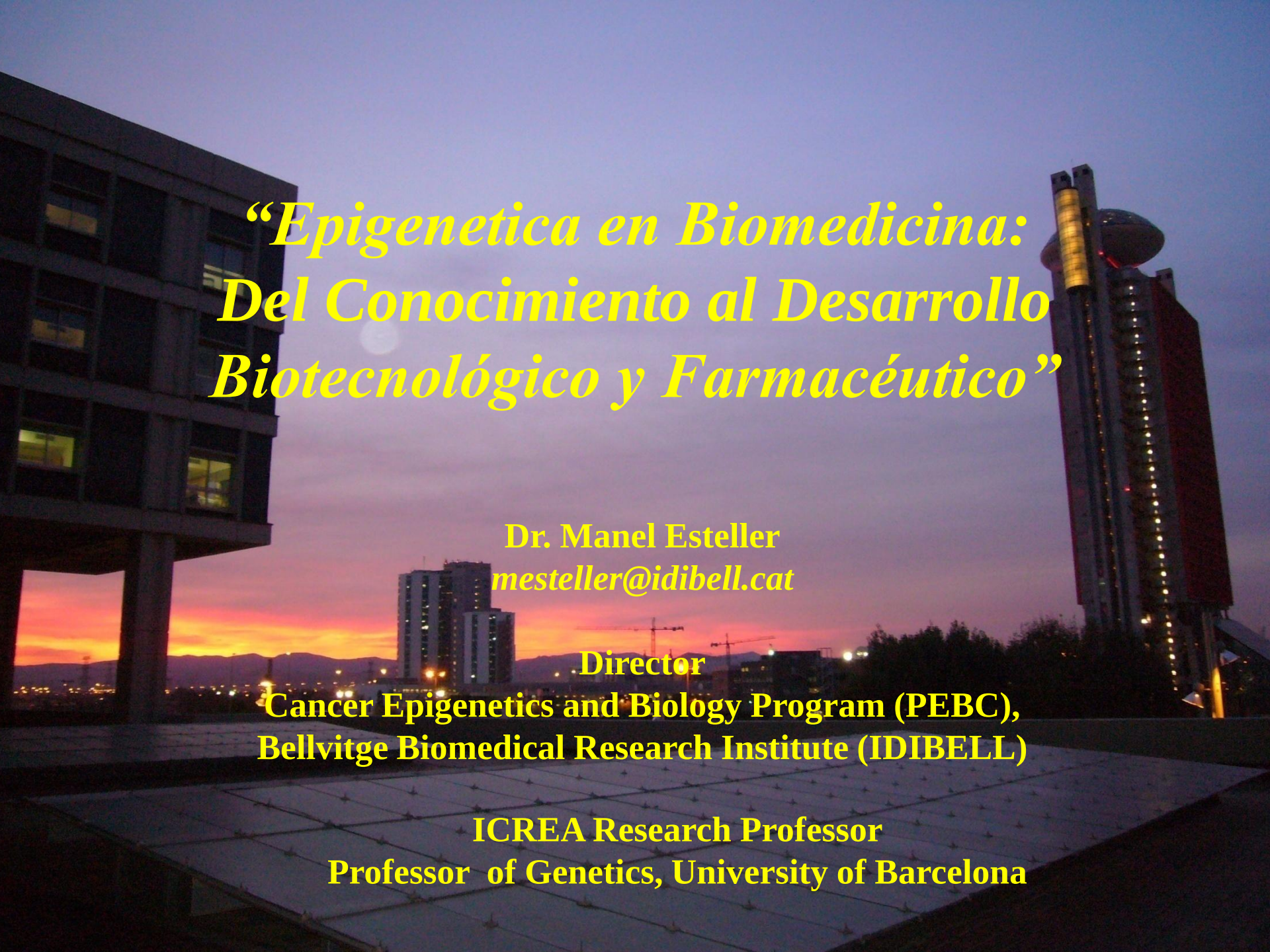

"Epigenetica en Biomedicina: Del Conocimiento al Desarrollo Biotecnológico y Farmacéutico"

Dr. Manel Esteller
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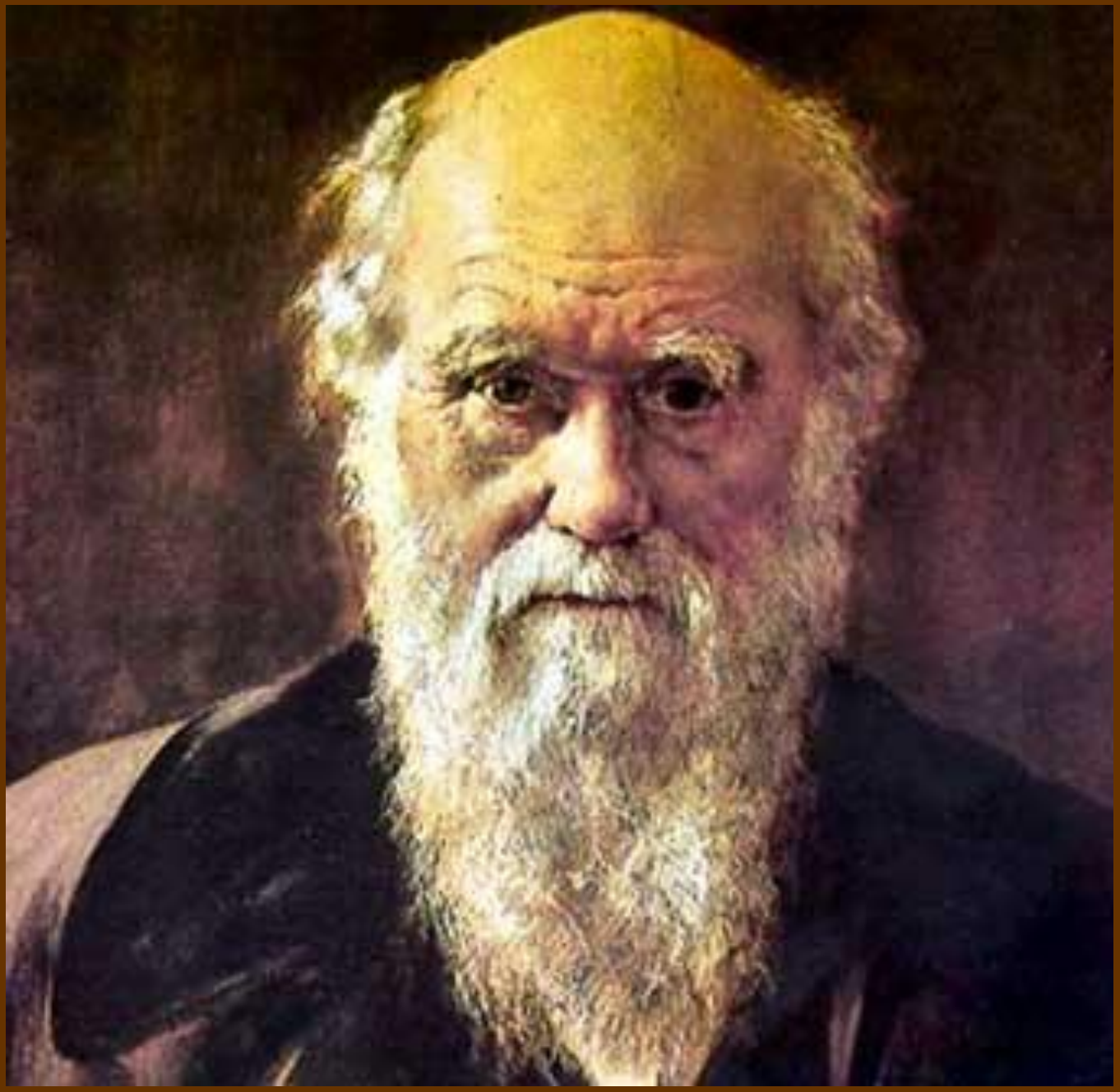
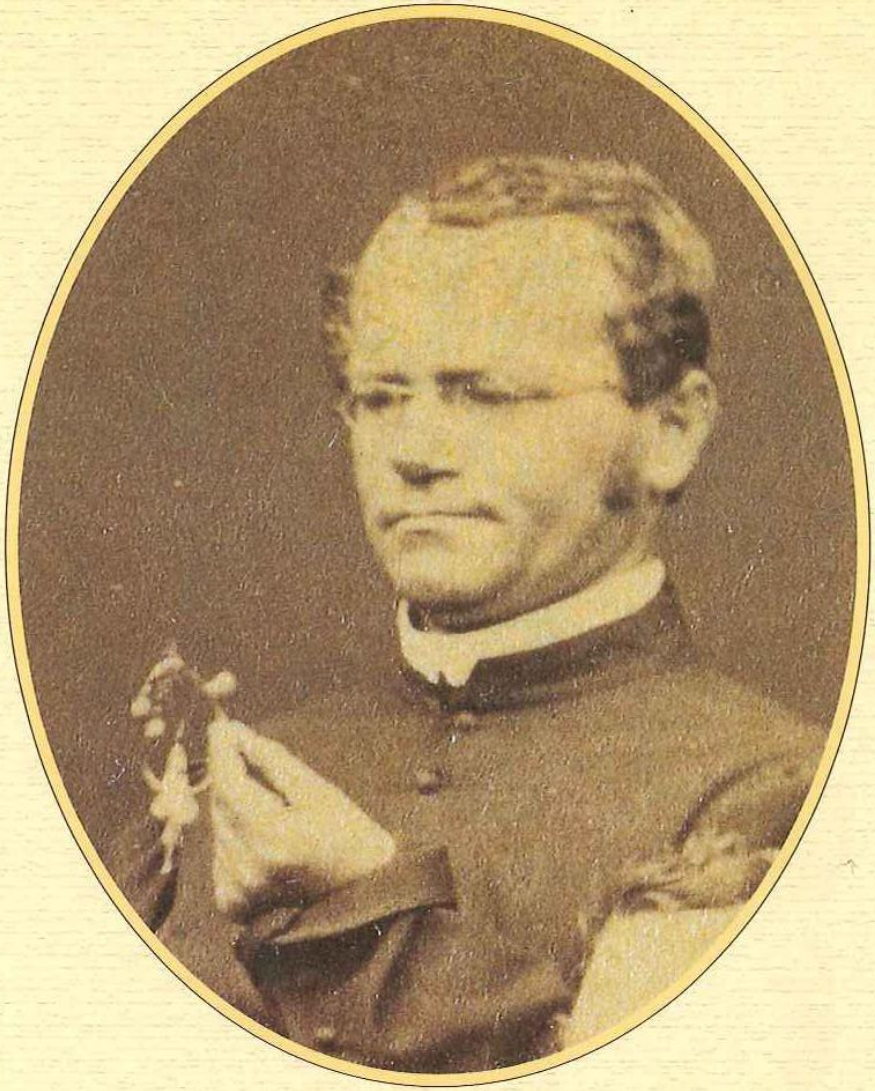
Director
Cancer Epigenetics and Biology Program (PEBC),
Bellvitge Biomedical Research Institute (IDIBELL)

ICREA Research Professor
Professor of Genetics, University of Barcelona



Gregor Johann Mendel (1822–1884)
The Genius of Genetics



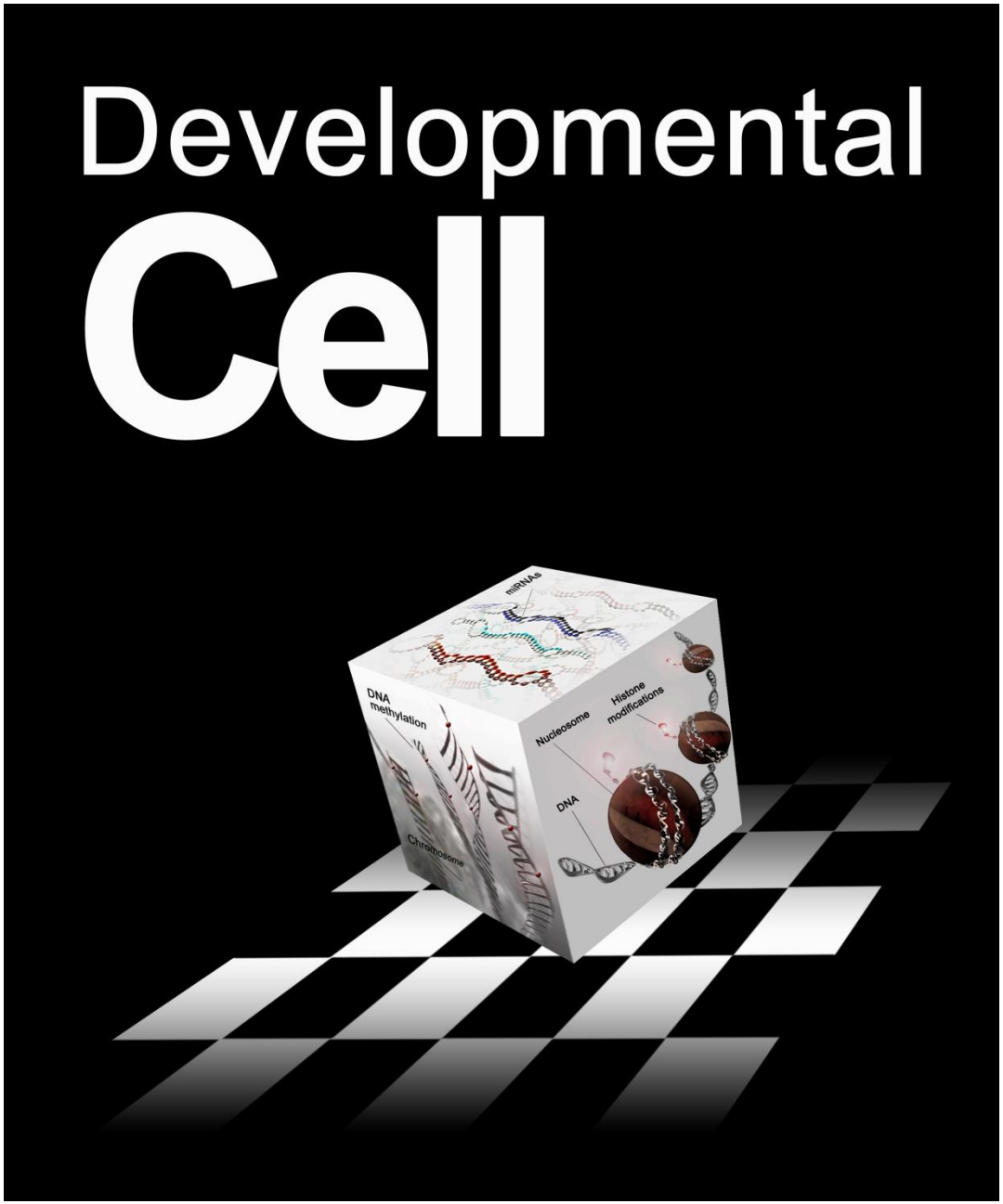
Brno, Czech Republic


Gregor
Mendel
Otevřeno
květen - říjen
denně 10h - 18h
listopad - duben
st - ne 10h - 16h
Open
May - October
daily 10am - 6pm
November - April
Wed - Sun 10am - 4pm

WE ARE MORE THAN OUR GENES !

inrecentyearsepigeneticalterationshavecometopr
ominenceincancerresearchinparticularhypermethy
lationofcpgislandslocatedinthepromoterregionso
ftumorsuppressorgenesisnowfirmlyestablishedasa
nimportantmechanismforgeneinactivationincancer
oneofthemostremarkableachievementsinthefieldha
sbeentheidentificationofthemethylcpgbindingdom
ainfamilyofproteinswhichprovidemechanisticlink
sbetweenspecificpatternsofdnamethylationandhis
tonemodificationsalthoughmanyofthecurrentdatai
ndicatethatmethylcpgbindingproteinsplayakeyrol
einmaintainingatranscriptionallyinactivestateo
fmethylatedgenesmbd4isalsoknowntobeinvolvedine
xcisionrepairoftgmismatchesthelatterisamembero
fthisfamilyofproteinsandappearstoplayaroleinre
ducingmutationsat5methylcytosinethisreviewexam
inesthecontributionofmethylcpgbindingproteinsi
ntheepigeneticpathwayofcancer

In recent years, epigenetic alterations have come to prominence in cancer research. In particular, hypermethylation of CpG islands located in the promoter regions of tumor-suppressor genes is now firmly established as an important mechanism for gene inactivation in cancer. One of the most remarkable achievements in the field has been the identification of the methyl-CpG-binding domain family of proteins, which provide mechanistic links between specific patterns of DNA methylation and histone modifications. Although many of the current data indicate that methyl-CpG-binding proteins play a key role in maintaining a transcriptionally inactive state of methylated genes, MBD4 is also known to be involved in excision repair of T:G mismatches. The latter is a member of this family of proteins and appears to play a role in reducing mutations at 5-methylcytosine. This review examines the contribution of methyl-CpG-binding proteins in the epigenetic pathway of cancer.



The Epigenetic Dice:

-DNA Methylation

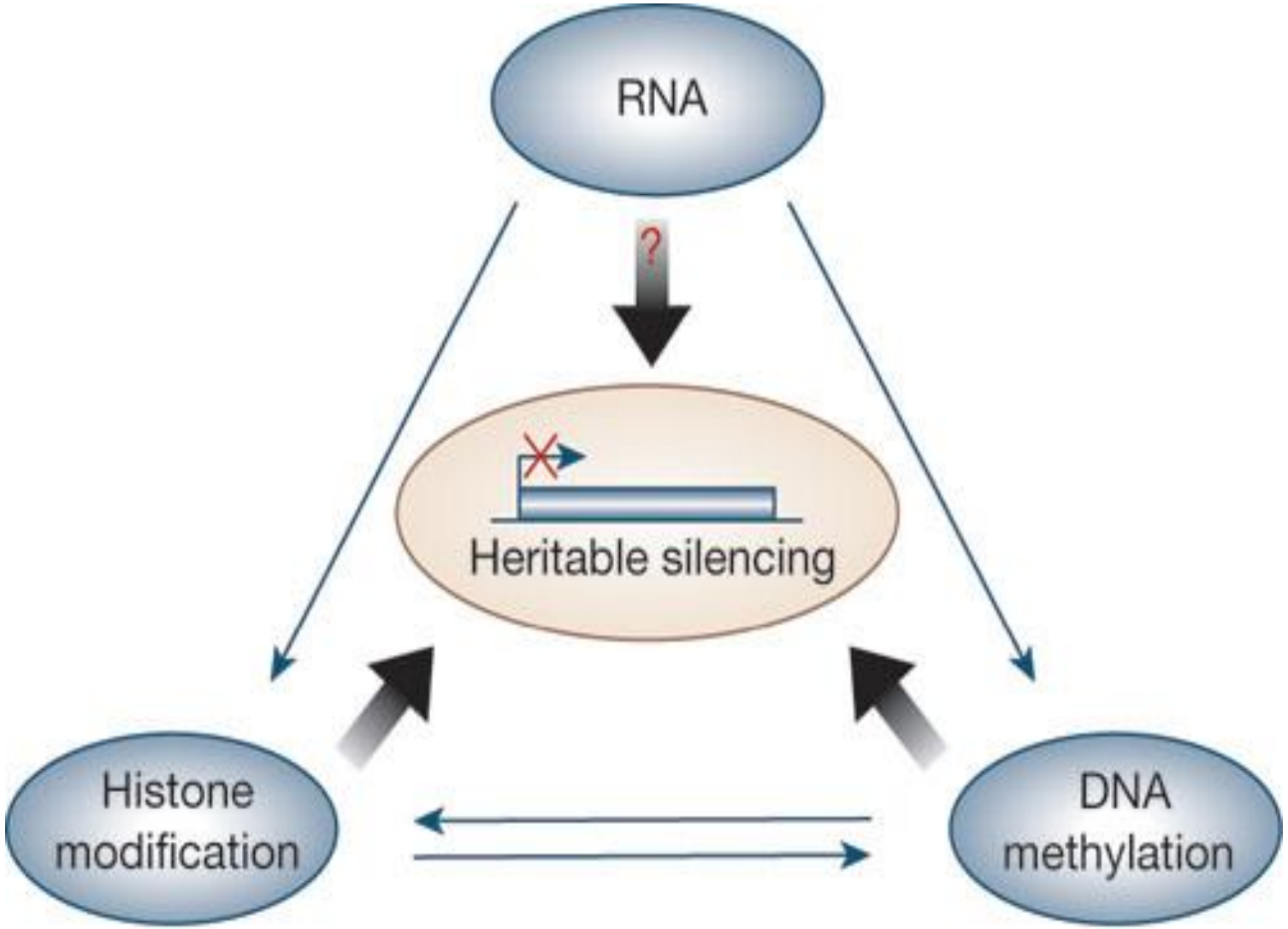
-Histone Modifications

-ncRNAs

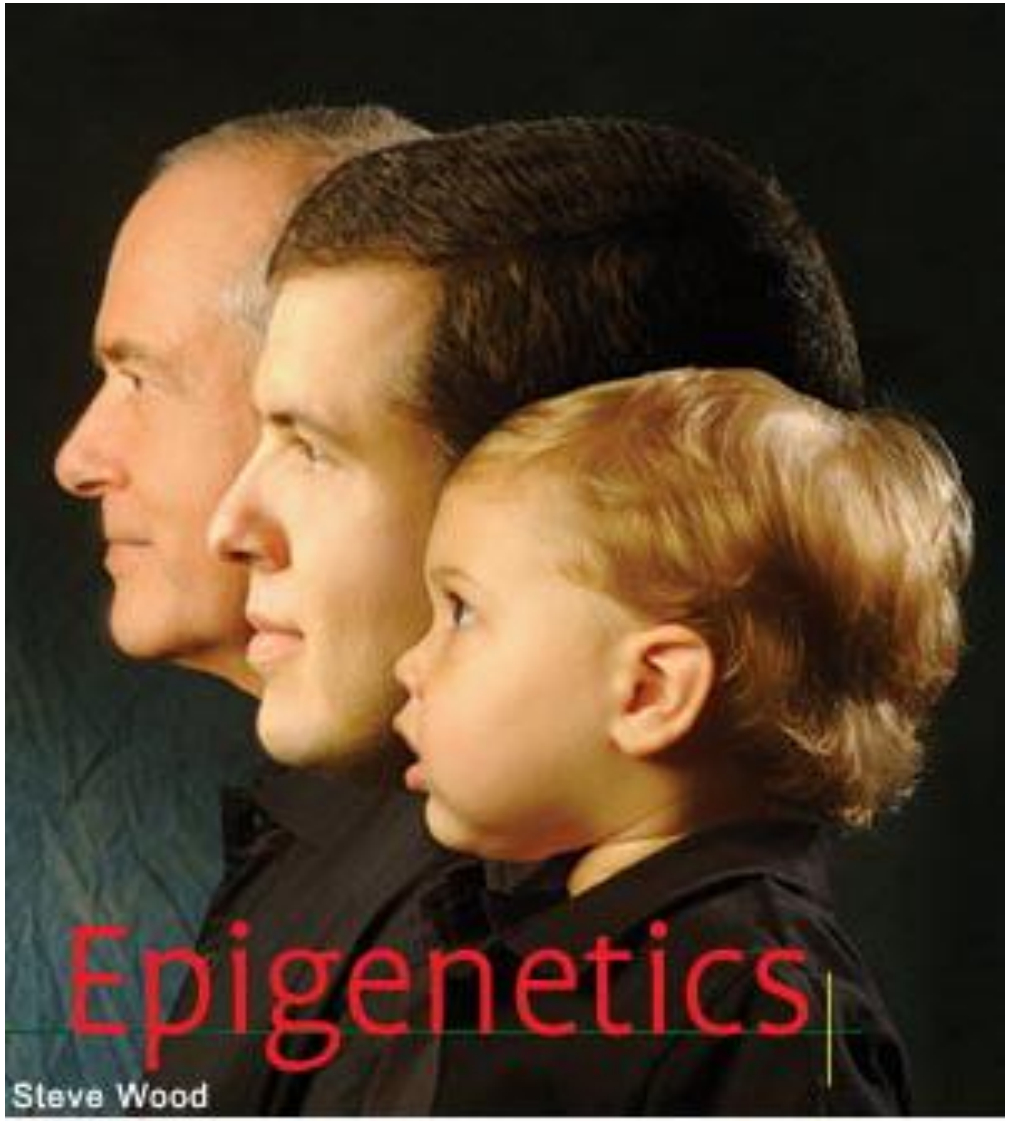
-….

