

IS IT POSSIBLE?

Imagine the future.....

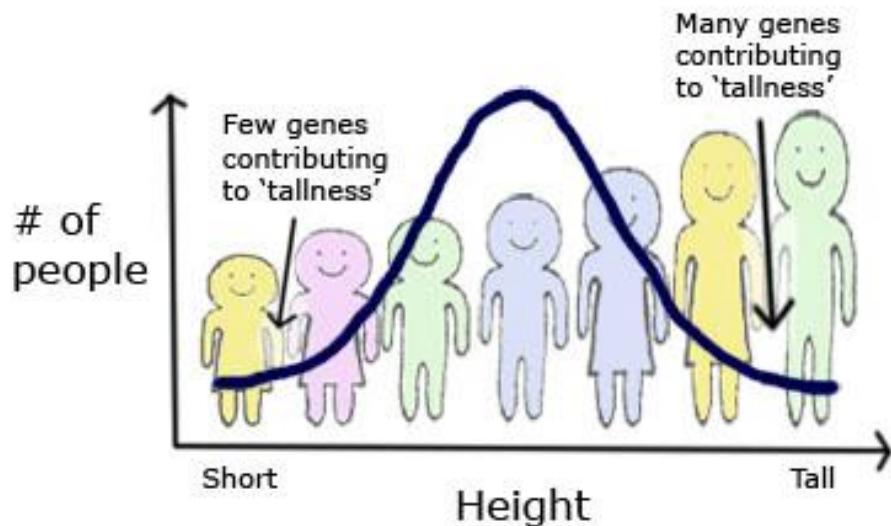
It is the year 2050. You have set IIT as your goal for your undergraduate degree. You enroll in one of the numerous coaching classes that have an excellent success rate for cracking the JEE.

The first day you show up to the coaching class, you are asked to give a sample of your blood, which is given to a genetic testing lab to test your intelligence and ability to be an engineer. After 2 days, the results of your genetic test shows that you have a 90% probability of being an outstanding engineer. You are admitted into IIT Bombay immediately!



The environment also plays a role

Genetic influence on height

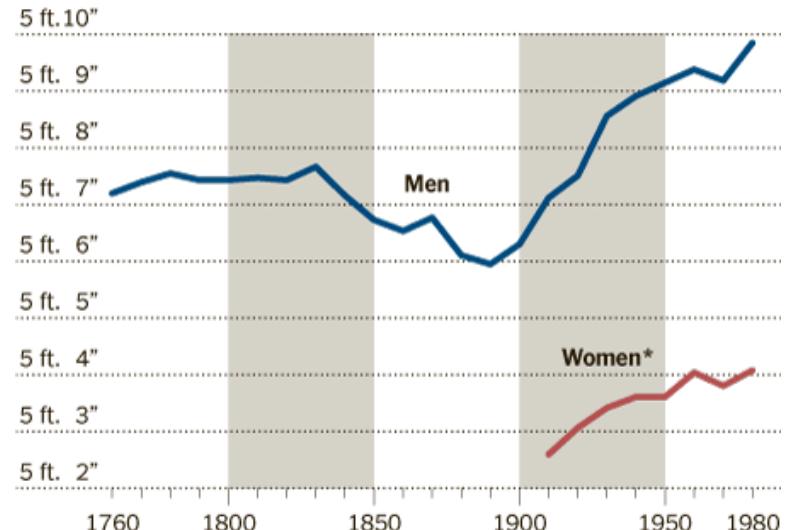


Environmental influence on height: Nutrition

The Growing American

A new book due out next month examines changes in body size of Western Europeans and Americans since the 1700s. The average height of native-born American men rose four inches between 1890 and 1980.

AVERAGE HEIGHT OF NATIVE-BORN AMERICANS



*Data not available for women prior to 1910.

Source: "The Changing Body," by Floud, Fogel, Harris and Hong



Association of *COMT* and *PRODH* gene variants with intelligence quotient (IQ) and executive functions in 22q11.2DS subjects[☆]

Miri Carmel ^{a,b,*}, Omer Zarchi ^{a,c,f}, Elena Michaelovsky ^{a,b}, Amos Frisch ^{a,b},
Miriam Patya ^{a,b}, Tamar Green ^{a,c,d}, Doron Gothelf ^{a,c}, Abraham Weizman ^{a,b,e}

^aSackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^bFelsenstein Medical Research Center, Petah Tikva, Israel

^cThe Child Psychiatry Unit, Edmond and Lily Safra Children's Hospital, Sheba MedicalCenter, Tel Hashomer, Ramat Gan, Israel

^dNes-Ziyyona-Ber Yaakov Mental Health Center, Beer Yaakov, Israel

^eGeha Mental-Health Center, Petah Tikva, Israel

^fRabin Medical Center, 49100 Petah Tikva, Israel

Proteins that play roles in your brain cells

ARTICLE INFO

Article history:

Received 27 January 2014

Received in revised form

23 April 2014

Accepted 24 April 2014

Keywords:

22q11.2DS

Intelligence quotient (IQ)

Executive function (EF)

COMT

ABSTRACT

The 22q11.2 deletion syndrome (22q11.2DS) carries the highest genetic risk factor for the development of schizophrenia. We investigated the association of genetic variants in two schizophrenia candidate genes with executive function (EF) and IQ in 22q11.2DS individuals.

Ninety two individuals with 22q11.2 deletion were studied for the genetic association between *COMT* and *PRODH* variants and EF and IQ. Subjects were divided into children (under 12 years old), adolescents (between 12 and 18 years old) and adults (older than 18 years), and genotyped for the *COMT* Val158Met (rs4680) and *PRODH* Arg185Trp (rs4819756) polymorphisms. The participants underwent psychiatric evaluation and EF assessment. Our main finding is a significant influence of the *COMT* Val158Met polymorphism on both IQ and EF performance. Specifically, 22q11.2DS subjects with Met allele displayed higher IQ scores in all age groups compared to Val carriers, reaching significance in both adolescents and adults. The Met allele carriers performed better than Val carriers in EF tasks, being statistically significant in the adult group. *PRODH* Arg185Trp variant did not affect IQ or EF in our 22q11.2DS cohort. In conclusion, functional *COMT* variant, but not *PRODH*, affects IQ and EF in 22q11.2DS subjects during neurodevelopment with a maximal effect at adulthood. Future studies should monitor the cognitive performance of the same individuals from childhood to old age.

Concept check! Q&A

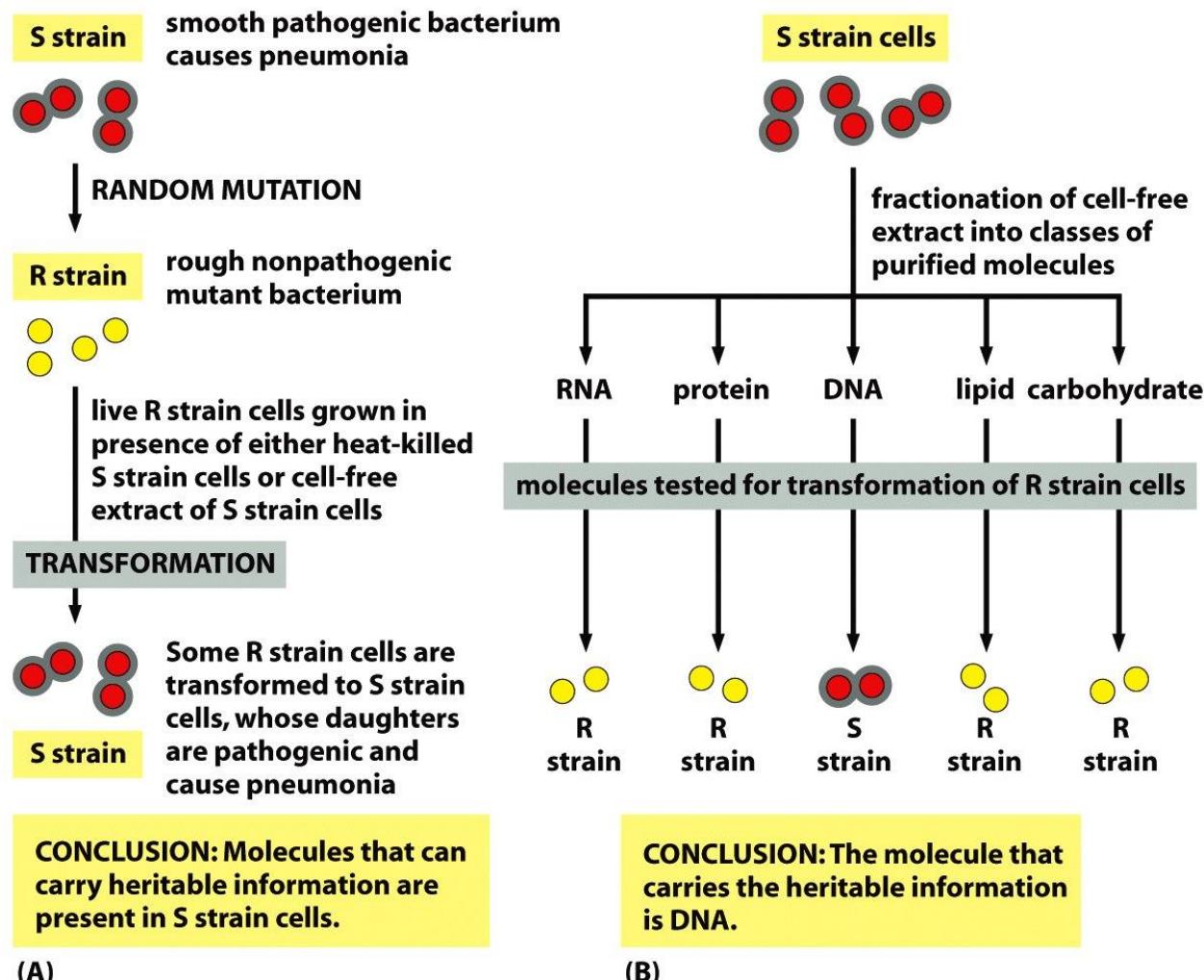
1. Which cells in your blood will you find DNA? The blood cells are: red blood cells (carry oxygen, no nucleus) and white blood cells (fight infection, nucleus).
2. Do you think your mother could have been an engineer as well?
3. What effect do you think your environment could have had on the results of the test?
4. Finally, is it possible???



Molecular basis of inheritance: exciting scientific detective story

- What is the molecular basis of Mendel's **heritable factors** and Morgan's **genes**?

