

# Genetics of Propionic Acidemia

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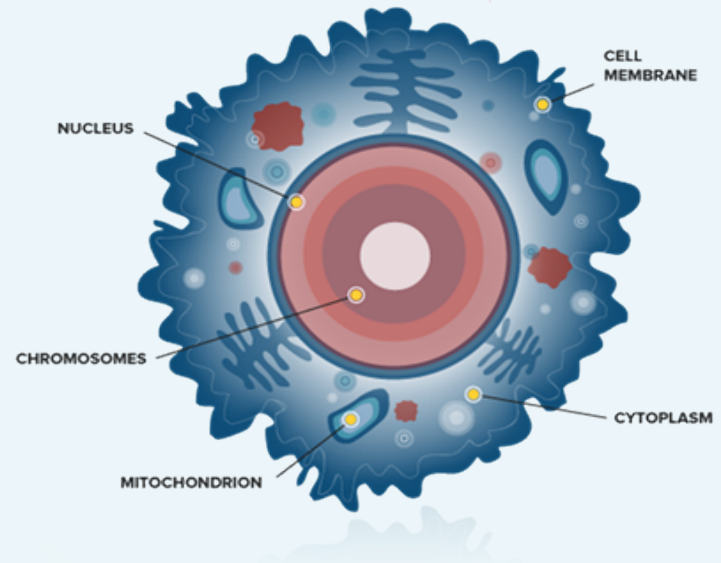
# Our Chromosomes, Genes, DNA

## The Human Body



The human body is made of some 50 trillion to 100 trillion cells, which form the basic units of life and combine to form more complex tissues and organs. Inside each cell, genes make up a blueprint for protein production that determines how the cell will function. Genes also determine physical characteristics or traits. The complete set of some 20,000 to 25,000 genes is called the genome. Only a tiny fraction of the total genome sets the human body apart from those of other animals.

## Cells



Most cells have a similar basic structure. An outer layer, called the cell membrane, contains fluid called cytoplasm. Within the cytoplasm are many different specialized "little organs" called organelles. The most important of these is the nucleus, which controls the cell and houses the genetic material in structures called chromosomes. Another type of organelle is mitochondrion. These cellular power plants have their own genome and do not recombine during reproduction.

Adapted from The National Geographic Genographic Project

<https://genographic.nationalgeographic.com/science-behind/genetics-overview/>

## Chromosomes

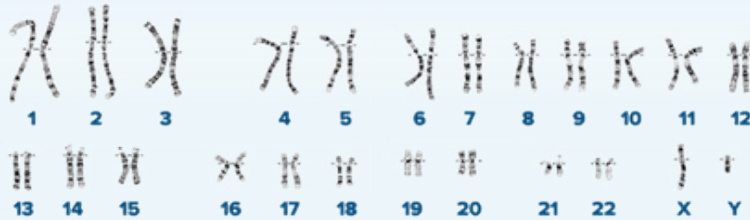
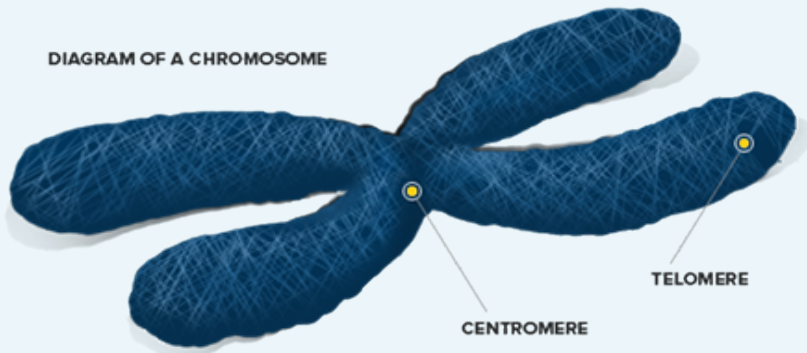
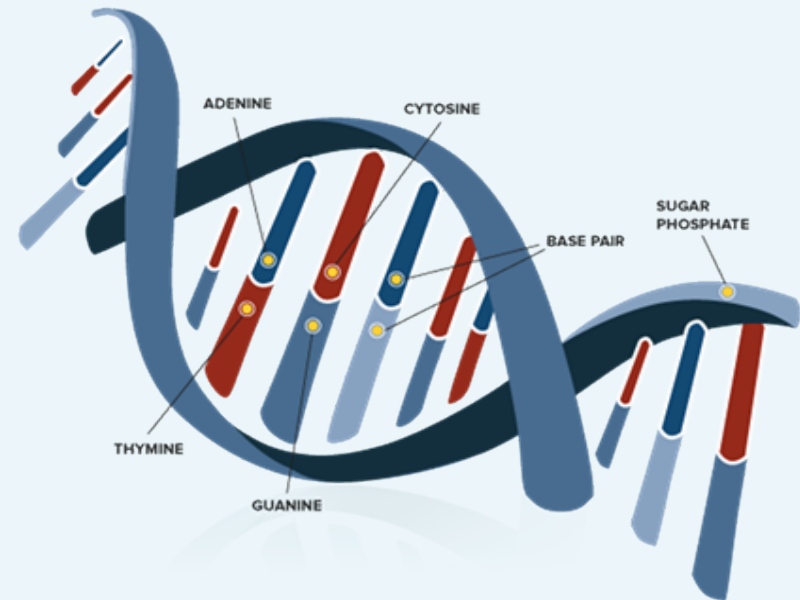


