

# Package ‘ICAMS’

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**Type** Package

**Title** In-depth Characterization and Analysis of Mutational Signatures

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**Author** Steve Rozen, Nanhai Jiang, Arnoud Boot

**Maintainer** Steve Rozen <steverozen@gmail.com>

**Description** A toolkit for analysis and visualization of experimentally elucidated mutational signatures -- the kind of analysis and visualization presented in Boot et al., "In-depth characterization of the cisplatin mutational signature in human cell lines and in esophageal and liver tumors", 2018 <<https://genome.cshlp.org/content/28/5/654.short>>. This package has functions to read in variant call files and to collate and plot the mutational spectra.

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BSgenome,  
BSgenome.Hsapiens.1000genomes.hs37d5,  
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data.table,  
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GenomicRanges,  
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**Collate** 'ICAMS.R'  
'INDELS\_related\_functions.R'  
'utility\_functions.R'  
'VCF\_to\_catalog\_functions.R'  
'data.R'  
'plot.R'  
'read\_write\_catalog.R'  
'test\_functions.R'

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CatalogRowOrder	<i>Canonical order of row names in a catalog</i>
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**Description**

Canonical order of row names in a catalog

**Usage**

catalog.row.order

**Format**

A list which contains string of characters indicating the canonical order of row names in a catalog.

**Note**

In the ID (insertion and deletion) catalog, deletion repeat size ranges from 0 to 5+, but for plotting and end user documentation it ranges from 1 to 6+.

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CollapseCatalog	<i>Collapse catalog functions</i>
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**Description**

Collapse a catalog matrix

**Usage**

Collapse192To96(catalog)  
Collapse1536To96(catalog)  
Collapse144To78(catalog)

**Arguments**

catalog	A catalog matrix to be collapsed whose row names indicate the mutation types while its columns show the occurrences of each mutation type of different samples.
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**Details**

Collapse192To96 Collapse a SNS 192 catalog matrix to a SNS 96 catalog matrix.  
Collapse1536To96 Collapse a SNS 1536 catalog matrix to a SNS 96 catalog matrix.  
Collapse144To78 Collapse a DNS 144 catalog matrix to a DNS 78 catalog matrix.

**Value**

A canonical catalog matrix whose row names indicate the mutation types while its columns show the occurrences of each mutation type of different samples.

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)
```

**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, cat various messages.

**Details**

This function is primarily for internal use, but we export it so that the logic behind it will be documented for users.

Example:

GGCTAGTT aligned to GGCTAGAACTAGTT with a deletion represented as:

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

Presumed repair mechanism leading to this:

```
....
GGCTAGAACTAGTT
CCGATCTTGATCAA
```

=>

```
....
GGCTAG      TT
CC      GATCAA
      ....
```

=>

```
GGCTAGTT
CCGATCAA
```

The deletion caller 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
                ***  -  ***  -
```

```
GGCTAG-----TT  GGCTAGTT  GGCTAG[AACTAG]TT
                ****  ****
```

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

```
GACTAGCTAGTT
GACTA----GTT  GACTAGTT  GACTA[GCTA]GTT
                ***  -***  -
```

is really a repeat

```
TODO(Steve): add check in code
GACTAG----TT  GACTAGTT  GACTAG[CTAG]TT
                ****  ----
```

```
GACT----AGTT  GACTAGTT  GACT[AGCT]AGTT
                **  ---*  --
```

**But the function only flags this with a -1 return; it does not figure out the repeat extent.**

In the implementation, the function finds:

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

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

## Value

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

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GetVAF	<i>Extract the VAFs (variant allele frequencies) from a VCF file.</i>
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### Description

Extract the VAFs (variant allele frequencies) from a VCF file.

### Usage

```
GetStrelkaVAF(vcf)
```

```
GetMutectVAF(vcf)
```

### Arguments

vcf                      said VCF as a data.frame.

### Value

A vector of VAFs, one for each row of vcf.

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ICAMS	<i>ICAMS: In-depth Characterization and Analysis of Mutational Signatures</i>
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### Description

A toolkit for analysis and visualization of experimentally elucidated mutational signatures – the kind of analysis and visualization presented 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://genome.cshlp.org/content/28/5/654.short>.

### Details

ICAMS can read in variant call files (VCFs) generated by Strelka or Mutect, and collate the mutations into "catalogs" of mutational spectra. ICAMS can plot the catalogs of mutational spectra and signatures.

ICAMS can build and plot catalogs of mutational spectra for single nucleotide substitutions (SNS), double nucleotide substitutions (DNS), and small insertions and deletions (ID). It can also read and write these catalogs.

