

## BRIEF REPORT

# A Mutation in the Thyroid Hormone Receptor Alpha Gene

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## SUMMARY

Thyroid hormones exert their effects through alpha ( $TR\alpha 1$ ) and beta ( $TR\beta 1$  and  $TR\beta 2$ ) receptors. Here we describe a child with classic features of hypothyroidism (growth retardation, developmental retardation, skeletal dysplasia, and severe constipation) but only borderline-abnormal thyroid hormone levels. Using whole-exome sequencing, we identified a de novo heterozygous nonsense mutation in a gene encoding thyroid hormone receptor alpha (*THRA*) and generating a mutant protein that inhibits wild-type receptor action in a dominant negative manner. Our observations are consistent with defective human  $TR\alpha$ -mediated thyroid hormone resistance and substantiate the concept of hormone action through distinct receptor subtypes in different target tissues.

**T**HYROID HORMONES HAVE DIVERSE ACTIONS, WHICH INCLUDE REGULATION of skeletal growth, maturation of the central nervous system, cardiac and gastrointestinal function, and energy homeostasis. In addition, thyroid hormones control their own production by feedback inhibition of hypothalamic thyrotropin-releasing hormone and pituitary thyroid-stimulating hormone, which direct their synthesis or release. These physiological effects are principally mediated by hormone action through nuclear receptor proteins that act as ligand-inducible transcription factors and either positively or negatively regulate the expression of target genes in different tissues in a hormone-dependent manner.

The receptors are encoded by two genes (*THRA* and *THRB*), each of which undergoes alternate splicing to generate receptor subtypes ( $TR\alpha 1$ ,  $TR\beta 1$ , and  $TR\beta 2$ ), with differing tissue distributions.  $TR\alpha 1$  is the predominant subtype in bone, the gastrointestinal tract, cardiac and skeletal muscle, and the central nervous system;  $TR\beta 1$  is most abundant in the liver and kidney; and  $TR\beta 2$  is more discretely expressed in the hypothalamus, pituitary, cochlea, and retina.<sup>1</sup> In the absence of hormone, thyroid receptors that are not bound to ligands repress or silence target-gene transcription by recruiting multiprotein complexes containing corepressors (e.g., nuclear receptor corepressor and silencing mediator of retinoic acid and thyroid hormone receptor), with histone deacetylase activity; triiodothyronine occupancy

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of the receptor results in dissociation of the co-repressor complex and recruitment of coactivator proteins, such as steroid receptor coactivator 1 (SRC-1), which mediate hormone-dependent transcriptional regulation.<sup>2</sup>

Here we describe a child with characteristic clinical features of hypothyroidism (growth retardation, developmental retardation, and chronic constipation) and near-normal circulating thyroid hormone levels. She is heterozygous for a de novo *THRA* mutation, generating a mutant protein that inhibits wild-type receptor function in a dominant negative manner, causing some target tissues to be resistant to the action of thyroid hormone.

#### CASE REPORT

A 6-year-old girl of white European origin, born to unrelated parents, presented with growth retardation. At the age of 18 months, her height had been 79 cm (10th percentile), and the deficit had persisted (Fig. 1A, and Fig. 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The child also had decreased subischial leg length with a normal sitting height, indicating that the growth deficit affected the lower segment of her body (Fig. 1B). Tooth eruption had been delayed; she had no teeth at 12 months of age, only eight deciduous teeth at 26 months, and no secondary dentition at the age of 6 years. Her weight for age (23.2 kg) was 1.0 SD above average (Fig. 1 in the Supplementary Appendix), resulting in a borderline-high body-mass index (the weight in kilograms divided by the square of the height in meters) of 23.5. Severe constipation was noted after weaning at 7 months, with infrequent bowel movements (every 3 to 7 days), despite combination laxative therapy with senna and macrogol. Mild hypermobility and ligamentous laxity was present in the ankle and knee. Muscle tone was reduced with normal power but with impairment in gross and fine motor coordination, resulting in a slow, broad-based gait, clumsiness, and difficulty with fine motor skills, including an inability to write or draw. Her affect was placid, with slow, monotonous speech, but with no receptive or expressive deficit. Neuropsychological assessment showed restricted adaptive behavior (Adaptive Behavior Assessment System standard score, 63; 0.7th percentile) and significant impairments in selected cognitive domains, with a standard score for visuospatial reasoning of 71 (3rd percentile) on the Wechsler

Intelligence Scale for Children, fourth edition, and a standard score for working memory of 77 (4th percentile), despite average verbal comprehension (standard score, 93; 32nd percentile).

