# Cyclosporine and methotrexate-related pharmacogenomic predictors of acute graft-*versus*-host disease

Isabelle Laverdière,[1] Chantal Guillemette,[1] Ryad Tamouza,[2] Pascale Loiseau,[2] Regis Peffault de Latour,[3] Marie Robin,[3] Félix Couture,[4] Alain Filion,[4] Marc Lalancette,[4] Alan Tourancheau,[1] Dominique Charron,[2] Gérard Socié,[3*] and Éric Lévesque[4*]

[1]Pharmacogenomics Laboratory, Centre Hospitalier de l'Université Laval (CHU de Québec) Research Center, Faculty of Pharmacy, Laval University, Québec, Canada; [2]INSERM UMRS 940, Institut Universitaire d'Hématologie, Université Paris-Diderot and Laboratoire d'Immunologie et d'Histocompatibilité, Hôpital Saint Louis, CIB-HOG, AP-HP, Paris, France; [3]Inserm UMRS 940, Institut Universitaire d'Hématologie, Université Paris-Diderot and Service d'Hématologie-Greffe de Moelle, Hôpital Saint-Louis, AP-HP, Paris, France; and [4]CHU de Québec Research Center; Faculty of Medicine, Laval University, Québec, Canada

**GS and EL contributed equally to this work.*

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*Correspondence: eric.levesque@crchuq.ulaval.ca or gerard.socie@paris7.jussieu.fr*

## Supplemental Methods

### *Polymorphisms selection*

The design of the present study involved two consecutive steps. An initial set of 219 haplotype-tagging SNPs (htSNPs) scattered along 20 candidate genes related to MTX/CsA pathways were initially selected in order to capture 935 allelic variations covering ≥80% of the genetic diversity in all genes, except for *NFAT1*, *NFAT2* and *UGT1A* (coverage of 79%, 47% and 69%, respectively) (**Figure 1**). In order to test the pertinence of the future SNPs to analyze in a large cohort of 420 HSCT recipient/donor pairs, we have firstly assessed this set of 219 htSNPs in an independent group of 104 HSCT recipient/donor pairs (**Supplementary Table 1**). The SNPs found to be associated with GvHD or risk of death with *p* values <0.10 were then genotyped in the large cohort of patients described below. After exclusion of SNPs not satisfying the Hardy-Weinberg proportions (*p* values <0.001) and having a minor allele frequency less than 5%, a remaining total of 59 SNPs (**Supplementary Table 2)** were subsequently studied.

### *Gene polymorphisms analyses*

EDTA or heparin-treated peripheral blood samples were collected before transplantation and stored at -80°C until DNA extraction. Genotyping was performed using iPLEX matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Sequanom, San Diego, CA, USA). For each run of analyses, negative controls was included and the robustness of assay was assessed by a random sample duplicates for 5% of patients with an overall replication rate of 99.5%.

**Supplementary Table 1. Patient, donor and transplant characteristics of the exploratory HSCT cohort (n=104).**

| Variables | Donors/Patients (n=104) | |
|---|---|---|
| **Patient age, n (%)** | | |
| <20 years | 19 | 18.3 |
| 20-50 years | 47 | 45.2 |
| >50 years | 38 | 36.5 |
| **Donor age, n (%)** | | |
| <20 years | 20 | (19.2) |
| 20-50 years | 43 | (41.3) |
| >50 years | 25 | (24.0) |
| Missing data | 16 | (15.4) |
| **Disease, n (%)** | | |
| Non-malignant haematological disorder | 10 | (9.6) |
| Haematological malignancy | 94 | (90.4) |
| **Donor type, n (%)** | | |
| Matched related | 87 | (83.7) |
| Mismatched related | 1 | (1.0) |
| Missing data | 16 | (15.4) |
| **Sex match (donor/patient), n (%)** | | |
| Male/male | 30 | (28.8) |
| Male /female | 20 | (19.2) |
| Female/male | 23 | (22.1) |
| Female/female | 15 | (14.4) |
| Missing data | 16 | (15.4) |
| **CMV match (donor/patient)** | | |
| Negative/negative | 35 | (33.7) |
| Negative/positive | 16 | (15.4) |
| Positive/negative | 6 | (5.8) |
| Positive/positive | 31 | (29.8) |
| Missing data | 16 | (15.4) |
| **Stem cell source, n (%)** | | |
| Bone marrow | 40 | (38.5) |
| Peripheral blood | 56 | (53.8) |
| Cord blood unit | 1 | (1.0) |
| Missing data | 7 | (6.7) |
| **Conditioning, n (%)** | | |
| Myeloablative | 81 | (77.9) |
| Non-myeloablative | 23 | (22.1) |
| **CsA prophylaxis, n (%)** | | |
| CSA ± others (without MTX) | 27 | (26.0) |
| CsA+MTX | 77 | (74.0) |
| **aGVHD grade II-IV, n (%)** | 30 | (28.8) |
| Time of occurrence, day (mean, range) | 26 | (11-75) |
| **cGVHD, n (%)** | 48 | (46.2) |
| Time of occurrence, day (mean, range) | 228 | (45-724) |
| **Survival status** | | |
| Alive | 66 | (63.5) |
| Dead | 35 | (33.7) |
| Missing data | 3 | (2.9) |
| **Follow-up of survivors, y (mean, range)** | 5.7 | (0.5-10) |

**Supplementary Table 2. SNPs selected and tested in the study cohort (n=420).**

| Gene(s) | SNP (n=74) | SNP position | Alleles | Maf (%) | Role | Amino acid change | Amino acid position |
|---|---|---|---|---|---|---|---|
| **ABCB1** | rs1055302 | chr7:87132916 | G/A | 10 | Downstream | - | - |
| | rs2235023 | chr7:87190452 | G/A | 11.1 | Intron | - | - |
| | rs4148732 | chr7:87234049 | A/G | 9.0 | Intron | - | - |
| | rs6950978 | chr7:87200467 | A/T | 24.3 | Intron | - | - |
| **ABCC1** | rs11075291 | chr16:16098475 | A/G | 41.2 | Intron | - | - |
| | rs17264736 | chr16:16116556 | T/G | 39.8 | Intron | - | - |
| | rs17579503 | chr16:16090801 | G/T | 9.7 | Intron | - | - |
| | rs212087 | chr16:16230290 | C/T | 38.9 | Intron (boundary) | - | - |
| | rs215073 | chr16:16085355 | G/A | 8.0 | Intron | - | - |
| | rs35597 | chr16:16158034 | G/A | 45.6 | Intron | - | - |
| | rs4148343 | chr16:16142358 | C/A | 14.4 | Intron | - | - |
| | rs4148355 | chr16:16174667 | A/G | 11.9 | Intron | - | - |
| | rs4781699 | chr16:16049633 | G/T | 32.3 | Intron | - | - |
| | rs4781712 | chr16:16103232 | G/A | 46.9 | Intron | - | - |
| | rs8054670 | chr16:16132134 | T/C | 21.2 | Intron | - | - |
| | rs8058040 | chr16:16107712 | A/G | 16.8 | Intron | - | - |
| **ABCC2** | rs3740065 | chr10:101605693 | T/C | 10.2 | Intron | - | - |
| | rs2002042 | chr10:101587931 | C/T | 28.3 | Intron | - | - |
| **ABCG2** | rs12505410 | chr4:89030841 | T/G | 38.5 | Intron | - | - |
| | rs13120400 | chr4:89033527 | T/C | 30.1 | Intron | - | - |
| **ATIC** | rs10191233 | chr2:216184222 | C/T | 35.6 | Intron | - | - |
| | rs12995526 | chr2:216197971 | C/T | 50.0 | Intron | - | - |
| | rs17514110 | chr2:216205484 | C/T | 7.5 | Intron | - | - |
| | rs2177735 | chr2:216207875 | T/C | 35.0 | Intron | - | - |
| | rs2372536 | chr2:216190020 | 347C/G | 27.5 | Coding exon | Thr/Ser | 116 |
| | rs7585489 | chr2:216181868 | C/T | 20.8 | Intron | - | - |
| **DHFR** | rs11951910 | chr5:79939471 | T/C | 7.5 | Intron | - | - |
| | rs34965641 | chr5:79942376 | C/T | 22.6 | Intron | - | - |
| **EEF1A1** | rs7751342 | chr6:74225145 | G/T | 27.9 | Downstream | - | - |
| **MTHFR** | rs1572151 | chr1:11857711 | A/G | 9.3 | Intron | - | - |
| | rs1801131 | chr1:11854476 | 1298A/C | 35.8 | Coding exon | Glu/Ala | 429 |
| | rs1801133 | chr1:11856378 | 677C/T | 31 | Coding exon | Ala/Val | 222 |
| | rs1994798 | chr1:11854755 | T/C | 46 | Intron (boundary) | - | - |
| | rs2274976 | chr1:11850927 | 1781G/A | 6.2 | Coding exon | Arg/Gln | 594 |
| | rs3737967 | chr1:11847449 | C/T | 6.9 | 3' UTR | - | - |
| | rs3753582 | chr1:11865542 | T/G | 12.5 | Intron | - | - |
| | rs3818762 | chr1:11851003 | C/G | 31.0 | Intron (boundary) | - | - |
| **NFATC1** | rs1017860 | chr18:77172206 | C/T | 19.9 | Intron | - | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | rs15350 | chr18:77211764 | T/C | 10.6 | Coding exon | Ser/Ser | 145 |
| | rs2036892 | chr18:77168536 | A/T | 45.0 | Intron | - | - |
| | rs304933 | chr18:77164443 | G/A | 19.0 | Intron | - | - |
| | rs7242726 | chr18:77209568 | G/C | 26.7 | Intron | - | - |
| | rs754093 | chr18:77246406 | T/G | 45.1 | Coding exon | Cys/Gly | 738 |
| | rs754505 | chr18:77226368 | G/A | 7.1 | Intron | - | - |
| | rs8090560 | chr18:77213155 | G/A | 20.4 | Intron | - | - |
| | rs8090692 | chr18:77163929 | A/G | 28.3 | Intron | - | - |
| | rs9953344 | chr18:77159355 | C/T | 9.3 | Intron | - | - |
| **NFATC2** | rs3787186 | chr20:50153344 | G/A | 36.4 | Intron | - | - |
| | rs3787193 | chr20:50109945 | G/C | 47.7 | Intron | - | - |
| | rs6123048 | chr20:50147400 | A/G | 5.3 | Intron | - | - |
| **PPIA** | rs11984372 | chr7:44841646 | A/C | 38.1 | 3' UTR | - | - |
| | rs6463247 | chr7:44839616 | T/C | 17.3 | Intron | - | - |
| **SLC19A1** | rs1051266 | chr21:46957794 | 80G/A | 43.8 | Coding exon | His/Arg | 27 |
| | rs4818789 | chr21:46948827 | T/G | 23.7 | Intron | - | - |
| | rs4819128 | chr21:46949649 | T/C | 41.6 | Intron | - | - |
| **TYMS** | rs2847153 | chr18:661647 | G/A | 17.7 | Intron | - | - |
| | rs9967368 | chr18:656020 | G/C | 35.7 | Promoter | - | - |
| **UGT1A** | rs17863795 | chr2:234651369 | T/C | 6.6 | Intron | - | - |
| | rs2018609 | chr2:234548576 | A/G | 31.4 | Intron | - | - |

