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Gene polymorphisms and thyroid hormone signaling: implication for the treatment of hypothyroidism

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Abstract

Introduction—Mutations and single nucleotide polymorphisms (SNPs) in the genes encoding the network of proteins involved in thyroid hormone signaling (TH) may have implications for the effectiveness of the treatment of hypothyroidism with LT4. It is conceivable that loss-of-function mutations or SNPs impair the ability of LT4 to be activated to T3, reach its targets, and ultimately resolve symptoms of hypothyroidism. Some of these patients do benefit from therapy containing LT4 and LT3.

Methods—Here, we reviewed the PubMed and examined gene mutations and SNPs in the TH cellular transporters, deiodinases, and TH receptors, along with their impact on TH signaling, and potential clinical implications.

Results—In some mechanisms, such as the Thr92Ala-DIO2 SNP, there is a compelling rationale for reduced T4 to T3 activation that limits the effectiveness of LT4 to restore euthyroidism. In other mechanisms, a potential case can be made but more studies with a larger number of individuals are needed.

Discussion/Conclusion—Understanding the clinical impact of the genetic makeup of LT4-treated patients may help in the preemptive identification of those individuals that would benefit from therapy containing LT3.

Keywords

deiodinase; polymorphism; thyroid; thyroxine; triiodothyronine; T3-signaling

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Introduction

The rationale for the treatment of hypothyroidism with L-thyroxine (LT4) monotherapy is that thyroxine (T4) is converted to the biologically active 3,5,3'-triiodothyronine (T3) by the deiodinases (DIO), restoring thyroid hormone (TH) economy and TH signaling throughout the body [1]. Nonetheless, the findings (i) that LT4 exhibits variable effectiveness in restoring clinical and biochemical euthyroidism [2–4], (ii) that Thr92Ala-DIO2 is associated with increased Body Mass Index (BMI) and relative insulin resistance in obese Caucasians [5], and with reduced quality of life and positive response to therapy for hypothyroidism containing LT4 + LT3 [6], put that rationale in check. Is it possible that single nucleotide polymorphisms (SNPs) in genes involved in TH signaling play a role in the variable effectiveness of treatment with LT4?

Here we review the impact of SNPs on several genes involved in TH signaling and the treatment of hypothyroidism. We searched PubMed using the following keywords: "deiodinase gene polymorphism", "thyroid hormone receptor gene polymorphism", "gene polymorphism", and "thyroid hormone signaling".

Thyroid hormone signaling

T3 is the biologically active TH, the molecule that interacts with the highest affinity to the TH receptors (TRs). Most T3 originates from the conversion of T4 (prohormone) to T3 that takes place outside the thyroid gland. A smaller portion (~20% in humans) of T3 is secreted directly by the thyroid gland. Most T4 and T3 circulate in the blood linked to "transport" proteins, and only the free hormone enters cells and triggers biological effects. Both T4 and T3 enter target cells via specific membrane transporters. These transporters are abundant (and redundant) but may be limiting for TH action in tissues such as the brain. Their expression is cell-specific, as well as their transport specificity, e.g. MCT8 preferentially transports T4 while MCT10 prefers T3 [7].

Once inside the cells, TH can be metabolized by two activating deiodinase pathways, the types I (D1) and II (D2) deiodinases, which mediate the conversion of T4 to T3, and an inactivating pathway, the type III deiodinase (D3), which inactivates TH (producing reverse T3 (from T4) and T2 (from T3)). D1 is inserted in the plasma membrane, hence T3 produced via D1 equilibrates rapidly with plasma. In contrast, D2 is present in the endoplasmic reticulum (ER), closely associated with the cell nucleus. D2-generated T3 remains within the cell for several hours, eventually binding to nuclear TRs and triggering biological effects; nonetheless, the D2 pathway is the main source of circulating T3 in normal individuals: ~65% of the extra-thyroidally produced T3 is contributed by D2 and the rest by D1 [7]. D3 is unique, in that it is located in the plasma membrane but undergoes constant internalization and recycling between the plasma membrane and early endosomes [8, 9]. In contrast to D2, the expression of D3 is thought to reduce TH signaling in a cell-specific fashion [10–12].

