Mutational processes moulding the genomes of human cancers

wellcome trust sanger institute

International Cancer Genome Consortium

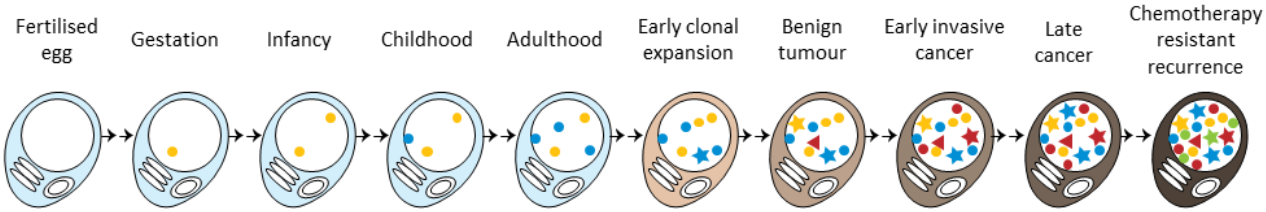
From fertilised egg to cancer cell

Chemotherapy resistant recurrence

From fertilised egg to cancer cell

Chemotherapy resistant recurrence

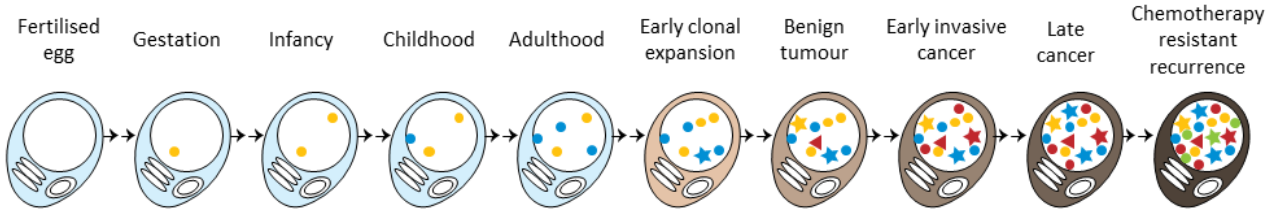
From fertilised egg to cancer cell



Mutational processes

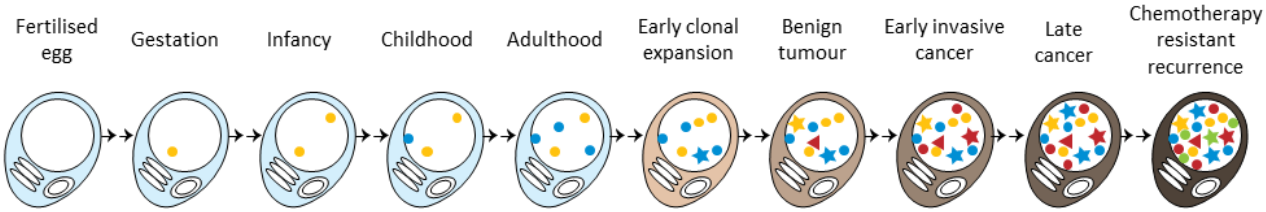
- DNA replication infidelity
- Exogenous exposures
- Endogenous exposures
- Defects of DNA repair
- Chemotherapy

From fertilised egg to cancer cell



From fertilised egg to cancer cell

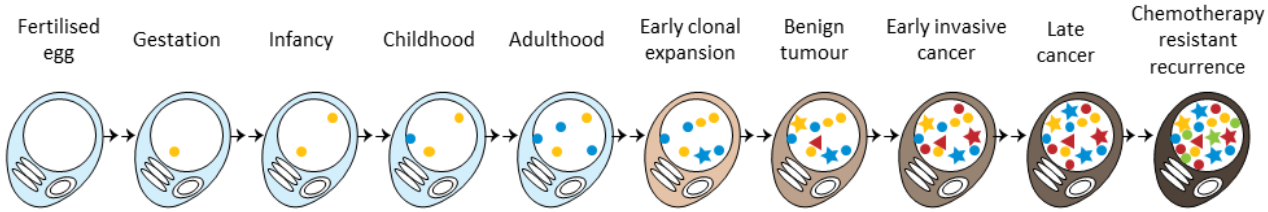
Mutational processes



A

From fertilised egg to cancer cell

Mutational processes



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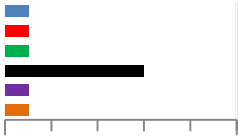

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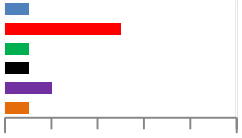

From fertilised egg to cancer cell

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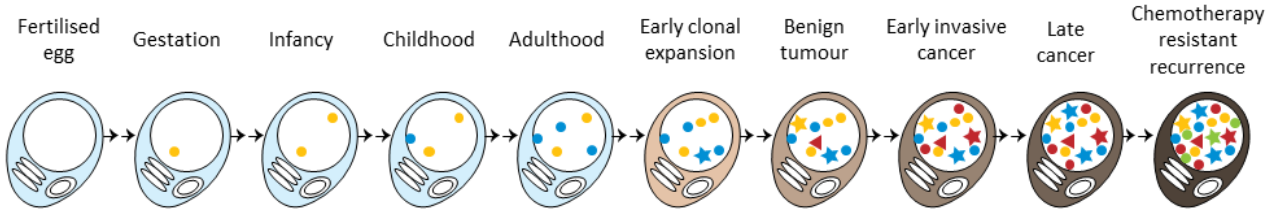

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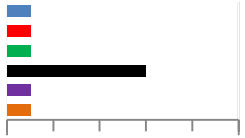

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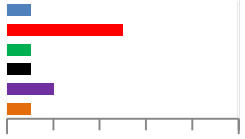

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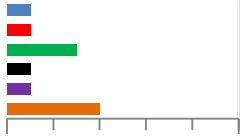
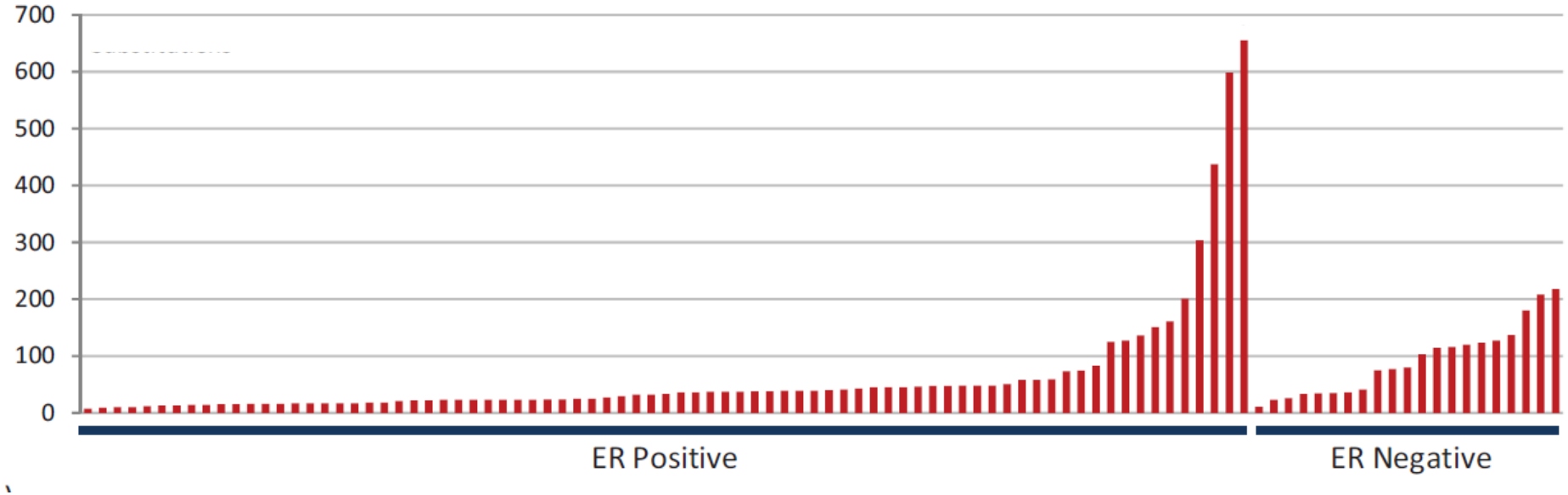


From fertilised egg to cancer cell

Processes of somatic mutation

- Genome-wide
- Localised

Prevalence of base substitutions in 100 breast cancers



Whole genome sequences of 21 breast cancers

ER+, HER2-	5
ER+, HER2+	2
ER-, HER2+	2
ER-, HER2-	3
BRCA1 null	5
BRCA2 null	4
Total	21

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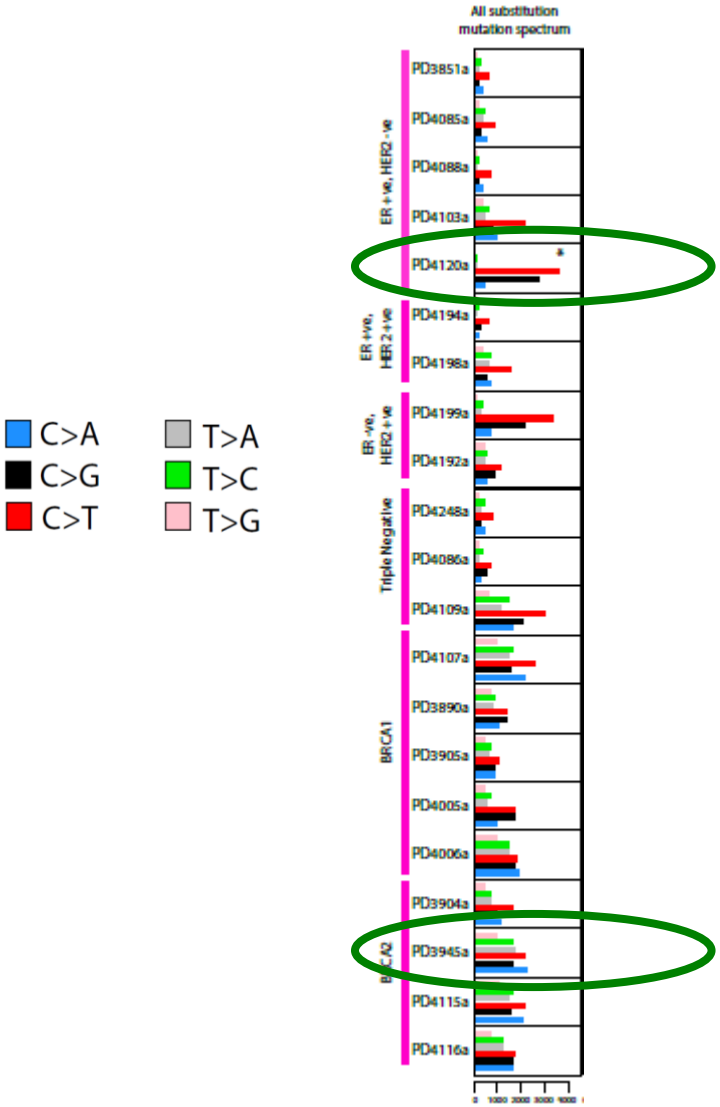
Genome-wide somatic substitutions

183,916

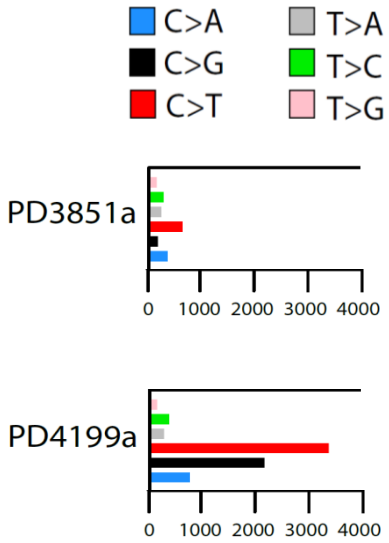
Genome-wide somatic indels

2,877

Mutational spectra of 21 breast cancers



Mutation signatures in breast cancer



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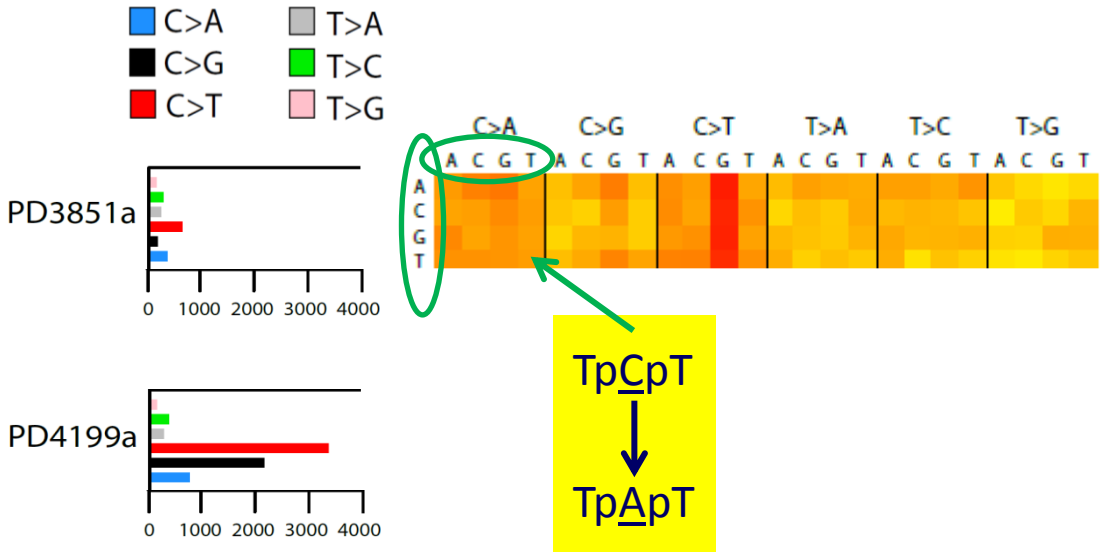

