A super quick introduction to molecular biology and genomics

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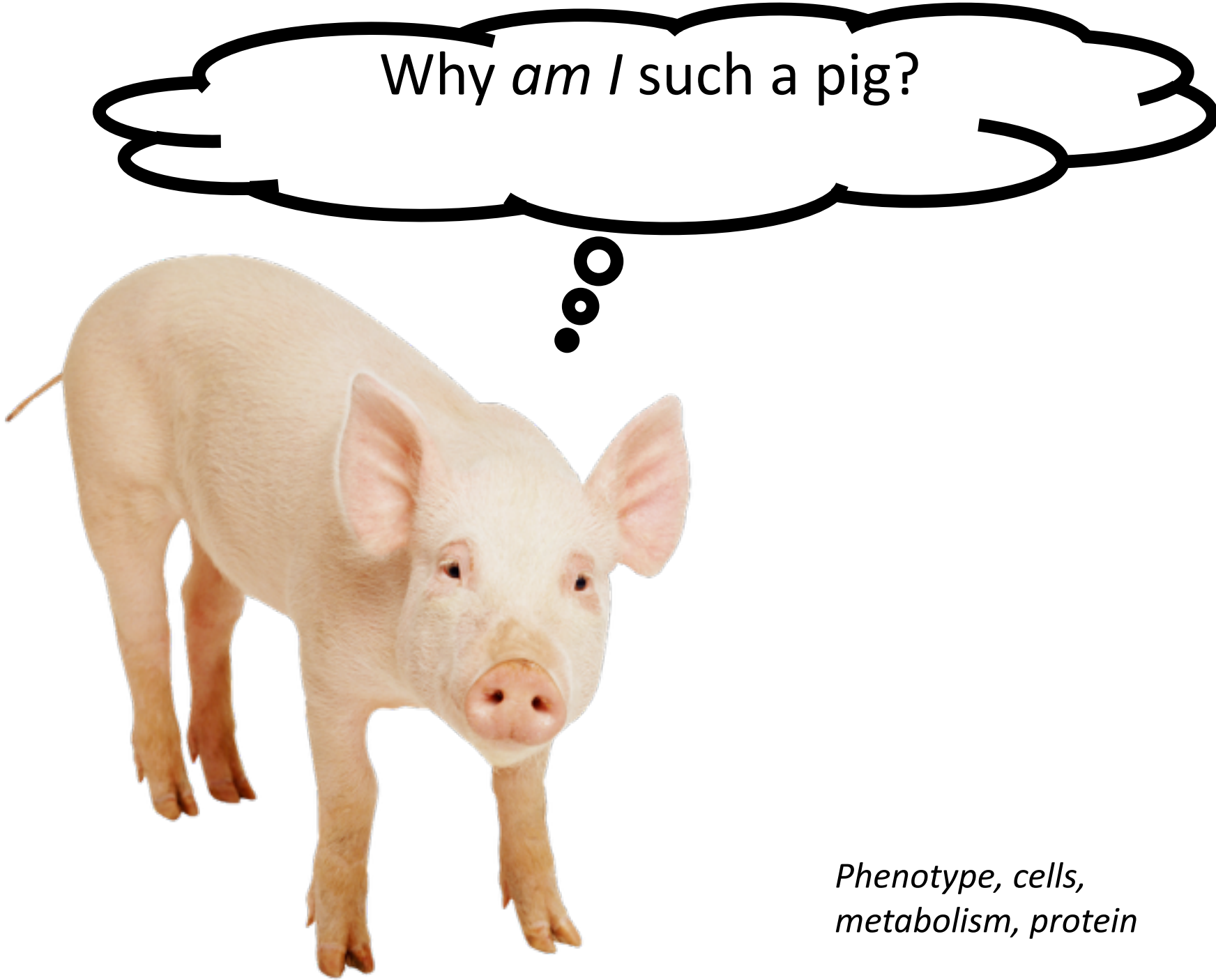
Key terms

- Genotype/Phenotype
- Cell
- Proteins
- Evolution: inheritance, selection, variation
- DNA/RNA
- Chromosome
- Gene
- Genome
- Replication
- Transcription
- Exon/Intron
- Translation
- Codon
- Central Dogma
- Gene Expression
- Regulation
- Epigenetics


Why are my children such pigs?



Phenotype, cells, metabolism, protein

Proteins

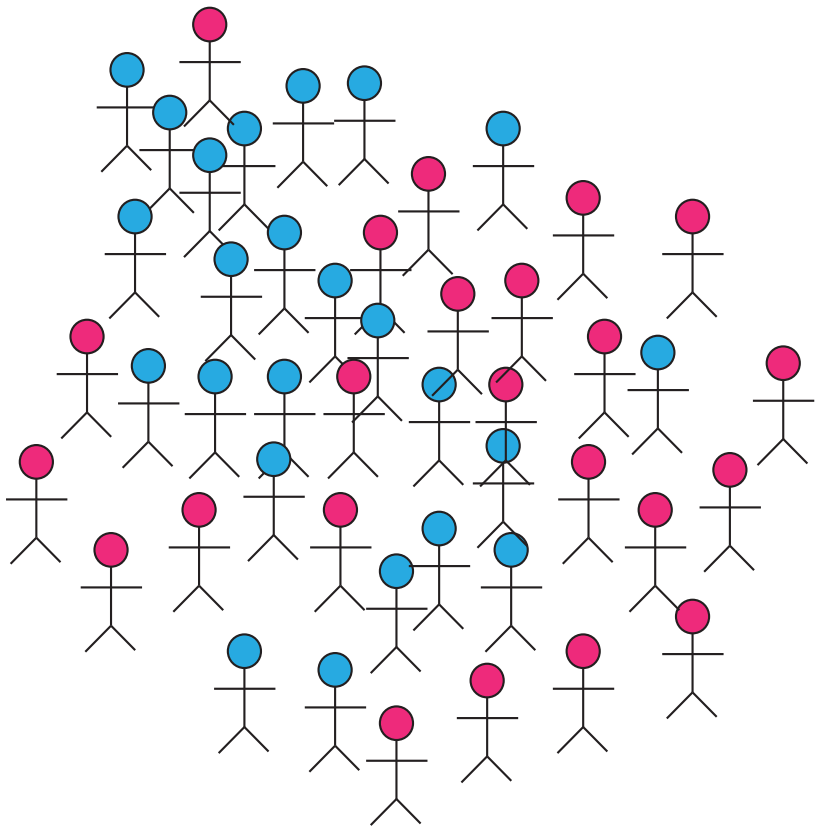
- *phenotype:* characteristics of an organism
- characteristics due to cellular structures and activities
  - mostly carried out by *proteins*
- Examples:

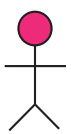
alpha-keratin	*component of hair*
insulin	*regulates blood glucose level*
actin & myosin	*muscle contraction*
hemoglobin	*oxygen transport*
DNA polymerase	*synthesis of DNA*
DNA glycosylases	*DNA repair*
matrix metalloproteinase	*extra-cellular matrix degradation*

Genetics

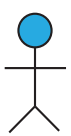
- *gene:* in classical genetics it was an abstract concept
  - a unit of inheritance passed from parent to offspring
  - specify proteins
- *genome* refers to the complete set of *genes*
- *genotype:* genetic characteristics of an individual

What is Genomics?



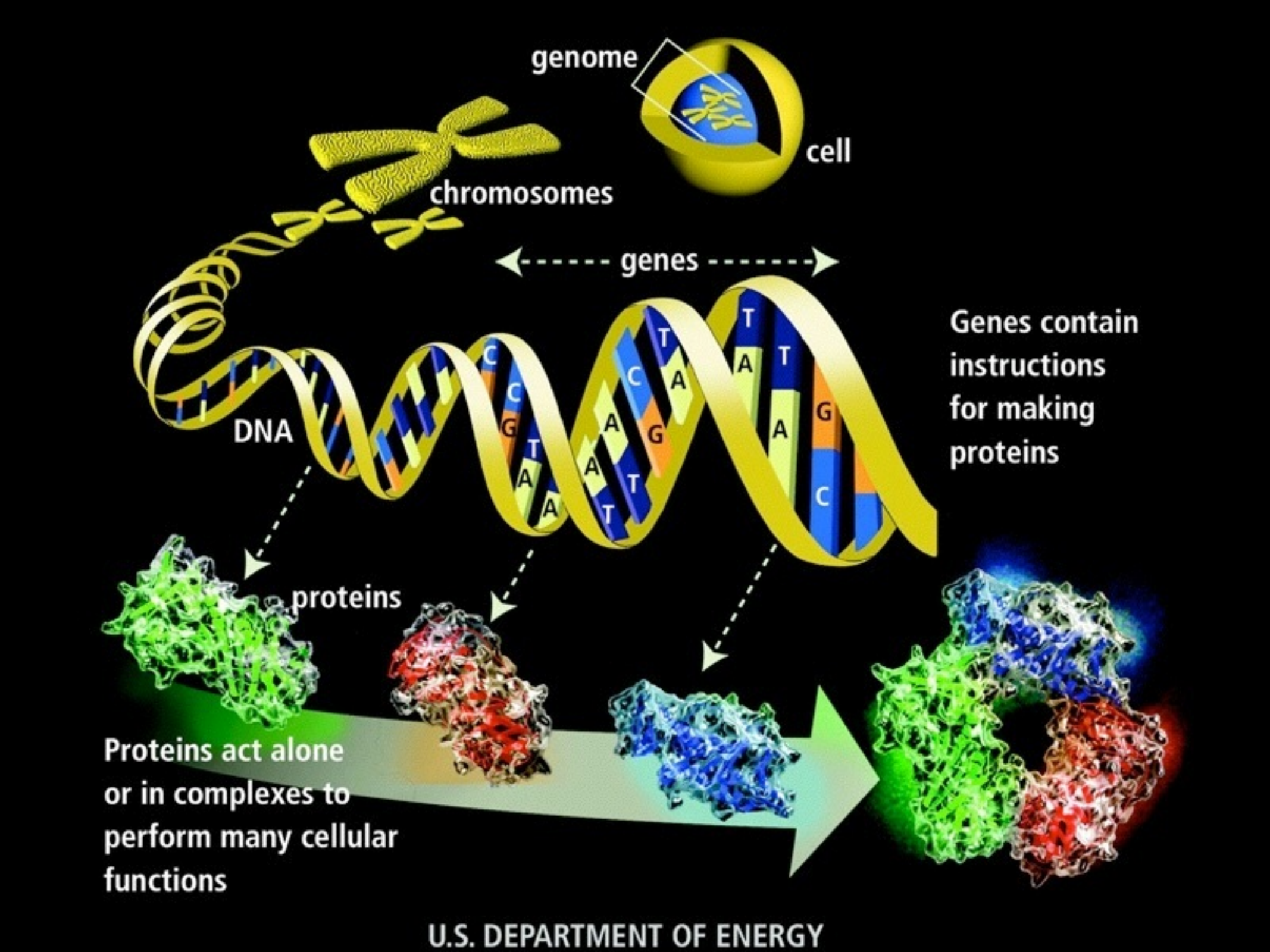


cancer



healthy

- Study the **molecular** basis of *variation* in development and disease
- Using **high-throughput** experimental methods
  - algorithms
  - ML
  - data management
  - modeling


genome
cell
chromosomes
genes
DNA
Genes contain instructions for making proteins
proteins
Proteins act alone or in complexes to perform many cellular functions
U.S. DEPARTMENT OF ENERGY

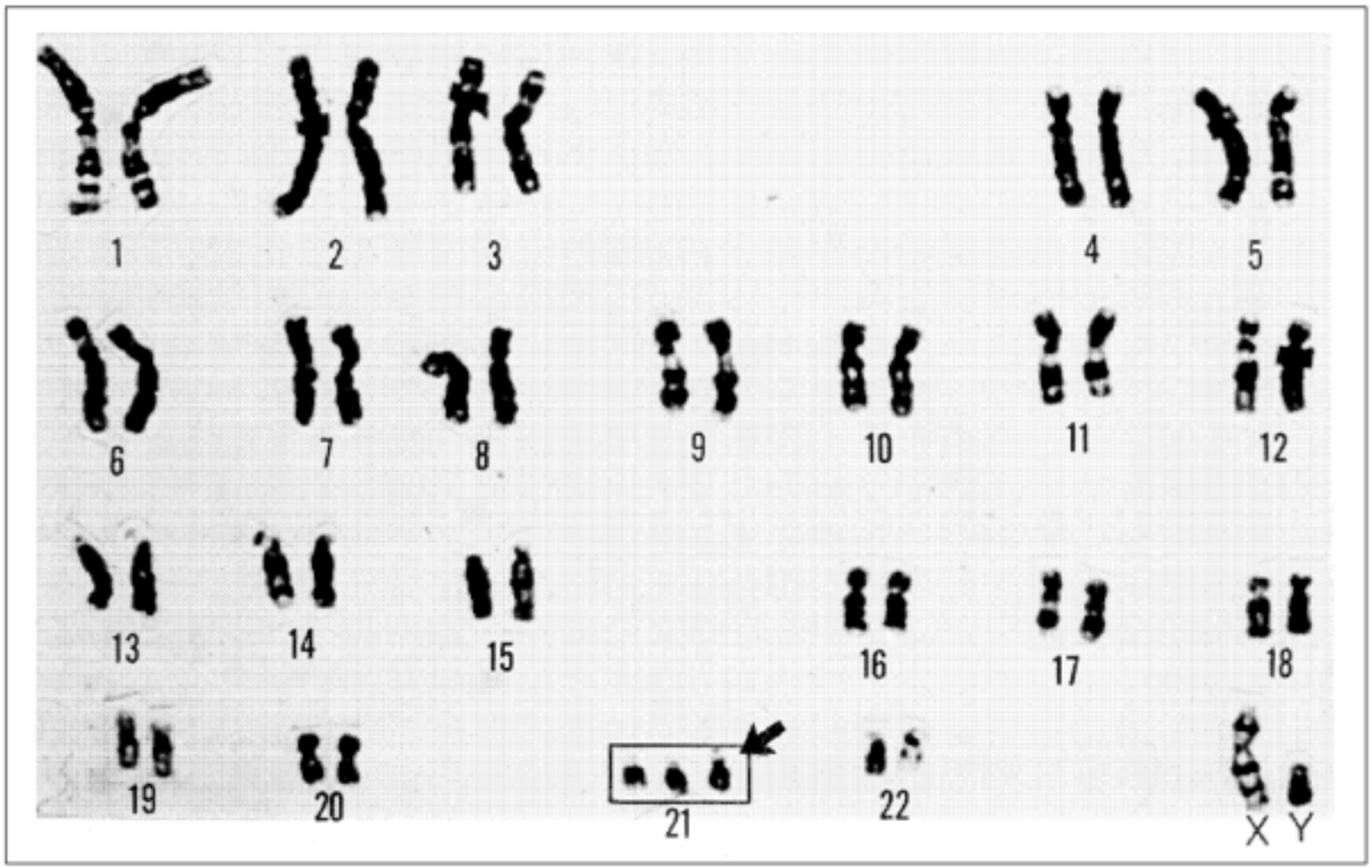
What is Genomics?

- Each cell contains a complete copy of an organism's genome, or blueprint for all cellular structures and activities.

- The genome is distributed along chromosomes, which are made of compressed and entwined DNA.

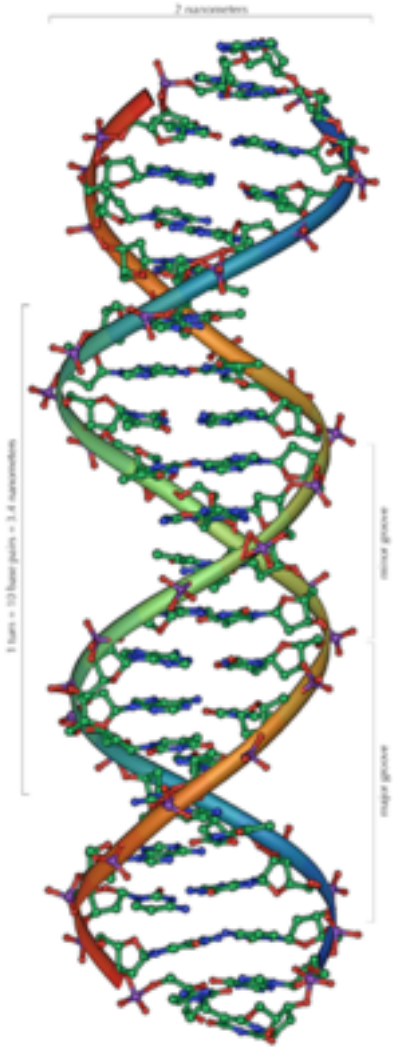
- Cells are of many different types (e.g. blood, skin, nerve cells), but all can be traced back to a single cell, the fertilized egg.

