# Ensembl Genome Browser Workshop

## Liverpool, United Kingdom

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**Ensembl, EMBL-EBI**

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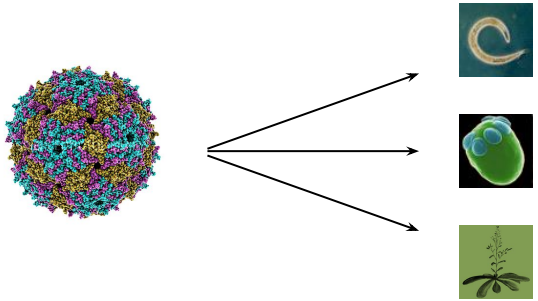
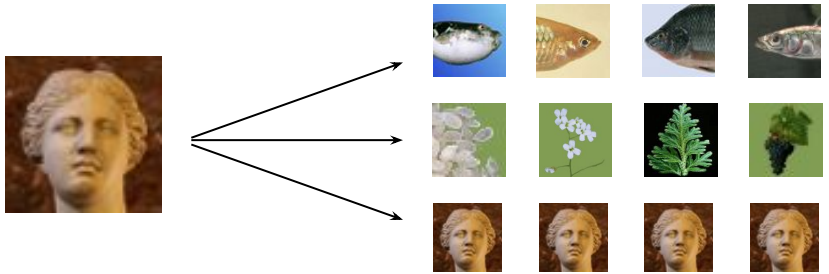
# Learning outcomes

- Differentiate the types of genomic data available in Ensembl
- Perform an analysis of a variation dataset using the Ensembl VEP
- View the output from the Ensembl VEP and filter to prioritise variants of interest
- Identify how to find the help and documentation pages for the available data types

# Sequencing genomes

- 1977: first genome sequenced (5 kb)
- 2004: first human genome sequenced (3 Gb)

