# Package 'ICAMS'

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Type Package

```
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Description Analysis and visualization of experimentally elucidated mutational
      signatures -- the kind of analysis and visualization in Boot et al.,
      ``In-depth characterization of the cisplatin mutational signature in
      human cell lines and in esophageal and liver tumors", Genome Research 2018,
      <doi:10.1101/gr.230219.117> and
      `Characterization of colibactin-associated mutational signature in an
      Asian oral squamous cell carcinoma and in other mucosal tumor types",
      Genome Research 2020 <doi:10.1101/gr.255620.119>.
      'ICAMS' stands for In-depth Characterization
      and Analysis of Mutational Signatures. 'ICAMS' has functions to read in
      variant call files (VCFs) and to collate the corresponding catalogs of
      mutational spectra and to analyze and plot catalogs of mutational spectra
      and signatures. Handles both ``counts-based" and ``density-based" (i.e.
      representation as mutations per megabase) mutational spectra or signatures.
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      dplyr,
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      graphics,
      grDevices,
```

Title In-Depth Characterization and Analysis of Mutational Signatures ('ICAMS')

2 R topics documented:

```
IRanges,
     lifecycle,
     RColorBrewer,
     stats,
     stringi,
     utils,
     zip
Depends R (>= 3.5),
RoxygenNote 7.1.2
Suggests BSgenome. Hsapiens. 1000 genomes. hs37d5,
     BSgenome. Hsapiens. UCSC. hg38,
     BSgenome.Mmusculus.UCSC.mm10,
     ggplot2,
     reshape2,
     rlang,
     testthat
```

# **R** topics documented:

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### **Description**

An R list with one element each for BSgenome.Hsapiens.1000genomes.hs37d5, BSgenome.Hsapiens.UCSC.hg38 and BSgenome.Mmusculus.UCSC.mm10. Each element is in turn a sub-list keyed by exome, transcript, and genome. Each element of the sub list is keyed by the number of rows in the catalog class (as a string, e.g. "78", not 78). The keys are: 78 (DBS78Catalog), 96 (SBS96Catalog), 136 (DBS136Catalog), 144 (DBS144Catalog), 192 (SBS192Catalog), and 1536 (SBS1536Catalog). So, for example to get the exome abundances for SBS96 catalogs for BSgenome.Hsapiens.UCSC.hg38 exomes one would reference all.abundance[["BSgenome.Hsapiens.UCSC.hg38"]][["exome"]][["96"]] or all.abundance\$BSgenome.Hsapiens.UCSC.hg38\$exome\$"96". The value of the abundance is an integer vector with the K-mers as names and each value being the count of that K-mer.

#### Usage

all.abundance

## **Format**

See Description.

```
all.abundance$BSgenome.Hsapiens.UCSC.hg38$transcript$`144`
# AA AC AG AT CA CC ...
# 90769160 57156295 85738416 87552737 83479655 63267896 ...
# There are 90769160 AAs on the sense strands of transcripts in # this genome.
```

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Add sequence context and transcript information to an in-memory DBS VCF
DBS VCF

## **Description**

Add sequence context and transcript information to an in-memory DBS VCF

## Usage

```
AnnotateDBSVCF(DBS.vcf, ref.genome, trans.ranges = NULL, name.of.VCF = NULL)
```

## **Arguments**

```
DBS.vcf An in-memory DBS VCF as a data.frame.

ref.genome A ref.genome argument as described in ICAMS.

trans.ranges Optional. If ref.genome specifies one of the BSgenome object

1. BSgenome.Hsapiens.1000genomes.hs37d5

2. BSgenome.Hsapiens.UCSC.hg38

3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

name.of.VCF Name of the VCF file.
```

## Value

An in-memory DBS VCF as a data.table. This has been annotated with the sequence context (column name seq.21bases) and with transcript information in the form of a gene symbol (e.g. "TP53") and transcript strand. This information is in the columns trans.start.pos, trans.end.pos, trans.strand, trans.Ensembl.gene.ID and trans.gene.symbol in the output. These columns are not added if is.null(trans.ranges).

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AnnotateIDVCF	Add sequence context to an in-memory ID (insertion/deletion) VCF,
	and confirm that they match the given reference genome

## **Description**

Add sequence context to an in-memory ID (insertion/deletion) VCF, and confirm that they match the given reference genome

# Usage

```
AnnotateIDVCF(
   ID.vcf,
   ref.genome,
   flag.mismatches = 0,
   name.of.VCF = NULL,
   suppress.discarded.variants.warnings = TRUE
)
```

#### **Arguments**

ID.vcf

An in-memory ID (insertion/deletion) VCF as a data.frame. This function expects that there is a "context base" to the left, for example REF = ACG, ALT = A (deletion of CG) or REF = A, ALT = ACC (insertion of CC).

ref.genome

A ref. genome argument as described in ICAMS.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants. See element discarded.variants in the return value for more details.

name.of.VCF Name of the VCF file.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### Value

A list of elements:

- annotated.vcf: The original VCF data frame with two new columns added to the input data frame:
  - seq. context: The sequence embedding the variant.
  - seq.context.width: The width of seq.context to the left.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.

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#### **Examples**

```
file <- c(system.file("extdata/Strelka-ID-vcf/",</pre>
                        "Strelka.ID.GRCh37.s1.vcf",
                       package = "ICAMS"))
ID.vcf <- ReadAndSplitVCFs(file, variant.caller = "strelka")$ID[[1]]</pre>
if (requireNamespace("BSgenome.Hsapiens.1000genomes.hs37d5", quietly = TRUE)) {
  list <- AnnotateIDVCF(ID.vcf, ref.genome = "hg19")</pre>
  annotated.ID.vcf <- list$annotated.vcf}</pre>
```

AnnotateSBSVCF

Add sequence context and transcript information to an in-memory SBS VCF

# **Description**

Add sequence context and transcript information to an in-memory SBS VCF

#### Usage

```
AnnotateSBSVCF(SBS.vcf, ref.genome, trans.ranges = NULL, name.of.VCF = NULL)
```

## **Arguments**

SBS.vcf An in-memory SBS VCF as a data. frame. ref.genome A ref. genome argument as described in ICAMS. trans.ranges Optional. If ref. genome specifies one of the BSgenome object 1. BSgenome. Hsapiens. 1000 genomes. hs37d5 2. BSgenome.Hsapiens.UCSC.hg38 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

Name of the VCF file. name.of.VCF

### Value

An in-memory SBS VCF as a data.table. This has been annotated with the sequence context (column name seq. 21bases) and with transcript information in the form of a gene symbol (e.g. "TP53") and transcript strand. This information is in the columns trans.start.pos, trans.end.pos, trans.strand, trans.Ensembl.gene.ID and trans.gene.symbol in the output. These columns are not added if is.null(trans.ranges).

```
file <- c(system.file("extdata/Strelka-SBS-vcf",</pre>
                        "Strelka.SBS.GRCh37.s1.vcf",
                        package = "ICAMS"))
list.of.vcfs <- ReadAndSplitVCFs(file, variant.caller = "strelka")</pre>
SBS.vcf <- list.of.vcfs$SBS[[1]]</pre>
```

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```
if (requireNamespace("BSgenome.Hsapiens.1000genomes.hs37d5", quietly = TRUE)) {
 annotated.SBS.vcf <- AnnotateSBSVCF(SBS.vcf, ref.genome = "hg19";</pre>
                                       trans.ranges = trans.ranges.GRCh37)}
```

as.catalog

Create a catalog from a matrix, data.frame, or vector

## **Description**

Create a catalog from a matrix, data. frame, or vector

## Usage

```
as.catalog(
  object,
  ref.genome = NULL,
  region = "unknown",
  catalog.type = "counts",
  abundance = NULL,
  infer.rownames = FALSE
```

## **Arguments**

object

A numeric matrix, numeric data.frame, or vector. If a vector, converted to a 1-column matrix with rownames taken from the element names of the vector and with column name "Unknown". If argument infer.rownames is FALSE then this argument must have rownames to denote the mutation types. See CatalogRowOrder for more details.

ref.genome

A ref. genome argument as described in ICAMS.

region

A character string designating a region, one of genome, transcript, exome, unknown; see ICAMS. If the catalog type is a stranded catalog type (SBS192 or DBS144), region = "genome" will be silently converted to "transcript".

catalog.type

One of "counts", "density", "counts.signature", "density.signature".

abundance

If NULL, then inferred if ref. genome is one of the reference genomes known to ICAMS and region is not unknown. See ICAMS. The argument abundance should contain the counts of different source sequences for mutations in the same format as the numeric vectors in all. abundance.

infer.rownames If TRUE, and object has no rownames, then assume the rows of object are in the correct order and add the rownames implied by the number of rows in object (e.g. rownames for SBS 192 if there are 192 rows). If TRUE, be sure the order of rows is correct.

## Value

A catalog as described in ICAMS.

8 Canonicalize1Del

#### **Examples**

Canonicalize1Del

Given a deletion and its sequence context, categorize it

## **Description**

This function is primarily for internal use, but we export it to document the underlying logic.

# Usage

```
Canonicalize1Del(context, del.seq, pos, trace = 0)
```

## **Arguments**

context	The deleted sequence plus ample surrounding sequence on each side (at least as long as del.seq).
del.seq	The deleted sequence in context.
pos	The position of del.sequence in context.
trace	If $> 0$ , then generate messages tracing how the computation is carried out.

## **Details**

```
See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7_indel_classification_2017_12_08.xlsx for additional information on deletion mutation classification.
```

This function first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACAC, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

# Value

A string that is the canonical representation of the given deletion type. Return NA and raise a warning if there is an un-normalized representation of the deletion of a repeat unit. See FindDelMH for details. (This seems to be very rare.)

```
Canonicalize1Del("xyAAAqr", del.seq = "A", pos = 3) # "DEL:T:1:2"
Canonicalize1Del("xyAAAqr", del.seq = "A", pos = 4) # "DEL:T:1:2"
Canonicalize1Del("xyAqr", del.seq = "A", pos = 3) # "DEL:T:1:0"
```

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CatalogRowOrder

Standard order of row names in a catalog

## **Description**

This data is designed for those who need to create their own catalogs from formats not supported by this package. The rownames denote the mutation types. For example, for SBS96 catalogs, the rowname AGAT represents a mutation from AGA > ATA.

## Usage

```
catalog.row.order
```

#### **Format**

A list of character vectors indicating the standard orders of row names in catalogs.

An object of class list of length 9.

#### **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

## Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+. In ID83 catalogs, deletion repeat sizes range from 0 to 5.

