Hypomethylation of the Prader-Willi imprinting control region associates with postnatal growth and visceral adiposity in healthy children

G. Carreras-Badosa[1], **B. Mas-Parés**[1], **A. Gómez-Vilarrubla**[1], **S. Xargay-Torrent**[1], **A. de Arriba Muñoz**[2], **E. Puerto-Carranza**[3], **A. Prats-Puig**[4], **F. de Zegher**[5], **L. Ibañez**[6], **J. Bassols**[1], **A. López-Bermejo**[1]

[1] Pediatrics, Girona Biomedical Research Institute, Girona, Spain; [2] Pediatric Endocrinology Unit, Miguel Servet Hospital, Zaragoza, Spain; [3] Pediatrics, Dr. Josep Trueta Hospital, Girona, Spain; [4] University School of Health and Sport (EUSES), University of Girona, Girona, Spain; [5] Department of Development & Regeneration, University of Leuven, Leuven, Belgium;[6] Endocrinology, Sant Joan de Déu Children's Hospital Pediatric Institute, University of Barcelona, Barcelona, Spain.

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Introduction

Children with Prader-Willi syndrome present with short stature and obesity. However, very little is known about the role of this imprinted control region in postnatal growth in the general population. This study aims to analyze the methylation status of the PWS imprinting control region (ICR) (**Figure 1**) in placenta and its association with postnatal growth and obesity parameters in healthy children.

Methodology

The methylation percentages of the PWS-ICR (**Figure 2**) were determined by Epytyper™ technology in placentas from 118 healthy newborns included in a cohort of mother-newborn pairs in Girona, a region in Northeastern Spain. Methylation values for the different studied cytosine-guanine nucleotides (CpG) within the PWS-ICR were correlated with anthropometric parameters (weight, height and body composition) in the offspring from birth to 6 years of age (**Table 1**).

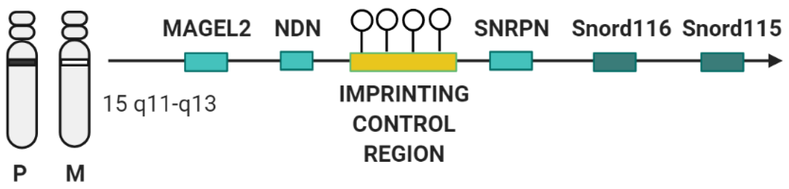

Figure 1: Studied Prader-Willi syndrome imprinted control region (PWS-ICR).

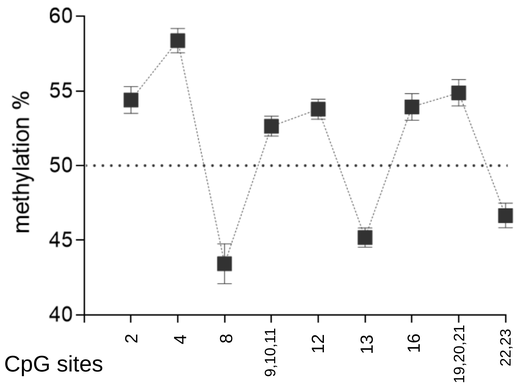

Figure 2: Placental methylation percentages of the studied CpG sites within the PWS-ICR.

Table 1: Descriptives of the studied variables

	All population	Lower birth-weight (below BW-sds median)	Higher birth-weight (over BW-sds median)
Newborn	**N=118**	**N=59**	**N=59**
Gestational age (weeks)	39,7 ± 1,3	39,7 ± 1,3	39,6 ± 1,3
Birth weight (g)	3354 ± 384	3097 ± 242	3612 ± 324 *
Birth weight SDS (z score)	0,18 ± 0,88	-0,50 ± 0,41	0,87 ± 0,66 *
Birth height (cm)	49,7 ± 1,7	48,8 ± 1,4	50,6 ± 1,5 *
Birth height SDS (z score)	-0,04 ± 1,01	-0,59 ± 0,74	0,52 ± 0,95 *
1st month weight (g)	4203 ± 477	3980 ± 398	4427 ± 445 *
1st month height (cm)	53,7 ± 1,9	53,0 ± 1,9	54,4 ± 1,6 *
Follow-up at 6 years of age	**N=109**	**N=54**	**N=55**
Age (years)	6,29 ± 0,87	6,37 ± 0,97	6,23 ± 0,78
Height (cm)	119,0 ± 8,0	118,5 ± 9,1	119,4 ± 7,0
Height SDS (z score)	0,22 ± 1,21	0,01 ± 1,18	0,43 ± 1,21
Visceral fat (cm)	5,34 ± 1,27	5,31 ± 1,22	5,37 ± 1,32

