Identification of germline mutations in familial and extremely early-onset urinary bladder cancer

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON41769

Source
ToetsingOnline

Brief title
Genetics of early-onset and familial bladder cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
bladder cancer, bladder papilloma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: Bladder cancer, Familial, Mutations, Whole exome sequencing

Outcome measures

Primary outcome

The main study parameters are the presence of rare, novel, high-penetrance mutations predisposing for familial or early-onset bladder cancer, and second-hit (somatic) mutations (found in tumor DNA).

Secondary outcome

The secondary study parameter is information on disease characteristics (tumor stage, tumor grade).

Study description

Background summary

Urinary bladder cancer (UBC) is a common disease, which has a significant impact on patients due to the high risk of multiple recurrences leading to frequent transurethral procedures in non-muscle invasive disease and major surgery in muscle invasive disease. A positive family history of UBC doubles the risk for UBC and suggests a role for germline, genetic variants in the etiology of UBC. Common genetic UBC variants were successfully tackled in genome-wide association studies in large populations of sporadic UBC cases and controls. However, we currently know little about rare genetic variants involved in bladder cancer predisposition. Identification of these variants leads to increased insight into the mechanisms of UBC biology, offering novel potential targets for therapeutic interventions and new diagnostic and prognostic markers. We will make use of a selection of UBC samples that are enriched for these rare, novel, high-penetrance variants: striking families and early-onset cases.

Study objective

The main objective of this study is to identify rare, high-penetrance germline mutations predisposing to familial and/or early onset UBC.

Study design

We will perform an observational family study using high-risk families and patient-parent trios. The duration of the study is four years. This study will be divided in three parts:
1. A nationwide recruitment of novel index patients and families including extremely early age-at-onset patients and their healthy parents. We will make use of our collection of UBC families (N=64). We will i) invite previously identified high-risk UBC families to a consultation with a clinical geneticist in order to update the information on family history of cancer and exposure to UBC risk factors in the family ii) extend the collection of peripheral blood from affected and unaffected UBC family members and iii) collect tumor material from UBC index patients and affected family members. If a new high-risk UBC family is identified, the clinical geneticist will draw a pedigree with information on family history of cancer, collect information on exposure to UBC risk factors in the family, and collect DNA of the index patient and selected family members.
We will also recruit extremely young UBC patients (<=30 years of age at time of UBC diagnosis) with help of the Netherlands Cancer Registry and of the treating physicians of the patients. From the early-onset patients and their healthy parents we will collect two EDTA blood tubes. From the early-onset patients we will also collect remaining tumor tissue.
2. Discovery of novel candidate UBC-predisposing mutations and genes. We will employ next generation whole exome sequencing (WES) on the germline DNA of two relatives with UBC from 20 stringently selected high-risk families, and 25 extremely young sporadic UBC patients and their unaffected parents (trios) to identify germline de novo mutations as well as variants that follow a recessive inheritance pattern. This will result in ~100 candidate genes for the third part of this study.
3. Substantiation of novel candidate UBC-predisposing genes in additional samples. Based on the selection of candidate genes obtained using WES, we will assemble a set of an anticipated 100 candidates to perform a high-throughput mutational screening using molecular inversion probe (MIP) technology. Our screening series comprises the germline DNAs of the entire set of index patients and relatives of UBC families (N=±145), the extremely early-onset bladder cancer patients (N=±150), and their unaffected parents. In addition, we will include tumor DNA from familial patients and early-onset patients for the detection of second-hit mutations and somatic changes in these selected candidate genes.

Study burden and risks

Burden and risk associated with participation
High-risk UBC families: The index patients of 64 high-risk UBC families (identified for a previous study) are contacted by the clinical geneticist involved in this project for a consultation, during which information on family

history and exposure to UBC risk factors in the family is updated. Affected family members (and selected non-affecteds) for whom no DNA has been collected yet, are asked to donate a blood (two 9mL EDTA tubes) or saliva sample. For new high-risk UBC families, the index patient will be invited to have a consultation with the clinical geneticist, during which a pedigree is drawn with information on family history of cancer and information on exposure to UBC risk factors in the family is collected. The index patient and selected family members are asked to donate a blood sample. The blood drawing will be performed at the outpatient clinic of the Genetics department at the Radboudumc, or one of the local Thrombosis Service Points in the country if deemed more convenient. Risks associated with giving a single blood sample are confined to fainting or bruising and are therefore negligible.
On the informed consent form participants give permission for genetic research with the chance of incidental findings (unless they state on the informed consent form that only research without the chance of incidental findings may be performed). Any incidental findings are discussed by an independent commission that decides whether returning the incidental finding is beneficial to the participant. If so, the participant is invited for a consultation with the clinical geneticist involved in this project.

Early-onset patients and their parents: The patients will be asked to fill out a detailed bladder cancer specific questionnaire about family history, medical history, socio-demographic data (age, gender, ethnicity, education, occupation) and lifestyle factors (e.g. smoking behaviour). The patients are asked to fill out the contact information of their parents on the questionnaire. The patients as well as their parents are asked to donate a blood (two 9mL EDTA tubes) or saliva sample. The blood drawing will be performed by a professional at one of the Thrombosis Service Points. Again, risks associated with giving a single blood sample are confined to fainting or bruising and are therefore negligible. Also, the early-onset patients and their parents give permission for genetic research with the chance of incidental findings (unless they state on the informed consent form that only research without the chance of incidental findings may be performed).

Benefit associated with participation
Participants can possibly benefit from this study if a mutation that underlies the bladder cancer (in their family) is identified. Family members (and any future children) can be genotyped for this mutation and periodically screened if needed. Furthermore, participants may consider the possible sequencing of their genetic material and the potential returns of incidental findings, a benefit.

Group relatedness
The research is (partially) focused on patients who are not yet 18 because the probability of an underlying mutation as genetic cause for the bladder tumor is greatest in the group of patients with a young age at onset. It is also in the interest of the young patients and their families (and any future children) to

include them in the study at a young age and allow for the identification of any causal mutation as soon as possible.

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)
Elderly (65 years and older)

Inclusion criteria

Newly identified high-risk UBC families:
- Hereditary UBC: A family with at least three first-degree relatives with UBC, or a family with two first-degree relatives with UBC with uncommon characteristics (such as young never-smoking women with high-stage disease).;Early-onset patients:
- Diagnosed with bladder cancer after 01-01-1989

- <= 30 years old at time of diagnosis

Exclusion criteria

High-risk UBC families:
- Unable to read or understand the invitation letter, information brochure and informed consent form;Early-onset patients:
- Unable to read or understand the invitation letter, information brochure and informed consent form
- Younger than 12 years at time of study invitation

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-07-2016
Enrollment:	585
Type:	Actual

Ethics review

Approved WMO

Date:	20-07-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL51321.091.14