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Genetic Susceptibility to Kidney Cancer

Minna Kankuri-Tammilehto

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Abstract

According to the latest knowledge, hereditary kidney cancers may account for 5–8% of all kidney cancers, and it may be more common than previously thought. Hereditary RCC is often characterized by an early age of onset (approximately 45 years), typical histological pattern, and frequently the bilaterality and multicentricity of the primary tumor. Wilms’ tumor (nephroblastoma) is the most common kidney tumor of childhood. More than 15 syndromes with inherited susceptibility to kidney cancer are known, and there are over 25 known genes associated with them. Most of these are dominantly inherited in which the offspring of the proband has a 50% chance of inheriting a gene mutation with susceptibility to kidney cancer. The aggressiveness of hereditary RCCs and recommended surgery varies depending on the syndrome and mutation type. Also, systemic therapy may be optional. Multigene next generation sequencing (NGS) panel technology allows genes of interest to be studied quickly and cost-effectively. Sequencing investigations have improved the accuracy of hereditary cancer diagnoses. Diagnostic utility has been hugely increased by multigene NGS panels. It is important to identify hereditary cancer susceptibility, because the risk of cancer in the mutation carriers can be reduced. In this review article, the latest literature on syndromes subjecting to hereditary kidney cancer and recommended follow-up is summarized.

Keywords: von Hippel-Lindau, hereditary papillary RCC, hereditary leiomyomatosis and RCC, Birt-Hogg-Dubé, Wilms’ tumor, hereditary kidney cancer syndromes, genetic susceptibility

1. Introduction

Kidney cancer is the 16th most common cancer worldwide with over 400,000 cases in 2018 representing approximately 2.2% of all diagnosed malignancies worldwide [1]. The majority of primary renal malignancies are renal cell carcinomas (RCCs) with most of the remaining comprising upper tract urothelial carcinoma (UTUC). The mean age of onset of RCC is
approximately 60–70 years. The most common kidney tumor of childhood is Wilms’ tumor (nephroblastoma). In the European Union, the estimated annual number of new kidney cancers is approximately 46,000 [2]. Etiologic risk factors for kidney cancer development are male sex, obesity, and tobacco, in addition to hypertension [3–5], acquired cystic kidney disease [6], and inherited susceptibility. Prognostic factors of different protein and gene expressions in RCC have been studied [7, 8].

According to the latest knowledge, hereditary kidney cancers may account for 5–8% of all kidney cancers [9], and it may be more common than previously thought [10]. In those RCC patients without clear cell RCC (ccRCC) subtype, the amount of germline high-risk mutations is greater, 12% [11]. Susceptibility to kidney cancer may be caused by high-risk, moderate-risk, or low-risk gene mutation [12]. Even the carriership of high-risk gene mutation does not always lead to kidney cancer. The risk for kidney cancer (penetrance) varies in different syndromes. In some cases, the predisposed genetic factor to kidney cancer is chromosomal aberration, for example, as in constitutional chromosomal 3 translocation with 6 or 8 of family (Table 2). In hereditary cancer, the impact of environmental factors is small.

More than 15 syndromes with inherited susceptibility to kidney cancer are known, and there are over 25 known genes associated with them. Most of these are dominantly inherited in which the offspring of the proband has a 50% chance of inheriting a gene mutation with susceptibility to kidney cancer.

2. Identifying hereditary kidney cancer

Hereditary kidney cancer syndrome is often characterized by an early age of onset (approximately 45 years) [30], typical histological pattern, and frequently the bilaterality and multicentricity of the primary tumor (Table 1). By evaluating the family history of diagnosed cancer cases, benign tumors, and diagnostic gene test results, it is possible to identify families with hereditary kidney cancer (Tables 2 and 3).

It is possible that there exists only a single hereditary cancer syndrome case in the family due to de novo mutations (autosomal dominant) which means that the person’s parents do not have the same mutation. There are hot spot regions in genes where mutation can easier develop during meiosis of germ cells. In addition to this, the risk of hereditary kidney cancer

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Table 1. Factors suggesting inherited cancer syndrome.

| Multiple close relatives with benign or malign tumors of the syndrome |
| Atypically young age of onset for tumors of the syndrome |
| Relative with two tumors of the syndrome (two examples below) |
| • RCC and uterine leiomyosarcoma |
| • Colon cancer or endometrial carcinoma in the uterus and upper tract urothelial carcinoma |
| Typical histological finding (e.g., rare subtype or multiplicity) or clinical picture |
is linked to some congenital multisystem syndromes, such as Beckwith-Wiedemann syndrome and tuberous sclerosis (Table 4). When such a multisystemic syndrome is detected, appropriate follow-up care is provided as with hereditary kidney cancer families.