Cover by Sanchez-Mut and Esteller, Dev Cell, November 15th 2010

Epigenetics Parameters

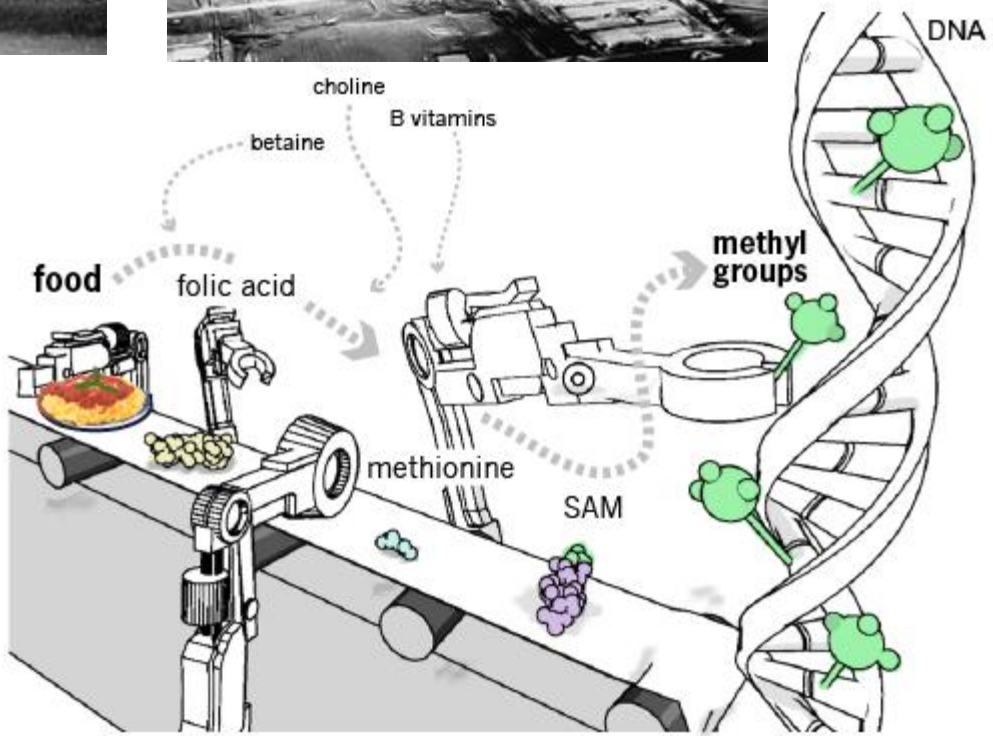


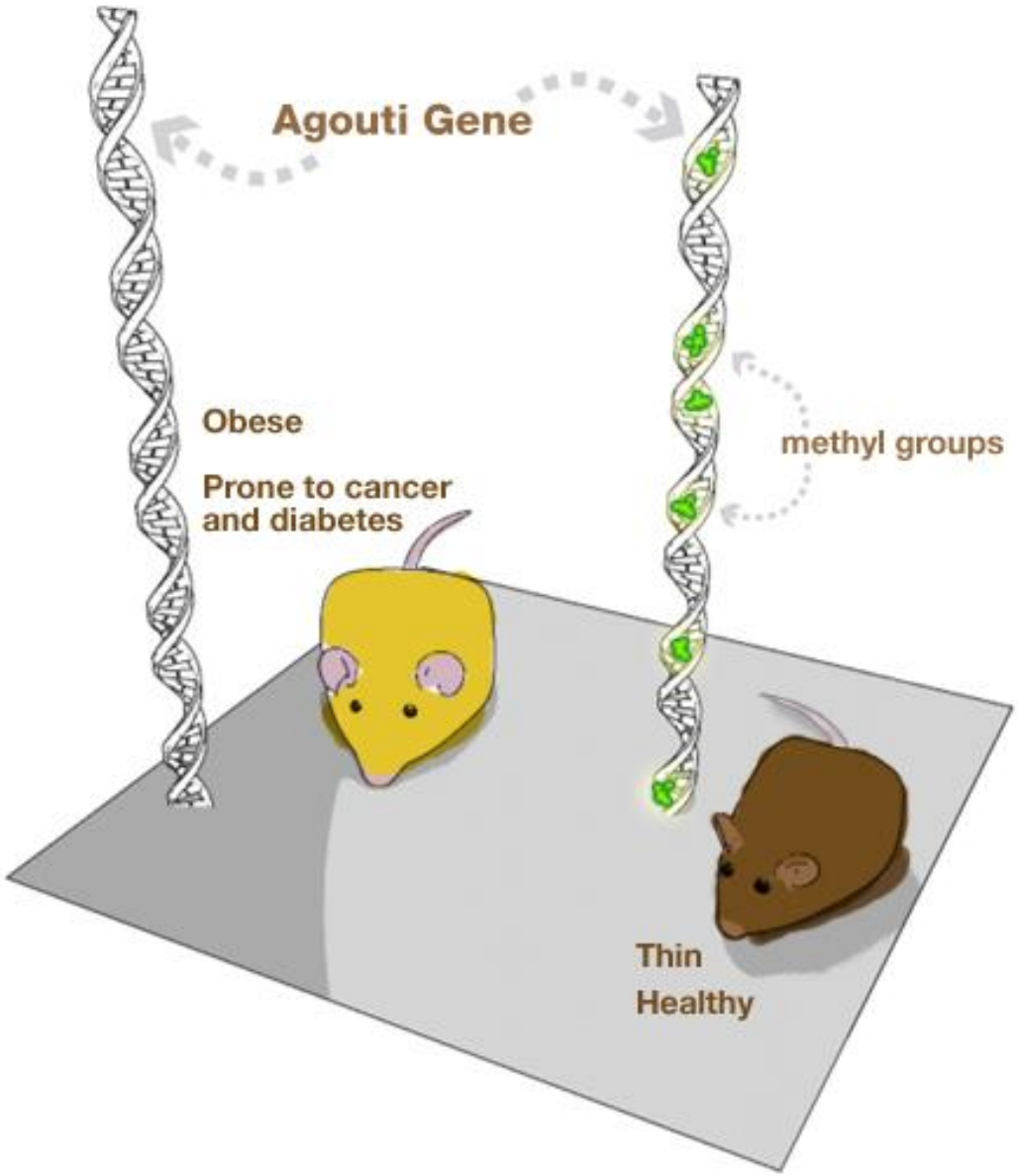
Nature, 429, 457-63, 2004



Going Beyond the Gene

Imprint of famine seen in genes of Second World War babies 60 years on

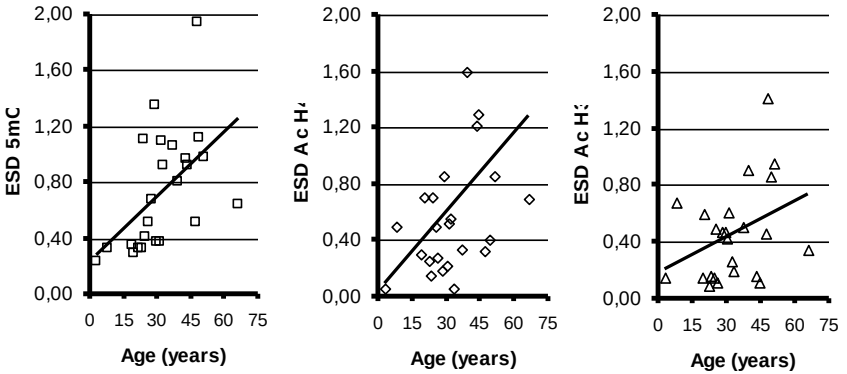



Agouti Gene
Obese
Prone to cancer
and diabetes
methyl groups
Thin
Healthy

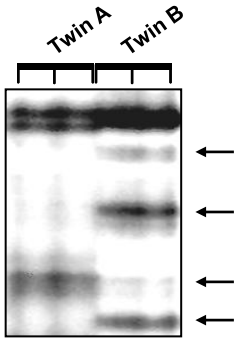
Towards the Human Epigenome

A

B

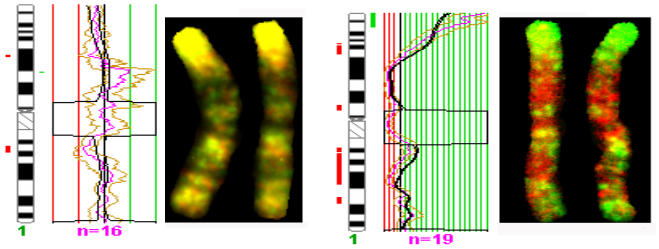


C



50-year-old

D



3-year-old twins

50-year-old twins

PNAS

Epigenetic differences arise during the lifetime of monozygotic twins

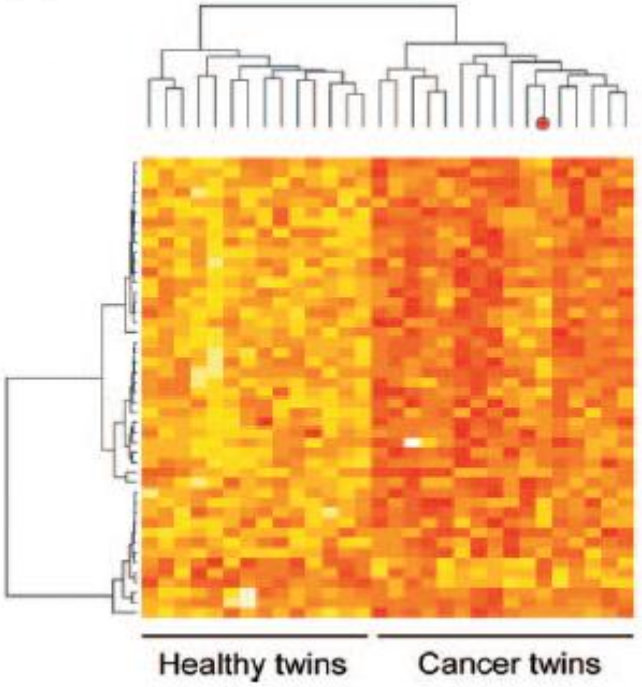
Mario F. Fraga*, Esteban Ballestar*, Maria F. Paz*, Santiago Ropero*, Fernando Setien*, Maria L. Ballestar†, Damia Heine-Suñer‡, Juan C. Cigudosa§, Miguel Urioste¶, Javier Benitez¶, Manuel Boix-Chornet†, Abel Sanchez-Aguilera†, Charlotte Ling||, Emma Carlsson||, Pernille Poulsen**, Allan Vaag**, Zarko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

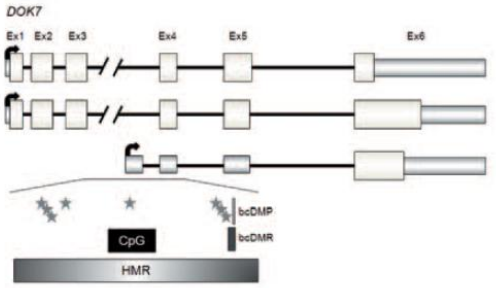
*Epigenetics, §Cytogenetics, and ¶Genetic Laboratories, Spanish National Cancer Centre (CNIO), Melchor Fernandez Almagro 3, 28029 Madrid, Spain; †Department of Behavioral Science, University of Valencia, 46010 Valencia, Spain; ‡Molecular Genetics Laboratory, Genetics Department, Son Dureta Hospital, 07014 Palma de Mallorca, Spain; ||Department of Clinical Sciences, University Hospital Malmö, Lund University, S-205 02 Malmö, Sweden; **Steno Diabetes Center, 2820 Gentofte, Denmark; ††Twin Research and Genetic Epidemiology Unit, St. Thomas' Hospital, London SE1 7EH, United Kingdom; and ‡‡Human Cancer Genetics Program, Department of Molecular Virology, Immunology, and Medical Genetics, Ohio State University, Columbus, OH 43210

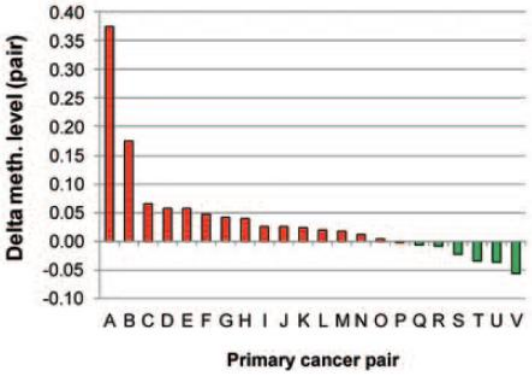
Edited by Stanley M. Gartler, University of Washington, Seattle, WA, and approved May 23, 2005 (received for review January 17, 2005)

Francis Collins, director of the National Human Genome Research Institute, said:
"Here's something where Mendel, Watson and Crick all seem to have missed some crucial goodies"

Discordant Twins for Breast Cancer



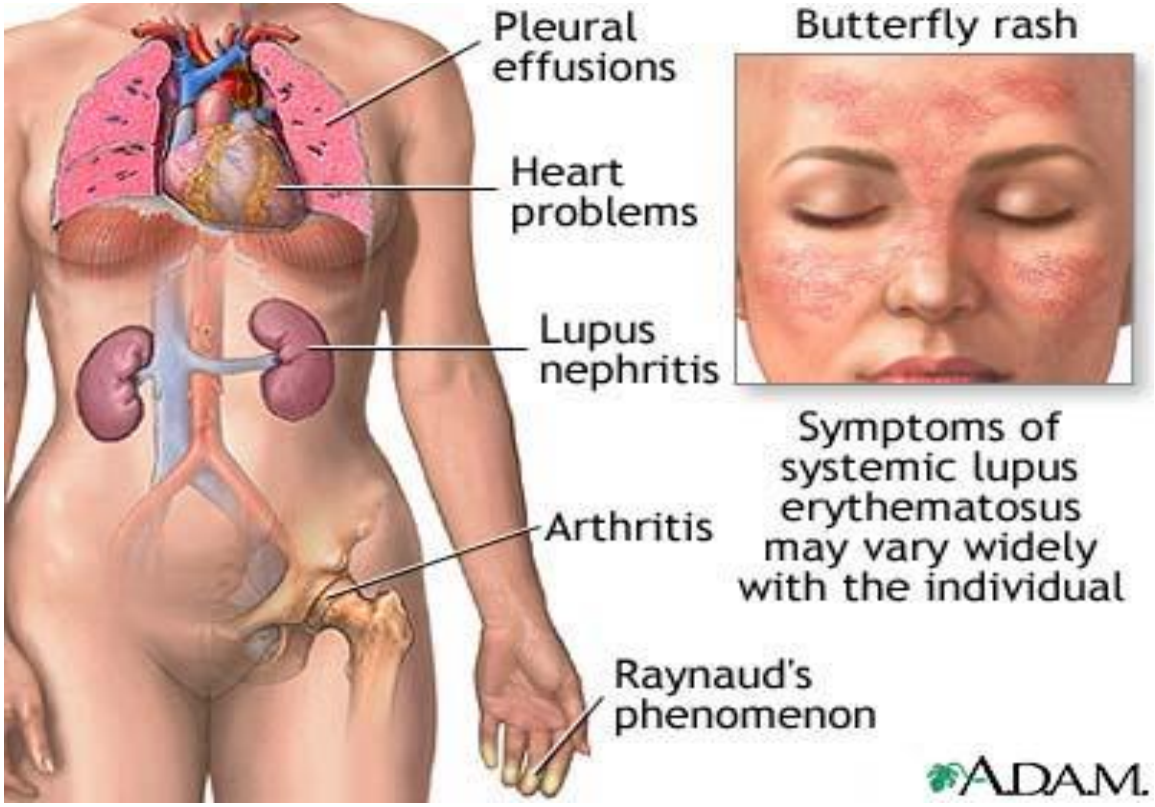




Heyn et al., Carcinogenesis 2012

Lupus eritematoso sistémico

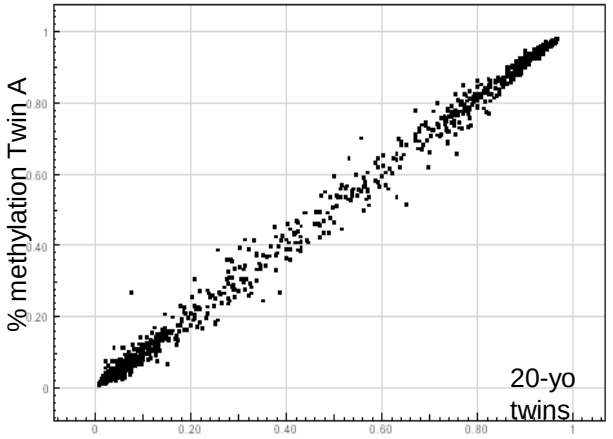
Autoimmune disease affecting many tissues and organs

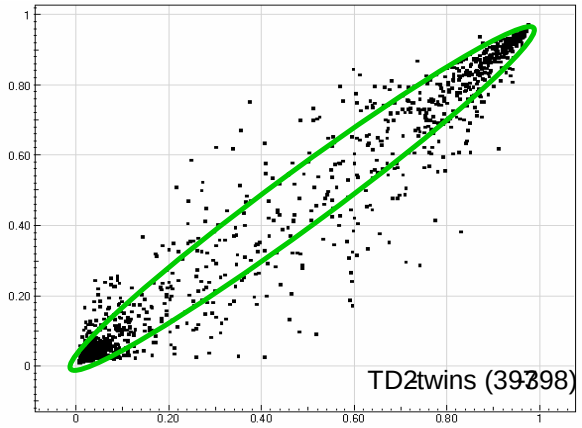


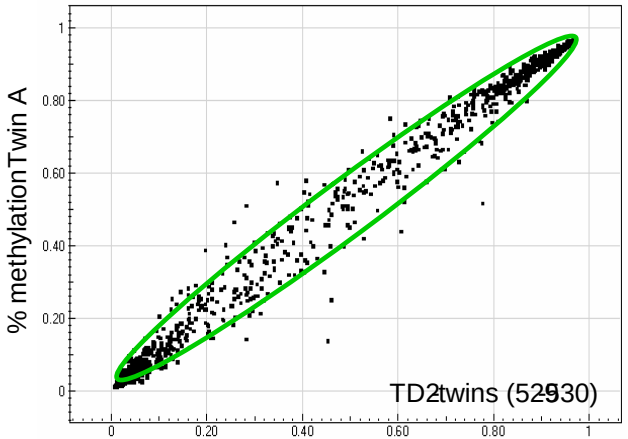
Autoantibodies against nuclear antigens, specially against DNA, histones and nucleosomes

