REVIEW

Congenital hypothyroidism and thyroid cancer

Gustavo Penna1,2, Ileana G S Rubio3,4,5, Ester Saraiva Brust3,4, Juliana Cazarin6, Fabio Hecht6, Nina Ramalho Alkmim2,7, Kamilla M A Brandão Rajão2,8 and Helton Estrela Ramos9,10,11

1Department of Clinical Medicine, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
2Endocrinology Service of Institute Orizonti, Belo Horizonte, Minas Gerais, Brazil
3Department of Biological Science, Molecular Thyroid Science Laboratory, Federal University of São Paulo, São Paulo, Brazil
4Biotechnology Post-graduation Program, Federal University of São Paulo, São Paulo, Brazil
5Structural and Functional Biology Program, Federal University of São Paulo, São Paulo, Brazil
6Laboratory of Endocrine Physiology, Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
7Post-Graduation Program Molecular Medicine, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil
8Endocrinology Service of Hospital das Clínicas, Federal University of Minas Gerais, Belo Horizonte, Brazil
9Department of Bioregulation, Health & Science Institute, Thyroid Study Laboratory, Federal University of Bahia, Salvador, Brazil
10Post-Graduation Program Medicine and Health, Faculty of Medical Sciences, Federal University of Bahia, Salvador, Bahia, Brazil
11Post-Graduate Program in Interactive Processes of Organs and Systems, Health & Science Institute, Federal University of Bahia, Salvador, Bahia, Brazil

Correspondence should be addressed to G Penna: gustavocpenna@gmail.com

Abstract

Differentiated thyroid carcinoma (DTC) combined with congenital hypothyroidism (CH) is a rare situation, and there is no well-established causal relationship. CH is a common congenital endocrine, while DTC occurring in childhood represents 0.4–3% of all malignancies at this stage of life. The association of CH with DTC could be related to dyshormonogenetic goiter (DHG) or developmental abnormalities. This review will explore the clinical features and the molecular mechanisms potentially associated with the appearance of DTC in CH: sporadic somatic driver mutations, chronic increase of thyroid-stimulating hormone (TSH) levels, higher concentrations of hydrogen peroxide (H2O2), cell division cycle associated 8 (Borelain/CDC8) gene mutations, and in others genes associated with CH – either alone or associated with the mechanisms involved in dyshormogenesis. There are some pitfalls in the diagnosis of thyroid cancer in patients with CH with nodular goiter, as the proper cytological diagnosis of nodules of patients with dyshormogenesis might be demanding due to the specific architectural and cytological appearance, which may lead to an erroneous interpretation of malignancy. The purpose of this article is to suggest an analytical framework that embraces the fundamental relationships between the various aspects of CH and CDT. In face of this scenario, the entire genetic and epigenetic context, the complex functioning, and cross talk of cell signaling may determine cellular mechanisms promoting both the maintenance of the differentiated state of the thyroid follicular cell and the disruption of its homeostasis leading to cancer. Whereas, the exact mechanisms for thyroid cancer development in CH remain to be elucidated.

Key Words
- congenital hypothyroidism
- goiter
- dyshormogenesis
- thyroid cancer
Introduction

Differentiated thyroid carcinoma (DTC) is a common malignancy within the endocrine system but a rare disease in children, accounting for up to 3% of cases in all childhood cancers, and with an annual incidence of 0.2–1 cases per million children (Paulson et al. 2019). The vast majority (>90%) of follicular-derived thyroid carcinomas is papillary thyroid carcinoma (PTC) (Nilsson & Fagman 2017). It has been previously shown that pediatric patients with a history of goiter or benign thyroid nodule are at increased risk of presenting DTC (Gupta et al. 2013). However, a potential study bias is that children with known congenital diseases including hypothyroidism are more strictly followed with serial thyroid ultrasound during life, leading to the early discovery of incidental PTCs.

The possibility of a causal association instead of a direct cause-effect link in cases of co-occurrence of congenital hypothyroidism and thyroid cancer should also be considered. Nevertheless, traditional risk factors well recognized in the development of DTC in children include iodine deficiency, autoimmune thyroid disease, and radiation exposure (Rose et al. 2012, Francis et al. 2015, Turcotte et al. 2017, Paulson et al. 2019, Pessôa-Pereira et al. 2019, Zirilli et al. 2019). Yet, it is true that Hashimoto’s thyroiditis could partially justify the association between higher serum thyroid-stimulating hormone (TSH) levels and an increased hazard of malignancy (Boelaert 2009). Undeniably, DTC has been further reported continuously in patients with congenital goiter (CG) or dysshormogenesis (DH), conjecturing that the uninterrupted TSH stimulus may perhaps contribute to the propensity of DTC; however, in reality, this association has been advised by some authors (Boelaert 2009, Fiore et al. 2010) and not recommended by others (Castro et al. 2011, Kim et al. 2011).

Thyroid dysgenesis (TD) is the foremost source of congenital hypothyroidism (CH), and it comprises several distinct phenotypes: (a) athyreosis, the most severe, in which no thyroid vestige can be found; (b) ectopic, frequently a primitive gland present outside the thyroid bed; (c) hypoplasia, considered a minuscule orthotopic gland and d) hemiagenesis, identified by the absence of one lobe, mostly meaning an ulceration evolution error (Ramos et al. 2008, Cerqueira et al. 2018).

