Three Japanese Patients from Two Families with Generalized Resistance to Thyroid Hormone with Mutations in Exon 9 of the Thyroid Hormone Receptor β Gene

Matsuo Taniyama, Yoshiyuki Ban, Naoko Momotani*, Fuminori Makino*, Koichi Ito* and Yoshio Ban

Abstract

Resistance to thyroid hormone (RTH) is a genetic disorder caused by mutations in the thyroid hormone receptor (TR) β gene. The mutations are clustered in two regions: exon 9 and exon 10. To date, only one patient with an exon 9 mutation has been reported in Japan. We herein report three patients from two Japanese families with RTH and mutations in exon 9. A 52-year-old woman and her 18-year-old daughter, both with inappropriate secretion of TSH (SITSH) were diagnosed simultaneously with generalized RTH. Molecular analysis revealed a G345D mutation. An 11-year-old girl with SITSH, whose only manifestation was a goiter, had an R338W mutation, which is frequently associated with pituitary RTH. Thus, RTH with mutations in exon 9 of the TR β gene is not so rare in Japan.

Key words: hyperthyroxinemia, inappropriate secretion of thyrotropin (SITSH), unresponsiveness of the tissue

Introduction

Resistance to thyroid hormone (RTH) is a genetic disorder characterized by poor responsiveness to thyroid hormone. In RTH, the pituitary gland is always resistant to TH, though peripheral tissues sometimes respond better than the pituitary gland, and the patients sometimes present with thyrotoxic manifestations such as tachycardia or irritability. Mutations of the thyroid hormone receptor (TR) β gene have been identified in the majority of patients with RTH (1). There are two clusters of mutations that are located in the hormone binding domain of the gene: one cluster is located in exon 9 and the other is located in exon 10 (2). In reported Japanese cases, the majority of mutations have been located in exon 10 (1), whereas only one mutation in exon 9 (R338W) has been reported (3). We newly identified mutations in exon 9 in three Japanese RTH patients from two families.

Case Reports

Patient 1
Patient 1 was a 52-year-old woman who visited a general practitioner because of a goiter at the age of 47. She had no manifestation of thyrotoxicosis. A diagnosis of Graves’ disease with hyperthyroxinemia was made. After antithyroid drug therapy was started, the goiter grew, and the patient was referred to Ito Hospital. Radioiodine (RI) therapy was performed followed by administration of methimazol. Four months after RI therapy, TSH level was assayed for the first time, and inappropriate secretion of TSH (SITSH) was found (total T3, 265 ng/dl, total T4, 18.1 µg/dl, TSH, 119.2 µU/ml). The patient stopped visiting the hospital, however. When she visited Ito Hospital again 3 years later, the SITSH was still present (Table 1). On physical examination, her heart rate was 60 beats per minute. A small goiter was observed. On TRH test, TSH levels responded, and an exaggerated PRL response was noted (Table 1). Urinary pyridinoline level, deoxy-pyridinoline level, and the ratio of urinary tetrahydrocortisone to tetrahydrocortisol (THE/THF) (4), which are markers of peripheral thyroid hormone activity, were not increased. Pituitary adenoma was not found by computed tomography. On the basis of these findings, as well as the presence of SITSH in the patient’s daughter, generalized RTH (GRTH) was diagnosed.

Patient 2
This 18-year-old woman was the daughter of Patient 1. She had noticed a goiter but had no thyrotoxic symptoms. She was diagnosed with Graves’ disease by the same general practitioner who treated her mother, and she was started on antithyroid drug therapy. Because her goiter had become enlarged, she visited Ito Hospital separately from her mother and had a thy-
Resistance to Thyroid Hormone

Table 1. Endocrinological Data

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (μU/ml) basal</td>
<td>0.3–3.5</td>
<td>1.00</td>
<td>4.00</td>
<td>2.70</td>
</tr>
<tr>
<td>after TRH</td>
<td></td>
<td>7.20</td>
<td>79.2</td>
<td>n.d.</td>
</tr>
<tr>
<td>F-T3 (pg/ml)</td>
<td>2.5–5.5</td>
<td>10.9</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>F-T4 (ng/dl)</td>
<td>0.80–1.90</td>
<td>7.01</td>
<td>4.44</td>
<td>3.71</td>
</tr>
<tr>
<td>PRL (ng/ml) basal</td>
<td>1.4–14.6</td>
<td>15</td>
<td>13</td>
<td>n.d.</td>
</tr>
<tr>
<td>after TRH</td>
<td></td>
<td>115</td>
<td>141</td>
<td>n.d.</td>
</tr>
<tr>
<td>U-pyr (μmol/molCr)</td>
<td>10–36</td>
<td>37</td>
<td>33</td>
<td>207*</td>
</tr>
<tr>
<td>U-DP (μmol/molCr)</td>
<td>2–7</td>
<td>5</td>
<td>5</td>
<td>40*</td>
</tr>
<tr>
<td>U-THE/THF</td>
<td>1.2–2.6</td>
<td>1.3</td>
<td>1.3</td>
<td>n.d.</td>
</tr>
</tbody>
</table>


roidectomy. SITSH (total T3, 280 ng/dl, total T4, 16.5 μg/dl, TSH, 133.6 μU/ml) was found 1 month after the surgery and was present 3 years later (Table 1). Pituitary adenoma was not found. TSH and PRL responses to TRH were exaggerated (Table 1). Markers for peripheral thyroid hormone activity were not increased. Because the patient's mother had SITSH, Patient 2 also was diagnosed with GRTH.

