The impact of genetic predisposition in pediatric renal cancer: genotypic and phenotypic characterization

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1. To determine the frequency of mutations in known and novel pediatric renal cancer predisposing genes.2. To structurally document phenotypic characteristics of children with renal cancer, to optimize genetic counseling and surveillance and...

Ethical review	Approved WMO
Status	Completed
Health condition type	Congenital and hereditary disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON46432

Source
ToetsingOnline

Brief title
WES-KidTs

Condition

- Congenital and hereditary disorders NEC
- Renal and urinary tract neoplasms malignant and unspecified

Synonym
kidney tumors, Renal tumors

Research involving
Human

Sponsors and support

Primary sponsor: Prinses Máxima Centrum voor Kinderoncologie
Source(s) of monetary or material Support: Stichting Kinderen Kankervrij (□KiKa□);KiKa

project number 278

Intervention

Keyword: Childhood cancer, Genetic predisposition, Pediatric renal tumors, Whole exome sequencing

Outcome measures

Primary outcome

Frequency of known and novel genetic causes of pediatric renal cancer.

Secondary outcome

To structurally document phenotypic characteristics of children with renal

cancer, to optimize genetic counseling and surveillance, and contribute to a

better detection of pediatric renal cancer predisposition.

Study description

Background summary

Cancer in children is sometimes caused by genetic predisposition. For pediatric renal tumors, a genetic predisposition is currently recognized or suspected in 10-20% of children. However, the true incidence of renal tumor predisposition in children is still unknown. Recognizing genetic predisposition is important to provide a targeted therapeutic approach, early genetic counseling and screening of family members at risk.

Wilms tumor is the most common renal tumor in childhood. This tumor is rare in adults, and can occur in children sporadically, or as a result of a renal tumor predisposition syndrome. Well known predisposition syndromes include Denys-Drash, WAGR and Beckwith-Wiedemann syndrome. Children with these syndromes can often be recognized by their appearance, a family history of cancer or congenital abnormalities. However, genetic predisposition has also been described in children without any of these features. It is therefore unclear who should be referred for genetic testing.

Also in non-Wilms tumors, germline genetic abberations have been identified that can explain the development of the renal tumor in a some of the children. Examples include the recently described DICER1 syndrome in children with a

cystic nephroma, and SMARCB1 mutations in children with a rhabdoid tumor of the kidney. Yet, information on phenotypic characteristics and the role of genetic predisposition in other renal tumors in childhood is scarce.

Study objective

1. To determine the frequency of mutations in known and novel pediatric renal cancer predisposing genes.

2. To structurally document phenotypic characteristics of children with renal cancer, to optimize genetic counseling and surveillance and contribute to a better detection of pediatric renal cancer predisposition.

Study design

All children with renal tumors in the Netherlands, and some adults with Wilms tumors, are treated in the Princess Máxima Center. They are referred to the clinical geneticist for genetic counseling, and will be registered in the WES-KidTs study.

WES-KidTs consists of standardized phenotyping, genetic characterization and the development of a guideline for genetic counseling and testing. Standardized phenotyping includes documentation of syndromic features, tumor type, psychomotor development and medical and family history. Based on this information, patients will be stratified into three categories:
a. Patients highly suspected for a specific renal cancer predisposition syndrome, which justifies direct testing with a gene-specific test
b. Patients with features/history suspect for genetic susceptibility without a clear candidate gene
c. Patients without suspicion for genetic predisposition

Patients in the first category, with a high suspicion of a predisposition syndrome, will be offered gene-specific testing as part of routine diagnostics. Patients with Wilms tumor will also be offered methylation analysis to test for Beckwith Wiedemann Syndrome.

Patients in whom gene-specific testing did not lead to a genetic diagnosis, and patients from the last two categories, will be asked to participate in whole exome sequencing (WES). WES will be performed in two steps:

Step 1: In this step, exome data will be analysed using a renal cancer predisposition gene filter, to minimize unsollicted findings. Only genes for which mutations are currently known to carry an increased risk of renal cancer are included in this filter.
Step 2: If the filtered WES-analysis has not identified a genetic predisposition, we can perform a trio-analysis in which we compare the

patient's complete WES data to WES data from both parents. Patients and/or parents can indicate on the informed consent form whether our analysis should be limited to the renal cancer gene filter (step 2) or whether a trio-analysis can be performed (step 3).

The results of this study will be used to develop a guideline for genetic counseling and testing in children with renal tumors. This will include recommendations on which patients need referral to a clinical geneticist, who needs genetic testing, which genes should be included with respect to specific phenotypes and/or tumor types, and how genetic testing should be performed. Moreover, we will evaluate the impact of extensive genetic testing on patients and parents. This information will be relevant for the implementation of next generation sequencing techniques in daily (pediatric oncology) care.

Study burden and risks

The only physical burden for patients is minimal since venipuncture is only needed in cases where blood was not previously stored for research. For children, this will be combined with punctures as part of the cancer treatment / follow up. There is a small risk of finding genetic predisposition for diseases other than cancer, a so called *unsolicited finding*. This risk is limited as much as possible by the renal cancer predisposition filter, and patients will be counseled about the risk of unsolicited findings by a clinical geneticist. The committee for unsolicited findings in the UMCU Genetics department will assess unsolicited findings for relevance to the patient/family.

Group relatedness: Pediatric renal tumors are genetically and biologically different from renal tumors in the adult population. Wilms tumor, the most common renal tumor in childhood, occurs at a median age of onset of 3.5 years, and even earlier in patients with a genetic predisposition. In this study, we are specifically interested in pediatric renal tumors.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- All patients diagnosed with and/or treated for a renal tumor in the Princess Máxima Center.
- Additional patients with rare renal tumors may be included from the International Society of Pediatric Oncology (SIOP) 2001 database.

Exclusion criteria

- Previously diagnosed cancer predisposition syndrome associated with the renal tumor
NB: These patients will not be included in whole exome sequencing, but will be registered in the WES-KidTs database.

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-06-2018
Enrollment:	120
Type:	Actual

Ethics review

Approved WMO Date:	13-03-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	08-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL62906.041.18

Study results

Date completed: 04-03-2021

Results posted: 10-08-2022

First publication
01-03-2022