

# Post-Transplant Complications Are Affected By Non-HLA Variations

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JR Schoenborn

Hematopoietic cell transplant (HCT) has successfully treated a large number of patients with various hematological disorders, such as leukemia. The number of patients able to be treated by HCT has greatly expanded because of the use of bone marrow or stem cells from unrelated individuals. However, recipients that receive unrelated donor cells are at a higher risk for post-transplant complications resulting from genetic differences between the donor and patient. These include graft-versus-host disease (GVHD), which occurs in up to 80% of all unrelated transplants. In GVHD, the donor cells recognize the recipient's body as foreign and attack their organs. To minimize the risk of complications such as these, unrelated patients and donors are matched for alleles of five genes within the major histocompatibility complex (MHC) on chromosome 6p21.3.

To address if genetic variation in other sites of chromosome 6p21.3 could contribute to post-transplant complications, Drs. Effie Petersdorf, Mari Malkki and Ted Gooley of the Clinical Research Division examined genetic variation in donors and recipients in a retrospective discovery-validation cohort of 4205 transplants. The authors identified two genetic loci that were highly predictive of disease-free survival and acute GVHD. Furthermore, genotyping of donor-recipient pairs demonstrated that most transplant recipients had at least one matched donor. Upcoming clinical trials will utilize these newly identified markers to determine if more refined genetic matching of patients will the lower incidence of GVHD.

The 6p21.3 genomic region is very gene-rich and encodes many molecules that are involved in the immune response. Petersdorf *et al.* genotyped 1120 single nucleotide polymorphisms (SNPs) in over 2100 donor-recipient transplant pairs to identify those that correlated with patients' clinical outcomes. SNPs represent variations in the DNA sequence among the human population, and may serve as markers for genetic differences in nearby genes. SNPs of the donor, recipient and the donor-recipient mismatch type were characterized both individually and in combination, and compared to clinical outcome. Only ten SNPs associated with patients' clinical outcomes, but these were independent of the HLA genotype, mismatch at an additional HLA locus (*HLA-DPB1*) or other clinical variables. Of these, two SNPs were validated in an additional cohort of over 1650 paired donor-

recipient transplant pairs. Most HLA-matched patients and donors were matched for one of these two SNPs, however only 60% of patients were matched for the second SNP variant. Because most patients have multiple HLA-matched donors and SNP-matched donors are relatively common, matching the donor-recipient genotypes for both HLA and SNP loci would be possible for most patients.

SNPs may occur within or outside of genes and may influence gene expression or function. The first SNP is within 2 kb of the HLA-DPB1 3' untranslated region and has previously been a marker for pediatric asthma, rheumatoid arthritis and Hodgkin lymphoma. The second SNP has previously been associated with autoimmune diseases such as type I diabetes, and may alter MHC class I protein expression. Future studies will identify and characterize genes near these SNP markers that correlate with outcome to determine how variation at non-classical HLA loci define transplant risk. Understanding how these genetic factors influence post-transplant complications and better predict low-risk donor-recipient matches will be beneficial to future hematopoietic transplants.

[Petersdorf EW, Malkki M, Gooley TA, Spellman SR, Haagenson MD, Horowitz MM, Wang T.](#) 2012. MHC-resident variation affects risks after unrelated donor hematopoietic cell transplantation. *Science Translational Medicine*. DOI: 10.1126/scitranslmed.3003974