Patient 3

This patient was an 11-year-old girl found by a medical doctor to have a small goiter and referred to Ito Hospital. She had no related symptoms or signs. She was 148.4 cm in height and 33.4 kg in weight. Her heart rate was 84 beats per minute. Initial examinations revealed SITSH (F-T3, 8.5 pg/ml, F-T4, 3.71 ng/dl, TSH, 2.70 μU/ml). Magnetic resonance imaging detected no pituitary adenoma. Total cholesterol was 161 mg/dl. Urinary pyridinoline and deoxy-pyridinoline levels were within normal limits considering the patients age. She was diagnosed with GRTH.

Molecular Analysis

Direct sequencing of amplified TRβ gene was performed by standard cycle sequencing using an automated sequencer. All patients gave their informed consent to this study and the investigation was performed in accordance with the principles of the Declaration of Helsinki. Patients 1 and 2 had a guanine to adenine transition at nucleotide position 1319, which yields an amino acid substitution at codon 345 (G345D). This mutation was confirmed by PCR-RFLP using restriction enzyme

Figure 1. PCR-RFLPs of two families. (A) Patients 1 and 2 had a mutated allele shown as extra band by Sau3a digestion. (B) Patient 3 had a mutated allele (faint band indicated by arrow) that was detected by Hsp92H digestion, however, neither parent had this allele.
The frequencies of the mutations in exon 9 and exon 10 of the TRβ gene are similar in the global survey (1). The majority of Japanese patients with RTH had mutations in exon 10, however, and only one Japanese patient was reported to have a mutation in exon 9 (3), whereas another patient had a mutation in exon 7 (5). We have presented 3 cases of mutations in exon 9 in 2 families. This suggests that mutations in exon 9 of TRβ gene, though not common, are not as rare in Japan as was previously thought (Fig. 2). The binding activities of the mutated receptors were generally not different between exon 9 and exon 10 mutations (1). Although loss of hormone binding was a common feature, differences in the clinical features between the exon 9 mutations and the exon 10 mutations have been reported (6).

When both the pituitary gland and peripheral tissues are equally resistant to thyroid hormone, patients appear euthyroid and are diagnosed as having GRTH. In contrast, some patients have thyrotoxic manifestations; this condition is clinically referred to as pituitary RTH (PRTH) (7). The present three patients were diagnosed with GRTH because they had no symptoms of thyrotoxicosis or laboratory findings suggesting thyroid hormone excess. Patient 3 had a R338W mutation, which is frequently associated with the clinical features of thyrotoxicosis (3, 8, 9) and the majority of patients with the R338W mutation, including another Japanese patient, were diagnosed with PRTH. Some peculiar mutations such as R429Q (10) and R383H (11), in which the corepressor release is impaired, have been reported to be associated with PRTH. It has been closed that the mutations associated with PRTH including R338W show a weaker negative dominant activity on TR-β2 isoform, which is expressed exclusively in the pituitary gland, than on TR-β1 isoform (12). These phenomena may explain why these mutant receptors manifest PRTH, however, some patients with these PRTH-associated mutations including the present patient 3 represented as GRTH (6, 9, 13). Further studies of the mechanisms behind the unresponsiveness of tissues in individual cases are needed.

Figure 2. Locations of reported thyroid hormone receptor β mutations in Japanese patients. The majority of the reported mutations are in exon 10. Only R338W has been reported for the exon 9 mutation. Two underlined mutations are the present cases. Sau3a (Fig. 1 upper panel). Patient 3 had a cytosine to thymine transition at nucleotide position 1297, resulting in an amino acid change (R338W). PCR-RFLP with Hsp92II was used to verify this mutation. Neither parents of Patient 3 had this mutation (Fig. 1 lower panel).

Discussion

The frequencies of the mutations in exon 9 and exon 10 of the TRβ gene are similar in the global survey (1). The majority of Japanese patients with RTH had mutations in exon 10, however, and only one Japanese patient was reported to have a mutation in exon 9 (3), whereas another patient had a mutation in exon 7 (5). We have presented 3 cases of mutations in exon 9 in 2 families. This suggests that mutations in exon 9 of TRβ gene, though not common, are not as rare in Japan as was previously thought (Fig. 2). The binding activities of the mutated receptors were generally not different between exon 9 and exon 10 mutations (1). Although loss of hormone binding was a common feature, differences in the clinical features between the exon 9 mutations and the exon 10 mutations have been reported (6).

When both the pituitary gland and peripheral tissues are equally resistant to thyroid hormone, patients appear euthyroid and are diagnosed as having GRTH. In contrast, some patients have thyrotoxic manifestations; this condition is clinically referred to as pituitary RTH (PRTH) (7). The present three patients were diagnosed with GRTH because they had no symptoms of thyrotoxicosis or laboratory findings suggesting thyroid hormone excess. Patient 3 had a R338W mutation, which is frequently associated with the clinical features of thyrotoxicosis (3, 8, 9) and the majority of patients with the R338W mutation, including another Japanese patient, were diagnosed with PRTH. Some peculiar mutations such as R429Q (10) and R383H (11), in which the corepressor release is impaired, have been reported to be associated with PRTH. It has been closed that the mutations associated with PRTH including R338W show a weaker negative dominant activity on TR-β2 isoform, which is expressed exclusively in the pituitary gland, than on TR-β1 isoform (12). These phenomena may explain why these mutant receptors manifest PRTH, however, some patients with these PRTH-associated mutations including the present patient 3 represented as GRTH (6, 9, 13). Further studies of the mechanisms behind the unresponsiveness of tissues in individual cases are needed.

References