

Insufficient gestational weight gain associated with higher DNA methylation in cord blood cells

CURRENT STATUS: UNDER REVISION

BMC Genomics  BMC Series

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DOI:

10.21203/rs.2.22196/v1

SUBJECT AREAS

Epigenetics & Genomics

KEYWORDS

Gestational weight gain, cord blood, DNA methylation, enhancer

Abstract

Background Gestational weight gain (GWG) is one of the crucial factors affecting fetal growth as well as the in utero environment, influencing fetal cell programming during development. We reported previously that GWG affected the occurrence of outlying CpG methylation values of placental DNA in a U-shaped manner, with the occurrence of outlying values from adequate GWG subjects positioned at the bottom of the curve. In the present study, we aimed to elucidate the effects of GWG on the infant epigenome by the view that the influence of insufficient GWG on infant DNA methylation may turn in some other direction at the borderline of the optimal weight gain.

Method We collected cord blood from 60 subjects with uncomplicated term delivery whose mean pre-pregnancy body mass index and mean GWG was 19.8 ± 1.9 and 8.1 ± 4.3 kg, respectively. Cord blood DNA was underwent analysis using the Infinium MethylationEPIC BeadChip to profile genome-wide methylation status.

Results GWG was continuously associated with cord blood DNA methylation at five CpG loci significantly (multiple test corrected p -value, 0.043) in the lower than upper limit of the recommended GWG group (n = 51). The significant association between DNA methylation levels and GWG was disappeared when added 9 subjects who gained weight more than upper limit of recommendation during pregnancy. The methylation plot of the five loci plateaued or traced a U-curve near the border of the upper limit of the GWG recommendation. Cord blood DNA methylation of these five still tended to be associated with GWG after considering gestational age as covariate with involving the other eleven CpG sites with the same p -value (multiple test corrected p -value, 0.056). The fifteen out of the identified 16 CpG sites showed negative association between GWG and DNA methylation levels and five of them colocalized at inferred enhancer region.

Conclusions It is known that demethylation at enhancer region in genome is one of the features during late fetal development. We found that insufficient GWG showed higher methylation status in some enhancer-candidate loci in cord blood cells, which may indicate incomplete demethylation during in utero development.

Full-text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed.

However, the manuscript can be downloaded and accessed as a PDF.

Tables

Table 1. Subject characteristics (N = 60)

Characteristic	Number	%
Maternal age, years		
30-35	28	46.7
36-40	26	43.3
41-45	6	10.0
Parity		
0	43	71.7
≥1	17	28.3
Gestational age at delivery, weeks		
37-40	56	93.3
>40	4	6.7
Infant birth weight, g		
<2500	8	13.3
2500-3499	52	86.7
Infant sex		
Male	32	53.3
Female	28	46.7
Gestational weight gain, kg (*JMWLW border line)		
<7; insufficient	22	36.7
≥7 to ≤12; adequate	29	48.3
>12; excessive	9	15.0
Pre-pregnancy BMI		
<18.5	17	28.3
≥18.5 to ≤25	43	71.7
>25	0	0
Caesarian section		
Yes	20	33.3
No	40	66.7
Maternal smoking		
Yes	0	0
No	60	100
Race		
Japanese	60	100

Table 2. The 5 CpG sites that were significantly associated with continuous GWG in ULO after adjustment for cell counts

TargetID	coe	P val (FDR-adjusted)	Genic region (Nearest TSS)	Gene Name	Chr	Position	Predicted Enhancer
cg00599163	-0.0056	1.04.E-07 (0.043)	promoter-TSS	LINC01806	2	162100495	Yes
cg19516245	-0.0034	1.14.E-07 (0.043)	Intergenic (-44,422 bp)	ZBTB10	8	81353432	
cg16530016	-0.0064	2.09.E-07 (0.043)	GeneBody intron 1 of 2	RAMP3	7	45215683	
cg03962019	-0.0029	2.47.E-07 (0.043)	Intergenic (-19,738 bp)	FOXO6	1	41807865	
cg10370704	-0.0033	2.82.E-07 (0.043)	GeneBody intron 26 of 36	CABIN1	22	24500452	Yes

* The association was observed only in ultrasound- based GA

Table 3. The 2 CpG sites that were significantly associated with continuous GA after adjustment for cell counts

