NEW DATA IN PRADER-WILLI SYNDROME AND PERSPECTIVES

Maithé Tauber
Reference centre for Prader-Wili syndrome and other rare causes of obesity
Children Hospital ,Toulouse
France

Disclosure :

Scientific board of Merck Serono, Novo-Nordisk , OT4B

Grant from Pfizer

Consultant for Pfizer, Millendo, Merck

3 patents for Oxytocin related products in Prader-Willi Syndrome

OUTLINE

-OVERVIEW OF PWS

-MENTAL HEALTH :

- -PWS as a model of addiction disorders
- -Epigenetics marks

-ENDOCRINE AND METABOLIC TROUBLES

- -increased IGFBP-7 a new marker of PWS ?
- -diabetes in the transition period

-SCOLIOSIS

- -is ghrelin a marker of the occurrence and severity of scoliosis ?

-COVID-19

- -people with PWS are not at high risk for severe COVID-19 as a group

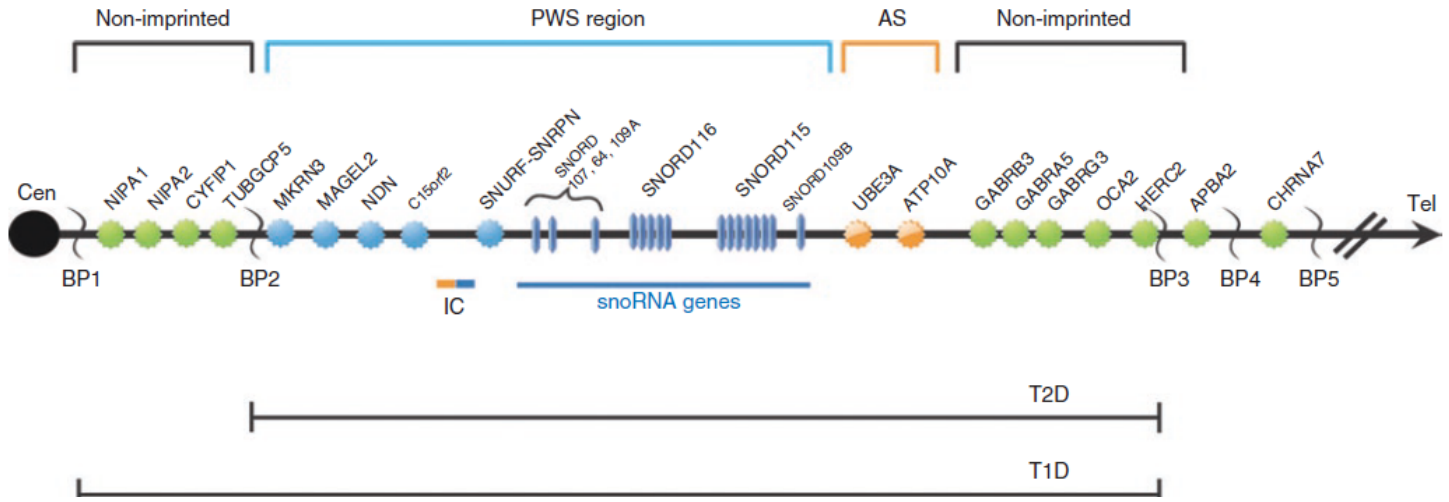
-THERAPEUTIC PERSPECTIVES

- -many drugs in development

PRADER-WILLI SYNDROME

Definition

PWS is a neurodevelopmental genetic disorder due to loss of expression of paternal inherited maternal imprinted alleles in the chromosome 15q11-q13.

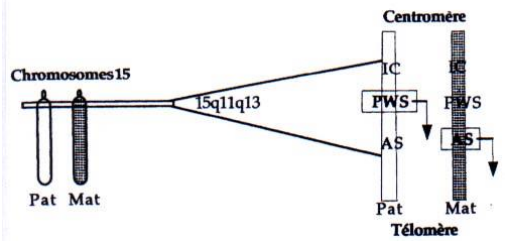


-50% paternal deletion (FISH +)

-45% maternal disomy

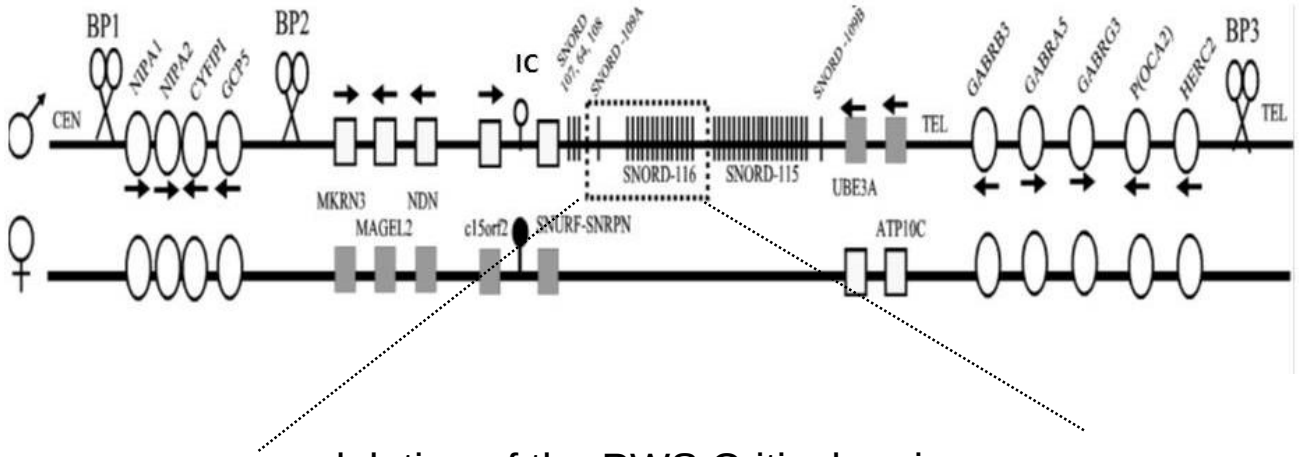
-< 2% imprinting déficit

-1-3%translocation



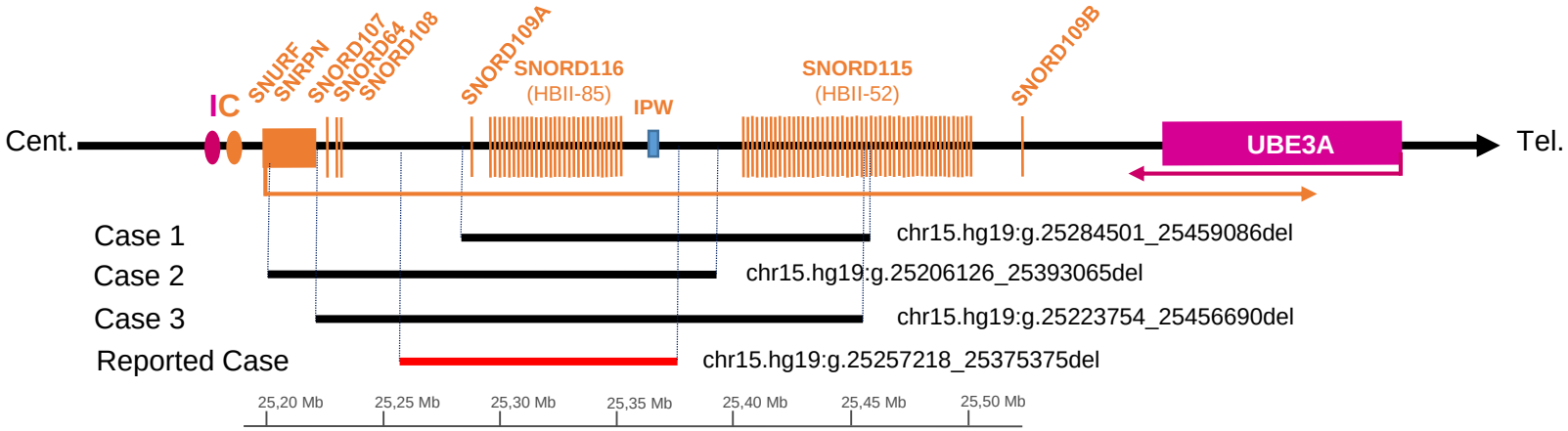
THE CRITICAL MINIMAL REGION

The hypothetical minimal paternal deletion region associated with PWS phenotype deduced from clinical cases with chromosomal translocations removes SNORD109A, the SNORD116 cluster (30 snoRNAs copies) and IPW.



deletion of the PWS Critical region reproduces PWS phenotype in mice

a



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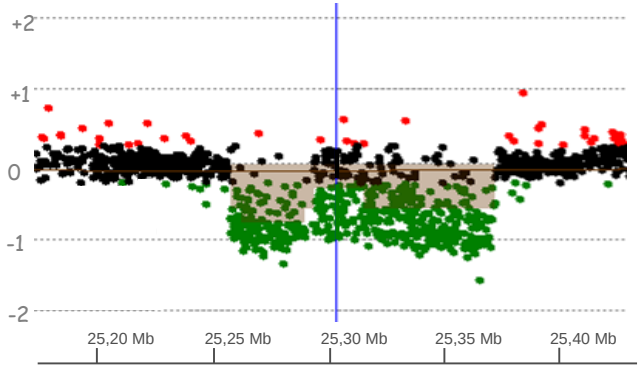

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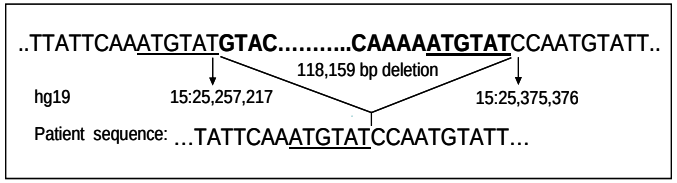


