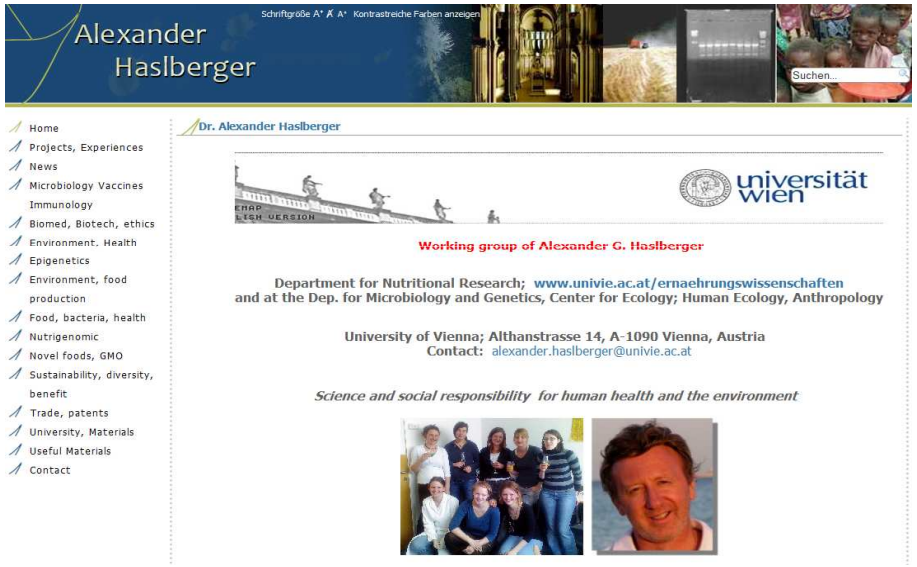
Psychoonkology, Sept. 2010
lifestyle factors and epigenetics



Alexander G. Haslberger

Dep. für
Ernährungswissenschaften
Univ. of Vienna

Working group:
Food, GI-Microbiology,
Epigenetics

universität wien

Content

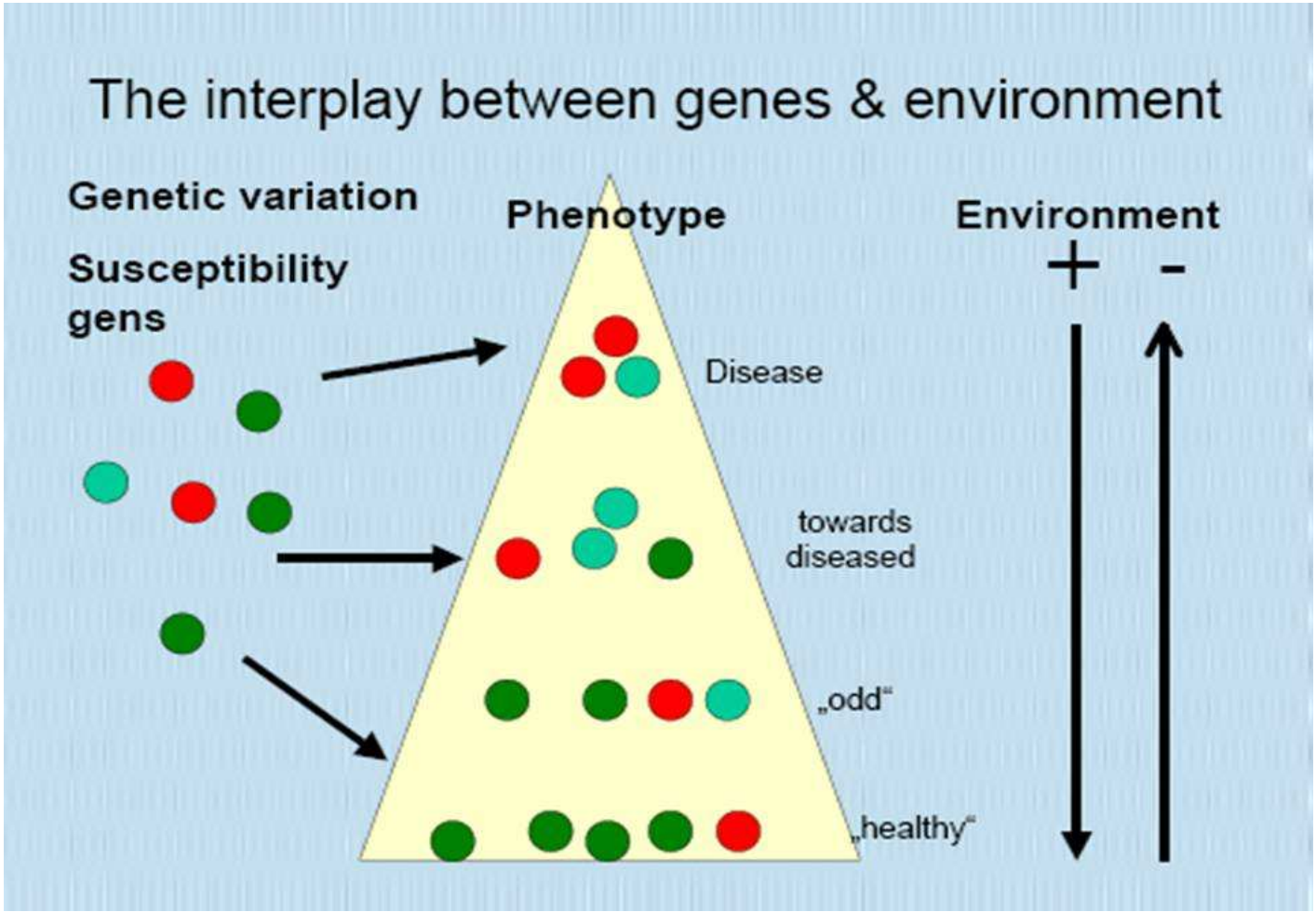
Health: Genetics/Epigenetics/ Environment

Epigenetics: Effects from the environment

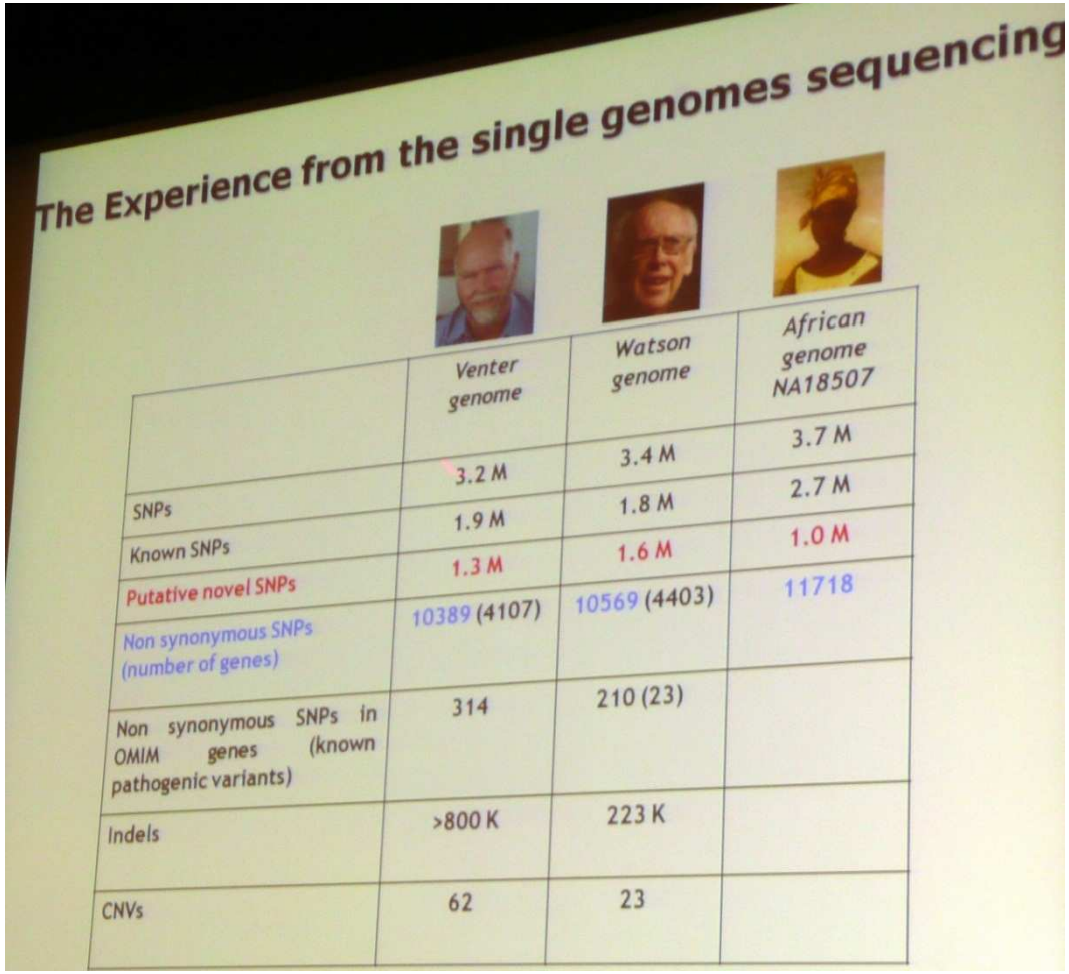
Epigenetics, cancer, prevention and therapy?

Conclusion

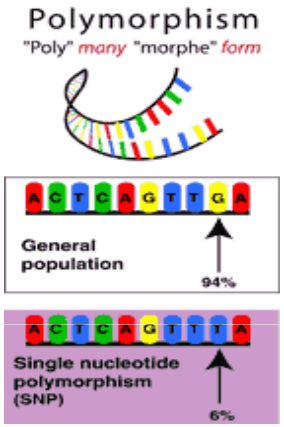
Health: interaction nature – nurture genetics- environment

