Centro Universitario Rivera

SEDE TACUAREMBÓ

CENUR NORESTE

UNIVERSIDAD DE LA REPÚBLICA URUGUAY

6ta Clase

EPIGENÉTICA

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CONTENIDO

EFECTOS DEL AMBIENTE EN EL CONTROL EPIGENÉTICO

- Dieta:
  - Humanos
  - Ratones

- Efectos paternos: compuestos químicos

- Cuidado materno

26 grados

Histone H3 lysine 27 (H3K27) demethylase KDM6B

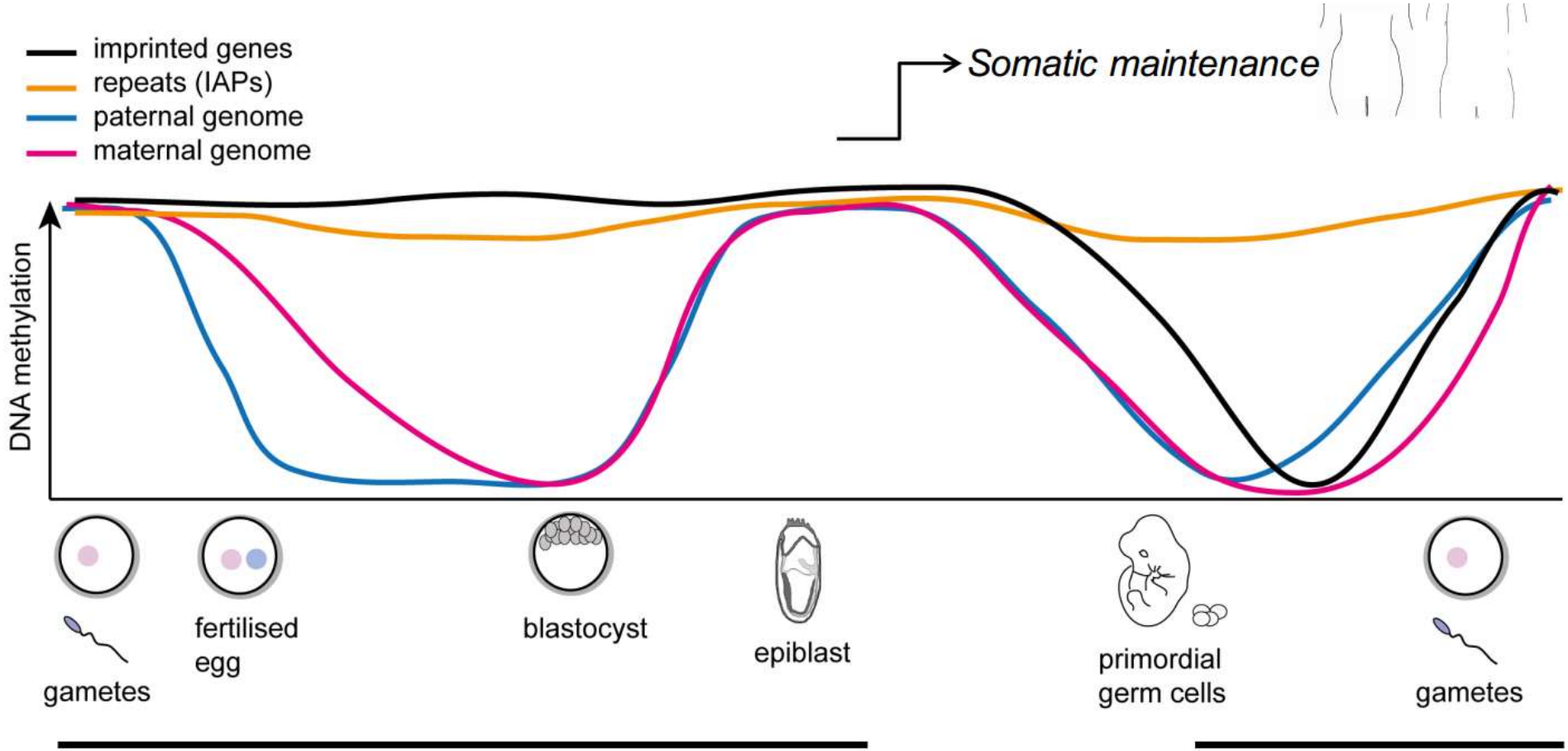
Elimina la trimetilation of H3K27

Dmrt1 = **Doublesex and mab-3 related transcription factor 1**

Jalea Real

Ácido graso: (*E*)-10-hidroxy-2-decenoico (10HDA).

HDACi
Inhibidor de deacetilasa de histonas


imprinted genes
repeats (IAPs)
paternal genome
maternal genome
Somatic maintenance
DNA methylation
gametes
fertilised egg
blastocyst
epiblast
primordial germ cells
gametes

HAMBRUNA HOLANDESA 1944 - 1945

580 calorías por día.

La poca ingesta de alimentos en el periodo periconcepcional se asoció con el aumento de trastornos metabólicos, diabetes, obesidad y enfermedades cardiovasculares en los hijos.

