

L7

Epigenetics

Cancer, Environment & Aging

1. Development of cancer
2. Knudsen 's „two hit hypothesis“
3. Epigenetic mechanisms and the development of cancer
4. Diagnostics using DNA methylation

Cancer is a complex genetic disease of cellular origin in which a combination of genetic and epigenetic alterations allow the abnormal use of developmental programs to promote uncontrolled differentiation and proliferation.

“All cancers arise due to alterations in DNA. Some cancer-causing mutations may be present in the germline, are therefore heritable and confer an elevated risk of developing cancer. Many, however, occur over the course of a person’s lifetime in individual cells of the body and are known as somatic (driver and passenger) mutations.”

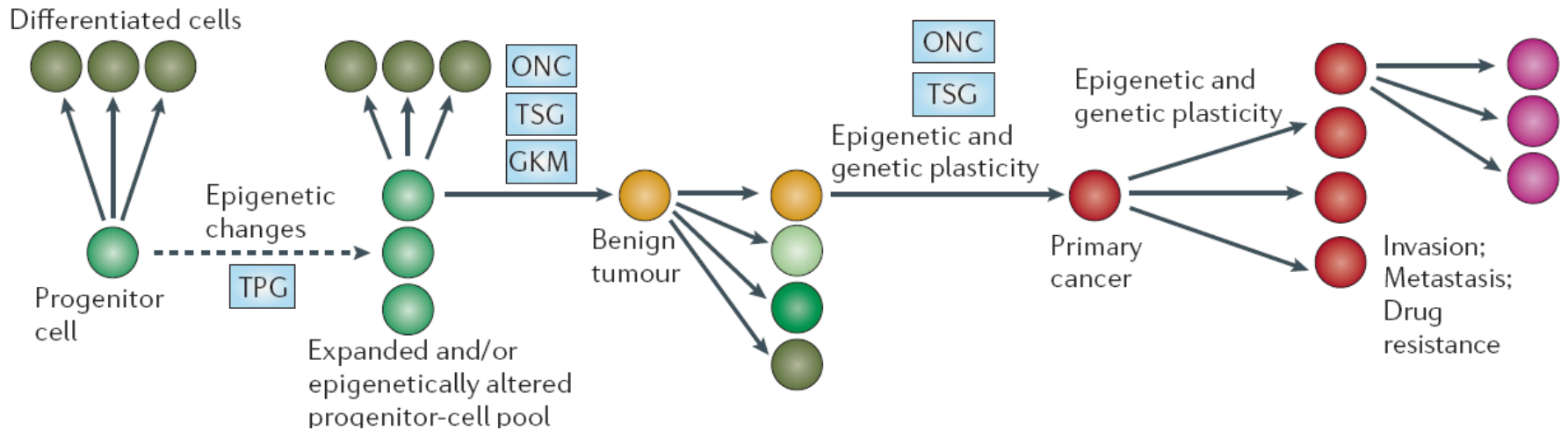
ICGC policy document: <http://icgc.org/icgc/goals-structure-policies-guidelines/introduction>

In cancer the „normal“ cell physiology is altered due to a deregulation of genetic programs by :

- Chromosomal mutations = amplifications or deletion = gain or loss of genes.
- Point-mutations (either somatic or germ line).
- Transcriptional silencing or activation of genes by epigenetic changes
- Genomic instability (e.g. activation of transposable elements) (epigenetic).

# Cancer development – a single cell progenitor model

(cancer stem cell model)



GKM: Gate Keeper Mutation, e.g.. tumor suppressor gene (TSG) or oncogene (ONC)

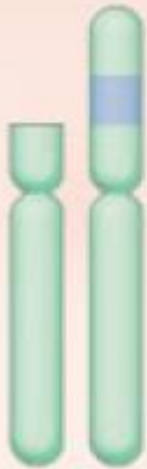
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# The Knudson's „Two hit hypothesis“ – extension by epigenetic silencing

Normal



Cancer



Cancer



Cancer



Sporadic cancer

Normal



Cancer



Cancer



Inherited cancer



Mutation



Methylation

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How can tumor suppressor genes become inactivated and oncogenes become activated?

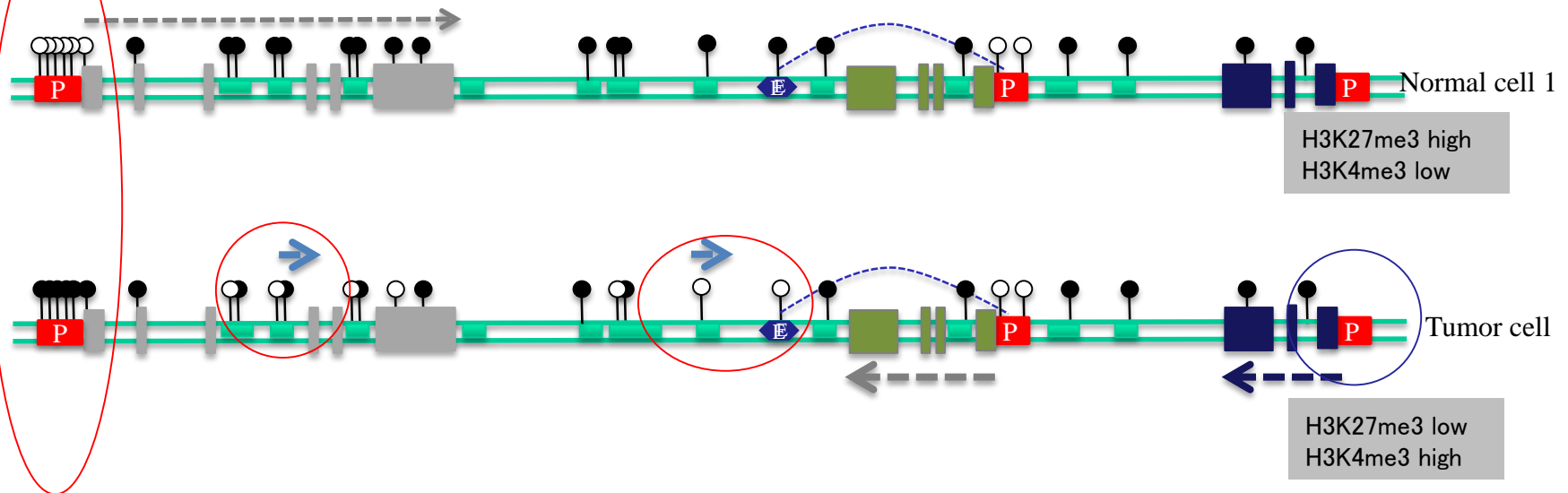
1. Genetic alterations (mutations)
2. Epigenetic silencing (epimutations)

# Which general epigenetic changes occur in cancer cells

De novo methylation of Housekeeping gene  
e.g. cell cycle regulator  
DNA-repair factor

Genome wide loss of  
DNA-methylation

Loss of silencing of  
developmental genes  
(e.g. embryonic  
cell proliferator)



Promoter **P**  
With CpG island

Repetitive  
Element

enhancer **E**  
CpG-

Promoter **P**  
CpG-poor

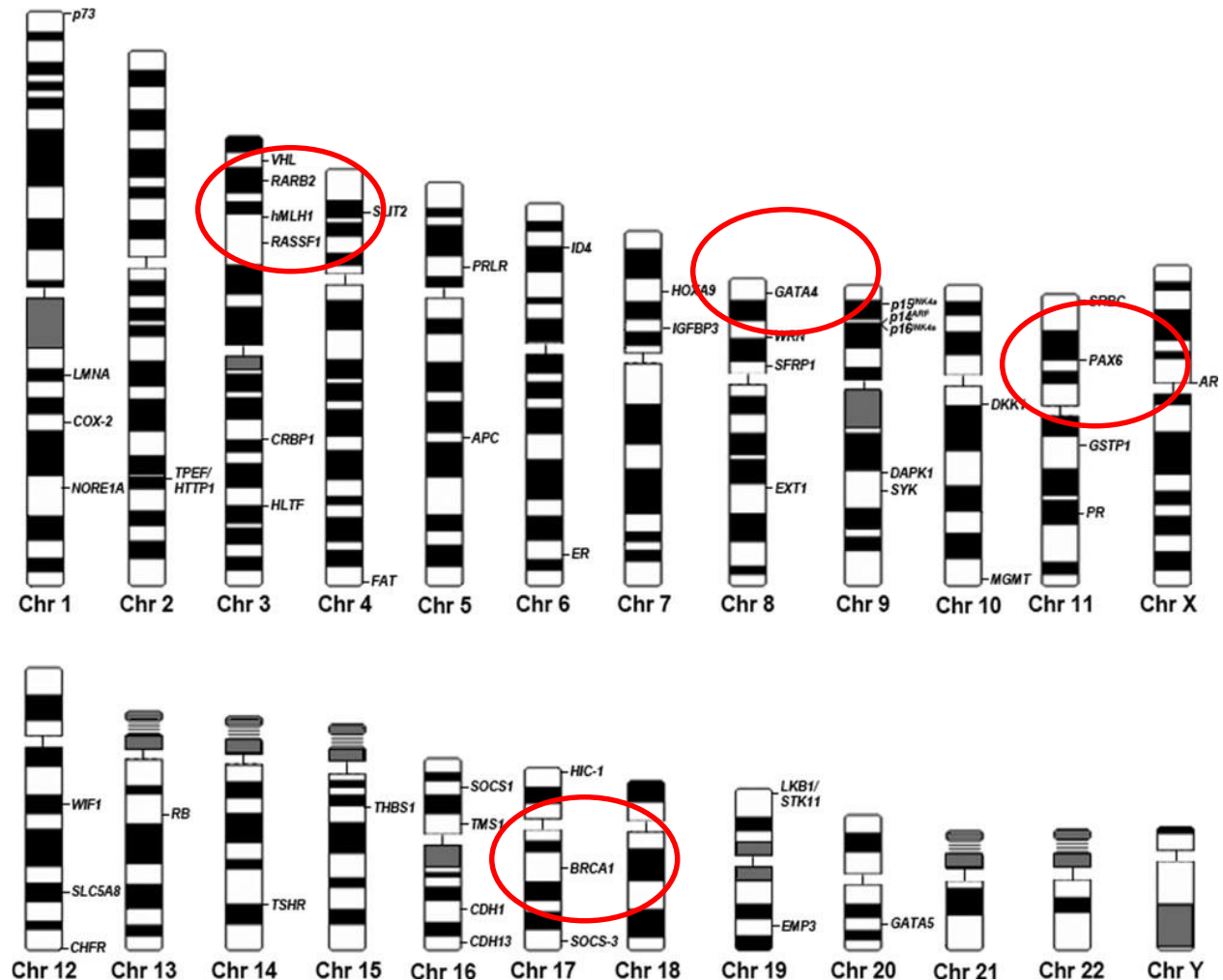
Promoter **P**  
No DNA-methylation  
control