The regulation of T3-responsive genes occurs through mechanisms that involve histone modification [13]. TRs are bound to specific DNA sequences known as TH-responsive

elements (TREs). In the absence of T3, TRs attract transcriptional co-repressors, silencing gene transcription. Upon T3 binding, T3-TRs activate gene transcription by releasing co-repressor and attracting transcriptional co-activators. Less is known about the suppression of gene expression by T3. There is also evidence that T4 can trigger some biological effects via non-genomic actions [14], and some of the mechanistic details have been worked out for the cardiovascular system [15].

In summary, TH signaling depends on the integrity and function of several proteins that cooperate to elicit TH actions. Understandably, gain- or loss-of-function modifications in the genes encoding any of these proteins may affect TH action with substantial clinical consequences for patients that are being treated for hypothyroidism.

Gene polymorphisms

A gene mutation is defined as any abnormal change in a DNA sequence, present in less than 1% of the population. A SNP is defined as a common variation in a DNA sequence, where the least common allele has a frequency of >1% [16]. Whereas many mutations have clear-cut clinical consequences, some of the findings obtained with SNPs might not be reproduced across different populations, raising the possibility that the phenotypic impact of SNPs may vary according to the genetic background of the population studied. Indeed, that mutations and SNPs can cause an array of phenotypic effects is well known, and these effects can be modulated by the environment and by other genes in the genome (the genetic background), and that interactions among mutations can also be heavily dependent on the genetic background in which they are studied [17–19].

Knowledge about mutations and SNPs is relevant to patients under treatment for hypothyroidism because they may potentially reduce the effectiveness of LT4 [20, 21]. This is particularly true if one considers that athyreotic patients appropriately treated with LT4 may have a deficiency of T3 [22], and that this deficiency becomes more prevalent when these patients carry a specific SNP in the DIO2 gene [23]. In this regard, many LT4-treated patients exhibit a relative deficiency of T3, i.e. upon normalization of serum TSH the T3/T4 ratio is lower than normal. What is more important is that ~15% of the LT4-treated patients exhibit an absolute deficiency of T3, with circulating values below the normal reference range despite normalization of serum TSH [21, 22]. This is explained by insufficient/absent thyroidal secretion of T3 and an imbalance between D2-generated T3 in the hypothalamus-pituitary unit versus D2-generated T3 in the tissues that contribute to the T3 in the circulation [20, 24]. Thus, combined with the T3 deficiency, any further impairment in TH signaling (such as caused by a gene mutation or critical SNPs) may tilt the balance between clinical euthyroidism and residual symptoms [25].

Thyroid hormone transporters

Different proteins can carry THs through cell membranes. Some of these proteins include monocarboxylate transporters (MCT), organic anion transporter polypeptides (OATP), large neutral amino acid transporters (LAT), and the sodium/taurocholate co-transporting polypeptide (SLC10A1, also known as NTCP) [26]. These transporters have different

specificities for T3 and T4 (in the uM range), however, the total concentration of THs in tissues is much lower (nM) and, due to binding to high-capacity low-affinity cytoplasmic proteins, the concentration of free T3 and free T4 is even lower (pM) (reviewed extensively elsewhere [27]). In other words, TH transporters are not working at their full capacity. Moreover, TH transporters are generally expressed in abundance and exhibit a great deal of redundancy. For example, some cells may express up to 16 cell membrane TH transporters [28, 29], and in many cases, no single one plays a dominant role.

T4 needs to get into cells to be activated to T3 by the deiodinases. Circulating T3 also needs to get into cells before reaching the cell nucleus and triggering biological effects. Given that LT4-treated patients have a relative (in 15% it is absolute) deficiency of T3, any further impairments in the mechanisms that trigger T3 effects may compromise the effectiveness of treatment with LT4. Several studies have attempted to assess whether SNPs in TH transporters may affect plasma TH levels [28, 30–32] or to find an association with cognitive phenotypes or clinical outcomes [31, 33, 34]. However, results have not been universally reproduced, so it has been difficult to conclude the physiological significance of most of these genomic variations. Below is a summary of the main genomic alterations identified in the different TH transporters families.

MCT

MCTs transport monocarboxylates (e.g., pyruvate, lactate, ketone bodies) [35]. Two members of this family act as TH transporters: MCT8 and MCT10 (encoded by *SLC16A2* and *SLC16A10*, respectively).

