

Use the Ensembl VEP online to analyse your variants through a simple point-and-click interface.

The web interface allows you to access the key features of the Ensembl VEP without using the command line. Interactively filter your results to find the data you want. Download your results in multiple data formats, easily share your results with others, and integrate your variation data with the powerful Ensembl web browser.

If you use the Ensembl VEP in your work, please cite **McLaren et. al.** ([doi:10.1186/s13059-016-0974-4](https://doi.org/10.1186/s13059-016-0974-4))

See our latest tutorial [Annotating and prioritizing genomic variants using the Ensembl Variant Effect Predictor – A tutorial](#) for more information on using the Ensembl VEP web interface.

Any questions? Send an email to the Ensembl developer's mailing list, dev@ensembl.org or contact the Ensembl Helpdesk at helpdesk@ensembl.org.



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When you reach the Ensembl VEP web interface, you will be presented with a form to enter your data and alter various options.

Note that the listed options change depending on the selected species.

Data input

1. First select the correct species for your data. Ensembl hosts many vertebrate genomes; genomes for plants, protists and fungi can be found at [Ensembl Genomes](#).
2. You can optionally choose a name for the data you upload - this can make it easier for you to identify jobs and files that you have uploaded to the Ensembl VEP at a later point.
3. You have three options for uploading your data:
 - **File upload** - click the "Choose file" button and locate the file on your system. Please ensure your files are sorted by location if you are using VCF or other input formats using location. This greatly improves speed of analysis
 - **Paste file** - simply copy and paste the contents of your file into the large text box
 - **File URL** - point the Ensembl VEP to a file hosted on a publically accessible address. This can be either a **http://** or **ftp://** address.

Once you have uploaded some data, you can select it as the input for future jobs by choosing the data from the drop down menu.

The format of your data is automatically detected; see the examples or the [input format](#) documentation.

4. For pasted data you can get an instant preview of the results of your first variant by clicking the button that appears when you paste your data. This quickly shows you the consequence type, the IDs of any overlapping variants, genes, transcripts and regulatory features, as well as SIFT and PolyPhen predictions. To see the full results set submit your job as normal.
5. For some species you can select which transcript database to use. The default is to use Ensembl transcripts, which offer the most rich annotation through Ensembl VEP.

GENCODE Basic is a subset of the GENCODE gene set, and is intended to provide a simplified, high-quality subset of the GENCODE transcript annotations that will be useful to the majority of users. GENCODE Basic includes all genes in the GENCODE gene set, with a representative subset of the transcripts (splice variants).

GENCODE Primary is a new transcript subset which covers all human exons in a minimal set of transcripts. This aims to enable annotation of all potential variant consequences without duplication across multiple transcripts.

You can also select to use RefSeq transcripts from the [otherfeatures database](#); note though that these transcripts are simply aligned to the reference genome and the database is missing much of the annotation found when using the main Ensembl database (e.g. protein domains, CCDS identifiers).

Species:

 Homo_sapiens

Assembly: GRCh38.p13
[Change species](#)
If you are looking for Ensembl VEP for Human GRCh37, please go to [GRCh37 website](#).

Name for this job (optional):

Input data:

Either paste data:

rs699
rs171
rs665

[Run instant Ensembl VEP for current line](#)

Examples: [Ensembl default](#), [VCF](#), [Variant identifiers](#), [HGVS notations](#), [SPDI](#)

Or upload file: No file chosen

Or provide file URL:

Transcript database to use:

☒ Ensembl/GENCODE transcripts
☐ Ensembl/GENCODE basic transcripts
☐ Ensembl/GENCODE primary transcripts
☐ RefSeq transcripts
☐ Ensembl/GENCODE and RefSeq transcripts

Identifiers

Ensembl VEP can provide additional identifiers for genes, transcripts, proteins and variants.

- **Gene symbol**
Add the gene symbol for the gene to the output. This will typically be, for example, the [HGNC](#) identifier for genes in human. Equivalent to `--symbol` in the Ensembl VEP script.
- **Transcript version**
Add the transcript version to the transcript identifier. Equivalent to `--transcript_version`.
- **CCDS**
Add the [Consensus CDS](#) transcript identifier where available. Equivalent to `--ccds`.
- **Protein**
Add the Ensembl protein identifier (ENSP). Equivalent to `--protein`.
- **UniProt**
Add identifiers for translated protein products from three [UniProt](#)-related databases (SWISSPROT, TrEMBL and UniParc). Equivalent to `--uniprot`.
- **HGVS**
Generate [HGVS](#) identifiers for your input variants relative to the transcript coding sequence (HGVSc) and the protein sequence (HGVS p). Equivalent to `--hgvs`.

Identifiers

Additional identifiers for genes, transcripts and variants

Identifiers

Gene symbol:	<input checked="" type="checkbox"/>
Transcript version:	<input checked="" type="checkbox"/>
CCDS:	<input type="checkbox"/>
Protein:	<input type="checkbox"/>
UniProt:	<input type="checkbox"/>
HGVS:	<input type="checkbox"/>

Variants and frequency data

Ensembl VEP can also search the Ensembl database for known variants that are co-located with variants from your input data.

- **Find co-located known variants** - report known variants from the Ensembl Variation database that overlap with your input. A list of variant sources imported can be viewed [here](#). Note that this feature is only available for species with an Ensembl Variation database. Equivalent to `--check_existing`.

Ensembl VEP will by default compares the alleles of your input variant to that of the existing variant; Ensembl VEP will only report the existing variant ID if none of the alleles in your input variant are novel.

For example, if your input variant has alleles A/G, and the existing variant has alleles A/T, then the existing variant will not be reported. If instead your input variant has alleles A/T, then the existing variant will be reported.

To disable this allele matching, select the option "Yes but don't compare alleles" for the option "Find co-located known variants".

For known variants Ensembl VEP can also provide PubMed IDs of publications citing the variant (equivalent to `--pubmed`).

- **Variant synonyms**
Report known synonyms for co-located variants.
- **Frequency data for co-located variants**
Ensembl VEP can also report allele frequency (AF) data for existing variants from several major genotyping projects, the [1000 Genomes Project](#), and [gnomAD](#); this only applies when you have selected human as your species.
 - **1000 Genomes global** - the combined phase 3 population (i.e. all individuals from all populations). Equivalent to `--af`
 - **1000 Genomes continental** - the four continent-level populations - AFR (African), AMR (American), ASN (Asian) and EUR (European). Equivalent to `--af_1kg`
 - **gnomAD exomes** - combined, AFR, AMR, ASJ, EAS, FIN, NFE, OTH, SAS populations. Equivalent to `--af_gnomadg`
 - **gnomAD genomes** - combined, AFR, AMR, AMI, ASJ, EAS, FIN, MID, NFE, OTH, SAS populations. Equivalent to `--af_gnomadg`
- **PubMed IDs for citations of co-located variants**
Report the PubMed IDs of any publications that cite the co-located variant(s).
- **Include flagged variants**
Variants flagged as failed by the Ensembl Variation quality control.

- **Paralogue variants**
Retrieves variants that overlap genomic coordinates corresponding to aligned amino acid positions in paralogous proteins. This functionality is provided by the [Paralogues](#) plugin.
- **Open Targets Genetics**
Returns locus-to-gene (L2G) scores to predict causal genes at GWAS loci from [Open Targets Genetics](#). This functionality is provided by the [OpenTargets](#) plugin.

Variants and frequency data
Co-located variants and frequency data

Variants and frequency data

Find co-located known variants:
Yes

Variant synonyms:
☐

Frequency data for co-located variants:
☒ 1000 Genomes global minor allele frequency
☐ 1000 Genomes continental allele frequencies
☐ gnomAD (exomes) allele frequencies
☐ gnomAD (genomes) allele frequencies

PubMed IDs for citations of co-located variants:
☒

Include flagged variants:
☐

Paralogue variants:
☒ Disabled
☐ Enabled

Open Targets Genetics:
☐

Additional annotations

- **DosageSensitivity**
Retrieves haploinsufficiency and triplosensitivity probability scores for affected genes from a dosage sensitivity catalogue published in paper - <https://www.sciencedirect.com/science/article/pii/S0092867422007887>.
- **LOEUF**
LOEUF stands for the 'loss-of-function observed/expected upper bound fraction'. This plugin adds constraint scores derived from gnomAD to Ensembl VEP. Equivalent to the Ensembl VEP plugin [LOEUF](#).
- **Transcript biotype**
Add the [transcript biotype](#) to the output. Equivalent to `--biotype` in the Ensembl VEP script.
- **Exon and intron numbers**
Report the exon or intron number that a variant falls in as NUMBER / TOTAL, i.e. exon 2/5 means the variant falls in the 2nd of 5 exons in the transcript. Equivalent to `--numbers`.
- **Transcript support level**
Report the [transcript support level](#) of the overlapped transcript. Equivalent to `--tsl`.
- **APPRIS**
Report the [APPRIS](#) score of the overlapped transcript. Equivalent to `--appris`.
- **Identify canonical transcripts**
Add a flag to the output indicating if the reported transcript is the [canonical transcript](#) for the gene. Equivalent to `--canonical`.
- **Upstream/Downstream distance (bp)**
Change the distance to assign the upstream and downstream consequences. Equivalent to `--distance`.
- **miRNA structure**
Determines where in the secondary structure of a miRNA a variant falls (only for Ensembl/GENCODE transcripts). Equivalent to `--mirna`.
- **NMD**
Predicts if a stop_gained variant allows the transcript to escape nonsense-mediated mRNA decay based on certain rules. This functionality is provided by the [NMD](#) plugin.
- **UTRAnnotator**
Annotates the effect of 5' UTR variant especially for variant creating/disrupting upstream ORFs. This functionality is provided by the [UTRAnnotator](#) plugin.

