Genome-wide investigation of DNA Methylation in peripheral T-cells from patients with CAH

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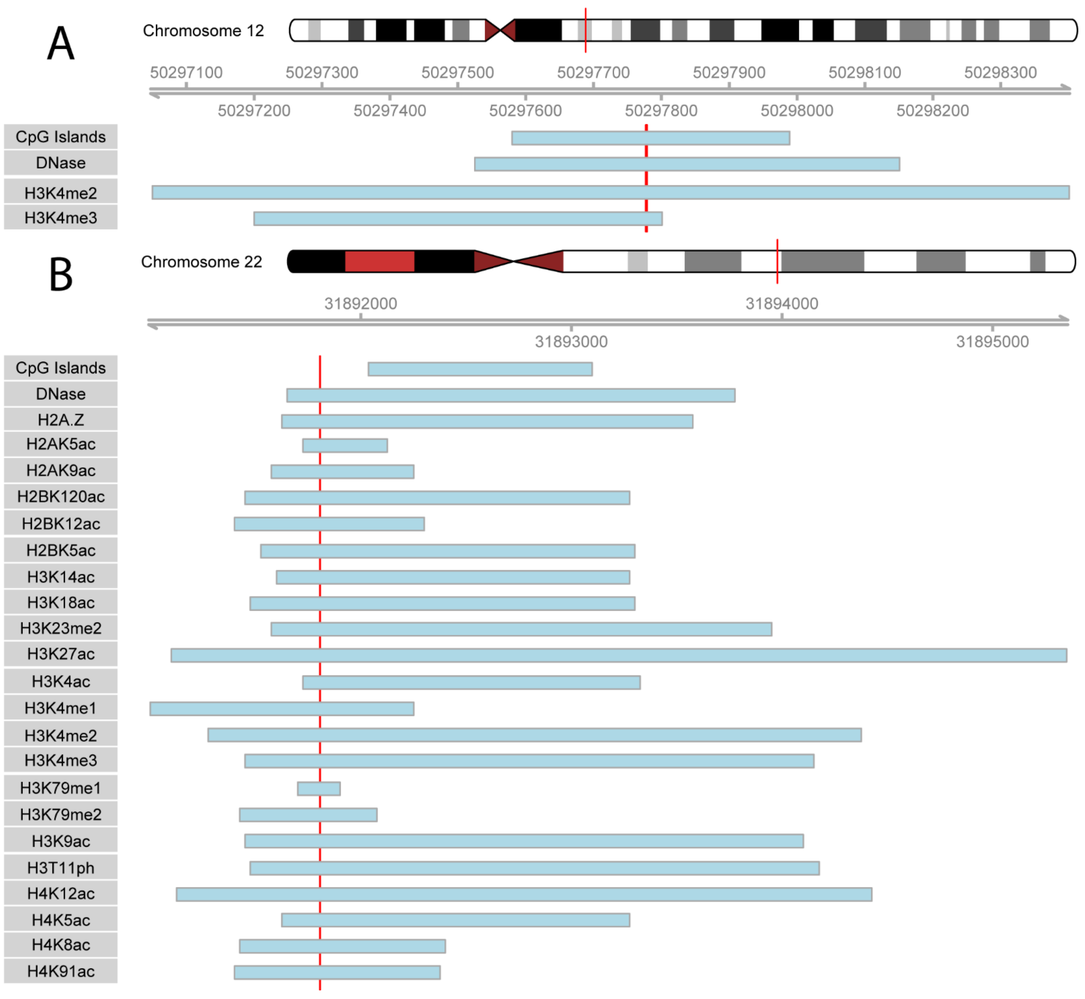

Figure 3. Genomic location and overlapping epigenomic features for cg18486102 (A) and cg02404636 (B). The red line indicates the location of the differentially methylated CpGs. Blue bars indicate regions enriched with specific epigenetic feutires.

