

Genetics: A Simple Overview.

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Calgary, Alberta
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Introduction.

- This presentation will provide an overview of the **basic** concepts of genetics.
- Genetics involves a lot of **concepts** and **jargon**:
 - We will try to use analogies to illustrate some of these complex ideas and explain things as we go.
- Genetics has greatly advanced over the years, but **many questions** still remain unanswered:
 - Genetic concepts get more **complicated** as you get more **specific**.
 - Many specific features still remain **obscure**.

Knowledge translation

- This talk is an example of **knowledge translation** (KT).
- KT is an important new tool in medical research.
- KT involves making a **bridge** of understanding between researchers, doctors and patients.
- Complex messages are lost if they are not easily understood. Our goal is to present information in a way that is **understandable** to all interested parties:
 - Patients can better understand research findings and judge information pertaining to them.
 - Health care providers and researchers can better understand patients and their needs.

Outline:

Part One: Overview of some basic chemistry.

Part Two: DNA carries the genetic code.

Part Three: The genetic code creates proteins.

Part Four: Genes.

Part Five: Chromosomes.

Part Six: Mating passes traits on through alleles.

Part Seven: Mutations.

Part Eight: A very simple genetic treatment.

Part Nine: Overview of Neuromuscular Illnesses (NMIs).

Part Ten: Conclusion.

Part One:
Overview of some basic chemistry.

Atoms set the stage.

- Genetics (and all life) is rooted in, and controlled by the basic “laws” of chemistry.
- Elements are formed from atoms:
 - Example: pure elemental gold consists only of gold atoms.
 - Common elements: **hydrogen, carbon, nitrogen, oxygen.**
- About 113 different elements are known:
 - The 4 elements listed in red comprise more than **95%** of all living matter.
 - Many elements are very rare, appearing in trace amounts.
- Each type of element (atom) has **unique basic properties** - gold and silver are different because gold atoms and silver atoms have different properties.

Example: Oxygen / hydrogen atoms.

Each type of atom has unique properties that determine how it will **behave**, especially, how it will **interact** with other atoms.



One
Hydrogen
atom



One
Oxygen
atom

Representation of whole individual atoms.

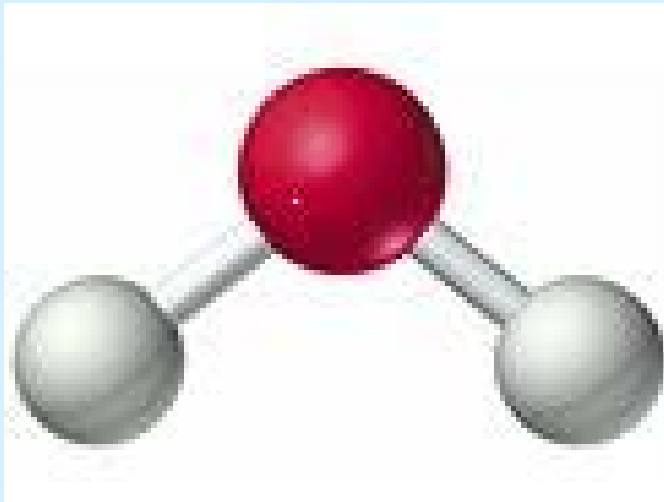
Molecules.

- Atoms join together to create **molecules**:
 - We can also refer to molecules as **chemicals**.
- Each atom's basic properties **limit** its interactions and determine what molecules can be formed:
 - Some types of atoms are naturally **attracted** to electrically join (bond) with each other.
 - Other atoms are **pushed away** from each other by their electrical properties and avoid joining.
- Molecules are made out of atoms that join together:
 - Water: 2 Hydrogen (**H**) atoms + 1 Oxygen (**O**) atom join together to form 1 water molecule (**H₂O**).

Example: A molecule of water.

One O
atom.

Two H
atoms.



One H₂O molecule.

Each hydrogen atom forms a connection (an **electrical bond**) with the single oxygen atom, shown in red.

The three atoms combine (bond together) to form one water molecule.

A drop of pure water consists of only H₂O molecules.

Based on the atoms present and their bonding, molecules display a unique three-dimensional shape.

Properties change.

- The atoms present in a molecule and how they fit together with each other determine the **chemical properties** of the molecule.
- Compared to atoms, molecules will display “new” and **different** properties after they form:
 - Sodium (Na) atoms make up a very reactive (nearly explosive) metal.
 - Chlorine (Cl) atoms exist as a toxic gas.
 - Sodium (Na) and chlorine (Cl) join together (bond) to form sodium chloride (NaCl), a molecule with the characteristic properties we know as table salt.
- Just as atoms interact based on their properties, molecules also display unique properties that will determine how they interact with other molecules.

Chemical hierarchies.

- Based upon their unique properties, molecules link together and interact with each other to form even larger, more complex **chemical compounds**.
- In turn, chemical compounds join or interact to form very complex networks of **chemical reactions** and substances, e. g., amino acids join to make proteins.
- On a larger scale, chemicals form a single **cell** and in turn, cells go on to form **tissues**, tissues go on to form **organs** and the scale and complexity keep increasing.
- All matter as we know it, and all life forms, are composed of complex chemical structures interacting with each other, governed by the laws of basic chemistry.

Chemistry as a complex logo set.

- Think of a big logo set – all of the different types of pieces have different sizes, shapes and colors.
 - Only certain pieces can be fit together with certain other pieces – there is a strict “rule book” (Mother Nature) that says what pieces can go together.
 - Very large & complex structures can be created – many sub-units can be made & fit into other sub-units.
 - Once put together, the structures take on a life of their own, moving pieces in and out, building new structures, using and making energy, etc.

Evolution reflects basic chemistry.

- Elements are common throughout the universe.
 - If the basic elements are present with favorable conditions (temperature, atmospheric pressure, etc.) then molecules will form and chemical reactions will take place.
 - In this way, life, basically as we know it, (DNA-based) could evolve anywhere in the universe.
 - Our genetic code and the chemistry of life are not random, nor are they unique to the earth: they arise from the basic properties of the elements interacting in favorable conditions.

Some Special Cases.

Proteins.

- Proteins are large chemical compounds made up of amino acids arranged in a linear chain and joined together by bonds. They fold into unique 3D shapes.
- The sequence of amino acids in each protein is specified by the genetic code as defined by a gene.
- Proteins can work together to achieve a particular function, and they often join together to form stable complexes that do different jobs in cells.
- Protein is a necessary part of our diet, since animals cannot synthesize all of the amino acids, we must obtain certain essential amino acids from food.
- Proteins are essential parts of all living organisms and participate in every process within cells.

Enzymes.

- A special group of proteins called **enzymes**, helps to make chemical reactions happen faster.
- The main job of enzymes is to **speed up** reactions that take place between chemicals:
 - You get home and discover you lost the door key. It will be hours before your wife comes home with the other key. Enzymes are like a locksmith who shows up and opens the door for you right away.
- Without enzymes, life would not be possible because the chemical reactions we depend upon would take too long.

Life's energy source.

- Plants and animals take advantage of a special chemical reaction to obtain **energy**.
- In these reactions, a chemical called adenosine triphosphate (**ATP**) is altered (1 phosphate is removed) to create adenosine diphosphate (**ADP**) and, in the process, produces significant energy.
- **All** of the activities in a cell that require energy use ATP as a source.
- Example: Muscles use ATP to fuel contractions.
- ATP is also a component of many other chemical reactions that are vital to life.

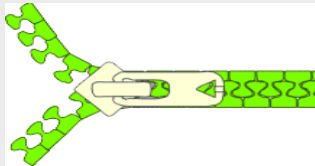
Part Two:
DNA carries the genetic code.

Basic DNA.

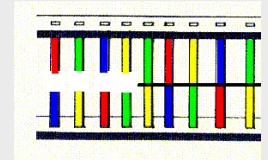
- **DNA**: deoxyribonucleic acid.

[dee-**OX**-see -- rye-bow -- new-**Clay**-ick acid]

- Our genetic information is carried as two long strands of chemicals – they join together like a long zipper.

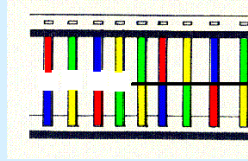


Chemicals on each strand join (bond) in the middle >

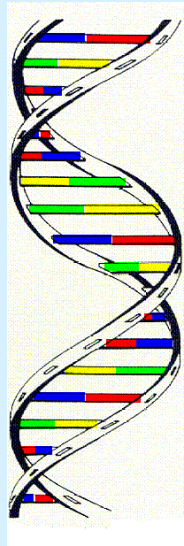


- Only **FOUR** different chemicals are used to make this message – think of each tooth in the zipper as one of these four chemicals.
- The 4 chemicals are called “**bases**” (or **nucleotides**):
A: adenine, **T: thymine**, **C: cytosine**, **G: guanine**

The DNA helix.



The two strands twist together to form a **helix** of DNA.

