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."

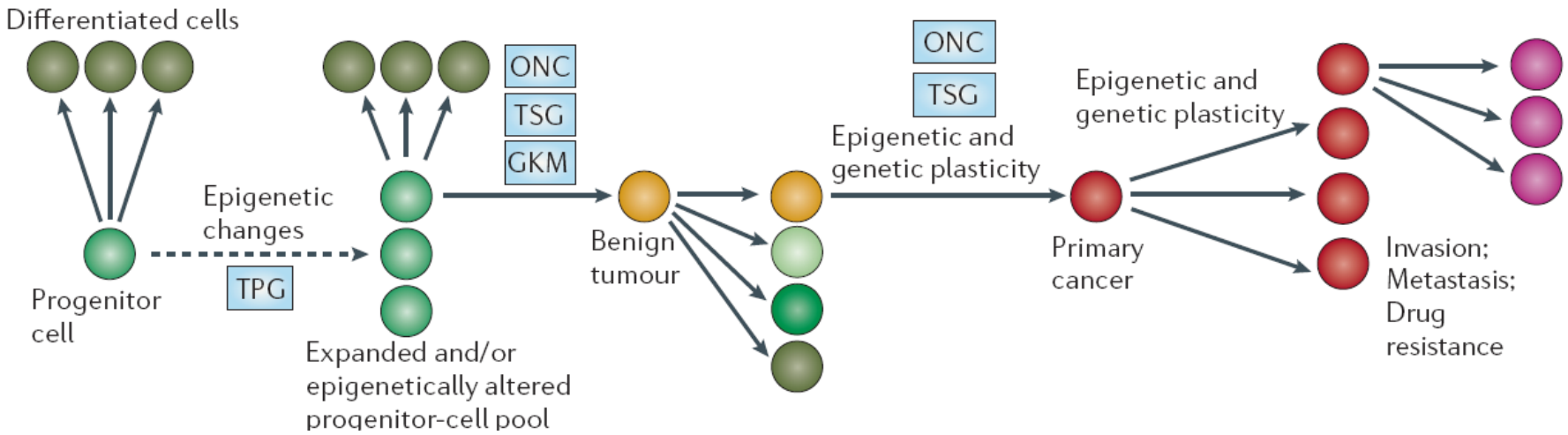
ICGC policy document: http://icgc.org/icgc/goals-structure-policies-guidelines/introduction

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 ny epigenetic changes
- Genomic instability (e.g. actiation 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)

Source: A. Feinberg et al. Nature reviews (2006) (7): 21–33

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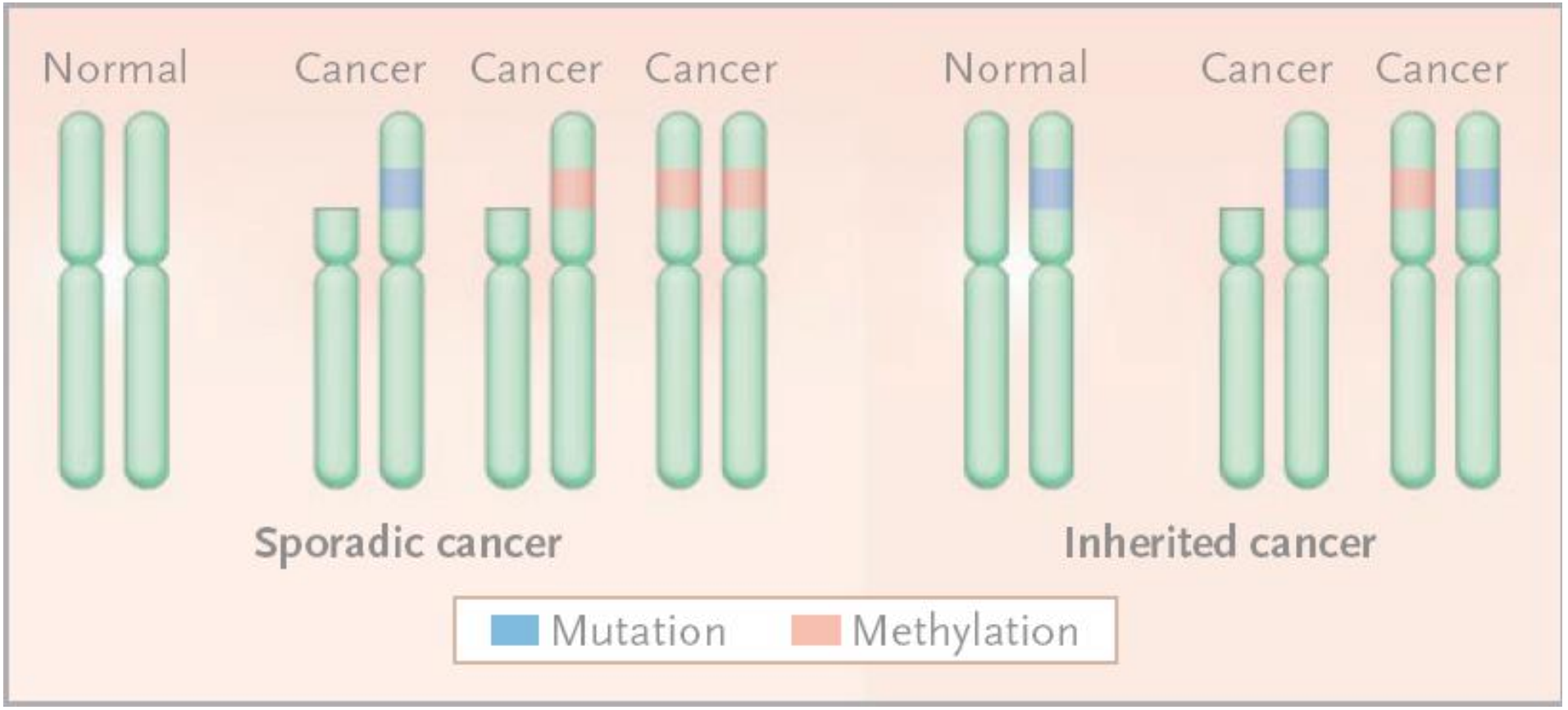
The Knudson‘s „Two hit hypothesis“ – extension by epigenetic silencing



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

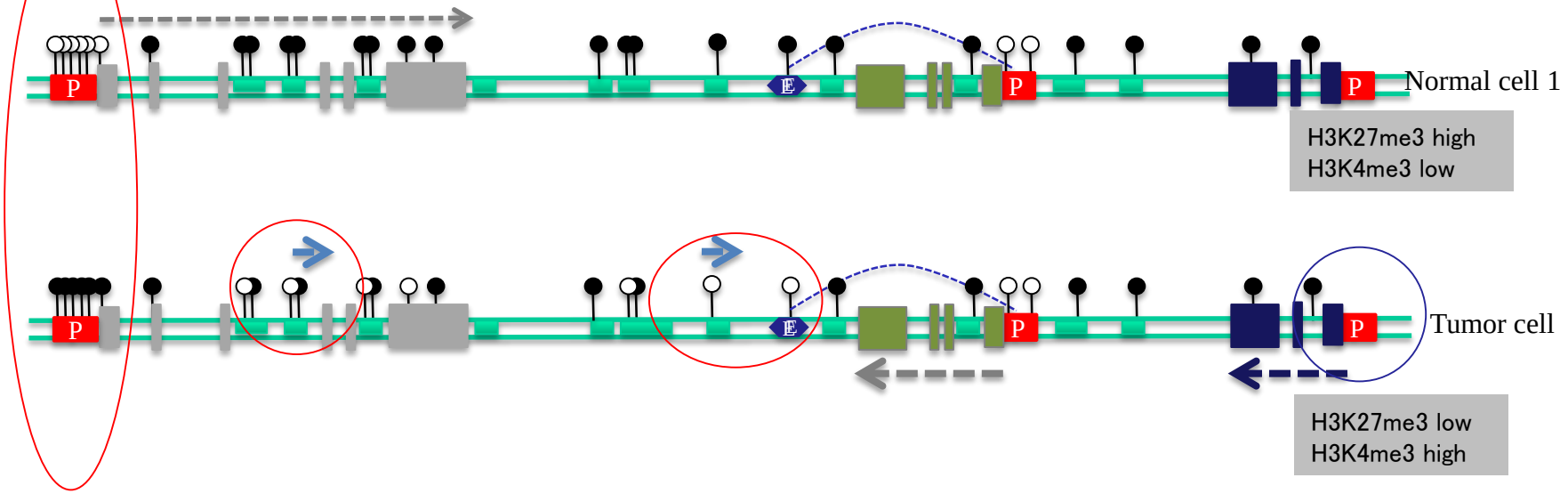
1. Genetic alterations (mutations)
2. Epigenetic silencing (epimutations)

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)



