

Overview of `ensemblVEP` Pre Ensembl 90

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Contents

1	Introduction	1
2	Results as R objects	1
3	Write results to a file	4
4	Configuring runtime options	4
5	<code>sessionInfo()</code>	5

1 Introduction

Ensembl provides the facility to predict functional consequences of known and unknown variants using the Variant Effect Predictor (VEP). The `ensemblVEP` package wraps Ensembl VEP and returns the results as R objects or a file on disk. To use this package the Ensembl VEP perl script must be installed in your path. See the package README for details.

NOTE: As of Ensembl version 88 the VEP script has been renamed from `variant_effect_predictor.pl` to `vep`. The `ensemblVEP` package code and documentation have been updated to reflect this change.

Downloads: <http://uswest.ensembl.org/info/docs/tools/vep/index.html>

Complete documentation for runtime options: http://uswest.ensembl.org/info/docs/tools/vep/script/vep_options.html

To test that Ensembl VEP is properly installed, enter the name of the script from the command line:

```
vep
```

2 Results as R objects

```
> library(ensemblVEP)
```

The `ensemblVEP` function can return variant consequences from Ensembl VEP as R objects (`GRanges` or `VCF`) or write them to a file. The default behavior returns a `GRanges`. Runtime options are stored in a `VEPParam` object and allow a great deal of control over the content and format of the results. See the man pages for more details.

```
> ?ensemblVEP
> ?VEPParam
```

The default runtime options can be inspected by creating a `VEPParam`.

```
> param <- VEPParam(version=88)
> param
```

```
class: VEPParam88
identifier(0):
colocatedVariants(0):
dataformat(0):
basic(0):
input(1): species
```

```

cache(3): dir, dir_cache, dir_plugins
output(1): terms
filterqc(0):
database(1): database
advanced(1): buffer_size
version: 88
scriptPath:

```

```
> basic(param)
```

```
$verbose
[1] FALSE
```

```
$quiet
[1] FALSE
```

```
$no_progress
[1] FALSE
```

```
$config
character(0)
```

```
$everything
[1] FALSE
```

```
$fork
numeric(0)
```

Using a vcf file from VariantAnnotation as input, we query Ensembl VEP with the default runtime parameters.

```

> fl <- system.file("extdata", "gl_chr1.vcf", package="VariantAnnotation")
> gr <- ensemblVEP(fl)

```

Consequence data are parsed into the metadata columns of the GRanges. To control the type and amount of data returned see the options in output(VEPParam()).

```
> head(gr, 3)
```

GRanges object with 3 ranges and 23 metadata columns:

	seqnames	ranges	strand	Allele					
	<Rle>	<IRanges>	<Rle>	<factor>					
	rs6054257	20 [14370, 14370]	*		A				
	20:17330_T/A	20 [17330, 17330]	*		A				
	rs6040355	20 [1110696, 1110696]	*		G				
		Consequence	IMPACT	SYMBOL	Gene				
		<factor>	<factor>	<factor>	<factor>				
	rs6054257	intergenic_variant	MODIFIER	<NA>	<NA>				
	20:17330_T/A	intergenic_variant	MODIFIER	<NA>	<NA>				
	rs6040355	upstream_gene_variant	MODIFIER	PSMF1	ENSG00000125818				
		Feature_type	Feature	BIOTYPE	EXON				
		<factor>	<factor>	<factor>	<factor>				
	rs6054257	<NA>	<NA>	<NA>	<NA>				
	20:17330_T/A	<NA>	<NA>	<NA>	<NA>				
	rs6040355	Transcript	ENST00000479715	processed_transcript	<NA>				
		INTRON	HGVSc	HGVSp	cDNA_position	CDS_position			
		<factor>	<factor>	<factor>	<factor>	<factor>			
	rs6054257	<NA>	<NA>	<NA>	<NA>	<NA>			
	20:17330_T/A	<NA>	<NA>	<NA>	<NA>	<NA>			
	rs6040355	<NA>	<NA>	<NA>	<NA>	<NA>			
		Protein_position	Amino_acids	Codons	Existing_variation				
		<factor>	<factor>	<factor>	<factor>				

```

rs6054257      <NA>      <NA>      <NA>      <NA>
20:17330_T/A   <NA>      <NA>      <NA>      <NA>
rs6040355     <NA>      <NA>      <NA>      <NA>

```

```

      DISTANCE  STRAND  FLAGS SYMBOL_SOURCE  HGNC_ID
      <factor> <factor> <factor>      <factor> <factor>
rs6054257     <NA>     <NA>     <NA>      <NA>     <NA>
20:17330_T/A  <NA>     <NA>     <NA>      <NA>     <NA>
rs6040355     2610      1        <NA>      HGNC HGNC:9571

```

```
-----
```

```
seqinfo: 1 sequence from genome
```

Next we use a vcf of structural variants as input

```
> fl <- system.file("extdata", "structural.vcf", package="VariantAnnotation")
```

and request that a VCF object be returned by setting the *vcf* option in the *dataformat* slot to TRUE.

```
> param <- VEPParam(dataformat=c(vcf=TRUE), version=88)
```

