Explaining the Down syndrome specific thyroid phenotype by epigenetics

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To provide further evidence for the role of long-term epigenetic effects of an extra chromosome 21 on HPT-axis associated genes as an explanation of DS associated thyroid phenotype, in a series of DS individuals in whom data on thyroid functioning...

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

Summary

ID

NL-OMON46203

Source
ToetsingOnline

Brief title
The Down syndrome thyroid phenotype and epigenetics

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Thyroid gland disorders

Synonym
Thyroid disorders in Down syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Down syndrome, Epigenetics, Thyroid

Outcome measures

Primary outcome

DNA methylation differences of HPT-axis associated genes in DS children with the most severe thyroid phenotype compared to those with the mildest thyroid phenotype.

Secondary outcome

Thyroid function tests (TSH, free T4, anti-TPO):

Data on thyroid function are available from the neonatal age up to 10 years. Although we do not expect the severity of the initial thyroid phenotype to have changed it is important to verify the initial thyroid phenotype with a recent measurement of thyroid function. It is also important to identify patients who may have developed autoimmune thyroiditis (anti-TPO positivity) since the age of 10 years because these patients would have to be excluded.

Study description

Background summary

Down syndrome (DS) is characterized by an extra chromosome 21 and is associated with various congenital malformations. DS is also associated with a specific thyroid phenotype characterised by mild plasma TSH elevation and slightly lower T4 concentrations. The reason for this different set of thyroid values in DS is unknown and whether or not this needs treatment remains a matter of debate. Previous studies have provided evidence that the extra chromosome 21 in trisomy 21 has epigenetic effects on loci outside this chromosome that are relevant to DS associated phenotypes. We hypothesize that the Down syndrome associated thyroid phenotype may be the result of the epigenetic effect of an extra chromosome 21 on genes associated with the hypothalamic-pituitary-thyroid

(HPT)-axis set point. In a recent (as yet unpublished) study we analysed DNA methylation patterns of 179 HPT-axis associated genes in 10 neonates with DS and found 151 genes to be significantly differently methylated compared to 10 controls. Data om thyroid phenotype were not available in this study (protocol 2015_211).

Study objective

To provide further evidence for the role of long-term epigenetic effects of an extra chromosome 21 on HPT-axis associated genes as an explanation of DS associated thyroid phenotype, in a series of DS individuals in whom data on thyroid functioning at birth are available.

Study design

Observational study with invasive measurements

Study burden and risks

The burden is limited to a single visit to the AMC and a single blood sampling (12 ml). The risks of this study are minimal for the participants and consists of possible hematoma.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)

Inclusion criteria

Between 1999 and 2001, a randomized clinical trial (RCT) was conducted at our centre in a cohort of Down syndrome infants to study the effects of thyroxin treatment versus placebo on psychomotor development. A follow-up study was performed in 2012 (at age 10.7 years). Since this is a cohort of children with Down syndrome that has been extensively phenotypically characterised including data on thyroid function, they provide an excellent opportunity to compare long-term effects.
For the purpose of this study only children from the placebo group will be included, and only in the group not on thyroid hormone treatment and without evidence of thyroid autoimmunity, to avoid influences of treatment and additional morbidity on the methylation pattern. Permission for re-contacting has been obtained in the past.

Exclusion criteria

Children from the treatment group in the original trial. Children currently on thyroid hormone treatment. Children with signs of thyroid autoimmunity.

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):	05-04-2016
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	08-01-2016
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	NL55622.018.15