Facioscapulohumeral muscular dystrophy (FSHD): Advanced diagnostics and extended molecular insights

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To determine whether DUX4 can be detected in epithelial or stem cells isolated from midstream urine and/or buccal brush biopsies and/or skin punch biopsies of FSHD patients. Hereby we will assess whether any of these biomaterials can be used as an...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON46477

Source
ToetsingOnline

Brief title
Advanced FSHD diagnostics

Condition

- Muscle disorders

Synonym
Facioscapulohumeral muscular dystrophy, FSH, FSHD, Landouzy-Dejerine myopathy

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Spieren voor spieren

Intervention

Keyword: Biomarkers, Diagnostic, DUX4, FSHD

Outcome measures

Primary outcome

-To assess whether DUX4 detection in urine-derived (epithelial, stem and myogenic) cells can be used as a diagnostic marker for FSHD;

-To assess whether DUX4 detection in (cells derived from) skin biopsies or buccal brush biopsies can be used as a diagnostic marker for FSHD;

-To generate (induced pluripotent) stem cell and epithelial cell cultures of FSHD patients, healthy individuals, and patients with an unrelated neuromuscular disease

-To identify novel biomarkers for FSHD severity in plasma from FSHD patients, healthy individuals, and patients with an unrelated neuromuscular disease.

Secondary outcome

- To determine whether DUX4 and DUX4 target genes (i.e. genes regulated by DUX4) are significantly higher expressed in urine-derived stem cells of FSHD patients, thus prior to differentiation to myogenic cells, compared to controls;

- To determine whether DUX4 and DUX4 target genes are significantly higher expressed in urine-derived epithelial cells of FSHD patients;

- To determine whether DUX4 and DUX4 target genes are significantly higher expressed in urine-derived cells of FSHD patients compared to controls after myogenic differentiation;

- To determine whether DUX4 and DUX4 target genes are significantly higher expressed in skin and epithelial cells from skin of FSHD patients compared to

controls;

- To determine whether DUX4 and DUX4 target genes are significantly higher expressed in cells derived from buccal brush biopsies of FSHD patients compared to control individuals;

-To correlate DUX4 transcript levels in cells derived from urine, skin punch biopsies, or buccal brush biopsies to the clinical severity score and results from manual muscle testing

-To correlate DUX4 transcript levels in cells derived from urine, skin punch biopsies, or buccal brush biopsies to D4Z4 sizing and D4Z4 methylation levels;

- To correlate DUX4 transcript levels in cells derived from urine, skin punch biopsies, or buccal brush biopsies to cytokine levels in plasma

- To assess the (epi)genetic regulation of DUX4 during development by differentiation of iPS cells into meso-, endo- and ectoderm cell types, or tissue specific cell lineages;

- To perform (single cell) RNA sequencing analysis on RNA isolated from cells derived from urine, blood, skin punch biopsies, or buccal brush biopsies of FSHD patients, and compare these results with already available RNA sequencing data obtained from RNA isolated from myoblasts or muscle biopsies of FSHD patients.

Study description

Background summary

Facioscapulohumeral muscular dystrophy (FSHD) is an inherited dystrophic myopathy characterized by progressive and irreversible weakness, mostly