An call to *ensemblVEP* results in an error.

```
> vcf <- ensemblVEP(fl, param)
2012-12-03 16:40:55 - Starting...
ERROR: Could not detect input file format
```

In most situations Ensembl VEP can auto-detect the input format. In this case, however, it cannot so we explicitly set the *format* option to 'vcf'.

```
> input(param)$format <- "vcf"
```

Try again.

```
> vep <- ensemblVEP(fl, param)
```

Success! When a VCF is returned, consequence data are included as an unparsed INFO column labeled *CSQ*.

```
> info(vep)$CSQ
```

```
CharacterList of length 0
```

The *parseCSQToGRanges* function parses these data into a *GRanges*. When the rownames of the original VCF are provided as *VCFRowID* a metadata column of the same name is included in the output.

```
> vcf <- readVcf(fl, "hg19")
> csq <- parseCSQToGRanges(vep, VCFRowID=rownames(vcf))
> head(csq, 3)
```

```
GRanges object with 0 ranges and 23 metadata columns:
```

```

seqnames  ranges strand | Allele Consequence  IMPACT  SYMBOL
  <Rle> <IRanges> <Rle> | <character> <character> <character> <character>
      Gene Feature_type  Feature  BIOTYPE  EXON  INTRON
<character> <character> <character> <character> <character> <character>
      HGVS  HGVS  cDNA_position CDS_position Protein_position
<character> <character> <character> <character> <character>
Amino_acids  Codons Existing_variation  DISTANCE  STRAND
<character> <character> <character> <character> <character>
      FLAGS SYMBOL_SOURCE  HGNC_ID
<character> <character> <character>

```

```
-----
```

```
seqinfo: no sequences
```

The *VCFRowID* columns maps the expanded *CSQ* data back to the rows in the *VCF* object. This index can be used to subset the original VCF.

```

> vcf[csq$"VCFRowID"]

class: CollapsedVCF
dim: 0 1
rowRanges(vcf):
  GRanges with 5 metadata columns: paramRangeID, REF, ALT, QUAL, FILTER
info(vcf):
  DataFrame with 10 columns: BKPTID, CIEND, CIPOS, END, HOMLEN, HOMSEQ, IMPR...
info(header(vcf)):
  Number Type Description
BKPTID . String ID of the assembled alternate allele in the asse...
CIEND 2 Integer Confidence interval around END for imprecise var...
CIPOS 2 Integer Confidence interval around POS for imprecise var...
END 1 Integer End position of the variant described in this re...
HOMLEN . Integer Length of base pair identical micro-homology at ...
HOMSEQ . String Sequence of base pair identical micro-homology a...
IMPRECISE 0 Flag Imprecise structural variation
MEINFO 4 String Mobile element info of the form NAME,START,END,P...
SVLEN . Integer Difference in length between REF and ALT alleles
SVTYPE 1 String Type of structural variant
geno(vcf):
  List of length 4: GT, GQ, CN, CNQ
geno(header(vcf)):
  Number Type Description
GT 1 String Genotype
GQ 1 Float Genotype quality
CN 1 Integer Copy number genotype for imprecise events
CNQ 1 Float Copy number genotype quality for imprecise events

```

3 Write results to a file

In the previous section we saw Ensembl VEP results returned as R objects in the workspace. Alternatively, these results can be written directly to a file. The flag that controls how the data are returned is the *output_file* flag in the *input* options.

When *output_file* is an empty character (default), the results are returned as either a *GRanges* or *VCF* object.

```

> input(param)$output_file

character(0)

```

To write results directly to a file, specify a file name for the *output_file* flag.

```

> input(param)$output_file <- "/mypath/myfile"

```

The file can be written as a *vcf* or *gvf* by setting the options in the *dataformat* slot to TRUE. If neither of *vcf* or *gvf* are TRUE the file is written out as tab delimited.

```

> ## Write a vcf file to myfile.vcf:
> myparam <- VEPParam(dataformat=c(vcf=TRUE),
+                       input=c(output_file="/path/myfile.vcf"), version=88)
> ## Write a gvf file to myfile.gvf:
> myparam <- VEPParam(dataformat=c(gvf=TRUE),
+                       input=c(output_file="/path/myfile.gvf"), version=88)
> ## Write a tab delimited file to myfile.txt:
> myparam <- VEPParam(input=c(output_file="/path/myfile.txt"), version=88)

```

4 Configuring runtime options

The Ensembl VEP web page has complete descriptions of all runtime options. http://uswest.ensembl.org/info/docs/tools/vep/script/vep_options.html Below are examples of how to configure the runtime options in the *VEP-Param* for specific situations. Investigate the differences in results using a sample file from *VariantAnnotation*.

```
> fl <- system.file("extdata", "ex2.vcf", package="VariantAnnotation")
```