Promote P
With CpG island

Repetetive
Element

enhancer E
CpG-

Promoter P
CpG-poor

Promoter P
No DNA-methylation
control

methyliertes CpG

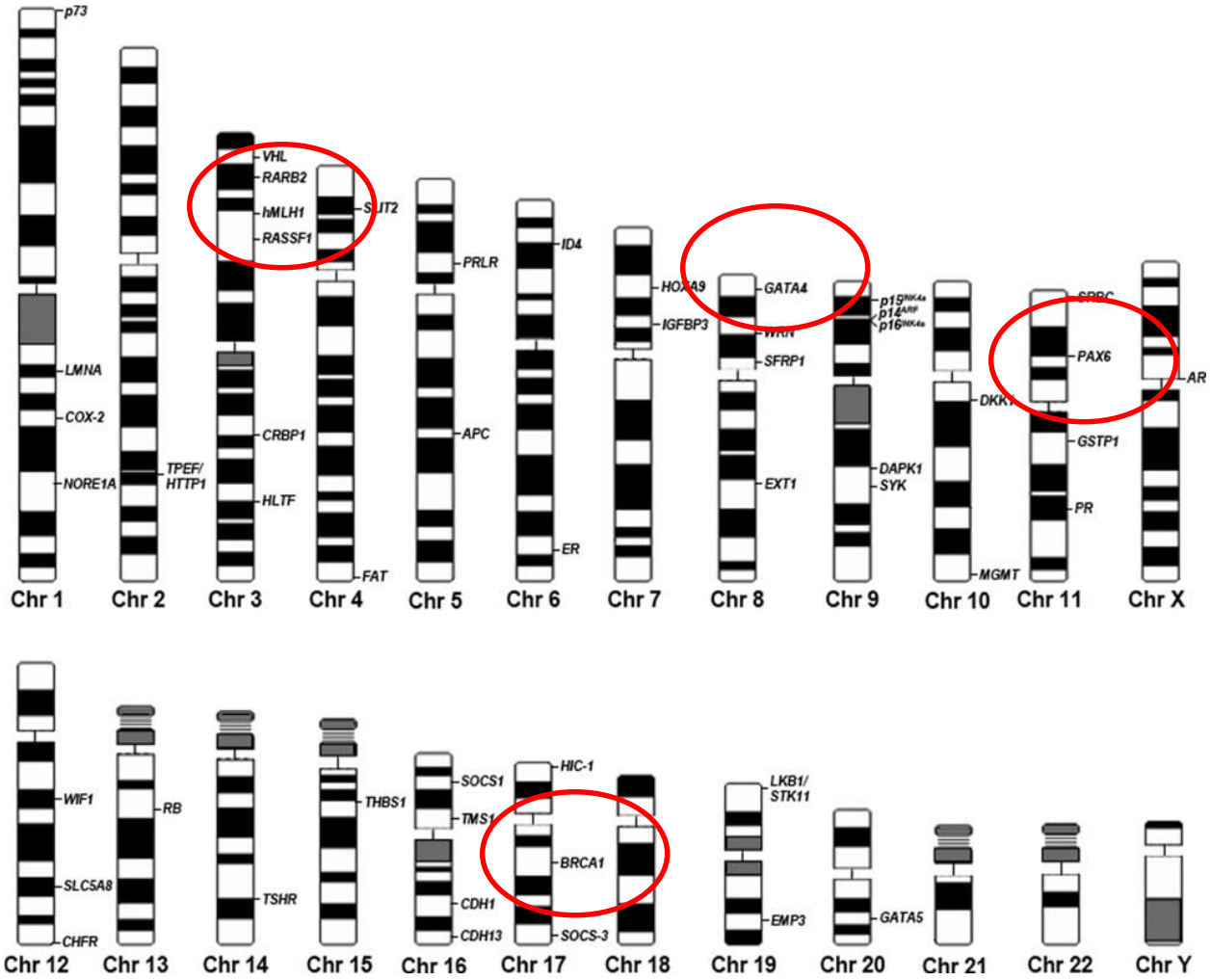
unmethyliertes CpG

Transkript

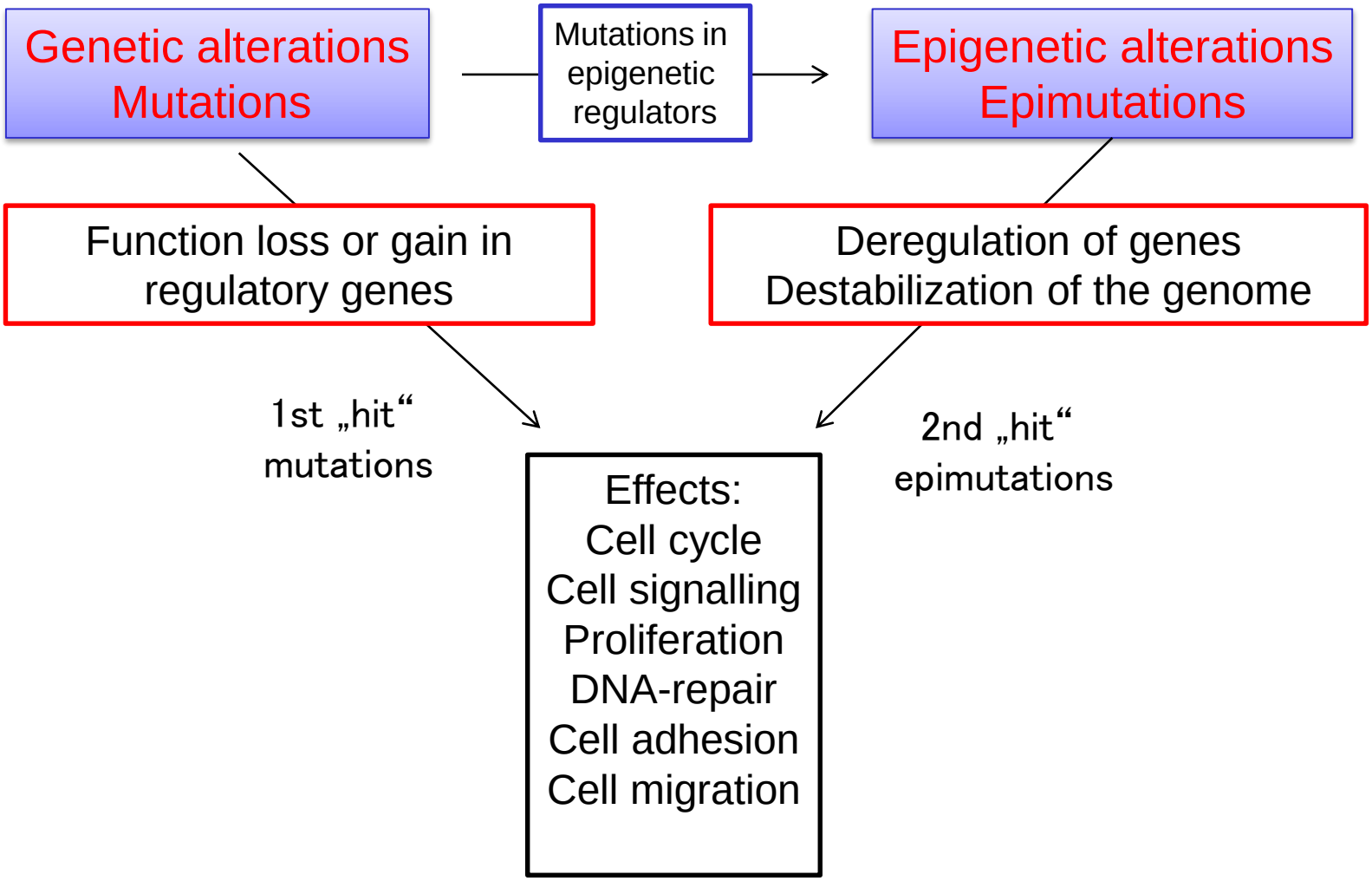
Exon

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



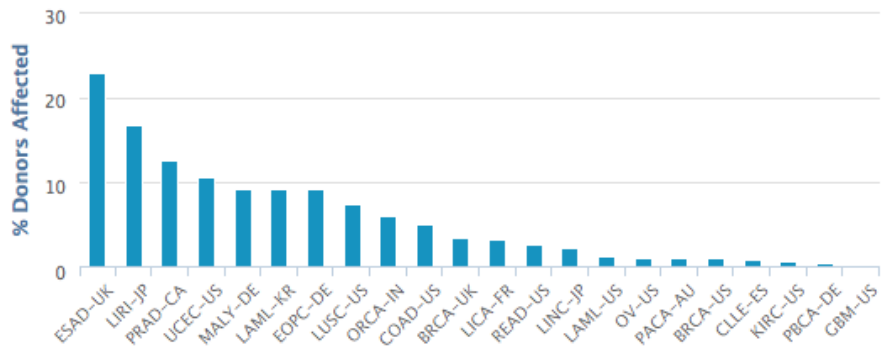
Genetic mutations of Tet1 in cancer

Tet1

Cancer Distribution

OPEN IN ADVAN

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



Showing **22** projects

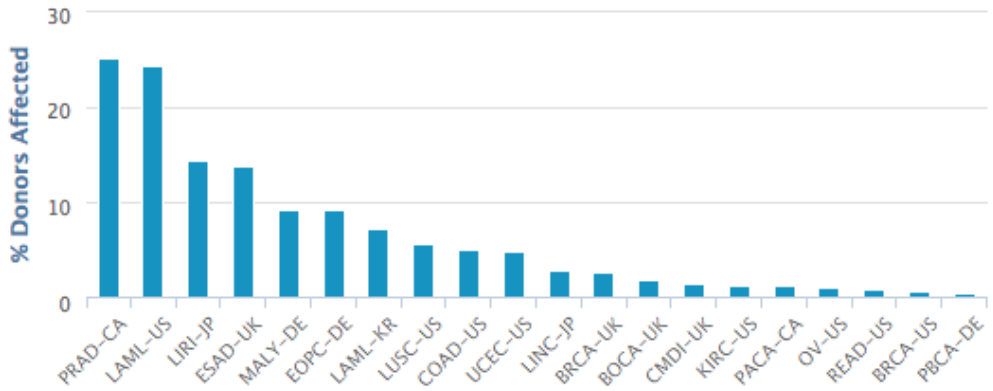
Project	Site	Tumour Type	Tumour Subtype	# Donors affected ▾	#
ESAD-UK	Esophagus	Esophageal Cancer	Esophageal Adenocarcinoma	5 / 22 *(22.73%)*	
LIRI-JP	Liver	Liver Cancer	Hepatocellular Carcinoma (Viru...	7 / 42 *(16.67%)*	
PRAD-CA	Prostate	Prostate Cancer	Adenocarcinoma	1 / 8 *(12.50%)*	
UCEC-US	Uterus	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

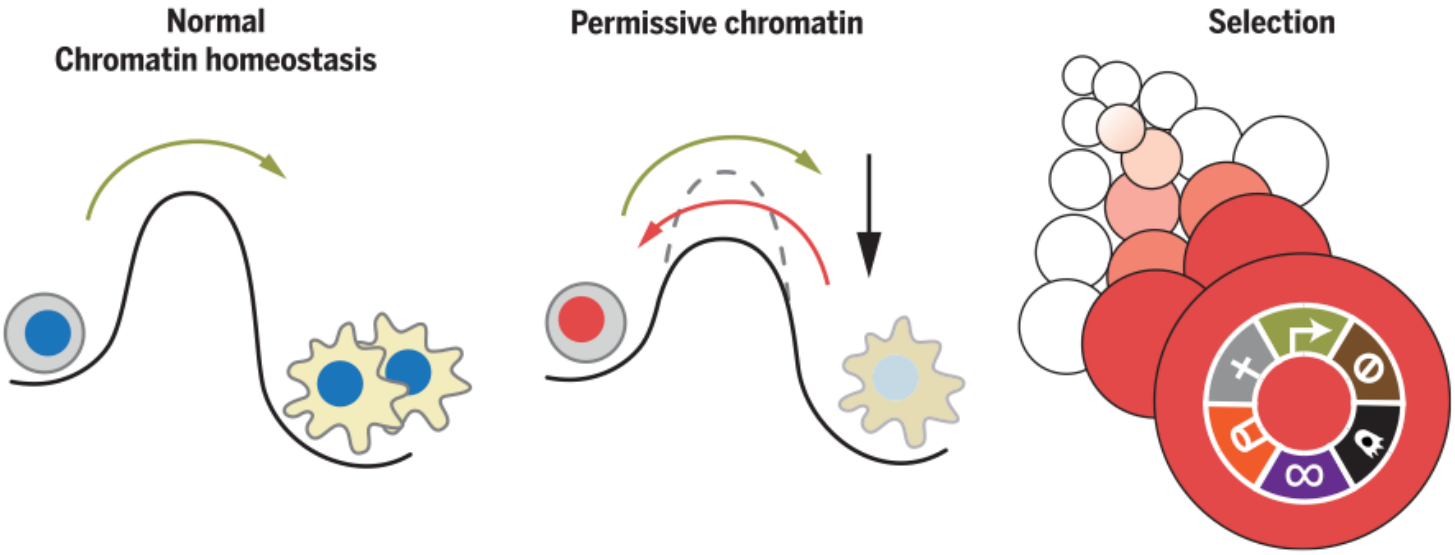
124 DONORS AFFECTED BY **113** MUTATIONS ACROSS **20** PROJECTS



Showing **20** projects

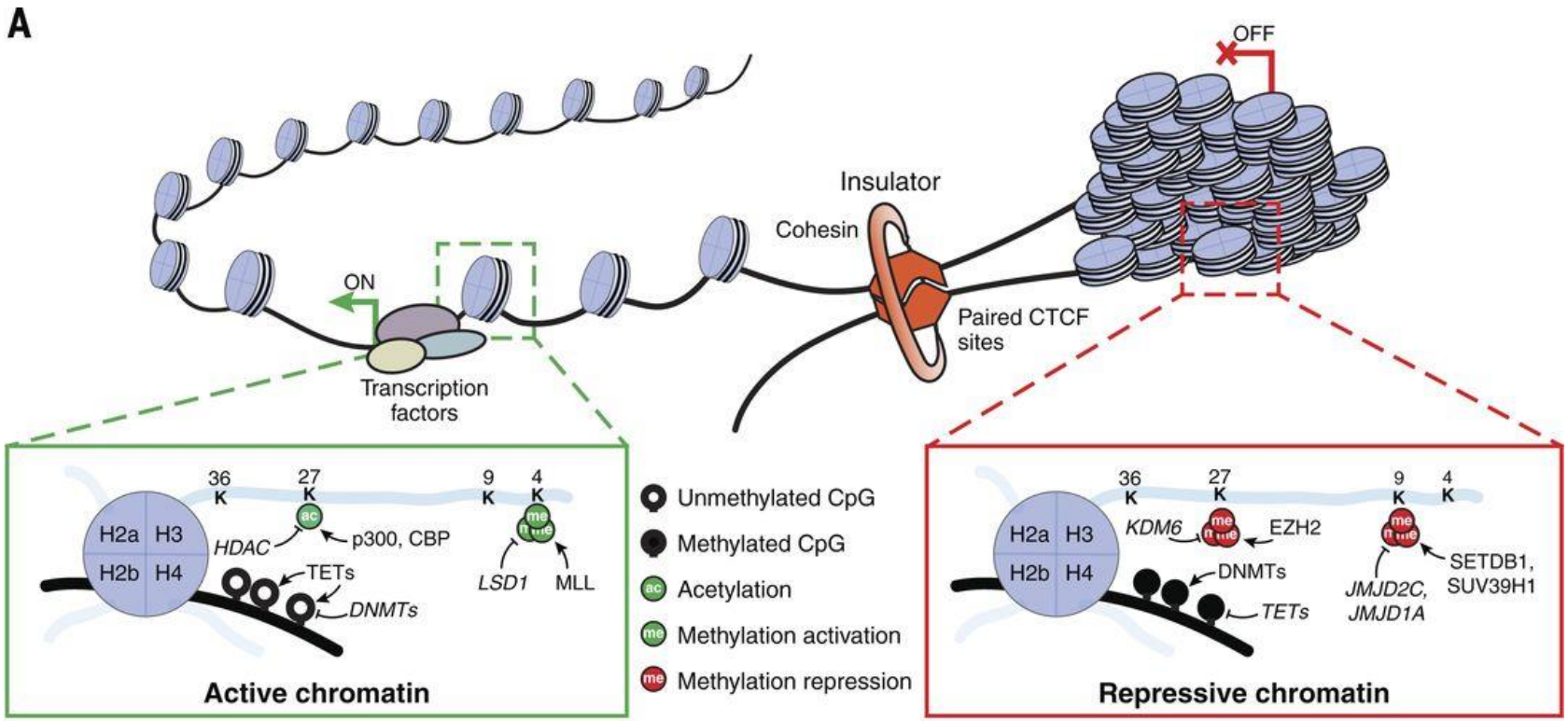
Project	Site	Tumour Type	Tumour Subtype	# Donors affected ▾	# Mutations
PRAD-CA	Prostate	Prostate Cancer	Adenocarcinoma	2 / 8 *(25.00%)*	2
LAML-US	Blood	Blood Cancer	Acute Myeloid Leukemia	41 / 170 *(24.12%)*	25
LIRI-JP	Liver	Liver Cancer	Hepatocellular Carcinoma (Viru...	6 / 42 *(14.29%)*	9
ESAD-UK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