● methyliertes CpG  
○ unmethyliertes CpG

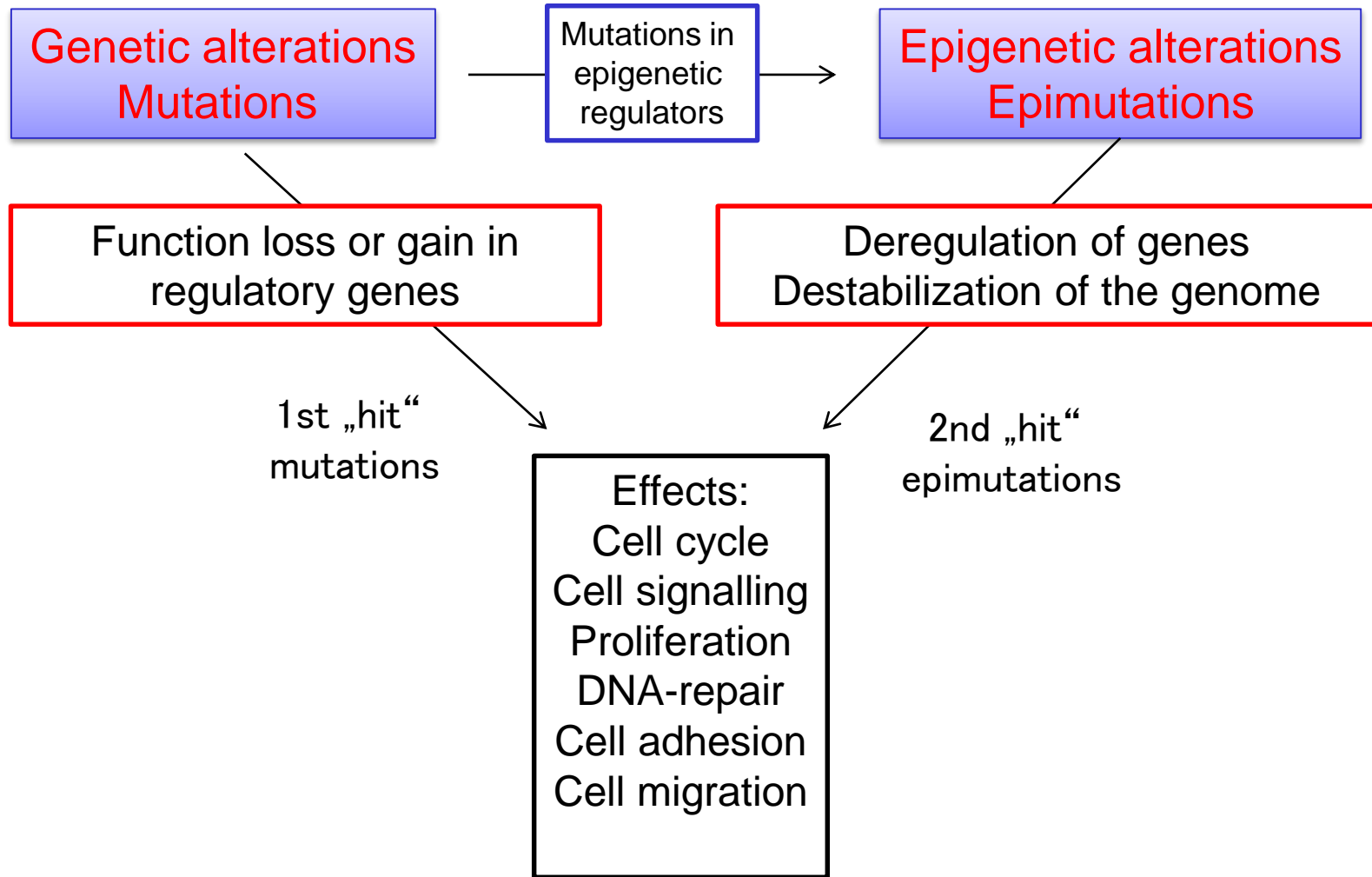
---> Transkript  
| Exon

# Frequently observed epigenetic silencing of tumor suppressor genes (CpG island hypermethylation)

50% of tumor suppressor genes are inactivated by epigenetic mechanisms.



# The complex interplay of genetic and epigenetic alterations in cancer development



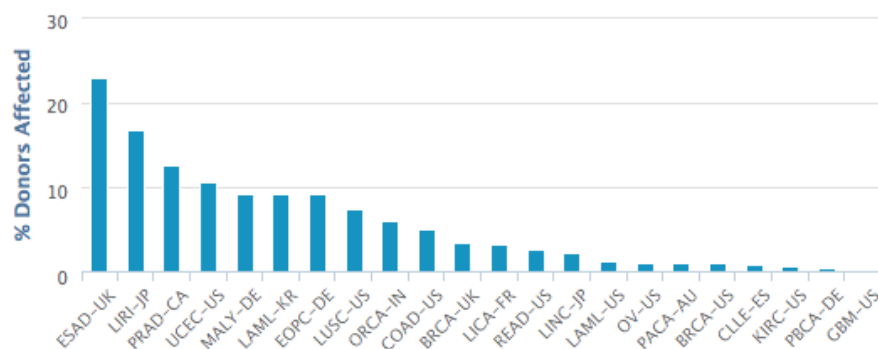
# Genetic mutations of Tet1 in cancer

## Tet1

### Cancer Distribution

[OPEN IN ADVAN](#)

**112** DONORS AFFECTED BY **167** MUTATIONS ACROSS **22** PROJECTS



Showing **22** projects

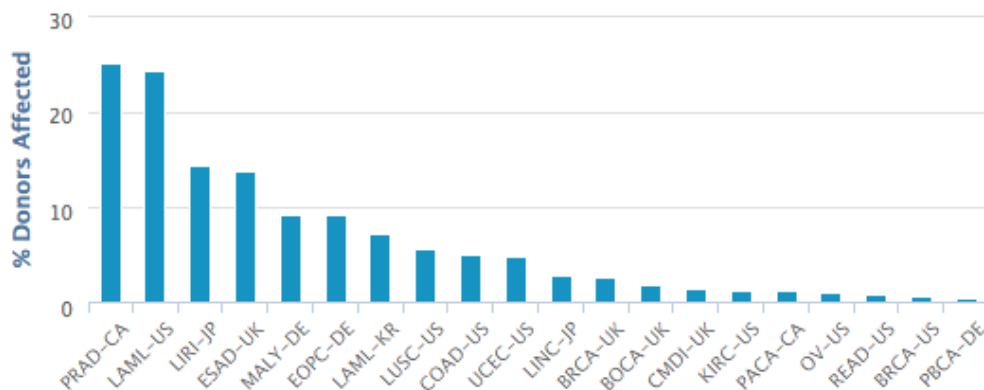
Project	Site	Tumour Type	Tumour Subtype	# Donors affected ▾	#
ESAD-UK	Esophagus	Esophageal Cancer	Esophageal Adenocarcinoma	5 / 22 (22.73%)	
LIRI-JP	Liver	Liver Cancer	Hepatocellular Carcinoma (Viru...	7 / 42 (16.67%)	
PRAD-CA	Prostate	Prostate Cancer	Adenocarcinoma	1 / 8 (12.50%)	
UCEC-US	Uterus	Endometrial Cancer	Uterine Corpus Endometrial Car...	26 / 246 (10.57%)	
MALY-DE	Blood	Malignant Lymphoma	Germinal Center B-cell Derived ...	4 / 44 (9.09%)	
LAML-KR	Blood	Blood Cancer	Acute Myeloid Leukemia	5 / 55 (9.09%)	

# Genetic mutations of DNMT3A in cancer

## Cancer Distribution

[OPEN IN ADVANCED SEARCH](#)

**124** DONORS AFFECTED BY **113** MUTATIONS ACROSS **20** PROJECTS

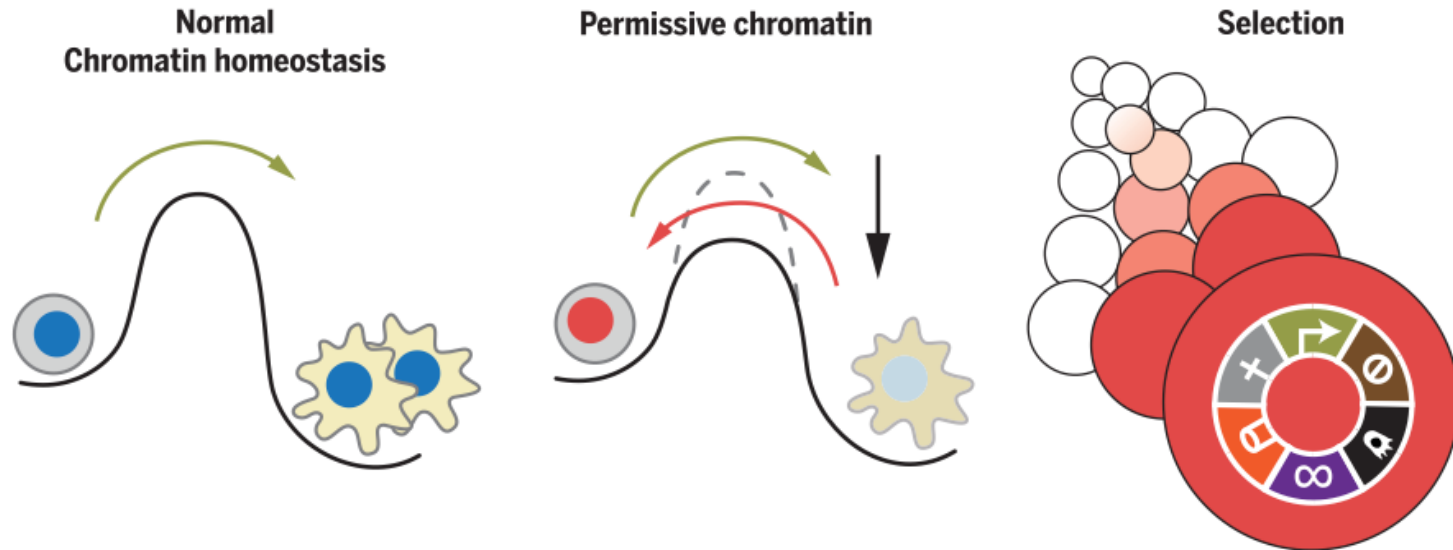


Showing **20** projects



Project	Site	Tumour Type	Tumour Subtype	# Donors affected ▼	# Mutations
<a href="#">PRAD-CA</a>	Prostate	Prostate Cancer	Adenocarcinoma	2 / 8 (25.00%)	2
<a href="#">LAML-US</a>	Blood	Blood Cancer	Acute Myeloid Leukemia	41 / 170 (24.12%)	25
<a href="#">LIRI-JP</a>	Liver	Liver Cancer	Hepatocellular Carcinoma (Viru...	6 / 42 (14.29%)	9
<a href="#">ESAD-UK</a>	Esophagus	Esophageal Cancer	Esophageal Adenocarcinoma	3 / 22 (13.64%)	4
<a href="#">MALY-DE</a>	Blood	Malignant Lymphoma	Germinal Center B-cell Derived	4 / 44 (9.09%)	5

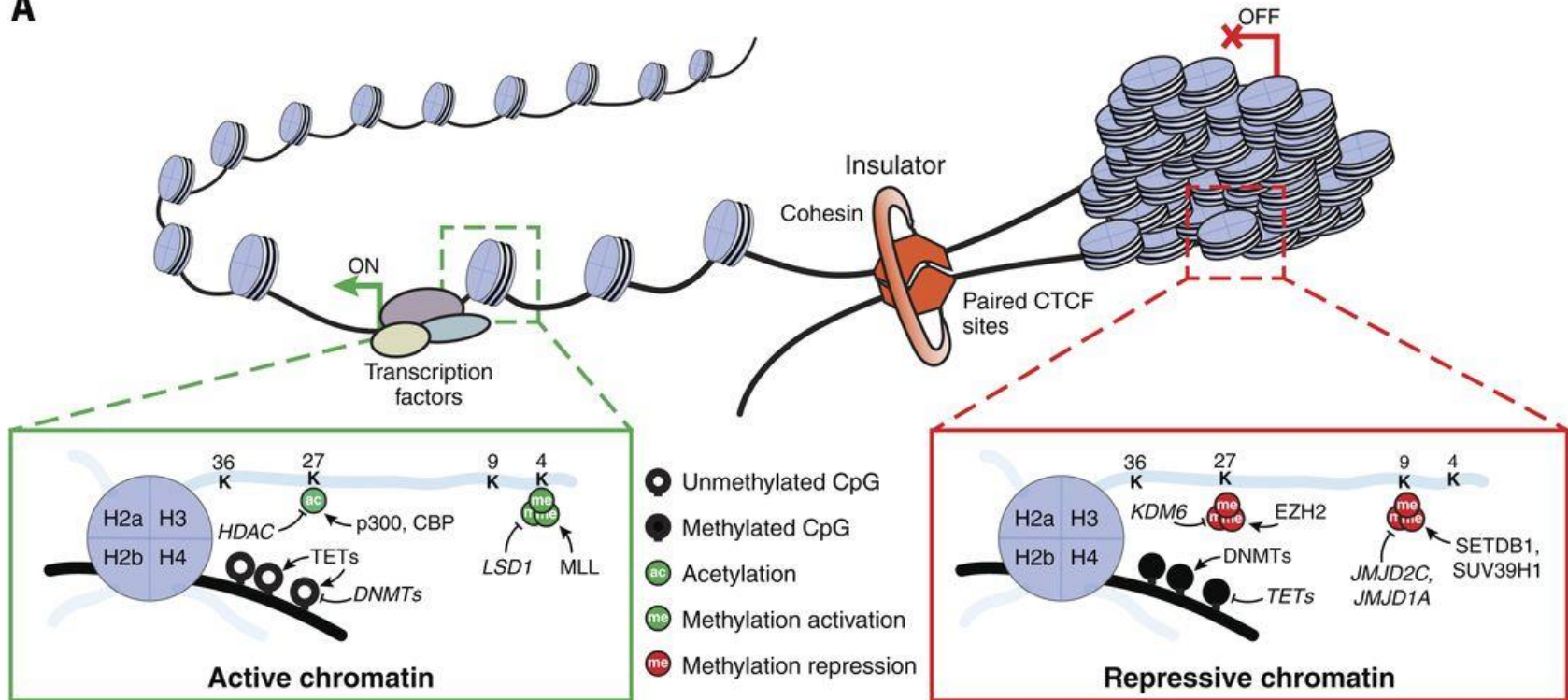
# Chromatin changes and cancer



**Epigenetic plasticity, selection, and cancer.** (Left) Normal chromatin and associated epigenetic mechanisms stabilize gene expression and cellular states while facilitating appropriate responses to developmental or environmental cues (blue nuclei represent normal cell state). Genetic, environmental, and metabolic insults that disrupt chromatin can lead to either restrictive or overly permissive chromatin states. (Center) Overly permissive chromatin results in epigenetic plasticity; this plasticity permits stochastic activation of alternate gene regulatory programs (red nuclei represent cancer-like cell state). (Right) Some stochastic changes will be inconsequential “passengers” while others will confer fitness and be selected as “drivers”; in this way, chromatin aberrations have the potential to fulfill each hallmark of cancer.