- **RiboseqORFs**

Annotates the consequences of variants overlapping Ribo-seq ORFs. This functionality is provided by the [RiboseqORFs](#) plugin.

- **Protein matches**

Shows the variant location on PDBe and AlphaFold protein structures in interactive 3d displays, where available. Report [protein domains](#) from [PDBe](#), [Pfam](#), [Prosites](#) and [InterPro](#) that overlap input variants. Equivalent to [--domains](#).

- **mutfunc**

[mutfunc](#) predicts destabilization effect of protein structure, interaction, regulatory region, etc. caused by a variant. This functionality is provided by the [mutfunc](#) plugin.

- **IntAct**

Reports relevant data for variants that falls within molecular interaction site as reported by [IntAct](#) database. This functionality is provided by the [IntAct](#) plugin.

- **MaveDB**

[MaveDB](#) holds experimentally determined measures of variant effect. This functionality is provided by the [MaveDB](#) plugin.

- **Get regulatory region consequences**

In addition to predicting consequences with overlapping transcripts, Ensembl VEP can find overlaps with known regulatory regions as determined in the [Ensembl Regulatory build](#).

Using this option, Ensembl VEP will also report if a variant falls in a transcription factor binding motif, and give a score that reflects whether the altered motif sequence is more or less similar to the consensus.

Get regulatory consequences is equivalent to [--regulatory](#).

- **Enformer**

Predictions of variant impact on gene expression. This functionality is provided by the [Enformer](#) plugin.

- **Phenotypes**

Report the phenotypic data overlapping the genomic features. This functionality is provided by the [Phenotypes](#) plugin.

For more information on the imported phenotypic data for genes, variation and QTLs see [our phenotype documentation](#).

Note: This web functionality is not reporting cancer phenotypic data this release. However the cancer phenotypic data is available in the command line version.

- **Gene Ontology**

Add terms to describe any overlapping gene's function, the cellular component in which the function is performed and the biological processes to which this contributes.

- **Geno2MP**

[Geno2MP](#) is a web-accessible database of rare variant genotypes linked to individual-level phenotypic profiles defined by human phenotype ontology (HPO) terms. This functionality is provided by the [Geno2MP](#) plugin.

- **Mastermind**

Uses the [Mastermind Genomic Search Engine](#) to report variants that have clinical evidence cited in the medical literature. This functionality is provided by the [Mastermind](#) plugin.

Note: This web functionality is only reporting the URL to the Mastermind Genomic Search Engine webpage.

Additional annotations ▾ *Additional transcript, protein and regulatory annotations*

Gene tolerance to change

DosageSensitivity:

☐

LOEUF:

☐

Transcript annotation

Transcript biotype:

☒

Exon and intron numbers:

☐

Transcript support level:

☒

APPRIS:

☒

MANE:

☒

Identify canonical transcripts:	<input type="checkbox"/>
Upstream/Downstream distance (bp):	<input type="text" value="5000"/>
miRNA structure:	<input type="checkbox"/>
NMD:	<input type="checkbox"/>
UTRAnnotator:	<input type="checkbox"/>
RiboseqORFs:	<input type="checkbox"/>
Protein annotation	
Protein matches:	<input type="checkbox"/>
mutfunc:	<input checked="" type="radio"/> Disabled <input type="radio"/> Enabled
Functional effect	
IntAct:	<input checked="" type="radio"/> Disabled <input type="radio"/> Enabled
MaveDB:	<input type="checkbox"/>
Regulatory data	
Get regulatory region consequences:	<input type="text" value="Yes"/>
Regulatory impact	
Enformer:	<input type="checkbox"/>
Phenotype data and citations	
Phenotypes:	<input type="checkbox"/>
Gene Ontology:	<input type="checkbox"/>
Mastermind:	<input type="checkbox"/>

Predictions

- **SIFT predictions**

[SIFT](#) predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids. Only available in popular species. For both SIFT and PolyPhen Ensembl VEP can report either a score between 0 and 1, a prediction in words, or both. Equivalent to [--sift](#).

- **PolyPhen predictions**

[PolyPhen](#) is a tool which predicts possible impact of an amino acid substitution on the structure and function of a human protein using straightforward physical and comparative considerations. Equivalent to [--polyphen](#).

- **dbNSFP**

Retrieves data for missense variants from [dbNSFP](#). Equivalent to the Ensembl VEP plugin [dbNSFP](#).

- **AlphaMissense**

[AlphaMissense](#) is a deep learning model developed by Google DeepMind that predicts the pathogenicity of single nucleotide missense variants. Equivalent to the Ensembl VEP plugin [AlphaMissense](#).

- **CADD**
[Combined Annotation Dependent Depletion \(CADD\)](#) is a tool for scoring the deleteriousness of single nucleotide variants and insertion/deletion variants in the human genome. CADD integrates multiple annotations into one metric by contrasting variants that survived natural selection with simulated mutations. CADD is only available here for non-commercial use. See [CADD website](#) for more information. Equivalent to the Ensembl VEP plugin [CADD](#).
- **REVEL**
[Rare Exome Variant Ensemble Learner \(REVEL\)](#) is an ensemble method for predicting the pathogenicity of missense variants based on a combination of scores from multiple individual tools. REVEL is only available here for non-commercial use. Equivalent to the Ensembl VEP plugin [REVEL](#).
- **ClinPred**
[ClinPred](#) is a prediction tool to identify disease-relevant nonsynonymous single nucleotide variants. The predictor incorporates existing pathogenicity scores and benefits from normal population allele frequencies. ClinPred is only available here for non-commercial use. Equivalent to the Ensembl VEP plugin [ClinPred](#).
- **EVE**
Adds information from [EVE](#) (evolutionary model of variant effect). Equivalent to the Ensembl VEP plugin [EVE](#).

-
- **dbscSNV**
Retrieves data for splicing variants from [dbscSNV](#). Equivalent to the Ensembl VEP plugin [dbscSNV](#).
 - **MaxEntScan**
Get splice site predictions from [MaxEntScan](#). Equivalent to the Ensembl VEP plugin [MaxEntScan](#).
 - **SpliceAI**
Pre-calculated annotations from [SpliceAI](#) a deep neural network, developed by Illumina, Inc that predicts splice junctions from an arbitrary pre-mRNA transcript sequence. Used for non-commercial purposes. This functionality is provided by the [SpliceAI](#) plugin. The pre-calculated annotations for all possible single nucleotide substitutions can be retrieved from:
 - Ensembl/GENCODE v24 canonical transcripts
Masked scores
 - Ensembl/GENCODE v37 MANE transcripts
Raw scores

Note: The pre-calculated annotations for 1 base insertions, and 1-4 base deletions are only available for Ensembl/GENCODE v24 canonical transcripts.

-
- **BLOSUM62**
Looks up the BLOSUM 62 substitution matrix score for the reference and alternative amino acids predicted for a missense mutation. Equivalent to the Ensembl VEP plugin [Blosum62](#).
 - **Ancestral allele**
Retrieves ancestral allele sequences from a FASTA file. Ensembl produces [FASTA file dumps](#) of the ancestral sequences of key species. Equivalent to the Ensembl VEP plugin [AncestralAllele](#).

Predictions Variant predictions, e.g. SIFT, PolyPhen

Pathogenicity predictions

SIFT:

Prediction and score

PolyPhen:

Prediction and score

dbNSFP:

Disabled

Enabled

AlphaMissense:

CADD:

REVEL:

ClinPred:

EVE:

Splicing predictions

dbSNV:	<input type="checkbox"/>
MaxEntScan:	<input type="checkbox"/>
SpliceAI:	<input checked="" type="radio"/> Disabled <input type="radio"/> Enabled
Conservation	
BLOSUM62:	<input type="checkbox"/>
Ancestral allele:	<input type="checkbox"/>

Filtering options

Ensembl VEP allows you to pre-filter your results e.g. by MAF or consequence type. Note that it is also possible to perform equivalent operations on the results page for Ensembl VEP, so if you aren't sure, don't use any of these options!

- By frequency**
 Filter variants by minor allele frequency (MAF). Two options are provided:
 - Exclude common variants**
 Filter out variants that are co-located with an existing variant that has a frequency greater than 0.01 (1%) in the 1000 Genomes global population. Equivalent to `--filter_common` in the Ensembl VEP script.
 - Advanced filtering**
 Enabling this option allows you to specify a population and frequency to compare to, as well whether matching variants should be included or excluded from the results.
- Return results for variants in coding regions only**
 Exclude variants that don't fall in a coding region of a transcript. Equivalent to `--coding_only`.
- Restrict results**
 For many variants Ensembl VEP will report multiple consequence types - typically this is because the variant overlaps more than one transcript. For each of these options Ensembl VEP uses consequence ranks that are subjectively determined by Ensembl. [This table](#) gives all of the consequence types predicted by Ensembl, ordered by rank. Note that enabling one of these options not only loses potentially relevant data, but in some cases may be scientifically misleading. Options:
 - Show one selected consequence**
 Pick one consequence type across all those predicted for the variant; the output will include transcript- or feature-specific information. Consequences are chosen by the canonical, biotype status and length of the transcript, along with the ranking of the consequence type according to [this table](#). This is the best method to use if you are interested only in one consequence per variant. Equivalent to `--pick`.
 - Show one selected consequence per gene**
 Pick one consequence type for each gene using the same criteria as above. Note that if a variant overlaps more than one gene, output for each gene will be reported. Equivalent to `--per_gene`.
 - Show only list of consequences per variant**
 Give a comma-separated list of all observed consequence types for each variant. No transcript-specific or gene-specific output will be given. Equivalent to `--summary`.
 - Show most severe per variant**
 Only the most severe of all observed consequence types is reported for each variant. No transcript-specific or gene-specific output will be given. Equivalent to `--most_severe`.