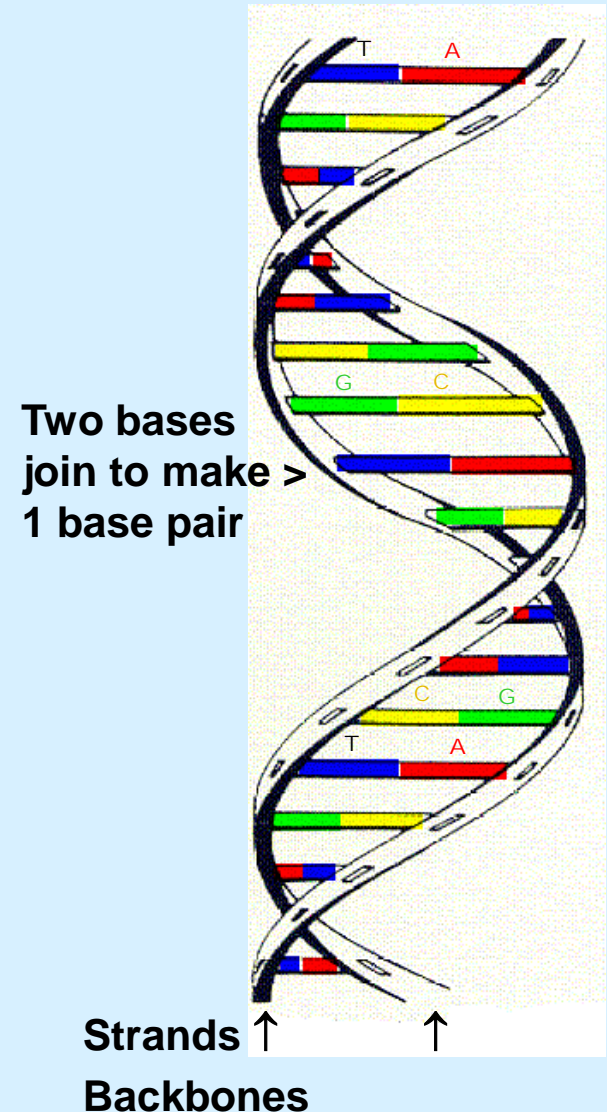


↑Helix

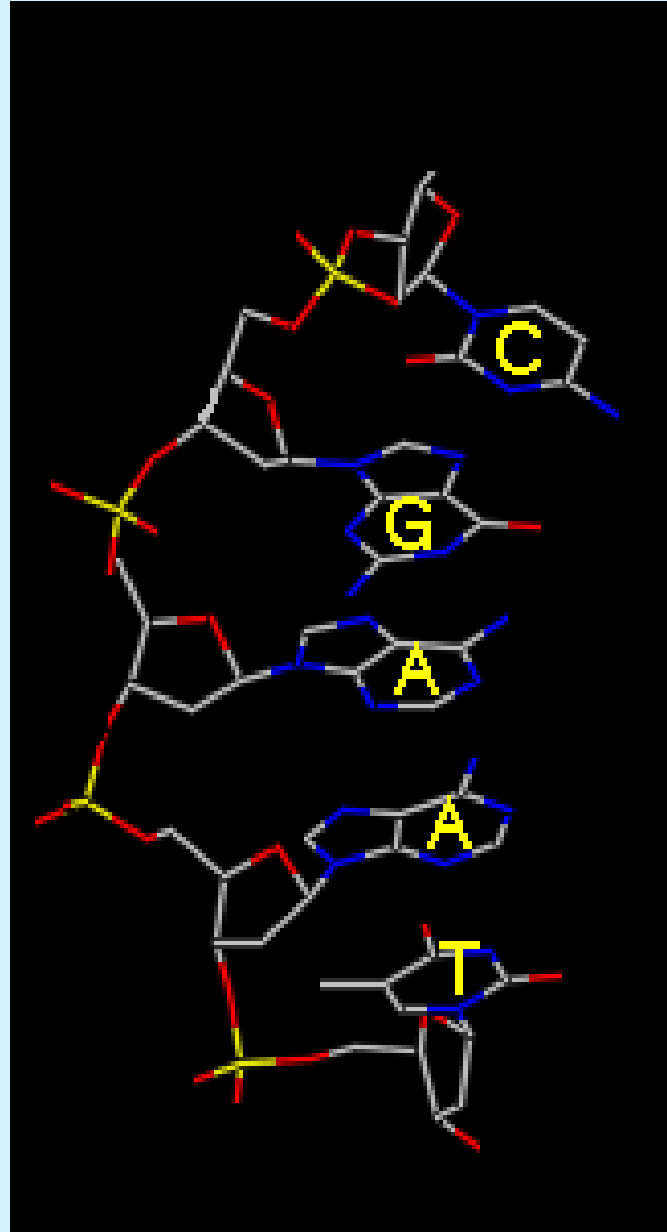
- The genetic message is the **sequence** (order) of the chemicals in the zipper.

- Part of the **complexity** comes from the sheer sizes involved:
- One “set” of human DNA has about 3 **billion** base pairs in the zipper (about 6 billion individual chemical “teeth”).
 - The largest single message yet found, the dystrophin gene (involved in causing **Duchenne** muscular dystrophy), has 2,220,223 bases on each side.

DNA Helix.



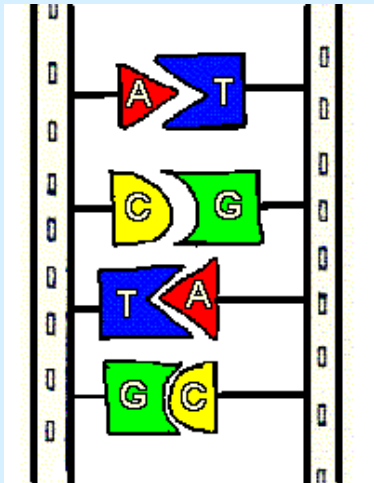
- On the left, we see the DNA **backbone** of one strand, shown in red, yellow and grey (it is mostly made out of sugar and phosphate molecules).



- In this diagram, on the right, we can see five **bases** attached in **sequence** (C G A A T)

Certain bases always pair up.

- Due to their chemical properties, certain bases on one strand **pair up** with certain bases on the other strand:
 - **A** always pairs with **T** and **T** always pairs with **A**
 - **C** always pairs with **G** and **G** always pairs with **C**.



- This pairing makes it easy: once researchers know the chemicals on one side of the zipper, they also know exactly what must be on the opposite side of the zipper.

Genetic code – Codons.

- The 4 letters in the DNA code – **A** **T** **C** and **G** – make up 3 letter “words,” called **codons**, that spell out the genetic messages.

Examples:

G G G **G G C** **A G T**

- There are **64** different combinations possible.
- The entire genetic code is made up of series of these 64 codons, presented in different combinations to form “sentences” – these are what we commonly refer to when we talk about **genes**.
- Each gene is a “sentence” of code spelling out the formula for one or more proteins in the body.

What does DNA do?

- DNA provides the basic information that allows cells to manufacture proteins.
- All life processes are made up of networks of proteins interacting together.
- In initial development, DNA directs the creation of the necessary proteins to form the various structures of the body – about 300,000 proteins in humans.
- During the life of an organism, proteins are continually being used up and a constant supply of new proteins must be provided.
- DNA also provides a mechanism for this information to be passed from generation to generation.

DNA summary.

- DNA is made up of two long strings of molecules made of sugar (**deoxyribose**) and phosphate links that form the outside backbone of each strand.
- The four base chemicals (also called **nucleotides**) attach along the inside of the backbone strands.
- Bases on opposite strands bond to each other in the middle, zipping the strands together into a **helix**.
- **Sequences of bases** form the genetic messages we commonly refer to as **genes** (we have ~ 23,000).
- Chemicals in the cell unzip and re-zip the DNA helixes as the genetic messages are needed by the cells.
- Most of the messages are used to make proteins.

Basic RNA.

- **RNA** stands for ribonucleic acid.
[rye-bow -- new -- **Clay**-ick acid]
- RNA is similar to DNA, except:
 - RNA has the same bases as DNA, except one – instead of **T = thymine** there is a **U = uracil**.
 - In RNA, the chemical backbone of the strand has a different type of **sugar** – it has a **ribose** sugar instead of a deoxyribose.
 - RNA is usually found as just a **single strand** – it usually does not form into a two stranded helix.
 - **Many** kinds of RNA have been identified, some are well understood, others, not at all.

The message has to be copied.

- The sequences of bases on the DNA are **not** directly used to make proteins.
- DNA is in the center of the cell (the **nucleus**) and it never leaves but **proteins** are made in the body of the cell.
- RNA acts as a **messenger**, making a copy of the sequence needed from the DNA and carrying it out of the cell's center into the body of the cell where it is used to make protein.

Here is an overall summary:

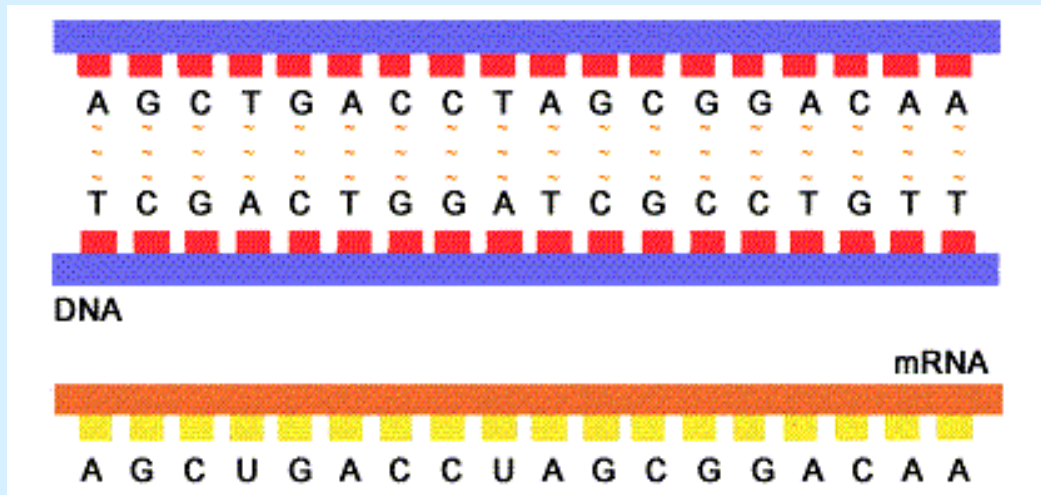
- **DNA - transcription--> RNA - translation--> Protein.**

Transcription.

- DNA to RNA **transcription** has four basic steps:
 - Step 1: The 2 strands of DNA **unzip**.
 - Step 2: Primary RNA “sees” a **start sign** (“**promoter**”) on the DNA strand and it joins on, copying the sequence of bases – the **reading frame** – until it hits a **stop signal**.
 - Step 3: This **primary RNA** now carries a complete copy of the base sequence of the DNA – it is now **edited** into **messenger RNA (mRNA)**.
 - Step 4: The final mRNA moves into the body of the cell and acts as a template for **protein synthesis**.

Copying the message.

- The two unwrapped DNA strands are shown in blue. The top strip – called “**sense**” (coding) DNA – is not used in the copying (“**transcription**”) process.



↑ This yellow strip is the newly formed primary RNA strand. Notice it comes out as an **exact copy** of the top DNA strip (but with **U** for **T**).

← The second blue strip is the **template strand** of DNA used to make the copy (this is the opposite side of the sense DNA strip, so it is called “**antisense**” (non-coding) DNA).

Genetic messages.

- Sections of base sequence are read as 3 letter words – **codons**, to form “sentences:” the gene’s message.
- In the next few slides, I am going to “cheat” a bit and use some common 3 letter English words to illustrate how the triplet genetic code makes sense and how mutations create problems.
- Remember, in “real life” there are just 4 letters in the genetic alphabet – **A T G** and **C** and the three letter codons they form don’t make much sense to us (but they **do** make sense to the protein factory in the cell).