Evidence that **DNA** is the **genetic material** (by Griffith, Avery, McCarty and Macleod)



(A)

(B)

Points to ponder about Griffith's experiment

- Why did Griffith and others kill the S strain before growing in the presence of live R strain?
- What extra experiment would you propose to confirm that the S strain was completely killed and not giving pathogenic effects itself?
- Mendel's experiments show transfer of genetic material through heredity, Griffith's experiments show transfer of genetic material from external sources
- Can you come with some properties of a good genetic material based on Mendel and Griffith's experiments? Does DNA fit your properties?

What Is a Gene? *Revisiting the Question*

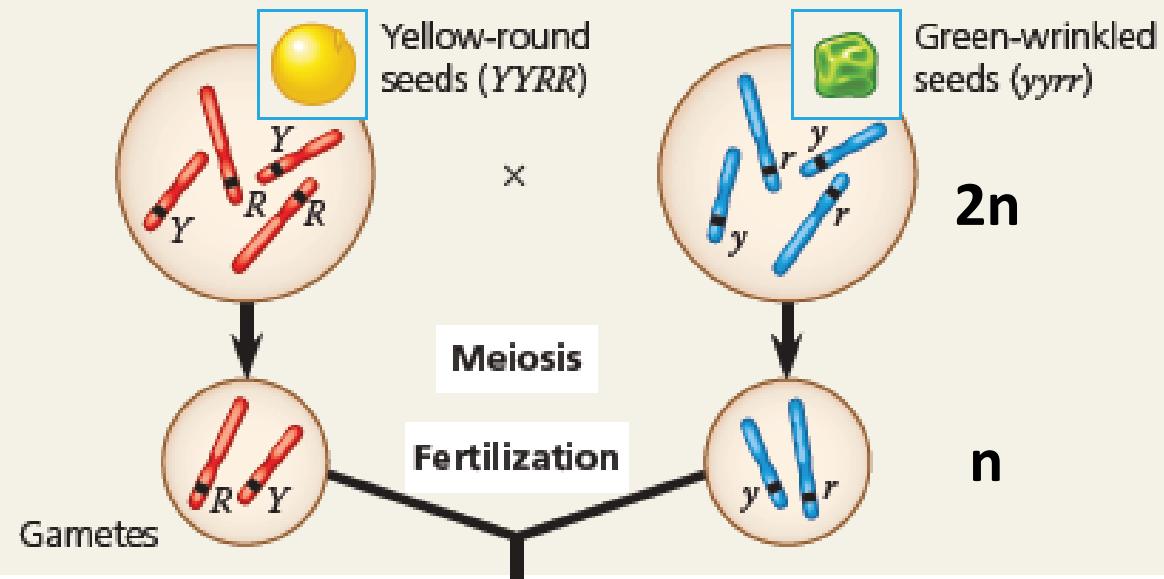
- The idea of the gene has evolved through the history of genetics
- We have considered a gene as
 - A discrete unit of inheritance
 - A region of specific nucleotide sequence in a chromosome
 - A DNA sequence that codes for a specific polypeptide chain

In summary, a gene can be defined as a region of DNA that can be expressed to produce a final functional product, either a polypeptide or an RNA molecule

Chromosomal basis of Mendel's laws

P Generation

Starting with two true-breeding pea plants, we will follow two genes through the F_1 and F_2 generations. The two genes specify seed color (allele Y for yellow and allele y for green) and seed shape (allele R for round and allele r for wrinkled). These two genes are on different chromosomes. (Peas have seven chromosome pairs, but only two pairs are illustrated here.)



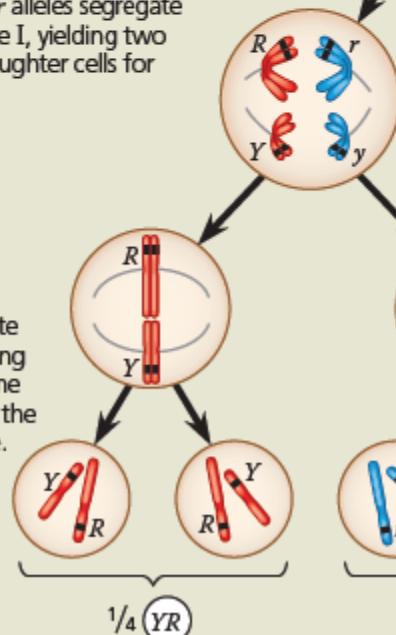
Chromosomal basis of Mendel's laws

F₁ Generation

LAW OF SEGREGATION

The two alleles for each gene separate during gamete formation. As an example, follow the fate of the long chromosomes (carrying R and r). Read the numbered explanations below.

- 1 The R and r alleles segregate at anaphase I, yielding two types of daughter cells for this locus.



- 2 Each gamete gets one long chromosome with either the R or r allele.

All F₁ plants produce yellow-round seeds (YyRr).

Meiosis

Two equally probable arrangements of chromosomes at metaphase I

Anaphase I

Metaphase II

$\frac{1}{4}$ (yr)

$\frac{1}{4}$ (Yr)

$\frac{1}{4}$ (yR)

$\frac{1}{4}$ (YR)

LAW OF INDEPENDENT ASSORTMENT

Alleles of genes on nonhomologous chromosomes assort independently during gamete formation. As an example, follow both the long and short chromosomes along both paths. Read the numbered explanations below.

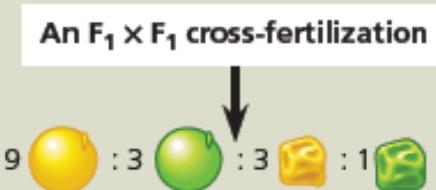
- 1 Alleles at both loci segregate in anaphase I, yielding four types of daughter cells, depending on the chromosome arrangement at metaphase I. Compare the arrangement of the R and r alleles relative to the Y and y alleles in anaphase I.

- 2 Each gamete gets a long and a short chromosome in one of four allele combinations.

Chromosomal basis of Mendel's laws

F₂ Generation

- ③ Fertilization recombines the *R* and *r* alleles at random.



- ③ Fertilization results in the 9:3:3:1 phenotypic ratio in the F₂ generation.

Now that you understand the chromosomal basis of Mendel's experiments, do you think he was lucky to get the clean results that he did?

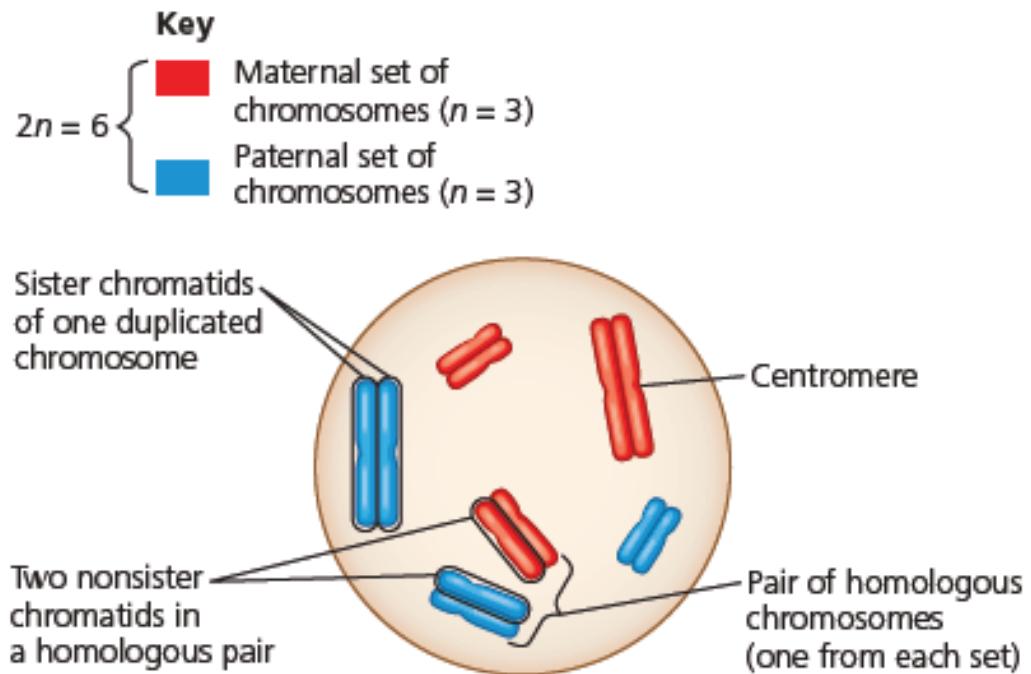
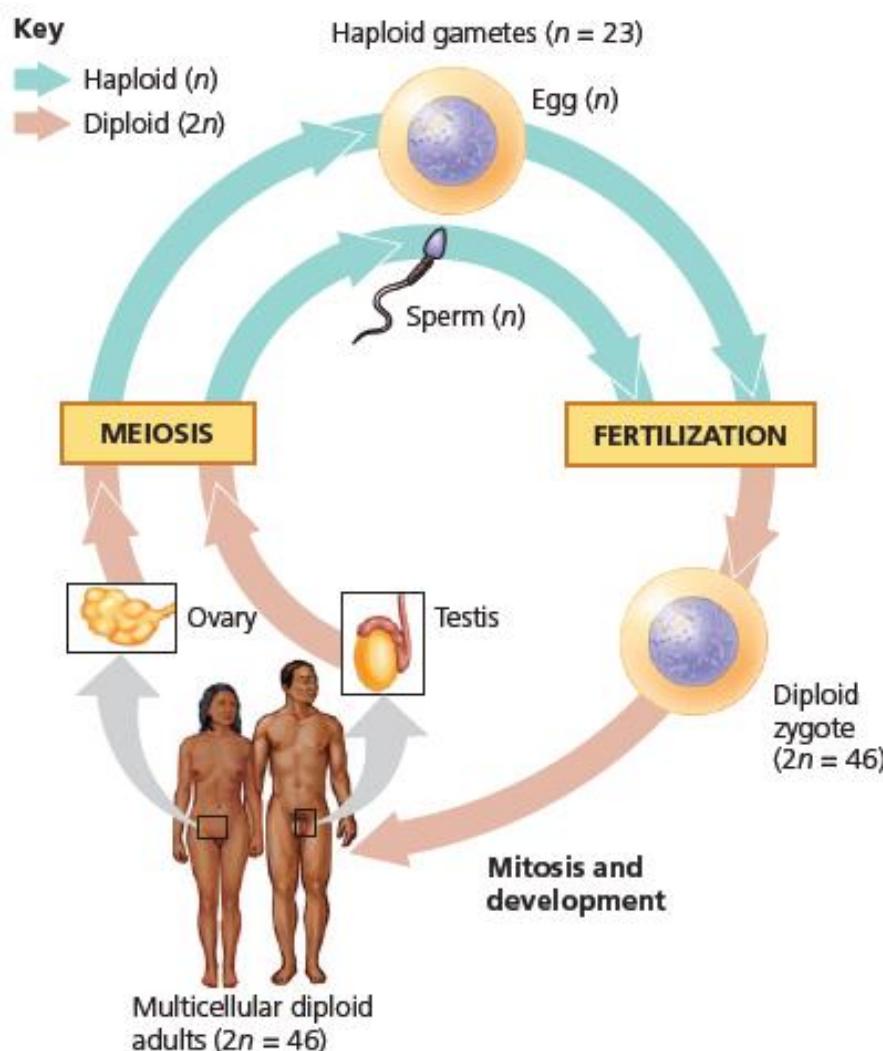
Points to ponder:

He chose clearly dominant alleles.

