

An Overview of Spinal Muscular Atrophy

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Our Goal.

- Our goal is to give a **general overview** of Spinal Muscular Atrophy (SMA).
- This talk is a **summary** of basic ideas.
- This talk will give a fair amount of **information** and background but in a simple and understandable way.
- The **basic** ideas are really pretty straightforward and we can get a pretty good sense of what its all about in just a few minutes.
- Scientific articles are full of very complex language. As much as possible, this talk is in **plain** English.

Knowledge Translation.

- This talk is an example of **knowledge translation** (KT).
- This is an important **new tool** in medical research.
- KT involves making a two way **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.
 - Doctors and researchers can better understand patients and their needs.

What is Spinal Muscular Atrophy?

- Usually called **Spinal Muscular Atrophy** (SMA).
- Caused by a genetic mutation that depletes a key protein leading to nerve loss and then muscle wasting.
- A “**motor neuron disorder**” (the nerve cells affected).
- A wide variation in the severity of symptoms is seen:
 - **Fatal** by two years of age in its most severe form.
 - Many intermediate **degrees** of impact on the body.
 - At its **mildest**, people lead almost normal lives.
- Affects about 1 in 6000 to 1 in 10,000 births. Leading genetic cause of infant mortality.

Types of Spinal Muscular Atrophy.

- **Five main types** are recognized.
- All five types have the **same** basic genetic cause.
- Five types described based on onset and severity:
 - SMA 0: a **very severe** form that begins before birth.
 - SMA I: (Werdnig-Hoffman) **severe**, evident at birth or within the first few months – 50% of cases.
 - SMA II: weakness between ages 6 and 12 months – **intermediate severity**.
 - SMA III: (Kugelberg-Welander) **milder** form that affects children over 1 and adolescents.
 - SMA IV: **mildest** type, develops in **adulthood**.

- SMA type 0:
 - Onset in the fetus.
 - First noticed between 30 - 36 weeks of gestation by reduced movement of the fetus .
 - **Profound** weakness and wasting of voluntary muscles, newborns show little movement and have difficulties swallowing and breathing.

SMA Types

- SMA type I [also called Werdnig-Hoffmann disease]:
 - Onset from **birth to 6 months**.
 - **Profound** weakness and wasting of voluntary muscles, child cannot sit without aid, swallowing problems, diaphragm weakened, respiratory problems cause **death**, usually within **2 years**.
- SMA type II:
 - Onset from **6 to 12 months**.
 - Variable symptom severity, child can sit alone, **various degrees** of muscle weakness. Variable life expectancy.

- SMA type III [Kugelberg-Welander disease]
 - Onset **after** 12 months.
 - Less weakness, usually have a normal life expectancy. The disorder progresses slowly, with the ability to walk usually lasting until into adolescence. A wheelchair is often required later in life.
- SMA type IV:
 - **Adult** onset (usually after age 30).
 - Much less common and **milder** than the other forms, it is characterized by a gradual onset and very slow progression.

Some SMA Symptoms.

- The muscles in the **proximal area** (the center of the body) and the **legs** are most affected. This includes the muscles that control **swallowing** and **breathing**.
- Problems eating, swallowing and digesting food are common.
- Osteoporosis (thinning of bones) is common.
- In severe cases, progression of weakness and loss of ambulation are linked to a marked deformation of the spine (**scoliosis**) often requiring surgery to correct.

Basic Problem.

- In SMA, a genetic mutation causes a problem in the production of an important protein needed by nerves.
 - Some of this key protein is made, but at a reduced level (if the mutation is so serious that it blocks **all** production, the fetus dies).
 - This causes **motor neuron cells** (MNs) in the spinal cord to die off.
 - These nerve cells are needed to pass on electrical signals from the brain to the muscles. Without these signals, the muscles cannot function properly – they are weakened and eventually **waste away**.

Nerves Stimulate Muscles.

- The **nervous system** uses a complex series of nerves and signals to control muscles. The nerves affected by SMA are the **lower motor neurons** in the anterior (front) horn of the spinal cord.
- The cell bodies of lower motor neurons are located in the brain stem, but their axons travel down the spinal cord and eventually **connect** with the body's muscles.
- When the brain sends a signal to move, it passes through the motor neurons to the **neuromuscular junction** at their end, where **acetylcholine** is released.
- Acetylcholine, a **neurotransmitter**, travels across the junction where it “excites” the muscle to contract.

Muscles Need Nerve Stimulation.