Maf: minor allele frequency (%) of HapMap-CEU population reports by the *Single Nucleotide Polymorphism Database* (dbSNP), available from: http//www.ncbi.nhl.nih.gov/SNP.

SNP's position, alleles, amino acid change and its position were obtained from SNPper/Bioinformatics Tools, available from http//:snpper.chip.org (A. Riva, I.S. Kohane, *SNPper: retrieval of human SNPs,* Bioinformatics, 2002:18:1681-1685).

**Supplementary Table 3. Clinically relevant factors and their association with risk of GvHD.**

| **Variable** | **Categories** | **aGvHD 0-I vs II-IV** *(p value)* | **aGvHD 0-II vs III-IV** *(p value)* |
|---|---|---|---|
| ATG | Prophylaxis with *vs* without ATG | **<0.0001** | **0.0002** |
| Donor age | ≤20, 20-50 *vs* >50 years | **0.0003** | **0.0032** |
| Recipient age | ≤20, 20-50 *vs* >50 years | **0.0275** | **0.0439** |
| CMV status match | -/-, +/+ *vs* +/-,-/+ | 0.4327 | 0.8437 |
| Hematological disease | Malignant *vs* non malignant | **<0.0001** | **<0.0001** |
| HLA compatibility | Match related *vs* matched unrelated donor | **<0.0001** | **0.0024** |
| Conditioning regimen | Myeloablative *vs* reduces intensity regimen | 0.1628 | 0.4869 |
| Gender compatibility | Female donor to male recipient *vs* other | 0.3217 | 0.5871 |
| Stem cells sources | Bone marrow *vs* peripheral blood | **0.0016** | **0.0026** |
| TBI | <12 *vs* ≥12 gy | **<0.0001** | **0.0024** |