Chromosomes



These are actually human. And for a down syndrome patient

DNA



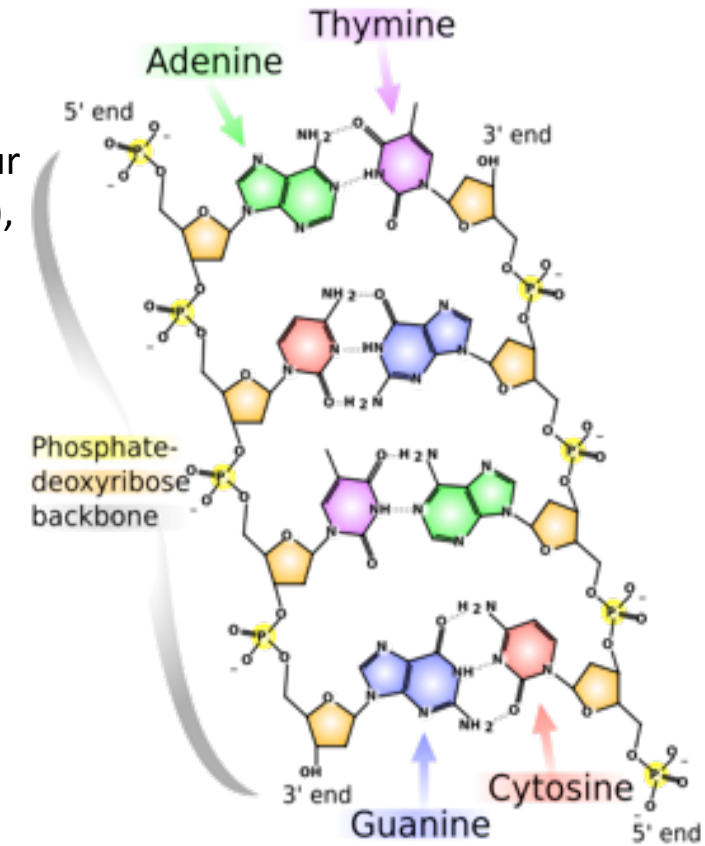
DNAs (Deoxyribonucleic acids) are molecules to store genetic information of a living organism.

DNA consists of two polymers made from four types of nucleotides: adenine (A) guanine (G), cytosine (C) and thymine (T).

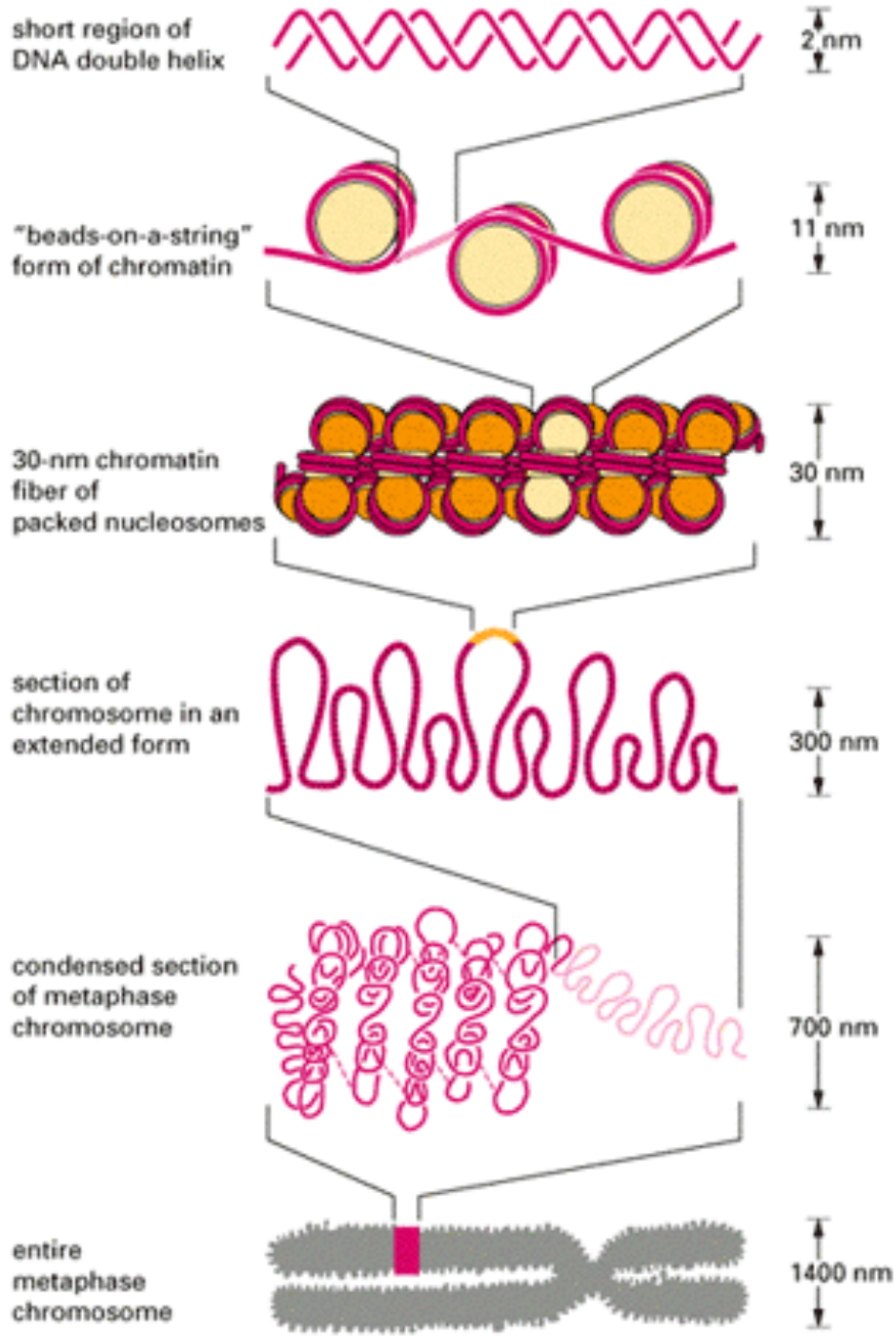
Purines: A, G; Pyrimidines: C, T

Two polymers are complementary to each other and from a double-helix structure

```
5′-ACCGTTCGACGGTAA-3′
   ||||||||||||||||
3′-TGGCAAGCTGCCATT-5′
```



Watson and Crick 1953


short region of
DNA double helix
2 nm
"beads-on-a-string"
form of chromatin
11 nm
30-nm chromatin
fiber of
packed nucleosomes
30 nm
section of
chromosome in an
extended form
300 nm
condensed section
of metaphase
chromosome
700 nm
entire
metaphase
chromosome
1400 nm

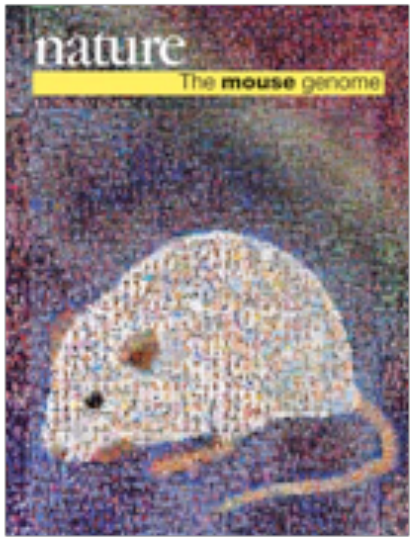
chromatin

Measurement

- For a small enough piece, we can measure the sequence of bases, referred to as *sequencing*
- Human Genome Project

D. melanogaster, *Science*, 2000

H. sapiens, *Nature*, 2000 and *Science*, 2000



M. musculus, *Nature*, 2002

Genome

TCAGTTGGAGCTGCTCCCCCACGGCCTCTCCTCACATTCCACGTCCTGTAGCTCTATGACCTCCACCTTTGAGTCCCTCCTCTCACACCTGAC
ATGAAAAGGCACATGAGGATCCTCAAATACCCCGTGATCAGTCTCAGGGTAGCTCTCATAGCCTGGACAGGGCCCCCCTCGGGGGTTGCGCCC
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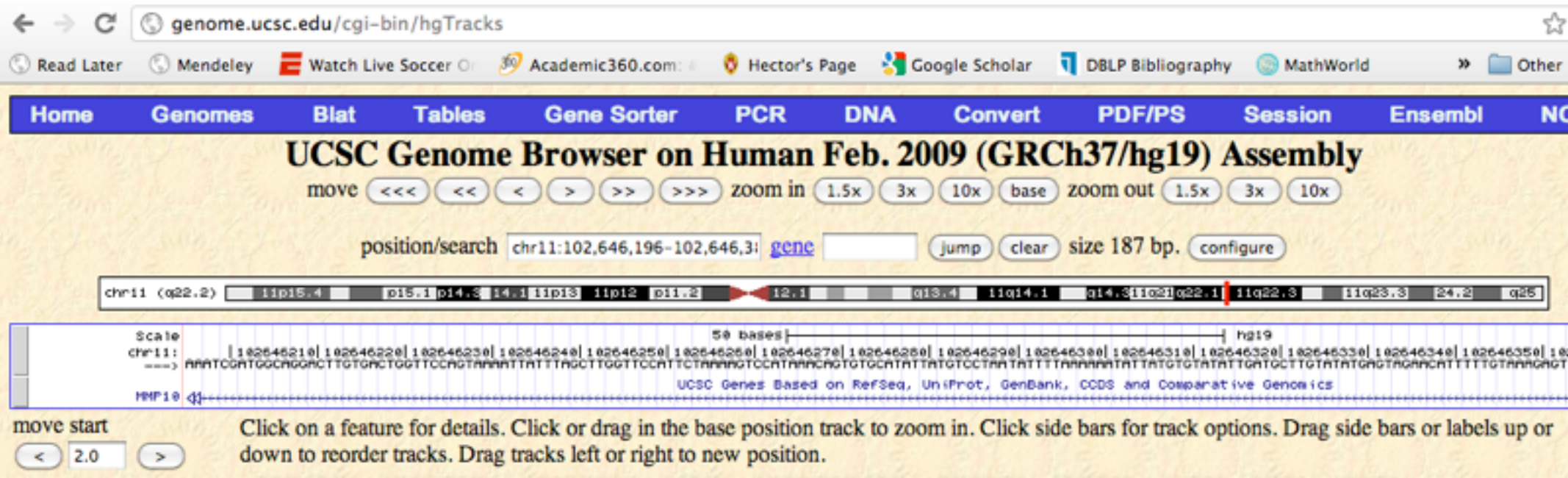
AATCAAATTCGGACCCTGCAAGCATCAGTACACCCAGCAGAGTGGACACAGCACCGTCCAGAACGGGAGCAAACATGTGCTCCAGAGCGAGCA
TAGCCCTGTGGTTCTTGTCCCCAATGGCTGTCAGAAAGGCCTGAACAAAGGAGAAAATTGACACGGTCACATTCTGGGTGTGGTAAAGTGCTC
AGCTGTGTCTATACTTGGGTTTTGTAT…

Total amount of DNA in human genome:
$3 * 10^9$ base pairs (bp)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gene
jump
clear
size 187 bp.
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chr11 (q22.2)
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UCSC Genes Based on RefSeq, UniProt, GenBank, CCDS and Comparative Genomics
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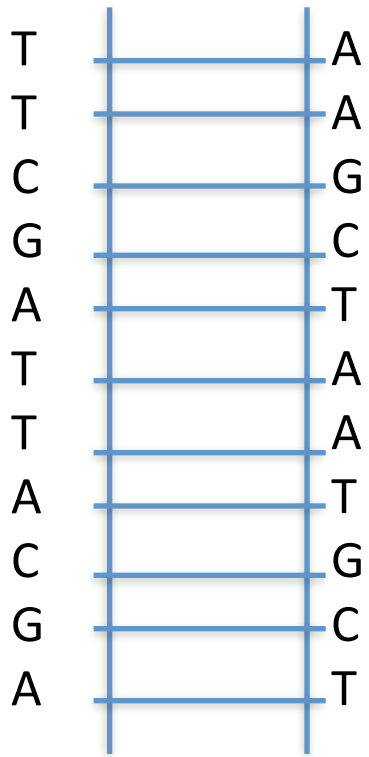
Replication



