



The Potential Contribution of Cancer Genomics Information to Community Investigations of Unusual Patterns of Cancer: A Workshop

Using Cancer Mutational Signatures to Explore Etiology of Pediatric Cancer

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Somatic Mutations, Mutational Signatures, and Human Cancer

- **Somatic mutations** accumulate daily in every cell of the human body. These mutations originate from lifestyle choices, defective cellular machineries, and even from normal cellular processes.
- **Cancer risk** can be strongly affected by mutagenesis. Lifestyle choices can cause somatic mutations and significantly affect the risk for developing cancer. For example, from 105 patients with lung squamous cell carcinomas only 1 has never smoked.
- **Mutational signatures** analysis is a machine learning approach that allows detecting the *unusual patterns of somatic mutations* generated by different mutagenic processes from DNA sequencing data.

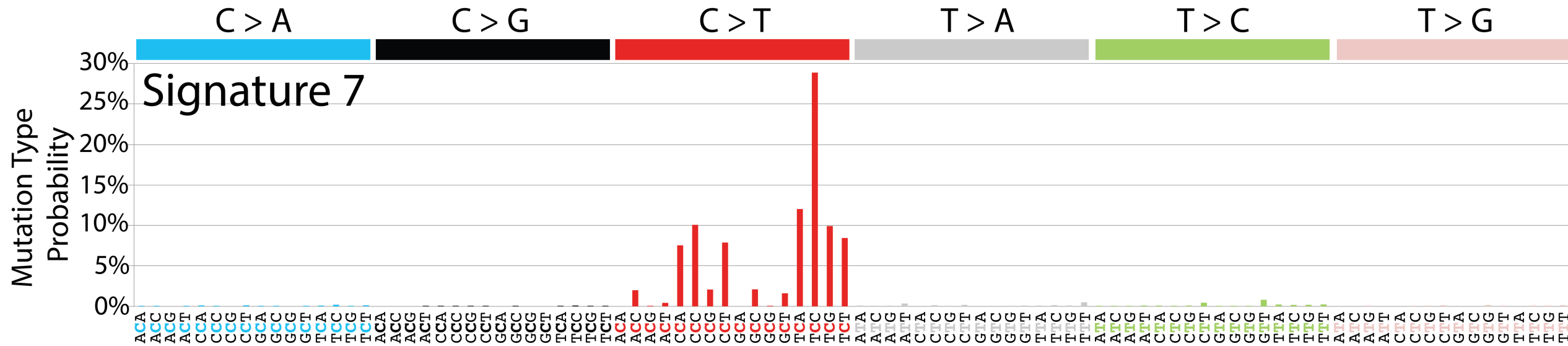
Human cancers and their origins



Skin Cancer



Majority caused by UV-light exposure



Mutational signature: a molecular fingerprint found in a cancer cell

Alexandrov et al., Nature 2013

Human cancers and their origins

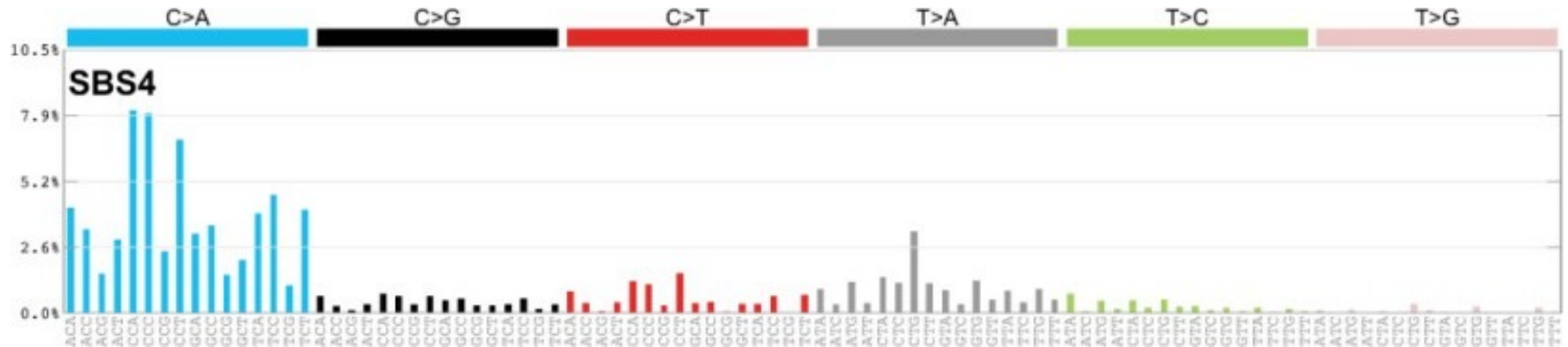


Lung Cancer



~80% caused by tobacco smoking

Predominately **C>A** somatic mutations



Mutation Signatures in Human Cancer



Proposed Etiology:

APOBEC activity
Deamination of 5'methycytosine
Reactive oxygen species
Polymerase η activity
POLE mutation

