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Identification of novel recessive *IGFALS* mutations and *INSR* variant in an obese Korean boy

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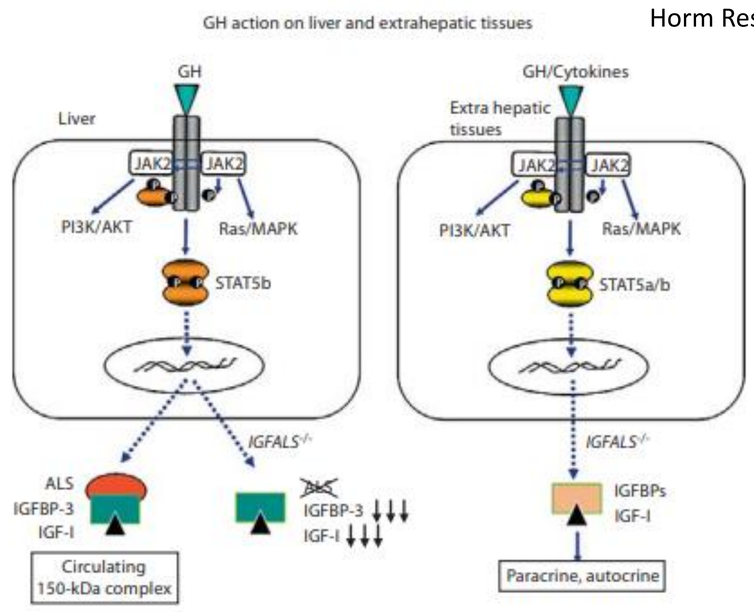
INTRODUCTION

- *IGFALS* gene is located in chromosome 16p13.3 encoding acid labile subunit which binds insulin like growth factors (IGFs) to increase their half-life and vascular localization.
- Biallelic defect of this gene leads to acid labile subunit deficiency (MIM#615961) characterized by postnatal growth retardation, insulin resistance, delayed puberty and no growth hormone deficiency.
- 21 cases have been reported in the literature so far, and all of the mutations occurred in exon 2 of *IGFALS*.
- Insulin-resistant diabetes mellitus with acanthosis nigricans (MIM#610549) can be caused by heterozygous, homozygous, or compound heterozygous mutation in the *INSR* gene (location: 19p13.2).
- Mutation of *INSR* impairs tyrosine kinase activity and the presence of mutant receptors appeared to have negative effects on the activity of the normal receptor.



METHOD & RESULT

Patient: An 5-year-old boy was presented with obesity and growth retardation. He was born to unrelated parents at 36 weeks and 6 days of gestational age with birth weight of 2.04kg through cesarean section, and had no specific perinatal history. The intrauterine growth retardation was identified during 2nd trimester.

Clinical findings: He showed rapid weight gain for 2 years. His height, weight, and body mass index was 104.7 cm (-1.3 SDS), 29.7 kg (2.9 SDS), and 27.1 kg/m^2 (3.2 SDS). The midparental height was 170.5 cm (-0.5 SDS). He had acanthosis nigricans on neck, axillary, and inguinal area. He had severe obesity, obstructive severe sleep apnea, and heavy snoring and picking habitus was observed.

Laboratory finding & Molecular analysis result

The methylation test for 15q11-12 was done for distinguishing of Prader-Willi syndrome and the result revealed normal. The laboratory finding showed very low level of Insulin growth like factor(IGF)-1 and IGF binding globulin 3(IGFBP3). The cortisol level at 8 AM was also low (3.90 ug/dL) and morning fasting insulin and glucose level was 91.49 uIU/mL and 99 mg/dL. The homeostasis model assessment of insulin resistance (HOMA-IR) was 22.4. The bone age was delayed for chronological age. Pituitary hormone deficiency was suspected but the result of anterior pituitary function test was normal. The targeted exome sequencing was done for growth hormone resistance syndrome in this subject. The result revealed novel biallelic mutations, c.680C>A (p.Ala227Glu) and c.1897C>T (p.Arg633Trp), in *IGFALS* gene. Each mutation was inherited from mother and father, respectively. Additionaly, c.1517G>A (p.Arg506Gln) in *INSR* was identified. This variant has not reported in gnomAD (http://gnomad.broadinstitute.org/) and the minor allele frequency in Asian was 0.0008%. This novel variant is predicted to be deleterious by SIFT (http://sift.jcvi.org/), PROVEAN (http://provean.jcvi.org/) and MutationTaster (http://www.mutationtaster.org/), respectively. *INSR* variant was inherited from mother. She also showed insulin resistance (Table 1).