MCT8 is highly specific for T4 and T3 transport but also transports rT3 and T2. Given the importance of MCT8 in the brain, loss-of-function mutations in *SLC16A2* result in severe psychomotor impairment and elevated serum T3 levels, a condition known as the Allan-Herndon-Dudley syndrome (AHDS) [36, 37]. *SLC16A2* mutations are distributed throughout the coding region, mainly in the transmembrane domains [38]. As mutations are less common in the extracellular and intracellular loops, missense mutations in these domains likely result in a milder phenotype, escaping detection [38, 39]. *SLC16A2* gene mutations range from single nucleotide substitutions to large deletions involving one or more exons, disrupting MCT8 synthesis and its function. For example, the single nucleotide deletion c.1212delT leads to a premature stop codon in position 416 that results in a non-functional protein [36]. In other cases, the mutation results in impaired trafficking into the membrane and/or decreases its affinity for TH [40, 41]. Since mutations in the *SLC16A2* gene have such profound effects, the question arises whether small changes in the *SLC16A2* gene may affect transport activity as well. Only three studies exist on the relationship between *SLC16A2* polymorphic variants and serum TH levels [28, 31, 32]. The variant rs6647476 is not associated with serum TH levels, MCT8 mRNA levels, or TH-responsive genes in white blood cells. Conversely, the variant rs5937843 is associated with lower free T4 in heterozygous males but not in the homozygous female [28] in the same population.

MCT10 is a transporter of aromatic amino acids (e.g., tyrosine and tryptophan) and also transports T3 and T4. Compared with MCT8, MCT10 is slightly more efficient

at transporting T3 and less efficient at T4 transport [42]. Considering its broad tissue distribution (intestine, kidney, liver, heart, skeletal muscle, and placenta) [43], it is conceivable that mutations or SNPs in *SLC16A10* may influence circulating TH levels and TH signaling [44]. However, a compilation of studies that analyzed the association of plasma TH levels and *SLC16A10* SNPs showed inconsistent results. In healthy individuals, the variant rs14399 (in the 3'-UTR region of the *SLC16A10* gene) and the variant rs14399 [31] are not associated with serum TH levels, and the variant rs17606253 exhibit a weak association with abnormal FT4 serum levels [45]. In athyreotic patients receiving levothyroxine (LT4) treatment, the variant rs17606253 does not affect the plasma fT3 levels.

The clinical relevance of these polymorphisms is unclear. There is only one study associating some of these polymorphisms with possible cognitive phenotypes and suggests an influence on cognitive domains such as attention, alertness, and planning (*SLC16A2* rs5937843 and rs6647476) and nonverbal reasoning abilities (*SLC16A10* rs14399) [33], unfortunately, in this study, the TH levels were not studied.

OATP

OATPs transport amphipathic organic compounds (e.g., steroids, bile salts). Among the ~40 OATPs identified, 8 human and 14 mouse proteins are active in TH transport in vitro [46], but in humans, their expression is generally very low. Virtually all OATPs transport numerous substrates except for OATP1C1. OATP1C1 in humans is mainly expressed in the blood-brain-barrier and transports T3, rT3, T4, and T4 sulfate with high specificity [47, 48]. Its clinical relevance is well illustrated in a case of a 15-year-old patient harboring a missense mutation (D252N) who exhibited progressive neurodegeneration and hypometabolism [49].

Several studies have examined human polymorphisms in *OATP1C1*. In patients with primary autoimmune hypothyroidism on LT4 treatment [50], the variants rs10770704 and rs10444412 are associated with fatigue and depression but not the variant rs36010656. However, no association with neurocognitive functioning or preference for combined LT4–LT3 therapy was found. In another study of patients with acute myocardial infarction [51], four OATP1C1 variants were studied: rs10444412, rs10770704, rs1515777, and rs974453. Only the homozygous rs1515777 was associated with a decrease in circulating FT3 and the ratio FT3/FT4. The wild-type OATP1C1 rs974453 has been associated with a higher odds ratio of symptoms of depression [52] and worst outcomes after ischemic stroke [53].

From the OATP1 family, the transporters OATP1A2, OATP1B1, and OATP1B3 also exhibit high affinity for T3 and T4 (similar to MCT8). However, its low specificity questions its physiological role in TH transport. Several studies have explored polymorphisms in these genes and their effect on plasma TH levels. OATP1A2 is expressed in the liver, brain, and kidney [54, 55]. The OATP1A2-Ile13Thr polymorphism is associated with higher plasma T3 levels in two different studies on healthy individuals [56, 57], but not the OATP1A2-Glu172Asp. However, both polymorphisms exhibited decreased TH transport in vitro [56, 58, 59].

