REVIEW

Congenital hypothyroidism and thyroid cancer

Gustavo Penna[1,2], Ileana G S Rubio[3,4,5], Ester Saraiva Brust[3,4], Juliana Cazarin[6], Fabio Hecht[6], Nina Ramalho Alkmim[2,7], Kamilla M A Brandão Rajão[2,8] and **Helton Estrela Ramos[9,10,11]**

[1]Department of Clinical Medicine, Federal University of Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[2]Endocrinology Service of Institute Orizonti, Belo Horizonte, Minas Gerais, Brazil
[3]Department of Biological Science, Molecular Thyroid Science Laboratory, Federal University of São Paulo, São Paulo, Brazil
[4]Biotechnology Post-graduation Program, Federal University of São Paulo, São Paulo, Brazil
[5]Estructural and Functional Biology Program, Federal University of São Paulo, São Paulo, Brazil
[6]Laboratory of Endocrine Physiology, Institute of Biophysics Carlos Chagas Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[7]Post-Graduation Program Molecular Medicine, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil
[8]Endocrinology Service of Hospital das Clínicas, Federal University of Minas Gerais, Belo Horizonte, Brazil
[9]Department of Bioregulation, Health & Science Institute, Thyroid Study Laboratory, Federal University of Bahia, Salvador, Brazil
[10]Post-Graduation Program Medicine and Health, Faculty of Medical Sciences, Federal University of Bahia, Salvador, Bahia, Brazil
[11]Post-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 (H_2O_2), 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 dyshormonogenesis. 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 dyshormonogenesis 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
- dyshormonogenesis
- thyroid cancer

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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 dyshormonogenesis (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 ulterior 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): organification 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_2O_2), cell division cycle associated 8 (Borelain/*CDC8*) 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-Gwiezdzinska *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

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not been considered an increased risk condition for malignant transformation (Klubo-Gwiezdzinska *et al.* 2011, Tian *et al.* 2014). The association between lingual thyroid and DTC was recently reviewed (Klubo-Gwiezdzinska *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 (Diaz-Arias *et al.* 1992, Pérez *et al.* 2003, Kennedy & Riefkohl 2007, Sevinç *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 cyst carcinoma and DTC at 19 years old (Şıklar *et al.* 2012).

Hemiagenesis (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) (Ghossein *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 (Grasberger & Refetoff 2011). Veritably, 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, Spitzweg & Morris 2010, Grasberger & 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 (Grasberger & 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, McGirr *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, Ozlük *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 anatomopathological examination, the association between dyshormonogenic goiter (DHG) and DTC has been increasing, as described by Ghoseein *et al.*, who observed a prevalence as high as 6% (Ghossein *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).

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Table 1 Cases of thyroid malignancy associated with dyshormonogenetic goiter and congenital hypothyroidism due to thyroid dysgenesis.

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

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Table 1 Continued.

