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Review Article

Advances and Perspectives in Genetics of Congenital Thyroid Disorders Associated with Thyroglobulin Gene Mutations

Abstract

Dyshormonogenesis due to *thyroglobulin* (*TG*) gene mutations is a rare cause of congenital hypothyroidism with an estimated incidence of approximately 1 in 100,000 newborns. The *TG* gene is organized in 48 exons, spanning over 270 kb on human chromosome 8q24. The human *TG* mRNA is 8.5 Kb long and the preprotein monomer is composed of a 19 amino acids signal peptide followed by a 2749 residues polypeptide. Until now, one hundred seventeen deleterious mutations in the human *TG* gene have been identified and characterized, originating structural changes in the protein that alter the normal protein folding, assembly and biosynthesis of thyroid hormones: 19 splice site mutations, 23 nonsense mutations, 57 missense mutations, 13 deletions (9 single nucleotide deletions, 2 multiple nucleotide deletions and 2 involving a large number of nucleotides), 4 single nucleotide insertions or duplication and 1 imperfect DNA inversion. The p.R277*, p.R1511*, p.A2215D, p.R2223H and p.R2317* mutations are the most frequently identified *TG* mutations in Caucasian population, whereas c.274+2T>G, p.C1058R, p.C1245R and p.C1977S are the most common mutations in Asian population.

TG mutations are inherited in an autosomal recessive manner and affected individuals are either homozygous or compound heterozygous for gene mutations and the parents should be carriers of one the *TG* mutation.

New approaches including the use of new sequencing technology, will eclipse traditional methods of detecting mutations and will allow the quick identification of mutations in remote regions as well as the detection of coexistence of multiple mutations in the same gene or in different thyroid genes.

Introduction

Thyroglobulin (TG) is a structural, ancestral and secretory protein with high specificity for the biosynthesis of thyroid hormones. Its main function is to provide the precursor for synthesis and storage of thyroid hormones [1-4]. It is also an important storage of iodine when external iodine availability is limited. Biosynthesis of thyroid hormones requires the integrity of a complex protein system, several sequential steps and is critically dependent upon the native three-dimensional structure of TG [1-4]. The central steps in thyroid hormone synthesis take place at the cell–colloid interface of follicular thyroid cells [1-4]. Iodine is covalently bound to Tyr amino acids within TG. Correctly folded TG homodimers are secreted into the follicular lumen where coupling between either two diiodotyrosine (DIT) residues, or between a DIT and a monoiodotyrosine (MIT) residues, results in the formation of 3,5,3´-triiodothyronine (T3) and 3,5,3´,5´-tetraiodothyronine (T4) [1-4]. The iodination and coupling reactions are mediated by thyroid peroxidase (TPO) with a source of hydrogen peroxide [1-4]. The H_2O_2 generation system of the thyroid involves a metabolic pathway which includes the dual oxidase 1 and 2 (DUOX1, DUOX2), and DUOX maturation factor 1 and 2 (DUOXA1, DUOXA2) proteins. The mature TG molecules remain in the lumen of thyroid follicles. Afterwards, TG is subjected to proteolysis, MIT and DIT are subsequently deiodinated by the iodotyrosine dehalogenase [1-4]. Thyroid gland produces predominantly T_4 together with a small amount of the T_3. The peripheral metabolism of thyroid hormone is determined by the action of the D1, D2 and D3 selenodeiodinases that catalyze the interconversion of T4 in T3 [5].

Thyroid hormones are essential for normal central nervous system development [6,7]. Untreated congenital hypothyroidism result in irreversible mental delay and short stature [6,7]. For over three decades, mutations in the human

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TG gene have been identified associated with congenital goiter [8-53] and also endemic and nonendemic goiter [54-56]. The clinical spectrum ranges from euthyroidism to permanent severe hypothyroidism [1,2,6,7]. Phenotypic variations among patients with the same mutations have been observed. In addition to iodine deficiency, other environmental and genetic factors may contribute to clinical variability.

In this review we summarize the most recent data related to thyroid disorders caused by mutations in the *TG* gene and provide data that have an impact on the disease management as well counseling benefits for the patients and their families.

