BRIEF REPORT

A Mutation in the Thyroid Hormone Receptor Alpha Gene

Elena Bochukova, D.Phil., Nadia Schoenmakers, M.B., Maura Agostini, Ph.D., Erik Schoenmakers, Ph.D., Odelia Rajanayagam, B.Sc., Julia M. Keogh, B.Sc., Elana Henning, B.Soc.Sc., Jana Reinemund, Ph.D., Evelien Gevers, M.D., Ph.D., Margarita Sarri, Ph.D., Kate Downes, Ph.D., Amaka Offiah, M.B., B.S., Ph.D., Assunta Albanese, M.Phil., David Halsall, Ph.D., John W.R. Schwabe, Ph.D., Murray Bain, Ph.D., Keith Lindley, Ph.D., Francesco Muntoni, M.D., Faraneh Vargha-Khadem, Ph.D., Mehul Dattani, M.D., I. Sadaf Farooqi, M.B., Ch.B., Ph.D., Mark Gurnell, M.D., Ph.D., and Krishna Chatterjee, B.M., B.Ch.

SUMMARY

Thyroid hormones exert their effects through alpha (TRα1) and beta (TRβ1 and TRβ2) 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 TRα-mediated thyroid hormone resistance and substantiate the concept of hormone action through distinct receptor subtypes in different target tissues.

From the University of Cambridge Metabolic Research Laboratories and National Institute for Health Research Cambridge Biomedical Research Centre, Institute of Metabolic Science (E.B., N.S., M.A., E.S., O.R., J.M.K., E.H., J.R., D.H., I.S.F., M.G., K.C.), and the Diabetes and Inflammation Laboratory, Cambridge Institute for Medical Research (K.D.), Addenbrooke's Hospital, Cambridge; the Academic Unit of Child Health, University of Sheffield, Sheffield (A.O.); and the Department of Biochemistry, University of Leicester, Leicester (J.W.R.S.) — all in the United Kingdom; and the Departments of Endocrinology (E.G., M.D.), Neuropsychology (M.S., F.V.-K.), and Gastroenterology (K.L.), Great Ormond Street Hospital for Children; the Department of Paediatric Endocrinology, St. George's Hospital (A.A., M.B.); and the Dubowitz Neuromuscular Centre, Institute of Child Health (F.M.) — all in London. Address reprint requests to Dr. Chatterjee or Dr. Farooqi at the Metabolic Research Laboratories, University of Cambridge, Box 289, Institute of Metabolic Science, Addenbrooke's Hospital, Hills Rd., Cambridge CB2 0QQ, United Kingdom, or at kkc1@mole.bio.cam.ac.uk or isf20@cam.ac.uk.

Drs. Bochukova and Nadia Schoenmakers contributed equally to this article.

This article (10.1056/NEJMoa1110296) was published on December 14, 2011, and updated on September 20, 2012, at NEJM.org.

N Engl J Med 2012;366:243-9.

THYROID 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 (TRα1, TRβ1, and TRβ2), with differing tissue distributions. TRα1 is the predominant subtype in bone, the gastrointestinal tract, cardiac and skeletal muscle, and the central nervous system; TRβ1 is most abundant in the liver and kidney; and TRβ2 is more discretely expressed in the hypothalamus, pituitary, cochlea, and retina.[1] 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

of the receptor results in dissociation of the corepressor complex and recruitment of coactivator proteins, such as steroid receptor coactivator 1 (SRC-1), which mediate hormone-dependent transcriptional regulation.[2]

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 visuoperceptual 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 TRα PROTEIN

After generation of the E403X mutant TRα by site-directed mutagenesis of wild-type receptor complementary DNA, we performed assays of radiolabeled 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 TRα1 and TRβ 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