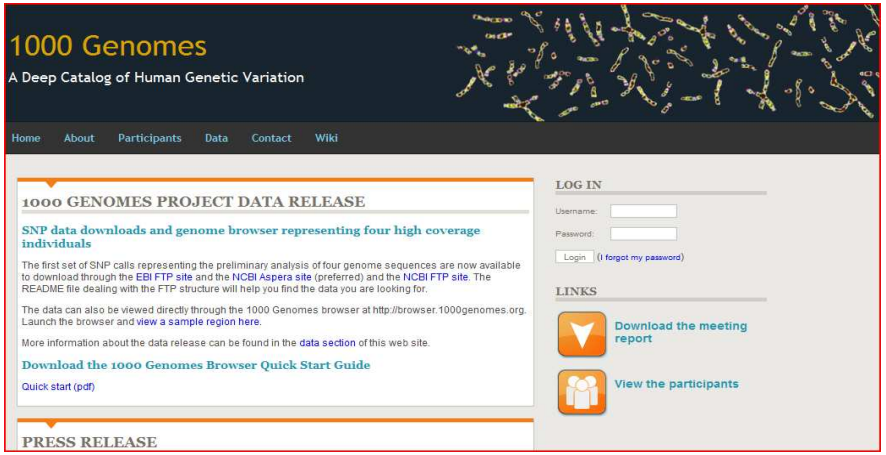


Individual, hereditary, genetic characteristics: mainly SNPs

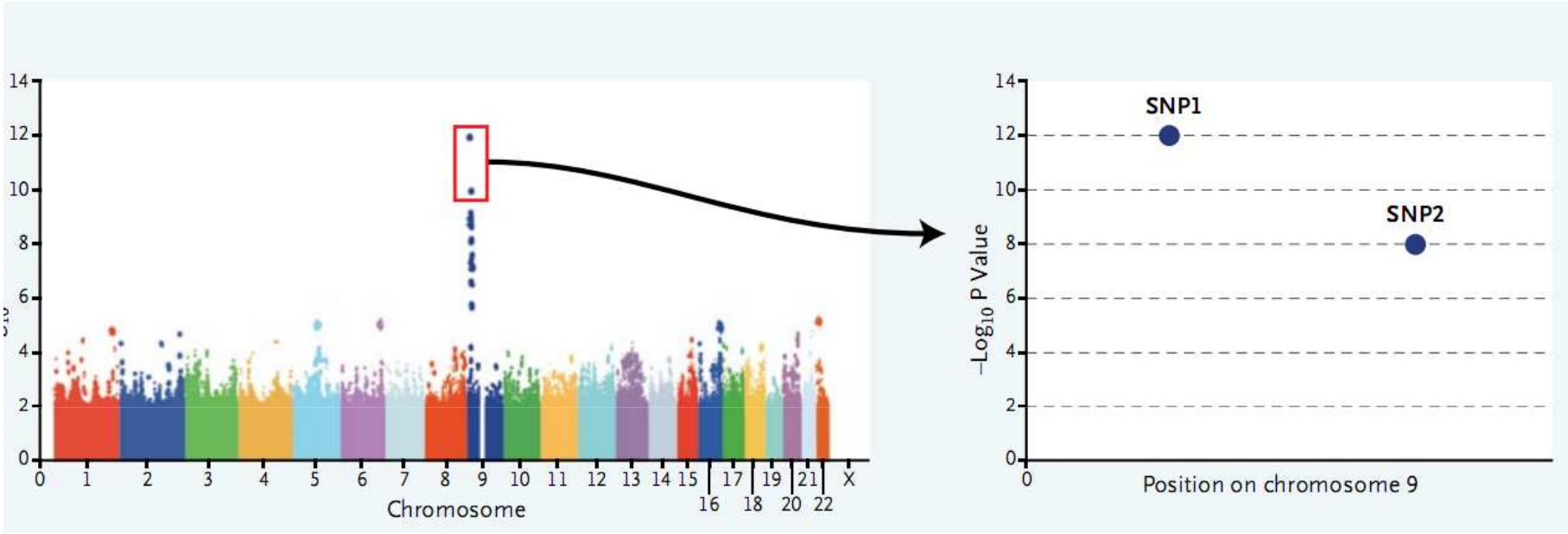


	Venter genome	Watson genome	African genome NA18507
SNPs	3.2 M	3.4 M	3.7 M
Known SNPs	1.9 M	1.8 M	2.7 M
Putative novel SNPs	1.3 M	1.6 M	1.0 M
Non synonymous SNPs (number of genes)	10389 (4107)	10569 (4403)	11718
Non synonymous SNPs in OMIM genes (known pathogenic variants)	314	210 (23)	
Indels	>800 K	223 K	
CNVs	62	23	





Genome wide association studies, Cancer



NATURE GENETICS | LETTER

Genome-wide association study identifies five new susceptibility loci for prostate cancer in the Japanese population

Ryo Takata, Shusuke Akamatsu, Michiaki Kubo, Atsushi Takahashi, Naoya Hosono, Takahisa Kawaguchi, Tatsuhiko Tsunoda, Johji Inazawa, Naoyuki Kamatani, Osamu Ogawa, Tomoaki Fujioka, Yusuke Nakamura & Hidewaki Nakagawa

Affiliations | Contributions | Corresponding author

Nature Genetics **42**, 751–754 (2010) | doi:10.1038/ng.635
Received 26 February 2010 | Accepted 06 July 2010 | Published online 01 August 2010

Prostate cancer is one of the most common malignancies in males throughout the world[1], and its incidence is increasing in Asian countries. We carried out a genome-wide association study and replication study using 4,584 Japanese men with prostate cancer and 8,801 control subjects. From the thirty-one associated SNPs reported in previous genome-wide association studies in European populations, we confirmed the association of nine SNPs at $P < 1.0 \times 10^{-7}$ and ten SNPs at $P < 0.05$ in the Japanese population. The remaining 12 SNPs showed no association ($P > 0.05$). In addition, we report here five new loci for prostate cancer susceptibility, at *5p15* (λ-corrected probability $P_{GC} = 3.9 \times 10^{-18}$), *GPRC6A/RFX6* ($P_{GC} = 1.6 \times 10^{-12}$), *13q22* ($P_{GC} = 2.8 \times 10^{-9}$), *C2orf43* ($P_{GC} = 7.5 \times 10^{-8}$) and *FOXP4* ($P_{GC} = 7.6 \times 10^{-8}$). These findings advance our understanding of the genetic basis of prostate carcinogenesis and also highlight the genetic heterogeneity of prostate cancer susceptibility among different ethnic populations.

Genome-wide association study provides evidence for a breast cancer risk locus at 6q22.33

Bert Gold[a], Tomas Kirchhoff[b], Stefan Stefanov[a], James Lautenberger[a], Agnes Viale[c], Judy Garber[d], Eitan Friedman[e], Steven Narod[f], Adam B. Olshen[g], Peter Gregersen[h], Kristi Kosarin[b], Adam Olsh[a], Julie Bergeron[i], Nathan A. Ellis[j], Robert J. Klein[k], Andrew G. Clark[l], Larry Norton[m], Michael Dean[a], Jeff Boyd[n], and Kenneth Offit[b,o]

[a]Laboratory of Genomic Diversity, Human Genetics Section, National Cancer Institute–Frederick, Frederick, MD 21702; [b]Clinical Genetics Service, Department of Medicine, [c]Genome Core Laboratory, [d]Breast Medicine Service, [g]Department of Biostatistics and Epidemiology, and [o]Cancer Biology and Genetics Program, Memorial Sloan–Kettering Cancer Center, New York, NY 10065; [e]Cancer Risk and Prevention Program, Dana–Farber Cancer Institute, Boston, MA 02115; [f]The Susanne Levy Gertner Oncogenetics Unit, Chaim Sheba Medical Center, Tel-Hashomer, and the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv 69978, Israel; [h]Centre for Research in Women's Health, Toronto, ON, Canada M5G 1N8; [k]Center for Genomics and Human Genetics, North Shore Long Island Jewish Research Institute, Manhasset, NY 11030; [l]Laboratory of Genomic Diversity, Human Genetics Section, SAIC-Frederick, Inc., Frederick, MD 21702; [i]Division of Gastroenterology, Department of Medicine, University of Chicago, Chicago, IL 60637; [j]Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY 14853; and [m]Anderson Cancer Institute, Memorial Health University Medical Center, Savannah, GA 31404

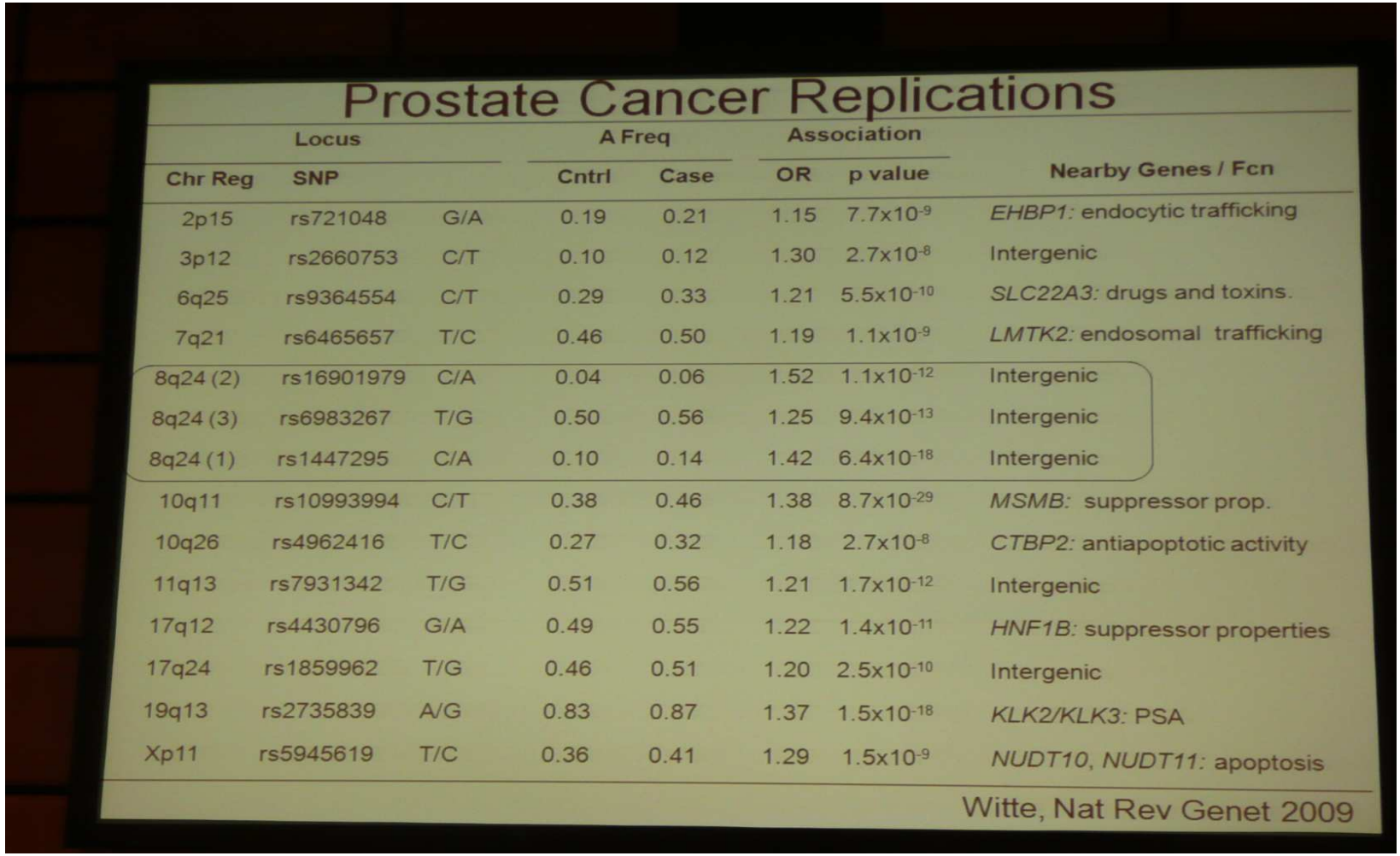
nature genetics

Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease

Jeffrey C Barrett[*1], Sarah Hansoul[2], Dan L Nicolae[3], Judy H Cho[4], Richard H Duerr[5,6], John D Rioux[7,8], Steven R Brant[9,10], Mark S Silverberg[11], Kent D Taylor[12], M Michael Barmada[6], Alain Bitton[13], Themistocles Dassopoulos[9], Lisa Wu Datta[9], Todd Green[9], Anne M Griffiths[14], Emily O Kistner[15], Michael T Murtha[6], Miguel D Regueiro[5], Jerome I Rotter[12], L Philip Schumm[15], A Hillary Steinhart[11], Stephan R Targan[12], Ramnik J Xavier[16], the NIDDK IBD Genetics Consortium[*2], Cécile Libioulle[2], Cynthia Sandor[2], Mark Lathrop[17], Jacques Belaiche[18], Olivier Dewit[19], Ivo Gut[17], Simon Heath[17], Debby Laukens[20], Myriam Mni[2], Paul Rutgeerts[21], André Van Gossum[22], Diana Zelenika[17], Denis Franchimont[22], Jean-Pierre Hugot[23], Martine de Vos[20], Severine Vermeire[21], Edouard Louis[18], the Belgian-French IBD Consortium[*3], the Wellcome Trust Case Control Consortium[*3,24], Jon R Cardon[1], Carl A Anderson[1], Hazel Drummond[25], Elaine Nimmo[25], Tariq Ahmad[25], Natalie J Prescott[26], Clive M Onnie[26], Sheila A Fisher[26], Jonathan Marchini[27], Jilur Ghori[28], Suzannah Bumpstead[28], Rhian Gwilliam[28], Mark Tremelling[29], Panos Deloukas[28], John Mansfield[30], Derek Jewell[31], Jack Satsangi[24], Christopher G Mathew[26], Miles Parkes[29], Michel Georges[2] & Mark J Daly[*,3,32]

Several risk factors for Crohn's disease have been identified in recent genome-wide association studies. To advance gene discovery further, we combined data from three studies on Crohn's disease (a total of 3,230 cases and 4,829 controls) and carried out replication in 3,664 independent cases with a mixture of population-based and family-based controls. The results strongly confirm 11 previously reported loci and provide genome-wide significant evidence for 21 additional loci, including the regions containing *STAT3*, *JAK2*, *ICOSLG*, *CDKAL1* and *ITLN1*. The expanded molecular understanding of the basis of this disease offers promise for informed therapeutic development.