```
catalog.row.order$SBS96
# "ACAA" "ACCA" "ACGA" "ACCA" "CCCA" "CCGA" "CCTA" ...
# There are altogether 96 row names to denote the mutation types
# in SBS96 catalog.
```

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CollapseCatalog

"Collapse" a catalog

## **Description**

- 1. Take a mutational spectrum or signature catalog that is based on a fined-grained set of features (for example, single-nucleotide substitutions in the context of the preceding and following 2 bases).
- 2. Collapse it to a catalog based on a coarser-grained set of features (for example, single-nucleotide substitutions in the context of the immediately preceding and following bases).

Collapse192CatalogTo96 Collapse an SBS 192 catalog to an SBS 96 catalog.

Collapse1536CatalogTo96 Collapse an SBS 1536 catalog to an SBS 96 catalog.

Collapse144CatalogTo78 Collapse a DBS 144 catalog to a DBS 78 catalog.

## Usage

```
Collapse192CatalogTo96(catalog)
Collapse1536CatalogTo96(catalog)
Collapse144CatalogTo78(catalog)
```

#### **Arguments**

catalog

A catalog as defined in ICAMS.

## Value

A catalog as defined in ICAMS.

## **Examples**

FindDelMH

Return the length of microhomology at a deletion

## **Description**

Return the length of microhomology at a deletion

## Usage

```
FindDelMH(context, deleted.seq, pos, trace = 0, warn.cryptic = TRUE)
```

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#### **Arguments**

context The deleted sequence plus ample surrounding sequence on each side (at least as

long as del. sequence).

deleted.seq The deleted sequence in context.

pos The position of del. sequence in context.

trace If > 0, then generate various messages showing how the computation is carried

out.

warn.cryptic if TRUE generating a warning if there is a cryptic repeat (see the example).

#### **Details**

This function is primarily for internal use, but we export it to document the underlying logic.

Example:

GGCTAGTT aligned to GGCTAGAACTAGTT with a deletion represented as:

```
GGCTAGAACTAGTT
GGCTAGTT GG[CTAGAA]CTAGTT
```

Presumed repair mechanism leading to this:

```
GGCTAGAACTAGTT
CCGATCTTGATCAA
```

=>

GGCTAG TT CC GATCAA

=>

GGCTAGTT CCGATCAA

Variant-caller software can represent the same deletion in several different, but completely equivalent, ways.

```
GGC----TAGTT GGCTAGTT GGC[TAGAAC]TAGTT

* --- * ---

GGCT----AGTT GGCTAGTT GGCT[AGAACT]AGTT

** -- ** --

GGCTA-----GTT GGCTAGTT GGCTA[GAACTA]GTT
```

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```
*** - *** -

GGCTAG----TT GGCTAGTT GGCTAG[AACTAG]TT

**** ****
```

This function finds:

- 1. The maximum match of undeleted sequence to the left of the deletion that is identical to the right end of the deleted sequence, and
- 2. The maximum match of undeleted sequence to the right of the deletion that is identical to the left end of the deleted sequence.

The microhomology sequence is the concatenation of items (1) and (2).

#### Warning

A deletion in a *repeat* can also be represented in several different ways. A deletion in a repeat is abstractly equivalent to a deletion with microhomology that spans the entire deleted sequence. For example;

```
GACTAGCTAGTT
GACTAGTT GACTAGTT GACTA[GCTA]GTT

*** -*** -

is really a repeat

GACTAG---TT GACTAGTT GACTAG[CTAG]TT

*** ----

GACT---AGTT GACTAGTT GACT[AGCT]AGTT

** --** --
```

This function only flags these "cryptic repeats" with a -1 return; it does not figure out the repeat extent.

## Value

The length of the maximum microhomology of del. sequence in context.

#### ID classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

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#### **Examples**

FindMaxRepeatDel

Return the number of repeat units in which a deletion is embedded

## **Description**

Return the number of repeat units in which a deletion is embedded

## Usage

```
FindMaxRepeatDel(context, rep.unit.seq, pos)
```

## **Arguments**

context A string that embeds rep.unit.seq at position pos

 $\label{eq:context} \textbf{A substring of context at pos to pos + nchar(rep.unit.seq) -1, which is the} \\$ 

repeat unit sequence.

pos The position of rep.unit.seq in context.

#### **Details**

This function is primarily for internal use, but we export it to document the underlying logic.

For example FindMaxRepeatDel("xyaczt", "ac", 3) returns 0.

If substr(context, pos, pos + nchar(rep.unit.seq) -1) != rep.unit.seq then stop.

If this functions returns 0, then it is necessary to look for microhomology using the function FindDelMH.

## Warning

This function depends on the variant caller having "aligned" the deletion within the context of the repeat.

For example, a deletion of CAG in the repeat

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```
GTCAGCAGCATGT

can have 3 "aligned" representations as follows:

CT---CAGCAGGT

CTCAG---CAGGT

CTCAGCAG---GT
```

In these cases this function will return 2. (Please not that the return value does not include the rep.uni.seq in the count.)

However, the same deletion can also have an "unaligned" representation, such as

```
CTCAGC---AGGT

(a deletion of AGC).

In this case this function will return 1 (a deletion of AGC in a 2-element repeat of AGC).
```

#### Value

The number of repeat units in which rep.unit.seq is embedded, not including the input rep.unit.seq in the count.

#### **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

#### **Examples**

```
\label{local_problem} Find MaxRepeat Del("xyACACzt", "AC", 3) \ \# \ 1 \\ Find MaxRepeat Del("xyACACzt", "CA", 4) \ \# \ 0
```

GeneExpressionData

Example gene expression data from two cell lines

# Description

This data is designed to be used as an example in function PlotTransBiasGeneExp and PlotTransBiasGeneExpToPdf.

# Usage

```
gene.expression.data.HepG2
gene.expression.data.MCF10A
```

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#### **Format**

A data.table which contains the expression values of genes.

An object of class data.table (inherits from data.frame) with 57736 rows and 4 columns.

An object of class data.table (inherits from data.frame) with 57736 rows and 4 columns.

## **Examples**

```
gene.expression.data.HepG2
# Ensembl.gene.ID gene.symbol counts TPM
# ENSG00000000003 TSPAN6 6007 33.922648455
# ENSG00000000005 TNMD 0 0.000000000
# ENSG00000000419 DPM1 4441 61.669371091
# ENSG00000000457 SCYL3 1368 3.334619195
# ENSG00000000460 C1orf112 916 2.416263423
```

GeneratePlotPFMmatrix Generate PFMmatrix (Position Frequency Matrix) from a given list of sequences

## **Description**

Generate PFMmatrix (Position Frequency Matrix) from a given list of sequences

## Usage

```
GeneratePlotPFMmatrix(
   sequences,
   indel.class,
   flank.length = 5,
   plot.dir = NULL,
   plot.title = NULL
)
```

# Arguments

sequences	A list of strings returned from SymmetricalContextsFor1BPIndel.
indel.class	A single character string that denotes a 1 base pair insertion or deletion, as taken from ICAMS::catalog.row.order\$ID. Insertions or deletions into or from 5+ base-pair homopolymers are not supported.
flank.length	The length of flanking bases around the position or homopolymer targeted by the indel.
plot.dir	If provided, make a dot-line plot for PFMmatrix.
plot.title	The title of the dot-line plot

## Value

A matrix recording the frequency of each base (A, C, G, T) on each position of the sequence.

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#### **Examples**

```
file <- c(system.file("extdata/Mutect-vcf",</pre>
                       "Mutect.GRCh37.s1.vcf",
                       package = "ICAMS"))
split.vcfs <- ReadAndSplitVCFs(file, variant.caller = "mutect")</pre>
ID.catalog <- VCFsToIDCatalogs(list.of.vcfs = split.vcfs$ID,</pre>
                                ref.genome = "hg19",
                                region = "genome",
                                return.annotated.vcfs = TRUE)
annotated.vcf <- ID.catalog$annotated.vcfs$Mutect.GRCh37.s1</pre>
extended.seq.contexts <-
  SymmetricalContextsFor1BPIndel(annotated.vcf = annotated.vcf,
                                   indel.class = "DEL:T:1:0")
GeneratePlotPFMmatrix(sequences = extended.seq.contexts,
                       indel.class = "DEL:T:1:0",
                       plot.dir = file.path(tempdir(), "test.pdf"),
                       plot.title = "Deletion of 1T from 1T")
```

GetVAF

Extract the VAFs (variant allele frequencies) and read depth information from a VCF file

#### **Description**

Extract the VAFs (variant allele frequencies) and read depth information from a VCF file

## Usage

```
GetStrelkaVAF(vcf, name.of.VCF = NULL)
GetMutectVAF(vcf, name.of.VCF = NULL, tumor.col.name = NA)
GetFreebayesVAF(vcf, name.of.VCF = NULL)
GetPCAWGConsensusVAF(vcf, mc.cores = 1)
```

## **Arguments**

vcf An in-memory VCF data frame.

name.of.VCF Name of the VCF file.

tumor.col.name Optional. Only applicable to Mutect VCF. Name or index of the column in

**Mutect** VCF which contains the tumor sample information. It **must** have quotation marks if specifying the column name. If tumor.col.name is equal to

NA(default), this function will use the 10th column to calculate VAFs.

mc.cores The number of cores to use. Not available on Windows unless mc.cores = 1.

## Value

The original vcf with two additional columns added which contain the VAF(variant allele frequency) and read depth information.

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#### Note

 ${\tt GetPCAWGConsensusVAF}\ is\ analogous\ to\ {\tt GetMutectVAF},\ calculating\ VAF\ and\ read\ depth\ from\ PCAWG7\ consensus\ vcfs$ 

## **Examples**

HaplotypePlot

Generate Haplotype plot from a given list of sequences

## **Description**

Generate Haplotype plot from a given list of sequences

## Usage