TargetID	coe	P val (FDR-adjusted)	Genic region	Gene Name	Chr	Position	45
cg11932158	-0.043	1.73.E-08 (0.013)	promoter-TSS200	PLCH1	3	155422129	Ye
cg21262198	-0.036	1.02.E-07 (0.038)	promoter-TSS200	PLCH1	3	155422159	N

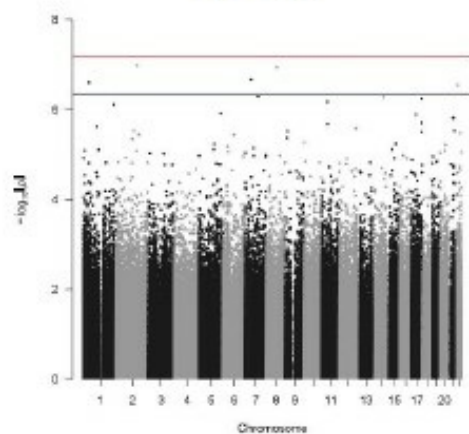
Table 4. The 16 CpG sites with the top FDR-adjusted P value that were associated with continuous GWG in ULO after adjustment for cell counts and GA

TargetID	coe	P val (FDR-adjusted)	Genic region (Nearest TSS)	Gene Name	Chr	Position	chromHM Enhance
cg19516245	-0.003	1.89E-07 (0.056)	Intergenic (-44,422 bp)	ZBTB10	8	81353432	
cg00599163	-0.005	2.30E-07 (0.056)	promoter-TSS	LINC01806	2	162100495	Yes
cg03962019	-0.003	2.49E-07 (0.056)	Intergenic (-19,738 bp)	FOXO6	1	41807865	
cg16530016	-0.006	3.71E-07 (0.056)	intron 1 of 2	RAMP3	7	45215683	
cg00445959	-0.006	5.93E-07 (0.056)	intron 1 of 23	XPO6	16	28220268	Yes
cg10370704	-0.003	6.04E-07 (0.056)	intron 26 of 36	SUSD2	22	24500452	Yes
cg03806175	-0.003	6.06E-07 (0.056)	intron 56 of 70	LOC10192755 0	7	98577593	
cg17714110	-0.001	6.08E-07 (0.056)	Intergenic (-2,610 bp)	FOXN3	14	90088104	Yes
cg24629380	-0.001	9.10E-07 (0.056)	intron 4 of 7	VANGL1	1	116214059	Yes
cg26970265	-0.001	9.11E-07 (0.056)	promoter-TSS	TTC3-AS1	21	38566282	
cg04032453	-0.001	9.12E-07 (0.056)	intron 3 of 11	TBC1D16	17	77960186	
cg21398491	-0.002	9.44E-07 (0.056)	Intergenic (+ 670,924 bp)	KCNJ3	2	156226017	
cg08538468	0.001	9.95E-07 (0.056)	promoter-TSS	SH3GL2	9	17579028	
cg21428460	-0.012	1.08E-06 (0.056)	promoter-TSS	C11orf96	11	43963367	
cg00949980	-0.003	1.16E-06 (0.056)	intron 1 of 3	SUMO3	21	46237117	
cg23702903	-0.004	1.18E-06 (0.056)	exon 15 of 20	GAA	17	78061443	

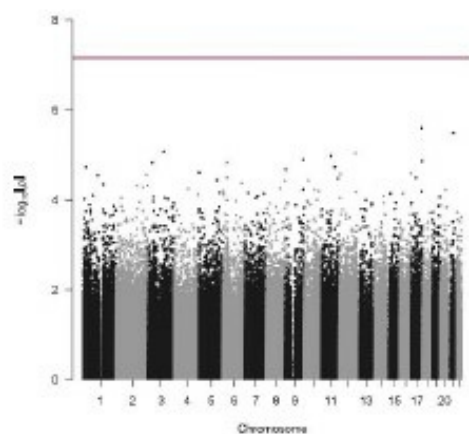
The association was observed only in ultrasound- based GA (*) and last menstrual period-estimated GA (\$), respectively, in Bohlin *et al*'s study.