He chose pea plants that are diploid and inferred the Law of Segregation (other plants can have more than 2 copies of each chromosomes!).

He chose traits whose genes were on different chromosomes and inferred the Law of Independent Assortment.

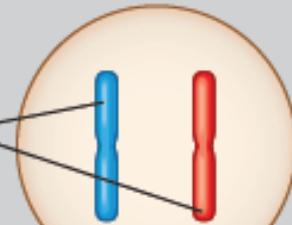
Understanding meiosis that produces gametes



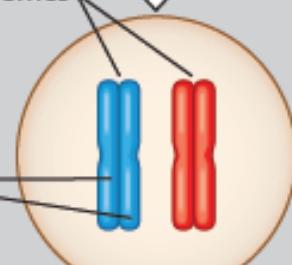
Understanding meiosis that produces gametes

Interphase

Pair of homologous chromosomes in diploid parent cell



Chromosomes duplicate

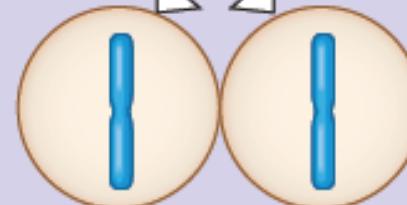


Sister chromatids

Diploid cell with duplicated chromosomes

Meiosis II

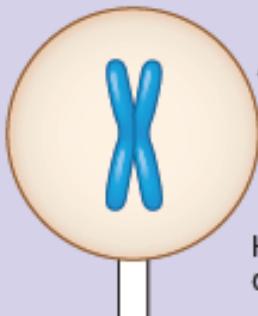
2 Sister chromatids separate



Haploid cells with unduplicated chromosomes

Meiosis I

1 Homologous chromosomes separate



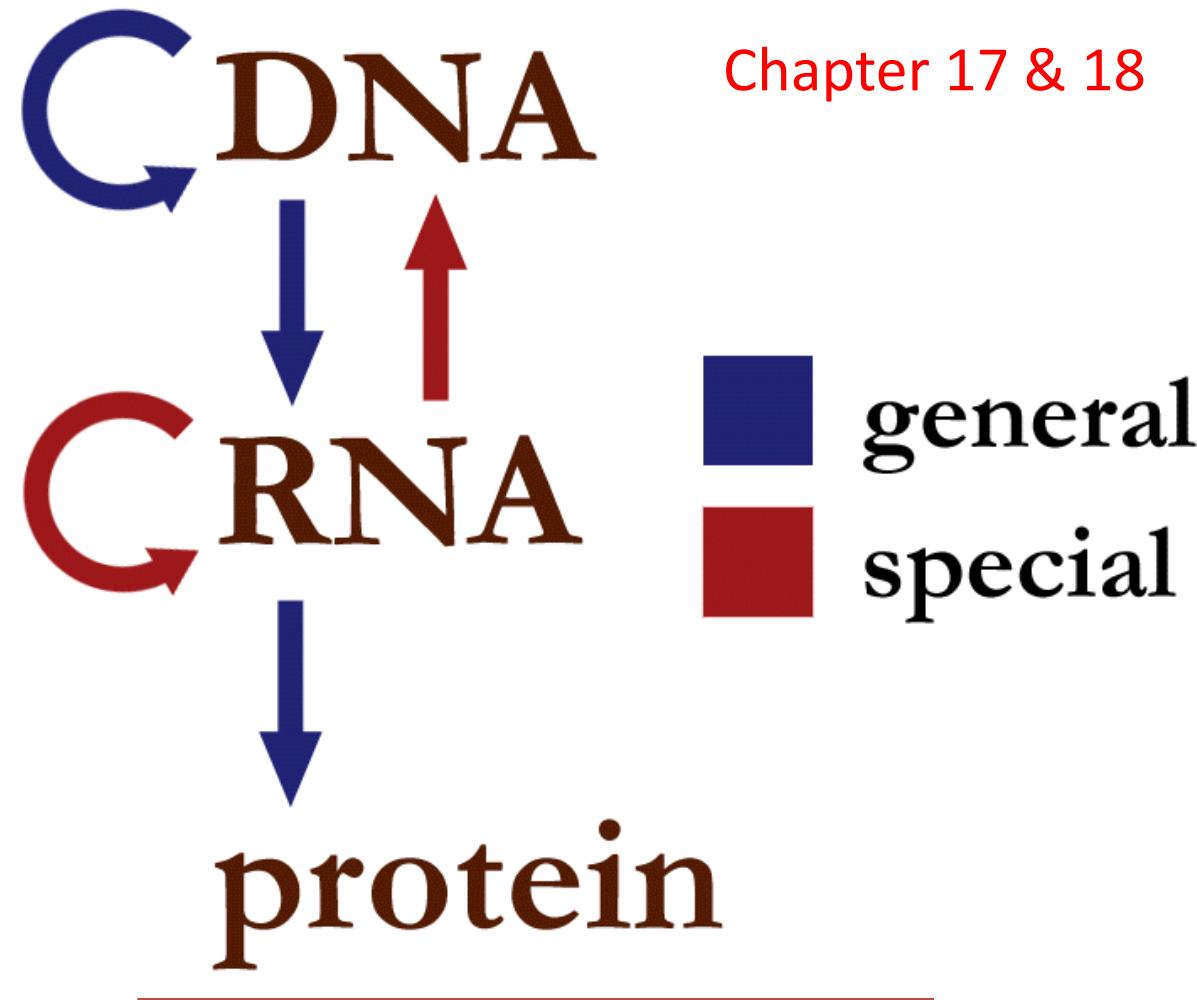
Haploid cells with duplicated chromosomes

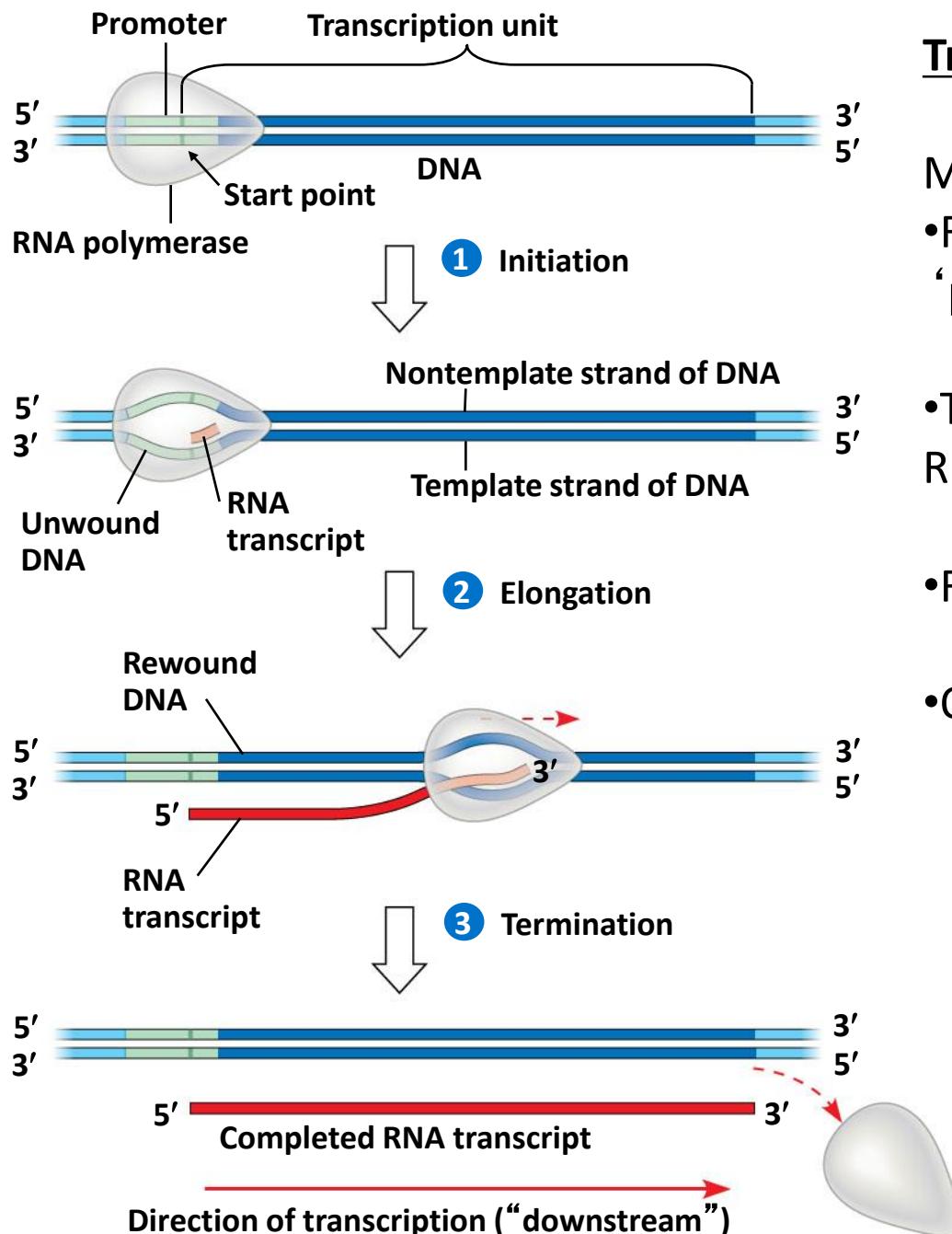
Meiosis reduces the number of chromosome sets from diploid to haploid

Imagine the future.....

Scenario # 1: Your genetic test says you are worthy of the IITs. How can your DNA result in traits like intelligence?

