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MDM2 polymorphisms and cancer risk in basal cell carcinoma

M.T. Boyd and **N. Vlatković**
MDM2/p53 Laboratory, School of Cancer Studies, University of Liverpool, UCD Building, Daulby Street, Liverpool L69 3GA, U.K.

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Sir, Wilkening *et al.* recently reported in this Journal that there was no association between a single nucleotide polymorphism (SNP) in the *MDM2* gene and the risk or age at onset of basal cell carcinoma (BCC).1 Given the functional consequence of the SNP, these results are predictable.2

MDM2 is a proto-oncogene that acquires oncogenicity through increased expression (for review see Iwakuma and Lozano3). Upregulation of *MDM2* has been shown to be a significant factor in a range of common cancers, and increased *MDM2* expression has been found to be associated with poor outcome in studies of several common cancers, e.g. of the bladder.4 *MDM2* interacts directly with p53 and most of the oncogenic effects of *MDM2* are due to its ability to negatively regulate the p53 tumour suppressor protein. Increased expression of *MDM2* often results from gene amplification, and tumours with *MDM2* gene amplification rarely harbour p53 mutations.5 p53 levels and activity are regulated by *MDM2* and it is increasingly clear that this is substantially due to the ability of *MDM2* to act as a ubiquitin ligase with specificity for, *inter alia*, p53. *MDM2* targets p53 for ubiquitination, leading to export of p53 from the nucleus and/or degradation by proteasomes. The importance of negative regulation of p53 by *MDM2* has been beautifully demonstrated in studies of knock-out mice which have shown that *MDM2* is an essential gene precisely because it is able to negatively regulate p53.6,7 The interplay between these two critical genes extends further, with p53 acting as a transcriptional regulator of *MDM2*, and thus an autoregulatory feedback loop connects these molecules.8

The discovery of a SNP (SNP309 T/G) in the *MDM2* gene that is associated with increased expression from the G haplotype has been shown to be linked with early onset of cancer in patients with wild-type p53.9 Not surprisingly, given what is known regarding the function of *MDM2* in negatively regulating p53, the SNP309 is not informative in patients with mutant p53. The study by Wilkening et al. failed to show any link between SNP309 status and BCC, but the authors did not take into account the p53 status of the patients studied. As the utility of SNP309 genotyping depends upon the status of p53, a re-analysis of the data that takes into account p53 mutational information is clearly warranted.

Analysis of SNP309 can prove highly informative, but not in the absence of information regarding p53 status, except perhaps in those cancers where p53 is rarely mutated. This is

mboyd@liv.ac.uk.
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not, however, the case for BCC where p53 mutation has been reported to occur in approximately 50% of cases.10

Thus the important question that should be asked by studies of this type is not whether SNP309 alone is associated with clinical parameters, but rather whether the SNP is informative in cases that retain wild-type p53.

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