The genetic determinants of renal allograft rejection

To the Editor:

We thank Massart et al for their comments1 on our recently published large-scale genome-wide association study of renal transplant outcomes,2 and we welcome the opportunity to examine their findings in more detail.

The 2 recipient genetic loci highlighted in their paper,3 rs10765602 (gene annotation CCDC67) and rs7976329 (gene annotation PTPRO), were well imputed in our study (INFO>0.95) and neither reached genome-wide significance in our reported analyses.2 To provide additional confidence, we have reanalyzed our data following reimputation to the 1000 Genomes phase 3 reference panel via the Sanger Imputation Service (www.imputation.sanger.ac.uk) using Eagle and the Positional Burrows-Wheeler Transform package.4 Table 1 indicates that neither single nucleotide polymorphism (SNP) reaches a nominal level of statistical significance in either donor or recipient genome for our broader definition of acute rejection (any acute rejection event recorded in the first 12 months after transplantation).

The lack of replication signal in our study, despite greater numbers of cases, may be due to a number of factors. We agree with Massart et al that one reason may be the differences in phenotype definition. Our study was primarily designed and powered to detect genetic variation in donor and recipient genomes associated with long-term graft survival, as this is the key unmet medical need in clinical renal transplantation outcomes, with currently no effective therapeutic options. Our acute rejection phenotype was established from reported national registry-based outcomes and was not specific to acute T cell–mediated rejection, and thus signal attenuation may be responsible for the difference. However, we note that in our study the recipient minor allele frequency differences between cases and controls are less than 1%, indicating almost complete attenuation. Alternatively, it is possible that the signals found by Ghisdal et al3 are false positives. Even genome-wide significant signals can be false positives, and as the authors used a pooled-DNA design, and employed a permutation-based joint test of association and linkage disequilibrium to determine the significance of hits in their discovery phase, it is difficult to determine the combined (discovery + replication) association p-values for their SNPs. We believe that further data are needed to resolve this issue.

We agree that genetic variation outside the HLA region is an important consideration in seeking to understand the pathogenesis of long-term graft survival and potentially identifying novel therapeutic targets to reduce cumulative allograft loss over time. We look forward to working with already established international collaborations5 to identify these genetic determinants of long-term graft survival for the benefit of our patients.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

Keywords

basic (laboratory) research/science, clinical research/practice, immunogenetics, informatics, kidney (allograft) function/~
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| Table 1 | Results from UKIRTC acute rejection GWAS for rs10765602 and rs7976329 |
|---------|---------------------------------------------------------------------|
| Test    | rsID  | AlleleA | AlleleB | Cases AA | Cases AB | Cases BB | Cases total | ctrls AA | ctrls AB | ctrls BB | ctrls total | MAF cases | MAF controls | P     | Beta  | SE    |
|---------|-------|---------|---------|----------|----------|----------|-------------|----------|----------|----------|-------------|-----------|--------------|-------|-------|-------|
| Recipient (null as missing) | rs10765602 | G | T | 36 | 152 | 209 | 398 | 73 | 319 | 426 | 818 | 0.283 | 0.284 | .702 | -0.039 | 0.102 |
| Recipient (null as missing) | rs7976329 | T | C | 171 | 177 | 50 | 398 | 359 | 359 | 100 | 818 | 0.349 | 0.342 | .636 | 0.046 | 0.098 |
| Recipient (null as control) | rs10765602 | G | T | 36 | 152 | 209 | 398 | 146 | 795 | 941 | 1881 | 0.283 | 0.289 | .676 | 0.039 | 0.092 |
| Recipient (null as control) | rs7976329 | T | C | 171 | 177 | 50 | 398 | 805 | 839 | 237 | 1881 | 0.349 | 0.349 | .823 | 0.020 | 0.087 |
| Donor (null as missing) | rs10765602 | G | T | 26 | 160 | 193 | 379 | 49 | 261 | 351 | 661 | 0.278 | 0.271 | .929 | 0.010 | 0.112 |
| Donor (null as missing) | rs7976329 | T | C | 150 | 185 | 44 | 379 | 278 | 300 | 83 | 661 | 0.361 | 0.352 | .361 | 0.097 | 0.106 |
| Donor (null as control) | rs10765602 | G | T | 26 | 160 | 193 | 379 | 117 | 623 | 821 | 1560 | 0.278 | 0.274 | .922 | -0.010 | 0.100 |
| Donor (null as control) | rs7976329 | T | C | 150 | 185 | 44 | 379 | 656 | 736 | 168 | 1560 | 0.361 | 0.343 | .323 | 0.095 | 0.097 |

Neither SNP was found to be significantly associated with the acute rejection phenotype in our analysis, in either recipients or donors. The SNPs were imputed to the 1000 Genomes Phase 3 reference panel and analyzed using SNPTEST (frequentist 1, method score). The first 5 principal components, the recruitment site, recipient age, donor age, recipient sex, donor sex, and the total number of HLA mismatches (at A, B, and DR) were included as covariates. Both SNPs, in both recipients and donors, were imputed to a high quality, with an info score and average maximum posterior call of greater than 0.95. Test = recipient/donor to indicate whether recipient or donor genotypes were tested (null as missing /control indicates whether blank records were treated as missing data, or as controls); rsID, SNP identifier; AlleleA, noneffect allele (coded as 0); AlleleB, effect allele (coded as 1); Cases/controls AA, number of cases/controls who were homozygous for allele A; cases/controls AB, number of cases/controls who were heterozygous; cases/controls BB, number of cases/controls who were homozygous for allele B; MAF, minor allele frequency (frequency of least common allele in the given dataset); beta, beta coefficient relating to the coded allele (AlleleB); SE, standard error of beta coefficient; P, P-value.