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The role of non-HLA gene polymorphisms in graft-versus-host disease

Akiyoshi Takami

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Abstract A large number of reports have associated various non-HLA gene polymorphisms with the risk and severity of graft-versus-host disease (GVHD). To date, candidate gene studies and genome-wide association studies have been performed to investigate such non-HLA gene polymorphisms in relation to GVHD. Candidate gene studies are hypothesis-driven and cost-effective, whereas genome-wide association studies have the potential to discover new gene polymorphisms, including possible biomarkers and therapeutic targets. Some gene polymorphisms have the potential to affect protein function or gene expression, or to encode minor histocompatibility antigens. Non-HLA genotyping for genes influencing GVHD prior to transplantation should provide useful information that will facilitate choosing the donor, type of graft, conditioning treatment, and GVHD prophylaxis. However, attention should be paid to the need for validation studies and ethical issues.

Keywords Candidate gene study · Genome-wide association study · Single nucleotide polymorphism

Introduction

Graft-versus-host disease (GVHD) is the main cause of early mortality and morbidity after allogeneic hematopoietic stem cell transplantation (SCT) [1–3]. Although HLA matching represents the major genetic determinant of the clinical outcome after allogeneic SCT [4–6], GVHD also occurs in HLA identical transplants, indicating that non-HLA immune-associated genes are also involved in the process. Middeleton et al. [7] were the first to report that non-HLA gene polymorphisms were associated with SCT outcomes, showing a potential role of *TNF* and *IL-10* polymorphisms in predicting acute GVHD. Since then, a large number of non-HLA genes, which mainly impact the individual immune response to infections and inflammatory reactions, have been reported to have polymorphisms associated with the risk and severity of GVHD [8–19]. These studies prompted us to better define the impact of non-HLA gene polymorphisms on the SCT outcomes and to incorporate these markers into routine pre- and post-transplant strategies. This review offers current knowledge on the contributions of non-HLA polymorphisms of the donor and recipient in GVHD after allogeneic SCT.

A. Takami (✉)
Department of Hematology and Oncology, Kanazawa University Hospital, 13-1 Takaramachi, Kanazawa 920-8641, Japan
e-mail: takami@staff.kanazawa-u.ac.jp

Classification of non-HLA gene polymorphisms

A gene polymorphism refers to an individual variation in the sequence of DNA found to cause a more than 1 % gene variation, which contrasts with a mutation, which is defined as an allele sequence found to have less than 1 % gene variation. A gene polymorphism occurs in non-coding regions more frequently than in coding regions. The non-HLA gene polymorphisms include single nucleotide polymorphisms (SNPs), tandem repeats (TRs) and copy number polymorphisms (CNPs), which are named in an allele-based manner (Fig. 1).

SNPs are individual variations of a DNA sequence, and more than 13 million SNPs have been identified through the 1000 genomes project [20]. A CNP is a difference in the copies of one or more sections of the DNA between individuals owing to duplication or deletion events, and affects a region one kbp to several Mbp in size [21–24].

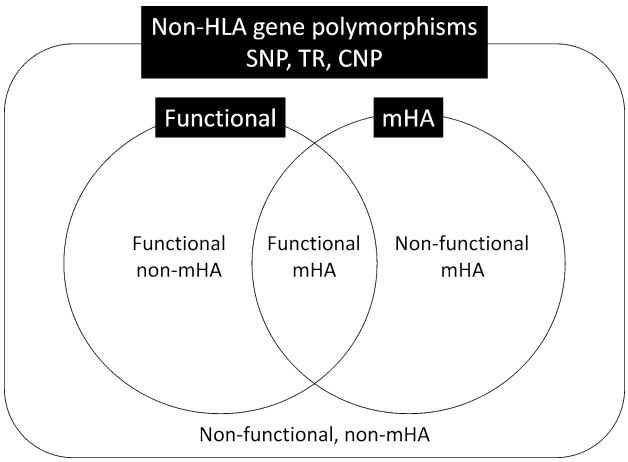

Fig. 1 A schematic diagram of the non-HLA gene polymorphisms

This is in contrast to the TR, such as minisatellites, microsatellites and short tandem repeats, in which a pattern of two to 1000 nucleotides is repeated and the repetitions are directly adjacent to each other.

Studies on the functional effects of gene polymorphisms will be helpful for demonstrating the pathways underlying GVHD. A gene polymorphism is considered to be functional when it affects the protein function or gene expression.

Some polymorphic genes encode proteins which are expressed on the cell surface and give an immunological response when the transplant donor and recipient are not identical, where the polymorphic genes are considered to encode minor histocompatibility antigens (mHAs). mHAs are short peptides that are presented on host HLA molecules and can stimulate alloreactive T-cell immune responses after SCT [25], which may lead to the development of GVHD. A polymorphic gene can encode mHAs that result in peptide sequences that can influence the intracellular processing or presentation of mHA peptides, and the stimulation of an alloreactive response if donors and recipients differ in their mHA genotypes.

Identification of non-HLA gene polymorphisms associated with GVHD

Two approaches are generally used to study non-HLA gene polymorphisms associated with GVHD, namely, candidate gene studies (CGS) and genome-wide association studies (GWAS). The CGS is the approach of choice to test a hypothesis and to confirm the findings of prior studies. Candidate genes are chosen based on their biological significance and/or previous reports showing their association with autoimmune diseases, infection immunity and organ transplant rejection. A genome-wide association study (GWAS) examines many gene polymorphisms with a hypothesis-free basis, and usually focuses on associations of SNPs and CNPs with diseases and traits. The major advantage of a CGS approach is its cost effectiveness and its focus on a particular gene polymorphism with known functional consequences, whereas a GWAS approach is expensive, and the results are often difficult to translate into functional knowledge. On the other hand, the CGS does not generally take into account the influence of confounding factors and considers only gene interactions, whereas the GWAS has the potential to uncover novel SNPs, such as possible biomarkers and therapeutic targets, with no bias.

For both the CGS and GWAS approaches, it is important that the association found in a discovery cohort is repeated using an independent cohort to validate the association. One interesting approach is validation of CGD results by a GWAS. Chien et al. [26] examined whether CGS-identified SNPs had a significant impact on the risk of acute GVHD in a GWAS using an independent cohort, and demonstrated the associations of the *IL-2*, *IL-6*, *IL-10*, *CTLA4*, *HPSE* and *MTHFR* genes with the development of acute GVHD. Validation of the GWAS results using a CGD approach and a functional investigation may also be promising.

Non-HLA polymorphisms associated with GVHD

The non-HLA gene polymorphisms demonstrated by large cohort studies to be associated with GVHD are summarized in Table 1. It should be noted that the polymorphic genes in the recipients are more commonly identified than those in the donors. Using a GWAS, Ogawa et al. [17] determined that there were more than half a million SNPs in 1598 recipient and unrelated donor pairs, and identified five novel SNPs (rs6937034, rs1137282, rs9657655, rs5998746 and rs11873016) associating with the risk of acute GVHD, which were all in the recipients. Compelling evidence from mouse models of GVHD and clinical data have indicated the importance of the cytokine storm in the pathophysiology of acute GVHD, and polymorphisms in cytokine and chemokine genes, such as *IFNG*, *IL-1*, *IL-2*, *IL-6*, *IL-10*, *IL-17* and *TNF*, predict the development and severity of acute GVHD, as well as increases in the circulating levels of these cytokines. Activation of inflammatory pathways through these mediators occurs before infusion of donor T cells, which may account for the findings that many gene recipient-derived polymorphisms were critical for the risk of GVHD. These findings may be beneficial when considering the treatment strategy prior to treatment or during the pathogenesis of acute GVHD.

