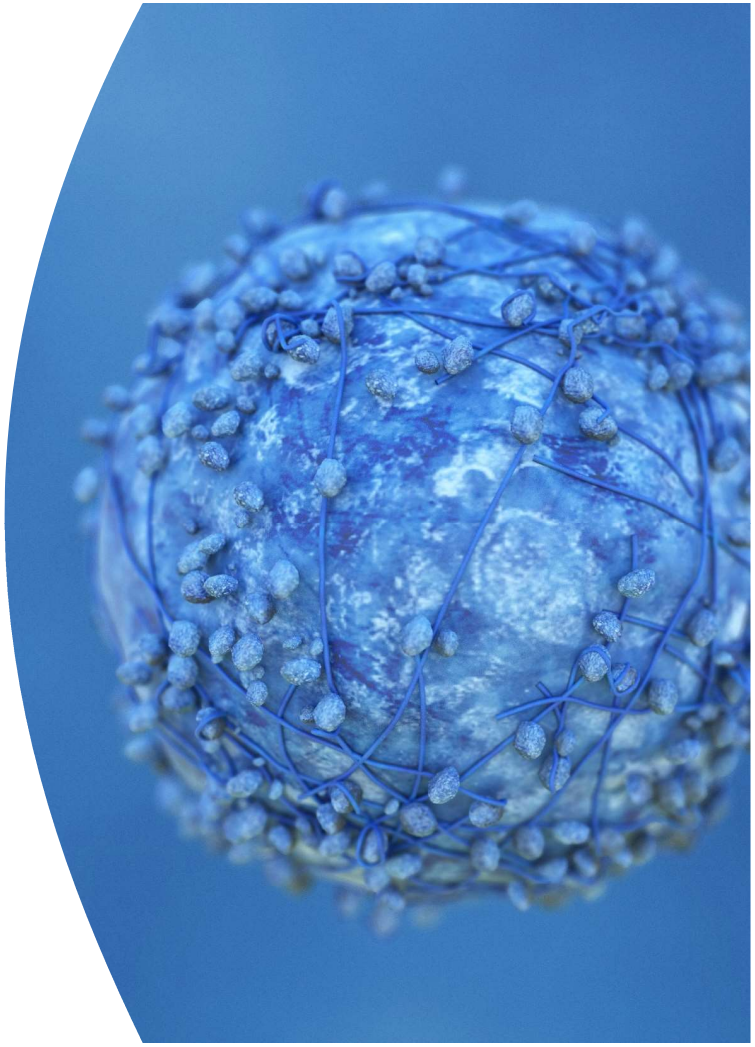
WHAT IS FUNCTIONAL GENOMICS?

Rory Stark

CRUK Bioinformatics Summer School

22 July 2020



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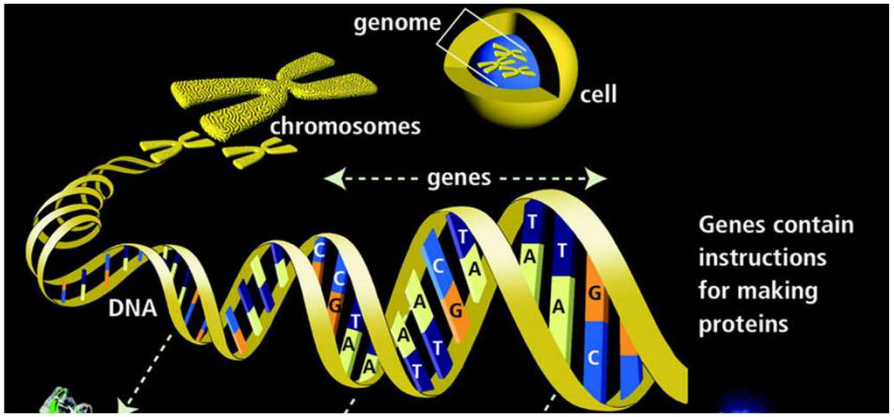
Together we will beat cancer

What is functional genomics?