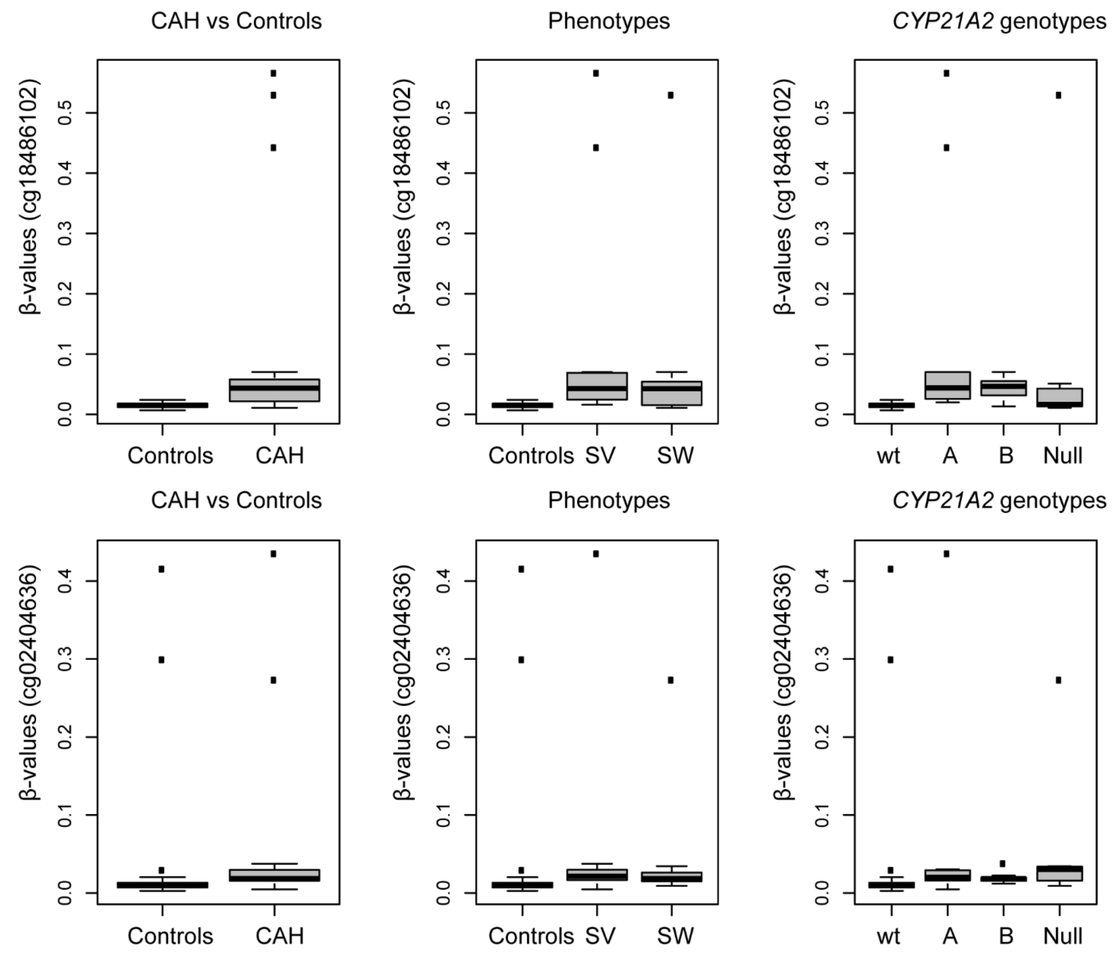

Figure 2. β-values for DMP's for cg18486102 and cg02404636.

Introduction

Patients with CAH (21OHD) are at risk of long term cognitive and metabolic sequelae. DNA methylation may be a possible mechanism which mediates long term outcome in patients.

Objective

To investigate genome-wide methylation in patients with CAH in order to find evidence for genomic reprogramming which may mediate long term outcome

Methods

CD4+ T-cell DNA from 28 patients with CAH (18.5±6.5 yrs) and 37 population controls (17.0±6.1 yrs) were analyzed with the Infinium-HumanMethylation450 BeadChip array (450K array) to measure genome-wide locus specific DNA methylation. Effects of CAH (phenotype and genotype) on methylation were investigated as well as the association between differentially methylated CpGs and metabolic and cognitive outcome.

Results

Patient phenotype correlated with two CpG sites: cg18486102 (rho=0.58, p=0.027) and cg02404636 (rho=0.58, p = 0.038). cg02404636 also correlated with genotype (rho = 0.59, p = 0.024). The level of methylation (β-values) for both differentially methylated probes (DMP) are shown in Figure 2. cg18486102 is located in the TSS200 region of the *FAIM2* gene and cg02404636 in the TSS1500 region of the *SFI1* gene. Both DMPs overlap with several epigenomic features (Figure 3). FAIM2 is involved in the inhibition of Fas Ligand activated apoptosis in neurons but has also been associated with BMI and blood lipid profile. SFI1 is a centrin binding protein involved in centrosome maturation and mitosis. No significant association was made between *FAIM2* TSS methylation and cognitive or metabolic outcome. However, *SFI1* TSS methylation was associated with plasma HDL-cholesterol levels.

Table 1. Associations between β-values in cg18486102 and cg02404636 and metabolic and cognitive outcome.

	cg18486102 (p)	cg18486102 x sex (p)	cg02404636 (p)	cg02404636 x sex (p)
BMI	0.100	0.317	0.431	0.277
Glucose homeostasis (Mean ± 1SD)				
Glucose (mmol/L) (P)	0.452	0.554	0.994	0.465
Insulin (mIE/L) (S)	0.473	0.925	0.202	0.178
C-peptide (nmol/L) (S)	0.458	0.642	0.953	0.579
HbA_{1c} (mmol/mol) (B)	0.684	0.756	0.282	0.336
Lipid profile (Mean ± 1SD)				
Triglycerides (mmol/L) (P)	0.359	0.739	0.798	0.436
Cholesterol (mmol/L) (P)	0.421	0.179	0.453	0.187
HDL-cholesterol (mmol/L) (P)	0.301	0.499	0.661	**0.035**
LDL-cholesterol (mmol/L) (P)	0.197	0.075	0.591	0.693
LDL/HDL Ratio	0.122	0.106	0.759	0.455
Cognitive performance (Mean ± 1SD)				
Coding (Sc)	0.858	0.099	0.356	0.530
Matrices (Sc)	0.895	0.373	0.983	0.176
Vocabulary (Sc)	0.653	0.094	0.108	0.069
Digit Span (Sc)	0.910	0.127	0.245	0.342
Stroop Int (Sc)	0.113	0.066	0.572	0.978

Conclusions

This is the first analysis of genome-wide DNA methylation in patients with CAH. We identified two CpGs, cg18486102 and cg02404636, to be associated with the severity of the disorder and *CYP21A2* genotype. The CpGs were located in the TSS region of the genes *FAIM2* and *SFI1*, respectively. Both genes are biologically relevant considering the long term metabolic and cognitive outcome in patients with CAH.

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Adrenals and HPA Axis

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