Classification and diagnosis of congenital hypothyroidism

Congenital hypothyroidism (CH) is the most frequent endocrine disease in infants, with prevalence of 1:2000 - 1:3000 newborns and is characterized by high levels of thyroid-stimulating hormone (TSH) as a consequence of reduced thyroid function [1,2,6,7]. It is also one of the most common preventable causes of cognitive and motor deficits. Prevention of CH is based on carrier identification, genetic counseling and prenatal diagnosis. In neonates a complete diagnosis of CH should include clinical examination, biochemical thyroid tests, thyroid ultrasound, radioiodine or technetium scintigraphy and perchlorate discharge test (PDT) [6,7]. In the last three decades, considerable progress has been made in identifying the genetic and molecular causes of CH. Knowing the prevalence of the mutations present in each population will facilitate greatly the molecular genetic testing. The classification based on the genetic alterations divides CH into two main categories caused: (a) by disorders of thyroid gland development (dysembriogenesis or thyroid dysgenesis group) or (b) by defects in any of the steps of thyroid hormone synthesis (dyshormonogenesis group) [1,2,6,7]. The dysembryogenesis or thyroid dysgenesis group, which accounts for the 80-85 % of the cases, results from a thyroid gland that is completely absent in orthotopic or ectopic location (agenesis or athyreosis), severely reduced in size but in the proper position in the neck (orthotopic hypoplasia) or located in an unusual position (thyroid ectopy) at the base of the tongue or along the thyroglossal duct [1,2,6,7]. In only 5% of the patients, CH is associated with mutations in genes responsible for the development or growth of thyroid cells: *NKX2.1* (also known as *TTF1* or *T/EBP*), *FOXE1* (also known as *TTF2* or *FKHL15*), *paired box transcription factor 8* (*PAX-8*), *NKX2.5*, and *TSHR* genes [1,2,6,7]. Epigenetic mechanisms leading to stochastic variations in the expression of multiple loci could be responsible for the sporadic characteristic of thyroid dysgenesis. Consequently, the genetic mechanisms underlying the defects in thyroid organogenesis in the majority of the cases remain to be elucidated.

Dyshormonogenesis, which accounts for the remaining 15-20% of the cases, has been linked to mutations in the *SLC5A* (*Na+/I_ symporter, NIS*) [57], *SLC26A4* (*Pendrine, PDS*) [58], *TPO* [59], *dual oxidasa2* (*DUOX2*), *DUOX maturation factor 1 and 2* (*DUOXA1* and *DUOXA2*) [60,61], *iodotyrosine dehalogenase 1* (*DEHAL1*) [62] and *thyroglobulin* (*TG*) [1-4,8-56] genes. These mutations produce a heterogeneous spectrum of congenital hypothyroidism, with an autosomal recessive inheritance. Thereafter, the patients are typically homozygous or compound heterozygous for the gene mutations and the parents, carriers of one mutation.

Dyshormonogenesis due to *TG* gene mutations is a rare cause of CH with an estimated incidence of approximately 1 in 100,000 newborns [1,2]. The patients with TG synthesis defects presents a congenital goiter or goiter appearing shortly after birth, clinical spectrum ranges from euthyroid to mild or severe permanent hypothyroidism, high iodide uptake, normal organification of iodide (negative PDT), elevated serum TSH with simultaneous low or normal serum T_4 and T_3 levels, and low serum TG concentration [1-2,8-53]. The presence of very low TG level and also negative PDT in a goitrous individual are the basis for the selection of patients for molecular studies in the *TG* gene [2]. Patients with iodotyrosine dehalogenase deficiency will also develop goiter with hypothyroidism, when dietary iodide is limiting. In these patients the PDT does not show increased release of radioiodine after administration of the competitor, indicating that the organification process itself is not affected, whereas the serum TG levels are frequently elevated [2,62]. Patients with an iodide transport defect by mutations in *SLC5A* gene have a normal-sized or somewhat enlarged thyroid gland, elevated plasma TG levels and no radio-iodide uptake [2,57]. Iodide organification defects are associated with mutations in the *TPO*, *DUOX2*, *DUOXA2* or *SLC26A4* genes and characterized by a positive PDT [2,59-61]. Mutations in *SLC26A4* gene cause Pendred syndrome characterized by congenital sensorineural hearing loss and goiter without or with hypothyroidism [2,58].

TG gene and its expression

Human *TG* gene is a single copy gene of 270 kb long that maps on chromosome 8q24 and contains an 8,459-8,468 nucleotides coding sequence (GenBank Accesion Number: NM_003235.4) divided into 48 exons (Figure 1a) [63-71]. *TG* gene expression is stimulated by TSH through the modulation of the intracellular level of cyclic adenosine monophosphate (cAMP) [1-3]. TSH exerts its function via a G protein-coupled receptor, the TSH receptor (TSHR), which relies on the associated G protein to transmit and amplify the signal inside the cell [1-3]. Transcription of the TG gene is under control of the coordinated action of a master set of transcription factors that includes the NKX2.1, FOXE1 and PAX8, by their binding to the *TG* promoter on their respective consensus sequences [1-3].