#### METHODS

##### GENETIC STUDIES

Our institutional ethics committee approved the study, and the patient's parents provided written informed consent. We performed high-throughput sequencing of a DNA sample from the patient after whole-exome capture (see the Methods section in the Supplementary Appendix). Bioinformatic analysis of sequence data identified novel variants that were linked to the patient's phenotype. Sanger sequencing verified variant genotypes in the patient and her family and analyzed other coding exons in *THRA*, including in 200 alleles from healthy white persons of the same ethnic background.

##### FUNCTIONAL ANALYSES OF E403X MUTANT TR $\alpha$ PROTEIN

After generation of the E403X mutant TR $\alpha$  by site-directed mutagenesis of wild-type receptor complementary DNA, we performed assays of radio-labeled triiodothyronine binding, transactivation, and dominant negative activity, along with the protein-protein (two-hybrid) interaction assay, as described previously (see the Methods section in the Supplementary Appendix).

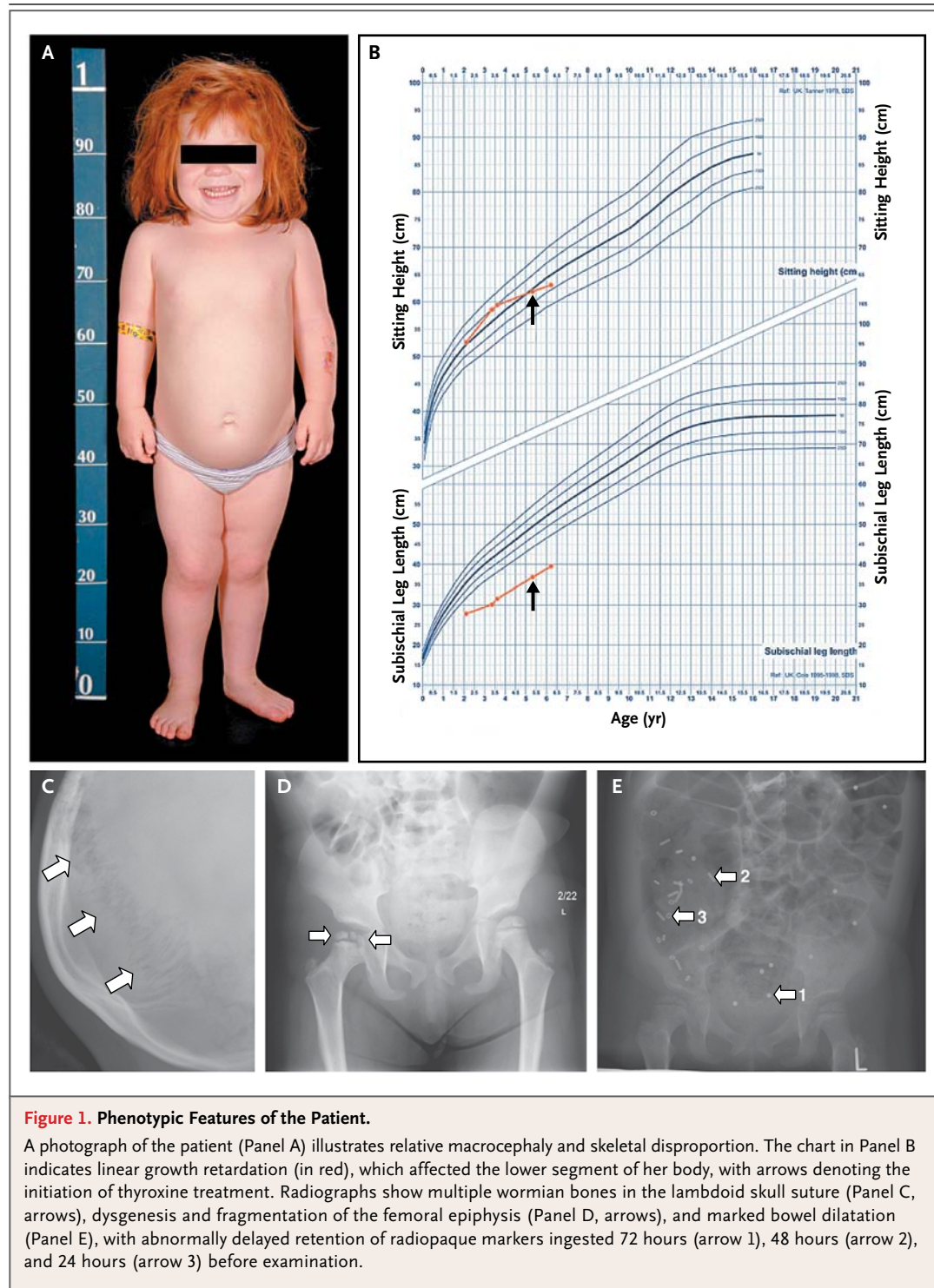
##### EX VIVO STUDIES OF PERIPHERAL-BLOOD MONONUCLEAR CELLS

We measured wild-type and E403X mutant TR $\alpha$ 1 and TR $\beta$  and Krüppel-like factor 9 (KLF9) messenger RNAs (mRNAs) in samples of peripheral-blood mononuclear cells (PBMCs) from the patient and control subjects using a quantitative polymerase-chain-reaction (PCR) assay with specific primers (see the Methods section in the Supplementary Appendix).

#### RESULTS

##### CLINICAL AND METABOLIC INVESTIGATION

Measurements of thyroid hormones in the patient showed low-normal or subnormal levels of total thyroxine and free thyroxine, high-normal or elevated levels of total triiodothyronine and free triiodothyronine, and normal levels of thyroid-stimulating hormone (Table 1, and Fig. 3A in the