Chromatin changes and cancer



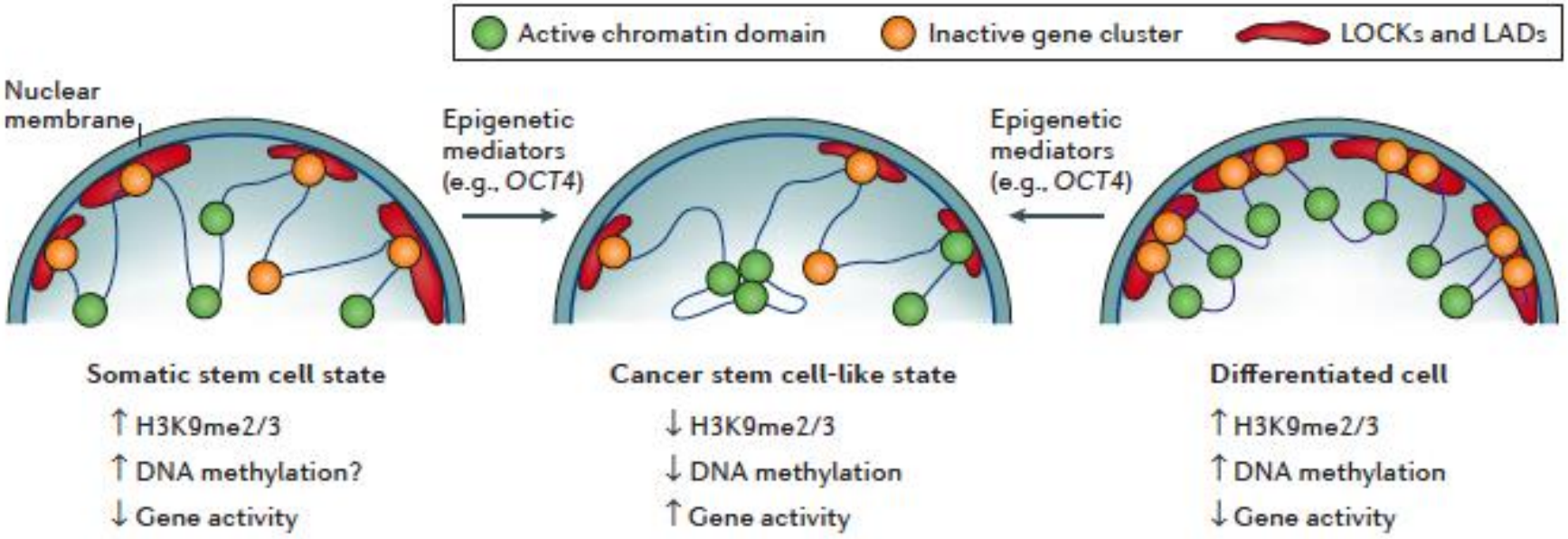
Epigenetic plasticity, selection, and cancer. (**Left**) Normal chromatin and associated epigenetic mechanisms stabilize gene expression and cellular states while facilitating appropriate responses to developmental or environmental cues (blue nuclei represent normal cell state). Genetic, environmental, 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



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[1], Michael A. Koldobskiy[1] and Anita Göndör[2]

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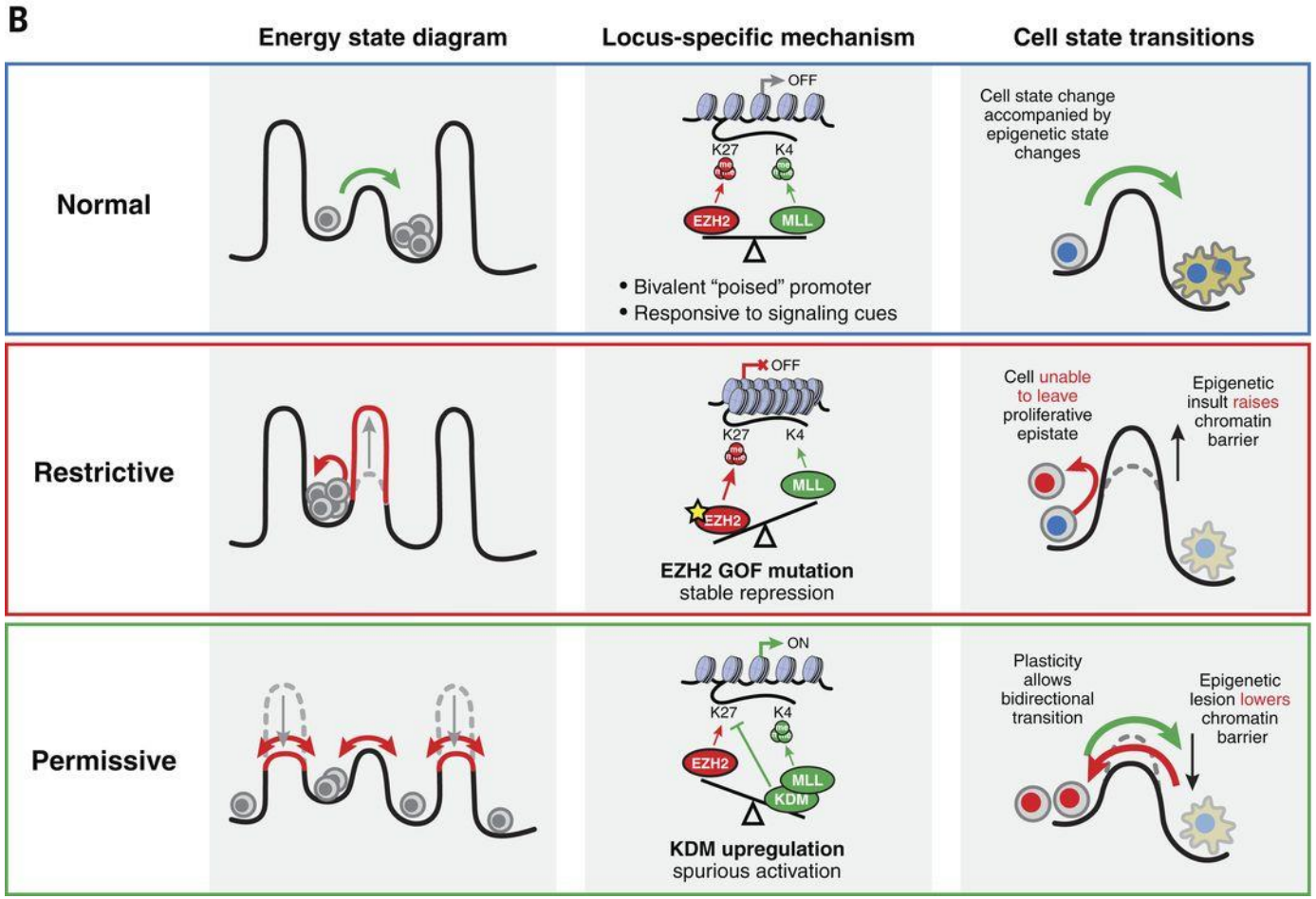

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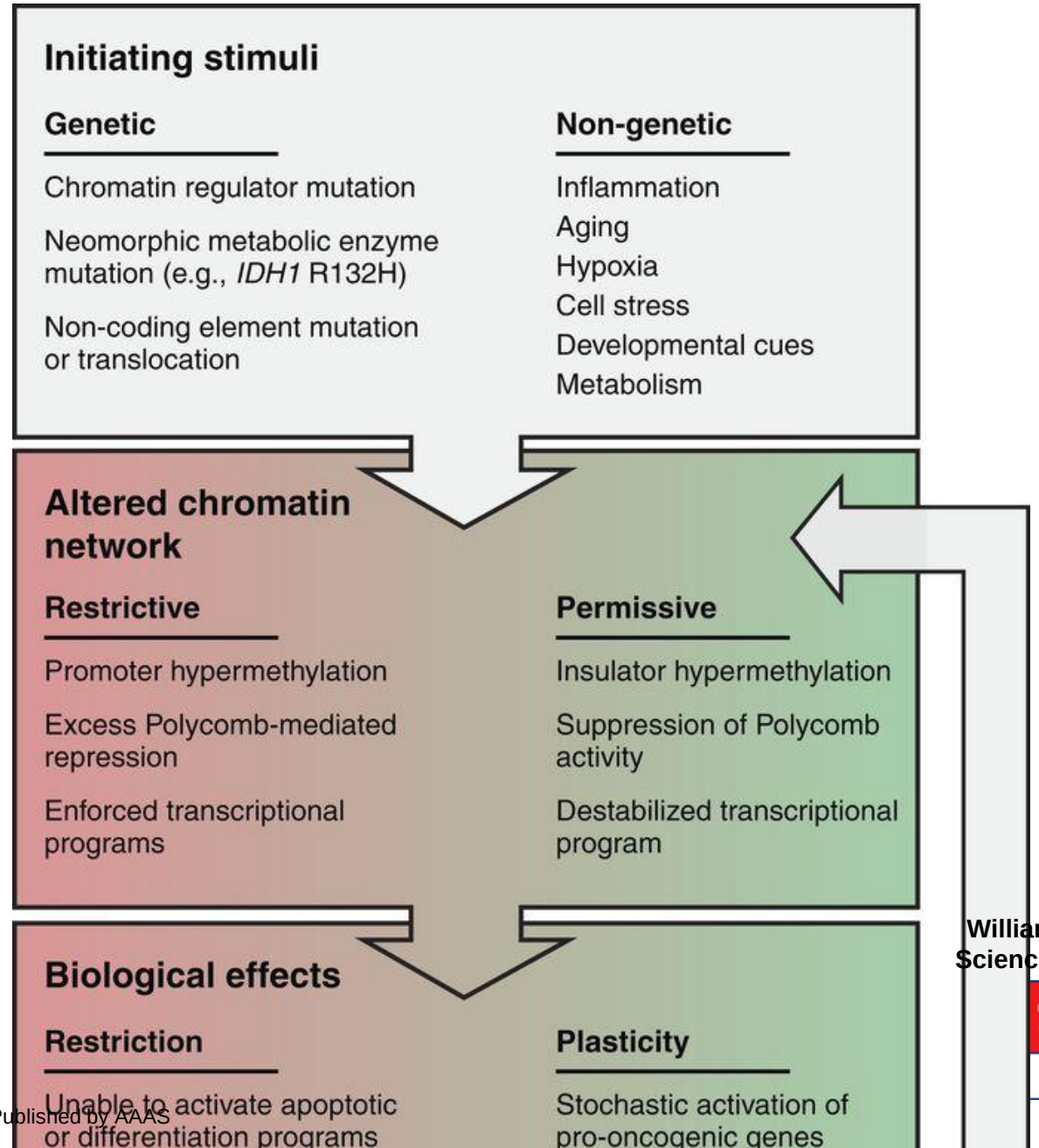
Chromatin programs are frequently disrupted in cancer.



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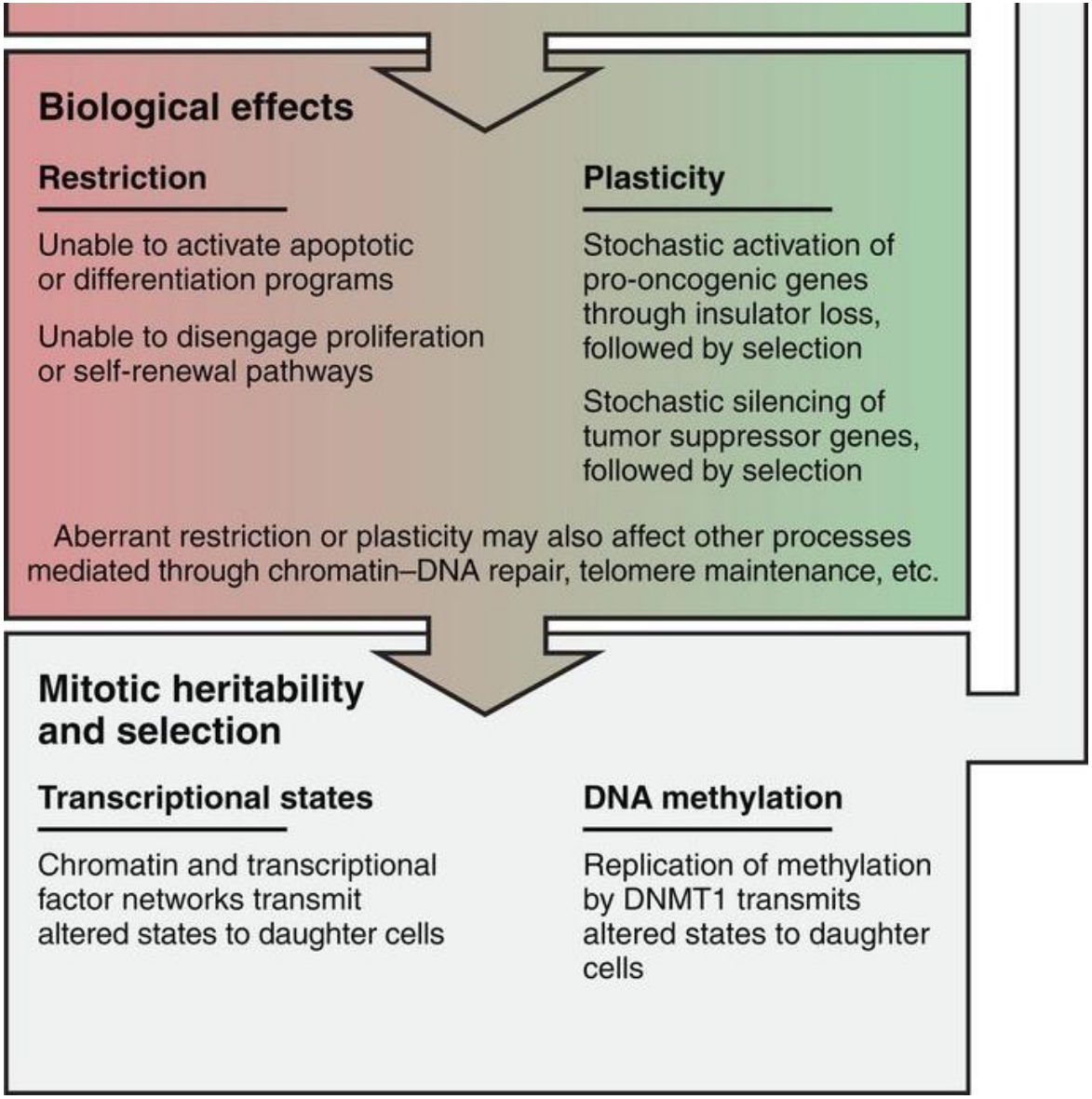