Penetrance: odds ratio small? <1.3

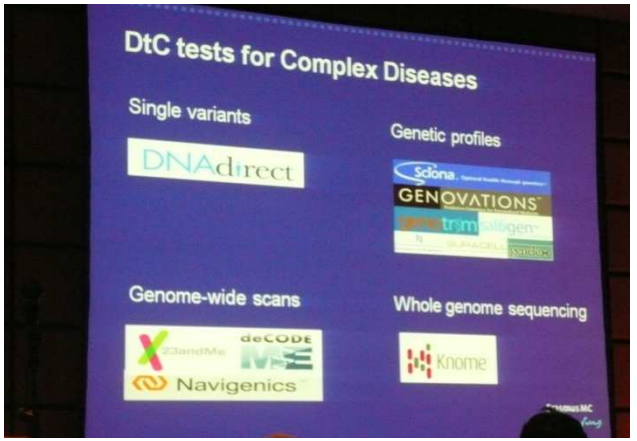


Prostate Cancer Replications

Locus			A Freq		Association		
Chr Reg	SNP		Cntrl	Case	OR	p value	Nearby Genes / Fcn
2p15	rs721048	G/A	0.19	0.21	1.15	7.7×10^{-9}	*EHBP1:* endocytic trafficking
3p12	rs2660753	C/T	0.10	0.12	1.30	2.7×10^{-8}	Intergenic
6q25	rs9364554	C/T	0.29	0.33	1.21	5.5×10^{-10}	*SLC22A3:* drugs and toxins.
7q21	rs6465657	T/C	0.46	0.50	1.19	1.1×10^{-9}	*LMTK2:* endosomal trafficking
8q24 (2)	rs16901979	C/A	0.04	0.06	1.52	1.1×10^{-12}	Intergenic
8q24 (3)	rs6983267	T/G	0.50	0.56	1.25	9.4×10^{-13}	Intergenic
8q24 (1)	rs1447295	C/A	0.10	0.14	1.42	6.4×10^{-18}	Intergenic
10q11	rs10993994	C/T	0.38	0.46	1.38	8.7×10^{-29}	*MSMB:* suppressor prop.
10q26	rs4962416	T/C	0.27	0.32	1.18	2.7×10^{-8}	*CTBP2:* antiapoptotic activity
11q13	rs7931342	T/G	0.51	0.56	1.21	1.7×10^{-12}	Intergenic
17q12	rs4430796	G/A	0.49	0.55	1.22	1.4×10^{-11}	*HNF1B:* suppressor properties
17q24	rs1859962	T/G	0.46	0.51	1.20	2.5×10^{-10}	Intergenic
19q13	rs2735839	A/G	0.83	0.87	1.37	1.5×10^{-18}	*KLK2/KLK3:* PSA
Xp11	rs5945619	T/C	0.36	0.41	1.29	1.5×10^{-9}	*NUDT10, NUDT11:* apoptosis

Witte, Nat Rev Genet 2009

Genetic association, testing ….?



ARTICLE

A Critical Appraisal of the Scientific Basis of Commercial Genomic Profiles Used to Assess Health Risks and Personalize Health Interventions

A. Cecile J.W. Janssens,[1,*] Marta Gwinn,[2] Linda A. Bradley,[2] Ben A. Oostra,[3] Cornelia M. van Duijn,[4] and Muin J. Khoury[2]

Predictive genomic profiling used to produce personalized nutrition and other lifestyle health recommendations is directly to consumers. By examining previous meta-analyses and HuGE reviews, we assessed the scientific evidence su ported gene-disease associations for genes included in genomic profiles offered online. We identified seven companies tive genomic profiling. We searched PubMed for meta-analyses and HuGE reviews of studies of gene-disease association 2000 through June 2007 in which the genotypes of people with a disease were compared with those of a healthy or ge control group. The seven companies tested at least 69 different polymorphisms in 56 genes. Of the 56 genes tested, 2 reviewed in meta-analyses. For the remaining 32 genes, we found 260 meta-analyses that examined 160 unique polyn associations, of which only 60 (38%) were found to be statistically significant. Even the 60 significant associations, w different polymorphisms and 28 different diseases, were generally modest, with synthetic odds ratios ranging from 0.5 tective variants and from 1.04 to 3.2 for risk variants. Furthermore, genes in cardiogenomic profiles were more frequentl noncardiovascular diseases than with cardiovascular diseases, and though two of the five genes of the osteogenomic significant associations with disease, the associations were not with bone diseases. There is insufficient scientific evid that genomic profiles are useful in measuring genetic risk for common diseases or in developing personalized diet an mendations for disease prevention.

Nature Medicine | Commentary

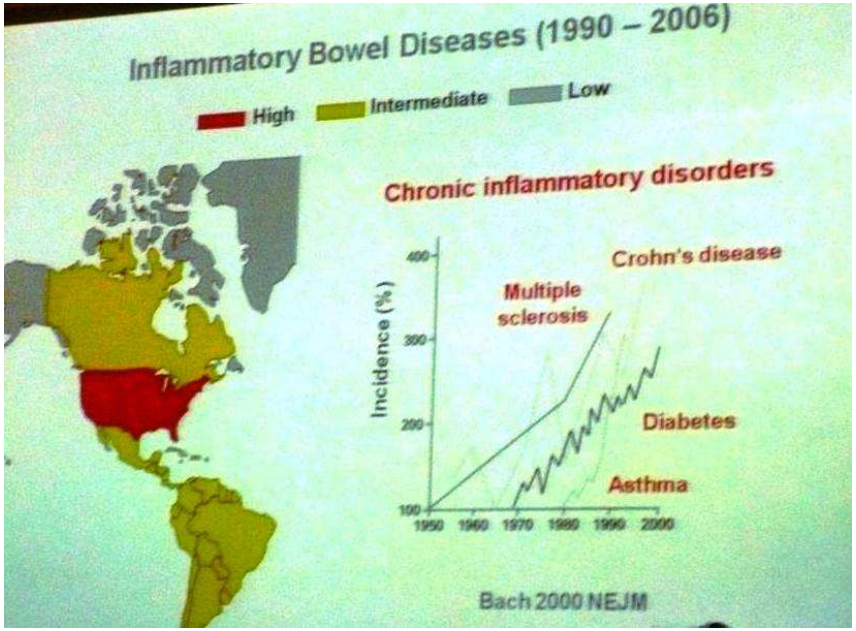
Christopher B Newgard & Alan D Attie

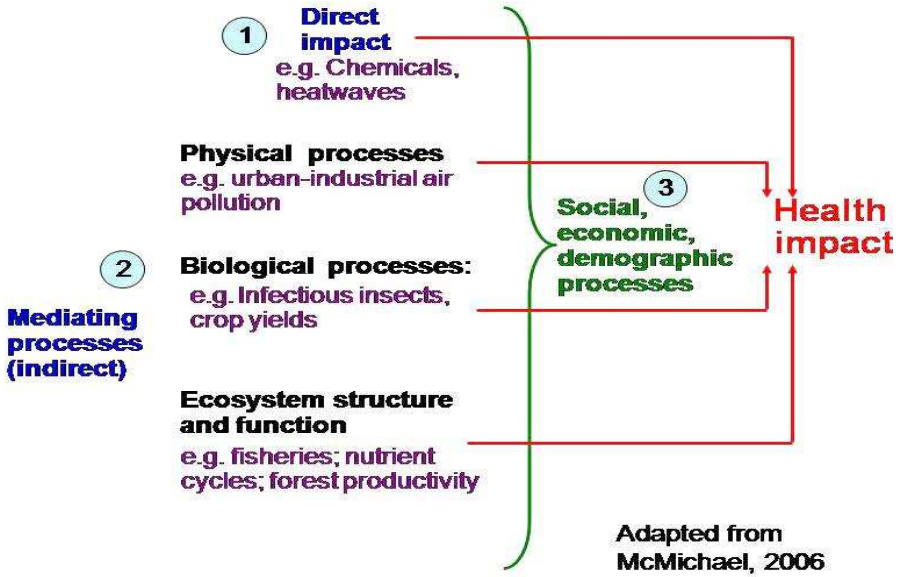
Getting biological about the genetics of diabetes

The first round of genome-wide association studies has not accounted for common human diseases to the extent that was expected. New phenotyping approaches and methods of data integration should bring these studies closer to their promised goals.

Nature Medicine Volume: 16, Pages: 388-391 Year published: (2010)

Effects f omthe Environment: complex interactions of natural, social environment, nutrition, lifestyle and our gut commensals





Why: limits of classical epidemiology ?

Towards causal understanding: molecular epidemiology ?

Complex diseases: The need to understand gene- environment interactions

Originally published in *Science* Express on 26 April 2007
Science 1 June 2007:
Vol. 316. no. 5829, pp. 1341 - 1345
DOI: 10.[illegible]ence.1142382

REPOR[illegible]

A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

Laura J. Scott,[1] Karen
Michael R. Erdos,[3] Hea
Ludmila Prokunina-Ol
Rui Xiao,[1] Xiao-Yi Li,[1]
Peggy P. White [1] Kurt

OPEN ACCESS Freely [illegible]line

PLoS one

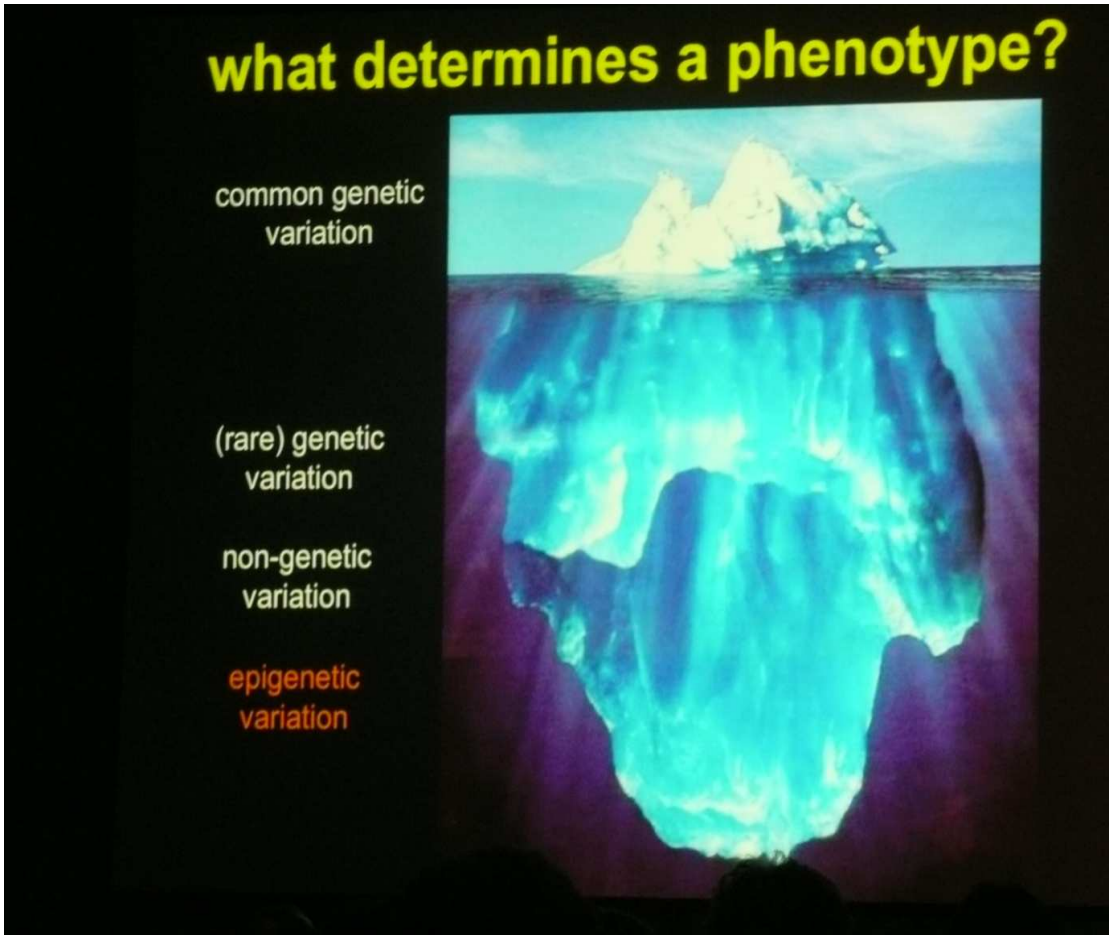
An Environment-Wide Association Study (EWAS) on Type 2 Diabetes Mellitus