Supplementary Appendix), resulting in markedly subnormal ratios of free thyroxine to free triiodothyronine (Fig. 3B in the Supplementary Appendix) and of total thyroxine to total triiodothy-

ronine (Fig. 3C in the Supplementary Appendix), with a very low level of circulating reverse triiodothyronine (Table 1). The level of serum thyroxine-binding globulin was normal ( $23.5 \mu\text{g}$  per liter

**Table 1. Biochemical and Metabolic Measurements in the Patient.\***

Variable	Baseline	After Thyroxine Treatment	Reference Values
Thyroxine ( $\mu\text{g}/\text{dl}$ )			
Total	3.3	10.6	7.4–12.1 <sup>†</sup>
Free	0.5	1.5	0.8–1.7 <sup>‡</sup>
Triiodothyronine			
Total (ng/dl)	155	260	130–221 <sup>†</sup>
Free (ng/dl)	0.4	0.7	0.3–0.5 <sup>‡</sup>
Reverse (ng/ml)	0.07	0.2	0.21–0.37 <sup>†</sup>
Thyroid-stimulating hormone (mU/liter)	1.04	<0.03	0.8–6.2 <sup>‡</sup>
Sex hormone-binding globulin (nmol/liter)	146	131	20–81 <sup>†</sup>
Insulin-like growth factor 1 (ng/ml)	59	96	67–257 <sup>†</sup>
Pulse (bpm) <sup>§</sup>	71	69	
Blood pressure (mm Hg) <sup>§</sup>	82/51	77/43	
Basal metabolic rate (MJ/day) <sup>¶</sup>	3.49	4.08	4.06

\* To convert the values for total thyroxine to nanomoles per liter or free thyroxine to picomoles per liter, multiply by 12.87. To convert the values for total triiodothyronine to nanomoles per liter, multiply by 0.01536. To convert the values for free triiodothyronine to picomoles per liter, multiply by 15.36. To convert the values for insulin-like growth factor 1 to nanomoles per liter, divide by 7.7.

<sup>†</sup> Values are from 23 healthy control subjects who were matched with the patient according to age, sex, and body-mass index.

