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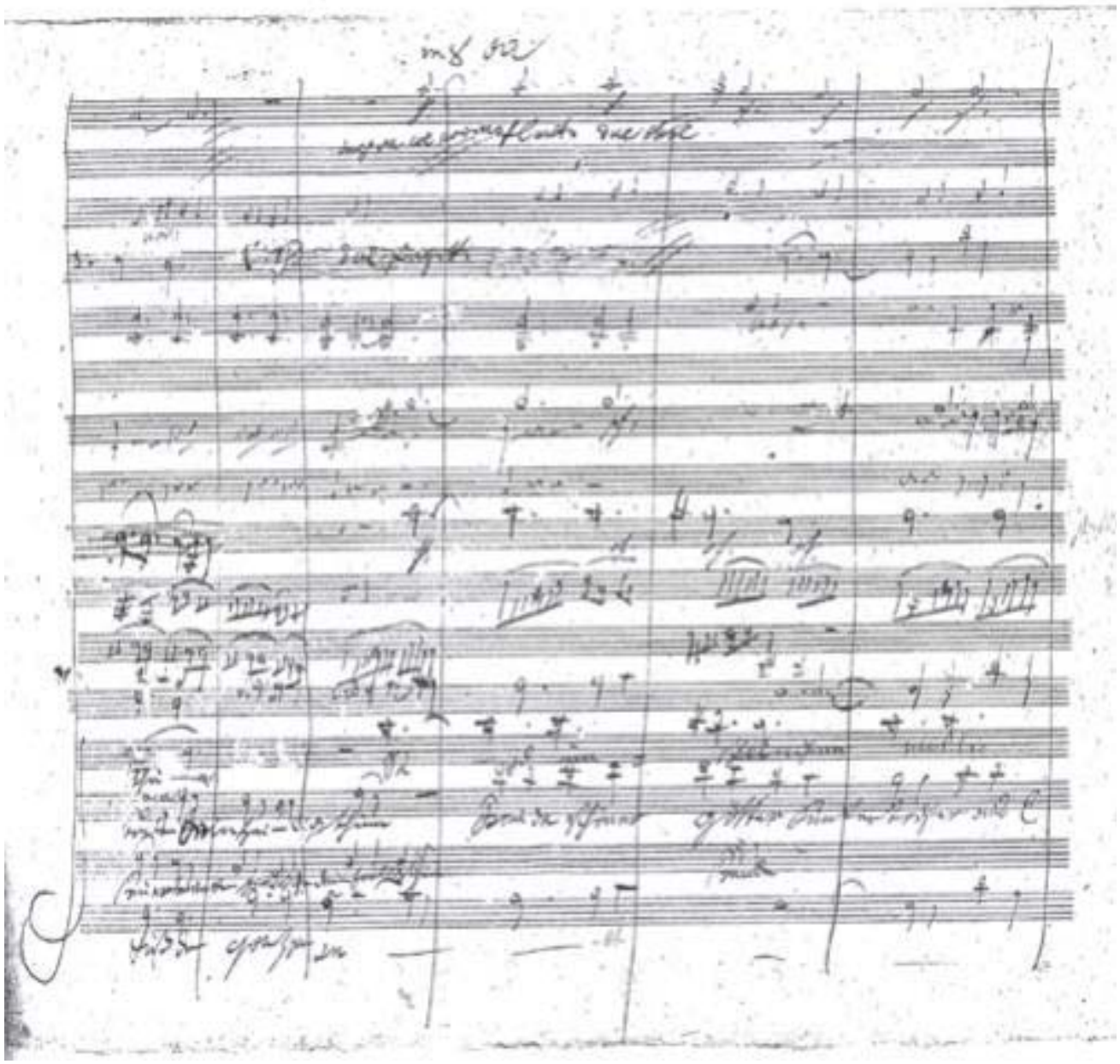
# EPIGENETICS AND BREAST CANCER

