GUEST EDITORIAL

Familial renal cell carcinoma: clinical and molecular genetic aspects

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Summary Renal cell carcinoma (RCC) accounts for 2% of all human cancer, but familial cases are infrequent. Riches (1963) and Griffin et al. (1967) found only 1% of cases were familial in their respective series. McLaughlin et al. (1984) in a population-based case-control study found a family history of renal cell carcinoma in 2.4% of affected patients compared to 1.4% of controls. Nevertheless the importance of inherited tumours in clinical practice and medical research is disproportionate to their frequency. In clinical practice recognizing familial RCC can provide opportunities to prevent morbidity and mortality by appropriate screening. In medical research recent advances in molecular genetics offer the prospect of isolating the genes involved in the pathogenesis of familial RCC and of the more common sporadic cases. In this article we review the clinical and molecular genetics of inherited renal cell carcinoma (adenocarcinoma or hypernephroma).

Clinical aspects

As with other inherited tumours, familial RCC is characterised by (i) an early age at onset compared to sporadic cases, (ii) frequent bilaterality and (iii) multicentricity. Mean age at diagnosis in familial cases is about 45 years, more than 15 years earlier than for sporadic cases (Maher et al., 1990a; Erlandsson et al., 1988). Two main groups of inherited RCC can be distinguished (i) those which occur as part of von Hippel-Lindau (VHL) disease and (ii) those with 'pure' inherited RCC and no additional features.

Von Hippel-Lindau disease

This is the most frequent cause of inherited RCC and subclinical evidence of VHL disease should be sought in all cases of inherited or multiple RCC. This autosomal dominant cancer syndrome has a heterozygote prevalence of 1 in 50,000 persons and 700 patients have been reported (Lamiell et al., 1989; Maher et al., 1990b). The characteristic manifestations of VHL disease are retinal, cerebellar and spinal haemangioblastomas, RCC, phaeochromocytoma, and renal, pancreatic and epididymal cysts. Infrequent complications include pancreatic tumours (APUDomas or carcinoma), supratentorial haemangioblastoma and angiomas in the spleen, adrenal glands or liver (Horton et al., 1976; Lamiell et al., 1989; Maher et al., 1990b). Conventional diagnostic criteria require that in the absence of a family history the diagnosis can be made in the presence of two or more haemangioblastomas or a single haemangioblastoma associated with a visceral lesion (Melmon & Rosen, 1964). When there is a family history of haemangioblastoma then only a single manifestation is necessary to make the diagnosis. Most patients with VHL disease present before age 40 years and almost all gene carriers can be identified by age 60 if appropriate screening is performed (Maher et al., 1990b). Although RCC is the presenting feature in only 10% of patients with VHL disease the risk of developing a RCC rises progressively from age 20 and is 70% by age 60 years (Maher et al., 1990b). Comprehensive screening programmes have been proposed (Huson et al., 1986; Jennings et al., 1988; Maher et al., 1990b; Lamiell et al., 1989) and annual renal imaging (ultrasound or CT scan) from age 20 years is mandatory for both affected patients and at risk relatives. Multiple renal cysts are frequent in VHL disease and have been found in up to 76% of patients (Horton et al., 1976). These cysts may be precancerous and in patients with multiple renal cysts a continuum from simple benign cysts to frank RCC may be seen (Solomon & Schwartz, 1988; Ibrahim et al., 1989). RCC in VHL disease patients has been reported to be bilateral and multicentric in up to 75% and 87% of patients respectively (Fill et al., 1979).