Determination of the relationship between an organism's genome and its phenotype



- Each cell contains a complete copy of the genome, distributed along chromosomes (compressed and entwined DNA)
- $3x10^9$ (3Gb) base pairs in human DNA: 5-6 meters in each cell!
- Encodes blueprint for all cellular structures and activities and which cells go where (somehow…)

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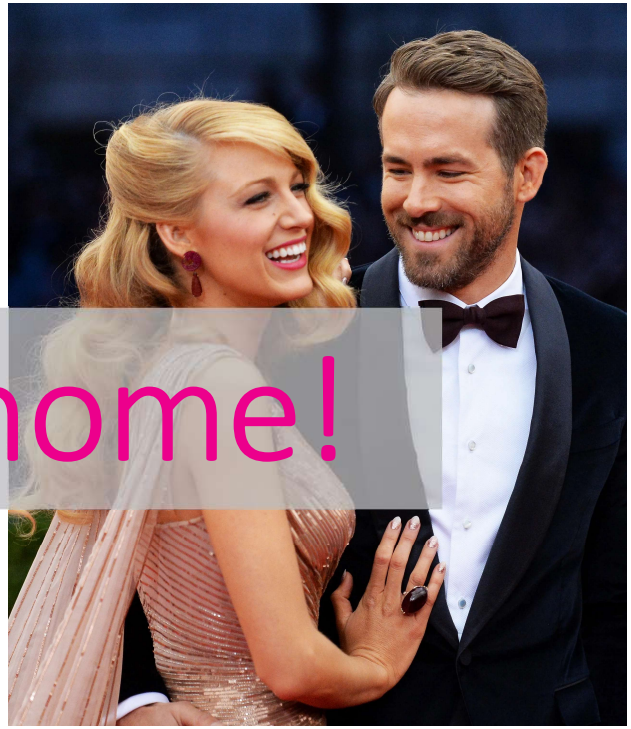
What accounts for differences in phenotype?



Different Genome!

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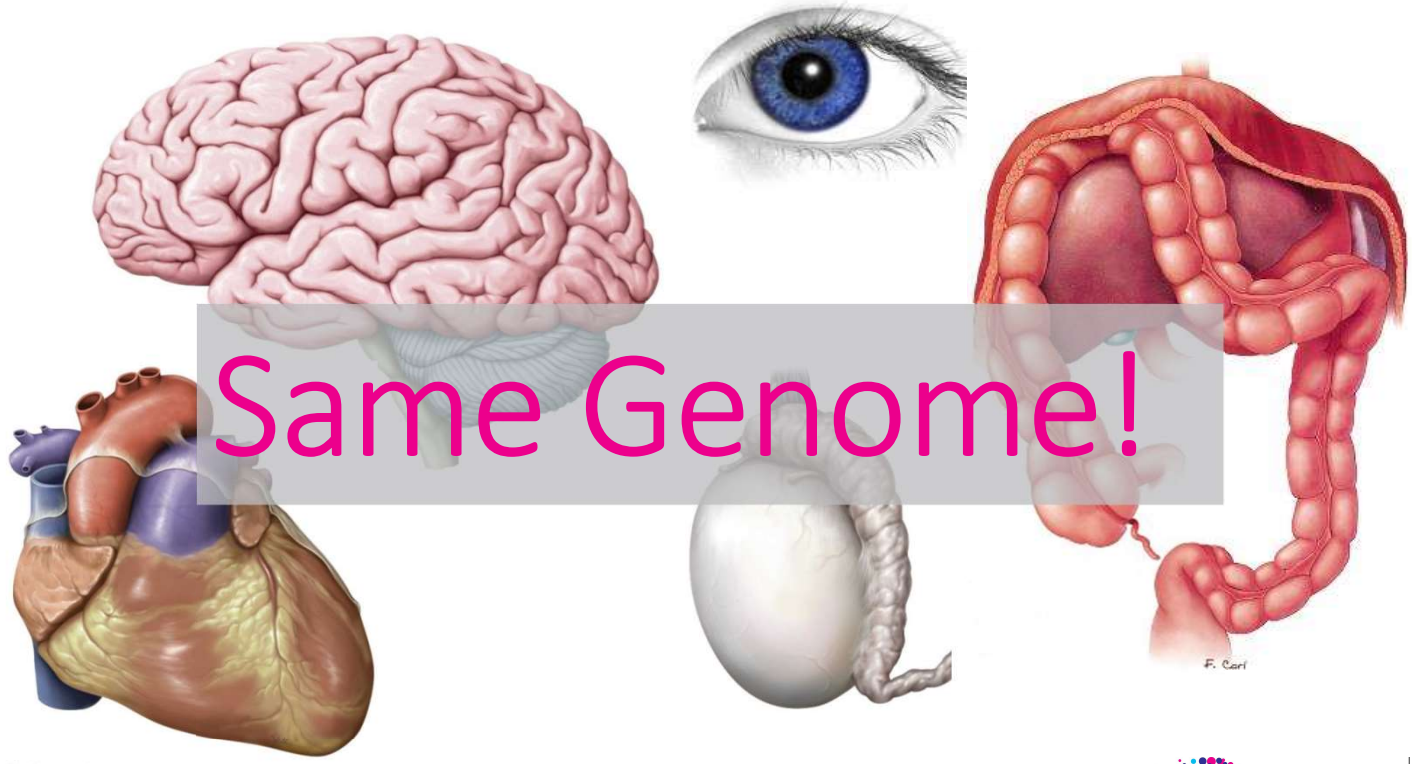
What accounts for differences in phenotype?