“Junk DNA.”

- The DNA sequence of bases contains the messages needed by the cell but not all of the DNA is used:
 - It is estimated that only about **3 percent** of the DNA consists of coding sequences used to make proteins. Example: Only 11,058 of the dystrophin gene's 2,220,223 bases are used in making protein.
 - At first, scientists believed the non-coding DNA sequences were some sort of left over material and they referred to it as “junk DNA.”
- Researchers now appreciate that this DNA plays important, if not critical roles, however, these roles are still not well understood. One idea is this DNA performs a regulatory or control function.

The message is edited.

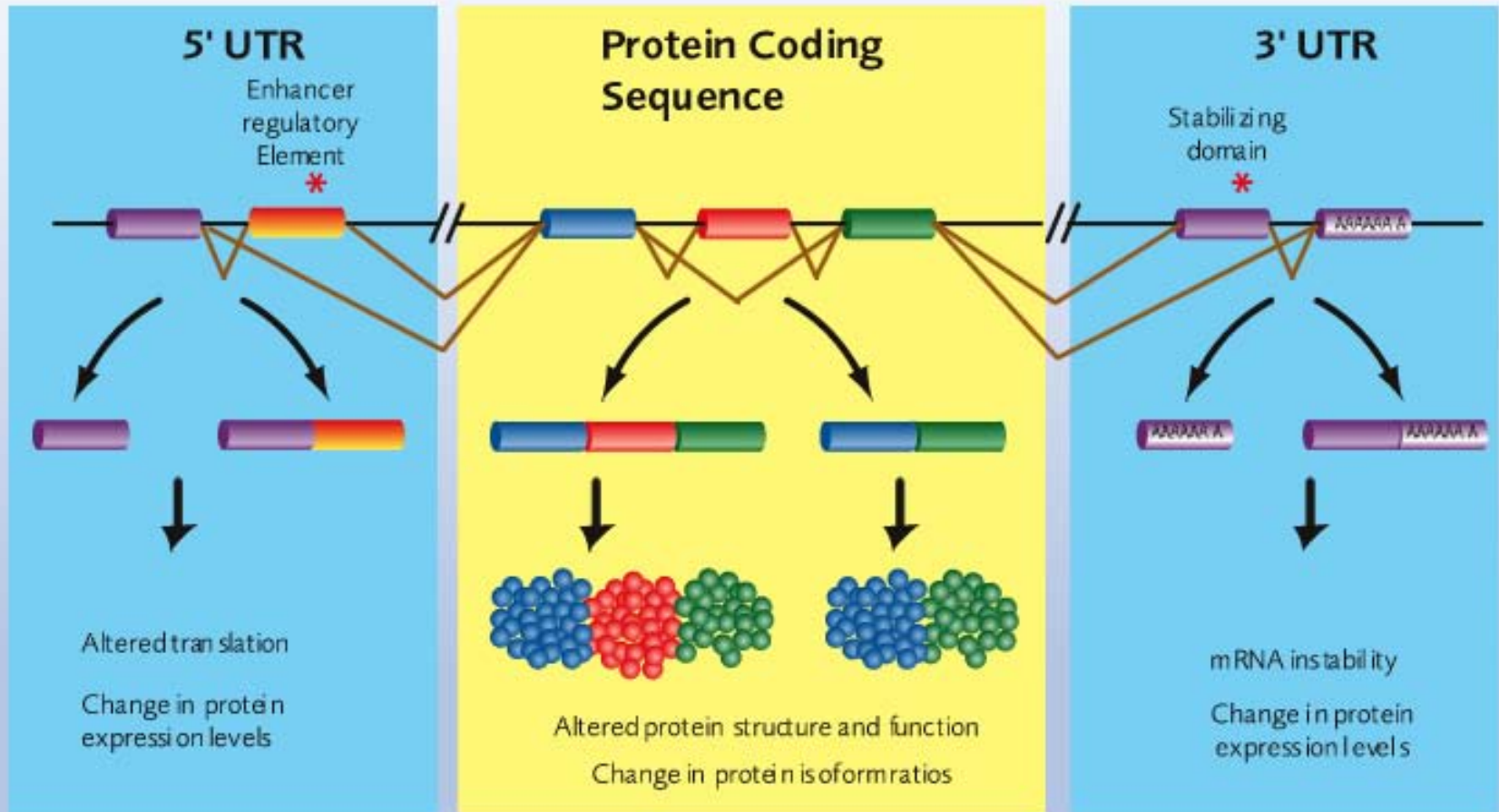
- The sequences of DNA bases used to make proteins are now edited:
 - As we have seen, the whole DNA sequence in a gene is initially **transcribed** into **primary RNA**:
 - This primary RNA is now **edited**, some parts of the code sequence are kept and other parts are removed from the final mRNA message.
 - The retained **coding sequences** are called **exons**.
 - The discarded, **untranslated sections** are called **introns**

Alternative splicing.

- Differences in how the final mRNA is edited allow one gene to make several **different** mRNAs and thus make several different proteins or to change other variables.
 - To create several mRNAs from one section of DNA, during editing, exons can either be kept in the final message or removed in different combinations: this is called **alternative splicing**.
 - Alternative splicing can affect the protein **coding region** of the RNA to produce proteins that differ in their sequence and thus differ in their properties & activities.
 - Alternative splicing within **non-coding regions** of the RNA can result in changes in **regulatory elements**, for example, affecting the level of protein expression: how much protein is actually produced and becomes active.

Alternative splicing.

The impact of alternative RNA splicing



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<http://www.exonhit.com/alternativesplicing/>

Summary from DNA to mRNA.

- To put a genetic message into action:
 - The DNA helix unzips into one sense strand (not used) and one template, antisense strand.
 - An RNA strand forms by moving along the template DNA strand and adding new bases corresponding to the sequence it finds.
 - When done, the 2 DNA strands zip back together.
 - The RNA is now edited before it moves out of the cell's center into the body of the cell.
 - Differences in editing allow a gene to make several different mRNAs & thus several different products.
- Proteins are made according to the sequences of code carried by the mRNAs that move into the cell.

Part Three:

The genetic code creates proteins.

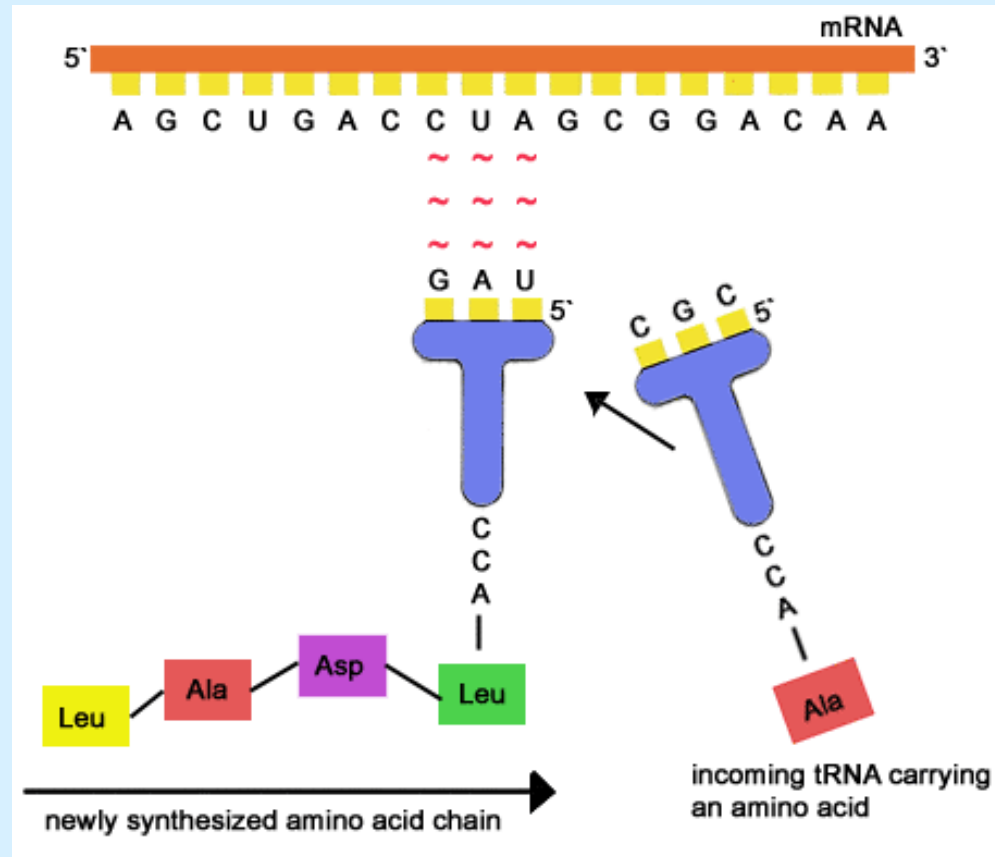
Protein is made.

- The normal operation of proteins is critical to the function of every system in the body.
- Estimates are there are ~300,000 proteins in humans.
- Each **edited** mRNA sequence spells out a protein.
- **Proteins** are made up out of chains of chemicals called **amino acids (AA)**.
- Proteins are made by “factories” in the cell called **ribosomes** that “read” the mRNA base sequence.
- Ribosomes assemble a sequence of amino acids into a new protein chain according to the mRNA sequence.
- There are **64** three “letter” **codons**: 61 represent different amino acids, 3 stand for stop signs.

Translation.

- There is some overlap as 61 codons specify just **20** different amino acids.
- As the mRNA is read, the code tells the factory what amino acid to add next in the new **protein chain**: this process is called **translation**.
- Proteins may contain from a few dozen to a few thousand amino acids.
- The largest protein yet found is Titin, a muscle protein with 26,926 amino acids strung together in one long single chain.

Translation.



- The **sequence** of amino acids defines the protein.

<http://library.thinkquest.org/C004535/media/translation.gif>

Post-translational processing.

- More flexibility (and more complexity) is added after the protein chain of amino acids is assembled:
 - Several **modifications** can be made at this stage that alter the final protein and how it functions.
 - This is extremely important for medical research:
 - It is not enough to know the genetic code and how it is edited, we also need to learn how proteins are modified after their amino acid sequence is assembled.
 - **Post-translational processing** is also another way that the cell can make several different proteins from a single gene.

Finished protein.

