# ClinVar

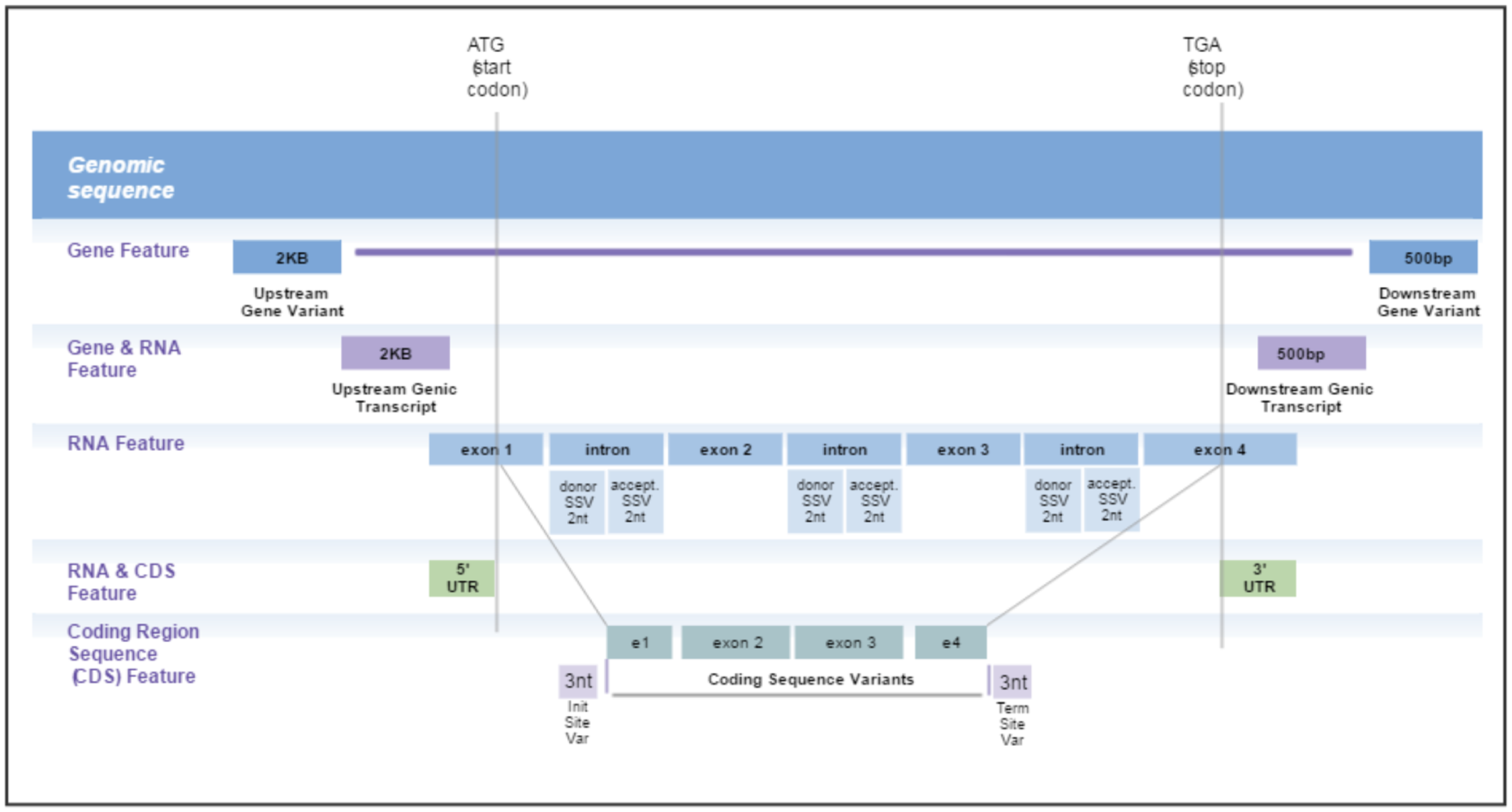



**Fig 1. Gene, RNA and Coding Region Sequence (CDS) feature locations used for assigning SO terms**

## Molecular consequence

Molecular consequence represents effects on protein products from the alterations in the coding nucleotide sequence. NCBI computes molecular consequence, and also assigns location-based ontology terms established by Sequence Ontology (SO), based on where the variant is located relative to gene, RNA and/or coding regions.