Filtering options
Pre-filter results by frequency or consequence type

Filters

Filter by frequency:

☐ No filtering
☐ Exclude common variants
☒ Advanced filtering

Exclude
variants with MAF greater than
0.01
in 1000 genomes (1KG) combined population

Return results for variants in coding regions only:

Restrict results:

☐

Show all results

NB: Restricting results may exclude biologically important data!

Advanced options

The Ensembl VEP web interface allows you to use/setup advanced options:

- **Buffer size**

By default Ensembl VEP process the variants by blocks of 5000 (i.e. what we call "buffer size").

In some cases, reducing the size of the blocks (buffer size) could prevent memory issues for large Ensembl VEP queries (e.g. use of regulatory data, many plugins or custom annotations).

This is why the maximum buffer size is automatically set to 500 on the Ensembl VEP Web interface when the "Regulatory data" option is selected.

- **Right align variants prior to consequence calculation**

By default Ensembl VEP performs consequence calculation at the given input coordinates.

Optionally, Ensembl VEP can shift insertions and deletions found within repeated regions as far as possible in the 3' direction, normalising output.

Advanced options ☐ Additional enhancements

Advanced options

Buffer size:

5000

NB: When the **Regulatory data** option is selected then due to the large amount of regulatory data available, the **maximum buffer size** is default value of **5000** to **500**. This reduces the memory requirement but might increase the run time. If you find that your jobs are still failing you can select a value **lower than 500**.


Right align variants prior to consequence calculation:

Right align relative to transcrip






Jobs



Once you have clicked **Run**, your input will be checked and submitted to the Ensembl VEP as a job. All jobs associated with your session or account are shown in the **Recent Tickets** table. You may submit multiple jobs simultaneously.
















The **Jobs** column of the table shows the current status of the job.

- **Queued** - your job is waiting to be submitted to the system
- **Running** - your job is currently running
- **Done** - your job is finished - click the [View results] link to be taken to the results page
- **Failed** - there is a problem with your job - click the magnifying glass icon  to see more details

The following actions are available for each job:

-  **Save icon**: save the job (you need to login with an Ensembl account).
-  **Edit icon**: resubmit a job (for example, to slightly tweak the data or parameters before re-running).
-  **Magnifying glass icon**: see summary of the options that you selected for your Ensembl VEP job, as well as data versions associated with this run.
-  **Share icon**: display URL to share with other users. You can also disable URL sharing here.
-  **Trash can icon**: delete a job.

Show	All	entries	Show/hide columns	Filter
Analysis	Jobs			Submitted at (GMT)
Ensembl Variant Effect Predictor	 Ensembl VEP analysis of pasted data in Bos_taurus	Done [View results]   		11/05/2023, 17:00
Ensembl Variant Effect Predictor	 Ensembl VEP analysis of pasted data in Ovis_aries	Done [View results]		11/05/2023, 16:55

Ensembl Variant Effect Predictor	 Ensembl VEP analysis of pasted data in Homo_sapiens Failed	11/05/2023, 16:54	   
Ensembl Variant Effect Predictor	 Ensembl VEP analysis of pasted data in Homo_sapiens Running	11/05/2023, 16:51	   
Ensembl Variant Effect Predictor	 Ensembl VEP analysis of pasted data in Homo_sapiens Queued	11/05/2023, 16:49	   

The Ensembl VEP presents a [summary](#) and a detailed [results preview](#) on its results page.

Summary

The summary panel on the Ensembl VEP results page gives a brief overview of the Ensembl VEP job, along with some basic statistics about the results.

Statistics

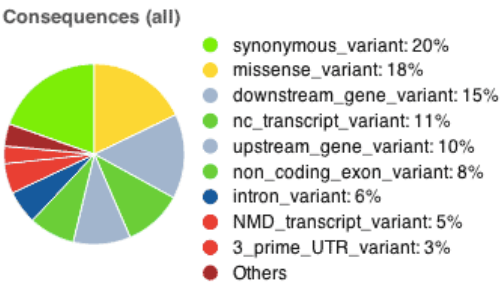
Various statistics are listed in a table, including:

- Variants processed - variants not parsed by Ensembl VEP are excluded from this count
- Variants remaining after [filtering](#)
- Novel / known variants - the number and percentage of novel variants vs existing variants in the input (see [input page documentation](#))
- Number of overlapped genes, transcripts and regulatory features

Category	Count
Variants processed	498955
Variants remaining after filtering	498955
Novel / known variants	-
Overlapped genes	825
Overlapped transcripts	2888
Overlapped regulatory features	7309

Pie charts

Pie charts are shown detailing the proportion of consequence types called across all variants in the results. The colour scheme of the pie chart matches the colours used to draw variants on the Ensembl region in detail view.



Results preview table

The results table shows one row per transcript and variant. By default all of the columns are shown; to temporarily hide columns, click the blue "Show/hide columns" button and select or deselect the columns you wish to view. The columns you select will be recalled when viewing other jobs.


Hover over a column title to see a description. See the [Ensembl VEP output format documentation](#) for more details on each of the results columns.

The table can be sorted by any column - click the column header to toggle sorting behaviour.

To download what you see in the table, hover over the spreadsheet icon in the top right corner of the table.

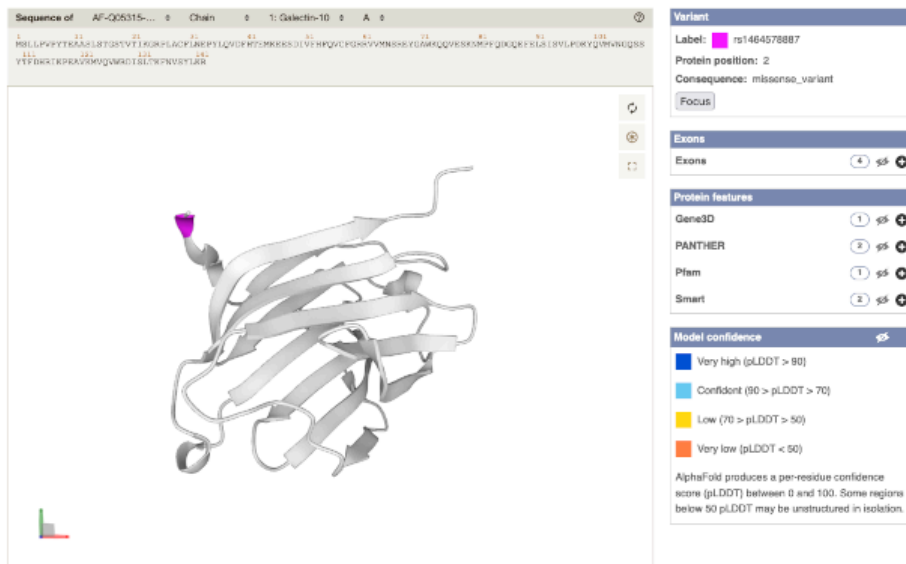
Several columns have special features for the data they contain:

- **Location** - click the link to navigate to the region in detail view for the region surrounding this variant
- **Gene, Feature and Existing Variation** - click the link to bring up a summary view of the gene, transcript, regulatory feature or variation, from which you can navigate to the main Ensembl page for it
- **Consequence** - hover over the consequence name to see the [Sequence Ontology](#) definition. See the [Ensembl Variation documentation](#) for a full list of consequence types used by Ensembl VEP and their definitions
- **SIFT and PolyPhen** - predictions and scores are coloured according to the nature of the prediction, with red indicating deleterious or damaging
- **Protein matches** - lists of matching protein domains and families are shown. Click on 'Protein Structure view' to see the variant on [PDB](#) structures or [AlphaFold](#) model to see the variant on a predicted structure

Show/hide columns 											
Uploaded variation	Location	Feature	Feature type	Consequence	CDS position	Protein position	Amino acids	Codons	SIFT	GMAF	
rs116383664	1:1115461	ENSR00000528523	RegulatoryFeature	regulatory_region_variant	-	-	-	-	-	T:0.0137	
rs116383664	1:1115461	ENST00000373317	Transcript	upstream_gene_variant	-	-	-	-	-	T:0.0137	
rs116383664	1:1115461	ENST00000486379	Transcript	upstream_gene_variant	-	-	-	-	-	T:0.0137	
rs116383664	1:1115461	ENST00000379289	Transcript	missense_variant	247	83	R/W	Cgg/Tgg	tolerated(0.06)	T:0.0137	
rs116383664	1:1115461	ENST00000460998	Transcript	upstream_gene_variant	-	-	-	-	-	T:0.0137	
rs116383664	1:1115461	ENST00000514695	Transcript	upstream_gene_variant	-	-	-	-	-	T:0.0137	
rs116383664	1:1115461	ENST00000379290	Transcript	missense_variant	247	83	R/W	Cgg/Tgg	tolerated(0.06)	T:0.0137	
rs116383664	1:1115461	ENST00000379288	Transcript	missense_variant	28	10	R/W	Cgg/Tgg	deleterious(0.03)	T:0.0137	

AlphaFold Predicted Model

Ensembl protein: ENSP00000221804

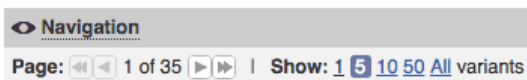


Navigating results

The navigation panel can be used to scroll through pages of results.

By default, the results for five variants are shown. Note that since a variant can overlap multiple transcripts, the table will often show **more than** five rows. To change the number shown, click the appropriate link. Be warned that if your input file is large, it is inadvisable to show all results unless you are sure you have applied sufficient filters - your browser may become unresponsive if it tries to display many thousands of rows in the table.

To navigate between pages of results, use the four arrow icons. Note that when any filters are enabled, it is not possible to navigate to the last page of results as the total number of results cannot be calculated.



Filtering results

You can apply any combination of filters to your results in order to identify interesting data. This is equivalent to using the [Ensembl VEP filtering script](#) on the command line.