Los hijos de quienes no estuvieron sometidos a la restricción de alimentos no presentaron estas caracteristicas.

Periodos sensibles, durante la embriogénesis/gametogenesis.

HAMBRUNA HOLANDESA 1944 - 1945

Se encontraron cambios en la metilación del ADN de algunos genes: *IGF2*, *GNAS* y *MEG* (genes de impronta).

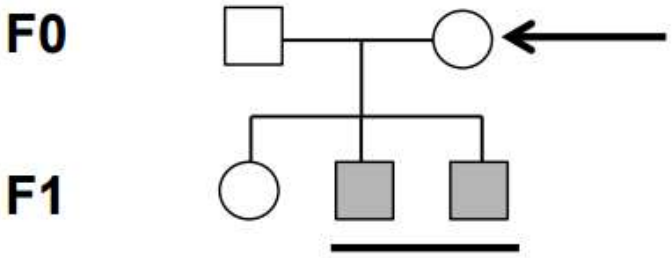
Los datos originales sugerían que había un efecto transgeneracional, pero estudios recientes sugieren que no.

EFECTOS PATERNOS: COMPUESTOS QUÍMICOS

Vinclozolina **(*RS*)-3-(3,5-Dichlorophenyl)-5-methyl-5-vinyloxazolidine-2,4-Dione**

Fungicida usado en la producción de frutas, vegetales y vino.

Es un disrruptor endocrino, anti-androgénico.

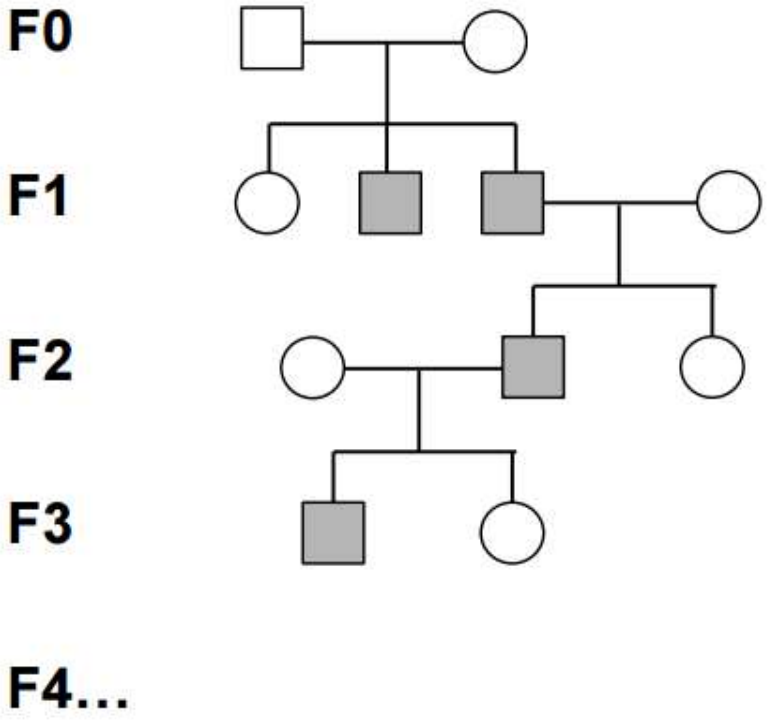


Exposición durante la mitad de la gestación

Produce subfertilidad, oligozoospermia, en 90% de los machos (alta penetrancia)

