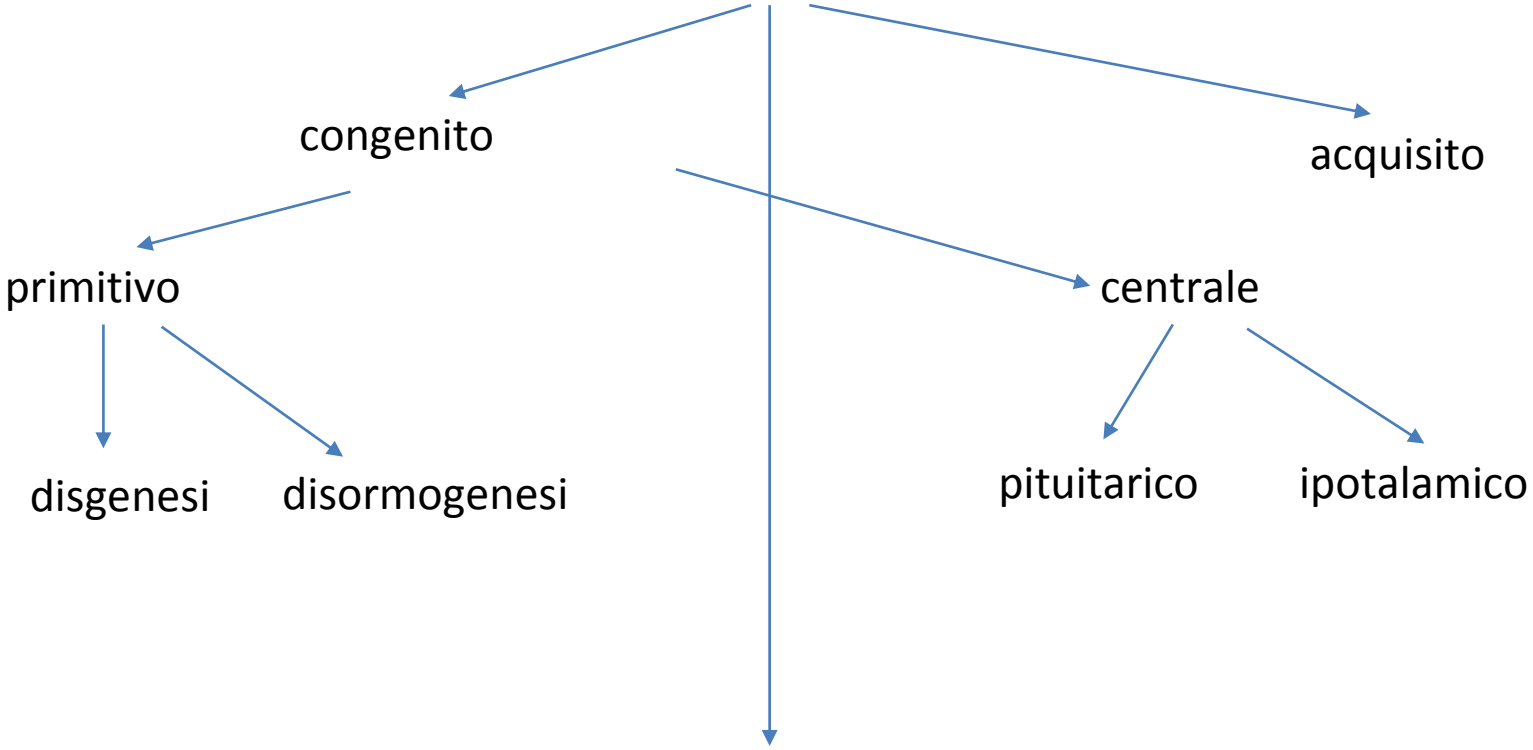
Novità in Endocrinologia Pediatrica
dalla Clinica alla Genetica

La genetica dell'ipotiroidismo congenito

Giorgio Radetti

14 maggio 2016, Cagliari

Ipotiroidismo

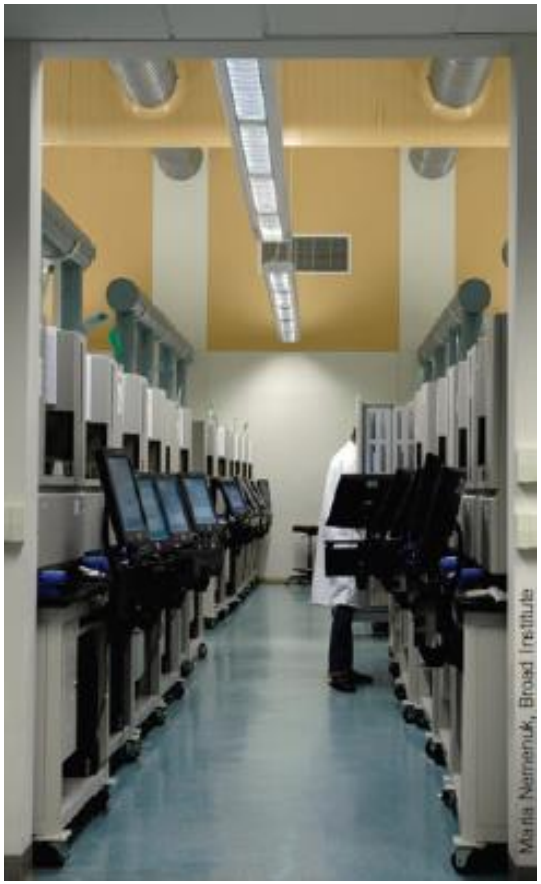


Da insensibilità tessutale agli ormoni tiroidei

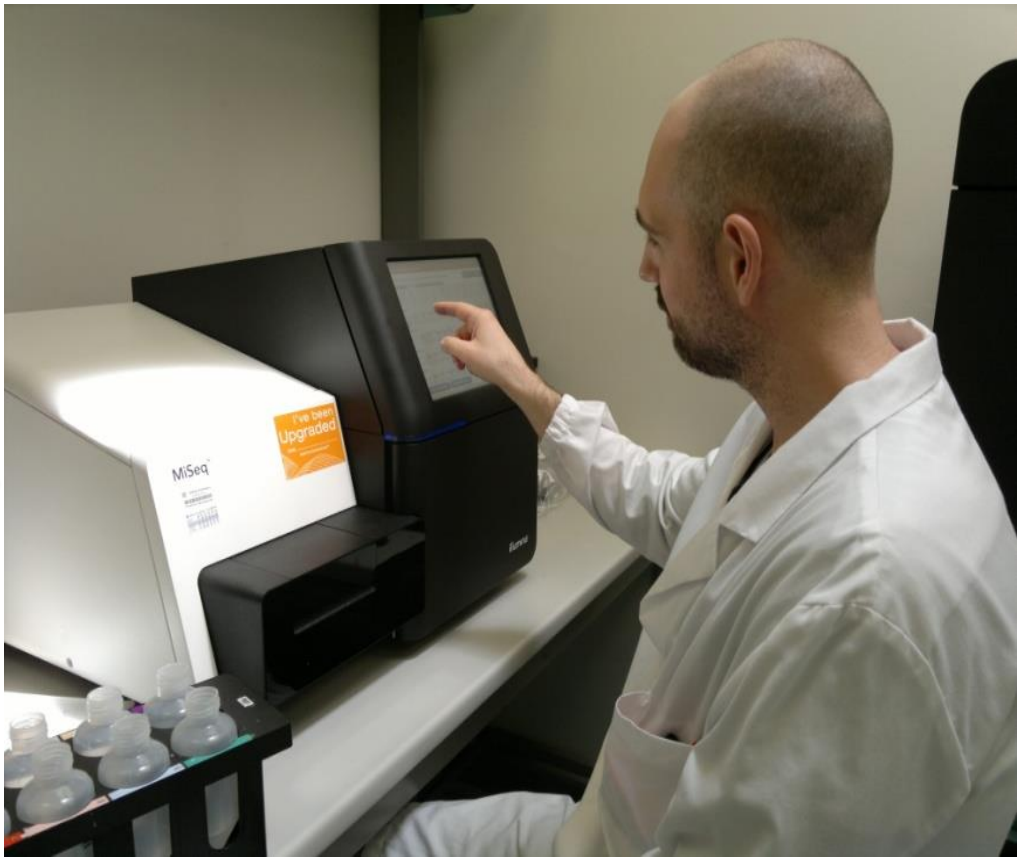
Next-generation sequencing transforms today's biology

Stephan C Schuster

| VOL.5 NO.1 | JANUARY 2008 | NATURE METHODS



Sequencing centers producing the Sanger sequence data for mammalian genome projects are factory-like outfits with a large number of personnel.



The latest next-generation sequencing instruments can generate as much data in 24 h as several hundred Sanger-type DNA capillary sequencers, but are operated by a single person.

