Gene and Polymorphism Content of the HLA Complex and Its Relevance to Transplantation

" *HLA Kompleks Gen ve Polimorfizmlerinin Transplantasyon ile İlişkisi* "

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Kingston University London

Istanbul, 29 March 2024

Kingston University London

Outline

HLA Complex and Its Unique Features

Gene and Polymorphism Update (2024)

Transplantation-related Gene Content

(Classical HLA genes; HLA-DP; HLA-F; HLA-G; MICA/MICB)

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History / Nostalgy

Histocompatibility Studies & H-2

Naming of HLA ("Antigens")

Solid Organ Transplantation

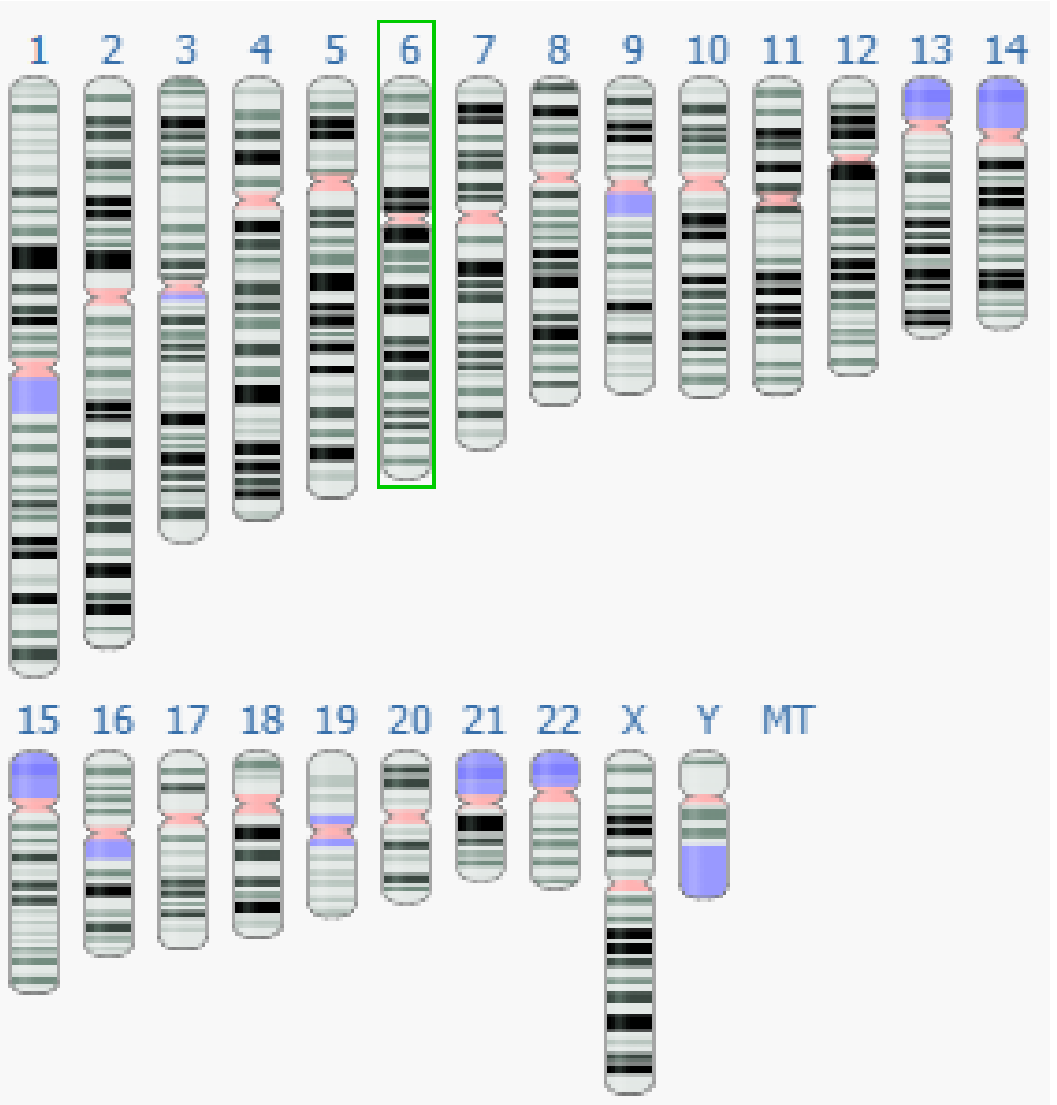
Bone Marrow Transplantation / HSCT

Immunosuppressives

.....

BMT 1992 Paper

Chromosome 6



MHC

TABLE 2 Sequenced cell lines and assembled haplotypes—summary of sequencing and assembly statistics

Cell line	MHC class II type	MHC assembly (bp)	MHC class II (bp)	MHC read depth			GenBank ID
				Nanopore	Illumina (WG)	PacBio (WG)	
APD	DR3	4.928.029	149.477	31,65	16,26	11,10	OK649231
DBB	DR4	5.048.108	260.711	20,03	12,91	11,50	OK649232
MANN	DR4	5.025.203	259.962	27,62	18,19	11,10	OK649234
SSTO	DR4	5.045.615	258.762	22,43	15,04	9,61	OK649236
KAS116	DR1	4.907.004	155.951	85,87	NA	11,10	OK649233
QBL	DR3	4.904.614	149.416	17,81	12,86	8,95	OK649235
COX	DR3	4.795.265	153.371	NA	NA	NA	GL000251.2
PGF	DR2	4.873.646	169.898	NA	NA	NA	chr6:28510120–33.480.575 (GRCh38)

Complete sequences of six major histocompatibility complex haplotypes, including all the major MHC class II structures

Torsten Houwaart[1] | Stephan Scholz[1] | Nicholas R. Pollock[2,3] | William H. Palmer[2,3] | Katherine M. Kichula[2,3] | Daniel Strelow[1] | Duyen B. Le[1] | Dana Belick[1] | Lisanna Hülse[1] | Tobias Lautwein[4] | Thorsten Wachtmeister[4] | Tassilo E. Wollenweber[4] | Birgit Henrich[1] | Karl Köhrer[4] | Peter Parham[5] | Lisbeth A. Guethlein[5] | Paul J. Norman[2,3] | Alexander T. Dilthey[1]

MHC

FIGURE 3 Multiple-sequence alignment visualization of *MHC class II* haplotype structures. Shown is a comparison of the eight completed *MHC class II* region sequences. Colors represent respective sequence similarity across haplotypes. Segments drawn underneath the respective plots represent inversions. The plot was created using Mauve[53] with parameter "seed weight" set to 22. Vertical lines connecting horizontally aligned homologous regions were edited for clarity.

Complete sequences of six major histocompatibility complex haplotypes, including all the major MHC class II structures

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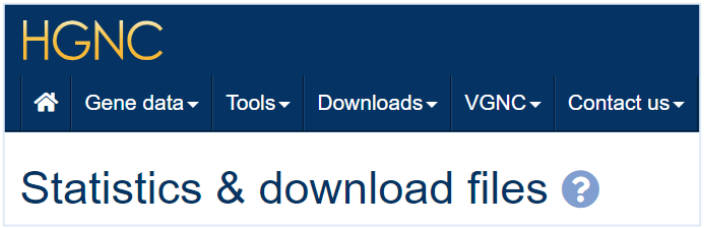
MHC

	A	B	C	D	E
1	**hgnc_id**	**symbol**	**name**	**locus_group**	**locus_type**
14	HGNC:35418	GTF2H2C_2	GTF2H2 family member C, copy 2	protein-coding g	gene with protein product
15	HGNC:4950	**HLA-DRB2**	major histocompatibility complex, class II, DR	pseudogene	pseudogene
16	HGNC:4951	**HLA-DRB3**	major histocompatibility complex, class II, DR	protein-coding g	gene with protein product
17	HGNC:4952	**HLA-DRB4**	major histocompatibility complex, class II, DR	protein-coding g	gene with protein product
18	HGNC:4955	**HLA-DRB7**	major histocompatibility complex, class II, DR	pseudogene	pseudogene
19	HGNC:4956	**HLA-DRB8**	major histocompatibility complex, class II, DR	pseudogene	pseudogene
20	HGNC:5923	IGLV5-39	immunoglobulin lambda variable 5-39	other	immunoglobulin gene
21	HGNC:6330	KIR2DL2	killer cell immunoglobulin like receptor, two Ig	protein-coding g	gene with protein product
22	HGNC:16345	KIR2DL5A	killer cell immunoglobulin like receptor, two Ig	protein-coding g	gene with protein product
23	HGNC:16346	KIR2DL5B	killer cell immunoglobulin like receptor, two Ig	protein-coding g	gene with protein product
24	HGNC:6604	LILRA3	leukocyte immunoglobulin like receptor A3	protein-coding g	gene with protein product
25	HGNC:42096	MTND1P13	MT-ND1 pseudogene 13	pseudogene	pseudogene
26	HGNC:27538	OR8U8	olfactory receptor family 8 subfamily U membe	protein-coding g	gene with protein product
27	HGNC:29166	OR8U9	olfactory receptor family 8 subfamily U membe	protein-coding g	gene with protein product
28	HGNC:31940	OR9G9	olfactory receptor family 9 subfamily G membe	protein-coding g	gene with protein product
29	HGNC:16376	**FAM8A5P**	family with sequence similarity 8 member A5,	pseudogene	pseudogene
30	HGNC:34393	PRAMEF22	PRAME family member 22	other	unknown
31	HGNC:33447	**PRKRAP1**	protein activator of interferon induced protein	pseudogene	pseudogene
32	HGNC:43788	PRSS3P2	PRSS3 pseudogene 2	pseudogene	pseudogene
33	HGNC:48421	**RNU1-79P**	RNA, U1 small nuclear 79, pseudogene	pseudogene	pseudogene



