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Defining Genetic Risk for GVHD and Mortality Following Allogeneic Hematopoietic Stem Cell Transplantation

John A Hansen, Jason W Chien, Edus H Warren, Lue Ping Zhao, and Paul J Martin

The Fred Hutchinson Cancer Research Center and the University of Washington School of Medicine

Abstract

Purpose of review—To explore what is known about the genetics of hematopoietic stem cell transplantation (HCT) and how genetic polymorphism affects risk of graft-versus-host disease (GVHD) and mortality.

Recent findings—Genetic variation found across the human genome can impact HCT outcome by 1) causing genetic disparity between patient and donor, and 2) modifying gene function. Single nucleotide polymorphisms (SNP) and structural variation can result in mismatching for cellular peptides known as histocompatibility antigens (HA). At least 25 to 30 polymorphic genes are known to encode functional HA in mismatched individuals, but their individual contribution to clinical GVHD is unclear. HCT outcome may also be affected by polymorphism in donor or recipient. Association studies have implicated several genes with GVHD and mortality, however results have been inconsistent most likely due to limited sample size, and differences in racial diversity and clinical covariates. New technologies using DNA arrays genotyping for a million or more SNPs promise genome-wide discovery of HCT associated genes, however adequate statistical power requires study populations of several thousand patient-donor pairs.

Summary—Available data offers strong preliminary support for the impact that genetic variation has on risk of GVHD and mortality following HCT. Definitive results however await future genome-wide studies of large multi-center HCT cohorts.

Keywords

Graft-versus-host disease (GVHD); histocompatibility antigens (HA); single nucleotide polymorphism (SNP); genome-wide association studies (GWAS); transplant-related mortality (TRM)

Introduction

A modern revolution in human genetics research began with publication ten years ago of the first edition sequence for the human genome [1,2]. During the subsequent decade, major advances have occurred in the development of DNA arrays and high density genotyping, parallel processing, next generation sequencing and bioinformatics. Clinical applications recently beyond reach are increasingly approachable, together with the promise that personalized medicine eventually can be translated from theory to practice [3,4]. The opportunity for the development of genomic strategies and tools for risk assessment, counseling and treatment planning are more compelling than ever before.

Genetic analysis has been an essential feature of clinical allogeneic hematopoietic stem cell transplantation (HCT) for more than nearly 40 years. Success in the early years and refinements in donor selection the last few years have been based on a detailed understanding of the genetics of the human major histocompatibility (MHC) and the development of DNA-based methods for high resolution genotyping of the highly polymorphic HLA genes. Mismatching for HLA has a adverse effect on HCT outcome and increases risk of severe GVHD, graft rejection and mortality[5–8], and prolongs the duration of chronic GVHD[9], while optimization of high resolution typing and allele-level donor and recipient HLA-matching has improved HCT outcome. [10] The role of non-HLA genes in generating alloimmune responses after HCT has been well defined for at least a few selected genes using T cell clones, but little progress has been made in completing a catalog of these genes across the genome. In this review we address current knowledge about the contribution of non-MHC polymorphisms to HCT biology, first discussing novel approaches to measuring genetic disparity between donor and recipient genome-wide, and then reviewing evidence that other common genetic variants in the donor or recipient can affect gene function and HCT outcome.

Genetic disparity and alloimmune response

Early pioneers in transplantation biology observed that genetic variation between individuals could induce immune responses in a recipient or donor and cause graft rejection or GVHD, and they hypothesized the existence of polymorphic genes encoding histocompatibility antigens (HA) capable of inducing both cellular and humoral immunity. [11,12] The strongest HA, also referred to as major HA, are encoded by the class I and class II HLA genes of the major histocompatibility complex (MHC). [11] Although greater risk of GVHD and mortality is associated with HLA mismatching, [5,8] clinically significant GVHD also occurs in HLA identical transplants, demonstrating that other genes in addition to HLA encode HA. [13] The strength of these non-HLA or minor HA may be relatively weak and they may activate only a limited number of T cells, but the overall response to minor HA encoded throughout the genome can induce a polyclonal T cell response capable of causing severe and life-threatening GVHD. The number of functional minor HA present in any donor-recipient pair is undetermined, but most probably exceeds the 25–30 currently known minor HA by a 100-fold or more.

Minor HA in related and unrelated donor transplants

Siblings share by common inheritance approximately 50% of all their genes, including those that encode minor HA, while unrelated individuals share far fewer genes. Therefore the burden of minor HA disparity must be greater in unrelated compared to related donor transplants. [14]

Minor HA and GVHD

There have been several published studies that have tested different minor HA for association with GVHD, however the results of these studies have been variable (summarized in a recent review by E.H. Warren in 2009).[15] Although studies in HCT recipients as well as in vitro studies have clearly demonstrated that minor HA genes are capable of eliciting clonal T cell responses, clinical association studies have been unable to consistently measure the individual effect of specific minor HA on GVHD risk.

Y-chromosome associated HA

In addition to the classical MHC and minor HA, cellular proteins encoded by the Y-chromosome can also induce an alloimmune response. [16,17] Disparity for the Y-chromosome occurs when male recipients receive HSC grafts from female donors (F→M).

The alloimmune response that follows is sufficiently strong to result in an increased risk of acute and chronic GVHD.[9,18–22] The strength of the anti-Y response can be explained in part by the presence of several genes on the Y chromosome that are found in strong linked disequilibrium and which encode multiple male-specific epitopes (*SMCY*, *UTY*, *DDX3Y*, *USP9Y*, *RPS4Y1*, *TMSB4Y*, and *ZFY*) that can elicit multiple CD4+ and CD8+ T cell, and B cell responses in F→M HCT. [16,17,19,23–32]

Structural polymorphisms and gene deletions

Another class of non-MHC genes affecting HCT outcome is illustrated by the recent study by McCarroll et al showing that deletion of the entire *UGT2B17* gene in the donor but not the recipient can result in an alloimmune response associated with acute GVHD. [33] This multi-center study initially examined six common deletions (*UGT2B17*, *UGT2B28*, *GSTT1*, *GSTM1*, *LCE3C* and *OR51A2*) in a phase I discovery study using 414 HLA MRD transplants. The association of the *UGT2B17* deletion with acute GVHD was validated in a phase II study of two additional cohorts with 336 and 595 HLA-identical sibling transplants respectively. The odds ratio for the overall association was 2.5 ($p=5\times 10^{-4}$). [33] The cumulative incidence of grade 2–4 acute GVHD associated with the *UGT2B17* deletion in the cohort of 595 matched sibling donor transplant recipients from our Center is illustrated in Figure 1. The *UGT2B17* gene is homozygously deleted in a variable proportion of every human population studied to date. [34] Several studies [35–37] have shown that HCT donors with homozygous deletion of *UGT2B17* make CD8+ *UGT2B17*-specific T cell responses in recipients who express at least one copy of the gene.