However, DH is the least frequent type of CH, representing 10 to 15% of all CH cases (Grasberger & Refetoff 2011). DH is caused by altered proteins involved in one of the crucial steps of thyroid hormone (TH) biosynthesis and secretion: (a) solute carrier family 5 member 5 (SLC5A5/NIS): iodide trapping from blood; (b) solute carrier family 26 member 4 (pendrin): iodide discharge beyond the apical membrane; (c) thyroid peroxidase (TPO), dual oxidase 2 (DUOX2) and dual oxidase maturation factor 2 (DUOXA2): organization of iodide within the follicular lumen; (d) thyroglobulin (TG): a substrate for TH production and e) iodotyrosine deiodinase (DEHAL1): the ability to recycle iodine (Grasberger & Refetoff 2011).

When associated with a congenital thyroid problem, pediatric DTC carries some unique dilemmas, both at the diagnostic and therapeutic levels, which need to be appropriately addressed to assure the best management and result. The purpose of this article is to suggest an analytical framework that embraces the primary relationships between the various aspects of congenital hypothyroidism and thyroid cancer. This review will explore the mechanisms involved in DH or TD, either alone or associated with the molecular features potentially associated with the appearance of CDT in CH – one or more of them: sporadic somatic driver mutations (constitutive activation of mitogen-activated protein kinase (MAPK), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PI3K)/AKR mice thymoma oncogene (AKT) activation), the chronic increase of TSH levels, higher concentrations hydrogen peroxide (H$_2$O$_2$), cell division cycle associated 8 (Borelain/CDCA8) gene mutations and others genes associated with CH.

Clinical aspects of thyroid cancer in sporadic forms of congenital hypothyroidism

Thyroid dysgenesis (TD)

Ectopic thyroid (ET) occurs when it is not located in the standard thyroid compartment, generally observed in the lingual/sublingual (in most cases), thyroglossal, laryngotracheal or lateral cervical areas (Klubo-Gwiazdzinska et al. 2011, Nilsson & Fagman 2017). It might be associated with an involution in size and hypofunction sometimes appearing in the neonatal period or later (puberty or adult life) (Ramos et al. 2008). Despite the ability of the ectopic thyroid to synthesize T4, it may be insufficient at some point in life leading to hypothyroidism and goiter, as observed in some of the patients (Camargo 2018). ET may be subjected to the same pathological processes as the normal orthotopic thyroid, such as autoimmune disease, hyperplasia, and tumorigenesis, albeit, it has...
not been considered an increased risk condition for malignant transformation (Klubo-Gwiedzinska et al. 2011, Tian et al. 2014). The association between lingual thyroid and DTC was recently reviewed (Klubo-Gwiedzinska et al. 2011, Huang et al. 2019). To our knowledge, the majority of DTC cases associated with ET are not related to a previous history of CH; although, in some cases, hypothyroidism has been observed or has become symptomatic during puberty, pregnancy, or menses (Díaz-Arias et al. 1992, Pérez et al. 2003, Kennedy & Riefkohl 2007, Seviç et al. 2010, Chen et al. 2013, Mogi et al. 2018). Yet, in relation to the thyroglossal duct associated with DTC, to the best of our knowledge, most cases are not linked to a previous history of CH. Siklar et al. described a patient who presented CH detected in the neonatal period and who, subsequently, developed synchronous thyroglossal duct carcinoma and DTC at 19 years old (Siklar et al. 2012).

Hemangioma (HG) is an uncommon congenital abnormality in which a thyroid lobe fails to develop (Ramos et al. 2008). The real prevalence of HG is unknown because it is typically detected incidentally in imaging obtained to assess other conditions, and a compensatory mechanism of thyroid hyperplasia with goiter formation might occur to balance the hormonal deficit. An unilateral goiter in the remnant lobe is commonly confounded with a thyroid nodule or mass (Castanet et al. 2005, Wu et al. 2012). The coexistence of HG and DTC has been reported in euthyroid adults (not in children with CH), and this condition was not consistently linked to an increased risk of tumorigenesis (McHenry et al. 1995, Huang et al. 2002, Pizzini et al. 2005, Niedziela 2006, Wang et al. 2014). The incidence of co-occurrence of DTC and HG has been estimated at 3%, but this does not seem to justify empirical thyroidectomy or active surveillance (Mikosch et al. 1999, Maiorana et al. 2003, Wu et al. 2010, 2012).

**Dyshormonogenesis (DH)**

DH is a rare disorder, with a worldwide incidence of 1:30,000 to 1:50,000 newborns, and it is often combined with goiter formation, sometimes occurring since the intrauterine period (CG, congenital goiter) (Ghosein et al. 1997, Rastogi & LaFranchi 2010). Commonly, the goiter is first diffused and gradually becomes nodular, with solid and fleshy consistency, essentially identified in patients from a non-endemic area. As previously mentioned, the increase in thyroid volume can also be observed at birth, without the maternal intake of goitrogenic substances (Deshpande & Bobhate 2005), or during fetal development (Huel et al. 2009).

