Rubinstein-Taybi syndrome and keloids

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON38183

Source
ToetsingOnline

Brief title
Rubinstein-Taybi syndrome and keloids

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Epidermal and dermal conditions

Synonym
itching scar, keloid

Research involving
Human

Sponsors and support

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

Intervention

Keyword: itching, Keloid, Rubinstein-Taybi syndrome, therapy

Outcome measures

Primary outcome

The clinical characteristics of keloids

The histological characteristics of keloids

The moleculair and cell-biological characteristics of keloids in RTS, mainly

the TGF beta pathway and HAT function

Secondary outcome

Not applicable

Study description

Background summary

Rubinstein-Taybi syndrome (RTS) is a multiple congenital anomalies-intellectual disability syndrome, caused by mutations in CREBBP or its homologue EP300. One of the complications in RTS is keloid formation occurring in 25-30% of individuals. Keloids are proliferative fibrous growths resulting from excessive tissue response to skin trauma. In RTS minimal or unrecognizable skin injuries can cause massive keloid formation, thereby affecting quality of life in RTS significantly due to their extensive itching.

Study objective

The present proposal aims at detecting the pathogenesis of keloids in RTS by studying 50 RTS individuals from 3 countries (Netherlands, Norway, UK) with keloids clinically, and take 3 biopsies in 5 of them from normal skin, edge of normal skin-keloid and keloid. Molecular studies (transcriptome analysis; HAT activity) and cell biological functions (TGFß-signalling pathway; expression studies) will be performed in frozen biopsies and cultured cells. Depending results a topical medication will be chosen and prepared for a future trial.

Study design

Comprehensive literature review
a. RTS
b. Keloids

c. Keloids in RTS
d. Keloids in RTS and itching

Clinical studies
1:. All RTS individuals known to support groups in the Netherlands, Norway and UK will be invited to participate through their national support groups (all support groups have agreed to do so).
2. Parents/other legal representatives of RTS individuals with keloids can indicate their willingness to participate at a dedicated e-mail address.
3. Check if mutation is known in RTS individual (studied in about 3/4 of individuals); if not this will be offered for free during attendance of the clinic. The clinical diagnosis in all members of the support groups of the three countries is already confirmed by one of us (RCMH).
4. All will be invited to visit a clinic (one in each country). Families are again informed in detail about the study, offered the opportunity to ask questions, and asked to sign the consent form.
5. The clinical history will be obtained using 3 validated questionnaires forwarded to participating families in advance (RTS; keloid; itching. See Appendices 1-3). Results will be discussed during the clinic, and additional questions asked in case of ambiguities.
6. Physical exam will be performed standardized using the Patient and Observer Scar Assessment Scale (van de Kar 2005). Three dimensions of keloids will be measured with a ruler. Standardized photographs will be taken of chest, shoulders and back. 10cc venoud blood will be drawn for itching parameters.
7. Biopsies (2mm) will be performed in 5 RTS individuals from 3 sites: healthy skin; active edge between keloid and healthy skin; keloid. The sites will be discussed in advance between the physician and RTS individual/family. All biopsies will be taken during anaesthesia needed for other reasons. Biopsies will be stored using HAM F10 or similar medium and forwarded to the lab within 24 hours. Photographs will be taken just before and after biopsying of the biopsy site. Follow-up will be offered to all 5 biopsied RTS individuals after 6 and 12 months, to check for new keloid formation which will be measured and photographed.

Molecular studies
a. Part of the biopsy material will be used for fibroblast cultures using standard protocols.
b. Other parts of the biopsies will be frozen to allow for mRNA and protein expression studies at the particular part of the skin (normal; edge normal skin-keloid; keloid).This will be done at T0, and after 1, 3 and 6 passages of fibroblast cultures.
c. Expression studies of CREBBP and EP300 in the frozen biopsies using quantitative PCR.
d. Transcriptome analysis in both cultured cells and frozen biopsies at mRNA using deep sequencing (Illumina/Solexa). Data analysis, involving fold-change calculations, standard statistical tests, including ANOVA analyses, and clustering will be performed. Analysis of the function of differentially

regulated gene sets will use both Bioconductor and in-house software that queries the Gene Ontology databases and assesses whether deregulated genes are over-represented in these pathways. Data will also be compared with previously established transcriptome sets in Growth factor stimulated T98G cells.
e. HAT function: we are presently testing which technique functions best to test this in CREBBP: a filter-binding assay measuring the transfer of radiolabeled acetate from acetyl-CoA to protein, or spectroscopic enzyme-coupled assays linking the HAT reaction to reduction of NAD+ by pyruvate or alpha-ketoglutarate dehydrogenase. Both techniques have specific characteristics (Berndsen et al 2005) and in a presently running pre-study we will determine which functions best for the present aims.
f. TGFß-signaling will be studied in cultured cells and frozen biopsies by analysis of nuclear localization of P-SMAD2 by immuno-fluorescence on cells or by immunohistochemistry. Also expression levels of TGFß, TFGBR (Alk5), P-Smad2 and expression of SMAD2 target genes (fibronectin, collagen type I, plasminogen activator inhibitor 1 and matrix metalloproteinase-2) will be studied by Western blotting and/or quantitative PCR.

Study burden and risks

Burden:
The patient will be asked to complete 3 questionnaires. A physical exam will be performed and the POSAS (Patient and Observer Scar Assessment Scale) will be completed. Three dimensions of keloids will be measured with a ruler. Standardized photographs will be taken of chest, shoulders and back. 10cc of peripheral blood will be taken for itching parameters. Biopsies (2 mm) will be performed in 5 RTS individuals from 3 sites: healthy skin, active edge between keloid and healthy skin, keloid. The sites will be discussed in advance between the physician and RTS individual/ family. All biopsies will be taken during anaesthesia needed for other reasons.

Risks:
The small biopsy wound taken from normal skin is unlikely to develop into a keloid scar as it will be taken from an area not known to develop keloids (i.e. lower limbs). The biopsies taken in the middle from the keloid will not cause an increase of the keloid. Only the biopsy taken from the edge normal skin-keloid might well cause an increase in size of the keloid of about 2mm. As especially a biopsy from this site is essential for the study and the extension of the already existing keloid is limited we think this is acceptable.

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

Patients with the Rubinstein Taybi syndrome
Patients with keloids
Age 18 years or above
Written informed consent
For the biopsy study: the patient needs general anaesthesia for a planned intervention for patient care reasons

Exclusion criteria

Insufficient understanding of the purpose of the study by parents / other legal representative
Age < 18 years

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-04-2012
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	10-01-2012
Application type:	First submission
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	NL33011.018.11