Collectively, analysis of the effect of recipient incompatibility for MHC and non-MHC genetic disparity demonstrates that the risk of GVHD and mortality associated with different genes spans a wide spectrum. HLA disparity generally has a strong effect, disparity for individual minor HA loci, e.g. *HA-I*, a much weaker effect, while disparity for the Y chromosome and the *UGT2B17* deletion has an intermediate effect most likely because the latter encode several distinct minor HA. Although HLA restriction of T cell responses is clearly defined for individual epitopes or peptides, larger blocks or segments of DNA such as that affected by the *UGT2B17* deletion can alter multiple immune epitopes and potentially induce a broad immune response. While T cell responses to single peptides, measured individually, would be relatively weak, the more complex deletions and Y chromosome encoded minor HA are stronger and significantly contribute to clinical GVH. The relative strength of these minor HA is illustrated in Figure 2.

Genome-wide assessment of minor HA disparity

Ogawa et al have published a preliminary summary of their experience using a GWAS approach to measuring genome-wide disparity. [38] They performed genome-wide SNP scans for 1598 HLA-A, B, C, DRB1 and DQB1 matched unrelated patient-donor pairs, and measured SNP-by-SNP donor-recipient disparity across the genome under the assumption that there was no HLA restriction operating. The scan revealed a single relatively strong signal associated with grade 2–4 acute GVHD which mapped to the HLA-DP region with a maximum p value of 1.81×10^{-9} for SNP rs6937034. No other signals were detected under the assumption of no HLA restriction, but when the association analysis was limited to patients expressing HLA-DQB1*0601 a signal was detected on chromosome number 12 (rs17473423; $p=3.99\times 10^{-13}$), and when the analysis was limited to patients expressing HLA-B*4403, another signal was detected on chromosome 9 (rs9657655; $p=8.56\times 10^{-10}$) (Figure 3B and 3C). [38] Overall, four additional loci were identified when the analysis was adjusted for restriction by DQB1*0501, Cw*0102, B85201 and Cw*1202.

Genetic variation affecting gene function, immune response and disease risk

In addition to the genetic variation that encodes disparity for HLA and minor HA, many genetic polymorphisms are functional variants that affect gene transcription and translation, and protein structure. Most of the polymorphism in the human genome exists as single nucleotide polymorphisms (SNP). More than 13 million single nucleotide polymorphisms (SNPs) have been identified through massive resequencing by several laboratories participating in the 1000 genomes project (<http://www.1000genomes.org/page.php>). Individual SNPs can be identified by various methods including PCR assays using specific primer pairs, and a million or more SNPs can be identified using DNA arrays.

Candidate gene studies

A candidate gene association study is usually the approach of choice when testing a specific hypothesis or replicating and confirming a prior study. This approach is generally efficient and cost effective when the task requires genotyping for one or a few dozen SNPs.

Genome-wide association studies (GWAS)

The advent of DNA array technology and parallel processing has allowed for simultaneous genotyping for a million or more SNPs [39,40] and the development of dense SNP marker maps across the genome, [39,41–43,43] making it possible to screen genes in an unbiased manner for polymorphisms that correlate with phenotype, disease status and relevant quantitative traits. As shown by multiple studies, the GWAS approach has been very successful in discovery and the identification of new genetic variation and genes associated with disease risk. [44] GWAS has uniquely contributed to the discovery of disease associated genes in diabetes, [45,46] rheumatoid arthritis, [47,48] and multiple sclerosis [49] by scanning the genomes of tens of thousands of individuals. A catalog of published GWAS results compiled by NIH is available at: www.genome.gov/gwastudies.

Results from candidate gene association studies

Previous candidate gene studies have reported polymorphisms implicating at least 18 genes as associated with GVHD and mortality (specific genes, SNPs and associations summarized in Table 1 [50–80]). Results however have not always been consistent, and followup studies have often failed to confirm findings of previous studies. The reasons for these differences may be explained by heterogeneity among patient populations for race and clinical variables, but most likely failure to replicate these early studies reflects problems with statistical power and inadequate sample size. As an example, we discuss two genes that belong to the same pathway, IL10 and IL10RB.

The IL10 pathway and GVHD

The IL10 gene has been subject of several studies, and although results are not consistent, the cumulative evidence indicates that there is an IL10 effect in HCT outcome. Middleton et al were the first to report an association for an IL10-linked microsatellite polymorphism (–1064) with severe acute GVHD. [66] This IL10 association with acute GVHD was expanded by the same group in a larger group of 144 MRD transplants to also include a SNP mapping to position –1082 in the IL10 5' promoter region (rs1800896). Socie et al analyzed three IL10 promoter region SNPs 100 MRD transplants and identified an association with acute GVHD for a promoter region haplotype defined by three SNPs (–1082/–819/–592). [56]

We began our studies of the IL10 gene with a discovery phase analysis of two promoter region SNPs, –592 (rs1800872) and –1082 (rs1800896), in 570 MRD transplants, and showed an association of SNP –592 in the patient with severe acute GVHD and TRM.[60]

Following successful replication in an independent cohort of 423 MRD transplants, we combined the cohorts and in a subsequent analysis of the total 993 transplant recipients showed that the presence in the patient of the IL10/−592*AA *genotype* compared with the CC *genotype* was associated with both a decreased risk of grade 3–4 acute GVHD (HR, 0.4; p=0.02) and risk of nonrelapse mortality (HR, 0.6; p=0.05). A haplotype analysis showed that the IL10/−592*A *allele* was a specific tag SNP for the promoter region haplotype T-C-A-T-A (SNPs at positions −3575, −2763, −1082, −819, and −592). [60]