OATP1B1 and OATP1B3 are expressed in the liver [60, 61], and albeit with very low specificity [46], they preferentially transport iodothyronine sulfates T4S, T3S, and rT3S exhibiting limited transport of nonsulfated T4, T3, and rT3 [62]. While polymorphisms in these genes have been extensively studied in the context of drug response [58, 63], only two studies associated the OATP1B1-Val174Ala (rs4149056) with higher T4S levels in healthy individuals [32] as a consequence of a ~40% decreased function of the transporter. The OATP1B3-Ser112Ala and -Met233Ile polymorphisms show no association with serum thyroid parameters [32].

SLC17

The SLC17 family are organic anion transporters. Currently, the SLC17A4 is the only member shown to transport TH and play a role in plasma TH level. One study that used genome-wide association analysis (GWAS) [30] identified SNPs in this gene and found that the SLC17A4 variants rs9356988 and rs137964359 are associated with changes in plasma FT4 levels. Further in vitro studies confirmed that the SLC17A4 encodes a new high-affinity T3 and T4 transporter.

No studies to date have been conducted to link SNPs in the family of the liver Na/taurocholate cotransporter, commonly known as NTCP, nor the L-type amino acid transporters (LAT1 and LAT2), to alterations in plasma TH levels or in their capacity to transport TH. Nonetheless, there are TH transporters in these families that are clinically relevant. For instance, there is suggestive evidence of individual vulnerability to schizophrenia related to the LAT1 SNP rs9936204 [64]. Another example is the mutations in the SLC10A1 gene, which encodes the Na +/taurocholate co-transporting polypeptide (NTCP), and in the SLC7A5 gene, which encodes the light chain of LAT1 [44]. Two distinct SLC7A5 mutations have been identified, resulting in decreased LAT1-mediated leucine transport. These mutations have been observed in patients with autism spectrum disorder, as well as delays in motor coordination and cognitive skills development. However, the impact of these mutations on TH transport remains to be elucidated [44].

TH deiodination

Studies in mice with targeted inactivation of the activating deiodinase genes revealed that deiodinase defects can be compensated for by changes in thyroidal secretion of T3. As a result, serum T3 levels remain unaffected, even if all three deiodinases have been inactivated [65, 66]. Therefore, it is likely that a substantial number of individuals with defects in deiodinases exist which remain well compensated for by adjustments in the thyroid secretion of T3. Nonetheless, these defects may become clinically relevant once these individuals develop hypothyroidism (and the ability of the thyroid gland to compensate is diminished or eliminated) and are treated with LT4. In the absence of a healthy thyroid gland, T3 homeostasis depends solely on the functionality of the deiodinases. Thus, any impairment in deiodinase function (e.g. loss-of-function SNPs or mutations) can compromise the effectiveness of treatment with LT4.

Deiodinases are selenoproteins, and as such they require a specialized pathway that directs the incorporation of selenocysteine into the nascent selenoprotein [67]. A key protein involved in this pathway is the selenocysteine insertion sequence-binding protein 2 (SECISBP2), the mutation of which can compromise the synthesis of all selenoproteins, including the three deiodinases [68]. Several pathogenic variants of SECISBP2 have been identified, including the homozygous variant p.Arg128Ter, which leads to early termination of protein synthesis [69], variants p.Arg120Ter and p.Arg770Ter [70], respectively a frame-shift variant causing a premature stop codon at amino acid 255, and a splicing defect resulting in the incorporation of additional intronic sequences between exon 6 and 7 in the other allele; and heterozygosity for the missense variant p.Cys691Arg [71]. Many other SECISBP2 mutations have been identified [72–74], all impacting TH metabolism to different degrees.

In addition to the pathway involved in selenoprotein synthesis, mutations and SNPs with potential impact on therapy with LT4 have been described for the three deiodinases.

