

# Package ‘HiLDA’

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**Type** Package

**Title** Conducting statistical inference on comparing the mutational exposures of mutational signatures by using hierarchical latent Dirichlet allocation

**Depends** R(>= 4.1), ggplot2

**Imports** R2jags, abind, cowplot, grid, forcats, stringr, GenomicRanges, S4Vectors, XVector, Biostrings, GenomicFeatures, BSgenome.Hsapiens.UCSC.hg19, BiocGenerics, tidyr, grDevices, stats, TxDb.Hsapiens.UCSC.hg19.knownGene, utils, methods, Rcpp

**Suggests** knitr, rmarkdown, testthat, BiocStyle

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**Description** A package built under the Bayesian framework of applying hierarchical latent Dirichlet allocation. It statistically tests whether the mutational exposures of mutational signatures (Shiraishi-model signatures) are different between two groups. The package also provides inference and visualization.

**License** GPL-3

**URL** <https://github.com/USCbiostats/HiLDA>,  
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**BugReports** <https://github.com/USCbiostats/HiLDA/issues>

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**Author** Zhi Yang [aut, cre],  
 Yuichi Shiraishi [ctb]  
**Maintainer** Zhi Yang <zyang895@gmail.com>

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---

boundaryTurbo\_F      *Check whether the parameter F is within the appropriate range*

---

**Description**

Check whether the parameter F is within the appropriate range

**Usage**

```
boundaryTurbo_F(turboF, fdim, signatureNum)
```

**Arguments**

turboF	F (converted for turboEM)
fdim	a vector specifying the number of possible values for each mutation signature
signatureNum	the number of mutation signatures

**Value**

a logical value

---

boundaryTurbo\_Q      *Check whether the parameter Q is within the appropriate range*

---

**Description**

Check whether the parameter Q is within the appropriate range

**Usage**

```
boundaryTurbo_Q(turboQ, signatureNum, sampleNum)
```

**Arguments**

turboQ	Q (converted for turboEM)
signatureNum	the number of mutation signatures
sampleNum	the number of cancer genomes

**Value**

a logical value

---

calcPMSLikelihood	<i>A function for calculating the log-likelihood from the data and parameters</i>
-------------------	---

---

**Description**

A function for calculating the log-likelihood from the data and parameters

**Usage**

```
calcPMSLikelihood(p, y)
```

**Arguments**

p	this variable includes the parameters for mutation signatures and membership parameters
y	this variable includes the information on the mutation features, the number of mutation signatures specified and so on

**Value**

a value

---

convertFromTurbo_F	<i>Restore the converted parameter F for turboEM</i>
--------------------	--

---

**Description**

Restore the converted parameter F for turboEM

**Usage**

```
convertFromTurbo_F(turboF, fdim, signatureNum, isBackground)
```

**Arguments**

turboF	F (converted for turboEM)
fdim	a vector specifying the number of possible values for each mutation signature
signatureNum	the number of mutation signatures
isBackground	the logical value showing whether a background mutaiton features is included or not

**Value**

a vector

---

convertFromTurbo\_Q     *Restore the converted parameter Q for turboEM*

---

**Description**

Restore the converted parameter Q for turboEM

**Usage**

```
convertFromTurbo_Q(turboQ, signatureNum, sampleNum)
```

**Arguments**

turboQ	Q (converted for turboEM)
signatureNum	the number of mutation signatures
sampleNum	the number of cancer genomes

**Value**

a vector

---

convertToTurbo\_F     *Convert the parameter F so that turboEM can treat*

---

**Description**

Convert the parameter F so that turboEM can treat

**Usage**

```
convertToTurbo_F(vF, fdim, signatureNum, isBackground)
```

**Arguments**

vF	F (converted to a vector)
fdim	a vector specifying the number of possible values for each mutation signature
signatureNum	the number of mutation signatures
isBackground	the logical value showing whether a background mutation features is included or not

