

Case report

A Case of Congenital Central Hypothyroidism Caused by a Novel Variant (Gln1255Ter) in *IGSF1* Gene

Running title: A Novel Variant in *IGSF1* Gene

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What is already known on this topic?

Mutations in *IGSF1* gene that mainly regulates pituitary thyrotrope function lead to X-linked hypothyroidism characterized with congenital hypothyroidism of central origin and testicular enlargement. The clinical features associated with *IGSF1* mutations are variable, but prolactin and/or growth hormone deficiency, and discordance between timing of testicular growth and rise of serum testosterone levels could be seen.

What this study adds?

Genetic analysis revealed a novel c.3763C>T variant in *IGSF1* gene. To our knowledge, this is the first reported case of *IGSF1* deficiency from Turkey. Additionally, as in our case early testicular enlargement but delayed testosterone rise should be evaluated in all boys with central hypothyroidism, as macroorchidism is usually seen in adulthood.

Abstract

Loss-of-function mutations in *immunoglobulin superfamily, member 1 (IGSF1)* gene cause X-linked central hypothyroidism, and therefore its mutation affects mainly males. Central hypothyroidism in males is the hallmark of the disorder, however some patients additionally present with hypoprolactinemia, transient and partial growth hormone deficiency, early/normal timing of testicular enlargement but delayed testosterone rise in puberty, and adult macroorchidism.

Here, we report a boy with congenital central hypothyroidism caused by a novel variant in *IGSF1* gene. In our patient, early testicular enlargement but delayed testosterone rise with central hypothyroidism and hypoprolactinemia were the most important clues for the diagnosis. In genetic analysis, we identified a novel hemizygous nonsense c.3763 C>T (Gln1255Ter) variant in *IGSF1* gene. To our knowledge, this is the first reported case of *IGSF1* deficiency from Turkey.

Keywords; central hypothyroidism, hypoprolactinemia, *IGSF1*

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Introduction

Congenital central hypothyroidism (CCH) is a rare disease characterized by impaired thyrotropin secretion with a normal thyroid gland. The pathogenic mechanism of CCH is heterogeneous and dysfunction of thyrotroph-specific genes such as the *thyroid-stimulating hormone β -subunit (TSH β)* and *TRH receptor (TRHR)* can result in isolated central hypothyroidism (1,2). Many CCH patients, however, have additional pituitary hormone deficiencies (3). Some patients with combined pituitary hormone deficiencies (CPHD) were reported to carry gene mutations of transcription factors involved in pituitary development including *POU1F1*, *PRO1*, *HESX1*, and *LHX3* (4). Recently, a loss-of-function mutations of *immunoglobulin superfamily, member 1 (IGSF1)* gene have been described in 2012 as a X-linked cause of congenital central hypothyroidism with an estimated prevalence of 1/100.000 (5,6). Central hypothyroidism in males is the hallmark of the disorder, however some patients additionally present with hypoprolactinemia, transient and partial growth hormone deficiency (GHD), early/normal timing of testicular enlargement but delayed testosterone rise in puberty resulting in delayed

adolescent growth spurt, and adult macro-orchidism (7). *IGSF1* gene resides on X-chromosome (Xq 26.2) and therefore its mutation affects mainly males, although some female heterozygous carriers may present central hypothyroidism (7). *IGSF1* encodes a plasma membrane immunoglobulin superfamily glycoprotein (8). After proteolytic cleavage, C-terminal portion traffics to plasma membrane where it is expressed as a large extracellular domain, suggesting a possible function in cell-cell adhesion or signaling (9). *IGSF1* is mainly expressed in Rathke's pouch, adult pituitary gland, and hypothalamus (5,10).

Here we report a boy with CCH caused by a novel variant in *IGSF1* gene. In our patient, early testicular enlargement but delayed testosterone rise with central hypothyroidism and hypoprolactinemia were the most important clues for the diagnosis. Additionally, to our knowledge, this is the first reported case of *IGSF1* deficiency from Turkey.

