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Primer in Genetics and Genomics, Article 1: DNA, Genes, and Chromosomes

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Abstract

Precision medicine refers to the practice of determining a patient's unique genetic, biomarker, and other characteristics for the purpose of improving his or her clinical outcomes. Not all patients with the same clinical diagnosis respond equally to identical treatment regimens. By examining patients at the molecular level, health-care providers will be better able to apply the most effective therapies that each individual requires. To understand precision medicine, nurses must have a solid understanding of genomics and proteomics. The purpose of this article is to (1) provide a historical review of what and how we have learned about the genome, particularly in the past century, (2) explain the processes whereby genetic information in cellular DNA is transcribed to messenger RNA and translated to protein, and (3) introduce genetic and epigenetic mechanisms that regulate gene expression.

Keywords

central dogma, precision medicine, epigenetics, history of DNA, gene, genome

During his State of the Union address on January 20, 2015, President Obama introduced the Precision Medicine Initiative designed "to give all of us access to the personalized information we need to keep ourselves and our families healthier" (as cited in Collins & Varmus, 2015, p. 793). Precision medicine refers to the practice of determining a patient's unique genetic, biomarker, and other characteristics for the purpose of improving his or her clinical outcomes. Not all patients with the same clinical diagnosis respond equally to identical treatment regimens. By examining patients at the molecular level, health-care providers will be better able to apply the most effective therapies that each individual requires.

In order for nurses to participate in the development and practice of precision medicine, they must acquire a solid understanding of genomics and proteomics. Genomics refers to the study of the entire genome of an organism, which consists of all the DNA in a cell, including its contents, organization, and function. All cells, with the exception of egg and sperm, carry an identical genome. Proteomics is the study of the complete set of proteins a given cell type produces. Thus, different cell types have different proteomes. The purpose of this article is to (1) provide a historical review of what and how we have learned about the genome, particularly in the past century, (2) explain the processes whereby genetic information in cellular DNA is transcribed to messenger RNA (mRNA) and translated to protein, and (3) introduce genetic and epigenetic mechanisms that regulate gene expression. All concepts we cover in this article are commonly included in standard genetics textbooks, such as *Essentials of Genetics* (Klug, Cummings, Spencer, & Palladino, 2013) or *Concepts of Genetics* (Brooker, 2016). We encourage the reader to consult such textbooks for additional information or clarification.

What Is DNA?

DNA, or deoxyribonucleic acid, was first described by James Watson and Francis Crick in "A Structure for Deoxyribose Nucleic Acid," a paper that appeared in *Nature* on April 25, 1953 (Watson & Crick, 1953). This publication marked a landmark achievement in science because, for the first time, scientists understood what a gene actually looked like. Scientists had previously known that genes were made of DNA and that they carried hereditary information that was passed on from one generation to the next, yet it was only when Watson and Crick made their discovery that scientists finally knew the structure of DNA, and hence, the structure of a gene.

DNA consists of two long polymer strands, each of which is made up of a series of nucleotides linked together, that form a double helix (Figure 1). Nucleotides have three components: (1) the sugar deoxyribose, (2) a phosphate group (PO_4), and (3) one of four different nitrogenous bases (i.e., adenine, guanine,