Results of other studies of IL10 gene, however have been variable and often contrary. Rocha et al found a significant association of IL10/−1082 with chronic GVHD in 107 HLA MRD, but no significant association with acute GVHD or TRM. Mullighan et al similarly found a significant association of the −592/−819/−1082 haplotype in the patient with chronic GVHD in 160 MRD transplants, but no significant association with acute GVHD or TRM. [54] Sivula et al found an association of the patient IL10/−592*AA *genotype* with an increased risk of acute GVHD in 309 MRD transplants,[70] an effect opposite to that reported by Lin et al.[60] Keen et al analyzed the IL10 gene in unrelated donor transplants and found an association of an extended haplotype consisting of the microsatellite marker IL10R2 together with the −1082/−819/−592 IL10 promoter region SNPs associated with an increased risk of TRM.[68] A study of IL10 promoter region SNPs in 936 unrelated donor transplants at our Center, however failed to show any significant association with GVHD or TRM. [69]

We have extended the genetic analysis of the IL10 pathway in GVHD to include the IL10RB gene encoding one of two IL-10 receptors. We genotyped for a SNP at cDNA position 238 in exon 2 of the IL10RB gene (*rs2834167*) that is known to regulate the expression of the IL10 receptor.[81] The presence of the IL10RB/c238*G *allele* in the donor was significantly associated with a lower risk of grades III–IV acute GVHD in MRD transplants, and a synergism was observed between IL10/−592*A and IL10RB/c238*G in reducing the overall risk of acute GVHD. [71] More recently, Sivula et al have reported a comparable effect for the c238 SNP with an association of the *AA *genotype* with an increased risk of acute GVHD in MRD transplants albeit in the patient and not the donor genome. [70] The inconsistency of the results for IL10 as detailed in this preceding section almost certainly apply to the other genes listed in Table 1. A more clear understanding and definitive analysis of the genetics of GVHD will require much larger population studies appropriately stratified to control for racial admixture and adjusted for clinical covariates that may be confounding the overall results.

Genome-wide association studies in HCT

Preliminary results from two GWAS-HCT projects related to HCT have been published. Ogawa et al are performing a GWAS of unrelated HCT patient-donor pairs transplanted through the Japanese Marrow Donor Program, [38] and our group has embarked upon a GWAS of GVHD and other HCT outcomes including opportunistic infection and organ specific complications. [82] From 3,177 patients undergoing HCT at our Center between 1992 and 2005 for whom DNA was available, we randomly selected a discovery cohort 1,560 donor-patient pairs (total of 3,120 samples), and reserved the remainder patient/donor pairs as the validation cohort. Samples were genotyped using the Affymetrix GeneChip® Genome-Wide Human SNP Array 5.0, which contains over 500,000 SNPs placed evenly across the genome.

Following the GWAS convention, we assessed SNP-allelic and genotypic associations with each of multiple clinical phenotypes. In the GWAS community, a generally accepted significance level is a p-value 10^{-8} (equivalent to the p-value of 1% with Bonferroni

correction for one million SNP comparisons). Since the significance level is influenced by linkage-disequilibrium structure, we performed 1,000 permutations on our own genomewide data, and established the significance threshold by controlling the average number of false discoveries to be less than 1 under the genomewide null hypothesis, resulting in a p-value of 10^{-6} as the threshold for significance in our cohort. With this criterion, we identified 65 SNPs among 12 HCT phenotypes as candidates for the replication studies (Table 2). As described by Chien et al, the gram negative bacteremia GWAS results have been tested for replication. [82] Of the 9 SNPs found to be significant in the initial GWAS, all in the genome of the patient, one was successfully replicated. Prompted by this disappointing finding, we re-examined the prior power estimations and explored the potential advantages of expanding the size of the phase I discovery analysis. We thus considered how the power for discovery might be affected by a 2.5-fold increase in sample size. Figure 4 shows the power curves for detecting dominant genetic associations with minor allele frequencies (MAF) of 10% and 25%, when the sample size is 1500 (dashed lines) and 4000 (solid lines). Increasing sample size uniformly improves power across a range of odds ratios from 1.2 to 2.0 (which is equivalent to a hazard ratio in a time-to-event analysis under rare disease assumption). Thus, it should be possible to achieve a more than doubling of the study power for detecting odds ratios of 1.5 across different allelic frequencies in the expanded cohort with a 2.5-fold increase in sample size. The improvement in power is even greater for an odds ratio ranging from 1.5 to 1.8, and power is also improved for lower incidence rates in the range of 10%. These power calculations suggest that expanding the sample size from 1,500 to 4000 cases as proposed should increase sensitivity and power for discovery and thereby broaden the ultimate utility of this dataset by identifying additional genetic variants that may be missed in the current study and yet are clinically meaningful.

Conclusion

Candidate gene studies performed to date have been far from conclusive and were largely limited in sample size, but they have nonetheless provided compelling evidence that genetic variation in the donor and patient can affect transplant outcome. Definitive utilization of GWAS and more adequately powered studies will require extensive multi-center participation, resources to prospectively collect pretransplant DNA, uniform eligibility requirements, standardized definition of clinical phenotypes and informed consent appropriate for performing genome-wide genetic studies. Achieving complex studies like this in the future will also require the careful planning, discipline and funding provided by large cooperative clinical trials.

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Abbreviations

GWAS	Genome-wide association studies
GVHD	graft-versus-host disease
HCT	hematopoietic stem cell transplant
HA	histocompatibility antigens
MRD	HLA matched related donor
HLA	Human leukocyte antigens

MHC	human major histocompatibility
SNP	complex single nucleotide polymorphism
TRM	transplant-related mortality
URD	unrelated donor