### Effect on protein products per transcript

For each RNA for which the variant coincides in part or completely within a coding region, we would assign one of the following molecular consequences, as a computed effect of a sequence change on a particular protein product.

| Public Term | SO id and value | VCF Tag |
|---|---|---|
| Stop Lost | SO:0001578:stop_lost | |
| Nonsense | SO:0001587:stop_gained | NSN |
| Synonymous | SO:0001819:synonymous_variant | SYN |
| Missense | SO:0001583:missense_variant | NSM |
| Frameshift | SO:0001589 :frameshift_variant | NSF |
| Inframe Insertion | SO:0001821:inframe_insertion | |
| Inframe Deletion | SO:0001822:inframe_deletion | |
| Inframe Indel | SO:0001820:inframe_indel | |

### Location-based Ontology Terms

Location-based Ontology Terms are assigned to a variant whenever any part of its deletion interval (per the representation of variants that considers them to be pairs of deletion and insertion intervals on a sequence) overlaps one of the Gene, RNA Feature or Coding regions (see illustration). If the variant overlaps more than one region or, if multiple transcripts are involved (as would be the case when the region is relative to a genomic location), all relevant SO terms are reported, in no particular order.

| Public Term | SO id and value | VCF Tag |
|---|---|---|
| 2KB Upstream | SO:0001636 :2KB_upstream_variant | R5 |
| 500 bp Downstream | SO:0001634:500B_downstream_variant | R3 |
| 3' UTR | SO:0001624 :3_prime_UTR_variant | U3 |
| 5' UTR | SO:0001623 :5_prime_UTR_variant | U5 |
| Coding Sequence Variant | SO:0001580 :coding_sequence_variant | |
| Initiator Codon | SO:0001582 :initiator_codon_variant | |
| Terminator Codon | SO:0001590:terminator_codon_variant | |
| 500 bp Downstream Genic Variant | SO:0002152:genic_downstream_transcript_variant | |
| 2KB Upstream Genic Variant | SO:0002153:genic_upstream_transcript_variant | |
| Intron | SO:0001627:intron_variant | INT |
| Non Coding Transcript Variant | SO:0001619 :non_coding_transcript_variant | |
| Splice Acceptor | SO:0001574 :splice_acceptor_variant | ASS |
| Splice Donor | SO:0001575 : splice_donor_variant | DSS |

The information was obtained from ClinVar: https://www.ncbi.nlm.nih.gov/variation/docs/glossary/

# ANNOVAR

| Value | Default precedence | Explanation | Sequence Ontology |
|---|---|---|---|
| exonic | 1 | variant overlaps a coding | exon_variant (SO:0001791) |
| splicing | 1 | variant is within 2-bp of a splicing junction (use -splicing_threshold to change this) | splicing_variant (SO:0001568) |
| ncRNA | 2 | variant overlaps a transcript without coding annotation in the gene definition (see Notes below for more explanation) | non_coding_transcript_variant (SO:0001619) |
| UTR5 | 3 | variant overlaps a 5' untranslated region | 5_prime_UTR_variant (SO:0001623) |
| UTR3 | 3 | variant overlaps a 3' untranslated region | 3_prime_UTR_variant (SO:0001624) |
| intronic | 4 | variant overlaps an intron | intron_variant (SO:0001627) |
| upstream | 5 | variant overlaps 1-kb region upstream of transcription start site | upstream_gene_variant (SO:0001631) |
| downstream | 5 | variant overlaps 1-kb region downtream of transcription end site (use -neargene to change this) | downstream_gene_variant (SO:0001632) |
| intergenic | 6 | variant is in intergenic region | intergenic_variant (SO:0001628) |

The value of the first column takes the following precedence (as of December 2010 and later version of ANNOVAR): exonic = splicing > ncRNA> > UTR5/UTR3 > intron > upstream/downstream > intergenic. The precedence defined above is used to decide what function to print out when a variant fit multiple functional categories. Note that:

1. the "exonic" here refers only to coding exonic portion , but not UTR portion, as there are two keywords (UTR5, UTR3) that are specifically reserved for UTR annotations.
2. "splicing" in ANNOVAR is defined as variant that is within 2-bp away from an exon/intron boundary by default, but the threshold can be changed by the --splicing_threshold argument. Before Feb 2013, if "exonic,splicing" is shown, it means that this is a variant within exon but close to exon/intron boundary; this behavior is due to historical reason, when a user requested that exonic variants near splicing sites be annotated with splicing as well. However, I continue to get user emails complaining about this behavior despite my best efforts to put explanation in the ANNOVAR website with details. Therefore, starting from Feb 2013 , "splicing" only refers to the 2bp in the intron that is close to an exon, and if you want to have the same behavior as before, add -exonicsplicing argument.
3. If a variant is located in both 5' UTR and 3' UTR region (possibly for two different genes), then the "UTR5,UTR3" will be p rinted as the output.
4. The term "upstream" and "downstream" is defined as 1-kb away from transcription start site or transcription end site, respectively, taking in account of the strand of the mRNA; the --neargene threshold can be used to adjust this threshold.
5. If a variant is located in both downstream and upstream region (possibly for 2 different genes), then the "upstream,downstream" will be printed as the output. In 2011 June version of ANNOVAR, the splicing annotation is improved. If the splicing site is in intron, then all isoforms and the corresponding base change will be printed.

