Expression QTLs with Opposing Effects on HLA-DR and -DQ Genes are Associated with Autoimmune Disorders:

Evidence for Mixed Isotype Heterodimer Formation?

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Outline

HLA class II genetic variation and susceptibility to autoimmunity

Results from a single study of PBMC

Replication attempts

HLA class II gene expression levels, hybrid isomers and autoimmunity

Conclusions

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Background

The HLA region harbours the strongest risk markers for susceptibility to autoimmune disorders (AIDs). Most GWAS top hits, including those for AIDs, are expression quantitative trait loci (eQTL).

It is generally accepted that one of the triggers of autoimmunity is increased HLA class II gene expression.

eLIFE elifesciences.org RESEARCH ARTICLE

Regulatory polymorphisms modulate the expression of HLA class II molecules and promote autoimmunity

Prithvi Raj[†1], Ekta Rai[1,2†], Ran Song[1], Shaheen Khan[1], Benjamin E Wakeland[1], Kasthuribai Viswanathan[1], Carlos Arana[1], Chaoying Liang[1], Bo Zhang[1], Igor Dozmorov[1], Ferdicia Carr-Johnson[1], Mitja Mitrovic[3], Graham B Wiley[4], Jennifer A Kelly[4], Bernard R Lauwerys[5], Nancy J Olsen[6], Chris Cotsapas[3], Christine K Garcia[7,8], Carol A Wise[8,9,10,11], John B Harley[12,13], Swapan K Nath[4], Judith A James[4], Chaim O Jacob[14], Betty P Tsao[15], Chandrashekhar Pasare[1], David R Karp[16], Quan Zhen Li[1], Patrick M Gaffney[4], Edward K Wakeland[1*]

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Expression level of risk genes of MHC class II is a susceptibility factor for autoimmunity: New insights

Carmen Gianfran [a], Laura Pisapia [b], Stefania Picascia [a], Maria Strazzullo [b], Giovanna Del Pozzo [b, *]

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Aim

We aimed to test the hypothesis that "increased levels of HLA-DR/DQ genes are associated with autoimmune disorders (AID)" by taking advantage of the known genetic associations and eQTL data.

To systematically examine the direction of the eQTL effects in relation to the direction of AID risk, we screened eQTLs for HLA-DR and -DQ expression in blood mononuclear cells, and GWAS catalogs for AID associations.

As a rare source of eQTL correlations with directions in peripheral blood mononuclear cells in an unbiased study of the whole genome, we primarily used the publicly accessible data from Kirsten et al (*Hum Mol Genet* 2015).

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Material & Methods

As a rare source of eQTL correlations with directions in peripheral blood mononuclear cells in an unbiased study of the whole genome, we primarily used the publicly accessible data from Kirsten et al (*Hum Mol Genet* 2015).

Dissecting the genetics of the human transcriptome identifies novel trait-related *trans*-eQTLs and corroborates the regulatory relevance of non-protein coding loci

Supplementary Data

Supplementary Data

- Supplementary Figures - pdf file
- Supplementary Tables - xlsx file
- Supplementary Table 2 - txt file
- Supplementary Table 12 - pdf file

Peripheral blood mononuclear cells of 2112 individuals (Supplementary Table 1)

Dissecting the genetics of the human transcriptome identifies novel trait-related *trans*-eQTLs and corroborates the regulatory relevance of non-protein coding loci

Holger Kirsten, Hoor Al-Hasani, Lesca Holdt, Arnd Gross, Frank Beutner, Knut Krohn, Katrin Horn, Peter Ahnert, Ralph Burkhardt, Kristin Reiche Jörg Hackermüller, Markus Löffler, Daniel Teupser, Joachim Thiery, Markus Scholz