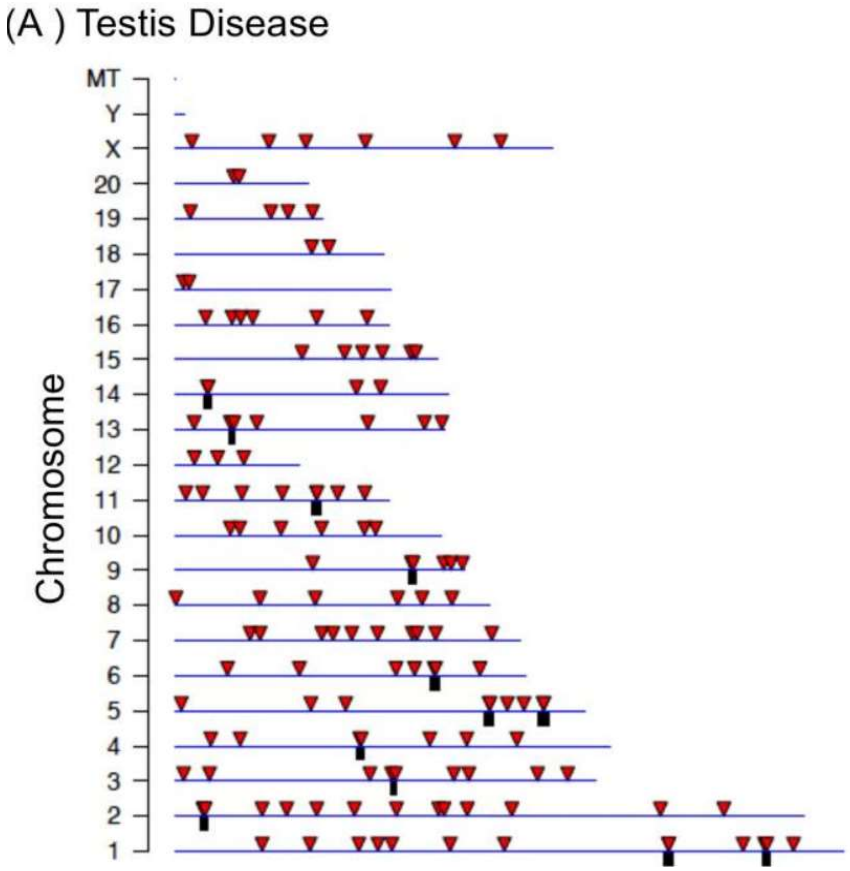
EFECTOS PATERNOS: COMPUESTOS QUÍMICOS

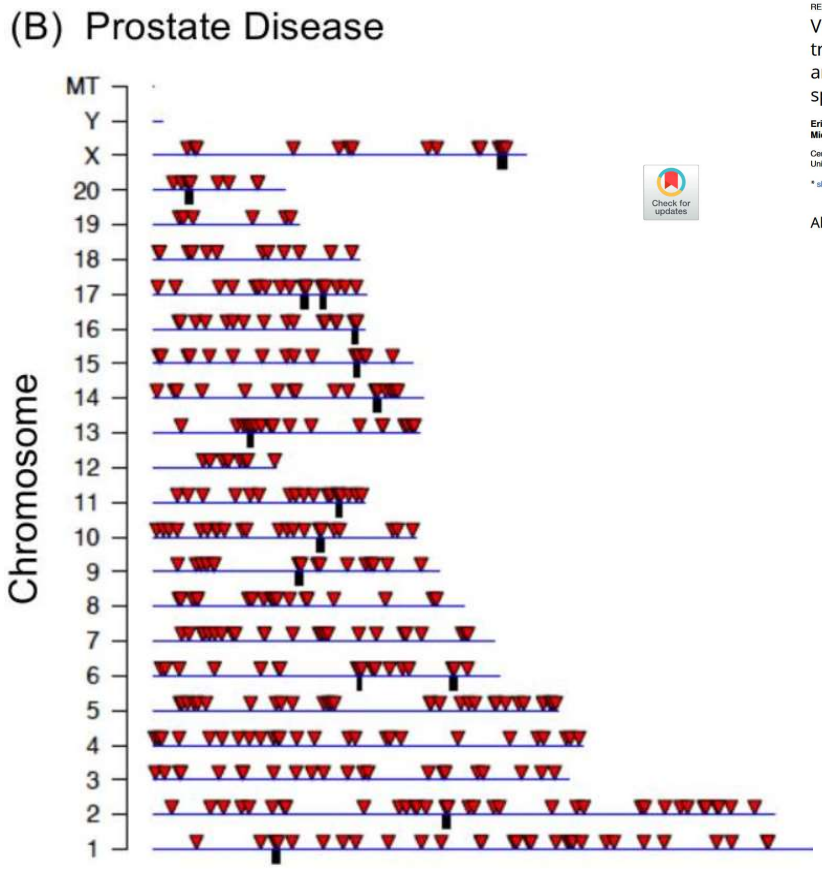
Vinclozolina (Ronilan, Curalan, Vorlan, Touche): **(*RS*)-3-(3,5-Dichlorophenyl)-5-methyl-5-vinyloxazolidine-2,4-Dione**



Desde F1-F4: oligozoospermia, en 90% de los machos (alta penetrancia)

Vinclozolina (Ronilan, Curalan, Vorlan, Touche): **(*RS*)-3-(3,5-Dichlorophenyl)-5-methyl-5-vinyloxazolidine-2,4-Dione**





PLOS ONE

RESEARCH ARTICLE

Vinclozolin induced epigenetic transgenerational inheritance of pathologies and sperm epimutation biomarkers for specific diseases

Eric Nilsson, Stephanie E. King, Margaux McBirney, Deepika Kubsad, Michelle Pappalardo, Daniel Beck, Ingrid Sadler-Riggleman, Michael K. Skinner*

Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, WA, United States of America

