Do mutations in the TBL1X gene alter sensitivity to thyroid hormone?

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To determine the effect of mutations in the TBL1X gene on TH dependent signalling in liver cells generated from iPSCs.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Endocrine disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON45797

Source
ToetsingOnline

Brief title
Mutations inTBL1X and sensitivity to thyroid hormone

Condition

- Endocrine disorders congenital

Synonym
Isolated central hypothyroidism; low thyroid hormone production caused by insufficient stimulation of the thyroid by the pituitary gland

Research involving
Human

Sponsors and support

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

Intervention

Keyword: TBL1X gene, Thyroid hormone

Outcome measures

Primary outcome

TH dependent signalling in hepatocytes carrying a mutation in the TBL1X gene.

Secondary outcome

Not applicable.

Study description

Background summary

Congenital central hypothyroidism is characterized by insufficient production of thyroid hormone (TH) due to inadequate stimulation by thyroid stimulating hormone (TSH) of an otherwise normal thyroid gland. Central hypothyroidism occurs either isolated, or in combination with other pituitary hormone deficiencies. Well-known genetic causes of isolated central hypothyroidism include mutations in the TSHB, TRHR and IGSF1 genes.

Using X-exome sequencing in three related patients with isolated central hypothyroidism, a novel mutation was identified in the Transducin *-like Protein 1, X-linked (TBL1X) gene.

Plasma TH concentrations are continuously monitored and regulated by the hypothalamic-pituitary-thyroid (HPT) axis, a multi-loop feedback system. Production of TH is stimulated by TSH from the pituitary, which - in turn - is stimulated by thyrotropin releasing hormone (TRH) from the hypothalamus. TRH and TSH are both suppressed by the active form of TH, triiodothyronine (T3), via so-called *negative regulation'. In this regulation, T3 suppresses hormone production by inhibiting transcription of the TRH and TSH encoding genes.

Corepressors (CoRs) and coactivators (CoAs) serve as coregulatory factors in T3-negative regulation for both gene transcription silencing and activation. The TBL1X product, TBL1, is an essential core subunit of the main CoRs in this pathway. TBL1 stabilises the binding of CoRs to the DNA for adequate transcriptional modification. Additionally, TBL1 mediates the dismissal of CoRs and recruitment of CoAs in the presence of T3. In genes negatively regulated by T3, including TSHB and TRH, CoRs are critical in activation of gene

transcription in absence of T3. The mechanism of this pathway, and the role of TBL1 herein, is still unknown.

In addition to the three above-mentioned patients, we found TBL1X mutations in six other patients with isolated central hypothyroidism from five families. The phenotype of these patients and several mutation carrying relatives with normal thyroid function has been extensively evaluated. Besides isolated central hypothyroidism, 11 of 16 mutation carriers were found to have mild high frequency hearing loss.

Central hypothyroidism is characterised by a too low plasma free thyroxine (FT4) concentration in combination with a normal TSH concentration. Although most mutation carrying patients had FT4 concentrations in the *hypothyroid range*, several patients had only mild, or no signs or symptoms of hypothyroidism. Mice expressing a mutated NCoR - another component of the CoR * were found to have low TH levels, but seemed clinically unaffected. Hereupon, it was speculated that these mice might be more sensitive to TH, and do well with lower plasma TH concentrations. Until now, this phenomenon has not been encountered in humans. With respect to the low FT4 concentrations found in our patients with mutations in TBL1X, we don*t know if they are harmful for cellular function.

Therefore, we would like to study the functional consequences of mutations in TBL1X in human liver cells, by generating such cells from induced pluripotent stem cells (iPSCs), derived from peripheral mononuclear white blood cells obtained from patients with a TBL1X gene mutation and their siblings (as controls). Performing functional studies at the cellular level will make it possible to test the hypothesis that patients with a (too) low plasma FT4 concentration due to a mutation in TBL1X are not hypothyroid at the target tissue level because of increased sensitivity to TH. These studies will provide the answer to the question patients with too low FT4 concentrations due to TBL1X mutations need to be treated with TH yes or no.

Study objective

To determine the effect of mutations in the TBL1X gene on TH dependent signalling in liver cells generated from iPSCs.

Study design

Prospective descriptive study. To assess TH dependent signalling in liver cells, induced pluripotent stem cells (iPSCs) will be generated from peripheral mononuclear white blood cells and transformed into hepatocytes. This will be done in collaboration with Prof. Hollenberg and Dr. Wilson, Harvard University/Boston Medical Center, Boston.
Peripheral mononuclear white blood cells will be isolated from a venous blood

sample and shipped to Boston. To this end, blood will be taken from patients on one occasion at a regular outpatient clinic visit. The remaining work - generation of iPSC/hepatocytes and functional studies/gene expression - will be done in Boston.

Study burden and risks

Confirmed carriers and non-mutation carrying first- or second-degree relatives will be invited to the department of paediatrics or internal medicine of the Academic Medical Center to undergo venous blood collection. As congenital central hypothyroidism is a rare condition, and many known patients are children, minors will be included in the study. Venous blood collection and placement of an intravenous cannula may be uncomfortable and carry a small risk of bruising and bleeding. The risks involved in participation are negligible and the burden is considered minimal. There are no other risks or benefits associated with participation.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

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

Isolated central hypothyroidism (low serum FT4, normal TSH concentration) caused by a mutation in the TBL1X gene,
First- or second-degree relative of a patient with central hypothyroidism caused by a mutation in the TBL1X gene, NOT carrying a TBL1X mutation.

Exclusion criteria

Carriers of other genetic defects known to cause isolated central hypothyroidism.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-05-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	14-11-2018
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	NL66178.018.18