# Chromatin structure affects cellular identity and state transitions

A

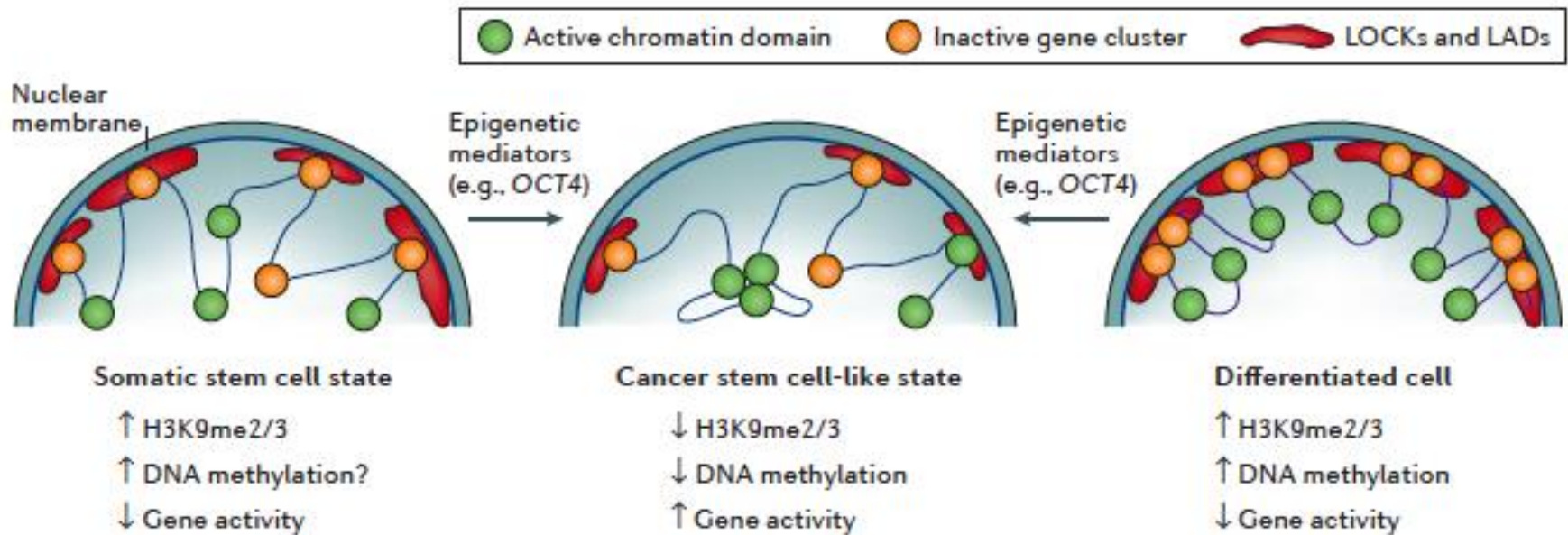


William A. Flavahan et al.  
Science 2017;357:eaal2380





# Disorganisation of chromatin in cancer cells

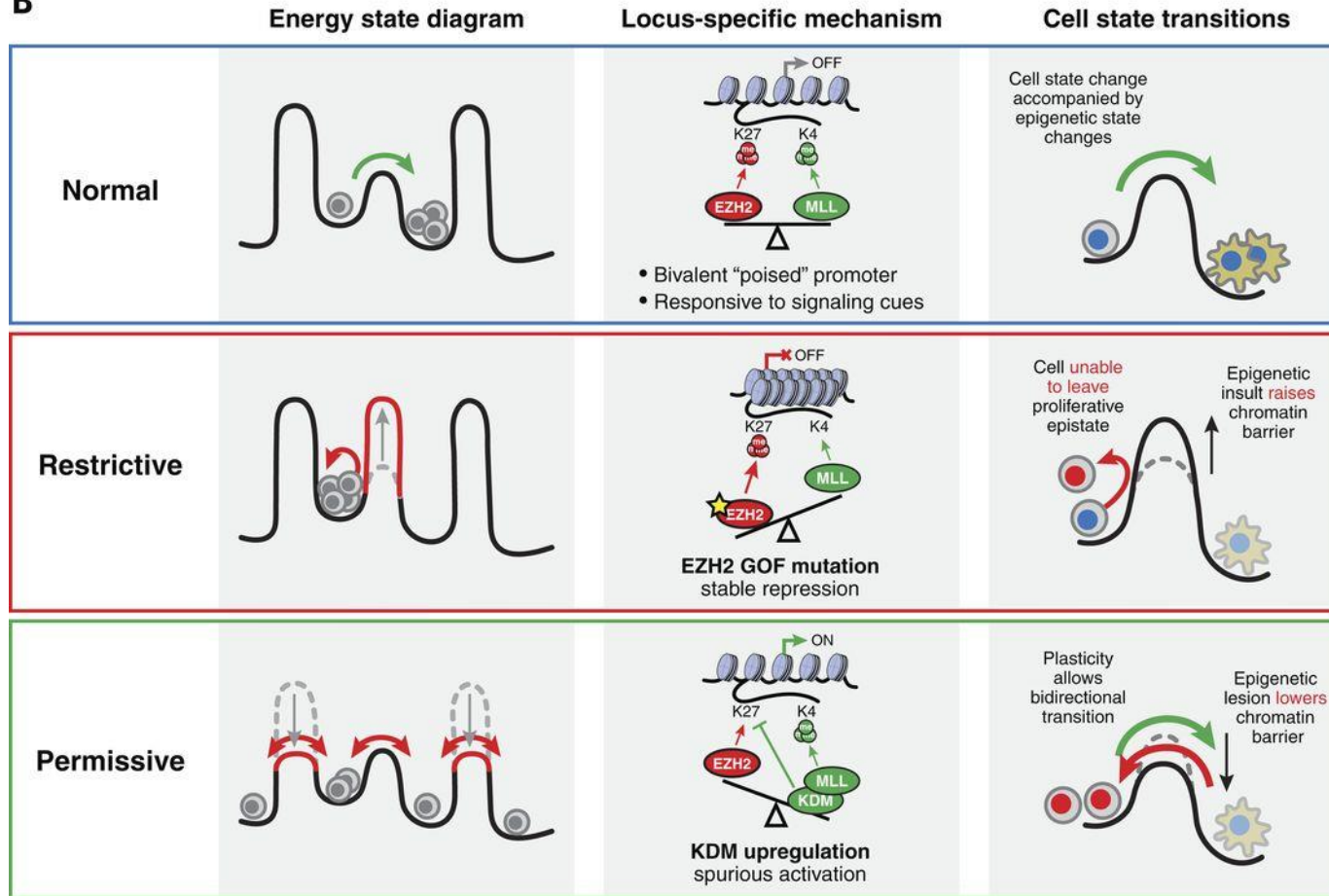


Epigenetic modulators, modifiers and mediators in cancer aetiology and progression

*Andrew P. Feinberg<sup>1</sup>, Michael A. Koldobskiy<sup>1</sup> and Anita Gondör<sup>2</sup>*

