Small-for-Gestational-Age Newborns Exhibit Altered Placental and Cord Blood Methylation of Genes Involved in Energy Homeostasis: Association with Fetal Growth and Postnatal Body Composition

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The authors have nothing to disclose

BACKGROUND

- Fetal growth is partly regulated by epigenetic factors, such as DNA methylation.
- Altered methylation status in placental genes has been related to gestational diabetes, preeclampsia and prematurity.
- However, the epigenetic mechanisms underlying fetal growth restraint in uncomplicated pregnancies remain unknown.

AIM

To identify new candidate genes related to fetal growth, by assessing DNA methylation profiling in placenta and cord blood -as well as expression levels of differentially methylated genes- in newborns born appropriate- (AGA) or small-for-gestational-age (SGA).

SUBJECTS AND METHODS

- Placentas and cord blood samples were collected from uncomplicated pregnancies delivering term AGA [birthweight, between -1.1 and 1.1 SD; N=30) or SGA [birthweight, <-2 SD; N=21) newborns.
- Placental methylation profiling was performed using Agilent DNA Methylation array design to detect CpG sites located within promoter regions of 14.475 genes. A first analysis of the array revealed that 39 genes were differentially methylated (all, p<0.009). Among those genes, we selected those related to energy homeostasis (n=8) which were validated by bisulfite pyrosequencing (BSP) and also analyzed in cord blood by BSP.
- A differential methylation pattern was confirmed in four of the eight genes; of those, three were hypermethylated (*GPR120, ATG2B*, and *NKX6.1*) and one was hypomethylated (*SLC13A5*). Placental and cord blood expression of the confirmed genes was performed by real-time PCR.
- Glucose, insulin and IGF-I were measured in cord blood; body composition was assessed by DXA at age 15 days.

RESULTS

Table 1. Bivariate correlations between placental and cord blood gene methylation and expression and selected parameters in all subjects.

	Methylation				Expression			
	Placenta		Cord Blood		Placenta		Cord Blood	
ATG2B	**β**	***P***	**β**	***P***	**β**	***P***	**β**	***P***
Birth weight	-0.316	0.03	-0.441	0.002	0.522	<0.0001	-	-
Birth length	-0.358	0.013	-0.435	0.002	0.495	<0.0001	-	-
HOMA-IR	-	-	-	-	-	-	-	-
IGF-I	-0.293	0.045	-	-	-	-	0.338	0.023
Fat Mass	-	-	-	-	0.442	0.001	-	-
Abdominal fat	-	-	-	-	0.416	0.003	-	-
Lean Mass	-0.334	0.022	-0.509	<0.0001	0.428	0.002	-	-
NKX6								
Birth weight	-0.358	0.025	-0.593	<0.0001	0.553	<0.0001	0.399	0.007
Birth length	-0.395	0.001	-0.581	<0.0001	0.473	<0.0001	0.329	0.027
Insulin	-	-	-0.310	0.046	-	-	-	-
HOMA-IR	-	-	-	-	-	-	-	-
IGF-I	-0.328	0.002	-0.420	0.003	0.448	0.001	0.327	0.028
Fat Mass	-0.492	0.001	-	-	0.324	0.02	-	-
Abdominal fat	-0.417	0.008	-0.313	0.031	0.325	0.02	-	-
Lean Mass	-0.324	0.044	-0.560	<0.0001	0.476	<0.0001	-	-
SLC13A5								
Birth weight	-0.560	<0.0001	-0.505	<0.0001	0.415	0.002	0.661	<0.0001
Birth length	-0.463	0.001	-0.477	0.001	0.498	<0.0001	0.597	<0.0001
Insulin	-	-	-0.330	0.031	-	-	0.346	0.027
HOMA-IR	-0.323	0.035	-	-	-	-	-	-
IGF-I	-0.393	0.004	-0.360	0.0011	0.386	0.005	0.629	<0.0001
Fat Mass	-0.313	0.025	-	-	0.458	0.001	0.435	0.003
Abdominal fat	-0.358	0.01	-0.305	0.033	0.488	<0.0001	0.410	0.005
Lean Mass	-0.557	<0.0001	-0.512	<0.0001	0.430	0.002	0.647	<0.0001
GPR120								
Birth weight	0.642	<0.0001	-0.621	<0.0001	-0.421	0.002	0.378	0.012
Birth length	0.592	<0.0001	-0.621	<0.0001	-0.407	0.003	-	-
Insulin	0.349	0.019	-0.325	0.036	-	-	-	-
HOMA-IR	0.331	0.03	-	-	-0.353	0.022	0.417	0.01
IGF-I	0.475	<0.0001	-0.414	0.004	-	-	0.445	0.004
Fat Mass	0.615	<0.0001	-	-	-0.295	0.038	0.514	<0.0001
Abdominal fat	0.588	<0.0001	-0.369	0.011	-0.421	0.002	0.431	0.003
Lean Mass	0.617	<0.0001	-0.615	<0.0001	-0.309	0.029	0.320	0.034

HOMA-IR: Homeostasis model assessment-insulin resistance; IGF-I: insulin-like growth factor-I

Figure 1. Methylation (top) and expression levels (bottom) of validated genes in placentas from infants born appropriate (AGA, n=30) or small-for-gestational age (SGA, n=21).

