Letters to the Editor

Minimal Region of Deletion on Chromosomal Arm 3p25.1-p25.2 in Uveal Melanoma

To the Editor:

Parrella et al. (1) have reported a novel minimal region of deletion (MRD) in uveal melanomas located on chromosome 3p25.1-p25.2. This is very interesting because in uveal melanoma, monosomy 3 is strongly correlated with metastatic disease (2). As loss of one chromosome 3 is probably one step toward inactivation of one or several tumor suppressor genes on this chromosome, tumors with partial deletions can help to narrow down the regions containing candidate tumor suppressor genes. In a previous study on 333 uveal melanomas, we detected partial chromosome 3 deletions in 13 tumors and these defined two MRDs (3). Although close to our MRD on 3p, the MRD on 3p25.1-p25.2 does not overlap, thus suggesting that there might be two candidate tumor suppressor gene regions on 3p. Only two of the markers that we had analyzed are located in 3p25.1-p25.2 and, therefore, we surmised that we might have missed the presence of allele loss in this region. Consequently, we investigated 67 readily available uveal melanomas from patients that referred to the Essen Department of Ophthalmology, for allelic loss at four markers mapped to the MRD reported by Parrella et al. using our reported methodology (3, 4). We found that all informative markers showed absolute or relative allele loss in all 27 tumors with monosomy 3. No allele loss was found in any of the 40 tumors with disomy 3. Quantitative analysis showed allelic imbalance in 8 of 180 comparisons of constitutional versus tumor genotypes, a figure to be expected because of stochastic variation (4). Obviously, it is difficult to reconcile the findings of Parrella et al. with our negative results. It has to be noted that Parrella et al. used DNA from microdissected paraffin-embedded specimens, whereas we used DNA from fresh frozen tumors. Almost clean allele loss in our tumors with monosomy 3 shows that we have little contamination by DNA from normal cells, which might cause false-negative findings. Moreover, we used fluorescence-based automated detection that ensures accurate quantitative evaluation and, therefore, lowers the risk of false-positive findings compared with visual inspection of autoradiographs. With regard to possible biological reasons for the discrepant results, it must be noted that all but two of our patients are Caucasians from western Europe, which might represent a more homogeneous background, compared with that of the patients investigated by Parrella et al. As the risk for uveal melanoma is dependent on ethnic background, it is not unlikely that genetic variation influences pathways of tumorigenesis. It will be interesting to find out why allele loss on 3p25.1-p25.2 is not present in the uveal melanomas from our patients.

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References


In Response:

We acknowledge Lohmann et al. for their careful analysis in a different patient population of our minimal region of deletion in uveal melanoma on chromosome 3p25.1-p25.2. In contrast to our results, they have found an absence of allelic loss of markers in our minimal region of deletion in 40 tumors with disomy 3. Their previous work had defined a minimal region of deletion slightly telomeric to ours. The high frequency of monosomy 3 in uveal melanoma makes it plausible that multiple tumor suppressor genes could be simultaneously inactivated by the loss of this chromosome. In fact, as an explanation for the discrepancy in our observations, we had suggested in our article that two closely spaced tumor suppressor genes could be important to the tumorigenesis of uveal melanoma.

With respect to technical differences, Lohmann et al. correctly noted that our study was done using DNA isolated from microdissected paraffin-embedded specimens whereas their study used DNA from fresh-frozen samples. However, we do not feel that this difference adequately explains the discrepancy as our allelic losses were also quite clean, as illustrated in our article. Although not specified in their letter, one must assume that the informativity of the markers used in their patient population was sufficient to confidently assess for allelic loss.

We agree with Lohmann et al. that a difference in ethnicity is a likely biological explanation for the discrepancy in our results, and we look forward, as they do, to the results of further studies of this important tumor type.

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