DIO1

A common theme in mouse models of natural Dio1 deficiency or targeted Dio1 inactivation is the elevation in serum rT3 levels [65, 66]. This knowledge led to the recent identification of individuals that carry (loss-of-function) pathogenic missense variants (p.Asn94Lys and p.Met201Ile) in DIO1 [75]. Whereas loss-of-function mutations in DIO1 can be compensated for by increased thyroid secretion of T3, this mechanism is absent in patients with hypothyroidism. While DIO1 mutations seem to be rare, DIO1 SNPs have been identified and also found to be associated with alterations in the free T3 to free T4 ratio [76]. The C-allele in this SNP correlated with increased D1 function, resulting in elevated free T3/T4 ratio and free T3 levels, as well as decreased free T4 and rT3 levels. Notably, another rs12095080 SNP in the DIO1 gene was linked to a higher risk of cardiac mortality following acute myocardial infarction (OR=3.97; 95% CI.=1.45–10.89; P=0.005), although it is not clear that this is connected with TH homeostasis [77]. Notably, in a prospective observational study, 196 LT4-treated hypothyroid subjects were assessed at baseline for well-being and common deiodinase SNPs. The minor genotypes of a few DIO1 SNPs (rs11206244, rs2294512, and rs4926616) were associated with reduced psychological well-being, but not those for DIO2 or DIO3 [78].

These findings are reminiscent of the observations that the DIO1 rs11206244 genotype was associated with lifetime major depression in white female subjects, in particular those from high-risk cohorts [79]. Along the same lines, after 168 patients were genotyped for ten DIO1–3 and OATP1C1 SNPs, the major allelic (wild-type) DIO1-rs12095080 genotype (AA) was found to be associated with a higher odds ratio of anxiety symptoms (OR = 5.16; 95% CI: 1.04–25.58; p = 0.045), but the DIO1-rs11206244 wild-type genotype (CC) and wild-type OATP1C1-rs1515777 allele containing the genotypes (AA + AG) were associated with a lower odds ratio of symptoms of anxiety (OR = 0.37; 95% CI: 0.14–0.96; p = 0.041 and OR = 0.30; 95% CI: 0.12–0.76; p = 0.011, respectively). The wild-type OATP1C1-rs974453 genotype (GG) was associated with a higher odds ratio of symptoms of depression (OR = 2.73; 95% CI: 1.04–7.12; p = 0.041). These findings support the idea that

SNPs in TH transporters and deiodinases may play a role in the effectiveness of treatment for hypothyroidism. Conversely, one other study failed to identify a correlation between variants of the DIO1 gene, which affect TH levels and DIO3 SNPs, with recurrent depressive disorders [80].

It is straightforward to appreciate how loss-of-function mutations and SNPs in DIO1 can compromise T3 production in LT4-treated patients, and contribute to a relative or absolute deficiency of T3. In addition, such genetic modifications in DIO1 may also explain anecdotal reports that the T3/rT3 ratio could be used to assess the effectiveness of therapy with LT4. Given that rT3 is cleared from the circulation via D1, any impairment in D1 activity can result in an accumulation of circulating rT3, decreasing further the T3/rT3 ratio.

Notably, the genetically-based variability in deiodinase genes may also play a role in the clinical effectiveness of LT3 when given as an adjuvant to antidepressant drugs. The use of antidepressants over 8 weeks in 64 patients treated with sertraline plus T3 or plus placebo was followed by a questionnaire. Among SNPs in DIO1 (DIO1-C785T, DIO1-A1814G) and DIO2 (DIO2-Thr92Ala and DIO2-ORFa-Gly3Asp), only the DIO1-785T genotype was associated with the efficacy of LT3 supplementation (DIO1 DIO1-785T has reduced activity) [81].

DIO2

D2 is a key enzyme to be considered in the treatment of hypothyroidism given that in LT4-treated patients, ~80% of the serum T3 is derived from the D2 pathway [82]. The Thr92Ala-DIO2 SNP (rs225014) is relatively common, with at least one allele present in ~45% of the population [16]. This SNP has been associated with various clinical syndromes, including increased BMI and relative insulin resistance [83], hypertension, type 2 diabetes, mental disorders, lung injury, bone remodeling, and autoimmune thyroid disease. However, its prominence in the management of hypothyroidism came from a possible link with the effectiveness of therapy with LT4 and responsiveness to LT4+LT3 [6] (As mentioned earlier, these associations have not been consistently replicated in all population studies [16]).

