Defects of Thyroid Hormone Synthesis and Action

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KEYWORDS

• Thyroid hormone receptors • Deiodinase • Resistance to thyroid hormone
• Congenital hypothyroidism • Goiter • Dyshormonogenesis • Dysgenesis

KEY POINTS

- Diagnosis of thyroid disease has evolved to involve sophisticated genetic testing of candidate genes to confirm the cause of the thyroid disease.
- Congenital hypothyroidism in the absence of a goiter points to thyroid-stimulating hormone receptor (*TSHR*), Paired Box Gene 8 (*PAX8*), *TTF1*, *FOXE1*, *NKX2-5*, and *DUOX2* gene mutations.
- Congenital hypothyroidism in the presence of a goiter and a low radioactive iodine uptake suggest a sodium iodine symporter mutation.
- Congenital hypothyroidism in the presence of a goiter and high uptake suggests a thyroperoxidase (*TPO*), thyroglobulin (*Tg*), *DUOX2* and *DUOXA2* and *DEHALI*, or *PDS* gene defect.
- Knowledge of the physiologic consequences of genetic mutations can help lead to rational recognition plans and treatment.

INTRODUCTION

In the beginning (before the genomic revolution) thyroid disorders were primarily diagnosed by the presence of a goiter and thought to be due to either deficiency or excess of iodine. Many years later, in 1956, an autoimmune cause was proposed.[1] The clinical tools available to the physicians in those years consisted of measurement of protein-bound iodine (PBI) in the serum as a marker of thyroid hormone (TH) concentration, use of a Geiger counter to measure iodine uptake into the gland with radioactive iodine, as well as measurements of radioiodine discharge after treatment with perchlorate and basal metabolic rates as a surrogate for TH action. Remarkably clinician

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scientists have mapped most pathways involved in TH synthesis and action based on these rudimentary tests. The sentinel observations of astute physicians more than 50 years ago are responsible for our current outlook on diagnosis and treatment of thyroid disease. Such individuals are Vaughan Pendred[2] who reported 2 sisters having goiter and deafness; John Stanbury and A.N. Hedge[3] who described 3 siblings with congenital hypothyroidism (CH) and goiter, likely due to a defect in organification of iodine; and Samuel Refetoff, Leslie DeGroot, and Laurence DeWind[4] who described a family with insensitivity to TH. As biochemical techniques developed and a clearer understanding of TH synthesis ensued, new pathways were discovered relating to TH synthesis and action. However, the notion that a defect was inherited predated any knowledge of molecular biology. Additionally, in so much as understanding the physiology has been informative with regard to identifying candidate genes (defects in TH receptors, defects in peroxidase), gene linkage and analysis has led to a deeper understanding of new mechanisms and pathways of TH synthesis and action (eg, *DUOXA,* Paired Box Gene 8 [*PAX8*], monocarboxylate transporter 8 [*MCT8*]). Furthermore, when discovering the involvement of a particular gene mutation as the cause of a thyroid defect, there needs to be convincing evidence of the structure-function relationship of the gene and proof that it is responsible for the phenotype (**Figs. 1** and **2**).

We are at a crossroad in diagnosing thyroid disease having evolved from PBI and iodine uptake to sophisticated chips that screen patients' DNA samples for a variety of common binding protein abnormalities or receptor mutations whether it be the TH receptor beta (*THRB*), thyroid-stimulating hormone (TSH) receptors (*TSHRs*), or something else. The purpose of this article is to present a succinct review of the genetic causes of abnormalities in TH synthesis and action exclusive of thyroid cancer,

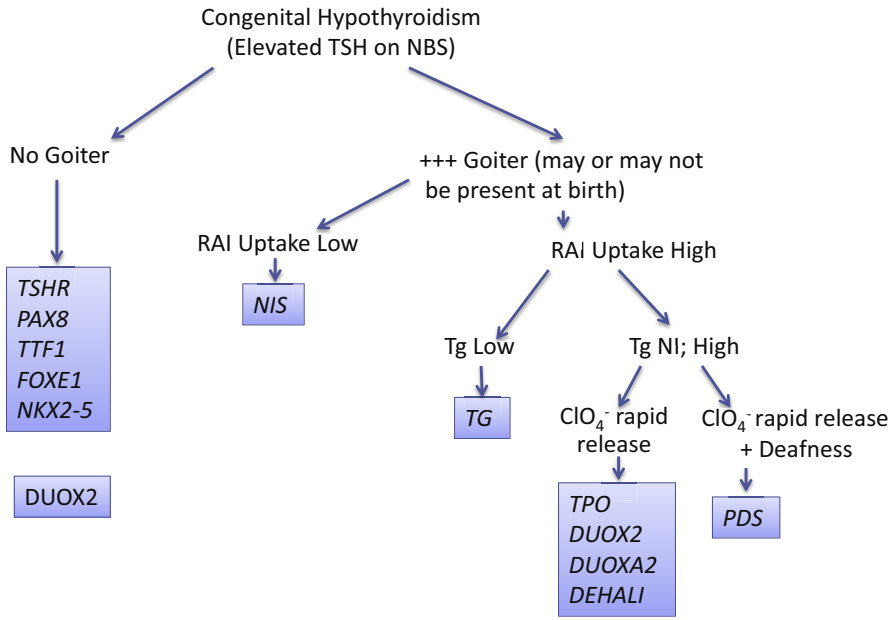

Fig. 1. Algorithm for genetic screening for disorders of TH synthesis. NBS, newborn screening; NI, normal; *NIS*, sodium iodine symporter; *PAX8*, Paired Box Gene 8; RAI, radioactive iodine; *Tg*, serum thyroglobulin; *TPO*, thyroperoxidase; TSH, thyroid-stimulating hormone; *TSHR*, thyroid-stimulating hormone receptor.