Bieth , Eddiry et al
Europ J Human Genet
2014

A NEURODEVELOPMENTAL TRAJECTORY WITH 3 DIMENSIONS NUTRITIONAL, ENDOCRINE AND METABOLISM AND BEHAVIOUR

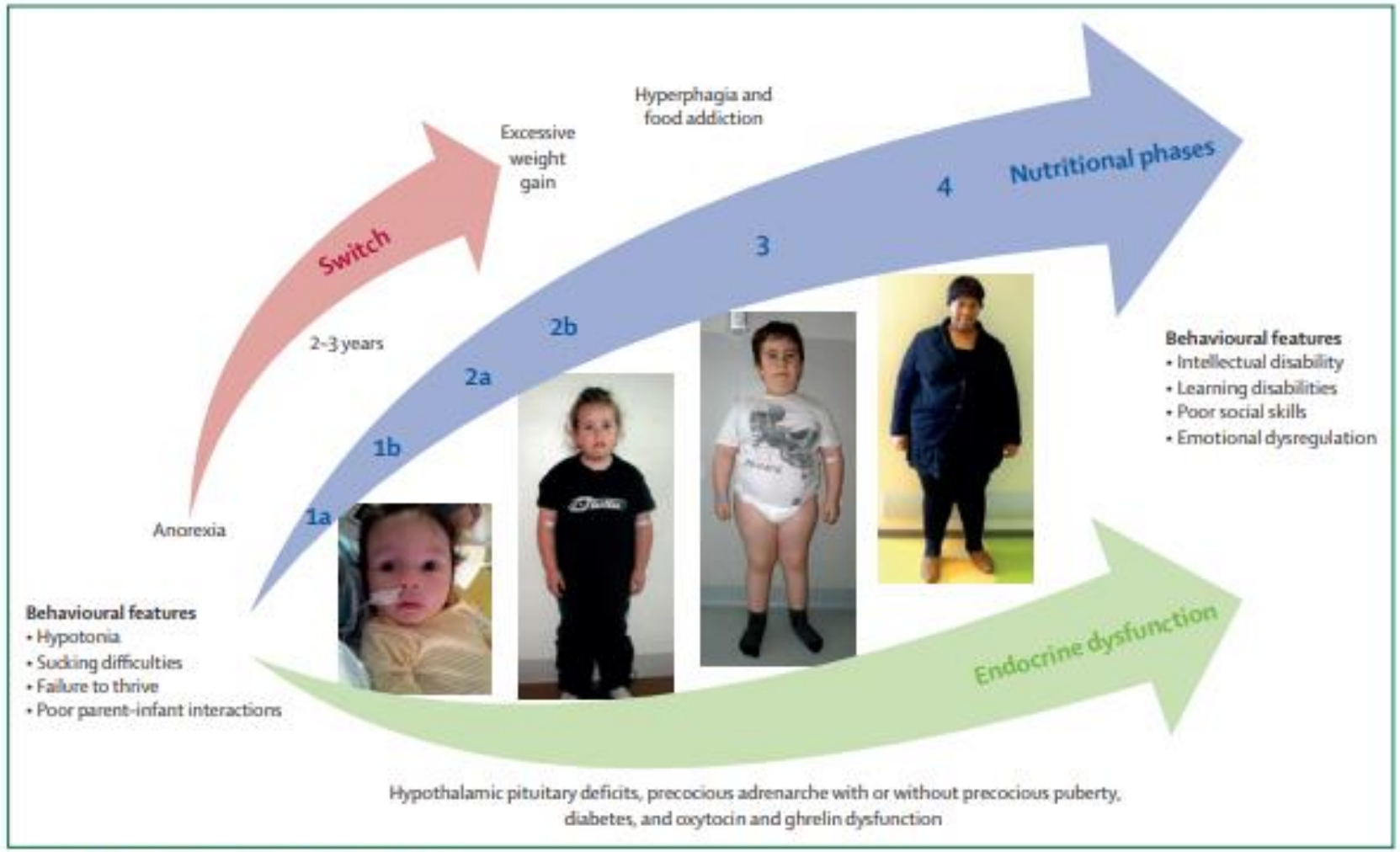
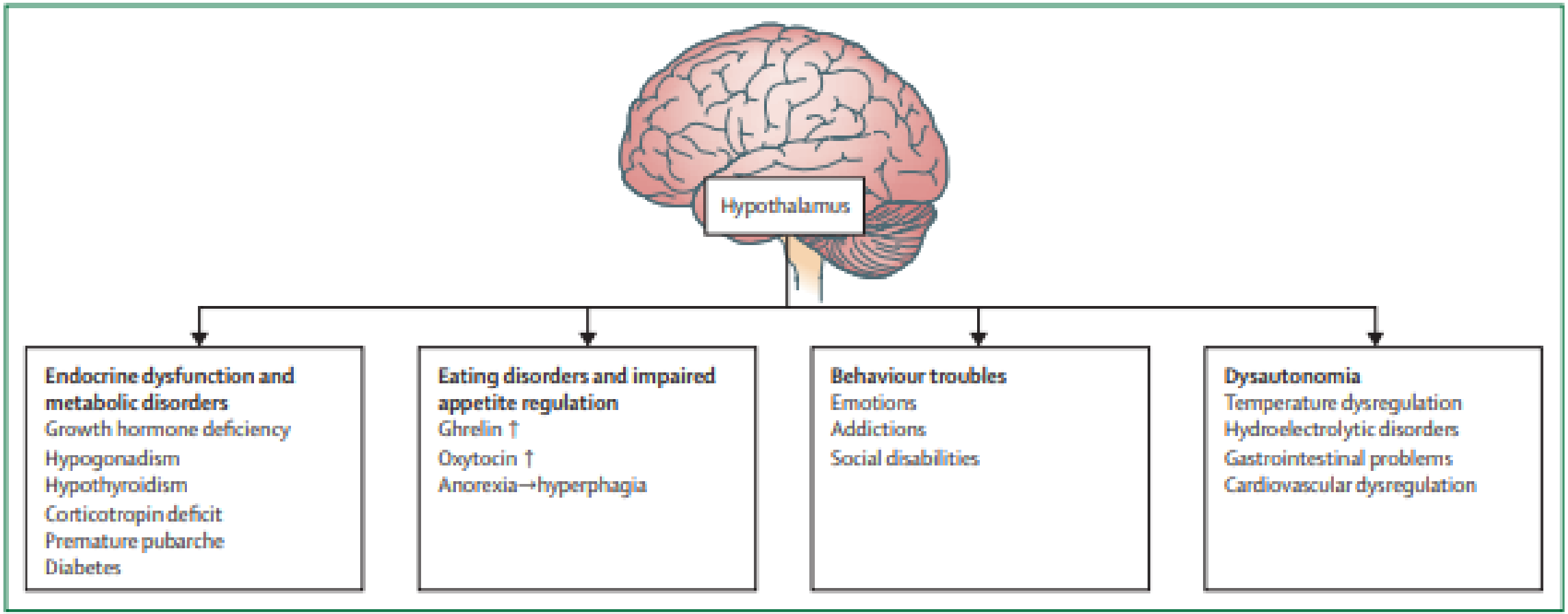


Figure 1: Natural history of Prader-Willi syndrome
Written informed consent was obtained from all patients or their guardians.

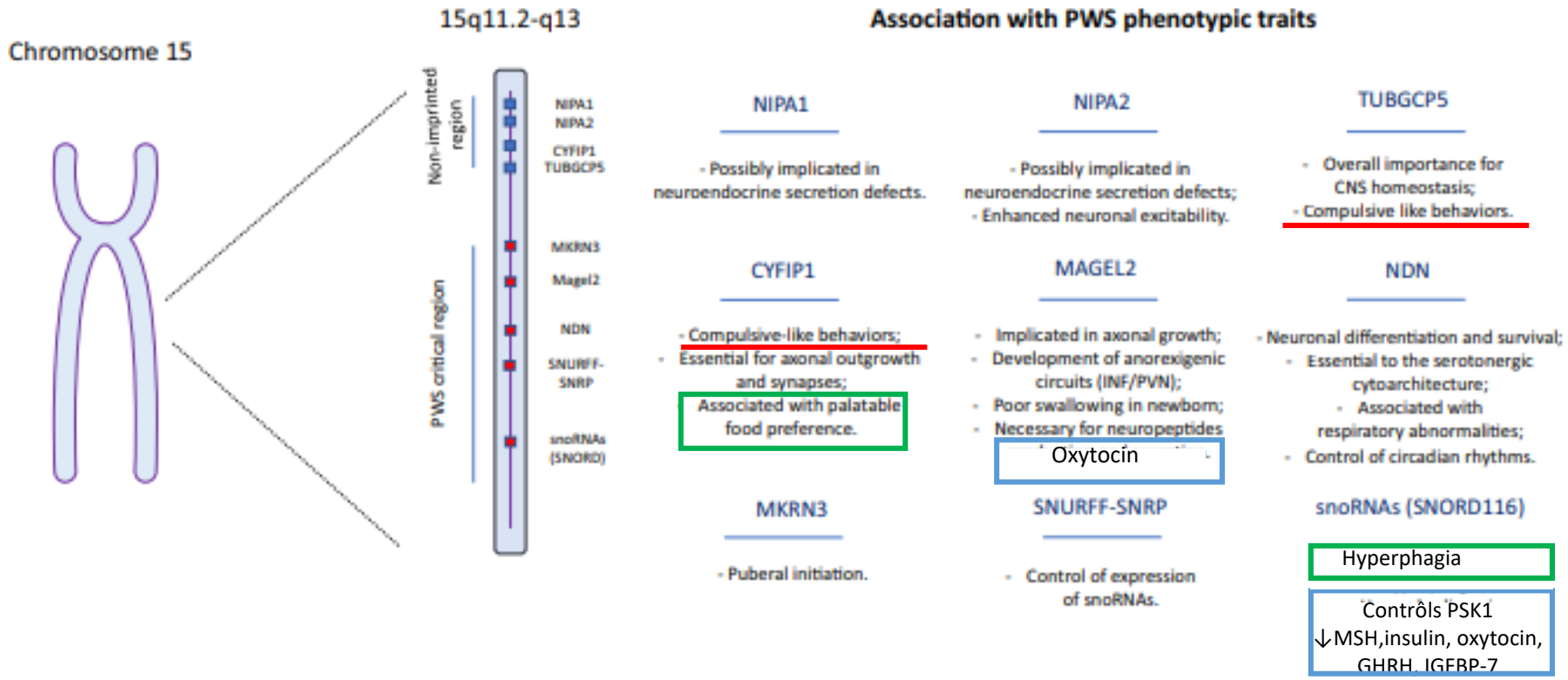
Tauber et al Lancet 2021

Impaired development and function of the hypothalamus explains most of the typical features of Prader-Willi syndrome



