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Case Report

Two siblings with congenital central hypothyroidism caused by a novel mutation in the *IGSF1* gene

Makiko Oguma[1], Mizuki Kobayashi[1], Masayo Yamazaki[1], Koji Yokoyama[1], Shuntaro Morikawa[2], Takeshi Yamaguchi[2], Takanori Yamagata[1], and Toshihiro Tajima[1]

[1]*Department of Pediatrics, Jichi Medical University, Tochigi, Japan*

[2]*Department of Pediatrics, Hokkaido University School of Medicine, Hokkaido, Japan*

Abstract. Genetic defects in the immunoglobulin superfamily member 1(IGSF1) protein are the cause of congenital central hypothyroidism (C-CH). Here we report two Japanese siblings with C-CH due to a novel *IGSF1* mutation. The youngest brother showed a failure to thrive, hypothermia, and neonatal icterus six days after birth. Further endocrine evaluations led to the diagnosis of C-CH. In addition, PRL deficiency was later detected. In contrast, the elder brother did not show symptoms of severe hypothyroidism during the neonatal period, but he had been followed up by doctors due to psychomotor developmental delays since the age of 1 yr. At the age of 3 yr, he had low thyroxine and PRL levels and was also diagnosed with C-CH. Because of the C-CH and PRL deficiency, an IGSF1 deficiency was suspected. Sequence analysis of the *IGSF1* gene identified a novel hemizygous mutation of p.Trp1173GlyfsTer8 (NM_001170961.1:c.3517del) in both siblings. In conclusion, the phenotypic severity of C-CH is different, even in siblings. Importantly, an IGSF1 deficiency may result in severe hypothyroidism during the neonatal period.

Key words: congenital central hypothyroidism, immunoglobulin superfamily 1, developmental delay

Introduction

Congenital central hypothyroidism (C-CH) is a rare disease characterized by impaired thyrotropin secretion with a normal thyroid gland. C-CH is caused by defects in the ß-subunit of the thyroid-stimulating hormone (TSH) or thyrotropin-releasing hormone (TRH) receptor or the immunoglobulin superfamily gene 1 (*IGSF1*) (1). In addition, a defect in the transducing ß-like protein 1 (*TBL1X*) has recently been reported to be associated with C-CH (2). Inheritance of C-CH caused by TSH ß-subunit (*TSHB*) and TRH receptor (*TRHR*) mutations is autosomal recessive. In contrast, inheritance of *IGSF1* and *TBL1X* mutations is X-linked recessive.

It is known that there are broad phenotypical differences among patients with an IGSF1 deficiency (3–9). The degree of CH in affected individuals is highly variable (1, 3, 4, 6, 8). Several patients with an IGSF1 deficiency have been diagnosed in infancy and childhood; however, in some patients with an IGSF1

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Corresponding author: Makiko Oguma, MD, Department of Pediatrics, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0498, Japan
E-mail: r0607mi@jichi.ac.jp

deficiency, the symptoms of hypothyroidism are mild and a diagnosis only made in adulthood. In addition, some patients also present with PRL and partial growth hormone deficiencies (3–9). Furthermore, macroorchidism is one of the characteristic features of an IGSF1 deficiency, but not all patients are affected (5, 8).

Here we report two siblings with C-CH caused by a novel mutation in the *IGSF1* gene. The younger brother developed severe symptoms of CH soon after birth representing the most severe case of C-CH caused by an IGSF1 deficiency reported to date.

Methods

Genetic study

The study was approved by the Bioethics Committee for Human Gene Analysis at Jichi Medical University. Written consent was obtained from the patients' parents.

Sequence analysis of IGSF1

Exon and exon-intron boundaries of the *IGSF1* gene were amplified from genomic DNA by PCR using primers reported previously (5). PCR products were sequenced directly with an ABI PRISM 373A automated fluorescent sequencer (Applied Biosystems Inc., Foster City, CA, USA).

Case Report

Patient 1

The patient was born by normal vaginal delivery after 37 weeks of gestation. His length and weight at birth were 50.2 cm (+ 1.4 standard deviation (SD) for normal Japanese boy) and 3,555 g (+ 2.2 SD for normal Japanese boy), respectively. He was the third child of non-consanguineous parents. There was no family history of thyroid disease, but his elder brother had been followed up by doctors since the age of 1 yr because of psychomotor developmental delays. His elder sister had no health problems. Six days after birth he was referred to the neonatal care unit due to poor activity and failure to thrive. Neonatal screening for hypothyroidism based on TSH measurement at 5 d post birth did not detect any abnormality.

At referral, his body weight was 3,020 g. His body temperature was 36.0ºC. His skin was dry and icteric, and he had marked abdominal distention. Stool frequency was once in two days after birth. His external genitalia were normal.