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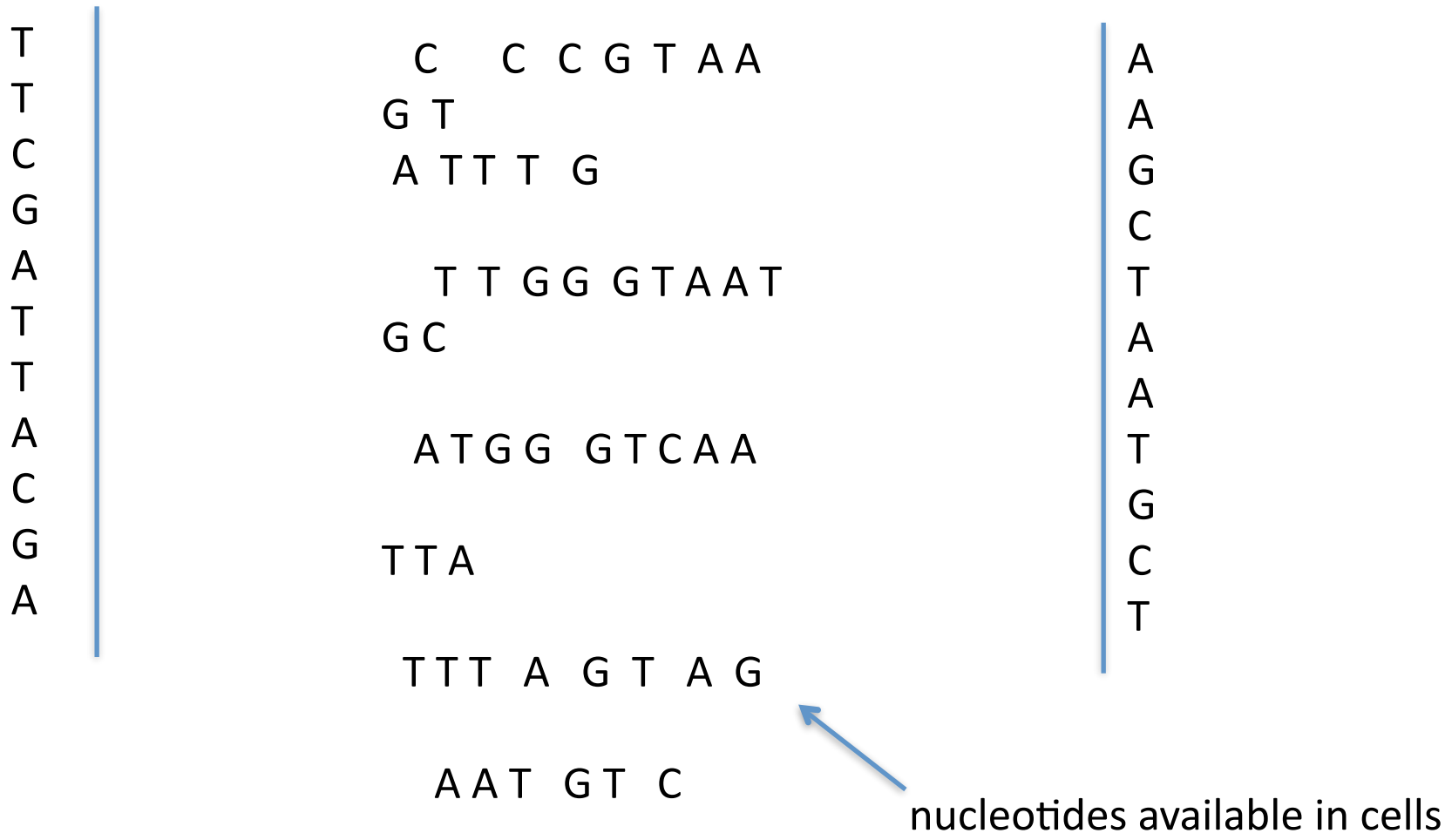
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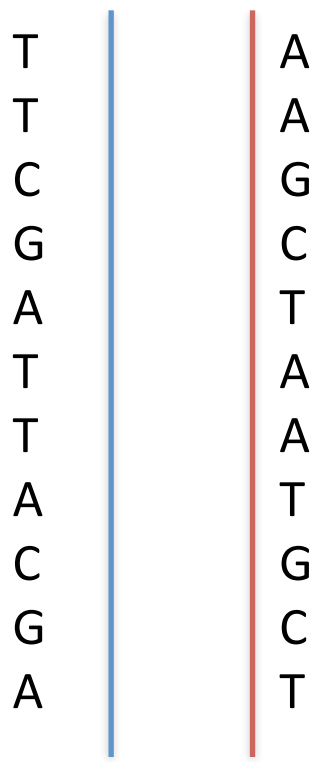
nucleotides available in cells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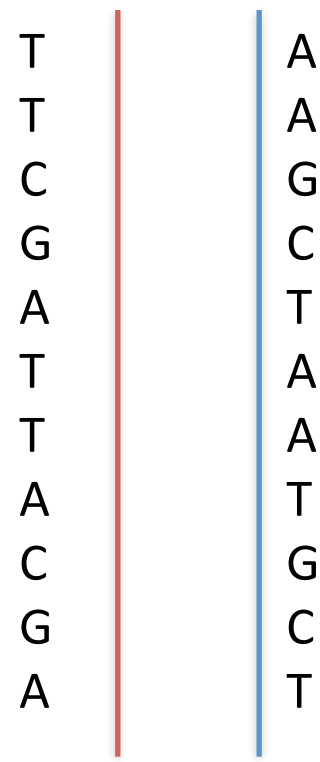
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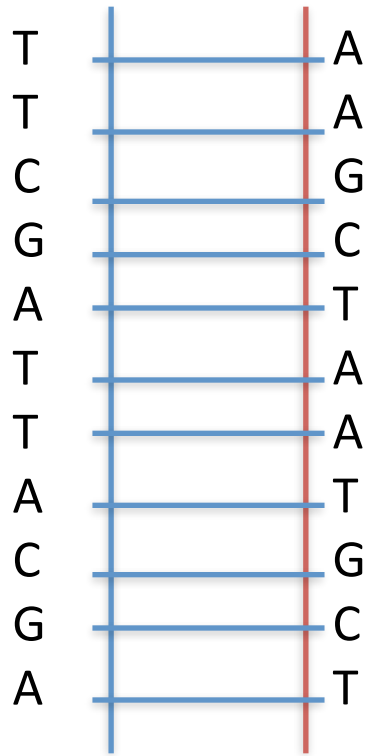
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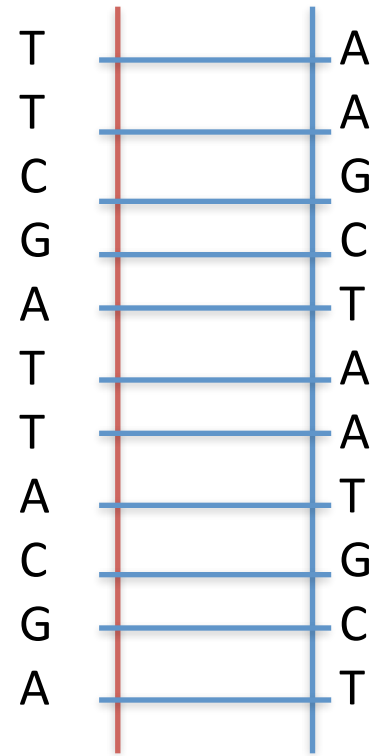
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G C
A T
T A
T A
A T
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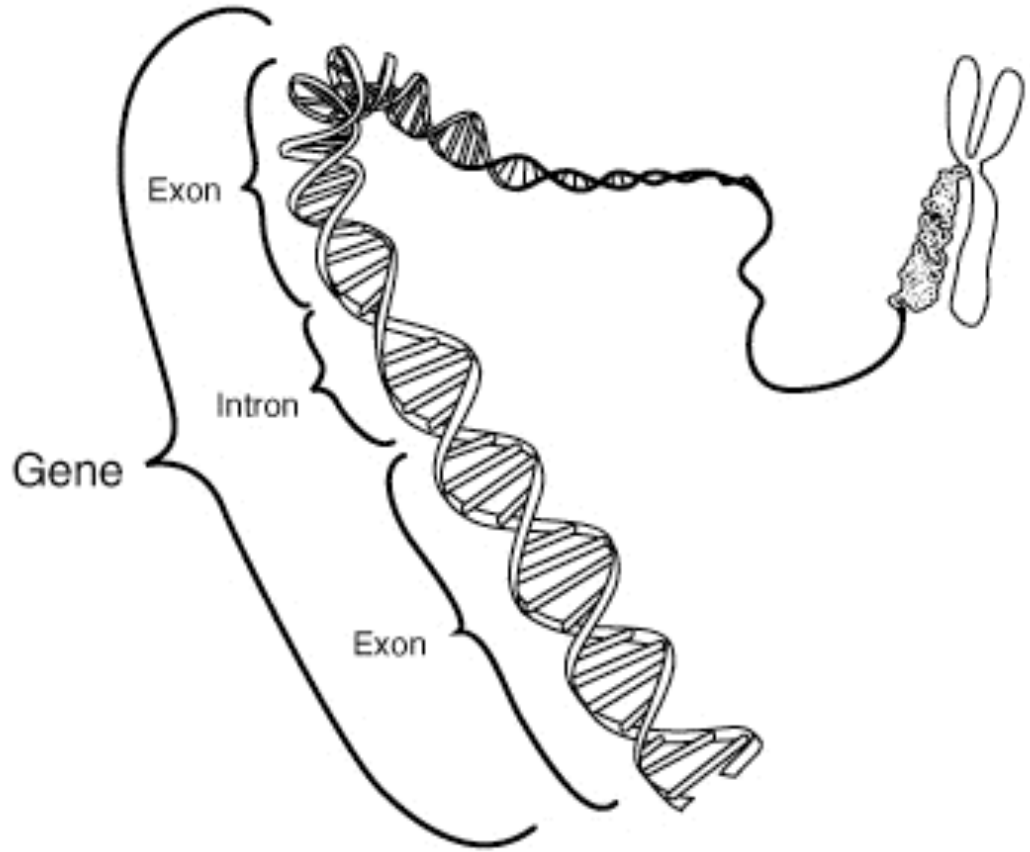
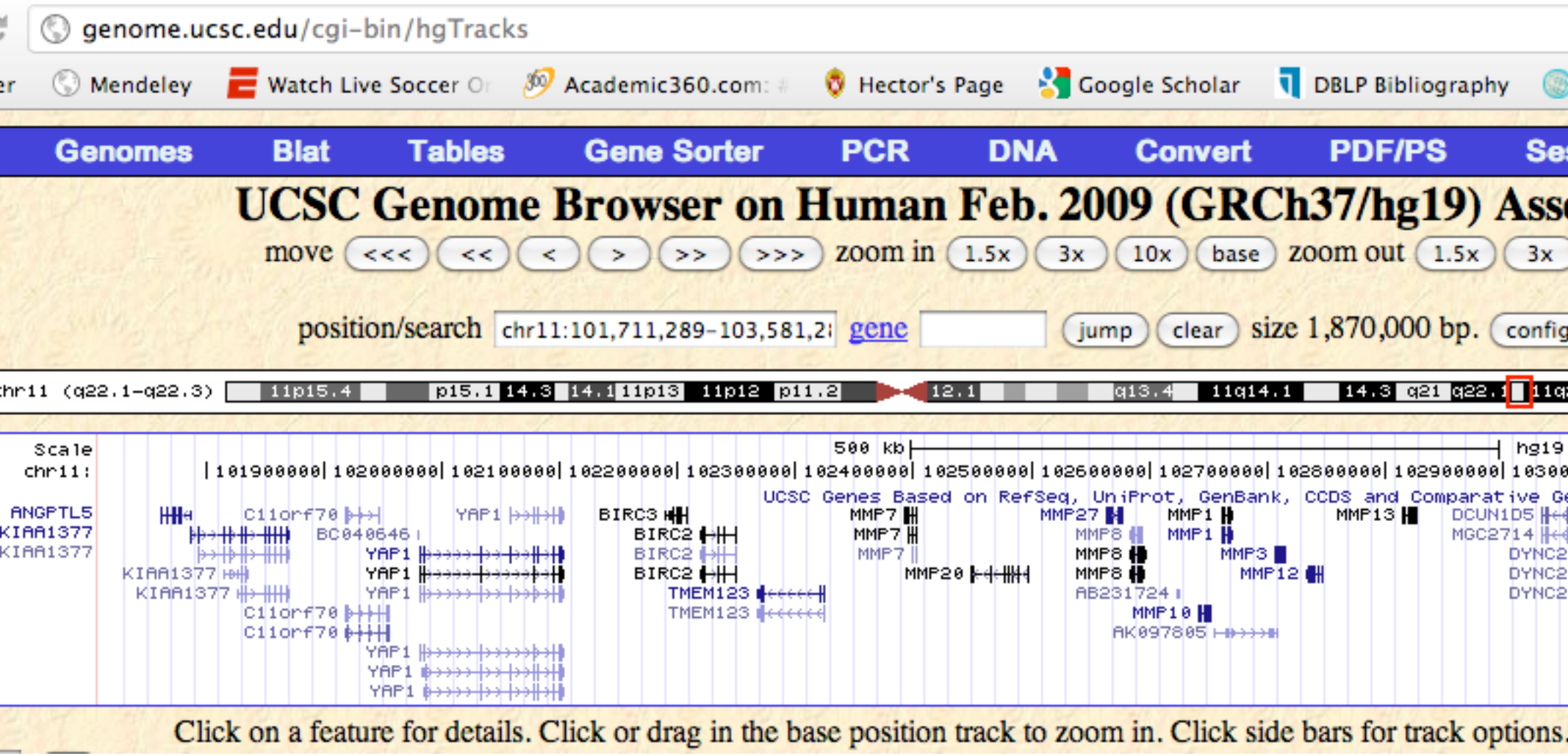
Why are these two different?

Differences explained by 1-10% difference in genome

Similarities explained by similar genes

Genes

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chr11:
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UCSC Genes Based on RefSeq, UniProt, GenBank, CCDS and Comparative Ge
ANGPTL5
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KIAA1377
C11orf70
BC040646
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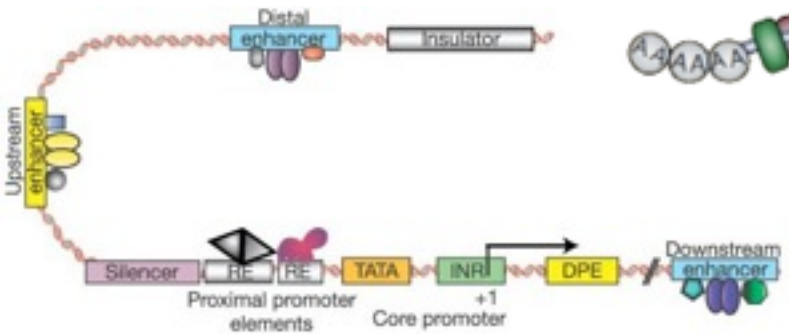
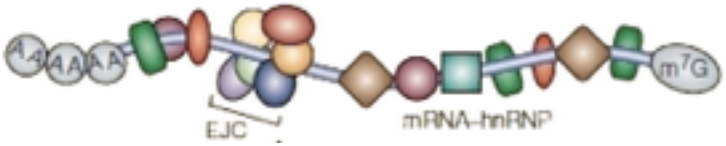
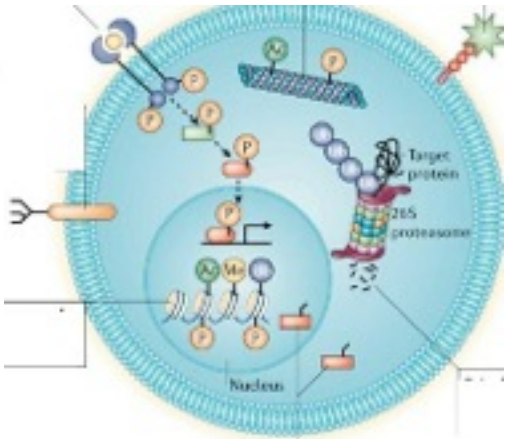
Central Dogma

Genes encode proteins which are transcribed into mRNA and translated into proteins.

genomics transcriptomics proteomics







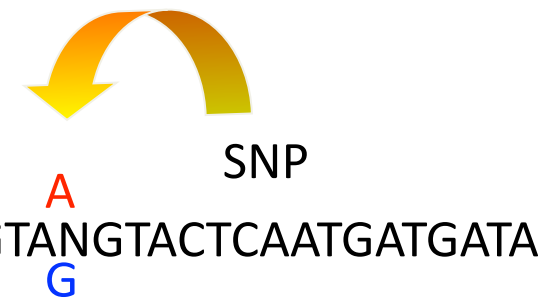
Major technological advances allow **unprecedented** data acquisition

What makes them different?

Much human variation is due to difference in ~ 6 million base pairs (0.1 % of genome) referred to as SNPs

Single Nucleotide Polymorphism (SNP)

Genomic DNA:



Three genotypes

AA

Mother

TACATAGCCATCGGTAAGTACTCAATGATGATA
ATGTATCGGTAGCCATTCATGAGTTACTACTAT

Father

TACATAGCCATCGGTAAGTACTCAATGATGATA
ATGTATCGGTAGCCATTCATGAGTTACTACTAT

AG

Mother

TACATAGCCATCGGTAAGTACTCAATGATGATA
ATGTATCGGTAGCCATTCATGAGTTACTACTAT

Father

TACATAGCCATCGGTAGGTACTCAATGATGATA
ATGTATCGGTAGCCATCCATGAGTTACTACTAT

GG

Mother

TACATAGCCATCGGTAGGTACTCAATGATGATA
ATGTATCGGTAGCCATCCATGAGTTACTACTAT

Father

TACATAGCCATCGGTAGGTACTCAATGATGATA
ATGTATCGGTAGCCATCCATGAGTTACTACTAT

From reads to evidence

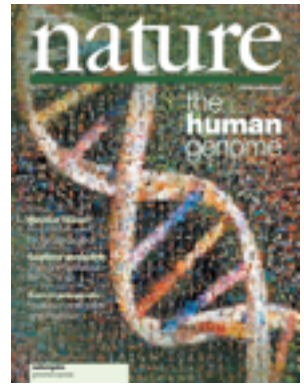
From reads to evidence

1. Comparative

Sequence-wise, individuals of a species are nearly identical

Well curated, annotated "reference" genomes exist

D. melanogaster, *Science*, 2000

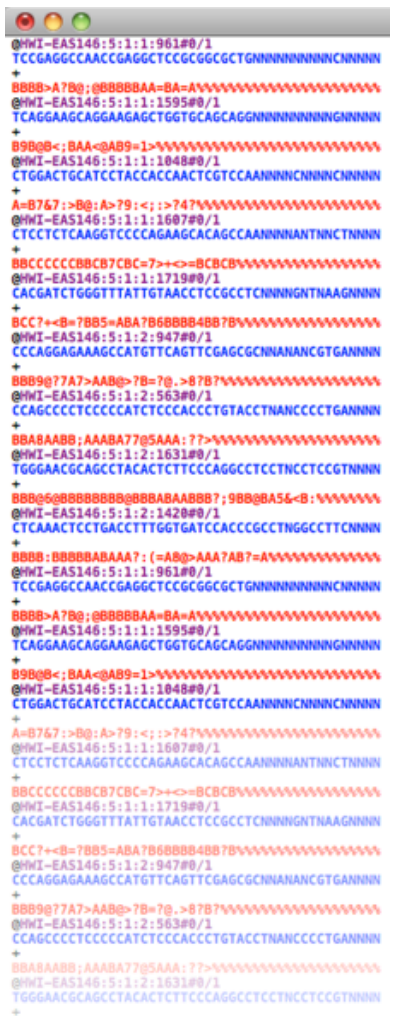


H. sapiens, *Nature*, 2000 and *Science*, 2000

M. musculus, *Nature*, 2002

Idea: "Map" reads to their point of origin with respect to a reference, then study differences

