A missense mutation in *MKRN3* in a Danish girl with central precocious puberty and her brother with early puberty

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Disclosure statement: The authors have nothing to disclose.

Background: Idiopathic central precocious puberty (ICPP) results from the premature reactivation of the hypothalamic-pituitary-gonadal axis leading to development of secondary sexual characteristics prior to 8 years in girls or 9 years in boys (1). Defects in the maternally imprinted gene *MKRN3* are the most frequent genetic cause of ICPP identified to date, with mutations found in patients with diverse ethnic backgrounds (2-6). It is therefore well-justified to screen this gene in ICPP patients from different populations. *MKRN3* expression decreases in the mouse arcuate nucleus at the beginning of puberty, suggesting its function towards GnRH secretion is inhibitory (2). The exact mechanism of action, however, remains unknown.

Aims:

- To investigate whether mutations in *MKRN3* contribute to the premature onset of puberty in Danish patients
- To find out if *MKRN3* is expressed in human adult hypothalamus

Methods:

- 29 Danish girls with ICPP were screened for mutations in *MKRN3*.
- Effects of the identified mutation were predicted by PolyPhen2, SIFT and Mutation Taster
- Expression of *MKRN3* in a human hypothalamic cDNA library was investigated by PCR and gel electrophoresis.

Results: One paternally inherited variant (c.1034G>A (p.Arg345His)) was identified in one girl with ICPP and in her brother with early puberty (**Figure 1**). The variant has been reported with a frequency of 1/8600 in the NHLBI ESP database and is predicted to be deleterious by three different in silico prediction programs. Expression of *MKRN3* was confirmed in the hypothalamic cDNA library (**Figure 2**).

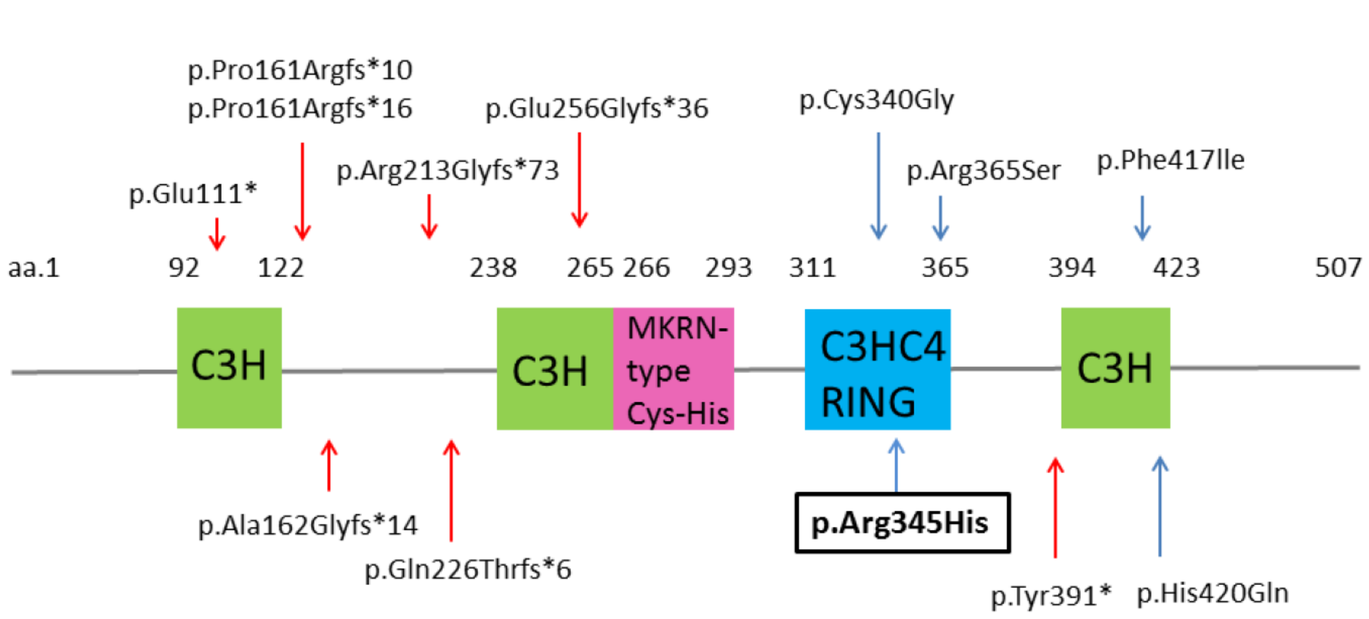

Figure 1. The *MKRN3* mutation identified in this study (boxed) and previously identified mutations.

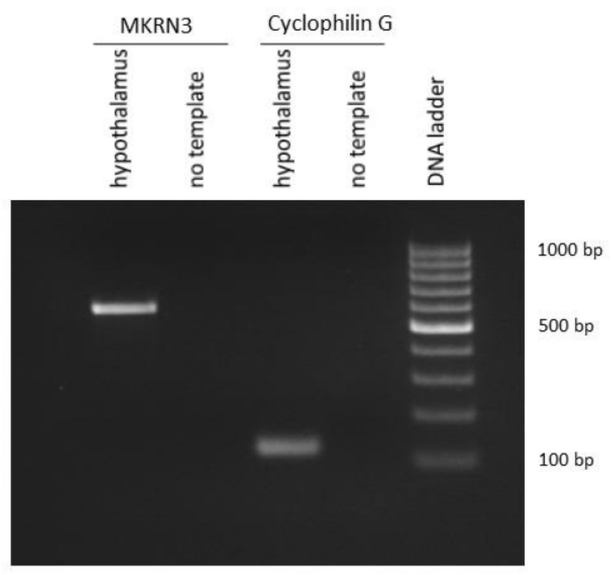

Figure 2. *MKRN3* is expressed in the human hypothalamus. A 598-bp fragment of transcript encoding MKRN3 was amplified from the human hypothalamic cDNA library. *Cyclophilin G* served as the housekeeping control gene. The PCR products were visualized on a 2.0% agarose gel.

Conclusion: Our results are in line with previous studies where paternally inherited *MKRN3* mutations have been found in both males and females with ICPP or early puberty. Expression of *MKRN3* in adult hypothalamus implies its function there is not limited to acting as a pubertal break.

References:

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ESPE 2015
121--P1
Puberty and Neuroendocrinology
Johanna Knskoski
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
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