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

1. [StrelkaSNSVCFFilesToCatalog](#), which creates 3 SNS catalogs (96, 192, 1536) and 3 DNS catalogs (78, 136, 144) from the Strelka SNS VCFs.
2. [StrelkaIDVCFFilesToCatalog](#), which creates ID (indels) catalog from the Strelka ID VCFs.
3. [MutectVCFFilesToCatalog](#), which creates 3 SNS catalogs (96, 192, 1536), 3 DNS catalogs (78, 136, 144) and ID (indels) catalog from the Mutect VCFs.

### Plotting catalogs

Functions for plotting catalogs of mutational spectra or of mutational signatures to a PDF file. Mutational *signatures* are similar to spectra, but where spectra consist of counts 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). [PlotCatalogToPdf](#)

### Writing catalogs

Functions for writing a catalog of mutational spectra or of mutational signatures to a file on disk. [WriteCatalog](#)

### Reading catalogs

Functions for reading files that contain catalogs of mutational spectra or of signatures in standardized format. [ReadCatalog](#)

### Transforming catalogs

There is a function to transform 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. 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 (million) source sequences. For example, a density-based catalog represents the proportion of ACCs mutated to ATCs, the proportion of ACGs mutated to ATGs, etc., as opposed to number of ACC-to-ATC mutations, the number of ACG-to-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). [TransformCatalog](#)

### Collapsing catalogs

Functions for collapsing a mutational spectrum or signature catalog based on a fined-grained set of features (for example, single-nucleotide substitutions in the context of the preceding and following 2 bases) 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). [CollapseCatalog](#)

### Exported data

1. [CatalogRowOrder](#) Canonical order of row names in a catalog.
2. [TranscriptRanges](#) Transcript ranges and strand information for a particular organism.

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MutectVCFFilesToCatalog

*Create SNS and DNS catalogs from Mutect VCF files*

---

### Description

Create 3 SNS catalogs (96, 192, 1536) and 3 DNS catalogs (78, 136, 144) from the Mutect VCFs specified by vector.of.file.paths

**Usage**

```
MutectVCFFilesToCatalog(vector.of.file.paths, genome, trans.ranges)
```

**Arguments**

```
vector.of.file.paths  A vector containing the paths of the Mutect VCF files.
genome                Name of a particular reference genome (without quotations marks).
trans.ranges          A data.table which contains transcript range and strand information.
```

**Details**

This function calls [VCFsToNSNCatalogs](#), [VCFsToDNSCatalogs](#) and [VCFsToIDCatalogs](#)

**Value**

A list of 3 SNS catalogs (one each for 96, 192, and 1536) , 3 DNS catalogs (one each for 78, 136, and 144) and ID catalog.

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PlotCatalogToPdf	<i>Plot catalog to pdf functions</i>
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**Description**

Plot mutation catalogs of various samples to a PDF file

**Usage**

```
PlotCatSNS96ToPdf(catalog, name, id = colnames(catalog),
  type = "density", grid = FALSE, upper = TRUE, xlabels = TRUE,
  abundance = NULL)

PlotCatSNS192ToPdf(catalog, name, id = colnames(catalog),
  type = "counts", cex = 0.8, abundance = NULL)

PlotCatSNS192StrandToPdf(catalog, name, id = colnames(catalog),
  type = "counts", cex = 1, abundance = NULL)

PlotCatSNS1536ToPdf(catalog, name, id = colnames(catalog), abundance)

PlotCatDNS78ToPdf(catalog, name, id = colnames(catalog),
  type = "density", abundance = NULL)

PlotCatDNS144ToPdf(catalog, name, id = colnames(catalog),
  type = "counts", cex = 1, abundance = NULL)

PlotCatDNS136ToPdf(catalog, name, id = colnames(catalog),
  type = "density", abundance = NULL)

PlotCatIDToPdf(catalog, name, id = colnames(catalog), type = "counts")
```



**Arguments**

catalog	A matrix of mutation counts. Rownames indicate the mutation types. Each column contains the mutation counts for one sample.
name	The name of the PDF file to be produced.
id	A vector containing the identifiers of the samples in catalog.
type	A vector of values indicating the type of plot for each sample. If type = "counts", the graph will plot the occurrences of the mutation types in the sample. If type = "signature", the graph will plot mutation signatures of the sample. If type = "density", the graph will plot the rates of mutations per million nucleotides for each mutation type. (Please take note there is no "density" type for PlotCatID-toPdf function and the option of type = "density" is not implemented for function PlotCatSNS192ToPdf, PlotCatSNS192StrandToPdf and PlotCatDNS144ToPdf at the current stage.)
grid	If TRUE, draw grid lines in the graph.
upper	If TRUE, draw horizontal lines and the names of major mutation class on top of graph.
xlabels	If TRUE, draw x axis labels.
abundance	A named numeric vector, see <a href="#">Abundance</a> , used only when type = "density".
cex	A numerical value giving the amount by which mutation class labels, y axis labels, sample name and legend (if it exists) should be magnified relative to the default.

