MKRN3 mutations and Central Precocious Puberty

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BACKGROUND

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.

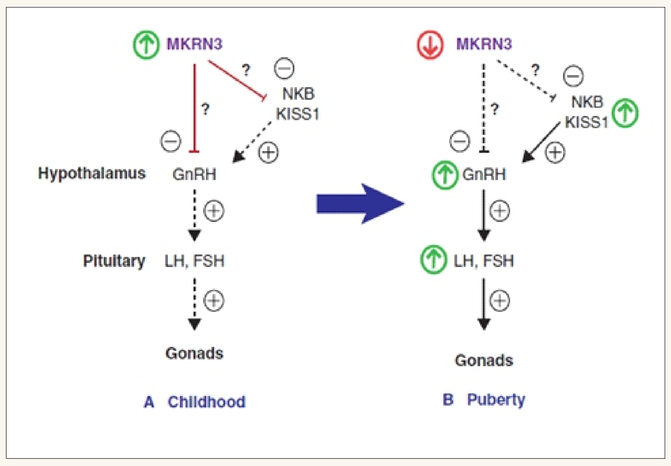
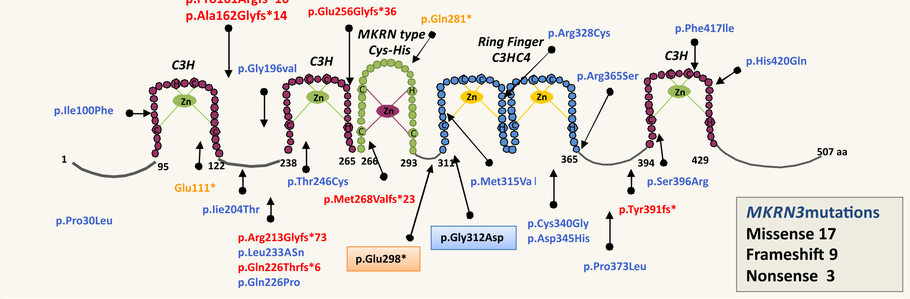


FIGURE 1. Mechanism of puberty initiation due to MKRN3 deficiency.



Abreu AP et al. 2013, N Engl Med – p.Arg213Glyfs*73, p.Tyr391fs*, p.Ala162Glyfs*14, p.Arg365Ser
Settas N et al. 2014, J Clin Endocrinol Metab – p.Cys340Gly
Macedo DB et al. 2014, J Clin Endocrinol Metab – p.Phe161Argfs10*, p.Phe161Argfs16*, p.Phe417Ile, p.Gln226Thrfs*6, p.Glu256Glyfs*36
Schreiner F et al. 2014, Horm Res Paediatr - p.Ala162Glyfs*14, p.Glu111*
de Vries L et al. 2014, Hum Reprod - p.His420Gln
Lee HS et al. 2016, Horm Res Paediatr (Epub May 2015) - p.Ile100Phe, p.Gly196Val, p.Ile204Thr, p.Gln226Pro, p.Leu233Asn, p.Ser396Arg, p.Gln281*
Neocleous V et al. 2016, Clin Endocrinol (Epub Aug 2015) – p.Gly312Asp
Kansakoski J et al. 2015, Pediatr Res (Epub Sep 2015) – p.Asp345His
Simon D et al. 2016, Eur J Endocrinol (Epub Oct 2015) – p.Pro30Leu, p.Thr246Cys, p.Met268Valfs*23, p.Met315Val, p.Arg328Cys, p.Pro373Leu
Grandone A et al. 2015, BMC Endocr Disord – p.Pro160Cysfs*14
Christophoridis et al. (manuscript in preparation) – p.Glu298*

FIGURE 2. MKRN3 reported mutations.

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.Glu298STOP
3) 1 Cypriot Sporadic patient was found to have the known p.M268Vfs*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.

Table 1 Hormonal and imaging data in the two sisters with CPP identified with the g.Gly312Asp mutation.

