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Mutation-in-Brief

A novel mutation of the THRB gene in a Japanese family with resistance to thyroid hormone

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Introduction

Resistance to thyroid hormone (RTH; OMIM 190160) is an inherited syndrome of reduced sensitivity to thyroid hormone. RTH, in majority, is caused by monoallelic inactivating mutation of *THRB*, which encodes the thyroid hormone receptor ß (TRß) (1). RTH is endocrinologically characterized by high serum thyroid hormones together with inappropriately normal TSH. The severity of hormonal resistance varies among different tissues in an affected individual, due to differences in the relative expression of TRß and thyroid hormone receptor alpha (TRα) in different tissues (2). To date, more than 100 THRB mutations have been reported among RTH patients. Most mutations are located in the ligand-binding domain of TR. They interfere with the function of the normal TR because of their dominant negative effect (1).

We report a novel mutation of the THRB gene in a family with RTH.

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Patients' Report

The proband, a 7-yr-old Japanese boy, visited our service due to a learning disability. He was born at full term and had no remarkable medical history. He had no symptoms suggesting hyperthyroidism or hypothyroidism. On examination, his height and weight were 125.2 cm (+1.2 SD) and 22.3 kg (–0.1 SD), respectively. His heart rate was 66 beats /min, which was in the normal range but relatively bradycardic. He was diagnosed as having attention-deficit/hyperactivity disorder (ADHD) using the ADHD rating scale. The Wechsler Intelligence Scale for Children was within the normal range (data not shown).

The 3-yr-old brother of the proband had speech delay. At that time, he could say some words but could not combine them. The 43-yr-old mother was healthy and had no specific

Table 1 Thyroid function tests

	Serum levels			Size of thyroid gland by ultrasonography
	Free T_4 (ng/dl)	Free T_3 (pg/ml)	TSH (μU/ml)	
Proband	2.62	8.29	1.78	Right lobe; >97.5th percentile* Left lobe; normal*
Brother	6.35	10.65	3.95	Normal
Mother	2.59	4.09	2.49	Normal
Maternal grandmother	2.72	4.51	1.32	
References for adult	0.9–1.7	2.3–4.3	0.5–5.0	

* We did not know the reason for the asymmetry.

complaints. The 67-yr-old maternal grandmother was being treated at another hospital due to thyroid goiter.

The proband, brother, mother and maternal grandmother had high serum thyroid hormone levels with an inappropriately normal serum TSH level (Table 1). Accordingly, all of them were diagnosed as having RTH, although we did not perform brain MRI to exclude a TSH-producing pituitary adenoma in the three generations.

Written informed consent for a genetic study of *THRB* for the proband's family (proband, brother, mother and father) was obtained from the parents. Analysis of the maternal grandmother was not permitted. This study was approved by the institutional review board of Keio University School of Medicine. We extracted genomic DNA and sequenced all coding exons and flanking introns of *THRB* using a standard PCR-based technique. We found a heterozygous *THRB* sequence variation in the proband, brother and mother, c.844A>G, p.R282G, in exon 8, but not in the father (Fig. 1A). This variation was not present in the Single Nucleotide Polymorphism database (dbSNP) or the Human Genetic Variation Database (HGVD). The sequence-based mutation prediction for R282G was probably damaging according to PolyPhen (http://genetics.bwh.harvard.edu/pph/).

We conducted a computational mutation prediction. Crystal structure data of TRß-T_3 complex was used as a reference wild-type structure (3). We modeled the structure of the mutation using a modeling software, the PyMOL Molecular Graphics System (http://www.pymol.org), to predict possible abnormal residue-ligand contact (Fig. 1B and 1C).

Discussion

We identified a novel mutation (c.844A>G, p.R282G) in exon 8 of the THRB gene in the family with RTH. The affected residue (R282) is located in the ligand-binding domain. p.R282S and p.R282T have been reported in the literature as mutations responsible for RTH (4, 5). With respect to serum freeT_4, freeT_3 and TSH, there were no differences among R282S, R282T and R282G. Moreover, R282G was judged as probably damaging and deleterious by sequence-based mutation prediction and computational mutation prediction, respectively.

