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Fibrosis, inflammation, Oxygenation of Renal Tissue In FabrY disease: The FORTIFY study

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Overreaching aim

The overall objective of this study is to investigate Fabry-associated renal organ involvement by using a novel magnetic resonance imaging (MRI) approach, focusing on changes in renal oxygen levels by blood oxygenation-level dependent (BOLD) imaging. Furthermore, to correlate renal oxygenation to the phenotypic presentation of patients with Fabry-associated nephropathy regarding circulating and imaging-derived biomarkers of kidney inflammation, fibrosis and injury as compared with healthy age- and sex-matched controls.

The study will achieve this by:

1) Using a non-invasive, contrast-free MRI protocol focusing on parameters of oxygenation, inflammation, fibrosis, and injury in the kidney.
2) Using an extensive, in-depth biomarker blood panel to investigate the pathological pathways associated with Fabry disease and Fabry-associated nephropathy.

Introduction

Fabry disease is a rare X-linked lysosomal disorder caused by mutations in the gene encoding the enzyme α-galA, an essential enzyme for normal cellular function. The enzyme deficiency causes progressive accumulation of glycosphingolipids, especially globotriaosylceramide (Gb3) in virtually all organs, leading to dysfunction and eventually leading to organ failure. Although, Fabry disease is caused by an X-linked genetic mutation and the clinical implication among men with a classic phenotype are most severe, Fabry disease affects both males and females [1]. Men with a non-classic phenotype and females present with a more heterogenous degree of organ involvement, however, these patients remain at increased risk of multisystem organ involvement and must be attend extensive screening, evaluated repeatedly in order to decide when and who are in need of treatment [2]. However, as evident in patients with the several known genotypes, which presents with no or very low α-galA-activity and develop early multi-organ involvement, one of the complication of greatest prognostic impact is an early involvement of the kidney [1].

Fabry nephropathy

Although, the etiology of kidney affection in Fabry disease in general is well established, the actual mechanisms of progression – and thus the targets of therapeutic approach – are largely unknown. Fabry nephropathy is characterized by the accumulation of Gb3 deposition in podocytes, epithelial cells and endothelial cells throughout the tubules, where kidney biopsies suggest healthy, functioning tissue is substituted with reparative diffuse fibrosis. Indeed, evidence shows a direct

association between Gb3 accumulation and both a decline in renal glomerular filtration rate and an increase in urinary albumin excretion – both clinically validated biomarkers of kidney injury and decline in function [3–5]. Given Gb3 accumulation in Fabry disease accounts for less than 5% of the total tissue volume at maximum [6,7], the disproportionate and devastating effects observed have led to the proposal of Gb3 having additional effects beyond mere storage [8–11]. Oxidative stress, endothelial dysfunction, and inflammation have been proposed as important mechanisms induced directly or indirectly by Gb3 accumulation, resulting in increased cell-death of functioning glomeruli with unamenable, reparative fibrosis as a result [9–12]. Furthermore, certain cells seems more susceptible to injury and less susceptible to the benefits expected from Fabry-specific treatment; an important example being renal podocytes [3].

Fabry nephropathy and Magnetic Resonance Imaging

Renal hypoxia is now considered to play a key role in the development of chronic kidney disease (CKD) [13–17]. Using a novel contrast-free, non-invasive magnetic resonance imaging (MRI) [16], our collaborative partners have reported renal hypoxia in subjects with type I diabetes and pathological urinary albumin/creatinine ratio (UACR) levels [18]. Recent advances in MRI thus, enables us to investigate the pathological mechanisms underlining Fabry nephropathy by non-invasively measurements of oxygenation, inflammation and fibrosis [13–16]. The kidney's oxidative capacity evaluated by R2*-related blood oxygenation level-dependent (BOLD) MRI has been validated as a parameter of renal cortical and medullar oxygen-partial pressure [13–16]. Furthermore, changes in dynamic R2*-signaling have been validated as a non-invasive, contrast-free measure of renal oxygenation capacity, which becomes reduced with presence of chronic kidney disease [14,16]. Concurrently, arterial spin labelling (ASL) is able to provide a reliable measure of total blood flow as well as regional blood flow in the renal artery and the kidney [14,16]. Finally, the inflammatory and fibrotic burden can be elucidated upon by diffusion-weighted sequences and native T1-mapping [13,16]. Therefore, this novel method provides information on kidney-specific shift in energetic oxygen-dependent capacity, ongoing inflammation, and accumulation of fibrosis, with changes not only portraying key aspects of kidney physiology, but changes expected to elucidate on the pathophysiology forming the very basis of Fabry nephropathy.