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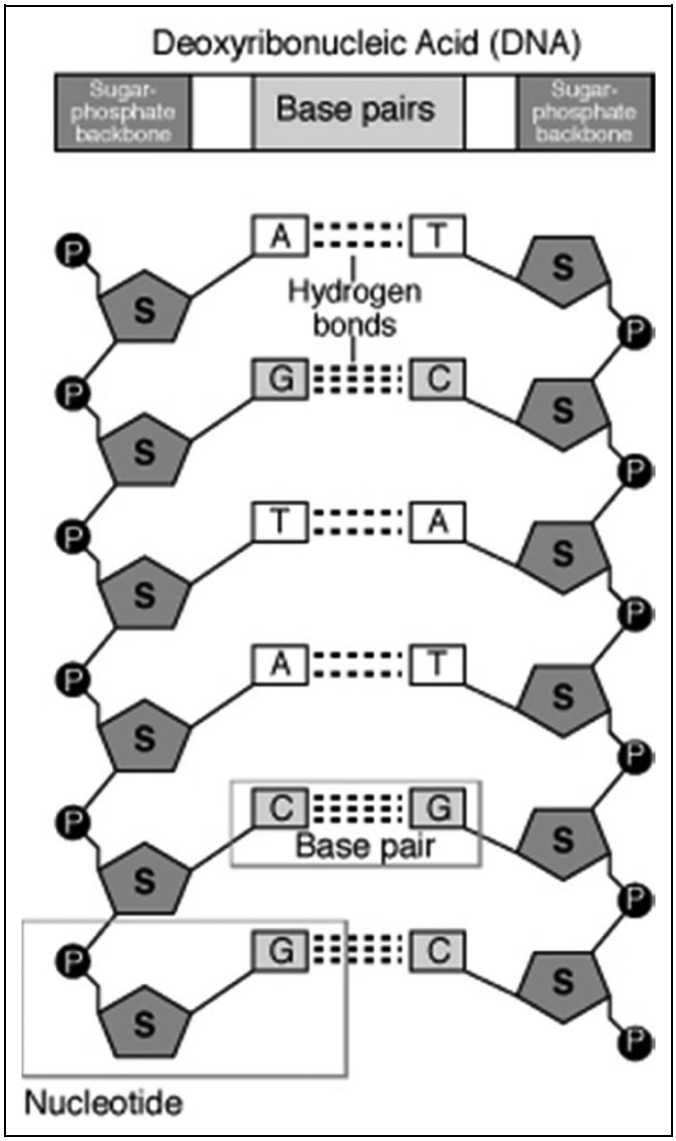

Figure 1. DNA double helix. The sugar molecules (S) are connected to one another by phosphodiester bonds (P) on the exterior of the double helix. The complementary bases (A, T, G, C) are connected to one another by hydrogen bonds on the interior of the double helix. A = adenine; C = cytosine; G = guanine; T = thymine. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. Author: Mirmillion. https://commons.wikimedia.org/wiki/File: Nucleotide.gif

cytosine, or thymine). The nucleotides on a DNA strand are connected to each other by covalent bonds between the 3′ hydroxyl group of one sugar molecule and the 5′ phosphate group of the next. Strands of DNA differ from one another only in terms of the order of bases they carry (i.e., their sequence), which are abbreviated as A, G, C, and T, respectively.

The two strands of DNA are linked together by hydrogen bonds that form between the bases, which are on the inside of the molecule (Figure 1). The sugar–phosphate backbones are on the outside of the molecule. Watson and Crick's model showed that every time A appeared on one strand, it was always paired with T on the other strand, and A and T were connected by two hydrogen bonds. If there was a C on one strand, it was always paired with G on the opposite strand, and C and G were connected by three hydrogen bonds. This feature of DNA, in which A always pairs with T and C always pairs with G, is known as complementary base pairing.

Every nucleated cell in our body, with the exception of egg and sperm, has a complete genome in its nucleus. Each time the cell divides by the process of mitosis, all the DNA in that cell is replicated, so that each of the two new daughter cells has its own copy of the entire genome. The mitochondria, which produce the energy required for all the cell's functions, contain a small circular DNA molecule that is also part of the genome. Every living organism has a complete genome in each of its cells. And the structure of all DNA is the same. The DNA in human cells has the same structure as the DNA in the cells of a butterfly, a whale, a flower, or a worm. What differs is simply the amount of DNA carried by each organism and the order of the nucleotides in each strand.

What Is a Gene?