Familial Renal Cell Carcinoma without additional features

The literature contains 23 reports of 105 patients with familial RCC (Clemmesen, 1942; Rusche, 1953; Krumbach & Ansell, 1959; Brinton, 1960; Riches, 1963; Griffin et al., 1967; Klinger, 1968; Pearson, 1969; Horn & Horn, 1971; Steinberg et al., 1972; Franksson et al., 1972; Guiguis, 1973; Valleteau de Mouillac et al., 1974; Braun, 1975; Lyons et al., 1977; Pilepich et al., 1978; Cohen et al., 1979; Goldman et al., 1979; Reddy, 1981; Li et al., 1982; Pathak et al., 1982; McLaughlin et al., 1984; Mathieson, 1986). The mean age at diagnosis of patients with inherited RCC is 48 years (Erlandsson et al., 1988) similar to the mean age of diagnosis of RCC in VHL disease. The most likely mode of inheritance is autosomal dominant with age-dependent penetrance, vertical transmission being observed in 17 of 29 families available for analysis. The kindred reported by Cohen et al. (1979) contained ten affected patients in three generations, but here there was an associated between RCC and a balanced 3;8 translocation with breakpoints at 3p14.2 and 8q24.1. RCC was only seen in translocation carriers, each of whom had an 87% risk of developing RCC by 60 years of age. There are no other reports of familial RCC being associated with constitutional chromosome translocations but sporadic cases associated with 3;12 and 3;6 translocations have been reported (Kovacs & Hoene, 1988; Kovacs et al., 1989a). Not all patients with familial RCC will have been karyotyped, but Kantor et al. (1982) did not find any constitutional chromosome 3 rearrangements in seven patients with familial tumours nor in five with bilateral disease or 23 with an early age at onset.

The multiple atypical renal cysts seen in VHL disease do not appear to be a prominent feature of other forms of inherited RCC. The family reported by Franksson et al. (1972) with RCC and polycystic kidneys may have had VHL disease. Apart from multicentricity the histopathological appearances of all forms of inherited RCC are similar to those of non-familial tumours. Early detection of RCC improves prognosis (Smith et al., 1989) and patients at risk for familial RCC should be screened annually from age 20 as in VHL disease (see above).

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Molecular genetics of inherited RCC

Although there is a rat model of dominantly inherited RCC (Eker et al., 1981), most recent research interest has focused on the molecular genetics of human inherited RCC and it is now clear that genes on the short arm of chromosome 3 are implicated in the pathogenesis of familial and non-familial cases of nonpapillary RCC (Kovacs et al., 1989b). Statistical analyses of RCC in VHL disease and other forms of familial RCC (Mager et al., 1990a; Erlandsson et al., 1988) suggests a single stage mutation model of tumourigenesis as in inherited retinoblastoma (Cavenee et al., 1983). Reports of cytogenetic deletions and allele loss in VHL disease tumours are compatible with the VHL gene functioning as a recessive tumour suppressor gene (King et al., 1987; Tordy et al., 1989). The precise localisation of the gene responsible for familial RCC is the subject of intense interest. Genetic linkage studies in families with VHL disease place the VHL locus at the tip of chromosome 3p (3p25–26) (Seizinger et al., 1988; Mager et al., 1990c, 1990d). However the breakpoint in the 3;8 translocation family reported by Cohen et al. (1979) is more proximal at 3p14.2 (Wang & Perkins 1984) (Figure 1). Although the c-myc oncogene situated at 8q24.1 is translocated, there is no evidence of any rearrangement or alteration of c-myc expression (Drabkin et al., 1989). Thus it has been presumed that the predisposition for RCC in this family results from the disruption of a gene (the 'first hit') at or close to the translocation breakpoint on chromosome 3p (Drabkin et al., 1989). Further support for this hypothesis is provided by Kovacs et al. (1989b), who described a patient with multiple bilateral RCC and a constitutional 3;6 translocation (breakpoint between 3p13 and 3p14), and Pathak et al. (1982) who reported a patient with familial RCC and normal constitutional karyotype, but a chromosome 3:11 translocation (breakpoint at 3p13 or 3p14) in tumour cells perhaps suggesting an inherited instability in this region. Kovacs and Hoene (1988) have reported a non-familial RCC in a patient with a constitutional 3:12 translocation with a breakpoint at 3q13:2 in whom the derivative chromosome containing 3p was lost from the tumour cells. In this case it may be that the translocation predisposes to RCC because of a tendency for the derivative chromosome to be lost when the 'first hit' has occurred on the normal chromosome. Alternatively the translocation may be more complex than it appears with involvement of the short arm of chromosome 3 as well as the long arm. Further molecular genetic studies of tumours associated with constitutional chromosome 3 rearrangements would be of interest.