It is suspected that hereditary kidney cancer is underdiagnosed. Identifying the families with increased risk for kidney cancer allows clinicians to improve the prognosis of persons with genetic cancer susceptibility. This review discussed the characteristics of inherited kidney cancer and how to improve their prognosis (Table 5).

### 3. Basic cancer genetics

In hereditary and sporadic cancer, the normal genome regulation is impaired [34], and cancer susceptibility is caused by both inherited germline gene mutations and somatic gene mutations in tissue that occurred over time. However, in sporadic cases the inherited gene mutations cause low risk for kidney cancer [35]. Of all clear cell-type RCCs (sporadic or hereditary), 75% have a somatic mutation in the von Hippel-Lindau tumor suppressor gene (VHL) in the short

<table>
<thead>
<tr>
<th>RCC subtype</th>
<th>von Hippel-Lindau (VHL)</th>
<th>Hereditary papillary RCC (HPRC)</th>
<th>Hereditary leiomyomatosis and RCC (HLRCC)</th>
<th>Birt-Hogg-Dubé (BHD)</th>
<th>Constitutional chromosomal 3 translocation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk for RCC</td>
<td>Clear cell carcinoma</td>
<td>Papillary type 1</td>
<td>Papillary type 2, collecting duct</td>
<td>Most often chromophobe ± oncocytoma</td>
<td></td>
</tr>
<tr>
<td>Gene</td>
<td>VHL</td>
<td>MET</td>
<td>FH</td>
<td>FLCN(BHD)</td>
<td></td>
</tr>
<tr>
<td>Typical age of onset for RCC</td>
<td>40 years</td>
<td>50–70 years</td>
<td>Less than 40 years</td>
<td>50 years</td>
<td></td>
</tr>
<tr>
<td>Biology of RCC</td>
<td>Bilaterality, multiple tumors</td>
<td>Bilaterality, multiple tumors, microscopic lesions as much as 1000</td>
<td>Unilaterality, solitarity, aggressive, highly potential to metastasize</td>
<td>Bilaterality, multiple tumors</td>
<td></td>
</tr>
<tr>
<td>Typical surgery</td>
<td>Minimal invasive</td>
<td>Minimal invasive or radical nephrectomy</td>
<td>Radical nephrectomy</td>
<td>Minimal invasive</td>
<td></td>
</tr>
<tr>
<td>Other signs of the syndrome than RCC</td>
<td>Retinal hemangioma/CNS hemangioblastoma, pheochromocytoma</td>
<td>None</td>
<td>Uterine leiomyomas in almost every patient, uterine leiomyosarcoma, cutaneous leiomyomas</td>
<td>Cutaneous hair follicle benign tumors and pulmonary cysts in almost every patient</td>
<td>Thyroid, bladder, pancreatic and gastric cancer</td>
</tr>
</tbody>
</table>

| Reference | [13, 14] | [15, 16] | [17–20] | [21, 22] | [23] |

Table 2. Hereditary cancer syndromes in which the kidney cancer risk is high.
<table>
<thead>
<tr>
<th>Hereditary Cancer Syndromes</th>
<th>Tuberous Sclerosis</th>
<th>Beckwith-Wiedemann Syndrome</th>
<th>Perlman Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney cancer subtype</strong></td>
<td>Clear cell, papillary, chromophobe</td>
<td>Wilms' tumor</td>
<td>Wilms' tumor</td>
</tr>
<tr>
<td><strong>Risk for kidney cancer</strong></td>
<td>Less than 5%</td>
<td>Around 5%</td>
<td>30–60%</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td>MLH1, MSH2, TSC1, TSC2</td>
<td>CDKN1C</td>
<td>PTEN</td>
</tr>
<tr>
<td><strong>Typical age of onset for kidney cancer</strong></td>
<td>Primarily in the first 8 years of life</td>
<td>35 years</td>
<td>Neonatally</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Autosomal dominant</td>
<td>Autosomal dominant, sporadic</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td><strong>Other signs of the syndrome than kidney cancer</strong></td>
<td>Mucocutaneous papules, hamartomas, peau rassee, thyroid cancer, uterine cancer, intestinal polyps</td>
<td>Ossifying jaw fibromas, renal cysts, parathyroid adenoma/carcinoma, uterine tumors</td>
<td>Brain tumor, sarcoma, leukemia and other cancer types</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>[24]</td>
<td>[25]</td>
<td>[26]</td>
</tr>
</tbody>
</table>