# Chromatin structure affects cellular identity and state transitions

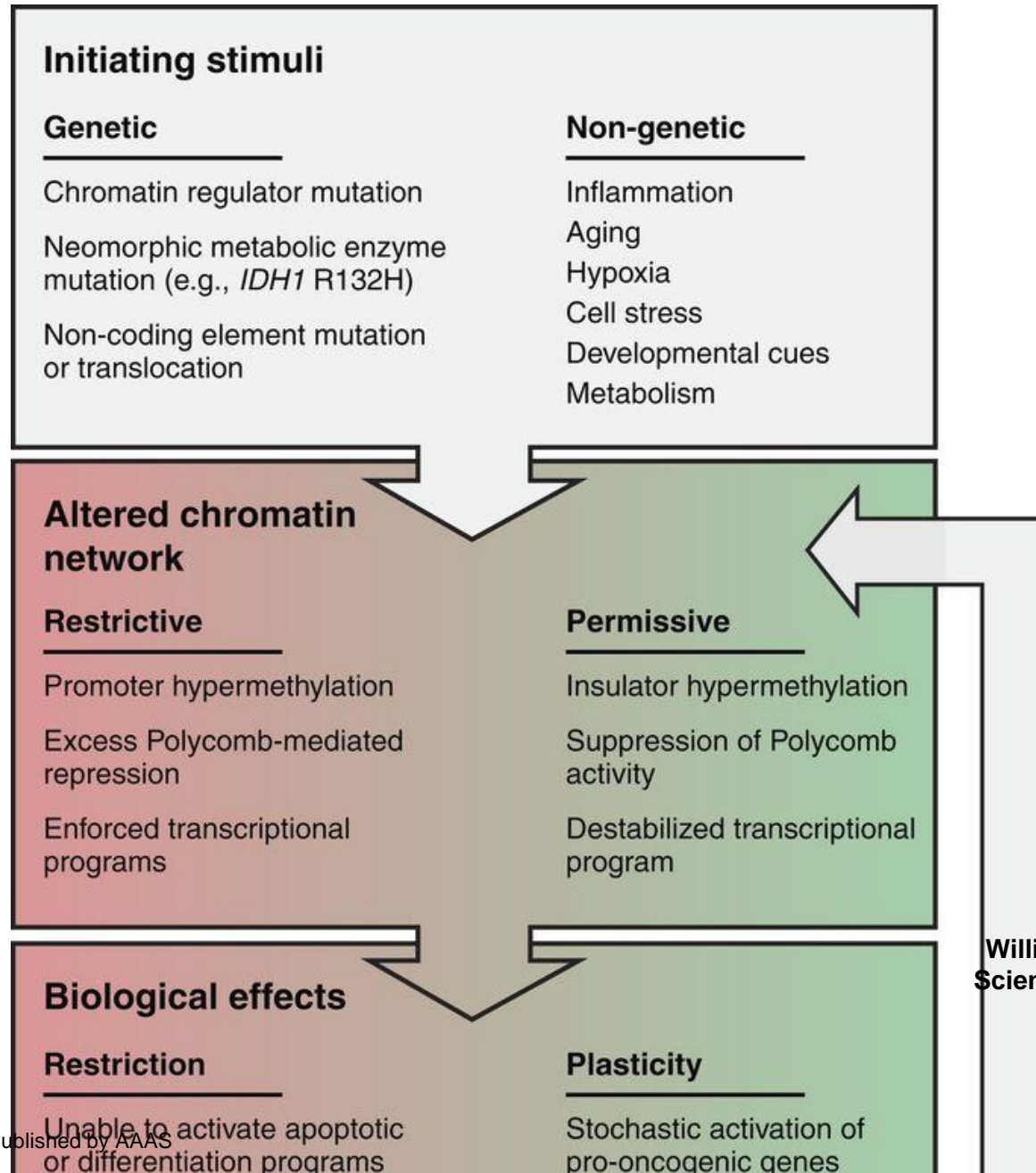
B



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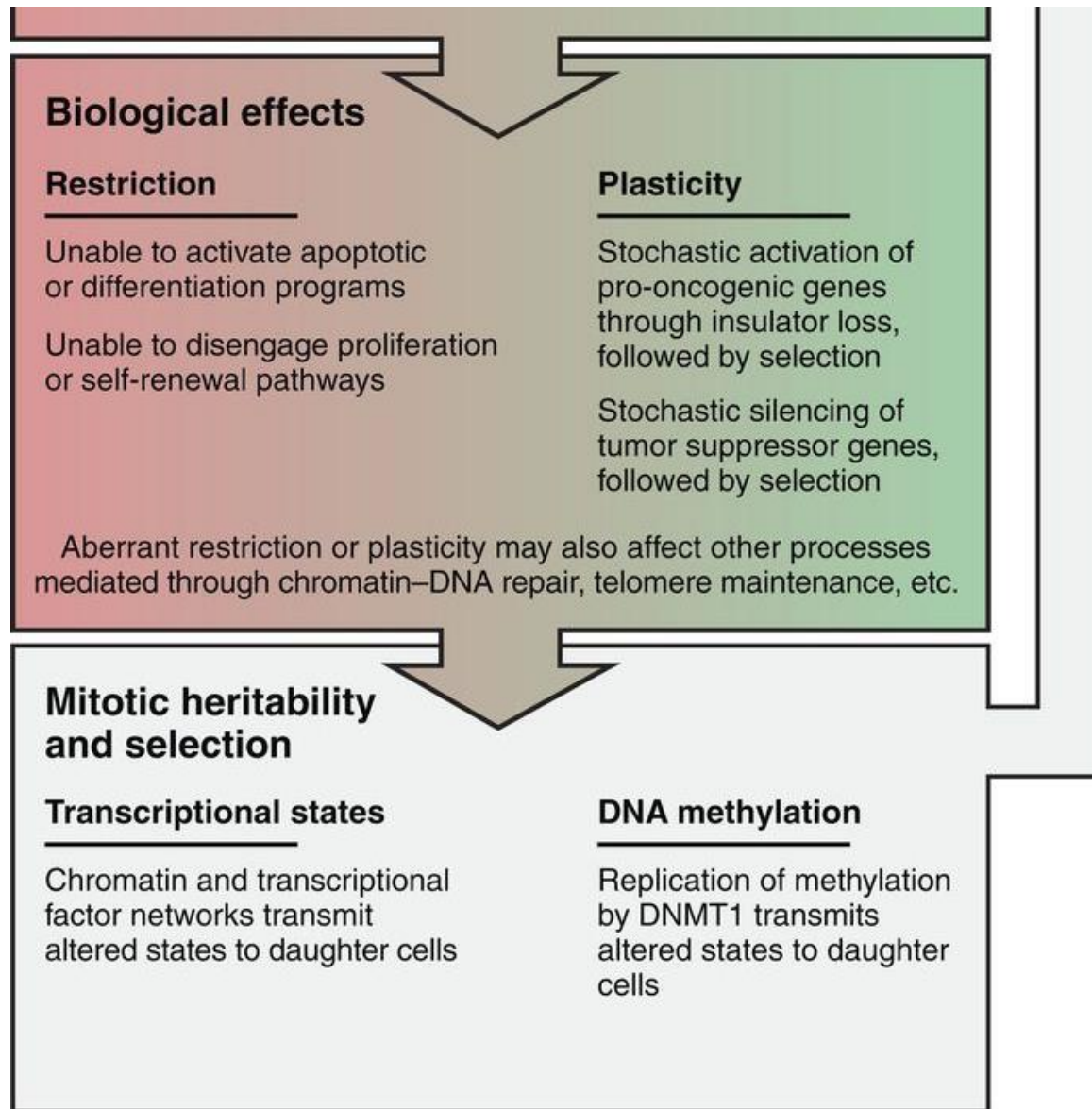
# Chromatin programs are frequently disrupted in cancer.



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# Chromatin programs are frequently disrupted in cancer.

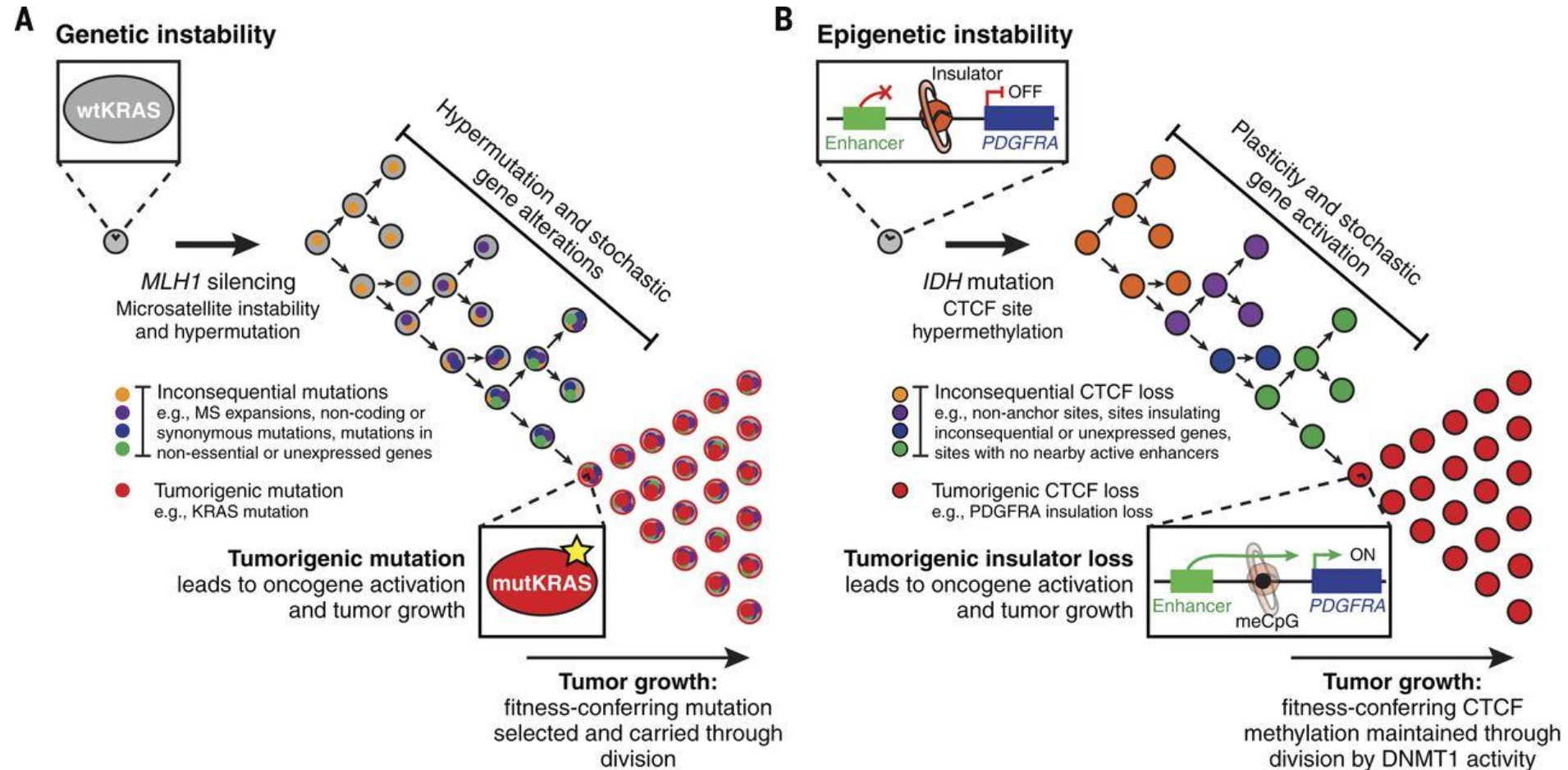


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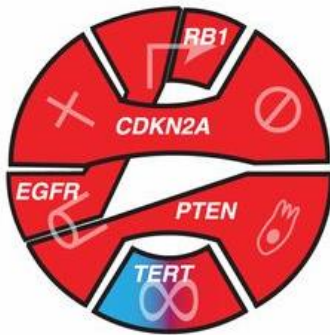
# Genetic and epigenetic contributions to the evolution in cancer.



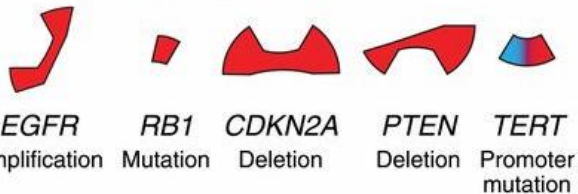
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# Genetic and epigenetic mechanisms variable the hallmarks of cancer

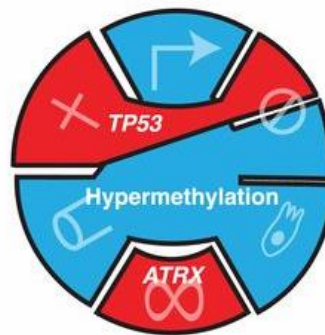
**B** Glioblastoma



Oncogenic alterations  
(genetic / epigenetic)



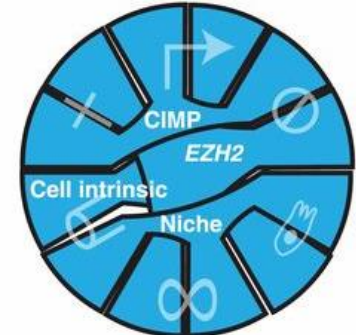
**C** Anaplastic astrocytoma



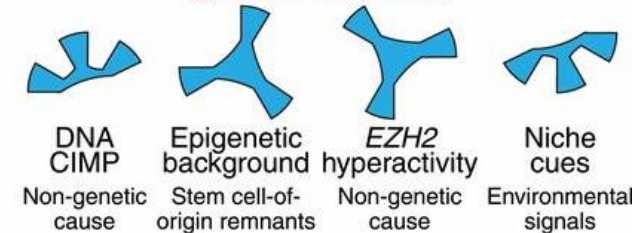
Oncogenic alterations  
(genetic / epigenetic)



**D** Ependymoma (EPN-A, balanced)



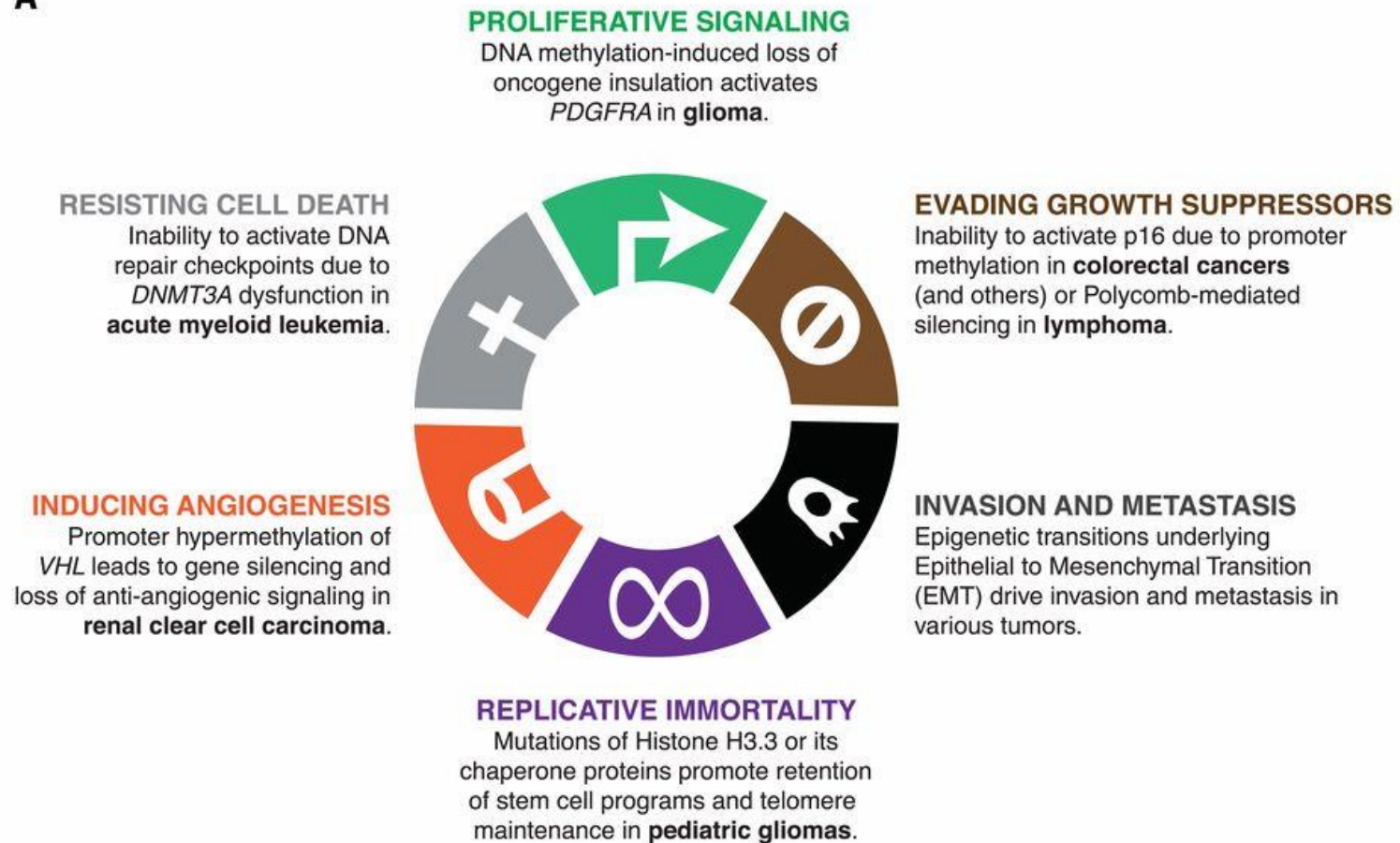
Oncogenic alterations  
(genetic / epigenetic)