Defective DNA MMR
Defective DNA BER
Defective DNA HRR

Temozolomide treatment
Platinum treatment
Azathioprine treatment

Haloalkane exposure
Aristolochic acid exposure
Aflatoxin exposure
Ultraviolet light exposure
Tobacco smoking

Example Mutational Signatures for Investigating Unusual Patterns of Cancer

Mutational Signatures for Discovery of Germline Predisposition Syndromes

nature
genetics

Analysis | Published: 09 November 2015

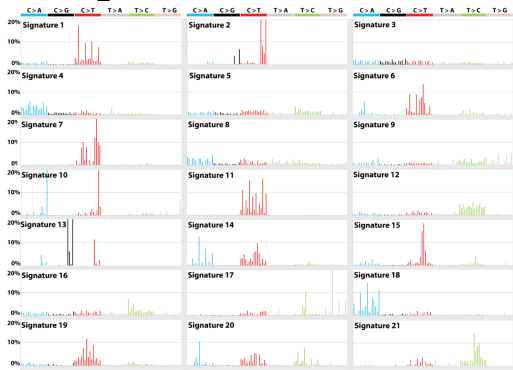
Clock-like mutational processes in human somatic cells

9 novel mutational signatures identified

Signature 30 discovered; etiology/cause unknown

Alexandrov *et al.*, Nature Genetics 2015

2013



First map of 21 mutational signatures identified in human cancer
Alexandrov *et al.*, Nature 2013

2015

2017

RESEARCH

CANCER

Use of CRISPR-modified human stem cell organoids to study the origin of mutational signatures in cancer

Signature 30 functionally associated with failure BER due to defective *NTHL1*.

Drost *et al.*, Science 2017

Cancer Cell

Mutational Signature Analysis Reveals *NTHL1* Deficiency to Cause a Multi-tumor Phenotype

Signature 30 found in 29 tumors from 7 organs in 17 families. *NTHL1* germline deficiency (SNPs & indels) found in all but one patient.

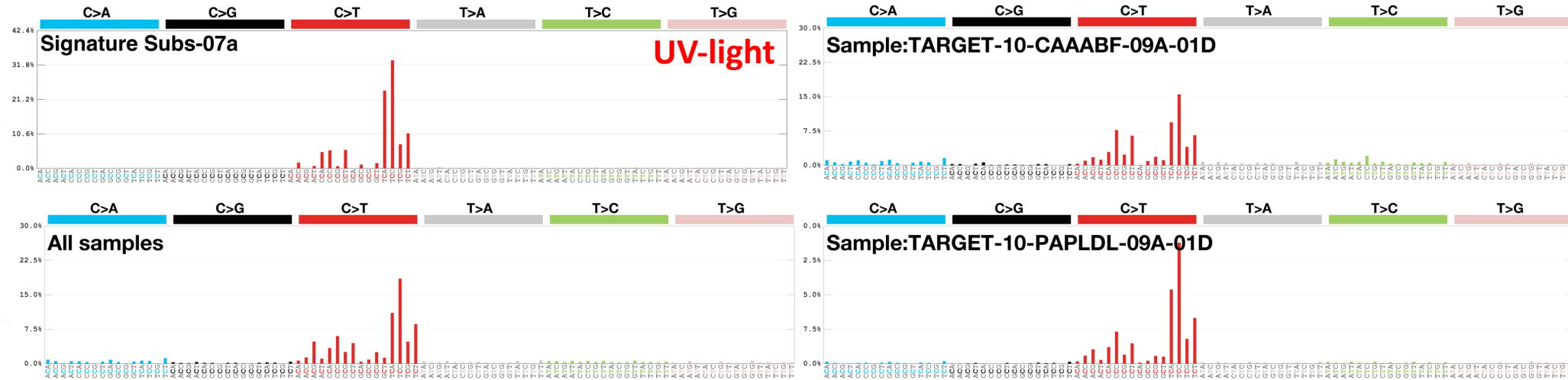
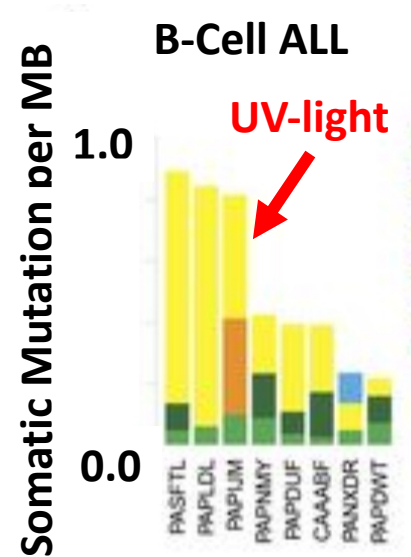
Grolleman *et al.*, Cancer Cell 2019

2019

Cancer Cell main conclusions:
“Mutational signature analyses can assist to identify germline DNA repair defects.”

“This study illustrates the power of mutational signature analysis in defining tumor phenotypes in rare cancer predisposition syndromes and provides **proof-of-principle for recognizing new patients** with cancer syndromes based on tumor sequence data.”

