Esposizione agli interferenti endocrini e meccanismi epigenetici

Lucia Migliore

Dipartimento di Ricerca Traslazionale e Nuove Tecnologie in Medicina e Chirurgia

Università di Pisa

e Azienda Ospedaliero Universitaria Pisana

lucia.migliore@med.unipi.it

Udine, 28 settembre 2024

Processi cellulari dovuti a meccanismi epigenetici

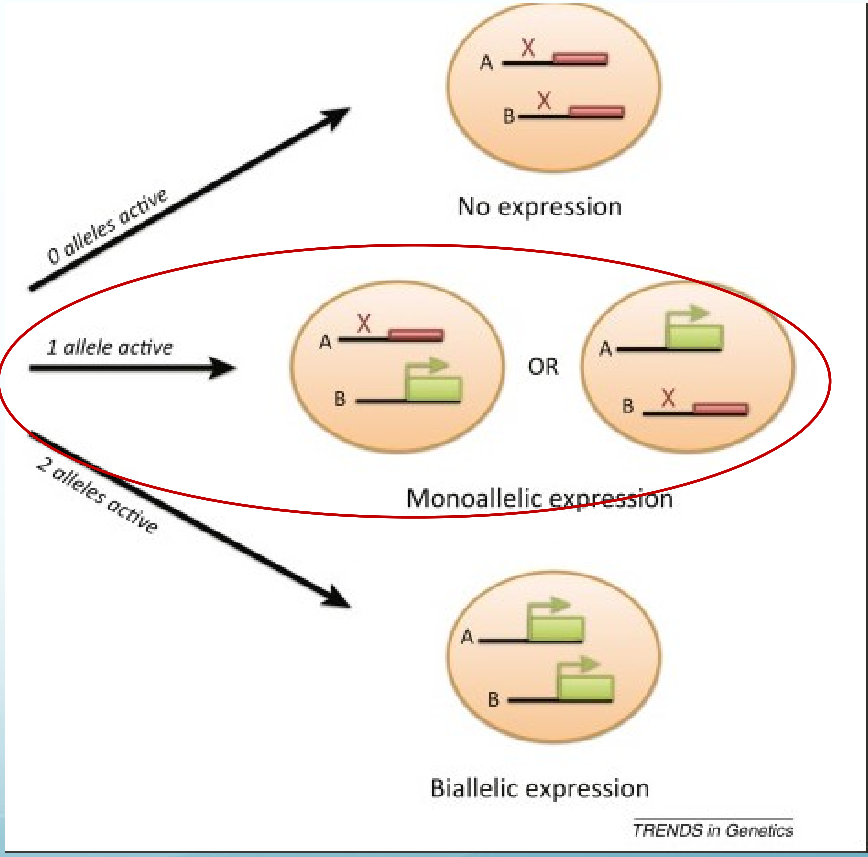
- Imprinting genomico (effetto parentale)
- Inattivazione di un cromosoma X nelle femmine

Imprinting genomico

L'effetto parentale in genetica viene evidenziato nella seconda metà del secolo scorso

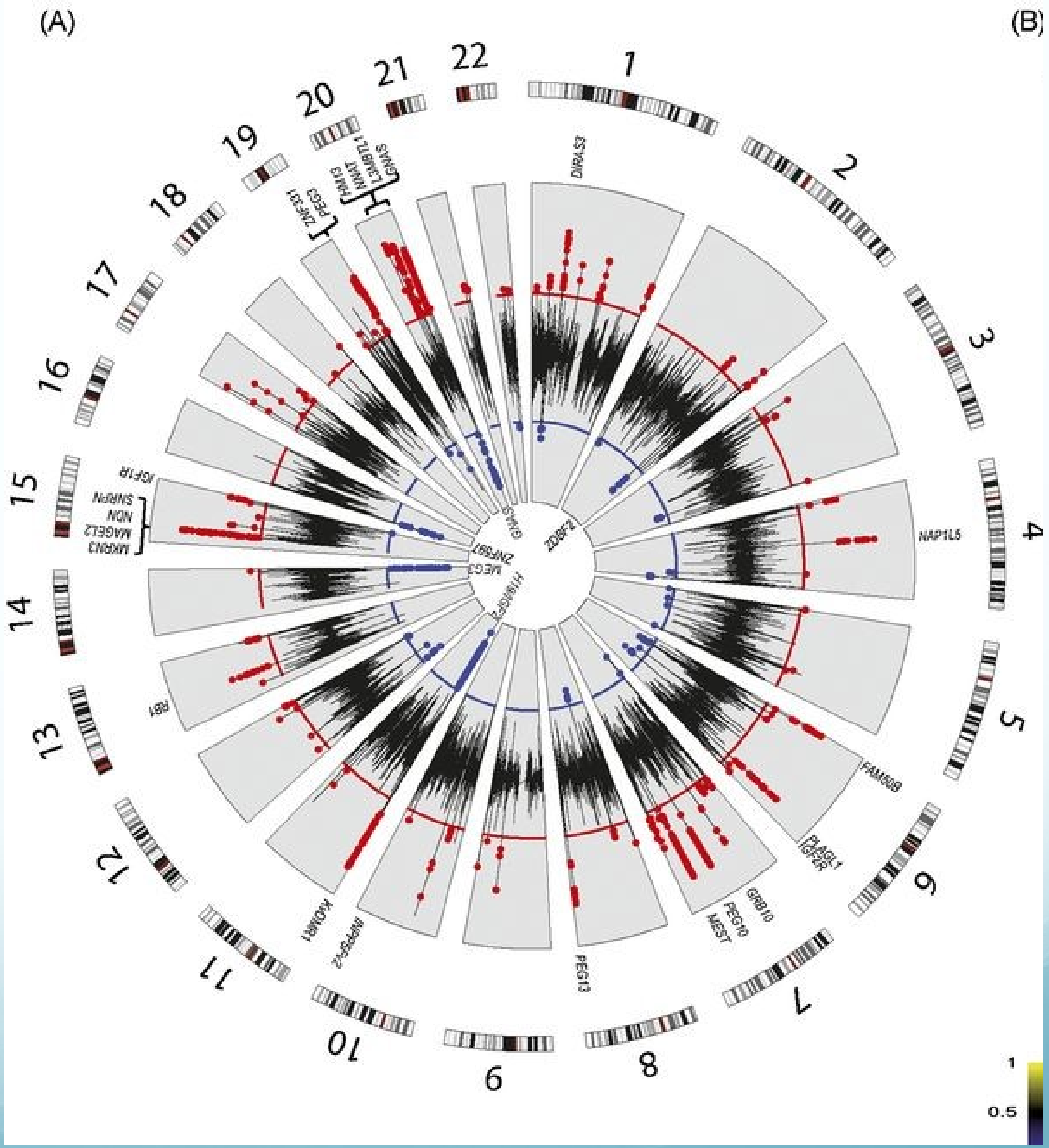
(Surani et al. 1984)

Consiste nell' espressione differenziale degli alleli ereditati per via paterna o materna



Imprintome

Molti geni *imprinted* sono stati identificati nel topo e nell’uomo



Insieme di geni **Materni**

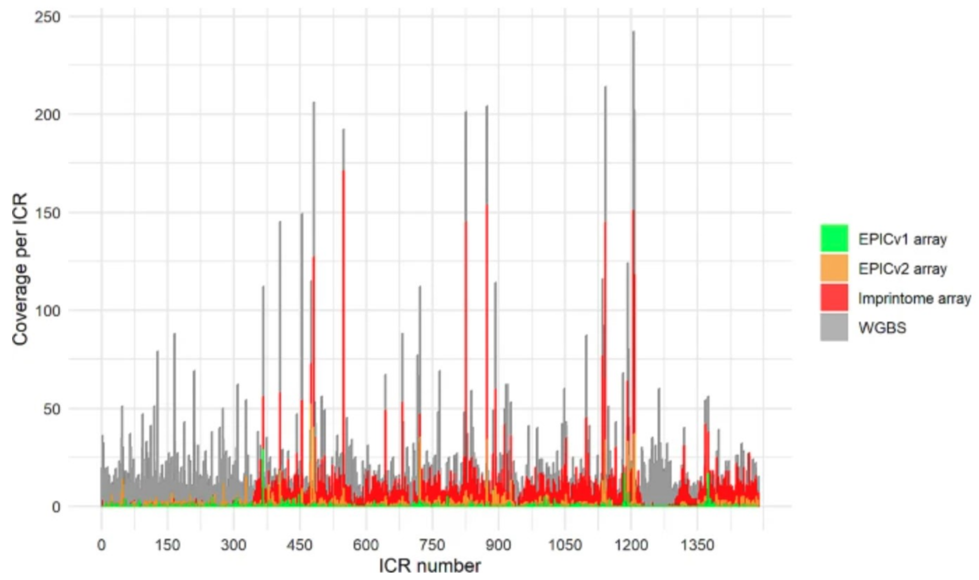
e **Paterni** silenziati

Court et al., Genome Research, 2014

Ad oggi (2024) nel genoma umano sono state identificate circa **1500 regioni** soggette ad imprinting (**ICR: Imprint Control Regions**). **Disfunzioni** dell'imprinting di queste regioni sono correlate a molte **condizioni patologiche**, e possono essere **modulate da fattori nutrizionali o ambientali**

Carreras-Gallo, N. *et al.*
Creation and validation of the first infinium DNA methylation array for the human imprintome.
Epigenetics Commun. **4**, 5 (2024)

Fig. 1



Coverage across Imprint Control Regions (ICRs) for each sequencing method. Whole genome bisulfite sequencing (WGBS) is the reference and it contains the 1,488 ICRs described [12], as well as the 22,157 probes mapped to these regions. The other sequencing methods have a lower number of ICRs and probes representing those ICRs

L'inattivazione del cromosoma X nelle femmine di mammifero

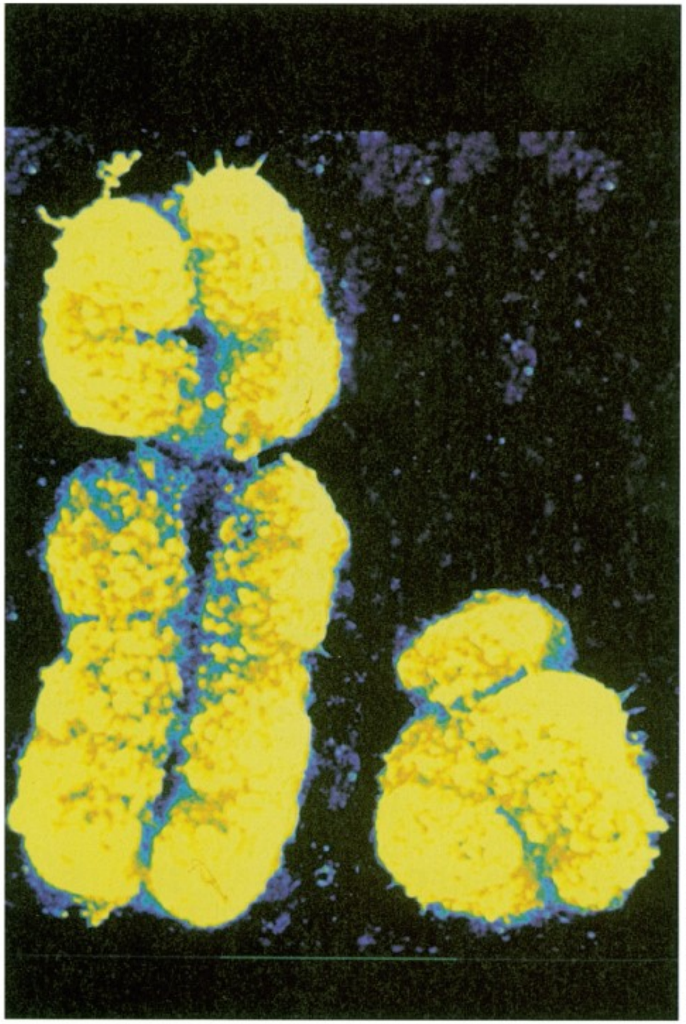
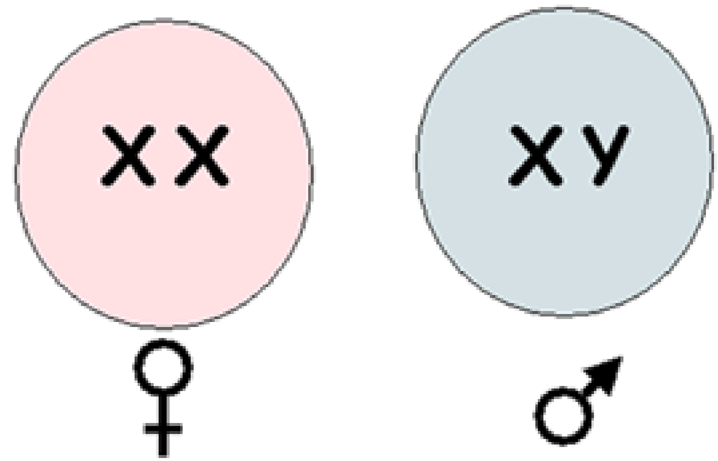
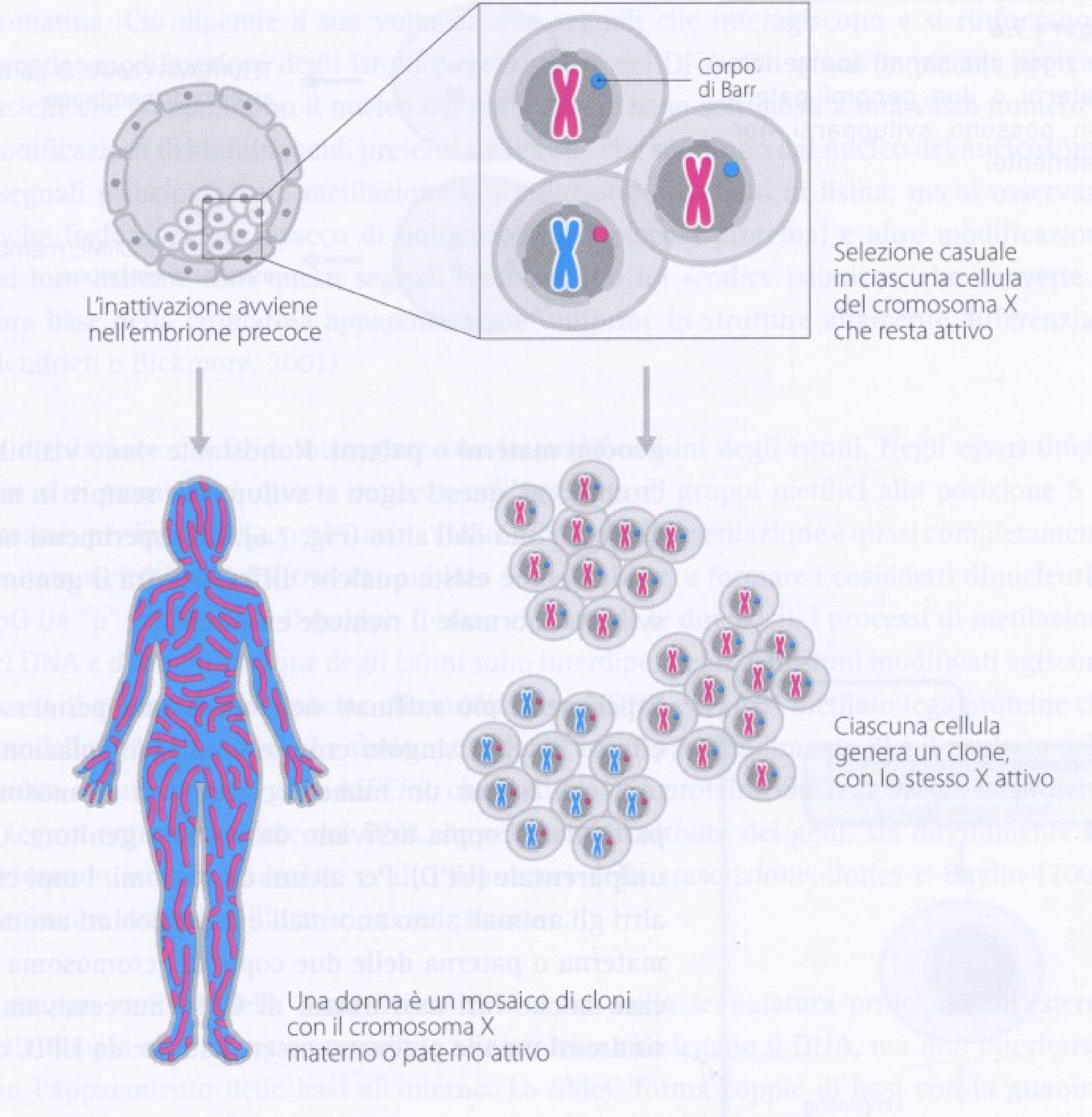