From genes to proteins & regulation of gene expression

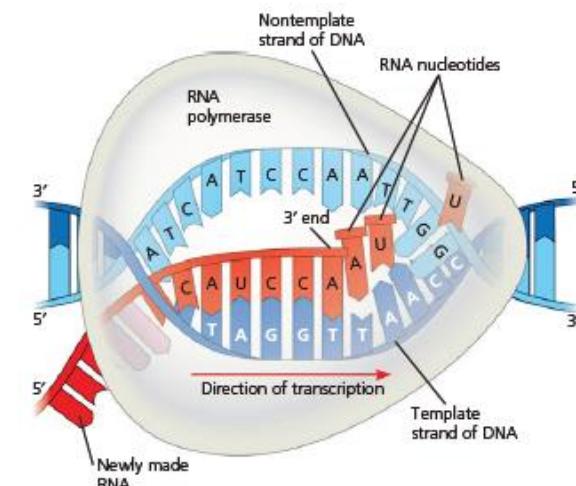




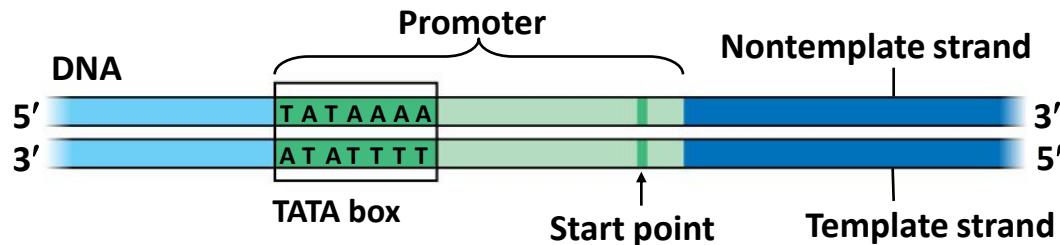
Transcription (RNA synthesis)

Main points:

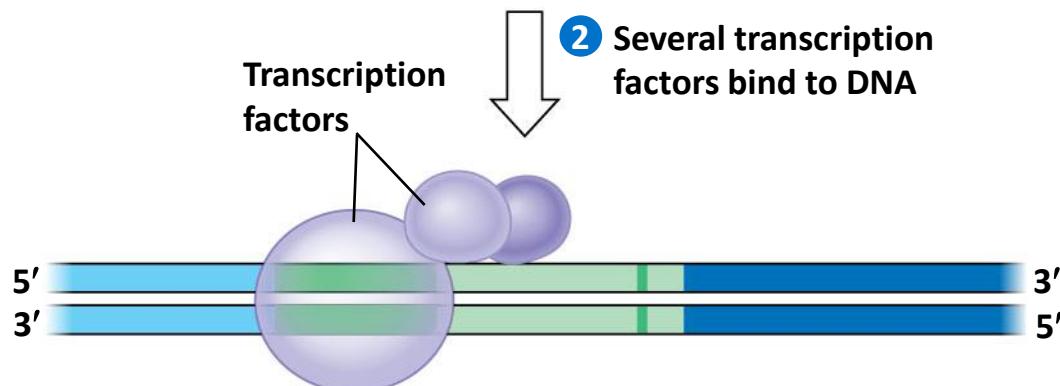
- RNA synthesis starts at a 'promoter' .
- The machinery for transcription is RNA polymerase.
- RNA synthesis is 5' to 3'
- One strand of a gene is transcribed.