Polymorphisms of immunoregulatory genes associated with GVHD

C–C chemokine receptor type (CCR) 5 is a chemokine receptor and its ligands include C–C motif ligand (CCL) 3,

Table 1 Non-HLA gene polymorphisms associated with GVHD

Gene	Polymorphism	Function, ref.	Cohort (cases)	Type of GVHD	Genome	Ref.
BAFF	rs16972217	U	MRD and URD (164)	Acute, chronic	R	[48]
BAFF	rs7993590	U	MRD and URD (164)	Acute, chronic	R	[48]
BAFF	rs12428930	Yes [49]	MRD and URD (164)	Acute, chronic	R	[48]
BAFF	rs2893321	U	MRD and URD (164)	Acute, chronic	R	[48]
BPI	rs4358188	U	MRD and URD (304)	Acute	D	[50]
CCL5	rs1800825	U	(72)	Chronic	R	[51]
CCR5	rs1799987	U	URD (1,370)	Acute	D	[27]
CCR6	rs2301436	U	MRD (161)	Chronic	D	[52]
CCR6	rs3093023	U	MRD (161)	Chronic	D	[52]
CTLA4	rs231775	Yes [53]	MRD (536)	Acute	D	[53]
CTLA4	rs231775	Yes [53]	MRD (225)	Chronic	D	[54]
CTLA4	rs3087243	Yes [55]	URD (322)	Acute	D	[28]
CTLA4	rs3087243	Yes [55]	URD (686)	Acute	R	[26]
DAAM2	rs2504082	U	MRD (228)	Acute	R	[56]
DARC	rs2814778	Yes [57]	MRD (105)	Acute	D	[58]
DARC	rs12075	U	MRD (105)	Acute	D	[58]
ERA	intron 1 (AT)n	U	MRD (108)	Acute	R	[59]
FAS	rs1800682	No [60]	MRD (160)	Acute	R	[61]
FCGR3A	rs396991	Yes [62]	URD (99)	Chronic	R	[9]
FCRL3	rs7528684	Yes [63]	MRD (123)	Chronic	R	[64]
HLA-G	(14 bp)n	Yes [65]	URD (53)	Acute	R	[66]
HMGB1	rs41376448	U	MRD and URD (422)	Acute	R	[67]
HPSE	rs4364254	Yes [68]	URD (414)	Acute, chronic	R	[69]
HPSE	rs4693608	Yes [68]	URD (414)	Acute, chronic	R	[69]
HPSE	rs4364254	Yes [68]	URD (686)	Acute	R	[26]
HSPA1L	rs2075800	U	MRD and URD (64)	Acute	R	[70]
H-Y	Y-chromosome	Yes [71]	MRD and URD (53,988)	Chronic	M	[44]
IFNG	intron 1 (CA)n	Yes [72]	MRD (80)	Acute	R	[73]
IFNG	intron 1 (CA)n	Yes [72]	MRD (80)	Acute	R	[73]
IMPD	rs2278294	U	MRD and URD (240)	Acute	R	[74]
IL-1A	rs1800587	Yes [75]	MRD (115)	Chronic	D	[76]
IL-1RA	(86 bp)n	Yes [77]	MRD (99)	Acute	D	[78]
IL-1RA	(86 bp)n	Yes [77]	MRD (107)	Acute	D	[79]
IL-2	rs2069762	Yes [80]	URD (95)	Acute, chronic	R	[80, 81]
IL-2	rs2069762	Yes [80]	URD (322)	Chronic	R	[28]
IL-2	rs2069762	Yes [80]	URD (686)	Acute	D	[26]
IL-6	rs1800795	Yes [82]	MRD (160)	Acute	D	[61]
IL-6	rs1800795	Yes [82]	MRD (80)	Chronic	R	[73]
IL-6	rs1800795	Yes [82]	MRD (100)	Chronic	R	[83]
IL-6	rs1800795	Yes [82]	MRD and URD (166)	Acute	R	[84]
IL-6	rs1800795	Yes [82]	MRD (93)	Acute	D	[85]
IL-6	rs1800795	Yes [82]	URD (686)	Acute	D	[26]
IL-6	rs1800795	Yes [82]	MRD (612)	Acute	R	[26]
IL-6	rs1800795	Yes [82]	MRD (612)	Acute	D	[26]
IL-10	rs1800872	Yes [86, 87]	MRD (309)	Acute	R	[88]
IL-10	rs1800872	Yes [86, 87]	MRD (100)	Acute	R, D	[83]
IL-10	rs1800872	Yes [86, 87]	MRD (100)	Acute	R	[89]
IL-10	rs1800872	Yes [86, 87]	MRD (953)	Acute	R	[90]

