IGSF1 deficiency syndrome
A newly uncovered endocrinopathy

Sjoerd D. Joustra,1,2,* A.S. Paul van Trotsenburg,3,* Yu Sun,4 Monique Losekoot,1 Daniel J. Bernard,3 Nienke R. Biermasz,3 Wilma Oostdijk1 and Jan M. Wit1,*

1Department of Pediatrics; Leiden University Medical Center; Leiden, The Netherlands; 2Department of Endocrinology and Metabolic Disorders; Leiden University Medical Center; Leiden, The Netherlands; 3Department of Pediatric Endocrinology; Emma Children’s Hospital; Academic Medical Center; University of Amsterdam; Amsterdam, The Netherlands; 4Center for Human and Clinical Genetics; Leiden University Medical Center; Leiden, The Netherlands; 5Department of Pharmacology and Therapeutics; McGill University; Montreal, QC Canada

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Abbreviations: BMI, body mass index; CH-C, congenital central hypothyroidism; CNS, central nervous system; FSH, follicle-stimulating hormone; FT4, free T4; GH, growth hormone; Ig, immunoglobulin; IgSF, immunoglobulin superfamily; IGSF1, immunoglobulin superfamily member 1; LH, luteinizing hormone; (N)CAM, (neural) cell adhesion molecules; NK cells, natural killer cells; TBG, thyroxine-binding globulin; TRH, thyrotropin-releasing hormone; TRHR, thyrotropin-releasing hormone receptor; TSH, thyroid-stimulating hormone

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*Correspondence to: Sjoerd D. Joustra; Email: S.D.Joustra@lumc.nl; A.S. Paul van Trotsenburg; Email: A.S.VanTrotsenburg@amc.uva.nl; Jan M. Wit; Email: J.M.Wit@lumc.nl

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As reported previously,1 IGSF1 encodes a plasma membrane immunoglobulin superfamily glycoprotein.2,3 The canonical IGSF1 protein possesses 12 immunoglobulin (Ig)-like loops of the C2 (constant region type 2) type, a transmembrane domain and a short intracellular C-tail. A hydrophobic linker, separating Ig-like loops 5 and 6, targets the protein for obligate co-translational proteolysis such that only the C-terminal domain traffics to the

**Introduction**

Recently, a large international and multidisciplinary consortium, headed by investigators from the Netherlands (Leiden and Amsterdam), Canada (Montreal) and the United Kingdom (Cambridge and London), reported on a novel X-linked syndrome caused by loss-of-function mutations or deletions in IGSF1 (OMIM #300888).1 The main characteristics of this syndrome, which we propose to call “IGSF1 deficiency syndrome,” are congenital hypothyroidism of central origin (CH-C) and macroorchidism. However, in a variable proportion of the affected male individuals several other features were observed, including prolactin deficiency (18/26), partial and transient growth hormone deficiency (4/26), disharmonious pubertal development (normal timing of testicular growth, but with a delayed rise of serum testosterone) and overweight. In this addendum, we wish to highlight several clinical and laboratory features of patients with this novel syndrome and speculate about the pathophysiology.

**Immunoglobulin Superfamily Member 1 (IGSF1)**

A recently uncovered X-linked syndrome, caused by loss-of-function of IGSF1, is characterized by congenital central hypothyroidism and macroorchidism, variable prolactin deficiency, occasional growth hormone deficiency, delayed pubertal testosterone secretion and obesity. We propose to call this endocrinopathy “IGSF1 deficiency syndrome.” Based on an estimated incidence of isolated congenital central hypothyroidism of 1:65,000, we predict that the incidence of IGSF1 deficiency related hypothyroidism is approximately 1:100,000. IGSF1 encodes a plasma membrane immunoglobulin superfamily glycoprotein that is highly expressed in pituitary and testis, but is of unknown function. The variable profile of pituitary dysfunction suggests that IGSF1 may play a role in pituitary paracrine regulation. The clinical significance of the syndrome, particularly the clinical consequences of untreated hypothyroidism, justifies screening family members of patients with IGSF1 mutations for carriership and to study potential carriers of IGSF1 mutations, including patients with idiopathic central hypothyroidism, combined GH and TSH deficiency, macroorchidism or delayed puberty.

**Immunoglobulin Superfamily Member 1 (IGSF1)**

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plasma membrane. ICAM and its mouse homolog Igsf1 mRNA is abundantly expressed in Rathke’s pouch (the developing pituitary primordium) and in adult pituitary gland and testis (for a review, see ref. 1). IGSF1 protein is detected in mouse pituitary thyrotropes, somatotropes and lactotropes, but not in gonadotropes or in testis.

