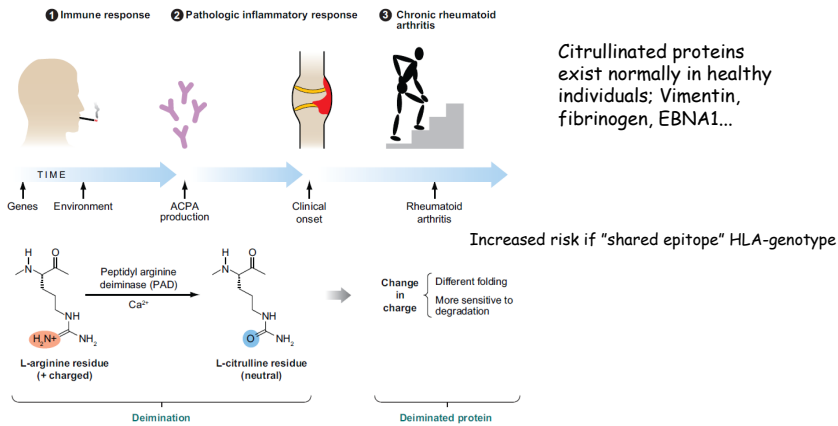


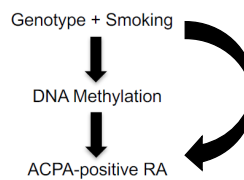
Environmental impact on development of ACPA and Rheumatoid Arthritis; smoking is key



Klareskog et al. Annu. Rev. Immunol. 2008. 26:651–75

Smoking, gene/environment interactions and RA risk?

Two RA cohorts.
One MS cohort
Genome wide methylation analysis,
but focus on the MHC cluster



Stage 1: Identification of significant interaction between genotype and smoking on DNA methylation (the EIRA cohort)

Stage 2: Replication the interaction (the EIMS cohort)

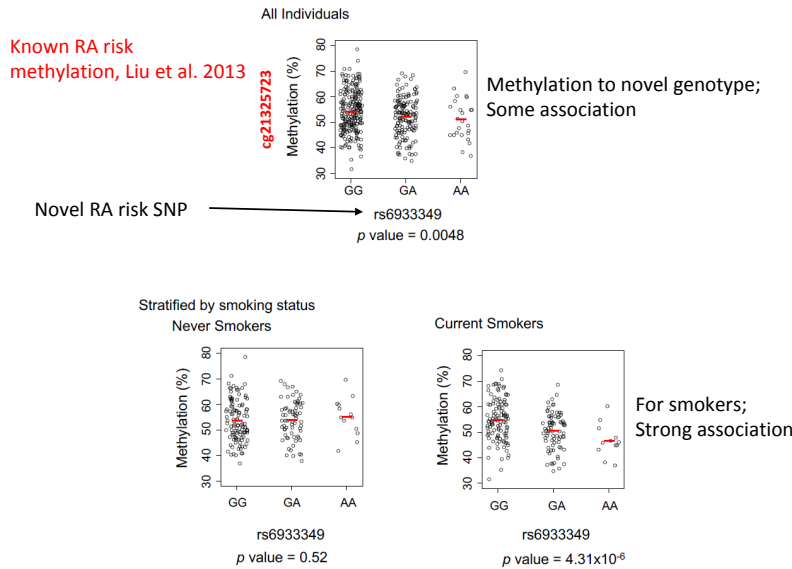
Stage 3: Study of genotype and smoking interaction on ACPA-positive RA (the EIRA and MyEIRA cohorts)

Stage 4: Study of DNA methylation as a mediator for genotype and smoking interaction on ACPA-positive RA (the EIRA cohort)