Known carcinogen in unexpected cancer types: **UV-light**



Similarity extends to strand bias, dinucleotide, and indel patterns. Confirmed in three other cohorts. Signature found only in white Caucasian children. Much lower mutation burden compared to skin cancer.



[Cancer Causes & Control](#)

October 2017, Volume 28, [Issue 10](#), pp 1075–1083 | [Cite as](#)

Residential exposure to ultraviolet light and risk of precursor B-cell acute lymphoblastic leukemia: assessing the role of individual risk factors, the ESCALE and ESTELLE studies

Authors

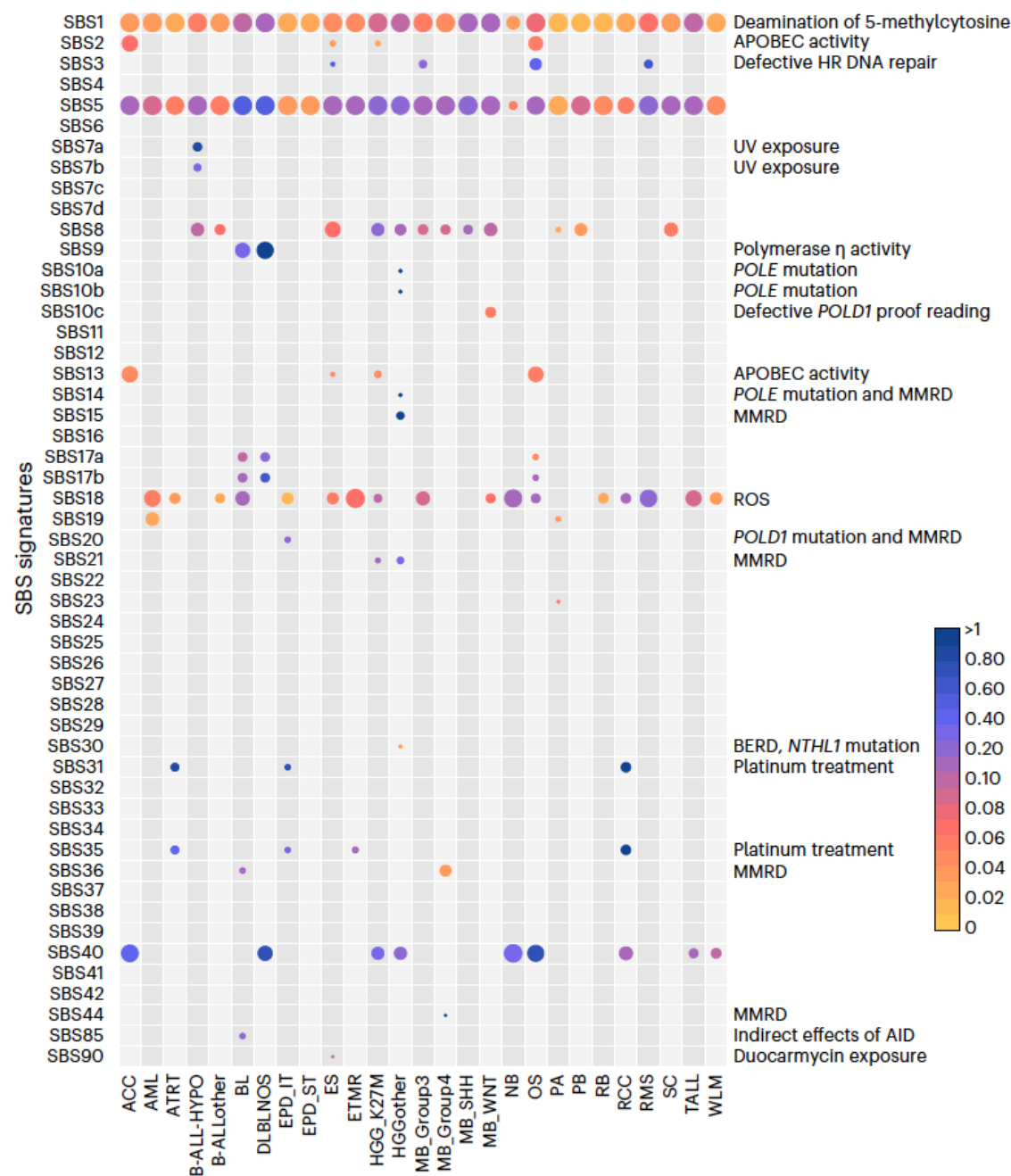
[Authors and affiliations](#)

Astrid Coste , Denis Hémon, Laurent Orsi, Mathieu Boniol, Jean-François Doré, Laure Faure, Jacqueline Clavel,