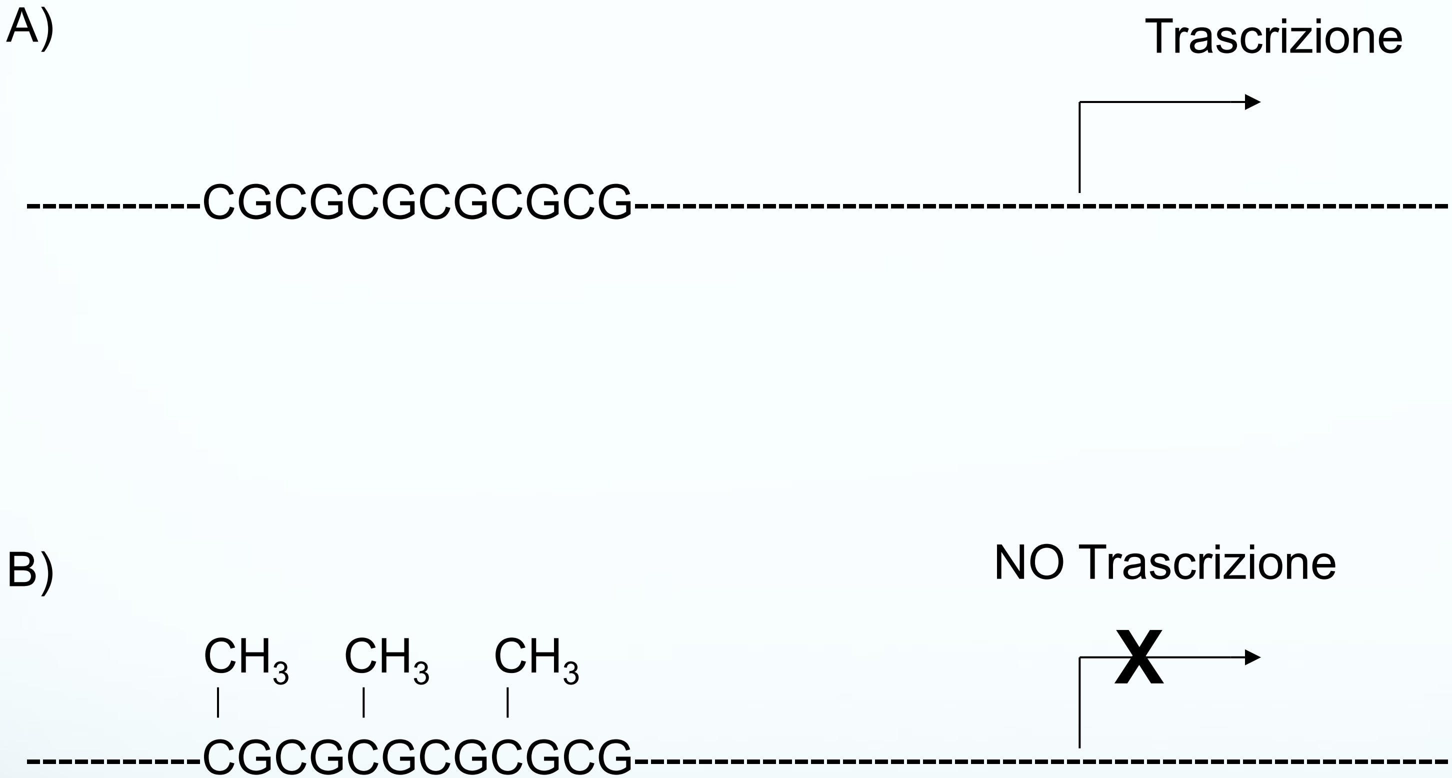
FIGURA 4.15 I cromosomi umani X (sinistra) e Y (destra). Questa fotografia "false color" di microscopia elettronica a scansione mostra le differenze tra i due cromosomi.

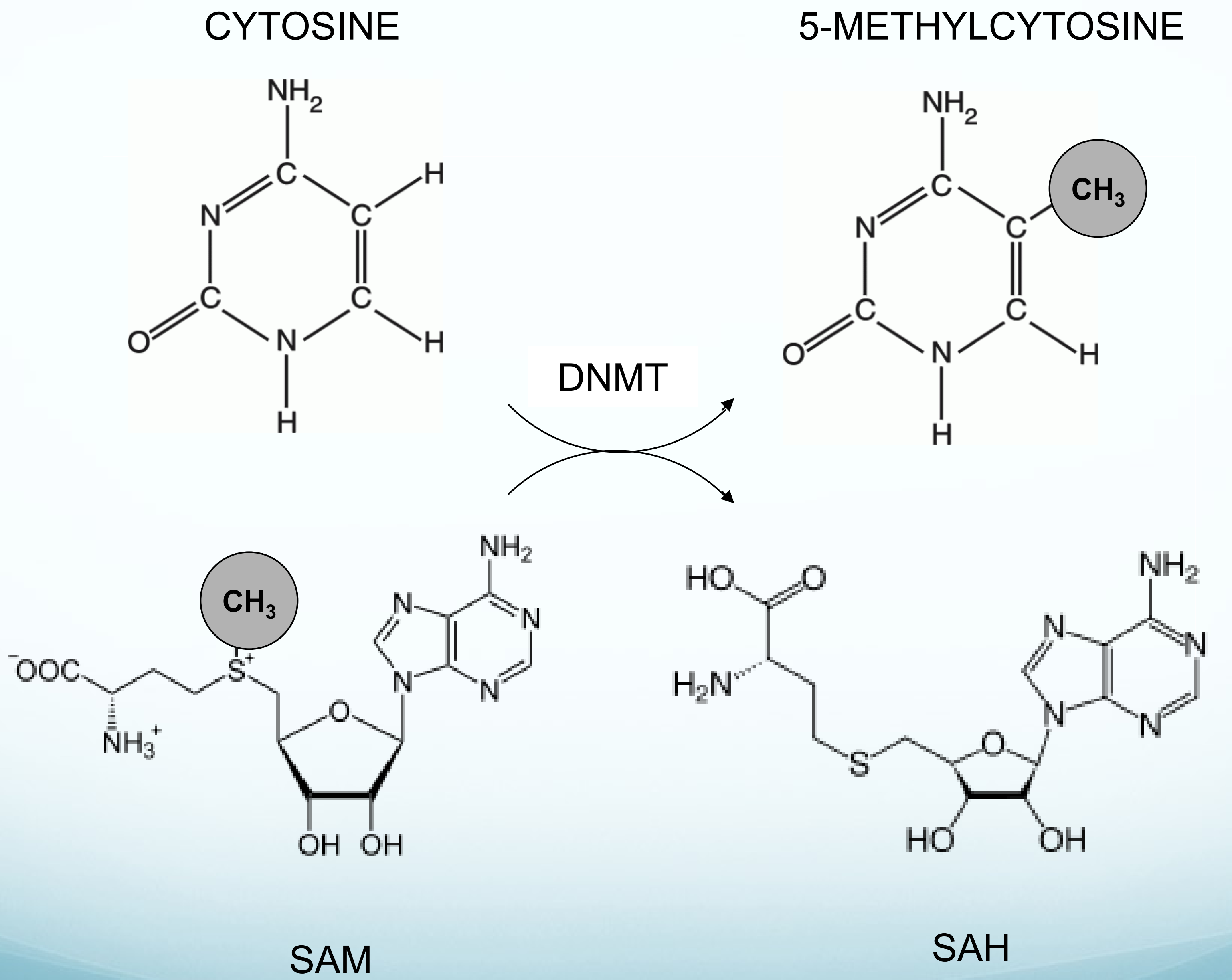


EdiSES
Michael R. Cummings
EREDITÀ
Principi e problematiche della genetica umana


Corpo
di Barr
L'inattivazione avviene
nell'embrione precoce
Selezione casuale
in ciascuna cellula
del cromosoma X
che resta attivo
Ciascuna cellula
genera un clone,
con lo stesso X attivo
Una donna è un mosaico di cloni
con il cromosoma X
materno o paterno attivo

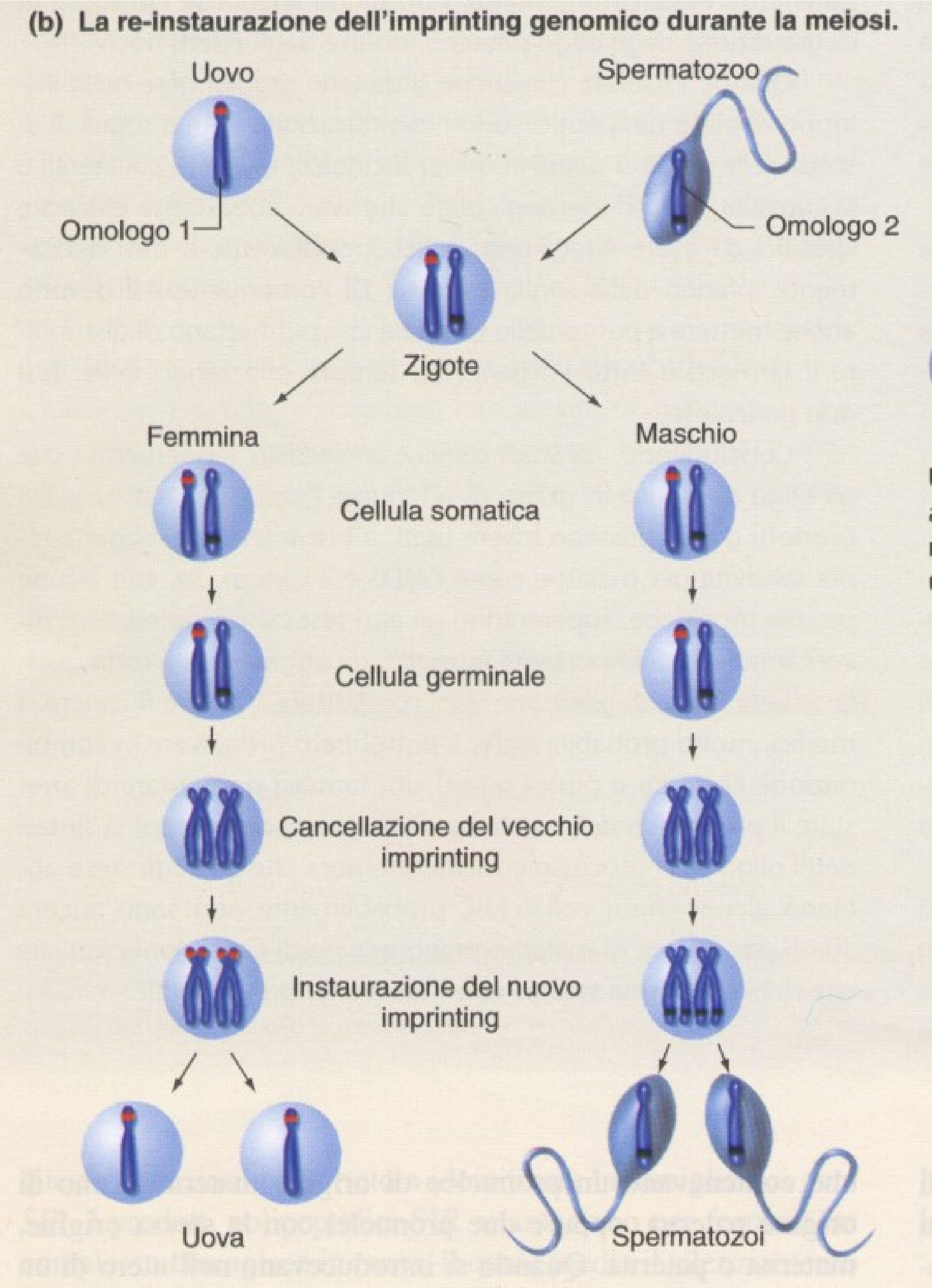
Imprinting genomico: meccanismo molecolare



