What are the genetic modifiers that explain the phenotypic variability in Lynch syndrome?

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Ethical review	Approved WMO
Status	Pending
Health condition type	Gastrointestinal tract disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON42727

Source
ToetsingOnline

Brief title
Genetic modifiers in Lynch Syndrome

Condition

- Gastrointestinal tract disorders congenital
- Gastrointestinal neoplasms malignant and unspecified

Synonym
hereditary colorectal cancer, HNPCC (hereditary non-poliposis colorectal cancer)

Research involving
Human

Sponsors and support

Primary sponsor: Klinische Genetica
Source(s) of monetary or material Support: Ministerie van OC&W,KWF Kankerbestrijding

Intervention

Keyword: Lynch, modifiers, NGS

Outcome measures

Primary outcome

We will establish a genetic profile of both cases and controls. We will focus

our analysis of the NGS data on a pre-determined set of 30-50 oncogenes..

Abnormalities can be found in genes that are weakly correlated to CRC or other

LS-related tumours. These may explain the variance of phenotype between family

members. These variants will be analysed in a segregation analysis between

family members to determine their role in the modification of cancer risk.

Secondary outcome

nvt

Study description

Background summary

Lynch syndrome (LS) is the most common form of heritable colorectal cancer (CRC). The genetic basis of LS has been traced back to mutations in the mismatch repair (MMR) genes, MLH1, MSH2, MSH6, PMS2 and the EPCAM gene through inactivation of MSH2. Although these genes are responsible for LS, there is a wide range in phenotype amongst patients. We hypothesise that this variation can be explained by both environmental factors and/or genetic modifiers. These modifiers might alter the risk for cancer posed by the MMR defect alone and thus result in a variation in penetrance of disease.

Study objective

We aim to recognise potential genetic modifiers for mutations in PMS2. This will be approached through comparing a selection of CRC-related genes in the exome of members of a PMS2 family who differ in age of onset and severity of disease.

Study design

We have designed this project as a case-control study. Confirmed carriers of mutations in the MMR genes will be compared to unaffected or less severely affected family members with regard to the clinical phenotype and genetic composition. The genetic information will be obtained through a next generation sequencing (NGS) based analysis of oncogenes and results will be derived from statistical modelling. NGS will be carried out on DNA that has previously been stored for research purposes with patient consent. The DNA of some individuals has not been stored previously or is of unsufficient quality or quantity to perform NGS. We will need to ask these individuals to donate blood for DNA extraction and their consent for the use of this DNA for research purposes. We will ask for informed consent specifically for the NGS in both groups as there is a chance of finding genetic variants that may have clinical implications.

Study burden and risks

The people participating in this study will be requested a maximum of one sample of blood for DNA extraction, only if the DNA currently stored is inadequate for NGS. This is a mildly intrusive procedure and from which we do not expect serious adverse effects.

The participants do need to be fully informed about the possibility of finding germline oncogene mutations beside the well-known MMR defect. Through NGS, their whole expressed genetic composition can be accessed. In this study we will, however, only access a pre-determined set of 30-50 genes. Still, a small chance remains that pathogenic mutations will be found that otherwise would not have been identified. These mutations can encompass abnormalities that are known to be related to CRC, which will always be reported to the patients. Other mutations that can be found in CRC-related genes will be variants of unknown significance (VUS), which are classified according to their assumed pathogenicity. VUS*s of category 4 will also be reported to patients, as these are the very likely to be pathogenic. Lastly, findings in genes not directly associated with cancer can be found. These will be included in the study for research purposes and not reported to the patients because of the uncertain clinical significance.

The possible clinical implications of identifying a pathogenic mutation will to be discussed with the participant before they give consent for NGS. Finding mutations that underlie preventable diseases, although not a goal of this study, will be beneficial for those individuals whom it concerns. Also, we believe that the small chance of finding variants will be outweighed by the added LS cancer risk knowledge. The current knowledge on the MMR gene defects provides an inadequate answer to the variability of LS phenotype. An extended genetic model needs to be established in order to allow better risk assessment for LS patients in the future. This study will contribute to the generation of

this polygenic model.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Over 18 years of age
- Member of an established PMS2 family
- Confirmed heterozygous mutation carrier
- Consent to be informed on findings that may have clinical implications

Exclusion criteria

- Under the age of 18
- Mentally handicapped
- Unable to consent to the study
- No consent to be informed on findings that may have clinical implications

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	04-05-2015
Enrollment:	331
Type:	Anticipated

Ethics review

Approved WMO

Date:	20-07-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	NL53277.058.15