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Universitatea de Medicină și Farmacie „Victor Babeș" din Timișoara

Centrul de medicină GENOMICA

SPITALUL CLINIC DE URGENȚĂ PENTRU COPII LOUIS ȚURCANU TIMIȘOARA

When to suspect Prader Willi Syndrome and how to diagnose it?

Dr Chirita-Emandi Adela
Dr Dobrescu Andreea
"Victor Babes"University of Medicine and Pahrmacy Timisoara
Emergency Hospital for Children "Louis Turcanu" Timisoara

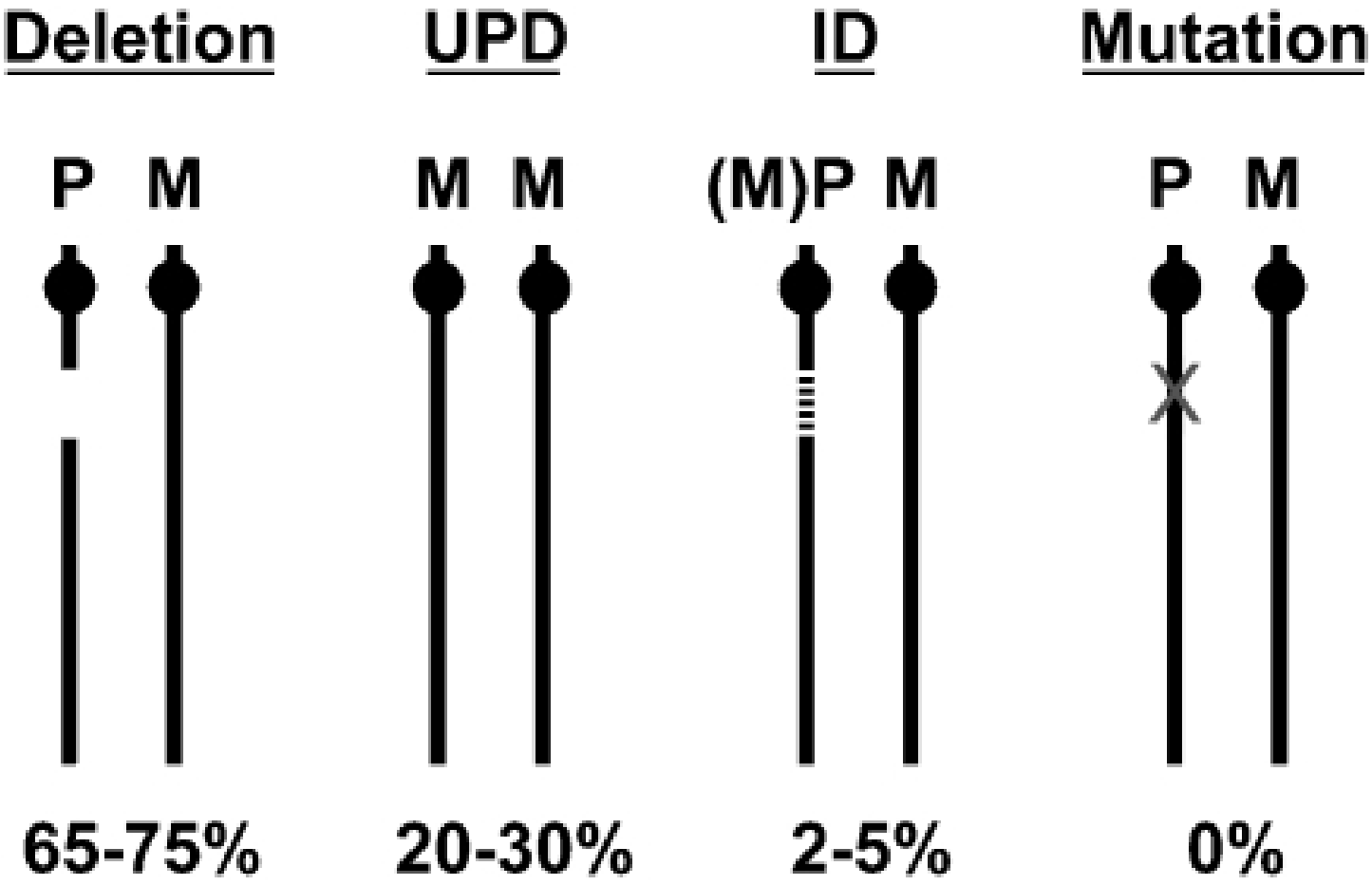
Summary

- Background: What is Prader Willi Syndrome?
- Clinical presentation
- Genetics diagnosis
- A few particular case reports

Background: What is PWS?

