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1. Introduction

1.1 Etiology of CH (Dyshormonogenesis / Dysgenesis)

1.1.1 Dyshormonogenesis

Thyroid dyshormonogenesis results from a defect in any one of the steps involved in the biosynthesis of thyroid hormone, from the transport of iodine across the apical membrane to its intracellular recycling from mono- and di-iodotyrosines. These defects are inherited as autosomal recessive traits and occur at higher frequency in consanguineous families. In population-based studies, mutations in activating the thyroperoxidase gene ($TPO$)\(^{1-4}\) and the dual oxidase-like domains 2 gene ($DUOX2$; see www.endocrine-abstracts.org/ea/0020/ea0020s14.2.htm) seem to be the most commonly involved.

1.1.2 Congenital Hypothyroidism from Thyroid Dysgenesis (CHTD) – The most frequent form

Congenital hypothyroidism from thyroid dysgenesis (CHTD) is a common disorder with a birth prevalence of 1 case in 4,000 live births \(^{5}\). CHTD is the consequence of a failure of the thyroid to migrate to its anatomical location (anterior part of the neck), which results in thyroid ectopy (lingual or sub-lingual) or of a complete absence of thyroid (athyreosis). The most common diagnostic category is thyroid ectopy (up to 80%). The majority of CHTD cases has no known cause, but is associated with a severe deficiency in thyroid hormones (hypothyroidism), which can lead to severe mental retardation if left untreated. Therefore, CHTD is detected by biochemical screening at 2 days of life, which enables initiation of thyroid hormone therapy during the second week of life. Even with early treatment (on average at 9 d), developmental delay may still be observed in severe cases (i.e., IQ loss of 10 points)\(^{6}\).

CHTD is predominantly non-syndromic and sporadic (i.e. 98% of cases are non-familial), has a discordance rate of 92% in MZ twins, and has a female and ethnic (i.e., Caucasian) predominance \(^{7,8}\). Moreover, germlinal mutations in thyroid related transcription factors NKX2.1, FOXE1, PAX-8, and NKX2.5 have been identified in only 3% of patients with sporadic CHTD \(^{9}\) and linkage analysis excluded these genes in some multiplex families with
Recent works have shown that (i) ectopic thyroids show a differential gene expression compared to that of normal thyroids (with enrichment for the Wnt signaling pathway) and (ii) cases of CHTD are associated with rare CNVs.

### 1.2 Thyroid embryology

In all vertebrates, the developing thyroid is first visible as a thickening of the endodermal epithelium emerging at the most anterior part of the foregut, named foramen caecum in humans. This structure, the median thyroid anlage, is evident by E8-8.5 day in mice, 24 hpf in zebrafish and by E20-22 day in humans. At this time, primitive thyroid cells already have a distinct molecular signature, with co-expression of four transcription factors Hhex, Tift1, Pax8 and Foxe1. Thereafter, the primitive thyroid moves progressively to reach its final location by the seventh week in humans (see Table 1 below for comparison between species).

<table>
<thead>
<tr>
<th>Species</th>
<th>Specification</th>
<th>Budding</th>
<th>Migration</th>
<th>Follicle formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>E20-22</td>
<td>E24</td>
<td>E25-50</td>
<td>E70</td>
</tr>
<tr>
<td>Mouse</td>
<td>E8.5</td>
<td>E10</td>
<td>E10.5-13.5</td>
<td>E15.5</td>
</tr>
<tr>
<td>Zebrafish</td>
<td>24 hpf</td>
<td>36-46 hpf</td>
<td>48-55 hpf</td>
<td>55 hpf</td>
</tr>
</tbody>
</table>

E, embryonic day; hpf, hours post-fertilization.

Table 1. Timing of key morphogenic events during thyroid development in different species (adapted from 13).