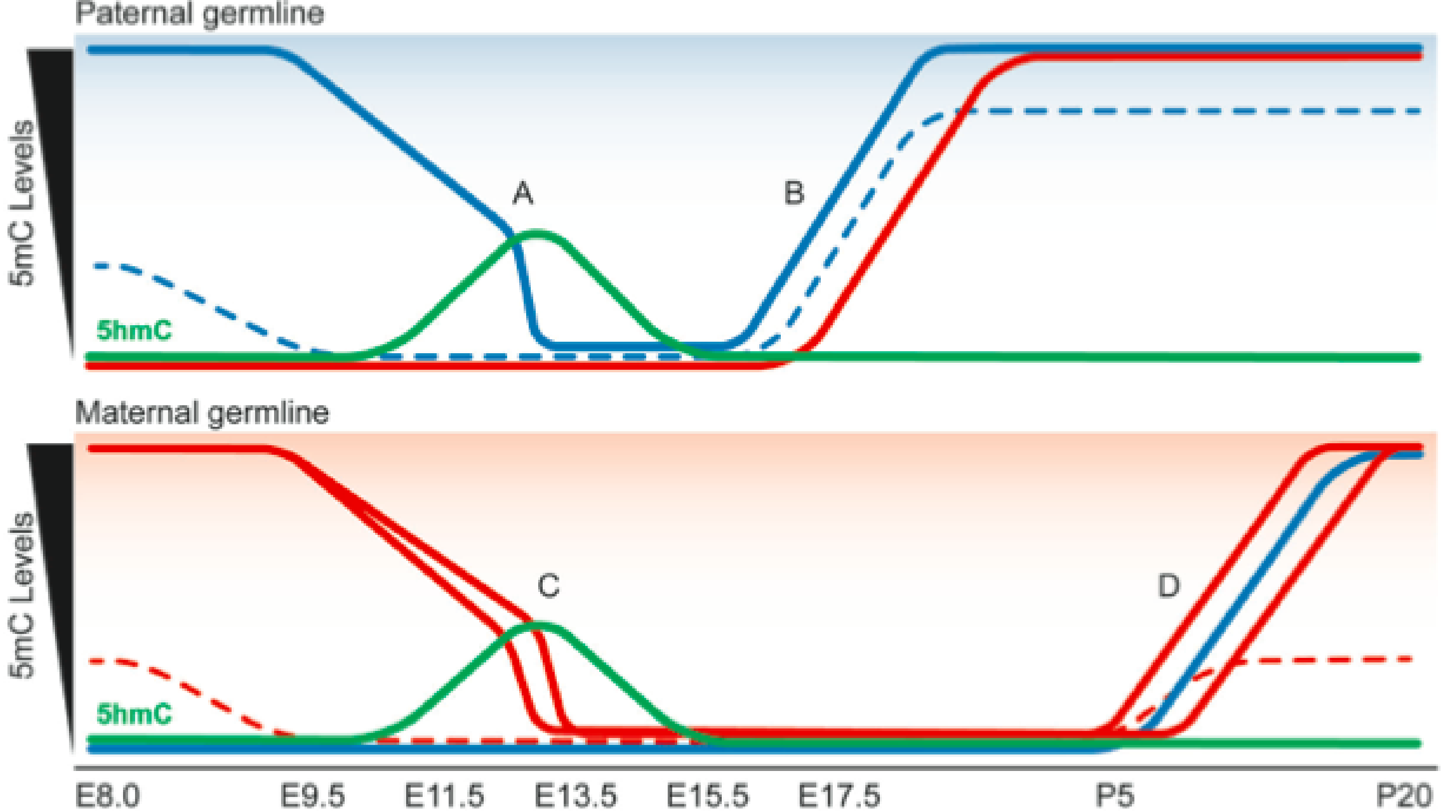


CYTOSINE
5-METHYLCYTOSINE
DNMT
SAM
SAH

L'imprinting è un fenomeno epigenetico e reversibile



Hartwell et al.,
GENETICA, Ed. McGraw Hill, 2004



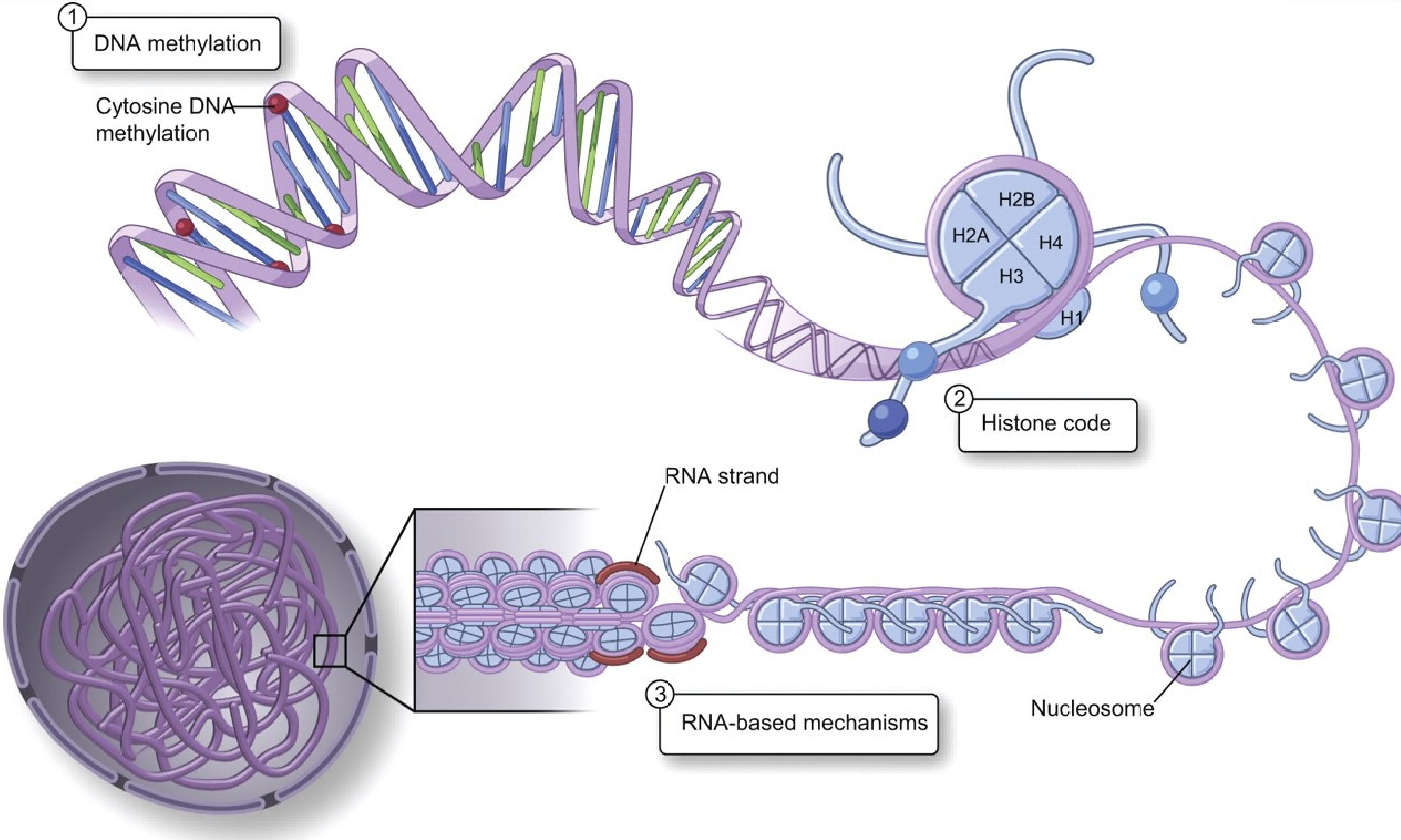
Imprinting: eliminazione ed acquisizione della metilazione nelle DMR

Nelle cellule germinali primordiali avviene la demetilazione seguita da rimetilazione specifica.

La demetilazione alle DMR è sia passiva (diminuzione attività de novo DNMT: Dnmt3a, Dnmt3b, and Dnmt3l, E8) sia attiva (intervento enzimi TET e produzione di 5hmeC, E10.5).

McDonald and Mann, Molecular Reproduction & Development, 81:126-140 (2014)

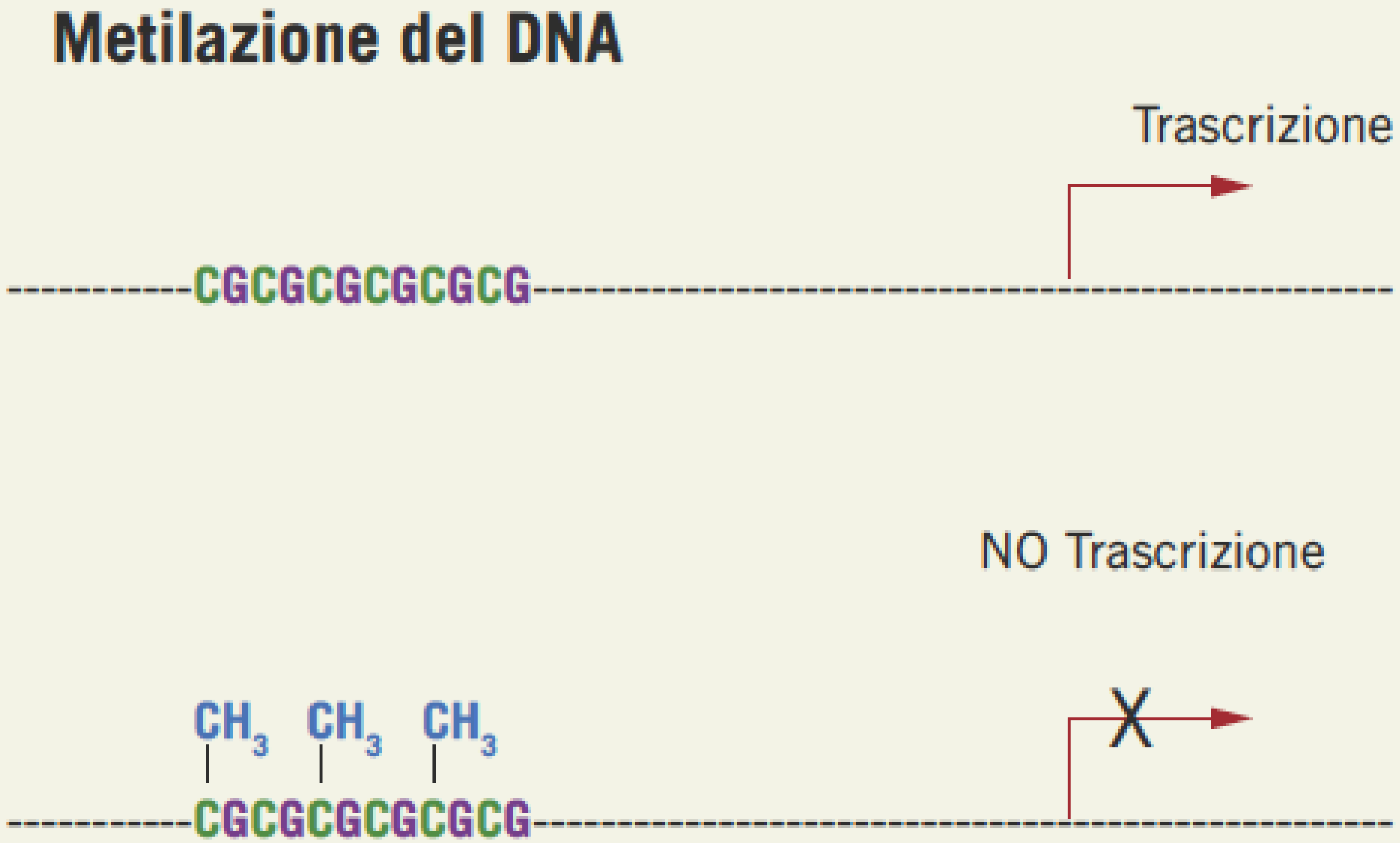
DAL CODICE GENETICO A QUELLO EPIGENETICO



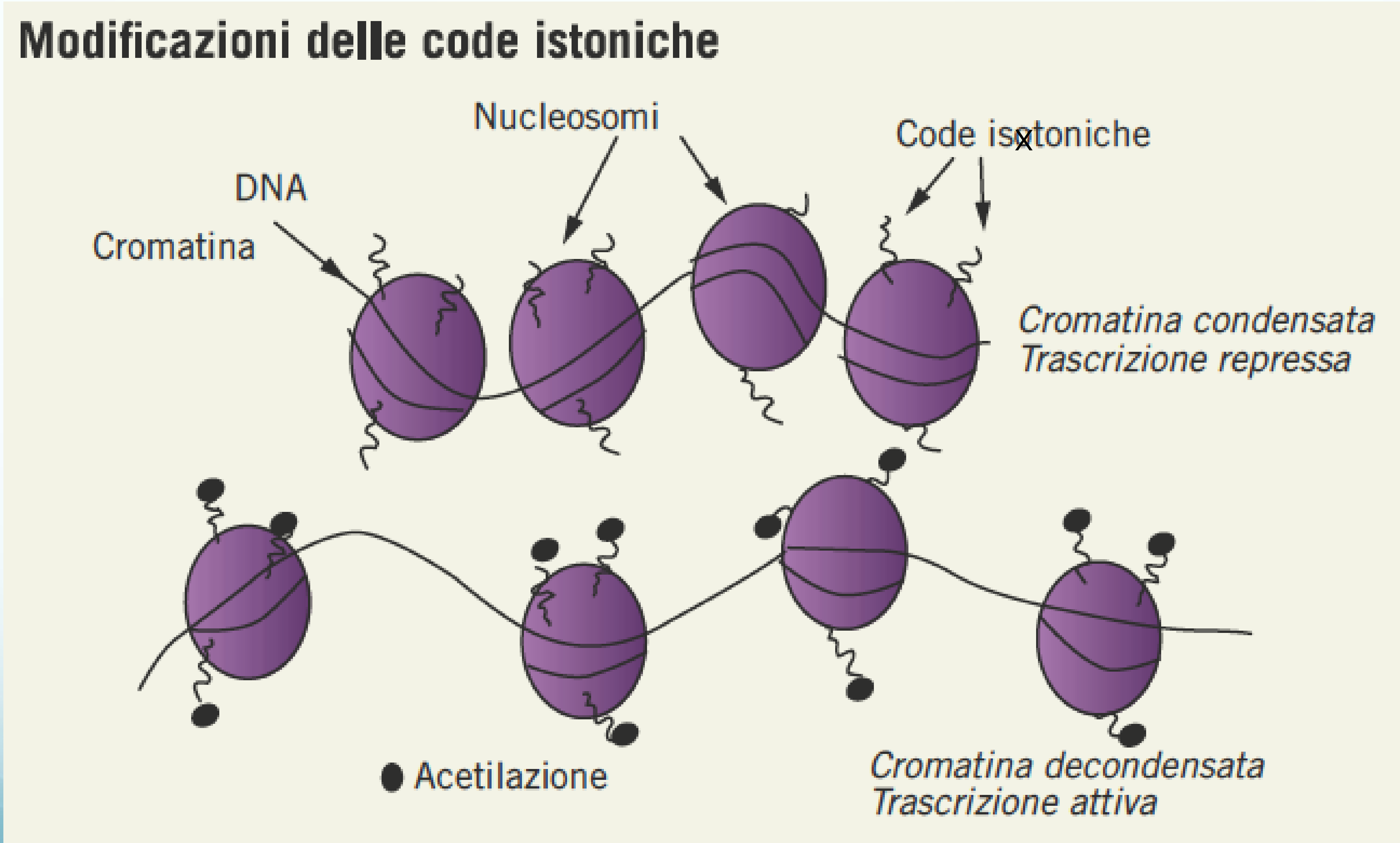
MECCANISMI EPIGENETICI

- 3 meccanismi per regolare l'espressione genica:

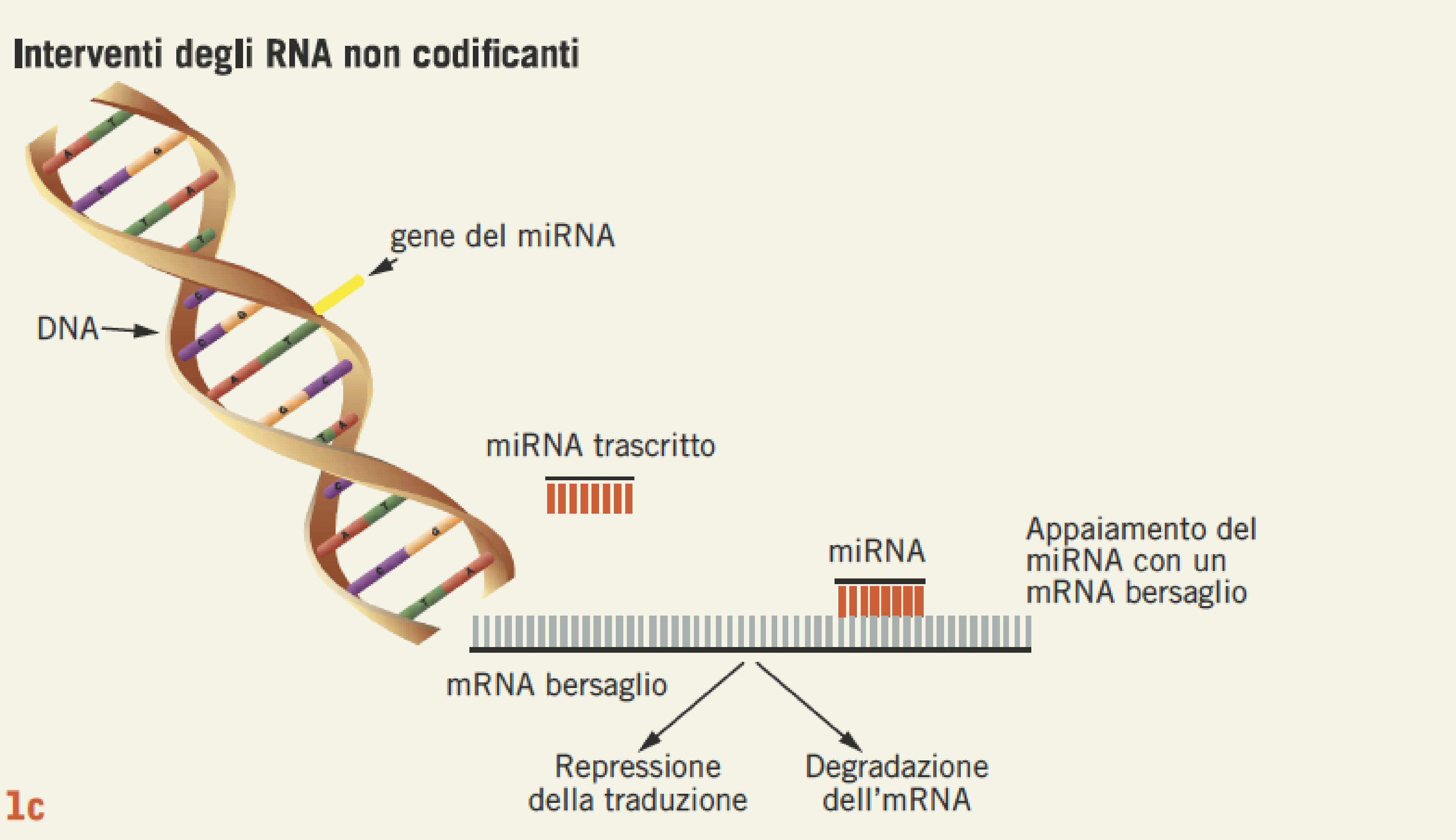
- ✓ metilazione del DNA
- ✓ modificazioni delle code istoniche
- ✓ interventi da parte dei ncRNA



L. Migliore, il Pediatra, ottobre 2016

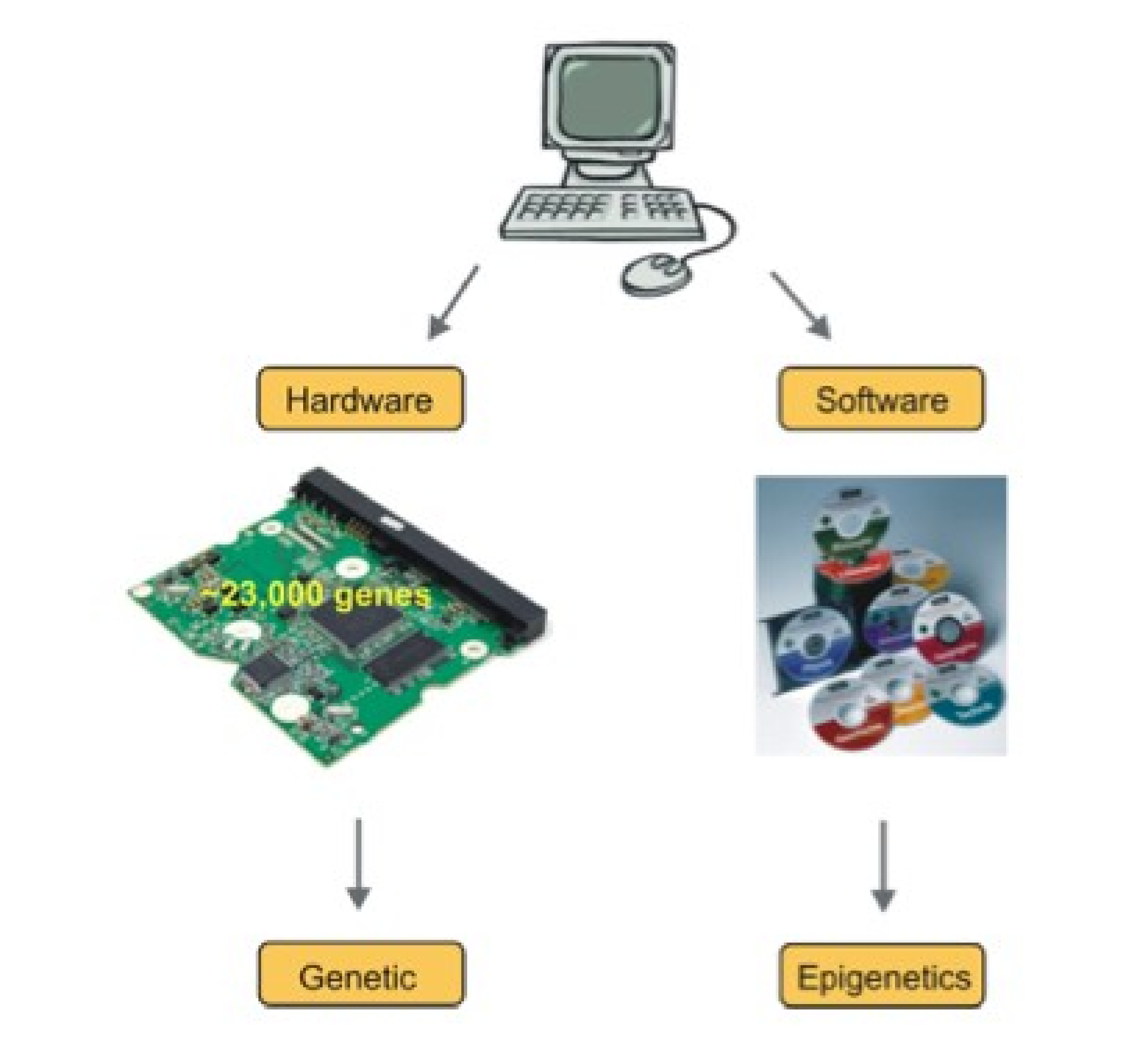


L. Migliore, il Pediatra, ottobre 2016



L. Migliore, il Pediatra, ottobre 2016

Genetica/Epigenetica



A. Hoffmann, D. Spengler / Neuroscience 264 (2014) 64–75

“Although the data are still sparse, early epigenetic studies have provided a proof of principle that experiences and the environment leave marks on genes, and thus suggest molecular and physical mechanisms for the epidemiological concept of gene-environment interaction”

(M. Szyf et al., *Epigenetics* 2016)

Disordini dell'imprinting genomico

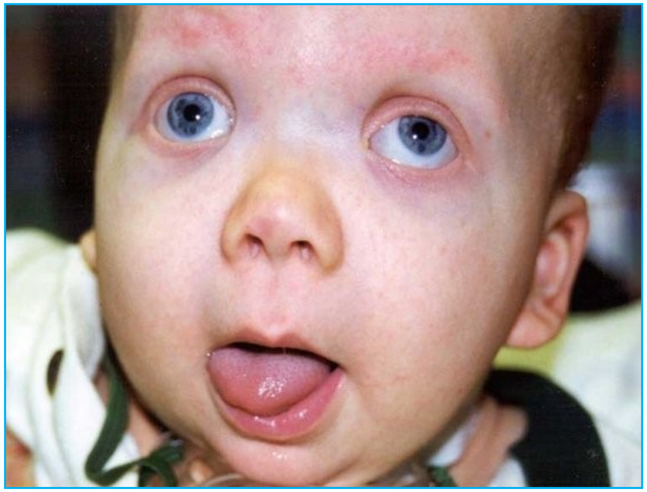
S. di Beckwith-Wiedemann

S. di Prader-Willi

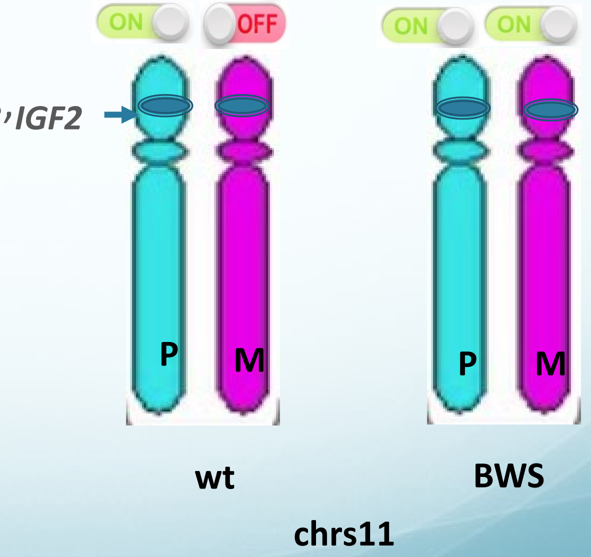
S. di Angelman

S. di Silver-Russell

Beckwith-Wiedemann syndrome



- Sporadic
- Prenatal overgrowth
- Macroglossia, omphalocele, visceromegaly, multiple angiomas, hemipertrophy,
- Neonatal hypoglycemia
- Increased incidence of childhood cancers (Wilms t.)
- Altered imprinting for growth regulatory genes (11p15 region including *IGF2*)



EPIGENETICA:
un ruolo nelle malattie genetiche complesse e nelle patologie correlate con l'età

Alterazioni della metilazione del DNA (es. ipermetilazione) o delle code istoniche della cromatina (es. ipoacetilazione) sono state correlate a molte malattie complesse (cancro, diabete, malattie cardiovascolari, malattie autoimmuni, autismo, schizofrenia, malattie neurodegenerative ………….)

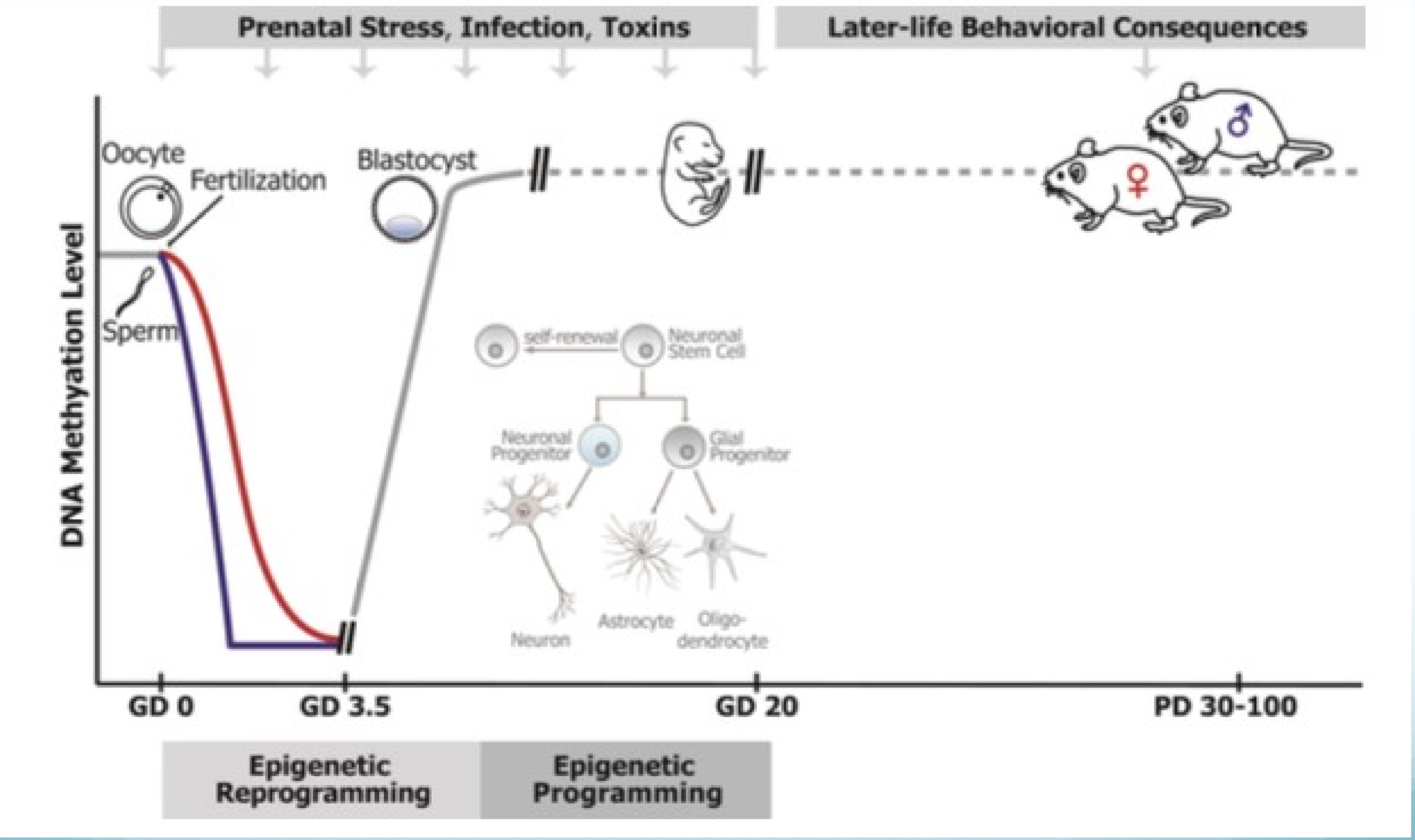
Epigenetics at the Epicenter of Modern Medicine

Andrew P. Feinberg JAMA. 2008;299(11):1345-1350

Epigenetica e ambiente

L'epigenoma è un importante bersaglio per le modificazioni indotte dall'ambiente

Esistono periodi critici per le modificazioni epigenetiche



Una teoria emergente: DOHaD

Developmental Origins of Health and Diseases

Sostiene che il rischio di malattie ad insorgenza nell’età adulta (“*non communicable diseases*”) è associato con condizioni ambientali avverse durante lo sviluppo embrio-fetale.

David Barker (1938 - 2013)

Barker DJ, Eriksson JG, Forsén T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. Int J Epidemiol. 2002 Dec;31(6):1235-9.