Roentgenological examination showed there was no epiphyseal nucleus of the distal femurs. His total bilirubin was 19.85 mg/dl and his direct bilirubin was 1.01 mg/dl. His thyroid function was as follows: serum TSH was 1.10 μU/ml (normal range for this age, 0.30–3.50 μU/ml), free T4 (FT4) was 0.38 ng/dl (normal range for this age, 1.40–1.74 ng/dl), and free T3 (FT3) was 1.09 pg/ml (normal range for this age, 3.51–4.90 pg/ml). His plasma adrenocorticotropic hormone was 31.9 pg/ml (normal range for this age, 17.6–35.5 pg/ml) and his serum cortisol was 15.9 μg/dl (normal range for this age, 9.3–17.9 μg/dl). Brain magnetic resonance imaging (MRI) showed that the brain and hypothalamic-pituitary regions were normal. Based on these findings, he was diagnosed with C-CH and levothyroxine supplementation (20 μg/day) was started at the age of 7 d. Phototherapy for neonatal icterus and intravenous infusion of 5% glucose were also initiated. At the age of 12 d, the levothyroxine dose was increased to 30 μg/d and the symptoms of hypothyroidism gradually disappeared until 14 d of age. His growth chart revealed that he was obese (Fig. 1A). His psychomotor development was normal. At the age of 4 yr, his serum PRL was low (1.0 ng/ml; normal range for this age: 2.0–19.6 ng/ml). He is currently 6 yr of age. His height is 117.2 cm (+ 0.81 SD for normal Japanese boy), his weight is 31.1 kg (+ 3.28 SD for normal Japanese boy), and his body mass index (BMI) is 22.6 kg/m^2. At the age of 6 years, his serum insulin-like growth facter 1 (IGF-1) was 54 ng/ml (normal range for this age, 55–215 ng/ml).

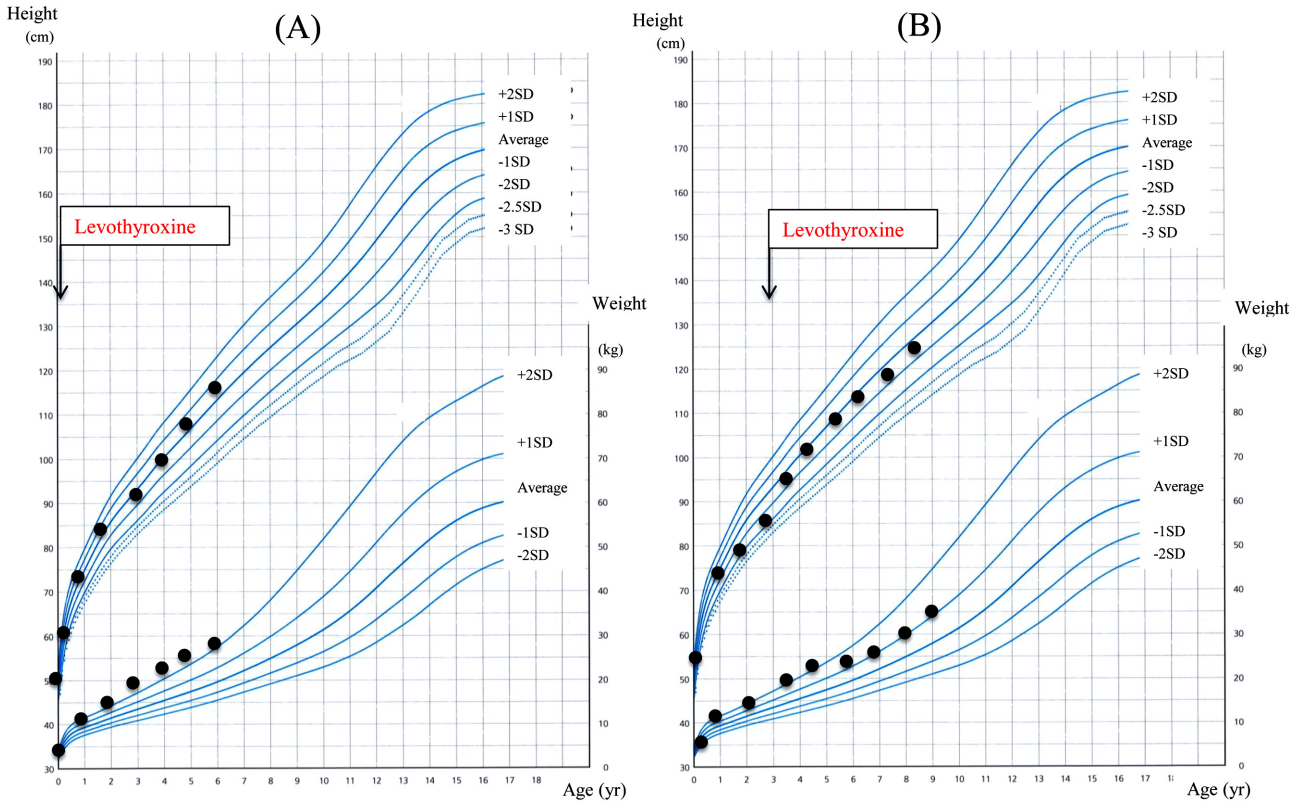

Fig. 1. Growth chart. (A) Young brother (patient 1), (B) Elder brother (patient 2).