- Each motor neuron controls a group of muscle cells – from 10s to 1000s of cells – known as a “**motor unit.**”
- A few signals are **always active** creating a continuous but partial contraction of the muscles – **muscle tone.**
- In SMA, MNs die and signals can't reach the muscle:
 - With poor signals, there is little, or no, muscle tone and the muscles have trouble contracting, contract slowly and cannot hold a contraction well when a signal does come in (they are weakened).
 - **Voluntary** movement is affected.
 - In addition, the **involuntary** control of muscles (respiration, breathing, etc) is also affected.

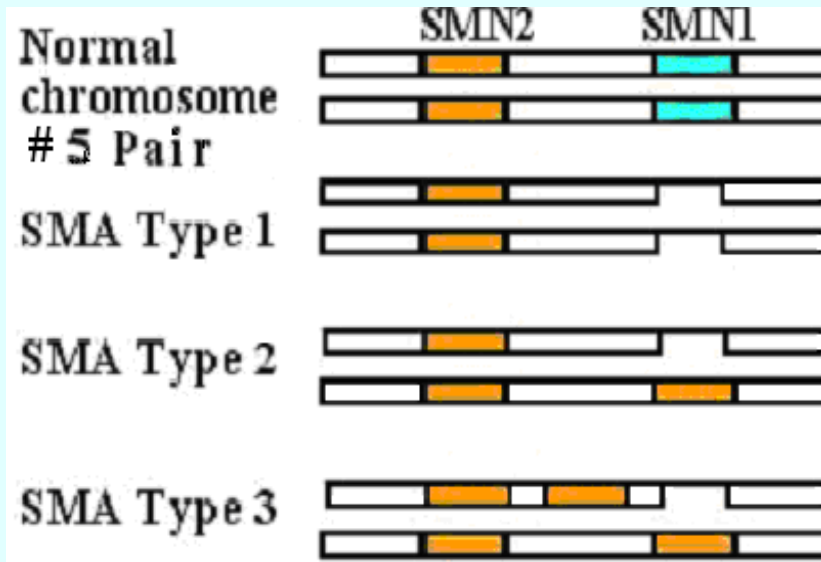
The Mutations in SMA.

- In the case of SMA, the gene affected is called the “survival of motor neuron 1, telomeric” (SMN1) gene.
 - It makes survival of motor neuron protein (SMN1).
 - Usually, each cell has 2 copies of the SMN1 gene.
- In SMA patients, both SMN1 gene copies are **deleted** or **defective**: they don't get enough SMN1 protein.
- A nearby gene called the SMN2 gene is **nearly** identical to the SMN1 gene and it also makes some SMN1 protein – **up to 30%** of what is needed.
- The exact genetic mechanisms involving these two genes is complex and the number of SMN2 genes present can vary quite a bit, even in “normal” people.

The Mutations in SMA.

- **Mutations** of SMN1 often **convert** it to a SMN2 gene.
- SMA patients therefore often are missing their SMN1 gene but have “**extra**” copies of the SMN2 gene:
 - People with SMA often have no SMN1 gene but they must have at least **one** SMN2 gene to make **some** SMN protein or they would not have survived gestation.
- SMA patients with **multiple** SMN2 genes end up with more SMN1 protein – the more SMN1 protein the cells get, the milder the SMA symptoms (as seen in the continuum of SMAII to SMAIV symptoms).

Illustration.



(Each normal cell has two copies of each gene as shown on the top pair of chromosomes)

- **SMN1: Normal gene | blue |**
- **SMN1 gene mutations:**
 - *Deletion* | / / yields the most severe SMA
 - *Conversion* of SMN1 to SMN2 gene | **yellow** | yields milder SMA
- **SMN2 gene | yellow |**
 - **All** SMA cases have at least 1 SMN2 gene
 - *Multiple copies* of SMN2 = milder SMA.
 - *SMN2 mutations alone* don't produce SMA.

Finkel type of SMA.

- The VAPB gene on chromosome 20, provides instructions for making a protein that is found in cells throughout the body. Little is known about the function of the VAPB protein.
- **Mutations** of the VAPB gene cause amyotrophic lateral sclerosis (ALS) type 8 and an adult-onset form of spinal muscular atrophy known as Finkel type.
- The symptoms of Finkel type are very similar to the symptoms of SMA IV.

Reference: <http://ghr.nlm.nih.gov/condition=spinalmuscularatrophy>

Spontaneous Mutations and Mosaicism. ¹⁷

- In some SMA cases, the mutation is new.
- **Spontaneous** (new) mutations, are not inherited from either Mom or Dad – the mutation arises in one of the early cells that divide to form the embryo.
 - There is usually no prior family history of SMA.
 - If the mutation was in an egg or sperm cell, the person may pass it on, if he or she has children.
- Some cases show **mosaicism**. This happens when a new mutation occurs in a single cell very early in development (the rest are OK). As this cell divides, its daughter cells carry the mutation. Thus, only some cells in the body have the mutation. The effect of SMA mosaicism varies widely in each person.

