NAMPT SNPs ASSOCIATED WITH VISFATIN/NAMPT LEVELS LOCATED NEARBY A PUTATIVE ENHANCER REGION ACTIVATED BY METFORMIN

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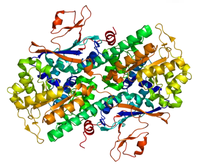
Introduction

Nicotinamide phosphoribosyltransferase (NAMPT) is a adipokine released by adipocytes and inflammatory cells.

NAMPT has potential to be a predictive biomarker or a therapeutic target for several diseases. **NAMPT is activated by Metformin**, the first-line therapy for type 2 diabetes.



Noncoding single nucleotide polymorphisms (SNPs) are also relevant for NAMPT levels. rs1319501 in *NAMPT* promoter region was found to be associated with plasma NAMPT levels, and are tightly linked with rs9770242 and rs61330082, which are located ~1,500bp upstream from the *NAMPT* transcription start site.

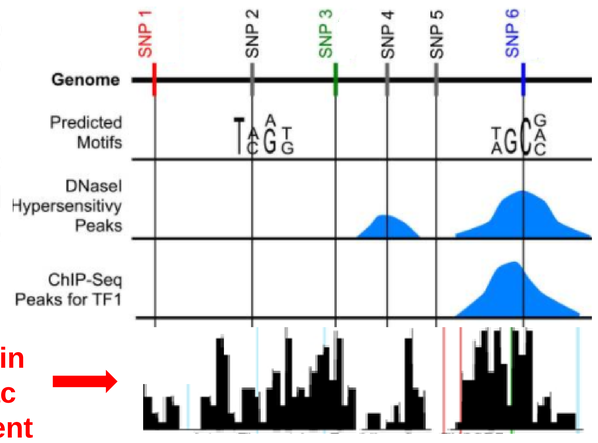
Hypothesis and Objectives

However, noncoding SNPs may overlap with functional regulatory elements, such as enhancers.

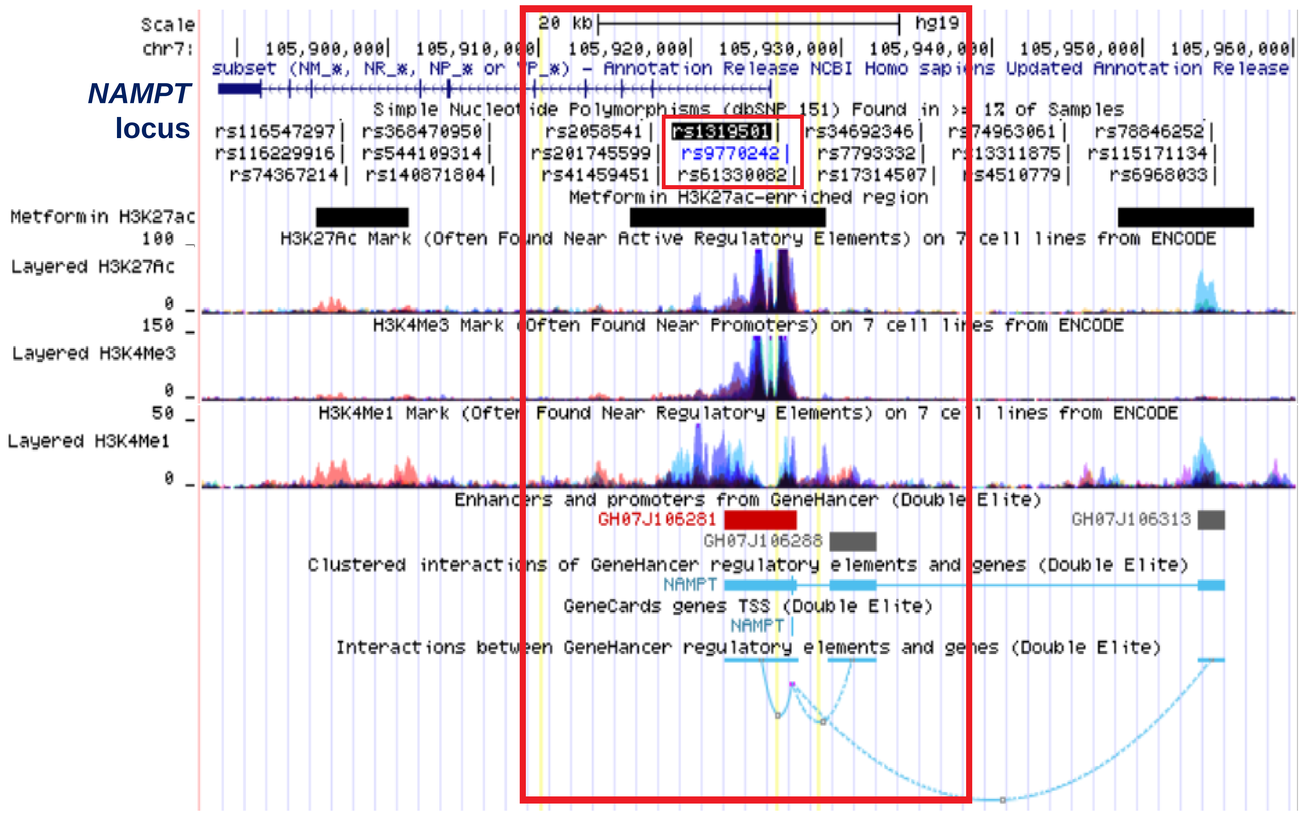
Thus, we searched for metformin-responsive regulatory elements in the *NAMPT* locus, and linked SNPs within them that may be associated with NAMPT levels.