Chirag J. Patel[1,2,3], Jayanta Bhattacharya[4], Atul J. Butte[1,2,3]*

1 Department of Pediatrics and Medicine, Stanford University School of Medicine, Stanford, California, United States of America, **2** Stanford Center for Biomedical Informatics Research, Stanford University School of Medicine, Stanford, California, United States of America, **3** Lucile Packard Children's Hospital, Palo Alto, California, United States of America, **4** Center For Primary Care and Outcomes Research, Stanford University School of Medicine, Stanford, California, United States of America

significant findings were validated with other cohorts. We discovered significant associations for the pesticide-derivative heptachlor epoxide (adjusted OR in three combined cohorts of 1.7 for a 1 SD change in exposure amount; $p<0.001$), and the vitamin γ-tocopherol (adjusted OR 1.5; $p<0.001$). Higher concentrations of polychlorinated biphenyls (PCBs) such as PCB170 (adjusted OR 2.2; $p<0.001$) were also found. Protective factors associated with T2D included β-carotenes (adjusted

link between genetic - environment missing ?



Environment

Epigenetic, first evidences

Epigenetic Transgenerational Actions of Endocrine Disruptors and Male Fertility

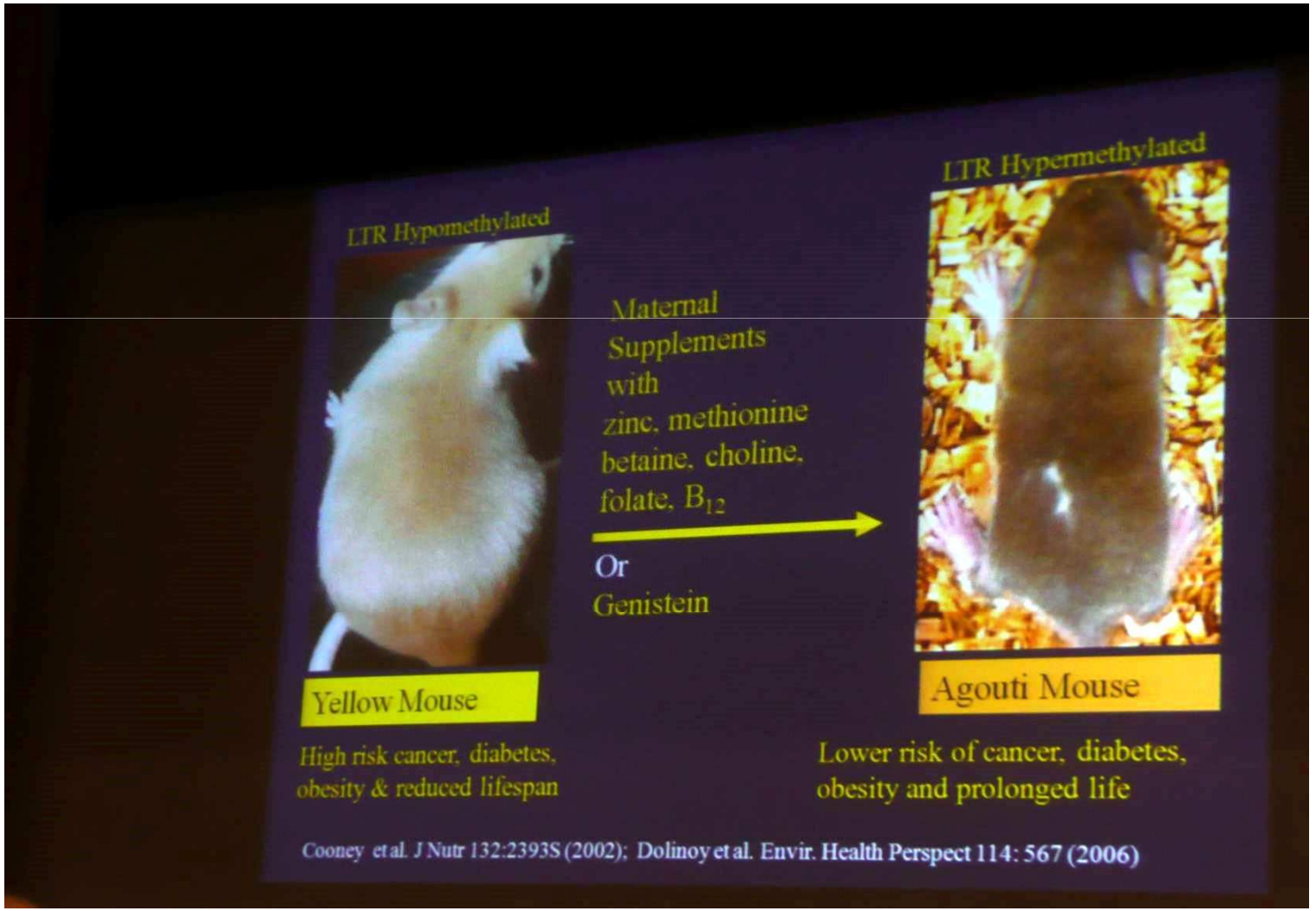
Matthew D. Anway, Andrea S. Cupp,* Mehmet Uzumcu,† Michael K. Skinner‡

Transgenerational effects of environmental toxins require either a chromosomal or epigenetic alteration in the germ line. Transient exposure of a gestating female rat during the period of gonadal sex determination to the endocrine disruptors vinclozolin (an antiandrogenic compound) or methoxychlor (an estrogenic compound) induced an adult phenotype in the F_1 generation of decreased spermatogenic capacity (cell number and viability) and increased incidence of male infertility. These effects were transferred through the male germ line to nearly all males of all subsequent generations examined (that is, F_1 to F_4). The effects on reproduction correlate with altered DNA methylation patterns in the germ line. The ability of an environmental factor (for example, endocrine disruptor) to reprogram the germ line and to promote a transgenerational disease state has significant implications for evolutionary biology and disease etiology.

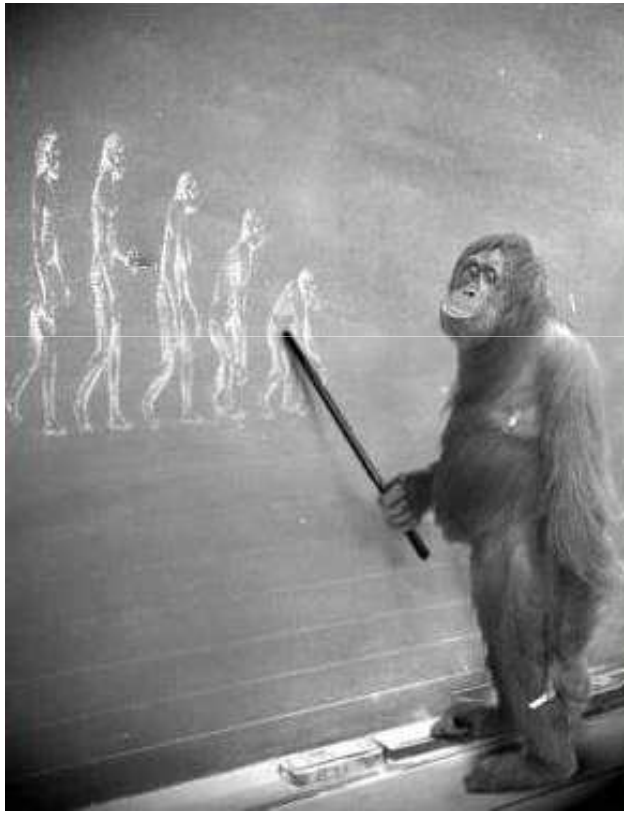
3 JUNE 2005 VOL 308 SCIENCE www.sciencemag.org

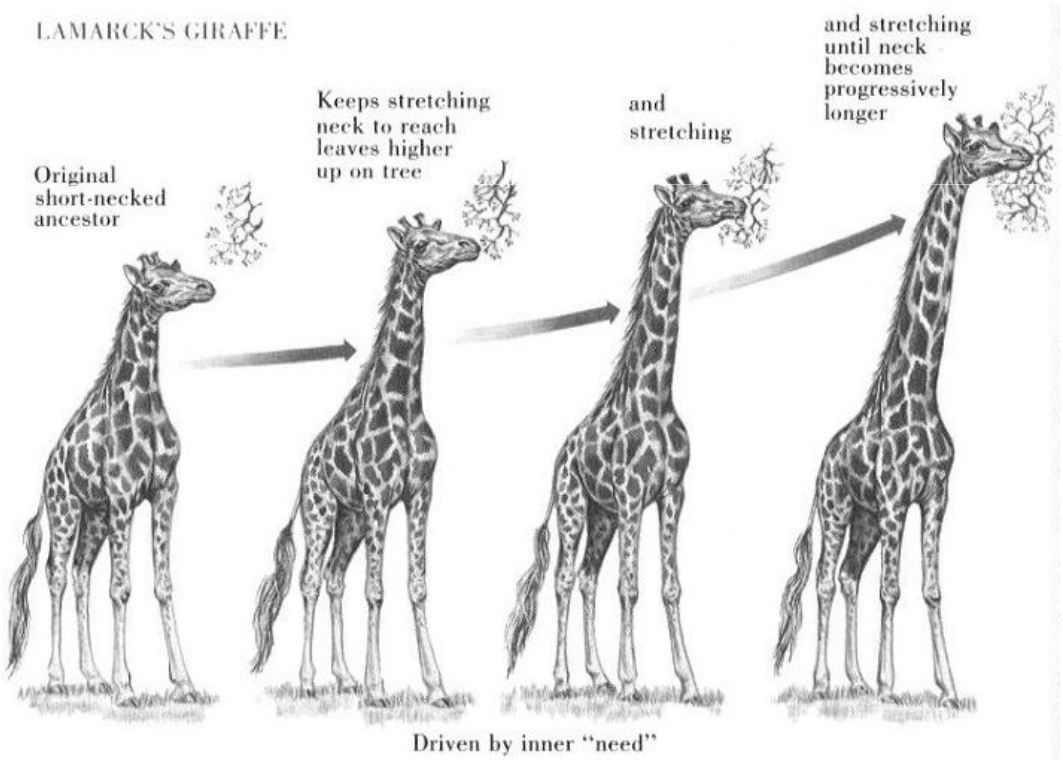
ENDOGENE DIRUPTORS
The fungicide vinclozolin,
which is sprayed on vineyards can cause fertility problems in male offspring of exposed rats.

Epigenetic first evidences, agouti



Darwin, LaMarck and epigenetics ?





