IBDome; Identification of rare variants in candidate genes and regulatory elements in familiar and sporadic early-onset IBD (inflammatory bowel disease) patients

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Primary Objective: Identification of rare variants in candidate genes and regulatory elements in pediatric IBD patients. Secondary Objective(s): To determine the functional consequences of identified genetic variants in IBD, we will correlate...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal inflammatory conditions
Study type	Observational invasive

Summary

ID

NL-OMON41478

Source
ToetsingOnline

Brief title
IBDome

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
inflammatory bowel disease, ulcerative colitis or Crohn

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: genetic testing, IBD, pediatric

Outcome measures

Primary outcome

Identification of rare variants in IBD candidate genes by analyzing the differences in genetic profile between patients and family members and between patients and controls. Major goal is to extend our understanding of genetic components in sporadic cases of early onset IBD with an emphasis on rare variants and to identify individual causative mutations in familial cases. We will correlate clinical information (age of onset, clinical data, associated diseases) with observed variants of candidate genes. In familiar cases, only affected family members will be sequenced by next generation sequencing. Unaffected family members will be sequenced by traditional Sanger sequencing for variants identified in the affected family members.

Secondary outcome

When we find novel diagnostic genes, the Diagnostic Section of Medical Genetics might include sequencing of the new gene(s) into their standard pipeline. This practical implementation of our study will be done according to their diagnostic standards and internal protocols.

Study description

Background summary

Crohn*s disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD) affecting 1 in 250 individuals of European ancestry. IBD is a chronic relapsing and remitting disease. Although the exact etiology of IBD is unknown, it is speculated that IBD occurs in genetically susceptible individuals as a result of dysregulated immune responses to gut flora after exposure to an as yet unidentified environmental stimulus.

The advances in science and technology now permit large scale genome-wide association studies (GWAS) to identify genetic risk factors for disease in a population and assess gene-environment interactions that can influence outcomes in disease. Furthermore, with the results of different genetic studies, functional studies of genetic risk factors have identified new pathways involved in the pathogenesis of IBD.

Recent IBD GWAS showed that single nucleotide polymorphisms (SNP) in the IL10 locus are associated with ulcerative colitis and to a lesser extent Crohn*s disease. Functional studies in patients with ulcerative colitis showed physiologically important defects in IL10 signalling in lamina propria mononuclear cells. These results imply that IL10 signalling plays an important role in regulation of intestinal inflammation.

GWAS published in last 2-3 years revealed numerous other candidate genomic loci involved in IBD. Nevertheless, the results of GWAS only explained part (~10-20%) of the inheritability. In upcoming years a lot of effort will be put into further analysis and sequencing of identified candidate loci to unravel causative rare variants and genes. Since most of these studies are performed on adult-onset IBD patients we will take advantage from our cohort of familiar/sporadic cases of early onset IBD patients, while approximately 1/10 to 1/5 of IBD patients are diagnosed or have onset of their symptoms under the age of 18. Due to a larger familial component and differences in phenotypic manifestation and severity compared to late onset adult IBD we expect a larger genetic component in pathogenesis of our cohort. In addition, we plan to sequence the whole coding part of 300 candidate genes which allows us to discover rare variants. Finally, we will take advantage from our flexible and cost-effective deep sequencing setup which allows us to sequence large numbers of candidate genes in numerous individuals for only small fraction of costs needed for Sanger sequencing or whole exome/genome deep sequencing. This gives us logistical advantage over competitors.

Study objective

Primary Objective: Identification of rare variants in candidate genes and

regulatory elements in pediatric IBD patients.
Secondary Objective(s): To determine the functional consequences of identified genetic variants in IBD, we will correlate clinical information (age of onset, clinical data, associated diseases) with observed variants of candidate genes and examine pathways involved in the pathophysiology of specific intestinal inflammatory diseases.

Study design

Patients with IBD diagnosed in childhood will be recruited in two academic centres, UMC Utrecht and Erasmus MC Rotterdam. Clinical data are already available. We will collect blood from the patients that were diagnosed as a child since 2005. We will also include newly diagnosed pediatric patients and phenotype these according to the EUROKIDS protocol.

All patients diagnosed as a child will be asked for participation, particularly patients with familial IBD and patients with a diagnosis before the age of 5 years. A venipuncture is one of the usual diagnostic procedures during periodical check up for IBD. We will ask for a sample of extra blood (max 10 ml) during this diagnostic venipuncture after informed consent is obtained. Affected and non-affected family members will be asked for participation and provide max 10ml blood. In case obtaining a blood sample from non-affected family members is a problem, DNA can also be extracted from sputum. Blood samples are max 10 ml from individuals of 5 years and older, 4-10 ml from children 1-5 years of age, and 2-5 ml from children < 1 year of age. This will be coordinated during routine blood draws where possible.

A follow up questionnaire will be used to complete data on patient*s disease progression that may have developed since diagnosis of IBD. Participating family members are also asked to fill out a questionnaire.

The objective of the present study is sequencing ~300 candidate genes in maximal 400 individuals, with the possibility to extend the range of sequencing to regulatory regions and whole exomes, this possible future extension will not require additional venipuncture.

The total duration of the study will be 3,5 years. After obtaining informed consent, DNA from patients and family members will be collected in our diagnostic DNA-lab followed by sequencing of ~300 candidate genes in maximal 400 individuals, with the possibility to extend range of sequencing to regulatory regions and whole exomes. Even though we pick up 300 candidate genes, there is a possibility that causative mutations are present elsewhere. Therefore in patients where we can't explain the disease by mutations in one of the 300 candidate genes, we'll perform whole exome sequencing (sequencing of all genes) and sequencing of regulatory elements to find the causative mutation. DNA and medical information will be stored for a maximum of 20 years.

Study burden and risks

Venous blood investigation is one of the usual diagnostic procedures during periodical check up for IBD. We will ask for some extra blood (max. 10 ml) during this diagnostic venipuncture. Affected and non-affected family members will be asked for max 10ml blood. In case obtaining a blood sample from non-affected family members is a problem, DNA can also be extracted from sputum. No increased risk is to be expected, however venipuncture can be an undesirable experience to a child, especially when the venipuncture is difficult to perform e.g. because of small vessels. This can be inconvenient for the patient. Therefore, we will refrain from taking the extra blood necessary for our research if the venipuncture is difficult to perform and/or the child is distressed.

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

(1) Diagnosis of IBD according to the IBD guidelines including endoscopic investigation with histologic abnormalities suspicious for IBD.
(2) Age at diagnosis between 0- 17 years
(3) Family member of pediatric IBD patient

Exclusion criteria

No informed consent obtained for present study. We will refrain from taking the extra blood for our research if the venipuncture is difficult to perform and/or the child is distressed.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-04-2015
Enrollment:	0
Type:	Actual

Ethics review

Approved WMO Date:	22-11-2013
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-02-2015
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	NL40100.041.12