The panel of genes for targeted NGS analysis

Gene	Function	Associated defects
TSHR	Thyroid stimulation	Variable TSH resistance
SLC26A4	Ion apical transport	Pendred syndrome (SHL + PIOD)
DUOX2	H_2O_2 production	Variable PIOD and degree of hypothyroidism
DUOXA2	H_2O_2 production	PIOD
TG	TH synthesis	TIOD with severe hypothyroidism + low sTg
TPO	Iodide organification	TIOD with severe hypothyroidism
GLIS3	Transcription factor	Variable dysgenesis + neonatal DM + polycystic kidneys
NKX2.1	Transcription factor	Brain-Lung-Thyroid syndrome
PAX8	Transcription factor	Variable dysgenesis
FOXE1	Transcription factor	Bamforth-Lazarus syndrome (athyreosis + cleft palate + spiky hair)
JAG1	Notch stimulation	Alagille syndrome (Thyroid hypoplasia in zebrafish)

- *In contrast with current understanding, novel/rare variations in the known candidate genes can contribute to the CH pathogenesis of a large number of affected patients.*
- *The systematic NGS approach reveals a frequent (>20% of cases) multigenic origin of CH, including unexpected variations in genes that would have been excluded a priori from screening on the basis of the clinical phenotype.*

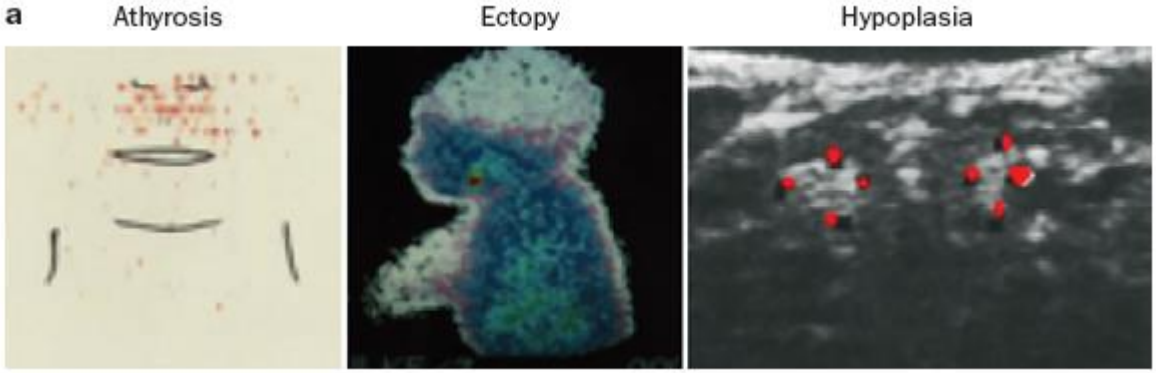
Etiology of CH

CH as a complex genetic disease with variable penetrance and expressivity…….

……. frequent multifactorial (genetic, epigenetic, environment) or multigenic origin

- *Amendola E et al 2005 A mouse model demonstrates a multigenic origin of congenital hypothyroidism. Endocrinology 146:5038–5047*
- *Vassart G, Dumont JE 2005 Thyroid dysgenesis: multigenic or epigenetic or both. Endocrinology 146:5035–5037*
- *Leger J et al 2002 Thyroid developmental anomalies in first degree relatives of children with congenital hypothyroidism. J Clin Endocrinol Metab 87, 575*
- *Amendola E et al 2010 A locus on mouse chromosome 2 is involved in susceptibility to Congenital Hypothyroidism and contains an essential gene expressed in thyroid. Endocrinology 151:1948-1958*

Ipotiroidismo primitivo: disgenesi



A causa della bassa frequenza di mutazioni nei pazienti con disgenesi tiroidea, L'analisi genetica dovrebbe essere fatta solamente se coesistono altri segni clinici (FOXE1, NKX2-1, NKX2-5) o ricorrenza familiare (PAX8 e TSHR)

- **FOXE1**: labiopalatoschisi, capelli dritti (spiky), ritardo mentale
- **NKX2-1**: modico ipotiroidismo, sintomi polmonari, coreoatetosi, atassia , ipotonia muscolare
- **NKX2-5**: difetto cardiaco nel 50%
- **PAX8**: ipoplasia tiroidea, lieve ipotiroidismo e agenesia renale unilaterale
- **TSHR**: espresso tardivamente, induce solo ipoplasia tiroidea oltre all'ipotiroidismo

JAG1 Loss-Of-Function Variations as a Novel Predisposing Event in the Pathogenesis of Congenital Thyroid Defects

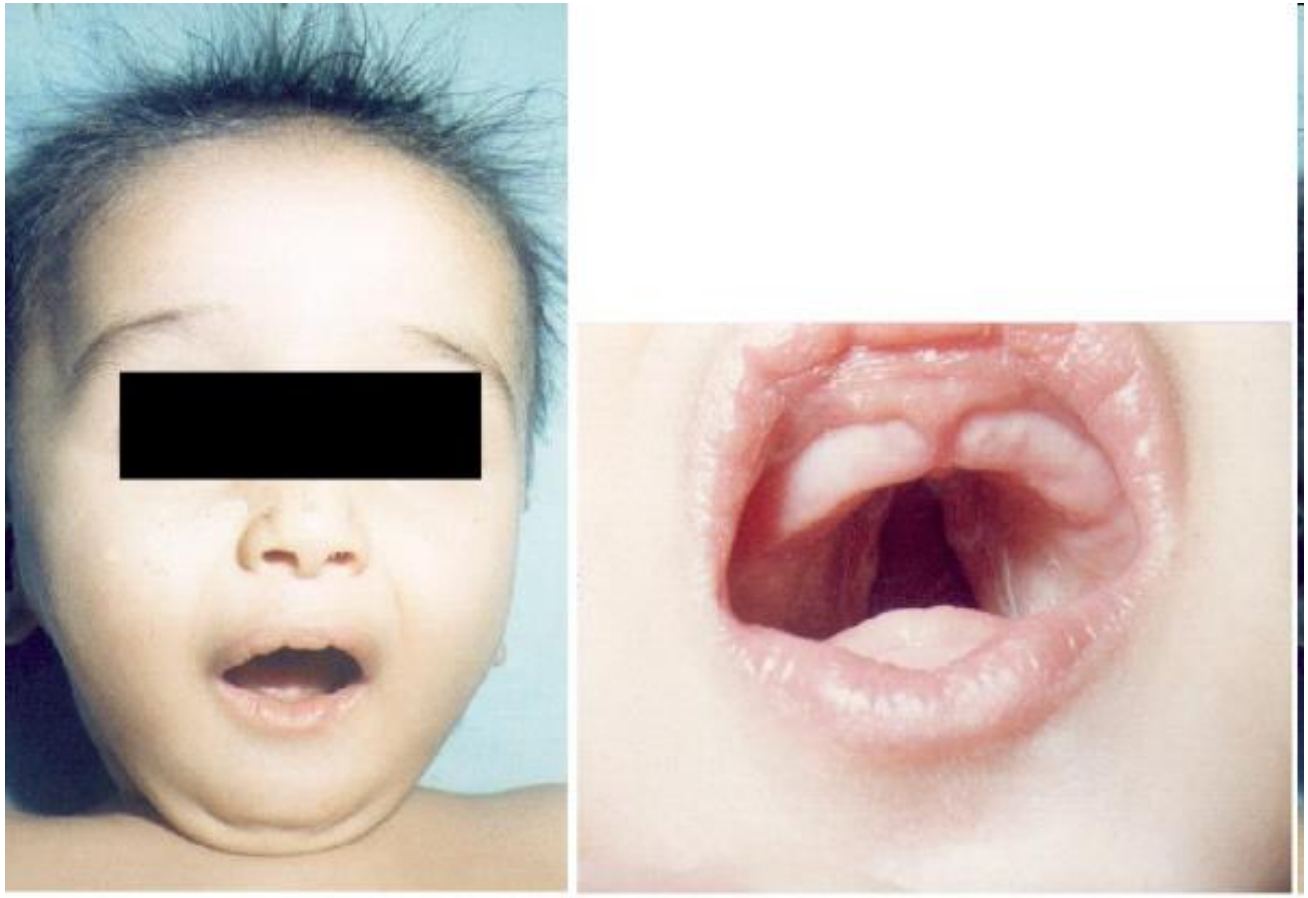
Tiziana de Filippis,* Federica Marelli,* Gabriella Nebbia, Patrizia Porazzi, Sabrina Corbetta, Laura Fugazzola, Roberto Gastaldi, Maria Cristina Vigone, Roberta Biffanti, Daniela Frizziero, Luana Mandarà, Paolo Prontera, Mariacarolina Salerno, Mohamad Maghnie, Natascia Tiso, Giorgio Radetti, Giovanna Weber, and Luca Persani†

JCEM 2016

Patients with FOXE 1 mutations, showing spiky hair, micrognathia, and hypertelorism (A), and cleft palate (B). From: *Castanet M, et al. A novel loss-of-function mutation in TTF-2 is associated with congenital hypothyroidism, thyroid agenesis, and cleft palate.*

Hum Mol Genet 2002;11:20521-9

Bamforth-Lazarus Syndrome



Park, S M et al. J Med Genet 2005;42:379-389

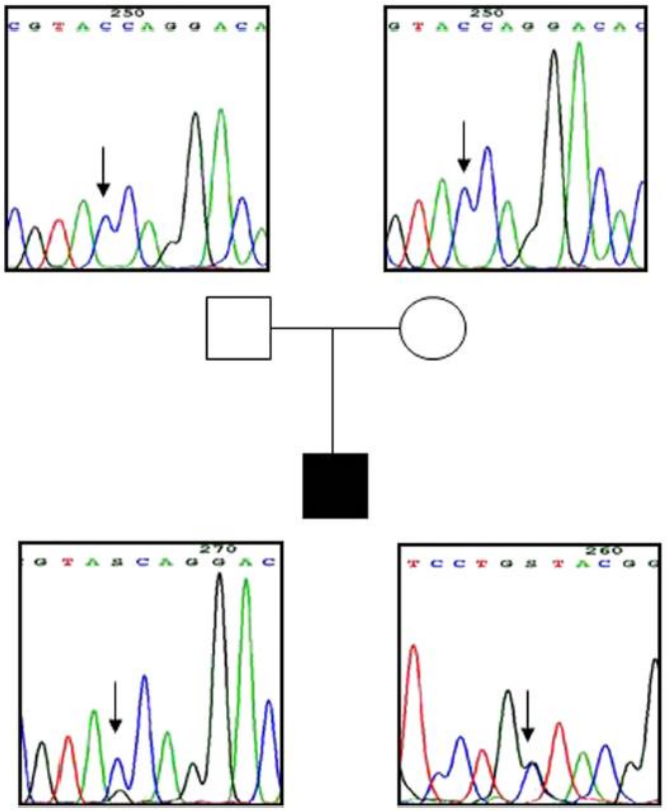
Monti *et al. Italian Journal of Pediatrics* (2015) 41:45
DOI 10.1186/s13052-015-0150-6

