A novel MKRN3 nonsense mutation causing familial central precocious puberty

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Disclosure Statement

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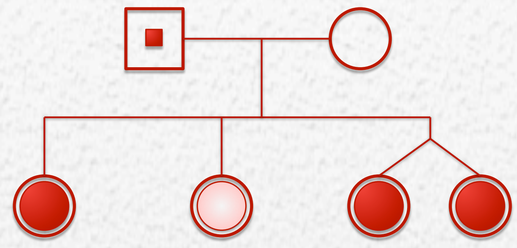
Case Report

Three out of four girls of a six-member Greek family were diagnosed with CPP. The parents were not consanguineous; mother had menarche at normal age (12.5 years), whereas father was considered as an "early developer" although without documentation.

The first girl was presented with thelarche in 2004 at the age of 6.5 years,the second girl was presented with thelarche at the age of 8.5 years, whereas the twin, non-monozygotic, younger girls exhibited precocious puberty recently with an interval of 5 months at the ages of 5.1 and 5.6 years, respectively.

In all affected girls, GnRH stimulation tests were performed by intravenous injection of GnRH at a dose of 2.5 μg/kg. Transabdominal pelvic ultrasound scans and magnetic resonance imaging (MRI) of the hypothalamic-pituitary are were performed in all three girls affected with CPP.



Age (years)	18	10	6	6
Thelarche (years)	6.5	8.5	5.6	5.1
LH peak (IU/L)	18.7	N/A	23.2	19.4
FSH peak (IU/L)	15.5	N/A	16.7	20.0
E2 (pg/ml)	22	N/A	25	5
Uterine length (cm)	4.4	N/A	4.0	4.1
Rt Ovary Vol (cm³)	2.8	N/A	2.7	2.8
Lt Ovary Vol (cm³)	2.9	N/A	2.7	2.7

Table 1. Hormonal and ultrasound data of all girls

Genomic DNA was extracted from peripheral blood leukocytes samples of all family members. The coding region of the intronless MKRN3 gene was amplified according to a cascade strategy of three overlapping fragments by PCR analysis using primers. The PCR products were analysed by Sanger sequencing using the ABI Prism Dye terminator sequencing kit and finally analysed on an ABI 3130XL apparatus.

Results

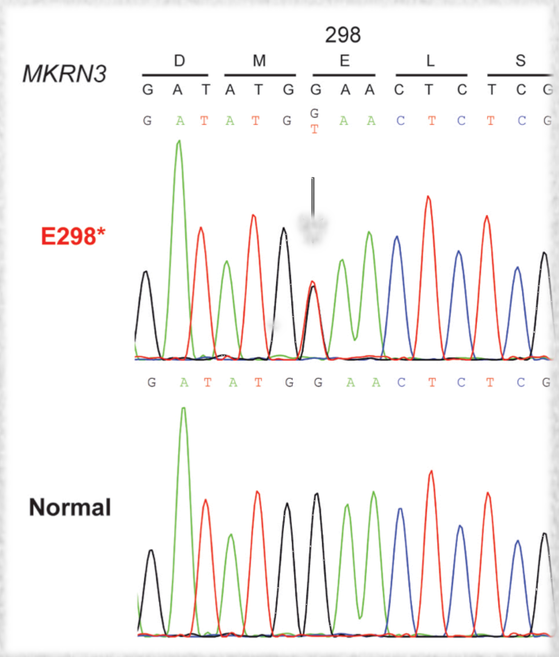


Figure 1. Sequence chromatograms of the *MKRN3* gene from a diseased and healthy genotype with the novel E298* nonsense mutation.

DNA sequencing of the four girls, three of them affected with CPP, identified the novel heterozygous nonsense p.Glu298Ter (E298*) mutation in the MKRN3 gene (Figure 1). The same mutation was identified in their father.

The novel nonsense mutation p.Glu298Ter is a premature stop codon located between zing fingers 2 and 3 (ZNF2 & ZNF3) completely removing half of the protein and two nucleotide binding regions (Figure 2).

