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Pathophysiological relevance of deiodinase polymorphism

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Abstract

Purpose of review—To assess new findings and clinical implications of deiodinase gene polymorphism. Deiodinases are enzymes that can activate or inactivate thyroid hormone molecules. Whereas the types 1 and 2 deiodinase (D1 and D2) activate thyroxine (T4) to 3,5,3'-triiodothyronine (T3) via deiodination of T4's outer ring, D1 and D3 inactivate both T4 and T3 and terminate thyroid hormone action via deiodination of T4's inner molecular ring. A number of polymorphisms have been identified in the three deiodinase genes; the most investigated and likely to have clinical relevance is the Thr92 substitution for Ala substitution in DIO2 (Thr92Ala-DIO2). There are a number of reports describing the association between the Thr92Ala-DIO2 polymorphism and clinical syndromes that include hypertension, type 2 diabetes, mental disorders, lung injury, bone turnover, and autoimmune thyroid disease; but these associations have not been reproduced in all population studies.

Recent findings—A new report indicates that carriers of the Thr92Ala-DIO2 polymorphism exhibit lower D2 catalytic activity and localized/systemic hypothyroidism. This could explain why certain groups of levothyroxine-treated hypothyroid patients have improved quality of life when also treated with liothyronine (LT3). Furthermore, Ala92-D2 was abnormally found in the Golgi apparatus, what could constitute a disease mechanism independent of T3 signaling. Indeed, brain samples of Thr92Ala-DIO2 carriers exhibit gene profiles suggestive of brain degenerative disease. In addition, African American carriers of Thr92Ala-DIO2 exhibit an about 30% higher risk of developing Alzheimer's disease.

Summary—The finding of deiodinase polymorphisms that can diminish thyroid hormone signaling and/or disrupt normal cellular function opens the door to customized treatment of hypothyroidism. Future studies should explore how the racial background modulates the clinical relevance of the *Thr92Ala-DIO2* gene polymorphism.

Keywords

deiodinase polymorphism; hypothyroidism; thyroid; thyroid hormone; thyroxine

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Conflicts of interest

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INTRODUCTION

Thyroid hormone regulates a wide array of developmental and physiologic processes, affecting virtually every tissue in the human body throughout all phases of life [1]. Both thyroxine (T4) and the biologically active 3,5,3'-triiodothyronine (T3) have stable levels in the circulation, a finding that at face value may seem to oppose the idea that these molecules initiate or terminate important biological processes. However, the modern paradigm of thyroid hormone action posits that thyroid hormone does have dynamic regulatory functions made possible by 'local' molecular mechanisms by which thyroid signaling can be altered at the level of the target cell – both in the short and long term – even as circulating levels remain stable [2]. This 'local' control model is based on three key factors. First, the lipid bilayer that constitutes the plasma membrane is not significantly permeable to T3 or T4, such that both molecules only enter cells through specific transporters that are embedded in the plasma membrane [3]. Second, once inside the target cells, thyroid hormones are activated or inactivated by deiodinases, enzymes that thereby control the intracellular level of T3. The type 2 deiodinase (D2) converts T4 to T3 and is the main activating deiodinase in humans, whereas the type 3 deiodinase (D3) inactivates both T4 and T3 [4]. The third factor is that intracellular T3 binds to and activates thyroid hormone receptors that modulate transcription of target genes. Additional local control at the receptor level is achieved via the existence of two different T3 receptors, TR α and TR β , which have distinct patterns of tissue-specific distribution; these receptors also control different sets of genes [5]. Ultimately, the thyroid-hormone dependent behavior of a cell or tissue depends not just on the supply of T3 and T4 from the plasma, but also on the unique blend of transporters, deiodinases, and receptor subtypes expressed in that cell.

