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A novel MKRN3 mutation discovered in a Korean girl with central precocious puberty

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INTRODUCTION

• Precocious puberty refers to early secondary sexual development before the age of 8 years in girls and 9 years in boys. Precocious puberty caused by activation of hypothalamic GnRH secretion is called central precocious puberty (CPP)

• Despite screening of many CPP subjects, mutations associated with CPP have been discovered in only two genes: KISS1 and KISS1R [4,5]. Recently, it was reported that mutations in MKRN3, the gene encoding makorin RING-finger protein 3, cause CPP.

• The aim of the present study was to examine variants of the MKRN3 gene in Korean girls with CPP.

METHODS

• In this study, 260 Korean girls with CPP were included. The mean pubertal onset age of the subjects was 7.7 years (2.0–7.9 years).

•Of 117 patients with available information on the family pubertal history, 23 subjects (19.6%) had familial CPP.

•CPP was defined as objective breast budding appearing before the age of 8 years, advanced bone age, and GnRH stimulated luteinizing hormone (LH) 5.0 IU/L on an immunoradiometric assay (IRMA).

Case History

• The proband was referred to our department at the age of 7.3 years because of breast enlargement, which had started 8 months earlier. A physical examination showed Tanner stage II for breast development and Tanner stage I for pubic hair development. Her height and weight were within the normal range for her age (height 118.3 cm, 5th percentile and weight 19.8 kg, 5th percentile). Bone age, evaluated by a left wrist X-ray was 9 years according to the Greulich and Pyle method.

•Her younger brother was examined when he was 11.8 years (height, 154.4 cm, SDS 1.06 on the basis of the Korean National Growth Chart). His bone age was 14 years, and physical examination showed Tanner stage III for pubic hair and a volume of 10cc for both testis.

•His father's height was 165 cm (-1.5 SDS on the basis of the Korean National Growth Chart), but he was unable to recall precisely his pubertal onset age.

RESULTS

• The conventional Sanger method was used to identify variants in the coding region of MKRN3 of the 260 Korean girls with CPP. One novel nonsense mutation (p.Gln281*) was detected and six kinds of missense variants (p.Ile100Phe, p.Gly196Val, p.Ile204Thr, p.Gln226Pro, p.Lys233Asn, and p.Ser396Arg), as shown in Table 1.

Table 1. One nonsense and six missense *MKRN3* mutations of the seven Korean girls with central precocious puberty And their clinical characteristics and results of GnRH stimulation test

DNA	Protein	dbSNP ID	PolyPhen-2	Time of Diagnosis (year)		LH (IU/L)		FSH (IU/L)		Peak LH/FSH ratio
				Age	Bone Age	Basal	Peak	Basal	Peak	
841C→T	Gln281*	-	-	7.3	9	3.2	28.7	5.6	15.6	1.83
587G→T	Gly196Val	rs183691859	Possibly damaging	8.9	11	2.7	9	2.6	12.8	0.7
298A→T	Ile100Phe	-	Benign	8.3	10	1.6	10.4	1.3	12.6	0.82
611T→C	Ile204Thr	-	Benign	7.8	10.5	0.9	26.8	3.2	11.3	2.37
677A→C	Gln226Pro	-	Benign	6.8	9.5	1.7	5.6	3	19.8	0.28
699G→C	Lys233Asn	-	Benign	7.8	10.5	0.8	11.6	0.8	9.4	1.23
1188C→A	Ser396Arg	-	Benign	8.8	10	1.3	9.5	1.3	10.1	0.64

The positions of the mutation are defiened according to NM_005664.3 for mRNA and NP_005655.1 for protein. PolyPhen-2 is prediction of functional effects of human nonsynonymous SNPs,

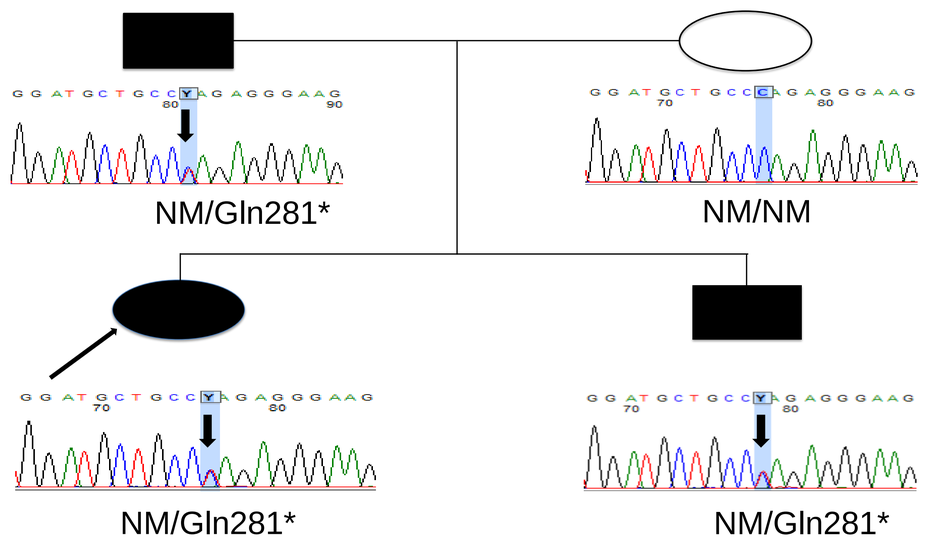

Figure 1. Pedigree and chromatogram of the family with *MKRN3* nonsense mutation. The position of the mutation is defined according to NM_005664.3 in this figure. NM denotes nonmutated.

CONCLUSION

We identified a paternal inherited MKRN3 mutation that appears to be associated with idiopathic CPP in girls. Our study supports that the polymorphism or mutation of MKRN3 gene could lead to precocious puberty.