ITALIAN JOURNAL OF PEDIATRICS

CASE REPORT Open Access

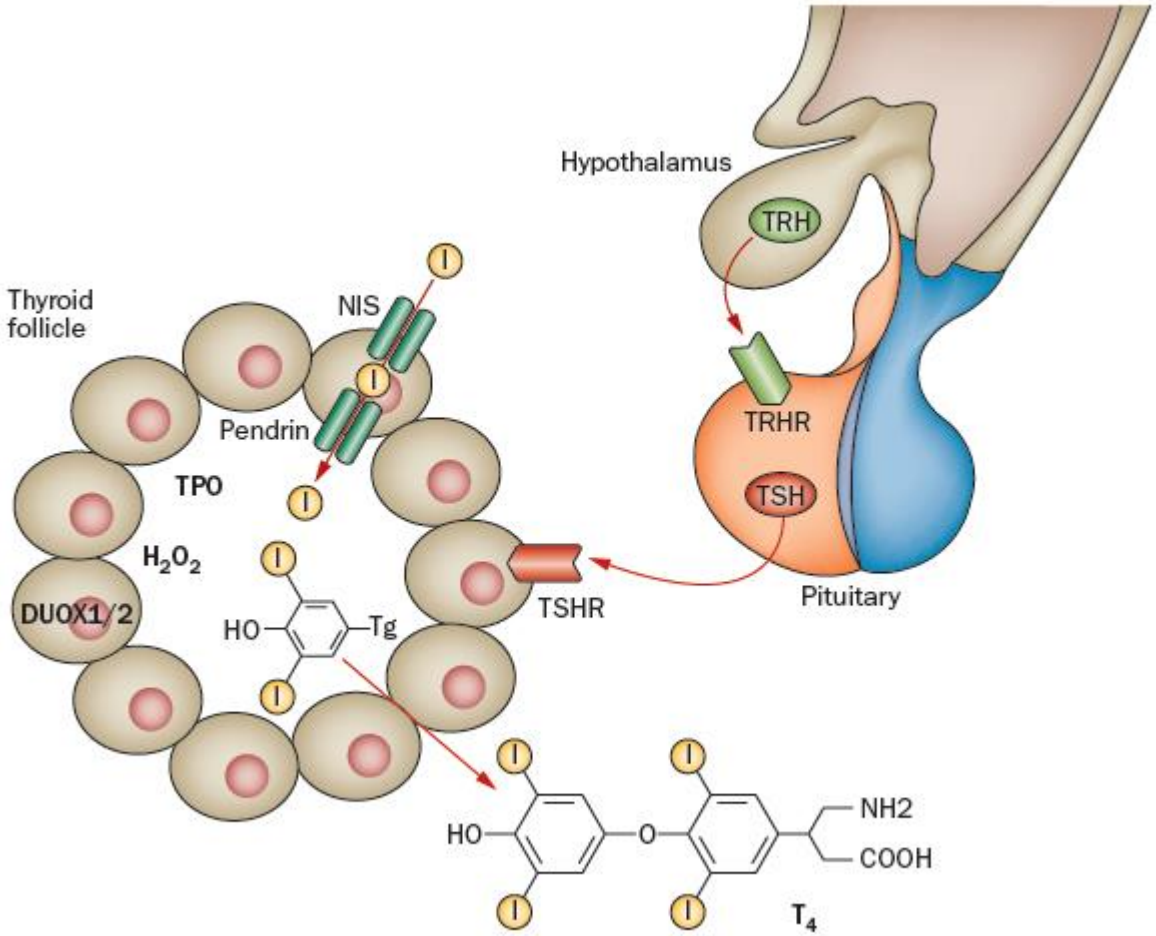
NKX2.1-Related Disorders: a novel mutation with mild clinical presentation

Sara Monti[1], Annalisa Nicoletti[1], Antonella Cantasano[1], Heiko Krude[2] and Alessandra Cassio[1,3*]



	4° d	10° d	8° m	13° m
TSH spot (mU/L)	10	4.4		
TSH serum (mU/L)			8.8	13.8
fT4 serum (pg/ml)			14.8	13.4
Choreoathetosis			+ -	+ +
Thyroid US		Norm		

Ipotiroidismo primitivo:disormogenesi



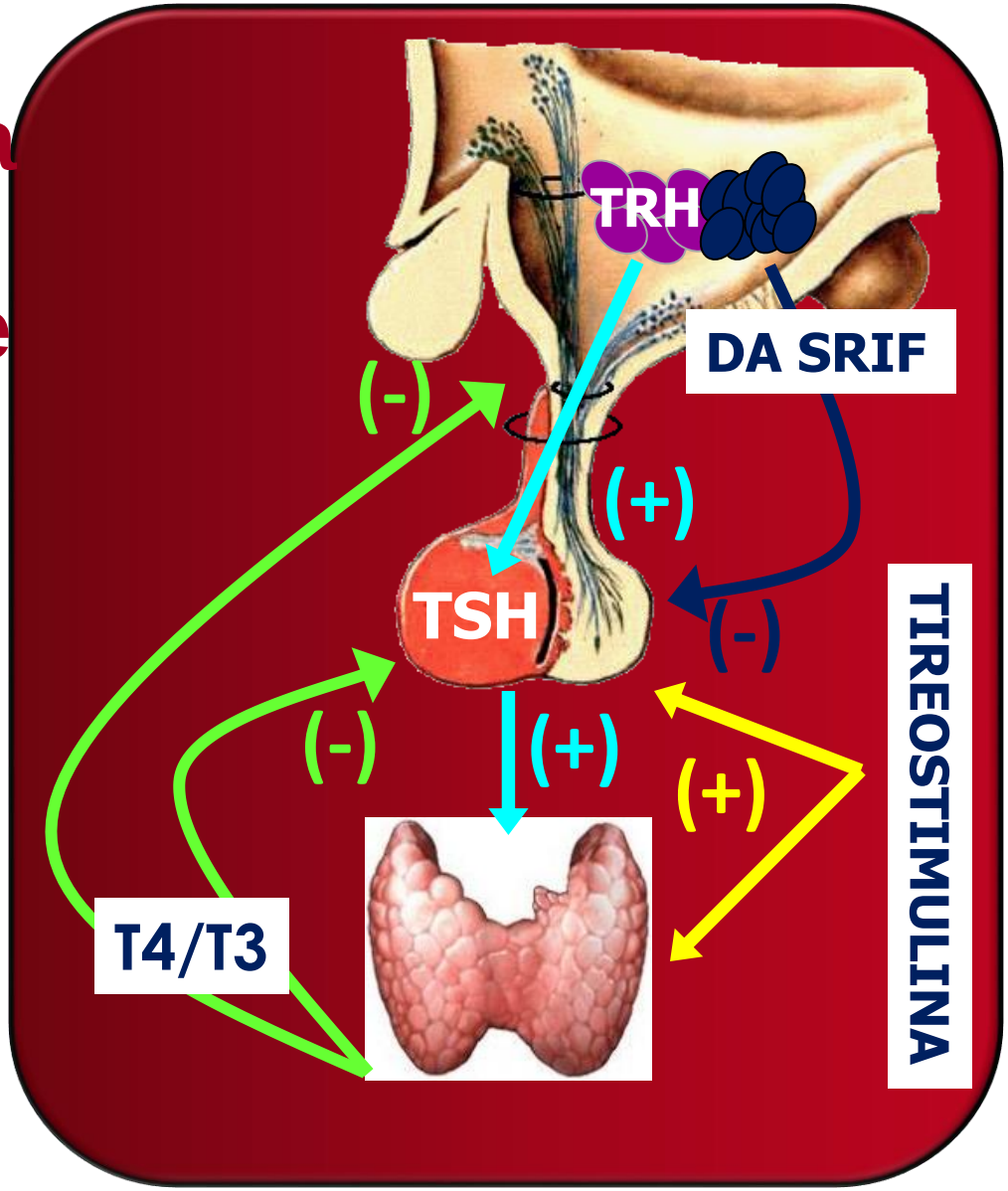
- **NIS**: trasporta attivamente lo iodio attraverso la membrana basale
- **Pendrina** (gene SLC26A4) facilita il passaggio dello iodio nel lume follicolare
- **Gene TG**: produzione di TG
- **TPO**: ossida lo iodio e lo lega ai gruppi tirosinici della tiroglobulina (MIT, DIT) e favorisce la loro associazione(T3, T4)
- **DUOX1 e 2**: provvedono alla produzione di H2O2 necessaria alla funzione della TPO
- **DUOXA1 e 2**: dimerizzano con il rispettivo DUOX e favoriscono l'uscita dal RE verso la membrana cellulare
- **DEHAL1**: ricicla lo iodio deiodinando le mono e diiodotironine
- **GNAS gene**: l' alterazione della G protein 〈 altera la trasmissione di segnale del TRH e del TSH

IPOTIROIDISMO CENTRALE

E' la forma di ipotiroidismo causata da un'insufficiente stimolazione da parte del TSH di una ghiandola tiroidea normale

PREVALENZA

1:16.000-100.000



Persani L, JCEM 2012

IPOTIROIDISMO CENTRALE

- La causa è una alterazione anatomica o funzionale della zona ipotalamo-ipofisaria

- La diagnosi è posta in presenza di bassi valori di fT4 e di valori di TSH inappropriatamente normali o modicamente elevati.