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What is functional genomics?

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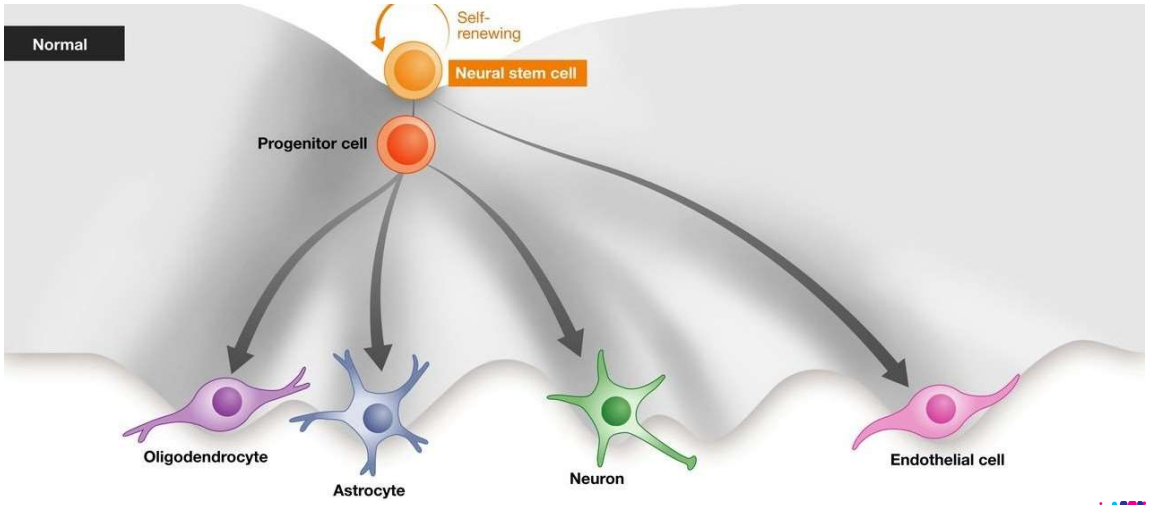

