The Repertoire of Mutational Signatures in Human Cancer

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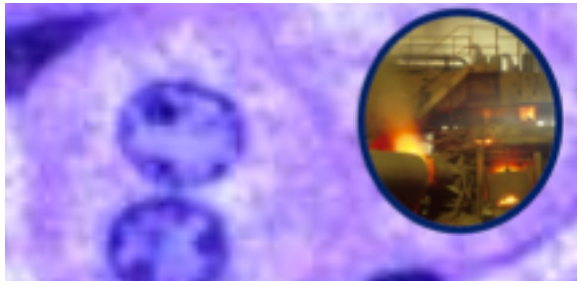
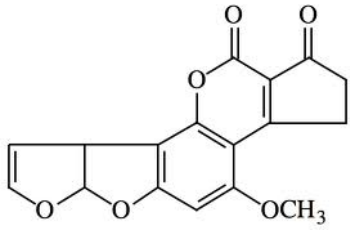
NCI Designated Comprehensive Cancer Center

UC San Diego Moores Cancer Center

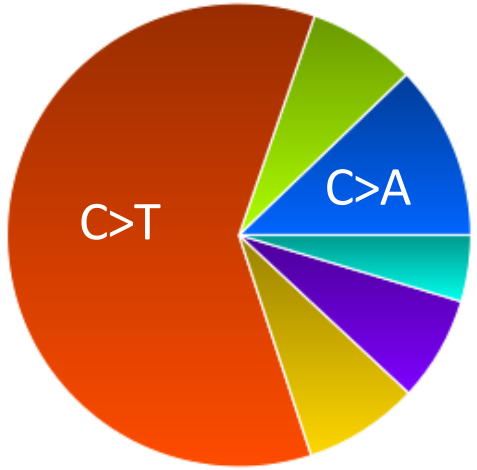
Somatic mutations occur in all cells of the body throughout life





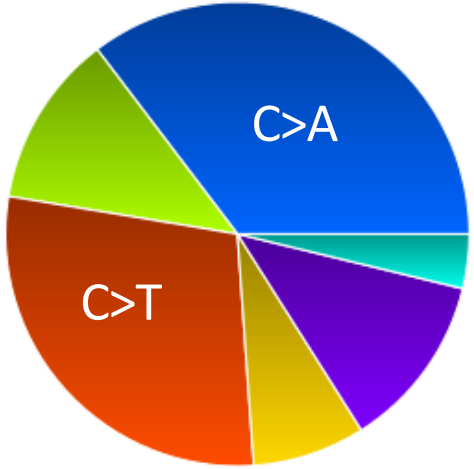
TP53 mutations in human cancer

686 skin cancers



Ultraviolet light
causes C>T mutations

1647 lung cancers



Tobacco carcinogens
cause C>A mutations

From fertilised egg to cancer cell

Chemotherapy
resistant
recurrence

From fertilised egg to cancer cell

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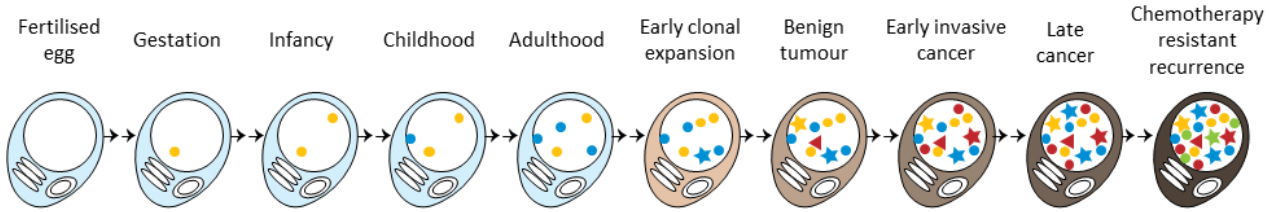
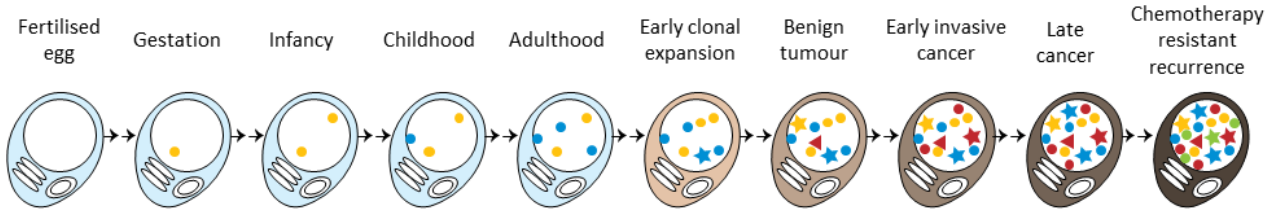
From fertilised egg to cancer cell



Mutational processes

A

From fertilised egg to cancer cell



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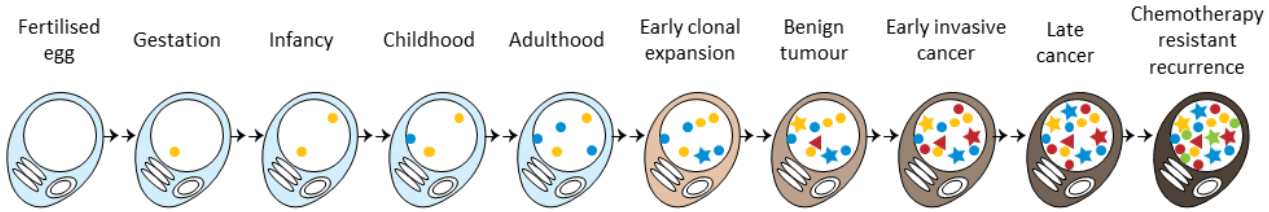

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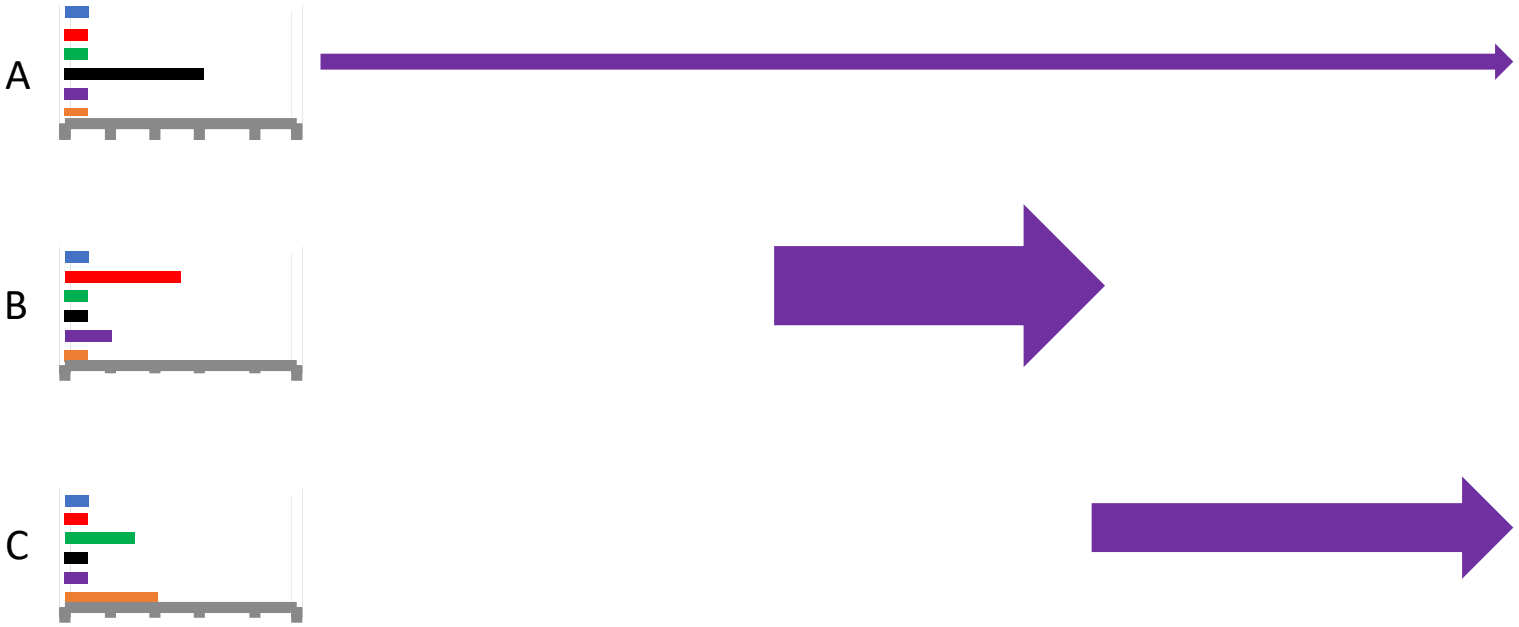

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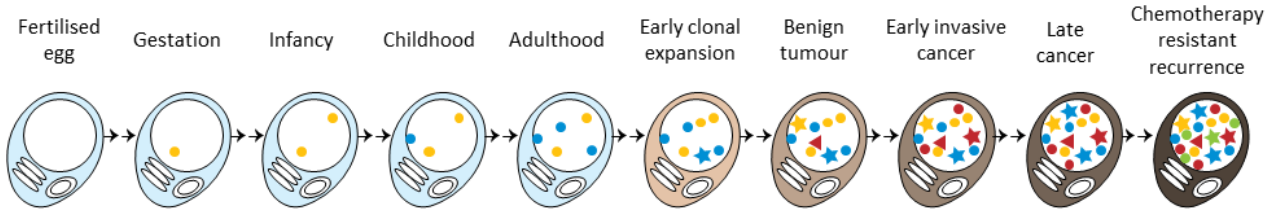

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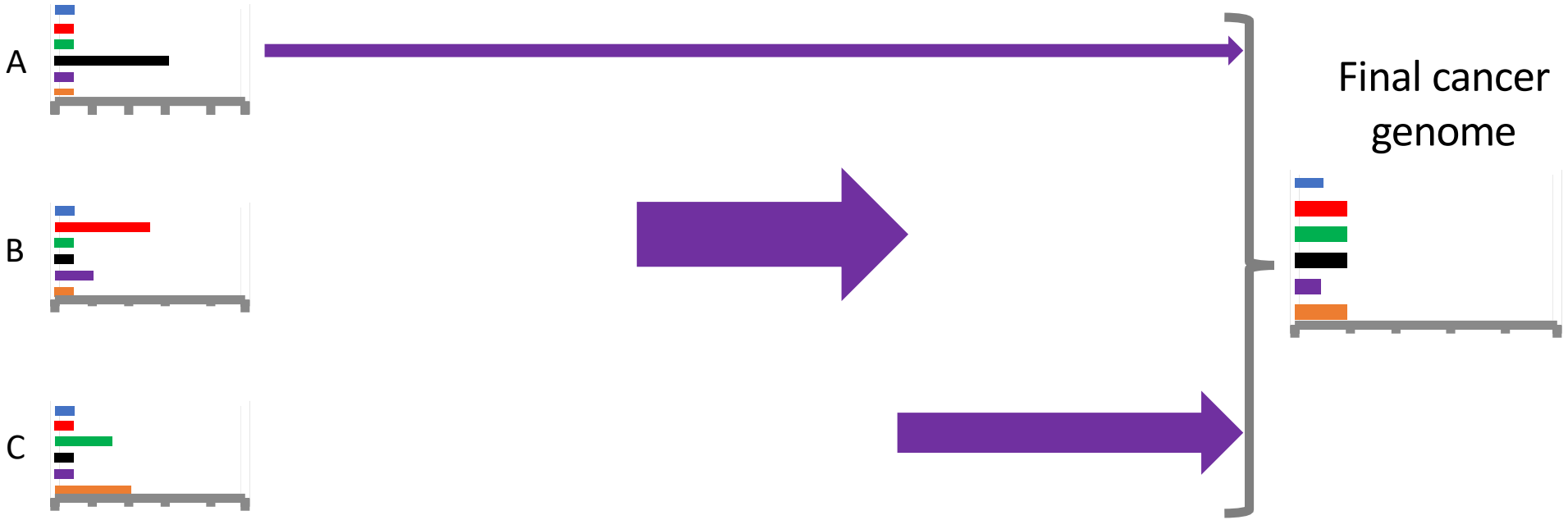
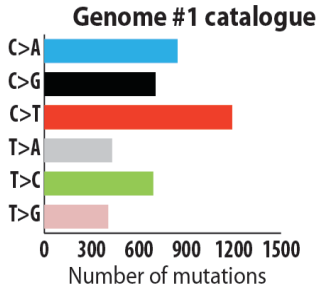
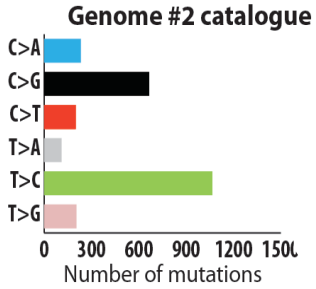
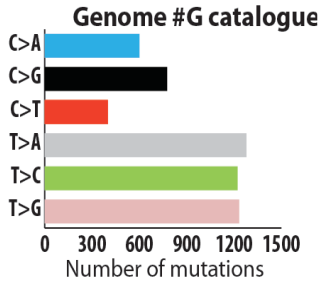


Mutational signatures derived from cancer genomes







NMF approach for extracting processes

$$M \approx P \times E$$

- Solving the blind source separation problem
  - Infinite solutions as a matrix can be approximately decompose in two matrices in infinite number of ways
  - BSS problem is usually solved by constraining the solutions
  - Intrinsic nonnegative constraints from our theoretical modal
  - Other constraints are possible (*e.g.* sparsity, independence, *etc.)* but we will ignore them for now

- Nonnegative matrix factorization as a method for decomposing the mutational spectrum matrix

Solved using the stochastic multiplicative update method

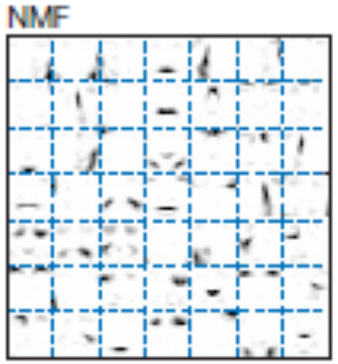
$$\min_{P \in \mathbb{R}_+^{K \times N}} \; \min_{E \in \mathbb{R}_+^{N \times G}} \; \frac{1}{2} || M - P \times E ||_F^2$$

Nonnegative 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*



Extracting mutational signatures from human cancers

30,874 cancer cases of 91 cancer types

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30,874 mutation catalogues = 183,099,289 somatic mutations

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Apply two independent NMF approaches to all samples (global) and samples in each cancer type (local)

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Extract mutational signatures of subs, dinucleotides, and indels

Extracting mutational signatures from human cancers

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30,874 mutation catalogues = 183,099,289 somatic mutations

Apply two independent NMF approaches to all samples (global) and samples in each cancer type (local)

Extract mutational signatures of subs, dinucleotides, and indels

Estimate the contribution of each mutational signature to the mutational catalogue of each of the 30,874 cancer genomes

The repertoire of mutational signatures in human cancer

Single base substitution (SBS) mutational signatures

Classification of base substitution mutations

C>T
C>A
C>G
T>A
T>C
T>G

6 mutation classes

Classification of base substitution mutations

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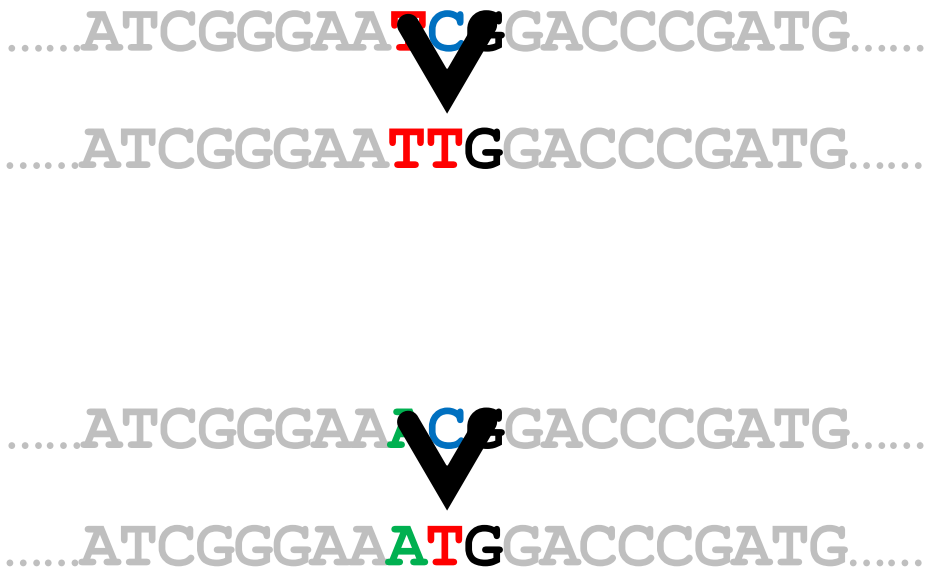
Classification of base substitution mutations



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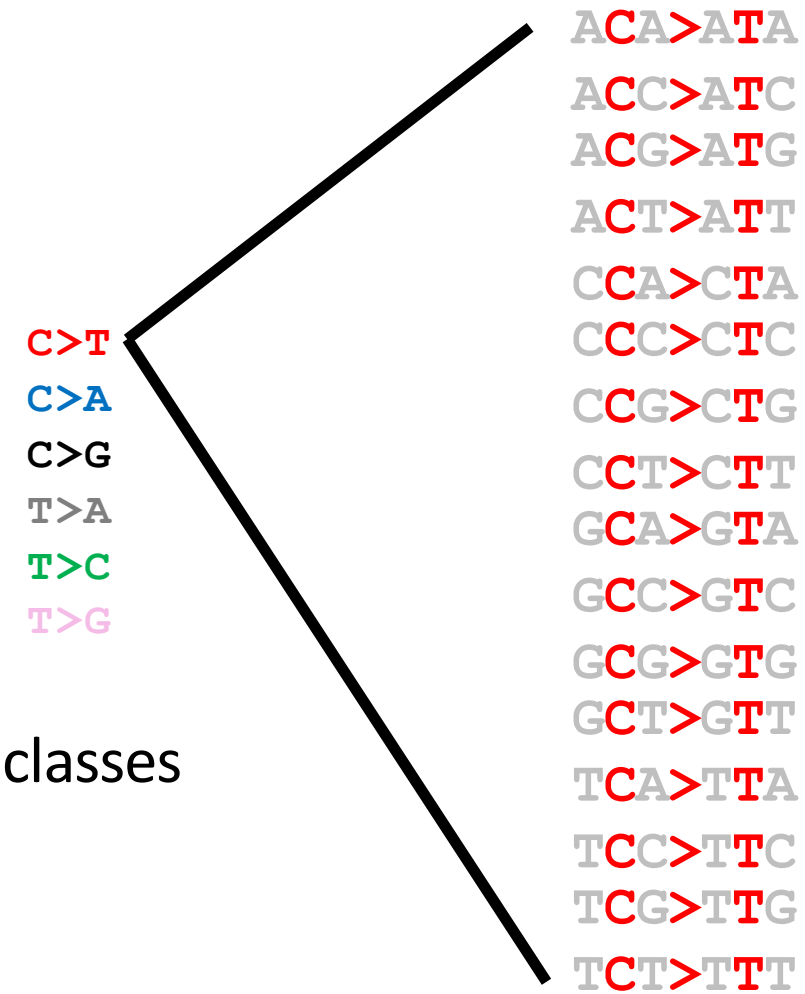

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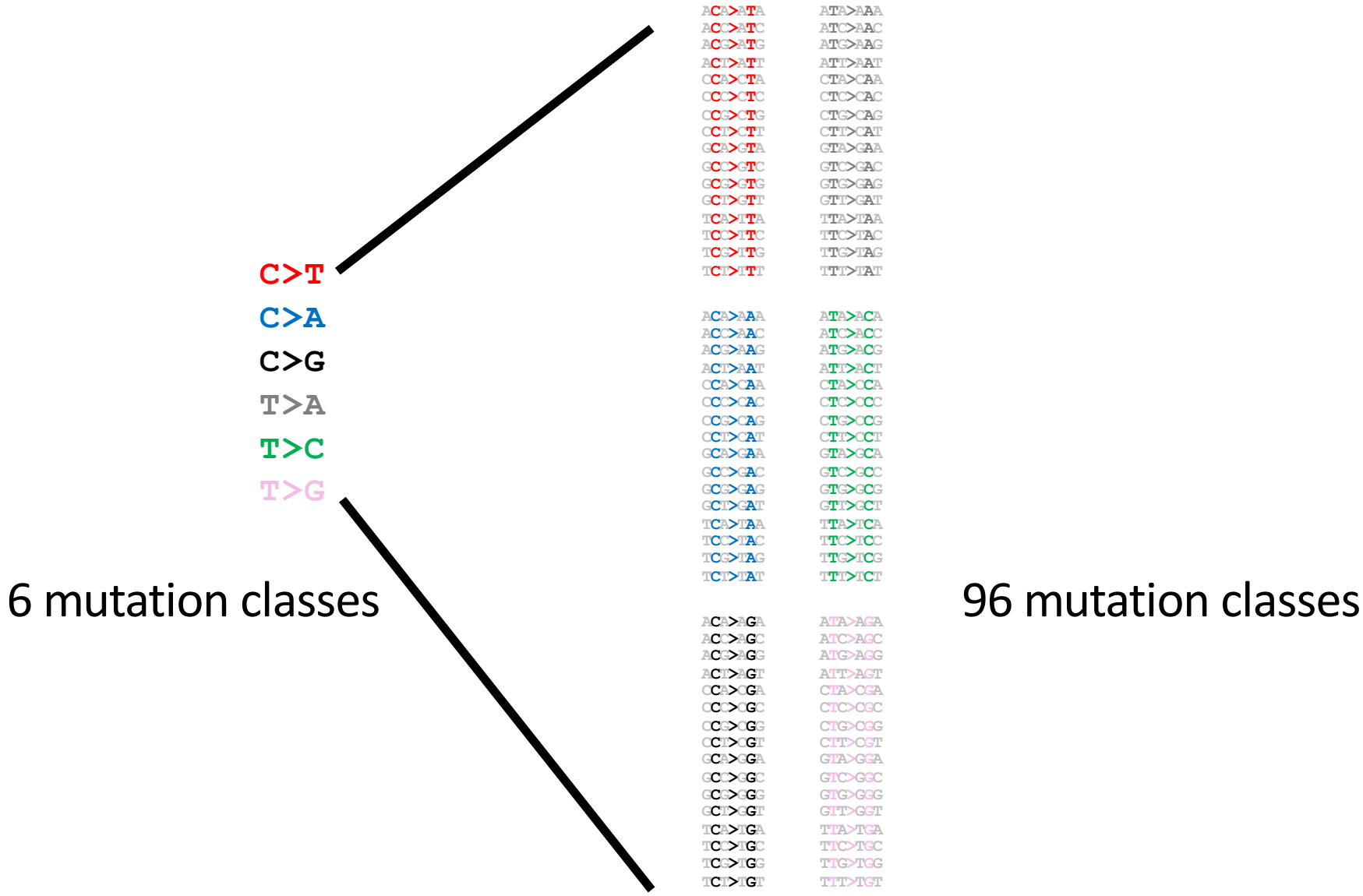
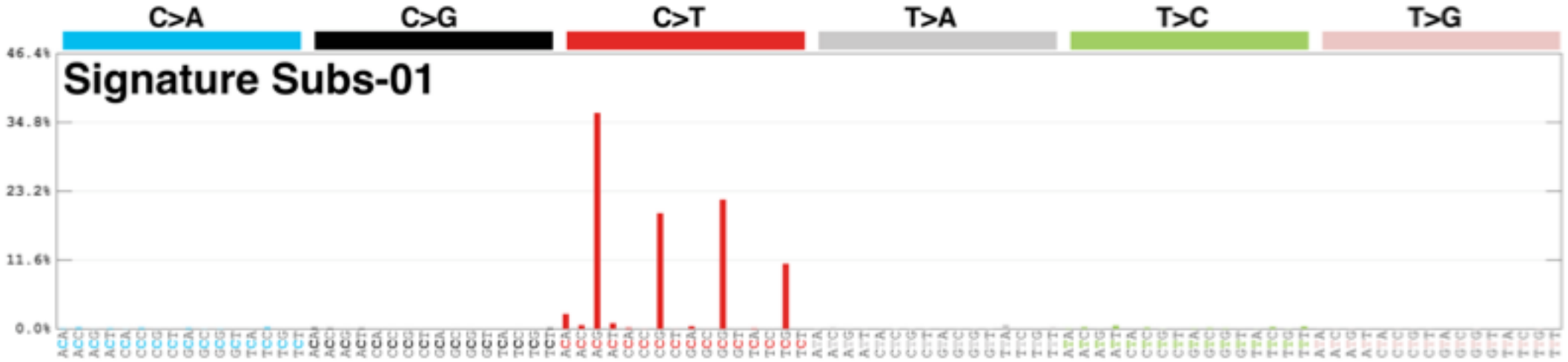