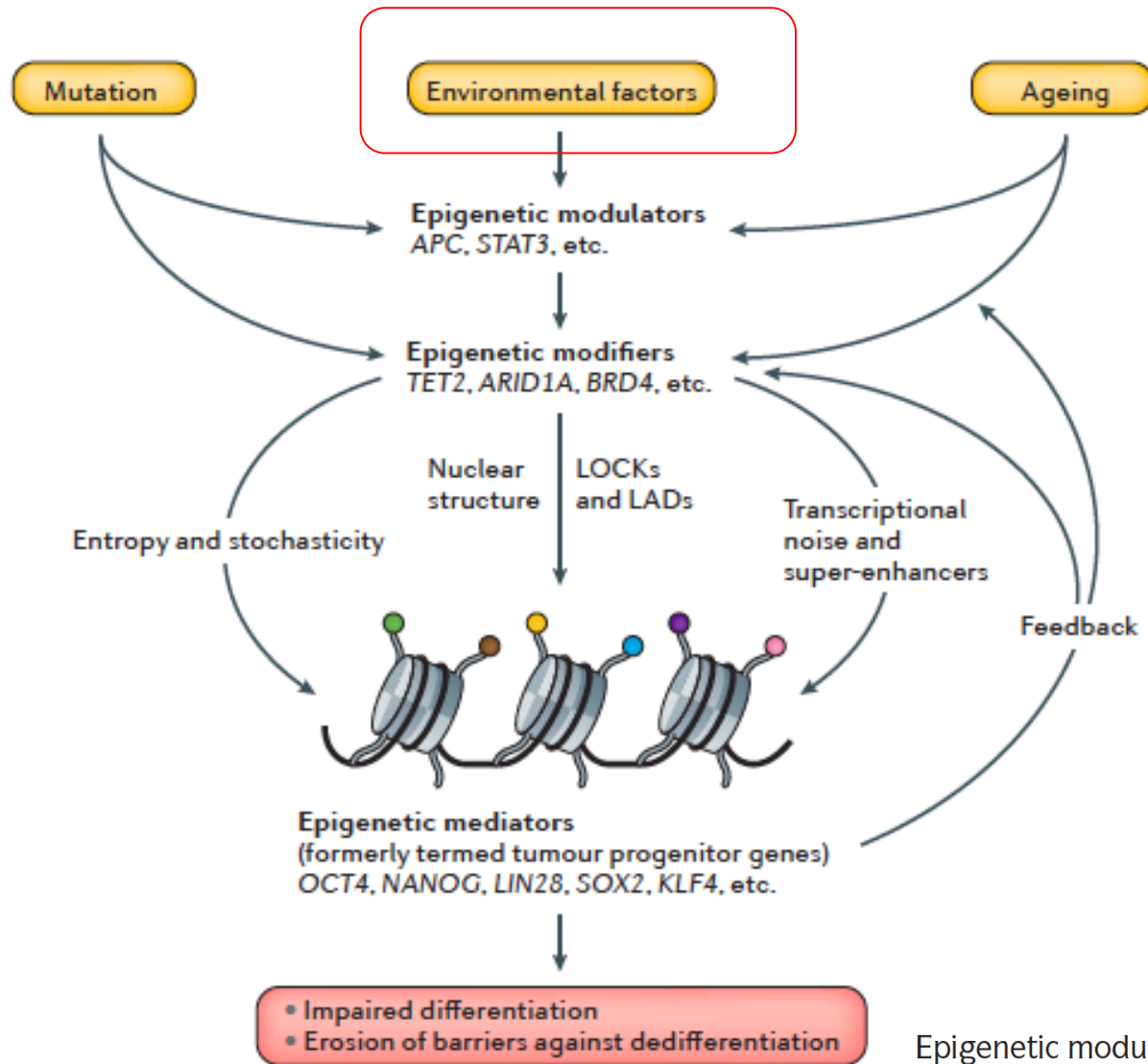
William A. Flavahan et al. Science 2017;357:eaal2380

# Genetic and epigenetic mechanisms underlie the hallmarks of cancer.

A



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Epigenetic modulators, modifiers and mediators in cancer aetiology and progression

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1. Development of cancer
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Table 1 | **Hypermethylated genes in cancer and their associated tissue types**

Gene name	Gene function	Cancer type
APC	WNT signalling	Prostate, colon, lung, bladder
AR	Androgen receptor signalling	Prostate
BRCA1		
BRCA2		
CDKN2A		
CDKN2B		
CDKN2C		
CDKN2D		
CDKN2E		
CDKN2F		
CDKN2G		
CDKN2H		
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CDKN2L		
CDKN2M		
CDKN2N		
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Table 1 | **Hypermethylated genes in cancer and their associated tissue types**

Gene name	Gene function	Cancer type
<i>APC</i>	WNT signalling	Prostate, colon, lung, bladder
<i>AR</i>	Androgen receptor signalling	Prostate
<i>BMAL1</i>	AHR signalling	Leukaemia, lymphoma
<i>BRCA1</i>	DNA damage response	Breast, ovarian
<i>CDH1</i>	Cell–cell adhesion	Breast, prostate
<i>CDH11</i>	Cell–cell adhesion	Colon, breast, oesophagus, gastric, liver
<i>CDH13</i>	Cell–cell adhesion	Lung, head and neck
<i>CDKN2A</i>	Cell cycle control	Lymphoma, colon, stomach, prostate
<i>CDKN2B</i>	Cell cycle control	Leukaemia
<i>DAPK1</i>	Programmed cell death control	Lung, head and neck, bladder
<i>EMP3</i>	Signal transduction	Glioma
<i>ESR1</i>	Oestrogen receptor signalling	Breast
<i>GSTP1</i>	Detoxification	Prostate, liver, lung
<i>IGFBP3</i>	Signal transduction	Colon, lung, ovarian, prostate
<i>LGALS3</i>	Extracellular matrix protein	Prostate
<i>MASPIN</i>	Peptidase inhibitor	Pancreas
<i>MGMT</i>	DNA repair	Colon, glioma, lymphoma, prostate, lung
<i>miR-148a</i>	Metastasis suppression	Metastasis
<i>miR-34b</i> and <i>miR-34c</i>	Metastasis suppression	Metastasis
<i>miR-9</i>	Metastasis suppression	Metastasis
<i>miR-200s</i>	Epithelial–mesenchymal transition	Colon, bladder, squamous cell carcinoma
<i>MLH1</i>	DNA repair	Colon, endometrium, stomach
<i>NORE1A</i>	Cell growth control	Colon, liver, lung, thyroid
<i>NSD1</i>	Nuclear receptor	Glioma, neuroblastoma
<i>PYCARD</i>	Apoptosis	Glioma, breast, colon, gastric, lung
<i>RARB</i>	Retinoic acid receptor	Breast, colon, prostate

# Cancer–Diagnostics

Mutations and epimutations in the MGMT gene

**MGMT: O6–Methylguanine–DNA methyltransferase**

MGMT detoxifies alkylated guanines – acts against chemotherapy

# The role of MGMT in cancer treatment

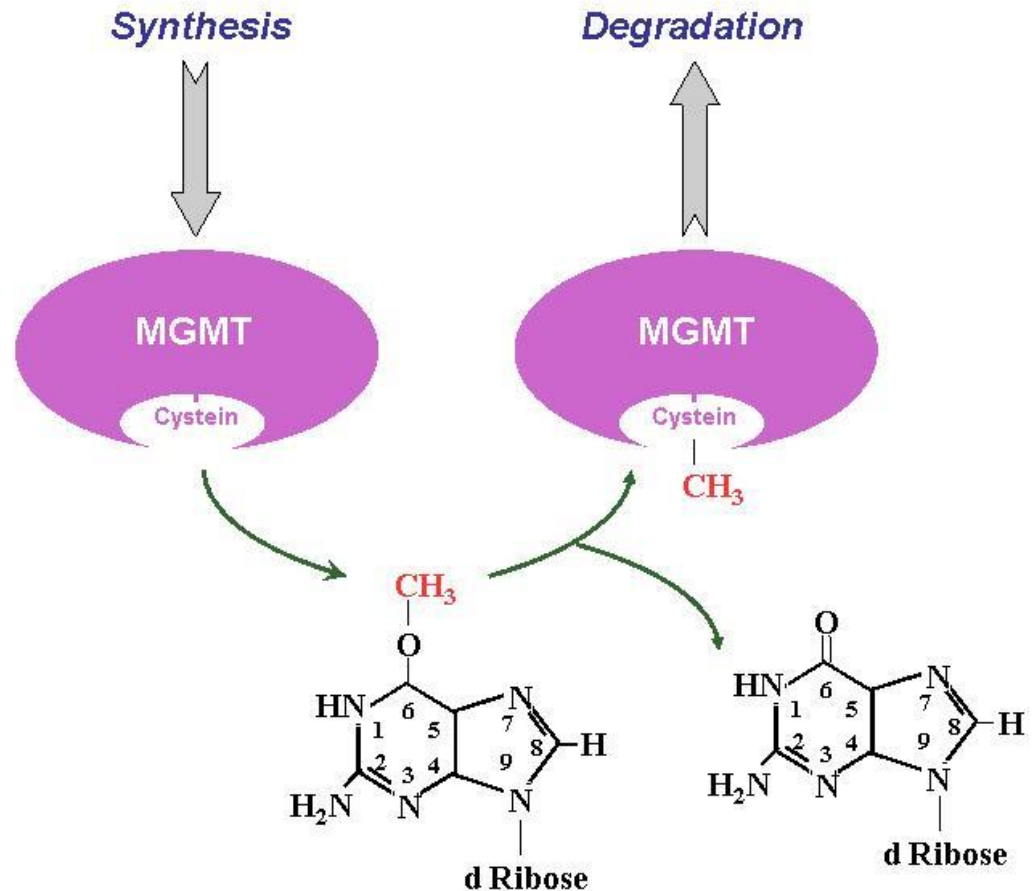
Chemotherapy often uses alkylating substances by modifying bases in the genome (i.e. addition von  $C_nH_{2n+1}$ ), e.g:

- Chemotherapeutics (Dacarbazine, Streptozotocin, Temozolomide),
  - Nutrition (Dimethylnitrosamine (DMNA))
  - Smoking (Nitrosononikotin (NNN); 4-Methylnitrosoamino-1-(3-pyridyl)-1-butanon (NNK))
- 
- One product is the O<sup>6</sup>methyl-Guanin which when not repaired, allows a „promiscuous base pairing“ with Thymidine during S-phase
  - This causes G-C to T-A point mutation
  - **Without MGMT the cell has increased mutation rates**

