

Nuclear Pedigree Criteria for the Identification of Individuals Suspected to be at Risk of an Inherited Predisposition to Renal Cancer

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Abstract

Renal clear cell carcinomas represent about 3% of all visceral cancers and account for approximately 85% of renal cancers in adults. Environmental and genetic factors are involved in the development of renal cancer. Although to date there are 19 hereditary syndromes described in which renal cell cancer may occur, only four syndromes with an unequivocal genetic predisposition to renal cell carcinoma have been identified: VHL syndrome (mutations in the VHL gene), hereditary clear cell carcinoma (translocations t(3:8), t(2:3)), hereditary papillary carcinoma (mutations in the MET protooncogene) and tuberous sclerosis (mutations in the TSC1 and TSC2 genes). Little is known genetically about the other forms of familial renal cell cancer. Since there is a growing awareness about the necessity of early intervention, clinical criteria have been developed that aid in the identification of hereditary forms of renal cancer. The aim of the current study was to identify minimal inclusion criteria so that nuclear pedigree families can be ascertained for risk assessment and/or kidney tumour screening. The results reveal that inclusion features described herein, such as (a) renal clear cell cancer diagnosed before 55 years of age, and (b) renal clear cell cancer and gastric cancer or lung cancer among first degree relatives, are useful in identifying suspected hereditary clear cell renal cancer patients.

Introduction

Renal clear cell carcinomas represent about 3% of all visceral cancers and account for 85% of renal cancers in adults. The tumours occur most often in older individuals, usually in the sixth and seventh decades of life, and are often diagnosed at incurable stages [1]. In Western countries the frequency of renal cancer remains relatively high,

there being approximately 30,000 new cases and 12,000 deaths per year from the disease [1]. The causes of kidney cancer are believed to be environmental (such as cigarette smoking, asbestos, petroleum products, heavy metals, unopposed oestrogen therapy, hypertension and obesity), genetic or a mixture of both [1]. To date there are 19 hereditary syndromes described in which renal cell cancer may occur (Table 1).

Table 1. Genetic syndromes characterised by an increased risk of renal cancer (Familial Cancer Database - FACD, <http://facd.uicc.org>)

Syndrome	Histological type of renal cancer	Gene	Mode of inheritance	Frequency of syndromes	References
A. VHL	Clear cell carcinoma	VHL	AD	1:36000	2, 3, 4, 5, 6, 7
B. Hereditary clear cell carcinoma	Clear cell carcinoma	FHIT? TRC?	AD	4 families reported	8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19
	Papillary carcinoma	MET	AD	?	20, 21, 22, 23, 24
C. Lynch (HNPCC)	Urothelial carcinoma	hMSH2 hMLH1	AD	1:2000	25, 26, 27, 28, 29, 30
D. Tuberous sclerosis	Clear cell carcinoma	TSC1 TSC2	AD	?	31, 32, 33, 34, 35
	Papillary carcinoma				
E. Bean	?	?	AD	simple families	36
F. Cowden	?	PTEN	AD	?	37
G. Gorlin	?	PTCH	AD	?	38
H. Fanconi anaemia	?	FANCA FANCC FANCD FANCG FANCE	AR	?	39, 40, 41
I. MEN1	Oncocytoma	MEN1	AD	?	42, 43, 44
J. Reed	?	?	AD	simple families	45
K. Werner	?	WRN	AR	simple families	46, 47, 48, 49
L. Birt-Hogg-Dube	?	?	AD	simple families	50
M. Syndrome of multiple adenomas and carcinoma of large bowel	?	CRAC1	AD	one family	51
N. 'Diffuse tubulocystic renal hyperplasia with renal cell carcinoma'	Tubulo-papillary carcinoma	?	<i>de novo</i>	two cases	52

The identification of genetic predispositions to renal cell cancer remains a priority since knowledge about the underlying molecular genetic basis of the disease will allow for a better understanding of the mechanisms giving rise to the disease and, perhaps more importantly, allow for the identification of individuals who are at risk of disease development.

There are two aspects of these criteria that can be problematic in the clinical setting with respect to the identification of familial renal cell cancer patients. The first is the difficulty in fulfilling criteria in countries where large families and extensive pedigrees are impossible to identify, for whatever reason, even though the

incidence of hereditary renal cell cancer may be quite high. Second, the criteria do not take into consideration the existence of family cancer syndromes where renal cell cancer may occur in association with an extra-gastric malignancy.

From a clinical perspective, there is a necessity to be able to identify hereditary renal cell cancer families with a minimum set of criteria that will provide a high likelihood of ascertainment. The aim of this study was to determine whether a minimum set of criteria could be established to identify suspected hereditary renal cell cancer patients when there is restricted information about the familial occurrence of disease.

Patients and methods

A total of 146 clear cell renal carcinoma (CCRC) patients comprising 3 groups were enrolled in the study.

Group A (familial renal cancer): comprising 46 patients affected by CCRC from 22 randomly selected families with at least two renal cancers among first or second degree relatives, independent of age at diagnosis of tumours. All families were registered in the International Hereditary Cancer Centre in Szczecin.

Group A1 (nuclear pedigree): comprising 25 patients affected by CCRC from Group A. None of the parents of these patients have been diagnosed as affected with renal cell cancer.

