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# ***Congenital central hypothyroidism caused by a novel IGSF1 variant identified in a French family***

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Short Title: Neonatal central hypothyroidism caused by a novel IGSF1 variant

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## Established Facts and Novel Insights

### Established Facts

- The phenotype of IGSF1 deficiency is variable. In addition to central hypothyroidism, IGSF1 deficiency can also lead to several other hormonal anomalies such as prolactin deficiency, transient partial GH deficiency in childhood and/or increased IGF-1 levels in adulthood, disharmonious puberty with premature testicular growth contrasting with a delayed testosterone rise and late adrenarche, adult macroorchidism, and increased BMI.
- Congenital central hypothyroidism (CCH) can be diagnosed in neonates as well as in asymptomatic adults, with variable inter- and intra-familial expressivity.

### Novel Insights

- We describe a novel pathogenic variant of the *IGSF1* gene (c.2485dup). The duplication changes the open reading frame, leading to a premature stop codon (p.Ala829Glyfs\*15). The affected part of IGSF1 is the C-terminal domain, the site of modifications in almost all reported pathogenic variants.
- Two brothers in this family presented symptoms of at birth in context of neonatal stress. The third brother, who had neither neonatal symptoms nor stress, was only diagnosed because of familial screening at 11 months of age. The misdiagnosis of CCH at birth in some family members provides insights into natural evolution of the disease without treatment.
- Family genetic screening is essential to identify and properly monitor carriers as central hypothyroidism can develop overtime.

## **Abstract (271 words)**

### **Introduction**

Central congenital hypothyroidism (CCH) is a rare disorder that can be caused by X-linked mutations in the immunoglobulin superfamily member 1 (*IGSF1*) gene. Here, we describe four familial cases with a variable presentation due to a novel *IGSF1* pathogenic variant.

### **Case presentation**

In the index case, investigation at birth of suspected brain-lung-thyroid syndrome surprisingly revealed a central hypothyroidism. Next-generation sequencing (NGS) uncovered a novel *IGSF1* pathogenic variant: a hemizygous single base duplication (G) resulting in a premature stop codon (NM\_001555.4: c.2485dup, p.Ala829Glyfs\*15). Further family investigations revealed missed neonatal CCH for the older brother who presented with prolonged jaundice (TSH 3.06 mUI/L, FT4 9.4 pmol/L, FT3 4.2 pmol/L). It also led to the diagnosis of CCH at 11 months of age for the younger brother, whose thyroid function was considered normal at birth. Neuropsychological evaluations showed no cognitive impairment for the eldest two brothers, but a slightly reduced processing-speed index compared with the other parameters for the oldest. Furthermore, a maternal uncle was diagnosed with biochemical CCH at 34 years of age, despite having few symptoms, and a complete work-up revealed prolactin deficiency and macroorchidism.

### **Discussion**

This report of a rare case of neonatal CCH caused by *IGSF1* deficiency highlights the importance of recognizing the neonatal signs of hypothyroidism to diagnose CCH as early as possible. Our results also show the importance of performing family genetic screening if a pathogenic variant is identified, to properly monitor carriers as CCH may develop over time. We suggest that these families should be followed up in the long-term to better understand the natural history of this syndrome and evaluate the need for hormone substitution.

## Introduction

Central congenital hypothyroidism (CCH) is a rare and heterogeneous disorder, due to insufficient stimulation of the thyroid gland by thyroid stimulating hormone (TSH). The molecular origin of CCH is sometimes difficult to assess, as it can be caused by pituitary and/or hypothalamic dysfunction. Mutations in genes involved in the TSH biosynthesis pathway such as those coding for thyroid stimulating hormone subunit  $\beta$  (*TSH $\beta$* ), thyrotropin-releasing hormone receptor (*TRHR*), immunoglobulin superfamily member 1 (*IGSF1*), and the more recently identified transducin-like protein 1 (*TBL1X*) and insulin receptor substrate 4 (*IRS4*), lead to isolated CCH [1,2]. More often however, when the defect affects genes coding for transcription factors involved in pituitary development (*POU1F1*, *PROP1*, *LHX3*, *LHX4*, *HESX1*, *OTX2*), CCH is associated with multiple pituitary hormone deficiency (MPHD) with or without extra-pituitary abnormalities [3,4].

