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JENNY LIND CHILDREN'S HOSPITAL

A novel mutation of *IGSF1* gene

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To provide every patient with the care we want for those we love the most

INTRODUCTION

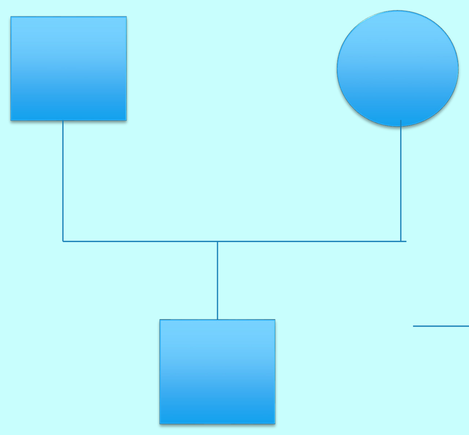
Mutations in *IGSF1* result in X-linked congenital central hypothyroidism, macroorchidism and a variable spectrum of anterior pituitary dysfunction, most commonly including hypoprolactinaemia. We identified a novel hemizygous *IGSF1* mutation (c.3191T>C, p.L1064P) in a 17 year-old adolescent, inherited from his heterozygous mother.

CASE

A 17 year-old male adolescent presented with long standing history of obesity, learning difficulties, macroorchidism, hypoprolactenemia and evidence of central hypothyroidism fT4 8pmol/L (8-21pmol/L), TSH 1.8 mU/L (0.35-3.5 mU/L). A novel hemizygous *IGSF1* mutation (c.3191T>C, p.L1064P) was identified by direct sequencing. This variant was novel, absent from the Exac database and predicted to be probably damaging by Polyphen2. *IGSF1* deficiency is almost universally associated with macroorchidism, and he exhibited testicular enlargement (volumes ~ 35ml). Additionally, he had hypoprolactinaemia 26 mIU/L (44 - 479 mIU/L), consistent with previous reports that basal prolactin is subnormal in ~60% affected males. His mother who was euthyroid was subsequently found to be heterozygous for the same variant. His father had 16p11.2 microdeletion which the proband, who was also obese (BMI 31.6 kg/m^2) and had learning difficulties, hasn't inherited.

16p11.2 microdeletion

heterozygous for *IGSF1* mutation (c.3191T>C, p.L1064P)



A novel hemizygous *IGSF1* mutation (c.3191T>C, p.L1064P)

- Central Hypothyroidism
- Macroorchidism
- Hypoprolactinaemia
- Obesity
- Learning difficulties

CONCLUSIONS

- We described a male with central hypothyroidism, macroorchidism and hypoprolactinaemia due to a maternally-inherited novel mutation in *IGSF1* (c.3191T>C, p.L1064P).
- X-linked *IGSF1* deficiency syndrome is the commonest cause of central hypothyroidism and should be considered in all cases of central hypothyroidism of unknown cause, especially when accompanied by: X-linked inheritance pattern, Prolactin +/- Growth Hormone deficiency, macroorchidism +/- disharmonious pubertal development, delayed adrenarche and obesity.
- A low index of suspicion is required in order to diagnose central hypothyroidism with borderline fT4 levels in children with stigmata of hypothyroidism
- Babies born to heterozygous female carriers of *IGSF1* mutations should undergo a FT4 and TSH measurement at birth since TSH-based CH screening protocols will not detect central hypothyroidism.

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