Summary: What We Need to Know.

- The DNA code ends up being used as a template for making different proteins in the body.
- Mutations in this DNA lead to altered protein function and are the usual culprits in most genetic disorders.
- SMA severity depends on the status of 2 genes.
- Two SMN1 genes make the normal protein we need, SMN2 genes make a little. In SMA, the SMN1 genes are deleted or defective. Mutations can also convert SMN1 into SMN2. The more SMN2 genes present, the more protein & the later the onset & milder the SMA.
- If both genes are severely impacted and little SMN1 protein is made, the results are usually rapidly fatal.

- In 2000, researchers created an SMA Mouse Model this will help speed SMA research.
- Efforts are underway to “tweak” the SMN2 gene to produce more of the normal SMN protein in order to further compensate and reduce symptoms.
- Several other approaches include:
 - Helping motor neurons survive with less SMN protein.
 - Develop drugs that have a positive effect on nerve cells and help in tissue-building.
 - Research on creatine, a substance that may help muscle or nerve cells produce energy more readily.

Recent Research.

- In March, 2005, a study showed that the pain reliever indoprofen and a drug called aclarubicin, increased the amount of SMN protein produced. Indoprofen treatment increased the amount of SMN by 13%. These drugs are promising avenues of research.
- In December, 2004, a study used a type of gene therapy to deliver SMN to cells in SMA mice, improving motor neuron survival and inducing a small but significant increase in survival.
- In November, 2003, a study of valproic acid in laboratory cells increased production of SMN protein.

Canadian Research.

- Canadians have been active in SMA research.
 - Dr. James R Bain McMaster University.
 - Dr. C. DiDonato: Ottawa Hospital Research Institute.
 - Dr. N. Gendron: Children's Hospital of Eastern Ontario.
 - Dr. R. K. Kothary: Ottawa Hospital.
 - Dr. A. MacKenzie: Children's Hospital of Eastern Ontario.
 - Dr. L. Simard, Hospital of Sainte-Justine, Montreal.

Other SMA Research.

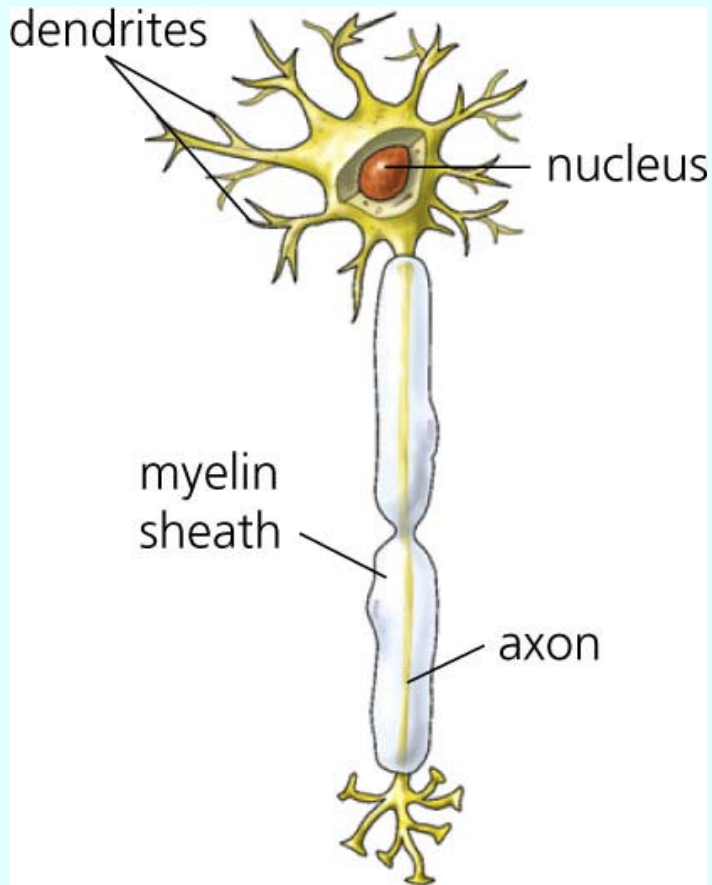
- AmSMART (American Spinal Muscular Atrophy Randomized Trials): <http://www.amsmart.org/>
 - An organization of 5 pediatric medical centers that perform clinical trials in children with SMA.
- A major research project is trying to develop methods to treat SMA:
 - The National Institute of Neurological Disorders and Stroke (NINDS) has established the SMA Project: A Collaborative Program to Accelerate Therapeutics Development for Spinal Muscular Atrophy (SMA). <http://www.smaproject.org/>

References.