While the recent advances in imaging present a unique possibility for early detection of Fabry nephropathy, there is a need for validation against clinically established biomarkers of risk such as pathologically increased UACR – currently the greatest predictor of progressive loss of glomerular function in regards to end-stage renal disease in general and in Fabry nephropathy [4,5]. Pathological UACR levels is considered the first clinical sign of Fabry nephropathy, with an estimated prevalence

of 50% among men aged 35 years. Even among women, which often less severely afflicted, up to 40% develop proteinuria and 15% experience a clinically significant renal event, thus, the prognostic importance of increased UACR in Fabry disease is evident [19–21]. Therefore, UACR levels is the key clinical parameter of Fabry nephropathy as recommended in guidelines [22].

Hypothesis

Impaired renal oxygenation is an early characteristic of Fabry nephropathy, which precedes established markers of renal decline such as estimated glomerular filtration rate or UACR.

Participants and methods

Study design

A cross-sectional study and will consist of a group of patients from the Danish National Fabry Cohort followed at the Danish National Fabry Centre, Department of Hormone and Metabolism, Copenhagen University Hospital, Rigshospitalet. Furthermore, a control group of healthy age- and sex-matched individuals will be included to comprise a contemporary control cohort and will undergo the same program.

Participants

We will enroll 40 participants with Fabry disease previously verified by genetic testing. The Fabry patients will be divided into two groups with and without renal involvement. Renal involvement is defined according to UACR levels and impairment of kidney function using the KDIGO classification [23].

- n=20: UACR ≥ 30 mg/g and eGFR < 60 ml/min/1.73m^2 (≥ CKD G3a/A2).
- n=20: UACR < 30 mg/g and eGFR ≥ 60 will be included (≤ CKD G2/A1).

A control group will consist of 20 healthy age- and sex-matched controls with no renal impairment (≤ CKD G2/A1: UACR < 30 mg/g and eGFR ≥ 60 ml /min).

Inclusion and exclusion criteria

Fabry cohort

Inclusion criteria

- Male and female individuals with a genetically-verified diagnosis of Fabry disease
- ≥ 18 years of age.

- Able to give informed consent

Exclusion criteria

- Any contraindication for magnetic resonance imaging according to standard checklist used in clinical routine, including claustrophobia or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MR compatible.
- Pregnancy

Control group

Inclusion criteria

- Male and female individuals (≥18 years of age)
- Able to give informed consent

Exclusion criteria

- A genetically-verified diagnosis of Fabry disease.
- Family member to a patient with a genetically-verified diagnosis of Fabry disease
- Cancer expected to influence life expectancy.
- Known heart failure, previous apoplexia or previously established kidney disease.
- Initiation or change of antihypertensive therapy within 3 months of enrolment
- Renal impairment as depicted by the CKD-EPI classification (≥ CKD G2/A1)
- Any contraindication for MRI according to standard checklist used in clinical routine, including claustrophobia or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MR compatible.
- Pregnancy

Endpoints

Primary endpoint

- A between-group difference in renal hypoxia (R*) evaluated by BOLD MRI when comparing the groups of patients with Fabry disease.

Secondary endpoints

- A between-group difference in renal hypoxia (R*) evaluated by BOLD MRI when comparing patients with Fabry disease irrespective of renal impairment with the control group.

- A between-group difference in perfusion of the renal cortex (mL/100g/min) when comparing patients with Fabry disease with the control group.
- A between-group difference in perfusion of the renal medulla (mL/100g/min) when comparing groups with Fabry disease patients with the control group.
- A between-group difference in renal blood flow (mL/min) when comparing groups with Fabry disease patients with the control group.
- A between-group difference in native T1 (ms) when comparing groups with Fabry disease patients with the control group.
- A between-group difference in diffusion-weigthed signaling when comparing groups with Fabry disease patients with the control group.