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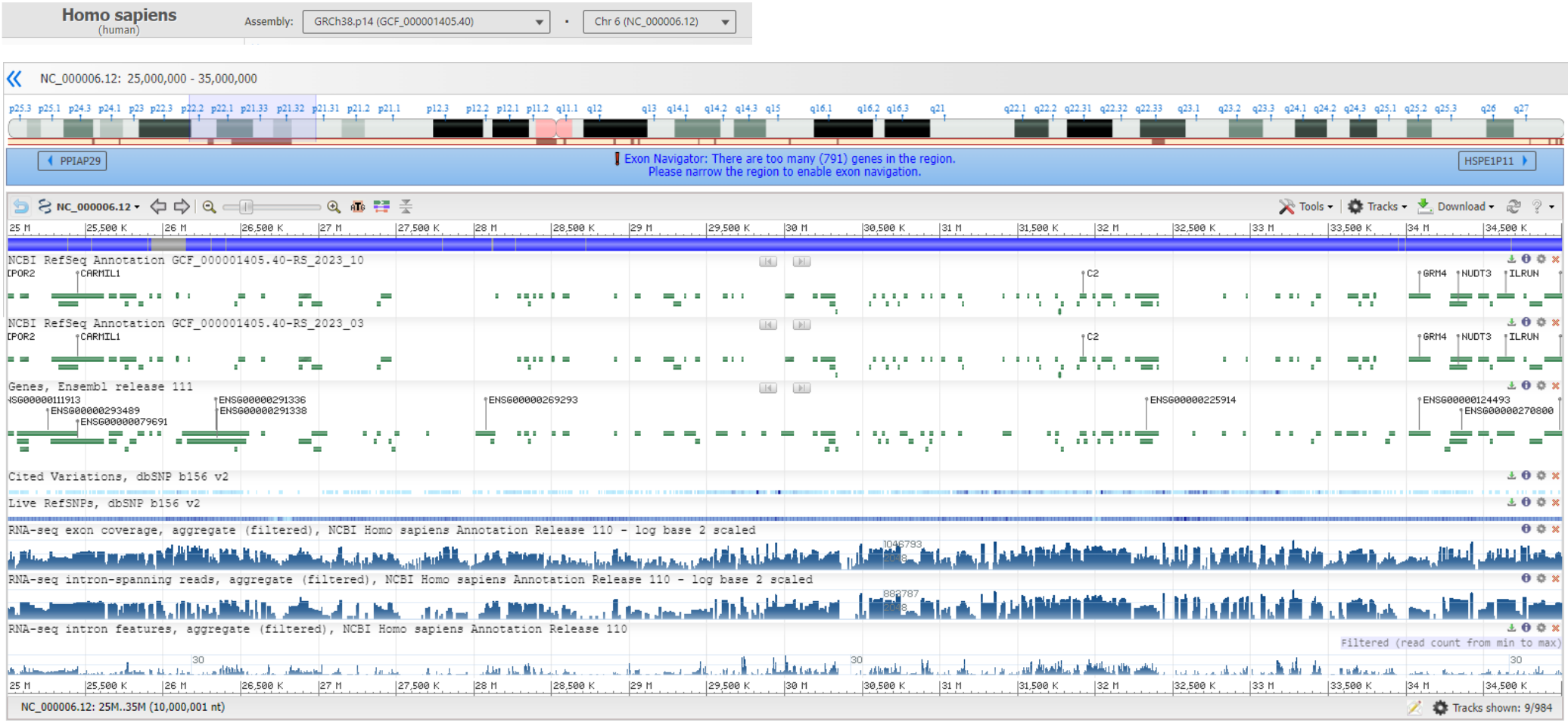
xMHC

Genome Data Viewer



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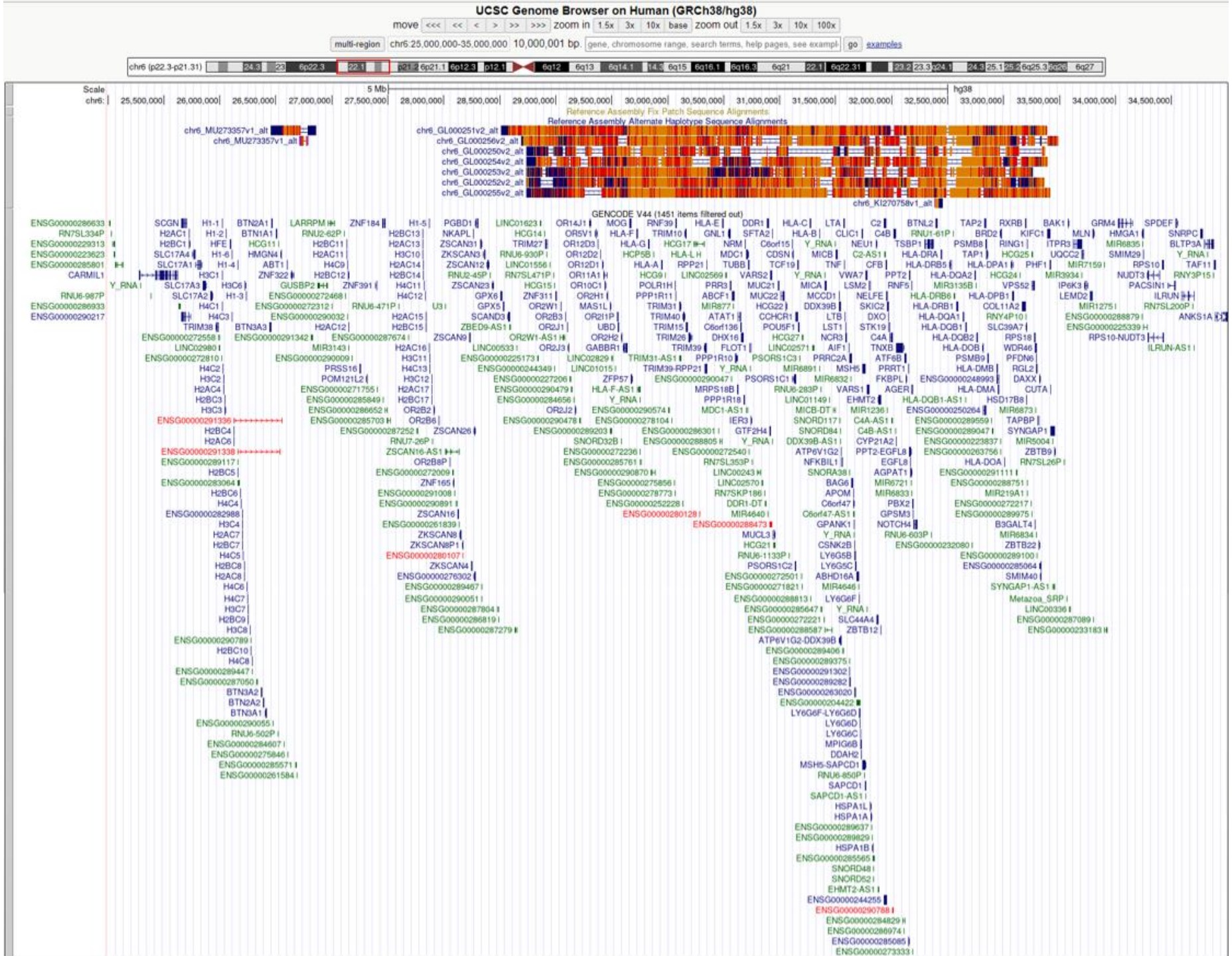
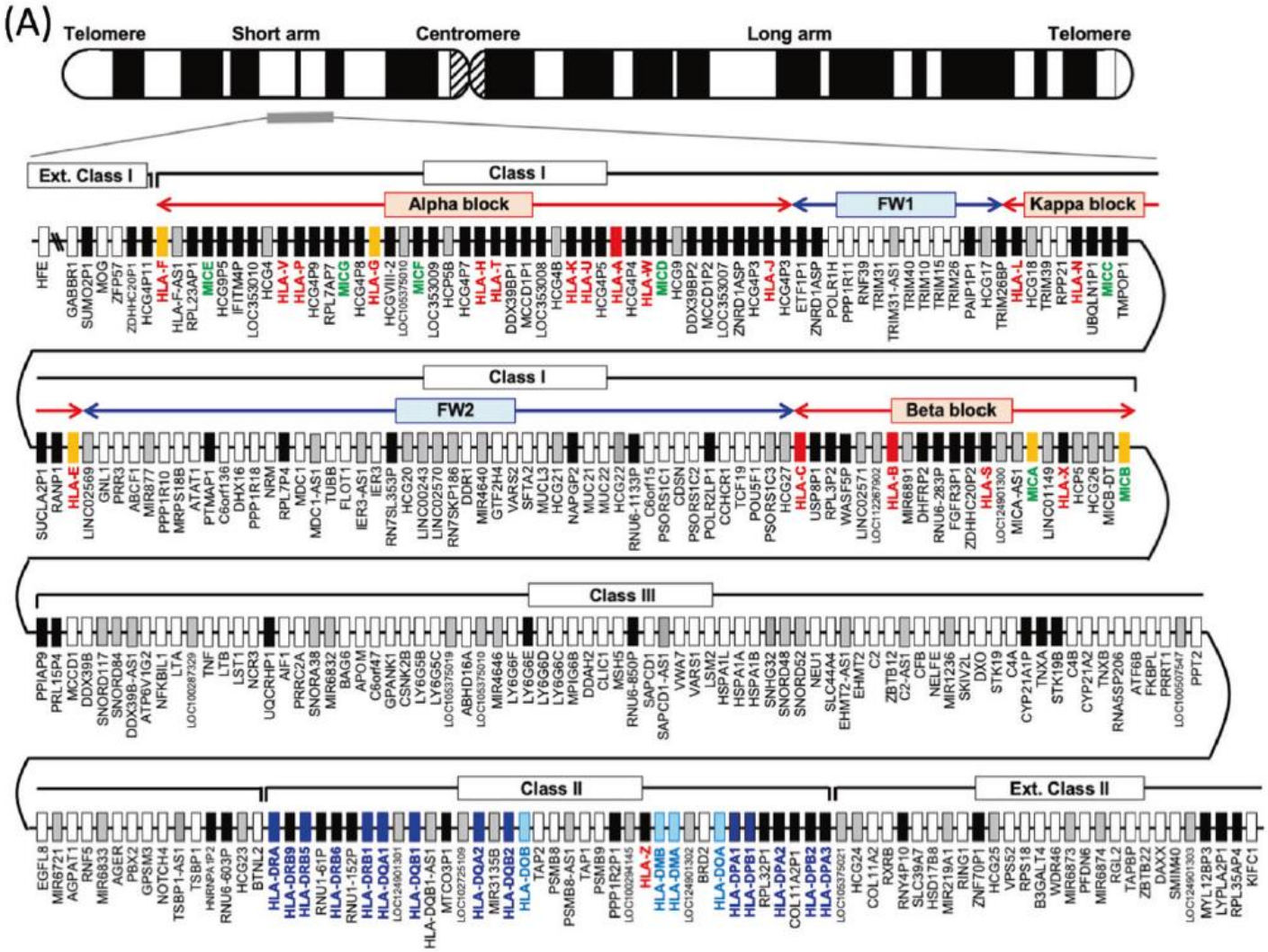
NIH National Library of Medicine
National Center for Biotechnology Information