Hypothalamic neuropeptides and neurocircuitries in Prader Willi syndrome

Felipe Correa-da-Silva[1,2,3] | Eric Fliers[1] | Dick F. Swaab[3] | Chun-Xia Yi[1,2,3]



Correa-da-Silva Journal of Neuroendocrinology 2021

Hypothalamic neuropeptides and neurocircuitries in Prader Willi syndrome

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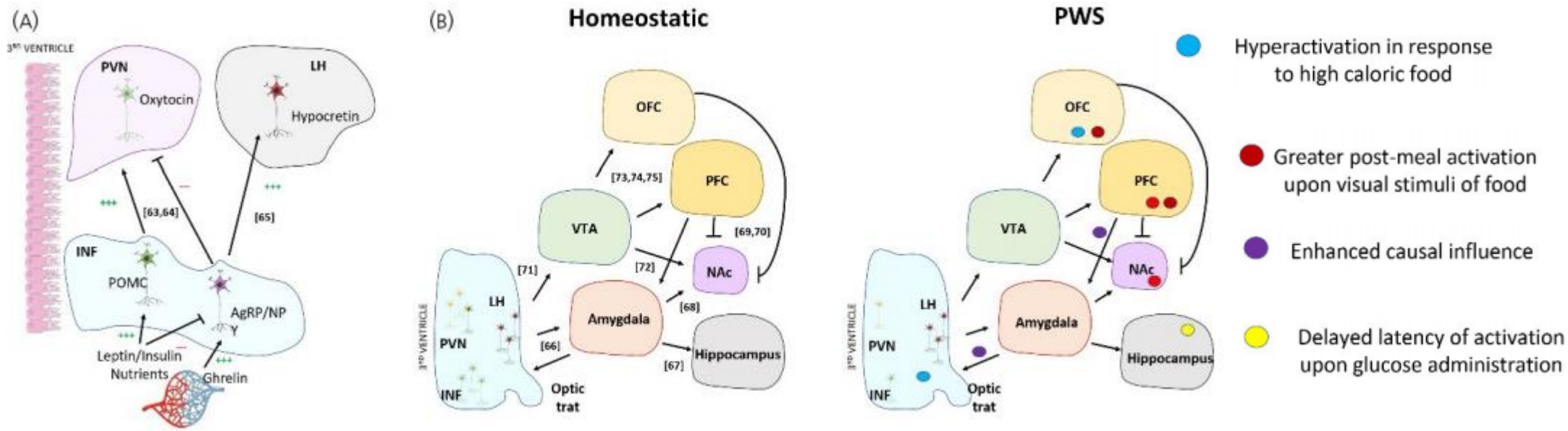

Damping of orexigenic (NPY) and anorexigenic (oxytocin and probably POMC) neurons with hyperactivation of circuits involved in food intake and motivation

HYPOTHALAMIC NEUROPEPTIDES

Neuropeptide	CNS	Hypoactivity/Hyperactivity	Plasma concentrations	Reference (##)
NPY	Decreased expression and cell count	Hypoactivity	–	103
AgRP	Decreased expression and unchanged cell count	Hypoactivity	–	103,121
Hypocretin	Unchanged cell count	Unaltered/ Hyperactivity (?)	Increased	130,131
POMC	Decreased expression	Hypoactivity	–	121
OXT	Decreased expression and cell count	Hypoactivity	Increased	102,142
BDNF	Decreased expression	Hypoactivity	Decreased	121,146

Abbreviations: AgRP, agouti related protein; BDNF, brain derived neurotrophic factor; NPY, Neuropeptide Y; OXT, oxytocin; POMC, proopiomelanocortin.

Correa-da-Silva Journal of Neuroendocrinology 2021

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WHAT IS HYPERPHAGIA?

-obsession with food and food-related items

-foraging and storing, stealing food, craving for food

-food impulsivity

-before and during meals :

-agitation and abnormal behaviours (excessive cleaning of the dishes, crumbs, over preocupation with others) , rituals

-either excessively slow or rapid eating with high risk of chocking and aspiration

-excessive quantities of food/drinking intake

Hyperphagia in Prader-Willi syndrome might be linked with addiction for food.

NON FOOD RELATED BEHAVIOURS

- other addictions : smoking +++alcohol rarely

-objects collections,

-global impulsivity

-thinking rigidity : difficulty to change mind

-disruptive behaviour

-perseverations, repetitions , rituals

-difficulty to evaluate quantities

Molecular Psychiatry
https://doi.org/10.1038/s41380-020-00917-x

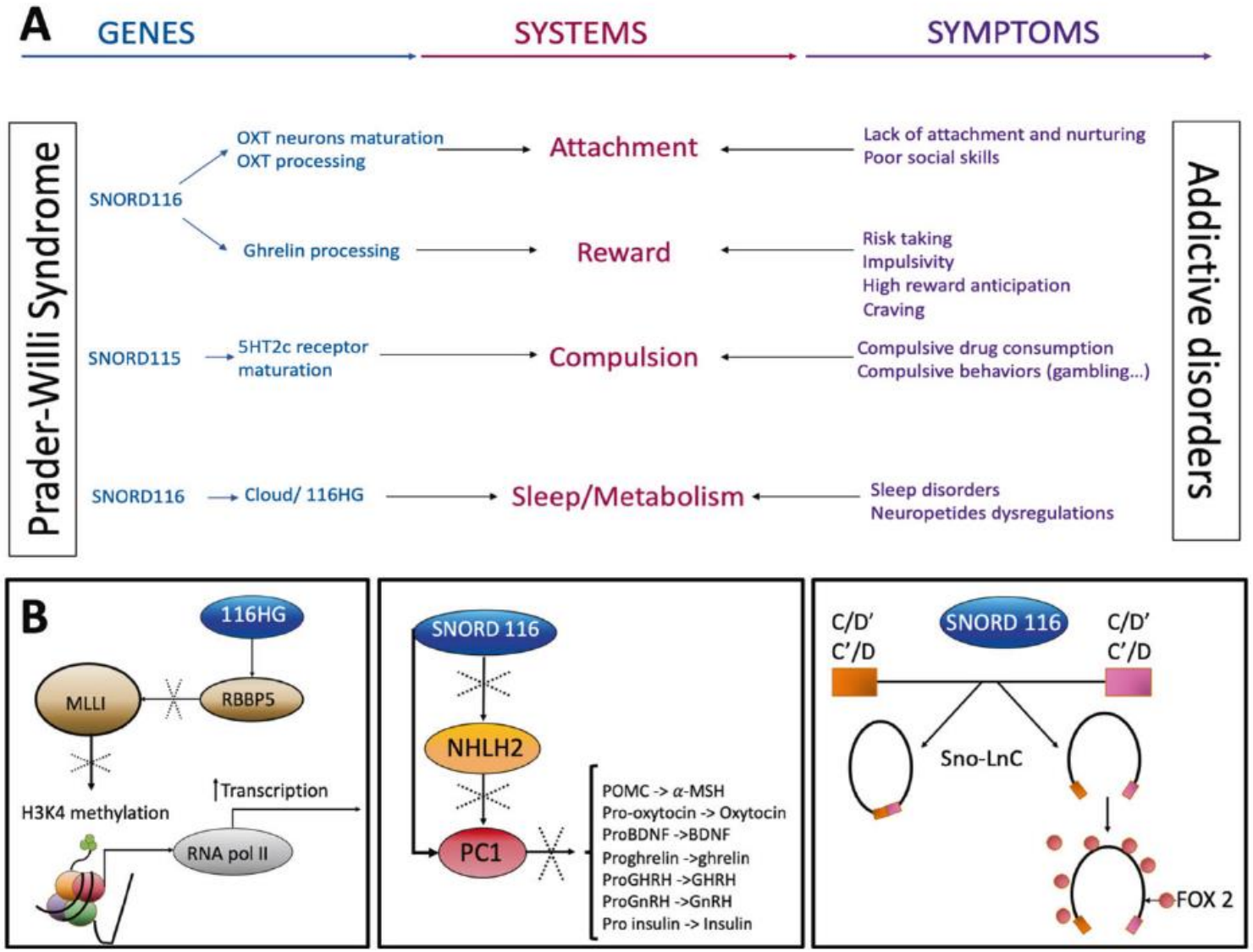
PERSPECTIVE

What can we learn from PWS and SNORD116 genes about the pathophysiology of addictive disorders?