```
HaplotypePlot(
  sequences,
  indel.class,
  flank.length = 5,
  title = "Haplotype Plot"
)
```

# Arguments

sequences A list of strings returned from SymmetricalContextsFor1BPIndel.

A single character string that denotes a 1 base pair insertion or deletion, as taken from ICAMS::catalog.row.order\$ID. Insertions or deletions into or from 5+ base-pair homopolymers are not supported.

The length of flanking bases around the position or homopolymer targeted by the indel.

The title of the haplotype plot

# Value

A ggplot2 object

18 ICAMS

**ICAMS** 

ICAMS: In-depth Characterization and Analysis of Mutational Signatures

#### **Description**

Analysis and visualization of experimentally elucidated mutational signatures – the kind of analysis and visualization in Boot et al., "In-depth characterization of the cisplatin mutational signature in human cell lines and in esophageal and liver tumors",

Genome Research 2018 https://doi.org/10.1101/gr.230219.117 and "Characterization of colibactinassociated mutational signature in an Asian oral squamous cell carcinoma and in other mucosal tumor types", Genome Research 2020, https://doi.org/10.1101/gr.255620.119. "ICAMS" stands for In-depth Characterization and Analysis of Mutational Signatures. "ICAMS" has functions to read in variant call files (VCFs) and to collate the corresponding catalogs of mutational spectra and to analyze and plot catalogs of mutational spectra and signatures.

## **Details**

"ICAMS" can read in VCFs generated by Strelka, Mutect or other variant callers, and collate the mutations into "catalogs" of mutational spectra. "ICAMS" can create and plot catalogs of mutational spectra or signatures for single base substitutions (SBS), doublet base substitutions (DBS), and small insertions and deletions (ID). It can also read and write these catalogs.

## **Catalogs**

A key data type in "ICAMS" is a "catalog" of mutation counts, of mutation densities (see below), or of mutational signatures.

Catalogs are S3 objects of class matrix and one of several additional classes that specify the types of the mutations represented in the catalog. The additional class is one of

- SBS96Catalog (strand-agnostic single base substitutions in trinucleotide context)
- SBS192Catalog (transcription-stranded single-base substitutions in trinucleotide context)
- SBS1536Catalog
- DBS78Catalog
- DBS144Catalog
- DBS136Catalog
- IndelCatalog
- ID166Catalog (genic-intergenic indel catalog)

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as.catalog is the main constructor.

Conceptually, a catalog also has one of the following types, indicated by the attribute catalog.type:

1. Matrix of mutation counts (one column per sample), representing (counts-based) mutational spectra (catalog.type = "counts").

- 2. Matrix of mutation **densities**, i.e. mutations per occurrences of source sequences (one column per sample), representing (density-based) mutational spectra (catalog.type = "density").
- 3. Matrix of mutational signatures, which are similar to spectra. However where spectra consist of counts or densities of mutations in each mutation class (e.g. ACA > AAA, ACA > AGA, ACA > ATA, ACC > AAC, ...), signatures consist of the proportions of mutations in each class (with all the proportions summing to 1). A mutational signature can be based on either:
  - mutation counts (a "counts-based mutational signature", catalog.type = "counts.signature"), or
  - mutation densities (a "density-based mutational signature", catalog.type = "density.signature").

Catalogs also have the attribute abundance, which contains the counts of different source sequences for mutations. For example, for SBSs in trinucleotide context, the abundances would be the counts of each trinucleotide in the human genome, exome, or in the transcribed region of the genome. See TransformCatalog for more information. Abundances logically depend on the species in question and on the part of the genome being analyzed.

In "ICAMS" abundances can sometimes be inferred from the catalog class attribute and the function arguments region, ref.genome, and catalog.type. Otherwise abundances can be provided as an abundance argument. See all.abundance for examples.

Possible values for region are the strings genome, transcript, exome, and unknown; transcript includes entire transcribed regions, i.e. the introns as well as the exons.

If you need to create a catalog from a source other than this package (i.e. other than with ReadCatalog or VCFsToCatalogs, VCFsToZipFile, etc.), then use as.catalog.

#### **Creating catalogs from variant call files (VCF files)**

• VCFsToCatalogs creates 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and ID (small insertions and deletions) catalog from the VCFs.

## Plotting catalogs

- PlotCatalog function plots mutational spectra for one sample or plot one mutational signature.
- PlotCatalogToPdf function plots catalogs of mutational spectra or of mutational signatures to a PDF file.

## Wrapper function to create catalogs from VCFs and plot the catalogs to PDF files

• VCFsToCatalogsAndPlotToPdf creates all types of SBS, DBS and ID catalogs from VCFs and plots the catalogs.

## Wrapper function to create a zip file which contains catalogs and plot PDFs from VCF files

 VCFsToZipFile creates a zip file which contains SBS, DBS and ID catalogs and plot PDFs from VCF files. 20 ICAMS

## The ref. genome (reference genome) argument

Many functions take the argument ref.genome.

To create a mutational spectrum catalog from a VCF file, "ICAMS" needs the reference genome sequence that matches the VCF file. The ref. genome argument provides this.

ref.genome must be one of

- 1. A variable from the Bioconductor BSgenome package that contains a particular reference genome, for example BSgenome. Hsapiens. 1000genomes. hs37d5.
- 2. The strings "hg38" or "GRCh38", which specify BSgenome. Hsapiens. UCSC. hg38.
- 3. The strings "hg19" or "GRCh37", which specify BSgenome. Hsapiens. 1000genomes. hs37d5.
- 4. The strings "mm10" or "GRCm38", which specify BSgenome. Mmusculus. UCSC. mm10.

All needed reference genomes must be installed separately by the user. Further instructions are at https://bioconductor.org/packages/release/bioc/html/BSgenome.html.

Use of "ICAMS" with reference genomes other than the 2 human genomes and 1 mouse genome specified above is restricted to catalog.type of counts or counts.signature unless the user also creates the necessary abundance vectors. See all.abundance.

Use available.genomes() to get the list of available genomes.

#### Writing catalogs to files

• WriteCatalog function writes a catalog to a file.

## Reading catalogs

• ReadCatalog function reads a file that contains a catalog in standardized format.

#### **Transforming catalogs**

TransformCatalog function transforms catalogs of mutational spectra or signatures to account for differing abundances of the source sequence of the mutations in the genome.

For example, mutations from ACG are much rarer in the human genome than mutations from ACC simply because CG dinucleotides are rare in the genome. Consequently, there are two possible representations of mutational spectra or signatures. One representation is based on mutation counts as observed in a given genome or exome, and this approach is widely used, as, for example, at https://cancer.sanger.ac.uk/signatures/, which presents signatures based on observed mutation counts in the human genome. We call these "counts-based spectra" or "counts-based signatures".

Alternatively, mutational spectra or signatures can be represented as mutations per source sequence, for example the number of ACT > AGT mutations occurring at all ACT 3-mers in a genome. We call these "density-based spectra" or "density-based signatures".

This function can also transform spectra based on observed genome-wide counts to "density"-based catalogs. In density-based catalogs mutations are expressed as mutations per source sequences. For example, a density-based catalog represents the proportion of ACCs mutated to ATCs, the proportion of ACGs mutated to ATGs, etc. This is different from counts-based mutational spectra catalogs, which contain the number of ACC > ATC mutations, the number of ACG > ATG mutations, etc.

This function can also transform observed-count based spectra or signatures from genome to exome based counts, or between different species (since the abundances of source sequences vary between genome and exome and between species).

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## Collapsing catalogs

## CollapseCatalog function

1. Takes a mutational spectrum or signature catalog that is based on a fined-grained set of features (for example, single-nucleotide substitutions in the context of the preceding and following 2 bases).

2. Collapses it to a catalog based on a coarser-grained set of features (for example, single-nucleotide substitutions in the context of the immediately preceding and following bases).

#### Data

- 1. CatalogRowOrder Standard order of rownames in a catalog. The rownames encode the type of each mutation. For example, for SBS96 catalogs, the rowname AGAT represents a mutation from AGA > ATA.
- 2. TranscriptRanges Transcript ranges and strand information for a particular reference genome.
- 3. all.abundance The counts of different source sequences for mutations.
- 4. GeneExpressionData Example gene expression data from two cell lines.

IsICAMSCatalog

Check whether an R object contains one of the ICAMS catalog classes

#### **Description**

Check whether an R object contains one of the ICAMS catalog classes

## Usage

```
IsICAMSCatalog(object)
```

# Arguments

object

An R object.

## Value

A logical value.

MutectVCFFilesToCatalog

[Deprecated, use VCFsToCatalogs(variant.caller = "mutect") instead] Create SBS, DBS and Indel catalogs from Mutect VCF files

### **Description**

[Deprecated, use VCFsToCatalogs(variant.caller = "mutect") instead] Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and Indel catalog from the Mutect VCFs specified by files

## Usage

```
MutectVCFFilesToCatalog(
   files,
   ref.genome,
   trans.ranges = NULL,
   region = "unknown",
   names.of.VCFs = NULL,
   tumor.col.names = NA,
   flag.mismatches = 0,
   return.annotated.vcfs = FALSE,
   suppress.discarded.variants.warnings = TRUE
)
```

## **Arguments**

files

Character vector of file paths to the Mutect VCF files.

ref.genome

A ref. genome argument as described in ICAMS.

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information

region

A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Vector of column names or column indices in VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the VCFs to calculate VAFs. See GetMutectVAF for more details.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls VCFsToSBSCatalogs, VCFsToDBSCatalogs and VCFsToIDCatalogs

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).
- catID: Matrix of ID (small insertions and deletions) catalog.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: **Non-NULL only if** return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class, DBS136.class and DBS144.class showing the mutation class for each DBS variant.
  - ID: ID VCF annotated by AnnotateIDVCF with one new column ID.class showing the mutation class for each ID variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

## ID classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

#### Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions. In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

#### **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

## **Examples**

 ${\tt MutectVCFFilesToCatalogAndPlotToPdf}$ 

[Deprecated, use VCFsToCatalogsAndPlotToPdf(variant.caller = "mutect") instead] Create SBS, DBS and Indel catalogs from Mutect VCF files and plot them to PDF

## **Description**

[Deprecated, use VCFsToCatalogsAndPlotToPdf(variant.caller = "mutect") instead] Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and Indel catalog from the Mutect VCFs specified by files and plot them to PDF

## Usage

```
MutectVCFFilesToCatalogAndPlotToPdf(
    files,
    ref.genome,
    trans.ranges = NULL,
    region = "unknown",
    names.of.VCFs = NULL,
    tumor.col.names = NA,
    output.file = "",
    flag.mismatches = 0,
    return.annotated.vcfs = FALSE,
    suppress.discarded.variants.warnings = TRUE
)
```

## **Arguments**

files Character vector of file paths to the Mutect VCF files.

ref.genome A ref.genome argument as described in ICAMS.

trans.ranges Optional. If ref.genome specifies one of the BSgenome object

1. BSgenome. Hsapiens. 1000 genomes. hs37d5

2. BSgenome. Hsapiens. UCSC. hg38

3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region A character string designating a genomic region; see as . catalog and ICAMS.

names.of.VCFs Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will

be used as the names of the VCF files.

tumor.col.names

Optional. Vector of column names or column indices in VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the VCFs to calculate

VAFs. See GetMutectVAF for more details.

output.file Optional. The base name of the PDF files to be produced; multiple files will be generated, each ending in x.pdf, where x indicates the type of catalog plotted

in the file.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls MutectVCFFilesToCatalog and PlotCatalogToPdf

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).

- catID: Matrix of ID (small insertions and deletions) catalog.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class,
     DBS136.class and DBS144.class showing the mutation class for each DBS variant.
  - ID: ID VCF annotated by AnnotateIDVCF with one new column ID. class showing the mutation class for each ID variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

#### Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions. In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

#### **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

#### **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

MutectVCFFilesToZipFile

[Deprecated, use VCFsToZipFile(variant.caller = "mutect") instead] Create a zip file which contains catalogs and plot PDFs from Mutect VCF files

## **Description**

[Deprecated, use VCFsToZipFile(variant.caller = "mutect") instead] Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and Indel catalog from the Mutect VCFs specified by dir, save the catalogs as CSV files, plot them to PDF and generate a zip archive of all the output files

## Usage

```
MutectVCFFilesToZipFile(
    dir,
    zipfile,
    ref.genome,
    trans.ranges = NULL,
    region = "unknown",
    names.of.VCFs = NULL,
    tumor.col.names = NA,
    base.filename = "",
    flag.mismatches = 0,
    return.annotated.vcfs = FALSE,
    suppress.discarded.variants.warnings = TRUE)
```

# **Arguments**

dir

Pathname of the directory which contains **only** the Mutect VCF files. Each Mutect VCF **must** have a file extension ".vcf" (case insensitive) and share the **same** ref.genome and region.

zipfile

Pathname of the zip file to be created.

ref.genome

A ref. genome argument as described in ICAMS.

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as . catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCFs listed in dir. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in dir and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Vector of column names or column indices in VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of VCFs listed in dir. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the VCFs to calculate VAFs. See GetMutectVAF for more details.

base.filename

Optional. The base name of the CSV and PDF files to be produced; multiple files will be generated, each ending in  $x.\operatorname{csv}$  or  $x.\operatorname{pdf}$ , where x indicates the type of catalog.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls MutectVCFFilesToCatalog, PlotCatalogToPdf, WriteCatalog and zip::zipr.

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144)
- catID: Matrix of ID (small insertions and deletions) catalog.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class, DBS136.class and DBS144.class showing the mutation class for each DBS variant.
  - ID: ID VCF annotated by AnnotateIDVCF with one new column ID.class showing the mutation class for each ID variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

# **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

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See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

#### Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions. In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

## **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

## **Examples**

PlotCatalog

Plot one spectrum or signature

## **Description**

Plot the spectrum of **one** sample or plot **one** signature. The type of graph is based on attribute("catalog.type") of the input catalog. You can first use TransformCatalog to get different types of catalog and then do the plotting.

## Usage

```
PlotCatalog(
  catalog,
  plot.SBS12 = NULL,
  cex = NULL,
  grid = NULL,
  upper = NULL,
  xlabels = NULL,
```

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```
ylabels = NULL,
ylim = NULL
)
```

#### **Arguments**

catalog	A catalog as defined in ICAMS with attributes added. See as.catalog for more details. catalog can also be a numeric matrix, numeric data.frame, or a vector denoting the mutation <b>counts</b> , but <b>must</b> be in the correct row order used in ICAMS. See CatalogRowOrder for more details. If catalog is a vector, it will be converted to a 1-column matrix with rownames taken from the element names of the vector and with column name "Unknown".
plot.SBS12	Only meaningful for class SBS192Catalog; if TRUE, generate an abbreviated plot of only SBS without context, i.e. C>A, C>G, C>T, T>A, T>C, T>G each on transcribed and untranscribed strands, rather than SBS in trinucleotide context, e.g. $ACA > AAA$ , $ACA > AGA$ ,, $TCT > TAT$ , There are 12 bars in the graph.
cex	Has the usual meaning. Taken from $par("cex")$ by default. Only implemented for SBS96Catalog, SBS192Catalog and DBS144Catalog.
grid	A logical value indicating whether to draw grid lines. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog.
upper	A logical value indicating whether to draw horizontal lines and the names of major mutation class on top of graph. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog.
xlabels	A logical value indicating whether to draw x axis labels. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog. If FALSE then plot x axis tick marks for SBS96Catalog; set par(tck = $\emptyset$ ) to suppress.
ylabels	A logical value indicating whether to draw y axis labels. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog.

