Multifocal renal cell carcinoma in sibs from a chromosome 9 linked (TSC1) tuberous sclerosis family

Julian R Sampson, Anup Patel, A David Mee

Abstract
Multifocal renal cell carcinomas (RCCs), together with angiomylipomas (AMLs) and renal cysts, were identified in early adult life in two sisters with tuberous sclerosis (TSC). They were members of a multigenerational tuberous sclerosis family showing strong evidence for a mutant TSC causing gene on chromosome 9 (TSC1). Previous reports of multifocal RCC in young patients with TSC suggest that constitutional mutations at the TSC loci may predispose to RCC. In the rat a germline mutation affecting the TSC2 gene is associated with transmission of multifocal RCC as an autosomal dominant trait. However, the cases reported here are the first to suggest a similar role for the TSC1 gene in renal cell carcinogenesis.

CASE 1
A 35 year old mother of three presented with right loin pain, dyspnoea on exertion, and a mass in the right flank. She had been diagnosed as having TSC eight years previously, when she and other members of her family were investigated following diagnosis of TSC in a cousin who developed epilepsy. Clinical and genetic investigation of her family (family 1013) has confirmed segregation of a tuberous sclerosis causing gene on chromosome 9 (the TSC1 gene) through her family for at least four generations.

Tuberous sclerosis (TSC) is an autosomal dominant disorder associated with the development of a wide variety of hamartomatous lesions in many tissues and organs.1 The birth frequency has been estimated at 1 in 5800.2 Two TSC causing genes have been localised to human chromosomes 9 (TSC1)3 and 16 (TSC2)4 but only the TSC2 gene has been isolated.5 Loss of heterozygosity at 9q34 and 16p13.3 in TSC associated hamartomas indicate that both the TSC1 and TSC2 genes act as tumour suppressor genes.57 In the kidneys, TSC is associated with the development of angiomylipomas (AML), cysts, and much less frequently renal cell carcinomas (RCCs) with clear cell or oncocytic histology.1 Here we report the occurrence of multifocal RCC in two sisters in early adult life. In one sister the RCCs were bilateral and metastatic. Genetic linkage studies showed that TSC in the family could be attributed to a mutation at the TSC1 locus on chromosome 9 (fig 1). These observations suggest a role for the TSC1 gene in the genesis of RCC, similar to that already reported for the TSC2 gene in an animal model, the Eker rat.910

Correspondence to:
Dr Sampson.
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Institute
of Medical Genetics,
University of Wales
College of Medicine,
Cardiff CF4 4XN, UK
J R Sampson

Department
of Surgery, Division
of Urology, UCLA
School of Medicine,
10833 Le Conte
Avenue, Los Angeles,
CA90024-1738, USA
A Patel

Department
of Surgery,
Charing Cross
Hospital, Fulham
Palace Road,
London W6 8RF, UK
A D Mee

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Figure 1 Pedigree of family 1013 with tuberous sclerosis. The sisters in whom renal cell carcinomas were diagnosed are indicated (case 1 and case 2). Previously reported linkage investigation has confirmed that the mutant TSC gene segregating in this family maps to chromosome region 9q34.4 The germline mutation is therefore of TSC1 type. Two point analysis versus a TSC1 linked dinucleotide repeat polymorphism in the argininosuccinate synthetase gene generated a lod score of 2.86 with no recombinant meioses.5 An affected only analysis yields a lod score of 8.71, while linkage to the TSC2 region has been excluded.11 Family member IV-5 had no symptoms of TSC, but was not included in the linkage analysis because age precluded consent to radiological investigation for asymptomatic evidence of TSC.

Figure 2 Abdominal computerised tomography (transverse plane) of case 2 at the time of diagnosis of renal cell carcinoma in her second (right) kidney. The complex cystic lesion with solid internal elements is arrowed. The large size of the right kidney reflects compensatory hypertrophy following left nephrectomy 11 years earlier. The high density signals marked "X" represent clips left on the left renal artery at previous surgery.

Discussion

In TSC, renal cysts, angiomyolipomas, and more rarely carcinoma may be found separately or may coexist, making evaluation difficult. Preoperative distinction between angiomyolipoma and renal cell carcinoma usually rests with imaging techniques such as sonography, computerised tomography, or magnetic resonance imaging, which identify a high fat content in angiomyolipoma. More subtle features including early arteriovenous shunting, anechoic rim or intratumoural cysts,12 or intraleisonal calcification may be suggestive of carcinoma. Particular difficulties in distinguishing carcinoma from AML arise when areas of haemorrhage or necrosis in a renal cell carcinoma give multiple echoes which are a characteristic of angiomyolipoma,13 or when arteriovenous shunting through an AML with early filling of the renal vein is incorrectly taken to suggest the presence of renal cell carcinoma.14 In contrast, the presence of solid elements within a renal cyst (as seen in one of the sisters described here) is suspicious of malignancy, and in these circumstances positive aspiration cytology may yield a more definitive diagnosis.

There have been no systematic studies of renal cell carcinoma in TSC, although at least 21 case reports have been published (references available from authors on request). In an unselected series of 256 TSC patients, one of us (JS) noted only two further cases of recognised renal cell carcinoma. Although published cases are likely to be subject to reporting bias, it is noteworthy that, among these, presentation was at a mean age of only 23.3 years (range 7–39 years) and that nine of 21 cases were bilateral. These observations are consistent with the TSC genes predisposing to renal cell carcinoma through a two-hit or analogous mechanism as first proposed for retinoblastoma by Knudson.15 The human TSC2 gene was recently isolated from chromosome 16 and has been shown to have the properties of a tumour suppressor gene, consistent with this hypothesis.57 Evidence that the TSC2 gene may be involved in renal cell carcinogenesis is provided by an animal model, the Eker rat. This strain carries an insertional mutation affecting the homologue of the human TSC2 gene18 and develops multifocal RCC as a dominant trait. Histologically the tumour cells are oncocytelike, eosinophilic, basophilic, or mixed, but not of clear cell type.16 In contrast, the human TSC1 gene has not yet been isolated from chromosome 9 and no animal model for TSC1 has been described. The cases reported here suggest that the TSC1 gene, as well as the TSC2 gene, can play a role in the genesis of RCC.

Although the first tumour occurring in case 2 of the present report showed penetration of the renal capsule, vascular invasion, and metastasis to regional lymph nodes, the patient has remained disease free for 15 years after complete surgical excision and radiotherapy. Some TSC patients with associated RCC have remained well on follow up, despite histological evidence for metastasis at presentation17,18 and only three of 21 previously reported cases are
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