Table 1 continued

Gene	Polymorphism	Function, ref.	Cohort (cases)	Type of GVHD	Genome	Ref.
IL-10	rs1800872	Yes [86, 87]	MRD (107)	Chronic	R	[79]
IL-10	rs1800872	Yes [86, 87]	MRD (612)	Acute	R	[26]
IL-10	rs1800871	Yes [86, 87]	MRD (612)	Acute	R	[26]
IL-10	(CA)n	U	MRD (49)	Acute	R	[7]
IL-10	(CA)n	U	MRD (144)	Acute	R	[91]
IL-10	(CA)n	U	MRD and URD (62)	Chronic	D	[92]
IL-10	(CA)n	U	MRD (88)	Acute	R	[93]
IL-10RB	rs2834167	Yes [86, 87]	MRD (309)	Acute	R	[88]
IL-10RB	rs2834167	Yes [86, 87]	MRD (953)	Acute	D	[90]
IL-17	rs2275913	Yes [17]	URD (510)	Acute	R	[16]
IL-17	rs2275913	Yes [17]	URD (438)	Acute	D	[17]
IL-23R	rs11209026	Yes [94]	MRD and URD (407)	Acute	D	[95]
IL-23R	rs11209026	Yes [94]	MRD and URD (231)	Acute	D	[96]
IL-23R	rs11209026	Yes [94]	MRD and URD (304)	Acute	D	[50]
MADCAM1	rs2302217	U	MRD (87)	Chronic	R	[97]
MTHFR	rs1801131	Yes [98]	MRD (159)	Acute	R	[10]
MTHFR	rs1801131	Yes [98]	MRD and URD (304)	Acute	R	[99]
MTHFR	rs1801131	Yes [98]	MRD (612)	Acute	R	[26]
MTHFR	rs1801133	Yes [98]	MRD (140), URD (53)	Acute, chronic	D	[100]
MTHFR	rs1801133	Yes [98]	MRD (140)	Acute	D	[101]
NKG2D	rs1049174	Yes [16]	URD (145)	Acute	D	[14]
NOD2	rs2066844	Yes [102]	URD (342)	Acute	D	[103]
	rs2066845					
	rs2066847					
NOD2	rs2066844	Yes [102]	MRD (403)	Acute	R, D	[104]
	rs2066845					
	rs2066847					
PARP1	rs1805410	U	URD (470)	Chronic	R	[105]
PECAM-1(CD31)	rs668	U	MRD (85)	Acute	D	[106]
PECAM-1(CD31)	rs668	U	MRD (102)	Acute	D	[107]
PECAM-1(CD31)	rs12953	U	MRD (112)	Acute	M	[108]
PECAM-1(CD31)	rs1131012	U	MRD (74)	Acute	D	[109]
PTPN22	rs2488457	U	URD (663)	Acute	R	[15]
PTPRC	rs17612648	Yes [110]	URD (44)	Acute	D	[110]
RFC1	rs6844176	U	URD (470)	Acute	R	[105]
TGFB1	rs1800470	Yes [111]	MRD and URD (24)	Acute	R	[112]
TGFB1	rs1800470	Yes [111]	MRD and URD (168)	Acute	R	[113]
TGFB1	rs1800470	Yes [111]	MRD (77)	Acute	D	[114]
TGFB1RII	rs2228048	U	MRD (77)	Acute	R	[114]
TLR1	rs4833079	U	MRD (305)	Acute	R	[115]
TLR4	rs4837656	U	MRD (305)	Acute	R	[115]
TLR4	rs17582214	U	MRD (305)	Acute	R	[115]
TLR4	rs4986791	Yes [116]	MRD (403)	Acute	R, D	[104]
TLR5	rs10737416	U	MRD (305)	Acute	R	[115]
TLR5	rs2800230	U	MRD (305)	Chronic	D	[115]
TLR5	rs2800237	U	MRD (305)	Chronic	D	[115]
TLR6	rs6531656	U	MRD (305)	Acute	D	[115]
TLR10	rs337629	U	MRD (305)	Acute	D	[115]

Table 1 continued

Gene	Polymorphism	Function, ref.	Cohort (cases)	Type of GVHD	Genome	Ref.
TNF	(TNFd)n	Yes [73]	MRD (49)	Acute	R	[7]
TNF	(TNFd)n	Yes [73]	MRD (80)	Acute	R	[73]
TNF	(TNFd)n	Yes [73]	MRD and URD (62)	Acute	D	[92]
TNF	rs1799964	Yes [117]	URD (922)	Acute	M	[28]
TNF	rs1800610	U	MRD (160)	Acute, chronic	R, D	[61]
TNF	rs1800630	No [118]	URD (462)	Acute	R, D	[119]
TNF	rs1799724	U	URD (462)	Acute	R, D	[119]
TNFRII	rs1061622	Yes [120]	MRD (104)	Acute	R	[120]
TNFRII	rs1061622	Yes [120]	MRD (104)	Chronic	D	[120]
TNFRII	rs1061622	Yes [120]	URD (462)	Chronic	D	[119]
TSER	(28 bp)n	Yes [121]	MRD and URD (304)	Acute	D	[99]
UGT2B17	129 kbp deletion	Yes [122]	MRD (1,345)	Acute	M	[41]
VDR	intron 8 CNP	Yes [123]	MRD (88)	Acute	R	[93]
VEGFA	rs699947	Yes [124, 125]	MRD (98)	Acute	R	[126]
VEGFA	rs833061	Yes [124, 125]	MRD (98)	Acute	R	[126]
U	rs6937034	U	URD (1,598)	Acute	M	[127]
KRAS	rs1137282	U	URD (1,598)	Acute	M	[127]
U	rs9657655	U	URD (1,598)	Acute	M	[127]
U	rs5998746	U	URD (1,598)	Acute	R	[127]
U	rs11873016	U	URD (1,598)	Acute	R	[127]

CNP copy number polymorphism, *TR* tandem repeat, *U* unknown, *MRD* matched-related donor, *URD* unrelated donor, *D* donor, *R* recipient, *M* mismatch between recipient and donor

CCL4, CCL5 and CCL3L1. A large cohort study demonstrated that the donor *CCL5* genotype significantly influenced the risk of severe acute GVHD and disease-free survival [27].

Harkensee et al. [28] reevaluated 41 previously documented SNPs in two independent, large cohorts, and showed an association of the *TNF* and *CTLA4* SNPs with acute GVHD and an association of the *IL-2* SNP with chronic GVHD.

The *PTPN22* gene encodes lymphoid-specific phosphatase (Lyp) and is an important negative regulator of T-cell activation involved in the dephosphorylation and inactivation of TCR-associated kinases. A SNP of the *PTPN22* promoter gene, rs2488457 (G/C), is associated with the susceptibility to autoimmune diseases. In unrelated bone marrow transplantation, the recipient C/C genotype is associated with a significantly lower incidence of grade II–IV acute GVHD and a higher incidence of relapse, which predict worse survival outcomes for patients with high-risk disease [15].

Functional polymorphisms

IL-17 is the hallmark cytokine of Th17 cells and plays important roles in the host defense, the pathophysiology of autoimmune diseases and organ allograft rejection. Although several studies using mouse models showed a significant impact of IL-17 on the development of acute GVHD [29–35], the results were not consistent. Espinoza et al. were the first to report an association of the rs2275913 SNP (G/A) in the promoter of the IL-17 gene with the development of acute GVHD [17, 36]. Notably, the rs2275913 SNP is located within a binding motif for nuclear factor activated T cells (NFAT), which is a critical regulator of the *IL-17* promoter [37]. The same group demonstrated that the A allele of the *IL-17* gene makes patients susceptible to acute GVHD because it correlates with more efficient IL-17 secretion through its higher affinity for NFAT than the G allele [17]. These findings suggest not only the functional relevance of the *IL-17* promoter SNPs with the development of acute GVHD, but also the involvement of IL-17 in the development of acute GVHD, leading to a hypothesis that IL-17-producing cells can modify the function of host dendritic cells (DCs) through unknown mechanisms. The direct interaction between IL-17 and host DCs may be supported by the fact that DCs express IL-17 receptors [38]. A better understanding of the molecular mechanism by which this promoter SNP controls the production of IL-17 may therefore offer some novel therapeutic insights into the mechanisms underlying the development of other IL-17-related diseases, including rheumatoid arthritis, periodontal disease,

multiple sclerosis, allergic rhinitis, psoriasis, inflammatory bowel disease and organ allograft rejection [39].

mHAs

McCarroll et al. [40] identified 1316 CNPs using genotyping arrays with higher SNPs density and copy number probes accompanied by newer algorithms. Among them, donor-negative and recipient-positive mismatch of the *UGT2B17* CNP showed an association with acute GVHD [41]. This is consistent with a previous report [42] showing that the protein encoded by the *UGT2B17* gene is a mHA that is selectively expressed in the liver, intestine and antigen-presenting cells, and that it plays a causative role in acute GVHD.

