A new user-friendly web application to implement mutational signature analysis

31st European Congress of Pathology
Nice, September 10th

MARCOS DÍAZ GAY
Mutational signatures marked a turning point in cancer diagnosis, prognosis, treatment, ...
Mutational signatures marked a turning point in cancer diagnosis, prognosis, treatment, ...
Mutational signatures marked a turning point in cancer diagnosis, prognosis, treatment, ...

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

HRDetect is a predictor of BRCA1 and BRCA2 deficiency based on mutational signatures

Helen Davies1,32, Dominik Glodzik1,32, Sandro Morgenella1, Lucy R Yates1,2, Johan Staf1, Xueqing Zou1, Manasa Ramakrishna1,2, Sancha Martin1, Sandrine Boyault5, Anieta M Sieuwerts6, Peter T Simpson7, Tari A King8, Keiran Raine1, Jorunn E Eyfjord9, Gu Kong10, Åke Borg1, Ewan Birney11, Hendrik G Stunnenberg12, Marc J van de Vijver13, Anne-Lise Børresen-Dale14,15, John W M Martens16, Paul N Span16,17, Sunil R Lakhani18, Anne Vincent-Salomon19,20, Christos Sotiriou21, Andrew Tutt22,23, Alastair M Thompson24, Steven Van Laere25,26, Andrea L Richardson27,28, Alain Viari29,30, Peter J Campbell1, Michael R Stratton1 & Serena Nik-Zainal1,31
Different bioinformatic packages allow mutational signatures implementation...

- pmSignature
- SomaticSignatures
- deconstructSigs
- MutationalPatterns
- SignatureAnalyzer
- ...
- MutSpec
- SigProfiler
... but it remains inaccessible for the majority of the research community
... but it remains inaccessible for the majority of the research community
Web applications to implement mutational signature analysis

Mutational signatures
  New paradigm in cancer genomics

Mutational Signatures in Cancer – MuSiCa
  Simplifying signature analysis

An open door to the future
  Updating to new algorithm and COSMIC framework
Web applications to implement mutational signature analysis

**Mutational signatures**  
**New paradigm in cancer genomics**

*Mutational Signatures in Cancer – MuSiCa*  
Simplifying signature analysis

An open door to the future  
Updating to new algorithm and COSMIC framework
There are different sources of DNA damage

Lifestyle choices
Tobacco smoking or chewing

Normal cellular activities
Spontaneous deamination of methylated cytosines

Failure in DNA replication or repair
Aberrant mismatch repair pathway
Prevalence of somatic mutations is highly variable among cancer classes
Pattern of mutations is defined by base substitutions and context

Six classes of single-base mutations
Reported by pyrimidine
Pattern of mutations is defined by base substitutions and context

Six classes of single-base mutations
Reported by pyrimidine

C > A  C > G  C > T  T > A  T > C  T > G
Pattern of mutations is defined by base substitutions and context

Six classes of single-base mutations
Reported by pyrimidine

Adding 5’ and 3’ adjacent bases
96 possibilities considering context
Pattern of mutations is defined by base substitutions and context

Six classes of single-base mutations
- Reported by pyrimidine

Adding 5’ and 3’ adjacent bases
- 96 possibilities considering context
Pattern of mutations is defined by base substitutions and context

Six classes of single-base mutations
Reported by pyrimidine

Adding 5’ and 3’ adjacent bases
96 possibilities considering context
Mutational record of a cancer patient is a mix of the different mutational processes
Mathematical models allows the *un-mixing* and the generation of signatures

Blind signal separation problem

Non-negative matrix factorization
Deciphering of *de novo* mutational signatures is different from signature refitting

Large number of samples → Set of consensus signatures
Deciphering of de novo mutational signatures is different from signature refitting

Single sample – clinical setting
Deciphering of *de novo* mutational signatures is different from signature refitting.

Single sample – clinical setting.
Web applications to implement mutational signature analysis

Mutational signatures
   New paradigm in cancer genomics

Mutational Signatures in Cancer – MuSiCa
   Simplifying signature analysis

An open door to the future
   Updating to new algorithm and COSMIC framework
Web applications to implement mutational signature analysis

Mutational signatures
New paradigm in cancer genomics

**Mutational Signatures in Cancer – MuSiCa**
Simplifying signature analysis

An open door to the future
Updating to new algorithm and COSMIC framework
MuSiCa is a web application built in Shiny and based on MutationalPatterns package
MuSiCa is a web application built in Shiny and based on MutationalPatterns package
MuSiCa is a web application built in Shiny and based on MutationalPatterns package.
MuSiCa is a web application built in Shiny and based on MutationalPatterns package.
MuSiCa is a web application built in Shiny and based on MutationalPatterns package.

MuSiCa is a web application built in Shiny and based on MutationalPatterns package.
MuSiCa is a web application built in Shiny and based on MutationalPatterns package.
MuSiCa refitting analysis is based on the 30 SBS COSMIC v2 signatures (2015)
MuSiCa application workflow allows single and multi-sample analysis.
MuSiCa application demo
MuSiCa has been widely used since its publication for signature analysis.

+1,300 unique users accessed web version
5 WoS citations
First 15 months since publication
Web applications to implement mutational signature analysis

Mutational signatures
New paradigm in cancer genomics

Mutational Signatures in Cancer – MuSiCa
Simplifying signature analysis

An open door to the future
Updating to new algorithm and COSMIC framework
Web applications to implement mutational signature analysis

Mutational signatures
New paradigm in cancer genomics

Mutational Signatures in Cancer – MuSiCa
Simplifying signature analysis

An open door to the future
Updating to new algorithm and COSMIC framework
SigProfiler tool is the gold standard tool to perform signature analysis...