<sup>‡</sup> Reference ranges in children from 1 to 5 years of age are from Kapelari et al.<sup>3</sup>

<sup>§</sup> Detailed reference values are shown in Figure 4 in the Supplementary Appendix.

<sup>¶</sup> The basal metabolic rate was measured by means of indirect calorimetry with the use of a ventilated hood. The reference value is the predicted basal metabolic rate of the patient on the basis of her age, sex, and body composition.

[normal range, 18 to 35]). Skeletal radiographs showed delayed fusion of cranial sutures with a patent anterior fontanelle (Fig. 2A in the Supplementary Appendix), multiple wormian bones (Fig. 1C), and delayed tooth eruption (Fig. 2B in the Supplementary Appendix), together with femoral epiphyseal dysgenesis (Fig. 1D) and delayed bone age (chronologic age, 6.3 years; bone age, 2.9 years). Abdominal radiography revealed bowel dilatation with abnormal retention of ingested marker pellets, confirming delayed intestinal transit (Fig. 1E). Colonic-pressure measurements showed negligible contractile responses to bisacodyl stimulation, and intestinal biopsy ruled out Hirschsprung's disease.

The child's heart rate and blood pressure were low, with a resting heart rate of 71 beats per minute (1st percentile) (Fig. 4A in the Supplementary Appendix) and blood pressure of 82/51 mm Hg (systolic, 0.4th percentile; diastolic, 25th percentile)

(Fig. 4B in the Supplementary Appendix). The basal metabolic rate (3.49 megajoules [MJ] per day) was below normal, but the level of serum sex hormone-binding globulin, a hepatic marker of thyroid hormone action, was markedly elevated (146 nmol per liter). A normal growth hormone response to provocative testing, with a glucagon test peak of 13.1  $\mu\text{g}$  per liter and a clonidine test peak of 11.7  $\mu\text{g}$  per liter (normal value, >10  $\mu\text{g}$  per liter), was associated with slightly subnormal levels of insulin-like growth factor 1 (IGF-1; 59 ng per milliliter) (Table 1).

