Familial Central Precocious Puberty Caused by a Novel MKRN3 Mutation

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Introduction

Mutations in the imprinted gene *MKRN3* have been associated with inherited central precocious puberty (CPP). *MKRN3* is a maternal imprinted gene and the disease is exclusively paternally transmitted . Although the mechanism is unclear, it has been suggested that MKRN3 inhibits hypothalamic GnRH release. Currently, MKRN3 mutations represent the most frequent known genetic causes of familial CPP.

Methodology

Six patients (3M, 3F) with CPP from highly consanguineous families were enrolled. CPP was diagnosed based on clinical and hormonal findings in 6 children belonging to 2 related families. Five patients were treated with GnRH analog. The age of pubertal onset in the girls ranged from 5 to 6.5 years and in the boys, from 7 to 8 years. *MKRN3* was sequenced for the proband and the identified mutation was screened in 13 family members.

Results

The familial occurrence of CPP raised the diagnosis of MKRN3 mutation; *MKRN3* sequencing revealed a novel heterozygous loss-of-function missense mutation, c.1033C>T; p.Arg345Cys.

This mutation is located within the zinc finger motif predicted to be involved in RNA binding, essential for protein function. Nine family members were heterozygous. Two children of family 1 were homozygous for the same mutation inherited both maternally and paternally. Two non-affected members were negative.

Figure 1: Clinical characteristics of the patients

Patient no. Family no.	**1** **I**	**2** **I**	**3** **II**	**4** **II**	**5** **II**	**6** **II**	**7** **III**	Normal range
Male/Female	M	F	F	M	M	F	F	
Age at puberty onset (y)	8	6	6	7.5	8.5	6	6.5	
Tanner stage at presentation	P3	B3, P1	B2-3, P1	P3	P3	B3, P1	B3, P2	
Δ BA–CA (y)	2	2	2	2.5	2.5	1.9	3	
Basal LH, FSH (mIU/L)	3, 5.4	1.3, 4.9	0.4, 1.6	2, 8.7	1.8, 3.6	1.3, 4.8	6, 7.3	
Testosterone (ng/mL)	2.6			7				2.41-8.7
Estradiol (pmol/L)			81			85	80.3	0-580
Age at initiation of GnRH-A (y)		7.4	8.5	9	9	7.5	7.5	

Conclusion

We report a novel MKRN3 mutation in highly consanguineous families with multiple patients with CPP. This is the first report of homozygosity for an MKRN3 mutation, indicating that the phenotype in these cases does not differ from the phenotype of heterozygous patients. *MKRN3* gene is paternally transmitted, so all affected patients with CPP inherited the mutation from their father. Sequencing of *MKRN3* is recommended in familial CPP.

Figure2: Family pedigree