

HLA-DRB1*07:01–HLA-DQA1*02:01–HLA-DQB1*02:02 haplotype is associated with a high risk of asparaginase hypersensitivity in acute lymphoblastic leukemia

Nóra Kutszegi,^{1,2} Xiaoqing Yang,³ András Gézsi,¹ Géza Schermann,¹ Dániel J. Erdélyi,² Ágnes F. Semsei,¹ Krisztina M. Gábor,⁴ Judit C. Sági,¹ Gábor T. Kovács,² András Falus,¹ Hongyun Zhang⁵ and Csaba Szalai^{1,6}

¹Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary; ²2nd Department of Paediatrics, Semmelweis University, Budapest, Hungary; ³BGI-Shenzhen, China; ⁴Department of Pediatrics and Pediatric Health Care Center, Faculty of Medicine, University of Szeged, Szeged, Hungary; ⁵BGI Clinical Laboratory, Shenzhen, China and ⁶Central Laboratory, Heim Pal Children Hospital, Budapest, Hungary

NK and XY contributed equally to this work.

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Correspondence: szalaics@gmail.com or zhanghy@genomics.cn

Online Supplementary Material

Text S1. Estimation of *HLA-DRB1*–*HLA-DQA1*–*HLA-DQB1* haplotypes by using Allele Frequency Net Database — HLA Haplotype Frequency Search. Testing the possible combinations of the given genotypes at the two loci (*HLA-DRB1* and *HLA-DQB1*, respectively), haplotypes were only adopted as a result if exactly two not overlapping haplotypes could be found in the specified database (i.e. in case of a patient for example with *HLA-DRB1**01:01/*HLA-DRB1**07:01 and *HLA-DQB1**05:01/*DQB1**02:02 genotypes, the possible combinations are: *HLA-DRB1**01:01–*HLA-DQA1**(any)–*HLA-DQB1**05:01, *HLA-DRB1**07:01–*HLA-DQA1**(any)–*HLA-DQB1**05:01, *HLA-DRB1**01:01–*HLA-DQA1**(any)–*HLA-DQB1**02:02 and *HLA-DRB1**07:01–*HLA-DQA1**(any)–*HLA-DQB1**02:02. Among these, only two already described haplotypes were in the database pertaining to Caucasoid origin: *HLA-DRB1**01:01–*HLA-DQA1**01:01–*HLA-DQB1**05:01 and *HLA-DRB1**07:01–*HLA-DQA1**02:01–*HLA-DQB1**02:02, therefore these were accepted as most likely haplotypes). Each search was specified to obtain any data regarding to the *HLA-DQA1* locus.

Table S1. Univariate and multivariate logistic regression analyses between cofactors and asparaginase hypersensitivity.

Covariate	Group	% Asparaginase hypersensitivity	Univariate p value	OR (95% CI)	Multivariate p value	OR (95% CI)
Gender	Male	38%	0.51	1.15 (0.75-1.76)	0.22	1.34 (0.84-2.14)
	Female	41%				
Immunophenotype	pre-B ALL	40%	0.87	1.05 (0.56-1.98)	0.82	0.92 (0.45-1.90)
	T-ALL	41%				
Age at diagnosis	<10 years	37%	0.14	1.46 (0.86-2.48)	0.28	1.41 (0.76-2.60)
	≥10 years	46%				
Risk group	Standard	39%	5.7x10⁻⁵	5.88 (2.85-12.15)	1.15x10⁻⁴	5.37 (2.29-12.63)
	Medium	31%				
	High	77%				
Treatment protocol	ALL-BFM 90	26%	3.36x10⁻³	4.18 (1.61-10.89)	0.03	3.14 (1.10-8.97)
	ALL-BFM 95	39%				
	ALL IC-BFM 2002 standard	44%				
	ALL IC-BFM 2002 experimental	60%				
	ALL IC-BFM 2009	40%				

Results under the statistical significance of $p \leq 0.05$ are in bold. OR, odds ratio; 95% CI, 95% confidence interval; ALL, acute lymphoblastic leukemia; IC, intercontinental; BFM, Berlin—Frankfurt—Münster.