IGSF1 was initially hypothesized to function as a pituitary inhibin co-receptor and named inhibin binding protein or p11.P However, IGSF1’s putative role as an inhibin co-receptor has been challenged by more recent binding and in vivo data. ICAM’s function in normal physiology has remained undefined.

Immunoglobulin domains are commonly found in eukaryotic proteins (e.g., in 765, 142 and 80 human, fly and roundworm proteins, respectively). Most members of the immunoglobulin superfamily (IgSF) are cell adhesion molecules (CAMs) and regulate signaling by cell surface receptors through modification of target recognition, differentiation and specialization of membrane microdomains and initiation and organization of signaling platforms. They can bind other IgSF members (homophilically or heterophilically) as well as other molecules.

The disproportionate increase in numbers of IgSF members from invertebrates to vertebrates parallels the evolution of the adaptive immune system. Indeed, many members (e.g., CD226, CD96) perform important functions on various immune cells, including recognition of molecules on cell surfaces or extracellular matrix. These immune cells include naïve T cells, cytotoxic T cells, NK cells, NK T cells, monocytes, dendritic cells and mast cells, as well as platelets and megakaryocytes.

Other IgSF members (e.g., the neural cell adhesion molecule (NCAM) and L1 subfamilies) are involved in the development of the central nervous system (CNS), facilitating neural cell migration, axon guidance and synapse formation. In adult life, they maintain synaptic connections, cell-cell contacts, neuronal-glial interactions and synaptic plasticity. Dysfunction of NCAM and L1 has been linked to schizophrenia, bipolar disorder, depression, anxiety, Alzheimer disease and autism. NCAM also plays an important role in neurogenesis in CNS trauma and degenerative diseases. An appreciation of the diverse actions of IgSF members in these and other cells or tissues may facilitate the dissection of IGSF1’s normal physiological function(s).

Incidence of IGSF1 Deficiency Syndrome

Why was IGSF1 deficiency syndrome only recently discovered? The most likely explanation is that the signature abnormality, CH-C, is only rarely detected, because most neonatal screening programs for congenital hypothyroidism are TSH based. The Netherlands is one of the few countries where screening consists of a stepwise approach starting with the measurement of blood thyroxine (T4), followed by the measurement of TSH and TBG, and in all affected eight Dutch families the index case was diagnosed through abnormal T4 levels in the neonatal screening program. In these cases, the levels of blood T4 and free T4 (FT4) were usually not far below the lower limit of the reference range for age, and most of the infants did not show clinical signs of hypothyroidism. In combination with the observation that other affected males in these families presented with a similar decrease in serum FT4 concentrations, this would suggest that the degree of hypothyroidism is rather mild (in most cases), so that it would escape detection on the basis of clinical features.

The Dutch screening program, using the T4+TSH+TBG approach, reported an CH-C incidence of 1:16,404. This represented 13.5% of the total number of patients with permanent CH, as detected by neonatal screening, and is greater than the incidence observed in the USA (1:55,656). In the Netherlands, three fourths of these children turned out to have multiple pituitary hormone deficiencies, suggesting that the incidence of isolated CH-C is likely close to 1:65,000. In our analysis, in 8 out of 11 index cases (male infants) with isolated CH-C an Igsf1 defect was detected (unpublished). Based on these considerations, we speculate that the incidence of IGSF1 related CH-C is approximately 1:100,000. The two previously known causes of inherited isolated CH-C (autosomal recessive mutations in the TRH receptor (TRHR) or TSH β subunit (TSHB)) are very rare and were found in none of the Dutch children with CH-C (Van Trotsenburg, personal communication).

The adult male carriers of IGSF1 mutations, who were found by follow up familial studies, had CH and macroorchidism, but did not display clinical features of hypothyroidism. In fact, most functioned well and several had university education and high paying jobs.

Pituitary Function in IGSF1 Deficiency

The combination of CH-C, variable hypoprolactinemia and occasional transient partial growth hormone (GH) deficiency strongly suggests that IGSF1 deficiency causes a special form of pituitary dysfunction. A role for IGSF1 in the pituitary is also suggested by its robust expression in the developing and adult gland. Furthermore, the profile of deficiencies suggests that IGSF1 plays a role in TRH signaling in thyrotropes, lactotrophs and somatotrophs, which is supported both by the expression of the protein in each of these lineages and by the downregulation of the Trhr in pituitaries of Igsf1-deficient mice. This however does not explain the dis harmoniously delayed puberal development in our patients (discussed below). We presently hypothesize that IGSF1 may play a role in paracrine communication within the pituitary (for a review on pituitary paracrinicity see ref. 16).

