MUNI
MED

Inflammation-induced mutagenesis

Petr Müller

Mutations

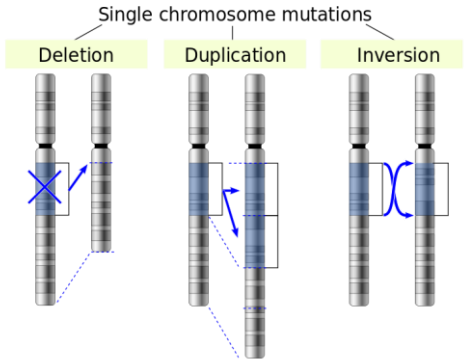
mutation is an alteration in the nucleotide sequence of the genome of an organism, virus, or extrachromosomal DNA

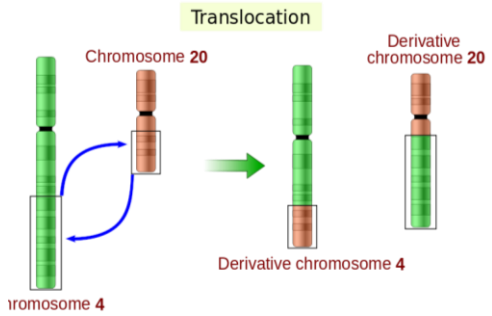
By effect on structure

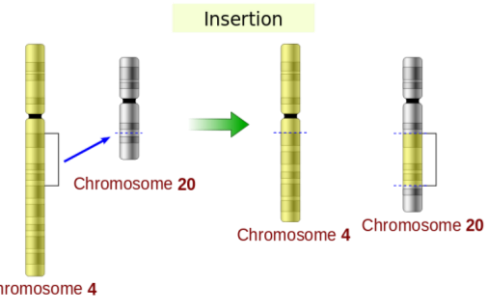
<u>Large scale mutations</u>
(Chromosomal abnormalities)

- **Deletion**
- **Duplication, amplification**
- **Inversion**
- **Translocation**
- **Insertion**

- **Loss of heterogisosity**
- **Aneuploidity**





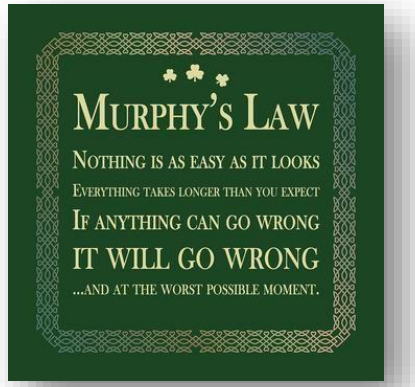


<u>Small-scale mutations</u>

- **Insertions**
- **Deletions**
- **Substitution mutations / point mutations**
  - **Missense**
  - **Nonsense**
  - **Silent**

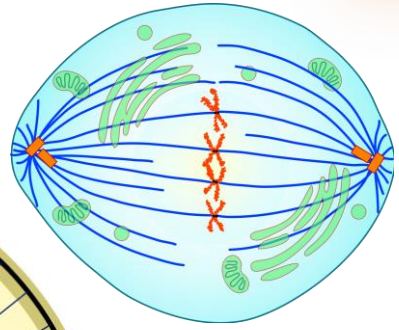
Spontaneous vs induced mutations

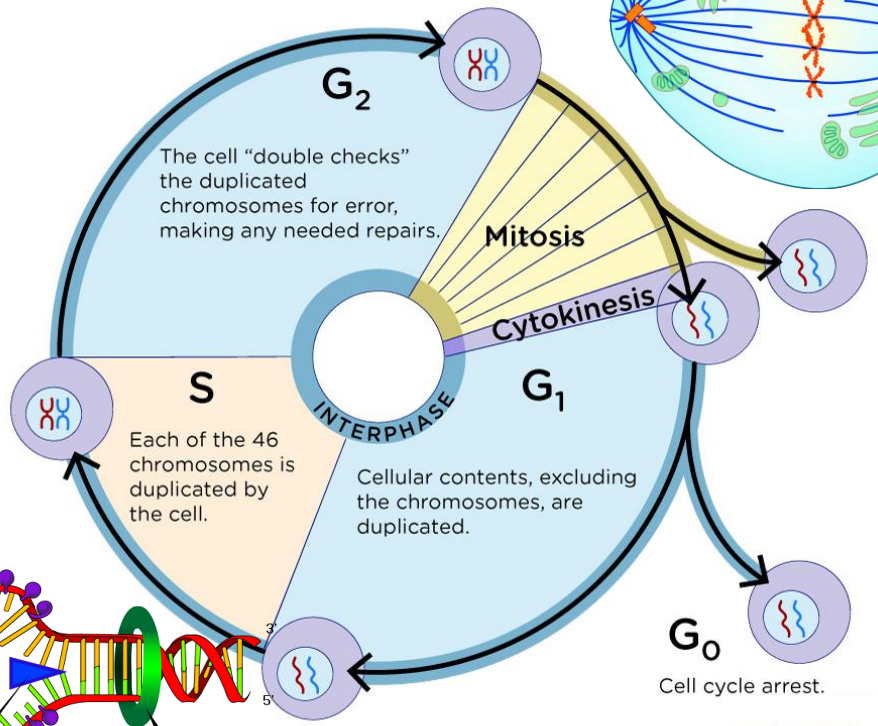
Tautomerism
Depurination
Deamination
Slipped strand mispairing
Replication slippage



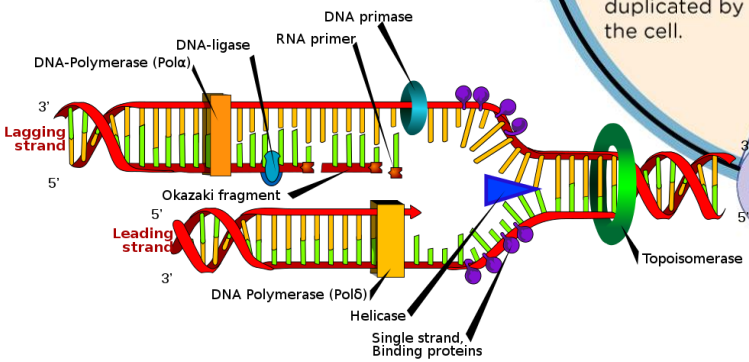
Chromosome abnormality
Amplification
Translocation
Aneuploidity

Mitosis
-chromosome segragation





DNA replication



DNA repair -> genomic instability

Double strand break repair
- BRCA1, BRCA2
- CHK2
- ATM

Mismatch repair (MMR)
- MLH1, MLH2, MLH3, PMS1, and PMS2

Nucleotide excision repair (NER)
- Xeroderma pigmentosum (XPC,..)

DNA polymerase
- POLD, POLE

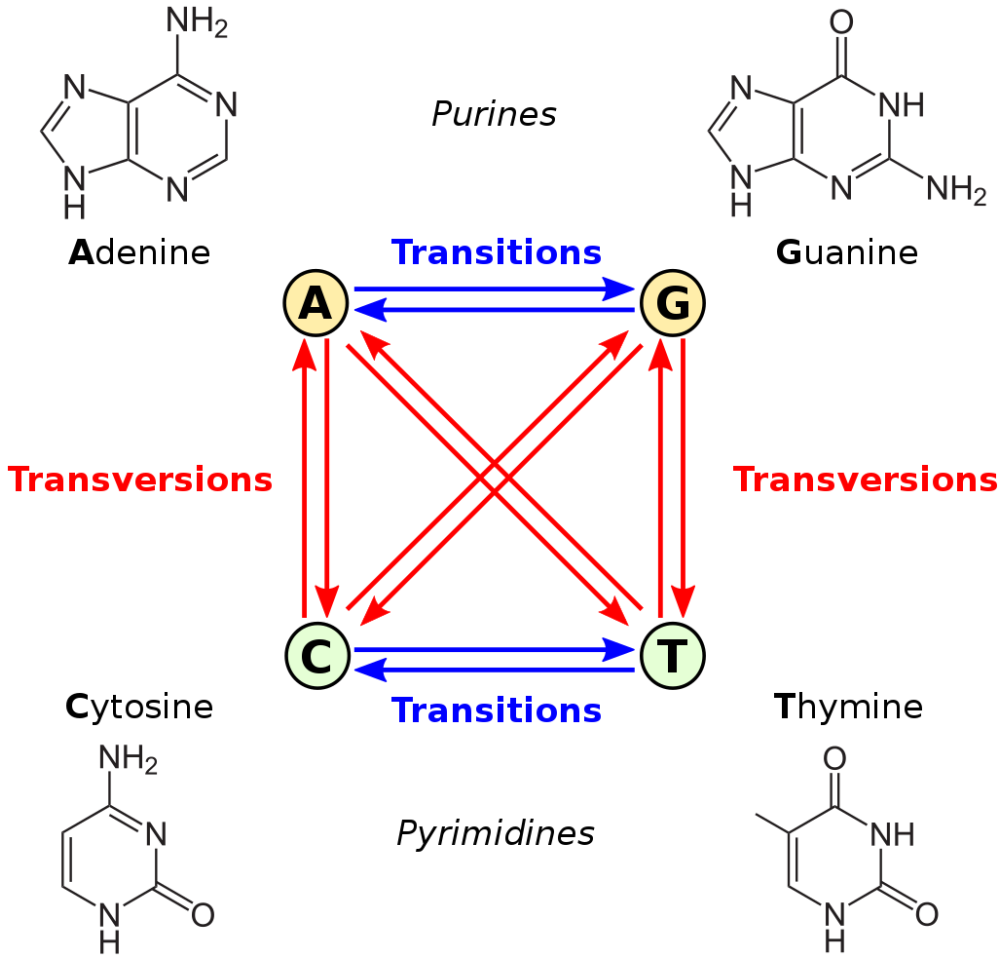
Point mutations

Transition

- mutation that changes a purine nucleotide to another purine (A ↔ G), or a pyrimidine nucleotide to another pyrimidine (C ↔ T).
- Approximately two out of three single nucleotide polymorphisms (SNPs) are transitions.
- Transitions can be caused by oxidative deamination and tautomerization.

Transversion

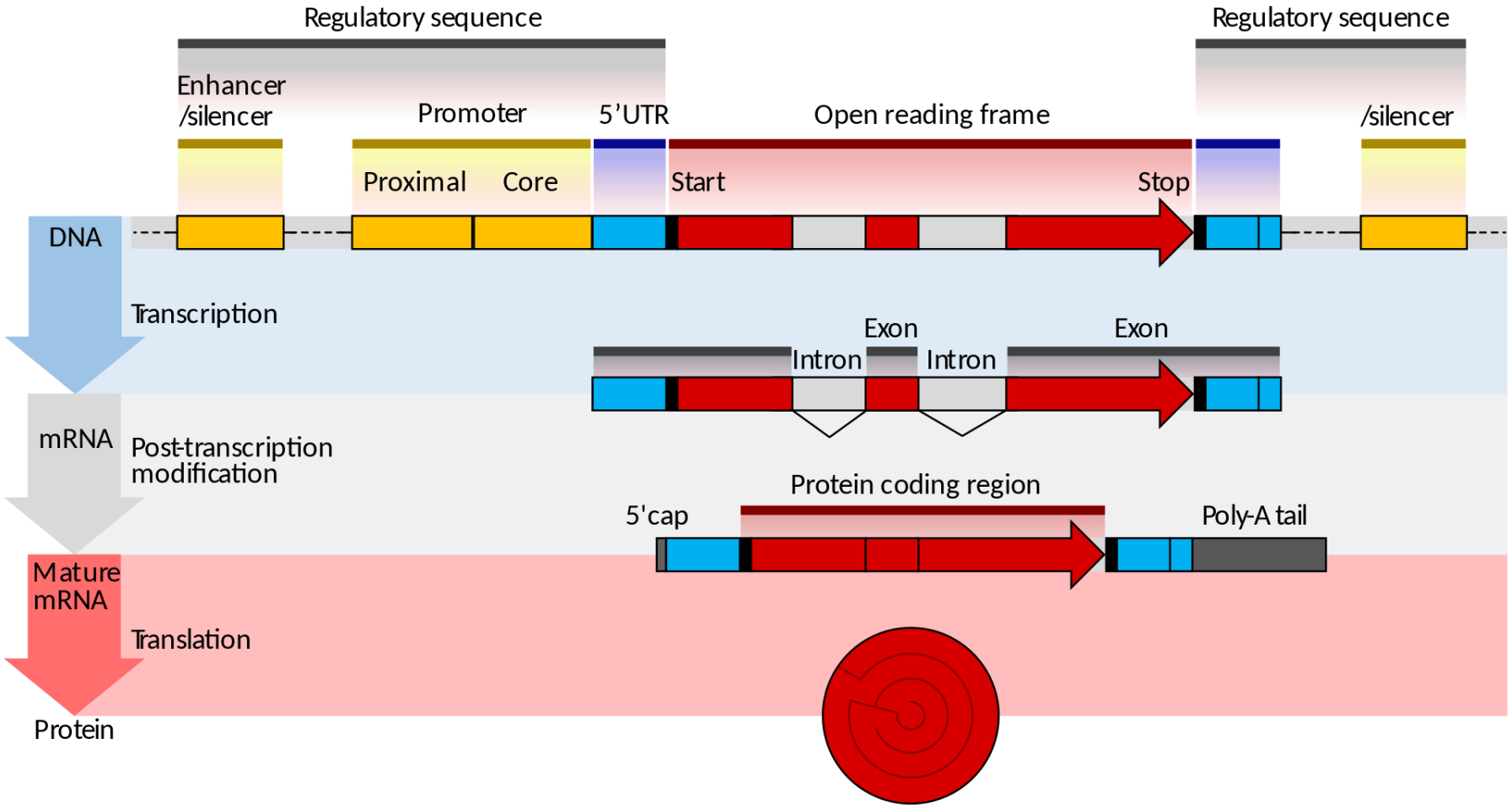
- mutation in DNA in which a single (two ring) purine (A or G) is changed for a (one ring) pyrimidine (T or C), or vice versa.
- A transversion can be spontaneous, or it can be caused by ionizing radiation or alkylating agents.



Mutations by impact on protein sequence

Coding region:

- **Point mutations**
  - Missense
  - Nonsense
  - Silent
- **Frameshift mutations**
  - Insertions
  - Deletions
  - (Indels)



Bad and good mutations

- Genetic variation is an important force in evolution as it allows natural selection to increase or decrease frequency of alleles already in the population.

- Genetic variation can be caused by mutation (which can create entirely new alleles in a population), random mating, random fertilization, and recombination between homologous chromosomes during meiosis (which reshuffles alleles within an organism’s offspring).

- Genetic variation is advantageous to a population because it enables some individuals to adapt to the environment while maintaining the survival of the population.