To add a filter, simply select the column you wish to filter on, select an "operator", and input a value for the filter to compare to.

To edit a filter, click the pencil icon . To remove a filter, click the cross icon .

When you have added more than one filter, you are given the option to match any or all of the rules shown; click the "Update" button once you have made your selection.

Certain columns when selected have special features:

- **Location** - for this column you may enter genomic coordinates in the format "chromosome:start-end". It is also possible to enter just a chromosome, e.g. enter "12" to show only variants on chromosome 12.

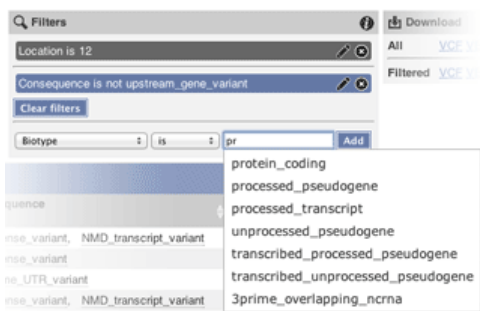
Adding multiple location filters allows you to select multiple regions - location filters are not affected by whether you select "Match all" or "Match any" (see above).

Users should note that enabling at least one location filter will greatly speed up the return of results (this is because [tabix](#) is used behind the scenes).

Location filters are not affected by the operator selected.

- **Allele, Feature type, Consequence, SIFT, PolyPhen and Biotype** - for these columns, autocomplete will help you fill in the value when you start typing
- **SIFT and PolyPhen** - these columns can contain both text (e.g. a SIFT prediction) and a number (e.g. a frequency value). Ensembl VEP allows you to filter on either part of this.

For example, you may enter "is" and "deleterious" for SIFT to return deleterious predictions, or "<" and "0.1" to find results with a SIFT score less than 0.1.

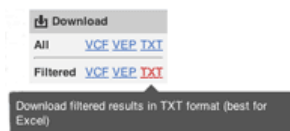


Downloading results

Ensembl VEP allows you to download either your full or filtered results set in a choice of data formats.

- **VCF** - [VCF](#) is a portable format for variant data. Consequence data is encoded as a series of delimited strings under the "CSQ" key in the VCF INFO field.
- **Ensembl VEP** - The default [Ensembl VEP output format](#) gives one row per variant and transcript overlap.
- **TXT** - Text format is a tab-delimited format, equivalent to what can be seen in the results table. Note that the columns you select to be visible in the table do not affect the downloaded file - all columns are outputted. This format is best if you intend to import the results into a spreadsheet program such as Microsoft Excel.

You can also send the genes or known variants in your current preview to BioMart. This allows you to easily retrieve any of BioMart's rich data associated with these genes (other database references, GO terms, orthologues/paralogues) and variants (phenotype annotations, synonyms, citations).



Input

Both the web and command line interfaces to Ensembl VEP can use the same input formats.

Supported input formats:

Format	Variant example	Structural variant example
Default Ensembl VEP input	1 881907 881906 -/C +	1 160283 471362 DUP +
VCF	1 65568 . A C . . .	1 7936271 . N N[12:58877476[. . SVTYPE=BND
HGVS identifiers	ENST00000618231.3:c.9G>C	X Not supported
Variant identifiers	rs699	nsv1000164
Genomic SPDI notation	NC_000016.10:68684738:G:A	X Not supported
REST-style regions	14:19584687-19584687:-1/T	21:25587759-25587769/DEL

Default Ensembl VEP input

The default format is a simple **whitespace-separated** format (columns may be separated by space or tab characters), containing five required columns plus an optional identifier column:

1. **chromosome** - just the name or number, with no 'chr' prefix
2. **start**
3. **end**
4. **allele** - pair of alleles separated by a '/', with the reference allele first (or [structural variant type](#)).
5. **strand** - defined as + (forward) or - (reverse). The alleles will be reverse complemented for mapping to the genome if the minus strand is provided.
6. **identifier** - this identifier will be used the output. If not provided, Ensembl VEP will construct an identifier from the given coordinates and alleles.

```

1 881907 881906 -/C +
2 946507 946507 G/C +
5 140532 140532 T/C +
8 150029 150029 A/T + var2
12 1017956 1017956 T/A +
14 19584687 19584687 C/T -
19 66520 66520 G/A + var1

```

An insertion (of any size) is indicated by start coordinate = end coordinate + 1. For example, an insertion of 'C' between nucleotides 12600 and 12601 on the forward strand of chromosome 8 is indicated as follows:

```

8 12601 12600 -/C +

```

A deletion is indicated by the exact nucleotide coordinates. For example, a three base pair deletion of nucleotides 12600, 12601, and 12602 of the reverse strand of chromosome 8 will be:

```

8 12600 12602 CGT/- -

```

Structural variants are also supported by indicating a [structural variant type](#) instead of the allele:

```

1 20000 30000 CN4 + cnv4
1 160283 471362 DUP + dup
1 1385015 1387562 DEL + del1
12 1017956 1017956 INV + inv
21 25587759 25587769 CN0 + del2

```

VCF

[VCF \(Variant Call Format\) version 4.0](#) is supported. This is a common format produced by many variant calling tools and is the recommended format for use with Ensembl VEP:

```

#CHROM POS ID REF ALT QUAL FILTER INFO FORMAT
1 65568 . A C . . . .
1 230710048 rs699 A G . . . .
2 265023 . C T . . . .
3 319780 . GA G . . . .
20 3 . C CAAG,CAAGAAG . PASS . .
21 43762120 rs1300 T A,C,G . . . .

```

Structural variants are also supported depending on [structural variant type](#).

Users using VCF should note a peculiarity in the difference between how Ensembl and VCF describe unbalanced variants. For any unbalanced variant (i.e. insertion, deletion or unbalanced substitution), the VCF specification requires that the base immediately before the variant should be included in both the reference and variant alleles. This also affects the reported position i.e. the reported position will be one base before the actual site of the variant.

In order to parse this correctly, Ensembl VEP needs to convert such variants into Ensembl-type coordinates, and it does this by removing the additional base and adjusting the coordinates accordingly. This means that if an identifier is not supplied for a variant (in the 3rd column of the VCF), then the identifier constructed and the position reported in Ensembl VEP output file will differ from the input.

This problem can be overcome with the following:

1. ensuring each variant has a unique identifier specified in the 3rd column of the VCF
2. using VCF format as output (`--vcf`) - this preserves the formatting of your input coordinates and alleles
3. using `--minimal` and `--allele number` (see [Complex VCF entries](#)).

The following examples illustrate how VCF describes a variant and how it is handled internally by Ensembl VEP. Consider the following aligned sequences (for the purposes of discussion on chromosome 20):

```
Ref: a t C g a // C is the reference base
1 : a t G g a // C base is a G in individual 1
2 : a t - g a // C base is deleted w.r.t. the reference in individual 2
3 : a t CAg a // A base is inserted w.r.t. the reference sequence in individual 3
```

Individual 1

The first individual shows a simple balanced substitution of G for C at base 3. This is described in a compatible manner in VCF and Ensembl styles. Firstly, in VCF:

```
20 3 . C G . PASS .
```

And in Ensembl format:

```
20 3 3 C/G +
```

Individual 2

The second individual has the 3rd base deleted relative to the reference. In VCF, both the reference and variant allele columns must include the preceding base (T) and the reported position is that of the preceding base:

```
20 2 . TC T . PASS .
```

In Ensembl format, the preceding base is not included, and the start/end coordinates represent the region of the sequence deleted. A "-" character is used to indicate that the base is deleted in the variant sequence:

```
20 3 3 C/- +
```

The upshot of this is that while in the VCF input file the position of the variant is reported as 2, in the output file in Ensembl VEP default format the position will be reported as 3. If no identifier is provided in the third column of the VCF, then the constructed identifier will be:

```
20_3_C/-
```

Individual 3

The third individual has an "A" inserted between the 3rd and 4th bases of the sequence relative to the reference. In VCF, as for the deletion, the base before the insertion is included in both the reference and variant allele columns, and the reported position is that of the preceding base:

```
20 3 . C CA . PASS .
```

In Ensembl format, again the preceding base is not included, and the start/end positions are "swapped" to indicate that this is an insertion. Similarly to a deletion, a "-" is used to indicate no sequence in the reference:

```
20 4 3 -/A +
```

Again, the output will appear different, and the constructed identifier may not be what is expected:

```
20_3_-/A
```

Using VCF format output, or adding unique identifiers to the input (in the third VCF column), can mitigate this issue.

Complex VCF entries

For VCF entries with multiple alternate alleles, Ensembl VEP will only trim the leading base from alleles if **all** REF and ALT alleles start with the same base:

```
20 3 . C CAAG,CAAGAAG . PASS .
```

This will be considered internally by Ensembl VEP as equivalent to:

```
20 4 3 -/AAG/AAGAAG +
```

Now consider the case where a single VCF line contains a representation of both a SNV and an insertion:

```
20 3 . C CAAAG,G . PASS .
```

Here the input alleles will remain unchanged, and Ensembl VEP will consider the first REF/ALT pair as a substitution of C for CAAG, and the second as a C/G SNV:

```
20 3 3 C/CAAG/G +
```

To modify this behaviour, with the commandline tool you can use `--minimal`. This flag forces Ensembl VEP to consider each REF/ALT pair independently, trimming identical leading and trailing bases from each as appropriate. Since this can lead to confusing output regarding coordinates etc, it is not the default behaviour. It is recommended to use the `--allele_number` flag to track the correspondence between alleles as input and how they appear in the output.

HGVS identifiers

See <https://varnomen.hgvs.org/> for details. These must be relative to genomic or Ensembl transcript coordinates.

It also is possible to use RefSeq transcripts, if they match the reference genome See [HGVS documentation](#)

Examples:

```
ENST00000618231.3:c.9G>C
ENST00000471631.1:c.28_33delTCGCGG
ENST00000285667.3:c.1047_1048insC
5:g.140532G>C
```

Examples using RefSeq identifiers (using `--refseq` in the command line or select the 'RefSeq transcripts' on the web interface:

```
NM_153681.2:c.7C>T
NM_005239.6:c.190G>A
NM_001025204.2:c.336G>A
```

HGVS protein notations may also be used, provided that they unambiguously map to a single genomic change. Due to redundancy in the amino acid code, it is not always possible to work out the corresponding genomic sequence change for a given protein sequence change. The following example is for a permissible protein notation in dog (*Canis familiaris*):

```
ENSCAF00000040171.1:p.Thr92Asn
```

Ambiguous gene-based descriptions

It is possible to use ambiguous descriptions listing only gene symbol or UniProt accession and protein change (e.g. PHF21B:p.Tyr124Cys, P01019:p.Ala268Val), as seen in the literature, though this is not recommended as it can produce multiple different variants at genomic level. The transcripts for a gene are considered in the following order:

1. [MANE Select transcript status](#)
2. [MANE Plus Clinical transcript status](#)
3. canonical status of transcript
4. [APPRIS isoform annotation](#)
5. [transcript support level](#)
6. biotype of transcript ("protein_coding" preferred)
7. CCDS status of transcript
8. consequence rank according to [this table](#)
9. translated, transcript or feature length (longer preferred)

and the first compatible transcript is used to map variants to the genome for annotation.

Variant identifiers

These should be dbSNP rsIDs (such as `rs699`), or any synonym for a variant present in the Ensembl Variation database. Structural variant identifiers (like `nsv1000164` and `esv1850194`) are also supported.

See [here](#) for a list of identifier sources in Ensembl.

Examples:

```
rs1156485833
rs1258750482
rs867704559
esv1815690
nsv1000164
```

Genomic SPDI notation

Genomic SPDI notation which uses four fields delimited by colons S:P:D:I (Sequence:Position:Deletion:Insertion) is also supported. In SPDI notation, the position refers to the base before the variant, not the base of the variant itself.

See [here](#) for details.

Examples:

```
NC_000016.10:68684738:G:A
NC_000017.11:43092199:GCTTTT:
NC_000013.11:32315789.:C
NC_000016.10:68644746:AA:GTA
16:68684738:2:AC
```

REST-style regions

The Ensembl VEP region REST endpoint requires variants are described as [chr]:[start]-[end]:[strand]/[allele].

This follows the same conventions as the [default input format](#), with the key difference being that this format does not require the reference (REF) allele to be included; this will be looked up using either a provided FASTA file (preferred) or Ensembl core database. Strand is optional and defaults to 1 (forward strand).

```
# SNP
5:140532-140532:1/C

# SNP (reverse strand)
14:19584687-19584687:-1/T

# insertion
1:881907-881906:1/C

# 5bp deletion
2:946507-946511:1/-
```

Structural variants are also supported by indicating a [structural variant type](#) in the place of the [allele]:

```
# structural variant: deletion
21:25587759-25587769/DEL

# structural variant: inversion
21:25587759-25587769/INV
```

Structural variant types

Ensembl VEP also predicts molecular consequences for structural variants using the following input formats:

- [Default Ensembl VEP input](#)
- [REST-style regions](#)
- [Variant identifiers](#)
- [VCF](#)

To recognise a variant as a structural variant, the allele string (or SVTYPE in the INFO column of the VCF format) must be set to one of the currently supported values:

- **INS** - insertion
 - **INS:ME** - insertion of mobile element
 - **INS:ME:ALU** - insertion of ALU element
 - **INS:ME:HERV** - insertion of HERV element
 - **INS:ME:LINE1** - insertion of LINE1 element
 - **INS:ME:SVA** - insertion of SVA element
- **DEL** - deletion
 - **DEL:ME** - deletion of mobile element
 - **DEL:ME:ALU** - deletion of ALU element
 - **DEL:ME:HERV** - deletion of HERV element
 - **DEL:ME:LINE1** - deletion of LINE1 element
 - **DEL:ME:SVA** - deletion of SVA element

- **DUP** - duplication
 - **DUP:TANDEM** - tandem duplication
 - **TDUP** - tandem duplication
- **INV** - inversion
- **CNV** - copy number variation
 - The copy number value can be specified like so:
 - CN0
 - CN=4
 - CN3, CN4, CN6
 - CN=0, CN=2, CN=4
 - **CNV:TR** - tandem repeats
 - Requires **INFO** fields describing the tandem repeat, such as **RUS** and **RN** – check [VCF 4.4 specification, section 5.7](#)
 - Currently, the **CIRUC** and **CIRB** **INFO** fields are ignored when calculating alternative alleles in tandem repeats
- **BND** - chromosome breakpoints
 - Breakpoint variants are composed by one or more breakends
 - In VCF, breakend replacements are inserted into the **ALT** column and need to meet the [HTS specifications](#), such as TG[12:58877476[
 - Single breakends can be specified in **ALT**, such as T. and .G
 - Multiple, comma-separated alternative breakends can be specified in **ALT**, such as A[22:22893780[,A[X:10932343[
 - Breakends are only supported for VCF input format

More information on how Ensembl VEP processes structural variants can be found [here](#).

Examples of structural variants encoded in VCF format

#CHROM	POS	ID	REF	ALT	QUAL	FILTER	INFO
1	160283	dup	.	<DUP>	.	.	SVTYPE=DUP;END=471362
1	1385015	del	.		.	.	SVTYPE=DEL;END=1387562
1	7936271	bnd	N	N[12:58877476[.	.	SVTYPE=BND

See the [VCF definition document](#) for more detail on how to describe structural variants in VCF format.

Output

Ensembl VEP can return the results in different formats:

- [Default Ensembl VEP output](#)
- [Tab-delimited output](#)
- [VCF](#)
- [JSON output](#)

Along with the results Ensembl VEP computes and returns some [statistics](#).

Default Ensembl VEP output

The default output format ("VEP" format when downloading from the web interface) is a 14 column tab-delimited file. Empty values are denoted by '-'. The output columns are:

1. **Uploaded variation** - as chromosome_start_alleles
2. **Location** - in standard coordinate format (chr:start or chr:start-end)
3. **Allele** - the variant allele used to calculate the consequence
4. **Gene** - Ensembl stable ID of affected gene
5. **Feature** - Ensembl stable ID of feature
6. **Feature type** - type of feature. Currently one of Transcript, RegulatoryFeature, MotifFeature.
7. **Consequence** - [consequence type](#) of this variant
8. **Position in cDNA** - relative position of base pair in cDNA sequence
9. **Position in CDS** - relative position of base pair in coding sequence
10. **Position in protein** - relative position of amino acid in protein
11. **Amino acid change** - only given if the variant affects the protein-coding sequence
12. **Codon change** - the alternative codons with the variant base in upper case
13. **Co-located variation** - identifier of any [existing variants](#). Switch on with `--check_existing`
14. **Extra** - this column contains extra information as key=value pairs separated by ";", see below.

Other output fields:

- **REF_ALLELE** - the reference allele (after minimisation)
- **UPLOADED_ALLELE** - the uploaded allele string (before minimisation)
- **IMPACT** - the impact modifier for the consequence type
- **VARIANT_CLASS** - Sequence Ontology [variant class](#)
- **SYMBOL** - the gene symbol
- **SYMBOL_SOURCE** - the source of the gene symbol
- **STRAND** - the DNA strand (1 or -1) on which the transcript/feature lies
- **ENSP** - the Ensembl protein identifier of the affected transcript
- **FLAGS** - transcript quality flags:
 - *cds_start_NF*: CDS 5' incomplete
 - *cds_end_NF*: CDS 3' incomplete
- **SWISSPROT** - Best match UniProtKB/Swiss-Prot accession of protein product
- **TREMBL** - Best match UniProtKB/TrEMBL accession of protein product
- **UNIPARC** - Best match UniParc accession of protein product
- **HGVSc** - the HGVS coding sequence name
- **HGVSp** - the HGVS protein sequence name
- **HGVSG** - the HGVS genomic sequence name
- **HGVS_OFFSET** - Indicates by how many bases the HGVS notations for this variant have been [shifted](#). Value must be greater than 0.
- **NEAREST** - Identifier(s) of nearest transcription start site
- **SIFT** - the SIFT prediction and/or score, with both given as prediction(score)
- **PolyPhen** - the PolyPhen prediction and/or score
- **MOTIF_NAME** - the source and identifier of a transcription factor binding profile aligned at this position
- **MOTIF_POS** - The relative position of the variation in the aligned TFBP
- **HIGH_INF_POS** - a flag indicating if the variant falls in a high information position of a transcription factor binding profile (TFBP)
- **MOTIF_SCORE_CHANGE** - The difference in motif score of the reference and variant sequences for the TFBP
- **CELL_TYPE** - List of cell types and classifications for regulatory feature
- **CANONICAL** - a flag indicating if the transcript is denoted as the canonical transcript for this gene
- **CCDS** - the CCDS identifier for this transcript, where applicable
- **INTRON** - the intron number (out of total number)
- **EXON** - the exon number (out of total number)
- **DOMAINS** - the source and identifier of any overlapping protein domains
- **DISTANCE** - Shortest distance from variant to transcript. *Note: DISTANCE of 0 is possible for insertions happening just before or after a transcript because variant coordinates are considered to be the flanking bases where insertion happens.*
- **IND** - individual name
- **ZYG** - zygosity of individual genotype at this locus
- **SV** - IDs of overlapping structural variants
- **FREQS** - Frequencies of overlapping variants used in filtering
- **AF** - Frequency of existing variant in 1000 Genomes
- **AFR_AF** - Frequency of existing variant in 1000 Genomes combined African population
- **AMR_AF** - Frequency of existing variant in 1000 Genomes combined American population
- **ASN_AF** - Frequency of existing variant in 1000 Genomes combined Asian population
- **EUR_AF** - Frequency of existing variant in 1000 Genomes combined European population
- **EAS_AF** - Frequency of existing variant in 1000 Genomes combined East Asian population
- **SAS_AF** - Frequency of existing variant in 1000 Genomes combined South Asian population
- **gnomADe_AF** - Frequency of existing variant in gnomAD exomes combined population
- **gnomADe_AFR_AF** - Frequency of existing variant in gnomAD exomes African/American population
- **gnomADe_AMR_AF** - Frequency of existing variant in gnomAD exomes American population
- **gnomADe_ASJ_AF** - Frequency of existing variant in gnomAD exomes Ashkenazi Jewish population
- **gnomADe_EAS_AF** - Frequency of existing variant in gnomAD exomes East Asian population
- **gnomADe_FIN_AF** - Frequency of existing variant in gnomAD exomes Finnish population
- **gnomADg_MID_AF** - Frequency of existing variant in gnomAD exomes Mid-eastern population
- **gnomADe_NFE_AF** - Frequency of existing variant in gnomAD exomes Non-Finnish European population
- **gnomADe_REMAINING_AF** - Frequency of existing variant in gnomAD exomes combined remaining combined populations
- **gnomADe_SAS_AF** - Frequency of existing variant in gnomAD exomes South Asian population
- **gnomADg_AF** - Frequency of existing variant in gnomAD genomes combined population
- **gnomADg_AFR_AF** - Frequency of existing variant in gnomAD genomes African/American population

- **gnomADg_AMI_AF** - Frequency of existing variant in gnomAD genomes Amish population
- **gnomADg_AMR_AF** - Frequency of existing variant in gnomAD genomes American population
- **gnomADg_ASJ_AF** - Frequency of existing variant in gnomAD genomes Ashkenazi Jewish population
- **gnomADg_EAS_AF** - Frequency of existing variant in gnomAD genomes East Asian population
- **gnomADg_FIN_AF** - Frequency of existing variant in gnomAD genomes Finnish population
- **gnomADg_MID_AF** - Frequency of existing variant in gnomAD genomes Mid-eastern population
- **gnomADg_NFE_AF** - Frequency of existing variant in gnomAD genomes Non-Finnish European population
- **gnomADg_REMAINING_AF** - Frequency of existing variant in gnomAD genomes combined remaining combined populations
- **gnomADg_SAS_AF** - Frequency of existing variant in gnomAD genomes South Asian population
- **MAX_AF** - Maximum observed allele frequency in 1000 Genomes, ESP and gnomAD
- **MAX_AF_POPS** - Populations in which maximum allele frequency was observed
- **CLIN_SIG** - ClinVar clinical significance of the dbSNP variant
- **BIOTYPE** - Biotype of transcript or regulatory feature
- **APPRIS** - Annotates alternatively spliced transcripts as primary or alternate based on a range of computational methods. NB: not available for GRCh37
- **TSL** - Transcript support level. NB: not available for GRCh37
- **GENCODE_PRIMARY** - Reports if transcript belongs to GENCODE primary subset
- **PUBMED** - Pubmed ID(s) of publications that cite existing variant
- **SOMATIC** - Somatic status of existing variant(s); multiple values correspond to multiple values in the Existing_variation field
- **PHENO** - Indicates if existing variant is associated with a phenotype, disease or trait; multiple values correspond to multiple values in the Existing_variation field
- **GENE_PHENO** - Indicates if overlapped gene is associated with a phenotype, disease or trait
- **ALLELE_NUM** - Allele number from input; 0 is reference, 1 is first alternate etc
- **MINIMISED** - Alleles in this variant have been converted to minimal representation before consequence calculation
- **PICK** - indicates if this block of consequence data was picked by `--flag_pick` or `--flag_pick_allele`
- **BAM_EDIT** - Indicates success or failure of edit using BAM file
- **GIVEN_REF** - Reference allele from input
- **USED_REF** - Reference allele as used to get consequences
- **REFSEQ_MATCH** - the RefSeq transcript match status; contains a number of flags indicating whether this RefSeq transcript matches the underlying reference sequence and/or an Ensembl transcript ([more information](#)).
 - *rseq_3p_mismatch*: signifies a mismatch between the RefSeq transcript and the underlying primary genome assembly sequence. Specifically, there is a mismatch in the 3' UTR of the RefSeq model with respect to the primary genome assembly (e.g. GRCh37/GRCh38).
 - *rseq_5p_mismatch*: signifies a mismatch between the RefSeq transcript and the underlying primary genome assembly sequence. Specifically, there is a mismatch in the 5' UTR of the RefSeq model with respect to the primary genome assembly.
 - *rseq_cds_mismatch*: signifies a mismatch between the RefSeq transcript and the underlying primary genome assembly sequence. Specifically, there is a mismatch in the CDS of the RefSeq model with respect to the primary genome assembly.
 - *rseq_ens_match_cds*: signifies that for the RefSeq transcript there is an overlapping Ensembl model that is identical across the CDS region only. A CDS match is defined as follows: the CDS and peptide sequences are identical and the genomic coordinates of every translatable exon match. Useful related attributes are: *rseq_ens_match_wt* and *rseq_ens_no_match*.
 - *rseq_ens_match_wt*: signifies that for the RefSeq transcript there is an overlapping Ensembl model that is identical across the whole transcript. A whole transcript match is defined as follows: 1) In the case that both models are coding, the transcript, CDS and peptide sequences are all identical and the genomic coordinates of every exon match. 2) In the case that both transcripts are non-coding the transcript sequences and the genomic coordinates of every exon are identical. No comparison is made between a coding and a non-coding transcript. Useful related attributes are: *rseq_ens_match_cds* and *rseq_ens_no_match*.
 - *rseq_ens_no_match*: signifies that for the RefSeq transcript there is no overlapping Ensembl model that is identical across either the whole transcript or the CDS. This is caused by differences between the transcript, CDS or peptide sequences or between the exon genomic coordinates. Useful related attributes are: *rseq_ens_match_wt* and *rseq_ens_match_cds*.
 - *rseq_mrna_match*: signifies an exact match between the RefSeq transcript and the underlying primary genome assembly sequence (based on a match between the transcript stable id and an accession in the RefSeq mRNA file). An exact match occurs when the underlying genomic sequence of the model can be perfectly aligned to the mRNA sequence post polyA clipping.
 - *rseq_mrna_nonmatch*: signifies a non-match between the RefSeq transcript and the underlying primary genome assembly sequence. A non-match is deemed to have occurred if the underlying genomic sequence does not have a perfect alignment to the mRNA sequence post polyA clipping. It can also signify that no comparison was possible as the model stable id may not have had a corresponding entry in the RefSeq mRNA file (sometimes happens when accessions are retired or changed). When a non-match occurs one or several of the following transcript attributes will also be present to provide more detail on the nature of the non-match: *rseq_5p_mismatch*, *rseq_cds_mismatch*, *rseq_3p_mismatch*, *rseq_ntran_mismatch*, *rseq_no_comparison*
 - *rseq_ntran_mismatch*: signifies a mismatch between the RefSeq transcript and the underlying primary genome assembly sequence. This is a comparison between the entire underlying genomic sequence of the RefSeq model to the mRNA in the case of RefSeq models that are non-coding.
 - *rseq_no_comparison*: signifies that no alignment was carried out between the underlying primary genome assembly sequence and a corresponding RefSeq mRNA. The reason for this is generally that no corresponding, unversioned accession was found in the RefSeq mRNA file for the transcript stable id. This sometimes happens when accessions are retired or replaced. A second possibility is that the sequences were too long and problematic to align (though this is rare).
- **OverlapBP** - Number of base pairs overlapping with the corresponding structural variation feature
- **OverlapPC** - Percentage of corresponding structural variation feature overlapped by the given input
- **CHECK_REF** - Reports variants where the input reference does not match the expected reference
- **AMBIGUITY** - IUPAC allele ambiguity code

Example of Ensembl VEP default output format:

11_224088_C/A	11:224088	A	ENSG00000142082	ENST00000525319	Transcript	missense_variant	742	71
11_224088_C/A	11:224088	A	ENSG00000142082	ENST00000534381	Transcript	5_prime_UTR_variant	-	-
11_224088_C/A	11:224088	A	ENSG00000142082	ENST00000529055	Transcript	downstream_variant	-	-
11_224585_G/A	11:224585	A	ENSG00000142082	ENST00000529937	Transcript	intron_variant	-	-
22_16084370_G/A	22:16084370	A	-	ENSR00000615113	RegulatoryFeature	regulatory_region_variant	-	-

The Ensembl VEP command line tool will also add a header to the output file. This contains information about the databases connected to, and also a key describing the key/value pairs used in the extra column.

```
## ENSEMBL VARIANT EFFECT PREDICTOR v115.0
## Output produced at 2017-03-21 14:51:27
## Connected to homo_sapiens_core_115_38 on ensembl.org
## Using cache in /homes/user/.vep/homo_sapiens/115_GRCh38
## Using API version 115, DB version 115
## polyphen version 2.2.2
## sift version sift5.2.2
## COSMIC version 78
## ESP version 20141103
## gencode version GENCODE 25
## genebuild version 2014-07
## HGMD-PUBLIC version 20162
## regbuild version 16
## assembly version GRCh38.p7
## ClinVar version 201610
## dbSNP version 147
## Column descriptions:
## Uploaded_variation : Identifier of uploaded variant
## Location : Location of variant in standard coordinate format (chr:start or chr:start-end)
## Allele : The variant allele used to calculate the consequence
## Gene : Stable ID of affected gene
## Feature : Stable ID of feature
## Feature_type : Type of feature - Transcript, RegulatoryFeature or MotifFeature
## Consequence : Consequence type
## cDNA_position : Relative position of base pair in cDNA sequence
## CDS_position : Relative position of base pair in coding sequence
## Protein_position : Relative position of amino acid in protein
## Amino_acids : Reference and variant amino acids
## Codons : Reference and variant codon sequence
## Existing_variation : Identifier(s) of co-located known variants
## Extra column keys:
## IMPACT : Subjective impact classification of consequence type
## DISTANCE : Shortest distance from variant to transcript
## STRAND : Strand of the feature (1/-1)
## FLAGS : Transcript quality flags
```

Tab-delimited output

The `--tab` specifies a tab-delimited output file.

This differs from the default output format in that each individual field from the "Extra" field is written to a separate tab-delimited column.

This makes the output more suitable for import into spreadsheet programs such as Excel.

Furthermore the header is the same as the one for the Ensembl VEP default output format and this is also the format used when selecting the "TXT" option on the Ensembl VEP web interface.

Example of tab-delimited output format:

<i>#Uploaded_variation</i>	<i>Location</i>	<i>Allele</i>	<i>Gene</i>	<i>Feature</i>	<i>Feature_type</i>	<i>Consequence</i>
11_224088_C/A	11:224088	A	ENSG00000142082	ENST00000525319	Transcript	missense_variant
11_224088_C/A	11:224088	A	ENSG00000142082	ENST00000534381	Transcript	downstream_gene_variant
11_224088_C/A	11:224088	A	ENSG00000142082	ENST00000529055	Transcript	downstream_gene_variant
11_224585_G/A	11:224585	A	ENSG00000142082	ENST00000529937	Transcript	intron_variant,NMD_transcript_v

The choice and order of columns in the output may be configured using `--fields`. For instance:

```
./vep -i examples/homo_sapiens_GRCh38.vcf --cache --force_overwrite --tab --fields "Uploaded_variation,Location,Allele,"
```

VCF output

The Ensembl VEP commandline tool can also generate VCF output using the `--vcf` flag.

Main information about the VCF output format:

- Consequences are added in the INFO field of the VCF file, using the key "**CSQ**" (you can change it using `--vcf_info field`).
- Data fields are encoded separated by the character "|" (pipe). The order of fields is written in the VCF header. Unpopulated fields are represented by an empty string.
- Output fields in the "CSQ" INFO field can be configured by using `--fields`.

- Each prediction, for a given variant, is separated by the character "," in the CSQ INFO field (e.g. when a variant overlaps more than 1 transcript)

Here is a list of the (default) fields you can find within the CSQ field:

```
Allele|Consequence|IMPACT|SYMBOL|Gene|Feature_type|Feature|BIOTYPE|EXON|INTRON|HGVSc|HGVSp|cDNA_position|CDS_position|P
```

Example command using the `--vcf` and `--fields` options:

```
./vep -i examples/homo_sapiens_GRCh38.vcf --cache --force_overwrite --vcf --fields "Allele,Consequence,Feature_type,Fea
```

VCFs produced by Ensembl VEP can be filtered using [filter_vep.pl](#) in the same way as standard format output files.

If the input format was VCF, the file will remain unchanged save for the addition of the CSQ field and the header (unless using any filtering). If an existing CSQ field is found, it will be replaced by the new annotation (use `--keep_csq` to preserve it).

Custom data added with `--custom` are added as separate fields, using the key specified for each data file.

Commas in fields are replaced with ampersands (&) to preserve VCF format.

```
##INFO=<ID=CSQ,Number=.,Type=String,Description="Consequence annotations from Ensembl VEP. Format: Allele|Consequence|I
#CHROM POS ID REF ALT QUAL FILTER INFO
21 26978790 rs75377686 T C . . CSQ=C|missense_variant|MODERATE|MRPL39|ENSG00000154719|Transcript
```

JSON output

Ensembl VEP can output serialised [JSON](#) objects using the `--json` flag. JSON is a serialisation format that can be parsed and processed easily by many packages and programming languages; it is used as the default output format for [Ensembl's REST server](#).

Each input variant is reported as a single JSON object which constitutes one line of the output file. The JSON object is structured somewhat differently to the other output formats, in that per-variant fields (e.g. co-located existing variant details) are reported only once. Consequences are grouped under the feature type that they affect (Transcript, Regulatory Feature, etc). The original input line (e.g. from VCF input) is reported under the "input" key in order to aid aligning input with output. When using a cache file, frequencies for co-located variants are reported by default (see `--af 1kg`, `--af gnomade`).

Here follows an example of JSON output (prettified and redacted for display here):

```
{
  "input": "1 1918090 test1 A G . . .",
  "id": "test1",
  "seq_region_name": "1",
  "start": 1918090,
  "end": 1918090,
  "strand": 1,
  "allele_string": "A/G",
  "most_severe_consequence": "missense_variant",
  "colocated_variants": [
    {
      "id": "COSV57068665",
      "seq_region_name": "1",
      "start": 1918090,
      "end": 1918090,
      "strand": 1,
      "allele_string": "COSMIC_MUTATION"
    },
    {
      "id": "rs28640257",
      "seq_region_name": "1",
      "start": 1918090,
      "end": 1918090,
      "strand": 1,
      "allele_string": "A/G/T",
      "minor_allele": "G",
      "minor_allele_freq": 0.352,
      "frequencies": {
        "G": {
          "amr": 0.5072,
          "gnomade_sas": 0.3635,
          "gnomade": 0.481,
          "gnomade_remaining": 0.4536,
          "gnomade_asj": 0.3939,
          "gnomade_nfe": 0.5042,
          "gnomade_afr": 0.0975,
          "afr": 0.053,
          "gnomade_amr": 0.5568,
          "gnomade_fin": 0.4751,
          "sas": 0.3906,
          "gnomade_eas": 0.4516,
          "eur": 0.4901,
          "eas": 0.4623,
          "gnomade_mid": "0.3306"
        }
      }
    }
  ]
}
```

```

    }
  }
],
"transcript_consequences": [
  {
    "variant_allele": "G",
    "consequence_terms": [
      "missense_variant"
    ],
    "gene_id": "ENSG00000178821",
    "transcript_id": "ENST00000310991",
    "strand": -1,
    "cdna_start": 436,
    "cdna_end": 436,
    "cds_start": 422,
    "cds_end": 422,
    "protein_start": 141,
    "protein_end": 141,
    "codons": "aTg/aCg",
    "amino_acids": "M/T",
    "polyphen_prediction": "benign",
    "polyphen_score": 0.001,
    "sift_prediction": "tolerated",
    "sift_score": 0.22,
    "hgvs_p": "ENSP00000311122.3:p.Met141Thr",
    "hgvs_c": "ENST00000310991.8:c.422T>C"
  }
],
"regulatory_feature_consequences": [
  {
    "variant_allele": "G",
    "consequence_terms": [
      "regulatory_region_variant"
    ],
    "regulatory_feature_id": "ENSR00000000255"
  }
]
}

```

In accordance with JSON conventions, all keys (except alleles) are lower-case. Some keys also have different names and structures to those found in the other Ensembl VEP output formats:

Key	JSON equivalent(s)	Notes
Consequence	consequence_terms	
Gene	gene_id	
Feature	transcript_id, regulatory_feature_id, motif_feature_id	Consequences are grouped under the feature type they affect
ALLELE	variant_allele	
SYMBOL	gene_symbol	
SYMBOL_SOURCE	gene_symbol_source	
ENSP	protein_id	
OverlapBP	bp_overlap	
OverlapPC	percentage_overlap	
Uploaded_variation	id	
Location	seq_region_name, start, end, strand	The variant's location field is broken down into constituent coordinate parts for clarity. "seq_region_name" is used in place of "chr" or "chromosome" for consistency with other parts of Ensembl's REST API
*_maf	*_allele, *_maf	
cDNA_position	cdna_start, cdna_end	
CDS_position	cds_start, cds_end	
Protein_position	protein_start, protein_end	
SIFT	sift_prediction, sift_score	
PolyPhen	polyphen_prediction, polyphen_score	

Statistics

Ensembl VEP writes an HTML file containing statistics pertaining to the results of your job; it is named **[output_file]_summary.html** (with the default options the file will be named **variant_effect_output.txt_summary.html**). To view it, please open the file in your web browser.

- To prevent Ensembl VEP writing a stats file, use [--no_stats](#).
- To get a machine-readable text file in place of the HTML file, use [--stats_text](#). You can get both a HTML file and plain text file by using both [--stats_text](#) and [--stats_html](#).
- To change the name of the stats file from the default, use [--stats_file \[file\]](#).

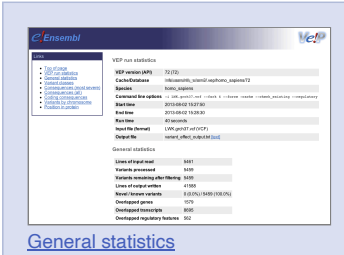
The page contains several sections:

General statistics

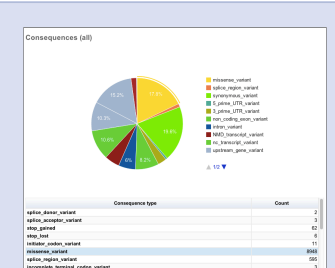
This section contains two tables. The first describes the cache and/or database used, the version of Ensembl VEP, species, command line parameters, input/output files and run time. The second table contains information about the number of variants, and the number of genes, transcripts and regulatory features overlapped by the input.

Charts and tables

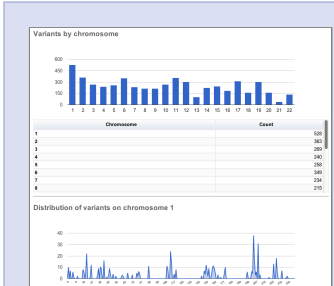
There then follows several charts, most with accompanying tables. Tables and charts are interactive; clicking on a row to highlight it in the table will highlight the relevant segment in the chart, and vice versa.



