HYPOMETHYLATION WITHIN THE IMPRINTED *DLK1 - DIO3* DOMAIN : A POTENTIAL REGULATORY MECHANISM OF PRE AND POSTNATAL GROWTH

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Introduction:

Genomic imprinting causes genes to be expressed or repressed depending on their parental origin. The 1-Mb *DLK1-DIO3* imprinted domain is located on human chromosome 14. Gene expression along this cluster is regulated by an intergenic differentially methylated imprinting control region ('IG-DMR'). In mice, altered gene dosage within this cluster is associated with abnormalities in embryonic and placental growth.

Objectives:

Study the association between *DLK1-DIO3* IG-DMR methylation and placental, fetal and postnatal growth in humans.

Methods:

We studied by means of pyrosequencing the DNA methylation of 18 CpG dinucleotides across the IG-DMR in placentae from 80 healthy mothers who delivered healthy infants. The studied chromosomal locations within the cluster were: Region 1: chr14:101270990-101271064; Region 2: chr14:101278037-101278081 and Region 3: chr14:101292465-101292596. At birth, placentas and infants were weighed (gestational age 39 1 weeks; birth weight z-score 0.31 0.89) and placenta samples were collected. Infants' weights were measured monthly during the first year of life.

Results:

Children with hypomethylation within region 3 showed lower birth weight-to-placental weight ratios (r=0.316; p=0.014) and higher increases in weight during the first year of life (r=-0.380; p=0.004). We also performed analyses of individual CpG sites within region 1 and 2. In region 1, lower levels of methylation were related to lower birth weight (r=0.270; 0.017) while two different CpGs in region 2 showed significant associations, respectively, with placental weight (position 1: r=-0.306; p=0.011) and weight increase during the first year of life (position 5; r=-0.301; 0.044) (Table 1). All these associations remained significant after adjusting for confounding variables (Table 2).

Table 1: Correlations of DLK1-DIO3 methylation percentages with growth variables in newborns (n= 80).

		Region 1	Region 2	Region 3
Birth weight	r	**0.270**	0.014	0.056
	p	**0.017**	0.922	0.658
Placental weight	r	-0.153	**-0.306**	-0.181
	p	0.264	**0.011**	0.167
Birth weight-to-placental weight	r	0.123	0.233	**0.316**
	p	0.370	0.090	**0.014**
Weight increases during the first year of life	r	0.067	**-0.301**	**-0.380**
	p	0.656	**0.044**	**0.004**

Table 2: Multiple regression analyses of DLK1-DIO3 methilation pecentages with growth variables in newborns (n= 80).

	Beta	Sig.	R2
Birth weight			
Region 1	0.243	0.035	0.080
Placental weight			
Region 2	-0.200	0.049	0.103
Birth weight-to-placental weight			
Region 3	0.262	0.028	0.050
Weight increases during the first year of life			
Region 2	-0.251	0.046	0.131
Region 3	-0.321	0.005	0.189

Conclusions:

For the first time, we show that placental hypomethylation at the *DLK1-DIO3* IG-DMR is associated with decreased fetal growth and increased placental weight and postnatal growth. We suggest that hypomethylation in the *DLK1-DIO3* imprinted domain may be a new mechanism regulating pre and postnatal growth in humans.

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