### 2. Epidemiology of CH

#### 2.1 Basics

Permanent primary congenital hypothyroidism is the most common form of congenital hypothyroidism, and is in fact the most common congenital endocrine disorder: estimates of its prevalence depend on the screening methods, algorithms and cut-offs used but average 1 in 2,500 newborn infants. Two thirds of the cases are due to thyroid dysgenesis (thyroid ectopy, athyreosis and thyroid hypoplasia) with a prevalence of 1 in 4,000 newborn infants, which has remained stable over the last 20 years in our jurisdiction and which is not influenced by seasonal factors. Ten to fifteen percent are due to recessively inherited defects in hormone synthesis resulting in goiter (birth prevalence of 1:30,000), while a growing number of cases, as a consequence of lower TSH cut-offs, are due to mild functional disorders with a normal thyroid gland in situ (15-20%, birth prevalence of 1:20,000 to 1:15,000).

#### 2.2 Controversies about neonatal screening program for CH

While screening for CH is an unqualified public-health success, a number of controversies mark the almost four decades since it was first implemented. All these controversies have
three points in common: (a) the biochemical identification of CH and the lack of agreement on the cutoffs used to detect CH \(^{16}\), (b) whether there is a correlation between neonatal TSH and \(T_4\) values and later mental development \(^{20, 21}\), and (c) the fact that CH encompasses a variety of different thyroid etiologies (dysgenesis, dyshormonogenesis with goiter, normal-size gland \textit{in situ}) \(^{12}\). Consequently, a uniform definition of CH is difficult considering the spectrum of pathologies and the continuous nature of the distribution of TSH levels \(^{22, 23}\).

2.2.1 Which biochemical test to use for neonatal CH screening?

The first controversy was about the nature of the biochemical test to use for neonatal CH screening. For technical reasons related to the precision of the measurements around the cutoff values, Dussault and Laberge had initially developed a screening program based on total \(T_4\) as the primary measurement \(^{24}\). However, because primary CH is at least 10-fold more common than central hypothyroidism, TSH is the most logical analyte to measure \(^{25}\). Technical improvements leading to accurate TSH measurements on eluates of blood collected on dried spots have led to the adoption of TSH-based screening by an increasing number of jurisdictions, including Québec since 1987.

2.2.2 Should there be specific guidelines for screening for CH in premature and/or (very) low birth weight newborns?

A second controversy relates to whether there should be specific guidelines for screening for CH in premature and/or (very) low birth weight (VLBW) newborns. These newborns generally have low \(T_4\) with normal TSH, a condition that has been named hypothyroxinemia of prematurity for which there is at present no evidence that it should be screened for or treated \(^{26}\). By contrast, transient primary CH has been convincingly shown to be more frequent in premature newborns only in areas with a borderline low iodine intake \(^{27}\) and attributed in large part to the use of iodine-containing disinfectants \(^{28}\). However, permanent CH from dysgenesis or dyshormonogenesis is not more frequent in premature newborns. On the contrary, it tends to be associated with prolonged gestation \(^{29}\) and with a skewing of the birth weight distribution to the right \(^{30}\). Nevertheless, the New England CH Cooperative reported in 2003 that a ‘delayed TSH rise’ occurred more often in VLBW newborns and suggested that a second sample be systematically obtained; scintigraphic scans to determine the possible cause of this delayed-onset hyperthyrotropinemia were not performed \(^{31}\) and a recent update on a subset of these VLBW newborns has shown that the problem was transient, with no evidence of benefit from treatment \(^{32}\). Other studies showed that lowering the TSH cutoff on the first blood sample increased the number of preterm infants labeled as having CH \(^{33-35}\). Our previous study did not support the need for a specific protocol for low birth weight infants \(^{36}\) and our more recent one confirms that the incidence of CH in LBW newborns has remained stable in spite of the decreased cutoff on the repeat screening specimen \(^{17}\). Additionally, we have not identified a single patient with trisomy 21 and CH at screening. This is consistent with the observations of van Trotsenburg \textit{et al.} \(^{37}\) that the rightward shift of the distribution of neonatal screening TSH is minimal (95% confidence intervals: 4.8-7.6 vs 3-3.1 mU/L in controls) and insufficient to result in these patients being identified as having CH with our screening algorithm.
2.2.3 Is CH incidence increasing?