UCSC Genome Browser on Human (GRCh38/hg38)
move <<< << < > >> >>> zoom in 1.5x 3x 10x base zoom out 1.5x 3x 10x 100x
multi-region chr6:25,000,000-35,000,000 10,000,001 bp. gene, chromosome range, search terms, help pages, see exampl go examples
chr6 (p22.3-p21.31)
Scale
chr6:
5 Mb
hg38
25,500,000 26,000,000 26,500,000 27,000,000 27,500,000 28,000,000 28,500,000 29,000,000 29,500,000 30,000,000 30,500,000 31,000,000 31,500,000 32,000,000 32,500,000 33,000,000 33,500,000 34,000,000 34,500,000
Reference Assembly Fix Patch Sequence Alignments
Reference Assembly Alternate Haplotype Sequence Alignments
chr6_MU273357v1_alt
chr6_MU273357v1_alt
chr6_GL000251v2_alt
chr6_GL000256v2_alt
chr6_GL000250v2_alt
chr6_GL000254v2_alt
chr6_GL000253v2_alt
chr6_GL000252v2_alt
chr6_GL000255v2_alt
chr6_KI270758v1_alt
GENCODE V44 (1451 items filtered out)

xMHC

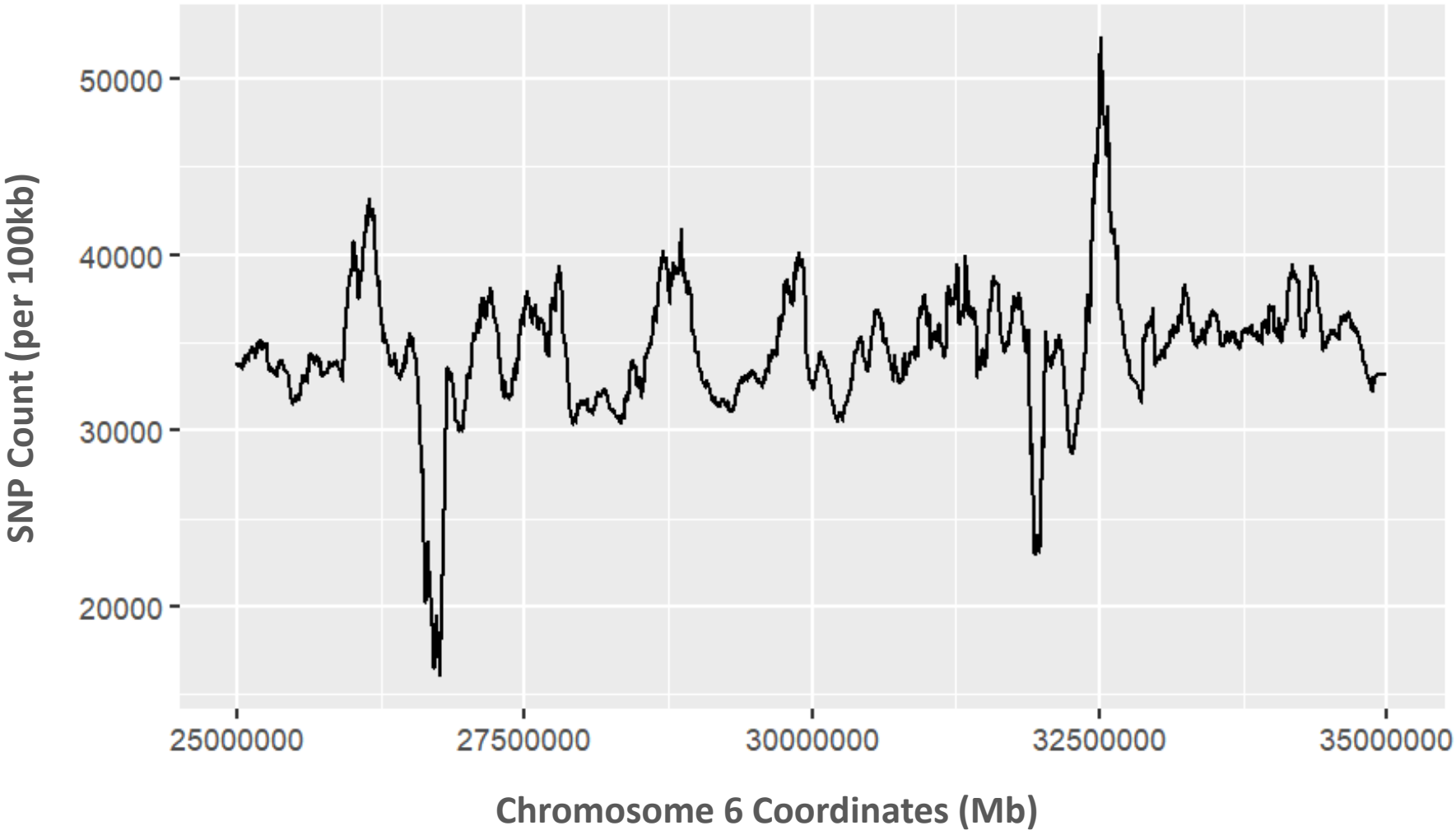


Human leukocyte antigen super-locus: nexus of genomic supergenes, SNPs, indels, transcripts, and haplotypes

Jerzy K. Kulski[1]✉, Shingo Suzuki[1] and Takashi Shiina[1]

Kingston University London

SNP Density



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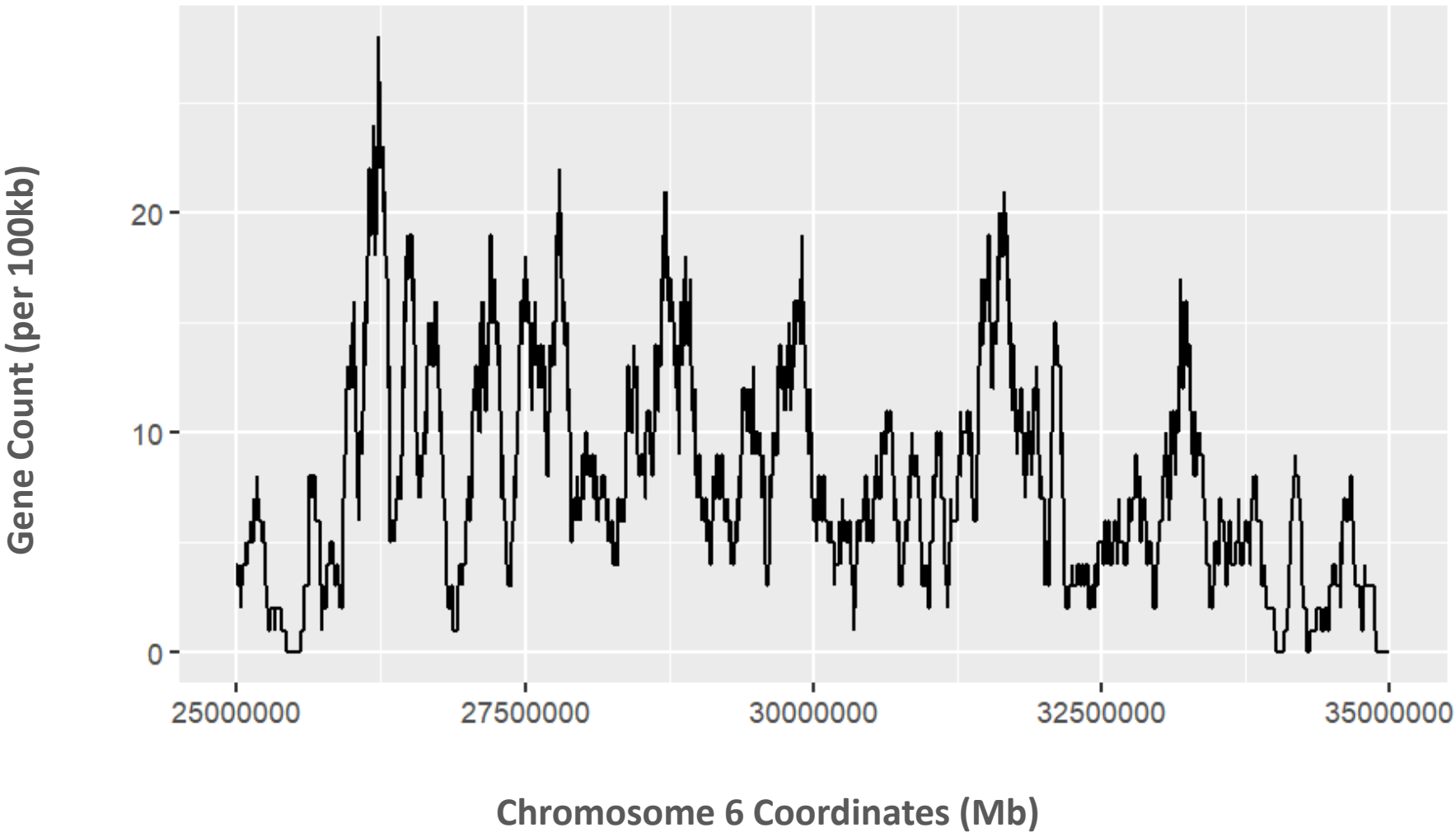
Gene Density



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xMHC: Unique Features

Genome (3.2Gb)	xHLA Region (25.7 to 33.4Mb)	Comparison
Total No of Genes 60155	Total No of Genes 674	...
Protein-coding genes 19881	Protein-coding genes 453	32.66 vs 67.21% *P*<0.0001
Non-coding RNA Genes 25411	Non-coding RNA Genes 54	42.63 vs 8.01% *P*<0.0001
Long non-coding RNA genes 15877	Long non-coding RNA genes 13	1.93 vs 26.39% *P*<0.0001
Small non-coding RNA genes 9534	Small non-coding RNA genes 7	1.04 vs 15.85% *P*<0.0001
Pseudogenes 14467	Pseudogenes 172	24.03 vs 25.52% *P* = 0.37

xHLA makes up 0.24% of the genome, but contains 0.40% of all SNPs in the human genome

A systematic analysis of the gene and variation content of the extended HLA region

Ertan KANBUR, Mustafa DOGAN, Mehmet Tevfik DORAK

Presented at EFI 2017

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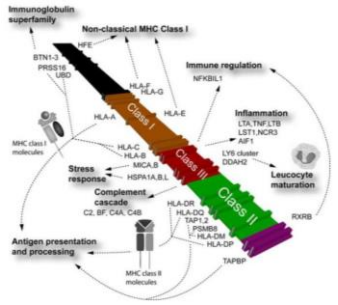
xMHC: Unique Features



- 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
- Highest genetic heritability estimates of DNA heritability
- Very strong selective coefficients
- 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

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xMHC: Unique Features

Heritability of DNA methylation

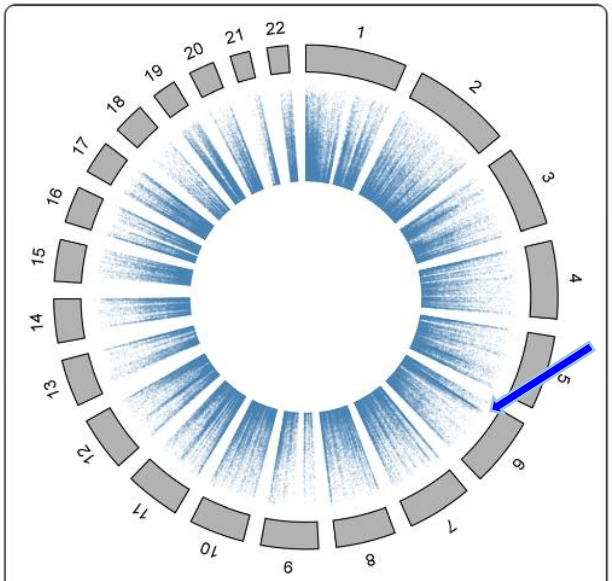


Figure 2 Distribution of genetic heritability estimates across the genome. The MHC region, which had the highest estimates of genetic heritability is clearly visible on chromosome 6. Telomeric regions show an increased density of probes with high genetic heritability, although this is primarily due to higher numbers of probes in these regions.

