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

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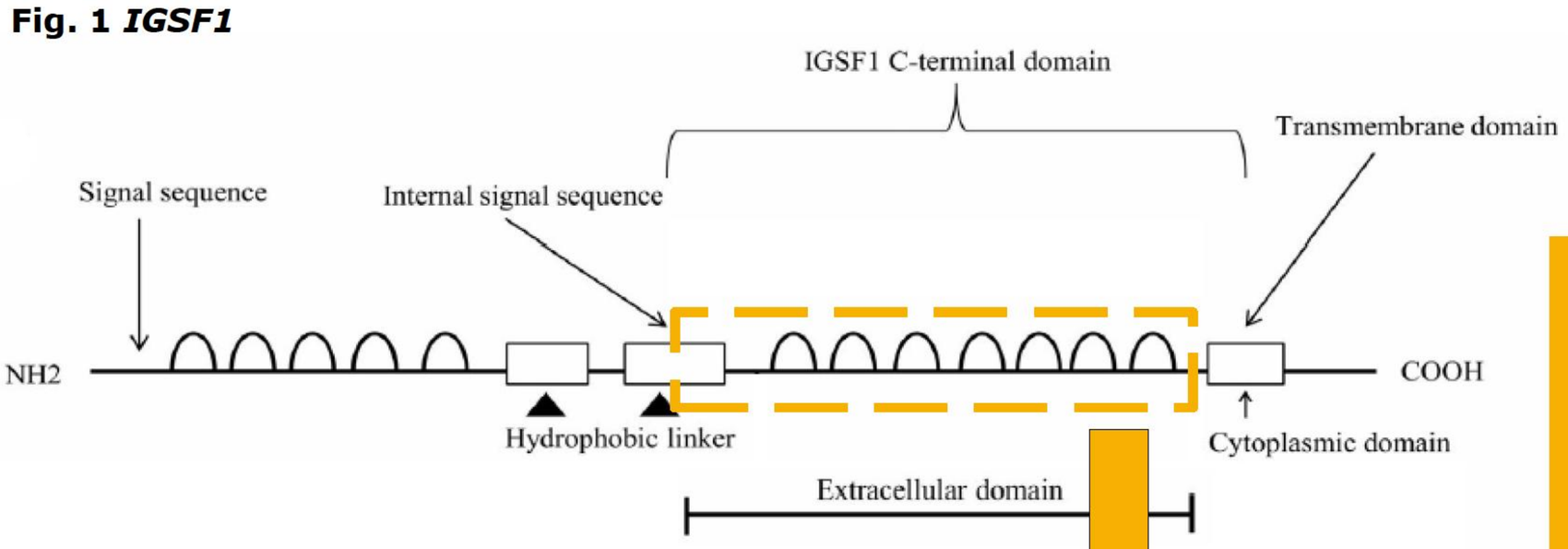
Fig. 1 *IGSF1*



CONCLUSION:
The combination of central hypothyroidism and growth hormone deficiency is explained by *IGSF1* defects in only a small minority of the patients

HYPOPIT STUDY

The Dutch HYPOthalamic and PITuitary gene (HYPOPIT) study investigates the causes of Isolated Growth Hormone Deficiency (IGHD) and Combined Pituitary Hormone Deficiency (CPHD).

Former projects within the HYPOPIT study showed that only a small minority of the Dutch IGHD and CPHD cases could be explained by mutations in *GH1, GHRHR, HMGA2* and *CDK6* (in IGHD) and *PROP1, HESX1, POU1F1, LHX3, LHX4, OTX2, SHH* and *HHIP* (in CPHD).

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.2, in black).

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

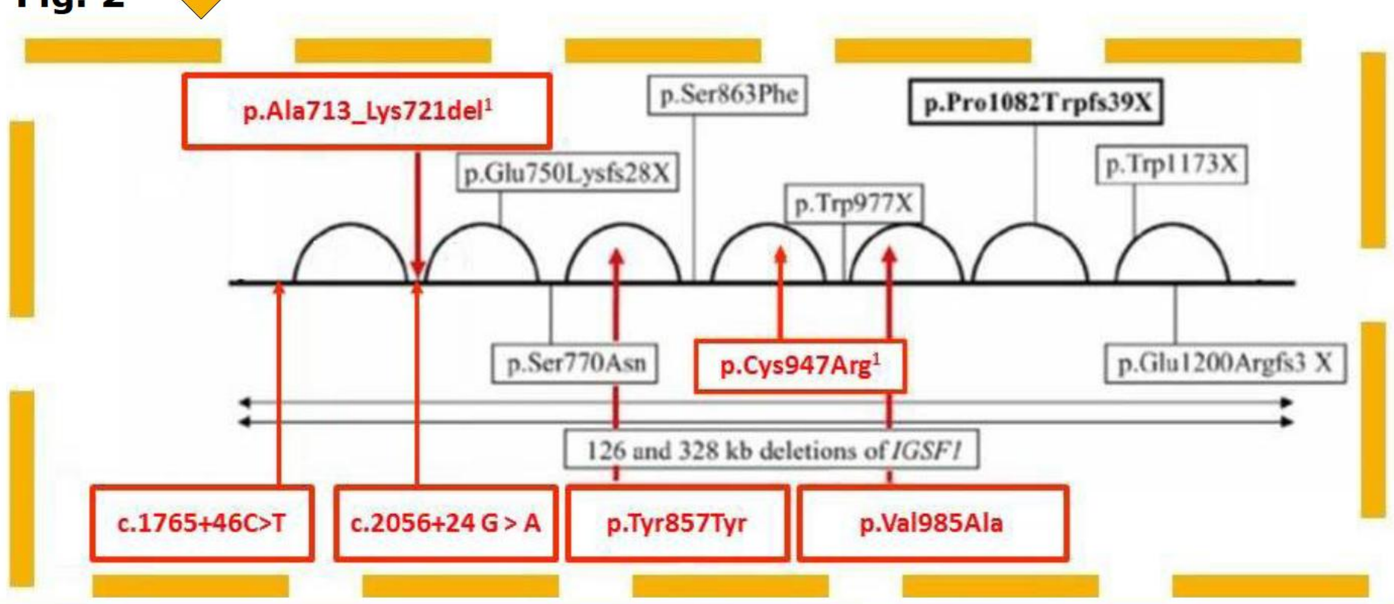
Later on, *IGSF1* mutations were also reported in patients without macro-orchidism, who had central hypothyroidism combined with other pituitary hormone deficiencies.

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.

Fig. 2



Variant	Count	Impact	Position	Reference
c.1765+46 C > T	1/80	Intronic	Intron 11-12	rs188854607
c.2056+24 G > A	4/80	Intronic	Intron 12-13	rs3810725
c.2137_2163del (p.Ala713_Lys721del)	1/80	27nt del	Exon 13	Sun Y. et al., (2012)
c.2571 T > C (p.Tyr857Tyr)	27/80	Silent	Exon 14	rs4830219
c.2839 T > C (p.Cys947Arg)	1/80	Missense	Exon 15	Sun Y. et al., (2012)
c.2954 T > C (p.Val985Ala)	2/80	Missense	Exon 16	rs147496468

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_Lys721 del) 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 , Loss-of-function mutations in IGSF1 cause an X-linked syndrome of central hypothyroidism and testicular enlargement Nat Genet 2012, 44:1375-1381)
[2]Zuben E. Sauna and Chava Kimchi-Sarfaty. Understanding the contribution of synonymous mutations to human disease. Nature Reviews Genetics 2011, 12: 683-691)

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