The function of DUX4 in the thymus

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

Summary

ID

NL-OMON48252

Source
ToetsingOnline

Brief title
DUX4 in the thymus

Condition

- Muscle disorders

Synonym
Facioscapulohumerale dystrofie, FSHD, Landouzy-Dejerine disease

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Prinses Beatrix Spierfonds en Marie Curie Individual Fellowship

Intervention

Keyword: DUX4, FSHD, neuromuscular disorder, Thymus

Outcome measures

Primary outcome

To detect germline and skeletal muscle DUX4 transcripts and DUX4 protein in

thymic tissue of control individuals.

Secondary outcome

• To identify which cell types in the thymus express DUX4.

• To determine the functional consequences of DUX4 expression in the thymus.

• To study downstream targets of DUX4 or related neuromuscular proteins for

their expression and function in the thymus.

Study description

Background summary

Facioscapulohumeral muscular dystrophy (FSHD) is an inherited myopathy characterized by progressive and irreversible weakness, mostly starting in the facial, shoulder, and upper arm muscles. FSHD is caused by misexpression of the cleavage stage transcription factor DUX4 in skeletal muscles. DUX4 expression is pathogenic for skeletal muscles, therefore several research groups are focusing on reducing DUX4 expression as a therapeutic strategy for FSHD. DUX4 expression is currently considered to be limited to the luminal cells of the testis and to cleavage stage embryos. However, a recent paper showed DUX4 expression in the thymus of a control individual, suggesting a function for DUX4 in thymic cells. It is important to know the function of DUX4 outside the germline since therapeutic strategies that block DUX4 may disturb this function. We therefore propose to establish the function of DUX4 in the thymus.

Study objective

The main goal of our study is to determine the function of DUX4 in the human thymus by obtaining residual tissue from inevitable (incomplete) thymectomies during open heart surgery in infants. Our primary objective is to detect germline and skeletal muscle DUX4 transcripts in the thymus. Our secondary objectives are to establish which cells in the thymus express DUX4 and to determine which genes are silenced or activated upon DUX4 expression in the

thymus. Besides DUX4 expression, we will measure the expression of other thymic genes that are related to FSHD but also to other skeletal muscle disorders. Studying genes involved in skeletal muscle disorders will give us more knowledge about the disease mechanisms involved in different skeletal muscle disorders and will determine whether the thymus has a more general function in skeletal muscle pathology.

Study design

This is an explorative, observational study on residual thymic tissue obtained from standard care operative procedures in children < 3 years undergoing open heart surgery for the first time. Thymic tissue will be collected perioperatively and immediately processed. We expect to complete this study within 3 years after start of inclusion.

Study burden and risks

As thymic tissue is removed during a first open heart surgery in infants < 3 years in a clinical care setting and is considered waste material, we do not expect additional burden and/or risk for the study population. In conclusion, we believe that the burden is minimal and in proportion to the potential value of this study for other patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

• Able to give informed consent in writing, signed by the parent(s) or legal guardian.
• Child <3 years planned for first-time elective open heart surgery.

Exclusion criteria

• Children suffering from (auto)immune*mediated inflammatory disorders.
• Children with a positive family history of a skeletal muscle disorder.
• Children of 3 years and older
• Children who have had open heart surgery previously
• Non-elective open heart surgery

Study design

Design

Study type: Observational non invasive

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2019
Enrollment:	24

Type:	Anticipated

Ethics review

Approved WMO Date:	21-11-2019
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	NL70879.058.19