A missense mutation in \textit{MKRN3} in a Danish girl with central precocious puberty and her brother with early puberty

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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 \textit{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. \textit{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 \textit{MKRN3} contribute to the premature onset of puberty in Danish patients
- To find out if \textit{MKRN3} is expressed in human adult hypothalamus

**Methods:**
- 29 Danish girls with ICPP were screened for mutations in \textit{MKRN3}.
- Effects of the identified mutation were predicted by PolyPhen2, SIFT and Mutation Taster
- Expression of \textit{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 \textit{MKRN3} was confirmed in the hypothalamic cDNA library (Figure 2).

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

**Figure 2.** \textit{MKRN3} is expressed in the human hypothalamus. A 598-bp fragment of transcript encoding MKRN3 was amplified from the human hypothalamic cDNA library. \textit{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 \textit{MKRN3} mutations have been found in both males and females with ICPP or early puberty. Expression of \textit{MKRN3} in adult hypothalamus implies its function there is not limited to acting as a pubertal break.

**References:**