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The Genetics of Retinoblastoma, Revisited

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The fact that all individuals are not identical in their risk for certain cancers has been known for many years. The factors responsible for the increased risk observed in certain individuals, families, or populations may be either environmental or genetic. The genetic risk factors identified to date generally result in a greatly increased relative risk – on the order of ten to one hundred thousand-fold in the case of familial retinoblastoma, for example. The major reason for the identification of genetic factors that result in such large increases in relative risk is that the transmission of such genes in families results in an easily identifiable pattern of inheritance and the concommitant ability to locate the gene resulting in increased risk by genetic linkage analysis. From our study of sporadic and familial retinoblastoma, we have identified a genetic factor whose action appears to result in a more modest increase in relative risk – on the order of one-hundred to one-thousand-fold. We believe that a locus that is responsible for this increase in relative risk lies on the human X-chromosome. Our data indicate that aberrant alleles at this locus not only appear to increase an individual's risk for a number of cancers, but also participate in the process of genome imprinting.

The epidemiological and genetic arguments in favor of the involvement of an X-linked "imprintor, mutator" gene in the generation of new, heritable, RB-1 mutations are given in detail in Naumova and Sapienza (1994). The pertinent data may be summarized as follows:

1. there is a significant excess-of-males among patients with bilateral sporadic but not unilateral sporadic retinoblastoma;
2. there is preferential retention of paternally-derived RB-1 alleles in bilateral, but not unilateral, sporadic retinoblastoma;
3. sex ratio bias in favor of males is observed among the offspring of male founders but not female founders of retinoblastoma pedigrees (i.e. the male founders fail to transmit their X-chromosomes with the expected frequency;
4. transmission ratio distortion in favor of affected individuals is observed among the offspring of male founders but not female founders, and

5. the affected male offspring of these male founders have families in which offspring are distributed equally among affected and unaffected boys and girls, as expected for an autosomal dominant trait, i.e. sex-ratio and transmission-ratio distortion are observed only among the offspring of male founders of retinoblastoma pedigrees.

We have developed a genetic model based on the process of genome imprinting that may explain these data, as well as related observations on other pediatric cancers and cancer prone syndromes.

REFERENCE:

1. Naumova A and Sapienza C (1994): The genetics of retinoblastoma, revisited. Amer J Hum Genet 54: 264-273.

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