

Epigenome-wide association study in Childhood Obesity: Searching for early markers of late disease risk

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Take-home Idea

EpiWAS for childhood obesity has revealed a potential causal locus (*SPATC1L*) for the disease where there seems to be a complex interaction between genetics and epigenetics.

Introduction

Here we analyzed DNA methylation profiles (Infinium MethylationEPIC BeadChip 850K) in whole blood from 26 obese (zBMI > 2) and 12 control lean pre-pubertal children (zBMI < 1). 109 CpG sites appeared differentially methylated between the two groups (methylation change >10% and FDR value <0.05).

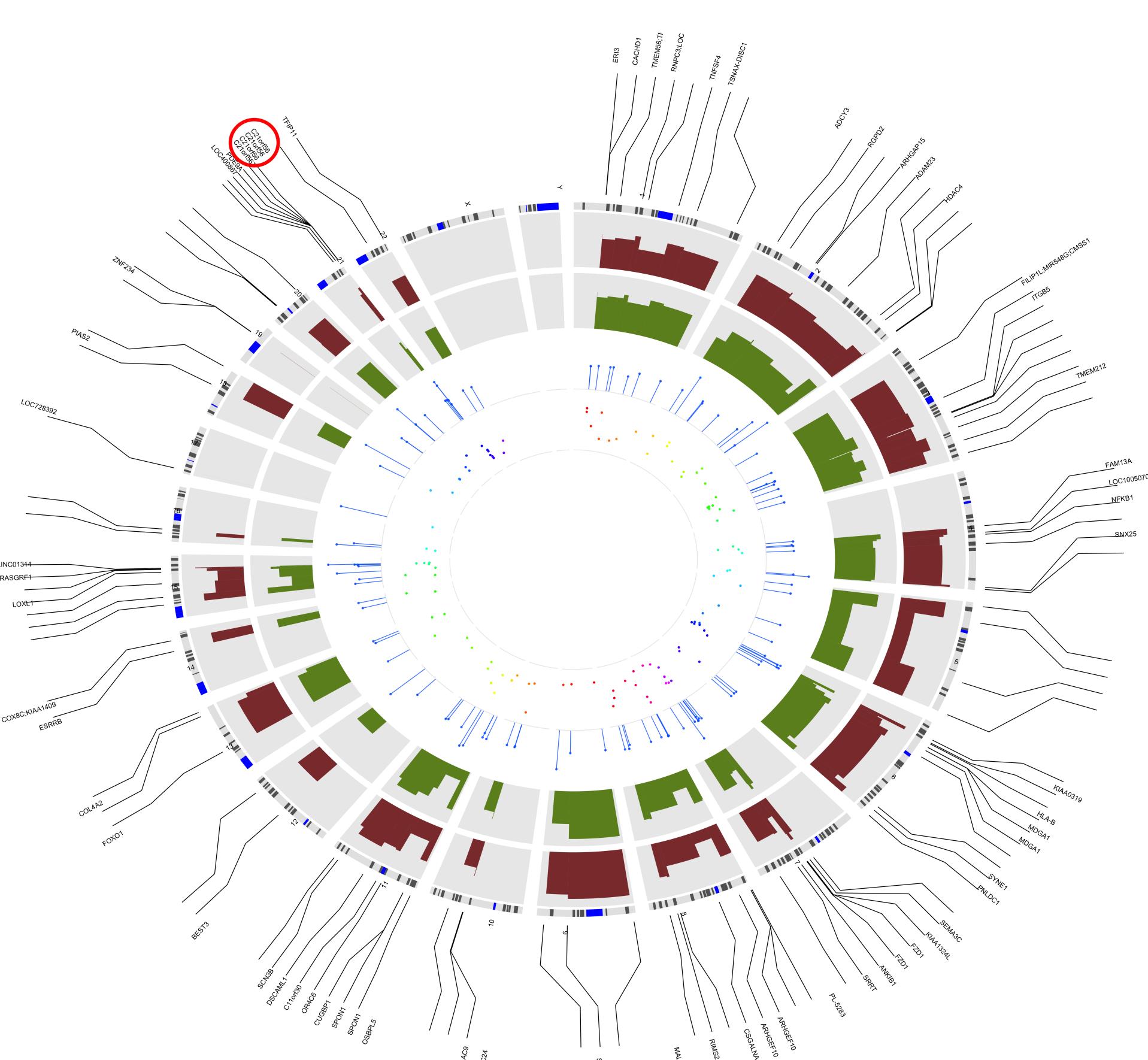


Figure: Circular plot, integrating the methylation data. Circular tracks from outside to inside: gene names, genome positions by chromosomes (black lines depict the cytobands), average of beta values for obese subjects, average of beta values for control subjects, effect size between the two groups, manhattan plot (for 109 CpG).