Table S2. HLA-DRB1 and HLA-DQB1 allelic odds ratios of asparaginase hypersensitivity reactions in ALL patients (n=359).

Gene	Allele	Allele Frequency	%Hypersensitivity: carrier ¹	%Hypersensitivity: noncarrier ²	OR ³	95% CI ⁴	p value ³
<i>HLA-DRB1</i>	*01:01	0.082	35.6	39.7	0.76	0.41-1.39	0.368
	*01:02	0.015	45.5	38.8	1.39	0.39-4.94	0.613
	*03:01	0.097	40.0	38.8	1.05	0.60-1.82	0.865
	*04:01	0.031	36.4	39.2	0.88	0.35-2.21	0.791
	*04:02	0.025	38.9	39.0	0.86	0.31-2.35	0.766
	*04:03	0.014	80.0	37.8	4.79	0.95-24.10	0.057
	*04:04	0.018	69.2	37.9	5.08	1.48-17.44	0.010
	*04:05	0.004	0.0	39.3	NA ⁵	NA ⁵	0.985
	*04:07	0.004	33.3	39.0	1.35	0.12-15.78	0.812
	*04:08	0.007	60.0	38.7	2.47	0.39-15.55	0.336
	*04:10	0.001	100.0	38.8	NA ⁵	NA ⁵	0.979
	*07:01	0.128	56.5	33.0	2.86	1.73-4.75	4.56x10⁻⁵
	*08:01	0.039	21.4	40.5	0.44	0.17-1.13	0.088
	*08:04	0.001	100.0	38.8	NA ⁵	NA ⁵	0.980
	*09:01	0.008	50.0	38.8	1.63	0.31-8.64	0.567
	*10:01	0.017	8.3	40.1	0.12	0.02-0.98	0.048
	*11:01	0.070	22.0	41.7	0.40	0.19-0.82	0.013
	*11:03	0.010	42.9	38.9	1.13	0.24-5.32	0.881
	*11:04	0.060	44.2	38.3	1.30	0.67-2.54	0.436
	*11:15	0.001	100.0	38.8	NA ⁵	NA ⁵	0.979
	*11:43	0.001	0.0	39.1	NA ⁵	NA ⁵	0.981
	*12:01	0.015	45.5	38.8	1.71	0.50-5.93	0.394
	*12:02	0.001	0.0	39.1	NA ⁵	NA ⁵	0.981
	*13:01	0.072	26.9	41.0	0.49	0.25-0.96	0.039
	*13:02	0.025	33.3	39.3	0.79	0.28-2.26	0.664
	*13:03	0.019	28.6	39.4	0.61	0.18-2.06	0.426
	*13:05	0.001	0.0	39.1	NA ⁵	NA ⁵	0.981
	*13:15	0.001	100.0	38.8	NA ⁵	NA ⁵	0.980