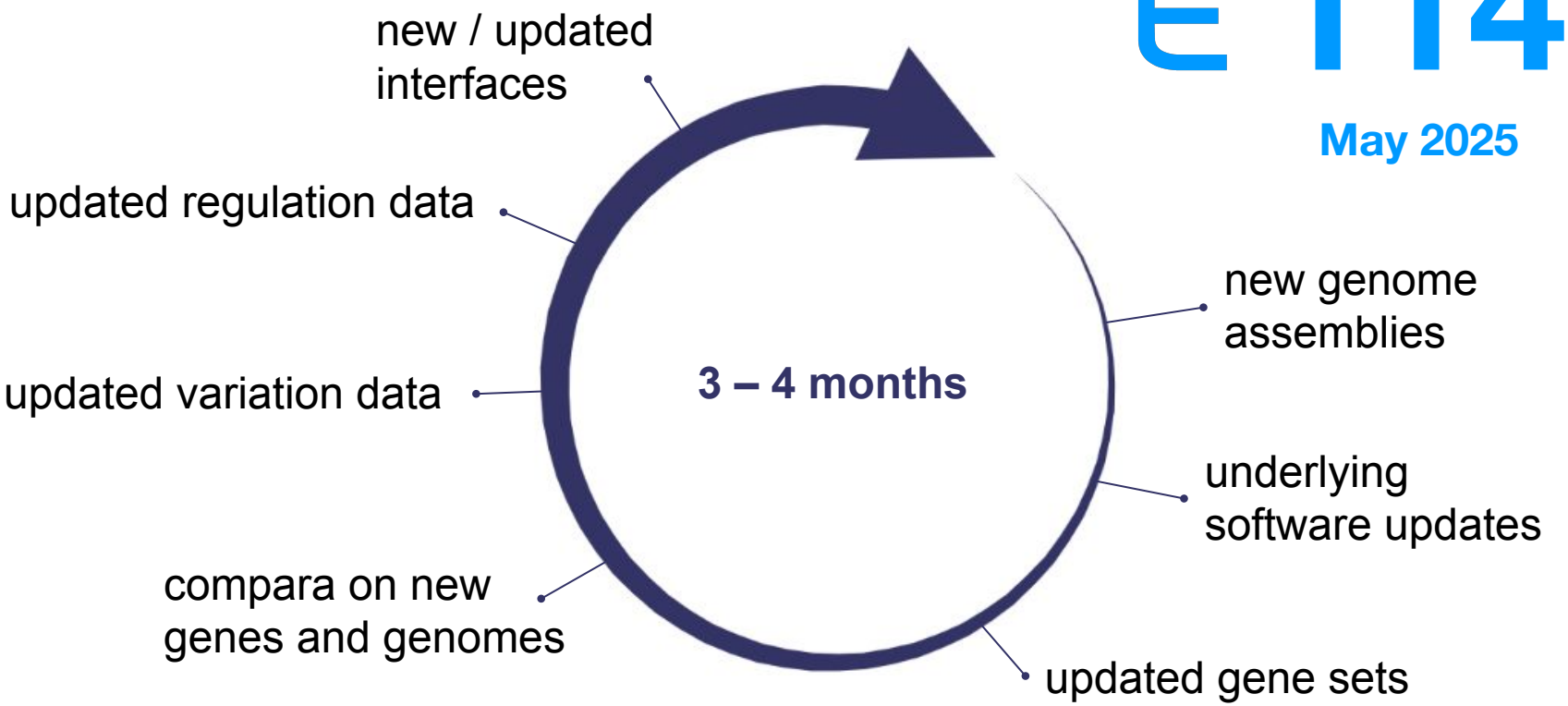




# Ensembl release cycle

E 114

May 2025

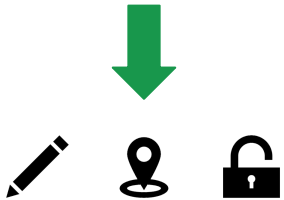


# Why do we need genome browsers?

# What is Ensembl?

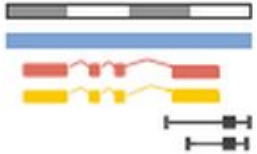
Ensembl annotates and maps genomic features from genome sequences, and brings together information from a wide range of other databases in a single site.

```
AGTGCTTAATGTGGCTAGTGGCACCGGTTTGGACAGCACAGCTGTAAAATGTTCCC
ATCCTCACAGTAAGCTGTTACCGTTCCAGGAGATGGGACTGAATTAGAATTCAAAC
AAATTTTCCAGCGCTTCTGAGTTTTACCTCAGTCACATAATAAGGAATGCATCCCT
GTGTAAGTGCATTTTGGTCTTCTGTTTTGCAGACTTATTTACCAAGCATTGGAGGA
ATATCGTAGGTAAAAATGCCTATTGGATCCAAAGAGAGGCCAACATTTTTTGAAAT
TTTTAAGACACGCTGCAACAAAGCAGGTATTGACAAATTTTATATAACTTTATAAA
TTACACCGAGAAAGTGTTTTCTAAAAAATGCTTGCTAAAAACCCAGTACGTCACAG
TGTTGCTTAGAACCATAAACTGTTCCTTATGTGTGTATAAATCCAGTTAACAACAT
AATCATCGTTTGCAGGTTAACCACATGATAAATATAGAACGTCTAGTGGATAAAGA
GGAAACTGGCCCCTTGACTAGCAGTAGGAACAATTACTAACAAATCAATTACTAAC
```



# Ensembl features

- Genomes and gene builds
- Comparative genomics (homologues, gene trees, alignments)
- Regulatory builds
- Data export with BioMart
- Tools for data processing, e.g. Ensembl VEP
- Display your own data
- Programmatic access via APIs
- Completely open-source (FTP, GitHub)



The mission of Ensembl is to provide a comprehensive and accurate annotation of genomes, integrating this information with other biological data and making it publicly accessible via the web.



# ENSEMBL

Genome data & annotation

About using Ensembl

**Species selector**

Create & manage your own species list

**Genome browser**

Look at genes & transcripts in their genomic context

**Entity viewer**

Get gene & transcript information

# Ensembl Beta

- New Ensembl genome browser platform with an app-based approach to functionality
- Infrastructure continues to provide the community with access to more intuitive interfaces and new feature developments
- Highly responsive and modern user interface
- User will have the ability to browse multiple species of interest simultaneously
- All Ensembl sites now in a single platform
- Currently under Beta testing - we want to hear the users' thoughts!

# Available human genome assemblies

99 human genome assemblies, including:

- GRCh37 (hg19)
- GRCh38 (hg38)
- T2T-CHM13
- Genomes of 48 individuals (96 haplotypes) from the Human Pangenome Reference Consortium (HPRC)

TOWARDS A COMPLETE REFERENCE OF HUMAN GENOME DIVERSITY

HUMAN PANGENOME

# New features to expect in Ensembl Beta

- Regulatory data (Available now!)
- Cross-references (XRefs) (Available now!)
- Additional genome assemblies and gene builds
- Gene expression, ontology and pathways
- Associated phenotypes
- Additional variation data

# The Ensembl Variant Effect Predictor (VEP)

## Ensembl Genome Browser Workshop

# Ensembl VEP

An analysis tool to predict the **molecular consequences** of variants and report essential information about a variant/ location.

