Ensembl Genome Browser Workshop

Liverpool, United Kingdom

Aleena Mushtaq

Ensembl, EMBL-EBI

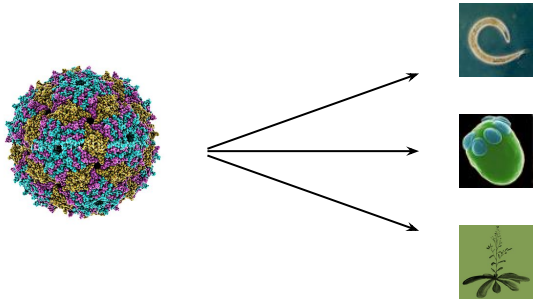
July 2025

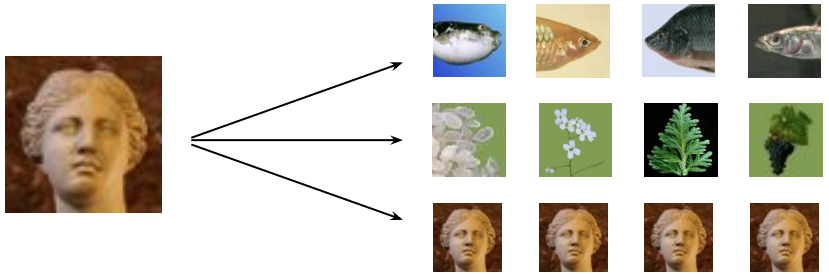
Learning outcomes

- 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)