DEIODINASE GENE POLYMORPHISM AND THYROID HORMONE SIGNALING

The purpose of this article is to review recent progress in the deiodinase field, focusing on single nucleotide polymorphisms (SNPs) of the deiodinase genes and their associated clinical syndromes. A gene polymorphism is a common variation in a DNA sequence in which the least common allele has a frequency of at least 1%. This is in contrast to a mutation, which is any change in a DNA sequence away from normal that is present in less than 1% of the population. The original study that shed light on the importance of deiodinase SNPs came as a result of molecular scanning of DIO2 in 50 obese Caucasians, which identified a Thr92Ala variant associated with lower glucose disposal rates [6]. Carriers of the Thr92Ala-DIO2 polymorphism exhibited strong association with insulin resistance and, in individuals who also carried the Trp64Arg ADRB3 variant, an increased BMI. Subsequent population-based studies have suggested associations between Thr92Ala-DIO2 with hypertension [7], insulin resistance [6,8], type 2 diabetes [9], bipolar disorder [10], mental retardation [11], low intelligence quotient (IQ)[12], recovery from lung injury [13], osteoarthritis[14], and increased bone turnover [15]. A recent study of autoimmune thyroid disease such as Graves' and Hashimoto's diseases revealed that Thr92-DIO2 genotype is less frequent in these patients, especially in Hashimoto's disease, when compared with controls [16]. Clinical phenotypes related to other deiodinase gene (*DIO1*,

DIO3) polymorphisms have been reported but have been less well studied to date (see [17] for review).

The Thr92Ala-DIO2 polymorphism is relatively common, present in 12–36% of the population [18]. Given the role of DIO2 in the tissue-specific determination of local thyroid hormone levels, it is particularly intriguing that the Thr92Ala-DIO2 polymorphism has been linked to altered responsiveness of hypothyroid patients to thyroid hormone replacement therapy [19,20]. Although most patients do well on replacement therapy with levothyroxine (LT4), a minority (about 15%) remain symptomatic despite being achieving normal thyroid-stimulating hormone (TSH) levels [21,22]. Residual clinical manifestations of hypothyroidism include objective parameters, that is, higher BMI, greater use of beta-blockers, statins or antidepressant medication [22], and lower energy expenditure [23], as well as subjective aspects, that is, difficulty in weight management, fatigue or low-energy levels, and problems with mood and memory [24]. In a study performed in the United Kingdom, carriers of the Thr92Ala-DIO2 polymorphism exhibited better quality of life outcomes in response to combination therapy with LT4 and LT3 as compared with LT4 alone [21]. One hypothesis to explain this association could be that carriers of the Thr92Ala-DIO2 polymorphism suffer from localized hypothyroidism, presumably related to defective local LT4 activation that can be overcome using LT3. Further evidence for a clinically relevant phenotype of this polymorphism comes from a Danish study of 45 overtly autoimmune, hypothyroid patients who participated in a prospective, double-blind, crossover study regarding combination therapy [25]. The Danish patients were randomized to receive either 3 months of LT4 therapy followed by 3 months of combination therapy or vice versa, adjusted to obtain normal serum TSH values. Clinical outcomes were evaluated considering polymorphisms in DIO2 (Thr92Ala-DIO2) and on the cellular membrane transport-facilitating monocarboxylate transporter (MCT10) gene (*rs17606253*). The major finding was that the combination of polymorphisms in Thr92Ala-DIO2 and MCT10 on the same patient enhanced patients' preference for LT4 combined with LT3 replacement therapy [25]. These findings suggest that LT4-treated thyroidectomized patients carrying the Thr92Ala-DIO2 polymorphism might be at a greater risk of systemic and/or localized hypothyroidism.

Perhaps unsurprisingly, the clinical syndrome associations with *DIO2* gene polymorphisms have not been reproduced in all population studies [4,18,26]. This type of study design is prone to false-positive findings, and of course racial and other background factors may play important roles in such associations. Studies with negative findings include a Dutch study in which the effects of the Thr92Ala-DIO2 polymorphism were evaluated in 12 625 individuals, including 364 patients on thyroid hormone replacement therapy. The analyses involved anthropometric data, medication use and existence of metabolic syndrome, quality of life assessed with the RAND 36-Item Health Survey, and executive function with the Ruff Figural Fluency Test. In this case, there was no association between the Thr92Ala-DIO2 polymorphism and thyroid parameters, quality of life, or cognitive functioning in the general population or in participants on either form of thyroid hormone replacement therapy [26]. In a similar study conducted in Korean patients, no associations were observed with SNPs in DIO2 or DIO3 and wellbeing in hypothyroid patients [27]. These negative findings remind one that SNP associations seen in one sub-population may not apply to another.