- Fallimento della "reflex TSH strategy”

- Il deficit di TSH raramente è isolato, più facilmente fa parte di un quadro di deficit combinato

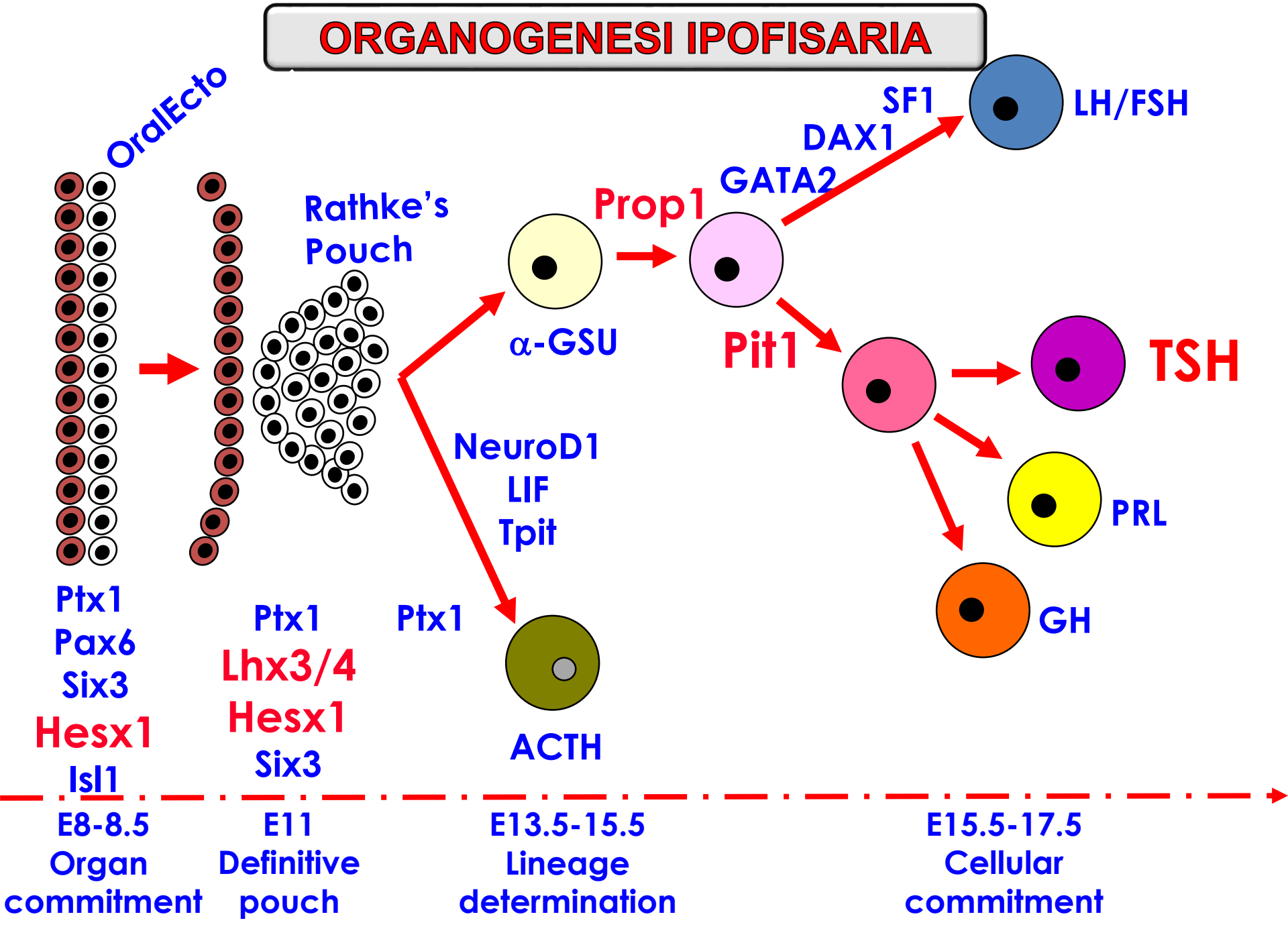
TABLE 1. Known causes of CH in a tentative order of frequency

Invasive or compressive lesions
Pituitary macroadenomas
Craniopharyngiomas
Meningiomas or gliomas
Rathke cleft cysts
Metastases
Empty sella
Carotid aneurysm
Iatrogenic factors
Cranial surgery or irradiation
Drugs (*e.g.* RXR selective ligands)
Injuries
Head traumas
Traumatic delivery
Vascular accidents
Pituitary apoplexy
Postpartum pituitary necrosis (Sheehan syndrome)
Subarachnoid hemorrhage
Autoimmune disease
Lymphocytic hypophysitis
Polyglandular autoimmune diseases
Infiltrative lesions
Iron overload (hemochromatosis, thalassemia major)
Sarcoidosis
Histiocytosis X
Inherited diseases
CPHD: pituitary transcription factor defects; *LEPR* mutations
Isolated CH: *TSHβ* or *TRHR* mutations
Infective diseases
Tuberculosis
Mycoses
Syphilis

TABLE 2. Genetic forms of CH

Gene (MIM no.)	Clues for diagnosis (MIM phenotype no.)	Inheritance
TSHβ (188540)	Severe isolated CH of neonatal onset with high α-GSU, pituitary hyperplasia (275100)	Recessive
TRH-R (188545)	Isolated CH with blunted TSH/PRL response to TRH and apparently uneventful infantile development, and with delayed diagnosis from childhood (growth retardation) to adulthood	Recessive
POU1F1 (173110)	Moderate/severe CH of neonatal to infantile onset combined with GH and PRL defects, prominent forehead, mid face hypoplasia, depressed nose (613038)	Dominant or recessive
PROP1 (601538)	Moderate/severe CH of neonatal to infantile onset, combined with GH, PRL, LH/FSH defects, and delayed ACTH deficiency, pituitary hypo-/hyperplasia (262600)	Recessive
HESX1 (601802)	Severe panhypopituitarism associated with septooptical dysplasia, supernumerary/hypoplastic digits (182230)	Dominant or recessive
LHX3 (600577)	Hypopituitarism with conserved ACTH function and associated with pituitary hypo- or hyperplasia, short/rigid cervical spine, vertebral abnormalities, and variable deafness or mental retardation (221750)	Recessive
LHX4 (602146)	Combined anterior pituitary defects associated with abnormalities of cerebellum and small sella turcica (262700)	Dominant
LEPR (601007)	Severe obesity and hyperphagia combined with delayed puberty and mild thyrotropin defect	Recessive

The reference numbers on the NCBI web site (http://www.ncbi.nlm.nih.gov/omim) are reported for each gene and phenotype (4).


ORGANOGENESI IPOFISARIA
OralEcto
Rathke's Pouch
Ptx1
Pax6
Six3
Hesx1
Isl1
Ptx1
Lhx3/4
Hesx1
Six3
Ptx1
α-GSU
Prop1
GATA2
SF1
DAX1
LH/FSH
Pit1
TSH
PRL
GH
NeuroD1
LIF
Tpit
ACTH
E8-8.5
Organ commitment
E11
Definitive pouch
E13.5-15.5
Lineage determination
E15.5-17.5
Cellular commitment

The IGSF1 Deficiency Syndrome: Characteristics of Male and Female Patients

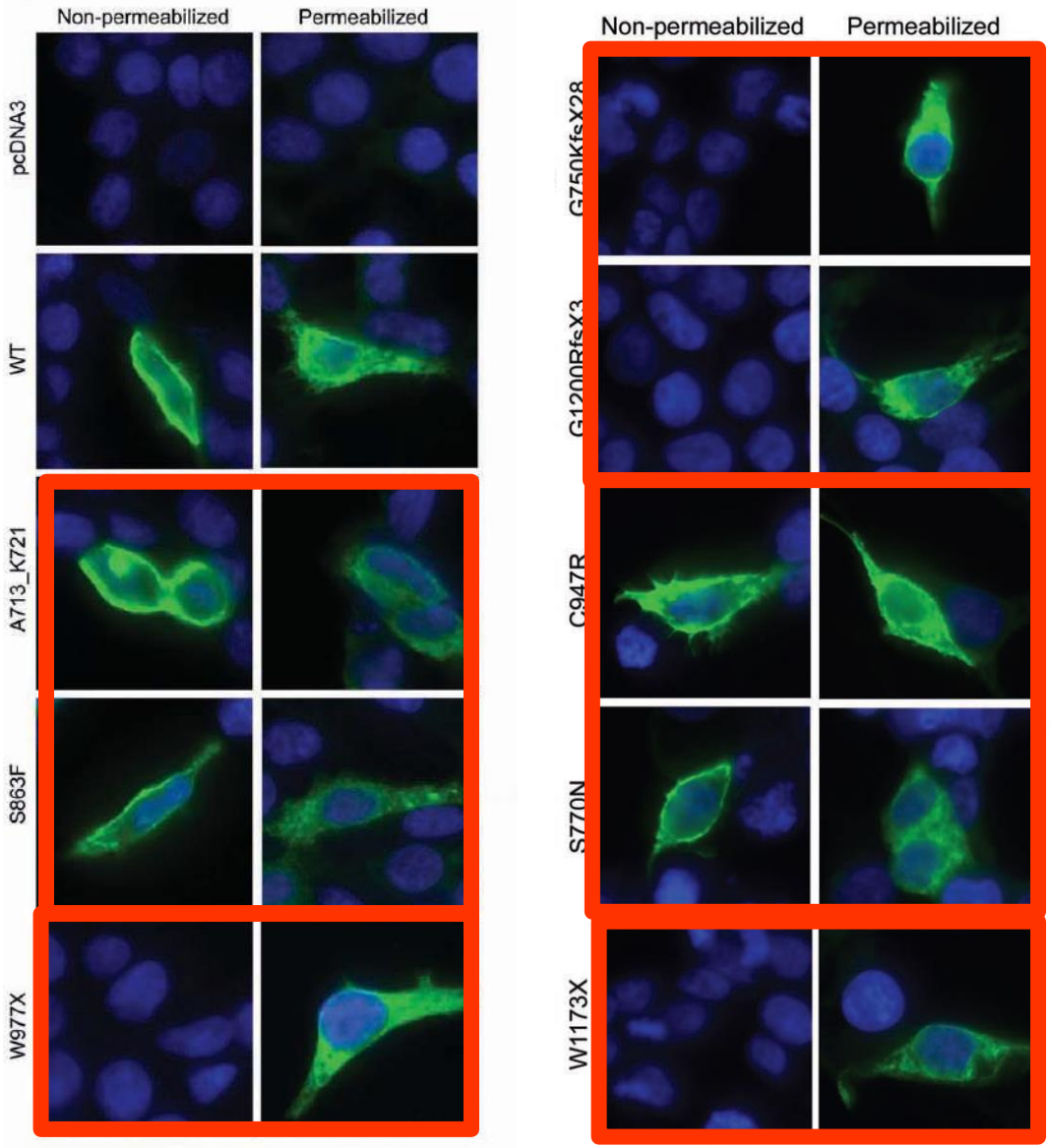
S. D. Joustra, N. Schoenmakers, L. Persani, I. Campi, M. Bonomi, G. Radetti, P. Beck-Peccoz, H. Zhu, T. M. E. Davis, Y. Sun, E. P. Corssmit, N. M. Appelman-Dijkstra, C. A. Heinen, A. M. Pereira, A. J. Varewijck, J. A. M. J. L. Janssen, E. Endert, R. C. Hennekam, M. P. Lombardi, M. M. A. M. Mannens, B. Bak, D. J. Bernard, M. H. Breuning, K. Chatterjee, M. T. Dattani, W. Oostdijk, N. R. Biermasz, J. M. Wit,*

