

Epigenome-wide association study in Childhood obesity

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1 Introduction

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

C21orf56 (SPATC1L)*

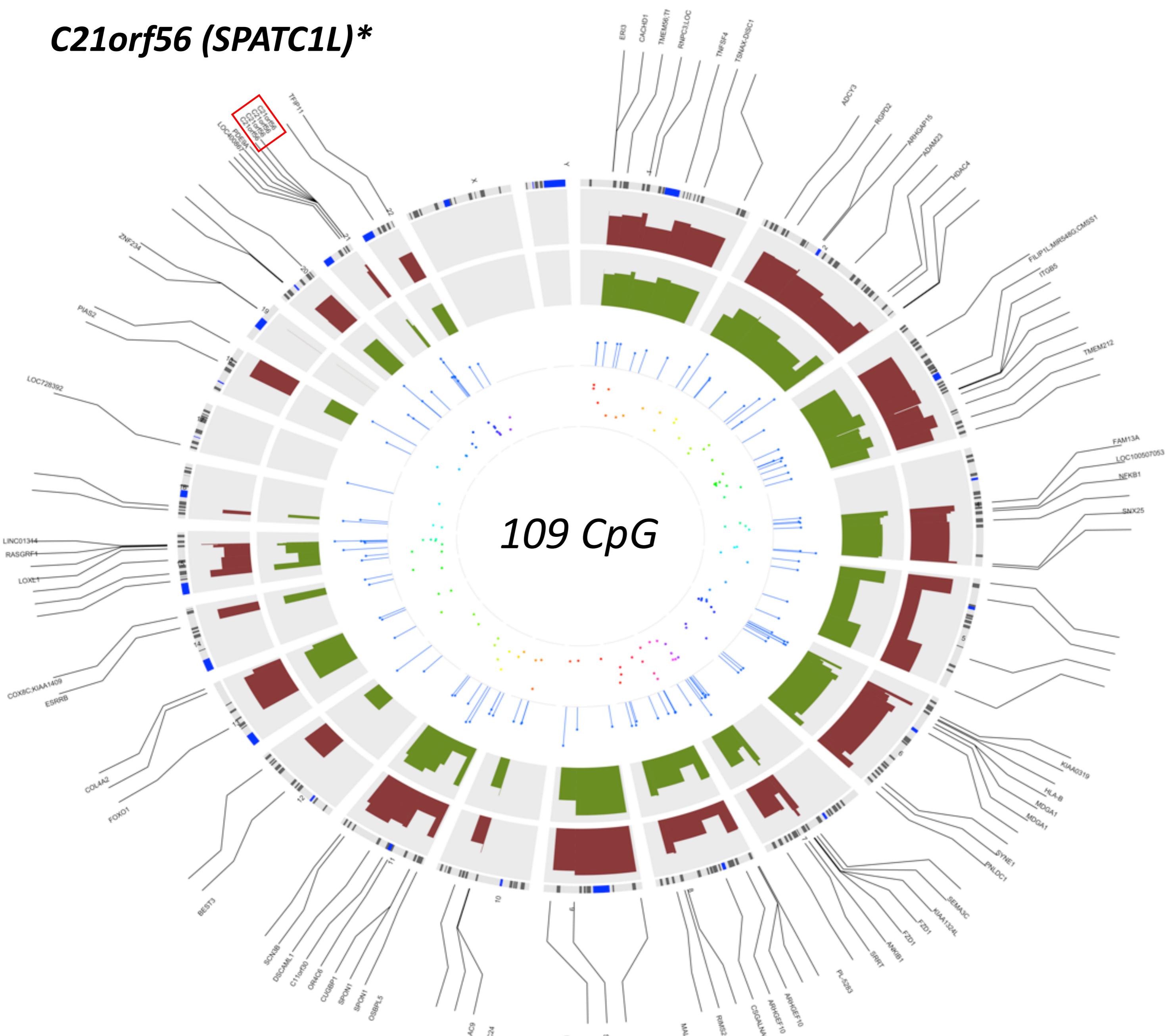
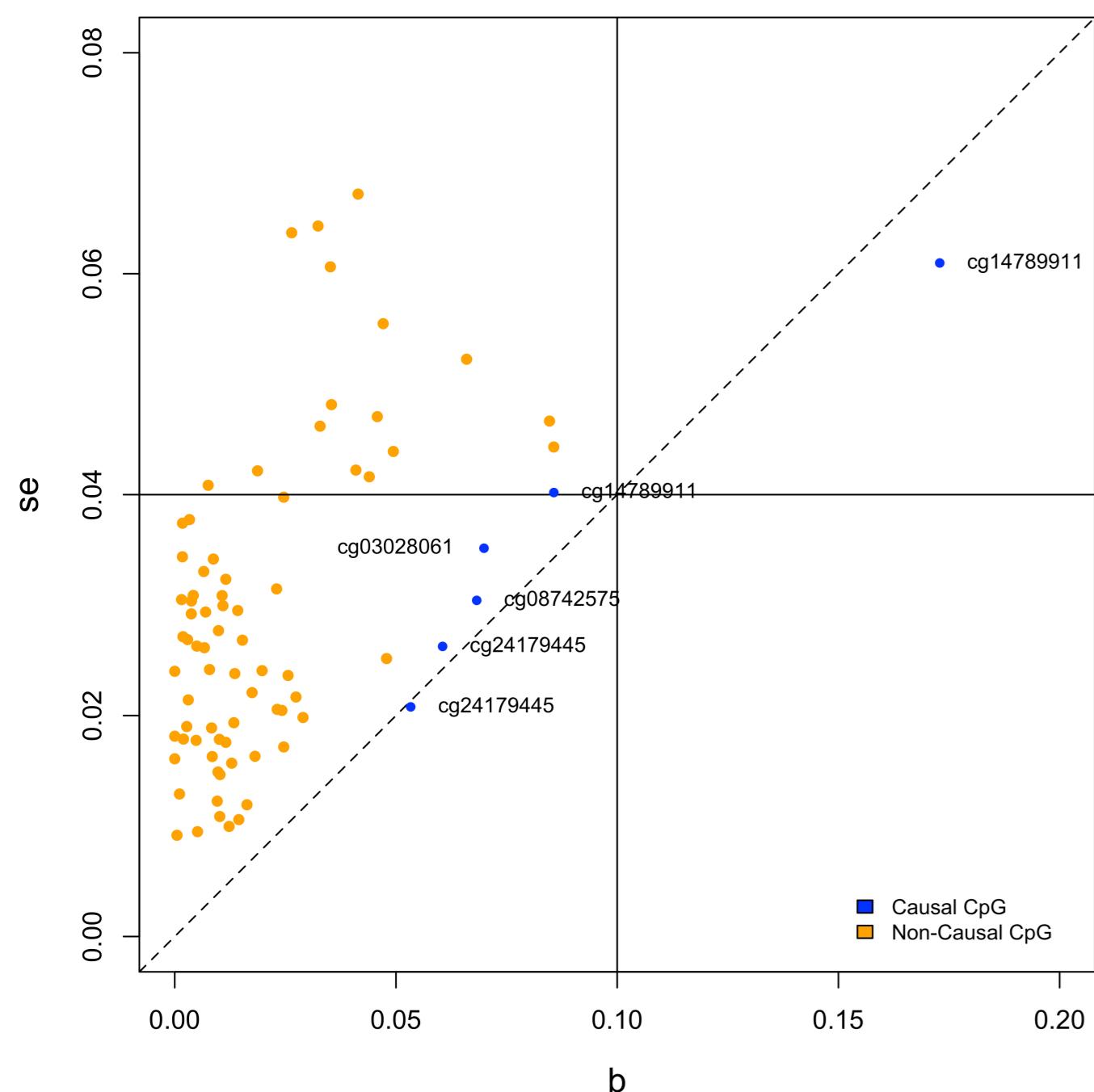