- One or more chains of amino acids are used to create a protein.
- The amino acids and their sequence in the chain help define the unique properties and the eventual shape of the final protein. In a complex series of steps, the chains gather together and fold into a unique **3 dimensional shape**. This final shape is critical to the protein's function.
- It does not take much of a mistake to cause trouble.
- Mutations in DNA leading to altered protein function are the **usual** culprit in most genetic disorders.

Finished protein.



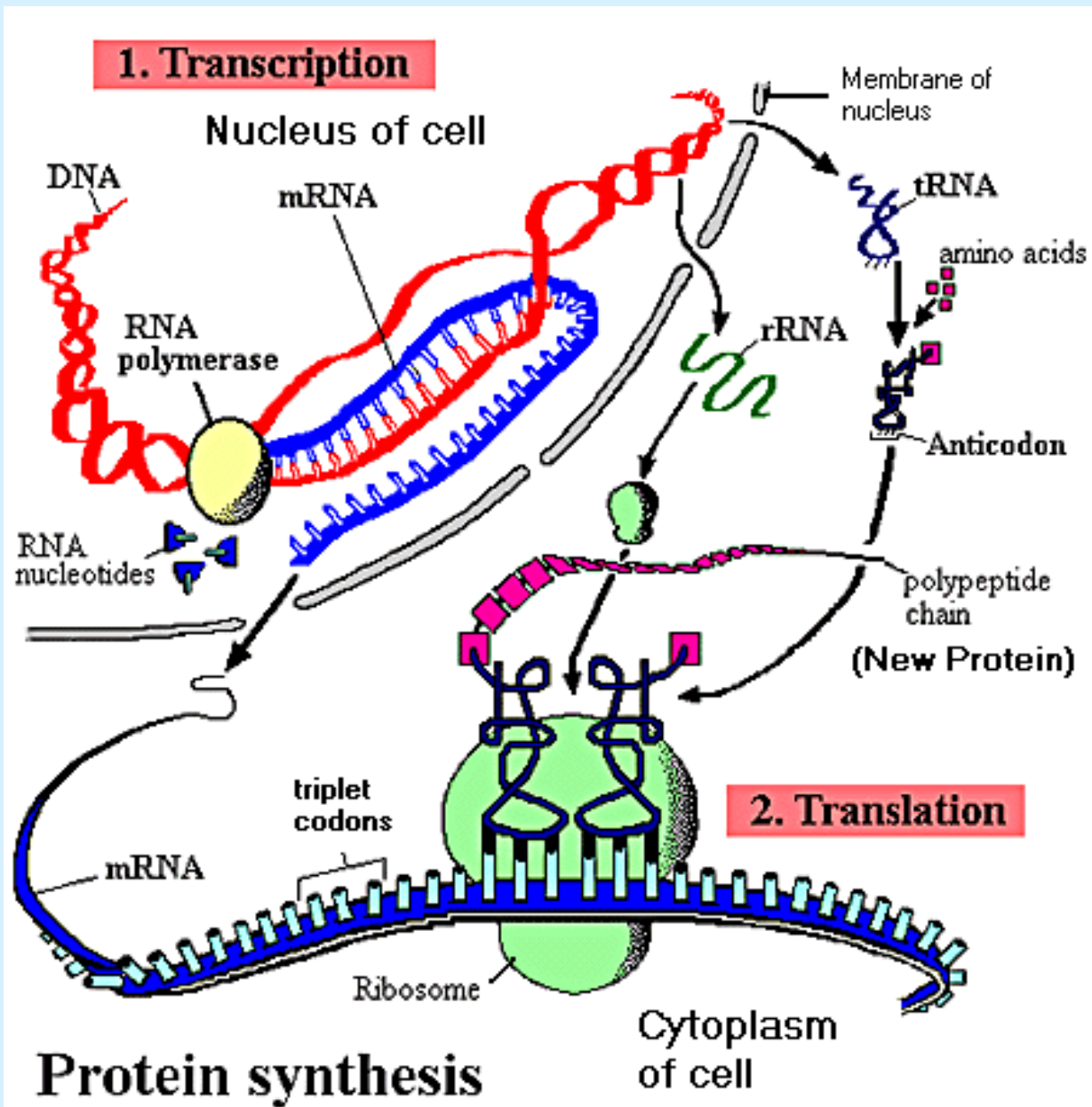
- There are 114 **billion** dystrophin molecules in one gram of muscle tissue.

<http://www.smdf.se/2005garcia.htm>

- Example: a diagram of dystrophin muscle protein, a protein containing 3685 amino acids.

▪ http://imbs.massey.ac.nz/Staff_images/dystrophin-web1.gif Dr Andrew Sutherland-Smith

Summary: Code to protein diagram.



- Epigenome: [EP – pee – gee – nome] The study of *heritable* changes in gene function that may occur without a change in the actual sequence of DNA.
- It was originally believed that only changes in the actual DNA code could be inherited – passed on to future generations.
- It is now recognized that some exceptions can occur.
- The control of genes and their protein products can be influenced by the environment and changes passed on to future generations without changes to the code.
- It is not yet clear how significant a factor this type of effect is in human genetics.

- A series of biochemical reactions control genes, turning them **on and off** and setting the **timing** and **amounts** of proteins they produce.
- The “settings” of these reactions are strongly influenced by the **environment** and they can also be **passed on** from generation to generation:
 - This partly explains why identical twins are different, their exact environments differ and thus so do their epigenomes, resulting in slightly different outcomes.
- It is also why the children and grandchildren of women who suffer severe malnutrition during pregnancy are likely to weigh less at birth – the mother’s “low food settings” were somehow inherited by the children.

Summary from code to protein.

- DNA carries the genetic code in sequences of chemicals that form genetic “messages.”
- A message is read by RNA and used as a template to make a unique sequence of amino acids.
- Chains of amino acid sequences form into proteins.
- Proteins then interact and form into complex structures that are the basis of all living matter.
- The code is not always final, some modifications can be made along the way that alter the final protein product and how it will function.
- To devise genetic treatments, doctors will have to understand this whole process in great detail.

Part Four: Genes.

Genes.

- Traditionally, the view was that 1 gene = 1 protein:
 - We now know that one gene sequence can be read in different ways to make different proteins (**one gene = a few proteins**).
 - Some genes **may also do other jobs** (not all genes make protein).
- The human genetic code contains about **23,000** genes (best estimate today):
 - The complexity of humans is not reflected in the **number** of genes: rice has about as many genes.
- All of the genes in a species are called a **genome** (**genomics**: the study of genomes).

Life is like an old pocket watch.

- Life operates on the basis of **complex interactions** and interconnections between many smaller sub-parts:
 - These sub-parts are rooted in the **chemicals** we have talked about.
- An old **pocket watch** is full of gears and levers that work together in unison to keep time:
 - If one gear breaks or one lever fails, the watch's whole function is disrupted and it can't keep time.
 - In this example, think of a watch being like a single cell and the gears and levers as the proteins that are working together to keep the cell running.

Life's pocket watch is dynamic.

- Genes are constantly **turning on and off**:
 - When a gene is turned off, the protein the gene makes is quickly used up and disappears.
 - When more protein is needed, the gene for that protein is turned on and the cell makes the protein.
 - “Gears and levers” are always coming and going.
 - There are several **layers of complexity**:
 - There are 1000s of proteins controlled by genes, constantly being turned “on and off” in every cell.
 - Each cell must work correctly.
 - As cells age and fail, they must be replaced.
 - Cells form tissues that form organs that do various jobs.
 - Trillions of cells work together simultaneously to create a single, functioning individual.

Genotype and phenotype.

- The genes in a person are called the **genotype**.
- Almost all genes interact with the environment and this may influence their expression:
 - Think of choosing paint at the store:
 - We carefully choose a color and the paint is mixed.
 - When we paint our room, the color looks just a bit different than it did in the store: the room has a small effect on the final color we see.
 - Genes are like this, their expression is slightly modified by the environment they find themselves expressed in.
 - This expressed form is called the **phenotype**.
 - Phenotype: the trait expressed that we can see, e.g. blue eyes.

Most traits are multigenic.

- Most genes tend to function in small groups and many traits are controlled by at least **several genes**.
 - Most complex traits and illnesses are controlled or influenced by groups of genes “working together.”
Examples: depression, cancer, heart disease.
 - The media is misleading when we read about “the gene for schizophrenia” being discovered – there is no single gene.
- Traits and disorders controlled by one gene are the exception.
- This complicates possible gene therapies.

Sequencing the genome.

- Recently, scientists published the whole gene code sequence of the **human genome**:
 - This was a big step toward understanding how things work (and someday being able to fix things when they go wrong).
 - But, the sequence itself is only part of the picture – now we need to see how the sequence is edited and how it is used.
 - Next, we have to understand how proteins are made and function and how they work together.
- The code sequence forms the foundation for the next steps . . .

Sequence to function.