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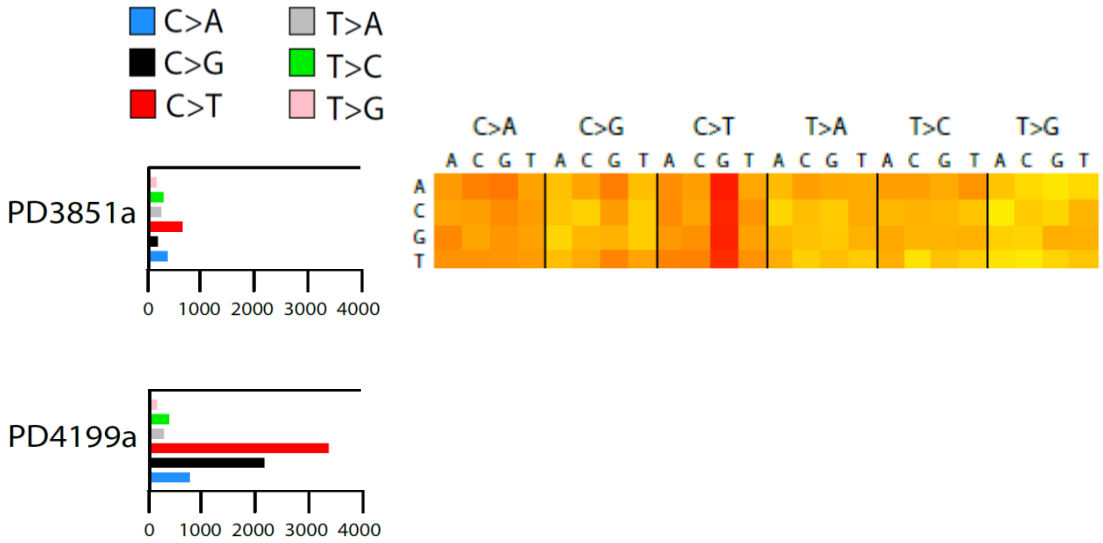

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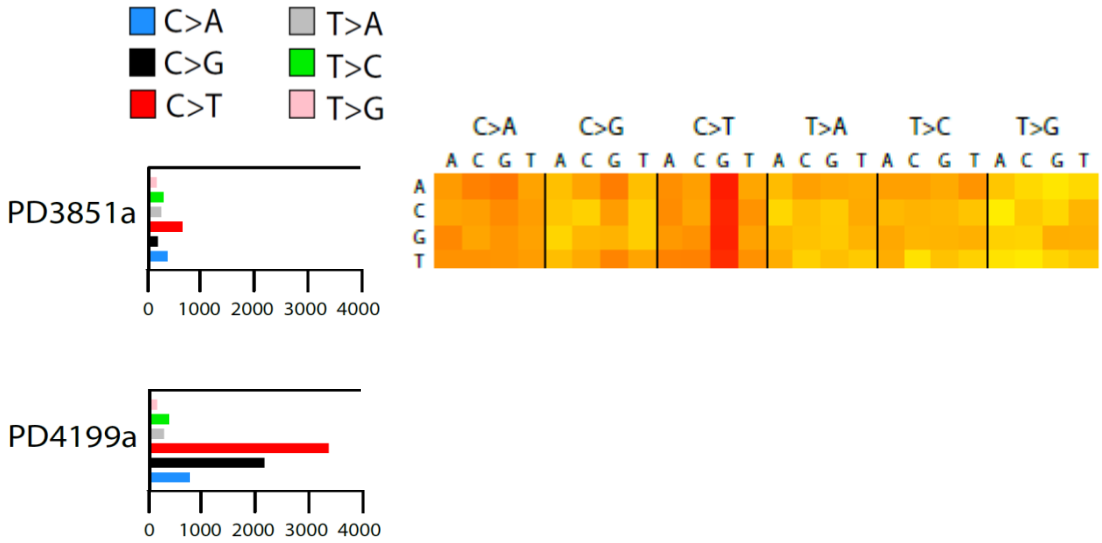
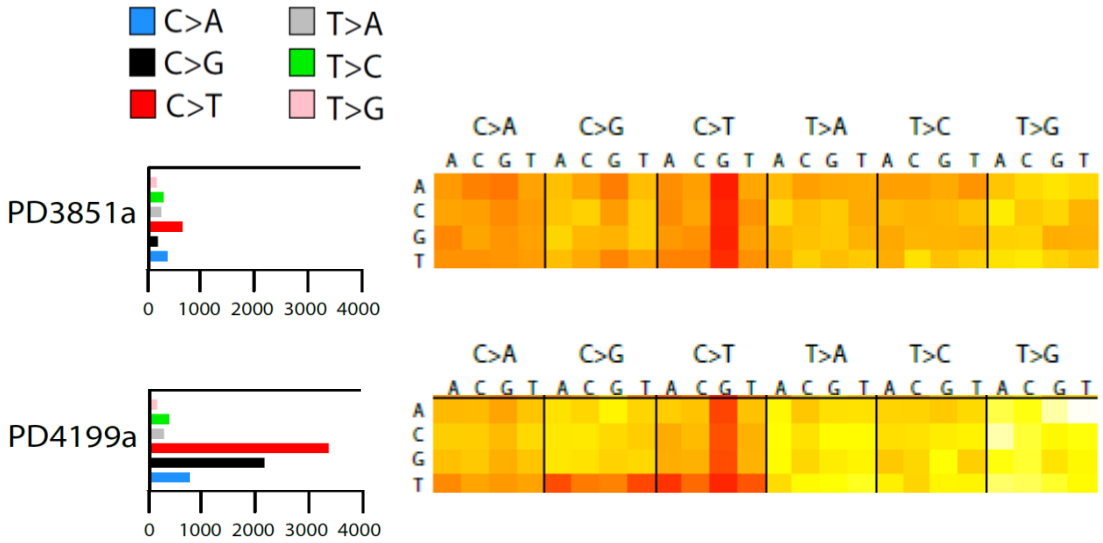


C>T at XpCpG

Mutation signatures in breast cancer



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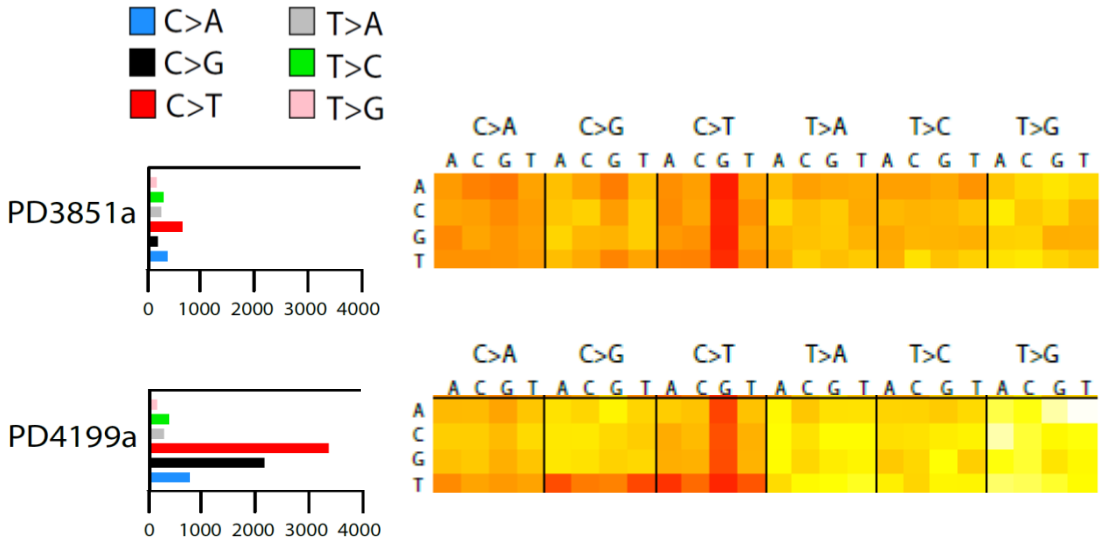
Mutation signatures in breast cancer



C>T at XpCpG

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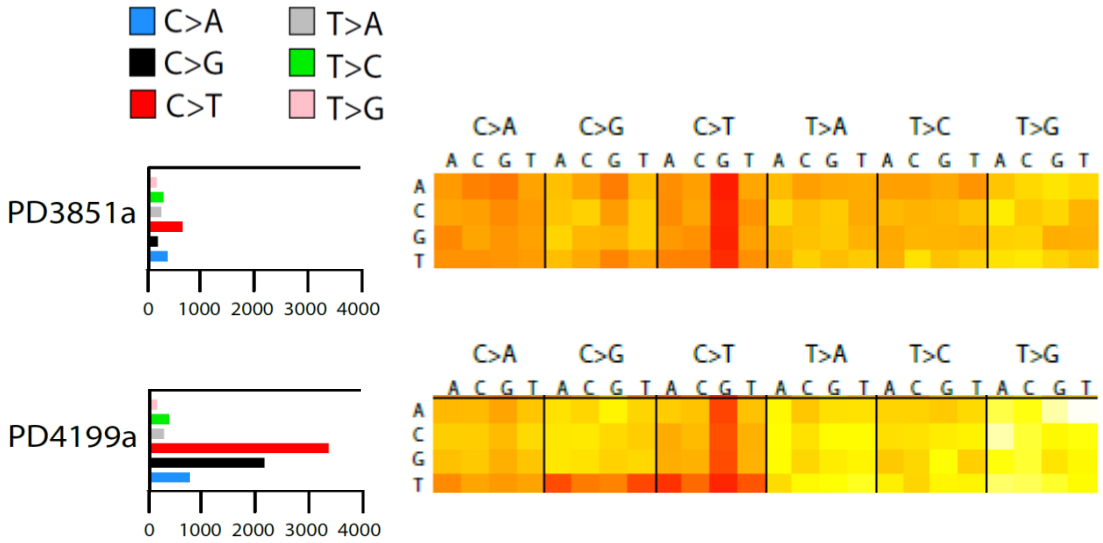
Mutation signatures in breast cancer



C>T at XpCpG

C>T at XpCpG

C>T at TpCpX

C>G at TpCpX

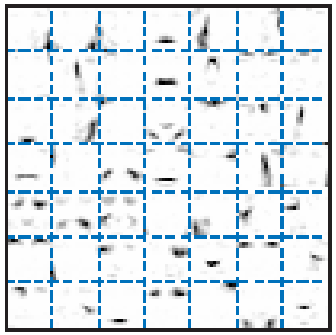
Non-negative matrix factorization (NMF)

Learning the parts of objects by non-negative matrix factorization

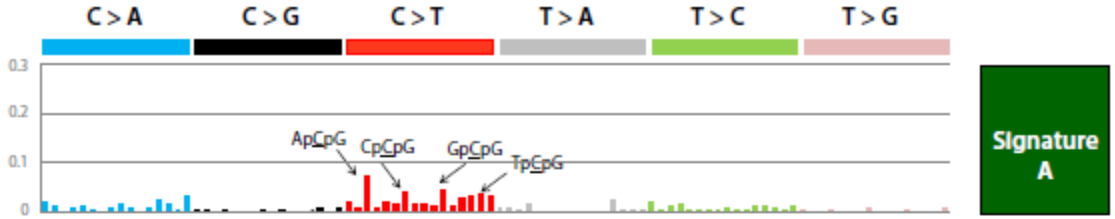
Daniel D. Lee* & H. Sebastian Seung*†

* *Bell Laboratories, Lucent Technologies, Murray Hill, New Jersey 07974, USA*
† *Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA*

Is perception of the whole based on perception of its parts? There is psychological[1] and physiological[2,3] evidence for parts-based representations in the brain, and certain computational theories of object recognition rely on such representations[4,5]. But little is known about how brains or computers might learn the parts of objects. Here we demonstrate an algorithm for non-negative matrix factorization that is able to learn parts of faces and



Mutation signatures detected by non-negative matrix factorization



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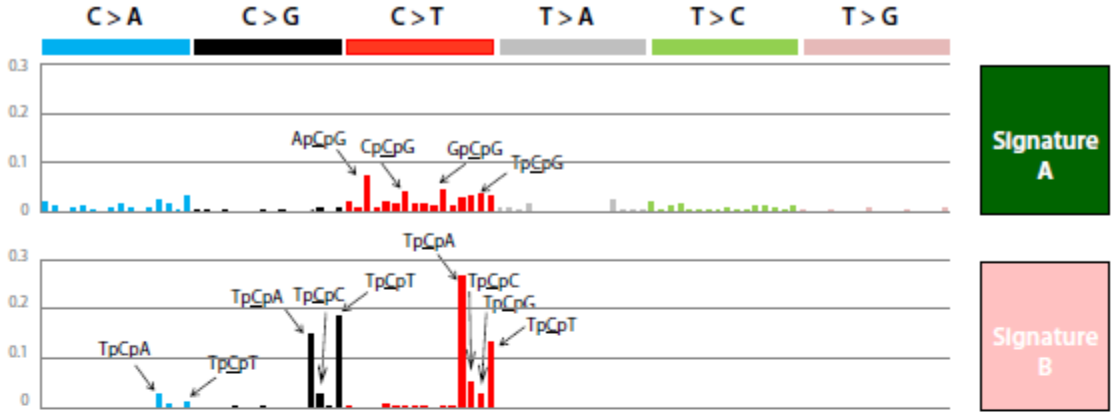