(a) UCSC Genome Browser *SPATC1L* locus.

Causality Analysis

Two-Sample Mendelian randomisation is a method to estimate the causal effect of an exposure on an outcome using summary statistics from genome wide association studies (GWAS). This approach is based on the association between SNPs and other exposure (CpGs in this case) to produce the phenotype. We identified 4 causal CpGs for several disorders, including Childhood Obesity and Type II Diabetes. The 2 CpG that are potentially causal for childhood obesity are **cg08742575** and **cg14789911** and map together in the *SPATC1L* locus (red circle in circular plot figure).

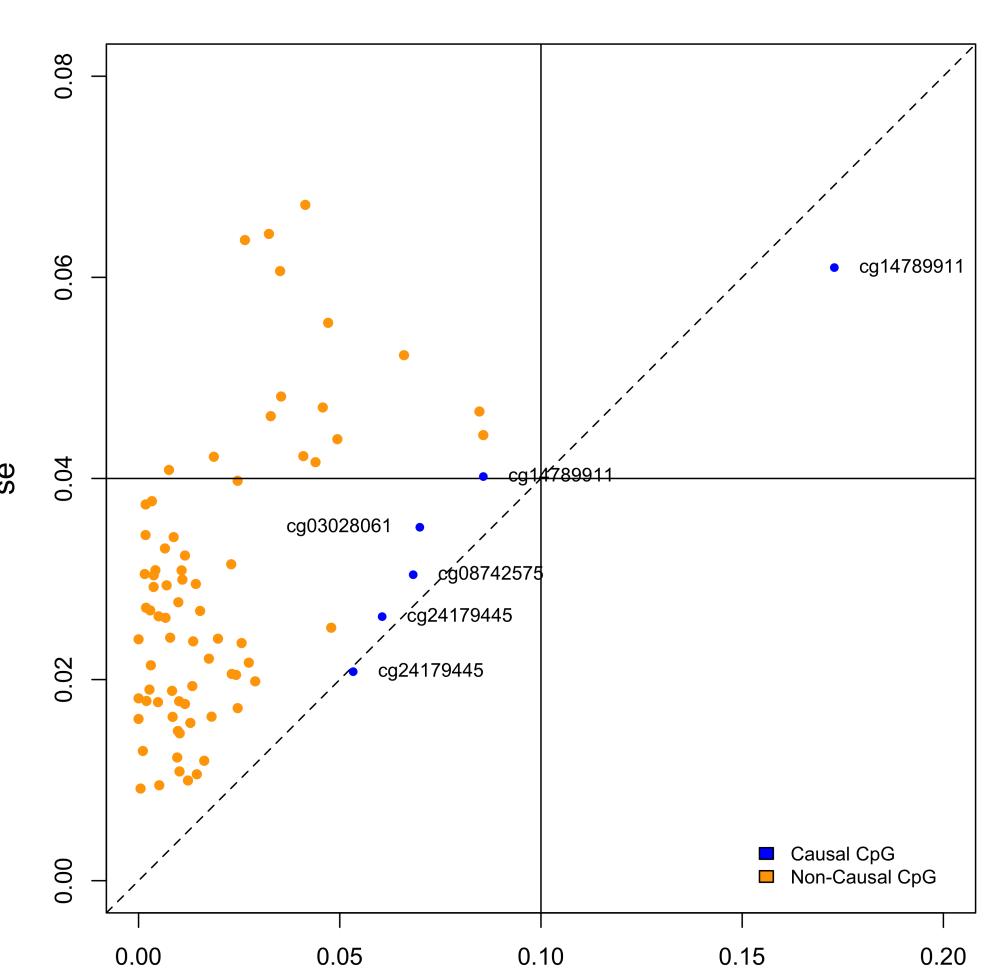


Figure: CpG sites that influences on the outcome according to results of the causality analysis. In orange, non-causal CpGs. In blue, CpGs that are significantly associated ($P < 0.05$) with a SNP and have an effect in outcome (causal CpGs).