Adaptive immunity and controled mutagenesis

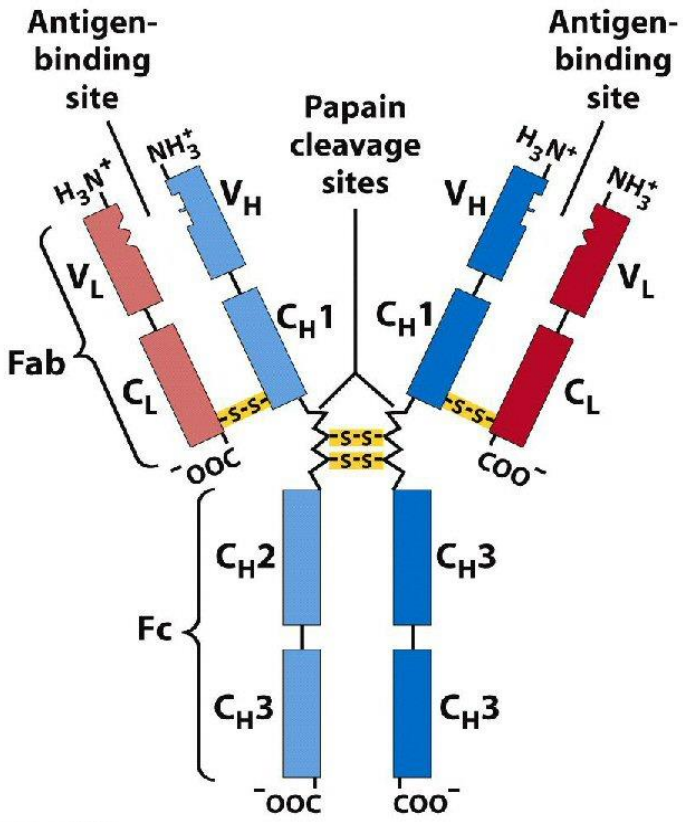
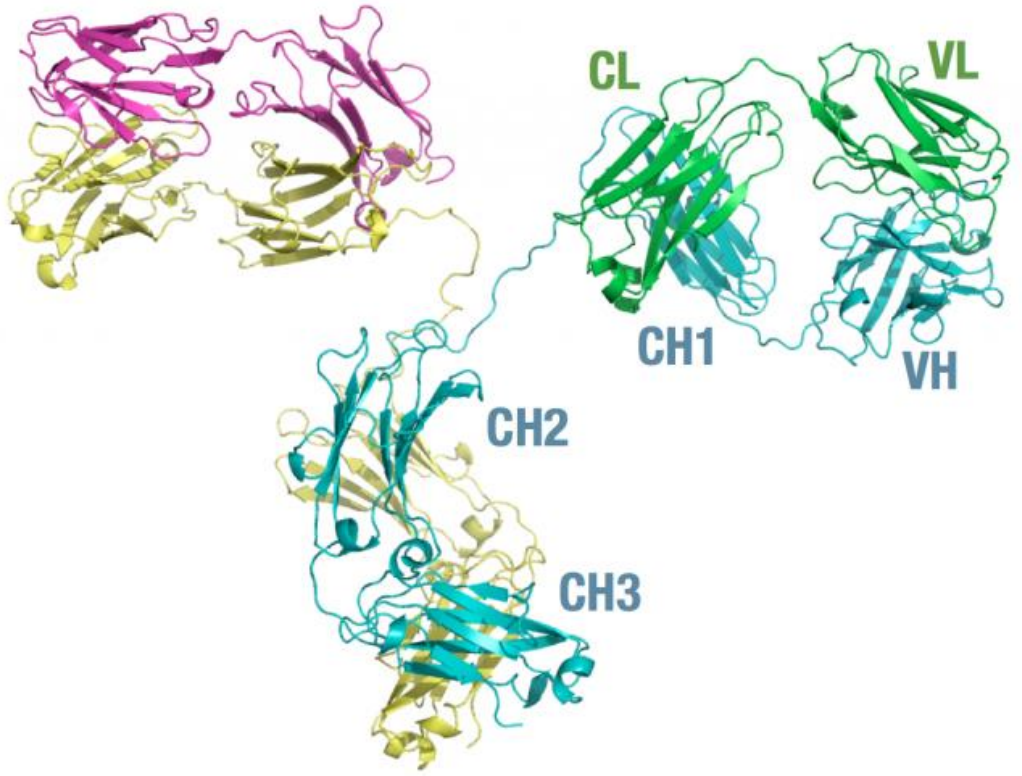
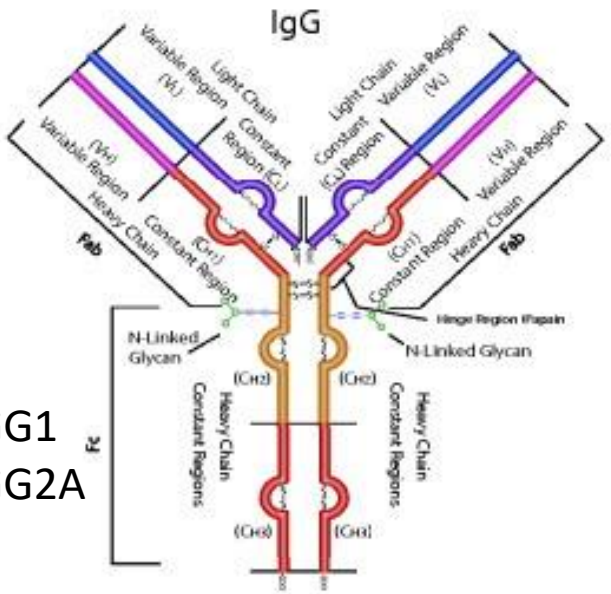


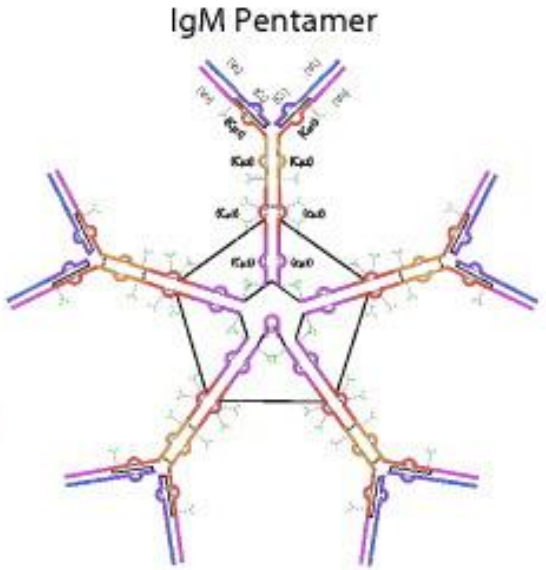
Figure 5-21a
Lehninger Principles of Biochemistry, Fifth Edition

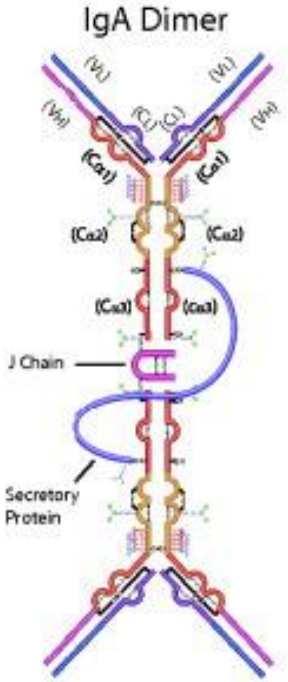


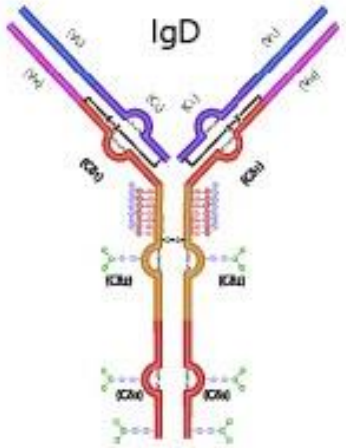
Antibody isotypes

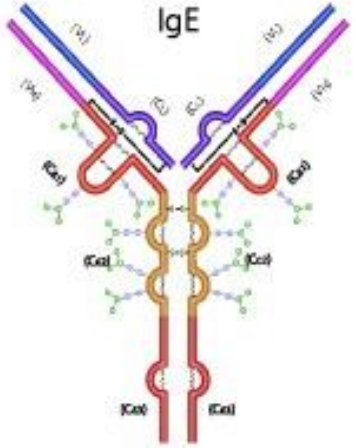
IGG1
IGG2A











Antibody genetics

IGH locus chr. 14
IGL kappa (κ) locus chr. 2
IGL lambda (λ) locus chr. 22

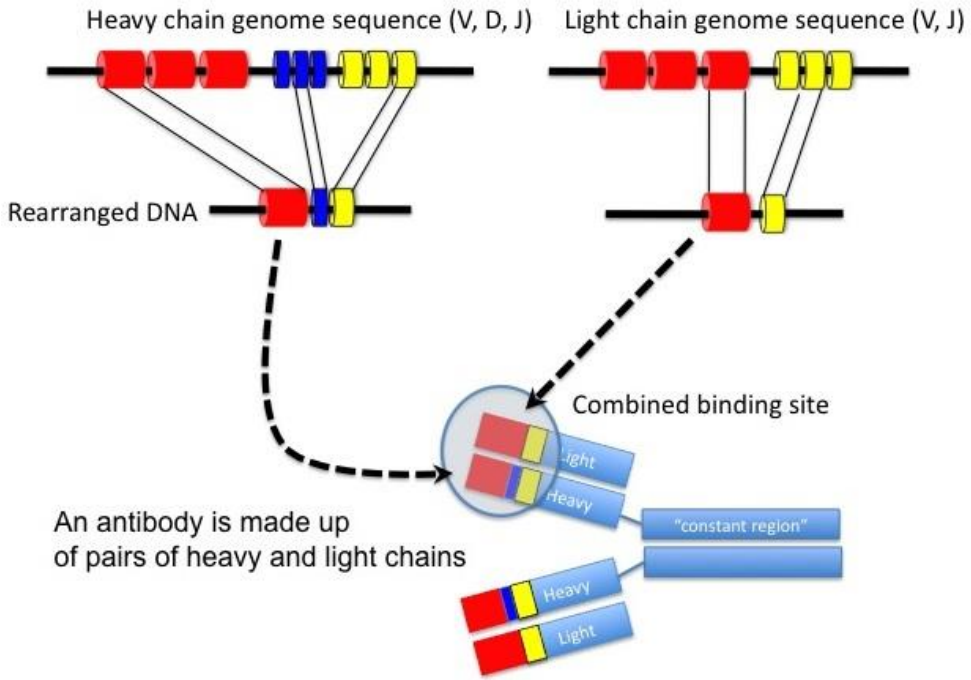
44V x 27D x 6J

Susumu Tonegawa
Nobel prize 1987

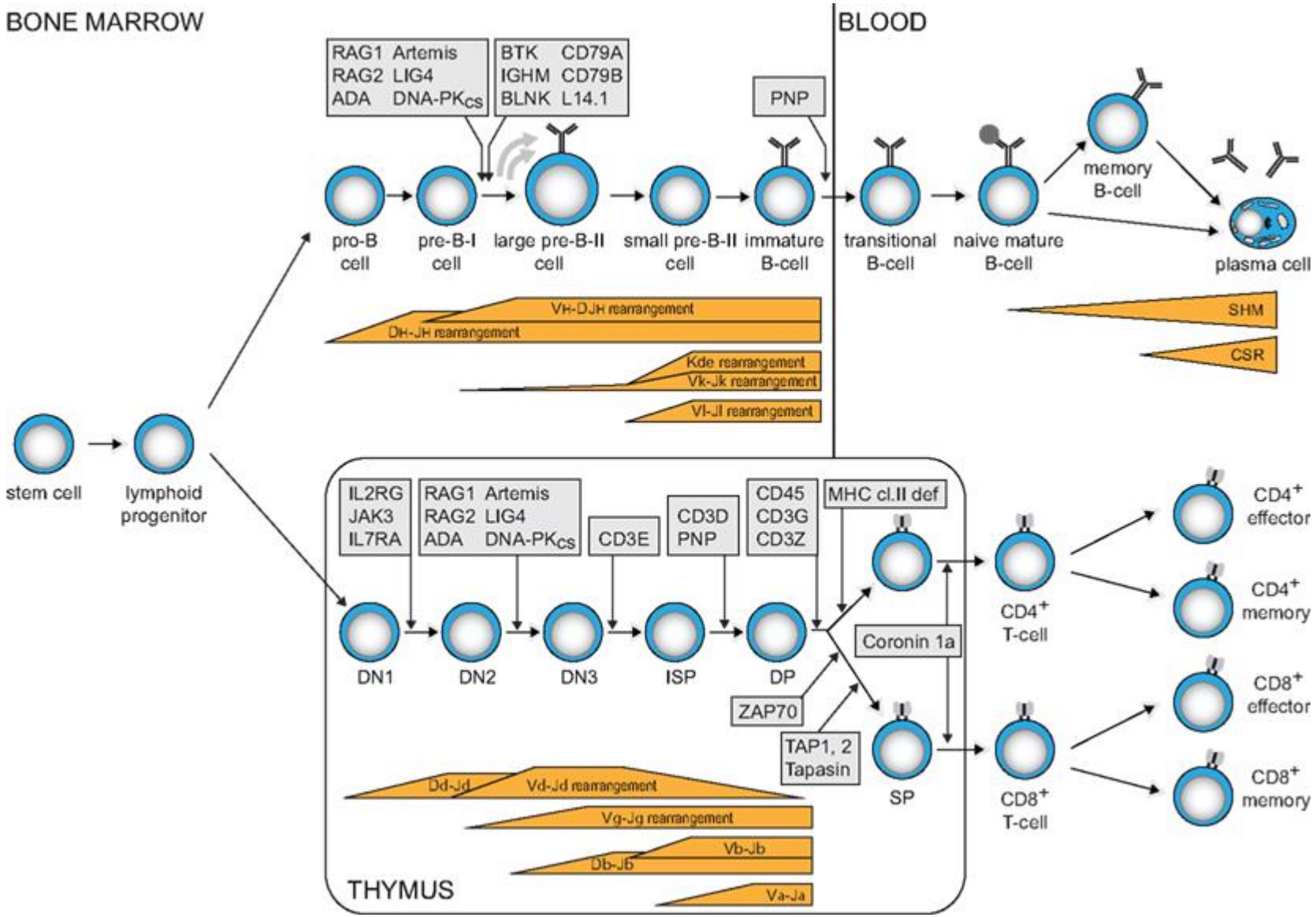
V(D)J recombination

Somatic hypermutation and affinity maturation

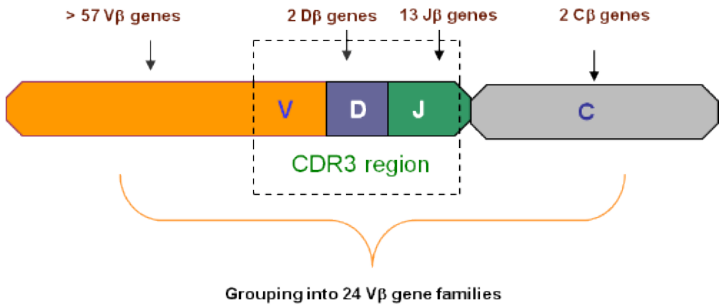
Class switching

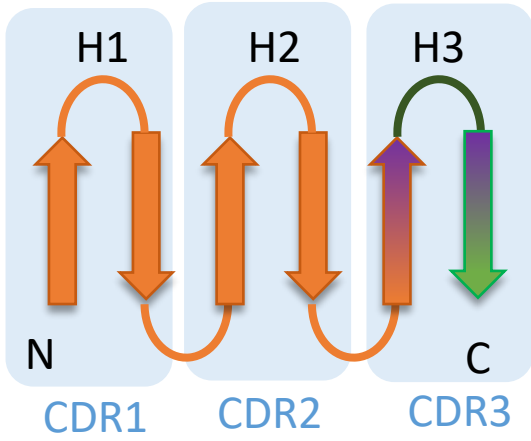


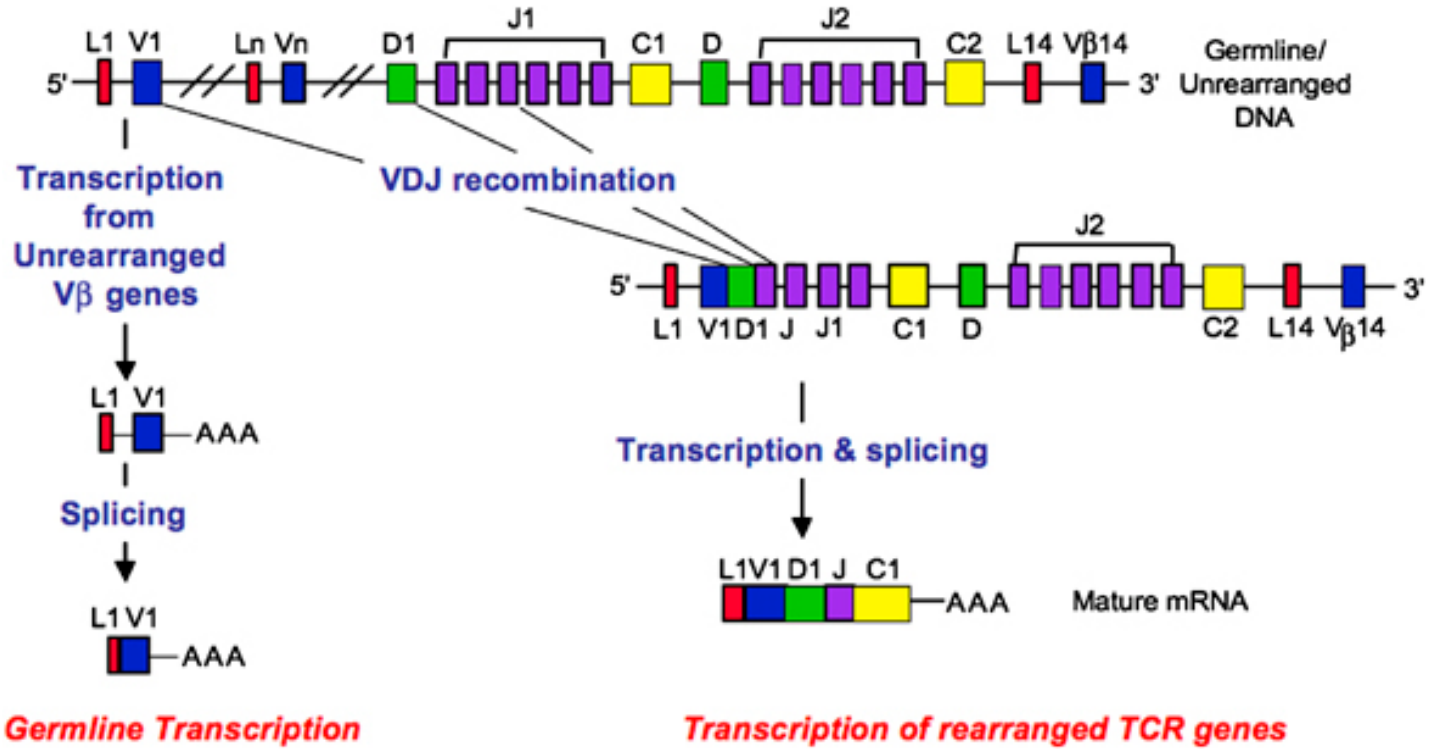
V(D)J recombinations in lymphocyte differentiation