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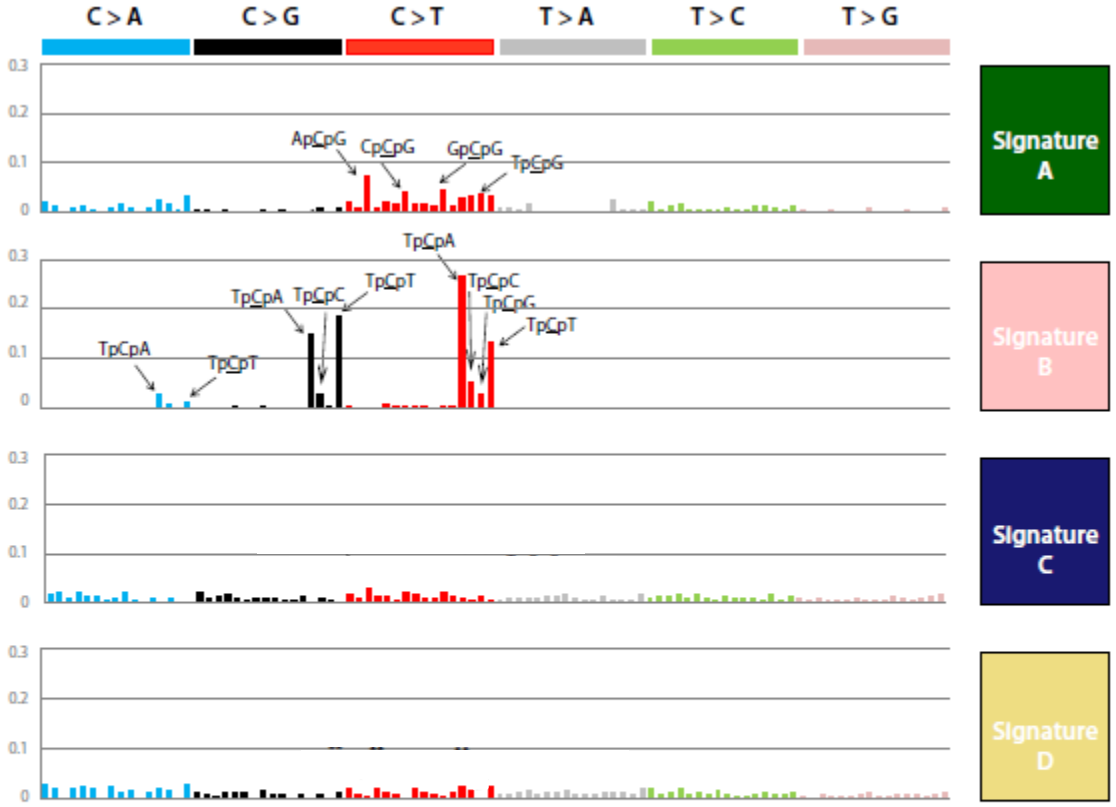

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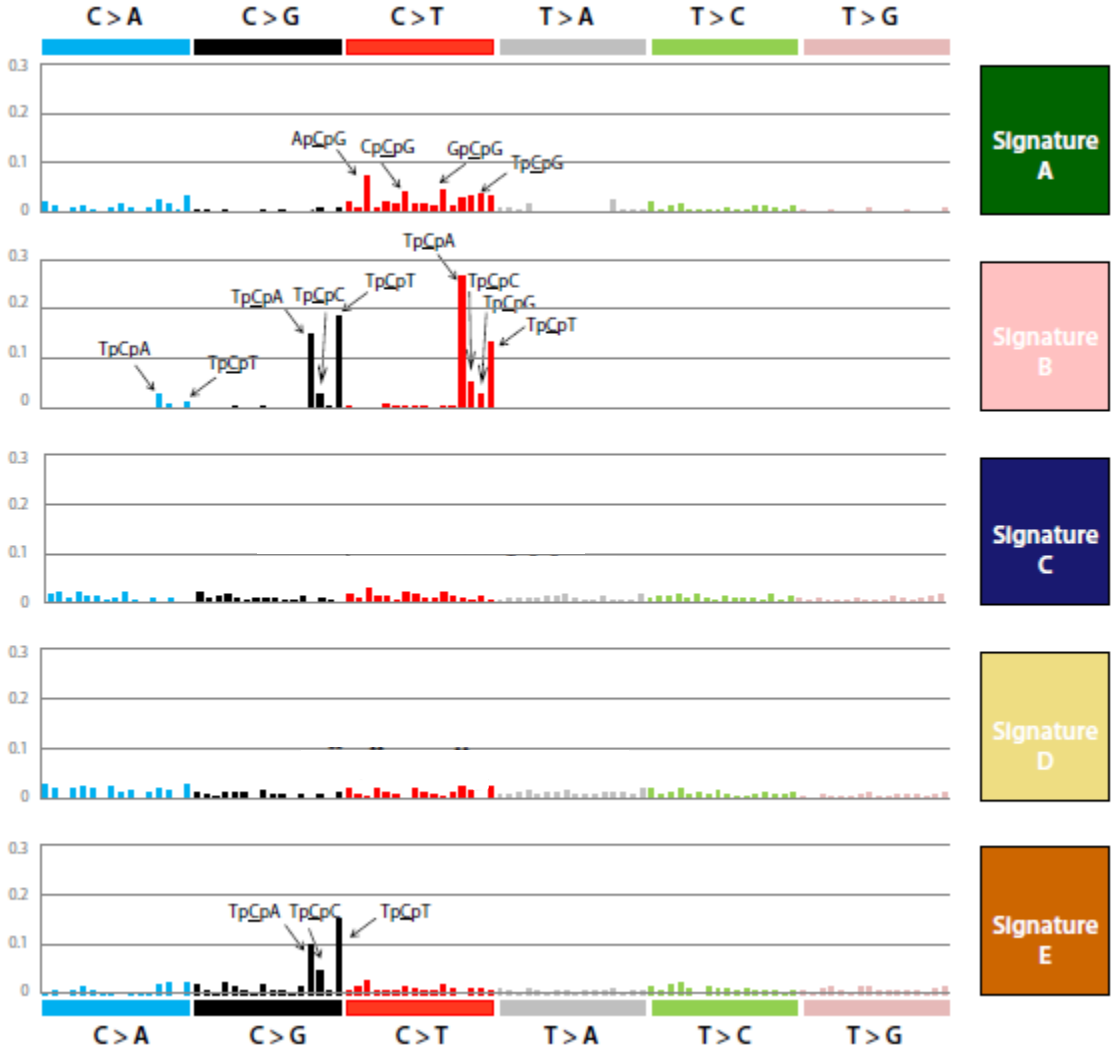
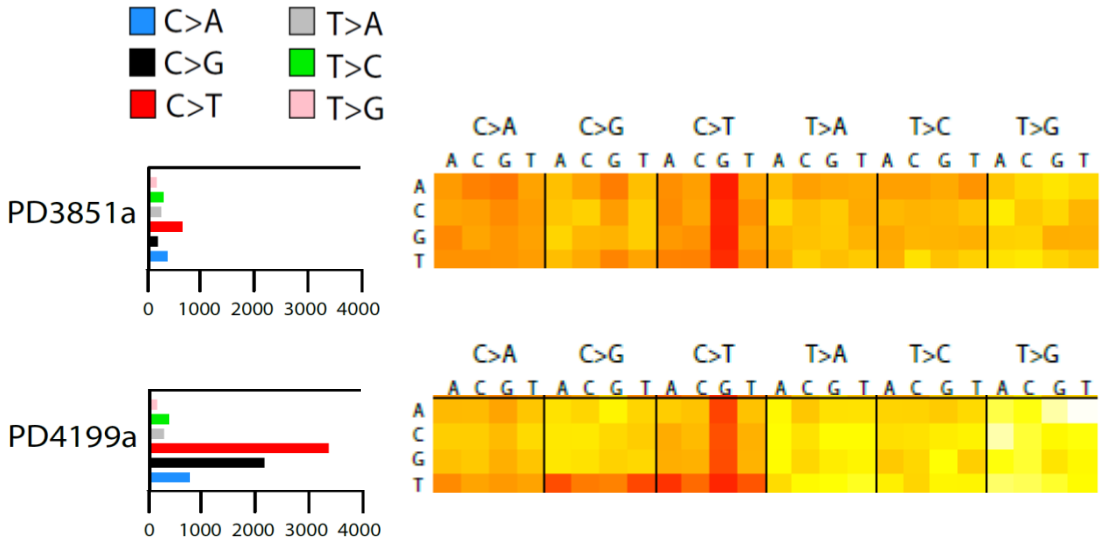


Contributions of mutation signatures to individual cancers



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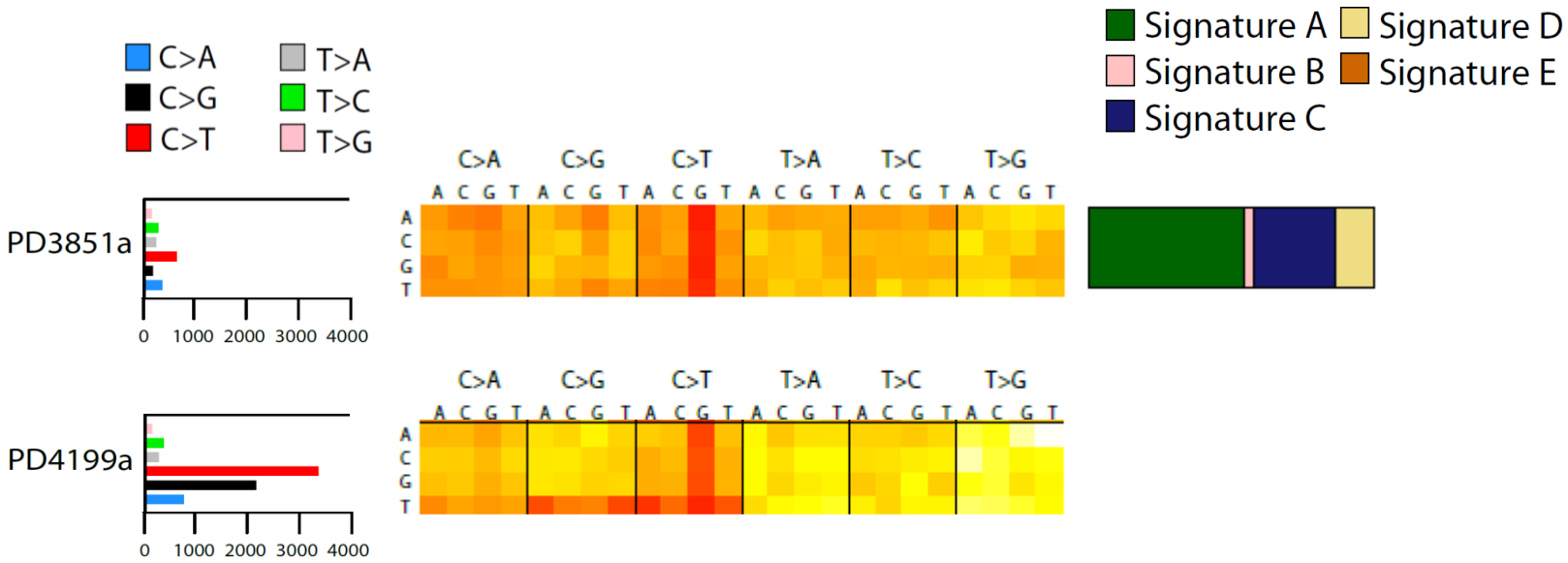

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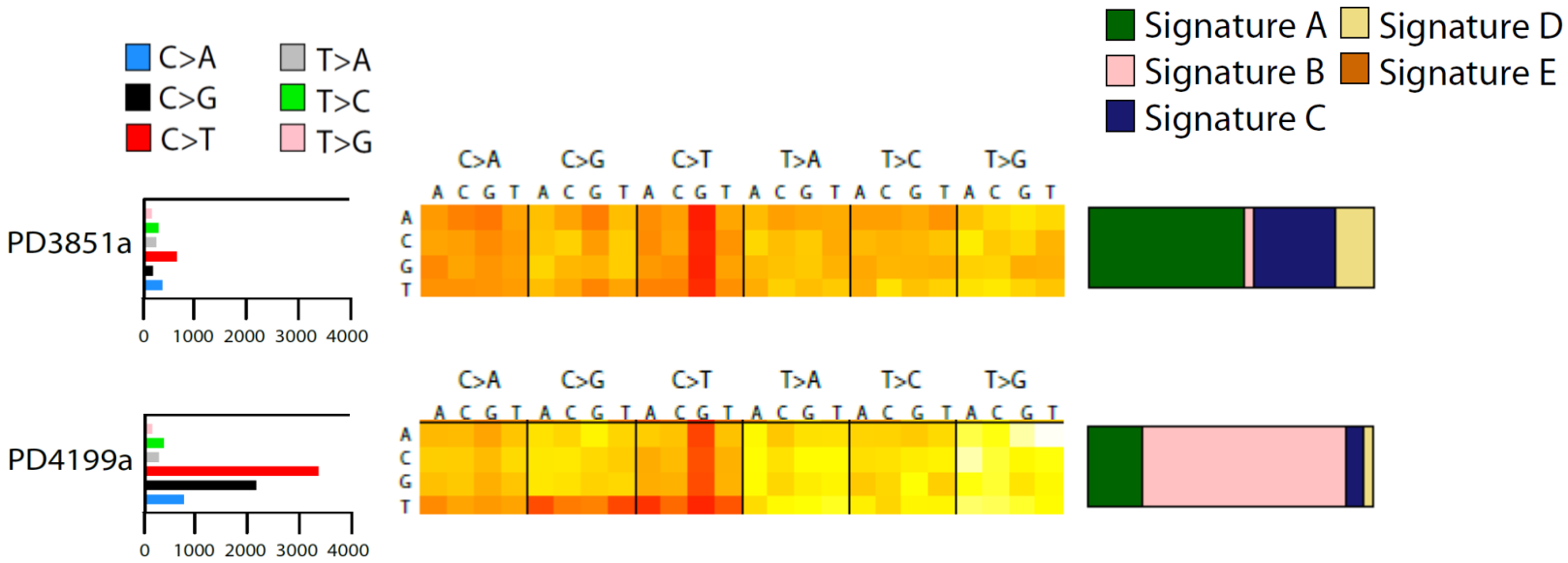

