MKRN3 mutations and Central Precocious Puberty

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Central precocious puberty (CPP) results from premature GnRH secretion due to untimely activation of the hypothalamic-pituitary-gonadal axis arising from:

1) gain-of-function mutations of the KISS1 and KISS1R genes.
2) loss-of-function mutations in the imprinted makorin RING-finger protein 3 (MKRN3) gene leading to MKRN3 protein deficiency.

**BACKGROUND**

**OBJECTIVE**

To identify loss-of-function mutations in the MKRN3 gene or gain-of-function mutations in the KISS1 and KISS1R genes and investigate genotype - phenotype correlations.

**METHODS**

Sanger sequencing was performed in a cohort of 24 girls with CPP in order to identify variations in MKRN3 and the KISS1 and KISS1R genes. Four of them reported familial history of CPP. The pathogenicity of the alterations at the protein level was verified via in silico structural modelling.

**RESULTS**

1) 2 Cypriot families were identified with the novel g.Gly312Asp
2) 1 Greek family was identified with the novel p.Glu268STOP
3) 1 Cypriot Sporadic patient was found to have the known p.M268Fs*23
4) Mutational analysis of the KISS1 and KISS1R did not identify any defect.
5) The imprinted novel MKRN3 mutations were also identified in the unaffected fathers following an imprinted mode of inheritance.
6) Age at the onset of puberty was similar among patients with MKRN3 mutations and was earlier compared to those without MKRN3 mutations.

The identification of mutations in the MKRN3 gene in children with a family history of CPP supports the role of MKRN3 in the onset of puberty and proves the fundamental task of this gene in the suppression of the hypothalamic GnRH neurons. Therefore, MKRN3 gene analysis should be considered as an additional critical tool for the diagnosis of familialCPP.