CASE REPORT

Nagoya J. Med. Sci. **85**. 369–374, 2023
doi:10.18999/nagjms.85.2.369

Eighteen-years follow-up of congenital hypothyroidism by *TSHR* gene p.Arg109Gln and p.Arg450His variants

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ABSTRACT

Congenital hypothyroidism (CH) is a common heterogeneous endocrine disorder. The thyroid-stimulating hormone receptor gene (*TSHR*) is one of the major candidate genes associated with CH. Studies have investigated the possible correlations between the specific clinical features and the presence of *TSHR* variants. However, only a few reports have focused on the long-term follow-up of patients with CH. Here we present a case of CH-associated *TSHR* p.Arg109Gln and p.Arg450His rare compound heterozygous variants, with a follow-up performed until adolescence. The patient had high serum TSH levels during newborn screening. Oral administration of levothyroxine (l-T4) was initiated at 1 month of age. The ultrasonogram revealed normal thyroid morphology and blood flow. Reduced uptake of I-123 and negative perchlorate test was observed. A small amount of l-T4 remained needed although l-T4 could be steadily reduced by puberty. The patient was diagnosed with orthotopic, nongoitrous, and permanent CH. He had no nonclassical TSH resistance. Patients with the *TSHR* p.Arg109Gln compound heterozygous variant exhibit permanent CH with high TSH levels and normal or slightly lower fT4 levels. In the future, genotype identification could help predict the long-term prognosis and reduce the requirement for detailed examinations. More case studies are needed to determine the relationship between genetic variants and clinical features in CH.

Keywords: congenital hypothyroidism, *TSHR*, p.Arg109Gln, genotype-phenotype, nonclassical TSH resistance

Abbreviations:
CH: congenital hypothyroidism
TSHR: thyroid-stimulating hormone receptor gene
l-T4: levothyroxine

INTRODUCTION

Congenital hypothyroidism (CH) is a common heterogeneous endocrine disorder, of which approximately 20% of cases are caused by a single gene variant. The thyroid-stimulating hormone receptor gene (*TSHR*) variants majorly contribute to the development of nongoitrous CH.[1] Several studies have investigated the phenotypes associated with specific *TSHR* variants. However, only a few reports have focused on the long-term follow-up of patients with CH. Thus, determining

Received: April 18, 2022; accepted: June 13, 2022

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the clinical features of CH in adolescents is difficult. Here, we report a case of CH that is associated with the *TSHR* p.Arg109Gln and p.Arg450His compound heterozygous variants, which was followed-up for 18 years.

CASE REPORT

An 18-year-old Japanese boy patient had a history of CH. He was born full-term at 40 weeks gestation with a birth weight of 2,818 kg. High serum TSH levels (22.7 μIU/mL) were detected during newborn screening although goiter was not observed. Both parents had normal thyroid function. The thyroid function tests of his father revealed that serum TSH, free T3, and free T4 levels were 0.196 μIU/mL, 4.44 pg/mL, and 1.59 ng/dL, respectively. Those of his mother were 1.44 μIU/mL, 3.09 pg/mL, and 1.19 ng/dL, respectively. The initial examination of thyroid function during detail tests revealed that serum TSH, free T3, free T4, and thyroglobulin levels were 41 μIU/mL, 4.29 pg/mL, 1.59 ng/dL, and 160 ng/mL, respectively. Oral levothyroxine (l-T4) administration was initiated at 1 month of age, which led to a TSH level reduction. The distribution of 18-year detailed clinical history, such as dose of l-T4 and serum TSH levels, is shown in Figure 1. The patient received l-T4 in oral doses of 8.37, 8.21, and 6.92 μg/kg/day at 1, 2, and 3 years of age, respectively. At 7 years of age, the patient underwent a diagnostic reevaluation, which revealed the serum TSH, free T3, free T4, and thyroglobulin levels as 47.59 μIU/mL, 3.44 pg/mL, 0.94 ng/dL, and 84.95 ng/mL, respectively. The ultrasonogram revealed normal thyroid morphology and blood flow, and the thyroid size of the right lobe was 27.3 × 8.0 × 8.8 mm, the left lobe was 22.1 × 10.3 × 8.3 mm, and the isthmus was 1.4 mm. Reduced uptake of I-123 (8.5%, 8.7%, and 7.8% at 3, 6, and 24 h, respectively) and negative perchlorate test were observed. The thyrotropin-releasing hormone stimulation test at 0, 15, 30, 45, 60, 90, and 120 min were 47.59, 171.2, 223.5, 218.1, 199.8, 145.9, and 124.6 μIU/mL, respectively. Additionally, the baseline and peak TSH levels were 47.59 and 223.5 μIU/mL, respectively.

