DNA, Heredity and Drug Resistance

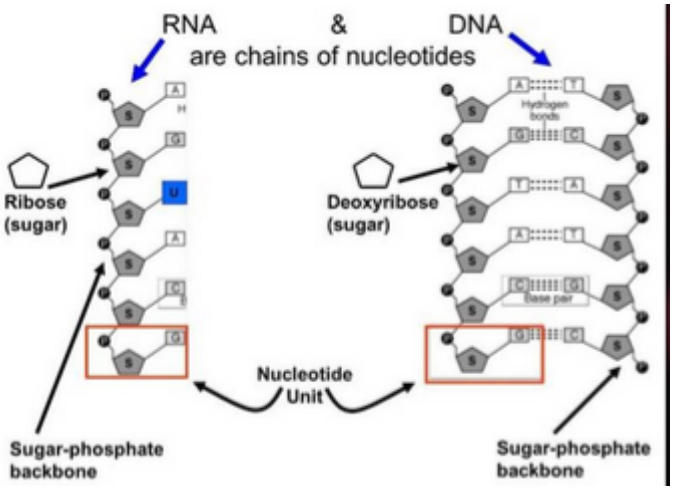
Chromosomes are molecules of DNA that provide the essential genetic code for all living organisms, and it is the code that directs the synthesis of proteins that define each organism's structure and function. Genetic factors contribute to causation of many diseases, such as breast cancer and heart disease. Understanding genetics also enables one to understand the major threats to health as a result of the development of drug resistance.

Learning Outcomes

1. Explain how DNA encodes genetic information and the role of messenger RNA and transfer RNA
2. Explain how DNA directs protein synthesis and roles of DNA and proteins in regulating cell function
3. Demonstrate how to predict the possible genotypes that could occur in an offspring provided one knows the genotype of both parents
4. Explain what a mutation is and give examples of how it might occur

DNA

Deoxyribonucleic acid (DNA) is an extremely long polymer made from units called nucleotides.

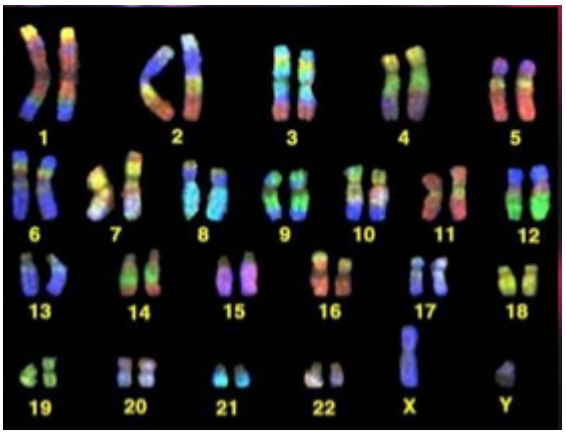


The backbone of each molecule is composed of alternating sugars (the pentagon with "S") and each sugar is also covalently bonded with one of the following nucleotide bases:

- Adenine (A)
- Thymine (T)
- Cystosine (C)
- Guanine (G)
- Uracil (U)

DNA and RNA differ in several ways:

- DNA is double stranded, while RNA is single stranded (though RNA forms loops by hydrogen-bonding to itself)
- DNA contains the sugar deoxyribose while RNA has the sugar ribose
- RNA contains the base uracil in place of thymine



The illustration above shows the 46 chromosomes that contain the human genome. There are 22 homologous pairs and 2 sex chromosomes in humans. Sex chromosomes are XX in females and XY in males. The XY chromosomes are physically different from one another in that the Y chromosome is much shorter, only containing about 9 gene loci that match those on the X chromosome. This means that, except for the sex chromosome, each gene has one chromosome is inherited from one's mother and one from the father. Each chromosome is a single molecule of DNA.

Since Y chromosomes are much shorter than those on the X chromosome, almost all of the alleles on a male's single X chromosome are expressed since there is no alternative dominant allele to mask them. This results in a distinct inheritance patter for traits that are encoded on the X chromosome. For example, color-blindness is a defective allele always carried on the X chromosome.