- Prader Willi Syndrome (PWS) is a highly variable genetic condition affecting multiple organs;
- It affects between 350,000 and 400,000 individuals worldwide;
- Most common cause of syndromic obesity.

Background: What is the cause of PWS?

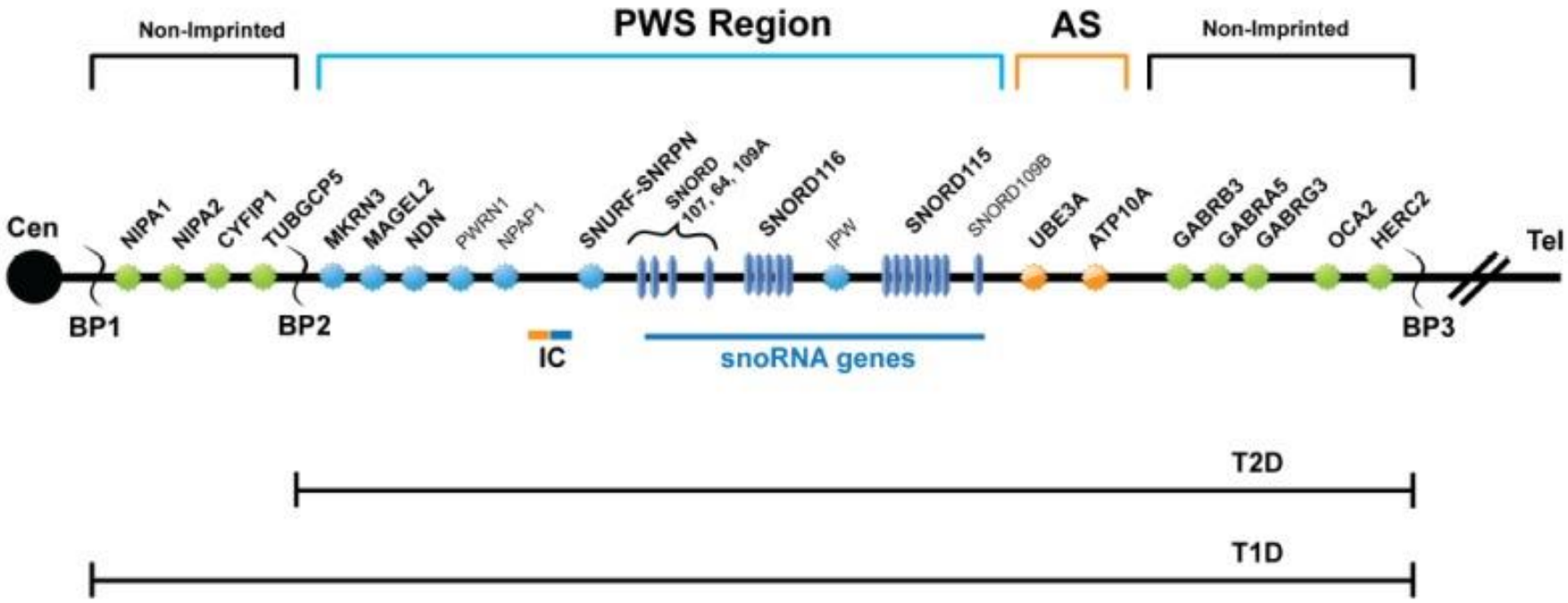


Deletion = 'de novo' deletion in the paternal chromosome; UPD=uniparental disomy, ID=imprinting defect

SB Cassidy, DJ Driscoll. Prader–Willi syndrome. Eur J Hum Genet. 2009 Jan; 17(1): 3–13.

Background: What is the cause of PWS?

- 15q11-13 chromosome region



D.Driscoll, JL Miller, SSchwartz, SB Cassidy. Prader-Willi Syndrome. GeneReviews 2017

Clinical presentation: How specific are the clinical criteria?