In turn, DH can be subcategorized based on radioiodine uptake and perchlorate test in (a) iodide transport defect (ITD) (Nicola et al. 2011), who has little or no uptake of radioiodine in the thyroid and (b) iodide organification defect (IOD) with normal radioiodine uptake (Nascimento et al. 2003). The patient’s phenotype depends on the severity of the inborn TH biosynthesis error. A severe defect will lead to neonatal CH, goiter, and developmental retardation if not properly treated (Grosberger & Refetoff 2011). Veritally, DH is present only in a minority of DH patients shortly after birth, and it is mainly attributed to relevant biallelic mutations in the TPO, NIS, TG, or pendrin (PDS) genes (Rubio & Medeiros-Neto 2009, Ris-Stalpers & Bikker 2010, Grosberger & Refetoff 2011, Wémeau & Kopp 2017). In contrast, weaker defects, typically attributed to DUOX2 gene mutations, might be present during adolescence or pregnancy as a minimal thyroid hypofunction (Grosberger & Refetoff 2011, Muzza & Fugazzola 2017).

Although rare, follicular carcinoma, papillary thyroid carcinoma, or microcarcinoma have been reported in the setting of DH (Table 1). Moreover, follicular thyroid carcinoma (FTC) has been reported more than other types (Potter & Morris 1935, McGrir & et al. 1959, Stanbury & Vickery 1962, Medeiros-Neto & Oliveira 1970, Illum 1978, Cooper et al. 1981, Abs et al. 1991, Medeiros-Neto et al. 1998, Ozcük et al. 1998, Camargo et al. 2001, Bashir et al. 2004, Kim et al. 2004, Alzahrani et al. 2006, Chertok Shacham et al. 2012). In fact, in the last few years, after improvements in the anatomicopathological examination, the association between dyshormonogenic goiter (DHG) and DTC has been increasing, as described by Ghosein et al., who observed a prevalence as high as 6% (Ghosein et al. 1997). Long-term follow-up and regular neck ultrasound imaging are being considered to prevent the late diagnosis of DTC in patients with DHG (Boelaert 2009), and the recent European consensus guidelines update recommends a periodical neck ultrasound every 2 to 3 years in children and adolescents with goitrous CH due to DHG, to identify nodules that may require fine-needle aspiration biopsy to rule out thyroid carcinoma (van Trotsenburg et al. 2021). In reality, most genetic defects in all known thyroid-specific factors required for the synthesis of thyroid hormones have been described in association with DTC (Table 1).
Table 1  Cases of thyroid malignancy associated with dyshormonogenetic goiter and congenital hypothyroidism due to thyroid dysgenesis.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex (F/M) and age (years) at surgery</th>
<th>Clinical, macroscopic and microscopic aspects</th>
<th>Histology (reported in the original publication)</th>
<th>Distant metastasis</th>
<th>Molecular defect (mutation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potter &amp; Morris 1935 (n = 5)</td>
<td>3F, 2M (14–19)</td>
<td>Goiter, encapsulated neoplasm or infiltration of connective tissue, vascular invasion</td>
<td>Adenocarcinoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>McHenry et al. 1995 (n = 1)</td>
<td>1F (age not reported)</td>
<td>Unsuspected hemiagenesis, Graves’s disease, marked hyperplasia of a single lobe, and isthmus</td>
<td>FTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Rickles 1947 (n = 2)</td>
<td>2F (10, 11)</td>
<td>Case 1: multiple adenomas, no invasion; Case 2: papillary adenocystoma</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Thieme 1957 (n = 2)</td>
<td>1M, 1F (24, 22)</td>
<td>Cases 1 and 2: deafness, MNG; Case 1: vascular emboli, capsular invasion</td>
<td></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Roberts 1957 (n = 1)</td>
<td>1M (9)</td>
<td>Deafness, MNG</td>
<td>Consistent with adenocarcinoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>McGirr et al. 1959 (n = 1)</td>
<td>1F (9)</td>
<td>MNG (100 g)</td>
<td>Adenocarcinoma</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Stanbury &amp; Vickery 1962 (n = 1)</td>
<td>1M (27)</td>
<td>MNG, vascular invasion</td>
<td>FTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Crooks et al. 1963 (n = 1)</td>
<td>1M (16)</td>
<td>MNG (90 g), vascular invasion</td>
<td>Hyperplasia with adenocarcinoma change</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Medeiros-Neto &amp; Oliveira 1970</td>
<td>1F (27)</td>
<td>MNG, capsular, and vascular invasion</td>
<td>FTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hayek et al. 1973 (n = 1)</td>
<td>1M (7)</td>
<td>MNG, trabeculae, and ribbons of irregular cells with large nuclei having coarse chromatin and frequent mitoses, vascular invasion</td>
<td>Suspected carcinoma</td>
<td>No</td>
<td>Suspect of PDS defect (no molecular study)</td>
</tr>
<tr>
<td>Illum 1978 (n = 1)</td>
<td>1F (38)</td>
<td>Adenomatous colloid goiter (initially), capsular, vascular and ETE with muscular invasion</td>
<td>FTC</td>