The last controversy arose from the reported increase in global incidence of CH in the United States 38. The cause of this increase is difficult to ascertain for the following reasons: (a) CH is a spectrum of different disorders which have only an elevated TSH in common, (b) newborn screening practices vary between jurisdictions, even within the same country, as does the documentation of the etiology or of the transient or permanent nature of CH, (c) most studies reporting an increased incidence of CH did not classify cases through the systematic use of thyroid scintigraphy 38-40.

In a recent study, we were able to assess the impact of a change (made in 2001) in screening practice on the incidence of CH, globally and by diagnostic sub-groups over a period of 20 years. Had the TSH cutoff remained unchanged in 2001, the incidence of CH (global and by diagnostic sub-groups) would have remained stable 17. Moreover, our lowering of the TSH cutoff at re-testing did not significantly increase the incidence of the most severe types of CH (athyreosis, ectopy and dyshormonogenesis with goiter). Rather, the additional cases identified predominantly had functional disorders with a normal-size gland in situ and a normal or low isotope uptake. Of note, even though these cases were associated with mild primary hypothyroidism, 86% were permanent. This finding is consistent with previous studies showing that even mild CH diagnosed after lowering the TSH cutoff was permanent in 75 to 89% of cases 33, 34, 41.

The next question is whether these cases of mild CH require L-T4 treatment to attain their full intellectual potential. The original purpose of screening for CH was to identify severe cases in which a benefit was clear (i.e., prevention of intellectual disability) 42. Over the last two decades, this original paradigm progressively shifted to the detection and treatment of all CH cases, including isolated hyperthyrotropinemas. With lower TSH cutoffs, additional cases are detected and treated but without evidence of benefit of this intervention on intellectual outcome. This lack of obvious benefit might be the reason why, in the United States, more than a third of children labeled as having CH on the basis of neonatal screening no longer receive treatment after age 4 years 43. If we are to treat patients and not numbers, there is an urgent need to come back to the original intent of screening for CH and, consequently, to evaluate whether newborns with mildly elevated TSH benefit from early diagnosis and treatment 26, 44, 45. Given that pediatric endocrinologists tend to recommend treatment, a controlled study to answer that question is unlikely to be performed. An alternative could be to track children with TSH levels in the upper 10% of the distribution of screening results but lower than the cutoff and to evaluate whether they have any evidence of intellectual disability. Such a ‘retrospective screening study’ was reported in 1984 by Alm and colleagues 46 and did not suggest any harm from transient and untreated neonatal hyperthyrotropinemia. Whether the same would be true of persistent infantile hyperthyrotropinemia remains to be determined.

2.3 CH and its impact on neurocognitive development

Before biochemical screening of newborn infants for hypothyroidism was introduced, the mean IQ of children with congenital hypothyroidism was 85 19, mainly because less than 20% of affected infants were diagnosed within three months after birth; even those with a normal IQ had deficits in fine motor control and learning disabilities 47. When biochemical
screening was implemented, it was rapidly shown that most infants with hypothyroidism treated soon after birth have normal psychomotor development. However, some controversy remains as to whether the consequences of very severe congenital hypothyroidism can be entirely avoided. Indeed, with early treatment, normalization of neurocognitive development is generally achieved, but a relative developmental delay is still observed in the most severely affected (i.e., IQ of 101 vs 111 in controls, loss of 10 points).

