

Overview of `ensemblVEP` Pre Ensembl 90

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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(2): host, 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>	<NA>	<NA>	
20:17330_T/A	<NA>	<NA>	<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>	<NA>	
20:17330_T/A	<NA>	<NA>	<NA>	<NA>	<NA>	<NA>	
rs6040355	<NA>	<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):
  SimpleList 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 3.4.3 (2017-11-30)
```

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

```
Running under: Ubuntu 16.04.4 LTS
```

```
Matrix products: default
```

```
BLAS: /home/biocbuild/bbs-3.6-bioc/R/lib/libRblas.so
```

```
LAPACK: /home/biocbuild/bbs-3.6-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_1.20.1	VariantAnnotation_1.24.5
[3]	Rsamtools_1.30.0	Biostrings_2.46.0
[5]	XVector_0.18.0	SummarizedExperiment_1.8.1
[7]	DelayedArray_0.4.1	matrixStats_0.53.1
[9]	Biobase_2.38.0	GenomicRanges_1.30.3
[11]	GenomeInfoDb_1.14.0	IRanges_2.12.0
[13]	S4Vectors_0.16.0	BiocGenerics_0.24.0

loaded via a namespace (and not attached):

[1]	Rcpp_0.12.16	compiler_3.4.3	pillar_1.2.1
[4]	prettyunits_1.0.2	GenomicFeatures_1.30.3	bitops_1.0-6
[7]	tools_3.4.3	zlibbioc_1.24.0	progress_1.1.2
[10]	biomaRt_2.34.2	digest_0.6.15	bit_1.1-12
[13]	BSgenome_1.46.0	RSQLite_2.0	memoise_1.1.0
[16]	tibble_1.4.2	lattice_0.20-35	rlang_0.2.0
[19]	Matrix_1.2-12	DBI_0.8	GenomeInfoDbData_1.0.0
[22]	rtracklayer_1.38.3	httr_1.3.1	stringr_1.3.0
[25]	bit64_0.9-7	grid_3.4.3	R6_2.2.2
[28]	AnnotationDbi_1.40.0	XML_3.98-1.10	RMySQL_0.10.14
[31]	BiocParallel_1.12.0	magrittr_1.5	blob_1.1.0
[34]	GenomicAlignments_1.14.1	assertthat_0.2.0	stringi_1.1.7
[37]	RCurl_1.95-4.10		