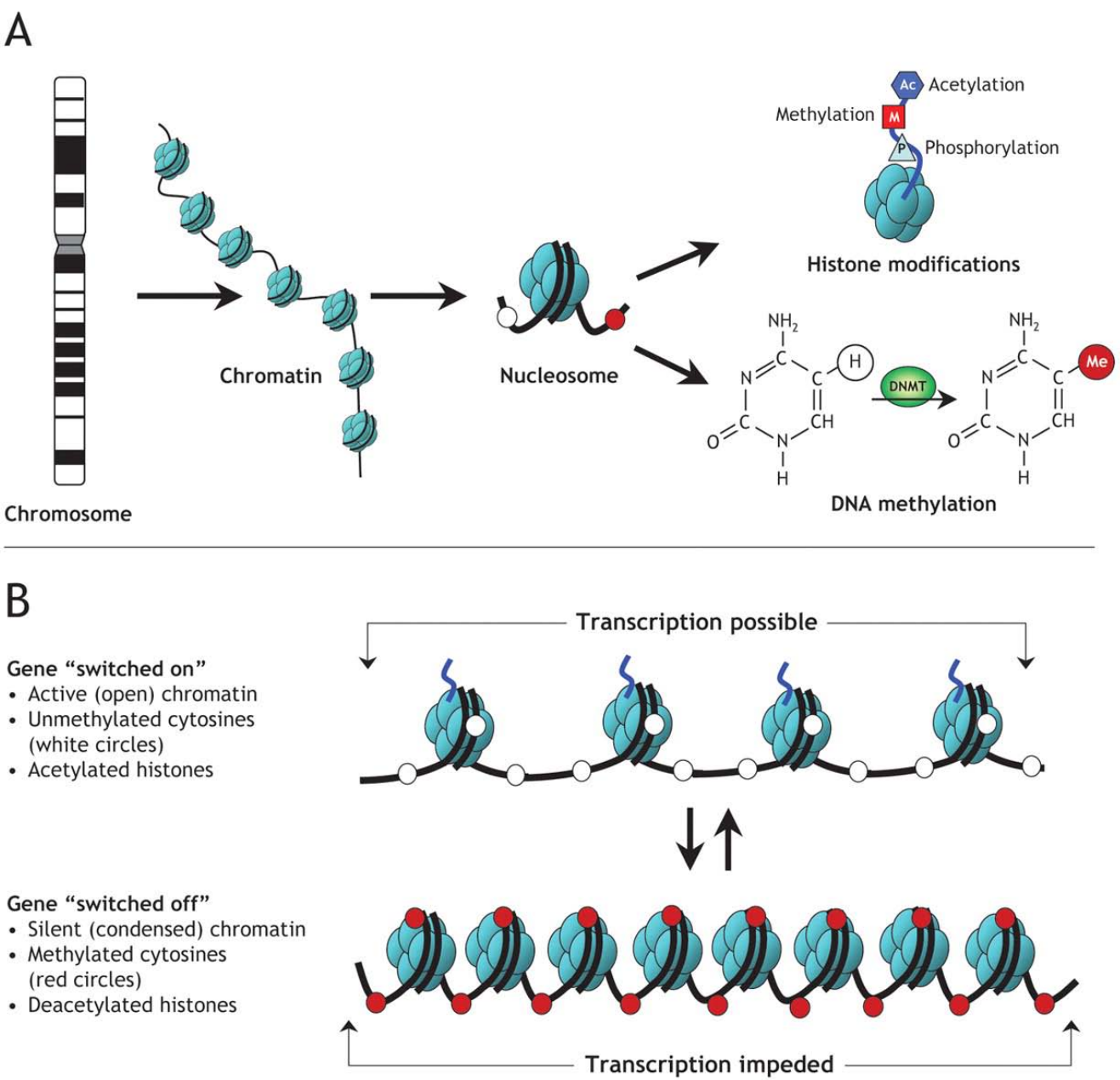
**27 September 2013**

**GISMA**

The iconic power of the double helix is related to its heuristic simplicity, particularly as a mechanism to explain inheritance.

However, the **script** needs to be interpreted and receives meaning only from the interplay with the environment **(interpretation of the script)**.




A
Chromosome
Chromatin
Nucleosome
Ac
Acetylation
Methylation
M
P
Phosphorylation
Histone modifications
NH2
H
DNMT
Me
DNA methylation
B
Gene "switched on"
• Active (open) chromatin
• Unmethylated cytosines (white circles)
• Acetylated histones
Transcription possible
Gene "switched off"
• Silent (condensed) chromatin
• Methylated cytosines (red circles)
• Deacetylated histones
Transcription impeded

# Epigenetics and Cancer

- **Growing data on the importance of epigenetics in the aetiology and pathogenesis of cancer**

**1. DNA methylation**

- **Gene specific hypermethylation (eg RASSF1, MLH1)**
- **Genome-wide hypomethylation (4% down to 2-3% of all cytosines)**

**2.Histone Modifications**

- **Active vs Inactive histone marks**
- **Polycomb group gene silencing (H3-K27-me3)**

Many cancer risk factors cause epigenetic modifications

# Epigenetics and The Environment

- Epigenetic changes can be inherited mitotically in somatic cells

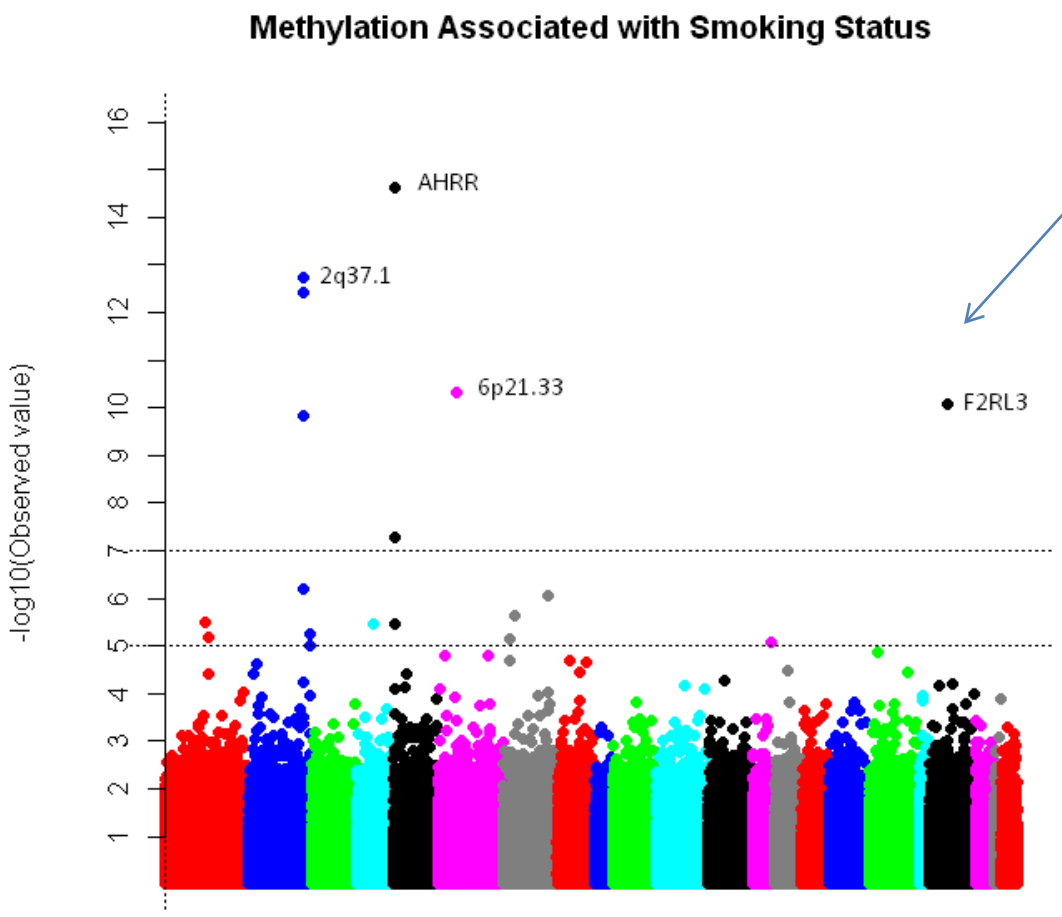
- Pre-natal and early post-natal exposures can result in changes in risk of developing disease
  - Nutrition
  - Xenobiotic chemicals
  - Behavioural Factors
  - Reproductive Factors, Hormonal Exposures