Figure 1. Circular plot, integrating the methylation data. Circular tracks from outside to inside: gene names, genome positions by chromosomes (black lines depict the cytobands), average of beta values for obese subjects, average of beta values for control subjects, effect size between the two groups, manhattan plot (for 109 CpG).

2 Causality analysis



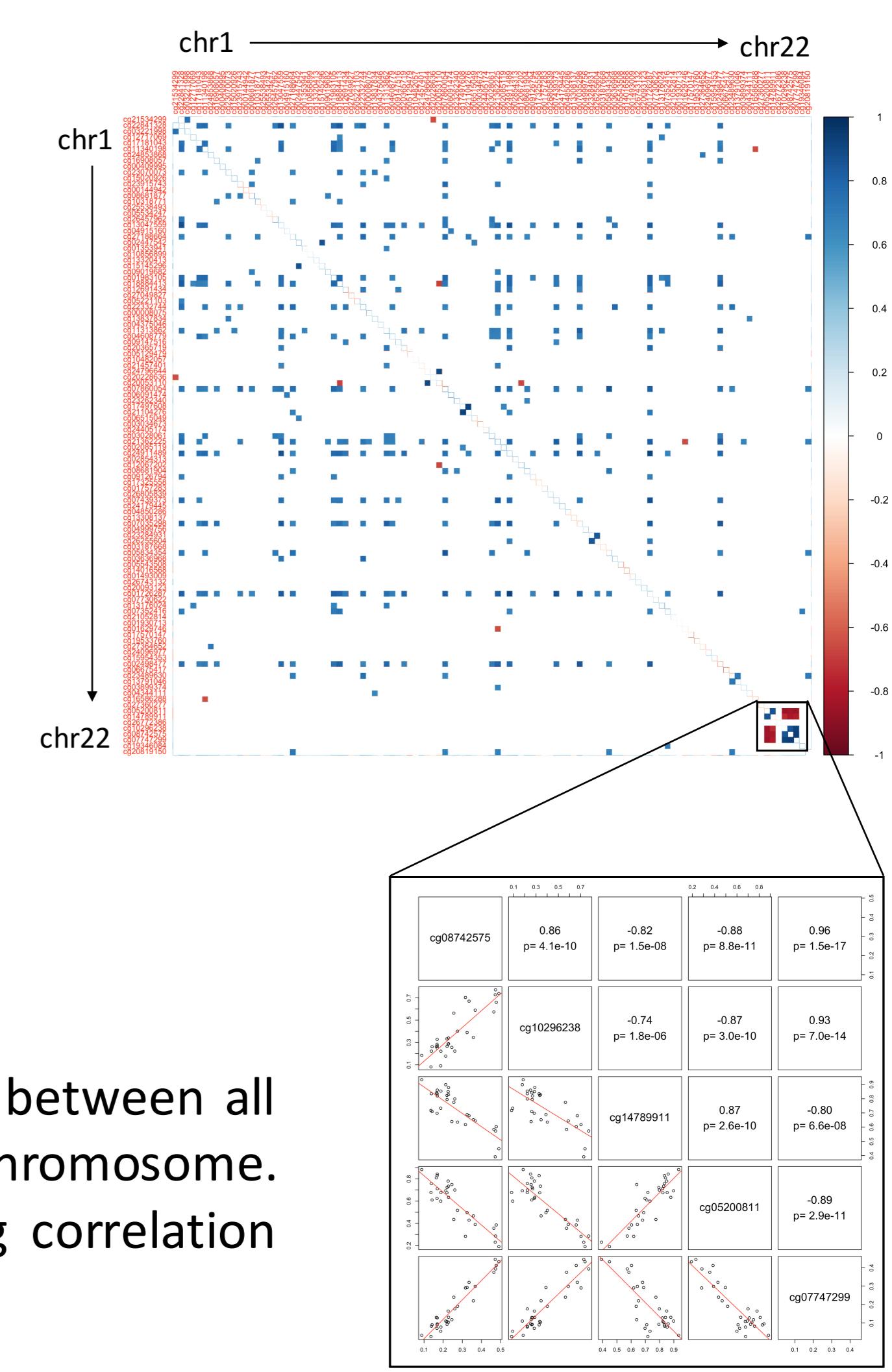
Two sample Mendelian randomisation is a method to estimate the causal effect of an exposure on an outcome using summary statistics from genome wide association studies (GWAS). We identified 4 causal CpGs for several disorders, including Childhood Obesity, Type 2 Diabetes, Ulcerative Colitis and Inflammatory Bowel Disease.