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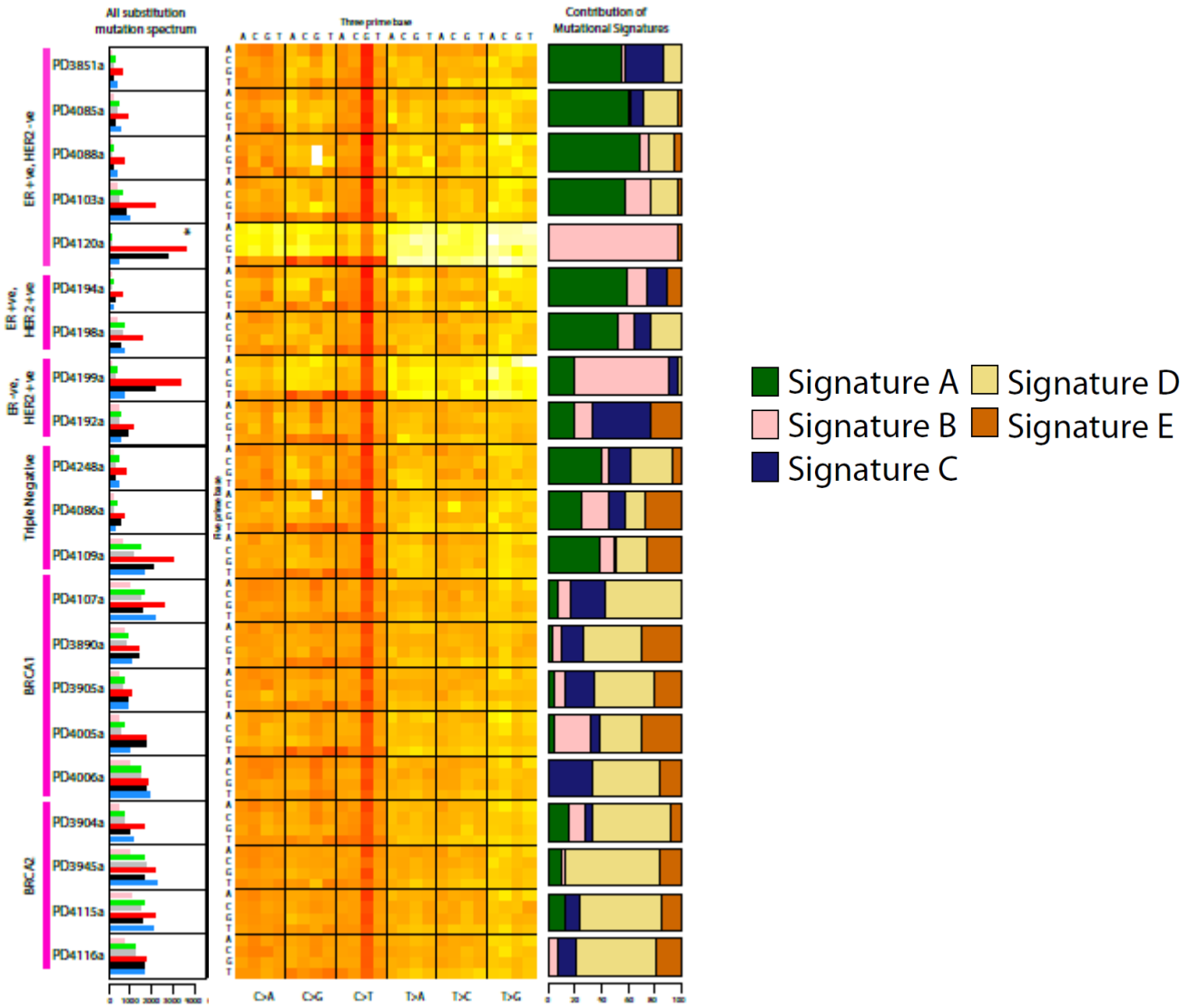
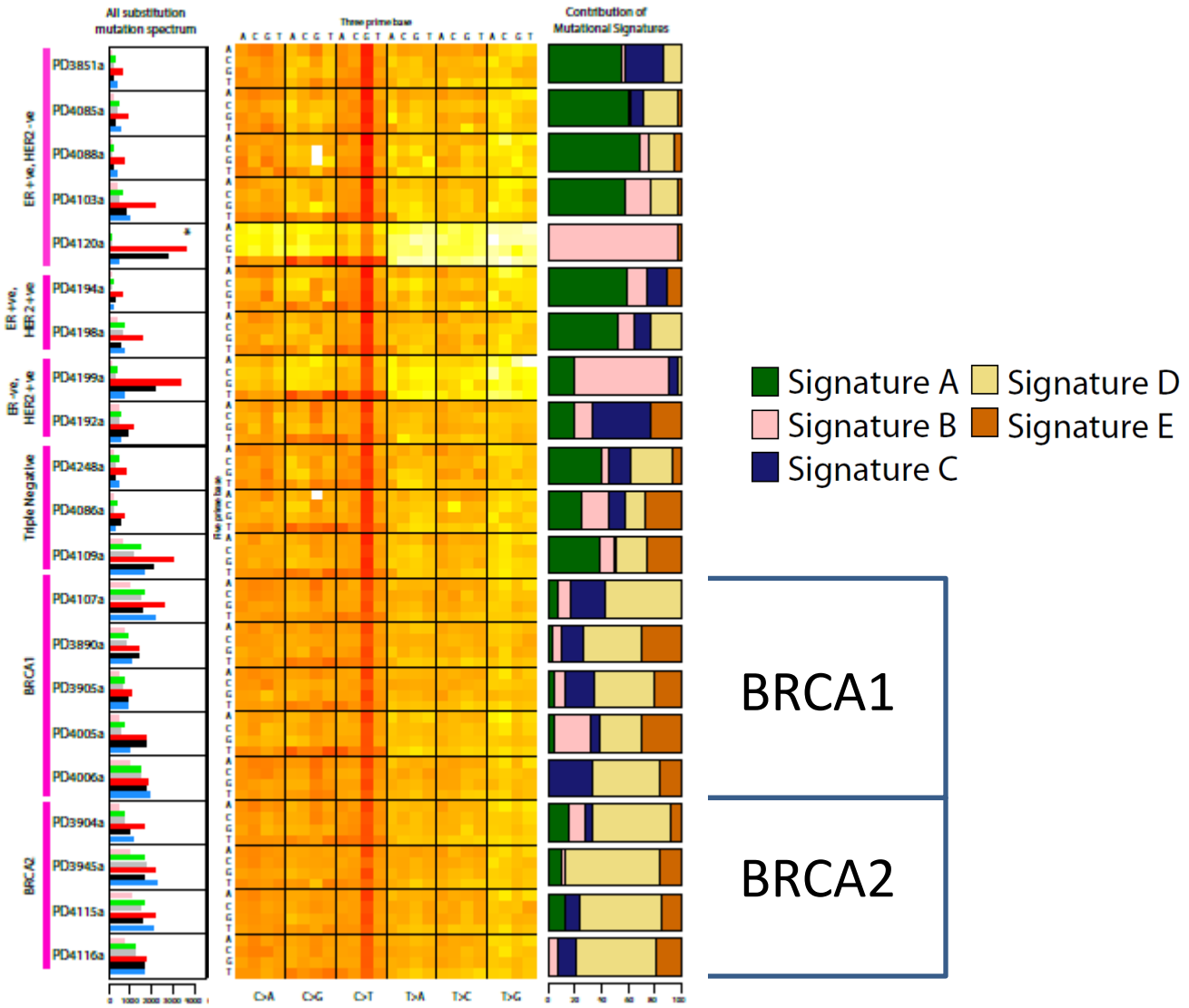
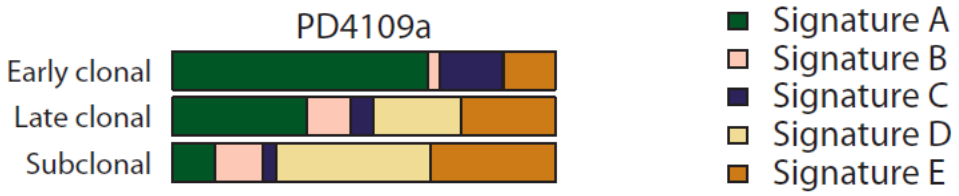


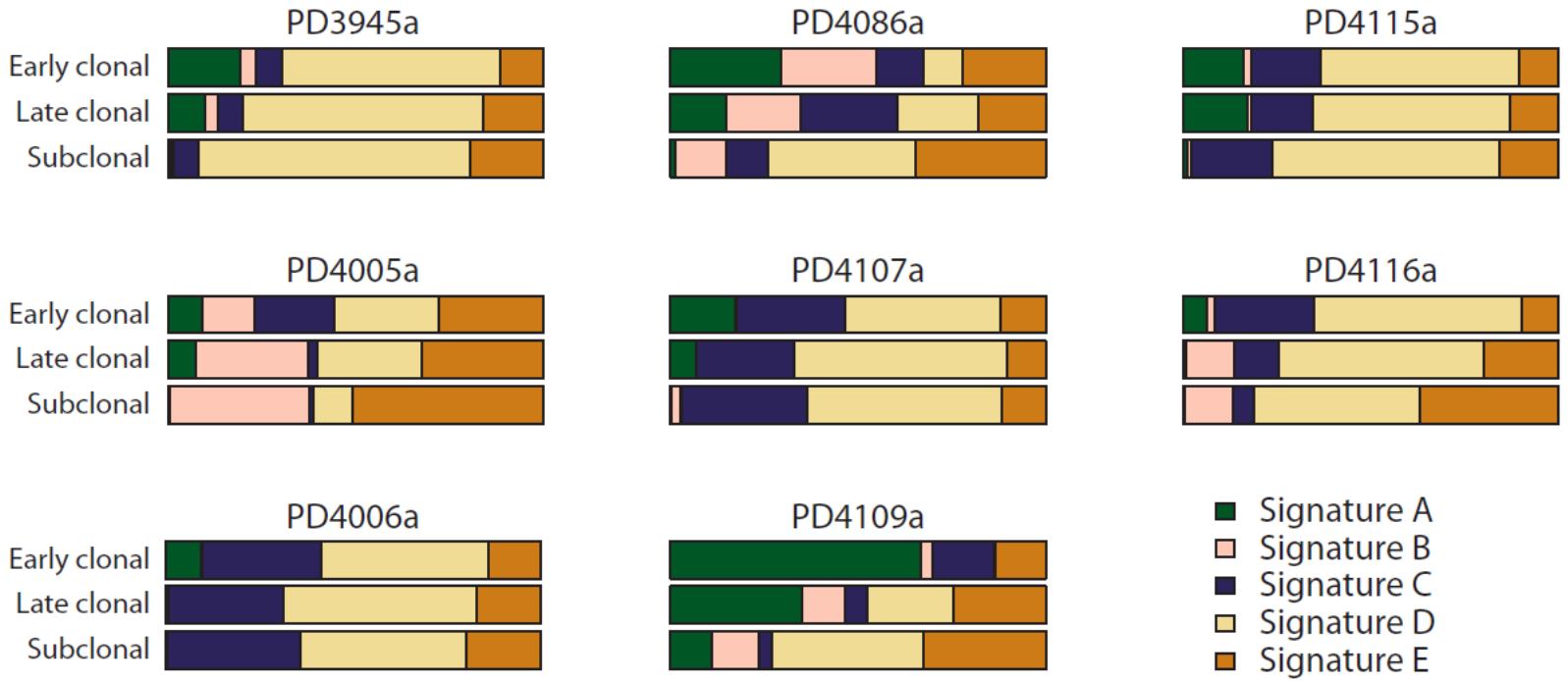
Mutational signatures in BRCA1 and BRCA2 null cancers