# MGMT is a suicide-enzyme

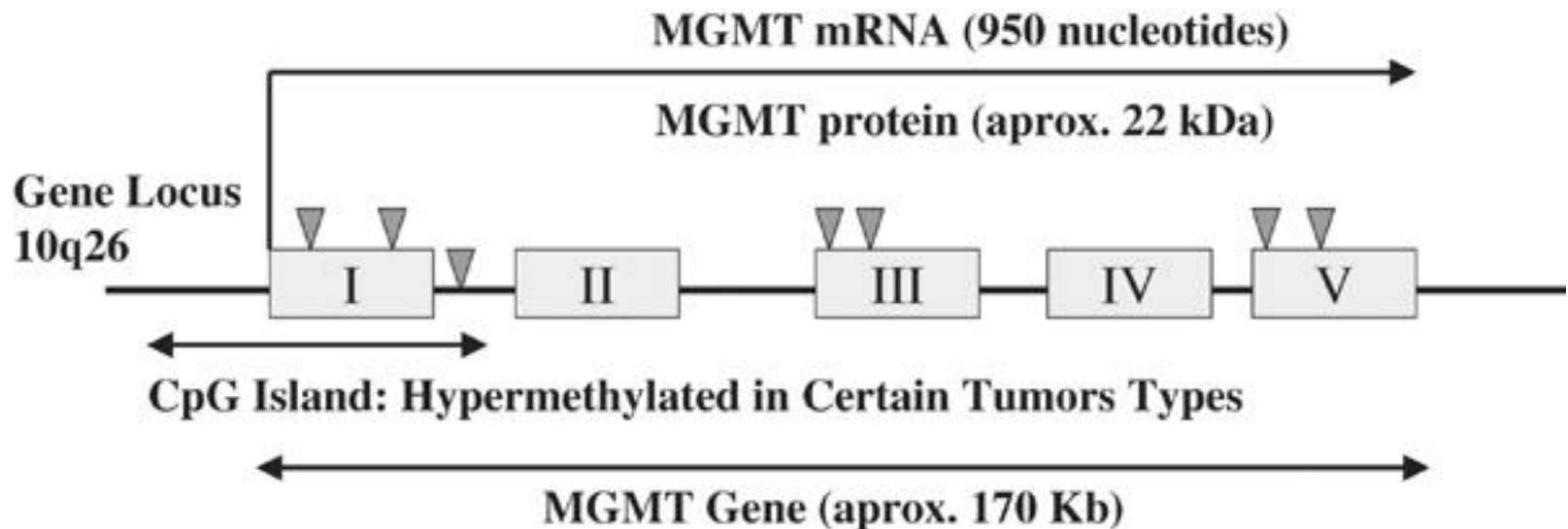
- MGMT receives alkyl-residue and is subsequently inactivated
- Ubiquitination and Proteasome-mediated degradation

„Suicide Reaction“



# MGMT Gene

## O<sup>6</sup>-Methylguanine DNA Methyltransferase (MGMT)



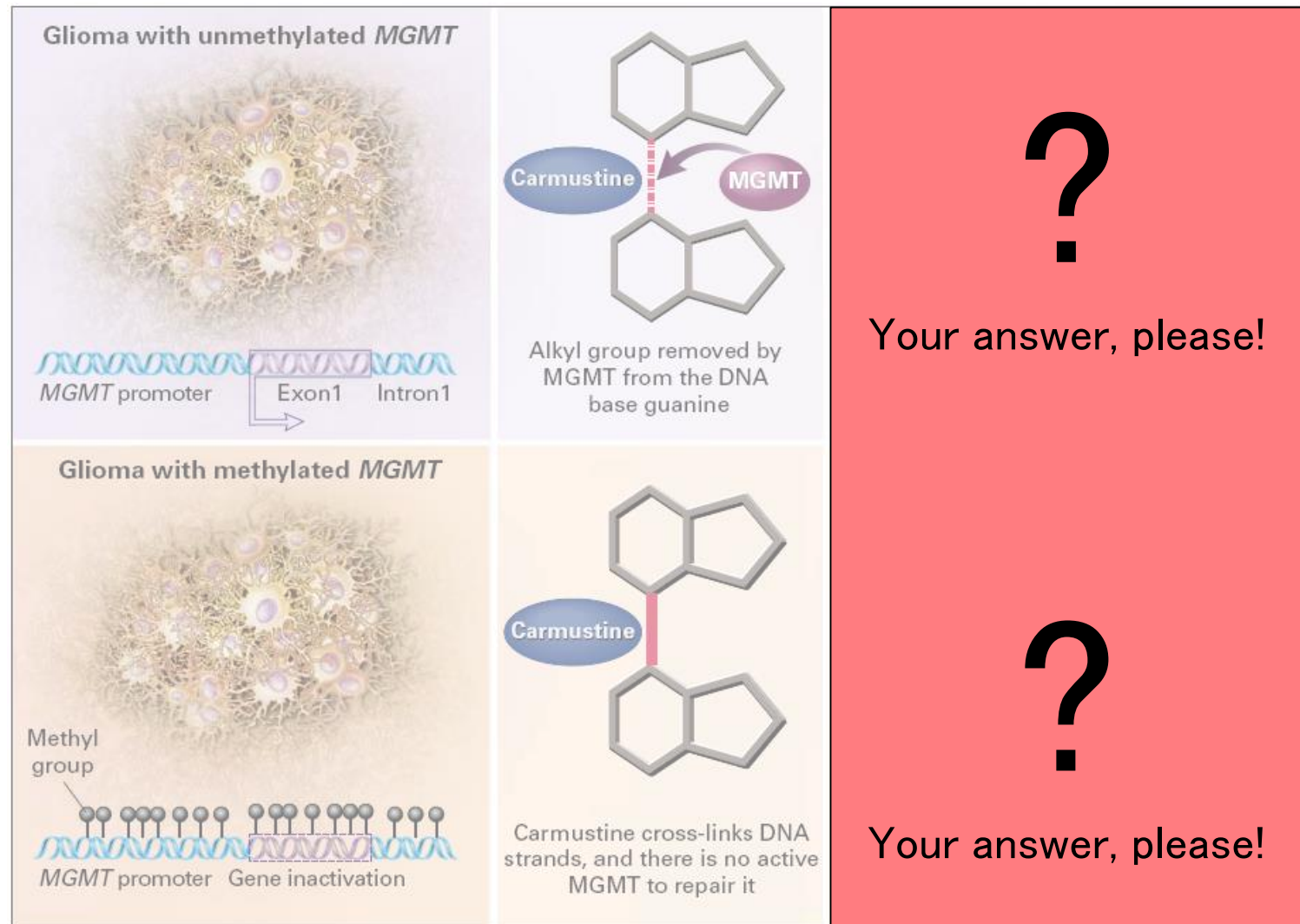
▼: Described Polymorphisms of Unknown Significance

MGMT and brain tumor treatment  
(chemotherapy) by Carmustin (an alkylating  
agent) to kill fast dividing tumor cells

The methylation status of the MGMT promoter is a molecular  
biomarker to predict responsiveness to chemotherapy!

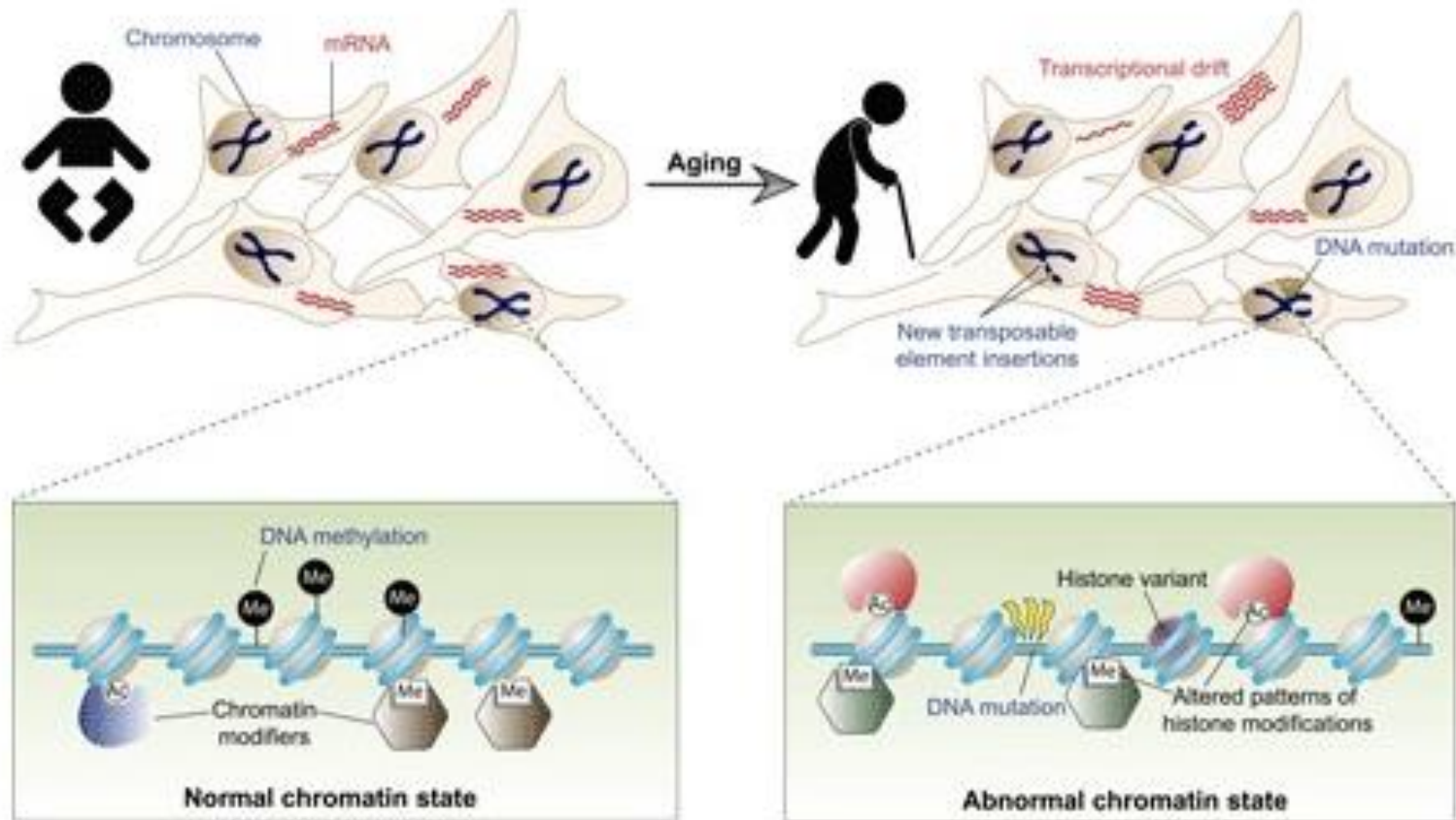


# MGMT and Glioma

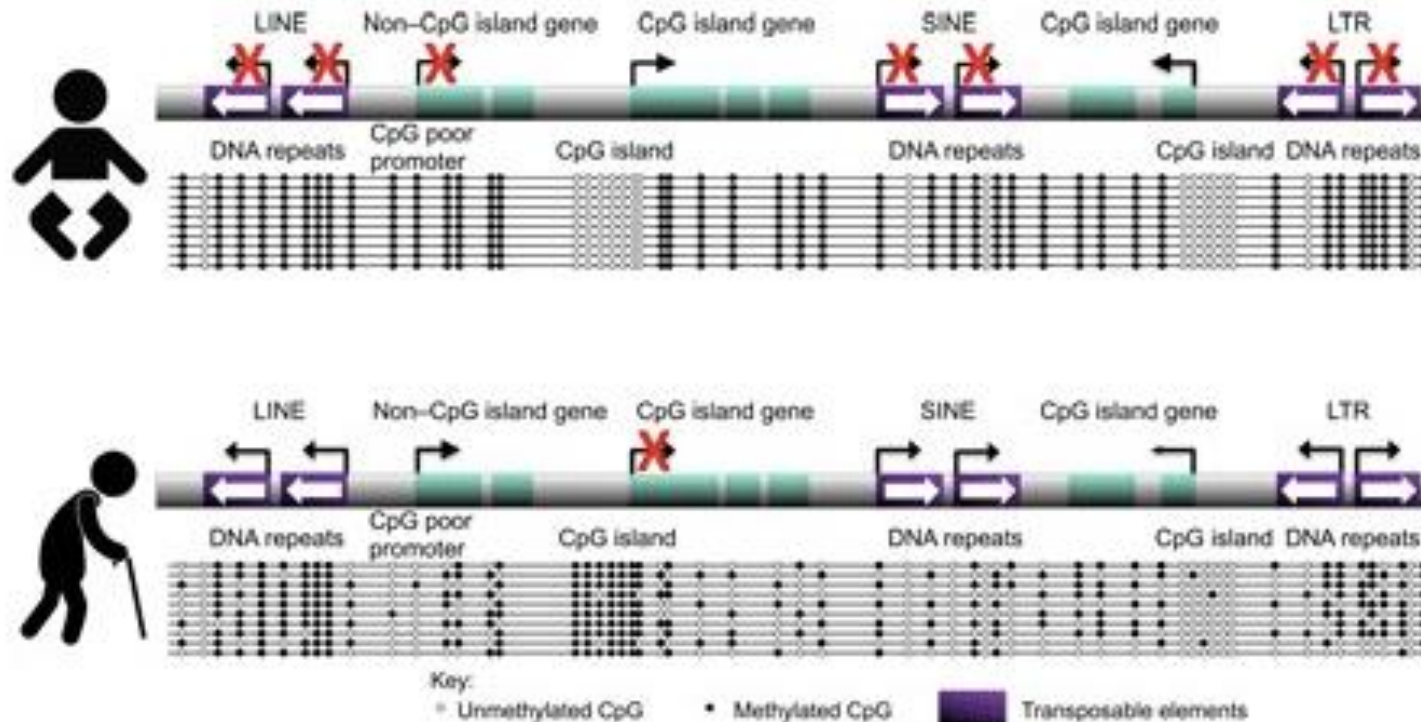


The methylation status of the MGMT promoter is a molecular biomarker to predict responsiveness to chemotherapy!