- Add regulatory region consequences:

```
> param <- VEPPParam(output=c(regulatory=TRUE), version=88)
> gr <- ensemblVEP(fl, param)
```

- Specify input file format as VCF, add HGNC gene identifiers, output SO consequence terms:

```
> param <- VEPPParam(input=c(format="vcf"),
+                     output=c(terms="so"),
+                     identifiers=c(symbol=TRUE), version=88)
> gr <- ensemblVEP(fl, param)
```

- Check for co-located variants, output only coding sequence consequences, output HGVS names:

```
> param <- VEPPParam(filterqc=c(coding_only=TRUE),
+                     colocatedVariants=c(check_existing=TRUE),
+                     identifiers=c(symbol=TRUE), version=88)
> gr <- ensemblVEP(fl, param)
```

- Add SIFT score and prediction, PolyPhen prediction only, output results as VCF:

```
fl <- system.file("extdata", "chr22.vcf.gz", package="VariantAnnotation")
param <- VEPPParam(output=c(sift="b", polyphen="p"),
                   dataformat=c(vcf=TRUE), version=88)
vcf <- ensemblVEP(fl, param)
csq <- parseCSQToGRanges(vcf)
```

```
> head(levels(mcols(csq)$SIFT))
[1] "deleterious(0.01)" "deleterious(0.02)" "deleterious(0.03)"
[4] "deleterious(0.04)" "deleterious(0.05)" "deleterious(0)"
```

```
> levels(mcols(csq)$PolyPhen)
[1] "benign"           "possibly_damaging" "probably_damaging"
[4] "unknown"
```

5 sessionInfo()

```
> sessionInfo()
```

```
R version 4.0.0 (2020-04-24)
```

```
Platform: x86_64-pc-linux-gnu (64-bit)
```

```
Running under: Ubuntu 18.04.4 LTS
```

```
Matrix products: default
```

```
BLAS: /home/biocbuild/bbs-3.11-bioc/R/lib/libRblas.so
```

```
LAPACK: /home/biocbuild/bbs-3.11-bioc/R/lib/libRlapack.so
```

```
locale:
```

```
[1] LC_CTYPE=en_US.UTF-8      LC_NUMERIC=C
[3] LC_TIME=en_US.UTF-8      LC_COLLATE=C
[5] LC_MONETARY=en_US.UTF-8  LC_MESSAGES=en_US.UTF-8
[7] LC_PAPER=en_US.UTF-8     LC_NAME=C
[9] LC_ADDRESS=C             LC_TELEPHONE=C
[11] LC_MEASUREMENT=en_US.UTF-8 LC_IDENTIFICATION=C
```

```
attached base packages:
```

```
[1] stats4    parallel  stats     graphics  grDevices  utils     datasets
[8] methods  base
```

other attached packages:

[1]	ensemblVEP_1.30.0	VariantAnnotation_1.34.0
[3]	Rsamtools_2.4.0	Biostrings_2.56.0
[5]	XVector_0.28.0	SummarizedExperiment_1.18.0
[7]	DelayedArray_0.14.0	matrixStats_0.56.0
[9]	Biobase_2.48.0	GenomicRanges_1.40.0
[11]	GenomeInfoDb_1.24.0	IRanges_2.22.0
[13]	S4Vectors_0.26.0	BiocGenerics_0.34.0

loaded via a namespace (and not attached):

[1]	progress_1.2.2	tidyselect_1.0.0	purrr_0.3.4
[4]	lattice_0.20-41	vctrs_0.2.4	BiocFileCache_1.12.0
[7]	rtracklayer_1.48.0	GenomicFeatures_1.40.0	blob_1.2.1
[10]	XML_3.99-0.3	rlang_0.4.5	pillar_1.4.3
[13]	glue_1.4.0	DBI_1.1.0	rappdirs_0.3.1
[16]	BiocParallel_1.22.0	bit64_0.9-7	dbplyr_1.4.3
[19]	GenomeInfoDbData_1.2.3	lifecycle_0.2.0	stringr_1.4.0
[22]	zlibbioc_1.34.0	memoise_1.1.0	biomaRt_2.44.0
[25]	curl_4.3	AnnotationDbi_1.50.0	Rcpp_1.0.4.6
[28]	BSgenome_1.56.0	openssl_1.4.1	bit_1.1-15.2
[31]	hms_0.5.3	askpass_1.1	digest_0.6.25
[34]	stringi_1.4.6	dplyr_0.8.5	grid_4.0.0
[37]	tools_4.0.0	bitops_1.0-6	magrittr_1.5
[40]	RCurl_1.98-1.2	RSQLite_2.2.0	tibble_3.0.1
[43]	crayon_1.3.4	pkgconfig_2.0.3	ellipsis_0.3.0
[46]	Matrix_1.2-18	prettyunits_1.1.1	assertthat_0.2.1
[49]	httr_1.4.1	R6_2.4.1	GenomicAlignments_1.24.0
[52]	compiler_4.0.0		