Correlation of clinical phenotype and genotype of Prader-Willi syndrome (PWS) and the deletion of paternal *MKRN3* allele in PWS patients with central precocious puberty

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Introduction

- Prader-Willi syndrome (PWS) is caused by a 5–6 Mb deletion of the paternally-derived chromosome 15q11–13, maternal uniparental disomy (mUPD) for chromosome 15, or an imprinting center mutation.
- Puberty is usually delayed or hypogonadotropic hypogonadism is often present in patients with PWS. However, central precocious puberty (CPP) or early puberty is rarely associated.
- Recent studies identified that patients with familial CPP harbored mutations in *MKRN3*, which is paternally expressed, imprinted gene located in the Prader-Willi syndrome critical region.
- *MKRN3* (makorin ring finger protein 3)
  - Encodes makorin ring finger protein 3 that is involved with ubiquitination and cell signaling.
  - Derived only from RNA transcribed from the paternally inherited copy of the gene due to maternal imprinting

Objectives

- We hypothesized that deletion of *MKRN3* could cause CPP in patients with PWS.
- This study was undertaken to correlate clinical features between PWS patients with deletion and those with UPD and to describe clinical characteristics of PWS patients with CPP according to *MKRN3* deletion.

Subjects and Methods

- 114 patients (70 males and 44 females) with Prader-Willi syndrome
  - Typical facial features and other clinical findings
  - Diagnosis was confirmed by methylation test and fluorescent in situ hybridization (FISH).
- Patients with central precocious puberty
  - Tanner stage, growth velocity, bone age
  - GnRH stimulation test in patients with precocious puberty
  - The presence of *MKRN3* deletion was determined by multiple ligation-dependent probe amplification (MLPA) analysis in patients with microdeletion of 15q11-q13 region.

Results

Clinical phenotypes at diagnosis according to the genotype

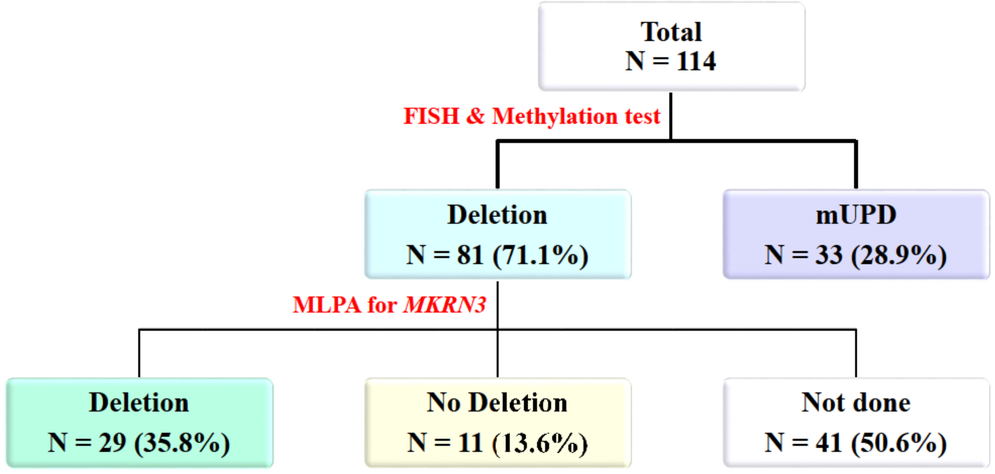

Fig. 1. Results of fluorescent in situ hybridization, methylation-specific polymerase chain reaction, and multiplex ligation-dependent probe amplification (MLPA) analysis.

Table 1. Comparison of clinical phenotype at diagnosis between patients with deletion and those with mUPD

Total (n=78)	Deletion (n=52)	mUPD (n=26)	*P* value
Neonatal hypotonia	24 (46.2%)	8 (30.8%)	0.145
Developmental delay	16 (30.8%)	6 (23.1%)	0.333
Short stature (Height < -2 SDS)	19 (36.5%)	5 (19.2%)	0.095
Genital hypoplasia	16 (30.8%)	6 (23.1%)	0.333
Feeding difficulty	15 (28.8%)	5 (19.2%)	0.264
Hypopigmentation	8 (15.4%)	0 (0%)	0.032

Table 2. Response to rhGH therapy between patients with deletion and those with mUPD

	Deletion (n=34/81, 42%)	mUPD (n=15/33, 45.5%)	*P* value
Before rhGH therapy			
Weight SDS	0.01 ± 1.68	0.32 ± 1.74	0.479
Height SDS	-0.80 ± 1.20	-0.91 ± 1.04	0.708
BMI (kg/m^2)	19.61 ± 5.92	20.61 ± 6.09	0.787
IGF-1 (ng/mL)	83.73 ± 80.52	73.41 ± 52.2	0.871
IGFBP-3 (ng/mL)	2451.74 ± 955.91	2355.27 ± 879.21	0.991
After 1 year of rhGH therapy			
Weight SDS	0.86 ± 1.27	0.42 ± 1.24	0.298
△Weight SDS	7.60 ± 7.44	5.29 ± 4.78	0.068
Height SDS	-0.14 ± 0.93	-0.48 ± 1.07	0.519
△Height SDS	17.11 ± 4.83	15.73 ± 3.72	0.298
BMI (kg/m^2)	20.88 ± 6.39	19.84 ± 48	0.618
IGF-1 (ng/mL)	434.29 ± 230.35	361.73 ± 175.62	0.298
IGFBP-3 (ng/mL)	3481.71 ± 1689.09	3176.53 ± 1048.54	0.879

