A case of familial central precocious puberty caused by a novel mutation in the makorin RING finger protein 3 gene

Anna Grandone[1]; Grazia Cantelmi[1]; Pierluigi Marzuillo[1]; Grazia Cirillo[1]; Caterina Luongo[1]; Flora Micillo[1]; Emanuele Miraglia del Giudice[1]; Laura Perrone[1]

[1]Department of woman and children and general and specialized surgery, Seconda Università degli Studi di Napoli, Naples, Italy.

Background

Central precocious puberty (CPP) is often familial but its genetic cause is largely unknown. Very recently, the makorin RING finger protein 3 (MKRN3) gene, located on chromosome 15 in the Prader-Willi syndrome (PWS)-associated region (15q11-q13), has been found mutated for the first time in 5 families with familial precocious puberty, with a peculiar kind of transmission. In fact, it is an imprinted gene which is expressed only if transmitted from the father. The function of this gene is not completely known and the phenotype of patients with mutations in MKRN3 gene is not yet completely elucidated. We report a new mutation (Pro160Cysfs*14) in the paternally imprinted MKRN3 gene causing familial CPP.

Case study

When the index case, a 7 years old girl, came to our observation, showed Tanner stage 3 and pubic hair stage 1. Her bone age evaluated by TW2 method was 10.3 years. Her laboratory data confirmed diagnosis of central precocious puberty (Table 1). Familial medical history revealed precocious puberty in a cousin on paternal side and in her paternal grandmother (Figure 1). Genetic analysis revealed a new mutation (Pro160Cysfs*14) in the paternally imprinted MKRN3. Puberty onset was at about 6 years in all affected female family members and the grandmother presented also premature menopause. Precocious puberty was well controlled by pharmacological therapy.

Table 1: Clinical features and biochemical characteristics at of the index case heterozygous for Pro160Cysfs*14 mutation.

Age (years)	7
Weight (kg)	28.9 (25-50th)
Height (cm)	136.6(>97th)
Bone age (years)	10.3
Tanner stage	PH1 B3
Hormonal profile	
Basal LH (IU/L)	4.1
Basal FSH (IU/L)	7.6
Estradiol (pg/mL)	29.7

Figure 1 :Pedigree genotype of the family members. The proband is indicated with an arrow.

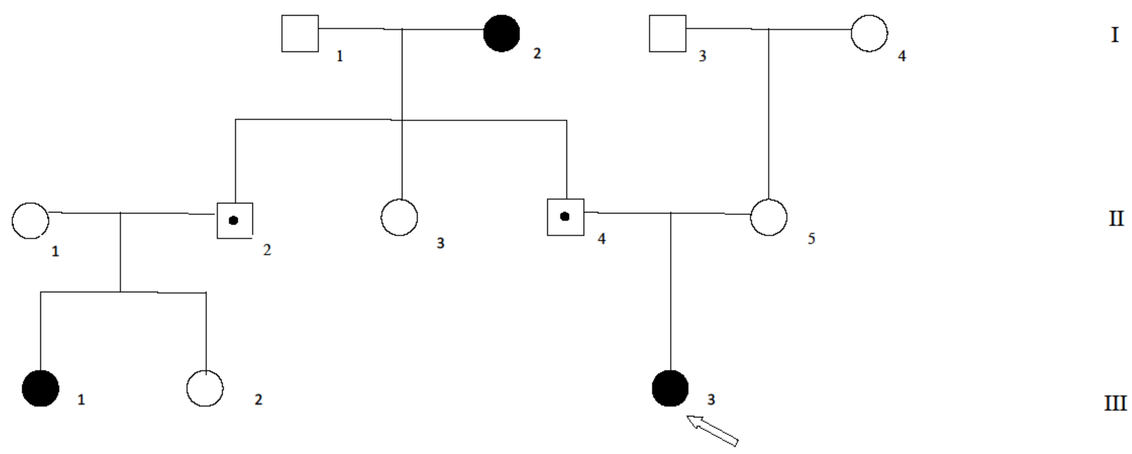

Figure 2: MKRN3 Domains and the Mutation Identified. Pro160Cysfs*14 consisted in a deletion of 8bp (c477_485del). It was a frameshift mutation and resulted in a premature stop codon leading to a truncated protein (Pro160Cysfs*14) and so predicting a truncated protein lacking two of the three C3H motifs, the C3HC4 RING motif and MKRN-specific Cys–His domain.

Conclusions

We expand the number of the MKRN3 gene CPP causative mutations and its clinical phenotype reporting a new mutation in a family with three affected members showing central precocious puberty and underlining the presence of premature menopause in one of these. We highlight the importance of an accurate family medical history to disclose the peculiar pattern of inheritance of this gene.

References

1. Abreu AP, Dauber A, Macedo DB, Noel SD, Brito VN, Gill JC et al. Central precocious puberty caused by mutations in the imprinted gene MKRN3. N Engl J Med 2013; 368: 467-2475
2. Bohne A, Darras A, D'Cotta H, Baroiller JF, Galiana-Arnoux D, Volff JN. The vertebrate makorin ubiquitin ligase gene family has been shaped by large-scale duplication and retroposition from an ancestral gonad-specific, maternal-effect gene. BMC Genomics 2010; 11: 721.
3. Macedo DB, Abreu AP, Reis AC, Montenegro LR, Dauber A, Beneduzzi D et al. Central precocious puberty that appears to be sporadic caused by paternally inherited mutations in the imprinted gene makorin ring finger 3. J Clin Endocrinol Metab 2014; 99:E1097–E1103.
4. Gross-Tsur V, Hirsch HJ, Benarroch F, Eldar-Geva T. The FSH-inhibin axis in prader-willi syndrome: heterogeneity of gonadal dysfunction. Reprod Biol Endocrinol. 2012 ;10: 39.

We have no conflicts of interest to declare.

ESPE 2015 540--P2

Puberty and Neuroendocrinology

Anna Grandone

DOI: 10.3252/pso.eu.54espe.2015

Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology

PosterSessionOnline.com