General statistics



Summary of called consequence types



Distribution of variants across chromosomes

For any questions not covered here, please send an email to the Ensembl [developer's mailing list](#) (public) or contact the [Ensembl Helpdesk](#) (private). Also you can report issues through our (public) Github repositories. For general Ensembl VEP issues you should use [ensembl-vep](#) repository and for specific plugins you should use [VEP_plugins](#) repository.

General questions

Q: Why has my insertion/deletion variant encoded in VCF disappeared from the output?

Ensembl treats unbalanced variants differently to VCF - your variant hasn't disappeared, it may have just changed slightly! You can solve this by giving your variants a unique identifier in the third column of the VCF file. See [here](#) for a full discussion.

Q: Why don't I see any co-located variants when using species X?

Not all species have variants and not all species that do are in the Ensembl variation resource - see [this document](#) for details. The [custom](#) option can be used in the commandline interface to include more variant sets

Q: Why do I see multiple known variants mapped to my input variant?

Ensembl VEP compares your input to known variants from the Ensembl variation database. In some cases one input variant can match multiple known variants:

- Germline variants from dbSNP and somatic mutations from COSMIC may be found at the same locus
- Some sources, e.g. HGMD, do not provide public access to allele-specific data, so an HGMD variant with unknown alleles may colocate with one from dbSNP with known alleles
- Multiple alternate alleles from your input may match different variants as they are described in dbSNP

See [here](#) for a full discussion.

Q: Ensembl VEP is not assigning a frequency to my input variant - why?

Ensembl VEP's cache contains frequency data only for specific studies. See [here](#) for a full discussion. The [custom](#) option can be used in the commandline interface to include more frequency sets

Q: Why do I see so many lines of output for each variant in my input?

While it would be convenient to have a simple, one word answer to the question "What is the consequence of this variant?", in reality biology is not this simple! Many genes have more than one transcript, so Ensembl VEP provides a prediction for each transcript that a variant overlaps. Ensembl VEP has options to help select results according to your requirements; the [--canonical](#) and [--mane](#) options indicate which transcripts are canonical and belong to the human MANE set respectively, while [--pick](#), [--per_gene](#), [--summary](#) and [--most_severe](#) allow you to give a more summary level assessment per variant.

Furthermore, several "compound" consequences are also possible - if, for example, a variant falls in the final few bases of an exon, it may be considered to affect a splicing site, in addition to possibly affecting the coding sequence.

Q: How do I reduce Ensembl VEP's memory requirement?

There are a number of ways to do this-

1. Ensure your input file is sorted by location. This can greatly reduce memory requirements and runtime
2. Consider reducing the buffer size. This reduces the number of variants annotated together in a batch and can be modified in both command line and web interfaces. Reducing buffer size may increase run time.
3. Ensure you are only using the options you need, rather than [--everything](#). Some data-rich options, such as regulatory annotation have an impact on memory use

Q: How to cite Ensembl VEP?

If you use Ensembl VEP, please cite our [latest publication](#) to continue to support Ensembl VEP development.

Ensembl VEP web interface questions

Q: How do I access the web version of the Ensembl Variant Effect Predictor?

You can find the Ensembl VEP web tool on the [Tools](#) page.

Q: Why is the output I get for my input file different when I use the Ensembl VEP web and command line interfaces?

Ensure that you are passing equivalent arguments to the command line tool that you are using in the web interface. If you are sure this is still a problem, please report it on the [ensembl-dev](#) mailing list.

Q: Is there a tutorial for the web tool?

Yes, see our latest tutorial [Annotating and prioritizing genomic variants using the Ensembl Variant Effect Predictor — A tutorial](#) for more information on using the Ensembl VEP web interface.

Ensembl VEP command line tool questions

Q: How can I make Ensembl VEP run faster?

There are a number of factors that influence how fast Ensembl VEP runs. Have a look at our [handy guide](#) for tips on improving runtime.

Q: Why am I not seeing the same variant from my input in the output?

Since the Ensembl 110 release, Ensembl VEP by default will minimise the input allele for display in the output. To see the exact allele representation you provided, use the `--uploaded_allele` option.

Q: Why do I see "N" as the reference allele in my HGVS strings?

Q: Why do I get errors related with Sequence.pm?

```
substr outside of string at /nfs/users/nfs_w/wm2/Perl/ensembl-variation/modules/Bio/EnsEMBL/Variation/Utils/Sequence.pm
Use of uninitialized value $ref_allele in string eq at /nfs/users/nfs_w/wm2/Perl/ensembl-variation/modules/Bio/EnsEMBL/
Use of uninitialized value in concatenation (.) or string at /nfs/users/nfs_w/wm2/Perl/ensembl-variation/modules/Bio/En
```

Both of these error types are usually seen when using a [FASTA file](#) for retrieving sequence. There are a couple of steps you can take to try to remedy them:

1. The index alongside the FASTA can become corrupted. Delete [fastafilename].index and re-run Ensembl VEP to regenerate it. By default this file is located in your \$HOME/.vep/[species]/[version]_[assembly] directory.
2. The FASTA file itself may have been corrupted during download; delete the fasta file and the index and re-download (you can use the [Ensembl VEP installer](#) to do this).
3. Older versions of BioPerl (1.2.3 in particular is known to have this) cannot properly index large FASTA files. Make sure you are using a later (>=1.6) version of BioPerl. The [Ensembl VEP installer](#) installs 1.6.924 for you.

If you still see problems after taking these steps, or if you were not using a FASTA file in the first place, please [contact us](#).

Q: Why are chromosomes not found in annotation sources or synonyms?

```
WARNING: Chromosome 21 not found in annotation sources or synonyms on line 160
```

This can occur if the chromosome names differ between your input variant and any annotation source that you are using (cache, database, GFF/GTF file, FASTA file, custom annotation file). To circumvent this you may provide a [synonyms file](#). A synonym file is included in Ensembl VEP's cache files, so if you have one of these for your species you can use it as follows:

```
./vep -i input.vcf -cache -synonyms ~/.vep/homo_sapiens/115_GRCh38/chr_synonyms.txt
```

The file consists of lines containing pairs of tab-separated synonyms. Order is not important as synonyms can be used in both "directions".

Q: Why do I get feature_type warnings from my GFF/GTF file?

```
WARNING: Ignoring 'five_prime utr' feature_type from Homo_sapiens.GRCh38.111.gtf.gz GFF/GTF file. This feature_type is
```

This can occur if you are using GFF/GTF file and the file contains a type that is not supported by Ensembl VEP. Those lines are simply ignored. However, in cases where the transcript model is incomplete the full model may be ignored.

Please try to use supported feature types as mentioned [here](#).

Q: Can I get gnomAD exomes and genomes frequencies in Ensembl VEP?

Yes, see [this guide](#).

Q: Why do I have issues connecting to Ensembl databases?

```
Could not connect to database homo_sapiens_core_63_37 as user anonymous using [DBI:mysql:database=homo_sapiens_core_63_37;host=ensembl.mysql.ensembl.org] (2) at $HOME/src/ensembl/modules/Bio/EnsEMBL/DBSQL/DBConnection.pm line 11.

----- EXCEPTION -----
MSG: Could not connect to database homo_sapiens_core_63_37 as user anonymous using [DBI:mysql:database=homo_sapiens_core_63_37;host=ensembl.mysql.ensembl.org] (2)
```

If you select the database option rather than using a cache Ensembl VEP will try to connect to the public MySQL server at [ensembl.mysql.ensembl.org](#). Occasionally the server may break connection with your process, which causes this error. This can happen when the server is busy, or due to various network issues. Consider using the [caching system](#). Using a cache and fasta file is the most efficient way to run Ensembl VEP.

Q: Can I use Ensembl VEP on Windows?

Yes - see the [documentation](#) for a few different ways to get the Ensembl VEP running on Windows.

Q: Can I use Ensembl VEP with species and assemblies which are not available in Ensembl?

Yes - you can run Ensembl VEP on any species you have data for by providing a custom gene annotation in [GFF/GTF](#) and genome sequence in [FASTA](#) file, like so:

```
./vep -i input.vcf --gff data.gff.gz --fasta genome.fa.gz
```

Q: Can I use Ensembl VEP with T2T-CHM13 and other human assemblies?

Yes - you can run Ensembl VEP using [Human Pangenome Reference Consortium \(HPRC\)](#) data by following the instructions on how to [use Ensembl VEP with HPRC assemblies](#).

Q: Can I download all of the SIFT and/or PolyPhen predictions?

The Ensembl Variation database and the human Ensembl VEP cache file contain precalculated SIFT and PolyPhen-2 predictions for every possible amino acid change in every translated protein product in Ensembl. Since these data are huge, we store them in a [compressed format](#).

There are different approaches to download SIFT/PolyPhen-2 data:

- Using the [PolyPhen_SIFT plugin](#):
 - For any species with predictions in our Ensembl databases, the plugin is able to download the predictions data into a local SQLite database for offline use. PolyPhen predictions are only available for human data.
 - We also provide a downloadable SQLite database containing PolyPhen/SIFT predictions based on [Human Pangenome Reference Consortium \(HPRC\)](#) and GRCh38 assemblies. For more information, refer to [Missense deleteriousness predictions](#) in HPRC assemblies.
- Using our **Perl API**:
 - Fetch a [ProteinFunctionPredictionMatrix](#) for your protein of interest and then call its [get_prediction\(\)](#) method to get the score for a particular position and amino acid, looping over all possible amino acids for your position.
 - You would need to work out which peptide position your codon maps to, but there are methods in the [TranscriptVariation](#) class that should help you (probably [translation_start\(\)](#) and [translation_end\(\)](#)).