Case report

A 10.1 year-old boy was referred to our pediatric endocrinology out-patient clinic for hypothyroidism. He has been followed up in another hospital due to congenital hypothyroidism, and using levothyroxine (62.5 mcg/day). In medical history, he was born term with 3240 g weight without perinatal hypoxia. His mental-motor development was normal. He had used short-term growth hormone therapy two years ago. His parents were not consanguineous, and had no history of hypothyroidism.

In physical examination, height was 135 cm (-0.55 SDS) and weight was 37 kg (+0.62 SDS). Thyroid gland was not palpable, bilateral testicular volumes were 6 ml, and penis stretched length was 4 cm without pubarche. Target height was 170 cm (-0.92 SDS). Laboratory findings were as follows; FT4: 0.59 ng/dl (0.61-1.68), FT3: 3.46 ng/dl (2.9-6.1), TSH 0.02 uIU/ml (0.37-5.1), thyroglobulin 10.7 µg/L (3.5-41), prolactin 0.76 µg/L (2.64-13.13), and thyroid auto-antibodies were negative. Thyroid ultrasonography revealed a hypoplastic thyroid gland with a total volume of 0.9 ml. Levothyroxine dosage was increased until euthyroidism was achieved. Bone age was 9 years. There was a 38 mm arachnoid cyst in the right temporal pole in brain MRI, and pituitary gland was normal in structure. Growth hormone deficiency was excluded on follow-ups. His growth rate and IGF-1 level (120.3 µg/L) were normal for his age. Total testosterone was low (0.01 µg/L), and other laboratory tests (morning basal values) were as follows; LH: 0.01 U/L, FSH: 0.65 U/L, ACTH: 8.9 ng/L (4.7-48.8), and cortisol: 7 µg/dl (6.7-22.6). Low dose ACTH stimulation test was performed, and peak cortisol level was found as normal (22.1 µg/dl). Additionally, in TRH stimulation test, peak TSH response was very low (0.01 uIU/ml) confirming the pituitary central hypothyroidism. Laboratory findings of the mother were found normal; FT4: 1.1 ng/dl, FT3: 4.2 ng/dl, TSH 3.3 uIU/ml and prolactin 16 µg/L. FT4, TSH and prolactin levels of the father and the two other siblings (one sister and one brother) were also normal.

At the age of 11.9, his bilateral testicular volumes were 6-8 ml without pubarche. Laboratory tests were as follows; total testosterone: 0.07 ng/ml (0.21-0.82), LH: 0.13 U/L, FSH: 1.85 U/L, DHEAS: 48 µg/dl (20-550), androstenedione: 0.3 ng/ml (0.3-0.6), 11-deoxycortisol: 0.41 ng/ml (0.2-1.5), 17-OH progesterone: 1.5 ng/ml (0.5-1.5), Anti-Mullerian hormone (AMH): 24.2 ng/ml (28.4-113.8). As a result, *IGSF1* gene mutation was considered in the patient with central hypothyroidism, hypoprolactinemia, and low testosterone level incompatible with testicular volume.

After written informed consents were provided from the parents, genetic analysis with Next Gene Sequencing (Illumina, NovaSeq, 6000) was performed. We identified a novel hemizygous nonsense c.3763C>T (G1n1255Ter) variant in *IGSF1* gene, **Figure 1**. We considered this variant as *pathogenic* by using American College of Medical Genetics (ACMG) criterias (11). According to ACMG criterias *IGSF1* c.3763 C>T variant was met the criteria for PVS1, PM2 and PP4. The explanations of these criteria are as follows; its nonsense nature and loss of function is a known mechanism for central hypothyroidism (PVS1), absence in population databases (PM2), and compatible clinical findings with *IGSF1* gene mutations (PP4). Sanger sequencing was performed to the patient's mother, and she was found as an obligate carrier, **Figure 2**. However, other relatives of the mother did not accept to make genetic analysis.

