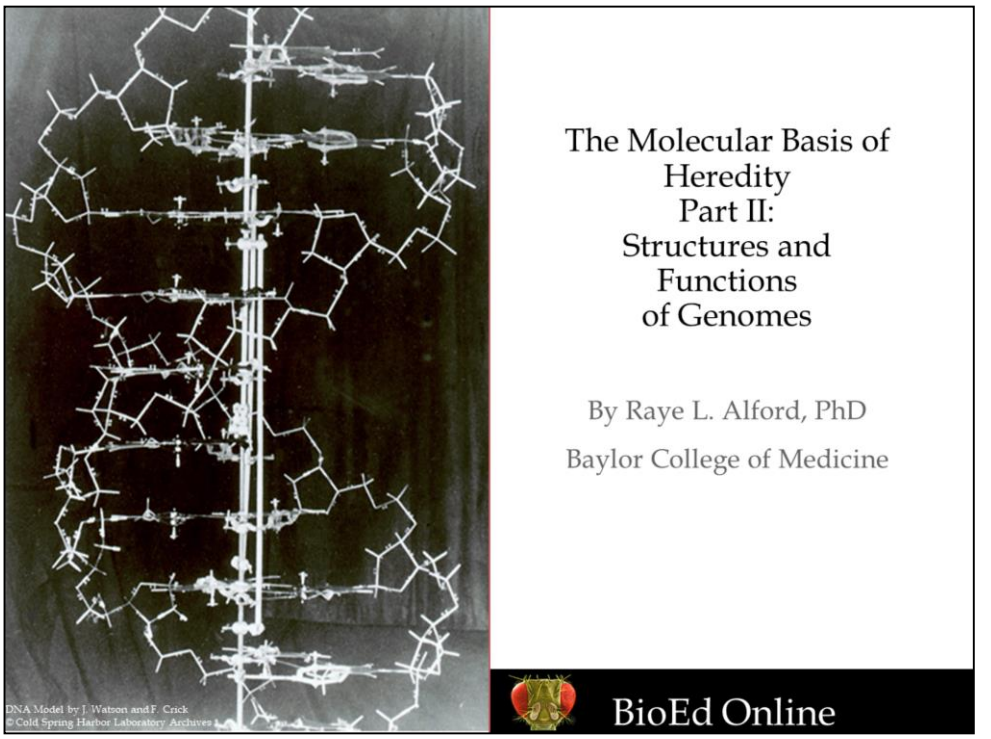


Structures and Functions of Genomes

In this slide set, we will explore the structures and functions of genomes, including the genomes of eukaryotes, prokaryotes and viruses. We also will explore the human genome in depth and learn how changes in the structure or number of chromosomes in the human genome lead to certain genetic disorders.

Illustration:

The image on this slide is a photograph of the model of the DNA molecule built by Drs. James Watson and Francis Crick in 1953. Drs. Watson and Crick used this model to depict their proposed structure for the DNA double helix. The hypothesized structure was derived from X-ray diffraction data produced by Drs. Maurice Wilkins and Rosalind Franklin. The model was constructed from metal scraps obtained from a machine shop.

Drs. Watson and Crick published their proposed DNA structure in the journal, *Nature*, on April 2, 1953 (Volume 171, page 737). For their work, Drs. Watson, Crick and Wilkins were awarded the Nobel Prize in Physiology or Medicine in 1962. Dr. Franklin died before 1962. Since Nobel Prizes are awarded only to living individuals, she could not be honored.

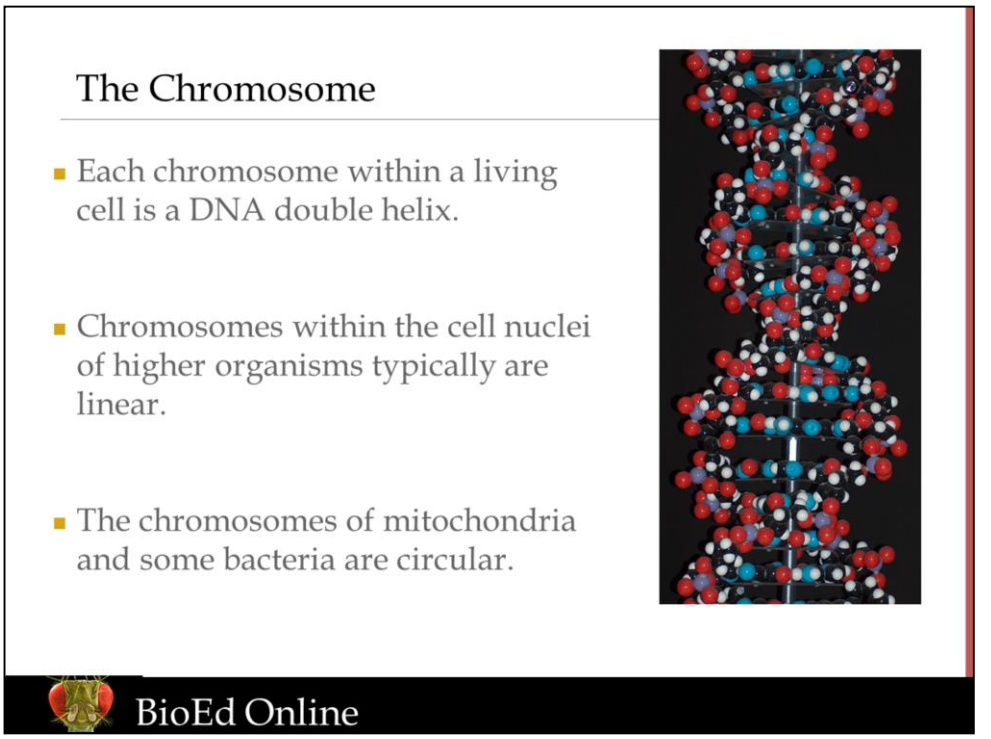
References:

The Chemical Heritage Foundation. (2002.) Chemical Achievers: James Watson, Francis Crick, Maurice Wilkins, and Rosalind Franklin. The Chemical Heritage

Foundation. Retrieved 2-28-2005 from
http://www.chemheritage.org/EducationalServices/chemach/ppb/cwwf.html

Image Reference:

The Dolan DNA Learning Center. (2002). *DNA model by J. Watson and F. Crick*, copyright Cold Spring Harbor Laboratory Archives. Cold Spring Harbor Laboratory, Cold Spring Harbor, New York. Retrieved 06-20-2005 from http://www.dnalc.org/



The Chromosome

Each chromosome of a living cell is a DNA double helix. The atoms that make up DNA are organized into two primary molecular components: bases and pentose sugars with attached phosphate groups. The bases are the key informational components of DNA, the letters of the DNA alphabet. The bases of DNA include adenine (A), cytosine (C), guanine (G), and thymine (T). Each base consists of a nitrogen-containing component called an amine. The side groups attached to the amines differ among the bases. The pentose sugars and phosphate groups serve as the links that connect the bases in a string, or strand, of DNA. When DNA strands form a double-stranded molecule, two strands of DNA are joined together through hydrogen bonds that form between the bases. In the double-stranded DNA molecule, an A base always pairs with a T base and a C base always pairs with a G base. Once joined, the bases are referred to as base pairs.

Embedded within the DNA sequence of each chromosome are the organism's genes. The chromosome can be thought of as the DNA scaffolding within which the genes reside. An organism's set of chromosomes is called its genome**.** Genes are interspersed unevenly along the lengths of most eukaryotic chromosomes. Across the human genome, for example, there are gene-rich regions and gene-poor regions.

The genomes of most eukaryotes are fairly large and often complex. In addition to genes themselves, most eukaryotic genomes also contain a variety of non-coding structural and regulatory elements and introns. Some of the genetic material also

serves as a fossil record, a history book written in biological terms and handed down from generation to generation.

In addition to the DNA inside the cell nucleus, eukaryotic cells have separate genetic material in certain organelles such as mitochondria and, in plants, chloroplasts. In general, organelles, prokaryotes and viruses have greater biological constraints than nuclei on the tolerable sizes of their genomes because of the small genome size that can be incorporated into the organelle, bacterial cell, or viral capsid. As such, the genes of mitochondria, bacteria and viruses typically lack many of the complex non-coding elements commonly found in the nuclear genes of eukaryotes.