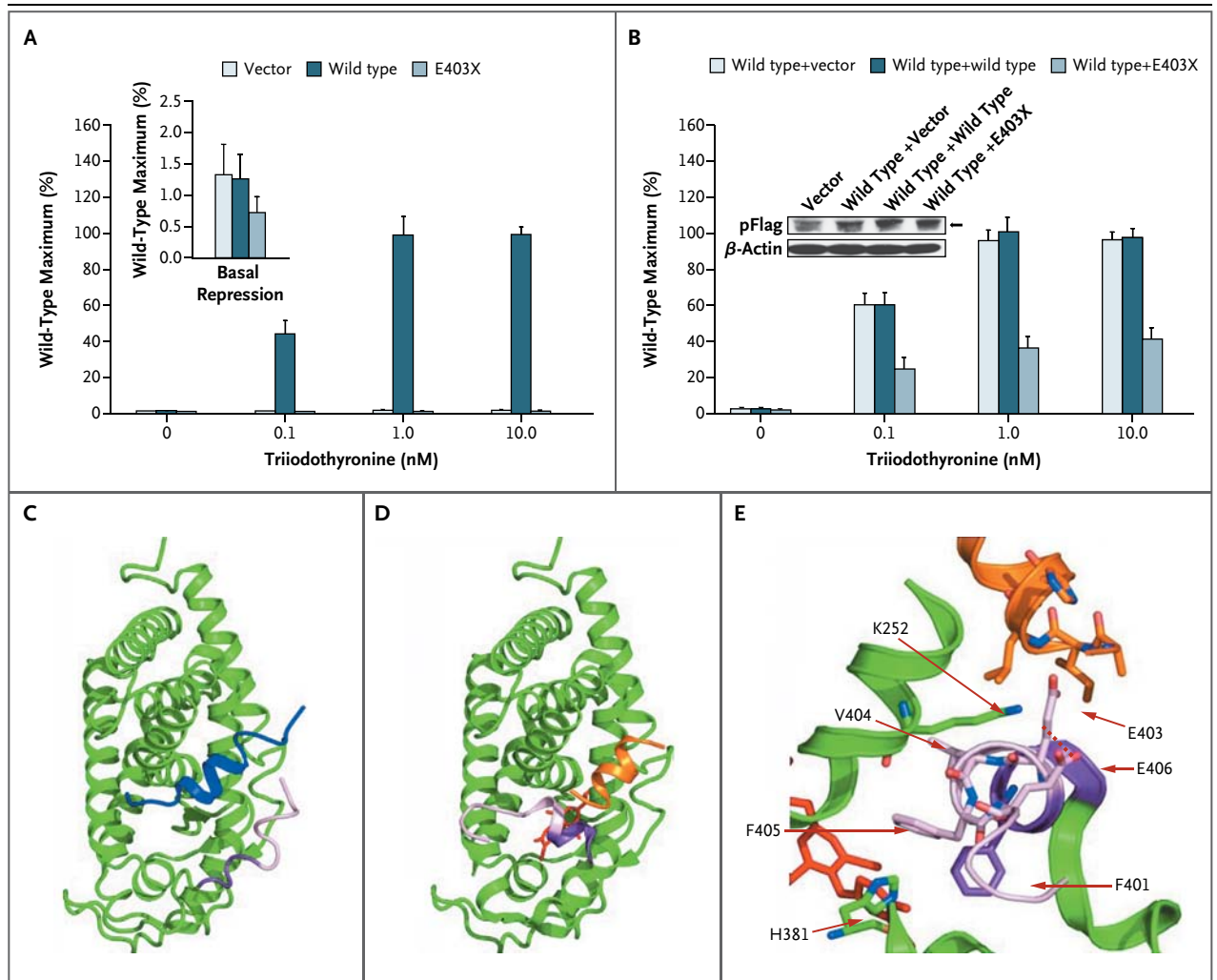
After thyroxine treatment (at a dose of 50  $\mu\text{g}$  daily for 9 months), levels of free thyroxine, free triiodothyronine, and IGF-1 rose to normal or supraphysiological levels, with full suppression of thyroid-stimulating hormone and normalization of the basal metabolic rate. However, the level of sex hormone-binding globulin remained high, and the pulse rate and blood pressure remained abnormally low (Table 1, and Fig. 4A and 4B in the Supplementary Appendix), as did the growth rate (Fig. 1B, and Fig. 1 in the Supplementary Appendix) and intestinal transit time (data not shown).

#### DE NOVO *THRA* MUTATION IN PROBAND

Whole-exome sequencing of a DNA sample from the patient identified many nonsynonymous variants inherited from either unaffected parent but only one heterozygous de novo mutation (c1207 G→T, p.E403X) in *THRA*, a finding that could explain the child's phenotype (Table 3 in the Supplementary Appendix). Sanger sequencing identified no other abnormalities in the *THRA* coding region. The mutation was present in DNA isolated from different cells (PBMCs, buccal epithelial tissue, hair follicle, and colon) obtained from the patient (Fig. 5A in the Supplementary Appendix) but was absent in published normal genomes and exomes (see the Supplementary Appendix) and in 200 control alleles (data not shown). The nucleotide change did not affect other transcripts (e.g., TR $\alpha$ 2 and Rev-erba) derived from the *THRA* locus (Fig. 5B in the Supplementary Appendix).

#### FUNCTIONAL CHARACTERIZATION OF E403X MUTANT TR $\alpha$

The abnormal receptor did not activate a thyroid hormone-responsive reporter gene (Fig. 2A) and mediated substantial repression of basal promoter activity (Fig. 2A, inset), findings that are consistent with negligible binding of radiolabeled triiodothyronine to E403X TR $\alpha$  (data not shown).