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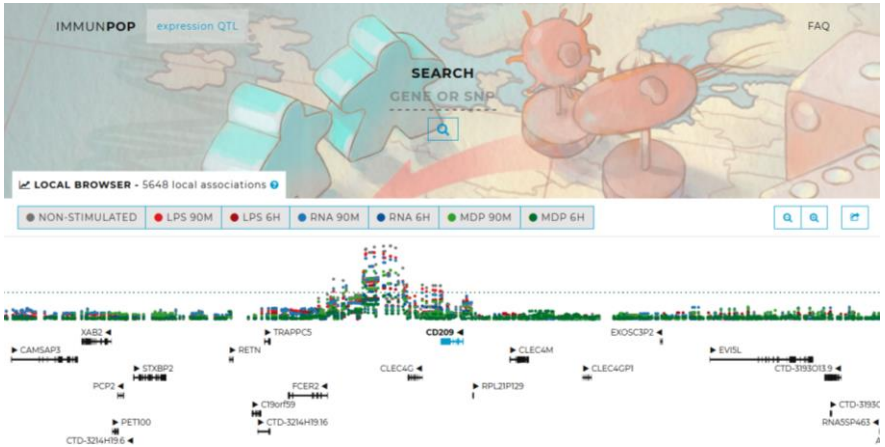
Material & Methods

Replication was sought in:

Cumulative results obtained from PhenoScanner (GRASP) and SNiPA Geuvadis Browser, FHS results via PheGenI, and published papers for RNA-seq-based results

… and the dedicated eQTL Btrowser for immunoregulatory SNPs:

ImmunPop eQTL Browser



Genetic regulatory effects modified by immune activation contribute to autoimmune disease associations

Sarah Kim-Hellmuth, Matthias Bechheim, Benno Pütz, Pejman Mohammadi, Yohann Nédélec, Nicholas Giangreco, Jessica Becker, Vera Kaiser, Nadine Fricker, Esther Beier, Peter Boor, Stephane E. Castel, Markus M. Nöthen, Luis B. Barreiro, Joseph K. Pickrell, Bertram Müller-Myhsok, Tuuli Lappalainen, Johannes Schumacher & Veit Hornung

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Results

As in most other traits, most GWAS hits for AIDs were eQTLs.

The direction of the correlation did not show consistency. Some AID risk markers correlated with increased, and some with decreased expression of HLA-DR/DQ mRNA.

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Results

When we focused on correlations with *DRA* and *DRB1* expression levels jointly in the same direction, we noted that the two strongest multiple sclerosis (MS) risk-associated SNPs were eQTLs with negative (rs3135388) or positive (rs3129889) correlations with both genes. Thus, changes in the DR antigen levels could not be the mechanism of these associations.

However, both SNPs also correlated with *HLA-DQA1* levels in the opposite direction: positive (rs3135388) and negative (rs3129889), which suggested that it is the effects at opposing directions on DR and DQ loci that may be the mechanism of the associations with MS risk.

Our Immunochip data on IHWG cell lines showed that both SNPs were exclusively on the same *DRB1*15:01 - DQA1*01:02* haplotypes.
These two alleles form a mixed isotype heterodimer in the pathogenesis of MS in an animal model (Kaushansky et al, 2015).

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Results

A genetic effect for changes in opposite directions in *HLA-DRA/B1* and *HLA-DQA1* expression levels might facilitate mixed isotype heterodimer between *DRB1*15:01 and DQA1*01:02*.

PNAS PNAS PNAS PNAS

Epistasis among *HLA-DRB1*, *HLA-DQA1*, and *HLA-DQB1* loci determines multiple sclerosis susceptibility

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Edited by Tak Wah Mak, Ontario Cancer Institute, Toronto, ON, Canada, and approved March 19, 2009 (received for review December 19, 2008)