# What can you do with Ensembl VEP?

**Variant input:**

- Alleles + location
- VCF
- HGVS
- Variant IDs
- SPDI


**Output:**

- Genes, transcripts affected
- Pathogenicity
- Frequency data
- Protein information
- PubMed citations

# Data input formats

**HGVS notation:**

```
ENST00000641515.2:c.4A>C
ENST00000272065.10:c.43+16C>T
ENST00000256509.7:c.5del
9:g.22125504G>C
```

**Variant IDs:**

```
rs1156485833
COSM327779
rs867704559
```

**SPDI:**

```
NC_000001.11:65567:A:C
NC_000002.12:265022:C:T
NC_000003.12:319780:A:
```

# Data input formats

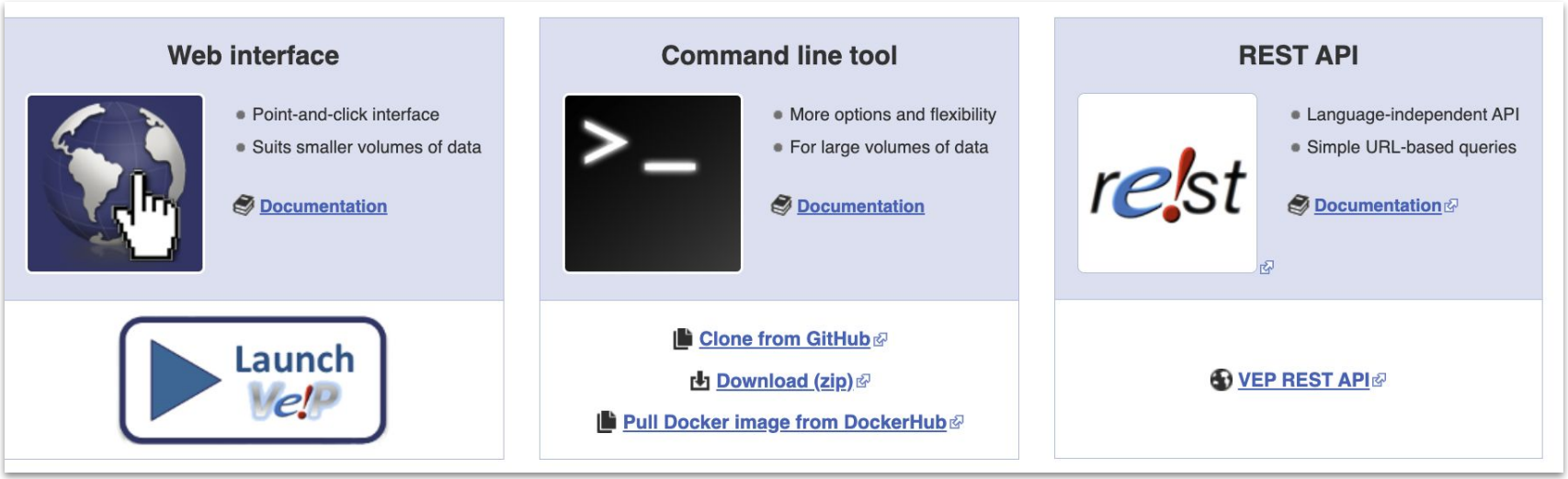
## Ensembl default input:

```
#chr    start   end allele strand id
1   65568   65568   A/C 1
2   265023  265023  C/T 1
3   319781  319781  A/- 1
```

## VCF:

```
#chr    pos id  ref alt qual    filt    info
1   65568   .   A   C   .   .   .
2   265023  .   C   T   .   .   .
3   319780  .   GA  G   .   .   .
```

# Ensembl VEP interfaces



# Ensembl VEP REST API

**`GET`** and **`POST`** requests are supported for single variants or small batches using HGVS notation, variant IDs or variant coordinates.

| Resource | Description |
|---|---|
| GET vep/:species/hgvs/:hgvs_notation | Fetch variant consequences based on a HGVS notation |
| POST vep/:species/hgvs | Fetch variant consequences for multiple HGVS notations |
| GET vep/:species/id/:id | Fetch variant consequences based on a variant identifier |
| POST vep/:species/id | Fetch variant consequences for multiple ids |
| GET vep/:species/region/:region/:allele/ | Fetch variant consequences |
| POST vep/:species/region | Fetch variant consequences for multiple regions |

