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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 Papillary carcinoma	TSC1 TSC2	AD	?	31, 32, 33, 34, 35
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	?	*de novo*	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.

References

1. Kumar V, Abbas AK and Fausto N. Pathologic basis of disease. 7th edition, Elsevier Saunders 2005; 1116-1119.
2. Choyke PL, Filling-Katz MR, Shawker TH, Gorin MB, Travis WD, Chang R, Seizinger BR, Dwyer AJ and Linehan WM. von Hippel-Lindau disease: radiologic screening for visceral manifestations. Radiology 1990; 174 (3 Pt 1): 815-820.
3. Neuman HP. Basic criteria for clinical diagnosis and genetic counselling in von Hippel-Lindau syndrome. Vasa 1988; 16: 220-226.
4. Neumann HP and Zbar B. Renal cysts, renal cancer and von Hippel-Lindau disease. Kidney Int 1997; 51 (1): 16-26.
5. Neumann HP, Bender BU, Berger DP, Laubenberger J, Schultze-Seemann W, Wetterauer U, Ferstl FJ, Herbst EW, Schwarzkopf G, Hes FJ, Lips CJ, Lamiell JM, Masek O, Riegler P, Mueller B, Glavac D and Brauch H. Prevalence, morphology and biology of renal cell carcinoma in von Hippel-Lindau disease compared to sporadic renal cell carcinoma. J Urol 1998; 160 (4): 1248-1254.
6. Maher ER, Yates JR, Harries R, Benjamin C, Harris R, Moore AT and Ferguson-Smith MA. Clinical features and natural history of von Hippel-Lindau disease. Q J Med 1990; 283: 1151-1163.
7. Poston CD, Jaffe GS, Lubensky IA, Solomon D, Zbar B, Linehan WM and Walther MM. Characterization of the renal pathology of a familial form of renal cell carcinoma associated with von

Hippel-Lindau disease: clinical and molecular genetic implications. J Urol 1995; 153: 22-26.
8. Bodmer D, Eleveld MJ, Ligtenberg MJ, Weterman MA, Janssen BA, Smeets DF, de Wit PE, van den Berg A, van den Berg E, Koolen MI and Geurts van Kessel A. An alternative route for multistep tumorigenesis in a novel case of hereditary renal cell cancer and t(2:3) (q35;q21) chromosome translocation. Am J Hum Genet 1998; 62 (6): 1475-1483.
9. Borówka A and Zajączek S. Rodzinne występowanie raka jasnokomórkowego nerki. Doniesienie zjazdowe: 26 Kongres PTU, Poznań 1996.
10. Braun WE, Strimlan CV, Negron AG, Straffon RA, Zachary AA, Bartee SL and Grecek DR. The association of W17 with familial renal cell carcinoma. Tissue Antigens 1975; 6: 101-104.
11. Cohen AJ, Li FP, Berg S, Marchetto DJ, Tsai S, Jacobs SC and Brown RS. Hereditary renal-cell carcinoma associated with a chromosomal translocation. N Engl J Med 1979; 301: 592-595.
12. Gemmill RM, West JD, Boldog F, Tanaka N, Robinson LJ, Smith DI, Li F and Drabkin HA. The hereditary renal cell carcinoma 3;8 translocation fuses FHIT to a patched-related gene, TRC8. Proc Natl Acad Sci USA 1998; 95: 9572-9577.
13. Koolen MI, van der Meyden AP, Bodmer D, Eleveld M, van der Looij E, Brunner H, Smits A, van den Berg E, Smeets D, Geurts van Kessel A. A familial case of renal cell carcinoma and a t(2;3) chromosome translocation. Kidney Int 1998; 53: 273-275.
14. Kovacs G, Brusa P and De Riese W. Tissue-specific expression of a constitutional 3;6 translocation: development of multiple bilateral renal-cell carcinomas. Int J Cancer 1989; 43: 422-427.
15. Li FP, Marchetto DJ and Brown RS. Familial renal carcinoma. Cancer Genet Cytogenet 1982; 7: 271-275.
16. Li FP, Decker HJ, Zbar B, Stanton VP Jr, Kovacs G, Seizinger BR, Aburatani H, Sandberg AA, Berg S, Hosoe S and Brown RS. Clinical and genetic studies of renal cell carcinomas in a family with a constitutional chromosome 3;8 translocation. Genetics of familial renal carcinoma. Ann Intern Med 1993; 118 (2): 106-111.
17. Maher ER and Yates JR. Familial renal cell carcinoma: clinical and molecular genetic aspects. Br J Cancer 1991; 63: 176-179.
