SHERLOCk: An integrative genomic approach to Solve tHe puzzle of sevERe (earLy-Onset) COPD

Published: 21-03-2017
Last updated: 16-04-2024

The aim of this study is to identify why a subset of COPD patients develops such a severe COPD at early age and with relatively few packyears smoking. This will need a functional genomics approach integrating both whole genome DNA sequencing data in...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Observational invasive

Summary

ID

NL-OMON55665

Source
ToetsingOnline

Brief title
SHERLOCk

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Severe COPD

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Genotyping, Phenotyping, Severe COPD, Susceptibility

Outcome measures

Primary outcome

To identify which genes and gene-networks are associated with severe

(early-onset) COPD.

Secondary outcome

- To determine which common and rare genetic variants are likely causally

related to the development and/or excessive progression of the disease

- To assess which COPD-associated genes and gene-networks are controlled by

miRNA?*s (micro-RNA*s) and DNA methylation sites.

Study description

Background summary

Chronic Obstructive Pulmonary Disease (COPD) is characterized by a chronic airflow limitation associated with an abnormal inflammatory response of the airways to inhaled noxious particles or gases. It is the third leading cause of death worldwide, accounting for approximately 3 million deaths each year and the prevalence is predicted to increase even further during the coming decade (WHO 2015). In the last two decades, there has been a disappointing lack of fundamental breakthroughs in the understanding of the pathophysiology of COPD and there is currently no pharmacological treatment available that halts its relentless progression. A clear alternative for describing COPD does not exist either, while the identification of subgroups of COPD patients based on clinical, genomic and epigenomic factors would be useful. A clinically relevant phenotype with high potential of having a genetic cause is severe early-onset COPD (SEO-COPD), defined by severe airflow obstruction (FEV1 <= 40% predicted) at a relatively young age (<=53 years). In the UMCG, we have a continuous flow of severe COPD patients who are referred to our hospital for bronchoscopic lung volume reduction treatment or lung transplantation. Approximately 40-50% of these patients fulfil the criteria for SEO-COPD. As part of a previously approved study (*Phenotyping in COPD*, METc 2014/102), these patients are

routinely characterized when they are willing to participate in this study and gave their written informed consent. Characterization is performed using lung function (i.e. spirometry, body box), clinical (i.e. questionnaires, physical examination, measurement of waist-hip ratio), radiologic (HRCT-scan) and systemic parameters (venous blood collection). Moreover, the following additional samples are being extracted: bronchial biopsies, bronchial brushes and nasal brushes.
There are two objectives this study adds. The primary objective is to identify the genetic and epigenetic mechanisms underlying SEO-COPD by using the bronchial brushes and biopsies that are already extracted from the SEO-COPD patients and add 125 patients with severe COPD. The secondary objective is to add two control groups (i.e. mild-moderate COPD group and healthy non-COPD control group) matched for age and smoking habits.
Hopefully, this will eventually explore COPD susceptibility and its genetic cause, resulting in a more tailored treatment of this COPD subset.

Study objective

The aim of this study is to identify why a subset of COPD patients develops such a severe COPD at early age and with relatively few packyears smoking. This will need a functional genomics approach integrating both whole genome DNA sequencing data in blood and transcriptomics data in the bronchial epithelium as well as epigenetic regulation. This will identify novel common and rare genetic variants, genes, miR*s, and DNA methylation sites that contribute to severe (early-onset) COPD.

Study design

This is a single-center, observational, cross-sectional study.

The 250 (ex-)smoking mild-moderate COPD patients and 150 (ex-) smokers without COPD are characterized during the following three visites:
Visit 1: demographics, medical history, physical examination, bodycomposition (waist-hip ratio), questionnaires (CCQ, CAT, SGRQ), peripheral blood, ECG, spirometry with reversibility and sputuminduction.
Visit 2: diffusion capacity, bodybox and IOS, PC20 methacholine, FeNO, PeXA, Multiple Breath Nitrogen Washout (MBNW), in- and expiration HRCT of the thorax.
Visit 3: nosebrushes, bronchoscopy.

Yearly visit: catch-up demographics, medical history, physical examination, spirometry and reversibility.
Exacerbation visit: Catch up demographics and medical history, physical examination, spirometry and sputum induction, nasal swab, peripheral blood collection.

The 125 patients with severe COPD are mainly characterized during routine

clinical care. When included in the study, patients will fill in extra questionnaires, do extra pulmonary function tests, will collect urine and stool samples and during the bronchoscopy, samples will be collected for the study. The bronchoscopy is performed for bronchoscopic lungvolume reduction therapy and not planned for participation in this study.

Study burden and risks

The risk for participant in this study are:
1. Dyspnea during sputum induction and provocation test with methacholine.
2. Bronchospasm during bronchoscopy and / or desaturation during the bronchoscopy
3. Bleeding during collection of bronchial biopsies, bronchial or nasal brushes.

Measures for treatment or prevention:
Ad 1. Before the sputum induction and after the methacholine provocation every subject will be given inhaled salbutamol to prevent or treat dyspnea. Patients with severe COPD or an FEV1 < 1,2 L will not do provocation tests or sputum induction.
Ad 2. If bronchospasms occur during the bronchoscopy the procedure will be stopped immediately and if necessary subject will be given extra bronchodilator medication by inhalation. This will treat bronchospasm properly. Monitoring oxygen saturation will be performed during the whole procedure. If necessary the bronchoscopy will be stopped.
Ad 3. If hemostasis is necessary, xylometazoline will be applied locally.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

All groups:
• Subjects must be able to adhere to the study visit schedule and other protocol requirements.
• Age between 40-75 years.
• Absence of asthma.
• >=5 packyears of smoking.

Inclusion for current-smoking mild-moderate COPD patients (n = 125)
• GOLD classification I or II according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post bronchodilator FEV1/FVC <0.7) (2).
• Average of at least 2 cigarettes/day during the last year.

Inclusion for ex-smoking mild-moderate COPD patients (n = 125)
• GOLD classification I or II according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post bronchodilator FEV1/FVC <0.7) (2).
• Cessation of smoking for >=6 months.

Inclusion for current-smoking non COPD control subjects (n = 75)
• Absence of COPD according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post bronchodilator FEV1/FVC <0.7 or FEV1/FVC < lower limit of normal) (2).
• Average of at least 2 cigarettes/day during the last year.

Inclusion for ex-smoking non COPD control subjects (n = 75)
• Absence of COPD according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post bronchodilator FEV1/FVC <0.7) (2).
• Cessation of smoking for >=6 months.

Inclusion criteria for severe COPD treated with bronchoscopic intervention (n=125):
• GOLD classification III or IV according to the Global initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post bronchodilator FEV1/FVC <0.7) (2).
• Scheduled for a bronchoscopy related to a lung volume reduction procedure (during which we will also perform the sampling - these patients will not be scheduled for a bronchoscopy only for this study)

Exclusion criteria

• Presence of acute infections (such as hepatitis, pneumonia, pyelonephritis) in the previous 3 months.
• Signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic or cerebral disease.
• Malignancy within the past 5 years (except for squamous or basal cell carcinoma of the skin that has been treated with no evidence of recurrence).
• Known recent substance abuse.
• Females of childbearing potential without an efficient contraception.

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):	17-10-2017
Enrollment:	525
Type:	Actual

Ethics review

Approved WMO Date:	21-03-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-02-2022
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
ClinicalTrials.gov	NCT04263961
CCMO	NL57656.042.16