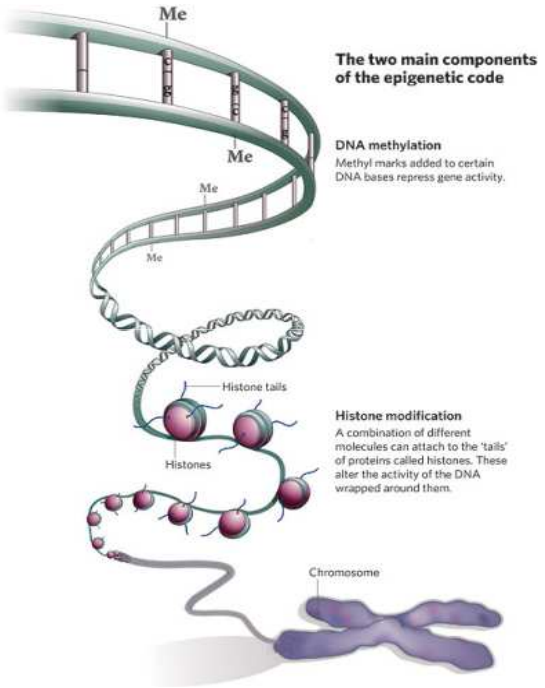
Three main types of epigenetic information

The three main types of epigenetic information

Cytosine DNA methylation is a covalent modification of DNA, in which a methyl group is transferred from *S-adenosylmethionine to the C-5 position of cytosine by a family of cytosine* (DNA-5)-methyltransferases. DNA methylation occurs almost exclusively at CpG nucleotides and has an important contributing role in the regulation of gene expression and the silencing of repeat elements in the genome.

Genomic imprinting is parent-of-origin-specific allele silencing, or relative silencing of one parental allele compared with the other parental allele. It is maintained, in part, by differentially methylated regions within or near imprinted genes, and it is normally reprogrammed in the germline.

Histone modifications — including acetylation, methylation and phosphorylation — are important in transcriptional regulation and many are stably maintained during cell division, although the mechanism for this epigenetic Inheritance is not yet well understood. Proteins that mediate these modifications are often associated within the same complexes as those that regulate DNA methylation.



RNA (interference)

Andrew P. Feinberg and Benjamin Tycko, 2004

Epigenetics

Epigenetics : C. H. Waddington in 1942 conceptual model of how genes might interact with their surroundings to produce a phenotype.

E*pigenetic*: heritable traits (over rounds of cell division and sometimes transgenerationally) that do not involve changes to the underlying DNA sequence

Epigenetic effects: Transgenerational

VOLUME 84, No. 2 *THE QUARTERLY REVIEW OF BIOLOGY* JUNE 2009

TRANSGENERATIONAL EPIGENETIC INHERITANCE: PREVALENCE, MECHANISMS, AND IMPLICATIONS FOR THE STUDY OF HEREDITY AND EVOLUTION

EVA JABLONKA

The Cohn Institute for the History and Philosophy of Science and Ideas, Tel-Aviv University, Tel-Aviv 69978, Israel

E-MAIL: JABLONKA@POST.TAU.AC.IL

GAL RAZ

The Graduate School of Medicine, Tel-Aviv University, Tel-Aviv 69978, Israel

E-MAIL: GALRAZ@POST.TAU.AC.IL

KEYWORDS

cell memory, epigenetics, induced heritable variations, Lamarckism, microevolution, macroevolution

ABSTRACT

This review describes new developments in the study of transgenerational epigenetic inheritance, a component of epigenetics. We start by examining the basic concepts of the field and the mechanisms that underlie epigenetic inheritance. We present a comprehensive review of transgenerational cellular epigenetic inheritance among different taxa in the form of a table, and discuss the data contained therein. The analysis of these data shows that epigenetic inheritance is ubiquitous and suggests lines of research that go beyond present approaches to the subject. We conclude by exploring some of the consequences of epigenetic inheritance for the study of evolution, while also pointing to the importance of recognizing and understanding epigenetic inheritance for practical and theoretical issues in biology.

Effects from the environment: Prenatal nutrition. the Dutch famine study

PNAS

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[a,f], P. Eline Slagboom[a], and L. H. Lumey[a,1]

Departments of [a]Molecular Epidemiology, [c]Medical Statistics, and [d]Gerontology and Geriatrics, Leiden University Medical Center, Leiden, The Netherlands; [b]Hubert Department of Global Health, Rollins School of Public Health, Emory University Atlanta, GA 30322; [e]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY 10032; and [f]New York State Psychiatric Institute, New York, NY 10032

Edited by Charles R. Cantor, Sequenom Inc., San Diego, CA, and approved September 17, 2008 (received for review July 7, 2008)

Table 2. *IGF2* DMR methylation among individuals exposed to famine late in gestation and their unexposed, same-sex siblings

IGF2 DMR methylation	Mean methylation fraction (SD)				Relative change exposed	Difference in SDs	*P*
	Exposed (n = 62)		Controls (n = 62)				
Average	0.514	0.045	0.519	0.036	−0.9%	−0.12	.64
CpG 1	0.460	0.044	0.464	0.048	−0.9%	−0.09	.68
CpG 2 and 3	0.462	0.039	0.471	0.039	−1.7%	−0.21	.46
CpG 4	0.602	0.085	0.612	0.073	−1.5%	−0.12	.30
CpG 5	0.529	0.060	0.531	0.060	−0.3%	−0.02	.77

P values were obtained using a linear mixed model and adjusted for age.

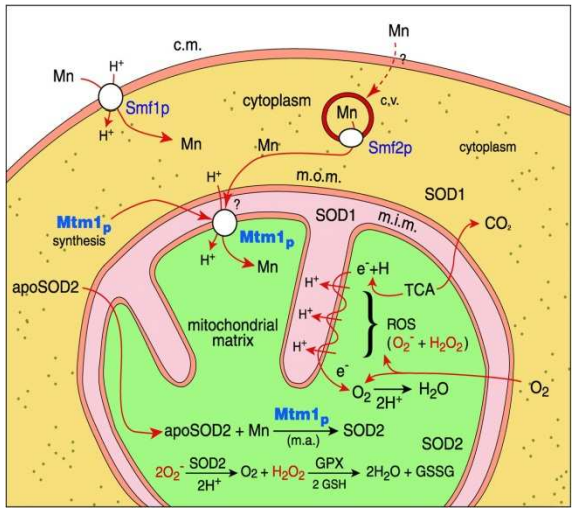
Effects from nutrition, adult: anti oxydative MnSOD

British Journal of Nutrition (2008), page 1 of 7
doi:10.1017/S0007114508047685

Epigenetic regulation of human buccal mucosa mitochondrial superoxide dismutase gene expression by diet

Roman Thaler[1], Heidrun Karlic[2,3], Petra Rust[1] and Alexander G. Haslberger[1]*

[1]*Department of Nutritional Sciences, University of Vienna, Althanstrasse 14, A-1090 Vienna, Austria*
[2]*Ludwig Boltzmann Institute for Leukaemia Research, Hanusch Krankenhaus, Vienna, Austria*
[3]*Hanuschkrankenhaus der Wiener Gebietskrankenkasse, Heinrich Collinstraße 30, A-1140 Vienna, Austria*



Effects from environment, toxins: epitoxicology

Epigenetics and environmental chemicals

Andrea Baccarelli and Valentina Bollati

Laboratory of Environmental Epigenetics, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, University of Milan and IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Milan, Italy

Correspondence to Andrea Baccarelli, MD, PhD, Center of Molecular and Genetic Epidemiology, Department of Environmental and Occupational Health, University of Milan and IRCCS Maggiore Hospital, Mangiagalli and Regina Elena Foundation, Via San Barnaba 8, 20122 Milan, Italy
Tel: +39 02 503 20145; fax: +39 02 503 20103;
e-mail: andrea.baccarelli@unimi.it

Current Opinion in Pediatrics 2009, 21:243–251

Purpose of review
Epigenetics investigates heritable changes in gene expression occurring without changes in DNA sequence. Several epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA expression, can change genome function under exogenous influence. Here, we review current evidence indicating that epigenetic alterations mediate toxicity from environmental chemicals.

Recent findings
In-vitro, animal, and human investigations have identified several classes of environmental chemicals that modify epigenetic marks, including metals (cadmium, arsenic, nickel, chromium, and methylmercury), peroxisome proliferators (trichloroethylene, dichloroacetic acid, and TCA), air pollutants (particulate matter, black carbon, and benzene), and endocrine-disrupting/reproductive toxicants (diethylstilbestrol, bisphenol A, persistent organic pollutants, and dioxin). Most studies conducted so far have been centered on DNA methylation, whereas only a few investigations have studied environmental chemicals in relation to histone modifications and microRNA.

Summary
For several exposures, it has been proved that chemicals can alter epigenetic marks, and that the same or similar epigenetic alterations can be found in patients with the disease of concern or in diseased tissues. Future prospective investigations are needed to determine whether exposed individuals develop epigenetic alterations over time and, in turn, which such alterations increase the risk of disease. Also, further research is needed to determine whether environmental epigenetic changes are transmitted transgenerationally.

Keywords
DNA methylation, environment, epigenetics, histone modification, microRNA

Curr Opin Pediatr 21:243–251

1040-8703

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RESEARCH ARTICLE OPEN ACCESS

Investigating the Epigenetic Effects of a Prototype Smoke-Derived Carcinogen in Human Cells

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Stella Tommasi[1], Sang-in Kim[1], Xueyan Zhong[1], Xiwei Wu[2], Gerd P. Pfeifer[1], Ahmad Besaratinia[1*]

1 Department of Cancer Biology, Beckman Research Institute of the City of Hope National Medical Center, Duarte, California, United States of America, **2** Division of Information Sciences, Beckman Research Institute of the City of Hope National Medical Center, Duarte, California, United States of America

To **add a note**, highlight some text. Hide notes
Make a general comment

Jump to
Abstract
Introduction

Effects from the social environment, stress

Review

Epigenetic programming of the stress response in male and female rats by prenatal restraint stress

Muriel Darnaudéry[a], *Stefania Maccari*[a,b,*,1]

[a]*Perinatal Stress Team, University of Lille 1, 59655 Villeneuve d'Ascq Cedex, France*
[b]*Department Human Physiology and Pharmacology, Sapienza University of Rome, Italy*

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ABSTRACT

Exposure to hostile conditions results in a series of coordinated responses aimed at enhancing the probability of survival. The activation of the hypothalamo-pituitary-adrenocortical (HPA) axis plays a pivotal role in the stress response. While the short-term activation of the HPA axis allows adaptive responses to the challenge, in the long run this can be devastating for the organism. In particular, life events occurring during the perinatal period have strong long-term effects on the behavioral and neuroendocrine response to stressors. In male and female rats exposed to prenatal restraint stress (PRS), these effects include a long-lasting hyperactivation of the HPA response associated with an altered circadian rhythm of corticosterone secretion. Furthermore, male animals exhibit sleep disturbances. In males, these HPA dysfunctions have been reported in infant, young, adult and aged animals, thus suggesting a permanent effect of early stress. Interestingly, after exposure to an intense inescapable footshock, female PRS rats durably exhibit a blunted corticosterone secretion response to stress. In male PRS rats exposed to an alcohol challenge, the HPA axis is similarly hyporesponsive. Rats exposed to PRS also show behavioral disturbances. Both male and female PRS rats show high anxiety levels and depression-like behavior during adulthood, although some studies suggest that female PRS rats present low anxiety levels. With ageing, male and female PRS rats exhibit memory impairments in hippocampus-dependent tasks, while female PRS rats improve their memory performance during adulthood. The gender effect on behavior seems to be related to a reduction in hippocampal plasticity in male PRS rats, and an increase in female PRS rats. Despite the permanent imprinting induced by early stress, the dysfunctions observed after PRS can be reversed by environmental or pharmacological strategies such as environmental enrichment or antidepressive and neurotrophic treatments. Mechanisms underlying the effects of PRS on the offspring remain largely unknown. However, previous studies have demonstrated that maternal glucocorticoids during pregnancy play an important role in the HPA disturbances reported

Epigenetic effects from social environment: care, stress

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Review

Epigenetic mechanisms and the transgenerational effects of maternal care

Frances A. Champagne *

Department of Psychology, Columbia University, Room 406, Schermerhorn Hall, 1190 Amsterdam Avenue, New York, NY 10017, USA

Available online 28 March 2008

Abstract

The transmission of traits across generations has typically been attributed to the inheritance by offspring of genomic information from parental generations. However, recent evidence suggests that epigenetic mechanisms are capable of mediating this type of transmission. In the case of maternal care, there is evidence for the behavioral transmission of postpartum behavior from mothers to female offspring. The neuroendocrine and molecular mediators of this transmission have been explored in rats and implicate estrogen–oxytocin interactions and the differential methylation of hypothalamic estrogen receptors. These maternal effects can influence multiple aspects of neurobiology and behavior of offspring and this particular mode of inheritance is dynamic in response to environmental variation. In this review, evidence for the generational transmission of maternal care and the mechanisms underlying this transmission will be discussed as will the implications of this inheritance system for offspring development and for the transmission of environmental information from parents to offspring.