Multiple sclerosis (MS), a common central nervous system inflammatory disease, has a major heritable component. Susceptibility is associated with the MHC class II region, especially *HLA-DRB5*0101–HLA-DRB1*1501–HLA-DQA1*0102–HLA-DQB1*0602* haplotypes (hereafter DR2), which dominate genetic contribution to MS risk. Marked linkage disequilibrium (LD) among these loci makes identification of a specific locus difficult. The once-leading candidate, *HLA-DRB1*15*, localizes to risk, neutral, and protective haplotypes. *HLA-DRB1*15* and *HLA-DQB1*0602*, nearly always located together on a small ancestral chromosome segment, are strongly MS-associated. One intervening allele on this haplotype, viz. *HLA-DQA1*0102*, shows no primary MS association. Two Canadian cohorts (n = 830 and n = 438 trios) genotyped for *HLA-DRB1*, *HLA-DQA1* and *HLA-DQB1* alleles were tested for association using TDT. To evaluate epistasis involving *HLA-DRB1*15*, transmissions from *HLA-DRB1*15*-negative parents were stratified by the presence/absence of *HLA-DRB1*15* in affected offspring. All 3 alleles contribute to MS susceptibility through novel epistatic interactions. *HLA-DQA1*0102* increased disease risk when combined with *HLA-DRB1*1501 in trans*, thereby unambiguously implicating *HLA-DQ* in MS susceptibility. Three-locus haplotypes demonstrated that *HLA-DRB1*1501* and *HLA-DQB1*0602* each influence risk. Transmissions of rare morcellated DR2 haplotypes showed no interaction with *HLA-DQA1*0102*. Incomplete haplotypes bearing only *HLA-DRB1*1501* or *HLA-DQB1*0602* did not predispose to MS. Balanced reciprocal transmission distortion can mask epistatic allelic association. These findings implicate epistasis among HLA class II alleles in human immune responses generally, provide partial explanation for intense linkage disequilibrium in the MHC, have relevance to animal models, and demonstrate key roles for DR2-specific interactions in MS susceptibility. MHC disease associations may be more generally haplotypic or diplotypic.

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Role of a Novel Human Leukocyte Antigen-DQA1*01:02; DRB1*15:01 Mixed Isotype Heterodimer in the Pathogenesis of "Humanized" Multiple Sclerosis-like Disease*

Received for publication, February 12, 2015, and in revised form, April 13, 2015 Published, JBC Papers in Press, April 24, 2015, DOI 10.1074/jbc.M115.641209

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Background: HLA-DR15 haplotype (DRB1*15:01-DQA1*01:02-DQB1*0602-DRB5*01:01) association with multiple sclerosis (MS) is conventionally attributed to effects from HLA-DRB1*15:01, with impact on MS risk from the neighboring HLA-DQ locus unclear.
Results: Functional studies show MS-like disease dependent on a novel DQA1*01:02;DRB1*15:01 mixed isotype heterodimer.
Conclusion: DQA1*01:02 within a mixed heterodimer may contribute to MS pathogenesis.
Significance: HLA class II/MS susceptibility models may require broader reinterpretation.

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Results

Too good to be true? These two SNPs are supposed to show the same effects (they are in absolute LD)

snp	snp_pos	beta_dqa1	gene_dqa1	beta_drb1	gene_drb1	beta_dra	gene_dra
rs3129889	32413545	-0.1966755	HLA-DQA1	2.377578	HLA-DRB1	0.0471586	HLA-DRA
rs3129889	32413545	-0.0838106	HLA-DQA1	3.954122	HLA-DRB1	0.0471586	HLA-DRA
rs3135388	32413051	0.0837451	HLA-DQA1	-3.954998	HLA-DRB1	-0.0471913	HLA-DRA
rs3135388	32413051	0.1966361	HLA-DQA1	-2.378109	HLA-DRB1	-0.0471913	HLA-DRA

HLA-DQA1 | ***HLA-DRA & DRB1***

In any case, they seem to have opposite effects on *DRA/DRB1* and *DQA1*.

Dissecting the genetics of the human transcriptome identifies novel trait-related *trans*-eQTLs and corroborates the regulatory relevance of non-protein coding loci

Holger Kirsten, Hoor Al-Hasani, Lesca Holdt, Arnd Gross, Frank Beutner, Knut Krohn, Katrin Horn, Peter Ahnert, Ralph Burkhardt, Kristin Reiche Jörg Hackermüller, Markus Löffler, Daniel Teupser, Joachim Thiery, Markus Scholz

Human Molecular Genetics, Volume 24, Issue 16, 15 August 2015, Pages 4746–4763, https://doi.org/10.1093/hmg/ddv194

Results

Multiple sclerosis risk associations with the minor alleles of rs3135388 (A) and rs3129889 (G)