McRae *et al. Genome Biology* 2014, **15**:R73
http://genomebiology.com/2014/15/5/R73

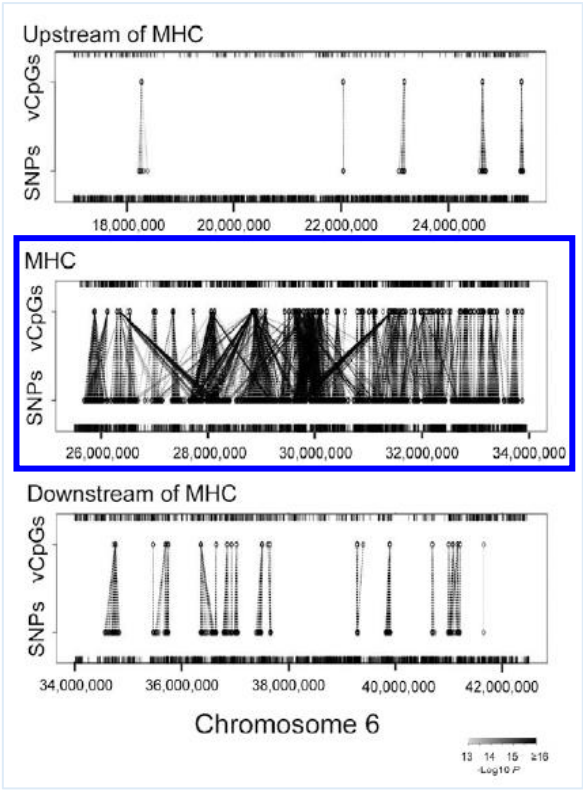
Genome Biology

RESEARCH Open Access

Contribution of genetic variation to transgenerational inheritance of DNA methylation

Allan F McRae[1,2*], Joseph E Powell[1,2], Anjali K Henders[3], Lisa Bowdler[3], Gibran Hemani[1,2], Sonia Shah[1,2], Jodie N Painter[3], Nicholas G Martin[3], Peter M Visscher[1,2†] and Grant W Montgomery[3†]

meQTL density



(E) Associations between CpG sites and SNPs upstream of (top panel), within (middle panel), or downstream of (bottom panel) the major histocompatibility complex (MHC) region. Each dashed line represents a significant association, and the shades of black indicate significance of the associations.

GeMes, Clusters of DNA Methylation under Genetic Control, Can Inform Genetic and Epigenetic Analysis of Disease

Yun Liu,[1,2,9] Xin Li,[1,2,9] Martin J. Aryee,[1,3] Tomas J. Ekström,[4,5] Leonid Padyukov,[4,6] Lars Klareskog,[4,6] Amy Vandiver,[1,2] Ann Zenobia Moore,[7] Toshiko Tanaka,[7] Luigi Ferrucci,[7] M. Daniele Fallin,[1,8,*] and Andrew P. Feinberg[1,2,*]

trans-eQTL density

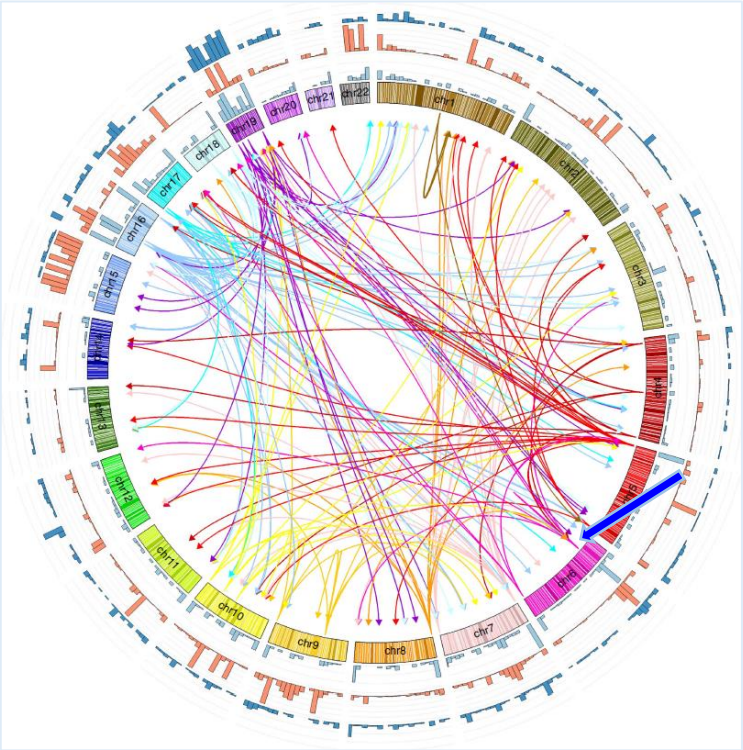


Figure 1 | Enrichment of features in regions harbouring SNPs involved in distal SNP–CpG associations. Outer histograms: number of SNPs involved in distal SNP–CpG associations (light blue), calculated in 7.5 Mb bins; number of piRNA sequences (orange); number of transcription factors (dark blue). Inner links: SNP regions associated with four or more CpG sites. Arrows are pointing from SNPs to the CpG sites they are associated with, and are coloured according to the chromosomes where the SNPs reside.

Long-range epigenetic regulation is conferred by genetic variation located at thousands of independent loci

Mathieu Lemire[1], Syed H.E. Zaidi[1], Maria Ban[2], Bing Ge[3], Dylan Aïssi[4,5,6], Marine Germain[4,5,6], Irfahan Kassam[7], Mike Wang[1], Brent W. Zanke[8], France Gagnon[7], Pierre-Emmanuel Morange[9,10,11], David-Alexandre Trégouët[4,5,6], Philip S. Wells[8], Stephen Sawcer[2], Steven Gallinger[12,13], Tomi Pastinen[3] & Thomas J. Hudson[1,14,15]

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xMHC: Unique Features

trans-eQTLs

	P Value	SNPName	SNPChr	SNPChrPos	ProbeName	ProbeChr	ProbeCenterChrPos	CisTrans	SNPType	Allele	OverallZScore
2	3.27167E-310	rs9268923	6	32432835	cg10154826	6	17601018	trans	C/T	T	61.2544774
3	3.27167E-310	rs2395185	6	32433167	cg10154826	6	17601018	trans	G/T	T	61.2544774
4	3.27167E-310	rs9268853	6	32429643	cg10154826	6	17601018	trans	T/C	C	61.1446653
5	3.27167E-310	rs477515	6	32569691	cg10154826	6	17601018	trans	G/A	A	58.2171575
6	3.27167E-310	rs4239020	17	80176641	cg07393940	7	158741793	trans	C/T	C	-55.4574242
7	3.27167E-310	rs12342831	9	33124872	cg20290983	6	43655494	trans	T/C	C	55.1041246
8	3.27167E-310	rs10813951	9	33128021	cg20290983	6	43655494	trans	A/G	G	55.0625727
9	3.27167E-310	rs12342831	9	33124872	cg04842962	6	43655513	trans	T/C	C	54.9486903
10	3.27167E-310	rs10813951	9	33128021	cg04842962	6	43655513	trans	A/G	G	54.9126278
11	3.27167E-310	rs3780486	9	33139453	cg20290983	6	43655494	trans	C/T	T	54.832052
12	3.27167E-310	rs3780486	9	33139453	cg04842962	6	43655513	trans	C/T	T	54.7699307
13	3.27167E-310	rs10813957	9	33153527	cg20290983	6	43655494	trans	G/T	T	54.7260295
14	3.27167E-310	rs10813957	9	33153527	cg04842962	6	43655513	trans	G/T	T	54.6814431
15	3.27167E-310	rs5756504	22	37467270	cg13737042	9	37806390	trans	C/T	T	-50.6708043
16	3.27167E-310	rs5756506	22	37467392	cg13737042	9	37806390	trans	G/C	C	-50.6605533
17	3.27167E-310	rs62103177	18	77624479	cg05926928	17	57297748	trans	G/A	A	49.4548764
18	3.27167E-310	rs8321	6	30032522	cg01620082	3	125678431	trans	A/C	C	-46.813694
19	3.27167E-310	rs2074977	19	3434028	cg08382705	11	45687343	trans	C/A	C	-46.6429193
20	3.27167E-310	rs8321	6	30032522	cg06606381	12	133084921	trans	A/C	C	-46.2606567

BIOS QTL browser

This web page accompanies the manuscripts titled ***'Disease variants alter transcription factor levels and methylation of their binding sites'***, by *Bonder & Luijk et al* and ***'Unbiased identification of regulatory modifiers of genetic risk factors'***, by *Zhernakova et al*, both have been submitted to Nature Genetics.
For further questions, contact the corresponding author: lude@ludesign.nl

Download meQTL results

You can download the full *cis-* and *trans-*meQTL and eQTMs, detected at a false-discovery rate of 0.05:
Cis-meQTLs
Cis-eQTMs
Trans-meQTLs

Sex-differential in trait associations

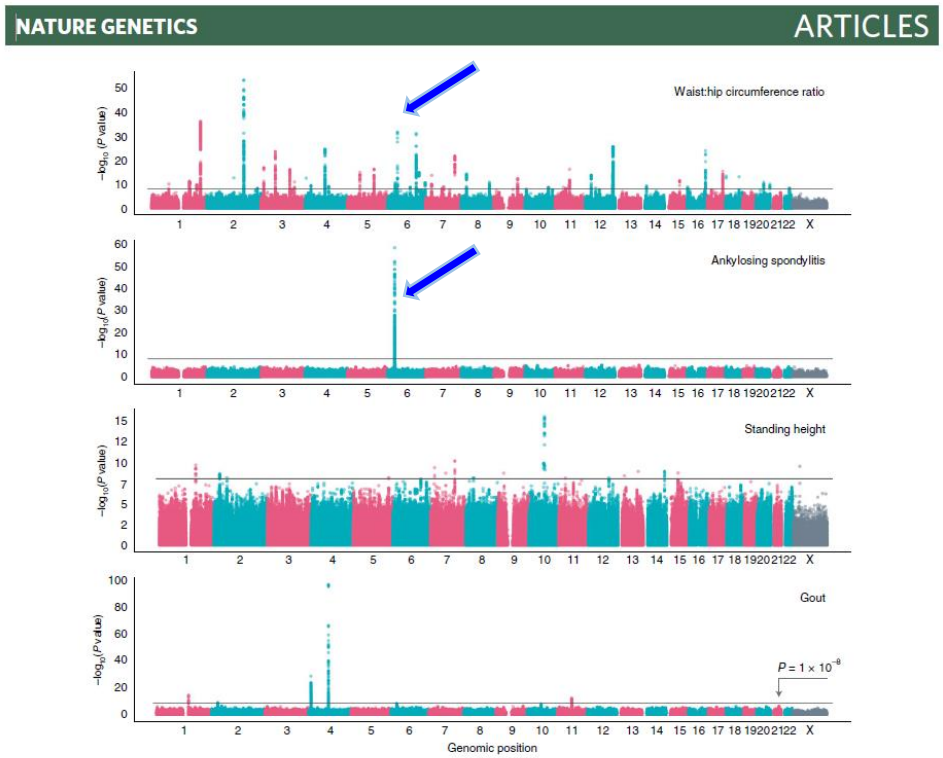

Fig. 3 | Manhattan plots for traits with most lead sdSNPs. The *x* axis corresponds to the genomic position in the genome and the *y* axis to the $-\log_{10}(P$ value) of the two-sided Student's *t*-test (Methods), for which the null hypothesis is that there is no difference between the sexes. Each point corresponds to a genetic variant. Points that go above the statistical significance line at $-\log_{10}(P) = 1 \times 10^{-8}$ are considered to be sdSNPs. Traits represented include: waist:hip circumference ratio, ankylosing spondylitis, standing height and gout.