Mutational signatures in human cancer



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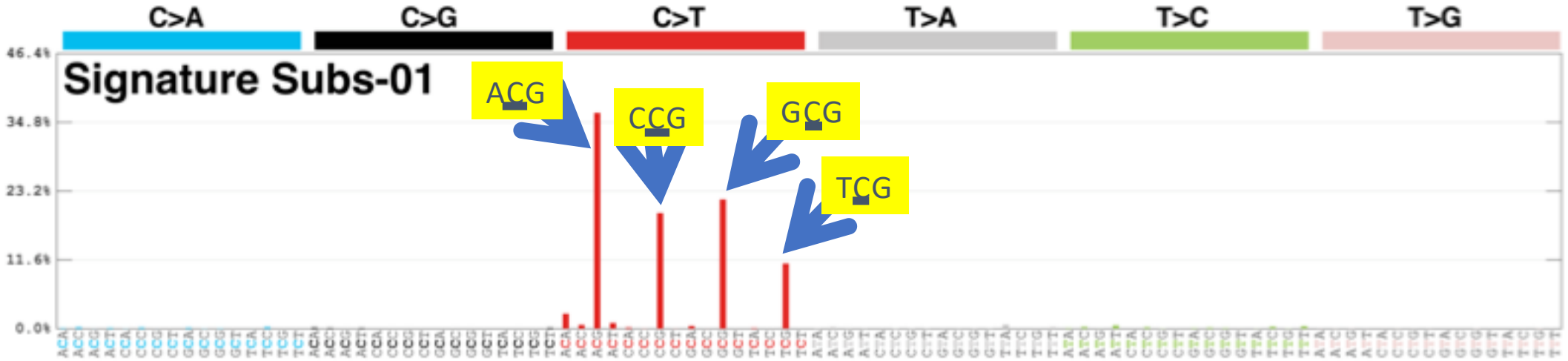

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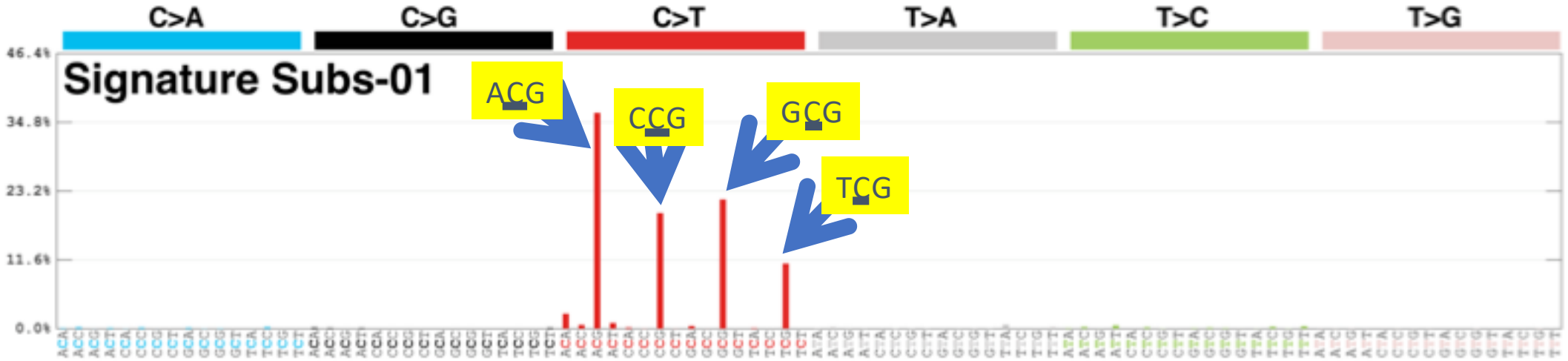

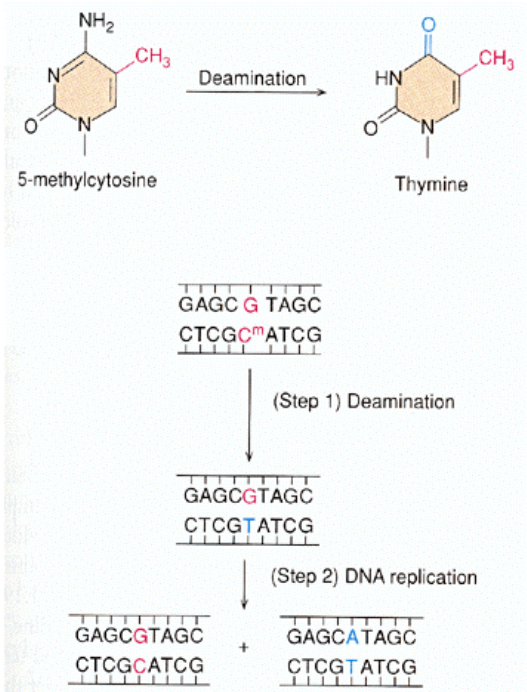

Repertoire of substitution signatures in human cancer

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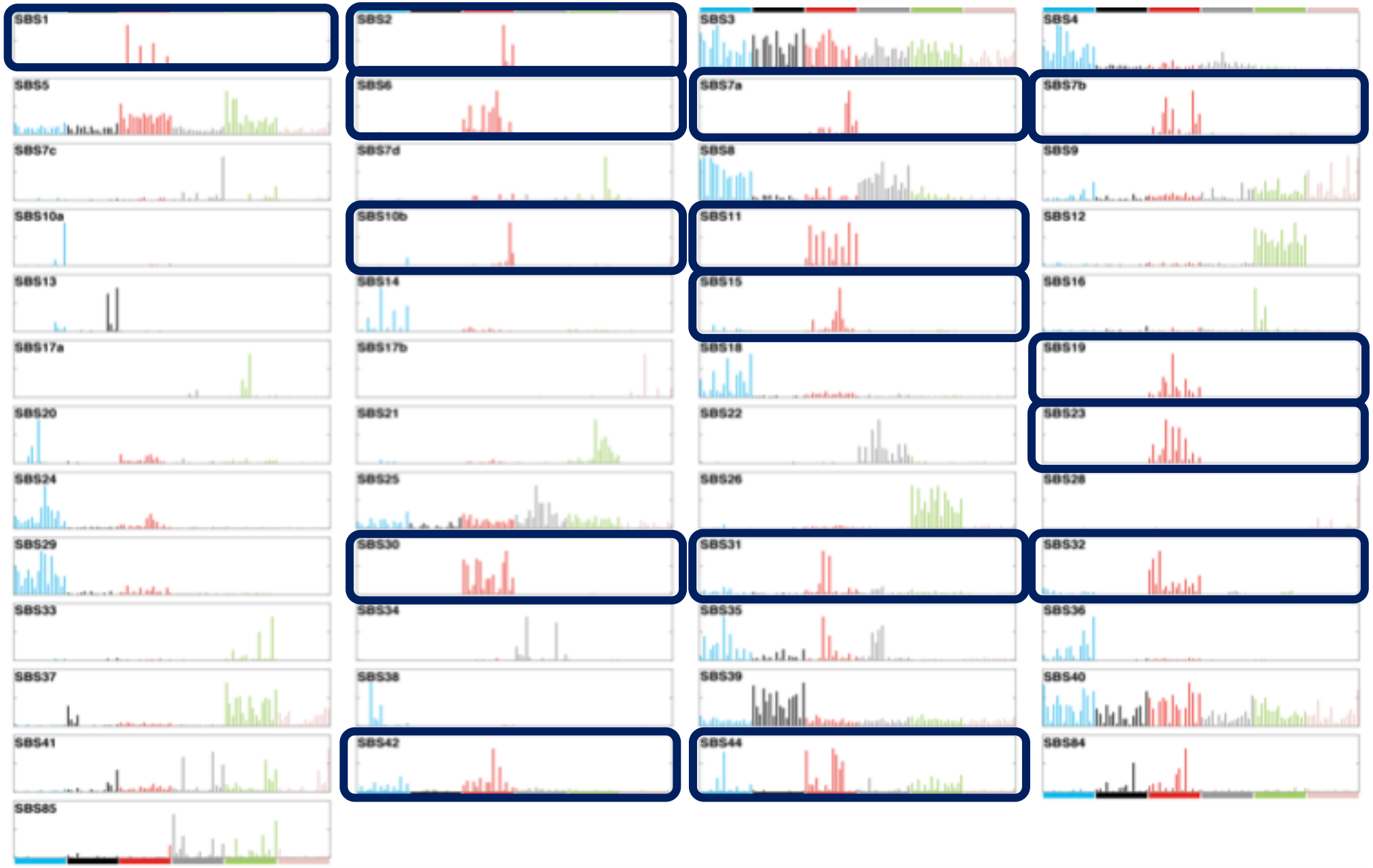
Repertoire of substitution signatures in human cancer

C>T



Repertoire of substitution signatures in human cancer

C>A

Repertoire of substitution signatures in human cancer

C>G

Repertoire of substitution signatures in human cancer

T>A

Repertoire of substitution signatures in human cancer

T>C

Repertoire of substitution signatures in human cancer

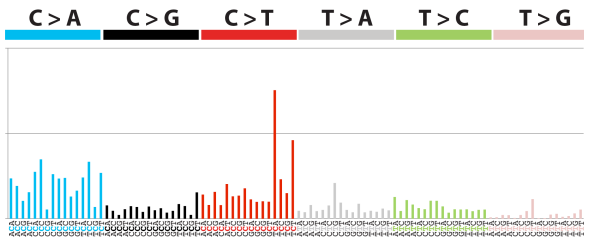
T>G

Contributions of mutational signatures to individual cancer cases

A single lung cancer genome

Contributions of mutational signatures to individual cancer cases

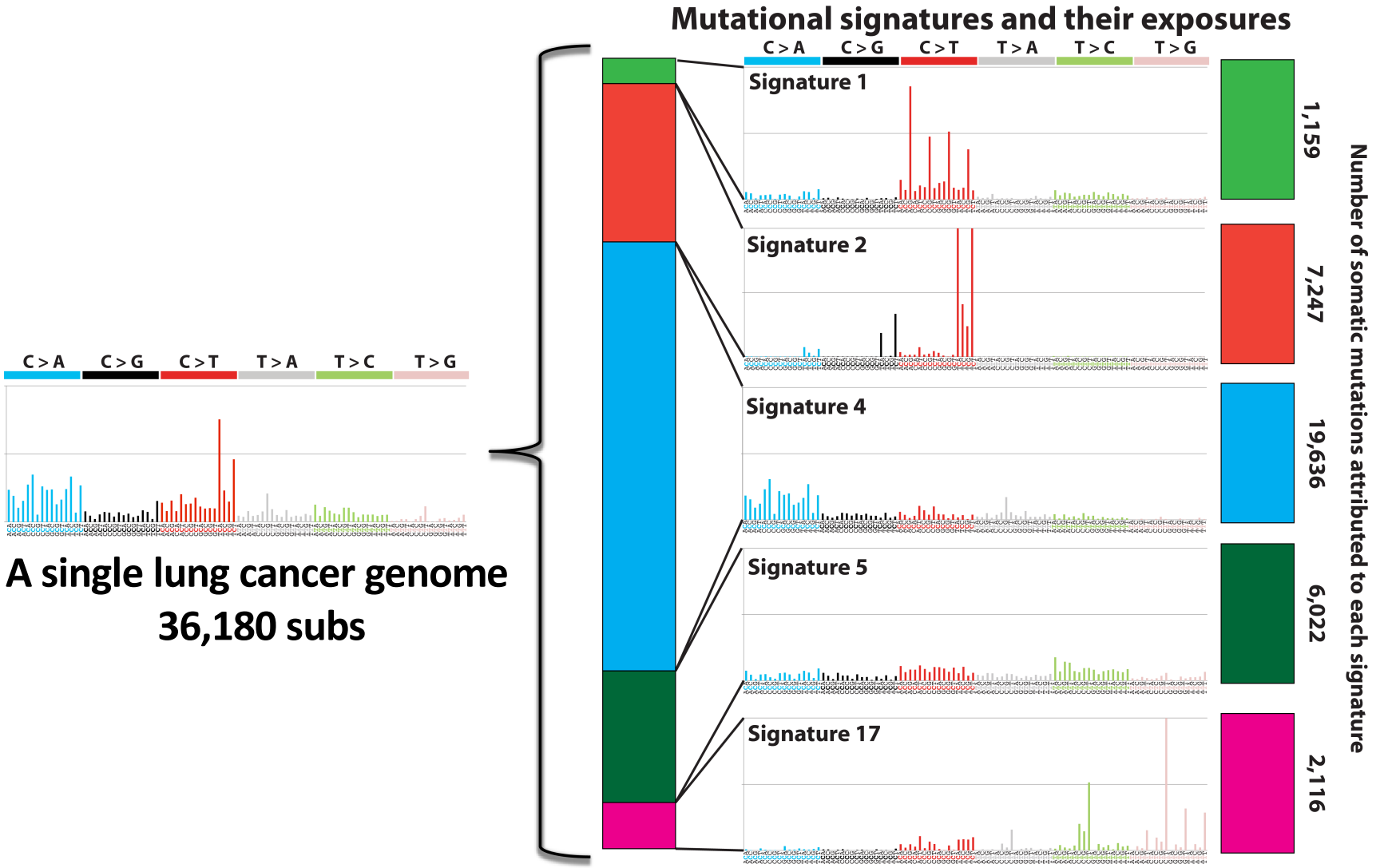
A single lung cancer genome



A single lung cancer genome
36,180 subs

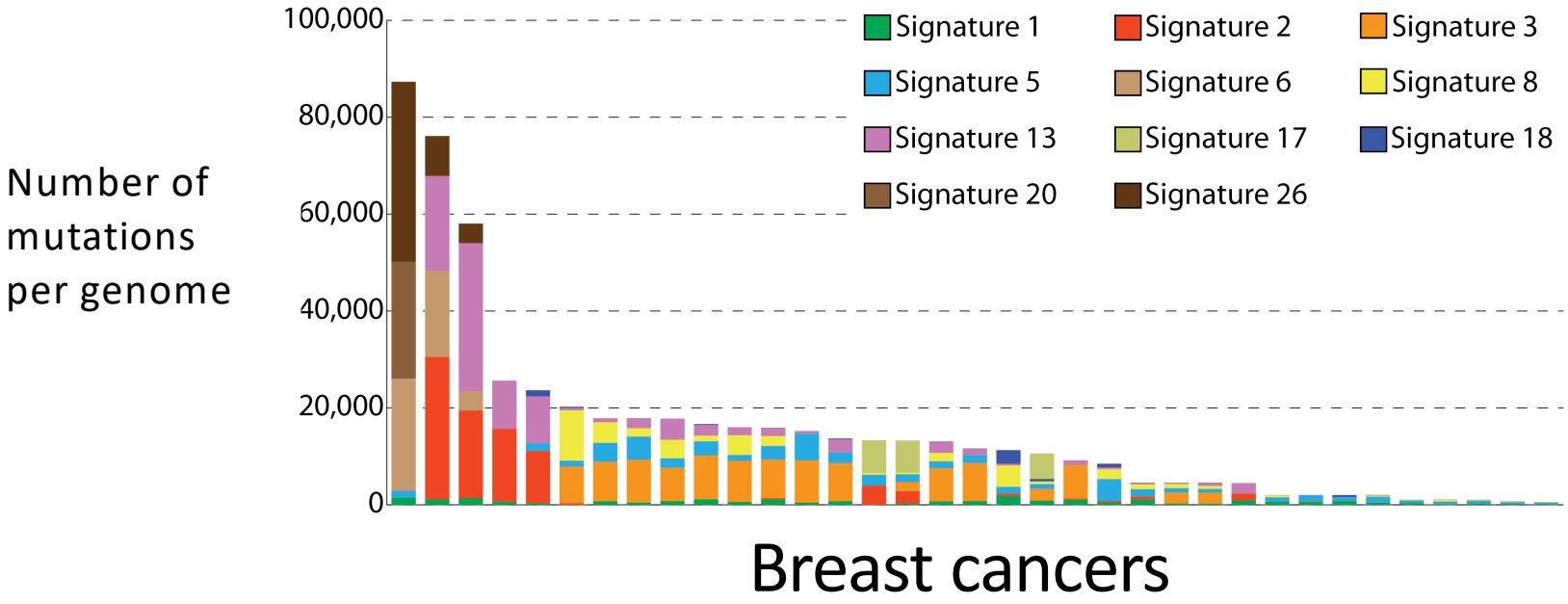
Contributions of mutational signatures to individual cancer cases

A single lung cancer genome



Contributions of mutational signatures to individual cancer cases

Mutational signatures in forty breast cancer genomes



Substitution signatures activity in highly curated samples

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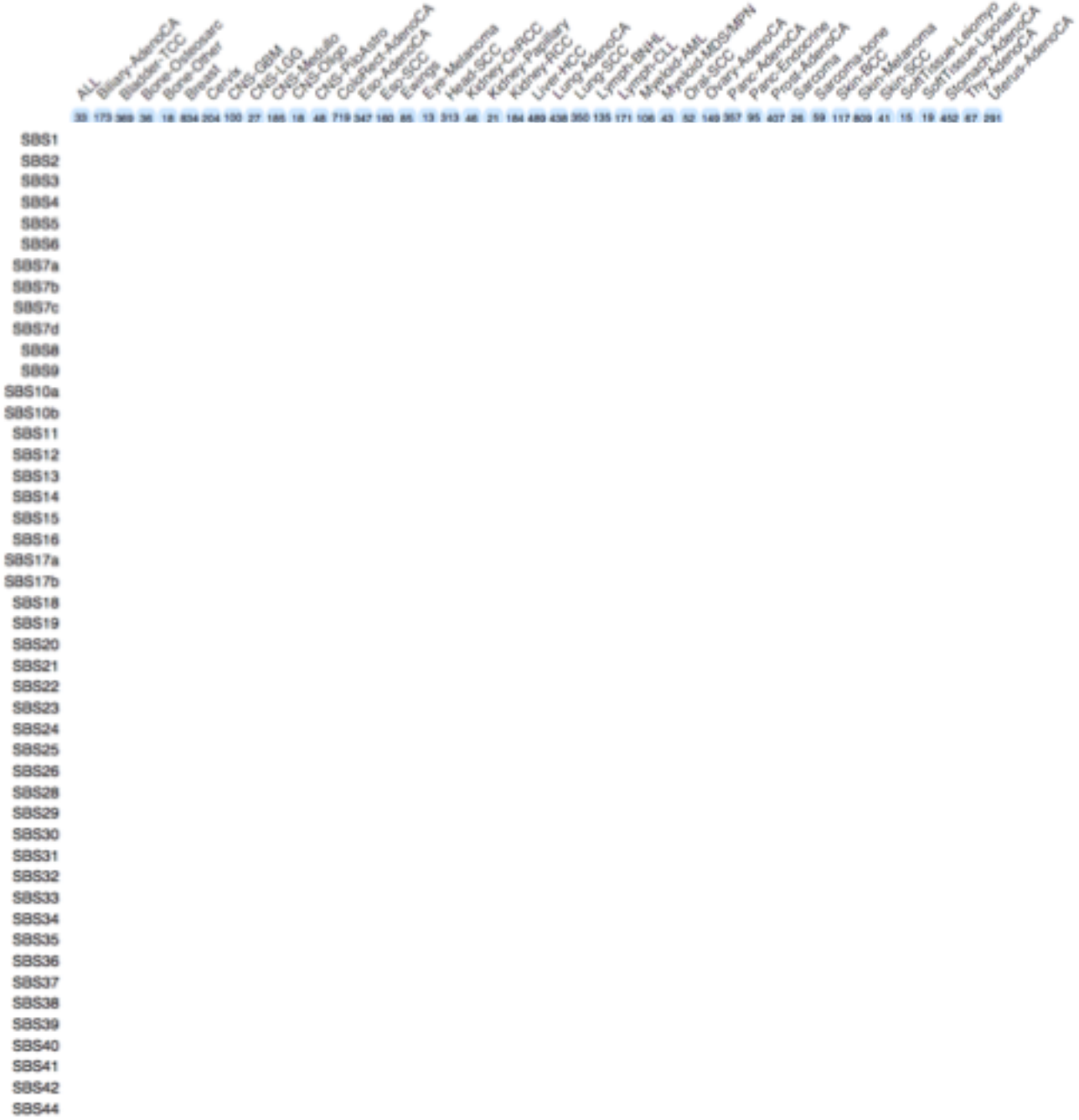

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100% of ALL samples have signature 1 0.032 median mutations per MB

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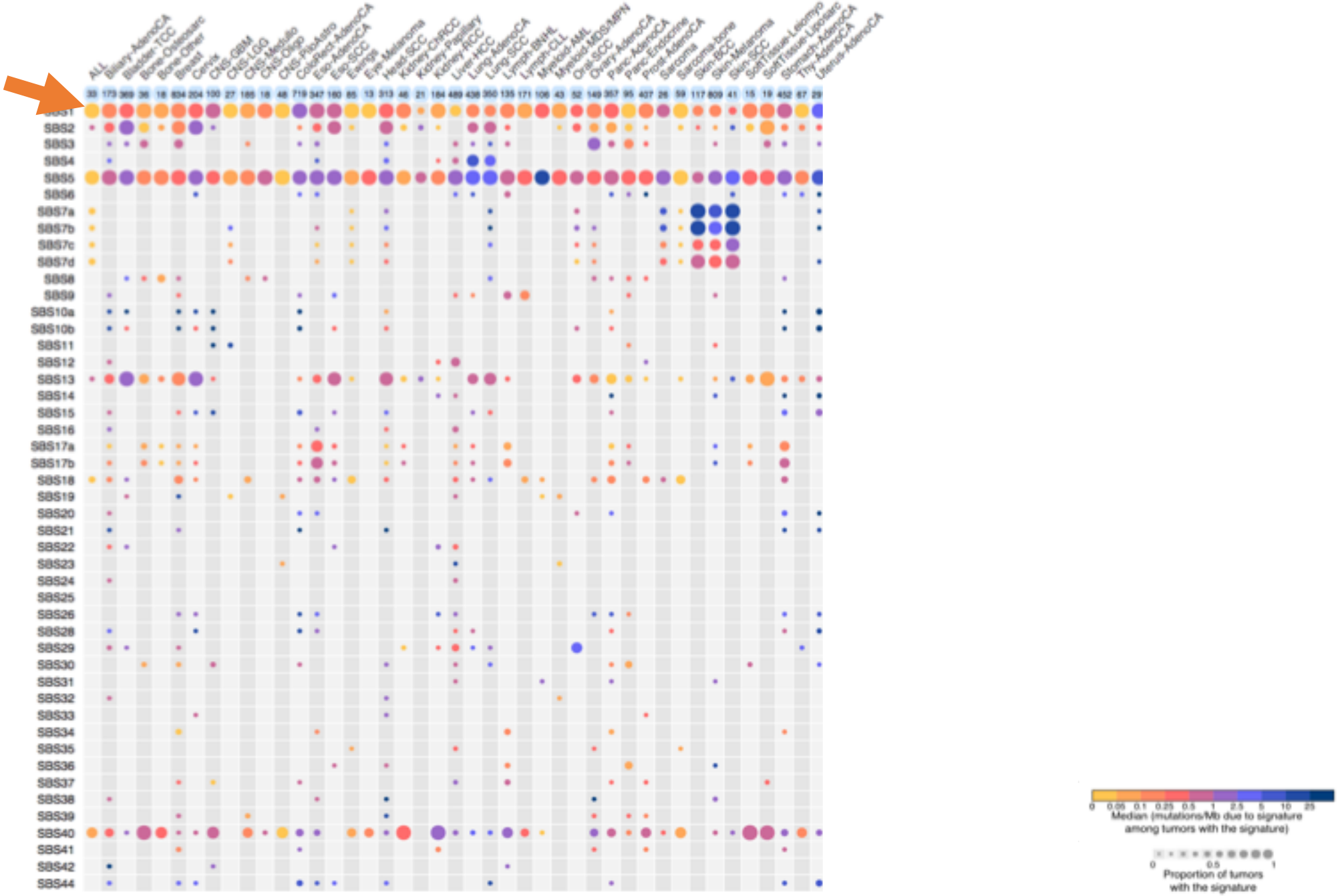