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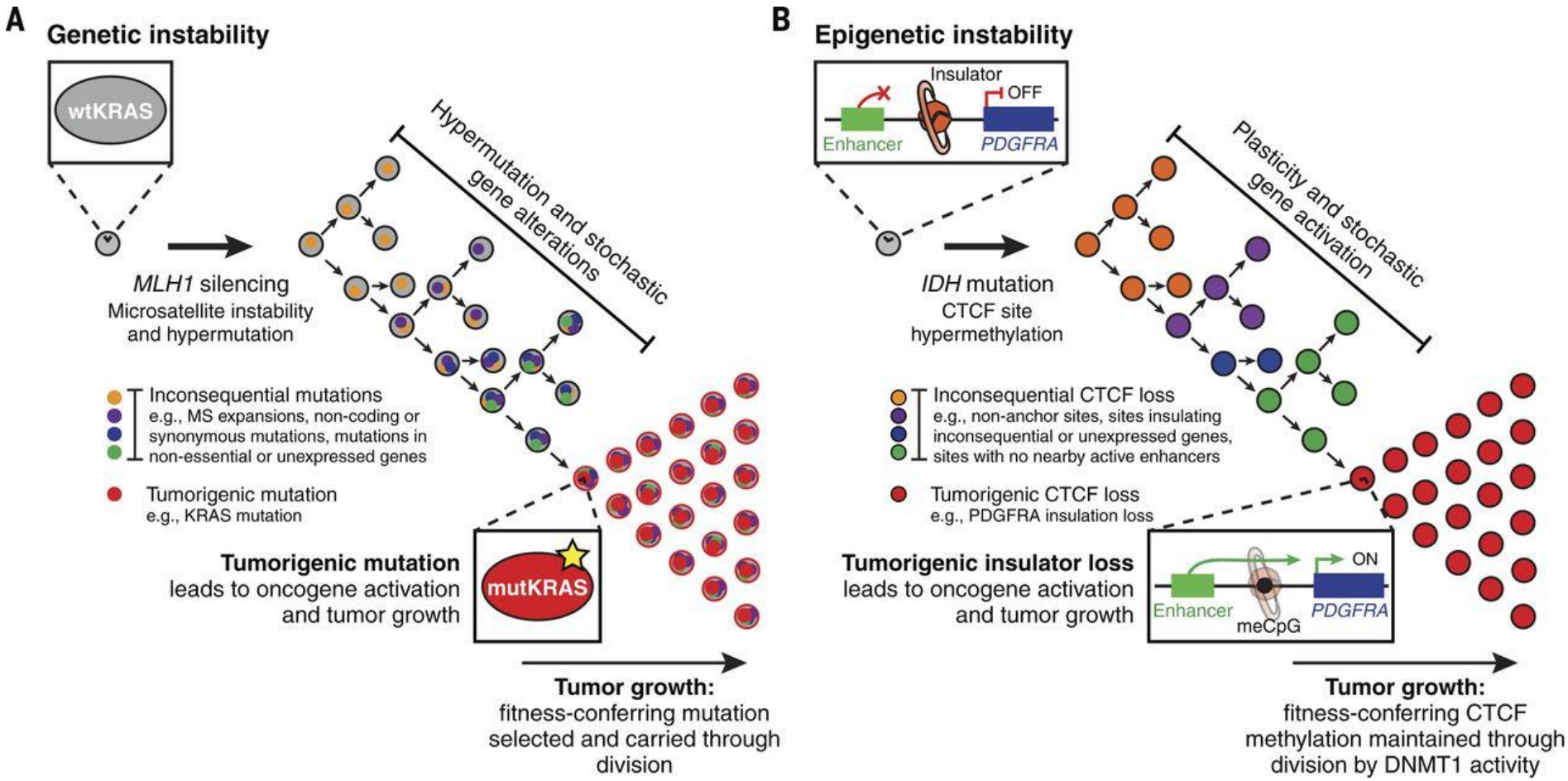
Genetic and epigenetic contributions to the evolution in cancer.



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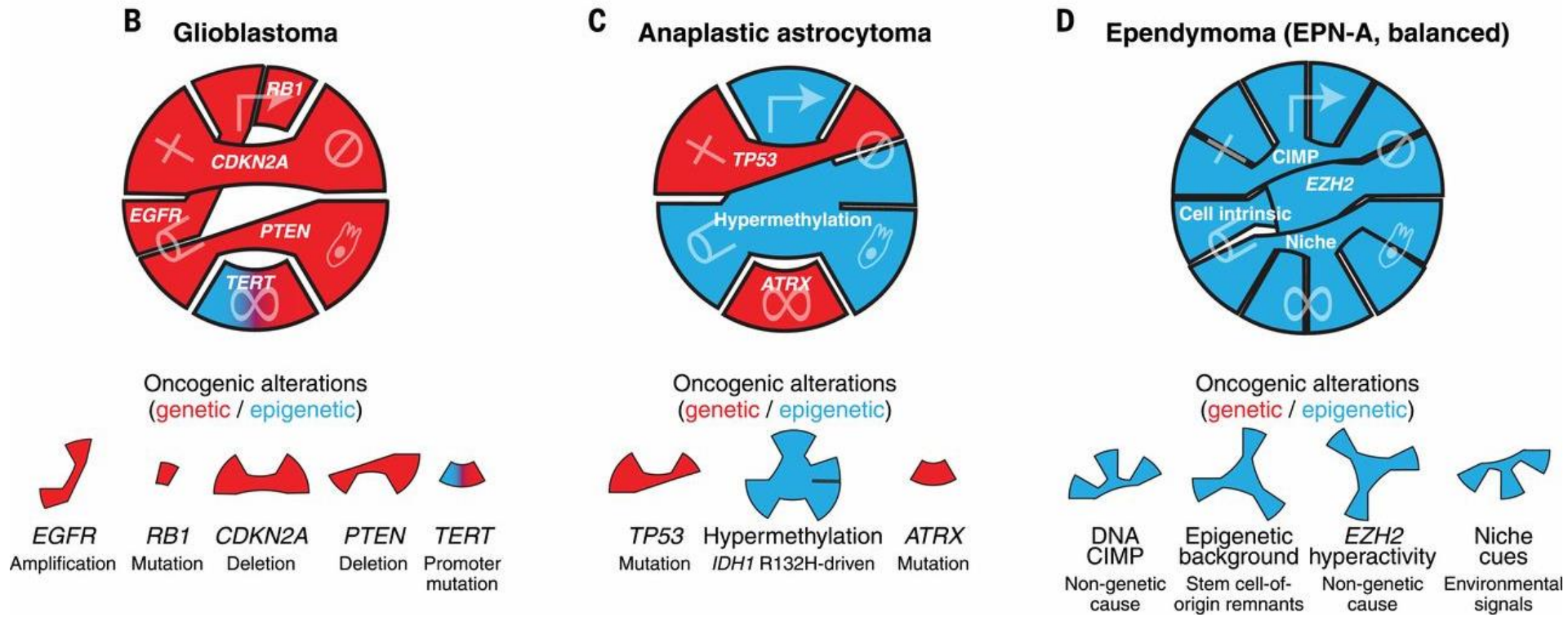
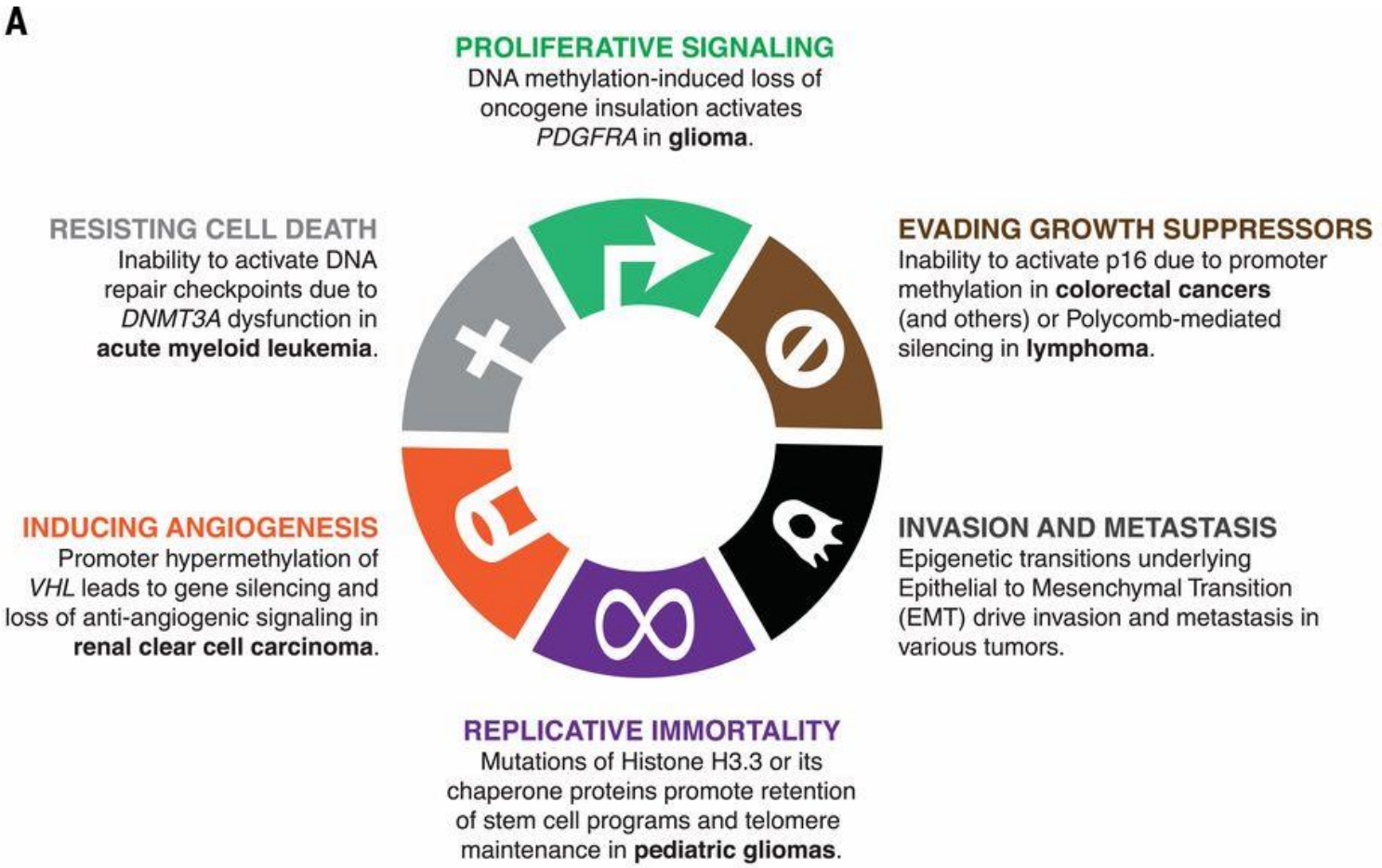
Genetic and epigenetic mechanisms variable the hallmarks of cancer



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

Published by AAAS

Genetic and epigenetic mechanisms underlie the hallmarks of cancer.



