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INFLUENCE OF DONOR AND RECIPIENT GENETIC POLYMORPHISMS ON THE OCCURRENCE OF DELAYED KIDNEY GRAFT FUNCTION

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Introduction: Delayed graft function (DGF) is a significant problem in kidney transplantation with deceased donors (DD), since it is frequent and leads to prolonged hospitalization, increased costs of transplantation, increased risk of acute rejection and poorer long-term graft survival. **Objective:** This study sought to investigate the association between genetic polymorphisms in donors (D) and recipients (R) with occurrence of DGF.

Material and Methods: R and D of all kidneys transplants (Tx) with DD performed in a single center, from 2007 to 2012, except those that met the exclusion criteria: age under 18 years, pre-transplant class I PRA ≥ 80% and lack of DNA samples stored in the lab. Among 579 Tx, 466 R and 312 D were included. D and R were of predominantly Caucasian ancestry. DGF was defined as the need for dialysis in the first week after Tx, and occurred in 303 Tx. A multiple regression analysis including clinical data from R and D and transplant variables, showed that only D serum creatinine (Cr) > 1.5 mg/dL before kidney removal remained associated with DGF (p=0.0005, OR=1.5). Selection of candidate genes in which to explore polymorphisms was based on a literature search of publications concerning (1) gene polymorphisms associated with DGF (17 studies) or acute kidney injury (1 systematic review); (2) genome-wide association study (GWAS) of polymorphisms and renal function (1 study); (3) differential gene expression in ischemia-reperfusion or acute kidney injury (6 reviews). Among the 122 candidate genes that came out of this search, 31 genes were selected for this study. For all genes, except for *TLR4* and those selected through the GWAS, we choose the SNPs using a prioritization system (SNPLogic - www.snplogic.org) based on SNP's potential to influence gene expression and their allelic frequencies in Caucasian populations. One SNP in 30 genes (*ANGPT2, ATF3, BAX, BCL2, CCL3, CX3CL1, CXCL1, CXCL1 ,CXCL8, EDN1, FABP1, GATM1, GSTM1, GSTP1, HAVCR1, HIF1A, HIF2A, HMOX1, ICAM1, JAG1, LCN2, LGALS3, MTHFR, NOS2, PARP1, SELP, SHROOM3, STC1, TLR4, UMOD* and *VEGFA), and two SNPs in TLR4 gene,* were genotyped with the TaqMan OpenArray™ Genotyping System® (Life Technologies).

Results: Out of the 32 SNPs included in the study, we were able to analyze 29, since the assays for the genes *CCL3, GSTPM* and *HIF1A* did not work. No deviation from Hardy-Weinberg equilibrium was observed for any of the polymorphisms. Only the SNP rs2146323, +7149 C>A intron 2 in *VEGFA* of donors (AA/AC vs CC genotypes: p=0.0004,

OR=2.3, 95% CI=1.5-3.6) and the SNP rs1871042, +2778 C>T intron 6 in *GSTP1* of recipients (TT/TC vs CC genotypes: p=0.0066, OR=1.7, 95% CI=1.16-2.4) were associated with DGF. These two SNPs are located at predicted transcription factors binding sites. A posterior multiple regression analysis, including the final Cr of the donor and the *VEGFA* and *GSTP1* SNPs, revealed that all three variables were independently associated with DGF.

Conclusion: Out of 29 SNPs investigated, only a SNP in the gene *VEGFA* (vascular endothelial growth factor A) of the donor, and a SNP in the gene *GSTP1* (glutathione S-transferases P1) of the recipient were found to be significantly associated with DGF.