- Lunn MR, et al “Indoprofen Upregulates the Survival Motor Neuron Protein through a Cyclooxygenase-Independent Mechanism.” *Chemistry & Biology*, November 2004, Vol. 11, pp. 1489-1493.
- Azzouz, M. et al “Lentivector-mediated *SMN* replacement in a mouse model of spinal muscular atrophy.” *J. Clin. Invest.* **114**:1726-1731 (2004).
- Sumner CJ, et al "Valproic acid increases SMN levels in spinal muscular atrophy patient cells." *Annals of Neurology* , Nov 2003, Volume 54, No. 5, pp. 647-654.
- See:
<http://ghr.nlm.nih.gov/condition=spinalmuscularatrophy>

- Background Information.

The Nerve Cell (A Neuron).



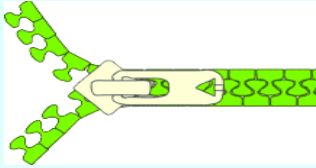
From The American
Heritage Dictionary

- A neuron has: 1). a **cell body** (with a center **nucleus**), 2). an **axon** – a long “cord” that carries an electrical signal & 3). dendrites – extensions that end in **synapses**.
- An axon can extent over 3 feet from a nerve body.
- Axons are wrapped in a **myelin** sheath of insulation.
- Where nerves meet muscle, there is a special **junction**.

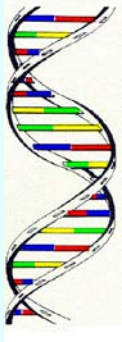
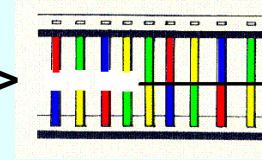
- The **genetic** cause of SMA was isolated in the 1990s.
- We will present some information on the **basic** genetic code and then discuss the problem that causes SMA.
- The **internet** contains a great deal of background information on all of these aspects.
- Again, it is the **basic ideas** that are important here, not the complex details.

Basic DNA.

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



Chemicals on each strand join in the middle >



- The two strands twist to form a **helix** of “DNA.”
- DNA**: deoxyribonucleic acid.

[dee-**O**X-see-rye-bow-noo-**C**lay-ick]

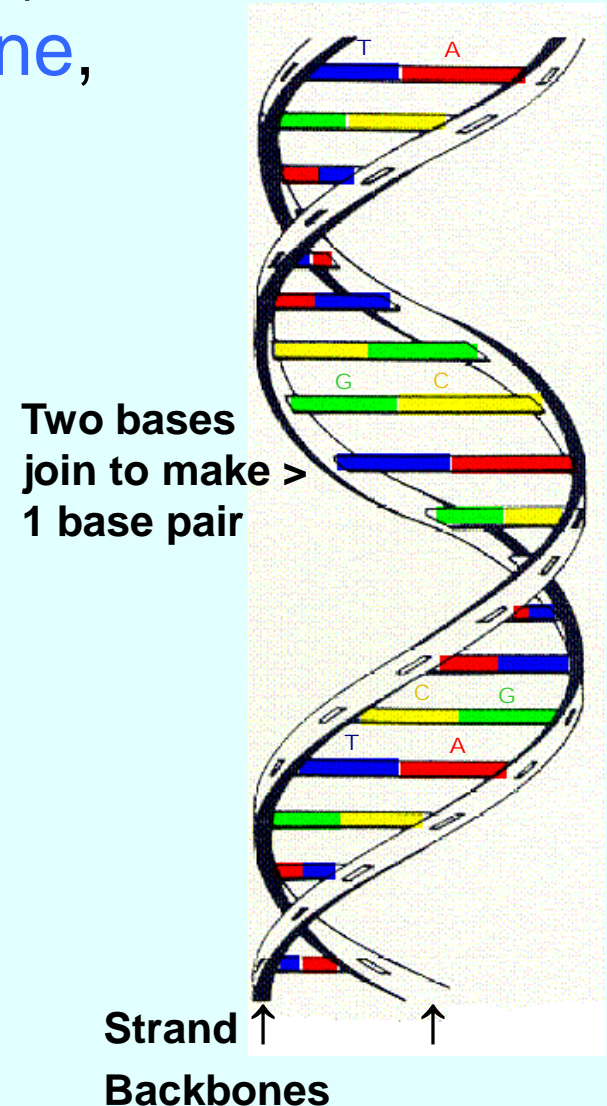
Helix ↑

- Only **FOUR** different chemicals are used to make this message – think of each tooth in the zipper as one of these four chemicals.
- The genetic message is the **sequence** (order) of the chemicals in the zipper.