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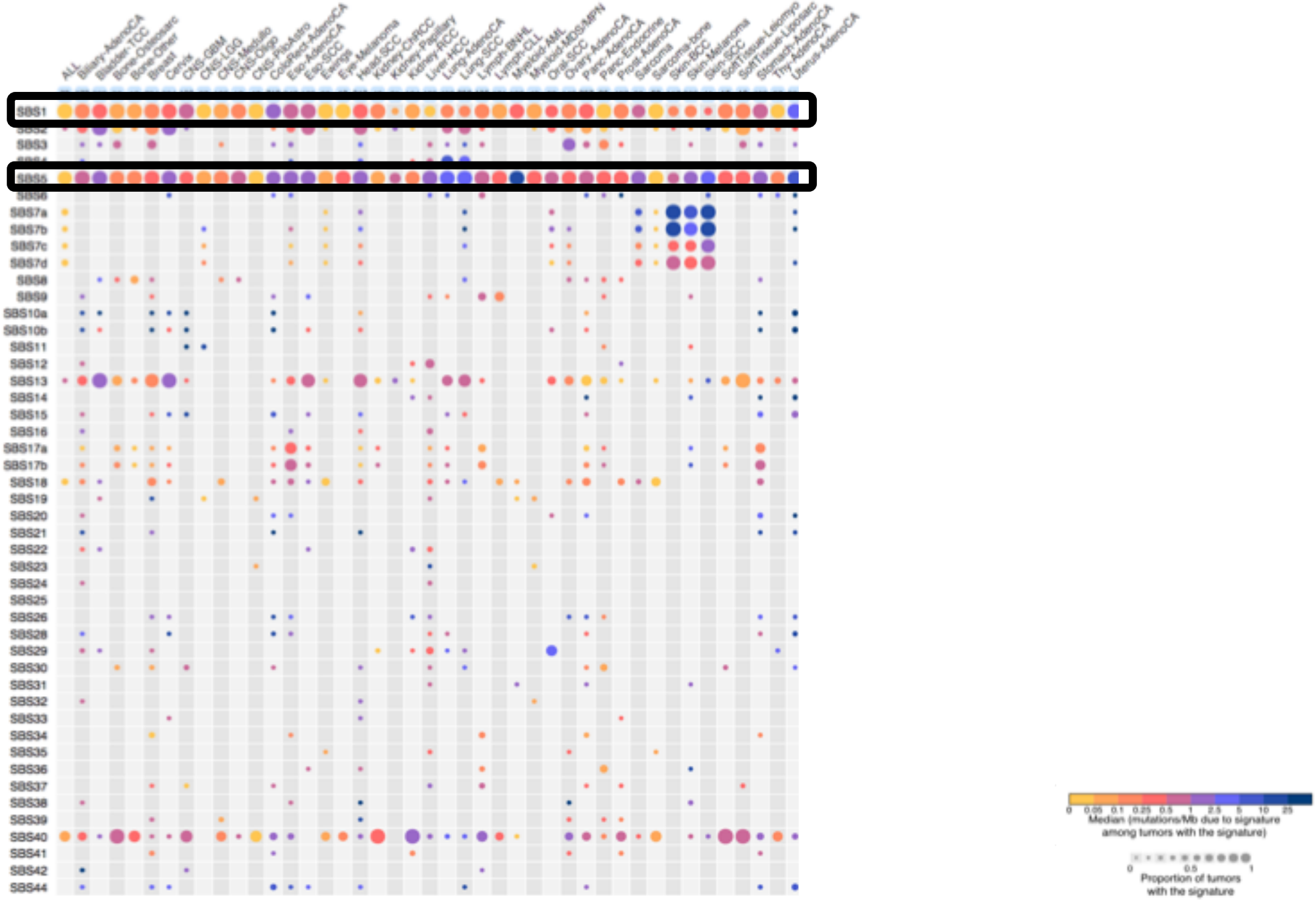

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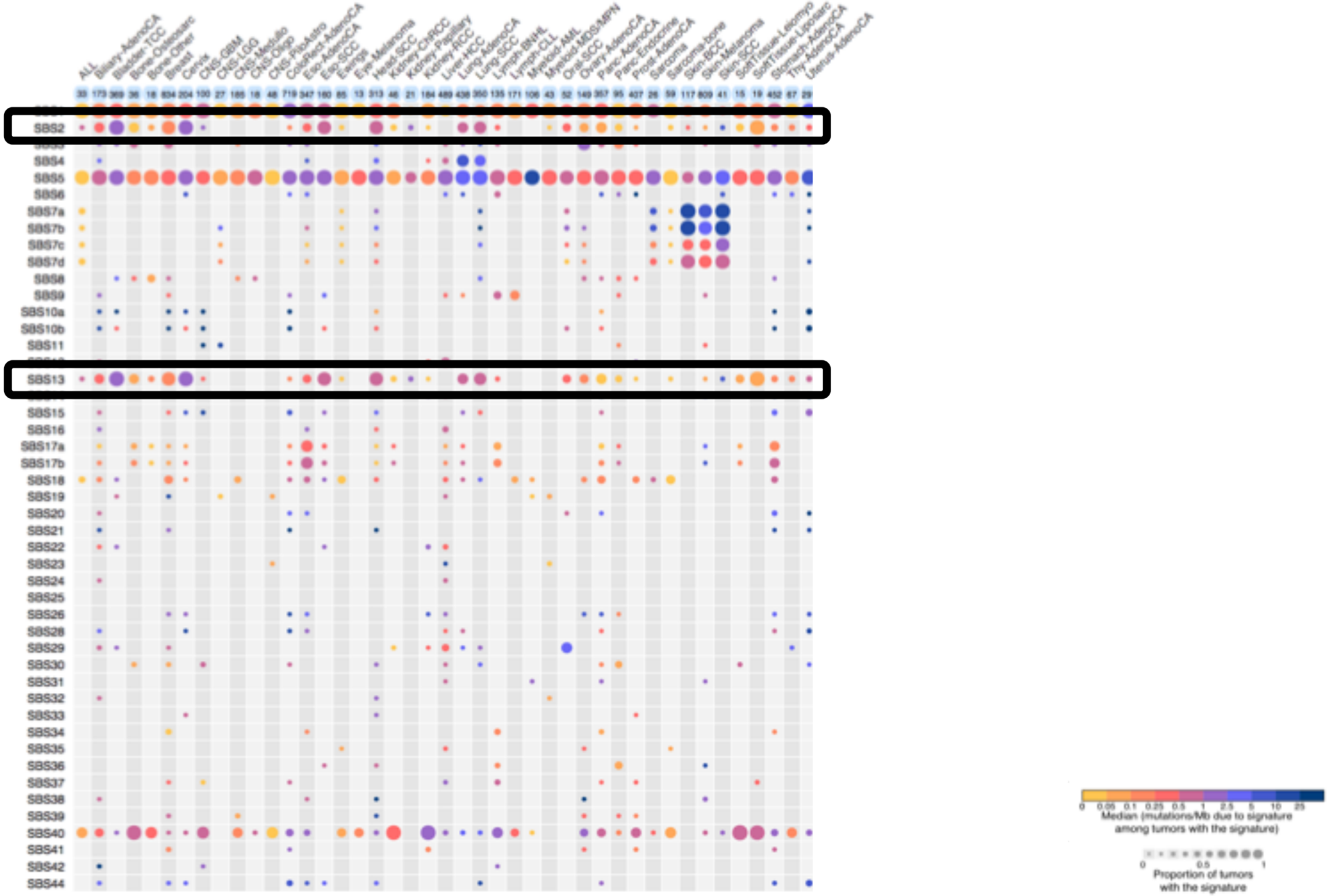

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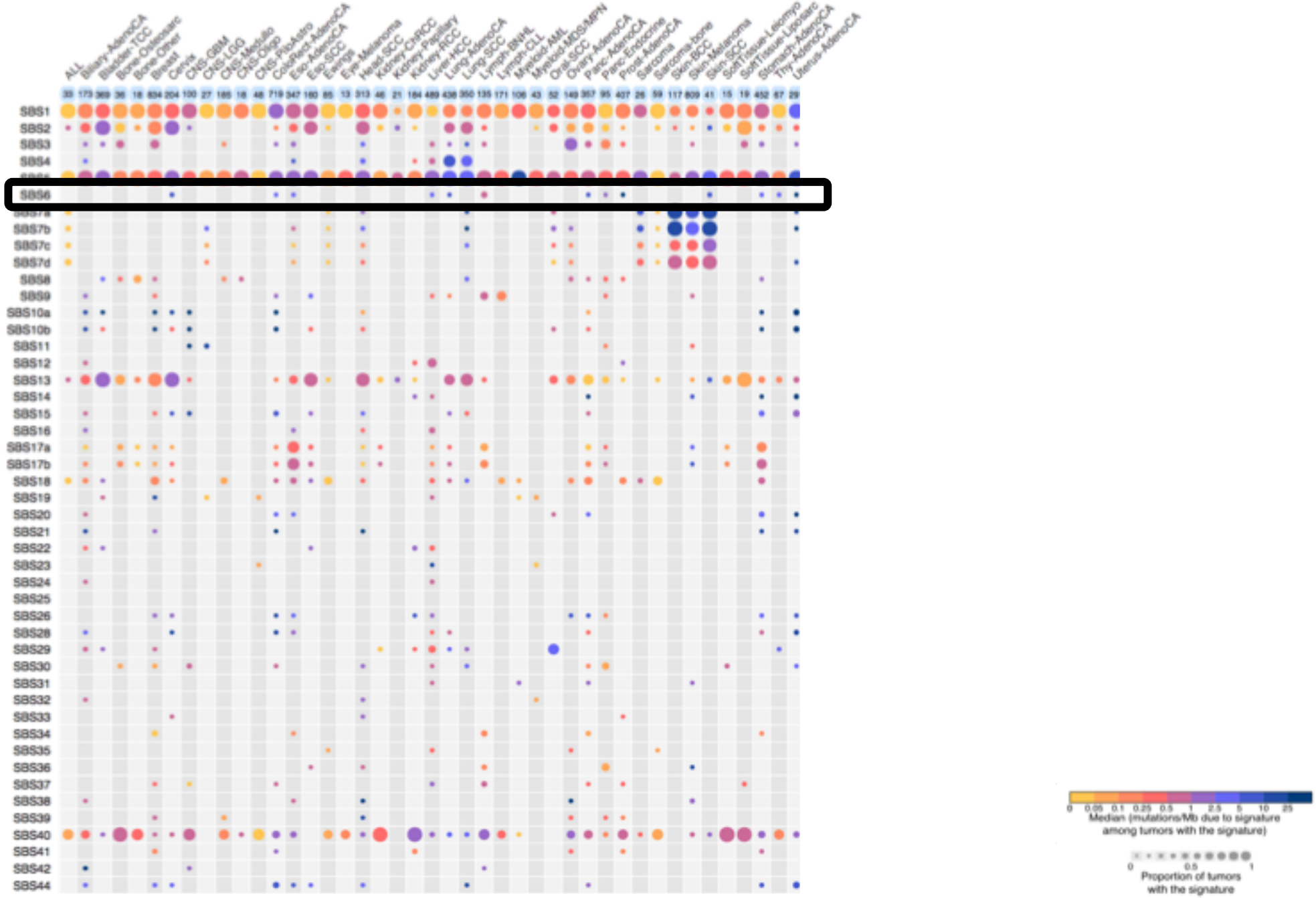

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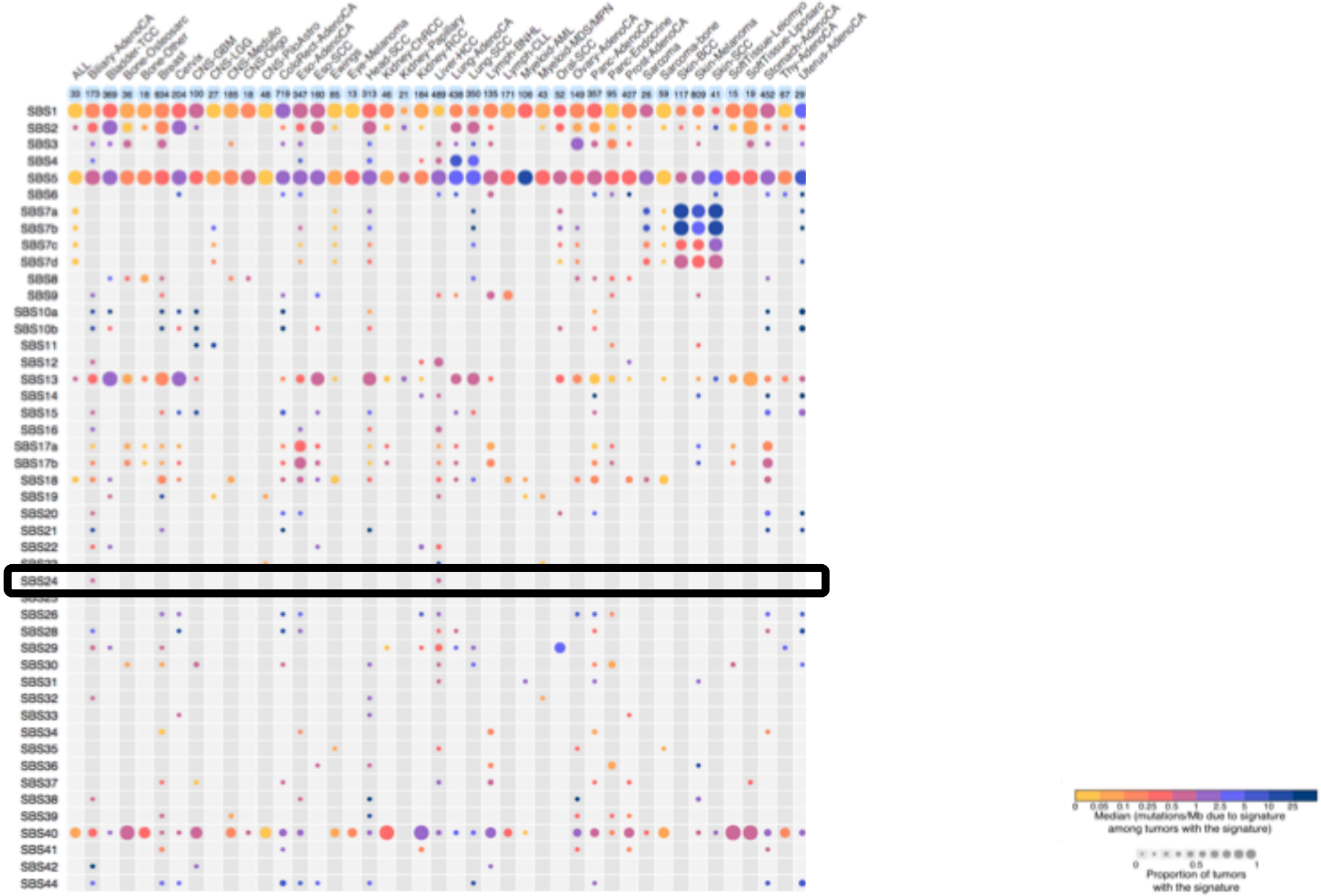

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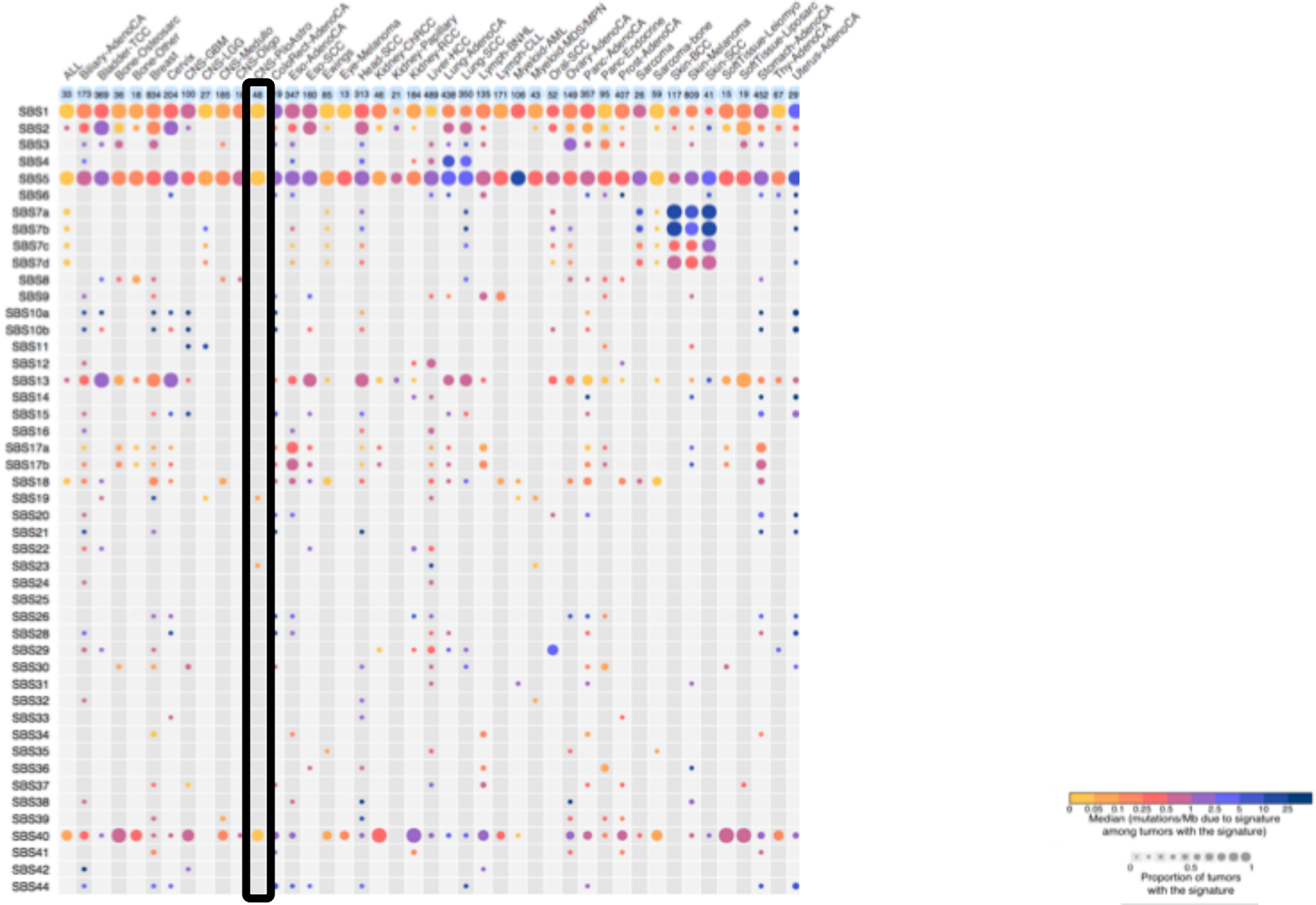

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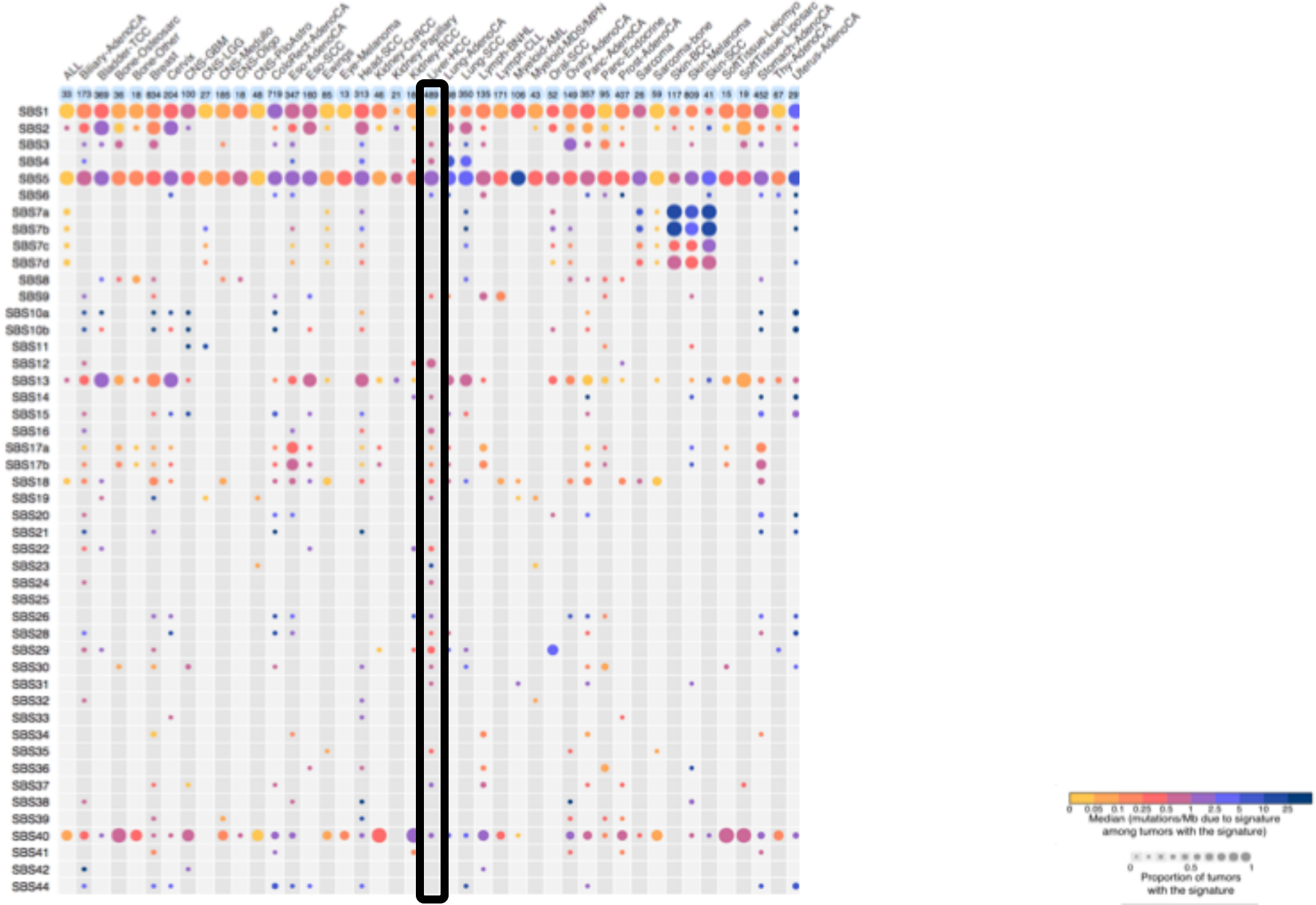

