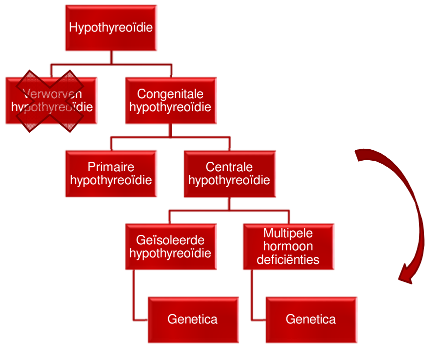
GENETISCHE ASPECTEN VAN CENTRALE HYPOTHYREOÏDIE

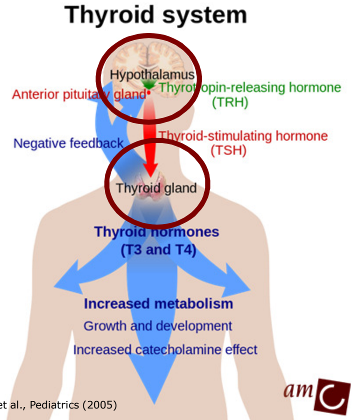
Charlotte Heinen
Arts-onderzoeker kinderendocrinologie
December 2016



Thyroid system

Congenitale Centrale Hypothyreoïdie
1:16.404

Congenitale Primaire Hypothyreoïdie
1:3.017



Lanting et al., Pediatrics (2005)

Neonatale screening

- Hielprik op leeftijd 3-7 dagen oud
- Nederlandse screening sinds 1995:
  - T4 in alle neonaten
  - TSH in laagste 20% T4
  - TBG in laagste 5% T4

Aanpak screening uniek voor Nederland

Detecteert primaire én centrale hypothyreoïdie

2.1 Interpretatie van de CH-uitslag en actie bij de eerste hielprik bij kinderen die niet voldoen aan de voorwaarden van de prematurenregeling

T4 (SD)[a] en T4/TBG ratio (SD/nmol)[b,c]	TSH (mE/l bloed)[d] Afwijkend (≥ 22)	Dubieus (8 t/m 21)	Negatief (≤ 7)
Afwijkend (T4 ≤ -3.0) én TBG> 40 nmol/l	*Verwijzen*	*Verwijzen*	*Verwijzen*
Dubieus (-3.0 < T4 ≤ -1.6 én T4/TBG ratio ≤ 17)	*Verwijzen*	*Tweede hielprik*	*Tweede hielprik*
Negatief (-3.0 < T4 ≤ -1.6 en T4/TBG ratio > 17 óf T4 ≤ -3,0 én TBG ≤ 40 nmol/l óf T4> -1,6	*Verwijzen*	*Tweede hielprik*	Geen actie

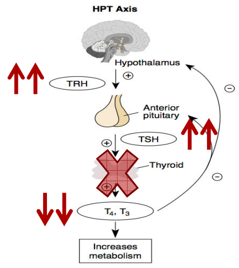
Suggestief voor CH-C

Laag T4 (≤-1,6 SD) + normaal TSH + lage T4/TBG ratio (≤17)

Aanmelding kinderendocrinologie: 14e levensdag

- Anamnese
- Lichamelijk onderzoek
- Venapunctie
  - **TSH, FT4**

Primaire Hypothyreoïdie



Patterns of thyroid function tests during assessment of thyroid function

Serum TSH	Serum free T4	Serum T3	Assessment
Normal hypothalamic-pituitary function			
Normal	Normal	Normal	Euthyroid
High	Low	Normal or low	Primary hypothyroidism
High	Normal	Normal	Subclinical hypothyroidism
Low	High or normal	High	Hyperthyroidism
Low	Normal	Normal	Subclinical hyperthyroidism
Normal or low*	Low or low-normal	Low or normal	Central hypothyroidism

T3: triiodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone.
* In central hypothyroidism, serum TSH may be low, normal, or slightly high.

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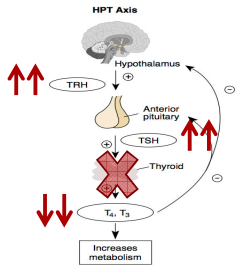
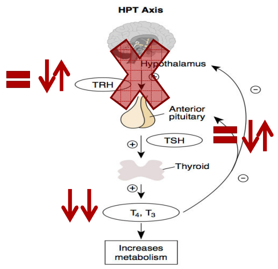
Primaire Hypothyreoïdie



Centrale Hypothyreoïdie



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Diagnose centrale hypothyreoïdie afhankelijk van FT4!

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Centrale hypothyreoïdie gediagnosticeerd… en nu?