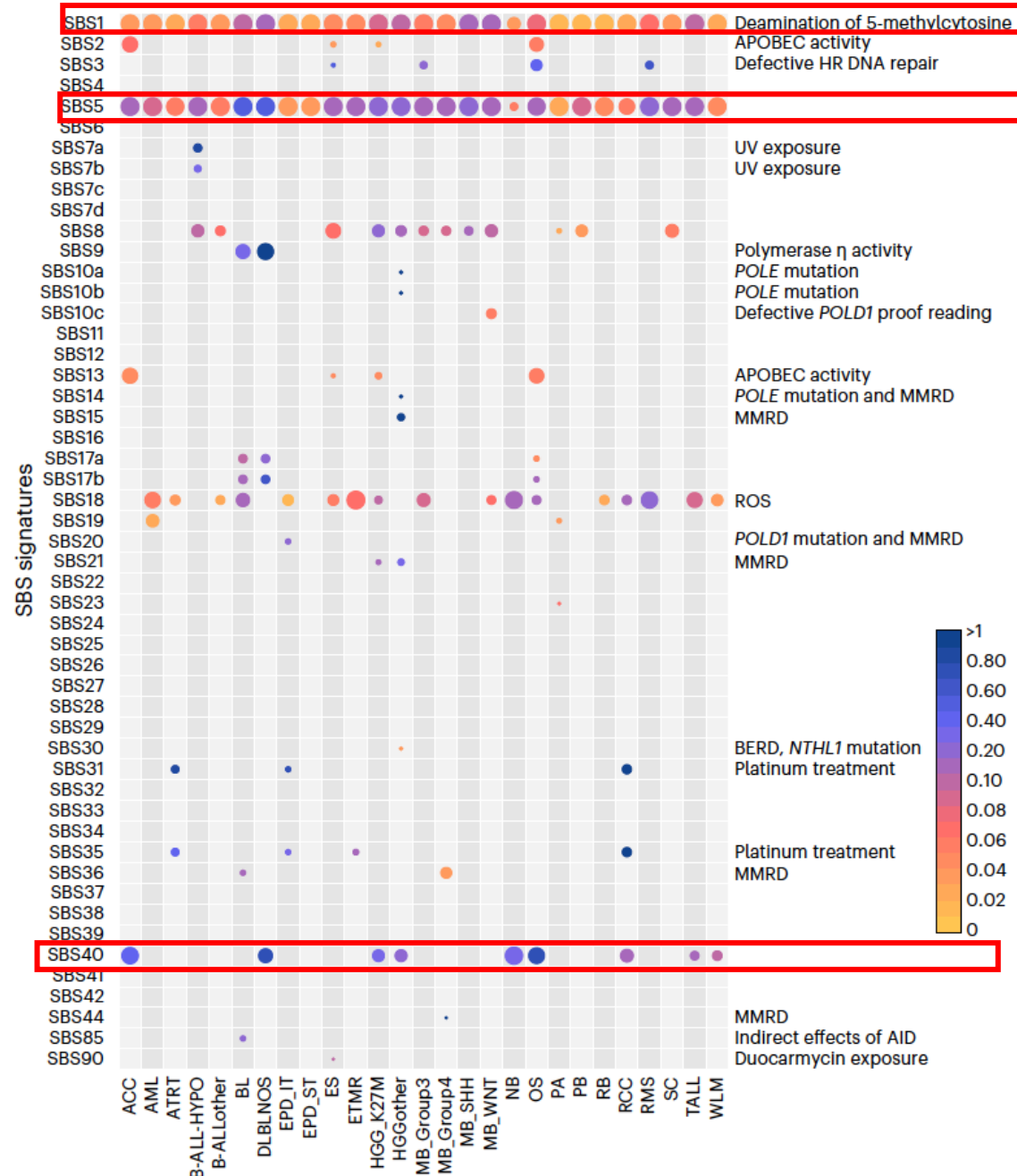
Stéphanie Goujon

Example Mutational Signatures for Investigating Unusual Patterns of Paediatric Cancer