In the patients with IGSF1 deficiency syndrome that we have investigated thus far, prolactin deficiency was always associated with CH-C, a similar combination as observed in patients with mutations of the TRH receptor (TRHR). Prolactin deficiency can also be part of multiple pituitary hormone deficiency, for example in patients with Pouif1, Prop1, Hesx1 or Lhx3 mutations (for a review, see ref. 18). It is generally assumed that prolactin deficiency in males is not associated with a clinical phenotype, but this hypothesis requires empirical validation. The hypothalamo-pituitary-adrenal axis appears to be intact in this syndrome, although some patients showed a delayed adrenarche (unpublished).
Pubertal Development

Based on longitudinal observations in various patients, testicular size in infancy appears normal, though usually in the upper half of the reference range (2 ml according to the Prader orchidometer). Pubertal testicular growth starts at a normal age, but volumes exceed the reference range from late adolescence onward (> 30 ml according to the Prader orchidometer, > 18 ml on ultrasound).19 Very high testicular volumes in two males of approximately 50 y (close to 50 ml by ultrasound) suggest that there may be further testicular growth from young to late adulthood. Ifs1-deficient mice show a normal testicular weight normalized to body weight; however, their unadjusted testicular weight is increased. Interestingly, in a recent case report on a male with an IGSF1 mutation the clinical phenotype did not include macroorchidism, in contrast to all evaluable patients in our cohort.20 The cause to this discrepancy is not clear, but could relate to differences in ethnicity.21

In contrast to the normal timing of testicular growth, testosterone secretion (and thus also pubic hair development) starts late in IGSF1-deficient males and in one case remained low up to the age of 15 y old. Thus, growth in adolescence resembles the pattern in boys with constitutional delay of growth and puberty, with growth retardation in early adolescence and a late pubertal growth spurt. However, at the end of the growth spurt, plasma testosterone is in the normal range.

Sertoli cell number and size, and thereby the size of the seminiferous tubules and amount of sperm production, determine the adult testis size. Therefore, increased Sertoli cell proliferation, for instance by dysfunction of the FMR1 gene in fragile X mental retardation syndrome (OMIM #300624), causes macroorchidism.22 Other examples of X-linked congenital syndromes associated with macroorchidism are the Shashi XLMR syndrome (OMIM #300238) and Clark Baraitser syndrome (OMIM 300602).24 FSH increases the rate of Sertoli cell proliferation and neonatal experimental suppression or stimulation of FSH in rats influences adult Sertoli cell number by a reduction of 40% or increase of 18–49%, respectively.25 In IGSF1 deficiency syndrome, serum FSH was always higher than serum LH (though both were within the reference range),1 possibly due to increased release of TRH or increased sensitivity of gonadotropes to TRH, which has been shown to increase FSH and not LH in a GnRH-independent fashion.26 In this event, the testicular phenotype may result from pituitary dysfunction. The hypoprolactinemia that is part of the IGSF1 deficiency syndrome, has to our knowledge never been associated with macroorchidism, although cases of hyperprolactinemia and macroorchidism have been reported.27

Another explanation might be sought in the effect of thyroid hormone on adult testis size, which is thought to have an even larger influence than FSH.25 Thyroid hormone (particularly T3) shortens the period of Sertoli cell proliferation and thereby influences the timing of maturation of Sertoli cells. Induction of neonatal hyper- or hypothyroidism in rats influences the final number of Sertoli cells in rats by a reduction of 50% or increase of 82–157%, respectively.23 In addition, a delay in pubertal testosterone rise but normal start of testicular enlargement (and even macroorchidism) has been described in patients with hypothyroidism diagnosed in late prepubertal years (usually due to Hashimoto’s disease),25 possibly by dysfunction of a T3-dependent increase in LH receptors on Leydig cells and a consequent failure of the LH-induced secretion of testosterone. Usually, treatment of CH-C started immediately after diagnosis at neonatal screening prevents this delay in testosterone production.26 However, IGSF1 (as well as TRH and TRHR25) is expressed in the testis; therefore, its local loss of function could alter normal testicular development and/or modify the local action of (thyroid) hormones on testicular cells.