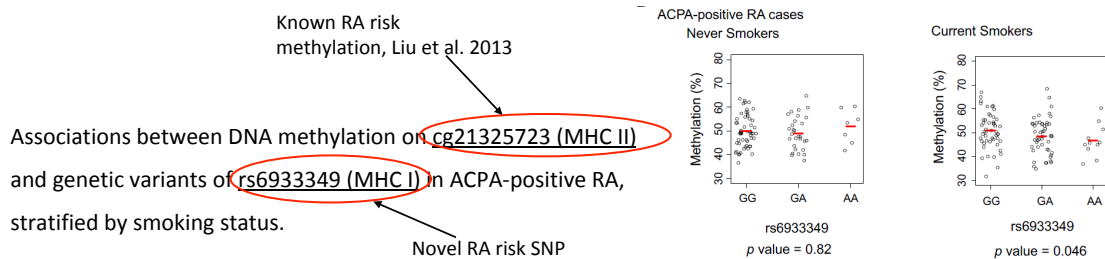
Meng et al. Arthr. Res. Ther. 2017

Associations of DNA methylation, genotype and smoking, in general...

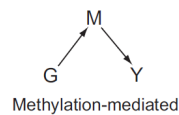
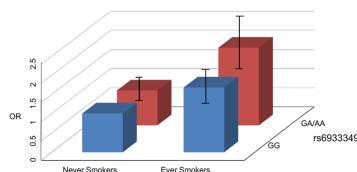


Meng et al. Arthr. Res. Ther. 2017

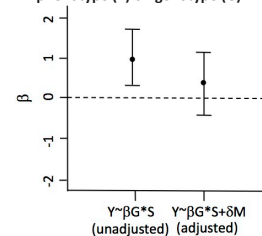
...and their association with risk for ACPA-RA



Increased risk for ACPA-positive RA in smokers and carriers of GA/AA genotypes.



β = "Dependence of rheumatoid arthritis phenotype (Y) on genotype (G)"



Meng et al. Arthr. Res. Ther. 2017

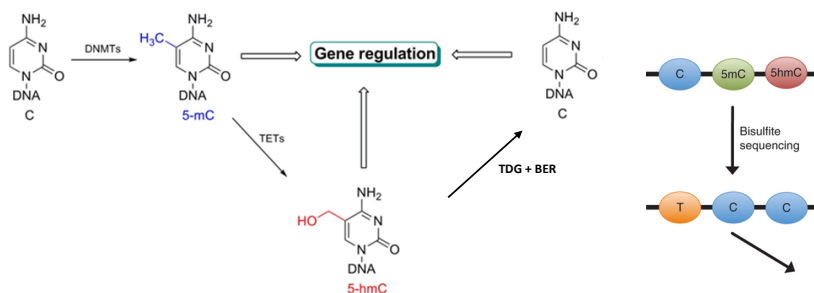
Smoking-induced inflammation related DNA methylation changes in the lung?



Is smoking associated with DNA demethylation?

Hypothesis: Oxidation of methylcytosine is a path to smoking induced demethylation

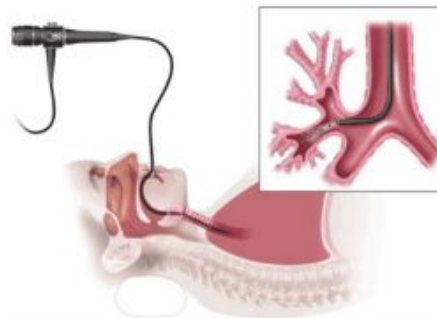
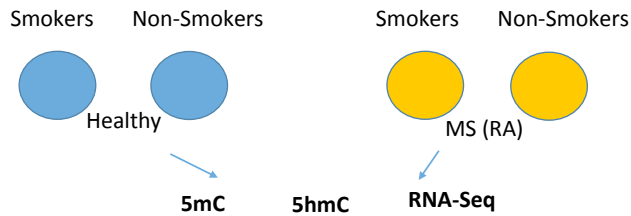
Induced by oxidative stress = caused by smoking?



CEGX, TrueMethyl, Oxidative bisulfite analysis

Epigenome wide analysis in BAL cells, Illumina EPIC, 850K

Tot. 64 individuals



Plasma proteinase inhibitor, α_2 -macroglobulin, A2M

A2M

A protease inhibitor and cytokine transporter.

