

PLACENTAL *FRAT-1* METHYLATION IN WOMEN WITH GESTATIONAL OBESITY IS ASSOCIATED WITH BODY COMPOSITION IN THE OFFSPRING AT 6 YEARS OF AGE

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INTRODUCTION

Gestational obesity can cause **metabolic programming** in the offspring. Epigenetic modifications such as **DNA methylation** have been suggested as potential mechanisms underlying this programming. ***FRAT-1*** is a gene involved in the **WNT signaling pathway**, which is an important regulator of adipose tissue development.

OBJECTIVES

The aims of this work were to study:

- The **methylation** status of ***FRAT-1*** in **placentas** of women with either normal weight or gestational obesity.
- Its association with **endocrine-metabolic parameters** in the offspring at **6 years of age**.

METHODOLOGY

A **global methylation array** (Infinium® Methylation EPIC BeadChip) was made in placental samples from 24 pregnant mothers with either normal weight gain or gestational obesity. **Two CpGs in *FRAT-1*** were significantly associated with increased maternal weight during gestation (FDR = 2.20x10⁻⁶ and OR = 0.91; FDR = 2.17x10⁻⁶ and OR = 0.94). The methylation status of these CpGs in ***FRAT-1*** was validated by pyrosequencing in a cohort of 64 pregnant women (39 with normal weight gain and 25 with gestational obesity) and its association with endocrine-metabolic parameters [weight, height, body mass index (BMI) and body composition] in the offspring at 6 years of age was assessed.

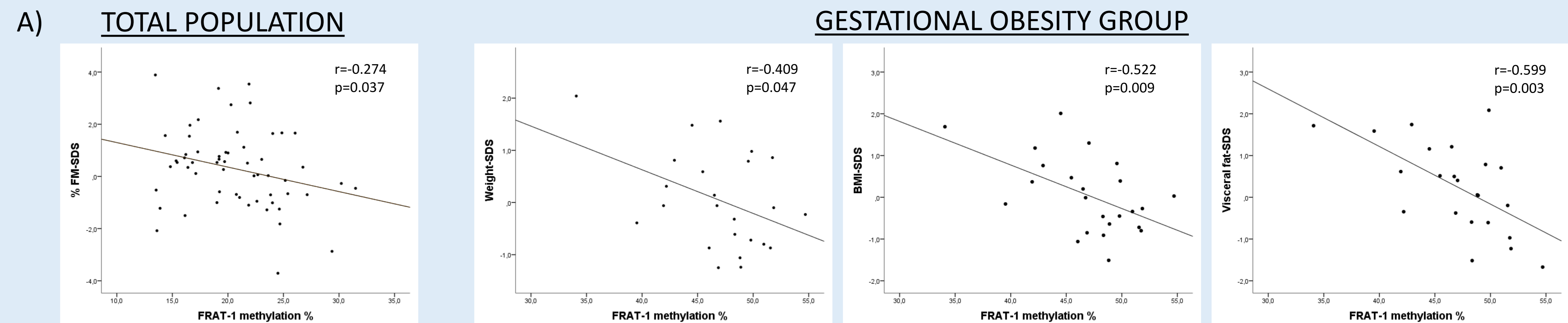


Figure 1: Schematic representation of the used methodology.

RESULTS

	Total population N=64	Normal weight gain N=39	Gestational obesity N=25	P-value
Mother				
Age (year)	30.80±4.17	30.85±4.43	30.72±3.79	n.s
Height (cm)	163.02±5.73	163.17±6.16	162.76±5.05	n.s
Weight 1st T (Kg)	67.80±13.85	64.45±13.72	73.50±12.36	0.012
Weight 2nd T (Kg)	72.52±12.45	67.76±10.41	79.75±11.95	<0.001
Weight 3rd T (Kg)	78.15±14.09	73.37±13.34	85.80±11.89	<0.001
GWG (Kg)	13.83±5.27	11.12±3.07	18.27±5.13	<0.001
Children 6y				
Age (year)	5.86±0.95	5.67±0.88	6.16±0.89	n.s
Weight (Kg)	22.43±5.07	21.89±5.36	23.25±4.55	n.s
Weight-SDS	0.13±1.16	0.13±1.26	0.12±1.00	n.s
Height (cm)	49.53±1.56	113.13±7.83	117.72±7.22	n.s
Height-SDS	-0.16±0.87	-0.19±1.21	0.12±1.13	n.s
BMI	16.83±2.37	16.95±2.60	16.66±1.99	n.s
BMI-SDS	0.22±1.11	0.31±1.22	0.09±0.92	n.s
% Fat mass	23.86±8.73	23.87±9.11	23.84±8.30	n.s
% Fat mass-SDS	0.30±1.49	0.34±1.57	0.24±1.40	n.s
Glucose (mg/dl)	82.42±7.99	81.46±7.88	83.92±8.10	n.s
Insulin (uU/ml)	5.58±2.30	5.57±2.46	5.59±2.07	n.s
Visceral Fat (cm ²)	5.19±1.13	5.10±1.17	5.34±1.07	n.s
Visceral fat-SDS	0.25±1.14	0.24±1.21	0.26±1.05	n.s

FRAT-1 methylation status was significantly associated with a **lower percentage of total fat mass SDS** ($r = -0.274$; $p = 0.037$) at 6 years of age. In women with gestational obesity, ***FRAT-1*** methylation was **negatively associated with weight-SDS, BMI-SDS, and visceral fat-SDS** (r from -0.409 to -0.599 ; all $p < 0.05$). In **multivariate analysis**, adjusted for confounding variables, the placental methylation status of ***FRAT-1*** was a predictor of the percentage of fat mass-SDS at 6 years of age ($\beta = -0.263$; $p = 0.041$; $R^2 = 0.140$); as well as of weight-SDS ($\beta = -0.552$; $p = 0.030$; $R^2 = 0.060$), BMI-SDS ($\beta = -0.713$; $p = 0.003$; $R^2 = 0.232$) and visceral fat-SDS ($\beta = -0.452$; $p = 0.042$; $R^2 = 0.319$) in the offspring of mothers with gestational obesity.



	Total population (N=64)		Gestational Obesity Group (N=25)			
	% FM -SDS		Weight-SDS	BMI-SDS	Visceral fat-SDS	
<i>FRAT-1</i> methylation %	β	p	β	p	β	p
Maternal age	0.263	0.047	-0.227	n.s	-0.153	n.s
Gestational weight gain	-0.106	n.s	0.092	n.s	0.088	n.s
Gestational age	0.008	n.s	-0.000	n.s	-0.188	n.s
Newborn weight	-0.264	n.s	0.207	n.s	-0.337	n.s
R2 model	0.140		0.060		0.232	0.319
R2 <i>FRAT-1</i>	0.059		0.129		0.240	0.328

Figure 2: A) Graphical representation of the correlations between ***FRAT-1*** methylation % and the endocrine-metabolic parameters of the 6 year children. B) Multivariate analysis adjusted for confounding variables.

CONCLUSIONS

Our results suggest that the **methylation of the *FRAT-1*** gene may play a role in **regulating the body composition** of the offspring at 6 years of age. This methylation may explain, at least in part, the **metabolic programming in the offspring caused by gestational obesity**.

Table 1: Descriptive analysis of the endocrine-metabolic parameters from both mothers and the offspring at 6 years of age.