Juliette Salles[1,2,3,4] · Emmanuelle Lacassagne[3] · Sanaa Eddiry[3] · Nicolas Franchitto[1,5] · Jean-Pierre Salles[3] · Maithé Tauber[1,3,4,6]

Received: 15 July 2020 / Revised: 16 September 2020 / Accepted: 5 October 2020

Published on line : 20 October 2020



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Salles et al. Clin Epigenet (2021) 13:159
https://doi.org/10.1186/s13148-021-01143-0

Clinical Epigenetics

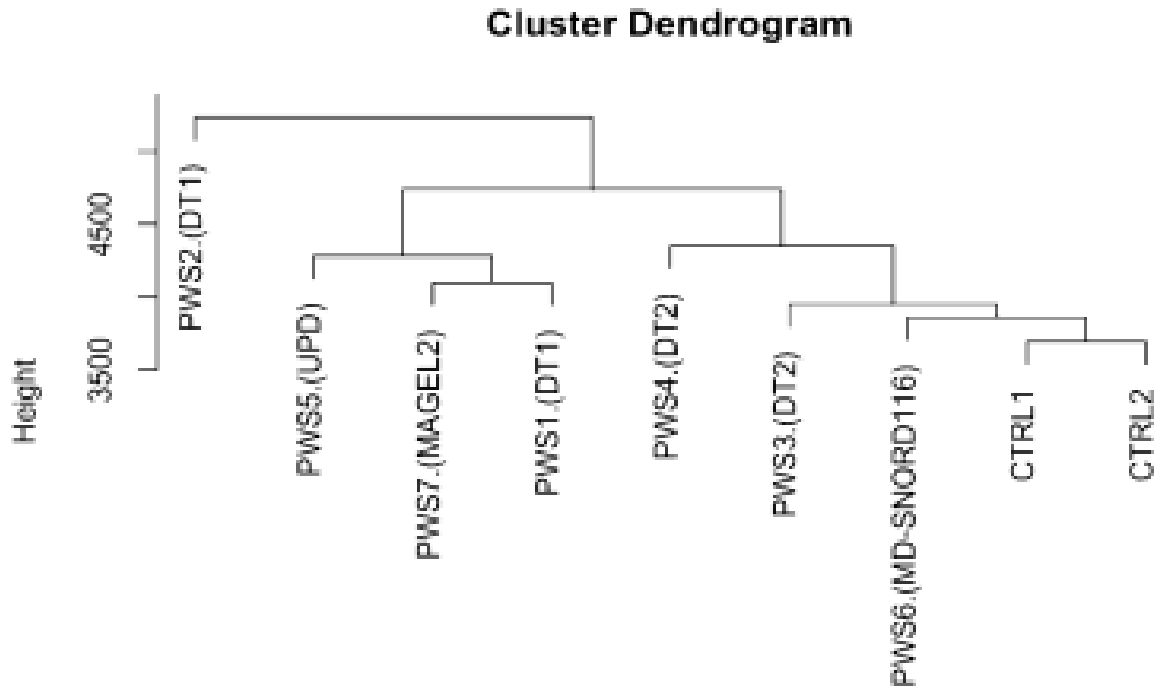
RESEARCH Open Access

Patients with PWS and related syndromes display differentially methylated regions involved in neurodevelopmental and nutritional trajectory

Juliette Salles[1,2,3,8*], Sanaa Eddiry[3], Emmanuelle Lacassagne[3], Virginie Laurier[4], Catherine Molinas[5], Éric Bieth[6], Nicolas Franchitto[7], Jean-Pierre Salles[3] and Maithé Tauber[3,5,8]

RESULTS: **29,234** differentially methylated cytosines, corresponding to **5,308** differentially methylated regions (DMRs), which matched with **2,280** genes. The DMRs in patients with PWS were associated with neurodevelopmental pathways, endocrine dysfunction, and social and addictive processes consistent with the key features of the PWS phenotype.

CONCLUSION: The PWS is associated with epigenetic modifications with differences in *SNORD116* and *MAGEL2* mutations, which seem to be relevant to the different associated phenotypes.



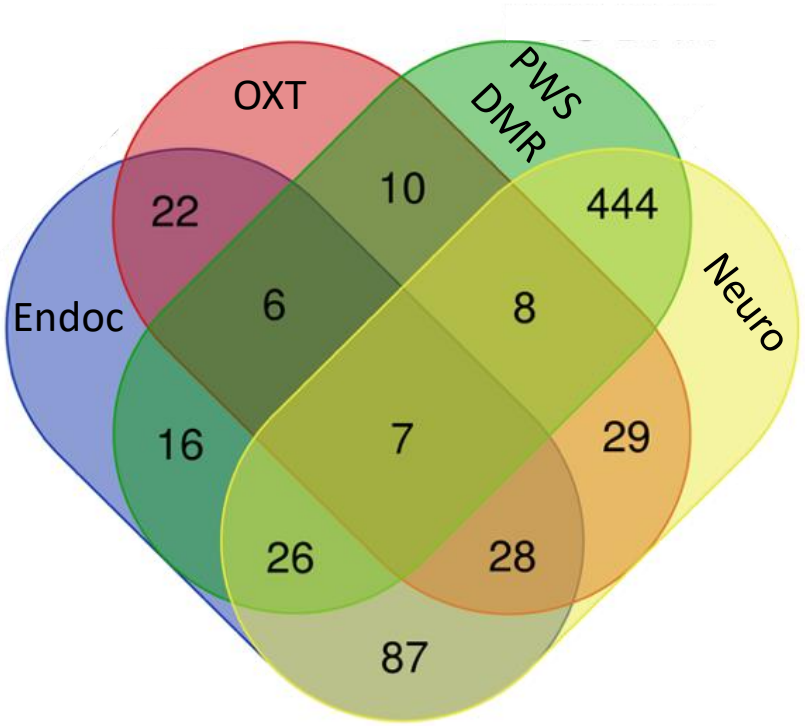
Results of hierarchical clustering; dendrogram including: PWS1: male infant patient with deletion type1, PWS2: male child patient with deletion type1, PWS3: female adult patient with deletion type2, PWS4: male adult patient with deletion type2 , PWS5: male infant patient with uniparental disomy (UPD), PWS6 (SNORD116 MD): female adult patient with SNORD116 deletion, PWS7 (MAGEL2): male adult patient with MAGEL2 mutation, CRTL1: male infant control, CTRL2: female infant control.

MAGEL2	Cellular macromolecule biosynthetic process	GO:0034645	2,83E-07
	Macromolecule biosynthetic process	GO:0009059	7,87E-07
	Organic substance biosynthetic process	GO:1901576	3,08E-06
	Biosynthetic process	GO:0009058	4,21E-06
	Cellular biosynthetic process	GO:0044249	9,83E-06
	Regulation of RNA metabolic process	GO:0051252	5,03E-05
	Nucleobase-containing compound metabolic process	GO:0006139	6,72E-05
	Nucleic acid metabolic process	GO:0090304	8,69E-05
SNORD116	Cellular metabolic process	GO:0044237	8,54E-09
	Nervous system development	GO:0007399	9,56E-09
	Metabolic process	GO:0008152	6,57E-08
	Primary metabolic process	GO:0044238	3,31E-07
	Nitrogen compound metabolic process	GO:0006807	5,41E-07
	Nucleic acid metabolic process	GO:0090304	9,97E-07
	Organic substance metabolic process	GO:0071704	1,15E-06
	Central nervous system development	GO:0007417	1,34E-06
	Hippo signaling pathway	KEGG:04390	6,29E-03
	Chronic myeloid leukemia	KEGG:05220	1,25E-02
	Neurotrophin signaling pathway	KEGG:04722	4,77E-02

The separate analysis for the *SNORD116* and *MAGEL2* deletions revealed that the DMRs associated with the *SNORD116* microdeletion were found in genes implicated in metabolic pathways and nervous system development, whereas *MAGEL2* mutations mostly concerned genes involved in macromolecule biosynthesis.

METHYLATION MARKS IN PWS

A



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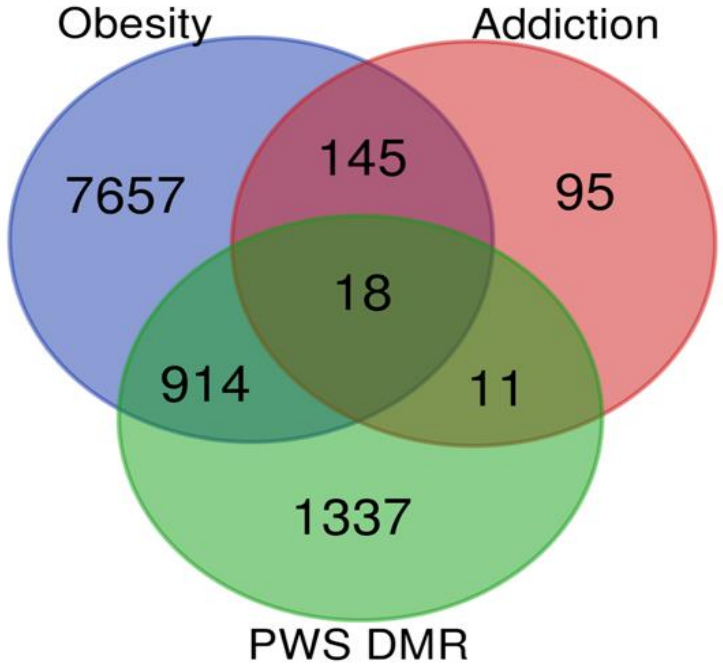
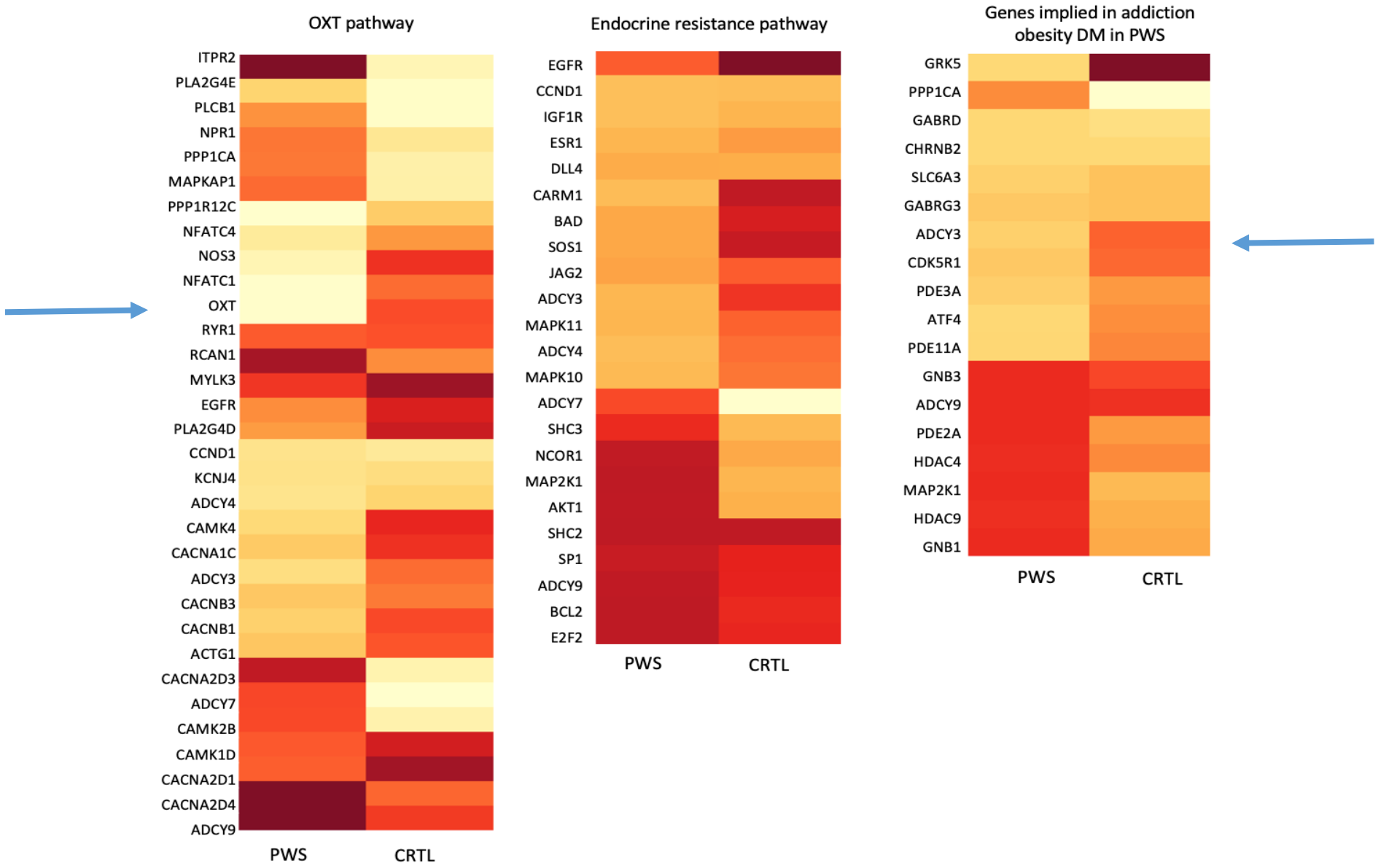


