GENETIC ASPECTS OF CHILDHOOD TUMOURS

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Present concepts on the etiology of childhood tumours are reviewed. The differences in clinical manifestations of the hereditary and nonhereditary types are illustrated with data on retinoblastoma and on nephroblastoma. Notwithstanding these differences it is most likely that the fundamental etiologic process is the same in both and that it consists in successive mutational events. The possible consequences of the association of retinoblastoma with a deletion of chromosome 13 in some cases are discussed. Several explanations for the association of Wilms' tumour and aniridia are also discussed.

Different mechanisms can play a role in the genesis of retinoblastoma on the one hand and of nephroblastoma or Wilms' tumour on the other.

As can be seen from the following summarizing table, three groups (I, II, III) can be considered.

I	Retinoblastoma & Wilms' tumour	*Hereditary* (40%): autosomal dominant — familial : unilateral bilateral — sporadic: most bilateral some unilateral *Nonhereditary* (60%) — sporadic: all unilateral	" Mutational"
II	Retinoblastoma	D deletion: 8 sporadic cases	Chromosomal
III	Wilms' tumour	Association with aniridia: 35 cases	?

I. The first group comprises hereditary and nonhereditary types of retinoblastoma and of Wilms' tumour, in which the etiologic events are thought to be mutational. In both diseases, around 40% of all the cases are considered to be hereditary, the mode of inheritance being autosomal dominant (Knudson 1971, Knudson and Strong 1972, Knudson et al. 1973).

The *hereditary* tumours can be familial or sporadic. Amongst the familial cases, there are unilateral as well as bilateral cases. The sporadic cases are mostly bilateral, sometimes unilateral. The hereditary sporadic cases are able to transmit the tumour to their offspring. On the contrary, the *nonhereditary* sporadic cases will not transmit the tumour to their offspring and are always unilateral. They represent 60% of all the cases.

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In retinoblastoma as well as in nephroblastoma the focality and time of onset is different in the hereditary and in the nonhereditary tumours.

The familial cases, which are of course hereditary, are usually bilateral. The sporadic cases, which comprise hereditary as well as nonhereditary cases, are more often unilateral than bilateral.

The median age at diagnosis is lower in the sporadic bilateral and in the familial cases (1-2 years), than in the sporadic unilateral cases (2-3 years in retinoblastoma and 3-4 years in Wilms' tumour). The difference amounts thus to about one year in retinoblastoma and two years in Wilms' tumour (Knudson 1971, Knudson and Strong 1972).

Knudson (1971) and Knudson and Strong (1972) explain these facts in the light of the hypothesis, according to which tumour formation can only start after *two or more mutational events* have occurred. The first step would be an "initiating" mutational event, only predisposing the cells to the action of a second mutational event, which really "promotes" active cell proliferation. Whereas the second event is probably the same in hereditary and nonhereditary tumours, the first event takes place at different moments in the two types. The cases of hereditary retinoblastoma and of hereditary Wilms' tumour, the familial as well as the sporadic ones, would be due to a germinal mutation, i.e., occurring during gametogenesis and present in the fertilizing gamete. This mutation will postzygotically be present in all the somatic cells, but tumour growth only starts after a somatic mutational event has taken place in one of the "initiated" retinal or renal cells respectively. When this second mutational event does not take place, the subject remains an unaffected carrier, who can nevertheless transmit the mutation to his offspring. On the other hand nonhereditary tumours would be due to two or more consecutive mutational events in the same somatic cell.

It is obvious that in hereditary cases, where all the cells already carry the first mutation and where only one somatic event must occur, the tumours can easily develop in more than one site and start earlier than in nonhereditary cases, where two somatic events are necessary.

The nature of the mutational events is as yet unclear (point mutation, gene deletion, gene duplication, incorporation of viral DNA?).

All hereditary tumours and tumour syndromes show tissue specificity. The mutated locus at a specific site of a specific chromosome apparently concerns a gene expressed specifically in one or more target tissues.

The main consequence of any mutation hypothesis is that all individual tumours should be derived from a single cell. This has indeed been found in tumours such as uterine leiomyomata (Linder and Gartler 1965), chronic myelocytic leukemia (Fialkow et al. 1967), lymphosarcoma, reticulum cell carcinoma and plasmacytoma (Fialkow 1972). Even tumours thought to be of viral origin such as warts (Murray et al. 1971) and Burkitt tumours (Fialkow et al. 1970) have been proven to be monocellular in origin. The method which demonstrated this is based on the random inactivation of one of the two X chromosomes in every normal female (Lyon 1962) and consists in the enzymatic analysis of women heterozygous for the X-linked enzyme G6PD, types A and B.

The two-mutational model can explain most data on retinoblastoma as well as on nephroblastoma, with one exception however: their occurrence in several sibships of the same family without expression in the parents. In order to explain this phenomenon Knudson and Strong (1972) advance the hypothesis of "premutation" or "delayed mutation": i.e., a vertical or hereditary passage of an unexpressed genetic change for one or more generations, following which the change becomes an expressed fixed germinal mutation.

II. The second group consists of eight cases of sporadic retinoblastoma, in which a deletion of chromosome 13 has been found (Lele et al. 1963, Thompson and Lyons 1965, Van Kempen 1966 and 1969, Taylor 1970, Gey 1970, Grace et al. 1971, Wilson et al. 1969 and 1973, Orye et al. 1971 and 1974).