DIAGRAM OF A CHROMOSOME



Chromosomes carry hereditary, genetic information in long strings of DNA called genes. Humans have 22 numbered pairs of chromosomes and a single pair of sex chromosomes—XX in females and XY in males. Each chromosomal pair includes one inherited from the father and one from the mother. If unwound, the microscopic DNA strands in one cell's nucleus would stretch to over six feet in length.

## DNA

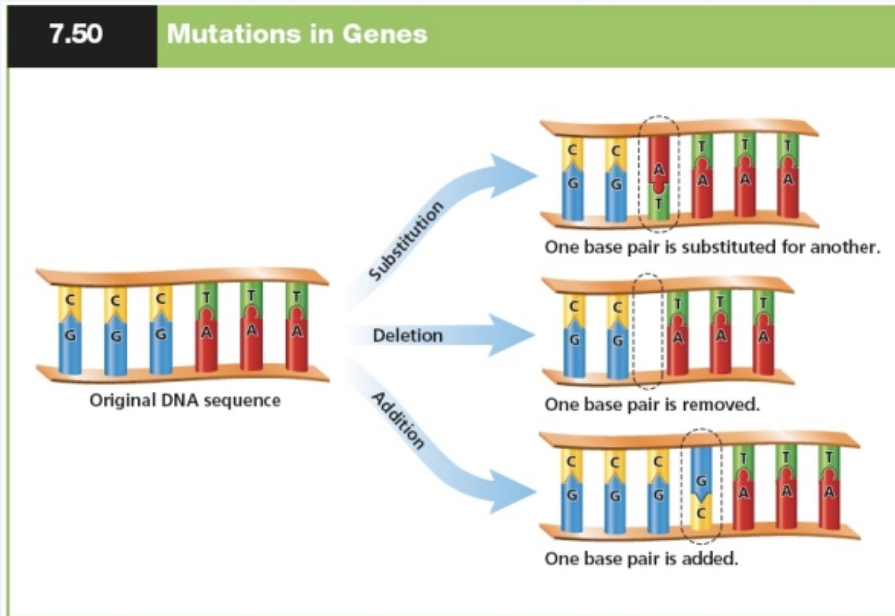


DNA (deoxyribonucleic acid) is the set of genetic instructions for creating an organism. DNA molecules are shaped like a spiral staircase called a double helix. Each stair is composed of the DNA bases A, C, T, and G. Some segments of these bases contain sequences, like A-T-C-C-G-A-A-C-T-A-G, which constitute individual genes. Genes determine which proteins individual cells will manufacture, and thus what function particular cells will perform.