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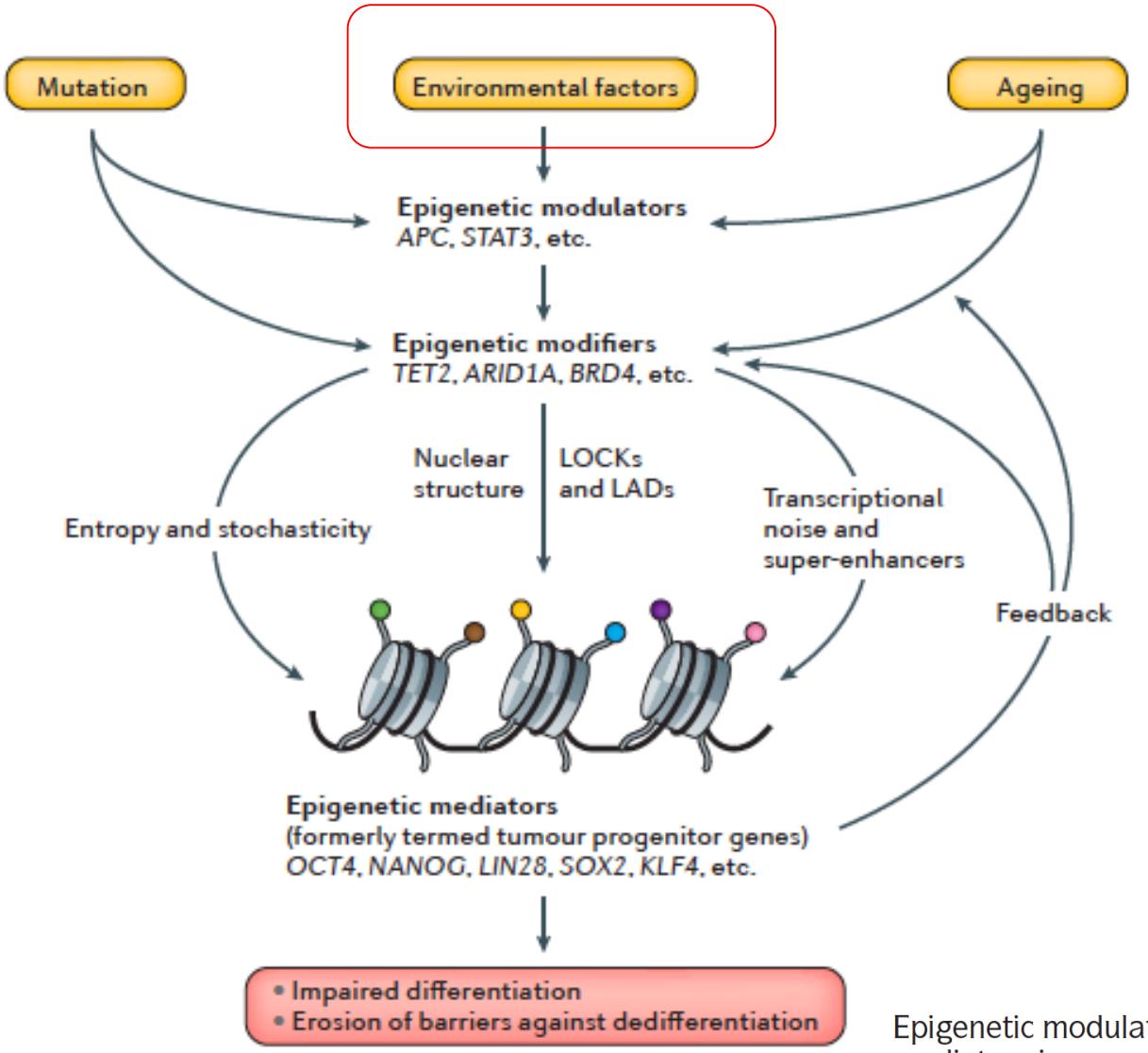

Epigenetic modulators, modifiers and mediators in cancer aetiology and progression

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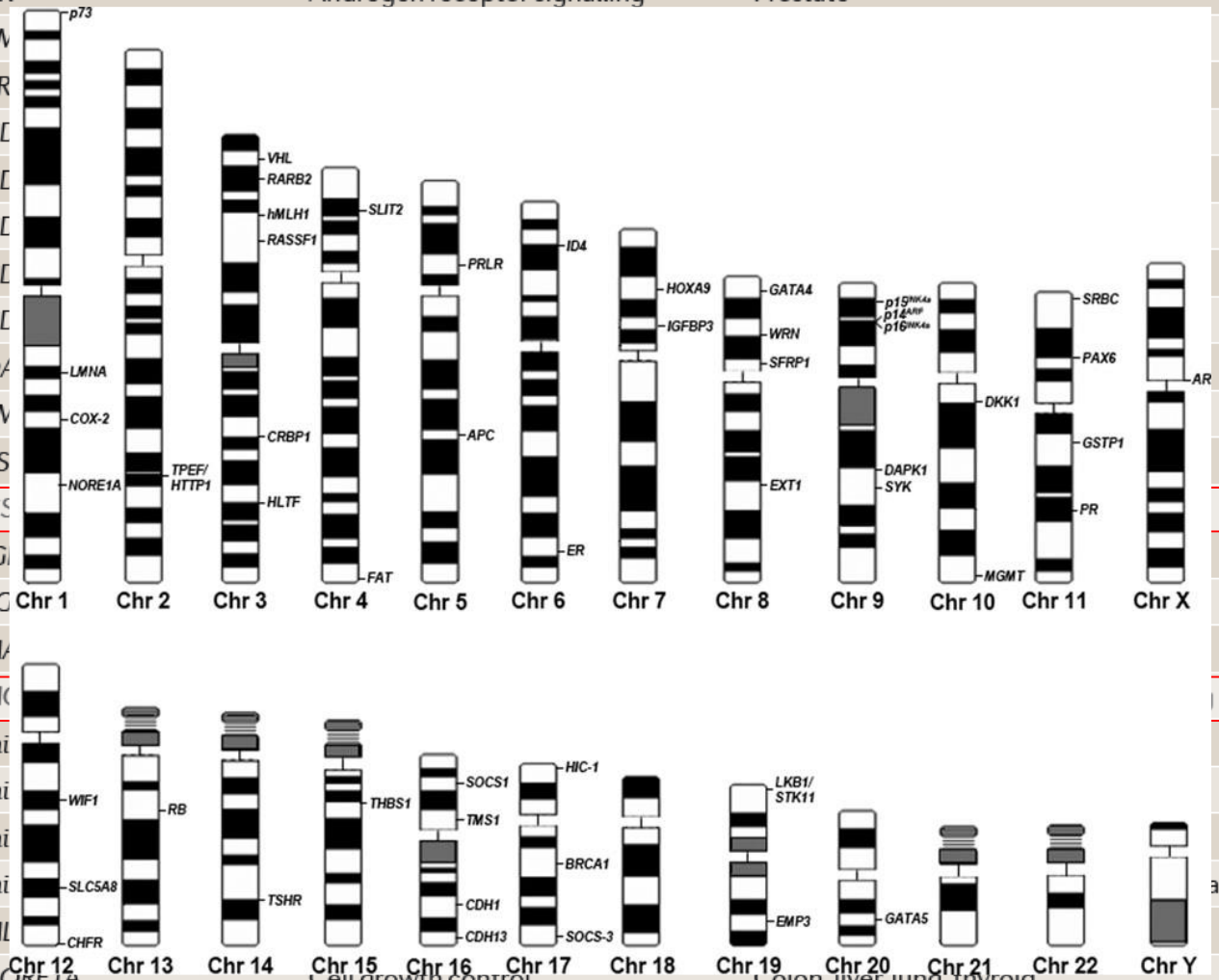
Table 1 | **Hypermethylated genes in cancer and their associated tissue types**

Gene name	Gene function	Cancer type
APC	WNT signalling	Prostate, colon, lung, bladder
AR	Androgen receptor signalling	Prostate
BM		
BR		
CD		
CD		
CD		
CD		
CD		
DA		
EM		
ES		
GS		
IG		
LC		
MA		
MC		
mi		
mi		
mi		
mi		
ML		
NORE1A	Cell growth control	Colon, liver, lung, thyroid
NSD1	Nuclear receptor	Glioma, neuroblastoma
PYCARD	Apoptosis	Glioma, breast, colon, gastric, lung
RARB	Retinoic acid receptor	Breast, colon, prostate



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Gene name	Gene function	Cancer type
APC	WNT signalling	Prostate, colon, lung, bladder
AR	Androgen receptor signalling	Prostate
BMAL1	AHR signalling	Leukaemia, lymphoma
BRCA1	DNA damage response	Breast, ovarian
CDH1	Cell–cell adhesion	Breast, prostate
CDH11	Cell–cell adhesion	Colon, breast, oesophagus, gastric, liver
CDH13	Cell–cell adhesion	Lung, head and neck
CDKN2A	Cell cycle control	Lymphoma, colon, stomach, prostate
CDKN2B	Cell cycle control	Leukaemia
DAPK1	Programmed cell death control	Lung, head and neck, bladder
EMP3	Signal transduction	Glioma
ESR1	Oestrogen receptor signalling	Breast
GSTP1	Detoxification	Prostate, liver, lung
IGFBP3	Signal transduction	Colon, lung, ovarian, prostate
LGALS3	Extracellular matrix protein	Prostate
MASPIN	Peptidase inhibitor	Pancreas
MGMT	DNA repair	Colon, glioma, lymphoma, prostate, lung
miR-148a	Metastasis suppression	Metastasis
miR-34b and *miR-34c*	Metastasis suppression	Metastasis
miR-9	Metastasis suppression	Metastasis
miR-200s	Epithelial–mesenchymal transition	Colon, bladder, squamous cell carcinoma
MLH1	DNA repair	Colon, endometrium, stomach
NORE1A	Cell growth control	Colon, liver, lung, thyroid
NSD1	Nuclear receptor	Glioma, neuroblastoma
PYCARD	Apoptosis	Glioma, breast, colon, gastric, lung
RARB	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 alkalyting 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.piridyl)-1-butanon (NNK))

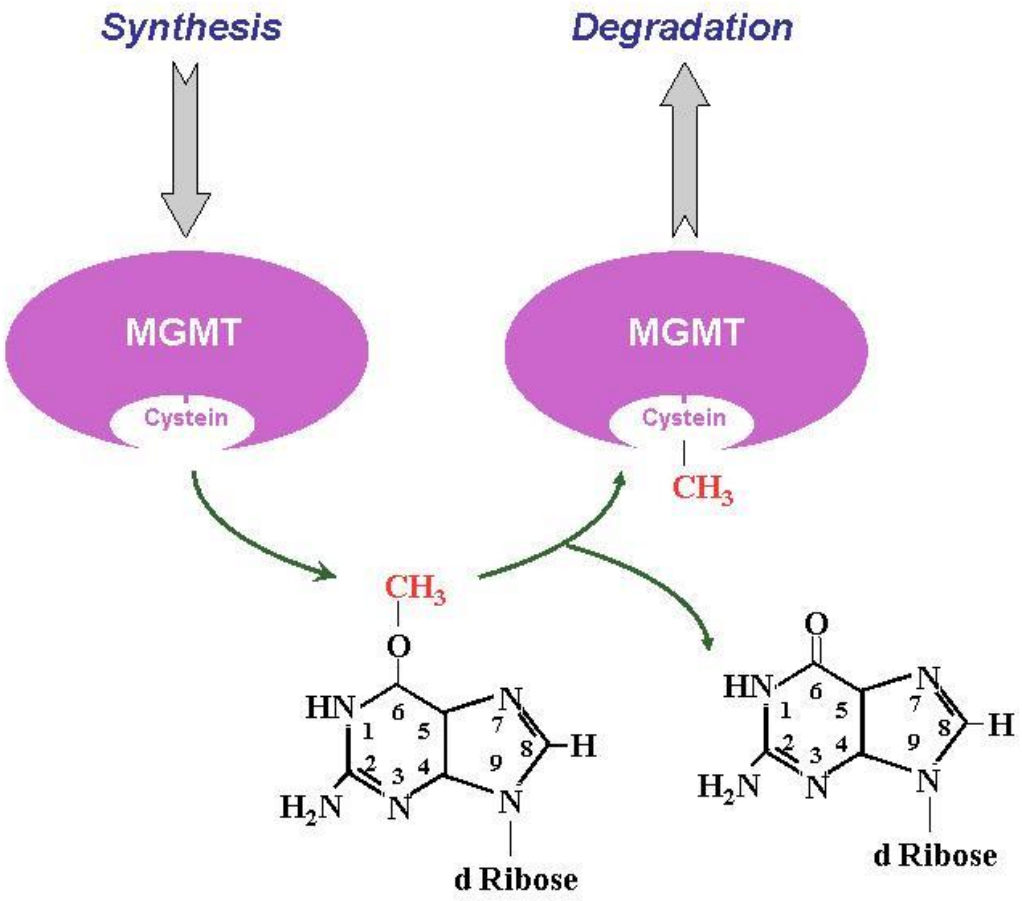
- One product is the O6methyl-Guanin which when not not repaired, allows a „promiscuous base pairing“ with Thymidine during S-phase
- This causes G-C to T-A point mutation
- Without MGMT the cell has increased mutation rates