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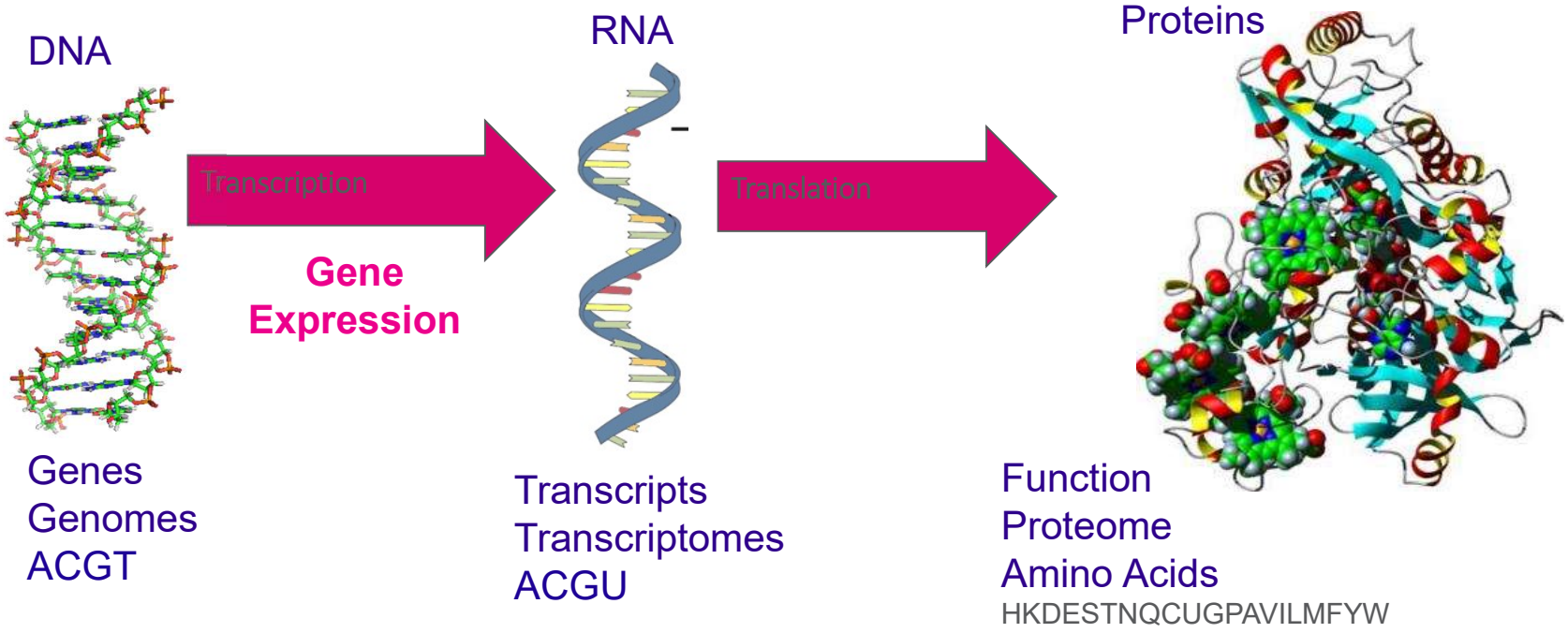
How do genomes determine function?



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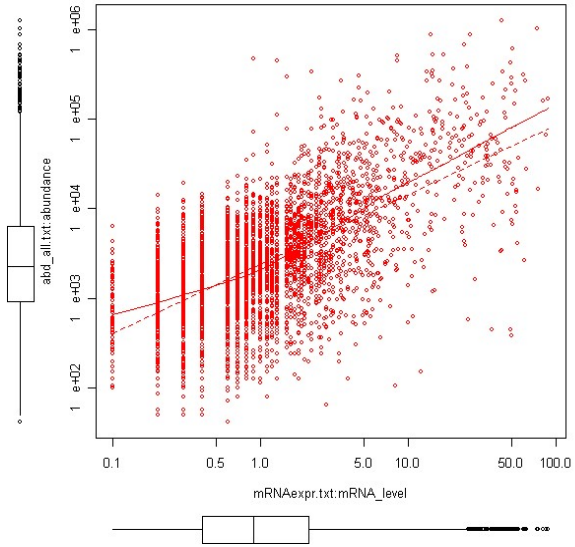
Gene expression

- Ideally, we'd measure all protein levels
- Instead, use mRNA ("transcript") levels as a proxy for protein levels
- Measure the expression levels of many genes in parallel
- Analyses:
  - Expression levels
  - Differences in expression levels (DE)
  - Patterns of expression
  - Splicing and isoforms

mRNA vs Protein levels in Yeast
R=0.44



Ghaemmaghami et al Nature 2003

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Comparing gene expression (DE)

- Different tissues, same organism
  - human brain/human liver
- Same tissue, different organism
  - human liver/mouse liver
  - wt/ko/CRISPR
- Same tissue, same organism, different condition
  - benign/tumour
  - treated/untreated
- Time course
- *In vivo* vs *In vitro*
- …

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Bulk (RNA-seq) vs single-cell (scRNA) analysis

