



# Commentary of Expertise on the Epigenetic Program during Intrauterine Development

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## ABSTRACT

Preterm infants reflect the influences of their early intrauterine environment at birth and are placed in a non-physiological environment after birth. We have studied the epigenetics of the Glucocorticoid Receptor (GR) and the Insulin-like Growth Factor 1 (IGF1) gene, which are important in later life. Our studies indicate that these genes are mainly modified epigenetically after birth. The postnatal environment overlaps the prenatal condition, causing modification of these genes. Our studies may imply an adult disease onset model and a critical view on transgenerational inheritance in humans through epigenetic changes in gametes.

**Keywords:** Insulin-like Growth Factor 1 (IGF1); Preterm infants; Intrauterine development

## DESCRIPTION

Human development is affected by the early environment through epigenetic modification of genes. The intrauterine period is the most crucial stage for the programming of later development of characteristics such as body size, metabolic activity, and stress reactivity. This intrauterine environment programming is known to lead to development of diabetes, cardiovascular disease, and hypertension in adulthood. The Glucocorticoid Receptor (GR) and Insulin-like Growth Factor 1 (IGF1) are important molecules, as their impairment leads to metabolic disorders later in life [1,2]. We have studied the relationship between early life environment in preterm infants and the epigenetic status of genes that encode them.

Dysregulation of the Hypothalamus-Pituitary-Adrenal (HPA) axis is an important risk factor for inflammatory disease, and psychiatric and metabolic disorders. HPA axis activity is regulated by the hypothalamic GR encoded by the nuclear receptor subfamily 3 group C member 1 (NR3C1), which mediates a negative feedback loop. We performed a longitudinal analysis of the methylation status within the GR gene promoter 1F region using the bisulfite amplicon method in 19 preterm infants born between 24 weeks and 28 weeks of gestation [3]. Methylation rates increased significantly between birth and postnatal 2 months at 11 of the 39 CpG sites. Intrauterine Growth Restriction (IUGR) and postnatal relative adrenal insufficiency were major factors resulting in high methylation of the GR gene. These results suggest that dysregulation of several genes induced by IUGR may increase susceptibility to complications after birth, particularly stressful

events, such as mechanical ventilation or repeated heel cut blood sampling, beyond adrenal glucocorticoid secretion.

IGF1 regulates body size in children and glucose tolerance in adults. High IGF1 gene methylation results in low IGF1 secretion and is seen in small full-term birth infants and in short children with poor growth hormone responsiveness. However, whether IGF1 gene methylation programming occurs during intrauterine life is unclear.

We analyzed the methylation status of the IGF1 gene P2 promoter region, the main IGF1 gene transcription regulator in preterm infants born between 22 and 32 weeks of gestation with and without IUGR. The methylation status of genes up to that time point is thought to reflect the intrauterine environment [4].

Our results showed that IGF1 secretion is epigenetically regulated to be high in infants with IUGR born before 32 weeks of gestation, in contrast to the secretion in term newborns and children, which is lower. This finding indicates that the IGF1 gene methylation process can respond to in utero malnutrition before 32 weeks of gestation and may be reset during gestational weeks 32 to 37.

We think that our research is meaningful in terms of the following two points:

## AS AN ADULT DISEASE ONSET MODEL

In addition to psychological disorders, impairment of the GR (1) and high methylation of the GR gene are known to cause metabolic disease [5]. Low IGF1 secretion (2), through high IGF1 gene promoter methylation, results in deregulated lipid metabolism,

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cardiovascular disease, and diabetes in adulthood [6]. Infants with IUGR are known to be at risk for these adult diseases. In our study, the GR and IGF1 gene methylation program in IUGR infants was not activated at preterm birth, suggesting that the IGF1 gene is also methylated by the postnatal environment in the same way as the GR gene. As preterm infants with IUGR and extra uterine rapid catch-up growth are known to be at risk for future adult diseases, nutrition status during the postnatal and infantile periods is an important factor driving this mechanism. Further longitudinal studies may reveal the process leading to the onset of adult diseases.

## AS A CRITICAL VIEW ON THE TRANS GENERATIONAL INHERITANCE MODEL IN HUMANS THROUGH EPIGENETIC CHANGES IN GAMETES

Acquired traits are inherited for two or more generations in plants, animals, and humans. Direct inheritance through epigenetic modification of gametes has been demonstrated in animals and plants, but remains controversial in humans [7]. Human height is highly hereditary across generations, but research on the association between the IGF1 gene and human stature has indicated that associated genetic factors such as allelic polymorphism and DNA mutations can only explain a minor part of the expected heritable fraction. On the other hand, epigenetic modifications can contribute to gene expression alterations in a heritable manner [8]. Therefore, programming of growth-related genes, including IGF1, may occur at least in part during an early embryonic stage such as the post-implantation stage. However, our study indicates that the epigenetic status of the IGF1 gene can adapt to the intrauterine environment, and that the nutritional status during the third trimester may reset this setting.

Taken together, our results suggest that the epigenetic status of the IGF1 gene can be affected by transgenerational transmission of (dietary) culture by communication, imitation, teaching, and learning during late pregnancy rather than by gamete-mediated transmission.

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