MGMT is a suicide-enzyme

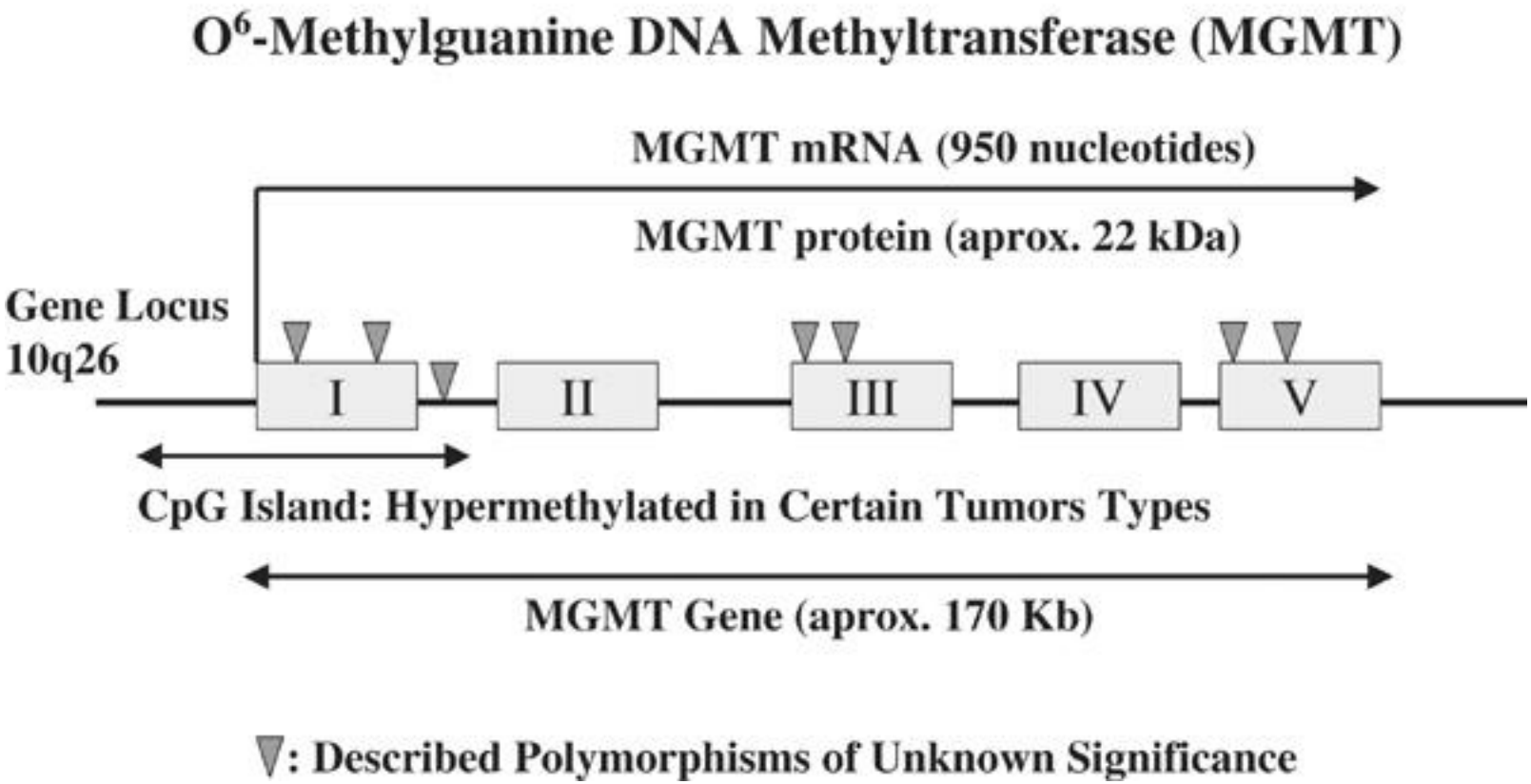
- MGMT receives alkyl-residue and is sub-sequently inactivated

- Ubiquitination and Proteasome-mediated degradation

„Suicide Reaction“



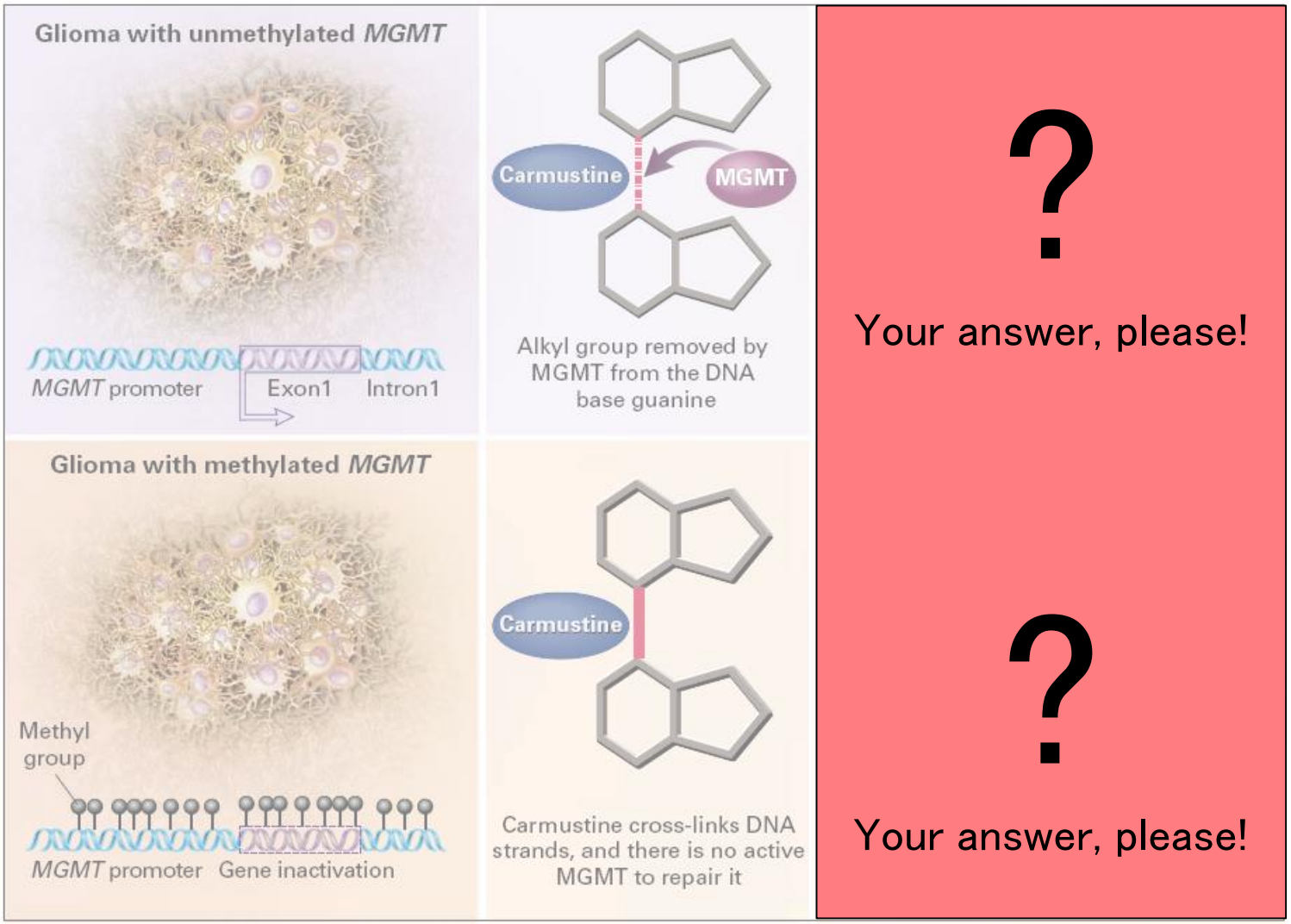
MGMT Gene


O6-Methylguanine DNA Methyltransferase (MGMT)
MGMT mRNA (950 nucleotides)
MGMT protein (aprox. 22 kDa)
Gene Locus
10q26
I
II
III
IV
V
CpG Island: Hypermethylated in Certain Tumors Types
MGMT Gene (aprox. 170 Kb)
: Described Polymorphisms of Unknown Significance

MGMT and brain tumor treatment (chemotherapy) by Carmustin (an alkalyting 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



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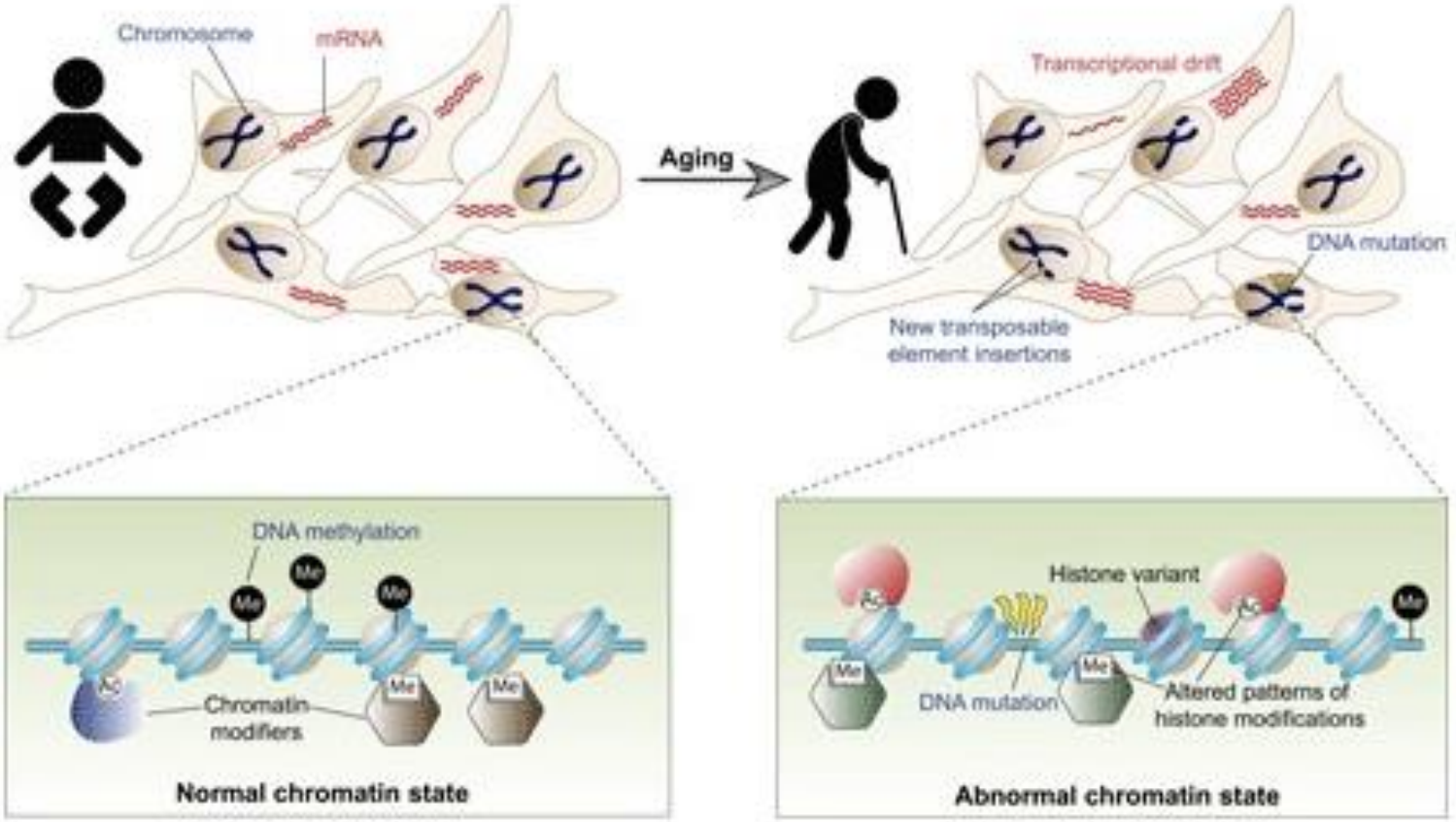
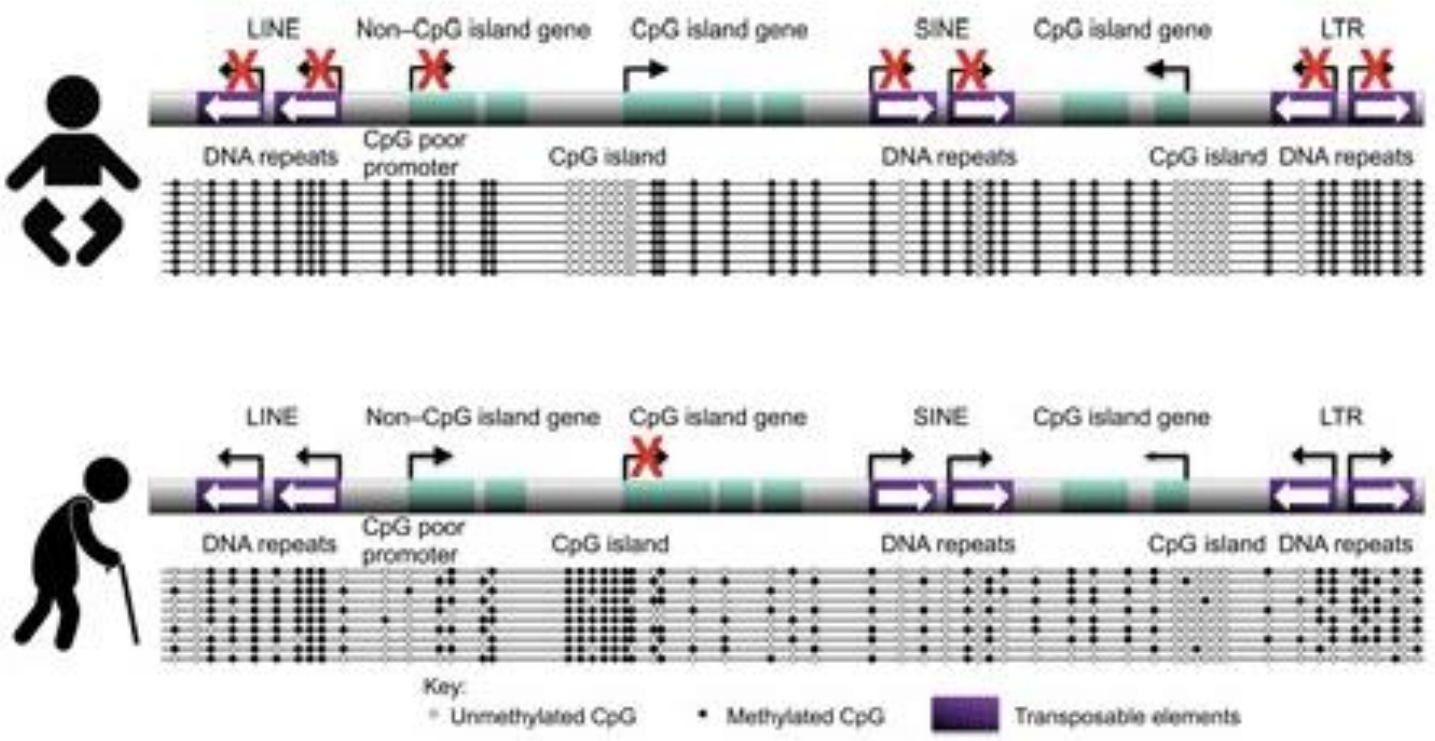
Epigenetics and aging



