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Functional Medicine

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PATHOPHYSIOLOGICAL RELEVANCE OF DEIODINASE POLYMORPHISM

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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.

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