**Details**

PlotCatSNS96ToPdf Plot the SNS 96 mutation catalog of various samples to a PDF file.

PlotCatSNS192ToPdf Plot the SNS 192 mutation catalog of various samples to a PDF file.

PlotCatSNS192StrandToPdf Plot the transcription strand bias graph of 6 SNS mutation types ("C>A", "C>G", "C>T", "T>A", "T>C", "T>G") of various samples to a PDF file.

PlotCatSNS1536ToPdf Plot the 1536 mutation catalog of  $\geq 1$  samples to a PDF file. The mutation types are in six-letters like CATTAT, first 2-letters CA refers to (-2, -1) position, third letter T refers to the base which has mutation, next second 2-letters TA refers to (+1, +2) position, last letter T refers to the base after mutation.

PlotCatDNS78ToPdf Plot the DNS 78 mutation catalog of various samples to a PDF file.

PlotCatDNS144ToPdf Plot the transcription strand bias graph of 10 major DNS mutation types ("AC>NN", "AT>NN", "CC>NN", "CG>NN", "CT>NN", "GC>NN", "TA>NN", "TC>NN", "TG>NN", "TT>NN") of various samples to a PDF file.

PlotCatDNS136ToPdf Plot the tetranucleotide sequence contexts of 10 major DNS mutation types ("AC>NN", "AT>NN", "CC>NN", "CG>NN", "CT>NN", "GC>NN", "TA>NN", "TC>NN", "TG>NN", "TT>NN") of various samples to a PDF file.

PlotCatIDToPdf Plot the insertion and deletion catalog of various samples to a PDF file. (Please take note that deletion repeat size ranges from 0 to 5+ in the catalog, but for plotting and end user documentation it ranges from 1 to 6+.)

**Value**

invisible(TRUE)

---

`ReadAndSplitMutectVCFs`*Read and split Mutect VCF files from paths*

---

**Description**

Read and split Mutect VCF files from paths

**Usage**

```
ReadAndSplitMutectVCFs(vector.of.file.paths)
```

**Arguments**

```
vector.of.file.paths
```

A vector containing the paths of the VCF files.

**Value**

A list with 3 in-memory VCFs and two left-over VCF-like data frames with rows that were not incorporated into the first 3 VCFs, as follows:

1. SNS VCF with only single nucleotide substitutions.
2. DNS VCF with only doublet nucleotide substitutions as called by Mutect.
3. ID VCF with only small insertions and deletions.
4. `other.subs` VCF like `data.frame` with rows for coordinate substitutions involving 3 or more nucleotides, e.g. `ACT > TGA` or `AACT > GGTA`.
5. `multiple.alternative.alleles` VCF like `data.frame` with rows for variants with multiple alternative alleles, for example `ACT` mutated to both `AGT` and `ACT` at the same position.

**See Also**

[MutectVCFFilesToCatalog](#)

---

`ReadAndSplitStrelkaSNSVCFs`*Read and split Strelka SNS VCF files from paths*

---

**Description**

Read and split Strelka SNS VCF files from paths

**Usage**

```
ReadAndSplitStrelkaSNSVCFs(vector.of.file.paths)
```

**Arguments**

```
vector.of.file.paths
```

A vector containing the paths of the VCF files.

**Value**

A list of 3 in-memory objects with the elements: SNS.vcfs: List of Data frames of pure SNS mutations – no DNS or 3+BS mutations DNS.vcfs: List of Data frames of pure DNS mutations – no SNS or 3+BS mutations ThreePlus: List of Data tables with the key CHROM, LOW.POS, HIGH.POS and additional information (reference sequence, alternative sequence, context, etc.) Additional information not fully implemented at this point because of limited immediate biological interest.

**See Also**

[StrelkaSNSVCFFilesToCatalog](#)

---

ReadCatalog

*Read Catalog Functions*


---

**Description**

Read a catalog in standardized format from path

**Usage**

```
ReadCatSNS96(path, strict = TRUE)
```

```
ReadCatSNS192(path, strict = TRUE)
```

```
ReadCatSNS1536(path, strict = TRUE)
```

```
ReadCatDNS78(path, strict = TRUE)
```

```
ReadCatDNS144(path, strict = TRUE)
```

```
ReadCatDNS136(path, strict = TRUE)
```

```
ReadCatID(path, strict = TRUE)
```

**Arguments**

path Path to a catalog on disk in the standardized format.