Epigenetics, Discordant Twins and Disease

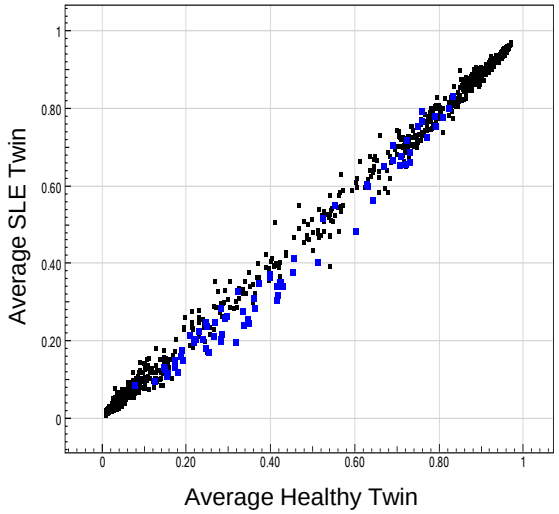
Diabetes Type 2, Target tissue: Fat

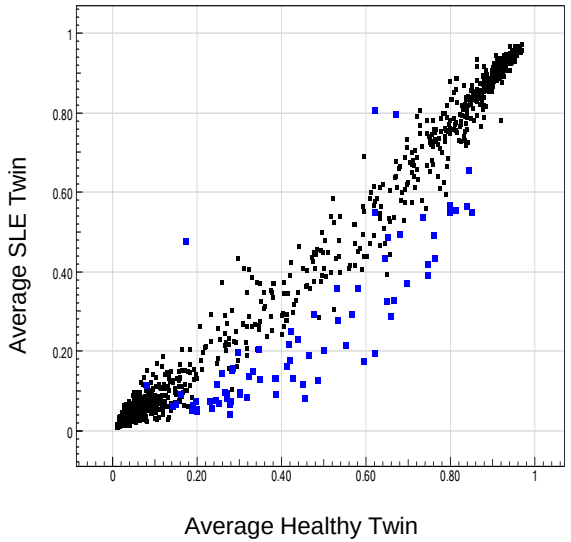


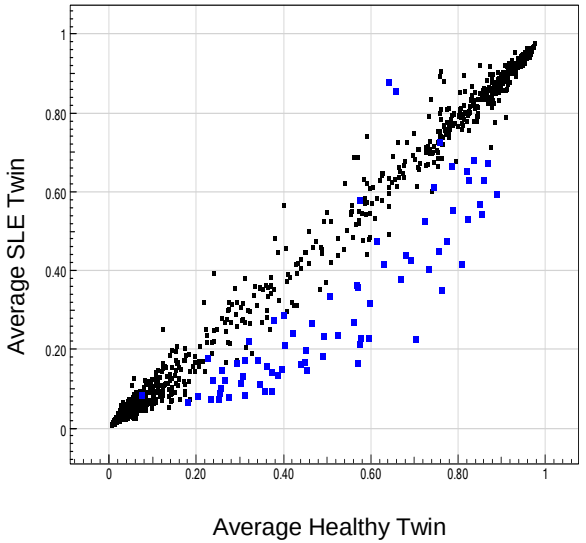




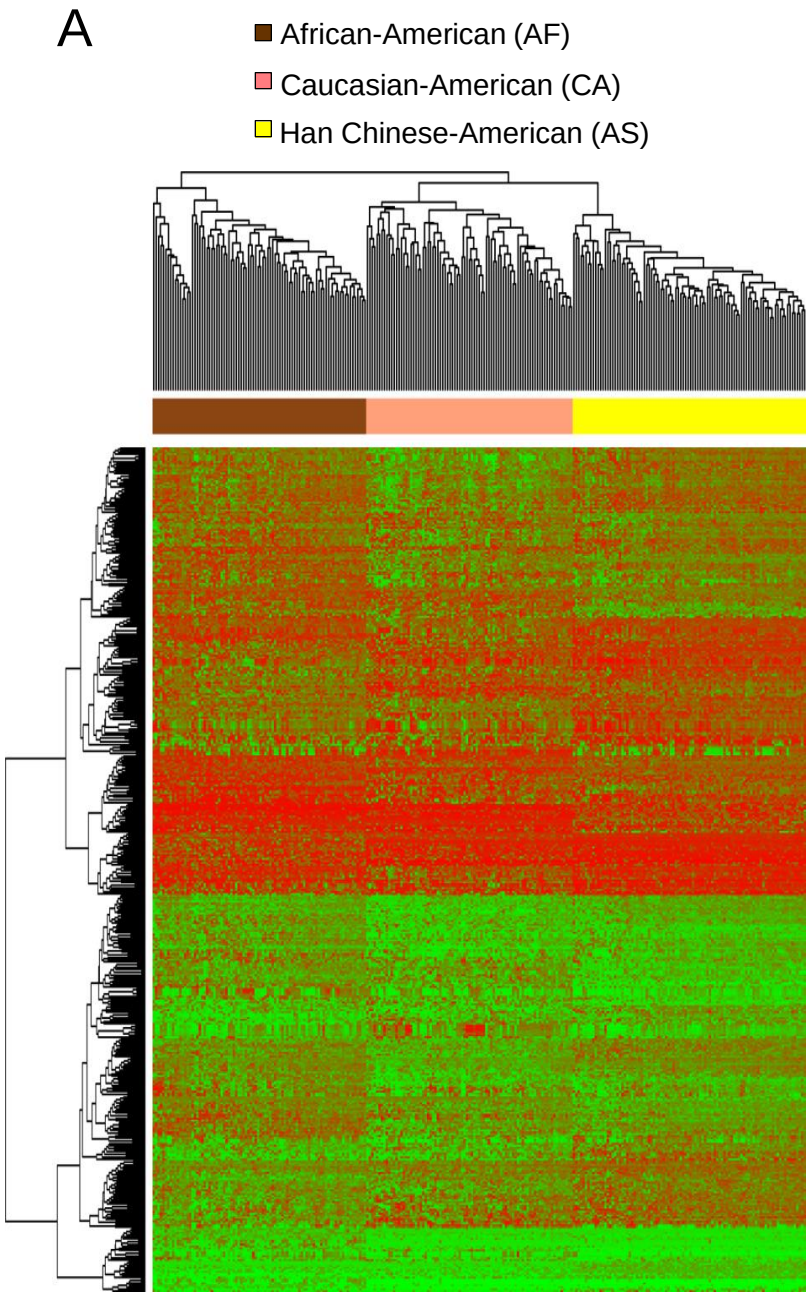
Systemic Lupus Erythematosus, Target tissue: Lymphocytes

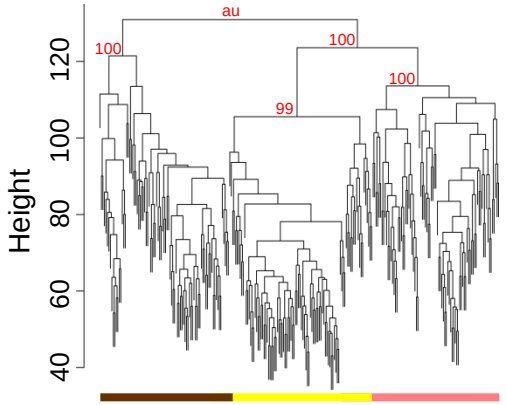


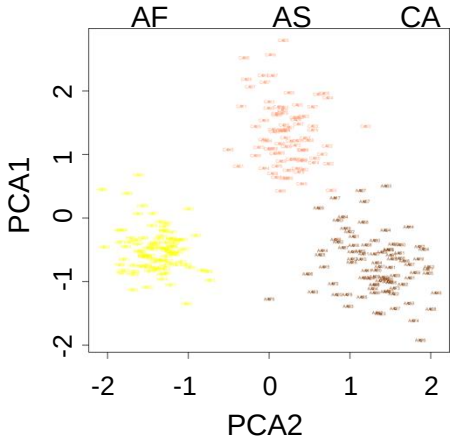


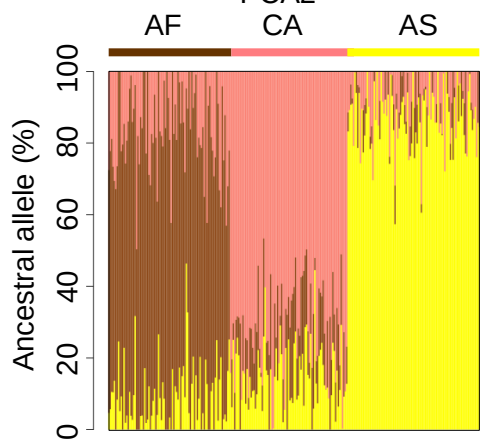


DNA methylation contributes to natural human variation

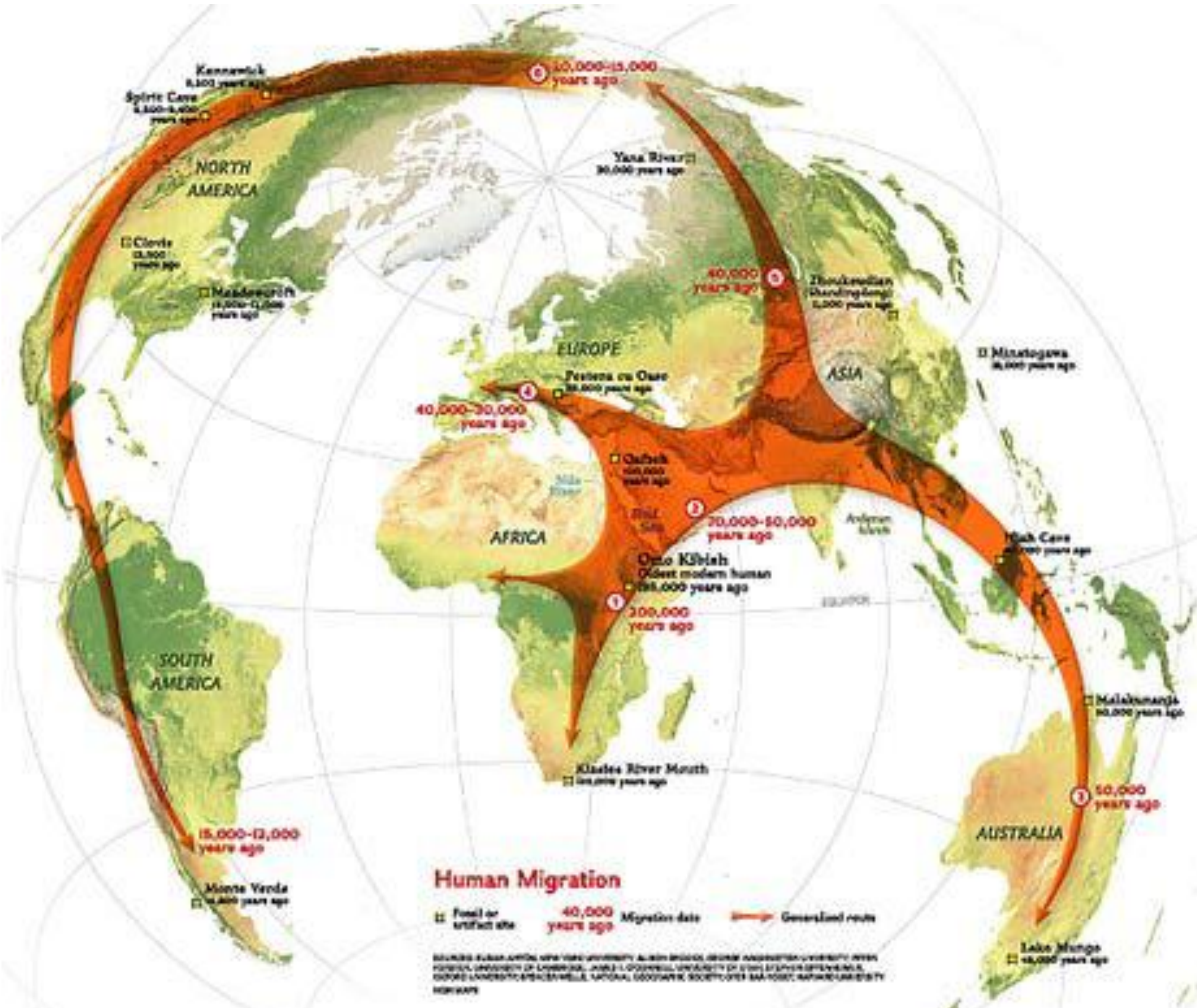








Heyn et al., Genome Research 2013



Kennewick
Spirit Cave
NORTH AMERICA
Clovis
20,000–15,000 years ago
Yana River
EUROPE
ASIA
AFRICA
SOUTH AMERICA
AUSTRALIA
40,000–30,000 years ago
40,000 years ago
70,000–50,000 years ago
200,000 years ago
50,000 years ago
15,000–12,000 years ago
Omo Kibish
Oldest modern human
Minatogawa
Niah Cave
Klasies River Mouth
Malakunanja
Monte Verde
Lake Mungo
Human Migration
Fossil or artifact site
40,000 years ago
Migration date
Generalized route

DNA methylation and natural human variation: pathways and diseases

DNA methylation and natural human variation: pathways and diseases

Taste

Skin Pigmentation

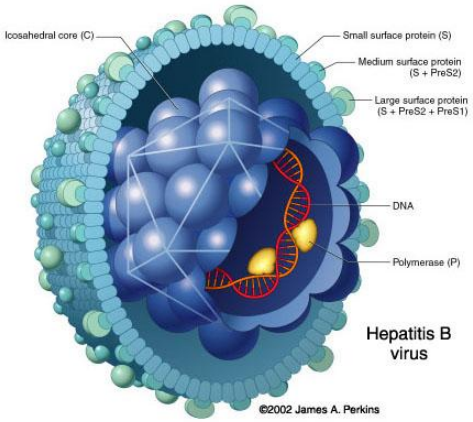
DNA methylation and natural human variation: pathways and diseases

Taste

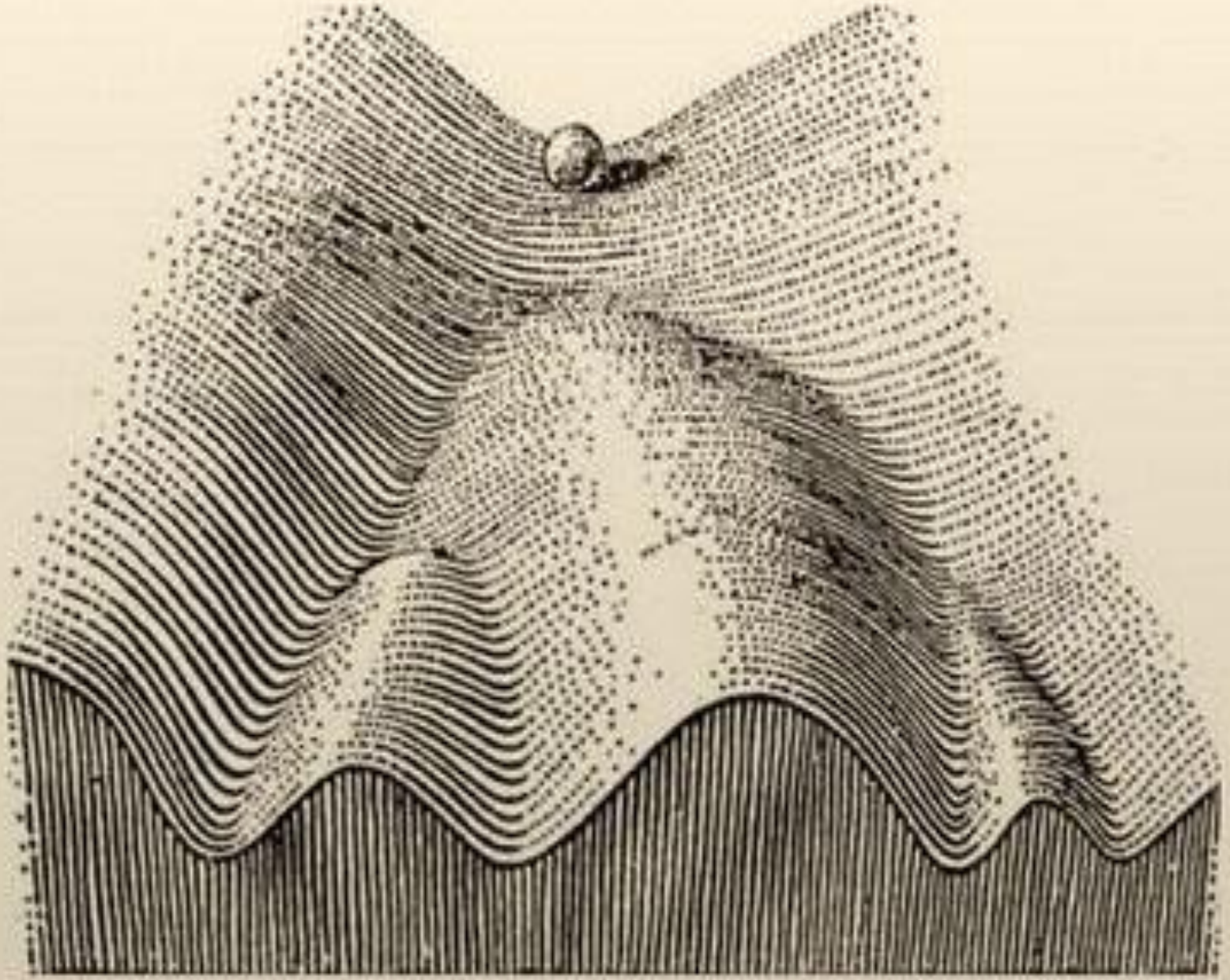
Skin Pigmentation

Diabetes

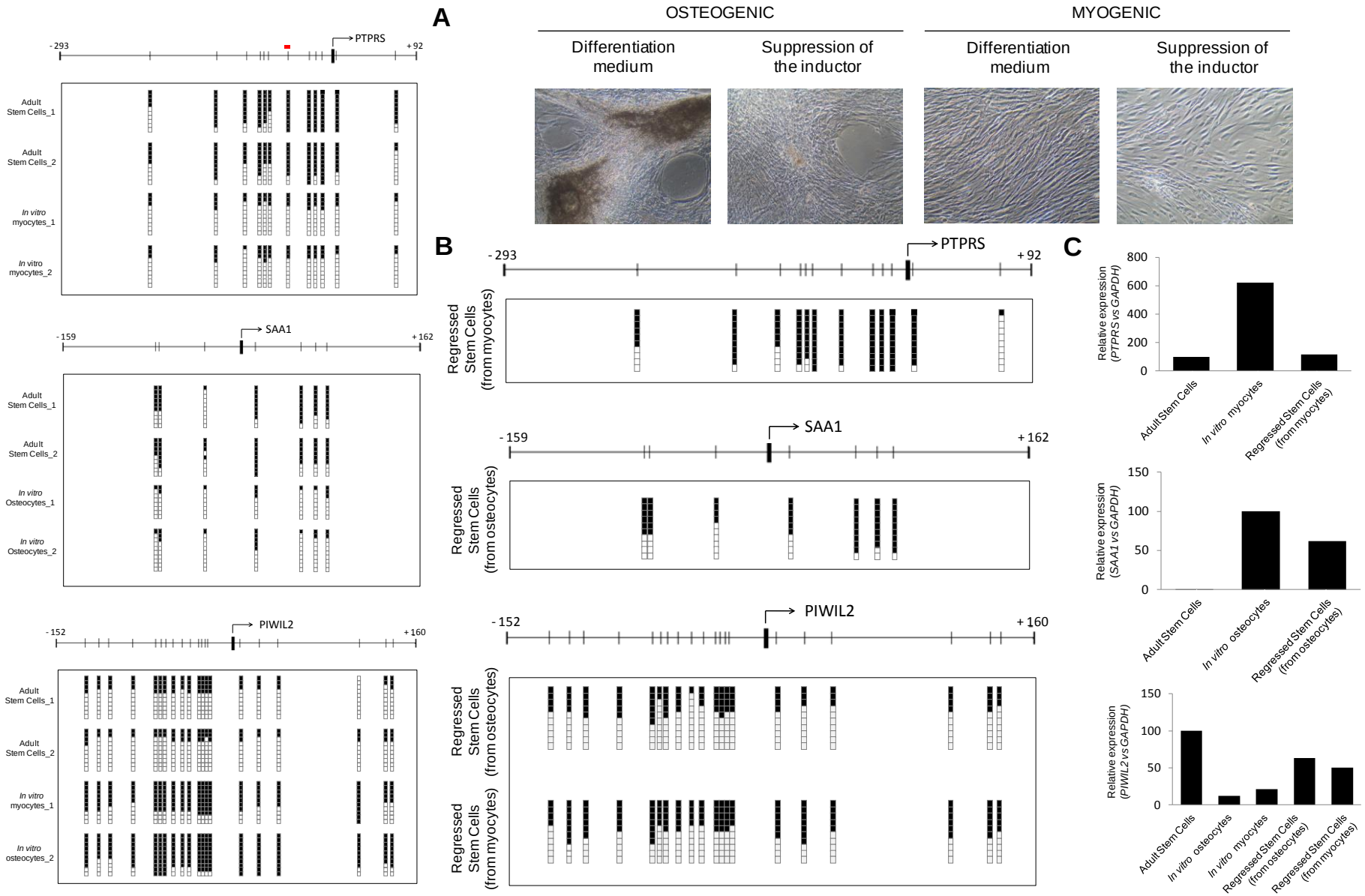
Parkinson's



Infection (HBV, HIV, Measles Virus, E. coli)



DNA methylation plasticity of human adipose-derived stem cells in lineage commitment



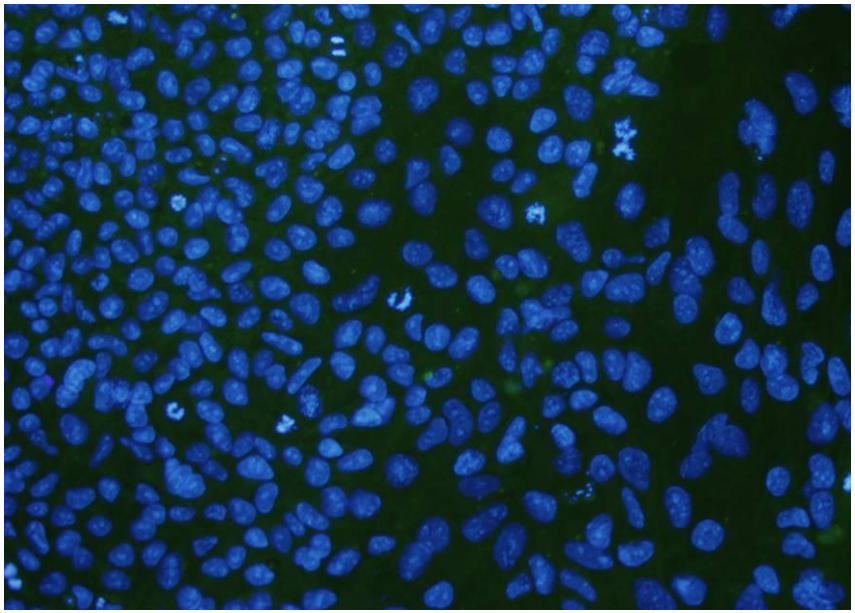
Berdasco et al., American Journal of Pathology 2012

Stem Cells and Sirtuins

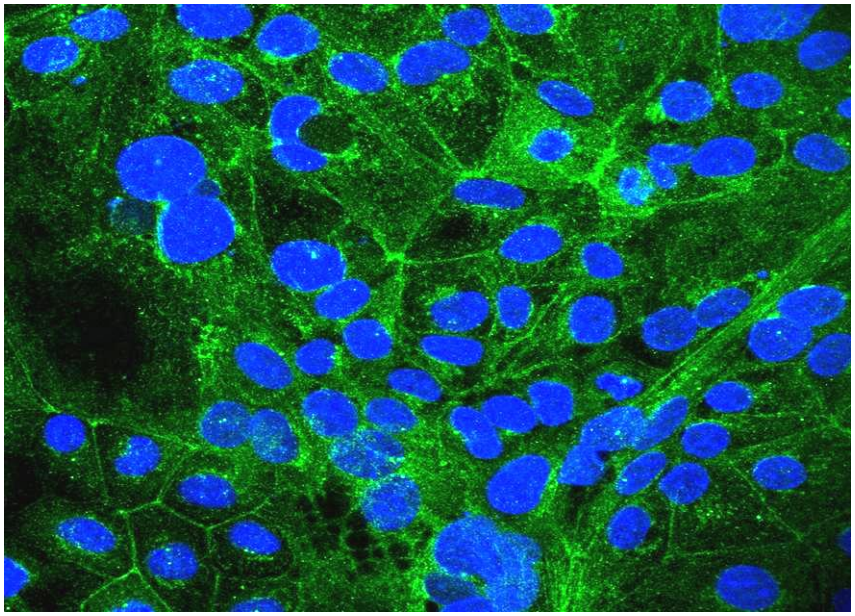
Blue: DAPI

Green: alpha-actin (mesodem)

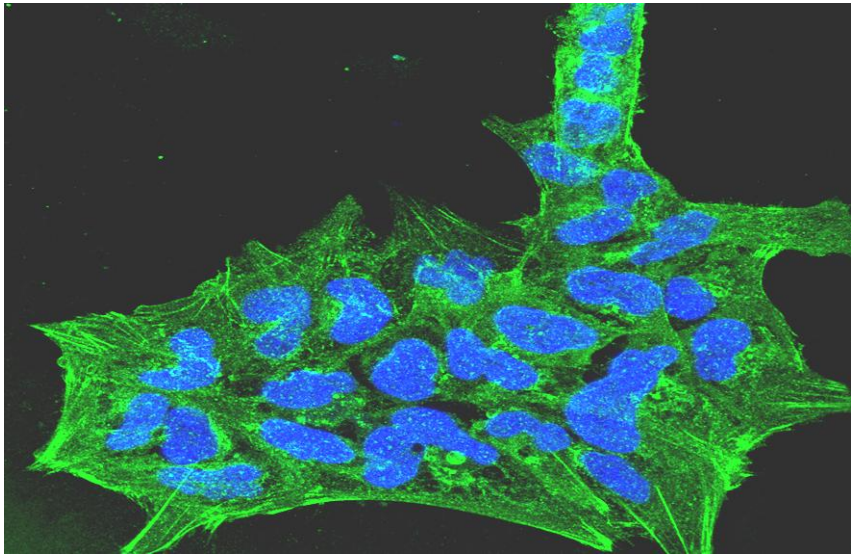
Embryonic Stem Cells (H-181)