Concepts in the 19th Century: Mendelian Ideas of Dominant Versus Recessive and Homozygosity Versus Heterozygosity

The concept of the gene can be traced back to Gregory Mendel, an Austrian monk who bred pea plants in the mid-1800s and carefully recorded the outcomes of his experiments. The plants he studied had seven different dichotomous characteristics. For instance, some had yellow seeds, other seeds were green. Some plants were tall, others were short. Observable characteristics such as seed color or height constitute a plant's phenotype.

Mendel noticed that when a pea plant self-fertilized, the offspring always had the same phenotype as the parent plant (known as true-breeding plants). He also began to cross-pollinate true-breeding plants with different phenotypes to see what would result. In the first generation of offspring produced, for example, by breeding plants with yellow seeds with those with green seeds, all of the new plants always had the same phenotype as only one of the parents (e.g., yellow seeds). But when the first-generation plants self-fertilized, both parental phenotypes appeared in the offspring and always with the same frequencies (e.g., 75% of the plants had yellow seeds and 25% had green seeds, or a phenotypic ratio of 3:1). Irrespective of the phenotype (e.g., seed color, pod shape, flower color, etc.), he always obtained the same results. Mendel concluded that the parental plants each carried a specific unit factor that was responsible for a phenotype, and these unit factors were transmitted to the next generation of plants.

We now know that the unit factors that Mendel discovered were genes. The plants he studied had a different gene for each observable phenotype. Because each phenotype was dichotomous, he reasoned that each gene had two forms. With regard to seed color, there was a yellow form and a green form. These different forms are now known as alleles.

Mendel further reasoned that each plant must carry two alleles for a given phenotype, or a genotype, which segregated during gamete formation, with the probability of one allele appearing in the gamete being equal to the probability of the other appearing in the gamete. Based on his observations of the results of true-breeding plants' self-fertilization, he reasoned that each of these plants' genotypes had two identical alleles, that is, they were homozygous. The first-generation plants produced by a cross between two true-breeding plants with different phenotypes had two different alleles, one from each parent; that is, they were heterozygous. These observations also gave rise to the notion of dominant and recessive. Because all plants in the first generation had the same phenotype of one of the parents, Mendel considered that to be the dominant trait. Since all the first-generation plants were heterozygous, it meant that only a single dominant allele was required to produce the dominant phenotype. The recessive trait appeared in the second generation because two recessive alleles are required for expression of the recessive phenotype.

Mendel's notion of a gene and the inheritance patterns he observed are still very relevant today. In fact, diseases caused by a mutation in a single gene are sometimes referred to as Mendelian disorders, and they are inherited with the same frequencies as those Mendel observed in his experiments.

Concepts in the 20th Century: Transcription of DNA to mRNA and Translation of mRNA Into Protein

During the time Watson and Crick made their discovery, the concept of a gene was reflected in what is known as the central dogma of genetics also called the central dogma of molecular biology (Figure 2). Scientists considered a gene to be a piece of DNA that carried the instructions to make a single protein. These instructions were stored in DNA but were transmitted by a carrier molecule known as mRNA. mRNA is made in the nucleus using DNA as a template in a process called transcription, and the mRNA produced is referred to as a transcript. Once generated, mRNA leaves the nucleus and enters the cytoplasm, where the protein-making machinery known as ribosomes reside. There, it serves as the template for its corresponding protein through the process of translation.

RNA has the same structure as DNA with a few exceptions. While DNA is a double helix, mRNA is always single stranded (Figure 3). This difference is due to the fact that, at any given time, only one of the two strands of DNA serves as a template; the other is the nontemplate strand, which represents the sequence of the gene. The beginning of each strand of DNA has a free phosphate group attached to the 5′ carbon of the sugar and the end has a free hydroxyl group attached to the 3′ carbon. The 5′ end of one strand of the double helix is paired with the 3′ end of the other. The two strands are said to be antiparallel. By convention, genes begin at the 5′ end and finish at the 3′ end. mRNA has the same 5′–3′ orientation. There are, however, two other differences between DNA and RNA. The sugar in RNA is ribose, not deoxyribose. And uracil (U) replaces thymine in RNA (Figure 3). For any given gene, where T is present in DNA, it will appear as U in mRNA.