Analysis of 785 Cancers from 27 **Paediatric** Cancer Types

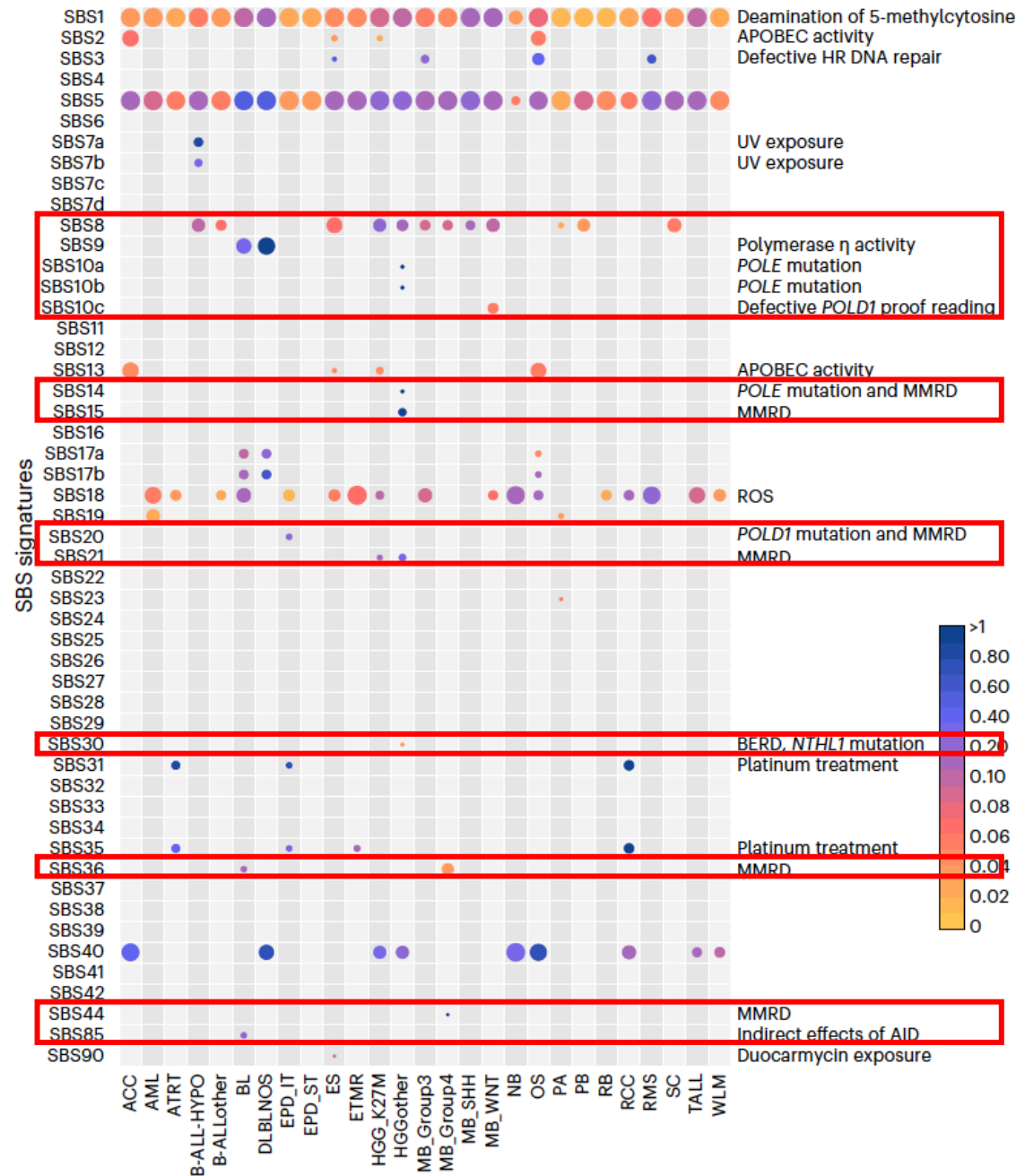


Analysis of 785 Cancers from 27 **Paediatric** Cancer Types



Clock-like mutational processes

Analysis of 785 Cancers from 27 Paediatric Cancer Types



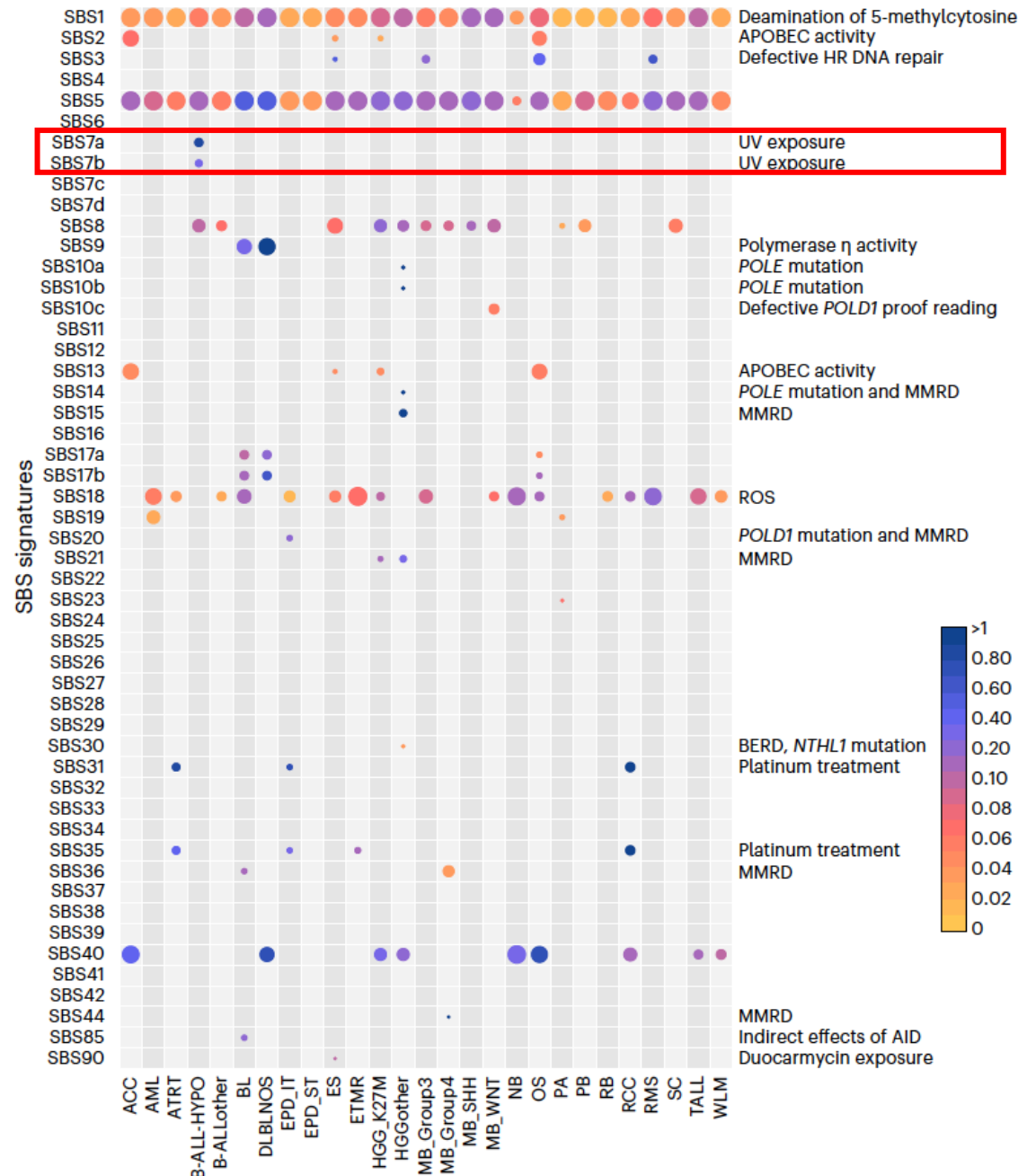
Failure or infidelity of DNA repair
machinery or DNA polymerases