Reference List

1. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome [erratum appears in Nature 2001 Aug 2;412(6846):565 Note: Szustakowski, J [corrected to Szustakowski, J]. Nature. 2001; 409:860–921. [PubMed: 11237011]
2. Venter JC, Adams MD, Myers EW, et al. The sequence of the human genome [erratum appears in Science 2001 Jun 5;292(5523):1838]. Science. 2001; 291:1304–1351. [PubMed: 11181995]
- 3**. Varmus H. Ten years on--the human genome and medicine. N Engl J Med. 2010; 362:2028–2029. A current review of the progress of the human genome project over the last decade, and important insights into human genetic variation that have resulted. [PubMed: 20505183]
- 4**. Collins F. Has the revolution arrived? Nature. 2010; 464:674–675. An important current editorial commenting on the progress and current priorities of the human genome project, and realistic future clinical applications. Complements well the review by H. Varmus. [3]. [PubMed: 20360716]
5. Beatty PG, Clift RA, Mickelson EM, et al. Marrow transplantation from related donors other than HLA-identical siblings. N Engl J Med. 1985; 313:765–771. [PubMed: 3897863]
6. Beatty PG, Anasetti C, Hansen JA, et al. Marrow transplantation from unrelated donors for treatment of hematologic malignancies: effect of mismatching for one HLA locus. Blood. 1993; 81:249–253. [PubMed: 8417795]
7. Flomenberg N, Baxter-Lowe LA, Confer D, et al. Impact of HLA class I and class II high resolution matching on outcomes of unrelated donor bone marrow transplantation: HLA-C mismatching is associated with a strong adverse effect on transplant outcome. Blood. 2004; 104:1923–1930. [PubMed: 15191952]
8. Petersdorf EW, Gooley TA, Anasetti C, et al. Optimizing outcome after unrelated marrow transplantation by comprehensive matching of HLA class I and II alleles in the donor and recipient. Blood. 1998; 92:3515–3520. [PubMed: 9808542]
9. Stewart BL, Storer B, Storek J, et al. Duration of immunosuppressive treatment for chronic graft-versus-host disease. Blood. 2004; 104:3501–3506. [PubMed: 15292060]
10. Lee SJ, Klein J, Haagenson M, et al. High-resolution donor-recipient HLA matching contributes to the success of unrelated donor marrow transplantation. Blood. 2007; 110:4576–4583. [PubMed: 17785583]
11. Snell, GD.; Dausset, J.; Nathenson, S. Histocompatibility. New York, NY: Academic Press; 1976.
12. Elkins WL. Cellular immunology and the pathogenesis of graft versus host reactions (Review). Prog Allergy. 1971; 15:78–187. [PubMed: 4151282]
13. Perreault C, Décary F, Brochu S, et al. Minor histocompatibility antigens. Blood. 1990; 76:1269–1280. [PubMed: 2207305]
14. Martin PJ. Increased disparity for minor histocompatibility antigens as a potential cause of increased GVHD risk in marrow transplantation from unrelated donors compared with related donors. Bone Marrow Transplant. 1991; 8:217–223. [PubMed: 1958902]
- 15**. Warren, EH. The human graft-versus-tumor response - and how to exploit it. In: Appelbaum, FR.; Forman, SJ.; Negrin, RS., et al., editors. Thomas' Hematopoietic Cell Transplantation. 4. Oxford, UK: Wiley-Blackwell; 2009. p. 232-247. A comprehensive review of the biology of minor histocompatibility antigens and their role as targets for GVHD and graft-vs.-tumor therapy. A valuable resource that summarizes the extensive literature describing the association or lack of association of disparity for minor histocompatibility antigens with risk of acute GVHD. The cumulative evidence unfortunately demonstrates that matching for individual minor

histocompatibility antigens has no measurable benefit in reducing the incidence or severity of acute GVHD

16. Wang W, Meadows LR, den Haan JM, et al. Human H-Y: a male-specific histocompatibility antigen derived from the SMCY protein. *Science*. 1995; 269:1588–1590. [PubMed: 7667640]
17. Warren EH, Gavin MA, Simpson E, et al. The human UTY gene encodes a novel HLA-B8-restricted H-Y antigen. *J Immunol*. 2000; 164 :2807–2814. [PubMed: 10679124]
18. Randolph SSB, Gooley TA, Warren EH, et al. Female donors contribute to a selective graft-versus-leukemia effect in male recipients of HLA-matched, related hematopoietic cell transplants. *Blood*. 2004; 103:347–352. [PubMed: 12969970]
19. Miklos DB, Kim HT, Miller KH, et al. Antibody responses to H-Y minor histocompatibility antigens correlate with chronic graft-versus-host disease and disease remission. *Blood*. 2005; 105:2973–2978. [PubMed: 15613541]
20. Loren AW, Bunin GR, Boudreau C, et al. Impact of donor and recipient sex and parity on outcomes of HLA-identical sibling allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant*. 2006; 12:758–769. [PubMed: 16785065]
21. Stern M, Passweg JR, Locasciulli A, et al. Influence of donor/recipient sex matching on outcome of allogeneic hematopoietic stem cell transplantation for aplastic anemia. *Transplantation*. 2006; 82:218–226. [PubMed: 16858285]
22. Stern M, Brand R, de Witte T, et al. Female-versus-male alloreactivity as a model for minor histocompatibility antigens in hematopoietic stem cell transplantation. *Am J Transplant*. 2008; 8:2149–2157. [PubMed: 18828773]
23. Meadows L, Wang W, den Haan JM, et al. The HLA-A*0201-restricted H-Y antigen contains a posttranslationally modified cysteine that significantly affects T cell recognition. *Immunity*. 1997; 6:273–281. [PubMed: 9075928]
24. Vogt MH, de Paus RA, Voogt PJ, et al. DFFRY codes for a new human male-specific minor transplantation antigen involved in bone marrow graft rejection. *Blood*. 2000; 95:1100–1105. [PubMed: 10648428]
25. Vogt MH, Goulmy E, Kloosterboer FM, et al. UTY gene codes for an HLA-B60-restricted human male-specific minor histocompatibility antigen involved in stem cell graft rejection: characterization of the critical polymorphic amino acid residues for T-cell recognition. *Blood*. 2000; 96:3126–3132. [PubMed: 11049993]
26. Vogt MH, van den Muijsenberg JW, Goulmy E, et al. The DBY gene codes for an HLA-DQ5-restricted human male-specific minor histocompatibility antigen involved in graft-versus-host disease. *Blood*. 2002; 99:3027–3032. [PubMed: 11929796]
27. Spierings E, Vermeulen CJ, Vogt MH, et al. Identification of HLA class II-restricted H-Y-specific T-helper epitope evoking CD4+ T-helper cells in H-Y-mismatched transplantation. *Lancet*. 2003; 362:610–615. [PubMed: 12944060]
28. Miklos DB, Kim HT, Zorn E, et al. Antibody response to DBY minor histocompatibility antigen is induced after allogeneic stem cell transplantation and in healthy female donors. *Blood*. 2004; 103:353–359. [PubMed: 14512314]
29. Zorn E, Miklos DB, Floyd BH, et al. Minor histocompatibility antigen DBY elicits a coordinated B and T cell response after allogeneic stem cell transplantation. *J Exp Med*. 2004; 199:1133–1142. [PubMed: 15096539]
30. Torikai H, Akatsuka Y, Miyazaki M, et al. A novel HLA-A*3303-restricted minor histocompatibility antigen encoded by an unconventional open reading frame of human TMSB4Y gene. *J Immunol*. 2004; 173:7046–7054. [PubMed: 15557202]
31. Ivanov R, Hol S, Aarts T, et al. UTY-specific TCR-transfer generates potential graft-versus-leukaemia effector T cells. *Br J Haematol*. 2005; 129:392–402. [PubMed: 15842664]
32. Rosinski KV, Fujii N, Mito JK, et al. DDX3Y encodes a class I MHC-restricted HY antigen that is expressed in leukemic stem cells. *Blood*. 2008; 111:4817–4826. [PubMed: 18299450]
- 33*. McCarroll SA, Bradner JE, Turpeinen H, et al. Donor-recipient mismatch for common gene deletion polymorphisms in graft-versus-host disease. *Nat Genet*. 2009; 41:1341–1345.
Homozygous deletions in an HCT donor that knock-out entire functional genes (eg, UTGB17 /) can result in disparity for multiple linked histocompatibility epitopes capable of inducing