MAJOR CRITERIA	% Documented	Sensitivity
Neonatal hypotonia	87.9	97.5
Feeding problems in infancy	77.8	95.7
Excessive weight gain	66.7	95.0
Facial features	88.4	49.4
Hypogonadism	51.1	95.6
Developmental delay	98.9	97.8
Hyperphagia	84.4	93.4
MINOR CRITERIA		
Decreased fetal activity	62.2	89.3
Behavior problems	86.7	82.1
Sleep disturbance/sleep apnea	75.6	36.8
Short stature	63.3	86.0
Hypopigmentation	73.3	47.0
Small hands and/or feet	87.8	74.7
Narrow hands/straight ulnar borders	82.2	69.0
Eye abnormalities	67.8	49.2
Thick viscous saliva	88.9	82.5
Articulation defects	80.0	93.1
Skin-picking	83.3	61.3

M. Gunay-Aygun, S. Schwartz, S. Heeger, MA O'Riordan, S.B. Cassidy. The Changing Purpose of Prader-Willi Syndrome Clinical Diagnostic Criteria and Proposed Revised Criteria. PEDIATRICS Vol. 108 No. 5 Nov. 2001

Clinical presentation: clinical criteria?

- The clinical diagnosis needs an evaluation of major and minor criteria:
- at least 5 points (4 major criteria) up to age 3 ys
- at least 8 points (5 major criteria) after age 3ys

Clinical presentation: clinical criteria

- Hypotonia can be a symptom of over 500 different genetic disorders.
- It can present as:

peripheral/ central/combined hypotonia

- necessity for rational and systematic diagnostic testing.

Lisi EC, Cohn RD. Genetic evaluation of the pediatric patient with hypotonia: perspective from a hypotonia specialty clinic and review of the literature.Dev Med Child Neurol. 2011 Jul;53(7):586-99.

Clinical presentation: clinical criteria

Birth to 2 years	Age 2-6 years	Age 6-12 years	Age 13 years to adulthood
Hypotonia with poor suck (neonatal period)	Hypotonia with history of poor suck Global developmental delay	History of hypotonia with poor suck (hypotonia often persists) Global developmental delay Excessive eating with central obesity if uncontrolled	Cognitive impairment, usually mild intellectual disability Excessive eating with central obesity if uncontrolled Hypothalamic hypogonadism Typical behavior problems

Clinical findings that should prompt diagnostic testing have been proposed based on analysis of diagnostic criteria met in individuals in whom the diagnosis of PWS has been molecularly confirmed [Gunay-Aygun et al 2001].

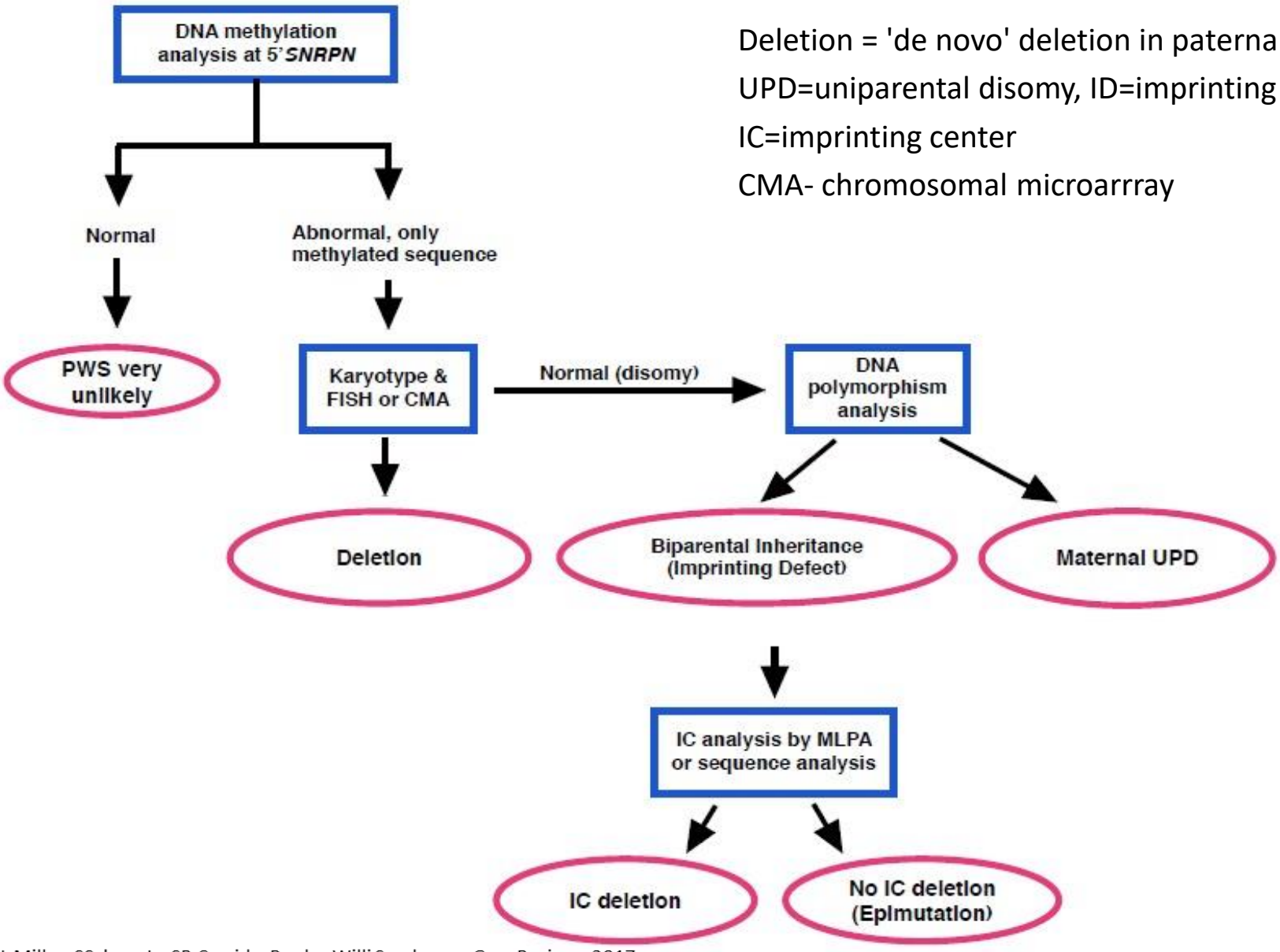
D.Driscoll, JL Miller, SSchwartz, SB Cassidy. Prader-Willi Syndrome. GeneReviews 2017