- Ipotiroidismo centrale
- Macroorchidismo post puberale
- Possibile deficit di PRL
- Inizio puberale normale, ma ritardato aumento del testosterone
- Sovrappeso
- Deficit GH parziale e transitorio

- Mutazioni del gene codificante IGFS1 causano una alterata espressione di IGFS1 a livello della membrana cellulare

- Ciò causa verosimilmente una alterata espressione dei recettori del TRH a livello pituitarico con conseguente alterata trasmissione del segnale

Alterato trafficking delle proteine mutate



Cellule HEK293 trasfettate con 100 ng di DNA; espressione analizzata in IF con anticorpo anti-IGSF1, controcolorazione con DAPI

Alcune forme mutate non sono presenti in membrana, ma la proteina appare comunque espressa.

Altre forme sono espresse in membrana.
Ulteriori studi (mediante cell surface biotinylation) indicano che tali forme raggiungono la membrana con minor efficienza rispetto al wt e con un pattern di glicosilazione più immaturo.

Sun et al, Nature Genetics 20

IGSF **ive Case**
Serie **lanagement**

S. D. Jc E. P. B. Ballieux,
M.-O. T rg, M. Losekoot,
L. Persa dijk,* on behalf of
the IGS

Table 3. Clinical Features of the X-Linked IGSF1 Deficiency Syndrome

Features	Values, %
Hemizygous males	
Central hypothyroidism	100
Low-normal T concentrations in adulthood	88
Adult macroorchidism	88
Delayed pubertal T rise, early/normal timing of testicular growth	75[a]
Mild problems with attentional control	75[a]
Small thyroid gland	74
Increased waist circumference in adults	59
Prolactin deficiency	61
Late biochemical adrenarche	50[a]
Increased waist circumference in children	57
Decreased DHEA in adulthood	40
Benign external hydrocephalus	33[a]
Increased birth weight	26
Hypocortisolism in infancy	21
Increased IGF-1 concentrations in adulthood	20
Increased head circumference	20
GHD in childhood	16
Heterozygous females	
Delayed age at menarche	31
Prolactin deficiency (non-symptomatic)	22
Central hypothyroidism	18

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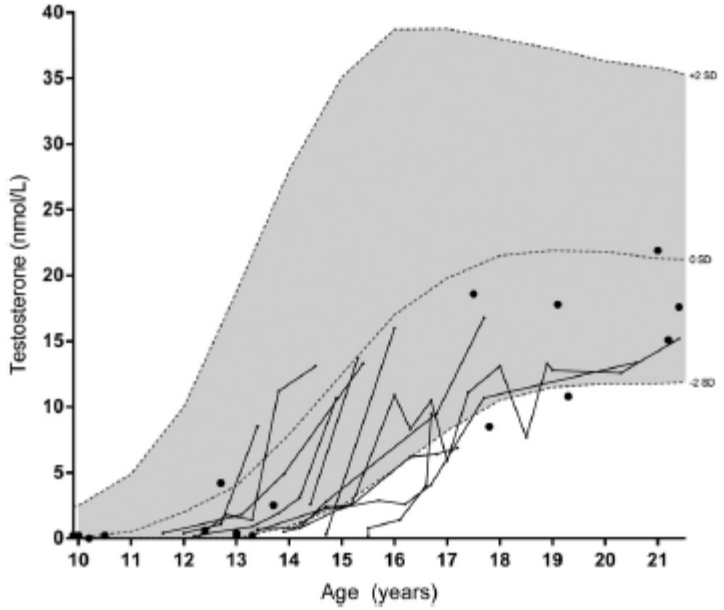


Figure 1. T concentrations in male patients. Lines represent longitudinal data and dots individual patients. Reference intervals were derived from Andersson et al (41).

(Supplemental Figure 6).

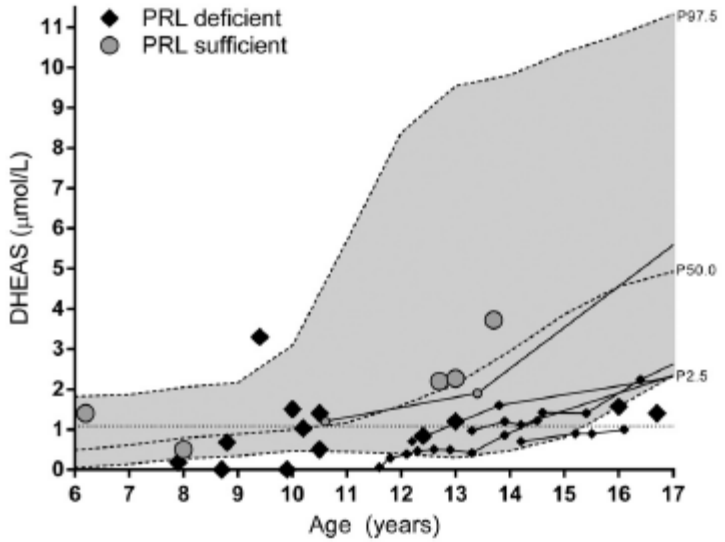
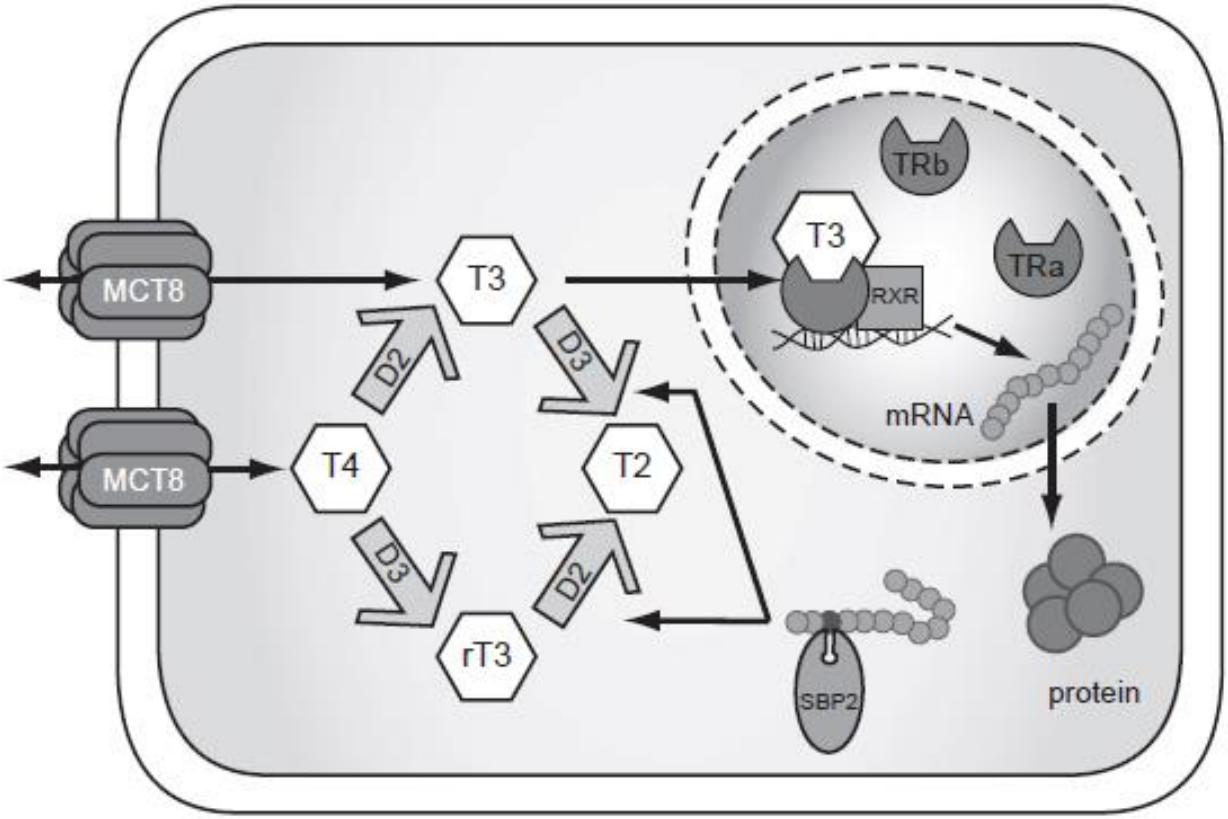


Figure 2. DHEAS concentrations in male patients around the age of biochemical adrenarche (1.084 µmol/L, dotted line). Lines represent longitudinal data, and the larger diamonds/dots are data from individual patients. Smoothed reference intervals were derived from Elmlinger et al (42). PRL, prolactin.