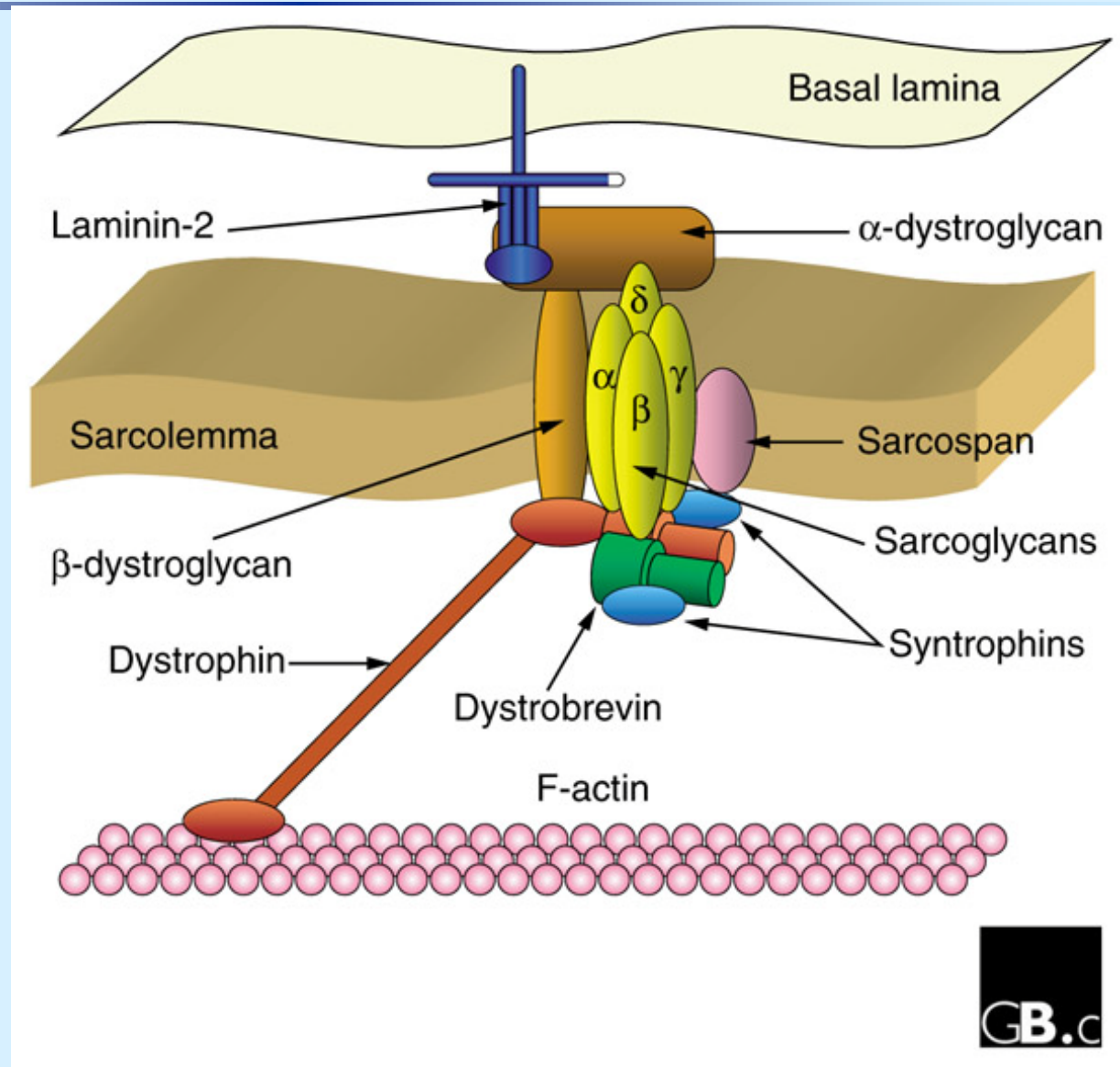
- Researchers now must link a function to each piece of code (called **annotating** the code):
 - What protein does this sequence of code make?
- We are interested in two aspects of proteins:
 - 1). How do normal proteins work and interact?
 - 2). How do proteins become defective in illness?
- Most illnesses will ultimately be traced back to some sort of protein-based abnormality.
- The **proteome**: all of the proteins we have, **proteomics** – the study of how the proteins work.

Protein “complexes.”

- **Functional proteomics**: the study of all protein functions and how proteins interact together.
 - Functional proteomics will be a critical area of study in understanding how cells work:
 - Most proteins work in “teams” called **complexes**.
 - Several protein complexes often work together to do specific jobs.
 - A single protein abnormality (for example, caused by a single mistake in the DNA code) can throw off a whole series of protein functions.

Proteins of the dystroglycan complex.

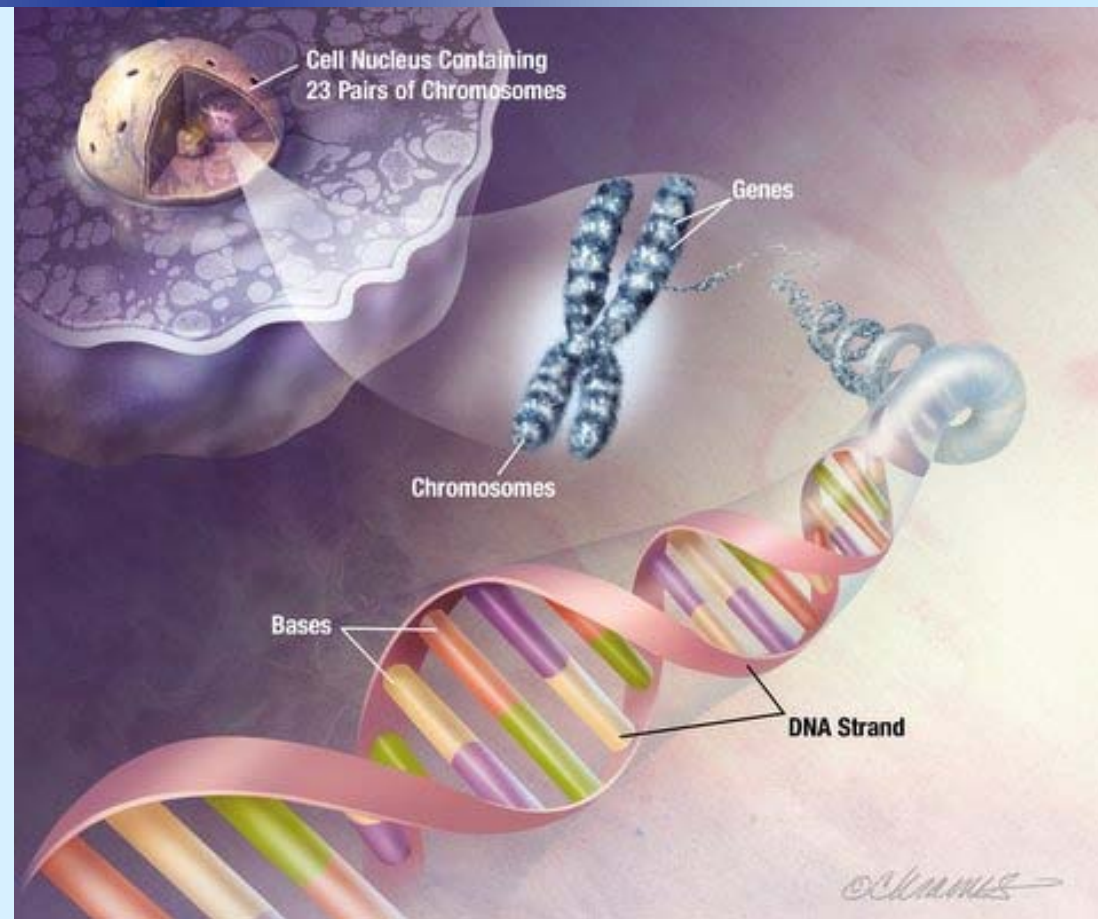
- The major muscle proteins fit together like the gears in a watch, in what is known as the **dystroglycan protein complex**.



Part Five:
Chromosomes.

DNA forms chromosomes.

- Each very long helix of DNA is tightly packed to form one **chromosome**.
- We **inherit** 23 from Dad & 23 from Mom. Each set of 23 contains about 23,000 genes with about 3.3 billion base pairs.



From: www.alzheimers.org/.../IMAGES/HIGH/Dna_high.jpg
National Institute on Aging, National Institutes of Health

- The chromosomes (**Chrome**-muh-soams) are found in the center of the cell – in the “nucleus.”

Chromosomes (abbreviated as Chrms). ⁶¹

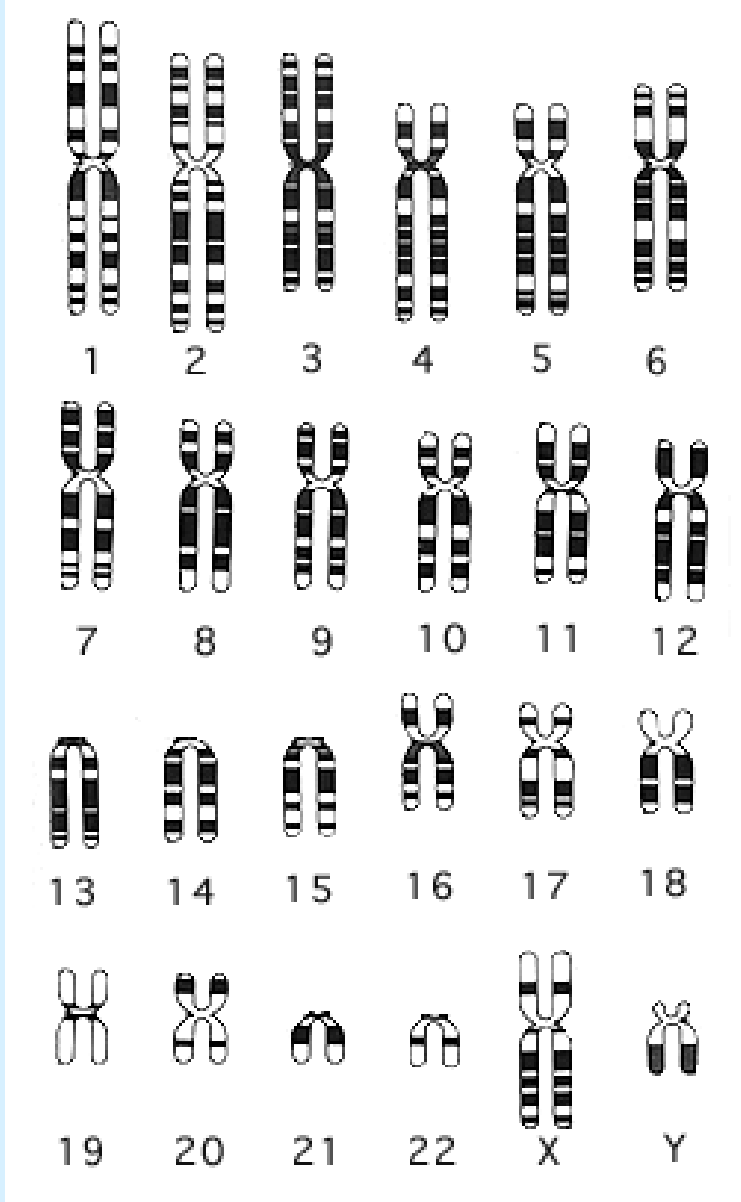
- Humans have **46** single chrms, found in 23 pairs:
 - 22 pairs are called **autosomes**.
 - There is one pair of **sex chrms** (always either **XY** or **XX**).
- Autosomes pair together and look like matching candlesticks – they look alike, the same size, etc.:
 - One chrms of each pair comes from the mother, the other chrms of the pair comes from the father.
 - The 2 chrms of each pair carry genes for the same traits (e.g., eye color) at the same location, but not necessarily the same version of that gene – these versions are called **alleles** (brown vs. blue eyes).