Proband	Age	LH basal IU/L	FSH basal IU/L	LH peak IU/L	FSH peak IU/L	Estradiol pg/ml	Bone Age	Uterine length cm	Rt ovar cm^3	Lt ovary cm^3
1	6	1.7	5.68	56.6	18.4	49.7	8 10/12	5.3	2.6	2.5
2	5.7	1.26	5.42	22.0	17.6	20.0	7 10/12	3.6	0.7	0.7

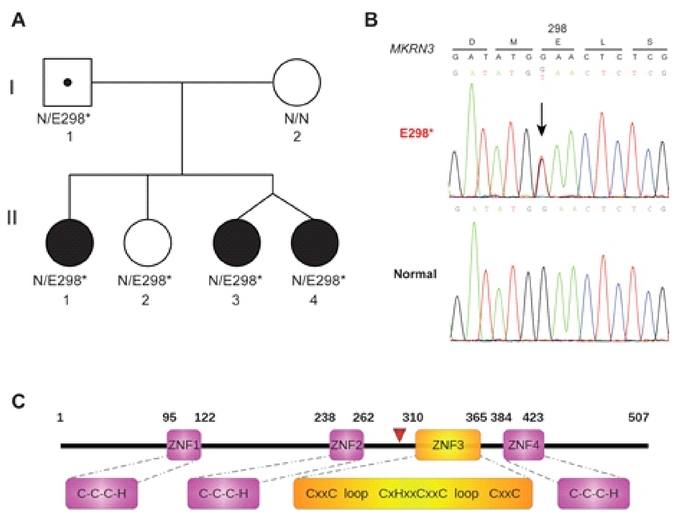


FIGURE 4. (A) Pedigree. (B) Sequence of MKRN3 of the novel E298* nonsense mutation. (C) Red arrow indicates the site of the truncation in the E298-stop mutant.

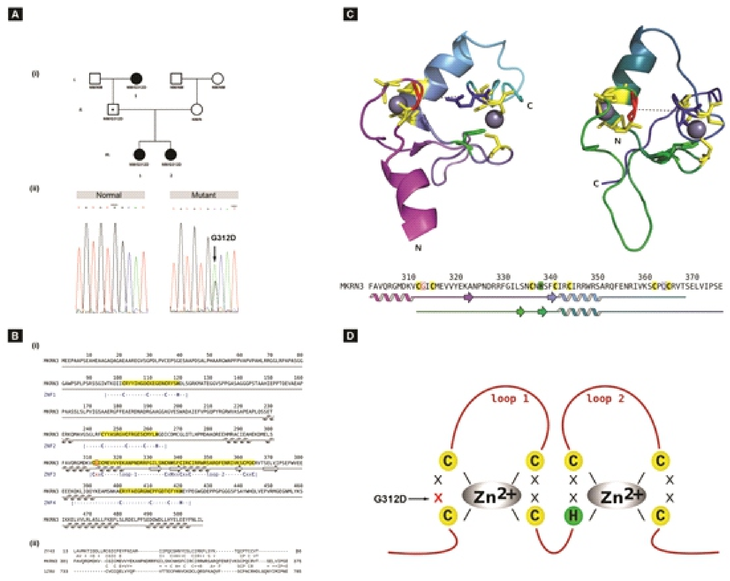


FIGURE 3. (A) Pedigree. (B) MKRN3 with the novel g.Gly312Asp. (C) Models of the MKRN3 ZNF3 domain. (D) 'cross brace' structure of the RING type Zinc finger motif. The glycine is the site of the replacement with the novel aspartic acid at position 312 is shown in red.

Table 2 Hormonal and imaging data in the four sisters identified with the p.Glu298Ter mutation.

Proband	Age	LH basal IU/L	FSH basa l IU/L	LH peak IU/L	FSH peak IU/L	Estradiol pg/ml	Bone age	Uterine length cm	Rt ovary cm^3	Lt ovary cm^3
II.1 Daughter	6.5	1.2	2.3	18.7	15.5	22	11	4.4	2.8	2.9
II.2 Daughter	8.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
II.3 Daughter	5.6	0.9	4.6	23.2	16.7	25	10	4.0	2.7	2.7
II.4 Daughter	5.1	<0.5	2.1	19.4	20.0	5	10	4.1	2.8	2.7

CONCLUSION

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 familial CPP.

Conflict of Interest: Nothing to declare