2. Eren E, Yapıcı Ş, Çakır ED, Ceylan LA, Sağlam H, Tarım Ö. Clinical course of hyperprolactinemia in children and adolescents: a review of 21 cases. J Clin Res Pediatr Endocrinol. 2011;3(2):65–9.
3. Gimm O, Armanios M, Dziema H, Neumann HP, Eng C. Somatic and occult germ-line mutations in SDHD, a mitochondrial complex II gene, in nonfamilial pheochromocytoma. Cancer Res. 2000;60(24):6822–5.
4. 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, et al. A map of human genome variation from population-scale sequencing. Nature. 2010;467(7319):1061–73.
5. Panizza E, Ercolino T, Mori L, Rapizzi E, Castellano M, Opocher G, et al. Yeast model for evaluating the pathogenic significance of SDHB, SDHC and SDHD mutations in PHEO-PGL syndrome. Hum Mol Genet. 2013;22(4):804–15.
6. Saskői É, Hujber Z, Nyírő G, Likó I, Mátyási B, Petővári G, et al. The SDHB Arg230His mutation causing familial paraganglioma alters glycolysis in a new Caenorhabditis elegans model. Dis Model Mech. 2020;13(10):dmm044925.
7. Guerrero Pérez F, Lisbona Gil A, Robledo M, Iglesias P, Villabona Artero C. Pituitary adenoma associated with pheochromocytoma/paraganglioma: a new form of multiple endocrine neoplasia. Endocrinol Nutr. 2016;63(9):506–8.

Soraya Lanes Iglesias[a,*], Alba Megido Armada[a], Luis Antonio Castaño González[b], Edelmiro Luis Menéndez Torre[b], Isolina Riaño Galán[b]

[a] *Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain*
[b] *Biocruces Bizkaia Health Research Institute, Barakaldo, Bizkaia, Spain*

* Corresponding author.
*E-mail address:* sorayalanes@gmail.com
(S. Lanes Iglesias).

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# IGSF1 mutation as a cause of isolated central hypothyroidism

## Mutación de IGFS1 como causa de hipotiroidismo central aislado

Hypothyroidism is a prevalent condition characterised by a deficiency in thyroid hormone production. Nearly all cases are of primary origin, meaning that they arise from thyroid gland abnormalities.

Central hypothyroidism has an incidence of one case per 16,000–30,000 population. It consists of a thyroid hormone deficiency as a result of dysfunction in the hypothalamus, pituitary gland or hypothalamic–hypophyseal portal circulation. It presents with decreased thyrotropin-releasing hormone (TRH), decreased thyroid-stimulating hormone (TSH) or both. TSH may be inappropriately decreased, normal for thyroxine levels or even mildly elevated since forms of TSH with limited biological activity are synthesised in some cases.[1]

Central hypothyroidism is most often seen in the context of panhypopituitarism. Isolated central hypothyroidism is a very uncommon condition, with an estimated prevalence of one out of every 65,000 people. Its primary causes are genetic and, therefore, congenital mutations. In the first report, it affected TSH subunit beta (TSHB). In subsequent reports, it affected others such as those of TRH receptor, immunoglobulin superfamily member 1 (IGSF1), transducin beta-like 1X (TBL1X) and insulin receptor substrate 4 (IRS4).[1,2] Out of them all, the most common is IGSF1 deficiency. It was first reported in 2012 and has recently been seen to account for up to 38% of cases of isolated central hypothyroidism.[3] It has an estimated incidence of one case per 100,000 population per year.[2]

We report the case of an 18-year-old male referred to endocrinology for hypothyroidism. He reported signs and symptoms of progressive asthenia and cold intolerance. His family history included autoimmune thyroiditis in his mother and maternal grandfather with isolated central hypothyroidism and primary hyperparathyroidism. Laboratory results included free thyroxine (T4) 0.48 mcg/dl (0.54–1.4) and TSH 1.11 mcIU/mL (0.38–5.3). A thyroid ultrasound yielded no findings of note, and the patient tested negative for peroxidase antibodies. All other baseline pituitary hormone levels were normal. The patient's condition was labelled isolated central hypothyroidism and replacement therapy with levothyroxine was started. Magnetic resonance imaging (MRI) of the pituitary gland revealed that the patient, like his grandfather, had a partially empty sella turcica.

When we reviewed his medical record, we saw that he had been followed up in paediatrics due to short stature, with a diagnosis of constitutional delay in growth and puberty at age 14, though with a testicular volume at the upper limit of normal (25 ml).