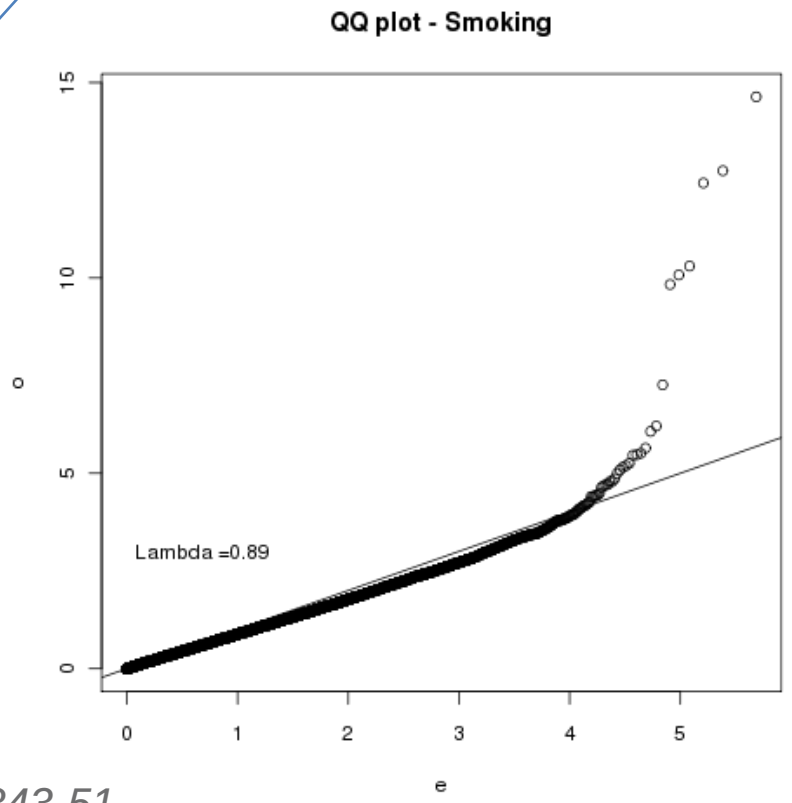
# Our own research at HuGeF and Imperial College

- **Smoking as an exposure alters DNA methylation detected in blood, and can be detected in Former Smokers up to 20 years later**
  - **Shenker et al., HMG 2013**
  - **Shenker et al., Epidemiology, 2013**
- **Fasting status influences the Epigenome, including the ATM methylation marker**
  - **Brennan et al, submitted**
- **Socio-economic status and gene methylation**
  - **Stringhini et al, submitted**
- **Intragenic ATM DNA methylation is associated with breast cancer risk**
  - **Flanagan et al., HMG 2009**
  - **Brennan et al., Cancer Research 2012**
- **Breast cancer: Global methylation EWAS (using 450K array data) as risk factor for breast cancer**
  - **Van Veldhoven et al, submitted ; Baglietto et al, submitted**