VDJ recombination

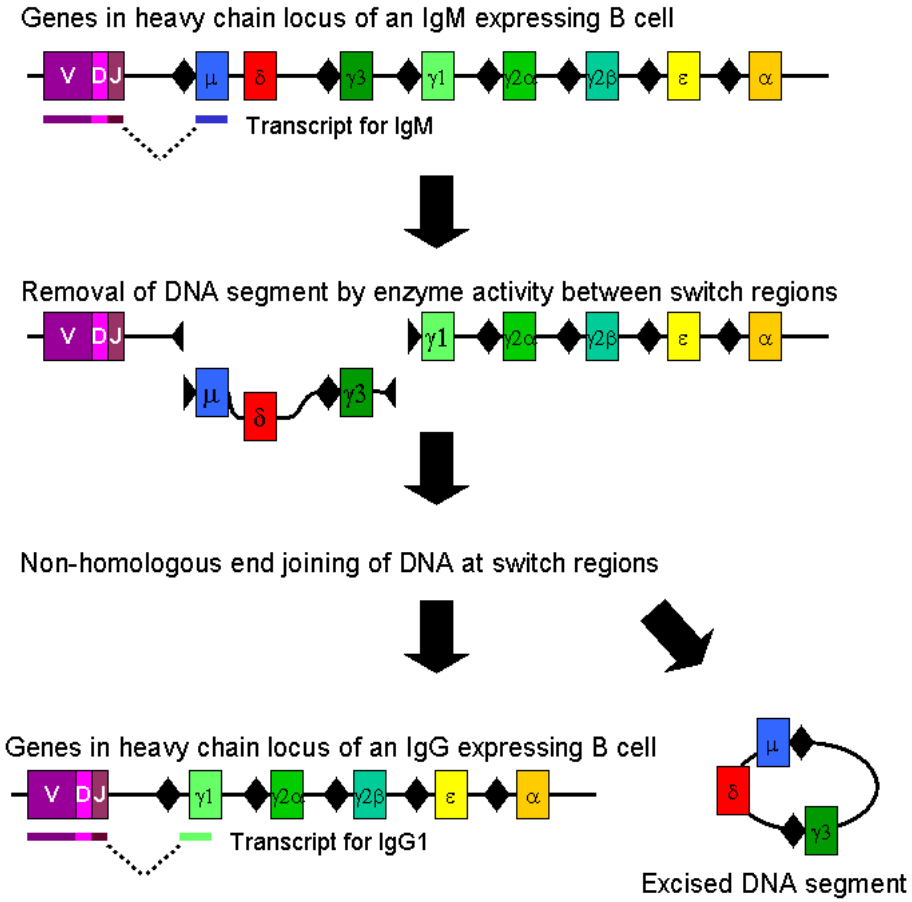






Class switching

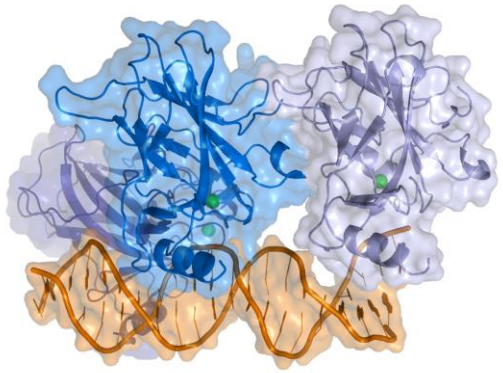
μ - IgM
δ - IgD
γ3 - IgG3
γ1 - IgG1
pseudogene
α1 - IgA1
γ2 - IgG2
γ4 - IgG4
ε - IgE
α2 - IgA2



Activation-Induced (Cytidine) Deaminase (AID),
Uracil DNA glycosylase
Apyrimidic/apurinic (AP)-endonucleases

S-region → DSB → NHEJ

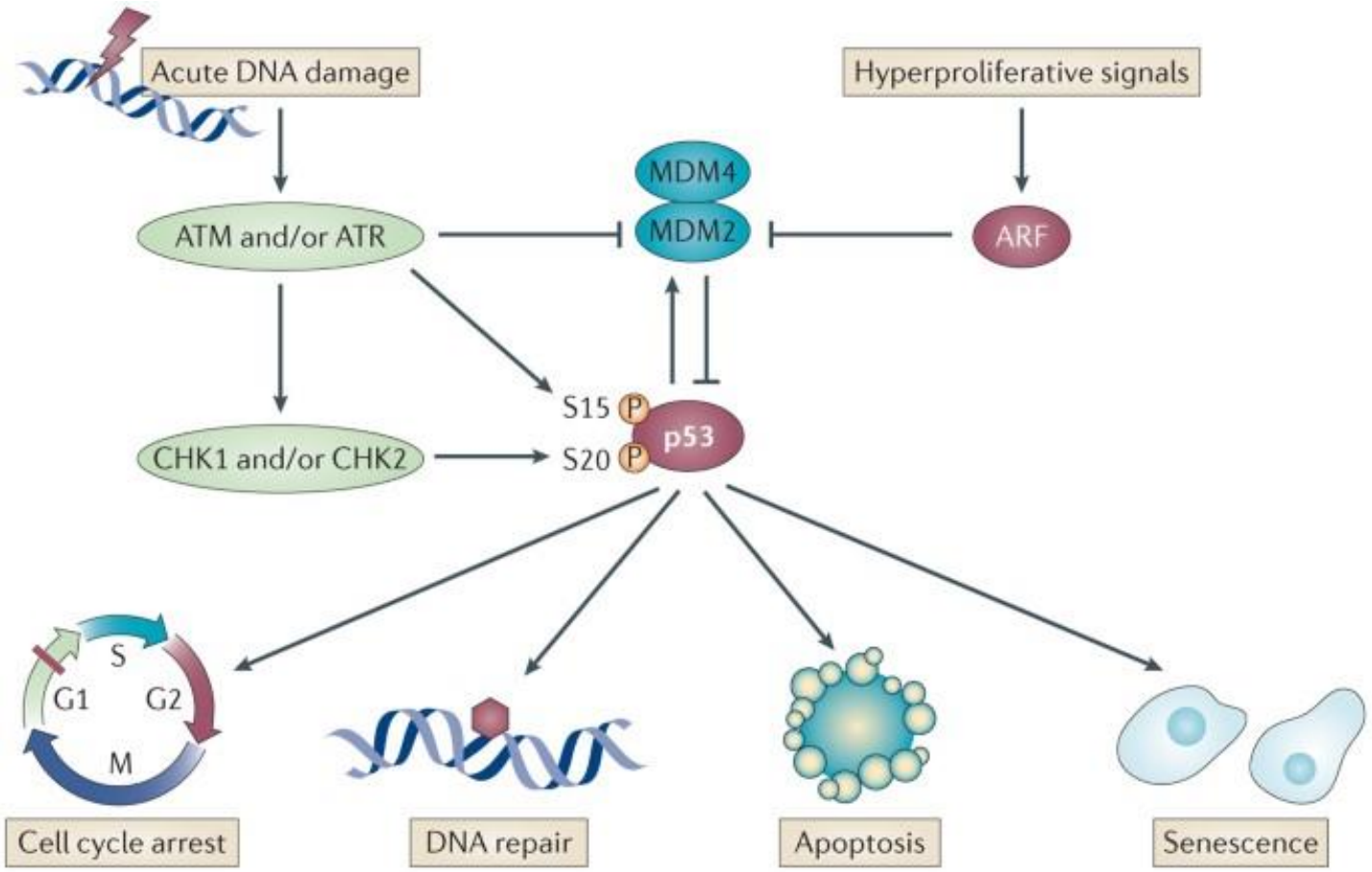
Tumor suppressor p53 - the guardian of genome



David Lane

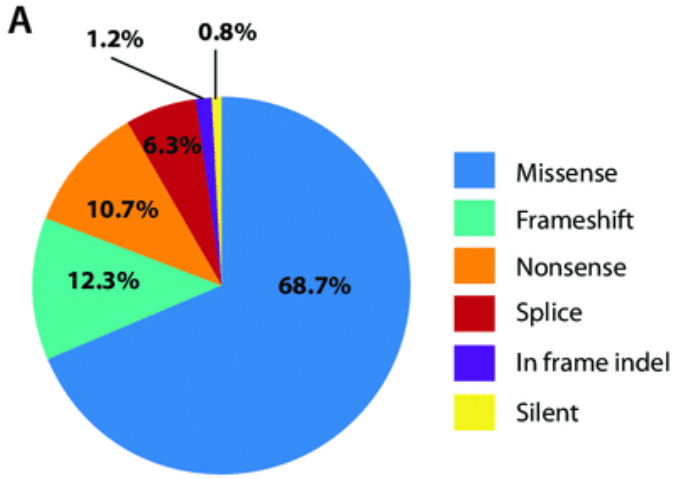
- Most frequently mutated gene in cancer
- Transcription factor
- Germline mutation cause Li-Fraumeni syndrome
- Tumor suppressor
- Both alleles lost in cancer – (lost of heterozygosity) LOH

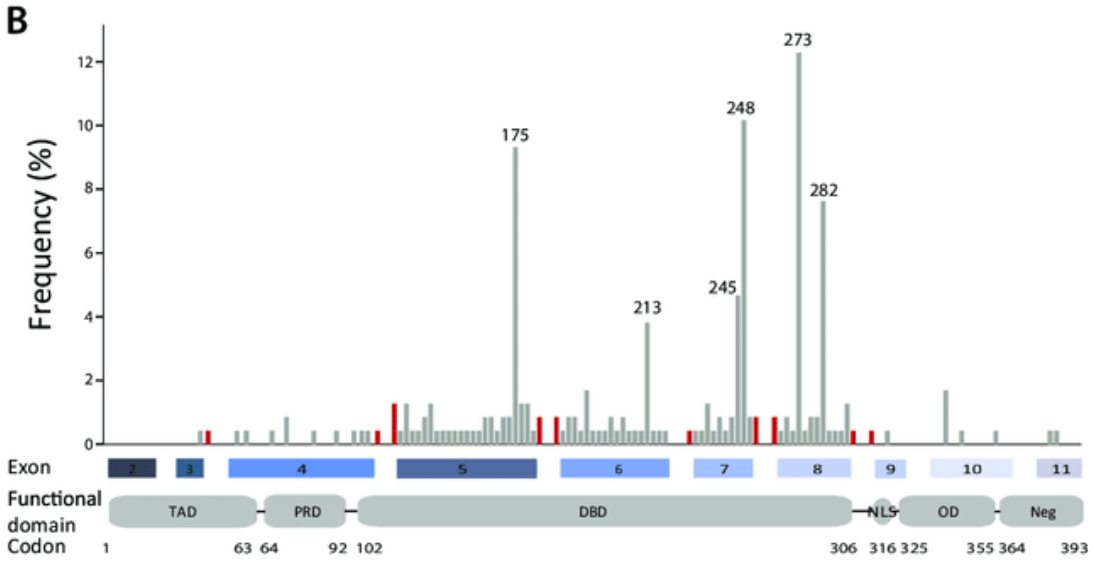
Tumor suppressor p53 - the guardian of genome

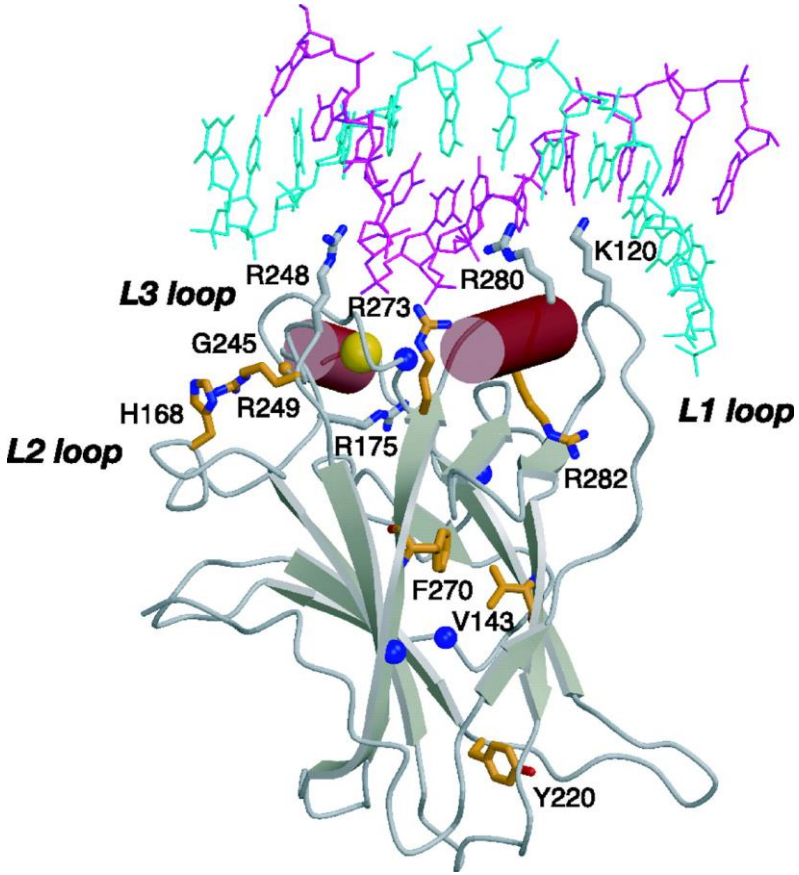


Nature Reviews | Cancer

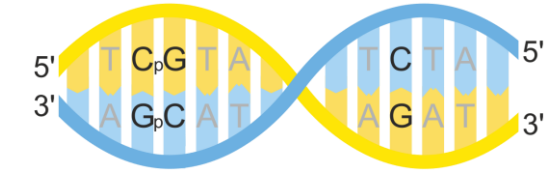
p53 mutational spectrum





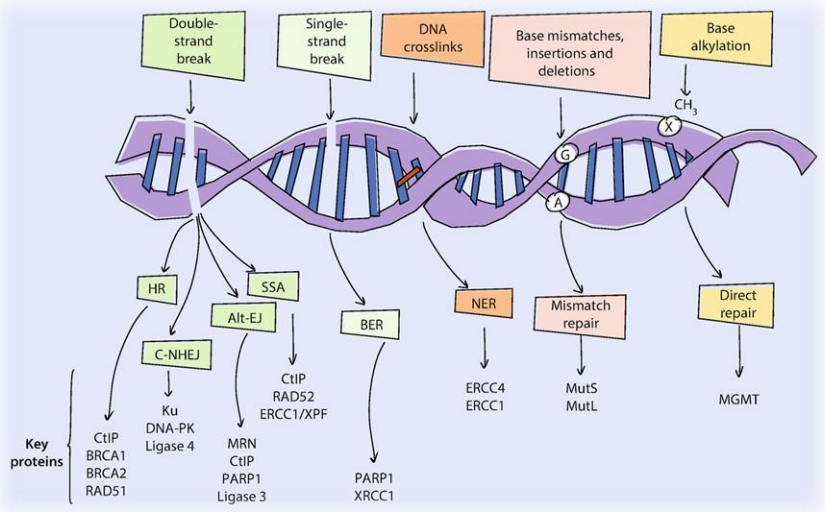


CGG -->Arg



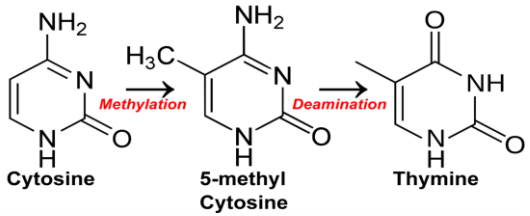
CpG island

Genomic instability



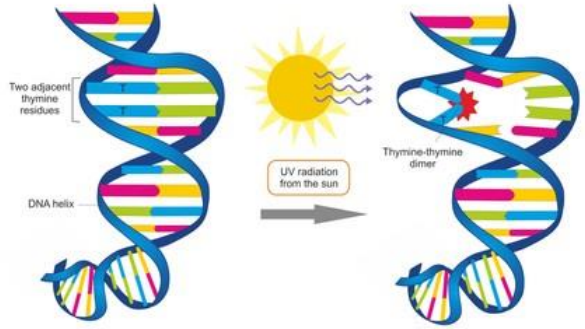
„Spontaneous“ mutations (aging and inflamation)