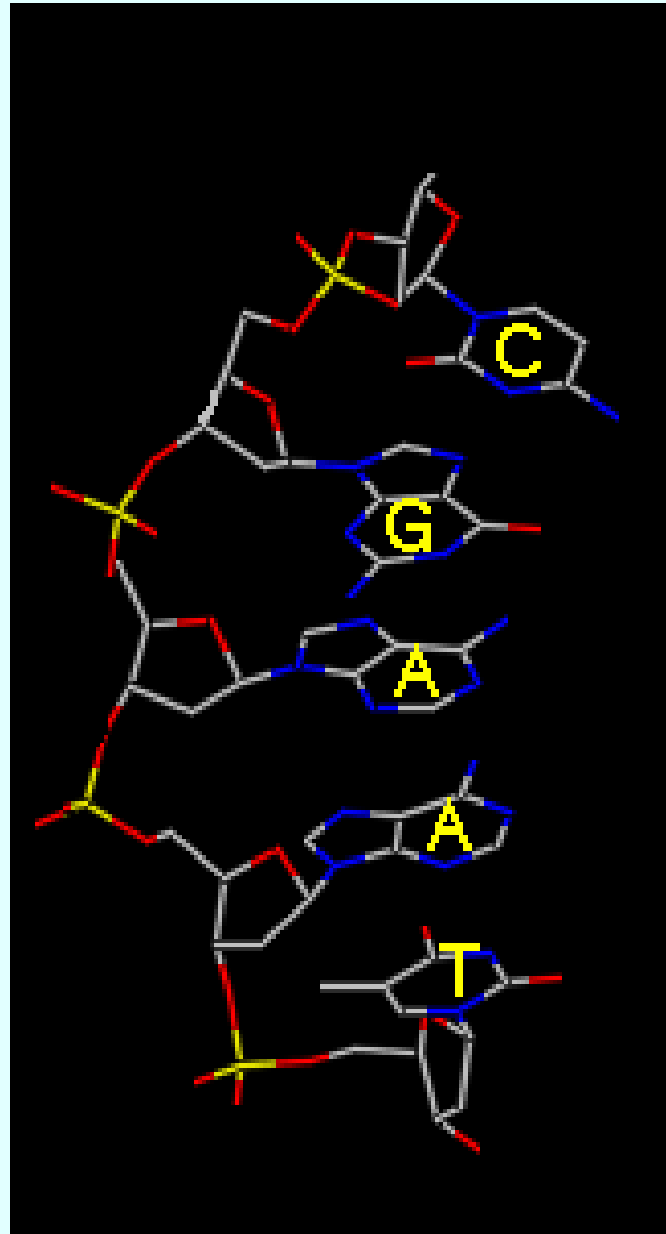
DNA Helix.

DNA Helix.

- The 4 chemicals are called “**bases**” (or **nucleotides**) **A** = adenine, **T** = thymine, **C** = cytosine, **G** = guanine
- Part of the **complexity** comes from the sheer sizes involved:
 - One piece of DNA can have **millions** of bases (chemical teeth) in the zipper.
 - The largest single message yet found, the gene involved in causing **Duchenne** MD, has 2,220,223 bases on each side.



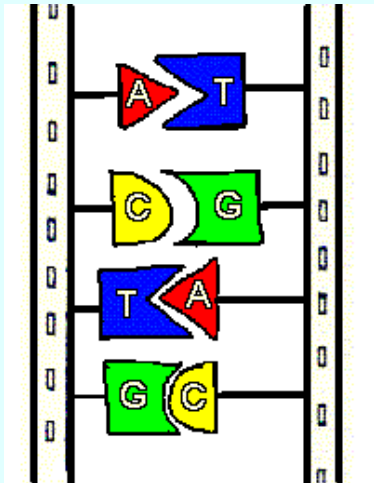
- On the left, we see the DNA **backbone** of one strand, shown in red, yellow and grey (it is mostly made out of sugar and phosphate molecules).



- 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 Doctors know the chemicals on one side of the zipper, they will know exactly what is 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.