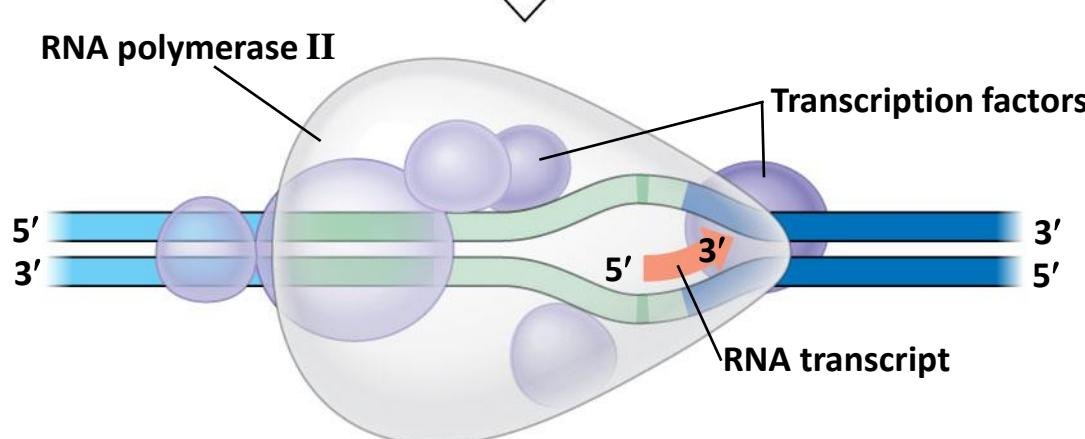
1 A eukaryotic promoter



2 Several transcription factors bind to DNA

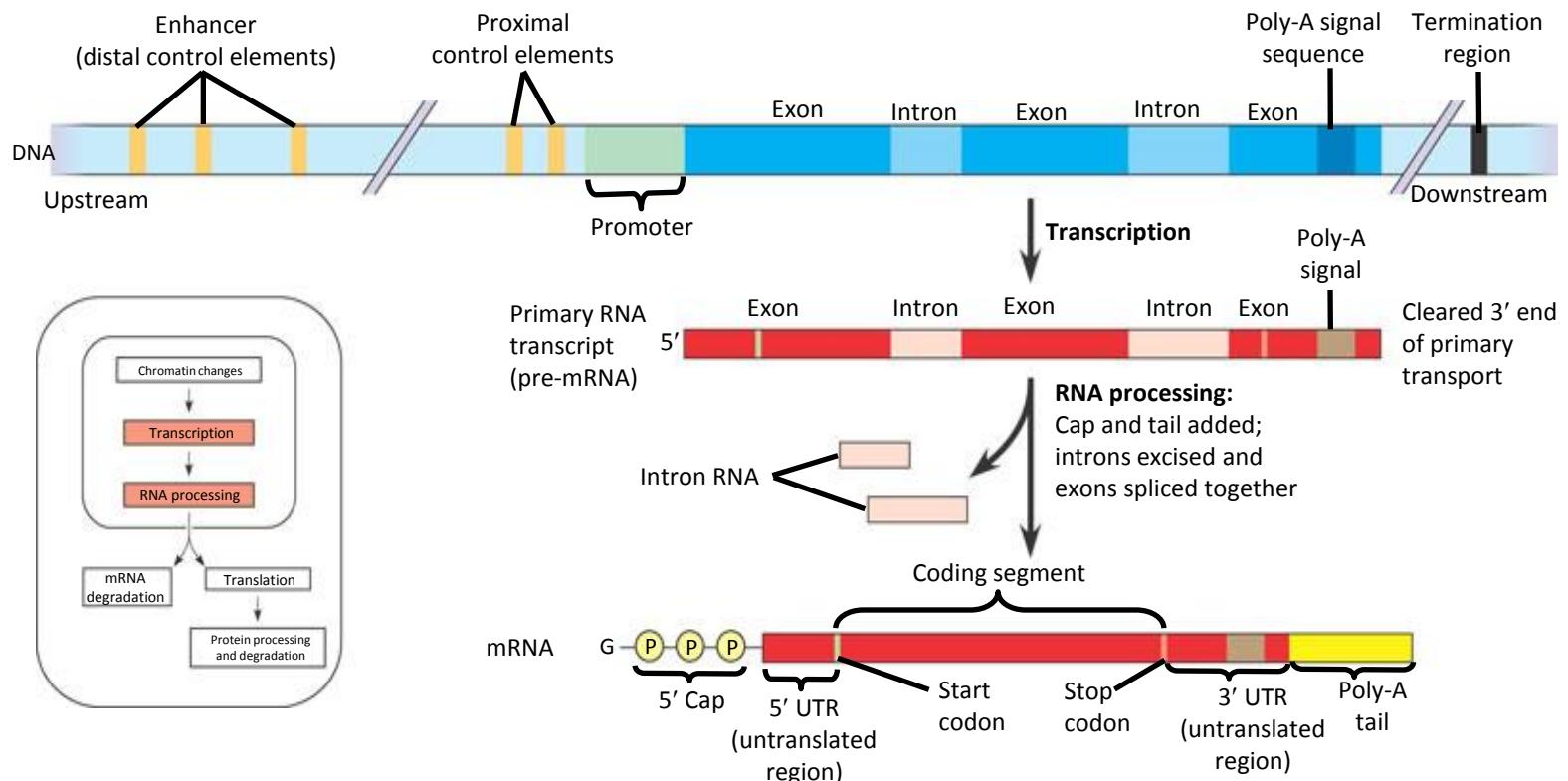


3 Transcription initiation complex forms

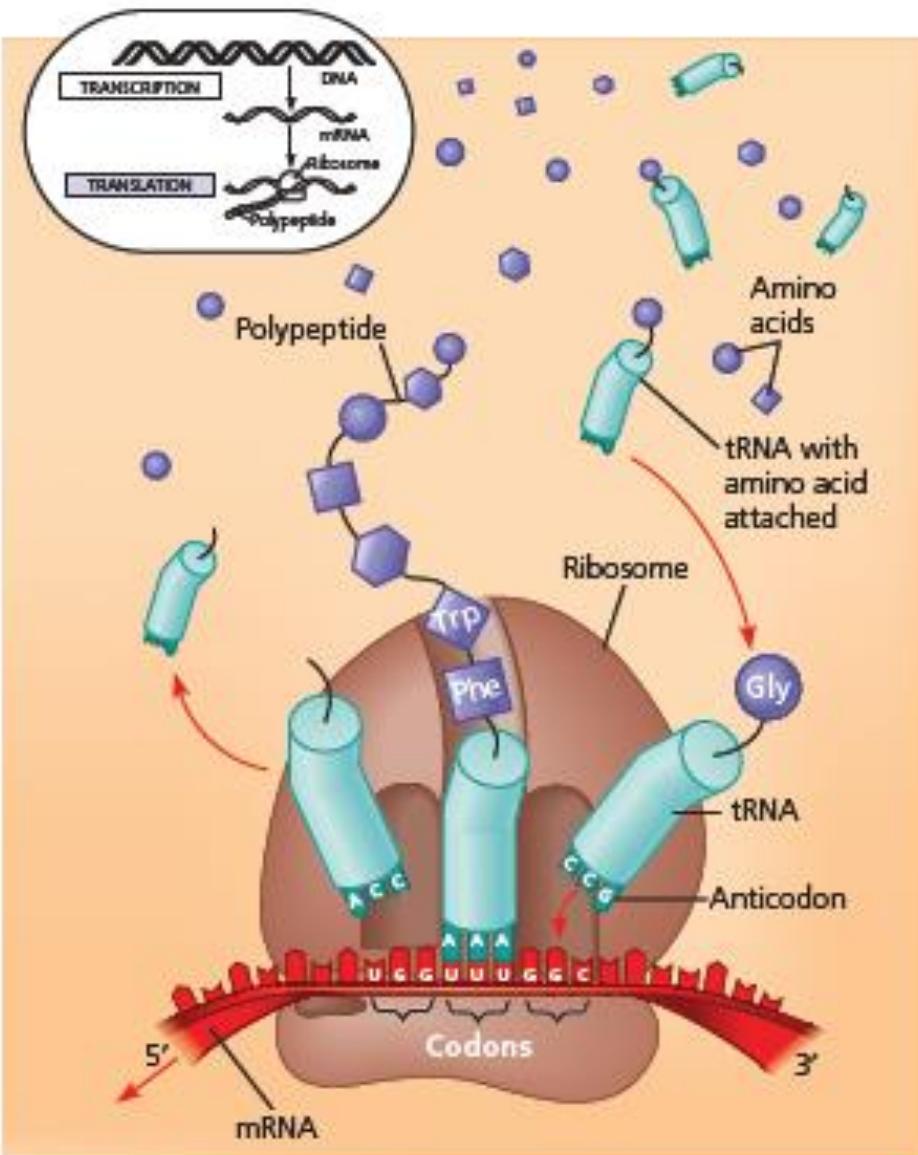


Organization of a Typical Eukaryotic Gene

- Associated with most eukaryotic genes are multiple control elements: Segments of non-coding DNA that help regulate transcription by binding certain proteins
- Eukaryotic RNAs have introns (RNA segments that are removed before translation) by splicing
- Eukaryotic RNAs have 5' caps and 3' tails



After Transcription, Translation: the ribosome uses mRNA for protein synthesis



Main points:

- Proteins are made of amino acids.
- Amino acids are joined by peptide bonds to give polypeptides.
- The machinery for translation is the ribosome.
- The information comes from RNA.
- Something has to ‘translate’ nucleic acid language into protein language: transfer RNA.
- Units of information are 3 nucleotides: codons.

After Transcription: Translation

		Second letter					
		U	C	A	G		
First letter	U	UUU UUC UUA UUG } Phe	UCU UCC UCA UCG } Ser	UAU UAC UAA UAG } Tyr Stop Stop	UGU UGC UGA UGG } Cys Stop Trp	U	C
	C	CUU CUC CUA CUG } Leu	CCU CCC CCA CCG } Pro	CAU CAC CAA CAG } His Stop Gln	CGU CGC CGA CGG } Arg	C	A
	A	AUU AUC AUA AUG } Ile	ACU ACC ACA ACG } Thr	AAU AAC AAA AAG } Asn Stop Lys	AGU AGC AGA AGG } Ser Stop Arg	C	A
	G	GUU GUC GUA GUG } Val	GCU GCC GCA GCG } Ala	GAU GAC GAA GAG } Asp Stop Glu	GGU GGC GGA GGG } Gly	U	G
		Third letter					

The genetic code:

RNA nucleotides are ‘read’ in units of 3 called codons.

All living organisms on the planet use the same genetic code!

There are 20 amino acids that are coded by 61 codons and three “STOP” codons.

Cracking the Code

- Deciphered by the mid-1960s
- Of the 64 triplets - 61 code for amino acids; 3 triplets are “stop” signals to end translation
- The genetic code is redundant but not ambiguous
- **Reading frame: AUG GGA TTA GCG ATT TGA**

Is the genetic code optimized?

If each of the 20 amino acids and the stop signal are to be assigned at least one codon there are more than 10^{84} alternative possibilities

1. Chemical constraints
2. Historical accidents
3. Evolutionary forces

Frozen accident hypothesis!

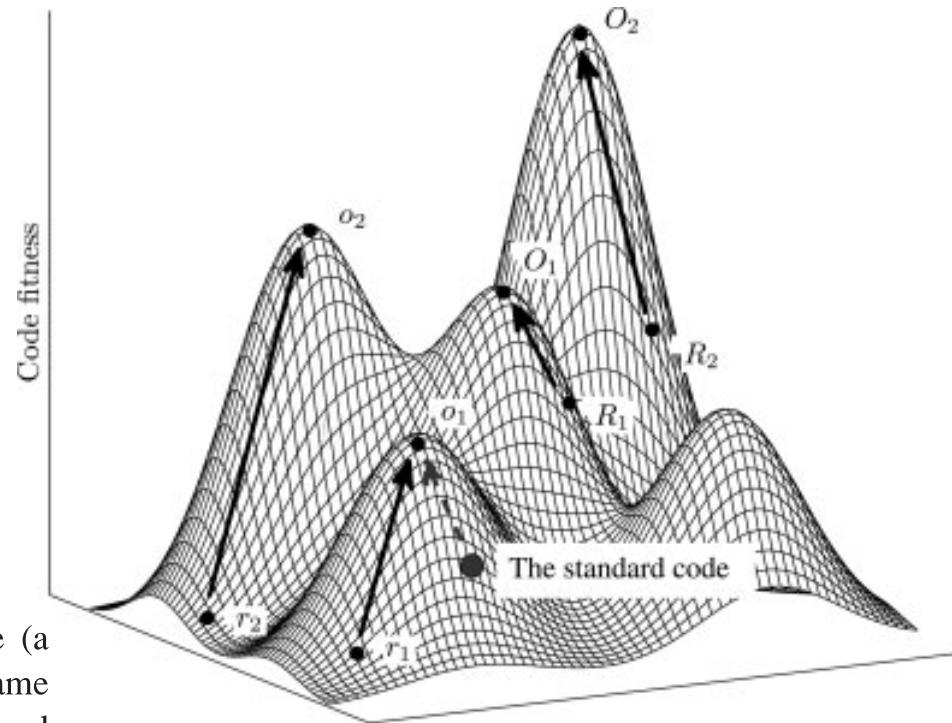
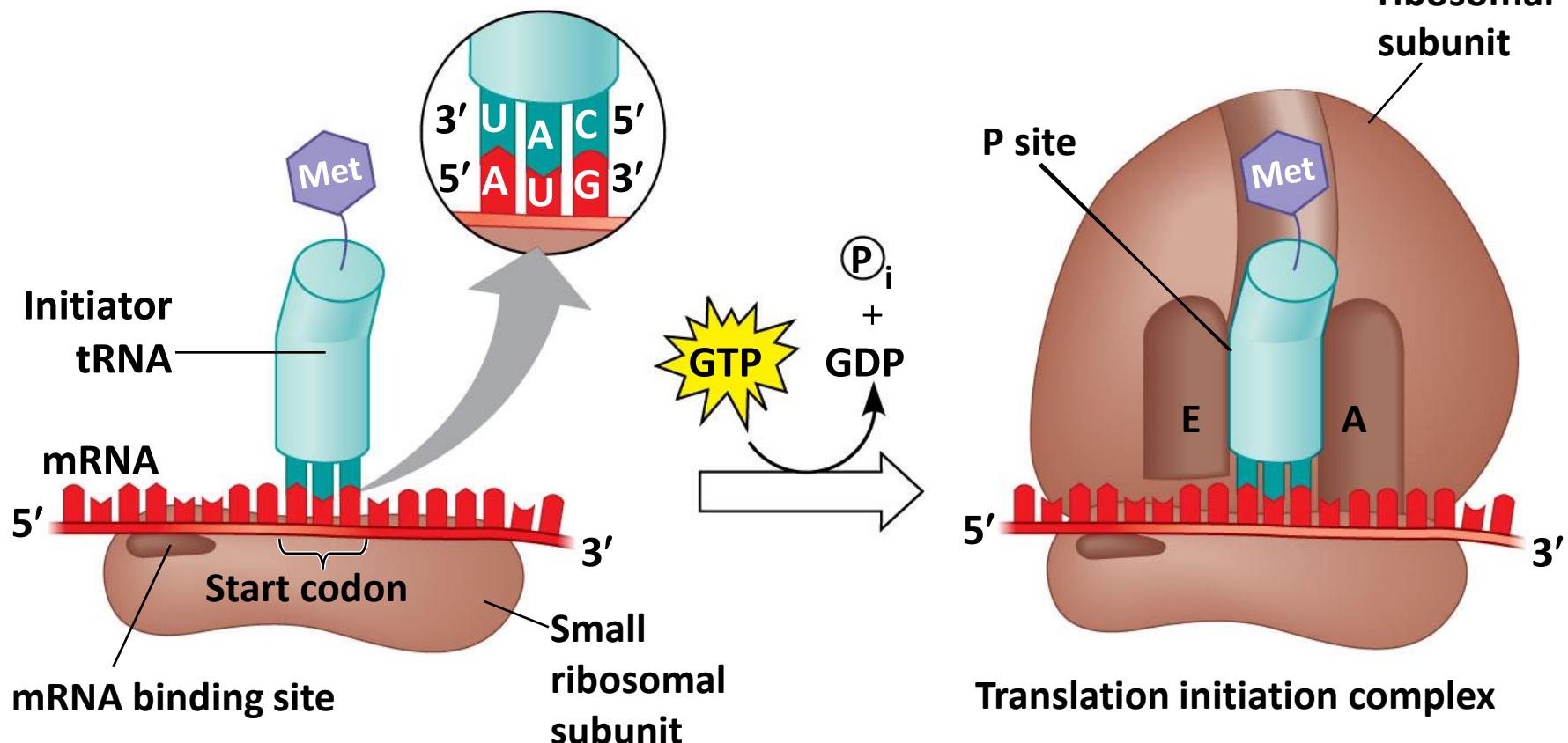


Figure 3. Evolution of codes in a rugged fitness landscape (a cartoon illustration). $r_1, r_2 \in \mathbf{r}$: random codes with the same block structure as the standard code, $o_1, o_2 \in \mathbf{o}$: codes obtained from $r_1, r_2 \in \mathbf{r}$ after optimization, $R_1, R_2 \in \mathbf{R}$: random codes with fitness values greater than the fitness of the standard code, $O_1, O_2 \in \mathbf{O}$: codes obtained from $R_1, R_2 \in \mathbf{R}$ after optimization. The figure is modified from (86).