IGSF1 deficiency, first described in 2012 by Sun *et al.*, has emerged as the leading cause of CCH [5–7]. *IGSF1* is located on the X chromosome (Xq26) and encodes a plasma membrane immunoglobulin superfamily glycoprotein with 12 Ig loops [5]. IGSF1 is expressed in the pituitary gland in Pit-1 cell lineages (i.e. somatotrophic, thyrotrophic and lactotrophic cells) or in thyrotrophic and gonadotrophic cells (depending on reports), and in the testes of rodents [5,8,9]. The variable endocrine phenotypes reported in the largest published series of IGSF1 deficiency-associated CCH include transient partial growth hormone (GH) deficiency in childhood, increased IGF-1 levels in adulthood, disharmonious puberty with premature testicular development leading to macroorchidism in adulthood but with late testicular and adrenal androgenic secretion, prolactin deficiency, and increased BMI [6].

CCH is difficult to detect at birth because the method used in neonatal hypothyroidism screening in France and most countries is TSH-based. The family described here is, to our knowledge, the first identified in France with CCH due to a novel *IGSF1* pathogenic variant. We discuss the difficulties in firmly diagnosing CCH, especially regarding neonatal stress and the consequences of diagnostic delay on childhood psychomotor development and adult cognitive function [10].

## CASE REPORT

### Patient 1 (IV-1)

The index case was the second child of non-consanguineous parents (Fig. 1). He was born by vaginal delivery at 37 weeks of gestation with a normal weight (3175 g) and length (51 cm) [11]. He immediately presented respiratory distress syndrome (RDS) due to hyaline membrane disease

(HMD), and had neonatal jaundice, which were treated with 48 h of mechanical ventilation, surfactant therapy, and phototherapy, respectively. His thyroid function was investigated at two days of age to identify the cause of associated hypotonia, breastfeeding difficulties, jaundice, and HMD in a term infant, in particular to investigate suspected brain-lung-thyroid syndrome. These tests revealed CCH, with low FT4 and FT3 (FT4: 6.2 pmol/L, FT3: 1.5 pmol/L; normal ranges for neonates: 12–32 and 3.1–6.8 pmol/L, respectively) with an inappropriately normal TSH level (3.8 mUI/L; normal range for neonates: 1.1–19; see Table 1). Levothyroxine replacement was started on day 4, leading to a normalization of FT4 levels at one month (21 pmol/L) and a collapse in TSH levels (<0.005 mUI/L) as expected in CCH [12]. There were no abnormalities in the pituitary work-up, including in baseline biochemical levels and MRI findings (Table 1).

Sanger sequencing at birth revealed no variants associated with congenital surfactant deficiency (*ABCA3*, *SFTPC* and *NKX2-1*) or isolated central hypothyroidism (*TSHB*).

At 7 weeks of age, the patient was hospitalized in a paediatric department for severe RSV infection, partial convulsive seizure and severe hyponatremia. SIADH and corticotroph deficiency were suspected. Hydrocortisone was administered for 10 days. ACTH deficiency was ruled out after interrupting hormone replacement therapy for two weeks (basal morning cortisol level: 712 nmol/). Brain MRI revealed bilateral hemispheric embolic lesions in the centrum ovale and posterior border zones. However, given the favourable clinical and neurological outcomes and the negative genetic work-up for brain-lung-thyroid syndrome (*NKX2-1*), no further investigations were performed.

Since no cause of CCH was found, and by analogy with the treatment of (sometimes transient) primary congenital hypothyroidism with eutopic thyroid gland, treatment was interrupted at 3.5 years of age to reassess the patients' thyroid function. Surprisingly, TSH levels had increased to 46 mUI/L with a FT4 level of 5.12 pmol/L (measured in an independent laboratory), raising questions about the diagnosis of CCH. L-thyroxine was resumed and thyroid function was reassessed in the hospital after a further treatment interruption (15 days). TSH levels were lower (TSH 5.3 pmol/L; FT4 3.9 pmol/L; FT3 < 1.5 pmol/L) (Table 1). Primary hypothyroidism was ruled out (negative antithyroid antibodies, non-inflammatory thyroid gland on ultrasonography and normal thyroid <sup>123</sup>I scintigraphy). Central congenital hypothyroidism was confirmed by a negative TRH stimulation test, with a defective response to hypothalamic stimulation (basal TSH: 4.98 mUI/L, peak: 7.84 mUI/L at 30 min) [13]. Prolactin response was normal (basal: 10.9 ng/mL, peak: 47 ng/mL at T30 min). Next-generation sequencing (NGS) revealed an *IGSF1* variant. Levothyroxine replacement therapy was resumed.