SPATC1L locus

Five out of the 109 targets, including the two potential causal CpG for childhood obesity, were located within the *SPATC1L* (Spermatogenesis and Centriole Associated 1 Like) gene. The diagram (a) shows that this region is very active in terms of histone binding, Dnase 1 hypersensitivity and binding of transcription factors.

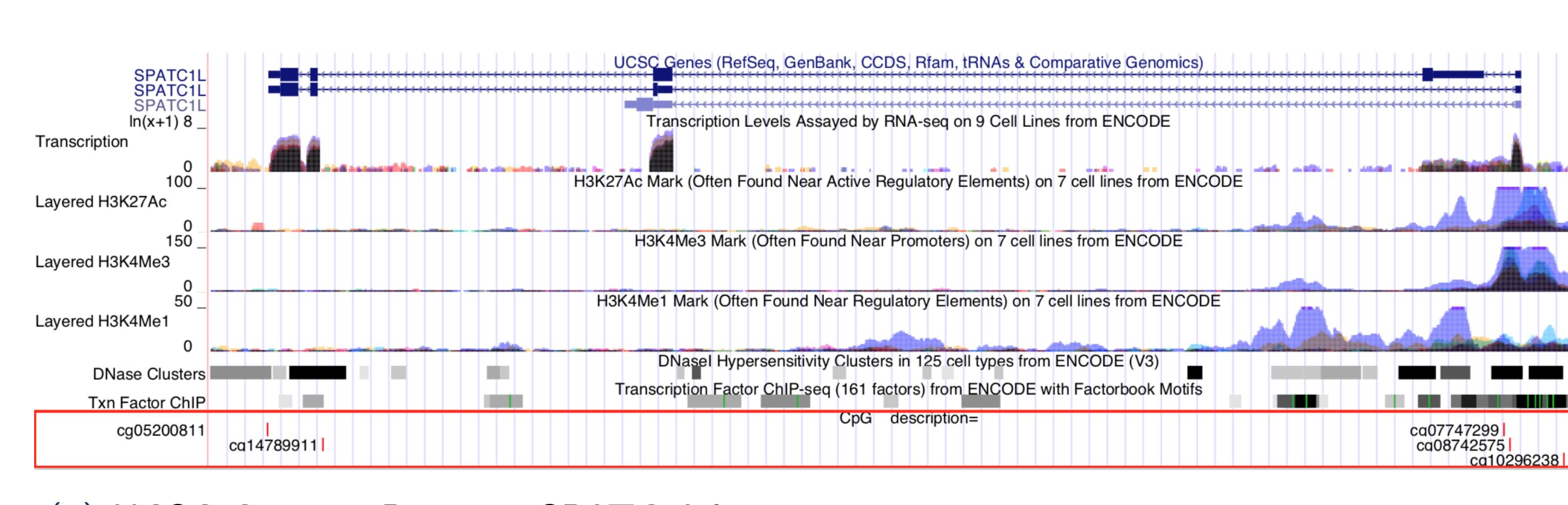


Figure: *SPATC1L* locus regulation and methylation

The five CpGs in this locus are extremely correlated (Bonferroni < 0.05) (b). This strong CpG correlation in the *SPATC1L* region could be explained by a co-regulation of methylation in this locus.

