

# MKRN3 levels in girls with central precocious puberty during GnRHa treatment: a longitudinal study.

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## Background

Recently, mutations of makorin RING-finger protein 3 (*MKRN3*) have been identified in familial central precocious puberty (CPP). Serum levels of this protein decline before the pubertal onset in healthy girls and boys and are lower in patients with CPP compared to prepubertal matched pairs. The aim of our study was to investigate longitudinal changes in *MKRN3* circulating levels in patients with CPP before and during GnRHa treatment.

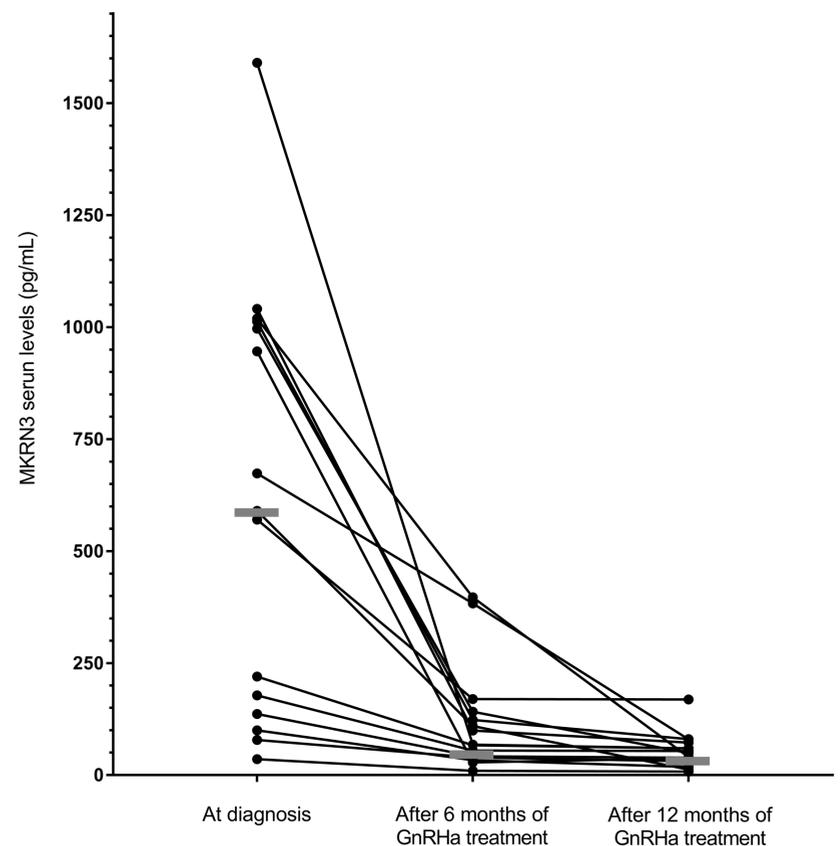
## Methods

We performed a longitudinal prospective study. We enrolled 15 patients with CPP aged 7.2 years (range: 2-8 years) with age at breast development onset <8 years and 12 control girls matched for time from puberty onset (mean age 11.8±1.2 years). Serum values of *MKRN3*, gonadotropins, (17)estradiol were evaluated before and during treatment with GnRHa (at 6 and 12 months). *MKRN3* gene was genotyped in CPP patients. Only basal levels were analyzed in control girls.

## Results

No *MKRN3* mutations were found among CPP patients. *MKRN3* levels declined significantly from baseline to 6 months of GnRHa treatment (p: 0.0007) and from 6 to 12 months of treatment (p: 0.003); *MKRN3* levels at six months were significantly lower than in control girls (p<0.0001).

	At diagnosis	After 6 months of GnRHa treatment	After 12 months of GnRHa treatment
BMI Z-score	0.1±0.42	-0.25±0.93	-0.14±0.81
LH (IU/L)	1.6±1.8	0.3±0.2	0.3±0.1
FSH (IU/L)	5.02±2.63	1.66±1.45	2.46±0.97
17-β-Estradiol (pg/mL)	21.03±13.93	<5	<5
MKRN3 (pg/mL)	612.67±476.54	117.9±119.47	54.19±39.03
MKRN3 (pg/mL) median (IQR)	590.25 (136.83-1012.64)	68.04 (39.32-141.48)	49.3 (31.2-72.8)



## Conclusion

We showed that girls with CPP had a decline in peripheral levels of *MKRN3* during GnRHa treatment. Our data suggest a suppression of *MKRN3* by pharmacological continuous administration of GnRHa. Further longitudinal studies on patients treated by long-acting GnRHa for different purposes (i.e. breast cancer or endometriosis) or in different ages could help to better understand the interplay among GnRH, gonadotropins, sexual hormones and *MKRN3*.

## References

- Abreu AP, Dauber A, Macedo DB, Noel SD, Brito VN, Gill JC, et al.: Central Precocious Puberty Caused by Mutations in the Imprinted Gene *MKRN3*. *N Engl J Med* 2013;368:2467–2475.
- Hagen CP, Sørensen K, Mieritz MG, Johannsen TH, Almstrup K, Juul A: Circulating *MKRN3* levels decline prior to pubertal onset and through puberty: a longitudinal study of healthy girls. *J Clin Endocrinol Metab* 2015;100:1920–6.
- Busch AS, Hagen CP, Almstrup K, Juul A: Circulating *MKRN3* Levels Decline During Puberty in Healthy Boys. *J Clin Endocrinol Metab* 2016;101:2588–2593.
- Varimo T, Dunkel L, Vaaralahti K, Miettinen PJ, Hero M, Raivio T: Circulating makorin ring finger protein 3 levels decline in boys before the clinical onset of puberty. *Eur J Endocrinol* 2016;174:785–90.
- Grandone A, Cirillo G, Sasso M, Capristo C, Tornese G, Marzuillo P, et al.: *MKRN3* levels in girls with central precocious puberty and correlation with sexual hormone levels: a pilot study. *Endocrine* 2018;59:203–208

No conflict of interest to declare

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