Sex differences in genetic architecture in the UK Biobank

Elena Bernabeu[1], Oriol Canela-Xandri[2], Konrad Rawlik[1], Andrea Talenti[1], James Prendergast[1] and Albert Tenesa[1,2]

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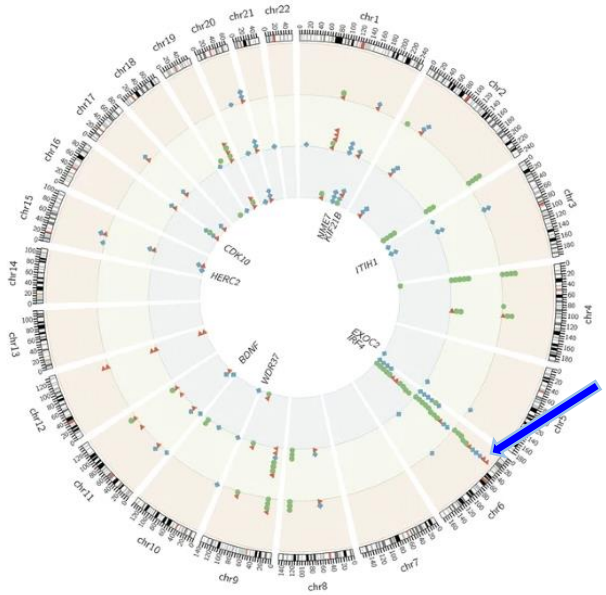
xMHC: Unique Features



Overview of PheWAS associations in the genome after functional annotation. **a** This matrix shows the number of functional SNPs for their respective phenotype. **b** The *Circos plot* showing the PheWAS associations in different types of functional data. *Red triangles* represent the associations in the GWAS Catalog only, *green circles* represent GWAS Catalog associations replicated by PheWAS ($P < 0.05$), and *blue diamonds* represent new phenotype associations identified by PheWAS ($P < 4.6 \times 10^{-6}$ or FDR < 0.1)

including:

- **Schizophrenia**
- **Alzheimer disease**
- **Parkinson disease**
- **Lung cancer**
- **Hodgkin lymphoma**

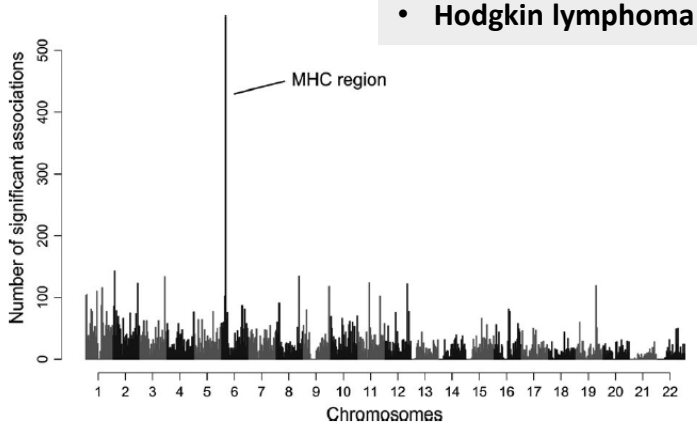


FIGURE 1 Number of significant GWAS associations along the genome. The chromosomal location of significant trait associations from GWAS (N = 18,682) is shown for all autosomes. Data from NHGRI GWAS catalog. Reproduced from "Lenz TL, Spirin V, Jordan DM, Sunyaev SR. Excess of Deleterious Mutations around HLA Genes Reveals Evolutionary Cost of Balancing Selection. Mol Biol Evol 2016;33(10):2555-64. https://doi.org/10.1093/molbev/msw127" by permission of Oxford University Press on behalf of the Society for Molecular Biology and Evolution

…. despite already showing the highest number of disease associations, the true extent of the involvement of the MHC region in disease genetics may not have been uncovered.

Zhao et al. Genome Medicine (2018) 10:7
DOI 10.1186/s13073-018-0513-x

Genome Medicine

RESEARCH Open Access

An integrative functional genomics framework for effective identification of novel regulatory variants in genome–phenome studies

Junfei Zhao[1†], Feixiong Cheng[2,3†], Peilin Jia[1], Nancy Cox[4,5], Joshua C. Denny[5,6] and Zhongming Zhao[1,7*]

Received: 9 March 2017 | Revised: 16 June 2017 | Accepted: 20 July 2017
DOI: 10.1111/iji.12332

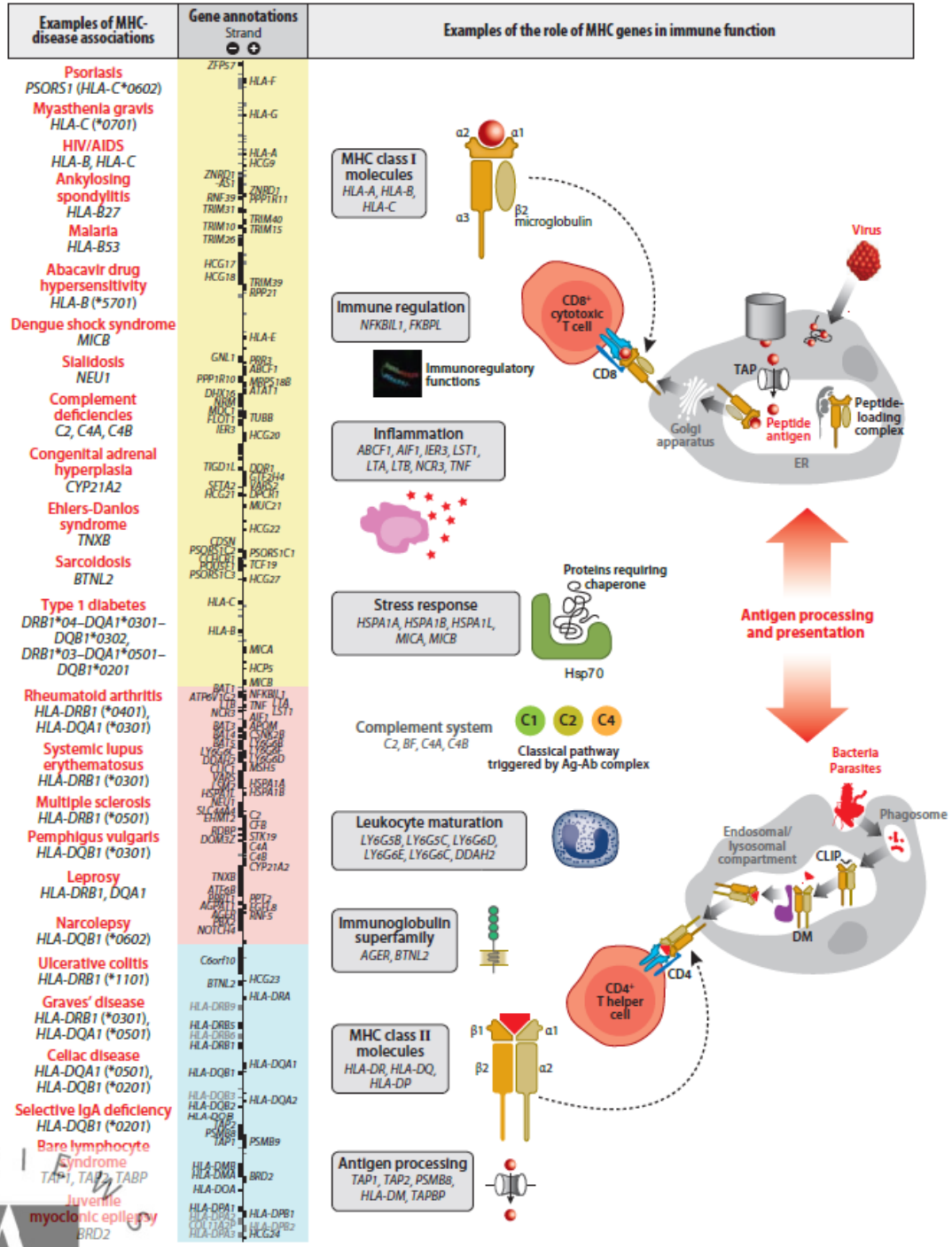
REVIEW

WILEY INTERNATIONAL JOURNAL OF IMMUNOGENETICS

What has GWAS done for HLA and disease associations?