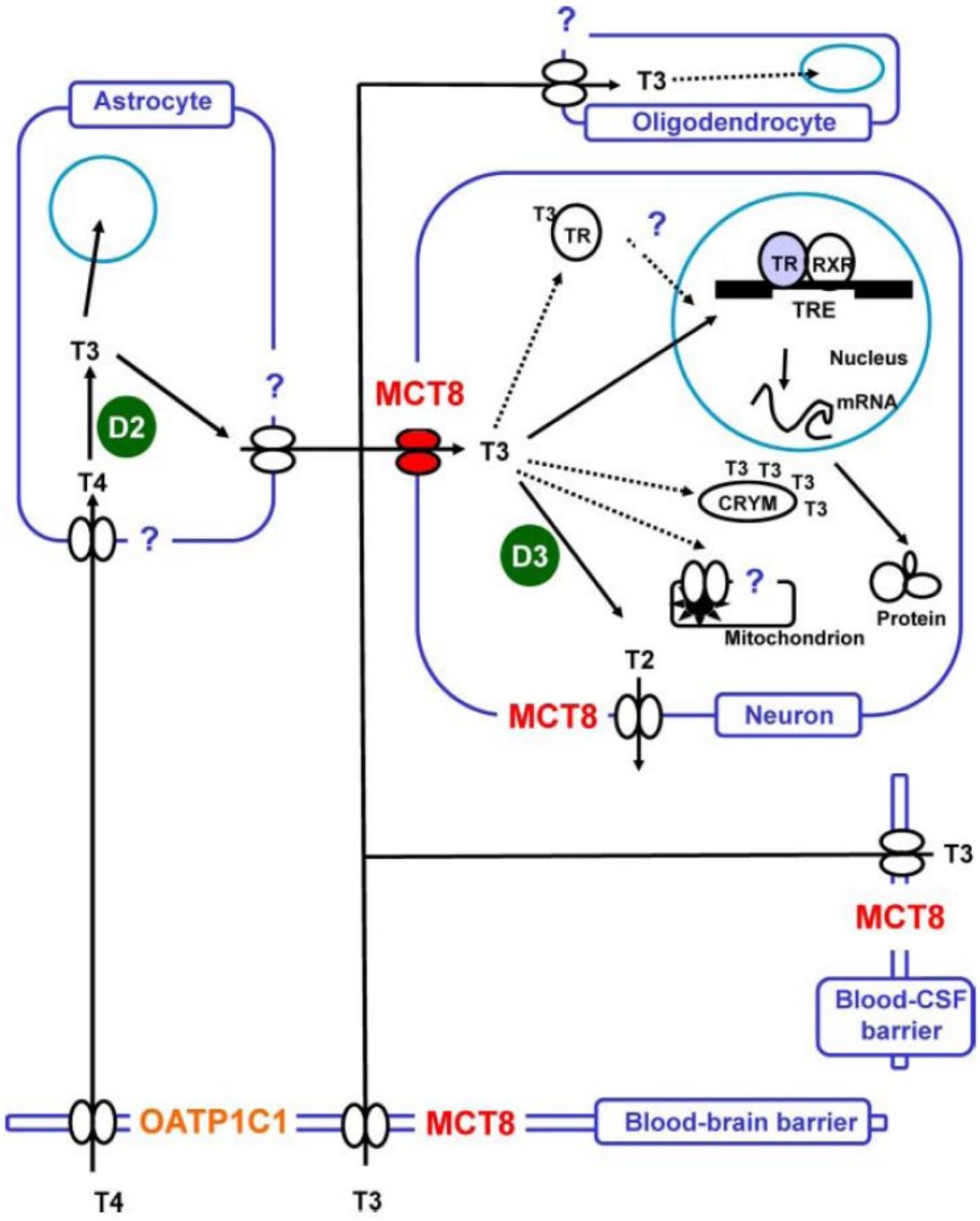
Sensibilità tessutale agli ormoni tiroidei



Alterato trasporto; deficit di MCT8

- **Clinica**: sindrome Allan-Herndon-Dudley: QI<40, ipotonia, convulsioni, difficoltà ad inghiottire, tetraparesi spastica
- Clinica: sindrome di Pelizeus-Mezbacher-like

- **Diagnostica**: fT4 lievemente basso, TSH marginalmente elevato, fT3 molto elevato
- **Sintomi** da eccesso di T3 (muscolo e fegato) e da deprivazione (cervello)


?
T3
Oligodendrocyte
Astrocyte
T3
TR
?
TR
RXR
TRE
Nucleus
mRNA
T3
D2
?
MCT8
T3
T4
T3 T3
T3
CRYM
T3
?
D3
Protein
Mitochondrion
T2
MCT8
Neuron
T3
MCT8
Blood-CSF barrier
OATP1C1
MCT8
Blood-brain barrier
T4
T3

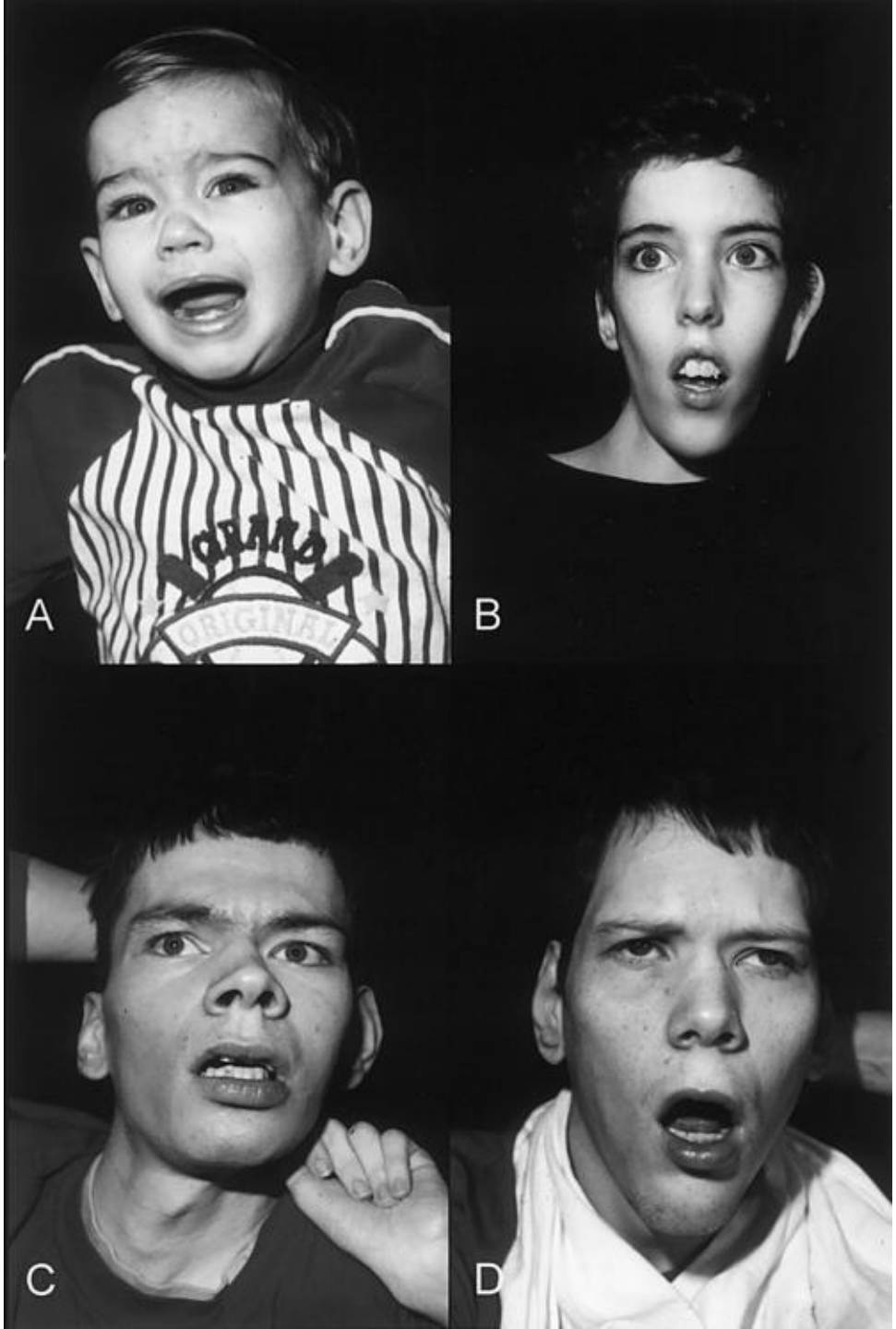

A
B
C
D

TABLE 1. Thyroid hormone transporters

Transporter[a]	Iodothyronine derivates	Specificity[b]	Reference
MCT8	T_3, T_4, rT_3, T_2	+++	17, 18
MCT10	T_3, T_4	++	57
Oatp1a1	T_3, T_4, rT_3, T_2, T_4S, T_3S, rT_3S, T_2S	+	8
OATP1A2	T_4, T_3, rT_3	+	102
Oatp1a3	T_4, T_3	+	103
Oatp1a4	T_4, T_3	+	7
Oatp1a5	T_4, T_3	+	7
OATP1B1	T_4, T_3, T_3S, T_4S, rT_3S	+	67, 104
Oatp1b2	T_3, T_4	+	105
OATP1B3	rT_3, T_4S, T_3S, rT_3S	+	13
OATP1C1	T_4, rT_3, T_3, T_4S	++	59
OATP2B1	T_4	+	61
OATP3A1_v1/v2	T_4	++	88
Oatp4a1	T_3, T_4, rT_3	+	102
OATP4C1	T_3, T_4	+	86
Oatp6b1	T_3, T_4	+	106
Oatp6c1	T_3, T_4	+	106
LAT1	T_3, T_4, rT_3, T_2	+	77
LAT2	T_3, T_4, rT_3, T_2	+	77
NTCP	T_4, T_3, T_4S, T_3S	++	8, 9
MDR1	T_3	+	10

A parte MCT8, per gli altri trasportatori non vi è evidenza di un ruolo patogenetico

MCT8 deficiency: terapia

- Tiroxina (aumenta ulteriormente i livelli di T3!)
- Propiltiouracile+tiroxina (?)
- Tiromimetici (DITPA, TRIAC, TETRAC)sono in fase di studio
  - Sembrano ridurre ulteriormente il T3 cerebrale!!!!!

