Unravelling intestinal inflammation: from Celiac Disease genotype to autoimmunity.

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

Summary

ID

NL-OMON44698

Source
ToetsingOnline

Brief title
CeD: From genotype to autoimmunity.

Condition

- Gastrointestinal inflammatory conditions
- Autoimmune disorders

Synonym
Celiac Disease, Gluten-intolerance

Research involving
Human

Sponsors and support

Primary sponsor: Genetica
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Celiac Disease, Gluten sensitivity, High-throughput profiling, Irritable Bowel Syndrome

Outcome measures

Primary outcome

The primary study parameters will be the data sets generated by the different

'omics' approaches and the results of the integration of these datasets.

Secondary outcome

These analyses will identify CeD biomarkers and the identification of these

will provide novel insights into the etiopathology of CeD. This will help in

the future with improving diagnostics and treatment, and hopefully the

prevention of CeD.

Study description

Background summary

About 50% of patients visiting gastroenterological clinics have symptoms that can be associated with a diversity of autoimmune diseases, including Celiac Disease (CeD) and Irritable Bowel Syndrome (IBS). We study the patho-mechanisms involved in CeD with the final aim to improve the diagnosis, prevention and treatment of CeD patients. CeD is a very common autoimmunity (incidence 1%) that is triggered by dietary gluten (the storage protein of wheat, barley and rye). CeD only develops in patients with a genetic susceptibility but the nature of all the genes involved in diseases susceptibility remains to be elucidated. We do know one major genetic risk factor (HLA) and 39 minor risk factors. The current diagnosis in CeD is based on symptomatic, serologic and histo-pathological features, but still only 1 out of 8 CeD patients is properly diagnosed. So far genetics, based on HLA, is only used to exclude CeD. The under-diagnosis of CeD is caused by the wide variety of clinical symptoms and the overlap with other phenotypes like IBS (incidence estimated between 10-30%; Roberts et al., 2013). The major consequence of misdiagnosing CeD is that patients do not follow a gluten-free diet, which severely increases the risk of complications and increases mortality.

We have been studying the genetics of CeD for over 15 years and have contributed to elucidating approx. 50% of the genetic factors involved in CeD (contributed by the 40 genetic factors mentioned above). The proposed studies will help CeD patients in two ways: (1) we will identify novel genetic markers that will improve diagnosis and predict who is at-risk for developing disease (and thereby contribute to disease prevention), (2) the genetic insights obtained, enhance our understanding of the disease process which ultimately will lead to the development of new ways to treat CeD.
We are currently at a stage at which we can start to translate genetic findings into insights in the disease process using state-of-the-art bioinformatic approaches, but for this we do need to study CeD patients and their immune cells (as CeD is an autoimmune disease) in much more detail. In particular we have to understand how multiple CeD genetic risk factors are jointly deregulating immune cells and how this eventually leads to disease. Since CeD manifests in the intestine it is also possible that there is an interaction between intestinal immune cells and the gut microbiome.
In summary, in order to be as succesful as possible we want to analyze the genetic profile of the patients, the symptoms involved in the disease, the activation potential of the patient's immune cells, metabolites associated with the disease, and the microbiome of the subjects. These different layers of information will then be integrated by bioinformatic analysis, to obtain novel insights into the pathologie of Celiac Disease.

Study objective

The primary aim of the current proposal is to get a better understanding of how CeD risk genes contribute to disease aetiology. To achieve this, we will apply a holistic approach in which we will study the behaviour of immune cells and the microbiome in CeD patients and compare that to non-patients using *omics* technology (i.e. the full repertoire of all transcripts, cytokine profiles, proteins, metabolites etc.) in the background of the genetic profile of each individual. To generate this information we for instance have to profile different immune cells from patients and controls. The datasets will be analysed and integrated using bioinformatics to develop insights into disease mechanism. The technology we apply can also be used for disease prediction. Hence the secondary aims are to (a) develop biomarker profiles that will improve diagnosis (preferentially before full blown manifestation of the disease), (b) to investigate whether disease specific biomarkers affect the biology of the cells and tissues involved in the disease, and (c) to investigate the commonalities and specificities of CeD when compared with other intestinal diseases. As we have to integrate information on genetics, immune cells and microbes, a panel of biomaterials (isolated from blood, urine, stool and buccal smears) will be sampled using non-invasive techniques (the most invasive being blood sampling). From these samples genomic, transcriptomic, epigenetic, serological, metabolomic, and microbiomic data will be generated and analysed. This will be complemented with phenotypic data acquired by examination of the study subjects at the time of presentation, medical records,

and from questionnaires that the subjects will be asked to complete.

Study design

This is a non-therapeutic study. Patients that visit the out-patient clinic of the Gastroenterology and Hepatology department of the UMCG will be recruited. Three extra tubes of blood (10ml) will be collected at the scheduled diagnostic venepuncture during their regular visit to the outpatient clinic of the department of Gastroenterology and Hepatology. Additionally, a buccal smear will be taken for identification of the microbiome of the oral cavity and the subject will be requested to exhale over a filter that will capture volatile organic compounds (metabolites). All contributors will be requested to provide a stool and urine sample which will be collected at home, and additionally to fill in a questionnaire.The data will be generated and analysed at the department of Genetics of the UMCG. Currently we are performing identical analyses in our *LifeLinesDeep* cohort, for which we are profiling 1.500 subjects in an identical manner. The LifeLinesDeep data will also provide the base-line values for our patient-derived data.

Study burden and risks

Three extra tubes of blood (10ml) will be collected at the scheduled diagnostic venepuncture during the regular visit to the outpatient clinic of the department of Gastroenterology and Hepatology. Additionally, a buccal smear will be taken and the subject will be requested to exhale in a bag. All contributors will be requested to provide a stool and urine sample which will be collected at home, and additionally to fill in a questionnaire.
The risk and burden associated with these procedures is negligible.

The study will not provide an immediate benefit for the participants, but the results will help in the future with improving diagnostics and treatment, and hopefully prevention of CeD.

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

Adults (patients and control subjects UMCG & Martini Ziekenhuis Groningen; controls Wilhelmina Ziekenhuis Assen):
-Patients suffering from CeD diagnosed by the treating physician according to established clinical, serological and pathological definitions.
- Patients suffering from IBS as diagnosed by the treating physician according to established clinical defined in the Rome II criteria.
-Spouses and 1st line family members of CeD patients
- >= 18- years old;Children (Patienten Wilhelmina Ziekenhuis Assen):
-Patients suffering from CeD diagnosed by the treating physician according to established clinical, serological and pathological definitions.
- <= 18- years old

Exclusion criteria

not applicable

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:	Recruiting
Start date (anticipated):	26-02-2015
Enrollment:	2500
Type:	Actual

Ethics review

Approved WMO Date:	24-06-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-04-2019
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL46789.042.13