18. Yao M and Shuin T. Familial renal cell carcinoma: review of recent molecular genetics.Int J Urol 1995; 2 (2): 61-70.
19. Zbar B and Lerman M. Inherited carcinomas of the kidney. Adv Cancer Res 1998; 75: 163-201.
20. Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, Scherer SW, Zhuang Z, Lubensky I, Dean M, Allikmets R, Chidambaram A, Bergerheim UR, Feltis JT, Casadevall C, Zamarron A, Bernues M, Richard S, Lips CJ, Walther MM, Tsui LC, Geil L, Orcutt ML, Stackhouse T, Lipan J, Slife L, Brauch H, Decker J, Niehans G, Hughson MD, Moch H, Storkel S, Lerman MI, Linehan WM and Zbar B. Germline and somatic mutations in the tyrosine kinase domain of MET proto-oncogene in papillary renal carcinomas. Nat Gen 1997; 16: 68-73.
21. Schmidt L, Junker K, Weirich G, Glenn G, Choyke P, Lubensky I, Zhuang Z, Jeffers M, Vande Woude G, Neumann H, Walther M, Linehan WM and Zbar B. Two north American families with hereditary papillary renal carcinoma and identical novel mutations in the MET proto-oncogene. Cancer Res 1998; 58: 1719-1722.
22. Zbar B and Lerman M. Inherited carcinomas of the kidney. Adv Cancer Res 1998; 75: 163-201.
23. Zbar B, Glenn G, Lubensky I, Choyke P, Walther MM, Magnusson G, Bergerheim US, Pettersson S, Amin M and Hurley K. Hereditary papillary renal cell carcinoma: clinical studies in 10 families. J Urol 1995; 153 (3 Pt 2): 907-912.
24. Zbar B, Tory K, Merino M, Schmidt L, Glenn G, Choyke P, Walther MM, Lerman M, Linehan WM. Hereditary papillary renal cell carcinoma. J Urol 1994; 151: 561-566.
25. Bronner CE, Baker SM, Morrison PT, Warren G, Smith LG, Lescoe MK, Kane M, Earabino C, Lipford J, Lindblom A, et al. Mutation in the DNA mismatch repair gene homologue hMLH1 is associated with hereditary non-polyposis colon cancer. Nature 1994; 368: 258-261.
26. Hofstra RMW, Wu Y, Berends MJW, Mensink RJG, Sijmons RH, van der Zee AGJ, et al. Frequent involvement of MSH6 germline mutations in HNPCC-suspected families with low microsatellite instability tumours. Am J Hum Genet 1998; 63 (4): A21.
27. Lubiński J, Górski B, Kurzawski G, Jakubowska A, Cybulski C, Suchy J, Dębniak T, Grabowska E, Lener M, Nej K. Molecular basis of inherited predispositions for tumors. Acta Biochim Pol 2002; 49 (3): 571-581.
28. Lynch HT and de la Chapelle A. Genetic susceptibility to non-polyposis colorectal cancer. J Med Gen 1999; 36: 801-818.
29. Park JG, Vasen HF, Park YJ, Park KJ, Peltomaki P, de Leon MP, Rodriguez-Bigas MA, Lubinski J, Beck NE, Bisgaard ML, Miyaki M, Wijnen JT, Baba S, Lindblom A, Madlensky L and Lynch HT. Suspected HNPCC and Amsterdam criteria II: evaluation of mutation detection rate, an international collaborative study. Int J Colorectal Dis 2002; 17 (2): 109-114.
30. Peltomaki P and Vasen HF. Mutations predisposing to hereditary nonpolyposis colorectal cancer: database and results of a collaborative study. The International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer. Gastroenterology 1997; 113 (4): 1146-1158.
31. van Baal JG, Fleury P and Brummelkamp WH. Tuberous sclerosis and the relation with renal angiomyolipoma. A genetic study on the clinical aspects. Clin Genet 1989; 35: 167-173.
32. van Baal JG, Smits NJ, Keeman JN, Lindhout D and Verhoef S. The evolution of renal angiomyolipomas in patients with tuberous sclerosis. J Urol 1994; 152: 35-38.
33. Bjornsson J, Short MP, Kwiatkowski DJ and Henske EP. Tuberous sclerosis-associated renal cell carcinoma. Clinical, pathological, and genetic features. Am J Pathol 1996; 149 (4): 1201-1208.
34. Sampson JR, Patel A and Mee AD. Multifocal renal cell carcinoma in sibs from a chromosome 9 linked (TSC1) tuberous sclerosis family. J Med Genet 1995; 32: 848-850.