Timing of mutational signatures in individual cancers



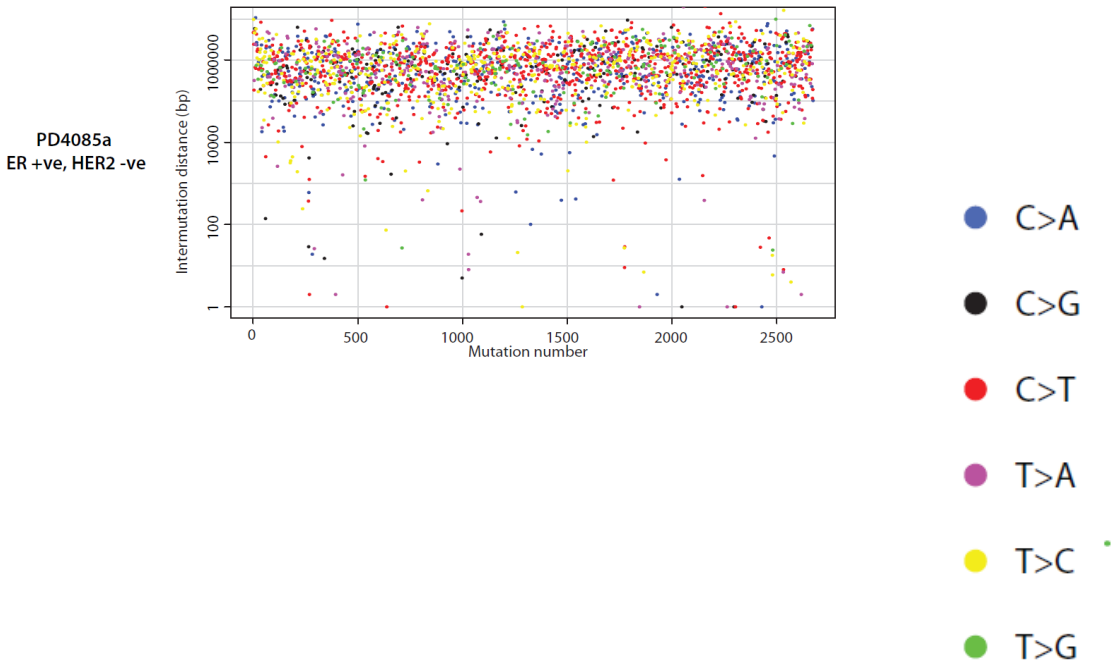
Timing of mutational signatures in individual cancers



Processes of somatic mutation

- Genome-wide
- Localised

Foci of substitution hypermutation, *kataegis,* occur in cancer genomes



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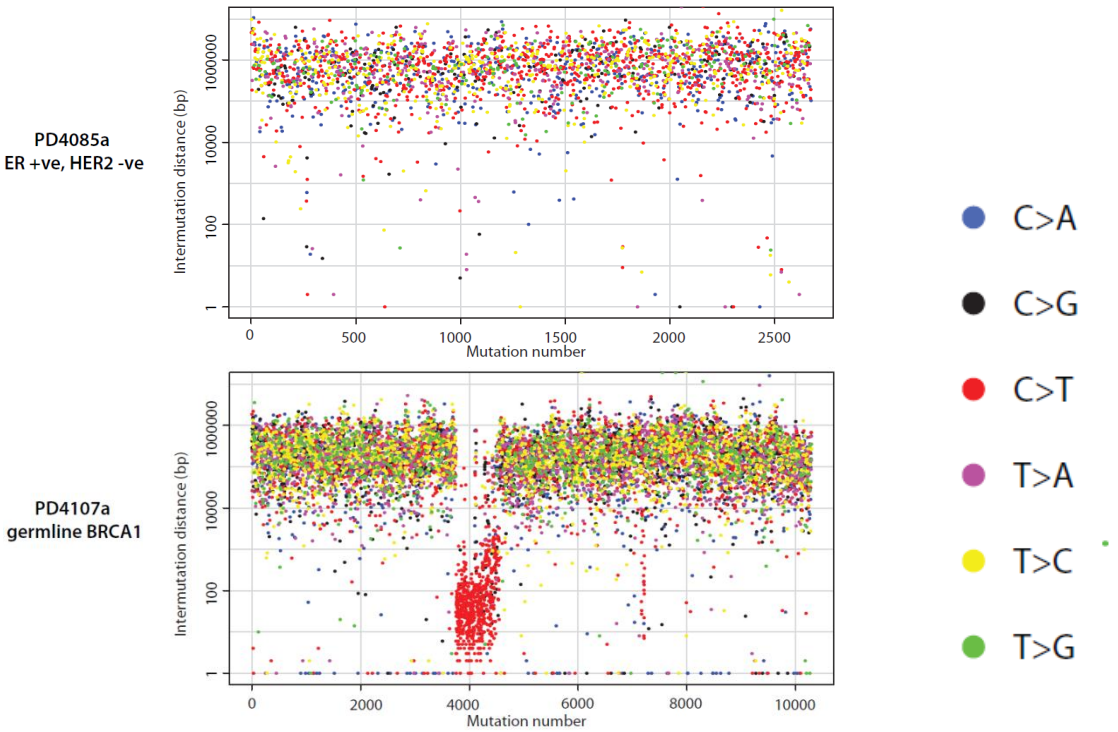

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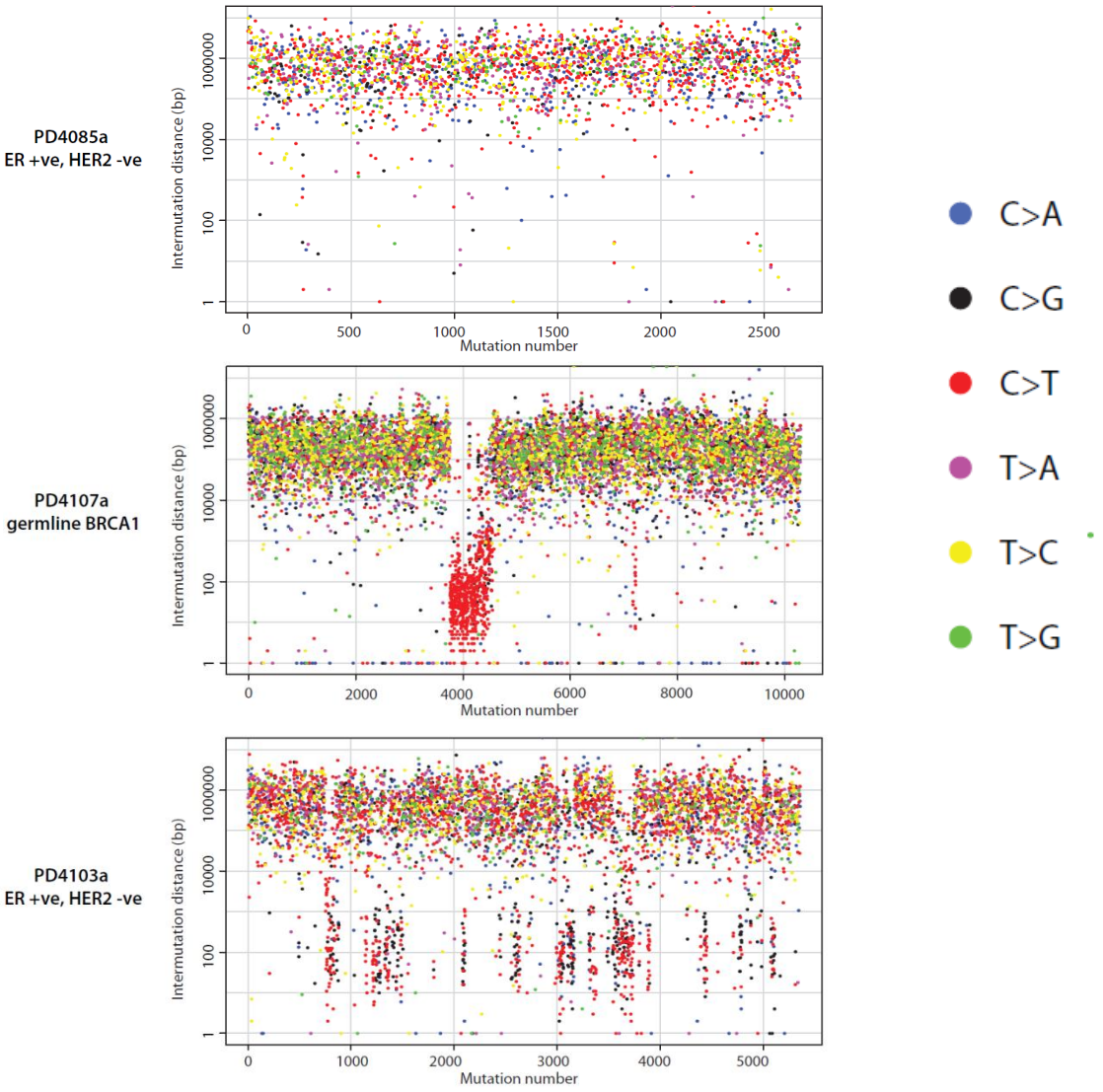
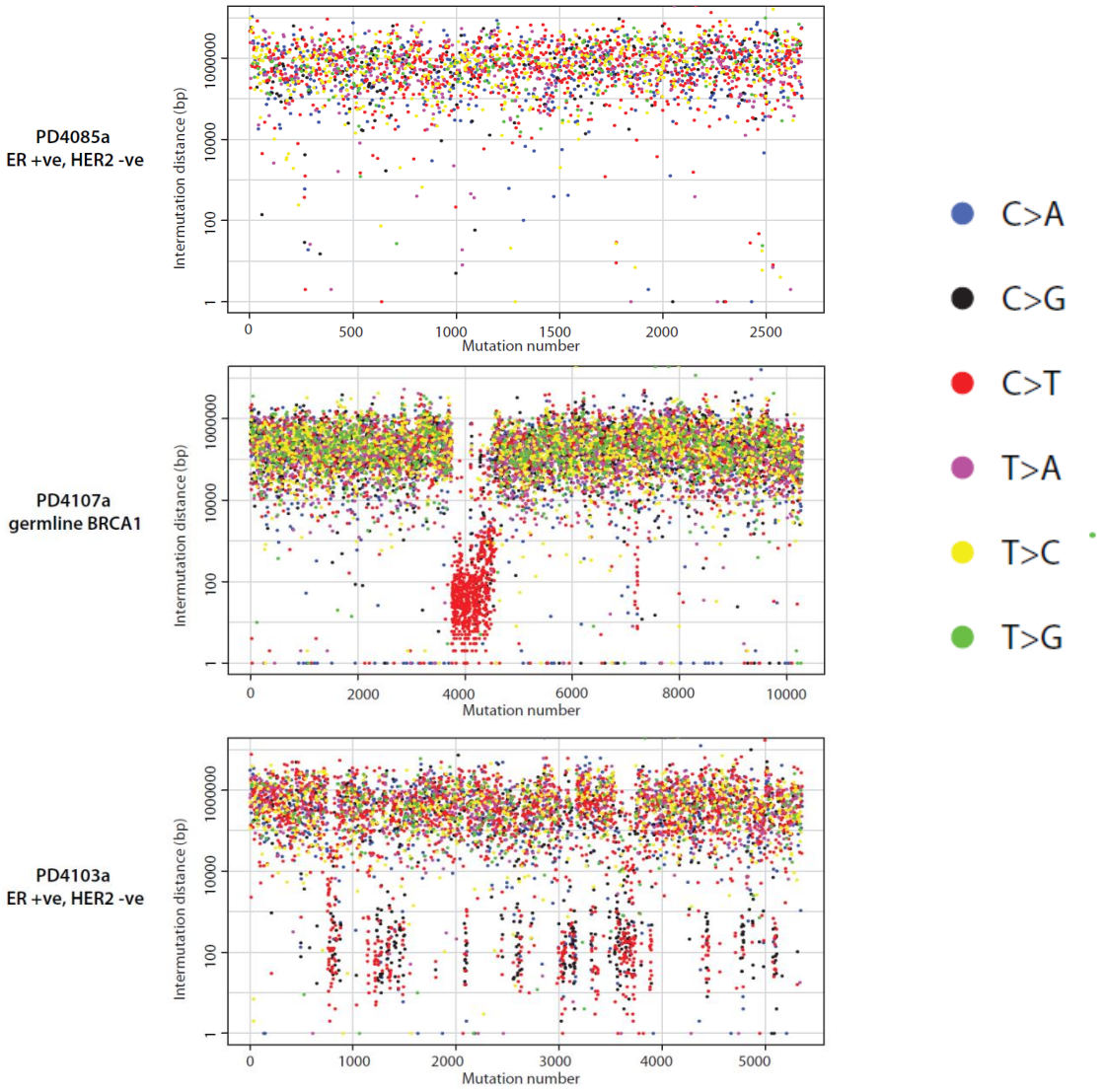
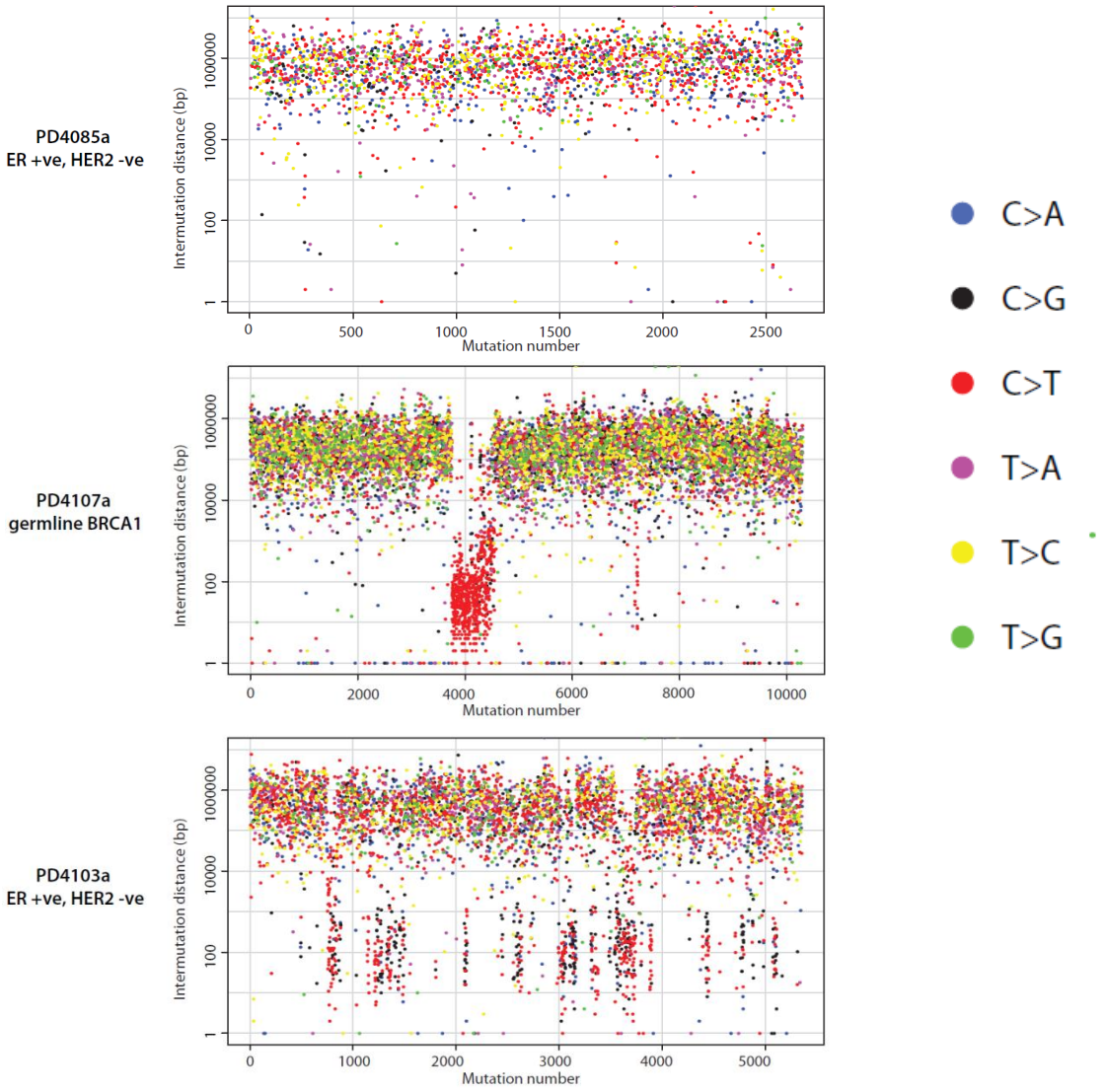