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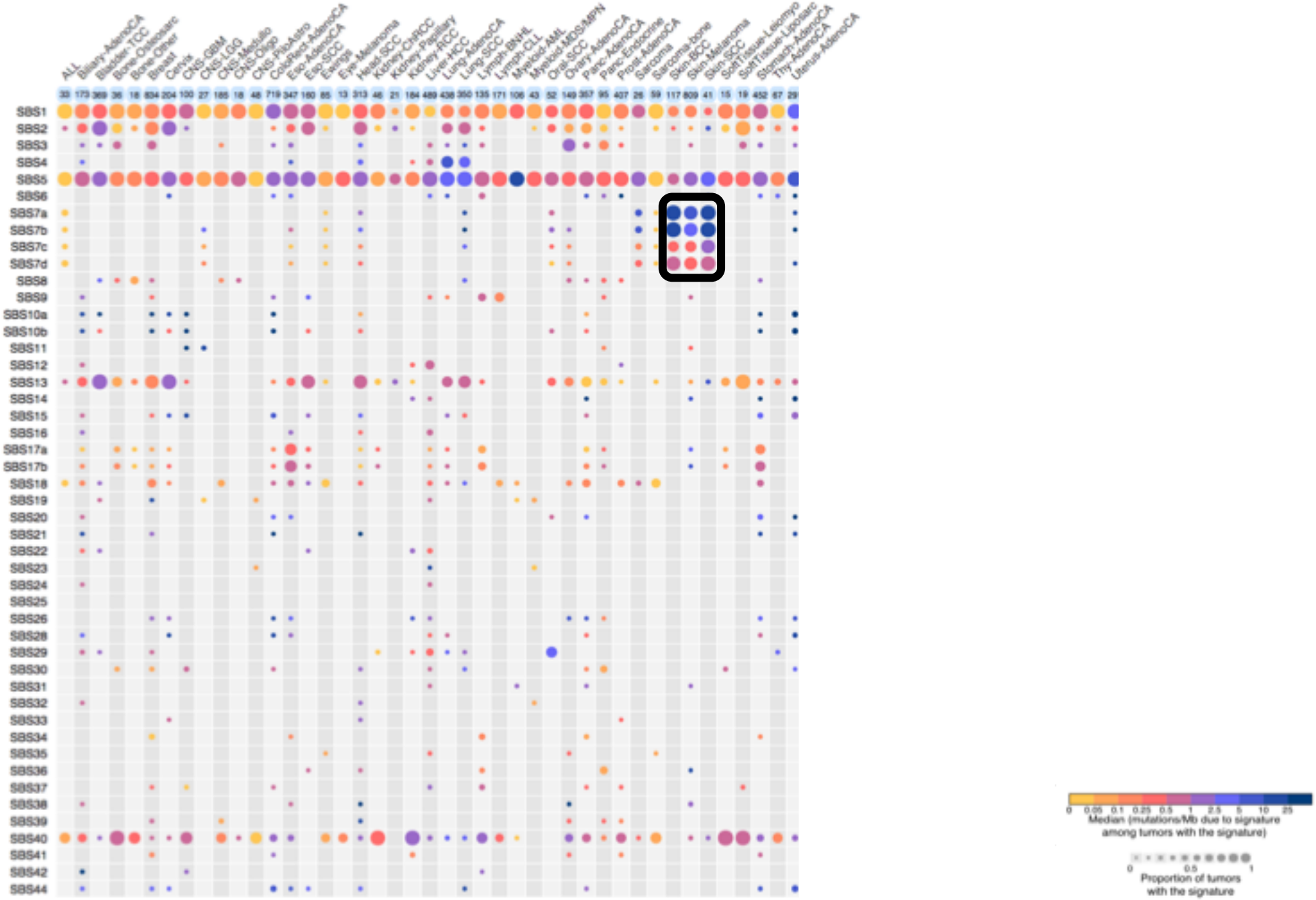
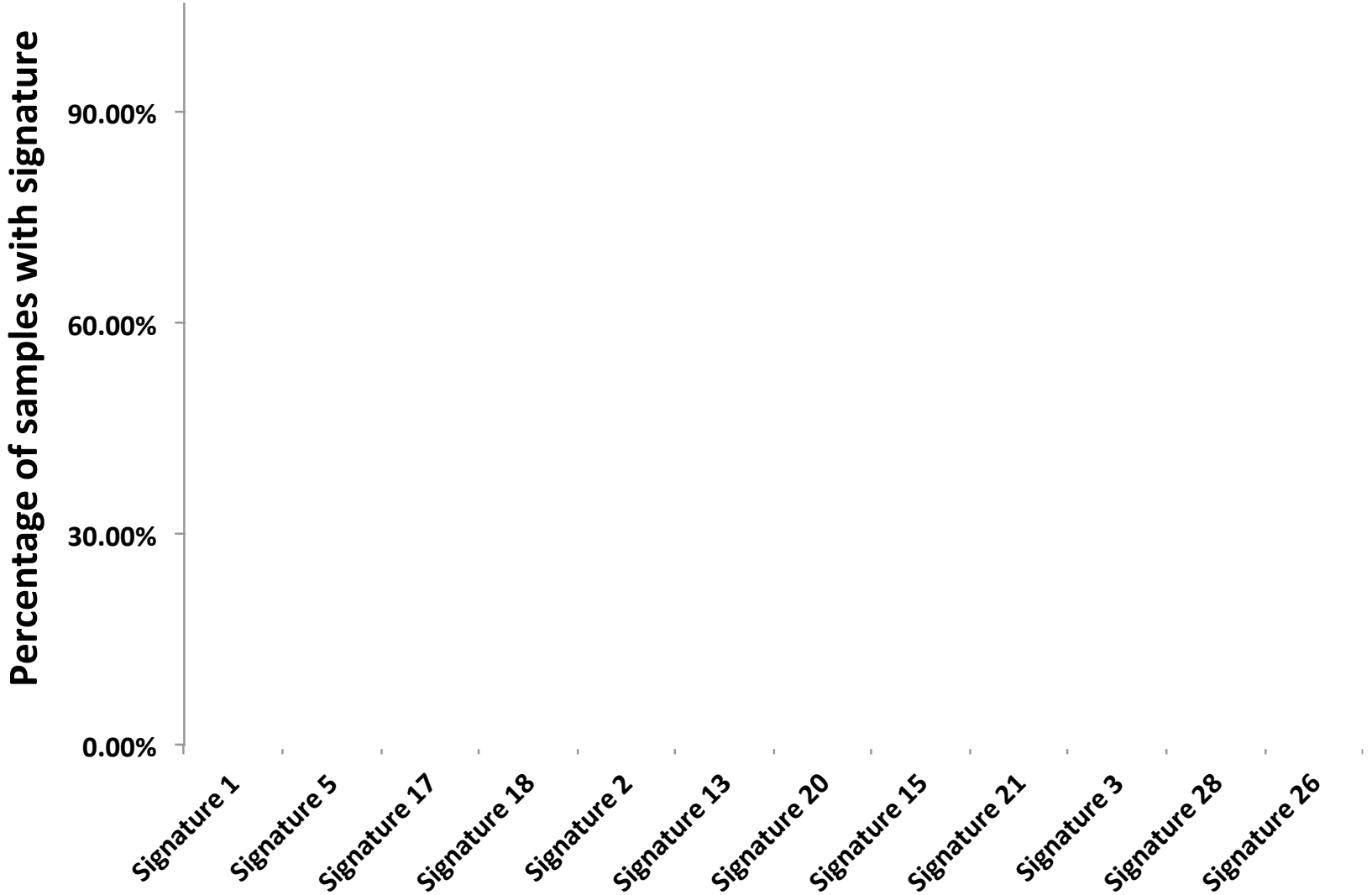


Cancer Type Example: Stomach Cancer



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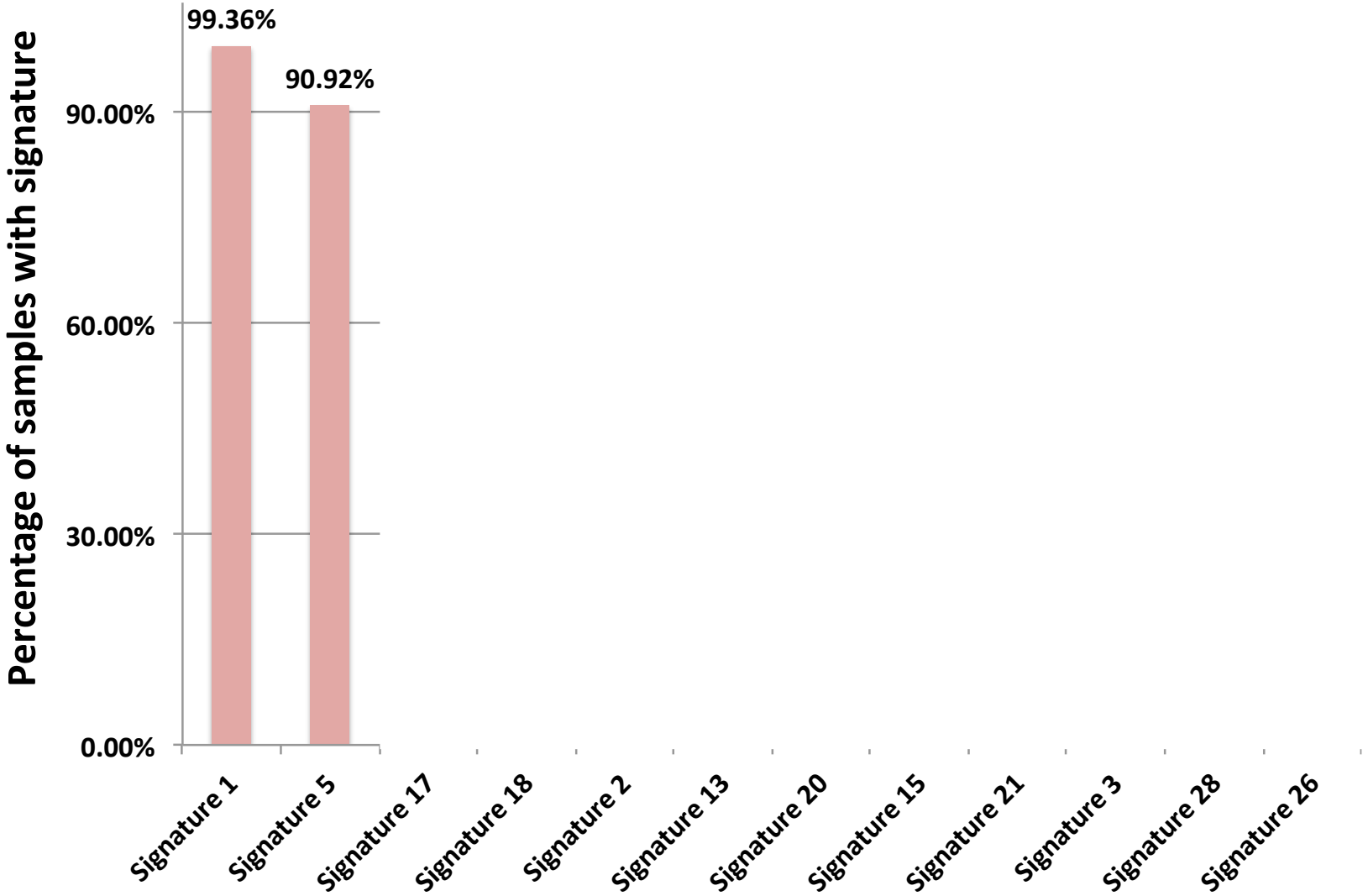

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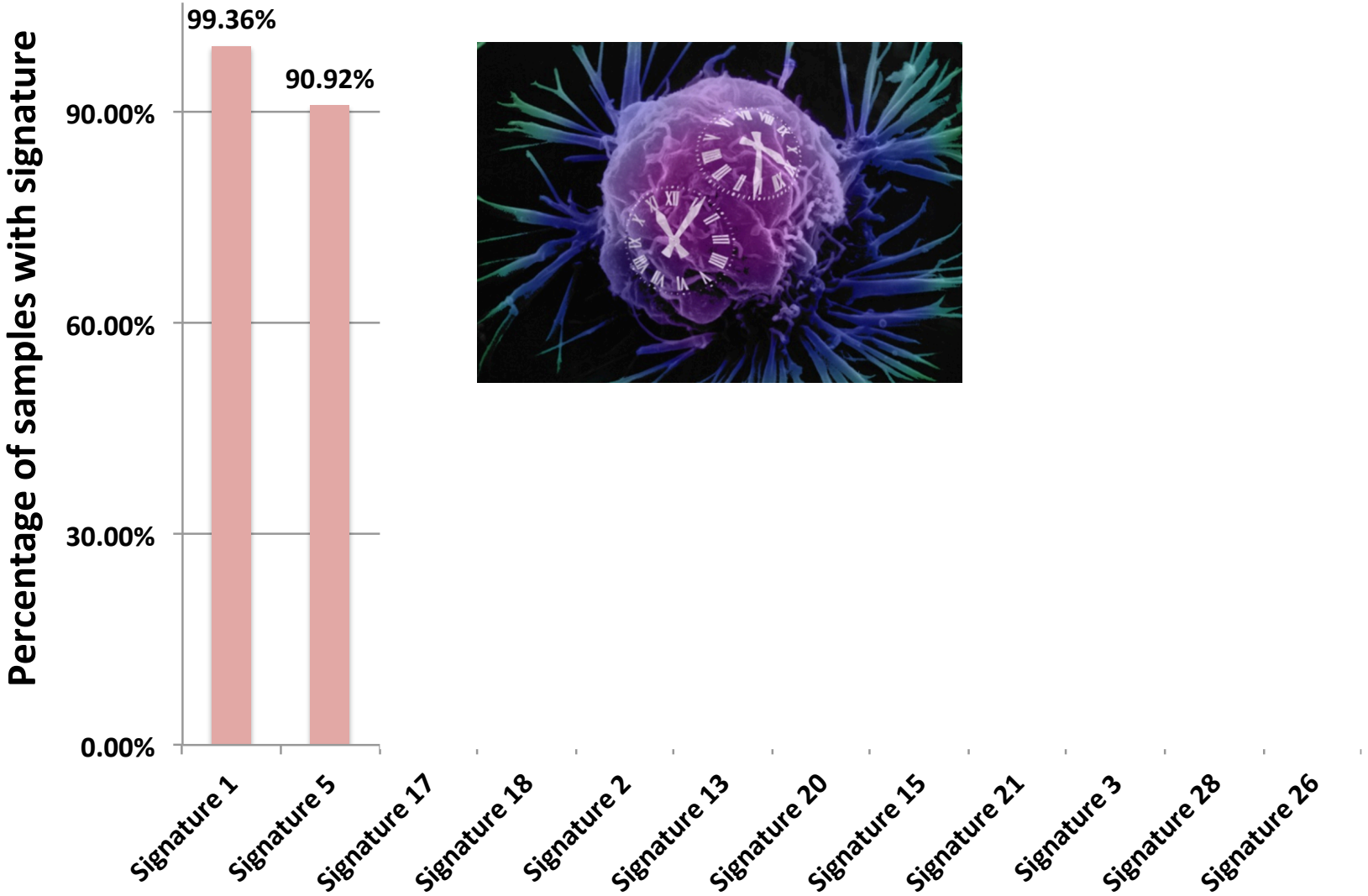

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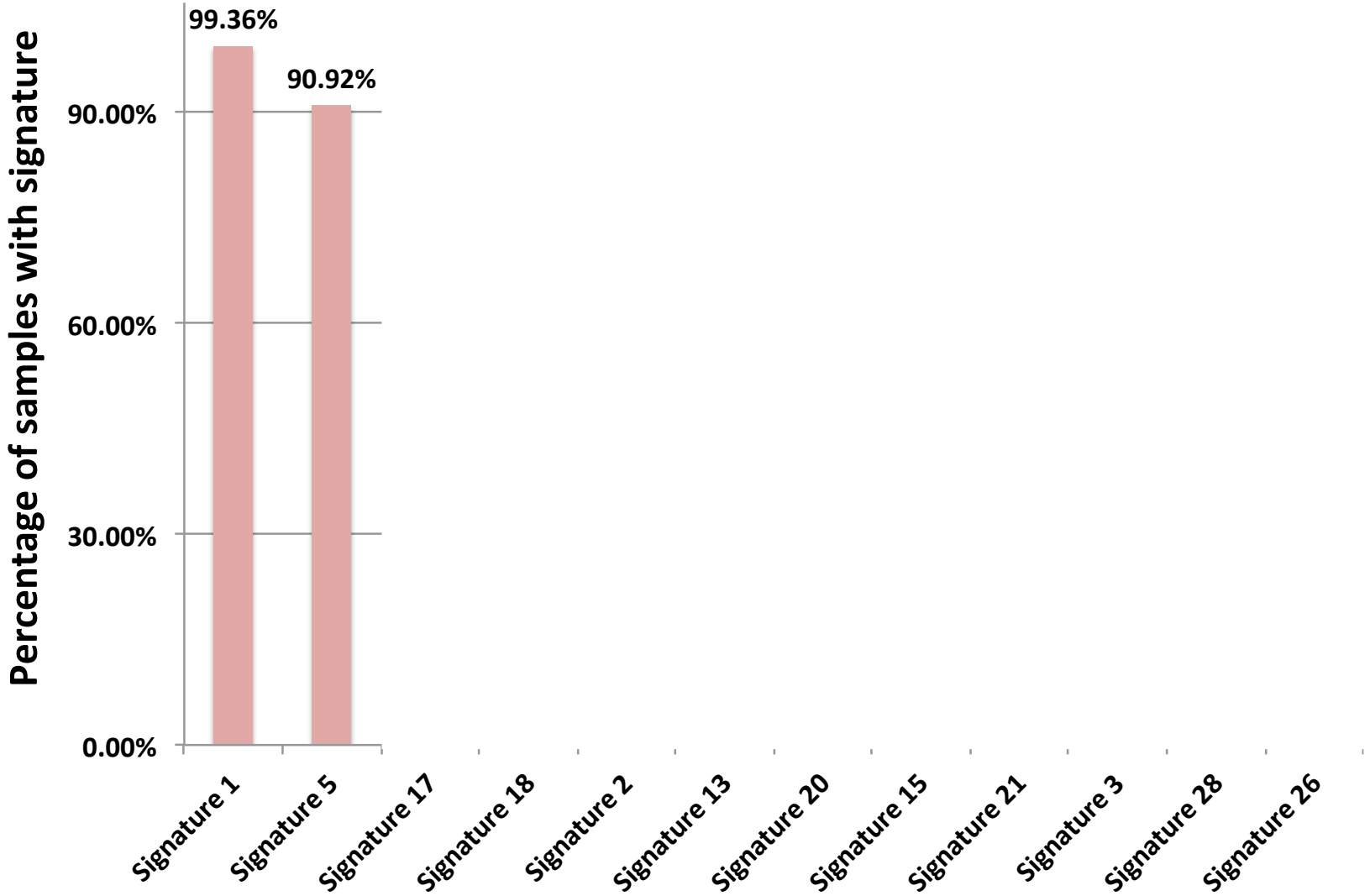

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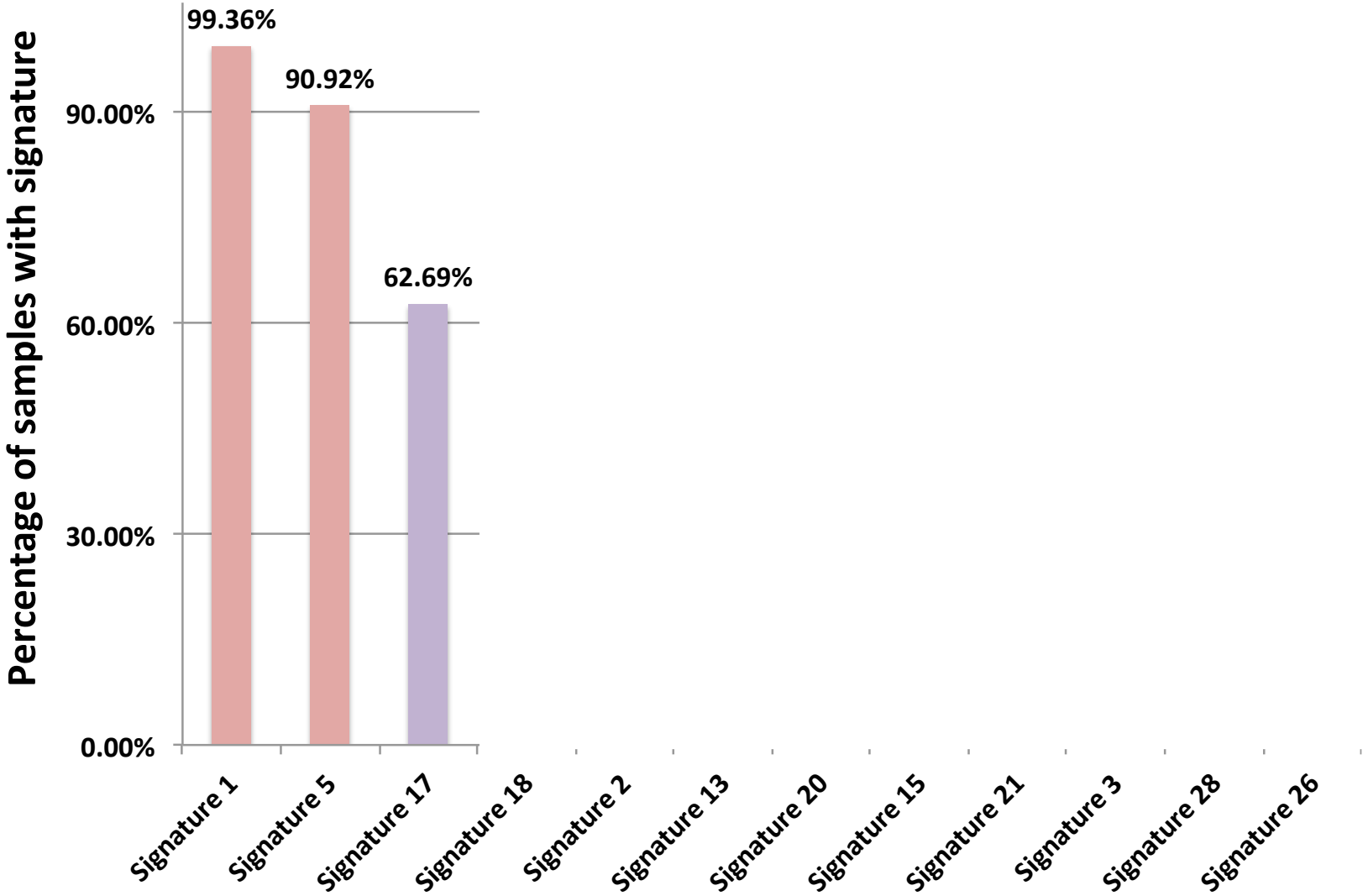

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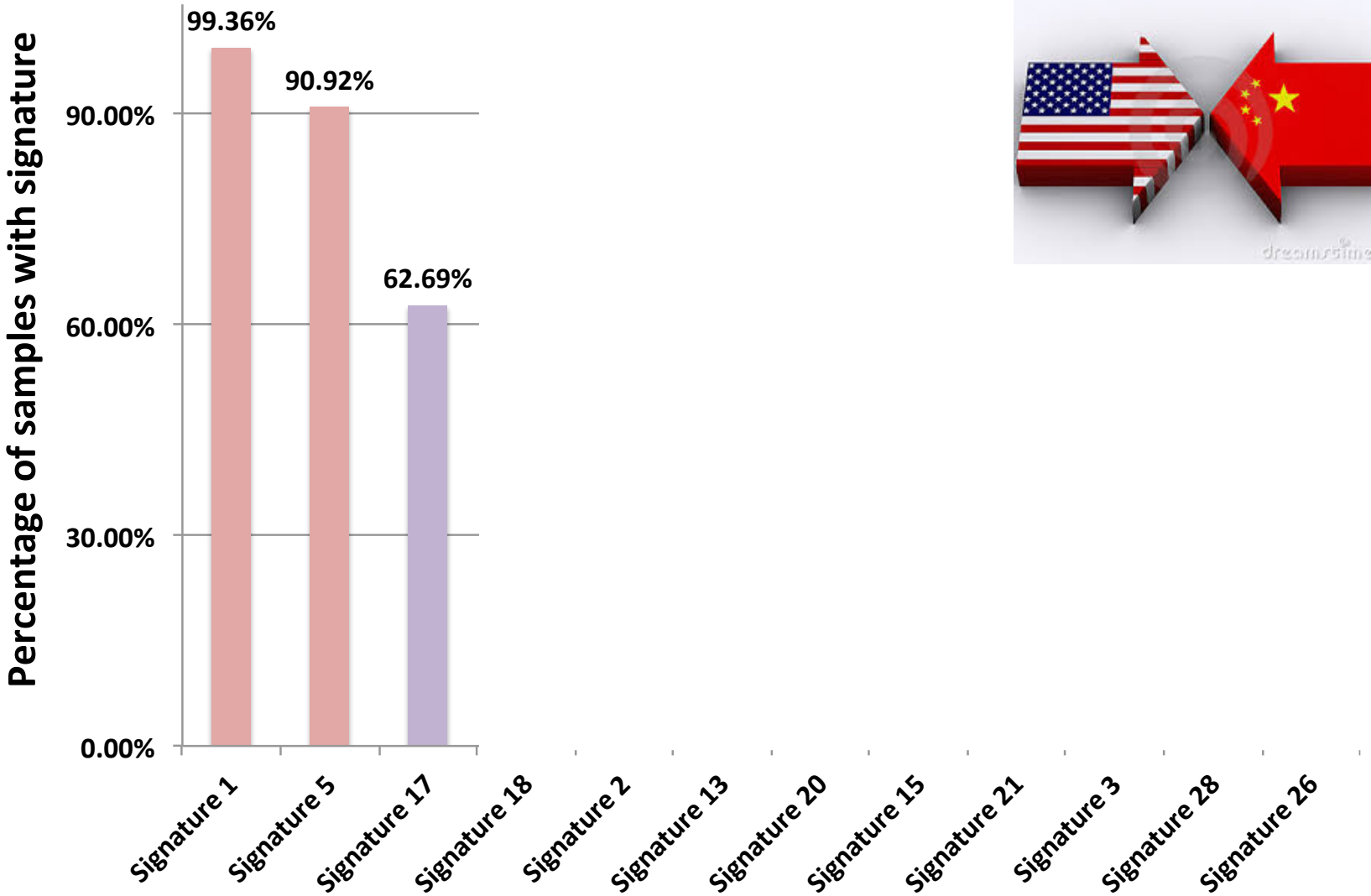