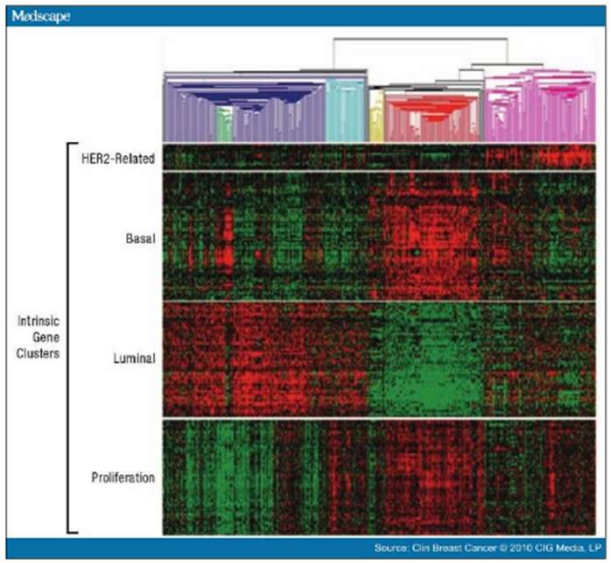
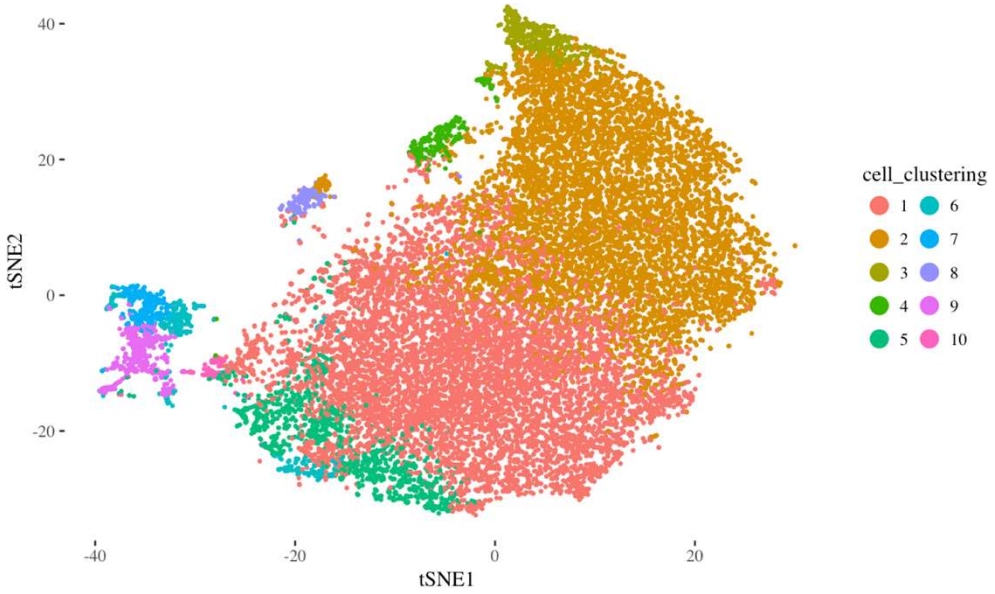


Figure 1.

Semi-Unsupervised Gene Expression Array Analysis of a Cohortof Breast Cancers Identifies Several Intrinsic SubtypesFigure

Shown are luminal A (outlined in dark blue), luminal B (pale blue), HER2-enriched (pink), basal-like (red), claudin-low (yellow), and normal-like (green) tumors. Heat map courtesy of CM Perou.