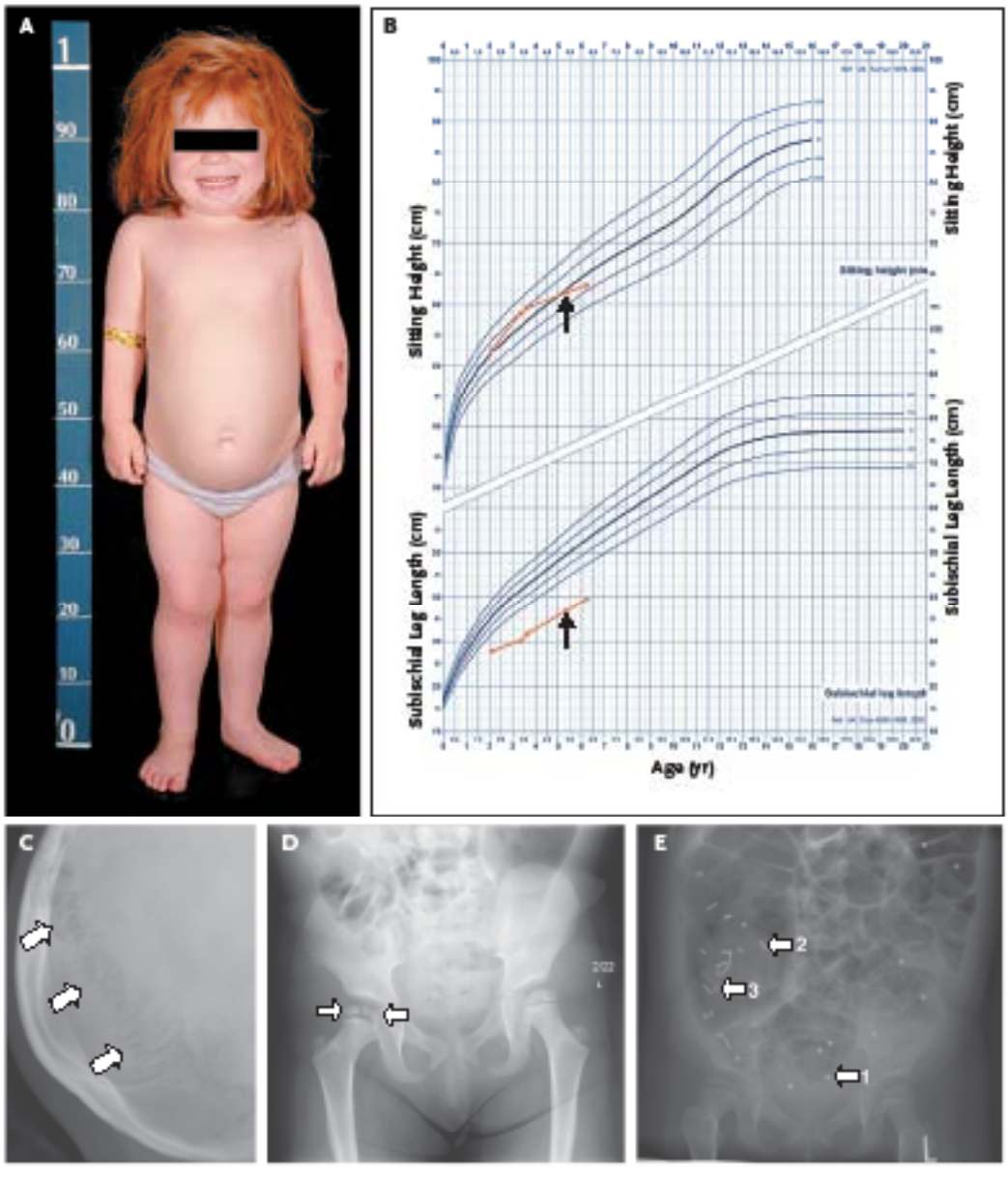

Figure 1. Phenotypic Features of the Patient.

A photograph of the patient (Panel A) illustrates relative macrocephaly and skeletal disproportion. The chart in Panel B indicates linear growth retardation (in red), which affected the lower segment of her body, with arrows denoting the initiation of thyroxine treatment. Radiographs show multiple wormian bones in the lambdoid skull suture (Panel C, arrows), dysgenesis and fragmentation of the femoral epiphysis (Panel D, arrows), and marked bowel dilatation (Panel E), with abnormally delayed retention of radiopaque markers ingested 72 hours (arrow 1), 48 hours (arrow 2), and 24 hours (arrow 3) before examination.