Analysis of 785 Cancers from 27 **Paediatric** Cancer Types



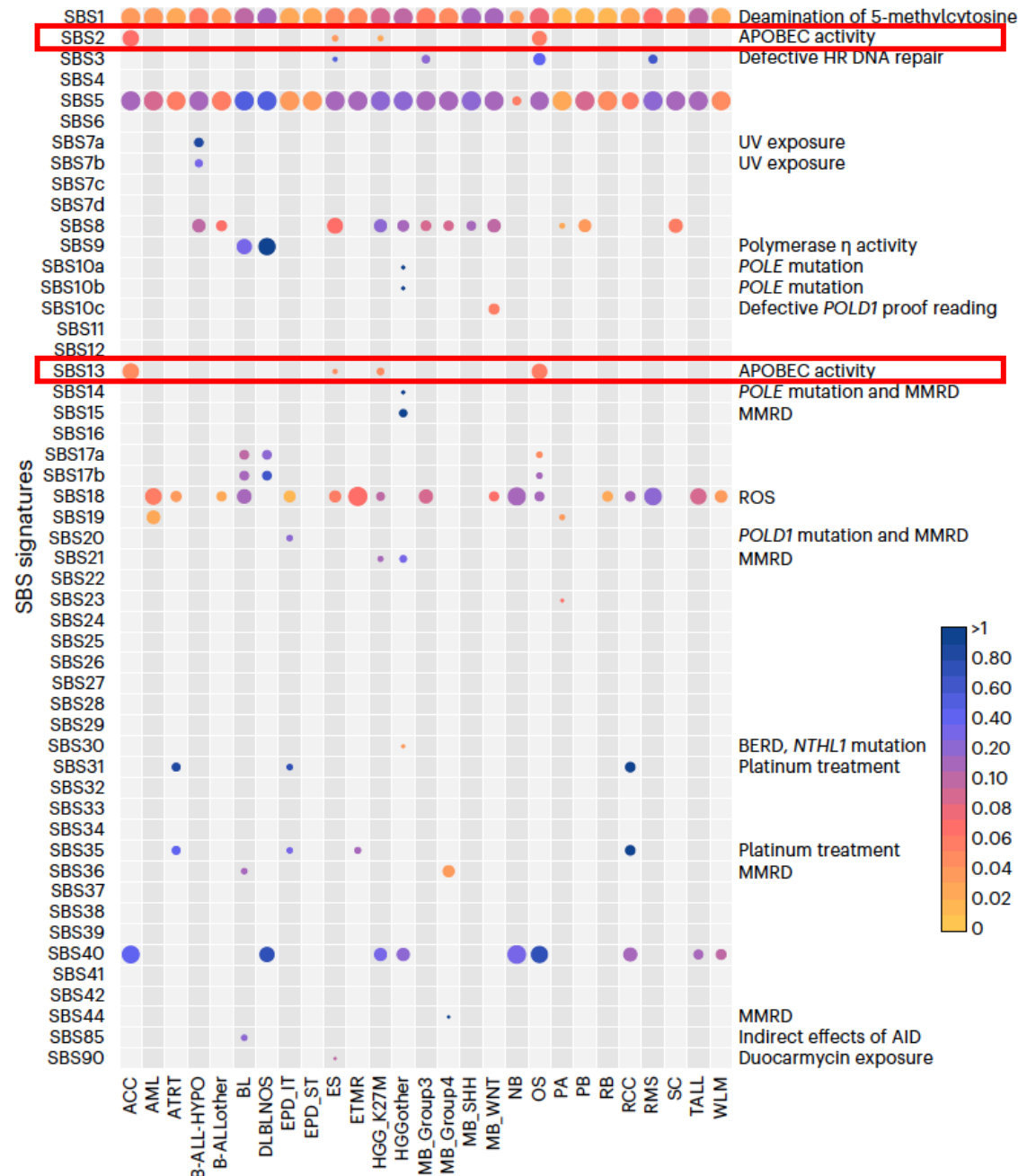
Secondary/recurrent cancers due primary anticancer therapy