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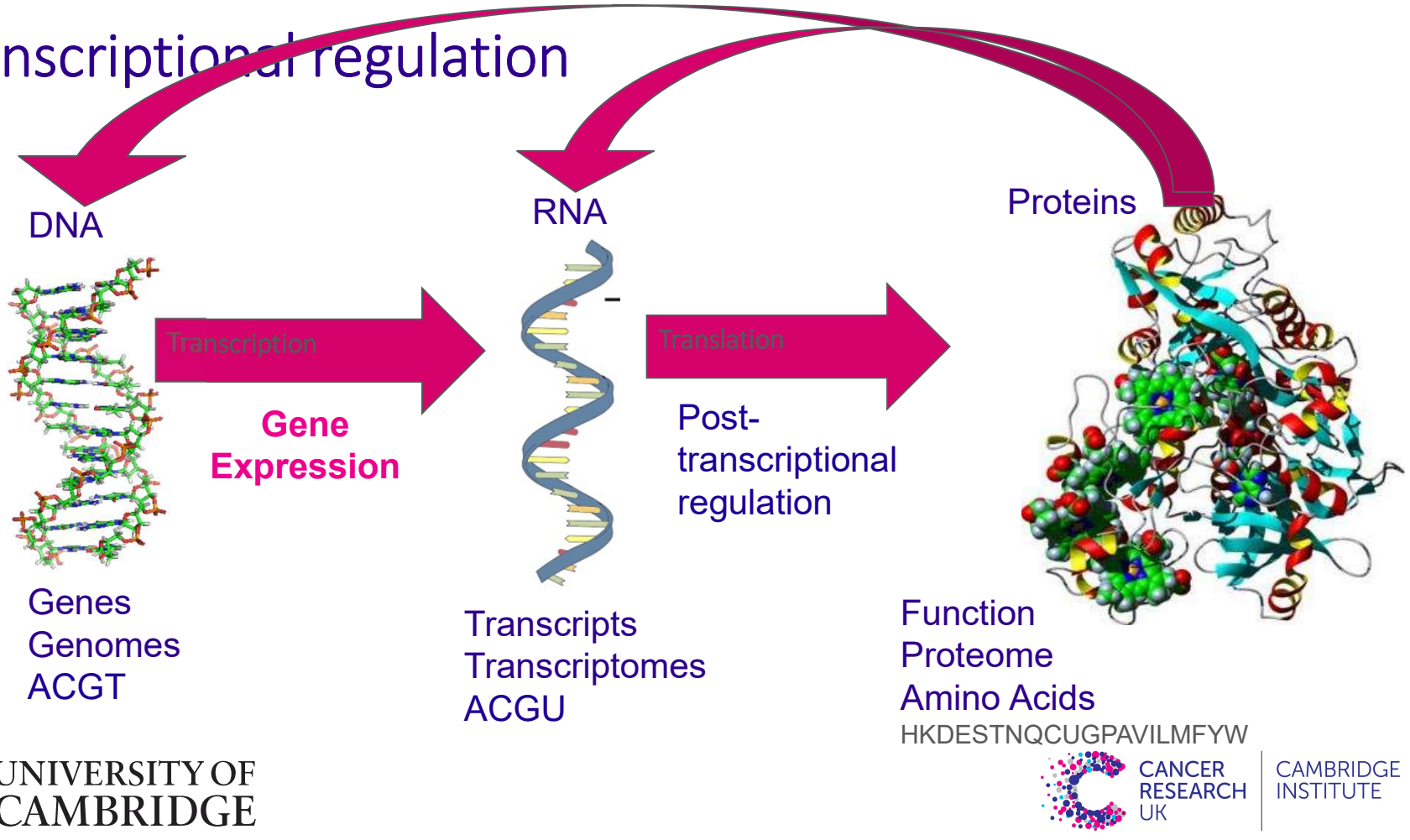
Transcriptional regulation



