Occasional abstract

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Recent views on genetic factors in retinoblastoma

In 1971 Knudson\(^1\) proposed that retinoblastoma was produced by two independent mutational events. The first of these could be germlinal, while the second event occurred in immature retinal cells. Patients with unilateral non-hereditary retinoblastoma had to have two new mutations occurring in a retinal cell, which would explain why their tumour developed later than hereditary tumours. Indeed, Knudson's conclusions were based on the age of onset distribution of bilateral versus unilateral tumours, the shape of these age of onset curves, and the observed numbers of tumours per gene carrier. Knudson also suggested that the germinal mutation could be delayed, to explain those pedigrees where two affected sibs have healthy parents. This idea of delayed mutation in retinoblastoma was later elaborated by Herrmann.\(^2\)

Recently this two-mutation hypothesis has been challenged by Matsunaga.\(^3\)–\(^5\) His hypothesis is that only one mutation (either a germlinal or a somatic one) is required and the expression of this mutated gene depends upon host resistance. The evidence for host resistance is threefold. Firstly, the age of appearance of the second tumour in bilaterally affected subjects is so close to that of the first tumour (even after allowing for the inevitable earlier diagnosis) that host factors influencing the age of appearance seems likely. These host factors are likely to be familial since the age of appearance of tumours is related to the degree of affection in the parent. Secondly, both the penetrance and the expressivity in offspring depends upon the expressivity in the gene carrying parent. For example, with a group of bilaterally affected parents, 0.49 of their children are overtly affected, nearly 90% of them having bilateral disease, whereas with a group of unaffected parents of familial cases, only 0.31 of their children are overtly affected, and of these only 54% have bilateral disease. Thirdly, the distribution of phenotypes (bilaterally affected, unilaterally affected, or unaffected) among children who have inherited the retinoblastoma gene does not fit the Poisson distribution, as would be expected if Knudson's second mutation occurred in them, but does fit the hypothesis of polygenic host resistance. Matsunaga envisages a multifactorial model with two thresholds: below the first threshold a gene carrier is unaffected, above the second threshold a gene carrier is bilaterally affected.

On Knudson's hypothesis the unilateral non-hereditary cases suffer from two new mutations. On Matsunaga's hypothesis they represent those subjects who are most susceptible to the development of retinoblastoma from a single initiating event occurring during retinal differentiation. Nearly everyone in the population will have some resistance to such an event, while those subjects who are non-manifesting gene carriers will have most resistance of all. However, this 'host resistance' would have to be specific for retinoblastoma since Matsunaga's most susceptible group, the unilateral non-hereditary cases, do not appear to have the same increased risk for developing cancers elsewhere as do familial cases, whether bilateral or not.\(^6\)–\(^7\) Perhaps the answer will come from studying a marker for resistance, or susceptibility, to retinoblastoma, if one is found. In any case the two protagonists should be applauded for the introduction of original genetic hypotheses into the perplexing puzzle of retinoblastoma.

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References


Note added in proof

A recent study from France\(^8\) has shown that the grandparents of retinoblastoma patients (those who

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were unilaterally affected as well as those who were bilaterally affected) have an increased incidence of cancers of various sorts. Very few of these grandparents were definite or possible gene carriers. It therefore seems likely that this increased familial susceptibility to cancer is the result of a genetic predisposition, caused by either a few or many genes, but not directly related to the main gene for retinoblastoma. This might support Matsunaga’s hypothesis.

Reference