Seleno cysteine insertion sequence binding protein 2 (SBP2)

- **Interviene** nella inserzione della selenocisteina nelle deiodinasi
- **Clinica**: ritardo di crescita, ritardo motorio e cognitivo, debolezza muscolare, ipoglicemia, sordità, infertilità
- **Diagnostica**: elevato T4 e rT3 e basso T3, TSH marginalmente elevato e bassi valori ematici di selenio

Resistenza agli ormoni tiroidei

- Prima descrizione nel 1967
- I pazienti presentano elevati valori di ormoni tiroidei e TSH inappropriatamente normale
- Sintomi: assenza, ipotiroidismo, ipertiroidismo
- La differente sensibilità a livello dei tessuti target spiega la clinica (forma generalizzata, pituitarica)
- Sono state rinvenute alterazioni a carico dei recettori per la T3 (TRβ1 and TRα1) codificati dai geni *THRB* e *THRA* rispettivamente.
- Si era pensato che la sindrome da resistenza fosse dovuta a mutazioni inattivanti il gene *THRB* (RTH-β), ma ultimamente si è visto che anche mutazioni nel gene *THRA (RTH*-α) causano un particolare quadro clinico.

Mutazioni gene THRB
(TRβ1, TRβ2; **RTH-β**)

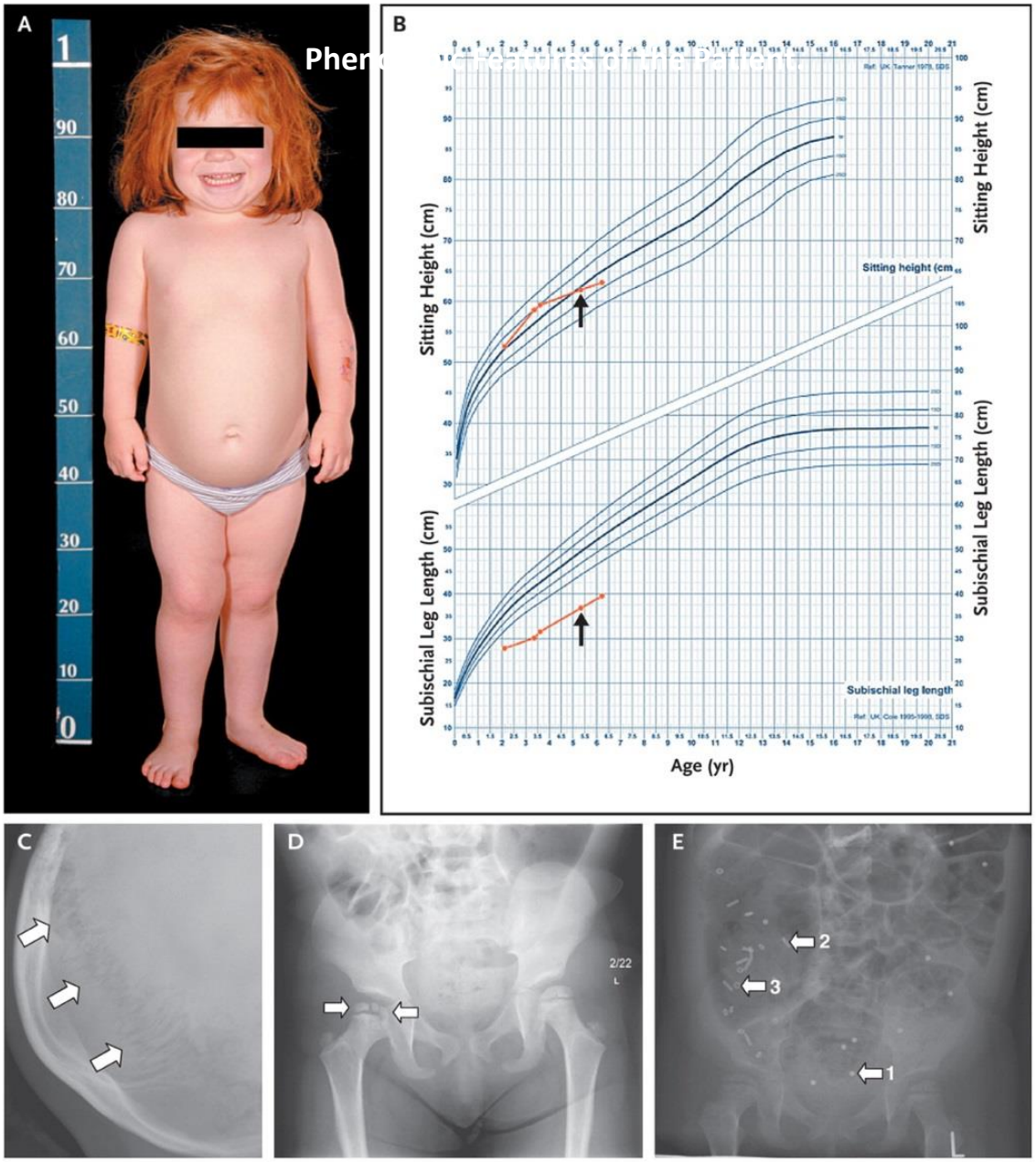
- Mutazioni in eterozigotismo esercitano una azione dominante negativa sul recettore wild type
- Delezioni si comportano secondo una trasmissione di tipo recessivo in quanto non vi è influenza negativa sul recettore wild type
- Mutazioni omozigoti sono rare e causano un fenotipo severo

Mutazioni gene *THRA* (TRa1; **RTH-α**)

- Il recettore mutato non trasmette il segnale ed inoltre reprime l'attività spontanea basale
- Inibisce con una azione dominante negativa il recettore wild-type TRα
- Probabilmente influenza anche l'attività deiodinasica: **D1** (T4 vs T3) o **D3** (T3 vs rT3)

- **Clinica**: ritardo di crescita (segmento inferiore), ritardo nell'apprendimento, stipsi, ipotono muscolare, incoordinazione motoria, ritardo nell'apprendimento

- **Laboratorio:** basso T4, elevato T3, basso rT3 e normale TSH, basso GH e IGF-1



Bochukova E et al. N Engl J Med 2012;366:243-249.

THYROID
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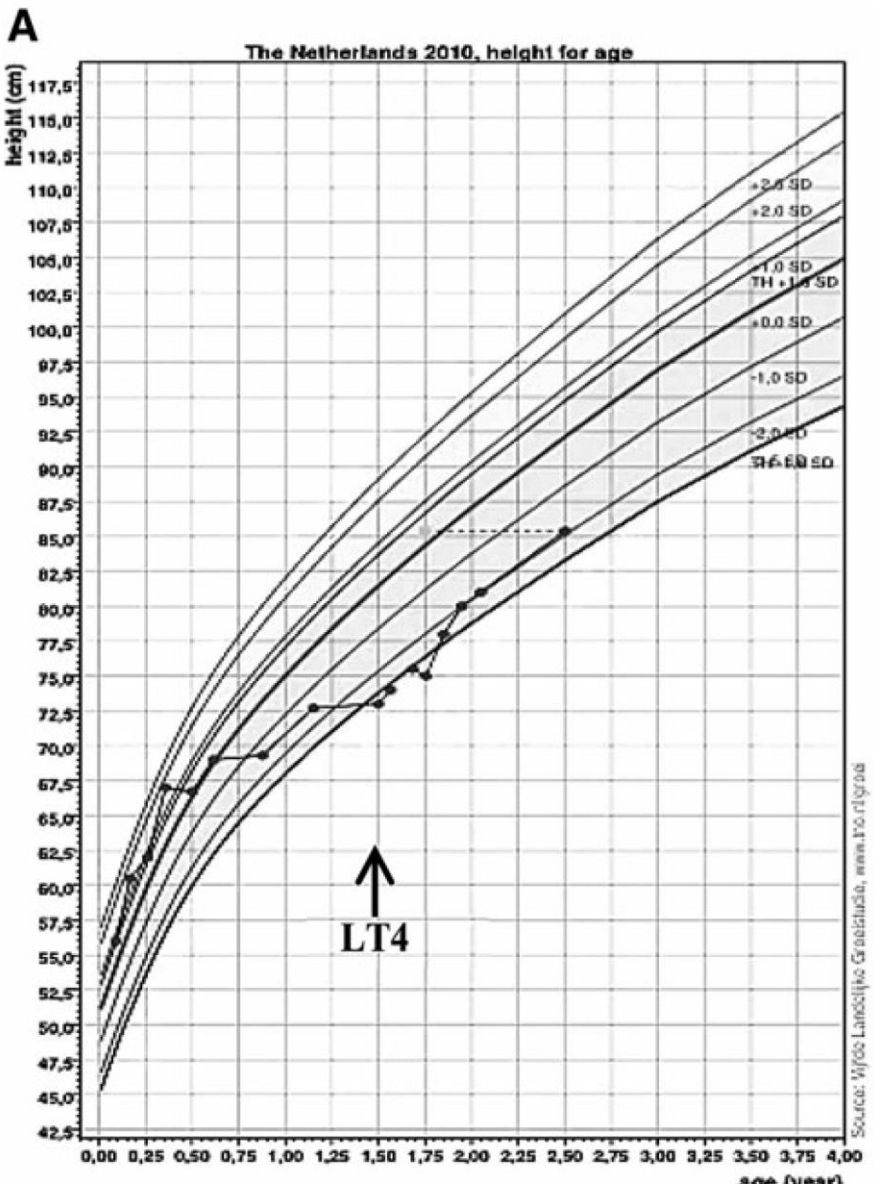
Resistance to Thyroid Hormone Alpha in an 18-Month-Old Girl: Clinical, Therapeutic, and Molecular Characteristics