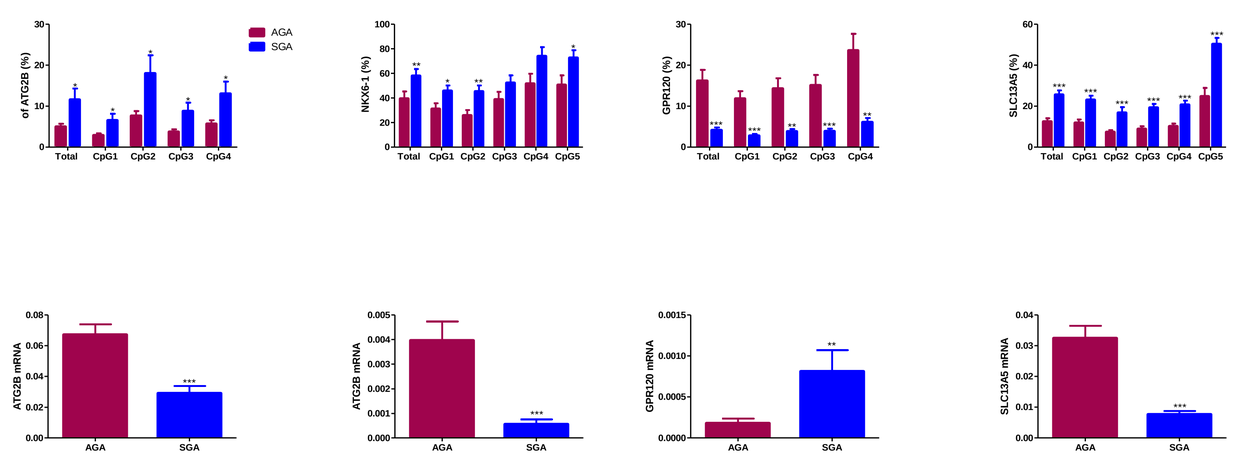
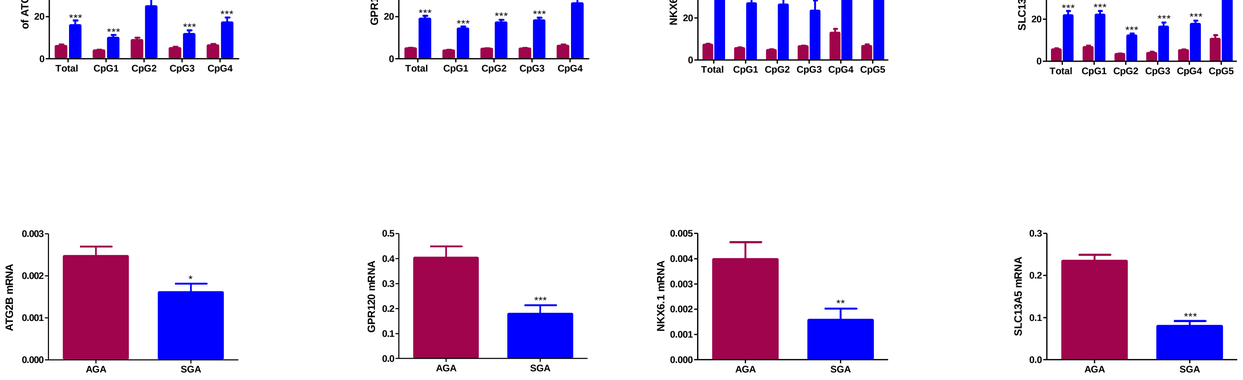


Figure 2. Methylation (top) and expression levels (bottom) of validated genes in cord blood from infants born appropriate (AGA, n=30) or small-for-gestational age (SGA, n=21).



Values are mean ± SEM. *p<0.05; **p<0.01; ***p<0,0001 *vs* SGA

CONCLUSION

Epigenetic modifications of placenta and cord blood-expressed genes related to energy homeostasis contribute to explain fetal growth restraint and postnatal fat mass gain in term SGA newborns from uncomplicated pregnancies.

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