

Package ‘ZygosityPredictor’

June 5, 2023

Type Package

Title Package for prediction of zygosity for variants/genes in NGS data

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Imports GenomicAlignments, GenomicRanges, Rsamtools, IRanges, VariantAnnotation, DelayedArray, dplyr, stringr, purrr, tibble, methods, igraph

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Description

The ZygosityPredictor allows to predict how many copies of a gene are affected by small variants. In addition to the basic calculations of the affected copy number of a variant, the ZygosityPredictor can integrate the influence of several variants on a gene and ultimately make a statement if and how many wild-type copies of the gene are left. This information proves to be of particular use in the context of translational medicine. For example, in cancer genomes, the ZygosityPredictor can address whether unmutated copies of tumor-suppressor genes are present. Beyond this, it is possible to make this statement for all genes of an organism. The ZygosityPredictor was primarily developed to handle SNVs and INDELs (later addressed as small-variants) of somatic and germline origin. In order not to overlook severe effects outside of the small-variant context, it has been extended with the assessment of large scale deletions, which cause losses of whole genes or parts of them.

RoxygenNote 7.2.3

Encoding UTF-8

biocViews BiomedicalInformatics, FunctionalPrediction, SomaticMutation, GenePrediction

Depends R (>= 4.3.0)

LazyData false

Suggests knitr, rmarkdown, testthat, BiocStyle

VignetteBuilder knitr

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aff_germ_copies	<i>calculates how many copies are affected by a germline small variant</i>
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Description

calculates how many copies are affected by a germline small variant
calculates how many copies are affected by a germline small variant

Usage

```
aff_germ_copies(chr, af, tcn, purity, sex, c_normal = NULL, af_normal = 0.5)  
  
aff_germ_copies(chr, af, tcn, purity, sex, c_normal = NULL, af_normal = 0.5)
```

Arguments

chr	chromosome of the variant (either format 1,2,...,X,Y or chr1,...,chrX)
af	Allele-frequency of the variant (numeric value between 0 and 1)
tcn	total-copynumber at position of the variant (numeric value >0)
purity	purity of the sample (numeric value between 0 and 1 indicating the fraction of relevant sample with control/unrelevant tissue)
sex	sex of the sample (character: "male", "female", "m", "f")

c_normal	expected copy number at position of the variant in normal tissue, 1 for gonosomes in male samples, and 2 for male autosomes and all chromosomes in female samples. (The function can also assess the c_normal parameter by itself, but then the following two inputs must be provided: chr and sex)
af_normal	Allele-frequency in normal tissue (numeric value between 0 and 1) 0.5 represents heterozygous variants in diploid genome, 1 would be homozygous. Could be relevant if germline CNVs are present at the position. Then also the c_normal parameter would have to be adjusted.

Value

A numeric value indicating the affecting copies for the variant

A numeric value indicating the affecting copies for the variant

Examples

```
library(dplyr)
library(purrr)
library(stringr)
aff_germ_copies(af=0.67, tcn=2, purity=0.9, chr="chrX", sex="female")
library(dplyr)
library(purrr)
library(stringr)
aff_germ_copies(af=0.67, tcn=2, purity=0.9, chr="chrX", sex="female")
```

aff_som_copies	<i>calculates how many copies are affected by a somatic small variant</i>
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Description

calculates how many copies are affected by a somatic small variant

calculates how many copies are affected by a somatic small variant

Usage

```
aff_som_copies(chr, af, tcn, purity, sex, c_normal = NULL)
```

```
aff_som_copies(chr, af, tcn, purity, sex, c_normal = NULL)
```

Arguments

chr	chromosome of the variant (either format 1,2,...,X,Y or chr1,...,chrX)
af	Allele-frequency of the variant (numeric value between 0 and 1)
tcn	total-copynumber at position of the variant (numeric value >0)
purity	purity of the sample (numeric value between 0 and 1 indicating the fraction of relevant sample with control/unrelevant tissue)

sex	sex of the sample (character: "male", "female", "m", "f")
c_normal	expected copy number at the position of the variant in normal tissue, 1 for gonosomes in male samples, and 2 for male autosomes and all chromosomes in female samples. (The function can also assess the c_normal parameter by itself, but then the following two inputs must be provided: chr and sex)