- polyclonal T cell and B cell responses in donor T cells when transplanted to a wild type (eg, UGTB17_{+/+}) or UGTB17_{+/}) recipient. [PubMed: 19935662]
34. Xue Y, Sun D, Daly A, et al. Adaptive evolution of UGT2B17 copy-number variation. *Am J Hum Genet.* 2008; 83:337–346. [PubMed: 18760392]
 35. Murata M, Warren EH, Riddell SR. A human minor histocompatibility antigen resulting from differential expression due to a gene deletion. *J Exp Med.* 2003; 197:1279–1289. [PubMed: 12743171]
 36. Terakura S, Murata M, Warren EH, et al. A single minor histocompatibility antigen encoded by UGT2B17 and presented by human leukocyte antigen-A*2902 and -B*4403. *Transplantation.* 2007; 83:1242–1248. [PubMed: 17496542]
 - 37**. Kamei M, Nannya Y, Torikai H, et al. HapMap scanning of novel human minor histocompatibility antigens. *Blood.* 2009; 113:5041–5048. A novel innovation for rapidly mapping new minor histocompatibility antigens recognized by T cell clones using a standard cell line panel that has been densely genotyped for SNPs across the genome by DNA array technology. Once these celllines have been transfected with the appropriate HLA restriction element, the location of the target gene is determined by linkage analysis. [PubMed: 18809759]
 - 38**. Ogawa S, Matsubara A, Onizuka M, et al. Exploration of the genetic basis of GVHD by genetic association studies (Review). *Biol Blood Marrow Transplant.* 2009; 15 (Suppl):39–41. This paper is one of the first publications demonstrating the utility of the genome-wide association study approach using high-density DNA arrays for discovery of previously unrecognized minor histocompatibility genes in unrelated patient-donor transplant pairs. [PubMed: 19147076]
 39. Steemers FJ, Chang W, Lee G, et al. Whole-genome genotyping with the single-base extension assay. *Nature Methods.* 2006; 3:31–33. [PubMed: 16369550]
 40. Gunderson KL, Steemers FJ, Lee G, et al. A genome-wide scalable SNP genotyping assay using microarray technology. *Nat Genet.* 2005; 37:549–554. [PubMed: 15838508]
 41. Matsuzaki H, Dong S, Loi H, et al. Genotyping over 100,000 SNPs on a pair of oligonucleotide arrays. *Nature Methods.* 2004; 1:109–111. [PubMed: 15782172]
 42. Miller RD, Phillips MS, Jo I, et al. High-density single-nucleotide polymorphism maps of the human genome. *Genomics.* 2005; 86 :117–126. [PubMed: 15961272]
 43. Gabriel SB, Schaffner SF, Nguyen H, et al. The structure of haplotype blocks in the human genome. *Science.* 2002; 296:2225–2229. [PubMed: 12029063]
 44. Kruglyak L. The road to genome-wide association studies (Review). *Nat Rev Genet.* 2008; 9:314–318. [PubMed: 18283274]
 45. Hakonarson H, Grant SF, Bradfield JP, et al. A genome-wide association study identifies KIAA0350 as a type 1 diabetes gene. *Nature.* 2007; 448:591–594. [PubMed: 17632545]
 46. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature.* 2007; 447:661–678. [PubMed: 17554300]
 47. Plenge RM, Cotsapas C, Davies L, et al. Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat Genet.* 2007; 39:1477–1482. [PubMed: 17982456]
 48. Thomson W, Barton A, Ke X, et al. Rheumatoid arthritis association at 6q23. *Nat Genet.* 2007; 39:1431–1433. [PubMed: 17982455]
 49. International Multiple Sclerosis Genetics Consortium. Evidence for polygenic susceptibility to multiple sclerosis--the shape of things to come. *Am J Hum Genet.* 2010; 86:621–625. [PubMed: 20362272]
 50. Perez-Garcia A, de la CR, Roman-Gomez J, et al. CTLA-4 polymorphisms and clinical outcome after allogeneic stem cell transplantation from HLA-identical sibling donors. *Blood.* 2007; 110:461–467. [PubMed: 17384200]
 51. Azarian M, Busson M, Lepage V, et al. Donor CTLA-4 +49 A/G*GG genotype is associated with chronic GVHD after HLA-identical haematopoietic stem-cell transplantations. *Blood.* 2007; 110:4623–4624. [PubMed: 18056853]
 52. Wu J, Tang JL, Wu SJ, et al. Functional polymorphism of CTLA-4 and ICOS genes in allogeneic hematopoietic stem cell transplantation. *Clin Chim Acta.* 2009; 403:229–233. [PubMed: 19332044]