# EWAS for smoking status – Discovery

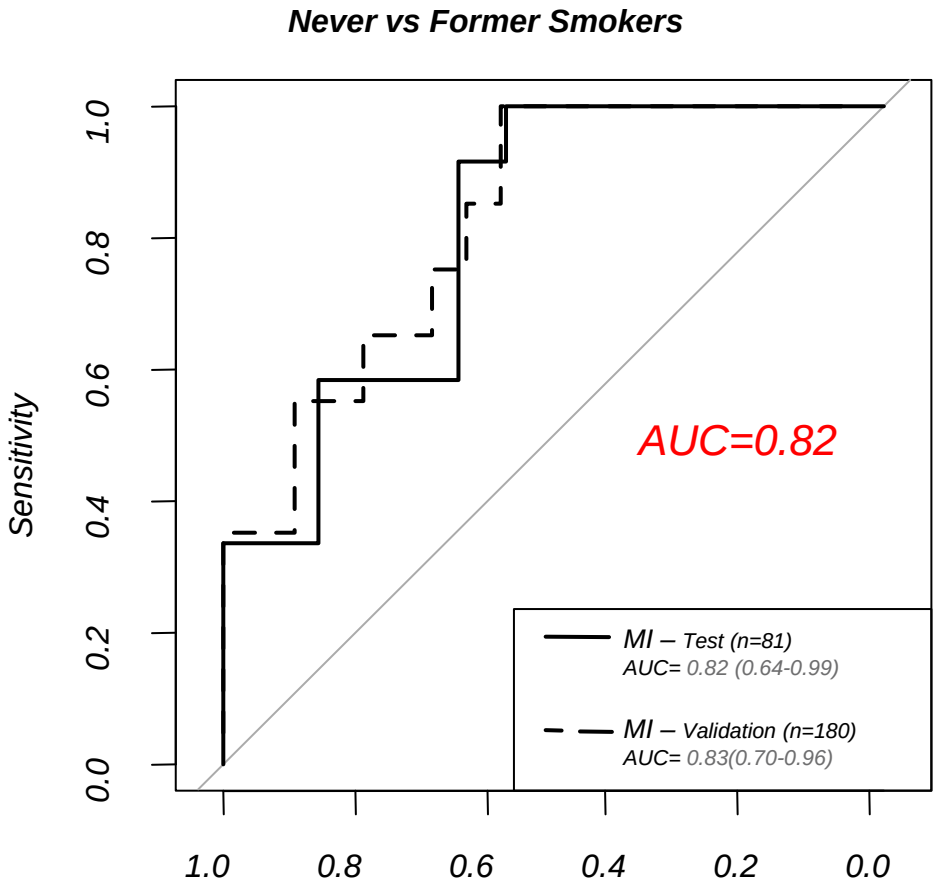
*Breitling et al AJHG April 2011*

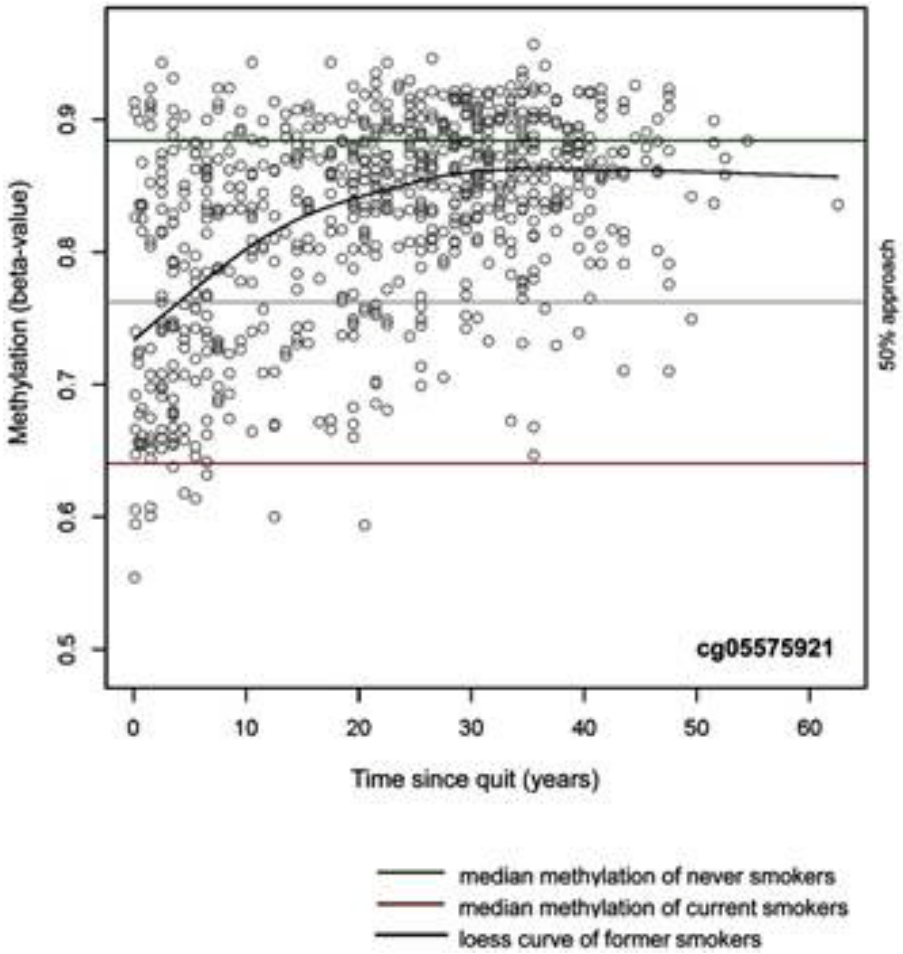



*Shenker NS et al., Hum Mol Genet. 2013 Mar 1;22(5):843-51.*

# Methylation Index to detect former smokers (or to quantify former exposure)

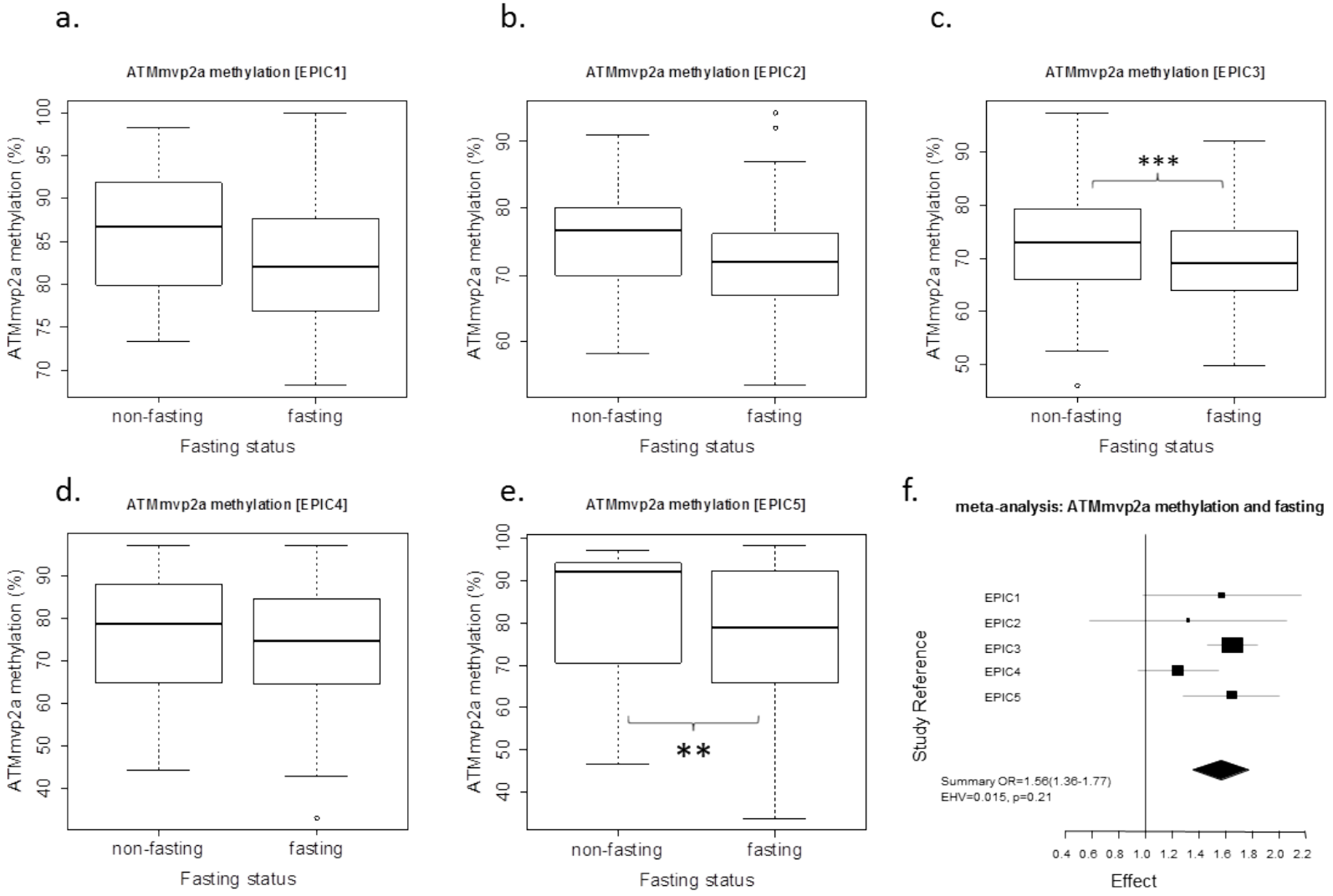



*Shenker et al, Epidemiology. 2013 Sep;24(5):712-6.*

*Zeilinger S, et al, PLoS One. 2013 May 17;8(5):e63812.*

# Fasting status




*Brennan, Flanagan et al., submitted*

# Dominance rank and expression level of pro-inflammatory genes (macaques)

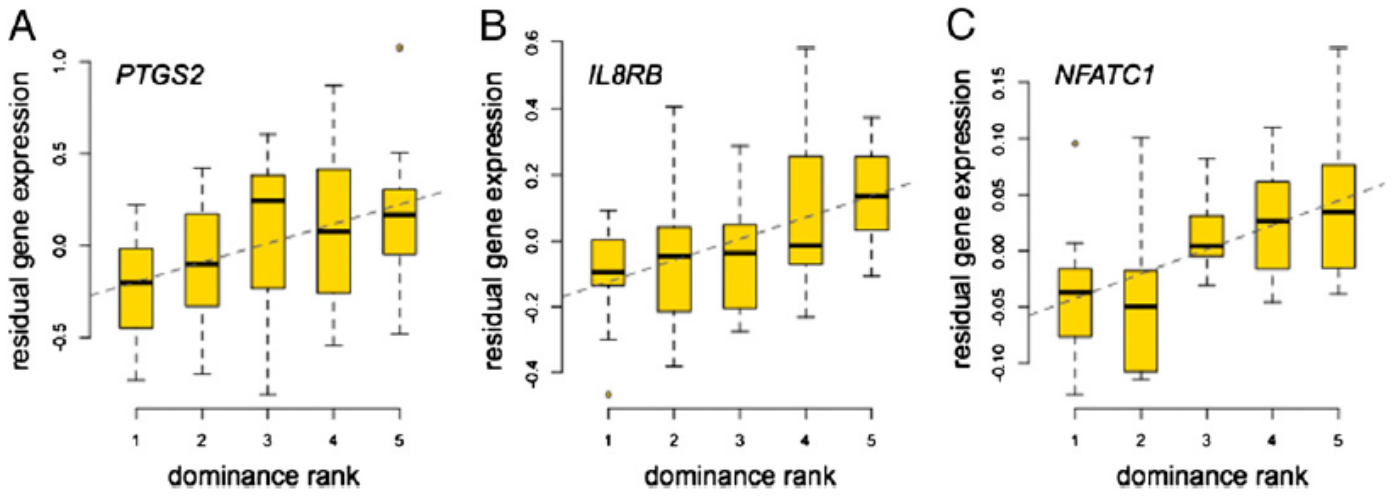
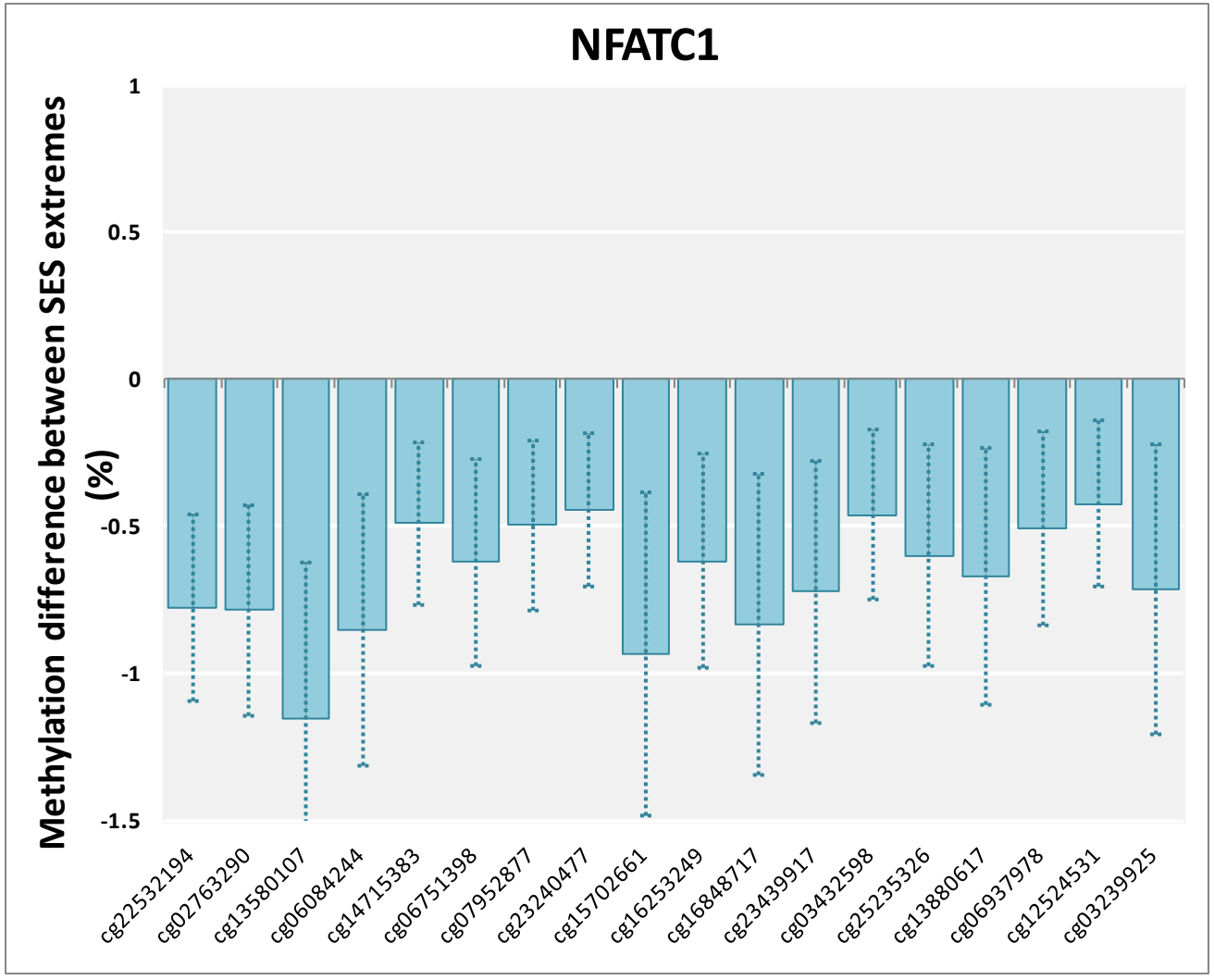



Fig. 2. Rank–gene expression associations among inflammation-related immune genes. Low-ranking females tend to overexpress inflammation-related genes: (*A*) *PTGS2* ($P = 0.004$); (*B*) *IL8RB* ($P = 0.003$); and (*C*) *NFATC1* ($P < 10^{-3}$).

**Tung et al. Social environment is associated with gene regulatory variation in the rhesus macaque immune system. Proc Natl Acad Sci U S A. 2012 Apr 24;109(17):6490-5.**

# SES and DNA methylation – EPIC Turin



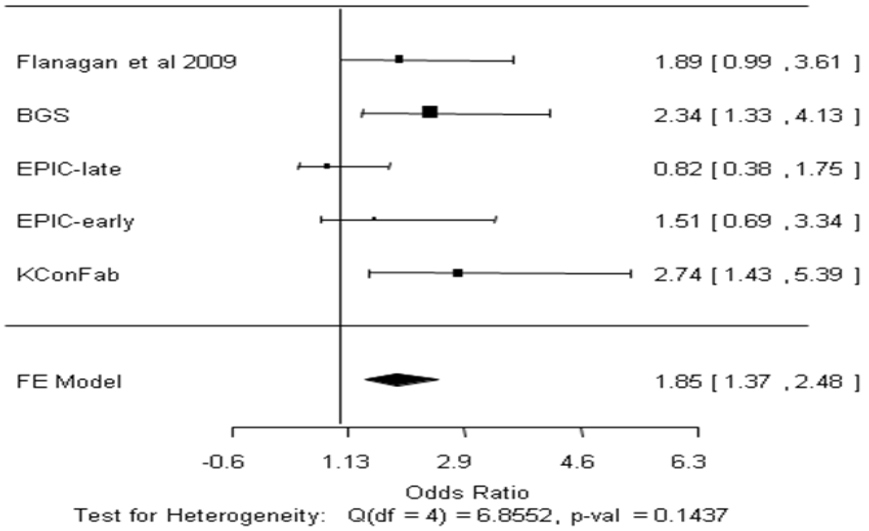

- NFATC1 is one of the three genes whose expression was more strongly associated with social rank in macaques (more expressed in macaques with low social rank)
- NFATC1 gene is involved in the expression of cytokine genes in T-cells, especially in the induction of the IL-2 or IL-4 gene transcription
- NFATC1 regulates not only the activation and proliferation but also the differentiation and programmed death of T-lymphocytes as well as lymphoid and non-lymphoid cells

# Breast cancer

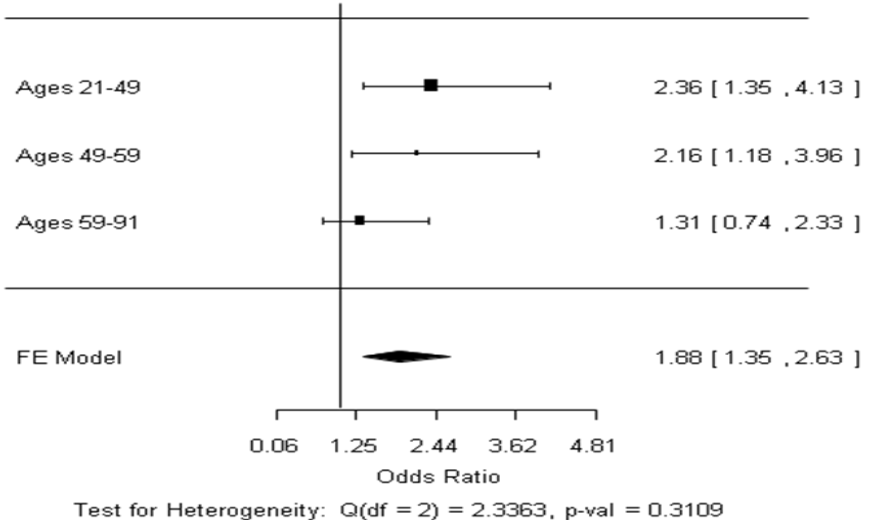
# Methylation of ATM and breast cancer.

Flanagan J, Vineis P et al. (Cancer Res,2012).

A




B

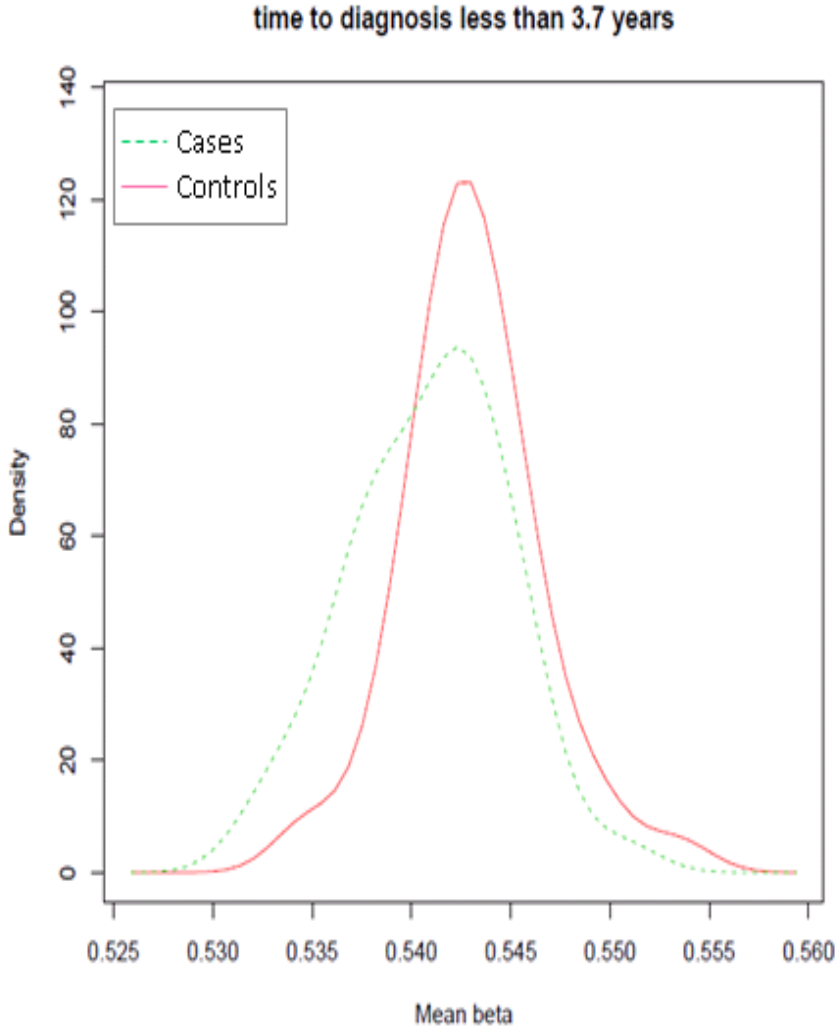


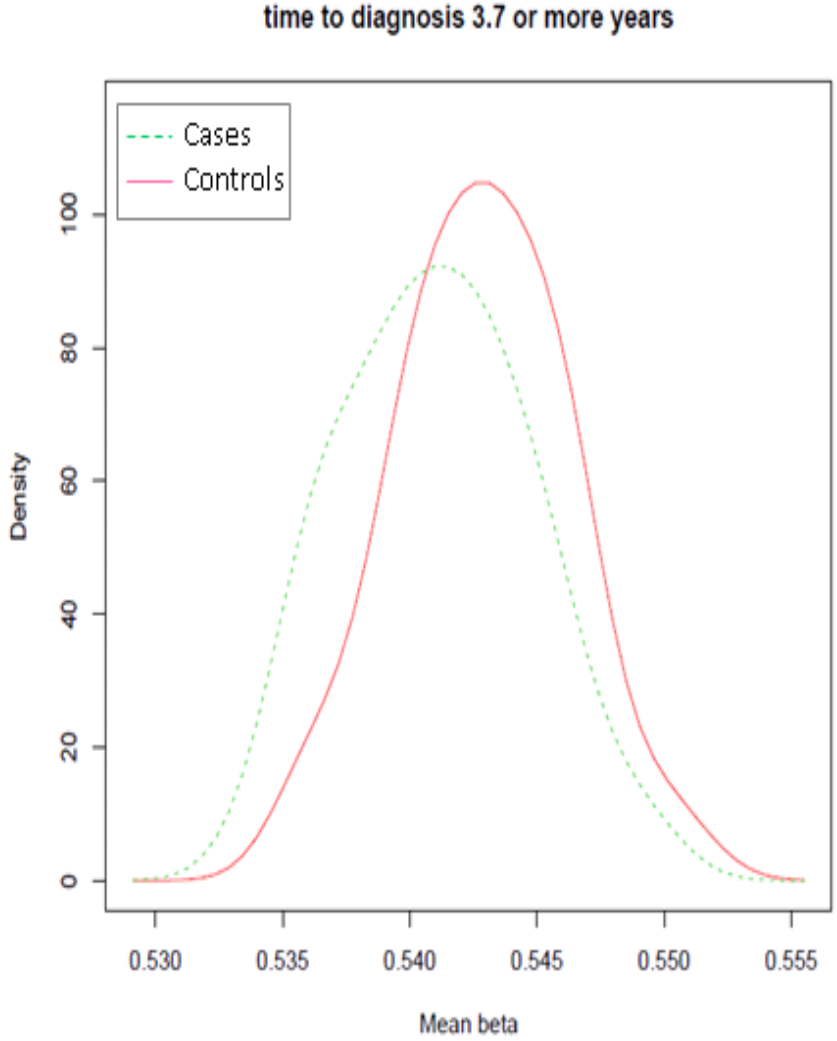
**HuGeF study on 450K genome-wide methylation and breast cancer (162 cases and 162 controls; nested, matched case-control study within the EPIC Italian cohort)**

**Global average hypomethylation is associated with BC**

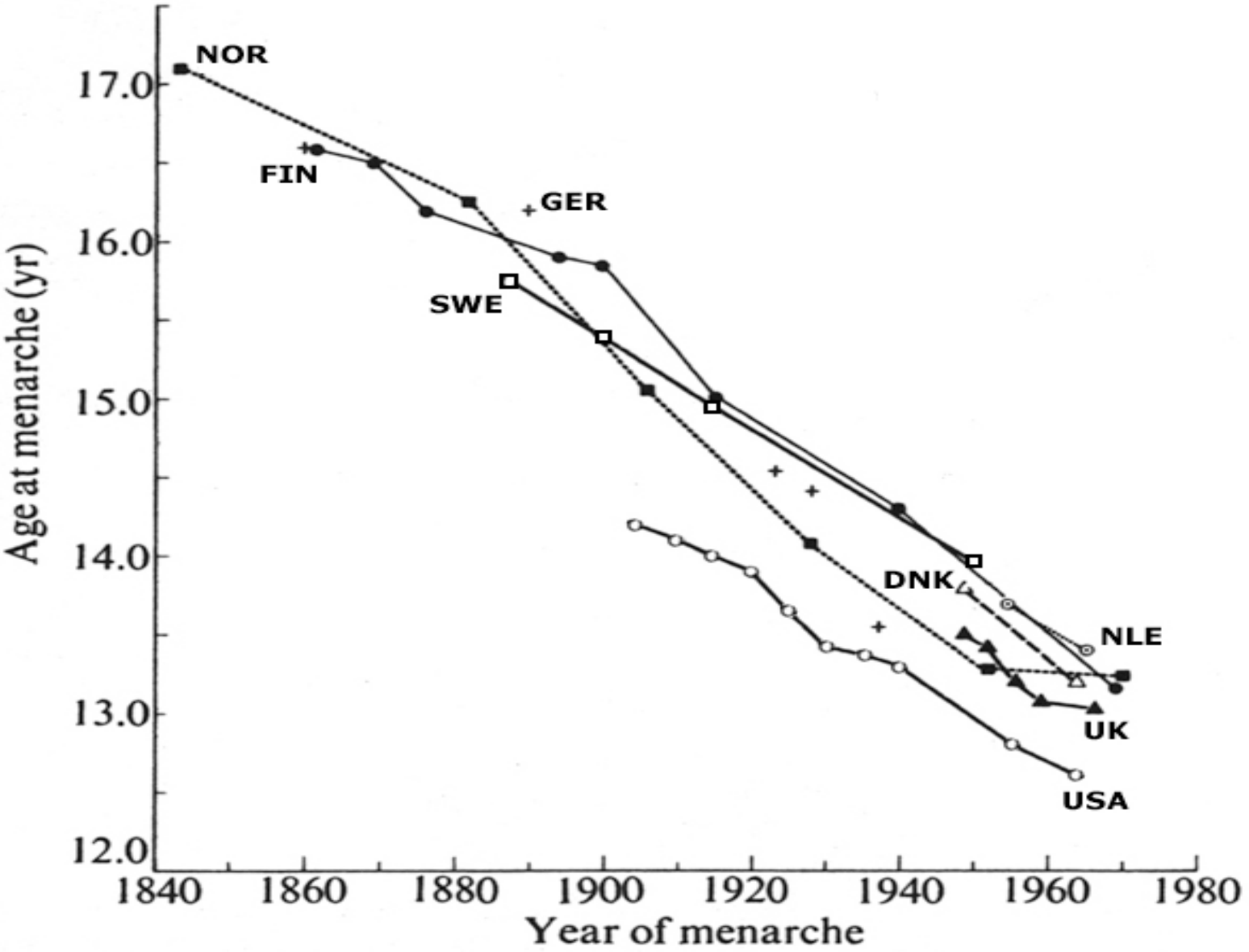
**(VanVeldhoven et al, submitted; results replicated in an Australian cohort, Baglietto et al, submitted)**

| | | OR | (95% CI) | p-value |
|---|---|---|---|---|
| **By quartiles** | ***Q1*** | **1.00** | | |
| | ***Q2*** | **0.31** | **(0.16 – 0.63)** | **0.001** |
| | ***Q3*** | **0.35** | **(0.18 - 0.69)** | **0.002** |
| | ***Q4*** | **0.19** | **(0.09 - 0.42)** | **0.00005** |
| | ***Per 1 SD*** | **0.51** | **(0.37 - 0.72)** | **0.00009** |
| **Time to Diagnosis** | ***<5*** | **0.55** | **(0.36 - 0.83)** | **0.004** |
| **(years)** | ***5-9*** | **0.61** | **(0.28 - 1.36)** | **0.23** |
| | ***≥10*** | **0.36** | **(0.16 - 0.82)** | **0.01** |


time to diagnosis less than 3.7 years
Cases
Controls
Density
0
20
40
60
80
100
120
140
0.525
0.530
0.535
0.540
0.545
0.550
0.555
0.560
Mean beta


time to diagnosis 3.7 or more years
Cases
Controls
Density
0
20
40
60
80
100
0.530
0.535
0.540
0.545
0.550
0.555
Mean beta

# Trends Towards Earlier Menarche

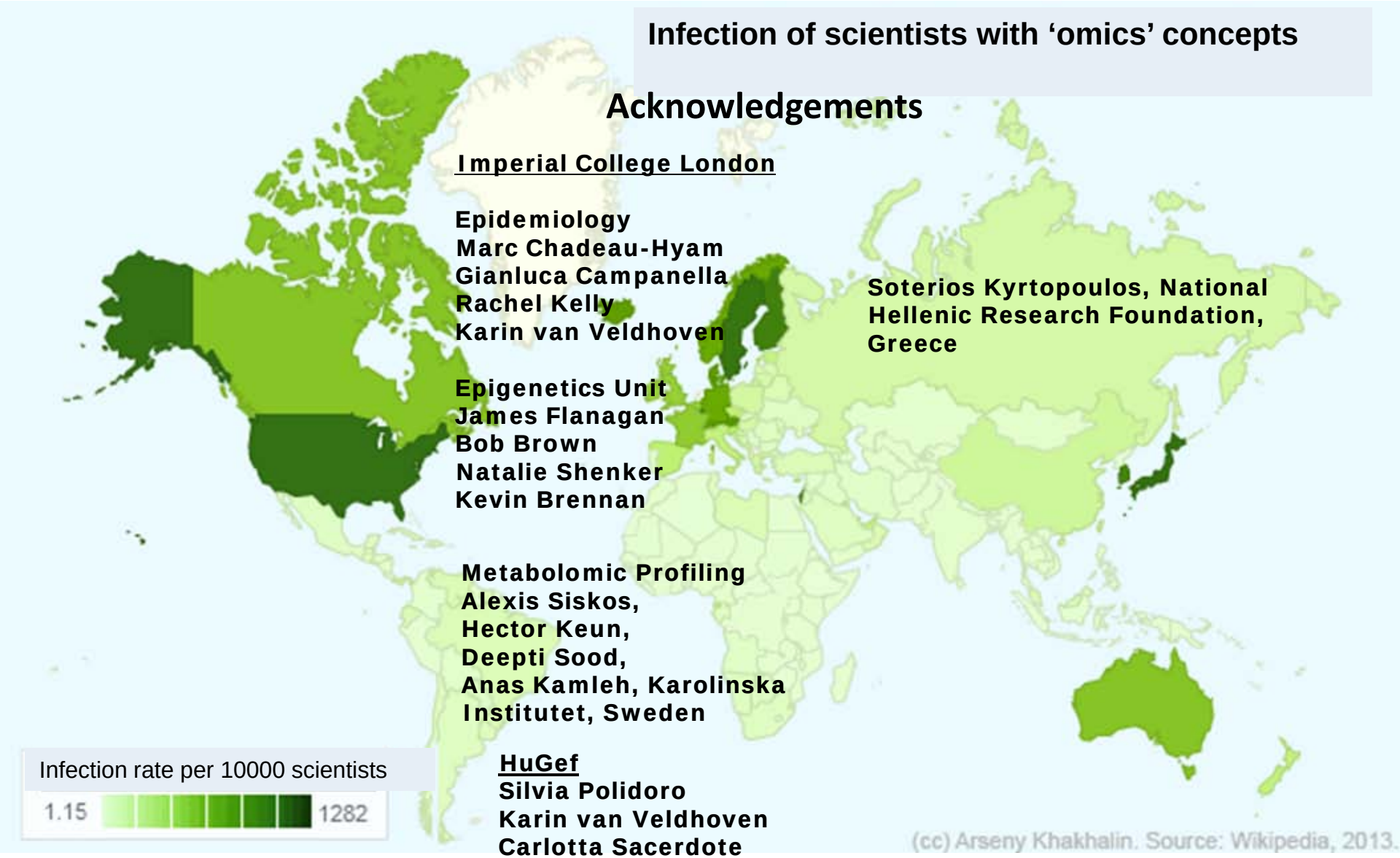



*From:* J.M. Tanner *Nature* 243: 95-96 (1973)

**Logistic Regression for percent global methylation (LUMA below vs. above median) binary variable by reproductive and other variables, including age at menarche as a categorical variable (376 cases and 376 controls from EPIC)**

| Variable | Adjusted OR | 95% Confidence Interval |
|---|---|---|
| Center | 0.99 | 0.97-1.02 |
| Plate number | 0.94 | 0.80-1.10 |
| Age at blood collection | 0.95* | 0.91-0.99 |
| Height | 0.96 | 0.92-0.99 |
| Weight | 1.01 | 0.98-1.03 |
| Total physical activity index – sex specific | 1.03 | 0.78-1.37 |
| Smoking status<br>-Never<br>-Past smoker<br>-Current smoker | 1.00<br>0.85<br>0.98 | 0.46-1.55<br>0.56-1.72 |
| Daily alcohol intake | 1.01 | 0.99-1.04 |
| Daily folate intake | 1.00 | 0.99-1.00 |
| Age at menarche | 1.32 | 1.14-1.53 |

# Infection of scientists with ‘omics’ concepts





## Acknowledgements

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**Karin van Veldhoven**

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**Deepti Sood,**
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