Gene	Allele	Allele Frequency	%Hypersensitivity: carrier ¹	%Hypersensitivity: noncarrier ²	OR ³	95% CI ⁴	p value ³
	*13:18	0.001	100.0	38.8	NA ⁵	NA ⁵	0.979
	*14:04	0.017	41.7	38.9	1.23	0.38-4.01	0.733
	*14:54	0.032	34.8	39.3	0.94	0.38-2.32	0.887
	*15:01	0.079	43.9	38.1	1.20	0.66-2.17	0.552
	*15:02	0.025	11.1	40.5	0.14	0.03-0.65	0.012
	*16:01	0.067	41.7	38.6	1.14	0.60-2.15	0.686
	*16:02	0.007	20.0	39.3	0.45	0.05-4.10	0.479
<i>HLA-DQB1</i>	*02:01	0.097	40.0	38.8	1.05	0.60-1.82	0.865
	*02:02	0.091	60.0	34.4	2.99	1.68-5.31	1.85x10⁻⁴
	*03:01	0.198	33.1	42.9	0.70	0.44-1.10	0.119
	*03:02	0.071	47.1	37.7	1.43	0.77-2.65	0.258
	*03:03	0.046	48.5	38.0	1.72	0.82-3.61	0.153
	*03:04	0.010	71.4	38.4	3.85	0.71-20.89	0.118
	*03:05	0.004	100.0	38.5	NA ⁵	NA ⁵	0.984
	*03:12	0.003	0.0	39.2	NA ⁵	NA ⁵	0.983
	*04:02	0.040	31.0	39.7	0.72	0.31-1.67	0.440
	*05:01	0.113	32.1	41.0	0.60	0.35-1.05	0.074
	*05:02	0.081	41.1	38.5	1.17	0.65-2.10	0.607
	*05:03	0.053	28.9	40.2	0.66	0.31-1.40	0.278
	*05:05	0.001	0.0	39.1	NA ⁵	NA ⁵	0.981
	*06:01	0.018	15.4	39.9	0.19	0.04-0.91	0.038
	*06:02	0.072	44.2	38.1	1.20	0.64-2.22	0.571
	*06:03	0.077	30.9	40.5	0.63	0.34-1.20	0.159
	*06:04	0.019	35.7	39.1	0.90	0.28-2.90	0.855
	*06:09	0.004	33.3	39.0	0.81	0.07-9.13	0.862
	*06:39	0.001	0.0	39.1	NA ⁵	NA ⁵	0.981

Results that reached the significance threshold ($p \leq 2.66 \times 10^{-4}$) are in bold. ¹Percent of patients with hypersensitivities to asparaginase with the allele defined in column 1 and 2. ²Percent of patients with hypersensitivities to asparaginase without the allele defined in column 1 and 2. ³For the association between the allele and asparaginase hypersensitivity. ⁴95% confidence interval for the estimated odds ratio. ⁵The odds ratios and confidence intervals were not estimated due to low allele frequency.

Table S3. HLA-DQA1 allelic and HLA-DRB1–HLA-DQA1– HLA-DQB1 haplotypic odds ratios of asparaginase hypersensitivity reactions in ALL patients (n=257).