References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

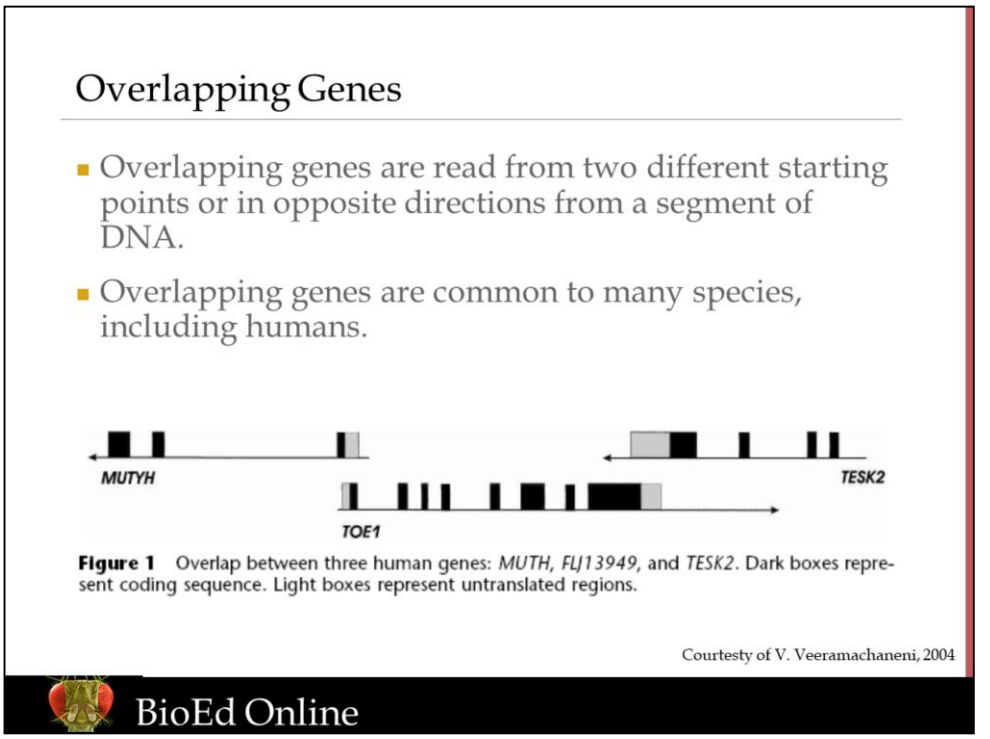
Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

Wells, S. (2003). *The journey of man: A genetic odyssey*. Princeton University Press.

Image Reference:

The image in this slide is a photograph of a space-filled molecular model of a DNA double helix. The model was purchased from Carolina Biological Supply for the exhibit "The Living Genome: Reading the Book of Life" at the Houston Museum of Natural Science (April 2003-December 2004). The photograph was taken by Raye L. Alford.



Overlapping Genes

The genes within an organism's genome are generally not evenly distributed along the length of that organism's DNA. The genes of mitochondria, bacteria and viruses often are immediately adjacent to one another, and frequently overlap. In eukaryotes, there are gene-rich and gene-poor regions within the genome where non-coding spacer regions span the distance between gene-rich areas. Within the gene-rich areas, overlapping genes are common. Overlapping genes are different genes whose nucleotide sequences overlap along a segment of DNA. The nucleotide sequence of overlapping genes is read by RNA polymerases in two or more reading frames or from opposite strands of the DNA molecule, thereby encoding different proteins within the same segment of DNA. Overlapping genes are found throughout nature, from bacteria and viruses to mammals, including humans.

References:

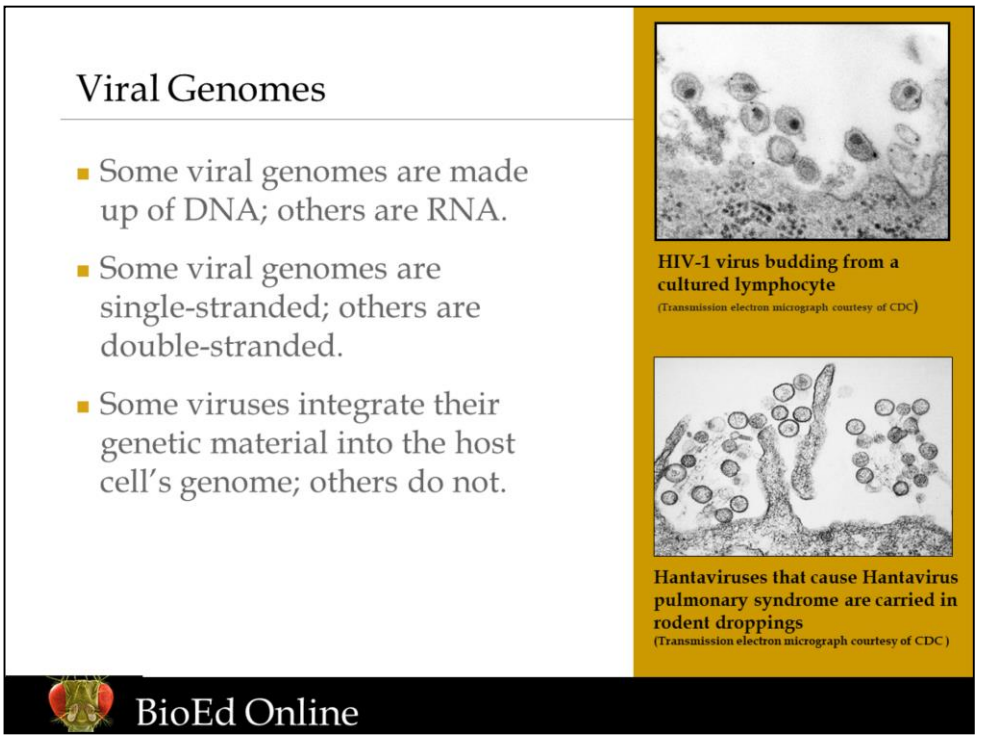
Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine, 6th ed., revised reprint*. Saunders, an imprint of Elsevier.

Image Reference:

Veeramachaneni,V, et al. (2004). Mammalian overlapping genes: The comparative perspective. *Genome Research*, 14 (280-286).



Viral Genomes

Viruses are not cells. They are genetic material encased in a protein coat, called a viral capsid. Some complex viruses also surround themselves with a viral envelope or membrane made up of lipids and glycoproteins. The genetic and biological characteristics of viruses vary widely.

Like bacterial genomes, the genomes of viruses are very small and typically do not contain introns (non-coding sections of DNA). However, despite their small sizes, the genomes of viruses can be quite complex in that the genes of viruses often overlap or lie immediately adjacent to one another. Like bacteria, some viruses encode multicistronic RNA molecules, which are RNA molecules that contain the coding sequences of more than one protein, usually arranged in sequential manner along the length of the RNA. A multicistronic RNA molecule encodes several proteins but is transcribed in a single RNA molecule. When the RNA is translated, one long polypeptide is made that is actually several proteins joined end-to-end. The polypeptide is processed by enzymatic cleavage to liberate the individual proteins from the larger polypeptide.

In addition, many viruses demonstrate temporal regulation of transcription. For example, early and late genes are expressed at different times during the course of a viral infection of a cell.

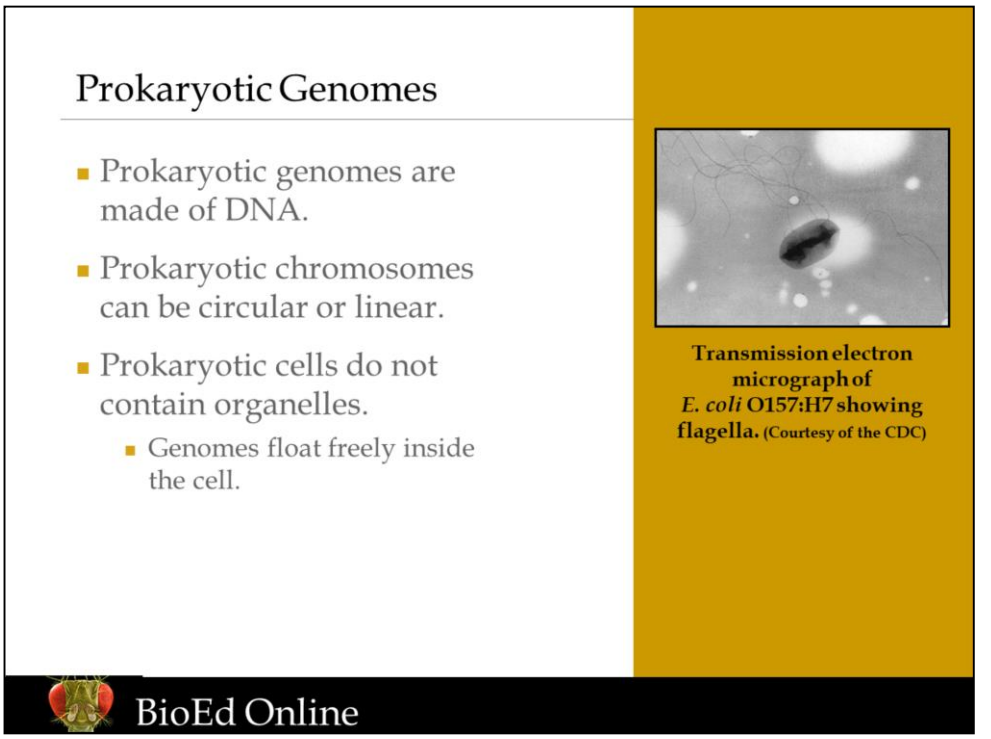
References:

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Image References:

CDC Public Health Image Library. HIV-1 virus (PHIL ID 1840). Retrieved 12-21-2004 from http://phil.cdc.gov/Phil/home.asp

CDC Public Health Image Library. Sin Nombre hanta virus (PHIL ID 1136). Retrieved 078-11-2005 from http://phil.cdc.gov/Phil/home.asp



Prokaryotic Genomes

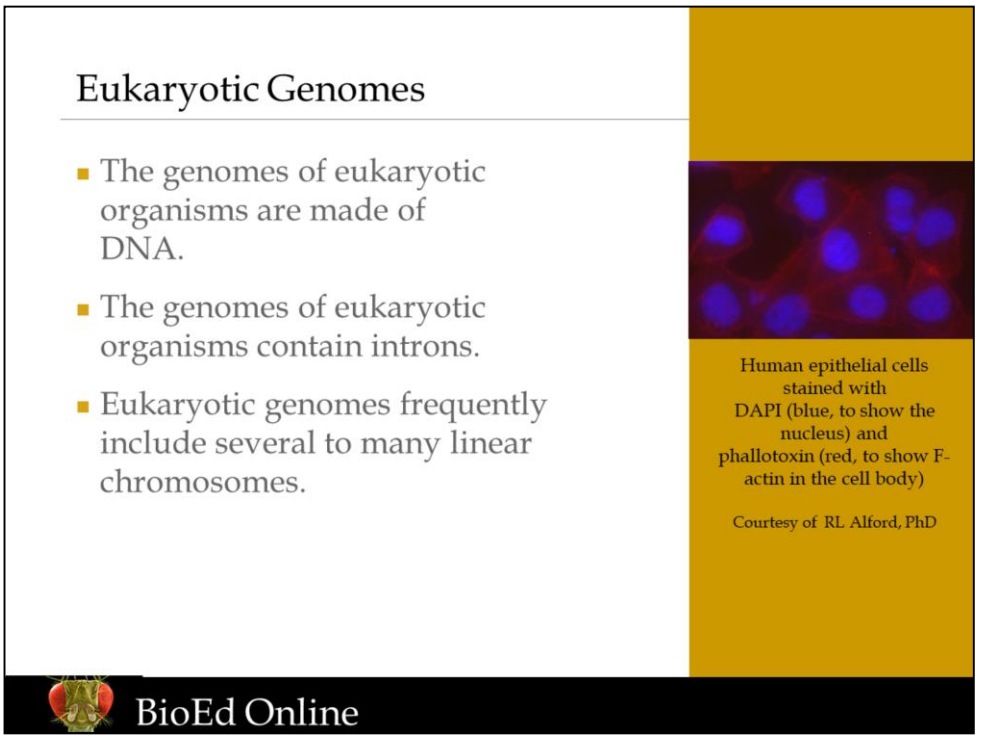
There are two domains of prokaryotes: bacteria and archaea. Members of these groups do not have a cell nucleus or organelles bounded by membranes. Although there are exceptions, bacterial genomes do not typically have introns. On the other hand, the genes of organisms in the domain Archaea are sometimes a bit more complex and can have introns and other structural and regulatory elements similar to those found in eukaryotes. Prokaryotic genome sizes can vary widely. Some may be as small as a a few hundred thousand base pairs or as large as several million base pairs.

References:

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Image References:

CDC Public Health Image Library (Elizabeth H. White, photographer). *E. coli* o157:H7 (PHIL ID 188). Retrieved 12-21-2004 from http://phil.cdc.gov/Phil/home.asp



Eukaryotic Genomes

Like the extensive diversity in life forms within the eukaryote domain, the genomes of eukaryotes also vary greatly in size and composition. For example, the yeast *Saccharomyces cerevisiae* genome is ~12.5 million base pairs in size, while the fern *Psilotum nudum* genome is ~250 billion base pairs in size. Further, most eukaryotic genomes encode complex genetic elements that preserve and maintain the structure of the genome, and regulate the transcription (expression) of eukaryotic genes.

Genomes of eukaryotes contain regions known as introns. Introns are non-coding segments of DNA, of variable size, that separate the coding segments, or exons, of the genes of eukaryotic organisms. During RNA processing, the introns are removed from RNA molecules in a complex process called splicing. In addition, the genetic material of eukaryotes is organized into one or more linear structures called chromosomes.

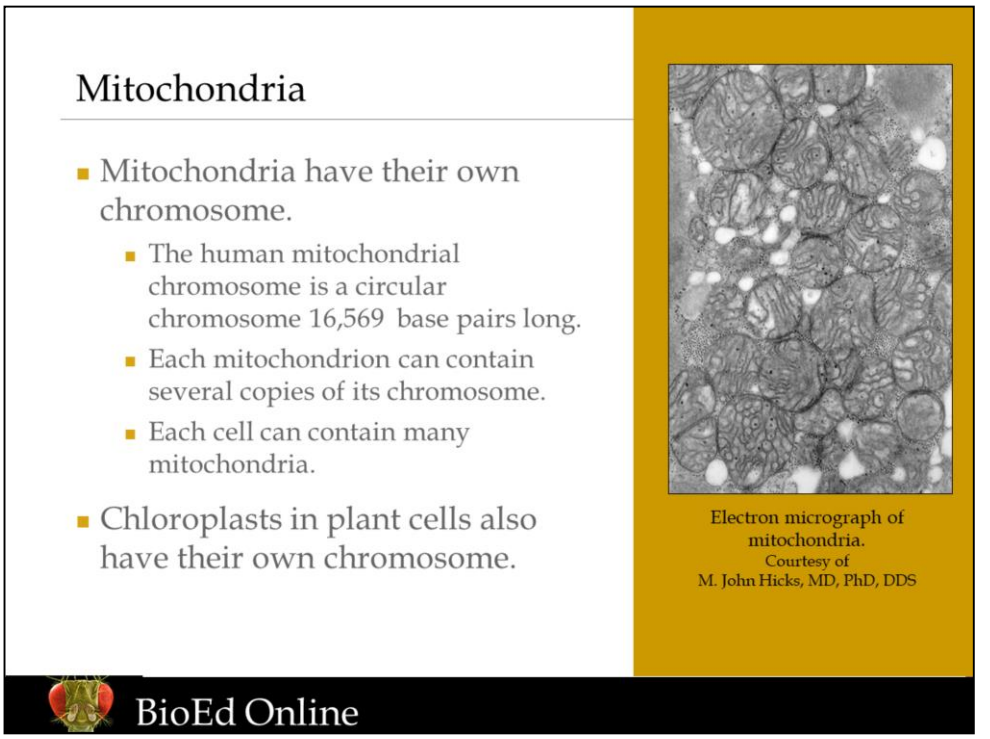
References:

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Kimball, J.W. (2005). *Kimball's Biology Pages*. Retrieved 07-11-2005 from http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/G/GenomeSizes.html

Image Reference:

Alford, RL. (2004). Human epithelial cells. The Bobby R. Alford Department of Otorhinolaryngology and Communicative Sciences, Baylor College of Medicine.



Mitochondria

Mitochondria are the power plants of cells: they provide cells with the chemical energy needed to perform the metabolic tasks associated with life. It is widely believed that mitochondria are the remnants of ancient energy-producing symbiotic bacterial cells that were assimilated into eukaryotic cells. Similarly, chloroplasts in green plants are believed to be remnants of photosynthetic bacteria.

The mitochondrial chromosome encodes 13 proteins, 2 rRNAs and 22 tRNAs. Mitochondria obtain many of their proteins from genes encoded in the nuclear genomes of cells. Nuclear encoded proteins are imported into the mitochondria after translation.

