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Case report

Identification of a Novel IGSF1 Variant in Two Malaysian Male Siblings with Central Hypothyroidism and Macroorchidism

IGSF1 Variant in Central Hypothyroidism

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What is already known on this topic?

- IGSF1 mutation is the most common cause of X-linked recessive mild to moderate isolated central hypothyroidism.
- It is associated with macroorchidism with delayed pubertal testosterone rise, large birth weight, increased body mass index, low prolactin and transient growth hormone deficiency

What this study adds?

- A novel IGSF1 c.3467T>A variant was found in 2 siblings with central hypothyroidism with macroorchidism, the first report in South East Asia.
- Genetic evaluation for IGSF1 variant is important in patients with unexplained isolated central hypothyroidism +/- macroorchidism to enable early detection and treatment of hypothyroidism in other similarly affected family members.

Abstract

IGSF1 mutation is the commonest cause of mild to moderate isolated central congenital hypothyroidism and has an X-linked recessive inheritance, primarily affecting males. Other notable clinical features are macroorchidism with delayed pubertal testosterone rise, large birth weight, increased body mass index, low prolactin, transient growth hormone deficiency and low prolactin. Two male siblings with central hypothyroidism were found to have a novel IGSF1 c.3467T>A variant that was likely pathogenic based on the family segregation study. The proband, aged 3 years presented at 18 days old with prolonged jaundice while his 16-year-old brother was only detected to have central hypothyroidism after the proband's genetic analysis result was known. Both siblings were obese, had large birth weights, macroorchidism and low prolactin. The proband's brother had intellectual disability while the proband had normal development. This case study highlights the importance of evaluation for the IGSF1 variant in patients with unexplained central hypothyroidism, especially when accompanied by X-linked inheritance and macroorchidism. Family segregation analysis allows detection of other affected family members or carriers who may also benefit from thyroxine treatment.

Keywords: IGSF1 variant, central hypothyroidism, macroorchidism

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Introduction

Central congenital hypothyroidism (CCH) is a thyroid disorder that is not readily detected in a TSH-based neonatal screening programme due to low levels of both thyroid stimulating hormone (TSH) and free thyroxine hormone (FT4). CCH is caused by a mutation in transcription factors that mediate pituitary gland development in most (60%) cases, e.g. POU1F1, PROP1, and HEX31, resulting in multiple pituitary hormone deficiencies.^{1,2} Isolated CCH is rare and can be due to genetic defects in the β -subunit of TSH and thyrotropin-releasing hormone (TRH) receptor.^{1,2,3} More recently, three other genes have been implicated in isolated central CH, namely, IGSF1, TBL1X and IRS4, all of which are of X-linked inheritance.¹

The IGSF1 gene resides on X-chromosome (Xq26.2) and is expressed in the pituitary gland, hypothalamus, and testes.^{1,2,4} It encodes a plasma membrane immunoglobulin superfamily glycoprotein that may be involved in the TRH receptor expression in the pituitary gland, and regulates TSH secretion via TRH signaling.^{1,2} Loss-of-function mutations in IGSF1 gene cause TSH deficiency and X-linked recessive mild to moderate central hypothyroidism (OMIM: #300888), affecting primarily males. Other reported clinical features are macroorchidism with delayed pubertal testosterone rise, delayed adrenarche, low prolactin, large birth weight and obesity.^{2,5} TSH and prolactin response to thyrotropin-releasing hormone (TRH) is normal or reduced.¹ The phenotype of carrier females ranges from being asymptomatic to having minor manifestations.⁵

The TBL1X protein forms part of the thyroid hormone receptor corepressor complex. TBL1X gene mutation results in hypothalamus and pituitary gland resistance to low FT4 levels and a negative shift of the FT4 setpoint.¹ TSH and prolactin response to TRH test is however normal.¹ Hemizygous males with TBL1X mutation have mild to moderate hypothyroidism and some affected individuals also have hearing deficits.¹ Patients with IRS4 gene mutation have isolated central hypothyroidism which is only mild with a blunted TSH response and normal/slightly low prolactin response to TRH.¹ Individuals with TBL1X and IRS4 mutations do not exhibit the other clinical features of IGSF1 mutations i.e. macroorchidism with delayed adrenarche or large birth weight. Like IGSF1 mutation, heterozygous females with TBL1X and IRS4 mutations are usually asymptomatic and have low-normal FT4 values.¹