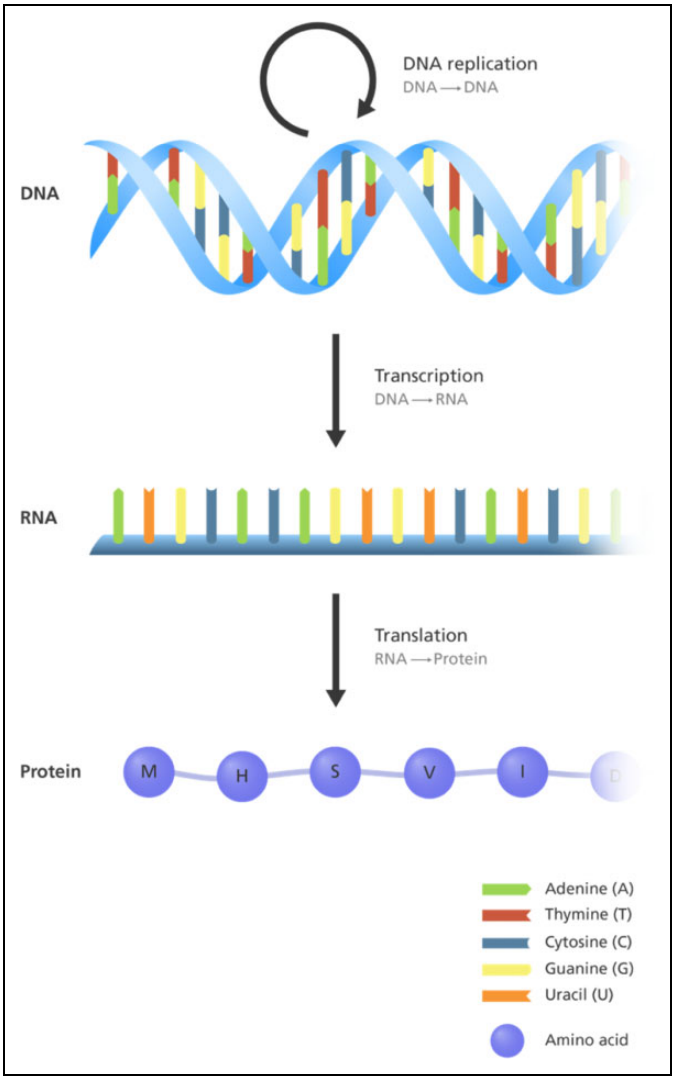

Figure 2. Central dogma of genetics. DNA is transcribed into RNA, which is subsequently translated into protein. D = aspartic acid; H = histidine; I = isoleucine; M = methionine; S = serine; V = valine. This image was obtained from the Creative Commons and was downloaded From Flickr on September 6, 2016. Author: Genome Research Limited. https://www.flickr.com/photos/yourgenome/26344048984

The last step the central dogma of genetics describes is the synthesis of a protein using mRNA as a template. The building blocks of proteins are amino acids, all of which have similar structures: a central carbon atom to which a hydrogen atom, an amino group (NH_3^+), a carboxyl group (COO^-), and an R group are covalently bound. It is the R group that differs among the 20 amino acids. The smallest amino acid is glycine because its R group is another hydrogen atom. The other amino acids have more complicated R groups, as shown in Figure 4.