**Value**

a vector

---

`convertToTurbo_Q`      *Convert the parameter Q so that turboEM can treat*

---

### Description

Convert the parameter Q so that turboEM can treat

### Usage

```
convertToTurbo_Q(vQ, signatureNum, sampleNum)
```

### Arguments

<code>vQ</code>	Q (converted to a vector)
<code>signatureNum</code>	the number of mutation signatures
<code>sampleNum</code>	the number of cancer genomes

### Value

a vector

---

EstimatedParameters-class

*An S4 class representing the estimated parameters*

---

### Description

An S4 class representing the estimated parameters

### Slots

<code>sampleList</code>	a list of sample names observed in the input mutation data
<code>signatureNum</code>	the number of mutation signatures specified at the time of estimation
<code>isBackGround</code>	the flag showing whether the background signature data is used or not.
<code>backGroundProb</code>	the background signatures
<code>signatureFeatureDistribution</code>	estimated parameters for mutation signatures
<code>sampleSignatureDistribution</code>	estimated parameters for memberships of mutation signatures for each sample
<code>loglikelihood</code>	the log-likelihood value for the estimated parameters

---

getLogLikelihoodC      *Calculate the value of the log-likelihood for given parameters*

---

**Description**

Calculate the value of the log-likelihood for given parameters

**Usage**

```
getLogLikelihoodC(  
  vPatternList,  
  vSparseCount,  
  vF,  
  vQ,  
  fdim,  
  signatureNum,  
  sampleNum,  
  patternNum,  
  samplePatternNum,  
  isBackground,  
  vF0  
)
```

**Arguments**

vPatternList	The list of possible mutation features (converted to a vector)
vSparseCount	The table showing (mutation feature, sample, the number of mutation) (converted to a vector)
vF	F (converted to a vector)
vQ	Q (converted to a vector)
fdim	a vector specifying the number of possible values for each mutation signature
signatureNum	the number of mutation signatures
sampleNum	the number of cancer genomes
patternNum	the number of possible combinations of all the mutation features
samplePatternNum	the number of possible combination of samples and mutation patterns
isBackground	the logical value showing whether a background mutation features is included or not
vF0	a background mutation features

**Value**

a value

---

```
getMutationFeatureVector
```

*Get mutation feature vector from context sequence data and reference and alternate allele information*

---

### Description

Get mutation feature vector from context sequence data and reference and alternate allele information

### Usage

```
getMutationFeatureVector(
  context,
  ref_base,
  alt_base,
  strandInfo = NULL,
  numBases,
  type
)
```

### Arguments

context	the context sequence data around the mutated position. This should be Biostrings::DNASTringSet class
ref_base	the reference bases at the mutated position.
alt_base	the alternate bases at the mutated position.
strandInfo	transcribed strand information at the mutated position. (this is optional)
numBases	the number of flanking bases around the mutated position.
type	the type of mutation feature vector (should be "independent" or "full").

### Value

a mutation feature vector

---

```
hildaBarplot
```

*Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions*

---

### Description

Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions

**Usage**

```
hildaBarplot(
  inputG,
  hildaResult,
  sigOrder = NULL,
  refGroup,
  sortSampleNum = TRUE,
  refName = "Control",
  altName = "Case",
  charSize = 3
)
```

**Arguments**

inputG	a MutationFeatureData S4 class output by the pmsignature.
hildaResult	a rjags class output by HiLDA.
sigOrder	the order of signatures if needed (default: NULL).
refGroup	the samples in the reference group (default: NULL).
sortSampleNum	whether to sort plots by number of mutations (default: TRUE).
refName	the name of reference group (default: Control)
altName	the name of the other group (default: Case)
charSize	the size of the character on the signature plot (default: 3)

**Value**

a list of a signature plot and a barplot of mutational exposures

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)

hildaBarplot(G, hildaLocal, refGroup=1:4)
```

---

hildaDiffPlot	<i>Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions</i>
---------------	---

---

**Description**

Read the raw mutation data with the mutation feature vector format, estimate and plot both mutation signatures and their fractions

**Usage**

```
hildaDiffPlot(inputG, hildaResult, sigOrder = NULL, charSize = 3)
```

**Arguments**

inputG            a MutationFeatureData S4 class output by the pmsignature.  
 hildaResult     a rjags class output by HiLDA.  
 sigOrder        the order of signatures if needed (default: NULL).  
 charSize        the size of the character on the signature plot (default: 3)

**Value**

a list of the signature plot and the mean difference plot.

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)

hildaDiffPlot(G, hildaLocal)
```

---

hildaGlobalResult     *Compute the Bayes factor*

---

**Description**

Compute the Bayes factor

**Usage**

```
hildaGlobalResult(jagsOutput, pM1 = 0.5)
```

**Arguments**

jagsOutput        the output jags file generated by the jags function from the R2jags package.  
 pM1                the probability of sampling the null (default: 0.5)

**Value**

a number for the Bayes factor

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
hildaGlobal <- hildaTest(inputG=G, numSig=3, refGroup=1:4, nIter=1000,
  localTest=TRUE)
hildaGlobalResult(hildaGlobal)
```

---

hildaLocalResult	<i>Extract the posterior distributions of the mean differences in muational exposures</i>
------------------	---

---

**Description**

Extract the posterior distributions of the mean differences in muational exposures

**Usage**

```
hildaLocalResult(jagsOutput)
```

**Arguments**

jagsOutput      the output jags file generated by the jags function from the R2jags package.

**Value**

a data frame that contains the posterior distributions of difference.

**Examples**

```
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)
hildaLocalResult(hildaLocal)
```

---

hildaPlotSignature	<i>Plot mutation signatures from HiLDA output</i>
--------------------	---

---

**Description**

Plot mutation signatures from HiLDA output

**Usage**

```
hildaPlotSignature(hildaResult, sigOrder = NULL, colorList = NULL, ...)
```

**Arguments**

`hildaResult` a rjags class output by HiLDA  
`sigOrder` the order of signatures if needed (default: NULL)  
`colorList` a vector of color for mutational exposures barplots  
`...` additional arguments passed on to visPMS

**Value**

a plot object containing all mutational signatures

**Examples**

```

inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)
hildaPlotSignature(hildaLocal)
  
```

---

`hildaReadMPFile`      *Read the raw mutation data of Mutation Position Format.*

---

**Description**

The mutation position format is tab-delimited text file, where the 1st-5th columns shows sample names, chromosome names, coordinates, reference bases (A, C, G, or T) and the alternate bases (A, C, G, or T), respectively. An example is as follows;

```

—
sample1 chr1 100 A C
sample1 chr1 200 A T
sample1 chr2 100 G T
sample2 chr1 300 T C
sample3 chr3 400 T C
—
  
```

Also, this function usually can accept compressed files (e.g., by gzip, bzip2 and so on) when using recent version of R.

**Usage**

```

hildaReadMPFile(
  infile,
  numBases = 3,
  trDir = FALSE,
  bs_genome = NULL,
  txdb_transcript = NULL
)
  
```

**Arguments**

<code>infile</code>	the path for the input file for the mutation data of Mutation Position Format.
<code>numBases</code>	the number of upstream and downstream flanking bases (including the mutated base) to take into account.
<code>trDir</code>	the index representing whether transcription direction is considered or not. The gene annotation information is given by UCSC knownGene (TxDb.Hsapiens.UCSC.hg19.knownGene object) When trDir is TRUE, the mutations located in intergenic region are excluded from the analysis.
<code>bs_genome</code>	this argument specifies the reference genome (e.g., BSgenome.Mmusculus.UCSC.mm10 can be used for the mouse genome). See <a href="https://bioconductor.org/packages/release/bioc/html/BSgenome.Mmusculus.UCSC.mm10/">https://bioconductor.org/packages/release/bioc/html/BSgenome.Mmusculus.UCSC.mm10/</a> for the available genome list
<code>txdb_transcript</code>	this argument specified the transcript database (e.g., TxDb.Mmusculus.UCSC.mm10.knownGene can be used for the mouse genome). See <a href="https://bioconductor.org/packages/release/bioc/html/AnnotationDb.Mmusculus.UCSC.mm10.knownGene/">https://bioconductor.org/packages/release/bioc/html/AnnotationDb.Mmusculus.UCSC.mm10.knownGene/</a> for details.

**Value**

The output is an instance of MutationFeatureData S4 class (which stores summarized information on mutation data). This will be typically used as the initial values for the global test and the local test.

**Examples**

```
inputFile <- system.file("extdata/esophageal.mp.txt.gz", package="HiLDA")
G <- hildaReadMPFile(inputFile, numBases=5, trDir=TRUE)
```

---

<code>hildaRhat</code>	<i>Output the maximum potential scale reduction statistic of all parameters estimated</i>
------------------------	---

---

**Description**

Output the maximum potential scale reduction statistic of all parameters estimated

**Usage**

```
hildaRhat(jagsOutput)
```

**Arguments**

<code>jagsOutput</code>	the output jags file generated by the jags function from the R2jags package.
-------------------------	--

**Value**

a number for the Rhat statistic.

**Examples**

```
inputFile <- system.file("extdata/hildaLocal.rdata", package="HiLDA")
hildaLocal <- readRDS(inputFile)
hildaRhat(hildaLocal)
```

---

hildaTest	<i>Apply HiLDA to statistically testing the global difference in burdens of mutation signatures between two groups</i>
-----------	--

---

**Description**

Apply HiLDA to statistically testing the global difference in burdens of mutation signatures between two groups

**Usage**

```
hildaTest(
  inputG,
  numSig,
  refGroup,
  useInits = NULL,
  sigOrder = NULL,
  nIter = 2000,
  nBurnin = 0,
  pM1 = 0.5,
  localTest = TRUE,
  ...
)
```

**Arguments**

inputG	a MutationFeatureData S4 class output by the pmsignature.
numSig	an integer number of the number of mutational signatures.
refGroup	the indice indicating the samples in the reference group.
useInits	a EstimatedParameters S4 class output by the pmsignature (default: NULL)
sigOrder	the order of the mutational signatures.
nIter	number of total iterations per chain (default: 2000).
nBurnin	length of burn (default: 0).
pM1	the probability of sampling the null (default: 0.5)
localTest	a logical value (default: TRUE)
...	Other arguments passed on to methods.

**Value**

the output jags file

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))

## with initial values
hildaLocal <- hildaTest(inputG=G, numSig=3, refGroup=1:4, nIter=1000,
  localTest=TRUE)
hildaGlobal <- hildaTest(inputG=G, numSig=3, refGroup=1:4, nIter=1000,
  localTest=FALSE)
```

---

MetaInformation-class *An S4 class to represent a mutation meta information common to many data types*

---

**Description**

@slot type type of data format (independent, full, custom) @slot flankingBasesNum the number of flanking bases to consider (only applicable for independent and full types) @slot transcriptionDirection the flag representing whether transcription direction is considered or not @slot possibleFeatures a vector representing the numbers of possible values for each mutation feature

---

MutationFeatureData-class

*An S4 class representing the mutation data*

---

**Description**

An S4 class representing the mutation data

**Slots**

featureVectorList a list of feature vectors actually observed in the input mutation data

sampleList a list of sample names observed in the input mutation data

countData a matrix representing the number of mutations and samples. The (1st, 2nd, 3rd) columns are for (mutation pattern index, sample index, frequencies).

mutationPosition a data frame containing position and mutations

---

mySquareEM	<i>A function for estimating parameters using Squared EM algorithm</i>
------------	--

---

**Description**

A function for estimating parameters using Squared EM algorithm

**Usage**

```
mySquareEM(p, y, tol = 1e-04, maxIter = 10000)
```

**Arguments**

p	this variable includes the parameters for mutation signatures and membership parameters
y	this variable includes the information on the mutation features, the number of mutation signatures specified and so on
tol	tolerance for the estimation (when the difference of log-likelihoods become below this value, stop the estimation)
maxIter	the maximum number of iteration of estimation

**Value**

a list

---

pmBarplot	<i>Plot both mutation signatures and their mutational exposures from pm-signature output</i>
-----------	--

---

**Description**

Plot both mutation signatures and their mutational exposures from pmsignature output

**Usage**

```
pmBarplot(
  inputG,
  inputParam,
  sigOrder = NULL,
  refGroup = NULL,
  sortSampleNum = TRUE,
  refName = "Control",
  altName = "Case",
  charSize = 3
)
```

**Arguments**

inputG	a MutationFeatureData S4 class output by the pmsignature.
inputParam	a estimatedParameters S4 class output by the pmsignature.
sigOrder	the order of signatures if needed (default: NULL).
refGroup	the samples in the reference group (default: NULL).
sortSampleNum	whether to sort by number of mutations (default: TRUE).
refName	the name of reference group (default: Control).
altName	the name of the other group (default: Case).
charSize	the size of the character on the signature plot (default: 3).

**Value**

a list of a signature plot and a barplot of mutational exposures

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)

pmPlots <- pmBarplot(G, Param, refGroup=1:4)
cowplot::plot_grid(pmPlots$sigPlot, pmPlots$propPlot, rel_widths = c(1,3))
```

---

pmgetSignature	<i>Obtain the parameters for mutation signatures and memberships</i>
----------------	--

---

**Description**

Obtain the parameters for mutation signatures and memberships

**Usage**

```
pmgetSignature(
  mutationFeatureData,
  K,
  numInit = 10,
  tol = 1e-04,
  maxIter = 10000
)
```

**Arguments**

mutationFeatureData	the mutation data (MutationFeatureData class (S4 class)) by the hildaReadMPFile.
K	the number of mutation signatures
numInit	the number of performing calculations with different initial values
tol	tolerance for the estimation (when the difference of log-likelihoods become below this value, stop the estimation)
maxIter	the maximum number of iteration of estimation

**Value**

The output is an instance of EstimatedParameters S4 class, which stores estimated parameters and other meta-information, and will be used for saving parameter values and visualizing the mutation signatures and memberships

**Examples**

```
## After obtaining G (see e.g., hildaReadMPFile function)
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)
```

---

pmMultiBarplot	<i>Plot both mutation signatures and their mutational exposures from pm-signature output for more than two groups</i>
----------------	---

---

**Description**

Plot both mutation signatures and their mutational exposures from pmsignature output for more than two groups

**Usage**

```
pmMultiBarplot(
  inputG,
  inputParam,
  sigOrder = NULL,
  groupIndices,
  sortSampleNum = TRUE,
  charSize = 3
)
```

**Arguments**

inputG	a MutationFeatureData S4 class output by the pmsignature.
inputParam	a estimatedParameters S4 class output by the pmsignature.
sigOrder	the order of signatures if needed (default: NULL).
groupIndices	a vector of group indicators.
sortSampleNum	an indicator variable on whether samples are sorted by the number of mutations (default: TRUE).
charSize	the size of the character on the signature plot (default: 3)

**Value**

a list of the signature plot and the mean difference plot.

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)

pmPlots <- pmMultiBarplot(G, Param, groupIndices=c(1, rep(2,3), rep(3,6)))
cowplot::plot_grid(pmPlots$sigPlot, pmPlots$propPlot, rel_widths = c(1,3))
```

---

pmPlotSignature	<i>Plot mutation signatures from pmsignature output</i>
-----------------	---

---

**Description**

Plot mutation signatures from pmsignature output

**Usage**

```
pmPlotSignature(inputParam, sigOrder = NULL, colorList = NULL, ...)
```

**Arguments**

inputParam	a estimatedParameters S4 class output by the pmsignature.
sigOrder	the order of signatures if needed (default: NULL).
colorList	a list of color to highlight the signatures (default: NULL).
...	additional arguments passed on to visPMS.

**Value**

a plot object containing all mutational signatures

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)
pmPlotSignature(Param)
```

---

PMSboundary	<i>A functional for generating the function checking the parameter (p) is within the restricted conditions or not</i>
-------------	---

---

**Description**

A functional for generating the function checking the parameter (p) is within the restricted conditions or not

**Usage**

```
PMSboundary(y)
```

**Arguments**

y	this variable includes the information on the mutation features, the number of mutation signatures specified and so on
---	--

**Value**

a functional

---

updateMstepFQC	<i>Update the parameter F and Q (M-step in the EM-algorithm)</i>
----------------	--

---

**Description**

Update the parameter F and Q (M-step in the EM-algorithm)

**Usage**

```
updateMstepFQC(
  vPatternList,
  vSparseCount,
  nTheta,
  fdim,
  signatureNum,
  sampleNum,
  patternNum,
  samplePatternNum,
  isBackground
)
```

**Arguments**

vPatternList	The list of possible mutation features (converted to a vector)
vSparseCount	The table showing (mutation feature, sample, the number of mutation) (converted to a vector)
nTheta	The parameters in the distribution
fdim	a vector specifying the number of possible values for each mutation signature
signatureNum	the number of mutation signatures
sampleNum	the number of cancer genomes
patternNum	the number of possible combinations of all the mutation features
samplePatternNum	the number of possible combination of samples and mutation patterns
isBackground	the logical value showing whether a background mutation features is included or not

**Value**

a vector

---

updatePMSPParam	<i>A function for updating parameters using EM-algorithm</i>
-----------------	--

---

**Description**

A function for updating parameters using EM-algorithm

**Usage**

```
updatePMSPParam(p, y)
```

**Arguments**

p	this variable includes the parameters for mutation signatures and membership parameters
y	this variable includes the information on the mutation features, the number of mutation signatures specified and so on

**Value**

a value

---

updateTheta\_NormalizedC

*Update the auxiliary parameters theta and normalize them so that the summation of each group sums to 1 (E-step), also calculate the current log-likelihood value*

---

### Description

Update the auxiliary parameters theta and normalize them so that the summation of each group sums to 1 (E-step), also calculate the current log-likelihood value

### Usage

```
updateTheta_NormalizedC(
  vPatternList,
  vSparseCount,
  vF,
  vQ,
  fdim,
  signatureNum,
  sampleNum,
  patternNum,
  samplePatternNum,
  isBackground,
  vF0
)
```

### Arguments

vPatternList	The list of possible mutation features (converted to a vector)
vSparseCount	The table showing (mutation feature, sample, the number of mutation) (converted to a vector)
vF	F (converted to a vector)
vQ	Q (converted to a vector)
fdim	a vector specifying the number of possible values for each mutation signature
signatureNum	the number of mutation signatures
sampleNum	the number of cancer genomes
patternNum	the number of possible combinations of all the mutation features
samplePatternNum	the number of possible combination of samples and mutation patterns
isBackground	the logical value showing whether a background mutation features is included or not
vF0	a background mutation features

**Value**

a value for theta

---

visPMS	<i>visualize probabilistic mutaiton signature for the independent model</i>
--------	---

---

**Description**

Generate visualization of mutation signatures for the model with substitution patterns and flanking bases represented by the indepenent representation.

**Usage**

```
visPMS(
  vF,
  numBases,
  baseCol = NA,
  trDir = FALSE,
  charSize = 5,
  isScale = FALSE,
  alpha = 2,
  charLimit = 0.25
)
```

**Arguments**

vF	a matrix for mutation signature
numBases	the number of flanking bases
baseCol	the colour of the bases (A, C, G, T, plus/minus strand)
trDir	the index whether the strand direction is plotted or not
charSize	the size of the character
isScale	the index whether the height of the flanking base is changed or not
alpha	the parameter for the Renyi entropy (applicable only if the isScale is TRUE)
charLimit	the limit of char size

**Value**

a plot of the input mutational signature

**Examples**

```
load(system.file("extdata/sample.rdata", package="HiLDA"))
Param <- pmgetSignature(G, K = 3)

sig <- slot(Param, "signatureFeatureDistribution")[1,,]
visPMS(sig, numBases = 5, isScale = TRUE)
```

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