Anja L.M. van Gucht,[1,2] Marcel E. Meima,[1,2] Nitash Zwaveling-Soonawala,[3] W. Edward Visser,[1,2] Eric Fliers,[4] Johanna M.B. Wennink,[5] Civile Henny,[6] Theo J. Visser,[1,2] Robin P. Peeters,[1,2,*] and A.S. Paul van Trotsenburg[3,*]


A
The Netherlands 2010, height for age
height (cm)
+2,0 SD
+2,0 SD
+1,0 SD
TH +1,0 SD
+0,0 SD
-1,0 SD
-2,0 SD
-2,5 SD
LT4
0,00 0,25 0,50 0,75 1,00 1,25 1,50 1,75 2,00 2,25 2,50 2,75 3,00 3,25 3,50 3,75 4,00
Source: Vijfde Landelijke Groeistudie, www.tno.nl/groei

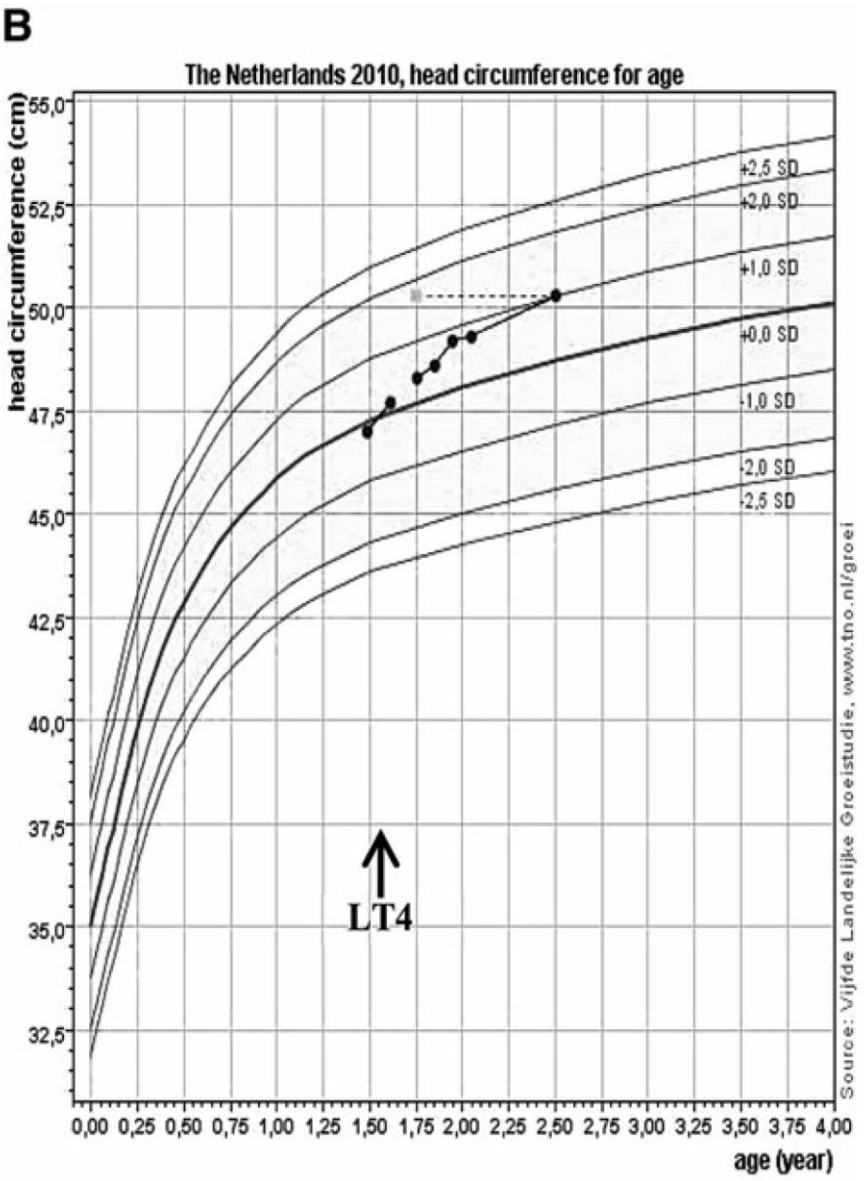

B
The Netherlands 2010, head circumference for age
head circumference (cm)
+2,5 SD
+2,0 SD
+1,0 SD
+0,0 SD
-1,0 SD
-2,0 SD
-2,5 SD
LT4
0,00 0,25 0,50 0,75 1,00 1,25 1,50 1,75 2,00 2,25 2,50 2,75 3,00 3,25 3,50 3,75 4,00
age (year)
Source: Vijfde Landelijke Groeistudie, www.tno.nl/groei

Table 1. Comparison of the clinical phenotype and serum thyroid hormone levels in patients with reduced sensitivity to thyroid hormone

			Nuclear receptors	
	Transport	Metabolism		
Mutated gene name	*MCT8*	*SBP2*	*THRB*	*THRA*
Clinical manifestations				
Neurological	Severe mental retardation and delayed motor and neurological development	(mild) delayed mental and motor development	ADHD, mental retardation in only minority of patients	Delayed motor and mental development
Growth	Decline in body weight during childhood	Delayed bone age and growth retardation	Delayed bone age and short stature in less than half of patients	Delayed bone age and growth retardation
Other	Feeding problems, X-linked	Immune deficiency, hypoglycaemia	Goitre, tachycardia	Constipation, low IGF1 levels
Laboratory findings				
TSH	Normal	Normal; slightly elevated	Normal or elevated	Normal
FT4	Low; low-normal	High	High	Low-normal
T3	High	Low; low-normal	Normal or elevated	High-normal
rT3	Low	High	High	Low

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Classification and Proposed Nomenclature for Inherited Defects of Thyroid Hormone Action, Cell Transport, and Metabolism

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Level of the defect			Phenotype	
Commonly used name[a]	*Synonyms*	*Gene involved and inheritance (OMIM)*	*Consistent (pathognomonic)*	*Common*
Thyroid hormone cell membrane transport defects (THCMTD)				
Monocarboxylate transporter 8 (MCT8) defect (8,9)	Allan-Herndon-Dudley syndrome	*MCT8 (SLC16A2)* gene (300095); X-chromosome linked	High T_3, low rT_3 and T_4, normal or slightly elevated TSH; low BMI; hypotonia, spastic quadriplegia; not walking or rarely ataxic gait; no speech or dysarthria, mental retardation	Hypermetabolism, paroxysmal dyskinesia, reduced muscle mass, seizures, poor head control, difficulty sitting independently
Idiopathic and other THCMTDs		To be determined	Unknown	
Thyroid hormone metabolism defects (THMD)				
Selenocysteine insertion sequence binding protein 2 (SBP2) defect (10)		*SBP2 (SECISBP2)* gene (607693); recessive	High T_4 and rT_3, low T_3, normal or slightly elevated TSH; growth retardation	Azoospermia, immunodeficiency, photosensitivity, delayed bone maturation, myopathy, hearing impairment, delayed developmental milestones
Idiopathic and other THMDs		To be determined	Unknown	
Thyroid hormone action defects (THAD): nuclear receptor and other				
Resistance to thyroid hormone (RTH)[b] (1–3)	Thyroid hormone unresponsiveness, generalized RTH, RTH beta; Refetoff syndrome	*THRB* gene (190160); dominant negative (rarely recessive)	High serum FT_4 and nonsuppressed TSH	High serum FT_3 and rT_3, high thyroglobulin, goiter, attention deficit hyperactivity disorder (ADHD), tachycardia
Non TR-RTH[c] (13)		Unknown	Same as above	Same as above
RTH alpha[d] (11,12)	Congenital nongoitrous hypothyroidism 6	*THRA* gene (190120); dominant negative	Low serum T_4/T_3 ratio; cognitive impairment, short lower limbs, delayed closure of skull sutures, delayed bone and dental development, skeletal dysplasia, macrocephaly; constipation; anemia	Low rT_3, seizures, placid behavior
Hypersensitivity to thyroid hormone (HTH)		Unknown	Low FT_4 and FT_3 with normal TSH and no serum transport defects	Normal thyroid gland
Idiopathic and other THADs		To be determined	Unknown	

[a]References are for first reported cases.
[b]Proposed future terminology: RTH β.
[c]RTH without mutations in the *THRB* gene.
[d]A single case with a mutation involving both TRα1 and TRα2 presented a more complex phenotype, including severe bone malformations, hypercalcemia with hyperparathyroidism, and diarrhea rather than constipation. It is unclear whether all observed abnormalities are due to the *THRA* gene mutation alone.
T_3, triiodothyronine; rT_3, reverse T_3; T_4, thyroxine; TSH, thyrotropin; FT_3, free T_3; FT_4, free T_4; BMI, body mass index; TR, thyroid hormone receptor.


Siete stati attenti???