* skinner@wsu.edu

Abstract

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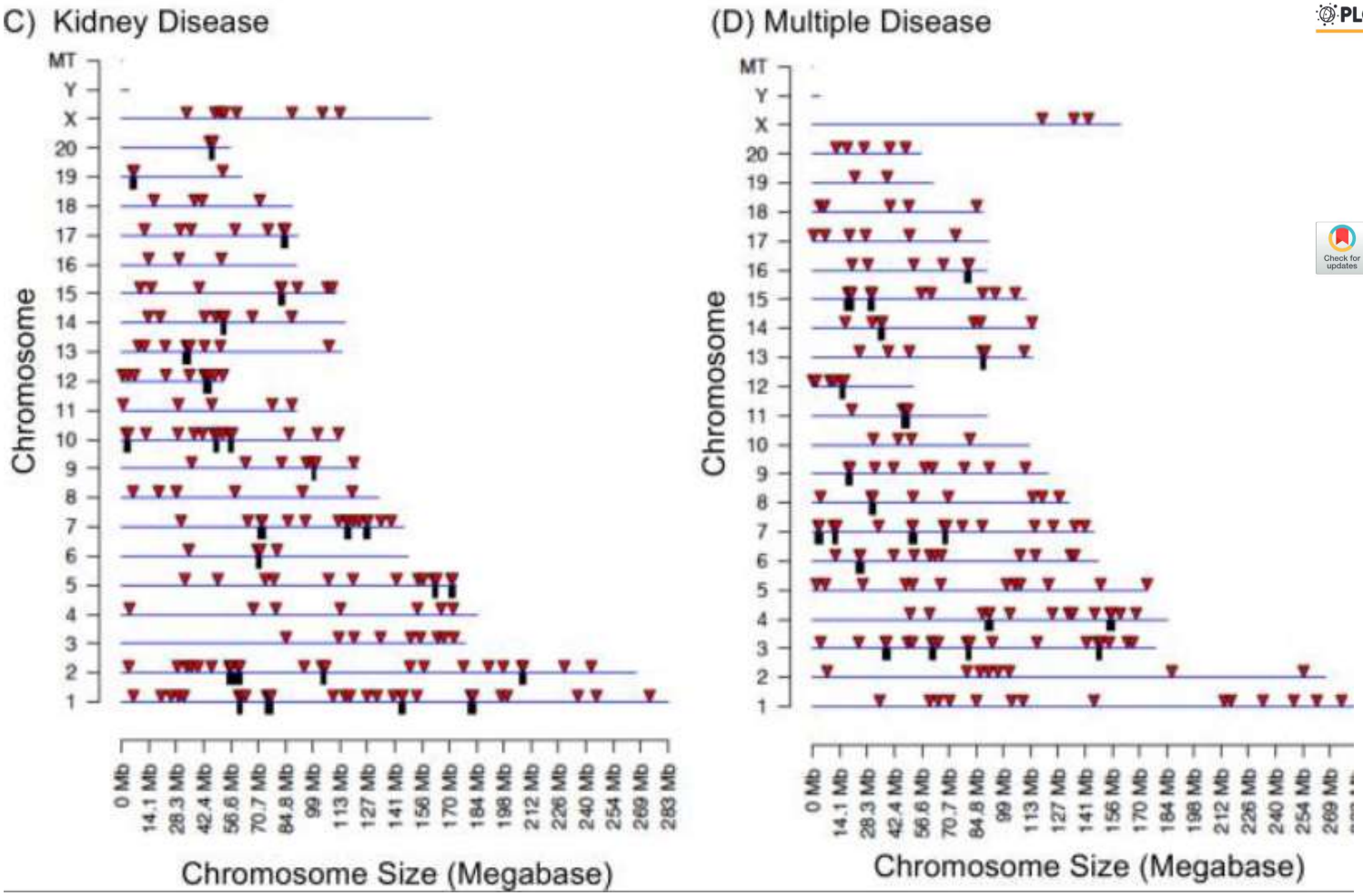

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Check for updates

Abstract

Metoxicloro: 1,1’-(2,2,2-Trichloroethane-1,1-diyl)bis(4-methoxybenzene)

Insecticida, pesticida usado en reemplazo del DDT.

Es un disrruptor endocrino estrogénico y anti-androgénico.

Asociado con disminución de la fertilidad, disminución en el tamaño de los ovarios, aumento en el ovario poliquístico.

Inhibe la producción de testosterona.

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PLOS ONE

Pesticide Methoxychlor Promotes the Epigenetic Transgenerational Inheritance of Adult-Onset Disease through the Female Germline

Mohan Manikkam, M. Muksitul Haque, Carlos Guerrero-Bosagna, Eric E. Nilsson, Michael K. Skinner*

Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, Washington, United States of America

Abstract

Environmental compounds including fungicides, plastics, pesticides, dioxin and hydrocarbons can promote the epigenetic transgenerational inheritance of adult-onset disease in future generation progeny following ancestral exposure during the critical period of fetal gonadal sex determination. This study examined the actions of the pesticide methoxychlor to promote the epigenetic transgenerational inheritance of adult-onset disease and associated differential DNA methylation regions (i.e. epimutations) in sperm. Gestating F0 generation female rats were transiently exposed to methoxychlor during fetal gonadal development (gestation days 8 to 14) and then adult-onset disease was evaluated in adult F1 and F3 (great-grand offspring) generation progeny for control (vehicle exposed) and methoxychlor lineage offspring. There were increases in the incidence of kidney disease, ovary disease, and obesity in the methoxychlor lineage animals. In females and males the incidence of disease increased in both the F1 and the F3 generations and the incidence of multiple disease increased in the F3 generation. There was increased disease incidence in F4 generation reverse outcross (female) offspring indicating disease transmission was primarily transmitted through the female germline. Analysis of the F3 generation sperm epigenome of the methoxychlor lineage males identified differentially DNA methylated regions (DMR) termed epimutations in a genome-wide gene promoters analysis. These epimutations were found to be methoxychlor exposure specific in comparison with other exposure specific sperm epimutation signatures. Observations indicate that the pesticide methoxychlor has the potential to promote the epigenetic transgenerational inheritance of disease and the sperm epimutations appear to provide exposure specific epigenetic biomarkers for transgenerational disease and ancestral environmental exposures.