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

**Details**

ReadCatSNS96 Read a 96 SNS catalog from path

ReadCatSNS192 Read a 192 SNS catalog from path

ReadCatSNS1536 Read a 1536 SNS catalog from path

ReadCatDNS78 Read a 78 DNS catalog from path

ReadCatDNS144 Read a 144 DNS catalog from path

ReadCatDNS136 Read a 136 DNS catalog from path

ReadCatID Read a ID (insertion/deletion) catalog from path Please take note that deletion repeat size ranges from 0 to 5+ in the catalog, but for plotting and end user documentation it ranges from 1 to 6+.

See also [WriteCatalog](#)

**Value**

A catalog in canonical in-memory format.

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ReadStrelkaIDVCFs	<i>Read Strelka ID (insertion and deletion) VCF files from paths</i>
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---

**Description**

Read Strelka ID (insertion and deletion) VCF files from paths

**Usage**

```
ReadStrelkaIDVCFs(vector.of.file.paths)
```

**Arguments**

```
vector.of.file.paths
```

A vector containing the paths of the VCF files.

**Value**

A list of vcfs from vector.of.file.paths.

**Note**

In the ID (insertion and deletion) catalog, deletion repeat size ranges from 0 to 5+, but for plotting and end user documentation it ranges from 1 to 6+.

---

revc	<i>Reverse complement every string in string.vec.</i>
------	---

---

**Description**

Reverse complement every string in string.vec.

**Usage**

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

**Arguments**

```
string.vec
```

a vector of type character.

**Value**

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

---

`StrelkaIDVCFFilesToCatalog`*Create ID (indel) catalog from Strelka ID VCF files*

---

**Description**

Create ID (indel) catalog from the Strelka ID VCFs specified by `vector.of.file.paths`

**Usage**

```
StrelkaIDVCFFilesToCatalog(vector.of.file.paths, genome)
```

**Arguments**

`vector.of.file.paths`

A vector containing the paths of the Strelka ID VCF files.

`genome`

Name of a particular reference genome (without quotations marks).

**Details**

This function calls [VCFsToIDCatalogs](#)

**Value**

An ID (indel) catalog

**Note**

In the ID (insertion and deletion) catalog, deletion repeat size ranges from 0 to 5+, but for plotting and end user documentation it ranges from 1 to 6+.

---

`StrelkaSNSVCFFilesToCatalog`*Create SNS and DNS catalogs from Strelka SNS VCF files*

---

**Description**

Create 3 SNS catalogs (96, 192, 1536) and 3 DNS catalogs (78, 136, 144) from the Strelka SNS VCFs specified by `vector.of.file.paths`

**Usage**

```
StrelkaSNSVCFFilesToCatalog(vector.of.file.paths, genome, trans.ranges)
```

**Arguments**

`vector.of.file.paths`

A vector containing the paths of the Strelka SNS VCF files.

`genome`

Name of a particular reference genome (without quotations marks).

`trans.ranges`

A `data.table` which contains transcript range and strand information.

Details

This function calls [VCFsToNSCatalogs](#) and [VCFsToDNSCatalogs](#)

Value

A list of 3 SNS catalogs (one each for 96, 192, and 1536) and 3 DNS catalogs (one each for 78, 136, and 144)

---

TranscriptRanges	<i>Transcript ranges data</i>
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---

Description

Transcript ranges and strand information for a particular organism

Usage

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

Format

A data.table which contains transcript range and strand information for a particular organism.

Details

`trans.ranges.GRCh37` A data.table which contains transcript range and strand information for **Human** GRCh37. It is derived from a raw **GFF3** format file, from which only the following four gene types are kept to facilitate transcriptional strand bias analysis: `protein_coding`, `retained_intron`, `processed_transcript` and `nonsense_mediated_decay`. It contains chromosome name, start, end position, strand information and gene name and is keyed by `chrom`, `chromStart`, and `chromEnd`. It can be used in function [StrelkaSNSVCFFilesToCatalog](#).

`trans.ranges.GRCh38` A data.table which contains transcript range and strand information for **Human** GRCh38. It is derived from a raw **GFF3** format file, from which only the following four gene types are kept to facilitate transcriptional strand bias analysis: `protein_coding`, `retained_intron`, `processed_transcript` and `nonsense_mediated_decay`. It contains chromosome name, start, end position, strand information and gene name and is keyed by `chrom`, `chromStart`, and `chromEnd`. It can be used in function [StrelkaSNSVCFFilesToCatalog](#).