Statistical analyses of the age at onset of non-familial RCC are compatible with a two stage mutation model of tumourigenesis as in retinoblastoma and Wilms' tumour (Mager et al., 1990a; Erlandsson et al., 1988; Knudson 1971; Knudson & Strong, 1972). In retinoblastoma non-familial tumours result from mutations at the same locus as familial tumours. For Wilms' tumour multiple loci exist: there are two loci on chromosome 11 (11p13 and 11p15) at which acquired mutations in both familial and non-familial tumours may occur. The locus for the inherited predisposition to Wilms' tumour has not yet been mapped but has been excluded from the short arm of chromosome 11 (Jeanpierre et al., 1990; Grundy et al., 1988).

Cytogenetic and molecular studies of sporadic RCC have consistently demonstrated chromosome 3p rearrangements (Zbar et al., 1987; Yoshida et al., 1986; Bergerheim et al., 1989; Kovacs et al., 1988). Furthermore, Shimizu et al. (1990) recently reported that the introduction of a normal chromosome 3p modulated the tumourigenicity of a human renal cell carcinoma cell line. In molecular genetic studies of sporadic RCC the most frequent change is allele loss from chromosome 3p21–pter (Zbar et al., 1987; Kovacs et al., 1988; Bergerheim et al., 1989). This includes the region to which the VHL disease gene has been localised (3p25–26) but the region of the 3:8 translocation breakpoint (3p14) is not always involved (Figure 1). However Teyssier et al. (1986) have described two sporadic RCC with an interstitial deletion of chromosome 3p which spared the region of the VHL disease gene. This suggests that at least two loci on chromosome 3p are involved in the pathogenesis of non-familial RCC. One locus is situated distally and may be the VHL disease gene itself, another is more proximal (3p13–21) and may be the site of the translocation breakpoints at 3p1–3p14. RCC seems to be similar to Wilms' tumour in that multiple loci are involved.

Human oncogenesis is a multistep process and activation of H-ras oncogenes and chromosome 11p allele loss have both been reported in human RCC (Fujita et al., 1988; Anglard et al., 1989). Nevertheless, the primary role of gene(s) on chromosome 3p in the pathogenesis of RCC is suggested by the observation that the introduction of a normal chromosome 11 into a human RCC cell line had no effect on tumourigenicity or cell growth (Shimizu et al. 1990). Several other human cancers are associated with chromosome 3p allele loss including small and non-small lung cell carcinoma, uterine and breast cancer. Recently, Naylor et al. (1989) and Erlandsson et al. (1990) have independently isolated the same gene from chromosome 3p21 and proposed it as a possible candidate gene for small cell lung carcinoma and for RCC respectively. Further research into the molecular pathology of inherited and sporadic RCC will be needed to elucidate the number and localisation of the

Figure 1 Indeogram of chromosome 3 showing (i) the region of the VHL disease locus (3p25–p26), (ii) location of the breakpoints in the 3:8 translocation family reported by Cohen et al. (1979) and the 3:6 translocation described by Kovacs et al. (1989a) (3p13–p14), (iii) the breakpoint in the 3;12 translocation reported by Kovacs and Hoene (1988) (3q13.2).
genes involved in the pathogenesis of these tumours and their possible relationship to those associated with other forms of human cancer.

Conclusions

Patients with familial or multicentric RCC should be investigated for subclinical evidence of VHL disease and for chromosome 3 rearrangements. At risk relatives should be identified and offered appropriate screening investigations. Molecular genetic research offers the prospect of reliable presymptomatic diagnosis for VHL disease being available in the near future, and blood and tumour samples for DNA analysis should be collected and stored from all affected patients. As the risk of recurrent tumours is high all such patients should receive lifelong follow-up.

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