Table 3. Hereditary cancer syndromes in which the kidney cancer risk is moderate or low.

<table>
<thead>
<tr>
<th>Hereditary Cancer Syndromes</th>
<th>Tuberous Sclerosis</th>
<th>Beckwith-Wiedemann Syndrome</th>
<th>Perlman Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney cancer subtype</strong></td>
<td>Upper tract urothelial carcinoma</td>
<td>Wilms' tumor and paraganglioma</td>
<td>Wilms' tumor</td>
</tr>
<tr>
<td><strong>Risk for kidney cancer</strong></td>
<td>Clear cell RCC, chromophobe RCC, oncocytoma</td>
<td>Around 5%</td>
<td>30–60%</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td>CDKN1C</td>
<td>CDKN1C</td>
<td>PTEN</td>
</tr>
<tr>
<td><strong>Typical age of onset for kidney cancer</strong></td>
<td>Primarily in the first 8 years of life</td>
<td>35 years</td>
<td>Neonatally</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>Autosomal dominant</td>
<td>Autosomal dominant, sporadic</td>
<td>Autosomal recessive</td>
</tr>
<tr>
<td><strong>Other signs of the syndrome than kidney cancer</strong></td>
<td>Renal angiomylipomas, hypopigmentation, seizures, learning difficulties, angiofibromas, shagreen patches, oral mucosal lesions, subependymal giant cell astrocytoma</td>
<td>Neonatal hypoglycemia, macrosomia, macroGLOSSIA, hemihyperplasia, omphalocele, renal abnormalities</td>
<td>Fetal ascites, macrosomia, visceromegaly, generalized hypertonia</td>
</tr>
<tr>
<td><strong>References</strong></td>
<td>[31, 32]</td>
<td>[33]</td>
<td>[34]</td>
</tr>
</tbody>
</table>

Table 4. Congenital multisystem syndromes with susceptibility for the kidney cancer.
arm of chromosome [36]. According to Vogelstein’s research group, chance has a major impact in the development of cancer-causing mutations during DNA replication in normal, noncancerous stem cells [37]. Current understanding is that about four to seven mutations in key driver genes is sufficient to cause cancer to develop [38].

Genes associated with cancer predisposition are oncogenes or tumor suppressor genes. Oncogenes act as gain of function. Mutation in the other allele is sufficient to produce the altered protein. An example of this is the MET oncogene, in which mutation predisposes to hereditary papillary renal cell carcinoma (HPRC) (Table 2). However, typically inherited cancer predisposition is caused by the loss of function of tumor suppressor gene. In nearly all cases, the mutations in tumor suppressor genes function recessively at the cellular level, following Knudson’s theory of two hits [39]. Therefore, both alleles must lose function before the carcinogenesis may occur. The first mutation associated with the syndrome, the germline mutation, passes the susceptibility to cancer to the next generation (nearly always) according to the autosomal dominant inheritance and is situated in all the persons’ cells. The mutation in the other allele in the same gene occurs during life. The penetrance of the inherited mutation is decreased. Therefore, only part of the mutation carriers will be affected, but the risk of cancer is many times higher than in an average population (Tables 2 and 3).

Caretaker genes are responsible for genomic stability by detecting damage to the genome, such as single- or double-stranded DNA breaks [40]. Disruption in these genes leads to genomic instability: an increase in the number of spontaneous mutations that cause new mutations in oncogenes and growth restriction genes. Mutations in the caretaker genes are responsible for a number of cancer susceptibility syndromes. For example, germline mutation in the growth restriction gene MLH1 exposes for Lynch syndrome, which is associated with a high risk of colon and endometrial carcinoma in the uterus and multiple risk for urothelial carcinoma compared to an average population [24, 41]. Gatekeeper genes control cell growth. Normally, a mutation in a gatekeeper gene activates the caretaker genes to participate in repair [34]. However, if this repair does not work, mutation in the gatekeeper gene will result in tumor formation. For example, p53 acts as a gatekeeper, and its mutation exposes it to several types of cancers, such as RCC (Table 3).