**Supplementary Table 4. Association of SNPs with grade II-IV aGVHD and competing risk of death prior aGVHD.**

| | | | | aGVHD ( grade II-IV) | | | | | Death prior aGVHD (grade II-IV) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | SNP | Maf (%) | [A]/[b] | Secondary mode[a] | | | | | Secondary model[a] | | | | |
| | | | | Mode | HR[b] | ( 95% CI ) | *p* value | *q* value | Mode | HR[b] | ( 95% CI ) | *p* value | *q* value |
| **RECIPIENT** | | | | | | | | | | | | | |
| ABCB1 | rs1055302 | 15 | G/A | Dom. | 1.18 | ( 0.85 - 1.63 ) | 0.318 | 0.523 | Dom. | 1.01 | ( 0.44 - 2.32 ) | 0.981 | 0.507 |
| | | | | Rec. | | | | | Rec. | | | | |
| ABCC1 | rs17264736 | 48 | G/T | Dom. | 0.72 | ( 0.51 - 1.03 ) | 0.073 | 0.339 | Dom. | 0.60 | ( 0.30 - 1.22 ) | 0.160 | 0.282 |
| | | | | Rec. | 0.69 | ( 0.51 - 0.95 ) | **0.021** | 0.211 | Rec. | 0.71 | ( 0.30 - 1.67 ) | 0.432 | 0.713 |
| ABCC1 | rs8054670 | 24 | T/C | Dom. | 0.91 | ( 0.68 - 1.20 ) | 0.493 | 0.645 | Dom. | 0.45 | ( 0.21 - 0.96 ) | **0.04** | 0.189 |
| | | | | Rec. | 1.10 | ( 0.67 - 1.80 ) | 0.713 | 0.365 | Rec. | 1.17 | ( 0.14 - 9.73 ) | 0.887 | 0.819 |
| ABCC1 | rs4148343 | 12 | C/A | Dom. | 0.81 | ( 0.58 - 1.12 ) | 0.199 | 0.500 | Dom. | 0.46 | ( 0.21 - 0.98 ) | **0.044** | 0.189 |
| | | | | Rec. | 0.95 | ( 0.34 - 2.64 ) | 0.925 | 0.384 | Rec. | 1.17 | ( 0.14 - 9.73 ) | 0.887 | 0.819 |
| ABCC2 | rs2002042 | 24 | C/T | Dom. | 0.95 | ( 0.71 - 1.29 ) | 0.759 | 0.738 | Dom. | 1.59 | ( 0.79 - 3.21 ) | 0.197 | 0.311 |
| | | | | Rec. | 1.97 | ( 1.02 - 3.78 ) | **0.042** | 0.211 | Rec. | 0.74 | ( 0.21 - 2.65 ) | 0.648 | 0.717 |
| ABCG2 | rs12505410 | 31 | T/G | Dom. | 0.73 | ( 0.55 - 0.97 ) | **0.029** | 0.191 | Dom. | 1.44 | ( 0.75 - 2.74 ) | 0.271 | 0.338 |
| | | | | Rec. | 0.79 | ( 0.50 - 1.26 ) | 0.325 | 0.314 | Rec. | 1.85 | ( 0.69 - 4.93 ) | 0.219 | 0.577 |
| ABCG2 | rs13120400 | 22 | T/C | Dom. | 0.68 | ( 0.51 - 0.92 ) | **0.011** | 0.087 | Dom. | 1.94 | ( 1.02 - 3.71 ) | **0.044** | 0.189 |
| | | | | Rec. | 0.67 | ( 0.36 - 1.22 ) | 0.188 | 0.282 | Rec. | 2.17 | ( 0.49 - 9.53 ) | 0.305 | 0.602 |
| ATIC | rs12995526 | 49 | C/T | Dom. | 0.94 | ( 0.69 - 1.28 ) | 0.685 | 0.721 | Dom. | 1.24 | ( 0.62 - 2.49 ) | 0.542 | 0.417 |
| | | | | Rec. | 0.77 | ( 0.55 - 1.07 ) | 0.119 | 0.261 | Rec. | 2.25 | ( 1.03 - 4.90 ) | **0.042** | 0.421 |
| ATIC | rs7585489 | 19 | C/T | Dom. | 1.09 | ( 0.81 - 1.47 ) | 0.559 | 0.645 | Dom. | 0.43 | ( 0.20 - 0.92 ) | **0.029** | 0.189 |
| | | | | Rec. | 0.87 | ( 0.44 - 1.70 ) | 0.682 | 0.361 | Rec. | 0.42 | ( 0.09 - 1.95 ) | 0.266 | 0.577 |
| NFATC1 | rs15350 | 24 | T/C | Dom. | 1.33 | ( 0.98 - 1.80 ) | 0.065 | 0.334 | Dom. | 0.65 | ( 0.31 - 1.36 ) | 0.253 | 0.329 |
| | | | | Rec. | | | | | Rec. | | | | |
| NFATC1 | rs2036892 | 46 | A/T | Dom. | 1.39 | ( 1.02 - 1.89 ) | **0.036** | 0.205 | Dom. | 1.04 | ( 0.50 - 2.17 ) | 0.923 | 0.486 |
| | | | | Rec. | 1.47 | ( 1.03 - 2.09 ) | **0.035** | 0.211 | Rec. | 1.07 | ( 0.51 - 2.24 ) | 0.863 | 0.819 |
| NFATC1 | rs754505 | 7 | G/A | Dom. | 1.12 | ( 0.77 - 1.64 ) | 0.555 | 0.645 | Dom. | 0.32 | ( 0.11 - 0.92 ) | **0.035** | 0.189 |
| | | | | Rec. | | | | | Rec. | | | | |
| NFATC1 | rs754093 | 48 | T/G | Dom. | 1.19 | ( 0.84 - 1.67 ) | 0.330 | 0.524 | Dom. | 0.92 | ( 0.47 - 1.80 ) | 0.801 | 0.445 |
| | | | | Rec. | 1.50 | ( 1.09 - 2.07 ) | **0.013** | 0.211 | Rec. | 1.58 | ( 0.73 - 3.40 ) | 0.243 | 0.577 |
| NFATC1 | rs8090692 | 32 | A/G | Dom. | 0.96 | ( 0.72 - 1.28 ) | 0.784 | 0.738 | Dom. | 1.31 | ( 0.66 - 2.62 ) | 0.443 | 0.380 |
| | | | | Rec. | 1.14 | ( 0.72 - 1.81 ) | 0.580 | 0.331 | Rec. | 6.11 | ( 1.33 - 28.05 ) | **0.020** | 0.413 |
| PPIA | rs11984372 | 29 | A/C | Dom. | 1.04 | ( 0.77 - 1.39 ) | 0.816 | 0.738 | Dom. | 0.90 | ( 0.46 - 1.74 ) | 0.751 | 0.434 |
| | | | | Rec. | 1.02 | ( 0.66 - 1.57 ) | 0.940 | 0.384 | Rec. | 0.08 | ( 0.02 - 0.40 ) | **0.002** | 0.093 |
| TYMS | rs9967368 | 37 | G/C | Dom. | 0.78 | ( 0.58 - 1.05 ) | 0.101 | 0.425 | Dom. | 0.38 | ( 0.19 - 0.79 ) | **0.009** | 0.189 |
| | | | | Rec. | 0.89 | ( 0.60 - 1.31 ) | 0.544 | 0.320 | Rec. | 1.02 | ( 0.44 - 2.36 ) | 0.956 | 0.844 |
| **DONOR** | | | | | | | | | | | | | |
| ABCC1 | rs4148343 | 12 | C/A | Dom. | 0.89 | ( 0.65 - 1.24 ) | 0.496 | 0.949 | Dom. | 0.37 | ( 0.18 - 0.77 ) | **0.008** | 0.377 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Rec. | | | | | | Rec. | | | | |
| ABCC2 | rs3740065 | 16 | T/C | Dom. | 1.00 | ( 0.73 - 1.38 ) | 0.999 | 0.999 | | Dom. | 0.52 | ( 0.22 - 1.20 ) | 0.126 | 0.587 |
| | | | | Rec. | 1.60 | ( 0.55 - 4.63 ) | 0.384 | 0.706 | | Rec. | 2.75 | ( 0.55 - 13.86 ) | 0.219 | 0.299 |
| ABCG2 | rs12505410 | 29 | T/G | Dom. | 0.89 | ( 0.67 - 1.19 ) | 0.445 | 0.949 | | Dom. | 1.54 | ( 0.70 - 3.36 ) | 0.282 | 0.650 |
| | | | | Rec. | 1.18 | ( 0.78 - 1.77 ) | 0.437 | 0.714 | | Rec. | 8.12 | ( 1.57 - 42.07 ) | **0.013** | 0.069 |
| ABCG2 | rs13120400 | 22 | T/C | Dom. | 0.92 | ( 0.69 - 1.22 ) | 0.549 | 0.949 | | Dom. | 1.01 | ( 0.50 - 2.06 ) | 0.976 | 0.786 |
| | | | | Rec. | 1.52 | ( 0.91 - 2.55 ) | 0.112 | 0.600 | | Rec. | 8.12 | ( 1.57 - 42.07 ) | **0.013** | 0.069 |
| ATIC | rs7585489 | 17 | C/T | Dom. | 1.05 | ( 0.76 - 1.43 ) | 0.775 | 0.952 | | Dom. | 0.89 | ( 0.46 - 1.71 ) | 0.719 | 0.753 |
| | | | | Rec. | 1.00 | ( 0.52 - 1.92 ) | 0.989 | 0.878 | | Rec. | 1.17 | ( 0.14 - 9.73 ) | 0.887 | 0.537 |
| EEF1A1 | rs7751342 | 40 | G/T | Dom. | 0.73 | ( 0.54 - 0.99 ) | **0.040** | 0.920 | | Dom. | 1.02 | ( 0.54 - 1.91 ) | 0.952 | 0.779 |
| | | | | Rec. | 0.97 | ( 0.63 - 1.49 ) | 0.876 | 0.866 | | Rec. | 3.02 | ( 1.13 - 8.08 ) | **0.028** | 0.127 |
| MTHFR | rs1801133 | 27 | C/T | Dom. | 0.98 | ( 0.73 - 1.33 ) | 0.908 | 0.957 | | Dom. | 1.12 | ( 0.55 - 2.30 ) | 0.747 | 0.753 |
| | | | | Rec. | 2.19 | ( 1.31 - 3.66 ) | **0.003** | 0.062 | | Rec. | 4.69 | ( 1.60 - 13.72 ) | **0.005** | 0.065 |
| NFATC1 | rs304933 | 25 | G/A | Dom. | 0.74 | ( 0.55 - 0.98 ) | **0.035** | 0.920 | | Dom. | 1.42 | ( 0.76 - 2.66 ) | 0.275 | 0.65 |
| | | | | Rec. | 0.95 | ( 0.55 - 1.62 ) | 0.837 | 0.866 | | Rec. | 6.16 | ( 1.83 - 20.74 ) | **0.003** | 0.065 |
| NFATC1 | rs754093 | 43 | T/G | Dom. | 1.18 | ( 0.84 - 1.65 ) | 0.335 | 0.949 | | Dom. | 1.96 | ( 0.89 - 4.29 ) | 0.093 | 0.482 |
| | | | | Rec. | 1.28 | ( 0.92 - 1.79 ) | 0.149 | 0.600 | | Rec. | 2.30 | ( 0.92 - 5.80 ) | 0.076 | 0.214 |
| NFATC1 | rs754505 | 8 | G/A | Dom. | 0.94 | ( 0.65 - 1.36 ) | 0.741 | 0.951 | | Dom. | 1.54 | ( 0.66 - 3.61 ) | 0.322 | 0.650 |
| | | | | Rec. | | | | | | Rec. | | | | |
| NFATC1 | rs8090560 | 29 | G/A | Dom. | 0.74 | ( 0.55 - 1.00 ) | **0.047** | 0.920 | | Dom. | 0.65 | ( 0.31 - 1.35 ) | 0.245 | 0.650 |
| | | | | Rec. | 1.33 | ( 0.81 - 2.18 ) | 0.257 | 0.642 | | Rec. | 0.89 | ( 0.28 - 2.85 ) | 0.841 | 0.521 |
| NFATC1 | rs9953344 | 14 | C/T | Dom. | 0.79 | ( 0.57 - 1.09 ) | 0.144 | 0.949 | | Dom. | 1.36 | ( 0.67 - 2.76 ) | 0.399 | 0.662 |
| | | | | Rec. | 1.00 | ( 0.45 - 2.19 ) | 0.992 | 0.878 | | Rec. | 12.0 | ( 1.74 - 82.93 ) | **0.012** | 0.069 |
| NFATC2 | rs3787186 | 31 | G/A | Dom. | 1.12 | ( 0.84 - 1.49 ) | 0.431 | 0.949 | | Dom. | 0.43 | ( 0.21 - 0.89 ) | **0.022** | 0.465 |
| | | | | Rec. | 1.39 | ( 0.92 - 2.09 ) | 0.117 | 0.600 | | Rec. | 0.84 | ( 0.35 - 2.05 ) | 0.709 | 0.495 |
| UGT1A | rs17863795 | 3 | T/C | Dom. | 1.05 | ( 0.60 - 1.85 ) | 0.854 | 0.957 | | Dom. | 0.31 | ( 0.10 - 0.95 ) | **0.041** | 0.465 |
| | | | | Rec. | | | | | | Rec. | | | | |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q values* ≤ 0.05 are in bold characters.

a, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

b, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD.

