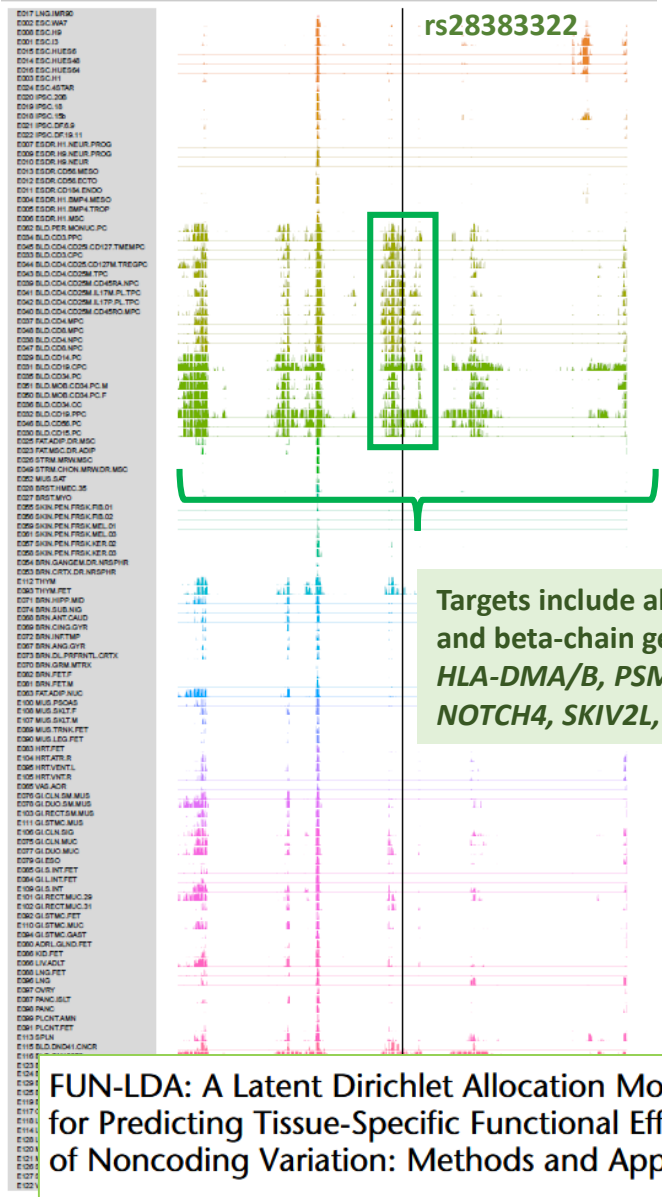
SNP	eQTL	meQTL	CTCF binding site
rs34831921	DQA1; DQB1	No	Yes
rs28383322	DRB1*	Strong effects across class II region	No

* Negative eQTL for a number of tissues, no effect on whole blood (*P* = 0.33; NES = -0.028)

Kingston University London

Results: FUN-LDA





Targets include all HLA class II alpha and beta-chain genes, *TAP1/2, HLA-DMA/B, PSMB8, BRD2*; and *C4, NOTCH4, SKIV2L, C6orf47*

GeneHancer

FUN-LDA: A Latent Dirichlet Allocation Model for Predicting Tissue-Specific Functional Effects of Noncoding Variation: Methods and Applications

Daniel Backenroth,[1] Zihuai He,[1] Krzysztof Kiryluk,[2] Valentina Boeva,[3,4] Lynn Pethukova,[5,6] Ekta Khurana,[7] Angela Christiano,[6,8] Joseph D. Buxbaum,[9,10] and Iuliana Ionita-Laza[1,*]

Kingston University London

Results: Gene Content of XL9

non-coding RNA loci within XL9

#	Symbol	Description		Location
1	HLA-DRB1	major histocompatibility complex, class II, DR beta 1	6	: 32,589,836 - 32,578,769
2	LOC107986589	uncharacterized LOC107986589	6	: 32,642,673 - 32,637,188
3	HLA-DQA1	major histocompatibility complex, class II, DQ alpha 1	6	: 32,637,406 - 32,654,846
4	LOC107987459	uncharacterized LOC107987459	6	
5	LOC107987449	uncharacterized LOC107987449	6	

Alternative haplotypes

Kingston University London

Conclusions

The two longevity-associated HLA region SNPs map to the super-enhancer XL9 in the HLA class II region.