**Figure 2. Functional Properties and Molecular Modeling of the E403X Mutation in Thyroid Hormone Receptor Alpha (TR $\alpha$ ).**

In Panel A, JEG-3 cells are transfected with empty vector or wild-type or mutant E403X TR $\alpha$ , together with a thyroid hormone–responsive reporter gene, in an assay of triiodothyronine-dependent activation. The inset shows the activity of a basal reporter gene in the absence of hormone. In Panel B, dominant negative inhibition is tested in cells cotransfected with reporter gene and equal combinations of epitope-tagged vectors, with receptor quantitation on Western blotting (inset). In Panel C, crystallographic modeling of unliganded TR $\alpha$  ligand-binding domain (LBD) shows displacement of its C-terminal  $\alpha$ -helix (H12) (dark purple), with absent residues (light purple) distal to the E403X mutation, together favoring corepressor recruitment (dark blue). In Panel D, modeling of TR $\alpha$  LBD bound to triiodothyronine (red) and coactivator (orange) shows the agonist-bound conformation of H12 (dark purple). In Panel E, key stabilizing amino acid interactions are detailed: E403 interacts with the coactivator peptide, F401 makes contact with ligand, V404 and F405 together with H381 contribute to the hydrophobic core of the LBD, and E406 forms a salt bridge with K252 (dotted line). Loss of these interactions in E403X TR $\alpha$  precludes hormone and coactivator binding, allowing constitutive binding to corepressor.

Furthermore, when coexpressed, the E403X receptor strongly inhibited transcriptional activation by wild-type TR $\alpha$  in a dominant negative manner (Fig. 2B). TR $\alpha$  was the predominant receptor subtype in PBMCs from the patient and the control subjects (Fig. 7A in the Supplementary Appendix), and quantitation of receptor transcripts in the patient's cells indicated that E403X TR $\alpha$  mutant mRNA was expressed with a frequency

similar to that of wild-type mRNA, with no evidence of nonsense-mediated decay (Fig. 6A, 6B, and 6C in the Supplementary Appendix). When studied *ex vivo*, both basal and triiodothyronine-induced expression of *KLF9*, a known thyroid hormone–responsive target gene,<sup>4</sup> was markedly reduced in PBMCs from the patient, as compared with those from control subjects (Fig. 7B in the Supplementary Appendix). Two-hybrid interaction assays showed

strong recruitment of corepressors (nuclear receptor corepressor and silencing mediator of retinoic acid and thyroid hormone receptor) by E403X mutant TR $\alpha$ , with failure of their hormone-dependent dissociation. Conversely, E403X TR $\alpha$  showed minimal triiodothyronine-dependent association with coactivator SRC-1 (Fig. 8A and 8B in the Supplementary Appendix).

Structural modeling provided a basis for these observations. The mutation that resulted in E403X prematurely truncated TR $\alpha$ , removing its C-terminal  $\alpha$ -helix (H12). Such loss of H12 exposes a hydrophobic cleft on the receptor surface that accommodates corepressor, facilitating its recruitment (Fig. 2C). The H12 deletion also entails loss of amino acids that are critical for hormone binding and coactivator recruitment (Fig. 2D and 2E),<sup>5</sup> with failure of these processes resulting in constitutive binding of corepressor by E403X mutant TR $\alpha$ , accounting for its potent transcription inhibitory (dominant negative) activity.

## DISCUSSION

Our patient had many clinical features that are typical of hypothyroidism but that paradoxically were associated with borderline low thyroxine levels and high triiodothyronine levels. Patent cranial sutures with wormian bones, delayed dentition, femoral epiphyseal dysgenesis, and retarded bone age are classic abnormalities in childhood myxedema,<sup>6,7</sup> and diminished colonic motility with megacolon or even ileus is recognized in hypothyroidism.<sup>8</sup> In addition, the child's cognitive deficits were consistent with those seen in congenital hypothyroidism.<sup>9</sup> Furthermore, her treatment with thyroxine was associated with responsiveness in some measurements (thyroid-stimulating hormone and basal metabolic rate) but with negligible change in growth, intestinal motility, or heart rate. Thus, the patient had differential sensitivity to thyroid hormone action, with retention of hormone responsiveness in the hypothalamic–pituitary axis and liver but skeletal, gastrointestinal, and myocardial resistance.

