Tissue responses to thyroid hormone in a kindred with resistance to thyroid hormone harboring a commonly occurring mutation in the thyroid hormone receptor β gene (P453T)

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Resistance to thyroid hormone (RTH) is a dominantly inherited syndrome of reduced tissue responsiveness to thyroid hormone (TH) usually due to mutations in the TH receptor β gene (*TR*β). We studied pituitary and peripheral tissue responses to graded doses of liothyronine (L-T_3) in 5 affected members (2 children and 3 adults) of a family with RTH due to the common *TR*β mutation P453T. Overall, the 5 subjects studied exhibited suppressed thyrotropin response to thyrotropin-releasing hormone of 51% ± 8%, 12.1% ± 1.5%, and 6.3% ± 3% of the 100% baseline on 50, 100, and 200 μg/dL L-T_3, respectively. This degree of suppression was greater than that observed in subjects with RTH due to other *TR*β mutations, indicating less resistance. Compared with normal subjects, however, the family described here demonstrated less suppression by L-T_3, compatible with their RTH, although of a mild magnitude. The 2 children with RTH demonstrated less L-T_3–mediated suppression of prolactin and cholesterol than the adults. Patients often receive thyroid ablative therapy before the diagnosis of RTH and are left with variable degrees of hypothyroidism. Our results demonstrate that graded doses of L-T_3 can be used to evaluate RTH patients, even under the condition of limited thyroid reserve, when results are compared with their baseline. We demonstrate that RTH patients can be evaluated either on or off thyroid hormone and still be distinguished from hypothyroid subjects without RTH. (J Lab Clin Med 2005;146:85–94)

Abbreviations: AUC = area under the curve; BMR = basal metabolic rate; CK = creatine kinase; FT_3I = free T_3 index; FT_4I = free T_4 index; GCRC = General Clinical Research Center; GRTH = generalized resistance to thyroid hormone; L-T_3 = liothyronine or L-3,3′, 5-triiodothyronine; LBD = ligand-binding domain; L-T_4 = levothyroxine; PCR = polymerase chain reaction; PRL = prolactin; PRTH = pituitary resistance to thyroid hormone; RTH = resistance to thyroid hormone; SHBG = sex hormone–binding globulin; TH = thyroid hormone; TR = thyroid hormone receptor; TRH = thyrotropin-releasing hormone; TSH = thyrotropin; TT_3 = total triiodothyronine; TT_4 = total thyroxine

Resistance to thyroid hormone (RTH) is a dominantly inherited syndrome of reduced tissue responsiveness to thyroid hormone (TH).[1] The clinical presentation of RTH is variable, but the common features include elevated serum levels of free thyroxine (T_4) and often free triiodothyronine (T_3), normal or slightly increased thyrotropin (TSH) level that responds to thyrotropin-releasing hormone (TRH), and goiter. The

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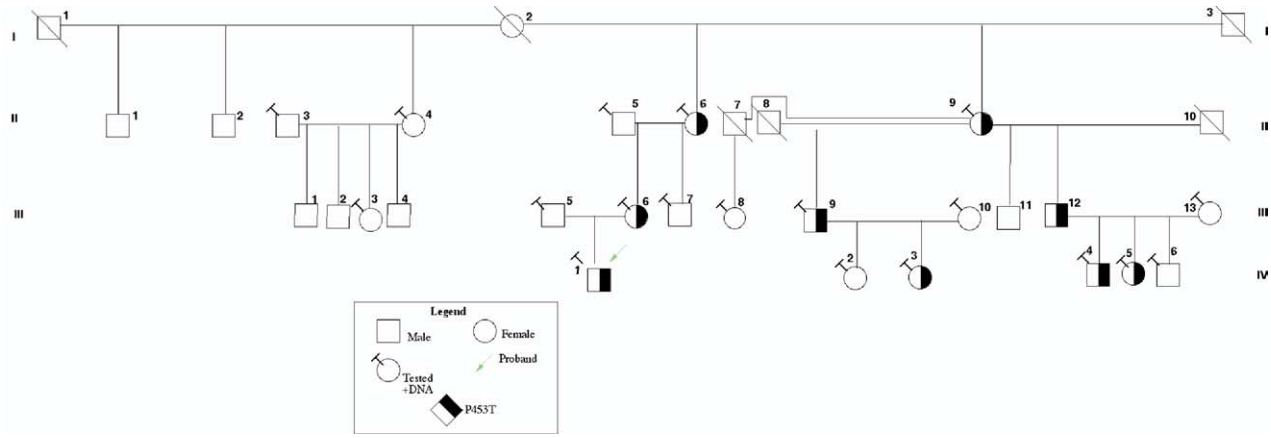