Procedures

Imaging procedure

MRI scanning of renal hemodynamics and oxygenation

The scanning protocol will consist of one scanning session (hereafter *RENOXY* scan) (Table 4). In brief, the RENOXY scan will consist of sequences of oxygenation (R2*-BOLD), perfusion (ASL), renal arterial flow (phase contrast), inflammation (T1), fibrosis (diffusion-weighted), preceded by a structural mapping sequence. In addition, a shorter version will be repeated during inhalation of 100% oxygen, including only structural mapping, BOLD, ASL and phase-contrast.

The entire session will last approximately 40-45 minutes (Table 1). If a participant is unable to endure the full scanning protocol a shortened version can be used. All scans will be performed on the same 3-T Philips Achieva.

Table 1: RENOXY scan

Procedures	Sequences	Time (app.)
Rest	30 minutes of rest prior to scanning sequence	
MRI session	- RENOXY scan - Hyperoxygenation scan	35 min 10 min

Clinical procedures

In addition to the imaging protocol, the participants will receive a full clinical work-up, fill out questionnaires in addition to blood and urine-sampling (Table 2).

Table 2: Clinical procedures	
Procedures	**Outcome**
Semi-structured interview	- Medical history, including concomitant chronic disease, current medication, and dietary supplements. - Alcohol, tobacco, and substance abuse - Socioeconomic status and educational background

Clinical examination	- Anthropomorphic measures (Age, height, weight, waist and hip circumference, body mass index [BMI, kg/m^2])
	- Office blood pressure and pulse
	- Electrocardiogram
	- Examination as specified in the
	  - Mainz Severity Score Index
	  - Fabry international prognostic index

Patient reported outcome	- ”Dit helbred og velbefindende” (SF-36®; *Quality of life*) -
Blood and urine samples	<u>Research Biobank focusing on</u> - Kidney function, inflammation, and fibrosis and cellular signaling in the kidney - Metabolic dysfunction - Risk markers of disease - Markers related to Fabry disease risk and progression <u>Establishing a biobank of future research</u> - Surplus biological material acquired will be kept in a biobank for future research. *See table 3 for overview of biomarkers*

Medical interview and clinical examination.

Participants will undergo a semi-structured interview to acquire relevant patient information such as, but no limited, to their previous medical history, established concomitant disease, current medication, their use of dietary supplements, their use of alcohol, tobacco and substance abuse, their socioeconomic, and educational background.

They will undergo a focused clinical examination acquiring basic anthropomorphic measures such as age, height, weight, hip- and waist circumference. Furthermore, the clinical examination will

consist of general health measures such as office blood pressure, pulse, electrocardiogram, and a physical examination specified to fulfill the elements of a modified Mainz Severity Score Index and the Fabry International Prognostic Index.

Patient reported outcome

Participants will be asked to answer health-related questionnaires and questionnaires regarding their current symptoms and their severity. These questionnaires are used and validated in Fabry disease and include:

- The SF36 Quality of Life-questionnaire

Blood and urine sampling

Participants will be required to undergo standard antecubital venipuncture to sample blood. The amount drawn will be 300 mL at the study visit. Regarding urine sampling, participants are to provide a first-voided, morning urine sample.

All samples, which are kept in the research biobank, are acquired and immediately frozen as aliquots and subsequently stored at -80 degrees (Celsius) until the end of the trial. The research biobank is to cease 6 months after last patient last visit; scheduled at 01.12.2025. At the day the research biobank ceases, the remaining material will be considered surplus and will be transferred to the biobank of future research. Regarding the research biobank, when performing the planned analysis, samples are to be thawed and analyzed in immediate succession, with repeat intra- and inter-assay analyses to determine and validate analysis-specific variation according to local laboratory standards. Postponing analysis until end of study is done to minimize time-dependent variation and is deemed necessary as part of trial conduct. Surplus material – both blood and urine – is stored and kept, comprising a biobank of future research. The biobank of future research is established and kept in accordance with the Danish laws on Data Protection and Data Security.

Biomarkers of interest to be analyzed on samples of blood or urine are specifically defined in protocol (table 3). Although all biomarkers are chosen due their prospective or established clinical value, further biomarkers may be necessary to be defined at a later date (e.g. omcis-based blood or urinary biomarker panel). If one or more biomarkers of interest are thought of post-hoc, a new informed consent is required. However, a relevant ethical committee can provide dispensation regarding renewed consent. . Separate consent forms will be signed in regard to the research biobank and the biobank of future research, respectively (SeeConsent forms).