53. Middleton PG, Norden J, Cullup H, 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 Transplant.* 2003; 32 :41–47. [PubMed: 12815477]
54. Mullighan C, Heatley S, Doherty K, et al. Non-HLA immunogenetic polymorphisms and the risk of complications after allogeneic hemopoietic stem-cell transplantation. *Transplantation.* 2004; 27:587–596. [PubMed: 15084940]
55. Cavet J, Middleton PG, Segall M, et al. Recipient tumor necrosis factor-alpha 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; 94:3941–3946. [PubMed: 10572111]
56. Socie G, Loiseau P, Tamouza R, et al. Both genetic and clinical factors predict the development of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Transplantation.* 2001; 72:699–706. [PubMed: 11544434]
57. Cullup H, Dickinson AM, Cavet J, et al. Polymorphisms of interleukin-1alpha constitute independent risk factors for chronic graft-versus-host disease after allogeneic bone marrow transplantation. *Br J Haematol.* 2003; 122:778–787. [PubMed: 12930389]
58. Mehta PA, Eapen M, Klein JP, et al. Interleukin-1 alpha genotype and outcome of unrelated donor haematopoietic stem cell transplantation for chronic myeloid leukaemia. *Br J Haematol.* 2007; 137:152–157. [PubMed: 17391495]
59. MacMillan ML, Radloff GA, Defor TE, et al. Interleukin-1 genotype and outcome of unrelated donor bone marrow transplantation. *Br J Haematol.* 2003; 121:597–604. [PubMed: 12752101]
60. Lin M-T, Storer B, Martin PJ, 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; 349:2201–2210. [PubMed: 14657427]
61. Cullup H, Dickinson AM, Jackson GH, et al. 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; 113:807–813. [PubMed: 11380474]
62. Rocha V, Franco RF, Porcher R, et al. Host defense and inflammatory gene polymorphisms are associated with outcomes after HLA-identical sibling bone marrow transplantation. *Blood.* 2002; 100:3908–3918. [PubMed: 12393699]
63. MacMillan ML, Radloff GA, Kiffmeyer WR, et al. High-producer interleukin-2 genotype increases risk for acute graft-versus-host disease after unrelated donor bone marrow transplantation. *Transplantation.* 2003; 76:1758–1762. [PubMed: 14688528]
64. Karabon L, Wysoczanska B, Bogunia-Kubik K, et al. 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; 66:700–710. [PubMed: 15993715]
65. Shamim Z, Ryder LP, Heilmann C, et al. Genetic polymorphisms in the genes encoding human interleukin-7 receptor-alpha: prognostic significance in allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2006; 37:485–491. [PubMed: 16435014]
66. Middleton PG, Taylor PRA, Jackson G, et al. Cytokine gene polymorphisms associating with severe acute graft-versus-host disease in HLA-identical sibling transplants. *Blood.* 1998; 92:3943–3948. [PubMed: 9808588]
67. Takahashi H, Furukawa T, Hashimoto S, et al. Contribution of TNF-alpha and IL-10 gene polymorphisms to graft-versus-host disease following allo-hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2000; 26:1317–1323. [PubMed: 11223972]
68. Keen LJ, Defor TE, Bidwell JL, et al. Interleukin-10 and tumor necrosis factor alpha region haplotypes predict transplant-related mortality after unrelated donor stem cell transplantation. *Blood.* 2004; 103 :3599–3602. [PubMed: 14701704]
69. Tseng L-H, Storer B, Petersdorf E, et al. IL 10 and IL 10 receptor gene variation and outcomes after unrelated and related hematopoietic cell transplantation. *Transplantation.* 2009; 87:704–710. [PubMed: 19295315]

70. Sivula J, Turpeinen H, Volin L, et al. 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 Immunology*. 2009; 10 :24. [PubMed: 19409109]
71. Lin M-T, Storer B, Martin 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 β genotype of donor. *Blood*. 2005; 106:3995–4001. [PubMed: 16109775]
72. Cardoso SM, Defor TE, Tilley LA, et al. Patient interleukin-18 GCG haplotype associates with improved survival and decreased transplant-related mortality after unrelated-donor bone marrow transplantation. *Br J Haematol*. 2004; 126:704–710. [PubMed: 15327523]
73. Elmaagacli AH, Koldehoff M, Landt O, et al. Relation of an interleukin-23 receptor gene polymorphism to graft-versus-host disease after hematopoietic-cell transplantation. *Bone Marrow Transplant*. 2008; 41:821–826. [PubMed: 18209723]
74. Gruhn B, Intek J, Pfaffendorf N, 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 Transplant*. 2009; 15:1571–1577. [PubMed: 19896081]
- 75**. Nguyen Y, Al Lehibi A, Gorbe E, et al. Insufficient evidence for association of NOD2/CARD15 or other inflammatory bowel disease-associated markers on GVHD incidence or other adverse outcomes in T-replete, unrelated donor transplantation. *Blood*. 2010; 115:3625–3631. The most recent in a series of candidate gene association studies reporting different findings or contradictions to previous studies. Data reported here found no significant association for SNPs in NOD2 or IL23R and transplant outcome. The reason for these differences remains unclear. It is not likely that future studies can resolve these inconsistencies until the size of study populations is substantially increased into the 1000's rather than 100's of cases, and that more rigorous standard adjustments for racial diversity and clinical covariates are routinely included in the analysis. [PubMed: 20177049]
76. Holler E, Rogler G, Herfarth H, et al. Both donor and recipient NOD2/CARD15 mutations associate with transplant-related mortality and GvHD following allogeneic stem cell transplantation. *Blood*. 2004; 104:889–894. [PubMed: 15090455]
77. Holler E, Rogler G, Brenmoehl J, et al. Prognostic significance of NOD2/CARD15 variants in HLA-identical sibling hematopoietic stem cell transplantation: Effect on long term outcome is confirmed in 2 independent cohorts and may be modulated by the type of gastrointestinal decontamination. *Blood*. 2006; 107:4189–4193. [PubMed: 16424393]
78. Holler E. The role of innate immunity in graft-versus-host disease and complications following allogeneic stem cell transplant (Review). *Biol Blood Marrow Transplant*. 2008; 15(Suppl):59–61. [PubMed: 19147080]
79. Stark GL, Dickinson AM, Jackson GH, et al. 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; 76:1742–1749. [PubMed: 14688526]
80. Middleton PG, Cullup H, Dickinson AM, 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 Transplant*. 2002; 30:223–228. [PubMed: 12203138]
81. Frodsham AJ, Zhang L, Dumpis U, et al. Class II cytokine receptor gene cluster is a major locus for hepatitis B persistence. *PNAS*. 2006; 103:9148–9153. [PubMed: 16757563]
- 82**. Chien JW, Zhao LP, Storer B, et al. Improving hematopoietic cell transplant outcomes in a new era of genomic research. *Biol Blood Marrow Transplant*. 2009; 15 (Suppl 1):42–45. A GWAS study of gram negative bacteremia (GNB) after allogeneic HCT that lead to the identification of genes that might explain why some transplant patients are at increased risk of GNB. [PubMed: 19147077]

Figure 1. Incidence of acute GVHD in patients receiving HSC grafts from an HLA identical sibling

Curves represent UGT2B17⁺ patients receiving HSC grafts from UGT2B17^{-/-} donors (solid line) compared with other patients receiving grafts from UGT2B17⁺ donors (dashed line). Figure adapted from McCarroll et al [33]

Figure 2. Relative strength of histocompatibility antigens

This figure illustrates the relative strength of the different known minor histocompatibility antigens beginning on the left with polymorphic genes that encode individual epitopes and ending on the right with the highly polymorphic and immunogenetic class I and class II HLA genes of the major histocompatibility complex.