Analysis of 785 Cancers from 27 **Paediatric** Cancer Types



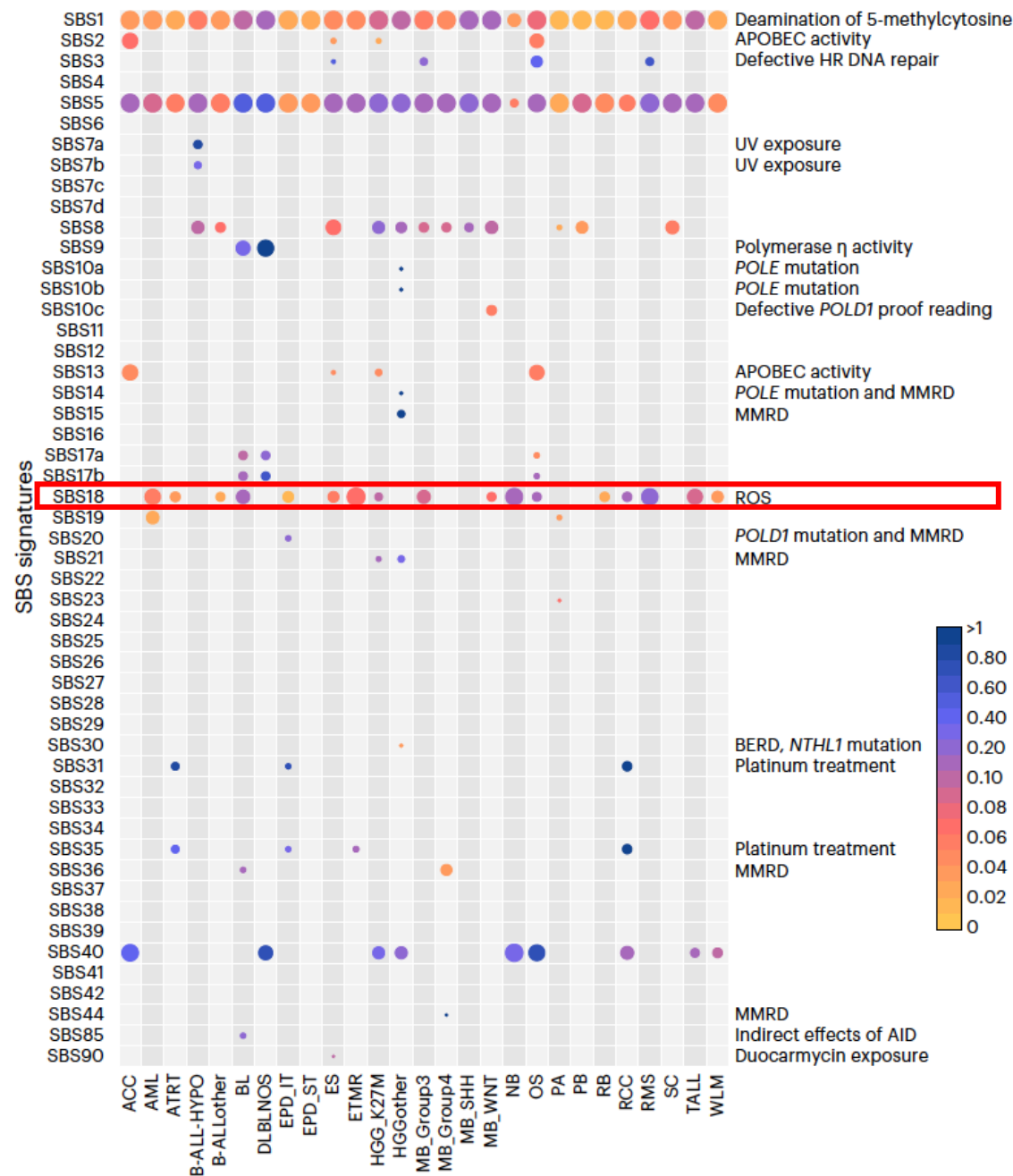
UV-light in B-cell ALL; the only signature of environmental mutagen found in paediatric cancers