TG is a large homodimeric secretory protein (660 kDa) with a high degree of glycosylation [1-4]. The human *TG* mRNA codes for a polypeptide chain of 2767 amino acids [63-65]. The monomeric TG preprotein has a leader peptide of 19 amino acids followed by 2748-amino-acid polypeptide (Figure 1b) [63-65]. Four hormonogenic acceptor tyrosine residues have been identified and localized at positions 5, 1291, 2554 and 2747 in human TG (Figure 1b) [1-4,72,73]. Each TG monomer contains 67 Tyr and 122 Cys residues, representing 2.44% and 4.44% of the total amino acids, respectively [63-65].

The internal protein organization makes *TG* an example of gene evolution by intragenic duplication events and gene fusions. The TG protein is composed of four structural and functional regions (Figure 1b). The N-terminal and the central part of the monomer includes three types of repetitive motifs,

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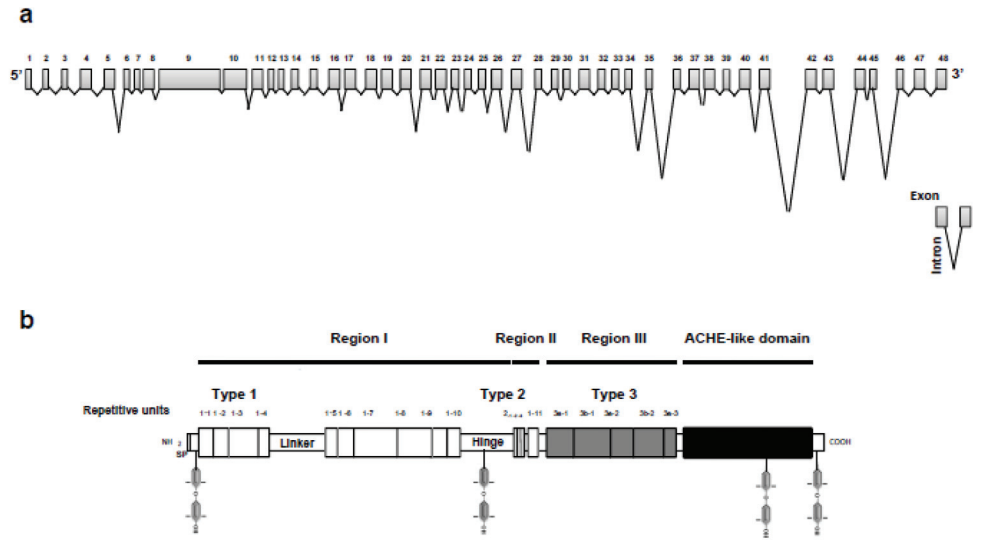

Figure 1: Schematic representation of the human *thyroglobulin* gene and protein.
a) Intron/exon organization of the *thyroglobulin* gene. Note the difference between scales used for introns and exons. Orientation is given according to the mRNA structure.
b) Primary structure of thyroglobulin. The signal peptide (SP), repetitive units of type 1, 2 and 3 and the acetylcholinesterase-homology domain (ACHE-like domain) are represented by boxes. The N-terminal and the central part of the monomer are organized in three regions (I, II and III). The N-terminal limit of repeat type 1-5 is ambiguous. The positions for T_4 (5, 1291 and 2747) and T_3 (2554) formation are shown.

called TG type-1, TG type-2, and TG type-3, organized in three regions (I, II and III) (Figure 1b) [1-4,74,75], are Cys-rich repeat domains covalently bound by disulfide bonds. TG monomer contains eleven elements of type-1 repetitive motif located between positions 12 - 1191 and between 1492 - 1546; three elements of type-2 repetitive motif located between amino acids 1437 and 1484, and five elements of type-3 repetitive motif between residues 1584 and 2168 [1-4,74,75]. Interestingly, type-1 repeats could function as binder and reversible inhibitors of protease and have been found as parts of six architecturally distinct protein groups: testicans, secreted modular calcium binding protein (SMOCs), trops, splice variant of the major histocompatibility complex class II–associated invariant chain, insulin-like growth factor–binding protein (IGFBP) and nidogen [76]. Each repeat TG type-1 is composed of approximately 60 amino acids, in which the positions of Cys, Pro and Gly residues are highly conserved. Some insertions of variable length are found in fixed positions. Region I comprises 10 of the 11 TG type-1 repeats, a linker, between repeat 1–4 and 1–5, and hinge segments (Figure 1b). Region II contains the 3 TG type-2 repeats and the 11th TG type-1 repeat (Figure 1b), whereas region III contains the five TG type-3 repeats (Figure 1b) [1-4,74,75]. The fourth region located in the carboxy-terminal, between residues 2192 to 2716, is a nonrepetitive domain that shows significant homology with the acetylcholinesterase (ACHE), named the ACHE-like or CheL domain (Figure 1b) [1-4,77-80]. ACHE-like domain is required for protein dimerization and consequently plays a critical structural and functional role in the TG protein that is essential for intracellular transport of TG to the site of its hormonogenesis [80]. This region functions as an intramolecular chaperone and as a molecular escort for TG regions I, II, and III [79].