Figure 3. Representative results of a GWAS performed by Ogawa et al [38] based on genotype mismatch

$-\log_{10}P$ values are plotted in genetic order. Results are presented for association tests for genotype mismatch under no HLA restriction (A), and under the restriction to HLA DQB1*0601 (B) and HLA B*4403 (C). Figure adapted from Ogawa et al (Biol Blood Marrow Transplant 2009, 15(Suppl.):39–41). [38].

Figure 4. Summary of power estimations for an expanded GWAS HCT study

Improvement in statistical power is achieved by increasing the sample size from 1500 samples (black lines) to 5000 samples (red lines). Horizontal grey lines indicate relative risks of 1.5 and 2.0. Panels show results for SNPs with minor allele frequencies (MAF) ranging between 0.10 and 0.40.

Table 1

Published data identifying genetic variation associated with acute GVHD, chronic GVHD, TRM and survival

Gene	Reference	Polymorphism		Study population ¹	Phenotype ²	Association ^{3,4}
		Alias or VNTR	SNP			
CTLA4	Perez-Garcia 2007 [50]	+49, CT60	rs231775, rs3087243	MRD (536)	aGVHD, relapse, survival	CT60*AA(d) with ↑acute GVHD; ↓relapse, ↑survival; +49, nsa
	Azarian 2007 [51]	+49, CT60	rs231775	MRD (225)	aGVHD, cGVHD, relapse, survival	+49/GG(d) with ↑chronic GVHD; CT60, nsa
	Wu 2009 [52]	-318, +49	rs5742909, rs231775	MRD (123)	aGVHD, cGVHD, relapse, DFS	-318*TT(d) with ↑relapse; +49, nsa
ESR1	Middleton 2003 [53]	VNTR (AT) _n ERα intron 1	- -	MRD (108)	aGVHD, survival	VNTR, P X hap (p) with ↑acute GVHD
FAS	Mullighan 2004 [54]	-670	- -	MRD (160)	aGVHD	-670G (p) with ↑acute GVHD
IFNG	Cavet 2001 [55]	VNTR (CA) _n Intron 1	- -	MRD (80)	aGVHD	IFNG 3/3 (p) with ↑acute GVHD
	Socie 2001 [56]	+874	- -	MRD (100)	aGVHD	IFNG +874 (p&d): nsa
IL1A	Cullup 2003 [57]	-899, VNTR	- - - -	MRD (115)	cGVHD	-899, VNTR
	Mehta 2007 [58]	-889	- -	URD (426)	aGVHD & TRM	-889
IL1B	MacMillan BJH 2003 [59]	-511	rs16944	MRD	aGVHD	-511 (p)
	L in 2003 [60]	-511, +3954	rs16944, rs1143634	MRD (570)	aGVHD	-511 and +3954 (p/d): nsa
IL1RN	Cullup 2001 [61]	VNTR	- -	MRD (99)	aGVHD	allele 2 (d) with ↓acute GVHD
	Rocha 2002 [62]	VNTR, intron 2	- -	MRD (107)	aGVHD, cGVHD, TRM	absence of allele 2 (d) with ↑acute GVHD; nsa with cGVHD or TRM
	L in 2003 [60]	9261	rs448341	MRD (570)	aGVHD	nsa (p/d)
IL2	MacMillan Transplant 2003 [63]	-330 (G,T)	rs2069762	URD (95)	aGVHD, cGVHD	-330*G (p) with ↑acute grade II-IV acute GVHD; nsa with cGVHD
IL6	Mullighan 2004 [54]	-174	rs1800795	MRD (160)	aGVHD	-174 (d) with ↑acute GVHD
	Karabon 2005 [64]	-174	rs1800795	ND (93)	aGVHD	-174 (p/d)

Gene	Reference	Polymorphism		Study population ¹	Phenotype ²	Association ^{3,4}
		Alias or VNTR	SNP			
IL7R	Cavet 2001 [55]	-174	rs1800795	MRD (80)	cGVHD	-174*G (p) trend rs1800896; significant ↑chronic GVHD
	Socie 2001 [56]	-174		MRD (100)	cGVHD	IL6 -174*G (p) with ↑chronic GVHD
	Lin 2003 [60]	-174	rs1800795	MRD (570)	aGVHD	Nsa
	Shamim 2006 [65]	+510,+1237,+2087,+3110	--	MURD (75)	aGVHD, cGVHD, TRM	+1237*G (d) with ↑TRM
	Shamim 2006 [65]	+510,+1237,+2087,+3110	--	MRD (100)	aGVHD, cGVHD, TRM	nsa
IL10	Middleton 1998 [66]	IL10G ⁻¹⁰⁶⁴ (5)	(CA) _n	MRD (49)	aGVHD	12-15 CA repeats with ↑acute GVHD
	Cavet 1999 [55]	IL10 ⁻¹⁰⁶⁴ (VNTR)	(CA) _n	MRD (144)	aGVHD, cGVHD, TRM	IL10 ⁻¹⁰⁶⁴ (p) with ↑acute GVHD
	Takahashi 2000 [67]	IL10G (VNTR)	(CA) _n	MRD & URD (62)	aGVHD, cGVHD	>13 repeats (d) with ↑chronic GVHD; nsa with acute GVHD
	Socie 2001 [56]	-1082/-819/-592	--	MRD (100)	aGVHD	IL10 GCC Hap (p/dr) with ↓acute GVHD
	Lin 2003 [60]	-592, -1082, -2763, -3575	rs1800872, rs1800896, rs1800890	MRD (993)	aGVHD, cGVHD, TRM	-592*G (p) with ↓acute GVHD, ↑TRM
IL10RB	Mullighan 2004 [54]	-1082/-819/-592	--	MRD (160)	aGVHD	nsa with acute GVHD; ATA hap(p) with ↑chronic GVHD
	Rocha 2002 [62]	-1082*G/G(p)	--	MRD (107)	aGVHD, cGVHD, TRM	nsa with aGVHD or TRM; -1082*G/G(p) with ↑chronic GVHD
	Keen 2004 [68]	IL10G(VNTR), -1082, -819, -592 hap	--	URD (182)	TRM	IL10R2-G-C-C hap (d) with ↑TRM
	Tseng 2009 [69]	-592, -1082, -2763, -3575	rs1800872, rs1800896, rs1800890	URD (936)	aGVHD, cGVHD, NRM	nsa
	Sivula 2009 [70]	IL10/-592	rs1800872	MRD (309)	aGVHD, cGVHD	IL10/-592*AA (p) with ↑acute GVHD
IL10RB	Lin 2005 [71]	c238 (A,G)	rs2834167	MRD (993)	aGVHD	c238*G (d) with ↓acute GVHD
	Tseng 2009 [69]	c238 (A,G)	rs2834167	URD (936)	aGVHD, cGVHD, NRM	nsa
	Sivula 2009 [70]	IL10RB c238	rs28341676	MRD (309)	aGVHD, cGVHD	c238*AA (p) with ↑acute GVHD