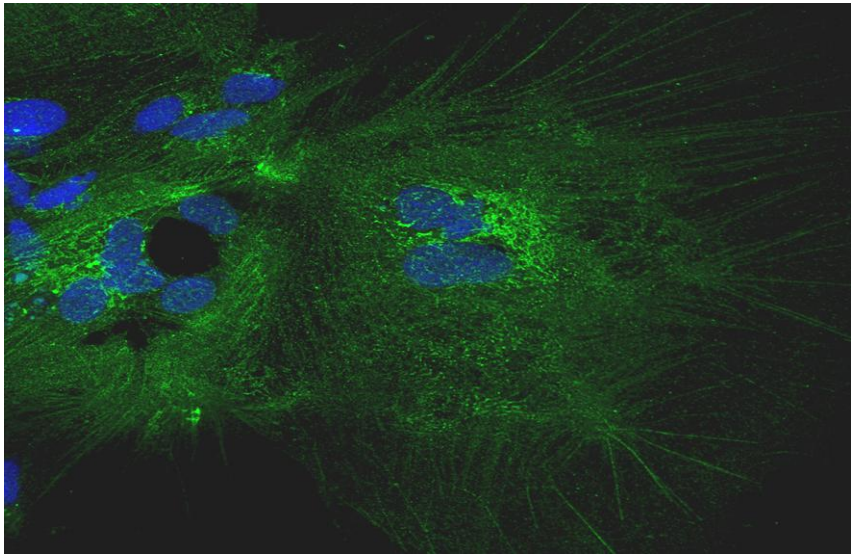
Differentiation upon siRNA of SIRT1



Differentiation upon Sirtinol treatment (24h)