Citation: Manikkam M, Haque MM, Guerrero-Bosagna C, Nilsson EE, Skinner MK (2014) Pesticide Methoxychlor Promotes the Epigenetic Transgenerational Inheritance of Adult-Onset Disease through the Female Germline. PLoS ONE 9(7): e102091. doi:10.1371/journal.pone.0102091

Editor: W. Steven Ward, John A. Burns School of Medicine, United States of America

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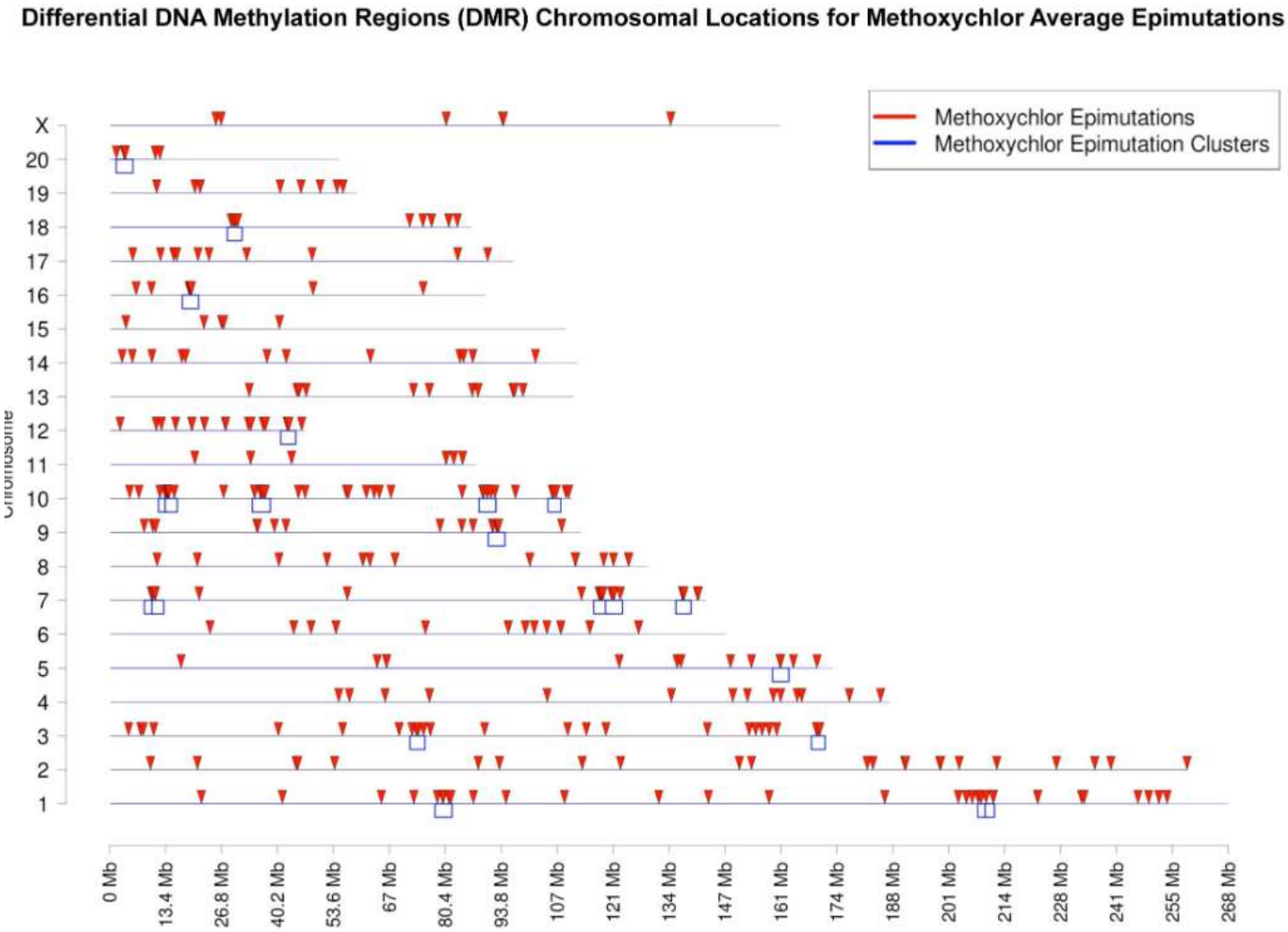

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Table 2. Pathway DMR associations.