CpG island



Exogenous mutagens

- Smoking
- UV light
- Alkylating agents
- aflatoxin



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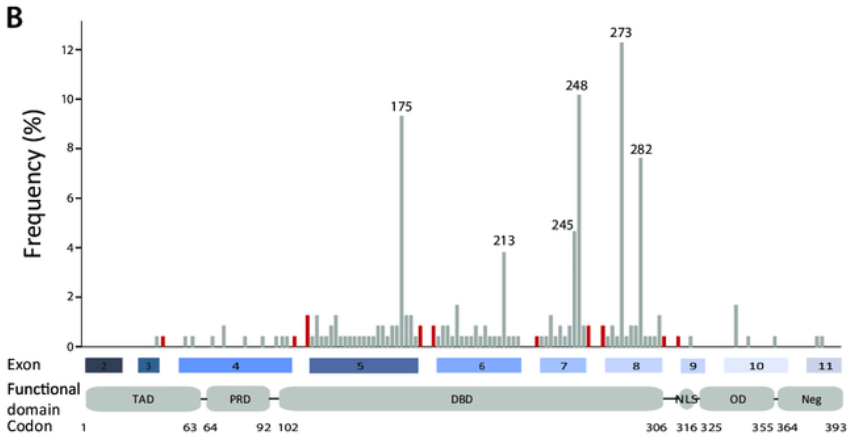
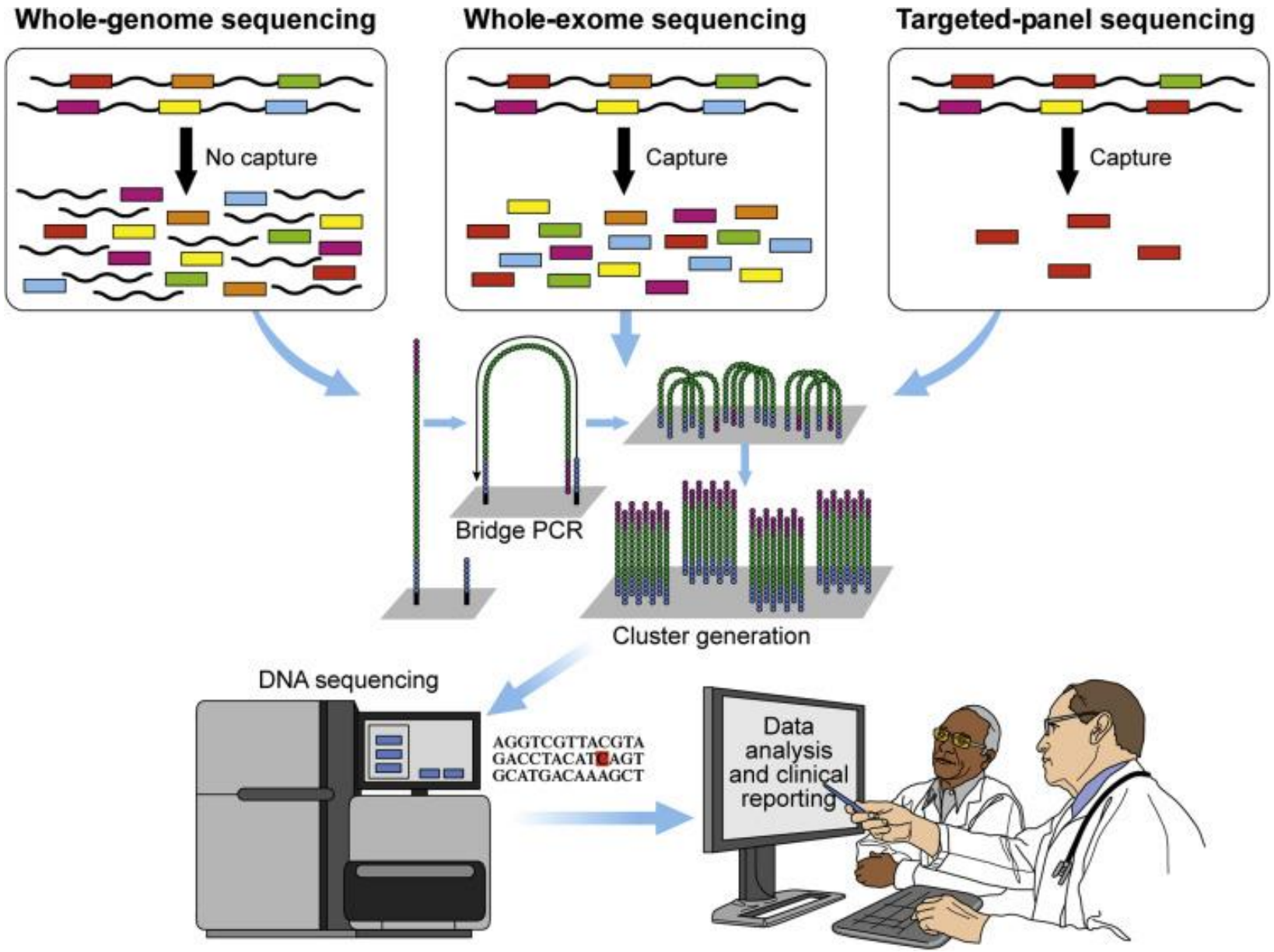
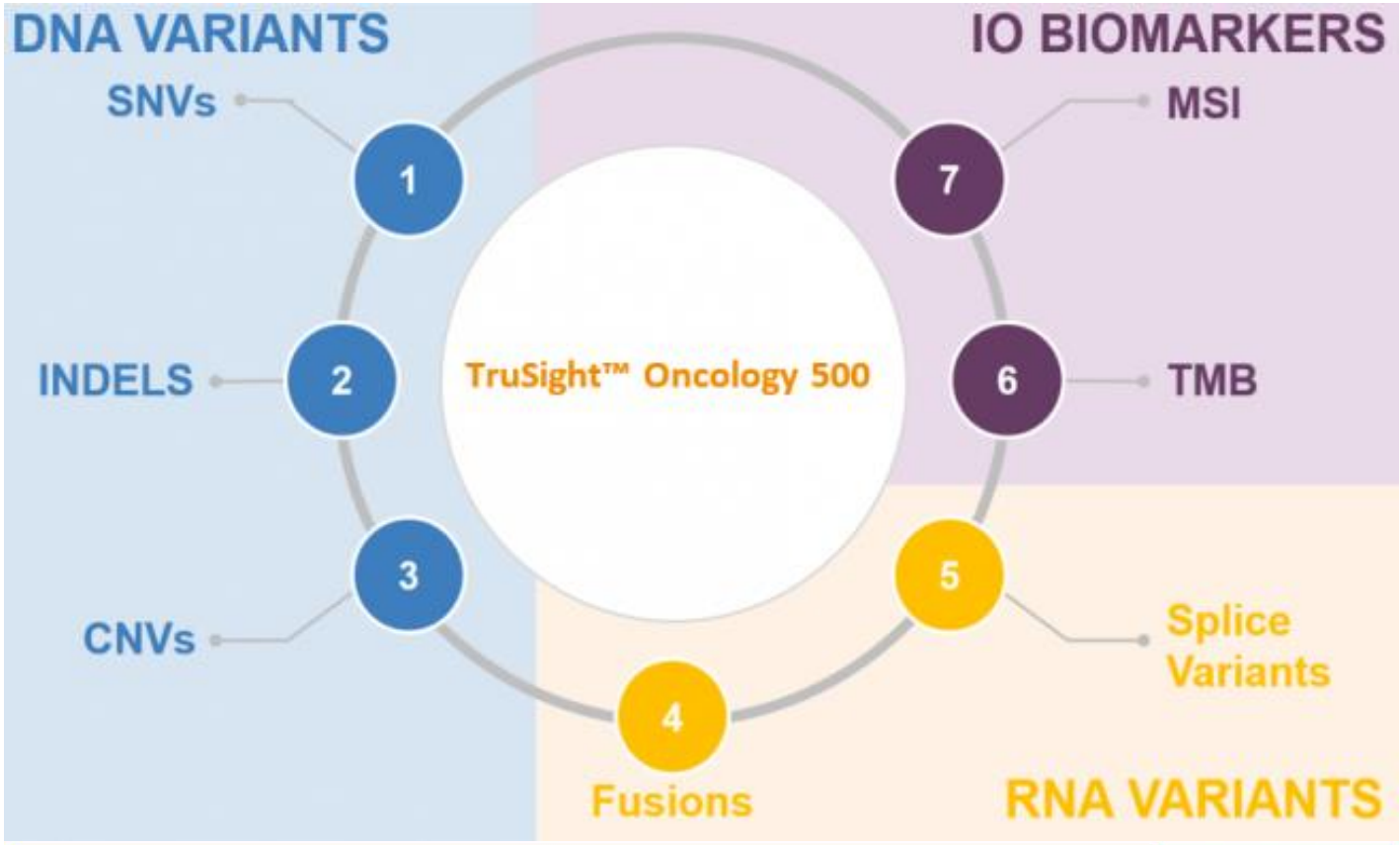
Mutation pattern
Mutational signatures



NGS
Next Generation Sequencing

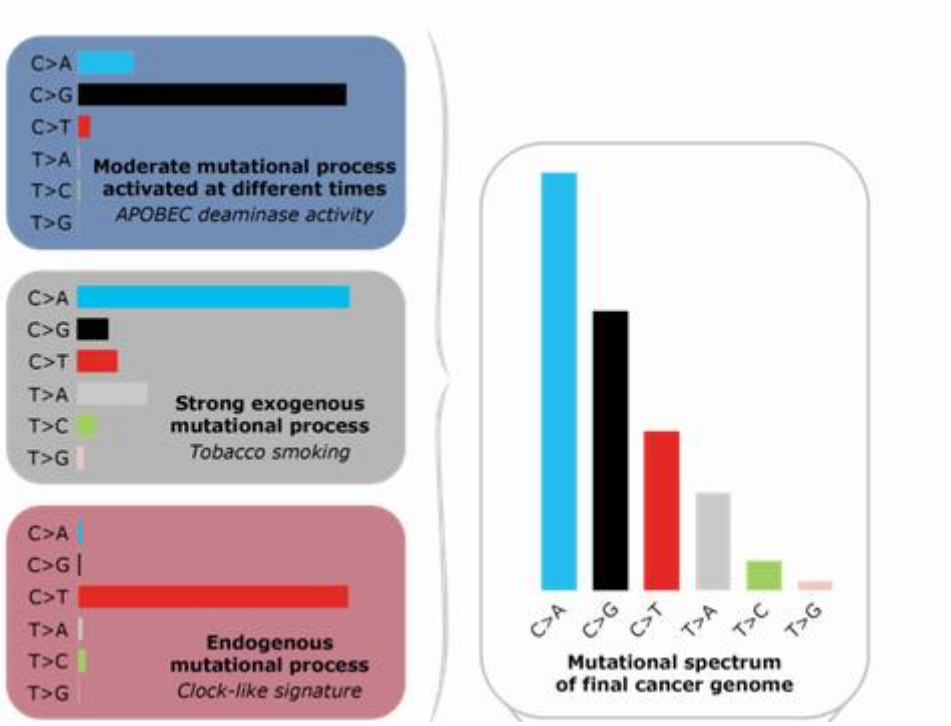


TruSight™ Oncology 500



Illumina					PierianDx
FFPE specimens	Sample	Library prep and enrichment	Sequence	Variant calling	Interpretation and reporting
Supports multiple tissue types	Commercial DNA/RNA* extraction kits	TruSight Oncology UMI kit DNA Probes (523 genes) RNA* Probes (55 genes) Automatable workflow	NextSeq™ System	TruSight Oncology 500 Local App	Powered by PierianDx Clinical Genomics Workspace