SNP	RAF	p-value	OR	Beta	CI	Region	Location	Functional class	Reported gene(s)	Mapped gene(s)	Reported trait	Study
rs3135388-A	0.22	4×10^{-225}	2.75		[2.46-3.07]	6p21.32	6:32445274	downstream_gene_variant	HLA-DRB1	HLA-DRA - HLA-DRB9	Multiple sclerosis	De Jager PL (PMID: 19525953), 2009
rs3135388-A	0.23	9×10^{-81}	1.99		[1.84-2.15]	6p21.32	6:32445274	downstream_gene_variant	HLA-DRA	HLA-DRA - HLA-DRB9	Multiple sclerosis	Hafler DA (PMID: 17660530), 2007

SNP	RAF	p-value	OR	Beta	CI	Region	Location	Functional class	Reported gene(s)	Mapped gene(s)	Reported trait	Study
rs3129889-G	0.20	1×10^{-206}	2.97		[NR]	6p21.32	6:32445768	downstream_gene_variant	HLA-DRB1	HLA-DRA - HLA-DRB9	Multiple sclerosis	Patsopoulos NA (PMID: 22190364), 2011

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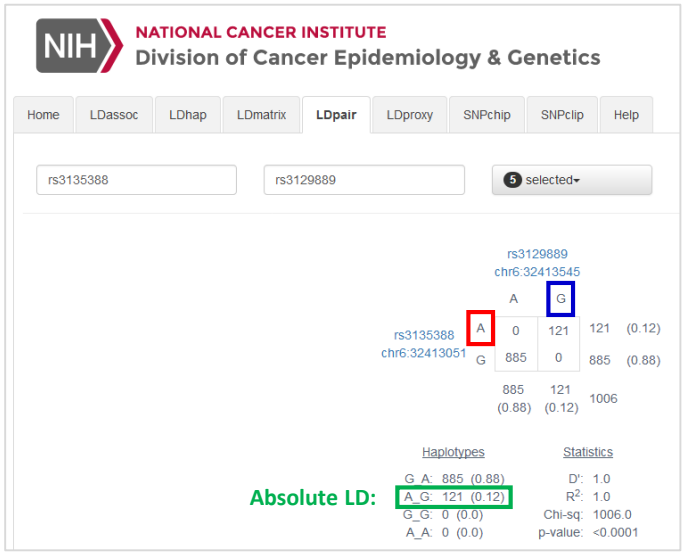
Results

HLA-DRA, *DRB1* and *DQA1* results passed quality control (but not *DQB1*).

SNP	expression_probe_ID	t.stat	FDR	R2	beta	beta_se	snp_chr	snp_pos	chr	strand	TSS	TSE	Entrez_ID	HGNC	potential_falsepos
rs2187668	ILMN_1808405	-15.8522562	4.67E-51	0.1064222	-0.4173034	0.02632454	6	32605884	6	+	32605183	32611428	3117	HLA-DQA1	FALSE
rs2187668	ILMN_3249667	-13.4896531	1.72E-37	0.0793949	-0.3887912	0.02882144	6	32605884	6	+	32605183	32611428	3117	HLA-DQA1	FALSE
rs2187668	ILMN_1715169	-11.3966886	4.90E-27	0.0579871	-1.1756696	0.10315887	6	32605884	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
rs2187668	ILMN_1697499	-6.52495132	5.02E-09	0.0197786	-0.7927972	0.1215024	6	32605884	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
rs2187668	ILMN_2157441	5.762147706	4.61E-07	0.0154919	0.04178188	0.00725109	6	32605884	6	+	32407619	32412821	3122	HLA-DRA	FALSE
rs3129889	ILMN_1697499	56.22363292	1.03E-304	0.5997038	3.95412227	0.07032847	6	32413545	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
rs3129889	ILMN_1715169	29.29031416	2.24E-155	0.289065	2.37757848	0.08117286	6	32413545	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
rs3129889	ILMN_3249667	-7.31979151	2.51E-11	0.0247642	-0.1966755	0.026869	6	32413545	6	+	32605183	32611428	3117	HLA-DQA1	FALSE
rs3129889	ILMN_2157441	7.211677046	5.35E-11	0.0240555	0.04715855	0.00653919	6	32413545	6	+	32407619	32412821	3122	HLA-DRA	FALSE
rs3129889	ILMN_1808405	-3.33139263	0.01859617	0.0052323	-0.0838106	0.02515783	6	32413545	6	+	32605183	32611428	3117	HLA-DQA1	FALSE
rs3135388	ILMN_1697499	-56.2490889	1.03E-304	0.5999211	-3.9549978	0.07031221	6	32413051	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
rs3135388	ILMN_1715169	-29.2978526	1.92E-155	0.2891708	-2.3781092	0.08117008	6	32413051	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
rs3135388	ILMN_3249667	7.317987757	2.54E-11	0.0247523	0.19663611	0.02687024	6	32413051	6	+	32605183	32611428	3117	HLA-DQA1	FALSE
rs3135388	ILMN_2157441	-7.21650878	5.17E-11	0.024087	-0.0471913	0.00653935	6	32413051	6	+	32407619	32412821	3122	HLA-DRA	FALSE
rs3135388	ILMN_1808405	3.32863924	0.01875637	0.0052237	0.08374508	0.02515895	6	32413051	6	+	32605183	32611428	3117	HLA-DQA1	FALSE