<td>No</td>
<td>Suspect of PDS defect (no molecular study)</td>
</tr>
<tr>
<td>Cooper et al. 1981 (n = 2)</td>
<td>1M, 1F (29, 23)</td>
<td>Case 1 (M): MNG, ETE (trachea and soft tissue), no vascular invasion; Case 2 (F): MNG (90 g), intermediate undifferentiation, no vascular invasion</td>
<td>FTC</td>
<td>Case 1: right scapula; Case 2: posterior ilium and lung</td>
<td>No</td>
</tr>
<tr>
<td>Yashiro et al. 1987 (n = 1)</td>
<td>1M (35)</td>
<td>MNG (108 g), vascular invasion</td>
<td>PTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Abs et al. 1991 (n = 1)</td>
<td>1F (52)</td>
<td>Deafness, toxic MNG, ETE</td>
<td>FTC</td>
<td>Mediastinum, bronchus, ribs, pelvis</td>
<td>No</td>
</tr>
<tr>
<td>Ghossein et al. 1997 (n = 3)</td>
<td>2M (33, 9), 1F (8)</td>
<td>Case 1 (M, 33 years): MNG (26 g), 0.7 cm; Case 2 (F, 8 years): MNG, 0.5 cm; Case 3 (M, 9 years): MNG (18 g), multifocal (0.8 and 0.5 cm)</td>
<td>MPTC</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex (F/M) and age (years) at surgery</th>
<th>Clinical, macroscopic and microscopic aspects</th>
<th>Histology (reported in the original publication)</th>
<th>Distant metastasis</th>
<th>Molecular defect (mutation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medeiros-Neto et al. 1998 (n = 1)</td>
<td>1F (7 days of age)</td>
<td>Solid cervical mass (74 g) with calcifications and ETE to the base of the tongue and hypopharynx, mediastinum and vascular invasion</td>
<td>FTC</td>
<td>Lung and bone (both femurs, right tibia)</td>
<td>TPO (c.1-bp ins., 2505C)</td>
</tr>
<tr>
<td>Ozluk et al. 1998 (n = 1)</td>
<td>1F (49)</td>
<td>Deafness, large goiter, capsular invasion, no vascular invasion, associated with breast invasive ductal carcinoma</td>
<td>FTC</td>
<td>No</td>
<td>Suspect of PDS defect (no molecular study)</td>
</tr>
<tr>
<td>Camargo et al. 2001 (n = 1)</td>
<td>1F (53)</td>
<td>Deafness, goiter (150 g), ETE, death by hemoptysis caused by tumor invasion</td>
<td>FTC with areas of anaplastic transformation</td>
<td>Lung</td>
<td>PDS (c.279delT)</td>
</tr>
<tr>
<td>Bashir et al. 2004 (n = 1)</td>
<td>1F</td>
<td>MNG</td>
<td>FTC</td>
<td>UN</td>
<td>PDS</td>
</tr>
<tr>
<td>Kim et al. 2004 (n = 1)</td>
<td>1M</td>
<td>Deafness, large goiter</td>
<td>Poorly differentiated FTC</td>
<td>UN</td>
<td>No</td>
</tr>
<tr>
<td>Pizzini et al. 2005 (n = 1)</td>
<td>1M (54)</td>
<td>Hemiagenesis of left thyroid lobe, with multinodular lesions in the right lobe, mediastinal extension, dysphagia</td>
<td>FTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Hishinuma et al. 2005 (n = 7)</td>
<td>6F (12, 17, 27, 28, 36, 38), 1M (35)</td>
<td>Goiter, BRAF&lt;sup&gt;V600E&lt;/sup&gt; and BRAF&lt;sup&gt;K600E&lt;/sup&gt; somatic mutations in tumors from two patients</td>
<td>6 PTC</td>
<td>No</td>
<td>TG (p.C1077R) (p.C1077R)</td>
</tr>
<tr>
<td>Alzahrani et al. 2006 (n = 1)</td>
<td>1M (21)</td>
<td>MNG, RAS mutation negative</td>
<td>FTC</td>
<td>Skull, abdomen, femur</td>
<td>TG (g.IVS5+1G&gt;A) (Stop codon)</td>
</tr>
<tr>
<td>Drut &amp; Moreno 2009 (n = 1)</td>
<td>1F (5)</td>
<td>MNG, malignant nodule with 0.7 cm, PTC at FNA cytology (nuclear changes, pseudoinclusions), vascular invasion, LN metastasis</td>
<td>PTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kallel et al. 2009 (n = 1)</td>
<td>1M (13)</td>
<td>Compressive MNG, multifocal PTC (dominant lesion, 0.6 cm), microfollicular pattern, lymph node metastasis (0.3 cm)</td>
<td>MFVPTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oguz et al. 2009 (n = 1)</td>
<td>1M (19)</td>
<td>Deafness, MNG, no capsular or vascular invasion</td>
<td>PTC</td>
<td>No</td>
<td>PDS</td>
</tr>
<tr>
<td>Raef et al. 2010 (n = 1)</td>
<td>1F (31)</td>
<td>MNG, two surgeries for DTC (first: two foci of MFVPTC, 0.5 cm), recurrence after 4 years of follow-up</td>
<td>PTC with follicular and oncocytic variants</td>
<td>Skull, pelvis and lung</td>
<td>TG (g.IVS5+1G&gt;A) (Stop codon)</td>
</tr>
<tr>
<td>Chertok Shacham et al. 2012 (n = 1)</td>
<td>1M</td>
<td>MNG with tracheal compression, no vascular invasion</td>
<td>FTC</td>
<td>No</td>
<td>TPO (c.875C&gt;T) (p.S292F)</td>
</tr>
<tr>
<td>Wu et al. 2012 (n = 7)</td>
<td>7 (age and sex not reported)</td>
<td>Hemiagenesis</td>
<td>PTC</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Sakurai et al. 2013 (n = 1)</td>
<td>1M (37)</td>
<td>Deafness, MNG (482 g), encapsulated follicular lesion, no vascular or LN invasion; twin brother with PDS mutation but benign MNG at surgery</td>
<td>FVPTC</td>
<td>No</td>
<td>PDS (c.2168A&gt;G; c.ins2110GCTGG)</td>
</tr>
<tr>
<td>Erden et al. 2013 (n = 1)</td>
<td>1F (17)</td>
<td>Recurrence of MNG 6 years after first operation</td>
<td>PTC</td>
<td>Lung</td>
<td>No</td>
</tr>
<tr>
<td>Zhu et al. 2015 (n = 1)</td>
<td>1F</td>
<td>Multifocal PTC, lymph node, and nerve invasion</td>
<td>PTC</td>
<td>No</td>
<td>TPO (c.2268–2269 insT)</td>
</tr>
</tbody>
</table>

