Genetic analysis of Café-au-Lait skin cells and their potential to develop into FD/MAS affected bones

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Objectives: (1) To find out in which skin layer (epidermis or dermis) and which skin cell type the Gs* mutation resides.(2) To determine osteogenic transdifferentiation- and mineralization characteristics of osteogenic cells that result from...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Musculoskeletal and connective tissue disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON49146

Source
ToetsingOnline

Brief title
A human bone model of FD/MAS from skin biopsies

Condition

- Musculoskeletal and connective tissue disorders congenital

Synonym
Fibrous Dysplasia (FD), McCune-Albright Syndrome (MAS)

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Fibrous Dysplasia, McCune-Albright Syndrome, osteoblastic transdifferentiation, post-zygotic GNAS mutation

Outcome measures

Primary outcome

The primary outcome of this study is the identification of the GNAS gene

mutation in epidermal and/or dermal cells from hyperpigmented skin (*Café

region*), non-hyperpigmented skin (*Lait region*) and from birthmarks, all

donated by FD/MAS patients.

Secondary outcome

The secondary outcome consists of the osteogenic transdifferentiation potential

and the functional characteristics of these osteogenic cells.

Study description

Background summary

Fibrous Dysplasia (FD) is a rare bone disease, characterized by a mutated G-protein alpha subunit (GNAS) gene. This mutation leads to abnormal bone matrix synthesis and thus to fibro-osseous bone lesions. Café-au-Lait skin macules are characteristic for patients with the McCune-Albright Syndrome, a variant of FD (FD/MAS). Patients with FD/MAS can experience intense pain and encounter a high risk of bone fractures and bone deformities during their whole life. On top of this, hyperfunctional endocrinopathies reduce their quality of life as well. To date, no cure exists.
Relatively little research has been conducted on this disease because of the invasiveness of bone biopsies, the risk of further expansion of the lesion after taking the biopsy, and the low number of patients. However, Micha et al. (2016) have recently shown the suitability of fibroblasts from skin biopsies to study aberrant bone formation in patients with Fibrodysplasia Ossificans Progressiva (FOP), another rare bone disease. To accomplish this, they transdifferentiated these fibroblasts towards the osteogenic lineage. We hypothesize that the same approach using skin biopsies from *Café* spots (hyperpigmented skin), control sites, i.e. *Lait* spots (non-hyperpigmented

skin) and those from birthmarks of FD/MAS patients (outside the Café spots) will allow us to study abnormal bone formation of FD/MAS patients.
Three 4 mm diameter skin biopsies (see above) per FD/MAS patient will be taken. The intended goal is to recruit five participants within three months. The Fibrous Dysplasia association, with whom the VUmc has close contact, will be asked to help in the recruitment. Recruitment will be done via the Amsterdam University Medical Centers, location VUmc, expertise center in rare bone diseases. The epidermal layer and dermis will be separated and studied for the presence of the GNAS mutation. Subsequently, osteogenic transdifferentiation possibilities of the cultured cells will be evaluated. To identify how FD/MAS affects osteoblastic differentiation, the functionality of the osteogenic cells resulting from transdifferentation will be compared between the three skin biopsy groups (*Café* region, *Lait* region and birthmark).

Study objective

Objectives:
(1) To find out in which skin layer (epidermis or dermis) and which skin cell type the Gs* mutation resides.
(2) To determine osteogenic transdifferentiation- and mineralization characteristics of osteogenic cells that result from transdifferentiated skin cells.
And to identify whether there is a link between pigmentation and the outcome of (the functionality of) osteogenic transdifferentation of skin cells.

Study design

Single center, non-randomized, analytical observational, cross-sectional pilot study

Study burden and risks

Participating patients will visit the hospital for skin biopsies. Patients may experience some pain after the skin biopsy. A pain reliever such as paracetamol (acetaminophen) can reduce pain. Sometimes a bruise develops. A minimal chance of infection is present. Small scars can form on the sites of biopsy collection. Participants are not restricted during their normal daily activities after the biopsy is taken. Our risk assessment is: low risk.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients who have been diagnosed with Mc-Cune Albright Syndrome (MAS) and are aged between 16 and 70.

Exclusion criteria

- Mentally incapable
- Hospitalized
- Using anticoagulants
- Coagulation disorder
- Viral infection
- Sudden health problems
- All Café-au-Lait skin macules have been treated with laser therapy
- Currently participating in another study parallel to this study
- Allergies for components of local anaesthesia

- Topical corticosteroids used less than two weeks prior to skin biopsies

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:	Recruiting
Start date (anticipated):	14-06-2021
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	18-12-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL71441.029.20