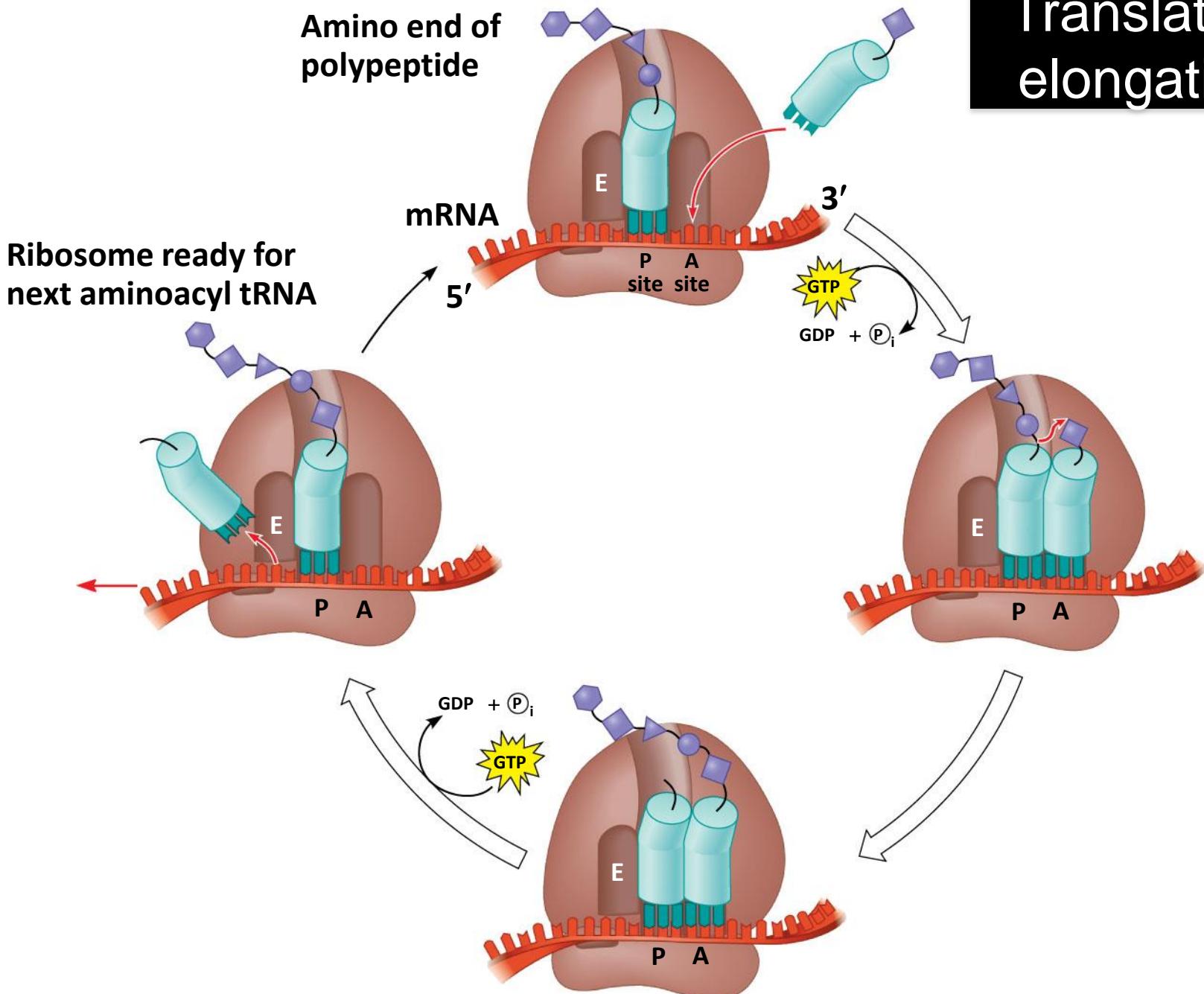
IUBMB Life, 61(2): 99–111, February 2009

Translation initiation: usually at an AUG codon

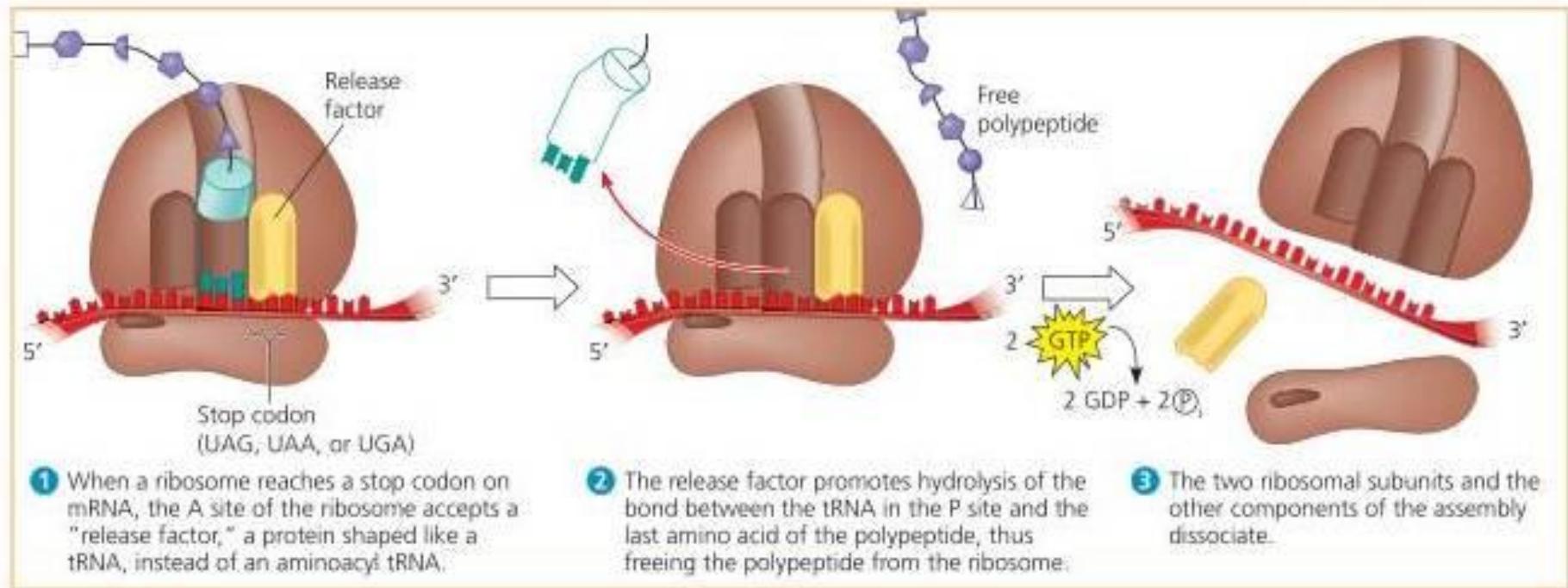


© 2011 Pearson Education, Inc.

Translation elongation

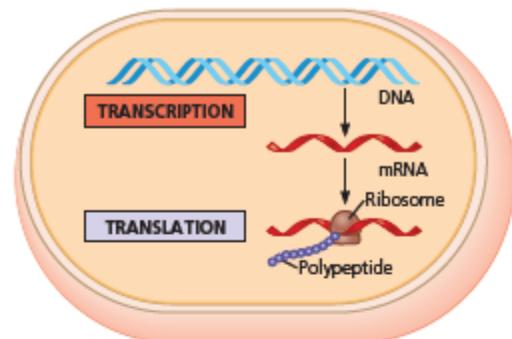


Translation termination is carried out by release factors

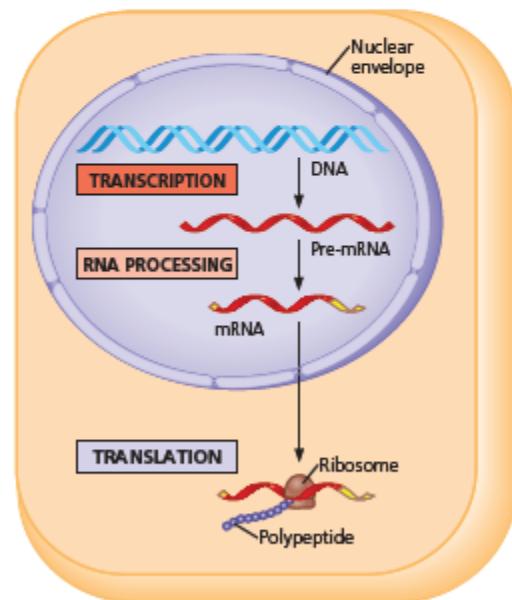


- Although bacterial and eukaryotic translation are very similar, the differences between the two are the basis of antibiotics

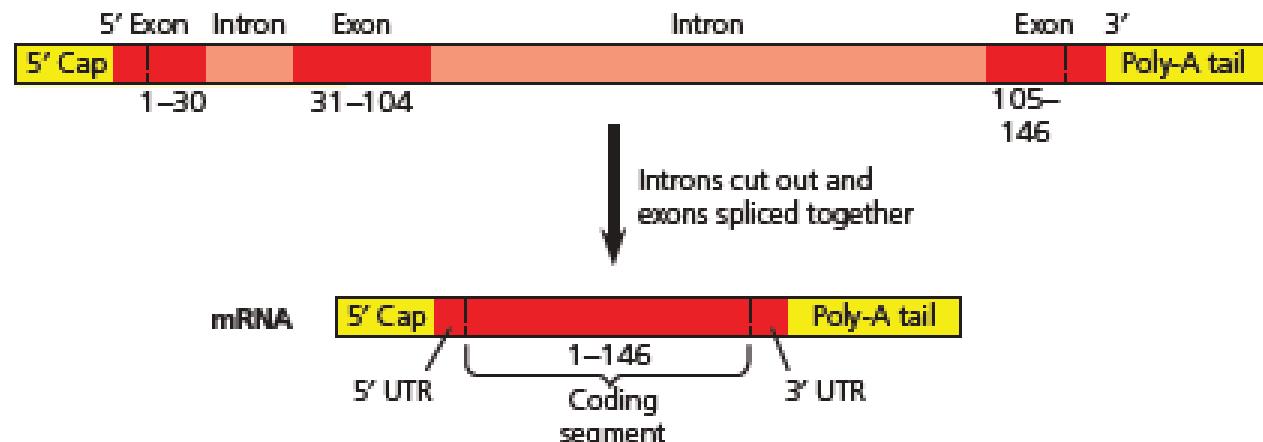
Gene expression : differences between bacterial and eukaryotic cells



(a) **Bacterial cell.** In a bacterial cell, which lacks a nucleus, mRNA produced by transcription is immediately translated without additional processing.



(b) **Eukaryotic cell.** The nucleus provides a separate compartment for transcription. The original RNA transcript, called pre-mRNA, is processed in various ways before leaving the nucleus as mRNA.