(Continued)
Molecular aspects of thyroid cancer associated with genetic forms of congenital hypothyroidism

Thyroid dysgenesis genetic defects

NK2 homeobox 1 (NKX2-1) is a crucial transcription factor for thyroid development, and germline mutations have been hypothesized as susceptibility elements of DTC (Ngan et al. 2009). In a genome-wide association study, a common variant near the NKX2-1 gene was associated with DTC (Gudmunsson et al. 2009). In one study, a frequent loss-of-function alteration of NKX-2-1 (p.A339V) was associated with PTC in patients harboring multinodular goiter (MNG) (Ngan et al. 2009). However, no mutations in the NKX2-1 gene have been described in patients with CH associated with DTC, and other studies have not confirmed NKX2-1 mutations as a risk factor for DTC in the clinical context of MNG (Cantara et al. 2010). Currently, the available data do not support a role for NKX2-1 in the predisposition to hereditary thyroid malignancy; therefore, we do not advise screening CH patients with NKX2-1 mutation for DTC (Villani et al. 2017).

Loss-of-function mutations in the forkhead box E1 (FOXE1) gene, another essential transcription factor for the migration of primordial thyroid cells, have been reported in patients with Bamforth–Lazarus syndrome, characterized by CH with TD (normally athyreosis), cleft palate, spiky hair, choanal atresia, and bifid epiglottis (Ramos et al. 2008, Carré et al. 2014). Notably, Landa and colleagues identified a causal variant within the FOXE1 promoter that was associated with PTC susceptibility (Landa et al. 2009). Previously, other sequence variant (9q22.33) near FOXE1 locus was associated with increased predisposition to papillary and follicular thyroid cancer (Gudmunsson et al. 2009). However, cases of DTC have not been reported in patients with CH due to mutations in the FOXE1 gene (Fernández et al. 2015).

Dyshormonogenesis genetic defects

As already described, DHG is related to TPO, NIS, TG, pendrin, and DUOX2 gene mutations (Rubio & Medeiros-Neto 2009, Bis-Stalpers & Bikker 2010, Spitzweg & Morris 2010, Grasberger & Refetoff 2011, Muzza & Fugazzola 2017, Wémeau & Kopp 2017). DTC cases in patients with TPO mutations were described (Medeiros-Neto et al. 1998, Chertok Shacham et al. 2012, Zhu et al. 2015). One of these mutations (c.875C>T, p.S292F) has also been described in 13 members of a Tunisian family; in which, only NIS with atypical oncogenic differentiation in two subjects has been reported (Bouagcha-Elleuch et al. 2015). Two single-nucleotide polymorphisms of TPO (SNP; rs2048722 and rs732609) were linked with the high-risk of DTC in two European populations (Cipollini et al. 2013). TG gene mutations were also reported (Hishinuma et al. 2005), including in association with an anaplastic thyroid cancer (Yoon 2020).

Homozygous deletion in the NIS protein associated with ITD was reported in a DTC patient who harbored a DHG with a late diagnosis, low adherence to LT4 treatment, and previous partial thyroidectomy (Agretti et al. 2016).

DUOX2 gene biallelic loss-of-function mutation phenotype includes normally localized thyroid gland, presenting regular to extended size, associated with normal or high serum levels of TSH and Tg (Pizzini et al. 2005, Niedziela 2006) but not associated with DTC. So far no germline mutations in the DUOX2 and DUOXA2 genes have been reported in DTC patients with DH (Carvalho & Dupuy 2013, Ameziane-El-Hassani et al. 2016, Azouzi et al. 2017, Muzza & Fugazzola 2017). A novel DUOX2 variant (DUOX2 Y1203H) was described as a gain-of-function mutation and could be investigated for being potentially implicated in redox upregulation related to DTC (Bann et al. 2019).