Sec-gen Sequencing for SNPs



Align

```
GTCGCAGTANCTGTCT
|||||||||  ||||||
GTCGCAGTATCTGTCT

GGATCTGCGATATACC
||||||  ||||||||||
GGATCT-CGATATACC

AATCTGATCTTATTTT
||||||||||||||||
AATCTGATCTTATTTT

ATATATATATATATAT
||||||||||||||||
ATATATATATATATAT

TCTCTCCCANNAGAGC
|||||||||  |||||
TCTCTCCCAGGAGAGC
```

"Pileup" or "Coverage plot"

"Depth of coverage" = 14

Call: HET A, G

```
      GTCGCAGTATCTGTCT
     GTCGCAGTATCTGTNN
    TGTCGCAGTATCTGTC
  TATGTCGCAGTATCTG
  TATATCGCAGTATCTT
  TATATCGCAGTATCTG
  NATATCGCAGTATNTG
 CCCTATATCGCAGTAT
ACACCCTATGTCGCA
ACACCCTATCTCGCA
ACACCCTATGTCGCA
GA-CACCCTATGTCGC
CCGGA-CACCCTATAT
CCGGA-CACCCTATAT
GCCGGA-CACCCTATG
```

"Coverage"

GTATTTTTCGTCTGGGGGGTATGCACGCGATAGCATTGCGAGACGCTGGAGCCGGAGCACCCTATGTCGCAGTATCTGTCTTTGATTCCTGCCTCATCCTATTATTTATCGC

Reference

(slide courtesy of Ben Langmead)

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CSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly

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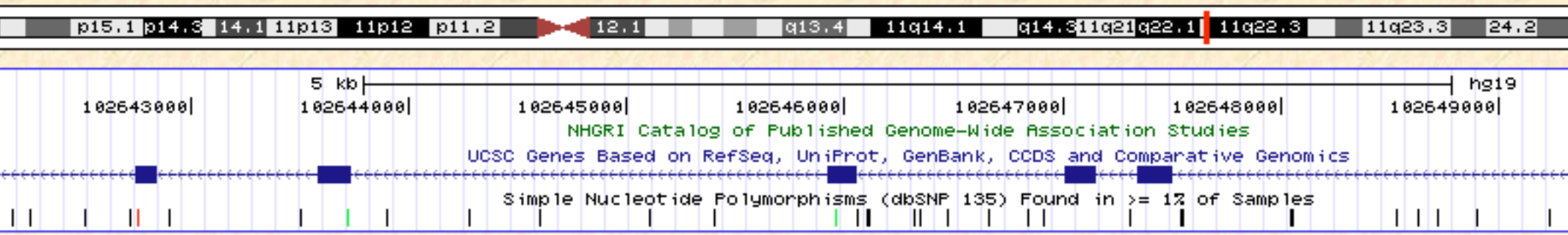
position/search chr11:102,641,234-102,651,3· gene jump clear size 10,111 bp. configure



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eorder tracks. Drag tracks left or right to new position.

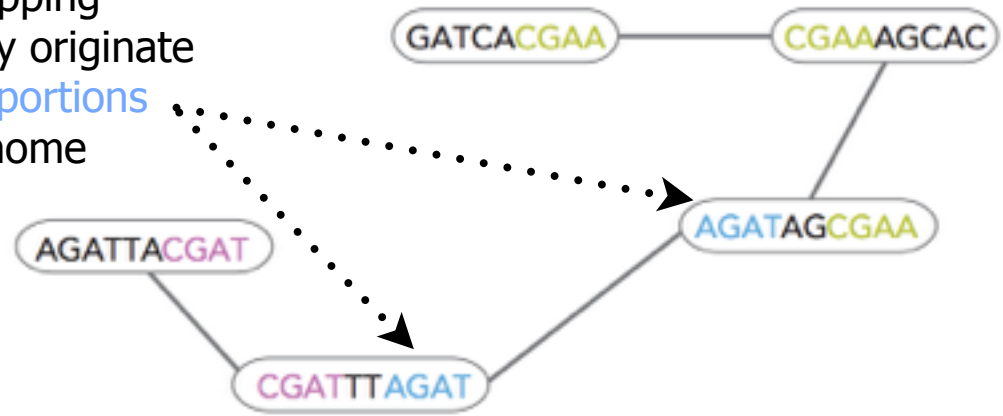
From reads to evidence

2. *de novo*

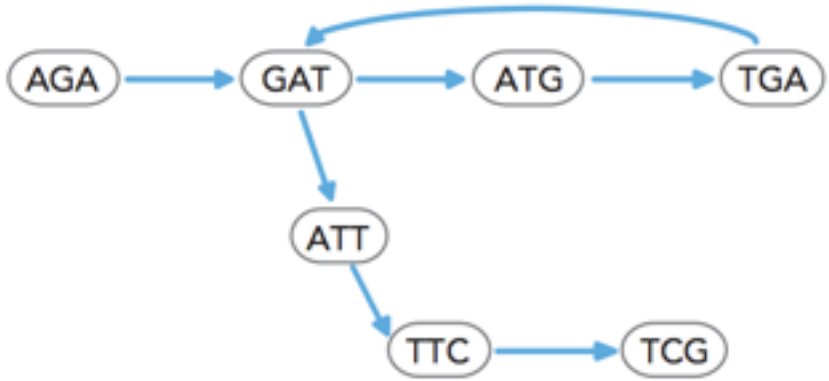
Assume nothing! - let reads tell us everything

Reads with overlapping sequence probably originate from overlapping portions of the subject genome

Encode overlap relationships as a graph



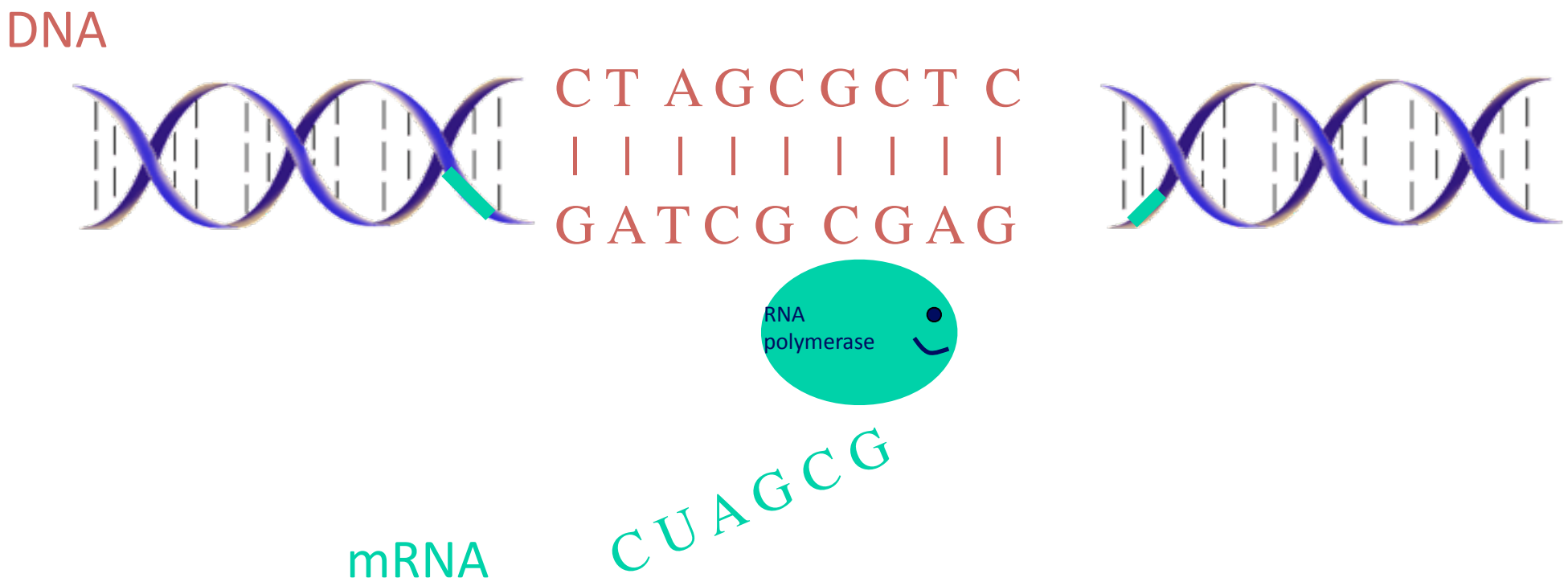
Source: De Novo Assembly Using Illumina Reads. Illumina. 2010

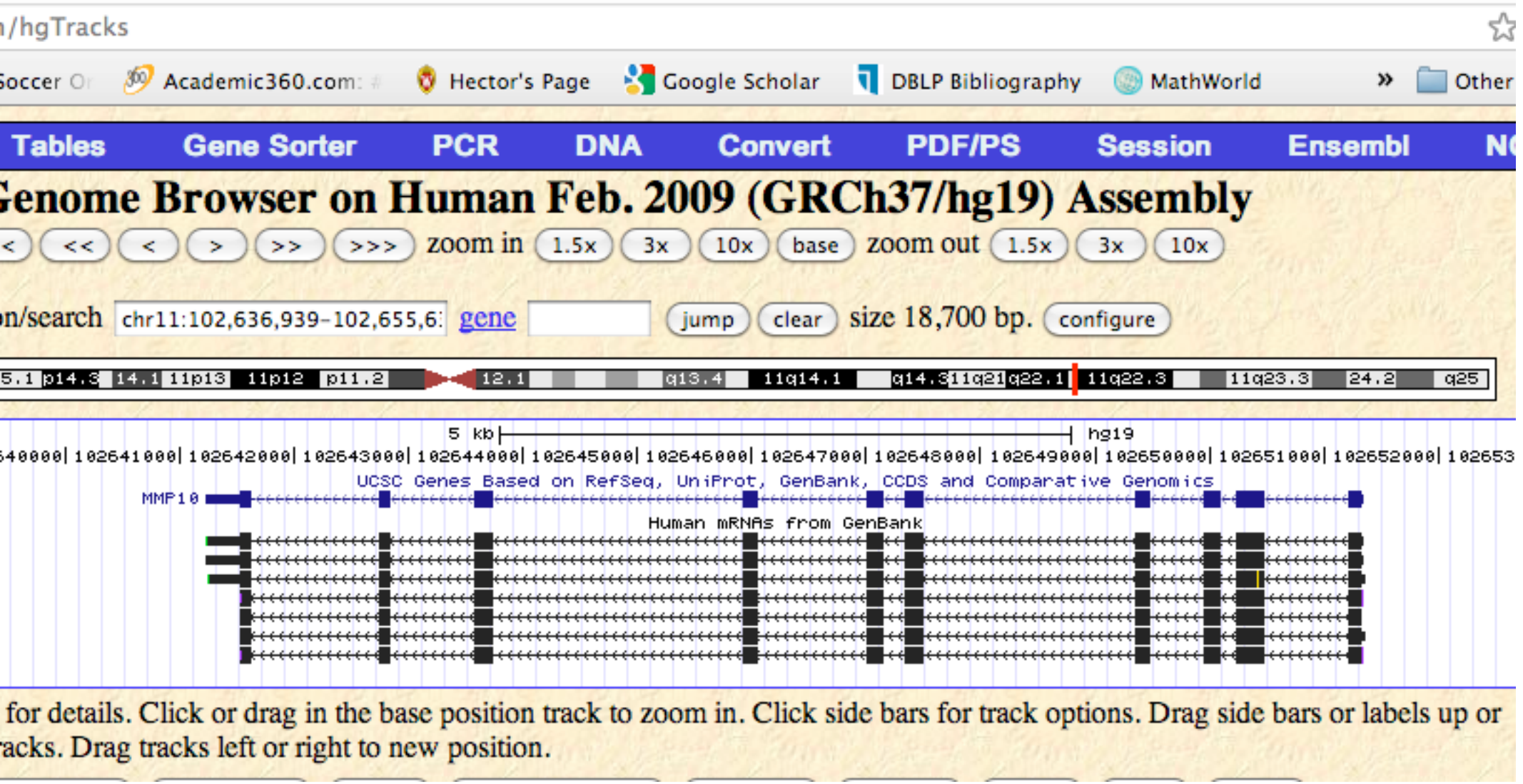


The full genome sequence is a "tour" of the graph

Source: De Novo Assembly Using Illumina Reads. Illumina. 2010
http://www.illumina.com/Documents/products/technotes/technote_denovo_assembly.pdf