In light of this molecular defect, the patient was follow-up closely. At the last examination at 6.3 years of age, the patient's height, BMI and testicular volume were in the normal ranges (+1.2 SD from target height, Prader orchidometer testicular volume: 4 mL). Neuropsychological test results were normal (Fig. 2).

### **Patient 2 (IV-2)**

Patient 2 was the first child of this family and the elder brother of Patient 1 (Fig.1). He was born at term by instrumental delivery because of foetal bradycardia during labour. He also had prolonged neonatal jaundice. Neonatal screening for congenital hypothyroidism based on elevated TSH levels revealed no abnormality. Thyroid test results were performed because of prolonged jaundice. Results were considered normal at the time despite revealing low FT4 (Table 1).

The *IGSF1* defect was diagnosed for his brother when he was 6.2 years of age. Thyroid function tests revealed moderate CCH including low FT4 with inappropriately normal level of TSH (Table 1). There were no obvious symptoms of hypothyroidism; the patient's height and BMI were normal (+0.61 SD and +0.91 SD respectively). Neuropsychological tests showed no cognitive impairment (note that the patient was from a high socioeconomic background), but his processing-speed index was slightly lower than the other parameters (Fig. 2). Levothyroxine therapy was started. IGF-1 concentrations decreased initially but then remained normal during follow-up, as did the patient's growth velocity. No GH stimulation test was performed. At 8 years of age, the patient's bone age was 5.5 years and testicular volume was 4 mL bilaterally.

### **Patient 3 (IV-3)**

Patient 3 was the third child of the family. He was born following a normal pregnancy, with a normal weight (3720 g) and length (51.5 cm). Since his brother was known to have CCH, thyroid function tests were performed at birth, with borderline results for FT4 (the laboratory's reference range, 11-19 pmol/l, was probably not adapted to his age; neonatal reference range in our laboratory, 11-32 pmol/l) and low FT3. Thyroid test results were considered normal at the time and no treatment was introduced. The *IGSF1* mutation was diagnosed in his brother a few months later, and genetic tests at 11 months of age confirmed the presence of the same variant. Thyroid function tests revealed moderate CCH (Table 1). Statural growth and cognitive development were normal but associated with overweight (BMI: 21 kg/m<sup>2</sup>, > 97<sup>th</sup> percentile for French references). Levothyroxine therapy was started. Interestingly, TSH levels had decreased significantly to 0.09 mUI/L 6 weeks later.

### **Patient 4 (III-2)**

The maternal uncle of the index case was 34 years old at first evaluation. He was referred to an endocrinologist after the *IGSF1* variant was identified by familial genetic screening (Fig. 1). The patient is socially and professionally integrated, without cognitive impairment, and is the father of two children. His height was 180 cm with a normal BMI (23.4 kg/m<sup>2</sup>). No obvious signs of hypothyroidism, notably learning disabilities, had been observed during childhood. The patient

reported having mild constipation and a sensitivity to cold. Clinical macroorchidism was confirmed by ultrasound measurements of testicular volume (right: 25 cc, left: 23 cc) with left asymptomatic varicocele [14]. Hormonal evaluation revealed biological CCH (FT4: 9 pmol/L (12–22 pmol/L), FT3: 2.6 pmol/L (2.9–4.9 pmol/L) and a normal TSH level (1.2 mUI/L)) with lactotroph deficiency (undetectable basal prolactin) (Table 1). Total cholesterol and LDL-cholesterol were elevated (6.38 mmol/L and 3.97 mmol/L respectively). Pituitary MRI findings were unremarkable, and the thyroid gland was small on ultrasonography. No neuropsychological assessment was performed. Six months of levothyroxine replacement therapy did not lead to any improvements in the patient's clinical symptoms.

### Family history

All the female carriers in this family were found to have normal thyroid function. Another family member (III-1; Fig. 1) had been treated since the age of 20 months for central hypothyroidism but he declined to participate in the study and undergo genetic screening.