Salles J et al Clinical epigenetics 2021



Representation of the methylation level of the genes of interest. The darkness of the color indicates the level of methylation (pale colors indicate low level of methylation, while dark colors indicate high level of methylation).

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GENETICS IN MEDICINE
An open access paper www.nature.com

Genet Med. 2021; 23(9): 1664–1672.
Published online 2021 May 26. doi: 10.1038/s41436-021-01185-y
PMCID: PMC8460435
PMID: 34040195

SNORD116 and growth hormone therapy impact IGFBP7 in Prader–Willi syndrome

Sanaa Eddiry,[1,2] Gwenaelle Diene,[3,4] Catherine Molinas,[1,3,4] Juliette Salles,[1,5] Françoise Conte Auriol,[1,2] Isabelle Gennero,[1] Eric Bieth,[6] Boris V. Skryabin,[7] Timofey S. Rozhdestvensky,[7] Lisa C. Burnett,[8] Rudolph L. Leibel,[9] Maithé Tauber,[1,3,4] and Jean Pierre Salles[✉1,2,4]

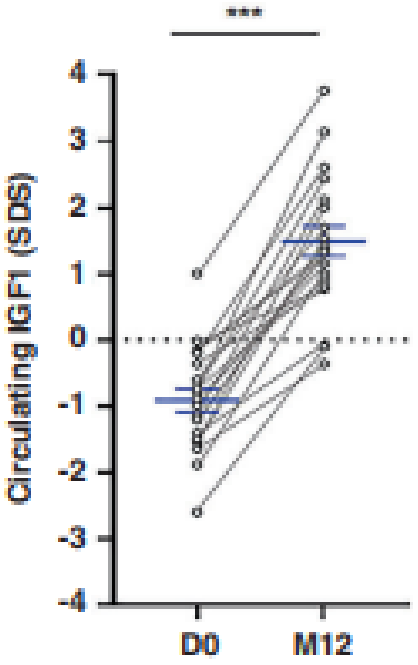
AIM : To clarify the role of SNORD116 in cellular and animal models with regard to growth hormone therapy (GHT).

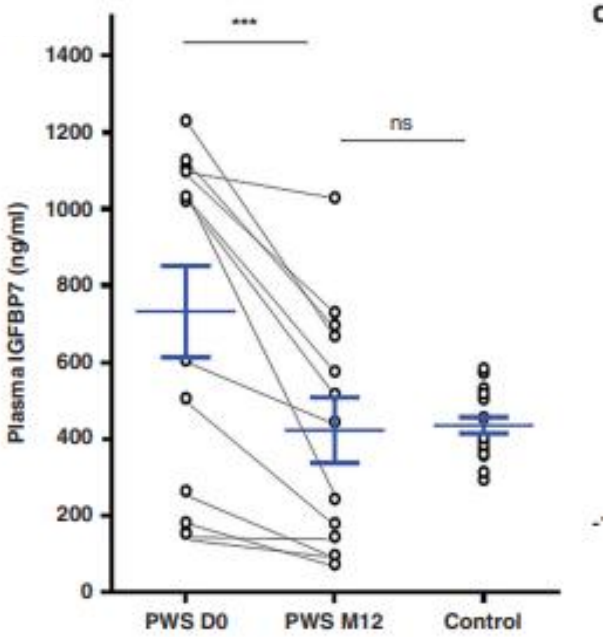
METHODS: We collected serums and induced pluripotent stem cells (iPSCs) from GH-treated PWS patients to differentiate into dopaminergic neurons, and in parallel used a Snord116 knockout mouse model. We analyzed the expression of factors potentially linked to GH responsiveness.

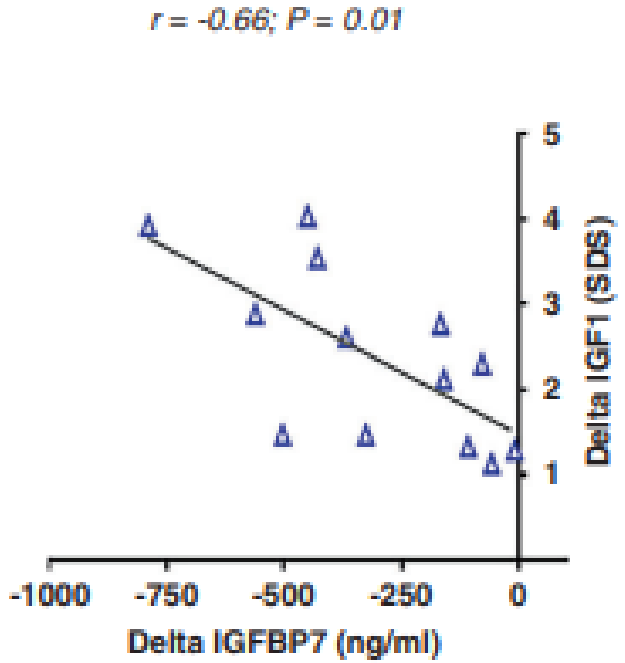
RESULTS: We found elevated levels of circulating IGFBP7 in naive PWS patients, with IGFBP7 levels normalizing under GHT.

CONCLUSION: SNORD116 deletion affects IGFBP7 levels, while IGFBP7 decreases under GHT in PWS patients. Modulation of the IGFBP7 level, which interacts with IGF1, has implications in the pathophysiology and management of PWS under GHT

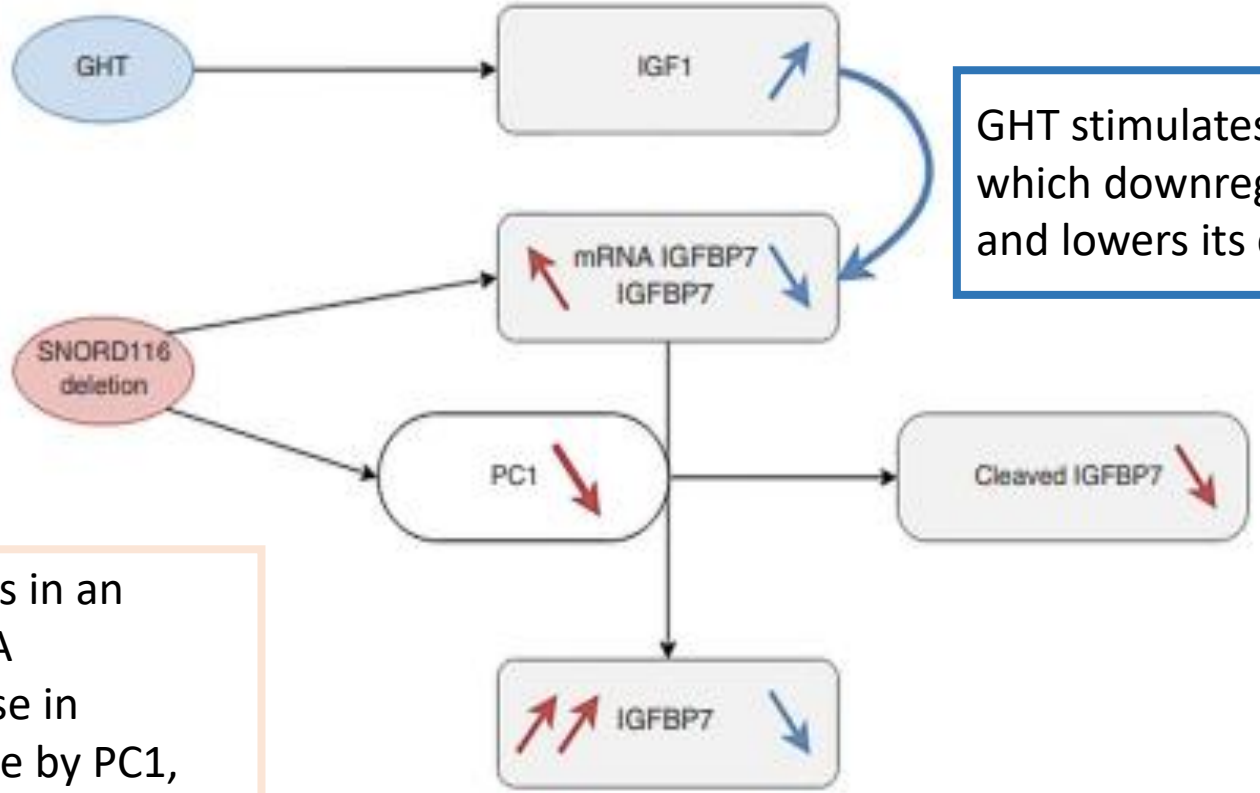
ELEVATED IGFBP7 PLASMA LEVELS DECREASE UNDER GROWTH HORMONE THERAPY (GHT) IN CHILDREN WITH PRADER–WILLI SYNDROME