After translation, intensive postranslational processes take place in the ER, Golgi aparatus, apical membrane and folicular lumen which include homodimers assembly, glycosylation, sialylation, sulfation, phosphorylation, iodination, multimerization and the formation of intrachain disulfide bonds [1-4]. Several ER enzymes and molecular chaperones, such as calnexin (CNX), calreticulin (CRT), GRP94, BiP, Protein Disulfide Isomerase (PDI), ERp57, ERp29, and ERp72 interact, both concurrently and sequentially, with TG during its folding and assembly and may serve to prevent export of improperly folded TG proteins [1-4].

Human thyroglobulin mutations

Molecular diagnosis of TG deficiency has been traditionally established by PCR-based approaches followed by systematic sequence analysis. Although these classical screenings are capable of detecting more than 90% of all point mutations, they do not detect large noncoding intragenic rearrangements or heterozygous deletions. The first-described human mutation causing a TG defect associated with CH was the mutation g.IVS3-3C>G [8]. Subcloning and sequencing of the cDNA fragments revealed that exon 4 is missing from the major TG transcript in the goiter [8]. Removal of exon 4 does not modify the reading frame of *TG* mRNA. However, exon 4 encodes tyrosine 130 which has been proposed as an important donor tyrosine involved in the synthesis of thyroxine, after coupling with the major acceptor tyrosine at position 5 [73]. The loss of the tyrosine 130 provides a coherent explanation to the hypothyroid status of the patient [8]. To date, one hundred seventeen deleterious mutations in the human *TG* gene have been identified and characterized: 19 splice site mutations, 23 nonsense mutations, 57 missense mutations, 13 deletions (9 single nucleotide deletions, 2 multiple nucleotide deletions and 2 involving a large number of nucleotides), 4 single nucleotide

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insertions or duplication and 1 imperfect DNA inversion (Table 1) [8-56]. The p.R277* [12,16,18,22,23,28,29,30,33,34,40,42,53], p.R1511* [9,16,23,32], p.A2215D [22,26,28,29,42], p.R2223H [14,29,31], p.R2317* [29,38,42,52] mutations are the most frequently identified *TG* mutations in Caucasian population, whereas c.274+2T>G [27,48,49], p.C1058R [17,20], p.C1245R [11,15,17,20,24,36] and p.C1977S [11,15,17,20] are the most common mutations in Asian population.

Exon skipping in the *TG* gene can be caused by nucleotide substitutions or deletion in acceptor or donor splice sites involving the -3/-2/-1 (c.275-3C>G, c.6563-2A>G, c.2762-1G>A, c.6200-1G>C, c.7998-1G>A) or +1/+2/+3/+4/+5/+6 position (c.638+1G>A, c.745+1G>A, c.4932+1G>C, c.5686+1G>T, c.5686+1G>A, c.5686+1G>C, c.6262+1delG, c.6876+1delG, c.274+2T>G, c.7036+2T>A, c.7862+2T>A, c.4159+3_+4delAT; c.3433+3_+6delGAGT, c.638+5G>A), respectively (Table 1) [8,10,13,16,19,20,26-28,30,36,39,40,44,46,48,49,53]. Recently, two exonic cryptic 5'splicing sites in exons 6 (c.745+1G>A) [46] and 19 (c.4159 + 3_+4delAT) [39] of the *TG* gene have been identified. The elimination of exons in the *TG* gene by aberrant splicing results in an altered ability to transfer an iodophenoxyl group from the donor site to the acceptor iodotyrosine.