The following two points merit brief comments. First, we did not determine that ADHD and speech delay in the proband and the brother were related to RTH. ADHD and speech delay have been reported to be well-known clinical features of RTH (1). Phenotypic variation has also been described within the same family, probably due to genetic variability other than TRß, which could modulate the phenotype of RTH (1). Second, the maternal grandmother must have the same mutation, although we had

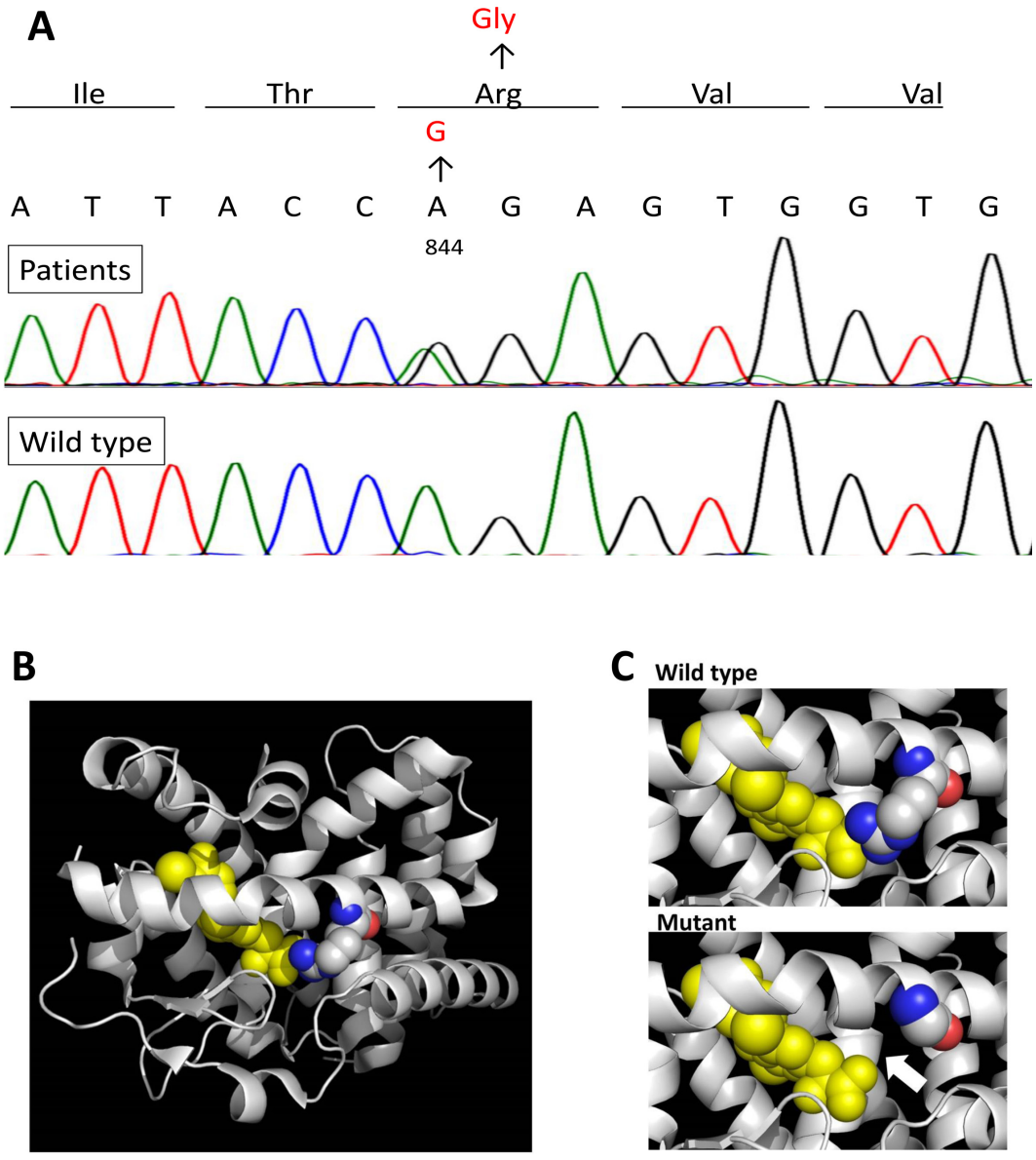

Fig. 1. Partial sequence of exon 8 of the THRB gene and computational mutation prediction of R282G. (A) The patients have a heterozygous mutation (c.844A>G, p.R282G) denoted by the arrow. (B) The three-dimensional structure of the TRß (ligand-binding domain)-T_3 complex is shown. A residue corresponding to Arg282 is shown with its side chain as spheres. (C) A modeled structure of R282G is shown in comparison with the wild type. The mutation was predicted to cause abnormal residue-ligand contact (arrow). Atom color code: red, oxygen; blue, nitrogen; grey, others. T_3 is colored yellow.

no chance to conduct a genetic analysis for her.

In conclusion, we identified a novel mutation of the THRB gene, c.844A>G, p.R282G, in a family with RTH.

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