Mutations in regions of *kataegis* are almost all C>T or C>G



Mutations in regions of *kataegis* are almost all at TpCpX trinucleotides



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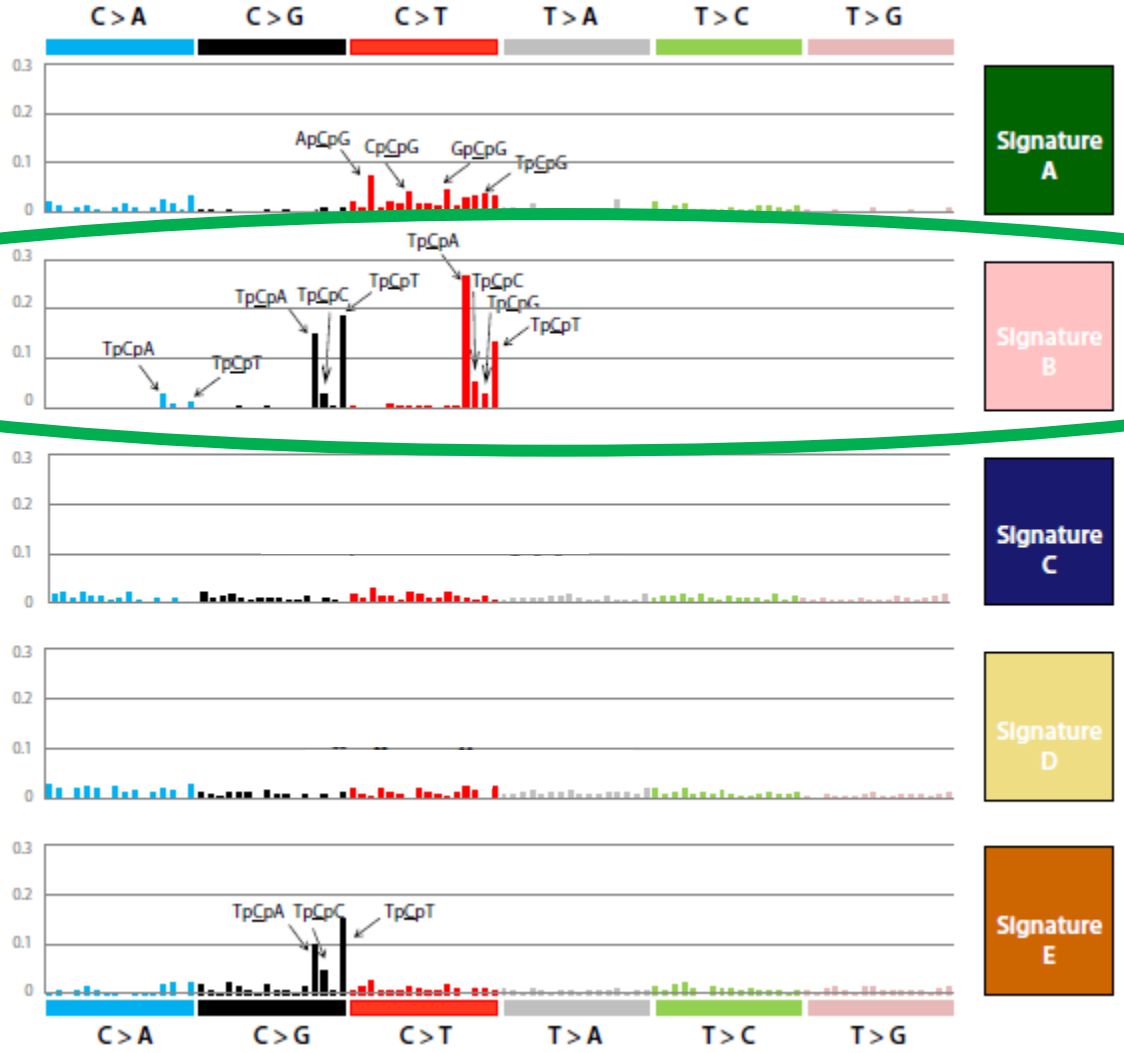
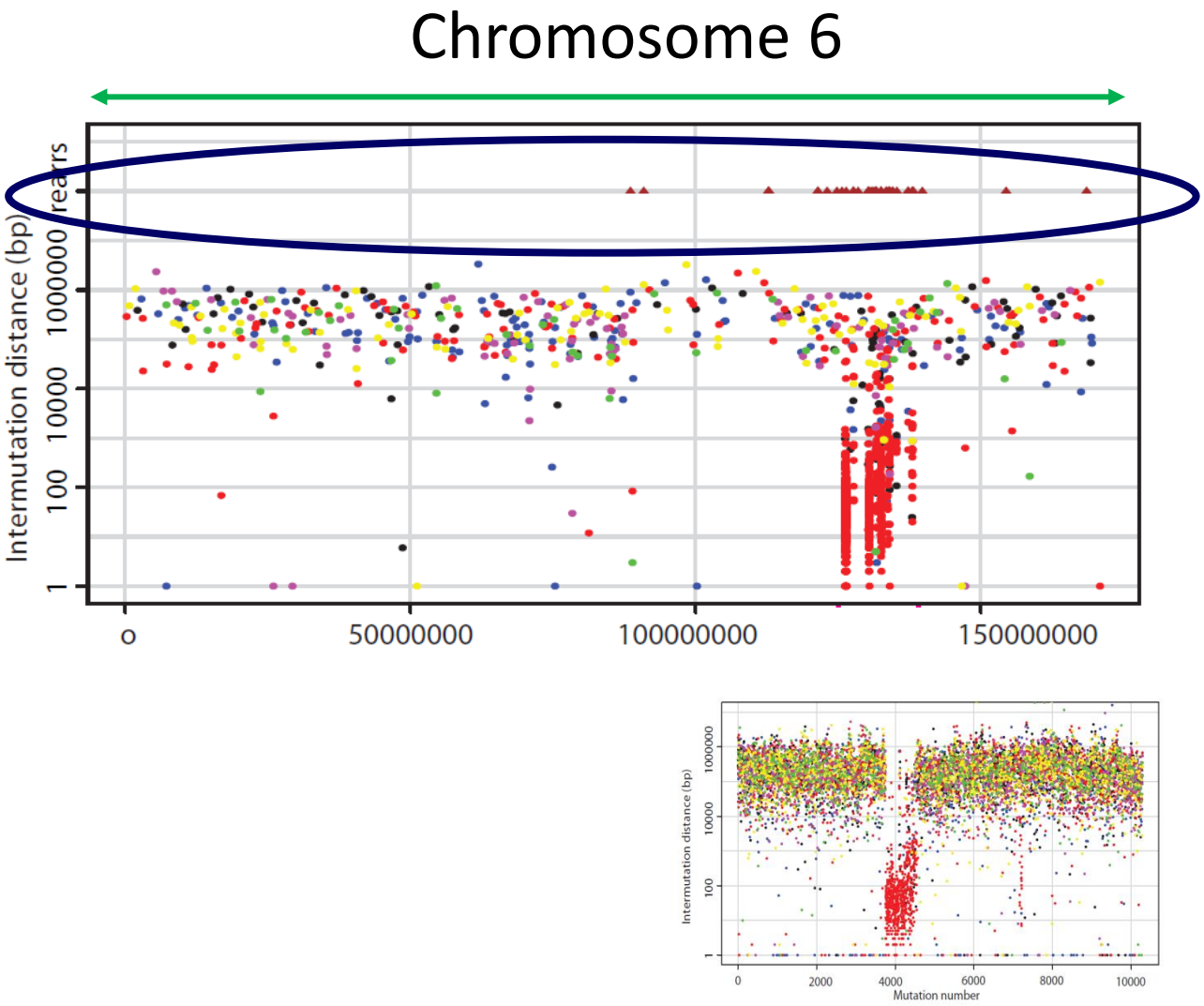


Regions of *kataegis* are characterised by dense aggregates of somatic genomic rearrangement

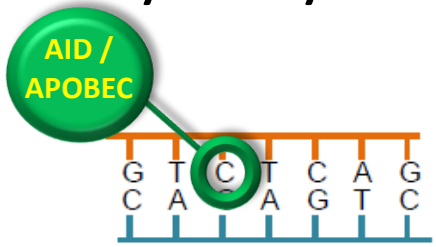


What biological processes are responsible for these genome-wide and localised signatures of somatic mutation?

The AID / APOBEC family of cytidine deaminases perform normal functions that require DNA editing

- AID plays a central role in somatic hypermutation and class switch recombination at the immunoglobulin loci
- APOBEC3A-H mutate HIV and Hepatitis B virus to restrict their activity and replication

DNA editing and rearrangement by the AID/APOBEC family of cytidine deaminases



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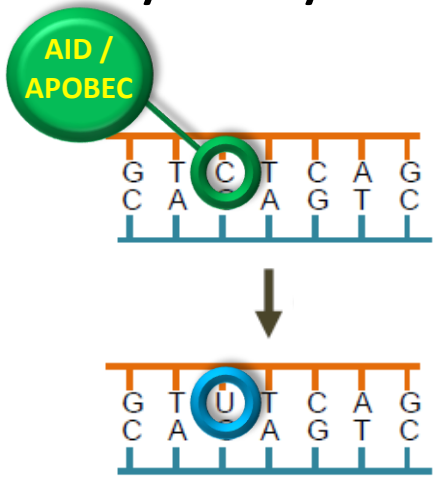

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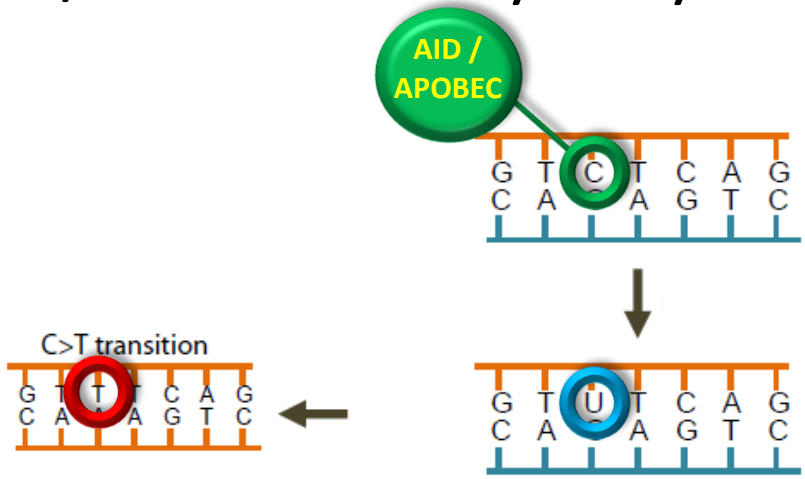