Data are not shown for bb genotype with low frequency (<2%).

**Supplementary Table 5. Association of SNPs with grade III-IV aGVHD and competing risk of death prior aGVHD.**

| | | | | aGVHD (grade III-IV) | | | | | | Death prior aGVHD (grade III-IV) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | SNP | Maf (%) | [A]/[b] | Secondary mode[a] | | | | | | Secondary model[a] | | | | | |
| | | | | Mode | HR[b] | ( | 95% CI | ) | *p* value | *q* value | Mode | HR[b] | ( | 95% CI | ) *p* value | *q* value |
| **RECIPIENT** | | | | | | | | | | | | | | | | |
| ABCC1 | rs4148343 | 12 | C/A | Dom. | 1.97 | ( | 1.02 - 3.82 | ) | **0.044** | 0.140 | Dom. | 0.69 | ( | 0.43 - 1.12 | ) 0.134 | 0.384 |
| | | | | Rec. | 1.94 | ( | 0.37 - 10.21 | ) | 0.436 | 0.100 | Rec. | 1.03 | ( | 0.14 - 7.72 | ) 0.981 | 0.857 |
| ABCC1 | rs4148355 | 14 | A/G | Dom. | 1.31 | ( | 0.65 - 2.64 | ) | 0.450 | 0.321 | Dom. | 1.69 | ( | 1.06 - 2.72 | ) **0.029** | 0.263 |
| | | | | Rec. | 1.44 | ( | 0.18 - 11.49 | ) | 0.730 | 0.122 | Rec. | 2.92 | ( | 0.62 - 13.71 | ) 0.174 | 0.483 |
| ABCC2 | rs2002042 | 24 | C/T | Dom. | 0.53 | ( | 0.29 - 1.00 | ) | **0.049** | 0.140 | Dom. | 1.37 | ( | 0.89 - 2.13 | ) 0.154 | 0.413 |
| | | | | Rec. | 1.97 | ( | 0.61 - 6.39 | ) | 0.261 | 0.083 | Rec. | 0.96 | ( | 0.37 - 2.48 | ) 0.929 | 0.857 |
| ATIC | rs12995526 | 49 | C/T | Dom. | 0.57 | ( | 0.25 - 1.28 | ) | 0.174 | 0.234 | Dom. | 1.55 | ( | 0.97 - 2.47 | ) 0.065 | 0.299 |
| | | | | Rec. | 0.91 | ( | 0.41 - 2.02 | ) | 0.814 | 0.126 | Rec. | 1.78 | ( | 1.08 - 2.91 | ) **0.023** | 0.266 |
| ATIC | rs17514110 | 8 | C/T | Dom. | 1.59 | ( | 0.62 - 4.03 | ) | 0.332 | 0.302 | Dom. | 0.58 | ( | 0.34 - 1.02 | ) 0.058 | 0.293 |
| | | | | Rec. | | | | | | | Rec. | | | | | |
| ATIC | rs2372536 | 28 | C/G | Dom. | 2.20 | ( | 1.14 - 4.24 | ) | **0.019** | 0.097 | Dom. | 0.93 | ( | 0.61 - 1.43 | ) 0.739 | 0.726 |
| | | | | Rec. | 2.04 | ( | 0.74 - 5.59 | ) | 0.167 | 0.068 | Rec. | 0.48 | ( | 0.25 - 0.93 | ) **0.028** | 0.266 |
| ATIC | rs7585489 | 19 | C/T | Dom. | 0.59 | ( | 0.30 - 1.15 | ) | 0.123 | 0.194 | Dom. | 0.92 | ( | 0.60 - 1.43 | ) 0.724 | 0.726 |
| | | | | Rec. | 0.03 | ( | 0.001 - 0.83 | ) | **0.039** | 0.065 | Rec. | 0.41 | ( | 0.17 - 1.01 | ) 0.053 | 0.286 |
| DHFR | rs34965641 | 30 | C/T | Dom. | 0.51 | ( | 0.28 - 0.95 | ) | **0.033** | 0.140 | Dom. | 1.48 | ( | 0.95 - 2.30 | ) 0.082 | 0.312 |
| | | | | Rec. | 0.79 | ( | 0.18 - 3.51 | ) | 0.754 | 0.123 | Rec. | 0.93 | ( | 0.47 - 1.84 | ) 0.835 | 0.857 |
| EEF1A1 | rs7751342 | 41 | G/T | Dom. | 0.72 | ( | 0.38 - 1.34 | ) | 0.294 | 0.275 | Dom. | 1.34 | ( | 0.86 - 2.09 | ) 0.201 | 0.454 |
| | | | | Rec. | 0.70 | ( | 0.30 - 1.60 | ) | 0.394 | 0.100 | Rec. | 2.03 | ( | 1.03 - 3.99 | ) **0.041** | 0.286 |
| NFATC1 | rs2036892 | 46 | A/T | Dom. | 1.42 | ( | 0.74 - 2.70 | ) | 0.293 | 0.275 | Dom. | 0.80 | ( | 0.52 - 1.24 | ) 0.313 | 0.530 |
| | | | | Rec. | 2.19 | ( | 1.02 - 4.71 | ) | **0.044** | 0.065 | Rec. | 0.93 | ( | 0.57 - 1.52 | ) 0.783 | 0.857 |
| NFATC1 | rs8090692 | 32 | A/G | Dom. | 0.87 | ( | 0.47 - 1.62 | ) | 0.662 | 0.418 | Dom. | 1.42 | ( | 0.90 - 2.25 | ) 0.130 | 0.384 |
| | | | | Rec. | 0.79 | ( | 0.37 - 1.72 | ) | 0.56 | 0.107 | Rec. | 2.74 | ( | 1.25 - 6.00 | ) **0.012** | 0.266 |
| NFATC1 | rs9953344 | 14 | C/T | Dom. | 0.51 | ( | 0.26 - 0.99 | ) | **0.046** | 0.140 | Dom. | 1.06 | ( | 0.69 - 1.65 | ) 0.780 | 0.741 |
| | | | | Rec. | 2.93 | ( | 0.36 - 24.1 | ) | 0.317 | 0.095 | Rec. | 3.07 | ( | 0.69 - 13.73 | ) 0.142 | 0.483 |
| PPIA | rs11984372 | 29 | A/C | Dom. | 0.45 | ( | 0.23 - 0.85 | ) | **0.014** | 0.088 | Dom. | 1.40 | ( | 0.93 - 2.10 | ) 0.109 | 0.356 |
| | | | | Rec. | 0.49 | ( | 0.21 - 1.14 | ) | 0.098 | 0.065 | Rec. | 0.79 | ( | 0.32 - 1.95 | ) 0.606 | 0.798 |
| TYMS | rs2847153 | 22 | G/A | Dom. | 0.53 | ( | 0.28 - 1.00 | ) | **0.050** | 0.140 | Dom. | 0.80 | ( | 0.52 - 1.22 | ) 0.293 | 0.516 |
| | | | | Rec. | 0.86 | ( | 0.25 3.01 | ) | 0.813 | 0.126 | Rec. | 3.42 | ( | 1.26 9.30 | ) **0.016** | 0.266 |
| **DONOR** | | | | | | | | | | | | | | | | |
| ABCB1 | rs4148732 | 13 | A/G | Dom. | 2.23 | ( | 1.14 - 4.34 | ) | **0.018** | 0.147 | Dom. | 1.03 | ( | 0.64 - 1.65 | ) 0.902 | 0.666 |
| | | | | Rec. | 6.89 | ( | 0.77 - 61.35 | ) | 0.084 | 0.343 | Rec. | 1.83 | ( | 0.41 - 8.23 | ) 0.430 | 0.921 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ABCC1 | rs11075291 | 45 | A/G | Dom. | 0.75 | ( 0.39 - 1.47 ) | 0.408 | 0.480 | Dom. | 1.06 | ( 0.70 - 1.59 ) | 0.785 | 0.643 |
| | | | | Rec. | 0.38 | ( 0.15 - 0.96 ) | **0.040** | 0.289 | Rec. | 1.06 | ( 0.59 - 1.92 ) | 0.846 | 0.957 |
| ABCC1 | rs215073 | 7 | G/A | Dom. | 1.93 | ( 0.74 - 5.03 ) | 0.181 | 0.349 | Dom. | 0.80 | ( 0.42 - 1.52 ) | 0.501 | 0.538 |
| | | | | Rec. | 13.9 | ( 1.31 - 149.25 ) | **0.029** | 0.289 | Rec. | 0.69 | ( 0.09 - 5.21 ) | 0.721 | 0.935 |
| ABCC1 | rs4148343 | 12 | C/A | Dom. | 0.54 | ( 0.28 - 1.03 ) | 0.063 | 0.228 | Dom. | 0.88 | ( 0.56 - 1.39 ) | 0.592 | 0.564 |
| | | | | Rec. | 1.02 | ( 0.25 - 4.08 ) | 0.978 | 0.752 | Rec. | 0.83 | ( 0.11 - 6.54 ) | 0.859 | 0.957 |
| ATIC | rs2177735 | 42 | T/C | Dom. | 1.96 | ( 1.00 - 3.85 ) | **0.049** | 0.220 | Dom. | 1.01 | ( 0.65 - 1.58 ) | 0.961 | 0.674 |
| | | | | Rec. | 1.06 | ( 0.53 - 2.11 ) | 0.871 | 0.752 | Rec. | 0.78 | ( 0.48 - 1.26 ) | 0.312 | 0.921 |
| EEF1A1 | rs7751342 | 40 | G/T | Dom. | 0.94 | ( 0.51 - 1.73 ) | 0.843 | 0.677 | Dom. | 1.12 | ( 0.74 - 1.7 ) | 0.583 | 0.564 |
| | | | | Rec. | 1.50 | ( 0.58 - 3.82 ) | 0.402 | 0.556 | Rec. | 2.45 | ( 1.33 - 4.49 ) | **0.004** | 0.189 |
| MTHFR | rs1801131 | 29 | A/C | Dom. | 1.12 | ( 0.63 - 2.00 ) | 0.703 | 0.645 | Dom. | 1.15 | ( 0.76 - 1.73 ) | 0.517 | 0.538 |
| | | | | Rec. | 0.37 | ( 0.14 - 0.99 ) | **0.047** | 0.289 | Rec. | 1.20 | ( 0.66 - 2.17 ) | 0.550 | 0.930 |
| MTHFR | rs2274976 | 4 | G/A | Dom. | 0.33 | ( 0.11 - 0.99 ) | **0.047** | 0.220 | Dom. | 2.12 | ( 1.15 - 3.89 ) | **0.016** | 0.310 |
| | | | | Rec. | | | | | Rec. | | | | |
| MTHFR | rs3737967 | 4 | C/T | Dom. | 0.33 | ( 0.11 - 0.99 ) | **0.047** | 0.220 | Dom. | 2.01 | ( 1.07 - 3.75 ) | **0.029** | 0.312 |
| | | | | Rec. | | | | | Rec. | | | | |
| MTHFR | rs3818762 | 26 | C/G | Dom. | 1.02 | ( 0.58 - 1.81 ) | 0.936 | 0.677 | Dom. | 1.16 | ( 0.77 - 1.74 ) | 0.493 | 0.538 |
| | | | | Rec. | 0.27 | ( 0.09 - 0.79 ) | **0.017** | 0.289 | Rec. | 1.17 | ( 0.63 - 2.18 ) | 0.625 | 0.930 |
| NFATC1 | rs754093 | 43 | T/G | Dom. | 1.70 | ( 0.90 - 3.24 ) | 0.104 | 0.297 | Dom. | 2.04 | ( 1.18 - 3.52 ) | **0.011** | 0.310 |
| | | | | Rec. | 2.00 | ( 1.00 - 4.01 ) | **0.050** | 0.289 | Rec. | 1.4 | ( 0.82 - 2.40 ) | 0.215 | 0.921 |
| NFATC1 | rs754505 | 8 | G/A | Dom. | 0.48 | ( 0.24 - 0.97 ) | **0.042** | 0.220 | Dom. | 1.24 | ( 0.68 - 2.28 ) | 0.478 | 0.538 |
| | | | | Rec. | | | | | Rec. | | | | |
| PPIA | rs11984372 | 30 | A/C | Dom. | 1.11 | ( 0.60 - 2.05 ) | 0.733 | 0.645 | Dom. | 1.63 | ( 1.04 - 2.53 ) | **0.031** | 0.312 |
| | | | | Rec. | 0.42 | ( 0.15 - 1.18 ) | 0.101 | 0.343 | Rec. | 0.50 | ( 0.17 - 1.47 ) | 0.209 | 0.921 |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q values* ≤ 0.05 are in bold characters.

a, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

b, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD.

Data are not shown for bb genotype with low frequency (<2%).

**Supplementary Table 6. Association between positive SNPs and clinical variables.**

| Variable (Additive model) | Recipient | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | *q value* | | | | | | | | | | |
| | rs17264736 | rs212087 | rs2177735 | rs2274976 | rs3737967 | rs3740065 | rs6950978 | rs8058040 | rs1017860 | rs12505410 | rs131204( |
| ATG | **0.0265** | 0.2463 | 0.2303 | 0.3221 | 0.3221 | 0.2990 | **0.0373** | 0.1103 | 0.2154 | 0.2463 | 0.1005 |
| Donor age | **0.0044** | **0.0486** | 0.2046 | **0.0147** | **0.0147** | **0.0027** | 0.1437 | **0.0177** | 0.3404 | 0.2043 | **0.0468** |
| Recipient age | **0.0219** | 0.2463 | 0.3398 | 0.3398 | 0.3398 | **0.0240** | 0.0692 | 0.1509 | 0.2399 | 0.2788 | 0.0784 |
| CMV status match | 0.3057 | 0.3398 | 0.2996 | 0.3377 | 0.3377 | 0.3549 | 0.2506 | 0.3392 | 0.2951 | 0.2963 | 0.2784 |
| Hematological disease | **0.0030** | 0.0864 | 0.0612 | 0.3398 | 0.3398 | **0.0314** | **0.0048** | **0.0139** | 0.3377 | **0.0092** | **0.0030** |
| HLA compatibility | **0.0027** | **0.0341** | 0.1103 | 0.3404 | 0.3406 | **0.0207** | 0.0784 | **0.0468** | 0.2784 | 0.0584 | **0.0030** |
| Conditioning regimen | 0.1689 | 0.0612 | 0.3599 | 0.3398 | 0.3398 | 0.1323 | 0.3791 | 0.2547 | 0.1906 | 0.1876 | 0.3377 |
| Gender compatibility | 0.1153 | 0.3110 | 0.2046 | 0.1689 | 0.1689 | 0.2974 | 0.2428 | **0.0030** | 0.3661 | 0.0677 | 0.0701 |
| Stem cells sources | **0.0314** | 0.2990 | 0.2043 | 0.3174 | 0.3174 | 0.3110 | **0.0147** | 0.1496 | 0.3377 | 0.2750 | 0.1689 |
| TBI | 0.0558 | **0.0179** | 0.3599 | 0.3174 | 0.3174 | 0.0558 | 0.3221 | 0.3211 | 0.1689 | 0.1208 | 0.0922 |

| Variable (Additive model) | Recipient | | | | | Donor | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *q value* | | | | | *q value* | | | | |
| | rs17514110 | rs4148732 | rs4781712 | rs6123048 | rs8090560 | rs4818789 | rs1051266 | rs34965641 | rs3787186 | rs4819128 |
| ATG | 0.3791 | 0.1861 | 0.3174 | 0.2428 | 0.3110 | 0.1689 | 0.1295 | 0.2043 | 0.2463 | 0.1437 |
| Donor age | 0.1617 | 0.0558 | 0.3057 | 0.2980 | **0.0476** | **0.0402** | 0.1515 | 0.3404 | **0.0030** | 0.1103 |
| Recipient age | 0.1926 | **0.0398** | 0.3385 | 0.2463 | 0.0502 | 0.1093 | 0.1689 | 0.3398 | **0.0179** | 0.0558 |
| CMV status match | 0.3795 | 0.2090 | 0.1732 | 0.2043 | 0.2506 | 0.3377 | 0.1617 | **0.0323** | 0.3791 | 0.1617 |
| Hematological disease | 0.3599 | **0.0080** | 0.3398 | 0.3110 | **0.0373** | 0.0584 | 0.2547 | 0.2703 | **0.0051** | **0.0439** |
| HLA compatibility | 0.1878 | 0.3398 | **0.0253** | 0.1437 | **0.0468** | 0.1230 | 0.3110 | 0.2703 | **0.0027** | 0.1295 |
| Conditioning regimen | 0.0758 | 0.2788 | 0.3110 | 0.2506 | **0.0398** | 0.0677 | 0.3110 | 0.2547 | 0.1509 | 0.3791 |
| Gender compatibility | 0.1876 | 0.1358 | 0.1876 | 0.2547 | 0.1437 | 0.0632 | 0.1732 | 0.3377 | 0.3404 | 0.2959 |
| Stem cells sources | 0.3791 | 0.2990 | 0.1615 | 0.3174 | 0.1153 | 0.2784 | 0.1295 | 0.2996 | **0.0114** | 0.1927 |
| TBI | 0.3599 | 0.3018 | 0.3221 | 0.2463 | 0.1876 | 0.1711 | 0.3280 | 0.3398 | **0.0369** | 0.1729 |

*q* values represent the statistical significance of association after correction for multiple comparison testing.