Chromosome.



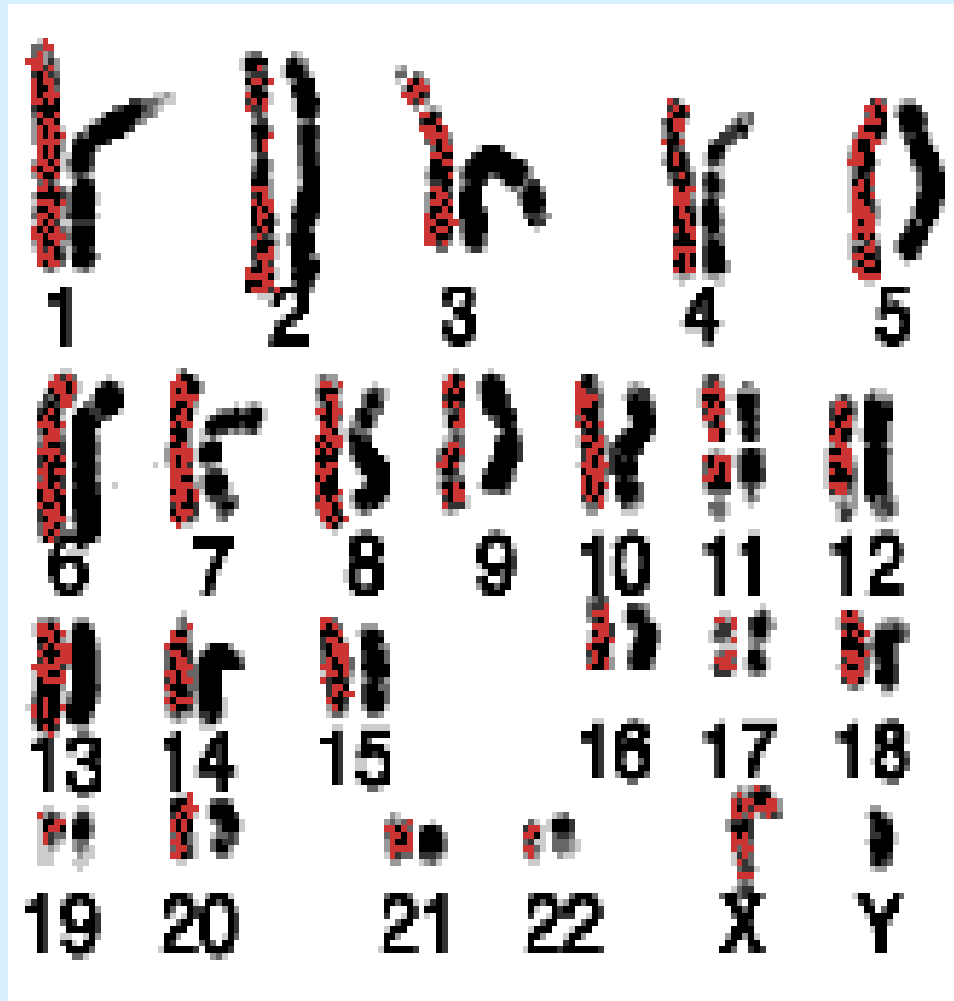
- The DNA (and our genes) are carried on chromosomes.
- Different chromosomes carry different genes.
- In this “drawing” of one chromosome, colored rings indicate individual genes.
- **Cytogenetics** (SIGHT-toe-genetics) is the study of chromosomes.

Chromosome map.



- Individual chromosomes can be “mapped” to show what genes each holds.
- This type of picture is called a **karyotype** (CARRY-oh-type).
- We can see 22 autosomes plus an X and Y pair here.

Karyotype - Another example.



- In this picture, red chrms are from mom, black ones from dad.

Sex chromosomes determine gender.

- The pairing of the sex chrms determines the **gender**.
- All early development starts out as female:
 - An XX pairing continues on to be a female.
 - In an XY pair, the **Y chrm** provided by Dad starts the process that switches development to a male.
- Mom always passes on an X chrm:
 - Eggs contain only 22 autosomes & an X (never Y).
- Dad passes on 22 autosomes and either:
 - an X (to make an XX – a girl),
 - or a Y (to make an XY – a boy).
- Sperm contains about 50 - 50 X and Y chrms.
- Only Dad can pass on a Y chrm to yield a boy.

Genes on the X chromosome.

- Sex chrms are unique and this has major implications for disorders involving **X-linked genes**:
 - The X chrm and the Y chrm always pair together.
 - However, unlike the autosomes (where chrm pairs carry 2 versions of each gene), the genes on the X are not duplicated on the Y:
 - Males (XY) have only one copy of the genes on the X chrm, there is no corresponding gene on the Y of the pair to compensate if there are problems, so in males, all of the genes on the X have to function correctly.
 - X-linked gene defects are a major problem for males – if there is a defect that causes an illness, the males will be affected in all cases.

X-linked genes in females.

- Females begin with one X from mom (X_m) and one X from dad (X_p) inside each cell:
 - Shortly after fertilization, one X in each cell is “chosen” and is turned off: **inactivated**.
 - Each cell ends up with one functioning X (the same “**dosage**” of X genes as males have).
 - Normally, half of the cells display an active X_m (from mom) and half show an active X_p (from dad). This pattern is called a “**mosaic**.”
 - This mosaic pattern of X chrms has some complex implications for females (beyond this introduction).

X-linked gene compensation (females). ⁶⁸

- If there is a defect on one X in a female, then usually, the same gene on her “other” X will be O.K. and will compensate (little or no signs of illness): the female is said to be a **carrier** of the defect.
 - Normally, inactivation is **random**: some healthy Xs are tuned off and so are some of the defective Xs (about a 50-50 ratio).
 - Enough healthy Xs are left functioning to compensate and to prevent major symptoms.
 - Women are called carriers because they may pass their defective X gene onto their children.

Skewed X inactivation.

- **Skewed** means tilted to one side: not random.
- If the initial inactivation of the X chrms is skewed towards the healthy X chr, then more healthy Xs will be inactivated compared to defective Xs.
- When this happens, there may not be enough healthy Xs left to support normal function and the female may show symptoms of the illness (called **a manifesting carrier**).
- In some females, 100% of the healthy X chrms are inactivated (random would be 50%):
 - In these **rare cases**, females show the same **severity of symptoms** of X-linked disorders as males.

Part Six:

Mating passes traits on through alleles.

Egg and sperm formation.

- “Normal” cells in the body contain 46 chrms arranged in 23 pairs.
- Egg and sperm cells (**gamete or germ cells**) must only carry only 23 chrms (so that when an egg and sperm cell join together, we end up with the correct number of 46).
- To accomplish this, when eggs and sperm form, a genetic “split” called **meiosis** takes place, reducing the 23 pairs of chrms to 23 singles.
- This reduction also involves a **shuffling** that creates variations in the gene sequences. These variations make the DNA in each sperm and egg genetically unique.

Somatic cells versus germ cells.

- An individual has the same genetic code in each cell in their body (called **somatic** cells), except in their eggs or sperm (the **gamete or germ cells**).
- Changes (**mutations**) in body cells over a person's lifetime are not passed on to children but can cause serious disorders during the person's lifetime (**cancer**).
- Only the genetic code carried in eggs or sperm is passed on to children (called the **germ line**).
 - Mutations in the DNA in eggs or sperm may be passed onto children.
- The formation of eggs & sperm is a critical step in human reproduction.

What is passed on.

- As we have explained, eggs pass on an X chrms and sperm can pass on either an X or a Y.
- Along with these 2 sex chrms, 22 autosomal chrms are also passed on to the children:
 - Mom passes on $22 + X = 23$ single chrms.
 - Dad passes on $22 + (X \text{ or } Y) = 23$ single chrms.
 - When an egg & sperm join, the first cell formed (the zygote) gets $23 + 23$ chrms = 46 singles (23 pairs).
 - This first set of 23 pairs is the individual's genotype and is now copied over & over. All cells in the person's body will carry copies of these 23 chrms pairs (with a couple of exceptions: red blood cells have no chrms, & sperm or eggs revert back to single, reshuffled sets).

Genetic variety from mom and dad.

- When eggs or sperm are formed, the gene sequences of the parent are shuffled, creating a slightly revised code in each egg or in each sperm.
- When an egg and a sperm join, they combine genes from two different parents creating a second opportunity for genetic revision/gene variety.
- A child is genetically **derived** from mom and dad's code (he/she has a .5 genetic relationship).
- These features create the variety seen in people, we often look like mom or dad and are related to them – we share their genetic predispositions .5, but we are also .5 different and therefore distinctly different.

Individual genetic variety.

- All people have basically the same genes:
 - Each gene has various forms in a population:
 - These alternate gene forms are called **alleles**.
 - Each person has 2 copies of most genes: one copy of a given gene on each chrm in a chrm pair.
- People have slightly different forms (.1%) of the same basic genes (otherwise we would all be identical).
- In different people, gene control may also vary:
 - Different genes may be turned on / off, genes may be turned on / off at different times or genes may be turned on / off at different rates. These differences also create variety among people.

How do alleles work?

- In the autosomes, the chrms & genes appear in pairs.
 - The two genes appear at the same location on each of the 2 chrms, but usually appear as alleles:
 - Alleles are slightly different versions of the same gene.
 - We have two alleles for most genes (one received from mom and one from dad).
 - Each allele may express a different version of a trait, the allele that is expressed will determine the **phenotype**: the actual trait that is expressed & that can be seen – for example, either blue eyes or brown.
 - There may be several allele versions in a population.
- In a pair of alleles, one will usually be **dominant** and the other **recessive**, the dominant one is expressed.

Dominant alleles.



- In describing traits, **dominant** alleles in a chrom pair are usually shown as capital letters.
- In this example, this gene may represent eye color: “a” = brown eyes and “A” = blue eyes. This person will have blue eyes as blue (“A”) is dominant in this pairing.

- Dominant traits are expressed if:
 - One dominant allele is present in a gene pair (**Aa**),
 - or, if both alleles of the pair are co-dominant (**AA**).

Recessive alleles.

- **Recessive** traits are usually shown as small letters.
- Recessive traits are not expressed if there is a dominant version (allele) of the same gene present on the other chromosome of the autosome pair:
 - The dominant trait “overpowers” the recessive one.
- If both alleles are recessive (**aa**), then the trait will be expressed – this is the **ONLY** way that a recessive trait can be expressed, with one exception:
 - All recessive genes on the male’s X gene will be expressed (he only has one copy of these genes, so they must be expressed).