Cellular Process or Pathway Name	Number of DMR Associated Genes	Number of Genes in Pathway	Fisher's Exact p-Value*
Olfactory transduction	6	15	3.24E-07
Steroid hormone biosynthesis	7	46	4.12E-05
Chemical carcinogenesis	6	35	0.000074
Ribosome	10	143	0.0007986
Drug metabolism - cytochrome P450	4	23	0.001175
Antigen processing and presentation	5	41	0.001508
Autoimmune thyroid disease	4	25	0.001625
Metabolic pathways	32	2435	0.00308
Phagosome	7	95	0.003587
Metabolism of xenobiotics by cytochrome P450	4	32	0.004123
Herpes simplex infection	8	126	0.004739
Graft-versus-host disease	3	17	0.004838
Endocytosis	8	139	0.008446
Allograft rejection	3	22	0.01015
Fatty acid elongation	3	22	0.01015
HTLV-I infection	10	205	0.01059
Type I diabetes mellitus	3	24	0.01294
Systemic lupus erythematosus	4	45	0.01385
Cell adhesion molecules (CAMs)	6	99	0.01699
Retinol metabolism	4	48	0.01724
Biosynthesis of unsaturated fatty acids	3	30	0.0237
Transcriptional misregulation in cancer	7	147	0.0336
Cardiac muscle contraction	4	60	0.03569
Viral myocarditis	3	38	0.04368
Phosphatidylinositol signaling system	3	39	0.04661
Wnt signaling pathway	5	98	0.05306

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BPA (Bisfenol – A)

Alteración en la espermatogénesis

Efecto transgeneracional

Alteración en la metilación de genes asociados con cáncer de próstata.

frontiers in Endocrinology

REVIEW
published: 30 July 2020
doi: 10.3389/fendo.2020.00453

Bisphenol A-Induced Epigenetic Changes and Its Effects on the Male Reproductive System

Federica Cariati[1,2], Luigi Carbone[3], Alessandro Conforti[3], Francesca Bagnulo[2], Stefania Ramona Peluso[2], Consolata Carotenuto[4], Cira Buonfantino[5], Erminia Alviggi[6], Carlo Alviggi[2,3,†] and Ida Strina[2,3†]*

[1] CEINGE-Biotecnologie Avanzate s.c.a.r.l., Naples, Italy, [2] Fertility Unit, Maternal-Child Department, AOU Policlinico Federico II, Naples, Italy, [3] Department of Neuroscience, Reproductive Sciences and Odontostomatology, Federico II University, Naples, Italy, [4] Molecular Medicine and Medical Biotechnology Department, Federico II University, Naples, Italy, [5] Department of Public Health, Federico II University, Naples, Italy, [6] GENERA Centers for Reproductive Medicine, Clinica Fuesch, Naples, Italy, [7] Endocrinology and Experimental Oncology Institute (IEOS), National Research Council, Naples, Italy

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TABLE 6 | Characteristics of the studies which analyzed the risk of prostate cancer induced by BPA exposure.

Epigenetic modification	Effects	Study type	Species	References
DNA methylation	Hypomethylation of the prostate cancer gene (PDE4D4)	*In vivo/In vitro*	Human	(59)
DNA methylation	• Aberrant NSBP1 promoter demethylation and transcriptional overexpression persisting in adult life • Aberrant HPCAL1 promoter hypermethylation and transcriptional suppression with a little degree of gene expression in adult life • High expression of DNMT3A and DNMT3B in early life, diminishing with aging • Involvement in early-life reprogramming of DNA methylation patterns in target genes such as NSBP1 or HPCAL1	*In vitro*	Rat	(63)
DNA methylation	DNA methylation-mediated gene expression of 6 genes linked to embryonic stem cell pluripotency	*In vivo*	Rat	(64)
DNA methylation	DNA hypomethylation of genes that confer carcinogenic risk	*In vivo*	Rat	(65)
DNA methylation	Deregulation of EZH2, DNMT1, DNMT3B and UHRF1	*In vitro*	Human	(66)
DNA methylation	• Expression levels of p16 gene decreased significantly after promoter hypermethylation • p16-related histone modifications • Dose-dependent promoter hypermethylation of tumor suppressor genes as BCR, PTGS2, TIMP3, and ZMYDN10 • Hypomethylation of PDLIM4 and PYCARD • Demethylation of GSTP1, LOX, MGMT, NEUROG, and TSC2 • Significant decrease of gene expression levels and downregulation of KDM5B and NSD1 measured in RT-PCR (real-time polymerase chain reaction)	*In vitro*	Human	(67)

BPA (Bisfenol – A)

