Whole Exome & Whole Genome Sequencing Analysis to Explore Familial Keratoconus

Published: 15-02-2023
Last updated: 31-12-2024

To identify genetic variants for the development and progression of keratoconus using Whole Exome Sequencing and Whole Genome Sequencing approaches on keratoconus families with index patients originating from the Rotterdam Eye Hospital and Erasmus...

Ethical review	Approved WMO
Status	Pending
Health condition type	Anterior eye structural change, deposit and degeneration
Study type	Observational invasive

Summary

ID

NL-OMON53921

Source
ToetsingOnline

Brief title
WES-WGS-KC

Condition

- Anterior eye structural change, deposit and degeneration

Synonym
eye bulging

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Combined Ophthalmic Research Rotterdam

Intervention

Keyword: genetics, Keratoconus, Whole exome sequencing, Whole genome sequencing

Outcome measures

Primary outcome

Genomic DNA will be extracted from saliva and/or blood according to standard protocols. Genetic sequencing will be performed according to standard protocols and quality control of the Erasmus MC Human Genomics Facility HuGe-F. We will perform an extensive quality control procedure which includes filtering on coverage (>10x) and quality of the detection variants. Next, we will annotate the variants using wAnnovar (wANNOVAR (wglab.org)). Segregation analysis will be performed, with cases being carriers and controls being non-carriers. We will look for variants shared across families and/or within each family, and we will evaluate these variants based on the biological information available to us such as the gene function and involvement with other diseases. This will help us identify the most likely causal variants.

In case of a suspected autosomal dominant inheritance pattern, we will focus on heterozygous variants. In case of a recessive inheritance pattern, we will focus on homozygous variants which are present in a heterozygous manner in the parents. As a first step, we will employ a candidate-gene approach using a panel of genes which previously have been associated with

keratoconus. This will be followed by an open exome approach to identify new genes.

To identify causal variants, we will perform a prioritization procedure using an allele frequency cut-off (<1%) in control databases such as gnomAD v3.1.2., GoNL (https://www.nlgenome.nl/) and TOPMed (https://topmed.nhlbi.nih.gov/). We will also assess the pathogenicity using several in silico prediction tools implemented in several annotation programs such as SIFT 6.2.1, PolyPhen-2, MutationTaster2021 and CADD v1.6. All variants will be confirmed using sanger sequencing and segregation analysis in other family members

Secondary outcome

Following ophthalmic imaging with Pentacam and Corvis, assessment of the scans will be performed using topographical maps and a selection of parameters provided by the default setting of the Pentacam and Corvis. Examples of such parameters are the degree of astigmatism, K1, K2, Kmax, final D and thinnest pachymetry. Corvis scans will also be analyzed in a similar fashion.

For the assessment of the association of environmental and genetic risk factors, an analysis of lifestyle, ocular history and systemic involvement will be performed.

Estimation of the heritability of corneal morphologic features as measured by Pentacam and Corvis will be performed, and an analysis of the morphologic features of the corneas of non-affected family

members of keratoconus patients will also be carried

out.

The association of corneal parameters (measured be Corvis or Pentcaam) with

specific genetic variants will be assessed as a

part of this study as well.

Study description

Background summary

Keratoconus is one of the most prevalent corneal disorders, leading to visual deterioration and necessitating in many cases corneal surgery. Multifactorial pathophysiology including both genetic and environmental factors is suspected. Currently, keratoconus is one of the most frequent indications for corneal transplantation (keratoplasty). Although keratoplasty is an effective treatment, it is a very intensive, time-consuming and expensive treatment modality. Relatively little is known about the causes and pathophysiology of keratoconus. There is evidence for a multifactorial etiology, including complex interactions of genetically determined mechanisms and environmental factors. In the meantime, the majority of genes and mutations involved still remain to be identified. By identifying new genes and mutations, more insight may be gained into the causal effects or mechanisms of some of the implicated environmental factors, as per further elucidating the molecular pathways involved. These findings can eventually aid in early prediction and prevention of keratoconus.

Study objective

To identify genetic variants for the development and progression of keratoconus using Whole Exome Sequencing and Whole Genome Sequencing approaches on keratoconus families with index patients originating from the Rotterdam Eye Hospital and Erasmus Medical Center

Study design

Case-control family-based study.

Study burden and risks

There is no direct benefit or compensation for participation, and besides some negligible or rare complications which are

associated with blood withdrawal, there is no major burden or risk for participants.
Ophthalmic measurements and WES or WGS will be performed for research purposes.
Incidental ophthalmic, karyotypic or
Genetic findings which are deemed by the researchers to be relevant for the patient or their families will be communicated with
the family physician and/or treating ophthalmologist as per the informed consent granted by every participant.

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)

Inclusion criteria

Keratoconus patients suspect of monogenetic course of disease and their healthy and affected family members

Exclusion criteria

keratoconus, non familial course

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:	Pending
Start date (anticipated):	01-03-2023
Enrollment:	0
Type:	Anticipated

Ethics review

Approved WMO

Date:	15-02-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL82389.078.22