Value

A numeric value indicating the affecting copies for the variant

A numeric value indicating the affecting copies for the variant

Examples

```
library(dplyr)
library(purrr)
library(stringr)
aff_som_copies(chr="chrX", af=0.67, tcn=2, purity=0.9, sex="female")
library(dplyr)
library(purrr)
library(stringr)
aff_som_copies(chr="chrX", af=0.67, tcn=2, purity=0.9, sex="female")
```

GR_GENE_MODEL	<i>germline small variant object</i>
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Description

germline small variant object

Usage

```
data(GR_GENE_MODEL)
```

Format

```
## 'GR_GENE_MODEL' GRanges object
```

GR_GERM_SMALL_VARS	<i>germline small variant object</i>
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Description

germline small variant object

Usage

data(GR_SOM_SMALL_VARS)

Format

'GR_SOM_SMALL_VARS' GRanges object

GR_SCNA	<i>copynumber object</i>
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Description

copynumber object

Usage

data(GR_SCNA)

Format

'GR_SCNA' GRanges object

GR_SOM_SMALL_VARS	<i>somatic small variant object</i>
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Description

somatic small variant object

Usage

data(GR_GERM_SMALL_VARS)

Format

'GR_GERM_SMALL_VARS' GRanges object

predict_zygosity	<i>predicts zygosity of a set of genes of a sample</i>
------------------	--

Description

predicts zygosity of a set of genes of a sample

predicts zygosity of a set of genes of a sample

Usage

```
predict_zygosity(  
  purity,  
  sex,  
  somCna,  
  geneModel,  
  bamDna,  
  somSmallVars = NULL,  
  germSmallVars = NULL,  
  bamRna = NULL,  
  ploidy = NULL,  
  colnameTcn = NULL,  
  colnameCnaType = NULL,  
  includeHomoDel = TRUE,  
  includeIncompleteDel = TRUE,  
  showReadDetail = FALSE,  
  printLog = FALSE,  
  assumeSomCnaGaps = FALSE,  
  byTcn = TRUE,  
  vcf = NULL,  
  distCutOff = 5000  
)
```

```
predict_zygosity(  
  purity,  
  sex,  
  somCna,  
  geneModel,  
  bamDna,  
  somSmallVars = NULL,  
  germSmallVars = NULL,  
  bamRna = NULL,  
  ploidy = NULL,  
  colnameTcn = NULL,  
  colnameCnaType = NULL,  
  includeHomoDel = TRUE,  
  includeIncompleteDel = TRUE,
```

```

    showReadDetail = FALSE,
    printLog = FALSE,
    assumeSomCnaGaps = FALSE,
    byTcn = TRUE,
    vcf = NULL,
    distCutOff = 5000
)

```

Arguments

purity	purity of the sample (numeric value between 0 and 1 indicating the fraction of relevant sample with control/unrelevant tissue)
sex	sex of the sample (character: "male", "female", "m", "f")
somCna	GRanges object containing all genomic regions with annotated total copynumber and cna_type as metadata columns. The total-copynumber column should be named "tcn" but also some other commonly used names. It should contain numeric values or characters that can be converted to numeric values. The cna_type column must contain the information about loss of heterozygosity (LOH). Therefore the term "LOH" must be explicitly mentioned in the column. If a genomic region is not present in the object, it will be taken as heterozygous with neutral TCN of 2.
geneModel	GRanges object containing the gene-annotation of the used reference genome with metadata column of the gene name (gene)
bamDna	path to bam-file
somSmallVars	GRanges object containing all somatic small variants (SNV and INDEL). Required metadata columns are reference base (ref/REF), alternative base (alt/ALT), annotation of the gene name (gene/GENE) and the allele-frequency (af/AF). If the object is not provided the tool assumes there are no somatic small variants.
germSmallVars	GRanges object containing all germline small variants (SNV and INDEL). Required metadata columns are reference base (ref/REF), alternative base (alt/ALT), annotation of the gene name (gene/GENE) and the allele-frequency (af/AF). If the object is not provided the tool assumes there are no germline small variants.
bamRna	optional; path to rna file (bam format)
ploidy	ploidy of the sample (numeric value)
colnameTcn	character indicating the name of the metadata containing the tcn information in the somCna object. If not provided the tool tries to detect the column according to default names
colnameCnaType	character indicating the name of the metadata containing cna type information in the somCna object. If not provided the tool tries to detect the column according to default names
includeHomoDel	default = TRUE; if FALSE homozygous deletions are excluded
includeIncompleteDel	default = TRUE; if FALSE heterozygous deletions are excluded
showReadDetail	default = FALSE; if TRUE a table is added to the output,