A. E. Kennedy[1] | U. Ozbek[2,3] | M. T. Dorak[4]

HLA

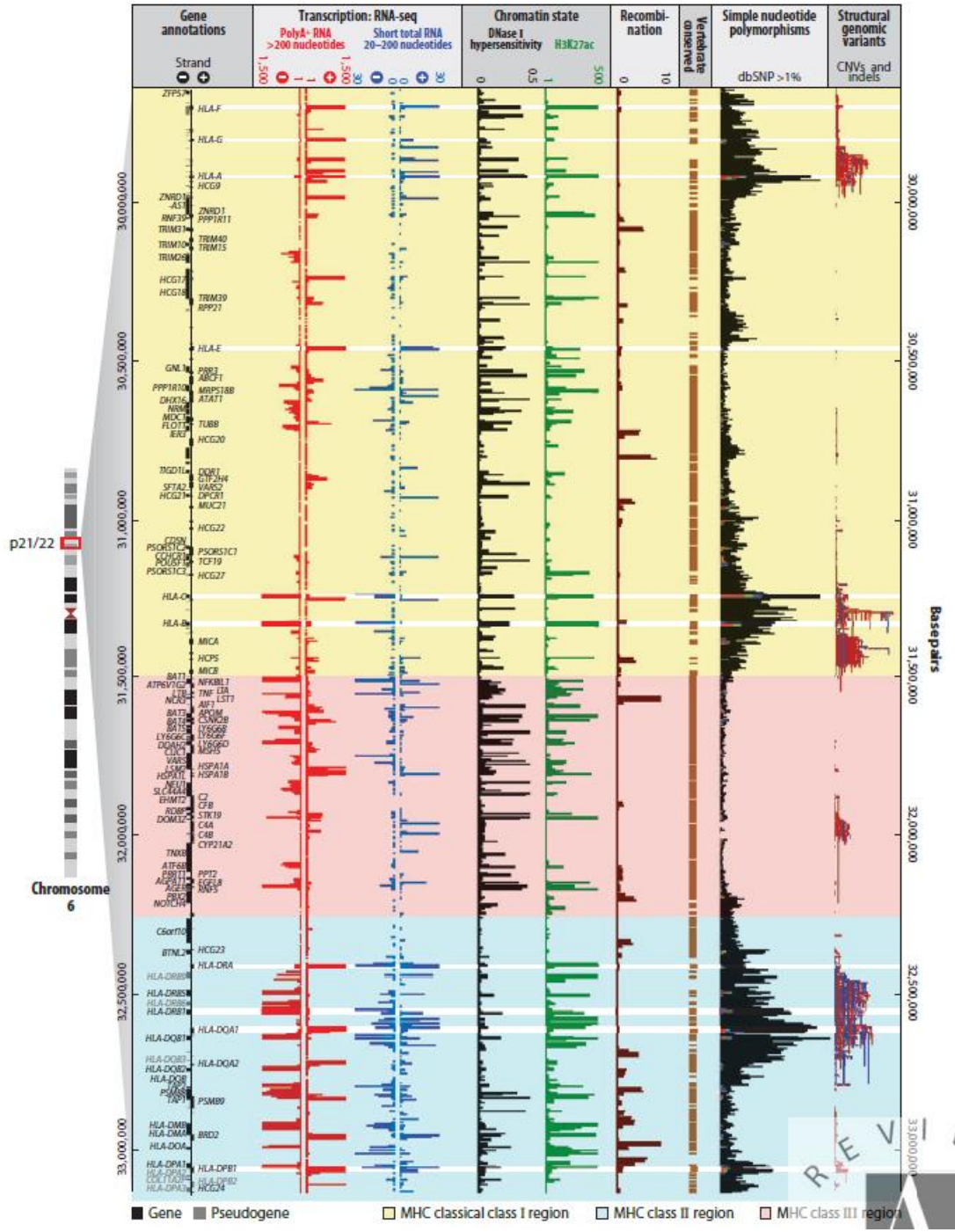


Major Histocompatibility Complex Genomics and Human Disease

John Trowsdale[1] and Julian C. Knight[2]

Annu. Rev. Genomics Hum. Genet. 2013. 14:16.1–16.23

HLA



Major Histocompatibility Complex Genomics and Human Disease

John Trowsdale[1] and Julian C. Knight[2]

Annu. Rev. Genomics Hum. Genet. 2013. 14:16.1–16.23

Transplant Success & xHLA

- **HLA genes** [**HLA-A/B/C/F/G; HLA-DP/DQ/DR**]
- **non-HLA genes within the xHLA** [**MICA/MICB**]
- **Other genes outside xHLA**
  - ✓ **Cytokine Genes:** Variations in genes encoding cytokines, which are signalling molecules involved in immune responses, may influence the inflammatory environment and immune reactions after transplantation.
  - ✓ **Adhesion Molecule Genes:** Genes encoding adhesion molecules on cell surfaces may affect the adhesion and migration of immune cells, influencing the immune response to the transplanted tissue.
  - ✓ **Genes Related to Fibrosis and Tissue Repair:** Variations in genes involved in fibrosis and tissue repair processes may influence the development of fibrotic reactions in the transplanted organ.
  - ✓ **Immunosuppressive Medication Metabolism Genes:** Genes involved in the metabolism of immunosuppressive medications used post-transplantation can impact drug efficacy and patient outcomes.
  - ✓ **Innate Immune System Genes:** Genes associated with the innate immune system, such as toll-like receptors, may influence the early responses to transplantation.

Transplant Success & non-HLA

Findings

59 268 nsSNPs affecting a transmembrane or secreted protein were analysed. The median number of nsSNP mismatches in immune-accessible transmembrane and secreted proteins between donors and recipients was 1892 (IQR 1850–1936). The degree of nsSNP mismatch was independently associated with graft loss in a multivariable model adjusted for HLA eplet mismatch (*HLA-A*, *HLA-B*, *HLA-C*, *HLA-DP*, *HLA-DQ*, and *HLA-DR*). Each increase by a unit of one IQR had an HR of 1·68 (95% CI 1·17–2·41, p=0·005). 5-year death censored graft survival was 98% in the quartile with the lowest mismatch, 91% in the second quartile, 89% in the third quartile, and 82% in the highest quartile (p=0·003, log-rank test). Customised peptide arrays verified a donor-specific alloimmune response to genetically predicted mismatched epitopes.

Interpretation

Genetic mismatch of non-HLA haplotypes coding for transmembrane or secreted proteins is associated with an increased risk of functional graft loss independently of HLA incompatibility. As in HLA alloimmunity, donor-specific alloantibodies can be identified against genotype derived non-HLA epitopes.

Genome-wide nsSNP mismatch in transmembrane and secreted proteins was independent of HLA mismatch, including *HLA-DP* mismatch and independently associated with transplant outcome.

Contribution of non-HLA incompatibility between donor and recipient to kidney allograft survival: genome-wide analysis in a prospective cohort

Roman Reindl-Schwaighofer, Andreas Heinzel*, Alexander Kainz, Jessica van Setten, Kira Jelencsics, Karin Hu, Bao-Li Loza, Michael Kammer, Georg Heinze, Petra Hruba, Alena Koňaříková, Ondrej Viklicky, Georg A Boehmig, Farsad Eskandary, Gottfried Fischer, Frans Claas, John C Tan, Tom J Albert, Jigar Patel, Brendan Keating, Rainer Oberbauer, for the iGeneTRAiN consortium†*

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Transplant Success & non-HLA

	Hazard ratio (95% CI)	p value
nsSNP mismatch in transmembrane and secreted (per IQR)	1·68 (1·17–2·41)	0·005
nsSNP mismatch (without transmembrane or secreted, per IQR)	0·90 (0·63–1·28)	0·543
Genome-wide SNP mismatch (without nsSNP, per IQR)	1·02 (0·85–1·22)	0·858
HLA eplet mismatch (per IQR)	1·43 (1·01–2·02)	0·042

nsSNP mismatch in transmembrane and secreted proteins was independently associated with graft loss, and exhibited a similar risk per IQR increase as HLA eplet mismatch. SNP=single nucleotide polymorphism. nsSNP=non-synonymous single nucleotide polymorphism.

Table 2: **Multivariable Cox proportional hazard model for death-censored kidney allograft loss**

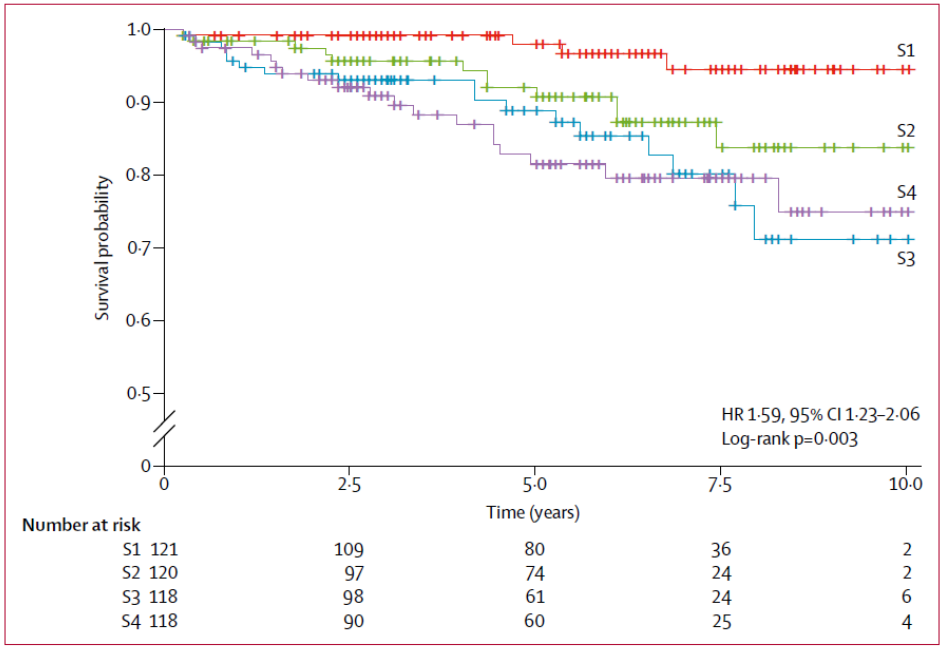

Figure 3: **Kaplan-Meier plot of functional renal allograft survival, stratified by quartiles of nsSNP mismatch coding for transmembrane and secreted proteins**
S1 denotes the lowest quartile and thus the lowest amount of mismatch, S4 the highest and thus the highest amount of mismatch. Differences between the survival curves were significant (log-rank p=0·003). nsSNP=non-synonymous single nucleotide polymorphism.

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Transplant Success & HLA-F

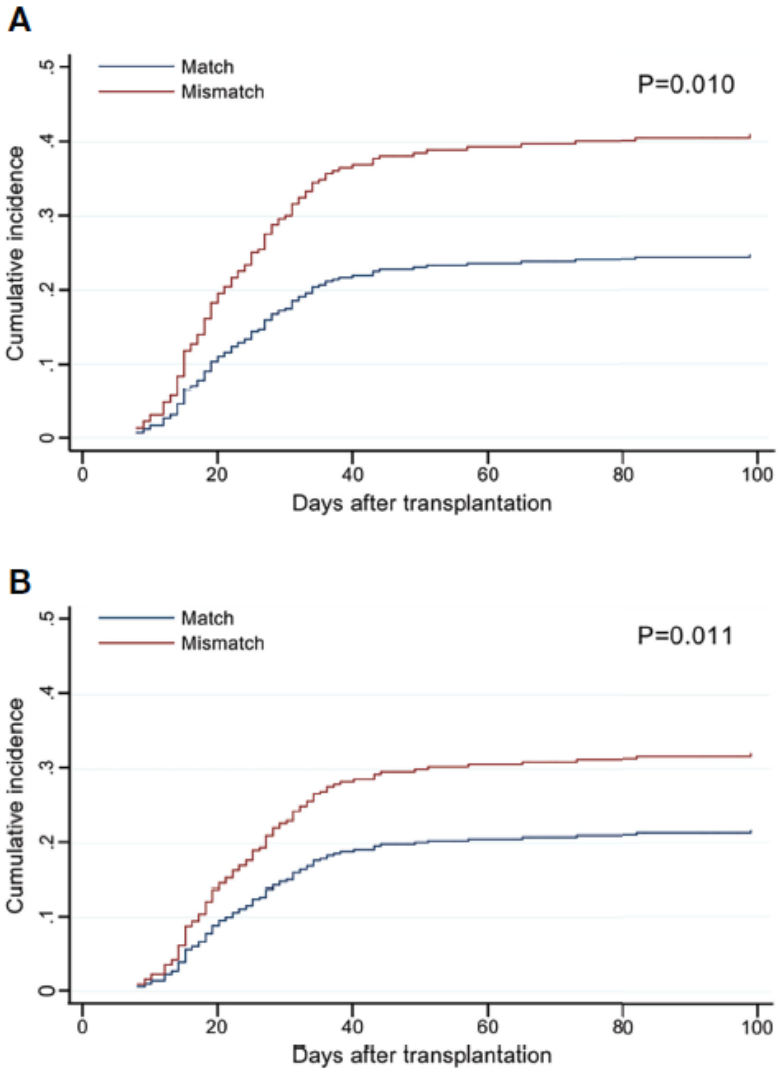

FIGURE 2 | Cumulative incidence of grade II–IV acute graft-versus-host disease (aGVHD) by the mismatch number of HLA-F-AS1 and HLA-DPB1 at the allele level in the GVH direction. (A, B) Cumulative incidence curves of HLA-F-AS1 and HLA-DPB1, respectively. Cumulative incidences at 100 days were HLA-F-AS1 match, 26% (95% CI, 21%–31%); HLA-F-AS1 mismatch, 42% (30%–55%); HLA-DPB1 match, 21% (15%–28%); and HLA-DPB1 mismatch, 34% (28%–41%).