Keywords: Maternal; Epigenetic; DNA methylation; Estrogen receptor α; Oxytocin; Environment; Cross-fostering

nature REVIEWS NEUROSCIENCE

Research Highlight

Nature Reviews Neuroscience **10**, 836 (December 2009) | doi:10.1038/nrn2768

Epigenetics: Stressed for life

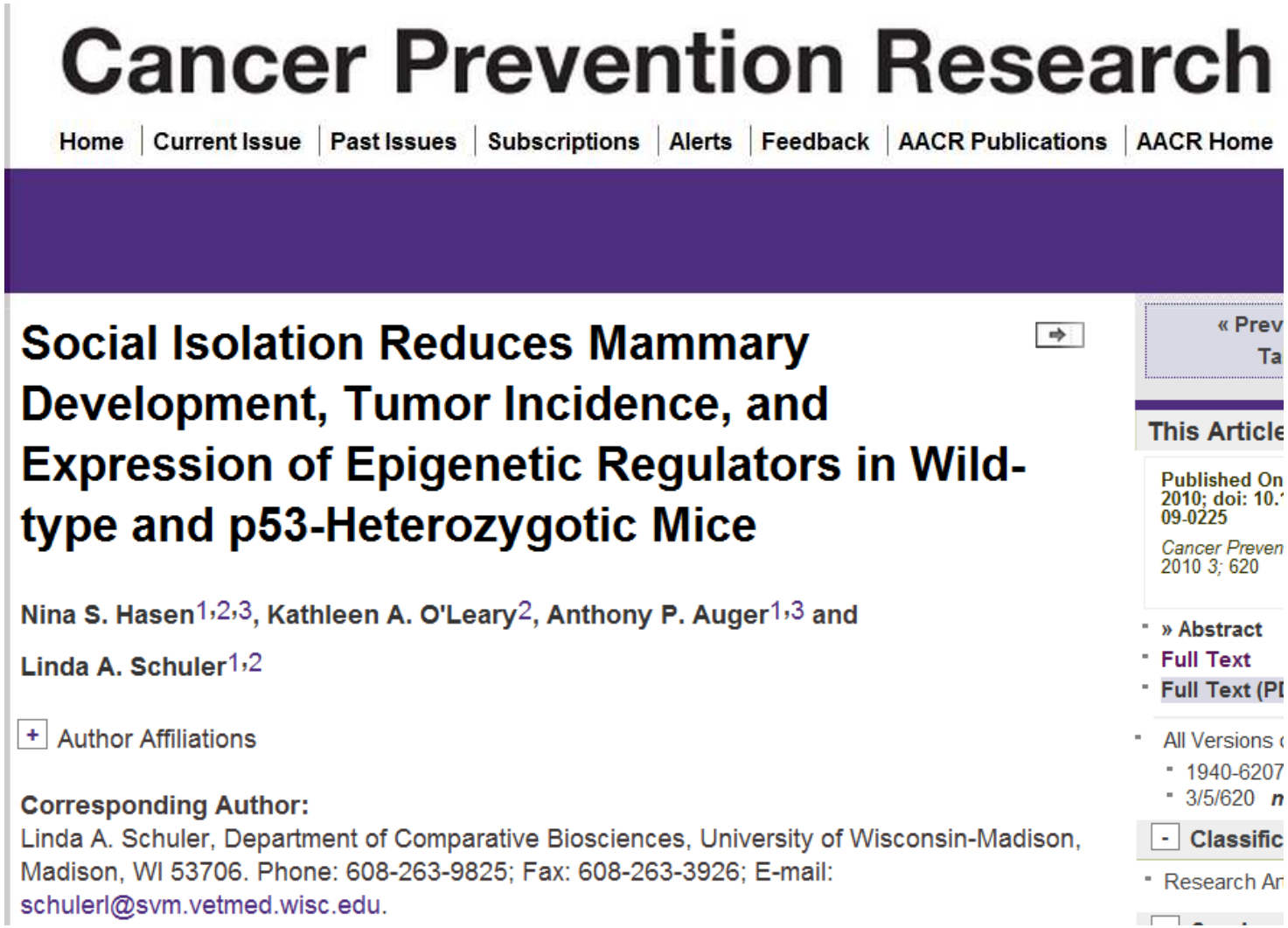
Leonie Welberg

Early-life stress (ELS) has long-lasting effects on the brain, and the epigenetic mechanisms underlying them are beginning to be unravelled. Murgatroyd *et al.* now show that methyl-CpG-binding protein 2 (MeCP2)-mediated regulation of arginine vasopressin (*Avp*) gene expression in parvocellular hypothalamus neurons contributes to the phenotype induced by maternal separation in mice.

PHOTOALTO

As in previous studies, daily 3-hour separation of mouse pups from their mother persistently altered the offspring's hormonal and behavioural responses to stress; this included elevated *Avp* mRNA levels in the hypothalamus. Importantly, treatment with an AVP V1b receptor antagonist reversed the mice's increased stress responses and impaired memory, indicating a central role for AVP in the ELS phenotype.

Soziale isolation changes expression of methyltransferases



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Social Isolation Reduces Mammary Development, Tumor Incidence, and Expression of Epigenetic Regulators in Wild-type and p53-Heterozygotic Mice

Nina S. Hasen[1,2,3], Kathleen A. O'Leary[2], Anthony P. Auger[1,3] and Linda A. Schuler[1,2]

+ Author Affiliations

Corresponding Author:
Linda A. Schuler, Department of Comparative Biosciences, University of Wisconsin-Madison, Madison, WI 53706. Phone: 608-263-9825; Fax: 608-263-3926; E-mail: schulerl@svm.vetmed.wisc.edu.

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Research Ar

Epigenetic effects from the social environment

Frances A. Champagne
Department of Psychology
Columbia University
Room 406 Schermerhorn Hall
1190 Amsterdam Avenue
New York, NY 10027
E-mail: fac2105@columbia.edu

Epigenetic Influence of Social Experiences Across the Lifespan

ABSTRACT: *The critical role of social interactions in driving phenotypic variation has long been inferred from the association between early social deprivation and adverse neurodevelopmental outcomes. Recent evidence has implicated molecular pathways involved in the regulation of gene expression as one possible route through which these long-term outcomes are achieved. These epigenetic effects, though not exclusive to social experiences, may be a mechanism through which the quality of the social environment becomes embedded at a biological level. Moreover, there is increasing evidence for the transgenerational impact of these early experiences mediated through changes in social and reproductive behavior exhibited in adulthood. In this review, recent studies which highlight the epigenetic effects of parent–offspring, peer and adult social interactions both with and across generations will be discussed and the implications of this research for understanding the developmental origins of individual differences in brain and behavior will be explored.* © *2010 Wiley Periodicals, Inc.* Dev Psychobiol

Keywords: *epigenetic; maternal; social; transgenerational; development*

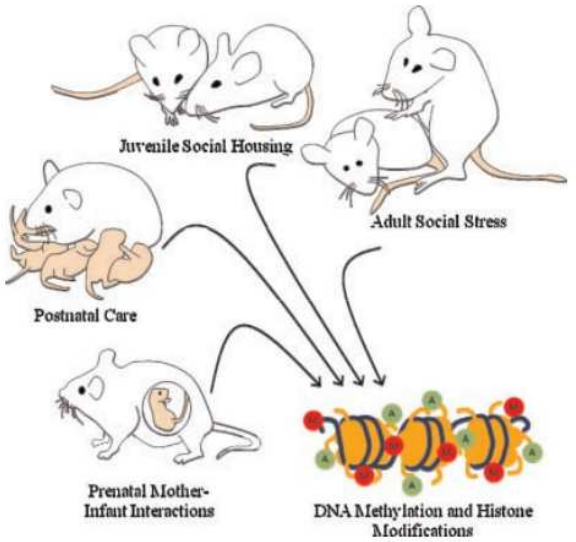


FIGURE 1 Epigenetic consequences of social experiences across the lifespan. Emerging evidence suggests that prenatal environmental exposures, postnatal mother–infant interactions, juvenile social rearing, and adult social stress can alter epigenetic processes such as DNA methylation (red circles) and histone acetylation (green circles)/methylation with long-term consequences for gene expression, physiology, and behavior.

Rev., Dev. Psychobiol. 2010

Live time: Epigenetic diversity: Twin studies

NAS

Epigenetic differences arise during the lifetime of monozygotic twins

Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling‖, Emma Carlsson‖, Pernille Poulsen**, Allan Vaag**, Zarko Stephan††, Tim D. Spector††, Yue-Zhong Wu‡‡, Christoph Plass‡‡, and Manel Esteller*§§

