

Circulating MKRN3 levels decline during puberty in healthy boys

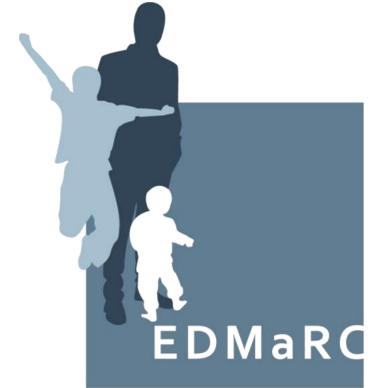
- Dynamics of a novel pathway in control of pubertal timing -

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Endocrine Disruption of Male Reproduction and Child Health

Background

Initiation and progression of puberty requires concerted action of activating and inhibiting factors. Recently, cases of central precocious puberty have been linked to loss-of-function mutations of makorin RING-finger protein 3 (MKRN3) indicating a pivotal inhibitory role of MKRN3 on GnRH secretion (1).

Objective

To investigate peripubertal circulating MKRN3 levels in healthy boys with regard to pubertal timing.

Method

Healthy boys (n=60) aged [median (range)] 9.3 (5.8-11.8) years at baseline were followed for 6.0 (0.5-7.6) years with blood sampling and clinical examinations every 6 months. Age at pubertal onset was approximated using the date between two visits when a boy's uni- or bilateral testicular volume increased from <4 to ≥4 ml. Serum levels of MKRN3 were measured: 623 samples, median (range) 12 (2-14) pg/ml per boy. Participants were genotyped for two SNP in the vicinity of *MKRN3* (rs12148769 and rs12439354).

Results

Circulating MKRN3 levels exhibited a broad variation during puberty (all samples, median: 122 pg/ml, range <25–1285 pg/ml) (Fig. 2D). MKRN3 levels declined prior to onset of puberty; the geometric mean (95% CI) 5 years prior to onset of puberty vs. last visit before onset of puberty was 216 (169–272) pg/ml vs. 128 (118–139) pg/ml ($p < 0.001$), respectively (Fig. 1, blue). MKRN3 levels continued to decrease as puberty progressed. Each boy seemed to maintain his individual MKRN3 set point during puberty. Mean prepubertal MKRN3 levels were not associated with age at onset of puberty ($r = -0.163$, $p = 0.213$). Age at onset of puberty did not differ significantly between prepubertal MKRN3 level tertiles ($p = n.s.$, Fig. 2D). Further, no significant correlations were observed between MKRN3 and gonadotropin levels nor total testosterone levels within each pubertal stage (Fig. 2ABC). When comparing our recent observations with our previously published (2) observations in girls (Fig. 1, red), mean circulating MKRN3 levels in boys were significantly lower ($p < 0.01$) at all overlapping time intervals. The two investigated SNPs were not associated with mean prepubertal MKRN3 levels.

Conclusion

Continuously declining MKRN3 levels prior to pubertal onset support MKRN3 as an inhibitor of GnRH secretion during mid-childhood in boys. Marked inter-individual variation of MKRN3 at time of pubertal onset suggests an individual set-point for reactivation of GnRH secretion.