### Genetic analysis

Genetic analysis was performed in the index case by NGS (Miseq V2 Reagent Kit 300 cycles) (Illumina®, San Diego, CA, USA) on three genes implicated in isolated CCH (*IGSF1*, *TRHR* and *TSHB*). We identified a novel hemizygous variant in *IGSF1*: a single base duplication in exon 14 (NM\_001555.4: c.2485dup) (Fig. 3). This variant was not listed in population database (GnomAD V2.1.1). This duplication changes the open reading frame, leading to a premature stop codon (p.Ala829Glyfs\*15) or to the degradation of aberrant mRNA through NMD (Nonsense-Mediated mRNA Decay). It is located in the C-terminal domain of the protein, where almost all pathogenic variants have been reported. According to American College of Medical Genetics (ACMG) criteria (PVS1+PM2) [15], this variant was initially classified as *likely pathogenic*. Sanger sequencing was performed for the patient's mother, two brothers, one maternal uncle, and two aunts. The mother and two maternal aunts were carriers. His two brothers and maternal uncle were found to carry the same variant in a hemizygous state, such that this variant can be classified as *pathogenic* (Fig. 1).

## DISCUSSION

We report a well-documented familial case of CCH related to a novel *IGSF1* defect. More than 45 *IGSF1* variants have been published since the first was described by Sun *et al.* in 2012, and *IGSF1* deficiency now appears to be the leading cause of CCH [5–7].

In this family, seven members had the identified single duplication in exon 14 (c.2485dup, p.Ala829Glyfs\*15) of *IGSF1* resulting in a frameshift and thus a premature stop codon, including three heterozygous asymptomatic females and four hemizygous symptomatic males. The clinical features of the affected family members highlight several pitfalls for physicians and the value of genetic screening for paucisymptomatic patients.

The laboratory results of our index case, i.e. a low serum concentration of FT4 associated with a normal TSH level, initially led us to the diagnosis of central hypothyroidism. However, this diagnosis was reassessed as the patient's TSH levels rose significantly after treatment was briefly discontinued. Distinguishing between CCH and mild primary hypothyroidism based on laboratory results can sometimes be challenging, since normal or elevated TSH levels with low FT4 can also be caused by a hypothalamic defect. This phenomenon has been described previously for CCH patients in the context of MPPHD [16], and has been documented in *IGSF1* deficiency by Garcia *et al.* [9]. The mechanism whereby *IGSF1* deficiency leads to central hypothyroidism is not yet fully understood but may involve impaired glycosylation of TSH and reduced bioactivity, or may be linked to a reduction in TRH receptor expression, as identified *in vitro* and in *IGSF1*-deficient mice [9,17].

A TRH test may be helpful in this context to differentiate hypothalamic and pituitary origins [13], although the value of TRH tests in pituitary assessments is debatable [13,18] and as was the case here, variable results have been reported in *IGSF1* deficiency [9,19–27].

The characteristics of this familial case suggest that the neonatal expression of CCH in *IGSF1* deficiency could depend on delivery-related stress. While the index patient was diagnosed at birth following RDS, having therefore experienced a high level of stress, and his elder brother with misdiagnosed neonatal CCH presented jaundice after instrumental delivery; the youngest brother experienced no such neonatal stress and his thyroid function, evaluated at birth based on family history, was considered normal. This younger brother was the only one without any symptoms of hypothyroidism at birth. The fact that *Igsf1* $\Delta$ 312 mice have normal thyroid function under physiological conditions but are more susceptible than wild-type mice to thyroid stress [17] suggests that *IGSF1* plays a modulatory role in stress response [28].

As has been reported previously [23–25,29,30], the phenotype of affected family members is highly variable. A number of asymptomatic or paucisymptomatic adults in the family were indeed identified by familial genetic screening following the diagnosis of the index case. In these cases, the French neonatal screening program for CH based solely on TSH failed to reveal CCH. Physicians must

therefore rely on classic neonatal signs of hypothyroidism (hypotonia, jaundice, failure to thrive, etc.), which are typically absent in mild forms, and perform a complete thyroid evaluation to diagnose CCH with certainty. This is how CCH was diagnosed for the index case. A complete thyroid work-up was also performed at birth for the elder brother (patient 2), to investigate neonatal jaundice, but in this case the results were misinterpreted as normal. This situation highlights the difficulties in interpreting the results of neonatal thyroid assessments [31,32].

A genetic approach is helpful for the management of isolated CCH in the neonatal period and for clinical follow-up. For instance, severe forms of isolated CCH due to variants of the *TSHB* gene are known to cause psychomotor retardation, which is likely to be reversible with treatment [33]. In *IGSF1* deficiency, CCH may worsen or develop over time as shown by the clinical and biochemical follow-up of the younger sibling (patient 3) and Tenenbaum-Rakover *et al.*'s description of an Israeli family [24]. Molecular diagnoses should be followed by close thyroid function monitoring, even in patients with normal thyroid function at birth [32]. Hypothyroidism should be diagnosed as early as possible to improve the neurodevelopmental outcomes of CCH patients. Just like patient 4 in the present family, most patients with a late diagnosis of *IGSF1* syndrome have normal cognitive function, as reported recently by Joustra *et al.* Some untreated male patients were nevertheless found to have mild deficits in attentional control [34]. *IGSF1* is expressed in the pituitary gland and hypothalamus but also in the cerebral cortex, subfornical organ, striatum and amygdala in adult rats and may therefore play a specific role in neurodevelopment [8,34]. This specific neurodevelopmental function has to be confirmed in human as results indicate that CCH is associated with light cognitive impairment: patients with early-detected and early treated isolated CCH have lower processing speeds than their siblings, but comparable overall cognitive performance, with 43% of these CCH cases being related to *IGSF1* variants [35]. Interestingly, the older sibling (patient 2) in the family, diagnosed later, was found to have a lower processing speed, than his brother (patient 1), who was treated right from birth (Fig. 2).

The natural history and physiopathology of *IGSF1* deficiency remain poorly understood. One of the specificities of this syndrome is its phenotypic variability: family members with the same *IGSF1* variant may not all present the same clinical signs [6]. In the present family, the main phenotypic presentation of *IGSF1* deficiency was CCH for the younger siblings and prolactin deficiency and macroorchidism for their uncle. We therefore plan to closely follow up these three siblings to anticipate potential deficits that may arise later in life, in particular their neuropsychological development in light of their thyroid disease. Long term follow-up may also highlight the benefits of levothyroxine replacement for apparently asymptomatic individuals, especially in terms of metabolic

parameters such as increased BMI and dyslipidaemia, and neurodevelopmental outcomes such as deficits in attentional control [6,25,34].

In countries where neonatal screening for congenital hypothyroidism is based on TSH alone, recognizing the neonatal signs of hypothyroidism is particularly important to diagnose CCH as early as possible. If a pathogenic variant is identified, family genetic screening is warranted to properly monitor carriers as CCH may develop over time. Finally, we advocate the long-term follow-up of these families to better understand the natural history of this syndrome and reevaluate needs for hormone replacement.

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### **Consent to publish statement**

Written informed consent was obtained from the patients' parents for publication of the details of their medical case.

Ethics approval and consent to participate: Non applicable

### **Conflict of interest statement**

The authors have no conflicts of interest to declare.

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### **Authors' contributions**

R. Fourneaux was a major contributor in writing the manuscript

S. Castets, analyzed and interpreted the patient data regarding the endocrinological disease and was a major contributor in writing the manuscript

A. Godefroy analyzed and interpreted the patient data regarding the endocrinological disease

M. Grelet analyzed and interpreted the patient data regarding the genetic disease

J. Abeillon, analyzed and interpreted the patient data regarding the endocrinological disease

A. Saveanu, analyzed and interpreted the patient data regarding the genetic disease and was a major contributor in writing the manuscript

F. Castinetti, analyzed and interpreted the patient data regarding the endocrinological disease  
R. Reynaud, analyzed and interpreted the patient data regarding the endocrinological disease  
and was a major contributor in writing the manuscript

### **Availability of data and material**

The patients' medical files are accessible for research purposes on approval by the local ethics committee from the Pediatric Endocrinology Unit, CHU Timone Enfants, Assistance Publique-Hôpitaux de Marseille, Marseille, France and from the Endocrinology Department, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, France.

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## Figure Legends

Fig.1: Pedigree of the French family with the novel IGSF1 pathogenic variant. Affected male patients with genetic data are indicated by black symbols, while the grey symbols represent affected male patients who did not undergo genetic testing. Heterozygous females are indicated by central black dots. Untested cases are shown in white.

Fig. 2: Neuropsychological evaluation of patient 1 (IV-1) using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV) at 4.8 years and patient 2 (IV-2) using the Wechsler Intelligence Scale for Children (WISC-V) at 6.5 years.

Fig. 3: Sanger sequencing of the *IGSF1* gene: a hemizygous single base duplication (G) resulting in a premature stop codon (NM\_001555.4: c.2485dup, p.Ala829Glyfs\*15).