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Transplant Rejection and Risk: In Search of the Genetic Dark Matter

William S. Oetting[1], **Pamala A. Jacobson**[1], and **Ajay K. Israni**[2]

[1]College of Pharmacy, University of Minnesota, Minneapolis, MN, USA

[2]Department of Medicine, Hennepin County Medical Center, University of Minnesota, Minneapolis, MN, USA

Cellular acute rejection (AR) is a major risk factor for allograft loss in solid organ transplantation. Identification of individuals at higher risk for AR would allow for the individualization of treatment, hopefully reducing the incidence of AR and resulting in the prolongation of allograft survival. One hypothesis is that some individuals are genetically predisposed to AR, increasing their risk for AR when taking standard immunosuppressant regimens. Based on this hypothesis, there have been numerous studies trying to identify genetic variants, mostly in the form of single nucleotide polymorphisms (SNPs), that may increase or decrease individual risk to AR. Studies have evaluated genetic variants in both the recipient and donor genomes of kidney, lung, liver and heart allografts. Most genes analyzed are thought to be involved in the immune response to the allograft or pharmacology of the immune suppressants. Though there have been many statistically positive associations reported in the literature, the validation of these results has been problematic. As an example, in our study of 969 kidney transplant recipients, we attempted to validate multiple SNPs that had been previously reported as being associated with AR, some having been reported in multiple publications. Of 23 variants tested, only one, the Leiden mutation in the factor 5 gene (rs6025), was replicated in our study [1]. As observed in many genome wide association studies (GWAS) in complex diseases, the initial study may identify one, or several SNPs with statistically significant associations to the phenotype, even after multiple testing is taken into account. Unfortunately, subsequent smaller sized studies many times fail to validate these SNPs and instead identify a different set of SNPs associated with the clinical phenotype. This scenario has even been given its' own term; “the winners' curse”. There may be several reasons for this subsequent lack of validation, including small sample sizes resulting in false positives or false negatives in the initial study, small effect sizes making validation less likely, even when truly positive, differences in phenotype definition or using a study population with a different ethnic having a different allelic profile. Even differences in environment or clinical care between centers may hinder replication. Current studies have analyzed common alleles with high minor allele frequencies in genes that are thought to be involved in AR. However, looking forward it may be important to focus more on specific biological pathways or rarer functional mutations instead of common alleles with a high allelic frequency.

Address for correspondence: William S. Oetting, PhD, Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN 55455. oetti001@umn.edu.

In this month's issue of the *Journal of Gastrointestinal and Liver Diseases*, Dr. Kamei and colleagues report on an association between a genetic variant of the transporter associated with antigen processing (TAP1) gene with AR in living donor liver transplantation based on 37 AR episodes [2]. They report that recipients who received a liver allograft having one or two copies of the glycine allele of the p.Asp697Gly polymorphism (rs1135261) were almost three times more likely to experience an AR event than receiving an allograft homozygous for the aspartic acid allele. The TAP1 gene is associated with antigen processing and presentation which plays a major role in the immune response. It has been shown that TAP1 works in cooperation with lipopolysaccharide signaling through toll-like receptor 4 (TLR4), which can increase the expression of TAP1 [3]. It is interesting that donor polymorphisms of TLR4 in liver allograft recipients have been associated with liver allograft failure [4]. It may be that perturbation of antigen processing and presentation results in a higher risk of AR and that genetic variants in genes involved in this pathway alter the efficiency of antigen presentation, resulting in an increased risk for AR. In both of these studies, it was the donor genotype that imparted the increased risk for AR. The authors speculate that donor class I-mediated antigen presentation to the recipient T lymphocytes may be altered. Though the association of the TLR4 SNP provides good biological support for the TAP1 SNP as an AR risk factor, the TAP1 SNP association still needs to be validated.

Candidate gene approaches assume that we know which pathways are important in transplant outcome. We are finding that this approach is not working and identification of a genetic variant that instills enough confidence to move into a clinical trial has yet to be identified. Current technologies now allow for the analysis of millions of SNPs in association studies and next generation sequencing will allow for the identification of all variants within a genome. For these technologies to be used appropriately, studies will require very large sample sizes to achieve the statistical power that will be needed to identify rare genetic variants or those with small effect sizes. Additionally, studies with uniform high quality clinical information will be required to make sure that all individuals are being ascertained using the same clinical phenotype. It is common for GWAS studies to have 10,000s of study subjects. To create studies in the transplant community with this number of subjects, large consortiums will be required, both for the initial discovery study, as well as the validation studies. This is a challenge since there is often large variation in institutional standards of practice and therefore uniform phenotypes could be difficult to create.

Though genetic variation, most likely, provides individual risk for AR, identifying this genetic ‘dark matter’ has been difficult. In the end, we will most likely identify risk profiles that consist of many genetic variants, each contributing a small risk to AR, instead of a single AR risk allele with a big effect. This view of complex genetic phenotypes was first proposed by R.A. Fisher in 1918 [5]. By working together on this problem, we can create the study cohorts needed to find variants associated with risks for differing transplant outcomes. Eventually we shall be able to identify profiles associated with an increased risk of adverse outcomes associated with transplantation, allowing us the opportunity to move towards personalized treatment of allograft recipients that minimize the adverse outcomes and maximize the life of the allograft.

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