We found elevated IGFBP7 levels in the brains of Snord116 knockout mice and in iPSC-derived neurons from a SNORD116-deleted PWS patient. ↑IGFBP7 in PWS patients may result from both ↑IGFBP7 expression and ↓IGFBP7 cleavage, by downregulation of the proconvertase PC1.



GHT stimulates IGF1 production,
which downregulates IGFBP7 mRNA expression
and lowers its circulating level.

Loss of SNORD116 results in an increase in IGFBP7 mRNA expression and a decrease in potential IGFBP7 cleavage by PC1, with high levels of secreted IGFBP7 in naive PWS patients

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Open Access Article

Diabetes Mellitus in Prader-Willi Syndrome: Natural History during the Transition from Childhood to Adulthood in a Cohort of 39 Patients

by Alice Clerc [1], Muriel Coupaye [2], Héléna Mosbah [2], Graziella Pinto [3], Virginie Laurier [4], Fabien Mourre [4], Christine Merrien [4], Gwenaëlle Diene [1,5], Christine Poitou [2,6] and Maithé Tauber [1,7,*]

AIM: was to describe the natural history of T2DM in patients with PWS before the age of 25 years and to develop screening and preventive strategies.

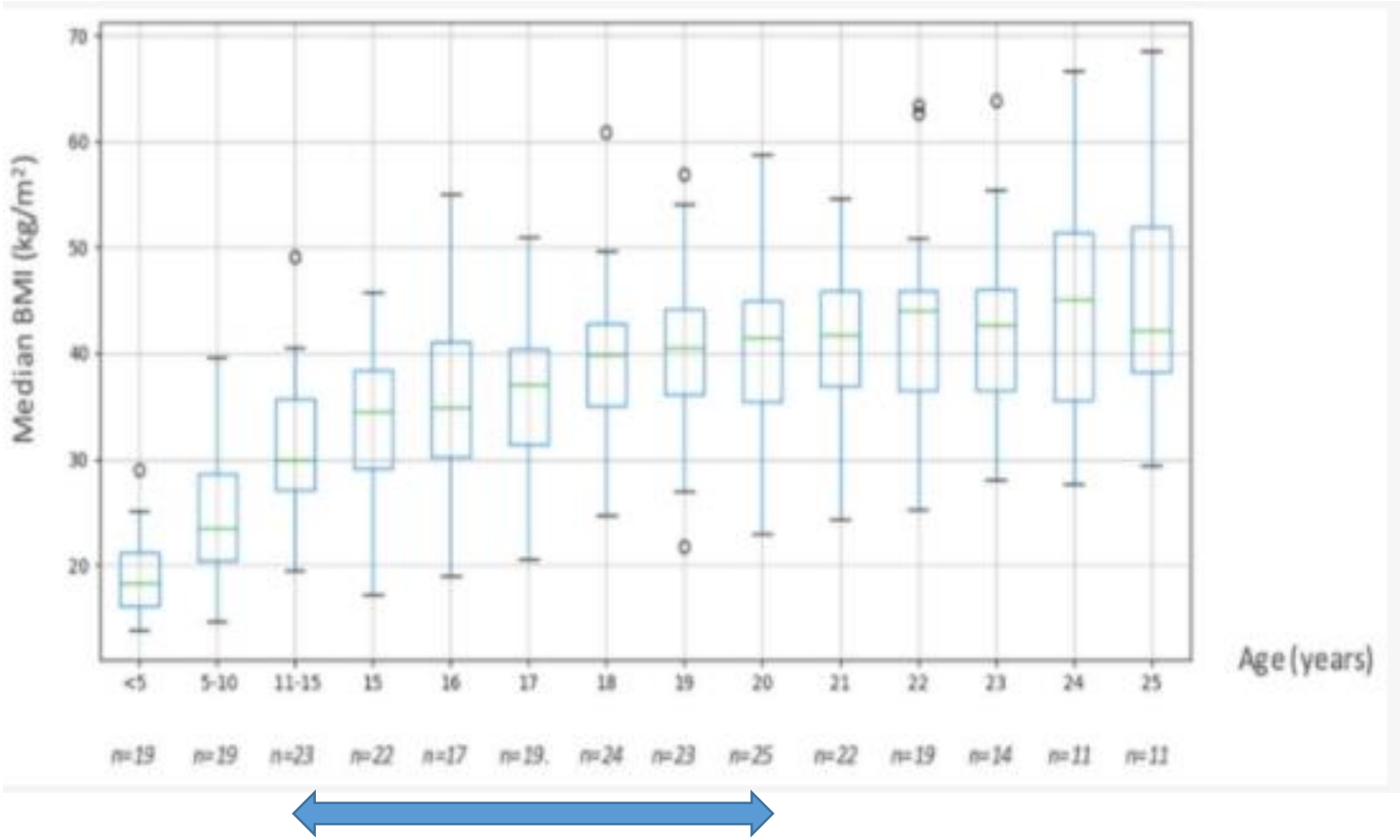
POPULATION :Thirty-nine patients followed in the French PWS Reference Center were included (25.6 years [23.7; 31.7]). Twenty-one had been treated with growth hormone (GH), fifteen had not, and three had an unknown status.

RESULTS: The median age at T2DM diagnosis was **16.8 years** (11–24) and **the median BMI was 39 kg/m²** [34.6; 45], with 34/35 patients living with obesity. The patients displayed frequent psychiatric (48.3% hospitalization,) and metabolic (56.4% hypertriglyceridemia,) comorbidities and **a parental history of T2DM (35.7%) or overweight (53.6%)** compared to the PWS general population. There was no difference in BMI and metabolic complications between the GH-treated and non-GH-treated groups at T2DM diagnosis.

CONCLUSIONS Patients with PWS who develop early T2DM have severe obesity, a high frequency of psychiatric and metabolic disorders, and a family history of T2DM and overweight. These results underline the need for **early identification of patients at risk, prevention of obesity, and repeated blood glucose monitoring during the transition period**.

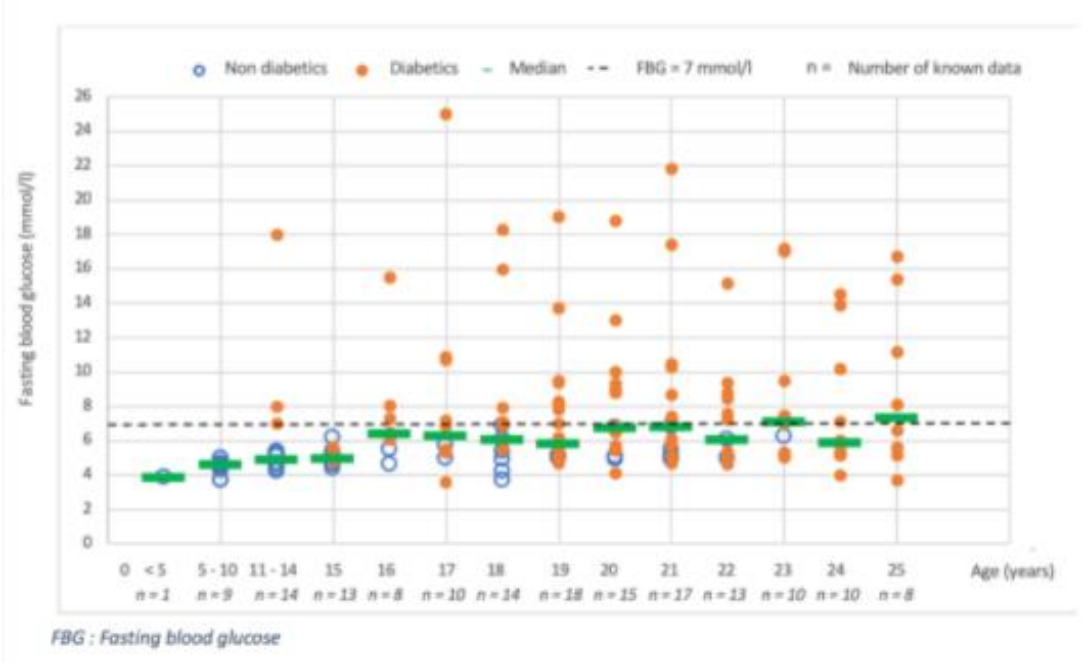
J. Clin. Med. **2021**, *10*(22), 5310

CHANGE IN BMI AS A FUNCTION OF AGE IN THE WHOLE POPULATION.