Table 3. Comparison of phenotype between patients with *MKRN3* deletion and those without deletion

Total	*MKRN3* deletion (n=29)	No *MKRN3* deletion (n=11)	*P* value
Neonatal hypotonia	13 (44.8)	3 (27.3)	0.261
Developmental delay	9 (31.0)	4 (36.4)	0.514
Short stature	8 (27.6)	7 (63.6)	0.042
Genital hypoplasia	7 (24.1)	3 (27.3)	0.568
Feeding difficulty	5 (17.2)	1 (9.1)	0.464
Hypopigmentation	3 (10.3)	1 (9.1)	0.7

Table 4. Response to rhGH therapy between patients with *MKRN3* deletion and those without deletion

Total	*MKRN3* deletion (n=13/29, 44.8%)	No *MKRN3* deletion (n=6/11, 54.5%)	*P* value
Before rhGH therapy			
Weight SDS	-0.30±1.54	0.15±1.37	NS
Height SDS	-0.86±1.28	-1.25±0.78	NS
BMI (kg/m^2)	18.57±5.83	18.66±3.03	NS
IGF-1 (ng/mL)	82.10±78.72	97.23±102.32	NS
IGFBP-3 (ng/mL)	2039.00±797.10	2182.00±1119.90	NS
After 1 year of rhGH therapy			
Weight SDS	0.72±1.20	0.79±1.28	NS
△Weight SDS	1.02±1.08	0.64±1.41	NS
Height SDS	-0.86±1.28	-1.24±0.78	NS
△Height SDS	0.90±0.83	0.68±1.09	NS
BMI (kg/m^2)	20.29±6.98	19.93±2.47	NS
IGF-1 (ng/mL)	370.70±168.95	314.97±172.85	NS
IGFBP-3 (ng/mL)	2581.77±828.83	2189.00±711.35	NS

Pubertal progression according to the genotype

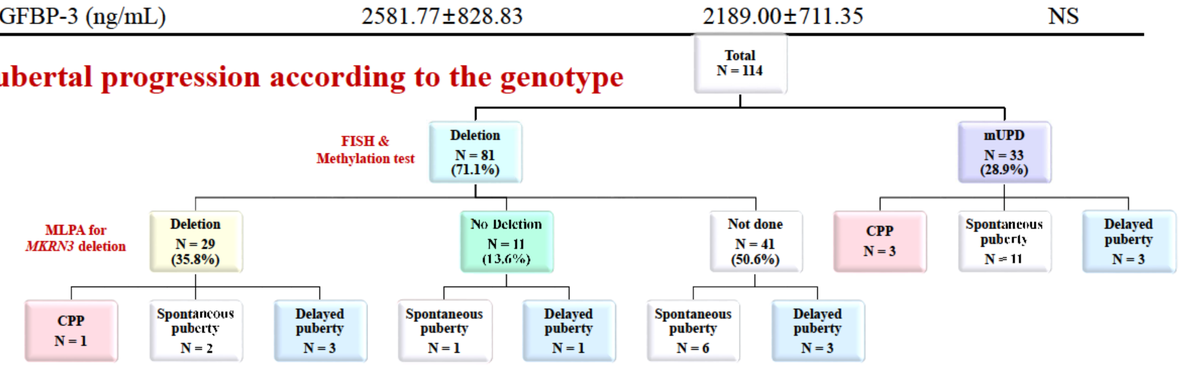

Fig. 2. Pubertal progression of PWS patients according to genotype and *MKRN3* deletion

Table 5. Clinical and endocrine characteristics of PWS patients with central precocious puberty

Subject No.	Genotype	Sex	Age at diagnosis (years)	Bone age (years)	Tanner Stage	GnRH stimulation test	Basal	After	Treatment
1	Deletion	M	8.3	13	P II	LH (mIU/ml)	0.89	21.0	GnRH agonist
						FSH (mIU/ml)	3.1	12.6	
						Testosterone (ng/ml)	0.18	0.82	
2	mUPD	F	7.6	11	B II	LH (mIU/ml)	1.3	17.9	GnRH agonist
						FSH (mIU/ml)	3.0	11.2	
						Estradiol (pg/ml)	11.9	12.6	
3	mUPD	M	9.7	12	P II	LH (mIU/ml)	1.6	9.9	GnRH agonist
						FSH (mIU/ml)	4.6	9.1	
						Testosterone (ng/ml)	0.31	0.79	
4	mUPD	M	9.8	13	P II	LH (mIU/ml)	3.9	21.9	GnRH agonist
						FSH (mIU/ml)	4.7	10.2	
						Testosterone (ng/ml)	2.4	4.5	

Conclusions

- Loss of function by mUPD or *MKRN3* deletion might contribute to the development of CPP in patients with PWS.
- *MKRN3* deletion is not necessary to cause PWS, but probable cause of early puberty.
- Therefore, CPP in PWS with mUPD or MKRN3 deletion is presumed to be caused by loss-of-function of *MKRN3*.
- Further study is needed to verify functional impact of *MKRN3* and influence of other adjacent genes in PWS patients with CPP.

Disclosure statement

The authors have nothing to declare.

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ESPE 2015 528--P2
Puberty and Neuroendocrinology
Jahyang Cho
DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
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