ABNORMAL CELLULAR PROPERTIES OF Thr92Ala-D2

How could the Thr92Ala-DIO2 polymorphism participate as a disease mechanism and/or affect clinical outcomes? The most obvious possibility is that Thr92Ala substitution affects D2 catalytic activity. Impaired T3 production would be predicted to cause either or both systemic/localized hypothyroidism. In this regard, the Thr92Ala substitution occurs at a residue that is relatively distant from the catalytic active site of the enzyme [28]. In-vitro studies show that Thr92Ala-D2 converts T4 to T3 with normal kinetics when transiently expressed in HEK-293 cells[29]. In fact, different laboratories have studied the Ala92-D2 enzyme extensively *in vitro* and no evidence of reduced catalytic activity have been reported [30]. In contrast, studies *in vivo* suggest that Thr92Ala-D2 might affect TSH secretion [31] and/or LT4 bioavailability [32]. More recently, a comparison of presurgical hormonal status of LT4-treated thyroidectomized individuals with their postsurgery status revealed an association between low FT3 values and Thr92Ala-DIO2 polymorphism[33]. In the same study, evidence of reduced Thr92Ala-D2 in-vivo activity was obtained in Ala92-D2-expressing murine myoblasts and in Ala92-D2-expressing primary cultures of pituitary cells from Dio2-null mice [33]. Thus, whether the Thr92Ala polymorphism affects the catalytic activity of the enzyme remains a subject of debate.

If altered catalysis is not the basis for clinical syndromes, another possibility is abnormal cell handling of the Thr92Ala-D2. D2 is a selenoprotein that resides in the endoplasmic reticulum (ER) [34,35]. Thanks to the physical proximity and functional relationship between ER and nuclear membrane, D2-generated T3 feeds the nuclear compartment with intracellularly generated T3. The D2 protein has not been crystalized but three-dimensional (3D) modeling based on hydrophobic cluster analyzes[28] identified a unique 18-residue 'instability' loop in the D2 molecule that mediates binding to ubiquitin ligases [36,37], hence D2 ubiquitination [38–40]. Subsequently, ubiquitinated D2 is retro-trans-located to the cytoplasm where it is degraded by the proteasomes [41]. This model has been substantiated via experiments in which D2's instability is transferrable to other proteins as seen when the otherwise stable protein Sec62 becomes unstable after fusion to D2's 18-residue instability loop[42]. Site-directed mutagenesis of this loop identified a conserved stretch of six amino acids critical for binding to ubiquitin ligases. Remarkably, the Thr92 to Ala substitution is contained within this six amino-acid stretch, and thus slows down the rate of D2 turnover via interference with ubiquitination[43]. Furthermore, electron microscopy studies of Ala92-D2-expressing cells have identified the ectopic presence of Ala92-D2 in the Golgi apparatus giving it a perturbed morphology, in contrast to Thr92-D2 that could not be found in the Golgi[43]. Cells expressing Ala92-D2 also exhibited alteration in expression of Golgi markers, a finding that was normalized with antioxidant treatment. Thus, although the obvious first pass hypothesis would be that DIO2 SNPs have pathophysiological effects mediated by alterations in local thyroid hormone signaling, it may also affect the cell via altering the Golgi apparatus.

One recent microarray-based study provides support for this 'non-T3 mediated' Golgi mechanism. Transcriptome profiling of cells that were engineered to express Thr92-D2 or Ala92-D2 and also brain samples of young adults carrying the Thr92Ala-DIO2 polymorphism who had died of trauma injuries identified unique modifications of gene

expression common to both the Ala92-D2-expressing cells and the temporal poles of carriers of the Thr92Ala-DIO2 polymorphism; these genes were not obviously related to T3 signaling and included evidence of upregulation of pathways related to the mitochondria, Golgi apparatus/ER transport, oxidative stress, and apoptosis [43]. Notably, in both models, there was molecular and physiological evidence of dysregulation in EGF receptor signaling, a pathway known to be altered in oxidative stress and play an important role in cognitive development and function [44]. Further studies are needed to understand the molecular consequences of ThrAla92-DIO2 accumulation in the Golgi apparatus.

