Multilocus inheritance determines predisposition to alpha-radiation induced bone tumourigenesis in mice.

In a recent study, we presented evidence for genetic predisposition governing radiation osteosarcomagenesis in mice. Following the incorporation of the bone-seeking alpha emitter (227)Th, 25% of the variance in osteosarcoma incidence was determined by inherited genetic factors. We have now mapped 5 susceptibility loci in crosses between the more susceptible BALB/c and the more resistant CBA/Ca strains. The major QTL on chromosome 14 overlaps with a locus that was already found in our previous study, using different strains of mice. Here, we investigate the effect by which the major susceptibility locus and 4 minor modifier loci interact to influence osteosarcoma predisposition. Following incorporation of the bone-seeking isotope, 100% of mice that harbour high-risk genotypes at all 5 susceptibility loci develop osteosarcoma with an average of 472 days latency times. In 10 mice inheriting exclusively low-risk genotypes only 1 osteosarcoma was found, arising after 733 days latency time. Inheritance of distinct combinations of BALB/c and CBA/Ca alleles at the susceptibility loci confer more extreme phenotypes in terms of susceptibility or resistance than observed in either of the two parental inbred strains. From the present study, we demonstrate that additive effects of multiple alleles, each making only a minor phenotypic contribution, can combine and
significantly alter tumour risk. This mechanism can be of particular importance in genetically heterogeneous populations such as man. (c) 2005 Wiley-Liss, Inc.