Figures

A Continuous GWG within upper limit of recommendation
(n = 51)



B Continuous GWG of whole subjects
(n = 60)



C Significantly associated 5 CpG sites

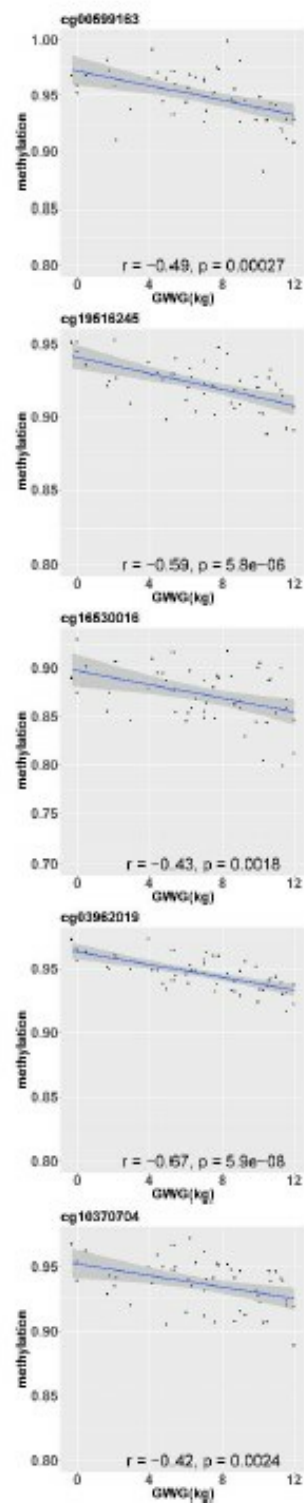


Figure 1. Kawai *et al.*

Figure 1

EWAS analysis with continuous GWG in UL O and whole subjects The results

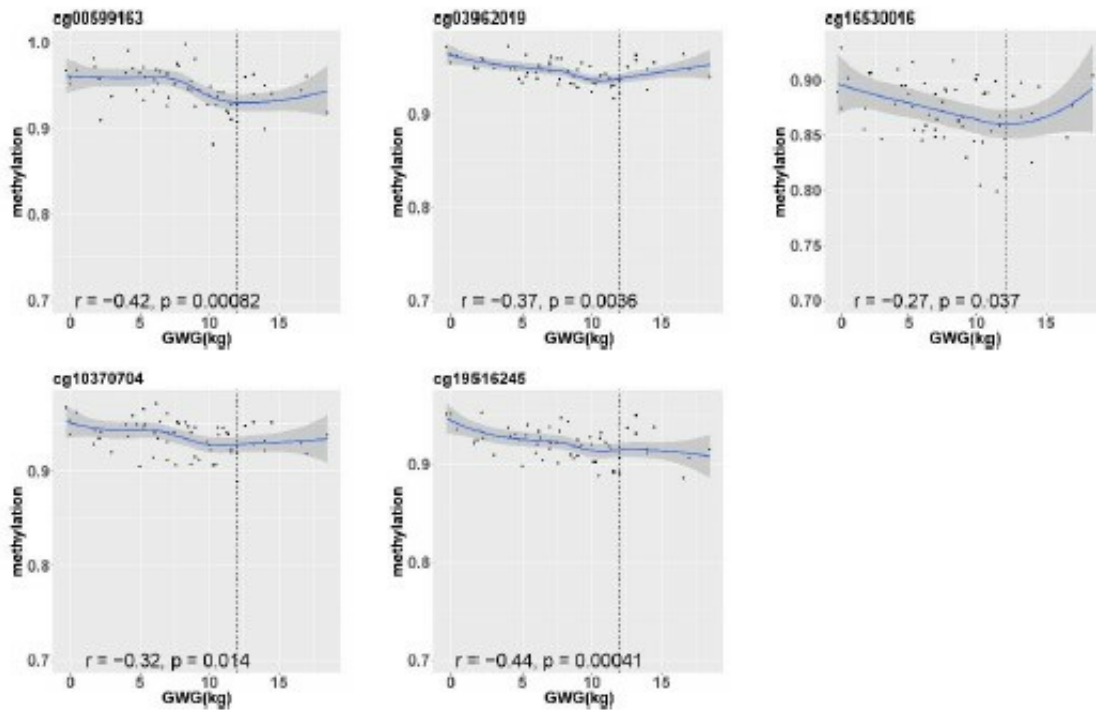


Figure 2

Methylation Plots of 5 CpG sites within whole subjects

Supplementary Files

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