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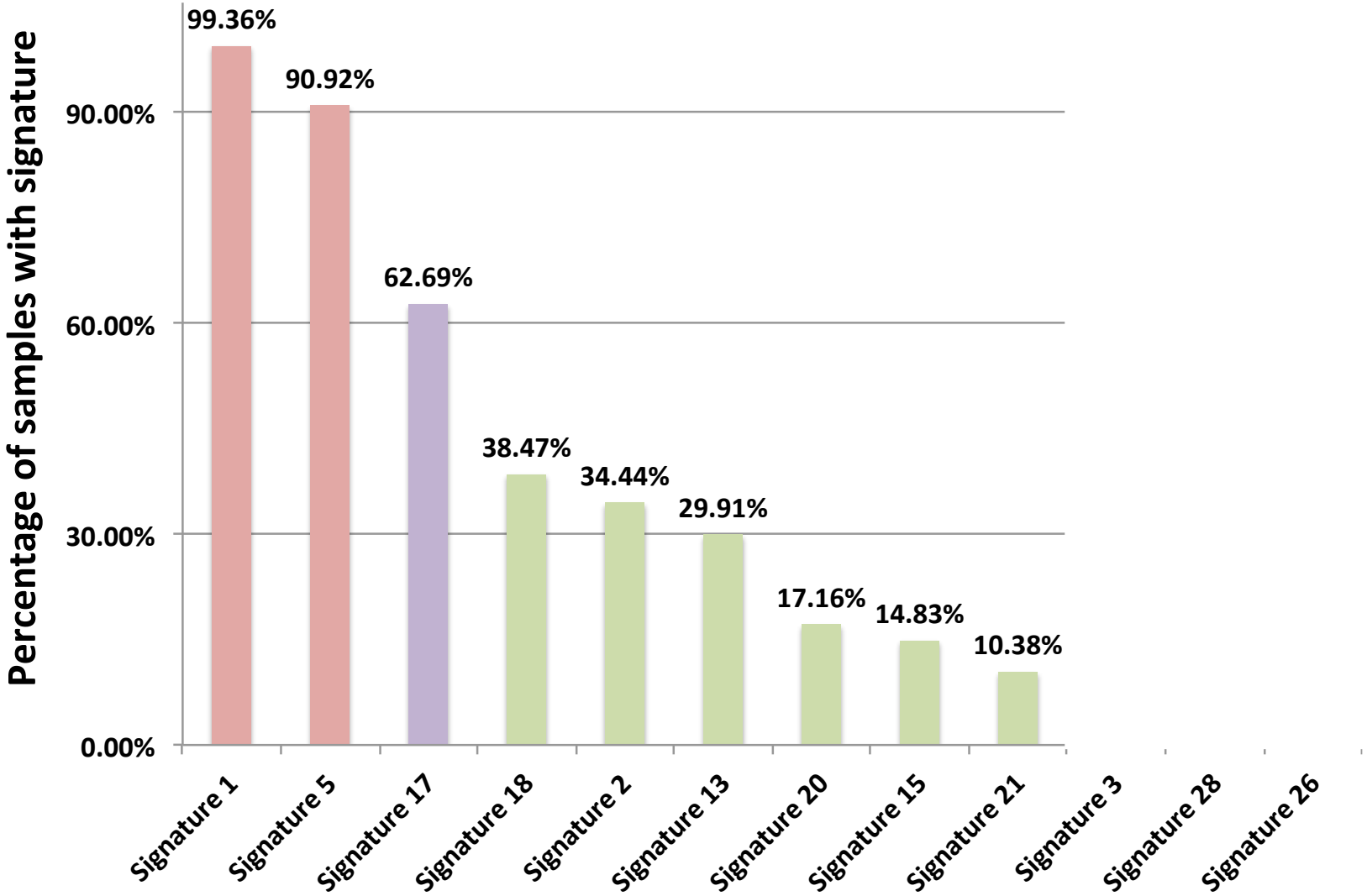

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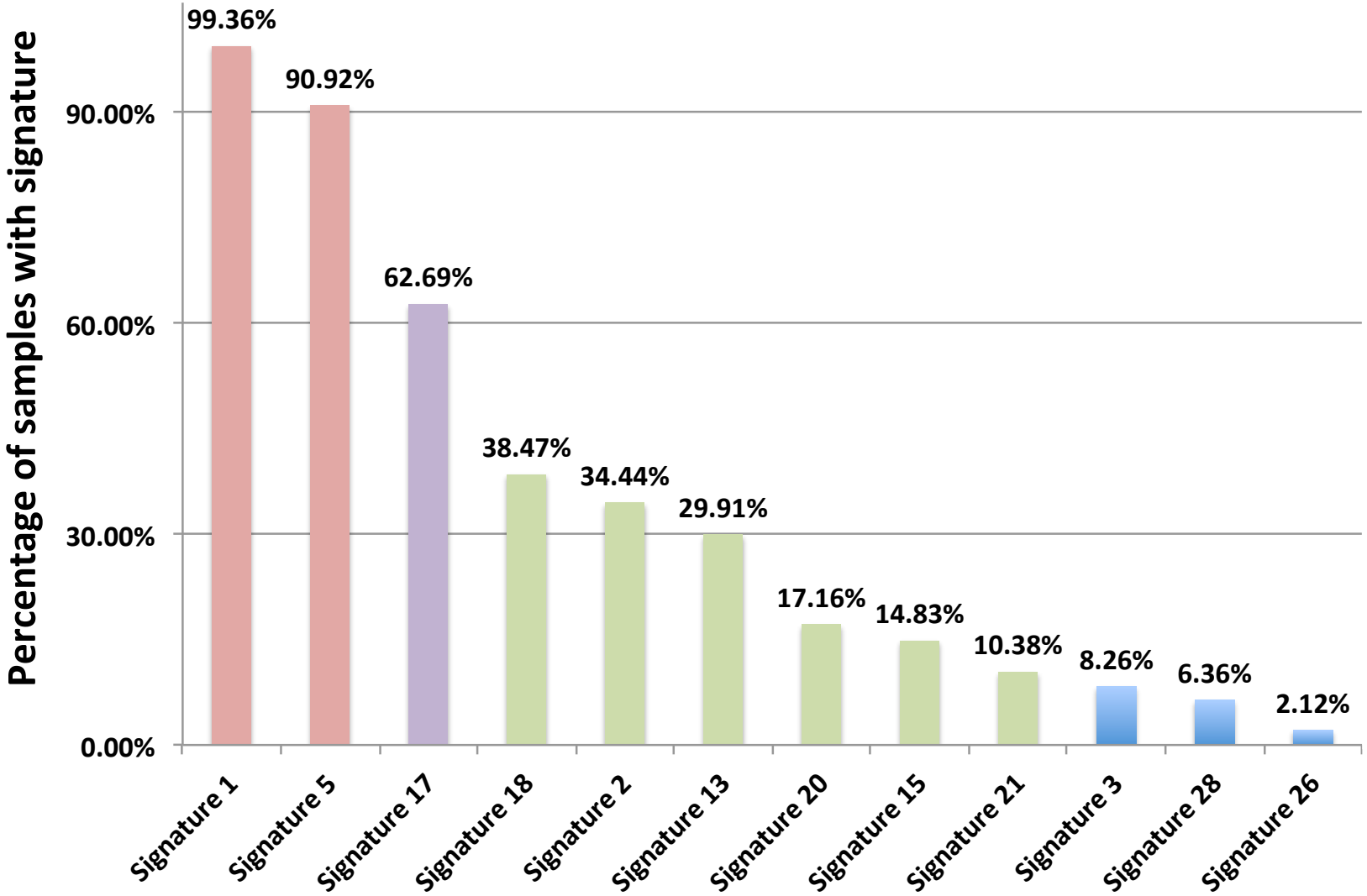

Aetiologies of SBS mutational signatures

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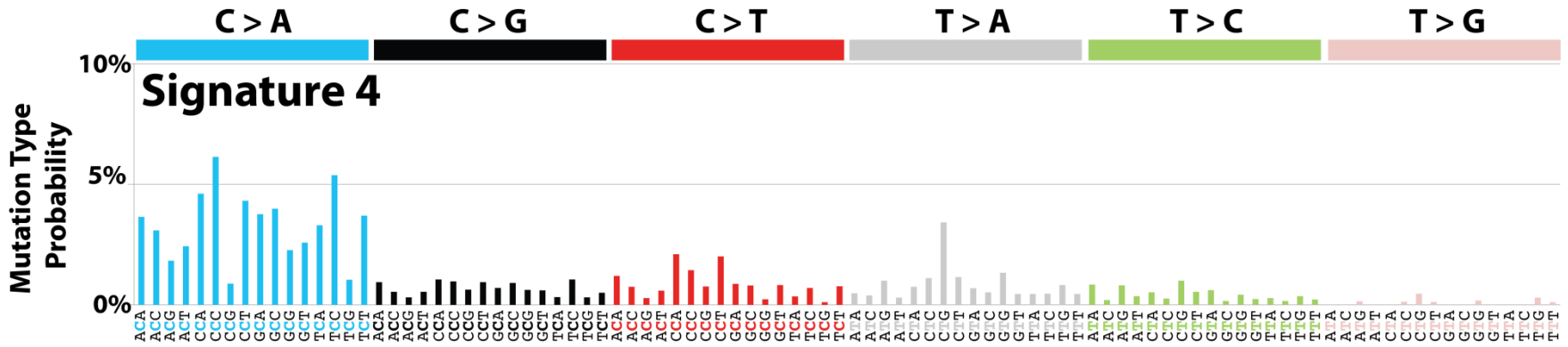
Tobacco smoking

How do you know these aetiologies?

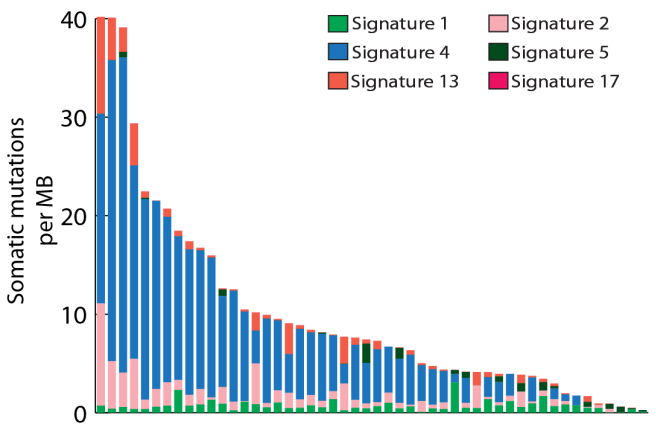
Signature 4 is likely due to tobacco smoking



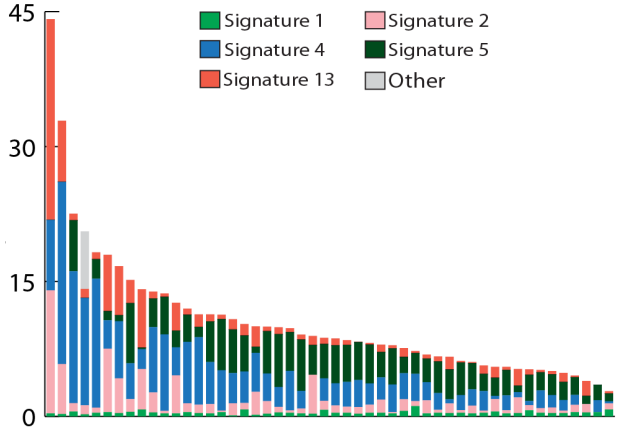
Contributions of mutational signatures to smoking induced and non-smoking induced cancer types

Smoking induced cancer types

Lung adenocarcinoma



Lung squamous carcinoma

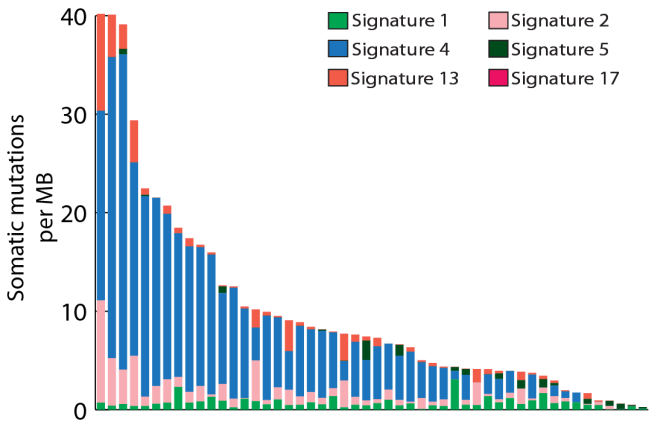


Contributions of mutational signatures to smoking induced and non-smoking induced cancer types

Smoking induced cancer types

Non-smoking induced cancer types

Lung adenocarcinoma



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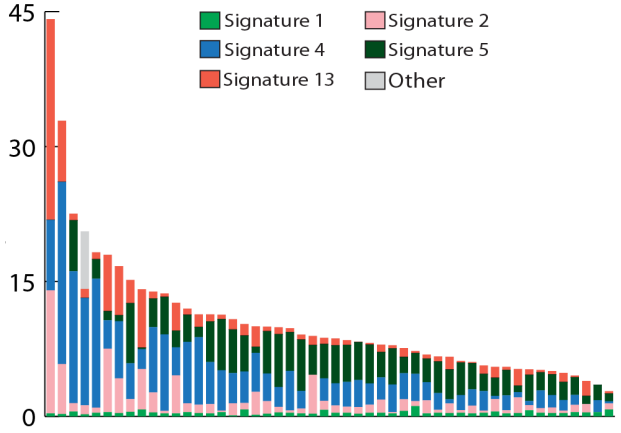
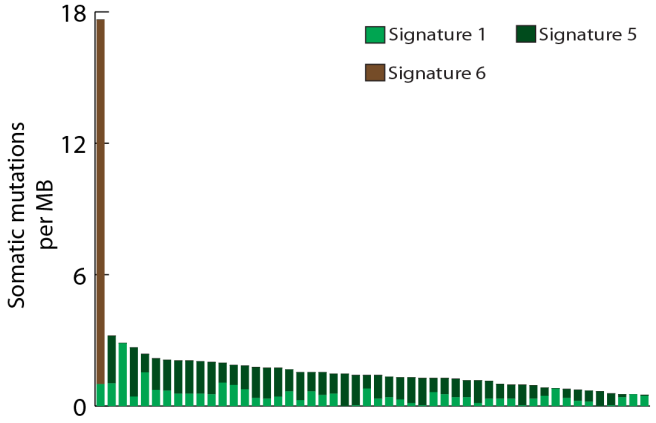
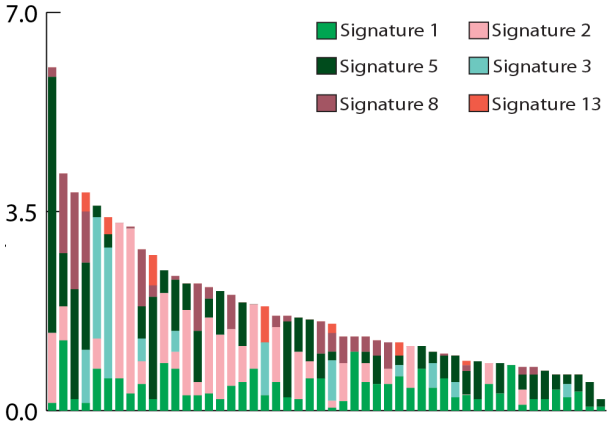


Low grade glioma



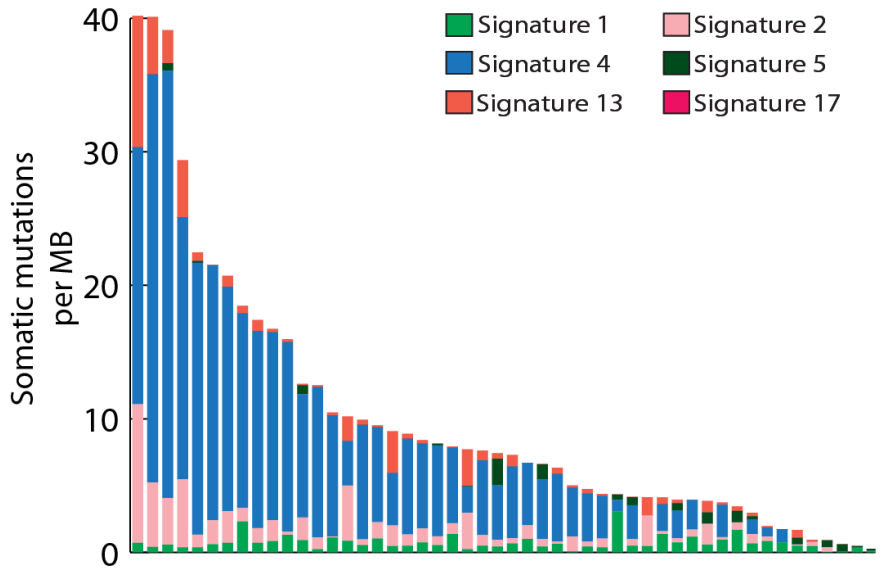
Breast cancer



Contributions of mutational signatures to lung adenocarcinomas

Contributions of mutational signatures to lung adenocarcinomas

Tobacco smokers



Contributions of mutational signatures to lung adenocarcinomas

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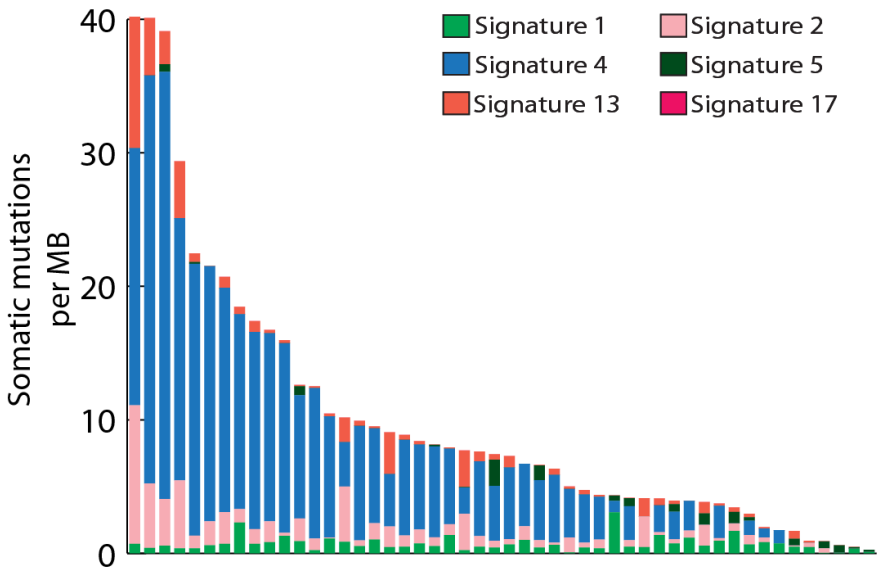
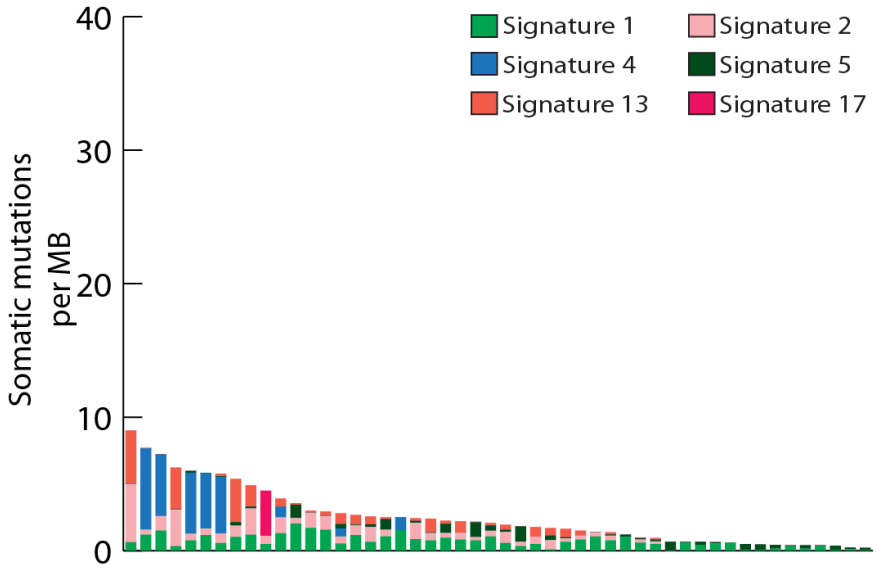
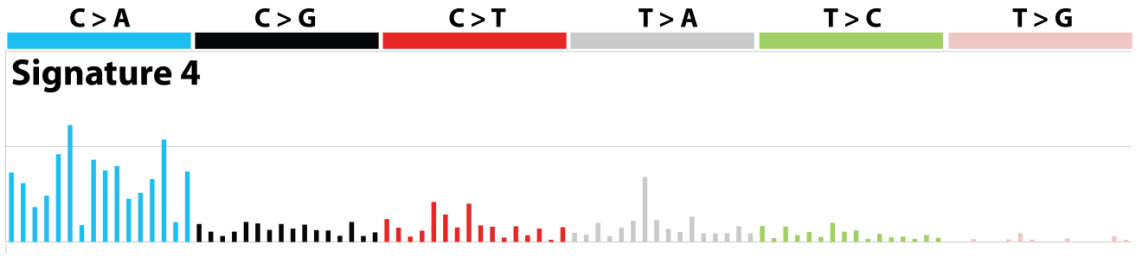


Life-long non-smokers



The mutational signature of *in vitro* benzo[*a*]pyrene exposure is similar to signature 4

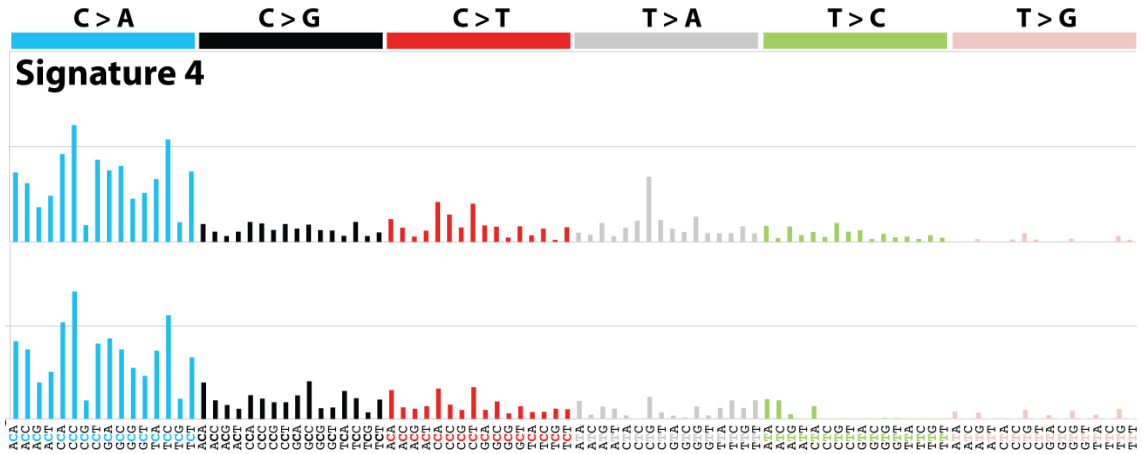
Signature 4 extracted from human cancers



The mutational signature of *in vitro* benzo[*a*]pyrene exposure is similar to signature 4

Signature 4 extracted from human cancers

Signature of benzo[*a*]pyrene exposure *in vitro*



Evidence for the aetiology of signature 4

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Identified only in cancer types epidemiologically known to be caused by tobacco smoking

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Highly enriched in tobacco smokers when compared to tobacco non-smokers

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Identified only in cancer types epidemiologically known to be caused by tobacco smoking

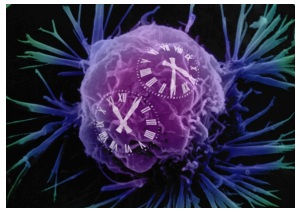
Highly enriched in tobacco smokers when compared to tobacco non-smokers

The pattern of signature 4 matches *in vitro* experimental results in which cells were exposed to known tobacco carcinogens