Intervention

Tonsilloadenoidectomy was performed for severe sleep apnea. After surgery, the recombinant human growth hormone therapy was started and the increasing height velocity and IGF-1 level was observed despite of short term treatment (Table 2).

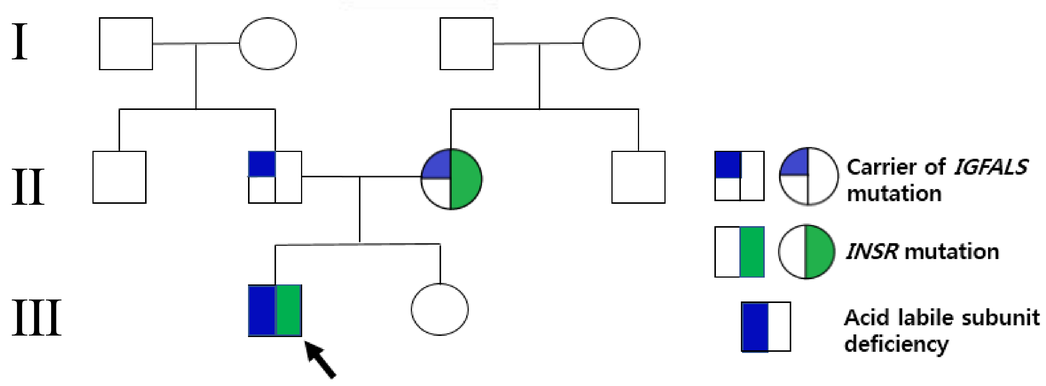


Figure 1. Pedigree and molecular analysis results of subject with acid labile subunit deficiency and insulin resistance.

Table 1. endocrine profile and genetic result of subject and his parents

	Proband	Mother	Father
IGF-1 (ng/mL)	4.55 (-2.5 SD)	183.4 (-0.7 SD)	44.6 (-4.4 SD)
IGFBP3 (ng/mL)	<500	3050	2340
HOMA-IR	22.4	4.42	5.9
Hb A1c (%)	5.4	5.0	5.6
Body Mass Index (kg/m^2)	27.1	24.7	27.9
IGFALS, c.680C>A (p.Ala227Glu) (exon2)	+	+	
IGFALS, c.1897C>T (p.Arg633Trp) (exon 2)	+		+
INSR, c.1517G>A (p.Arg506Gln) (exon 7)	+	+	

Table 2. Clinical course according to growth hormone therapy

	At start of GHT	1 mo after GHT	3 mo after GHT
IGF-1 (ng/mL)	6.7	37.53	60.72
IGFBP3 (ng/mL)	<500	<500	<500
Insulin* (uIU/mL)	126	11.1	76.6
glucose* (mg/dL)	110	88	99
Height (cm)	106	107.7	109
Weight (kg)	29.7	31.5	31.5
BMI (kg/m^2)	27.1	27.1	26.5

*fasting, GHT; growth hormone therapy.

CONCLUSION

- Here in, we report a Korean boy with novel compound mutations of *IGFALS* and likely pathogenic variant of *INSR* presenting with growth retardation, acanthosis nigricans and severe obesity.
- Long-term effect of IGFs dysfunction on glucose metabolism, growth, puberty and obesity in this subject should carefully be follow-up and we will assess the effectiveness of growth hormone.

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