Comprehensive detection of childhood cancer predisposing genes using exome sequencing:
The next step towards personalized treatment and cancer prevention.

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To detect high-risk pathogenic mutations in germline DNA of children with childhood cancer that are suggestive of genetic predisposition, using NGS-based whole-exome sequencing, resulting in novel targets for future functional and translational...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37736

Source
ToetsingOnline

Brief title
Detection of childhood cancer predisposing genes using exome sequencing

Condition

- Other condition
- Congenital and hereditary disorders NEC
- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
childhood cancer, pediatric tumors

Health condition

kanker op de kinderleeftijd

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cancer susceptibility, childhood cancer, exome sequencing, genetics

Outcome measures

Primary outcome

Mutations in known and novel pediatric cancer predisposing genes.

Secondary outcome

The results of this exome sequencing project will likely result in novel

clinical, molecular genetic, and functional studies in order to explore the

impact on clinical practice and to investigate novel functional pathways in

childhood cancer initiation and development.

Study description

Background summary

It has been estimated that up to 10% of all childhood malignancies result from a genetic predisposition. This figure likely represents an underestimation since it is primarily based on patients with a recognizable clinical syndrome or a positive family history for cancer. Overall, it is difficult to discern hereditary from non-hereditary cases, especially when cancer arises from de novo or recessive germline mutations or when no recognizable clinical phenotype is apparent.
Early recognition of a genetic predisposition in a child with cancer can be of major benefit for the patient and its family, as it may lead to better treatment choices and early detection of second primary tumors. Additionally,

family members can be advised about specific surveillance options. Until recently, the identification of cancer predisposing genes was laborious. With recent rapid technological developments in next generation sequencing (NGS) including whole-exome sequencing, the identification of cancer predisposing genes in single patients has become a reality, thus providing enormous challenges as well as opportunities for patient care.
We hypothesize that a genetic predisposition for childhood cancer is more likely to be present in children diagnosed with cancer and one ore more of the following characteristics: intellectual disability, congenital anomalies, an adult type of cancer in a child or a family history for the same type of cancer.

Study objective

To detect high-risk pathogenic mutations in germline DNA of children with childhood cancer that are suggestive of genetic predisposition, using NGS-based whole-exome sequencing, resulting in novel targets for future functional and translational studies.

Study design

We will offer genetic counseling and exome sequencing on germline DNA of individuals with childhood cancer who meet the inclusion criteria and their parents. Exome sequencing data will be filtered by exclusion of common variants from international databases and our continuously growing in-house Radboud Genetics variant database, which is thus far assembled from 600 exome sequences. Candidate causative variants (nonsense and frameshift mutations, highly conserved nonsynonymous missense mutations and canonical splice site mutations) will be selected for further analysis that will be performed in a fixed order:
a) At first instance we will analyze those variants identified in a set of approximately 150 genes with a known correlation with cancer predisposition. If no pathogenic aberrations are found in this list of genes we will:
b) Screen for genes recurrently targeted by rare candidate variants in the childhood cancer patient cohort. In the final stage of the project this analysis will be expanded by dedicated pathway analysis based on the genes that are known or identified at that time. DNA of the parents will be tested using Sanger sequencing to determine whether the variant is de novo.
c) Test a recessive model by selecting candidate causative variants that are present in a homozygous or compound heterozygous form in a single gene. Parental origin of the biallelic configuration of each selected candidate variant will be tested in DNA of the parents using Sanger sequencing.
d) Test a de novo model by comparing exome sequences of the child and its parents.

For a detailed description of the study see the research protocol.

Study burden and risks

Coincidental findings
We will apply a strict order of analyzing the data to minimize the chance of finding aberrations in genes not related to the malignancy. Moreover we will keep these samples (and their analysis) separate from our in-house Radboud Genetics variant database to prevent incidental findings in the future. Incidental findings might still give information about susceptibility for diseases later in life. In case such
coincidental findings are encountered despite all our preventive measures, we have a protocol in place how to proceed. This protocol was previously approved by the ethical review board of the UMC St Radboud for diagnostic exome sequencing. As part of this protocol, a committee is in place in our hospital to judge the health benefits of sharing any information from incidental findings emanating from the sequencing procedure with the child and the parents. Of course, the informed consent procedure for this study will extensively address this subject by clinical geneticists, who will perform the inclusion.

Venapuntures
Most often venapunctures will be combined with venapunctures as part of the treatment process and will therefore not be an extra burden for the children.

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

Individuals diagnosed with any form of childhood cancer and one of the following characteristics will be included:
• Intellectual disability,
• Congenital anomalies,
• Adult type of cancer in a child
• First or second degree relative with the same type of cancer.
• Second primary malignancy
as well as their parents

Exclusion criteria

A known genetic defect in the family for a cancer unrelated condition, of which the child might be a carrier but about which the child/parents do not want to be informed.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2013
Enrollment:	180
Type:	Anticipated

Ethics review

Approved WMO Date:	03-01-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2017
Application type:	Amendment
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	NL40012.091.12