Aetiologies of SBS mutational signatures

Aetiologies of SBS mutational signatures

Clock-like processes



Aetiologies of SBS mutational signatures

Tobacco smoking

Aetiologies of SBS mutational signatures

Tobacco chewing

Aetiologies of SBS mutational signatures

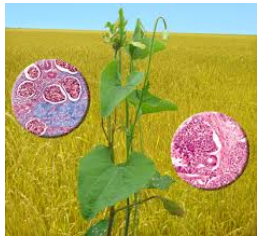
Ultraviolet light

Aetiologies of SBS mutational signatures

Aflatoxin

Aetiologies of SBS mutational signatures

Aristolochic acid



Aetiologies of SBS mutational signatures

Aetiologies of SBS mutational signatures

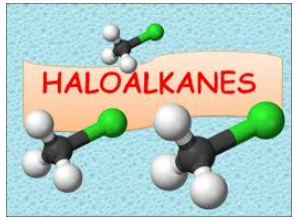
Platinum therapy

Aetiologies of SBS mutational signatures

Azathioprine

Aetiologies of SBS mutational signatures

Haloalkanes

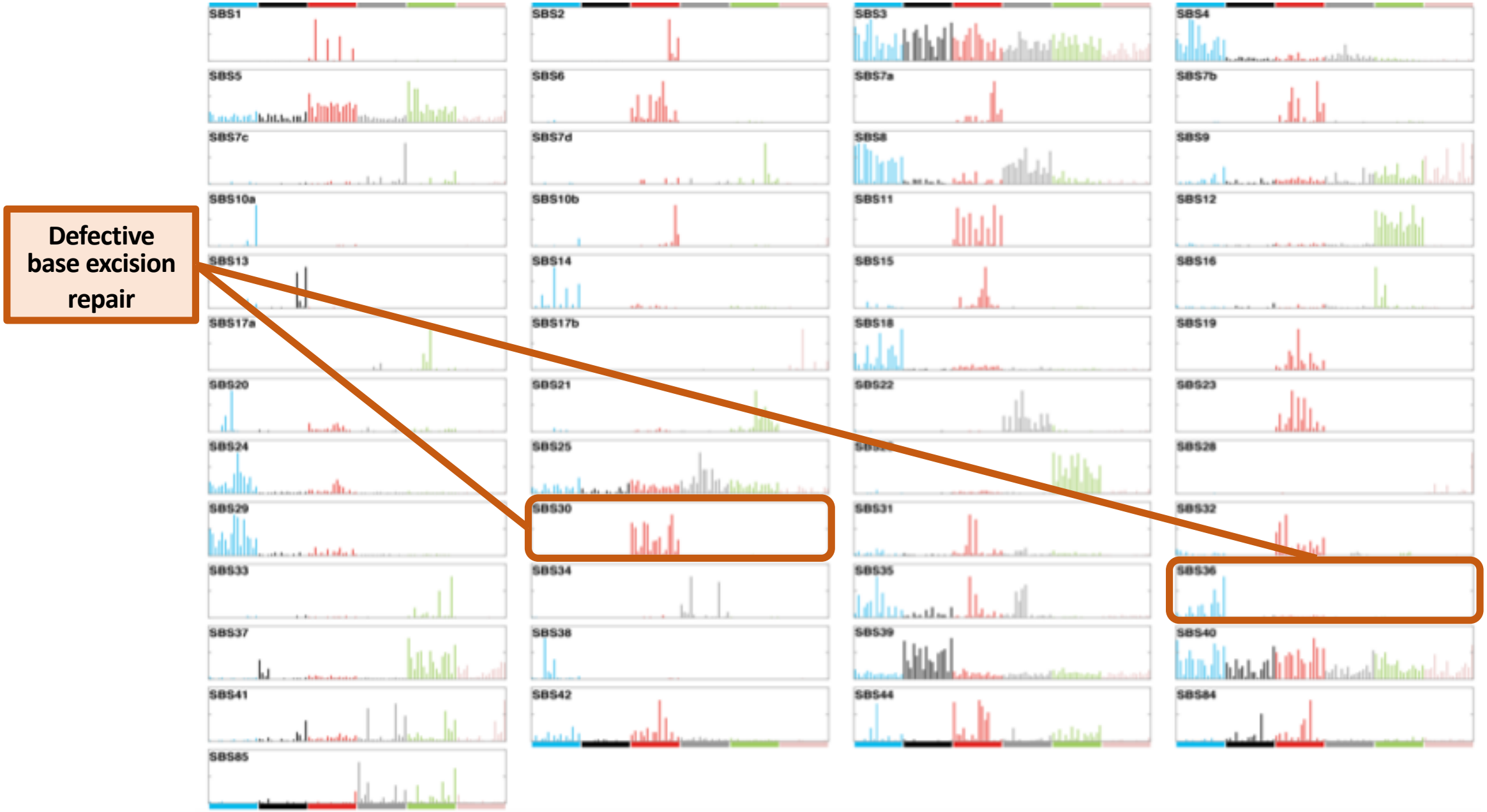


Aetiologies of SBS mutational signatures

Aetiologies of SBS mutational signatures

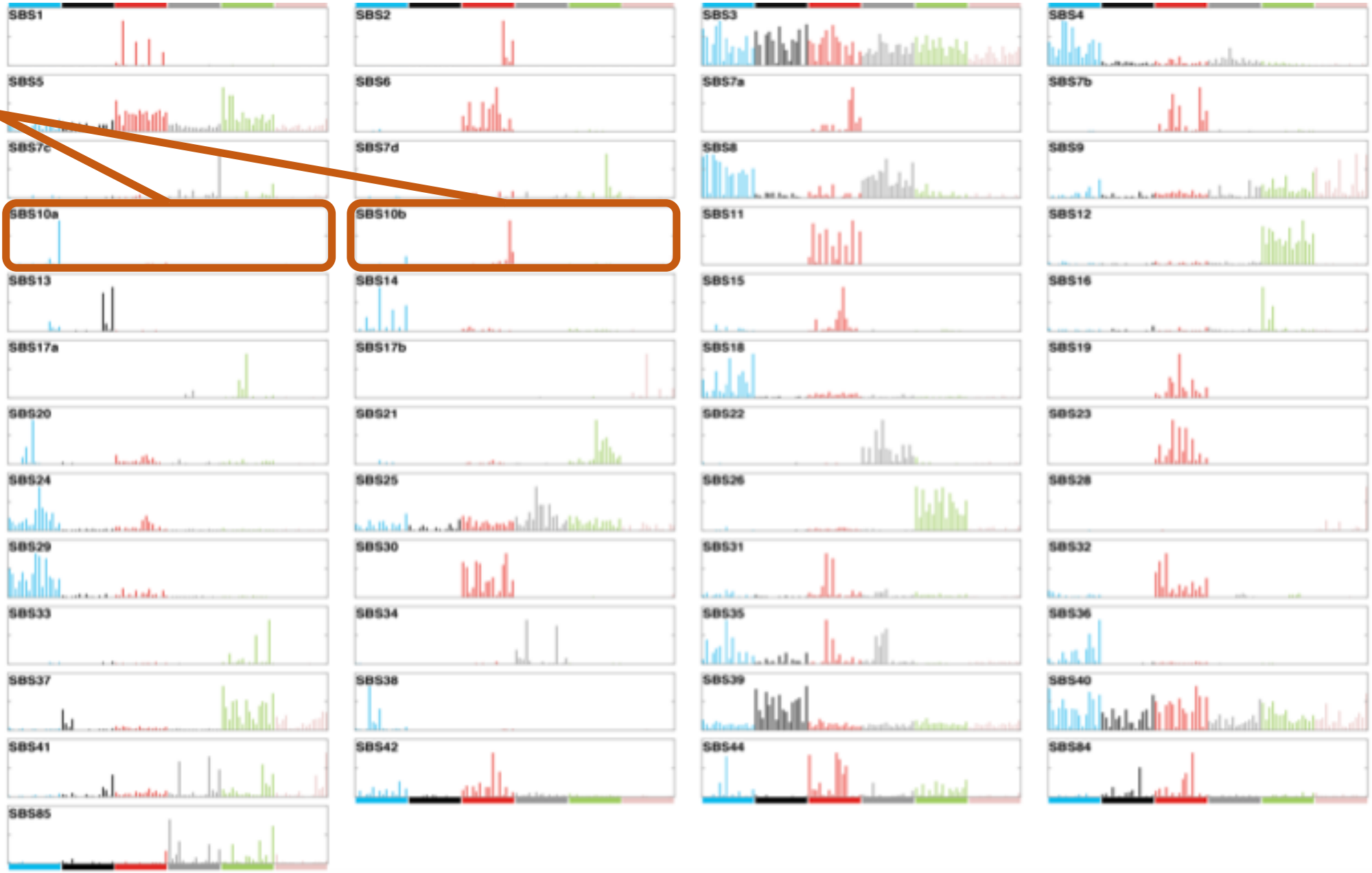
Defective BRCA1, BRCA2, homologous recombination repair

Aetiologies of SBS mutational signatures



Aetiologies of SBS mutational signatures

Defective polymerase epsilon activity



Aetiologies of SBS mutational signatures

Infidelity of polymerase eta activity

Aetiologies of SBS mutational signatures

Aetiologies of SBS mutational signatures

Aetiologies of SBS mutational signatures

Unknown aetiologies
18/49

Aetiologies of SBS mutational signatures

Unknown aetiologies 18/49

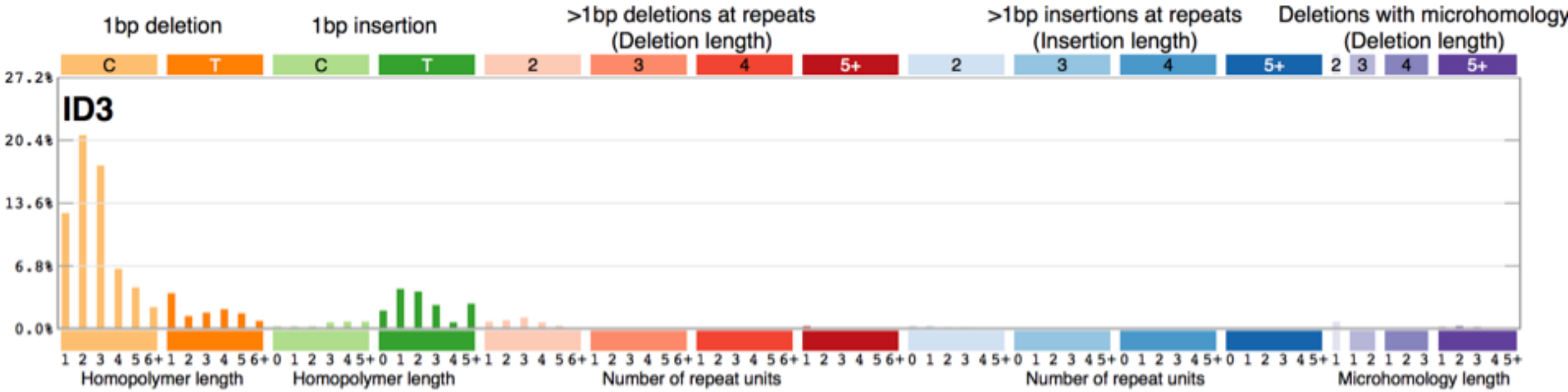
36 additional substitution signatures that are either known artifacts (20) or possible artifacts (16)

The repertoire of mutational signatures in human cancer

Indel (ID) mutational signatures

Example pattern of an ID mutational signature

Example pattern of an ID mutational signature



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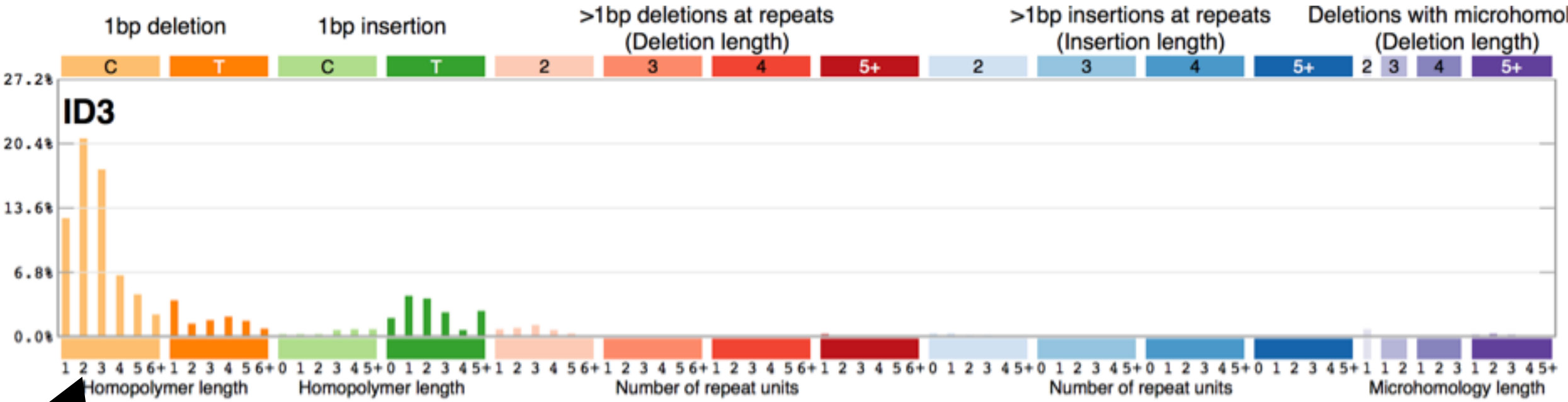
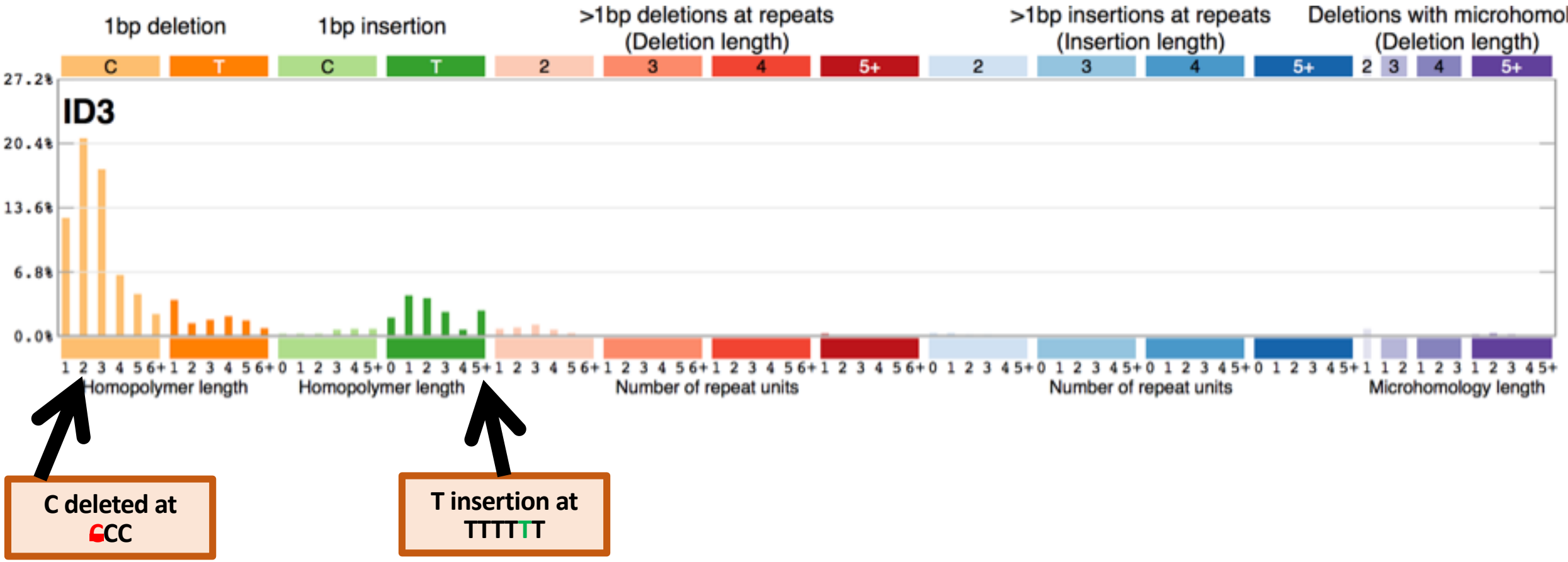


C deleted at CCC

Example pattern of an ID mutational signature



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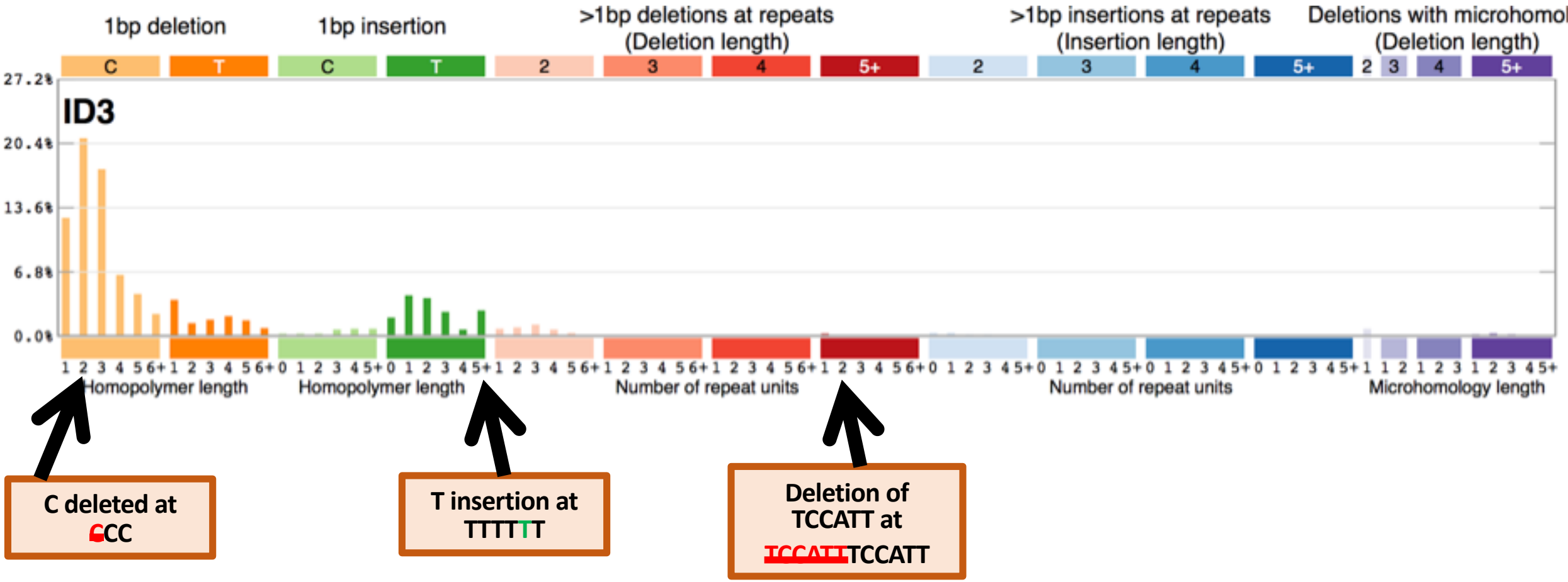

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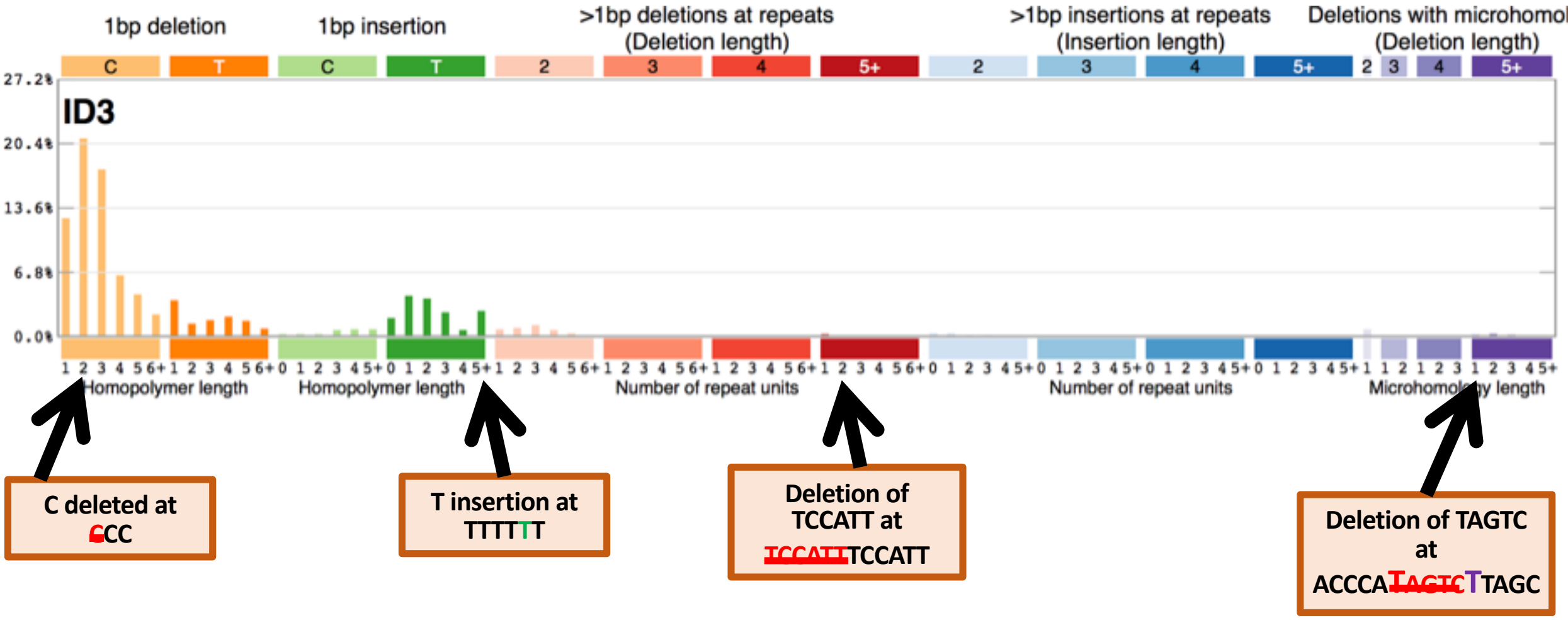

Aetiologies of ID signatures in human cancer

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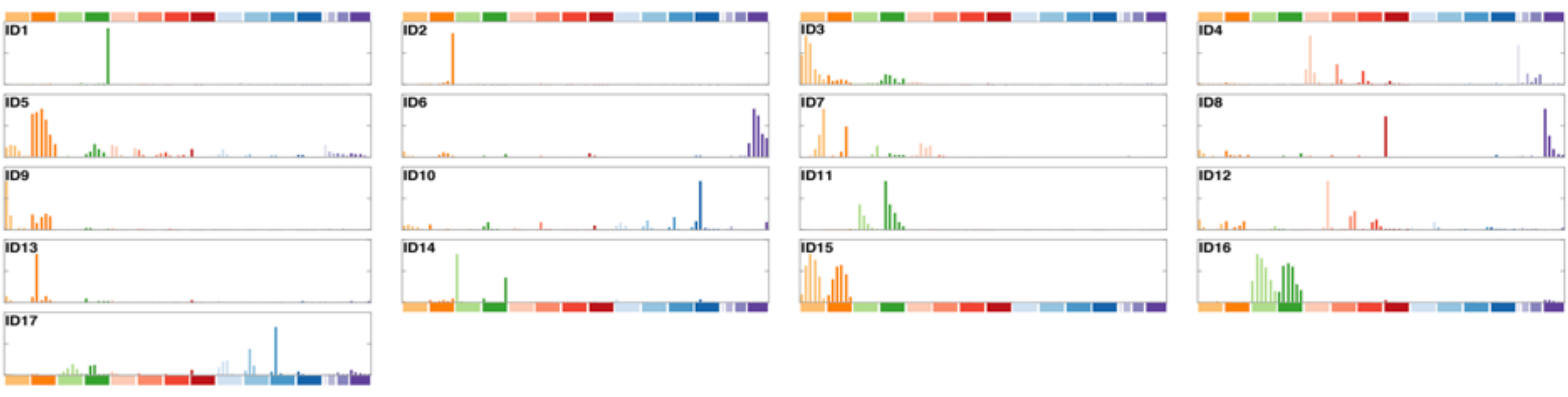
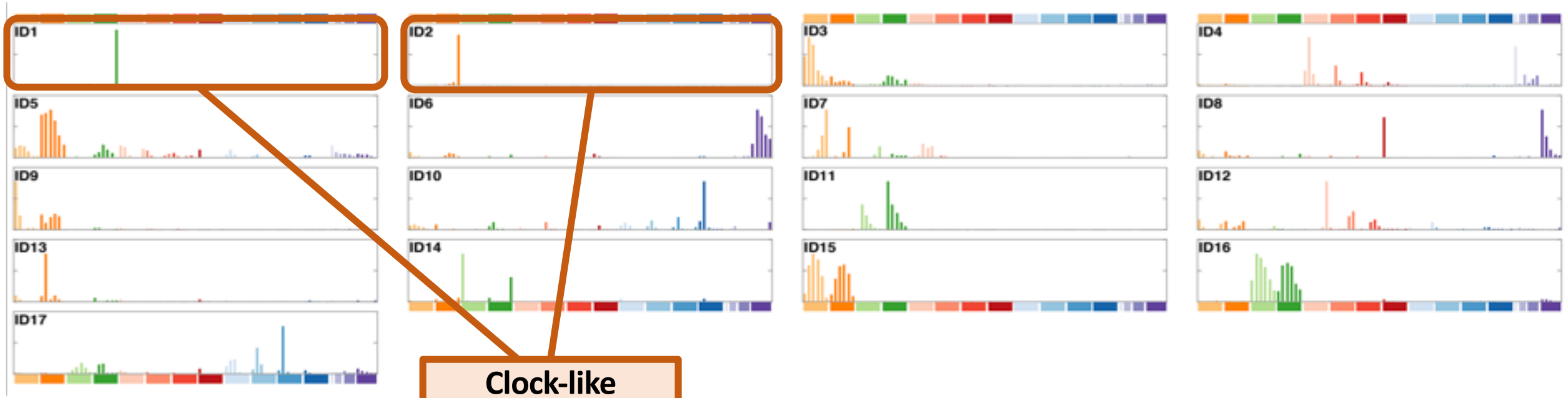
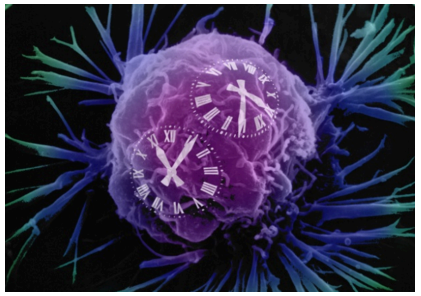