Reference (*n*, number of cases)	**Sex** (F/M) **and age** (years) **at surgery**	**Clinical, macroscopic and microscopic aspects**	**Histology** (reported in the original publication)	**Distant metastasis**	**Molecular defect** (mutation)
Medeiros-Neto *et al.* 1998 (*n* = 1)	1F (7 days of age)	Solid cervical mass (74 g) with calcifications and ETE to the base of the tongue and hypopharynx, mediastinum and vascular invasion	FTC	Lung and bone (both femurs, right tibia)	TPO (c.1-bp ins., 2505C)
Ozlük *et al.* 1998 (*n* = 1)	1F (49)	Deafness, large goiter, capsular invasion, no vascular invasion, associated with breast invasive ductal carcinoma	FTC	No	Suspect of PDS defect (no molecular study)
Camargo *et al.* 2001 (*n* = 1)	1F (53)	Deafness, goiter (150 g), ETE, death by hemoptysis caused by tumor invasion	FTC with areas of anaplastic transformation	Lung	PDS (c.279delT)
Bashir *et al.* 2004 (*n* = 1)	1F	MNG	FTC	UN	Suspect of PDS defect (no molecular study)
Kim *et al.* 2004 (*n* = 1)	1M	Deafness, large goiter	Poorly differentiated FTC	UN	PDS
Pizzini *et al.* 2005 (*n* = 1)	1M (54)	Hemiagenesis of left thyroid lobe, with multinodular lesions in the right lobe, mediastinal extension, dysphagia	PTC	No	No
Hishinuma *et al.* 2005 (*n* = 7)	6F (12, 17, 27, 28, 36, 38), 1M (35)	Goiter, $BRAF^{V600E}$ and $BRAF^{K600E}$ somatic mutations in tumors from two patients	6 PTC 1FTC	No	TG (p.C1077R) (p.C1264R) (p.C1996S) (p.G2375R)
Alzahrani *et al.* 2006 (*n* = 1)	1M (21)	MNG, RAS mutation negative	FTC	Skull, abdomen, femur	TG (g.IVS5+1G>A) (Stop codon)
Drut & Moreno 2009 (*n* = 1)	1F (5)	MNG, malignant nodule with 0.7 cm, PTC at FNA cytology (nuclear changes, pseudoinclusions), vascular invasion, LN metastasis	PTC	No	No
Kallel *et al.* 2009 (*n* = 1)	1M (13)	Compressive MNG, multifocal PTC (dominant lesion, 0.6 cm), microfollicular pattern, limph node metastatis (0.3 cm)	MFVPTC	No	No
Oguz *et al.* 2009 (*n* = 1)	1M (19)	Deafness, MNG, no capsular or vascular invasion	PTC	No	PDS
Raef *et al.* 2010 (*n* = 1)	1F (31)	MNG, two surgeries for DTC (first: two foci of MFVPTC, 0.5 cm), recurrence after 4 years of follow-up	PTC with follicular and oncocytic variants	Skull, pelvis and lung	TG (c.6725G>A; p.R2223H)
Chertok Shacham *et al.* 2012 (*n* = 1)	1M	MNG with tracheal compression, no vascular invasion	FTC	No	TPO (c.875C>T) (p.S292F)
Wu *et al.* 2012 (*n* = 7)	7 (age and sex not reported)	Hemiagenesis	PTC (*n* = 5) FTC (*n* = 1) Mixed PTC/FTC (*n* = 1)	No	No
Sakurai *et al.* 2013 (*n* = 1)	1M (37)	Deafness, MNG (482 g), encapsulated follicular lesion, no vascular or LN invasion; twin brother with PDS mutation but benign MNG at surgery	FVPTC	No	PDS (c.2168A>G; c.ins2110GCTGG)
Erden *et al.* 2013 (*n* = 1)	1F (17)	Recurrence of MNG 6 years after first operation	PTC	Lung	No
Zhu *et al.* 2015 (*n* = 1)	1F	Multifocal PTC, lymph node, and nerve invasion	PTC	No	TPO (c.2268–2269 insT)

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Table 1 Continued.

Reference (*n*, number of cases)	**Sex** (F/M) **and age** (years) **at surgery**	**Clinical, macroscopic and microscopic aspects**	**Histology** (reported in the original publication)	**Distant metastasis**	**Molecular defect** (mutation)
(Agretti *et al.* 2016) (*n* = 1)	1F (37)	Recurrent MNG (two operations), malignancy at second operation (multifocal FVPTC, ETE: fibro-muscular tissue infiltration)	FVPTC	No	NIS (c.970_1526del557; Y324LfsX12)
(Tong *et al.* 2016) (*n* = 11)	2 M (23, 34), 9 F (15, 22, 34, 37, 41, 49, 53, 54, 64)	Deafness, MNG, extensive fibrosis, hyperplastic nodule with papillary hyperplasia, solid growth pattern or insular/ trabecular growth	FVPTC	No	PDS (c.412G>T) (c.1001+1G>A)
(Yoon *et al.* 2020) (*n* = 1)	1 F (46)	Large heterogeneous and hypoechoic nodule with internal calcification (6 cm) in the right lobe, as well as dense calcification in the left lobe (0.9 cm)	ATC	Lung, bone and liver	TG (c.3790T>C; c.7070T>C)

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 *NKX2-1* (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, Ris-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 MNG with atypical oncocytic differentiation in two subjects has been reported (Bougacha-Elleuch *et al.* 2015). Two single-nucleotide polymorphisms of *TPO* (SNP; rs2048722 and rs732609) were linked the with 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 LT_4 treatment, and previous partial thyroidectomy (Agretti *et al.* 2016).