The information was obtained from ANNOVAR: https://annovar.openbioinformatics.org/en/latest/user-guide/gene/?#switching-to-ucscensembl-gene-annotation

# SnpEff

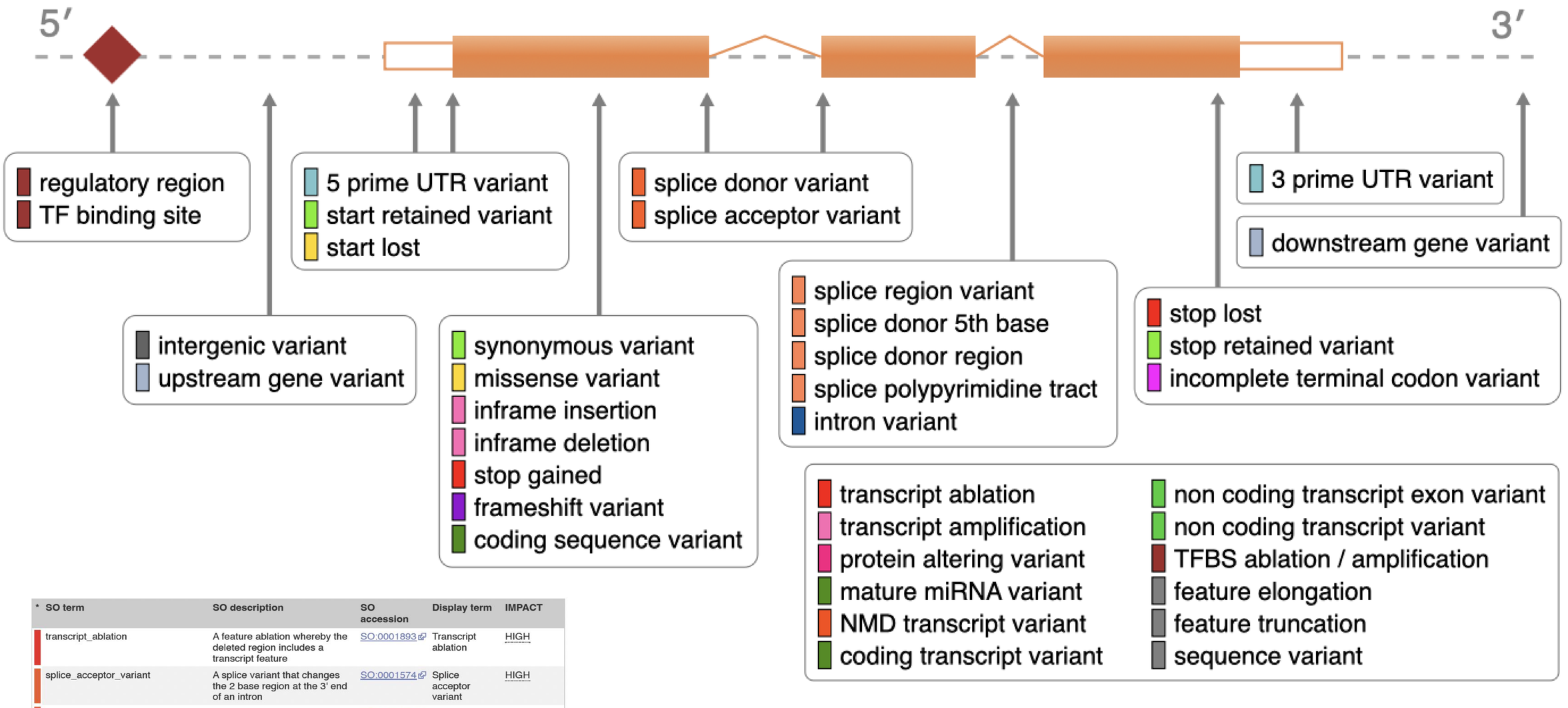
**Table 2.** Detailed effect list from SnpEff

