CHAPTER 3

GENETICS OF WILMS TUMOR

INTRODUCTION

Most Wilms tumors are unilateral and sporadic, but approximately 5-10% are bilateral and a further 1-2% show familial recurrence. The observation that Wilms tumor, like retinoblastoma (a childhood tumor of the retina), can be unilateral or bilateral at presentation, has been of particular interest in view of Knudson and Strong’s proposed two-hit model for the development of certain cancers. In 1971, Knudson compared the incidence of unilateral versus multiple retinoblastomas in children with a positive family history and subsequently calculated the number of events required for tumor development. Based on the Poisson distribution for rare events, he predicted that retinoblastoma develops as a consequence of two rate-limiting cellular events. A year later, a similar model was put forward for the development of Wilms tumor. This hypothesis predicts that most or all Wilms tumors will contain either one or two mutant Wilms tumor suppressor alleles and no wild-type allele. The first hit referred to in the two-hit hypothesis will result in a mutation in one Wilms tumor suppressor allele. The cell undergoing this mutation will still be phenotypically normal but will be predisposed to tumor initiation following a second hit. The number of mutant alleles in the tumor will depend upon whether the second hit, which results in loss of the wild-type allele, occurs through chromosome loss, non disjunction, mitotic recombination or a second mutation (Fig. 3.1).

The “two-hit” hypothesis suggests that there are heritable and non-heritable forms of cancer. In the heritable* form, the first cellular

*Heritable Wilms tumor should not be confused with familial Wilms tumor. Unlike retinoblastoma, only 1-2% of Wilms tumors are familial. Siblings of an affected child with heritable Wilms tumor are, in the large majority of cases, not at increased risk of developing Wilms tumor, as the germline mutation usually occurs de novo and therefore is not inherited from an affected parent.

event is prezygotic, leading to a constitutional or germline mutation that will be present in all cells of the resultant embryo. A single second event in any one cell of a susceptible target tissue (retina or kidney, for example) will lead to tumor development. The model predicts that individuals who carry a germline mutation are not only at risk of developing multiple tumors, since all the cells will carry the first event and only one additional event is required to allow tumorigenesis, but also that these individuals will

![Diagram](image)

**Fig. 3.1.** Mechanisms leading to phenotypic expression of a recessive WT1 mutation. The first “hit” involves a mutation that inactivates one WT1 allele. The second “hit” can involve mitotic recombination which will lead to a loss of heterozygosity for all genes distal to the recombination event. A second mechanism involves gene conversion/inactivation or a second mutation which will affect only the WT1 gene. Chromosome nondisjunction will result in two copies of the chromosome carrying the mutation while chromosome loss will result in a single copy of the mutant chromosome.