Group B: a total of 100 individuals diagnosed with CCRC between the years 1993 and 1997 irrespective of family history were collected from the city of Szczecin (total population 400,000).

The following inclusion features (IF) for the identification of suspected hereditary forms of clear cell renal cancer were used and compared against one another for their sensitivity and specificity:

IF 1: at least one of the parents of the patient with CCRC was affected by lung cancer

IF 2: at least one of the parents of the patient with CCRC was affected by gastric cancer

IF 3: CCRC diagnosed at the age of 45 years or younger

IF 4: CCRC diagnosed at the age of 50 years or younger

IF 5: CCRC diagnosed at the age of 55 years or younger

Statistical analysis

Univariate statistical analysis (Chi-squared, odds ratio (OR), and sensitivity and specificity of selection were performed using the SAS and LOGIT programs.

Results

The comparison of the five IFs was undertaken to identify the most consistent criteria that can be

employed in a clinical setting for the identification of suspected hereditary renal cell cancer, based on nuclear pedigree data. The first comparison was between Group A (associated with a genetic predisposition to disease) compared to unselected cases from Group B (Table 2). The results indicate that all inclusion features are more frequent in Group A (OR 1.62-4.88). There is no statistically significant difference for inclusion features IF1, IF2 and IF3.

The second comparison was performed between Group A1 and Group B (Table 3). The results indicate that there is a very strong correlation between hereditary (familial) predisposition to CCRC and occurrence of at least one of the following IFs: IF1, IF2 or IF5 - OR 13.4; $p < 0.00001$.

Discussion

The recognition of features that can be used for the identification of familial predispositions to CCRC in situations where extensive pedigree analysis is unknown or impossible to ascertain but the prevalence of the disease is relatively high in the population will aid in the identification of individuals at increased risk of developing CCRC.

By using the criteria described herein and the consequent recognition of significant odds ratios for some of the inclusion features to identify CCRC families, we believe that the identification of additional genes associated with this malignancy will be expedited.

Of particular interest are the odds ratio values for the inclusion features IF5 between groups A1 and B and IF 1 between groups A1 and B, which were relatively high (6.21 and 6.09, respectively). Since these inclusion features are significant we have a relatively high degree of confidence that the reported observations are not biased and are an accurate reflection of the validity of our approach for the identification of hereditary CCRC families. Indeed, these criteria have been tested in our

Table 2.

Criteria	Group A (n=46)	Group B (n=100)	OR	CI	Sensitivity	Specificity	P
IF1	5	7	1.62	0.5-5.2	10.87	93.00	0.4291
IF2	7	6	2.81	0.9-8.5	15.22	94.00	0.0693
IF3	7	6	2.81	0.9-8.5	15.22	94.00	0.0693
IF4	15	12	3.54	1.5-8.3	32.61	88.00	0.0029
IF5	23	17	4.88	2.3-10.6	50.00	83.00	0.000

Table 3.

Criteria	Group A1 (n=25)	Group B (n=100)	OR	CI	Sensitivity	Specificity	P
IF1	5	7	3.32	1.0-11.0	20.00	93.00	0.04840
IF2	7	6	6.09	1.9-19.5	28.00	94.00	0.00130
IF3	5	6	3.92	1.2-13.4	20.00	94.00	0.02710
IF4	9	12	4.13	1.5-11.2	36.00	88.00	0.00410
IF5	14	17	6.21	2.5-15.8	56.00	83.00	0.00010
IF1V IF2	12	13	6.16	2.4-16.2	48.00	87.00	0.00010
IF1V IF5	16	18	8.10	3.1-20.9	64.00	82.00	0.00000
IF2V IF5	18	22	9.12	4.1-24.1	72.00	78.00	0.00000
IF1V IF2 V IF3	15	16	7.88	3.1-20.4	60.00	84.00	0.00000
IF1V IF2 V IF3	18	20	10.29	4.3-27.4	72.00	80.00	0.00000
IF1V IF2 V IF5	20	23	13.40	5.5-38.3	80.00	77.00	0.00000

outpatient clinics to successfully identify hereditary CCRC. Therefore if we have families matching IF1 or IF2 or IF5, we are confident that a diagnosis of familial CCRC can be made.

At present it seems reasonable to offer the option of ultrasonography examination to all individuals identified by the use of our inclusion features beginning at the age of 5 to 10 years before the youngest CCRC identified within the patient's family. Such surveillance should only be an option and not a recommendation because the efficiency of such management procedures has not been rigorously determined to reduce morbidity and/or mortality. With respect to surveillance the real value of this will have to be established by studies on large cohorts of individuals from families matching pedigree and clinical criteria of suspected hereditary CCRC with identified constitutional DNA variants associated with genetic predispositions.

So far, the list of genetic changes associated with CCRC is somewhat limited but should be extended in the near future as more knowledge is gained about the genetic factors associated with altered CCRC predisposition.

In summary, we advocate the use of our criteria for suspected hereditary clear cell renal cancer identified in this report in order to:

a. offer an ultrasound examination option,

- b. create repositories of nuclear clear cell renal cancer families for future studies on the efficiency of surveillance for individuals with genetic predispositions to renal cancer,
- c. perform further studies to aid in the identification of genetic factors associated with CCRC.

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