# Value

ylim

ID166Catalog.

An **invisible** list whose first element is a logic value indicating whether the plot is successful. For SBS96Catalog, SBS192Catalog, DBS78Catalog, DBS144Catalog and IndelCatalog, the list will have a second element, which is a numeric vector giving the coordinates of all the bar midpoints drawn, useful for adding to the graph. For **SBS192Catalog** with "counts" catalog.type and non-NULL abundance and plot.SBS12 = TRUE, the list will have an additional element which is a list containing the strand bias statistics.

Has the usual meaning. Only implemented for SBS96Catalog, IndelCatalog,

## **Comments**

For **SBS192Catalog** with "counts" catalog.type and non-NULL abundance and plot . SBS12 = TRUE, the strand bias statistics are Benjamini-Hochberg q-values based on two-sided binomial tests of the mutation counts on the transcribed and untranscribed strands relative to the actual abundances of C and T on the transcribed strand. On the SBS12 plot, asterisks indicate q-values as follows \*, Q < 0.05; \*\*, Q < 0.01; \*\*\*, Q < 0.001.

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#### Note

The sizes of repeats involved in deletions range from 0 to 5+ in the mutational-spectra and signature catalog rownames, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

## **Examples**

PlotCatalogToPdf

Plot catalog to a PDF file

# Description

Plot catalog to a PDF file. The type of graph is based on attribute("catalog.type") of the input catalog. You can first use TransformCatalog to get different types of catalog and then do the plotting.

## Usage

```
PlotCatalogToPdf(
  catalog,
  file,
  plot.SBS12 = NULL,
  cex = NULL,
  grid = NULL,
  upper = NULL,
  xlabels = NULL,
  ylabels = NULL,
  ylim = NULL
)
```

## **Arguments**

catalog

A catalog as defined in ICAMS with attributes added. See as.catalog for more details. catalog can also be a numeric matrix, numeric data.frame, or a vector denoting the mutation **counts**, but **must** be in the correct row order used in ICAMS. See CatalogRowOrder for more details. If catalog is a vector, it will be converted to a 1-column matrix with rownames taken from the element names of the vector and with column name "Unknown".

file

The name of the PDF file to be produced.

plot.SBS12

Only meaningful for class SBS192Catalog; if TRUE, generate an abbreviated plot of only SBS without context, i.e. C>A, C>G, C>T, T>A, T>C, T>G each on transcribed and untranscribed strands, rather than SBS in trinucleotide context, e.g. ACA > AAA, ACA > AGA, ..., TCT > TAT, ... There are 12 bars in the graph.

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cex	for SBS96Catalog, SBS192Catalog and DBS144Catalog.
grid	A logical value indicating whether to draw grid lines. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog.
upper	A logical value indicating whether to draw horizontal lines and the names of major mutation class on top of graph. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog.
xlabels	A logical value indicating whether to draw x axis labels. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog. If FALSE then plot x axis tick marks for SBS96Catalog; set $par(tck = 0)$ to suppress.
ylabels	A logical value indicating whether to draw y axis labels. Only implemented for SBS96Catalog, DBS78Catalog, IndelCatalog, ID166Catalog.
ylim	Has the usual meaning. Only implemented for SBS96Catalog, IndelCatalog, ID166Catalog.

#### Value

An **invisible** list whose first element is a logic value indicating whether the plot is successful. For **SBS192Catalog** with "counts" catalog.type and non-null abundance and plot.SBS12 = TRUE, the list will have a second element which is a list containing the strand bias statistics.

#### **Comments**

For **SBS192Catalog** with "counts" catalog.type and non-NULL abundance and plot . SBS12 = TRUE, the strand bias statistics are Benjamini-Hochberg q-values based on two-sided binomial tests of the mutation counts on the transcribed and untranscribed strands relative to the actual abundances of C and T on the transcribed strand. On the SBS12 plot, asterisks indicate q-values as follows \*, Q < 0.05; \*\*, Q < 0.01; \*\*\*, Q < 0.001.

#### Note

The sizes of repeats involved in deletions range from 0 to 5+ in the mutational-spectra and signature catalog rownames, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

PlotTransBiasGeneExp Plot transcription strand bias with respect to gene expression values

### **Description**

Plot transcription strand bias with respect to gene expression values

#### Usage

```
PlotTransBiasGeneExp(
   annotated.SBS.vcf,
   expression.data,
   Ensembl.gene.ID.col,
   expression.value.col,
   num.of.bins,
   plot.type,
   damaged.base = NULL,
   ymax = NULL
)
```

# Arguments

annotated.SBS.vcf

An SBS VCF annotated by AnnotateSBSVCF. It **must** have transcript range information added.

expression.data

A data. table which contains the expression values of genes.

See GeneExpressionData for more details.

Ensembl.gene.ID.col

Name of column which has the Ensembl gene ID information in expression.data.

expression.value.col

Name of column which has the gene expression values in expression.data.

 $\verb"num.of.bins"$ 

The number of bins that will be plotted on the graph.

plot.type

A character string indicating one mutation type to be plotted. It should be one of "C>A", "C>G", "C>T", "T>A", "T>C", "T>G".

damaged.base

One of NULL, "purine" or "pyrimidine". This function allocates approximately equal numbers of mutations from damaged.base into each of num.of.bins bin by expression level. E.g. if damaged.base is "purine", then mutations from A and G will be allocated in approximately equal numbers to each expression-level bin. The rationale for the name damaged.base is that the direction of strand bias is a result of whether the damage occurs on a purine or pyrimidine. If NULL, the function attempts to infer the damaged.base based on mutation

counts.

ymax

Limit for the y axis. If not specified, it defaults to NULL and the y axis limit equals 1.5 times of the maximum mutation counts in a specific mutation type.

#### Value

A list whose first element is a logic value indicating whether the plot is successful. The second element is a named numeric vector containing the p-values printed on the plot.

#### Note

The p-values are calculated by logistic regression using function glm. The dependent variable is labeled "1" and "0" if the mutation from annotated SBS vcf falls onto the untranscribed and transcribed strand respectively. The independent variable is the binary logarithm of the gene expression value from expression data plus one, i.e.  $log_2(x+1)$  where x stands for gene expression value.

#### **Examples**

PlotTransBiasGeneExpToPdf

Plot transcription strand bias with respect to gene expression values to a PDF file

## **Description**

Plot transcription strand bias with respect to gene expression values to a PDF file

#### Usage

```
PlotTransBiasGeneExpToPdf(
   annotated.SBS.vcf,
   file,
   expression.data,
   Ensembl.gene.ID.col,
   expression.value.col,
   num.of.bins,
   plot.type = c("C>A", "C>G", "C>T", "T>A", "T>C", "T>G"),
   damaged.base = NULL
)
```

#### **Arguments**

```
annotated.SBS.vcf
```

An SBS VCF annotated by AnnotateSBSVCF. It **must** have transcript range information added.

file The name of output file.

```
expression.data
```

A data. table which contains the expression values of genes. See GeneExpressionData for more details.

Ensembl.gene.ID.col

Name of column which has the Ensembl gene ID information in expression.data.

expression.value.col

Name of column which has the gene expression values in expression.data.

num.of.bins The number of bins that will be plotted on the graph.

plot.type A vector of character indicating types to be plotted. It can be one or more types

from "C>A", "C>G", "C>T", "T>A", "T>C", "T>G". The default is to print all

the six mutation types.

damaged.base

One of NULL, "purine" or "pyrimidine". This function allocates approximately equal numbers of mutations from damaged.base into each of num.of.bins bin by expression level. E.g. if damaged.base is "purine", then mutations from A and G will be allocated in approximately equal numbers to each expression-level bin. The rationale for the name damaged.base is that the direction of strand bias is a result of whether the damage occurs on a purine or pyrimidine. If NULL, the function attempts to infer the damaged.base based on mutation counts.

#### Value

A list whose first element is a logic value indicating whether the plot is successful. The second element is a named numeric vector containing the p-values printed on the plot.

## Note

The p-values are calculated by logistic regression using function glm. The dependent variable is labeled "1" and "0" if the mutation from annotated SBS vcf falls onto the untranscribed and transcribed strand respectively. The independent variable is the binary logarithm of the gene expression value from expression data plus one, i.e.  $log_2(x+1)$  where x stands for gene expression value.

```
file <- c(system.file("extdata/Strelka-SBS-vcf/",</pre>
                       "Strelka.SBS.GRCh37.s1.vcf",
                       package = "ICAMS"))
list.of.vcfs <- ReadAndSplitVCFs(file, variant.caller = "strelka")</pre>
SBS.vcf <- list.of.vcfs$SBS[[1]]</pre>
if (requireNamespace("BSgenome.Hsapiens.1000genomes.hs37d5", quietly = TRUE)) {
  annotated.SBS.vcf <- AnnotateSBSVCF(SBS.vcf, ref.genome = "hg19",
                                       trans.ranges = trans.ranges.GRCh37)
  PlotTransBiasGeneExpToPdf(annotated.SBS.vcf = annotated.SBS.vcf,
                             expression.data = gene.expression.data.HepG2,
                             Ensembl.gene.ID.col = "Ensembl.gene.ID",
                             expression.value.col = "TPM",
                             num.of.bins = 4,
                             plot.type = c("C>A","C>G","C>T","T>A","T>C"),
                             file = file.path(tempdir(), "test.pdf"))
}
```

ReadAndSplitMutectVCFs

[Deprecated, use ReadAndSplitVCFs(variant.caller = "mutect") instead] Read and split Mutect VCF files

#### **Description**

[Deprecated, use ReadAndSplitVCFs(variant.caller = "mutect") instead] Read and split Mutect VCF files

## Usage

```
ReadAndSplitMutectVCFs(
   files,
   names.of.VCFs = NULL,
   tumor.col.names = NA,
   suppress.discarded.variants.warnings = TRUE
)
```

#### **Arguments**

files

Character vector of file paths to the Mutect VCF files.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Vector of column names or column indices in VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the VCFs to calculate VAFs. See GetMutectVAF for more details.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### Value

A list containing the following objects:

- SBS: List of VCFs with only single base substitutions.
- $\bullet\,$  DBS: List of VCFs with only doublet base substitutions as called by Mutect.
- ID: List of VCFs with only small insertions and deletions.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.