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Pendred syndrome (PS) is caused by biallelic mutations in the *SLC26A4/PDS* gene. Very few patients with PS have been diagnosed with DTC, mostly associated with iodine deficiency or sustained TSH elevations (Illum 1978, Abs *et al.* 1991, Ozlük *et al.* 1998, Camargo *et al.* 2001, Kim *et al.* 2004, Oguz *et al.* 2009, Sakurai *et al.* 2013). PS patients with MNG should be monitored regularly with sporadic ultrasound assessment and FNA in suspicious nodules (Wémeau & Kopp 2017, van Trotsenburg *et al.* 2021).

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)

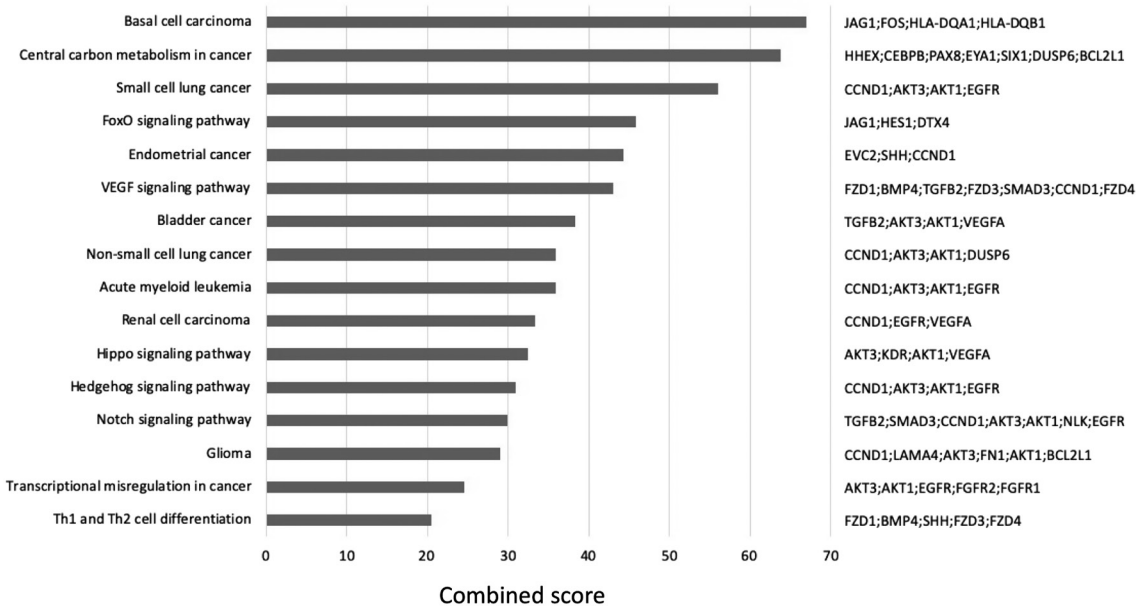


Figure 1
KEEG enrichment analysis of candidate genes in congenital hipothyroidism. Score bar plots and genes from the input that were found to be associated with each term (*P*-value < 0.05) (Kuleshov *et al.* 2016). AKT1, AKT serine/threonine kinase 1; AKT3, AKT serine/threonine kinase 3; BCL2L1, BCL2 like 1; BMP4, bone morphogenetic protein 4; CCND1, cyclin D1; CEBPB, CCAAT enhancer binding protein beta; DTX4, deltex E3 ubiquitin ligase 4; DUSP6, dual specificity phosphatase 6; EVC2, EvC ciliary complex subunit 2; EYA1, EYA transcriptional coactivator and phosphatase 1; FGFR1, fibroblast growth factor receptor 1; FGFR2, fibroblast growth factor receptor 2; FN1, fibronectin 1; FOS, Fos proto-oncogene, AP-1 transcription factor subunit; FZD1, frizzled class receptor 1; FZD3, frizzled class receptor 3; FZD4, frizzled class receptor 4; HES1, Hes family BHLH transcription factor 1; HHEX, hematopoietically expressed homeobox; HLA-DQA1, major histocompatibility complex, class II, DQ alpha 1; HLA-DQB1, major histocompatibility complex, class II, DQ beta 1; JAG1, jagged canonical notch ligand 1; KDR, kinase insert domain receptor; LAMA4, laminin subunit alpha 4; NLK, Nemo like kinase; PAX8, paired box 8; SHH, sonic Hedgehog signaling molecule; SIX1, SIX homeobox 1; SMAD3, SMAD family member 3; TGFB2, transforming growth factor beta 2; VEGFA, vascular endothelial growth factor A.