Gene/Haplotype	Allele	Allele Frequency	%Hypersensitivity: carrier ¹	%Hypersensitivity: noncarrier ²	OR ³	95% CI ⁴	p value ³
<i>HLA-DRB1</i>	*07:01	0.128	60.6	31.9	3.69	1.99-6.84	3.45x10⁻⁵
<i>HLA-DQB1</i>	*02:02	0.088	68.1	32.9	5.00	2.43-10.29	1.22x10⁻⁵
<i>HLA-DQA1</i>	*01:01	0.128	33.3	41.4	0.64	0.34-1.20	0.163
	*01:02	0.202	46.0	35.5	1.49	0.89-2.51	0.128
	*01:03	0.091	23.4	42.9	0.33	0.15-0.71	0.004
	*02:01	0.128	60.6	31.9	3.69	1.99-6.84	3.45x10⁻⁵
	*03:01	0.088	46.7	37.7	1.41	0.71-2.81	0.330
	*04:01	0.053	25.9	40.9	0.52	0.20-1.34	0.178
	*05:01	0.309	32.8	45.8	0.75	0.49-1.15	0.185
<i>HLA-DRB1*01:01–HLA-DQA1*01:01–HLA-DQB1*05:01</i>	NA	0.088	37.8	39.6	0.84	0.42-1.69	0.624
<i>HLA-DRB1*01:02–HLA-DQA1*01:01–HLA-DQB1*05:01</i>	NA	0.019	40.0	39.3	1.15	0.29-4.47	0.843
<i>HLA-DRB1*03:01–HLA-DQA1*05:01–HLA-DQB1*02:01</i>	NA	0.115	40.7	38.9	1.08	0.58-2.02	0.800
<i>HLA-DRB1*04:01–HLA-DQA1*03:01–HLA-DQB1*03:01</i>	NA	0.016	25.0	39.8	0.46	0.09-2.42	0.358
<i>HLA-DRB1*04:01–HLA-DQA1*03:01–HLA-DQB1*03:02</i>	NA	0.006	0.0	39.8	NA ⁵	NA ⁵	0.985
<i>HLA-DRB1*04:02–HLA-DQA1*03:01–HLA-DQB1*03:02</i>	NA	0.021	27.3	39.8	0.46	0.11-1.91	0.285
<i>HLA-DRB1*04:03–HLA-DQA1*03:01–HLA-DQB1*03:02</i>	NA	0.006	100.0	38.6	NA ⁵	NA ⁵	0.985
<i>HLA-DRB1*04:03–HLA-DQA1*03:01–HLA-DQB1*03:04</i>	NA	0.002	100.0	39.1	NA ⁵	NA ⁵	0.987
<i>HLA-DRB1*04:03–HLA-DQA1*03:01–HLA-DQB1*03:05</i>	NA	0.004	100.0	38.8	NA ⁵	NA ⁵	0.987
<i>HLA-DRB1*04:04–HLA-DQA1*03:01–HLA-DQB1*03:02</i>	NA	0.019	60.0	38.5	3.76	0.97-14.65	0.056
<i>HLA-DRB1*04:05–HLA-DQA1*03:01–HLA-DQB1*03:02</i>	NA	0.002	0.0	39.5	NA ⁵	NA ⁵	0.986
<i>HLA-DRB1*04:07–HLA-DQA1*03:01–HLA-DQB1*03:01</i>	NA	0.004	50.0	39.2	3.80	0.21-68.33	0.366
<i>HLA-DRB1*07:01–HLA-DQA1*02:01–HLA-DQB1*02:02</i>	NA	0.091	68.1	32.9	5.00	2.43-10.29	1.22x10⁻⁵
<i>HLA-DRB1*07:01–HLA-DQA1*02:01–HLA-DQB1*03:03</i>	NA	0.037	42.1	39.1	1.19	0.44-3.19	0.736
<i>HLA-DRB1*08:01–HLA-DQA1*04:01–HLA-DQB1*04:02</i>	NA	0.051	23.1	41.1	0.46	0.17-1.25	0.128