The 23 inactivating mutations that generates truncated proteins have been localized in exons 4 (p.Y107*, p.R140*) 7 (p.R277*), 9 (p.R432*, p.S509*, p.Q611*, p.W618*, p.Q636*, p.Q692*),10 (p.Q717*, p.Q752*, p.R768*, p.Q810*),13 (p.C1032*) 20 (p.W1418*), 22 (p.R1511*), 27 (p.Q1765*, p.Q1777*), 31 (p.Y1903*) 37 (p.Q2142*), 40 (p.R2317*), 46 (p.Q2638*) and 47 p.R2688*) of the *TG* gene (Table 1) [9,12,16,18,20,22,23,27-29,30,32-34,36-38,40-42,45,47,49,51-53]. The p.R277X by p.R277* mutation is the most frequently reported mutation in the *TG* gene and affected individuals have either homozygous or compound heterozygous mutations. This mutation has been found in families from Brazil, Argentina, Galicia and France (Table 1) [12,16,18,22,23,28-30,33,34,40,42,53]. The functional consequences of p.R277X by p.R277* truncated protein are a complete loss of the central and carboxy-terminal hormonogenic domains and consequently, limited ability to generate thyroid hormone. However, p.R277X by p.R277* TG peptide retains its ability for T_4 synthesis because it still harbors both the acceptor Tyr 5 and the donor Tyr 130. The p.R277X by p.R277* mutation was identified in members of unrelated families with history of CH from Brazil, Argentina and France (Table 1) [9,16,23,32]. The p.R277X by p.R277* mutation is removed from the transcripts by exon skipping using an alternative splicing [9]. The elimination of mutated exon 22 in the pre-mRNA restores the reading frame allowing translation to reach the normal stop codon and results in an in-frame deletion of 57 amino acid residues [9]. The c.886C>T and c.4588C>T nonsense mutations occur in a CpG dinucleotide sequence and could be caused by deamination of a methylated cytosine resulting in a thymine. The CGA arginine codon is considered a hot spot for mutations in mammalian DNA. Truncated protein can be also caused by nucleotide deletions (Table 1) [14,20,27,35,36,42,49,53,56] and insertions or duplication (Table 1) [22,33,36,39] in the *TG* gene. Recently, genetic analysis using an Inverse-PCR (I-PCR) -based approach in three brothers of Turkish origin born from consanguineus parents and affected by CH, goiter and low levels of serum TG, showed a DNA inversion of 16,962 bp in the *TG* gene associated with two deleted regions at both sides of the inversion limits [43]. The inversion region includes the first 9 bp of exon 48, 1015 bp of intron 47, 191 bp of exon 47, 1523 bp of intron 46, 135 bp of exon 46 and the last 14,089 bp of intron 45 [43]. The proximal deletion corresponds to 27 bp of *TG* intron 45, while the distal deletion spans the last 230 bp of *TG* exon 48 and the first 588 bp of intergenic region downstream TG end [43]. The parents were heterozygous carriers of the complex rearrangement.

Sequencing analysis of the *TG* gene revealed sixteen missense mutations that involved wild-type Cys residue: p.C141S, p.C164Y, p.C175G, p.C707Y, p.C1058R, p.C1245R, p.C1262Y, p.C1474Y, p.C1491F, p.C1588F, p.C1878Y, p.C1885G, p.C1977S, p.C1981W, p.C1987Y and p.C2135Y (Table 1) [11,15,17,20-22,24,36,42,49,53]. The loss of Cys residues can eliminate disulfide bonds and alter the normal conformational structure of the TG, possibly preventing the interaction of hormonogenic acceptor and donor sites.

The first report of a missense mutation in the ACHE-homology domain of TG in humans was observed in a French family with two affected siblings with congenital goitrous hypothyroidism [14]. A fetal goiter was diagnosed in both patients by ultrasound at the sixth month of gestation [14]. Percutaneous umbilical vein blood sampling was carried out under ultrasound guidance showing severe fetal hypothyroidism. The sequencing analysis showed a new compound heterozygous mutations, the mutation p.R2223H located in the ACHE-homology domain is associated with a mutation at nucleotide position 1143 in exon 9 (p.362fsX382) [14]. Later 8 new missense mutations were reported in the ACHE homology domain: p.A2215D, p.G2300D, p.R2317Q, p.G2355V, p.G2356R, p.L2528Q, p.R2566W and p.W2666L (Table 1) [17,20-22,24,26,28,29,42,49,50,53]. Functional analysis suggests that the p.A2215D mutation results in retention of the TG protein inside the ER and degradation via the proteasome system [28], as already observed in the *cog/cog* congenital goiter mouse and the WIC-rdw non-goitrous CH rat [81-83]. ER quality control system prevents misfolded TG protein export from ER to Golgi and consequently fails to be transported to the site of thyroid hormone synthesis [84]. These gives rise to a distention of ER, abnormality called as ER-Storage Disease (ERSD) [85]. Consequently, misfolded TG proteins are degraded by the ER-associated degradation (ERAD) pathway.

Animal thyroglobulin mutations

TG mutation have been described in Afrikander cattle [86], Dutch goats [87], cog/cog mouse [81], WIC-rdw rats [82,83] and Wistar Hannover GALAS rats [88].