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 triiodothyronine (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 μg per liter

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

Variable	Baseline	After Thyroxine Treatment	Reference Values
Thyroxine (μg/dl)			
Total	3.3	10.6	7.4–12.1†
Free	0.5	1.5	0.8–1.7‡
Triiodothyronine			
Total (ng/dl)	155	260	130–221†
Free (ng/dl)	0.4	0.7	0.3–0.5‡
Reverse (ng/ml)	0.07	0.2	0.21–0.37†
Thyroid-stimulating hormone (mU/liter)	1.04	<0.03	0.8–6.2‡
Sex hormone–binding globulin (nmol/liter)	146	131	20–81†
Insulin-like growth factor 1 (ng/ml)	59	96	67–257†
Pulse (bpm)§	71	69	
Blood pressure (mm Hg)§	82/51	77/43	
Basal metabolic rate (MJ/day)¶	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.
† Values are from 23 healthy control subjects who were matched with the patient according to age, sex, and body-mass index.
‡ Reference ranges in children from 1 to 5 years of age are from Kapelari et al.[3]
§ Detailed reference values are shown in Figure 4 in the Supplementary Appendix.
¶ 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 μg per liter and a clonidine test peak of 11.7 μg per liter (normal value, >10 μg 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 μg 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., TRα2 and Rev-erbα) derived from the *THRA* locus (Fig. 5B in the Supplementary Appendix).

FUNCTIONAL CHARACTERIZATION OF E403X MUTANT TRα

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 TRα (data not shown).