Homozygous / Heterozygous.

- To summarize: most chrms and genes come in pairs.
 - Genes in a pair are usually not exact copies, they are usually slightly different versions (called alleles).
- **Heterozygous**: When the two versions (alleles) of a gene differ slightly: one version is usually dominant over the other (the other one is recessive).
 - The dominant gene is shown as a capital letter, the recessive, as a small letter: Aa (or other letters) – in this case, the A version of the trait is expressed.
- **Homozygous**: When both versions of the gene (alleles) are the same – the trait will be expressed: the pair can be either dominant (AA) or recessive (aa).

How alleles work – An example.

- Blood type is based on the presence or absence of two proteins (called A and B) in red blood cells.
- Four blood types are seen in people (the **phenotype**):
 - Type A: Only type A protein is present.
 - Type B: Only type B protein is present.
 - Type AB: Both proteins are present.
 - Type O: Neither protein is present.
- The type of protein present is determined by three **alleles** forming six **genotypes** . . .

Blood type alleles.

- Three gene **alleles** control blood type (A, B and O).
- We each have 2 copies of these 3 alleles, so there are 6 possible **genotypes**: (**AA, Ao, BB, Bo, AB and oo**).
- Alleles A & B are each co-dominant over O.
 - **AA** or **Ao**: Both of these genotypes make type A protein (type **A** blood).
 - **BB** or **Bo**: Both of these genotypes make type B protein (type **B** blood).
 - **AB**: This genotype makes both proteins (type **AB**).
 - **oo**: This genotype makes no protein (type **O** blood).
 - **Four phenotypes of blood (Type A, B, AB, O).**

Autosomal dominant disorders.

- An autosomal dominant condition involves a mutation of a dominant gene on an autosomal chromosome.
- Example: **Myotonic dystrophy** is an autosomal dominant condition; this means that only 1 copy of the mutated gene (from either mom or dad) is necessary for DM to occur in a person (the other gene copy is usually healthy but it can't help out because it is recessive).
- Because the disorder is genetically dominant, a parent with the defect has a 50% chance of transmitting the mutation to each child – in other words, each child has a 50% chance of inheriting the defect from a parent with the mutation.

- An autosomal recessive condition involves a mutation of a recessive gene on an autosomal chromosome.
- Example: Spinal Muscular Atrophy (SMA) is **autosomal recessive**; two copies of the mutated gene (1 from mom, 1 from dad) are necessary for SMA to occur in a person (if you only inherit one copy, you are a carrier and you generally do not suffer symptoms but you can pass this defective gene onto your children).
- Because the disorder is genetically recessive, for each pregnancy, if both parents are carriers, there is a **25%** chance of a child inheriting two copies of the mutation and having SMA, a 25% chance they will be OK and a 50% chance of being a carrier.

Part Seven: Mutations.

Code is always being copied.

- Most of the body's cells carry a complete copy of all of an individual's DNA.
- As each cell is formed, the DNA in the parent cell is **copied** and put into the daughter cell:
 - DNA is carried on as cells die and are replaced.
- This replenishment process goes on at an extremely **high rate** in many types of cells:
 - Examples: in skin, in the reproductive system and in the gastrointestinal tract.
- This process is extremely reliable and there are mechanisms to check for accuracy but only one mistake in code reproduction can be disastrous.

Code is “dumb” but crucial.

- A sequence of code is like a phone number:
 - The code (number) represents some other target:
 - 911: represents the police, fire and ambulance
 - 411: represents directory assistance
 - Just as a phone number leads us to our target, DNA specifies the cell's targets – the **proteins** that the cell produces and that are so critical to life.
 - We can see that a difference in just one letter can change the meaning significantly:
 - If we use 411 instead of 911 we get the wrong target.

Common mutations.

- Changes in the normal (“wild”) code are **mutations**.
- Mutations **usually** affect the structure of proteins, altering their function & usually leading to disorders.
- Example: A mutation that adds or deletes even one letter can shift the triplet reading frame and garble the message – a **frameshift mutation**:
 - Using our example: **|THE OLD CAT WAS FAT|**
If we delete the T, the frame shifts right, giving:
|HEO LDC ATW ASF AT|
- The protein factory in the cell makes the protein spelled out by this odd message and the protein does not work the way it should, leading to a disorder.

Frameshift: A severe mutation.

- Because a frameshift mutation usually garbles the message so badly, it is commonly a very **devastating** type of mutation with severe consequences.
- The protein produced is often misshaped and cannot function or interact with other proteins (think of the example of the gears in a clock needing to all work together).
- This usually leads to very serious physical symptoms.
- An example is Duchenne muscular dystrophy.

Nonsense mutations.

- Recall that the mRNA will continue to copy the DNA code until it sees a stop signal.
- Some mutations can create an “accidental” stop sign in the middle of the message and the mRNA stops copying the message too soon.
- This type of mutation is called a **nonsense mutation**. The result is that only part of the correct message is made and, in turn, only part of the protein is made:
 - From our example: **|THE OLD CAT WAS FAT|**
The nonsense mutation product code looks like:
|THE OLD CAT|

Missense mutations.

- Mutations can sometimes change the DNA code to create a different amino acid in a specific location.
- These changes often alter the way the protein works.
- This type of mutation is called a **missense mutation**. The new message is readable but slightly changed:
 - From our example: **|THE OLD CAT WAS FAT|**
The missense mutation product code looks like:
|THE OLD HAT WAS FAT|
- The effect of this type of mutation can vary in severity depending upon the protein in question.
- Sickle cell anemia involves a missense mutation.

Introns can play a role?

- **Intron code** – untranslated regions (UTR) – are not kept in the mRNA & are not used to make proteins.
- Until recently, this untranslated intron code was thought to play no role and was called “**junk DNA**.”
- The majority of DNA (97%) is made up of intron code.
- Recently, it has been shown that some of this material plays a **crucial role** in switching on and off genes.
- Another clue to the importance of introns is found in some disorders, e.g., in myotonic dystrophy, the genetic defect is in an untranslated section of code.
- Overall, the role of this untranslated code and how it operates is not well understood yet.

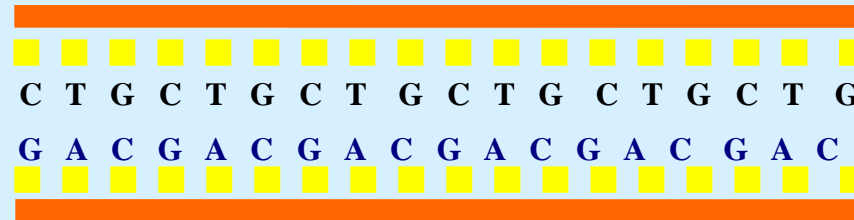
Base pair repeats.

- It is **normal** to see triplets or quadruplets – 3 or 4 bases together – repeated a number of times in a row, either within a gene or in the intronic code.
- When 3 chemicals are repeated, it's called a **trinucleotide** repeat:
Example: **CTG CTG CTG CTG CTG CTG CTG**
- There is normally some variation between different people, re: how many repeats are present and the number is stable over generations (children have roughly the same number as their parents).
- If the number of repeats is within **“normal” limits**, they do not cause problems.

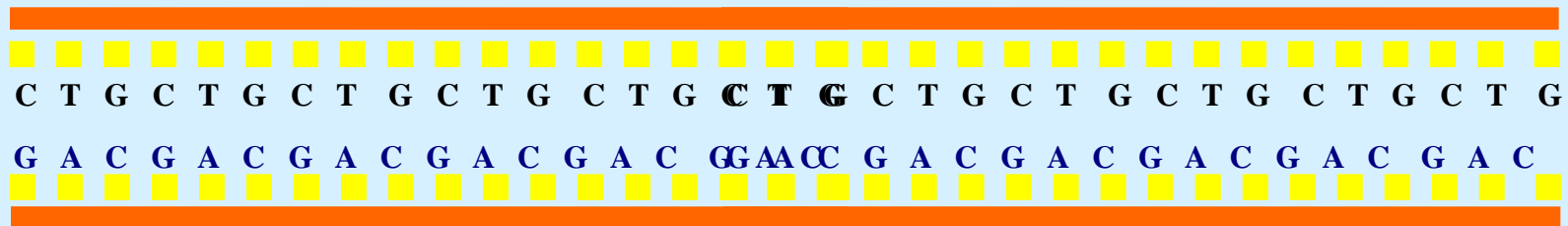
Repeat related mutations.

- Sometimes a mutation can occur that **deletes** repeats or that creates **extra** repeats. If a section of repeats becomes too small or too large, it leads to problems.
 - Example: In the most common type of Myotonic Dystrophy (DM1), an untranslated repeat of **CTG** is “expanded.”
 - People normally have fewer than 50 repeats.
 - People with DM1 may have from 50 to 2000 repeats. People with the very serious Congenital Myotonic Dystrophy may have up to 4000 repeats. (In the medical research, these numbers vary a bit.)

Illustration: Myotonic dystrophy.



Normal: fewer than 50 repeats.



Myotonic Dystrophy type 1: 50 to 2000 repeats.

Congenital Myotonic Dystrophy: up to 4000 repeats.

- With each new generation, the number of extra repeats often increases. Because the number of repeats varies over generations, this is called an “**unstable mutation.**”
- This phenomena is also called **genetic anticipation:**
 - With successive generations, the size of the repeated section increases and patients commonly show symptoms at an earlier age and / or they may show more severe symptoms.

Common repeat disorders include:

- Fragile X syndrome: the most common cause of inherited mental retardation (IQ ~ 35-70).
 - Caused by extra **C G G** repeats in an exon on the X chromosome.
- Huntington disease is caused by extra **C A G** repeats in an exon in the Huntington gene on chromosome 4.
- Friedreich ataxia is a neurodegenerative disorder caused by extra **G A A** repeats, located in an untranslated region of code on chromosome 9.
- Myotonic dystrophy (DM1 and DM2) a common muscle disorder, involves an expansion of repeats on chrm. #19 (DM1) and on chromosome #3 (DM2).

Other repeat disorders include . . .