**Supplementary Table 7. SNPs associated with grade II-IV aGvHD after exclusion of patients receiving mismatched unrelated transplant.**

| Gene | SNP | A/b | Genomic model[a] | | | | Secondary model[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mode | HR[c] | 95% CI | *p* value | Mode | HR[c] | 95% CI | *p* value |
| **aGVHD (grade II-IV)** | | | | | | | | | | |
| **RECIPIENT** | | | | | | | | | | |
| ATIC | rs17514110 | C/T | [Ab] [bb] | 1.94 | (1.21 - 3.12) | **0.006** | Dom. Rec. | 1.94 | (1.21 - 3.12) | **0.006** |
| MTHFR | rs2274976 | G/A | [Ab] [bb] | 2.66 | (1.48 - 4.79) | **0.001** | Dom. Rec. | 2.66 | (1.48 - 4.79) | **0.001** |
| MTHFR | rs3737967 | C/T | [Ab] [bb] | 2.66 | (1.48 - 4.79) | **0.001** | Dom. Rec. | 2.66 | (1.48 - 4.79) | **0.001** |
| NFATC1 | rs1017860 | C/T | [Ab] | 1.49 | (1.06 - 2.08) | **0.021** | Dom. | 1.53 | (1.10 - 2.13) | **0.011** |
| | | | [bb] | 2.45 | (0.98 - 6.14) | 0.056 | Rec. | 2.10 | (0.85 - 5.20) | 0.110 |
| NFATC2 | rs6123048 | A/G | [Ab] [bb] | 2.46 | (1.48 - 4.10) | **0.001** | Dom. Rec. | 2.46 | (1.48 - 4.10) | **0.001** |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q values* ≤ 0.05 are in bold characters.

a, Genomic model= [AA] vs. [Ab] and [bb], reference group=[AA] (HR fixed at 1.00).

b, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

c, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD. Data are not shown for bb genotype with low frequency (<2%).

**Supplementary Table 8. SNPs associated with the competing risk of death prior grade II-IV aGVHD after exclusion of patients receiving mismatched unrelated transplar**

| Gene | SNP | A/b | Genomic model[a] | | | | Secondary model[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mode | HR[c] | 95% CI | *p* value | Mode | HR[c] | 95% CI | *p* value |
| **Death prior aGVHD (grade II-IV)** | | | | | | | | | | |
| **RECIPIENT** | | | | | | | | | | |
| ATIC | rs17514110 | C/T | [Ab] | 0.36 | (0.10 - 1.33) | 0.125 | Dom. | 0.41 | (0.12 - 1.40) | 0.154 |
| | | | [bb] | | | | Rec. | | | |
| MTHFR | rs2274976 | G/A | [Ab] | 0.64 | (0.14 - 2.80) | 0.549 | Dom. | 0.85 | (0.23 - 3.24) | 0.817 |
| | | | [bb] | 3.93 | (0.28 - 54.34) | 0.307 | Rec. | | | |
| MTHFR | rs3737967 | C/T | [Ab] | 0.64 | (0.14 - 2.80) | 0.549 | Dom. | 0.85 | (0.23 - 3.24) | 0.817 |
| | | | [bb] | 3.93 | (0.28 - 54.34) | 0.307 | Rec. | | | |
| NFATC1 | rs1017860 | C/T | [Ab] | 2.30 | (1.00 - 5.28) | **0.049** | Dom. | 1.87 | (0.84 - 4.15) | 0.125 |
| | | | [bb] | 0.79 | (0.18 - 3.43) | 0.752 | Rec. | 0.56 | (0.14 - 2.21) | 0.407 |
| NFATC2 | rs6123048 | A/G | [Ab] | 0.82 | (0.29 - 2.27) | 0.698 | Dom. | 0.82 | (0.29 - 2.27) | 0.698 |
| | | | [bb] | | | | Rec. | | | |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q value*s ≤ 0.05 are in bold characters.

a, Genomic model= [AA] vs. [Ab] and [bb], reference group=[AA] (HR fixed at 1.00).

b, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

c, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD. Data are not shown for bb genotype with low frequency (<2%).

**Supplementary Table 9. SNPs associated with grade III-IV aGvHD after exclusion of patients receiving mismatched unrelated transplant.**

| Gene | SNP | A/b | Genomic model[a] | | | | Secondary model[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mode | HR[c] | 95% CI | *p* value | Mode | HR[c] | 95% CI | *p* value |
| **aGVHD (grade III-IV)** | | | | | | | | | | |
| **RECIPIENT** | | | | | | | | | | |
| ABCB1 | rs4148732 | A/G | [Ab] | 0.84 | (0.42 - 1.71) | 0.636 | Dom. | 0.92 | (0.46 - 1.83) | 0.819 |
| | | | [bb] | 6.60 | (0.71 - 61.49) | 0.097 | Rec. | 6.76 | (0.73 - 62.40) | 0.092 |
| ABCB1 | rs6950978 | A/T | [Ab] | 0.53 | (0.22 - 1.27) | 0.155 | Dom. | 0.76 | (0.37 - 1.60) | 0.473 |
| | | | [bb] | 1.45 | (0.53 - 3.97) | 0.466 | Rec. | 1.70 | (0.62 - 4.69) | 0.303 |
| ABCC1 | rs17264736 | G/T | [Ab] | 0.73 | (0.27 - 2.02) | 0.548 | Dom. | 0.50 | (0.21 - 1.15) | 0.103 |
| | | | [bb] | 0.41 | (0.17 - 1.01) | **0.052** | Rec. | 0.49 | (0.24 - 1.00) | **0.050** |
| ABCC1 | rs212087 | C/T | [Ab] | 1.09 | (0.54 - 2.18) | 0.816 | Dom. | 1.12 | (0.57 - 2.20) | 0.747 |
| | | | [bb] | 1.31 | (0.44 - 3.91) | 0.627 | Rec. | 1.24 | (0.46 - 3.35) | 0.668 |
| ABCC1 | rs4781712 | A/G | [Ab] | 1.01 | (0.40 - 2.53) | 0.987 | Dom. | 0.64 | (0.29 - 1.42) | 0.275 |
| | | | [bb] | 0.46 | (0.19 - 1.13) | 0.089 | Rec. | 0.46 | (0.22 - 0.97) | **0.040** |
| ABCC1 | rs8058040 | A/G | [Ab] | 3.39 | (1.45 - 7.95) | **0.005** | Dom. | 3.61 | (1.60 - 8.15) | **0.002** |
| | | | [bb] | 6.92 | (0.53 - 90.03) | 0.139 | Rec. | 7.06 | (0.55 - 89.84) | 0.132 |
| ABCC2 | rs3740065 | T/C | [Ab] | 3.15 | (1.34 - 7.41) | **0.009** | Dom. | 3.15 | (1.34 - 7.41) | **0.009** |
| | | | [bb] | | | | Rec. | | | |
| ABCG2 | rs12505410 | T/G | [Ab] | 0.80 | (0.36 - 1.77) | 0.576 | Dom. | 0.63 | (0.32 - 1.26) | 0.194 |
| | | | [bb] | 0.39 | (0.11 - 1.35) | 0.135 | Rec. | 0.40 | (0.11 - 1.40) | 0.151 |
| ABCG2 | rs13120400 | T/C | [Ab] | 0.99 | (0.48 - 2.05) | 0.988 | Dom. | 0.75 | (0.38 - 1.44) | 0.384 |
| | | | [bb] | 0.28 | (0.06 - 1.32) | 0.108 | Rec. | 0.28 | (0.06 - 1.32) | 0.108 |
| ATIC | rs2177735 | T/C | [Ab] | 2.26 | (1.01 - 5.06) | **0.047** | Dom. | 2.33 | (1.09 - 4.97) | **0.028** |
| | | | [bb] | 2.59 | (0.76 - 8.86) | 0.129 | Rec. | 1.85 | (0.57 - 5.97) | 0.306 |
| NFATC1 | rs8090560 | G/A | [Ab] | 1.82 | (0.85 - 3.87) | 0.123 | Dom. | 1.99 | (1.00 - 3.94) | **0.050** |
| | | | [bb] | 2.35 | (0.97 - 5.66) | 0.057 | Rec. | 1.80 | (0.81 - 3.97) | 0.147 |
| **DONOR** | | | | | | | | | | |
| DHFR | rs34965641 | C/T | [Ab] | 0.39 | (0.19 - 0.80) | **0.011** | Dom. | 0.38 | (0.19 - 0.77) | **0.008** |
| | | | [bb] | 0.34 | (0.08 - 1.45) | 0.144 | Rec. | 0.61 | (0.16 - 2.34) | 0.467 |
| NFATC2 | rs3787186 | G/A | [Ab] | 1.05 | (0.48 - 2.29) | 0.911 | Dom. | 1.35 | (0.65 - 2.78) | 0.425 |
| | | | [bb] | 2.81 | (1.06 - 7.48) | **0.038** | Rec. | 2.74 | (1.14 - 6.59) | **0.024** |
| SLC19A1 | rs1051266* | G/A | [Ab] | 0.32 | (0.15 - 0.70) | **0.004** | Dom. | 0.40 | (0.19 - 0.82) | **0.012** |
| | | | [bb] | 0.64 | (0.26 - 1.54) | 0.316 | Rec. | 1.41 | (0.70 - 2.88) | 0.338 |
| SLC19A1 | rs4818789 | T/G | [Ab] | 0.21 | (0.08 - 0.54) | **0.001** | Dom. | 0.33 | (0.16 - 0.71) | **0.004** |
| | | | [bb] | 0.55 | (0.23 - 1.31) | 0.176 | Rec. | 1.15 | (0.52 - 2.54) | 0.730 |
| SLC19A1 | rs4819128 | T/C | [Ab] | 0.28 | (0.13 - 0.63) | **0.002** | Dom. | 0.39 | (0.19 - 0.79) | **0.009** |
| | | | [bb] | 0.66 | (0.28 - 1.55) | 0.338 | Rec. | 1.45 | (0.71 - 2.98) | 0.311 |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q value*s ≤ 0.05 are in bold characters.