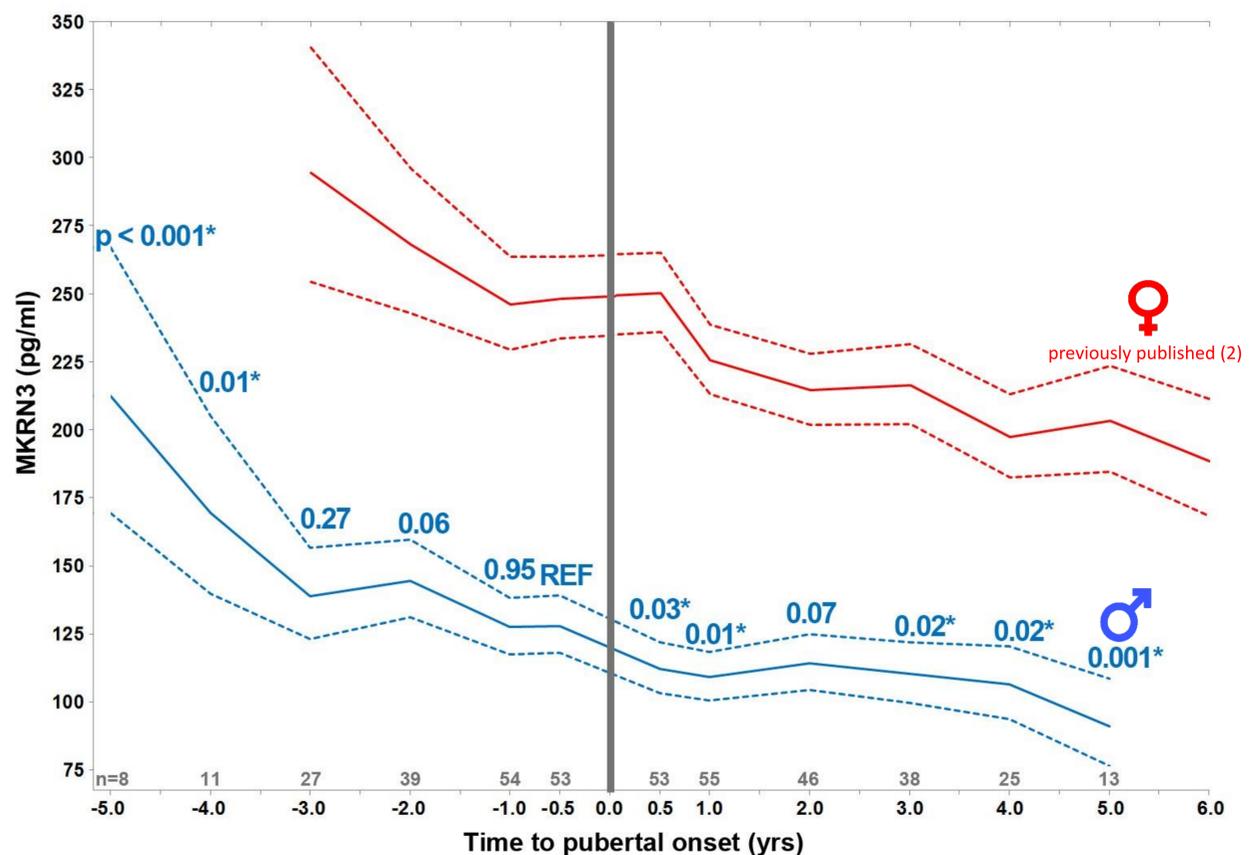


Figure 1. Variance component model of serum MKRN3 levels according to time to pubertal onset based on longitudinal data. Present data of boys is marked as blue, whereas previously published data in girls is marked as red (2)