Table 5. How to improve prognosis in the carriers of hereditary gene mutation.

- In the carriers of Lynch syndrome mutation, removal of colon adenomas decreases the risk of colon cancer
- In the carriers of Lynch syndrome mutation, removal of uterus by menopause decreases the risk of endometrial carcinoma in uterus
- In the carriers of p53 mutation, radiation therapy and X-ray imaging will be avoided

Occurrence can be prevented by removing the precursors identified in the monitoring
Occurrence can be prevented by surgical procedures

The aim is to improve the early detection of cancer
Occurrence can be prevented by removing the precursors identified in the monitoring
Genetics of cancer is only partially known. Advanced technological methods can detect previously unknown mutations in germline and tumors. Knowledge of the biology of hereditary cancer also increases the understanding of sporadic cancers, as the same disease genes are found in hereditary and non-hereditary cancers: e.g., mutated \textit{MET} is a driver gene in hereditary and sporadic papillary renal carcinomas [42], and mutated \textit{WT1} is observed both in sporadic and hereditary Wilms’ tumor. Novel genes and variants may be explored by whole exome (WES) or genome research (WGS), where also noncoding regions are examined, in scientific research projects. Identifying low-risk variants requires data from thousands of patients and controls, which are investigated in genome-wide association studies (GWAS).

4. Genetic counseling and supporting families with hereditary cancer

It is important to identify hereditary cancer susceptibility, because the risk of cancer, morbidity, and mortality in the mutation carriers can be reduced both in cancer patients and healthy relatives in the family. If the family mutation is known, healthy family members with mutation can participate in preventive studies. If the person does not have the known family mutation, there is no need to have follow-up care because the risk of the cancer is the same as for an average population.

Diagnostic gene testing on cancer patients is carried out in the clinical genetic units, but diagnostic genetic testing can also be ordered by a treating oncologist or surgeon for patients with kidney cancer. There are established principles for considering genetic testing in the case of suspected hereditary cancer susceptibility (Table 6) [43]. If there is a genetic test that is appropriate for the situation, the American Society of Clinical Oncology (ASCO) recommends access to genetic testing. Before testing the individuals, informed consent should be requested after adequate information and counseling [44]. For genetic testing the patient’s peripheral blood, lymphocyte DNA is examined for identifying a possible hereditary mutation.

The investigation for finding the family mutation is always started with the affected person. A medical geneticist will determine who could have mutation with increased kidney cancer risk.

Hereditary cancer is suspected
The result of the gene test should be adequately interpreted

Gene testing has one of the following benefits:

- Improves diagnosis
- Guides to the appropriate medical surveillance for the carriers of gene mutation
- Provides information about strategies for prevention in the carriers of gene mutation

The ASCO has provided guidance on when genetic testing for cancer families should be considered [43]. The following three conditions should be met. If the family mutation is found, the access for healthy relatives to genetic counseling should be arranged.

| Table 6. ASCO 2010 criteria for genetic testing. |
in the family. If there are no surviving cancer patients in the family, with the permission of the relative, from the pathology department, a sample of the deceased person may be requested to have healthy tissue DNA for genetic examination.

The result of the genetic testing gives information about the cancer risk of relatives. Healthy at-risk relatives should have access to genetic counseling and predictive genetic testing after counseling if they decide (Council of Europe’s The Convention on Human Rights and Biomedicine in Article 12, 1997). The clinical genetics units offer this service. The geneticist will have the opportunity to provide the laboratory with reliable information about the family mutation and arrange for the laboratory the DNA sample of the family’s index patient, which is a control sample, positive control, to obtain a reliable test result. Counseling before predictive genetic testing is nondirective and includes insight of the patient and the family. In counseling, the patient and family receive not only information but also support. Increased anxiety or distress has been documented in both counselors and their families around testing when investigating hereditary VHL susceptibility [45]. The Genetic Information Nondiscrimination Act of the Council of Europe’s Convention in Article 11, in 1997, was passed to prevent forms of genetic discrimination by employment and health insurance. The Council of Europe’s Convention prohibits the transfer of genetic information to employers in order to prevent employment discrimination. Insurance discrimination is discussed in counseling. In Finland, genetic testing is organized by public health care, which is why very few gene tests are conducted privately.

Participation in predictive genetic testing has been studied in the Finnish Lynch syndrome families, which are at high risk for colorectal cancer and endometrial carcinoma in the uterus. Approximately 80% of the members of the family participated in genetic counseling, and 95% of them performed genetic prediction [46]. The main reasons for participating in predictive genetic testing are the potential for cancer detection in surveillance monitoring, improved treatment options in many Lynch syndrome cancer types, and improved cancer prognosis.

After the genetic testing, the counselor should always receive an interpretation of the significance of the genetic test result [43, 44]. Different mutations in the same disease gene, for example, in the inherited VHL gene, can have varying effects on cancer risk and prognosis [47]. The genetic practitioner will assess the significance of the result for each family separately. It is useful to wait until the age of 18 to allow an offspring to reach an age of consent in those inherited syndromes in which the age of onset is in adulthood. However, the early age of onset in condition like VHL could have devastating complications without early detection and management, and therefore in this syndrome predictive testing is recommended to at-risk children in family.

5. Genotype-phenotype correlation in kidney cancer

*VHL* is divided to subgroups for academic purposes according to the phenotype based on the likelihood of pheochromocytoma or renal cell carcinoma. In the following some examples are described. For example, a reduced risk for renal cell carcinoma in individuals has been observed with a deletion of *VHL* [13]. A *MET* variant due to a mutation is associated with early-onset HPRC disease [16]. The *WT1* gene mutation may cause hereditary Wilms’ tumor
without syndrome or with syndrome, like Denys-Drash, Frasier, or nephrotic syndrome type 4. WT1 protein plays an important role in renal and gonadal development, due to which genital abnormalities can be seen in Denys-Drash and Frasier syndrome. In Frasier syndrome patients have progressive nephrotic syndrome, but incidence of Wilms’ tumor is rare. Mutations that are responsible for Frasier syndrome are located in intron 9 in \( WT1 \) (an alternative splicing site). In Denys-Drash syndrome, patients’ typical symptoms are progressive nephrotic syndrome that early progresses to renal failure less than the age of 4 years. A majority of the Denys-Drash patients have mutations located in exons 8 and 9. The risk of Wilms’ tumor is very high (90%).

6. The diagnostic impact of gene testing evolution

Multigene next generation sequencing (NGS) panel technology allows genes of interest to be studied quickly and cost-effectively. By focused massive parallel sequencing, it is possible to examine those exons of the genome’s genes that are of interest in diagnosing the cause of inherited kidney cancer. The method can also investigate boundaries between exons and introns. A gene panel for hereditary kidney cancer covers approximately 25 genes and can be ordered from different companies. Clinical picture may sometimes indicate a mutation in particular gene or genes, which can be separately examined. However, often hereditary mutation may be in many different genes according to patient and family history, and then multigene panel-based NGS will be more economical than Sanger or NGS sequencing of several different genes. Sequencing results are obtained in about 4 weeks. The gene content of the panels is regularly updated by laboratories as information on genes associated with kidney cancer is published continuously. A limitation of parallel sequencing is that they cannot recognize large intrinsic deletions or duplicates, and for this another method is required that investigates exome CNVs. A majority of hereditary mutations are located in the exome region. The whole genome NGS is not yet a routine method, but it is used in scientific studies. By the NGS method, the diagnostic utility of hereditary cancers has been hugely improved.