Dissecting the genetics of the human transcriptome identifies novel trait-related *trans*-eQTLs and corroborates the regulatory relevance of non-protein coding loci

Holger Kirsten, Hoor Al-Hasani, Lesca Holdt, Arnd Gross, Frank Beutner, Knut Krohn, Katrin Horn, Peter Ahnert, Ralph Burkhardt, Kristin Reiche Jörg Hackermüller, Markus Löffler, Daniel Teupser, Joachim Thiery, Markus Scholz

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Results

Detailed results confirm there is no mixup with strand assignment, and for each SNP two different probes give the same result.

SNP	expression_probe_ID	t.stat	FDR	R2	beta	beta_se	snp_chr	snp_pos	chr	strand	TSS	TSE	Entrez_ID	HGNC	potential_falsepos
rs3129889	ILMN_1697499	56.22363292	1.03E-304	0.5997038	3.95412227	0.07032847	6	32413545	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
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rs3135388	ILMN_1715169	-29.2978526	1.92E-155	0.2891708	-2.3781092	0.08117008	6	32413051	6	-	32546549	32557562	3123	HLA-DRB1	FALSE
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rs3135388	ILMN_2157441	-7.21650878	5.17E-11	0.024087	-0.0471913	0.00653935	6	32413051	6	+	32407619	32412821	3122	HLA-DRA	FALSE
rs3129889	ILMN_1808405	-3.33139263	0.01859617	0.0052323	-0.0838106	0.02515783	6	32413545	6	+	32605183	32611428	3117	HLA-DQA1	FALSE
rs3135388	ILMN_1808405	3.32863924	0.01875637	0.0052237	0.08374508	0.02515895	6	32413051	6	+	32605183	32611428	3117	HLA-DQA1	FALSE

snp	snp_pos	beta_dqa1	gene_dqa1	beta_drb1	gene_drb1	beta_dra	gene_dra
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rs3135388	32413051	0.0837451	HLA-DQA1	-3.954998	HLA-DRB1	-0.0471913	HLA-DRA
rs3135388	32413051	0.1966361	HLA-DQA1	-2.378109	HLA-DRB1	-0.0471913	HLA-DRA

HLA-DQA1 | HLA-DRA & DRB1

Dissecting the genetics of the human transcriptome identifies novel trait-related *trans*-eQTLs and corroborates the regulatory relevance of non-protein coding loci

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Kingston University London

Results

When the top GWAS hits for all AIDs were examined, we found a strong trend for opposing effects on *DRA* and *DRB1*, especially for type 1 diabetes (T1D)-associated SNPs.