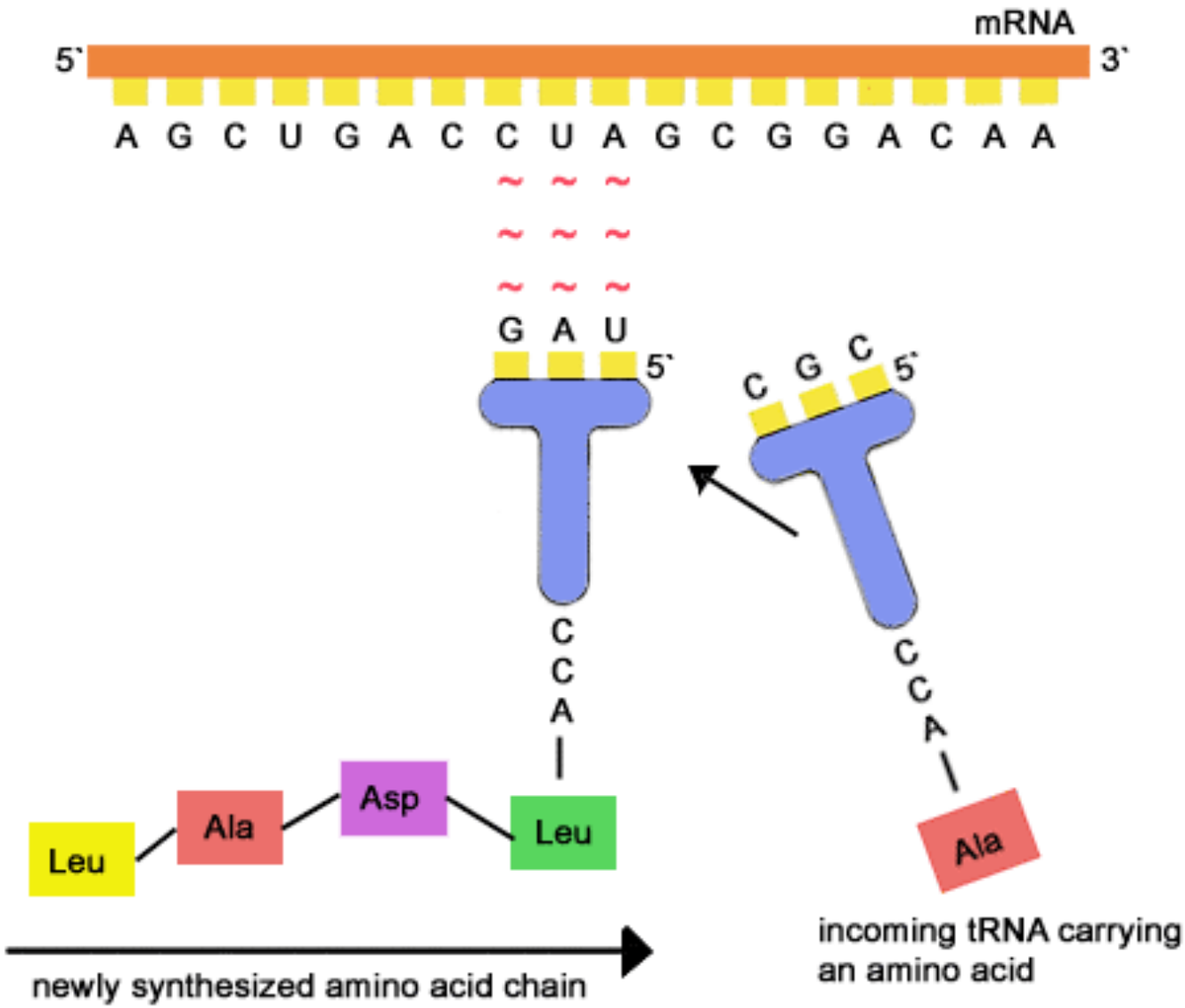
Transcription





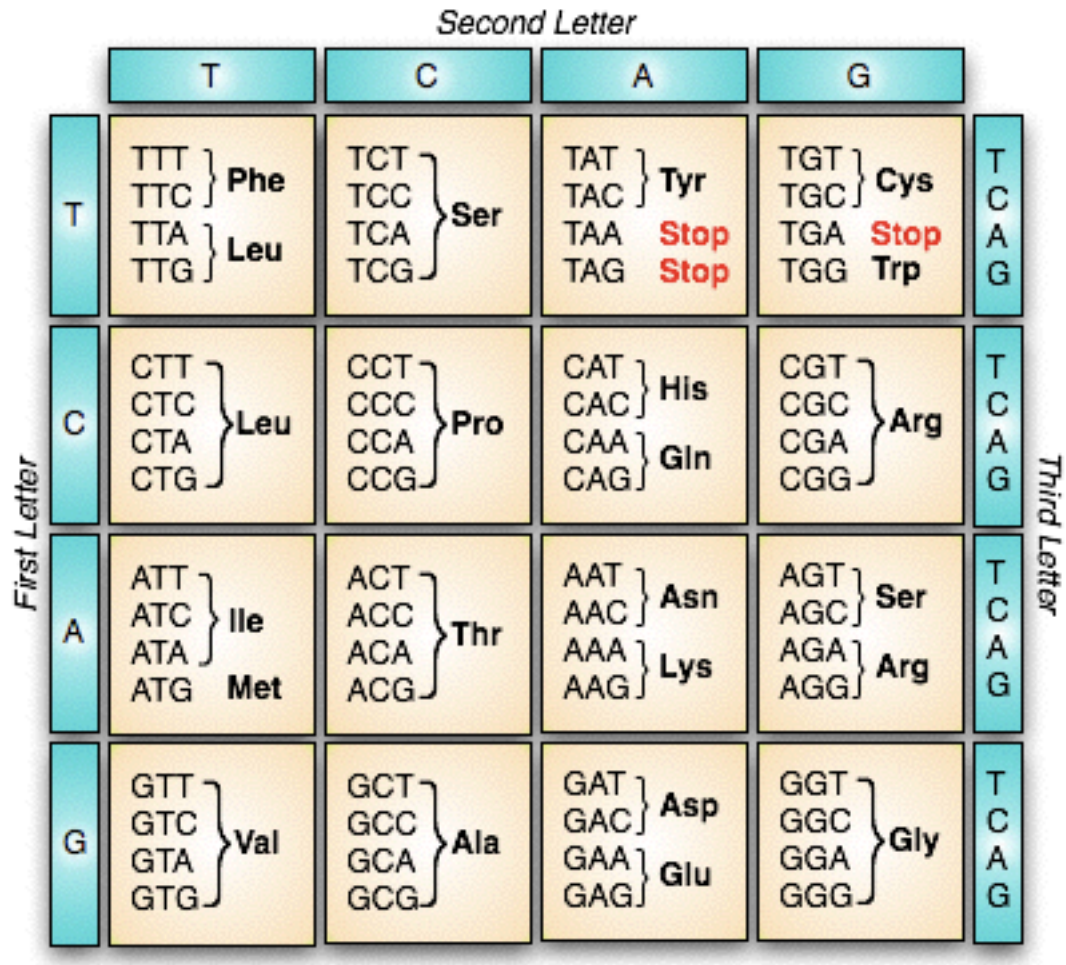
http://www.uniprot.org/uniprot/P09238

Translation

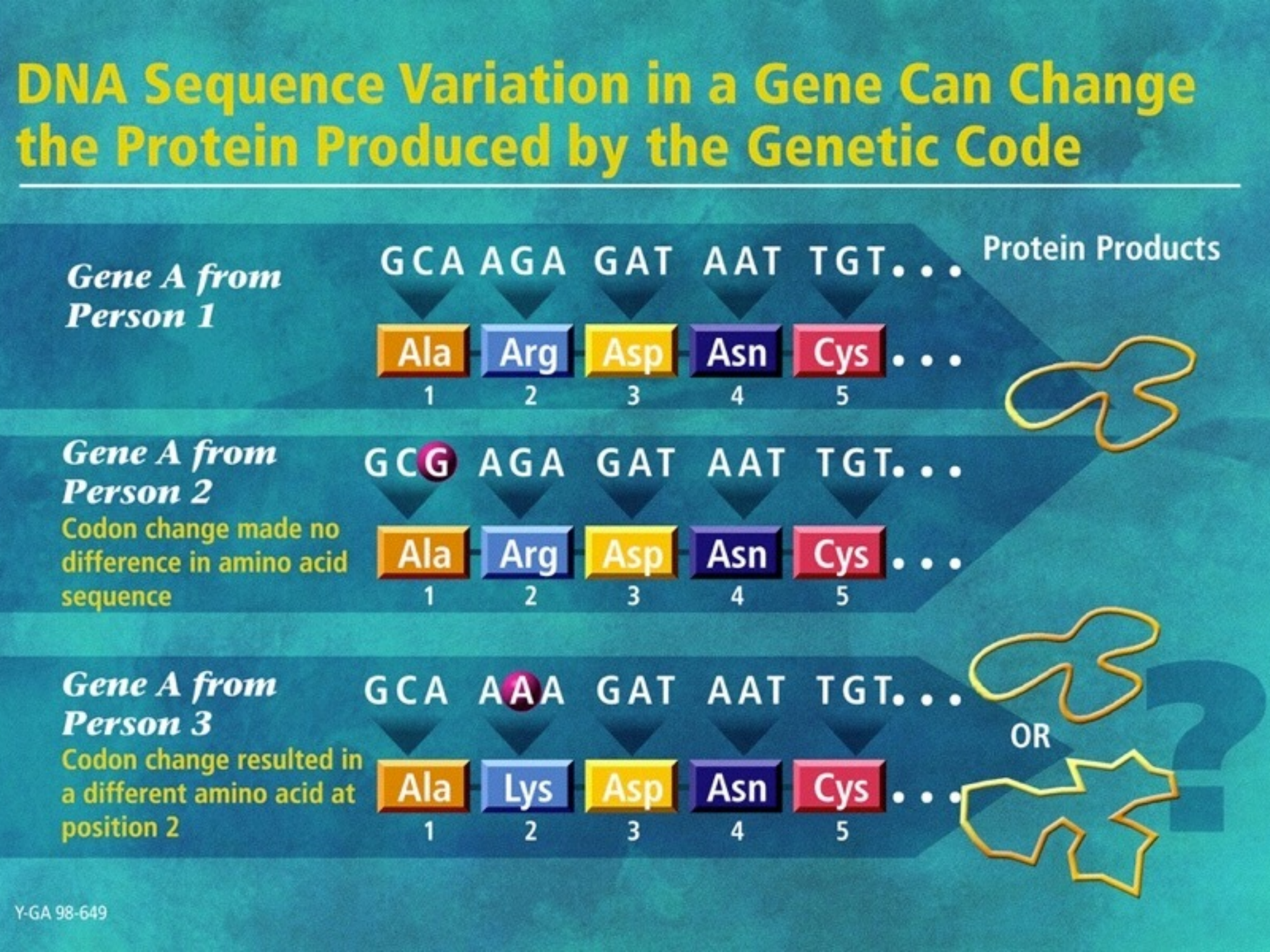


http://gel.ym.edu.tw/~ycl6/sc2005/images/translation.gif

The genetic code



DNA Sequence Variation in a Gene Can Change the Protein Produced by the Genetic Code



Y-GA 98-649

Health or Disease?

DNA Sequence

Person 1 A A A T T T

Normal protein

Some DNA variations have no negative effects

Person 2 A A T T T T

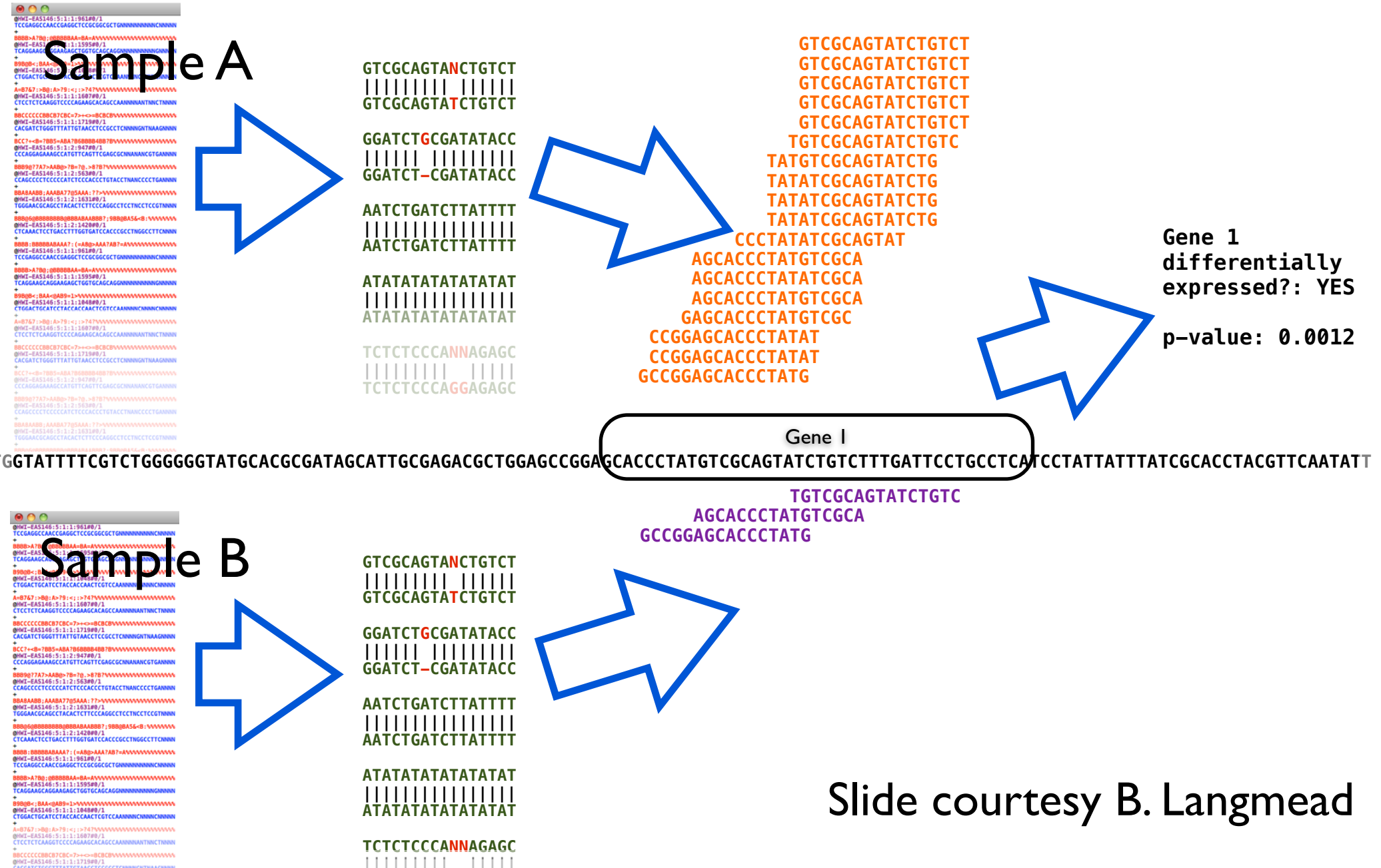
Low or nonfunctioning protein

Person 3 A A C T T T

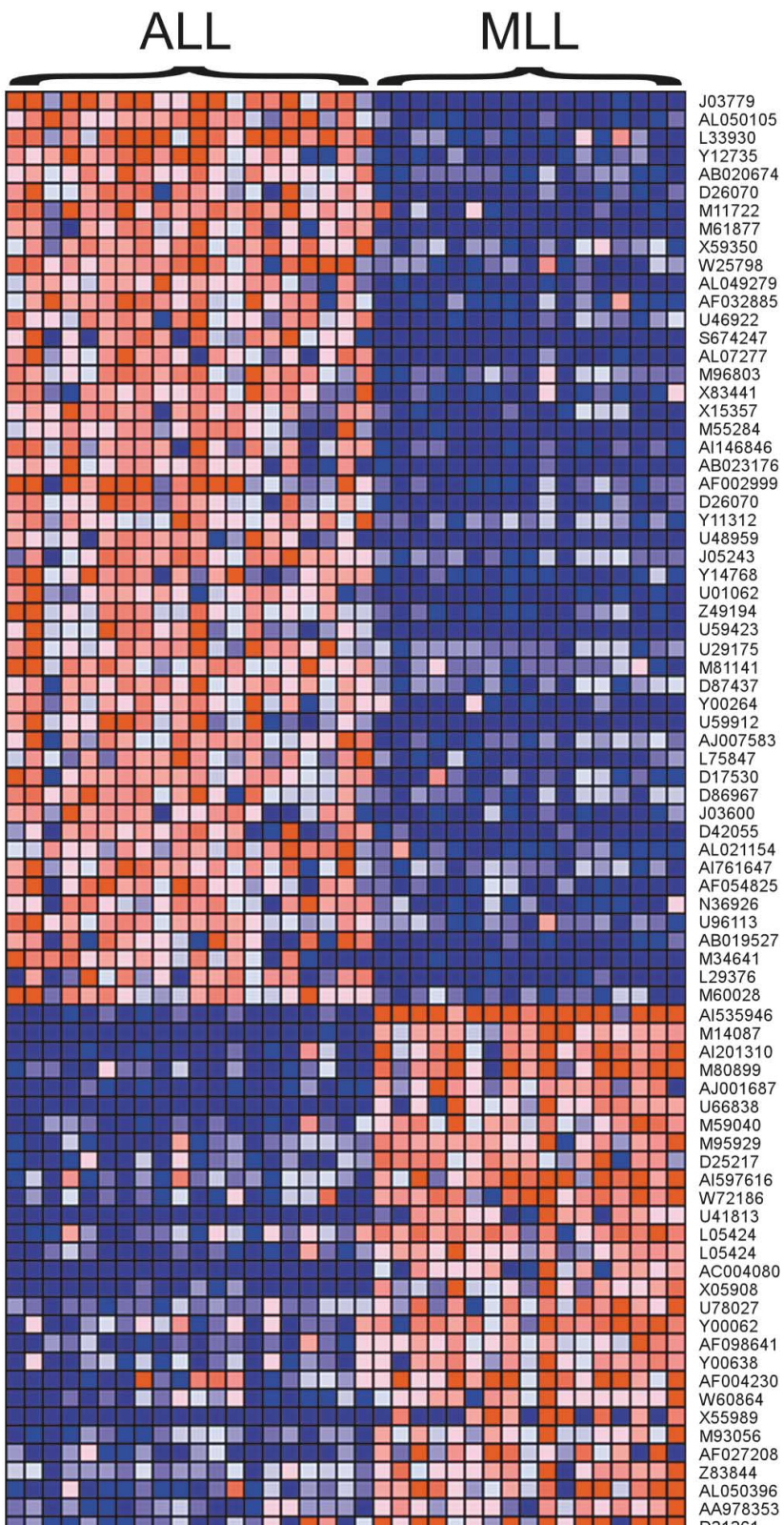
Other variations lead to disease (e.g., sickle cell) or increased susceptibility to disease (e.g., lung cancer)

YGG-00-0480

RNA-seq differential expression



Slide courtesy B. Langmead

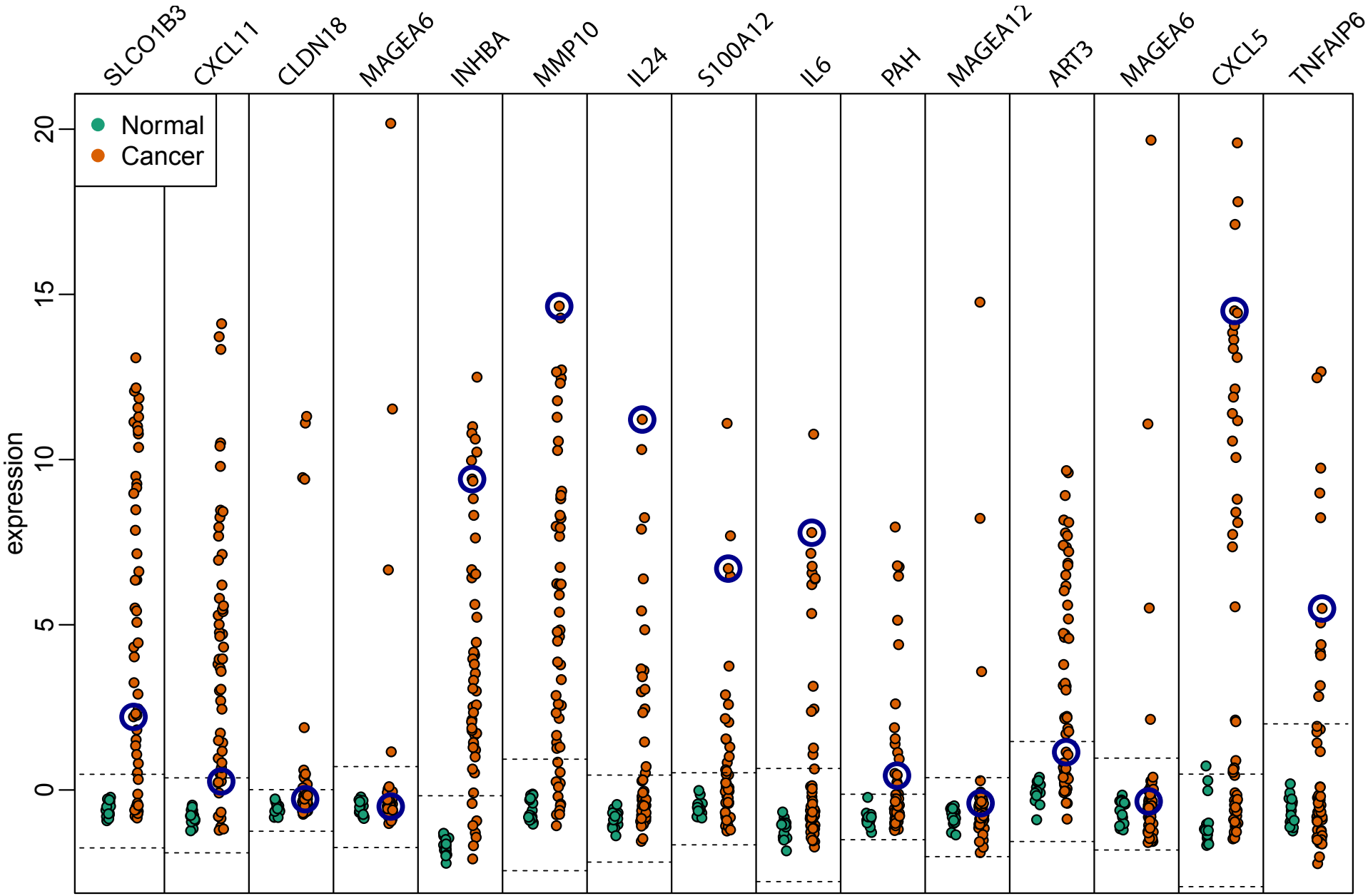


MLL translocations specify a distinct gene expression profile that distinguishes a unique leukemia

Scott A. Armstrong[1–4], Jane E. Staunton[5], Lewis B. Silverman[1,3,4], Rob Pieters[6], Monique L. den Boer[6], Mark D. Minden[7], Stephen E. Sallan[1,3,4], Eric S. Lander[5], Todd R. Golub[1,3,4,5*] & Stanley J. Korsmeyer[2,4,8*]

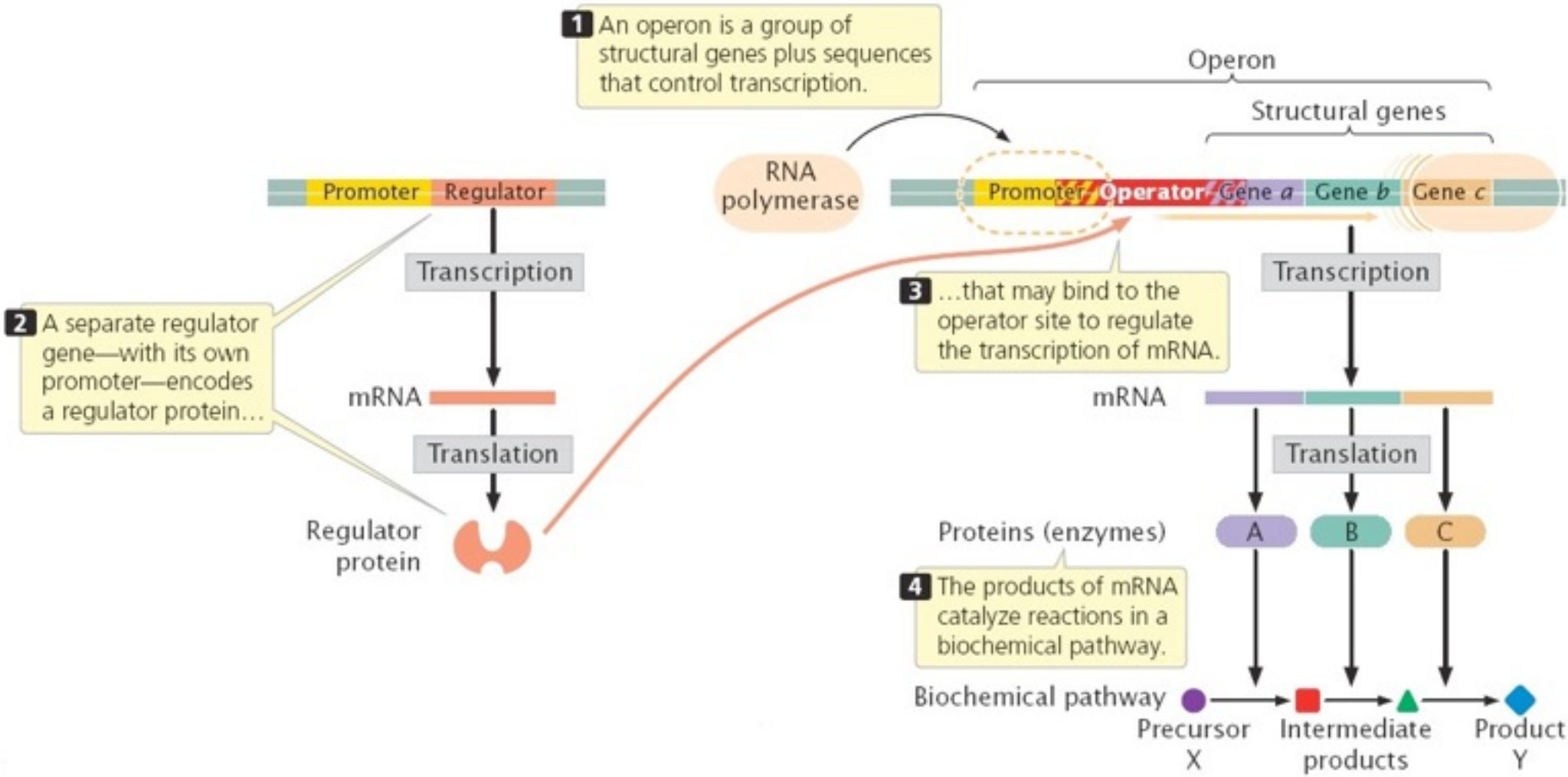
**These authors contributed equally to this work.*

Published online: 3 December 2001, DOI: 10.1038/ng765

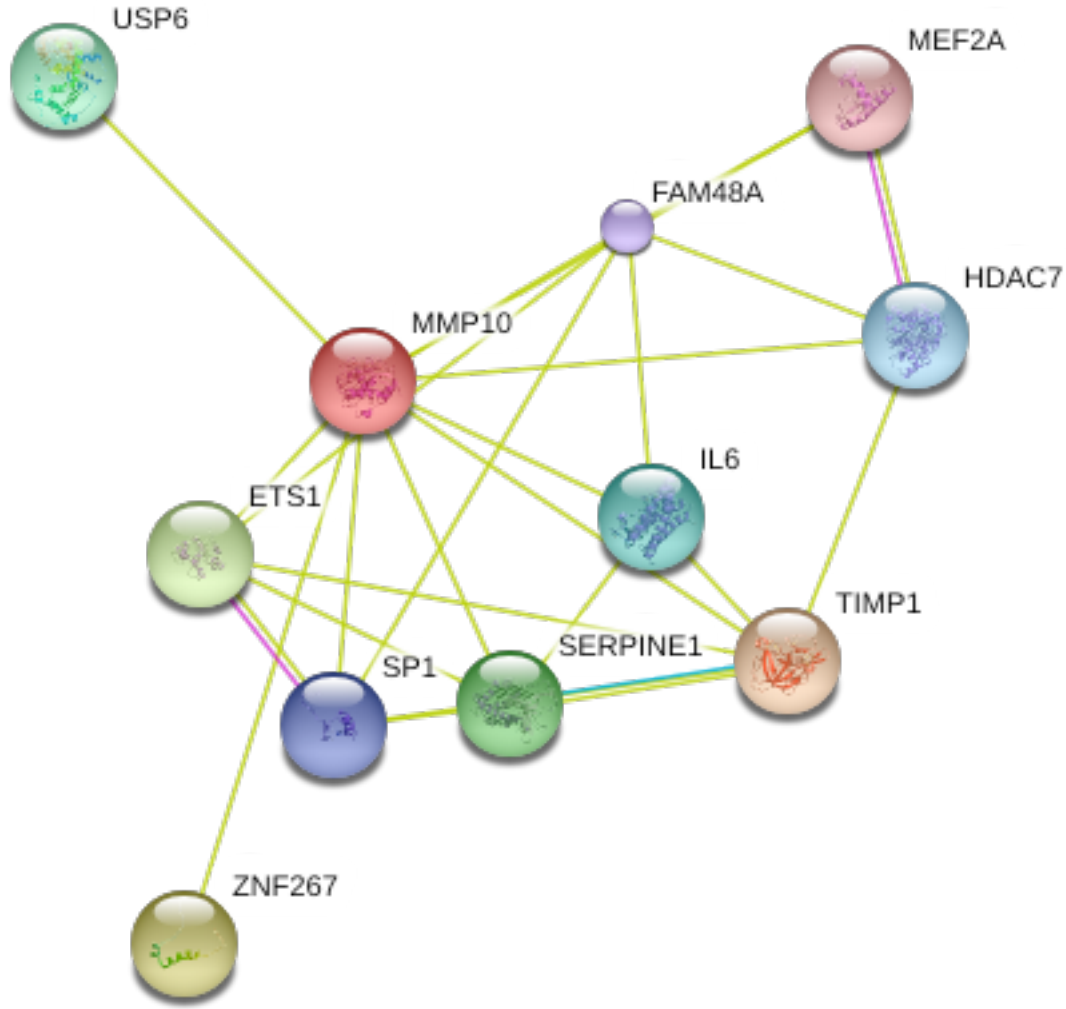


[Corrada Bravo, et al. Gene expression anti-profiles. *BMC Bioinformatics*.]

gene regulation

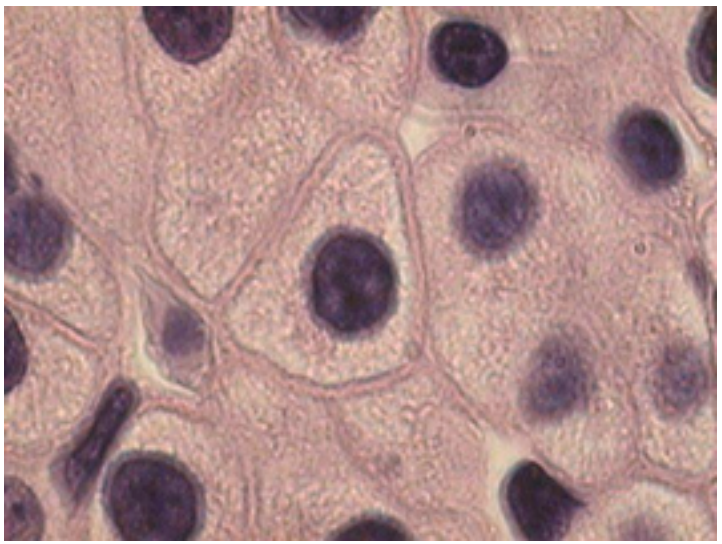


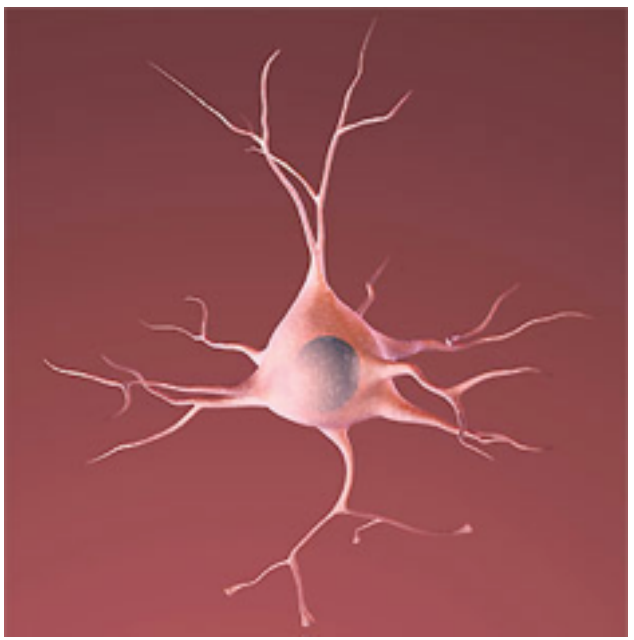
gene regulation

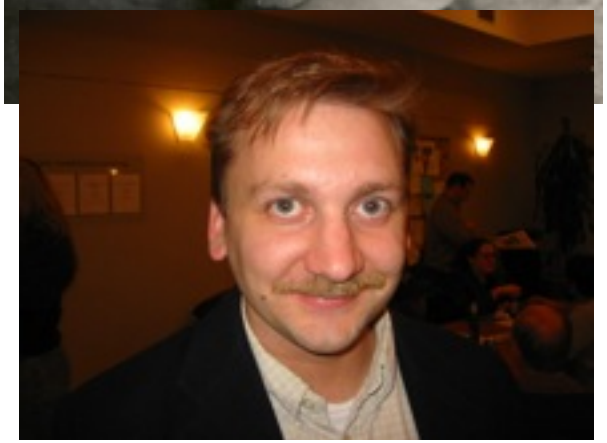


http://string-db.org/version_9_0/newstring_cgi/show_network_section.pl?identifier=9606.ENSP00000279441&all_channels_on=1&network_flavor=evidence&targetmode=proteins

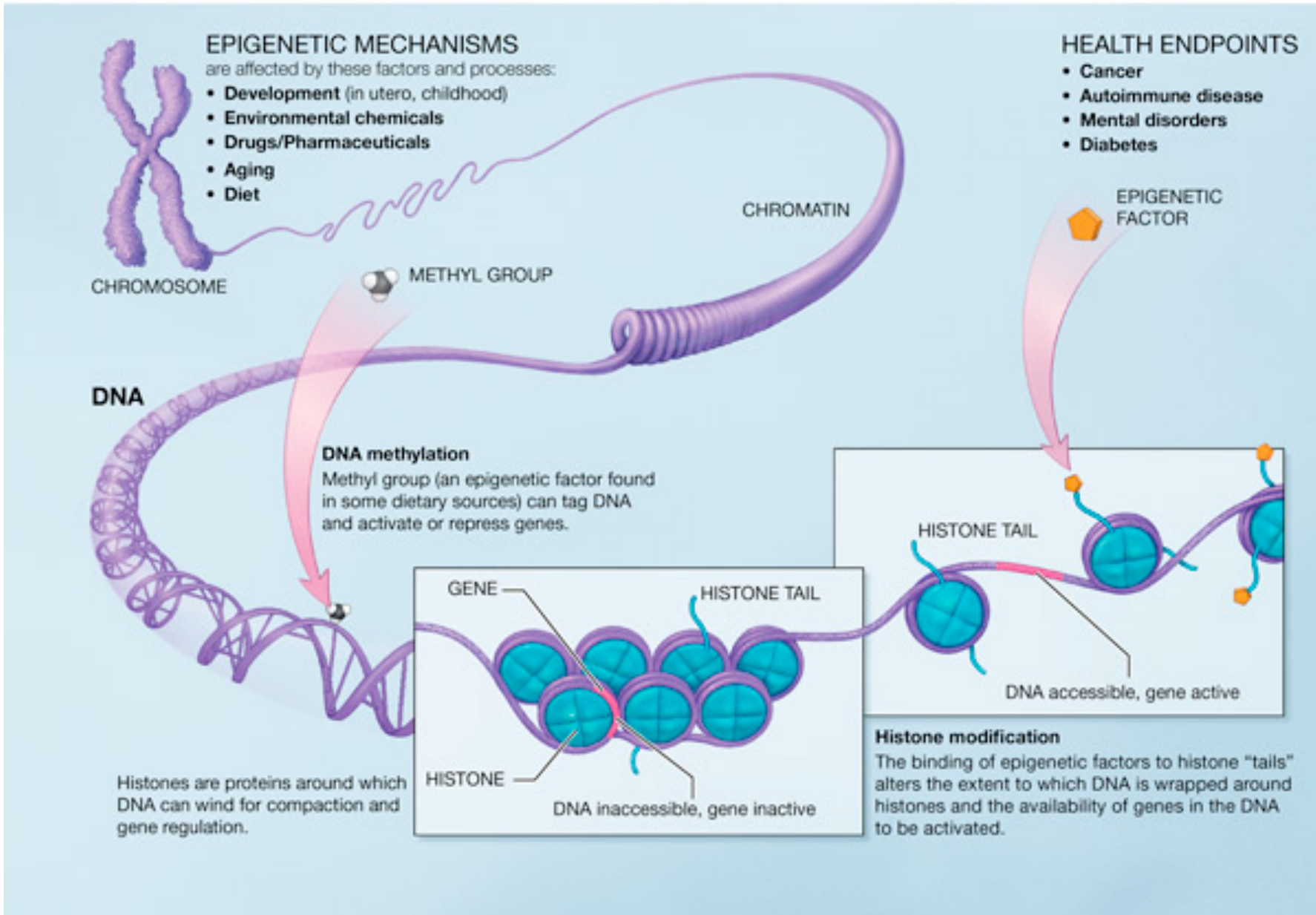
How many basepair differences?





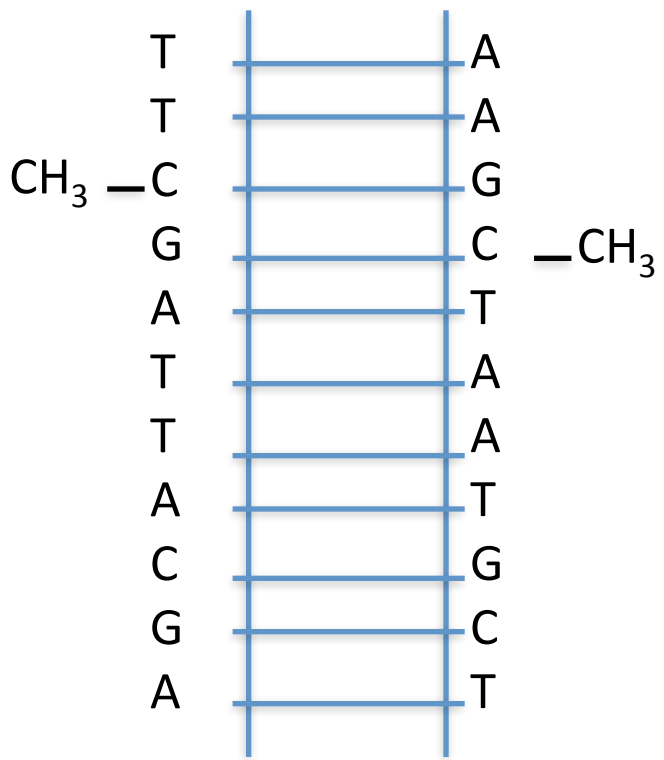


Epigenetics



http://nihroadmap.nih.gov/EPIGENOMICS/images/epigeneticmechanisms.jpg

DNA Methylation

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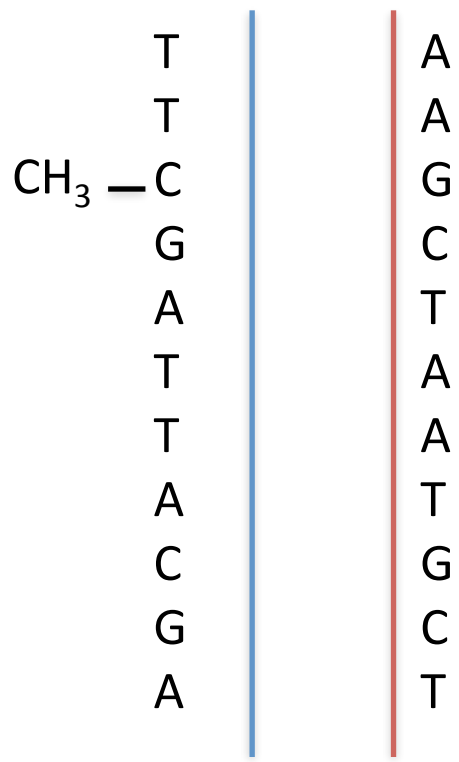
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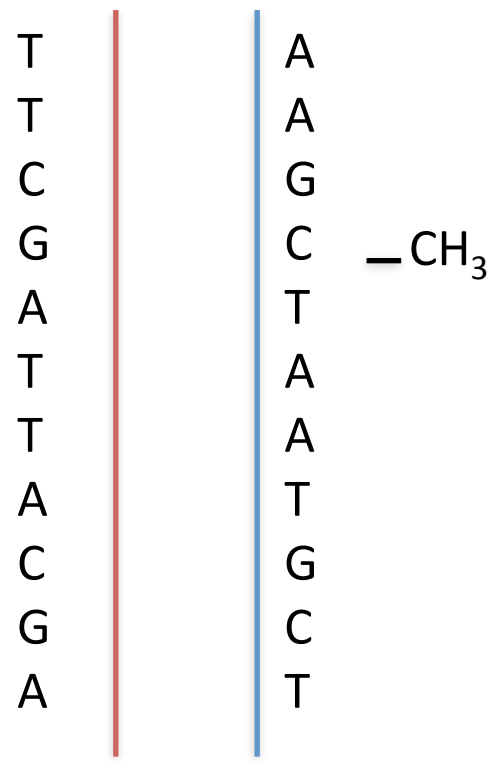
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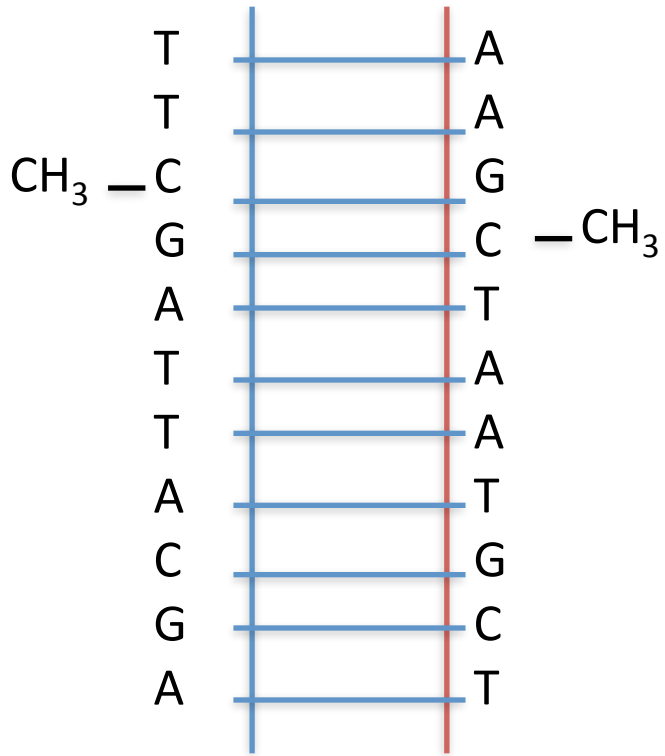
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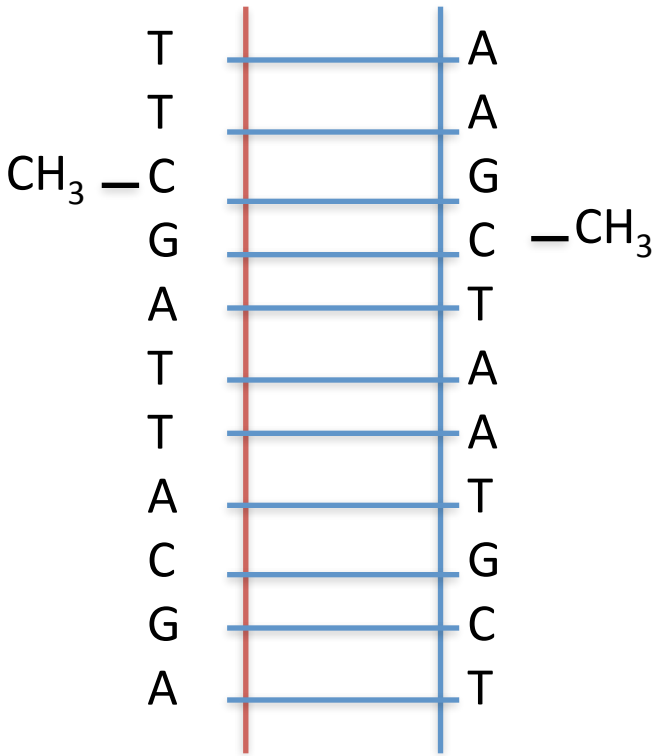
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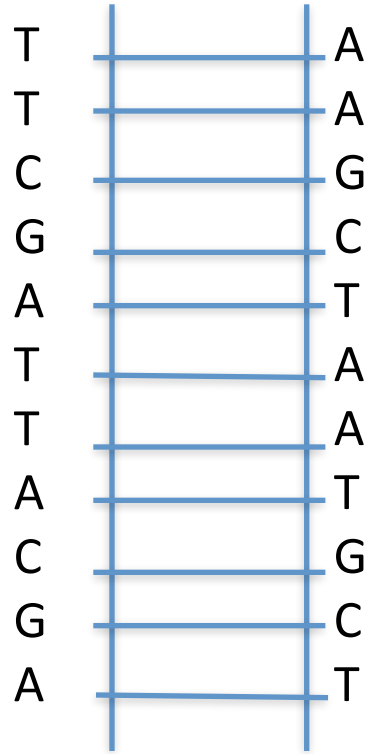
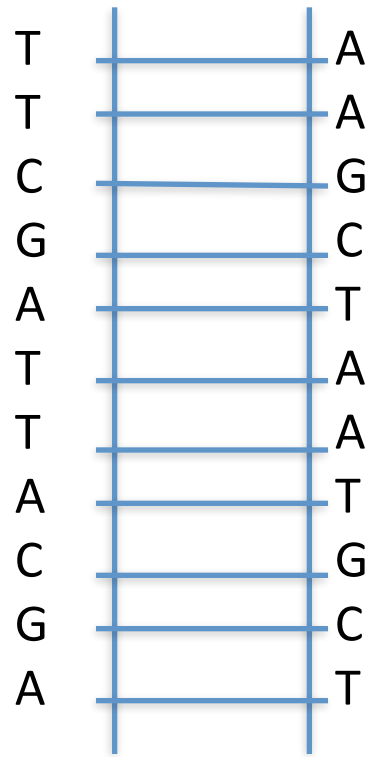
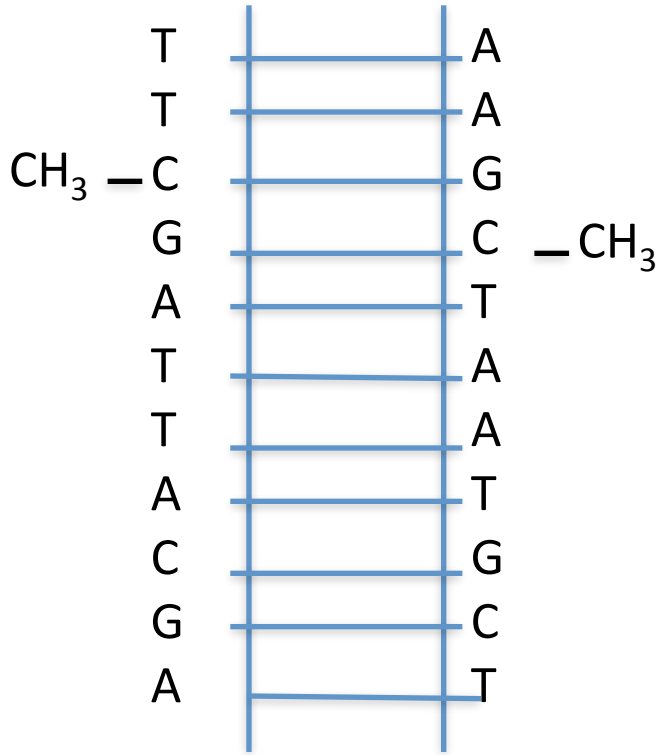
Liver



Brain



Liver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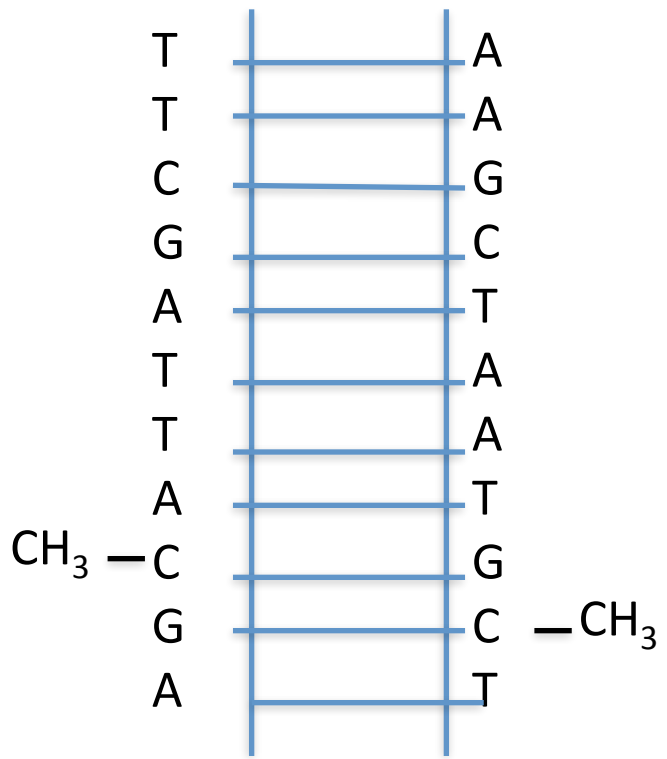
Brain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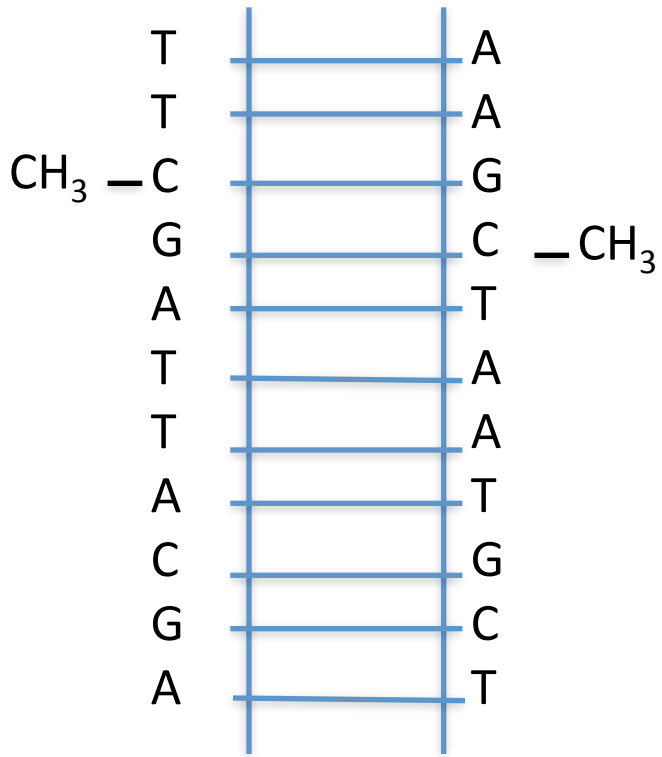
Liver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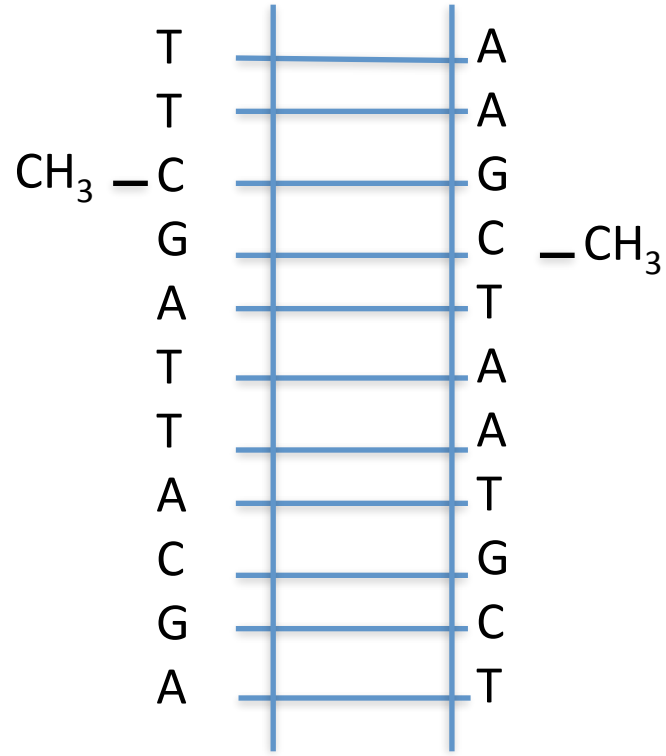
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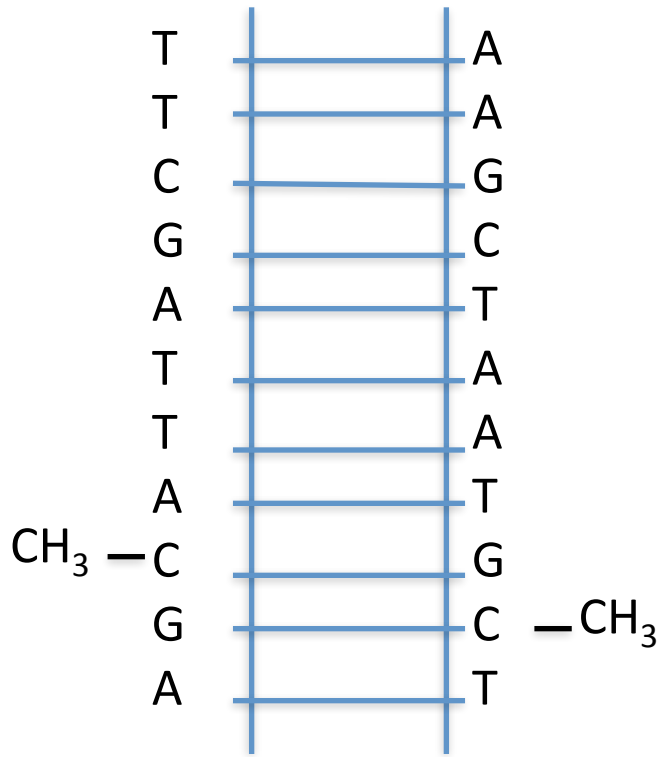
Brain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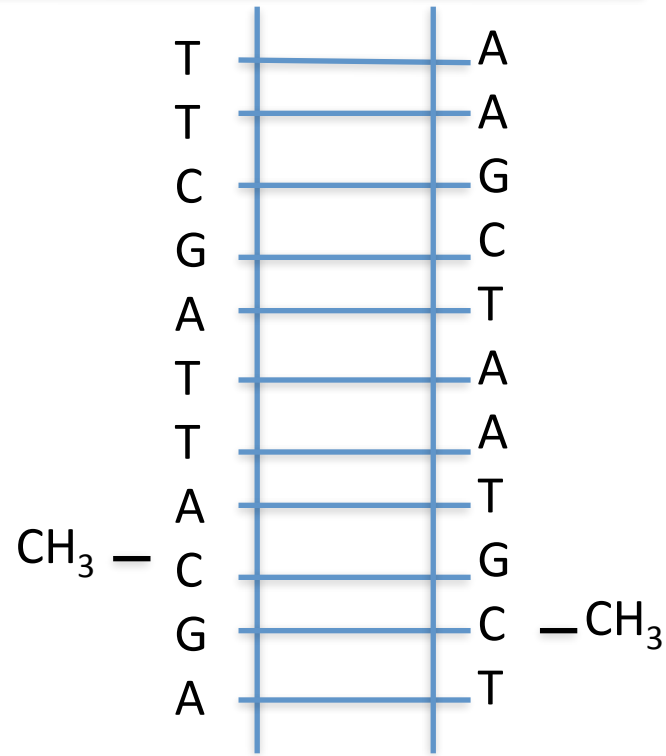
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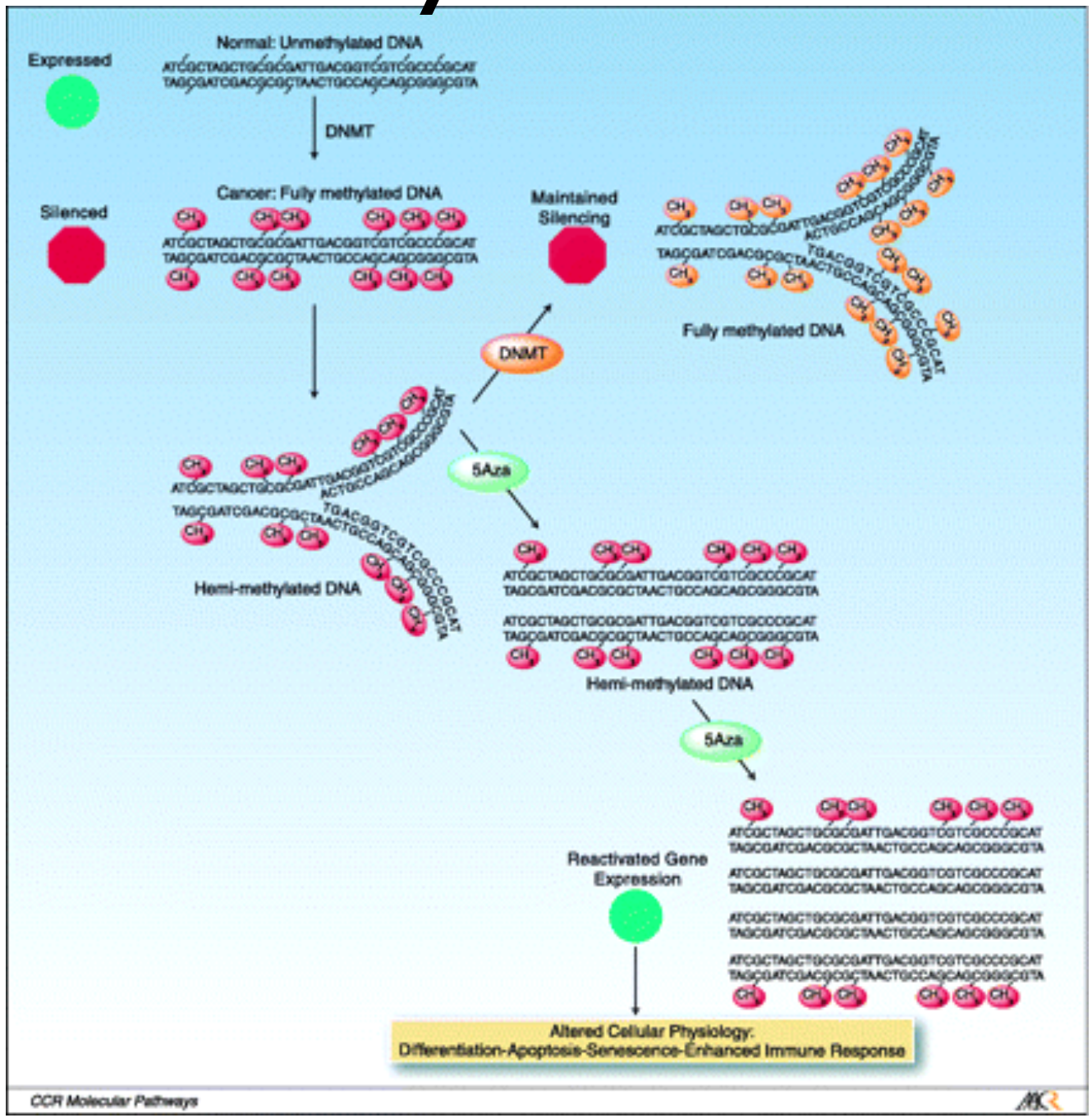
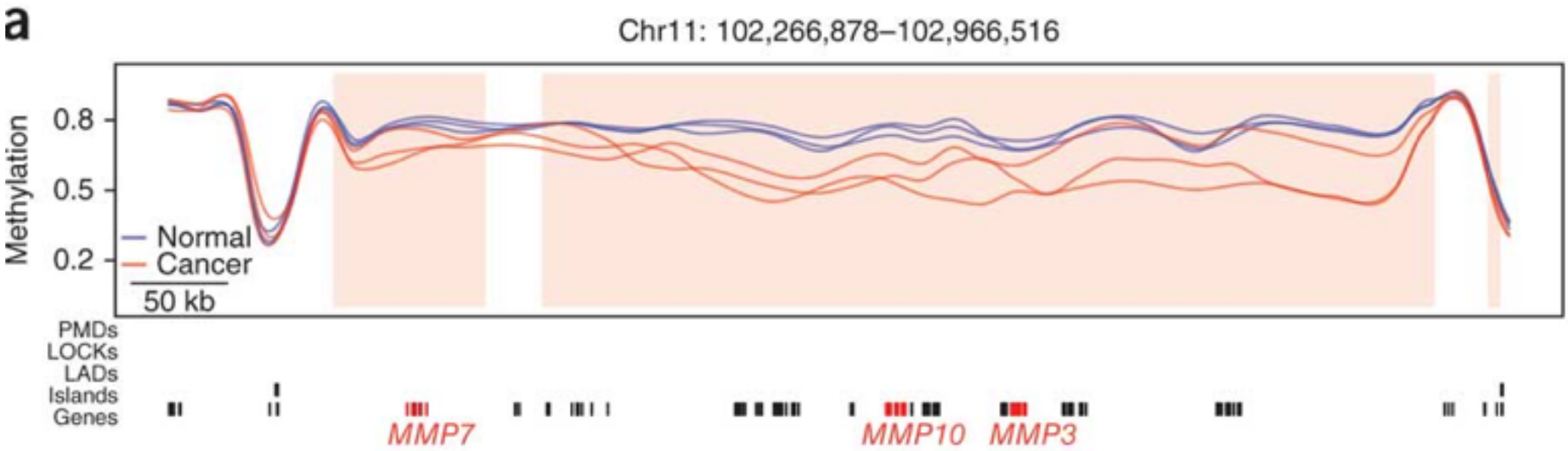
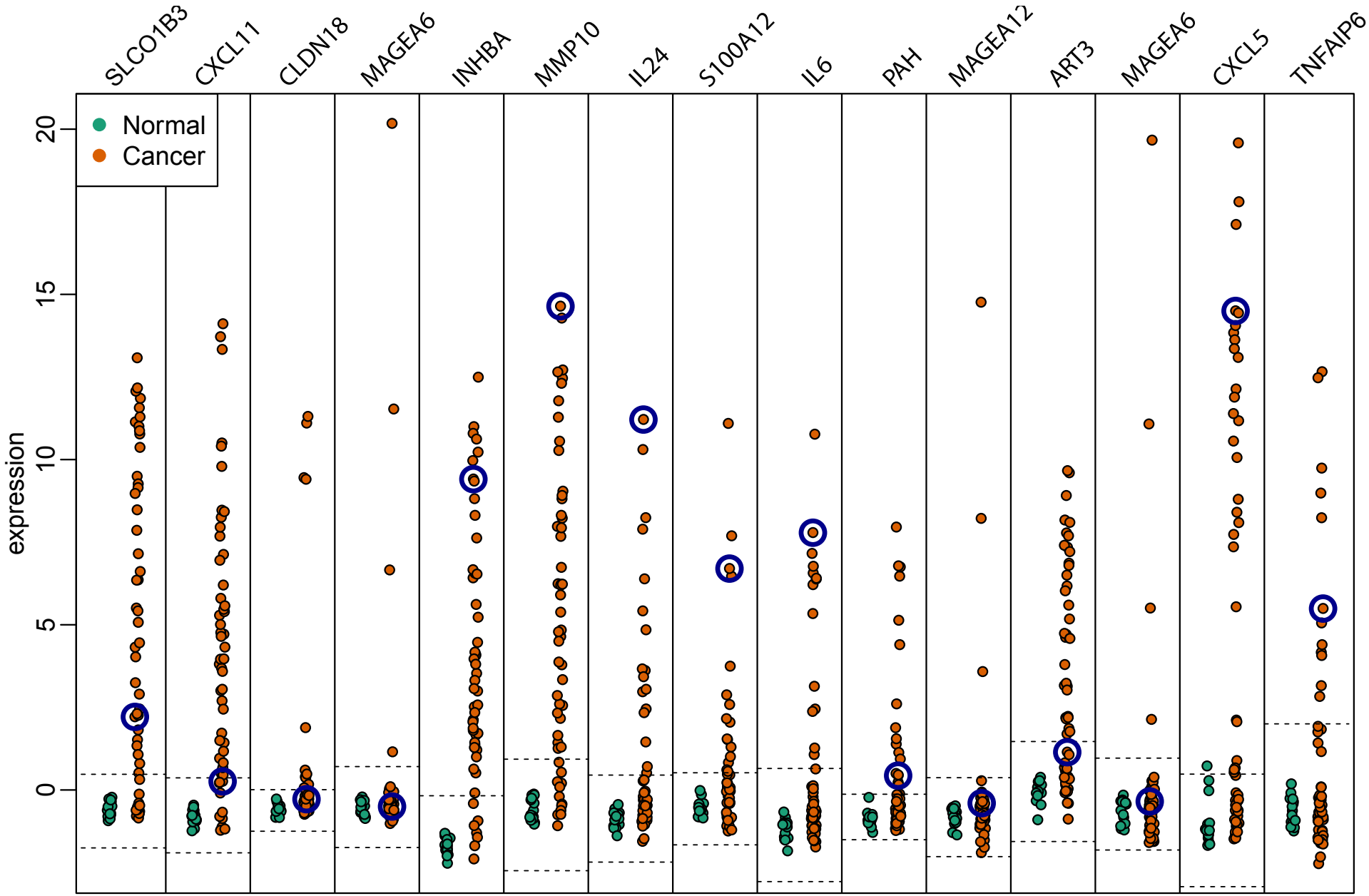
— CH3

DNA Methylation in cancer





[Hansen et al. Nature Genetics 2011]



[Corrada Bravo, et al. Gene expression anti-profiles. *BMC Bioinformatics*]