Table 3: Pre-specified biomarkers in research biobank		
Sample	Biomarker	Volume
Blood	*Circulating biomarkers specific to Fabry's Disease* - α-gal A activity in leucocytes, Lyso-Gb3 and Gb3, and urine Gb3 *Kidney function, fibrosis and inflammation, and cellular signaling in the kidney* - Creatinine, GDF-15, TGF-β, FGF-21, and FGF-23, VEGF, collagens *Clinical biomarkers of metabolic dysfunction* - fasting plasma glucose, insulin, 3-OH-hydroxybutyrate, HbA1c, and lipid profile. *Biomarkers of cardiorenal risk* - *NT-proBNP, TnI, hsTnT, proANP, proCNP*	300 mL
Urine	*Urinary excretion* - urinary podocyte excretion, ACR	200 mL

Study visits

Participants eligible for inclusion in the study will be required to attend 1 study visit to participate in the study program. However, if the participant is unable to attend a full study visit at any one day, the scanning protocol can be performed on a separate day from the remaining procedures.

Statistical considerations

Justification of sample size

From our previous study, we found that the mean baseline R2* was 23 with (SD=4). A between-group difference in R2* of 2.0 units can be considered a clinically important difference [24]. In the cohort, a difference of 2.0 units, an SD of the difference of 2, 80% power, a type 1 error of 5%, and wanting to compare groups independently results in a need of randomizing 51 participants 1:1:1 – corresponding to 17 participants in each group. Accounting for incident claustrophobia causing an unexpected loss of data, we aim to include 20:20:20 participants (Fabry w/ renal impairment; Fabry w/o renal impairment; age- and sex-matched controls).

The current study is an observational cross-sectional study, and the power calculation is performed to investigate the relationship between the presence of renal impairment with the phenotypic presentation of Fabry nephropathy. As the current Danish National consists of 100 individuals, of which approximately 40% have a history albuminuria, a study size consisting of 40 patients with genitically-verified Fabry disease will be feasible in the current patient population.

Furthermore, a simultaneously included control cohort of 20 healthy age- and sex-matched control, will constitute a basis for an in-depth comparison on the clinical implication of biomarkers

not readily available as part of routine clinical screening and is considered necessary as part of study conduct.

Risks and discomforts

There can be unexpected risks and discomforts attributable to participation in the study, which cannot be predicted prior to trial conduct. The following will elaborate on known risks and discomforts.

Risks related to clinical procedures

Blood sampling

Venipuncture to acquire blood samples can be uncomfortable but is considered safe and performed as a routine procedure in standard medical practice. Although a small hematoma may occur, and a minimal risk of infection is present, proper technique will be applied to ensure a minimal level of risks. In comparison to blood donation, where 500 mL is drawn, the current study will require a sample of 300 mL and may induce slight, transient lightheadedness, but is otherwise not associated with any known risk.

Additional risks related to scanning procedures

Magnetic resonance imaging

MRI is considered safe and is not related to short- or long-term risk. If a participant becomes claustrophobic and wants to terminate an ongoing exam, the physician is obliged to do so. In relation to the scanning procedure, participants are required to breathe while inhaling 100% oxygen during imaging. This procedure is not associated with any known short-term or long-term risks or discomforts.

Studies have shown fetus heart rate increases while performing MRI scans. This change is interpreted as a sign of fetal stress, why pregnancy is a contraindication to trial participation.

Data protection of Personal Information in the Study

All legislations, regulations, and laws on Data Protection and Data Security and the directives of the Danish Protection Agency will be complied with during the conduct of the trial. Permission to handle personal data will be sought and approved by the Danish Data Protection Agency. All data are stored pseudo-anonymized and analyzed electronically and no unauthorized access to data is allowed.

Original data is filed according to a unique participant number. REDCap, hosted by OPEN (Open Patient data Explorative Network) will be used for registration of clinical data. REDCap meets the safety requirements set by the Danish Data Protection Agency for storage of person-sensitive data; prescribed medication, medical history, height, weight are examples of such data. Data will be encrypted and stored for 15 years in accordance with recommendations on data storage from the Danish Data Protection Agency and thereafter transferred to the Danish Data Archives.