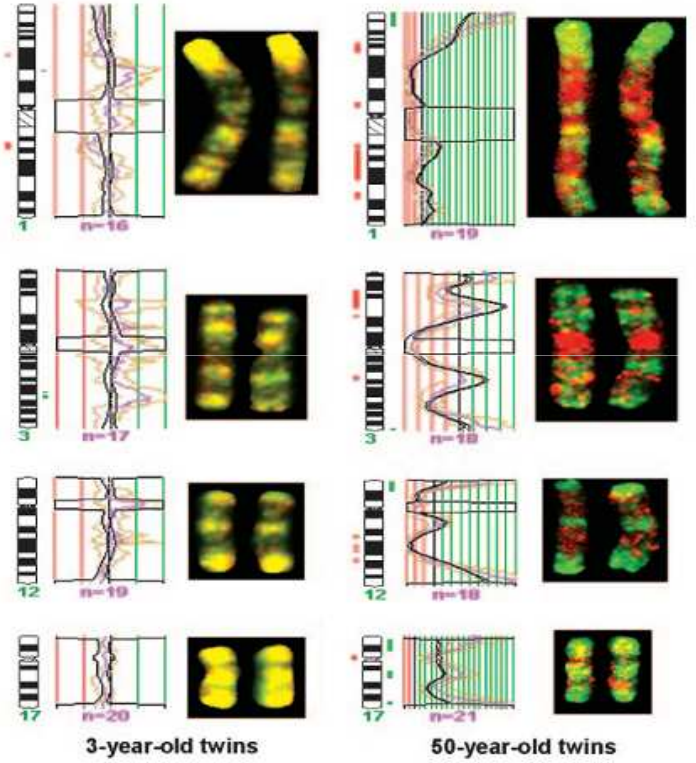
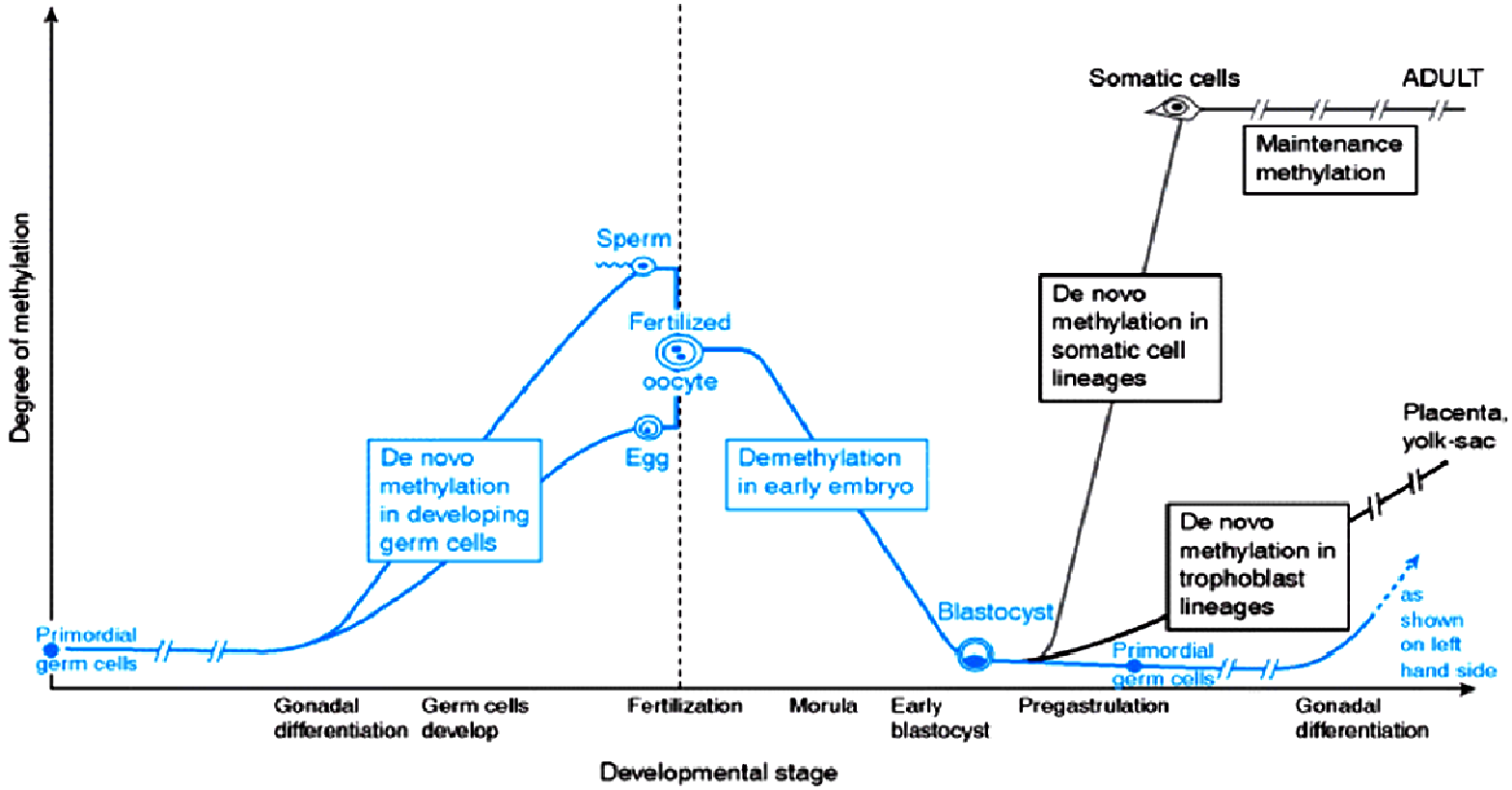


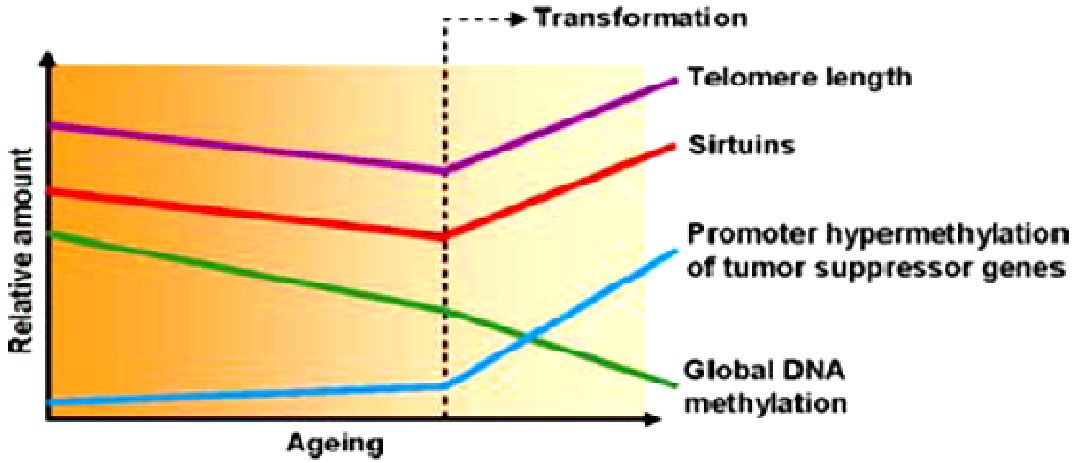
Fig. 3. Mapping chromosomal regions with differential DNA methylation in MZ twins by using comparative genomic hybridization for methylated DNA. Competitive hybridization onto normal metaphase chromosomes of the AIMS products generated from 3- and 50-year-old twin pairs. Examples of the hybridization of chromosomes 1, 3, 12, and 17 are displayed. The 50-year-old twin pair shows abundant changes in the pattern of DNA methylation observed by the presence of green and red signals that indicate hypermethylation and hypomethylation events, whereas the 3-year-old twins have a very similar distribution of DNA methylation indicated by the presence of the yellow color obtained by equal amounts of the green and red dyes. Significant DNA methylation changes are indicated as thick red and green blocks in the ideograms.

Life time Changes in DNA methylation /



Ageing and epigenetics

- A decreased DNA global methylation inversely correlates to an increased genome instability as seen during aging



- Aberrant gene methylation promotes the development of diseases. Hypermethylation of promoters of tumor suppressor genes triggers tumor genesis.
- Epigenetic marks can be seen as an additional (alterable) information level to the genome sequence

Epigenetic changes and neoplastic transformation, progenitor model

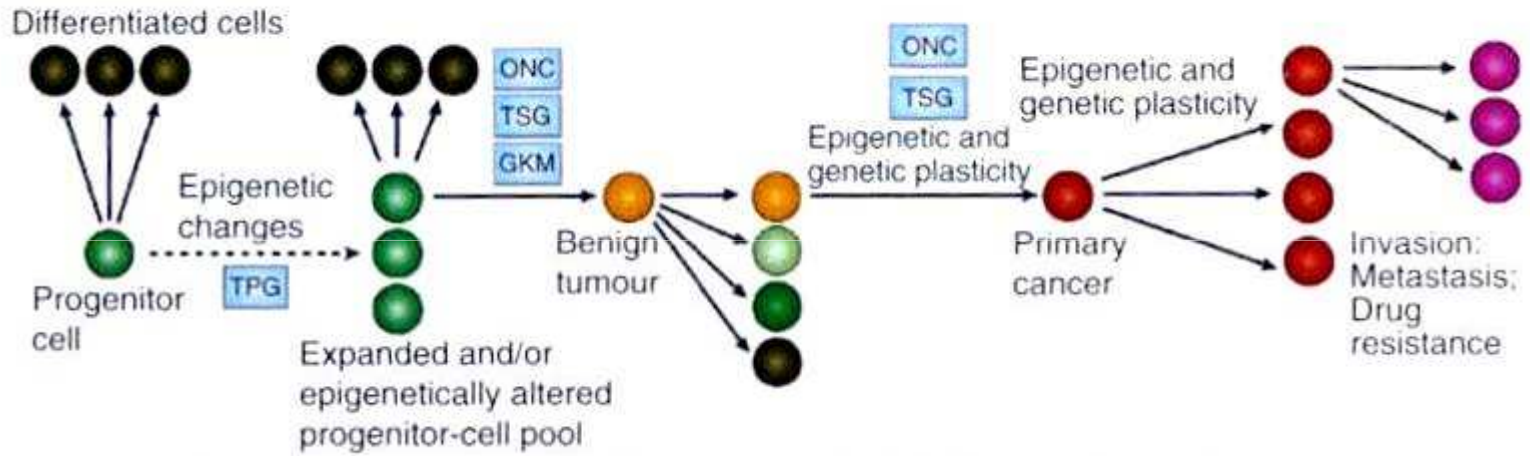


Figure 16.3 The epigenetic progenitor model increases the risk of cancer when such a

Progressive methylation of DNA and subsequent silencing of a subset of genes occurs in normal tissues along side age and time dependent events which predispose these normal cells to neoplastic transformation.

Genome wide methylation: specific genes

Recent Cancer methylation studies predict that hundreds of CPG islands could be methylated in a tumor cell.

However, it is clear that both the genome-wide methylation studies and candidate gene approaches that each tumor type may have its own set of cancer cell type specific genes that are more susceptible to methylation.

Thus each cancer type may have the potential to be typed or classified according to methylation profile.

Different methylation of regulator genes in cancers, markers

P15/P16 Methylation in cancer

Aberrant methylation of cycline dependent kinase inhibitor P16 INK 4a has been frequently detected in many human cancers.

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Gene	Function	Methylation frequency	Rationale	Refs
VHL	Invasion	5–15% renal; 0% prostate; 0% bladder	Tumour suppressor, early, RCC specific	20,109
GSTP1	DNA repair	70–90% prostate; 5–10% bladder; 5–10% renal	Frequent, early, tumour cell specificity tested in multiple studies	14,20,30, 31
INK4a	Cell cycle	3–13% prostate; 7–14% bladder; 10% renal	Tumour suppressor	18,20,110
ARF	Cell cycle	Rare prostate; 8–35% bladder; 17% renal	Tumour suppressor	14,19,20
TIMP3	Invasion	Rare prostate; rare bladder; 58–78% renal	Frequent in RCC	20,111
RARβ2	Growth factor response	53% prostate; 15–68% bladder; 12% renal	Frequent	17,18,20
RASSF1A	RAS signalling	38–53% prostate; 35–54% bladder; 27–45% renal	Frequent, early	17,18,20, 85,112,113
Laminin 5	Invasion	18–44% prostate; 8–45% bladder; NK renal	Tumour cell specificity tested	39,53
APC	Invasion	27–38% prostate; 10–69% bladder; 8–14% renal	Tumour suppressor	14,17,18,20
DAPK	Apoptosis	Rare prostate; 8–45% bladder; rare renal	One of the first genes found to be methylated in cancer	14,17,18,20
REPRIMO	Cell cycle	54% prostate; 19% bladder; NK renal	Adds coverage for prostate cancer	40,114
CDH1	Invasion	27% prostate; 36–63% bladder; 11% renal	Adds coverage for bladder cancer	17,18,20
MGMT	DNA repair	Rare prostate; 5% bladder; 10% renal	One of the first genes found to be methylated in cancer	17,18,20

The frequency of methylation of a given gene can vary between studies because of differences in the overall number, as well as the proportion of cell type, grade and stage of tumours examined. Differences in primer sequences and technology used to determine methylation status also contribute to variation between studies. NK, not known; RCC, renal cell carcinoma.

Epigenetic Therapies?

- Targeting DNA methylation and histone acetylation.
- Decitabine drug (5 – AZa-2 deoxycytidine) has been widely used as a demethylating agent *in vitro* and is used clinically in the treatment of acute leukemias and myelodysplasia.
- Therapeutic strategy was preceded in animal model using anti-sense oligonuleotides against DNA methyl transferase. The studies showed an inhibition of tumor growth and re-expression of p16 in treated animals.
- Combination of histone deacetylase inhibitors (HDAC) e.g. Trichostatin and DNA methy-transferase inhibitor decitabine exerts a synergistic effect on the re-expression of hyper methylated silenced genes such as p15, TIMP and DNA mismatch repair genes.

Diets for prevention and Co- Therapy ?

Diet and Epigenetics

Examples of dietary ingredients with epigenetic and chromatin remodeling properties

- Sulforanes from Brassica – HDAC inhibitors
- EGCG from green tea – DNA demethylation
- Genistein from soy – DNA methylation/demethylation
- Resveratrol from red grapes – affects NAD^+- dependent histone deacetylases (i.e., SIRT1) that deacetylates histones and regulatory proteins like PGC-1α
- Lunasin from soy – chromatin binding peptide and inhibitor of histone acetylation

Understanding cancer and epigenetics: also histones, miRNAS,...a long way to go ?