Epigenetics and aging

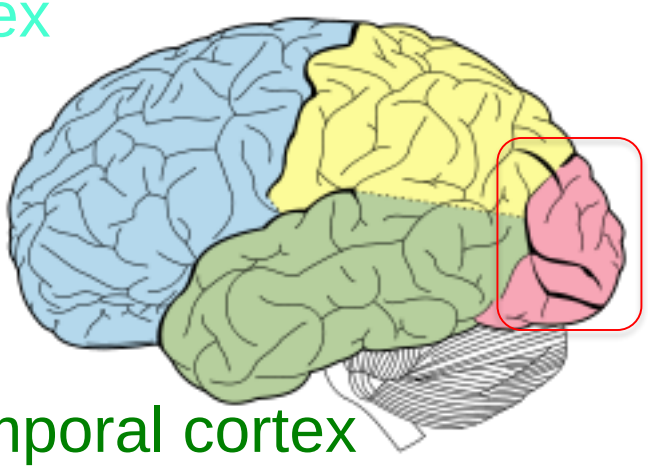


Sci Adv. 2016 Jul; 2(7): e1600584.
Published online 2016 Jul 29. doi: 10.1126/sciadv.1600584

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

Frontal cortex
(early)

(Lunnon et al 2014)
(De Jager et al 2014)

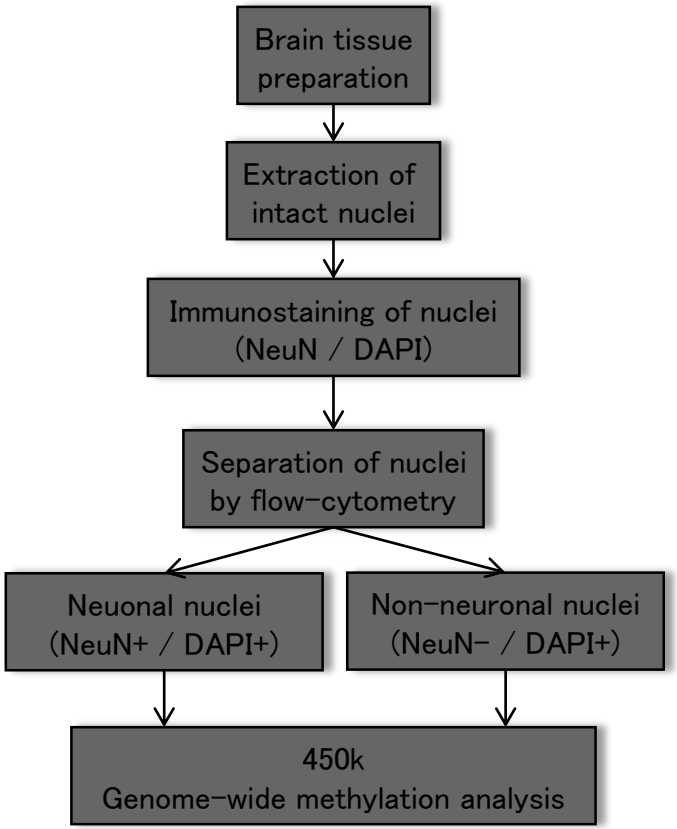


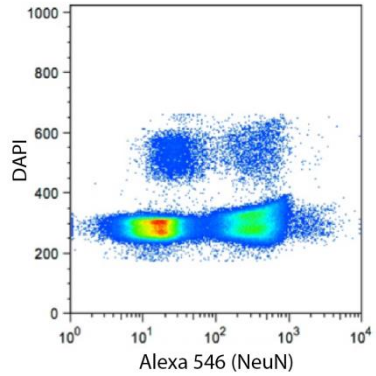
Occipital lobe
(late onset)

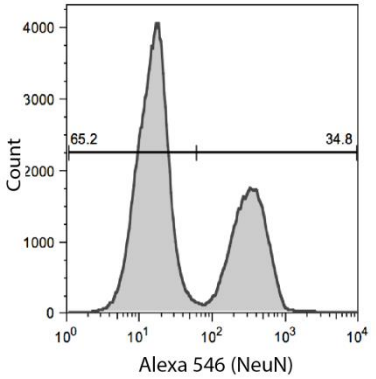
Temporal cortex
(middle)

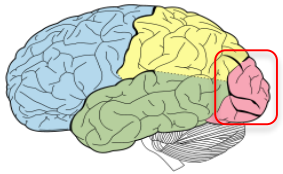
German Human Brain Bank
Prof. Dr. H. Kretzschmar

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





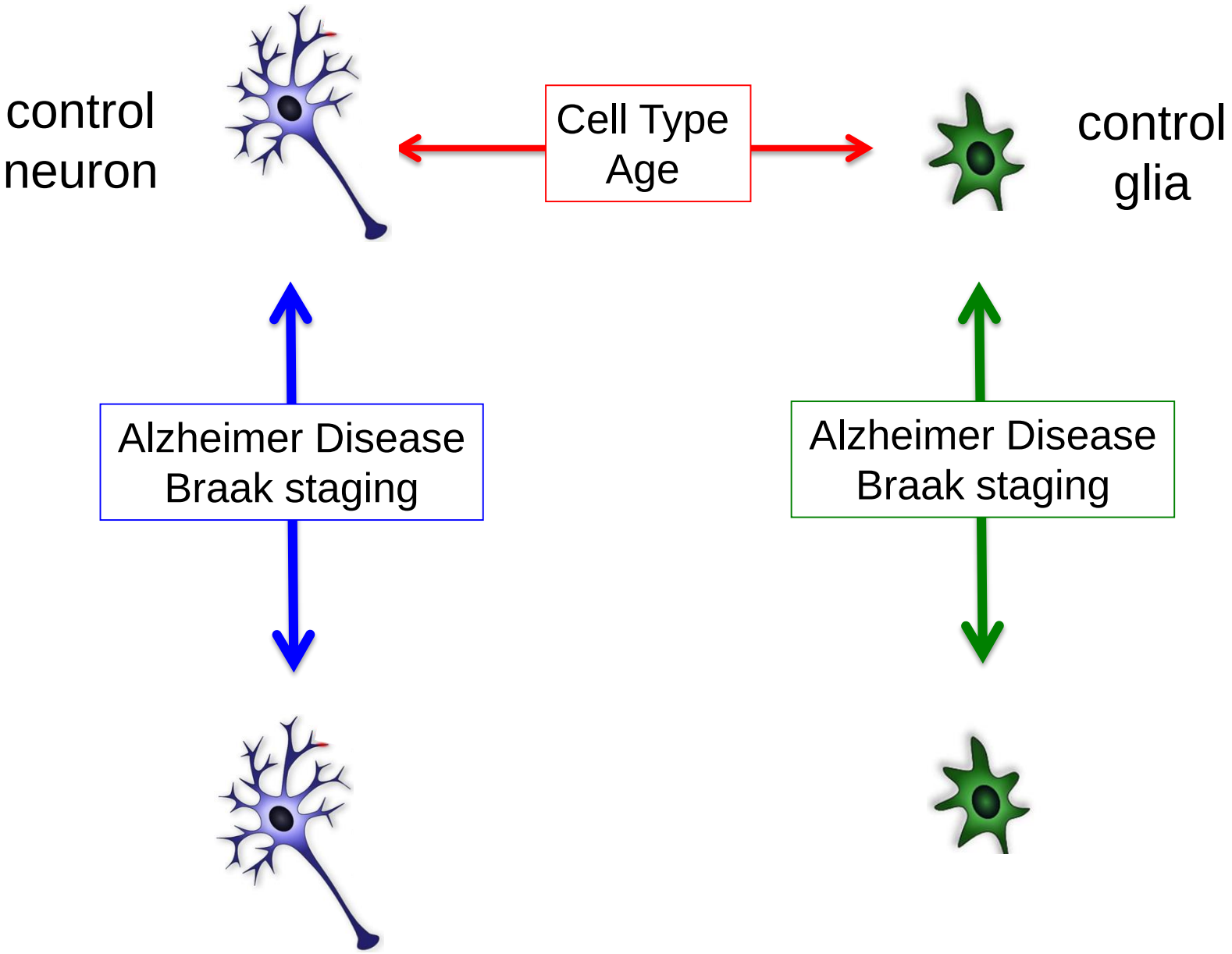




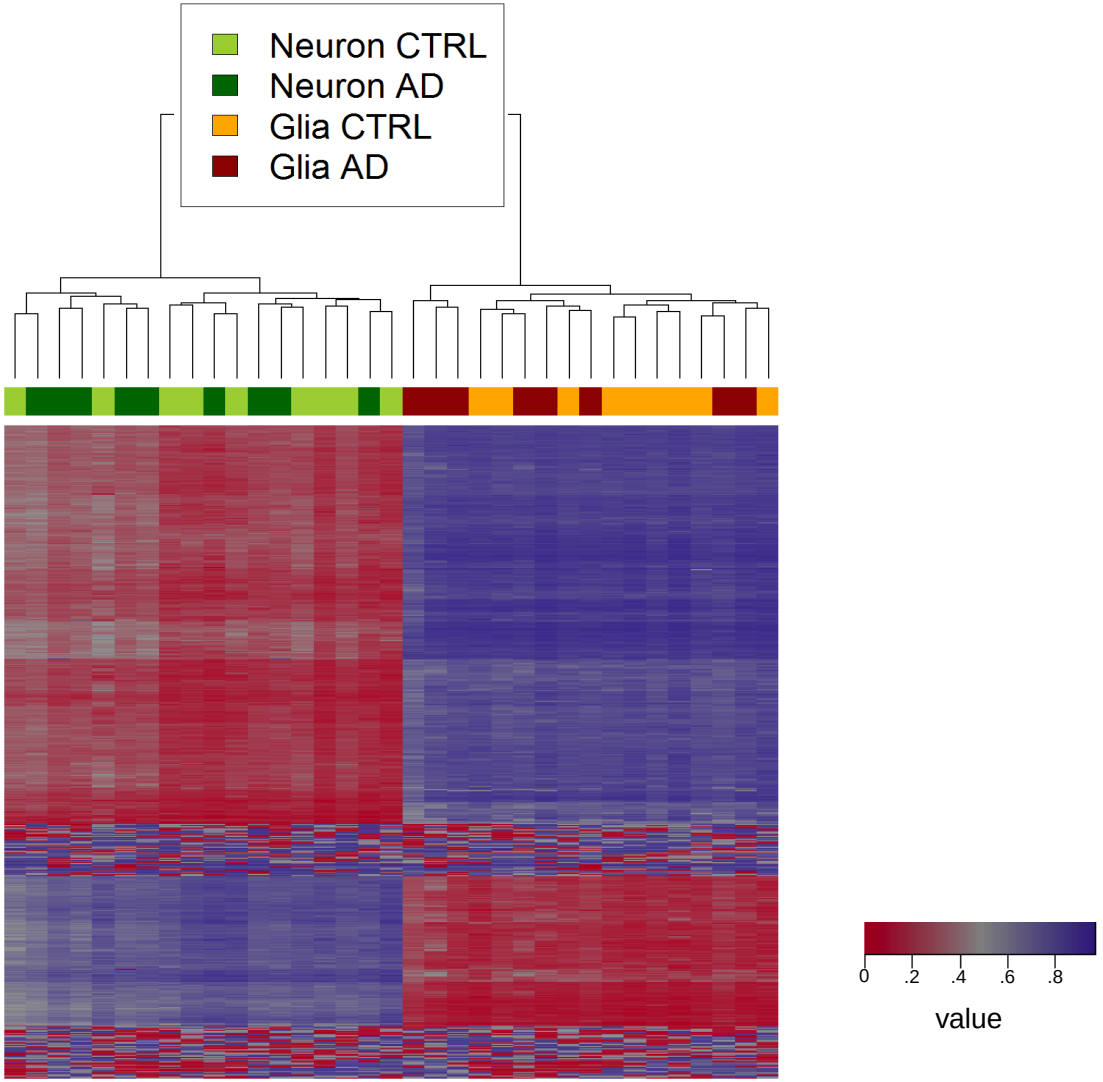
Occipital lobe
(late onset)