D2 is an ER-resident protein with a relatively short half-life due to ubiquitination and subsequent proteasomal degradation. D2 is normally a cargo protein in ER Golgi intermediary compartment (ERGIC) vesicles, recycling between ER and Golgi. This characteristic is attributed to a unique 18-residue loop that facilitates binding to two ubiquitin ligases [7]. In contrast, Ala-D2 exhibits a reduction in its catalytic activity, has a longer half-life, and is ectopically present in the Golgi apparatus [84, 85]. Ala-D2 expression caused ER stress and activates the unfolded protein response (UPR). Ala92-D2 accumulated in the trans-Golgi. The latter could explain why African American carriers of the Thr92AlaD2 polymorphism have been found at higher risk of developing Alzheimer’s disease [86].

An important finding that helped in the understanding of the Thr92Ala-DIO2 SNP was that Ala-D2 is 20–40% less catalytically active [23, 85]. The immediate consequence of these findings is that TH signaling may be compromised in LT4-treated patients carriers of

the SNP. This defect in TH signaling could be systemic (given that serum T3 levels were reported to be lower in carriers of the Thr92Ala-DIO2 SNP) [23] or localized, in tissues that depend on locally generated T3 via D2 (such as the brain).

An Ala-Dio2 SNP-carrying mouse was created to assess the impact of this SNP on therapy with LT4 [85]. The mouse refrained from physical activity, slept more, and required additional time to memorize objects. Indeed, the Ala-Dio2 SNP-carrying mouse exhibited UPR and hypothyroidism in distinct brain areas [85]. Enhancing T3 signaling in the brain with LT3 improved cognition, whereas restoring proteostasis with the chemical chaperone 4-PBA eliminated the Ala-Dio2 phenotype. In contrast, primary hypothyroidism intensified the Ala92-Dio2 phenotype, with only partial response to LT4 therapy. Disruption of cellular proteostasis and reduced Ala92-D2 activity may help explain the failure of LT4 therapy in patients with hypothyroidism that carry the Thr92Ala-DIO2 allele [85].

Subsequent studies with the Ala-Dio2 SNP-carrying mouse revealed that a more severe impairment in cognition was found in female mice, and in older male mice (7–8-month-old), which extended to different aspects of declarative and working memories. There were no structural alterations in the prefrontal cortex (PFC) and hippocampus of the Thr92Ala-Dio2 mouse. Nonetheless, in both male and female PFC, there was an enrichment in genes associated with TH-dependent processes, ER stress, and Golgi apparatus, while in the hippocampus there was additional enrichment in genes associated with inflammation and apoptosis. Reduced TH signaling remains a key mechanism of disease given that short-term treatment with L-T3 rescued the cognitive phenotype observed in males and females. Thus, female sex and age seem to be additional risk factors for cognitive impairment associated with the Thr92Ala-DIO2 polymorphism. In addition to reduced TH signaling, ER stress, and involvement of the Golgi apparatus, hippocampal inflammation, and apoptosis were identified as potentially important mechanisms of disease [87].

Although not universally reproduced [88], it is intriguing that carriers of the Thr92Ala-DIO2 SNP exhibit clinical improvement when LT3 is added to LT4 therapy [6]. This seems to be particularly true for patients that exhibit residual symptoms while on therapy with LT4 [89], or when an association with the MCT10 SNP rs17606253 was also considered [90]. Residual clinical manifestations of hypothyroidism include higher BMI, increased use of beta-blockers, statins, or antidepressant medications, and lower energy expenditure, in addition to reports of difficulty controlling weight, fatigue or low energy levels, and mood problems and memory [91]. These manifestations could be explained at least in part by an incomplete normalization of T3 signaling in LT4-treated patients, but more studies are needed.

New exciting evidence suggests that previous inconsistent results on the effect of Thr92Ala-DIO2 SNP could have been due to low statistical power. When anxiety and depression scores were assessed in 52,609 individuals (6, 906 with the Thr92Ala substitution), of whom 1569 had a history of LT4 use (194 with the Thr92Ala substitution), the Thr92Ala substitution was present in 13% of the population and was not associated with increased scores in individuals not on LT4. After all the necessary adjustments, individuals on LT4 who were non-homozygous for Thr92Ala were 22% more likely than those not on LT4 to

reach the threshold for anxiety caseness, while homozygous individuals were 208% more likely. The authors concluded that individuals homozygous for DIO2 Thr92Ala on LT4 have significantly reduced quality of life compared to those non-homozygous, but there is no effect in the absence of LT4. Since individuals are not aware of their genotype, this provides strong objective evidence for a biological basis for the persistence of symptoms in some individuals on LT4 [92].