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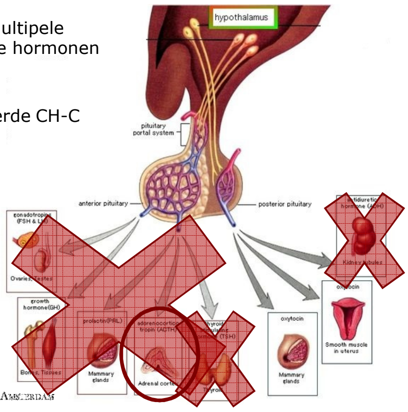
Uitval multipele hypofyse hormonen (MPHD)
80%

Geïsoleerde CH-C
20%



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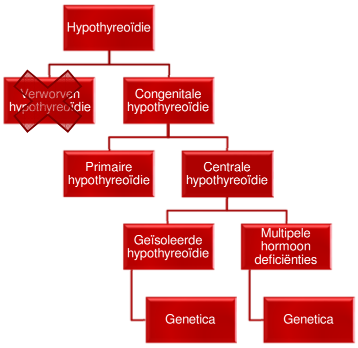
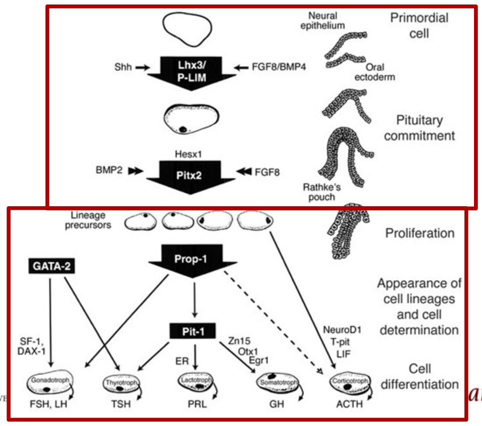
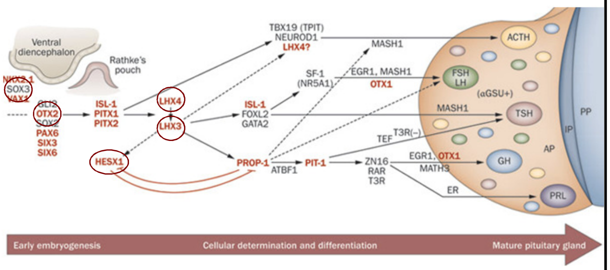
Gene with mutation	Inheritance	Hormone deficits	Additional features	MRI
TSHB	AR	TSH	–	E, N
TRHR	AR	TSH	–	N
Isolated TSH Deficiency or combined pituitary hormone deficiency				
IGSF1	XL[a]	TSH ± PRL, GH (transient)	Macroorchidism (males) Ovarian cysts (females)	N
Combined pituitary hormone deficiency				
POU1F1	AR, AD	GH, TSH, PRL	–	APH
PROP1	AR	GH, TSH, LH, FSH, PRL, evolving ACTH deficiencies	–	APH (may be transient), N, E
Specific Syndrome				
HESX1	AR, AD	Panhypopit GH and evolving TSH, ACTH, LH/FSH deficiency	Septo-optic dysplasia and its variants	APH, EPP, ACC, ONH
LHX3	AR	GH, TSH, LH, FSH, PRL (ACTH)	Limited neck rotation, short cervical spine, sensorineural deafness	APH, N, E
LHX4	AD	GH, TSH, ACTH, variable gonadotrophin deficiencies	Cerebellar abnormalities	APH, EPP
SOX3	XL	GH,TSH, ACTH, LH, FSH	Variable mental retardation	APH, EPP Persistent craniopharyn-geal canal
OTX2	AD	GH, TSH, ACTH, LH, FSH	Uni/Bilat. Anophthalmia Retinal dystrophy	N, APH, EPP





Vroege ontwikkeling



University of Amsterdam Prince et al., Nature Reviews (2011)

Vroege ontwikkeling

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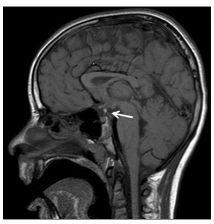
University of Amsterdam Mehta et al., Best Practice & Research (2008)

Vroege ontwikkeling

SOX3
- Mentale retardatie
- MPHD

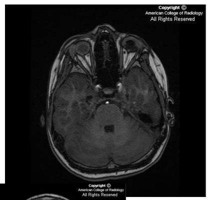


OTX2
- Oogafwijkingen
- MPHD

University of Amsterdam Tajima et al., JCEM (2009)
Stagi et al., Hormones (2014)

