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Title: Characterization of a major colon cancer susceptibility locus (Ccs3) on mouse chromosome 3

#### ABSTRACT

Treatment of mice with the carcinogen azoxymethane (AOM) induces a number of lesions in the colon, including hyperplastic lesions, as well adenomas and carcinomas in situ. Inbred strains of mice show different responses to AOM-induced carcinogenesis. A/J mice are highly susceptible and develop a greater number of hyperplastic lesions and tumors (15-70 tumors/mouse) than resistant C57BL/6J mice (0-6 tumors/mouse). Susceptibility to AOM-induced tumors segregates as a co-dominant trait in (A x B6)F1 hybrids. Using a set of 23 AcB and BcA recombinant congenic mouse strains derived from A/J (S) and B6 (R) parents, we observe that the number of hyperplastic lesions and tumors induced by AOM are under different genetic controls in AcB/BcA strains. The multiplicity of AOM-induced tumors is controlled by a major locus that we have mapped on the distal portion of chromosome 3, to which we have given the temporary designation Colon cancer susceptibility locus 3 (Ccs3). B6 and A/J alleles at Ccs3 are associated with resistance and susceptibility, respectively. Haplotype analysis in key informative AcB/BcA strains restricts the size of the Ccs3 locus to a 14 Mb segment that contains 94 annotated genes. The expression level of all these genes in normal colon has been established by transcript profiling with microarrays, and has led to the identification of a subset of positional candidates that are expressed at high levels in this tissue. The 4q and 1p human chromosomal segments sharing syntenic homology with the mouse Ccs3 segment are known to be associated with inflammatory bowel diseases and colorectal tumors in humans, suggesting that the study of the mouse Ccs3 locus may help further the pathogenesis of these human conditions.