With the exception of red blood cells (which lost their nucleus) each cell in the human body has all 46 chromosomes, so there are about 3 billion base pairs. The single chromosome of a bacterium is located diffusely in the cytoplasm, but chromosomes of higher species are contained with a membrane-bound nucleus. If we were to take the physical human chromosome and stretch it out, it would be about 5 centimeters, or all 46 would be about 2 meters laid end to end.

One of the helical strands of DNA is the coding strand. The coding strand of a chromosome has thousands of genes along its length (segments which contain genetic code for specific cellular proteins).

Genes and Inheritance

Each chromosome contains thousands of genes. This takes up up only 3-5% of our DNA, while the rest of DNA is considered "non-coding areas." Altogether 23 pairs of chromosomes carry the code for 20k-25k genes. Most genes are transcribed into "messenger RNAs" (mRNA) that provide a template that is used to translate the code into specific proteins. About 100 genes are transcribed into "ribosomal RNAs" and "transfer RNAs" that also play a vital role in the synthesis of proteins.

The sequence of bases in DNA can be though of as "letters" that provide the basis for all genetic code for proteins synthesized by our bodies, which provide the basis of structure of all our cells, enzymes and our traits and characteristics. The production of cellular proteins requires two major processes: transcription followed by translation.

Transcription and Translation

Transcription occurs in eukaryotic cells within the nucleus where DNA is used as a template to create mRNA with the help of RNA Polymerase. The initial transcript has coding segments (exons) and alternating non-coding segments (introns).

Splicing happens in 3 stages: Initiation, elongation, and termination. During initiation the polymerase binds to the promoter region of the template, the DNA "unwinds" and opens. During elongation the polymerase links complimentary bases to the new RNA molecule until it reaches the termination part of the gene and the polymerase and mRNA strand dissociate from DNA.

Before the mRNA leaves the nucleus the inrons are removed from the transcript by a process called RNA splicing. Extra nucleotides are then added to the ends of the transcript; these non-coding "caps" and "tails" protect the mRNA from attack by cellular enzymes and aid in recognition by ribosomes. Helper proteins assemble at these caps and form a splicing machine, or splicisome. It brings exons close together and cuts the intron loop off before disassembling. Then in translation, which occurs in the cytoplasm of the cell at the ribosomes, the information in mRNA is used to create a polypeptide.