Patient 2

Patient 2 was the elder brother of patient 1. He was the second child of this family and was vaginally delivered at 39 wk gestation. His body length and weight at birth were 52.7 cm (+ 2.0 SD for normal Japanese boy) and 4,255 g (+ 2.9 SD for normal Japanese boy), respectively. The neonatal screening for CH was based on a measurement of TSH alone which was within the normal range. He had prolonged icterus, but it naturally resolved at 4 mo of age. From the interview with the mother, stool frequency was once a day during this period. At that time, the thyroid function was not evaluated. Because he showed psychomotor developmental delays and hypotonia, he was regularly followed up. His developmental milestones were as follows: head control at 5 mo of age, sitting alone at 11 mo of age, rolling over and crawling at 12 mo of age, standing alone at 15 mo of age, walking alone at 2 yr and 3 mo, and ability to say 2 or 3 words at 18 mo of age. Because his younger brother was diagnosed with C-CH, he was referred to our pediatric endocrinology clinic at the age of 3 yr. At that time, his height was 97.8 cm (+ 0.6 SD for normal Japanese boy) and his body weight was 19.8 kg (+ 3.1 SD for normal Japanese boy). His abdomen was distended, and the mother complained that he had been suffering from constipation since the infantile period. His growth chart showed that he had been obese since he was 10 months of age (Fig. 1B). His endocrine profile was as follows: serum TSH was 0.67 μIU/ml (normal range for this age, 0.02–4.89 μU/ml), FT4 was 0.57 ng/dl (normal range for this age, 1.09–1.55 ng/dl), and FT3 was 2.38 pg/ml (normal range for this age, 3.90–5.12 pg/ml). The brain and hypothalamic-pituitary regions were normal by brain MRI. Based on the clinical findings and a low FT4 despite

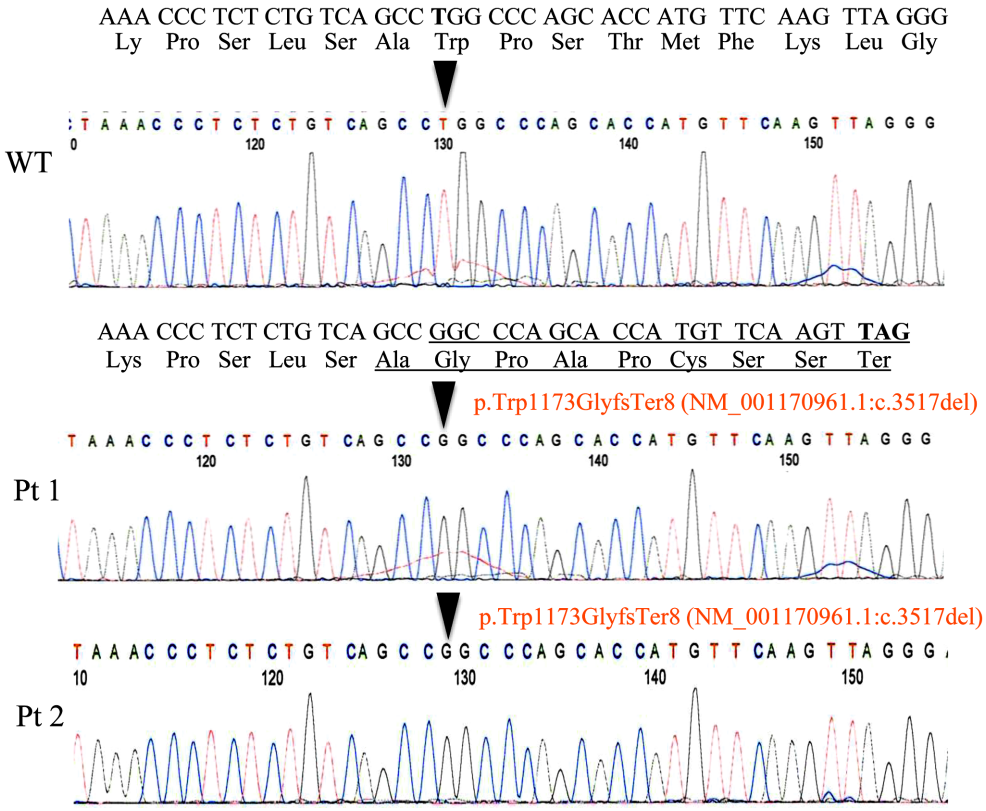

Fig. 2. Sequence of *IGSF1*. In both patients, a hemizygous single base (T) deletion in exon 18 resulted in a premature stop codon p.Trp1173GlyfsTer8 (NM_001170961.1:c.3517del). Arrowheads denote the deletion site of the T base.

