Gene variation among kidney donors associated with graft failure

April 6 2010

Among kidney transplant donors, variation of a gene that is an inhibitor of the development of fibrous connective tissue is significantly associated with an increased risk of graft failure, according to a study in the April 7 issue of *JAMA*.

The gene CAV1 is involved in tissue fibrosis as well as vascular proliferation, important contributors to kidney transplant failure, according to information in the article. "No studies to date have addressed whether genetic variation of CAV1 increases propensity toward fibrosis in general or renal fibrosis specifically," the authors write.

Jason Moore, B.M.B.S., of the Renal Institute of Birmingham and University Hospital Birmingham, England, and colleagues conducted a study to assess the role of CAV1 variants in the development of kidney allograft fibrosis and in kidney transplantation outcome. Gene variation among both donors and recipients was investigated because cells derived from both may contribute to allograft fibrosis. The study included genomic DNA from 785 white kidney transplant donors and their respective recipients (transplantations in Birmingham, England, between 1996 and 2006; median [midpoint] follow-up, 81 months). DNA samples were analyzed for common variation in CAV1. Validation of positive findings was sought in an independent kidney transplant donor-recipient group (transplantations in Belfast, Northern Ireland, between 1986 and 2005; n = 697; median follow-up, 69 months). Analysis assessed any association between genotype and allograft failure.

The researchers found that analysis of allograft failure revealed significant differences in graft survival between donor genotypes for the tag single nucleotide polymorphism (SNP) rs4730751, with poorer graft survival in recipients whose donors displayed genotype AA. Overall, graft failure rates were 38.6 percent for donor genotype AA, 22.3 percent for donor genotype CC, and 22.2 percent for donor genotype AC. No other donor or recipient tag SNPs were associated with graft failure.

Data from the Belfast validation group indicated significant differences in graft survival between donor genotypes, and, as in the Birmingham group, poorer graft survival was seen in recipients whose donors displayed genotype AA. Overall graft failure rates were 67 percent for donor genotype AA, 42 percent for donor genotype CC, and 44 percent for donor genotype AC.

"Although a minority of donors displayed the AA genotype (approximately 10 percent), this gene variant nevertheless shows potential in identifying a subpopulation at higher risk of allograft failure, and further investigation of its role in the etiology of renal fibrosis may be warranted," the authors write.

"This finding has implications for renal transplantation with regard to the mechanisms underlying graft failure and in the identification of genetic biomarkers. In addition, because renal transplantation may be viewed as an in vivo model of accelerated tissue fibrosis, this study may have relevance for other renal and nonrenal diseases characterized by tissue fibrosis. Finally, this study may also have implications for other conditions in which CAV1 is thought to play a role, in particular vascular disease and neoplasia."

More information: JAMA. 2010;303[13]:1282-1287.