# 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[1].
- Genetic mutations were initially described in kiss-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[2].

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

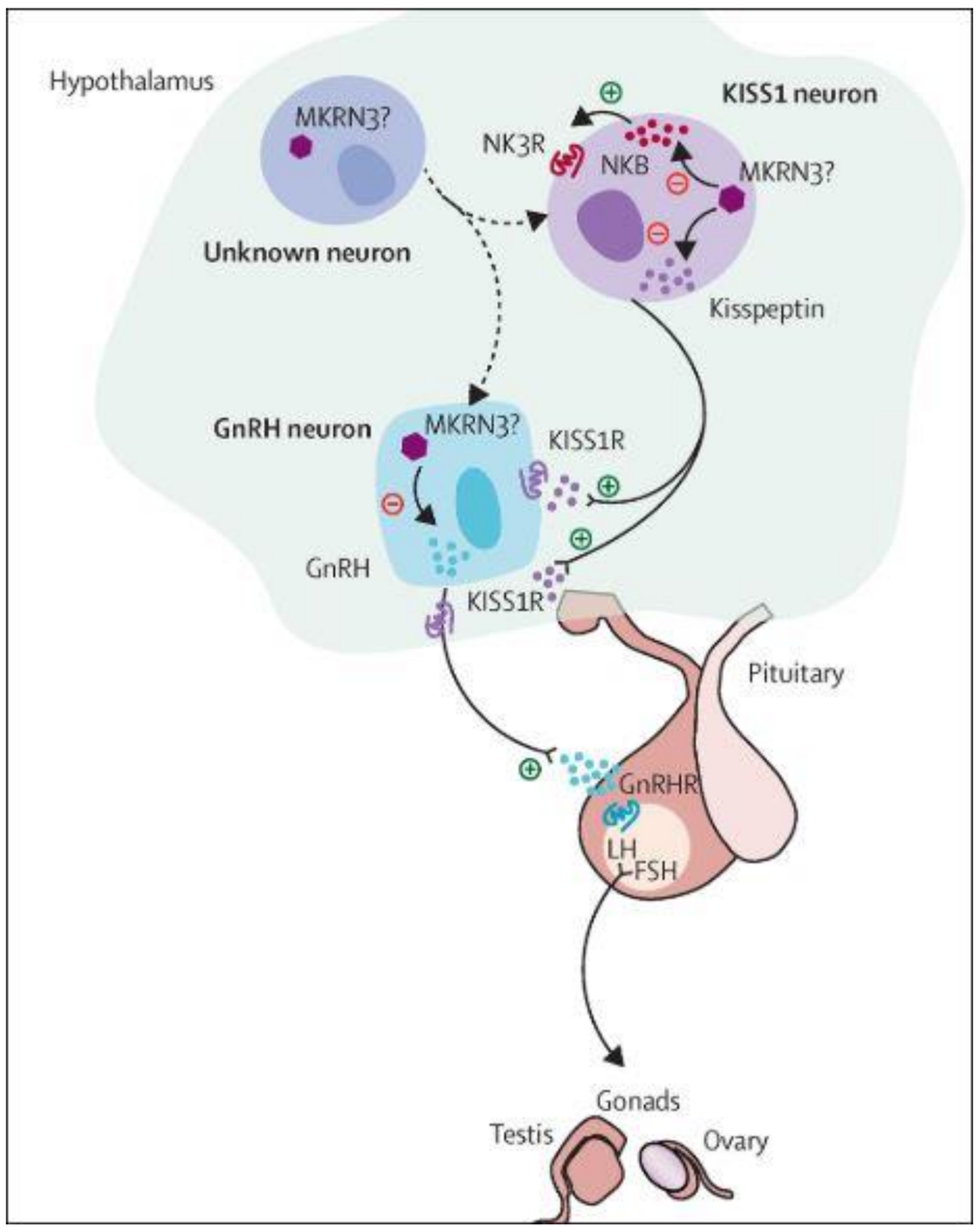


**Figure 1.** ***Mechanisms of action of the genetic factors involved in the control of puberty onset[6].*** Dashed lines represents proposed pathway.

## 2. Case:

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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.

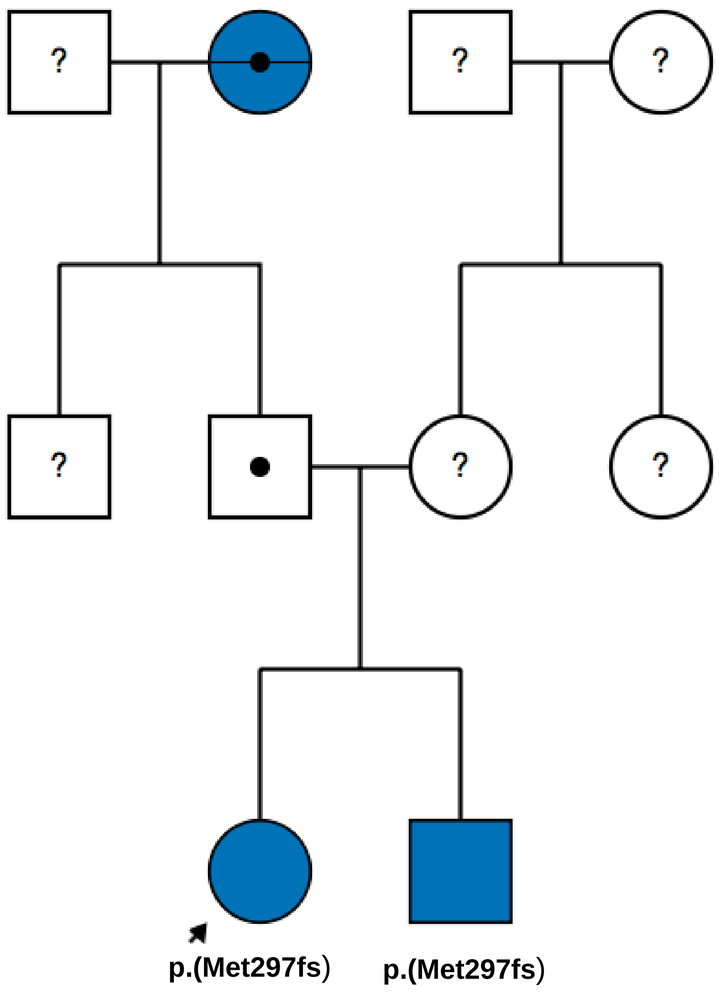


**Figure 2. Pedigree of our family:**

- Clinically affected family members,
- • Family members with genetic testing awaited,
- ? Family members whose phenotype is unknown,
- ↗ The proband.

## 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[3] 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[4].
- Multiple loss of function mutations have been described in patients with CPP[5] 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:

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