Renal Cell Cancer: Chromosome 3 Translocations as Risk Factors

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Renal cell cancer (RCC) is relatively rare, with overall incidence rates of approximately five per 100,000 (1). The disease can be cured only by surgery if detected early and clinically restricted to the organ, that is, without metastasis. Usually, RCCs occur as sporadic tumors, but hereditary RCCs have also been reported in particular as a consequence of von Hippel–Lindau (VHL) disease (2). Until recently, two families with RCC and with balanced chromosomal translocations were reported. In the first family, a constitutional translocation t(3;8)(p14;q24) (i.e., a genetic exchange between position p14 of chromosome 3 and position q24 of chromosome 8) was found in several family members, including 10 patients with RCC (3). In the second family, a constitutional t(3;6)(p13;q25) was found in three consecutive generations. As yet, constitutional t(3;6)(p13;q25) was found in several family members, including 10 patients with RCC (3). In the second family, a constitutional translocation t(3;6)(p13;q25) was found in three consecutive generations. As yet, only the oldest member of this family developed bilateral RCC (4). In addition, a single sporadic case of RCC has been reported carrying a constitutional

t(3;12)(q13;q24) (5). Recently, we added another hereditary case to this list, a t(2;3)(q35;q21) in several family members over three generations, including four patients with RCC (6). Via allele segregation and loss-of-heterozygosity analyses in this family, a modification of the standard two-step model of tumorigenesis was proposed in which the initial event, loss of the translocation-derived chromosome 3 through nondisjunction, was predicted to lead to chromosomal mosaicism (7). Subsequently, cells lacking this chromosome might have a second hit in the form of a random somatic mutation that initiates tumorigenesis. In support of this model, it was found that the VHL gene, which maps to this chromosome, carried different mutations in different RCCs, even in tumors from the same individual. In addition, it was hypothesized that the risk of developing RCC could be associated with the extent of somatic (kidney) mosaicism resulting from the initial chromosomal loss (7).

As a corollary of this model, we set out to evaluate whether familial chromosome 3 translocations may predispose to RCC development, irrespective of the location of the breakpoint in chromosome 3 and/or the translocation partner involved. Therefore, a series of 10 translocation families (Fig. 1, #1 to #10), referred to our Department of Human Genetics for other disorders and characterized by cytogenetic analysis as detailed earlier (6), was evaluated by use of written questionnaires and, if required, oral interviews. Relevant information could be obtained from a total of 57 chromosome 3 translocation carriers (>25 years of age; others excluded). Within this cohort, four patients (one male and three females; age range, 51–62 years) with clinically confirmed RCC of the clear cell type were encountered in two different families, three patients in family #6 with t(3;6)(q12;q15) and one patient in family #4 with t(3;4)(p13;p16). Based on the age- and sex-specific incidences of RCC in the Dutch population (8), only 0.204 cases of RCC were expected among the carriers. The incidence in this cohort is, therefore, increased with a factor of 19.6 (95% confidence interval = 5.3–50.2).

In families #1, #2, #3, and #10, eight, six, nine, and four translocation carriers over three generations were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively. In families #5, #7, #8, and #9, one, one, two, and three translocation carriers were identified, respectively.

Fig. 1. Diagram showing human chromosome 3, the familial translocations, and the positions of the respective breakpoints. Left: familial cases of renal cell carcinoma known from the literature (3–6). Right: families included in this study (#1 to #10). The two novel translocations (#4 and #6; unpublished) and the published translocations are enclosed in boxes.
in the literature (Fig. 1; unpublished and published, respectively) indicate that the overall incidence of RCC in chromosome 3 translocation families is strikingly high, in particular, when taking into account the fact that our series includes several small families with only a few translocation carriers at a relatively young age (i.e., #5, #7, #8, and #9) and the expected wide range in penetrance as based on the concept of somatic mosaicism (7). Another interesting observation is that the familial translocations at risk exhibit breakpoints in the proximal p- and q-arms of chromosome 3. Taking into consideration the fact that the 3p-arm is thought to harbor several tumor suppressor loci relevant to RCC development (positioned in the region 3p25–p14) (9), one might speculate that breakpoints more distal on 3p (#1 and #2) may interfere with the above-mentioned two-step model. In analogy, distal breakpoints on 3q (#9 and #10) would, according to the proposed two-step model, lead to somatic loss of the major part of chromosome 3. Such a loss may not be compatible with the survival of (renal) epithelial cells, thus explaining the absence of RCCs in this set of families. This latter suggestion is in full agreement with observations made in sporadic cases of RCC (10). Alternative options are that mitotic recombination (11) and/or genes located at or near the pericentromeric chromosome 3 translocation breakpoints [e.g., the fragile histidine triad gene (12)] may play a critical role(s) in tumor development.

Taken together, our findings strongly indicate a substantial increase in the risk of RCC development in carriers of (familial) reciprocal chromosome 3 translocations, in particular when the translocation breakpoints are located pericentromerically. This notion may have consequences for the identification of persons at risk, for the development of genetic counseling strategies, and for the clinical management of patients. Therefore, periodic echoscopic screening and counseling are already being actively pursued in the families at risk whom we have identified, thus allowing early RCC detection and surgical intervention. Our observations also call for cytogenetic analysis of familial cases of RCC, patients with bilateral and/or multifocal RCC, and patients with RCC at a relatively young age.

**References**


**Notes**

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