| Effect | Note |
|---|---|
| INTERGENIC | The variant is in an intergenic region |
| UPSTREAM | Upstream of a gene (default length: 5K bases) |
| UTR_5_PRIME | Variant hits 5'UTR region |
| UTR_5_DELETED | The variant deletes and exon which is in the 5'UTR of the transcript |
| START_GAINED | A variant in 5'UTR region produces a three base sequence that can be a START codon |
| SPLICE_SITE_ACCEPTOR | The variant hits a splice acceptor site (defined as two bases before exon start, except for the first exon) |
| SPLICE_SITE_DONOR | The variant hits a Splice donor site (defined as two bases after coding exon end, except for the last exon) |
| START_LOST | Variant causes start codon to be mutated into a non-start codon |
| SYNONYMOUS_START | Variant causes start codon to be mutated into another start codon |
| CDS | The variant hits a CDS |
| GENE | The variant hits a gene |
| TRANSCRIPT | The variant hits a transcript |
| EXON | The vairant hist an exon |
| EXON_DELETED | A deletion removes the whole exon |
| NON_SYNONYMOUS_CODING | Variant causes a codon that produces a different amino acid |
| SYNONYMOUS_CODING | Variant causes a codon that produces the same amino acid |
| FRAME_SHIFT | Insertion or deletion causes a frame shift |
| CODON_CHANGE | One or many codons are changed |
| CODON_INSERTION | One or many codons are inserted |
| CODON_CHANGE_PLUS_CODON_INSERTION | One codon is changed and one or many codons are inserted |
| CODON_DELETION | One or many codons are deleted |
| CODON_CHANGE_PLUS_CODON_DELETION | One codon is changed and one or more codons are deleted |
| STOP_GAINED | Variant causes a STOP codon |
| SYNONYMOUS_STOP | Variant causes stop codon to be mutated into another stop codon |
| STOP_LOST | Variant causes stop codon to be mutated into a non-stop codon |
| INTRON | Variant hist and intron. Technically, hits no exon in the transcript |
| UTR_3_PRIME | Variant hits 3'UTR region |
| UTR_3_DELETED | The variant deletes and exon which is in the 3'UTR of the transcript |
| DOWNSTREAM | Downstream of a gene (default length: 5K bases) |
| INTRON_CONSERVED | The variant is in a highly conserved intronic region |
| INTERGENIC_CONSERVED | The variant is in a highly conserved intergenic region |

The information was obtained from Cingolani Pet al. A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila melanogaster strain w1118; iso-2; iso-3. Fly (Austin). 2012. 6(2):80-92. doi: 10.4161/fly.19695.

# VEP

See below a diagram showing the location of each display term relative to the transcript structure:




| * | SO term | SO description | SO accession | Display term | IMPACT |
|---|---|---|---|---|---|
| | transcript_ablation | A feature ablation whereby the deleted region includes a transcript feature | SO:0001893 | Transcript ablation | HIGH |
| | splice_acceptor_variant | A splice variant that changes the 2 base region at the 3' end of an intron | SO:0001574 | Splice acceptor variant | HIGH |
| | splice_donor_variant | A splice variant that changes the 2 base region at the 5' end of an intron | SO:0001575 | Splice donor variant | HIGH |
| | stop_gained | A sequence variant whereby at least one base of a codon is changed, resulting in a premature stop codon, leading to a shortened transcript | SO:0001587 | Stop gained | HIGH |
| | frameshift_variant | A sequence variant which causes a disruption of the translational reading frame, because the number of nucleotides inserted or deleted is not a multiple of three | SO:0001589 | Frameshift variant | HIGH |
| | stop_lost | A sequence variant where at least one base of the terminator codon (stop) is changed, resulting in an elongated transcript | SO:0001578 | Stop lost | HIGH |
| | start_lost | A codon variant that changes at least one base of the canonical start codon | SO:0002012 | Start lost | HIGH |
| | transcript_amplification | A feature amplification of a region containing a transcript | SO:0001889 | Transcript amplification | HIGH |
| | feature_elongation | A sequence variant that causes the extension of a genomic feature, with regard to the reference sequence | SO:0001907 | Feature elongation | HIGH |
| | feature_truncation | A sequence variant that causes the reduction of a genomic feature, with regard to the reference sequence | SO:0001906 | Feature truncation | HIGH |
| | inframe_insertion | An inframe non synonymous variant that inserts bases into in the coding sequence | SO:0001821 | Inframe insertion | MODERATE |
| | inframe_deletion | An inframe non synonymous variant that deletes bases from the coding sequence | SO:0001822 | Inframe deletion | MODERATE |
| | missense_variant | A sequence variant, that changes one or more bases, resulting in a different amino acid sequence but where the length is preserved | SO:0001583 | Missense variant | MODERATE |
| | protein_altering_variant | A sequence_variant which is predicted to change the protein encoded in the coding sequence | SO:0001818 | Protein altering variant | MODERATE |
| | splice_donor_5th_base_variant | A sequence variant that causes a change at the 5th base pair after the start of the intron in the orientation of the transcript | SO:0001787 | Splice donor 5th base variant | LOW |
| | splice_region_variant | A sequence variant in which a change has occurred within the region of the splice site, either within 1-3 bases of the exon or 3-8 bases of the intron | SO:0001630 | Splice region variant | LOW |
| | splice_donor_region_variant | A sequence variant that falls in the region between the 3rd and 6th base after splice junction (5' end of intron) | SO:0002170 | Splice donor region variant | LOW |
| | splice_polypyrimidine_tract_variant | A sequence variant that falls in the polypyrimidine tract at 3' end of intron between 17 and 3 bases from the end (acceptor -3 to acceptor -17) | SO:0002169 | Splice polypyrimidine tract variant | LOW |
| | incomplete_terminal_codon_variant | A sequence variant where at least one base of the final codon of an incompletely annotated transcript is changed | SO:0001626 | Incomplete terminal codon variant | LOW |
| | start_retained_variant | A sequence variant where at least one base in the start codon is changed, but the start remains | SO:0002019 | Start retained variant | LOW |
| | stop_retained_variant | A sequence variant where at least one base in the terminator codon is changed, but the terminator remains | SO:0001567 | Stop retained variant | LOW |
| | synonymous_variant | A sequence variant where there is no resulting change to the encoded amino acid | SO:0001819 | Synonymous variant | LOW |
| | coding_sequence_variant | A sequence variant that changes the coding sequence | SO:0001580 | Coding sequence variant | MODIFIER |
| | mature_miRNA_variant | A transcript variant located with the sequence of the mature miRNA | SO:0001620 | Mature miRNA variant | MODIFIER |
| | 5_prime_UTR_variant | A UTR variant of the 5' UTR | SO:0001623 | 5 prime UTR variant | MODIFIER |
| | 3_prime_UTR_variant | A UTR variant of the 3' UTR | SO:0001624 | 3 prime UTR variant | MODIFIER |
| | non_coding_transcript_exon_variant | A sequence variant that changes non-coding exon sequence in a non-coding transcript | SO:0001792 | Non coding transcript exon variant | MODIFIER |
| | intron_variant | A transcript variant occurring within an intron | SO:0001627 | Intron variant | MODIFIER |
| | NMD_transcript_variant | A variant in a transcript that is the target of NMD | SO:0001621 | NMD transcript variant | MODIFIER |
| | non_coding_transcript_variant | A transcript variant of a non coding RNA gene | SO:0001619 | Non coding transcript variant | MODIFIER |
| | coding_transcript_variant | A transcript variant of a protein coding gene | SO:0001968 | Coding transcript variant | MODIFIER |
| | upstream_gene_variant | A sequence variant located 5' of a gene | SO:0001631 | Upstream gene variant | MODIFIER |
| | downstream_gene_variant | A sequence variant located 3' of a gene | SO:0001632 | Downstream gene variant | MODIFIER |
| | TFBS_ablation | A feature ablation whereby the deleted region includes a transcription factor binding site | SO:0001895 | TFBS ablation | MODIFIER |
| | TFBS_amplification | A feature amplification of a region containing a transcription factor binding site | SO:0001892 | TFBS amplification | MODIFIER |
| | TF_binding_site_variant | A sequence variant located within a transcription factor binding site | SO:0001782 | TF binding site variant | MODIFIER |
| | regulatory_region_ablation | A feature ablation whereby the deleted region includes a regulatory region | SO:0001894 | Regulatory region ablation | MODIFIER |
| | regulatory_region_amplification | A feature amplification of a region containing a regulatory region | SO:0001891 | Regulatory region amplification | MODIFIER |
| | regulatory_region_variant | A sequence variant located within a regulatory region | SO:0001566 | Regulatory region variant | MODIFIER |
| | intergenic_variant | A sequence variant located in the intergenic region, between genes | SO:0001628 | Intergenic variant | MODIFIER |
| | sequence_variant | A sequence_variant is a non exact copy of a sequence_feature or genome exhibiting one or more sequence_alteration | SO:0001060 | Sequence variant | MODIFIER |

* Corresponding colours for the Ensembl web displays.

Missense variants may have further annotation on their effect on the protein function, using a number of algorithms.

The information was obtained from Ensembl:
https://asia.ensembl.org/info/genome/variation/prediction/predicted_data.html