Assess the mtDNA mutation load in mesoangioblasts of mtDNA mutation carriers

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The primary objectives of this project are to assess the mtDNA mutation load in carriers of a mtDNA mutation and identify patients and/or mutations with no/low mtDNA mutation load in mesoangioblasts. Secondary objectives aim at determining the...

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

Summary

ID

NL-OMON49928

Source
ToetsingOnline

Brief title
mtDNA mutation load analysis MABs

Condition

- Muscle disorders

Synonym
mitochondrial muscle disease, mitochondrial myopathy

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: Interreg EMR

Intervention

Keyword: mesoangioblasts, mitochondrial myopathy, mtDNA

Outcome measures

Primary outcome

Assess the mtDNA mutation load in skeletal muscle derived mesoangioblasts

Secondary outcome

- Assess mtDNA copy number and OXPHOS capacity in mesoangioblasts

- Assess proliferation capacity of mesoangioblasts

- Assess myogenic differentiation capacity of mesoangioblasts

- Assess mtDNA mutation load in satellite cells

- Assess inflammation status mtDNA mutation carriers (TNFa, CK, IL6 blood)

Study description

Background summary

Mitochondrial diseases caused by defects in oxidative phosphorylation (OXPHOS) due to heteroplasmic mitochondrial DNA (mtDNA) mutations are rare (frequency 1/5,000), but severe multisystem disorders. Clinical manifestations are highly variable, but predominantly affect energy demanding tissues, like brain and muscle. Myopathy is a common feature of mtDNA disorders, being present in more than 50% of the mtDNA mutation carriers, and seriously affects patients* general well-being and quality of life. Currently, no treatment is available for these patients, although the induction of muscle regeneration by exercise treatment has been shown to alleviate the myopathy in patients. This implies that the patients can produce muscle fibres, which perform better, most likely because the mutation load is lower. Mesoangioblasts are myogenic precursors that have been recognized as a source for development of a systemic myogenic stem-cell therapy, and allogeneic transplantation has been successfully applied to mice and dogs with Duchene muscular dystrophy, followed by an ongoing trial in affected boys. For mtDNA mutation carriers, autologous stem-cell therapy could be feasible to treat myopathy, as our previous study of 25 carriers of 6 different mtDNA mutations demonstrated that the mtDNA mutation was (nearly) absent (<10%) in mesoangioblasts of nearly half of the mtDNA mutation carriers.

However, there are many more mtDNA mutations in the 16.5kb mtDNA that cause myopathy and the aim of this project is to determine the mtDNA mutation load in mesoangioblasts of other mtDNA mutation carriers and identify the patients or mutations for which this is a feasible approach.

Study objective

The primary objectives of this project are to assess the mtDNA mutation load in carriers of a mtDNA mutation and identify patients and/or mutations with no/low mtDNA mutation load in mesoangioblasts. Secondary objectives aim at determining the proliferation, myogenic differ-entiation and OXPHOS capacity of mesoangioblasts and systemic inflammation status.

Study design

Mono-centre observation study

Study burden and risks

All participants will visit the Maastricht UMC one time. At this visit, a blood sample (~20ml) and a skeletal muscle sample (~30 mg) will be collected. With respect to burden and risk associated with participation, in total 1 venous blood sample and 1 vastus lateralis/biceps brachii skeletal muscle sample will be collected. Blood collections are routinely performed in the clinic. Muscle biopsies can be painful in some cases. Infections and bleeding afterwards are possible, but rare. To minimize patient burden, muscle biopsies will be collected using the Pro-Mag I / Mission core 14G automatic biopsy instrument, which is a fast and routinely used procedure at the Maastricht UMC to harvest a small muscle fragment with patient burden being limited to the time of the procedure (anecdotes multiple patients).

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

- Written informed consent
- Age: 18+
- Sex: male/female
- Carriers of a heteroplasmic mtDNA mutation load >1% in blood or >20% in muscle

Exclusion criteria

- No informed consent
- Use of anti-coagulants, anti-thrombotics and other medication influencing coagulation
- Have a weekly alcohol intake of >= 35 units (men) or >= 24 units (women)
- Current history of drug abuse
- A history of strokes
- Significant concurrent illness
- Ongoing participation in other clinical trials that contain an intervention
- Major surgery within 4 weeks of the visit
- Pregnant or lactating women
- Patients unable and/or unwilling to comply with treatment and study instructions
- Any other factor that in the opinion of the investigator excludes the patient from the study

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-12-2022
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	24-12-2021
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	03-09-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL78411.068.21
Other	nog niet bekend