Case Presentation

A 3-year-old boy was diagnosed with central hypothyroidism at 18 days old during a workup for prolonged jaundice. He was the sixth child of non-consanguineous parents. His newborn screening cord TSH was 3.997mIU/L (normal). He was a term infant with a birth weight of 4.3kg born to a mother with gestational diabetes. He required five days of invasive respiratory support at birth for respiratory distress

syndrome. He was later readmitted at 18 days old for nosocomial pneumonia and was detected to have prolonged jaundice. A thyroid function test (TFT) performed at that time revealed a normal TSH of 4.3mIU/L (1.7-9.1mIU/L) and a low normal FT4 10.8pmol/L (10.5-30pmol/L). Serial monitoring of thyroid function showed a declining trend in FT4 down to 7.8pmol/L, with TSH 3.5mIU/L at 48 days old. He was commenced on L-thyroxine 4mcg/kg/day daily at two months of age. His thyroxine dose was gradually weaned down from five months of age as his TSH was very low (< 0.5mIU/L) with FT4 levels at the upper range of normal. Thyroxine was later stopped at one year of age due to low thyroxine requirement (1mcg/kg/day). However, it was restarted one month later as FT4 fell to 9.4pmol/L (10-17.6pmol/L) with a lack of TSH response (TSH 5.08mIU/L) without thyroxine replacement, suggesting central hypothyroidism.

His developmental milestones were normal. Serial growth monitoring revealed weight following the 97th percentile since infancy while height was on the 50th percentile. His calorie intake was excessive for his age and consisted of rice/noodles with meat and vegetables for his three main meals with three servings of snacks (biscuits/bread/ fresh milk) in a day. His present height, weight and body mass index (BMI) at 3 years of age are 93.9cm (-0.28SD), 17.8kg (+1.82SD) and 20.2kg/m² (+2.71SD) respectively. Bilateral testicular enlargement (\geq 4ml) was observed as early as 2.2 years of age. The right testis increased to 10ml while the left to 6ml at 3 years of age. There were no other signs of puberty. He had no midline defects or other system abnormalities. His hormonal profile was prepubertal (unstimulated luteinising hormone (LH) was <0.12 IU/L; follicular stimulating hormone (FSH) 2.21 IU/L and serum testosterone < 0.45nmol/L). His serum prolactin was low 57.2mIU/L (72-592mIU/L). Peak cortisol was 656.8nmol/L (normal > 500nmol/L) post synacthen test. Genetic testing by whole-exome sequencing (WES) by commercial diagnostic genetic laboratory (3billion, South Korea), identified a novel hemizygous missense variant c.3467T>A (p.Val1156Glu) in the IGSF1 gene (NM_001555.5) with uncertain significance.

Family segregation study

Seven family members (the proband's parents and five siblings) consented to genetic testing. Blood samples were taken for DNA extraction for targeted Sanger sequencing (by 1st BASE, Malaysia) and screening TFT. The genotype and phenotype of the family pedigree are presented in Figure 1.

The proband's 16-year-old elder brother (II2) was found to carry the same c.3467T>A variant (Fig. 1). His screening TFT revealed central hypothyroidism. Like the proband, he was relatively large at birth and had normal newborn cord blood TSH screening. He had speech delay and psychomotor retardation since preschool age. He was a slow learner and had poor social interaction with others. His present height, weight and BMI are 168.8cm (-0.62SD), 100.4kg (+2.39SD) and 35.2kg/m² (+2.43SD) respectively at 16 years of age. His puberty Tanner staging is genitalia 4, public hair 3, and both testes are enlarged (>25ml). He had normal pubertal levels of LH (2.13IU/L), FSH (9.67IU/L), and serum testosterone (16.64nmol/L). Serum prolactin was also low, <17.22mIU/L (72-592mIU/L). His fasting lipid profile and fasting blood glucose were normal. He was commenced on L-thyroxine 1mcg/kg/day daily upon detecting central hypothyroidism. Since then, he has shown improvement in his mental processing and social functioning with normalisation of FT4.

The probands' mother (I2) and 8-year-old sister (II5) who were carriers for the IGSF1 variant, c.3467T>A, had normal TFT and were also obese (BMI 35.9kg/m² and 21.5kg/m²(+1.74SD), respectively). Other siblings (II1, II3, II4) who did not carry the IGSF1 variant had normal TFT but variable nutritional status. His 17-year-old sister (II1) was overweight (BMI 28.5kg/m²), while his 14-year-old brother (II3) and 12-year-old sister (II4) had normal BMI. The proband's unaffected siblings had lower birth weights ranging from 3.0-3.9kg.