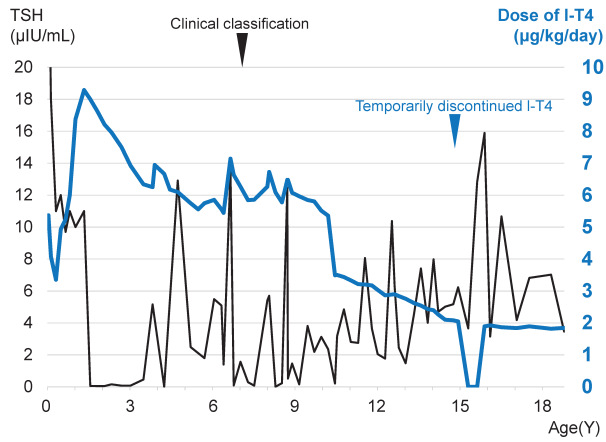

Fig. 1 Clinical course of our patient
At infancy, he was administered 6–9 μg/kg/day of l-T4. At 7 years of age, he received a diagnosis for the clinical classification. His oral dosage of l-T4 was 5–7 μg/kg/day until 10 years of age, after which, the dosage was changed to 3–4 μg/kg/day. At 15 years of age, treatment with l-T4 was temporarily discontinued, which resulted in elevated TSH levels. At 18 years of age, he was orally administered 100 μg/day of l-T4.

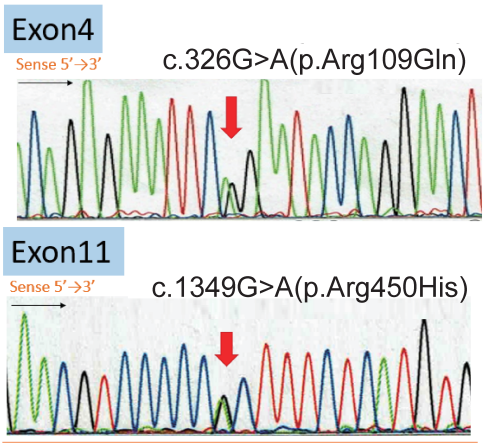

Fig. 2 Direct sequence *TSHR* gene analysis
Sense 5'→3' direction; the case exhibits a heterozygous variant of c.326G > A (p.Arg109Gln) and c.1349G > A (p.Arg450His) in exons 4 and 10, respectively.

The patient was diagnosed with orthotopic, nongoitrous, and permanent CH. Other defects, such as aplasia, hypoplasia, ectopic thyroid gland, defective hormone organification, and iodine concentration deficiency were not observed. The patient continued taking l-T4 after undergoing a clinical examination at 7 years of age. At age 15 years, l-T4 in oral doses of 2.04 μg/kg/day was temporarily discontinued, which resulted in increased TSH levels (15.9 μIU/mL). Thereafter, the patient resumed the treatment, and his TSH levels returned to normal. Genetic analysis was conducted to analyze the *TSHR* variant. Direct *TSHR* sequencing revealed p.Arg109Gln and p.Arg450His compound heterozygous variants, which were passed on from the father harboring p.Arg109Gln and mother harboring p.Arg450His, respectively (Figure 2). At 18 years of age, the patient was 173.5 cm tall and weighed 54.2 kg, and he had oral administration of l-T4 at a dose of 100 μg/day. He had not taken other medicines. His growth and psychomotor development were within the normal range. Genetic *TSHR* analysis was useful to predict his further thyroid function; therefore, he could understand the need for thyroid replacement therapy.

DISCUSSION

We report the case of a rare compound heterozygous variant associated with CH, where, for the first time, the patient was followed-up till adolescence. This report reveals the clinical CH features that are associated with *TSHR* p.Arg109Gln and p.Arg450His compound heterozygous variants.

