Tutorial Genomic variant interpretation & prioritisation for clinical research

ISMB/ECCB 2025

20 July 2025
Liverpool, UK

PDBe Protein Data Bank in Europe

Open Targets

wellcome sanger institute

DECIPHER GRCh38

G2P

UniProt

e!Ensembl

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Learning outcomes

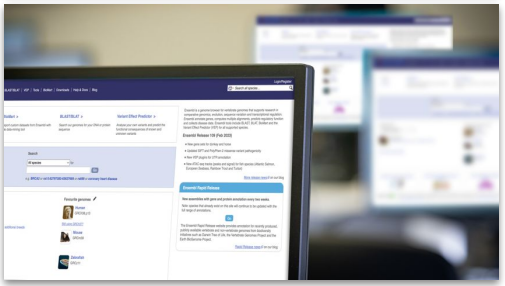
By the end of the tutorial, we expect you will be able to:

- **Explore human variation types** in commonly used bioinformatics file formats
- **Compare experimental methods** for variant effect analysis and understand the specific strengths of each
- **Navigate bioinformatics knowledge bases** to explore information about genetic variants and to contrast different approaches to see how they can be combined for interpretation
- **Evaluate evidence** from multiple sources supporting variant effect and impact in the context of research and study design
- **Investigate the impact** of variant interpretation on clinical diagnostics and drug tractability

Workshop structure

- Lectures and hands-on activities on key themes
  - Genome annotation & variation
  - Variant effects on proteins
  - Experimental methods
  - Clinical applications & resources
- Group projects & presentations
- Lunch and refreshment breaks

Full info:
https://www.iscb.org/ismbeccb2025/programme-agenda/tutorials#ip3



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Materials for this tutorial

- Github: https://bit.ly/3TNy43U

Agenda for today

09:15-09:30	Lecture 1: Introduction - The challenge of variant interpretation: Variation in context of human health
09:30-10:00	Lecture 2: Genomic Annotation for variation datasets: Public annotation datasets, Variation sources, Transcript based annotations, Non-coding variation, Structural variation
10:00-10:45	Hands-on 1: Annotating and predicting molecular variant effect: Variant prioritisation and scoring methods
10:45-11:00	Break
11:00-11:15	Lecture 3: Understanding Variant Effects Using Protein Structure Protein position, interaction and complexes for variant interpretation, Alphafold3 and predicted structures
11:15-11:45	Lecture 4: Understanding Variant Effects Using Protein Function Combining functional, structural and population annotations to contextualise variant effects in proteins
11:45-12:15	Hands-on 2: Using protein databases to investigate variant impact: Using structural information to interpret variant effect
12:15-12:45	Lecture 5: Deep Mutational Scanning: Genome Editing for Variant Analysis

Agenda for today

12:45-14:00	Lunch Break
14:00-14:30	Lecture 6: Utilising clinical data in variant prioritisation and classification, Applications for disease research and genomic diagnosis, DECIPHER, G2P, and GWAS Catalog
14:30-15:00	Lecture 7: Target tractability and drug associations: Target prioritisation for drug discovery, Case studies
15:00-16:00	Group Projects: Hands on activity using bioinformatics resources for variant interpretation
16:00-16:15	Break
16:15-17:00	Group Projects: Hands on activity using bioinformatics resources for variant interpretation
17:00-17:45	Presentations from groups: Present to peers to discuss ideas and future work
17:45-18:00	Closing Remarks

Meet your trainers

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Open Targets

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Introduction The challenge of variant interpretation