The study is reported to the Danish Data Protection Agency in Region H and will be handled according to the regulations of the General Data Protection Regulation: GDPR: REGULATION (EU) 2016/679 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27th of April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC and the Act on Processing of Personal Data. Data is stored for 15 years.

Procedures for recruiting participants and informed consent

Initial contact

Fabry patients are recruited from the Department of Hormone and Metabolism, Copenhagen University Hospital, Rigshospialet. The department is assigned as the national center concerning the treatment and monitoring of patients with Fabry disease. Eligibility to participate is evaluated by the doctor or other personnel of the patient's usual care at a regularly scheduled outpatient visit. Eligibility is evaluated using a confirmed diagnosis of Fabry disease using the current clinical standard, UACR and eGFR, and these three parameters (i.e. the inclusion criteria) will be transferred to the project doctor – UACR and eGFR are key parameters of renal function for the inclusion to the project. Patients who fulfill the inclusion criteria and none of the exclusion criteria will be informed of the study by the personnel at the department involved in their usual care. By acceptance, they will receive a written patient information. If the patient favors contact initiated by an investigator from the study and provides oral consent, the patients contact information (name, email, phone number) will be forwarded to an investigator. The oral information for the study is then presented by a medical doctor, who is a member of the study group at the department, given in quiet surroundings. Individuals acting as controls in the study will be recruited from varies homepages (sundhed.dk, facebook, and forsoegspersonen.dk), where contact information on investigators can be found. The recruitment material will be reviewed and approved by the Ethics Committee prior to use. Potential participants can contact the Departments of Hormone and Metabolism, Copenhagen University Hospital, Rigshospitalet by email or telephone. Regarding advertisements on Facebook,

any advertisement/post will have its ability to be shared or write a comment to the advertisement/post disabled. In addition to the written information pertaining to the study, it will be accompanied by the brochure: "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt" (Your rights as a participant in medical research) and "Dit væv, din ret" (Your tissue, your right). If the individual accepts further information on the study, a meeting in a quiet, undisturbed room will be scheduled with one of the investigators, and the person will be informed of the right to have a bystander present at that moment. The patient will be offered at least 24 hours reflection period before signing the consent form. The informed consent to participate in the study gives the research responsible doctors, sponsor and their representatives, and potential control authorities access to the information on kidney function, and relevant medical information for the study from the patient's medical record.

Scheduled meeting

At the scheduled meeting, the individual will receive additional oral information, from an investigator, and it will be clarified whether the patient fulfill the general participation criteria. The patient will be informed about the terms and restrictions of the form of 'informed written consent'. The investigator will ensure that the patient is adequately informed about the study background and design both orally and in writing. It will be made clear that the patient can withdraw from the study at any time without repercussions.

Acquisition of informed consent

If the patient is interested in participating in the study after the initial information meeting and after the allotted deciding time, a meeting will be scheduled where oral and written informed consent will be obtained. After consent to participate in the study has been obtained, the first study visit will be scheduled. No study-related examinations will be conducted prior the acquisition of informed consent. Investigators will only access electronic hospital records to transfer or record information after acquisition of written informed consent.

Informed consent

The participant will be required to sign the individual forms of informed consent applicable.

<u>Consent regarding study participation</u>

The participant's consent includes the right to read and transfer information from electronical hospital records to RED-Cap by investigators. The data transferred include information such as medical history, blood and urine test results, prescribed and over-the-counter medication. Further,

the informed consent includes permission to establish a research biobank regarding the analyses of biomarkers specified in the protocol. In addition, consent gives direct access to electronic hospital records for the primary investigator, the sponsor or their representatives, as well as authorized auditors in order to retrieve the health-related information necessary to perform the study and to perform quality control and monitoring. The access to electronic hospital records gives access to information from previous clinical evaluations performed by doctors or other hospital staff in relation to hospitalizations or outpatient visits as well as previously performed diagnostic analysis (e.g. biochemical analysis of blood, urine or other tissue samples), image-based evaluations (e.g. by ultrasound, computer-tomography or magnetic resonance imaging), and previous and current use of prescribed medication. These sources of information are vital in order to acquire a sufficient image of the patient's current medical health status.

The informed consent will be valid for the duration of the study.