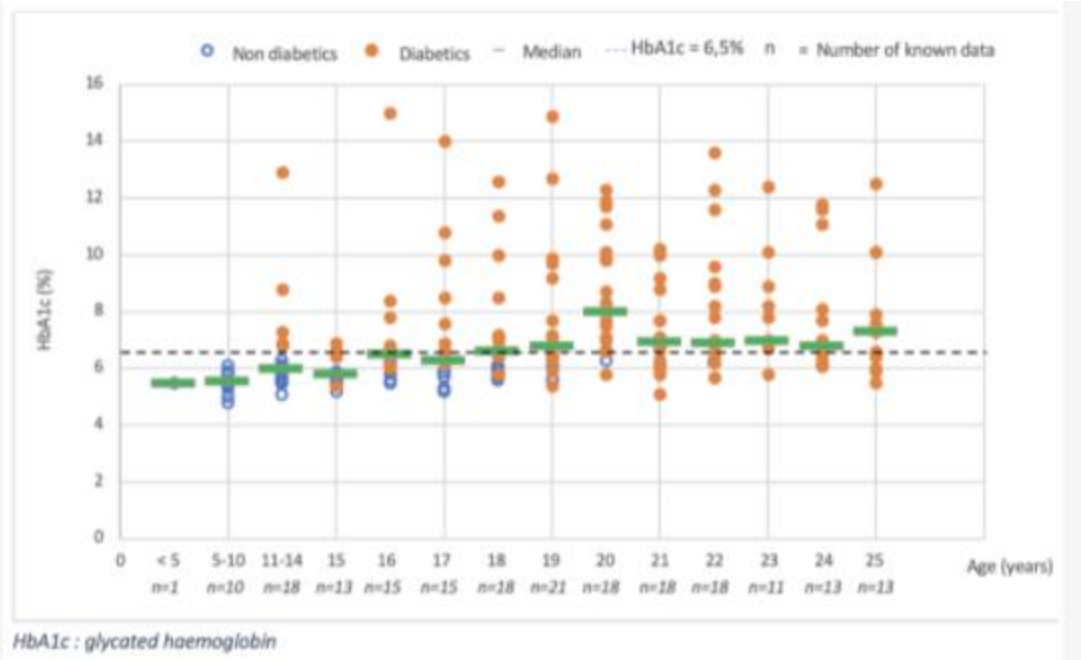


TRANSITION PERIOD : A STRONG NEED TO CONTROL BMI

EVOLUTION OF FASTING BLOOD GLUCOSE AND HBA1C AS A FUNCTION OF AGE.



FBG : Fasting blood glucose



HbA1c : glycated haemoglobin

Glycemic control is more difficult to achieve in patients with PWS and diabetes than in patients with diabetes but no PWS. Metformin treatment, which was prescribed for 94.7% of patients, was often insufficient as a monotherapy. Insulin was or had been used in 70.3% of the cases and the patients had a **median of three anti-diabetic treatments** [2; 3]. **SGLT-2 inhibitors** show promising results as they allow for significant weight loss along with improved blood sugar control. Three cases of an SGLT-2 inhibitor prescribed in combination with a GLP-1 agonist have been described in PWS, with marked improvement in HbA1c and significant weight loss following initiation of treatment

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RESEARCH Open Access

Is ghrelin a biomarker of early-onset scoliosis in children with Prader–Willi syndrome?

Dibia Liz Pacoricona Alfaro[1], Gwenaelle Diene[1,2,3], Graziella Pinto[4], Jean-Pierre Salles[2,5,6], Isabelle Gennero[5,7], Sandy Faye[2,3,8], Catherine Molinas[2,3,5,8], Marion Valette[1,2,3,8], Catherine Arnaud[1,9] and Maithé Tauber[2,3,5*]

BACKGROUND: To explore (1) whether ghrelin levels differ between children with PWS with and without EOS and correlate with scoliosis severity, and (2) whether ghrelin levels in the first year of life are associated with the later development of EOS.

METHODS: We used a case control study design for the first question and a longitudinal design for the second.
Thirty children<10 years old with EOS and 30 age- and BMI-matched controls without EOS from our database were included. The Cobb angle at diagnosis was recorded. In addition, 37 infants with a ghrelin measurement in the first year of life were followed until 4 years of age and assessed for EOS.

RESULTS: EOS children had an AG/UAG ratio statistically significantly lower than controls. The Cobb angle was positively correlated with Total Ghrelin and UAG. TG and AG in the first year of life were higher in infants who later develop EOS without reaching a statistically significant difference.

CONCLUSIONS: Our results suggest that ghrelin may play a role in the pathophysiology of EOS in PWS.
Higher ghrelinemia in the first year of life required careful follow-up for EOS.

Table 1 Clinical characteristics and TG, AG, UAG and AG/UAG of PWS children with and without EOS

	PWS children with EOS (cases) n = 30	PWS children without EOS (controls) n = 30	*p* value
Sex—girls, n (%)	20 (66.7)	16 (53.3)	0.285
Age—years, median (IQR)	3.7 (2.0–5.2)	3.9 (2.3–5.0)	–
BMI—WHO z-score, median (IQR)	0.0 (− 0.8–1.4)	0.1 (− 0.9–1.4)	–
Genetic subtype—deletion, n (%)	12 (40.0)	19 (63.3)	0.090
Age at start GH—months, median (IQR)	12 (9–13)	13 (10–16)	0.043
GH dose—mg/kg/d, median (IQR)	0.0263 (0.0215–0.0334)	0.0277 (0.0184–0.0321)	0.614
IGF-1—z-score, median (IQR)[a]	1.4 (0.3–2.5)	0.7 (− 0.2–1.7)	0.065
HbA1c—%, median (IQR)[a]	5.4 (5.2–5.6)	5.4 (5.2–5.8)	0.364
Insulin—μUI/ml, median (IQR)[a]	5.2 (2.5–8.2)	4.9 (3.0–7.2)	0.084
TG—pg/ml, median (IQR)	314.0 (207.2–481.0)	317.1 (231.7–618.4)	0.797
AG—pg/ml, median (IQR)	161.3 (89.6–210.6)	194.6 (154.2–256.8)	0.079
UAG—pg/ml, median (IQR)	152.3 (81.7–263.5)	120.1 (71.2–219.2)	0.382
AG/UAG, median (IQR)	0.783 (0.559–1.993)	1.589 (1.166–2.433)	0.005
Age at EOS diagnosis—years, median (IQR)	3.4 (1.8–5.2)		
Cobb angle at diagnosis—degrees, median (IQR)[b]	20 (12–27)		

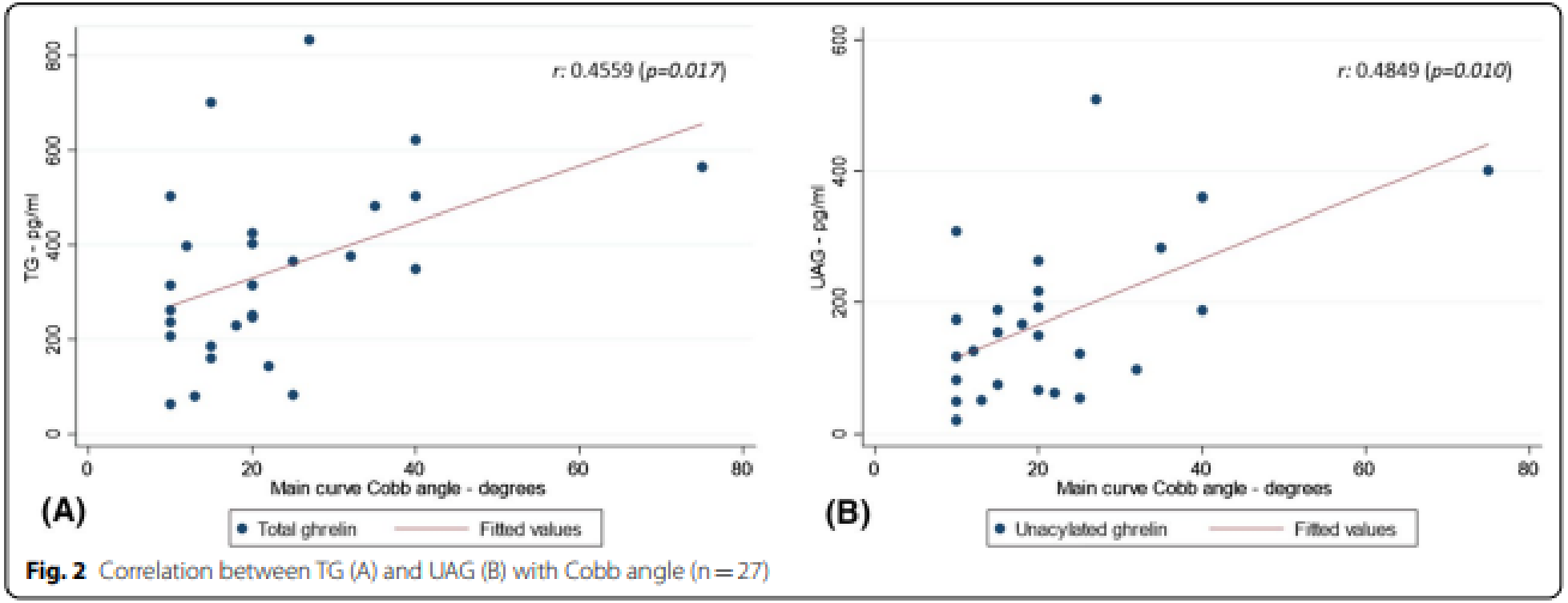

Fig. 2 Correlation between TG (A) and UAG (B) with Cobb angle (n = 27)