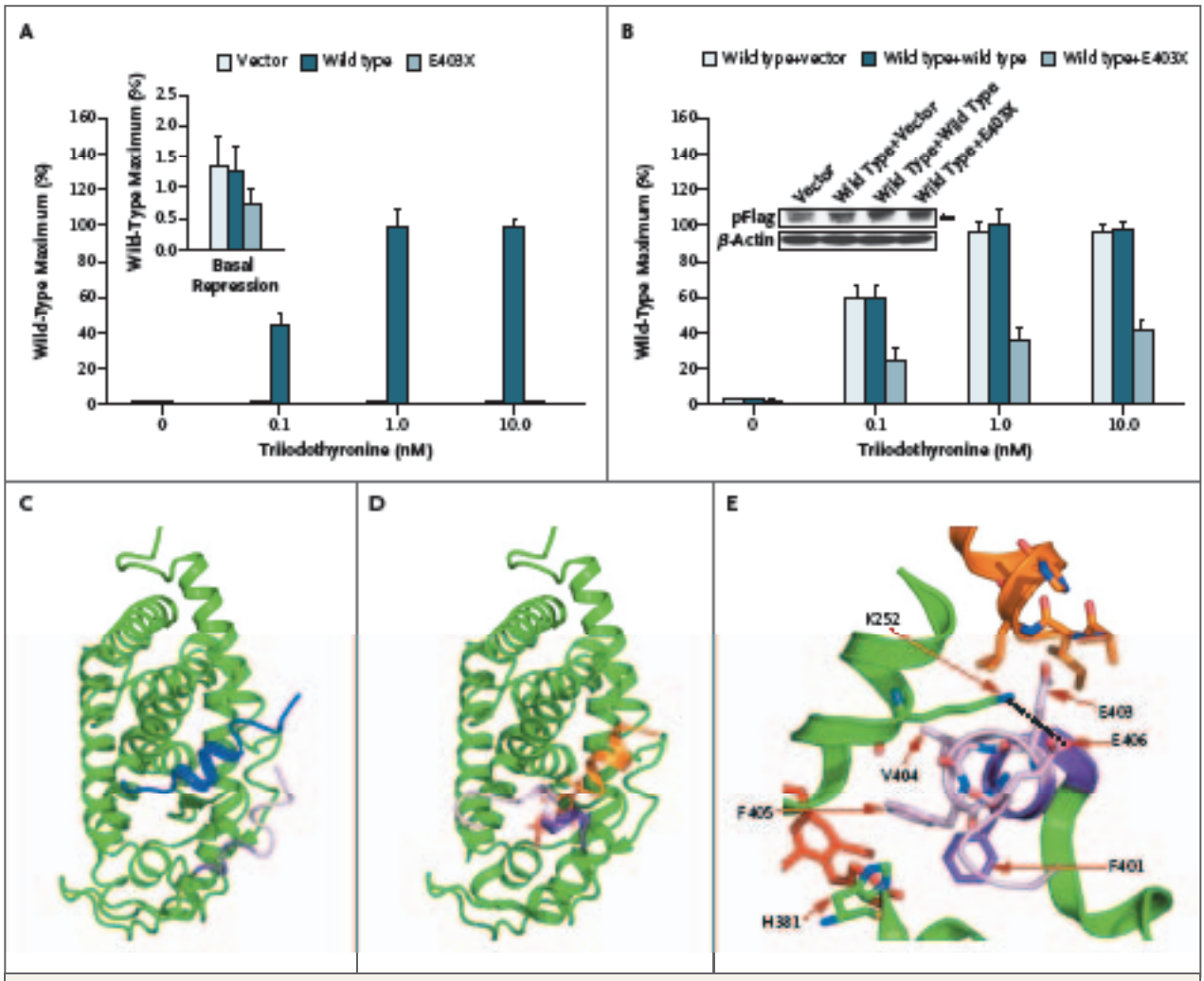

Figure 2. Functional Properties and Molecular Modeling of the E403X Mutation in Thyroid Hormone Receptor Alpha (TRα).

In Panel A, JEG-3 cells are transfected with empty vector or wild-type or mutant E403X TRα, 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 TRα ligand–binding domain (LBD) shows displacement of its C-terminal α-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 TRα 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 TRα precludes hormone and coactivator binding, allowing constitutive binding to corepressor.

Furthermore, when coexpressed, the E403X receptor strongly inhibited transcriptional activation by wild-type TRα in a dominant negative manner (Fig. 2B). TRα 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 TRα 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,[4] 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 TRα, with failure of their hormone-dependent dissociation. Conversely, E403X TRα 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 TRα, removing its C-terminal α-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),[5] with failure of these processes resulting in constitutive binding of corepressor by E403X mutant TRα, 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,[6,7] and diminished colonic motility with megacolon or even ileus is recognized in hypothyroidism.[8] In addition, the child's cognitive deficits were consistent with those seen in congenital hypothyroidism.[9] 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 TRα was a potent, dominant negative inhibitor of wild-type thyroid hormone 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.[10,11] 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 TRα was the predominant subtype. Conversely, organs containing mainly TRβ (e.g., pituitary and liver) remained sensitive to thyroid hormone.

TRα1 null mice do not have the abnormalities seen in our patient,[12] 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 TRα mutations (TRα1PV, TRα1L400R, and TRα1R384C), which are associated with skeletal abnormalities (delayed tooth eruption, linear growth retardation, patent cranial sutures, and epiphyseal dysgenesis), as seen in our patient.[13-15] Intestinal contractility is lost in mice with a disrupted *Thra* locus but with residual production of dominant negative receptor isoforms,[16] with intestinal dysmotility in TRα1L400R mice similar to that in hypothyroid Pax8-null animals.[15] 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.[14,17]

Free triiodothyronine levels in our patient were either high normal or slightly raised, as in TRαPV mice,[18] 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 TRαPV mice.[18] Alternatively, reduced tissue levels of type 3 deiodinase, which catabolizes triiodothyronine and whose expression is

predominantly regulated by TRα, may also be a contributory factor.[19]

The incidence of resistance to thyroid hormone is estimated to be approximately 1 in 40,000,[20] with de novo *THRB* mutations in 27% of cases.[21] 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 TRα mutant mice.[18,22] The phenotype of mice harboring different TRα mutations is not uniform,[22] 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 thyroid 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 TRα-selective thyromimetic agents[23] may be necessary to avoid hyperthyroidism in TRβ-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,[24] may be an alternative therapeutic strategy.

Supported by grants from the Wellcome Trust, the National Institutes of Health Research Cambridge Biomedical Research Centre, the Medical Research Council Centre for Obesity and Related Metabolic Disease (to Drs. Farooqi, Gurnell, and Chatterjee), and the Great Ormond Street Children's Charity (to Drs. Muntoni and Dattani).