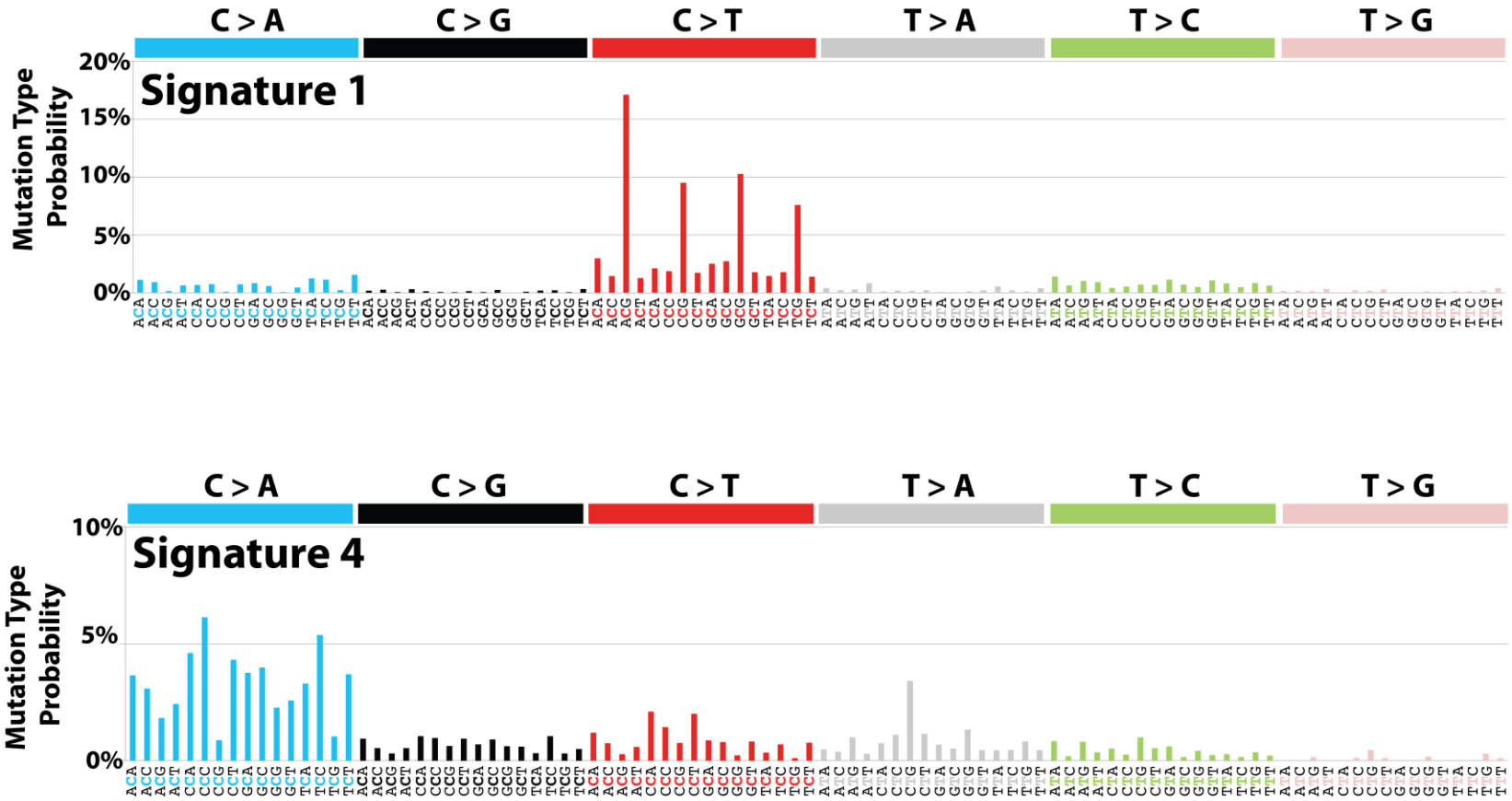
Mutational Signatures



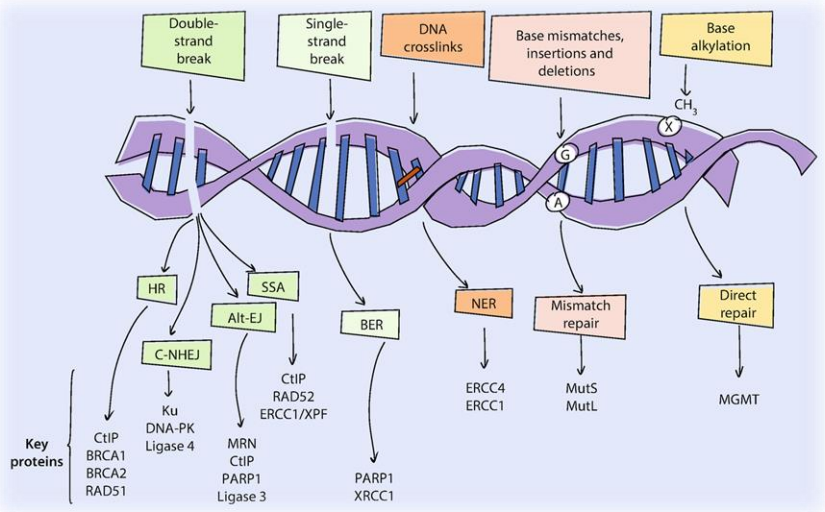
https://cancer.sanger.ac.uk/signatures/

Mutational signatures

Endogenous mutational process initiated by spontaneous deamination of 5-methylcytosine

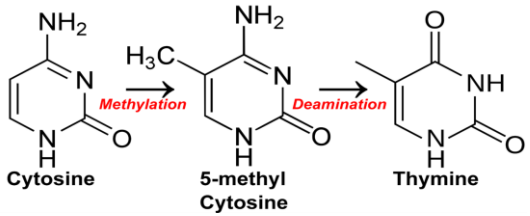


Genomic instability



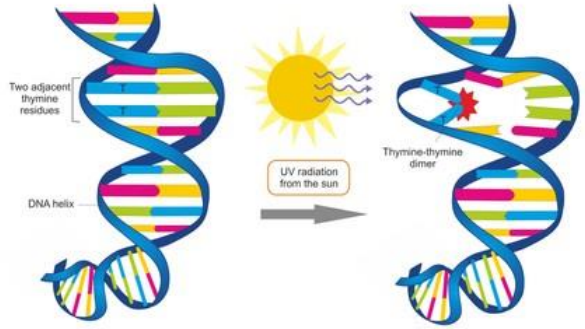
„Spontaneous“ mutations (aging and inflamation)

CpG island



Exogenous mutagens

- Smoking
- UV light
- Alkylating agents
- aflatoxin



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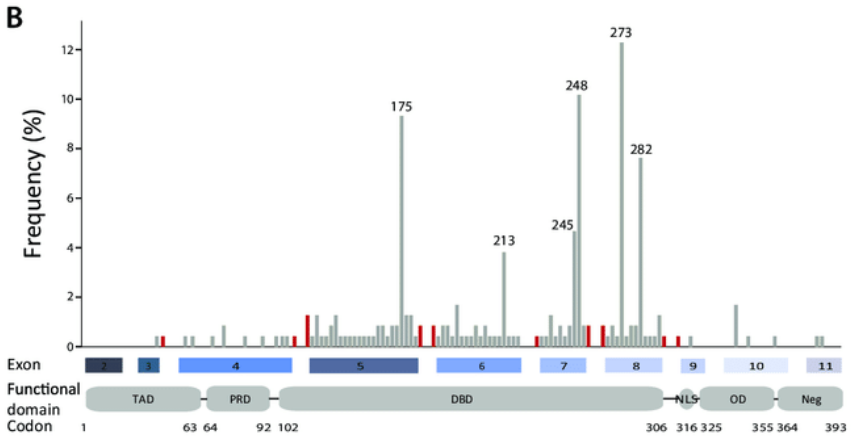
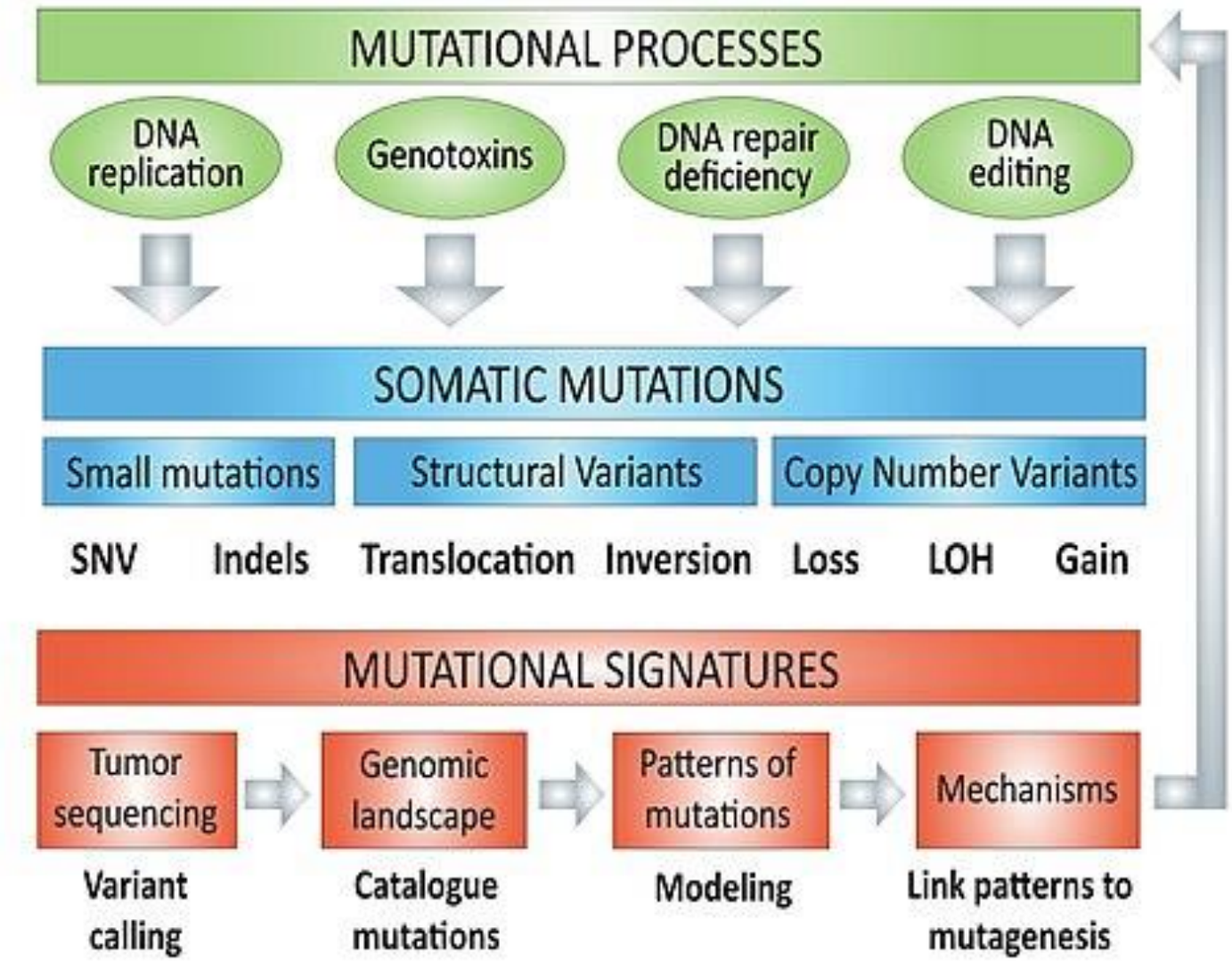
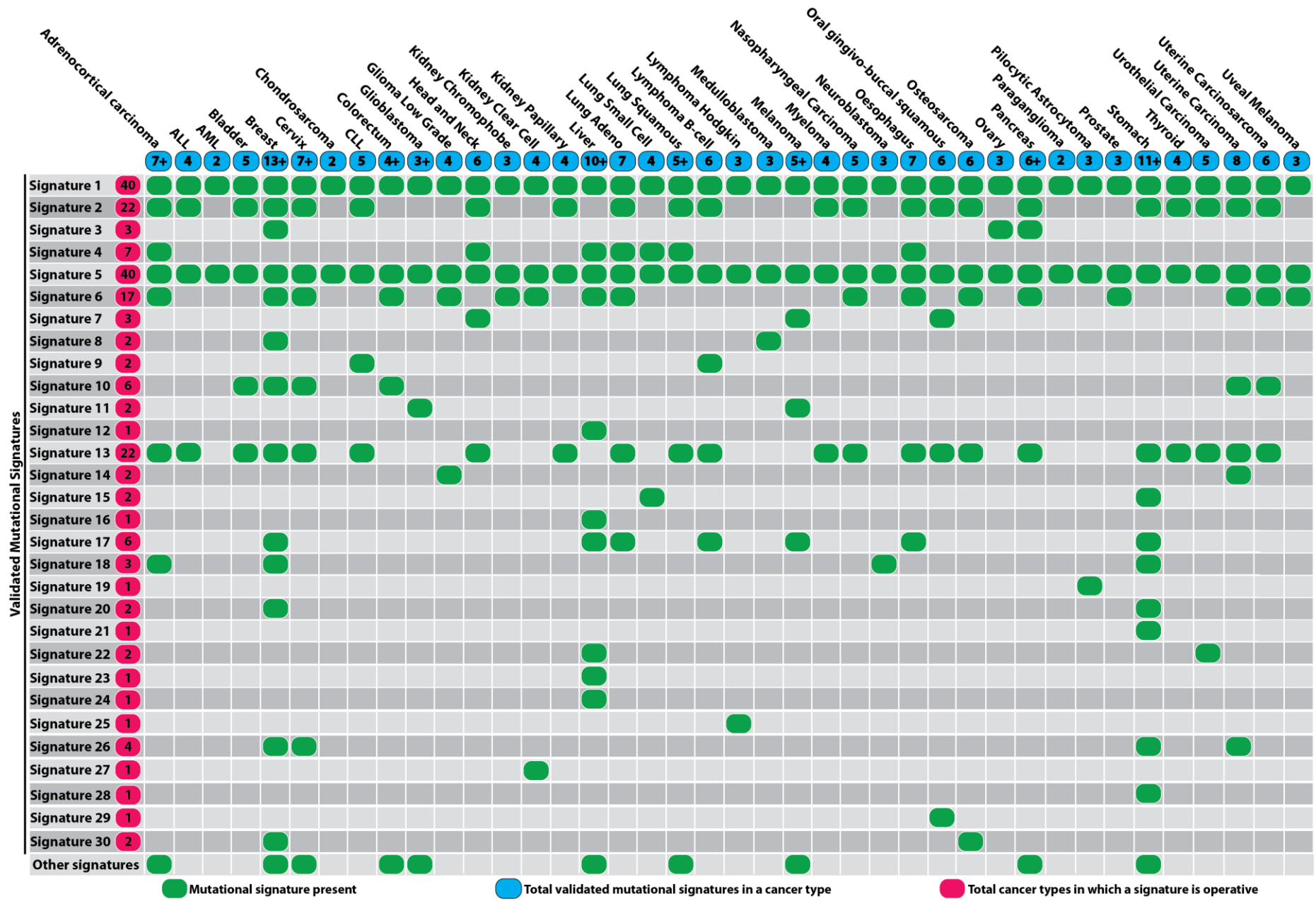
Mutation pattern
Mutational signatures



IDENTIFICATION OF MUTATIONAL SIGNATURES



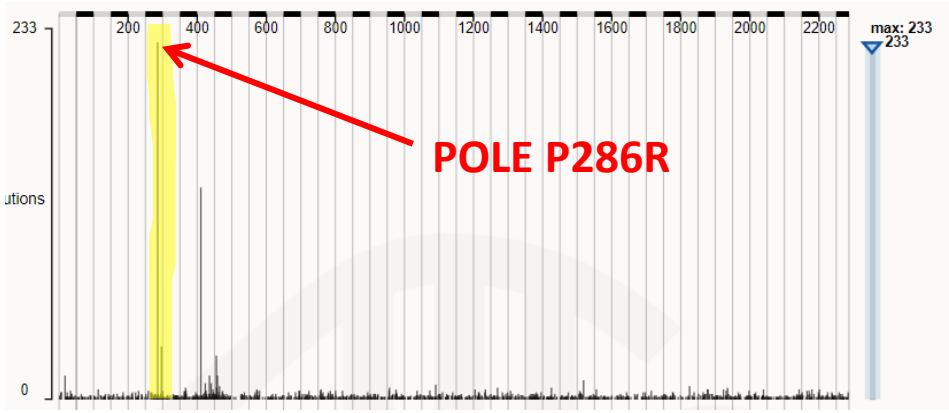

Adrenocortical carcinoma
ALL
AML
Bladder
Breast
Cervix
Chondrosarcoma
CLL
Colorectum
Glioblastoma
Glioma Low Grade
Head and Neck
Kidney Chromophobe
Kidney Clear Cell
Kidney Papillary
Liver
Lung Adeno
Lung Small Cell
Lung Squamous
Lymphoma B-cell
Lymphoma Hodgkin
Medulloblastoma
Melanoma
Myeloma
Nasopharyngeal Carcinoma
Neuroblastoma
Oesophagus
Oral gingivo-buccal squamous
Osteosarcoma
Ovary
Pancreas
Paraganglioma
Pilocytic Astrocytoma
Prostate
Stomach
Thyroid
Urothelial Carcinoma
Uterine Carcinoma
Uterine Carcinosarcoma
Uveal Melanoma
7+ 4 2 5 13+ 7+ 2 5 4+ 3+ 4 6 3 4 4 10+ 7 4 5+ 6 3 3 5+ 4 5 3 7 6 6 3 6+ 2 3 3 11+ 4 5 8 6 3
Validated Mutational Signatures
Signature 1 40
Signature 2 22
Signature 3 3
Signature 4 7
Signature 5 40
Signature 6 17
Signature 7 3
Signature 8 2
Signature 9 2
Signature 10 6
Signature 11 2
Signature 12 1
Signature 13 22
Signature 14 2
Signature 15 2
Signature 16 1
Signature 17 6
Signature 18 3
Signature 19 1
Signature 20 2
Signature 21 1
Signature 22 2
Signature 23 1
Signature 24 1
Signature 25 1
Signature 26 4
Signature 27 1
Signature 28 1
Signature 29 1
Signature 30 2
Other signatures
Mutational signature present
Total validated mutational signatures in a cancer type
Total cancer types in which a signature is operative

