SIX NOVEL VARIANTS IN THE MKRN3 GENE CAUSING CENTRAL PRECOCIOUS PUBERTY: CHARACTERISTICS OF TEN PATIENTS AND THEIR AFFECTED RELATIVES

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INTRODUCTION

In 2013, Abreu et al identified loss-of-function mutation in the MKRN3 gene of fifteen patients from five families with idiopathic central precocious puberty (iCPP), highlighting the implication of this maternally imprinted gene in this still poorly understood condition (4). Since this study, other mutations have been described and now represent the most common genetic cause of iCPP.

AIM

The objective of the study was to document the clinical course of puberty in nine girls and one boy harbouring pathogenic MKRN3 variants.

RESULTS

We identified eight different variants predicted to be deleterious by in silico analysis in the MKRN3 gene of ten patients with iCPP from eight unrelated families.

Six of the eight pathogenic variants are novel: two of them are missense, three are nonsense and one is a frameshift variant.

In 3/8 families, we could document that the mutation was inherited from the father.

The 4 year-old twin brothers of one patient were also carriers but still prepubertal.

The ten reported patients had a very rapid pubertal development and frank LH peak after GnRH test.

Final height of affected adult relatives were within target in males but below target height in females.

METHOD

We report the clinical and hormonal data of ten patients with iCPP due to MKRN3 variant.

A common clinical feature seems to be the marked LH peak after GnRH test and the very rapid pubertal progression. An MKRN3 defect should be considered in all patient with iCPP at a young age, rapid progression, marked LH response to GnRH or with a history of CPP in the paternal family.

The identification of an MKRN3 variant in these patients has clinical implications:

1. It allows family segregation studies and early detection of other cases of CPP.
2. It allows to avoid unnecessary CNS MRI at diagnosis.
3. CPP seems to impact adult height in females’ adult relatives carrying MKRN3 mutations unlike males, but this remains to be confirmed because only a few adults could be studied.

CONCLUSIONS

Observational case series study of patients with iCPP and MKRN3 variants followed in our center.

REFERENCES


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CONTACT INFORMATION

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Table 1. Clinical and Hormonal Data of Ten Patients with iCPP carrying an MKRN3 variant.

Table 2. Clinical Data of the Affected Relatives at the time of diagnosis.

Figure 1. Overview of the MKRN3 network showing the location of the mutations in its interacting partners (adapted from the Human Protein Reference Database (HPRD) and the Human Protein Atlas (HPA)).