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

REFERENCES

1. Lazar MA. Thyroid hormone receptors: multiple forms, multiple possibilities. Endocr Rev 1993;14:184-93.
2. Horlein AJ, Heinzel T, Rosenfeld MG. Gene regulation by thyroid hormone receptors. Curr Opin Endocrinol Diabetes 1996;3:412-6.
3. Kapelari K, Kirchlechner C, Högler W, Schweitzer K, Virgolini I, Mancavo R. Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. BMC Endocr Disord 2008;8:15.
4. Denver RJ, Williamson KE. Identification of a thyroid hormone response element in the mouse Krüppel-like factor 9 gene to explain its postnatal expression in the brain. Endocrinology 2009;150:3935-43.
5. Barettino D, Vivanco Ruiz MM, Stunnenberg HG. Characterization of the ligand-dependent transactivation domain of thyroid hormone receptor. EMBO J 1994; 13:3039-49.
6. Hüffmeier U, Tietze H-U, Rauch A. Severe skeletal dysplasia caused by undiagnosed hypothyroidism. Eur J Med Genet 2007;50:209-15.
7. Beierwaltes WH. Incomplete growth associated with hypothyroidism. J Clin Endocrinol Metab 1954;14:1551-9.
8. Ebert EC. The thyroid and the gut. J Clin Gastroenterol 2010;44:402-6.
9. Rovet JF, Foley TP, Nakhla M. Hypothyroidism. In: Wondisford FE, Radovick S, eds. Clinical management of thyroid disease. Philadelphia: Saunders, 2009:123-42.
10. Chatterjee VKK, Nagaya T, Madison LD, Rentoumis A, Jameson JL. Thyroid hormone resistance syndrome: inhibition of normal receptor function by mutant thyroid receptors. J Clin Invest 1991;87:1977-84.
11. Refetoff S, Weiss RE, Usala SJ. The syndromes of resistance to thyroid hormone. Endocr Rev 1993;14:348-99.
12. Wikström L, Johansson C, Saltó C, et al. Abnormal heart rate and body temperature in mice lacking thyroid receptor α1. EMBO J 1998;17:455-61.
13. O'Shea PJ, Bassett JHD, Sriskantharajah S, Ying H, Cheng S, Williams GR. Contrasting skeletal phenotypes in mice with an identical mutation targeted to thyroid hormone receptor α1 or β. Mol Endocrinol 2005;19:3045-59.
14. Tinnikov A, Nordström K, Thorén P, et al. Retardation of post-natal development caused by a negatively acting thyroid hormone receptor α1. EMBO J 2002;21: 5079-87.
15. Quignodon L, Vincent S, Winter H, Samarut J, Flamant F. A point mutation in the activation function 2 domain of thyroid hormone receptor α1 expressed after CRE-mediated recombination partially recapitulates hypothyroidism. Mol Endocrinol 2007;21:2350-60.
16. Fraichard A, Chassande O, Plateroti M, et al. The T3Rα gene encoding a thyroid hormone receptor is essential for postnatal development and thyroid hormone production. EMBO J 1997;16:4412-20.
17. Esaki T, Suzuki H, Cook M, et al. Cardiac glucose utilization in mice with mutated α- and β-thyroid hormone receptors. Am J Physiol Endocrinol Metab 2004;287: E1149-E1153.
18. Kaneshige M, Suzuki H, Kaneshige K, et al. A targeted dominant negative mutation of the thyroid hormone α1 receptor causes increased mortality, infertility, and dwarfism in mice. Proc Natl Acad Sci U S A 2001;98:15095-100.
19. Barca-Mayo O, Liao X-H, Alonso M, et al. Thyroid hormone receptor α and regulation of type 3 deiodinase. Mol Endocrinol 2011;25:575-83.
20. LaFranchi SH, Snyder DB, Sesser DE, et al. Follow-up of newborns with elevated screening T4 concentrations. J Pediatr 2003;143:296-301.
21. Refetoff S, Dumitrescu AM. Syndromes of reduced sensitivity to thyroid hormone: genetic defects in hormone receptors, cell transporters and deiodination. Best Pract Res Clin Endocrinol Metab 2007;21:277-305.
22. Vennström B, Mittag J, Wallis K. Severe psychomotor and metabolic damages caused by a mutant thyroid hormone receptor alpha 1 in mice: can patients with a similar mutation be found and treated? Acta Paediatr 2008;97:1605-10.
23. Ocasio CA, Scanlan TS. Design and characterization of a thyroid hormone receptor α (TRα)-specific agonist. ACS Chem Biol 2006;1:585-93.
24. Kuendgen A, Schmid M, Schlenk R, et al. The histone deacetylase (HDAC) inhibitor valproic acid as monotherapy or in combination with all-trans retinoic acid in patients with acute myeloid leukemia. Cancer 2006;106:112-9.