Figure 2. Results for the causality analysis investigating whether DNA methylation of the sentinel CpG sites influences outcome. For each sentinel CpG site, we identified the *cis* SNP (1 Mb) most closely associated with DNA methylation levels. For each SNP, we then determined its effect on outcome predicted via methylation (x axis) and standard deviation of this prediction (y axis). Orange, CpGs that are not significantly associated with a SNP or that are significantly associated with a SNP but have no effect in outcome (non-causal CpGs). Blue, CpGs that are significantly associated with a SNP with effect in outcome ($P < 0.05$). Consequently, the blue sentinels are the causal CpGs.

3 Correlations

The correlation plot shows significant correlation between CpG taking into account both phenotypes. We speculate that joint regulation of these CpG sites could be due to: 1) physical interaction during the methylation and/or 2) to *upstream* methylation mechanisms, altered in obese individuals. The strong correlation in the cluster of 5 CpGs in the *SPATC1L* region proved the joint regulation of this region, which contains the two causal CpG.

Figure 3. Correlation plot (Bonferroni < 0.05) between all significative CpGs. CpGs are ordered by chromosome. Zoom in for *SPATC1L* locus, that has a strong correlation cluster of 5 CpGs.



4 SPATC1L locus*

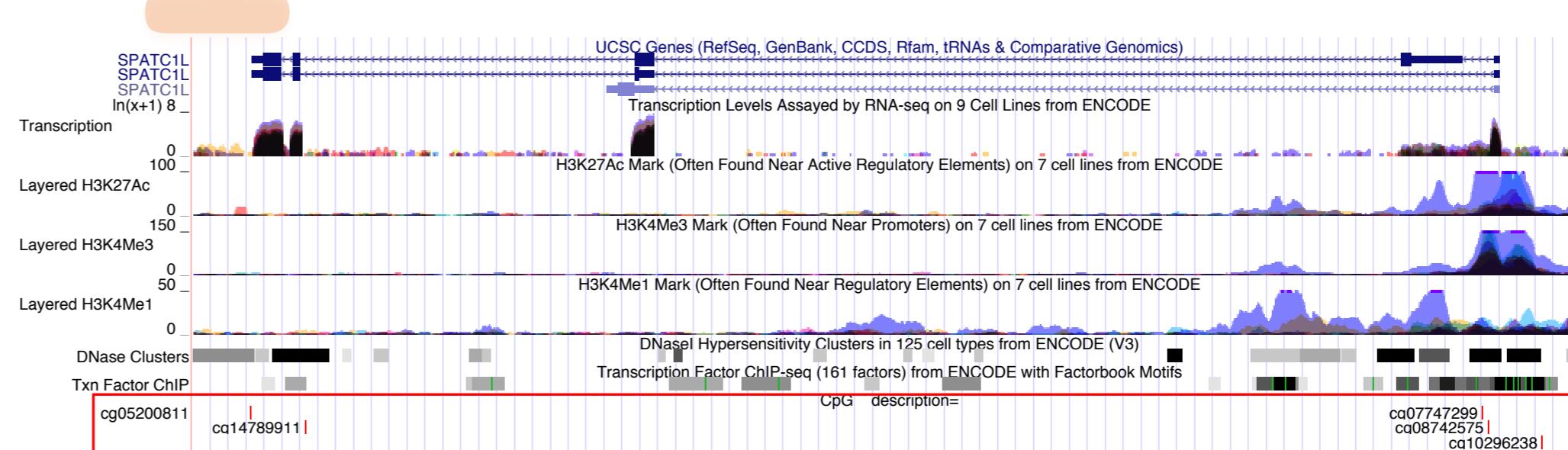


Figure 4. *SPATC1L* locus visualized in UCSC Genome Browser including personalized tracks. The 5 CpG sites are included in the red box.

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

5 Neighbouring genes expression

The 4 genes neighbouring *SPATC1L*: *COL6A2* (Collagen Type VI Alpha 2 Chain), *LSS* (Lanosterol Synthase), *YBEY* (YbeY Metallopeptidase) and *C21orf58* are differentially expressed in whole blood samples from Obese vs. Control subjects. In contrast, the expression of *FTCD* (Formimidoyltransferase Cyclodeaminase) and *MCM3AP* (Minichromosome Maintenance Complex Component 3 Associated Protein) was similar between groups ($P < 0.05$).

