

New genetic clues to why most bone marrow transplant patients develop graft-versus-host disease

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A team of scientists led by a bone marrow transplant researcher at Fred Hutchinson Cancer Research Center has shed new light on why most bone marrow transplant patients who receive tissue-matched cells from unrelated donors still suffer acute graft-versus-host disease (GVHD). The answer appears to lie in the discovery of previously undetected genetic differences in the DNA of patients and unrelated marrow donors.

The laboratory-based study findings by Effie Petersdorf, M.D., and colleagues soon will be translated to the clinic when a Hutchinson Center transplant protocol – the first of its kind – opens at Seattle Cancer Care Alliance later this year to test patients and donors for these genetic differences. The goal is to further refine the tissue-matching process to reduce the incidence of GVHD, which affects about 80 percent of patients and has been a longtime, vexing challenge for transplant doctors.

GVHD occurs when the donor immune system (the graft) begins to circulate in the patient's bloodstream and recognizes the host's (the patient's) tissue as foreign. When this happens, the new immune system attacks the recipient's tissues such as the liver, gastrointestinal system and skin.

[Bone marrow](#) and [stem cell transplants](#) are used to treat a variety of malignant blood diseases such as leukemia. Hematopoietic cell transplantation was pioneered at the Hutchinson Center in the 1970s and continues to be a major focus of research and clinical trials to improve survival and reduce side effects.

Published recently in *Science Translational Medicine*, the study details how researchers identified two specific single-nucleotide polymorphisms, also called SNPs (pronounced "snips"), within the major histocompatibility

complex (MHC) in human DNA that are markers for either [acute GVHD](#) or disease-free survival. These markers are distinct from the human leukocyte antigens (HLA), found on the same chromosome as the MHC, that are traditionally used to match recipients and donors, a process called tissue typing.

Researchers found that if a patient and donor have different SNPs, the patient was at increased risk of GVHD or a lower chance of disease-free survival. The scientists surmised that genes located near these SNPs must be involved in that process.

"The question I wanted to ask with this study is whether there could be genes we don't know about that are located close to the major histocompatibility complex that could be influencing GVHD risk," said Petersdorf, a member of the Hutchinson Center's Clinical Research Division. "Now that we know what to test for we can begin screening for the presence of the SNPs in patients and donors and select the optimal donor whose SNP profile will benefit the patient the most."

SNP genotyping is only beneficial for patients when they have multiple matched unrelated donors in order to determine which donor is the optimal match. Fortunately, this is fairly common, according to the study. Of 230 patients who had two or more HLA-matched donors, significant percentages also had at least one donor who was SNP-matched.

A SNP is a base change that involves two or more of the four bases (A, C, T and G) that comprise DNA, and is the simplest form of DNA variation on the human genome. SNPs serve as signposts or markers for nearby genes that are the actual drivers for the effect that they have on disease.

The next step for researchers is to sequence the

MHC region of genes close to the SNP locations in order to identify which genes are directly responsible for the correlations of survival and GVHD.

"Once we discover those genes we will characterize them and then we may be able to further refine donor matching," Petersdorf said.

For this study, researchers conducted a retrospective discovery-validation study that examined DNA from more than 4,000 former transplant [patients](#) nationwide. They studied 1,120 SNPs in the MHC on chromosome 6 – the region where all tissue typing and immune function genes are densely packed. They narrowed those SNPs to two that appeared to correlate with disease-free survival and acute GVHD.

More information: The *Science Translational Medicine* paper, "MHC-Resident Variation Affects Risks After Unrelated Donor Hematopoietic Cell Transplantation," stm.sciencemag.org/content/4/144/144ra101.full

Provided by Fred Hutchinson Cancer Research Center

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