Improving genetic and phenotypic screening of patients with renal tubulopathy-related disorders

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Ethical review	Approved WMO
Status	Pending
Health condition type	Renal and urinary tract disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON57415

Source
ToetsingOnline

Brief title
Genstudi

Condition

- Renal and urinary tract disorders congenital
- Nephropathies

Synonym
Renal tubulopathy-related disorders; kidney disorders

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Genetic screening, renal tubulopathy

Outcome measures

Primary outcome

* Patient data, including but not limited to primary phenotype, original clinical diagnosis, family history, age, and sexs

* Genetic profiles of patients, as obtained using previous (routine) genetic testing, or newly obtained whole exome sequencing, mitochondrial DNA screening, and whole genome sequencing data

Secondary outcome

* To determine the ion transporter function of the patients in specific parts of the renal tubules based on different tests, e.g., the thiazide, furosemide, furosemide-fludrocortisone, and DDAVP tubular function tests. These tests will be performed based on the patient's specific phenotype, or after a genetic variant (either an already known variant or a VUS) was found that is thought to hamper tubule function. To get a better understanding of the phenotype as well as the effect of the variant on the phenotype and the specific parts of the renal tubules.

* To identify and investigate novel mutations both within and outside of the standard renal WES panel.

* In case of a mitochondrial variant with unknown significance, to determine the heteroplasmy level of a mtDNA variant in blood, urine, and fibroblasts of participants, as well as the mitochondrial function based on fibroblast culture from skin biopsies.

* To investigate the use of advanced urine diagnostics to improve screening of patients using urinary extracellular vesicles (uEVs) and adult stem cells (ASCs).

* Laboratory parameters will mainly be retrieved from the patient records by the treating physician and anonymously shared with the research team. When the necessary evaluations are not recent or not available, blood will be drawn for these laboratory evaluations at the Radboudumc. For each analysis, the values will be compared to normal reference values.

Study description

Background summary

Renal tubulopathy-related disorders are a heterogenous group of genetic disorders, in which the renal tubular transport is disturbed. Consequently, patients present with disruption of the water, electrolyte, and/or acid-base balance, resulting in a wide-range of symptoms. Diagnosis of renal tubulopathy-related disorders is most often based on a combination of clinical symptoms (phenotyping) and genetic screening. However, in a subset of patients, the genetic diagnosis cannot be established. Nowadays the screening is most often done with either gene-specific testing or with whole exome sequencing (WES) using subsequent gene panel filters that include genes known to be related to renal diseases. Nevertheless, this only includes nuclear encoded genes known to cause kidney disease. As a consequence, gene mutations in mitochondrial DNA, mutations outside of the exons, and mutations outside the gene panel, are currently being missed. The lack of diagnosis results in basic treatment of the symptoms, which can be enough but when the causative mechanism is not known, the proper treatment is not always found. In addition, lack of diagnosis is both a psychological burden and a practical problem (sick leave, insurance issues) for patients. Thus, improving genetic screening will not only increase our knowledge about current (and possible novel) renal tubulopathy-related disorders, but it will also affect patient quality of life and improve (future) treatment options

Study objective

In this study, we aim to improve the genetic diagnosis of patients with genetic renal tubulopathy-related disorders. We hypothesize that a higher diagnostic yield can be obtained by genetic re-screening of patients using the updated renal gene panel, expanding the genetic screening to include whole exome, whole genome, and mitochondrial DNA screening. The secondary objective is to identify and investigate novel mutations both within and outside of the previously applied genetic screening. Furthermore, if applicable, we will broaden the phenotyping by doing additional (clinical, functional, or histological) tests and we will investigate advanced urine diagnostics.

Study design

Exploratory study

Study burden and risks

For some patients there will be no physical risk at all, due to the use of previously obtained genetic data and/or previously obtained material. Depending on the patient, the study procedure will have different steps and patients can opt-out at all moments. The physical risk of this study is mainly determined by the tubular ion transport function tests, due to administration of e.g., thiazide, which is low. The Radboudumc Expertise Center for Rare Kidney Disorders has validated protocols for such renal tubular tests, which include instructions on how to prevent and/or detect these complications. The rest of this study has little physical risk but does have some physical burden, such as collection of blood samples and 24-hour urine, if applicable a skin biopsy, as well as potential extra hospital visits. In addition, there is also a psychological burden connected to the study. Although all patients have been genetically tested by the Radboudumc, not all are currently actively followed at our outpatient clinic. So, they will have to be contacted again, which could be unexpected for these patients. The genetic testing also carries some psychological burden, such as chance of secondary findings or lack of diagnosis after testing. Patients that agree to accessing their genetic material, are not obliged to continue in any of the other steps, whether this is additional genetic testing or functional testing, and can of course retract consent at any time during or after this study. Next to this, an up-to-date bioinformatic filter will be used to reduce the chance of secondary findings by hiding known pathogenic variants (not related to renal tubulopathies) that otherwise would have to be reported to the patient. Lastly, all patients will be informed either by the researchers under supervision of a clinical geneticist or by a clinical geneticist, about the risk of secondary findings.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* The patient must have had genetic screening that did not result in a genetic diagnosis explaining the phenotype, performed at the Radboudumc
* The patient must have clinical proof of renal loss of salts, HCO3-, acid, glucose, amino acids, low molecular weight proteins, and/or water, as such presenting with a phenotype that suggests a renal tubulopathy is present

Exclusion criteria

Patients with a previous (genetic) diagnosis fully explaining their renal tubulopathy-related phenotype

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2024
Enrollment:	100
Type:	Anticipated

Ethics review

Approved WMO

Date:	16-04-2025
Application type:	First submission
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	NL87808.091.24