# Command-line Ensembl VEP

- Simple installation
- Can handle genome-wide data
- Can work 100% offline
- Highly customisable
- Data bundles (caches) available for GRCh38 / hg38, GRCh37 / hg19, T2T-CHM13 and more

# Deleteriousness predictions

Ensembl VEP plugins are available to integrate predictive scores from tools including:

- Missense variant scores:
  - AlphaMissense
  - REVEL
  - EVE
  - ClinPred
- Genome wide change tolerance:
  - CADD
- Splicing impact:
  - SpliceAI
  - MaxEntScan
- Impact on gene expression:
  - Enformer

# Phenotype/functional evidence plugins

Phenotype and functional information is available from sources including :


results of highly parallel assays into cellular variant effect


evidence of variant impact on interactions

NHGRI-EBI GWAS Catalog

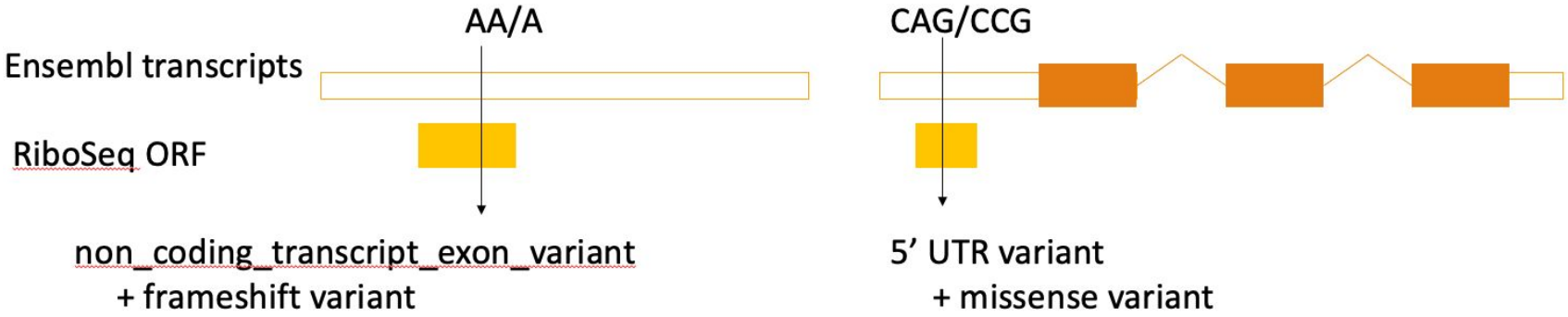
disease associations


the function, the cellular location and the associated biological processes of the product of any gene a variant lies within

# Additional analysis

Ensembl VEP plugins can run additional analysis, for example-

- Prediction of molecular consequences with respect to open reading frames discovered via RiboSeq

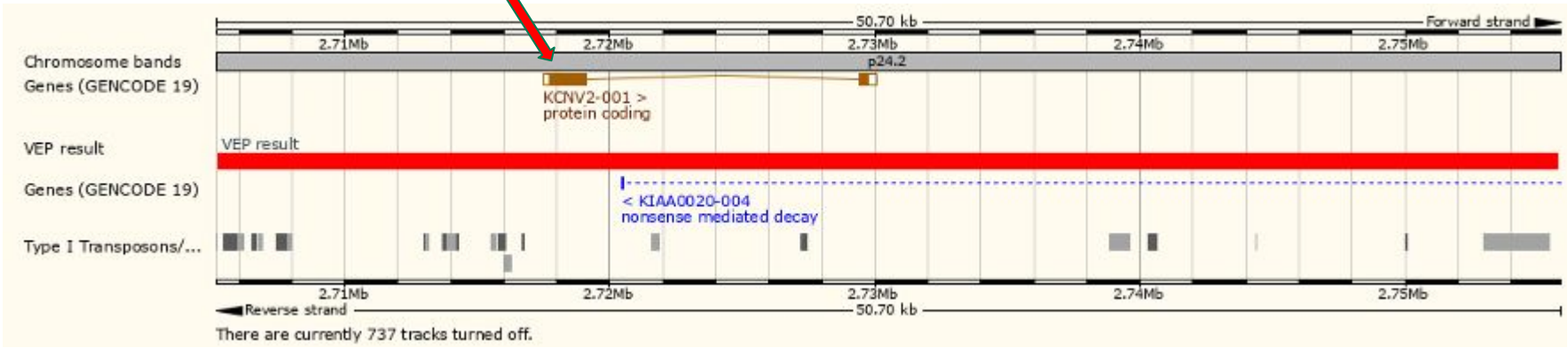



- Reporting ClinVar assertions associated with locations in paralogous genes

# Structural variant annotation

Ensembl VEP annotates SVs, reporting when transcripts and regulatory elements are deleted, truncated, amplified etc