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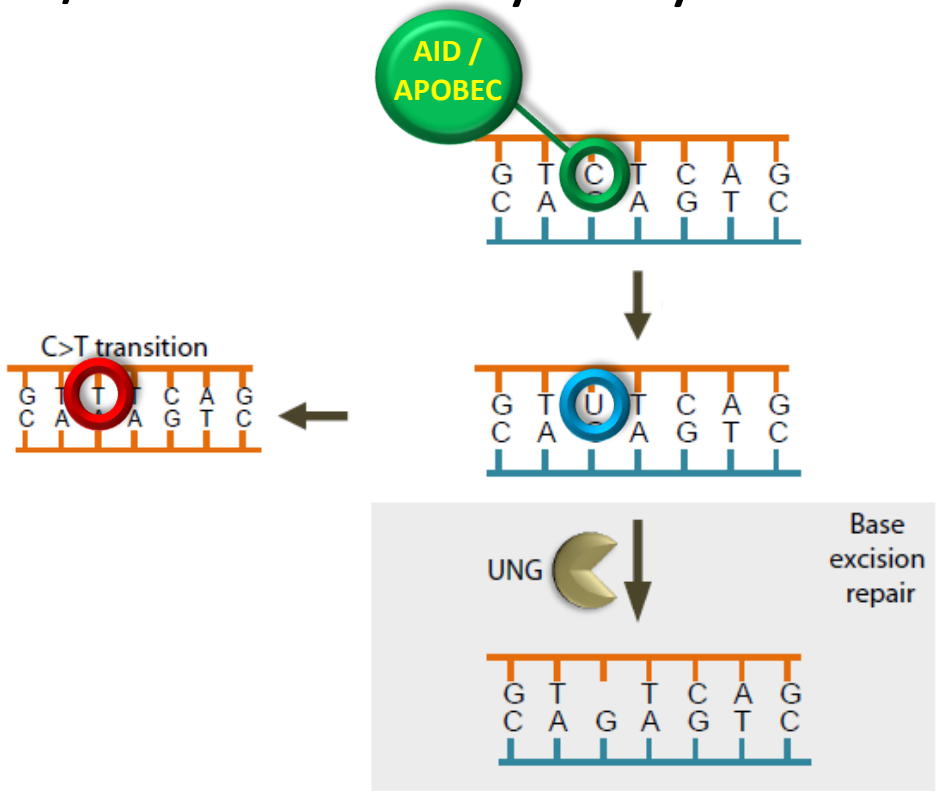

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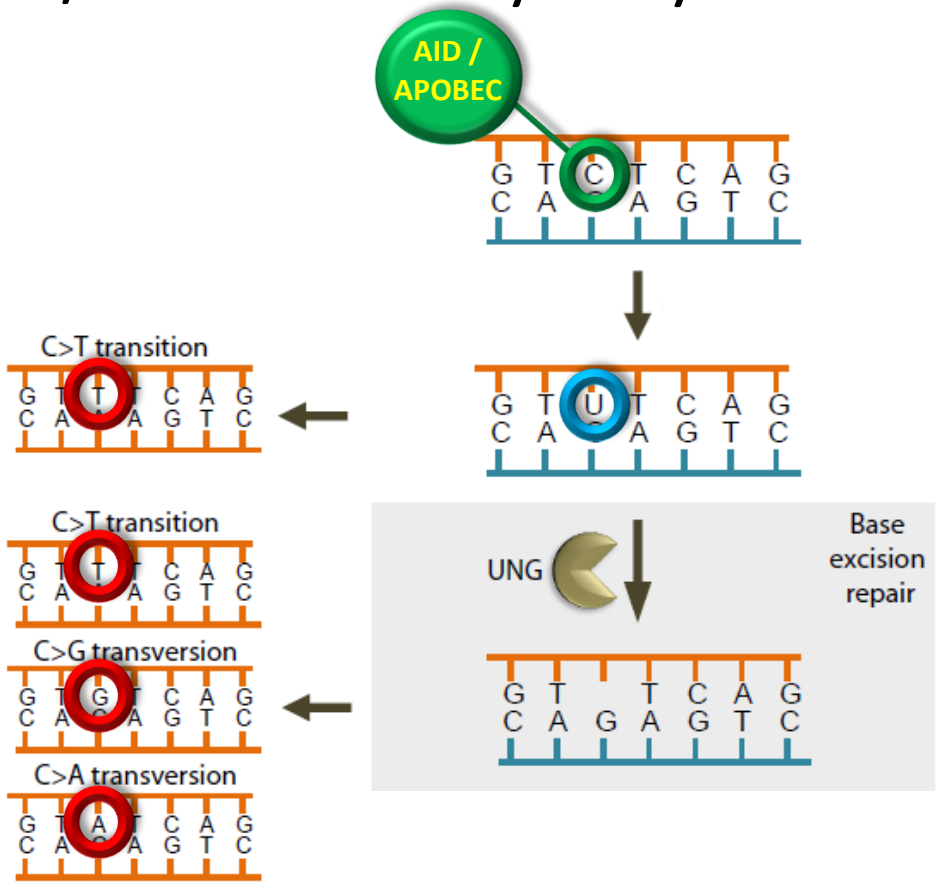

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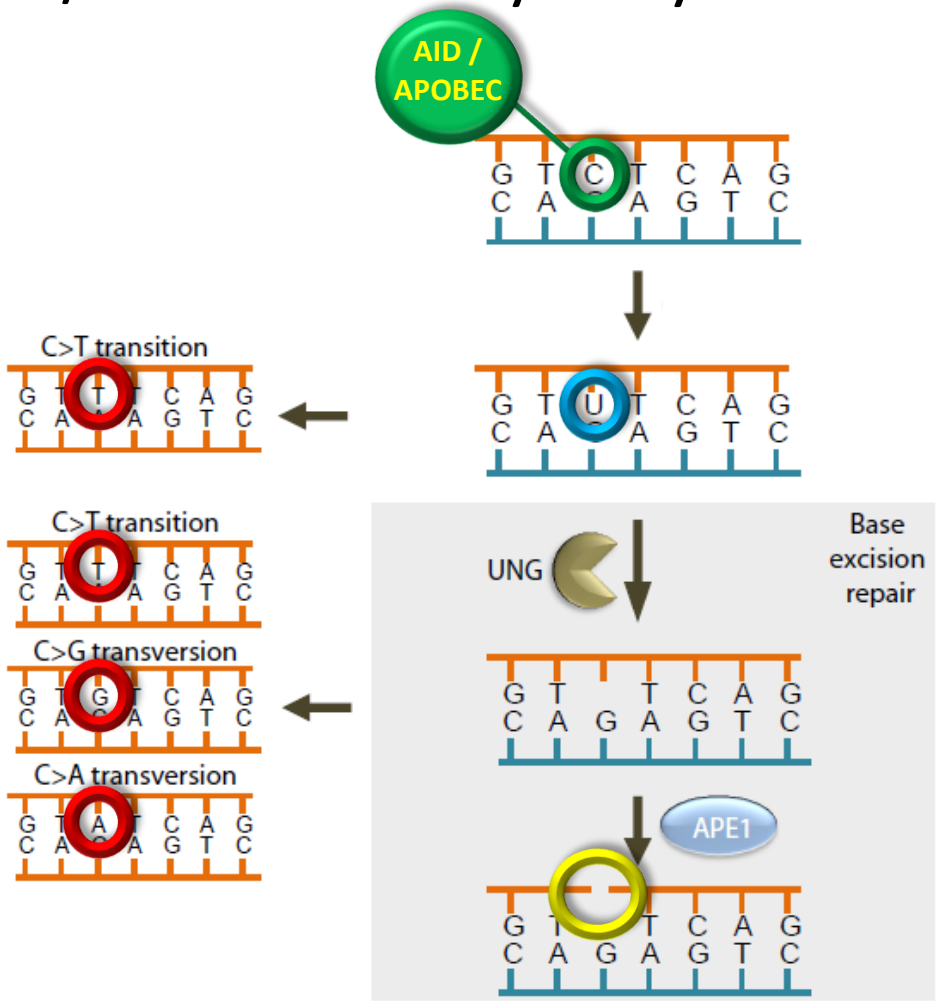

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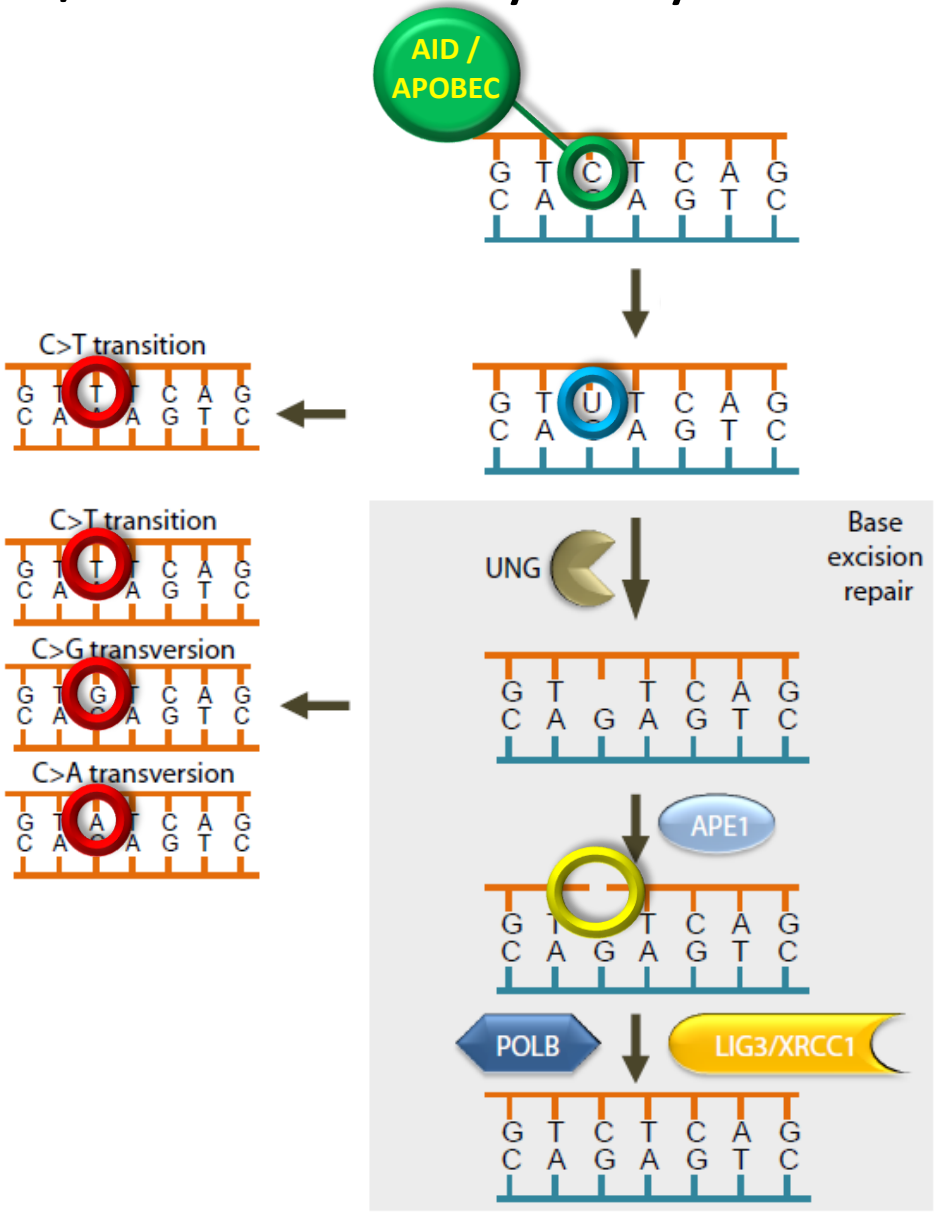

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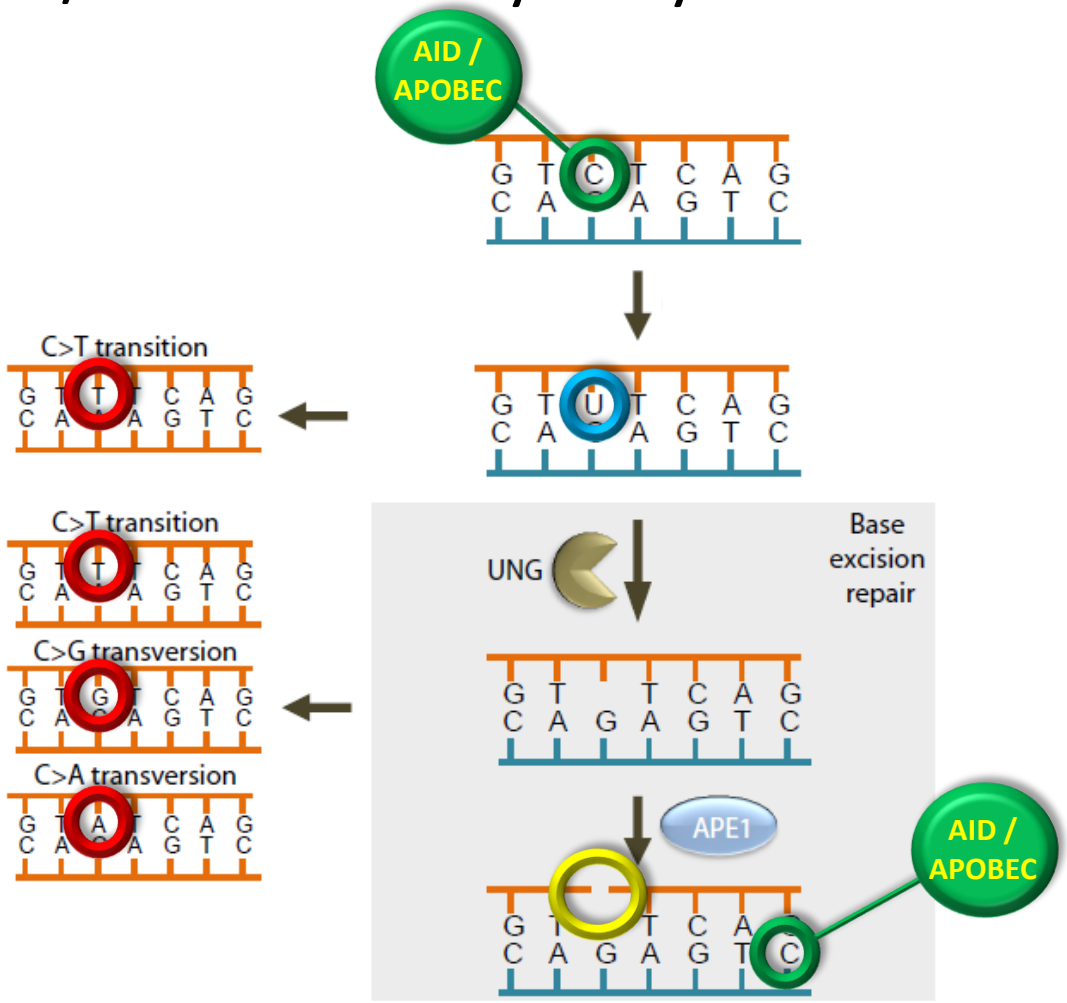