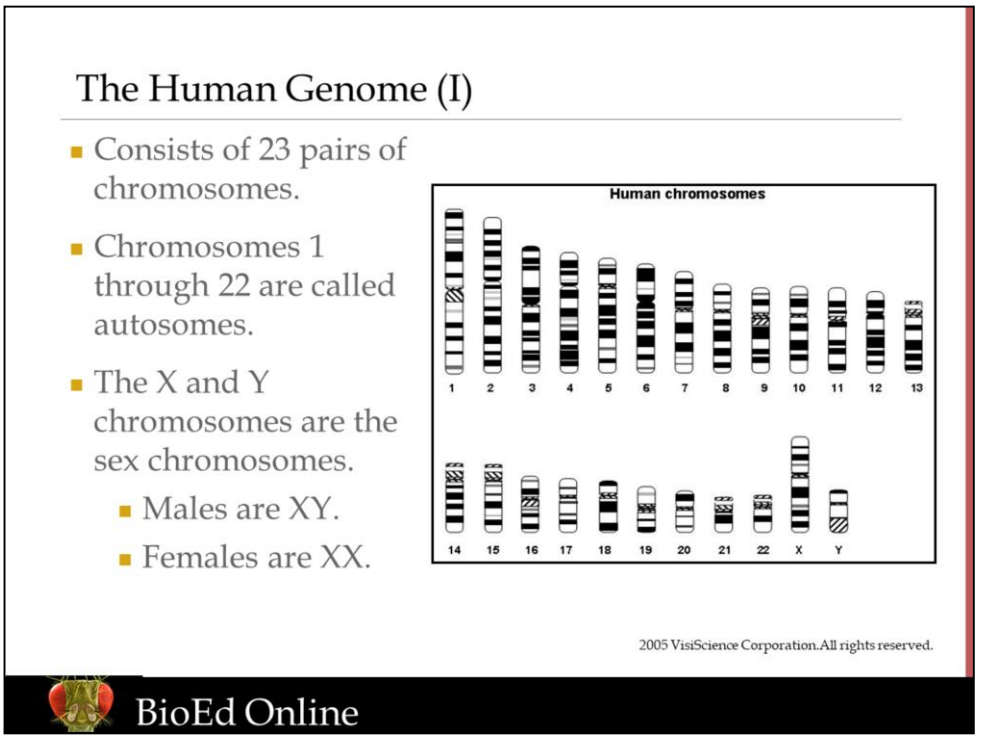
References:

Brandon, M. C., Lott, M. T., Nguyen, K. C., Spolim, S., Navathe, S. B., Baldi, P. & Wallace, D. C. (2004). MITOMAP: a human mitochondrial genome database--2004 update. *Nucleic Acids Research* 33 (Database Issue):D611-613, 2005. URL: http://www.mitomap.org.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Image Reference:

Hicks. J.M. Electron micrograph of mitochondria. Director of Surgical and Ultrastructual Pathology, Texas Children's Hospital and Department of Pathology, Baylor College of Medicine.



The Human Genome (I)

The haploid human genome consists of 23 different chromosomes. The diploid human genome consists of 23 pairs of chromosomes. One of each pair of chromosomes is inherited from each parent. For example, each of us carries two copies of chromosome 1: one from our mother, the other from our father. The first 22 pairs of human chromosomes are called autosomes. The 23rd pair of human chromosomes determine gender. Human females carry two X chromosomes: one inherited from the mother, one from the father. Human males carry one X chromosome and one Y chromosome. Males inherit their X chromosome from their mothers and their Y chromosome from their fathers.

In addition to the nucleus, the mitochondria of human cells also carry one or more copies of a small, circular DNA molecule. The mitochondrial chromosomes are inherited through the egg. Sperm do not contribute mitochondria to embryos. As a result, genetic diseases caused by mutations in genes on the mitochondrial chromosome are passed through the maternal lineage, from mothers to all their children. Children of fathers affected by mitochondrially transmitted genetic disorders are not at risk for inheriting the diseases. However, because mitochondria also import proteins encoded by nuclear genes, the inheritance of diseases of the mitochondria do not always follow this pattern. Examples of mitochondrially transmitted genetic diseases include MERFF (myoclonic epilepsy with ragged red [muscle] fibers), LHON (Leber hereditary optic neuropathy), a form of dementia called MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), MIDD (maternally inherited diabetes and deafness) syndrome, and genetic susceptibility to aminoglycoside ototoxicity (aminoglycosides are a group of antibiotics that include

gentamicin, streptomycin, tobramycin, kanamycin, neomycin, amikacin, and others). In general, observable effects of mitochondrial mutations are believed to be a reflection of how sensitive particular tissues (central nervous system, skeletal muscles, heart, kidney, and liver) are to energy metabolism.

References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

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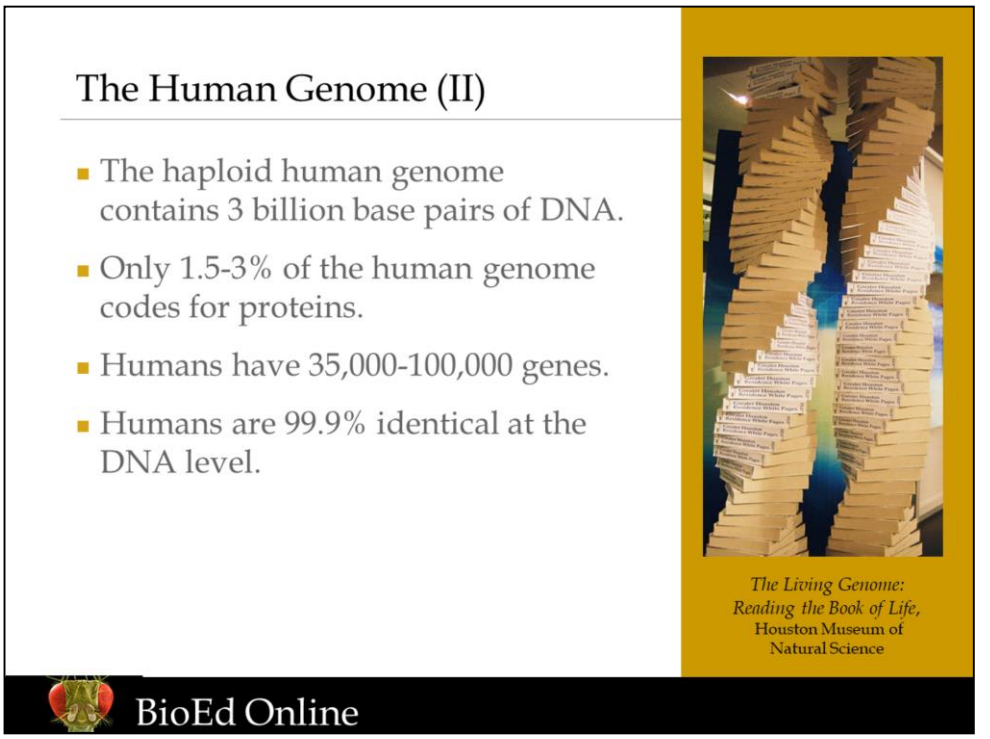


The Human Genome (II)

The haploid human genome (23 chromosomes) contains ~3 billion base pairs of DNA. The diploid human genome (23 pairs of chromosomes) contains ~6 billion base pairs of DNA.

Only 1.5-3% of the human genome codes for proteins. It is believed that much of the rest of the human genome serves regulatory and structural functions. The exact number of genes carried by humans is not yet known, but is likely to be somewhere between 35,000 and 100,000.

Humans are more than 99% identical to each other at the DNA level. Only identical twins possess identical genomic DNA. It is the <1% variability in our DNA that makes each of us unique. In recent years, the variability in human DNA has been used as a fossil record to study human history and trace the migration of humans out of Africa as we spread across and populated the Earth. What we have learned from our DNA is clear: every human on the planet today is related to every other human. We all are descended from the same trunk of the human family tree: brothers and sisters separated only by time and geography.

The photograph in this slide is of twin stacks containing a total of eighty-nine Houston telephone books, spiraled to mimic the shape of the DNA double helix. Together the two stacks of telephone books contain approximately the same number of characters as the haploid human genome (23 chromosomes) contains base pairs.

References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

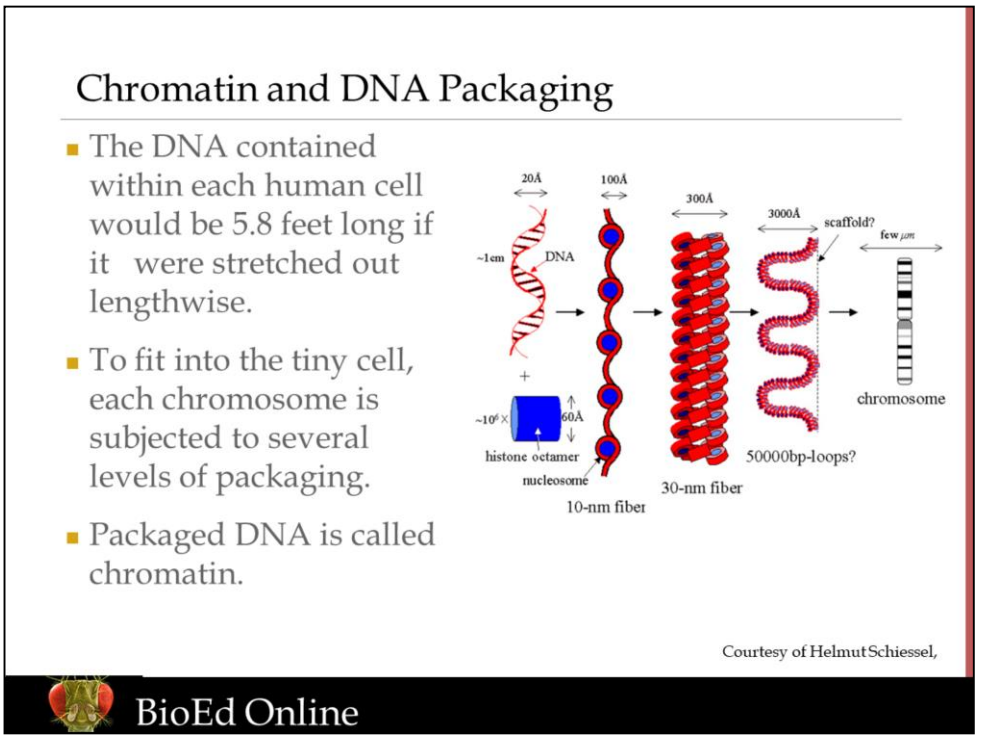
Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

Wells, S. (2003). *The journey of man: A genetic odyssey*. Princeton University Press.