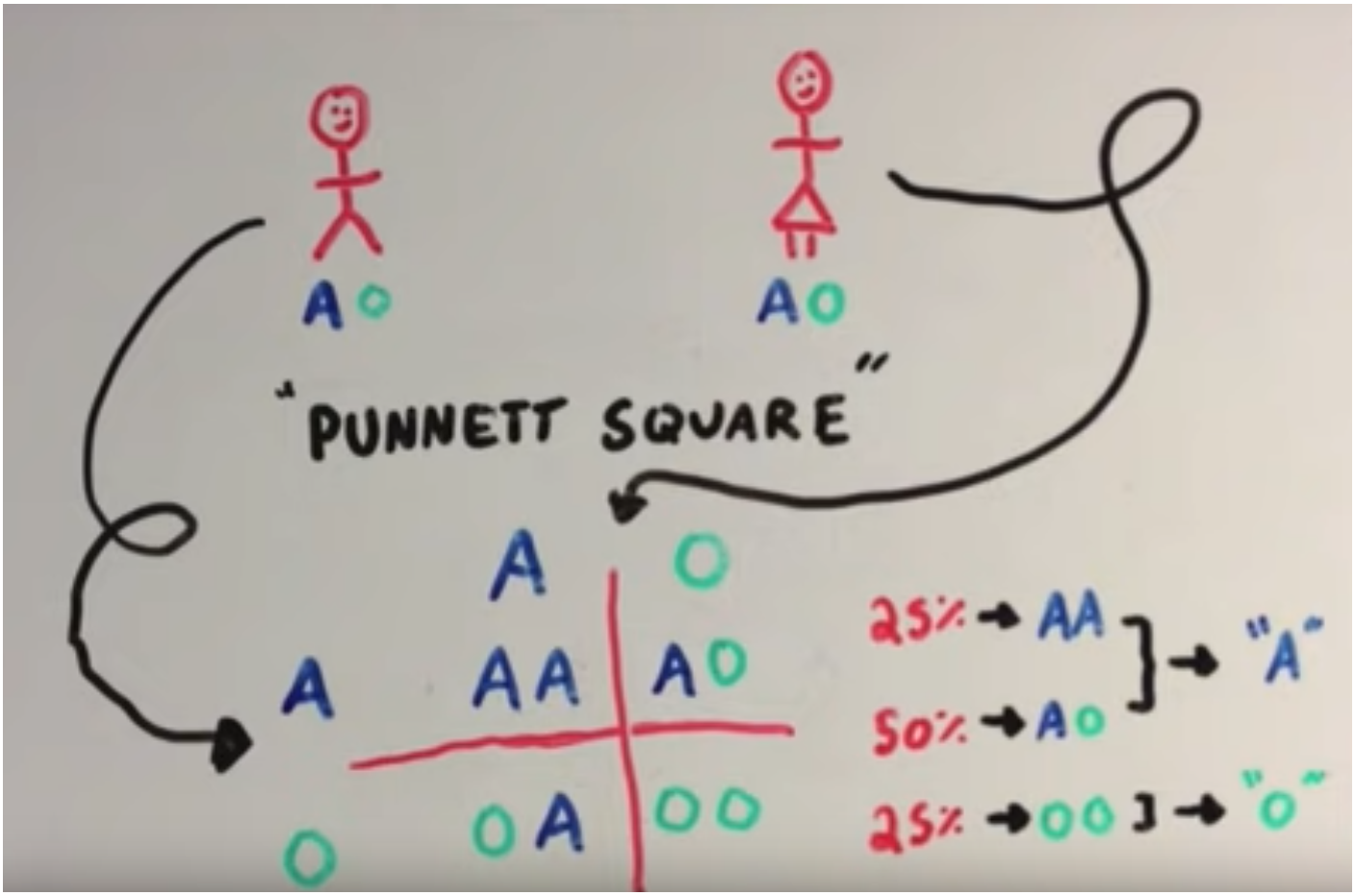
Alleles

The sequence of bases in the human genome is remarkably similar from person to person, but over hundreds of years of evolution mutations have been introduced to the human gene pool. Some are fatal, while others are passed down between generations, and they provide the basis for many variations in phenotype that make us all special. Over time, mutations have created variants of genes that are responsible for differences in the color of our hair, eyes, skin, how fast we can run, height, etc. Mutations introduce gene variants that encode for slightly different proteins, which in

turn influence all aspects of our phenotype. Note though, that an individual's phenotype is not solely the result of their genome, and could be a result of interaction with their environment.

Mutations have introduced gene variants that encode for slightly different proteins, influencing all aspects of our physical characteristics (phenotype). When mutations create variants of a particular gene the alternative gene forms are referred to as alleles. Some genes have a few alleles, while others have many.

Recall also that chromosomes come in pairs with the same gene in both members of a given pair. The two genes together can be referred to as the genotype. Genes are either dominant or recessive, and dominant genes are chosen. Also, different genotypes can create the same phenotype and blending a phenotype can occur with 2 dominant traits. Punnett squares are used to determine gene dominance.



There is an allele that contains genetic code for blood type. In the above A is the dominant trait and O is a regressive trait. A person can have 2 alleles for the same blood type, which is called homozygous, and they would have that blood type. Alternatively, a person could have an A and an O blood type allele, called heterozygous, and the dominant allele would win.

Dominant vs Recessive Inheritance Patterns

Some diseases are inherited, and the pattern of appearance within a family tree will depend on whether the faulty allele is dominant or recessive compared to the normal allele.

For example, the allele for Huntington's disease is dominant. If a man with a heterozygous Huntington's disease gene (Hh) has children with a woman with no Huntington's Disease gene (hh). Their children will have a 50% chance of having the disease. When diseases have dominant alleles it will occur quite frequently in the family tree.