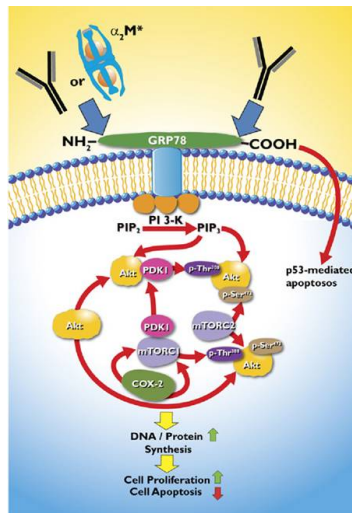
Inhibits a broad spectrum of proteases, including collagenase.

Inhibits inflammatory cytokines, and thus inflammatory cascades.

A major non-immunoglobulin plasma binding protein for TGF-beta.

Induces matrix metalloproteinase 9.

MMPs are elevated in arthritis; degrade non-collagen matrix components of the joints.



Extracellular GRP78 (BiP);

Anti-inflammatory

Development of tolerogenic DCs

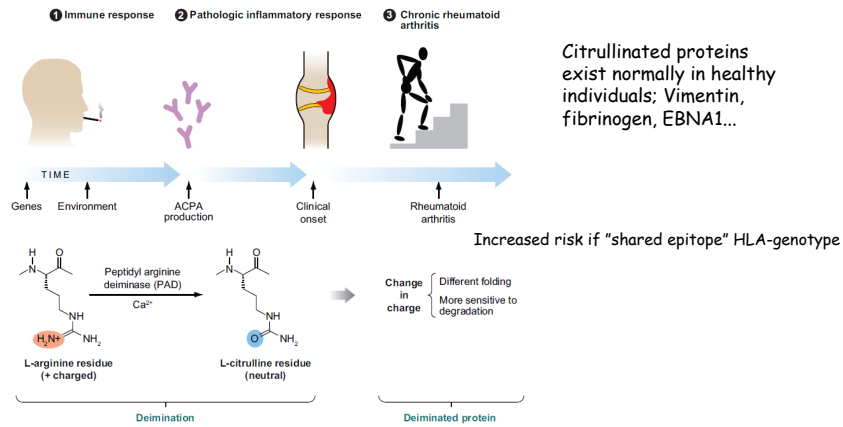
Induction of regulatory T-cells

Abrogation of osteoclast development and function

Induction of anti-inflammatory cytokine production

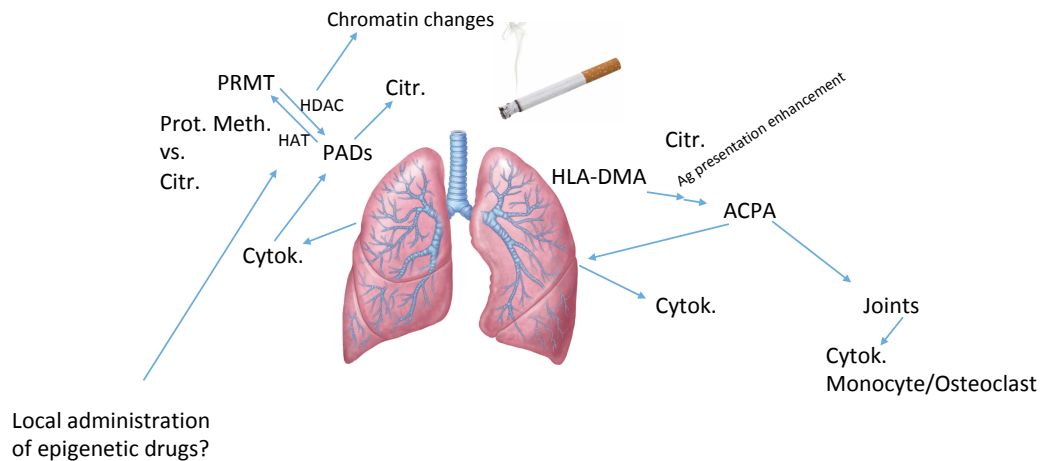
These functions help **drive the resolution of inflammation.**