The IGSF1 variant (c.3467T>A) was reclassified as likely pathogenic based on the American College of Medical Genetics and Genomics criteria and cosegregation data interpretation in pathogenicity classification (Table 1).⁶⁷

Discussion

The first cases of IGSF1 variant were reported among 11 unrelated families in 2012 with central hypothyroidism, testicular enlargement, and prolactin deficiency.⁸ Hitherto, this is the most common cause of mild to moderate isolated CCH among males and females and has an incidence rate of approximately 1:100000.¹⁹ Patients with IGSF1 variants have been known to have a broad spectrum of clinical manifestations.^{5,10,11} Central hypothyroidism of variable severity is the main finding in all males with IGSF1 variant, presenting with symptoms of hypothyroidism at different stages in life.^{5,10,11} The proband (II6) had mild to moderate CCH when he presented in early infancy with prolonged jaundice. The proband's brother (II2) had a later presentation with speech delay and psychomotor retardation at preschool age and was only found to have moderate CCH in his teens.

Both siblings share the classical phenotype of IGSF1 variant reported in the literature, such as increased birth weight, obesity, macroorchidism and prolactin deficiency.⁵ Other studies have also reported these patients to be overweight or obese despite thyroid hormone replacement.^{5,12} The mechanism of increased birth weight and obesity is unknown. The relatively high FSH levels in the proband and untreated hypothyroidism in the affected brother could have contributed to the macroorchidism.¹³ As IGSF1 is also expressed in the testes, it is postulated that loss-of-function mutations in IGSF1 cause the testicular enlargement.¹³

Hypoprolactinaemia associated with IGSF1 mutation is yet to be understood but it can affect adrenal function.¹³ Prolactin receptors are expressed in the adrenal gland and work synergistically with ACTH to augment adrenal androgen secretion.¹⁴ Delayed adrenarche is a finding often associated with IGSF1 mutation with prolactin deficiency.⁵ However, pituitary-adrenal axis in IGSF1 mutation is usually intact with adequate cortisol response in ACTH stimulation test as shown by the proband.⁵ The affected brother (II2) did not have ACTH stimulation test but he had no history to suggest adrenal insufficiency. Fertility has reportedly been preserved in individuals with IGSF1 mutations.⁵ Clinical and biochemical monitoring for adrenarche and puberty would be required for the proband.

The degree of central hypothyroidism varies in individuals with IGSF1 mutation, and it is unclear at what FT4 levels patients are affected by hypothyroidism. While some untreated adults generally have normal cognitive functioning with normal height, children with prolonged jaundice, obesity, dyslipidemia, and poor growth respond to the initiation of thyroxine therapy.⁵ In the case of II2, improvement in mental processing and social functioning was observed after thyroxine replacement. As for the proband, his normal development is likely attributed to the early initiation of treatment. It is recommended that treatment be started in all male children with IGSF1 variant and a treatment trial be given to all male adults and female carriers with low FT4 concentrations.⁵

Conclusion

This case study describes the phenotype of 2 male siblings with a novel IGSF1 variant, c.3467T>A, that is likely pathogenic based on the family segregation study. It highlights the importance of genetic testing for the IGSF1 variant in patients with unexplained central hypothyroidism, especially when X-linked inheritance, macroorchidism without pubarche, high birth weight, obesity or prolactin deficiency are present. Furthermore, a positive result of IGSF1 genetic testing of probands enables the detection of other seemingly asymptomatic family members who may also benefit from thyroxine replacement.

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Statement of Ethics

The proband's family have given written consent for the family segregation study and to publish their case.

Ethical Approval

The Universiti Putra Malaysia Ethics Committee deemed the study exempt from review.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

YLL, KHL, THT conceptualized the study; YLL collected the clinical data and wrote the paper; CTL, NHM, TK, KHL performed the genetic analysis; TK, THT interpreted the family segregation data. All authors reviewed the paper and approved the final manuscript.

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Table 1: *IGSF1* (c.3467T>A) classification according to American College of Medical Genetics and Genomics criteria

Evidence	Category	Description
PM2	Moderate	Absent from controls (or at extremely low frequency if recessive) in Exome Sequencing Project, 1000 Genomes Project, or Exome Aggregation Consortium.
PP1	Strong	Cosegregation with disease in multiple affected family members in a gene definitively known to cause the disease.

Classification: Likely pathogenic by fulling American College of Medical Genetics and Genomics criteria

Fig. 1. (a) Family pedigree. Filled black symbols represent central hypothyroidism affected individuals. The present age in years (y) is shown below the symbols. The genotype is shown below the present age. BW; birth weight, BMI; body mass index TSH; thyroid stimulating hormone(mIU/L), FT4; Free thyroxine hormone(pmol/L). A red arrow indicates the proband. (b) Representative chromatograms for targeted Sanger sequencing of the *IGSF1* gene variants identified in the family