a, Genomic model= [AA] vs. [Ab] and [bb], reference group=[AA] (HR fixed at 1.00).

b, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

c, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD. Data are not shown for bb genotype with low frequency (<2%).

**Supplementary Table 10. SNPs associated with the competing risk of death prior grade III-IV aGVHD after exclusion of patients receiving mismatched unrelated transpla**

| Gene | SNP | A/b | Genomic model[a] | | | | Secondary model[b] | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mode | HR[c] | 95% CI | *p* value | Mode | HR[c] | 95% CI | *p* value |
| **Death prior aGVHD (grade III-IV)** | | | | | | | | | | |
| **RECIPIENT** | | | | | | | | | | |
| ABCB1 | rs4148732 | A/G | [Ab] | 0.56 | (0.33 - 0.96) | **0.035** | Dom. | 0.60 | (0.36 - 1.01) | **0.053** |
| | | | [bb] | 1.78 | (0.41 - 7.80) | 0.444 | Rec. | 2.14 | (0.49 - 9.32) | 0.309 |
| ABCB1 | rs6950978 | A/T | [Ab] | 0.50 | (0.30 - 0.84) | **0.009** | Dom. | 0.55 | (0.34 - 0.90) | **0.018** |
| | | | [bb] | 1.25 | (0.48 - 3.24) | 0.644 | Rec. | 1.95 | (0.79 - 4.80) | 0.147 |
| ABCC1 | rs17264736 | G/T | [Ab] | 0.47 | (0.27 - 0.84) | **0.011** | Dom. | 0.50 | (0.29 - 0.87) | **0.014** |
| | | | [bb] | 0.58 | (0.29 - 1.15) | 0.118 | Rec. | 1.06 | (0.62 - 1.78) | 0.841 |
| ABCC1 | rs212087 | C/T | [Ab] | 1.92 | (1.15 - 3.23) | **0.013** | Dom. | 1.51 | (0.95 - 2.40) | 0.082 |
| | | | [bb] | 0.82 | (0.36 - 1.88) | 0.642 | Rec. | 0.68 | (0.30 - 1.53) | 0.352 |
| ABCC1 | rs4781712 | A/G | [Ab] | 0.48 | (0.26 - 0.88) | **0.018** | Dom. | 0.52 | (0.29 - 0.93) | **0.027** |
| | | | [bb] | 0.61 | (0.31 - 1.22) | 0.164 | Rec. | 1.10 | (0.66 - 1.84) | 0.705 |
| ABCC1 | rs8058040 | A/G | [Ab] | 1.10 | (0.68 - 1.77) | 0.709 | Dom. | 1.13 | (0.71 - 1.81) | 0.599 |
| | | | [bb] | 1.84 | (0.61 - 5.59) | 0.281 | Rec. | 1.75 | (0.60 - 5.12) | 0.309 |
| ABCC2 | rs3740065 | T/C | [Ab] | 0.97 | (0.57 - 1.63) | 0.900 | Dom. | 1.02 | (0.62 - 1.70) | 0.927 |
| | | | [bb] | 3.21 | (0.62 - 16.61) | 0.165 | Rec. | | | |
| ABCG2 | rs12505410 | T/G | [Ab] | 1.99 | (1.21 - 3.27) | **0.006** | Dom. | 1.93 | (1.20 - 3.12) | **0.007** |
| | | | [bb] | 1.62 | (0.65 - 4.07) | 0.302 | Rec. | 1.17 | (0.48 - 2.82) | 0.735 |
| ABCG2 | rs13120400 | T/C | [Ab] | 2.17 | (1.32 - 3.56) | **0.002** | Dom. | 2.12 | (1.30 - 3.46) | **0.003** |
| | | | [bb] | 1.55 | (0.45 - 5.37) | 0.492 | Rec. | 1.00 | (0.30 - 3.33) | 0.999 |
| ATIC | rs2177735 | T/C | [Ab] | 0.65 | (0.39 - 1.08) | **0.098** | Dom. | 0.57 | (0.35 - 0.93) | **0.023** |
| | | | [bb] | 0.40 | (0.20 - 0.79) | **0.008** | Rec. | 0.53 | (0.29 - 0.96) | **0.038** |
| NFATC1 | rs8090560 | G/A | [Ab] | 0.72 | (0.44 - 1.18) | 0.192 | Dom. | 0.79 | (0.50 - 1.27) | 0.332 |
| | | | [bb] | 1.59 | (0.59 - 4.31) | 0.361 | Rec. | 1.77 | (0.66 - 4.75) | 0.255 |
| **DONOR** | | | | | | | | | | |
| DHFR | rs34965641 | C/T | [Ab] | 1.17 | (0.74 - 1.87) | 0.496 | Dom. | 1.07 | (0.69 - 1.66) | 0.769 |
| | | | [bb] | 0.70 | (0.29 - 1.72) | 0.437 | Rec. | 0.66 | (0.28 - 1.59) | 0.355 |
| NFATC2 | rs3787186 | G/A | [Ab] | 0.65 | (0.41 - 1.05) | 0.076 | Dom. | 0.72 | (0.46 - 1.12) | 0.148 |
| | | | [bb] | 1.42 | (0.61 - 3.29) | 0.414 | Rec. | 1.77 | (0.79 - 3.98) | 0.166 |
| SLC19A1 | rs1051266* | G/A | [Ab] | 0.67 | (0.39 - 1.16) | 0.154 | Dom. | 0.78 | (0.48 - 1.27) | 0.320 |
| | | | [bb] | 0.96 | (0.54 - 1.68) | 0.876 | Rec. | 1.20 | (0.74 - 1.94) | 0.472 |
| SLC19A1 | rs4818789 | T/G | [Ab] | 0.48 | (0.28 - 0.81) | **0.006** | Dom. | 0.60 | (0.37 - 0.97) | **0.036** |
| | | | [bb] | 1.37 | (0.61 - 3.07) | 0.440 | Rec. | 1.69 | (0.75 - 3.78) | 0.202 |
| SLC19A1 | rs4819128 | T/C | [Ab] | 0.61 | (0.36 - 1.06) | 0.081 | Dom. | 0.76 | (0.47 - 1.22) | 0.251 |
| | | | [bb] | 0.98 | (0.56 - 1.70) | 0.929 | Rec. | 1.25 | (0.76 - 2.05) | 0.374 |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q value*s ≤ 0.05 are in bold characters.

a, Genomic model= [AA] vs. [Ab] and [bb], reference group=[AA] (HR fixed at 1.00).

b, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

c, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD. Data are not shown for bb genotype with low frequency (<2%).