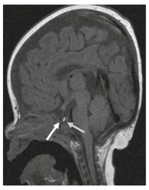
Vroege ontwikkeling

HESX1 (Septo-optische dysplasie)
- N. opticus
- Septum pellucidum
- Hypofyse



Vroege ontwikkeling

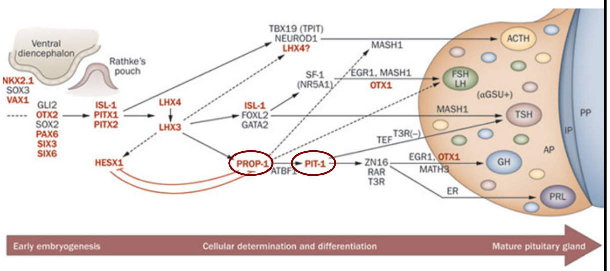
LHX3
- Rigide cervicale wervelkolom
- MPHD



LHX4
- Aanlegstoornissen hersenen
- MPHD

Bonfig et al., Eur J Pediatr (2011)
Cohen et al., JCEM (2016)

Cel differentiatie



Prince et al., Nature Reviews (2011)

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Mehta et al., Best Practice & Research (2008)

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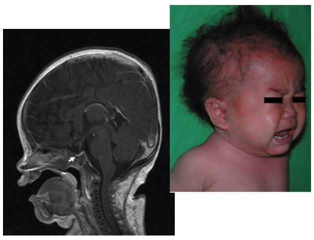
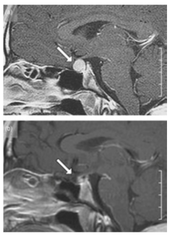
Cel differentiatie

POU1F1/PIT-1
- MPHD



PROP-1
- MPHD



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Lee et al., J Formos Med Assoc (2011)
Cohen et al., JCEM (2016)

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Behandeling

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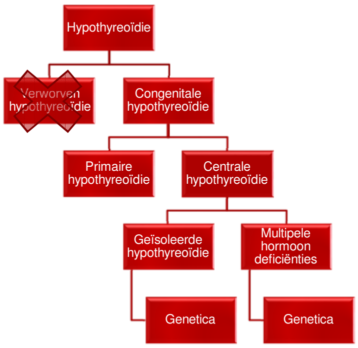

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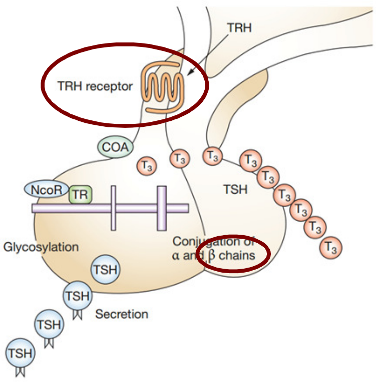
Mehta et al., Best Practice & Research (2008)



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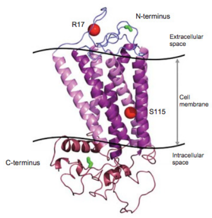
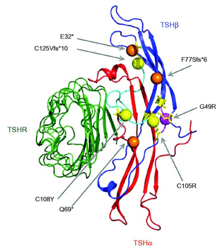
Yamada et al., Nat Clin Pract Endocrinol Metab (2008)

Geïsoleerde CH-C

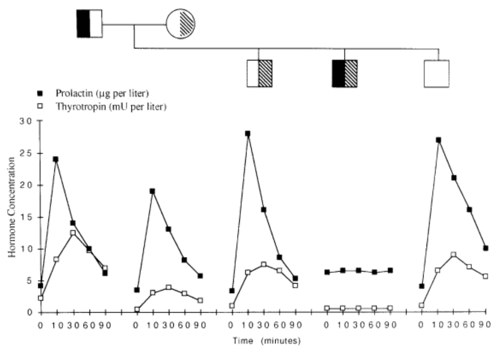
TRHR



TSHB



University of Amsterdam Schoenmakers et al., JoE (2015)



University of Amsterdam Collu et al., JCEM (1997)

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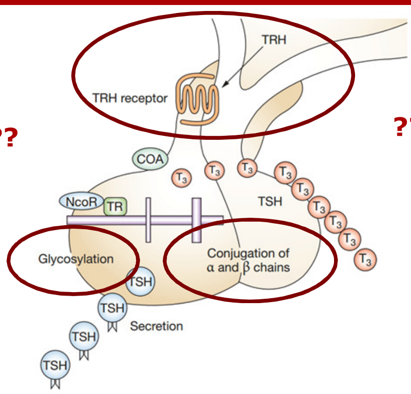

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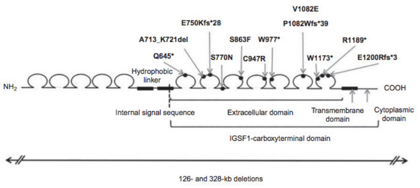
University of Amsterdam Yamada et al., Nat Clin Pract Endocrinol Metab (2008)