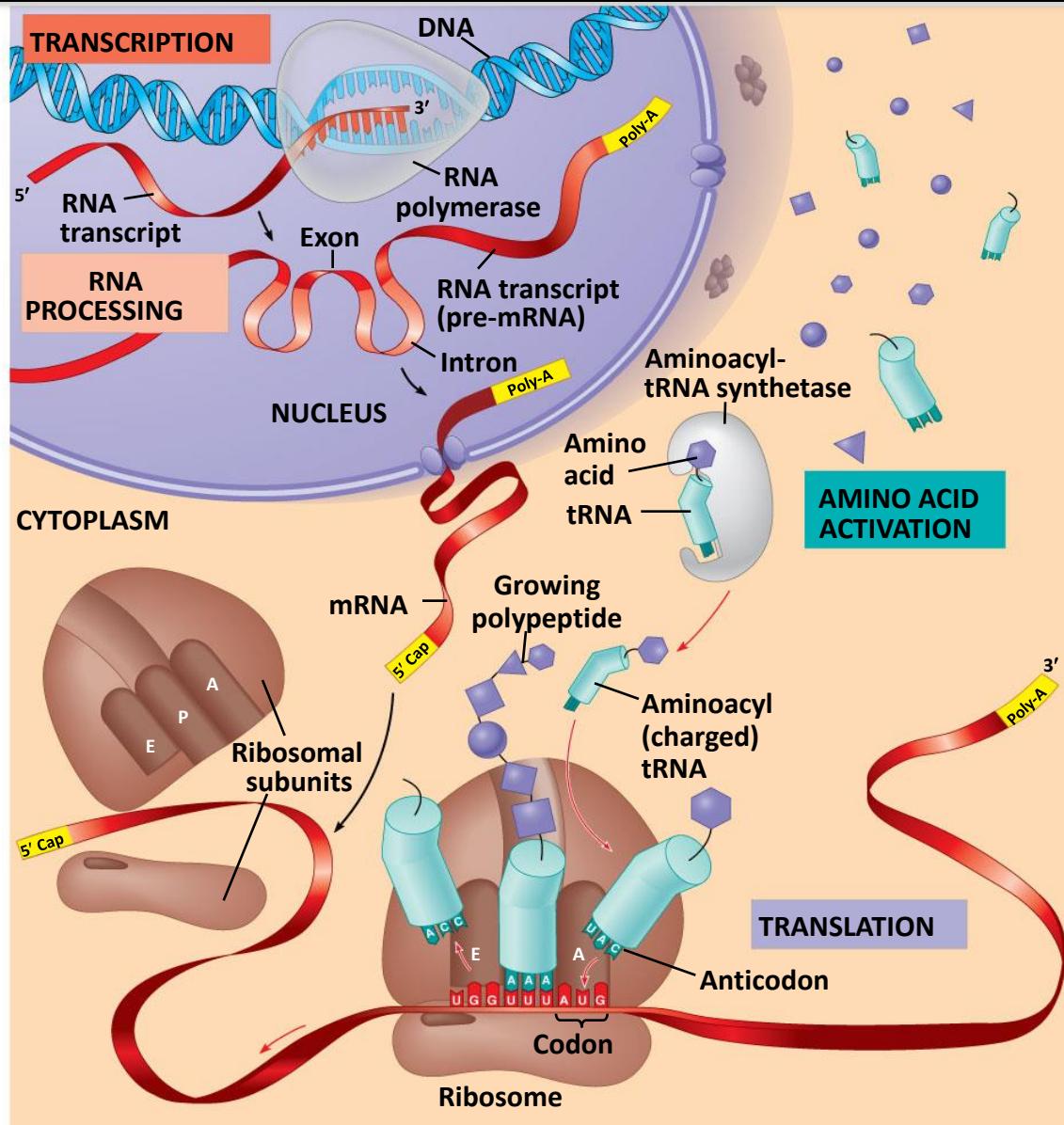


In bacteria, as there is no nucleus, transcription and translation are coupled.

In eukaryotes, the RNA is made in the nucleus and transported out to the cytosol where translation takes place (on the ER).

In eukaryotes, RNA has intervening segments (introns) that are removed by splicing.

Summary of transcription and translation in eukaryotic cells



Despite our differences, gene expression is remarkably similar on this planet!

Genes from one organism can be introduced into another and be expressed.

This is the basis of genetically modified (GM) crops.



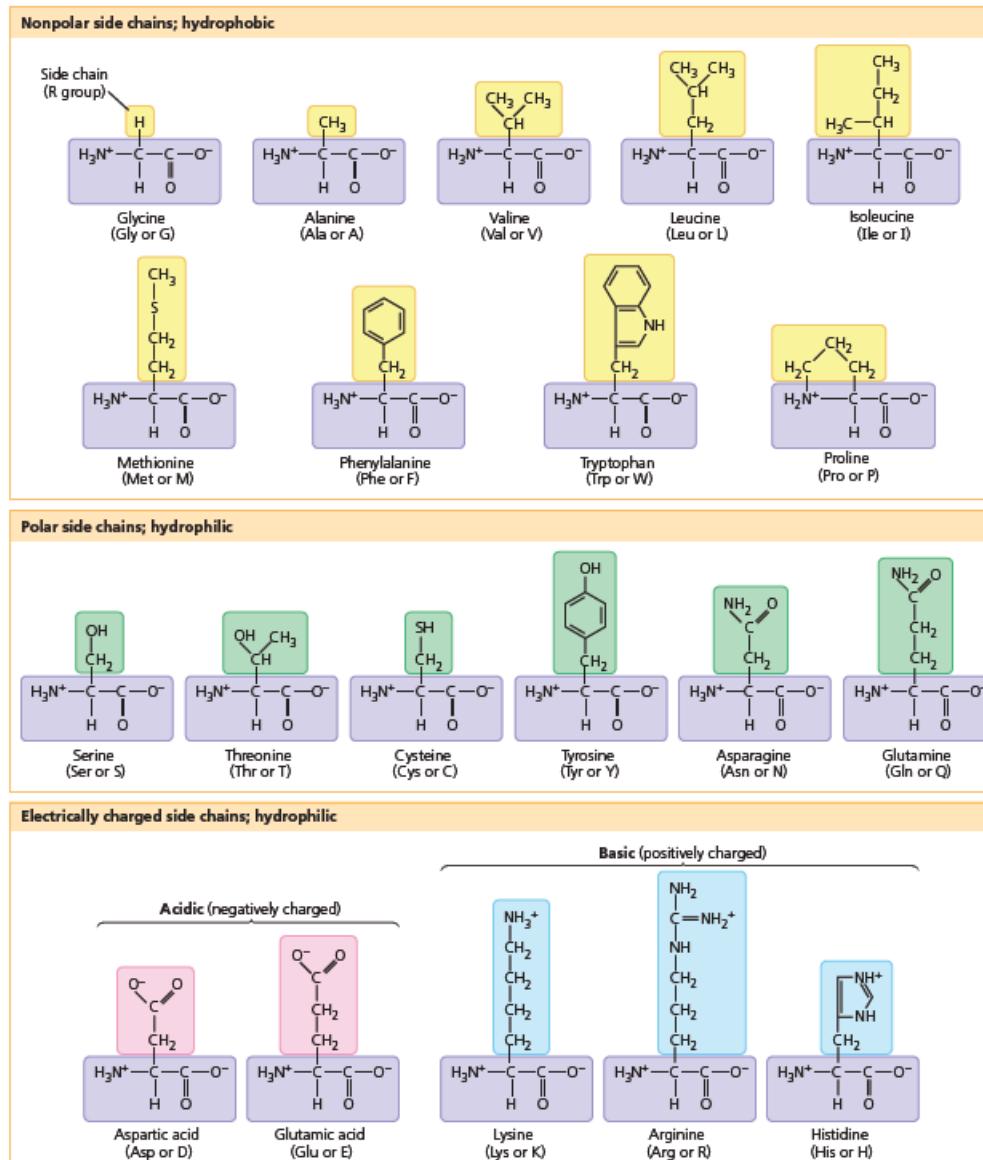
(a) **Tobacco plant expressing a firefly gene.** The yellow glow is produced by a chemical reaction catalyzed by the protein product of the firefly gene.

(b) **Pig expressing a jellyfish gene.** Researchers injected the gene for a fluorescent protein into fertilized pig eggs. One of the eggs developed into this fluorescent pig.

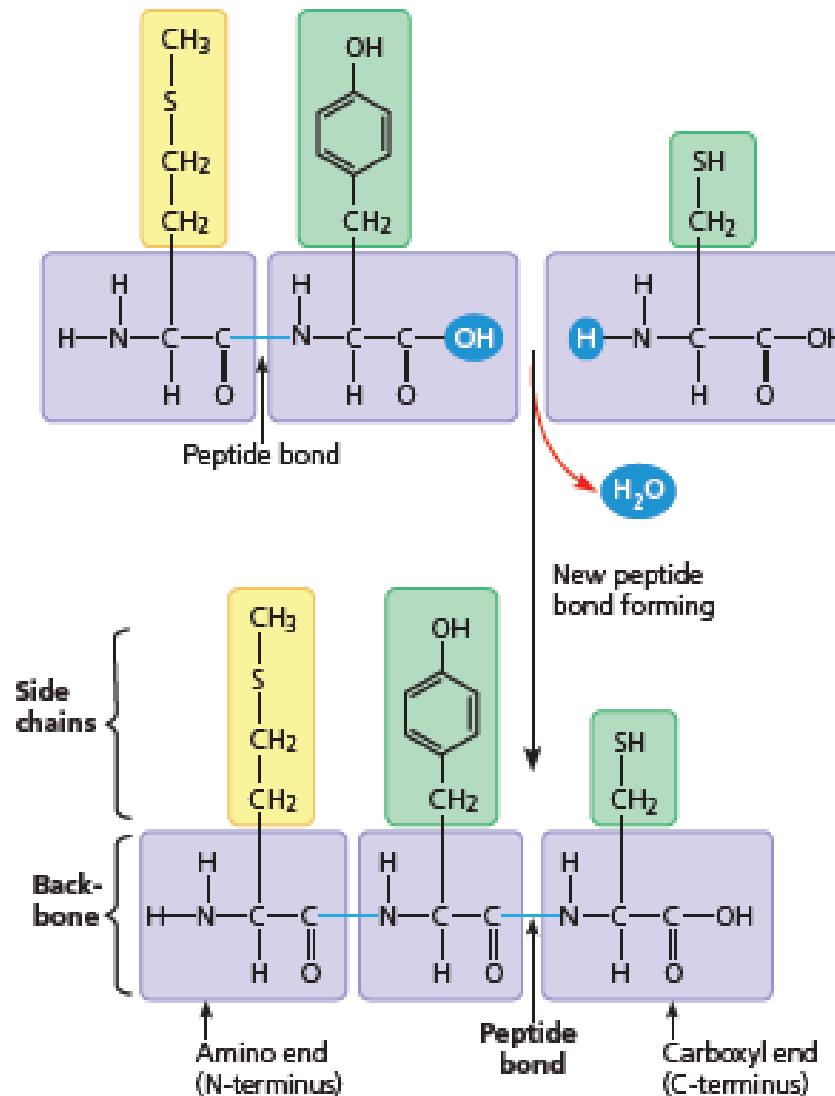
Translation features were predicted by Francis Crick based on the structure of DNA

- Crick proposed an adapter molecule such as tRNA
- The translation between the nucleic acid code to the amino acid code needs a molecule that has both. Does the structure of tRNA fit with this requirement?
- The translation code is a triplet code. Could nature have evolved a code with two nucleotides to specify an amino acid? The number of bases is 4 and the number of amino acids is 20.