Example is provided in the Figure:

(adapted from: Schaub MA., et al. *Genome Research*, 2012):



Results



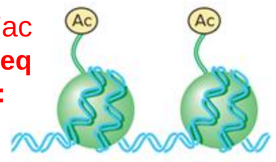
The SNPs rs1319501, rs9770242 and rs61330082 overlap with a metformin-responsive region enriched for the active histone mark H3K27ac upon metformin treatment, which is located nearby an enhancer element according to GeneHancer (**GH07J106288**). Notably, rs61330082 and rs11977021 were in perfect linkage disequilibrium in a cohort of obese children and are associated with visfatin level and adverse cardiometabolic parameters. According to **GTEx**, these SNPs are eQTLs for NAMPT in heart tissue.

Methods

We examined publicly available ChIP-seq data for active (H3K27ac) and silenced (H3K27me3) histone marks on human hepatocytes treated with metformin. We used **GeneHancer** to identify active regulatory elements, and several cis-regulatory elements assignment tools from the **Encyclopedia of DNA Elements (ENCODE)** to identify enhancers around the *NAMPT* locus. Next, we performed the functional annotation of noncoding SNPs located in *NAMPT* locus using the **Genotype-Tissue Expression (GTEx)** project data for SNPs linked to *NAMPT* expression.

ENCODE

H3K27ac **ChIP-seq data:**

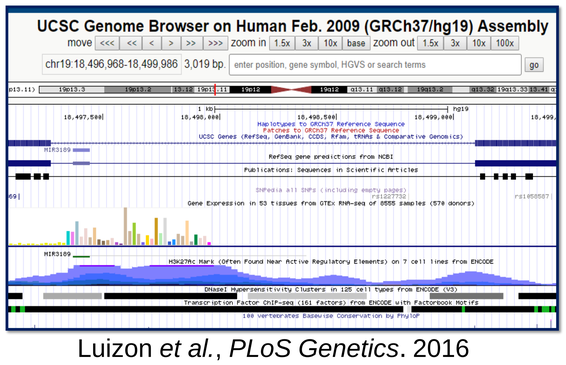


GeneHancer ENHANCERS & TARGET GENES

GTEx Portal "Viewing Gene Expression Data on the GTEx Portal"

Active mark.bed file...

... as custom track at UCSC Genome Browser



Luizon *et al.*, *PLoS Genetics*. 2016

Discussion and Conclusions

To understand the regulation of *NAMPT* expression is crucial to reveal its biological functions and the variations under physiological and pathophysiological contexts, which could help to define NAMPT as a biomarker.

These data support that noncoding variation within a metformin-activated enhancer may increase NAMPT expression.

The perspectives are to functionally characterize these noncoding *NAMPT* SNPs, which could be used to predict NAMPT levels in patients with type 2 diabetes treated with Metformin.

References: : Schaub MA., et al. *Genome research*, 2012.; Luizon *et al.*, *PLoS Genetics*. 2016; ENCODE PROJECT CONSORTIUM et al. The ENCODE (ENCyclopedia of DNA elements) project. ***Science***, 2004.

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