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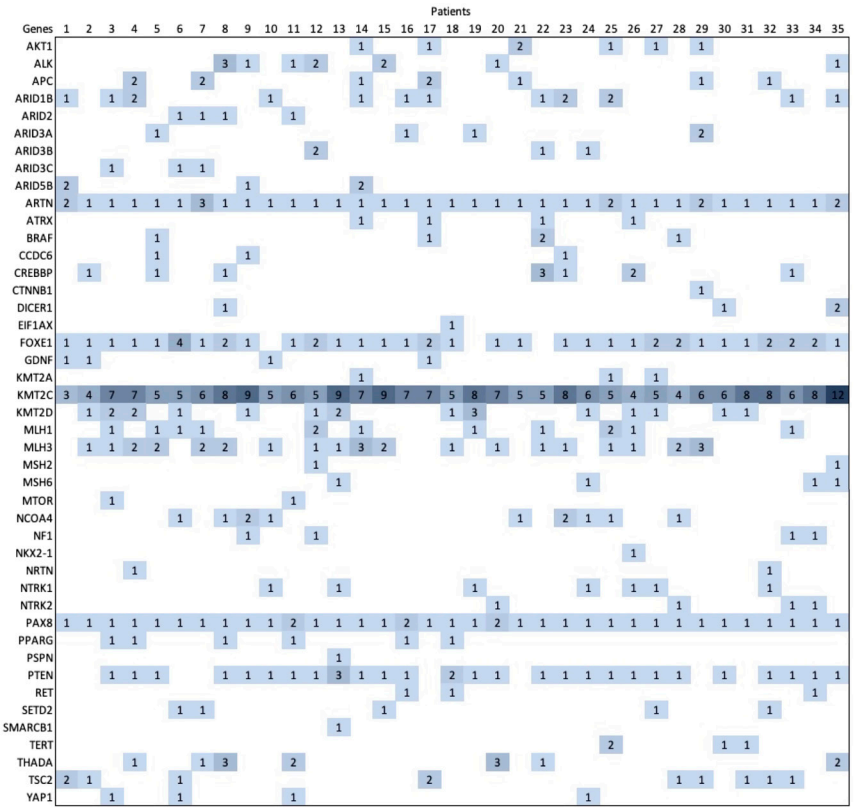


Figure 2
Genetic alterations in driver genes directly related with DTC subtypes (Santoro & Carlomagno 2016) identified in TD patients. AKT1, AKT serine/threonine kinase 1; ALK, ALK receptor tyrosine kinase; APC, APC regulator of WNT signaling pathway; ARID1B, AT-rich interaction domain 1B; ARID2, AT-rich interaction domain 2; ARID3A, AT-rich interaction domain 3A; ARID3B, AT-rich interaction domain 3B; ARID3C, AT-rich interaction domain 3C; ARID5B, AT-rich interaction domain 5B; ARTN, Artemin; ATRX, ATRX chromatin remodeler; BRAF, B-Raf proto-oncogene, serine/threonine kinase; CCDC6, coiled-coil domain containing 6; CREBBP, CREB binding protein; CTNNB1, catenin beta 1; DICER1, Dicer 1, ribonuclease III; EIF1AX, eukaryotic translation initiation factor 1A X-linked; FOXE1, forkhead box E1; GDNF, glial cell-derived neurotrophic factor; KMT2A, lysine methyltransferase 2A; KMT2C, lysine methyltransferase 2C; KMT2D, lysine methyltransferase 2D; MLH1, MutL homolog 1; MLH3, MutL homolog 3; MSH2, MutS homolog 2; MSH6, MutS homolog 6; MTOR, mechanistic target of rapamycin kinase; NCOA4, nuclear rceptor coactivator 4; NF1, neurofibromin 1; NKX2.1, NK2 homeobox 1; NRTN, neurturin; NTRK1, neurotrophic receptor tyrosine kinase 1; NTRK2, neurotrophic receptor tyrosine kinase 2; PAX8, paired box 8; PPARG, peroxisome proliferator activated receptor gamma; PSPN, persephin; PTEN, phosphatase and tensin homolog; RET, Ret proto-oncogene; SETD2, SET domain containing 2, histone lysine methyltransferase; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1; TERT, telomerase reverse transcriptase; THADA, THADA armadillo repeat containing; TSC2, TSC complex subunit 2; YAP1, Yes1 associated transcriptional regulator.