Consent regarding establishment of a biobank of future research

A separate form of informed consent gives permission of the establishment of a biobank of future research consisting of extra material, if any, acquired at the initial visit of the core program. The aim of the biobank for future research is to ensure the ability to answer contemporary research questions in a rapidly evolving field. Future analyses may therefore include, but not be limited to analyses of circulating levels of hormones, proteins, DNA-excerpts, not specified in the current protocol. Future analyses will be required to be approved by the regional ethics committee prior to analysis.

The informed consent will be valid for the duration of the study.

Time schedule

- Ethics committee approval 01.08.2023
- First patient first visit Q4, 2023
- Last patient last visit Q2, 2025
- Cessation of Research Biobank 01.12.2025
- End of data analysis and manuscript submission Q4, 2025

Data acquired is stored for 15 years after acquisition. The biobank of future research is created at the date of cessation of the research biobank.

Funding

The study will be funded by external independent private and public foundations. Any funding is deposited in a research account administered at Rigshospitalet, Copenhagen University Hospital -

Rigshospitalet, Denmark. None of the investigators or departments will have any financial gain from conducting the study. As funding is secured, the ethical committee (VEK) and the included patients will be informed, and the patient information will be accordingly updated to include the information on funding sources.

Patient insurance and reimbursement

The study is conducted at the Department of Hormone and Metabolism, Rigshospitalet and covered by the departments insurance. Participants in the trial are covered by the existing patient insurance (”Patienterstatningen”). The participants will not receive payment. If the study requires extra visits to the department, transportation cost will be covered according to the guidelines for voluntary research subject’s appendix 1 of the National Scientific Committee (NVK) . Furthermore, expenses as to their nutritional need during visits will be provided for.

Ethical considerations and clinical implications

The study will be conducted in accordance with the Helsinki II declaration, the regulations of the General Data Protection Regulation, and will follow the directives of the laws on Data Security (‘Datasikkerhed’) and on Data Protection (‘Databeskyttelsesloven’). The study will be approved by the Danish Data Protection Agency and the Regional Ethics Committee of Copenhagen Denmark. Furthermore, the trial will be conducted following the current clinical research standard. The study is to undergo independent monitoring ensuring trial conduct in accordance with the guidelines of Good Clinical Practice (GCP). By following GCP, it is ensured that the data collected is valid, complete, and well-documented. Anonymity of the participants is explicitly guaranteed.

Kidney disease is one of the complications with the greatest clinical impact in Fabry disease. Using a cutting-edge MRI-based approach, we will uncover and broaden the understanding of renal pathophysiology and its involvement in Fabry disease. All scheduled procedures, with the exception of the MRI scan, are a part of the current clinical observational program for patients with Fabry Disease at the Danish National Fabry Center. The addition of magnetic resonance imaging of the kidneys – the main focus of this trial – is considered a safe procedure and carries no additional risk. We believe the planned program will provide evidence of incremental value in a rare genetic disease associated with impairment of multiple organ systems, which progress faster, and leads to organ failure at an earlier age than seen in the general population. Therefore, we believe the current study will improve the diagnostic approach and the ability to detect patient in early stages of disease. Furthermore, we find that the potential therapeutic gain for the participants and future patients

outweigh the risks and discomforts of participating in the study, and therefore, we believe conducting the study is justified.

Dissemination of results

The investigators oblige themselves to publish all clinically relevant findings in peer-reviewed journals irrespective of their ability to achieve statistical significance – i.e. publishing all results irrespective of being positive, neutral, or negative. Results will be published following the International Committee of Medical Journal Editors (ICMJE) recommendations.

The investigators will present findings at national and international conferences with an aim to strengthen the current understanding of, to substantiate or challenge the current clinical approach to Fabry disease. Furthermore, the authors will disseminate the results of the overreaching aims among patients with Fabry disease through patient organizations on the national level.

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Overview of Appendix

- Informed consent form
    - Participation in study (Patient with Fabry)
    - Participation in study (Healthy control)
    - Biobank of future research
- Documentation of Primary
- Curriculum Vitae of Primary
- Participant information
- Information Pamphlets
    - “Forsøgspersonens rettigheder i et sundhedsvidenskabeligt forskningsprojekt”
    - “Dit væv, din ret”
- Questionnaires
    - SF-36 Quality of Life questionnaire