Genomic insights of congenital hypothyroidism and differentiated thyroid carcinoma association

Borealin/CDC8 gene mutations were associated to thyroid dysgenesis. Borealin is a major component of the chromosomal passenger complex (CPC) with functions in mitosis. The authors showed that the identified mutations decreased adhesion and migration (Carré et al. 2017). Thus, variants in this gene may participate in cellular mechanisms related to cancer. In a previous study, a list of genes described as candidate genes in congenital hypothyroidism containing an entire spectrum of possible causative defects of CH pathology was described (Camargo et al. 2018). When those 190 genes set was submitted to the enrichment analyses (Kuleshov et al. 2016), it generated a list including 16 pathways associated with cancer development or progression (Fig. 1), implying that genes associated with congenital hypothyroidism may also be involved in the pathology of thyroid cancer. Furthermore, when rare variants (frequency lower than 1% or without data in The 1000 Genomes Project population)
in exons and regulatory regions (5′UTRs) identified in the genome of 35 TD patients were analyzed through a list of 44 driver genes directly related to the development of medullary, papillary, and follicular types of DTC (Santoro & Carlomagno 2016) a high number of genetic alterations associated to the etiology of DTC (Fig. 2) (Brust & Rubio unpublished observations). Nevertheless, a great number of these variants were those without information on their population frequency; thus, comparative and even functional studies are needed to clarify their real meaning.

Alternative mechanisms of oncogenic activation

Somatic driver mutations

Constitutive activation of MAPK is considered crucial for the initiation of PTC, mainly through mutations in the BRAF and RAS genes or gene fusions of tyrosine receptor kinases such as RET/PTC, NTRK, and ALK. On the other hand, PI3K/AKT activation is critical for the development of follicular adenoma and progression to FTC due to mutations in RAS, PI3KCA, and AKT1 and by inactivating PTEN, which negatively regulates this pathway (Xing 2013, Zaballos & Santisteban 2017). However, few studies have molecularly characterized the thyroid cancer of CH patients, and only BRAFV600E mutations were detected (Table 1).

Chronic raised TSH

Increased risk of neoplastic transformation in children with DHG and elevated TSH over a long period were proposed earlier (Medeiros-Neto & Stanbury 1994). Up to now, only one study examined CH linked to TG gene mutations associated with DTC in seven patients with long-standing goiters, in a context of long-standing TSH stimulation and BRAFV600E somatic mutations (Hishinuma et al. 2005).
The cooperation of BRAF$^{V600E}$ mutation and TSHR signaling activation has been investigated in mouse models (Lu et al. 2010). The genetic contribution of TSHR variants in TSH levels and cancer risk through GWAS metaanalyses in 119,715 individuals identified 99 independent variants linked to TSH levels and 18 variants associated with DTC (Zhou et al. 2020). Therefore, the association between high TSH serum levels and DTC in patients with CH is not yet consensual and fully established, albeit, in a certain genetic context, it could be plausible.

**Oxidative stress**

H$_2$O$_2$ is required for thyroid hormone synthesis and may be involved in carcinogenesis via many mechanisms, including oxidative damage to DNA, gene expression, cell apoptosis, signaling, and proliferation (Carvalho & Dupuy 2013, Ameziane-El-Hassani et al. 2016). At higher concentrations, H$_2$O$_2$ induces oxidative stress, DNA oxidation, and damage-causing mutagenic and neoplastic events due to the activation of proto-oncogenes or inactivation of tumor suppressors genes combined with its proliferative effects (Stone 2004). A hypothetical model of the process of carcinogenesis of a dyshormonogenic thyrocyte, that includes the oxidative stress, chronic increase of TSH, increased ROS production, and mutation/polymorphisms of genes as Borealin/CDC8, TG, and TPO, is illustrated in Fig. 3.

Indeed, a functional interaction, at the plasma membrane, between DUOX and TPO regulates the extracellular H$_2$O$_2$ levels and may limit its diffusion into the cells as a protection from oxidative damage (Fortunato 2010). It is not known that if lack of a functional TPO could potentially be involved in neoplastic events in CH patients with TPO loss-of-function mutations (El Hassani 2019).

In human thyroid cells, NOX4 is overexpressed and positively regulated by TSH at transcriptional levels and is mainly expressed in intracellular compartments. NOX4 produces ROS in the perinuclear region of thyroid cells, probably exposing the nucleus to oxidative stress and inducing DNA damage (Weyemi 2010). The BRAF$^{V600E}$ mutation, the most frequent genomic alteration found in DTCs, upregulates NOX4 via the TGF-b1-SMAD3 pathway in thyroid cancer cells and downregulates NIS expression. It was suggested that NIS and other genes associated with thyroid differentiation might be silenced by a mechanism controlled by NOX4-derived ROS (Azouzi et al. 2017). The expression of NOX4 in CH patients with chronic elevated TSH has never been evaluated.