Notably, rs2187668, a risk marker for ten AIDs including T1D and Celiac disease (CD) in the risk direction, correlated with expression of *DRA* (negatively) and *DRB1* (positively) in opposite directions.

snp	snp_pos	beta_dqa1	gene_dqa1	beta_drb1	gene_drb1	beta_dra	gene_dra
rs2187668	32605884	-0.4173034	HLA-DQA1	-1.17567	HLA-DRB1	0.0417819	HLA-DRA
rs2187668	32605884	-0.3887912	HLA-DQA1	-0.7927972	HLA-DRB1	0.0417819	HLA-DRA

***HLA-DQB1* results did not pass quality control steps in the original study**

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Human Molecular Genetics, Volume 24, Issue 16, 15 August 2015, Pages 4746–4763, https://doi.org/10.1093/hmg/ddv194

Results

We located the variant allele of this SNP to the ancestral haplotypes 8.1, 18.2 and 58.1 (all carrying *DRB1*03; DQA1*05:01; DQB1*02:01*) as well as *DRB1*14:02*; *DQA1*05:03; DQB1*03:01-bearing* haplotypes, implicated in mixed isotype heterodimer formation in the pathogenesis of T1D and CD.

Genotype effects and epistasis in type 1 diabetes and HLA-DQ trans dimer associations with disease

BPC Koeleman[1,2], BA Lie[3], DE Undlien[4], F Dudbridge[5], E Thorsby[3], RRP de Vries[1], F Cucca[6], BO Roep[1], MJ Giphart[1] and JA Todd[7]

*Alleles of HLA class II genes DQB1, DQA1, and DRB1 in the MHC region are major determinants of genetic predisposition to type 1 diabetes (T1D). Several alleles of each of these three loci are associated with susceptibility or protection from disease. In addition, relative risks for some DR-DQ genotypes are not simply the sum or product of the single haplotype relative risks. For example, the risk of the DRB1*03-DQB1*02/DRB1*0401-DQB1*0302 genotype is often found to be higher than for the individual DRB1*03-DQB1*02 and DRB1*0401-DQB1*0302 homozygous genotypes. It has been hypothesized that this synergy or epistasis occurs through formation of highly susceptible trans-encoded HLA-DQ(α1, β1) heterodimers. Here, we evaluated this hypothesis by estimating the disease associations of the range of DR-DQ genotypes and their inferred dimers in a large collection of nuclear families. We determined whether the risk of haplotypes in DRB1*0401-DQB1*0302-positive genotypes relative to the DRB1*03-DQB1*02-positive genotypes is different from that of DRB1*01-DQB1*0501, which we used as a baseline reference. Several haplotypes showed a different risk compared to DRB1*01-DQB1*0501, which correlated with their ability to form certain trans-encoded DQ dimers. This result provides new evidence for the potential importance of trans-encoded HLA DQ molecules in the determination of HLA-associated risk in T1D.*

Genes and Immunity (2004) **5**, 381–388. doi:10.1038/sj.gene.6364106

Gluten-Specific T Cells Cross-React between HLA-DQ8 and the HLA-DQ2α/DQ8β Transdimer

Yvonne Kooy-Winkelaar,* Menno van Lummel,* Antonis K. Moustakas,† Joachim Schweizer,‡ M. Luisa Mearin,‡ Chris J. Mulder,§ Bart O. Roep,* Jan W. Drijfhout,* George K. Papadopoulos,¶ Jeroen van Bergen,* and Frits Koning*