ISMB/ECCB 2025

Mallory Freeberg

Human Genomics Team Lead

20 July 2025 - Liverpool, UK

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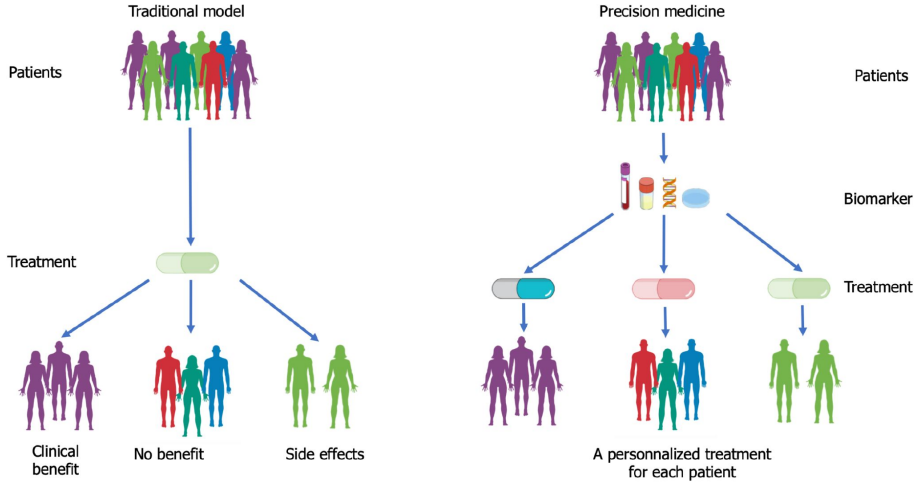
Variant interpretation is crucial for understanding health

- Genetic variation underpins both health and disease
- Interpreting variants is critical for:
  - Faster diagnosis
  - Understanding disease progression
  - Identifying drug targets
  - Personalising treatments

→ Improved health outcomes and societal and clinical benefits



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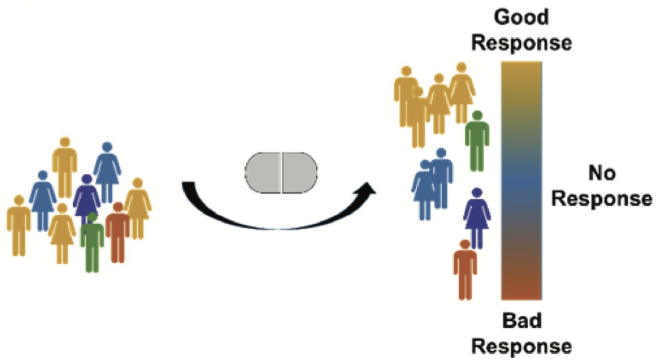
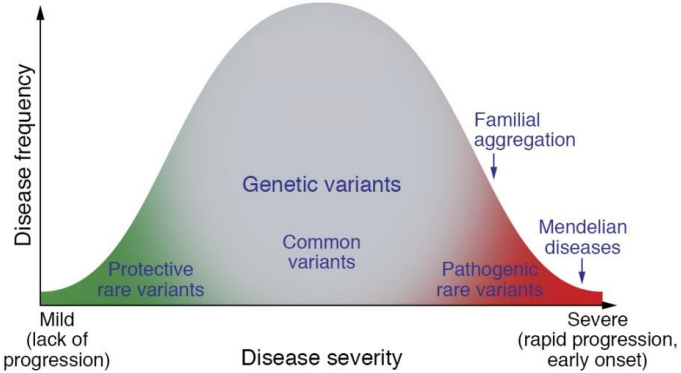
Variant interpretation is crucial for understanding health

