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

C. GERNAY [1], C. BRACHET [1], E. BOROS[1], C. LIBIOULLE[2], S. TENOUTASSE[1], C. HEINRICHS[1]

1. Paediatric Endocrinology Unit, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium
2. Department of Genetics, Centre Hospitalier Universitaire du Sart-Tilman, Université de Liège, Liège, Belgium

ESPE 2021
The 59th Annual Meeting Online
22-26 September 2021

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.

METHOD

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

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.

Family/ Patient number	Sex	Ethnicity	Age at pubertal onset, y	Age at diagnosis, y	Tanner stage at diagnosis	Height at diagnosis, SDS	ΔHeight-TH, SDS	ΔFH - TH, SDS	BMI, SDS	ΔBA-CA, y	Basal LH / Post-stimulated LH, IU/L	Basal FSH / Post-stimulated FSH, IU/L	E2, ng/L T, nmol/L	MKRN3 variant
1 / III-5	F	Caucasian	7.0	9.0	A2P4M4	1.8	2.3	0.5	0.7	3	20.3 >200	6.7 53.2	170	c.555_556delCA, p.Asp185Glufs*20 Frameshift
2 / III-8	F	Caucasian	7.3	7.6	A1P1M2	2	1.2	/	0	1.9	0.1 9.17	2.1 14.63	<5	c.1153C>T, p.Gln385* Nonsense c.1235T>G, p.Phe412Cys Missense
3 / V-2	F	Caucasian	6.4	6.5	A1P1M2	0.9	1.7	/	0.5	1.3	0.8 15.3	4.5 10.38	<25	c.983G>A, p.Arg328His Missense
4 / II-1	M	Center-African	?	11.7	A3P3G4	0.4	1	/	1.2	2	2.8 40	4.9 11.2	15.7	c.1076A>G, p.Lys359Ar Missense
4 / II-2	F	Center-African	6.8	7.2	A2P2M2	1.5	2.1	/	1.3	2.8	2.9 16.4	8.7 15.4	45	c.1076A>G, p.Lys359Ar Missense
4 / II-3	F	Center-African	6.8	7.2	A1P1M2	0.1	0.7	/	0	1.5	<1 13.9	2.4 17.3	<25	c.1076A>G, p.Lys359Ar Missense
5 / III-3	F	Caucasian	7.3	8.3	A1P1M3 -4	1.5	0.2	1.2	1.6	2.1	3.4 40.1	4.7 10.1	29	c.983G>A, p.Arg328His Missense
6 / IV-2	F	Caucasian	7	8.7	A2P3M3	0.9	0.5	/	0.3	2.3	2.6 23.4	5.4 11.4	46	c.268C>T, p.Arg90* Nonsense
7 / II-5	F	North-African	8.4	8.7	A2P2M3	-0.8	0.3	/	1.1	2.3	3.1 104.8	5.5 33.8	12	c.547G>T, p.Glu183* Nonsense
8 / II-4	F	South-African	6	6.8	A1P1M3	2.7	2.4	/	1.6	4.2	1.64 20.64	4.86 12.55	52	c.982C>T, p.Arg328Cys Missense

Table 1. Clinical and Hormonal Data of the 10 Patients with CPP carrying an *MKRN3* variant

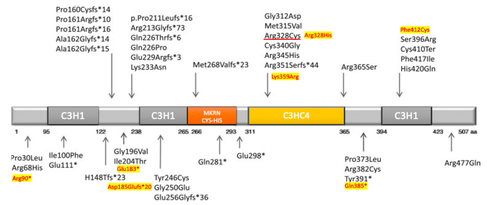

Figure 1. Structure of the MKRN3 human protein showing the location of the mutations in coding sequence from Valadares et al. in 2019 (11). The variants we report are added in red.

Family / Relative	Sex	Age at menarche (F) /recalled pub onset (M)	Final Height, SDS	Target Height, SDS
1 / I-2	F	8	-1.5 (reported)	Unknown
1 / III-1	F	8	Unknown	Unknown
2 / I-2	F	8	-0.6 (reported)	Unknown
2 / II-7	F	8	-2.5 (reported)	-0.4
2 / II-12	M	9.5	-0.3 (measured)	-0.4
2 / III-1	F	10	-0.6 (reported)	Unknown
2 / III-2	F	9	Not reached yet	Unknown
2 / III-6	F	9.5	Not reached yet	Unknwon
3 / IV-3	F	M2 at 6	Unknown	-1
3 / IV-4	F	M2 at 7.8	Not reached yet	-1
3 / IV-5	F	6.5	-2.8 (reported)	-1.5
3 / IV-6	M	9	-1.1 (measured)	-1.5
5 / I-2	F	9	-1.6 (reported)	Unknown
5 / III-1	F	9	-1.5 (reported)	-1.1
7 / II-3	M	9-10	-1.6 (reported)	-1.3
7 / II-4	F	9	-2.8 (reported)	-1.3

Table 2. Clinical Data of the affected relatives of the cases

CONCLUSIONS

We report the clinical and hormonal data of ten patients with CPP 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 CPP 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
Finally, iCPP 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.

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ACKNOWLEDGEMENTS

Thank you to all my team at HUDERF, patients and their families.

CONTACT INFORMATION

Caroline GERNAY

caroline.GERNAY@huderf.be