Because susceptibility to celiac disease is associated strongly with HLA-DQ2 (*DQA1*05/DQB1*02*) and weakly with HLA-DQ8 (*DQA1*03/DQB1*03*), a subset of patients carries both HLA-DQ2 and HLA-DQ8. As a result, these patients may express two types of mixed HLA-DQ2/8 transdimers (encoded by *DQA1*05/DQB1*03* and *DQA1*03/DQB1*02*) in addition to HLA-DQ2 and HLA-DQ8. Using T cells from a celiac disease patient expressing HLA-DQ8*trans* (encoded by *DQA*0501/DQB*0302*), but neither HLA-DQ2 nor HLA-DQ8, we demonstrate that this transdimer is expressed on the cell surface and can present multiple gluten peptides to T cell clones isolated from the duodenum of this patient. Furthermore, T cell clones derived from this patient and HLA-DQ2/8 heterozygous celiac disease patients respond to gluten peptides presented by HLA-DQ8*trans*, as well as HLA-DQ8, in a similar fashion. Finally, one gluten peptide is recognized better when presented by HLA-DQ8*trans*, which correlates with preferential binding of this peptide to HLA-DQ8*trans*. These results implicate HLA-DQ8*trans* in celiac disease pathogenesis and demonstrate extensive T cell cross-reactivity between HLA-DQ8 and HLA-DQ8*trans*. Because type 1 diabetes is strongly associated with the presence of HLA-DQ8*trans*, our findings may bear relevance to this disease as well. *The Journal of Immunology*, 2011, 187: 5123–5129.

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HLA-DQA1 and *HLA-DQB1* in Celiac disease predisposition: practical implications of the HLA molecular typing

Francesca Megiorni* and Antonio Pizzuti

Abstract

Celiac disease (CD) is a multifactorial disorder with an estimated prevalence in Europe and USA of 1:100 and a female:male ratio of approximately 2:1. The disorder has a multifactorial etiology in which the triggering environmental factor, the gluten, and the main genetic factors, Human Leukocyte Antigen *(HLA)-DQA1* and *HLA-DQB1* loci, are well known. About 90-95% of CD patients carry DQ2.5 heterodimers, encoded by *DQA1*05* and *DQB1*02* alleles both in *cis* or in *trans* configuration, and DQ8 molecules, encoded by *DQB1*03:02* generally in combination with *DQA1*03* variant. Less frequently, CD occurs in individuals positive for the DQ2.x heterodimers (*DQA1≠*05* and *DQB1*02*) and very rarely in patients negative for these DQ predisposing markers. HLA molecular typing for Celiac disease is, therefore, a genetic test with a negative predictive value. Nevertheless, it is an important tool able to discriminate individuals genetically susceptible to CD, especially in at-risk groups such as first-degree relatives (parents, siblings and offspring) of patients and in presence of autoimmune conditions (type 1 diabetes, thyroiditis, multiple sclerosis) or specific genetic disorders (Down, Turner or Williams syndromes).

Keywords: Celiac disease, *HLA-DQA1*, *HLA-DQB1*, HLA typing, Disease risk

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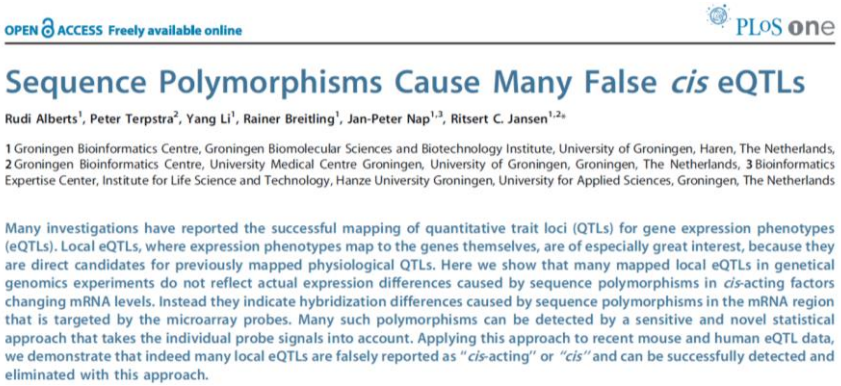
Conclusion

The AID-associated GWAS hits are indeed eQTLs for HLA class II genes, but some may act in different directions for their isotypes suggesting that they may contribute to AID development by facilitating mixed isotype heterodimer formation rather than ectopic or increased expression on antigen-presenting cells.

These preliminary results need confirmation and validation preferably by RNA-sequencing and at the protein level (bearing in mind the false-positive result possibility with probe-based methods in highly polymorphic regions of the genome).