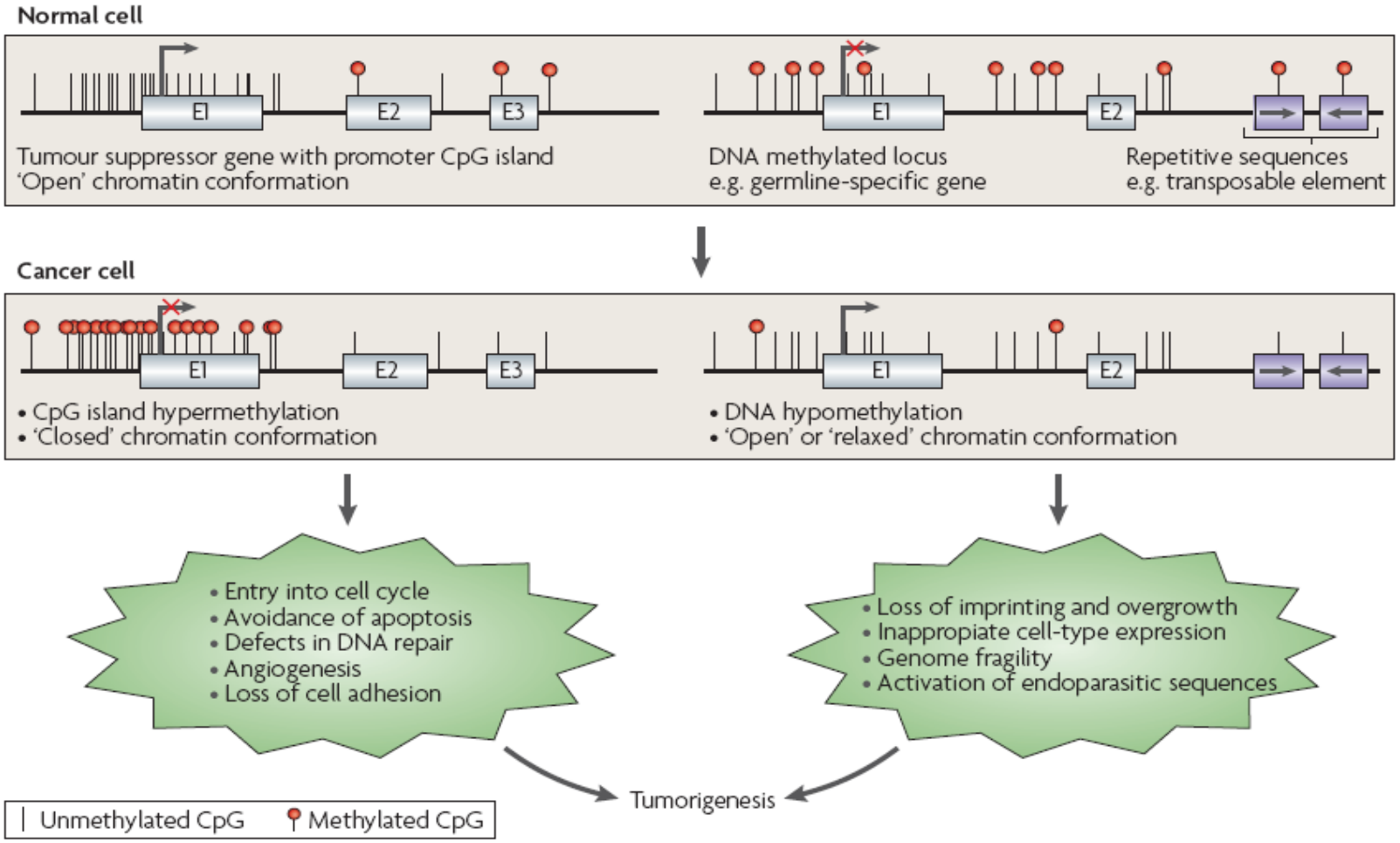


Differentiation upon bFGF withdrawal

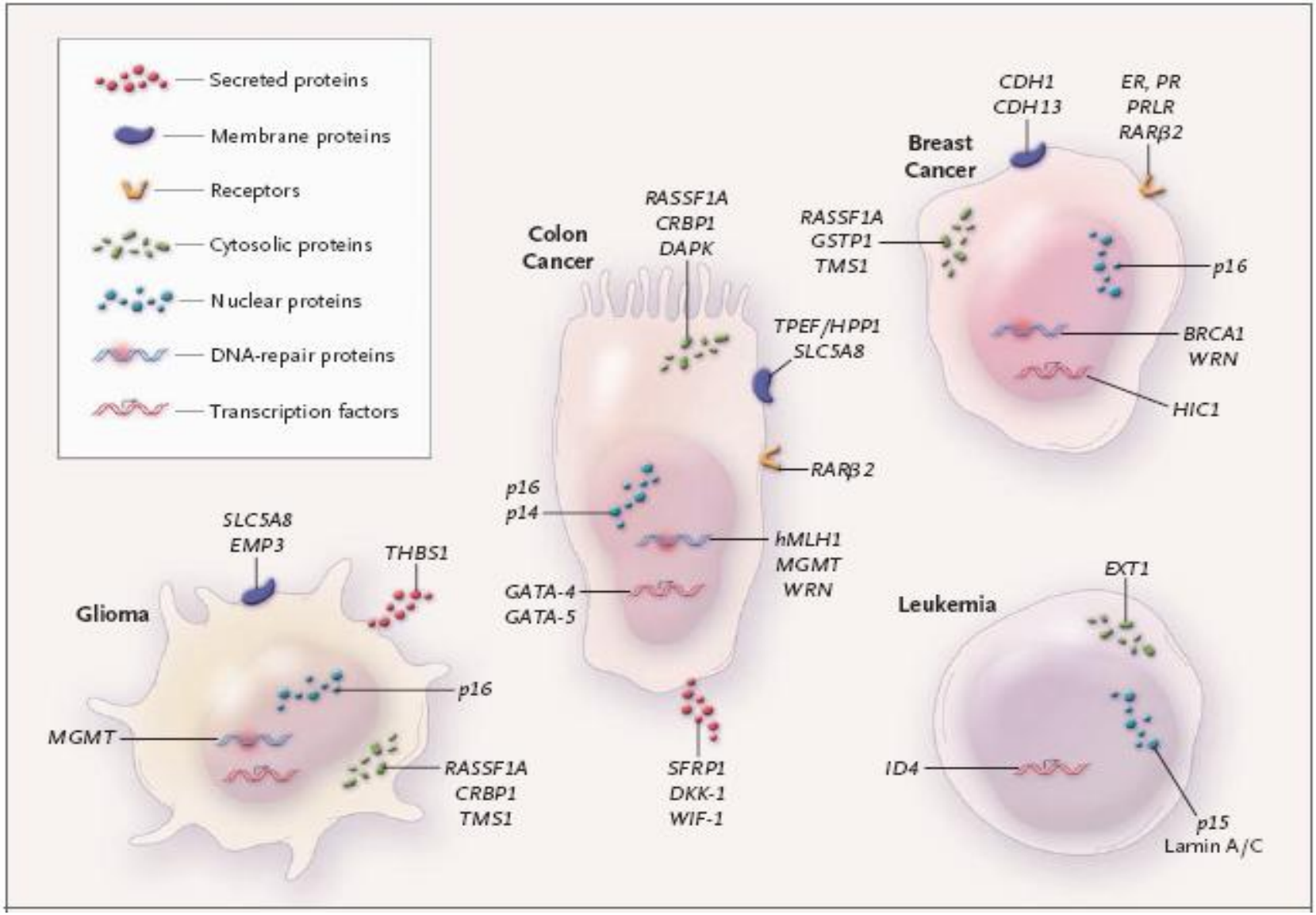


Epigenetic Marks

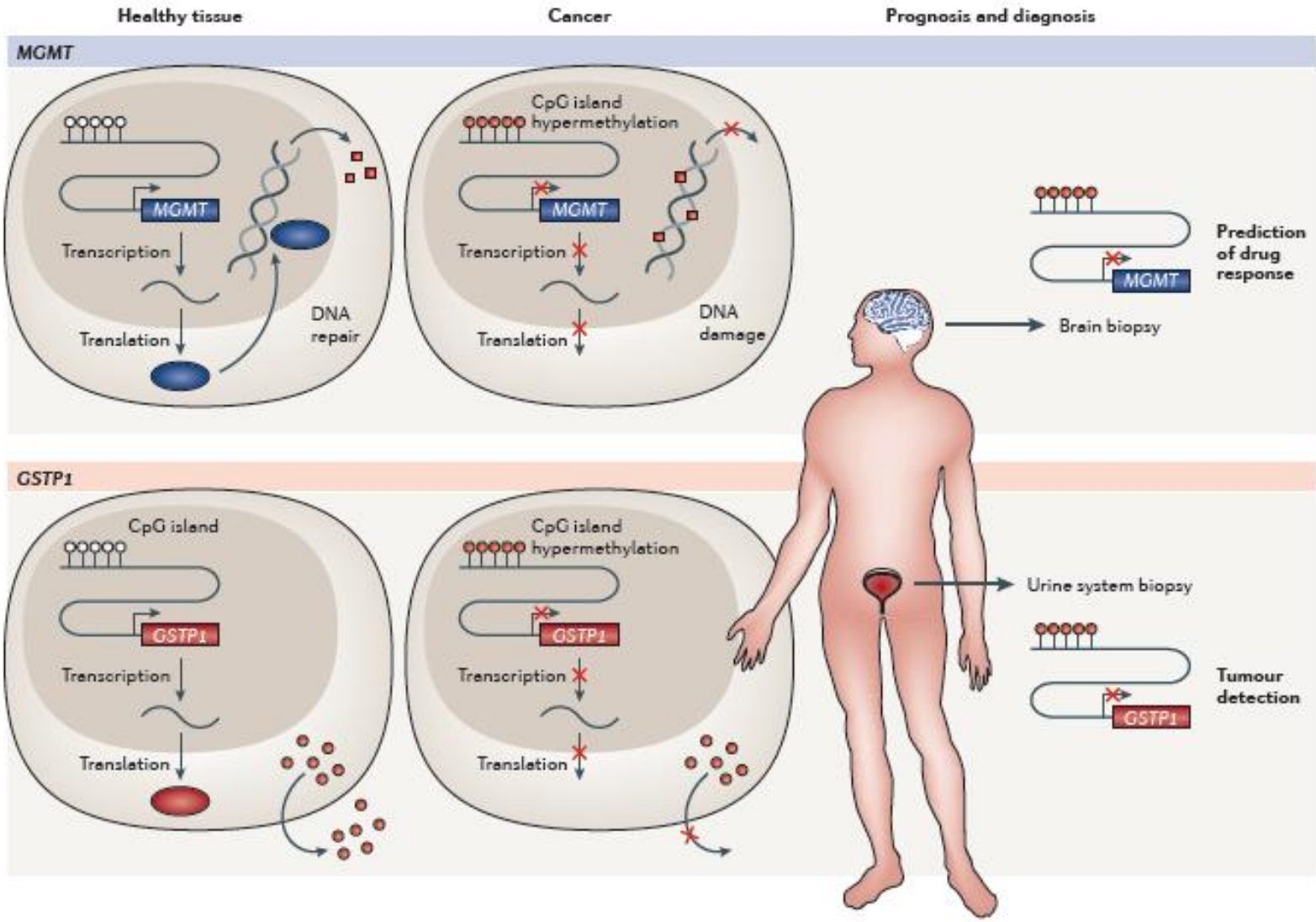
The Epigenetic Marks: DNA Methylation



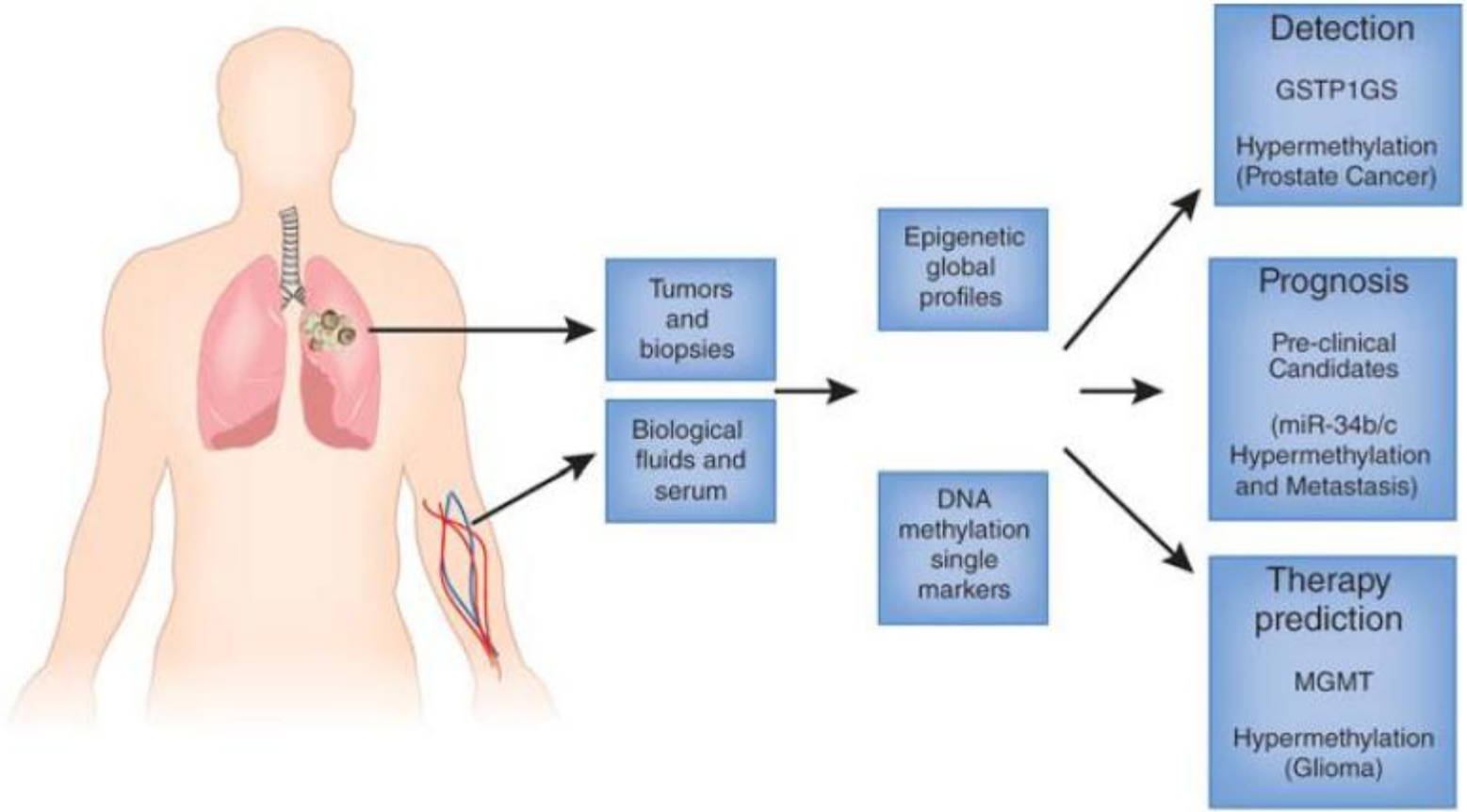
Esteller, Nat Rev Genet 2007



Esteller, New England Journal of Medicine, 2008

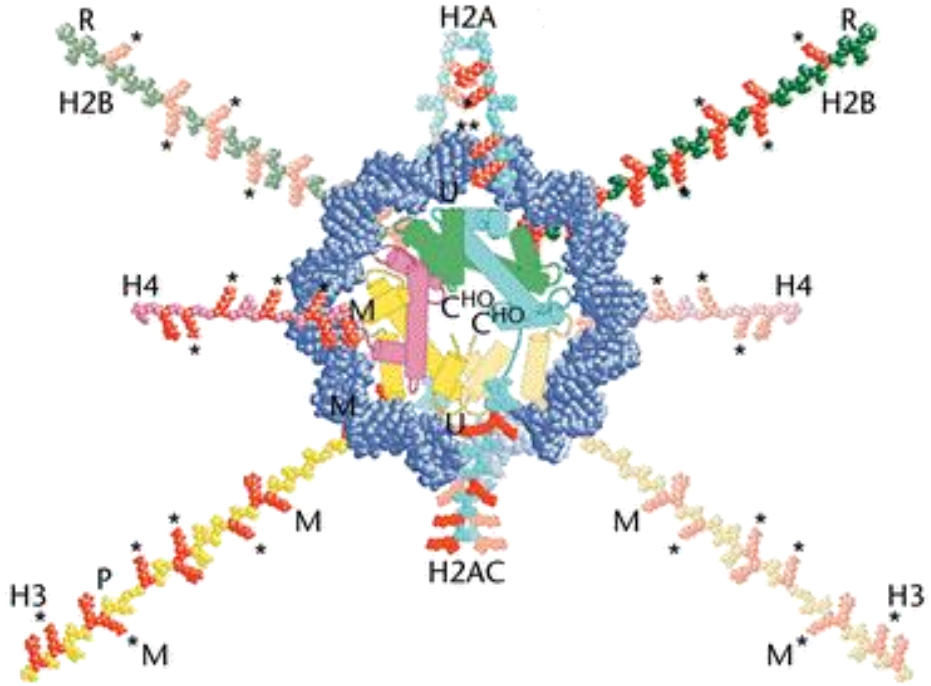


Heyn and Esteller, Nature Review Genetics, 2012



Roriguez-Paredes and Esteller, Nature Medicine, 2011

THE HISTONE CODE



H3, N-terminus

H4, N-terminus

activation

silencing

Me Ac P Ac

4 9 10 14 18 23 27 36

ARTKQTARKSTGGKAPRKQLATKAARKSAPATGGVKKPH-

Me

Me Ac Ac Ac Ac

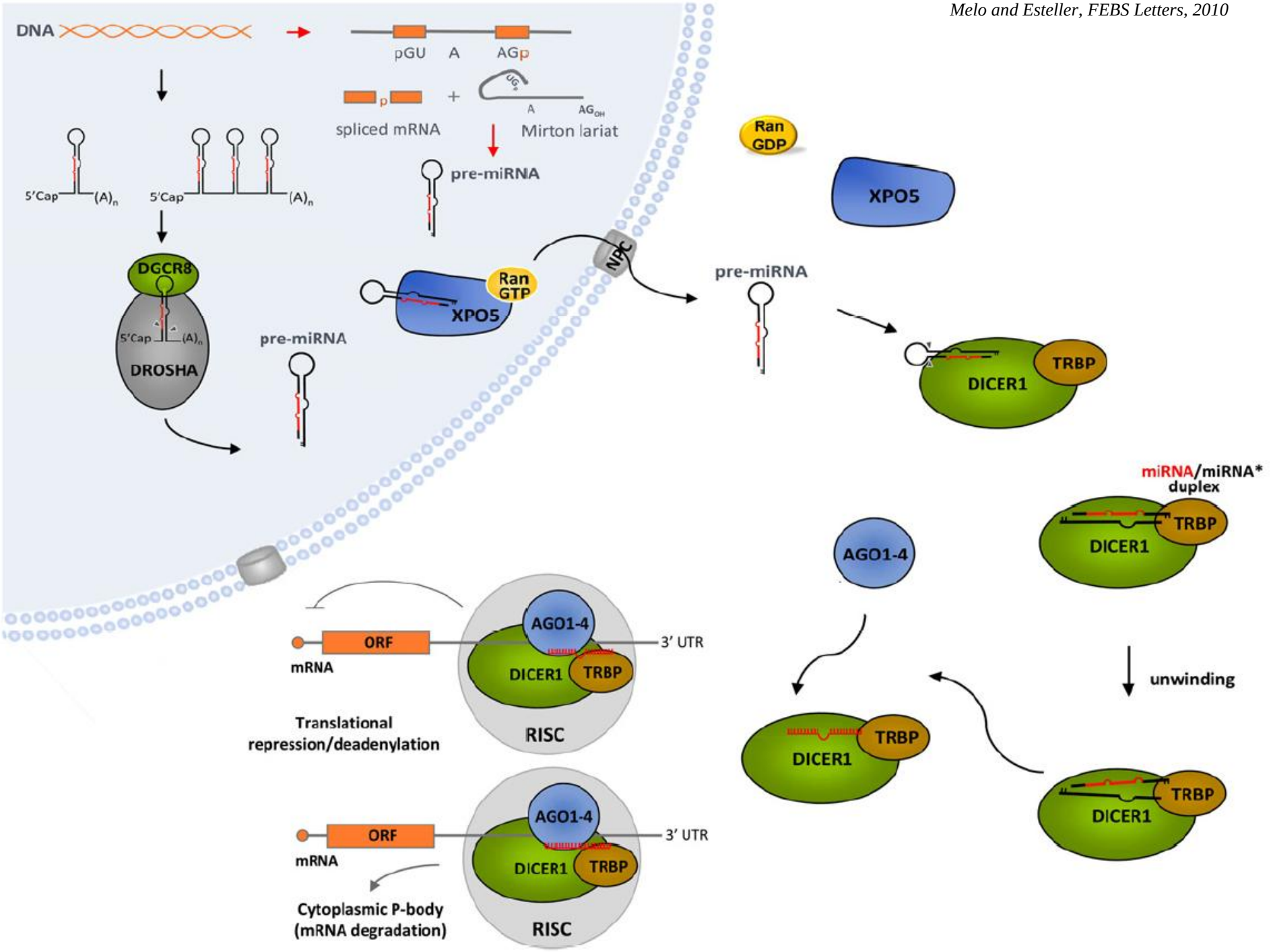
5 8 12 16 20

SGRGKGGKGLGKGGAKRHRKVLRDN-

Ac

The Dark Genome

Melo and Esteller, FEBS Letters, 2010



Melo and Esteller, FEBS Letters, 2010

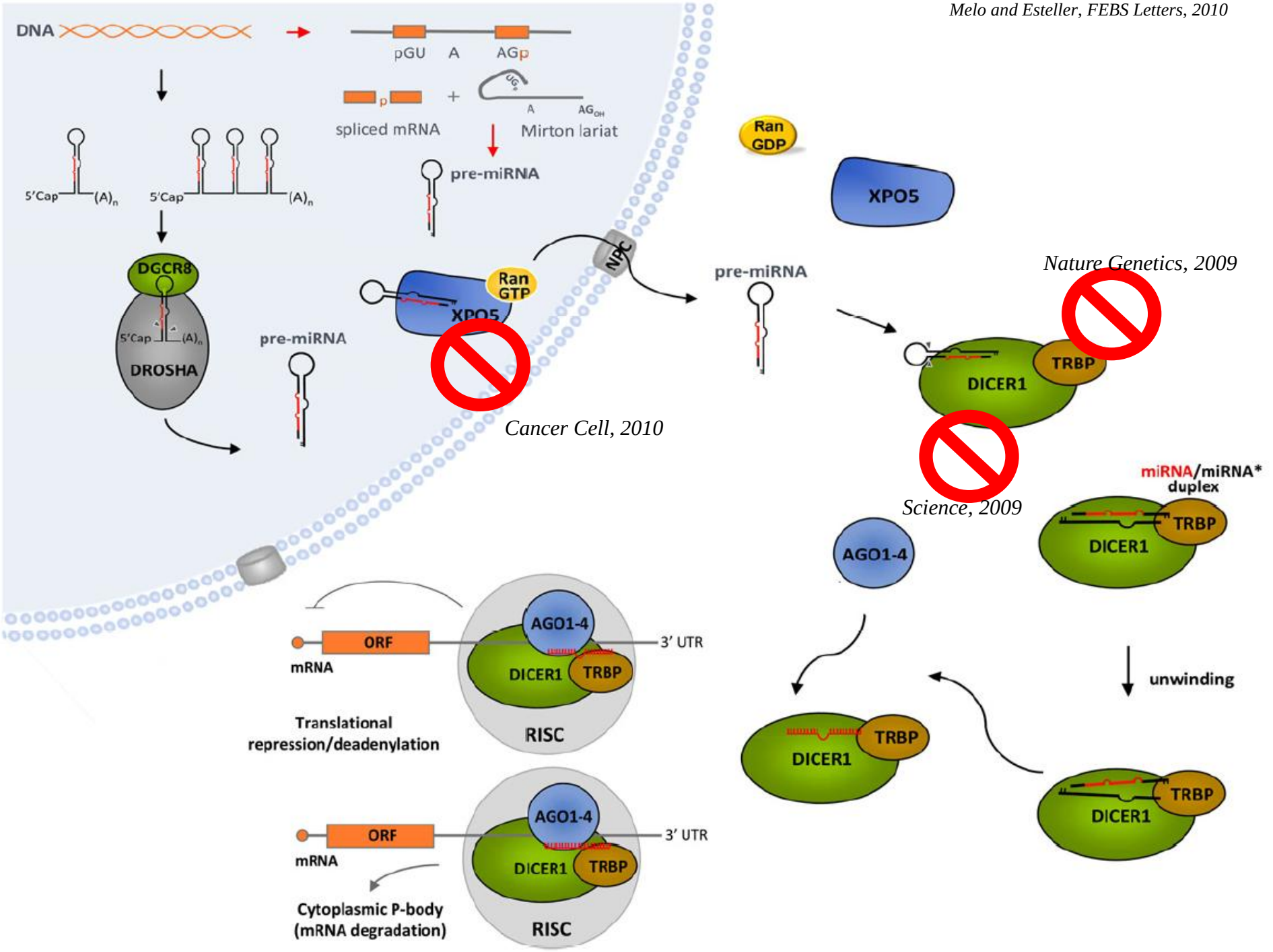
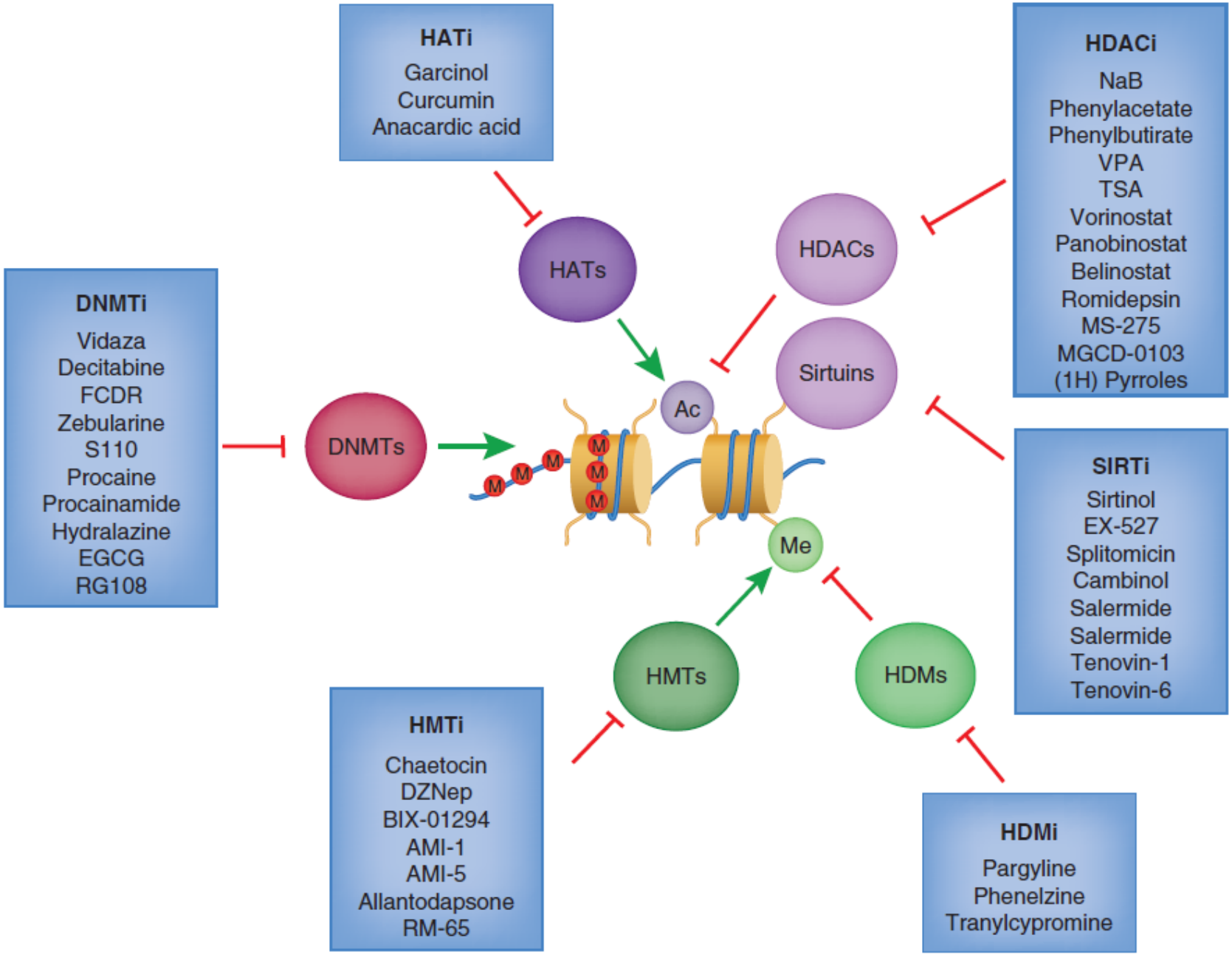


Table 1 | **Types of ncRNAs***

Name	Size	Location	Number in humans	Functions	Illustrative examples	Refs
Short ncRNAs						
miRNAs	19–24 bp	Encoded at widespread locations	>1,424	Targeting of mRNAs and many others	miR-15/16, miR-124a, miR-34b/c, miR-200	3–8
piRNAs	26–31bp	Clusters, intragenic	23,439	Transposon repression, DNA methylation	piRNAs targeting *RASGRF1* and LINE1 and IAP elements	13–19
tiRNAs	17–18bp	Downstream of TSSs	>5,000	Regulation of transcription?	Associated with the *CAP1* gene	37
Mid-size ncRNAs						
snoRNAs	60–300 bp	Intronic	>300	rRNA modifications	U50, SNORD	20–22
PASRs	22–200 bp	5′ regions of protein-coding genes	>10,000	Unknown	Half of protein-coding genes	10
TSSa-RNAs	20–90 bp	–250 and +50 bp of TSSs	>10,000	Maintenance of transcription?	Associated with *RNF12* and *CCDC52* genes	35
PROMPTs	<200 bp	–205 bp and –5 kb of TSSs	Unknown	Activation of transcription?	Associated with *EXT1* and *RBM39* genes	36
Long ncRNAs						
lincRNAs	>200 bp	Widespread loci	>1,000	Examples include scaffold DNA–chromatin complexes	*HOTAIR*, *HOTTIP*, *lincRNA-p21*	2,28–30
T-UCRs	>200 bp	Widespread loci	>350	Regulation of miRNA and mRNA levels?	uc.283+, uc.338, uc160+	31–34
Other lncRNAs	>200 bp	Widespread loci	>3,000	Examples include X-chromosome inactivation, telomere regulation, imprinting	*XIST*, *TSIX*, TERRAs, *p15AS*, *H19*, *HYMAI*	2,23–25

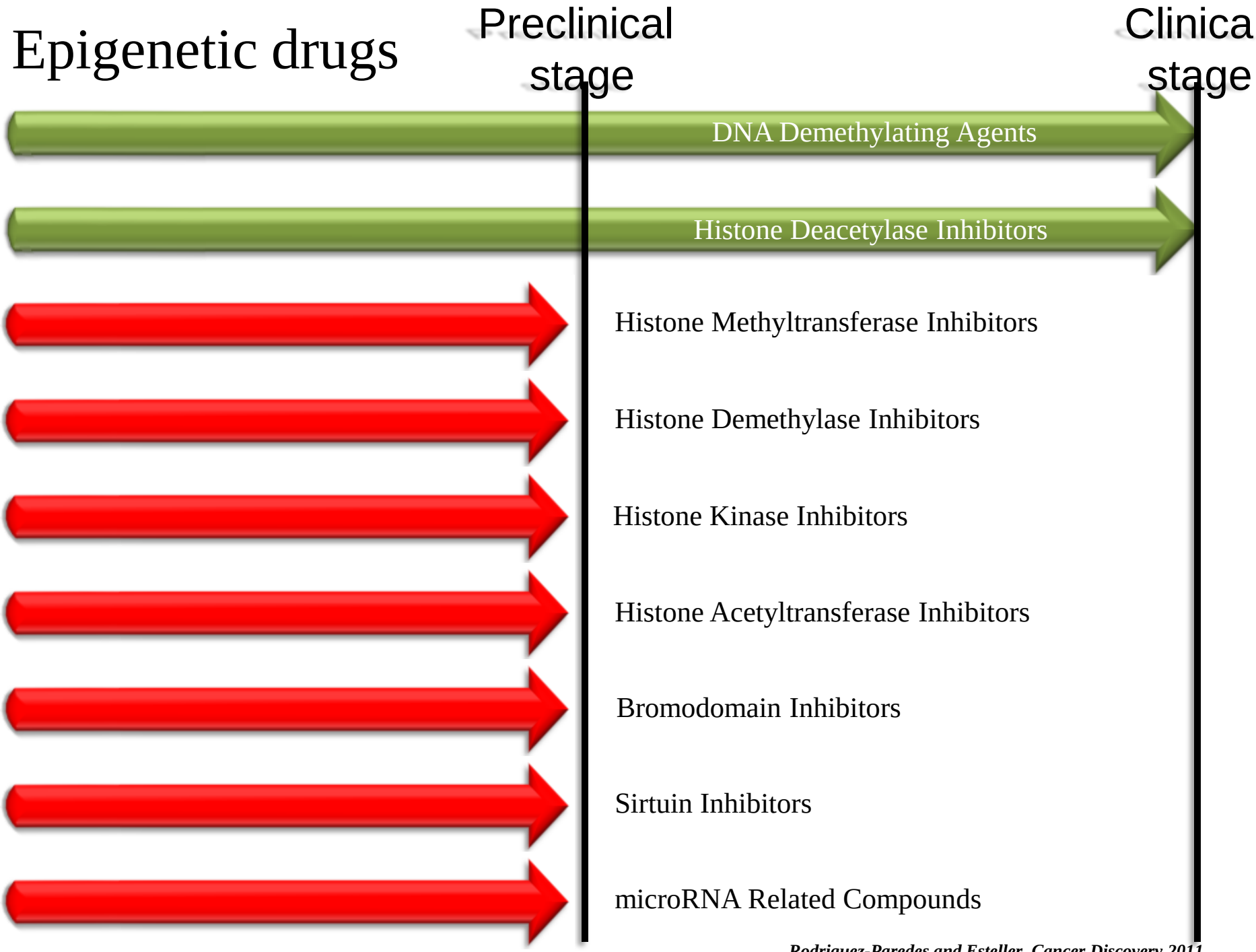
*There is not necessarily a clear delineation between classes of non-coding RNA (ncRNA); for example, X-inactivation specific transcript (*XIST*) and its antisense transcript *TSIX* could be considered as large intergenic non-coding RNAs (lincRNAs). In the 'Location' column, '–' represents the number of base pairs upstream of the transcription start site (TSS) and '+' represents the number of base pairs downstream of the TSS. *CAP1*, CAP, adenylate cyclase-associated protein 1; *CCDC52*, coiled-coil domain containing 52 (also known as *SPICE1*); *EXT1*, exostosin 1; *HOTAIR*, homeobox (HOX) transcript antisense RNA; *HOTTIP*, HOXA distal transcript antisense RNA; *HYMAI*, hydatidiform mole associated and imprinted; IAP, intracisternal A-particle; lncRNA, long non-coding RNA; miRNAs, microRNAs; piRNAs, PIWI-interacting RNAs; PASRs, promoter-associated small RNAs; PROMPTs, promoter upstream transcripts; *RASGRF1*, RAS-protein-specific guanine nucleotide-releasing factor 1; *RBM39*, RNA-binding motif protein 39; *RNF12*, ring finger protein 12 (also known as *RLIM*); snoRNAs, small nucleolar RNAs; TERRAs, telomeric repeat containing RNAs; tiRNAs, transcription initiation RNAs; TSSa-RNAs, TSS-associated RNAs; T-UCRs, transcribed ultraconserved regions.

Esteller, Nature Reviews Genetics 2011



Rodriguez-Paredes and Esteller, Nature Medicine, 2011

Epigenetic drugs



Rodriguez-Paredes and Esteller, Cancer Discovery 2011

Outside Cancer

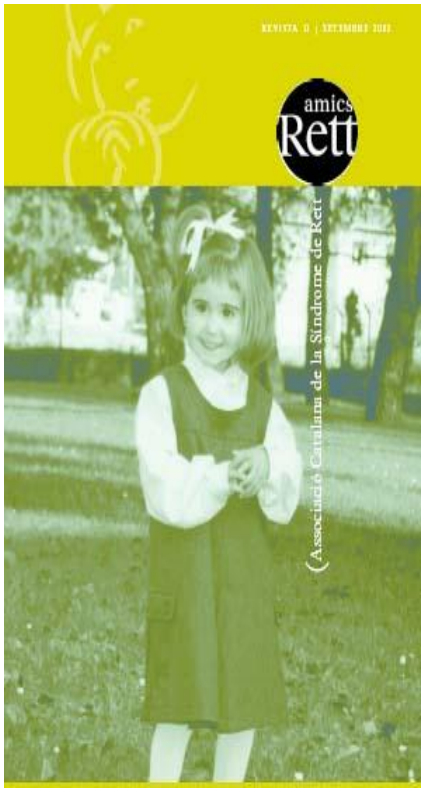
Rett Syndrome

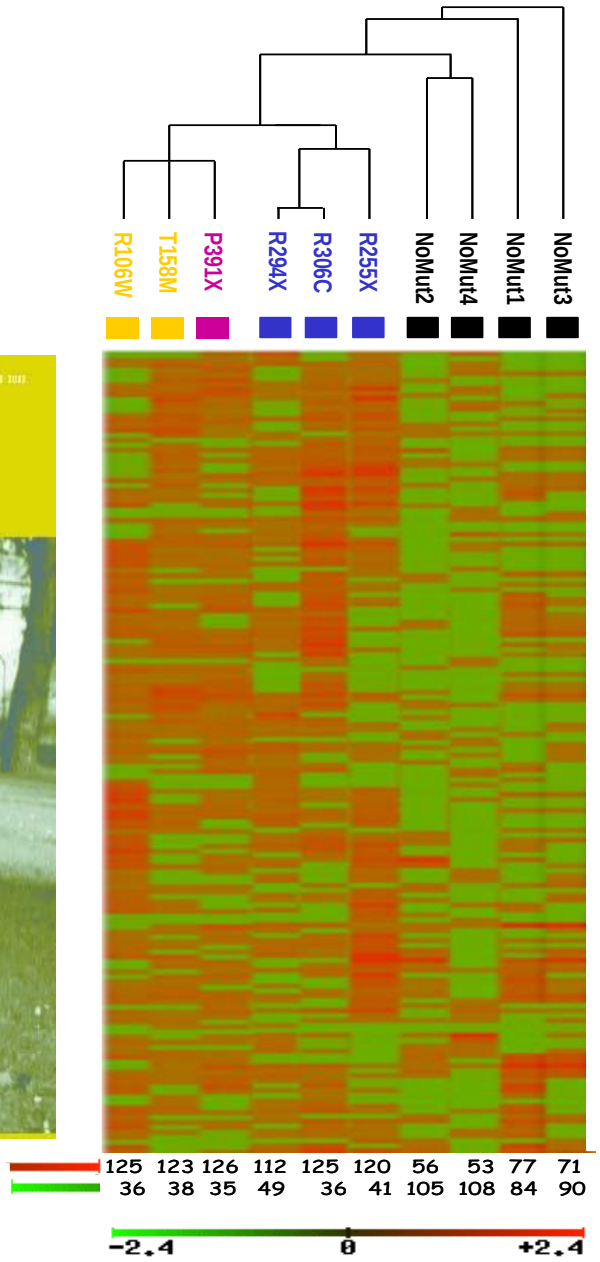
Rett Syndrome (RS) is a neurodevelopmental disorder believed to affect 1 in 10,000 females..

Germline mutations in MECP2 (Methyl-CpG Binding Protein-2) found in 65% of Rett patients. MECP2 is located in Xq28.

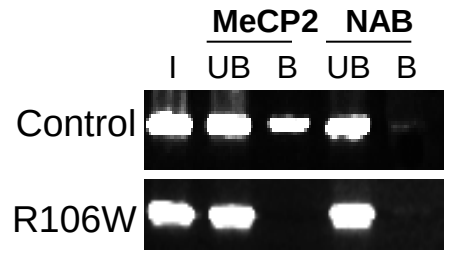
Girls with Rett Syndrome appear to develop normally until 6 to 18 months of age. They then enter a period of regression, losing speech and hand skills they had acquired. Most girls develop seizures, repetitive hand movements, irregular breathing and motor-control problems. A slowing of the rate of head growth also becomes apparent. Most researchers agree that RS is a developmental disorder rather than a progressive, degenerative disorder. The girls can live to adulthood, but most never regain the ability to use their hands or to speak.