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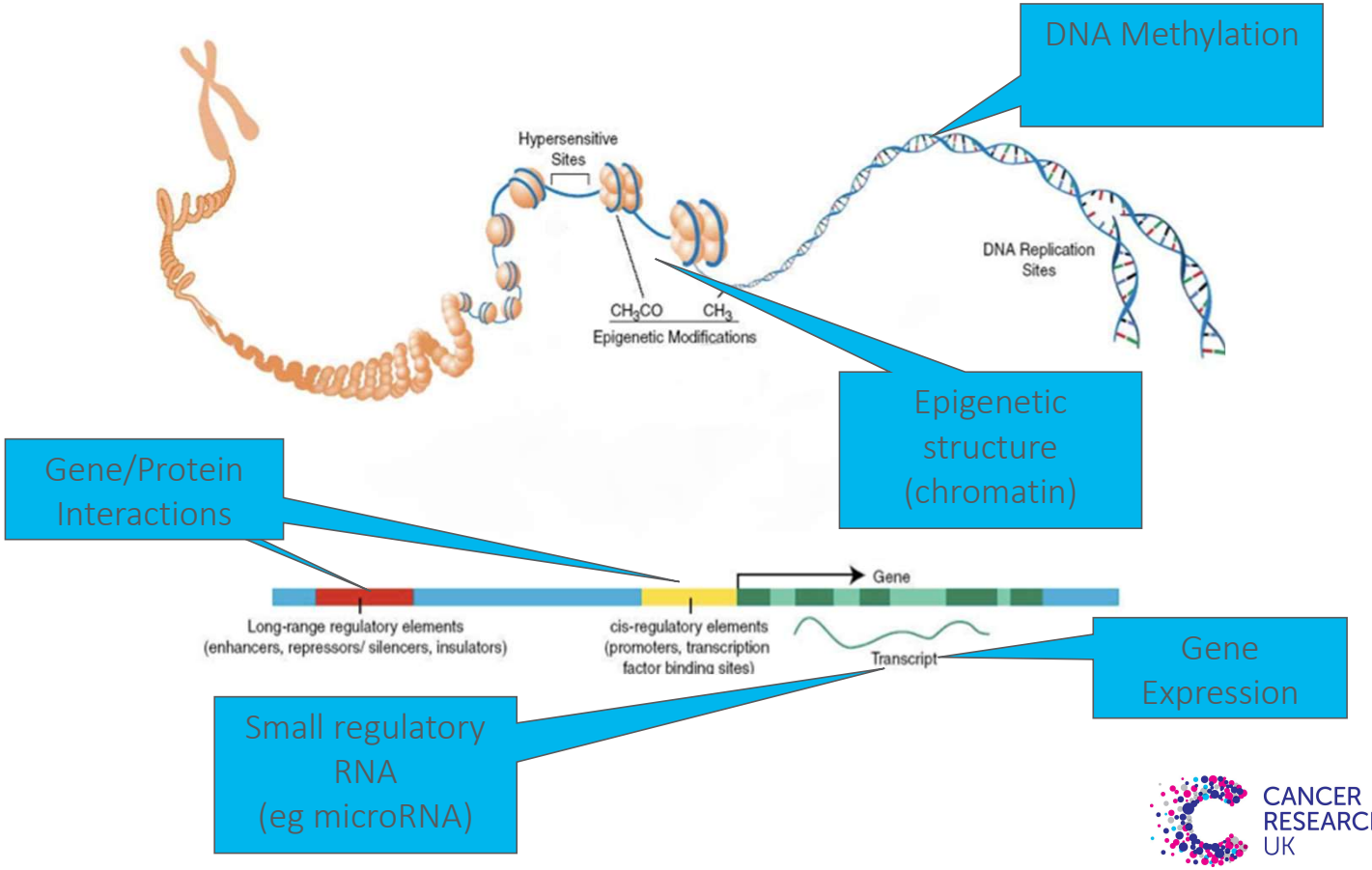
Transcriptional regulatory elements



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Transcriptional regulatory elements