International Society for
Developmental Origins of Health and Disease
www.dohadsoc.org

Alterazioni epigenetiche correlate a specifiche esposizioni ambientali prenatali

- **Metalli pesanti (As, Cd, Pb..)**
- **Interferenti endocrini, *obesogeni***
- **Dieta, alcol, farmaci (VPA, DES..)**
- **Stress**

Influence of environmental factors on the epigenome

REVIEWS

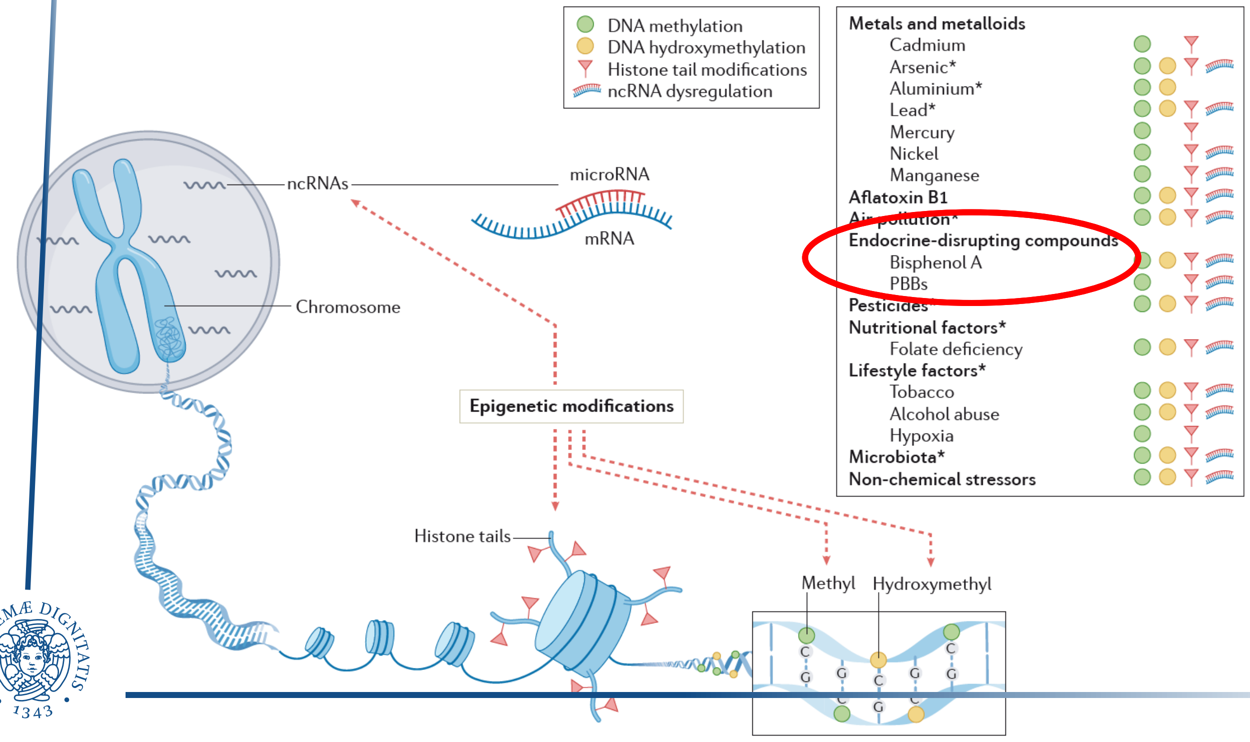
Check for updates

Gene–environment interactions in Alzheimer disease: the emerging role of epigenetics

Lucia Migliore[1,2] and Fabio Coppedè[1]

. Nat Rev Neurol. 2022 Nov;18(11):643-660.

Fig 1



Asterisks indicate environmental factors that are particularly relevant to Alzheimer disease

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

RESEARCH **Open Access**

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]

DNA methylation correlates with

- ✓ smoking (cotinine blood levels) and
- ✓ smoking-related genes

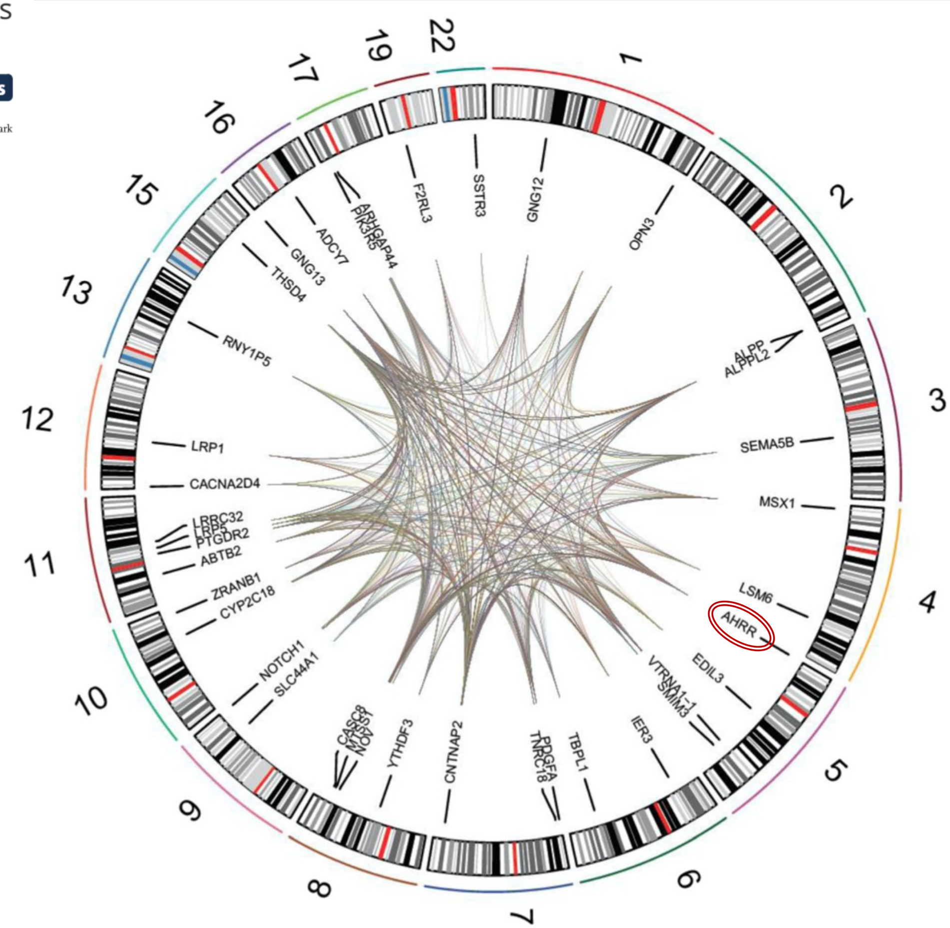
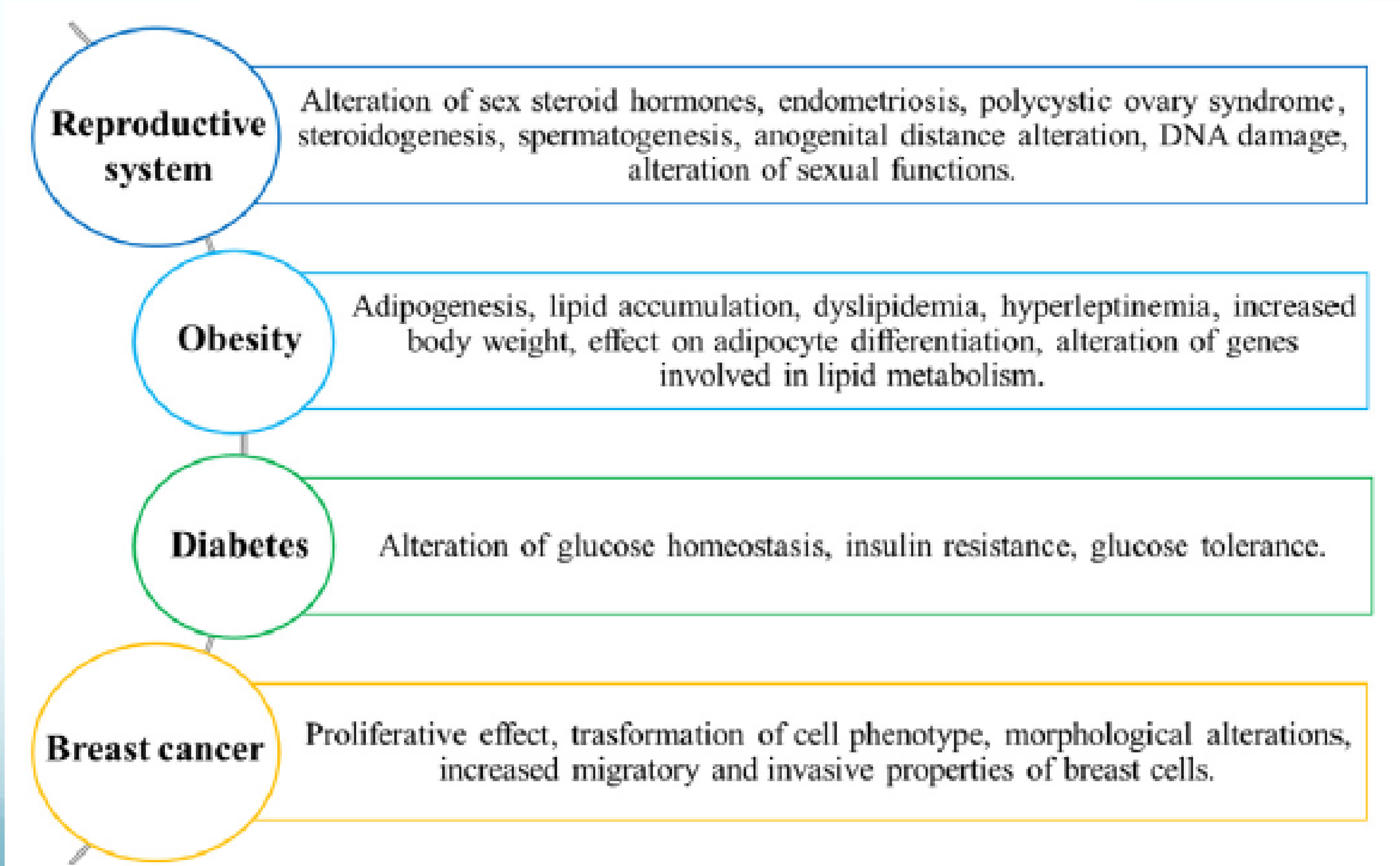


Fig. 3 Circos plot showing the presence of methylation quantitative trait loci among the 55 highlighted CpG sites and SNPs in 40 highlighted genes

Gupta *et al. Clinical Epigenetics* (2019) 11:1

Effects of EDC on human health



M. Giulivo et al. / Environmental Research 151 (2016) 251–264

Ci sono sempre più evidenze che la attuale epidemia di obesità **sia causata dall’ambiente**

Secondo le nuove prospettive l'obesità e le complicanze correlate sono associate **ad una componente ambientale,** multifattoriale, che include **farmaci, stress, nutrizione, microbioma, infezioni, i cicli di sonno-veglia, l'illuminazione notturna, composti chimici diffusi nell'ambiente (obesogeni)**, che possono far aumentare la suscettibilità ad acquistare peso ed alle altre conseguenze metaboliche, attraverso **modificazioni epigenetiche**.

Heindel et al. Environmental Health (2015) 14:54

L'ipotesi degli "obesogeni"

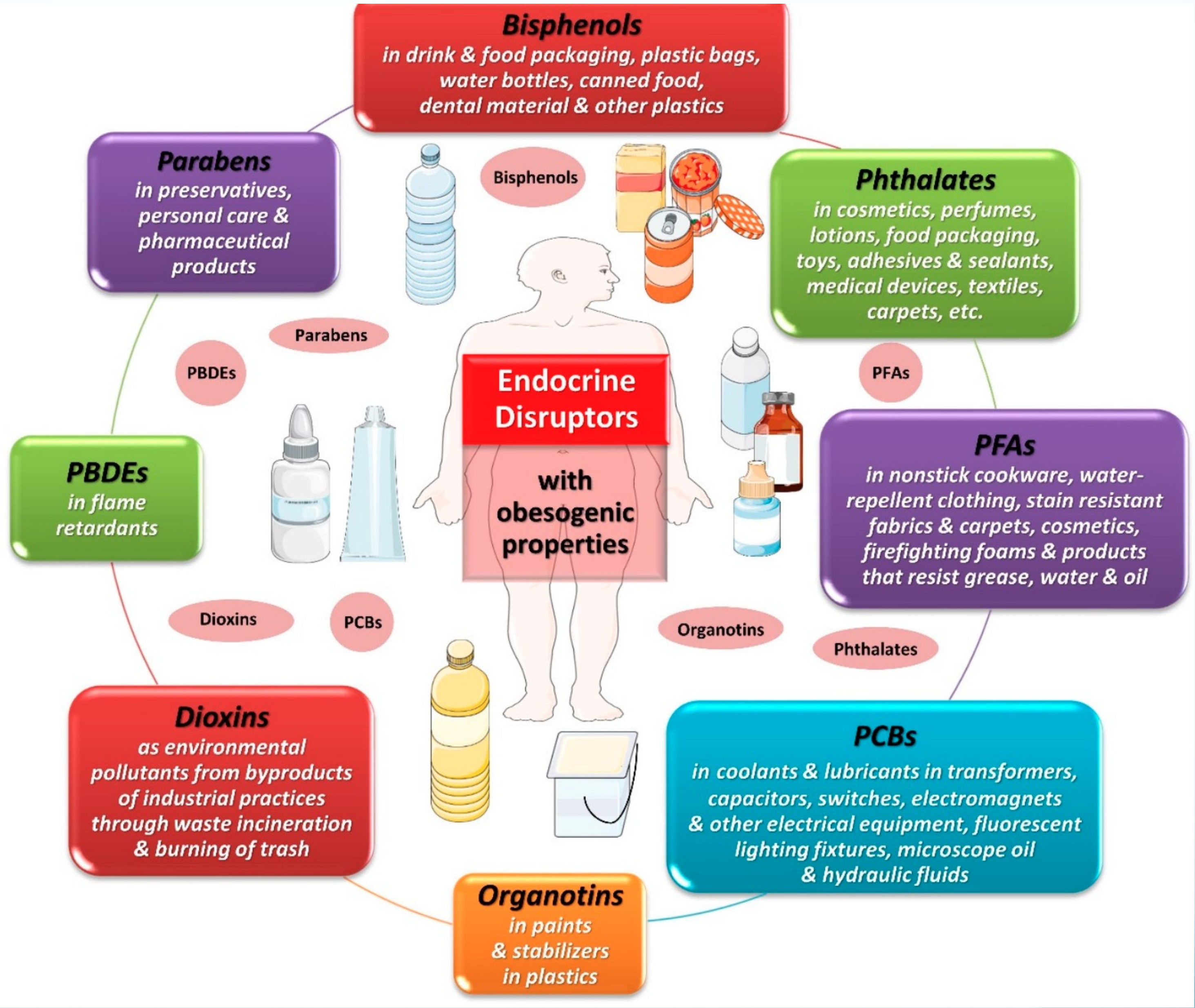
Nel 2006 Grün and Blumberg formularono "the *obesogen hypothesis*", secondo cui la pandemia di obesità che si sta verificando in questi ultimi tempi sarebbe, almeno in parte, conseguenza della diffusione nell'ambiente (specialmente nelle catene alimentari), di **xenobiotici** capaci di agire come **interferenti endocrini**, principalmente **durante il *fetal programming***: promuovendo l'iperplasia degli adipociti; facilitando i pathway dell'adipogenesi; disturbando l'omeostasi lipidica; interferendo con i meccanismi feedback dell'appetito e della sazietà

Che cosa è un “obesogeno”?