Cellular proteins encoded by the Y-chromosome can also operate as mHAs when male recipients receive SCT grafts from female donors [43, 44].

Conclusion

The determination of the non-HLA genotypes associated with GVHD prior to transplantation will provide patients an opportunity to receive optimal strategies in terms of the selection of the donor, type of graft, conditioning treatment and GVHD prophylaxis. However, several issues remain unresolved that need to be addressed before mainstream non-HLA genotyping can be implemented in clinical practice. First, the abundance of non-HLA gene polymorphisms identified should be validated by individual, multiracial cohorts irrespective of whether CGS and GWAS approaches were used, because the study populations may critically impact on results, as has also been seen in HLA association studies [4, 45, 46]. Second, whether a polymorphic gene has a functional role and mHA nature should be determined to obtain a better understanding of the molecular mechanisms by which the gene polymorphism can influence the GVHD, offering novel therapeutic insights into GVHD, as well as other autoimmune diseases in which the polymorphic gene is involved. There is also a possibility that the gene polymorphism of interest may coordinate with other genes, and/or have close linkage with another gene with functional and/or immunogenic properties. Finally, systemic discovery of new genetic biomarkers using GWAS will add weight in the decade ahead, but informed consent and privacy protection remain issues that need specific attention, because GWAS create a large amount of individual-specific digital information that is easy to share across international borders [47].

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Conflict of interest The authors declare no competing financial interests.

References

1. Gratwohl A, Brand R, Frassoni F, Rocha V, Niederwieser D, Reusser P, et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. Bone Marrow Transpl. 2005;36(9):757–69.
2. Munakata W, Sawada T, Kobayashi T, Kakihana K, Yamashita T, Ohashi K, et al. Mortality and medical morbidity beyond 2 years after allogeneic hematopoietic stem cell transplantation: experience at a single institution. Int J Hematol. 2011;93(4):517–22.
3. Sato T, Ichinohe T, Kanda J, Yamashita K, Kondo T, Ishikawa T, et al. Clinical significance of subcategory and severity of chronic graft-versus-host disease evaluated by National Institutes of Health consensus criteria. Int J Hematol. 2011;93(4):532–41.
4. Kawase T, Morishima Y, Matsuo K, Kashiwase K, Inoko H, Saji H, et al. High-risk HLA allele mismatch combinations responsible for severe acute graft-versus-host disease and implication for its molecular mechanism. Blood. 2007;110(7):2235–41.
5. Morishima S, Ogawa S, Matsubara A, Kawase T, Nannya Y, Kashiwase K, et al. Impact of highly conserved HLA haplotype on acute graft-versus-host disease. Blood. 2010;115(23):4664–70.
6. Hatanaka K, Fuji S, Ikegame K, Kato R, Wake A, Hidaka M, et al. Low incidences of acute and chronic graft-versus-host disease after unrelated bone marrow transplantation with low-dose anti-T lymphocyte globulin. Int J Hematol. 2012;96(6):773–80.
7. Middleton PG, Taylor PR, Jackson G, Proctor SJ, Dickinson AM. Cytokine gene polymorphisms associating with severe acute graft-versus-host disease in HLA-identical sibling transplants. Blood. 1998;92(10):3943–8.
8. Tanabe T, Yamaguchi N, Matsuda K, Yamazaki K, Takahashi S, Tojo A, et al. Association analysis of the NOD2 gene with susceptibility to graft-versus-host disease in a Japanese population. Int J Hematol. 2011;93(6):771–8.
9. Takami A, Espinoza JL, Onizuka M, Ishiyama K, Kawase T, Kanda Y, et al. A single-nucleotide polymorphism of the Fcgamma receptor type IIIA gene in the recipient predicts transplant outcomes after HLA fully matched unrelated BMT for myeloid malignancies. Bone Marrow Transpl. 2011;46(2):238–43.
10. Sugimoto K, Murata M, Onizuka M, Inamoto Y, Terakura S, Kuwatsuka Y, et al. Decreased risk of acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation in patients with the 5,10-methylenetetrahydrofolate reductase 677TT genotype. Int J Hematol. 2008;87(5):451–8.
11. Paczesny S, Hanauer D, Sun Y, Reddy P. New perspectives on the biology of acute GVHD. Bone Marrow Transpl. 2010;45(1):1–11.
12. Nakata K, Takami A, Espinoza JL, Matsuo K, Morishima Y, Onizuka M, et al. The recipient CXCL10 + 1642C>G variation