The amino acids in a protein are covalently linked together by peptide bonds, which are formed during the process of translation (Figure 2). The correspondence between the sequence of nucleotides in mRNA and the sequence of amino

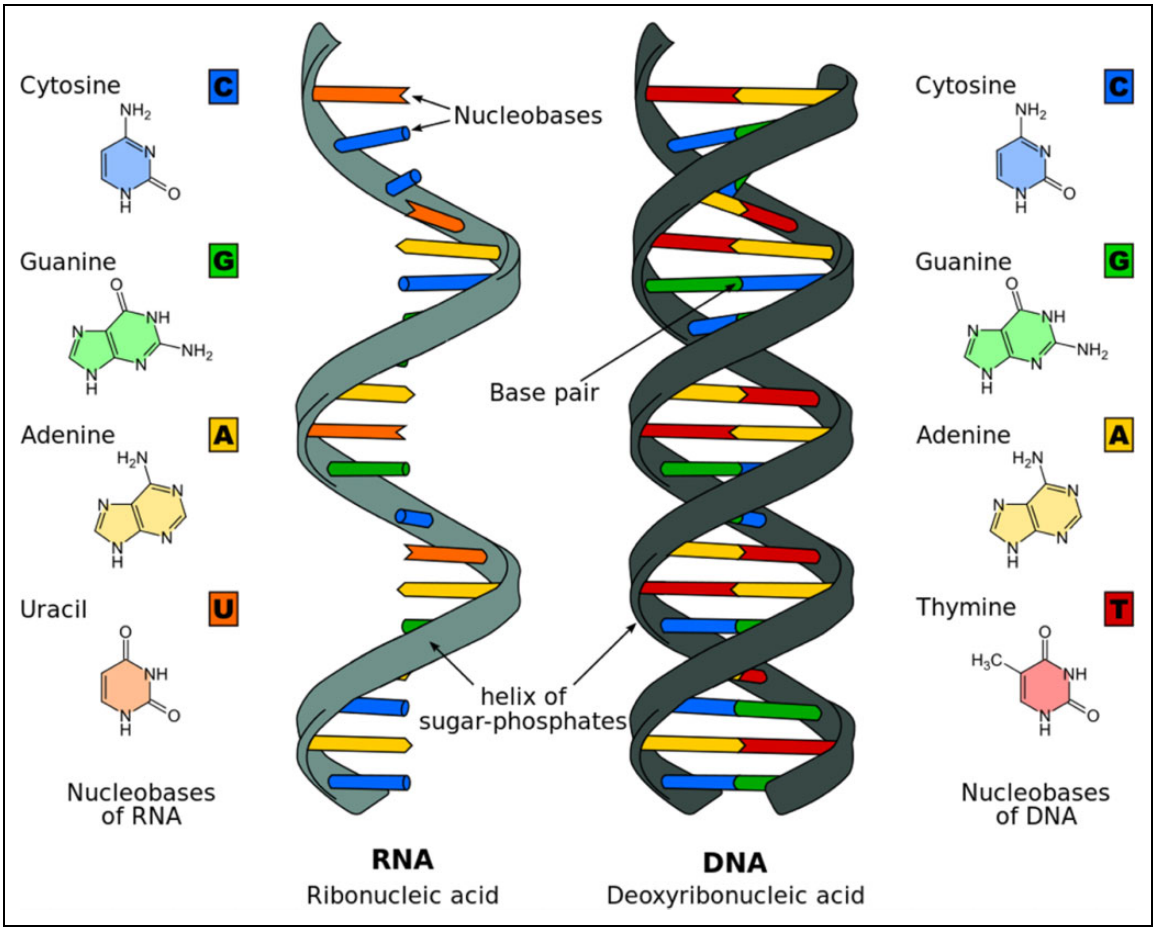

Figure 3. DNA versus RNA. DNA is always double stranded; RNA is often single stranded. The sugar in DNA is deoxyribose; the sugar in RNA is ribose. Thymine in DNA is replaced by uracil in RNA. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. https://commons.wikimedia.org/wiki/File: Difference_DNA_RNA-EN.svg

acids in a protein is called the genetic code (Figure 5). Because there are 20 amino acids, each of which is specified by using just four different bases (i.e., A, G, T, C), scientists determined that the genetic code must be a triplet code. Every three nucleotides, a grouping that is called a codon in mRNA, represents one and only one amino acid. So, if the codon is UUU, for example, then the amino acid that will become part of the protein is phenylalanine. Some amino acids may be specified by more than one codon, which is a safeguard against mutations. If a mutation occurs, particularly in the third nucleotide of a codon, the codon may still represent the same amino acid as the original codon, thus it may not lead to a change in the amino acid sequence of a protein. As all living organisms use the same genetic code, it is considered universal.