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Sequence Polymorphisms Cause Many False *cis* eQTLs

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Many investigations have reported the successful mapping of quantitative trait loci (QTLs) for gene expression phenotypes (eQTLs). Local eQTLs, where expression phenotypes map to the genes themselves, are of especially great interest, because they are direct candidates for previously mapped physiological QTLs. Here we show that many mapped local eQTLs in genetical genomics experiments do not reflect actual expression differences caused by sequence polymorphisms in *cis*-acting factors changing mRNA levels. Instead they indicate hybridization differences caused by sequence polymorphisms in the mRNA region that is targeted by the microarray probes. Many such polymorphisms can be detected by a sensitive and novel statistical approach that takes the individual probe signals into account. Applying this approach to recent mouse and human eQTL data, we demonstrate that indeed many local eQTLs are falsely reported as "*cis*-acting" or "*cis*" and can be successfully detected and eliminated with this approach.

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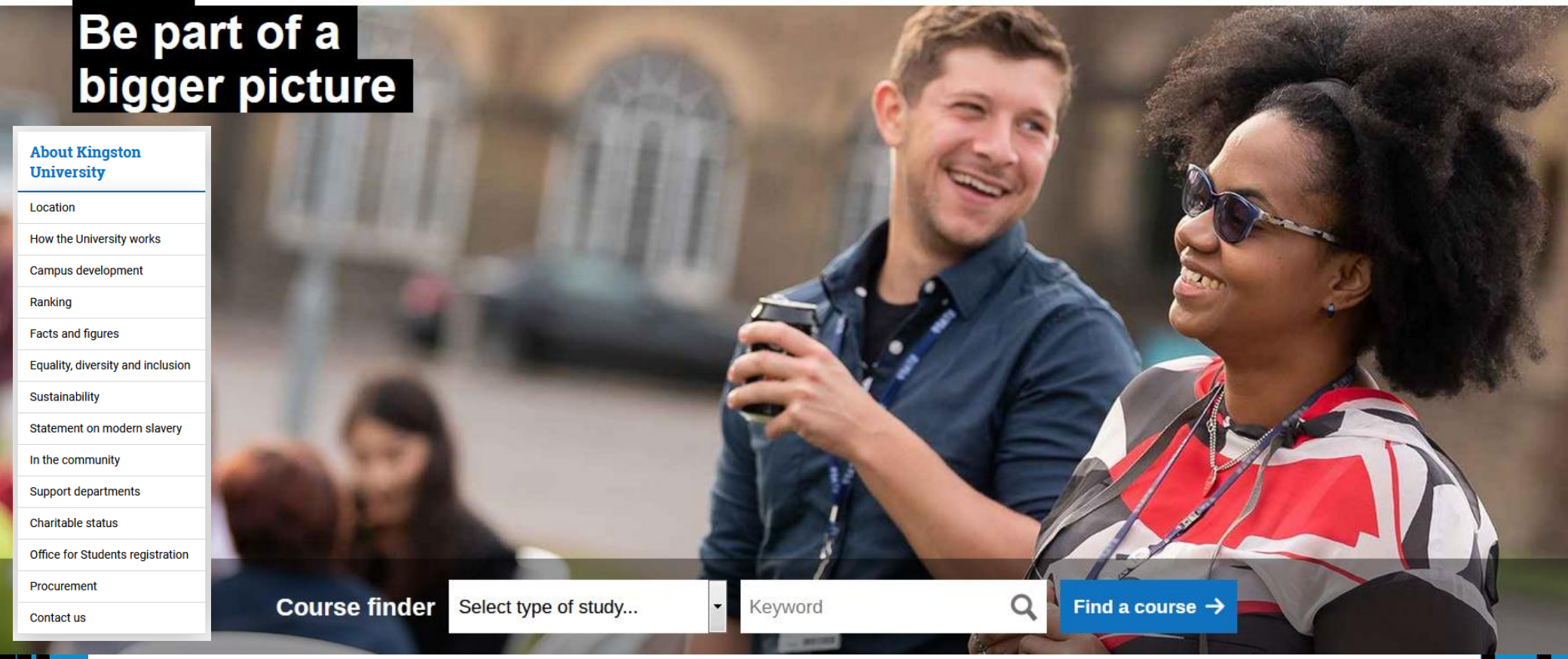

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