2.4 From epidemiology to molecular mechanisms

CHTD is predominantly not inherited (98% of cases are non-familial), it has a high discordance rate of 92% in monozygotic (MZ) twins, and it has a female and ethnic (i.e., Caucasian) predominance. Germinal mutations in thyroid-related transcription factors NKX2.1, FOXE1, PAX-8, and NKX2.5 have been identified by candidate gene screening in a small subset (3%) of patients with sporadic CHTD. Linkage analysis has excluded these genes in rare multiplex families with CHTD. Moreover, evidence of non-penetration of mutations in close relatives of patients (e.g. NKX2.5) suggests that modifiers, possibly additional de novo germline mutations such as copy number variants (CNVs) and/or somatic mutations, are associated with CHTD. Therefore, we hypothesize that the lack of clear familial transmission of CTHD may result from a requirement for two different genetic hits in genes involved in thyroid development. The first hit could be a rare inherited or de novo mutation in the germline, while the second mutation, in a different gene, could be germinal or somatic.

3. Genetic determinants of CHTD

3.1 Thyroid dysgenesis and genes, a complex duet

Currently, 26 genes (see Table 2) have been directly implicated in thyroid development, based on animal models and/or on their role in known human syndromes including CHTD. At the present time, systematic sequencing of four candidate genes (i.e., thyroid related transcription factors TITF-1/NKX2.1, FOXE1, PAX-8, and NKX2.5) identified mutations in only 3% of human CHTD. Evidence from animal models to date suggests that the embryonic development of the gland and its normal migration are dependent on the interplay among several transcription factors. In mice, the simultaneous expression of Tif1, Foxe1 and Pax8 is required for thyroid survival and migration, and all knockouts present with athyreosis at birth, although Foxe1 -/- mouse embryos at E11.5 have either thyroid ectopy (50%) or athyreosis (50%)12. Tif1, Foxe1 and Pax8 expression in thyroid follicular cells persist into adulthood. A multigenic model has been proposed based on studies of different strains of mice heterozygous for Pax8 and Tif1 genetic ablation. The two strains showed a differential predisposition to CHTD depending on several single-nucleotide polymorphisms in a third locus. Furthermore, inactivation of endodermic genes implicated in thyroid bud formation (i.e Hoxa5, Hoxa3, Hoxb3, Hoxd3, Shh and Hes1) or of genes implicated in cardiac (i.e. Nkx2.5, Nkx2.6, Hhex, Tbx1, Fibulin-1, Isl1 and Chordin) or musculoskeletal malformations (Shh inversion in short digits mice, Fgf10) point to
new candidate genes in humans with CHTD. Genes implicated in congenital heart malformations or in musculoskeletal malformations are of particular interest, as these conditions occur in up to 8% of CHTD cases \(^{73, 74}\). Another animal model, the zebrafish, has recently been used to study the origin of the thyroid by fate-mapping. Embryonic progenitor of thyroid cells stem from the definitive endoderm \(^{75}\) and inactivation of genes implicated in endoderm formation (e.g. *bon*, *cas*, and *oop*) subsequently impair thyroid gland formation in zebrafish \(^{76}\). In contrast to human and mice, TSH-TSHR axis seem to be necessary at early steps of thyroid morphogenesis \(^{15}\). Moreover, work in zebrafish also highlights the role of tissue-tissue interactions in normal thyroid development. For example, impaired activity of the transcription factor *hand2* in cardiac mesoderm has been shown to result in defective thyroid development \(^{77}\).

In humans, mutations have been found in leukocyte DNA of CHTD patients in the genes encoding transcription factors *TITF-1/NKX2.1* \(^{57, 58, 78, 79}\), *FOXE1* \(^{59, 60}\), *PAX8* \(^{61}\), and *NKX2.5* \(^{55}\). In these genes, all reported mutations so far were heterozygous and patients presented with thyroid gland hypoplasia; *except for FOXE1 mutations which have been found exclusively in the homozygous state in patients presenting with athyreosis, cleft palate and spiky hair* \(^{59}\). *TITF-1/NKX2.1* mutations are almost always *de novo*, whereas *PAX8* and *NKX2.5* mutations are often inherited with incomplete penetrance (*i.e.* a mutation-carrier parent is unaffected) \(^{55, 57-61}\). Other genes (*GLIS3, URB1, SALL1* and *TBX1*) are mutated in syndromes where thyroid dysfunction is associated with other dysmorphisms and is generally mild, except for *GLIS3* patients, which can have severe CH \(^{80, 81}\).