Transcription Factors
- ChIP

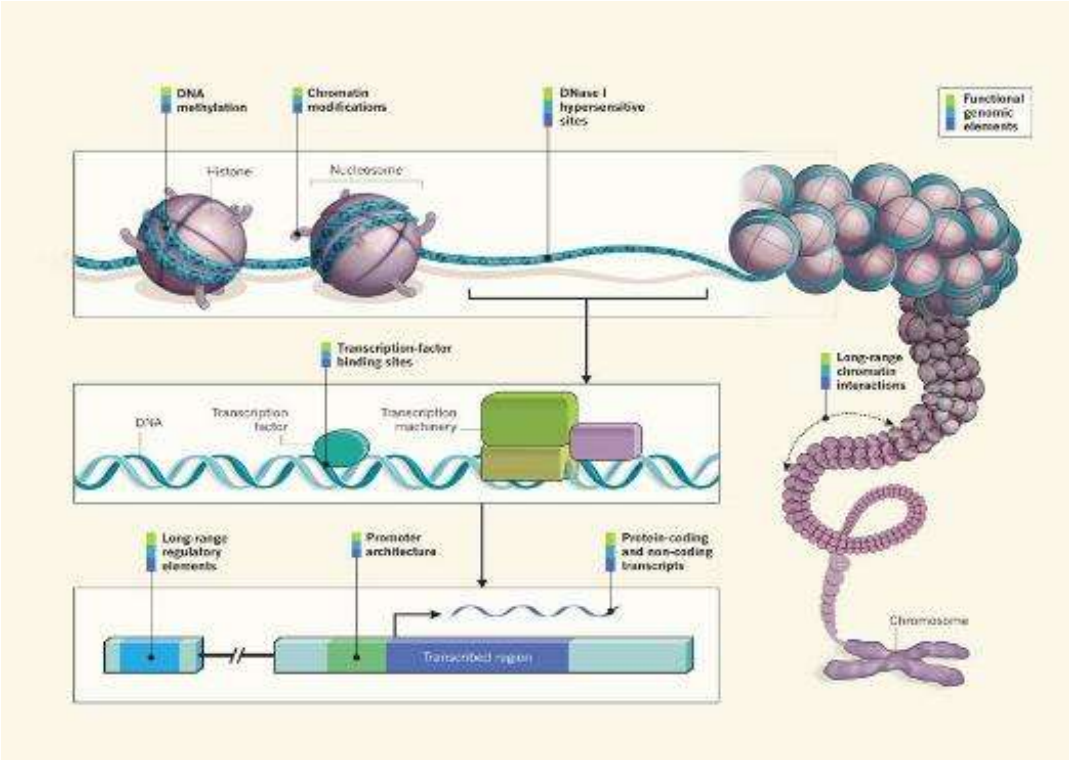
Histone marks
- ChIP

DNA Methylation
- RRBS
- MeDIP

Open chromatin
- ATAC

Çhromatin structure
- HiC

RNA Polymerase
- Pol II ChIP



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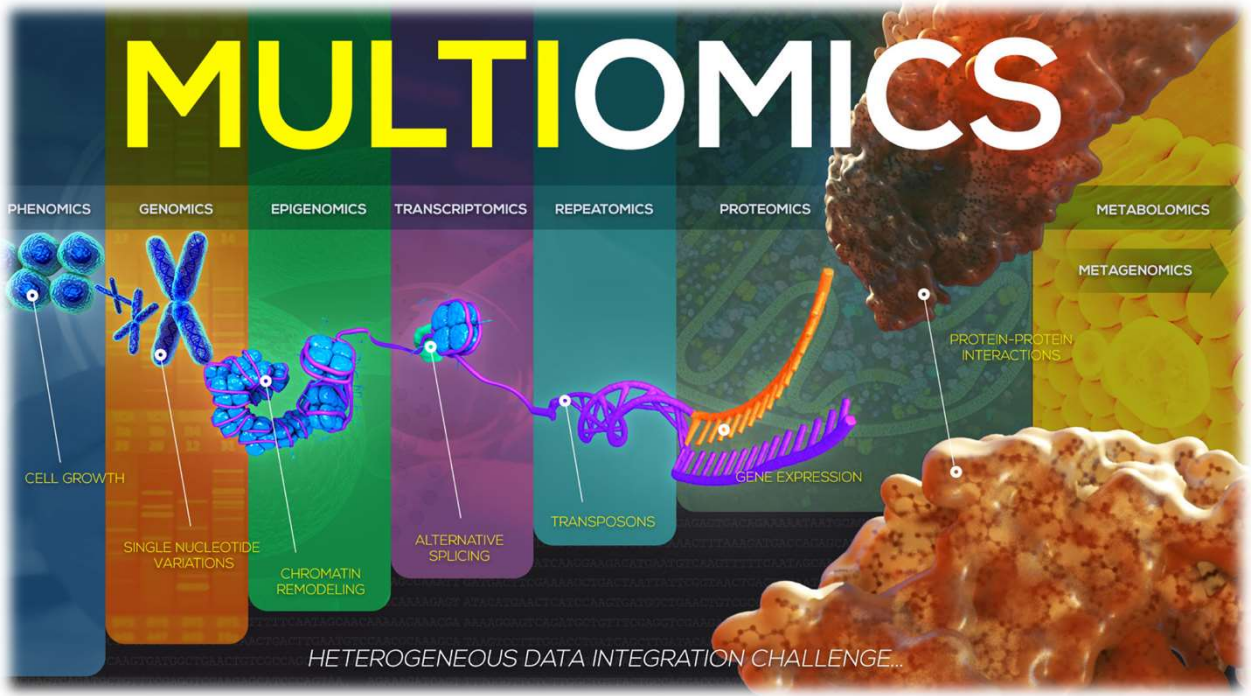
Functional genomics: the ultimate challenge



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