Environmental impact on development of ACPA and Rheumatoid Arthritis; smoking is key

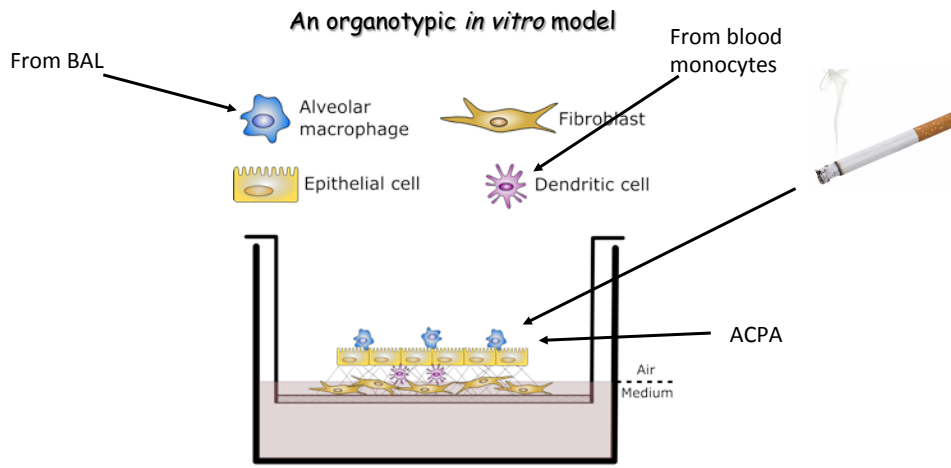


Klareskog et al. Annu. Rev. Immunol. 2008. 26:651-75

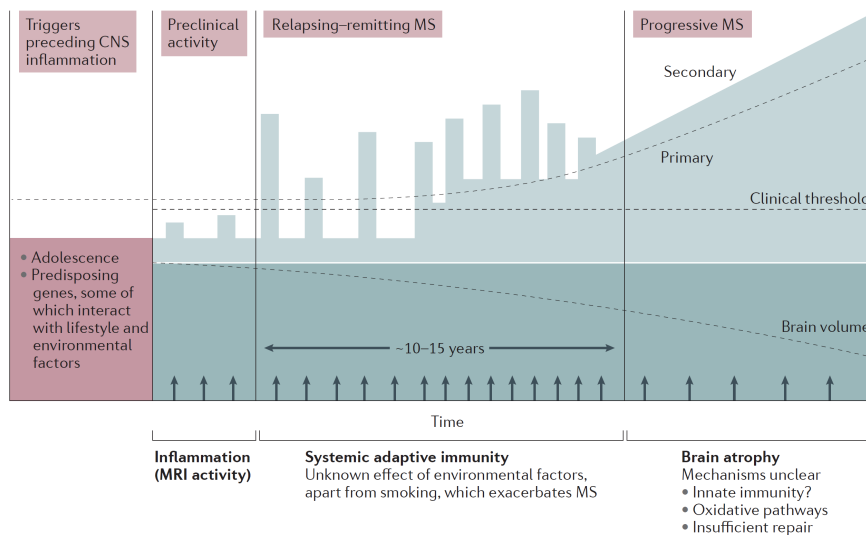
Hypothetical landscape for epigenetic control of immune related smoking effects



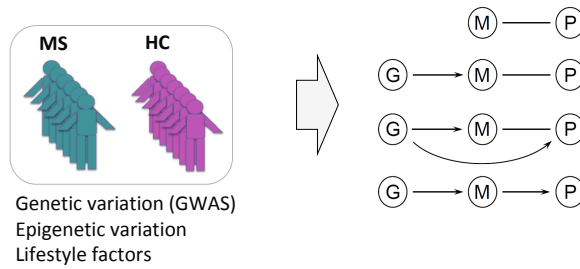
Environmental impact on development of ACPA and Rheumatoid Arthritis; it starts in the lungs



