A novel mutation of IGSF1 gene

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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, hypoprolactenaemia 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/m²) 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)

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.

REFERENCES