The delay of testosterone action might also primarily affect Sertoli cell maturation in IGSF1 deficiency syndrome, since patients with androgen insensitivity syndrome show features of Sertoli cells immaturity.25 In addition, non-hormonal factors (e.g., numerous growth factors) are presumed to play a physiological role in the proliferation or function of Sertoli cells, indicating that dysfunction of cell-contact, a common function of IgSF members, may play a role in the cessation of proliferation of Sertoli cells.29

Lastly, absence of (the influence of) germ cells has been proposed to delay the formation of inter-Sertoli cell tight junctions, change their secretory function or de-differentiate Sertoli cells.29 Interestingly, IGSF4 influences adhesion of spermatogenic cells to Sertoli cells,30 and IgSF-member NCAM is expressed on immature Sertoli cells and has been proposed to influence gonocyte adhesion during intratubular migration to basement membrane.31 Although we have no data on sperm quality in IGSF1 deficiency syndrome, the pedigrees show that fertility is not affected. This is true for Ifs1-deficient mice as well.7 However, communication between germ cells and Sertoli cells might still be compromised, possibly affecting Sertoli cell function. Awaiting laboratory data on Ifs1-deficient mice, we can only speculate on Sertoli cell function in IGSF1 deficiency syndrome. So far, however, there are no biochemical clues indicating profound Sertoli cell dysfunction in patients, since we found normal serum concentrations of inhibin B (though usually in the upper half of the reference range) and anti-mullerian hormone levels (though mostly low or in the lower half of the reference range).1

Obesity

Body mass index and fat percentage are elevated in most male carriers of IGSF1 mutations. This is not only observed in hypothyroid adults detected through family studies, who had not been substituted with thyroxine, but also in individuals treated with thyroxine since early infancy. Therefore it appears unlikely that hypothyroidism per se causes the obesity. Interestingly, serum lipoproteins are generally normal (Joustra et al., in preparation). At present, we have no explanation for the elevated adiposity in these patients. It is noteworthy, however, that body weight is also elevated in Ifs1-deficient mice.1

Genotype-Phenotype Correlation

In the 11 families we described,1 we identified 8 distinct mutations and 2 deletions
in IGSF1. The mutations included submicroscopic in-frame deletions, single-nucleotide deletions, nonsense mutations, missense mutations and a single-nucleotide duplication. Examining expression and post-translational regulation of IGSF1 mutants in heterologous HEK293 cells, we showed that the identified mutations block or substantially impair IGSF1 C-terminal domain plasma membrane trafficking.\(^1\) So, all mutations in these 11 families appear to cause a loss of protein function. To date, we have not observed any clear genotype-phenotype correlation. Indeed, it is notable that even within families, there were important differences in clinical features, also in the degree of hypothyroidism.

Besides these pathogenic mutations, we have found a large number of IGSF1 variants without apparent functional clinical consequences (Sun and Losekoot, personal communication). It cannot be excluded, however, that missense variants that traffic normally to the plasma membrane may otherwise change protein functionality (e.g., by modifying protein-protein interactions). It is also conceivable that there may be activating mutations of IGSF1, but these have not yet been described.

**Indications for Genetic Testing for IGSF1**

The clinical significance of the syndrome, particularly the possible consequences of untreated hypothyroidism or growth hormone deficiency, justifies the screening of family members of patients with IGSF1 mutations for carriership and to study patients with unexplained central hypothyroidism, combined GH and TSH deficiency, macroorchidism or delayed puberty for the presence of IGSF1 mutations. We expect that screening more patients will extend the phenotype beyond what we have learned from the 26 patients we recently described.\(^1\) A particularly interesting group consists of patients with GH deficiency in whom overt CH develops after GH treatment. In fact, after our publication, we found a case with this phenotype (unpublished). Furthermore, the syndrome is not limited to males. In approximately 25% of female heterozygous carriers of IGSF1 mutations, we observed central hypothyroidism of similar degree as found in hemizygous male carriers.\(^1\)

**Conclusion**

The IGSF1 deficiency syndrome is a novel and fascinating clinical syndrome involving multiple endocrine systems. Unraveling the physiologic role of IGSF1 in the pituitary and testis, and possibly other tissues, may uncover so far unexplored regulatory mechanisms, which may have implications for the understanding of other human disorders.

**Disclosure of Potential Conflicts of Interest**

No potential conflict of interest was disclosed.

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