Current knowledge on possible causes of CHTD suggests multiple loci that interact with modifiers such as sex and genetic background whereas environmental factors seem to have little impact. CHTD is sporadic in 98% of cases (*i.e.* nonetheless, 2% of cases are familial) \(^{82}\). A systematic survey of monozygotic (MZ) twins, which yielded a discordance rate of 92% \(^{7}\), as well as the documented ethnic (Caucasian) \(^{53}\) and female predominance in CHTD (*i.e.* 2:1 female:male) \(^{73}\) suggest that the genetic predisposition to CHTD is complex. Our published studies, showing no temporal or seasonal trends for CHTD and no effect of maternal folate supplementation on CHTD incidence, suggest that major environmental co-factors are unlikely \(^{5, 17}\).

### 3.2 Rationale to study genetic determinants of thyroid dysgenesis

Another sporadic congenital endocrine disorder that is much less common than thyroid dysgenesis, focal hyperinsulinism, has been shown to result from a two-hit model combining a germline mutational hit (consistent with the rare occurrence of familial cases \(^{83}\)) with a somatic loss of genomic imprinting \(^{84}\); in the pancreatic lesions found in these patients, a paternally inherited mutation in the SUR1 or KIR6.2 gene is found together with loss of the maternal 11p15 allele (loss of heterozygosity), a locus which contains many imprinted genes. The loss of heterozygosity is a somatic event restricted to the pancreatic lesion, which explains why focal congenital hyperinsulinism is a sporadic disease with a genetic etiology. A two-hit model combining inherited susceptibility polymorphisms with germ line or somatic mutation at a second locus in threshold-sensitive genes has recently been shown to be relevant for a severe form of mental retardation \(^{85}\).
<table>
<thead>
<tr>
<th>Gene</th>
<th>Features</th>
<th>Species</th>
<th>Thyroid phenotype</th>
<th>Additional phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>acv</td>
<td>growth factor, fgf8</td>
<td>zebrafish</td>
<td>Hydropsyse</td>
<td>Lack of cerebellum and hindbrain-boundry</td>
</tr>
<tr>
<td>bon</td>
<td>mixer TF</td>
<td>zebrafish</td>
<td>Hydropsyse</td>
<td>Overall reduction of the endoderm</td>
</tr>
<tr>
<td>cas</td>
<td>sox TF</td>
<td>zebrafish</td>
<td>Hydropsyse</td>
<td>Absence of endoderm</td>
</tr>
<tr>
<td>cyc</td>
<td>nodal ligand</td>
<td>zebrafish</td>
<td>Hydropsyse</td>
<td>Overall reduction of the endoderm, neural tubes defects, cyclopia</td>
</tr>
<tr>
<td>fse</td>
<td>GATAs TF</td>
<td>zebrafish</td>
<td>Hydropsyse or hypothyrosis</td>
<td>Aplasia of liver, pancreas, thymus, heart, pharynx, proctoral defects</td>
</tr>
<tr>
<td>han2</td>
<td>bHLH TF</td>
<td>zebrafish</td>
<td>Hydropsyse or hypothyrosis</td>
<td>Liver aplasia</td>
</tr>
<tr>
<td>hhex</td>
<td>Homeodomain TF</td>
<td>zebrafish</td>
<td>Hydropsyse or hypothyrosis</td>
<td>Forebrain defect</td>
</tr>
<tr>
<td>nkel (pax2.1)</td>
<td>Pariod-box TF</td>
<td>zebrafish</td>
<td>Hydropsyse</td>
<td>Lack of pronephric duct and absence of endoderm</td>
</tr>
<tr>
<td>mouse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chordin</td>
<td>Extracellular BMP</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Cardiac outflow tract defects, aplasia of thymus, parathyroid</td>
</tr>
<tr>
<td>Eein</td>
<td>Endothelin signalin peptide</td>
<td>mouse</td>
<td>Hydropsyse, absent iris</td>
<td>Craniofacial, cardiac and thymus defects</td>
</tr>
<tr>
<td>Eya1</td>
<td>Eya TF</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Aplasia of kidneys, thymus, parathyroid</td>
</tr>
<tr>
<td>Fgf10</td>
<td>Growth factor</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Aplasia of limbs, lungs, phylary, salivary glands</td>
</tr>
<tr>
<td>Flium-1</td>