Image Reference:

This telephone book stack was constructed as a part of "The Living Genome: Reading the Book of Life" exhibit at the Houston Museum of Natural Science (April 2003-December 2004). This photograph was taken by Ella Moore.



Chromatin and DNA Packaging

If the DNA contained within a single human cell were laid out lengthwise, with each chromosome arranged end to end, the DNA would be 5.8 feet, or almost two meters, long. However, it would be very thin, only ~24 angstroms wide. It would take 26 million DNA molecules arranged side by side to measure 1 inch wide.

To fit into the microscopic nucleus of a human cell, the length of DNA must be packaged very precisely. In the first level of packaging, the DNA double helix is wound tightly around proteins called histones. Histones are made up of eight component proteins and often are referred to as histone octamers. The packaging of DNA around histones gives DNA a beads-on-a-string appearance. Histone-packaged DNA results in a 10 nanometer (nm) fiber: remember, the native DNA double helix is only 24 angstroms wide, so this 100 angstrom, or 10 nm, fiber is four times wider, and quite a bit shorter than the native double helix would be.

The histone-packaged DNA is further wound into 30 nm fibers. These fibers are then packaged into loops of DNA believed to be anchored to the cytoskeleton within the nucleus of the cell. DNA that is completely packaged is referred to as chromatin.

References:

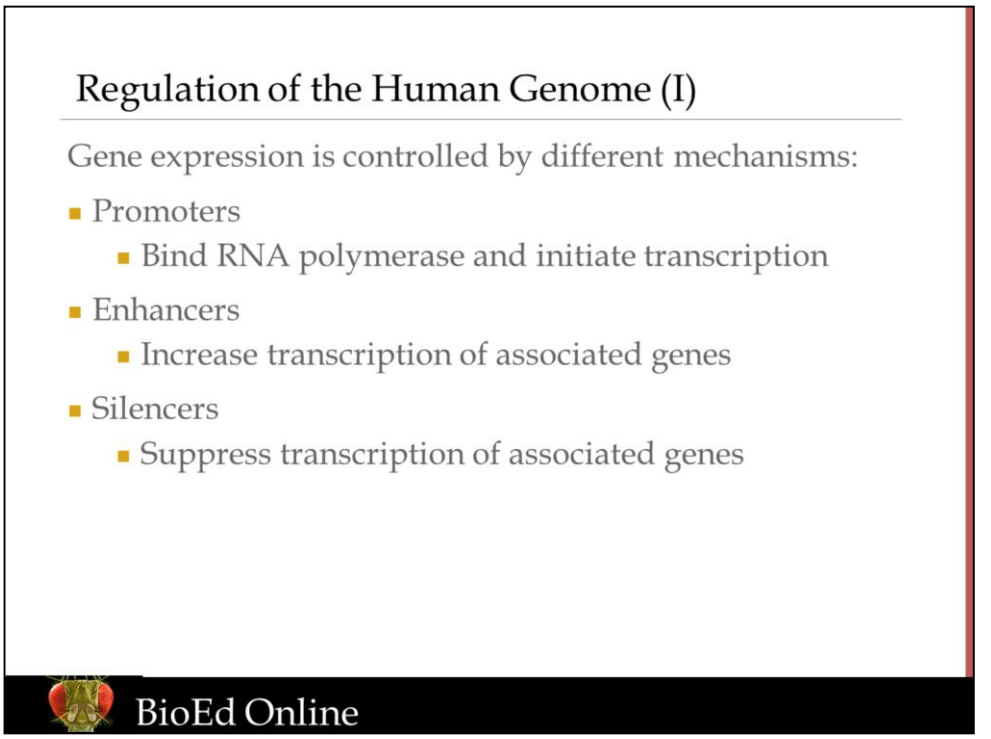
Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine, 6th ed., revised reprint*. Saunders, an imprint of Elsevier.

Image References:

Schiessel, H. (2003). *The physics of chromatin*. Retrieved 07-22-2005 from http://www.lorentz.leidenuniv.nl/~schiessel/chromatin.html.



Regulation of the Human Genome (I)

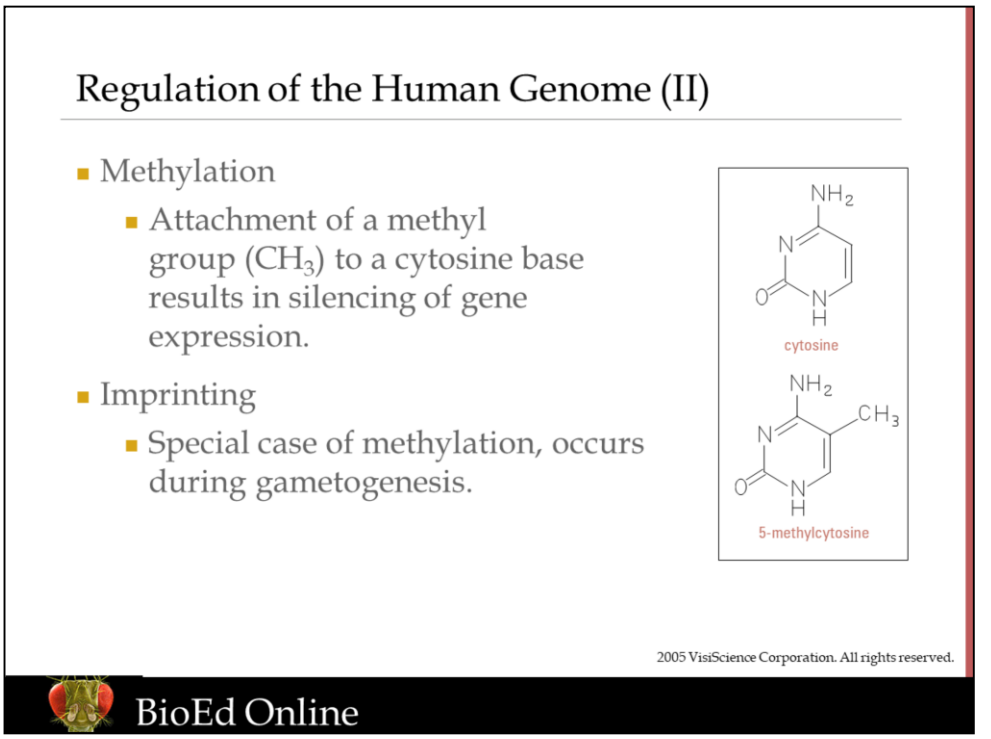
The expression of genes within the human genome is controlled by a number of different mechanisms. Promoters, enhancers and silencers are segments of DNA that regulate the rate and amount of transcription, or expression, of nearby genes. Transcription is the process of synthesizing RNA as a messenger in order to implement the instructions encoded within DNA. Promoters are generally located immediately upstream from the first exon (coding segment of DNA) of a gene. Enhancers are genetic elements that increase transcription of associated genes. Silencers are genetic elements that suppress transcription of associated genes. Enhancers and silencers can be located some distance away from a promoter, may be upstream or downstream of the promoter on which they act, and can be effective even at considerable genetic distances.

References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.



Regulation of the Human Genome (II)

Methylation is another mechanism of gene regulation. In methylation, portions of the DNA molecule, particularly regions of the DNA that control transcription are chemically modified through the action of enzymes called DNA methyltransferases. DNA methyltransferases attach a methyl group (CH_3) to the 5^{th} position carbon of cytosine bases, typically when cytosines occur in the context of C-G dinucleotides, sometimes referred to as CpG islands. Methylation of DNA usually results in the silencing or suppression of gene expression. Alternatively, a lack of methylation is usually associated with an active state of gene expression. Methylation is crucial for the regulation of gene expression and control of cellular growth throughout life, from embryonic development to adulthood. Methylation also is crucial for X-chromosome inactivation and imprinting.

Imprinting is a form of gene silencing whereby individual genes or groups of genes are methylated during gametogenesis to impart parent of origin effects on gene expression. For example, if a gene is maternally imprinted, (that is silenced in the maternal copy during female gametogenesis) only the paternal copy of the gene is expressed in the child. Paternal imprinting of genes also occurs. During gametogenesis, parental imprints are erased and reset in a manner consistent with whether the gametogenesis is occurring in a male or a female. A number of human genetic diseases occur because of mutations in imprinted genes or in the genetic control sequences responsible for setting, resetting or controlling imprinted regions. Such diseases include Angelman syndrome and Prader-Willi syndrome, which occur because of mutations in imprinted genes or errors in imprinting of genes on chromosome 15. These disorders also can be caused when errors in mitosis or meiosis produce a child who inherits both copies of his or her chromosome 15 from a single parent, resulting in inheritance of only imprinted copies of the genes involved and no active copy. This phenomenon is called uniparental disomy, or UPD.