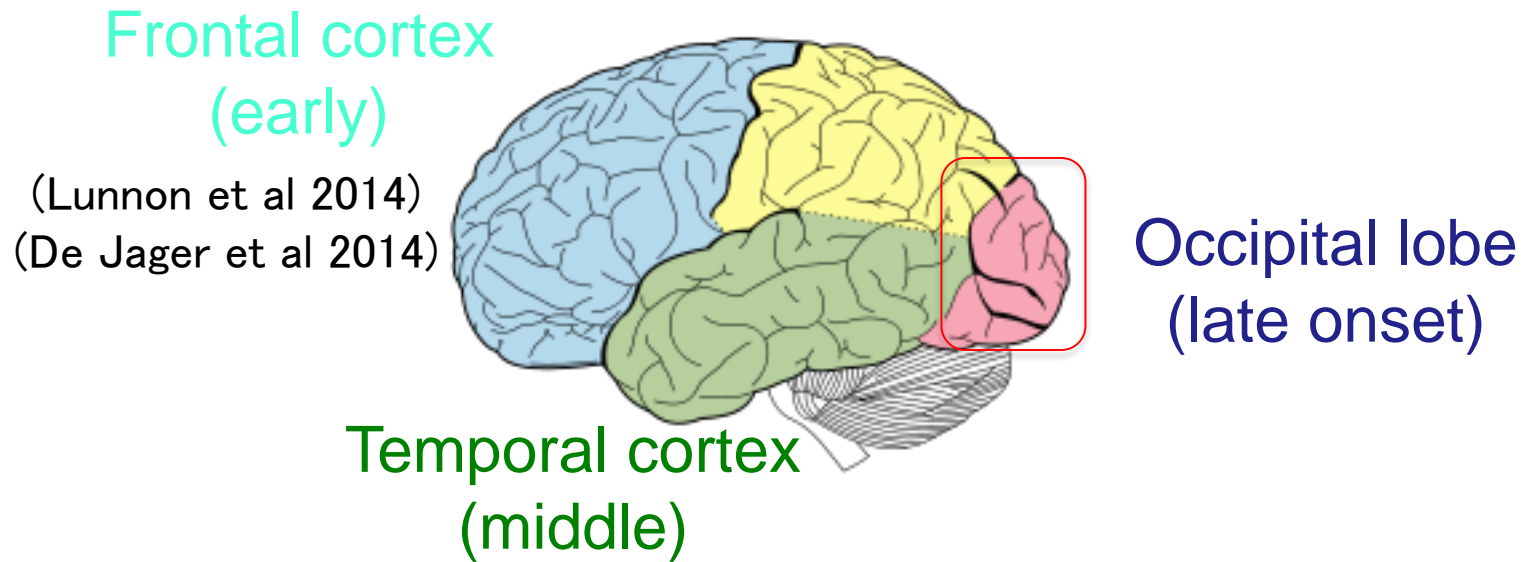
# Epigenetics and aging



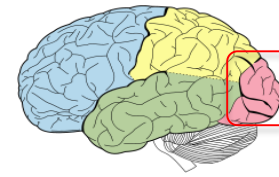
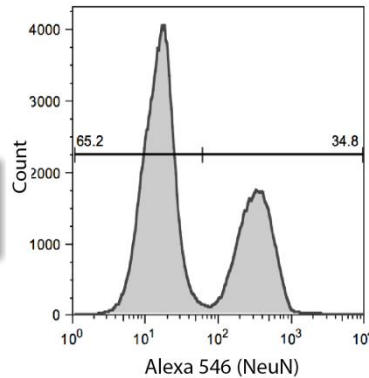
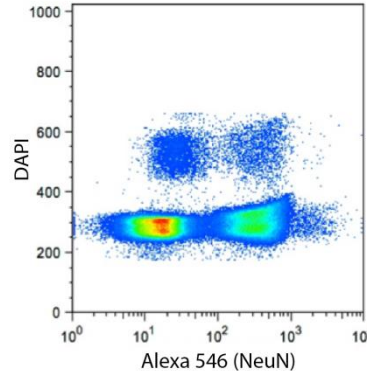
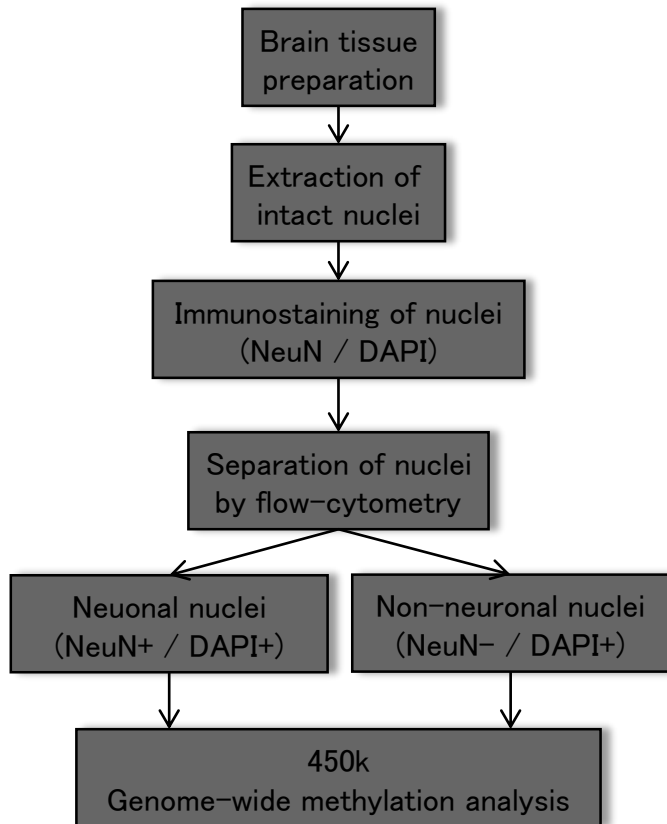
# Epigenetics and aging



# DNA-methylation in Alzheimers disease: analysis of human brain samples



# Separation of nuclei from Healthy and Alzheimers post mortem samples into neuron and glia fractions



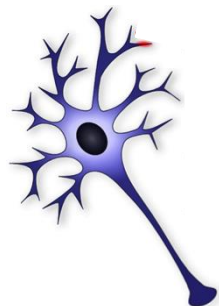
Occipital lobe  
(late onset)