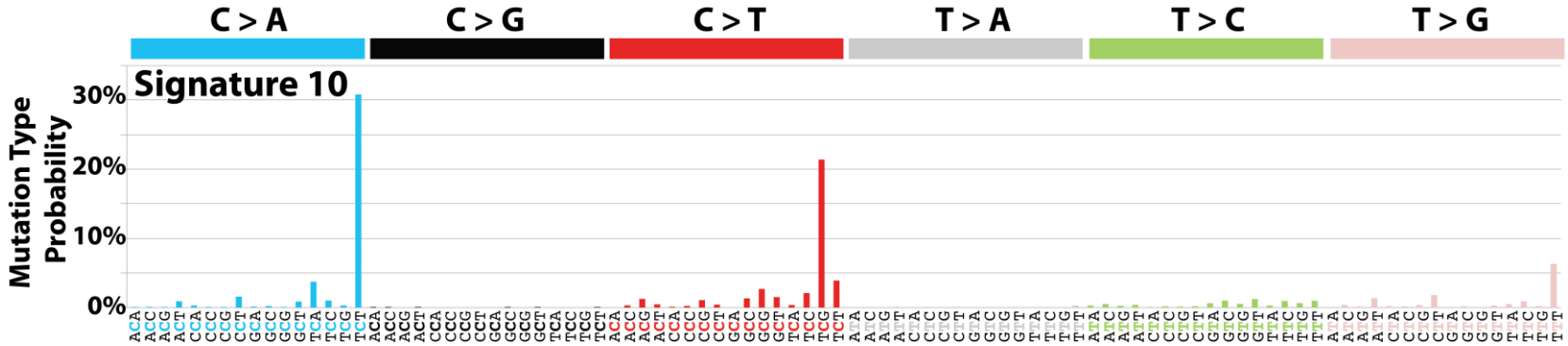
CLINICALLY RELEVANT RESULTS

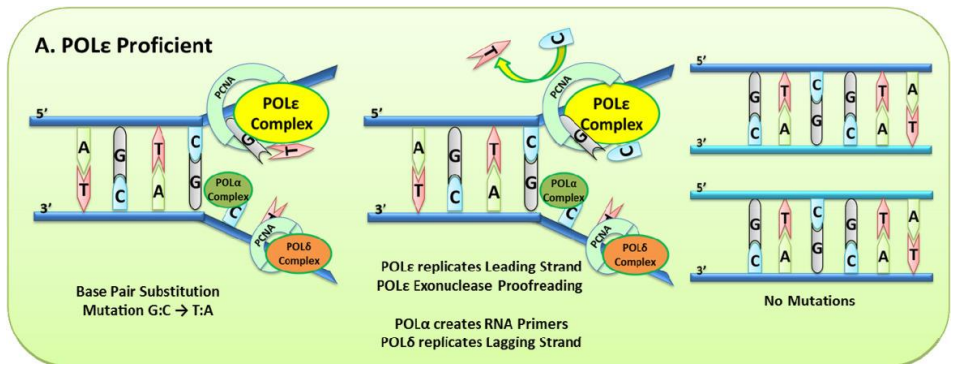
Tumor Mutational Burden: 242.632568
# of unstable microsatellite loci: 3
Usable MSI Sites (%): 2.7%

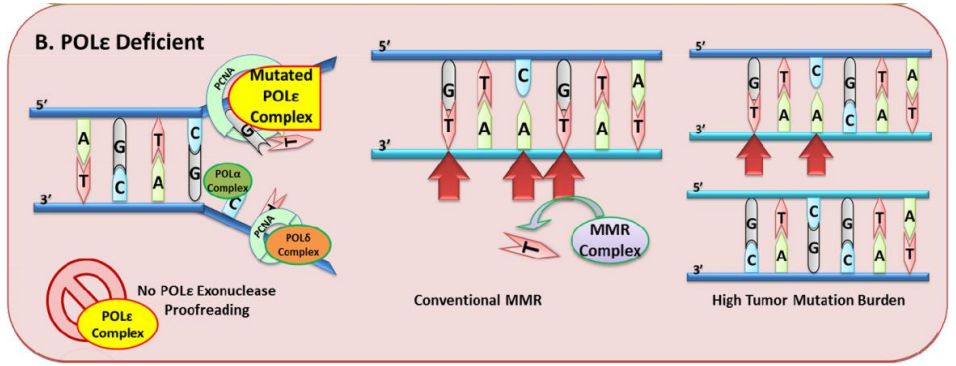
Tier I - Variants of Strong Clinical Significance

Level A
MSH2
p.E580*
c.1738G>T
NM_000251.2
VAF: 28.2%

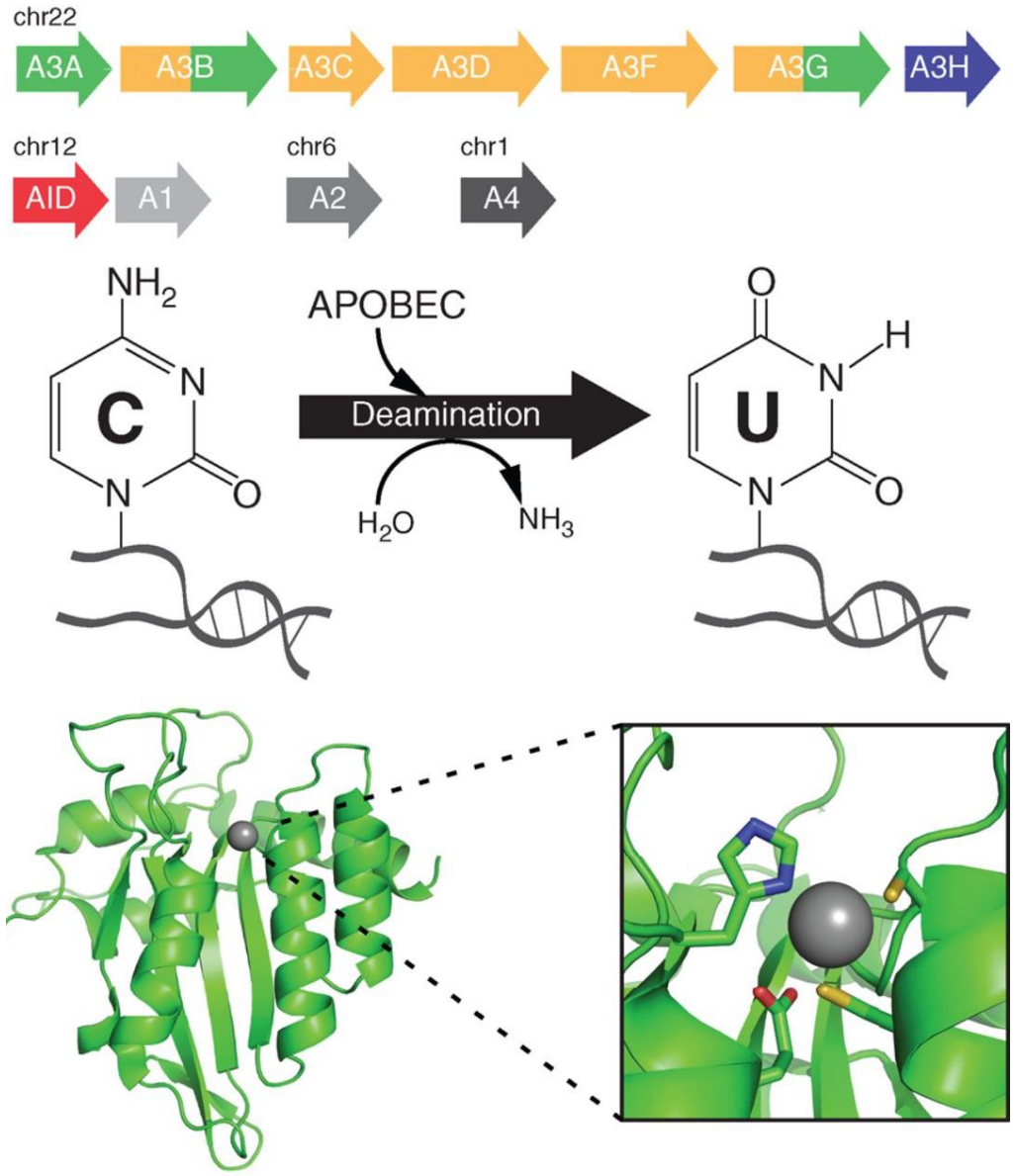






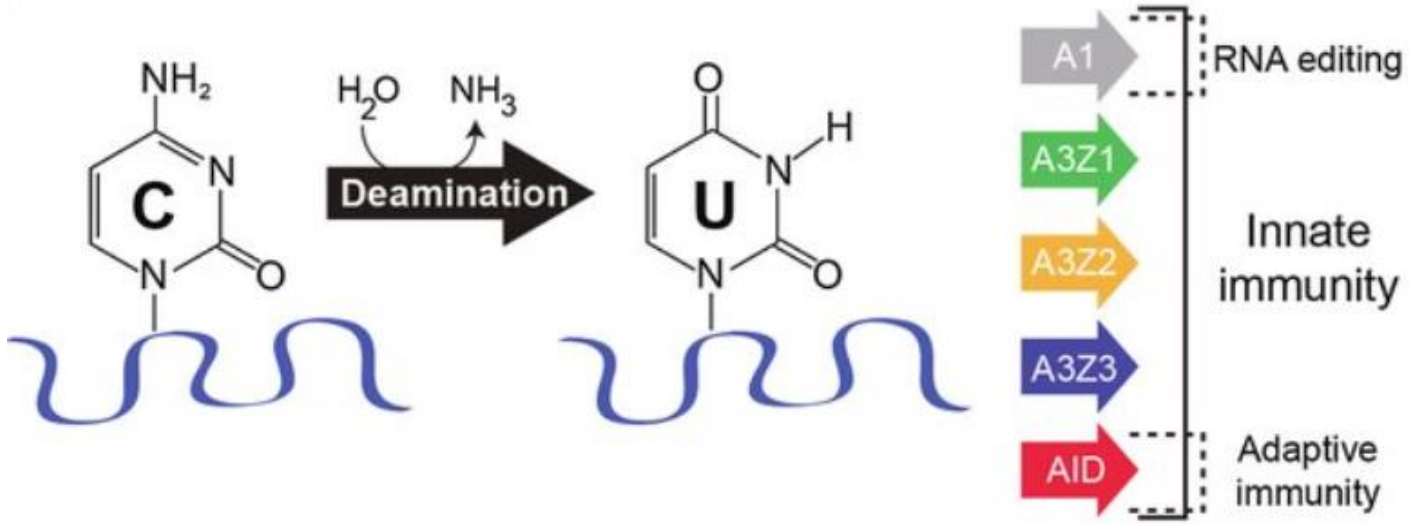


Cells are able to actively induce mutations



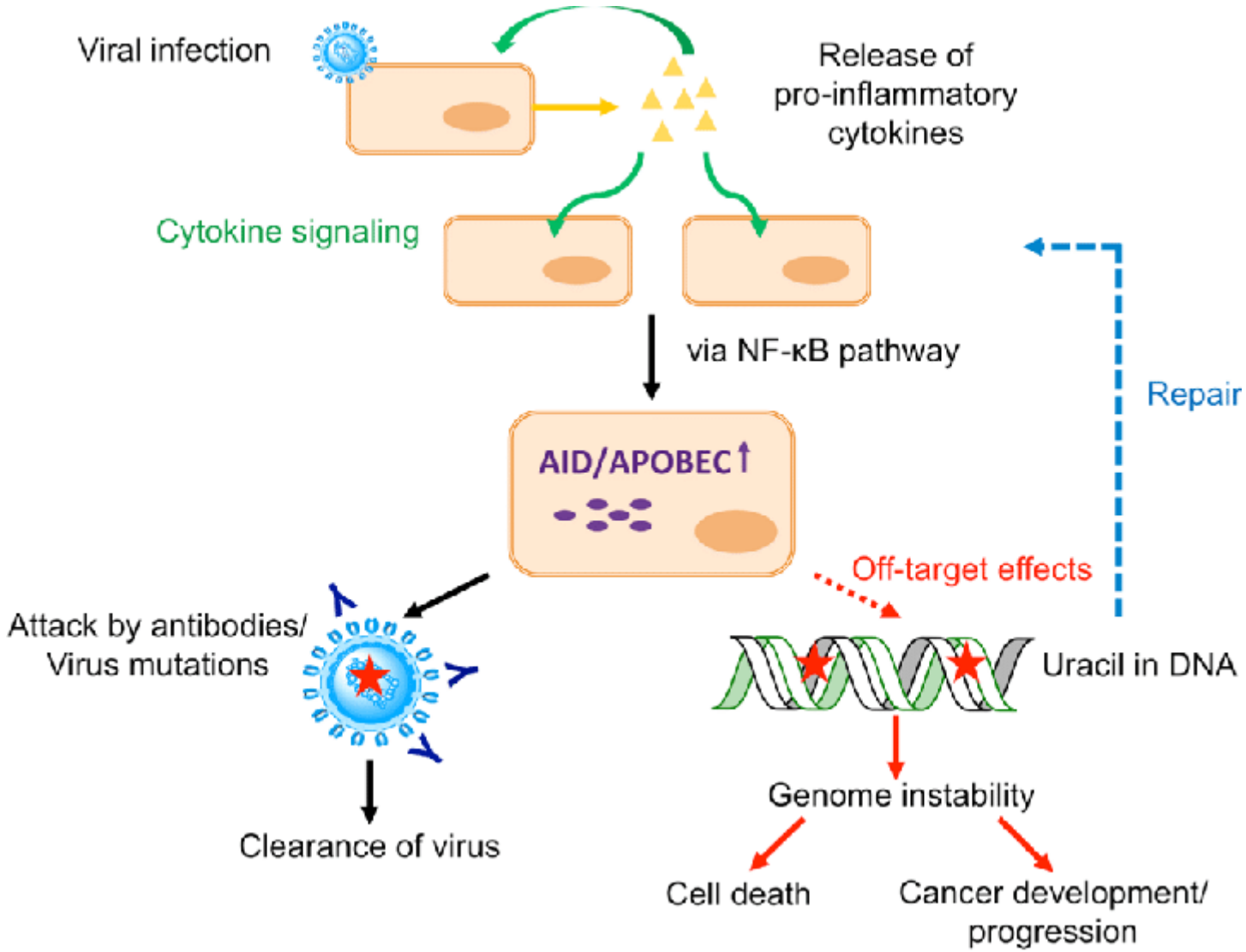
APOBEC family members

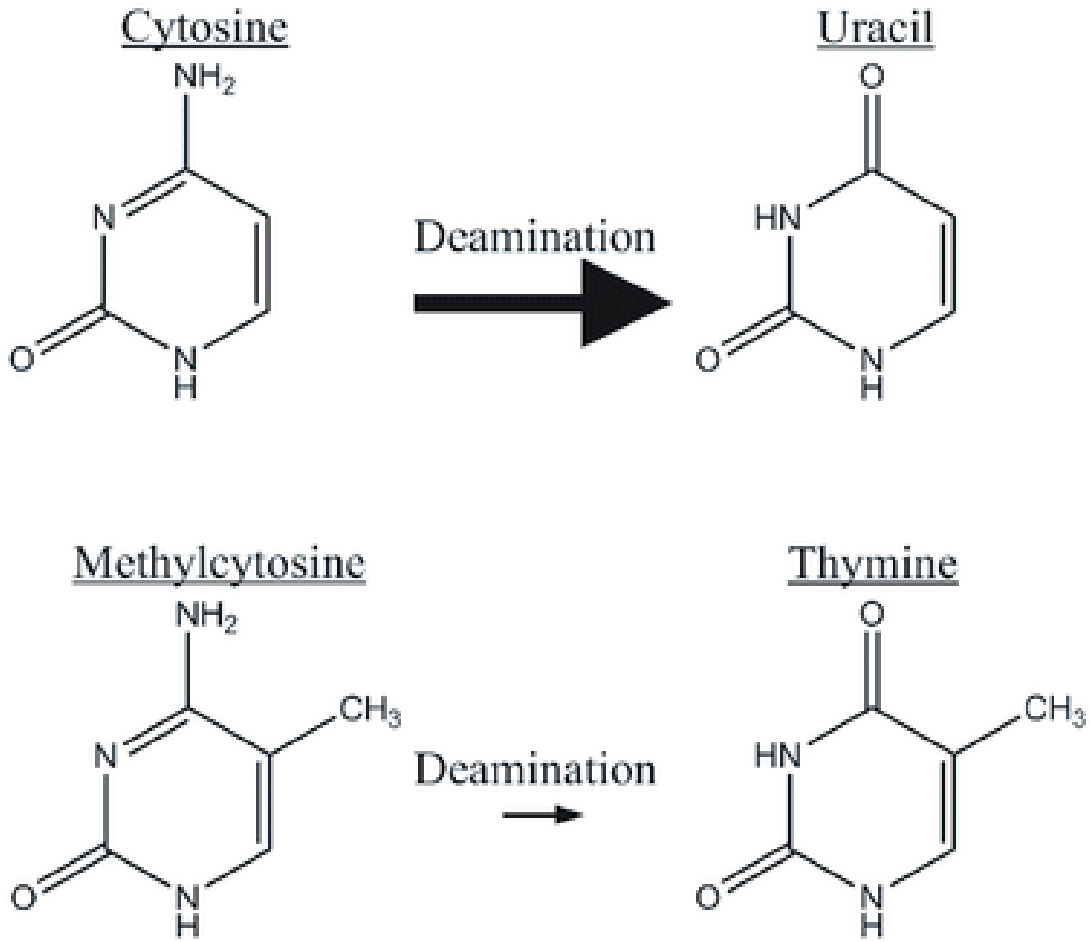
- APOBEC ("apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like") is a family of evolutionarily conserved cytidine deaminases.
- Discovered due to their ability to eliminate HIV infection
- When misregulated, are a major source of mutation in numerous cancer types.
- AID is a part of adaptive immunity; it is responsible for hypermutation of variable immunoglobulin regions in lymphocytes