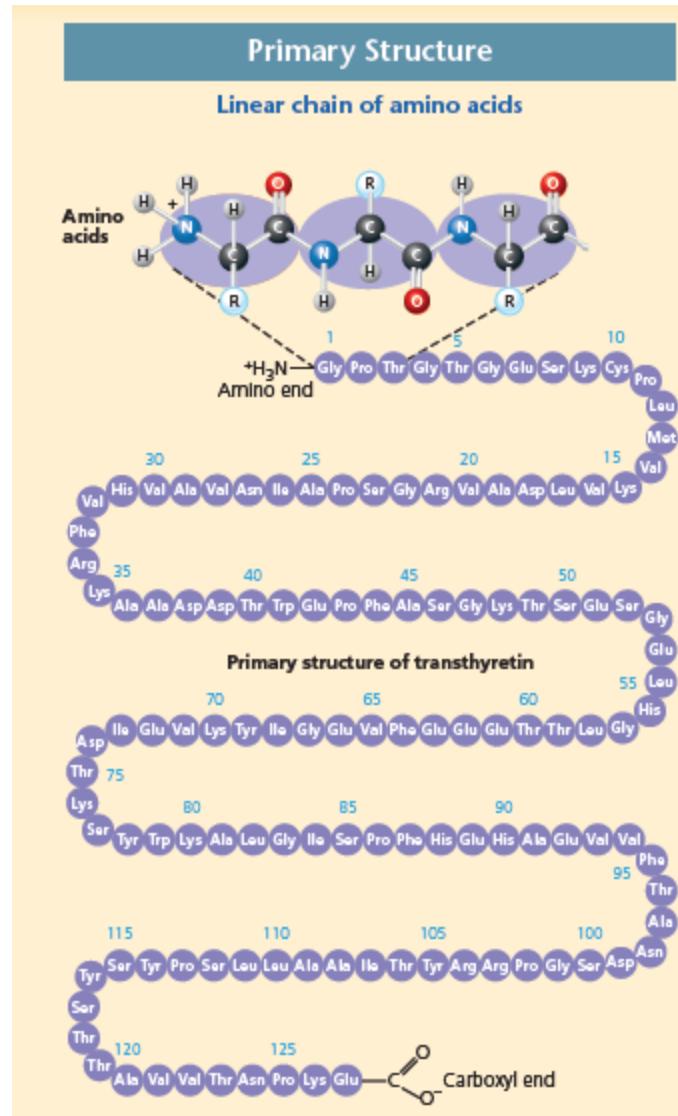
There are 20 amino acids, grouped according to the chemistry of their side chains



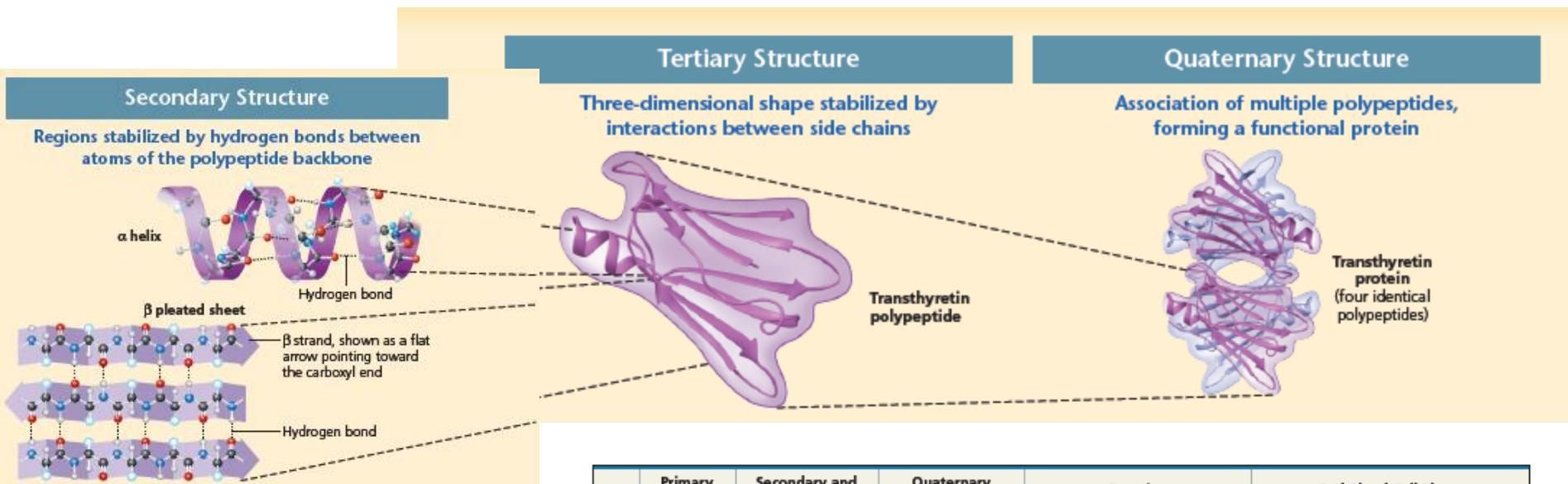
Proteins are polymers of amino acids joined by peptide bonds



Primary structure of proteins: the linear polypeptide

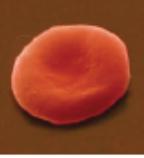


Secondary, tertiary and quaternary structures of proteins



Protein structure is crucial for protein function!

Sickle cell anemia

	Primary Structure	Secondary and Tertiary Structures	Quaternary Structure	Function	Red Blood Cell Shape
Normal hemoglobin	1 Val 2 His 3 Lou 4 Thr 5 Pro 6 Glu 7 Glu	β subunit	Normal hemoglobin	Molecules do not associate with one another; each carries oxygen.	Normal red blood cells are full of individual hemoglobin molecules, each carrying oxygen.  10 μ m
Sickle-cell hemoglobin	1 Val 2 His 3 Lou 4 Thr 5 Pro 6 Val 7 Glu	Exposed hydrophobic region β subunit	Sickle-cell hemoglobin	Molecules interact with one another and crystallize into a fiber; capacity to carry oxygen is greatly reduced.	Fibers of abnormal hemoglobin deform red blood cell into sickle shape.  10 μ m

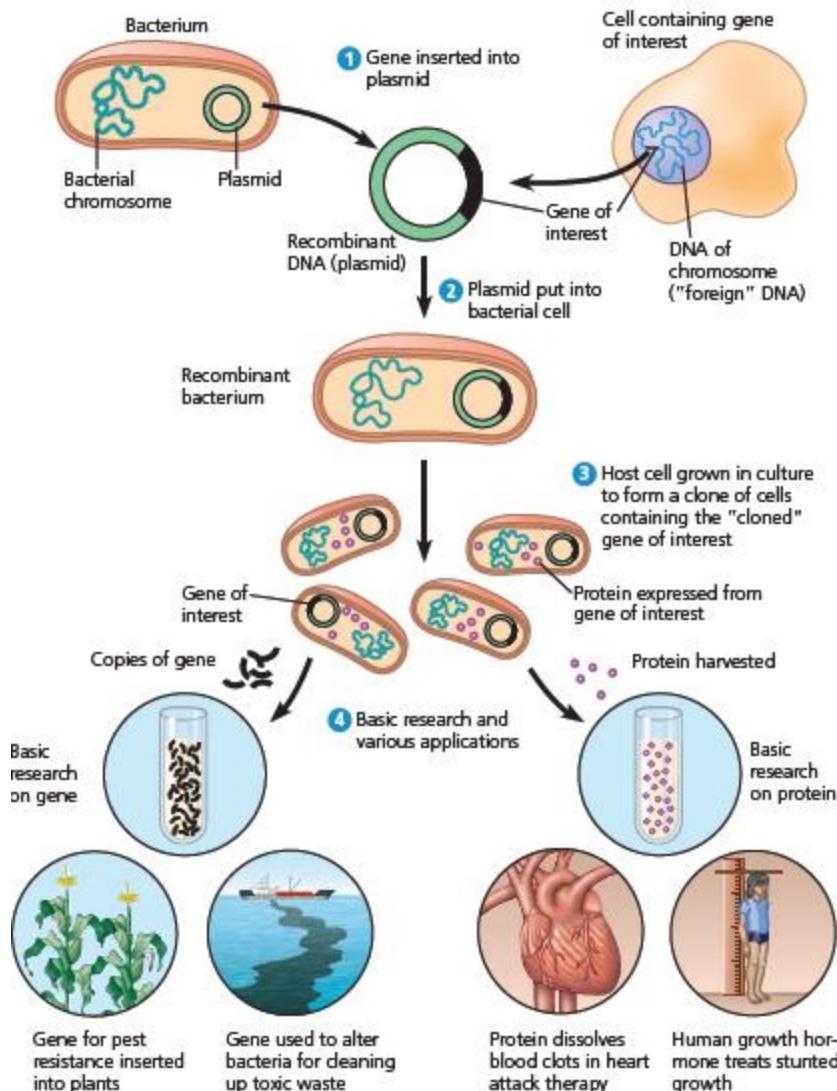
▲ Figure 5.21 A single amino acid substitution in a protein causes sickle-cell disease.

What is the biology behind GM brinjals?

Scenario: You go to the market to buy brinjals and are told that there is new variety of brinjals that is genetically modified to resist insects and worms. The genetic modification uses a gene from a bacteria that kills insects and worms. How can a bacterial gene protect brinjals? Will GM brinjals be bad for you as well?



What is the biology behind GM brinjals?



Many proteins are transferred from one organism to another.

This is done by using recombinant DNA technology.

Small circular DNA molecules (found in bacteria) are used to carry genes and express proteins.

The genes can be introduced into other organisms and the proteins can be purified and used as therapeutics.

What effect do the genes have on your body if you eat GM crops?

What effect do the genes have on the environment?