Extractor    SingleSample
SigProfiler tool is the gold standard tool to perform signature analysis... but lacks a GUI

Extractor

SingleSample

SigProfiler

Extractor

Python
SigProfiler tool is the gold standard tool to perform signature analysis... but lacks a GUI
SigProfiler tool is the gold standard tool to perform signature analysis... **but lacks a GUI**
New refitting algorithm considers biological rules to assign signatures

Complete set of mutational signatures

S2: Consider signatures extracted from this tumor type

S1: Examine an individual sample

S3: Apply rules for mutational signatures

S4: Evaluate sample with all N remaining signatures

S5: Exclude each of the N signatures and evaluate the sample with N-1 signatures

S6: Evaluate sample with the remaining M signatures

S8: Include each of the remaining signatures from the global set of signatures and evaluate the sample with M+1 signatures

S7: Consider all other signatures

S9: Output the results

Signature rules (only SBSs)
1) Exclude signatures if they lack the appropriate statistically significant strand bias: applied to signatures 4, 8, 7a/b/c/d, 11, 12, 16, 22, 23, 24, 25, 27, 31, 32, 33, 35, 42
2) Exclude 10a/b if sample has < 10^5 SBSs in WGS
3) Exclude 6, 14, 15, 20, 21, 26 if sample has < 10^4 SBSs in WGS

1) For SBS, add SBS1 and SBS5 if addition improves cosine similarity
2) For DBS, ID, and SBS signatures other than 1 or 5, add most contributing signature if addition increases cosine similarity > 0.05
3) "Connected signature inclusion rules" for SBSs; see Methods
Signatures are now based on new COSMIC v3 ...
Signatures are now based on new COSMIC v3 ...

49 SBS signatures
11 DBS signatures
17 Indel signatures
Signatures are now based on new COSMIC v3 ...

Mutational Signatures (v3 - May 2019)

Introduction

Somatic mutations are present in all cells of the human body and occur throughout life. They are the consequence of multiple mutational processes, including the intrinsic slight infidelity of the DNA replication machinery, exogenous or endogenous mutagen exposures, enzymatic modification of DNA and defective DNA repair. Different mutational processes generate unique combinations of mutation types, termed "Mutational Signatures".

In the past few years, large-scale analyses have revealed many mutational signatures across the spectrum of human cancer types. However, as the number of mutational signatures grows the need for a curated census of signatures has become apparent. Here, we deliver such a resource by providing the profiles of, and additional information about, known mutational signatures.

Vignettes

As the number of mutational signatures has increased it has become increasingly difficult to keep in mind their mutational features, aetiology, and other attributes. We therefore provide a summary "vignette" for each mutational signature. The vignettes include mutational profiles and notes on potential aetiology, associated mutational signatures, how the signature has changed during iterations of analysis and other pertinent comments. These are intended to be short, very high level, “aides-memoire” for key elements of what we know, suspect or has been widely discussed for each signature. They are not intended to be comprehensive summaries of everything reported in the scientific literature and they are not referenced.

These pages present vignettes for three sets of signatures:

- Single Base Substitution (SBS) Signatures
- Doublet Base Substitution (DBS) Signatures
- Small Insertion and Deletion (ID) Signatures
Signatures are now based on new COSMIC v3 ... where SigProfilerWeb will be available soon

Mutational Signatures (v3 - May 2019)

Introduction

Somatic mutations are present in all cells of the human body and occur throughout life. They are the consequence of multiple mutational processes, including the intrinsic slight infidelity of the DNA replication machinery, exogenous or endogenous mutagen exposures, enzymatic modification of DNA and defective DNA repair. Different mutational processes generate unique combinations of mutation types, termed "Mutational Signatures".

In the past few years, large-scale analyses have revealed many mutational signatures across the spectrum of human cancer types. However, as the number of mutational signatures grows the need for a curated census of signatures has become apparent. Here, we deliver such a resource by providing the profiles of, and additional information about, known mutational signatures.

Vignettes

As the number of mutational signatures has increased it has become increasingly difficult to keep in mind their mutational features, aetiology, and other attributes. We therefore provide a summary "vignette" for each mutational signature. The vignettes include mutational profiles and notes on potential aetiology, associated mutational signatures, how the signature has changed during iterations of analysis and other pertinent comments. These are intended to be short, very high level, "aides-memoire" for key elements of what we know, suspect or has been widely discussed for each signature. They are not intended to be comprehensive summaries of everything reported in the scientific literature and they are not referenced.

These pages present vignettes for three sets of signatures:

- Single Base Substitution (SBS) Signatures
- Doublet Base Substitution (DBS) Signatures
- Small Insertion and Deletion (ID) Signatures
Web applications to implement mutational signature analysis

Mutational signatures
New paradigm in cancer genomics

Mutational Signatures in Cancer – MuSiCa
Simplifying signature analysis

An open door to the future
Updating to new algorithm and COSMIC framework
Web applications to implement mutational signature analysis

Mutational signatures
New paradigm in cancer genomics

Mutational signatures are a promising biomarker for diagnosis, prognosis and treatment of different cancer types

Mutational Signatures in Cancer – MuSiCa
Simplifying signature analysis

MuSiCa is a user-friendly web tool to perform signature analysis in a clinical-based environment

An open door to the future
Update to new algorithm and COSMIC version

SigProfilerWeb adds an improved refitting algorithm and the support for new signatures and variant types
Science is never a one-person job...
Thank you!
A new user-friendly web application to implement mutational signature analysis

31\textsuperscript{st} European Congress of Pathology
Nice, September 10\textsuperscript{th}

MARCOS DÍAZ GAY