Graft Vs Host Disease in Stem Cell Tx Tied to Gene Variant

High expression of HLA-DPB1 increased risk of GVHD, death

The risk of graft versus host disease (GVHD) after allogeneic stem cell transplant increased significantly in recipients with a genetic variant associated with increased expression of the HLA-DPB1 gene, a large genotyping study showed.

Patients with the high-expression rs9277534G allele had a 54% greater risk of GVHD after HLA-mismatched transplantation as compared with patients who had the low-expression rs9277534A allele. The risk of death from causes other than disease recurrence was 25% higher in transplant recipients with the high-expression allele.

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Recipients with the high-expression allele had an increased risk of GVHD even with grafts from donors with the low-expression allele, as reported Aug. 13 in the [*New England Journal of Medicine*](http://www.nejm.org/).

"Our data provide new information on the role of HLA-DPB1 expression in transplantation associated risks that can be used to guide the selection of donors for future transplant recipients in order to minimize the risk of acute GVHD," [Effie W. Petersdorf, MD](https://www.fredhutch.org/en/labs/profiles/petersdorf-effie-wang.html), of Fred Hutchinson Cancer Research Center in Seattle, and co-authors said in conclusion. "We discovered that if rs9733534 genotypes had been known at the time of the search for an unrelated donor, almost 55% of recipients with rs9277534AG would have had suitable donors, and mismatching for their G-linked HLA-DPB1 allele could have been avoided."

"Fully HLA-compatible donors remain the donors of choice for recipients with rs9733534GG. Taken together, these data support rs9277534 and HLA-DPB1 genotyping for donor selection."

The introduction of polymerase chain reaction (PCR) assays revolutionized the ability to assess HLA-DP incompatibility and investigate its biologic relevance in transplantation. Studies involving PCR technology, DNA-based typing of HLA-A, B, C, DRB1, and DQB1-matched recipients and donors showed HLA-DPB1 mismatch in 85% of transplantations. Unidentified HLA-DPB1 mismatching can lead to life-threatening GVHD, the authors noted.

[Previous studies](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Science+translational+medicine%22%5BJour%5D+AND+2012%5Bpdat%5D+AND+Petersdorf+EW%5Bfirst+author%5D&cmd=detailssearch) showed an association of rs2281389 with acute GVHD, but the variant resides in a noncoding DNA region, making it an unlikely direct mediator of GVHD, the authors continued. In contrast, rs9277534 is linked to the HLA-DPB1 exon 2 allele that defines the HLA-DP-beta protein and tissue type. Moreover, both variants are in proximity to HLA-DPB1 and each other.

"The close relationship between rs2281389 and rs9277534 across haplotypes makes the rs9277534 expression variant a plausible marker for the risk of GVHD," the authors said.

To investigate a possible role of rs9277534 in GVHD, the authors genotyped the variant in 3,505 persons to define rs9277534-DPB1 haplotypes. They retrospectively determined linkage of the rs9277534 A and G alleles to mismatched HLA-DPB1 in 1,441 stem-cell recipients with a single HLA-DPB1 mismatch, and they used a PCR assay to assess HLA-DPB1 expression.

Investigators compared the risk of acute GVHD among recipients with the HLA-DPB1 high-expression rs9277534G allele versus recipients with the low-expression rs9277534A allele. Recipients with rs9277534G-associated HLA-DPB1 mismatches had a hazard ratio for GVHD of 1.54 (95% CI 1.25 to 1.89, *P*<0.001) and a hazard ratio of 1.25 for death by causes other than disease recurrence (95% CI 1.00 to 1.57, *P*=0.05).

The data showed that recipients with rs9277534G-linked HLA-DPB1 mismatches had a significantly increased risk of grade II, III, or IV acute GVHD (HR 1.32, 95% CI 1.13 to 1.55,*P*<0.001) and grade III or IV acute GVHD (HR 1.34, 95% CI 1.08 to 1.69, *P*=0.009). These analyses showed that the risk was limited to transplants involving patients with rs9277534G-linked HLA-DPB1 and donors with rs9277534A-linked HLA-DPB1.

The rs9277534G-linked mismatch was associated with a lower risk of relapse as compared with the rs9277534A-linked mismatches (HR 0.80, 95% CI 0.64 to 0.99, *P*=0.04), an observation consistent with a graft-versus-leukemia affect.

"The higher risk of GVHD was balanced by the lower risk of relapse, leading to similar overall mortality (HR 1.03, *P*=0.70)," the authors reported.