Clinical presentation: nutritional phases

Phase 0	Decreased fetal movements and lower birth weight than sibs
Phase 1a	Hypotonia with difficulty feeding (0–9 months)
	Needs assistance with feeding either through feeding tubes [nasal/oral gastric tube or gastrostomy tube] or orally with special, widened nipples
	Decreased appetite
Phase 1b	No difficulty feeding and normal growth (9–25 months)
Phase 2a	Weight increasing without appetite increase (2.1–4.5 years)
	Will become obese if given the recommended daily allowance for calories
	Typically needs to be restricted to 60–80 % of RDA to prevent obesity
Phase 2b	Weight and appetite are increased (4.5–8 years)
	Will become obese if allowed to eat what they want
Phase 3	Hyperphagic, rarely feels full (8 years-adulthood)
	Constantly thinking about food with temper tantrums related to food
Phase 4	Appetite is no longer insatiable (adulthood)
	Improvement in control of appetite and temper tantrums
	Most adults have not gone into this phase and maybe some (most?) never will

M. A. Angulo, M. G. Butler, M. E. Cataletto. Prader-Willi syndrome: a review of clinical, genetic, and endocrine findings. J Endocrinol Invest. 2015; 38: 1249–1263.

Genetic Diagnosis algorithm in PWS



Deletion = 'de novo' deletion in paternal chr;

UPD=uniparental disomy, ID=imprinting defect

IC=imprinting center

CMA- chromosomal microarrray

D.Driscoll, JL Miller, SSchwartz, SB Cassidy. Prader-Willi Syndrome. GeneReviews 2017

Genetic Diagnosis algorithm in PWS

Test Method	Genetic Mechanisms Detected	Proportion of PWS Detected by Test Method
DNA methylation	Deletions, UPD & ID	>99%
MS-MLPA	Deletions, UPD & ID	>99%
FISH test	Deletions	65%-75%
Chromosomal microarray arrayCGH	Deletions	65%-75%
Chromosomal microarray-SNP array	Deletions & some UPDs	80%-90%
DNA polymorphisms	UPD and ID	20%-30%
DNA sequence	ID with IC deletions	<1%

FISH=fluorescent in situ hybridization, UPD=uniparental disomy, ID=imprinting defect, IC- imprinting center

D.Driscoll, JL Miller, SSchwartz, SB Cassidy. Prader-Willi Syndrome. GeneReviews 2017

3 very short case reports of some particular features in people with PWS

1. Case presentation - history

- 14 years old male, the **first** child of healthy parents;
- Pregnancy uncomplicated, normal birth, weight 3200 g,