The congenital goiter of Afrikander cattle is an autosomal recessive disease characterized by a TG synthesis defect [86]. The inactive mutation is a c.2146C>T in exon 9 that generates a stop codon at amino acid position 697 (p.R697X by p.R697*) [86]. The nonsense mutation is thus removed from the transcripts by exon skipping, and there is a preferential accumulation in the goiter of a *TG* mRNA lacking exon 9 [86]. The original reading frame is maintained in the alternative spliced mRNA, which, as it lacks the mutated exon, is translatable into a potentially

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Table 1: Spectrum of thyroglobulin mutations.

Exon/Intron position	Nucleotide position	Amino acid position	References
Exon 2	c.113G>A	p.R19K	[25,49]
Exon 3	c.262C>T	p.R69W	[49]
Intron 3	c.274+2T>G (g.IVS3+2T>G)	Skipping of exon 3	[27,48,49]
Intron 3	c.275-3C>G (g.IVS3-3C>G)	Skipping of exon 4	[8]
Exon 4	c.378C>A	p.Y107*	[42]
Exon 4	c.475C>T	p.R140*	[53]
Exon 5	c.479G>C	p.C141S	[53]
Exon 5	c.548G>A	p.C164Y	[22]
Exon 5	c.580T>G	p.C175G	[20]
Intron 5	c.638+1G>A (g.IVS5+1G>A)	Skipping of exon 5	[19,40]
Intron 5	c.638+5G>A (g.IVS5+5G>A	NA	[53]
Intron 6	c.745+1G>A (g.IVS6 + 1G>A),	Skipping of exon 6 or partially included by use of cryptic 5′ splice site	[46]
Exon 7	c.759_760insA (c.759dupA)	p.L235Tfs*3	[22]
Exon 7	c.799C>T	p.L248F	[49]
Exon 7	c.886C>T	p.R277*	[12,16,18,22,23,28,29,30,33,34,40,42,53]
Exon 8	c.925A>G	p.T290A	[49]
Exon 8	c.967G>T	p.G304C	[37]
Exon 8	c.986A>C	p.Q310P	[20,40]
Exon 9	c.1143delC	p.G362Gfs*21	[14]
Exon 9	c.1345_1346insC (c.1345dupC)	p.P430Pfs*36	[33]
Exon 9	c.1348delT	p.S431Pfs*29	[27]
Exon 9	c.1351C>T	p.R432*	[27,37,53]
Exon 9	c.1382C>T	p.T442I	[49]
Exon 9	c.1583C>A	p.S509*	[53]
Exon 9	c.1712delT	p.L552Pfs*25	[27]
Exon 9	c.1888C>T	p.Q611*	[45]
Exon 9	c.1911G>A	p.W618*	[45]
Exon 9	c.1963C>T	p.Q636*	[51]
Exon 9	c.2115_2116insT (c.2115dupT)	p.V687Cfs*2	[36]
Exon 9	c.2131C>T	p.Q692*	[20]
Exon 10	c.2177G>A	p.C707Y	[53]
Exon 10	c.2206C>T	p.Q717*	[34]
Exon 10	c.2222C>T	p.T722M	[49]
Exon 10	c.2276A>G	p.Y740C	[53]
Exon 10	c.2281C>T	p.P742S	[50]
Exon 10	c.2311C>T	p.Q752*	[53]
Exon 10	c.2359C>T	p.R768*	[33,41,42]
Exon 10	c.2485C>T	p.Q810*	[36]
Exon 10	c.2610G>T	p.Q851H	[40,53,54,55]
Exon 10	c.2687G>A	p.R877Q	[38]
Exon 10	c.2736delG	p.R893Rfs*54	[42]
Intron 10	c.2762-1G>A (g.IVS10-1G>A)	NA	[20,40]
Exon 11	c.2969G>A	p.S971I	[20]
Exon 12	c.3022C>T	p.R989C	[20]
Exon 12	c.3035C>T	p.P993L	[20,49,50]
Exon 13	c.3149G>T	p.W1031L	[53]
Exon 13	c.3153T>A	p.C1032*	[49]
Exon 14	c.3229T>C	p.C1058R	[17,20]
Exon 15	c.3332C>G	p.T1092R	[49]
Exon 15	c.3416C>T	p.S1120L	[51]
Intron 15	c.3433+3_+6delGAGT (g.IVS15+3_+6delGAGT)	NA	[53]
Exon 17	c.3780delG	p.G1241Gfs*3	[36]
Exon 17	c.3788_3789insT (c.3788dupT)	p.I1244Ifs*3	[39]
Exon 17	c.3790T>C	p.C1245R	[11,15,17,20,24,36]
Exon 17	c.3808C>T	p.R1251C	[49]
Exon 17	c.3842G>A	p.C1262Y	[42]
Intron 19	c.4159+3_+4delAT(g.IVS19+3_+4delAT)	Skipping of exon 19 or partially included by use of cryptic 5′ splice site	[39]
Exon 20	c.4310G>A	p.W1418*	[20]
Exon 20	c.4378G>A	p.V1441I	[51]
Exon 21	c.4397G>A	p.S1447N	[20]
Exon 21	c.4478G>A	p.C1474Y	[53]
Exon 21	c.4493C>T	p.T1479M	[50]
Exon 22	c.4529G>T	p.C1491F	[36]
Exon 22	c.4537delG	p.D1494Tfs*54	[20]
Exon 22	c.4575G>T	p.Q1506H	[49]
Exon 22	c.4588C>T	p.R1511* Skipping of exon 22	[9,16,23,32]
Exon 22	c.4604A>G	p.D1516G	[49]
Exon 24	c.4820G>T	p.C1588F	[20]
Exon 24	c.4859C>T	p.T1601M	[50]
Exon 24	c.4930C>G	p.Q1625E	[53]
Intron 24	c.4932+1G>C (g.IVS24+1G>C)	NA	[20]
Exon 26	c.5071C>T	p.R1672C	[53]
Exon 26	c.5176C>T	p.L1707F	[49]
Exon 27	c.5299_5301delGAT	p.D1748del	[33]
Exon 27	c.5318C>A	p.A1754D	[49]
Exon 27	c.5350C>T	p.Q1765*	[27]
Exon 27	c.5386C>T	p.Q1777*	[32]
Exon 28	c.5466delA	p.K1803Kfs*30	[42]
Intron 30	c.5686+1G>T (g.IVS30+1G>T)	Skipping of exon 30	[10,13,26,28]
Intron 30	c.5686+1G>A (g.IVS30+1G>A)	NA	[20]
Intron 30	c.5686+1G>C (g.IVS30+1G>C)	Skipping of exon 30	[44]
Exon 31	c.5766C>A	p.Y1903*	[47,49]
Exon 31	c.5690G>A	p.C1878Y	[20,21]
Exon 31	c.5791A>G	p.I1912V	[20,49]
Exon 31	c.5710T>G	p.C1885G	[49]
Exon 33	c.5986T>A	p.C1977S	[11,15,17,20]
Exon 33	c.6000C>G	p.C1981W	[42]
Exon 33	c.6017G>A	p.C1987Y	[20]
Exon 33	c.6047delA	p.Q1997Rfs*2	[27]
Exon 34	c.6130C>T	p.R2025C	[51]
Intron 34	c.6200-1G>C (g.IVS34-1G>C)	Skipping of exon 35	[16,40]
Intron 35	c.6262+1delG (g.IVS35+1delG)	Skipping of exon 35	[30]
Exon 36	c.6360delC	p.T2101Tfs*33	[53]