DIO3

DIO3 is an imprinted gene in humans and could be involved in the pathogenesis of the syndrome linked to the uniparental disomy of chromosome 14 (Temple and Kagami-Ogata syndromes). Notably, DIO3 imprinting may be variable as it was found to be paternally imprinted in neonatal skin, whereas in adult skin, the allele preferentially expressed is inherited from the mother [93]. DIO3 is relevant for the treatment of hypothyroidism, given that mood and cognitive functions are affected by TH signaling, and that DIO3 is highly expressed in neurons and limits the TH actions in the brain [94, 95]. Thus, it is straightforward to conceive a scenario in which SNPs that affect D3 activity could modulate the effectiveness of the treatment of hypothyroidism. Unfortunately, to our knowledge studies to assess the impact of DIO3 SNPs on the therapy for hypothyroidism have not been reported.

Nonetheless, therapy with LT3 can increase plasma T3 levels and trigger TH signaling in the brain, despite the presence of D3 in neurons. Using a compartmentalized microfluid device allowed for the identification of a novel neuronal pathway of T3 transport and action that involves axonal T3 uptake into clathrin-dependent, endosomal/non-degradative lysosomes (NDLs). NDLs-containing T3 are retrogradely transported via microtubules, delivering T3 to the cell nucleus, and triggering T3 actions. The NDLs also contain Mct8 and D3, but most T3 gets away from degradation because D3's active center is oriented toward the cytosol, sparing T3 from deiodination. This mechanism is so effective that T3 implanted in specific mouse brain areas can trigger selective signaling in distant locations, as far as the contralateral hemisphere [96].

Conjugation of TH

In addition to deiodination, glucuronidation, and sulfation are other important pathways of iodothyronine metabolism. During glucuronidation, the phenolic hydroxyl group (4′–OH) is conjugated with glucuronic acid, and the reaction is mediated by the UDP-glucuronosyltransferases (UGTs). Glucuronidation of T4 (T4 to T4G) contributes significantly to T4 homeostasis in humans. The use of antiepileptic drugs that increase hepatic T4 glucuronidation is associated with decreased serum T4 levels [97], and when these drugs were administered to patients on replacement therapy, they required a higher LT4 dosage [98]. No significant T3 glucuronidation has been observed in humans [99].

Several studies have studied the effects of SNPs in the UGTs on their ability to glucuronidate T4. The variant UGT1A1*28 affects the in vitro glucuronidation of T4 in human livers. A series of studies in patients with differentiated thyroid cancer associated

UGT SNPs with changes in the LT4 dose required to normalize their TSH, with the carriers of the UGT1A1–53 requiring less LT4 [100]. The UGT1A1 rs8175347 and the UGTA3 variants rs3806596 and rs1983023 were associated with changes in the LT4 + LT3 dose required to suppress TSH secretion [101]. In the same study, the carriers of rs11563250G required ~5–12% more LT4, which agrees with in vitro studies showing that this variant increases the UGT1A1 activity [102]. Other studies in patients with total thyroidectomy and ablation by ^{131}I show that carriers of the UGT1A1 variant rs8175347 require lower LT4 doses but not with the UGT1A3 rs3806596 and rs1983023 [103].

Sulphation is the conjugation of the phenolic hydroxyl group (4′–OH) with sulfate, and the reaction is catalyzed by phenol sulfotransferase. In humans, the sulfotransferases that have an affinity for TH are SULT1A1, - SULT1A2, SULT1A3, SULTB1, SULT1C1, and SULT1E1 [104]. Sulphation of T4 and T3 aids deiodination by D1. D1 can generally perform inner and outer ring deiodination equally well, but if T4 is sulfated (T4S), it blocks outer ring deiodination by D1, resulting in the irreversible inactivation of TH and the production of rT3S [105]. Sulphation also increases the water solubility of TH, which helps to eliminate sulfated TH through the bile and urine. However, the levels of sulfated TH in serum, bile, and urine are typically low in normal physiological conditions, indicating that D1 preferentially metabolizes sulfated TH. In humans, the sulfotransferase shows a strong preference for T2, but the biological significance of this reaction is not fully understood. Only one study shows that a splice variant in the SULT1C3 results in a higher specificity for TH [106]. At the moment, studies to assess the impact of SNPs in the sulphatases on the variable effectiveness of therapy with LT4 have not been reported.