Evolution of Multiple Sclerosis, MS

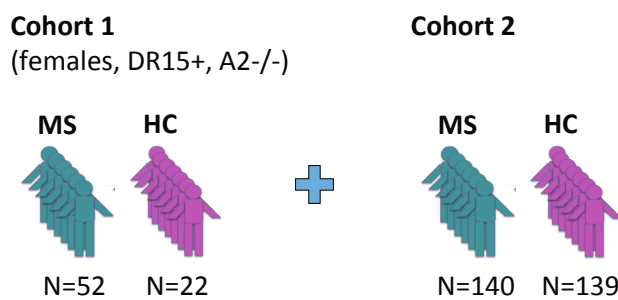


Mechanisms of known risk factors and identification of novel factors



- Examples:
- Genetic mediation
 - Smoking
 - Vitamin D

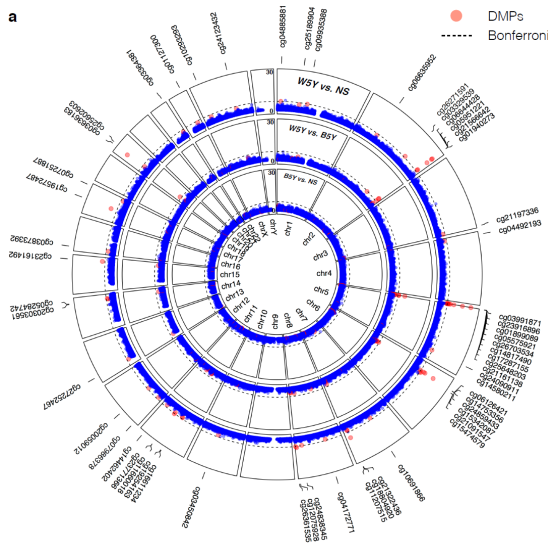
Smoking-induced mechanisms in MS



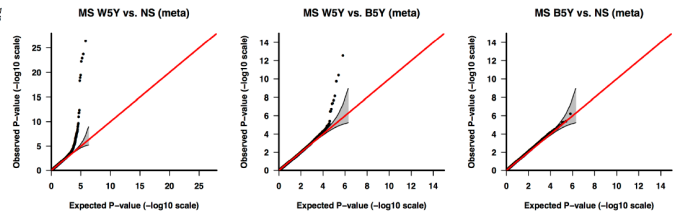
- Smoking status: current, past, never, passive smoker
- Illumina Infinium 450K Human Methylation arrays on blood DNA

Marabita F et al. *Scientific Reports*, 2017

Smoking induces DNA methylation changes in Multiple Sclerosis patients with exposure-response relationship

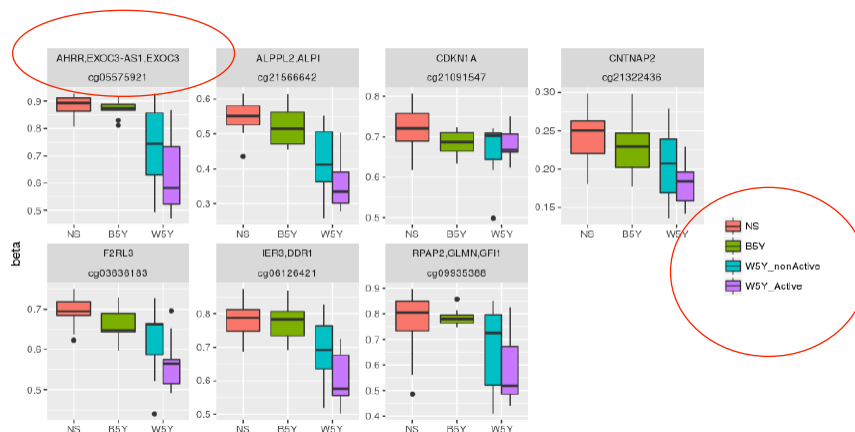


What Happens When You Quit Smoking?