Epigenetic modifications	Effects	Study type	Species	References
Histone methylation	• Decrease of DNMT • Reduction in the global DNA methylation levels in spermatogonia	*In vitro*	Mouse	(30)
DNA methylation	• No effect on DNA methylation of imprinted genes (IGF2, IGF2R, PEG3. and H19) in germ cells • Increase in ERα expression • Impairment of meiotic progression of germ cells • Decrease in quality and quantity of spermatozoa	*In vivo*	Mice	(31)
DNA methylation	• Reduction in DNA replication capacity • Alteration of the genome-wide DNA methylation level in GC-2 cells • Alteration of DNMT expression levels • Regulation of MYBPH and PRKCD methylation	*In vivo*	Mouse	(32)
DNA methylation	Promotion of the DNA methylation process in the testes by novo synthesis of glutathione and oxidative stress	*In vivo*	Fish	(33)
DNA methylation	Alteration of the global DNA methylation level of gonads	*In vivo*	Fish	(34)
DNA methylation	• Alteration of the global DNA methylation level of gonads • Transcriptional change of genes (DNMTS, GNMT, and TEST)	*In vivo*	Fish	(35)
DNA methylation	Variation in DNA methylation levels	*In vivo*	Fish	(36)
DNA methylation	Hypermethylation of global DNA in the testes	*In vivo*	Fish	(37)
DNA methylation	Global DNA demethylation	*In vivo*	Fish	(38)
DNA methylation	• Decrease of spermatocytes • Increase in apoptosis • Downregulation of CCNB1 and SYCP3 • Upregulation of GPER1 and ESRRGA receptors • Miss-regulation of epigenetic remodeling enzyme transcripts • DNA hypermethylation • H3K27me3 demethylation • Increase in histone acetyltransferase activity	*In vitro*	Fish	(39)
DNA methylation	• Di-methylation of lysine K4 on histones H3 • Impairment of motility, concentration, and mitochondrial activity in sperm	*In vivo*	Human	(40)
DNA methylation	Trimethylation of histone 3 (H3K27me3, H3K4me2, or H3K4me3) in sperm	*In vivo*	Human	(41)
DNA methylation	Hypomethylation of LINE-1	*In vivo*	Human	(42)
DNA methylation	• Decrease in sperm LINE-1 methylation status • Association between BPA urinary levels and low semen quality	*In vivo*	Human	(43)
DNA methylation	• Correlation between 5hmC rates of AChE and low sperm motility • Correlation between HoxC4 promoters and sperm concentration	*In vivo*	Human	(44)

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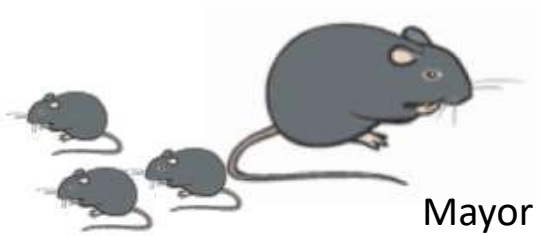
CUIDADO MATERNO Y EPIGENÉTICA