Sequence Variations Within *HLA-G* and *HLA-F* Genomic Segments at the Human Leukocyte Antigen Telomeric End Associated With Acute Graft-Versus-Host Disease in Unrelated Bone Marrow Transplantation

Shingo Suzuki[1], Satoko Morishima[2], Makoto Murata[3], Masafumi Tanaka[1], Atsuko Shigenari[1], Sayaka Ito[1], Uma Kanga[4], Jerzy K. Kulski[1,5], Yasuo Morishima[6,7] and Takashi Shiina[1]

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Transplant Success & MICA/MICB

- **Role in Graft-versus-Host Disease (GVHD):** Polymorphisms in MICA and MICB genes have been associated with an increased risk of GVHD, a condition where transplanted immune cells attack the recipient's tissues. This is particularly relevant in the context of hematopoietic stem cell transplantation (HSCT).
- **NK Cell Recognition:** MICA and MICB molecules are ligands for NK cell receptors, such as NKG2D. Variations in MICA and MICB can affect the interaction between these ligands and receptors, influencing NK cell activation and responses to transplanted tissues.
- **Influence on Immune Response:** Polymorphisms in MICA and MICB may impact the immune response to transplanted organs or tissues, contributing to variations in graft acceptance or rejection.
- **Donor-Recipient Matching:** Matching MICA and MICB profiles between donors and recipients is an area of interest in transplantation. Some studies suggest that considering MICA and MICB polymorphisms in addition to traditional HLA matching may provide additional information for predicting transplant outcomes.

Transplant Success & MICA/MICB

All patients and donors were high-resolution HLA-typed and matched for 10/10 (n = 1379), 9/10 (n = 636), or 8/10 (n = 157) HLA alleles.

Mismatches at the MICA locus as well as MICA-129 increased with the number of HLA mismatches.

Adverse OS was observed in the 10/10 match group if MICA-129 was mismatched (HR, 1.8; CI, 1.2 to 2.6; *P* = 0.003).; a significantly worse outcome for DFS (HR, 1.8; CI 1.3 to 2.5; *P* = 0.001).

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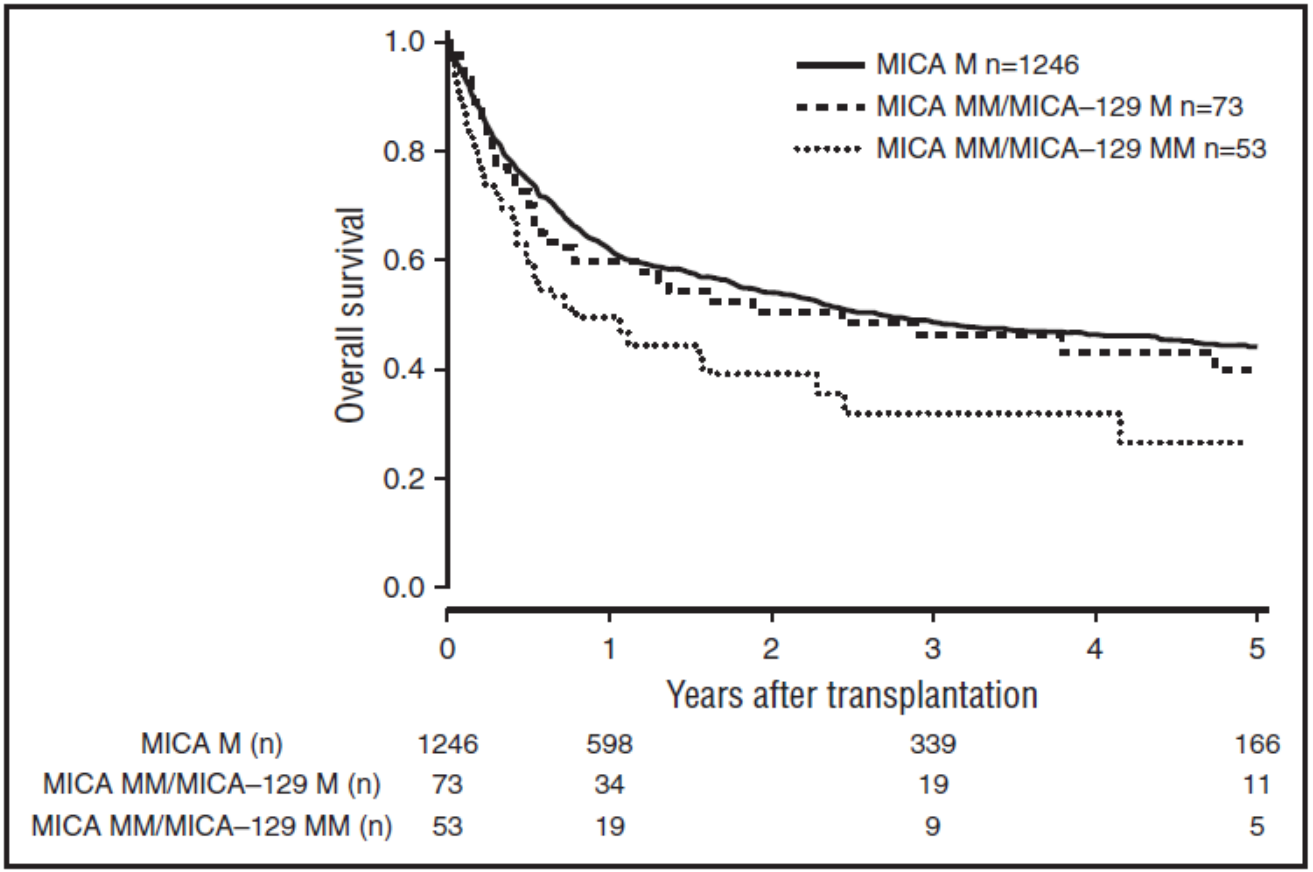
Matching for the MICA-129 polymorphism is beneficial in unrelated hematopoietic stem cell transplantation

Daniel Fuerst,[1,2] Christine Neuchel,[1,2] Dietger Niederwieser,[3] Donald Bunjes,[4] Martin Gramatzki,[5] Eva Wagner,[6] Gerald Wulf,[7] Bertram Glass,[8] Michael Pfreundschuh,[9] Hermann Einsele,[10] Renate Arnold,[11] Gernot Stuhler,[12] Kerstin Schaefer-Eckart,[13] Sebastian Freitag,[14] Jochen Casper,[15] Martin Kaufmann,[16] Mohammed Wattad,[17] Bernd Hertenstein,[18] Stefan Klein,[19] Mark Ringhoffer,[20] Daphne Mytilineos,[2] Chrysanthi Tsamadou,[1,2] Carlheinz Mueller,[21,22] Hubert Schrezenmeier,[1,2] and Joannis Mytilineos[1,2,22]

Transplant Success & MICA/MICB



MICA M (n)	1246	598	339	166
MICA MM/MICA–129 M (n)	73	34	19	11
MICA MM/MICA–129 MM (n)	53	19	9	5

Figure 1. Overall survival of patients with 10/10 compatible donors transplanted with a MICA matched donor (solid black line), a MICA mismatched/MICA-129 matched donor (dashed line), and a MICA mismatched/MICA-129 mismatched donor (dotted line) (P = 0.04).

Matching for the MICA-129 polymorphism is beneficial in unrelated hematopoietic stem cell transplantation

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Transplant Success & MICA/MICB

MICA **mismatches were associated with decreased graft survival (HR, 2.12; 95% CI: 1.5 to 3.1; *P* < 0.001).**

Both before and after transplantation anti-MICA donor-specific antibodies (DSA) were strongly associated with increased antibody-mediated rejection (ABMR) (HR, 3.8; 95% CI: 1.9 to 7.4; *P* < 0.001; HR, 9.9; 95% CI: 7.4 to 13.2; *P* < 0.001, respectively).

This effect was synergetic with that of anti-HLA DSA before and after transplantation (HR, 25.7; 95% CI: 3.3 to 199.4; *P* = 0.002; HR, 82.7; 95% CI: 33.7 to 203.0; *P* < 0.001, respectively).

De novo-developed anti-MICA DSA were the most harmful because they were also associated with reduced graft survival (HR, 1.3; 95% CI: 1.1 to 1.6; *P* = 0.014).

Finally, the damaging effect of anti-MICA DSA on graft survival was confirmed in an independent cohort of 168 patients with ABMR (HR, 1.7; 95% CI: 1.0 to 2.9; *P* = 0.04).