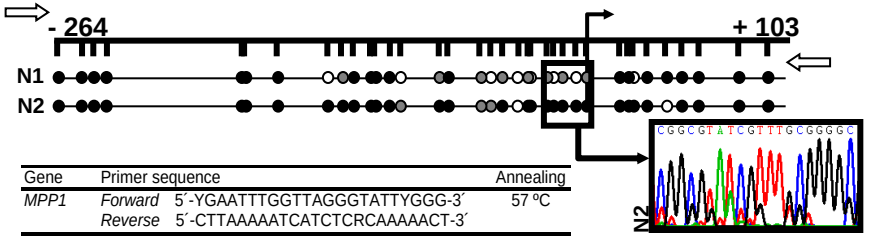
Clustering expression analysis and release of MeCP2- Silencing in Rett Syndrome Patients



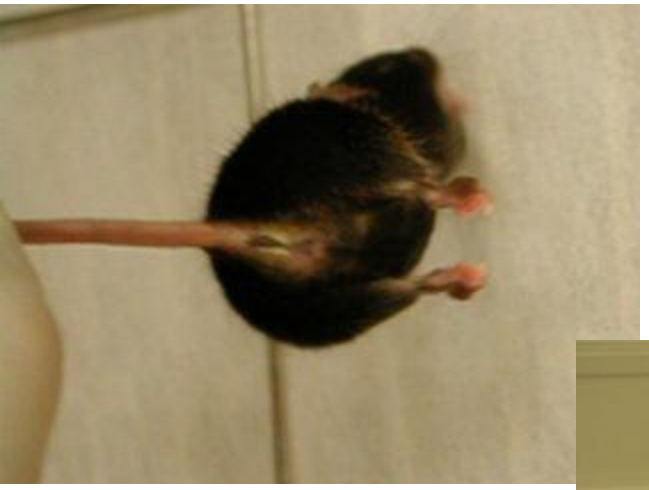


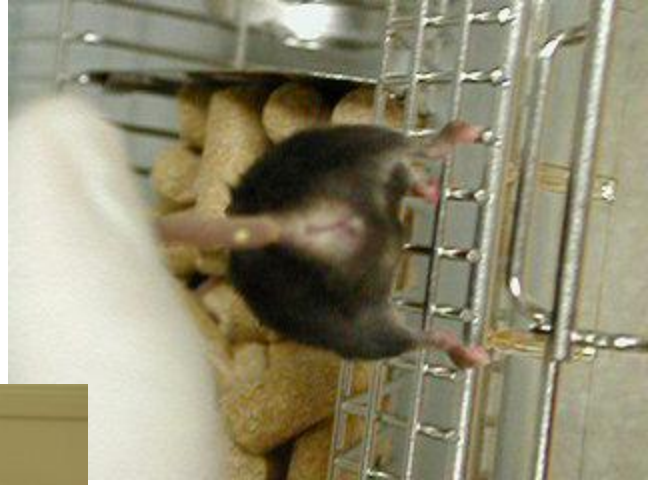
MPP1

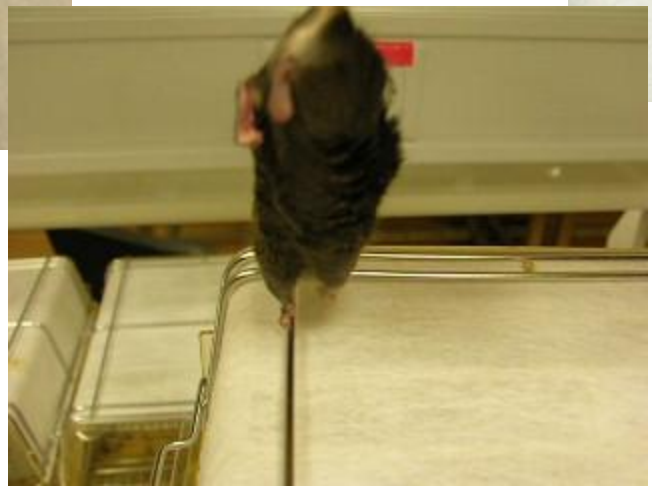


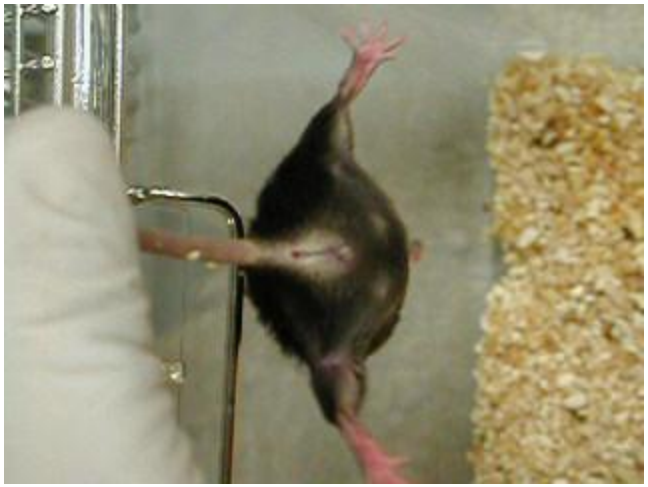


Human Mutation, 2005





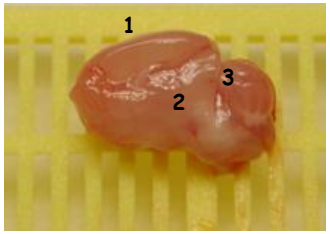




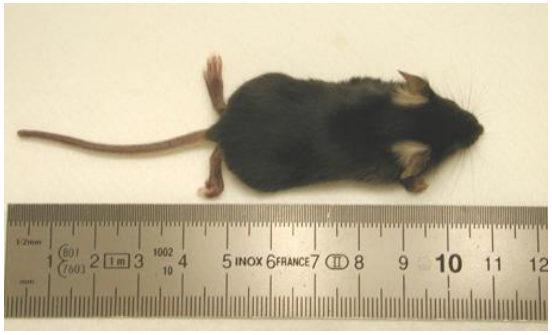
Mouse Model of Rett

7.5gr/10.25cms

299mg



1.-Encéfalo
2.-Mesencéfalo
3.-Cerebelo



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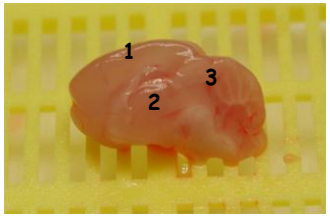
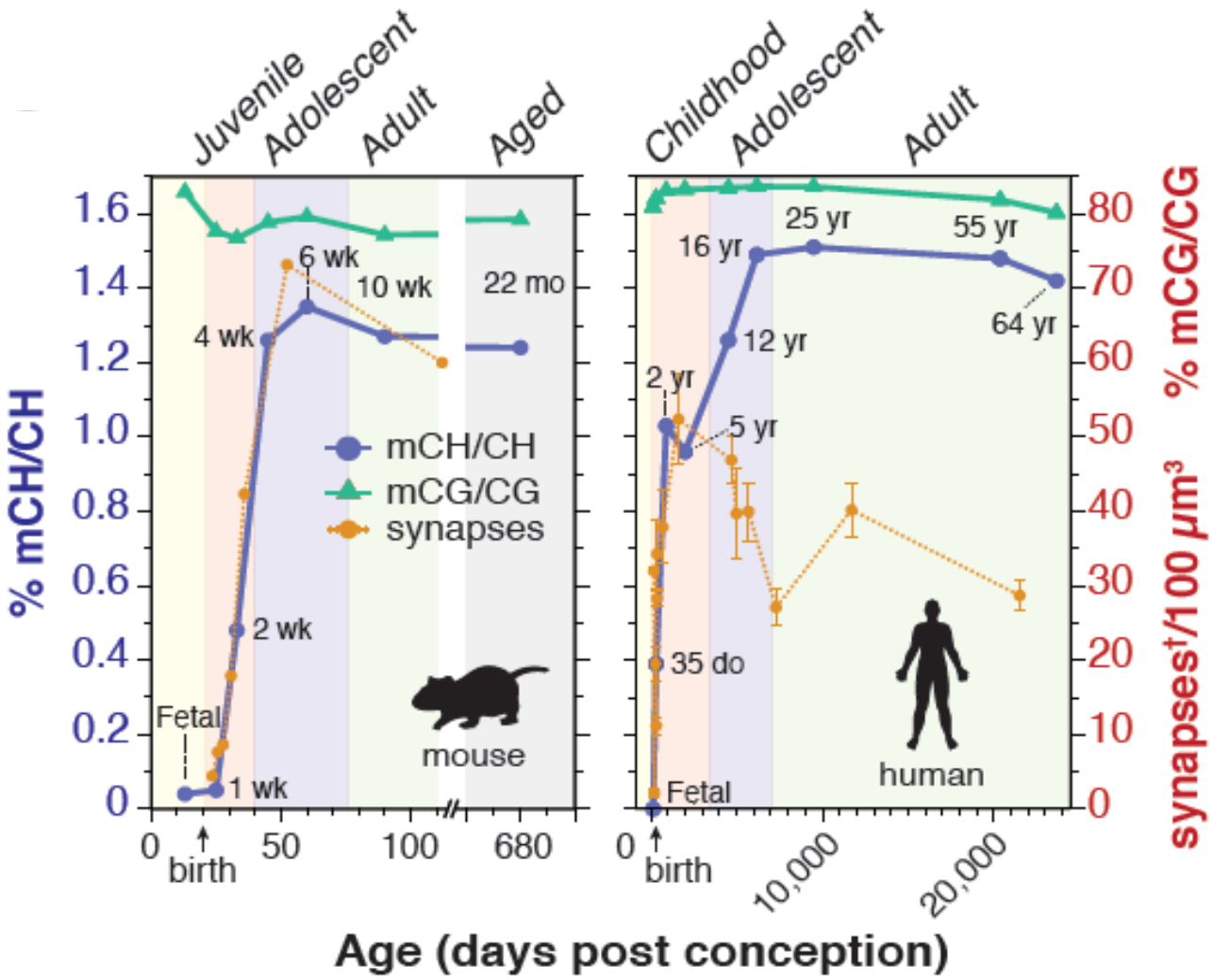
310mg



Dynamic DNA Methylation Reconfiguration During Brain Development



Lister et al., Science 2013

•DNA Methylation and Schizophrenia

1: Dong E, Agis-Balboa RC, Simonini MV, Grayson DR, Costa E, Guidotti A. Related Articles, Links

Reelin and glutamic acid decarboxylase67 promoter remodeling in an epigenetic methionine-induced mouse model of schizophrenia.
Proc Natl Acad Sci U S A. 2005 Aug 30;102(35):12578-83. Epub 2005 Aug 19.
PMID: 16113080 [PubMed - indexed for MEDLINE]

2: Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A, Costa E. Related Articles, Links

Reelin promoter hypermethylation in schizophrenia.
Proc Natl Acad Sci U S A. 2005 Jun 28;102(26):9341-6. Epub 2005 Jun 16.
PMID: 15961543 [PubMed - indexed for MEDLINE]

3: Veldic M, Guidotti A, Maloku E, Davis JM, Costa E. Related Articles, Links

In psychosis, cortical interneurons overexpress DNA-methyltransferase 1.
Proc Natl Acad Sci U S A. 2005 Feb 8;102(6):2152-7. Epub 2005 Jan 31.
PMID: 15684088 [PubMed - indexed for MEDLINE]

4: Noh JS, Sharma RP, Veldic M, Salvacion AA, Jia X, Chen Y, Costa E, Guidotti A, Grayson DR. Related Articles, Links

DNA methyltransferase 1 regulates reelin mRNA expression in mouse primary cortical cultures.
Proc Natl Acad Sci U S A. 2005 Feb 1;102(5):1749-54. Epub 2005 Jan 25.
PMID: 15671176 [PubMed - indexed for MEDLINE]

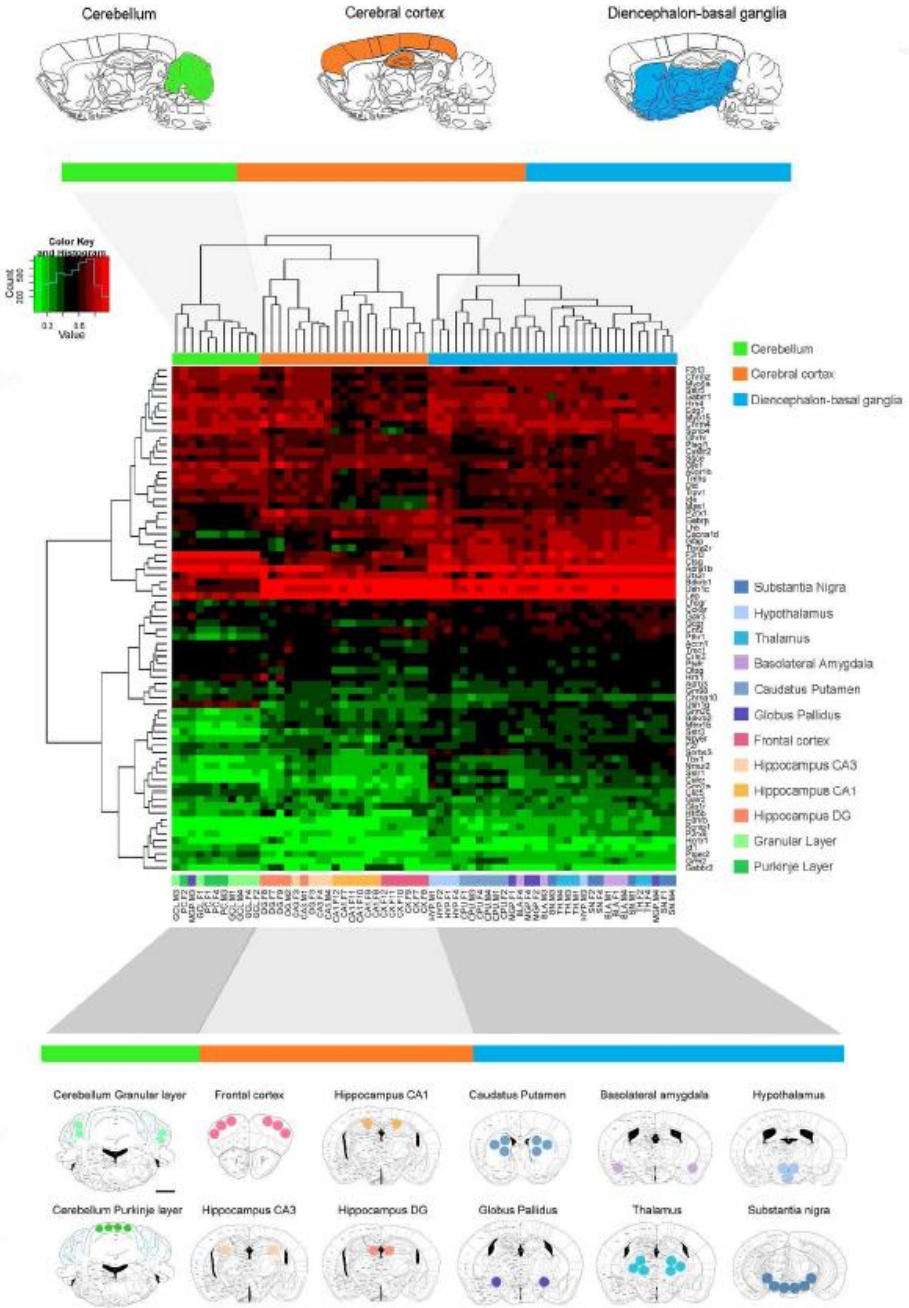
5: Veldic M, Caruncho HJ, Liu WS, Davis J, Satta R, Grayson DR, Guidotti A, Costa E. Related Articles, Links

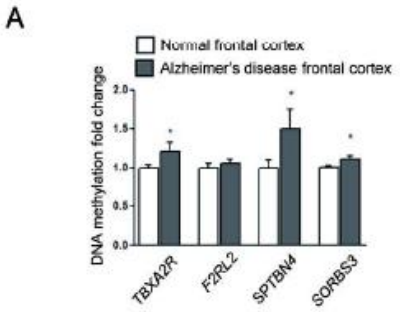
DNA-methyltransferase 1 mRNA is selectively overexpressed in telencephalic GABAergic interneurons of schizophrenia brains.
Proc Natl Acad Sci U S A. 2004 Jan 6;101(1):348-53. Epub 2003 Dec 18.
PMID: 14684836 [PubMed - indexed for MEDLINE]

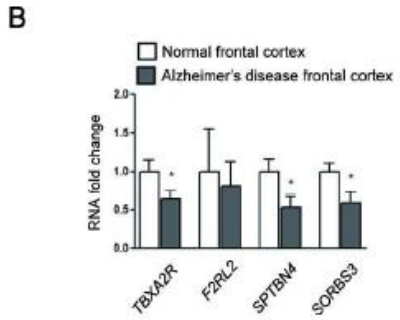
6: Tremolizzo L, Carboni G, Ruzicka WB, Mitchell CP, Sugaya I, Tueting P, Sharma R, Grayson DR, Costa E, Guidotti A. Related Articles, Links

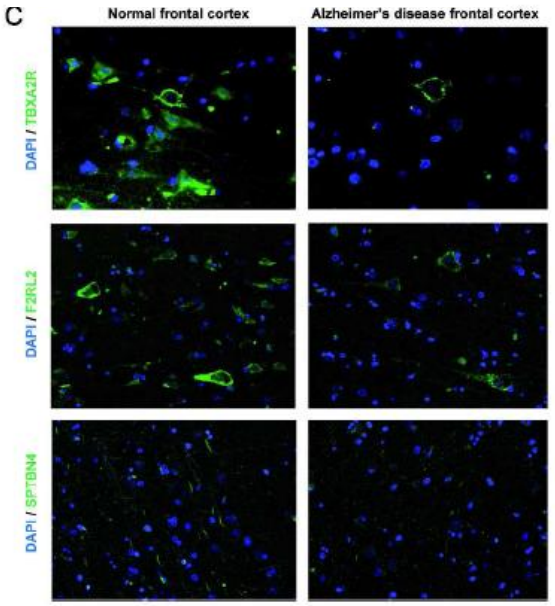
An epigenetic mouse model for molecular and behavioral neuropathologies related to schizophrenia vulnerability.
Proc Natl Acad Sci U S A. 2002 Dec 24;99(26):17095-100. Epub 2002 Dec 12.
PMID: 12481028 [PubMed - indexed for MEDLINE]

DNA Methylation Map of Mouse Brain Identifies Targets of Epigenetic Disruption in Alzheimer's Disease



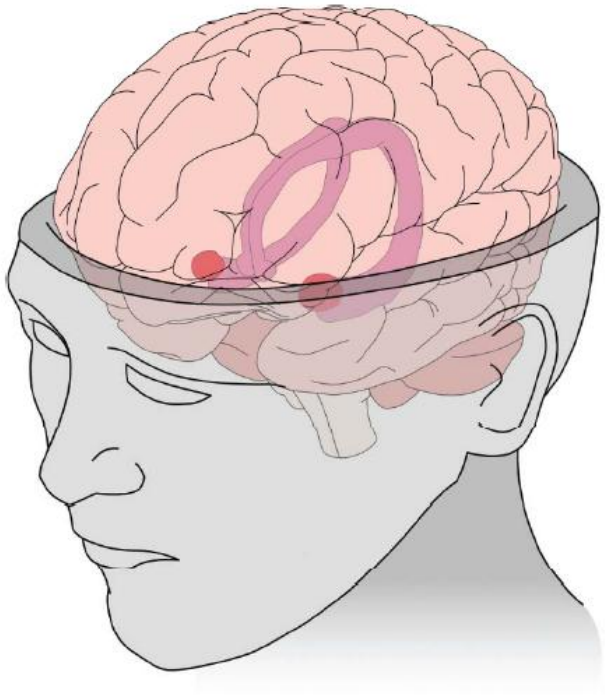


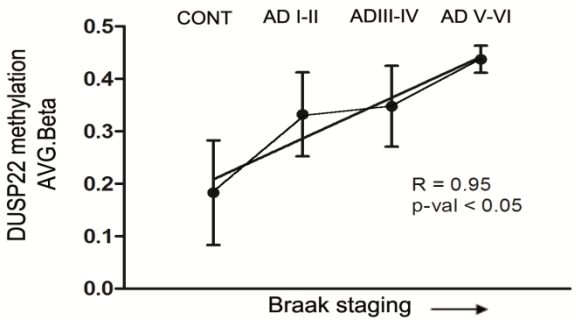


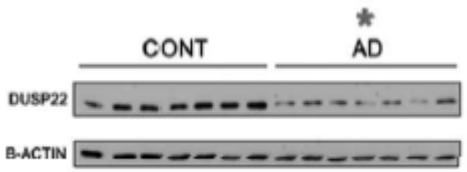


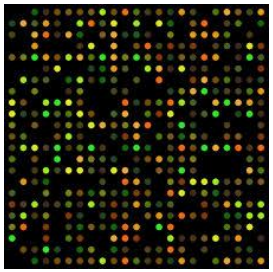
Sanchez-Mut et al., Brain 2013

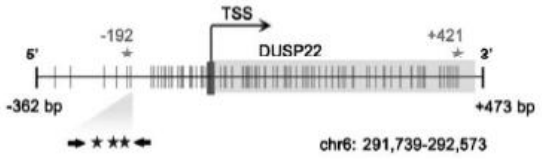
Promoter hypermethylation of the phosphatase DUSP22 mediates PKA-dependent TAU phosphorylation and CREB activation in Alzheimer's disease

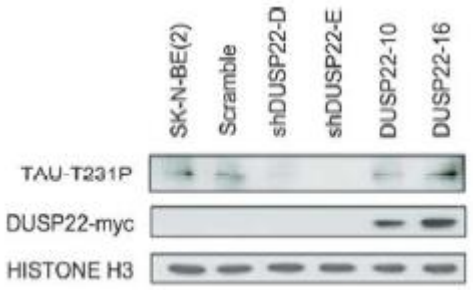






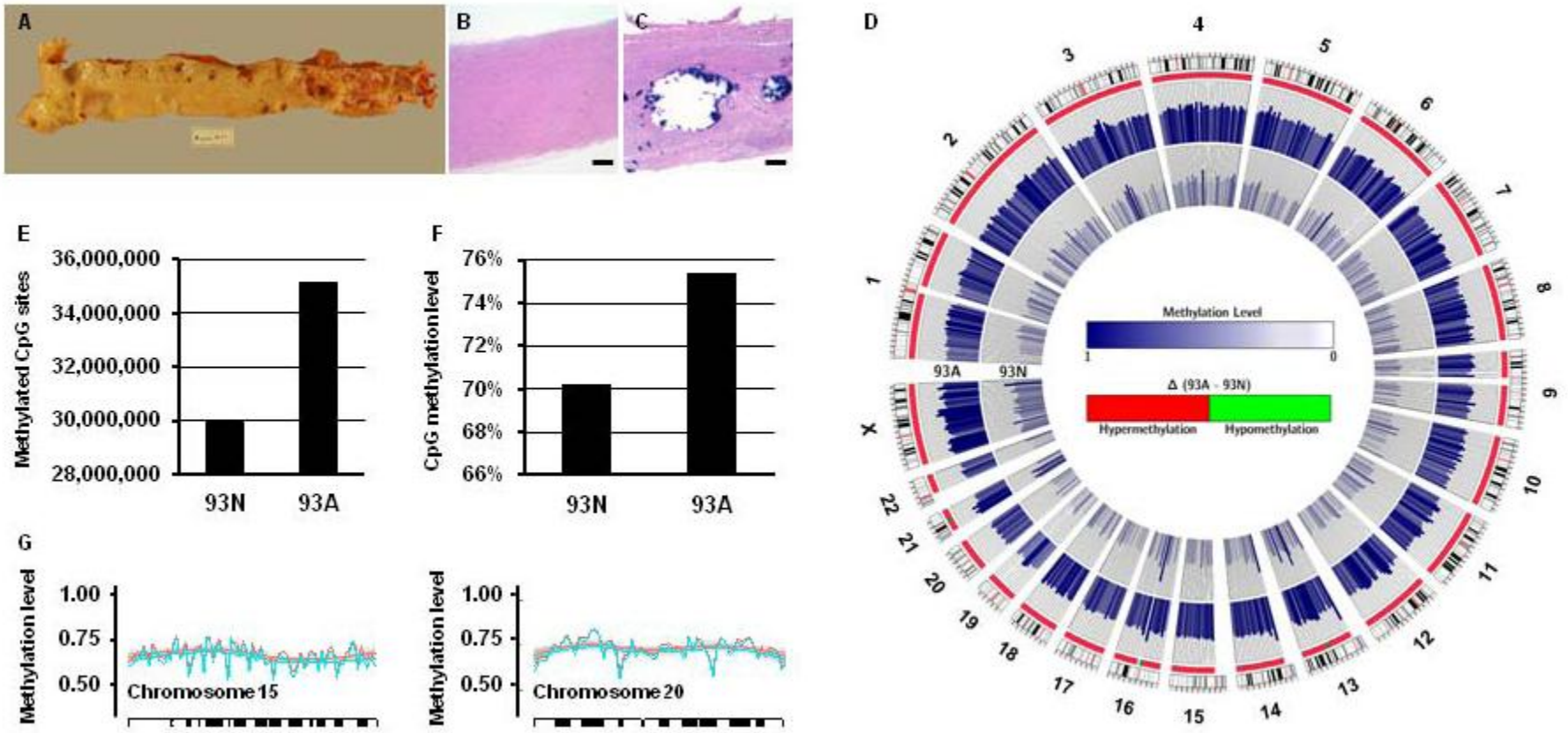






Sanchez-Mut et al., Hippocampus 2013

DNA Methylation Profiling of Human Atheroesclerosis



Zaina et al., Circulation: Cardiovascular Genetics 2014

…Epigenomes

“The Book of Life” (Almost…)