In addition to mRNA, translation requires transfer RNA (tRNA), as shown in Figure 6, as well as organelles called ribosomes (Figure 7). All tRNA has the same general cloverleaf structure. What differs among tRNAs are the amino acids attached to the acceptor stem and the three-nucleotide anticodon, which is complementary to the codons in mRNA. So, for example, the codon 5′-UGG-3′, which represents the amino acid tryptophan, would be read by a tRNA molecule that is attached to tryptophan and has the anticodon 5′-CCA-3′. This "reading" occurs when mRNA is in between the large and small subunits of a ribosome (Figure 7). During translation, mRNA moves through the ribosome like ticker tape, with codon-anticoding pairings dictating the sequence of amino acids in the growing polypeptide chain. In addition to the 61 codons that reflect amino acids, there are three stop codons—UAA, UAG, and UGA. When one of these codons passes through the ribosome, translation stops because there are no tRNAs with anticodons that are complementary to these three codons.

Concepts in the 21st Century: Genetic and Epigenetic Regulation of Gene Expression

We now know that only about 1% of our genome encodes proteins. Alternative splicing is the primary mechanism by which our approximately 20,000 genes can code for hundreds of thousands of proteins. Alternative splicing refers to modification of the primary mRNA produced during transcription (Figure 8). Only a portion of the transcript contains sequences that are translated into a protein. Introns, or intervening sequences, are removed after transcription, and the remaining