Modulating drug response



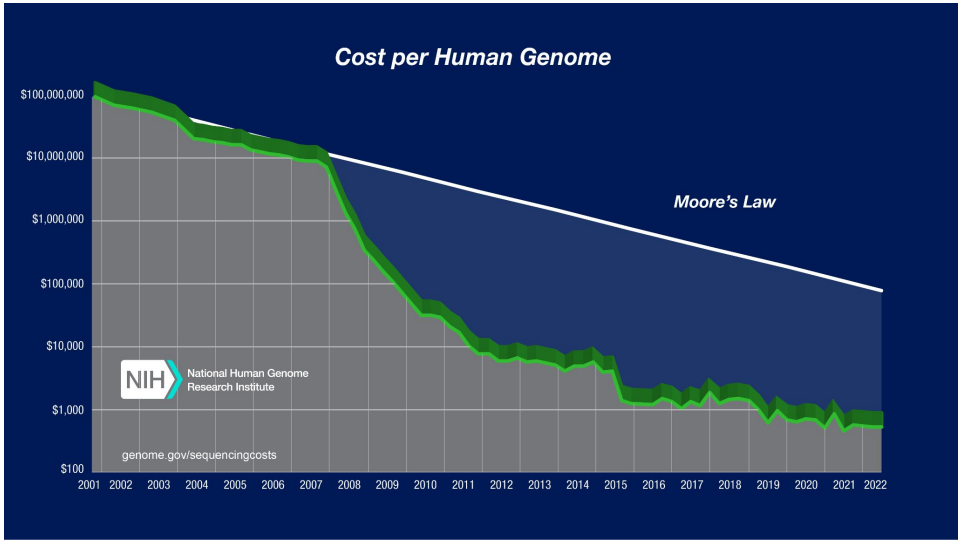
Dictating disease prognosis



http://dx.doi.org/10.1093/bioinformatics/btz023; https://doi.org/10.1172/JCI93556

Genomic data explosion brings benefits and challenges

- Sequencing is faster and cheaper
- Genome sequencing part of healthcare in some countries
- Millions of variants per genome → interpretation remains a bottleneck



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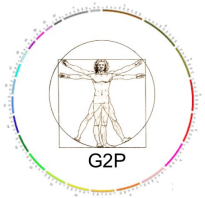
Variant interpretation is challenging in many aspects

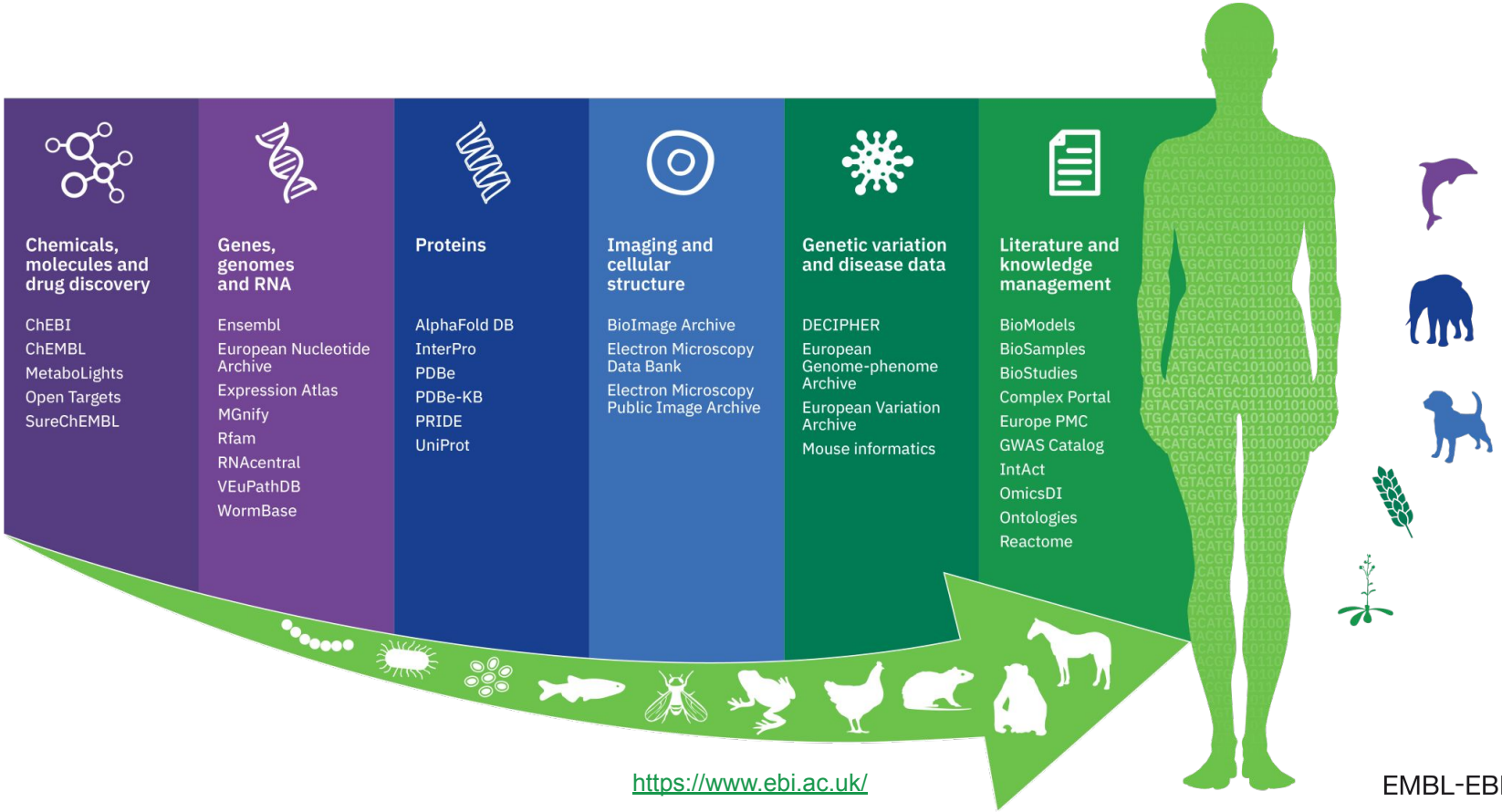
- Variants are diverse
  - Rare vs common
  - Coding vs non-coding
  - Single vs structural vs complex
- Functional effects can be population-specific and context-dependent
- *Diversity in mechanisms of action at gene and protein levels → not always obvious what is causing observations!*
- Information can be missing, incomplete, conflicting