## See Also

MutectVCFFilesToCatalog

## **Examples**

Read And Split Strelka SBSVCFs

[Deprecated, use ReadAndSplitVCFs(variant.caller = "strelka") instead] Read and split Strelka SBS VCF files

## **Description**

[Deprecated, use ReadAndSplitVCFs(variant.caller = "strelka") instead] The function will find and merge adjacent SBS pairs into DBS if their VAFs are very similar. The default threshold value for VAF is 0.02.

# Usage

```
ReadAndSplitStrelkaSBSVCFs(
  files,
  names.of.VCFs = NULL,
  suppress.discarded.variants.warnings = TRUE)
```

## **Arguments**

files

Character vector of file paths to the Strelka SBS VCF files.

 ${\tt names.of.VCFs}$ 

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

# Value

A list of elements as follows:

- SBS.vcfs: List of data.frames of pure SBS mutations no DBS or 3+BS mutations.
- DBS.vcfs: List of data.frames of pure DBS mutations no SBS or 3+BS mutations.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.

# See Also

StrelkaSBSVCFFilesToCatalog

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## **Examples**

ReadAndSplitVCFs

Read and split VCF files

# **Description**

Read and split VCF files

# Usage

```
ReadAndSplitVCFs(
   files,
   variant.caller = "unknown",
   num.of.cores = 1,
   names.of.VCFs = NULL,
   tumor.col.names = NA,
   filter.status = DefaultFilterStatus(variant.caller),
   get.vaf.function = NULL,
   ...,
   max.vaf.diff = 0.02,
   suppress.discarded.variants.warnings = TRUE,
   always.merge.SBS = FALSE
)
```

# **Arguments**

files Character vector of file paths to the VCF files.

variant.caller Name of the variant caller that produces the VCF, can be either "strelka",

"mutect", "freebayes" or "unknown". This information is needed to calculate the VAFs (variant allele frequencies). If variant caller is "unknown" (default) and get.vaf.function is NULL, then VAF and read depth will be NAs. If variant

caller is "mutect", do not merge SBSs into DBS.

num.of.cores The number of cores to use. Not available on Windows unless num.of.cores =

1.

names. of . VCFs Character vector of names of the VCF files. The order of names in names. of . VCFs

should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) and file paths without extensions (and the leading dot) will be used as the

names of the VCF files.

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tumor.col.names

Optional. Only applicable to **Mutect** VCFs. Vector of column names or column indices in **Mutect** VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of **Mutect** VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the **Mutect** VCFs to calculate VAFs. See GetMutectVAF for more details.

filter.status

The character string in column FILTER of the VCF that indicates that a variant has passed all the variant caller's filters. Variants (lines in the VCF) for which the value in column FILTER does not equal filter.status are silently excluded from the output. The internal function DefaultFilterStatus tries to infer filter.status based on variant.caller. If variant.caller is "unknown", user must specify filter.status explicitly. If filter.status = NULL, all variants are retained. If there is no FILTER column in the VCF, all variants are retained with a warning.

get.vaf.function

Optional. Only applicable when variant.caller is "unknown". Function to calculate VAF(variant allele frequency) and read depth information from original VCF. See GetMutectVAF as an example. If NULL(default) and variant.caller is "unknown", then VAF and read depth will be NAs.

.. Optional arguments to get.vaf.function.

max.vaf.diff

**Not** applicable if variant.caller = "mutect". The maximum difference of VAF, default value is 0.02. If the absolute difference of VAFs for adjacent SBSs is bigger than max.vaf.diff, then these adjacent SBSs are likely to be "merely" asynchronous single base mutations, opposed to a simultaneous doublet mutation or variants involving more than two consecutive bases. Use negative value (e.g. -1) to suppress merging adjacent SBSs to DBS.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

always.merge.SBS

If TRUE merge adjacent SBSs as DBSs regardless of VAFs and regardless of the value of max.vaf.diff and regardless of the value of get.vaf.function. It is an error to set this to TRUE when variant.caller = "mutect".

# Value

A list containing the following objects:

- SBS: List of VCFs with only single base substitutions.
- DBS: List of VCFs with only doublet base substitutions.
- ID: List of VCFs with only small insertions and deletions.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.

#### See Also

VCFsToCatalogs

40 ReadCatalog

## **Examples**

ReadCatalog

Read catalog

# **Description**

Read a catalog in standardized format from path.

# Usage

```
ReadCatalog(
   file,
   ref.genome = NULL,
   region = "unknown",
   catalog.type = "counts",
   strict = NULL,
   stop.on.error = TRUE
)
```

# **Arguments**

file

Path to a catalog on disk in a standardized format. The recognized formats are:

- ICAMS formatted SBS96, SBS192, SBS1536, DBS78, DBS136, DBS144, ID, ID166 (see CatalogRowOrder).
- SigProfiler-formatted SBS96, DBS78 and ID83 catalogs; see https://github.com/AlexandrovLab/SigProfilerExtractor.
- COSMIC-formatted SBS96, SBS192 (a.k.a. TSB192), DBS78, ID83 catalogs; see https://cancer.sanger.ac.uk/signatures/.

ref.genome A ref.genome argument as described in ICAMS.

region A character string designating a genomic region; see as.catalog and

ICAMS.

catalog.type One of "counts", "density", "counts.signature", "density.signature".

strict Ignored and deprecated.

stop.on.error If TRUE, call stop on error; otherwise return a 1-column matrix of NA's with

the attribute "error" containing error information. The number of rows may not

be the correct number for the expected catalog type.

## **Details**

See also WriteCatalog

# Value

A catalog as an S3 object; see as.catalog.

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#### **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

#### Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

# **Examples**

ReadStrelkaIDVCFs

[Deprecated, use ReadAndSplitVCFs(variant.caller = "strelka") instead] Read Strelka ID (small insertions and deletions) VCF files

# **Description**

[Deprecated, use ReadAndSplitVCFs(variant.caller = "strelka") instead] Read Strelka ID (small insertions and deletions) VCF files

# Usage

```
ReadStrelkaIDVCFs(files, names.of.VCFs = NULL)
```

# **Arguments**

files

Character vector of file paths to the VCF files.

 ${\tt names.of.VCFs}$ 

Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

#### Value

A list of data frames containing data lines of the VCF files.

#### Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

## See Also

```
StrelkaIDVCFFilesToCatalog
```

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## **Examples**

```
## Not run:
file <- c(system.file("extdata/Strelka-ID-vcf",</pre>
                        "Strelka.ID.GRCh37.s1.vcf",
                        package = "ICAMS"))
list.of.vcfs <- ReadStrelkaIDVCFs(file)</pre>
## End(Not run)
```

ReadVCFs

Read VCF files

# **Description**

Read VCF files

## Usage

```
ReadVCFs(
  files,
  variant.caller = "unknown",
  num.of.cores = 1,
  names.of.VCFs = NULL,
  tumor.col.names = NA,
  filter.status = DefaultFilterStatus(variant.caller),
  get.vaf.function = NULL,
```

# **Arguments**

files

Character vector of file paths to the VCF files.

variant.caller Name of the variant caller that produces the VCF, can be either "strelka", "mutect", "freebayes" or "unknown". This information is needed to calculate the VAFs (variant allele frequencies). If variant caller is "unknown" (default) and get.vaf.function is NULL, then VAF and read depth will be NAs. If variant caller is "mutect", do not merge SBSs into DBS.

num.of.cores

The number of cores to use. Not available on Windows unless num. of.cores =

names.of.VCFs

Character vector of names of the VCF files. The order of names in names . of . VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Only applicable to Mutect VCFs. Vector of column names or column indices in Mutect VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of Mutect VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the Mutect VCFs to calculate VAFs. See GetMutectVAF for more details.

revc 43

filter.status

The character string in column FILTER of the VCF that indicates that a variant has passed all the variant caller's filters. Variants (lines in the VCF) for which the value in column FILTER does not equal filter.status are silently excluded from the output. The internal function DefaultFilterStatus tries to infer filter.status based on variant.caller. If variant.caller is "unknown", user must specify filter.status explicitly. If filter.status = NULL, all variants are retained. If there is no FILTER column in the VCF, all variants are retained with a warning.

get.vaf.function

Optional. Only applicable when variant.caller is "unknown". Function to calculate VAF(variant allele frequency) and read depth information from original VCF. See GetMutectVAF as an example. If NULL(default) and variant.caller is "unknown", then VAF and read depth will be NAs.

... Optional arguments to get.vaf.function.

## Value

A list of data frames storing data lines of the VCF files with two additional columns added which contain the VAF(variant allele frequency) and read depth information.

# **Examples**

revc

Reverse complement every string in string.vec

## **Description**

Based on reverseComplement. Handles IUPAC ambiguity codes but not "u" (uracil). (see <a href="https://en.wikipedia.org/wiki/Nucleic\_acid\_notation">https://en.wikipedia.org/wiki/Nucleic\_acid\_notation</a>).

# Usage

```
revc(string.vec)
```

# **Arguments**

string.vec A character vector.

#### Value

A character vector with the reverse complement of every string in string.vec.

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# **Examples**

```
revc("aTgc") # GCAT

# A vector and strings with ambiguity codes
revc(c("ATGC", "aTGc", "wnTCb")) # GCAT GCAT VGANW

## Not run:
revc("ACGU") # An error
## End(Not run)
```

SimpleReadVCF

Read a VCF file into a data frame with minimal processing.

# **Description**

Read a VCF file into a data frame with minimal processing.

# Usage

```
SimpleReadVCF(file)
```

# **Arguments**

file

The name/path of the VCF file, or a complete URL.

# **Details**

Header lines beginning "##" are removed, and column "#CHROM" is renamed to "CHROM". Other column names are unchanged. Columns "#CHROM", "POS", "REF", and "ALT" must be in the input.

## Value

A data frame storing mutation records of a VCF file.

SplitListOfVCFs 45

SplitListOfVCFs	Split each VCF into SBS, DBS, and ID VCFs (plus VCF-like data
	frame with left-over rows)

# **Description**

Split each VCF into SBS, DBS, and ID VCFs (plus VCF-like data frame with left-over rows)

# Usage

```
SplitListOfVCFs(
  list.of.vcfs,
  variant.caller,
  max.vaf.diff = 0.02,
  num.of.cores = 1,
  suppress.discarded.variants.warnings = TRUE,
  always.merge.SBS = FALSE
)
```

## **Arguments**

list.of.vcfs List of VCFs as in-memory data frames. The VCFs should have VAF and read.depth information added. See ReadVCFs for more details.

variant.caller Name of the variant caller that produces the VCF, can be either "strelka", "mutect", "freebayes" or "unknown". If variant caller is "mutect", do **not** merge SBSs into DBS.

max.vaf.diff
The maximum difference of VAF, default value is 0.02. If the absolute difference of VAFs for adjacent SBSs is bigger than max.vaf.diff, then these adjacent SBSs are likely to be "merely" asynchronous single base mutations, opposed to a

simultaneous doublet mutation or variants involving more than two consecutive bases. Use negative value (e.g. -1) to suppress merging adjacent SBSs to DBS.

num.of.cores The number of cores to use. Not available on Windows unless num.of.cores = 1.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

always.merge.SBS

If TRUE merge adjacent SBSs as DBSs regardless of VAFs and regardless of the value of max.vaf.diff and regardless of the value of get.vaf.function. It is an error to set this to TRUE when variant.caller = "mutect".