References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics:*

Origins, peoples & disease. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

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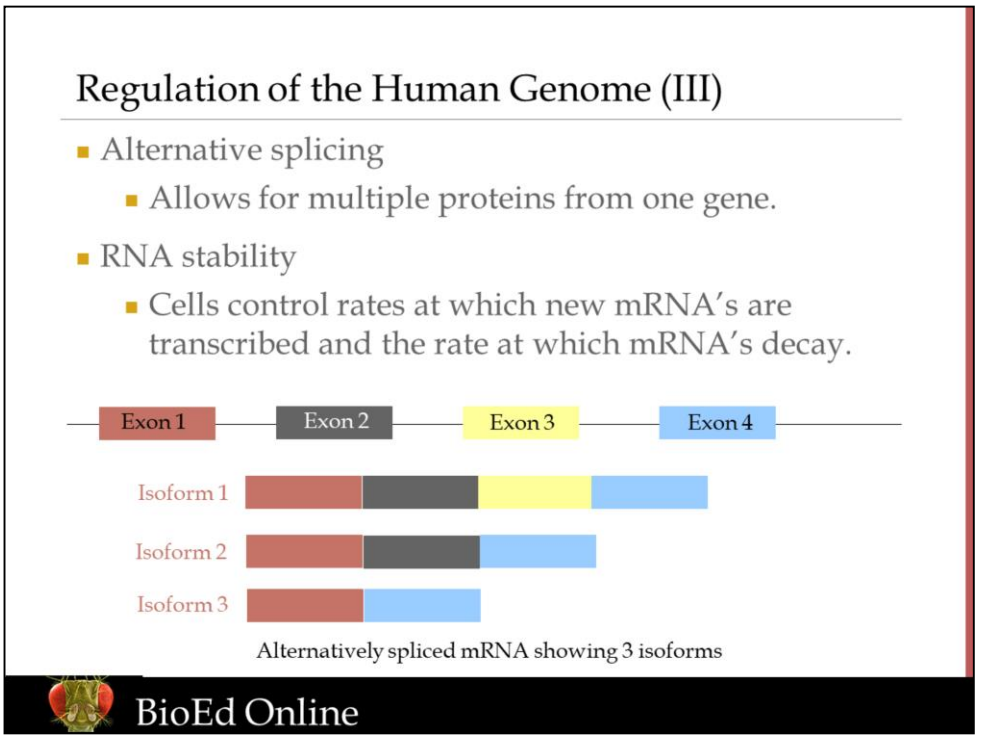


Regulation of the Human Genome (III)

Another type of genetic regulation is exerted at the level of RNA processing through a mechanism called alternative splicing. In alternative splicing, certain exons (coding segments of DNA) of a gene may be alternately included in the final mRNA product. In this way, inclusion of particular exons only in certain tissues or only at certain times during development permits cells to modify the performance characteristics of a particular protein, thereby altering the function or effect of a protein in a cell or tissue. As shown in the graphic, this precursor RNA is alternatively spliced into 3 different isoforms. Isoform 1 contains all 4 exons; isoform 2 contains only exons 1, 2, and 4; and, isoform 3 contains only exons 1 and 4.

Various factors, including DNA sequences, also contribute to the rate of production and stability of mRNAs. By controlling the rate at which new mRNAs are transcribed from a particular gene and the decay kinetics of a mRNA (the rate at which a mRNA is degraded within a cell), cells exert control over the amount of protein that is made from an mRNA, thereby influencing the level of particular proteins within cells and tissues. Different mRNAs have different decay kinetics, meaning that some are degraded very quickly and others are degraded much more slowly. For example, the mRNAs of many cellular growth factors and transcription factors are degraded very quickly, resulting in tight control of the temporal aspects of their cellular signaling properties. On the other hand, mRNAs that encode enzymes can be much longer lived.

References:

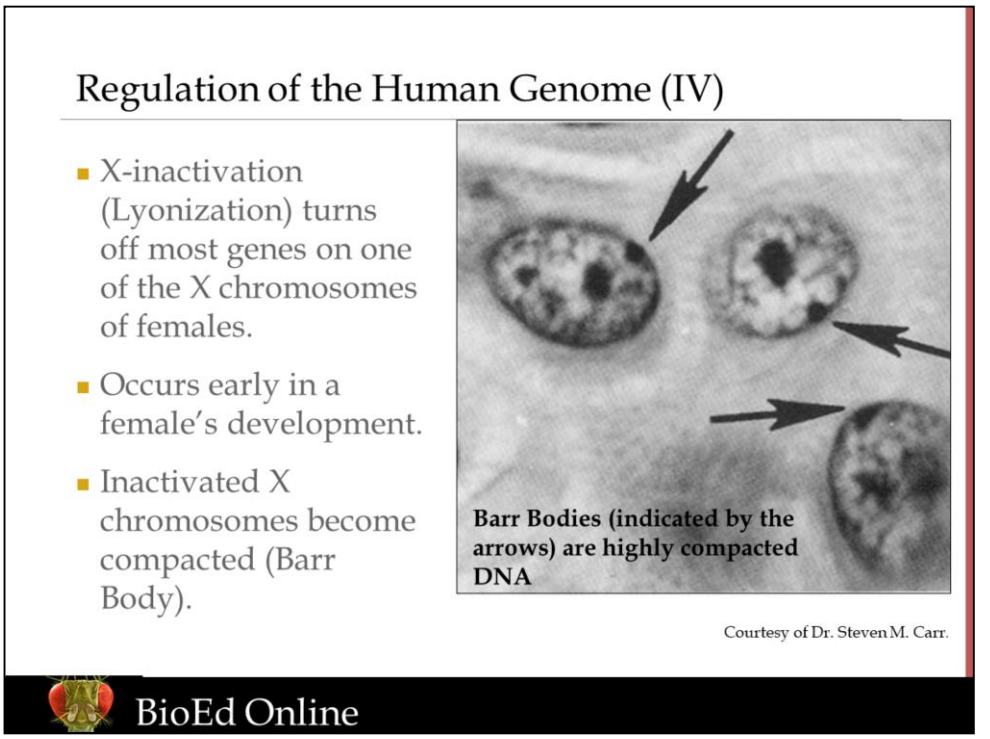
Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics:*

Origins, peoples & disease. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier

Wang, Y.,et al. (2002). Precision and functional specificity in mRNA decay. *Proceedings of the National Academy of Sciences*, 99(9):5860-5865.



Regulation of the Human Genome (IV)

During X-inactivation, most genes on one of the X chromosomes of a female are inactivated in a mechanism that provides dosage compensation to equalize the level of gene expression of most X-linked genes in females to that of males who have only one X chromosome. This process, often called Lyonization, results in the formation of a Barr body, the highly compacted, inactive X chromosome. In the photograph, Barr bodies are shown by arrows. The form of DNA in the inactive X-chromosome is called heterochromatin.

In human females, one X chromosome or the other is inactivated in each cell early in development. As a result, some human female cells have one X chromosome active, while the rest of the cells have the other X chromosome active. Typically, X-inactivation is random, or near random, meaning that roughly half of a female's cells express the genes of one X chromosome and the other half of her cells express genes from the other X chromosome. However, in some females, X-inactivation is not random, but skewed. In cases of nonrandom, or skewed X-inactivation, all or most cells of a female express X-linked genes from a single X chromosome. In reality, nonrandom X-inactivation may be less representative of the process of X-inactivation than of reduced survival of cells with a particular X chromosome inactivated, making it appear that X-inactivation was nonrandom.

In some cases, females who carry X-linked genetic diseases can be affected by those diseases, if X-inactivation is not random. For example, if a structural abnormality disrupts the pattern of X-inactivation, then most or all of a female's cells will express genes from a single X chromosome. If there are genes that are disrupted by the

structural abnormality, and those genes cause a disorder, the female can show symptoms of the disorder. For many X-linked disorders, females will show mild to moderate symptoms. This milder manifestation of an X-linked disorder in females may be related, in part, to the fact that most females have, in addition to a large number of cells expressing the abnormal gene, a large number of cells expressing the normal gene. Symptoms remain milder than those seen in affected males who carry no normal copy of the gene because they carry only a single X chromosome.

Some genes on the inactive X chromosome escape inactivation and remain active in females. These genes are believed to be responsible for many traits of normal females. The lack of these genes in females missing all or parts of a second X chromosome, as occurs in many cases of Turner syndrome, are thought to be associated with many of the clinical features of the syndrome.