Analysis of 785 Cancers from 27 **Paediatric** Cancer Types



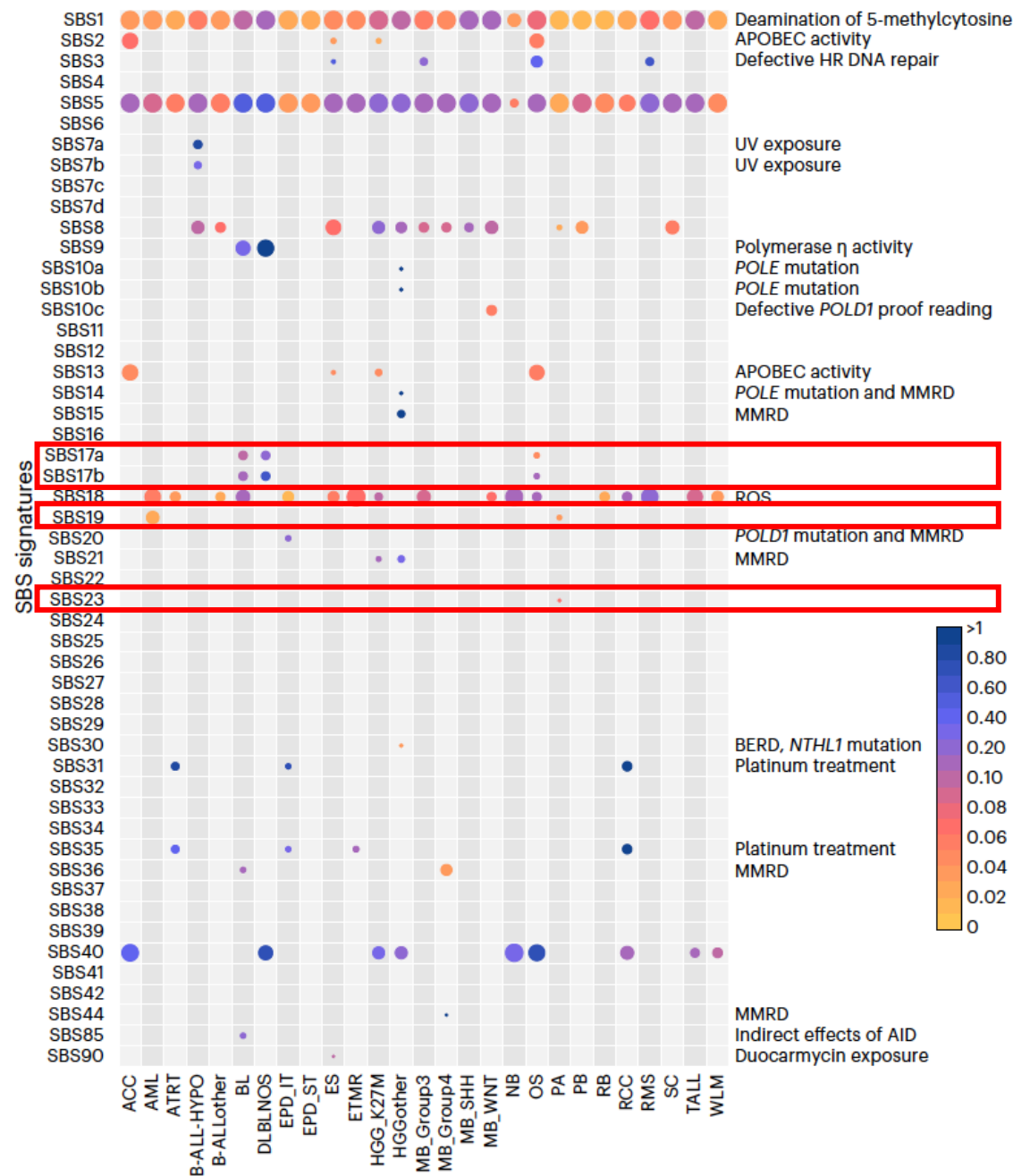
APOBEC family of deaminases. These enzymes can be activated by viruses, inflammation, and other endogenous and exogenous mechanisms.

Analysis of 785 Cancers from 27 **Paediatric** Cancer Types



Reactive oxygen species

Analysis of 785 Cancers from 27 **Paediatric** Cancer Types



Signatures with unknown aetiology

Summary

- Mutational signatures are a machine learning approach that allows detecting the aetiologies of cancers from cancer genomics data
- There are many examples in adult cancers of mutational signatures associated with environmental mutagens and lifestyle choices
- The majority of mutational signatures in paediatric cancers are attributed to endogenous mutagenic processes
- The potential mutational signatures of interest for environmental exposures are:
 - UV-light in B-cell acute lymphoblastic leukaemia (ALL)
 - APOBEC signatures
 - Signatures with unknown aetiologies



Thank you!