predicts survival outcomes after HLA fully matched unrelated bone marrow transplantation. Clin Immunol. 2013;146(2):104–11.
13. Espinoza JL, Takami A, Nakata K, Yamada K, Onizuka M, Kawase T, et al. Genetic variants of human granzyme B predict transplant outcomes after HLA matched unrelated bone marrow transplantation for myeloid malignancies. PLoS One. 2011;6(8): e23827.
14. Espinoza JL, Takami A, Onizuka M, Sao H, Akiyama H, Miyamura K, et al. NKG2D gene polymorphism has a significant impact on transplant outcomes after HLA-fully-matched unrelated bone marrow transplantation for standard risk hematologic malignancies. Haematologica. 2009;94(10):1427–34.
15. Espinoza JL, Takami A, Onizuka M, Morishima Y, Fukuda T, Kodera Y, et al. Recipient PTPN22 -1123 C/C genotype predicts acute graft-versus-host disease after HLA fully matched unrelated bone marrow transplantation for hematologic malignancies. Biol Blood Marrow Transpl. 2013;19(2):240–6.
16. Espinoza JL, Takami A, Onizuka M, Kawase T, Sao H, Akiyama H, et al. A single nucleotide polymorphism of IL-17 gene in the recipient is associated with acute GVHD after HLA-matched unrelated BMT. Bone Marrow Transpl. 2011;46(11):1455–63.
17. Espinoza JL, Takami A, Nakata K, Onizuka M, Kawase T, Akiyama H, et al. A genetic variant in the IL-17 promoter is functionally associated with acute graft-versus-host disease after unrelated bone marrow transplantation. PLoS One. 2011; 6(10):e26229.
18. Ting C, Alterovitz G, Merlob A, Abdi R. Genomic studies of GVHD-lessons learned thus far. Bone Marrow Transpl. 2013; 48(1):4–9.
19. Hansen JA, Chien JW, Warren EH, Zhao LP, Martin PJ. Defining genetic risk for graft-versus-host disease and mortality following allogeneic hematopoietic stem cell transplantation. Curr Opin Hematol. 2010;17(6):483–92.
20. Available: http://www.1000genomes.org/. Accessed 1 May 2013.
21. Sebat J, Lakshmi B, Troge J, Alexander J, Young J, Lundin P, et al. Large-scale copy number polymorphism in the human genome. Science. 2004;305(5683):525–8.
22. Schrider DR, Hahn MW. Gene copy-number polymorphism in nature. Proc Roy Soc B-Biol Sci. 2010;277(1698):3213–21.
23. Feuk L, Carson AR, Scherer SW. Structural variation in the human genome. Nat Rev Genet. 2006;7(2):85–97.
24. Kamada Y, Sakata-Yanagimoto M, Sanada M, Sato-Otsubo A, Enami T, Suzukawa K, et al. Identification of unbalanced genome copy number abnormalities in patients with multiple myeloma by single-nucleotide polymorphism genotyping microarray analysis. Int J Hematol. 2012;96(4):492–500.
25. Goulmy E. Human minor histocompatibility antigens. Curr Opin Immunol. 1996;8(1):75–81.
26. Chien JW, Zhang XC, Fan W, Wang H, Zhao LP, Martin PJ, et al. Evaluation of published single nucleotide polymorphisms associated with acute GVHD. Blood. 2012;119(22):5311–9.
27. McDermott DH, Conway SE, Wang T, Ricklefs SM, Agovi MA, Porcella SF, et al. Donor and recipient chemokine receptor CCR5 genotype is associated with survival after bone marrow transplantation. Blood. 2010;115(11):2311–8.
28. Harkensee C, Oka A, Onizuka M, Middleton PG, Inoko H, Hirayasu K, et al. Single nucleotide polymorphisms and outcome risk in unrelated mismatched hematopoietic stem cell transplantation: an exploration study. Blood. 2012;119(26): 6365–72.
29. Yi T, Chen Y, Wang L, Du G, Huang D, Zhao D, et al. Reciprocal differentiation and tissue-specific pathogenesis of Th1, Th2, and Th17 cells in graft-versus-host disease. Blood. 2009;114(14):3101–12.
30. Yi T, Zhao D, Lin CL, Zhang C, Chen Y, Todorov I, et al. Absence of donor Th17 leads to augmented Th1 differentiation and exacerbated acute graft-versus-host disease. Blood. 2008; 112(5):2101–10.
31. Tawara I, Maeda Y, Sun Y, Lowler KP, Liu C, Toubai T, et al. Combined Th2 cytokine deficiency in donor T cells aggravates experimental acute graft-vs-host disease. Exp Hematol. 2008;36(8):988–96.
32. Kappel LW, Goldberg GL, King CG, Suh DY, Smith OM, Ligh C, et al. IL-17 contributes to CD4-mediated graft-versus-host disease. Blood. 2009;113(4):945–52.
33. Iclozan C, Yu Y, Liu C, Liang Y, Yi T, Anasetti C, et al. Th17 cells are sufficient but not necessary to induce acute graft-versus-host disease. Biol Blood Marrow Transpl. 2009. PubMed PMID: 19804837. Epub 2009/10/07. Eng.
34. Carlson MJ, West ML, Coghill JM, Panoskaltsis-Mortari A, Blazar BR, Serody JS. In vitro-differentiated TH17 cells mediate lethal acute graft-versus-host disease with severe cutaneous and pulmonary pathologic manifestations. Blood. 2009;113(6): 1365–74.
35. Nishimori H, Maeda Y, Teshima T, Sugiyama H, Kobayashi K, Yamasuji Y, et al. Synthetic retinoid Am80 ameliorates chronic graft-versus-host disease by down-regulating Th1 and Th17. Blood. 2012;119(1):285–95.
36. Espinoza JL, Takami A, Onizuka M, Kawase T, Sao H, Akiyama H, et al. A single nucleotide polymorphism of IL-17 gene in the recipient is associated with acute GVHD after HLA-matched unrelated BMT. Bone Marrow Transpl. 2011. PubMed PMID: 21217785. ENG.
37. Liu XK, Lin X, Gaffen SL. Crucial role for nuclear factor of activated T cells in T cell receptor-mediated regulation of human interleukin-17. J Biol Chem. 2004;279(50):52762–71.
38. Antonysamy MA, Fanslow WC, Fu F, Li W, Qian S, Troutt AB, et al. Evidence for a role of IL-17 in organ allograft rejection: IL-17 promotes the functional differentiation of dendritic cell progenitors. J Immunol. 1999;162(1):577–84.
39. Miossec P, Korn T, Kuchroo VK. Interleukin-17 and type 17 helper T cells. N Engl J Med. 2009;361(9):888–98.
40. McCarroll SA, Kuruvilla FG, Korn JM, Cawley S, Nemesh J, Wysoker A, et al. Integrated detection and population-genetic analysis of SNPs and copy number variation. Nat Genet. 2008; 40(10):1166–74.
41. McCarroll SA, Bradner JE, Turpeinen H, Volin L, Martin PJ, Chilewski SD, et al. Donor-recipient mismatch for common gene deletion polymorphisms in graft-versus-host disease. Nat Genet. 2009;41(12):1341–4.
42. Murata M, Warren EH, Riddell SR. A human minor histocompatibility antigen resulting from differential expression due to a gene deletion. J Exp Med. 2003;197(10):1279–89.
43. Takami A, Sugimori C, Feng X, Yachie A, Kondo Y, Nishimura R, et al. Expansion and activation of minor histocompatibility antigen HY-specific T cells associated with graft-versus-leukemia response. Bone Marrow Transpl. 2004;34(8):703–9.
44. Stern M, Brand R, de Witte T, Sureda A, Rocha V, Passweg J, et al. Female-versus-male alloreactivity as a model for minor histocompatibility antigens in hematopoietic stem cell transplantation. Am J Transpl. 2008;8(10):2149–57.
45. Kawase T, Matsuo K, Kashiwase K, Inoko H, Saji H, Ogawa S, et al. HLA mismatch combinations associated with decreased risk of relapse: implications for the molecular mechanism. Blood. 2009;113(12):2851–8.
46. Crocchiolo R, Zino E, Vago L, Oneto R, Bruno B, Pollichieni S, et al. Nonpermissive HLA-DPB1 disparity is a significant independent risk factor for mortality after unrelated hematopoietic stem cell transplantation. Blood. 2009;114(7):1437–44.

