To the editor:

Genetic variants in **XRCC5** may predict development of venous thrombotic events in myeloma patients on thalidomide

We read with great interest the recent findings by Johnson et al indicating that genetic variants in DNA repair genes, in particular **XRCC5**, may play a crucial role in identifying myeloma patients on thalidomide treatment who are at high risk of acquiring treatment-related venous thrombotic events (VTEs). The authors used a comprehensive selection strategy for identifying single nucleotide polymorphisms (SNPs) and have reported an association between the high risk of VTE and genetic variants located in **XRCC5**.

In a recent publication from our group, we performed extensive genotyping using a haplotype tagging strategy in 306 myeloma patients and 263 controls and identified a rare homozygous variant in the SNP rs1051685 in the **XRCC5** gene. This SNP is located in an exon splice enhancer sequence (ESE) in the 3'UTR and can possibly alter splicing by affecting spliceosome assembly. This SNP is in high linkage disequilibrium (LD) with the SNPs rs1051677 and rs6941 reported in the Johnson study (D' = 1; Figure 1), thus we suggest that both of these studies are potentially identifying a locus for disease susceptibility.

The other SNP rs2440 reported by Johnson et al was also associated with disease susceptibility in our study albeit with a lower rate of linkage disequilibrium.

Figure 1. D' LD plot for the **XRCC5** gene was calculated using CEU genotype data for the markers genotyped across this region. Prefixes to SNP IDs denote the studies that SNPs were genotyped in: HT_ for the Hayden/Tewari study and J_ for the Johnston et al study. LD (linkage disequilibrium) blocks were defined using the 4 gamete rule. D' = 1 between the SNPs rs1051677, rs1051685, and rs6941.
weak signal ($P = 0.047$; odds ratio 0.58; 95% confidence interval [0.35-0.96]). Our findings highlight the involvement of genetic variants in the 3′UTR of the XRCC5 gene in myeloma. Johnson et al have also reported potential association for several other SNPs in the intronic region flanking the 3′UTR. Furthermore, we investigated the genomic region harboring the SNPs reported in both studies and found it to be highly conserved (77% sequence identity), in a spectrum of mammalian species including opossum, mouse, and dog, providing further evidence for potential functional significance. Taken together, these data strongly suggest that this genomic region plays a crucial role in contributing to myeloma etiology.

XRCC5 is a DNA repair gene that encodes Ku86, part of the Ku heterodimer involved in binding and stabilizing DNA double-strand breaks (DSBs) and along with the catalytic subunit PRKDC, forms the activated DNA-protein (DNA-PK) complex. This complex then recruits the ligation complex for repairing DSBs through nonhomologous end joining. Any alteration in binding could affect the assembly of the DNA-PK complex, leading to inefficient processing by the ligation complex, resulting in accumulation of unprocessed DSBs and recruitment of the apoptotic machinery. This could partially explain the hypersensitivity of myeloma patients to DNA damaging agents and also account for the enhanced effect in patients treated with thalidomide in the MRC and Hovon-50 studies (where cyclophosphamide or doxorubicin/adriamycin were included in the treatment regimen). The combined effect of these drugs could result in release of prothrombotic factors, priming an increase in thrombotic events in concert with the enhanced antitumor effect.

The application of thalidomide and immunomodulatory drugs has dramatically altered clinical outcome for myeloma patients; however, the risk of developing VTE needs to be addressed in the context of contributing to treatment-related mortality and morbidity. Our findings and those of Johnson et al highlight the significance of identifying genetic susceptibility loci in myeloma patients who contribute to increased disease risk and permit delineation of key genetic variants that could help guide clinical management and therapeutic intervention for high-risk patients.

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