Gene	Reference	Polymorphism		Study population ¹	Phenotype ²	Association ^{3,4}
		Alias or VNTR	SNP			
IL18	Cardoso 2004 [72]	-137/-607/-656		URD (157)	aGVHD, survival	GCG hap(p) with ↓TRM; nsa with aGVHD
IL23R	Elmaagacil 2008 [73]	+1142 (G,A)	Arg381Gln	MRD (221), URD (186)	aGVHD, NRM	1142*A (p) with ↓aGVHD and ↓NRM
	Gruhn 2009 [74]	+1142 (G,A)	- -	MRD & URD (231 children)	aGVHD, survival	1142*A (p) with ↓aGVHD
	Nguyen 2010 [75]		rs11209026; rs11465804	URD (390)	aGVHD, cGVHD & TRM	variant allele vs. wt, either SNP: nsa
NOD2	Holler 2004 [76,77]	SNP8,12,13	rs2066844, rs2066845, rs2066847	MRD & URD (169)	aGVHD & TRM	Mutations (d/p) with ↑acute GVHD & ↑TRM
	Holler 2006 [76,77]	SNP8,12,13	rs2066844, rs2066845, rs2066847	MRD (225)	aGVHD & TRM	Mutations (d/p) with ↑acute GVHD & ↑TRM
	Holler 2008 [78]	SNP8,12,13	- -	URD (342)	aGVHD & TRM	SNP13(d) with ↑acute GVHD & ↑TRM
	Elmaagacil 2008 [73]	SNP8,12,13	- -	MRD (403)	aGVHD, relapse, TRM	Mutations (p/d) with ↑acute GVHD
TNF	Nguyen 2010 [75]	SNP8,12,13	- -	URD (390)	aGVHD, cGVHD & TRM	nsa
	Middleton 1998 [66]	-308 SNP, TNFd (VNTR) ⁶	rs1800629, d3 allele	MRD (49)	aGVHD	-308: nsa, TNFd3/d3 (p/ d) ⁷ with ↑acute GVHD
	Cavet 1999 [55]	TNFd (VNTR)	- -	MRD (144)	aGVHD, cGVHD, TRM	TNFd3/d3 (p/d) ⁷ with ↑TRM
	Takahashi 2000 [67]	TNF -308	- -	MRD & URD (62)	aGVHD, cGVHD	-308, allele 2 (d) with ↑acute GVHD
	Socie 2001 [56]	TNFA -308, -238; TNFd (VNTR)	- -	MRD (100)	aGVHD, cGVHD	nsa
	Rocha 2002 [62]	TNFA -308, TNFB -252		MRD (107)	aGVHD, cGVHD, TRM	nsa
	L in 2003 [60]	-308	rs1800629	MRD (570)	aGVHD	nsa
	Mullighan 2004 [54]	-308, -238	rs1800629	MRD (160)	aGVHD	nsa
	Mullighan 2004 [54]	488	rs1800610	MRD (160)	aGVHD & TRM	TNF488A (p/d) ⁷ with ↑acute GVHD and ↑mortality
	Keen 2004 [68]	TNFd (VNTR) & -1031	- -	URD (182)	TRM	TNFd4 allele & TNF-1031C ↑TRM
TNFR2	Stark 2003 [79]	codon 196 (R,M)	- -	MRD (104)	aGVHD, cGVHD	196*R (p) with ↑acute GVHD; 196*RR (d) with ↑chronic GVHD

Gene	Reference	Polymorphism		Study population ¹	Phenotype ²	Association ^{3,4}
		Alias or VNTR	SNP			
VDR	Middleton 2002 [80]	VNTR, intron 8		MRD (88)	aGVHD & TRM	A allele (d) with ↑acute GVHD and mortality

¹ Study population: “MRD”, HLA matched related donor; “ND”, not defined; “URD”, unrelated donor.

² Phenotype: “aGVHD”, GVHD; “cGVHD”, chronic GVHD; “NRM”, non-relapse mortality; “TRM”, transplant-related mortality.

³ “nsa”, indicates no significant association.

⁴ “p”, patient; “d”, donor; “p/d”, patient or donor.

⁵ IL10^{−1064} is a microsatellites located in the IL10 promoter region.

⁶ TNFδ is a microsatellite in the TNF region.

⁷ MRD patients and donors share the same MHC and TNF genotypes.

Table 2

Numerical Summary of I Discovery SNPs Associated with HCT Outcome Phenotypes (n=1,593 HCT Cases)

HCT Phenotype	Phase I SNP Associations		Total	Highest p-value, $-\log_{10}$
	Patient	Donor		
Acute GVHD, grade 2–4	1	0	1	6.000
Acute GVHD, grade 3–4	1	0	1	6.560
Chronic GVHD	3	4	7	7.622
Tolerance	1	0	1	6.122
Acute lung injury (IPS)	1	2	3	6.850
Acute kidney injury	7	6	13	7.441
Airflow obstruction (BOS)	4	3	7	6.814
Gram negative bacteremia	9	0	9	8.100
CMV activation	8	5	13	8.194
Overall survival (OS)	4	1	5	6.883
Transplant-related mortality	1	1	2	6.988
(TRM)				
Relapse	3	0	3	6.471
Total	43	22	65	--