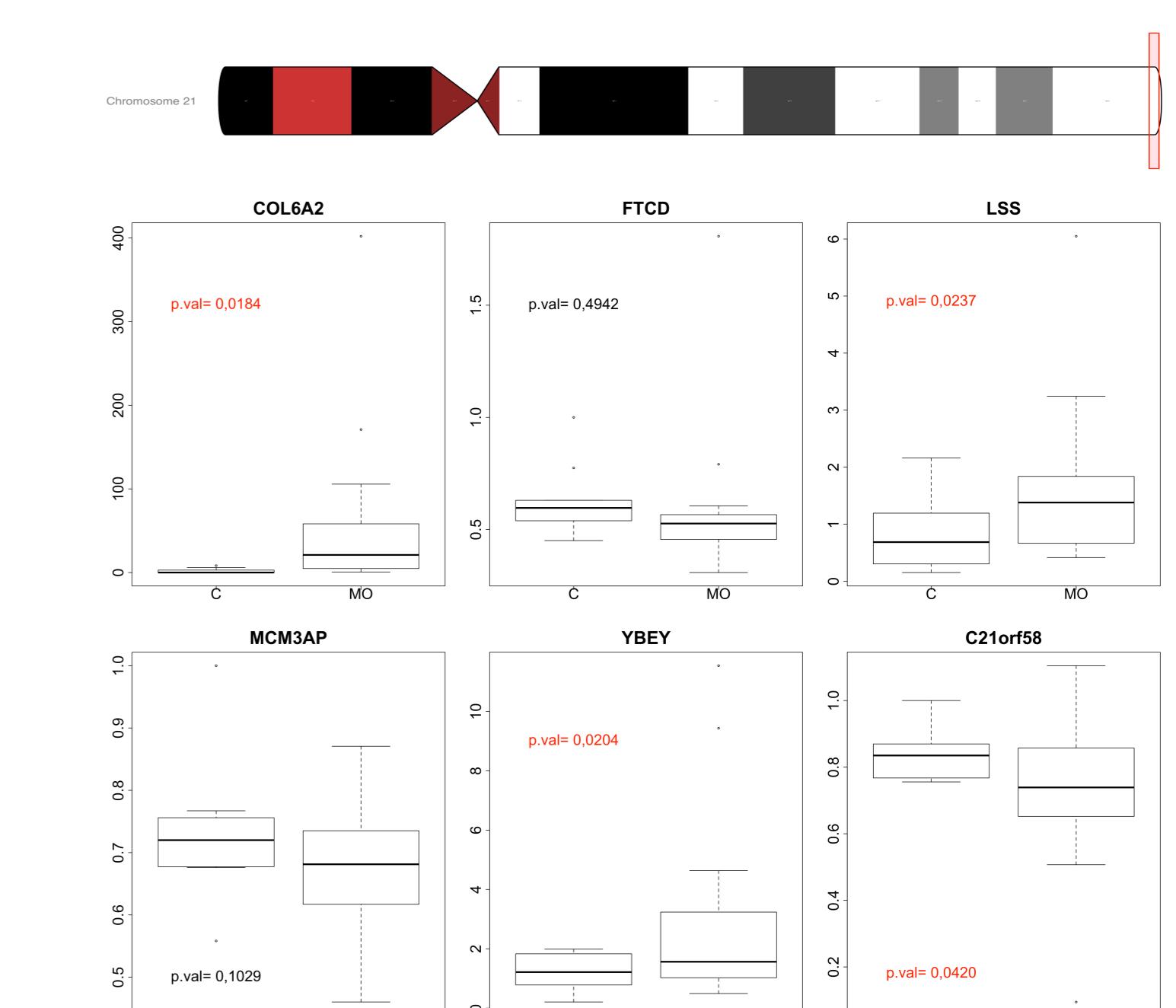


Figure 5. Chromosome 21 showing the *SPATC1L* locus (red box). Expression (mRNA relative abundance) of *COL6A2*, *FTCD*, *LSS*, *MCM3AP*, *YBEY* and *C21orf58* genes in Control and Obese subjects. ($P < 0.05$; t test)

6 Conclusions

- We show that childhood obesity is associated to a small change in DNA methylation (109 CpG sites).
- Only 2 CpG sites appeared to play a causative role in the development of the disease.
- We hypothesize that these CpG sites might mediate disease risk by modulating the expression of physically close genes (*COL6A2*, *LSS*, *YBEY* and *C21orf58*).