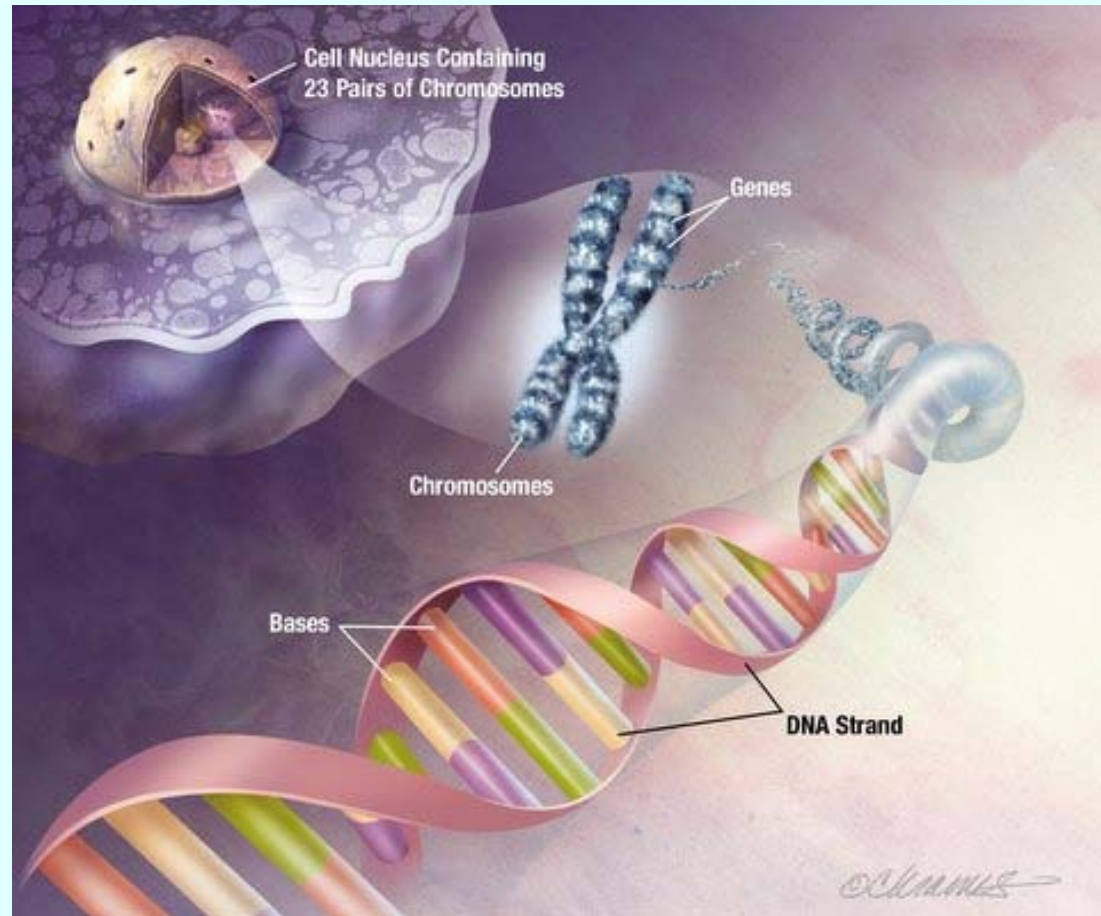
Examples:

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.

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 25,000 genes with about 3.2 billion base pairs.
- The chromosomes (Chrome-muh-soams) are found in the center of the cell – the “**nucleus**.”



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

DNA Summary.

- DNA is made up of a two long strings of sugar (**deoxyribose**) and phosphate links (molecules) 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 our 25 to 30,000 **genes**.
- DNA forms **chromosomes**: we get 23 from each parent, these are then copied for the rest of our lives.
- Chemicals in the cell can unzip and re-zip the helix as the genetic messages are needed by the cells.

Basic RNA.

- **RNA** stands for **ribonucleic acid**.
[rye-bow-noo-**Clay**-ick]
- 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** 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: 1.

- The sequences on the DNA are **not** directly used to make proteins.
- DNA is in the center of the cell (the **nucleus**) and it never leaves.
- **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:

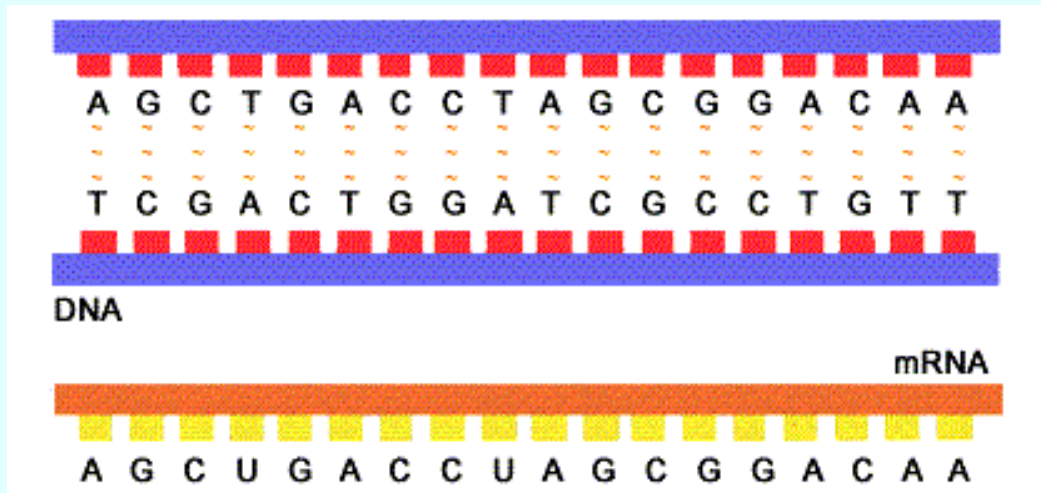
- **DNA - transcription--> RNA - translation-->Protein.**

The Message Has To Be Copied: 2.