47. Kaye J, Boddington P, de Vries J, Hawkins N, Melham K. Ethical implications of the use of whole genome methods in medical research. Eur J Hum Genet EJHG. 2010;18(4):398–403.
48. Clark WB, Brown-Gentry KD, Crawford DC, Fan K-H, Snavely J, Chen H, et al. Genetic variation in recipient B-cell activating factor modulates phenotype of GVHD. Blood. 2011;118(4): 1140–4.
49. Novak AJ, Slager SL, Fredericksen ZS, Wang AH, Manske MM, Ziesmer S, et al. Genetic variation in B-cell-activating factor is associated with an increased risk of developing B-cell non-hodgkin lymphoma. Cancer Res. 2009;69(10):4217–24.
50. Wermke M, Maiwald S, Schmelz R, Thiede C, Schetelig J, Ehninger G, et al. Genetic variations of interleukin-23R (1143A>G) and BPI (A645G), but not of NOD2, are associated with acute graft-versus-host disease after allogeneic transplantation. Biol Blood Marrow Transpl. 2010;16(12):1718–27.
51. Kim DH, Jung HD, Lee NY, Sohn SK. Single nucleotide polymorphism of CC chemokine ligand 5 promoter gene in recipients may predict the risk of chronic graft-versus-host disease and its severity after allogeneic transplantation. Transplantation. 2007;84(7):917–25.
52. Broen K, van der Waart AB, Greupink-Draaisma A, Metzig J, Feuth T, Schaap NPM, et al. Polymorphisms in CCR6 are associated with chronic graft-versus-host disease and invasive fungal disease in matched-related hematopoietic stem cell transplantation. Biol Blood Marrow Transpl. 2011;17(10):1443–9.
53. Perez-Garcia A, De la Camara R, Roman-Gomez J, Jimenez-Velasco A, Encuentra M, Nieto JB, et al. CTLA-4 polymorphisms and clinical outcome after allogeneic stem cell transplantation from HLA-identical sibling donors. Blood. 2007; 110(1):461–7.
54. Azarian M, Busson M, Lepage V, Charron D, Toubert A, Loiseau P, et al. Donor CTLA-4 +49 A/G*GG genotype is associated with chronic GVHD after HLA-identical haematopoietic stem-cell transplantations. Blood. 2007;110(13):4623–4.
55. Maier LM, Anderson DE, De Jager PL, Wicker LS, Hafler DA. Allelic variant in CTLA4 alters T cell phosphorylation patterns. Proc Natl Acad Sci. 2007;104(47):18607–12.
56. Yi H, Piao C, Kim I, Kim H, Oh S, Kim J, et al. DAAM2 polymorphism is closely related to the clinical outcomes of allogeneic hematopoietic stem cell transplantation. Ann Hematol. 2012;91(4):571–6.
57. Daniels G. The molecular genetics of blood group polymorphism. Hum Genet. 2009;126(6):729–42.
58. Sellami MH, Chaabane M, Kaabi H, Torjemane L, Ladeb S, Othmane TB, et al. Evidence that erythrocyte DARC-positive phenotype can affect the GVHD occurrence after HLA-identical sibling HSCT. Transpl Immunol. 2011;25(2–3):148–52.
59. Middleton PG, Norden J, Cullup H, Cavet J, Jackson GH, Taylor PR, et al. Oestrogen receptor alpha gene polymorphism associates with occurrence of graft-versus-host disease and reduced survival in HLA-matched sib-allo BMT. Bone Marrow Transpl. 2003;32(1):41–7.
60. Sibley K, Rollinson S, Allan JM, Smith AG, Law GR, Roddam PL, et al. Functional FAS promoter polymorphisms are associated with increased risk of acute myeloid leukemia. Cancer Res. 2003;63(15):4327–30.
61. Mullighan C, Heatley S, Doherty K, Szabo F, Grigg A, Hughes T, et al. Non-HLA immunogenetic polymorphisms and the risk of complications after allogeneic hemopoietic stem-cell transplantation. Transplantation. 2004;77(4):587–96.
62. Koene HR, Kleijer M, Algra J, Roos D, von dem Borne AEGKr, de Haas M. FcγRIIIa-158V/F Polymorphism influences the binding of IgG by natural killer cell FcγRIIIa, independently of the FcγRIIIa-48L/R/H phenotype. Blood. 1997;90(3):1109–14.
63. Kochi Y, Yamada R, Suzuki A, Harley JB, Shirasawa S, Sawada T, et al. A functional variant in FCRL3, encoding Fc receptor-like 3, is associated with rheumatoid arthritis and several autoimmunities. Nat Genet. 2005;37(5):478–85.
64. Shimada M, Onizuka M, Machida S, Suzuki R, Kojima M, Miyamura K, et al. Association of autoimmune disease-related gene polymorphisms with chronic graft-versus-host disease. Br J Haematol. 2007;139(3):458–63.
65. Chen XY, Yan WH, Lin A, Xu HH, Zhang JG, Wang XX. The 14 bp deletion polymorphisms in HLA-G gene play an important role in the expression of soluble HLA-G in plasma. Tissue Antigens. 2008;72(4):335–41.
66. La Nasa G, Littera R, Locatelli F, Lai S, Alba F, Caocci G, et al. The human leucocyte antigen-G 14-basepair polymorphism correlates with graft-versus-host disease in unrelated bone marrow transplantation for thalassaemia. Br J Haematol. 2007; 139(2):284–8.
67. Kornblit B, Masmas T, Petersen SL, Madsen HO, Heilmann C, Schejbel L, et al. Association of HMGB1 polymorphisms with outcome after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2010;16(2):239–52.
68. Ostrovsky O, Korostishevsky M, Shafat I, Mayorov M, Ilan N, Vlodavsky I, et al. Inverse correlation between HPSE gene single nucleotide polymorphisms and heparanase expression: possibility of multiple levels of heparanase regulation. J Leuk Biol. 2009;86(2):445–55.
69. Ostrovsky O, Shimoni A, Rand A, Vlodavsky I, Nagler A. Genetic variations in the heparanase gene (HPSE) associate with increased risk of GVHD following allogeneic stem cell transplantation: effect of discrepancy between recipients and donors. Blood. 2010;115(11):2319–28.
70. Bogunia-Kubik K, Lange A. HSP70-hom gene polymorphism in allogeneic hematopoietic stem-cell transplant recipients correlates with the development of acute graft-versus-host disease. Transplantation. 2005;79(7):815–20.
71. Wang W, Meadows LR, den Haan JM, Sherman NE, Chen Y, Blokland E, et al. Human H-Y: a male-specific histocompatibility antigen derived from the SMCY protein. Science. 1995; 269(5230):1588–90.
72. Pravica V, Asderakis A, Perrey C, Hajeer A, Sinnott PJ, Hutchinson IV. In vitro production of IFN-γ correlates with CA repeat polymorphism in the human IFN-γ gene. Eur J Immunogenet. 1999;26(1):1–3.
73. Cavet J, Dickinson AM, Norden J, Taylor PRA, Jackson GH, Middleton PG. Interferon-γ and interleukin-6 gene polymorphisms associate with graft-versus-host disease in HLA-matched sibling bone marrow transplantation. Blood. 2001;98(5): 1594–600.
74. Cao W, Xiao H, Lai X, Luo Y, Shi J, Tan Y, et al. Genetic variations in the mycophenolate mofetil target enzyme are associated with acute GVHD risk after related and unrelated hematopoietic cell transplantation. Biol Blood Marrow Transpl. 2012;18(2):273–9.
75. Um JY, Rim HK, Kim SJ, Kim HL, Hong SH. Functional polymorphism of IL-1 alpha and its potential role in obesity in humans and mice. PLoS One. 2011;6(12):e29524.
76. Cullup H, Dickinson AM, Cavet J, Jackson GH, Middleton PG. Polymorphisms of interleukin-1α constitute independent risk factors for chronic graft-versus-host disease after allogeneic bone marrow transplantation. Br J Haematol. 2003;122(5): 778–87.
77. Danis VA, Millington M, Hyland VJ, Grennan D. Cytokine production by normal human monocytes: inter-subject variation and relationship to an IL-1 receptor antagonist (IL-1Ra) gene polymorphism. Clin Exp Immunol. 1995;99(2):303–10.

78. Cullup H, Dickinson AM, Jackson GH, Taylor PR, Cavet J, Middleton PG. Donor interleukin 1 receptor antagonist genotype associated with acute graft-versus-host disease in human leucocyte antigen-matched sibling allogeneic transplants. Br J Haematol. 2001;113(3):807–13.
79. Rocha V, Franco RF, Porcher R, Bittencourt H, Silva WA Jr, Latouche A, et al. Host defense and inflammatory gene polymorphisms are associated with outcomes after HLA-identical sibling bone marrow transplantation. Blood. 2002;100(12): 3908–18.
80. MacMillan ML, Radloff GA, Kiffmeyer WR, DeFor TE, Weisdorf DJ, Davies SM. High-producer interleukin-2 genotype increases risk for acute graft-versus-host disease after unrelated donor bone marrow transplantation. Transplantation. 2003; 76(12):1758–62.
81. MacMillan ML, Radloff GA, DeFor TE, Weisdorf DJ, Davies SM. Interleukin-1 genotype and outcome of unrelated donor bone marrow transplantation. Br J Haematol. 2003;121(4): 597–604.
82. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest. 1998;102(7):1369–76.
83. Socie G, Loiseau P, Tamouza R, Janin A, Busson M, Gluckman E, et al. Both genetic and clinical factors predict the development of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Transplantation. 2001;72(4):699–706.
84. Ambruzova Z, Mrazek F, Raida L, Jindra P, Vidan-Jeras B, Faber E, et al. Association of IL6 and CCL2 gene polymorphisms with the outcome of allogeneic haematopoietic stem cell transplantation. Bone Marrow Transpl. 2009;44(4):227–35.
85. Karabon L, Wysoczanska B, Bogunia-Kubik K, Suchnicki K, Lange A. IL-6 and IL-10 promoter gene polymorphisms of patients and donors of allogeneic sibling hematopoietic stem cell transplants associate with the risk of acute graft-versus-host disease. Hum Immunol. 2005;66(6):700–9.
86. Suarez A, Castro P, Alonso R, Mozo L, Gutierrez C. Interindividual variations in constitutive interleukin-10 messenger RNA and protein levels and their association with genetic polymorphisms. Transplantation. 2003;75(5):711–7.
87. Crawley E, Kay R, Sillibourne J, Patel P, Hutchinson I, Woo P. Polymorphic haplotypes of the interleukin-10 5′ flanking region determine variable interleukin-10 transcription and are associated with particular phenotypes of juvenile rheumatoid arthritis. Arthr Rheum. 1999;42(6):1101–8.
88. Sivula J, Turpeinen H, Volin L, Partanen J. Association of IL-10 and IL-10Rbeta gene polymorphisms with graft-versus-host disease after haematopoietic stem cell transplantation from an HLA-identical sibling donor. BMC Immunol. 2009;10:24.
89. Lin M-T, Storer B, Martin PJ, Tseng L-H, Gooley T, Chen P-J, et al. Relation of an interleukin-10 promoter polymorphism to graft-versus-host disease and survival after hematopoietic-cell transplantation. N Engl J Med. 2003;349(23):2201–10.
90. Lin MT, Storer B, Martin PJ, Tseng LH, Grogan B, Chen PJ, et al. Genetic variation in the IL-10 pathway modulates severity of acute graft-versus-host disease following hematopoietic cell transplantation: synergism between IL-10 genotype of patient and IL-10 receptor beta genotype of donor. Blood. 2005; 106(12):3995–4001.
91. Cavet J, Middleton PG, Segall M, Noreen H, Davies SM, Dickinson AM. Recipient tumor necrosis factor-α and interleukin-10 gene polymorphisms associate with early mortality and acute graft-versus-host disease severity in HLA-matched sibling bone marrow transplants. Blood. 1999;94(11):3941–6.
92. Takahashi H, Furukawa T, Hashimoto S, Suzuki N, Kuroha T, Yamazaki F, et al. Contribution of TNF-alpha and IL-10 gene polymorphisms to graft-versus-host disease following allohematopoietic stem cell transplantation. Bone Marrow Transpl. 2000;26(12):1317–23.
93. Middleton PG, Cullup H, Dickinson AM, Norden J, Jackson GH, Taylor PR, et al. Vitamin D receptor gene polymorphism associates with graft-versus-host disease and survival in HLA-matched sibling allogeneic bone marrow transplantation. Bone Marrow Transpl. 2002;30(4):223–8.
94. Hazlett J, Stamp LK, Merriman T, Highton J, Hessian PA. IL-23R rs11209026 polymorphism modulates IL-17A expression in patients with rheumatoid arthritis. Genes Immun. 2012;13(3): 282–7.
95. Elmaagacli AH, Koldehoff M, Landt O, Beelen DW. Relation of an interleukin-23 receptor gene polymorphism to graft-versus-host disease after hematopoietic-cell transplantation. Bone Marrow Transpl. 2008;41(9):821–6.
96. Gruhn B, Intek J, Pfaffendorf N, Zell R, Corbacioglu S, Zintl F, et al. Polymorphism of interleukin-23 receptor gene but not of NOD2/CARD15 is associated with graft-versus-host disease after hematopoietic stem cell transplantation in children. Biol Blood Marrow Transpl. 2009;15(12):1571–7.
97. Ambruzova Z, Mrazek F, Raida L, Stahelova A, Faber E, Indrak K, et al. Possible impact of MADCAM1 gene single nucleotide polymorphisms to the outcome of allogeneic hematopoietic stem cell transplantation. Hum Immunol. 2009;70(6):457–60.
98. Frosst P, Blom HJ, Milos R, Goyette P, Sheppard CA, Matthews RG, et al. A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase. Nat Genet. 1995;10(1):111–3.
99. Robien K, Schubert MM, Chay T, Bigler J, Storb R, Yasui Y, et al. Methylenetetrahydrofolate reductase and thymidylate synthase genotypes modify oral mucositis severity following hematopoietic stem cell transplantation. Bone Marrow Transpl. 2006;37(8):799–800.
100. Murphy N, Diviney M, Szer J, Bardy P, Grigg A, Hoyt R, et al. Donor methylenetetrahydrofolate reductase genotype is associated with graft-versus-host disease in hematopoietic stem cell transplant patients treated with methotrexate. Bone Marrow Transpl. 2006;37(8):773–9.
101. Murphy NM, Diviney M, Szer J, Bardy P, Grigg A, Hoyt R, et al. The effect of folinic acid on methylenetetrahydrofolate reductase polymorphisms in methotrexate-treated allogeneic hematopoietic stem cell transplants. Biol Blood Marrow Transpl. 2012;18(5):722–30.
102. Brenmoehl J, Herfarth H, Glück T, Audebert F, Barlage S, Schmitz G, et al. Genetic variants in the NOD2/CARD15 gene are associated with early mortality in sepsis patients. Intens Care Med. 2007;33(9):1541–8.
103. Holler E, Rogler G, Brenmoehl J, Hahn J, Greinix H, Dickinson AM, et al. The role of genetic variants of NOD2/CARD15, a receptor of the innate immune system, in GvHD and complications following related and unrelated donor haematopoietic stem cell transplantation. Int J Immunogenet. 2008;35(4–5): 381–4.
104. Elmaagacli AH, Koldehoff M, Hindahl H, Steckel NK, Trenschel R, Peceny R, et al. Mutations in innate immune system NOD2/CARD 15 and TLR-4 (Thr399Ile) genes influence the risk for severe acute graft-versus-host disease in patients who underwent an allogeneic transplantation. Transplantation. 2006; 81(2):247–54.
105. Arora M, Lindgren B, Basu S, Nagaraj S, Gross M, Weisdorf D, et al. Polymorphisms in the base excision repair pathway and graft-versus-host disease. Leukemia. 2010;24(8):1470–5.

106. Goodman RS, Ewing J, Evans PC, Craig J, Poulton K, Dyer PA, et al. Donor CD31 genotype and its association with acute graft-versus-host disease in HLA identical sibling stem cell transplantation. Bone Marrow Transpl. 2005;36(2):151–6.
107. Sellami MH, Torjemane L, Ladeb S, Kaabi H, Ahmed AB, Cherif G, et al. Investigation of the effect of donor platelet endothelial cell adhesion molecule 1 polymorphism on the graft-vs.-host disease occurrence in Tunisian recipients of hematopoietic stem cells. Clin Biochem. 2011;44(8–9):699–703.
108. Sellami MH, Ladeb S, Kaabi H, Cherif G, Torjemane L, Othman TB, et al. Acute graft-vs.-host disease correlates with the disparity for the PECAM-1 S536N polymorphism only in the HLA-B44-like positive Tunisian recipients of HSCs. Cell Immunol. 2010;265(2):172–8.
109. Cavanagh G, Chapman CE, Carter V, Dickinson AM, Middleton PG. Donor CD31 genotype impacts on transplant complications after human leukocyte antigen-matched sibling allogeneic bone marrow transplantation. Transplantation. 2005;79(5):602–5.
110. Samaan S. Guérin-El Khourouj V, Auboeuf D, Peltier L, Pédron B, Ouachée-Chardin M, et al. Outcome of children treated with haematopoietic-stem cell transplantations from donors expressing the rare C77G variant of the PTPRC (CD45) gene. Br J Haematol. 2011;153(1):47–57.
111. Yokota M, Ichihara S, Lin T-L, Nakashima N, Yamada Y. Association of a T29 → C polymorphism of the transforming growth factor-β1 gene with genetic susceptibility to myocardial infarction in Japanese. Circulation. 2000;101(24):2783–7.
112. Tambur AR, Yaniv I, Stein J, Lapidot M, Shabtai E, Kfir B, et al. Cytokine gene polymorphism in patients with graft-versus-host disease. Transpl Proc. 2001;33(1–2):502–3.
113. Noori-Daloii MR, Rashidi-Nezhad A, Izadi P, Hossein-Nezhad A, Sobhani M, Derakhshandeh-Peykar P, et al. Transforming growth factor-beta1 codon 10 polymorphism is associated with acute GVHD after allogenic BMT in Iranian population. Ann Transpl. 2007;12(4):5–10.
114. Hattori H, Matsuzaki A, Suminoe A, Ihara K, Nagatoshi Y, Sakata N, et al. Polymorphisms of transforming growth factor-beta1 and transforming growth factor-beta1 type II receptor genes are associated with acute graft-versus-host disease in children with HLA-matched sibling bone marrow transplantation. Bone Marrow Transpl. 2002;30(10):665–71.
115. Sivula J, Cordova ZM, Tuimala J, Jaatinen T, Partanen J, Volin L, et al. Toll-like receptor gene polymorphisms confer susceptibility to graft-versus-host disease in allogenic hematopoietic stem cell transplantation. Scand J Immunol. 2012;76(3):336–41.
116. Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, et al. TLR4 mutations are associated with endotoxin hyporesponsiveness in humans. Nat Genet. 2000;25(2):187–91.
117. Cay HF, Sezer I, Dogan S, Felek R, Aslan M. Polymorphism in the TNF-alpha gene promoter at position -1031 is associated with increased circulating levels of TNF-alpha, myeloperoxidase and nitrotyrosine in primary Sjogren's syndrome. Clin Exp Rheumatol. 2012;30(6):843–9.
118. Uglialoro AM, Turbay D, Pesavento PA, Delgado JC, McKenzie FE, Gribben JG, et al. Identification of three new single nucleotide polymorphisms in the human tumor necrosis factor-alpha gene promoter. Tissue Antigens. 1998;52(4):359–67.
119. Ishikawa Y, Kashiwase K, Akaza T, Morishima Y, Inoko H, Sasazuki T, et al. Polymorphisms in TNFA and TNFR2 affect outcome of unrelated bone marrow transplantation. Bone Marrow Transpl. 2002;29(7):569–75.
120. Stark GL, Dickinson AM, Jackson GH, Taylor PR, Proctor SJ, Middleton PG. Tumour necrosis factor receptor type II 196M/R genotype correlates with circulating soluble receptor levels in normal subjects and with graft-versus-host disease after sibling allogeneic bone marrow transplantation. Transplantation. 2003;76(12):1742–9.
121. Mandola MV, Stoehlmacher J, Zhang W, Groshen S, Yu MC, Iqbal S, et al. A 6 bp polymorphism in the thymidylate synthase gene causes message instability and is associated with decreased intratumoral TS mRNA levels. Pharmacogenet Genom. 2004;14(5):319–27.
122. Hirata H, Hinoda Y, Zaman MS, Chen Y, Ueno K, Majid S, et al. Function of UDP-glucuronosyltransferase 2B17 (UGT2B17) is involved in endometrial cancer. Carcinogenesis. 2010;31(9):1620–6.
123. Morrison NA, Qi JC, Tokita A, Kelly PJ, Crofts L, Nguyen TV, et al. Prediction of bone density from vitamin D receptor alleles. Nature. 1994;367(6460):284–7.
124. Brogan IJ, Khan N, Isaac K, Hutchinson JA, Pravica V, Hutchinson IV. Novel polymorphisms in the promoter and 5′ UTR regions of the human vascular endothelial growth factor gene. Hum Immunol. 1999;60(12):1245–9.
125. Prior SJ, Hagberg JM, Paton CM, Douglass LW, Brown MD, McLenithan JC, et al. DNA sequence variation in the promoter region of the VEGF gene impacts VEGF gene expression and maximal oxygen consumption. Am J Physiol-Heart C. 2006;290(5):H1848–55.
126. Kim DH, Lee NY, Lee M-H, Sohn SK. Vascular endothelial growth factor gene polymorphisms may predict the risk of acute graft-versus-host disease following allogeneic transplantation: preventive effect of vascular endothelial growth factor gene on acute graft-versus-host disease. Biol Blood Marrow Transpl. 2008;14(12):1408–16.
127. Ogawa S, Matsubara A, Onizuka M, Kashiwase K, Sanada M, Kato M, et al. Exploration of the genetic basis of GVHD by genetic association studies. Biol Blood Marrow Transpl. 2009;15(1 Suppl):39–41.