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TIME COURSE OF CENTRAL PRECOCIOUS PUBERTY DEVELOPMENT CAUSED BY AN *MKRN3* GENE MUTATION: A PRISMATIC CASE

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Background & Objetive

- Loss-of-function mutations in the imprinted gene *MKRN3* represent the most common known genetic defects associated with central precocious puberty (CPP).
- The penetrance of these mutations remains to be established.
- To date, all reported individuals with *MKRN3* mutations were already in puberty or postpubertal and were identified retrospectively.
- We report the first case of a prepubertal child with an *MKRN3* mutation who was followed prospectively and developed CPP.

Patient & Methods

- We describe the complete clinical and laboratory features of a female patient carrying an *MKRN3* mutation, detected in childhood, followed until the development of pubertal signs.

Results

- The patient was screened at the age of 4 years because of positive family history – her sister developed CPP at the age of 6 years and was found to harbor the *MKRN3* p.Pro161Argfs*16 mutation, inherited from their asymptomatic father (**FIGURE 1**).

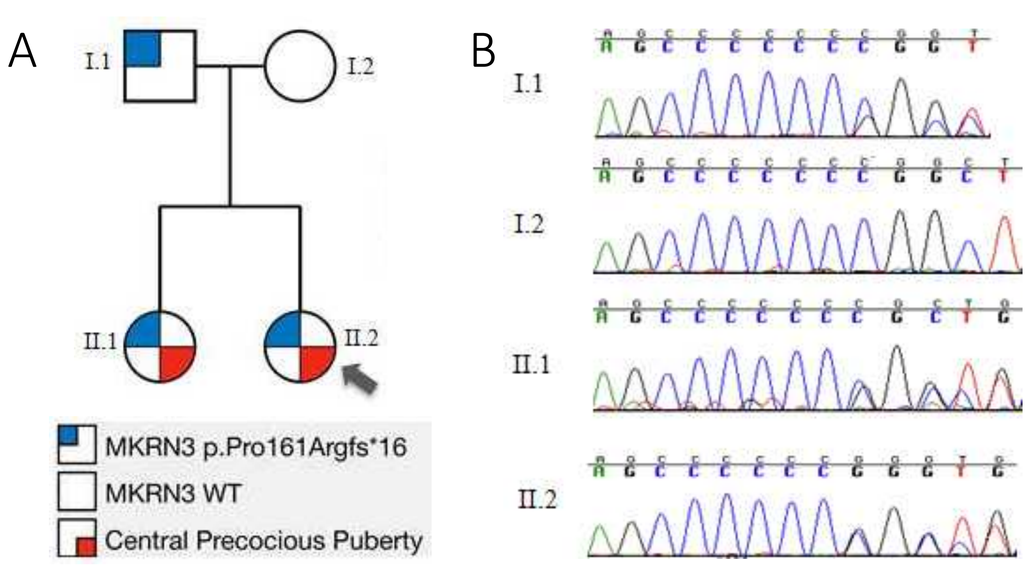

FIGURE 1A and 1B. Family pedigree and sequencing showing the paternal origin of the *MKRN3* p.Pro161Argfs*16 mutation in the patient (II.2) and in her older sister with CPP.

Table 1. Time course of the clinical and laboratory features of this prepubertal girl, carrying a loss-of-function *MKRN3* mutation, who developed CPP.

Age (years)	Height (z-score)	Growth rate (cm/yr)	Tanner Stage	LH (mIU/mL)	FSH (mIU/mL)	Estradiol (pg/mL)	Δ Bone age (years)
5.7	0.4	NA	B1 PH1	ND	ND	ND	ND
6.0	0.5	9.0	B1 PH1	0.1	1.3	49.7	0.6
6.3	0.6	7.5	B1 PH1	0.4	5.9	41.3	ND
6.7	0.8	12	B3 PH1	0.9	3.3	54.1	0.7

NA: Not available. B: Breast. PH: Pubic hair. ND: Not done.
Normal prepubertal reference values (ICMA): LH <0.3 mIU/mL; Estradiol <20 pg/mL.

Results

- During close follow-up, this young girl initially developed increased growth velocity at age of 6 years (9 cm/year) (**FIGURE 2** and **TABLE 1**).

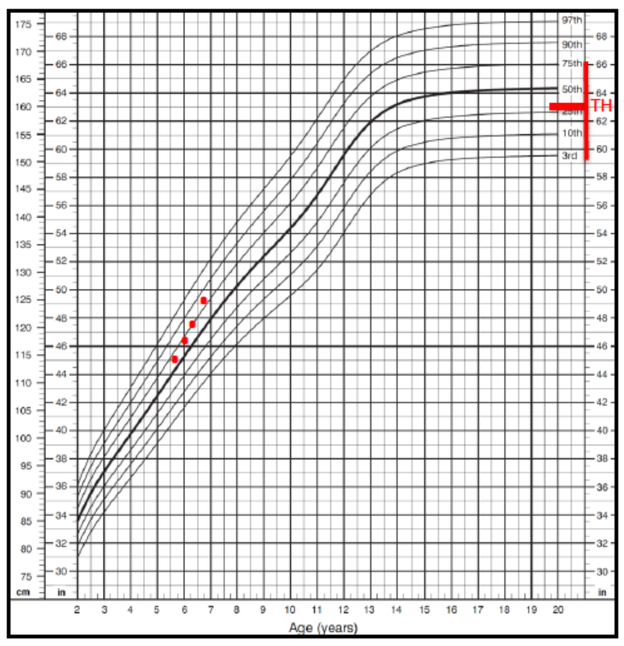

FIGURE 2. Girl's stature-for-age growth chart (CDC) showing the accelerated growth in the patient (II.2) with CPP caused by the *MKRN3* p.Pro161Argfs*16 mutation.

- Rapid growth was followed by a slightly increased basal LH level (0.4 mIU/mL) and, ultimately, by clinical thelarche, with rapid progression (Tanner stage 1 to 3) between the ages of 6.3 and 6.7 years, when LH level became clearly pubertal (0.9 mIU/mL) **(TABLE 1** and **FIGURE 3**).

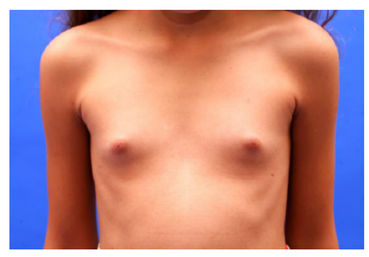

FIGURE 3. Rapid breast development (Tanner 3) in a 6.7-year-old girl with CPP caused by the *MKRN3* p.Pro161Argfs*16 mutation.
*The exhibition of this picture was authorized by the patient's parents.

- **FOLLOW-UP**: In the context of a loss-of-function *MKRN3* mutation and a positive family history, these features established the diagnosis of CPP and supported the initiation of treatment with GnRH analog, with complete regression of thelarche after 6 months of therapy.

Conclusions

- ***MKRN3* mutations likely present with full penetrance.**
- **The identification of carriers of *MKRN3* mutations may contribute to early diagnosis, facilitating treatment decisions, and guiding genetic counselling and prompt interventions.**
- **This case illustrates how genetic testing can be useful in the clinical setting.**

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