- DNA to RNA **transcription** has four basic steps:
 - Step 1: The 2 strands of DNA unwind and **unzip**.
 - Step 2: Primary RNA “sees” a **start sign** (“promoter”) on the DNA strand and it joins on, copying the sequence of the four bases – the **reading frame** – until it hits a **stop signal**.
 - Step 3: This primary RNA 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).

The Sequence Contains the Message.

- 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 – it is not clear what the rest does, but there is a growing appreciation that it probably plays important roles.
- Recall, the whole DNA sequence in the gene is initially **transcribed** into **primary RNA**:
 - Primary RNA is then **edited**, some parts are kept (the actual **coding sequences** called **exons**) and the other parts (**untranslated regions** called **introns**) are removed from the final mRNA message.

The Sequence is Edited.

- An illustration:

- Sequence:

exons	↓	introns	↓									
dek		THE	dke	OLD	dute	CAT	yji	WAS	khy	FAT		ert

- The sequence is now **edited** – the introns are removed to yield the **final mRNA message**:

| THE OLD CAT WAS FAT |

This message is now **translated** into a protein.

- In the illustration above, the start and the end of the **reading frame** is shown as **| |**

- The **sequence of exons** between these bookends is the critical message used to make a protein.

Introns 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 **disorders**, e. g., in FSHD, the genetic defect is in an untranslated section of the intron code.
- Overall, the role of this untranslated code and how it operates is **not well understood** yet.

Summary From DNA to mRNA.

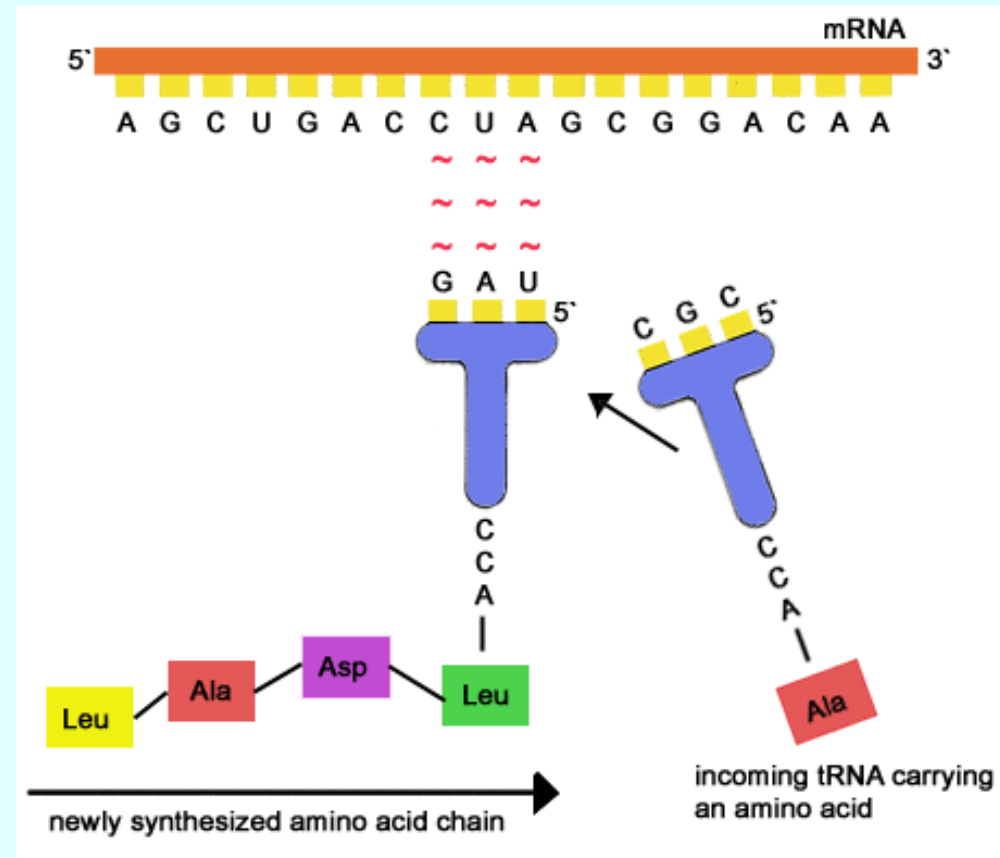
- To put a genetic message into action:
 - The DNA helix unzips into one sense strand (not used) and one template, antisense strand.
 - An RNA strand forms by moving along the template DNA strand and adding new bases corresponding to the sequence it finds.
 - When done, the 2 DNA strands zip back together.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

Protein is Made.