References:

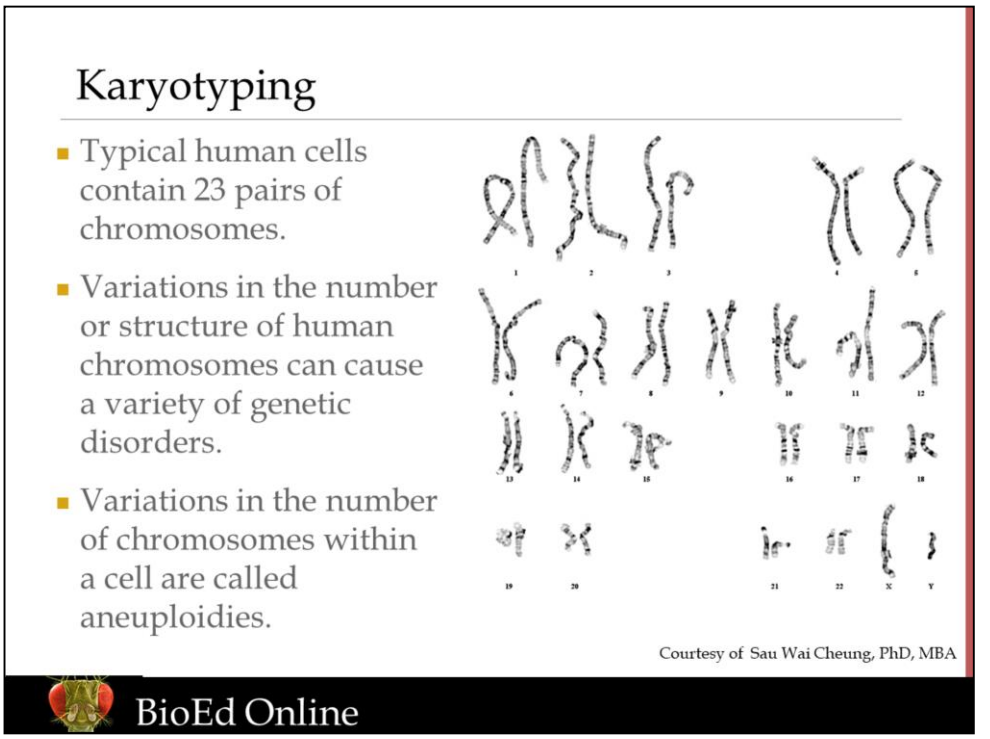
Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier

Image Reference:

This photograph is taken from the web site of Dr. Steven M. Carr at the Genetics, Evolution, and Molecular Systematics Laboratory, Department of Biology, Memorial University of Newfoundland, St. John's NF, Canada (http://www.mun.ca/biology/scarr/Directory.htm; http://www.mun.ca/biology/scarr/Barr_Bodies.jpg)



Karyotyping

The image in the slide shows the karyotype from a normal human male (note one X and one Y chromosome). Karyotyping is a laboratory technique which allows microscopic visualization of the number and gross structure of the chromosomes within a cell. This karyotype would be abbreviated 46,XY: 46 for the number of chromosomes and XY for the sex chromosome makeup. If this karyotype were from a normal female, there would be two X chromosomes and no Y chromosome. A normal female would be designated 46,XX.

The signs and symptoms of genetic disorders caused by disruptions in the structure or number of chromosomes in the human genome are extremely variable and typically related to the particular chromosomal abnormality involved. In the case of structural rearrangements of chromosomes, most effects are likely due to disrupted expression or regulation of genes at or near the sites of structural rearrangements. In the case of chromosomal aneuploidies (the condition of having more or less than the normal number of chromosomes), alteration of the normal copy number of genes on the involved chromosome are likely the cause of most abnormalities.

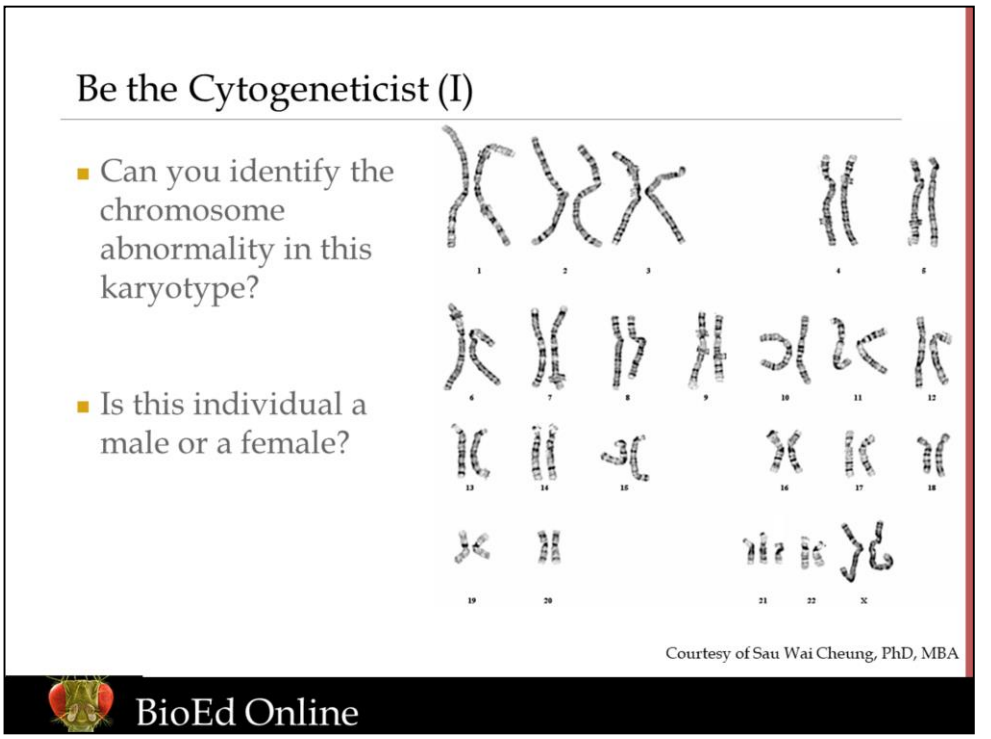
References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

Image Reference:

Karyotype provided by Sau Wai Cheung, PhD, MBA, Director of the Kleberg Cytogenetics Laboratory, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, USA.



Be the Cytogeneticist (I)

This individual is a female: note the two X chromosomes and the lack of a Y chromosome. This individual carries three copies of chromosome 21. This chromosomal aneuploidy is called Trisomy 21 syndrome, or Down syndrome. Down syndrome is caused by the presence of an extra copy of chromosome 21. This karyotype would be abbreviated 47,XX,+21.

Individuals with Down syndrome can have a variety of abnormalities including mental retardation, speckling of the irises of the eyes, poor muscle tone (hypotonia), characteristic appearance of the face, cardiac abnormalities, loose skin in the back of the neck, and fine, soft hair. Individuals with Down syndrome also are prone to leukemia, premature aging, and Alzheimer's disease.

Down syndrome affects approximately 1 in every 800 live births. Approximately 75% of Down syndrome fetuses spontaneously abort during gestation. Of babies born with Down syndrome, most carry an extra chromosome 21. The extra chromosome most often occurs as the result of an error in cell division during meiosis, the process during which germ cell precursors divide to create eggs and sperm. During meiosis, there are occasional sorting errors wherein the chromosomes do not get properly assorted to the dividing cells. This can result in a sperm or egg with an improper number of chromosomes. Most of the meiotic non-disjunction events that result in Down syndrome occur during maternal meiosis.

In some cases of Down syndrome, however, the extra copy of chromosome 21 is

attached to the end of another chromosome. Chromosomal rearrangements in which all or a portion of one chromosome becomes attached to another chromosome are called translocations. Translocation cases account for approximately 3% of Down syndrome cases. The source of the extra chromosomal material, whether it is derived from a parental translocation chromosome or as the result of a meiotic non-disjunction event, is important for estimating the chance of another child with Down syndrome being born in a family.

The risk for a woman to have a child with Down syndrome rises with age, and increases significantly after age 35, a phenomenon called maternal age effect. Despite this maternal age effect, most babies with Down syndrome are born to women under 35, because more babies are born to women under 35 overall, than are born to women over 35.

References:

National Association for Down Syndrome. (2005). Retrieved 07-11-2005 from http://www.nads.org/pages/facts.htm.