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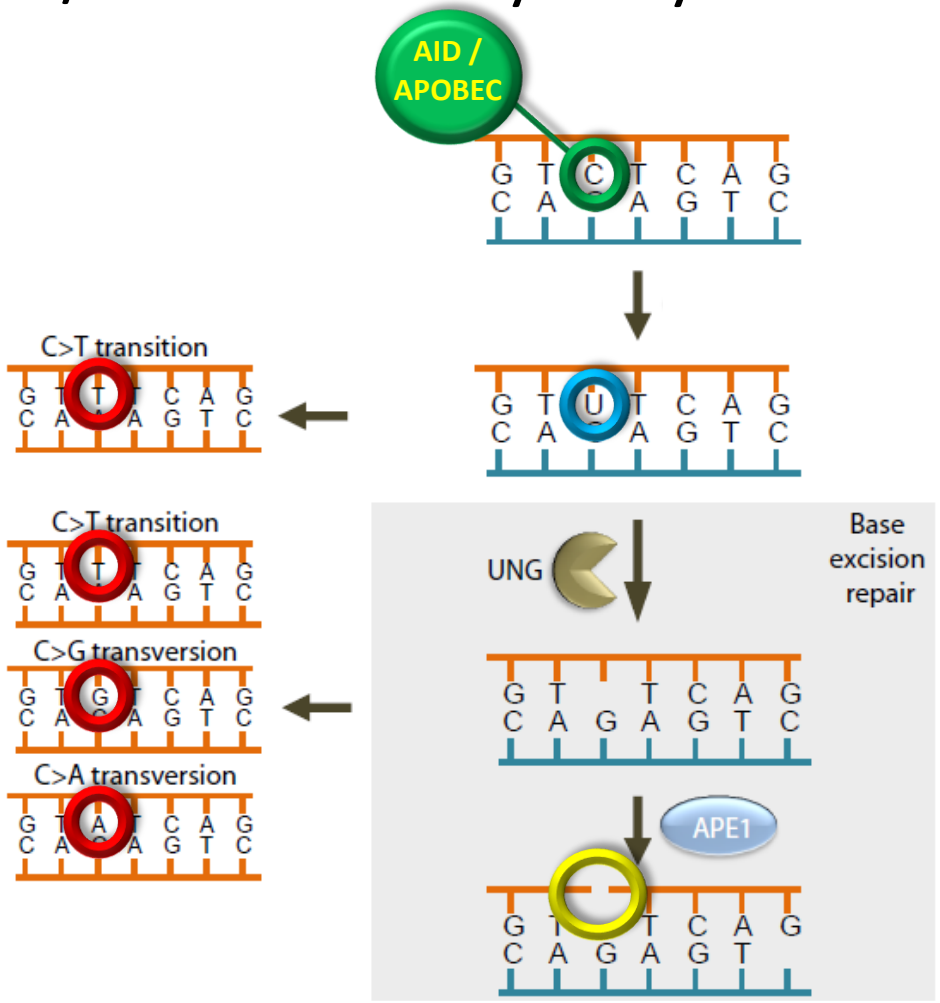

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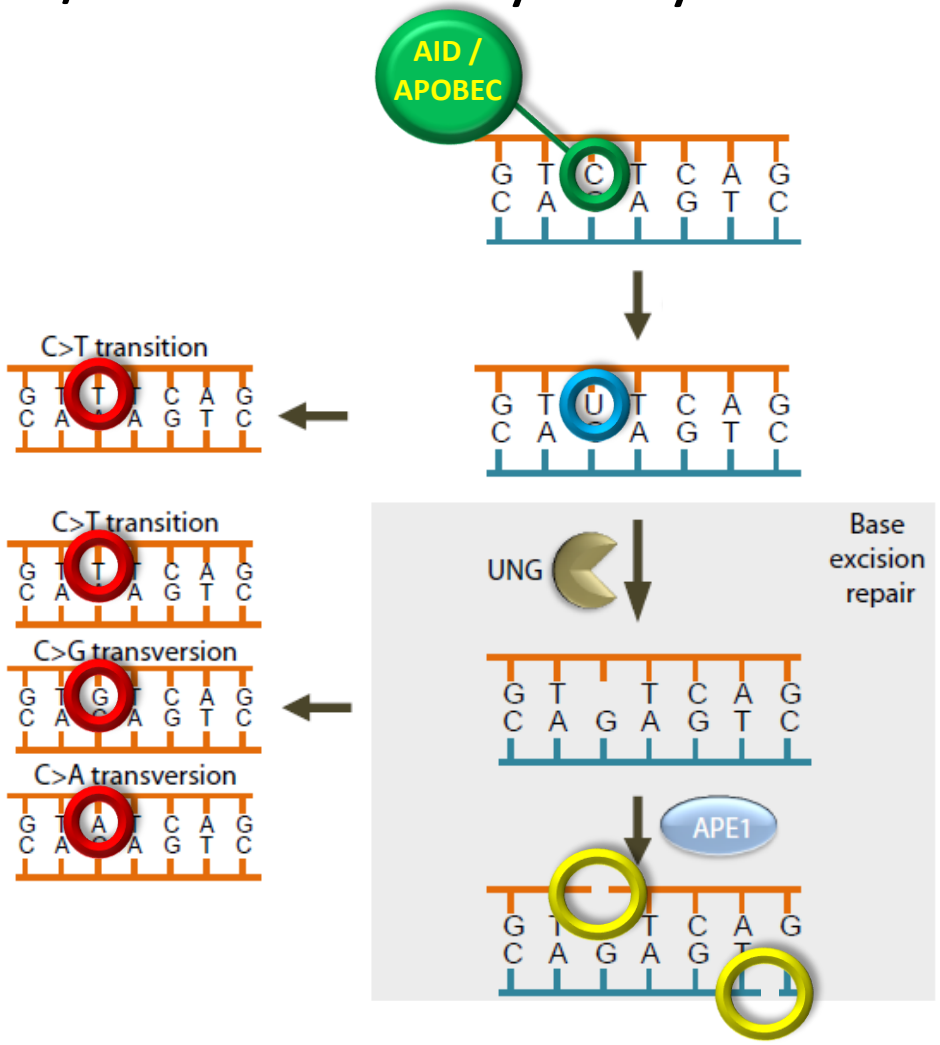

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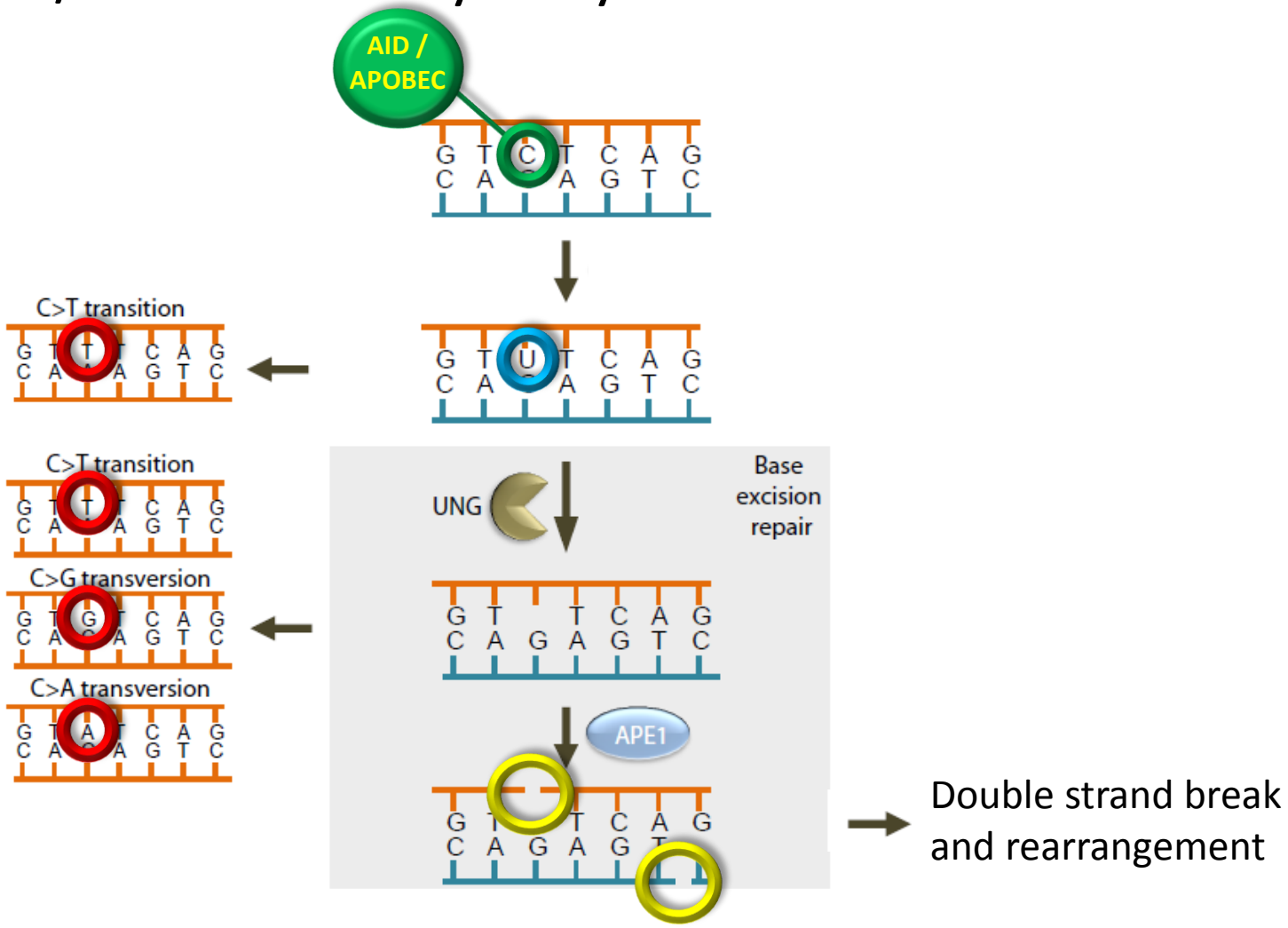
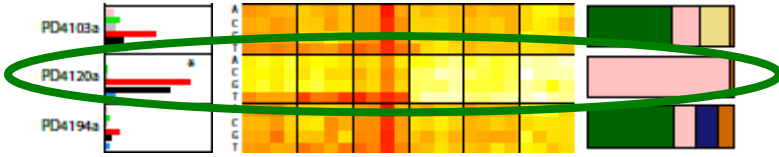


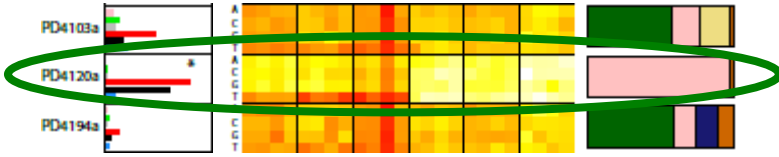
Why does the AID/APOBEC family of cytidine deaminases mutate some breast cancers?

- Why do members of the AID/APOBEC family cause genome-wide global hypermutation?

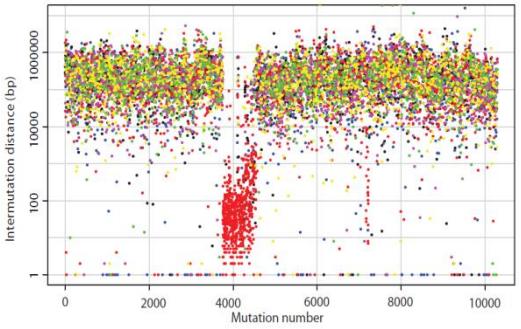


Why does the AID/APOBEC family of cytidine deaminases mutate some breast cancers?

- Why do members of the AID/APOBEC family cause genome-wide global hypermutation?



- Why do members of the AID/APOBEC family become targeted to specific regions of the genome in *kataegis?*



Summary

- Multiple processes of somatic mutation have contributed to the genesis of breast cancer
- Processes contribute to a different extent to different individual cancers
- Processes operate at different time points during oncogenesis
- A process of localised hypermutation, termed *kataegis*, exists in some breast cancer genomes
- The mechanisms underlying these mutational processes are unknown but AID/APOBEC DNA editing enzymes likely play a role

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