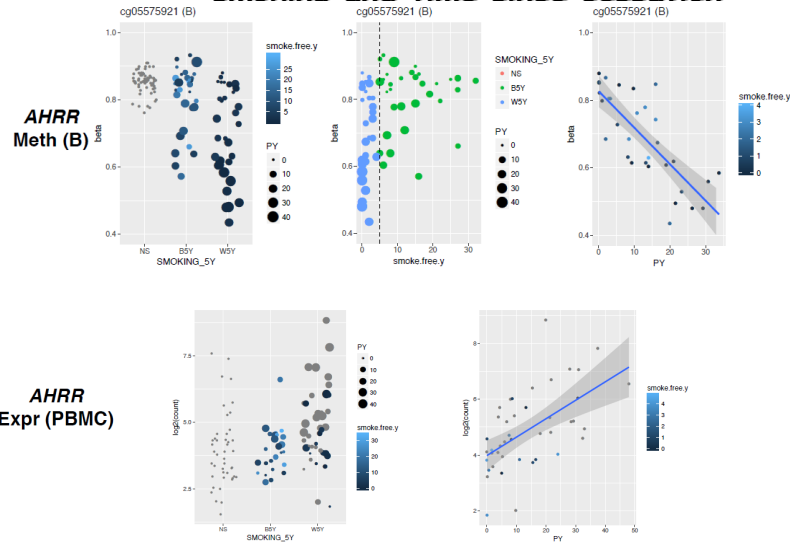
Marabita et al. Sci. Rep. 2017

The effect of smoking on DNA methylation for active smokers



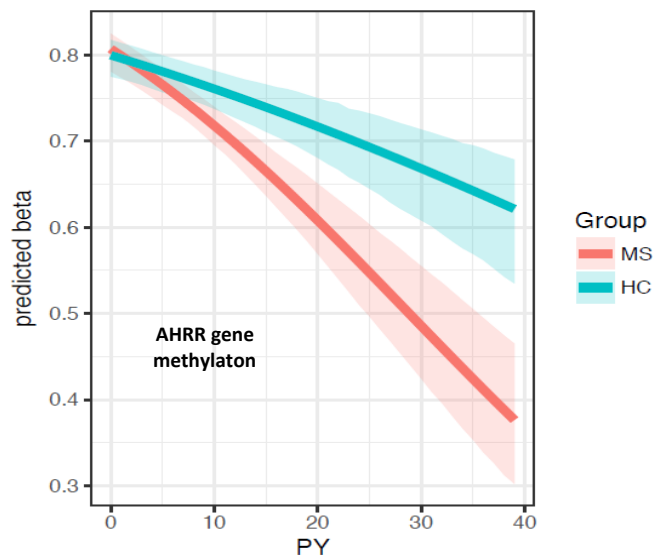
Marabita et al. Sci. Rep. 2017

Reversal of effects depends on the amount of smoking and time since cessation



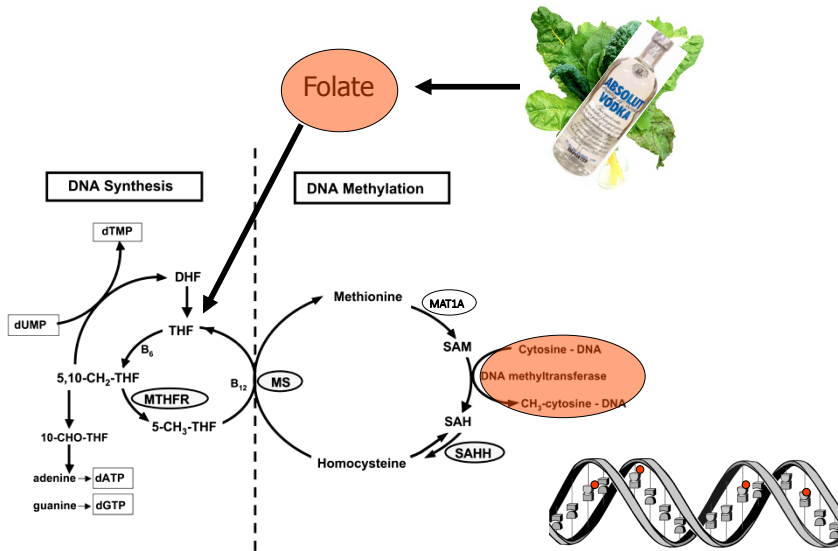
Marabita et al. Sci. Rep. 2017

Smoking load interacts with MS associated processes



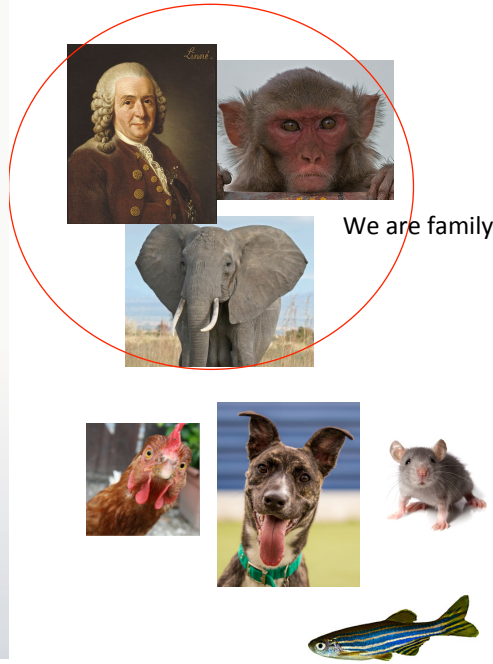
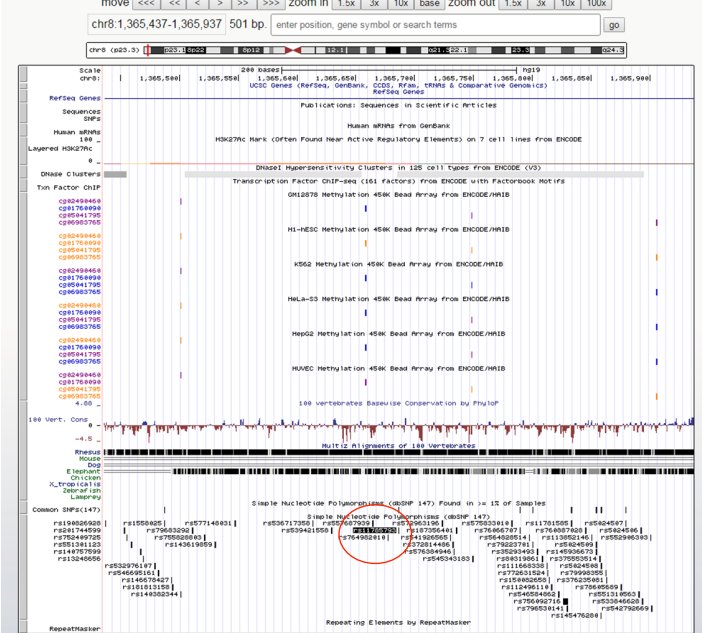
Marabita et al. Sci. Rep. 2017

Alcohol, nutritional and toxicological impact



Karolinska Institutet

UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly



Conclusions

Gene-environment interactions involve DNA methylation from early development to adult life, and maybe over generations.

The study of genetic variations together with epigenetics may reveal higher resolution genomic association pictures.

Study of RA and MS revealed genetic/epigenetic associations, new risk/protective genotypes in MS and genotype/epigenotype interactions with smoking in the risk risk for disease.

Smoking affects DNA methylation and hydroxymethylation of specific genes in bronchoalveolar lavage cells (macrophages). May be crucially important to separate 5-mC from 5-hmC.

The chronic alcoholic brain demonstrates genotype dependent DNA methylation close to the *DLGAP2* gene, whose product is implicated in glutamatergic transmission. Therapy for alcohol dependence may involve the newly found target.

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