Si lamía

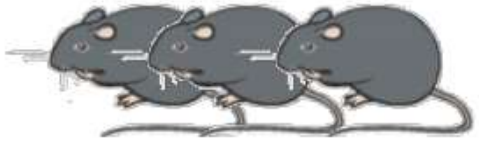
Menos metilación del **GR**

No lamía

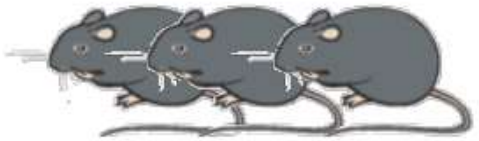


Mayor metilación del **GR**

Presentaron cambios en los **GR** del hipocampo

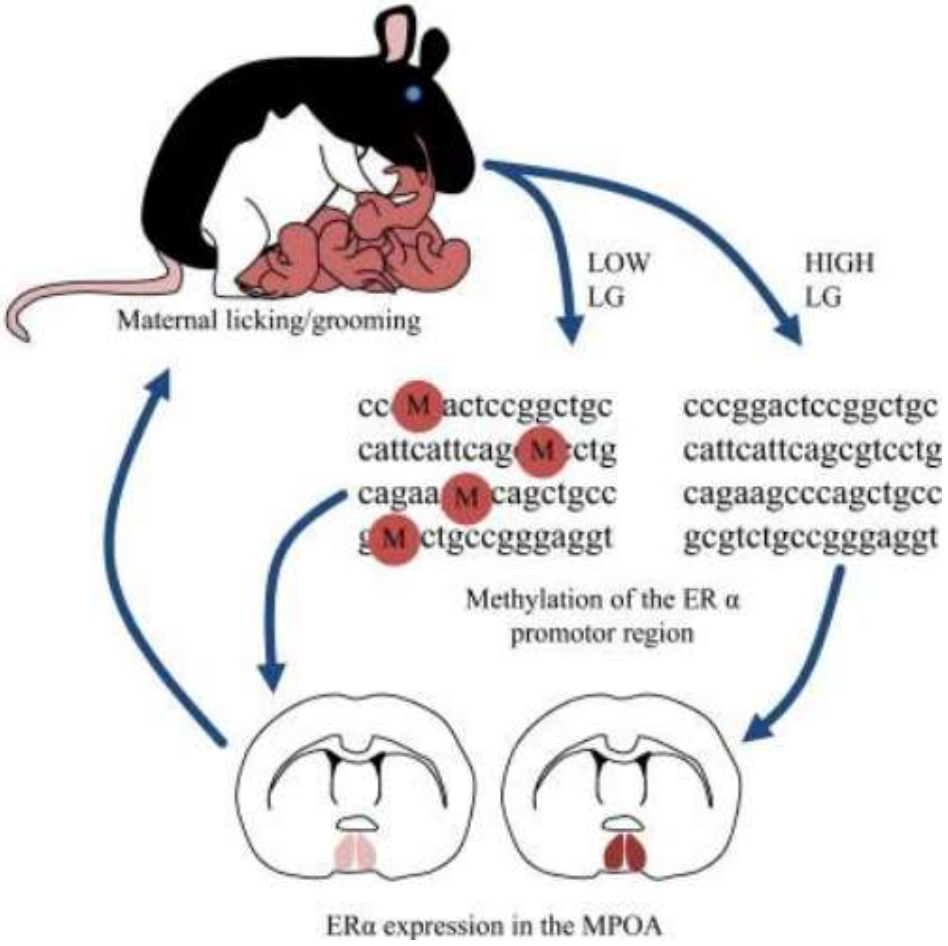


Adultos menos estresados



Adultos estresados

CUIDADO MATERNO Y EPIGENÉTICA

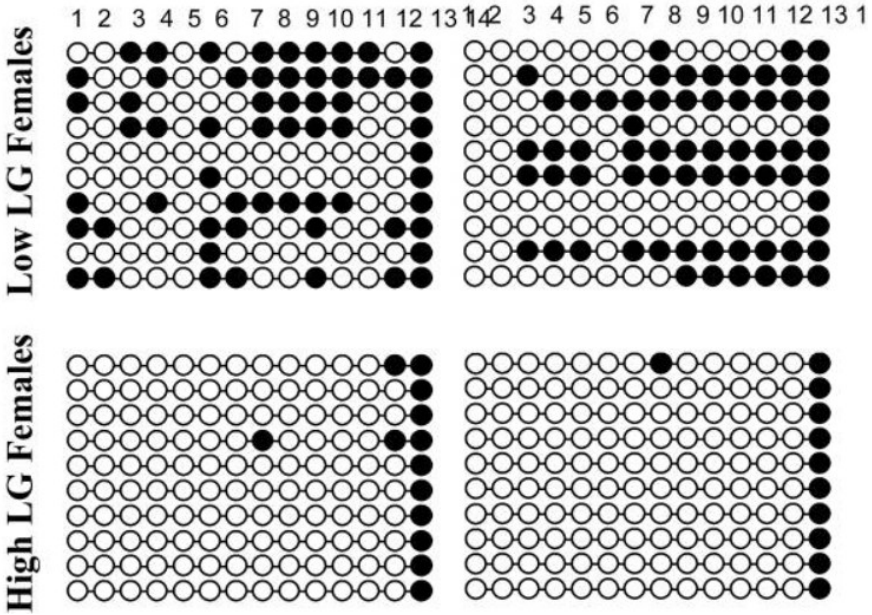


Epigenetic Mechanisms and the Transgenerational Effects of Maternal Care

Frances A. Champagne
Department of Psychology, Columbia University, New York NY 10027

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.



PREGUNTAS

¿Qué proporción del genoma es sensible a los factores ambientales?

¿Qué proporción de la población es genéticamente susceptible?

¿Podrían las alteraciones genéticas estar relacionadas con las epigenéticas?

¿Qué proporción de cambios pueden ser heredados?

Hum Genet (2012) 131:1565–1589
DOI 10.1007/s00439-012-1189-8

REVIEW PAPER

Environmental epigenetics: prospects for studying epigenetic mediation of exposure–response relationships

Victoria K. Cortessis · Duncan C. Thomas · A. Joan Levine · Carrie V. Breton · Thomas M. Mack · Kimberly D. Siegmund · Robert W. Haile · Peter W. Laird

Received: 21 February 2012 / Accepted: 7 June 2012 / Published online: 28 June 2012

Abstract Changes in epigenetic marks such as DNA methylation and histone acetylation are associated with a broad range of disease traits, including cancer, asthma, metabolic disorders, and various reproductive conditions. It seems plausible that changes in epigenetic state may be induced by environmental exposures such as malnutrition, tobacco smoke, air pollutants, metals, organic chemicals, other sources of oxidative stress, and the microbiome, particularly if the exposure occurs during key periods of development. Thus, epigenetic changes could represent an important pathway by which environmental factors influence disease risks, both within individuals and across generations. We discuss some of the challenges in studying epigenetic mediation of pathogenesis and describe some unique opportunities for exploring these phenomena.

Abbreviations

ART	Assisted reproductive technologies
ASM	Allele-specific DNA methylation
ChIP	Chromatin immunoprecipitation
CIMP	CpG island methylator phenotype
CpG	Cytosine-phosphate-guanine dinucleotide
CRC	Colorectal cancer
DES	Diethylstilbestrol
feNO	Fractional exhaled nitric oxide
FFPE	Formalin-fixed paraffin-embedded
HDAC	Histone deacetylases
iNOS	Inducible nitric oxide synthase
IUGR	Intra-uterine growth restriction
IVF	In vitro fertilization
PBMCs	Peripheral blood mononuclear cells
PTS	Maternal smoking during pregnancy
SNP	Single nucleotide polymorphism

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