Data shown as mean ± standard deviation SD; *p < 0,001

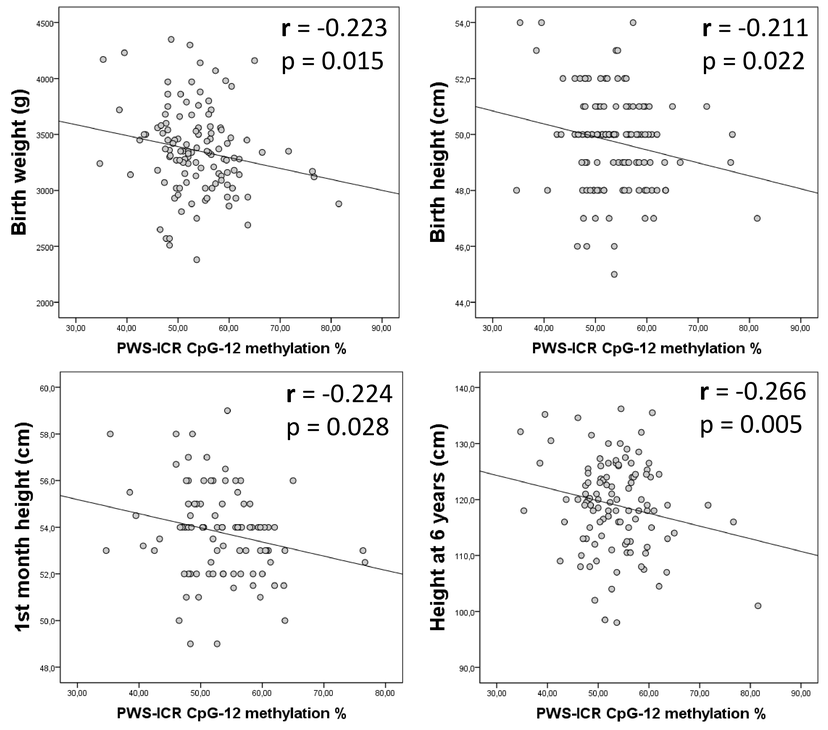

Figure 3: Birth weight and height, 1st month height and height at 6 years is related to placental methylation of PWS-ICR.

Results

The methylation status of the PWS-ICR was inversely and independently correlated to weight and height at birth, height during the first month of life, and with height at 6 years of age (**Figure 3**) as well as with visceral fat mass. All inverse associations between PWS-ICR methylation and growth and visceral adiposity parameters were more pronounced in children who had been heavier at birth (those with birthweight above the median; adjusted multivariate models $0.40 > R^2 > 0.30$), especially the association with the visceral fat mass at 6 years of age (**Figure 4**).

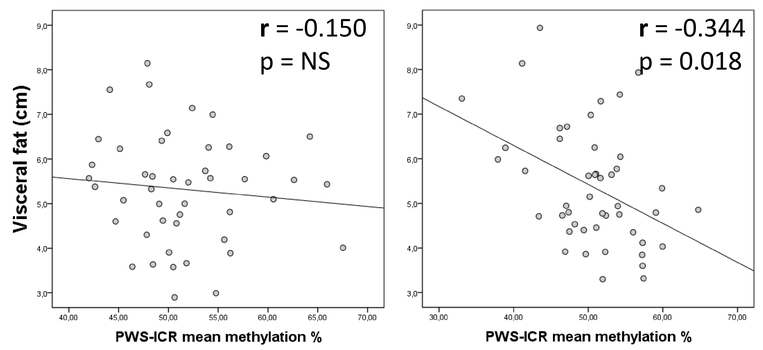

Figure 4: Visceral fat and PWS-ICR placental methylation association is pronounced in children who had been heavier at birth.

Conclusion

Placental PWS-ICR methylation status associates with growth parameters in healthy children from birth to school age as well as with higher visceral adiposity at 6 years of age. As shown for PWS patients, PWS-ICR methylation could similarly be involved in postnatal growth and visceral accumulation in healthy infants, especially in those who already accumulated more fat at birth.