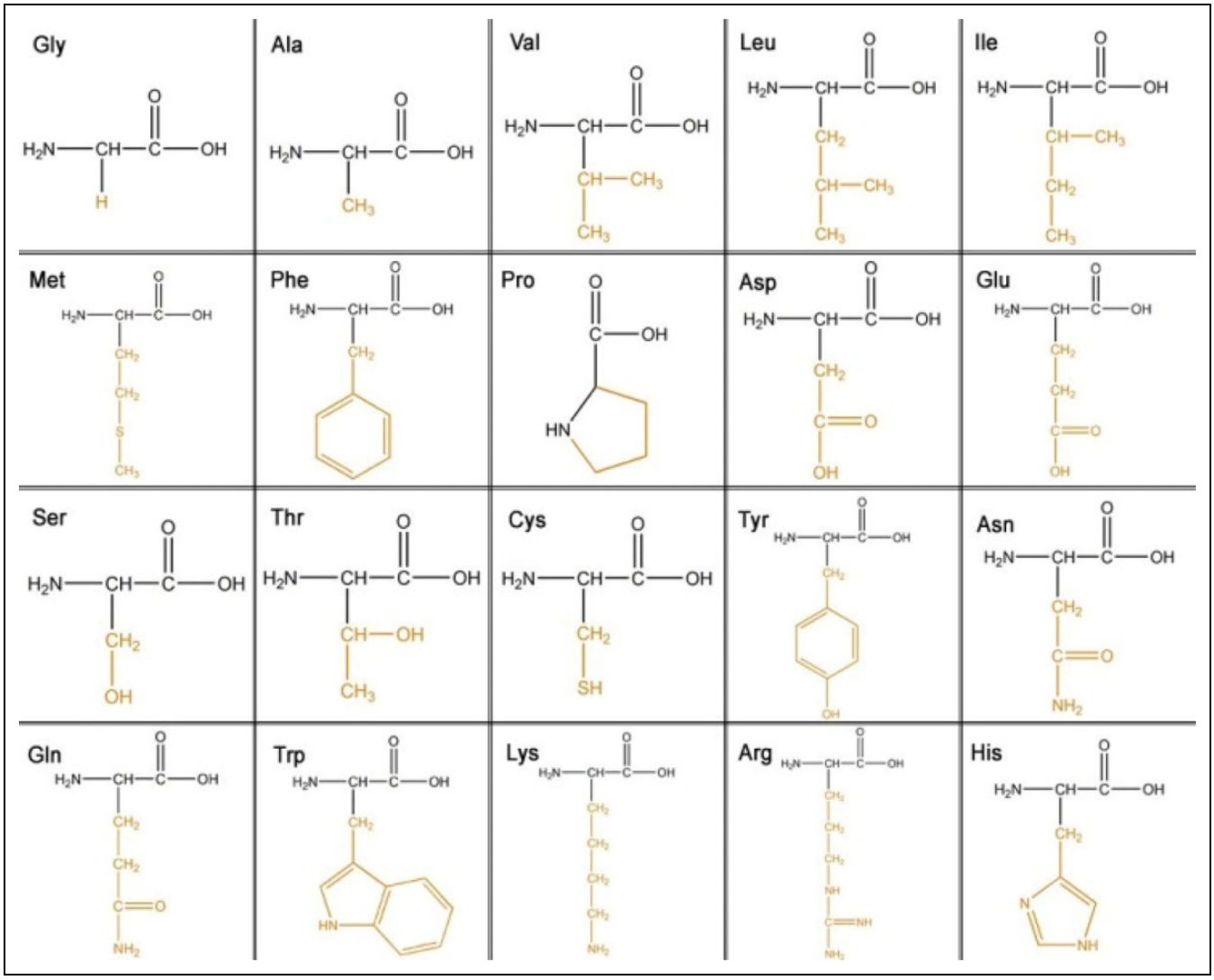

Figure 4. The structure of 20 amino acids. All amino acids have an amino group (NH2) and a carboxylic acid group (COOH). What differs among them is the R group (e.g., H for glycine, CH_3 for alanine, etc.). Gly = glycine; Ala = alanine; Val = valine; Leu = leucine; Ile = isoleucine; Met = methionine; Phe = phenylalanine; Pro = proline; Asp = aspartic acid; Glu = glutamic acid; Ser = serine; Thr = threonine; Cys = cysteine; Tyr = tyrosine; Asn = asparagine; Gln = glutamine; Trp = tryptophan; Lys = lysine; Arg = arginine; His = histidine. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. Author: Dalibor Bosits. https://commons.wikimedia.org/wiki/File: Tablica_aminokiselina.jpg

sequences, known as exons, are spliced together. One transcript can be processed in multiple ways, such that different combinations of exons can be spliced together, producing many different proteins from the same primary transcript. The discovery of alternative splicing has changed our thinking about the central dogma because we now know that the concept of one gene encoding one protein is not true.

If only 1% of our genome codes for protein, what is the function of the other 99%? A gene is really much more than the sequence of nucleotides that is reflected in the protein it generates. At the beginning and end of that sequence are long stretches of nucleotides that regulate transcription. At the beginning of a gene, which starts in the 5′ region, are promoter sequences that control where transcription will begin and how fast and how much of a transcript will be made. For example, the sequence 5′-TATAA-3′ is in the 5′ region of many genes, "upstream" of where transcription actually begins. Transcription factors that bind to DNA recognize this sequence and use it to correctly position RNA polymerase, the enzyme that actually generates the transcript. Other sequences, called enhancers and repressors, speed up and slow down, respectively, the rate of transcription. Enhancer and repressor sequences can be quite distant from the gene's coding region. Other transcription factors recognize these sequences and further control how much and how fast mRNA is generated. All of these sequences are part of a gene and are required to generate the many proteins that control the overall maintenance and general metabolism of all of our cells. Genes that are expressed in all cell types, such as RNA polymerase and transcription factors, are called housekeeping genes.