normal TSH, he was also diagnosed with C-CH and treatment with levothyroxine (30 μg/d) was initiated. Thereafter, his constipation improved, and his development gradually improved to normal standards. At 7 yr of age, his PRL was less than 0.5 ng/ml (normal range for this age, 1.5–12.7 ng/ml). He is currently 9 yr old. At the age of 9 yr, his serum IGF-1 was 81 g/ml (normal range for this age, 84–350 ng/ml). We were unable to evaluate his developmental progress or intellectual quotient in detail due to a lack of consent from his parents. However, his development appeared to be mildly delayed and he seemed hyperactive.

Results

Based on the diagnosis of C-CH and a PRL deficiency, the siblings were suspected to have an IGSF1 deficiency. Genetic analysis was performed when the elder and younger brothers were 7 yr and 3 yr old, respectively. Sequence analysis of the *IGSF1* gene showed a single base deletion in exon 18 (NM_001170961.1:c.3517del) as a hemizygous mutation in both siblings. This deletion resulted in a change in the open reading frame, leading to a premature stop codon eight codons downstream from the deletion (p.Trp1173GlyfsTer8) (Fig. 2). This mutation was located in the twelfth immunoglobulin loop. This single base deletion is not registered in the Human Genetic Variation Database. The mother did not agree to the analysis of the *IGSF1* gene in herself or the elder sister.

Discussion

Here we report two siblings with C-CH caused by an IGSF1 deficiency. In these siblings, a novel hemizygous mutation in the p.Trp1173GlyfsTer8 locus was identified. The mutation was mapped to the C-terminal region, similar to most of the mutations resulting in an IGSF1 deficiency identified thus far (3, 6). The mutation consisted of a single base deletion, which resulted in a change in the open reading frame and the introduction of a premature stop codon. Therefore, C-CH may have been caused by this mutation.

These patients presented with C-CH, PRL deficiency, and large body weight at birth which are consistent with symptoms of an IGSF1 deficiency. Regarding birth weight, Asakura et al. reported that Japanese patients with an IGSF1 deficiency are born larger than the mean for their gestational age (7). Therefore, a heavy birth weight is an indication of a possible IGSF1 deficiency in patients with C-CH. It is known that patients with an IGSF1 deficiency are overweight despite appropriate thyroid hormone replacement (4). Similarly, the two cases reported here were obese despite thyroid hormone replacement. The mechanisms underlying heavy birth weight and obesity in patients with an IGSF1 deficiency are not clear; however, metabolic parameters should be carefully monitored in these patients.

Patient 2 showed developmental delays prior to treatment, but his development improved after thyroid hormone replacement therapy. However, he was not completely normal and was hyperactive. Mild attention deficits have been reported in 10% of patients with C-CH and these deficits do not improve with thyroid hormone replacement therapy (10). Tenebaum-Rakover *et al*. reported that several patients showed hypotonia, delayed psychomotor development, and attention deficit disorder despite thyroid hormone replacement (11). As *IGSF1* is expressed in the brain (12, 13), the neurological deficits may be due to a direct effect of IGSF1 deficiency. Attention and cognitive deficits have been observed in patients with CH due to low prenatal thyroid hormone levels and/or suboptimal replacement doses of levothyroxine (14, 15). Indeed, treatment using levothyroxine in patient 2 was delayed until he was 3 yr of age. This delay in treatment, in addition to the direct effects of IGSF1 deficiency, may have influenced his current neurological status.

Finally, it is noteworthy that a marked difference in the degree of clinical symptoms of hypothyroidism was observed between the siblings. The younger brother showed severe symptoms soon after birth and very low levels of thyroid hormone. To our knowledge, this is the youngest patient reported so far with a severe clinical presentation of C-CH (3, 5–9, 11, 13, 16). Sun *et al.* reported a patient diagnosed at 1 week of age, but no clinical details were described (3) and the case was likely to have been identified through the neonatal screening of T4 levels in The Netherlands (3).

In conclusion, the cases reported here illustrate the varying levels of severity of C-CH, even in siblings. It should also be noted that some IGSF1-deficient patients may develop severe hypothyroidism in the neonatal period.

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