<td>ECM protein</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Craniofacial, cardiac and thymus defects</td>
</tr>
<tr>
<td>Fgfe</td>
<td>Forkhead TF</td>
<td>mouse</td>
<td>Ectopy or atrophyse</td>
<td>Cleft palate</td>
</tr>
<tr>
<td>Fgf</td>
<td>Transducer of FGF</td>
<td>mouse</td>
<td>Hypothyrosis, bilobation defect</td>
<td>Thymi and parathiroid defects</td>
</tr>
<tr>
<td>Hes1</td>
<td>Basic helix-loop-helix protein</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Forebrain truncations, liver aplasia, complex heart malformations</td>
</tr>
<tr>
<td>Hhex</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Hypothyplastic UBB</td>
</tr>
<tr>
<td>Hhexa3</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Hydropsyse, bilobation defect</td>
<td>Cardiovascular and skeletal defects</td>
</tr>
<tr>
<td>Hhexa5</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Empty thyroid follicle</td>
<td></td>
</tr>
<tr>
<td>Hhexb3</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Ectopy in Hhexa3, Hhexb3 double mutants</td>
<td>Cardiovascular and skeletal defects, Thymi and parathyroid agenesis</td>
</tr>
<tr>
<td>Hhexc3</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Ectopy in Hhexa3, Hhexb3 double mutants</td>
<td>Heart, pancreas and neural defects</td>
</tr>
<tr>
<td>Isl1</td>
<td>LIM homeodomain TF</td>
<td>mouse</td>
<td>Hypothyplasia of thyroid plaque</td>
<td>Thoracic defects, spectrum of midline defect, ophryogastric</td>
</tr>
<tr>
<td>Nke2.1</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Pulmonary aplasia, neural defects,</td>
</tr>
<tr>
<td>Nke2.5</td>
<td>Homeodomain TF</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Only in the Nke2.5, Nke2.5 double heterozygous mice</td>
</tr>
<tr>
<td>Pax3</td>
<td>Paired-box TF</td>
<td>mouse</td>
<td>Hypothyplasia, bilobation defects</td>
<td>Thymi and parathyroid defects</td>
</tr>
<tr>
<td>Pax8</td>
<td>Paired-box TF</td>
<td>mouse</td>
<td>Hydropsyse</td>
<td>Reproductive tract defects</td>
</tr>
<tr>
<td>Sihh</td>
<td>Secreted morphogen</td>
<td>mouse</td>
<td>Hemangiosis</td>
<td>Holopsycenopelia, midline defects, aberrant carotid arteries and short digits</td>
</tr>
<tr>
<td>Tbx1</td>
<td>T-box TF</td>
<td>mouse</td>
<td>Hypothyplasia, bilobation defect</td>
<td>Cardio outflow tract defects, aplasia of thymus, parathyroid</td>
</tr>
<tr>
<td>Twisted</td>
<td>modulator of BMP</td>
<td>mouse</td>
<td>Loss of Hhex expression at bud-stage</td>
<td>Vertebral defects, spectrum of midline defect, ophryogastric</td>
</tr>
<tr>
<td>human</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOXE1 (TITF2)</td>
<td>Forkhead TF</td>
<td>human</td>
<td>Hydropsyse</td>
<td>Cleft palate, choanal atresia, Spiky hair</td>
</tr>
<tr>
<td>GLIS3</td>
<td>Human</td>
<td>human</td>
<td>Hydropsyse</td>
<td>Neonatal diabetes, cystic kidneys, cholestatis.</td>
</tr>
<tr>
<td>Nkx2.5</td>
<td>Homeodomain TF</td>
<td>human</td>
<td>Thyroid in situ with primary hypothyroidism</td>
<td>Congential heart malformations</td>
</tr>
<tr>
<td>Pax8</td>
<td>Paired-box TF</td>
<td>human</td>
<td>Hydropsyse</td>
<td>Unilateral renal agenesis</td>
</tr>
<tr>
<td>Sall1</td>
<td>Zinc finger TF</td>
<td>human</td>
<td>Thyroid in situ with primary hypothyroidism</td>
<td>Townsen-Brooks syndrome</td>
</tr>
<tr>
<td>Tbx1</td>
<td>T-box TF</td>
<td>human</td>
<td>Thyroid in situ with primary hypothyroidism</td>
<td>DiGeorge with congenital heart malformations</td>
</tr>
<tr>
<td>TITF2 (Nkx2.1)</td>
<td>Homeodomain TF</td>
<td>human</td>
<td>Thyroid in situ with mild primary hypothyroidism</td>
<td>Respiratory failure, cheiroathoestasis</td>
</tr>
<tr>
<td>UVRB1</td>
<td>E3 ubiquettin ligases of the N-end rule pathway</td>
<td>human</td>
<td>Thyroid in situ with primary hypothyroidism</td>
<td>Johnson-Blizzard Syndrome</td>
</tr>
</tbody>
</table>