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# Genes → Variants → Disorders



The color of the hair is green.  
*Original gene sequence.*

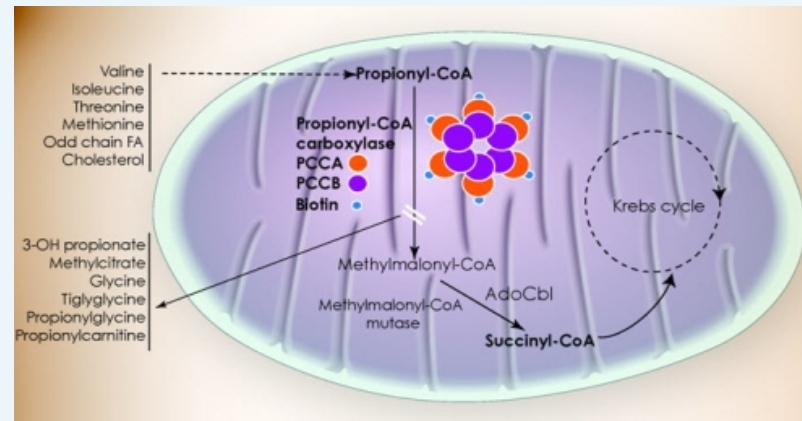
The colour of the hair is green.  
*Benign gene sequence variant.*

The folor of the hair is green.  
*Pathogenic gene sequence variant.*

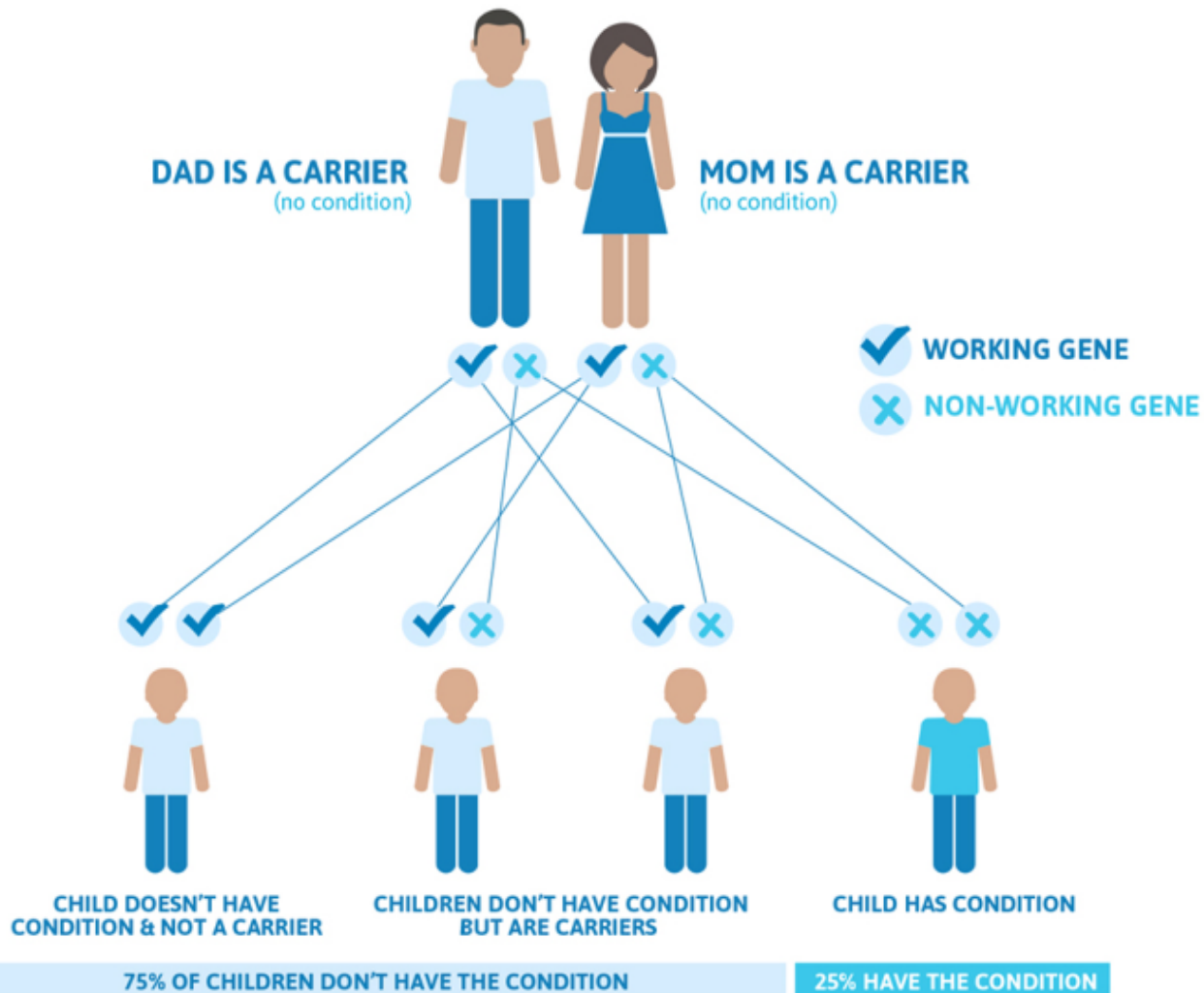
- Gene variants are simply differences in the original DNA sequence of a gene
- Benign variants do not affect the gene's function and do not lead to significant health problems. The harmless changes in our DNA sequences make us unique.
- Pathogenic gene variants affect the gene's function and lead to health problems. These variants are what we previously referred to as mutations. In propionic acidemia, pathogenic gene variants results in little to no working enzyme, causing the features of the disorder.