Fig 1. Pedigree of the kindred Mgg. Circles, females; squares, males. Half-shaded symbols indicate the confirmation of *TRβ* P453T. The Roman numerals identify the generational number, and the Arabic numerals identify the individual. A line through the symbol indicates that the subject is deceased. Blood was obtained from all subjects indicated as "tested."

incidence has been estimated to be 1 case per 40,000–50,000 live births.[2,3] The molecular basis for the syndrome in most patients is mutations localized to the ligand-binding domain (LBD) and adjacent hinge region of the TH receptor β gene (*TRβ*).[4–6]

The severity of reduced TH sensitivity ranges from clinically asymptomatic and euthyroid to variable stigmata compatible with thyrotoxicosis and hypothyroidism. This variation is likely due to the magnitude of functional impairment of the mutant *TRβ* and the relative level of tissue expression of the mutant *TRβ* and other unidentified cofactors. Some RTH subjects may exhibit symptoms and signs of TH deficiency in 1 tissue while manifesting findings of thyrotoxicosis in another tissue. Reports of subjects with RTH usually describe the molecular basis for the condition and the thyroid function tests as a reflection of the sensitivity of the hypothalamic-pituitary-thyroid axis to TH feedback. There is a paucity of data on pituitary and peripheral tissue action of TH in multiple subjects with an identical mutation. Furthermore, the ability to assess RTH by a challenge with TH in subjects with limited thyroidal reserve has not been evaluated.

We report a large family with RTH caused by a single nucleotide change in exon 10 of the *TRβ* gene resulting in the substitution of threonine for proline at codon 453 (the P453T mutation). This is a relatively common *TRβ* gene mutation that has been previously described in 8 families[4,7–16] and characterized extensively in vitro. The purpose of this study was to compare patterns of TH responsiveness of individuals harboring the same mutation within the same kindred. The opportunity to study several subjects with identical mutations and similar genetic backgrounds but different thyroidal reserve due to previous ablative treatment provided the opportunity to evaluate the validity of a standard protocol applied to various baseline thyroid states.

PATIENTS AND METHODS

Patients. The propositus was a 5-year-old male (IV-1) (Fig 1) who presented in 2003 with significant asthma, allergic rhinitis, and a history of recurrent episodes of otitis media. He was hyperactive and had a short attention span, as well as a small goiter. Thyroid function tests demonstrated elevated serum free T_4 and T_3 levels and TSH concentration at the upper limit of normal.

Other affected family members included the mother (III-6) and maternal grandmother (II-6) of the propositus. III-6 was a 29-year-old female noted to have abnormal thyroid function tests as a teenager. She was subsequently started on levothyroxine (L-T_4) therapy by her outside physician for presumed hypothyroidism secondary to autoimmune thyroid disease. On presentation to us, she was taking 175 μg L-T_4 daily, as well as oral contraceptive pills. Her medical history was significant for allergic rhinitis. She had a heteroechogenic thyroid gland that was twice the normal size.

II-6 was a 48-year-old female, mother of III-6 and grandmother of IV-1. She was treated with ^{131}I several years ago for presumed hyperthyroidism. He medical history was significant for hyperlipidemia, hypertension, asthma, allergic rhinitis, and gastroesophageal reflux disease. She denied any significant symptoms of hyperthyroidism or hypothyroidism. On presentation, she was taking 75 μg liothyronine (L-T_3) daily, as well as antihypertensive agents and inhaled steroids for asthma. Her thyroid gland was heteroechogenic and of twice-normal size.

A 30-year-old male (III-9), a first cousin of III-6, was found to have abnormal thyroid function tests as a teenager. His test abnormalities were interpreted as Graves' disease,