beginning in the facial, shoulder and upper arm muscles. There is no cure for FSHD and treatment options are limited. FSHD is caused by contraction of the D4Z4 repeat (FSHD1), or by mutations in SMCHD1 or DNMT3B (FSHD2), both resulting in D4Z4 chromatin relaxation and leading to the misexpression of the transcription factor DUX4 in muscle. Due to the complex genetic mechanism, FSHD genetic testing is cumbersome and currently not amenable to current routine (for example, next generation sequencing) technologies. Recent studies show that it is possible to isolate epithelial and stem cells from midstream urine and that these cells, directly, or after transdifferentiation into myogenic cells, can be used for the diagnosis of a number of limb girdle muscular dystrophies. FSHD has not yet been tested, but DUX4 detection in cells from urine could provide an appealing alternative for FSHD diagnostics. In addition, our FSHD mouse models reveal relatively high DUX4 levels in the epidermal layer of the skin (epithelial cells; likely keratinocytes), and preliminary studies suggest that this expression pattern reflects that of FSHD patients. To simplify diagnosis and because of the limited invasiveness, we therefore propose to assess whether epithelial or stem cells from urine, buccal brush biopsies or skin punch biopsies can be used as an alternative for FSHD diagnosis. In addition to serving a diagnostic purpose, identification of novel stem or somatic cell populations expressing DUX4 (without apparent detrimental effect as seen in muscle) will provide a novel source of cells that can help us to understand the basic pathological mechanism of FSHD. Furthermore, detection of DUX4 (and detection of the target genes DUX4 regulates) in any of these tissues may also serve as a biomarker for disease severity or in upcoming clinical trials with drugs that aim to suppress DUX4. Next to DUX4, cytokines may serve as biomarkers for FSHD development and progression, as an increasing number of studies point towards a role for the immune system in FSHD pathogenesis. Therefore, we also propose to measure cytokine levels in blood samples from FSHD patients, healthy individuals, and patients with an unrelated neuromuscular disease with the goal to identify novel biomarkers that can be used for natural history studies and future clinical trials.

Study objective

To determine whether DUX4 can be detected in epithelial or stem cells isolated from midstream urine and/or buccal brush biopsies and/or skin punch biopsies of FSHD patients. Hereby we will assess whether any of these biomaterials can be used as an attractive alternative for FSHD diagnosis. The secondary objectives are to investigate the role and regulation of DUX4 in these cell populations in order to get a better understanding of the pathological mechanisms underlying FSHD, and to identify novel biomarkers for FSHD development and severity.

Study design

Exploratory, case-control observational study

Study burden and risks

As stated in the introduction, FSHD is an irreversible and disabling disease which leads to functional impairment. Genetic testing is cumbersome and diagnosis of FSHD subtypes (FSHD1, FSHD2) requires different testing methods. DUX4 detection in either urine, skin punch biopsies, or buccal brush biopsies offer attractive new diagnosis methods. The generation of cellular models, like iPS cells, will lead to more insight in the disease mechanism and facilitate pre-clinical therapeutic tests. Finally, the identification of cytokines that may serve as biomarkers for development and progression of the disease is important for natural history studies and future clinical trials.
Considering the suffering of patients with FSHD, the burden of participants is relatively small and this study can be classified as a study with a negligible risk. One visit to the LUMC Leiden is required. For collection of blood (DNA, RNA and plasma), blood samples will be taken through venepuncture, a procedure with only minor risks. At the site of injection, some redness and swelling may appear and the individual might experience malaise. For collection of urine, participants will be asked to collect their urine in a special container. A skin punch biopsy will be performed, which is minimally invasive and carries the risk of hematoma and/or local hypoesthesia. Furthermore, a buccal brush biopsy will be obtained. Participants are given the opportunity to object against taking a skin punch biopsy or a buccal brush biopsy.

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

1.FSHD patients:
- 18 years or older
- Genetically proven FSHD or;
- Clinical FSHD diagnosis and permission for genetic testing to confirm the diagnosis;2. Healthy volunteers
- 18 years or older;3. Patients with an unrelated neuromuscular disease
- 18 years or older
- Confirmed neuromuscular disease, like Inclusion Body Myositis (IBM), Ocular pharyngeal muscular dystrophy (OPMD), Myasthenia Gravis (MG) and Lambert Eaton Myasthenic Syndrome (LEMS)

Exclusion criteria

Healthy volunteers: In order to be eligible to participate in this study, a healthy control must not have:
- A muscle disorder
- A neurological disorder
- A history of a urinary tract disorder interfering with urine sample acquisition

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2019
Enrollment:	200
Type:	Actual

Ethics review

Approved WMO

Date:	03-01-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL63765.058.18

Study results