---

TransformCatalog	<i>Transform catalog function</i>
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---

**Description**

Transform catalog function

**Usage**

```
TransformCatalog(catalog, source.abundance, target.abundance = NULL,
  which.n, source.type, target.type = source.type)
```

**Arguments**

catalog	A matrix of mutation counts/signature. Rownames indicate the mutation types. Each column contains the mutation counts/signature for one sample.
source.abundance	Either an abundance variable or string specifying an abundance.
target.abundance	Either an abundance variable or string specifying an abundance.
which.n	The n for the n-mers, one of 2, 3, 4, 5 for 2-mers, 3-mers, etc.
source.type	A character specifying the type of the input catalog ("counts", "signature" or "density")
target.type	A character specifying the type of the output catalog ("counts", "signature" or "density")

**Value**

A matrix of mutation counts/signature. Rownames indicate the mutation types. Each column contains the mutation counts/signature for one sample.

---

VCFsToDNSCatalogs	<i>Create DNS catalogs from VCFs</i>
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---

**Description**

Create a list of 3 catalogs (one each for DNS78, DNS144 and DNS136) out of the contents in list.of.DNS.vcfs. The VCFs must not contain any type of mutation other than DNSs.

**Usage**

```
VCFsToDNSCatalogs(list.of.DNS.vcfs, genome, trans.ranges)
```

**Arguments**

list.of.DNS.vcfs	List of in-memory data frames of pure DNS mutations – no SNS or 3+BS mutations. The list names will be the sample ids in the output catalog.
genome	Name of a particular reference genome (without quotations marks).
trans.ranges	A data frame containing transcript ranges.

**Value**

A list of 3 catalogs, one each for DNS78, DNS144, DNS136: catDNS78 catDNS144 catDNS136

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VCFsToIDCatalogs	<i>Create ID (insertion and deletion) catalog from ID VCFs</i>
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---

**Description**

Create ID (insertion and deletion) catalog from ID VCFs

**Usage**

```
VCFsToIDCatalogs(list.of.vcfs, genome)
```

**Arguments**

list.of.vcfs	List of in-memory VCFs. The list names will be the sample ids in the output catalog.
genome	Name of a particular reference genome (without quotations marks).

**Value**

An ID (indel) catalog

---

VCFsToSNSCatalogs	<i>Create SNS catalogs from SNS VCFs</i>
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---

**Description**

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

**Usage**

```
VCFsToSNSCatalogs(list.of.SNS.vcfs, genome, trans.ranges)
```

**Arguments**

list.of.SNS.vcfs	List of in-memory data frames of pure SNS mutations – no DNS or 3+BS mutations. The list names will be the sample ids in the output catalog.
genome	Name of a particular reference genome (without quotations marks).
trans.ranges	A data frame containing transcript ranges.

**Value**

A list of 3 catalogs, one each for 96, 192, 1536: catSNS96 catSNS192 catSNS1536



**Description**

Write a mutation catalog to a file on disk

**Usage**

```
WriteCatSNS96(ct, path, strict = TRUE)
```

```
WriteCatSNS192(ct, path, strict = TRUE)
```

```
WriteCatSNS1536(ct, path, strict = TRUE)
```

```
WriteCatDNS78(ct, path, strict = TRUE)
```

```
WriteCatDNS144(ct, path, strict = TRUE)
```

```
WriteCatDNS136(ct, path, strict = TRUE)
```

```
WriteCatID(ct, path, strict = TRUE)
```

**Arguments**

ct	A matrix of mutation catalog.
path	The path of the file to be written on disk.
strict	If TRUE, do additional checks on the input, and stop if the checks fail.

**Details**

WriteCatSNS96 Write a SNS 96 mutation catalog to a file on disk

WriteCatSNS192 Write a SNS 192 mutation catalog to a file on disk

WriteCatSNS1536 Write a SNS 1536 mutation catalog to a file on disk

WriteCatDNS78 Write a DNS 78 mutation catalog to a file on disk

WriteCatDNS144 Write a DNS 144 mutation catalog to a file on disk

WriteCatDNS136 Write a 136 DNS catalog from path

WriteCatID Write a ID (insertion/deletion) catalog to a file on disk Please take note that deletion repeat size ranges from 0 to 5+ in the catalog, but for plotting and end user documentation it ranges from 1 to 6+.

See also [ReadCatalog](#)

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