Table 2. Human genes and animal models of thyroid dysgenesis (adapted from 13).
3.3 Discordance between MZ twins for CHTD argues for association of somatic mutations with CHTD

Discordance between MZ twins argues against a germline mutation of high penetrance. However, the occurrence of familial cases (2%, 15 times more than expected by chance alone) and evidence of non-penetrance of mutations in close relatives of patients (e.g. NKX2.5) suggests that modifiers, possibly additional de novo germline mutations such as copy number variants (CNVs) and/or somatic mutations are associated with CHTD. Postzygotic (somatic) mutations, resulting in mosaicism, has been associated with discordance in MZ pairs for genetic conditions such as otopalatodigital syndrome spectrum disorders or Dravet’s syndrome. Classical twin studies (i.e., studies of affected vs unaffected MZ pairs) have limitations because: (i) the process of twining might itself be a risk factor for congenital birth defects (CHTD included) and (ii) a differential extent of chimerism in blood versus other tissues could interfere with detection of clear genetic differences between MZ twins using leukocyte-derived DNA. These limitations are potentially overcome by studying the genomes in somatic tissue of MZ twins discordant for CHTD.

4. Conclusion: Thyroid dysgenesis is a model disorder for congenital malformations and neurocognitive development

CHTD is a common disorder with a birth prevalence of 1 case in 4,000 live births. Even with early treatment (on average at 9 d), developmental delay is still observed in some patients (with an average IQ reduction of 10 points). The severity of the hypothyroidism is not solely responsible for this. Therefore, molecular markers are necessary to identify patients with possible susceptibility for mental retardation (i.e. genes involved both in neuronal and thyroid migration during development, such as NKX2.1). Patients in this category will benefit from earlier intervention to stimulate their neurocognitive development. The next logical goals will be (i) to determine whether mutations of discovered genes are associated with poor neurocognitive outcome, by sequencing these genes in CHTD patients with significant intellectual disabilities (need of special educational support) and (ii) to assess if patients in this category will benefit from earlier intervention to stimulate their neurocognitive development.

More generally, unraveling the etiology of CHTD may shed light on other more complex and less easily treatable congenital malformations (e.g. of the brain and heart) and provides a prototype approach for the study of congenital disorders currently unexplained by classical genetics.

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6. References


Congenital Hypothyroidism due to Thyroid Dysgenesis: From Epidemiology to Molecular Mechanisms

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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