Gene/Haplotype	Allele	Allele Frequency	%Hypersensitivity: carrier ¹	%Hypersensitivity: noncarrier ²	OR ³	95% CI ⁴	p value ³
<i>HLA-DRB1*08:04-HLA-DQA1*04:01-HLA-DQB1*04:02</i>	NA	0.002	100.0	39.1	NA ⁵	NA ⁵	0.987
<i>HLA-DRB1*09:01-HLA-DQA1*03:01-HLA-DQB1*03:03</i>	NA	0.008	75.0	38.7	5.61	0.53-58.84	0.150
<i>HLA-DRB1*10:01-HLA-DQA1*01:01-HLA-DQB1*05:01</i>	NA	0.043	9.1	40.7	0.17	0.02-1.39	0.098
<i>HLA-DRB1*11:01-HLA-DQA1*05:01-HLA-DQB1*03:01</i>	NA	0.089	21.7	43.1	0.37	0.17-0.81	0.013
<i>HLA-DRB1*11:03-HLA-DQA1*05:01-HLA-DQB1*03:01</i>	NA	0.012	33.3	39.4	0.67	0.11-3.94	0.661
<i>HLA-DRB1*11:04-HLA-DQA1*05:01-HLA-DQB1*03:01</i>	NA	0.054	46.4	38.4	1.40	0.61-3.19	0.429
<i>HLA-DRB1*12:01-HLA-DQA1*05:01-HLA-DQB1*03:01</i>	NA	0.016	50.0	39.0	1.91	0.44-8.24	0.384
<i>HLA-DRB1*13:01-HLA-DQA1*01:03-HLA-DQB1*06:03</i>	NA	0.070	25.0	41.6	0.42	0.19-0.97	0.041
<i>HLA-DRB1*13:02-HLA-DQA1*01:02-HLA-DQB1*06:04</i>	NA	0.027	35.7	39.5	0.90	0.27-3.02	0.870
<i>HLA-DRB1*13:02-HLA-DQA1*01:02-HLA-DQB1*06:09</i>	NA	0.006	33.3	39.4	0.74	0.06-8.48	0.810
<i>HLA-DRB1*13:03-HLA-DQA1*05:01-HLA-DQB1*03:01</i>	NA	0.043	18.2	40.2	0.36	0.07-1.84	0.219
<i>HLA-DRB1*13:05-HLA-DQA1*05:01-HLA-DQB1*03:01</i>	NA	0.002	0.0	39.5	NA ⁵	NA ⁵	0.988
<i>HLA-DRB1*15:01-HLA-DQA1*01:02-HLA-DQB1*05:02</i>	NA	0.008	25.0	39.5	0.42	0.04-4.71	0.479
<i>HLA-DRB1*15:01-HLA-DQA1*01:02-HLA-DQB1*06:02</i>	NA	0.076	53.8	36.7	2.15	1.04-4.46	0.039
<i>HLA-DRB1*15:01-HLA-DQA1*01:02-HLA-DQB1*06:03</i>	NA	0.002	100.0	39.1	NA ⁵	NA ⁵	0.986
<i>HLA-DRB1*15:02-HLA-DQA1*01:03-HLA-DQB1*06:01</i>	NA	0.021	18.2	40.2	0.21	0.04-1.06	0.058
<i>HLA-DRB1*16:01-HLA-DQA1*01:02-HLA-DQB1*05:02</i>	NA	0.074	42.1	38.8	1.21	0.58-2.51	0.609
<i>HLA-DRB1*16:02-HLA-DQA1*01:02-HLA-DQB1*05:02</i>	NA	0.010	20.0	39.7	0.47	0.05-4.32	0.503

Results that reached the significance threshold ($p \leq 2.66 \times 10^{-4}$) are in bold. ¹Percent of patients with hypersensitivities to asparaginase with the allele defined in column 1 and 2. ²Percent of patients with hypersensitivities to asparaginase without the allele defined in column 1 and 2. ³For the association between the allele and asparaginase hypersensitivity. ⁴95% confidence interval for the estimated odds ratio. ⁵The odds ratios and confidence intervals were not estimated due to low allele frequency.

Table S4. Regrouping of uncertain *HLA-DQA1* allele results.

Haplotype		<i>DQA1</i> allele
<i>HLA-DRB1*04:01-HLA-DQA1*03:01/*03:02-HLA-DQB1*03:01</i>		
<i>HLA-DRB1*04:01-HLA-DQA1*03:01/*03:02-HLA-DQB1*03:02</i>		
<i>HLA-DRB1*04:03-HLA-DQA1*03:01/*03:02-HLA-DQB1*03:02</i>	→	03:01 ^a
<i>HLA-DRB1*04:05-HLA-DQA1*03:01/*03:02-HLA-DQB1*03:02</i>		
<i>HLA-DRB1*04:07-HLA-DQA1*03:01/*03:02-HLA-DQB1*03:01</i>		
<i>HLA-DRB1*09:01-HLA-DQA1*03:01/*03:02-HLA-DQB1*03:03</i>		
<i>HLA-DRB1*10:01-HLA-DQA1*01:01/*01:04-HLA-DQB1*05:01</i>	→	01:01 ^a
<i>HLA-DRB1*13:01-HLA-DQA1*01:02/*01:03-HLA-DQB1*06:03</i>	→	01:03 ^b
<i>HLA-DRB1*13:03-HLA-DQA1*05:01/*05:05-HLA-DQB1*03:01</i>	→	05:01 ^a