Thyroid hormone receptors

The clinical implications of inactivating mutations in the genes encoding the THRα or THRβ are well known, with the development of the syndromes of resistance to TH (RTH) [38, 107]. In general, affected patients exhibit a tissue-specific reduction in TH signaling depending on the predominant form of the receptor expressed in each tissue. The clinical implications of having RTHβ may also include pregnancy outcomes (in pregnant women with RTHβ) [108, 109] and tissue TH responsiveness in healthy off-spring of these pregnancies [110].

However, little is known about the potential for SNPs in THR to affect the effectiveness of therapy for hypothyroidism. An analysis of the THR loci in 52 randomly identified individuals led to the identification of 15 SNPs that were subsequently studied in healthy Danish twins, and related to thyroid parameters [111]. One SNP in THRβ was also studied in the elderly population of the Rotterdam Scan Study. No associations between SNPs and TH levels were found. THRβ-in9-G/A was significantly associated with higher serum TSH (p(lnTSH) = 0.01) in the Danish twins, but not in elderly subjects of the Rotterdam Study (although it showed a similar trend) [111].

The analysis of 5 SNPs in THRα in the Lille Alzheimer's Disease (AD) case-control study (710 cases/597 controls), revealed that subjects bearing the rs939348 TT genotype tended to have a higher risk of developing AD (adjusted OR [95%CI] = 1.71 [0.99–2.95] $p = 0.06$).

Similar trends were observed in three other independent AD case-control studies. When combining the 4 studies (1749 cases/1339 controls), there was an overall higher risk of AD in TT subjects (adjusted OR [95%CI] = 1.42 [1.03–1.96], $p = 0.03$) compared to the carriers of the C allele. However, when these data were combined with 2 American GWAS studies on AD, there was only a weak (not significant) association (OR = 1.19 [0.97–1.45], $p = 0.10$) [112].

THRα gene sequencing of an obese woman (index case) revealed an SNP (rs12939700) in a critical region involved in THRα alternative processing. This led to the evaluation of THRα gene variants in 3 independent Europid populations (i) in two population cohorts at baseline (n=3417 and n=2265), 6 years later (n=2139) and (ii) in 4734 high cardiovascular risk subjects. Remarkably, the minor allele of the index case SNP (rs12939700), despite having a very low frequency (4%), was significantly associated with higher BMI (P=0.042) in subjects with high cardiovascular risk. A more frequent THRα SNP (rs1568400) was associated with higher BMI in subjects from the population (P=0.00008 and P=0.05) after adjusting for several confounders. Rs1568400 was also strongly associated with fasting triglycerides (P dominant = 3.99 × 10(−5)). In the same sample, 6 years later, age and sex-adjusted risk of developing obesity were increased in GG homozygotes (odds ratio 2.93 (95% confidence interval, 1.05–6.95)). In contrast, no association between rs1568400 and BMI was observed in subjects with high cardiovascular risk, in whom obesity was highly prevalent [113]. In a subsequent study, the THRα rs939348 SNP was associated with L-T4 dose and central obesity among patients with hypothyroidism [114].

Conclusion

In conclusion, our examination of mutations and SNPs in genes encoding the various components of the TH signaling revealed in some cases (i.e. Thr92Ala-DIO2) a mechanistic explanation for the reduced effectiveness of therapy with LT4 for hypothyroidism; in other cases, there is a potential for such a role but more studies are needed. Notably, such genetic modifications may remain silent while the patient has a healthy thyroid (due to thyroid-based compensatory mechanisms) and only later assume clinical significance after individuals develop hypothyroidism and undergo treatment with LT4. Along with other important factors, such as comorbidities and menopausal status, knowledge about the genetic makeup of patients may allow the future development of a diagnostic tool to identify patients who are likely to remain symptomatic while on LT4 and possibly benefit from therapy containing LT3 [89]. Further research is warranted in this area, paving the way for universally effective management of hypothyroidism, ultimately improving outcomes and patient well-being.

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