Aetiologies of ID signatures in human cancer



Clock-like processes



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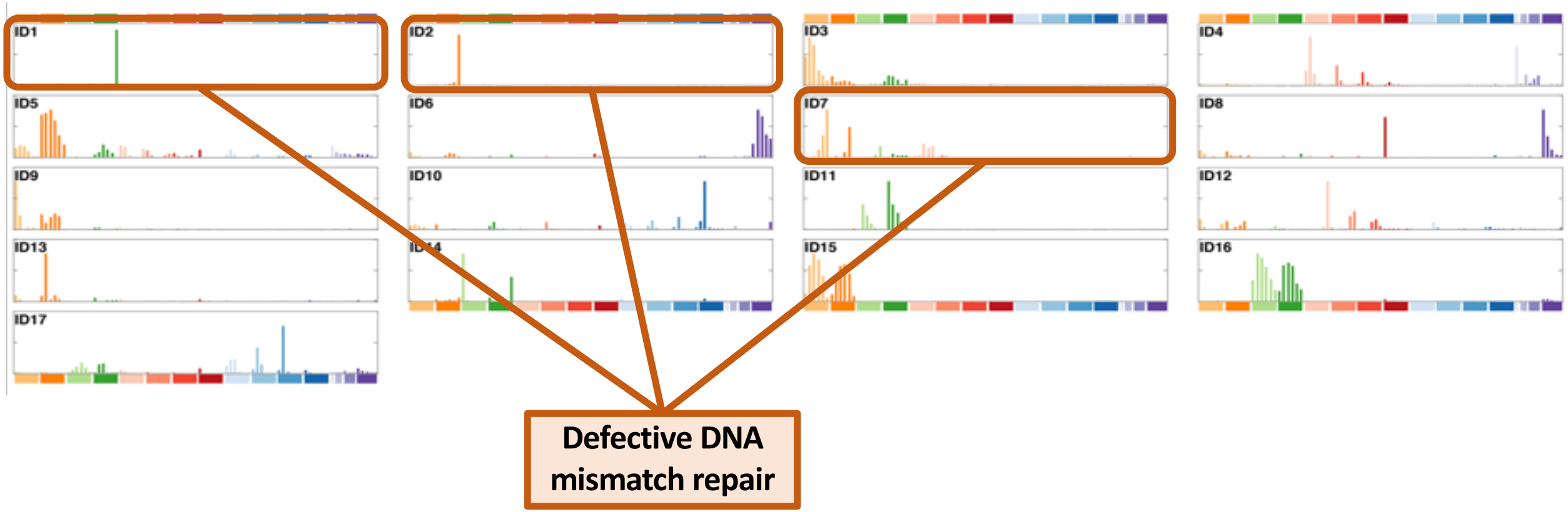

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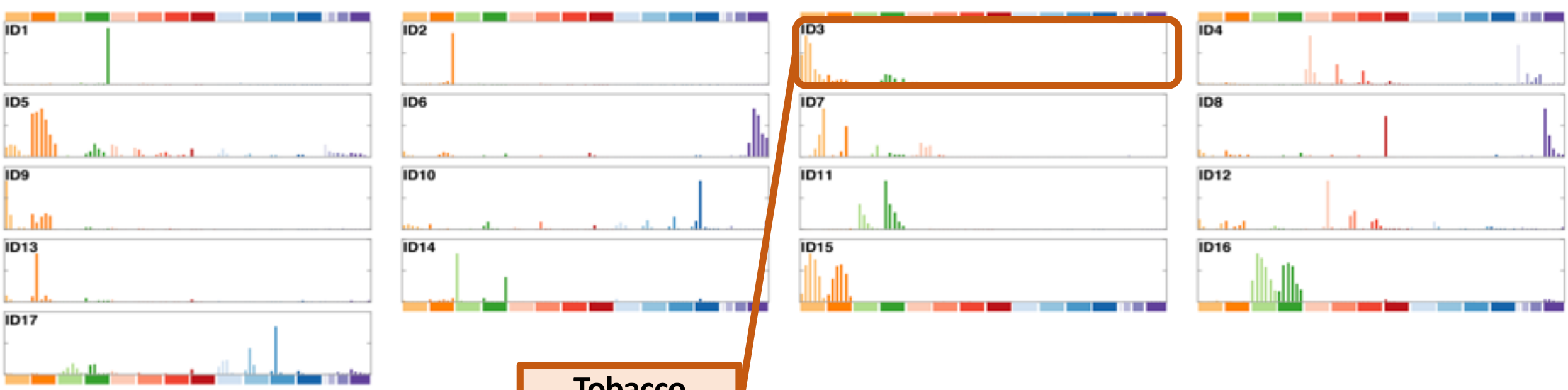
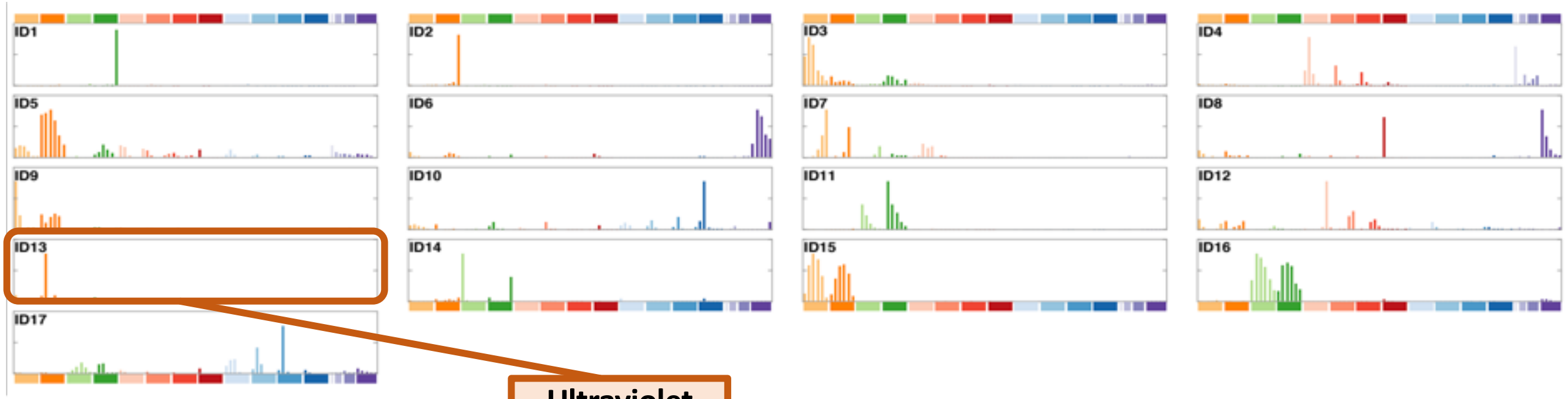


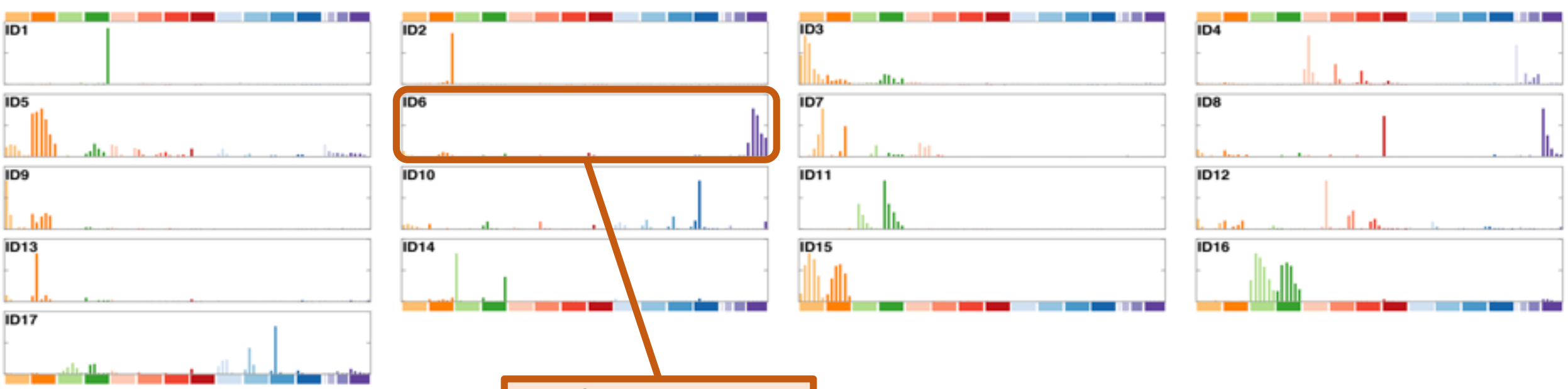
Tobacco smoking

Aetiologies of ID signatures in human cancer



Ultraviolet light

Aetiologies of ID signatures in human cancer



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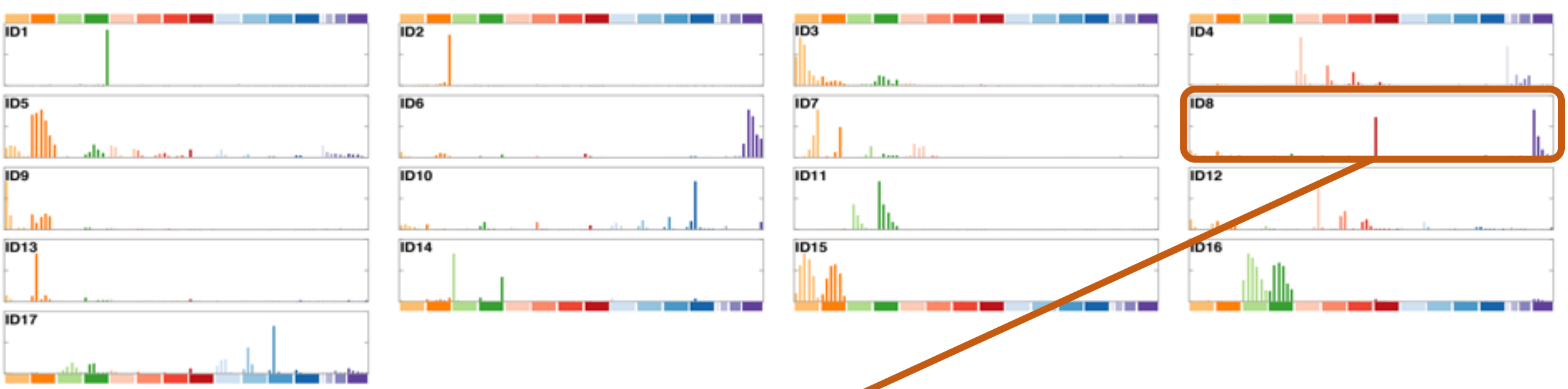
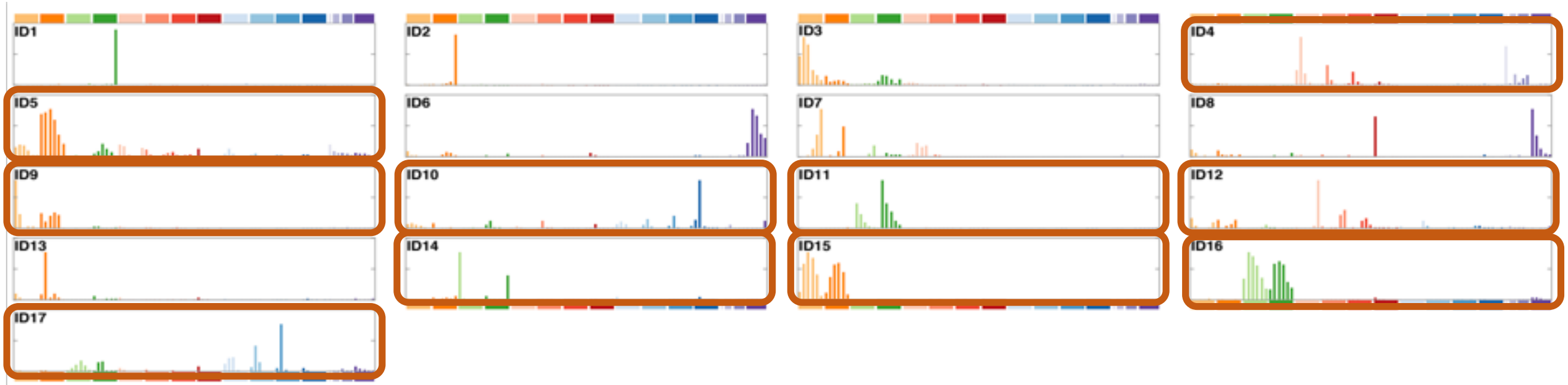
Aetiologies of ID signatures in human cancer



Radiation exposure

Aetiologies of ID signatures in human cancer



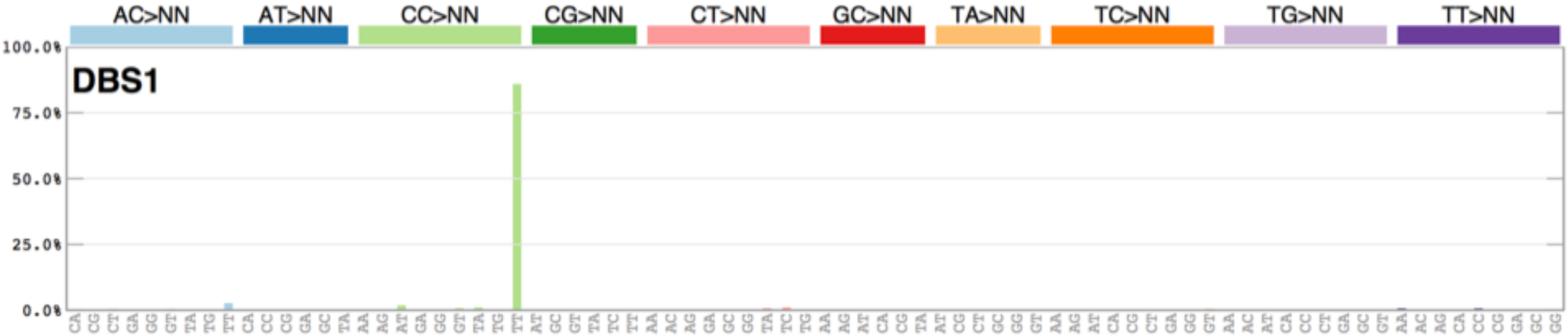
Unknown aetiologies 10/17

The repertoire of mutational signatures in human cancer

Double base substitutions (DBS) mutational signatures

Example pattern of a DBS mutational signature

Example pattern of a DBS mutational signature



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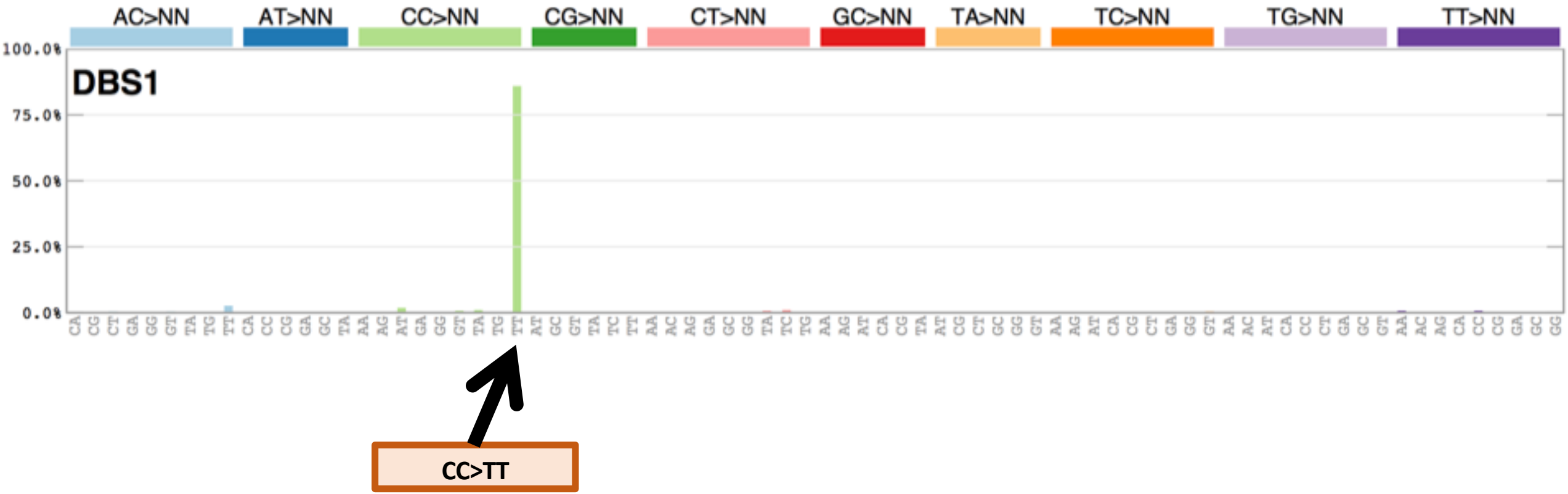
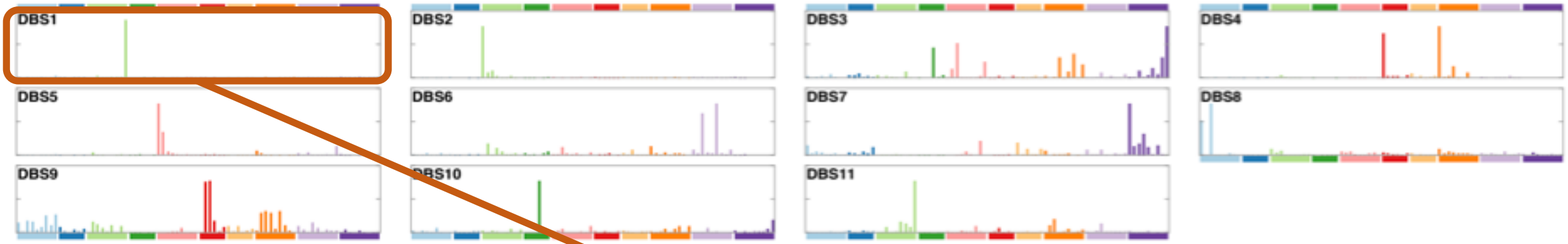


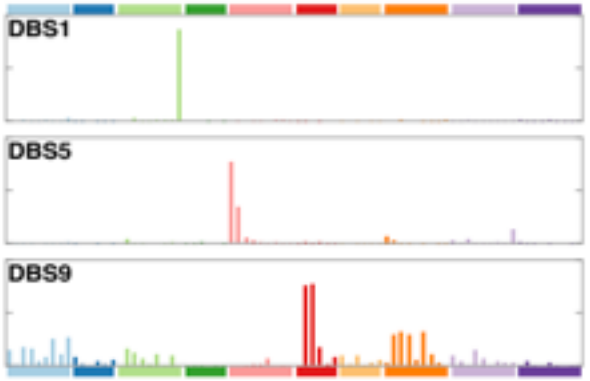
CC>TT

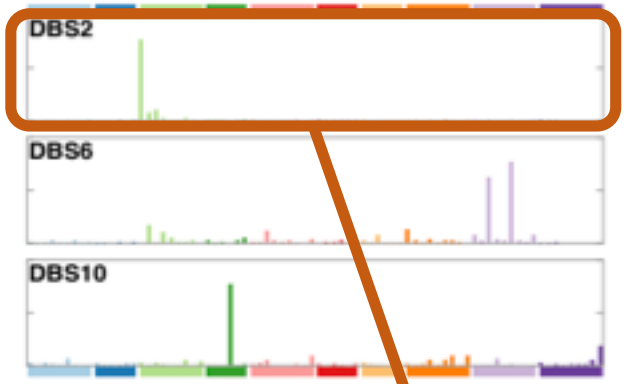
Aetiologies of DBS signatures in human cancer