**Thyroid cancer diagnostic pitfalls in patients with congenital hypothyroidism with nodular goiter**

Adequate cytological diagnosis in nodules of patients with dyshormogenesis might be demanding as a result of specific architectural and cytological appearances that may lead to an erroneous interpretation of the malignancy. The main findings are summarized in Table 2 (Matos et al. 1994, Mahajan et al. 2019). The cytological approach needs much refinement, encompassing the discernment of many conditions, such as hyperplastic nodule, post-radioiodine changes, follicular neoplasm, and non-invasive follicular thyroid neoplasm with papillary-like nuclear features (Matos et al. 1994, Mahajan et al. 2019). There may also be foci of papillary hyperplasia and mitotic activity, which could again lead to overdiagnosis of DTC. It is not rare for the cytological conclusion to be atypia of undetermined significance/follicular lesion of undetermined significance,
combined with focal cytological and architectural atypia (Matos et al. 1994, Mahajan et al. 2019). Hence, the histological examination must be largely scrupulous since lifelong TSH stimulation might be a powerful driver of many architectural changes and cellular pleomorphism (Table 2) (Ghossein et al. 1997, Fadda et al. 1999, Pedrinola et al. 2001, Drut & Moreno 2009, Kallel et al. 2009). In contrast, features such as capsular or vessel invasion, papillary-like arrangement, nuclear pseudo inclusions or grooves drive the diagnosis of DTC (Ghossein et al. 1997, Fadda et al. 1999, Pedrinola et al. 2001, Deshpande & Bobhate 2005, Drut & Moreno 2009, Kallel et al. 2009). The nuclear changes noticed are most common in the inter-nodular areas rather than in the nodules themselves, and it is essential to highlight that the perception of analogous features in the epithelium of the thyroid follicles outside the nodules is a tremendous aid for proper judgment of interpretation (Camargo et al. 1998, Fadda et al. 1999, Baloch & LiVolsi 2006, Braham et al. 2013). Follicular adenoma can be distinguished, and its capsule may appear focally disrupted; in this case, some observers advise that diagnosis of malignancy can only be made if the metastasis is documented (Rastogi & LaFranchi 2010). Occasionally, the DTC diagnosis can be challenging and guaranteed only in some cases that present vascular invasion (much more critical than capsular invasion), extra-thyroid extension or lymph node metastasis (Cooper et al. 1981). If trabecular, solid, insular or cribriform growth patterns are observed, the differential diagnosis must cover an undifferentiated carcinoma, and awareness of the possible DH problem will be extremely helpful (Deshpande & Bobhate 2005). It is a fact that these confounders’ aspects are typically more expected in patients who have not been diagnosed early and who, secondary to a prolonged TSH boost effect, present a palpable goiter (Fadda et al. 1999).

The possible peculiarities in the therapy of thyroid cancer occurring in the context of congenital hypothyroidism are surgical difficulties in a tumor that are in ectopic or hyperplastic tissue. Nevertheless, the overall management in the therapy of thyroid cancer occurring in the context of congenital hypothyroidism does not have differences and peculiarities/ particularities in relation to the treatment in pediatric thyroid cancer that does not have an association with congenital hypothyroidism (Francis et al. 2015).

**Conclusions**

The development of CDT combined with CH is a rare situation, with no well-established causal relationship. In association with dyshormonogenesis, as explained above, it has been suggested that one of the factors involved is the long exposure to elevated serum TSH levels, as well as stimulating factors or a lack of tumor-suppressor genes, type of mutation, patient’s iodine intake, others genetic and environmental factors and the presence of congenital goiter. It is important to remember that these patients are under greater surveillance, do more ultrasound, and this can be a bias for the association between CH and CDT.

This review warns the possibility of the occurrence of DTC in this group of patients with CH, and that it is advisable for a long-term follow-up by regular neck ultrasonographic imaging followed by fine-needle aspiration, if indicated, is recommended to avoid a delayed diagnosis of thyroid carcinoma in these cases. The mechanism that might lead to DTC in patients with CH still needs better elucidation. Elevated TSH, increased ROS production, and mutation/polymorphisms of genes as Borealin/CDC8, TG, and TPO have been associated with increased cancer risk or pro-tumoral cell behavior and might be potentially involved in this process.
Finally, these associations highlighted in this review are not yet consensual and fully established. A better characterization of the genetic and epigenetic background of CH patients in the future will lead to a better mechanistic insight into how this condition might or not predispose to thyroid cancer.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding
This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements
The authors thank FAPESP 2014/24549-4, Sao Paulo State Research Foundation, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