| Uploaded variant | Location | Consequence | Symbol | Gene | Feature type | Feature | Biotype | Exon | Intron |
|---|---|---|---|---|---|---|---|---|---|
| 9_2705212_deletion | 9:2705211-2755784 | transcript_ablation | KCNV2 | ENSG00000168263 | Transcript | ENST00000382082 | protein_coding | 1-2/2 | 1/1 |
| 9_2705212_deletion | 9:2705211-2755784 | 3_prime_UTR_variant, intron_variant, NMD_transcript_variant, feature_truncation | KIAA0020 | ENSG00000080608 | Transcript | ENST00000490444 | nonsense_mediated_decay | 4/4 | 3/3 |
| 9_2705212_deletion | 9:2705211-2755784 | regulatory_region_ablation, regulatory_region_variant | - | - | RegulatoryFeature | ENSR00001445356 | - | - | - |
| 9_2705212_deletion | 9:2705211-2755784 | regulatory_region_ablation, regulatory_region_variant | - | - | RegulatoryFeature | ENSR00001445357 | - | - | - |



# More information

Publications:

Hunt SE, Moore B, Amode RM, et al. Annotating and prioritizing genomic variants using the Ensembl Variant Effect Predictor - A tutorial. Human Mutation. 2022 Aug;43(8):986-997. DOI: 10.1002/humu.24298. PMID: 34816521; PMCID: PMC7613081.

McLaren W, Gil L, Hunt SE, et al. The Ensembl Variant Effect Predictor. Genome Biology. 2016 Jun;17(1):122. DOI: 10.1186/s13059-016-0974-4. PMID: 27268795; PMCID: PMC4893825.

# Demonstration

We're going to use Ensembl VEP to look at a set of variant:

14 73219188 73219188 C/T
6 161785778 161785778 A/C
7 117480097 117480097 G/T
7 117587806 117587806  G/A
10 62813413 62813413 G/A

# Recommend us

**Browser course**
One day course on the Ensembl browser, aimed at wet-lab scientists.

**REST API course**
Half day course on the Ensembl REST API, aimed at bioinformaticians.

**Train the trainer course**
One day course on delivering the Ensembl browser course.

We can teach an Ensembl course at any institute for free (plus trainers' expenses in high income countries).

helpdesk@ensembl.org

https://training.ensembl.org/hosting

# Reach out to us

/Ensembl.org

/EnsemblGenomeBrowser

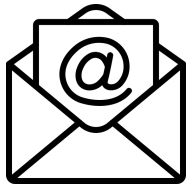
@Ensembl

www.ensembl.info

# Help and documentation

| | |
|---|---|
| Courses online | https://www.ebi.ac.uk/training/ |
| Tutorials | https://www.ensembl.org/info/website/tutorials/ |
| Flash animations | https://www.youtube.com/user/EnsemblHelpdesk |
| | https://youku.com/u/UMzM1NjkzMTI0 |

| | |
|---|---|
| Email | helpdesk@ensembl.org |
| Mailing lists | dev@ensembl.org |
| | announce@ensembl.org |



# Publications

- List of Ensembl publications: https://www.ensembl.org/info/about/publications.html
- Topic-specific articles mentioned throughout the workshop

Harrison PW, Amode MR, Harrison PW, Austine-Orimoloye O et al. Ensembl 2024. Nucleic Acids Research. 2024 Jan;52(D1):D891-D899. DOI: 10.1093/nar/gkad1049. PMID: 37953337; PMCID: PMC10767893.

Yates AD, Allen J, Amode RM, et al. Ensembl Genomes 2022: an expanding genome resource for non-vertebrates. Nucleic Acids Research. 2022 Jan;50(D1):D996-D1003. DOI: 10.1093/nar/gkab1007. PMID: 34791415; PMCID: PMC8728113.

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UKRI Medical Research Council
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NIH National Institute of Allergy and Infectious Diseases
NIH National Institute of General Medical Sciences

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# Training materials

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