**Supplementary Table 11. Association of SNPs with cGVHD and competing risk of death prior cGVHD.**

| | | | | cGVHD | | | | | Death prior cGVHD | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Gene | SNP | Maf (%) | [A]/[b] | Secondary mode[a] Mode | HR[b] | 95% CI | *p* value | *q* value | Secondary model[a] Mode | HR[b] | 95% CI | *p* value | *q* value |
| **RECIPIENT** | | | | | | | | | | | | | |
| ABCC1 | rs4781699 | 34 | G>T | Dom. | 0.66 | ( 0.47 - 0.92 ) | **0.015** | 0.378 | Dom. | 0.74 | ( 0.47 - 1.17 ) | 0.197 | 0.463 |
| | | | | Rec. | 0.88 | ( 0.54 - 1.44 ) | 0.609 | 0.574 | Rec. | 0.93 | ( 0.36 - 2.41 ) | 0.885 | 0.994 |
| ABCC2 | rs2002042 | 24 | C>T | Dom. | 0.80 | ( 0.57 - 1.12 ) | 0.189 | 0.535 | Dom. | 1.61 | ( 1.03 - 2.53 ) | **0.037** | 0.463 |
| | | | | Rec. | 1.23 | ( 0.65 - 2.33 ) | 0.519 | 0.574 | Rec. | 0.82 | ( 0.23 - 2.96 ) | 0.763 | 0.994 |
| MTHFR | rs1572151 | 9 | A>G | Dom. | 1.28 | ( 0.82 - 1.99 ) | 0.276 | 0.535 | Dom. | 1.08 | ( 0.63 - 1.85 ) | 0.792 | 0.566 |
| | | | | Rec. | | | | | Rec. | | | | |
| MTHFR | rs1801133 | 32 | C>T | Dom. | 1.50 | ( 1.05 - 2.15 ) | **0.027** | 0.378 | Dom. | 1.35 | ( 0.86 - 2.11 ) | 0.190 | 0.463 |
| | | | | Rec. | 0.95 | ( 0.59 - 1.56 ) | 0.851 | 0.687 | Rec. | 1.12 | ( 0.54 - 2.31 ) | 0.756 | 0.994 |
| NFATC2 | rs6123048 | 5 | A>G | Dom. | 1.77 | ( 1.06 - 2.94 ) | **0.028** | 0.378 | Dom. | 0.87 | ( 0.50 - 1.50 ) | 0.611 | 0.495 |
| | | | | Rec. | | | | | Rec. | | ( ) | | |
| NFATC1 | rs8090692 | 32 | A>G | Dom. | 1.17 | ( 0.84 - 1.63 ) | 0.361 | 0.547 | Dom. | 1.08 | ( 0.68 - 1.71 ) | 0.746 | 0.559 |
| | | | | Rec. | 1.13 | ( 0.63 - 2.04 ) | 0.688 | 0.608 | Rec. | 3.01 | ( 1.48 - 6.12 ) | **0.002** | 0.125 |
| SLC19A1 | rs4818789 | 24 | T>G | Dom. | 0.93 | ( 0.66 - 1.31 ) | 0.683 | 0.601 | Dom. | 1.52 | ( 0.99 - 2.34 ) | 0.059 | 0.463 |
| | | | | Rec. | 0.70 | ( 0.38 - 1.31 ) | 0.264 | 0.574 | Rec. | 1.00 | ( 0.47 - 2.13 ) | 0.994 | 0.994 |
| TYMS | rs9967368 | 37 | G>C | Dom. | 0.94 | ( 0.68 - 1.31 ) | 0.722 | 0.601 | Dom. | 1.00 | ( 0.65 - 1.56 ) | 0.991 | 0.624 |
| | | | | Rec. | 0.51 | ( 0.31 - 0.84 ) | **0.008** | 0.295 | Rec. | 1.09 | ( 0.61 - 1.96 ) | 0.763 | 0.994 |
| **DONOR** | | | | | | | | | | | | | |
| ABCC1 | rs8058040 | 21 | A>G | Dom. | 1.18 | ( 0.84 - 1.68 ) | 0.339 | 0.814 | Dom. | 1.22 | ( 0.76 - 1.94 ) | 0.415 | 0.757 |
| | | | | Rec. | 1.74 | ( 0.81 - 3.74 ) | 0.152 | 0.750 | Rec. | 6.11 | ( 1.72 - 21.8 ) | **0.005** | 0.173 |
| DHFR | rs11951910 | 9 | T>C | Dom. | 0.64 | ( 0.41 - 0.99 ) | **0.044** | 0.814 | Dom. | 1.17 | ( 0.64 - 2.12 ) | 0.614 | 0.757 |
| | | | | Rec. | | | | | Rec. | | | | |
| DHFR | rs34965641 | 26 | C>T | Dom. | 0.69 | ( 0.49 - 0.96 ) | **0.028** | 0.814 | Dom. | 1.07 | ( 0.68 - 1.68 ) | 0.776 | 0.762 |
| | | | | Rec. | 1.04 | ( 0.37 - 2.98 ) | 0.935 | 0.995 | Rec. | 0.66 | ( 0.29 - 1.52 ) | 0.327 | 0.516 |
| MTHFR | rs1801131 | 29 | A>C | Dom. | 0.93 | ( 0.67 - 1.29 ) | 0.664 | 0.861 | Dom. | 0.68 | ( 0.43 - 1.05 ) | 0.084 | 0.684 |
| | | | | Rec. | 0.96 | ( 0.55 - 1.69 ) | 0.891 | 0.995 | Rec. | 1.46 | ( 0.75 - 2.84 ) | 0.265 | 0.516 |
| MTHFR | rs1994798 | 45 | T>C | Dom. | 0.82 | ( 0.58 - 1.17 ) | 0.277 | 0.814 | Dom. | 0.64 | ( 0.38 - 1.05 ) | 0.077 | 0.684 |
| | | | | Rec. | 0.94 | ( 0.59 - 1.49 ) | 0.795 | 0.995 | Rec. | 1.44 | ( 0.82 - 2.53 ) | 0.205 | 0.516 |
| MTHFR | rs3818762 | 26 | C>G | Dom. | 0.81 | ( 0.58 - 1.12 ) | 0.195 | 0.814 | Dom. | 0.65 | ( 0.42 - 1.01 ) | 0.057 | 0.684 |
| | | | | Rec. | 0.96 | ( 0.52 - 1.77 ) | 0.897 | 0.995 | Rec. | 1.15 | ( 0.57 - 2.32 ) | 0.700 | 0.569 |
| NFATC1 | rs304933 | 25 | G>A | Dom. | 0.85 | ( 0.61 - 1.19 ) | 0.351 | 0.814 | Dom. | 1.09 | ( 0.70 - 1.71 ) | 0.698 | 0.757 |
| | | | | Rec. | 0.49 | ( 0.24 - 0.98 ) | **0.045** | 0.750 | Rec. | 2.42 | ( 1.15 - 5.08 ) | **0.020** | 0.223 |
| NFATC1 | rs8090692 | 29 | A>G | Dom. | 0.83 | ( 0.59 - 1.16 ) | 0.280 | 0.814 | Dom. | 1.16 | ( 0.73 - 1.84 ) | 0.525 | 0.757 |
| | | | | Rec. | 0.63 | ( 0.34 - 1.17 ) | 0.146 | 0.750 | Rec. | 3.15 | ( 1.25 - 7.92 ) | **0.015** | 0.223 |

Maf: minor allele frequency, [A]: major allele, [b]: minor allele, Dom.: Dominant mode, Rec.: recessive mode, *p and q values* ≤ 0.05 are in bold characters.

a, Dominant model=[AA] vs. [Ab+bb], reference group=[AA] (HR fixed at 1.00); Recessive model=[AA+Ab] vs. [bb], reference group=[AA+Ab] with HR fixed at 1.00.

b, Models adjusted for sex mismatch, diagnosis, source of cells, age of recipient and its donor, donor type and conditioning regimen. Incidence of GvHD was estimated by competing-risk analysis with death as competing risk for GvHD.

Data are not shown for bb genotype with low frequency (<2%).