Taking into account the tendency towards macroorchidism and the maternal grandfather's history of isolated central hypothyroidism, IGSF1 deficiency was suspected. Specific genetic testing was performed using next-generation sequencing (NGS) of the entire coding region and the intronic flanking regions of the IGSF1, FOXE1, NKX2-5, PAX8 and TSHR genes associated with hypothyroidism. This testing was positive for IGSF1 mutation (NM_001170961.1:c.2431_2432del p.(Met811Glufs*). Given these findings, the doctor responsible for the outpatient follow-up of the grandfather was notified; whether he agreed to undergo genetic testing is unknown.

IGSF1 deficiency has X-linked inheritance and is mainly associated with congenital isolated central hypothyroidism of variable severity (variable TSH, low free T4 and low free T3) and macroorchidism. A disharmonious puberty may also accompany it with a regular increase in testicular size but a delayed increase in pubertal luteinising hormone (LH) and follicle-stimulating hormone (FSH), as well as a secondary, delayed increase in testosterone, resulting in a later pubertal growth spurt.

It is also associated with obesity and attention deficit disorder despite early appropriate replacement therapy. Other associated hormone deficiencies are prolactin deficiency and growth hormone deficiency. In addition, in some cases, low serum testosterone levels have been seen in adults, though this would not seem to have any repercussions for fertility. Finally, one published case reported an association with congenital nystagmus due to a mutation in the FRMD7 gene, which is explained by this gene being in a locus close to the IGSF1 gene in the long arm of the X chromosome.[4]

Although IGSF1 deficiency is known to cause central hypothyroidism, its pathophysiology is unclear. IGSF1 encodes a transmembrane glycoprotein expressed in Rathke's pouch, the pituitary gland and the testicles, suggesting that IGSF1 is involved in TRH regulation or TSH secretion and probably plays a role in pituitary paracrine signalling. IGSF1 deficiency leads to decreased TSH due to decreased TRH signalling in thyrotropic cells. Further studies are needed to elucidate the pathophysiological mechanisms that cause macroorchidism, as well as increased weight in newborns or increased body mass index.[1,2]

This condition is underdiagnosed due to the difficulty of detecting it in newborns since most neonatal screening programmes include TSH measurement only. Furthermore, the degree of hypothyroidism may be highly variable, and there is no clear correlation between genotype and phenotype, meaning that, in many cases, patients will not show obvious signs and symptoms, even in adulthood.[2] There is no consensus on the need to perform specific neonatal screening due, on the one hand, to low incidence and, on the other hand, to the fact that many patients will have a very mild course with unaffected neurological development. However, screening in relatives of IGSF1 mutation carriers appears to be justified as it aids in diagnosing other affected individuals and in predicting other pituitary hormone deficiencies.[5]

In conclusion, genetic testing should rule out mutations and deletions in the IGSF1 gene in isolated central hypothyroidism, especially in the presence of concomitant macroorchidism, even in adult patients.

## Conflicts of interest

There were no conflicts of interest in the drafting of this article.

## References

1. Tajima T, Nakamura A, Oguma M, Yamazaki M. Recent advances in research on isolated congenital central hypothyroidism. Clin Pediatr Endocrinol. 2019;28(3):69–79, http://dx.doi.org/10.1297/cpe.28.69.
2. Joustra SD, van Trotsenburg AS, Sun Y, Losekoot M, Bernard DJ, Biermasz NR, et al. IGSF1 deficiency syndrome: a newly uncovered endocrinopathy. Rare Dis. 2013;1:e24883, http://dx.doi.org/10.4161/rdis.24883.
3. Cherella CE, Wassner AJ. Update on congenital hypothyroidism. Curr Opin Endocrinol Diabetes Obes. 2020;27:63–9, http://dx.doi.org/10.1097/MED.0000000000000520.
4. Reynaert N, Braat E, de Zegher F. Congenital nystagmus and central hypothyroidism. Int J Pediatr Endocrinol. 2015;2015:7, http://dx.doi.org/10.1186/s13633-015-0003-5.
5. Schoenmakers N, Alatzoglou KS, Chatterjee VK, Dattani MT. Recent advances in central congenital hypothyroidism. J Endocrinol. 2015;227:R51–71, http://dx.doi.org/10.1530/JOE-15-0341.

Julia Costas Eimil*, Paula Sánchez-Sobrino

*Servicio de Endocrinología y Nutrición, Complejo Hospitalario Universitario de Pontevedra, Pontevedra, Spain*

* Corresponding author.
*E-mail address:* julia.costas.eimil@sergas.es
(J. Costas Eimil).

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