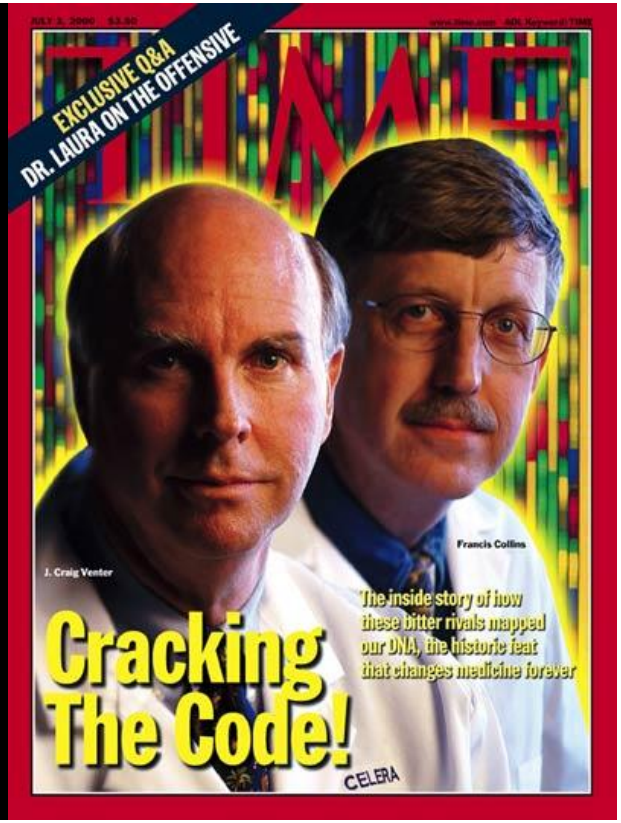
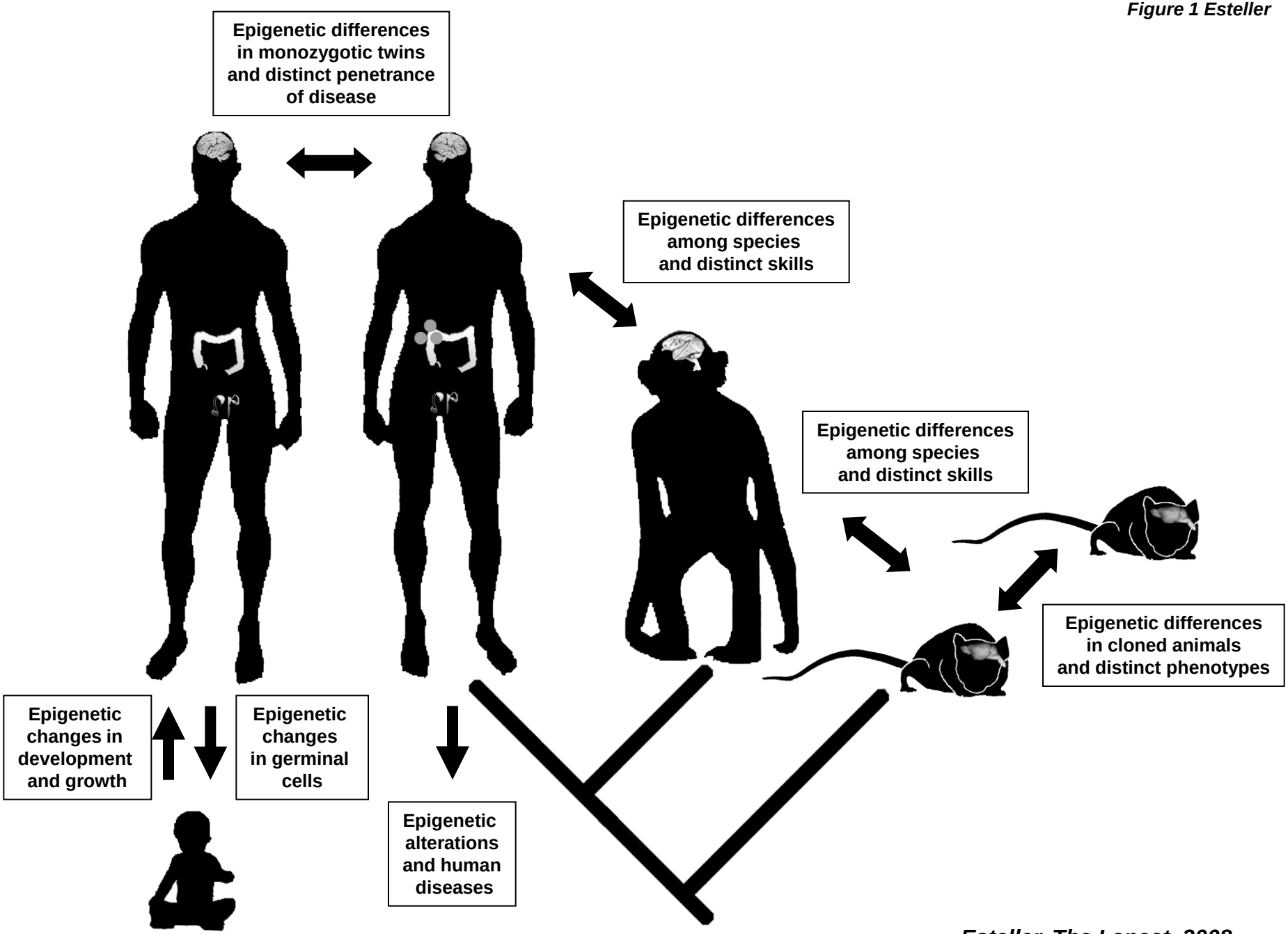


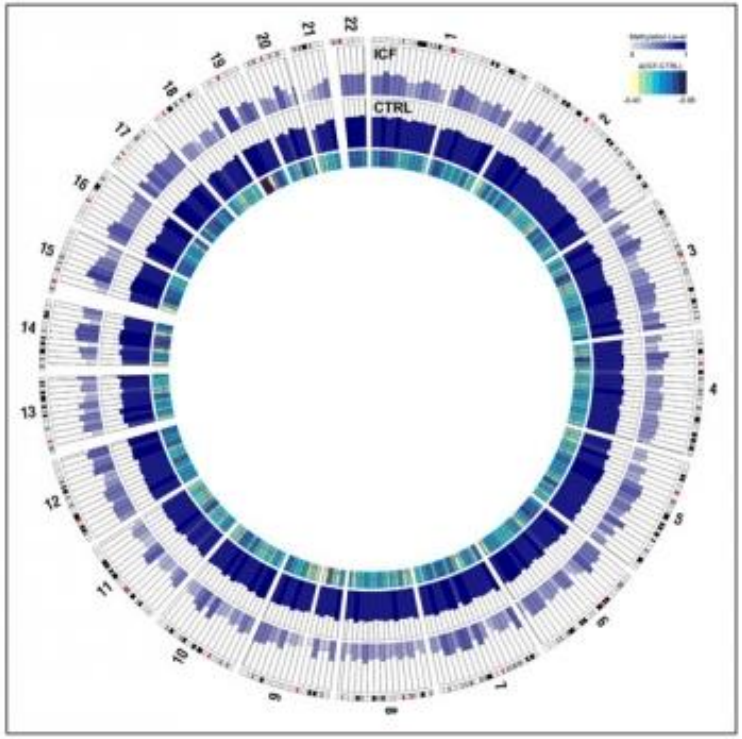
Figure 1 Esteller



Esteller, The Lancet, 2008

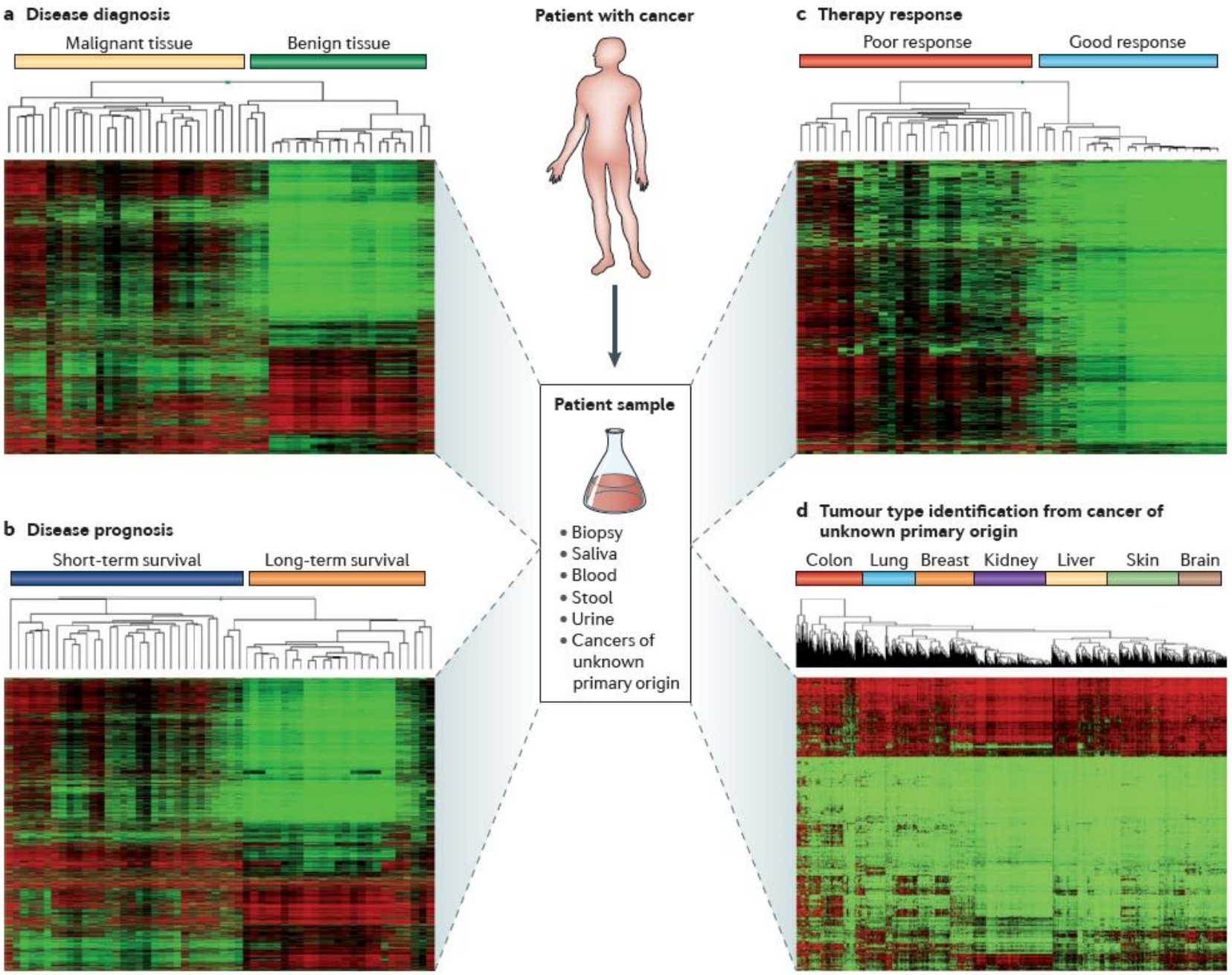
epigenetics

Volume 7 • Issue 6 • June 2012



Issue Highlights:
DNA methylation in an ICF syndrome patient (Heyn et al.)
Standardization and quality control for MeDIP (Lisanti et al.)
On diet, lifestyle and DNA methylation (Zhang et al.)

LANDES
BIOSCIENCE



Heyn and Esteller, Nature Reviews Genetics, 2012

Table 3 | **Hypermethylated genes predict drug sensitivity**

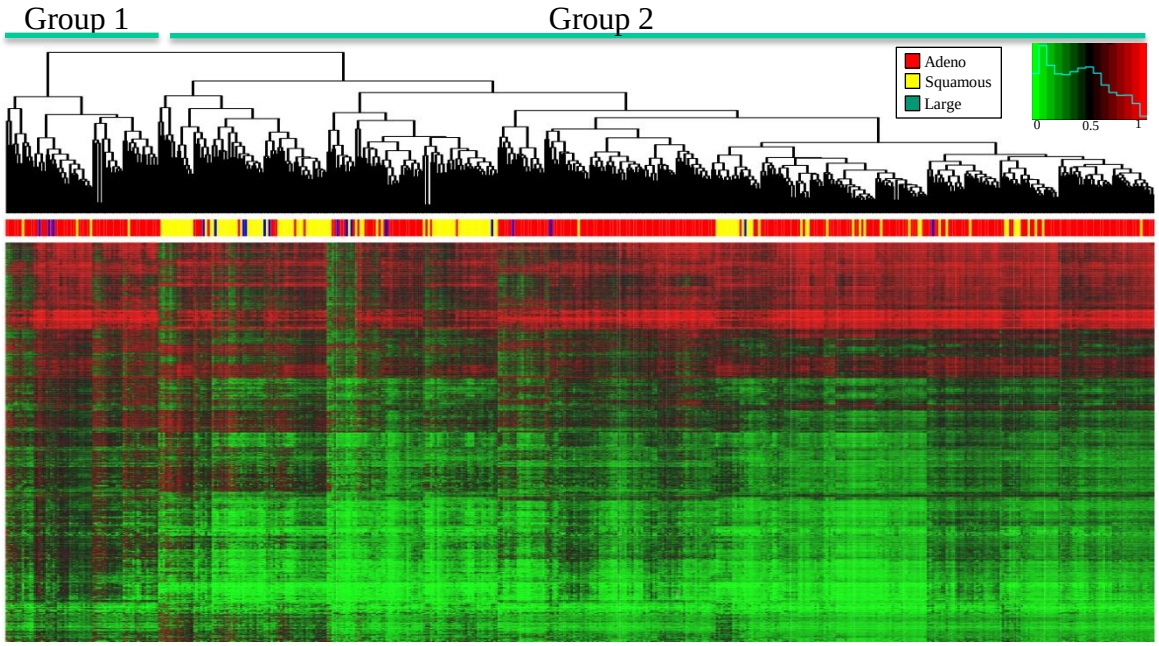
Gene name	Gene function	Therapeutical consequences	Tumour type application	Example refs
ABCB1	Protein transport	Sensitivity to doxorubicin	Breast	120
APAF1	Apoptotic activator	Resistance to adriamycin	Melanoma	121
BRCA1	DNA damage response	Sensitivity to PARP inhibitors and alkylating agents	Breast, ovary	81
CDK10	Cell cycle control	Resistance to anti-oestrogens	Breast	122
CHFR	Ubiquitin protein ligase	Sensitivity to paclitaxel and docetaxel	Ovary, endometrium, stomach	123
ESR1	ER signalling	Resistance to anti-oestrogens	Breast	124
FANCF	DNA damage response	Sensitivity to cisplatin	Ovarian	125
GSTP1	Detoxification	Sensitivity to doxorubicin	Prostate, breast, kidney	126
IGFBP3	Signal transduction	Resistance to cisplatin	Lung	127
LINE1	Repetitive element	Resistance to fluoropyrimidines	Colon	22
MGMT	DNA repair	Sensitivity to temozolomide, BCNU, ACNU, procarbazine	Glioma, colon, lung, lymphoma	5
MLH1	DNA repair	Resistance to cisplatin	Colon, stomach, endometrium, ovary	128
MT1E	Antioxidant	Sensitivity to cisplatin	Melanoma	129
PITX2	Transcriptional regulator	Resistence to tamoxifen	Breast	130
PLK2	Cell division	Sensitivity to paclitaxel and carboplatin	Ovary	131
PRKCDBP	Signal transduction	Resistance to TNFα	Colon	132
SFN	Signal transduction	Sensitivity to cisplatin and gemcitabine	Lung	133
SLC19A1	Folate transporter	Resistance to methotrexate	Lymphomas	134
SULF2	Heparin signalling	Sensitivity to camptothecin	Lung	135
TFAP2E	Transcriptional regulator	Sensitivity to fluorouracil	Colon	136
TGM2	Apoptosis	Resistance to doxorubicin and cisplatin	Lung, breast, ovary	137
TP73	Stress response	Sensitivity to cisplatin	Renal, melanoma	138
WRN	DNA helicases	Sensitivity to irinotecan	Colon	139
ERCC5	DNA repair	Resistance to nemorubicin	Ovary	140

ABCB1, ATP-binding cassette, subfamily B (MDR/TAP), member 1; ACNU, (1-4-amino-2-methyl-5-pyrimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride; *APAF1*, apoptotic activator; BCNU, bis-chloroethylnitrosourea; *BRCA1*, breast cancer 1, early onset; *CDK10*, cyclin-dependent kinase 10; *CHFR*, checkpoint with forkhead and ring finger domains, E3 ubiquitin protein ligase; *ERCC5*, excision repair cross-complementing rodent repair deficiency, complementation group 5; *ESR1*, oestrogen receptor 1; *FANCF*, Fanconi anaemia, complementation group F; *GSTP1*, glutathione *S*-transferase pi 1; *IGFBP3*, insulin-like growth factor binding protein 3; *MGMT*, O^6-methylguanine-DNA methyltransferase; *MLH1*, mutL homologue 1, colon cancer, nonpolyposis type 2; *MT1E*, metallothionein 1E; *PITX2*, paired-like homeodomain 2; *PLK2*, polo-like kinase 2; *PRKCDBP*, protein kinase C, delta binding protein; *SFN*, stratifin; *SLC19A1*, solute carrier family 19; *SULF2*, sulphatase 2; *TFAP2E*, transcription factor AP-2 epsilon (activating enhancer binding protein 2 epsilon); *TGM2*, transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyl-transferase); *TP73*, tumour protein p73; TNFα, tumour necrosis factor-α; *WRN*, Werner syndrome, RecQ helicase-like.

Heyn and Esteller, Nature Reviews Genetics, 2012

A 450,000 CpG Site Prognostic Classifier of 500 Non-Small Cell Lung Cancer Patients

A.



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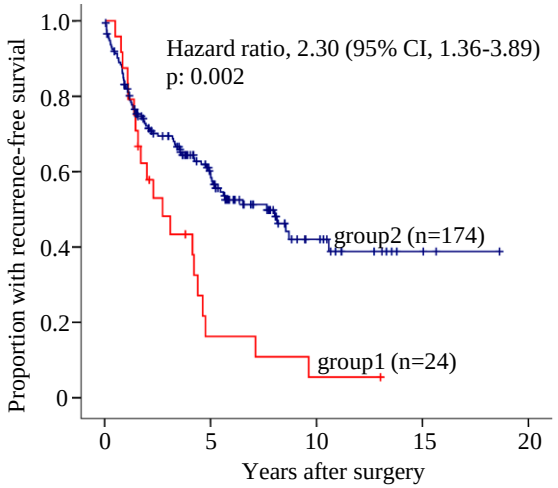
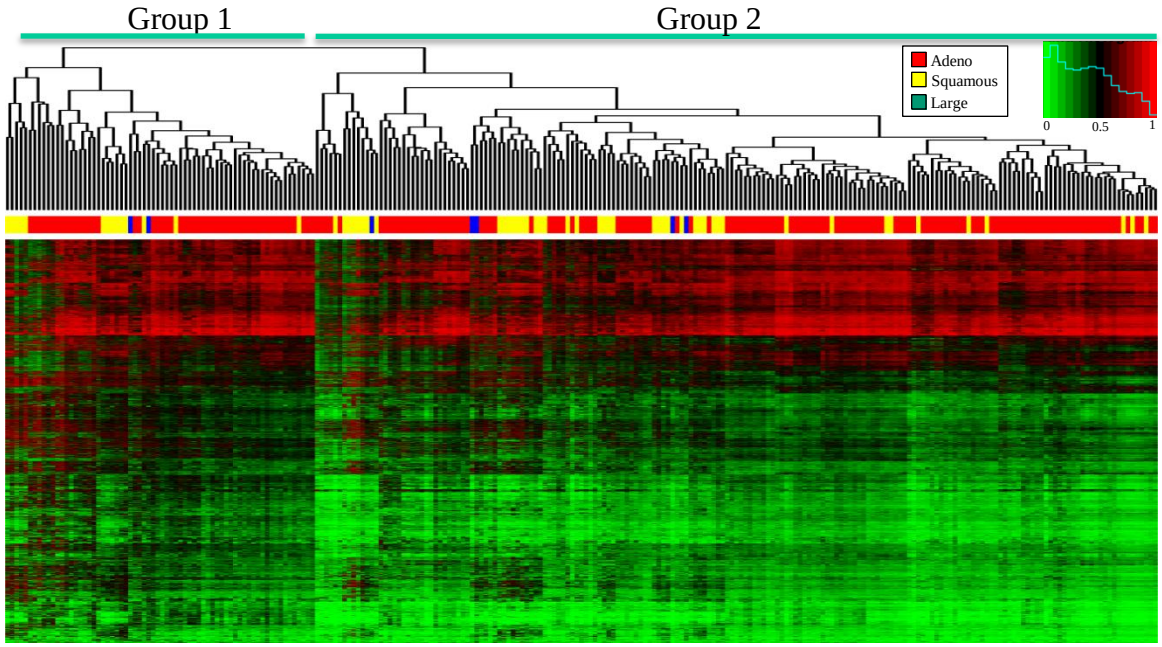


C.