Information on the clinical significance associated with mutations is reviewed in registers (e.g., InSiGHT and ClinVar) [48]. With the development of research techniques, more variants of uncertain significance (VUS) are now observed. Currently, these are also variants of which it is unknown whether they are benign or pathogenic and explain the patient’s predisposition to cancer. In some situations, the variant may be classified as likely pathogenic. Prediction programs can be used to evaluate a variant’s ability to cause disease (in silico analysis) [49, 50]. For example, the ExAC database can be used to check the prevalence of the variant in the population. As techniques evolve, it is increasingly possible to study the functional change in RNA structure caused by VUS alteration, which would be relevant to the quality of the resulting protein. In order to clarify the nature of the uncertain variants, the geneticist may arrange the so-called segregation analysis in family [49]. Finding the same hereditary variant from several relatives with cancer would strengthen the conclusion that the variant explains the cases in the family. Information is being collected internationally as laboratories collect VUS they observe into databases and doctors publish case reports. However, in already well-known genes such as BRCA and Lynch syndrome genes, VUS alterations are relatively rarely detected.
During counseling, the geneticist will inform what is known about the significance of the identified variant. If the significance of the variant remains open, the geneticist and laboratory experts may reclassify the change after few years. The increased use of multigene NGS panels in patient work expands the knowledge on the different pathogenic variants in the human DNA. The number of VUS changes will therefore decrease in the next few years [50]. It is important that counseling provides reliable information on the examination results and therefore VUS modifications are not used as a basis for prophylactic surgery or to determine the risk of relatives’ cancer.

7. Treatment in hereditary kidney cancer

For several RCC syndromes, studies have found that conservative management appears to preserve renal function without increased mortality. In certain syndromes, such as HLRCC, early and aggressive treatment may be preferable [17, 20]. Each subtype of RCC may need to be treated differently by systemic therapy, but no phase III clinical trial data exist from distinct treatments [51, 52]. The prognosis was inferior for papillary metastatic RCC (mRCC) compared to clear cell mRCC when patients were treated with the same evidence-based treatment in a study by Staehler [52]. The understanding of the metabolic and epigenetic abnormalities underlying the symptoms of hereditary kidney cancer-associated genes may lead to the development of novel diagnostic biomarkers and novel treatment modalities for kidney cancer [53].

8. Surveillance in hereditary kidney cancer families

Recommendations for follow-up care should correspond to the level of risk associated with the genetic variant tested [43]. The aim of the monitoring is to improve the early detection of cancer in families with hereditary renal cancer. Monitoring recommendations includes regular kidney imaging; the healthy carrier of a gene mutation predisposing to kidney cancer will usually undergo abdominal MRI scans on a regular basis (Table 7). The frequency of follow-up depends on the biological nature of the family syndrome. Several monitoring planes have been proposed for hereditary kidney cancer syndromes, for example, by Freifeld [54] and Carlo [10]. Also, PDQ Cancer Information Summaries [55] has a suggestion for surveillance in certain syndromes predisposing to hereditary renal cancer.

Tracking intervals may be less frequent, for example, for HPRC, and more frequent for others, such as HLRCC in the case of an early onset of 10 years [56] and several reported cases among children. However, the estimated risk of developing RCC before age 20 is estimated to be only around 1–2%, whereas the lifetime risk of RCC among FH mutation carriers is approximately 15% [25]. In 2014, consensus guidelines from an international HLRCC symposium recommended annual renal MRI starting at age 8 to 10 years, as also recommended by the HLRCC Family Alliance and the French National Cancer Institute [25]. The starting age is still variable. In HPRC patients, if the tumor smaller than 3 cm is found, imaging should be repeated within the first year to assess the growth rate [55]. Generally, patients with renal
tumors associated with HPRC are candidates for radiologic surveillance until one or more
tumors reach 3 cm. Ultrasound is not sufficient in surveillance of hereditary kidney cancer
syndromes [10, 25, 54, 55]. In the near future, more evidence on effective monitoring in
different kidney cancer syndromes will be gathered. If the gene mutation has not been identi-
fied but the family has a significantly increased risk of kidney cancer, a regular renal imaging
examination in the first-degree relative of the patient with renal cancer may be considered on a
case-by-case basis. Other surveillance procedures depend on the risks of the specific symptoms
in observed gene mutation. In multisystem syndromes, monitoring practices depend on the
probability of the kidney cancer, and ultrasound may be used in monitoring.

In Lynch syndrome, which is a high risk for upper tract ureotelic carcinoma, the risk of
colorectal cancer can be reduced by removing intestinal adenomas at regular checkups, which
results in the same mortality to colorectal cancer in the carriers of Lynch gene mutation as in
the general population.