Many resources available to tackle these challenges

- Data, annotations, and tools can help us understand variant effects
  - Bioinformatics tools & pipelines
  - Experimental assays
  - Genomic & proteomic data resources
  - Clinical databases



EMBL European Bioinformatics Institute (EMBL-EBI)



https://www.ebi.ac.uk/

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Agenda for today TO ADD

Questions?

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Next up:

Lecture 1 Genomic annotation for variation datasets

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Share your Feedback!

Scan the QR code to let us know your thoughts on this tutorial. Thank you!

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EMBL-EBI resources

https://www.ebi.ac.uk/services/data-resources-and-tools

The European Molecular Biology Laboratory

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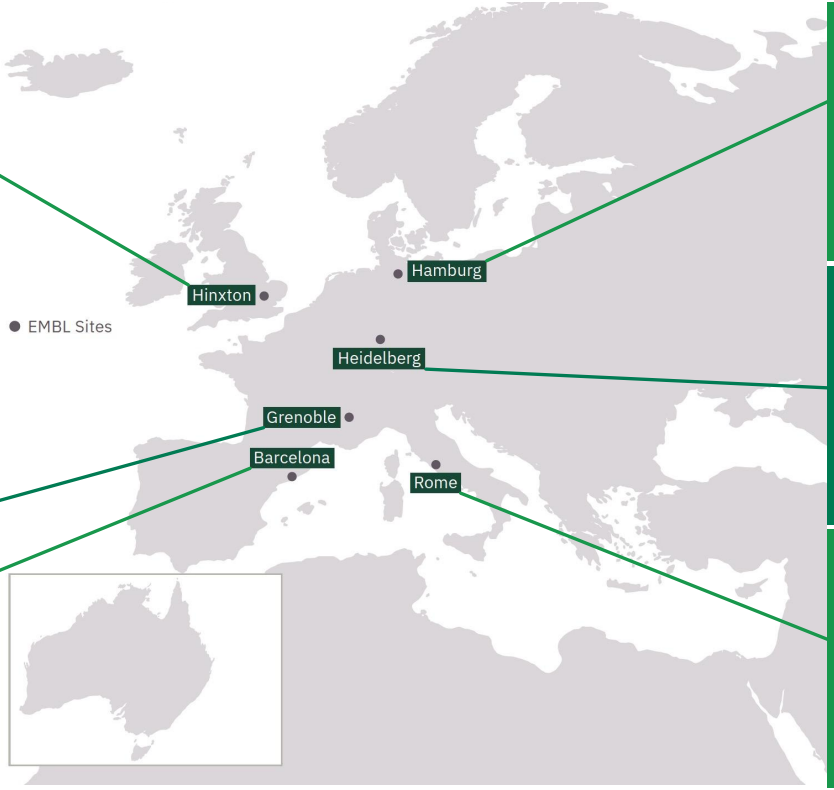
Bioinformatics