The haplotype formed by the two longevity- associated alleles "rs28383322-T and rs34831921-A" is exclusive to *DRB1*13:01/02* and *08:03:02* haplotypes.

The two longevity-associated XL9 SNPs show eQTL or meQTL effects across the HLA II region.

The presence of three non-coding RNA loci within XL9 is intriguing. Identification of their functions and targets together with next-gen sequencing-based disease association studies should unravel the exact role of XL9 in genome biology.

Kingston University London

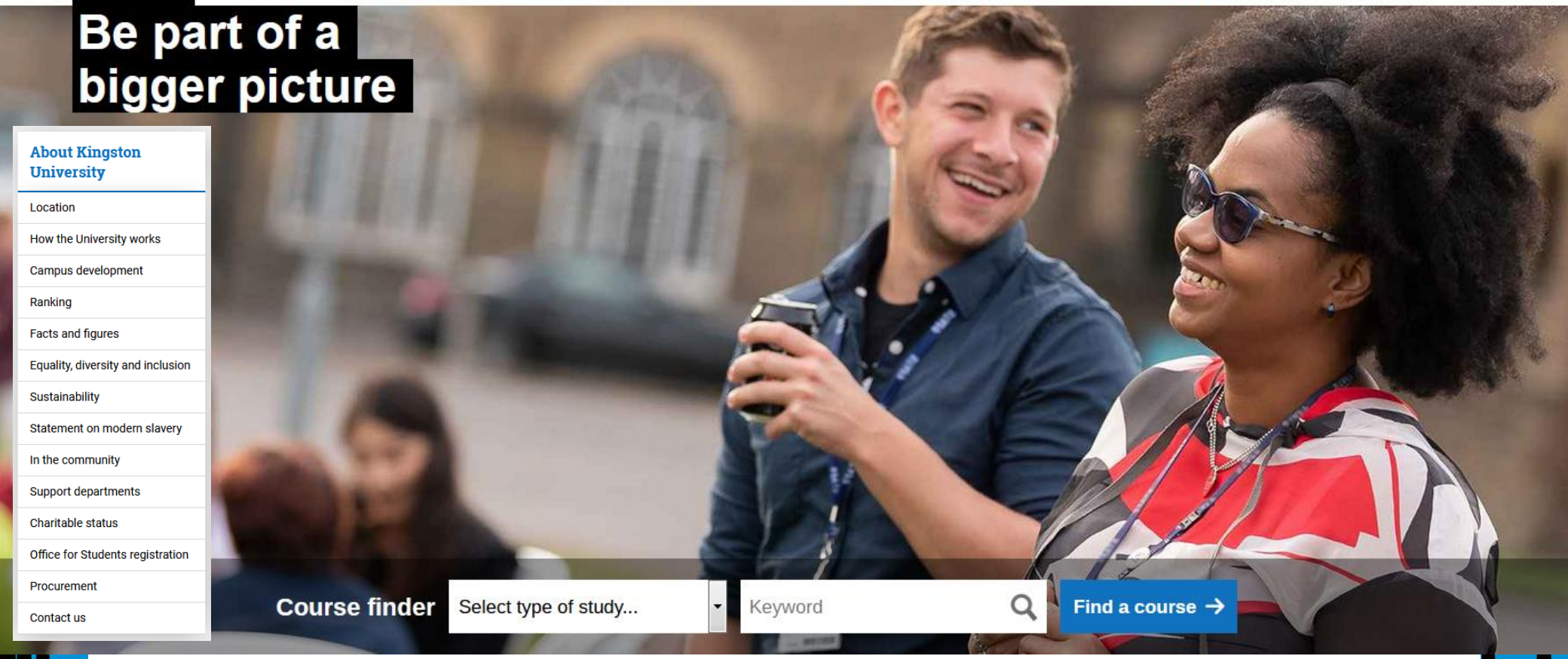
Kingston University London

Courses News Events Faculties and schools Services for business Giving Jobs About us How to find us Contact us

Site search

Undergraduate study Postgraduate study International students Research Alumni

Be part of a bigger picture



About Kingston University

- Location
- How the University works
- Campus development
- Ranking
- Facts and figures
- Equality, diversity and inclusion
- Sustainability
- Statement on modern slavery
- In the community
- Support departments
- Charitable status
- Office for Students registration
- Procurement
- Contact us

Course finder | Select type of study... | Keyword | Find a course →

Kingston University London