35. Weinblatt ME, Kahn E and Kochen J. Renal cell carcinoma in patients with tuberous sclerosis. Pediatrics 1987; 80 (6): 898-903.
36. Hoffman T, Chasko S and Safai B. Association of blue rubber bleb nevus syndrome with chronic lymphocytic leukemia and hypernephroma. Johns Hopkins Med J 1978; 142 (3): 91-94.
37. Haibach H, Burns TW, Carlson HE, Burman KD and Deftos LJ. Multiple hamartoma syndrome (Cowden's disease) associated with renal cell carcinoma and primary neuroendocrine carcinoma of the skin (Merkel cell carcinoma). Am J Clin Pathol 1992; 97 (5): 705-712.
38. Gorlin RJ. Nevoid basal-cell carcinoma syndrome. Medicine 1987; 66 (2): 98-113.
39. Deeg HJ, Socie G, Schoch G, Henry-Amar M, Witherspoon RP, Devergie A, Sullivan KM, Gluckman E and Storb R. Malignancies after marrow transplantation for aplastic anemia and Fanconi anemia: a joint Seattle and Paris analysis of result in 700 patients. Blood 1996; 87 (1): 386-392.
40. Swift M, Caldwell RJ and Chase C. Reassessment of cancer predisposition of Fanconi anemia heterozygotes. J Natl Cancer Inst 1980; 65 (5): 863-867.

41. Alter BP. Fanconi's anemia and malignancies. Am J Hematol 1996; 53: 99-110.
42. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, Debelenko LV, Zhuang Z, Lubensky IA, Liotta LA, Crabtree JS, Wang Y, Roe BA, Weisemann J, Boguski MS, Agarwal SK, Kester MB, Kim YS, Heppner C, Dong Q, Spiegel AM, Burns AL and Marx SJ. Positional cloning of the gene for multiple endocrine neoplasia-type 1. Science 1997; 276 (5311): 404-407.
43. Duquenne M, Weryha G, Leclere J, Duriez T and Schneegans O. Oncocytome renal au cours d'une neoplasie endocrinienne multiple de type I (letter). Presse Med 1992; 21 (27): 1293-1294.
44. Jeddi A, Vasse N, Prunet D, Buzelin F, Bouchot O and Buzelin JM. Wermer syndrome associated with a bilateral renal tumor. Prog Urol 1996; 6 (1): 103-106.
45. Reed WB, Walker R and Horowitz R. Cutaneous leiomyomata with uterine leiomyomata. Acta Derm Venerol 1973; 53: 409-416.
46. Epstein CJ, Martin GM, Schultz AL and Motulsky AG. Werner's syndrome: a review of its symptomatology, natural history, pathologic features, genetics and relationship to the natural aging process. Medicine 1966; 45 (3): 177-221.
47. Goto M, Miller RW, Ishikawa Y and Sugano H. Excess of rare cancers in Werner syndrome (adult progeria). Cancer Epidemiol Biomarkers Prev 1996; 5 (4): 239-246.
48. Ishii T and Hosoda Y. Werner's syndrome: autopsy report of one case, with a review of pathologic findings reported in the literature. J Am Geriatr Soc 1975; 23 (4): 145-154.
49. Ishikawa Y, Sugano H, Matsumoto T, Furuichi Y, Miller RW and Goto M. Unusual features of thyroid carcinomas in Japanese patients with Werner syndrome and possible genotype-phenotype relations to cell type and race. Cancer 1999; 85 (6): 1345-1352.
50. Birt AR, Hogg GR and Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatol 1977; 113: 1674-1677.
51. Cohen PR and Kurzrock R. Miscellaneous genodermatoses: Beckwith-Wiedemann syndrome, Birth-Hogg-Dube syndrome, familial atypical multiple mole melanoma syndrome, hereditary tylosis, incontinentia pigmenti, and supernumerary nipples. Dermatol Clin 1995; 13 (1): 211-229.
52. Tomlinson I, Rahman N, Frayling I, Mangion J, Barfoot R, Hamoudi R, Seal S, Northover J, Thomas HJ, Neale K, Hodgson S, Talbot I, Houlston R and Stratton MR. Inherited susceptibility to colorectal adenomas and carcinomas: evidence for a new predisposition gene on 15q14-q22. Gastroenterology 1999; 116: 789-795.
53. Henske EP, Thorner P, Patterson K, Zhuang Z and Bernstein J. Renal cell carcinoma in children with diffuse cystic hyperplasia of the kidneys. Pediatr Dev Pathol 1999; 2 (3): 270-274.