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Exon 36	c.6391_6394delTTGT	p.L2112Rfs*21	[49]
Exon 37	c.6461G>A	p.C2135Y	[20]
Exon 37	c.6481C>T	p.Q2142*	[28]
Intron 37	c.6563-2A>G (g.IVS37-2A>G)	NA	[36]
Exon 38	c.6605C>G	p.P2183R	[42]
Exon 38	c.6701C>A	p.A2215D	[22,26,28, 29,42]
Exon 38	c.6725G>A	p.R2223H	[14,29,31]
Intron 39	c.6876+1delG (g.IVS39+1delG)	NA	[49]
Exon 40	c.6956G>A	p.G2300D	[20]
Exon 40	c.7006C>T	p.R2317*	[29,38,42,52]
Exon 40	c.7007G>A	p.R2317Q	[20,21]
Intron 40	c.7036+2T>A (g.IVS40+2T>A)	Skipping of exon 40	[46]
Exon 41	c.7121G>T	p.G2355V	[20]
Exon 41	c.7123G>A	p.G2356R	[17,20,24]
Exon 44	c.7640T>A	p.L2528Q	[53]
Exon 44	c.7753C>T	p.R2566W	[49,50]
Intron 45	c.7862+2T>A (g.IVS45+2T>A)	NA	[20]
Exon 46	c.7969C>T	p.Q2638*	[20]
Intron 46	c.7998-1G>A (g.IVS46-1G>A)	NA	[28]
Exon 47	c.8054G>T	p.W2666L	[53]
Exon 47	c.8119C>T	p.R2688*	[47,49]
Deletion in the 5' region of the TG gene that involves promoter region and 11 first exons.			[56]
Deletion of 9,908 bp that includes exon 45			[35]
DNA inversion of 16,962 bp from exon 48 to intron 45 in the TG gene associated with two deleted regions at both sides of the inversion limits.			[43]

