Lecture 6: Finish GWAS + Intro to RNA sequencing

ECE 365

Announcements:

- Lab 3 (GWAS) released (due 03/25)
- Quiz 1 – 03/23
  - Material includes everything up to (and including) GWAS

Revisiting Logistic Regression

- Can we use Logistic Regression for GWAS?

- Problem: Number of SNPs can be $\sim 10^6$

GWAS via *univariate* logistic regression

- Run a separate logistic regression for each SNP

	SNP 1			x_i	SNP m		phenotype
person 1	0	1	1	0	0	1	0
	1	0	2	1	0	2	0
	1	1	1	0	0	0	1
	0	0	0	2	1	1	1
	1	1	1	0	0	0	1
	0	2	0	0	1	0	0
person n	1	1	0	1	0	2	1

$$p(1 \mid x_i) = \frac{1}{1 + e^{-(\beta_0 + \beta_i x_i)}}$$

captures association between i^{th} SNP and phenotype

- Use this to identify small subset of SNPs associated with phenotype
- Let's look at some examples on a Jupyter notebook

GWAS via *univariate* logistic regression

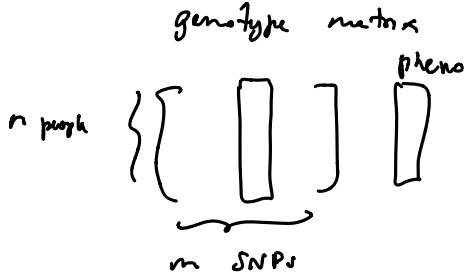
- Idea: combine all beta coefficients into a single model:

$$\underbrace{\ln\left(\frac{p(1|x)}{1-p(1|x)}\right)}_{\text{LOR}} = \beta_0 + \beta_1 x_1 + \cdots + \beta_m x_m$$

- Problems with this approach:
  - Since m is very large, some β_is will be large **by chance**
  - Some x_is are correlated

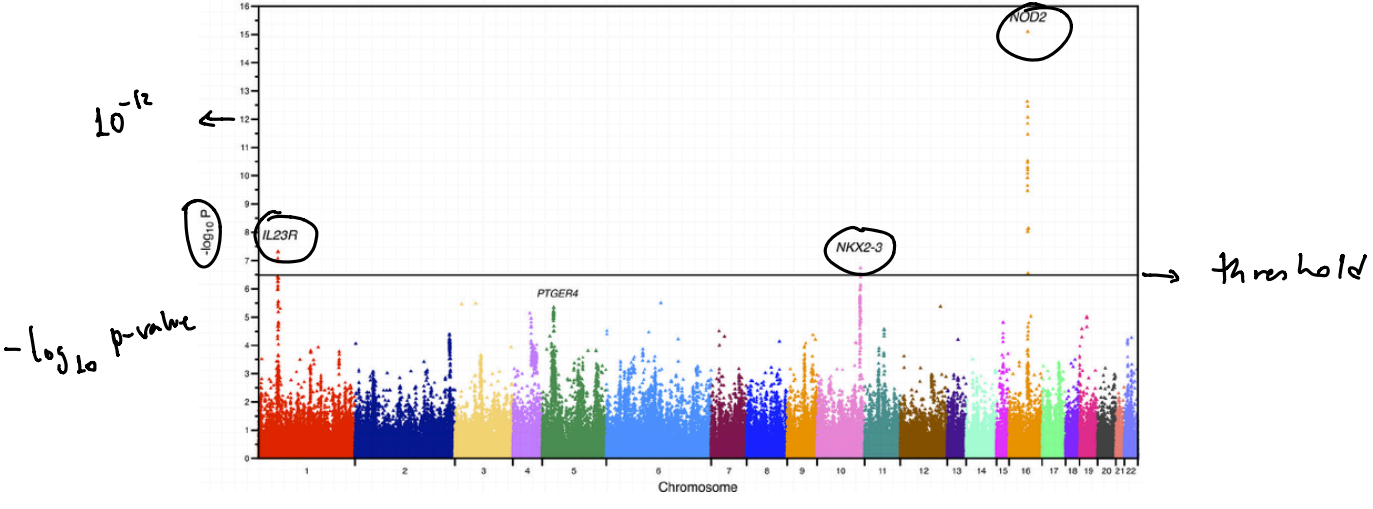
(e.g., anyone with $x_3 = 1$ has $x_4 = 1$)

Manhattan plots



- Allow us to see the significance of all SNPs in the genome
- We plot $-\log_{10}(p-\text{value})$

Manhattan plot of SNP association with Irritable Bowel Disease



GWAS via *univariate* logistic regression

- Idea: combine all beta coefficients into a single model:

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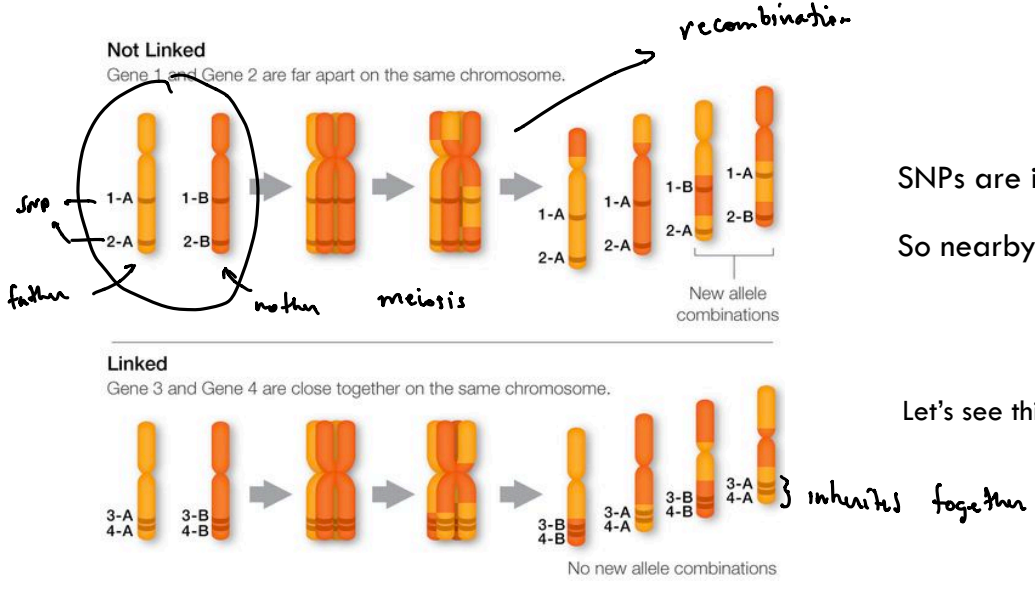
- Problems with this approach:
  - Since m is very large, some β_is will be large **by chance** (use p-values to select β_is)
  - Some x_is are correlated

Correlation between SNPs

- SNPs can be correlated due to genetic linkage



SNPs are inherited in blocks.

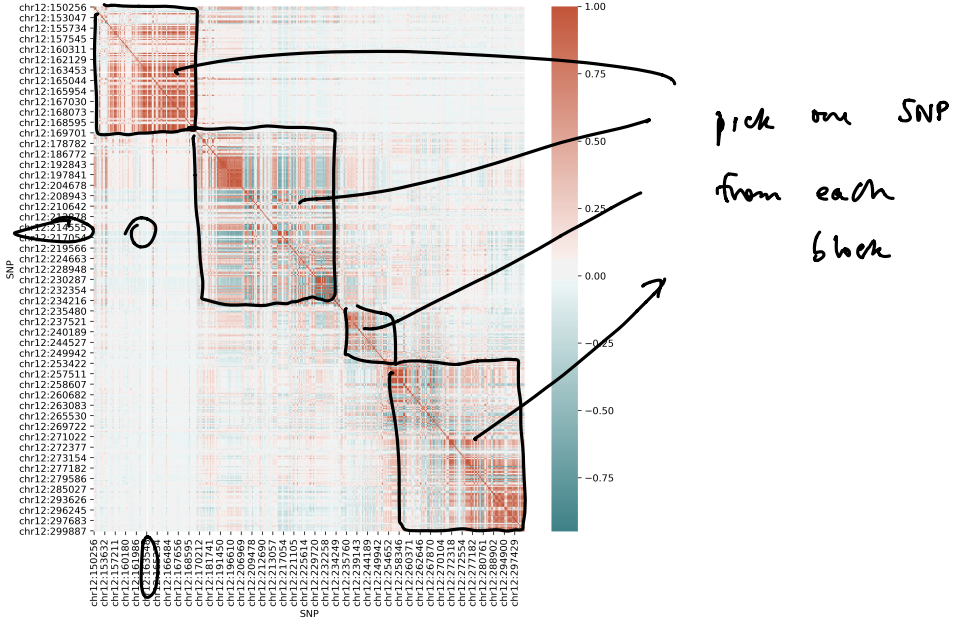
So nearby SNPs are more correlated.

Let's see this in the data!

https://learn.genetics.utah.edu/content/pigeons/geneticlinkage/

Correlation between SNPs

- In practice, SNPs that are "close" to each other are discarded



Final predictive model from GWAS

$$\ln\left(\frac{p(1|x)}{1-p(1|x)}\right) = \beta_0 + \beta_5 x_5 + \beta_{981} x_{981} + \cdots + \beta_{150127} x_{150127}$$

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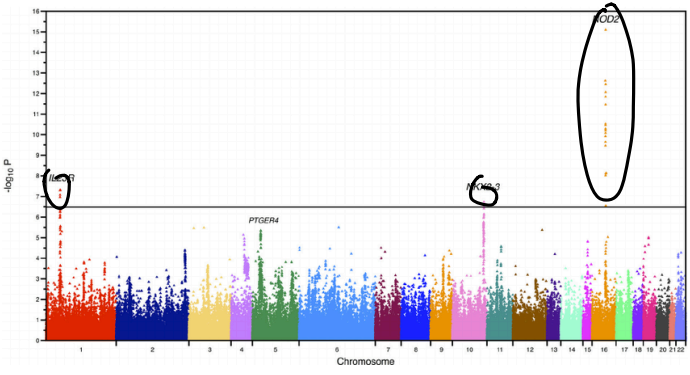
Only SNPs with high statistical significance



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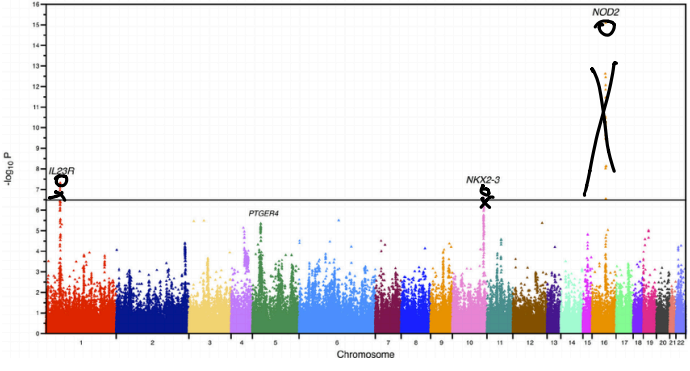
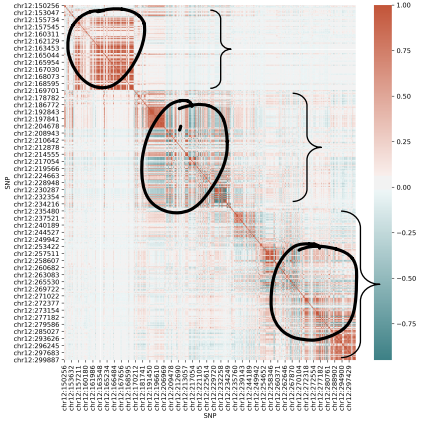
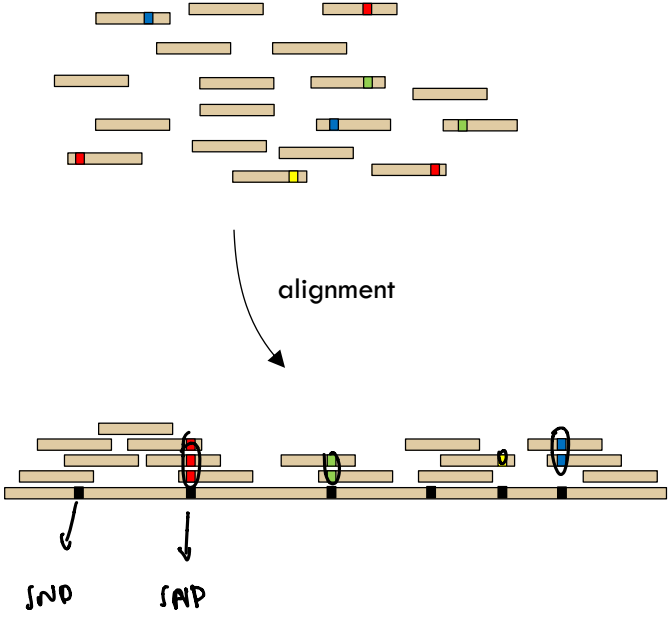
Only SNPs with high statistical significance

SNPs that are distant from each other (small correlation)





Big picture:



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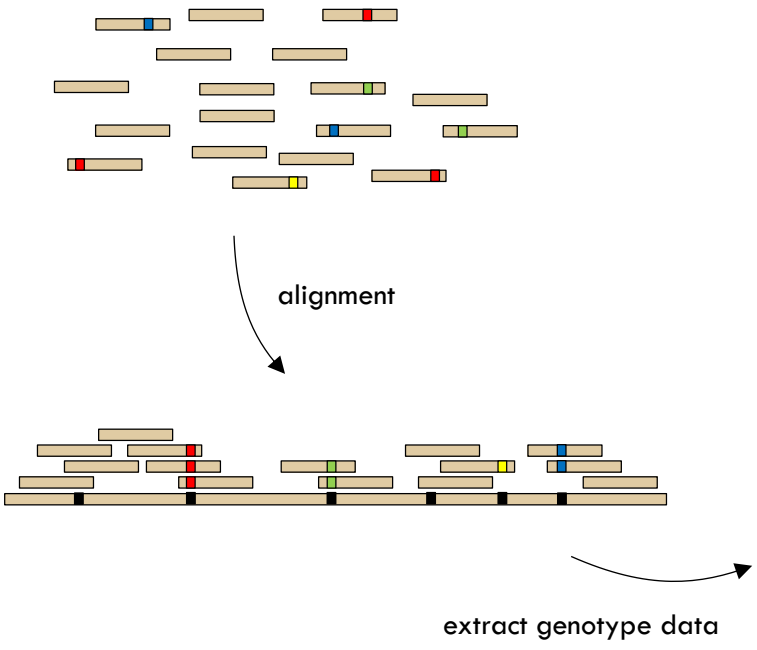


person 1

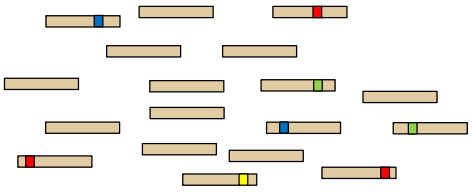
person n

$$\begin{bmatrix} 0 & 1 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 1 & 0 & 1 \end{bmatrix} \qquad \begin{bmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 1 \end{bmatrix}$$

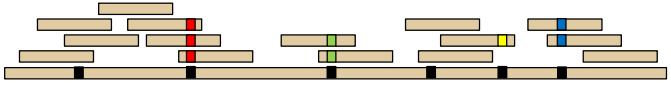
genotype

phenotype

Big picture:



alignment



extract genotype data

$$\ln\left(\frac{p(1|x)}{1-p(1|x)}\right) = \beta_0 + \beta_5 x_5 + \cdots + \beta_{981} x_{981}$$

GWAS

person 1

$$\begin{bmatrix} 0 & 1 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 & 0 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \\ 1 & 1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 1 & 1 & 0 & 1 & 0 & 1 \end{bmatrix} \qquad \begin{bmatrix} 0 \\ 0 \\ 1 \\ 1 \\ 1 \\ 0 \\ 1 \end{bmatrix}$$

person n

genotype

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Part II: RNA sequencing data analysis

ECE 365

The central dogma of molecular biology

- DNA → RNA → protein

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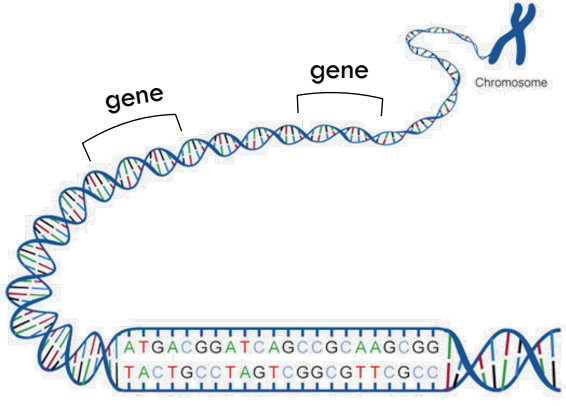

The central dogma of molecular biology

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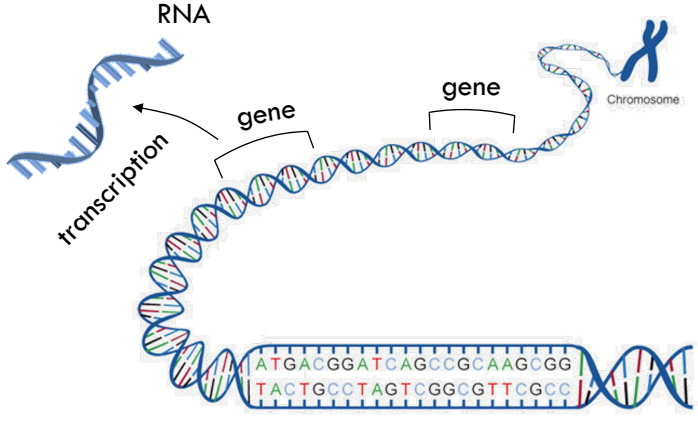

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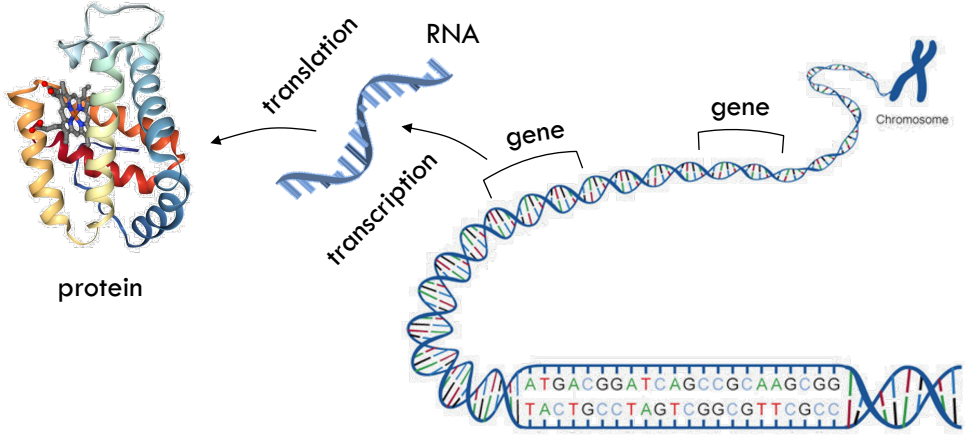

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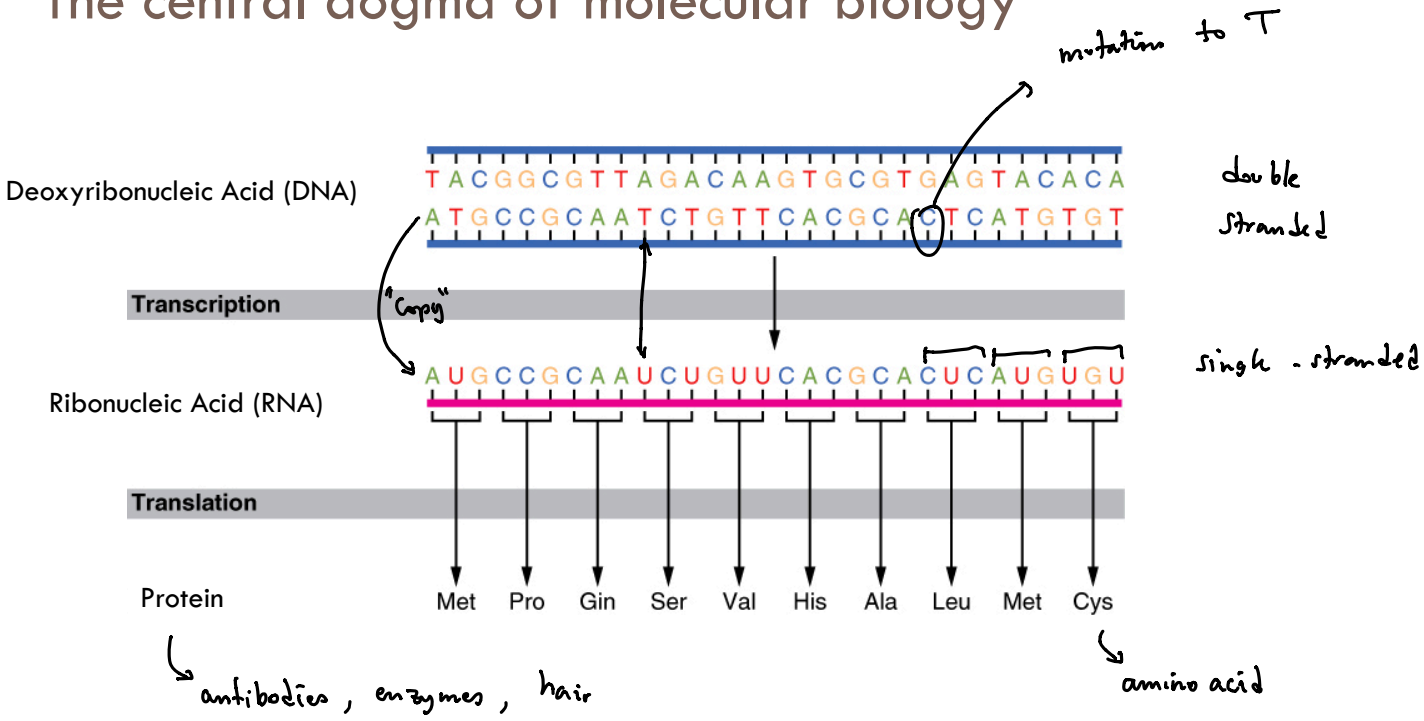

Why do we care about RNA?

- Different genes are *expressed* in different cell types

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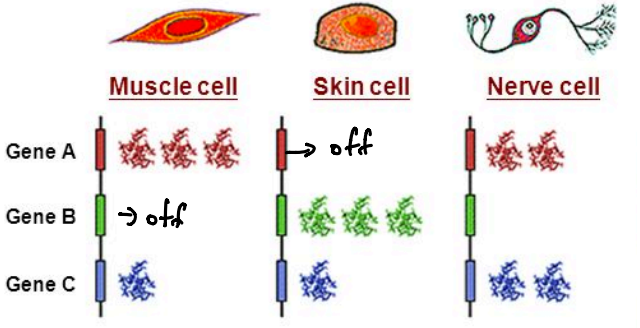

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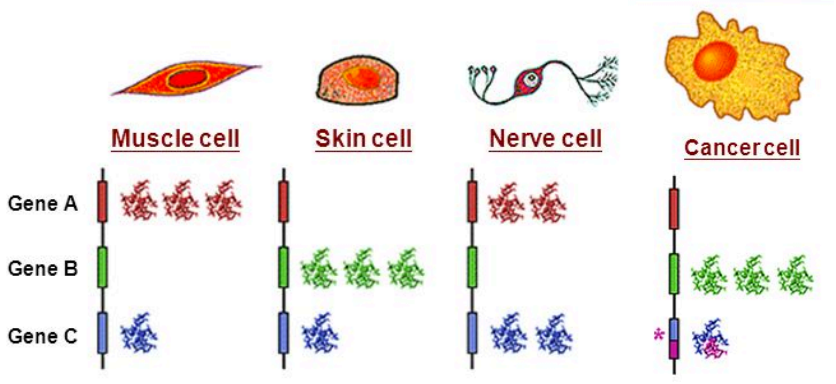

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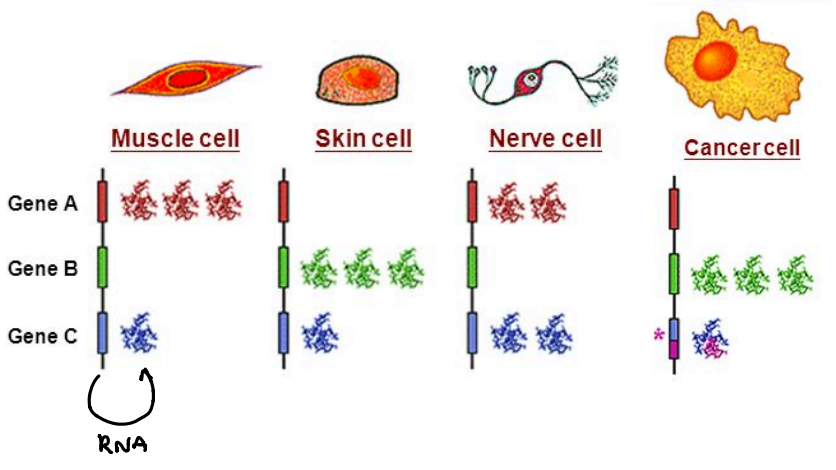
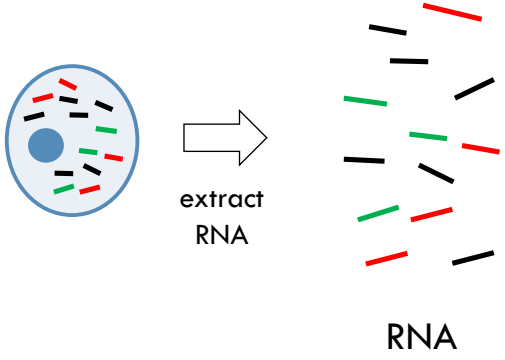


- RNA is an "intermediate step" between genes and proteins
- RNA levels in a cell can tell us which genes are "on/off"

How do we sequence RNA?



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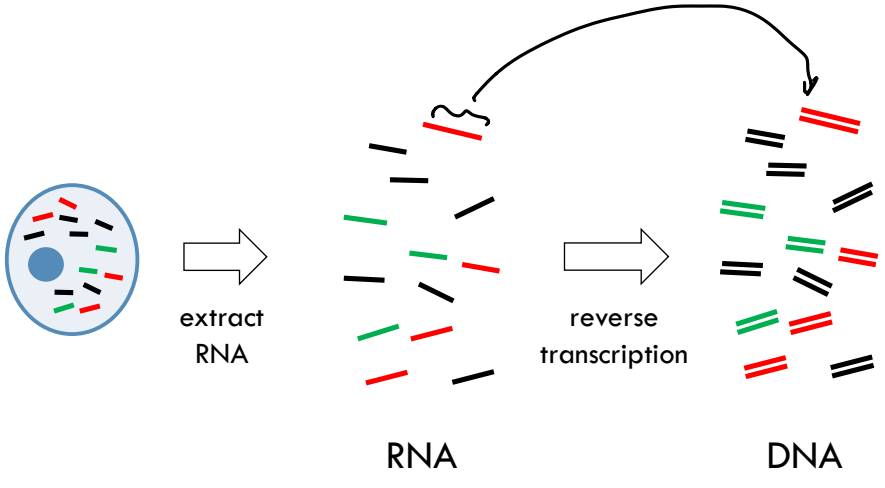

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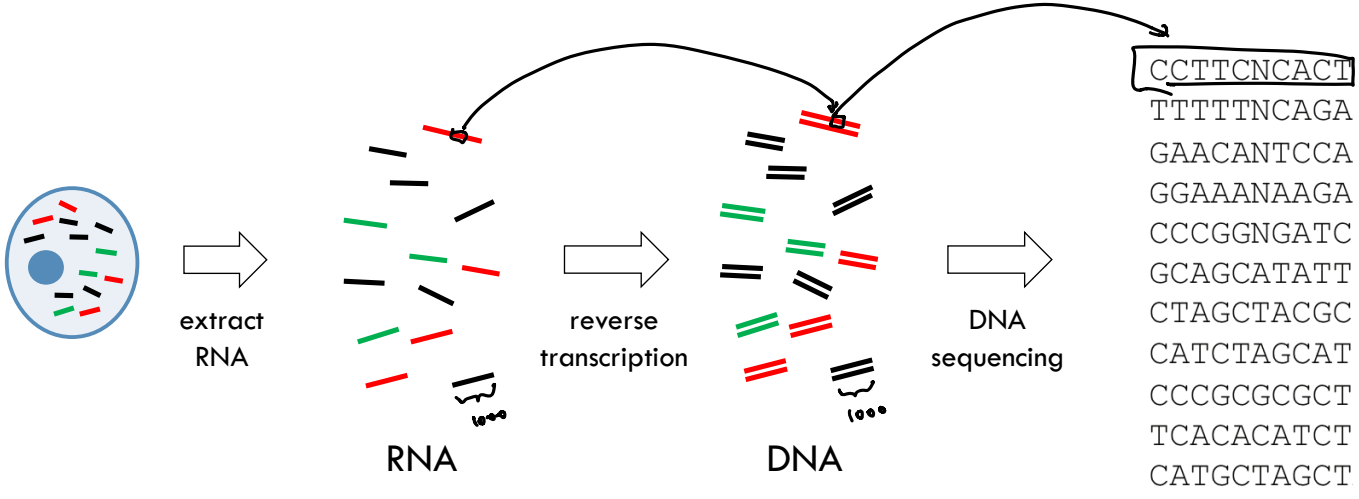

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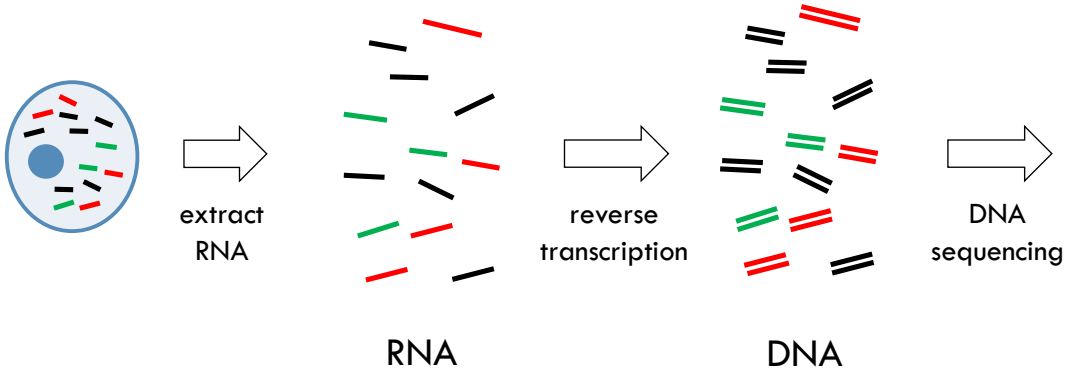

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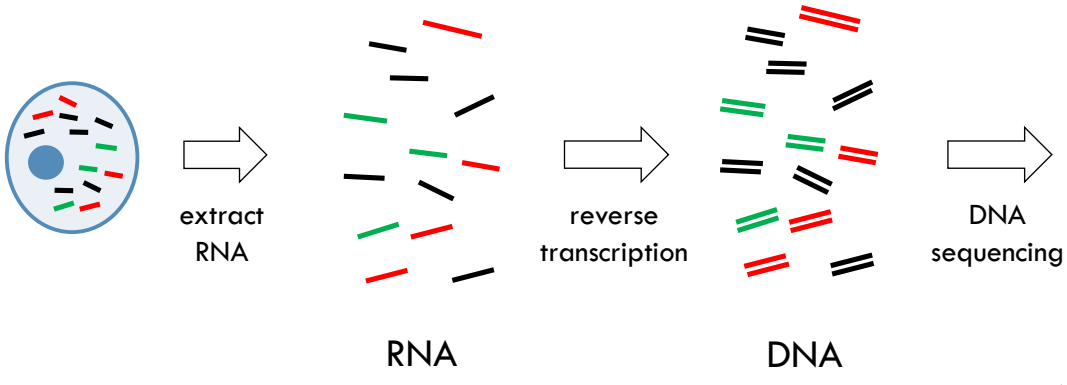

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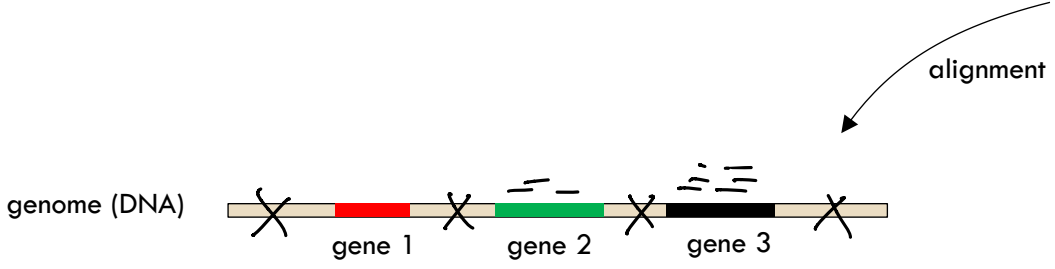
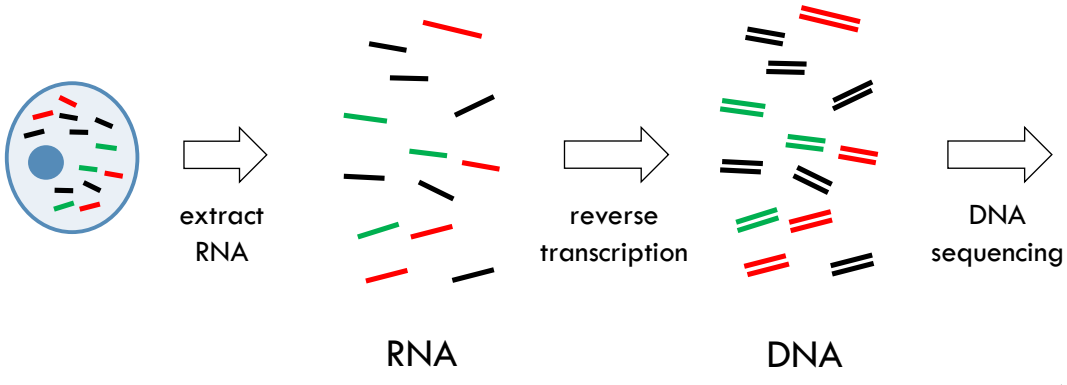
CCCGGNGATC
GCAGCATATT
CTAGCTACGC
CATCTAGCAT
CCCGCGCGCT
TCACACATCT
CATGCTAGCT



Our first goal: RNA quantification



GAACANTCCA
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alignment

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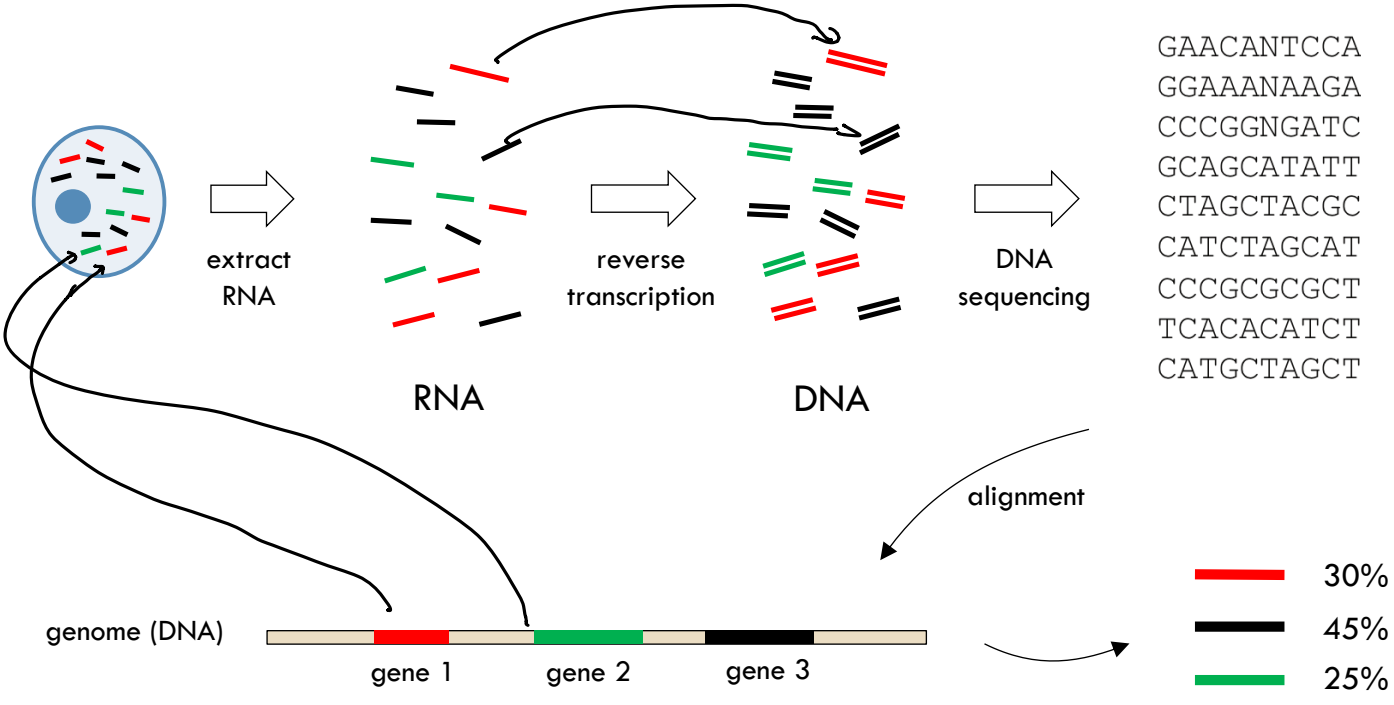

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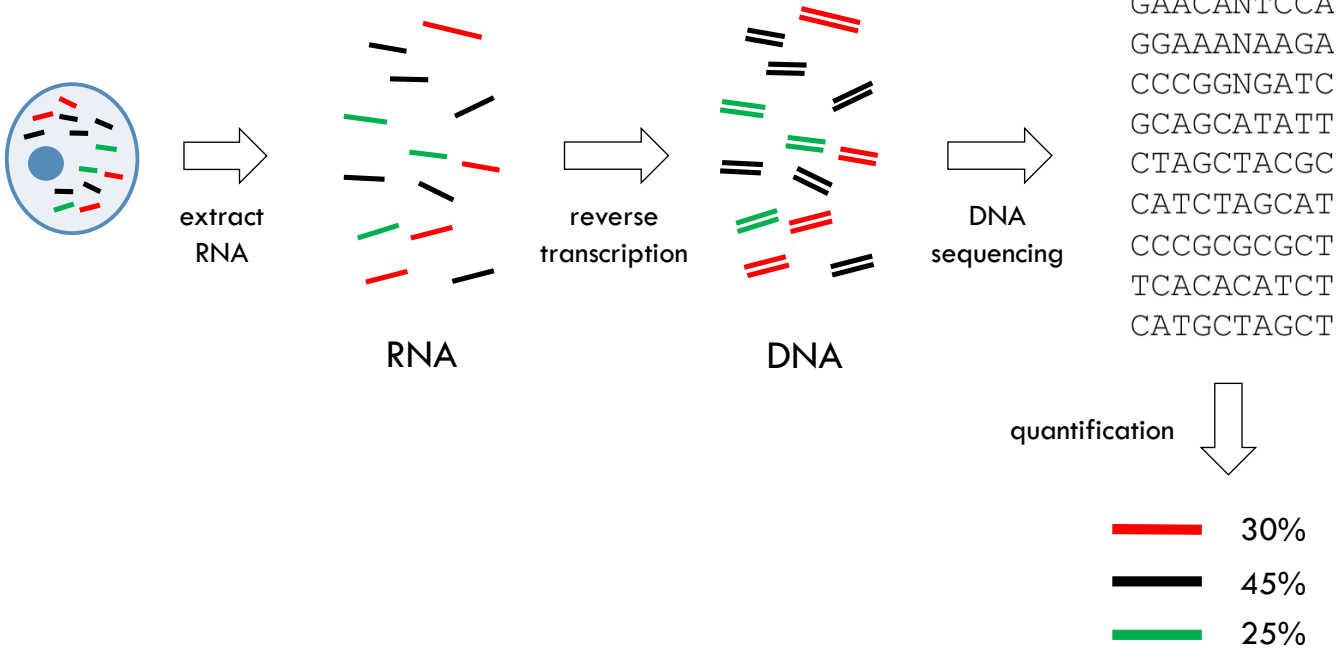

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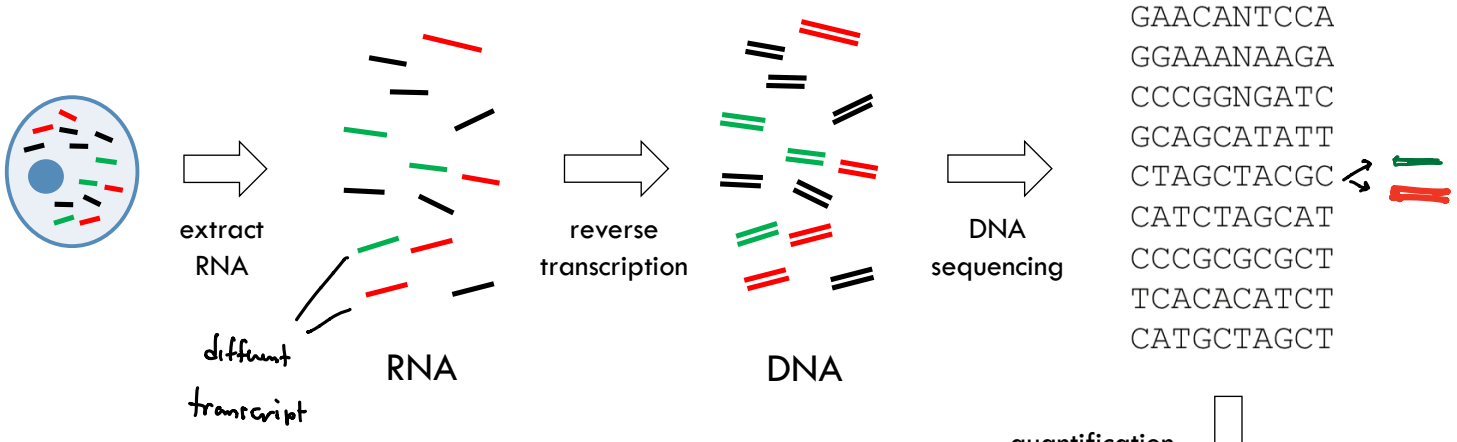

Why is this hard? Because transcripts may "look alike"