- The normal operation of proteins is critical to the function of every system in the body.
- Estimates are there are >100,000 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 (**ribosomes**) that “read” the mRNA base sequence.
- Ribosomes assemble the different amino acids into the new 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 is called **translation**.
- Proteins usually contain from tens to a few thousand amino acids.
- The largest protein yet found is Titin, a muscle protein with 26926 amino acids strung together in one long single chain.

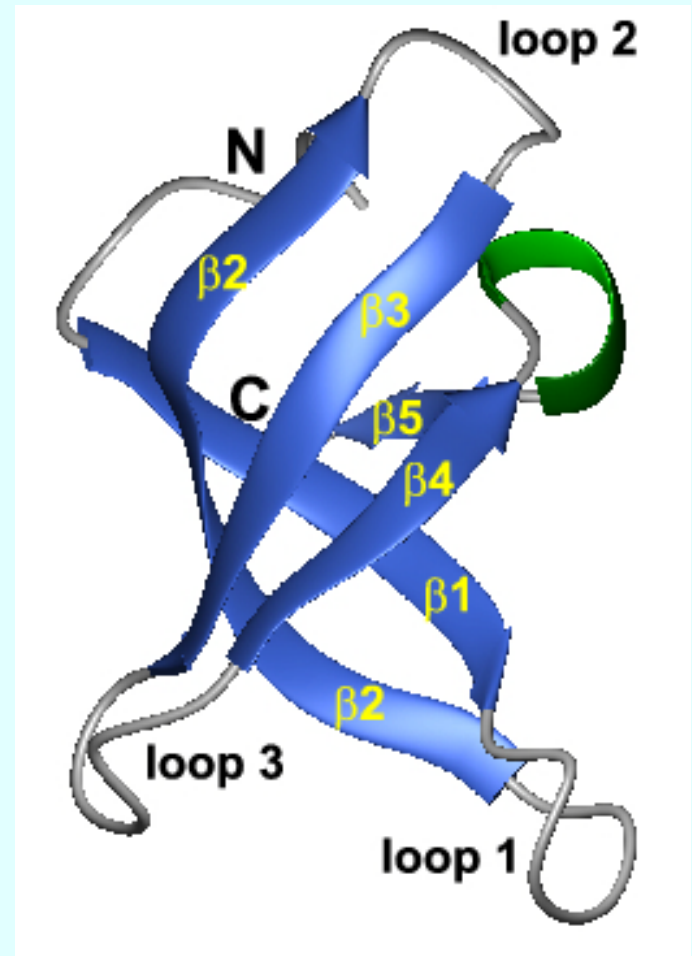


- The **sequence** of amino acids defines the protein.

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

Finished Protein.

- One or more chains of AAs are used to form a protein. In a complex series of steps, the cell gathers the strand(s) into a final **folded, 3-D shape**.
- This shape is critical to the protein's ability to 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.



- Example: a diagram of SMN1 protein.
 - *Nature Structural Biology* 8, 27 - 31 (2001)

Synopsis.

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

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 sequence are called **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 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 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 **F**AT WAS FAT|
- The effect of this type of mutation can vary in severity depending upon the protein in question.
- Missense mutations are often **seen** in SMA.

Autosomes.

- Our 46 **chromosomes** carry the DNA code.
- The 46 chromosomes are found in 22 pairs called **autosomes** and one pair of sex chromosomes.
- Different genes are located on different chromosomes.
- Each pair of autosomes holds **two copies** of a given gene, one inherited from Dad, the other from Mom.
- We are focused on the pair of # 5 chromosomes, this is where the SMN genes are.
- [The composition of pair # 23 determines sex: boys have an XY; X from Mom, Y from Dad and girls have an XX; one X from Mom and one X from Dad.]

Autosomal Recessive Inheritance.

- SMA is inherited as an **autosomal recessive** condition; this means that **two copies** of the gene with the genetic mutation (inherited from **both** Mom or Dad) are necessary for SMA to occur in a person. If a person only inherits one copy, they are a **carrier** and do not suffer symptoms but they can pass this defective gene onto their children – up to 1 in 40 people are carriers).
- Because the disorder is genetically recessive, for each pregnancy, if both parents carry the mutation, 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 becoming a **carrier**.