A paternally inherited familial precocious puberty caused by a novel MKRN3 frameshift variant
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1. Introduction:
- Central precocious puberty (CPP)(OMIM# 615346) results from early activation of the hypothalamic-gonadal axis.
- One third of idiopathic CPP is reported to be familial.
- Genetic mutations were initially described in kis-peptin-1 (KISS1) and the gene encoding its receptor (KISS1R).
- More recently, Abreu et al identified heterogeneous mutations in the makorin RING finger 3 (MKRN3)(OMIM#603856) gene.

OBJECTIVE: To describe a case of familial precocious puberty with a novel frameshift variant in MKRN3.

2. Case:
A 5 year old presented with breast bud development, aged 5.8 years.
- Peak luteinizing hormone (LH) and follicle stimulating hormone (FSH) were 28.3 IU/L and 12.6 IU/L respectively, confirming gonadotrophin-dependent precocious puberty (PP).
- No abnormality of pituitary/hypothalamus seen on MRI;
- Bone age was advanced by 3 years.

Her brother was assessed at 8.3 years with signs of precocious puberty:
- 8ml testicular volumes
- pubic hair
- muscular appearance
- body odour

- LHRH stimulation test was positive (peak LH and FSH were 24.0IU/L and 6.3IU/L respectively) confirming gonadotrophin-dependent PP;
- No abnormality of pituitary/hypothalamus seen on MRI.

3. Treatment:
Both were commenced on a LHRH analogue.

4. Genetic Investigations:
Exploration of family history suggested a paternal ‘parent of origin’ effect. Their father did not enter puberty early however the paternal grandmother and paternal great-aunt had menarche at 8 years:
- KISS1R analysis did not identify a mutation in either child.
- MKRN3 analysis using exome sequencing identified a heterozygous frameshift variant p.(Met297fs) (c. 890_893del) in exon 1 in both children.

5. Discussion:
- The mechanism that reactivates pulsatile gonadotrophin-releasing hormone (GnRH) secretion to initiate puberty is poorly understood.
- MKRN3 defects in sporadic CPP have been identified supporting a fundamental role for this peptide in the initiation of puberty.
- MKRN3 is a paternally expressed, imprinted gene located in the Prader-Willi critical region (chromosome 15q11-q13) and mutations represent an uncommon mode of transmission in CPP; exclusively paternal transmission is reported in only 1% of familial precocious puberty.
- Multiple loss of function mutations have been described in patients with CPP suggesting an important inhibitory effect of MKRN3 peptide on GnRH secretion.
- To our knowledge, the frameshift variant identified in the MKRN3 gene in our cases has not previously been described.
- Identification of further mutations in MKRN3 causing CPP may help to elucidate the mechanism of action of this important regulator in pubertal initiation.

OMIM Numbers: CPP2 615346, MKRN3: 603856

References: