CSFT 2019

13e congrès de la Société Francophone de Tabacologie

21 au 22 novembre 2019 | Ajaccio

# Impact transgénérationnel du tabagisme: le jeu de l'épigénétique

22/11/2019

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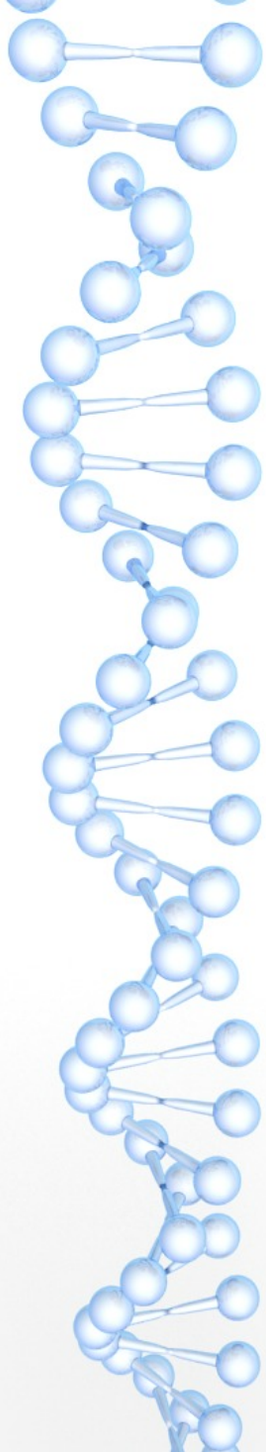
L'auteur n'a pas de lien d'intérêt



# Plan

- Epigénétique : késako?
- Comprendre l‘effet épigénétique du tabac
- Effets épigénétiques sur la/les prochaine(s) génération(s)
- Résumé

- Connaissances très récentes → pour le moment

impossible d'appliquer en pratique, à part notre devoir

d'informer les individus que nous suivons….

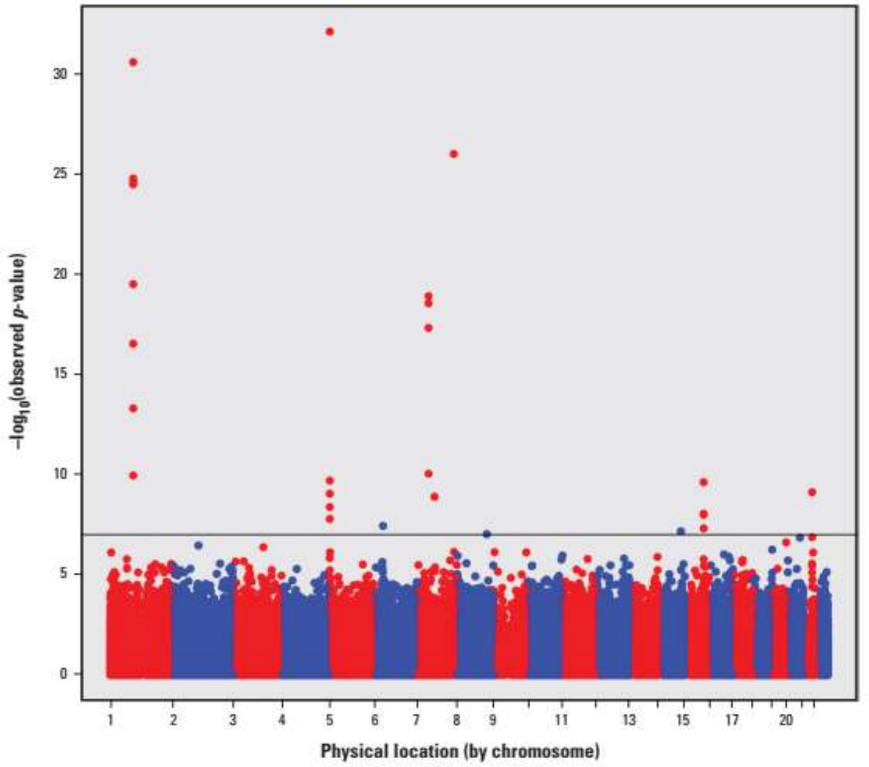



**Figure 1.** Epigenome-wide association between maternal cotinine and methylation of 473,844 CpGs measured in cord blood from the MoBa cohort. Twenty-six CpGs (10 genes) reached Bonferroni-corrected

**Table 2.** Differential methylation in cord blood DNA in relation to maternal cotinine in the MoBa study population: CpGs with Bonferroni-corrected statistical significance ($p < 1.06 \times 10^{-7}$), sorted by chromosome and position.

| Chr[a] | Gene | Distance to gene[b] | CpG | Position[c] | Unadjusted Coef[d] | Unadjusted SE[e] | Unadjusted p-Value | Adjusted[f] Coef | Adjusted[f] SE | Adjusted[f] p-Value | Rank[g] | Median methylation by cotinine category[h] Undetectable | Low | Medium | High |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | *GFI1* | 3688 | cg10399789 | 92945668 | −0.07 | 0.01 | 4.08E-13 | −0.065 | 0.010 | 1.10E-10 | 14 | 0.759 | 0.755 | 0.727 | 0.716 |
| 1 | *GFI1* | 3224 | cg09662411 | 92946132 | −0.111 | 0.012 | 2.26E-20 | −0.106 | 0.013 | 2.96E-17 | 11 | 0.730 | 0.733 | 0.669 | 0.654 |
| 1 | *GFI1* | 3169 | cg06338710 | 92946187 | −0.112 | 0.013 | 1.34E-18 | −0.106 | 0.014 | 5.02E-14 | 12 | 0.801 | 0.800 | 0.754 | 0.733 |
| 1 | *GFI1* | 2656 | cg18146737 | 92946700 | −0.28 | 0.024 | 2.42E-30 | −0.271 | 0.026 | 3.30E-25 | 6 | 0.877 | 0.875 | 0.771 | 0.738 |
| 1 | *GFI1* | 2531 | cg12876356 | 92946825 | −0.182 | 0.016 | 2.29E-30 | −0.176 | 0.017 | 1.70E-25 | 4 | 0.731 | 0.732 | 0.627 | 0.605 |
| 1 | *GFI1* | 2321 | cg18316974 | 92947035 | −0.243 | 0.024 | 6.43E-24 | −0.238 | 0.026 | 3.16E-20 | 7 | 0.921 | 0.923 | 0.856 | 0.841 |
| 1 | *GFI1* | 1768 | cg09935388 | 92947588 | −0.196 | 0.015 | 1.05E-38 | −0.188 | 0.016 | 2.68E-31 | 2 | 0.708 | 0.707 | 0.580 | 0.564 |
| 1 | *GFI1* | 1395 | cg14179389 | 92947961 | −0.184 | 0.017 | 5.38E-28 | −0.181 | 0.017 | 2.63E-25 | 5 | 0.242 | 0.246 | 0.154 | 0.158 |
| 5 | *AHRR* | 19617 | cg23067299 | 323907 | 0.075 | 0.012 | 4.21E-10 | 0.072 | 0.012 | 4.12E-09 | 20 | 0.789 | 0.789 | 0.813 | 0.837 |
| 5 | *AHRR* | 64157 | cg03991871 | 368447 | −0.057 | 0.008 | 2.04E-11 | −0.054 | 0.009 | 1.99E-10 | 15 | 0.841 | 0.839 | 0.820 | 0.818 |
| 5 | *AHRR* | 69088 | cg05575921 | 373378 | −0.202 | 0.015 | 2.85E-39 | −0.198 | 0.017 | 8.03E-33 | 1 | 0.883 | 0.874 | 0.829 | 0.784 |
| 5 | *AHRR* | 95070 | cg21161138 | 399360 | −0.045 | 0.007 | 1.52E-11 | −0.043 | 0.007 | 8.91E-10 | 18 | 0.718 | 0.715 | 0.701 | 0.679 |
| 6 | *HLA-DPB2* | 11549 | cg11715943 | 33091841 | −0.053 | 0.009 | 1.00E-08 | −0.054 | 0.010 | 3.63E-08 | 23 | 0.842 | 0.833 | 0.824 | 0.820 |
| 7 | *MYO1G* | 16417 | cg19089201 | 45002287 | 0.083 | 0.013 | 3.22E-10 | 0.088 | 0.014 | 9.13E-11 | 13 | 0.925 | 0.926 | 0.932 | 0.944 |
| 7 | *MYO1G* | 16218 | cg22132788 | 45002486 | 0.18 | 0.021 | 1.98E-18 | 0.184 | 0.021 | 4.82E-18 | 10 | 0.932 | 0.935 | 0.951 | 0.966 |
| 7 | *MYO1G* | 15968 | cg04180046 | 45002736 | 0.073 | 0.008 | 8.76E-20 | 0.076 | 0.008 | 2.85E-19 | 9 | 0.441 | 0.446 | 0.484 | 0.508 |
| 7 | *MYO1G* | 15785 | cg12803068 | 45002919 | 0.145 | 0.016 | 8.51E-19 | 0.149 | 0.016 | 1.25E-19 | 8 | 0.713 | 0.721 | 0.774 | 0.813 |
| 7 | *ENSG00000225718* | 198306 | cg04598670 | 68697651 | −0.063 | 0.009 | 1.29E-11 | −0.061 | 0.010 | 1.27E-09 | 19 | 0.623 | 0.607 | 0.597 | 0.574 |
| 7 | *CNTNAP2* | 854 | cg25949550 | 145814306 | −0.075 | 0.007 | 4.15E-30 | −0.073 | 0.007 | 1.02E-26 | 3 | 0.113 | 0.109 | 0.097 | 0.092 |
| 8 | *EXT1* | −33821 | cg03346806 | 119157879 | −0.038 | 0.007 | 3.08E-08 | −0.039 | 0.007 | 9.34E-08 | 26 | 0.801 | 0.795 | 0.793 | 0.779 |
| 14 | *TTC7B* | 274756 | cg18655025 | 91008005 | −0.041 | 0.007 | 2.07E-08 | −0.042 | 0.008 | 6.76E-08 | 25 | 0.854 | 0.847 | 0.841 | 0.836 |
| 15 | *CYP1A1* | −1266 | cg05549655 | 75019143 | 0.064 | 0.01 | 2.96E-10 | 0.065 | 0.010 | 2.38E-10 | 16 | 0.189 | 0.188 | 0.221 | 0.226 |
| 15 | *CYP1A1* | −1374 | cg22549041 | 75019251 | 0.096 | 0.016 | 4.52E-09 | 0.098 | 0.017 | 8.88E-09 | 21 | 0.385 | 0.379 | 0.414 | 0.475 |
| 15 | *CYP1A1* | −1406 | cg11924019 | 75019283 | 0.044 | 0.008 | 2.62E-08 | 0.044 | 0.008 | 4.78E-08 | 24 | 0.434 | 0.430 | 0.457 | 0.475 |
| 15 | *CYP1A1* | −1425 | cg18092474 | 75019302 | 0.066 | 0.012 | 1.10E-08 | 0.068 | 0.012 | 9.95E-09 | 22 | 0.510 | 0.504 | 0.549 | 0.573 |
| 21 | RUNX1 | 1746 | cg12477880 | 36259241 | 0.159 | 0.026 | 1.02E-09 | 0.163 | 0.026 | 7.55E-10 | 17 | 0.088 | 0.102 | 0.110 | 0.158 |

[a]Chromosome. [b]Distance from CpG to transcription start site of the nearest gene. [c]Chromosomal position based on NCBI human reference genome assembly Build 37.3. [d]Regression coefficient. [e]Standard error for regression coefficient. [f]Adjusted for maternal age, maternal education, parity, and asthma. [g]Rank order based on the adjusted *p*-value. [h]Maternal plasma cotinine (nmol/L) measured around gestational week 18 (undetectable: ≤ 0; low: > 0–56.8; moderate: > 56.8–388; high: > 388). Values > 56.8 nmol/L indicate active smoking.

Joubert, B. R.; et al. 450K Epigenome-Wide Scan Identifies Differential DNA Methylation in Newborns Related to Maternal Smoking during Pregnancy. *Environ. Health Perspect.* **2012**, *120* (10), 1425–1431.

# Epigénétique: késako?

## 1942 Conrad Waddington

"the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" [1]

© Peter Lofts Photography / National Portrait Gallery, London

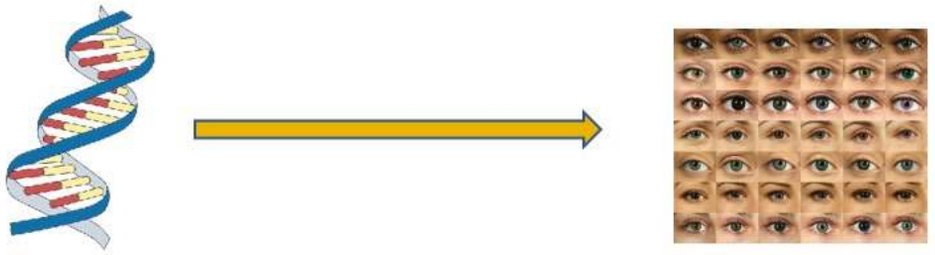
## 2001 Science

"the study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence." [2]


(1) Waddington, C. H. The Epigenotype. *Endeavour* **1942**, *1*, 18–20.

(2) Wu, C. T.; Morris, J. R. Genes, Genetics, and Epigenetics: A Correspondence. *Science* **2001**, *293* (5532), 1103–1105.

# Epigénétique: changement de paradigme



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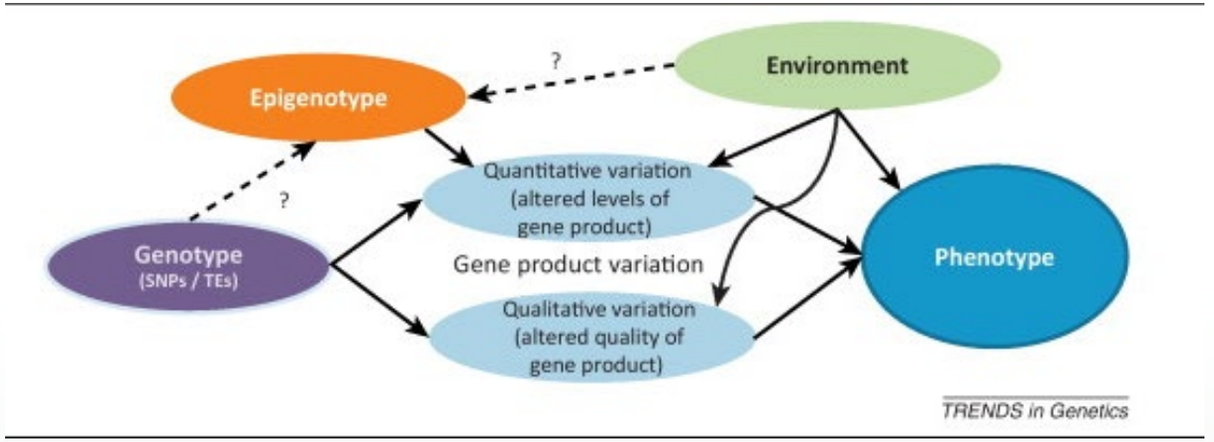
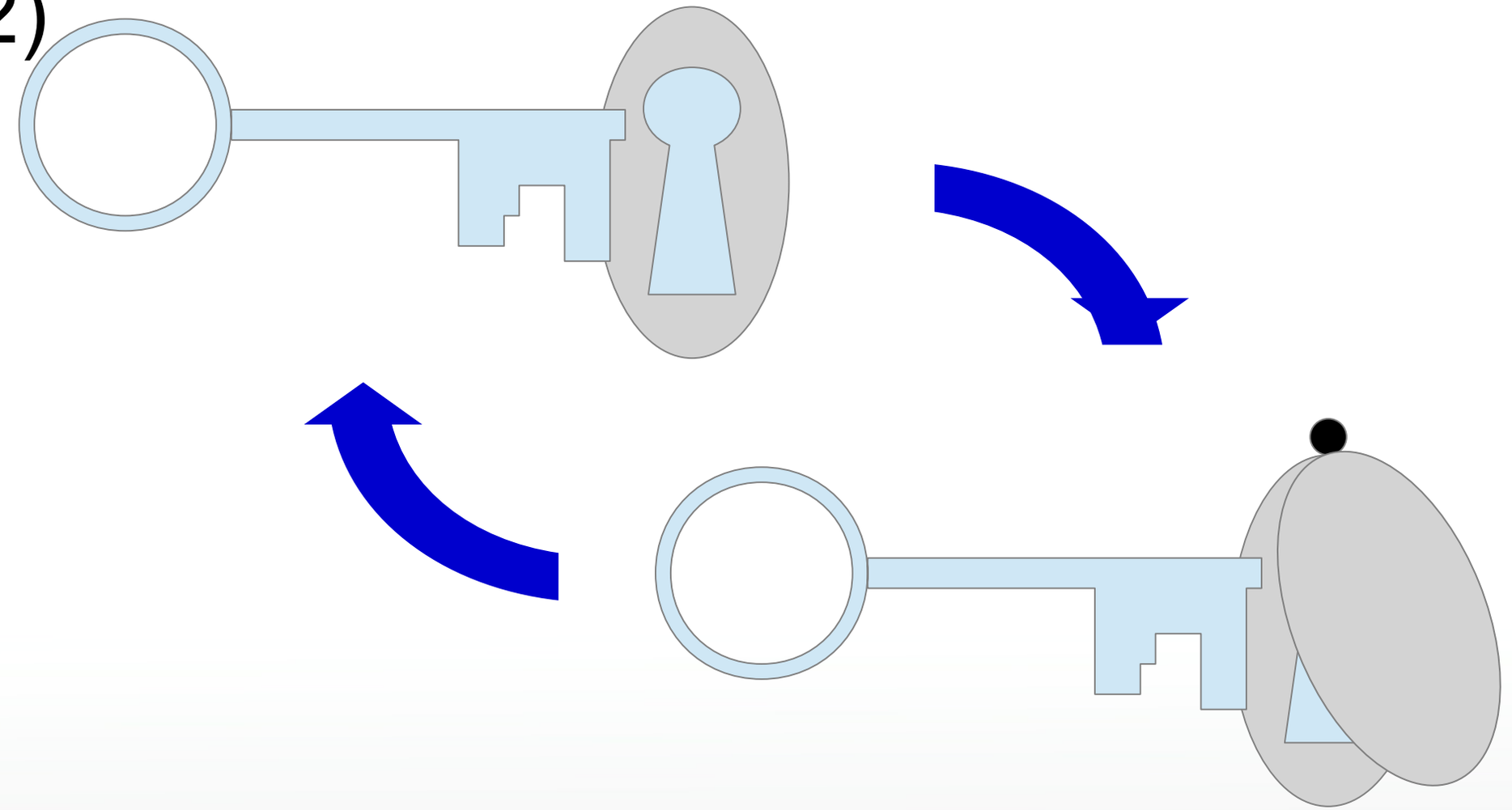


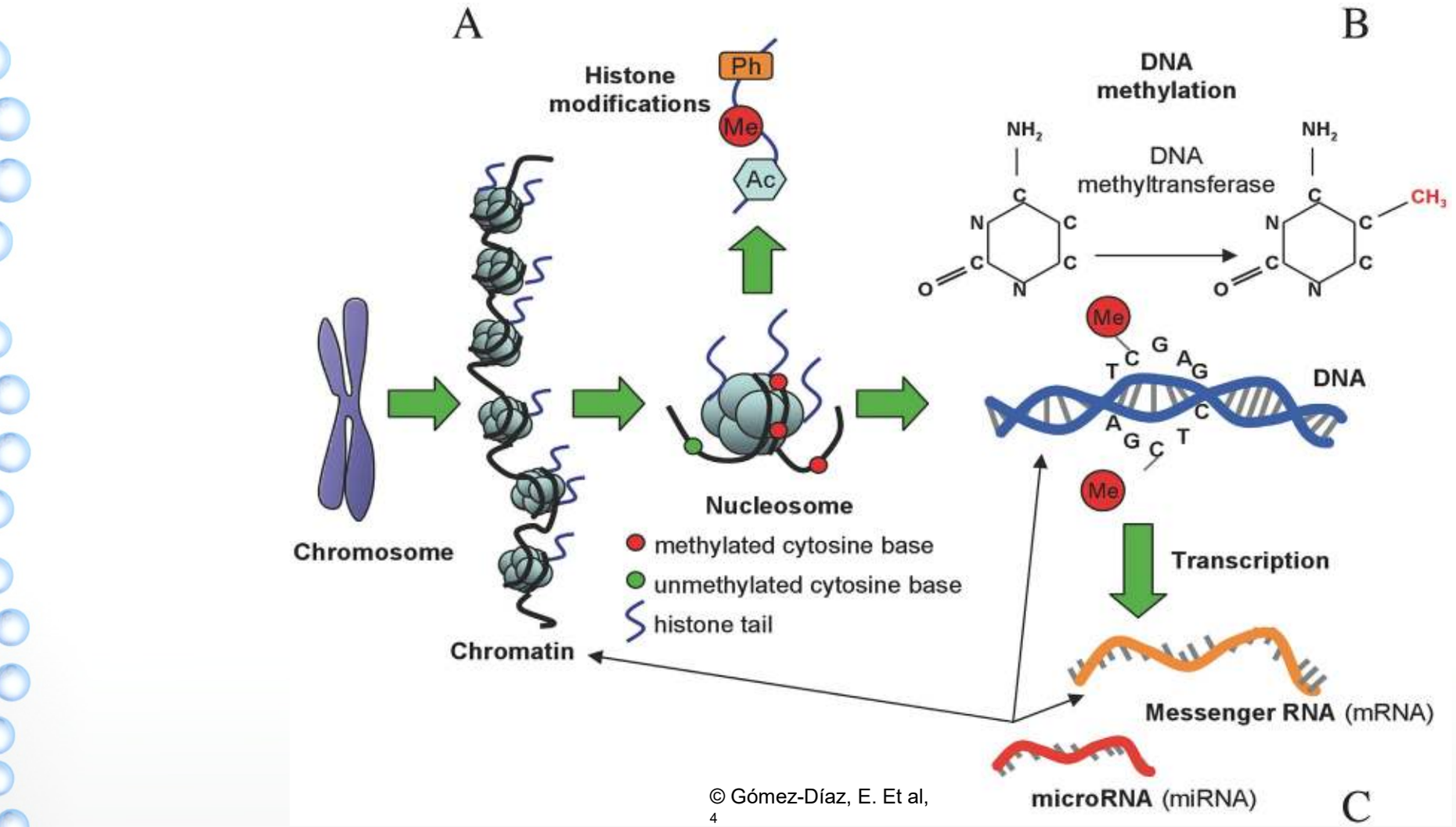

© Springer, N. M.[3]

(3) Springer, N. M. Epigenetics and Crop Improvement. *Trends in Genetics* **2013**, *29* (4), 241–247. https://doi.org/10.1016/j.tig.2012.10.009.

# Epigénétique: changement de paradigme (2)



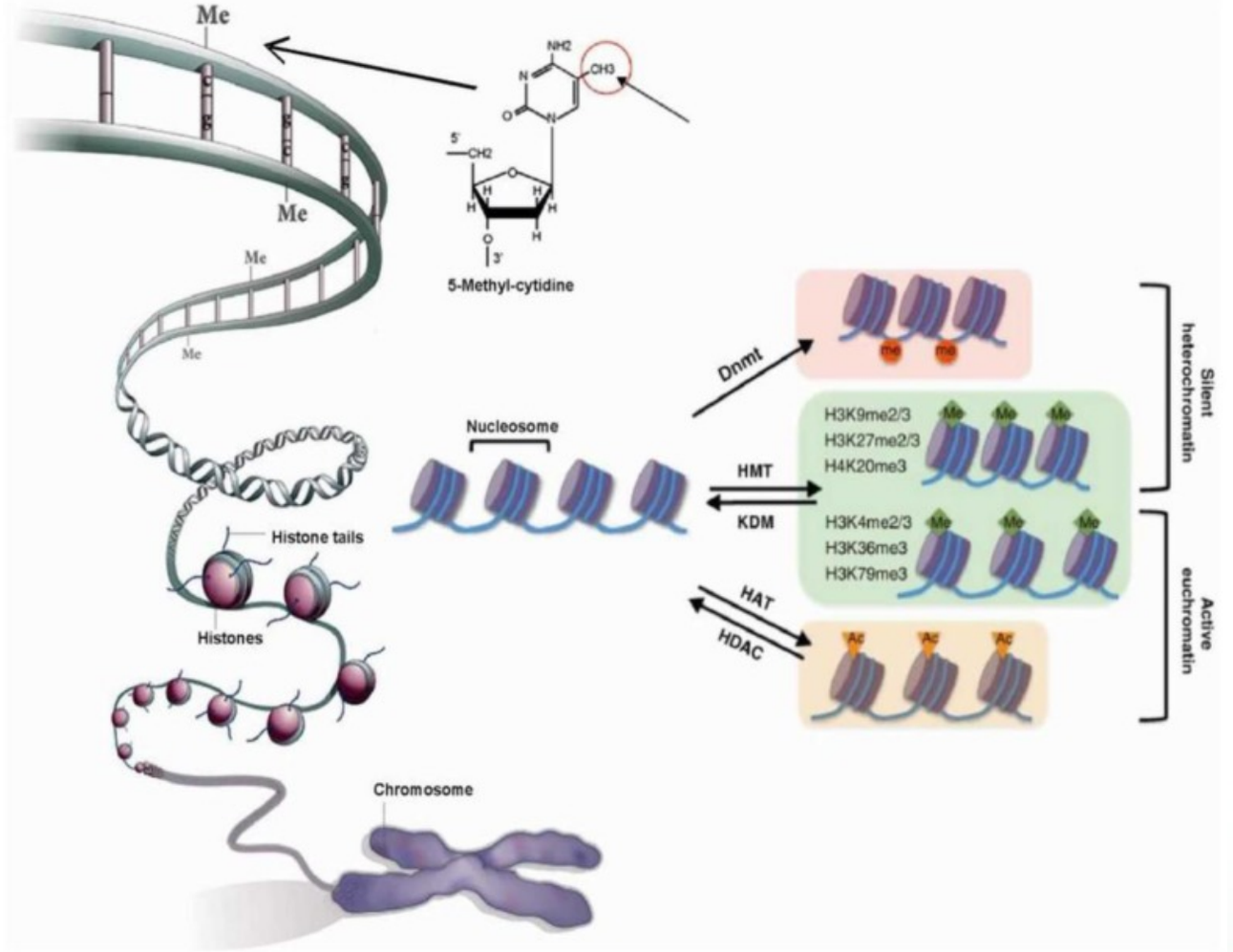
# Epigénétique: comment?






(4) Gómez-Díaz, E.; Jordà, M.; Peinado, M. A.; Rivero, A. Epigenetics of Host–Pathogen Interactions: The Road Ahead
and the Road Behind. *PLOS Pathogens* **2012**, *8* (11), e1003007

# Epigénétique: quel effet?

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Heterochromatine
=
chromatine
silencieuse

Euchromatine
=
chromatine
active



(5) Romanowska, J.; Joshi, A. From Genotype to Phenotype: Through Chromatin. *Genes (Basel)* **2019**, *10* (2). https://doi.org/10.3390/genes10020076.

# Epigénétique: ça s'hérite?

- divisions **mitotiques** → chaque cellule differéntiée passe ses marques à ses cellules filles

- divisions **meiotiques** → à priori méthylation remise à zéro sauf pour les loci « protégés » , histones : probablement oui, même pour le sperme, ARN: peut-être[6]

- les mitochondries → oui, avec des effets sur plein de processus, mal connu pour le moment (absence de histones)[7]

(6) Skvortsova, K.; Iovino, N.; Bogdanović, O. Functions and Mechanisms of Epigenetic Inheritance in Animals. *Nat. Rev. Mol. Cell Biol.* **2018**, *19* (12), 774–790.

(7) Stimpfel, M.; Jancar, N.; Virant-Klun, I. New Challenge: Mitochondrial Epigenetics? *Stem Cell Rev Rep* **2018**, *14* (1),

# Le tabac et l‘épigénétique



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## Epigenetic Signatures of Cigarette Smoking

Roby Joehanes, Allan C. Just, Riccardo E. Marioni, Luke C. Pilling, Lindsay M. Reynolds, Pooja R. Mandaviya, Weihua Guan, Tao Xu, Cathy E. Elks, Stella Aslibekyan, Hortensia Moreno-Macias, Jennifer A. Smith, Jennifer A. Brody, Radhika Dhingra, Paul Yousefi, James S. Pankow, Sonja Kunze, Sonia H. Shah, Allan F. McRae, Kurt Lohman, Jin Sha, Devin M. Absher, Luigi Ferrucci, Wei Zhao, Ellen W. Demerath, Jan Bressler, Megan L. Grove, Tianxiao Huan, Chunyu Liu, Michael M. Mendelson, Chen Yao, Douglas P. Kiel, Annette Peters, Rui Wang-Sattler, Peter M. Visscher, Naomi R. Wray, John M. Starr, Jingzhong Ding, Carlos J. Rodriguez, Nicholas J. Wareham, Marguerite R. Irvin, Degui Zhi, Myrto Barrdahl, Paolo Vineis, Srikant Ambatipudi, André G. Uitterlinden, Albert Hofman, Joel Schwartz, Elena Colicino, Lifang Hou, Pantel S. Vokonas, Dena G. Hernandez, Andrew B. Singleton, Stefania Bandinelli, Stephen T. Turner, Erin B. Ware, Alicia K. Smith, Torsten Klengel, Elisabeth B. Binder, Bruce M. Psaty, Kent D. Taylor, Sina A. Gharib, Brenton R. Swenson, Liming Liang, Dawn L. DeMeo, George T. O'Connor, Zdenko Herceg, Kerry J. Ressler, Karen N. Conneely, Nona Sotoodehnia, Sharon L. R. Kardia, David Melzer, Andrea A. Baccarelli, Joyce B. J. van Meurs, Isabelle Romieu, Donna K. Arnett, Ken K. Ong, Yongmei Liu, Melanie Waldenberger, Ian J. Deary, Myriam Fornage, Daniel Levy, and Stephanie J. London Show less Authors

**Originally published** 20 Sep 2016 | https://doi.org/10.1161/CIRCGENETICS.116.001506 | Circulation: Cardiovascular Genetics. 2016;9:436–447

Other version(s) of this article

## Abstract

### Background—

DNA methylation leaves a long-term signature of smoking exposure and is one potential mechanism by which tobacco exposure predisposes to adverse health outcomes, such as cancers, osteoporosis, lung, and cardiovascular disorders.

### Methods and Results—

To comprehensively determine the association between cigarette smoking and DNA methylation, we conducted a meta-analysis of genome-wide DNA methylation assessed using the Illumina BeadChip 450K array on 15 907 blood-derived DNA samples from participants in 16 cohorts (including 2433 current, 6518 former, and 6956 never smokers). Comparing current versus never smokers, 2623 cytosine–phosphate–guanine sites (CpGs), annotated to 1405 genes, were statistically significantly differentially methylated at Bonferroni threshold of $P<1\times10^{-7}$ (18 760 CpGs at false discovery rate <0.05). Genes annotated to these CpGs were enriched for associations with several smoking-related traits in genome-wide studies including pulmonary function, cancers, inflammatory diseases, and heart disease. Comparing former versus never smokers, 185 of the CpGs that differed between current and never smokers were significant $P<1\times10^{-7}$ (2623 CpGs at false discovery rate <0.05), indicating a pattern of persistent altered methylation, with attenuation, after smoking cessation. Transcriptomic integration identified effects on gene expression at many

Details Related References Figures


October 2016
Vol 9, Issue 5

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# Combien de temps ça reste ?

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Epigenetic signatures of starting and stopping smoking

Daniel L. McCartney[a], Anna J. Stevenson[a], Robert F. Hillary[a], Rosie M. Walker[a,d], Mairead L. Bermingham[a], Stewart W. Morris[a], Toni-Kim Clarke[b], Archie Campbell[a], Alison D. Murray[c], Heather C. Whalley[b], David J. Porteous[a,d], Peter M. Visscher[d,e], Andrew M. McIntosh[a,b,d], Kathryn L. Evans[a,d], Ian J. Deary[d,f], Riccardo E. Marioni[a,d,*]

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DOI: https://doi.org/10.1016/j.ebiom.2018.10.051 | Check for updates

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Abstract

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Background

Multiple studies have made robust associations between differential DNA methylation and exposure to cigarette smoke. But whether a DNA methylation phenotype is established immediately upon exposure, or only after prolonged exposure is less well-established. Here, we

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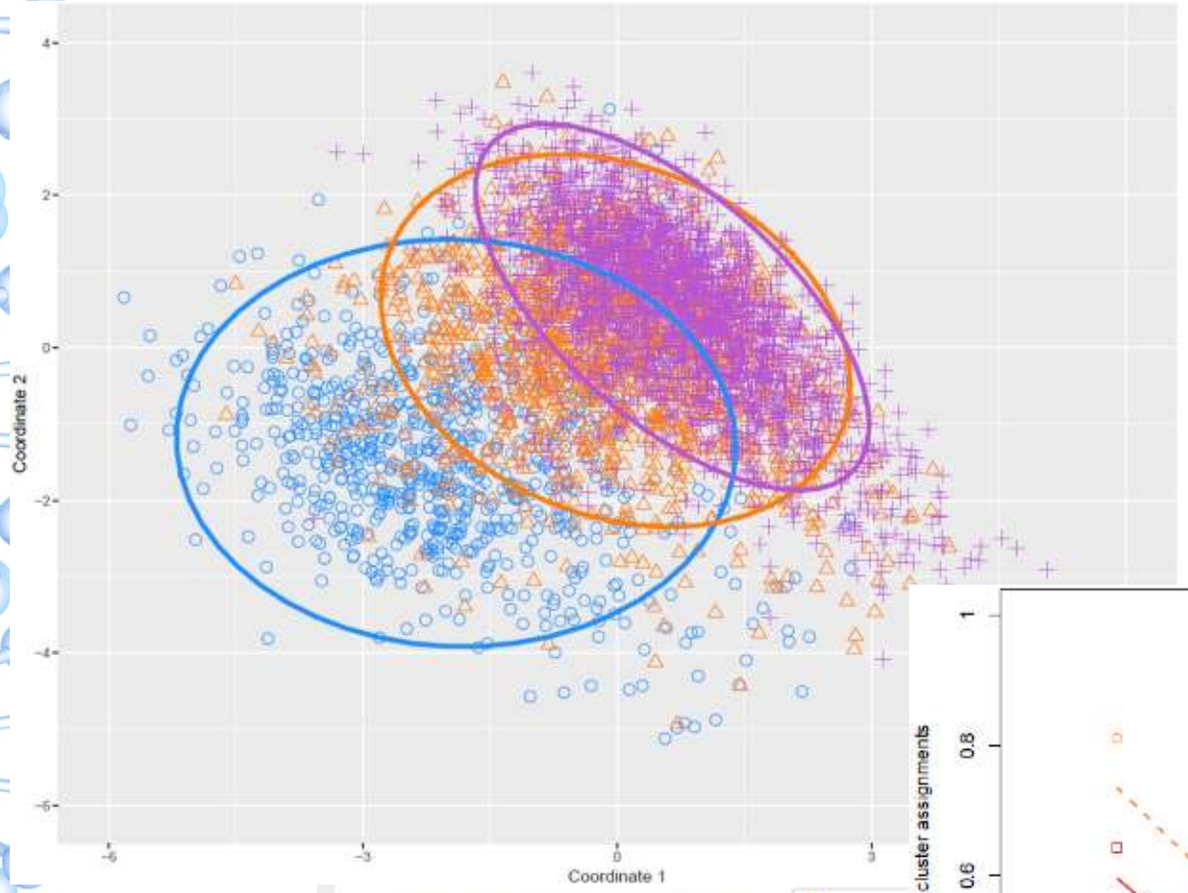


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Information for Authors

Group
Current smoker
Former smoker
Never smoker

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DOI: https://doi.org/10.1016/j.ebiom.2018.10.051 |

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Jun

## Abstract

### Background

Multiple studies have made robust associations betv
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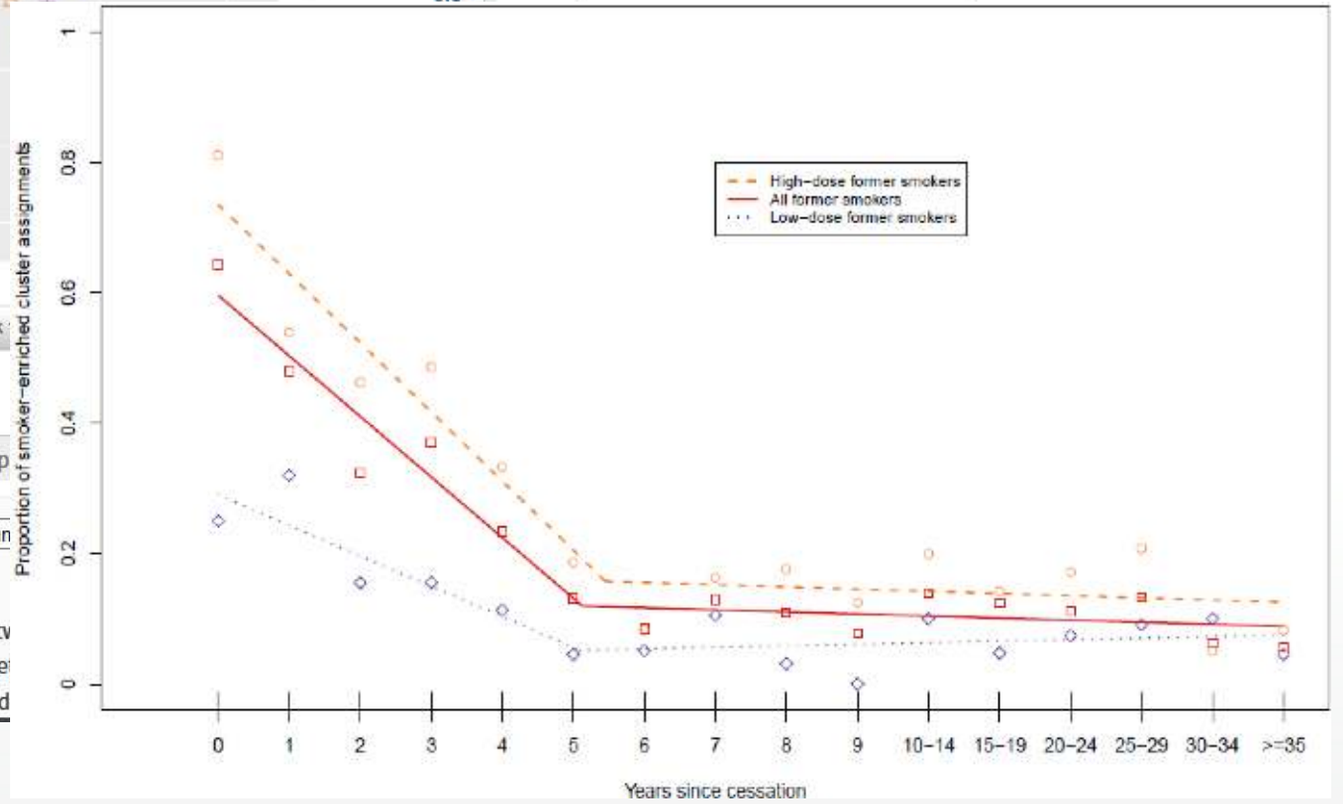
immediately upon exposure, or only after prolonged



# Tous égaux face au(x effets épigénétiques du) tabac?

< Articles

ORIGINAL RESEARCH ARTICLE

Front. Genet., 10 December 2018 | https://doi.org/10.3389/fgene.2018.00622

## Methylation of *MTHFR* Moderates the Effect of Smoking on Genomewide Methylation Among Middle Age African Americans

Allan M. Andersen[1], Man-Kit Lei[2,3], Robert A. Philibert[1,4] and Steven R. H. Beach[3,5]*

[1]Department of Psychiatry, University of Iowa, Iowa City, IA, United States
[2]Department of Sociology, University of Georgia, Athens, GA, United States
[3]Center for Family Research, University of Georgia, Athens, GA, United States
[4]Behavioral Diagnostics, Coralville, IA, United States

Gupta *et al. Clinical Epigenetics* (2019) 11:1
https://doi.org/10.1186/s13148-018-0606-9

Clinical Epiger

RESEARCH Open

## Epigenome-wide association study of serum cotinine in current smokers reveals novel genetically driven loci

Richa Gupta[1*], Jenny van Dongen[2], Yu Fu[1], Abdel Abdellaoui[2], Rachel F. Tyndale[3], Vidya Velagapudi[1], Dorret I. Boomsma[2], Tellervo Korhonen[1,4], Jaakko Kaprio[1,4], Anu Loukola[1,5] and Miina Ollikainen[1,4]

Elliott *et al. Clinical Epigenetics* 2014, 6:4
http://www.clinicalepigeneticsjournal.com/content/6/1/4

CLINICAL EPIGENETICS

RESEARCH Open Access

## Differences in smoking associated DNA methylation patterns in South Asians and Europeans

Hannah R Elliott[1*], Therese Tillin[2,3], Wendy L McArdle[1], Karen Ho[1], Aparna Duggirala[1], Tim M Frayling[4], George Davey Smith[1], Alun D Hughes[2,3], Nish Chaturvedi[2,3] and Caroline L Relton[1,5]

# Entretemps chez la femme enceinte



## 450K Epigenome-Wide Scan Identifies Differential DNA Methylation in Newborns Related to Maternal Smoking during Pregnancy

*Bonnie R. Joubert,[1] Siri E. Håberg,[2] Roy M. Nilsen,[3] Xuting Wang,[1] Stein E. Vollset,[2,4] Susan K. Murphy,[5] Zhiqing Huang,[5] Cathrine Hoyo,[5] Øivind Midttun,[6] Lea A. Cupul-Uicab,[1] Per M. Ueland,[4] Michael C. Wu,[7] Wenche Nystad,[2] Douglas A. Bell,[1] Shyamal D. Peddada,[1] and Stephanie J. London[1]*

[1]Division of Intramural Research, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, USA; [2]Norwegian Institute of Public Health, Oslo, Norway; [3]Haukeland University Hospital, Bergen, Norway; [4]University of Bergen, Bergen, Norway; [5]Duke University School of Medicine, Durham, North Carolina, USA; [6]Bevital A/S, Laboratoriebygget, Bergen, Norway; [7]Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina, USA

**Background:** Epigenetic modifications, such as DNA methylation, due to *in utero* exposures may play a critical role in early programming for childhood and adult illness. Maternal smoking is a major risk factor for multiple adverse health outcomes in children, but the underlying mechanisms are unclear.

**Objective:** We investigated epigenome-wide methylation in cord blood of newborns in relation to maternal smoking during pregnancy.

**Methods:** We examined maternal plasma cotinine (an objective biomarker of smoking) measured during pregnancy in relation to DNA methylation at 473,844 CpG sites (CpGs) in 1,062 newborn cord blood samples from the Norwegian Mother and Child Cohort Study (MoBa) using the Infinium HumanMethylation450 BeadChip (450K).

**Results:** We found differential DNA methylation at epigenome-wide statistical significance ($p$-value < $1.06 \times 10^{-7}$) for 26 CpGs mapped to 10 genes. We replicated findings for CpGs in *AHRR*, *CYP1A1*, and *GFI1* at strict Bonferroni-corrected statistical significance in a U.S. birth cohort. *AHRR* and *CYP1A1* play a key role in the aryl hydrocarbon receptor signaling pathway, which mediates the detoxification of the components of tobacco smoke. *GFI1* is involved in diverse developmental processes but has not previously been implicated in responses to tobacco smoke.

**Conclusions:** We identified a set of genes with methylation changes present at birth in children whose mothers smoked during pregnancy. This is the first study of differential methylation across the genome in relation to maternal smoking during pregnancy using the 450K platform. Our findings implicate epigenetic mechanisms in the pathogenesis of the adverse health outcomes associated with this important *in utero* exposure.

**Key words:** epigenetics, epigenome-wide, *in utero*, maternal smoking, methylation. *Environ Health Perspect* 120:1425–1431 (2012). http://dx.doi.org/10.1289/ehp.1205412 [Online 31 July 2012]

Maternal smoking during pregnancy is a major risk factor for adverse health outcomes in children including low birth weight, some childhood cancers, reduced lung function, and early respiratory illnesses (Office of the

methylation. A few human studies have examined epigenetic alterations in relation to maternal smoking during pregnancy and reported it to be associated with global methylation of leukocyte DNA using a [$^3$H]-

Infinium HumanMethylation450 Beadchip (450K; Illumina Inc.), which measures CpG methylation at > 470,000 CpGs, we evaluated the relationship between maternal smoking and DNA methylation in 1,062 infant cord blood samples from a birth cohort in Norway. We assessed maternal smoking objectively by measuring cotinine, a sensitive biomarker, in maternal plasma samples, and replicated our findings in an independent birth cohort study from the U.S. To our knowledge, this is the largest human study of any *in utero* exposure in relation to DNA methylation at birth using the 450K platform with improved epigenome-wide coverage.

### Methods

Participants in the current analysis were selected from a substudy of the Norwegian Mother and Child Cohort Study (MoBa) (Magnus et al. 2006; Ronningen et al. 2006) that evaluated the association between maternal plasma folate during pregnancy and childhood

Address correspondence to S.J. London, 111 T.W. Alexander Drive, Rall Bldg, A306, Research Triangle Park, NC 27709 USA. Telephone: (919) 541-5772. Fax: (919) 541-2511. E-mail: london2@niehs.nih.gov

Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1205412).

We are grateful to the participating families in Norway who take part in this ongoing cohort study. We thank R.E. Kolstad, A. Sunde, and K. Harbak

# Entretemps chez la femme ence

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## 450K Epigenome-Wide Scan Identifies Differential DNA Methylation in Newborns Related to Maternal Smoking during Pregnancy

*Bonnie R. Joubert,[1] Siri E. Håberg,[2] Roy M. Nilsen,[3] Xuting Wang,[1] Stein E. Vollset,[2,4] Susan K. Murphy,[5] Zhiqing Huang,[5] Cathrine Hoyo,[5] Øivind Midttun,[6] Lea A. Cupul-Uicab,[1] Per M. Ueland,[4] Michael C. Wu,[7] Wenche Nystad,[2] Douglas A. Bell,[1] Shyamal D. Peddada,[1] and Stephanie J. London[1]*

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**Background:** Epigenetic modifications, such as DNA methylation, due to *in utero* exposures may play a critical role in early programming for childhood and adult illness. Maternal smoking is a major risk factor for multiple adverse health outcomes in children, but the underlying mechanisms are unclear.

**Objective:** We investigated epigenome-wide methylation in cord blood of newborns in relation to maternal smoking during pregnancy.

**Methods:** We examined maternal plasma cotinine (an objective biomarker of smoking) measured during pregnancy in relation to DNA methylation at 473,844 CpG sites (CpGs) in 1,062 newborn cord blood samples from the Norwegian Mother and Child Cohort Study (MoBa) using the Infinium HumanMethylation450 BeadChip (450K).

**Results:** We found differential DNA methylation at epigenome-wide statistical significance ($p$-value < $1.06 \times 10^{-7}$) for 26 CpGs mapped to 10 genes. We replicated findings for CpGs in *AHRR*, *CYP1A1*, and *GFI1* at strict Bonferroni-corrected statistical significance in a U.S. birth cohort. *AHRR* and *CYP1A1* play a key role in the aryl hydrocarbon receptor signaling pathway, which mediates the detoxification of the components of tobacco smoke. *GFI1* is involved in diverse developmental processes but has not previously been implicated in responses to tobacco smoke.

**Conclusions:** We identified a set of genes with methylation changes present at birth in children whose mothers smoked during pregnancy. This is the first study of differential methylation across the genome in relation to maternal smoking during pregnancy using the 450K platform. Our findings implicate epigenetic mechanisms in the pathogenesis of the adverse health outcomes associated with this important *in utero* exposure.

**Key words:** epigenetics, epigenome-wide, *in utero*, maternal smoking, methylation. *Environ Health Perspect* 120:1425–1431 (2012). http://dx.doi.org/10.1289/ehp.1205412 [Online 31 July 2012]

Maternal smoking during pregnancy is a major risk factor for adverse health outcomes in children including low birth weight, some childhood cancers, reduced lung function, and early respiratory illnesses (Office of the

methylation. A few human studies have examined epigenetic alterations in relation to maternal smoking during pregnancy and reported it to be associated with global methylation of leukocyte DNA using a [$^3$H]-

Infinium HumanMethylation450 Beadchip (450K; Illumina Inc.), which measures CpG methylation at > 470,000 CpGs, we evaluated the relationship between maternal smoking and DNA methylation in 1,062 infant cord blood samples from a birth cohort in Norway. We assessed maternal smoking objectively by measuring cotinine, a sensitive biomarker, in maternal plasma samples, and replicated our findings in an independent birth cohort study from the U.S. To our knowledge, this is the largest human study of any *in utero* exposure in relation to DNA methylation at birth using the 450K platform with improved epigenome-wide coverage.

### Methods

Participants in the current analysis were selected from a substudy of the Norwegian Mother and Child Cohort Study (MoBa) (Magnus et al. 2006; Ronningen et al. 2006) that evaluated the association between maternal plasma folate during pregnancy and childhood

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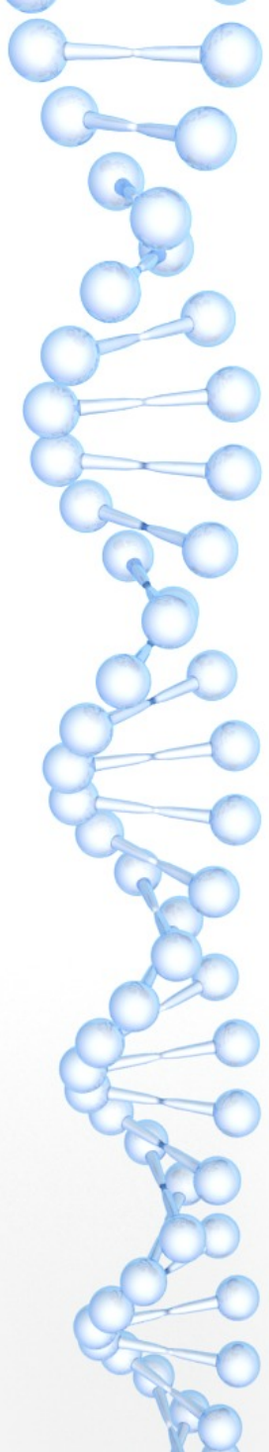
Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1205412).

We are grateful to the participating families in Norway who take part in this ongoing cohort study. We thank R.E. Kolstad, A. Sunde, and K. Harbak

| Chr[a] | Gene | t |
|---|---|---|
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 1 | *GFI1* | |
| 5 | *AHRR* | |
| 5 | *AHRR* | |
| 5 | *AHRR* | |
| 5 | *AHRR* | |
| 6 | *HLA-DPB2* | |
| 7 | *MYO1G* | |
| 7 | *MYO1G* | |
| 7 | *MYO1G* | |
| 7 | *MYO1G* | |
| 7 | *ENSG00000225718* | |
| 7 | *CNTNAP2* | |
| 8 | *EXT1* | |
| 14 | *TTC7B* | |
| 15 | *CYP1A1* | |
| 15 | *CYP1A1* | |
| 15 | *CYP1A1* | |
| 15 | *CYP1A1* | |
| 21 | RUNX1 | |



# De

Witt *et al. BMC Genor*
https://doi.org/10.118

RESEARCH

# Impact
# smokin
# by DNA

Stephanie H. Witt
Verena Peus[2], Bar
Helene Dukal[1], Ja
Michael Deuschle

**Abstract**

**Background:** Ci
who smoke duri
birth weight wh
have revealed th
that DNA methy
were to replicate
for the first time
known sex-speci

**Table 2** Top differentially methylated CpGs (associated with maternal smoking after correction for multiple testing)

| Name | Chromosome | Chromosomal position | UCSC RefGene name | UCSC RefGene group | Relation_to_UCSC CpG_Island | Difference[a] | *P*-value | FDR[b] |
|---|---|---|---|---|---|---|---|---|
| cg04865726 | 1 | 1365911 | | | S_Shelf | 0,033 | 5,39E-05 | 1,65E-02 |
| cg09662411 | 1 | 92946132 | GFI1 | Body | Island | -0,115 | 3,69E-07 | 3,98E-04 |
| cg06338710 | 1 | 92946187 | GFI1 | Body | Island | -0,099 | 2,26E-05 | 8,94E-03 |
| cg18146737 | 1 | 92946700 | GFI1 | Body | Island | -0,128 | 7,51E-07 | 5,19E-04 |
| cg12876356 | 1 | 92946825 | GFI1 | Body | Island | -0,178 | 1,07E-06 | 6,55E-04 |
| cg18316974 | 1 | 92947035 | GFI1 | Body | Island | -0,057 | 4,32E-07 | 3,98E-04 |
| cg09935388 | 1 | 92947588 | GFI1 | Body | Island | -0,194 | 2,72E-09 | 7,52E-06 |
| cg14179389 | 1 | 92947961 | GFI1 | Body | Island | -0,061 | 5,07E-08 | 9,34E-05 |
| cg11641006 | 2 | 235213874 | | | | 0,078 | 1,40E-05 | 6,45E-03 |
| cg23067299 | 5 | 323907 | AHRR | Body | S_Shore | 0,031 | 7,71E-05 | 2,17E-02 |
| cg23916896 | 5 | 368804 | AHRR | Body | N_Shore | -0,025 | 2,12E-04 | 4,22E-02 |
| cg11902777 | 5 | 368843 | AHRR | Body | N_Shore | -0,005 | 1,99E-04 | 4,22E-02 |
| cg05575921 | 5 | 373378 | AHRR | Body | N_Shore | -0,075 | 1,24E-15 | 6,85E-12 |
| cg21161138 | 5 | 399360 | AHRR | Body | | -0,043 | 2,63E-05 | 9,68E-03 |
| cg25325512 | 6 | 37142220 | PIM1 | 3'UTR | S_Shelf | -0,062 | 1,52E-04 | 3,65E-02 |
| cg23594693 | 6 | 41703970 | TFEB | 5'UTR;TSS1500;1stExon | S_Shore | 0,027 | 1,32E-04 | 3,46E-02 |
| cg02227813 | 6 | 130524018 | SAMD3; SAMD3 | Body | | 0,040 | 7,86E-05 | 2,17E-02 |
| cg07249149 | 7 | 1035363 | | | | -0,051 | 1,77E-04 | 3,91E-02 |
| cg19089201 | 7 | 45002287 | MYO1G | 3'UTR | Island | 0,028 | 1,29E-05 | 6,45E-03 |
| cg22132788 | 7 | 45002486 | MYO1G | Body | Island | 0,019 | 2,14E-04 | 4,22E-02 |
| cg04180046 | 7 | 45002736 | MYO1G | Body | Island | 0,063 | 5,31E-07 | 4,19E-04 |
| cg12803068 | 7 | 45002919 | MYO1G | Body | S_Shore | 0,109 | 1,56E-05 | 6,64E-03 |
| cg25949550 | 7 | 145814306 | CNTNAP2 | Body | S_Shore | -0,009 | 8,90E-08 | 1,23E-04 |
| cg15578140 | 7 | 147718109 | MIR548F3;CNTNAP2 | Body | | 0,054 | 8,01E-06 | 4,43E-03 |
| cg11813497 | 10 | 14372879 | FRMD4A | TSS200 | | 0,043 | 1,39E-04 | 3,49E-02 |
| cg26033520 | 10 | 74004071 | | | | -0,026 | 2,63E-04 | 4,84E-02 |
| cg08699196 | 12 | 53591398 | ITGB7 | Body | Island | 0,028 | 2,50E-04 | 4,77E-02 |
| cg05549655 | 15 | 75019143 | CYP1A1 | TSS1500 | Island | 0,021 | 4,76E-05 | 1,56E-02 |
| cg13859324 | 17 | 33474692 | UNC45B | TSS200;TSS200 | | 0,032 | 4,79E-05 | 1,56E-02 |
| cg11043990 | 17 | 74235759 | RNF157 | Body | Island | 0,017 | 1,60E-04 | 3,69E-02 |

[a]Beta-Value Mean-Differences between Smoking vs Non-Smoking group
[b]False discovery rate

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Research paper

## Association of maternal prenatal smoking *GFI1*-locus and cardio-metabolic phenotypes in 18,212 adults

Priyanka Parmar [a,b], Estelle Lowry [a,b], Giovanni Cugliari [c,d], Matthew Suderman [e], Rory Wilson [f,g], Ville Karhunen [h], Toby Andrew [i], Petri Wiklund [a,h,j], Matthias Wielscher [h], Simonetta Guarrera [c,d], Alexander Teumer [k,l], Benjamin Lehne [h], Lili Milani [m,n], Niek de Klein [o], Pashupati P. Mishra [p,q], Phillip E. Melton [r,s], Pooja R. Mandaviya [t], Silva Kasela [m], Jana Nano [g,u], Weihua Zhang [h,v], Yan Zhang [w], Andre G. Uitterlinden [t,u], Annette Peters [f,g,x], Ben Schöttker [w,y], Christian Gieger [f,g,x], Denise Anderson [z], Dorret I. Boomsma [aa], Hans J. Grabe [ab,ac], Salvatore Panico [ad], Jan H. Veldink [ae], Joyce B.J. van Meurs [t], Leonard van den Berg [ae], Lawrence J. Beilin [af], Lude Franke [o], Marie Loh [h,ag,ah], Marleen M.J. van Greevenbroek [ai], Matthias Nauck [l,aj], Mika Kähönen [ak,al], Mikko A. Hurme [am], Olli T. Raitakari [an,ao], Oscar H. Franco [u], P.Eline Slagboom [ap], Pim van der Harst [o,aq,ar], Sonja Kunze [f,g], Stephan B. Felix [l], Tao Zhang [as,at], Wei Chen [as], Trevor A. Mori [af], Amelie Bonnefond [i,au], Bastiaan T. Heijmans [ap], for the BIOS Consortium, Taulant Muka [u], Jaspal S. Kooner [v,aw,h,ay], Krista Fischer [m], Melanie Waldenberger [f,g,x], Philippe Froguel [i,au], Rae-Chi Huang [z], Terho Lehtimäki [p,q], Wolfgang Rathmann [ax], Caroline L. Relton [e], Giuseppe Matullo [c,d], Hermann Brenner [w,y], Niek Verweij [aq], Shengxu Li [ay], John C. Chambers [h,v,av,az], Marjo-Riitta Järvelin [a,b,h,ba,**,1], Sylvain Sebert [a,b,bb,*,1], for the GLOBAL Meth QTL

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Research paper

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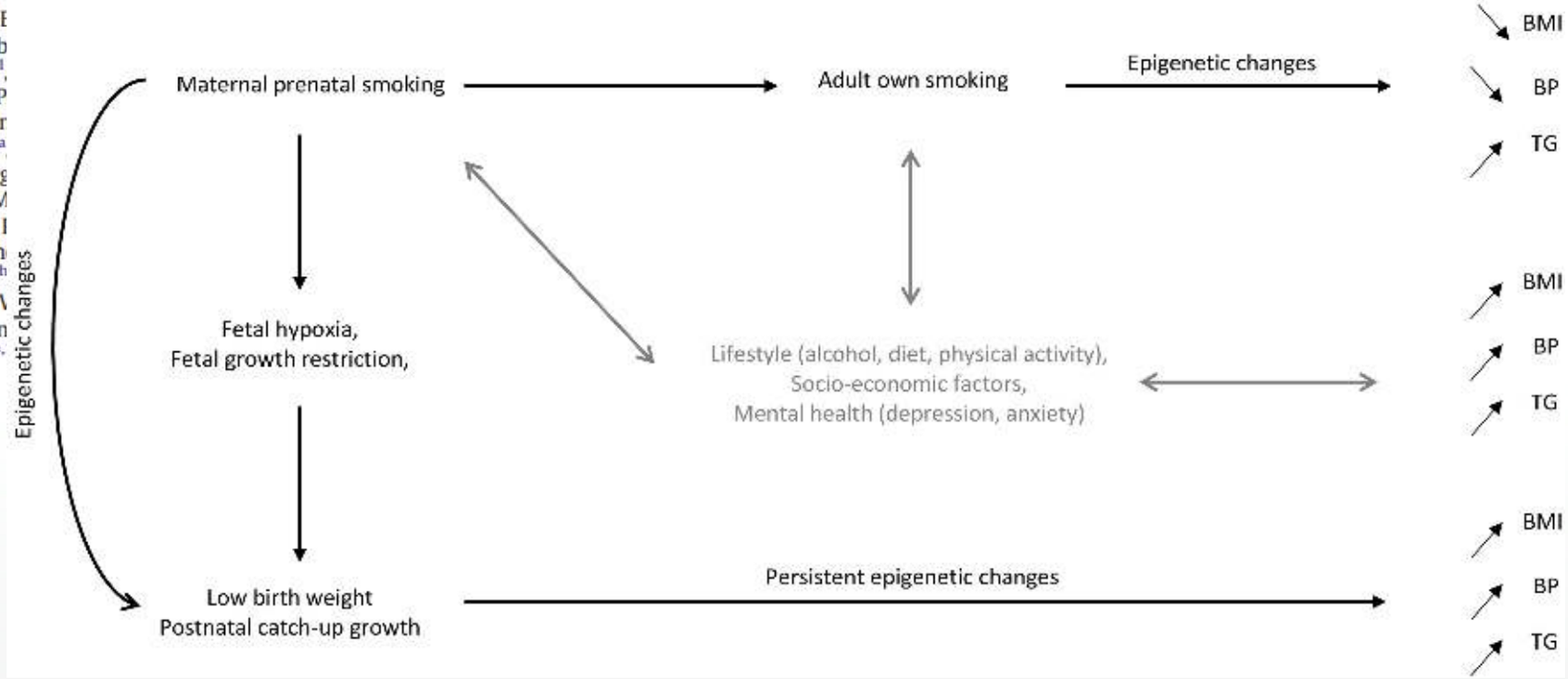
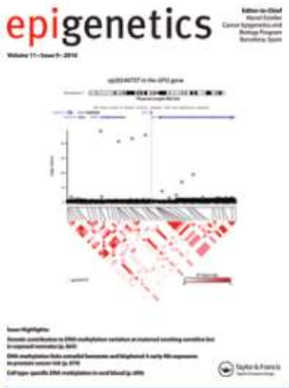
Jaspal S. Kooner [v,aw,h
Terho Lehtimäki [p,q], V
Niek Verweij [aq], Shen
Sylvain Sebert [a,b,bb,*]



# Tous (les nouveaux-nés) égaux face au tabac?



Epigenetics

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## Genetic contribution to variation in DNA methylation at maternal smoking-sensitive loci in exposed neonates

Semira Gonseth (Dr.), Adam J. de Smith, Ritu Roy, Mi Zhou, Seung-Tae Lee, Xiaorong Shao, Juhi Ohja, Margaret R. Wrensch, Kyle M. Walsh, Catherine Metayer & Joseph L. Wiemels

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# Effet du sevrage lors de la grossesse

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SCIENTIFIC REPORTS

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## Association between DNA methylation in cord blood and maternal smoking: The Hokkaido Study on Environment and Children's Health

Kunio Miyake[1], Akio Kawaguchi[2], Ryu Miura[3], Sachiko Kobayashi[3], Nguyen Quoc Vuong Tran[1], Sumitaka Kobayashi[3], Chihiro Miyashita[3], Atsuko Araki[3], Takeo Kubota[4], Zentaro Yamagata[1] & Reiko Kishi[3]

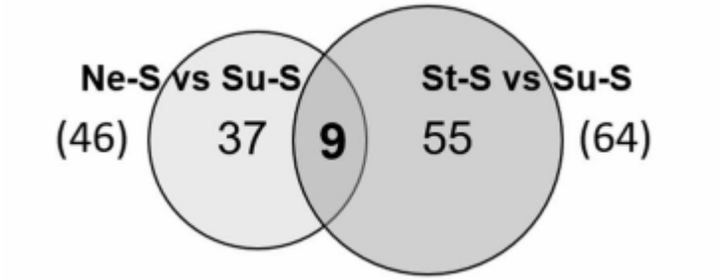
Maternal smoking is reported to cause adverse effects on the health of the unborn child, the underlying mechanism for which is thought to involve alterations in DNA methylation. We examined the effects of maternal smoking on DNA methylation in cord blood, in 247 mother–infant pairs in the Sapporo cohort of the Hokkaido Study, using the Infinium HumanMethylation 450K BeadChip. We first identified differentially methylated CpG sites with a false discovery rate (FDR) of $<0.05$ and the magnitude of DNA methylation changes ($|\beta| > 0.02$) from the pairwise comparisons of never-smokers (Ne-S), sustained-smokers (Su-S), and stopped-smokers (St-S). Subsequently, secondary comparisons between St-S and Su-S revealed nine common sites that mapped to *ACSM3*, *AHRR*, *CYP1A1*, *GFI1*, *SHANK2*, *TRIM36*, and the intergenic region between *ANKRD9* and *RCOR1* in Ne-S vs. Su-S, and one common CpG site mapping to *EVC2* in Ne-S vs. St-S. Further, we verified these CpG sites and examined neighbouring sites using bisulfite next-generation sequencing, except for *AHRR* cg21161138. These changes in DNA methylation implicate the effect of smoking cessation. Our findings add to the current knowledge of the association between DNA methylation and maternal smoking and suggest future studies for clarifying this relationship in disease development.

**These changes in DNA methylation implicate the efect of smoking cessation.**

# Effet du sevrage lors de la grossesse

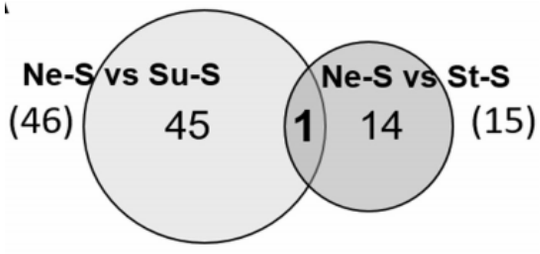
**Association between DNA methylation in cord blood and maternal smoking: The Hokkaido Study on Environment and Children's Health**

Kunio Miyake[1], Akio Kawaguchi[2], Ryu Miura[3], Sachiko Kobayashi[3], Nguyen Quoc Vuong Tran[1], Sumitaka Kobayashi[3], Chihiro Miyashita[3], Atsuko Araki[3], Takeo Kubota[4], Zentaro Yamagata[1] & Reiko Kishi[3]




jamais vs tabac  Arrêt vs tabac

En partie la signature d'une mère fumeuse s'efface lors d'un sevrage en début de grossesse




jamais vs tabac  jamais vs arrêt

Ces enfants portent la signature d'une mère fumeuse en début de grossesse

# Le tabagisme paternel

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## Cigarette smoking significantly alters sperm DNA methylation patterns

T. G. Jenkins, E. R. James, D. F. Alonso, J. R. Hoidal, P. J. Murphy, J. M. Hotaling, B. R. Cairns, D. T. Carrell, K. I. Aston

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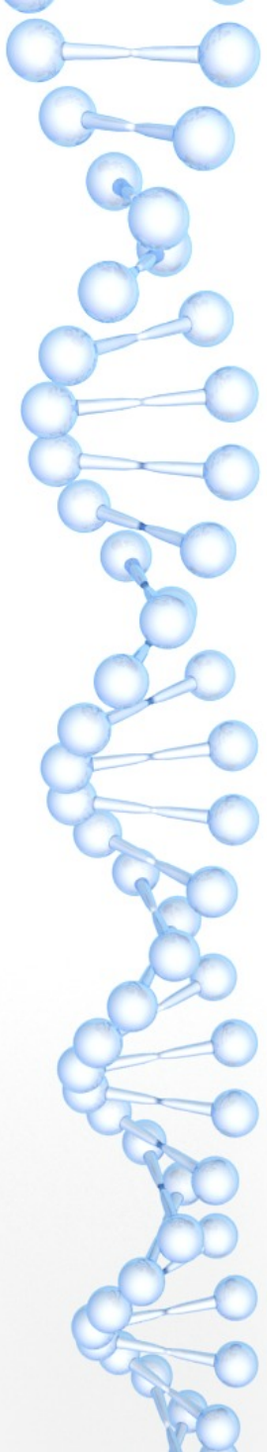
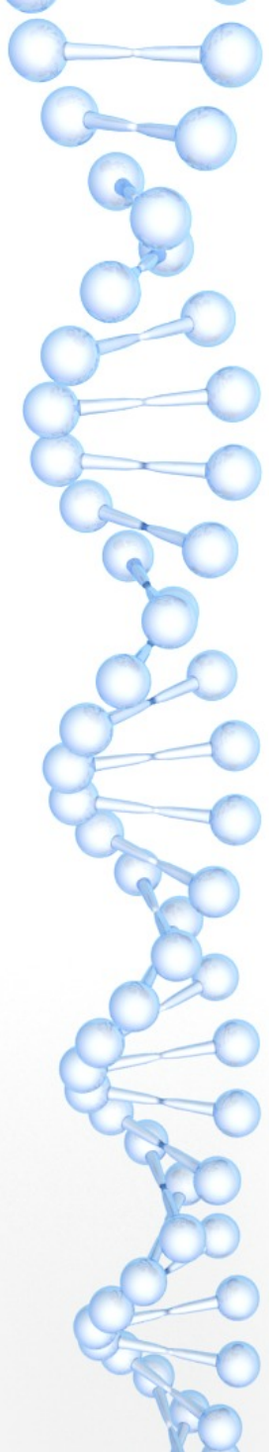
# En résumé

- Des composantes de la fumée de tabac ont des effets sur la transcription des gènes
- Ces effets sont variables d‘une personne à une autre
- Le foetus subit des effets parfois spécifiques qui peuvent perdurer longtemps
- Le sevrage peut atténuer l‘ampleur de ces effets

→ vivement qu‘on arrive à une proportion moindre de FEF à la naissance



Merci!



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