References
Boelaert K 2009 The association between serum TSH concentration and thyroid cancer. Endocrine-Related Cancer 16 1065–1072. (https://doi.org/10.1677/ERC-09-0130)
Carvalho DP & Dupuy C 2013 Role of the NADPH oxidases DUOX1 and NOX4 in thyroid oxidative stress. European Thyroid Journal 2 160–167. (https://doi.org/10.1007/s40035-013-0070-0)
Castanet M, Leenhardt L, Léger J, Simon-Carré A, Lyonnet S, Pelet A, Czernichow P & Polak M 2005 Thyroid hemiagenesis is a rare variant of thyroid dysgenesis with a familial component but without Pax8 mutations in a cohort of 22 cases. Pediatric Research 57 906–913. (https://doi.org/10.1203/01.PDR.0000161409.04177.36)
Chertok Shacham E, Ishay A, Irir E, Pohlenz J & Tenenbaum-Rakover Y 2012
Minimally invasive follicular thyroid carcinoma developed in
dyshormonogenetic multinodular goiter due to thyroid peroxidase gene
variants and risk of differentiated thyroid carcinoma in two European
doi.org/10.1002/ijc.28317)
Cooper DS, Axelrod L, DeGroot LJ, Vickery AL & Maloof F 1981
Congenital goiter and the development of metastatic follicular
carcinoma with evidence for a leak of nonhormonal iodide: clinical,
pathological, kinetic, and biochemical studies and a review of the
(https://doi.org/10.1210/jcem-52-2-294)
Crooks J, Greig K & Branwood AW 1963 Dyshormonogenesis and
(https://doi.org/10.1177/003693306300800802)
Deshpande AH & Bobhate SK 2005 Cytological features of
dyshormonogenetic goiter: case report and review of the literature.
Díaz-Arias AA, Bickel JT, Loy TS, Croll GH, Puckett CL & Havey AD 1992
Follicular carcinoma with clear cell change arising in lingual thyroid.
*Oral Surgery, Oral Medicine, and Oral Pathology* **74** 206–211. (https://doi.org/
10.1003/t030-1422(92)90384-3)
Drut R & Moreno A 2009 Papillary carcinoma of the thyroid developed in
congenital dyshormonogenetic hypothyroidism without goiter:
diagnosis by FNAB. *Diagnostic Cytopathology* **37** 707–709. (https://doi.org/
10.1002/dc.20916)
El Hassani RA, Buffet C, Leboulieux S & Dupuy C 2019 Oxidative stress in
tyroid carcinomas: biological and clinical significance. *Endocrine-
Erden ES, Babayigit C, Davran R, Akin M, Karazincir S, Isagogullari N, Demirkose M & Genc S 2013 Papillary thyroid carcinoma
with lung metastasis arising from dyshormonogenetic goiter: a case report.
*Case Reports in Medicine* **2013** 813167. (https://doi.org/10.1155/2013/813167)
Fadda G, Baloch ZW & LiVolsi VA 1999 Dyshormonogenetic goiter
pathology: a review. *International Journal of Surgical Pathology* **7**
125–131. (https://doi.org/10.1016/S1056-8752(99)00030-1)
Fernández LP, López-Márquez A & Santisteban P 2015 Thyroid
transcription factors in development, differentiation and disease.
*Nature Reviews: Endocrinology* **11** 29–42. (https://doi.org/10.1038/nnrendo.2014.186)
Fiore E, Rago T, Provenzale MA, Scutari M, Ugolini C, Basolo F, Di
Coscio G, Miccoli P, Grasso L, Pinchera A, Dinauer CA, Hamilton J, Hay ID, Luster M,
Klubo-Gwiezdzinska J, Manes RP, Chia SH, Burman KD, Stathatos NA,
Koplev S, Jenkins SL, Jagodnik KM, Lachmann A, Welti-Chanes L, Cinzone G,
Kim KW, Park YJ, Kim EH, Park DJ, Jang HC & Cho BY 2011 Elevated risk of papillary thyroid cancer in
corelating patients with hashimoto’s thyroiditis. *Head and Neck* **33**
691–695. (https://doi.org/10.1002/hed.21518)
Kluco-Gwiezdzinska J, Manes RP, Chia SH, Burman KD, Stathatos NA,
Deeb ZE & Wartofsky L 2011 Ectopic cervical thyroid carcinoma -
review of the literature with illustrative case series. *Journal of Clinical
Endocrinology and Metabolism* **96** 2684–2691. (https://doi.org/10.1210/
c.2011-0611)
Kuleshov MV, Jones MR, Rouillard AD, Fernandez NF, Duan Q, Wang Z,
a comprehensive gene set enrichment analysis web server 2016 update.
Landa I, Ruiz-Llorente S, Montero-Conde C, Ingaldia-Pérez L, Schiavi F,
rs1867277 in FOXE1 gene controls thyroid cancer susceptibility
through the recruitment of USF1/USF2 transcription factors. *Plos
Genetics* **5** e1000637. (https://doi.org/10.1371/journal.pgen.1000637)


Ris-Stalpers C & Bikkert H 2010 Genetics and phenomics of hypothyroidism and goiter due to TPO mutations. *Molecular and Cellular Endocrinology* 322 38–43. (https://doi.org/10.1016/j.mce.2010.02.008)

Roberts KD 1957 Thyroid carcinoma in childhood in Great Britain. *Archives of Disease in Childhood* 32 88–90. (https://doi.org/10.1136/adc.32.161.58)


Endocrine Journal 60 805–811. ([https://doi.org/10.1507/endocr.j.12-0396](https://doi.org/10.1507/endocr.j.12-0396))

Santoro M & Cazzolamagno F 2016 Pathogenesis of thyroid carcinoma. In Thyroid Diseases. Endocrinology. Eds P Vitti & L Hegedus. Cham: Springer. ([https://doi.org/10.1007/978-3-319-29919-6_20-1](https://doi.org/10.1007/978-3-319-29919-6_20-1))


Spitzweg C & Morris JC 2010 Genetics and phenomics of hypothyroidism and goiter due to NIS mutations. Molecular and Cellular Endocrinology 322 56–63. ([https://doi.org/10.1016/j.mce.2010.02.007](https://doi.org/10.1016/j.mce.2010.02.007))


Xing M 2013 Molecular pathogenesis and mechanisms of thyroid cancer 2013. Nature Reviews: Cancer 13 184–199. ([https://doi.org/10.1038/nrc3431](https://doi.org/10.1038/nrc3431))


Zaballas MA & Santisteban P 2017 Key signaling pathways in thyroid cancer. Journal of Endocrinology 235 R43–R61. ([https://doi.org/10.1530/JOE-17-0266](https://doi.org/10.1530/JOE-17-0266))


Received in final form 12 May 2021
Accepted Manuscript published online 17 June 2021