printLog	default = FALSE; if TRUE the gene which is evaluated is printed in console, containing the query-name of each read which was used to perform haplotype-phasing and the info into which class it was assigned.
assumeSomCnaGaps	(logical, default=FALSE) Only required if the somCna object lacks copy number information for genomic segments on which small variants are detected. By default, variants in such regions will be excluded from the analysis as required information about the copy number is missing. These variants will be attached to the final output list in a separate tibble. To include them, this flag must be set TRUE and the ground ploidy must be given as an input. This ground ploidy will then be taken as tcen in the missing regions. If no ploidy is given the tool will assume the ground ploidy of 2 when this flag is TRUE.
byTcen	logical, default=TRUE; optional if includeHomoDel or includeIncompleteDel is TRUE. If FALSE the tool will not use tcen as a criterion to assign large deletions. It will use the cna_type column and check for indicating strings like HOMDEL/HomoDel/DEL. Some commonly used strings are covered. It is recommended to leave this flag TRUE
vcf	character; path to variant call file (.vcf.gz format). Will be used (if provided) for extended SNP phasing if variants on the same gene are too far away from each other for direct haplotype phasing
distCutoff	numeric, default=5000; if input vcf is provided and SNP phasing is performed, this will limit the distance at which the SNP phasing should not be tried anymore. As the probability of finding overlapping reads at such a long distance is very low and the runtime will increase exponentially.

Value

A list of dataframes. Those are the evaluation per variant, the evaluation per gene and, if performed, the info about the haplotype-phasing.

A list of dataframes. Those are the evaluation per variant, the evaluation per gene and, if performed, the info about the haplotype-phasing.

Examples

```
cnvs = GenomicRanges::GRanges(
  dplyr::tibble(
    chr = "chr17",
    start = c(170060, 34520990),
    end = c(34520990, 83198614),
    tcen = c(2, 1),
    cna_type = c("neutral", "LOH")
  )
)
somatic_vars = GenomicRanges::GRanges(
  dplyr::tibble(
    chr="chr17",
    start = 7675088,
    end = 7675088,
    ref = "C",
```

```

      alt = "T",
      af = 0.65,
      gene = "TP53"
    )
  )
  germline_vars = GenomicRanges::GRanges(
    dplyr::tibble(
      chr="chr17",
      start = 41771694,
      end = 41771694,
      ref = "GTGT",
      alt = "G",
      af = 0.95,
      gene = "JUP"
    )
  )
  reference = GenomicRanges::GRanges(
    dplyr::tibble(
      chr = "chr17",
      start = c(7661778, 41754603),
      end = c(7687538, 41786931),
      gene = c("TP53", "JUP")
    )
  )
  sex = "female"
  purity = 0.9
  bamfile <- system.file("extdata", "ZP_example.bam",
    package = "ZygosityPredictor")
  predict_zygosity(purity = purity, sex = sex,
    somCna = cnvs,
    somSmallVars = somatic_vars,
    germSmallVars = germline_vars,
    geneModel = reference,
    bamDna = bamfile
  )
  cnvs = GenomicRanges::GRanges(
    dplyr::tibble(
      chr = "chr17",
      start = c(170060, 34520990),
      end = c(34520990, 83198614),
      tcn = c(2, 1),
      cna_type = c("neutral", "LOH")
    )
  )
  somatic_vars = GenomicRanges::GRanges(
    dplyr::tibble(
      chr="chr17",
      start = 7675088,
      end = 7675088,
      ref = "C",
      alt = "T",
      af = 0.65,
      gene = "TP53"
    )
  )

```

```

    )
  )
  germline_vars = GenomicRanges::GRanges(
    dplyr::tibble(
      chr="chr17",
      start = 41771694,
      end = 41771694,
      ref = "GTGT",
      alt = "G",
      af = 0.95,
      gene = "JUP"
    )
  )
  reference = GenomicRanges::GRanges(
    dplyr::tibble(
      chr = "chr17",
      start = c(7661778, 41754603),
      end = c(7687538, 41786931),
      gene = c("TP53", "JUP")
    )
  )
  sex = "female"
  purity = 0.9
  bamfile <- system.file("extdata", "ZP_example.bam",
    package = "ZygosityPredictor")
  predict_zygosity(purity = purity, sex = sex,
    somCna = cnvs,
    somSmallVars = somatic_vars,
    germSmallVars = germline_vars,
    geneModel = reference,
    bamDna = bamfile
  )

```

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