Gli **obesogeni** possono essere definiti da un punto di vista funzionale come composti chimici che interferiscono impropriamente con **l’omeostasi dei lipidi** e promuovono l’**adipogenesi**.

Grün F, Blumberg B (2007) Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev Endocr Metab Disord 8:161-71

Dalamaga et al., Int. J. Mol. Sci. **2024, *25*, 675**



Obesogenic endocrine-disrupting chemicals.
(PBDEs: polybrominated diphenyl ethers; PCBs: polychlorinated biphenyls;
PFAs: perfluoroalkyl substances.

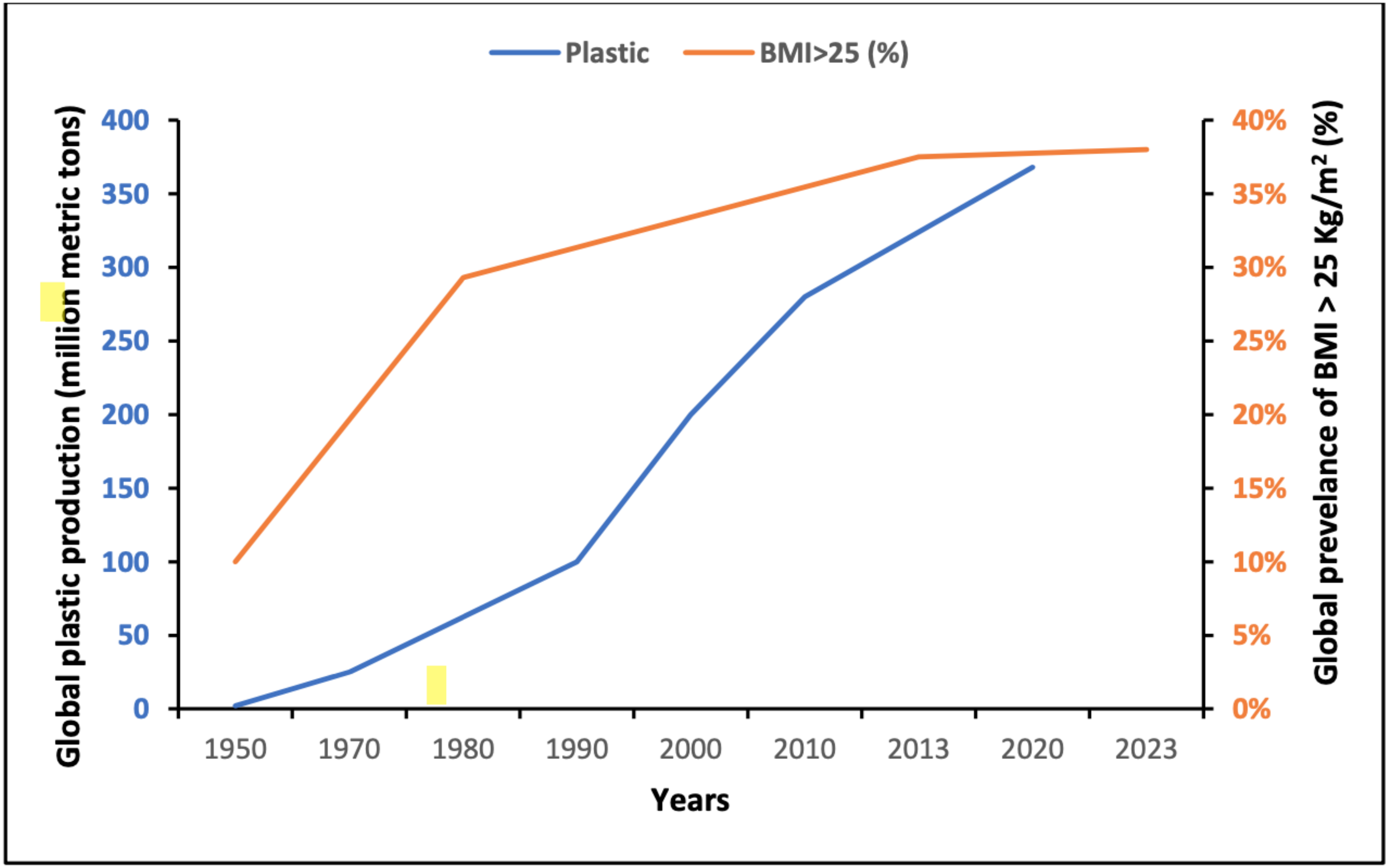
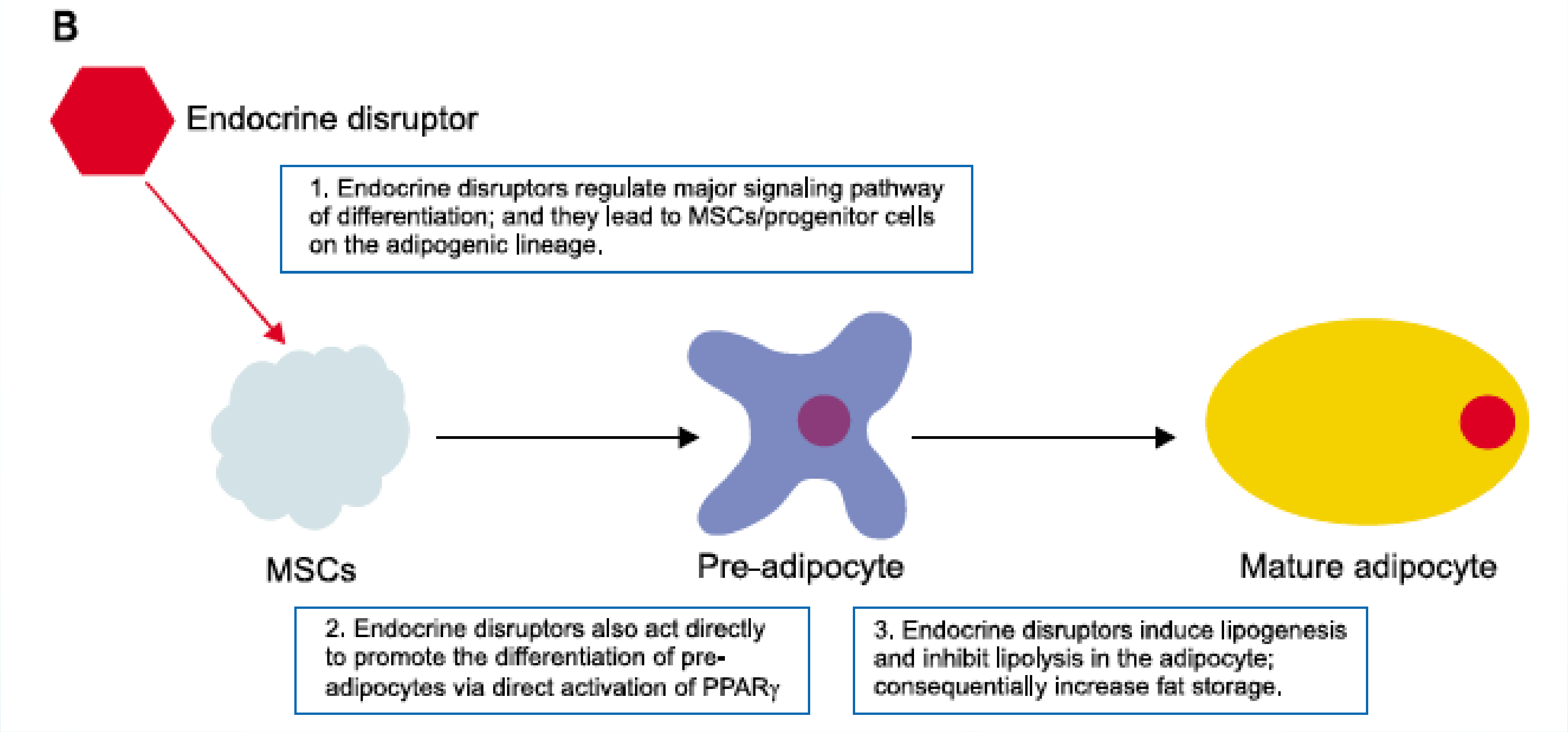


Figure 2. Worldwide plastic production in million metric tons and prevalence of excess body weight (BMI: >25 kg/m^2) in percentage (%). Figure is based on data from [1,36,37].

Dalamaga et al., Int. J. Mol. Sci. 2024, *25*, 675

Interferenti Endocrini come Obesogeni



Quando il target degli IE è l'adipocita, gli IE si comportano come obesogeni.

In questo caso, gli obiettivi specifici sono il recettore gamma attivato dai proliferatori dei perossisomi (PPAR-γ) sulle cellule mesenchimali o cellule progenitrici

Yang et al., J Canc Prev, 20:1, March 2015

Gli obesogeni (interferenti endocrini) agiscono mediante meccanismi epigenetici

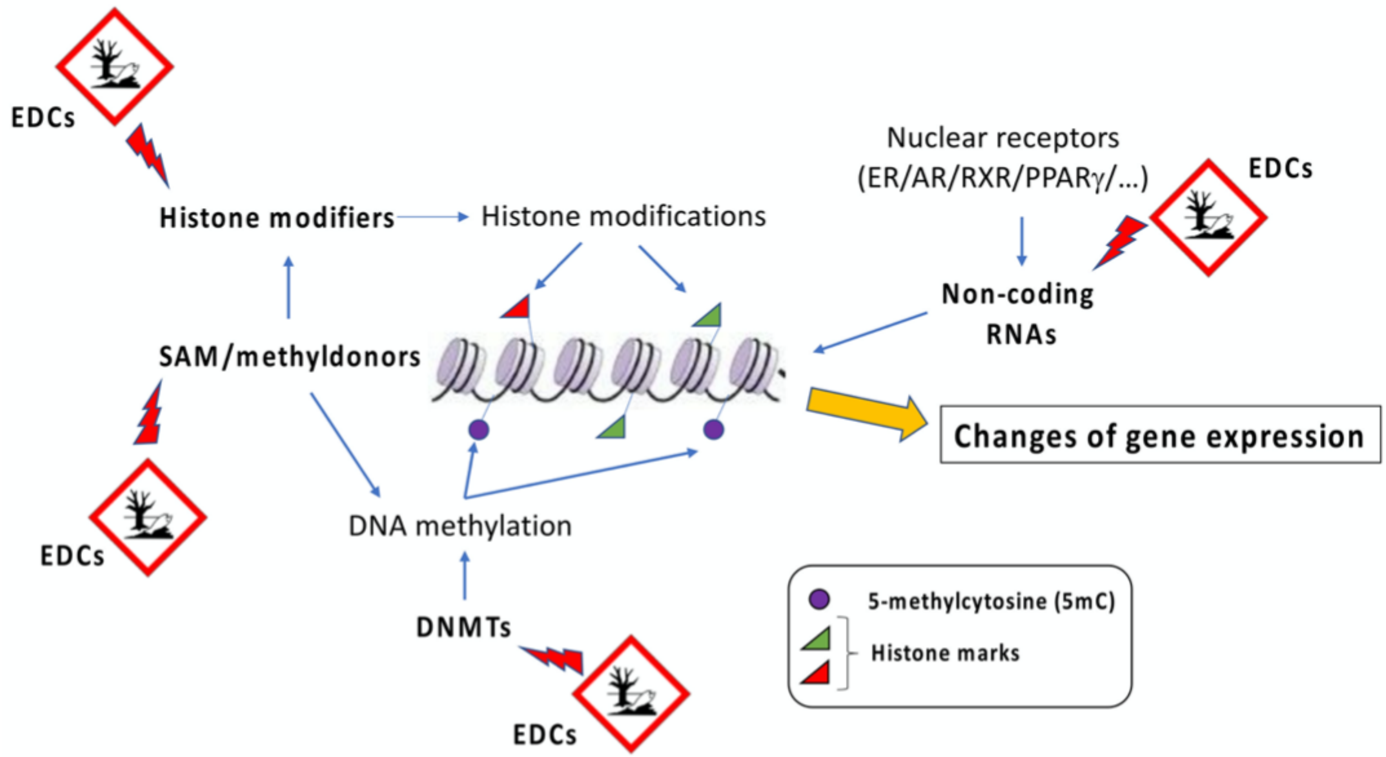


Figure 2. EDCs-induced epigenetic alterations. EDCs exposure may alter the levels of DNA methyltransferase (DNMT), histone modifiers, and SAM, as well as non-coding RNAs. All these events modify DNA methylation patterns and chromatin state and expression at specific genomic loci, determining changes in gene expression. SAM = s-adenosylmethionine.

Nettore et al., Biomedicines, 2021

Table 1. Characteristics and epigenetic effects of the main obesogenic EDCs.

Endocrine Disruptor	Description	Obesogenic Actions	Epigenetic Effects	Refs.
Bisphenol A (BPA)	Synthetic organic compound used in polycarbonate and resins. Commonly detected in water bottles, food containers, and metal-based cans.	Stimulation of adipogenesis Induction of insulin resistance Alteration of pancreatic beta-cell function Hepatotoxicity Induction of adulthood hepatic steatosis Reduction in mitochondrial function	Reduction in global DNA methylation Changes in histone marks (H3Ac, H4Ac, H3K4me2, H3K36me3)	[60] [61] [62]
Diethylstilbestrol (DES)	Synthetic estrogen used to prevent adverse pregnancy outcomes.	Stimulation of markers of adiposity (leptin and proinflammatory cytokines, [IL-6]) Alteration in glucose metabolism and pancreatic beta-cell hyperplasia	Increased expression of long non-coding RNA HOTAIR.	[63] [64] [65] [66]
Phthalates	Diesters of phthalic acid, widely used in the production of plastic products (children's toys, food packaging, medical devices, and furnishings).	Increased adipogenesis and insulin resistance Strong correlation between urinary levels of phthalates' metabolites and obesity	Increased DNA methylation at level of genes related to metabolism Increased expression of miR-34a-5p and of long non-coding RNA H19 and its downstream pathway	[67] [68] [69] [67] [70]
Organochlorine (OCPs) and Organophos-phate (OPPs) Pesticides	OCPs are chlorinated hydrocarbons used from the 1940s to the 1960s and are still detected in tap water. OPPs represent up to 50% of all the insecticide use worldwide.	Stimulation of adipogenesis OPPs accumulate in adipose tissue and influence PPARγ gene expression and production of inflammatory cytokines	Decreased global DNA methylation in both adipose-derived stromal cells (ADSCs) and 3T3-L1 preadipocytes Increased demethylation of lysine 27 on histone H3 (H3K27me3)	[71] [72] [73] [60] [74] [75]
Inhaled pollutants	Toxic environmental particles originate from a variety of sources (industrial pollution, automobile traffic, natural disasters).	Stimulation of the classic systemic inflammatory response associated with obesity, type 2 diabetes, insulin resistance, and metabolic syndrome	Altered DNA methylation status of PPARγ and PPARγ target genes	[76] [77] [78] [79]
Flame retardants	Group of compounds that prevent or slow the further development of ignition.	Stimulation of adipocytes differentiation Strong association between polybrominated diphenyl ethers (PBDEs) exposure and body mass index	Reduction in global DNA methylation	[80]

Nettore et al., Biomedicines, 2021

Current Obesity Reports (2023) 12:482–501
https://doi.org/10.1007/s13679-023-00526-z

REVIEW

Genetics and Epigenetics in Obesity: What Do We Know so Far?

