New syndromes in old genes; phenotypes caused by CREBBP and EP300 mutations but not resembling Rubinstein-Taybi syndrome

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To gain insight into the biological pathways that are influenced by the CEEx30/31 mutations.

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

Summary

ID

NL-OMON46364

Source
ToetsingOnline

Brief title
CEEx study

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
at the end of exon 30 or beginning of exon 31), intellectual disability due to mutations in CEEx30/31 (CREBBP or EP300

Research involving
Human

Sponsors and support

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

Intervention

Keyword: CREBBP, EP300, Genotype-phenotype correlation, Intellectual disability

Outcome measures

Primary outcome

We will compare the effects of the variants in CEEx30/31 with those of RSTS patients (CREBBP loss-of-function), patients with a duplication of CREBBP (CREBBP gain-of-function), and healthy controls on i) gene expression by RNA-Seq, ii) activity of DNA segments by ATAC-Seq, and iii) protein interactions with DNA using ChIP-seq.

Secondary outcome

n.a.

Study description

Background summary

We recently evaluated twenty-four patients with intellectual disability who had a mutation in CREBBP or EP300. Although mutations in these genes usually cause Rubinstein-Taybi syndrome (RSTS), the typical signs of RSTS, consisting of specific facial features, broad thumbs and broad big toes were absent, implying that the patients had different, previously unknown syndromes. All patients had a mutation in exon 30 or 31 of CREBBP/EP300 (*CEEx30/31*), a region in which, thus far, no mutations had been found in patients with RSTS.
Interestingly, the facial characteristics of patients with mutations at the 3* end of the CEEx30/31 region resembled those of patients with a duplication of CREBBP. Therefore, the mutations may result in a gain-of-function, in contrast to the loss-of-function that causes RSTS. The characteristics of patients with mutations at the 5* end of the CEEx30/31 region did not resemble one-another markedly. We therefore hypothesize that these mutations perturb other of the numerous functions of CREBBP/EP300 (both important cofactors of transcription).

Study objective

To gain insight into the biological pathways that are influenced by the

CEEx30/31 mutations.

Study design

Observational study with invasive measurements

Study burden and risks

The risk and burden associated with a single skin biopsy are negligible, especially when taken during surgery using the surgical incision that already needs to be made for clinical care reasons.

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)
Children (2-11 years)

Elderly (65 years and older)

Inclusion criteria

1. Individuals with either a) a mutation in CEEx30/31, b) RSTS, c) a dup 16p13.3, d) a dup 22q13.2, and e) healthy age-, and sex-matched controls.
2. availability of stored fibroblasts or a planned surgical intervention for patient care reasons
3. Patients and/or parent(s)/caregiver(s)/legal representatives able to provide written permission

Exclusion criteria

none

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-08-2018
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO

Date:	10-08-2018
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	NL65113.018.18