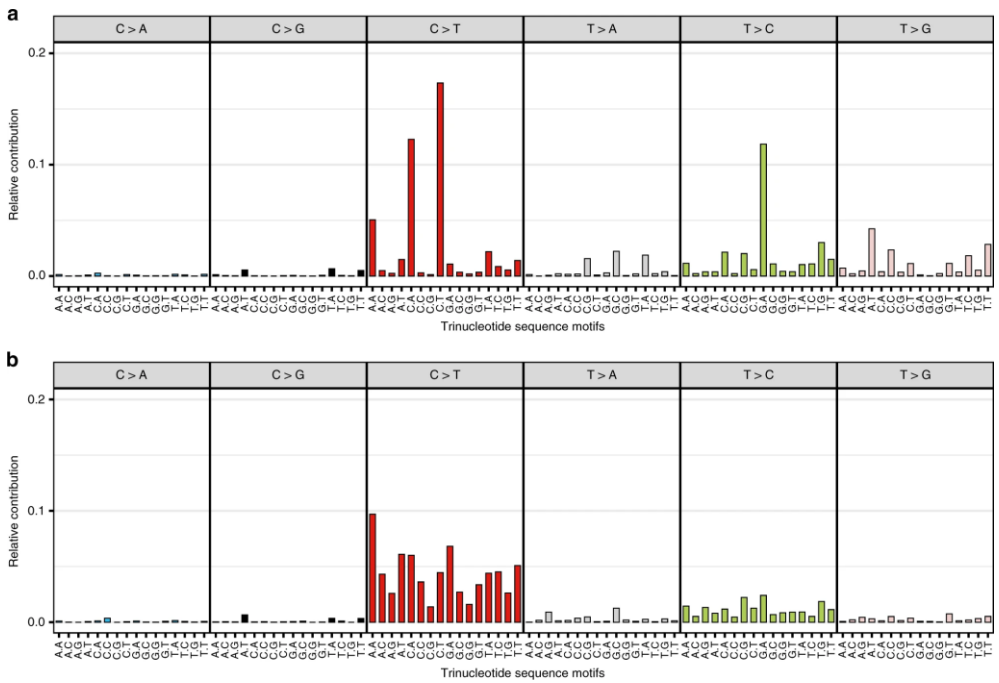
APOBEC1
APOBEC2
APOBEC3A
APOBEC3B
APOBEC3C
APOBEC3D
APOBEC3F
APOBEC3G
APOBEC3H
APOBEC4
AID (activation induced deaminase)

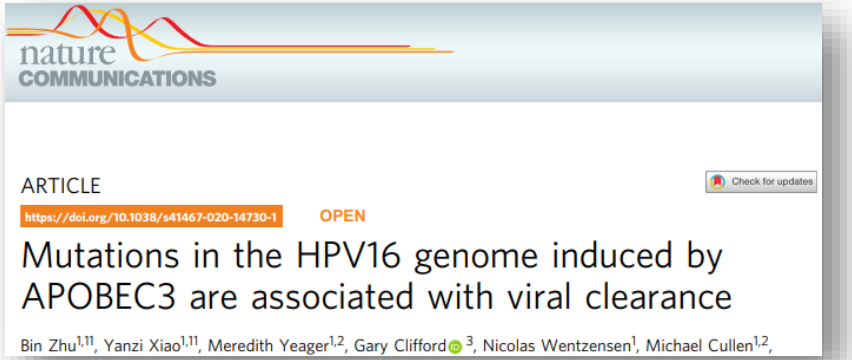
Cells are able to actively induce mutations

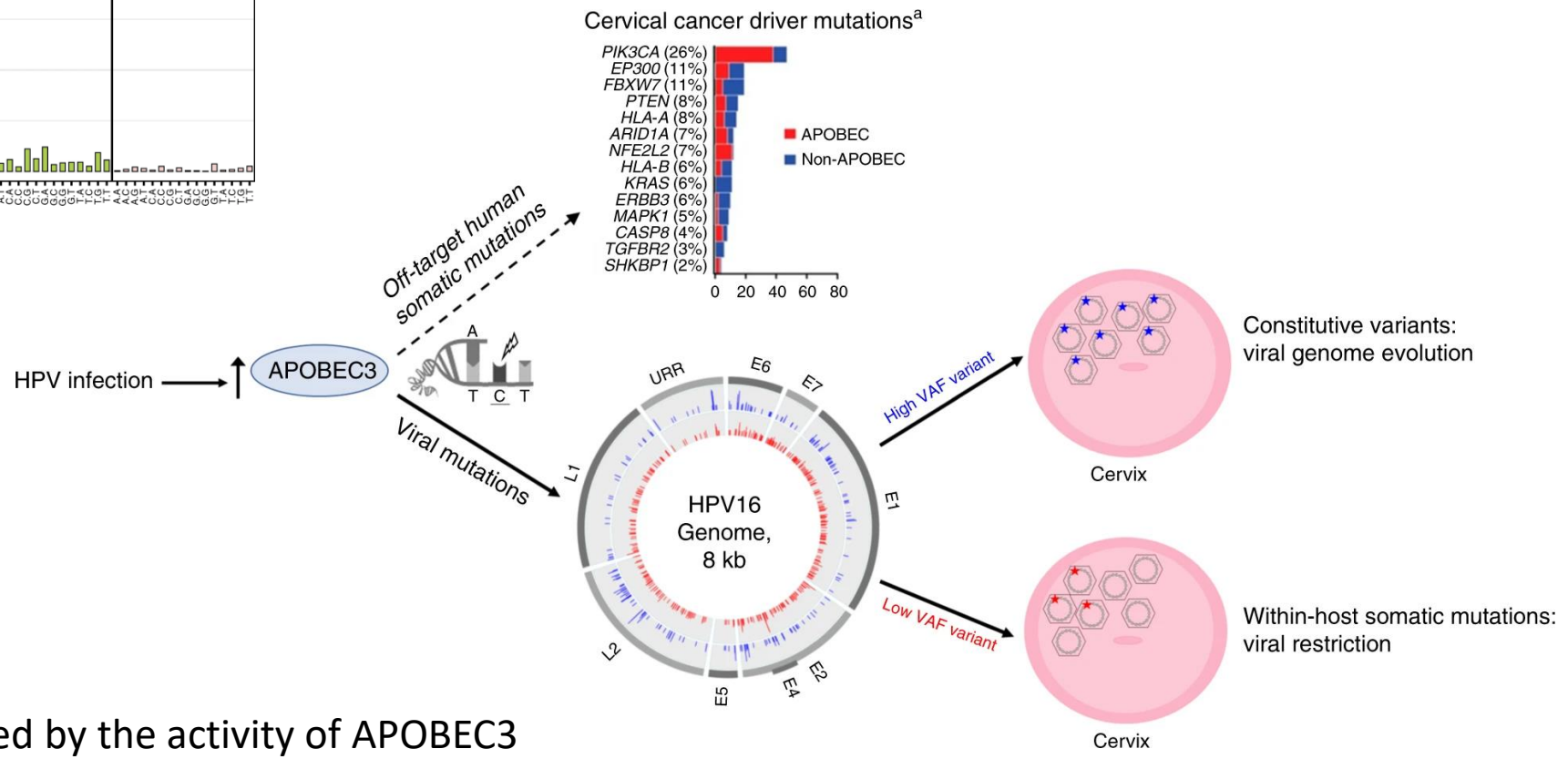



Cytosine
NH2
N
O
N
H
Deamination
Uracil
O
HN
O
N
H
Methylcytosine
NH2
CH3
N
O
N
H
Deamination
Thymine
O
CH3
HN
O
N
H

The role of APOBEC3







The effects of mutations induced by the activity of APOBEC3

Mechanisms of innate immunity

(fast but non-specific response)

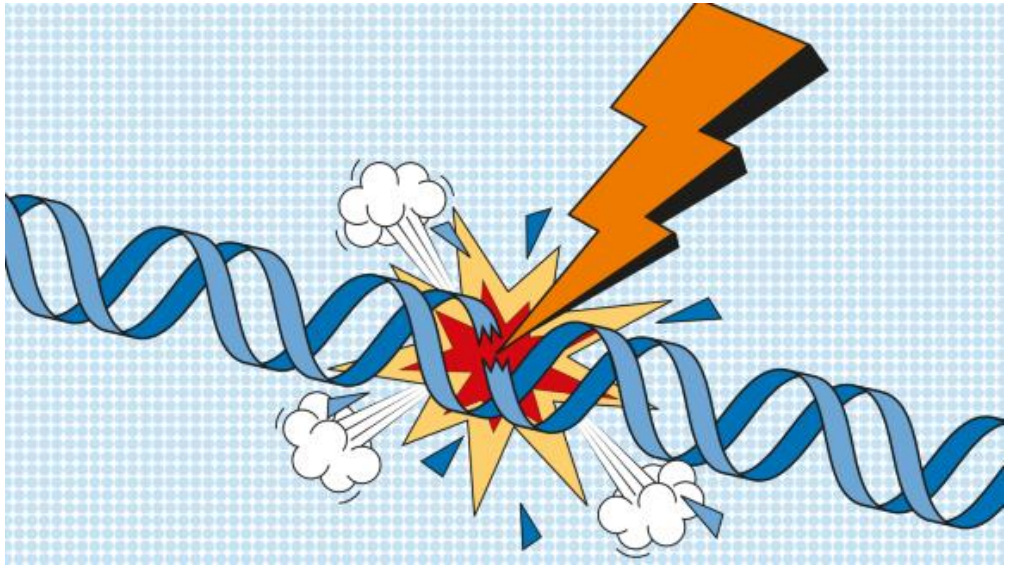
Detection of pathogenic microorganisms

- Membrane receptors
- Intracellular receptors of foreign nucleic acids
- Cytokine signalling

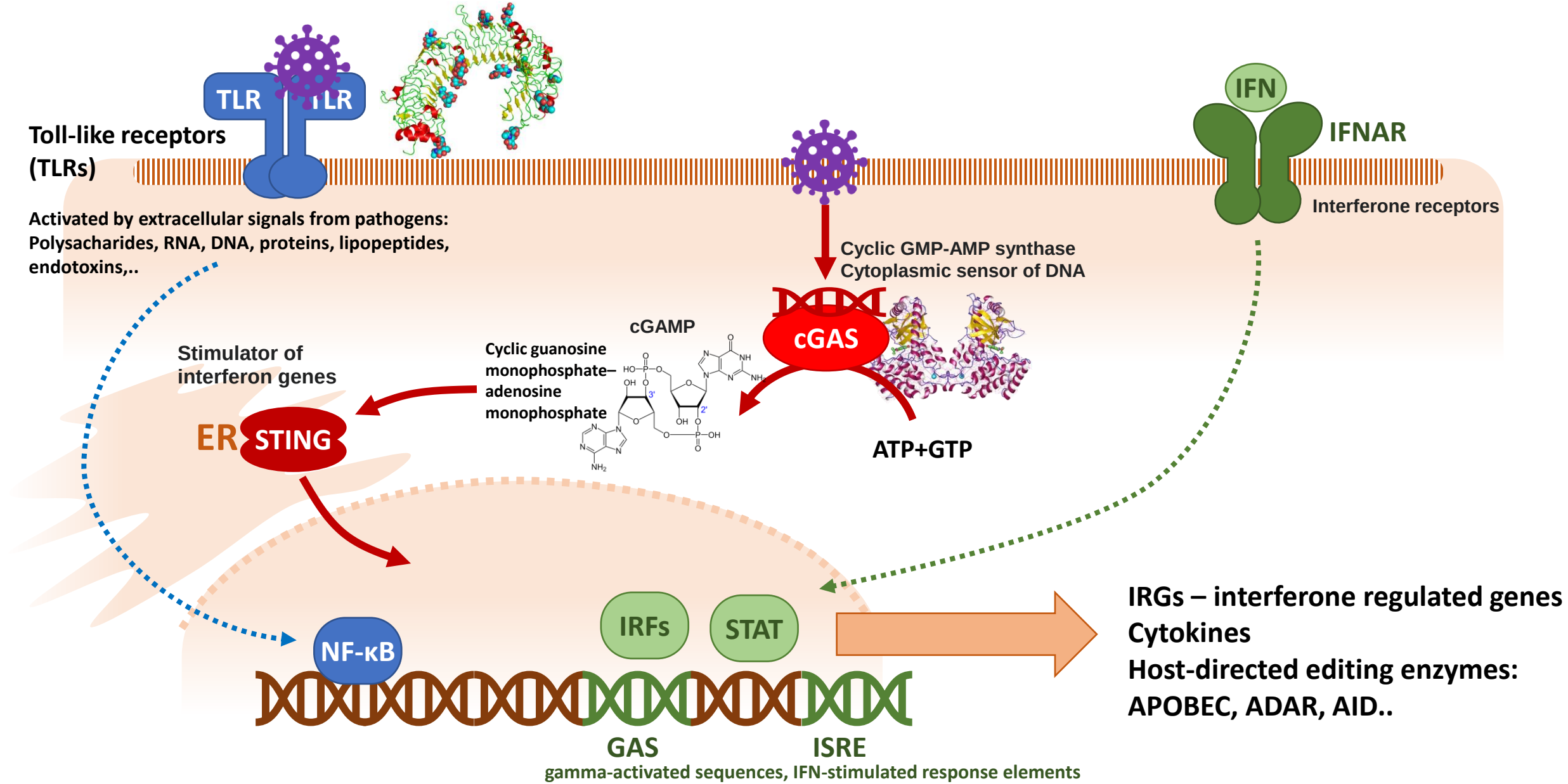
Intracellular signalling pathways

Activation of transcription / gene expression

- Expression of cytokines
- Activation of specific immune response
- Elimination of microorganisms
- Use of gene