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 $BRAF^{V600E}$ 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 $BRAF^{V600E}$ somatic mutations (Hishinuma *et al.* 2005).

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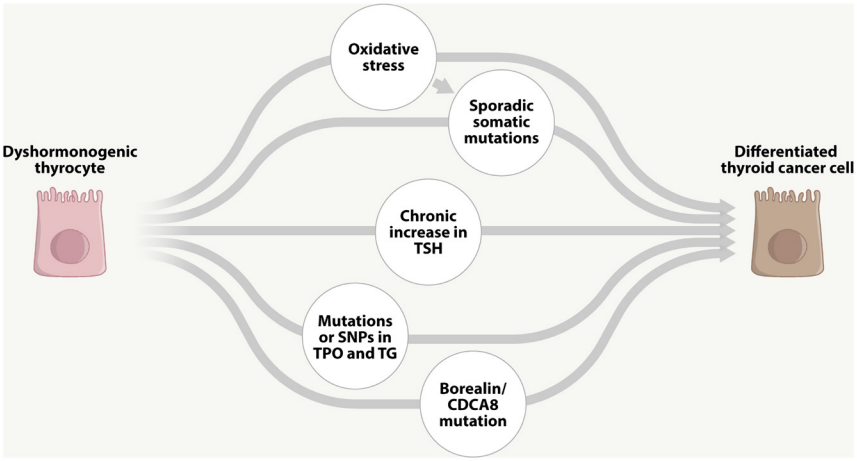


Figure 3
Hypothetical model of the process of carcinogesis of a dyshormonogenic thyrocyte. Borealin/CDCA8, cell division cycle associated 8 (Borealin/*CDC8*); SNP, single-nucleotide polymorphism; TG, thyroglobulin; TGO, thyroperoxidase; TSH, thyroid-stimulating hormone.

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 metanalyses 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_2O_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_2O_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_2O_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 dyshormonogenesis 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,

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Table 2 Cytological and anatomopathological features observed in dyshormonogenetic goiter (Fadda *et al.* 1999, Baloch & LiVolsi 2006).

Cytological findings on FNA
Architecture showing syncytial fragments, cohesive clusters, solid or microfollicular pattern with empty follicles devoid of colloid
Papillary and insular formations
Hyperplastic cells in sheets and large clumps with crowding and nuclear overlap
Exaggerated papillary infoldings of hyperplastic follicles mimicking papillary carcinoma
Representative stromal fragments of fibrosis
Background with thin colloid or decreased to absent colloid
Nuclei with anisonucleosis, mild enlargement, crowding, and overlapping
Chromatin may be normo- to hypo- to hyperchromic
Macroscopic and microscopic findings on histology
Thyroid gland is asymmetrically magnified and multinodular
Irregular demarcation at the capsular margin
Fibrous bands encapsulate individual nodules
Foci of thyroid cystic degeneration, thyroid hemorrhages or myxoid changes
Vascular pseudoinvasion: encroachment into vessel walls with subintimal invagination
Capsular pseudoinvasion: irregularities at the edge of the nodules simulating capsular invasion
Cytoarchitectural features on histology
Marked cellular pleomorphism: follicular cells can be cuboidal, columnar, or polygonal
Nuclei atypia, including bizarre and markedly enlarged, round to oval, hyperchromatic or vesicular nuclei (rare), is observed more in the internodular zone

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, Deshpande & Bobhate 2005, 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 or 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.

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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.

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