Geïsoleerde CH-C

IGSF1
- CH-C, evt PRL en GH deficientie
- Macroorchidie
- Vertraagde puberteit



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Sun et al., Nat Genet (2012)
Schoenmakers et al., JoE (2015)

amc

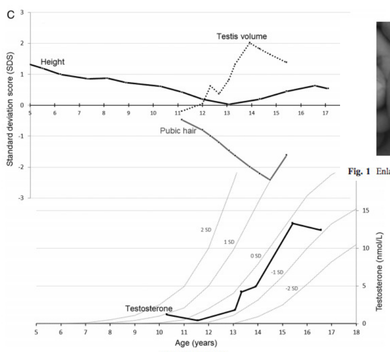

Figure 3. Continued.

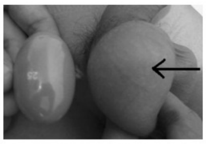

Fig. 1 Enlarged right testis with a testicular volume of 25 ml

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Joustra et al., JCEM (2016)
Rustagi et al., Indian J Pediatr (2011)

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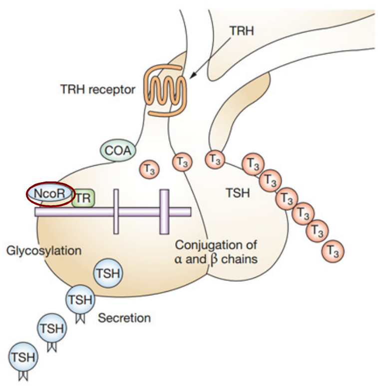

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Yamada et al., Nat Clin Pract Endocrinol Metab (2008)

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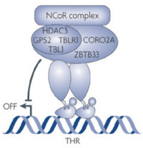
Geïsoleerde CH-C

TBL1X

- Kernonderdeel van het **NCoR/SMRT corepressor complex**
- Corepressor complexen reguleren het aflezen van DNA
- NCoR/SMRT reguleert het aflezen van “T3-target genes”
  - TRH gen
  - TSHB gen

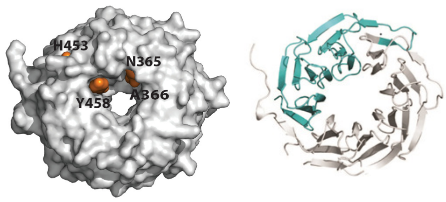


Yoon HG et al, EMBO J (2003)

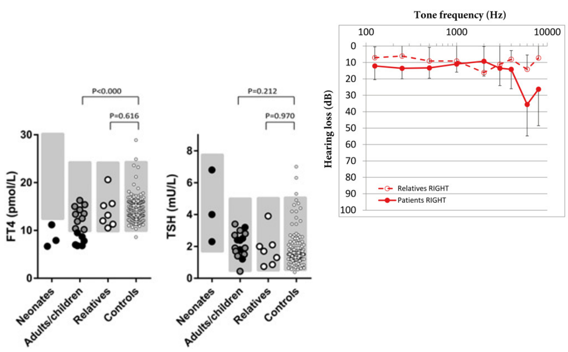
Geïsoleerde CH-C

TBL1X

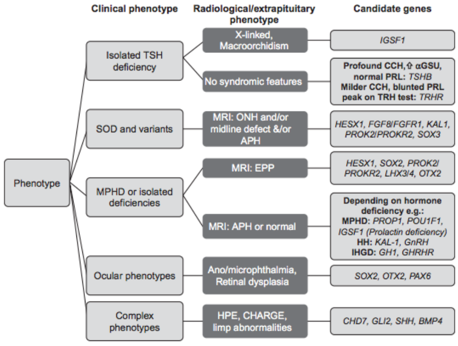
- CH-C
- Gehoorverlies



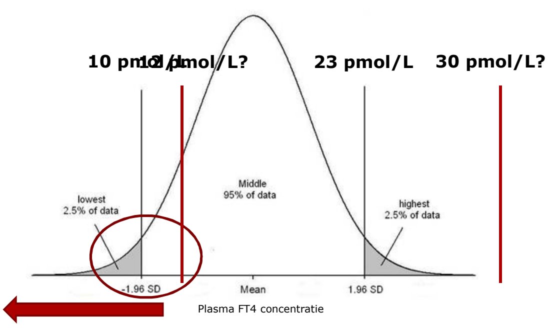
Heinen et al., JCEM (2016)



Heinen et al., JCEM (2016)



Waarom eigenlijk genetisch onderzoek?



Hypothyreoïdie

Genetisch onderzoek

Patient
- Bevestiging van diagnose CH-C
- Bevestiging aan- of afwezigheid andere afwijkingen
- Counseling bij kinderwens

Wetenschap
- Meer inzicht in mechanisme schildklierhormoon productie