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The MHC class I *MICA* gene is a histocompatibility antigen in kidney transplantation

Raphael Carapito[1,2,3,4,5] ✉, Ismail Aouadi[1,2,3,5], Martin Verniquet[1,2,3,5], Meiggie Untrau[1,2,3,5], Angélique Pichot[1,2,3,5], Thomas Beaudrey[1,2,5,6], Xavier Bassand[1,2,5,6], Sébastien Meyer[1,2,3,5], Loic Faucher[2,7], Juliane Posson[8,9], Aurore Morlon[2,10], Irina Kotova[2,10], Florent Delbos[2,11], Alexandre Walencik[2,11], Alice Aarnink[12], Anne Kennel[12], Caroline Suberbielle[2,13], Jean-Luc Taupin[2,13], Benedict M. Matern[14], Eric Spierings[14], Nicolas Congy-Jolivet[2,15,16], Arnaud Essaydi[17], Peggy Perrin[1,2,5,6], Antoine Blancher[2,15,16], Dominique Charron[2,5,13], Nezih Cereb[18], Myriam Maumy-Bertrand[2,5,19], Frédéric Bertrand[2,5,19], Valérie Garrigue[2,20], Vincent Pernin[2,20], Laurent Weekers[21], Maarten Naesens[22], Nassim Kamar[2,23], Christophe Legendre[2,24], Denis Glotz[2,8,9], Sophie Caillard[1,2,5,6], Marc Ladrière[25], Magali Giral[2,7], Dany Anglicheau[2,24,26], Caner Süsal[27,28] and Seiamak Bahram[1,2,3,4,5] ✉

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Transplant Success & MICA/MICB

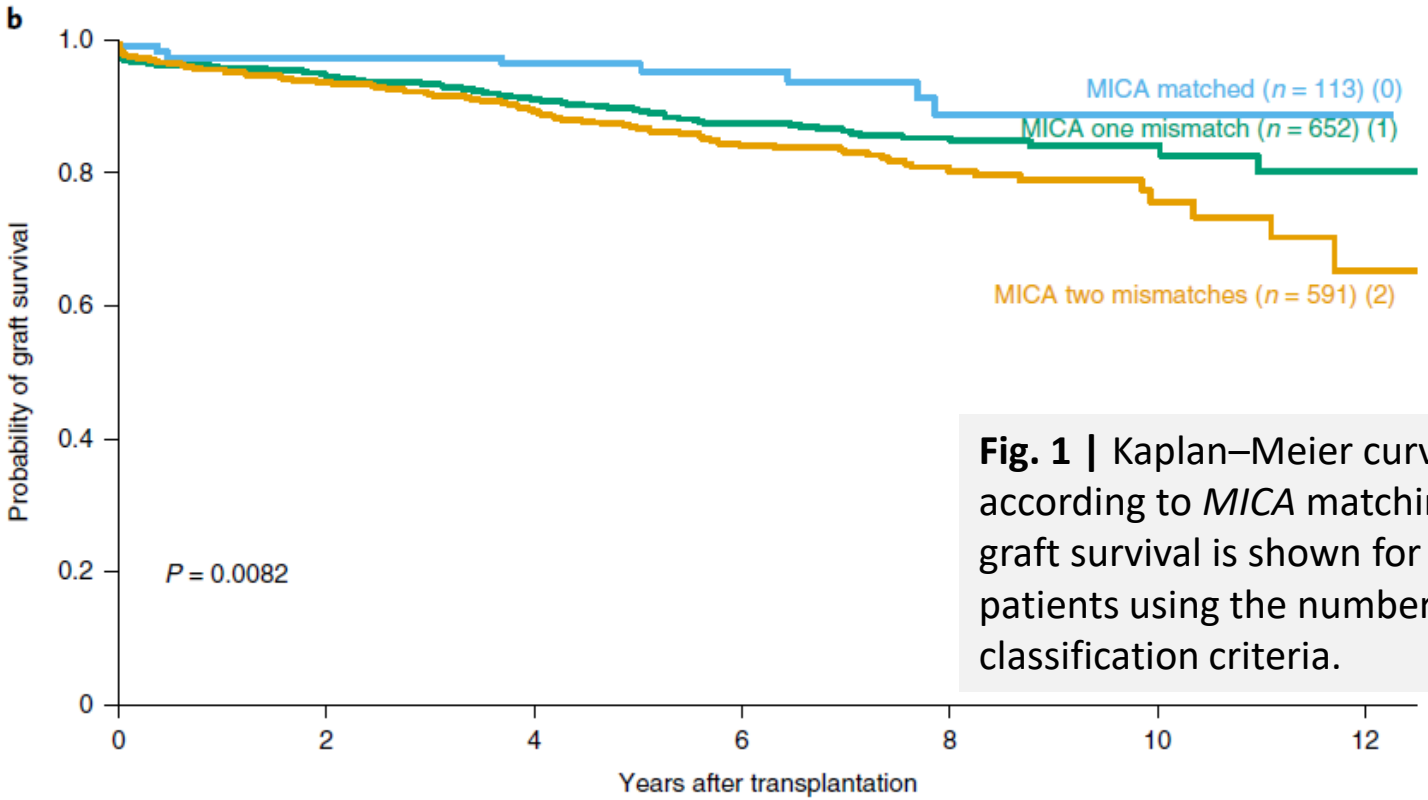

Fig. 1 | Kaplan–Meier curves for kidney graft survival according to *MICA* matching status. The probability of graft survival is shown for matched versus mismatched patients using the number of mismatches (**b**) as classification criteria.

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Transplant Success & MICA/MICB

The lower graft survival can be explained by an increased rate of ABMR, which is independently associated with anti-MICA DSA.

The present data formally define MICA as a bona fide transplantation antigen
in kidney organ transplants and provide the rationale for
including *MICA* genotyping and immunization monitoring in the pre- and post-transplantation workup (but not *MICA* eplet mismatches instead of global *MICA* mismatches *).

[* Close to 400 *MICA* alleles have been reported to date]

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Transplant Success & HLA-G

- HLA-G contributes to immune tolerance (incl. fetal-maternal tolerance) and resisting rejection: Soluble HLA-G levels correlate with maternal-fetal tolerance
- 3' UTR 14bp insertion/deletion polymorphism is associated with transplant rejection and soluble HLA-G levels
- HLA-G is thought to be involved in transplantation immune tolerance by protecting the organ from rejection
- In pathological situations, the molecule is observed in tumors and correlated to bad prognosis and is associated to autoimmune diseases and viral infection susceptibility, creating an unbalanced and pathologic environment
- HLA-G expression is also regulated by cytokines: IL-4 and IL-10 upregulates; IL-2 and IL-6 downregulates; IFN-γ and IL-10 maintains high expression

Biological Characteristics of HLA-G and Its Role in Solid Organ Transplantation

Siqi Liu[1], Nicolaas A. Bos[1], Erik A. M. Verschuuren[2], Debbie van Baarle[3] and Johanna Westra[1]*

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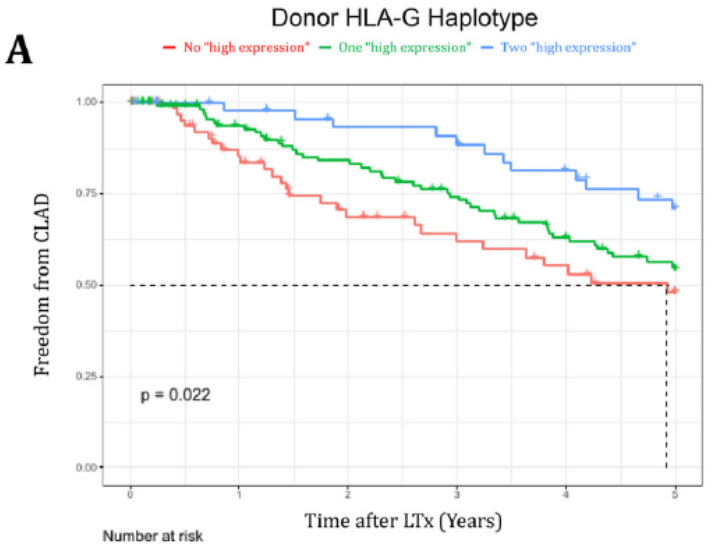
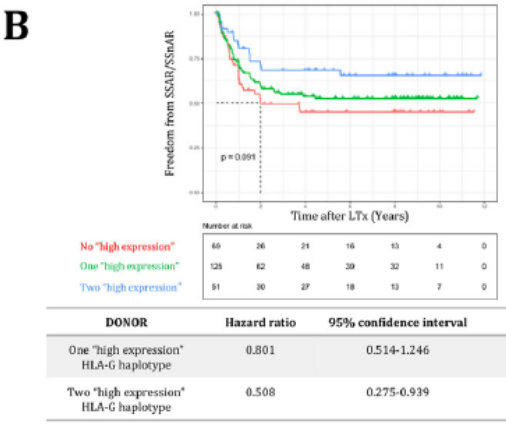
Transplant Success & HLA-G

Donor and recipient human leukocyte antigen-G polymorphisms modulate the risk of adverse immunologic events following lung transplantation

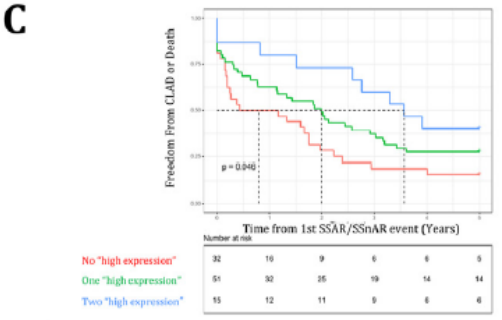
Peter Riddell [1], Jin Ma [2], Julieta Lozarte [2], Daniella Birriel [1], Ambily Ulahannan [1], Rasheed Ghany [1], Diego Delgado [4], Vivek Rao [3], Shof Keshavjee [1], Tereza Martinu [1], Iussi Tikkanen [1],



DONOR	Hazard ratio	95% confidence interval	P value
One "high expression" HLA-G haplotype	0.733	0.455-1.180	0.201
Two "high expression" HLA-G haplotype	0.392	0.198-0.774	0.007



DONOR	Hazard ratio	95% confidence interval	P value
One "high expression" HLA-G haplotype	0.801	0.514-1.246	0.325
Two "high expression" HLA-G haplotype	0.508	0.275-0.939	0.031



DONOR	Hazard ratio	95% confidence interval	P value
One "high expression" HLA-G haplotype	0.664	0.403-1.094	0.108
Two "high expression" HLA-G haplotype	0.414	0.193-0.885	0.023

Figure 1. HLA-G haplotypes were characterized as exhibiting low or high HLA-G expression based on the reported effects of each haplotype or by extrapolating the effects of individual SNPs on overall haplotype function. With this characterization, we performed Kaplan–Meier analysis to assess the effect of donor HLA-G haplotype on (A) the time to CLAD (censored at 5 years post-LTx), (B) the time to first SSAR/SSnAR, and (C) the time from first SSAR/SSnAR to either CLAD or death (analysis censored at 5 years post-SSAR/SSnAR). Below each graph, we report the numbers at risk and univariable Cox proportional hazards ratios. The comparator group is where both donor haplotypes exhibit low HLA-G expression. CLAD, chronic lung allograft dysfunction; HLA-G, human leukocyte antigen-G; LTx, lung transplantation; SNP, single nucleotide polymorphisms; SSAR, spirometrically significant acute rejection event; SSnAR, spirometrically significant nonacute rejection event.

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Conclusions

The HLA complex contains disproportional number of genes and polymorphisms

The extra-ordinary features of the HLA complex will certainly continue to create surprises in human genetics

Full (10/10) HLA antigen matching is a desirable feature for transplant success, but there is still room for further improvement

Some non-HLA polymorphisms within and outside the HLA complex may contribute to variable outcomes even in 10/10-matched transplant recipients

There are calls for MICA to be considered as a transplant antigen

The involvement of HLA-G via induction of immune tolerance in transplant outcomes (as in pregnancy) promises interesting prospects

Thank You

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