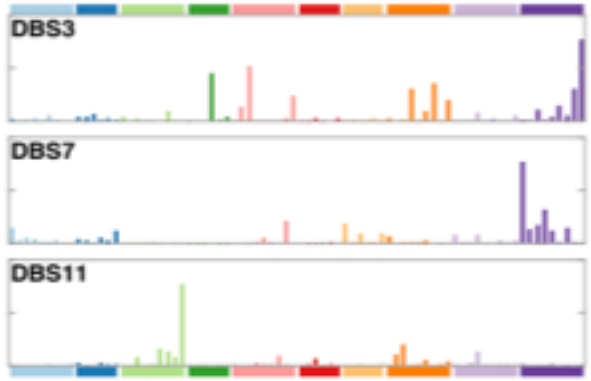


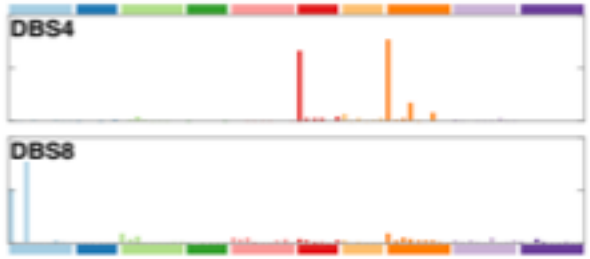
Ultraviolet light

Aetiologies of DBS signatures in human cancer

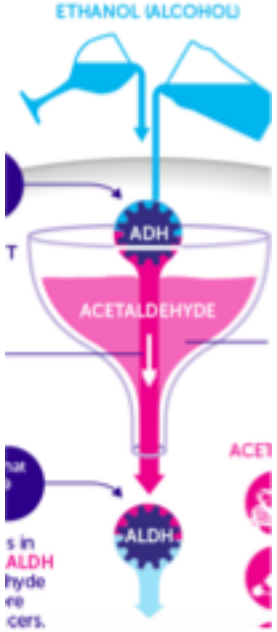




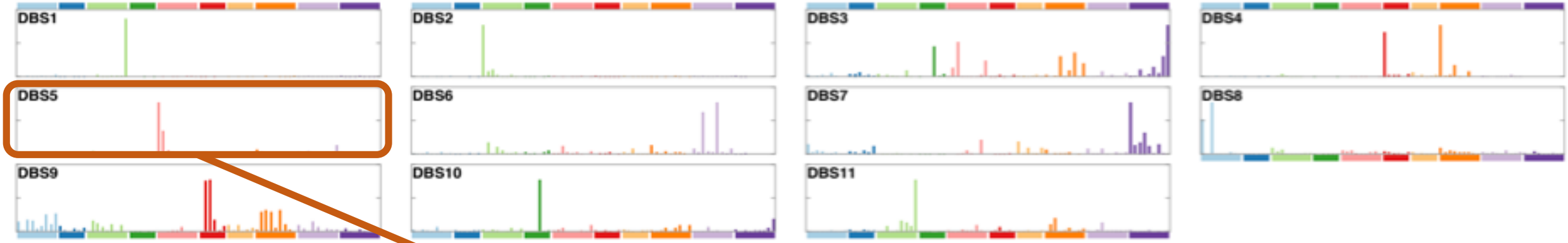




Acetaldehyde

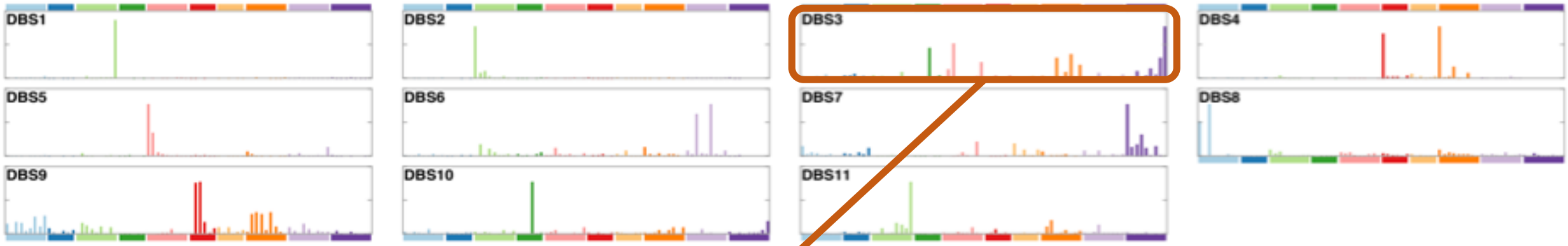


Aetiologies of DBS signatures in human cancer



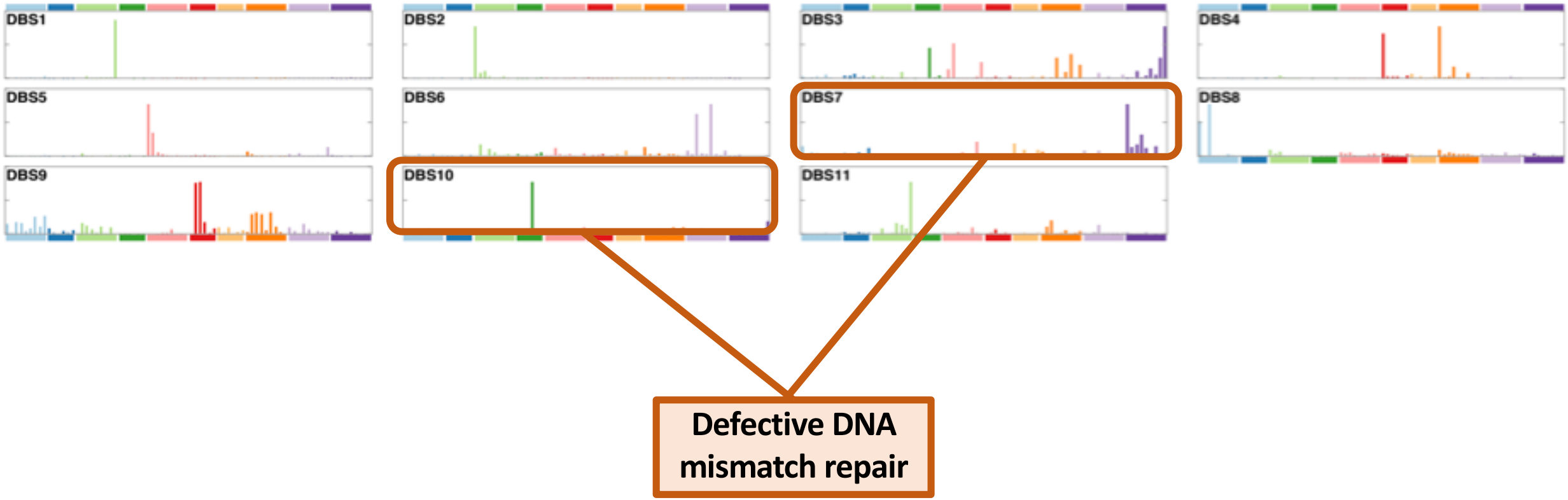
Platinum therapy

Aetiologies of DBS signatures in human cancer

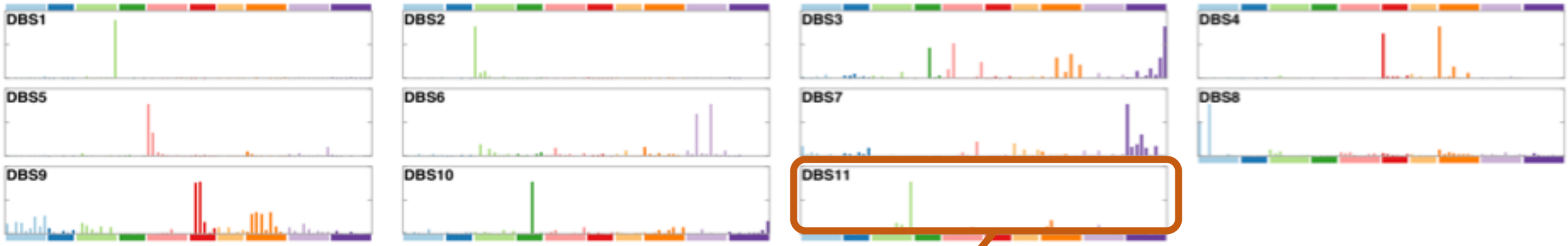


Defective polymerase epsilon activity

Aetiologies of DBS signatures in human cancer



Aetiologies of DBS signatures in human cancer



APOBEC 3A/B cytosine deamination

Aetiologies of DBS signatures in human cancer

Unknown aetiologies 4/11

Summary

Summary

- There are at least **85** SBS signatures, **17** ID signatures, and **11** DBS signatures in human cancer
- Some signatures are due to technical artefacts, known mutagenic exposures, or known defects in DNA maintenance but the cause of many is unknown
- Understanding the mutational processes underlying mutational signatures will inform on cancer causation, prevention and treatment

Summary

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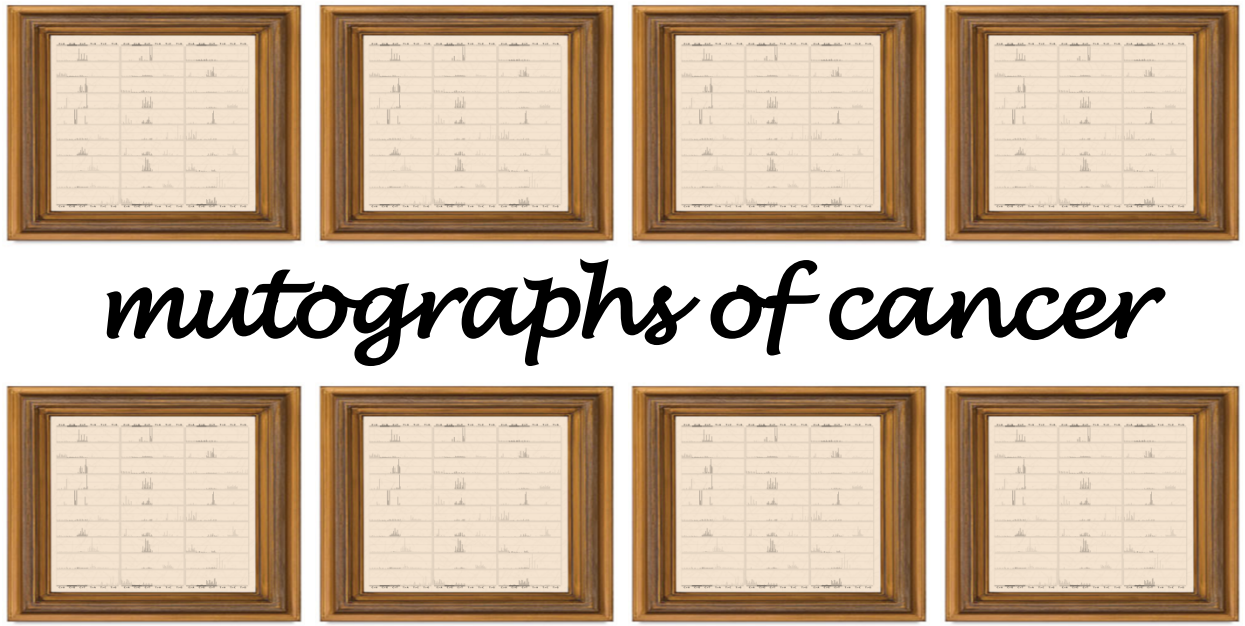
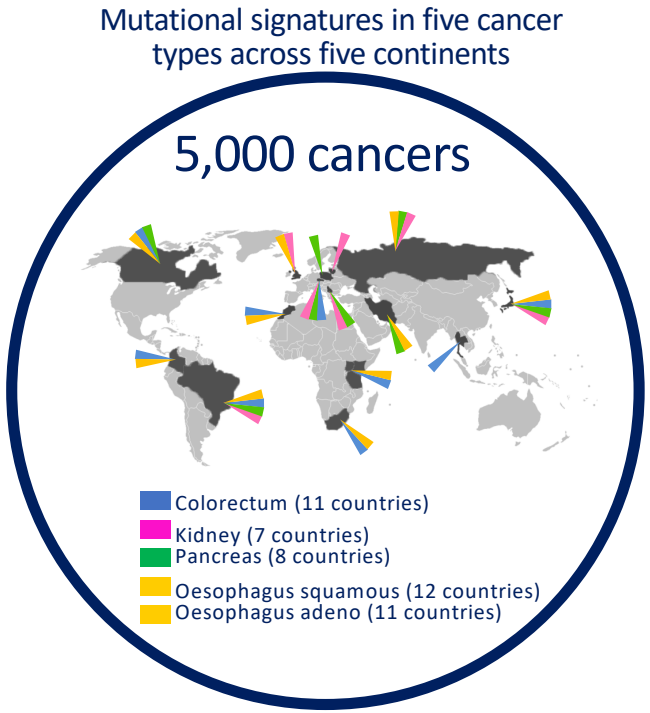


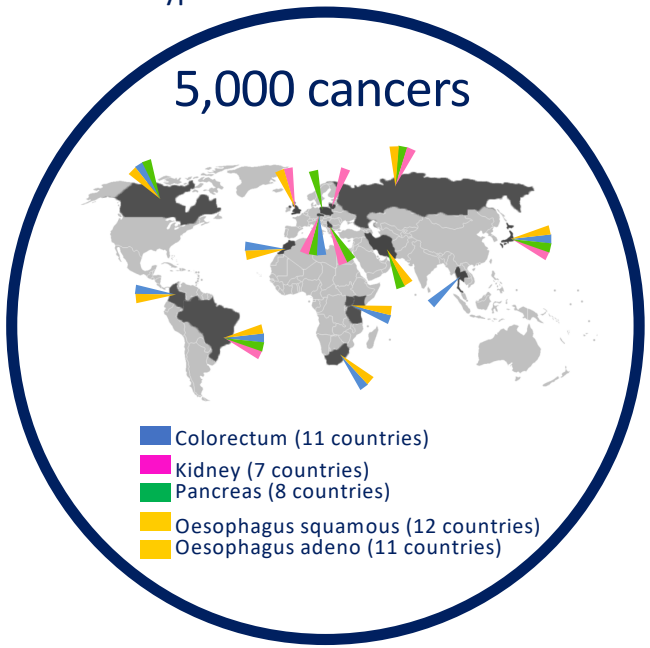
mutographs of cancer

Research plan

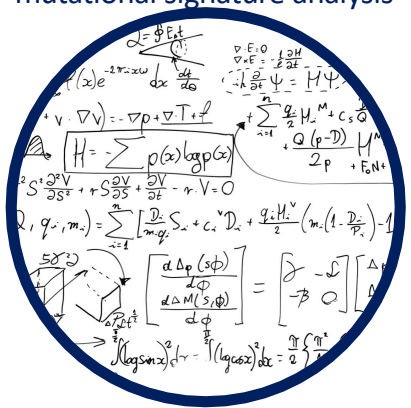


Research plan

Mutational signatures in five cancer types across five continents



Development of computational approaches for mutational signature analysis

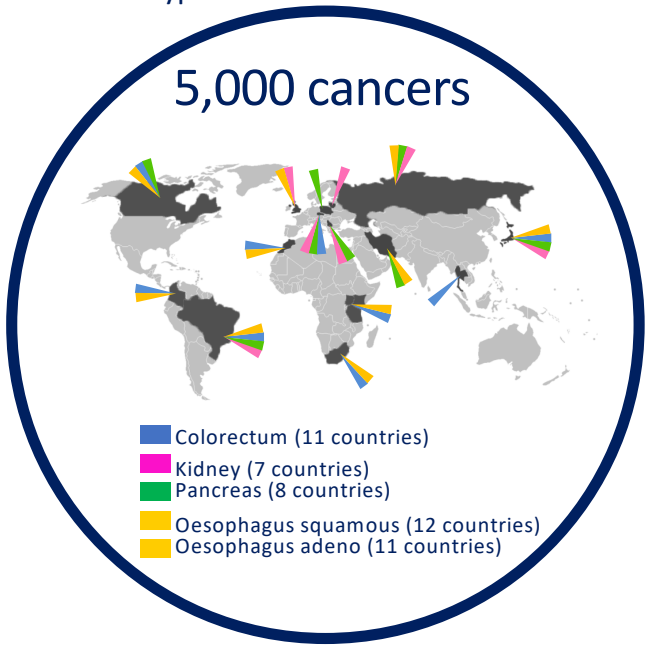


Research plan

Mutational signatures of cancer development in rodents exposed to known or suspected carcinogens

Establishing a compendium of mutational signatures through exposure of cells in culture to defined mutagens

Mutational signatures in five cancer types across five continents



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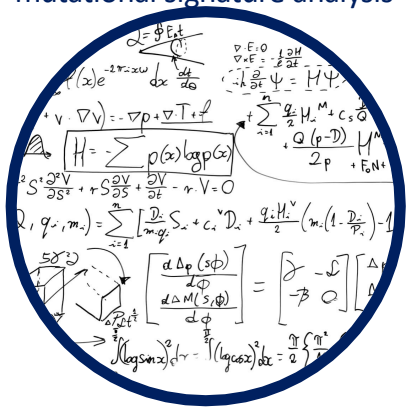

Research plan

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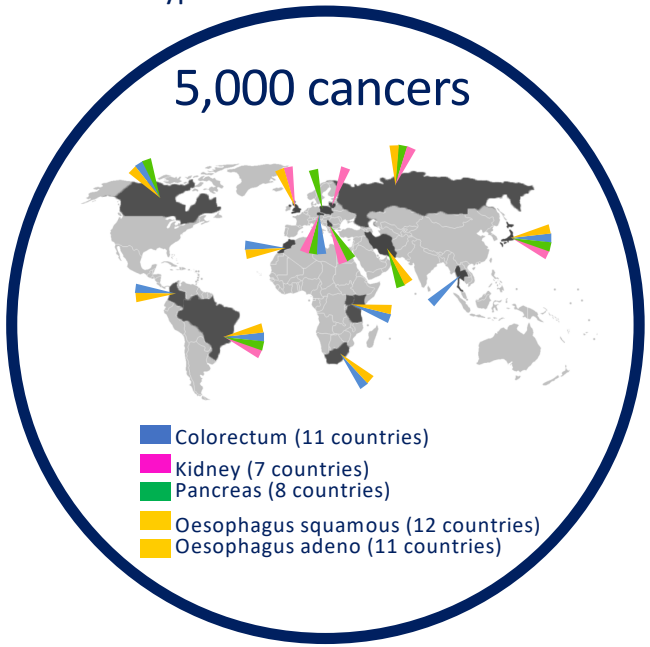
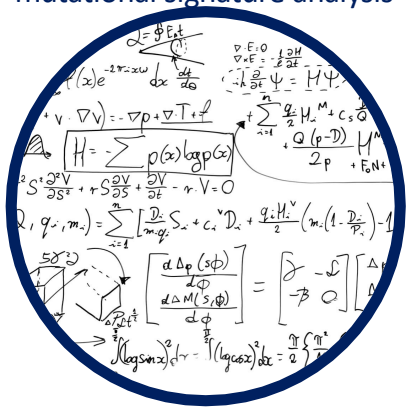


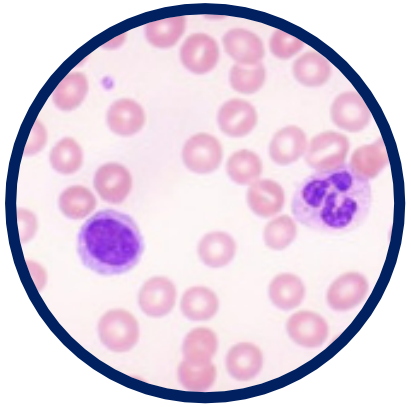
Understanding mutation burdens and mutational signatures in non-cancer tissues

Establishing a compendium of mutational signatures through exposure of cells in culture to defined mutagens

Development of computational approaches for mutational signature analysis



Surveying mutagenic exposures and endogenous mutation rates in normal white blood cells



The illustrative example of aristolochic acid

Aristolochia clematis

The illustrative example of aristolochic acid

Aristolochia clematis

California Poppy and Birthwort Liquid Extract, Cali
Californica) and Birthwort (Aristolochia Clematitis)

by HawaiiPharm

$34.95 ($8.74/Fl Oz)

FREE Shipping on eligible orders

The illustrative example of aristolochic acid

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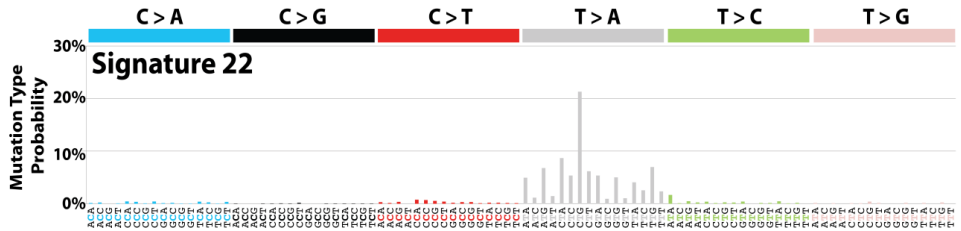

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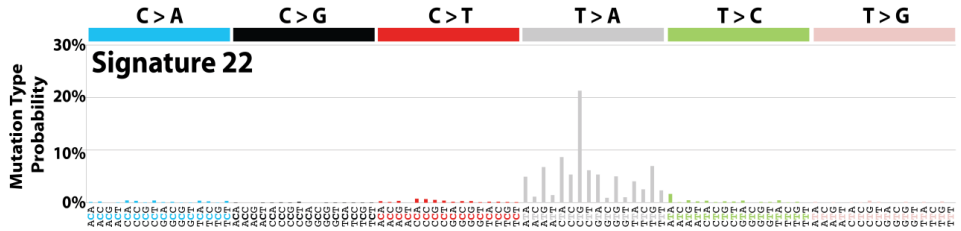
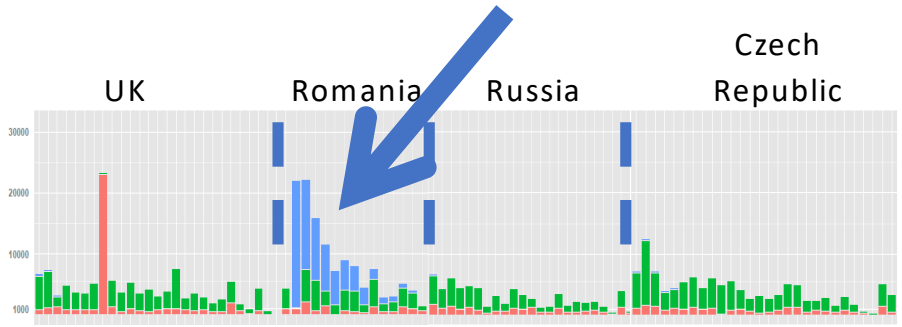


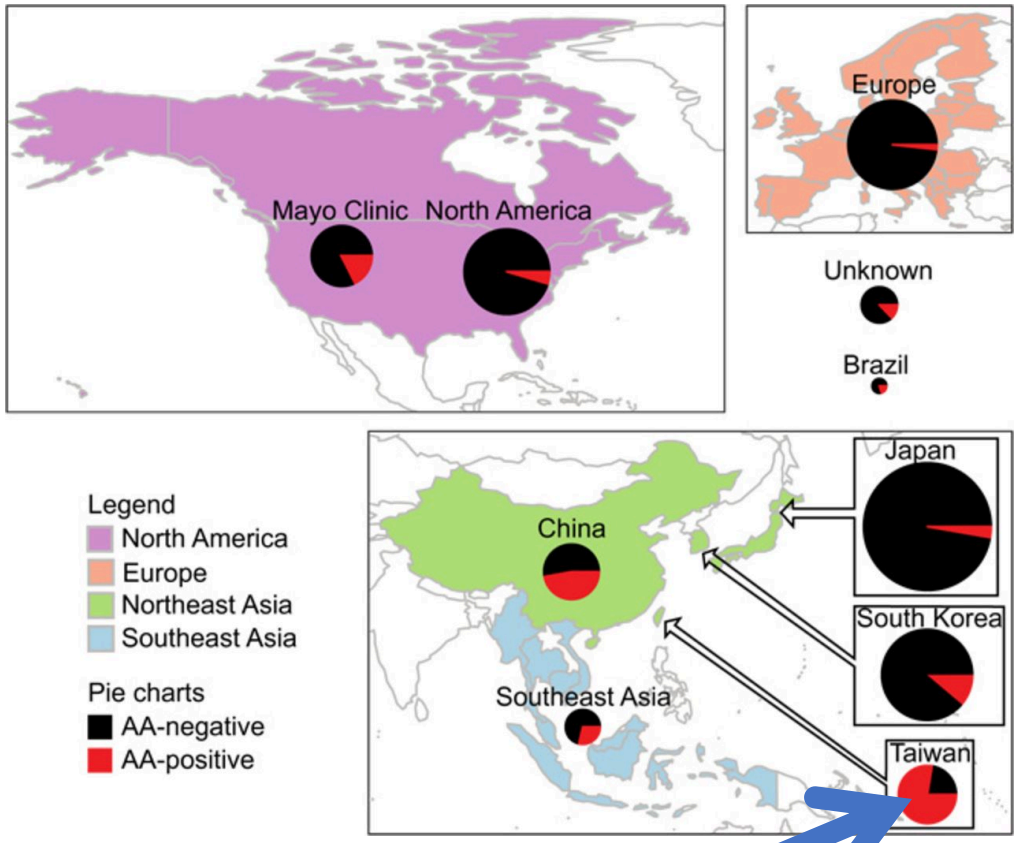
Renal clear cell cancers

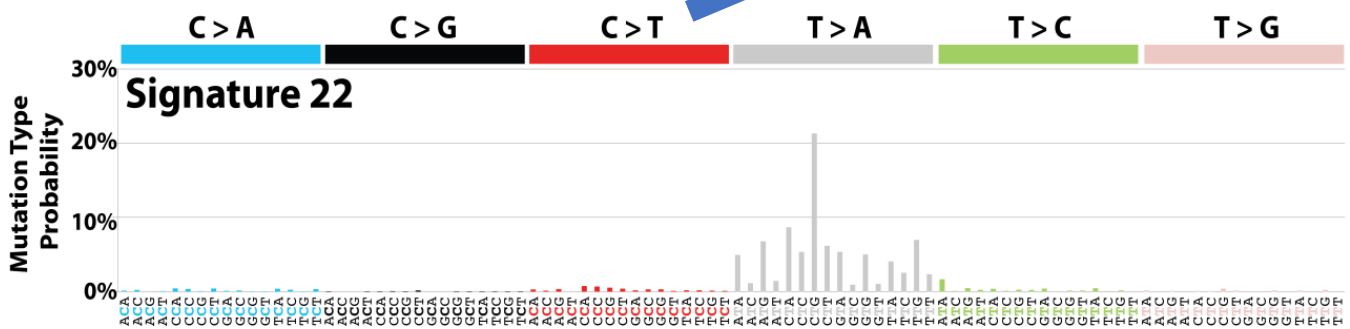


Signature 1 Signature 5 Signature 22

Aristolochic acid and liver cancer across the world

Aristolochic acid and liver cancer across the world





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