CH-associated *TSHR* p.Arg109Gln is a very rare variant. Clifton-Bligh et al first reported that the *TSHR* p.Arg109Gln variant may lead to CH, with moderate functional deterioration.[2] We identified six previous studies that reported *TSHR* p.Arg109Gln (Table 1).[1-6] None of them involved follow-up of patients until adolescence. No significant differences in sex were found in the patients (males, 3; females, 4; unknown, 1). Patients with the *TSHR* p.Arg109Gln compound heterozygous variant exhibit permanent CH,[1,2,6] with high TSH levels and normal or slightly lower fT4 levels. They are usually diagnosed during newborn screening. Patients with *TSHR*

Table 1 *TSHR* p.Arg109Gln variants in a previous report

Authors (year)	Country	Age	Sex	Variants	Diagnostic period	TSH* (μIU/mL)	fT4* (ng/dL)	CP
Clifton-Bligh[2] (1997)	UK	3	M	*TSHR* p.R109Q /p.W546X	NBS	92	0.78	N/D
		N/D	F	*TSHR* p.R109Q/Wt	FA	3.9	0.87	N
Camilot[3], Rapa[4] (2005, 2009)	Italy	N/D	N/D	*TSHR* p.R109Q/Wt	Infancy	7.35	Normal level	S
Nicoletti[5] (2009)	Italy	N/D	F	*TSHR* p.R109Q/Wt	Infancy	5.7	Normal level	S
		N/D	F	*TSHR* p.R109Q/Wt	FA	5.6	Normal level	N
		N/D	F	*TSHR* p.R109Q/Wt	FA	6.0	Normal level	N
Fu[6] (2016)	China	N/D	M	*TSHR* p.R109Q/Wt *DUOX2* p.K530X	NBS	100<	0.69	P
Sugisawa[1] (2018)	Japan	12	M	*TSHR* p.R109Q /p.R450H	NBS	13	1.2	P
Our case	Japan	18	M	*TSHR* p.R109Q /p.R450H	NBS	41	1.59	P

N/D: not detected
M: male
F: female
R: Arg
Q: Gln
W: Trp
X: Xaa
K: Lys
H: His
Wt: wild type
NBS: newborn screening
FA: family analysis
CP: clinical phenotype
N: normal
S: subclinical CH
P: permanent CH
* result at diagnosis

p.Arg109Gln monoallelic variants exhibit normal or subclinical CH with normal or slightly higher TSH and normal fT4 levels.[3-5] The father, harboring *TSHR* p.Arg109Gln heterozygous variant, in this case, had normal thyroid function in practice. CH-associated *TSHR* p.Arg109Gln may be moderate in severity, as shown in previous functional analysis.[1,2]

Thus far, only one case of permanent CH-associated *TSHR* p.Arg109Gln and p.Arg450His compound heterozygous variants has been reported in a 12-year-old Japanese boy.[1] Our case was similar to this case because the patient had orthotopic, nongoitrous, and permanent CH; however, the I-123 uptake study results were different. The characteristic clinical feature was nonclassical

TSH resistance, which is characterized by paradoxical I-123 uptake elevation. Nonclassical TSH resistance is associated with genotype and TSH value.[1] The patients had the same genotype and a high TSH value (47 μIU/mL); however, I-123 uptake had some differences. Our case may provide useful information to elucidate the factors that are involved in nonclassical TSH resistance.

We performed the difficult task of following up on a patient with a rare variant for 18 years. Hypothyroidism may become more apparent during puberty because of the increased thyroid hormone demand.[7] Our case showed that a small l-T4 amount was still needed although l-T4 could be steadily reduced by puberty. In the future, genotype identification could help predict the long-term prognosis and reduce the requirement for detailed examinations.

Our report may not be novel enough because both p.Arg109Gln and p.Arg450His have been reported in the literature. Particularly, the *TSHR* p.Arg450His allele seems a relatively common variant site in permanent CH. Moreover, the *TSHR* p.Arg450His accounts for approximately 70% of the total *TSHR* identified variants among Japanese patients.[8] However, further case studies of this kind are required to determine the relationship between gene variants and clinical features.[9] More case studies are needed to determine the relationship between genetic variants and clinical features in CH.

CONCLUSION

TSHR variant identification has provided important genetic information regarding CH. Patients with *TSHR* p.Arg109Gln and p.Arg450His compound heterozygous variants exhibit permanent CH with high TSH and normal or slightly low free-T4 levels. Patients with CH should be followed-up in the long-term and genotype-phenotyped to contribute to future analysis.

AUTHOR CONTRIBUTION

Daisuke Watanabe wrote the first draft of this manuscript.

ETHICAL STANDARDS AND INFORMED CONSENT

We received ethical committee approval from our hospital and informed consent from the patient's parents. Written informed consent was obtained from the patient for publication of this case report.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

No grant or payment was received to produce this manuscript.

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