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Editor's Summary

30 June 2005

Histones in cancer

Reports of altered epigenetic histone modifications in cancer cells have focused on individual gene promoters and so far none of these changes has been related to clinical outcome. Now aberrations of 'global' histone modification have been observed in prostate tumour patients. These do relate to clinical outcome, and suggest a useful means of prognosis.

NEWS AND VIEWS

Cancer: A changing global view

Barbara Marte

doi: 10.1038/4351172b

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LETTER

Global histone modification patterns predict risk of prostate cancer recurrence

David B. Seligson, Steve Horvath, Tao Shi, Hong Yu, Sheila Tze, Michael Grunstein and Siavash K. Kurdistani

doi: 10.1038/nature03672

First paragraph | Full Text | PDF (356K) | Supplementary information

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miRNA: The New Gene Silencer: miRNA and Cancer Progression

Authors and Disclosures

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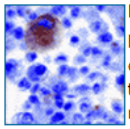
miRNA and Cancer Progression

A series of studies published during the last 2 to 3 years have revealed the association of miRNA expression with adverse outcome in a variety of human tumors.[3] The profiles of miRNA expression have been linked to aggressive cancers with advanced disease detected at diagnosis.[36] The study of miRNAs and cancer progression has focused on 3 major biologic pathways: cell adhesion, angiogenesis, and cell matrix digestion and signaling.[3]

Cell Adhesion

Integrins, CD44, and E-cadherin have been widely studied in breast cancers.[37] Gain of E-cadherin expression has been associated with the lobular phenotype in invasive breast cancer, whereas loss of E-cadherin expression in invasive ductal carcinoma is linked to high tumor grade and poor patient outcome.[38] Loss of E-cadherin expression has also been associated with an adverse prognosis in a wide variety of gastrointestinal, endocrine, pulmonary, and genitourinary carcinomas. To date, the miRNA, mir-9, has been found to regulate E-cadherin expression.[3] However, studies of mir-9 expression in human cancers have not reached consensus, with increased mir-9 expression associated with breast carcinoma[16] and with lung cancer in 1 study[34] but down-regulated in another lung cancer study.[15] Loss of E-cadherin expression is an adverse prognostic factor in melanoma[39] and is a candidate for miRNA association Figure 3.

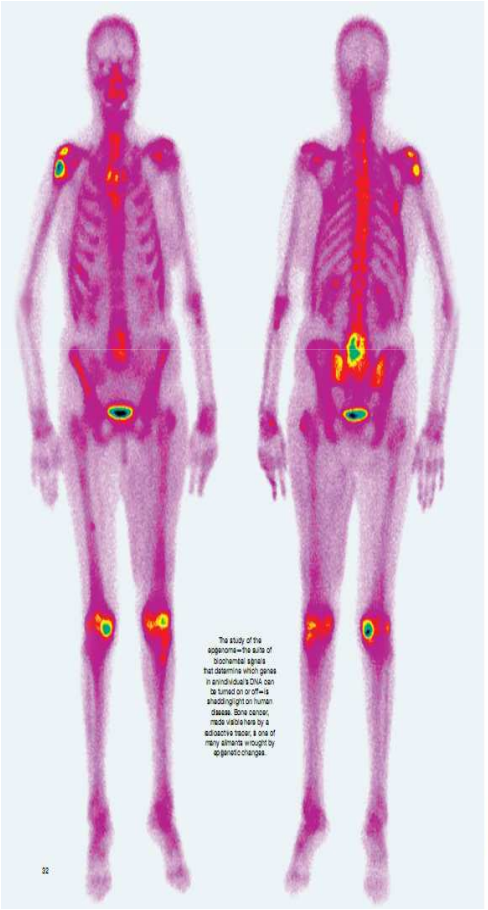


(Enlarge Image)

Figure 3.

E-cadherin protein expression regulated by microRNA (miRNA), miR-200c, in the human breast cell line, MDA-MB-231. miR-200c has variable expression in mammalian cell lines and is believed to target the zinc finger transcription factor TCF8 (ZEB1, ÔEF-1), whose expression down-regulates E-cadherin expression.[46] The human breast cancer line MDA-MB-231 (estrogen receptor–negative breast cancer) expresses TCF8 and does not express miR-200c or E-cadherin (A, E-cadherin, ×200). The ectopic expression of miR-200c in this cell line reduced levels of TCF8 and restored E-cadherin expression (B, ×400). If loss of miR-200 has a role in the transition from in situ to invasive carcinoma, restoration of miRNA expression could be potential therapy for some patients with breast cancer.

Conclusions



The study of the epigenome—the suite of biochemical signals that determine which genes in an individual's DNA can be turned on or off—is shedding light on human disease. Bone cancer, made visible here by a radioactive tracer, is one of many ailments wrought by epigenetic changes.

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DNA IS NOT DESTINY

The new science of epigenetics rewrites the rules of disease, heredity, and identity

By Ethan Watters

Back in 2000, Randy Jirtle, a professor of radiation oncology at Duke University, and his postdoctoral student Robert Waterland designed a groundbreaking genetic experiment that was simplicity itself. They started with pairs of fat yellow mice known to scientists as agouti mice, so called because they carry a particular gene—the agouti gene—that in addition to making the rodents ravenous and yellow renders them prone to cancer and diabetes. Jirtle and Waterland set about to see if they could change the unfortunate genetic legacy of these little creatures.

Typically, when agouti mice breed, most of the offspring are identical to the parents: just as yellow, fat as pincushions, and susceptible to life-shortening disease. The parent mice in Jirtle and Waterland's experiment, however, produced a majority of offspring that looked altogether different. These young mice were slender and mousy brown. Moreover, they did not display their parents' susceptibility to cancer and diabetes and lived to a sorry old age. The effects of the agouti gene had been virtually erased.

Remarkably, the researchers effected this transformation without altering a single letter of the mouse's DNA. Their approach instead was radically straightforward—they changed the moms' diet. Starting just before conception, Jirtle and Waterland fed a test group of mother mice a diet rich in methyl donors, small chemical clusters that can attach to a gene and turn it off. These molecules are common in the environment and are found in many foods, including onions, garlic, beets, and in the food supplements often given to pregnant women. After being consumed by the mothers, the methyl donors worked their way into the developing embryos' chromosomes and onto the critical agouti gene. The mothers passed along the agouti gene to their children intact, but thanks to their methyl-rich pregnancy diet, they had added to the gene a chemical switch that dimmed the gene's deleterious effects.

"It was a little eerie and a little scary to see how something as subtle as a nutritional change in the pregnant mother rat could have such a dramatic impact on the gene expression of the baby," Jirtle says. "The results showed how important epigenetic changes could be."

Our DNA—specifically the 25,000 genes identified by the Human Genome Project—is now widely regarded as the instruction book for the human body. But genes themselves need instructions for what to do, and where and when to do it. A human liver cell contains the same DNA as a brain cell, yet somehow it knows to code only those proteins needed for the functioning of the liver. Those instructions are found not in the letters of the DNA itself but on it, in an array of chemical markers and switches, known collectively as the epigenome, that lie along the length of the double helix. These epigenetic switches and markers in turn help switch on or off the expression of particular genes. Think of the epigenome as a complex software code, capable of inputing the DNA hardware to manufac-

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Learn:

Role of epigenetic methylation, histones, mi RNAs
In tissues, ageing, toxins…..

Cooperation between genetics, epigenetics and environment

Transgenerational epigenetics: responsibility !

Thank you,….

Epigenetics and Human Health
Linking Hereditary, Environmental and Nutritional Aspects

Editor: DR. ALEXANDER HASLBERGER
University of Vienna, Austria

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The consequences of hereditary factors on human health and their interaction with environmental, nutritional and life style factors are topics which are at the center of public, governmental and scientific interest.

This handbook and ready reference work features an holistic introduction by Paolo Vineis and 19 contributions from leading scientists. After introducing the concept of epigenetics, the book provides a multidisciplinary overview of the main research on epigenetics. The volume includes transdisciplinary links between molecular epidemiology, nutrigenomics, biobank research, toxicology, environmental health, nutrition and medical progress in cancer and neurodegenerative diseases. It also covers methods, strategies and research developments in epigenetics. A special focus of the book is on disease prevention and treatment.

This invaluable reference work is of interest to all healthcare-related professionals as well as nutritionists, and the medical community concerned with disease prevention.

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Epigenetics and Human Health

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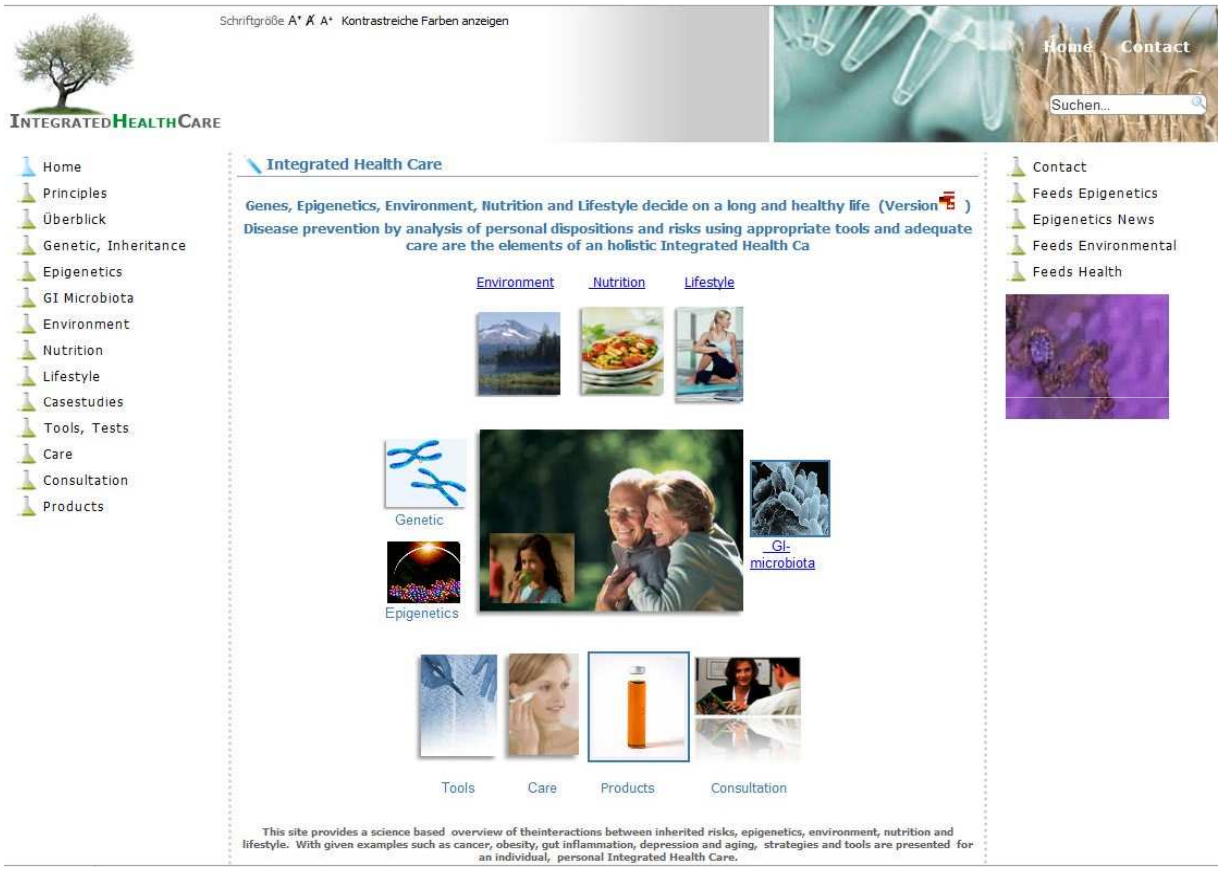

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