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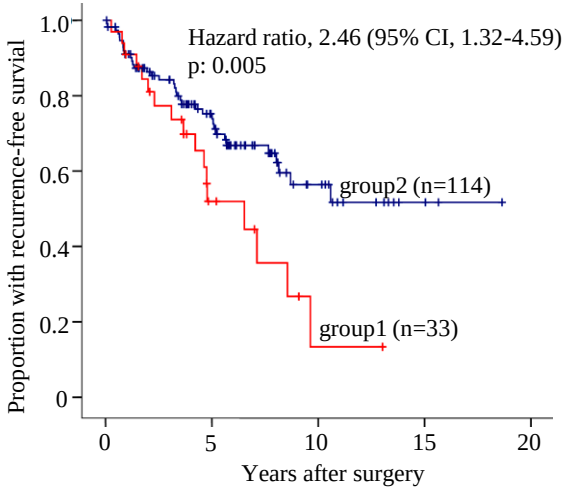
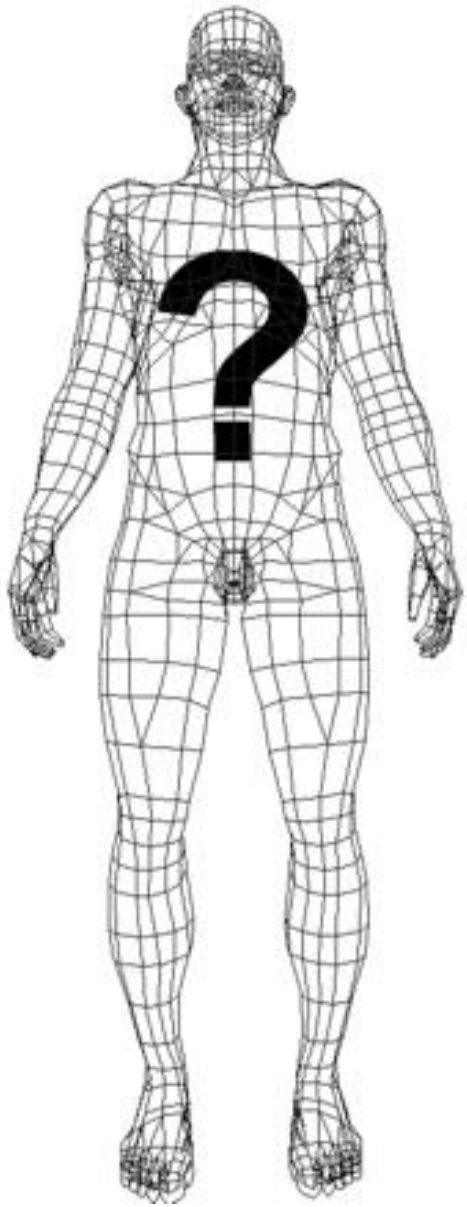
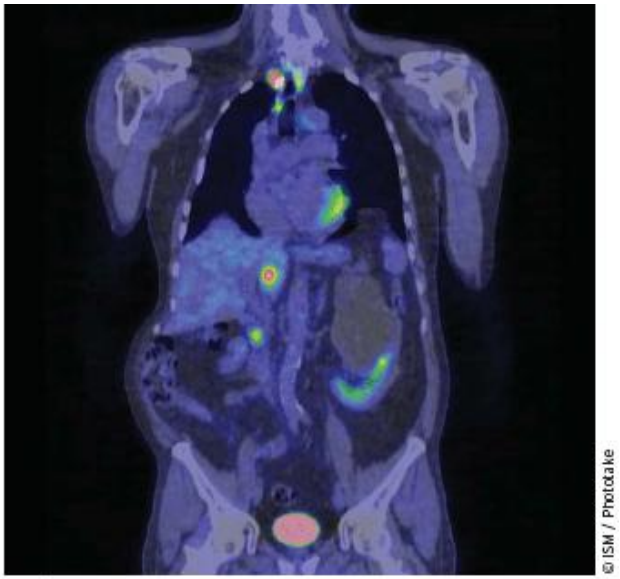


Cancer of Unknown Primary





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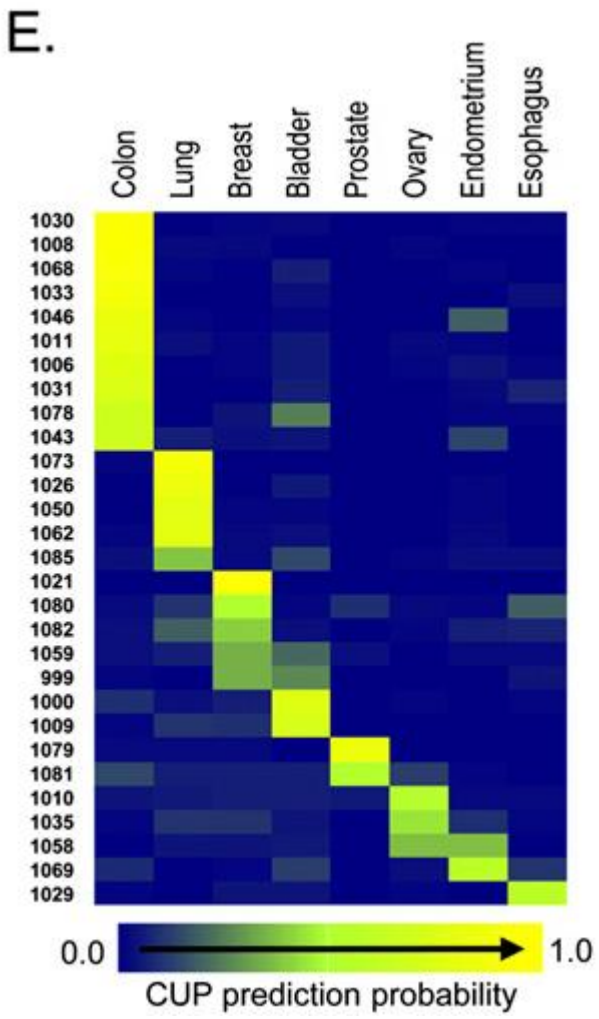
PET/CT of the thorax showing metastases.



Ferrer International
Av. Diagonal, XXX
Barcelona, Spain 08XXX
Tel: +(34) 9X XXX XXX
Fax: +(34) 9X XXX XXX
www.epitype.es

EpiType Logo

Sample ID:

Age:

Sex:

Test Report Date: 13 Oct 2014

Version: ESS 8.0

Processing ID: 5723654015_R04C01

PATIENT INFORMATIO

Requisition ID:

Biopsy Site:

Date Specimen Collected:

Date Specimen Recieved:

PHYSICIANS INFORMATION

Tel:

Fax:

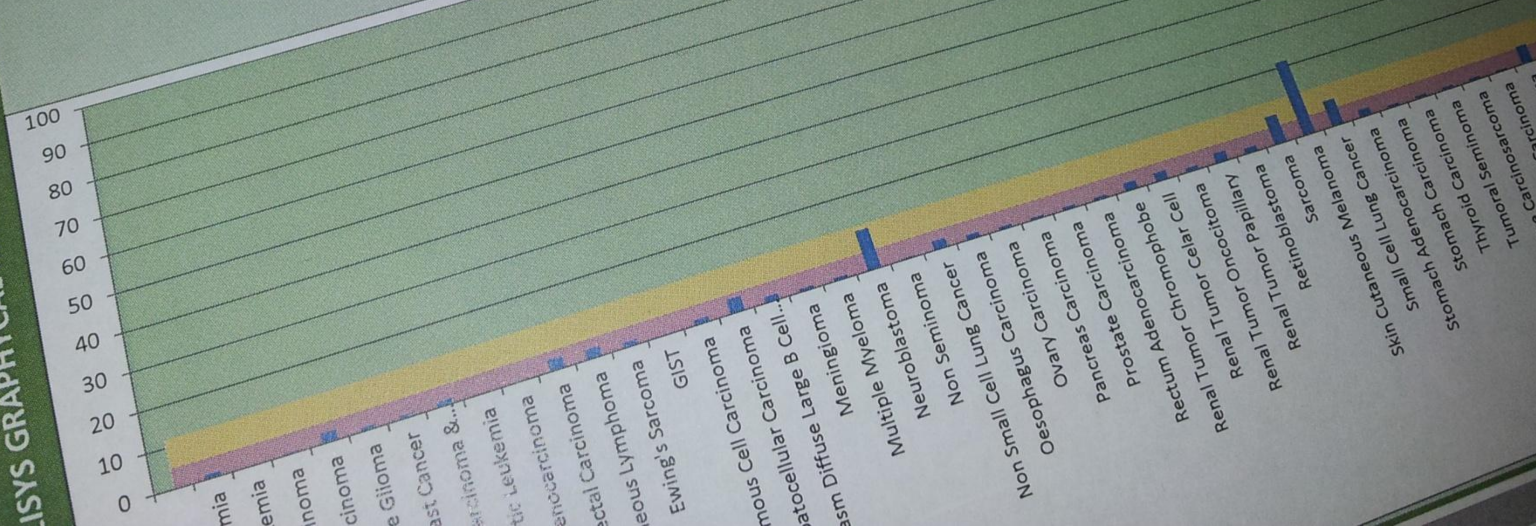
MOST LIKELY TUMOR TYPE

Skin Cutaneous Melanoma

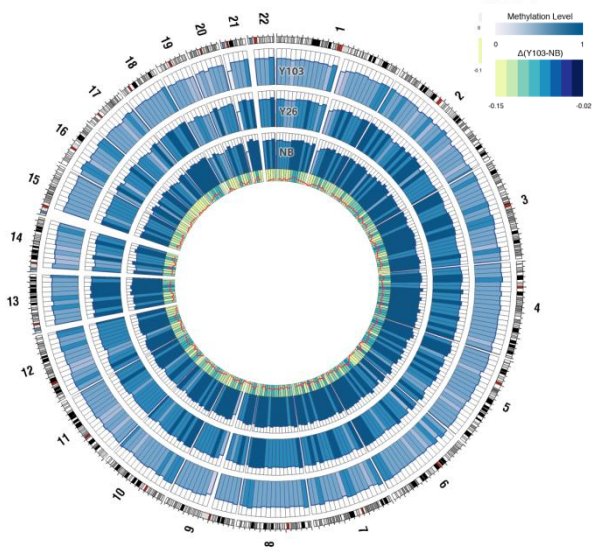
DEGREE OF CONFIDENCE

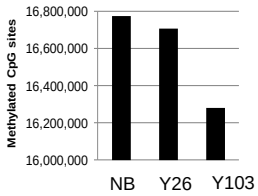
HIGH

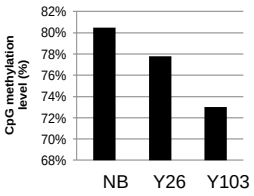
...LISYS GRAPHYCAL RESULTS

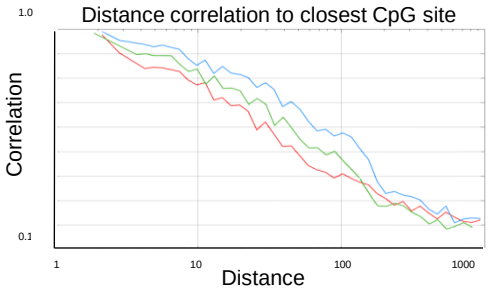


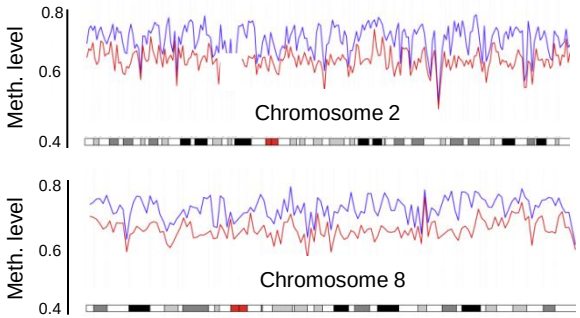
The Distinct DNA Methylomes of Newborns and Centenarians

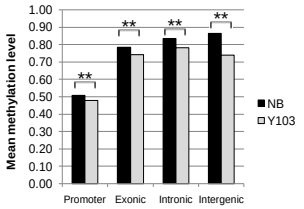


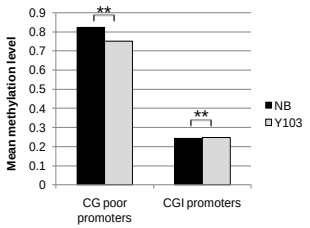


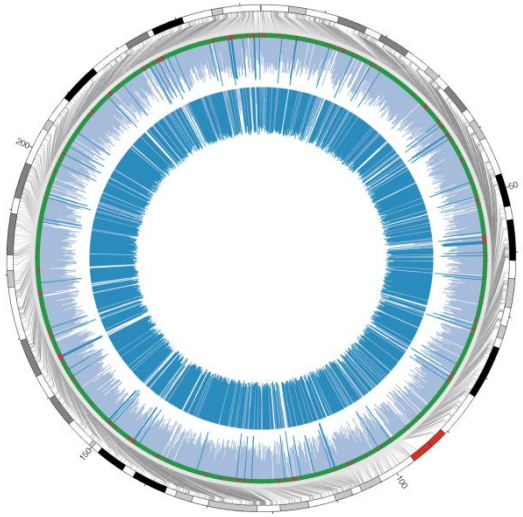


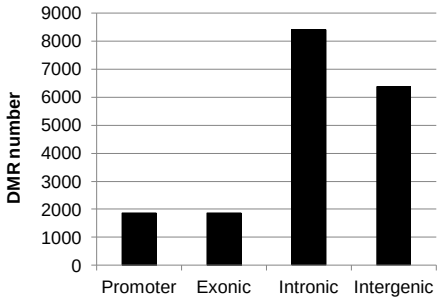


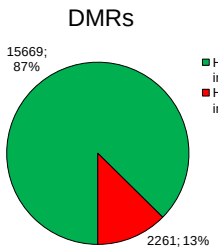


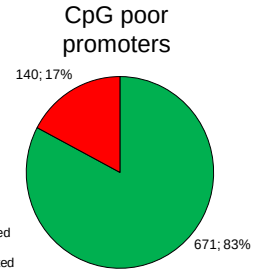


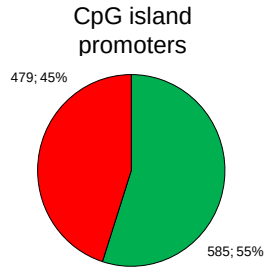


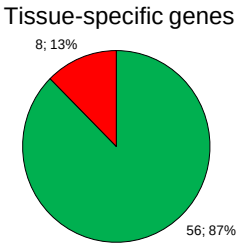


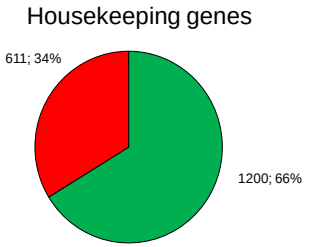






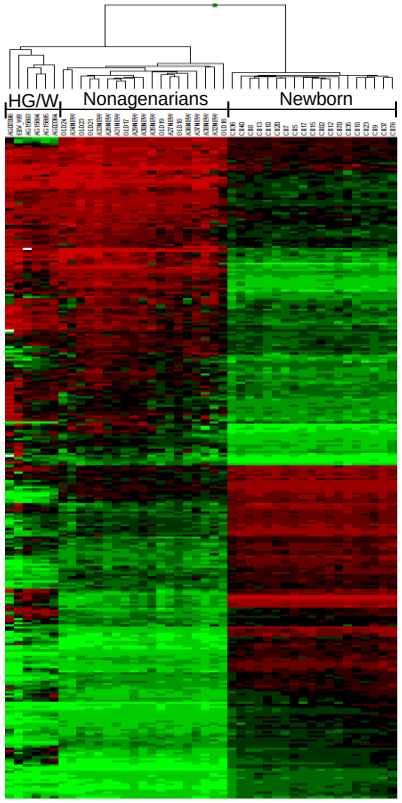




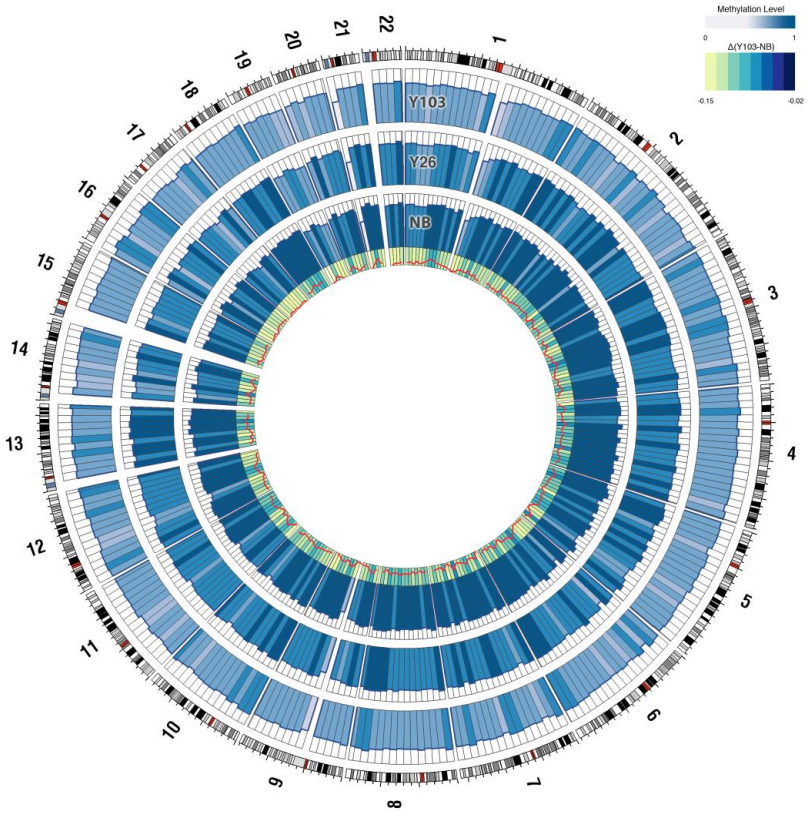


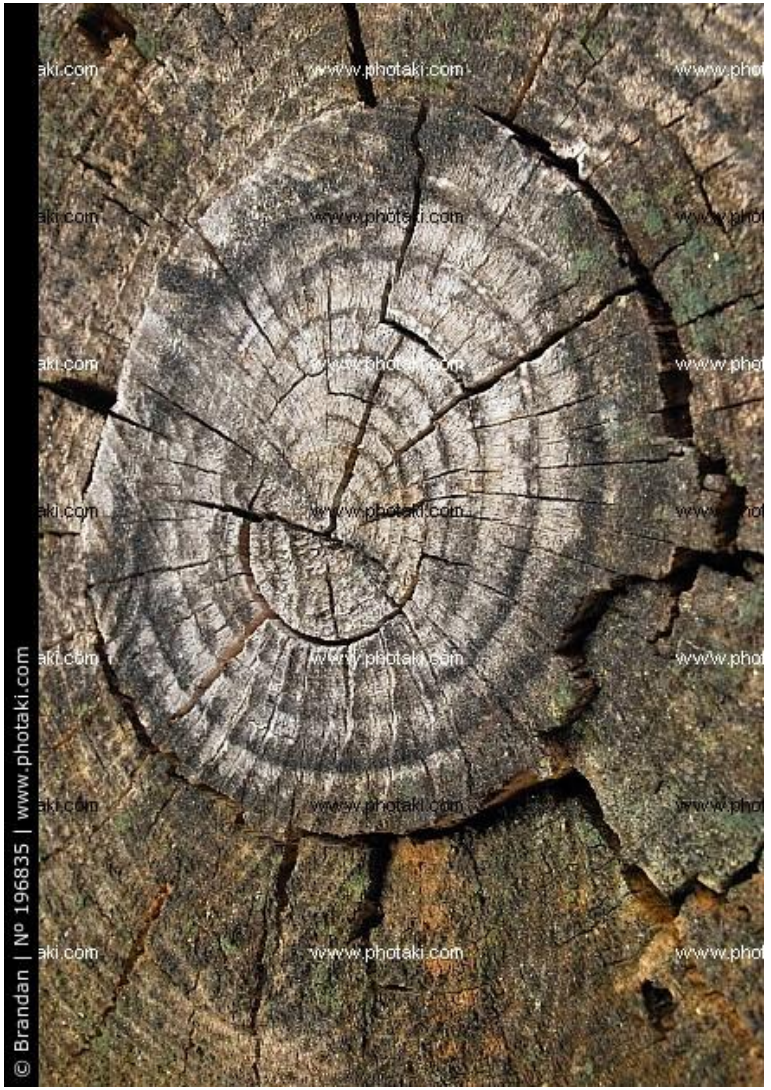
Proc Natl Acad Sci USA, 2012

Diseases Associated with Premature Aging: Hutchinson-Gilford Progeria and Werner syndrome

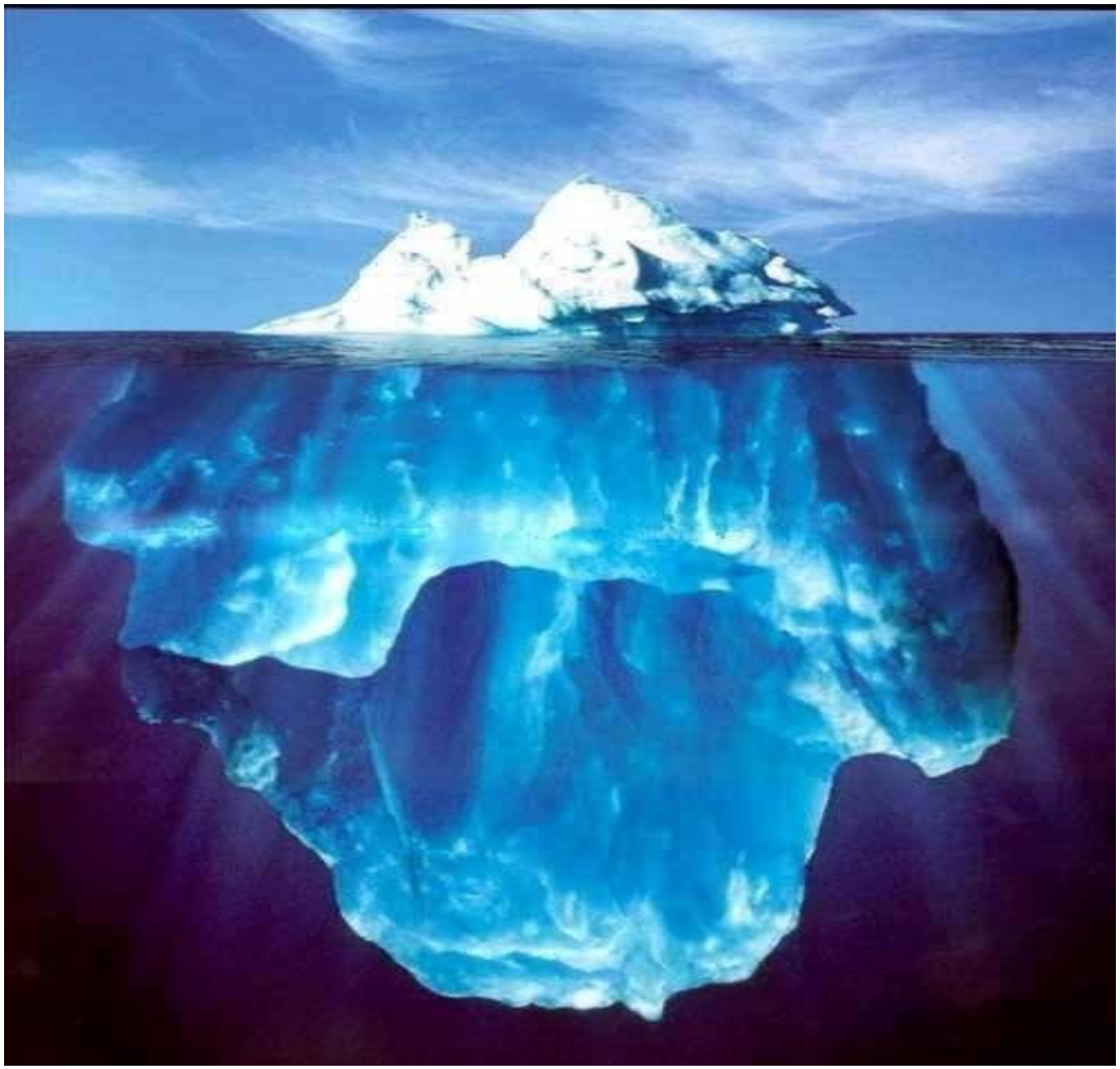


Prediction of Biological Age Using DNA Methylation





The Biomedical Iceberg



The Genome

The Epigenome

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Manel Esteller, 2014