SNP Models

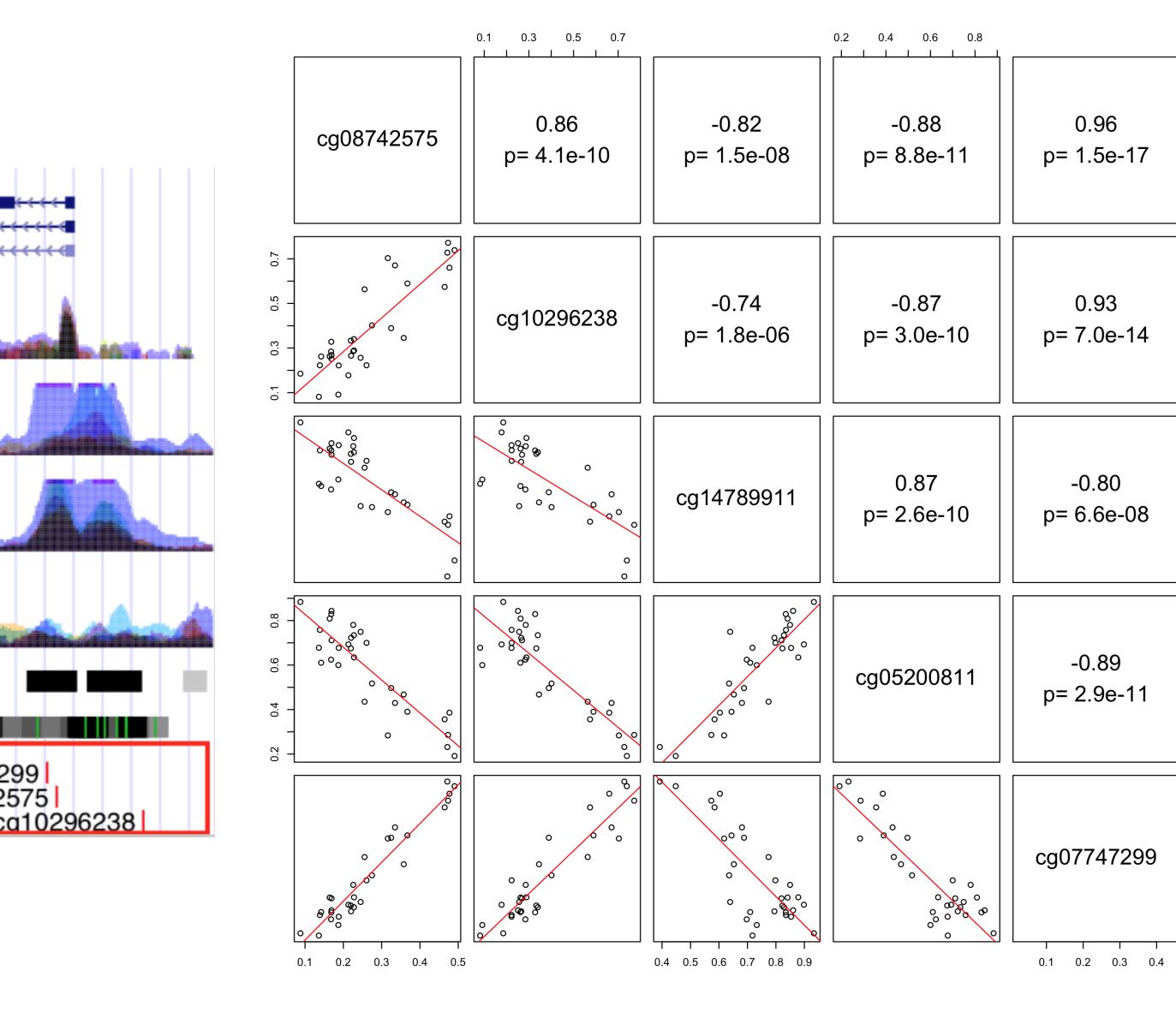
Other authors suggest that *SPATC1L* locus is an example of the connection between epigenetic and genetic marks [1]. We have analyzed the SNPs **rs151193360**, **rs62215189** and **rs8133082** of this region. Only SNP **rs62215189** had variability between the two phenotypes.

$$\text{logit}(P) = \ln \left(\frac{P}{1 - P} \right) \quad (1)$$

Results of the logistic regression model above:

- SNP rs62215189 as an outcome and five individual CpGs as predictors: **CpG cg10296238 and CpG cg05200811 may be associated with the rs62215189 SNP.**
- **SNP are not associated with our two causal CpGs.**
- Phenotype as outcome and the SNP rs62215189 as a predictor: **combination A/T of the SNP rs62215189 may be associated with the obese phenotype.**

Variable	Estimate	Std. Error	z value	Pr(> z)
rs62215189 A/T	0.887	0.449	1.976	0.048 *
cg10296238	4.647	2.419	1.921	0.055 .
cg05200811	-5.712	2.789	-2.048	0.041 *



(b) Correlations between *SPATC1L* CpGs.

Gene Expression

SPATC1L gene is differentially expressed between control and obese samples. Some genes around *SPATC1L* locus (+/-250kb) are also differently expressed between the two phenotypes. *COL6A1* ($p=0.193$) and *COL6A2* ($p=0.002$) are altered in obesity patients [2], particularly in subcutaneous adipocytes of adult subjects [2, 3].