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

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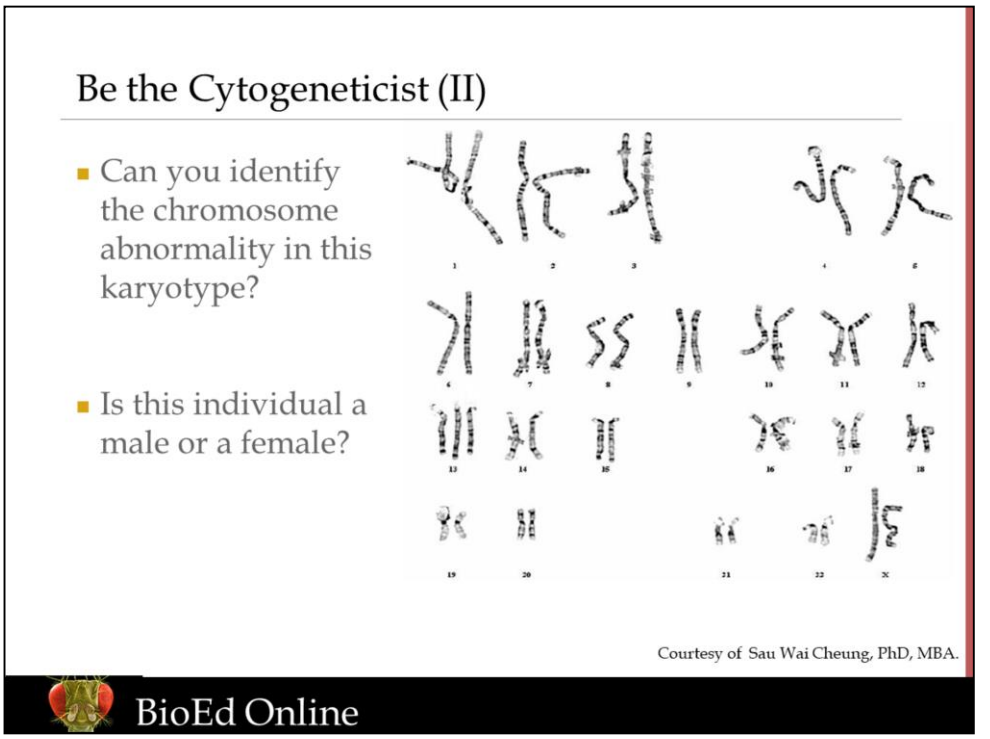

Be the Cytogeneticist (II)

This individual is a female: note the two X chromosomes and the lack of a Y chromosome. This individual carries three copies of chromosome 13, a chromosomal aneuploidy called Trisomy 13 syndrome or Patau syndrome. The syndrome is caused by the presence of an extra copy of chromosome 13. This karyotype would be abbreviated 47,XX,+13.

Babies with Trisomy 13 can have a variety of congenital abnormalities including incomplete development of the forebrain, olfactory and optic nerves, seizures, apnea, mental retardation, deafness, microcephaly (small head), sloping forehead, cleft lip and/or cleft palate, skin abnormalities, congenital heart defects, additional fingers and toes, prominence of the heels of the feet, thin or missing ribs, and other abnormalities.

Trisomy 13 syndrome occurs in approximately 1 of every 5,000 live births. More than 95% of fetuses that are trisomic for chromosome 13 spontaneously abort during gestation. Most babies with Trisomy 13 that are born alive die within the first few months of life.

About 20% of cases of Trisomy 13 are caused by a translocation, that is when all or a portion of chromosome 13 is attached to another chromosome (often chromosome 14). More often, the extra copy of chromosome 13 is the result of an error in cell division during meiosis, the process during which germ cell precursors divide to create eggs and sperm. During meiosis, there are occasional sorting errors wherein the chromosomes do not get properly assorted to the dividing cells. This can result in a

sperm or egg with an improper number of chromosomes. Most of the meiotic non-disjunction events that result in Trisomy 13 syndrome occur during maternal meiosis. The source of the extra chromosomal material, whether it is derived from a parental translocation chromosome or as the result of a meiotic non-disjunction event, is important for estimating the chance of another child with Trisomy 13 syndrome being born into a family.

References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier

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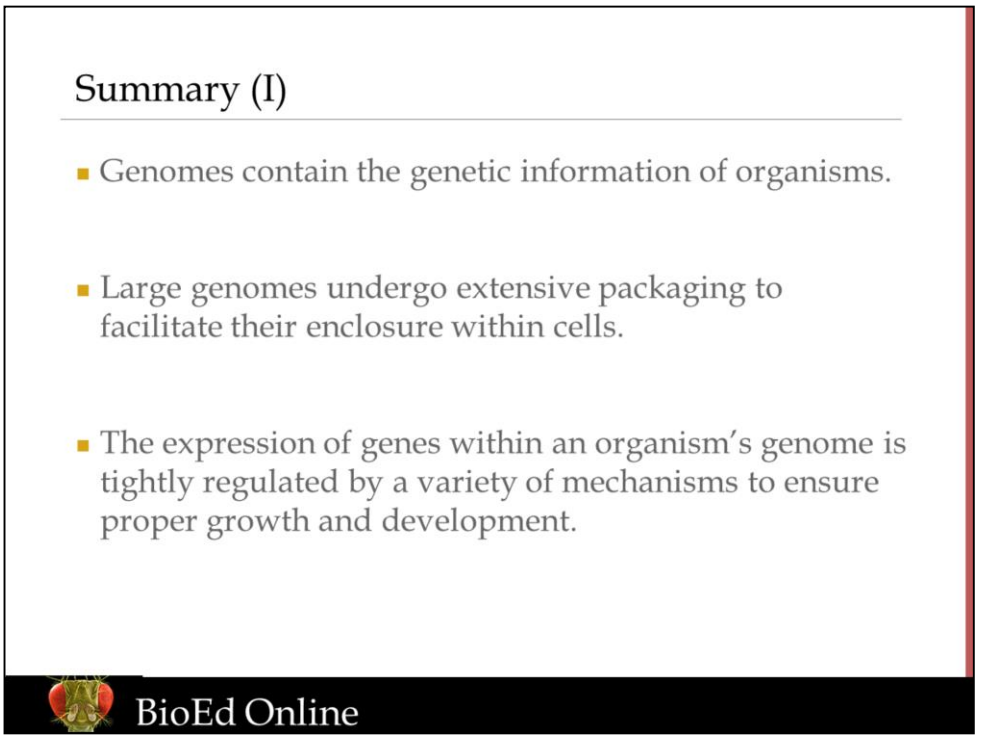


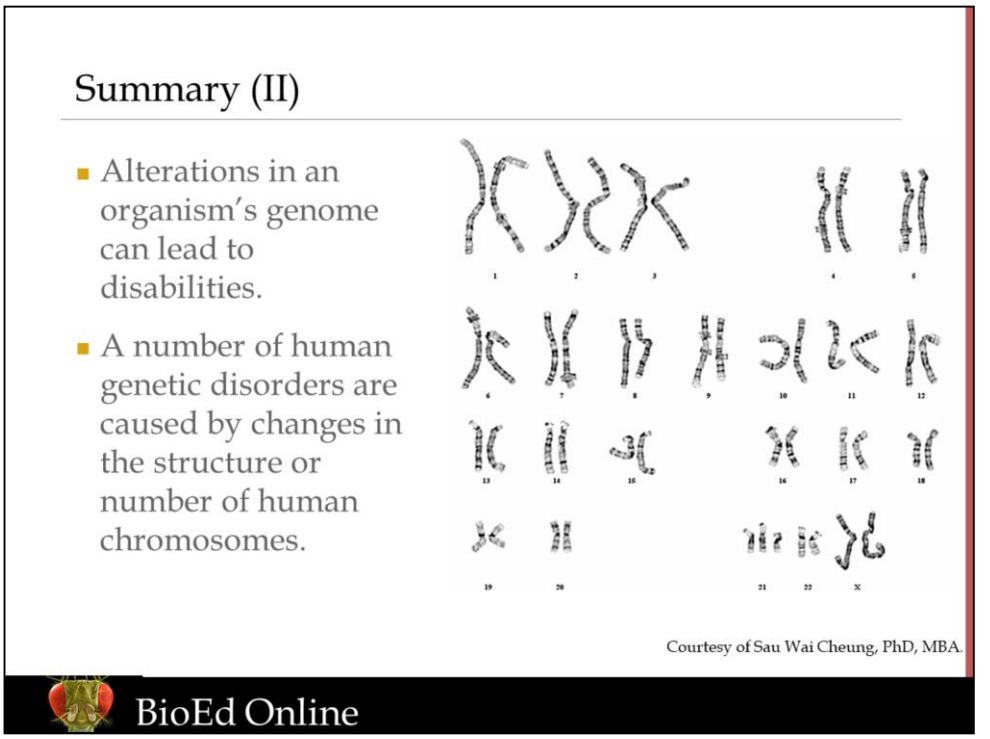
References:

Jobling, M.A., Hurles, M.E., & Tyler-Smith, C. (2004). *Human evolutionary genetics: Origins, peoples & disease*. Garland Science, Taylor and Francis Group.

Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

Wells, S. (2003). *The journey of man: A genetic odyssey*. Princeton University Press.



References:

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Lewin, B. (2004). *Genes VIII*. Pearson Prentice Hall.

Nussbaum, R.L., McInnes, R.R., & Willard, H.F. (2004). *Thompson & Thompson: Genetics in medicine (6th ed.), revised reprint*. Saunders, an imprint of Elsevier.

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