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Early and late genetic changes in clear cell renal carcinoma

Renal cell carcinoma is characterized by an accumulation of complex chromosomal alterations during tumor progression [1, 2]. Chromosome 3p deletions are known to occur early in carcinogenesis. However, the nature of subsequent events, their interrelationships, and sequence are poorly understood, as one usually only obtains a single "view" of the dynamic process of tumor development in a particular cancer patient. To address this limitation, we used comparative genomic hybridization (CGH) analysis in combination with a *distance-based* and a *branching* tree method to search for tree models of the oncogenesis process of 116 conventional (clear cell) renal carcinomas [3, 4, 5]. This provides a means to analyze and model cancer development processes in a more dynamic fashion, including the presence of multiple pathways, as compared to the fixed linear model first proposed by Vogelstein et al. in 1988 for colorectal cancer. The most common DNA losses involved 3p (61%), 4q (50%), 6q (40%), 9p (35%), 13q (37%), and Xq (21%). The most common gains were seen at chromosome 17p and 17q (20%). The tree model derived from the distance-based method is consistent with the established theory that -3p is an important early event in conventional (clear cell) renal cancer and supports the prediction made from the branching tree method that -4q is another important early event. Both tree models suggest that there may be two groups of clear cell renal cancers: one characterized by -6q, +17q, and +17p, and another by -9p, -13q, and -18q. Putative prognostic parameters were -9p and -13q. The distance-based tree clarifies that -8p (present in 12% of tumors) is a late event, largely independent of other events. In summary, tree modeling of CGH data provided new information on the inter-relationships of genetic changes in renal cancer, their possible order, as well as a clustering of these events. Using tree analysis, one can derive a more in-depth understanding of the renal cancer development process than is possible by simply focusing on the frequencies of genetic events in a given cancer type.

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