Infinium  
Hi Scan  
450 K array

Armin Theo Kraus  
Heinrich Leonhardt  
LMU München

control  
neuron

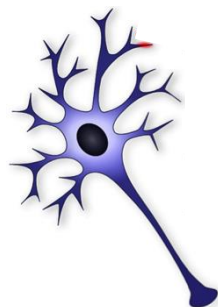


Cell Type  
Age



control  
glia

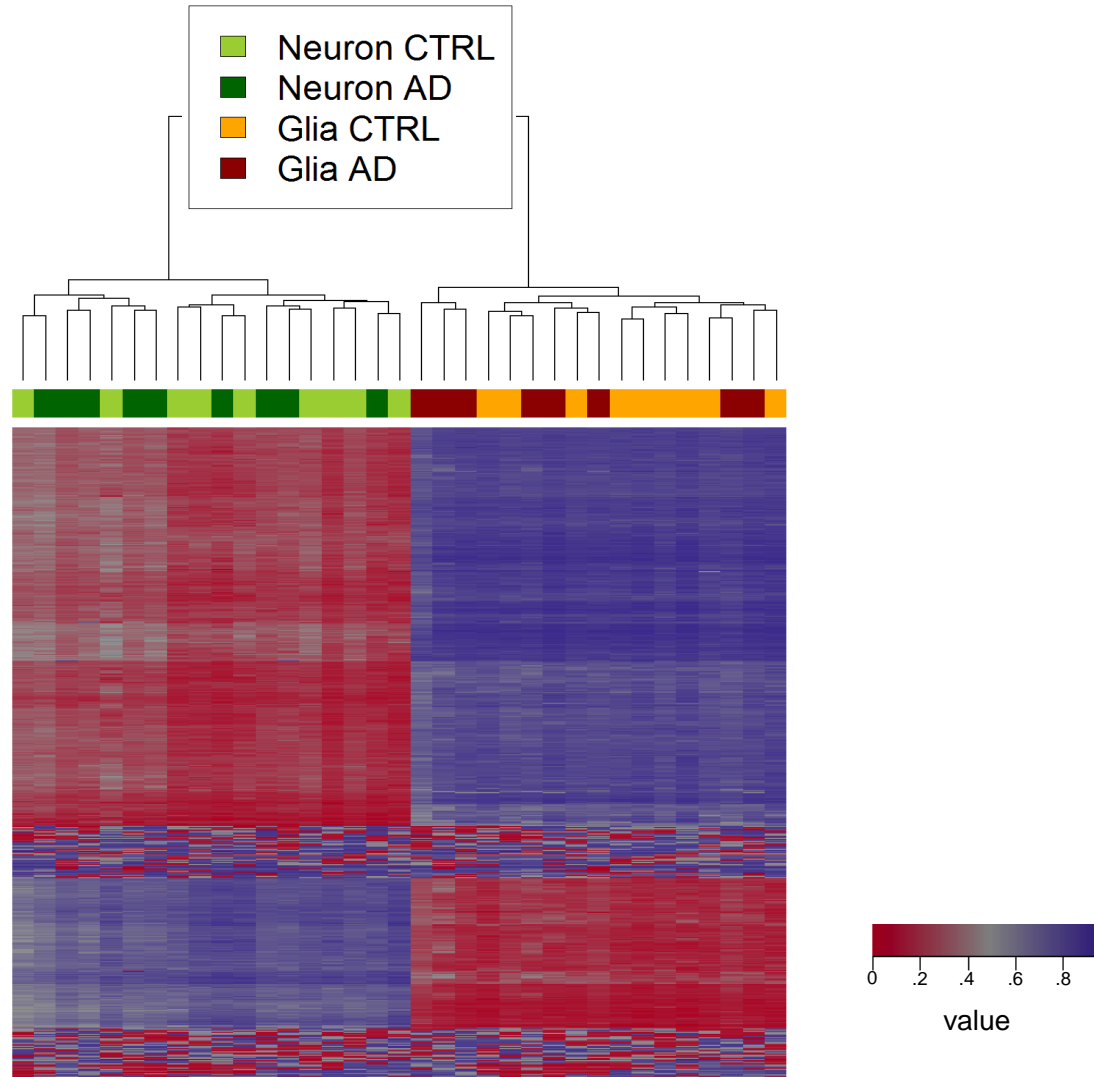
Alzheimer Disease  
Braak staging



Alzheimer Disease  
Braak staging

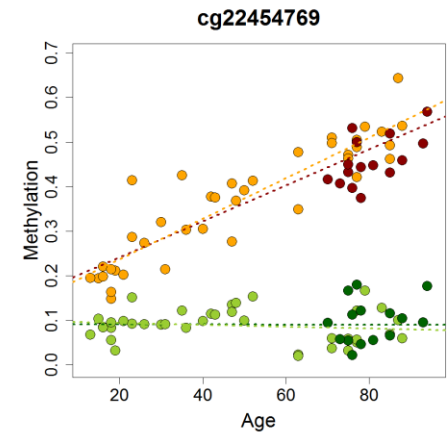
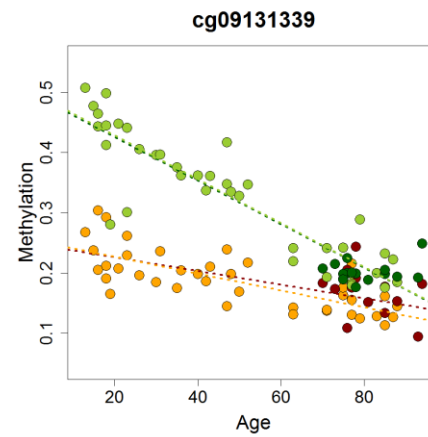
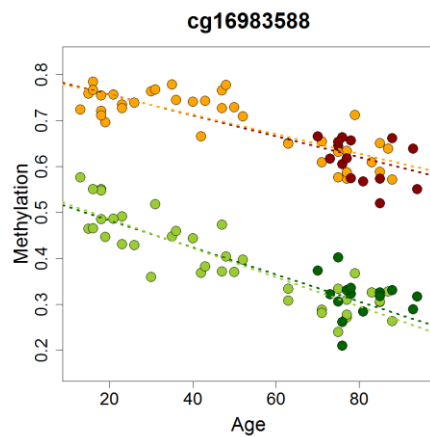
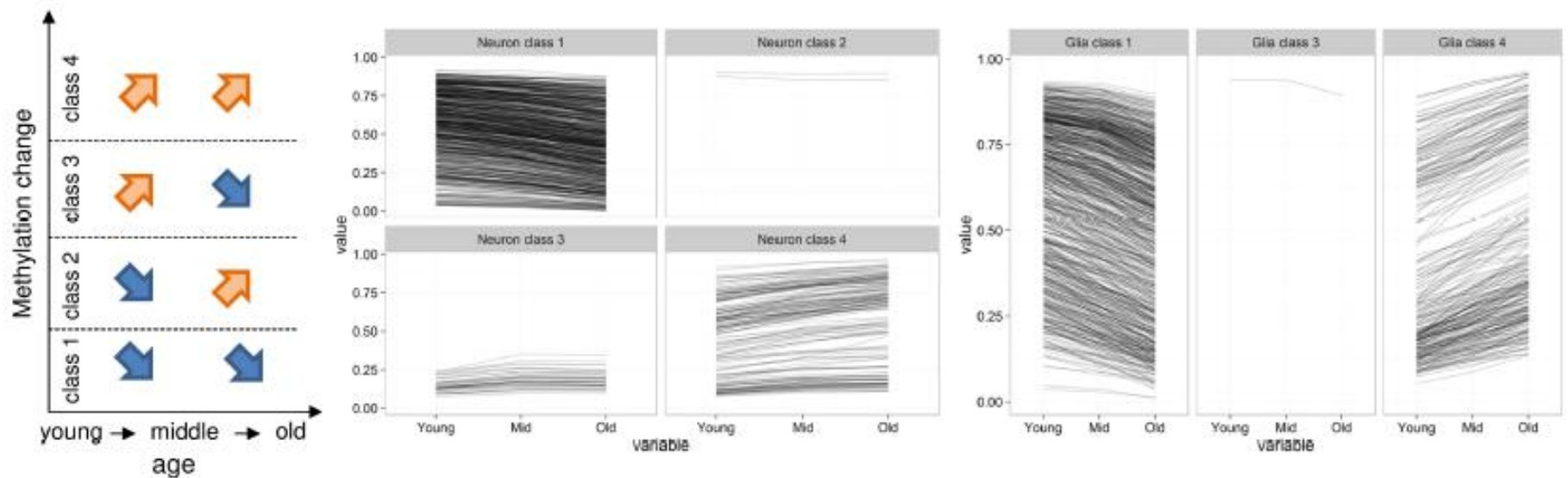


# Neuronal and glial cell populations have distinct methylomes



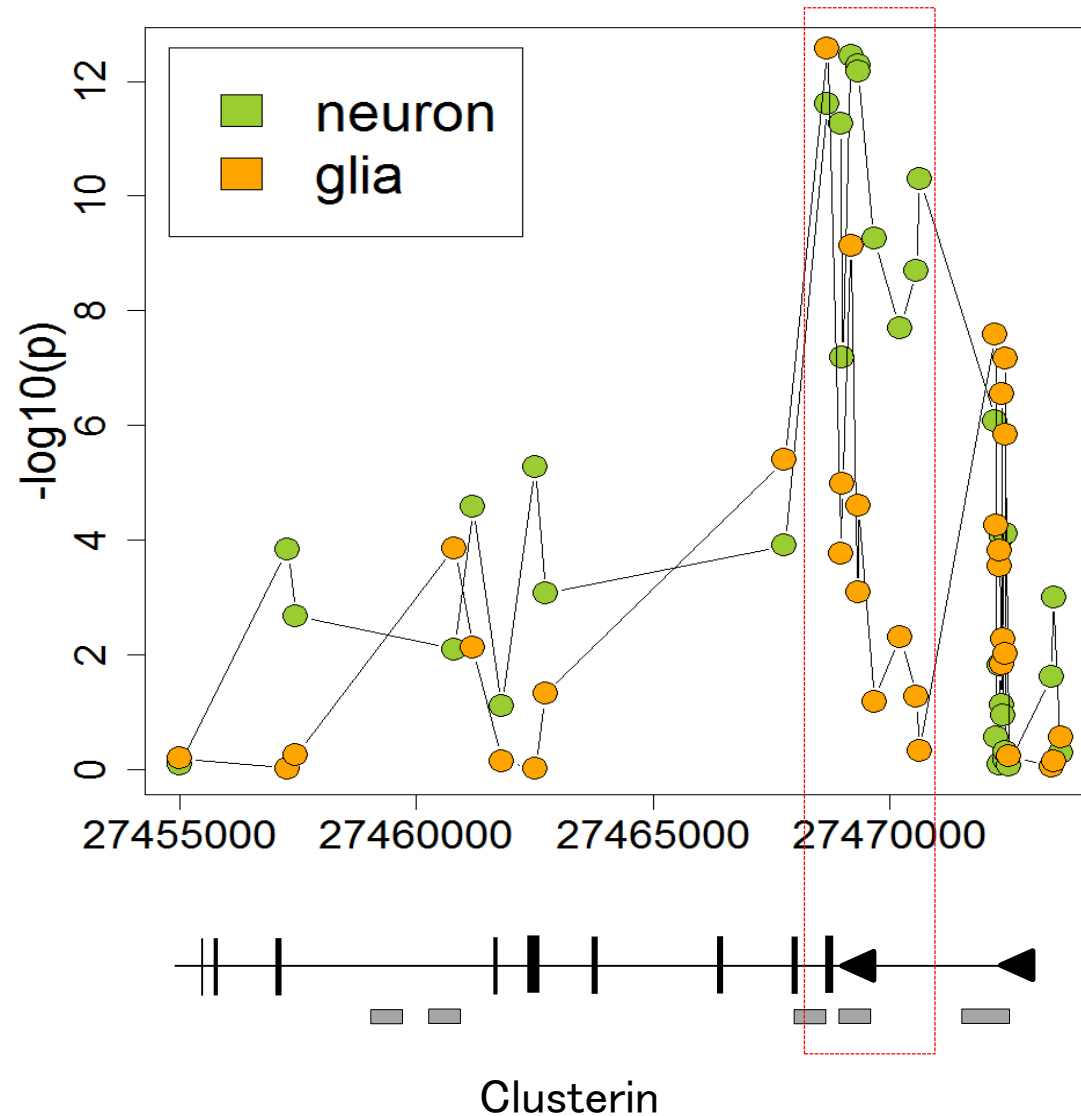


# Neuronal and glial cells have distinct patterns of aging





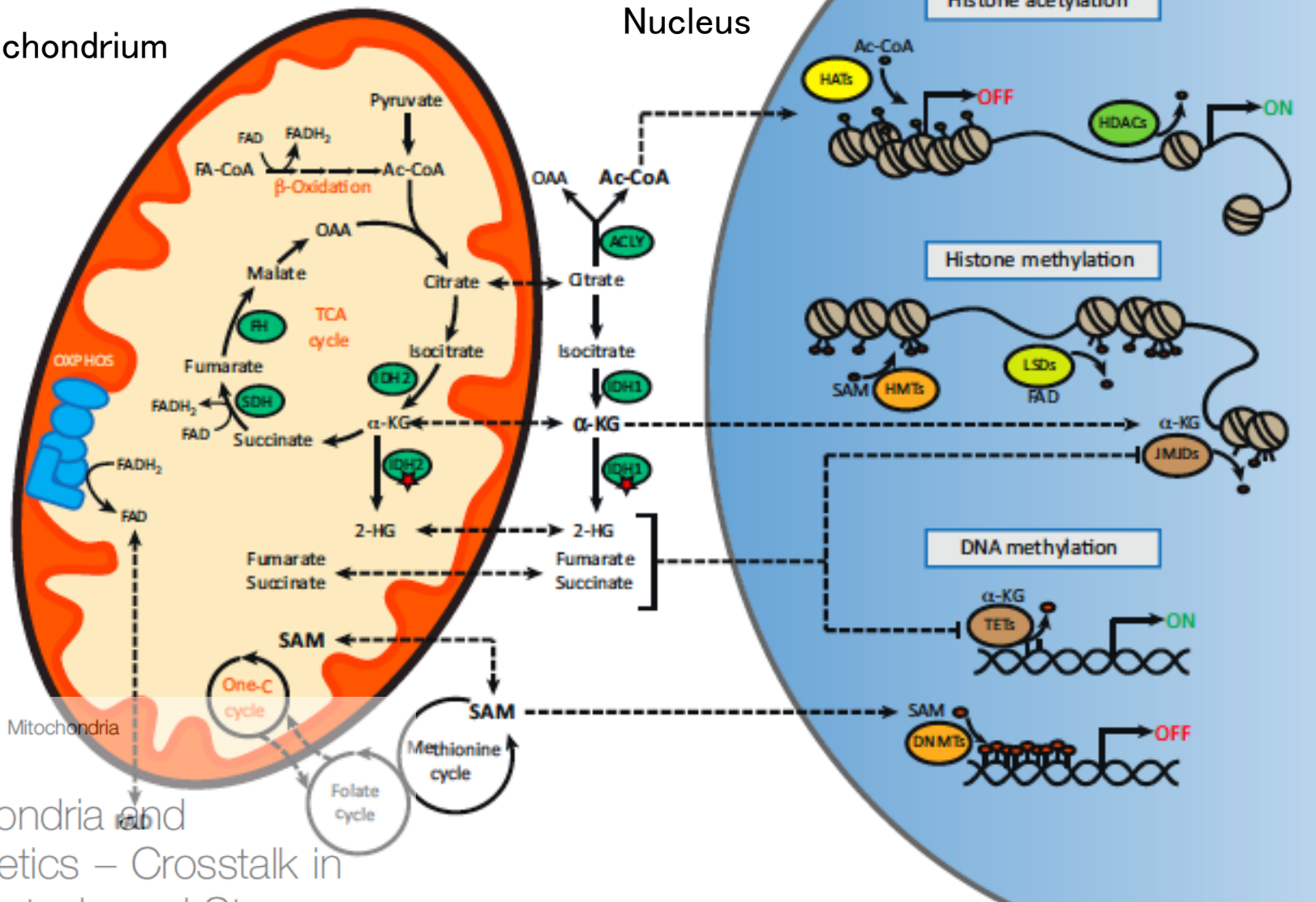
The AD risk gene ***Clusterin*** shows a clear epigenetic aging signature in neurons



# Epigenetics and (altered) metabolism in cancer

Mitochondrion

Nucleus



Special Series: Mitochondria

Review

Mitochondria and Epigenetics – Crosstalk in Homeostasis and Stress

Olli Matilainen,<sup>1,2</sup> Pedro M. Quirós,<sup>1,2</sup> and Johan Auwerx<sup>1,\*</sup>