- Another type of muscular dystrophy called **Facioscapulohumeral Muscular Dystrophy** (FSHD) is also a repeat disorder:
 - About 95% of people with FSHD have a mutation in a section of intronic DNA on chrm 4 made up of a series of repeats. The mutation **deletes** repeats. The smaller the repeat left, the more severe the disorder tends to be and the earlier the onset.
 - Normal repeat range: 10 to >100 copies
 - Borderline repeat range: 9 or 10 copies
 - FSHD repeat range: 1 to 8 copies.

Stable vs new mutations.

- Some genetic defects are “stable,” they exist in a population and are passed on by mating:
 - If the carriers of defects could be **screened**, and mating limited to producing only healthy children, these disorders could theoretically be eliminated (e.g., cystic fibrosis).
- In some disorders (like Duchenne MD), there is a very high rate (30%) of **new mutations** constantly popping up in each generation:
 - Disorders like this could not be eliminated by genetic screening.

Part Eight:

A very simple genetic treatment.

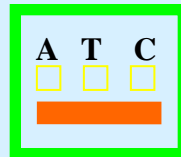
- If a piece of DNA is faulty, the RNA will copy the mistake & pass it on to the protein production phase.
- If doctors can see the DNA mistake, they can easily figure out the sequence of the corresponding final sense strand of mRNA that the cell makes.
- Doctors can create a piece of **antisense mRNA** in the lab to “mirror” this faulty section of sense mRNA.
 - This piece of antisense mRNA can be inserted into the cell where it will lock onto to the corresponding section of mRNA and “cover up” the faulty section.
 - This allows the mRNA to “skip” the mistake and prevent passing the mistake on from the DNA to the protein production phase.

Antisense blockage.



Here is a sense strand of mRNA. In this example, let's say the mRNA has copied a mutated section of DNA code – UAG – in the red box.

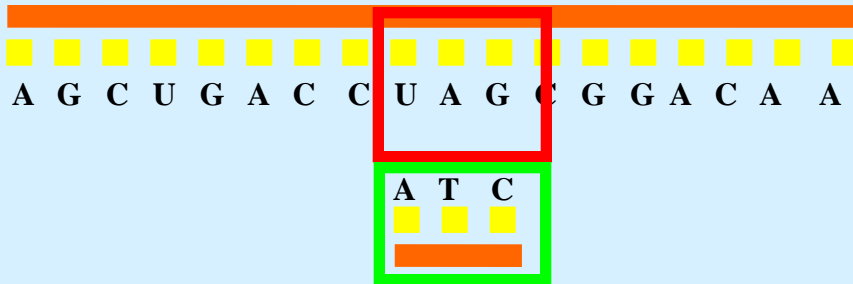
The antisense code is the opposite of the sense.



U = A,
A = T,
G = C

Doctors make this little piece of **antisense oligonucleotide** (AON) in the laboratory and put it into the cell – it attaches to the sense RNA.

- The mistake is in the red box:



- A short section of RNA (green box) is introduced, blocking out the mistake.
- If the mistake (like an extra section of repeats) can be blocked, maybe the problem can be helped or solved and the correct function restored.

- Think of a scratch on an old LP record. The needle comes to it and can't play the rest of the song. Here, doctors cover up the scratch & the needle jumps over it to finish the song. The song may not be perfect, but may be close enough to get the job done.

Part Nine:
Overview of Neuromuscular Illnesses (NMIs).

Neuromuscular Illness (NMI).

- To operate correctly, muscles must be stimulated by electrical signals received from the brain via nerves.
- Two major types of disorder are seen:
 - 1). “**Neuro**” related:
 - A). Problems with signal transmission in the nerves.
 - B). Problems getting the signal transferred from the nerve “across” into the muscle fibres (muscle cells).
 - 2). **Muscle** related:
 - Problems within the muscle itself.
- One in three thousand people have some type of neuromuscular disorder (BMJ, Oct. 98).

Nervous system.

- There are two main divisions in the nervous system:
 - **Central nervous system** (CNS): brain & spinal cord.
 - **Peripheral nervous system** (PNS):
 - 1). Sensation messages from **sensory neurons** in all parts of the body are carried by peripheral nerves to the spinal cord and then **up** to the brain (afferent – up).
[Peripheral means out toward the arms and legs.]
 - 2). Action messages from the brain go **down** the spinal cord through **motor neurons** that connect to muscles and glands (efferent – down).
 - The **spinal cord** contains both sensory & motor neurons, carrying signals to and from the brain.

Nerve cells – Neurons.

- **Neuron**: a special type of cell that conducts electrical impulses (“**nerve impulses**” or “action potentials”).
 - Neurons have three parts:
 - The **cell body**: the usual parts found inside any cell.
 - The **axon**: a long “cord” that carries the signals, covered in a special insulation called **myelin**.
 - **Dendrites**: branch-like projections on the neuron’s end that use **chemicals** to transmit the electrical signals from one neuron on to the next.
- **Myelin**: A protein that covers & “insulates” the axons.
 - Helps maintain the strength and speed of the electrical signals as they pass along the nerve.

Major disorders related to the nerves.

- CNS myelin related disorders:
 - Multiple Sclerosis (MS).

- Peripheral nerve disorders:
 - Charcot-Marie-Tooth (CMT).
 - Hereditary Motor Sensory Neuropathies (HMSM).

- CNS / Spinal cord disorders (motor neurons affected):
 - Amyotrophic Lateral Sclerosis (ALS).
 - Spinal muscular atrophy (SMA).
 - Polio (and Post-Polio syndrome).

Nerve – muscle connection.

- **Neuromuscular junction (NMJ)**: The gap between the end of a motor neuron (nerve) & a muscle fibre (cell):
 - The ends of motor nerves contain thousands of “containers” filled with a chemical called **acetylcholine** (ACh) {ah-SEAT-toe-coe-line}
 - When the brain wants a muscle to move, the signal reaches the nerve’s end & its containers **discharge** Ach.
 - Ach moves across the junction and fills up “special” Ach receptors on the muscle fibre (these are like a lock & key).
 - When the muscle receives enough Ach, it **contracts** (“fires”).
 - After the muscle contraction, another chemical “cleans out” the Ach from the muscle cell’s receptors, the muscle **relaxes** and returns to normal, ready for the next signal/contraction.

Major disorders of the NMJ.

- **Myasthenia Gravis:**
 - A type of autoimmune disorder – chemicals in the body (autoantibodies) fill the Ach receptors on the muscle cells and block the proper action of Ach.
- Lambert-Eaton Syndrome (LES)
 - Caused when antibodies interfere with the discharge of Ach from the nerve.
- Congenital Myasthenic Syndrome (CMS)
 - A genetic disorder where a mutation in the genes for the Ach receptors interferes with their function.

Muscle proteins.

- Muscles are made out of a complex network of **proteins** that all must function and work together:
 - Think of the gears in an old clock:
 - A few big gears turn many smaller ones and each one plays a critical role in keeping time.
 - As muscles work, proteins break apart & must be replaced – this is a normal, ongoing process.
- Proteins are made by the cells from **genetic instructions** carried in the **DNA**.
- A common cause of these muscle illnesses is a mistake (**mutation**) in the genetic information that causes a problem with a muscle-related protein.

Major protein disorders of the muscle.

- There are many different types of **muscular dystrophy** (MD), each caused by a different specific problem:
 - **Most** are caused by **genetic mutations** associated with different muscle proteins and most have characteristic patterns of symptoms.
 - Some major types:
 - **Duchenne** (DMD) & **Becker** muscular dystrophy (BMD).
 - **Myotonic** muscular dystrophy (DM).
 - **Limb Girdle** muscular dystrophy (LGMD).
 - **Facioscapulohumeral** muscular dystrophy (FSHMD).
 - **Emery-Dreifuss** muscular dystrophy (EDMD).
 - **Congenital** muscular dystrophy (CMD).
 - **Oculopharyngeal** muscular dystrophy (OPMD).

Other types of muscle disorders.

- **Inflammatory Myopathies:**
 - Cause unknown, muscles become inflamed and deteriorate over time.
 - Dermatomyositis, Polymyositis, Inclusion Body Myositis.
- **Other types of muscle myopathy:**
 - Inherited forms of Inclusion Body Myopathy.
- Muscles need **energy**: fuel is created by a complex biochemical reaction – part of our basic **metabolism**:
 - **Defects** in metabolism may cause disorders like Mitochondrial Myopathy and Carnateen deficiency.
- There are also several other types of rare NMIs that arise because of other types of defects in the muscle.

Classification analogy.

- The following illustration uses an **electric train** (like many rapid transit trains seen today) to illustrate the three main types of problems seen in neuromuscular illness.
- **1). Problems in the transmission of electrical signals along the nerves – the overhead power lines in our analogy.**
- **2). Problems getting the electrical signal from the nerve to the muscle: the neuromuscular junction – connection between the power line & the train.**
- **3). Problems in the muscle – the train's engine.**

◆ *Nerves (Overhead Wires)*

□ **Electrical impulses**

★ **Nerve Disorders**

◆ *Nerve – Muscle
Junction (Bridge from
Train to Wires)*

□ **Chemicals (Ach)**

★ **Junction Disorders**

◆ *Muscles (Train)*

□ **Proteins**

★ **Muscle Disorders**



◆ *Structures involved*

□ **Key component involved**

★ **Types of disorders**

Part Ten:
Conclusion.

Conclusion.

- Genetics is a complex topic in medicine.
- Great strides are being made in understanding genetics, but we still have a long way to go.
- Having a basic understanding of genetics is important for people dealing with genetically based illnesses.
- The internet contains a great deal of material for those interested, if you are not sure about the reliability of a source, compare its information with other sources.
- A paper on genetics (again, trying to present concepts in easy to understand ways) can be found at:
<http://members.shaw.ca/copingwithillness/>

Pronunciations.

- Alleles: AL-eels
- Chromosome: Chrome-muh-soam.
- Cytogenetics: SIGHT-toe-genetics
- Deoxyribonucleic: dee-OX-see-rye-bow-new-CLAY-ick
- Gamete: GAM-mate
- Genome: GEE-nome
- Genomics: GEE-nom-icks
- Heterozygous: HET-ter-roe-zag-us
- Karyotype: CARRY-oh-type
- Meiosis: ME-oh-sis
- Mitosis: MY-toe-sis
- Proteome: PRO-tea-ohmm.
- Proteomics: PRO-tea-nom-icks
- Cytogenetics (SIGHT-toe-genetics)

Sources.

- I believe that all illustrations are in the public domain - here are the sources used:
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