DNA Methylation Signatures Associated With Prenatal Dexamethasone Treatment

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Introduction

Dexamethasone (DEX) is used to prevent virilization in female fetuses at risk of CAH. Given that treatment has to be started before the genotype is known, 7 out of 8 fetuses will be exposed to DEX without benefit. Long-term follow-up of risk benefit is therefore crucial.

Objective

To investigate genome-wide methylation in DEX treated individuals as a proof of long lasting genomic programming.

Methods

CD4+ T-cell DNA from 42 DEX treated subjects (31 without CAH, mean age=16.5, sd=5.9; 7 girls with CAH mean age=17.7, sd=5.8; 4 boys with CAH mean age=23.5, sd=1.9), 28 untreated CAH controls (mean age=18.9, sd=6.7) and 38 population controls (mean age=17.7, sd=5.7) were analysed with the Infinium-HumanMethylation450 BeadChip array (450K array) to measure genome-wide locus specific DNA methylation.

The GREAT annotation tool (GREAT version 3.0.0) was used to investigate the functional relevance of differentially methylated CpG sites.

Targeted analysis of probes from a subset of functionally and clinically important candidate genes were performed independently with the same linear model as for the genome-wide methylation analysis, and with age and gender as covariates.

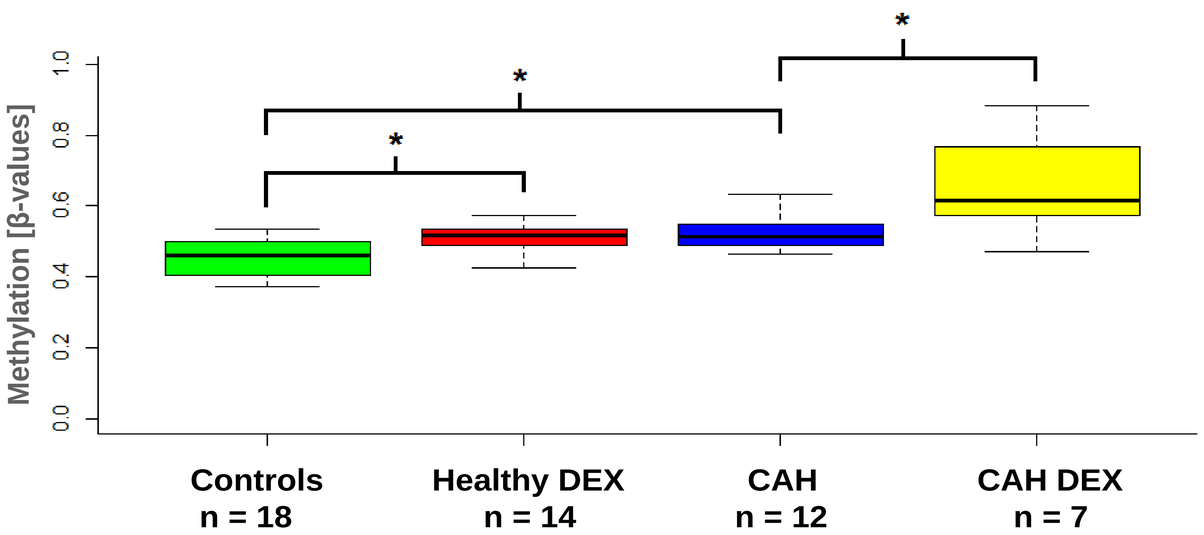

Figure 1: Targeted gene analysis shows a significant increase in methylation in a CpG located in the TSS200 region of *CYP21A2* in female subjects. * Significant (alpha level of .05).

Disclosure statement: The authors have nothing to disclose.

Conclusions

Our findings show that prenatal dexamethasone treatment gives long-lasting changes in DNA methylation. The DEX effects are mostly related to the immune system but also engages other biological processes such as the steroidogenic pathway. These results show that prenatal DEX treatment programs the fetus and affects the individual several decades later. More specifically, these changes may predispose the child to an increased risk of developing immune related disorders and/or result in an impaired steroidogenesis.

Enriched Gene Ontology terms from GREAT	DEX effect	DEX x GENDER
interleukin-1 secretion		
interleukin-1 beta secretion		
interleukin-1 production		
regulation of cytokine secretion involved in immune response		
alpha-beta T cell receptor complex		
T cell receptor complex		
CCR1 chemokine receptor binding		
CCR4 chemokine receptor binding		
chemokine receptor antagonist activity		
lipase activator activity		
phosphatidylinositol-5-phosphate binding		
phospholipase activator activity		
positive regulation of interleukin-1 beta secretion		
positive regulation of natural killer cell chemotaxis		
regulation of interleukin-1 beta secretion		

Table 1: Data from GREAT analysis showing 15 prominently enriched GO terms associated with DEX or with the DEX x GENDER. **Green:** Enriched. **Red:** Not enriched.

Results

We present data on genome-wide methylation effects in first trimester DEX treated individuals without CAH. 159 Gene Ontology terms (GO, including molecular functions, biological processes or cellular components) were significantly enriched and associated with prenatal DEX treatment or with the DEX x GENDER interaction. Most notably, GO terms related to the immune system were enriched, such as interleukin production and secretion as well as proteins involved in the T-cell receptor complex (Table 1).

Moreover, in our targeted analysis (Figure 1), the TSS200 region for several genes coding for steroidogenic enzymes were differentially methylated in first trimester treated subjects. The 21-hydroxylase gene (*CYP21A2*) was differentially methylated in all female subjects irrespective of duration of DEX-treatment. The largest effect was observed in full term treated CAH girls.

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