- motor development *reported as normal*
- development delay, behavioral problems (with poor social interaction, attention deficit, poor language; excessive irritability)
- rapid weight accumulation between 1 and 6 years, due to marked hyperphagia

1. Case presentation - phenotype

- Particular phenotype: narrow bi-frontal diameter, almond shaped eyes, small mouth, thin upper lip, down turned corners of the mouth, thick saliva, small hands
- **Marked obesity,** age 12 ys: W=103 kg, H=161 cm, BMI=39,7 kg/m^2
- Hypogonadism
- Sleep apnea, hepatomegaly and steatosis
- low bone density and increased risk for bone fracture (lumbar spine Tscore=-2.6)
- Mild mental retardation;
- **Severe behavior problems** sleep disturbances, language difficulties, (tantrums, violent reactions, obsessive attitude, opposition, stubbornness, lying, stealing).

1. Case presentation – clinical score

	% Affected
Major criteria	
Neonatal hypotonia	88
Feeding problems in infancy	79
Excessive weight gain	67
Facial features	88
Hypogonadism	51
Developmental delay	99
Hyperphagia	84

	% Affected
Minor criteria	
Decreased fetal activity	62
Behavior problems	87
Sleep disturbance/sleep apnea	76
Short stature	63
Hypopigmentation	73
Small hands and/or feet	88
Narrow hands/straight ulnar borders	82
Eye abnormalities	68
Thick viscous saliva	89
Articulation defects	80
Skin-picking	83

The clinical PWS diagnosis clinical score in patient = 8.

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1. Case presentation - phenotype

- the methylation analysis:

a positive methylation test for SNRPN gene locus

- the FISH analysis Specific PWS probe**:**

no deletion of the 15q11-q13 region

- **47, XYY karyotype**

1. Case presentation – discussion

- The co-existence of Prader Willi syndrome and a 47,XYY karyotyope has been previously reported in two cases.
- The first case was reported by Honma et al. in 1999 and presented a 26 month old boy with 47,XYY and maternal uniparental heterodisomy for chromosome 15.
- The second case, a 26 years old male with Prader Willi and 47,XYY was reported by Odent et al. in 2001. In this case the Prader Willi syndrome was due to a paternal deletion 15q11-13.

1. Case presentation – take home message

- **This is a rare case showing the evolution of a patient having a rare association of two chromosomal aberrations Prader Willi Syndrome and 47, XYY karyotype.**

- **The rare association of genetic anomalies shows how the phenotypic effect is modulated by the two.**

2. Case presentation – history

- 17 years old male, presented with neonatal hypotonia
- Diagnosed at 10 years
- Negative FISH test, positive methylation test
- Has very mild cognitive delay mostly in verbal skills, good school performance
- At 17ys W=95kg, H=180cm, BMI=29.3kg/m^2
- Has growth hormone treatment since age 12 ys and alternative therapies for cognitive stimulation, physio-kineto-therapy

2. Case presentation – take home message

- Although diagnosed very late….
- he has good cognitive development,
- few behavioural issues
- acceptable weight

3. Case presentation – history

- 6 years old male, presented with neonatal hypotonia
- Diagnosed before age 1 year
- Negative FISH test, positive methylation test
- Has mild cognitive delay
- At 6ys W=20kg, H=115cm, BMI=15.5kg/m^2
- Has particular nutritional behaviour very selective with food, constantly wants something new, refuses food outside time of meals, prefers to receive toys versus food.

3. Case presentation – take home message

Early diagnosis in this child made possible :

- well implemented, early nutritional education
- This could explain the particular behaviour related to food, however this could change with later age

Conclusions

- Diagnosis is possible within the first months of life because these infants display severe hypotonia, and neonatologists recognize this sign alone, sufficient to suggest genetic study
- **Early diagnosis** and **adequate multidisciplinary care are crucial** for the infant's outcome as they ensure parental guidance and support, including comprehensive advice to prevent obesity, and stimulation of cognitive and adaptive skills .
- In addition, we very recently reported positive effects of an early short course of oxytocin treatment in infants with PWS younger than 5 months

1.Bar C, Diene G, Molinas C, Bieth E, Casper C, Tauber M. Early diagnosis and care is achieved but should be improved in infants with Prader-Willi syndrome.Orphanet J Rare Dis. 2017 Jun 28;12(1):118.
2.The Use of Oxytocin to Improve Feeding and Social Skills in Infants With Prader-Willi Syndrome. Tauber M, Boulanouar K, Diene G, et al Pediatrics. 2017 Feb; 139(2)