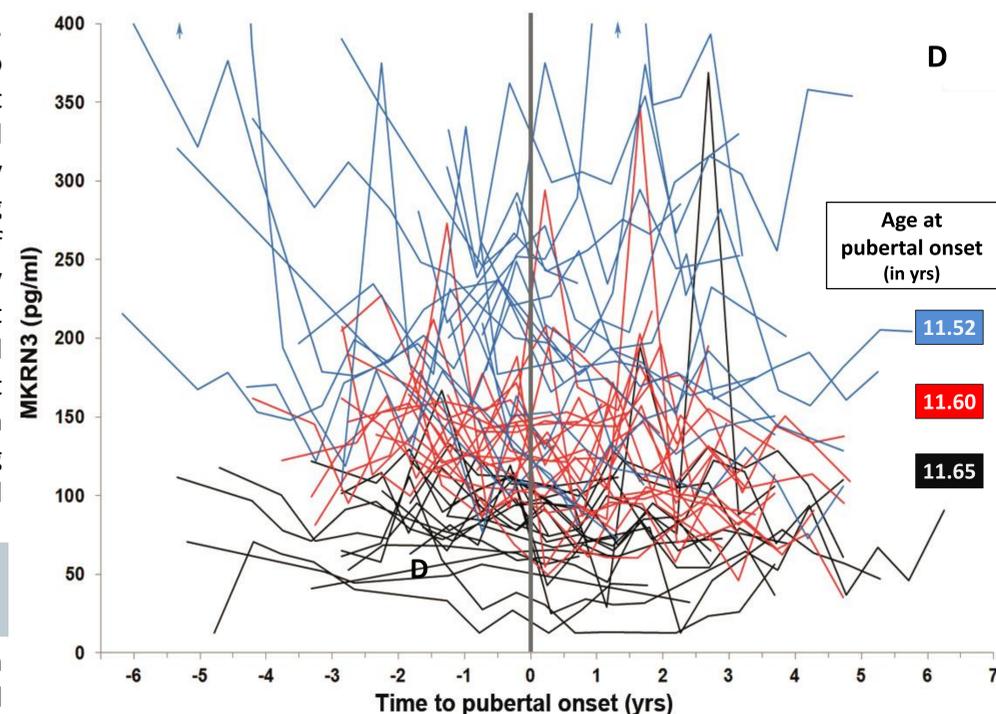
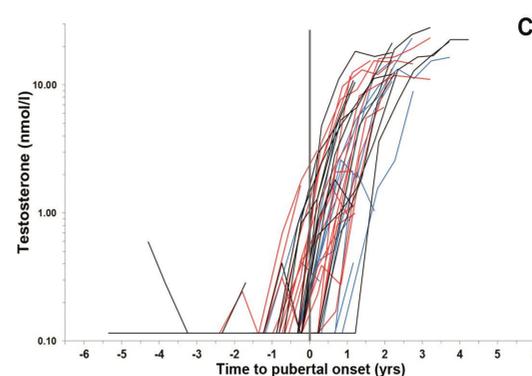
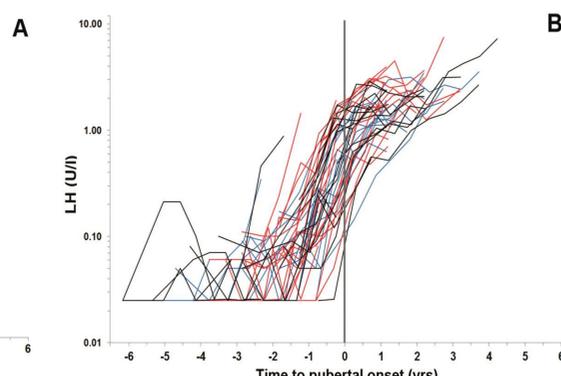
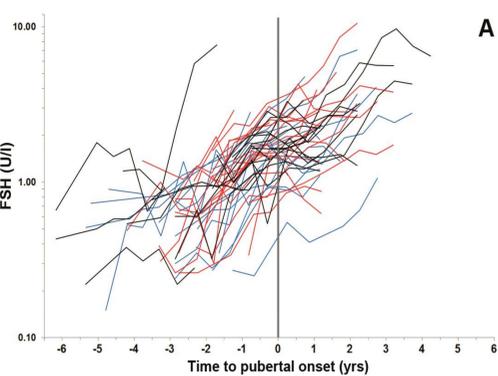


Figure 2. Serum levels of FSH (A), LH (B), total testosterone (C) and MKRN3 (D, raw data) levels in healthy boys according to time to pubertal onset. Each line represents consecutive measurements from the same boy. Measurement are grouped to tertiles of mean prepubertal MKRN3 levels and are marked in blue (highest tertile), red (middle tertile) and black (lowest tertile) - corresponding mean age at pubertal onset is shown in boxes. The blue arrows in (D) indicate single MKRN3 measurements of 1285 pg/ml 5.35 years and 604 pg/ml 1.33 years prior to pubertal onset, respectively.



- References:
 (1) Abreu AP et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. NEJM 2013
 (2) Hagen CP et al. Circulating MKRN3 levels decline prior to pubertal onset and through puberty: a longitudinal study of healthy girls. JCEM 2015



Poster presented at:

