vaRHC

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Contents

1. Introduction

Variant classification is a manual complex long process that combines information of distinct nature. An accurate classification is necessary to ensure a proper genetic counselling and personalized risk estimation.

In 2015, the American College of Molecular Genetics and Genomics (ACMG) together with the Association of Molecular Pathologists published generic guidelines to standardize and provide an objective framework to evaluate variant pathogenicity in Mendelian disease. Later, specific guidelines have been published for some genes by collaborative groups.

Moreover, it has been demonstrated that the combination of criteria in ACMG/AMP guidelines is compatible with a quantitative Bayesian formulation(Tavtigian et al., 2018) and a naturally scaled point system has been further abstracted (Tavtigian et al., 2020). Additionally, CanVIG-UK consensus recommendations has proposed some limitations to overlapping criterion combination to avoid double counting of evidence (Garrett et al., 2021).

In the last 5 years, some programs have been developed with the aim to semi-automatize the process of variant classification. Most tools are based on ACMG-AMP general rules but others focus on a set of genes.

`vaRHC` has been developed to automate as much as possible the process of variant classification in hereditary cancer (HC). The aim is to streamline the work of biologists and avoid possible manual error following gene-specific guidelines for *ATM*, *CDH1*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *PTEN* and *TP53* and the updated general ACMG rules for the remaining cancer susceptibility genes. The final classification is obtained according to Tatigian's natural scoring Bayesian-based metastructure (Tavtigian et al., 2020) but also considering the CanVIG-UK incompatibilities proposal. vaRHC gives the oportunity to export the output in a .xlsx file as a user-friendly way to examine and store the results allowing non-bioinformatic users to work with them, and even modify the file adding their considerations or information regarding the non-automatable criteria.

The current version of the package is based on the GRCh37 assembly of the human genome and works for single substitutions, deletions and insertions up to 25 bp, intronic variants and 5' or 3'-UTR variants 25 bp beyond the coding sequence.

2. Installation

vaRHC can be downloaded from GitHub using the remotes package:

```
if(!require("remotes", quietly = TRUE)) install.packages('remotes') ## Only the first time
library(remotes)
devtools::install_github("emunte/vaRHC")
```

Next, it has to be loaded into the workspace:

```
library("vaRHC")
```

3. Main functions

The package consists of two main functions ***vaR()*** and ***vaRbatch()***.

3.1 vaR()

3.1.1 Input

3.1.1.1 Parameters Using a **gene** and a **variant** name (in coding DNA nomenclature) as input variables, ***vaR()*** gathers relevant information from different sources. Gene-specific ACMG/AMP guidelines are then applied in order to calculate whether the variant of interest meets different criteria. The output also provides an explanation of the reason for applying or rejecting each criterion. Additionally, it returns a final classification of the variant using Tavtigian Bayesian metastructure and also considering most of CanVIG-UK recommendations.

The following example shows how to call the **vaR()** function for the variant c.1137+1G>A in *CDH1* gene.

```
eg.gene <- "CDH1"
eg.variant <- "c.1137+1G>A"


var.information <- vaR(gene = eg.gene, variant = eg.variant)
```

3.1.1.2 Optional parameters Optional parameters of *vaR()* are described below.

3.1.1.2.1 NM and CCDS

- ***NM***: Accession number of the transcrit and mRNA from RefSeq. By default is NULL and vaRHC will consider the ones detailed above. Be careful if you use a different NM because the program has not been validated for it. If you provide a different NM, CCDS must also be provided.The transcript accession number is retrieved from RefSeq. By default, this function parameter is set to NULL. vaRHC will consider the NMs listed in the Supplementary Table 1. If a different NM is used than the ones described in the table, it must be noted that the program has not been validated yet for it. In this case, a CCDS ID is also required.
- ***CCDS***: Consensus CDS ID retrieved from NCBI CCDS database (which can be found in the following link https://www.ncbi.nlm.nih.gov/projects/CCDS/CcdsBrowse.cgi). By default is set to NULL. vaRHC will consider the IDs detailed in the table above. Again, it must be noted that if a different CCDS ID is provided, the program has not been validated yet for it. In this case, NM accession number is required.

3.1.1.2.2 gene.specific.df **gene.specific.df**: By default the parameter is set to NULL as it considers the gene-specific cutoffs, frequencies and additional parameters queried in the IDIBELL database as described in the paper *vaRHC: an R package for semi-automation of variant classification in hereditary cancer genes according to ACMG/AMP and gene-specific ClinGen guidelines [Manuscript submitted for publication].* This table contains gene-specific information for applying the following criteria: BA1, BS1, BS2, PM2, predictors cut-off and BP7. If the user wants to modify any of these criteria or specify another additional gene, a table containing all these criteria can be loaded to the R environment, and set as the gene.specific.df parameter. A template of how the table needs to be can be downloaded from GitHub (https://github.com/emunte/vaRHC/blob/main/data/gene_specific.txt) or it can be found at the package documentation. Column names cannot be modified. See below the default table and the explanation of each column:

[illegible]
ATM 0.95 0.005 0.0005 NA NA NA NA NA 1e-05 NA NA NA NA NA NA NA NA NA < > 0.2 0.733 <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
CDH1 0.999 0.002 0.001 FLOSSIES [illegible] healthy 05 NA NA NA NA NA NA NA NA NA NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
CHEK2 0.95 0.01 0.005 100 NA 1e-05 5e-05 < >= 6.6 6.66 NA < >= 0.7 0.700 <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
general 0.99 0.01 0.002 50 FLOSSIES GNOMAD [illegible] healthy non_cancer 05 05 NA < >= 0.7 0.700 <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
MLH1 0.95 0.001 0.0010 NA homo_healthy NA 2e-05 NA NA NA NA NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
MSH2 0.95 0.001 0.0010 NA homo_healthy NA 2e-05 NA NA NA NA NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
MSH6 0.95 0.0022 0.0022 NA homo_healthy NA 2e-05 NA NA NA NA NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
PMS2 0.95 0.0028 0.0028 NA homo_healthy NA 2e-05 NA NA NA NA NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
PTEN 0.99 0.001 0.0002 10 FLOSSIES GNOMAD homo_healthy non_cancer 1e-05 < >= 0.1 0.10 = 1 NA NA NA NA NA NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 NA NA NA NA NA NA NA NA <=>= 0.1
TP53 0.999 0.001 0.0003 FLOSSIES homo_healthy >= 6.6 6.66 NA NA NA NA NA <=> 0.5 0.5 > <= - -2.5 2.5 < >= 0.16 0.16 <=>= 15 25 <=>= 0.1

- **BA1**: *float number.* Cut-off used to assign BA1 criterion.
- **BS1**: *float number.* Cut-off used to assign BS1 criterion.
- **IC**: *float number.* Interval of confidence used to assign BA1 and BS1 criterion
- **alleles**: *int number.* Minimum number of alleles needed in the subpopulation (it will only be considered when IC is not specified).
- **BS2**: *int number.* Minimum number of individuals that need to carry the variant to assign BS2.
- **BS2_sup**: *int number.* Minimum number of individuals that need to carry the variant to assign BS2_sup.
- **BS2_db**: *character* Db to be queried for BS2 criterion. Please introduce one of the following options *FLOSSIES*, *GNOMAD_non_cancer*, *GNOMAD_non_neuro* or *NA*. .
- **status**: *character* Type of zigosity asked for BS2 criterion. Please introduce one of the following options *homo_healthy*, *hete_healthy*, *NA*.
- **PM2**: float number. Cut-off used to assign PM2 criterion.
- **PM2_sup**: float number. Cut-off used to assign PM2_supporting criterion.
- **predictors section**: Predictors shown are: nucleotide conservation(**phylop, phastcons, gerp**), protein level (**revel, VEST4, provean, bayesDel_noAF, agvgd, polyphen, MAPP, prior_utah_prot**) and splicing predcitors (**spliceai, trap**). See references in the tool paper. For each predictor there are 4 columns:
  - **op_predictor_ben**: *character* Operator to use for benign cut-off. The possible options to introduce are <, >, =<, => or *!=*.

  - **op_predictor_pat** : *character* Operator to use for pathogenic cut-off. The possible options to introduce are <, >, =<, => or !=.
  - **predictor_ben** : *float number*. Benign cut-off to use with this predictor
  - **predictor_pat** : *float number*. Pathogenic cut-off to use with this predictor

  Be careful, changing a predictor cut-off will only be considered when the guidelines specify to use that predictor.

- **BP7_splicing**: *character* Wheter the BP7 criteria is dependent on splicing prediction not being altered or not. Possible options are *dependent*, *indpendent*.

```
eg.gene <- "CDH1"
eg.variant <- "c.1137+1G>A"
data("gene_specific")
eg.gene.specific <- gene_specific

var.information <- vaR(gene = eg.gene, variant = eg.variant, gene.specific.df = eg.gene.specific)
```

3.1.1.2.3 Connecting to webpages using javascript Insight database needs to be queried using RSelenium package. However, we have detected that some Institutes have unabled the possibility to connect to a remote server. The ****remotes*** parameter allows to decide if the user wants to allow this capability (TRUE) or not (FALSE). If it is set to FALSE the user will not collect information from insight database. The ***browser*** parameter is used to set which browser to start Rselenium server. By default is "firefox" (the recommended). If you do not have firefox installed try either "chrome" or "phantomjs" (but they have not been tested for this package).

3.1.1.2.4 SpliceAI related parameters

- ***spliceai.program*** : *Logical*. By default is FALSE , assuming that SpliceAI program is not installed in your computer. If this parameter is FALSE, the program will only classify substitutions and simple deletion variants considering a spliceAI distance of 1000 and will show masked results. If you want to classify other variants please install SpliceAI (https://pypi.org/project/spliceai/) and set the parameter to TRUE.
- ***spliceai.referenc*** : Path to the Reference genome hg19 fasta file. It can be downloaded from http://hgdownload.cse.ucsc.edu/goldenPath/hg19/bigZips/hg19.fa.gz . By default is NULL and it will only be taken into account if spliceai.program is set to TRUE.
- ***spliceai.annotation*** : Path to gene annotation file. By default it uses the file stored in package docs folder: "../docs/gencode.v38lift37.annotation.txt"
- ***spliceai.distance*** : *Integer*. Maximum distance between the variant and gained/lost splice site (default: 1000)
- ***spliceai.masked*** : Mask scores representing annotated acceptor/donor gain and unannotated acceptor/donor loss (default: 1, that is masked)

3.1.1.2.5 Provean related parameters

- ***provean***: *Logical*. By default is FALSE and it is assumed that provean program is not installed in your computer. Set to TRUE if you want to compute provean locally.
- ***provean.sh***: Path to the provean.sh file. It will only be considered when provean is set to TRUE.

3.1.1.2.6 Report related parameters

- ***excel.results*** : *Logical*. By default is FALSE and the excel file will not be created. If TRUE and excel file will be saved.
- ***path.original.file***: If excel.results param is set to TRUE, path.original.file must contain the path to the excel template. By default is the template located in the package docs folder.

3.1.1.2.7 Output dir

- ***output.dir***: By default is NULL and the output will be saved in the working directory. If yu want to save the output in another folder please enter here the path.

3.1.2 Output The result is stored in a list but it can also be exported in a xlsx file. The list has to dimensions.

3.1.2.1 vaRinfo Where all the information retrieved is stored. The names of the list elements are the following.

```
names(var.information$vaRinfo)
#>  [1] "Variant.Info"                 "Variant.Info.other"
#>  [3] "variant.correction"           "gene.specific.info"
#>  [5] "gnomAD"                       "flossies.db"
#>  [7] "clinVar"                      "predictors"
#>  [9] "codon.stop"                   "second.met"
#> [11] "insight.info"                 "functional.assays"
#> [13] "google.scholar.30.references" "cancer.hotspots"
#> [15] "class.info"
```

- **Variant.Info**: a data.frame containing a summary of variant location, different nomenclatures and variant consequences.

```
#> 'data.frame':    1 obs. of  19 variables:
#>  $ gene                      : chr "CDH1"
#>  $ NM                        : chr "NM_004360.5"
#>  $ initial.var               : chr "c.1137+1G>A"
#>  $ variant                   : chr "c.1137+1G>A"
#>  $ protein                   : chr "p.?"
#>  $ genomic                   : chr "NC_000016.9:g.68846167G>A"
#>  $ chr                       : chr "16"
#>  $ start                     : int 68846167
#>  $ end                       : int 68846167
#>  $ ref                       : chr "G"
#>  $ alt                       : chr "A"
#>  $ strand                    : int 1
#>  $ exon_intron               :'data.frame':   1 obs. of  1 variable:
#>   ..$ exon: int 8
#>  $ ensembl.id                : chr "ENST00000261769"
#>  $ most.severe.consequence   : chr "splice_donor_variant"
#>  $ most.severe.consequence.1: chr NA
#>  $ most.severe.consequence.2: chr NA
#>  $ CCDS                      : chr "CCDS10869.1"
#>  $ domain.info               : chr [1, 1:2] "Cadherin 3" "Cadherin"
```

- **Variant.Info.other**: only for *TP53* and *CDK2NA* other transcripts.
- **variant.correction**: output obtained by quering Mutalyzer.
- **gene.specific.info**: variant gene specificities used
- **gnomAD**: a list containing gnomAD v2.1.1 variant nomeclature, coverage and alleles information for non_cancer and non_neuro datasets. See below examples of how to obtain the gnomAD data

```
#nomenclature
var.information$vaRinfo$gnomAD$nomenclature
#> [1] "16-68846167-G-A"
#coverage
var.information$vaRinfo$gnomAD$coverage
#> $exomes
#> [1] 92.4
#>
#> $genomes
#> [1] 33.94
#information from exomes non cancer separated by subpopulations
knitr::kable(var.information$vaRinfo$gnomAD$info$exomes$non.cancer$subpopulations)
```

	AC	AN	nhomalt	AF	CI
non_cancer_nfe	0	102722	0	0	0
non_cancer_fin	0	21630	0	0	0
non_cancer_amr	0	34260	0	0	0
non_cancer_afr	0	14902	0	0	0
non_cancer_sas	0	30526	0	0	0
non_cancer_eas	0	17692	0	0	0
non_cancer_asj	0	9570	0	0	0
non_cancer_oth	0	5618	0	0	0

```
#information from exomes + genomes non neuro overall frequency
knitr::kable(var.information$vaRinfo$gnomAD$info$exomes.genomes$non.neuro$overall)
```

rowname	AC	AN	nhomalt	AF	CI
.	1	229382	0	4.4e-06	0

- **flossies.db**: a dataframe containing information obtained from FLOSSIES database.
- **clinVar**: a list containing information of the variant of interest and if it is a missense also information from other missense variants located at the same codon.
- **predictors**: a dataframe with all the predictors information stored. Only the predictors where use column is yes will be considered to calculate criteria.

	type	predictor	classification	use	values	position	operator.benign	benign.cutoff	operator.pathogenic	pathogenic.cutoff
Phylop	Nucleotide conservation	Phylop	NA	no	9.31715	NA	NA	NA	NA	NA
Phastcons	Nucleotide conservation	Phastcons	NA	no	1.00000	NA	NA	NA	NA	NA

	type	predictor	classification	use	values	position	operator.benign.cut.off	benign.cut.off	operator.pathogenic.cut.off	pathogenic.cut.off
Gerp	Nucleotide conservation	Gerp	NA	no	5.72000	NA	NA	NA	NA	NA
Revel	Protein effect	Revel	NA	no	NA	NA	NA	NA	NA	NA
VEST4	Protein effect	VEST4	NA	no	NA	NA	<=	0.5	>	0.50
Provean	Protein effect	Provean	NA	no	NA	NA	>	-2.5	<=	-2.50
BayesDel_noAF	Protein effect	BayesDel_noAF	NA	no	0.14100	NA	NA	NA	NA	NA
aGVGD_zebrafish	Protein effect	aGVGD_Zebrafish	NA	no	NA	NA	NA	NA	NA	NA
PolyPhen	Protein effect	PolyPhen	NA	no	NA	NA	NA	NA	NA	NA
MAPP	Protein effect	MAPP	NA	no	NA	NA	NA	NA	NA	NA
Prior_utah(MAPP/PP2)	Protein effect	Prior_utah(MAPP/PP2)	NA	no	NA	NA	NA	NA	NA	NA
Prior_utah_splicing_reference	Splicing Predictor	Prior_utah_splicing_reference	NA	no	NA	NA	NA	NA	NA	NA
Prior_utah_splicing_de_novo	Splicing Predictor	Prior_utah_splicing_de_novo	NA	no	NA	NA	NA	NA	NA	NA
SpliceAI-AcceptorGain	Splicing Predictor	SpliceAI-AcceptorGain	Benign	yes	0.01000	322	<=	0.15	>=	0.50
SpliceAI-AcceptorLoss	Splicing Predictor	SpliceAI-AcceptorLoss	Benign	yes	0.00000	-129	<=	0.15	>=	0.50
SpliceAI-DonorGain	Splicing Predictor	SpliceAI-DonorGain	Pathogenic	yes	0.56000	-84	<=	0.15	>=	0.50
SpliceAI-DonorLoss	Splicing Predictor	SpliceAI-DonorLoss	Pathogenic	yes	0.99000	-1	<=	0.15	>=	0.50
TraP	Splicing Predictor	TraP	NA	no	NA	NA	<=	0.459	>=	0.93

- **codon.stop**: a list with the following elements:
  - **variant.exon**: contains the exon where the variants is located and its coordinates.

transcript	exon	V1	V2	cStart	cStop	cdna.var.pos
LRG_301t1	8	68846038	68846166	1009	1137	1

- **premature.ter.codon**: for frameshifts and nonsense variants it contains the exon where the stop codon is produced and its coordinates.
- **length.transcript**: total number of coding nucleotides that the transcript has
- **porc.prot**: percentatge of protein conserved
- **canonical.skip.pred**: only for canonical splice variants. It contains information from the predicted skipping variant, its consequence and percentatge of protein conserved.

variant	protein	most.severe.consequence	porc.prot.splicing
c.1009_1137del	p.(Ser337_Thr379del)	inframe_deletion	0.0524805

- **exons**: exon coordinates according to LRG transcript. In genomic and coding dna nomenclature.

transcript	exon	V1	V2	cStart	cStop
LRG_301t1	1	68771195	68771366	-124	48
LRG_301t1	2	68772200	68772314	49	163
LRG_301t1	3	68835573	68835796	164	387
LRG_301t1	4	68842327	68842470	388	531
LRG_301t1	5	68842596	68842751	532	687
LRG_301t1	6	68844100	68844244	688	832
LRG_301t1	7	68845587	68845762	833	1008
LRG_301t1	8	68846038	68846166	1009	1137
LRG_301t1	9	68847216	68847398	1138	1320
LRG_301t1	10	68849418	68849662	1321	1565
LRG_301t1	11	68853183	68853328	1566	1711
LRG_301t1	12	68855904	68856128	1712	1936
LRG_301t1	13	68857302	68857529	1937	2164
LRG_301t1	14	68862077	68862207	2165	2295
LRG_301t1	15	68863557	68863700	2296	2439
LRG_301t1	16	68867193	68869444	2440	*2038

- **second.met**: only for start codon variants. It returns second metionine position and clinVar variants between first and second metionine.
- **insight.info**: information from INSIGHT database classifications and MMR Integrative Evaluation (http://www.insight-database.org/classifications/ and http://www.insight-database.org/classifications/mmr_integrative_eval.html)
- **functional.assays**: a list containing information from functional assays. Further details are explained in the tool article.
- **cancer.hotspots**: information obtained from Cancer Hotspots (http://www.insight-database.org/classifications/mmr_integrative_eval.html)

3.1.2.2 vaRclass All the assigned and denied criteria are stored in this list as well as final classification.

The list has the following items:

```
names(var.information$vaRclass)
#> [1] "final.classification" "final.criteria"
```

The final.classification element contains:

- **final.class**: variant's final classification
- **criteria.assingned**: a vector containing all the criteria that are assigned to the variant
- **sum.criteria**: Tavtigian's Bayesian score
- **discrep.reason**: wheter there are discrepances or not and the reason.

The final.criteria element contains: + *Criteria.res*: a matrix with all the criteria assigned(1), denied (0), not applicable (NA) or not calculated (NC). + *Criterion name + .message*: reasoning for the criterion being assigned or denied.

	very_strong	strong	moderate	supporting
PVS1	0	1	0	0
PS1	NA	NA	NA	NA
PS2	NC	NC	NC	NC
PS3	NC	NC	NC	NC
PS4	NC	NC	NC	NC
PM1	NA	NA	NA	NA
PM2	NA	NA	0	1
PM3	NC	NC	NC	NC
PM4	NA	NA	NC	NA
PM5	NC	NC	0	1
PM6	NC	NC	NC	NC
PP1	NC	NC	NC	NC
PP2	NA	NA	NA	NA
PP3	NA	NA	NA	NA
PP4	NC	NC	NC	NC
PP5	NA	NA	NA	NA
BA1	0	NA	NA	NA
BS1	NA	0	NA	NA
BS2	NC	0	NC	0
BS3	NC	NC	NC	NC
BS4	NC	NC	NC	NC
BP1	NA	NA	NA	NA
BP2	NA	NA	NA	0
BP3	NC	NC	NC	NC
BP4	NA	NA	NA	NA
BP5	NC	NC	NC	NC
BP6	NA	NA	NA	NA
BP7	NA	NA	NA	0
external	NC	NC	NC	NC

```
#> $PVS1.message
#> [1] "PVS1_strong is assigned according to site-specific recomendations in the splicing table (CDH1 Gu
#>
#> $PS1.message
#> [1] "PS1 does not apply for this variant."
#>
#> $PS3.message
#> [1] "PS3 is not assigned because variant is not found in the automated functional studies. Please che
#>
#> $BS3.message
#> [1] "BS3 is not assigned because variant is not found in the automated functional studies. Please che
#>
#> $PM1.message
#> [1] "As PVS1 is assigned, PM1 is not calculated"
#>
#> $PM2.message
#> [1] "PM2_supporting is assigned because the variant is observed in 4e-06 frequency which is < 9.99995
#>
#> $PM4.message
#> [1] "As PVS1 is assigned, PM4 is not calculated"
#>
#> $PM5.message
```

```
#> [1] "PM5_supporting is assigned according to site-specific recommendations for canonical splicing va
#>
#> $PP2.message
#> [1] "PP2 does not apply for this variant or gene."
#>
#> $PP3.message
#> [1] "PP3 is not calculated because PVS1 is met and co-usage is not permitted"
#>
#> $BA1.message
#> [1] "Freq gnomAD all non-cancer v2.1.1 = 0.00037% (MCAF 99.99% = 0.00037%)..Max freq in afr subpopula
#>
#> $BS1.message
#> [1] "The location is well covered in gnomAD (at least in exomes) but the variant is found in AF <  0
#>
#> $BS2.message
#> [1] "BS2 is not assigned taking into account the db queried. Please check if there exist more."
#>
#> $BP1.message
#> [1] "Not automated criteria"
#>
#> $BP2.message
#> [1] "BP2 is denied because the variant is not observed in homozygous state in gnomAD v2.1.1 non_canc
#>
#> $BP4.message
#> [1] "BP4 is not calculated because PVS1 is met and co-usage is not permitted."
#>
#> $BP7.message
#> [1] "BP7 is denied bc.1399T>Cecause variants must be positioned at or beyond  +7/-21."
#>
#> $PP5.message
#> [1] "According to ClinGen PP5 should not be applied since variants in reputable sources are not alwa
#>
#> $BP6.message
#> [1] "According to ClinGen BP6 should not be applied since variants in reputable sources are not alwa
#>
#> $PS2.message
#> [1] "Not automated criteria"
#>
#> $PS4.message
#> [1] "Not automated criteria"
#>
#> $PM3.message
#> [1] "Not automated criteria"
#>
#> $PM6.message
#> [1] "Not automated criteria"
#>
#> $PP1.message
#> [1] "Not automated criteria"
#>
#> $PP4.message
#> [1] "Not automated criteria"
#>
#> $BS4.message
```

```
#> [1] "Not automated criteria"
#>
#> $BP3.message
#> [1] "Not automated criteria"
#>
#> $BP5.message
#> [1] "Not automated criteria"
```

3.1.2.3 Excel file The excel file has the following sheets:

- **Classification summary**: variant summary and criteria assigned.
- **Evidence**: justification of every evidence given to a variant.
- **Frequency control**: population dta from gnomAD v2.1.1 non_cancer, non_neuro, FLOSSIES database and cancer hotspots
- **ClinVar**: variant information from ClinVar.
- **ClinVar variants**: List of variants in ClinVar at the same codon(only for missense variants).
- **ClinVar + variant name**: One sheet per variant listed in the previous sheet containing all the information provided by ClinVar.
- **Predictors**: Variant scores for the predictors listed and its cut-offs.
- **NMD**: Information for loss of function variants due to frameshift, nonsense or canonical splice site alterations.
- **Start Codon**: for start codon variants: list of ClinVar variants upstream the second in-frame metionine
- **Bibliography vaRCH**: a string containing all possible variant nomenclature to put in a search engine such as google. It also returns the 30 first articles listed in google scholar. Be careful because Google scholar has a limited of searches per day. When this searches are overpasses an Error 429 is returned.

3.1 vaRbatch()

vaRbatch() allows to perform vaR function in batch.

3.1.1 Input The input is a data frame containing gene and variant column. See and example below. This function only works for the NM described in 3.1.1.2.1 section.

```
#Example 1
data("example_input_vaRbatch")
example_input_vaRbatch[] <- lapply(example_input_vaRbatch, as.character) #convert to character
all <- vaRbatch( all.variants = example_input_vaRbatch, spliceai.program = TRUE, splieai.reference= "./

#Example2
eg.variants <- data.frame(gene=c("ATM", "MSH6", "BRCA1"), variants = c("c.8420A>T", "c.1559G>A", "c.211
batch.results <- vaRbatch( all.variants = eg.variants, spliceai.program =FALSE, print.data.frame = FALS
```

3.1.2 Output It returns a list containing vaR() output for all variants. The user can choose to print a data frame (***print.data.frame***) to store classification results in a csv file. The function also returns a log file, with the detailed time execution and any error that may occur explained. The log file is stored in a log folder in the working directory.

4. Legal advice and privacy policy for users

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The application only uses its session cookies for technical purposes.

You will be able to request more information on the processing of data performed and exercise access rights, rectification, deletion, opposition, portability, and limitation of the process by sending a request through the email address dataprotection@idibell.cat. You will also be able to contact the data protection delegate of the IDIBELL via dpd@ticsalutsocial.cat.

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5. Supplementary Tables

ST1

ensembltranscriptID	namegene	NM	NC	CCDS
ENST00000318602	A2M	NM_000014.6	NC_000012.11	CCDS44827.1
ENST00000642412	A4GALT	NM_017436.7	NC_000022.10	CCDS14041.1
ENST00000261772	AARS1	NM_001605.2	NC_000016.9	CCDS32474.1
ENST00000374736	ABCA1	NM_005502.4	NC_000009.11	CCDS6762.1
ENST00000650372.1	ABCB11	NM_003742.4	NC_000002.11	CCDS46444.1
ENST00000265316.9	ABCB6	NM_005689.4	NC_000002.11	CCDS2436.1
ENST00000253577.9	ABCB7	NM_004299.6	NC_000023.10	CCDS14428.1
ENST00000647814.1	ABCC2	NM_000392.5	NC_000010.10	CCDS7484.1
ENST00000645237.2	ABCC4	NM_005845.5	NC_000013.10	CCDS9474.1
ENST00000205557.12	ABCC6	NM_001171.6	NC_000016.9	CCDS10568.1
ENST00000389817.8	ABCC8	NM_000352.6	NC_000011.9	CCDS31437.1
ENST00000261200	ABCC9	NM_020297.2	NC_000012.11	CCDS8693.1
ENST00000218104.6	ABCD1	NM_000033.4	NC_000023.10	CCDS14728.1
ENST00000237612.8	ABCG2	NM_004827.3	NC_000004.11	CCDS3628.1
ENST00000405322.8	ABCG5	NM_022436.3	NC_000002.11	CCDS1814.1
ENST00000272286.4	ABCG8	NM_022437.3	NC_000002.11	CCDS1815.1
ENST00000644371.2	ABHD5	NM_016006.6	NC_000003.11	CCDS2711.1
ENST00000318560.6	ABL1	NM_005157.6	NC_000009.11	CCDS35166.1
ENST00000611156	ABO	NM_020469.3	NC_000009.11	-
ENST00000281182.9	ACAD8	NM_014384.2	NC_000011.9	CCDS8498.1
ENST00000370841.9	ACADM	NM_000016.5	NC_000001.10	CCDS668.1
ENST00000358776.7	ACADSB	NM_001609.3	NC_000010.10	CCDS7634.1
ENST00000265838.9	ACAT1	NM_000019.4	NC_000011.9	CCDS8339.1

ensembltranscriptID	namegene	NM	NC	CCDS
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ENST00000368122.4	ACKR1	NM_002036.4	NC_000001.10	CCDS1183.1
ENST00000648477.1	ACP5	NM_001611.5	NC_000019.9	CCDS12265.1
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ENST00000224784.10	ACTA2	NM_001613.2	NC_000010.10	CCDS7392.1
ENST00000646664.1	ACTB	NM_001101.3	NC_000007.13	CCDS5341.1
ENST00000290378.6	ACTC1	NM_005159.4	NC_000015.9	CCDS10041.1
ENST00000394419.9	ACTN1	NM_001130004.1	NC_000014.8	CCDS45130.1
ENST00000366578.6	ACTN2	NM_001103.4	NC_000001.10	CCDS1613.1
ENST00000388922.9	ACVRL1	NM_000020.2	NC_000012.11	CCDS31804.1
ENST00000372874	ADA	NM_000022.2	NC_000020.10	CCDS13335.1
ENST00000399837.8	ADA2	NM_001282225.2	NC_000022.10	CCDS13742.1
ENST00000310823.8	ADAM17	NM_003183.6	NC_000002.11	CCDS1665.1
ENST00000371929.7	ADAMTS13	NM_139025.4	NC_000009.11	CCDS6970.1
ENST00000368474.9	ADAR	NM_001111.5	NC_000001.10	CCDS1071.1
ENST00000297323.12	ADCY1	NM_021116.4	NC_000007.13	CCDS34631.1
ENST00000405460.9	ADGRV1	NM_032119.4	NC_000005.9	CCDS47246.1
ENST00000241356.5	ADORA3	NM_000677.3	NC_000001.10	CCDS839.1
ENST00000280155.4	ADRA2A	NM_000681.4	NC_000010.10	CCDS7569.2
ENST00000269143.8	AFG3L2	NM_006796.2	NC_000018.9	CCDS11859.1
ENST00000649286.2	AGK	NM_018238.4	NC_000007.13	CCDS5865.1
ENST00000220592	AGO2	NM_012154.3	NC_000008.10	CCDS6380.1
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ENST00000279146	AIP	NM_003977.2	NC_000011.9	CCDS8168.1
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ENST00000373449.7	AK2	NM_013411.3	NC_000001.10	CCDS373.1
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ENST00000389048	ALK	NM_004304.4	NC_000002.11	CCDS33172.1
ENST00000613296	ALMS1	NM_015120.4	NC_000002.11	CCDS42697.1
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ENST00000264276.11	ALS2	NM_020919.4	NC_000002.11	CCDS42800.1
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ENST00000284268.8	ANKH	NM_054027.6	NC_000005.9	CCDS3885.1
ENST00000371697.4	ANKRD1	NM_014391.2	NC_000010.10	CCDS7412.1
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ENST00000320560.13	ANO6	NM_001025356.3	NC_000012.11	CCDS31782.1
ENST00000296511.10	ANXA5	NM_001154.4	NC_000004.11	CCDS3720.1
ENST00000337619.11	AP1S1	NM_001283.5	NC_000007.13	CCDS47669.1
ENST00000255194.11	AP3B1	NM_003664.4	NC_000005.9	CCDS4041.1
ENST00000643116.3	AP3D1	NM_001261826.3	NC_000019.9	CCDS58638.1
ENST00000261842.10	AP4E1	NM_007347.5	NC_000015.9	CCDS32240.1
ENST00000649063.2	AP5Z1	NM_014855.3	NC_000007.13	CCDS47528.1
ENST00000257430	APC	NM_000038.5	NC_000005.9	CCDS4107.1
ENST00000236850.5	APOA1	NM_000039.1	NC_000011.9	CCDS8378.1
ENST00000319136.8	APOL1	NM_145343.2	NC_000022.10	CCDS13925.1
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ENST00000199280	AQP2	NM_000486.5	NC_000012.11	CCDS8792.1
ENST00000297991.6	AQP3	NM_004925.5	NC_000009.11	CCDS6542.1
ENST00000374690.9	AR	NM_000044.6	NC_000023.10	CCDS14387.1
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ENST00000349830	ARHGEF10	NM_014629.2	NC_000008.10	CCDS34794.1
ENST00000324856.13	ARID1A	NM_006015.4	NC_000001.10	CCDS285.1
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ENST00000244769.8	ATXN1	NM_000332.3	NC_000006.11	CCDS34342.1
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ENST00000674280.1	ATXN7	NM_001377405.1	NC_000003.11	CCDS43102.1
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ENST00000651292.1	B3GALNT1	NM_033169.3	NC_000003.11	CCDS3193.1
ENST00000379198.5	B3GALT6	NM_080605.4	NC_000001.10	CCDS13.1
ENST00000261499.10	B9D1	NM_015681.6	NC_000017.10	CCDS11205.1
ENST00000369085.8	BAG3	NM_004281.3	NC_000010.10	CCDS7615.1
ENST00000460680	BAP1	NM_004656.3	NC_000003.11	CCDS2853.1
ENST00000260947	BARD1	NM_000465.3	NC_000002.11	CCDS2397.1
ENST00000650064.2	BBS10	NM_024685.4	NC_000012.11	CCDS9014.2
ENST00000270233.12	BCAM	NM_005581.4	NC_000019.9	CCDS12644.1
ENST00000648566.1	BCL10	NM_003921.5	NC_000001.10	CCDS704.1
ENST00000333681.5	BCL2	NM_000633.3	NC_000018.9	CCDS11981.1

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ENST00000342274.8	BCOR	NM_001123383.1	NC_000023.10	CCDS14250.1
ENST00000218147	BCORL1	NM_021946.4	NC_000023.10	CCDS14616.1
ENST00000305877.13	BCR	NM_004327.4	NC_000022.10	CCDS13806.1
ENST00000392111.7	BCS1L	NM_004328.4	NC_000002.11	CCDS2419.1
ENST00000373886.8	BICC1	NM_001080512.3	NC_000010.10	CCDS31206.1
ENST00000316724.10	BIN1	NM_139343.3	NC_000002.11	CCDS2138.1
ENST00000263464.9	BIRC3	NM_001165.5	NC_000011.9	CCDS8315.1
ENST00000355112.8	BLM	NM_000057.2	NC_000015.9	CCDS10363.1
ENST00000224337.10	BLNK	NM_013314.3	NC_000010.10	CCDS7446.1
ENST00000433642.3	BLOC1S3	NM_212550.4	NC_000019.9	CCDS12656.1
ENST00000220531.9	BLOC1S6	NM_012388.3	NC_000015.9	CCDS10126.1
ENST00000295379.2	BMP10	NM_014482.1	NC_000002.11	CCDS1890.1
ENST00000649409.2	BMPER	NM_001365308.1	NC_000007.13	CCDS5442.1
ENST00000372037	BMPR1A	NM_004329.2	NC_000010.10	CCDS7378.1
ENST00000374580.10	BMPR2	NM_001204.6	NC_000002.11	CCDS33361.1
ENST00000646891.1	BRAF	NM_004333.4	NC_000007.13	CCDS5863.1
ENST00000357654	BRCA1	NM_007294.3	NC_000017.10	CCDS11453.1
ENST00000544455	BRCA2	NM_000059.3	NC_000013.10	CCDS9344.1
ENST00000259008	BRIP1	NM_032043.2	NC_000017.10	CCDS11631.1
ENST00000360796.10	BSCL2	NM_001122955.3	NC_000011.9	CCDS44627.1
ENST00000353555.9	BSG	NM_198589.3	NC_000019.9	CCDS12034.1
ENST00000651561.1	BSND	NM_057176.3	NC_000001.10	CCDS602.1
ENST00000256015.5	BTG1	NM_001731.3	NC_000012.11	CCDS9043.1
ENST00000308731.8	BTK	NM_000061.2	NC_000023.10	CCDS14482.1
ENST00000287598	BUB1B	NM_001211.5	NC_000015.9	CCDS10053.1
ENST00000374642.8	C1QA	NM_015991.2	NC_000001.10	CCDS226.1
ENST00000314933	C1QB	NM_000491.3	NC_000001.10	CCDS228.1
ENST00000374639.7	C1QC	NM_001114101.1	NC_000001.10	CCDS227.1
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ENST00000360817.10	C1S	NM_001734.3	NC_000012.11	CCDS31735.1
ENST00000299367.10	C2	NM_000063.4	NC_000006.11	CCDS4728.1
ENST00000245907.11	C3	NM_000064.2	NC_000019.9	CCDS32883.1
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ENST00000435363.7	C4B	NM_001002029.3	NC_000006.11	CCDS47405.1
ENST00000367070.8	C4BPA	NM_000715.4	NC_000001.10	CCDS1477.1
ENST00000367078.8	C4BPB	NM_001017365.3	NC_000001.10	CCDS1476.1
ENST00000223642.3	C5	NM_001735.2	NC_000009.11	CCDS6826.1
ENST00000392122	C6	NM_000065.2	NC_000005.9	CCDS3936.1
ENST00000313164.10	C7	NM_000587.2	NC_000005.9	CCDS47201.1
ENST00000361249.4	C8A	NM_000562.2	NC_000001.10	CCDS606.1
ENST00000371237.9	C8B	NM_000066.2	NC_000001.10	CCDS30730.1
ENST00000371634.7	C8G	NM_000606.3	NC_000009.11	CCDS7017.1
ENST00000263408.5	C9	NM_001737.3	NC_000005.9	CCDS3929.1
ENST00000380003.8	C9orf72	NM_018325.5	NC_000009.11	CCDS6522.1
ENST00000649794.3	CA5A	NM_001739.2	NC_000016.9	CCDS10965.1
ENST00000638009.2	CACNA1A	NM_001127221.1	NC_000019.9	CCDS45999.1
ENST00000399655.6	CACNA1C	NM_000719.6	NC_000012.11	CCDS44794.1
ENST00000356860.8	CACNA2D1	NM_000722.2	NC_000007.13	CCDS5598.1
ENST00000324631.13	CACNB2	NM_201596.3	NC_000010.10	CCDS7125.1
ENST00000300105.7	CACNG2	NM_006078.5	NC_000022.10	CCDS13931.1
ENST00000361010.7	CALCA	NM_001033953.2	NC_000011.9	CCDS31432.1

ensembltranscriptID	namegene	NM	NC	CCDS
ENST00000426151.7	CALCR	NM_001742.4	NC_000007.13	CCDS5631.1
ENST00000291295.14	CALM3	NM_005184.4	NC_000019.9	CCDS33061.1
ENST00000316448.10	CALR	NM_004343.3	NC_000019.9	CCDS12288.1
ENST00000269881.8	CALR3	NM_145046.4	NC_000019.9	CCDS12344.1
ENST00000397163.8	CAPN3	NM_000070.3	NC_000015.9	CCDS45245.1
ENST00000396946.9	CARD11	NM_032415.7	NC_000007.13	CCDS5336.2
ENST00000648509.2	CARD14	NM_001366385.1	NC_000017.10	CCDS11768.1
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ensembltranscriptID	namegene	NM	NC	CCDS
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ensembltranscriptID	namegene	NM	NC	CCDS
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ensembltranscriptID	namegene	NM	NC	CCDS
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ensembltranscriptID	namegene	NM	NC	CCDS
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ENST00000261024.7	SLC40A1	NM_014585.5	NC_000002.11	CCDS2299.1
ENST00000612814	SLC46A1	NM_080669.3	NC_000017.10	CCDS74020.1
ENST00000262418.12	SLC4A1	NM_000342.4	NC_000017.10	CCDS11481.1
ENST00000488495.3	SLC52A3	NM_033409.4	NC_000020.10	CCDS13007.1
ENST00000397528.8	SLC7A7	NM_001126105.2	NC_000014.8	CCDS9574.1
ENST00000256958.3	SLCO1B1	NM_006446.4	NC_000012.11	CCDS8685.1
ENST00000310926.11	SLCO2A1	NM_005630.3	NC_000003.11	CCDS3084.1
ENST00000674182.1	SLFN14	NM_001129820.2	NC_000017.10	CCDS45650.1
ENST00000647374.2	SLITRK6	NM_032229.3	NC_000013.10	CCDS41903.1
ENST00000294008.4	SLX4	NM_032444.2	NC_000016.9	CCDS10506.2
ENST00000342988	SMAD4	NM_005359.5	NC_000018.9	CCDS11950.
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ENST00000349721.8	SMARCA2	NM_003070.5	NC_000009.11	CCDS34977.1
ENST00000344626.10	SMARCA4	NM_003072.5	NC_000019.9	CCDS12253.1
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ENST00000644036.2	SMARCB1	NM_003073.3	NC_000022.10	CCDS13817.1
ENST00000375340.10	SMC1A	NM_001281463.1	NC_000023.10	CCDS75985.1
ENST00000361804.5	SMC3	NM_005445.3	NC_000010.10	CCDS31285.1
ENST00000444870.7	SMIM1	NM_001163724.3	NC_000001.10	CCDS57966.1
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ENST00000249373.8	SMO	NM_005631.5	NC_000007.13	CCDS5811.1
ENST00000379494.4	SMPX	NM_014332.3	NC_000023.10	CCDS14200.1
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ENST00000363593	SNORD118	NR_033294.2	NC_000017.10	-
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ENST00000401959.6	SNU13	NM_001003796.2	NC_000022.10	CCDS33653.1
ENST00000330871.3	SOCS3	NM_003955.4	NC_000017.10	CCDS11756.1
ENST00000270142.11	SOD1	NM_000454.4	NC_000021.8	CCDS33536.1
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ENST00000301691.3	SOST	NM_025237.3	NC_000017.10	CCDS11468.1
ENST00000396884.8	SOX10	NM_006941.3	NC_000022.10	CCDS13964.1
ENST00000258381	SOX2	NM_003106.2	NC_000003.11	CCDS3239.1
ENST00000373578	SP110	NM_080424.2	NC_000002.11	CCDS2475.1
ENST00000315285.9	SPAST	NM_014946.3	NC_000002.11	CCDS1778.1
ENST00000256084.8	SPINK5	NM_006846.3	NC_000005.9	CCDS43382.1
ENST00000504102.6	SPOP	NM_001007228.2	NC_000017.10	CCDS11551.1
ENST00000643759.2	SPTA1	NM_003126.3	NC_000001.10	CCDS41423.1
ENST00000644917.1	SPTB	NM_001355436.2	NC_000014.8	CCDS32099.1
ENST00000262554.7	SPTLC1	NM_006415.2	NC_000009.11	CCDS6692.1
ENST00000216484.7	SPTLC2	NM_004863.3	NC_000014.8	CCDS9865.1
ENST00000392485	SRC	NM_198291.2	NC_000020.10	CCDS13294.1
ENST00000265729.7	SRI	NM_003130.3	NC_000007.13	CCDS5612.1
ENST00000642900.1	SRP72	NM_006947.4	NC_000004.11	CCDS3506.1
ENST00000422622	SRSF2	NM_003016.4	NC_000017.10	CCDS11749.1
ENST00000242729	SSPN	NM_001135823.1	NC_000012.11	CCDS44850.1
ENST00000218089.13	STAG2	NM_001042749.2	NC_000023.10	CCDS43990.1
ENST00000361099.8	STAT1	NM_007315.3	NC_000002.11	CCDS2309.1
ENST00000314128.9	STAT2	NM_005419.4	NC_000012.11	CCDS8917.1

ensembltranscriptID	namegene	NM	NC	CCDS
ENST00000264657.10	STAT3	NM_139276.2	NC_000017.10	CCDS32656.1
ENST00000293328.8	STAT5B	NM_012448.3	NC_000017.10	CCDS11423.1
ENST00000300134.8	STAT6	NM_003153.5	NC_000012.11	CCDS8931.1
ENST00000300737.8	STIM1	NM_003156.3	NC_000011.9	CCDS7749.1
ENST00000330794.9	STING1	NM_198282.4	NC_000005.9	CCDS4215.1
ENST00000326873	STK11	NM_000455.4	NC_000019.9	CCDS45896.1
ENST00000372806.8	STK4	NM_006282.2	NC_000020.10	CCDS13341.1
ENST00000367568.5	STX11	NM_003764.3	NC_000006.11	CCDS5205.1
ENST00000221283.10	STXBP2	NM_006949.2	NC_000019.9	CCDS12181.1
ENST00000369902	SUFU	NM_016169.3	NC_000010.10	CCDS7537.1
ENST00000674285.1	SVOPL	NM_001139456.2	NC_000007.13	CCDS47721.1
ENST00000367255.10	SYNE1	NM_182961.4	NC_000006.11	CCDS5236.2
ENST00000555002.6	SYNE2	NM_182914.3	NC_000014.8	CCDS9761.2
ENST00000324444.9	SYNE4	NM_001039876.3	NC_000019.9	CCDS42553.1
ENST00000629380.3	SYNGAP1	NM_006772.3	NC_000006.11	CCDS34434.2
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ENST00000313288.9	TACC3	NM_006342.3	NC_000004.11	CCDS3352.1
ENST00000601016	TAFAZZIN	NM_000116.5	NC_000023.10	CCDS14748.1
ENST00000354258.5	TAP1	NM_000593.6	NC_000006.11	CCDS4758.1
ENST00000374897.4	TAP2	NM_001290043.2	NC_000006.11	CCDS78129.1
ENST00000434618.7	TAPBP	NM_003190.4	NC_000006.11	CCDS34426.1
ENST00000240185.8	TARDBP	NM_007375.3	NC_000001.10	CCDS122.1
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ENST00000332710.8	TBX1	NM_080647.1	NC_000022.10	CCDS13767.1
ENST00000408931.4	TBX20	NM_001077653.2	NC_000007.13	CCDS43568.1
ENST00000644296.1	TBX4	NM_001321120.2	NC_000017.10	CCDS82180.1
ENST00000310346.8	TBX5	NM_000192.3	NC_000012.11	CCDS9173.1
ENST00000375190.10	TBXA2R	NM_001060.5	NC_000019.9	CCDS42467.1
ENST00000650822.1	TBXAS1	NM_001130966.2	NC_000007.13	CCDS5855.1
ENST00000309889.3	TCAP	NM_003673.3	NC_000017.10	CCDS11342.1
ENST00000359486.8	TCF20	NM_005650.4	NC_000022.10	CCDS14033.1
ENST00000367882.5	TCF21	NM_003206.3	NC_000006.11	CCDS5167.1
ENST00000588136.7	TCF3	NM_001136139.4	NC_000019.9	CCDS45899.1
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ENST00000215838.8	TCN2	NM_000355.2	NC_000022.10	CCDS13881.1
ENST00000602385	TERC	NR_001566.1	NC_000003.11	-
ENST00000300086.5	TERF2IP	NM_018975.4	NC_000016.9	CCDS32491.1
ENST00000310581.10	TERT	NM_198253.2	NC_000005.9	CCDS3861.2
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ENST00000233156.9	TFPI	NM_006287.6	NC_000002.11	CCDS2294.1
ENST00000222543.11	TFPI2	NM_006528.4	NC_000007.13	CCDS5632.1
ENST00000238682.8	TGFB3	NM_003239.2	NC_000014.8	CCDS9846.1
ENST00000359013.4	TGFBR2	NM_001024847.2	NC_000003.11	CCDS33727.1
ENST00000377103	THBD	NM_000361.2	NC_000020.10	CCDS13148.1
ENST00000647395.1	THPO	NM_000460.4	NC_000003.11	CCDS3265.1
ENST00000248244.6	TICAM1	NM_182919.3	NC_000019.9	CCDS12136.1
ENST00000267415.12	TINF2	NM_001099274.3	NC_000014.8	CCDS41936.1
ENST00000377245.9	TJP2	NM_004817.4	NC_000009.11	CCDS6627.1
ENST00000296795.8	TLR3	NM_003265.2	NC_000004.11	CCDS3846.1
ENST00000355622.8	TLR4	NM_138554.5	NC_000009.11	CCDS6818.1
ENST00000380659	TLR7	NM_016562.4	NC_000023.10	CCDS14151.1

ensembltranscriptID	namegene	NM	NC	CCDS
ENST00000322914.7	TMC6	NM_007267.6	NC_000017.10	CCDS32748.1
ENST00000318430.10	TMC8	NM_152468.4	NC_000017.10	CCDS32749.1
ENST00000432959.1	TMEM127	NM_017849.3	NC_000002.11	CCDS2018.1
ENST00000334888.9	TMEM216	NM_001173991.3	NC_000011.9	CCDS86205.1
ENST00000306077.5	TMEM43	NM_024334.2	NC_000003.11	CCDS2618.1
ENST00000453321.8	TMEM67	NM_153704.5	NC_000008.10	CCDS6258.2
ENST00000556029.6	TMPO	NM_001032283.2	NC_000012.11	CCDS31879.1
ENST00000332149.10	TMPRSS2	NM_005656.4	NC_000021.8	CCDS33564.1
ENST00000346753.9	TMPRSS6	NM_153609.4	NC_000022.10	CCDS74856.1
ENST00000586569.3	TNFRSF11A	NM_003839.2	NC_000018.9	CCDS11980.1
ENST00000261652.7	TNFRSF13B	NM_012452.2	NC_000017.10	CCDS11181.1
ENST00000291232.5	TNFRSF13C	NM_052945.3	NC_000022.10	CCDS14024.1
ENST00000162749.7	TNFRSF1A	NM_001065.3	NC_000012.11	CCDS8542.1
ENST00000379236.4	TNFRSF4	NM_003327.4	NC_000001.10	CCDS11.1
ENST00000293825.11	TNFSF12	NM_003809.3	NC_000017.10	CCDS11109.1
ENST00000232975.8	TNNC1	NM_003280.2	NC_000003.11	CCDS2857.1
ENST00000381911.6	TNNI2	NM_003282.4	NC_000011.9	CCDS31333.1
ENST00000344887.10	TNNI3	NM_000363.4	NC_000019.9	CCDS42628.1
ENST00000326637.8	TNNI3K	NM_015978.3	NC_000001.10	CCDS664.1
ENST00000588981.6	TNNT1	NM_003283.6	NC_000019.9	CCDS12917.1
ENST00000656932.1	TNNT2	NM_001276345.2	NC_000001.10	CCDS73003.1
ENST00000278317.11	TNNT3	NM_006757.4	NC_000011.9	CCDS7727.1
ENST00000351698.5	TOR1A	NM_000113.3	NC_000009.11	CCDS6930.1
ENST00000269305	TP53	NM_000546.5	NC_000017.10	CCDS11118.1
ENST00000264731.8	TP63	NM_003722.5	NC_000003.11	CCDS3293.1
ENST00000396705.10	TPI1	NM_000365.6	NC_000012.11	CCDS8566.1
ENST00000403994.9	TPM1	NM_001018005.2	NC_000015.9	CCDS45273.1
ENST00000378292.9	TPM2	NM_213674.1	NC_000009.11	CCDS6586.1
ENST00000323144.12	TPM3	NM_001043353.2	NC_000001.10	CCDS41401.1
ENST00000643579.2	TPM4	NM_003290.3	NC_000019.9	CCDS12338.1
ENST00000309983.5	TPMT	NM_000367.5	NC_000006.11	CCDS4543.1
ENST00000299427.12	TPP1	NM_000391.4	NC_000011.9	CCDS7770.1
ENST00000376052.5	TPP2	NM_001330588.2	NC_000013.10	CCDS81777.1
ENST00000409012.6	TPRN	NM_001128228.3	NC_000009.11	CCDS56594.1
ENST00000392745.8	TRAF3	NM_145725.2	NC_000014.8	CCDS9975.1
ENST00000368761.11	TRAF3IP2	NM_147686.4	NC_000006.11	CCDS5093.1
ENST00000648948.2	TRAPPC9	NM_031466.8	NC_000008.10	CCDS55278.1
ENST00000373113.8	TREM2	NM_018965.3	NC_000006.11	CCDS4852.1
ENST00000625293.3	TREX1	NM_033629.6	NC_000003.11	CCDS2769.1
ENST00000450136.2	TRIM32	NM_012210.3	NC_000009.11	CCDS6817.1
ENST00000374272.4	TRIM63	NM_032588.3	NC_000001.10	CCDS273.1
ENST00000251607.11	TRNT1	NM_182916.3	NC_000003.11	CCDS2561.2
ENST00000646667.1	TRPM7	NM_017672.6	NC_000015.9	CCDS42035.1
ENST00000261740.7	TRPV4	NM_021625.4	NC_000012.11	CCDS9134.1
ENST00000298552	TSC1	NM_000368.4	NC_000009.11	CCDS6956.1
ENST00000219476	TSC2	NM_000548.3	NC_000016.9	CCDS10458.1
ENST00000298171.7	TSHR	NM_000369.2	NC_000014.8	CCDS9872.1
ENST00000368608	TSPYL1	NM_003309.3	NC_000006.11	CCDS34518.1
ENST00000358746.7	TTC37	NM_014639.3	NC_000005.9	CCDS4072.1
ENST00000319190.11	TTC7A	NM_020458.4	NC_000002.11	CCDS33193.1
ENST00000589042	TTN	NM_001267550.1	NC_000002.11	CCDS59435.1
ENST00000237014.8	TTR	NM_000371.3	NC_000018.9	CCDS11899.1

ensembltranscriptID	namegene	NM	NC	CCDS
ENST00000217133.2	TUBB1	NM_030773.3	NC_000020.10	CCDS13475.1
ENST00000400521.7	TXNRD2	NM_006440.3	NC_000022.10	CCDS42981.1
ENST00000525621.6	TYK2	NM_003331.4	NC_000019.9	CCDS12236.1
ENST00000395680.6	TYMP	NM_001257988.1	NC_000022.10	CCDS14096.1
ENST00000323274.15	TYMS	NM_001071.2	NC_000018.9	CCDS11821.1
ENST00000262629.9	TYROBP	NM_003332.3	NC_000019.9	CCDS12482.1
ENST00000380276.6	U2AF1	NM_001025203.1	NC_000021.8	CCDS33574.1
ENST00000450554	U2AF2	NM_007279.2	NC_000019.9	CCDS12933.1
ENST00000646651.1	UBE2T	NM_014176.4	NC_000001.10	CCDS1425.1
ENST00000438097	UBE3A	NM_130838.1	NC_000015.9	CCDS32177.1
ENST00000338222	UBQLN2	NM_013444.3	NC_000023.10	CCDS14374.1
ENST00000305208.10	UGT1A1	NM_000463.2	NC_000002.11	CCDS2510.1
ENST00000335765.9	UNC119	NM_005148.3	NC_000017.10	CCDS11233.1
ENST00000207549.9	UNC13D	NM_199242.2	NC_000017.10	CCDS11730.1
ENST00000227471.7	UNC93B1	NM_030930.2	NC_000011.9	CCDS73334.1
ENST00000242576.7	UNG	NM_080911.1	NC_000012.11	CCDS9124.1
ENST00000246337.9	UROD	NM_000374.5	NC_000001.10	CCDS518.1
ENST00000368797.10	UROS	NM_000375.3	NC_000010.10	CCDS7648.1
ENST00000219281.8	USB1	NM_024598.3	NC_000016.9	CCDS10791.1
ENST00000614341.5	USH1G	NM_173477.5	NC_000017.10	CCDS32725.1
ENST00000372429.8	USP20	NM_001110303.4	NC_000009.11	CCDS43892.1
ENST00000475243.6	VAPB	NM_004738.4	NC_000020.10	CCDS33498.1
ENST00000211998.10	VCL	NM_014000.2	NC_000010.10	CCDS7341.1
ENST00000358901.11	VCP	NM_007126.3	NC_000009.11	CCDS6573.1
ENST00000256474	VHL	NM_000551.3	NC_000003.11	CCDS2597.1
ENST00000557658.6	VIPAS39	NM_001193315.2	NC_000014.8	CCDS9862.1
ENST00000394975.3	VKORC1	NM_024006.6	NC_000023.10	CCDS10703.1
ENST00000330374.7	VMA21	NM_001017980.3	NC_000008.10	CCDS35430.1
ENST00000358544.7	VPS13B	NM_017890.4	NC_000001.10	CCDS6280.1
ENST00000620676.6	VPS13D	NM_015378.4	NC_000015.9	CCDS30588.1
ENST00000333371.8	VPS33B	NM_018668.4	NC_000001.10	CCDS10369.1
ENST00000644510.2	VPS45	NM_007259.5	NC_000014.8	CCDS944.1
ENST00000261405.10	VWF	NM_000552.5	NC_000012.11	CCDS8539.1
ENST00000376701.5	WAS	NM_000377.2	NC_000023.10	CCDS14303.1
ENST00000448612.6	WDR27	NM_182552.5	NC_000006.11	CCDS47520.2
ENST00000226760.5	WFS1	NM_006005.3	NC_000004.11	CCDS3386.1
ENST00000362057.4	WHRN	NM_015404.4	NC_000009.11	CCDS6806.1
ENST00000359761.7	WIPF1	NM_001077269.1	NC_000002.11	CCDS2260.1
ENST00000315939.11	WNK1	NM_018979.4	NC_000012.11	CCDS8506.1
ENST00000316024.9	WRAP53	NM_018081.2	NC_000017.10	CCDS11119.1
ENST00000298139.7	WRN	NM_000553.4	NC_000008.10	CCDS6082.1
ENST00000332351	WT1	NM_024426.3	NC_000011.9	CCDS7878.2
ENST00000381174.10	XG	NM_175569.3	NC_000023.10	CCDS14120.1
ENST00000371199.8	XIAP	NM_001167.3	NC_000023.10	CCDS14606.1
ENST00000378616.5	XK	NM_021083.4	NC_000023.10	CCDS14241.1
ENST00000375128.5	XPA	NM_000380.3	NC_000009.11	CCDS6729.1
ENST00000285021	XPC	NM_004628.4	NC_000003.11	CCDS46763.1
ENST00000262887.10	XRCC1	NM_006297.2	NC_000019.9	CCDS12624.1
ENST00000359321.2	XRCC2	NM_005431.2	NC_000007.13	CCDS5933.1
ENST00000373477.9	YARS1	NM_003680.3	NC_000001.10	CCDS368.1
ENST00000264972.10	ZAP70	NM_001079.3	NC_000002.11	CCDS33254.1
ENST00000230122.4	ZBTB24	NM_014797.2	NC_000006.11	CCDS34509.1

ensembltranscriptID	namegene	NM	NC	CCDS
ENST00000374423.9	ZDBF2	NM_020923.3	NC_000002.11	CCDS46501.1
ENST00000376335.8	ZIC2	NM_007129.5	NC_000013.10	CCDS9495.1
ENST00000372759.4	ZMPSTE24	NM_005857.3	NC_000001.10	CCDS449.1
ENST00000253144.13	ZNF331	NM_018555.6	NC_000019.9	CCDS33102.1
ENST00000301744.7	ZNF597	NM_152457.3	NC_000016.9	CCDS10505.1
ENST00000433976.7	ZNF778	NM_001201407.1	NC_000016.9	CCDS73928.1
ENST00000307771.8	ZRSR2	NM_005089.3	NC_000023.10	CCDS14172.1

6. Session info

```
sessionInfo()
#> R version 4.2.1 (2022-06-23)
#> Platform: x86_64-pc-linux-gnu (64-bit)
#> Running under: Ubuntu 20.04.4 LTS
#>
#> Matrix products: default
#> BLAS:   /usr/lib/x86_64-linux-gnu/blas/libblas.so.3.9.0
#> LAPACK: /usr/lib/x86_64-linux-gnu/lapack/liblapack.so.3.9.0
#>
#> locale:
#>  [1] LC_CTYPE=en_US.UTF-8       LC_NUMERIC=C
#>  [3] LC_TIME=en_GB.UTF-8        LC_COLLATE=en_US.UTF-8
#>  [5] LC_MONETARY=en_GB.UTF-8    LC_MESSAGES=en_US.UTF-8
#>  [7] LC_PAPER=en_GB.UTF-8       LC_NAME=C
#>  [9] LC_ADDRESS=C               LC_TELEPHONE=C
#> [11] LC_MEASUREMENT=en_GB.UTF-8 LC_IDENTIFICATION=C
#>
#> attached base packages:
#> [1] stats     graphics  grDevices utils     datasets  methods   base
#>
#> other attached packages:
#> [1] vaRHC_0.0.0.9000 dplyr_1.0.10
#>
#> loaded via a namespace (and not attached):
#>  [1] Rcpp_1.0.8.3                lattice_0.20-45
#>  [3] binman_0.1.2                Rsamtools_2.12.0
#>  [5] Biostrings_2.64.0           assertthat_0.2.1
#>  [7] digest_0.6.29               utf8_1.2.2
#>  [9] R6_2.5.1                    GenomeInfoDb_1.32.2
#> [11] stats4_4.2.1                evaluate_0.15
#> [13] highr_0.9                   httr_1.4.2
#> [15] pillar_1.7.0                zlibbioc_1.42.0
#> [17] rlang_1.0.4                 rstudioapi_0.13
#> [19] S4Vectors_0.34.0            Matrix_1.4-1
#> [21] rmarkdown_2.13              RMySQL_0.10.23
#> [23] BiocParallel_1.30.3         RSelenium_1.7.7
#> [25] wdman_0.2.5                 stringr_1.4.0
#> [27] RCurl_1.98-1.7              DelayedArray_0.22.0
#> [29] compiler_4.2.1              rtracklayer_1.56.1
#> [31] xfun_0.30                   pkgconfig_2.0.3
```

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#> [33] askpass_1.1                 BiocGenerics_0.42.0
#> [35] htmltools_0.5.2             openssl_2.0.0
#> [37] tidyselect_1.1.2            SummarizedExperiment_1.26.1
#> [39] tibble_3.1.6                GenomeInfoDbData_1.2.8
#> [41] IRanges_2.30.0              codetools_0.2-18
#> [43] matrixStats_0.62.0          XML_3.99-0.10
#> [45] fansi_1.0.3                 crayon_1.5.1
#> [47] GenomicAlignments_1.32.1    bitops_1.0-7
#> [49] grid_4.2.1                  jsonlite_1.8.0
#> [51] lifecycle_1.0.1             DBI_1.1.2
#> [53] semver_0.2.0                magrittr_2.0.3
#> [55] cli_3.4.1                   stringi_1.7.6
#> [57] XVector_0.36.0              xml2_1.3.3
#> [59] ellipsis_0.3.2              generics_0.1.2
#> [61] vctrs_0.4.1                 rjson_0.2.21
#> [63] restfulr_0.0.15             tools_4.2.1
#> [65] Biobase_2.56.0              glue_1.6.2
#> [67] purrr_0.3.4                 MatrixGenerics_1.8.1
#> [69] parallel_4.2.1              fastmap_1.1.0
#> [71] yaml_2.3.5                  GenomicRanges_1.48.0
#> [73] caTools_1.18.2              knitr_1.38
#> [75] BiocIO_1.6.0
```