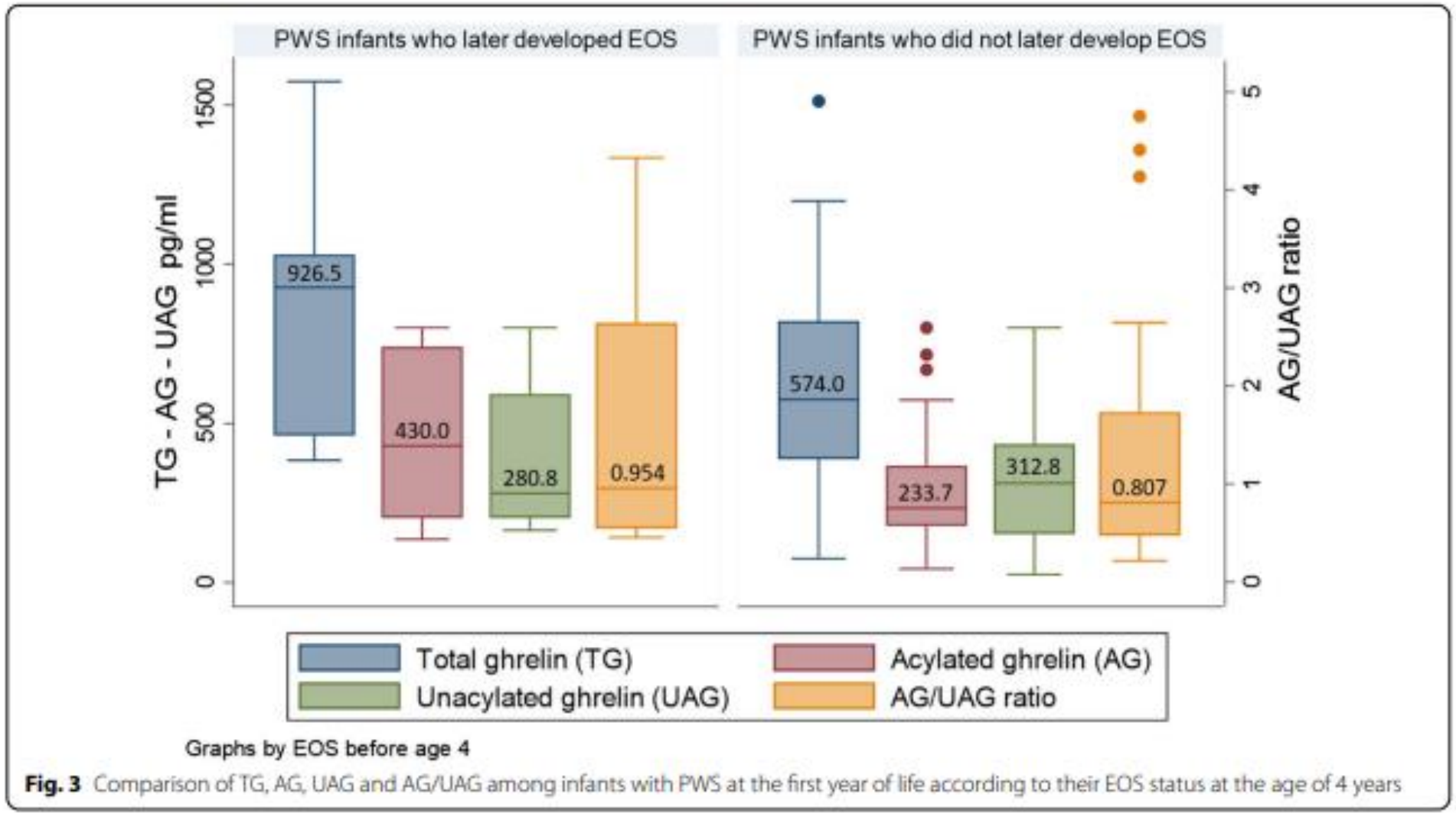

Fig. 3 Comparison of TG, AG, UAG and AG/UAG among infants with PWS at the first year of life according to their EOS status at the age of 4 years

OUTLINE

-OVERVIEW OF PWS

-MENTAL HEALTH :
- -PWS as a model of addiction disorders
- -Epigenetics marks

-ENDOCRINE AND METABOLIC TROUBLES
- -increased IGFBP-7 a new marker of PWS ?
- -diabetes in the transition period

-SCOLIOSIS
- -is ghrelin a marker of the occurrence and severity of scoliosis ?

-COVID-19
- -people with PWS are not at high risk for severe COVID-19 as a group

-THERAPEUTIC PERSPECTIVES
- -many drugs in development

RESEARCH Open Access

Paradoxical low severity of COVID-19 in Prader-Willi syndrome: data from a French survey on 647 patients

Muriel Coupaye[1*], Virginie Laurier[2], Grégoire Benvegnu[3,4], Christine Poitou[1,5], Pauline Faucher[1], Héléna Mosbah[1], Gwenaelle Diene[3,6], Graziella Pinto[7], Laura González Briceño[7], Christine Merrien[2], Ana Camarena Toyos[2], Emilie Montastier[8], Maithé Tauber[3,9] and Fabien Mourre[2]

BACKGROUND: To assess prevalence and medical course of SARS-CoV-2 infection in children and adults with PWS. From November 2020 to January 2021, we performed a detailed medical survey on 342 adults and 305 children with PWS followed in the French reference center.

RESULTS: We obtained responses from 288 adults (84%) and 239 children (78%). Thirty height adults (13.2%) and 13 children (5.4%) with PWS had SARS-CoV-2 infection. Mean age of **adults** was 34.1±11.9 years and mean body mass index was 40.6±12.7 kg/m2 ; **82% had obesity and 37% had diabetes**. Only 3 children (23%) had obesity and none had diabetes. The most frequent symptoms of COVID-19 were asthenia, fever, cough, headache and shortness of breath. **All patients had a favorable outcome**.

CONCLUSION: PWS itself is **not a risk factor for severe COVID-19** in children and adults. On the contrary, evolution of SARS-CoV-2 infection in adults with PWS seems more favorable than expected, given their comorbidities

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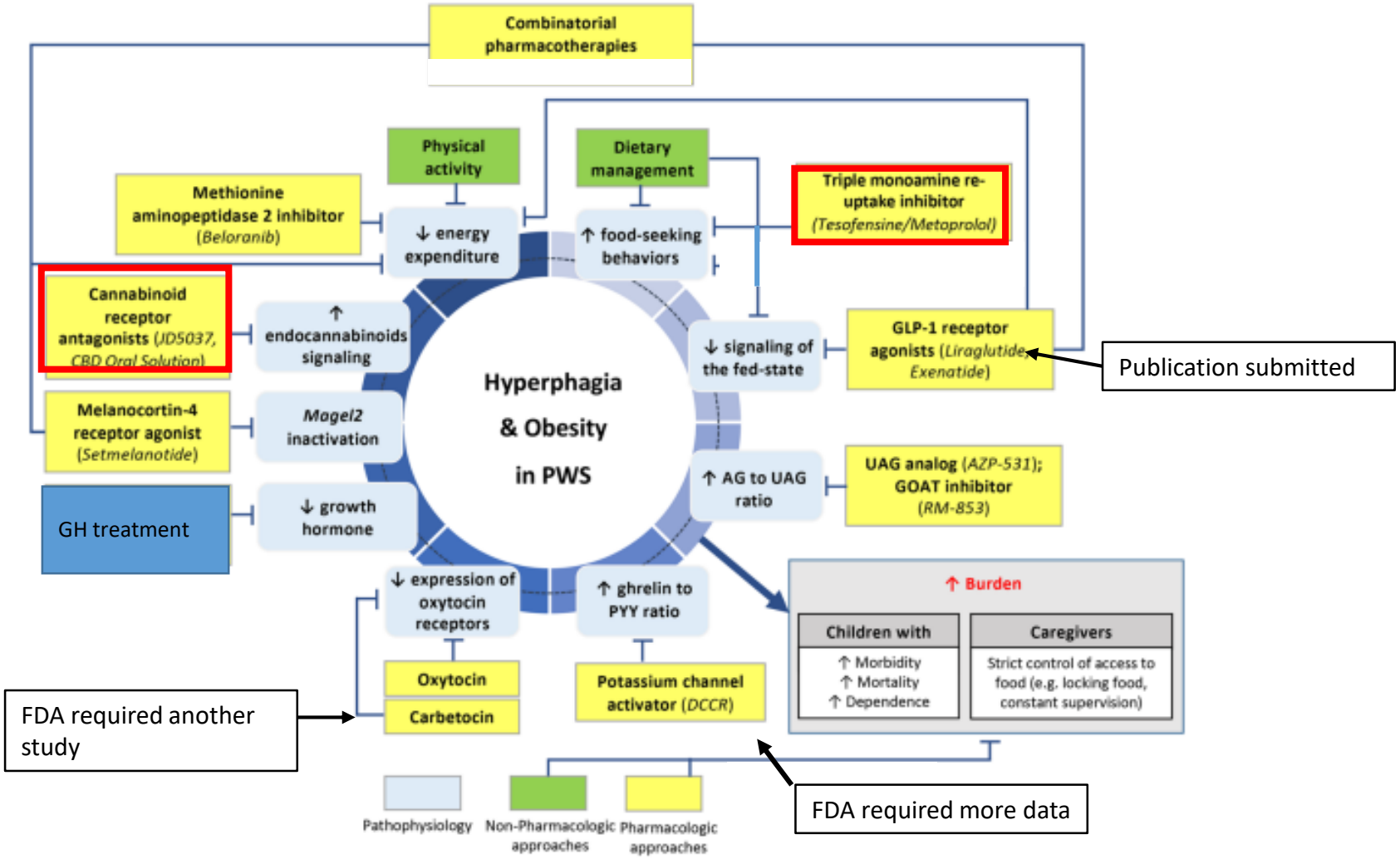
Current and emerging therapies for managing hyperphagia and obesity in Prader-Willi syndrome: A narrative review

Qiming Tan[1] | Camila E. Orsso[2] | Edward C. Deehan[2] | Lucila Triador[1] | Catherine J. Field[2] | Hein Min Tun[3] | Joan C. Han[4] | Timo D. Müller[5,6] | Andrea M. Haqq[1,2]



Publication submitted

FDA required another study

FDA required more data

Obesity Reviews 2020

CONCLUSIONS AND PERSPECTIVES

-What can we learn from addictive disorders ?

-How to use the new markers IGFBP-7 and ghrelin ?

-A challenge for preventing and treat diabetes in the transition period

-How to explain the « good outcome » of Covid19?

-What drug and what target?

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