Molecular studies identified a nonsense mutation in *THRA*, which is highly likely to be causal because the defect occurred de novo, was functionally deleterious, and was identified in a candidate gene that was closely linked to the patient's phenotype. Consistent with heterozygosity for the mutation, E403X TR $\alpha$  was a potent, dominant negative inhibitor of wild-type thyroid hor-

none receptor action in vitro. Impaired induction of a triiodothyronine-dependent target gene (*KLF9*) in PBMCs from the patient suggested that such dominant negative inhibition occurred in vivo. Resistance to thyroid hormone, a highly analogous disorder with refractoriness to hormone action in hypothalamic–pituitary and hepatic pathways, is associated with heterozygous *THRB* defects, resulting in diverse abnormal receptors that inhibit the function of wild-type receptors in a dominant negative manner.<sup>10,11</sup> Accordingly, we suggest that dominant negative inhibition of wild-type thyroid hormone receptors mediated resistance to thyroid hormone action and hypothyroidism in our patient, with such effects being most evident in tissues (e.g., skeleton, gastrointestinal tract, and myocardium) in which TR $\alpha$  was the predominant subtype. Conversely, organs containing mainly TR $\beta$  (e.g., pituitary and liver) remained sensitive to thyroid hormone.

TR $\alpha$ 1 null mice do not have the abnormalities seen in our patient,<sup>12</sup> which suggests that her phenotype was not caused by receptor insufficiency alone. On the other hand, her features mirror those of mice with dominant negative TR $\alpha$  mutations (TR $\alpha$ 1PV, TR $\alpha$ 1L400R, and TR $\alpha$ 1R384C), which are associated with skeletal abnormalities (delayed tooth eruption, linear growth retardation, patent cranial sutures, and epiphyseal dysgenesis), as seen in our patient.<sup>13–15</sup> Intestinal contractility is lost in mice with a disrupted *Thra* locus but with residual production of dominant negative receptor isoforms,<sup>16</sup> with intestinal dysmotility in TR $\alpha$ 1L400R mice similar to that in hypothyroid Pax8-null animals.<sup>15</sup> The bradycardia and low blood pressure seen in our patient have also been observed in murine models and may reflect myocardial thyroid hormone resistance or central autonomic dysfunction.<sup>14,17</sup>

Free triiodothyronine levels in our patient were either high normal or slightly raised, as in TR $\alpha$ PV mice,<sup>18</sup> with circulating free thyroxine being disproportionately low, resulting in a markedly abnormal, reduced ratio of free thyroxine to free triiodothyronine. This abnormal ratio, together with very low reverse triiodothyronine levels, may reflect altered metabolism of thyroid hormone in our patient. In this context, we note that hepatic levels of type 1 deiodinase enzyme, which converts thyroxine to triiodothyronine, were markedly raised in TR $\alpha$ PV mice.<sup>18</sup> Alternatively, reduced tissue levels of type 3 deiodinase, which catabolizes triiodothyronine and whose expression is

predominantly regulated by TR $\alpha$ , may also be a contributory factor.<sup>19</sup>

The incidence of resistance to thyroid hormone is estimated to be approximately 1 in 40,000,<sup>20</sup> with de novo *THRB* mutations in 27% of cases.<sup>21</sup> Since both thyroid receptor proteins are highly homologous, the occurrence of human *THRA* defects may be similar, albeit possibly limited by impaired fertility and increased mortality, which has been observed in both sexes of dominant negative TR $\alpha$  mutant mice.<sup>18,22</sup> The phenotype of mice harboring different TR $\alpha$  mutations is not uniform,<sup>22</sup> suggesting that the human disorder may also be variable. Nevertheless, we suggest that the combination of hypothyroid features and near-normal thyroid hormone levels but a subnormal ratio of thyroxine to triiodothyronine and low reverse triiodothyronine levels may be a hallmark of the disorder.

On the basis of the patient's intermittently low levels of thyroxine and the responsiveness to thy-

roid hormone in murine models, she was treated with thyroxine, and her levels of IGF-1 normalized, although there was little improvement in growth and gastrointestinal function. Higher-dose thyroxine therapy or the use of TR $\alpha$ -selective thyromimetic agents<sup>23</sup> may be necessary to avoid hyperthyroidism in TR $\beta$ -expressing tissues. However, given the triiodothyronine resistance of a target gene in her PBMCs, hormone-mediated relief of repression may not prove to be possible. We speculate that the use of histone deacetylase inhibitors, such as in the treatment of promyelocytic leukemia mediated by a dominant negative nuclear receptor fusion protein,<sup>24</sup> may be an alternative therapeutic strategy.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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