DIO POLYMORPHISMS IN NEURODEGENERATIVE DISEASE

One of the more intriguing observations from the transcriptome-focused recent studies in young adults who died of trauma injuries is that Thr92A-laDIO2 carriers exhibit transcriptional alterations in processes typically associated with neurodegenerative diseases, such as amyloid-beta ($A\beta$) peptide processing [43]. The hypothesis that carriers of the Thr92Ala-DIO2 polymorphism have an increased risk for incident Alzheimer's disease has been investigated in a subsequent study, with a number of circumstantial findings supporting an association. For example, the epidemiology and tissue pathology of Alzheimer's disease vary by ethnicity in parallel with Thr92Ala-DIO2 [45]. There is higher incidence and prevalence of Alzheimer's disease in African Americans compared with European Americans [46,47]; in studies that involved 3054 African Americans and 9304 European American subjects, the Thr92Ala-DIO2 polymorphism was found to be more prevalent in African Americans than European Americans, and to be associated with the development of Alzheimer's disease in African Americans but not European Americans [48]. These findings were based on large, well characterized primary and replication population studies containing both African American and European American participants in addition to a complimentary molecular analysis of both African American and European American brain samples. One negative study showing that Thr92Ala-DIO2 was not identified in a genome-wide association study (GWAS) with African American participants [49] may have been underpowered to detect the link because of its moderate effect size. Future studies will be needed to examine whether Thr92AlaD2 is a risk factor for neurodegenerative disease in African Americans and that Thr92AlaD2 may represent one factor contributing to racial discrepancies in incident Alzheimer's disease.

Altered Golgi trafficking of amyloid precursor protein (APP) is implicated in development of Alzheimer's disease as $A\beta$ peptide accumulation causes Golgi structural defects that further affect APP trafficking and processing [50]. Thus, it is conceivable that the cellular and Golgi perturbation associated with Thr92AlaD2 expression could promote dysfunction in cellular pathways involved in $A\beta$ peptide processing and contribute to development of Alzheimer's disease. Another possibility may be that the polymorphism promotes mitochondrial dysfunction: mitochondrial dysfunction and $A\beta$ accumulation likely contribute to oxidative stress in Alzheimer's disease [51]. Indeed, mitochondrial dysfunction and oxidative stress markers were present in the transcriptomes of human temporal pole samples from Thr92AlaD2 carriers and in the cell model of Thr92AlaD2 expression; some of these alterations in Thr92AlaD2-expressing cells were reversed upon antioxidant treatment [43]. Of course, it must be remembered that there could be yet unidentified causal

markers that could be contributing to the racially dependent phenotype. Ultimately, understanding the mechanisms underlying the Thr92Ala-DIO2 association with neurodegenerative disease may prove to be important for disease prevention.

CONCLUSION

A number of polymorphisms have been identified in the three deiodinase genes. The most investigated and likely to have clinical relevance is *Thr92Ala-DIO2*. It is questionable whether the Thr92 substitution for Ala affects the catalytic activity of the enzyme and causes localized/systemic hypothyroidism. If confirmed, this could explain why certain populations of hypothyroid patients exhibit better clinical outcomes when treated with combination therapy containing LT3. On the other hand, the in-vitro data clearly indicates that this polymorphism is associated with ectopic localization in the Golgi apparatus, what could constitute a disease mechanism per se. Indeed, temporal pole samples of carriers of the Thr92Ala-DIO2 polymorphism exhibit a transcriptome that is suggestive of brain degenerative disease. Future studies should confirm these results and further explore how the racial background modulates the clinical relevance of the *Thr92Ala-DIO2* gene polymorphism. This avenue of research may someday allow us to understand why some patients seem to fail T4 monotherapy, and help guide prevention strategies for neurodegenerative disease.

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KEY POINTS

- The Thr92Ala-DIO2 polymorphism might reduce thyroid hormone signaling and cause systemic and/or localized hypothyroidism.
- The central nervous system of carriers of the Thr92Ala-DIO2 polymorphism exhibit changes in gene profile suggestive of brain degenerative disease.
- African American carriers of the Thr92Ala-DIO2 polymorphism have are at a 30% higher risk of developing Alzheimer's disease.