These eight patients are a minority compared to the overwhelming majority of retinoblastoma patients who have a normal caryotype. Needless to say that the caryotype discussed here concerns the *patient's* caryotype and not the caryotype of the tumour cells cultured after extirpation. The latter can be abnormal even when the patient's caryotype is normal (Yoneda and Van Herrick 1963).

In the cases of retinoblastoma associated with a deletion the following etiologic mechanisms have been suggested:

(1) the removal of a normal allele might facilitate the expression of a mutated gene on the intact homologue (Lele et al. 1963);

(2) the presence of only one allele on one chromosome might be insufficient for normal retinal development (Hamerton 1971).

At present we do not know which of these hypotheses is correct.

Partial deletion of the long arm of chromosome 13 is associated with a characteristic malformation syndrome (mental and physical retardation, finger abnormalities, dermatoglyphic anomalies, etc.).

It is possible that all retinoblastomas are associated with a chromosomal deletion, but that in subjects with an apparently normal caryotype the deletion is limited to a single locus or to a few loci too small to be optically detected or to produce other congenital anomalies.

III. The third group comprises 35 nephroblastoma cases who, besides the renal tumour, also have aniridia (Brusa and Torricelli 1953, Miller et al. 1964: 6 cases; Fontana et al. 1965, Zimmerman and Font 1966, Faure and Lange 1967, Schweisgut et al. 1967: 4 cases; Fraumeni and Glass 1968: 5 cases; Mackintosh et al. 1968, Flanagan and Di George 1969, Woodard and Levine 1969, Miller 1969: 2 cases; Gandhi et al. 1970, Ledlie et al. 1970, Haiken and Miller 1971, Le Marec et al. 1971, Neidhardt 1972, Ladda et al. 1974; pers. obs.: 1 case).

The aniridia is usually severe. Aniridia, on the one hand, and Wilms' tumour, on the other, can both be autosomal dominant conditions. The association of Wilms' tumour and aniridia can thus be due to a *germinal mutation* of a single gene with pleiotropic effect or of two or more interacting genes (Fraumeni 1969).

As most of the cases have, besides the renal tumour and the aniridia, also other congenital anomalies, the syndrome could also be the result of a *chromosomal deletion*, which includes not only the aniridia locus but also the Wilms' tumour locus and some other adjacent loci. However, routine chromosomal analysis in five cases revealed a normal caryotype (Fraumeni and Glass 1968). The deletion is perhaps too small to be detected. Nevertheless, in a recent publication Ladda et al. (1974) described a chromosome translocation t(8p +; 11q —) in a patient with aniridia and Wilms' tumour. Computer analysis of scanning profiles revealed the translocation to be unbalanced, due to the loss of an interstitial segment of the short arm of chromosome 8.

The fact that in all 35 cases the renal tumour occurred sporadically and that only one of them belonged to an aniridia family, suggest the possiblity of an *environmental* effect during embryogenesis in at least 34 of the cases (Fraumeni 1969).

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RIASSUNTO

Aspetti Genetici dei Tumori dell'Infanzia

Vengono analizzate le attuali concezioni sull'eziologia dei tumori dell'infanzia. I dati clinici su retinoblastoma e nefroblastoma illustrano le differenze cliniche fra i tipi ereditari e non ereditari. Malgrado queste apparenti differenze, è probabile che i meccanismi eziologici siano fondamentalmente identici nei due tipi e consistano in una successione di avvenimenti mutazionali. Vengono discusse le eventuali conseguenze dell'associazione del retinoblastoma ad una delezione del cromosoma 13 in alcuni casi. Vengono enunciate diverse ipotesi per spiegare l'associazione del nefroblastoma con l'aniridia.

RÉSUMÉ

Aspects Génétiques des Tumeurs de l'Enfance

Les conceptions actuelles sur l'étiologie des tumeurs de l'enfance sont analysées. Les données cliniques sur le rétinoblastome et le néphroblastome illustrent les différences cliniques entre les types héréditaires et non-héréditaires. Malgré ces différences apparentes, les mécanismes étiologiques sont probablement fondamentalement identiques dans les deux types et consistent en une succession d'événements mutationnels. Les conséquences éventuelles de l'association du rétinoblastome à une délétion du chromosome 13 dans certains cas sont discutées. Plusieurs hypothèses sont énoncées pour expliquer l'association du néphroblastome avec l'aniridie.

ZUSAMMENFASSUNG

Erblichkeit der Tumore im Kindesalter

Analyse der derzeitigen Konzepte über die Aetiologie der Tumore im Kindesalter. Die klinischen Erhebungen über Retinoblastome und Nephroblastome zeigen die klinischen Unterschiede zwischen erblichen und nichterblichen Krankheitstypen. Trotz dieser scheinbaren Unterschiede ist der Ursprungsmechanismus bei beiden Typen wahrscheinlich derselbe, und zwar besteht er in einer Reihe von Mutationsvorgängen. Es folgt eine Erörterung über die evtl. Folgen der in einigen Fällen beobachteten Verbindung von Retinoblastom mit Chromosom-13-Delektion; sodann werden verschiedene Hypothesen unterbreitet, um die Verbindung von Nephroblastom und Aniridie zu erklären.

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