Infinium
Hi Scan
450 K array

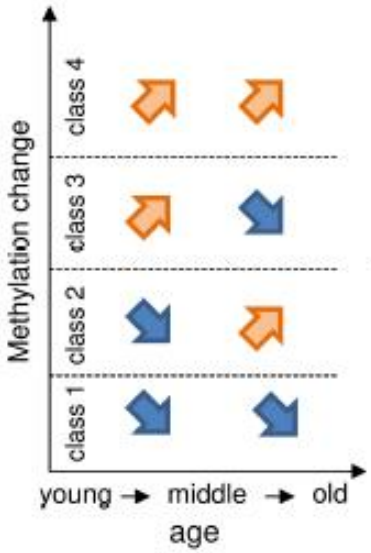
Armin Theo Kraus
Heinrich Leonhardt
LMU München

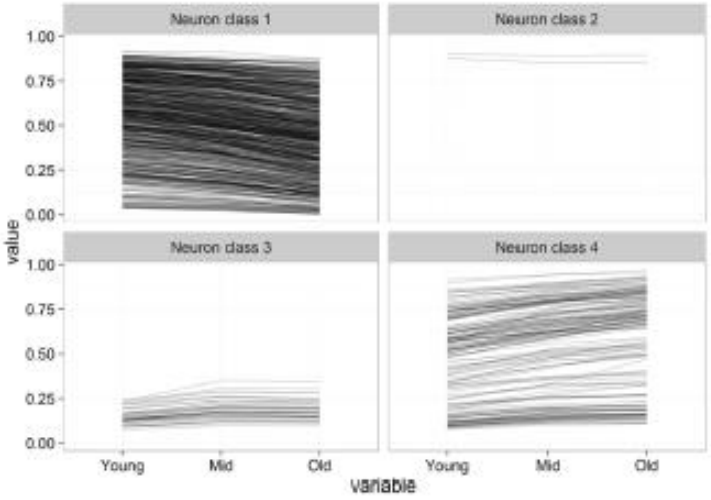

control
neuron
Cell Type
Age
control
glia
Alzheimer Disease
Braak staging
Alzheimer Disease
Braak staging

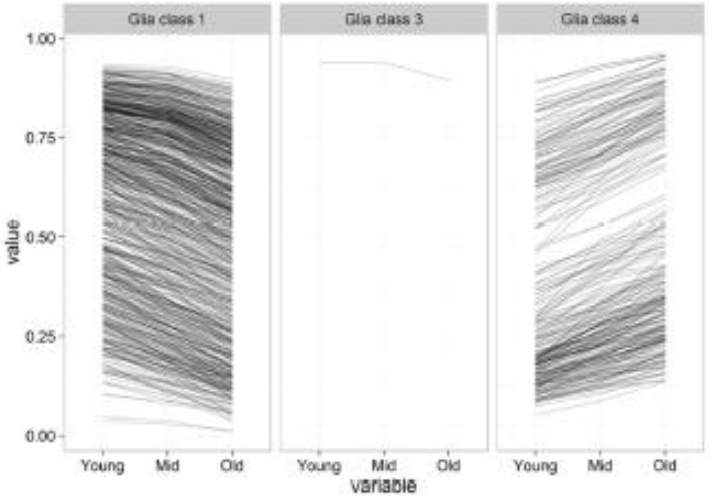
Neuronal and glial cell populations have distinct methylomes

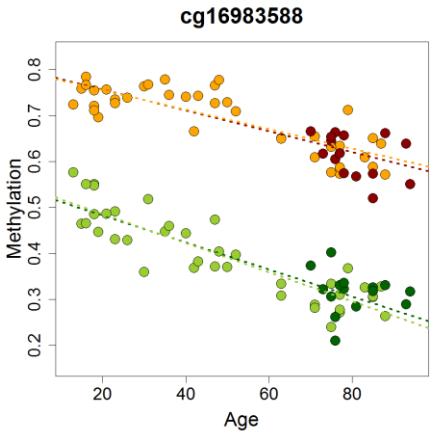


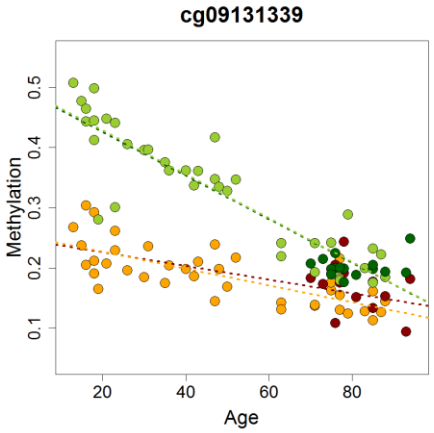
Neuronal and glial cells have distinct patterns of aging

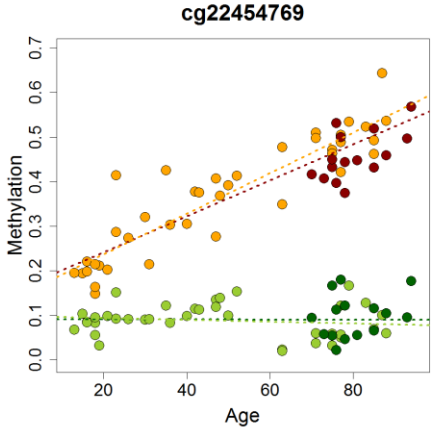




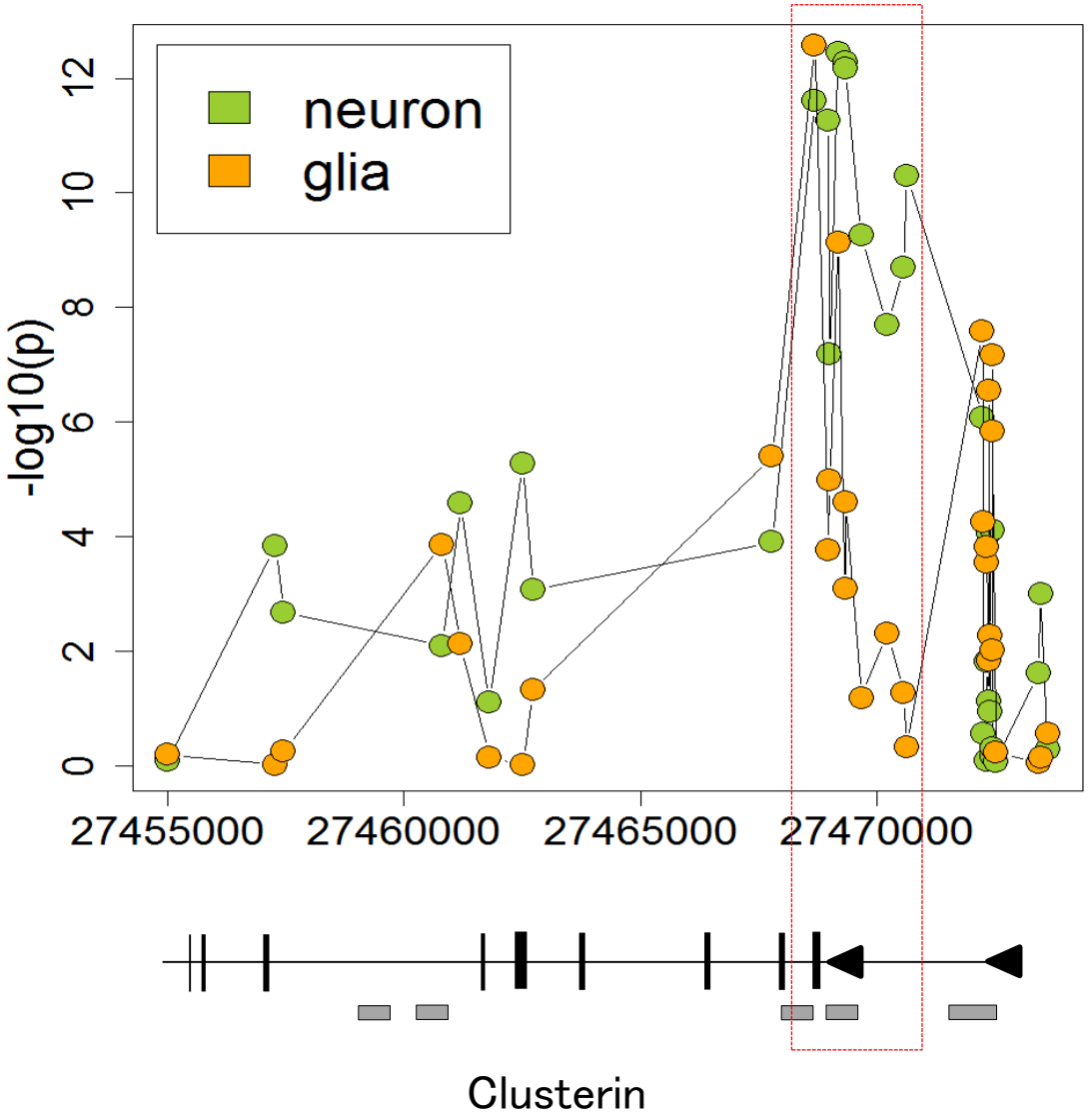




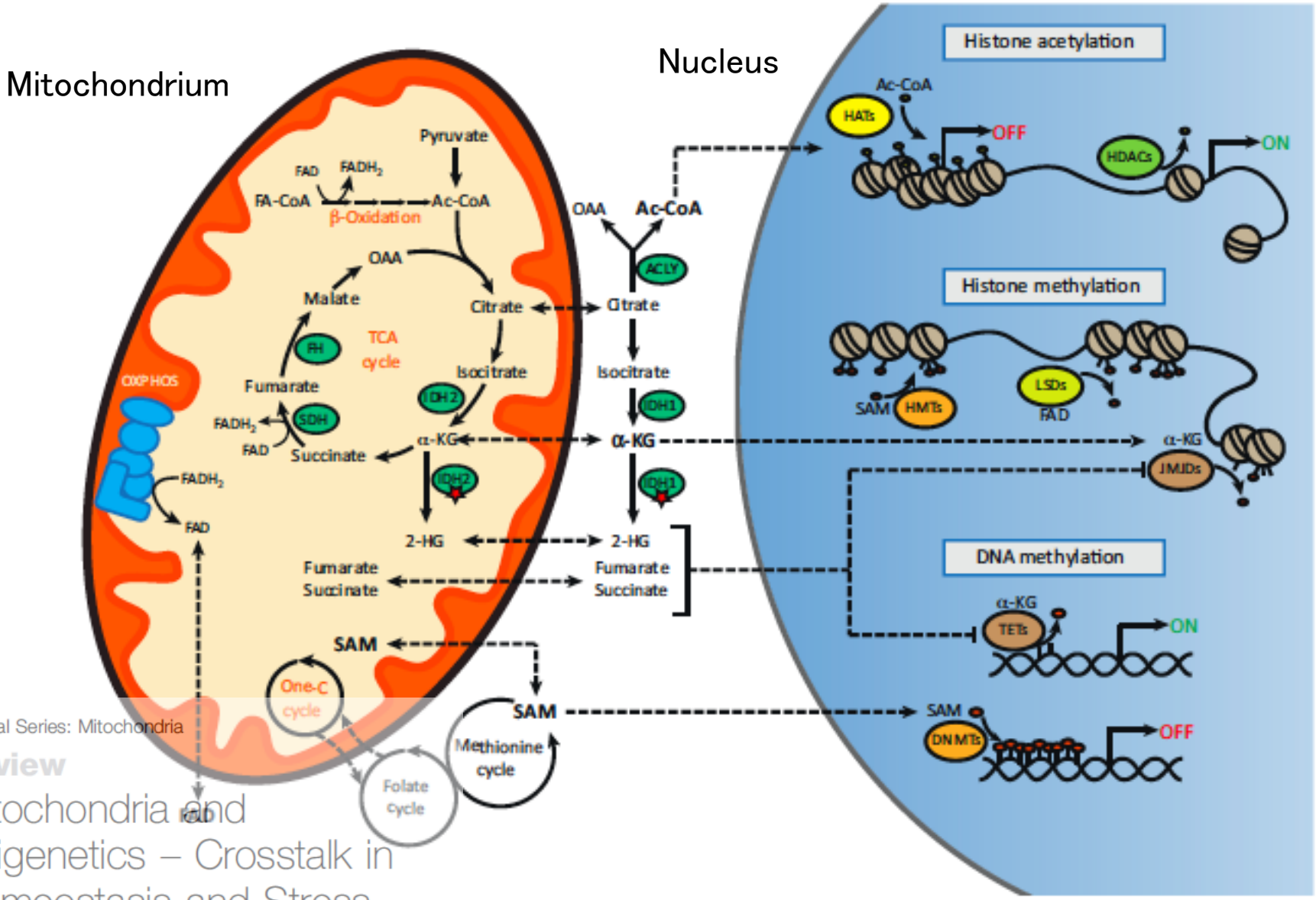




The AD risk gene ***Clusterin*** shows a clear epigenetic aging signature in neurons



Epigenetics and (altered) metabolism in cancer



Special Series: Mitochondria

Review

Mitochondria and Epigenetics – Crosstalk in Homeostasis and Stress

Olli Matilainen,[1,2] Pedro M. Quirós,[1,2] and Johan Auwerx[1,*]

Trends in Cell Biology