Maria Keller[1,2] · Stina Ingrid Alice Svensson[3] · Kerstin Rohde-Zimmermann[1,2] · Peter Kovacs[1] · Yvonne Böttcher[3,4]

Springer

Table 1 (continued)

Study reference	PMID	Clinical trait	Ethnicity	*N*/females; age in years	Tissue	Main findings	Multi-omics	Meta-analysis
Wu et al. (2022) [111]	35,882,828	WHR	Northern Han Chinease	120/n.a ø52	Blood	The study identified numerous CpG sites whose methylation levels associate with WHR		
Taylor et al. (2023) [112]	36,479,596	BMI	African American	239/239 ø31	Saliva, blood	A combined sex and female-only meta-analyses discovered multiple CpG sites associated with BMI		Yes
Do et al. (2023) [113•]	36,649,705	BMI	Caucasian/European, Asian, African	17,034/n.a n.a	Blood	This study identified ~ 700 novel CpG sites associated with BMI and that 397 CpG sites explained 32% of the variance in BMI		Yes

This table summarises 45 studies identified by using the following criteria: We performed a PubMed search (dated 08/03/2023) for studies published during the last 10 years (2013–2023) using

International Journal of *Environmental Research and Public Health* 2023

MDPI

Review

Inherited Epigenetic Hallmarks of Childhood Obesity Derived from Prenatal Exposure to Obesogens

María Á. Núñez-Sánchez [1], Almudena Jiménez-Méndez [2], María Suárez-Cortés [3], María A. Martínez-Sánchez [1], Manuel Sánchez-Solís [4,5], José E. Blanco-Carnero [2,6], Antonio J. Ruiz-Alcaraz [7,*] and Bruno Ramos-Molina [1,*]

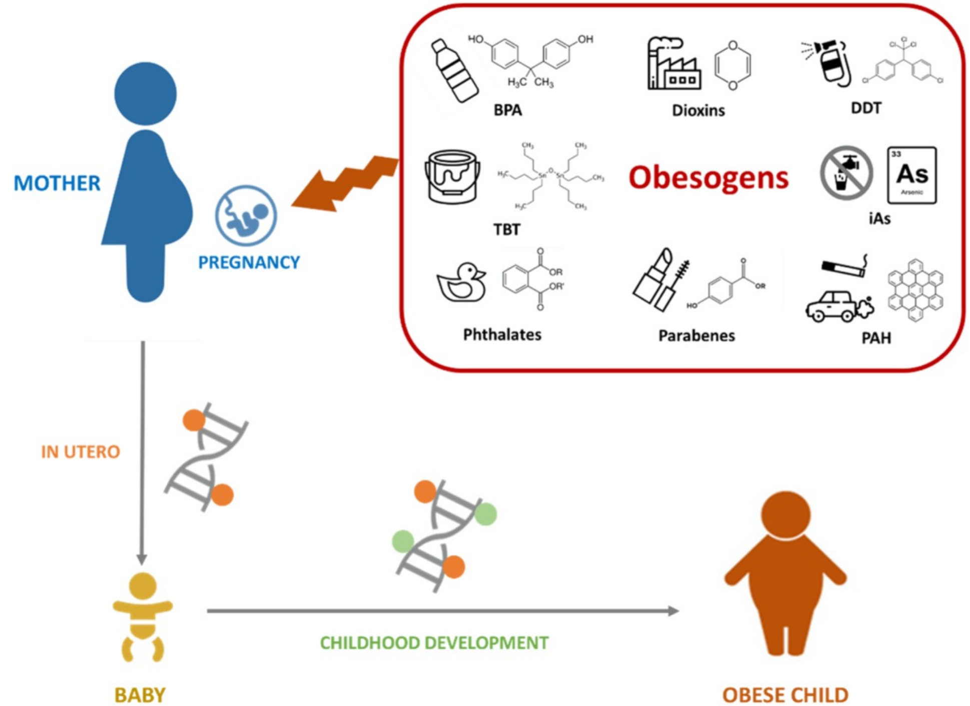


Figure 2. Schematic effect of obesogens on epigenetic hallmarks leading to childhood obesity. Several environmental pollutants may alter the inherited epigenetic profiles during pregnancy, which would contribute to the later development of childhood obesity and other metabolic related diseases. BPA, bisphenol A; DDT, dichlorodiphenyltrichloroethane; iAs, inorganic arsenic; PAH, polycyclic aromatic hydrocarbons; and TBT, tributyltin.

Table 1. Animal studies on transgenerational inheritance of obesity epiphenotypes after ancestral exposure to obesogenic non-persistent pollutants.

Compound	Model	Treatment	Outcomes in Progeny	Reference
Bisphenol A (BPA)	CD1 mice	Dams administered 50 mg/kg/day i.p. of BPA or sesame oil daily to gestating F0 CD1 females from embryonic day E7.5 to E13.5.	↑ 60% and 97% obesity in the male F2 and F4 progeny, respectively. Obesity phenotype transmittable up to F6. ↑ Visceral WAT and adipocyte size. ↑ Circulating leptin levels. ↑ Food intake. Altered light/dark respiratory exchange ratio. Demethylation in a cis-regulatory element of the *Fto* gene.	[21]
Bisphenol A (BPA)	BALB/c mice	Dams exposed to BPA (5 µL of BPA/mL of drinking water) 1 week before mating until delivery of the offspring.	↑ BW and fat mass. ↓ *Mest* methylation with increased *Mest* mRNA expression.	[22]
Bisphenol A (BPA)	CD-1 mice	Pregnant CD-1 mice (F0) dosed orally with 0, 5 (low-BPA group), or 500 (high-BPA group) µg/kg/day of BPA in tocopherol-stripped corn oil or vehicle during gestational days 9 to 18.	↑ Whole BW in males F1 (low-BPA group). ↑ Gonadal fat in F1 males (low-BPA group). ↓ Methylation of *Fggy* promoter in F1 males (low-BPA group). ↑ *Fggy* mRNA expression in F1 males (low-BPA group). No differences in F1 female mice between the groups.	[23]

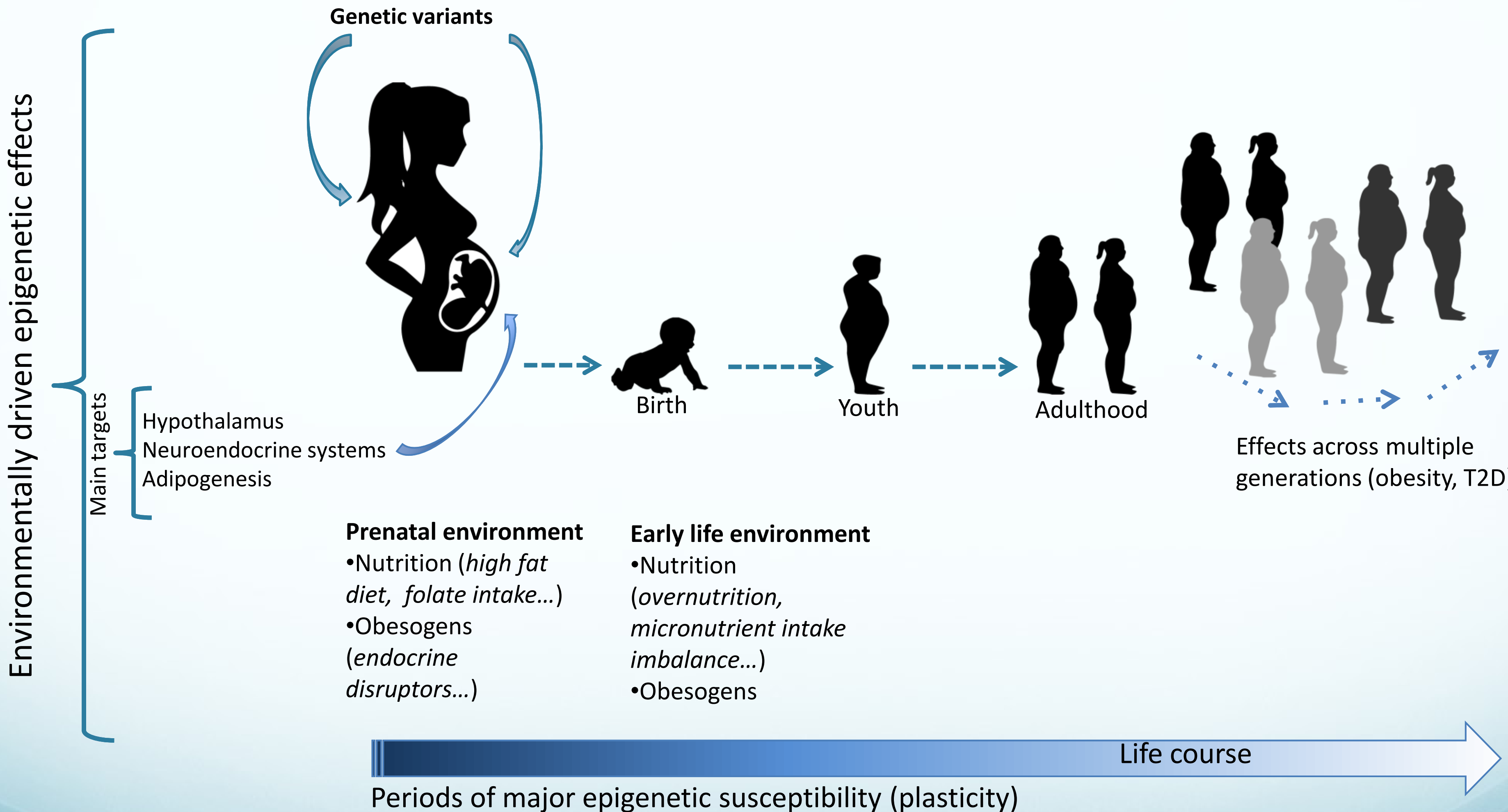
Nunez-Sanchez et al., Int.J.Environ.Res.Public Health 2023. 20, 4711

Table 3. Epidemiological studies addressing epigenomic changes related to childhood obesity development after maternal exposure to obesogens.

Compound	Cohort and Sample Size	Objective	Measures	Outcomes	References
Bisphenol A (BPA)	Mother–child pairs (LINA mother–child-study, N = 420). (#046–2006, #206–12-02072012, University of Leipzig).	To analyze epigenetic alterations in the cord blood of BPA prenatally exposed children and their potential link to overweight development.	BPA concentration: urine from gestating women (week 34). DNA methylation: cord blood. Infant's follow-up: 1 and 6 years.	↓ Methylation of CpG (cg17580798) in the *MEST* promoter. ↓ Methylation of cg23117250 (*RAB40B*). ↑ *MEST* mRNA levels. BPA prenatal exposure related to longitudinal weight development.	[22]
Bisphenol A (BPA)	Children exposed prenatally to low or high BPA levels based on 80th percentile of maternal BPA levels (N = 59). (IRB No. 1201-010-392).	To identify differentially methylated CpG sites due to prenatal BPA exposure.	BPA concentration: urine from gestating women collected during the second trimester of pregnancy. DNA methylation: infants' whole blood at 2 and 6 years old. Infants' follow-up: 2, 4, 6, and 8 years old.	↑ Methylation in cg19196862 (*IGF2R*) associate with ↑ BMI at 2 years of age. ↑ BMI during 4–8 years of age associated with hypermethylation in cg19196862 in girls. ↑ Methylation at cg19249811 (*SVIL*) not associated with BMI.	[33]
Di-2-ethylhexyl phthalate (DEHP)	Mother–child pairs (Hokkaido study) (N = 203) (reference no. 14, 22 March 2012, Hokkaido University Center for Environmental and Health Sciences).	To elucidate the relation between prenatal DEHP exposure and cord blood DNA methylation, as well as the association between DNA methylation and ponderal index (PI) at birth.	Mono(2-theylhexyl)phthalate concentration (MEHP) as indicator of DEHP exposure: maternal blood samples. DNA methylation: cord blood.	Maternal MEHP levels positively correlated to methylation levels in CpG located at 200 bases from the transcription start with of *ZC3H10* (cg26409978) and another mapped to *SDK1* (cg00564857). Enrichment of metabolic pathways, MAPK, Notch, and GnRH signaling pathways, renin secretion, and cortisol synthesis and secretion. ↑ Methylation levels at cg27433759 (*PIK3CG*), cg10548708 (*ACAA1*), and cg07002201 (*FUT9*) related to high levels of MEHP and lower PI.	[34]
Parabens	Mother–newborn pairs (ENVIRONAGE cohort, N = 229) (reference no. B371201216090 and B371201524537).	To determine the association between placental paraben levels and cord blood metabolic biomarkers, epigenetic alterations, and childhood trajectories of BMI z-scores.	Parabens concentrations (methyl (MeP), ethyl (EtP), propyl (PrP and butyl (BuP) parabens): placenta. DNA methylation: cord blood. Infants' follow up: up to 29 months after birth.	Correlation between higher levels of EtP and hypermethylation of cg08612779 (annotated to *GGT7*). EtP related to decreased longitudinal BMI z-scores.	[35]

ACAA1, acetyl-CoA acyltransferase 1; BMI, body mass index; BPA, bisphenol A; BuP, butylparaben; DEHP, diethylhexyl phthalate; EtP, ethylparaben; *FUT9*, fucosyltransferase; GGT7, gamma-glutamyltransferase 7; GnRH, gonadotropin-releasing hormone; MAPK, mitogen-activated protein kinase; MEHP, mono(2-theylhexyl)phthalate; MeP, methylparaben; *MEST*, mesoderm-specific transcript; PI, ponderal index; *PIK3CG*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma; *SDK1*, sidekick cell adhesion molecule 1; *SVIL*, supervillin; and *ZC3H10*, zinc finger CCH-type containing 10; ↑, increase; ↓ decrease.

Importanza degli effetti epigenetici determinati dall'ambiente durante il corso della vita e conseguenze intergenerazionali.



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Methylome analysis in girls with idiopathic central precocious puberty

Stefania Palumbo[1*†], Domenico Palumbo[2†], Grazia Cirillo[1], Giorgio Giurato[2], Francesca Aiello[1], Emanuele Miraglia del Giudice[1] and Anna Grandone[1]

Abstract

Background Genetic and environmental factors are implicated in many developmental processes. Recent evidence, however, has suggested that epigenetic changes may also influence the onset of puberty or the susceptibility to a wide range of diseases later in life. The present study aims to investigate changes in genomic DNA methylation profiles associated with pubertal onset analyzing human peripheral blood leukocytes from three different groups of subjects: 19 girls with central precocious puberty (CPP), 14 healthy prepubertal girls matched by age and 13 healthy pubertal girls matched by pubertal stage. For this purpose, the comparisons were performed between pre- and pubertal controls to identify changes in normal pubertal transition and CPP versus pre- and pubertal controls.

