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,1 Judit C. Sági,2 Gábor T. Kovács,2 András Falus,1 Hongyun Zhang5 and Csaba Szalai1,6

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
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≤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 | %Hypersensitivity: noncarrier | OR   | 95% CI   | p value |
|----------|---------|------------------|-----------------------------|-------------------------------|------|----------|---------|
| *HLA-DRB1* | *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   | NA       | 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   | NA       | 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   | NA       | 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   | NA       | 0.979   |
|          | *11:43* | 0.001            | 0.0                         | 39.1                          | NA   | NA       | 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   | NA       | 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   | NA       | 0.981   |
|          | *13:15* | 0.001            | 100.0                       | 38.8                          | NA   | NA       | 0.980   |
| Gene       | Allele | Allele Frequency | %Hypersensitivity: carrier<sup>1</sup> | %Hypersensitivity: noncarrier<sup>2</sup> | OR<sup>3</sup> | 95% CI<sup>4</sup>       | p value<sup>5</sup> |
|------------|--------|-----------------|-------------------------------------|----------------------------------------|-------------|--------------------------|---------------------|
| *13:18     | 0.001  | 100.0           | 38.8                                | NA<sup>5</sup>                         | NA<sup>5</sup> | 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                    |
| HLA-DQB1   | *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<sup>-4</sup>    |
| *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<sup>5</sup>                         | NA<sup>5</sup> | 0.984                    |
| *03:12     | 0.003  | 0.0             | 39.2                                | NA<sup>5</sup>                         | NA<sup>5</sup> | 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<sup>5</sup>                         | NA<sup>5</sup> | 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<sup>5</sup>                         | NA<sup>5</sup> | 0.981                    |

Results that reached the significance threshold (p≤2.66 x 10<sup>-4</sup>) are in bold. <sup>1</sup>Percent of patients with hypersensitivities to asparaginase with the allele defined in column 1 and 2. <sup>2</sup>Percent of patients with hypersensitivities to asparaginase without the allele defined in column 1 and 2. <sup>3</sup>For the association between the allele and asparaginase hypersensitivity. <sup>4</sup>95% confidence interval for the estimated odds ratio. <sup>5</sup>The odds ratios and confidence intervals were not estimated due to low allele frequency.
| Gene/Haplotype | Allele | Allele Frequency | %Hypersensitivity: carrier<sup>1</sup> | %Hypersensitivity: noncarrier<sup>2</sup> | OR<sup>3</sup> | 95% CI | p value<sup>3</sup> |
|---------------|--------|-----------------|-------------------------------------|-------------------------------------|------------|--------|-----------------|
| **HLA-DRB1**  | *07:01 | 0.128           | 60.6                                | 31.9                                | 3.69       | 1.99-6.84 | 3.45x10<sup>-5</sup> |
|               | *02:02 | 0.088           | 68.1                                | 32.9                                | 5.00       | 2.43-10.29 | 1.22x10<sup>-5</sup> |
| **HLA-DQB1**  | *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<sup>-5</sup> |
|               | *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           |
|               | *06:01 | 0.115           | 40.7                                | 38.9                                | 1.08       | 0.58-2.02 | 0.800           |
|               | *06:02 | 0.016           | 25.0                                | 39.8                                | 0.46       | 0.09-2.42 | 0.358           |
|               | *06:03 | 0.006           | 0.0                                 | 39.8                                | NA<sup>5</sup> | NA<sup>5</sup> | 0.985           |
|               | *06:04 | 0.021           | 27.3                                | 39.8                                | 0.46       | 0.11-1.91 | 0.285           |
|               | *06:05 | 0.006           | 100.0                               | 38.6                                | NA<sup>5</sup> | NA<sup>5</sup> | 0.985           |
|               | *06:06 | 0.002           | 100.0                               | 39.1                                | NA<sup>5</sup> | NA<sup>5</sup> | 0.987           |
|               | *06:07 | 0.004           | 100.0                               | 38.8                                | NA<sup>5</sup> | NA<sup>5</sup> | 0.987           |
|               | *06:08 | 0.019           | 60.0                                | 38.5                                | 3.76       | 0.97-14.65 | 0.056           |
|               | *06:09 | 0.002           | 0.0                                 | 39.5                                | NA<sup>5</sup> | NA<sup>5</sup> | 0.986           |
|               | *06:10 | 0.004           | 50.0                                | 39.2                                | 3.80       | 0.21-68.33 | 0.366           |
|               | *07:01 | 0.091           | 68.1                                | 32.9                                | 5.00       | 2.43-10.29 | 1.22x10<sup>-5</sup> |
|               | *07:02 | 0.037           | 42.1                                | 39.1                                | 1.19       | 0.44-3.19 | 0.736           |
|               | *08:01 | 0.051           | 23.1                                | 41.1                                | 0.46       | 0.17-1.25 | 0.128           |

<sup>1</sup> HLA-DQA1 allelic and HLA-DRB1–HLA-DQA1–HLA-DQB1 haplotypic odds ratios of asparaginase hypersensitivity reactions in ALL patients (n=257).

<sup>2</sup> Gene/haplotype %Hypersensitivity: carrier<sup>1</sup> and %Hypersensitivity: noncarrier<sup>2</sup> for asparaginase hypersensitivity reactions in ALL patients (n=257).

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

Results that reached the significance threshold (p≤2.66 x 10^-2) are in bold. <sup>1</sup>Percent of patients with hypersensitivities to asparaginase with the allele defined in column 1 and 2. <sup>2</sup>Percent of patients with hypersensitivities to asparaginase without the allele defined in column 1 and 2. <sup>3</sup>For the association between the allele and asparaginase hypersensitivity. <sup>4</sup>95% confidence interval for the estimated odds ratio. <sup>5</sup>The odds ratios and confidence intervals were not estimated due to low allele frequency.
Table S4. Regrouping of uncertain HLA-DQA1 allele results.

| Haplotype                                      | DQA1 allele |
|------------------------------------------------|-------------|
| HLA-DRB1*04:01–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:01 | 03:01^a     |
| HLA-DRB1*04:01–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:02 |             |
| HLA-DRB1*04:03–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:02 | 03:01      |
| HLA-DRB1*04:05–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:02 |             |
| HLA-DRB1*04:05–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:02 | 03:01      |
| HLA-DRB1*09:01–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:03 |             |
| HLA-DRB1*09:01–HLA-DQA1*03:01/*03:02–HLA-DQB1*03:03 | 03:01      |
| HLA-DRB1*10:01–HLA-DQA1*01:01/*01:04–HLA-DQB1*05:01 | 01:01^a     |
| HLA-DRB1*13:01–HLA-DQA1*01:02/*01:03–HLA-DQB1*06:03 | 01:03^b     |
| HLA-DRB1*13:03–HLA-DQA1*05:01/*05:05–HLA-DQB1*03:01 | 05:01^a     |