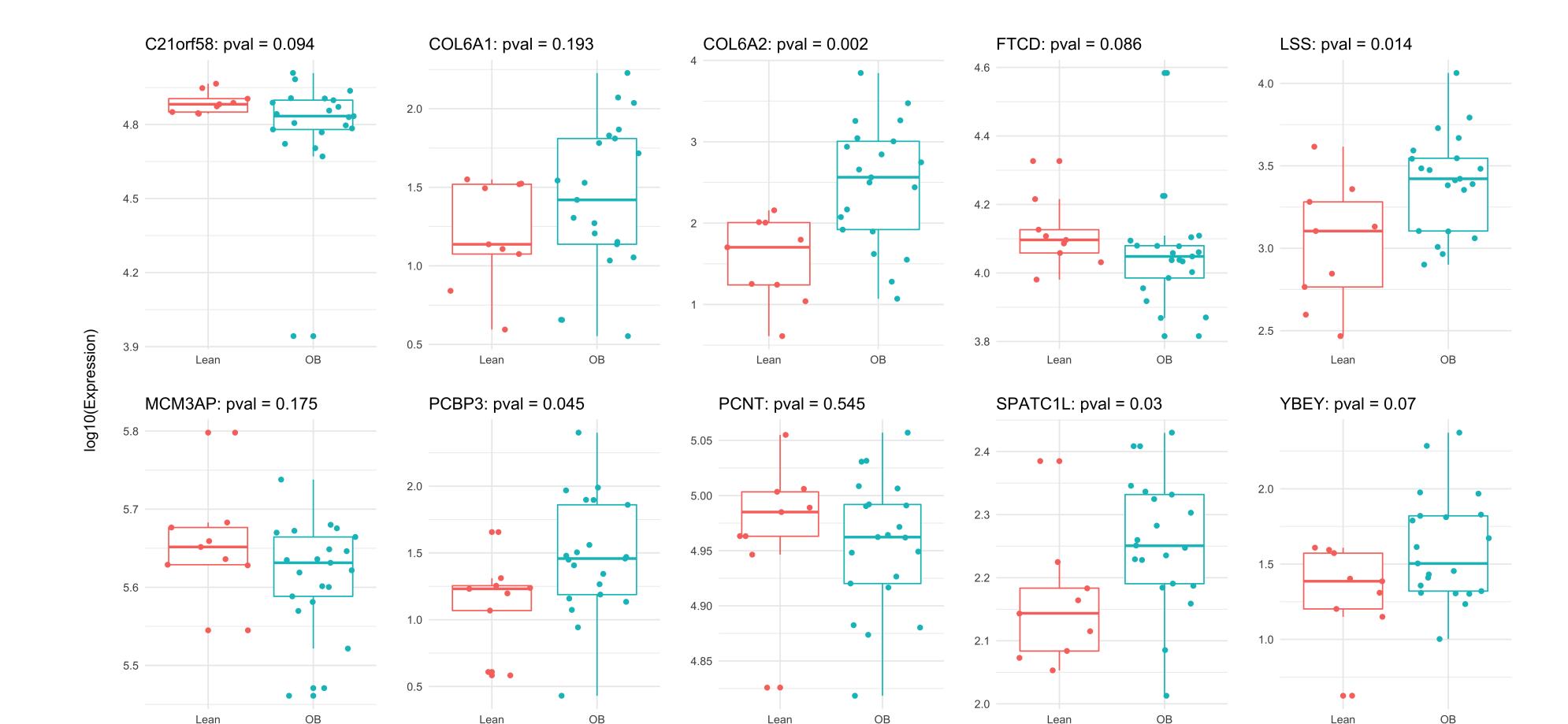


Figure: Whole blood expression (qPCR) of genes within *SPATC1L* locus. P-values come from ttest or Mann-Whitney U test depending on variable distribution).

Conclusions

- Childhood obesity is associated to a small change in DNA methylation (109 CpG sites).
- Gene expression and DNA methylation of *SPATC1L* locus are altered in childhood obesity.
- Two CpGs in the *SPATC1L* locus could play a causative role in childhood obesity.

References

- [1] Heyn, H., et. al. DNA methylation contributes to natural human variation. *Genome research*, 2013.
- [2] Lee, Y. H., et. al. Microarray profiling of isolated abdominal subcutaneous adipocytes from obese vs non- obese Pima Indians: increased expression of inflammation-related genes. *Diabetologia*, 2005.
- [3] Oñate, B., et. al. Stem cells isolated from adipose tissue of obese patients show changes in their transcriptomic profile that indicate loss in stemcellness and increased commitment to an adipocyte-like phenotype. *BMC genomics*, 2013.

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