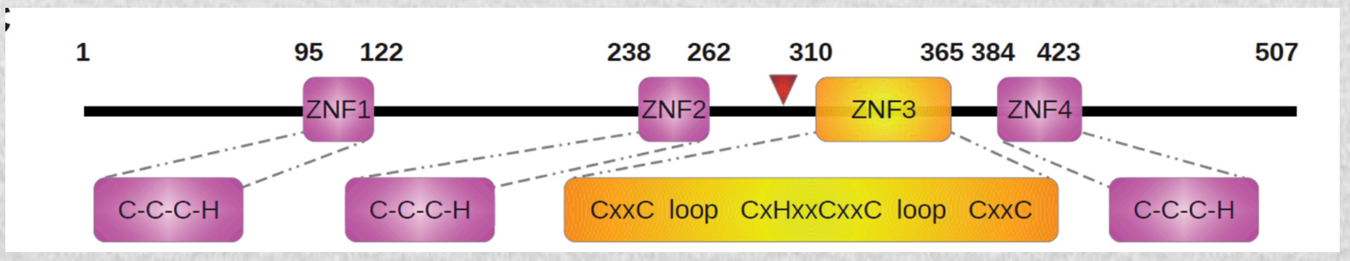


Figure 2. Domain arrangment of MKRN3 with RING-finger motifs shown below. ZNF boundaries defined from uniprot ID Q13064, magenta indicate a RING-type Zinc finger domain and orange indicate C3H1-type 1 subclass of Zinc finger domain. Red arrow indicates the site of the truncation in the E298-stop mutant.

Discussion

- 29 mutations in MKRN3 gene have been reported so far (August 2016 update – Figure 3):
  - 9 frameshift (**blue** letters)
  - 17 missense (**orange** letters)
  - 3 nonsense (**red** letters - including ours).

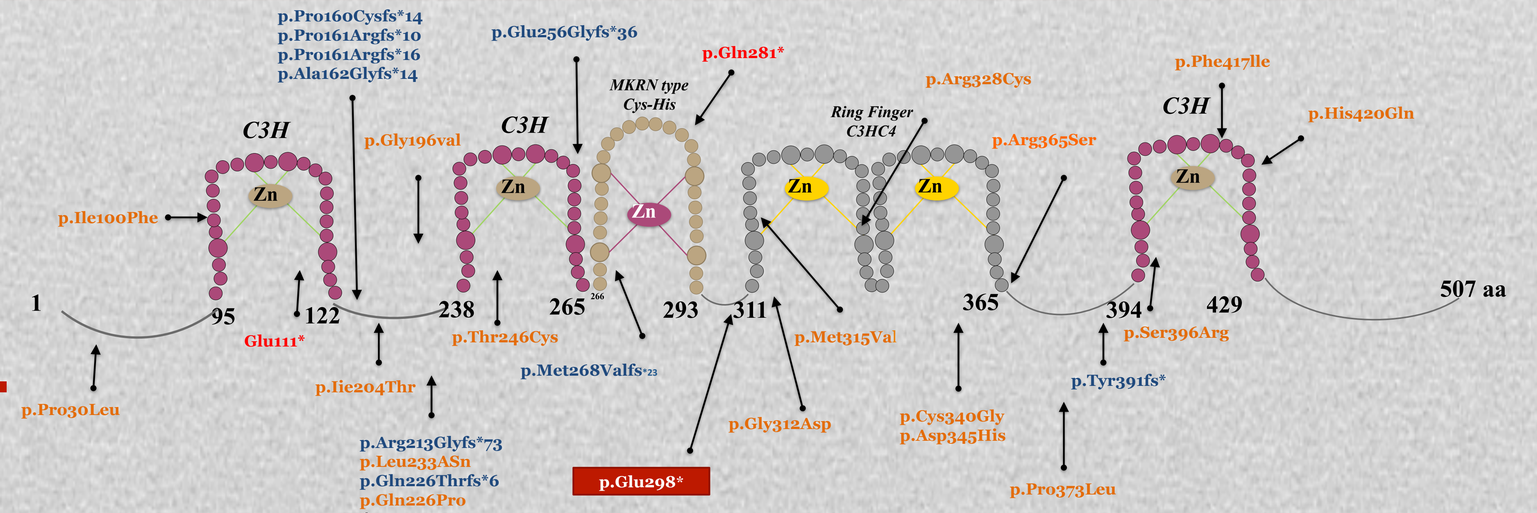


Figure 3. Overview of all reported mutations in the MKRN3 gene so far.

Conclusion

- We report a novel nonsense mutation of the MKRN3 gene in a Greek family of four sisters and their father following an imprinted mode of inheritance
- MKRN3 gene analysis should be considered as an important tool for the investigation of CPP and especially in familial cases with unaffected mothers

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