# Propionic Acidemia Genes

- Propionyl-CoA Carboxylase enzyme
  - Enzyme involved in breaking down certain proteins and fats
- 2 different subunits (parts) come together to make a working enzyme
- PCCA and PCCB are the genes that make the 2 different subunits
- Pathogenic variants in both copies of a person's PCCA gene or both copies of their PCCB gene will result in not making enough working propionyl-CoA carboxylase enzyme and result in having the disorder.
- Having a pathogenic variant in only one copy of the PCCA gene or one copy of the PCCB gene means you are a carrier but do not develop features of the condition.



## Autosomal Recessive Inheritance Pattern

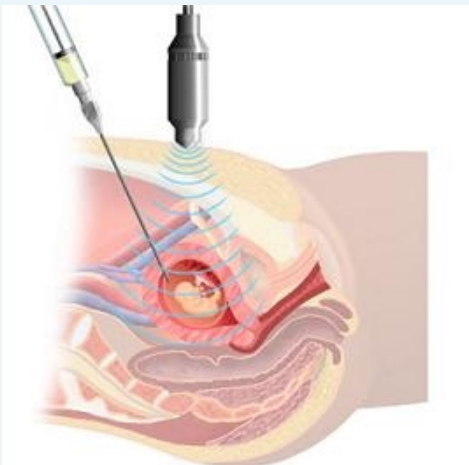
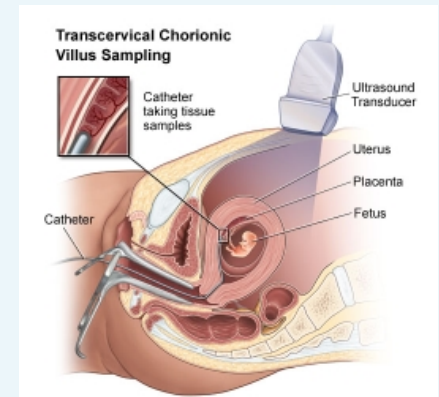


# Family Planning

- No testing before or during pregnancy
  - Testing of infant shortly after delivery
- Prenatal Diagnosis
- Preimplantation Genetic Diagnosis
- Egg or Sperm Donation
  - Donor can undergo gene testing to reduce likelihood that they are a carrier
- Adoption

# Prenatal Diagnosis

- PA gene mutation must be known
- Both methods have genetic test accuracy of >99%
- Both methods can provide additional information such as chromosome disorders and sex of the infant
- Chorionic Villus Sampling (CVS)
  - Performed between 10 – 12 weeks of pregnancy
  - 1/200 chance of miscarriage



- Amniocentesis
  - Performed after 15 weeks of pregnancy
  - 1/400 chance of miscarriage
    - some centers quote risk as low as 1/1000

# Preimplantation Genetic Diagnosis

- Requires in vitro fertilization
- Genetic testing performed on 1 – 2 cells from the embryo
- IVF performed at local center and genetic testing performed by one of several centers across the country
  - Genesis Genetics (Detroit, MI) and Reprogenetics (Livingston, NJ)
    - Now both own by parent company Cooper Genomics
    - Pioneers in PGD – offering PGD since 1990s.
    - <http://www.coopergenomics.com/>
  - Natera - Spectrum
    - Offering PGD since 2011
    - <https://www.natera.com/spectrum-pgs-pgd>
- May not be covered by your insurance plan
- Can also obtain information regarding chromosome disorders and sex of infant
- Recommend CVS or amniocentesis for confirmation of PGD results since there is a chance for error

