Screening of IGSF1 in Dutch patients with Central Hypothyroidism and GH deficiency

Meliza Elizabeth\(^1\), Anita C.S. Hokken-Koelega\(^1,3\), Theo J. Visser\(^2\), Robin P Peeters\(^2\), Laura C.G. de Graaff\(^1,2\)

1Dutch Growth Research Foundation, The Netherlands; 2Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands. 3Pediatrics, Subdiv. Endocrinology, Erasmus University, Rotterdam, The Netherlands

l.degraaff@erasmusmc.nl

**INTRODUCTION**

The immunoglobulin superfamily member 1 (IGSF1) gene encodes a plasma membrane glycoprotein mainly expressed in pituitary and testes. Mutations in the extracellular region of IGSF1 have recently been associated with central hypothyroidism (Fig. 1, in black).

Initially, IGSF1-mutations were only described in patients with central hypothyroidism combined with macro-orchidism.

Later on, IGSF1 mutations were also reported in patients without macro-orchidism, who had central hypothyroidism combined with other pituitary hormone deficiencies.

Therefore, we chose to study IGSF1 as a new candidate gene for patients with the combination of central hypothyroidism and growth hormone deficiency.

**METHODS**

We screened 80 male patients with the combination of central hypothyroidism and growth hormone deficiency for genetic defects in exons 10 to 17, encoding the extracellular region of IGSF1.

**RESULTS**

We found one known mutation, one known deletion and four known SNPs in the extracellular regions of IGSF1 (Fig. 2, in red).

The deletion (p.Ala713_Lys721del) and the mutation (p.Cys947Arg) were present in male patients with central hypothyroidism, GH deficiency and macro-orchidism, formerly described by Sun Y. et al\(^1\).

Interestingly, the minor allele of rs4830219 was associated with a more severe growth hormone deficiency. Patients carrying the minor allele had lower GH peak levels during arginine test (mean 3.1 vs. 8.4 mU/L, p = 0.005) and clonidine test (mean 3.1 vs. 6.9 mU/L, p = 0.05) and lower IGF-I SDS (mean -3.3 vs. -5.3, p = 0.019). Thyroid hormone levels and Inhibin B levels did not differ between the groups.

Although until recently, synonymous changes were thought to have no effect on the protein, several studies have shown that synonymous nucleotide changes can affect protein folding and function or affect splicing of precursor mRNAs\(^2\). Further studies are needed to confirm and clarify the functional impact of rs4830219.

---

1 Sun Y. et al., Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement Nat Genet 2012, 44:1375-1381