## Value

A list containing the following objects:

- SBS: List of VCFs with only single base substitutions.
- DBS: List of VCFs with only doublet base substitutions as called by Mutect.
- ID: List of VCFs with only small insertions and deletions.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.

## **Examples**

StrelkaIDVCFFilesToCatalog

[Deprecated, use VCFsToCatalogs(variant.caller = "strelka") instead] Create ID (small insertions and deletions) catalog from Strelka ID VCF files

# **Description**

[Deprecated, use VCFsToCatalogs(variant.caller = "strelka") instead] Create ID (small insertions and deletions) catalog from the Strelka ID VCFs specified by files

# Usage

```
StrelkaIDVCFFilesToCatalog(
  files,
  ref.genome,
  region = "unknown",
  names.of.VCFs = NULL,
  flag.mismatches = 0,
  return.annotated.vcfs = FALSE,
  suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

files Character vector of file paths to the Strelka ID VCF files.

ref.genome A ref.genome argument as described in ICAMS.

region A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs Optional. Character vector of names of the VCF files. The order of names in

names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will

be used as the names of the VCF files.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls VCFsToIDCatalogs

#### Value

A **list** of elements:

- catalog: The ID (small insertions and deletions) catalog with attributes added. See as.catalog for more details.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: **Non-NULL only if** return.annotated.vcfs = TRUE. A list of data frames which contain the original VCF's ID mutation rows with three additional columns seq.context.width, seq.context and ID.class added. The category assignment of each ID mutation in VCF can be obtained from ID.class column.

## **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

## Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

 ${\tt StrelkaIDVCFFilesToCatalogAndPlotToPdf}$ 

[Deprecated, use VCFsToCatalogsAndPlotToPdf(variant.caller = "strelka") instead] Create ID (small insertions and deletions) catalog from Strelka ID VCF files and plot them to PDF

# **Description**

[Deprecated, use VCFsToCatalogsAndPlotToPdf(variant.caller = "strelka") instead] Create ID (small insertions and deletions) catalog from the Strelka ID VCFs specified by files and plot them to PDF

# Usage

```
StrelkaIDVCFFilesToCatalogAndPlotToPdf(
   files,
   ref.genome,
   region = "unknown",
   names.of.VCFs = NULL,
   output.file = "",
   flag.mismatches = 0,
   return.annotated.vcfs = FALSE,
   suppress.discarded.variants.warnings = TRUE
)
```

## **Arguments**

files Character vector of file paths to the Strelka ID VCF files.

ref.genome A ref.genome argument as described in ICAMS.

region A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs Optional. Character vector of names of the VCF files. The order of names in

names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will

be used as the names of the VCF files.

output.file Optional. The base name of the PDF file to be produced; the file is ending in

catID.pdf.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls StrelkaIDVCFFilesToCatalog and PlotCatalogToPdf

#### Value

A **list** of elements:

- catalog: The ID (small insertions and deletions) catalog with attributes added. See as.catalog for more details.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: **Non-NULL only if** return.annotated.vcfs = TRUE. A list of data frames which contain the original VCF's ID mutation rows with three additional columns seq.context.width, seq.context and ID.class added. The category assignment of each ID mutation in VCF can be obtained from ID.class column.

## **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

## Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

StrelkaIDVCFFilesToZipFile

[Deprecated, use VCFsToZipFile(variant.caller = "strelka") instead] Create a zip file which contains ID (small insertions and deletions) catalog and plot PDF from Strelka ID VCF files

## **Description**

[Deprecated, use VCFsToZipFile(variant.caller = "strelka") instead] Create ID (small insertions and deletions) catalog from the Strelka ID VCFs specified by dir, save the catalog as CSV file, plot it to PDF and generate a zip archive of all the output files.

# Usage

```
StrelkaIDVCFFilesToZipFile(
    dir,
    zipfile,
    ref.genome,
    region = "unknown",
    names.of.VCFs = NULL,
    base.filename = "",
    flag.mismatches = 0,
    return.annotated.vcfs = FALSE,
    suppress.discarded.variants.warnings = TRUE
)
```

## **Arguments**

dir Pathname of the directory which contains **only** the Strelka ID VCF files. Each

Strelka ID VCF must have a file extension ".vcf" (case insensitive) and share

the **same** ref.genome and region.

zipfile Pathname of the zip file to be created.

ref.genome A ref.genome argument as described in ICAMS.

region A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs Optional. Character vector of names of the VCF files. The order of names in

names.of.VCFs should match the order of VCFs listed in dir. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in dir and file paths without extensions (and the leading dot) will

be used as the names of the VCF files.

base.filename Optional. The base name of the CSV and PDF file to be produced; the file is

ending in catID.csv and catID.pdf respectively.

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls StrelkaIDVCFFilesToCatalog, PlotCatalogToPdf, WriteCatalog and zip::zipr.

## Value

A **list** of elements:

- catalog: The ID (small insertions and deletions) catalog with attributes added. See as.catalog for more details.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: **Non-NULL only if** return.annotated.vcfs = TRUE. A list of data frames which contain the original VCF's ID mutation rows with three additional columns seq.context.width, seq.context and ID.class added. The category assignment of each ID mutation in VCF can be obtained from ID.class column.

## **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

# Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

StrelkaSBSVCFFilesToCatalog

[Deprecated, use VCFsToCatalogs(variant.caller = "strelka") instead] Create SBS and DBS catalogs from Strelka SBS VCF files

## **Description**

[Deprecated, use VCFsToCatalogs(variant.caller = "strelka") instead] Create 3 SBS catalogs (96, 192, 1536) and 3 DBS catalogs (78, 136, 144) from the Strelka SBS VCFs specified by files. The function will find and merge adjacent SBS pairs into DBS if their VAFs are very similar. The default threshold value for VAF is 0.02.

# Usage

```
StrelkaSBSVCFFilesToCatalog(
   files,
   ref.genome,
   trans.ranges = NULL,
   region = "unknown",
   names.of.VCFs = NULL,
   return.annotated.vcfs = FALSE,
   suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

files Character vector of file paths to the Strelka SBS VCF files.

ref.genome

A ref. genome argument as described in ICAMS.

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### **Details**

This function calls VCFsToSBSCatalogs and VCFsToDBSCatalogs.

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class, DBS136.class and DBS144.class showing the mutation class for each DBS variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

## Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions.

## **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

 ${\tt StrelkaSBSVCFFilesToCatalogAndPlotToPdf}$ 

[Deprecated, use VCFsToCatalogsAndPlotToPdf(variant.caller = "strelka") instead] Create SBS and DBS catalogs from Strelka SBS VCF files and plot them to PDF

## **Description**

[Deprecated, use VCFsToCatalogsAndPlotToPdf(variant.caller = "strelka") instead] Create 3 SBS catalogs (96, 192, 1536) and 3 DBS catalogs (78, 136, 144) from the Strelka SBS VCFs specified by files and plot them to PDF. The function will find and merge adjacent SBS pairs into DBS if their VAFs are very similar. The default threshold value for VAF is 0.02.

# Usage

```
StrelkaSBSVCFFilesToCatalogAndPlotToPdf(
  files,
  ref.genome,
  trans.ranges = NULL,
  region = "unknown",
  names.of.VCFs = NULL,
  output.file = "",
  return.annotated.vcfs = FALSE,
  suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

files Character vector of file paths to the Strelka SBS VCF files.

ref.genome A ref.genome argument as described in ICAMS.

trans.ranges Optional. If ref.genome specifies one of the BSgenome object

1. BSgenome. Hsapiens. 1000 genomes. hs37d5

2. BSgenome.Hsapiens.UCSC.hg38

3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

output.file

Optional. The base name of the PDF files to be produced; multiple files will be generated, each ending in x. pdf, where x indicates the type of catalog plotted in the file.

```
return.annotated.vcfs
```

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

## **Details**

This function calls StrelkaSBSVCFFilesToCatalog and PlotCatalogToPdf

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class,
     DBS136.class and DBS144.class showing the mutation class for each DBS variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

# Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions.

#### **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

StrelkaSBSVCFFilesToZipFile

[Deprecated, use VCFsToZipFile(variant.caller = "strelka") instead] Create a zip file which contains catalogs and plot PDFs from Strelka SBS VCF files

## **Description**

[Deprecated, use VCFsToZipFile(variant.caller = "strelka") instead] Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) from the Strelka SBS VCFs specified by dir, save the catalogs as CSV files, plot them to PDF and generate a zip archive of all the output files. The function will find and merge adjacent SBS pairs into DBS if their VAFs are very similar. The default threshold value for VAF is 0.02.

# Usage

```
StrelkaSBSVCFFilesToZipFile(
    dir,
    zipfile,
    ref.genome,
    trans.ranges = NULL,
    region = "unknown",
    names.of.VCFs = NULL,
    base.filename = "",
    return.annotated.vcfs = FALSE,
    suppress.discarded.variants.warnings = TRUE)
```

# **Arguments**

dir

Pathname of the directory which contains **only** the Strelka SBS VCF files. Each Strelka SBS VCF **must** have a file extension ".vcf" (case insensitive) and share the **same** ref.genome and region.

zipfile

Pathname of the zip file to be created.

ref.genome

A ref. genome argument as described in ICAMS.

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCFs listed in dir. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in dir and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

base.filename Optional. The base name of the CSV and PDF files to be produced; multiple files will be generated, each ending in x.csv or x.pdf, where x indicates the type of catalog.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

## **Details**

 $This function calls {\tt StrelkaSBSVCFFilesToCatalog, PlotCatalogToPdf, WriteCatalog and {\tt zip::zipr.}}$ 

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class,
     DBS136.class and DBS144.class showing the mutation class for each DBS variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

#### Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions.

## **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

SymmetricalContextsFor1BPIndel

Get all the sequence contexts of the indels in a given 1 base-pair indel class from a VCF

# **Description**

Get all the sequence contexts of the indels in a given 1 base-pair indel class from a VCF

# Usage

```
SymmetricalContextsFor1BPIndel(annotated.vcf, indel.class, flank.length = 5)
```

# **Arguments**

annotated.vcf	An in-memory data.frame or similar table containing "VCF" (variant call format) data as created by VCFsToIDCatalogs with argument return.annotated.vcfs = TRUE.
indel.class	A single character string that denotes a 1 base pair insertion or deletion, as taken from ICAMS::catalog.row.order\$ID. Insertions or deletions into or from 5+ base-pair homopolymers are not supported.
flank.length	The length of flanking bases around the position or homopolymer targeted by the indel.

# Value

A list of all sequence contexts for the specified indel.class.

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TranscriptRanges	

Transcript ranges data

# **Description**

Transcript ranges and strand information for a particular reference genome.

## Usage

```
trans.ranges.GRCh37
trans.ranges.GRCh38
trans.ranges.GRCm38
```

#### **Format**

A data.table which contains transcript range and strand information for a particular reference genome. colnames are chrom, start, end, strand, Ensembl.gene.ID, gene.symbol. It uses one-based coordinates.

An object of class data.table (inherits from data.frame) with 19083 rows and 6 columns.

An object of class data.table (inherits from data.frame) with 19096 rows and 6 columns.

An object of class data.table (inherits from data.frame) with 20325 rows and 6 columns.

## **Details**

This information is needed to generate catalogs that depend on transcriptional strand information, for example catalogs of class SBS192Catalog.