Discussion

The *IGSF1* protein contains 12 immunoglobulin domains in two clusters which are separated by a linker segment and followed by a transmembrane and a cytoplasmic region (12). Lack of *IGSF1* protein impairs glycosylation and trafficking of the protein to the cell surface. Therefore, mutations in *IGSF1* gene that mainly regulates pituitary thyrotrope function lead to X-linked hypothyroidism characterized with congenital hypothyroidism of pituitary origin. The clinical features associated with *IGSF1* mutations are variable, but prolactin and/or growth hormone deficiency, discordance between timing of testicular growth and rise of serum testosterone levels, and abnormal weight gain could be seen (5). In a recent study, pituitary central hypothyroidism is found as the cardinal finding of the disease (100% in the cases), however only 62% had prolactin deficiency, and the remaining patients had normal prolactin secretion. Interestingly, prolactin deficiency is not consistent in patients from the same family who carry the same mutations. The reason for this variability is unknown but might be caused by interplay of several gene polymorphisms (13). In the same study, transient GH deficiency was found as 11%. Surprisingly, all children with GH deficiency had normal IGF-1 levels, whereas adults had higher than normal IGF-1 levels. Many of children with GH deficiency were retested in adulthood and found normal in GH

stimulation tests. Additionally, delayed pubertal testosterone rise, and early/normal timing of testicular growth was found in 75% of the patients in this cohort. In our case, pubertal testicular volume without pubarche and with low testosterone level prompted us to consider IGSF1 deficiency.

Another important issue in these patients is the adrenal functions. Hypocortisolism was diagnosed in 21% of newborns; however this condition finally accepted as transient within a few years in all cases (13). The late adrenarche in patients with prolactin deficiency is another clue for adrenal dysfunction, however, it is considered as a result of prolactin deficiency. As it is known, prolactin receptors are highly expressed in adrenal gland and stimulated by ACTH to increase adrenal androgen secretion (14). Furthermore, as known DHEAS level is usually found elevated in hyperprolactinemia, and lowering of prolactin concentration decreases DHEAS level. In our case, the patient has delayed pubarche with low DHEAS and androstenedione levels for his age without adrenal insufficiency.

A small proportion of heterozygous females may also show central hypothyroidism, prolactin deficiency and delayed menarche. Heterozygous females carrying *IGSF1* mutations generally exhibit FT4 levels in the lower tertile of the normal range with nearly 20% fulfilling the criteria for central hypothyroidism. Up to 20% of the cases demonstrate hypoprolactinemia, and four females reported to have surgery for benign ovarian cysts until now (13). In our case, the mother was an obligate carrier, and had neither hypothyroidism nor hypoprolactinemia.

In conclusion, in the present case, genetic analysis revealed a novel c.3763C>T variant in *IGSF1* gene. To our knowledge, this is the first reported case of *IGSF1* deficiency from Turkey. Early testicular enlargement but delayed testosterone rise with central hypothyroidism and hypoprolactinemia were the most important clues for the diagnosis. Importantly, as in our case early testicular enlargement but delayed testosterone rise should be evaluated in all boys with central hypothyroidism, as macroorchidism is usually seen late in adulthood. Additionally, although the current clinical findings of the patient are sufficient for the diagnosis and treatment of central hypothyroidism, genetic diagnosis played a key role in management and follow-up of the patient.

Ethics

Ethics Committee Approval:

Informed Consent:

Authorship Contributions

Surgical and Medical Practices: --

Concept: Doga Turkkahraman

Design: Doga Turkkahraman

Data Collection or Processing: Doga Turkkahraman, Nadide Cemre Randa

Analysis or Interpretation: Doga Turkkahraman, Nadide Cemre Randa

Literature Search: Doga Turkkahraman, Nimet Karatas Torun

Writing: Doga Turkkahraman, Nimet Karatas Torun, Nadide Cemre Randa

Conflict of Interest: No conflict of interest

Financial Disclosure: No financial disclosure

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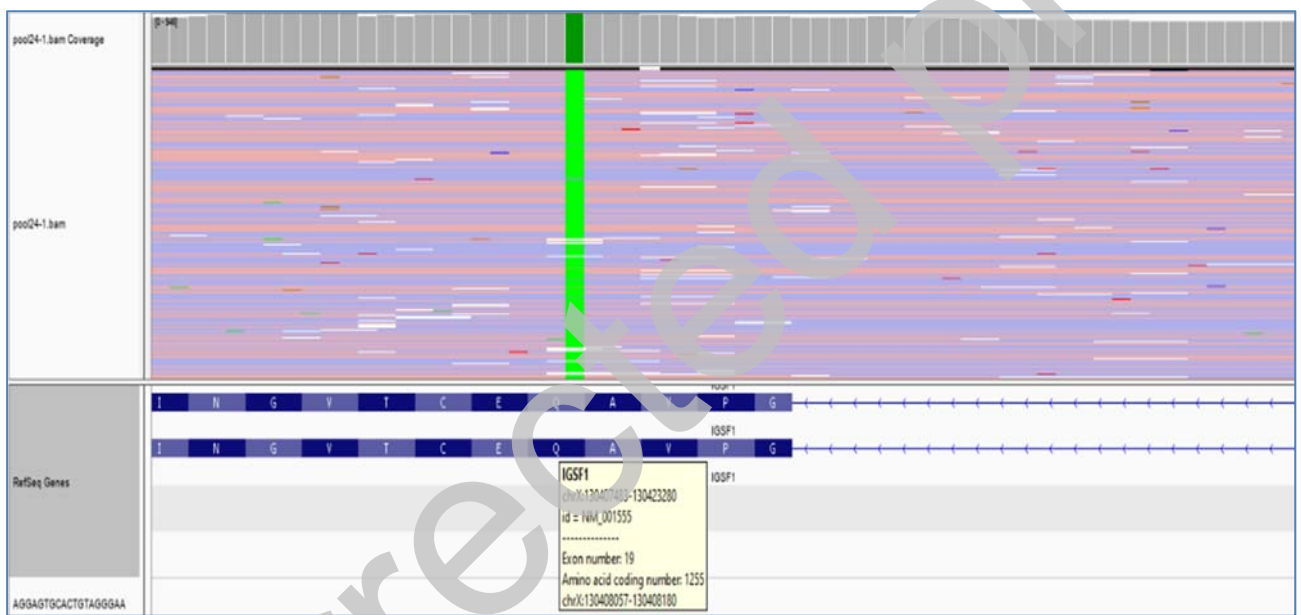


Figure 1. Next Gene Sequencing image of the novel hemizygous c.3763C > T change in *IGSF1* gene of the patient.

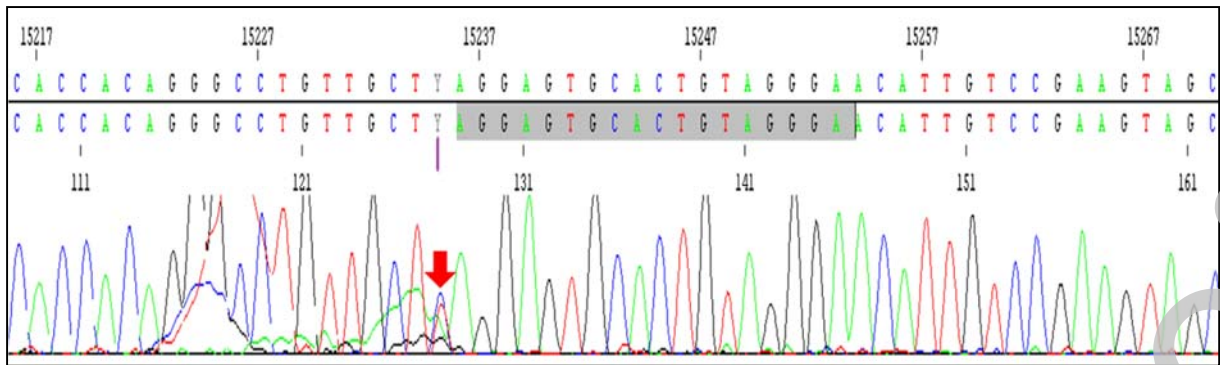


Figure 2. Sanger sequencing image of heterozygous c.3763C>T change in *IGSF1* gene of the patient's mother.