In comparison, cystic fibrosis is caused by a recessive allele, meaning that individuals who are heterozygous for the gene (Cc) will not manifest signs or symptoms. As a result the cystic fibrosis allele can be passed along a family tree with only sporadic appearance of the disease.

Binary Fission

Prokaryotes reproduce by the relatively simple process of binary fission. The single chromosome replicates and each copy attaches to a different location on the cell membrane. The cell membrane then begins to invigilate and eventually separates into two genetically identical bacteria. A similar process is used to replicate mitochondria within eukaryotic cells, but the overall process is more complicated in eukaryotes.

Mitosis

Mitosis is the process by which eukaryotic cells replicate by dividing into two genetically identical cells. It is the process by which new cells are formed in the embryo and after birth, and mitosis also replaces cells that have died or shed. In humans some cells retain the capacity to divide throughout life. Benign and malignant tumors also grow through mitosis.

Meiosis

Meiosis is the specialized process by which gametes (sperm and eggs) are produced for sexual reproduction in the ovaries and testes. Each gamete has 23 chromosomes and joins with the other gamete to create a mixture of genetic information from both parents.

Meiosis produces sperm and eggs with novel mixtures of the original parental chromosomes due to:

Random Assortment - Separation of homologous pairs of maternal and paternal chromosomes results in each gamete randomly getting some maternal chromosomes and some paternal. Random assortment of 23 pairs of chromosomes can produce > 8 million possible combinations.

Crossing Over - After maternal and paternal chromosomes match up as homologous pairs they exchange sections of DNA, this further shuffles the genetic deck.

Epigenetics

Our genome is established when fertilization takes place, and the code remains unchanged throughout our life except for certain mutations that may occur in individual cells.

We now know that many external factors (epigenetics) can affect the timing of the gene expression, the degree expression, and the eventual phenotype that is expressed. These external

factors can produce small modifications to DNA, such as addition or removal acetyl or methyl groups to DNA, or to the histones that control the wrapping and packing of DNA. Attachment of methyl groups appears to reduce transcription or even shut it off. attachment of acetyl groups to histones turns genes on or off.

These biological changes to the genome is known as 'epigenetic factors', changes above the level of the genome. In essence, the DNA in our cells provide the code for making functional proteins, and the epigenetic factors act as switches to turn genes on and off.

Certain genes that predispose an individual to being lean, however the individual might still become fat due to overeating.

Mutations and Drug Resistance

All humans have the same set of genes and the sequence of our base pairs in remarkably similar. However this doesn't mean we have all the same nucleotide sequence in our genome. If this were the case, then all humans would be clones having exactly the same genetic code. While DNA replication is remarkably precise, errors occasionally occur and produce changes in the base sequence.

Mutations are random changes in the sequence of base pairs in DNA and metagens are factors that cause mutations (chemicals or radiation). Mutagens result four patterns of alteration in the base sequence:

- Replacement (substitution) of a single base pair
- Addition of one or more base pairs
- Deletion of one or more base pairs
- Relocation of a segment of base pairs

Addition or deletion of pairs can be substantially disruptive, since mRNA transcript is read in 3 letter codons a shift could throw off the entire sequence.

Mutations can result in:

- Inconsequential changes which do not alter protein product
- Small changes that alter the protein product to some degree
- Small changes that alter phenotype markedly
- Very large changes in base sequence that arise from insertion or deletion of a base pair, or relocation of a segment of nucleotides.

The term ""anti-microbial" is a generall term that encompasses drugs, chemicals, or other substances that kill or slow the growth of microbes. These include:

- Anti-bacterials (antibiotics)

- Anti-virals
- Anti-fungals
- Anti parasitics

Alexander Fleming is widely credited with the discovery of penicillin in 1928, though there are earlier reports of mold killing bacteria. Penicillin became widely used, and with it resistant strains of bacteria emerged. At first these problems were dismissed but by the 1980s it had become a clear problem. Exposure to antibiotics kill susceptible bacteria, but the resistant strains spread their genes. Bacteria can also spread the strand of DNA which contains antibiotic resistance to other bacteria.

To avoid antibiotic resistant bacteria we can focus preventing infection, and appropriate use of antibiotics.

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