The nucleotide position is designated according to TG mRNA reference sequences reported in National Center for Biotechnology Information (NCBI), accession number: NM_ 003235.4. The A of the ATG of the initiator methionine codon is denoted nucleotide +1. The amino acid positions are numbered after subtracting the 19-amino acid signal peptide. Intronic nucleotides located upstream of the exon have negative numbering, while those located downstream have positive numbering. Splicing mutations are annotated by using cDNA sequences and old nomenclature (g.IVS) is included. Frameshifting mutations are designated by "fs" after a description of the first amino acid affected by the nucleotide change (insertion or deletion) and the stop codon with "*", followed by indication of the length of the shifted open reading frame from the first affected amino acid to the new stop codon. NA, Not Available.

functional protein and preexisting as a minor mRNA species in normal animals [86].

An inbred Dutch goat strain with congenital hypothyroidism and goiter was extensively studied by de Vijlder et al [87]. The hereditary TG synthesis defect in Dutch goats is caused by a c.945C>G that changes a triplet TAC coding for Tyr in exon 8 into a triplet TAG giving a stop codon (p.Y296X by p.Y296*) [87].

The cog/cog trait originally appeared as a spontaneous autosomal recessive phenotype in the inbred AKR/J strain of mouse [81]. Congenital hypothyroidism with goiter was observed in the cog/cog mouse, suggesting a defect of the TG synthesis [81]. Kim et al. identified a missense mutation, contained within the ACHE-like domain of the TG coding sequence, as the molecular basis for congenital hypothyroid goiter in the cog/cog mouse [81]. Direct sequencing of the cog *TG* cDNA showed a c.6848T>C mutation), generating the p.L2263P mutation in the mature cog TG protein [81]. Transient expression of the proteins indicated that cog TG exhibits a severe defect in the exit from the ER, whether the correction of this missense mutation restores the normal TG secretion [81].

The WIC-rdw rat is a hereditary hypothyroid variant derived from the Wistar-Imamichi strain [82,83]. In contrast to human patients and others animal models of congenital hypothyroidism, the WIC-rdw rat presents a hypoplastic thyroid gland, despite elevated circulating levels of TSH and reduced serum T_3 and T_4 [82,83]. The possibility that the mutant proteins may be cyto-toxic for thyroid growth and proliferation may be hypothesized [83]. Additional experiments are clearly needed to determine the mechanism by which WIC-rdw rat presents a hypoplastic thyroid gland. The sequencing of the WIC-rdw rat TG cDNA revealed a c.6958G>C mutation [82,83]. The corresponding amino acid substitution in the ACHE-like domain of the WIC-rdw TG was p.G2300R [82,83]. As in the cog/cog mouse models, the WIC-rdw TG was retained inside the ER in cells. [82,83]. Experimental studies showed that when mutant TG was co-expressed with wild-type TG, the two proteins cross-dimerized, and secretion of WIC-rdw TG was partially restored.

Finally, Wistar Hannover Galas rat showed two distinct spontaneous abnormalities: goiter and dwarfism [88]. The responsible mutation is a guanine to thymine transversion at the acceptor site of intron 6 of the *TG* gene (749-1G>T) that induces a complete missing of exon 7 from the *TG* transcript [88]. Interestingly, homozygotes manifested both dwarfism and goiter, while heterozygotes had only a goiter, suggesting that the mutant phenotype is inherited as an autosomal semi-dominant trait [88].

Perspectives and Conclusions

Recent technological advances in instrumentation, computer hardware and software for next-generation sequencing (NGS) platforms [89] have led to the identification of new mutations in the *TG* gene [47-51,53]. The new technologies allow also the identification in the same patient with CH the coexistence of multiple mutations in different thyroid genes; for instances mutations in *TG* associated with mutations in *DUOX2* [47,50,53] or *TPO* [53] or *TSHR* [48].

In the present paper, we discussed remarkable advances in the understanding of the pathophysiology of the CH associated with TG defects as well as in the identification of the mutations responsible for the disease. However, the impact of several mutations on the development of this disorder remains to be elucidated. The introduction of NGS approaches, characterized by a marked increase in the yield of DNA sequencing and the ability to analyze large populations will probably allow a change in the traditional understanding of the molecular and genetic bases of CH and the genotype-phenotype correlation. The identification of the coexistence of multiple mutations in the same gene or in different thyroid specific genes could contribute to the accurate diagnosis and classification of the defects. Moreover, the massive identification of mutations

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could be of greatly importance in the near future, since preimplantation of genetic diagnosis will be available for families in which the genetic defects responsible for the CH have been previously identified.

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