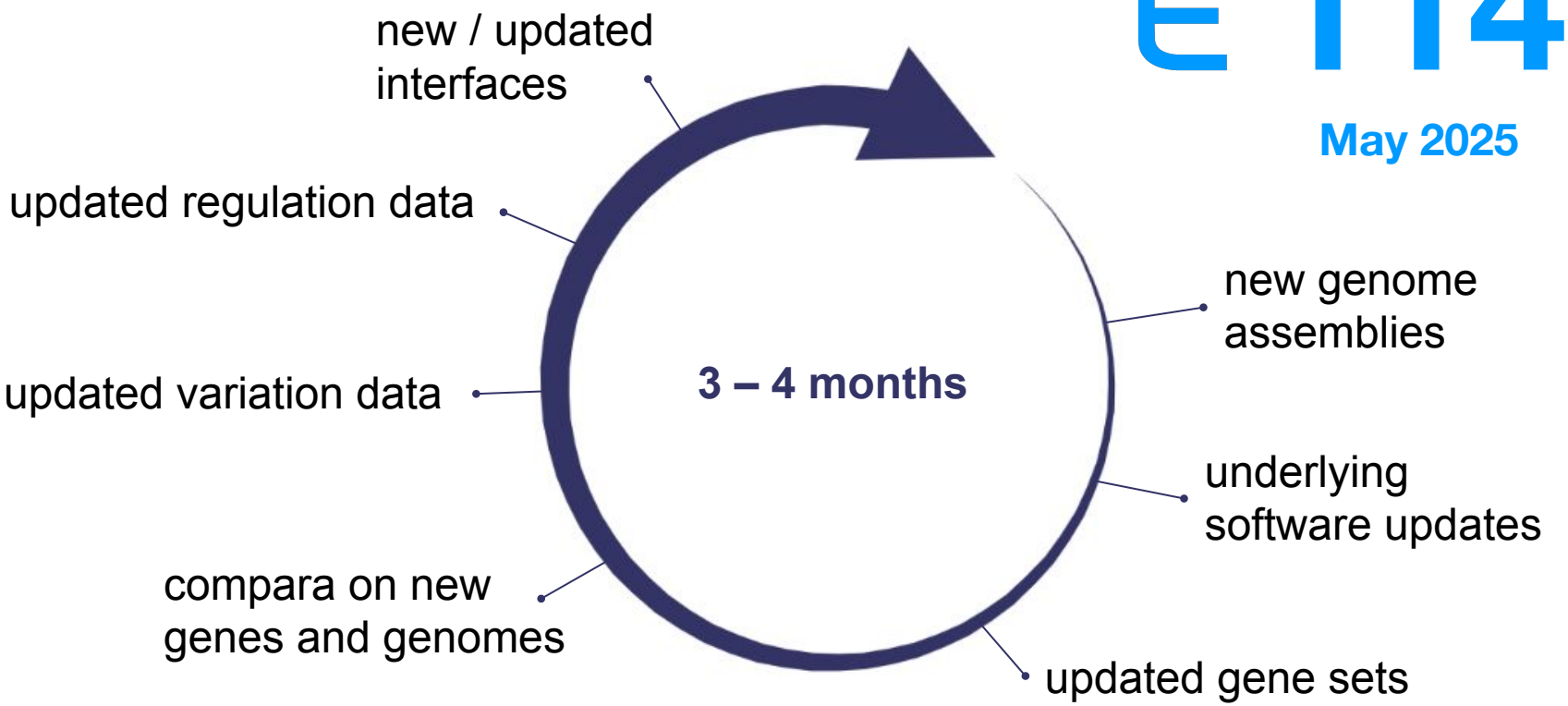




Ensembl release cycle

E 114

May 2025

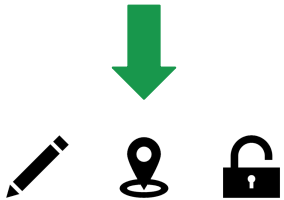


Why do we need genome browsers?

What is Ensembl?

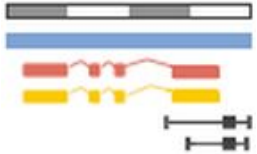
Ensembl annotates and maps genomic features from genome sequences, and brings together information from a wide range of other databases in a single site.

```
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

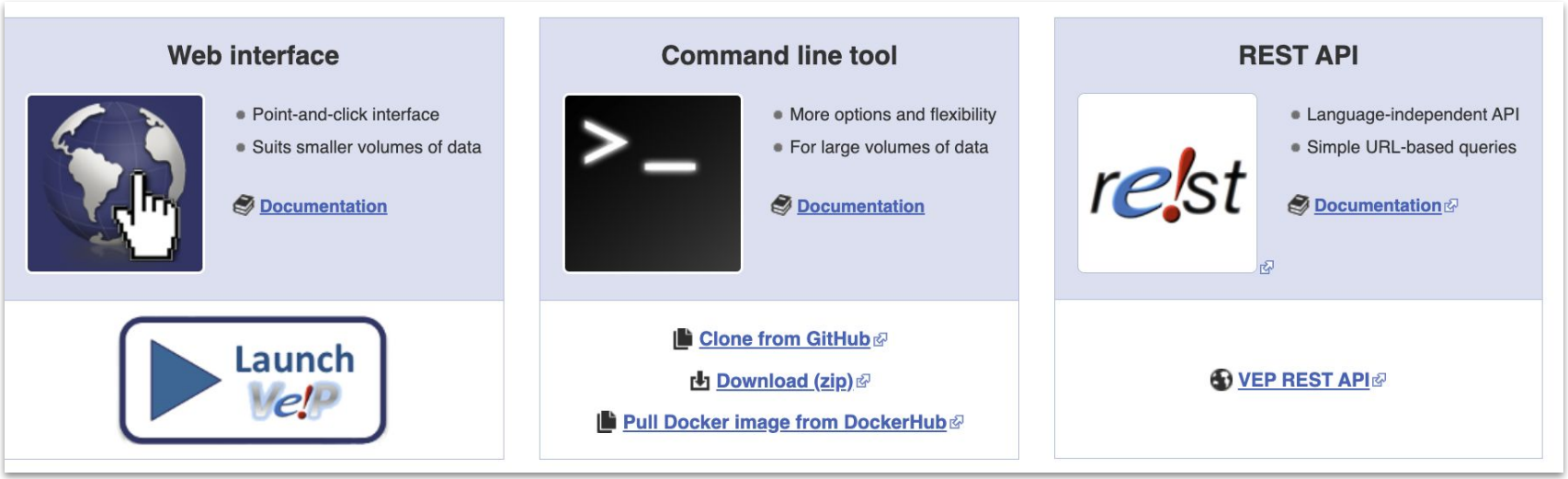
Ensembl default input:

```
#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

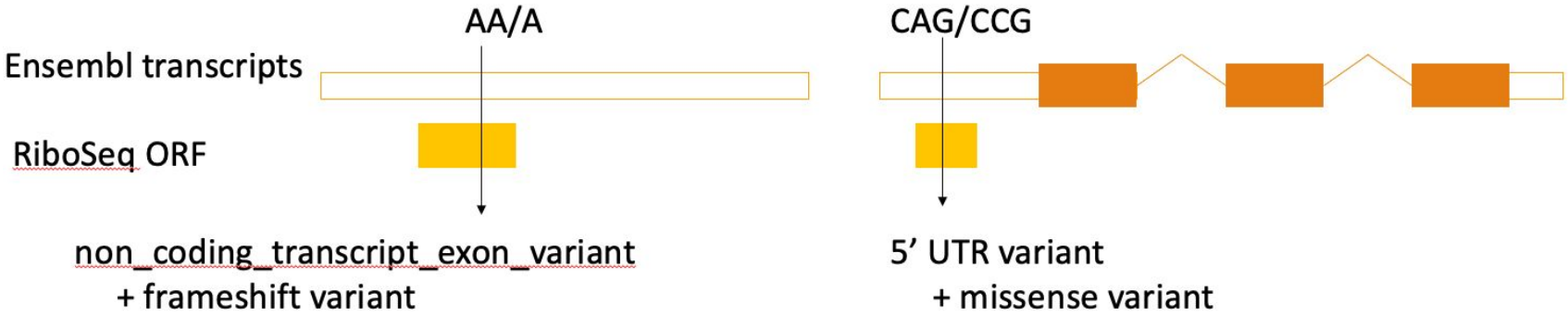
disease associations

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

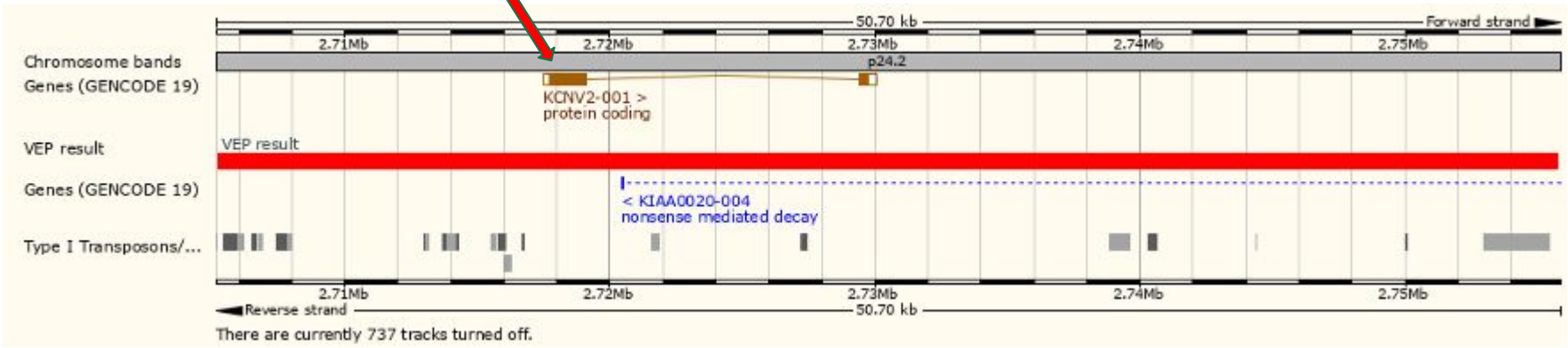


- Reporting ClinVar assertions associated with locations in paralogous genes

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

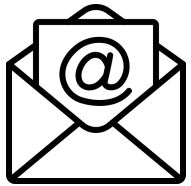
@Ensembl

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.

Acknowledgements and funding

wellcome

EMBL

TRANSFORMING GENETIC MEDICINE INITIATIVE

National Human Genome Research Institute (NHGRI)

National Institute of Allergy and Infectious Diseases (NIAID)

Open Targets

UK Research and Innovation

elixir

Funded by the European Union

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