Diseasy Severity in patients with heterozygous COL4A3 or COL4A4 pathogenic Variants and Exploration of Risk factors.

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To accomplish this aim we will address the following objectives:1. Define kidney disease heterogeneity within and between families carrying heterozygous COL4A3/COL4A4 pathogenic variants and evaluate hearing loss as non-renal phenotype;2. Analyze...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hearing disorders
Study type	Observational invasive

Summary

ID

NL-OMON51423

Source
ToetsingOnline

Brief title
DisCOLver

Condition

- Hearing disorders
- Nephropathies

Synonym
Alport Syndrome, Thin Basal Membrane Nephropathy

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Nierstichting

Intervention

Keyword: Alport syndrome, Phenotype, Thin Basal Membrane Nephropathy, Type IV-collagene

Outcome measures

Primary outcome

Proportion of participants with pathogenic variants in COL4A3/COL4A4 and

no/mild/ /severe kidney disease.

Secondary outcome

• Environmental factors associated with disease severity

• Hearing loss within patients with COL4A3/COL4A4 genetic variants

• Number of patients with intronic and somatic COL4A3/COL4A4 pathogenic variants

• Number of patients with additional podocyte-associated pathogenic genetic

variants

• Overall risk stratification for categorisation in phenotype (mild/ severe)

Study description

Background summary

Alport syndrome (AS) is a hereditary disorder of type IV collagen and is characterized by the combination of kidney injury, hearing loss, and eye abnormalities. Three genes encode the type IV collagen chains of the glomerular basement membrane. The majority AS cases are caused by mutations in the COL4A5 gene on the X chromosome. Autosomal Alport syndrome is caused by pathogenic variants in either COL4A3 or COL4A4 gene. Classically, patients with two pathogenic variants (homozygous or compound heterozygous) developed Alport syndrome, whereas patients with one variant (heterozygous) developed

(non-progressive) thin basement membrane nephropathy (TBMN). Recent advances in genetic diagnostic testing have resulted in the identification of heterozygous COL4A3/COL4A4 genetic variants in patients with chronic kidney disease (CKD) who were not diagnosed with AS or TBMN. Remarkably, there is marked heterogeneity between and within families with respect to the clinical course, and very few patients have extrarenal signs/symptoms. This heterogeneity is a serious limitation in patient care, and prohibits adequate counselling of patients.
The aim of the project is to find explanations for intra- and inter-familial heterogeneity among patients with established COL4A3/COL4A4 heterozygous variants.
The central hypothesis of the project is that phenotypic heterogeneity in patients with one heterozygous COL4A3/COL4A4 pathogenic variant is at least partly explained by hitherto unrecognized second hits. The unrecognized second hits may be environmental or genetic, either localized in the COL4A3 or COL4A4 genes (intronic variants or somatic variants in the kidney), or in other podocyte-associated genes.

Study objective

To accomplish this aim we will address the following objectives:
1. Define kidney disease heterogeneity within and between families carrying heterozygous COL4A3/COL4A4 pathogenic variants and evaluate hearing loss as non-renal phenotype;
2. Analyze environmental factors explaining variations in disease severity;
3. Depending on the outcome of obj. 2: Investigate the presence of intronic and somatic COL4A3/COL4A4 pathogenic variants;
4. Depending on the outcome of obj. 2 and 3: Investigate the presence of rare variants in other podocyte-associated genes.

Study design

Observational cross-sectional study.

Study burden and risks

Risks associated with participation are minimal. One clinic visit to the outpatient clinic is required to collect blood and urine samples (and a hearing test for index patients) and one additional urine sample will be sent by post. No additional interventions are required. There is no direct benefit for the patients.
The benefit for patients and families with heterozygous COL4A3/COL4A4 pathogenic variants is the potential insights in risk factors (lifestyle and genetic factors) contributing to the development of kidney failure. This can lead to optimal counselling strategies in the future.

Disclosure of individual results
Participants will be informed about the possible results and consequences of genetic testing. Since we will only focus on COL4A-genes and podocyte-associated genes and not perform open whole-exome sequencing chances of other secondary findings are extremely limited. Results of genetic testing will only be disclosed if individual results have a clinical impact for the individual: likely pathogenic or pathogenic variants based on the joint guideline of the Association of Clinical Genetic Laboratory Diagnostics (VKGL) and Association for Clinical Genetic Science (ACGS).

A clinical genetic specialist will always be involved when informing a participant about the results of genetic testing with implications for the health of the participant or family.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Patients (probands) & family members
• with a likely or proven pathogenic variant in COL4A3 or COL4A4

2. Family members
• First or second-degree relatives of a patient with a likely or proven pathogenic variant in COL4A3 or COL4A4 who have not undergone genetic analysis yet

3. COL4A5 validation group:
• Patients with a proven pathogenic variant in COL4A5

Exclusion criteria

• Inability to provide informed consent
• Age below 18 years

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-01-2023
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO Date:	03-08-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-11-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL80142.091.22