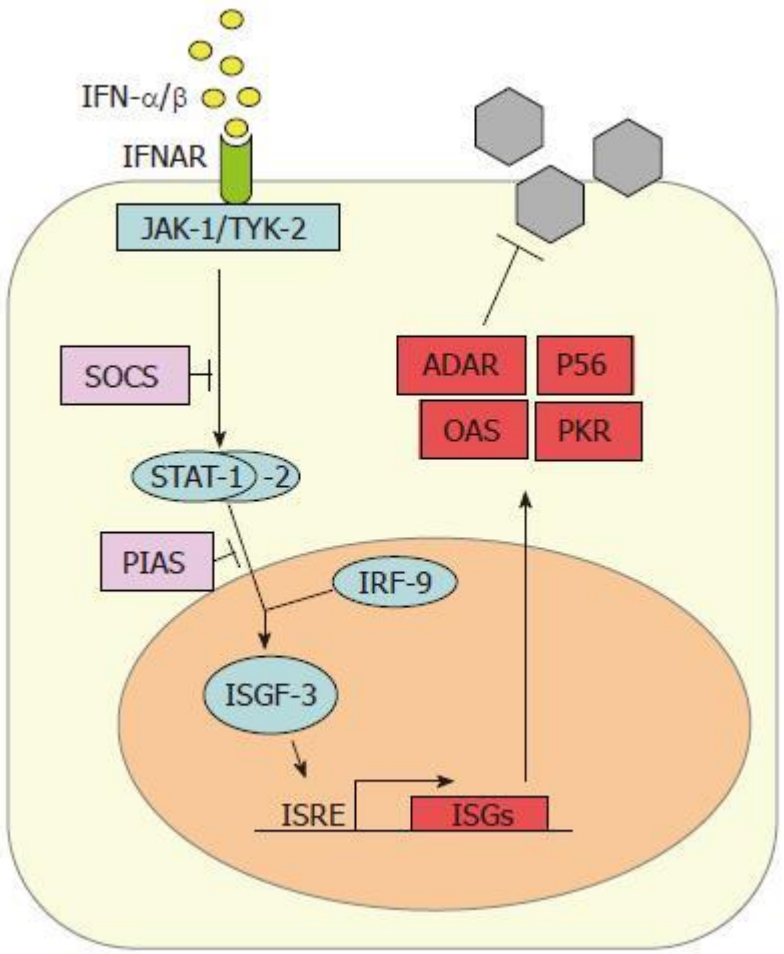
Mechanisms of innate immunity

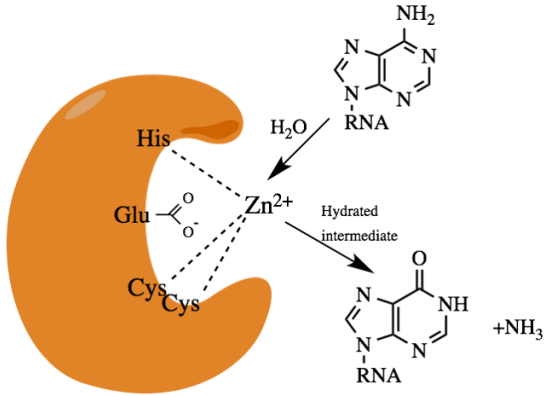


ADAR - adenosine deaminase acting on RNA

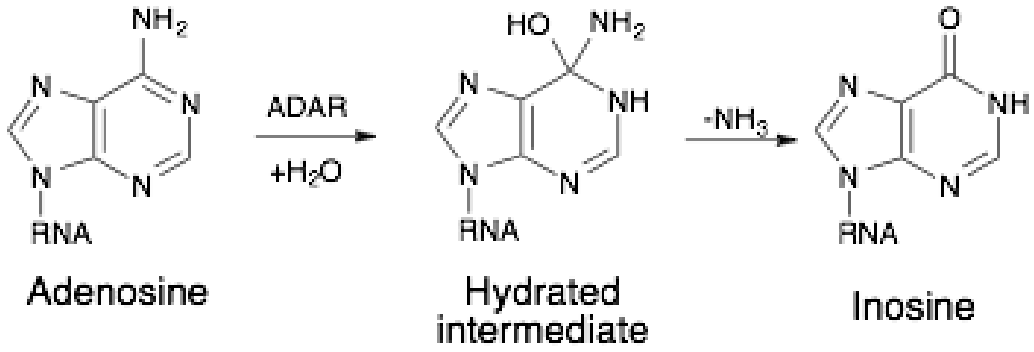
responsible for binding to double stranded RNA (dsRNA) and converting adenosine (A) to inosine (I) by deamination. ADAR protein is a RNA-binding protein, which functions in RNA-editing through post-transcriptional modification of mRNA transcripts by changing the nucleotide content of the RNA

Dysregulation associated with: Aicardi–Goutières syndrome and Bilateral Striatal Necrosis/Dystonia, cancer (HCC)





Mechanism of action:
Deamination of adenosine to inosine
Destabilize RNA
Mismatch pairing when replicated



viruses

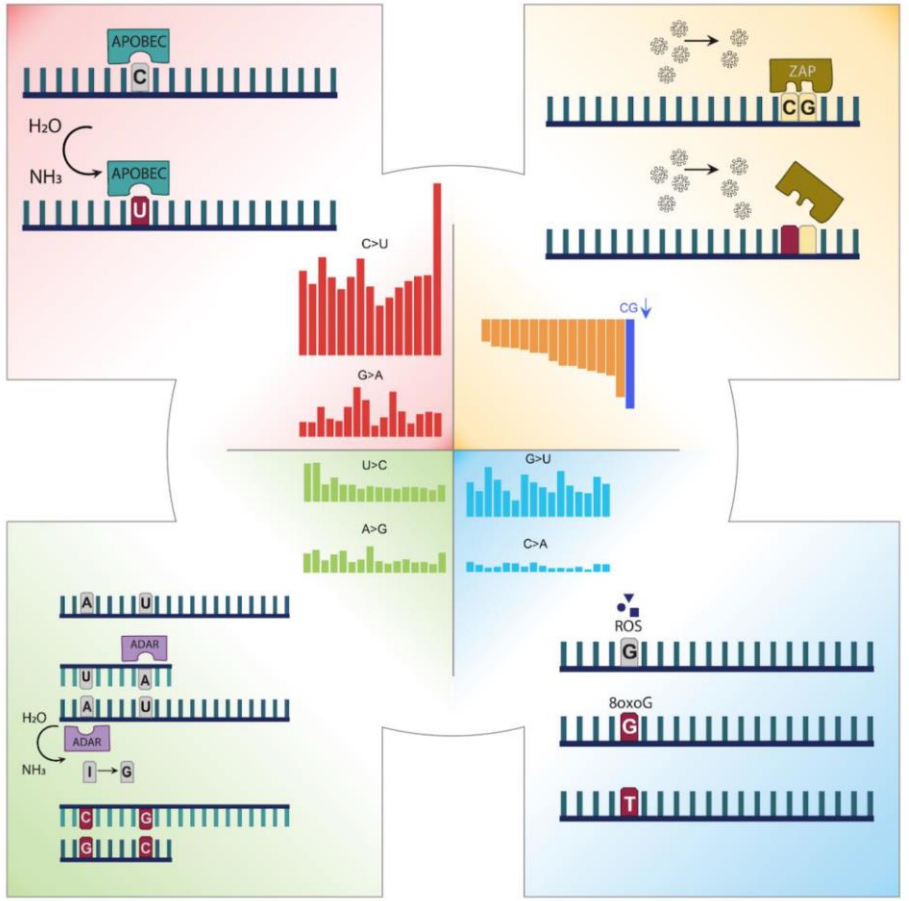
MDPI

Article

The Mutation Profile of SARS-CoV-2 Is Primarily Shaped by the Host Antiviral Defense

Cem Azgari, Zeynep Kilinc, Berk Turhan, Defne Circi and Ogun Adebali *

The results suggest that the heterogeneous mutation patterns are mainly reflections of host (i) antiviral mechanisms that are achieved through APOBEC, ADAR, and ZAP proteins, and (ii) probable adaptation against reactive oxygen species.



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Host-directed editing of the SARS-CoV-2 genome

Tobias Mourier [a, **, 1], Mukhtar Sadykov [a, 1], Michael J. Carr [b, c], Gabriel Gonzalez [b, c], William W. Hall [b, c, d], Arnab Pain [a, c, *]

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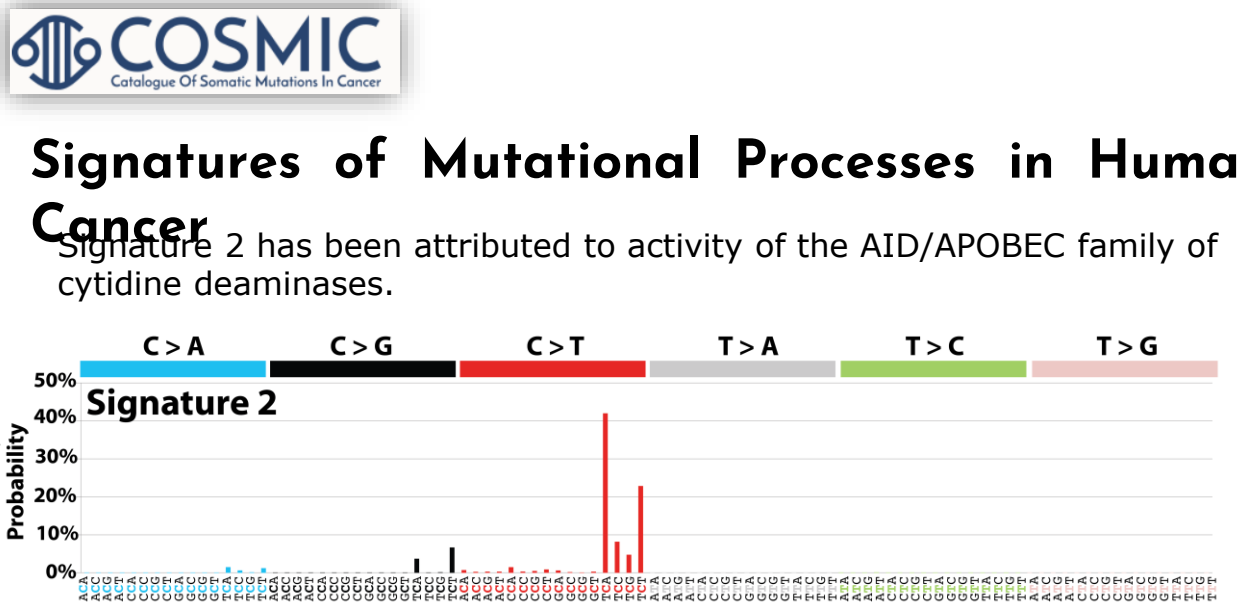
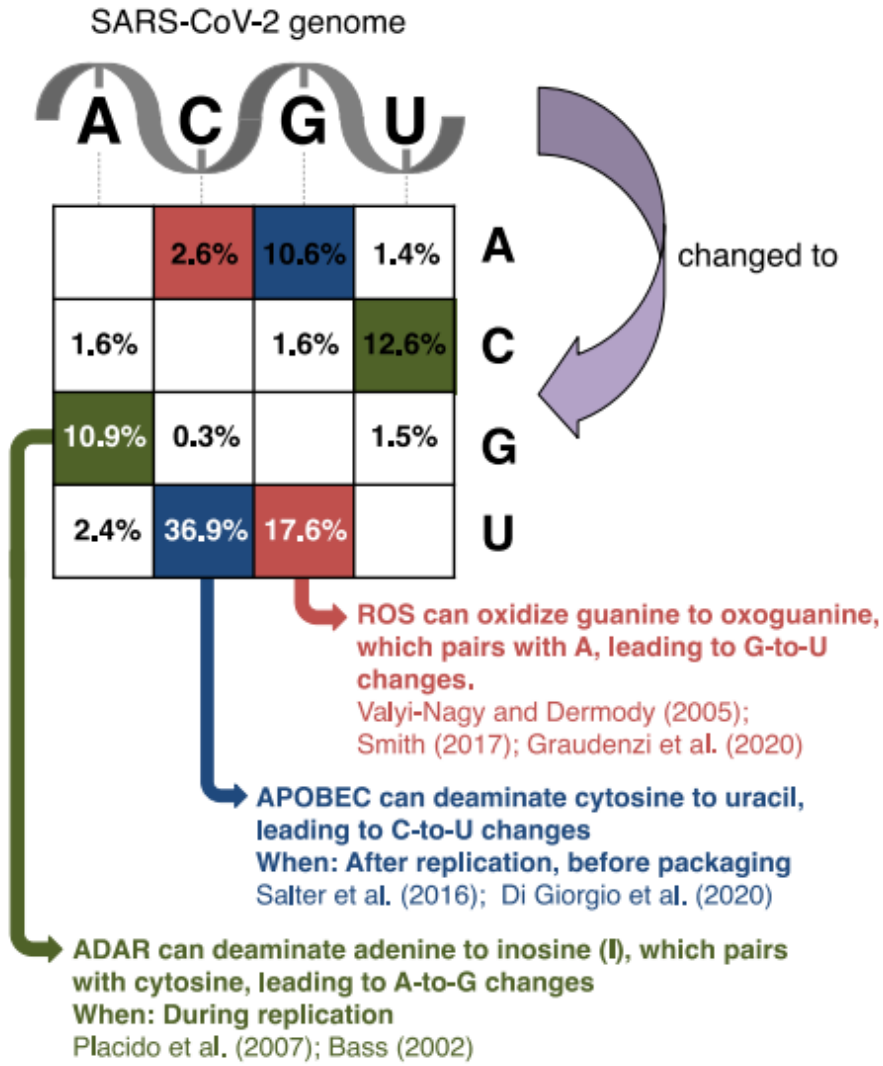
[d] Global Virus Network (GVN), 801 W. Baltimore St., Baltimore, MD, 21201, USA



Signatures of Mutational Processes in Human Cancer

Signature 2 has been attributed to activity of the AID/APOBEC family of cytidine deaminases.



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Article

Six reference-quality genomes reveal evolution of bat adaptations

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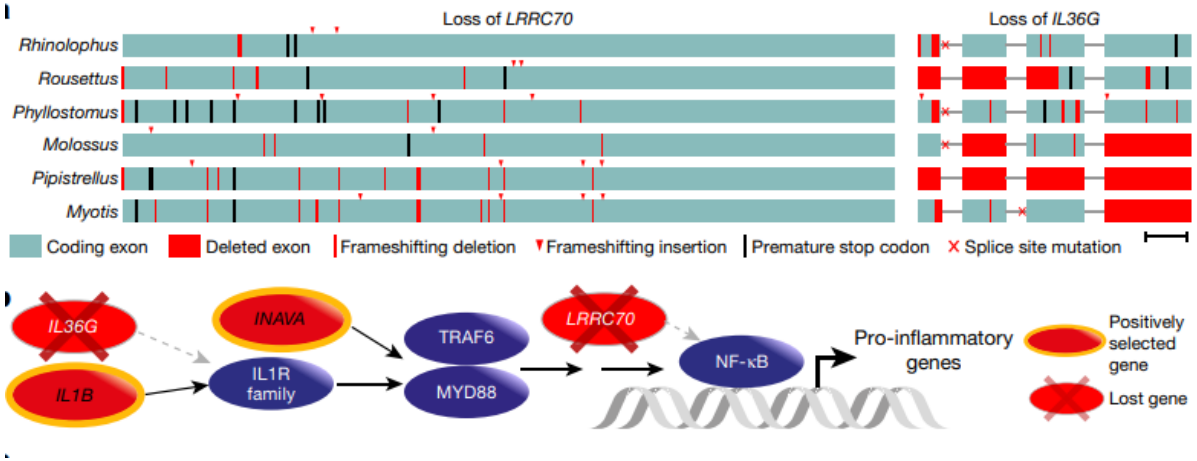
David Jebb[1,2,3,25], Zixia Huang[4,25], Martin Pippel[1,3,25], Graham M. Hughes[4], Ksenia Lavrichenko[5], Paolo Devanna[5], Sylke Winkler[1], Lars S. Jermiin[4,6,7], Emilia C. Skirmuntt[8], Aris Katzourakis[8], Lucy Burkitt-Gray[9], David A. Ray[10], Kevin A. M. Sullivan[10], Juliana G. Roscito[1,2,3], Bogdan M. Kirilenko[1,2,3], Liliana M. Dávalos[11,12], Angelique P. Corthals[13], Megan L. Power[4], Gareth Jones[14], Roger D. Ransome[14], Dina K. N. Dechmann[15,16,17], Andrea G. Locatelli[4], Sébastien J. Puechmaille[18,19], Olivier Fedrigo[20], Erich D. Jarvis[20,21,22], Michael Hiller[1,2,3,26]✉, Sonja C. Vernes[5,23,26]✉, Eugene W. Myers[1,3,24,26]✉ & Emma C. Teeling[4,26]✉

Loss of genes in NF-κB signalling pathway



Expansion of the APOBEC3 gene locus