Grenoble

Structural biology

Barcelona

Tissue biology and disease modelling

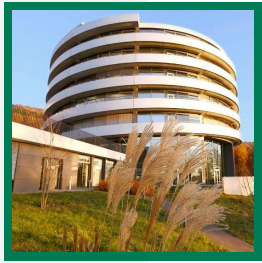


Hamburg

Structural biology

Heidelberg

Life sciences



Rome

Epigenetics and neurobiology

https://www.embl.org/

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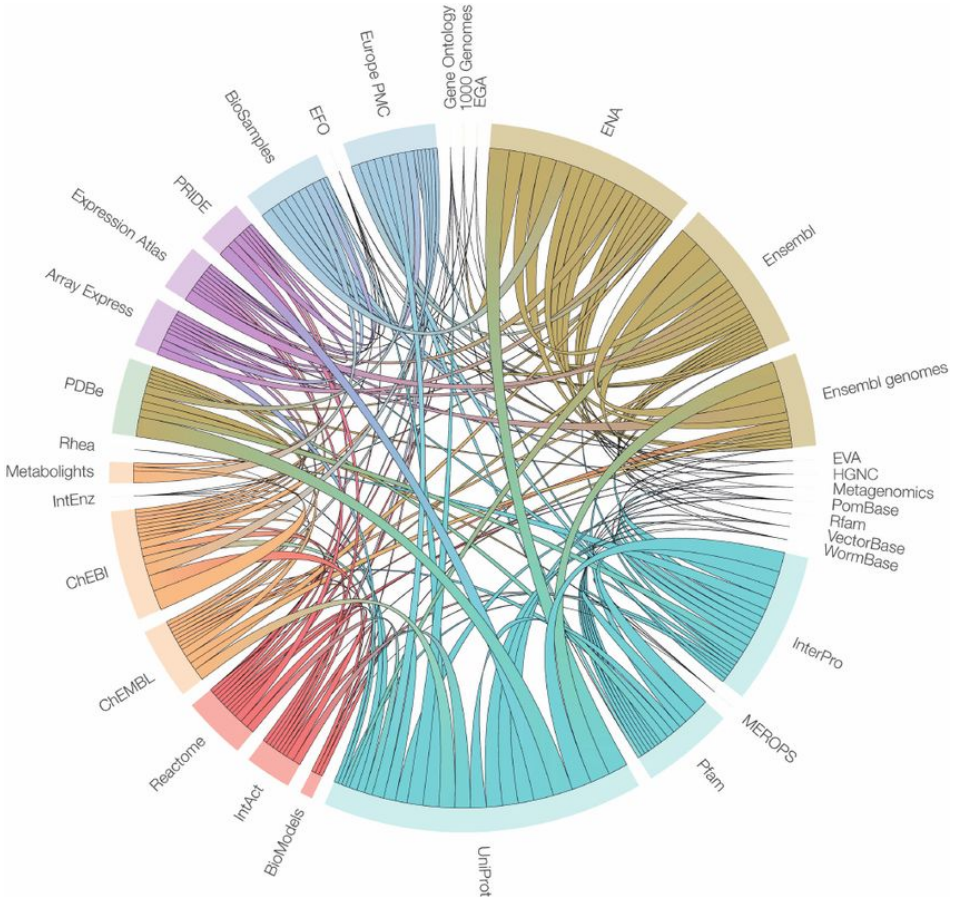
EMBL-EBI services and resources share data



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