```
trans.ranges.GRCh37: Human GRCh37. trans.ranges.GRCh38: Human GRCh38. trans.ranges.GRCm38: Mouse GRCm38.
```

For these two tables, only genes that are associated with a CCDS ID are kept for transcriptional strand bias analysis.

This information is needed for StrelkaSBSVCFFilesToCatalog, StrelkaSBSVCFFilesToCatalogAndPlotToPdf, MutectVCFFilesToCatalog, MutectVCFFilesToCatalogAndPlotToPdf, VCFsToSBSCatalogs and VCFsToDBSCatalogs.

## **Source**

```
ftp://ftp.ebi.ac.uk/pub/databases/gencode/Gencode_human/release_30/GRCh37_mapping/
gencode.v30lift37.annotation.gff3.gz
ftp://ftp.ebi.ac.uk/pub/databases/gencode/Gencode_human/release_30/gencode.v30.annotation.
gff3.gz
ftp://ftp.ebi.ac.uk/pub/databases/gencode/Gencode_mouse/release_M21/gencode.vM21.
annotation.gff3.gz
```

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## **Examples**

```
trans.ranges.GRCh37
         start
# chrom
                   end strand Ensembl.gene.ID gene.symbol
          65419 71585 + ENSG00000186092
                                                      OR4F5
     1
     1 367640 368634 + ENSG00000235249
1 621059 622053 - ENSG00000284662
#
                                                      0R4F29
#
                                                      OR4F16
     1 859308 879961
#
                            + ENSG00000187634
                                                      SAMD11
#
     1 879583 894689
                              - ENSG00000188976
                                                      NOC2L
   . . .
            . . .
                     . . .
                                            . . .
                                                         . . .
```

TransformCatalog

Transform between counts and density spectrum catalogs and counts and density signature catalogs

# **Description**

Transform between counts and density spectrum catalogs and counts and density signature catalogs

# Usage

```
TransformCatalog(
  catalog,
  target.ref.genome = NULL,
  target.region = NULL,
  target.catalog.type = NULL,
  target.abundance = NULL
)
```

# **Arguments**

catalog

An SBS or DBS catalog as described in ICAMS; must **not** be an ID (small insertions and deletions) catalog.

target.ref.genome

A ref.genome argument as described in ICAMS. If NULL, then defaults to the ref.genome attribute of catalog.

target.region A region argument; see as.catalog and ICAMS. If NULL, then defaults to the region attribute of catalog.

target.catalog.type

A character string acting as a catalog type identifier, one of "counts", "density", "counts.signature", "density.signature"; see as.catalog. If NULL, then defaults to the catalog. type attribute of catalog.

target.abundance

A vector of counts, one for each source K-mer for mutations (e.g. for strandagnostic single nucleotide substitutions in trinucleotide – i.e. 3-mer – context, one count each for ACA, ACC, ACG, ... TTT). See all.abundance. If NULL, the function tries to infer target.abundace from the class of catalog and the value of the target.ref.genome, target.region, and target.catalog.type.

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#### **Details**

Only the following transformations are legal:

 counts -> counts (deprecated, generates a warning; we strongly suggest that you work with densities if comparing spectra or signatures generated from data with different underlying abundances.)

- 2. counts -> density
- 3. counts -> (counts.signature,density.signature)
- 4. density -> counts (the semantics are to infer the genome-wide or exome-wide counts based on the densities)
- 5. density -> density (a null operation, generates a warning)
- 6. density -> (counts.signature, density.signature)
- 7. counts.signature -> counts.signature (used to transform between the source abundance and target.abundance)
- 8. counts.signature -> density.signature
- 9. counts.signature -> (counts, density) (generates an error)
- 10. density.signature -> density.signature (a null operation, generates a warning)
- 11. density.signature -> counts.signature
- 12. density.signature -> (counts, density) (generates an error)

## Value

A catalog as defined in ICAMS.

# Rationale

The TransformCatalog function transforms catalogs of mutational spectra or signatures to account for differing abundances of the source sequence of the mutations in the genome.

For example, mutations from ACG are much rarer in the human genome than mutations from ACC simply because CG dinucleotides are rare in the genome. Consequently, there are two possible representations of mutational spectra or signatures. One representation is based on mutation counts as observed in a given genome or exome, and this approach is widely used, as, for example, at https://cancer.sanger.ac.uk/cosmic/signatures, which presents signatures based on observed mutation counts in the human genome. We call these "counts-based spectra" or "counts-based signatures".

Alternatively, mutational spectra or signatures can be represented as mutations per source sequence, for example the number of ACT > AGT mutations occurring at all ACT 3-mers in a genome. We call these "density-based spectra" or "density-based signatures".

This function can also transform spectra based on observed genome-wide counts to "density"-based catalogs. In density-based catalogs mutations are expressed as mutations per source sequences. For example, a density-based catalog represents the proportion of ACCs mutated to ATCs, the proportion of ACGs mutated to ATGs, etc. This is different from counts-based mutational spectra catalogs, which contain the number of ACC > ATC mutations, the number of ACG > ATG mutations, etc.

This function can also transform observed-count based spectra or signatures from genome to exome based counts, or between different species (since the abundances of source sequences vary between genome and exome and between species).

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## **Examples**

VCFsToCatalogs

Create SBS, DBS and Indel catalogs from VCFs

## **Description**

Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and Indel catalog from the Mutect VCFs specified by files

# Usage

```
VCFsToCatalogs(
    files,
    ref.genome,
    variant.caller = "unknown",
    num.of.cores = 1,
    trans.ranges = NULL,
    region = "unknown",
    names.of.VCFs = NULL,
    tumor.col.names = NA,
    filter.status = DefaultFilterStatus(variant.caller),
    get.vaf.function = NULL,
    ...,
    max.vaf.diff = 0.02,
    return.annotated.vcfs = FALSE,
    suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

files Character vector of file paths to the VCF files.

ref.genome A ref.genome argument as described in ICAMS.

variant.caller Name of the variant caller that produces the VCF, can be either "strelka", "mutect", "freebayes" or "unknown". This information is needed to calculate the VAFs (variant allele frequencies). If variant caller is "unknown" (default) and get.vaf.function is NULL, then VAF and read depth will be NAs. If variant caller is "mutect", do not merge SBSs into DBS.

num.of.cores The number of cores to use. Not available on Windows unless num.of.cores =

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trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Only applicable to **Mutect** VCFs. Vector of column names or column indices in **Mutect** VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of **Mutect** VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the **Mutect** VCFs to calculate VAFs. See GetMutectVAF for more details.

filter.status

The character string in column FILTER of the VCF that indicates that a variant has passed all the variant caller's filters. Variants (lines in the VCF) for which the value in column FILTER does not equal filter.status are silently excluded from the output. The internal function DefaultFilterStatus tries to infer filter.status based on variant.caller. If variant.caller is "unknown", user must specify filter.status explicitly. If filter.status = NULL, all variants are retained. If there is no FILTER column in the VCF, all variants are retained with a warning.

get.vaf.function

Optional. Only applicable when variant.caller is "unknown". Function to calculate VAF(variant allele frequency) and read depth information from original VCF. See GetMutectVAF as an example. If NULL(default) and variant.caller is "unknown", then VAF and read depth will be NAs.

Optional arguments to get.vaf.function.

max.vaf.diff

**Not** applicable if variant.caller = "mutect". The maximum difference of VAF, default value is 0.02. If the absolute difference of VAFs for adjacent SBSs is bigger than max.vaf.diff, then these adjacent SBSs are likely to be "merely" asynchronous single base mutations, opposed to a simultaneous doublet mutation or variants involving more than two consecutive bases. Use negative value (e.g. -1) to suppress merging adjacent SBSs to DBS.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

## **Details**

This function calls VCFsToSBSCatalogs, VCFsToDBSCatalogs and VCFsToIDCatalogs

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#### Value

A list containing the following objects:

• catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).

- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).
- catID: Matrix of ID (small insertions and deletions) catalog.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class, DBS136.class and DBS144.class showing the mutation class for each DBS variant.
  - ID: ID VCF annotated by AnnotateIDVCF with one new column ID.class showing the mutation class for each ID variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

#### ID classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

## Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions. In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

## **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

VCFsToCatalogsAndPlotToPdf

Create SBS, DBS and Indel catalogs from VCFs and plot them to PDF

# **Description**

Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and Indel catalog from the VCFs specified by files and plot them to PDF

# Usage

```
VCFsToCatalogsAndPlotToPdf(
  files,
 output.dir,
  ref.genome,
  variant.caller = "unknown",
  num.of.cores = 1,
  trans.ranges = NULL,
  region = "unknown",
  names.of.VCFs = NULL,
  tumor.col.names = NA,
  filter.status = DefaultFilterStatus(variant.caller),
  get.vaf.function = NULL,
  . . . ,
 max.vaf.diff = 0.02,
 base.filename = "",
 return.annotated.vcfs = FALSE,
  suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

files Character vector of file paths to the VCF files.

output.dir The directory where the PDF files will be saved. ref.genome A ref.genome argument as described in ICAMS.

rer genome A rer genome argument as described in Teams

variant.caller Name of the variant caller that produces the VCF, can be either "strelka", "mutect", "freebayes" or "unknown". This information is needed to calculate the VAFs (variant allele frequencies). If variant caller is "unknown" (default) and get.vaf.function is NULL, then VAF and read depth will be NAs. If variant

caller is "mutect", do not merge SBSs into DBS.

num.of.cores The number of cores to use. Not available on Windows unless num.of.cores =

trans.ranges Optional. If ref.genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCF file paths in files. If NULL(default), this function will remove all of the path up to and including the last path separator (if any) in files and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Only applicable to **Mutect** VCFs. Vector of column names or column indices in **Mutect** VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of **Mutect** VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the **Mutect** VCFs to calculate VAFs. See GetMutectVAF for more details.

filter.status

The character string in column FILTER of the VCF that indicates that a variant has passed all the variant caller's filters. Variants (lines in the VCF) for which the value in column FILTER does not equal filter.status are silently excluded from the output. The internal function DefaultFilterStatus tries to infer filter.status based on variant.caller. If variant.caller is "unknown", user must specify filter.status explicitly. If filter.status = NULL, all variants are retained. If there is no FILTER column in the VCF, all variants are retained with a warning.

get.vaf.function

Optional. Only applicable when variant.caller is "unknown". Function to calculate VAF(variant allele frequency) and read depth information from original VCF. See GetMutectVAF as an example. If NULL(default) and variant.caller is "unknown", then VAF and read depth will be NAs.

.. Optional arguments to get.vaf.function.

max.vaf.diff

**Not** applicable if variant.caller = "mutect". The maximum difference of VAF, default value is 0.02. If the absolute difference of VAFs for adjacent SBSs is bigger than max.vaf.diff, then these adjacent SBSs are likely to be "merely" asynchronous single base mutations, opposed to a simultaneous doublet mutation or variants involving more than two consecutive bases. Use negative value (e.g. -1) to suppress merging adjacent SBSs to DBS.

base.filename

Optional. The base name of the PDF files to be produced; multiple files will be generated, each ending in x.pdf, where x indicates the type of catalog plotted in the file.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

 ${\tt suppress.discarded.variants.warnings}$ 

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

## **Details**

This function calls VCFsToCatalogs and PlotCatalogToPdf

# Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).
- catID: Matrix of ID (small insertions and deletions) catalog.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class, DBS136.class and DBS144.class showing the mutation class for each DBS variant.
  - ID: ID VCF annotated by AnnotateIDVCF with one new column ID. class showing the mutation class for each ID variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

## **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

#### Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions. In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

# Comments

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

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VCFsToDBSCatalogs

Create DBS catalogs from VCFs

## **Description**

Create a list of 3 catalogs (one each for DBS78, DBS144 and DBS136) out of the contents in list.of.DBS.vcfs. The VCFs must not contain any type of mutation other then DBSs.

# Usage

```
VCFsToDBSCatalogs(
  list.of.DBS.vcfs,
  ref.genome,
  num.of.cores = 1,
  trans.ranges = NULL,
  region = "unknown",
  return.annotated.vcfs = FALSE,
  suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

list.of.DBS.vcfs

List of in-memory data frames of pure DBS mutations – no SBS or 3+BS mutations. The list names will be the sample ids in the output catalog.

ref.genome

A ref. genome argument as described in ICAMS.

num.of.cores

The number of cores to use. Not available on Windows unless num. of. cores = 1

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome. Hsapiens. 1000 genomes. hs37d5
- 2. BSgenome. Hsapiens. UCSC. hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

# Value

A list containing the following objects:

VCFsToIDCatalogs 69

• catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).

- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: **Non-NULL only if** return.annotated.vcfs = TRUE. DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class, DBS136.class and DBS144.class showing the mutation class for each DBS variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

## **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

#### Note

DBS 144 catalog only contains mutations in transcribed regions.

# **Examples**

VCFsToIDCatalogs

Create ID (small insertions and deletions) catalog from ID VCFs

# **Description**

Create ID (small insertions and deletions) catalog from ID VCFs

# Usage

```
VCFsToIDCatalogs(
   list.of.vcfs,
   ref.genome,
   num.of.cores = 1,
   region = "unknown",
   flag.mismatches = 0,
   return.annotated.vcfs = FALSE,
   suppress.discarded.variants.warnings = TRUE
)
```

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# **Arguments**

list.of.vcfs List of in-memory ID VCFs. The list names will be the sample ids in the output

catalog.

ref.genome A ref.genome argument as described in ICAMS.

num.of.cores The number of cores to use. Not available on Windows unless num.of.cores =

1.

region A character string acting as a region identifier, one of "genome", "exome".

flag.mismatches

Deprecated. If there are ID variants whose REF do not match the extracted sequence from ref.genome, the function will automatically discard these variants and an element discarded.variants will appear in the return value. See AnnotateIDVCF for more details.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

#### Value

## A **list** of elements:

- catalog: The ID (small insertions and deletions) catalog with attributes added. See as.catalog for details.
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: **Non-NULL only if** return.annotated.vcfs = TRUE. A list of data frames which contain the original VCF's ID mutation rows with three additional columns seq.context.width, seq.context and ID.class added. The category assignment of each ID mutation in VCF can be obtained from ID.class column.

## Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

# ID classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

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# **Examples**

VCFsToSBSCatalogs

Create SBS catalogs from SBS VCFs

# Description

Create a list of 3 catalogs (one each for 96, 192, 1536) out of the contents in list.of.SBS.vcfs. The SBS VCFs must not contain DBSs, indels, or other types of mutations.

## Usage

```
VCFsToSBSCatalogs(
  list.of.SBS.vcfs,
  ref.genome,
  num.of.cores = 1,
  trans.ranges = NULL,
  region = "unknown",
  return.annotated.vcfs = FALSE,
  suppress.discarded.variants.warnings = TRUE
)
```

# **Arguments**

list.of.SBS.vcfs

List of in-memory data frames of pure SBS mutations – no DBS or 3+BS mutations. The list names will be the sample ids in the output catalog.

ref.genome

A ref. genome argument as described in ICAMS.

num.of.cores

The number of cores to use. Not available on Windows unless num.of.cores = 1

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome.Hsapiens.1000genomes.hs37d5
- 2. BSgenome.Hsapiens.UCSC.hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as.catalog and ICAMS.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

suppress.discarded.variants.warnings

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

## Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- discarded.variants: **Non-NULL only if** there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

## **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

## Note

SBS 192 catalogs only contain mutations in transcribed regions.

# **Examples**

VCFsToZipFile

Create a zip file which contains catalogs and plot PDFs from VCFs

## **Description**

Create 3 SBS catalogs (96, 192, 1536), 3 DBS catalogs (78, 136, 144) and Indel catalog from the VCFs specified by dir, save the catalogs as CSV files, plot them to PDF and generate a zip archive of all the output files.

## Usage

```
VCFsToZipFile(
  dir,
  files.
  zipfile,
  ref.genome,
  variant.caller = "unknown",
  num.of.cores = 1,
  trans.ranges = NULL,
  region = "unknown",
  names.of.VCFs = NULL,
  tumor.col.names = NA,
  filter.status = DefaultFilterStatus(variant.caller),
  get.vaf.function = NULL,
  max.vaf.diff = 0.02,
  base.filename = "",
  return.annotated.vcfs = FALSE,
  suppress.discarded.variants.warnings = TRUE
)
```

## **Arguments**

dir

Pathname of the directory which contains VCFs that come from the **same** variant caller. Each VCF **must** have a file extension ".vcf" (case insensitive) and share the **same** ref. genome and region.

files

Character vector of file paths to the VCF files. Only **one** of argument dir or files need to be specified.

zipfile

Pathname of the zip file to be created.

ref.genome

A ref. genome argument as described in ICAMS.

variant.caller

Name of the variant caller that produces the VCF, can be either "strelka", "mutect", "freebayes" or "unknown". This information is needed to calculate the VAFs (variant allele frequencies). If variant caller is "unknown" (default) and get.vaf.function is NULL, then VAF and read depth will be NAs. If variant caller is "mutect", do **not** merge SBSs into DBS.

num.of.cores

The number of cores to use. Not available on Windows unless num.of.cores = 1

trans.ranges

Optional. If ref. genome specifies one of the BSgenome object

- 1. BSgenome.Hsapiens.1000genomes.hs37d5
- 2. BSgenome.Hsapiens.UCSC.hg38
- 3. BSgenome.Mmusculus.UCSC.mm10

then the function will infer trans.ranges automatically. Otherwise, user will need to provide the necessary trans.ranges. Please refer to TranscriptRanges for more details. If is.null(trans.ranges) do not add transcript range information.

region

A character string designating a genomic region; see as. catalog and ICAMS.

names.of.VCFs

Optional. Character vector of names of the VCF files. The order of names in names.of.VCFs should match the order of VCFs listed in dir. If NULL(default),

this function will remove all of the path up to and including the last path separator (if any) in dir and file paths without extensions (and the leading dot) will be used as the names of the VCF files.

tumor.col.names

Optional. Only applicable to **Mutect** VCFs. Vector of column names or column indices in **Mutect** VCFs which contain the tumor sample information. The order of elements in tumor.col.names should match the order of **Mutect** VCFs specified in files. If tumor.col.names is equal to NA(default), this function will use the 10th column in all the **Mutect** VCFs to calculate VAFs. See GetMutectVAF for more details.

filter.status

The character string in column FILTER of the VCF that indicates that a variant has passed all the variant caller's filters. Variants (lines in the VCF) for which the value in column FILTER does not equal filter.status are silently excluded from the output. The internal function DefaultFilterStatus tries to infer filter.status based on variant.caller. If variant.caller is "unknown", user must specify filter.status explicitly. If filter.status = NULL, all variants are retained. If there is no FILTER column in the VCF, all variants are retained with a warning.

get.vaf.function

Optional. Only applicable when variant.caller is "unknown". Function to calculate VAF(variant allele frequency) and read depth information from original VCF. See GetMutectVAF as an example. If NULL(default) and variant.caller is "unknown", then VAF and read depth will be NAs.

Optional arguments to get.vaf.function.

max.vaf.diff

**Not** applicable if variant.caller = "mutect". The maximum difference of VAF, default value is 0.02. If the absolute difference of VAFs for adjacent SBSs is bigger than max.vaf.diff, then these adjacent SBSs are likely to be "merely" asynchronous single base mutations, opposed to a simultaneous doublet mutation or variants involving more than two consecutive bases. Use negative value (e.g. -1) to suppress merging adjacent SBSs to DBS.

base.filename

Optional. The base name of the CSV and PDF files to be produced; multiple files will be generated, each ending in  $x.\,\mathrm{csv}$  or  $x.\,\mathrm{pdf}$ , where x indicates the type of catalog.

return.annotated.vcfs

Logical. Whether to return the annotated VCFs with additional columns showing mutation class for each variant. Default is FALSE.

 $\verb|suppress.discarded.variants.warnings|\\$ 

Logical. Whether to suppress warning messages showing information about the discarded variants. Default is TRUE.

# **Details**

This function calls VCFsToCatalogs, PlotCatalogToPdf, WriteCatalog and zip::zipr.

#### Value

A list containing the following objects:

- catSBS96, catSBS192, catSBS1536: Matrix of 3 SBS catalogs (one each for 96, 192, and 1536).
- catDBS78, catDBS136, catDBS144: Matrix of 3 DBS catalogs (one each for 78, 136, and 144).

- catID: Matrix of ID (small insertions and deletions) catalog.
- discarded.variants: Non-NULL only if there are variants that were excluded from the analysis. See the added extra column discarded.reason for more details.
- annotated.vcfs: Non-NULL only if return.annotated.vcfs = TRUE. A list of elements:
  - SBS: SBS VCF annotated by AnnotateSBSVCF with three new columns SBS96.class, SBS192.class and SBS1536.class showing the mutation class for each SBS variant.
  - DBS: DBS VCF annotated by AnnotateDBSVCF with three new columns DBS78.class,
     DBS136.class and DBS144.class showing the mutation class for each DBS variant.
  - ID: ID VCF annotated by AnnotateIDVCF with one new column ID.class showing the mutation class for each ID variant.

If trans.ranges is not provided by user and cannot be inferred by ICAMS, SBS 192 and DBS 144 catalog will not be generated. Each catalog has attributes added. See as.catalog for more details.

#### **ID** classification

See https://github.com/steverozen/ICAMS/raw/master/data-raw/PCAWG7\_indel\_classification\_ 2021\_09\_03.xlsx for additional information on ID (small insertions and deletions) mutation classification.

See the documentation for Canonicalize1Del which first handles deletions in homopolymers, then handles deletions in simple repeats with longer repeat units, (e.g. CACACACA, see FindMaxRepeatDel), and if the deletion is not in a simple repeat, looks for microhomology (see FindDelMH).

See the code for unexported function CanonicalizeID and the functions it calls for handling of insertions.

## Note

SBS 192 and DBS 144 catalogs include only mutations in transcribed regions. In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

#### **Comments**

To add or change attributes of the catalog, you can use function attr. For example, attr(catalog, "abundance") <-custom.abundance.

76 WriteCatalog

WriteCatalog	Write a catalog
--------------	-----------------

# **Description**

Write a catalog to a file.

# Usage

```
WriteCatalog(catalog, file, strict = TRUE)
```

# **Arguments**

catalog A catalog as defined in ICAMS; see also as.catalog.

file The path to the file to be created.

strict If TRUE, do additional checks on the input, and stop if the checks fail.

## **Details**

See also ReadCatalog.

## Note

In ID (small insertions and deletions) catalogs, deletion repeat sizes range from 0 to 5+, but for plotting and end-user documentation deletion repeat sizes range from 1 to 6+.

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