Results Analysis of methylation changes associated with normal pubertal transition identified 1006 differentially methylated CpG sites, 86% of them were found to be hypermethylated in prepubertal controls. Some of these CpG sites reside in genes associated with the age of menarche or transcription factors involved in the process of pubertal development. Analysis of methylome profiles in CPP patients showed 65% and 55% hypomethylated CpG sites compared with prepubertal and pubertal controls, respectively. In addition, interestingly, our results revealed the presence of 43 differentially methylated genes coding for zinc finger (ZNF) proteins. Gene ontology and IPA analysis performed in the three groups studied revealed significant enrichment of them in some pathways related to neuronal communication (semaphorin and gustation pathways), estrogens action, some cancers (particularly breast and ovarian) or metabolism (particularly sirtuin).

Conclusions The different methylation profiles of girls with normal and precocious puberty indicate that regulation of the pubertal process in humans is associated with specific epigenetic changes. Differentially methylated genes include ZNF genes that may play a role in developmental control. In addition, our data highlight changes in the methylation status of genes involved in signaling pathways that determine the migration and function of GnRH neurons and the onset of metabolic and neoplastic diseases that may be associated with CPP in later life.

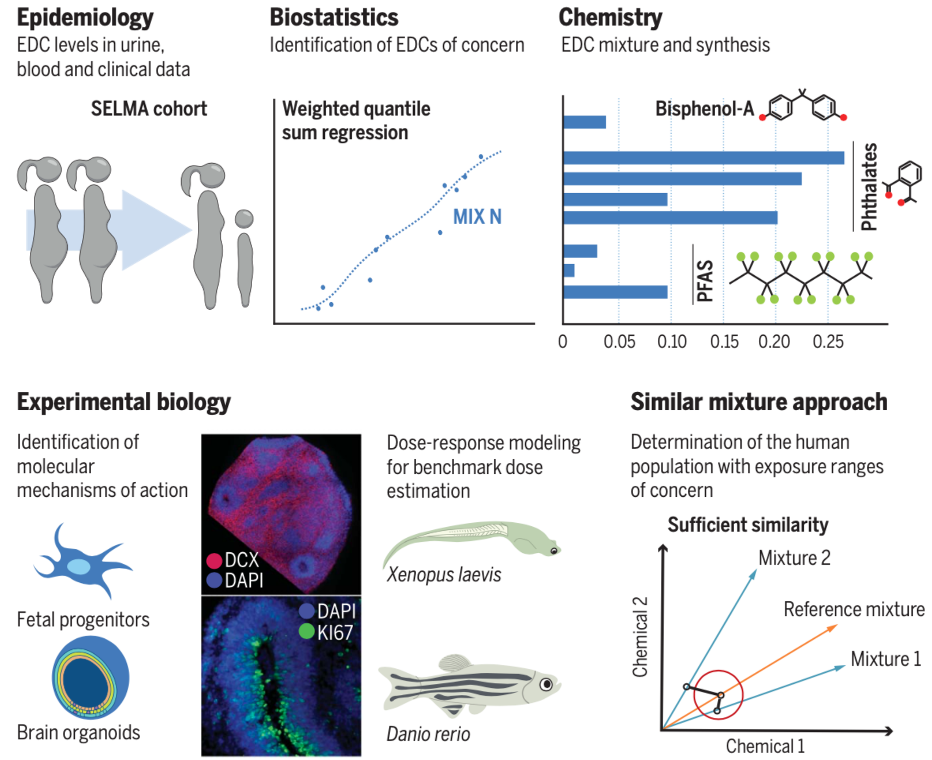
Keywords Epigenetics, Puberty, Differential methylation, Central precocious puberty, CPP, CpG

RESEARCH ARTICLE

ENVIRONMENTAL TOXINS

From cohorts to molecules: Adverse impacts of endocrine disrupting mixtures

Caporale *et al.*, *Science* **375**, eabe8244 (2022)   18 February 2022



Integrando studi sperimentali (human brain organoids, *Xenopus leavis* e *Danio rerio*) ed epidemiologici (The SELMA study: A birth cohort study in Sweden following more than 2000 mother-child pairs), sono state evidenziate (in vivo) correlazioni positive tra l'esposizione intrauterina ad una miscela di EDC e aumento delle probabilità di ritardo del linguaggio nella prole fino al 54% delle donne in gravidanza, e (in vitro) deregolazione di geni coinvolti nell'autismo

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ENVIRONMENTAL EPIGENETICS

Environmental Epigenetics, 2020, 1–12

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Research Article

RESEARCH ARTICLE

Maternal environmental exposure to bisphenols and epigenome-wide DNA methylation in infant cord blood

Carolyn F. McCabe [1], Vasantha Padmanabhan [2,3,4], Dana C. Dolinoy [1,2], Steven E. Domino[3], Tamara R. Jones[2], Kelly M. Bakulski [5] and Jaclyn M. Goodrich [2,*]

Maternal prenatal exposures, including bisphenol A (BPA), are associated with offspring's risk of disease later in life. Alterations in DNA methylation may be a mechanism through which altered prenatal conditions (e.g. maternal exposure to environmental toxicants) elicit this disease risk. In the Michigan Mother and Infant Pairs Cohort, maternal first-trimester urinary BPA, bisphenol F, and bisphenol S concentrations were tested for association with DNA methylation patterns in infant umbilical cord blood leukocytes ($N = 69$). We used the Illumina Infinium MethylationEPIC BeadChip to quantitatively evaluate DNA methylation across the epigenome; 822 020 probes passed pre-processing and quality checks. Single-site DNA methylation and bisphenol models were adjusted for infant sex, estimated cell-type proportions (determined using cell-type estimation algorithm), and batch as covariates. Thirty-eight CpG sites [false discovery rate (FDR) <0.05] were significantly associated with maternal BPA exposure. Increasing BPA concentrations were associated with lower DNA methylation at 87% of significant sites. BPA exposure associated DNA methylation sites were enriched for 38 pathways significant at FDR <0.05. The pathway or gene-set with the greatest odds of enrichment for differential methylation (FDR <0.05) was type I interferon receptor binding. This study provides a novel understanding of fetal response to maternal bisphenol exposure through epigenetic change.

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Networks of placental DNA methylation correlate with maternal serum PCB concentrations and child neurodevelopment

Julia S. Mouat[a,b,c,d], Xueshu Li[e], Kari Neier[a,b,c,d], Yihui Zhu[a,b,c,d], Charles E. Mordaunt[a,b,c,d], Michele A. La Merrill[b,f], Hans-Joachim Lehmler[e], Michael P. Jones[g], Pamela J. Lein[b,d,h], Rebecca J. Schmidt[b,d,i], Janine M. LaSalle[a,b,c,d,*]

Esposizione specifica (PCB), metilazione del DNA placentare e rischio di ASD

L'esposizione gestazionale a bifenili policlorurati (PCB) è stata associata a un rischio elevato di disturbi dello sviluppo neurologico nella prole. Gli alterati livelli di metilazione del DNA placentare sono stati associati ai livelli di PCB materni e allo sviluppo neurologico infantile. La metilazione di *CSMD1* e *AUTS2* potrebbe rappresentare un marcatore di alterata funzionalità placentare e/o rischio di ASD a seguito di esposizione materna a PCB.

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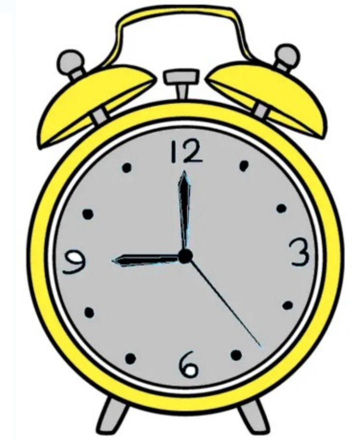
Article

Sex-Specific Associations between Prenatal Exposure to Bisphenols and Phthalates and Infant Epigenetic Age Acceleration

Gillian England-Mason [1,2], Sarah M. Merrill [3,4,5], Jiaying Liu [6], Jonathan W. Martin [7], Amy M. MacDonald [8], David W. Kinniburgh [6,8], Nicole Gladish [4,5], Julia L. MacIsaac [4,5], Gerald F. Giesbrecht [1,2,9,10], Nicole Letourneau [1,2,10,11,12,13], Michael S. Kobor [4,5,14] and Deborah Dewey [1,2,10,13,*]



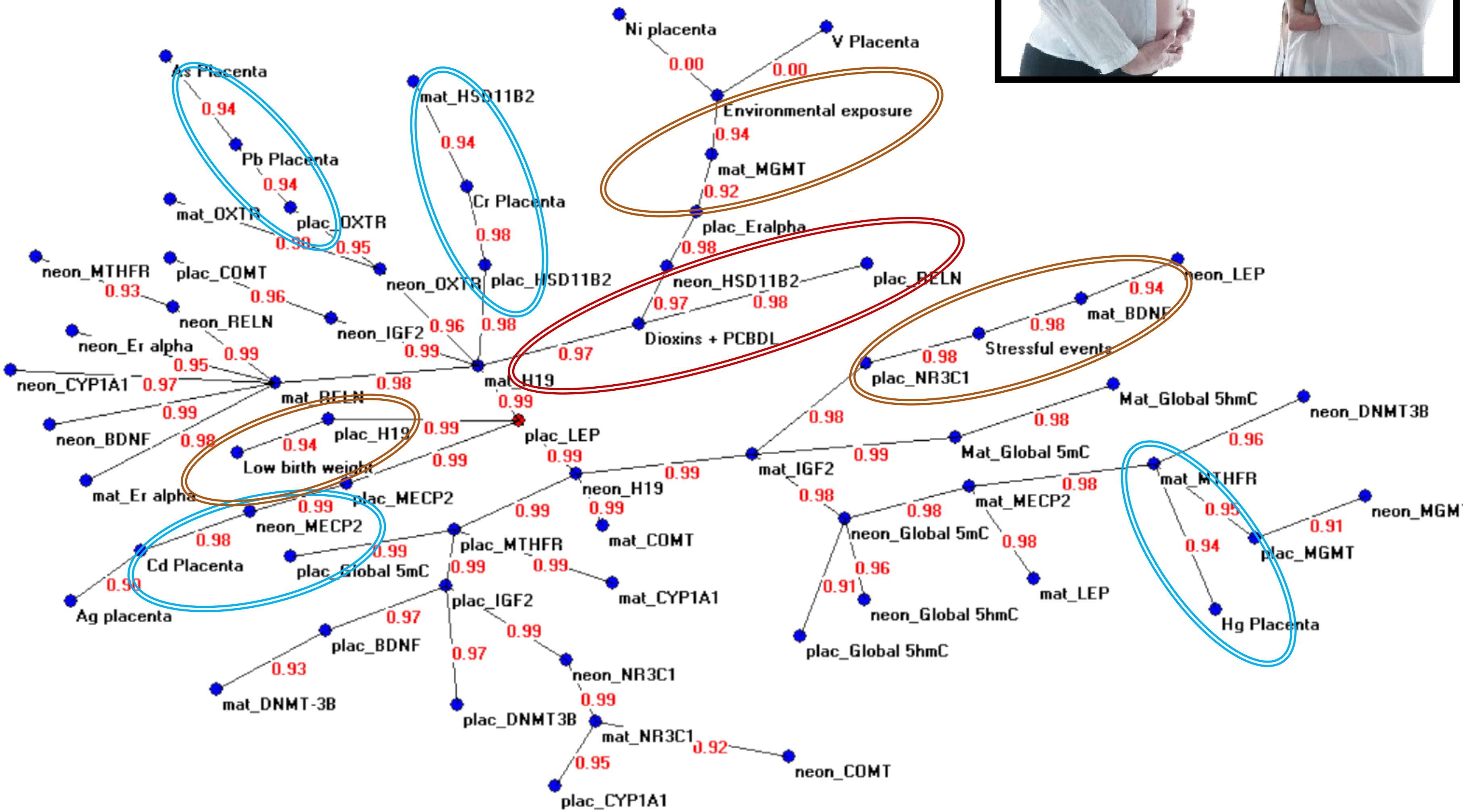
Abstract: We examined whether prenatal exposure to two classes of endocrine-disrupting chemicals (EDCs) was associated with infant epigenetic age acceleration (EAA), a DNA methylation biomarker of aging. Participants included 224 maternal–infant pairs from a Canadian pregnancy cohort study. Two bisphenols and 12 phthalate metabolites were measured in maternal second trimester urines. Buccal epithelial cell cheek swabs were collected from 3 month old infants and DNA methylation was profiled using the Infinium MethylationEPIC BeadChip. The Pediatric-Buccal-Epigenetic tool was used to estimate EAA. Sex-stratified robust regressions examined individual chemical associations with EAA, and Bayesian kernel machine regression (BKMR) examined chemical mixture effects. Adjusted robust models showed that in female infants, prenatal exposure to total bisphenol A (BPA) was positively associated with EAA ($B = 0.72$, 95% CI: 0.21, 1.24), and multiple phthalate metabolites were inversely associated with EAA (Bs from −0.36 to −0.66, 95% CIs from −1.28 to −0.02). BKMR showed that prenatal BPA was the most important chemical in the mixture and was positively associated with EAA in both sexes. No overall chemical mixture effects or male-specific associations were noted. These findings indicate that prenatal EDC exposures are associated with sex-specific deviations in biological aging, which may have lasting implications for child health and development.

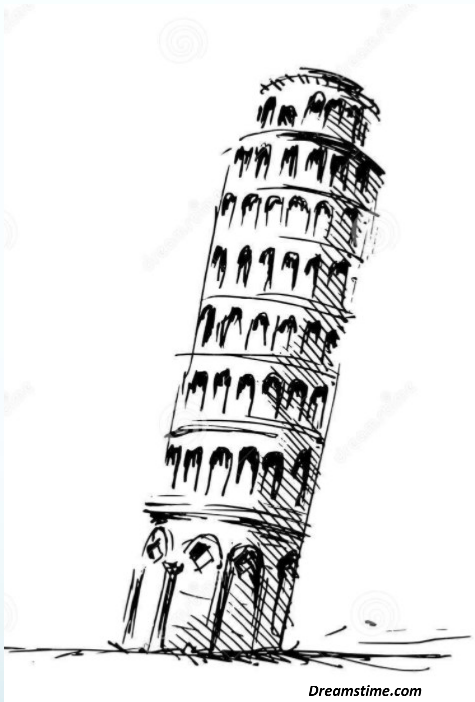
genes 2023 MDPI

Article

Prenatal environmental stressors and DNA methylation levels in placenta and peripheral tissues of mothers and neonates evaluated by applying Artificial Neural Networks

Andrea Stoccoro[1]†, Vanessa Nicolì[1]†, Fabio Coppedè[1], Enzo Grossi[2], Giorgio Fedrizzi[3], Simonetta Menotta[3], Francesca Lorenzoni[4], Marta Caretto[5], Arianna Carmignani[6], Sabina Pistolesi[7], Ernesto Burgio[8], Vassilios Fanos[9], Lucia Migliore[1,10]*





Grazie per l'attenzione!