### 9. Future perspectives

The contents of routine gene panels are based on the knowledge on kidney cancer susceptibil-
ity genes. If a patient’s DNA sequencing has failed to identify the hereditary mutation, RNA
sequencing may identify the specific diagnosis [57]. If there are three patients in the family, trio
exome analysis may be a pivotal method. Potentially, tumor tissue-only test would be a useful
method to find out novel kidney cancer susceptibility genes and mutations in kidney cancer

<table>
<thead>
<tr>
<th>RCC subtype</th>
<th>Hereditary papillary RCC (HPRC)</th>
<th>Hereditary leiomyomatosis and RCC (HLRCC)</th>
<th>Birt-Hogg-Dubé (BHD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>von Hippel-Lindau (VHL)</td>
<td>Clear cell carcinoma</td>
<td>Papillary type 1</td>
<td>Most often chromophobe/oncocytoma</td>
</tr>
<tr>
<td>Risk for RCC</td>
<td>40%</td>
<td>Nearly 100%</td>
<td>30%</td>
</tr>
<tr>
<td>Gene</td>
<td>VHL</td>
<td>MET</td>
<td>FLCN/BHD</td>
</tr>
<tr>
<td>Typical age of onset for RCC</td>
<td>40 years</td>
<td>50–70 years</td>
<td>50 years</td>
</tr>
<tr>
<td>Abdominal magnetic imaging</td>
<td>Annually starting at the age of 10</td>
<td>Annually starting at the age of 30</td>
<td></td>
</tr>
<tr>
<td>Other surveillance</td>
<td>Biannual brain and spine MRI starting at the age of 11</td>
<td>None</td>
<td>Dermatological and gynecological exam</td>
</tr>
<tr>
<td></td>
<td>Ophthalmological and audiological exam</td>
<td>Annualy starting at the age of 5–20 years</td>
<td>Dermatological exam and CT of the chest</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>Dermatological exam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plasma-free metanephrines/ urinary metanephrines</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Follow-up care recommendations in hereditary cancer syndromes in which the kidney cancer risk is high [10, 25, 54].
patients, as the knowledge on hereditary kidney cancer genes is still limited. This investigation is not available currently.

Tumor tissue-only gene tests by next generation sequencing with targeted genes may be soon routinely used for cancer patients’ pharmacogenetic genotyping and analyzing their tumor tissue’s somatic mutations to tailor their medical treatment [58]. The same method could be also a first step analysis for identifying the hereditary cancer mutation in a gene that is known in literature as a susceptibility gene. An additional test of patient’s peripheral lymphocyte should then be used to confirm the susceptible mutation as hereditary mutation.

The growing knowledge on the biology of hereditary kidney cancer produces information about driver genes in kidney cancer tumorigenesis and may develop diagnostics and therapeutic methods for kidney cancer in general [59]. Knowledge on evidence-based medicine in metastatic hereditary kidney cancer [60] is under active study. Analysis of induced pluripotent stem cells (iPSC) from HPRC pointed that drug screening and precision medicine are possible for hereditary kidney cancer [61]. Preventive medicine may be achieved for healthy persons with familial mutation predisposing to kidney cancer [61]. Prospective studies about the method of follow-up in healthy persons with family kidney cancer susceptibility mutation are warranted. The optimal onset to start follow-up in FH-related hereditary kidney cancer families should be clarified as currently there is no consensus. It is known that the prognosis in early-stage kidney cancer disease is better than in later stages [62]. Studies about long-term effect of surveillance in healthy carriers in hereditary kidney cancer families are needed. Additionally, further research is needed to understand the actual impact of genetic testing on young family members [63].

10. Conclusion

Knowledge on the clinical significance of mutations helps to improve prognosis in families with hereditary cancer. Understanding of hereditary kidney cancer syndromes on their molecular basis improves the utility of specific diagnosis [64]. In the future, increased knowledge of cancer genetics is likely to enable the development of targeted drug therapies. Today, hereditary mutations are detected by DNA testing of white blood cell lymphocytes. Tumor tissue-only tests to identify the hereditary kidney cancer are not yet available.

Author details

Minna Kankuri-Tammilehto\textsuperscript{1,2*}

*Address all correspondence to: mikanku@utu.fi

1 Department of Clinical Genetics, Turku University Hospital, Finland
2 Institute of Biomedicine, University of Turku, Finland
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