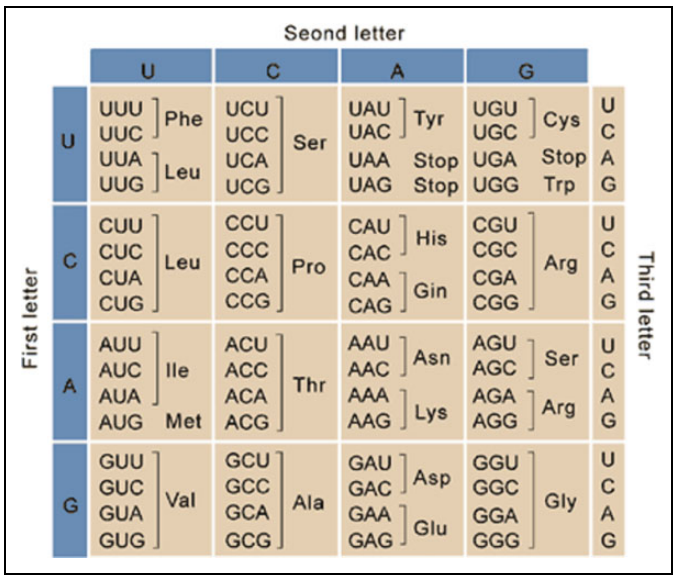

Figure 5. The genetic code. Each nucleotide triplet represents a codon. Each codon represents an amino acid (e.g, UUU = phenylalanine, UCU = serine, etc.). Three codons (UAA, UAG, and UGA) do not represent any amino acid. Rather, these are stop sequences that terminate protein synthesis. A = adenine; C = cytosine; G = guanine; U = uracil. This image was obtained from the Creative Commons and was downloaded from Wikimedia on September 6, 2016. (The label for the top horizontal row should read "Second letter.") https://commons.wikimedia.org/wiki/Category:Genetic_code#/media/File:06_chart_pu3.png

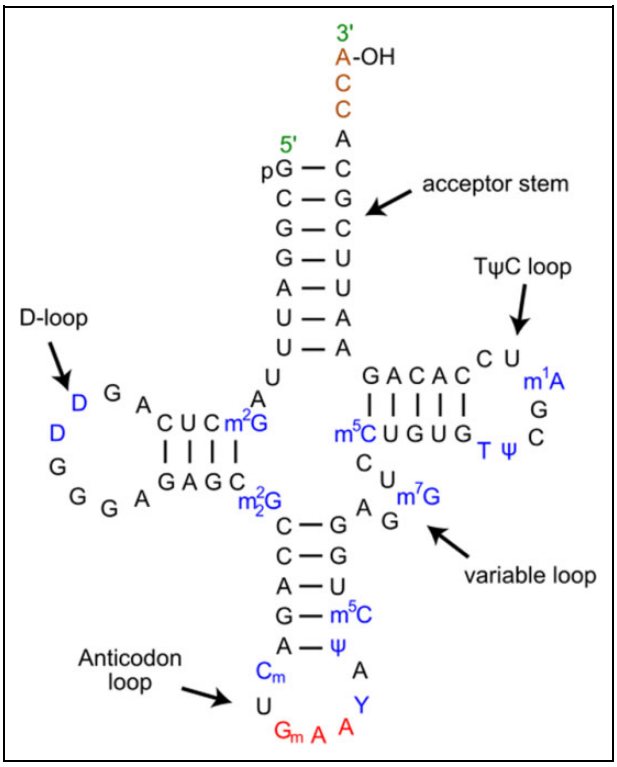

Figure 6. The structure of transfer RNA (tRNA). tRNA has a cloverleaf structure. The acceptor stem is attached to an amino acid, which corresponds to a codon in messenger RNA that is complementary to the nucleotides in the anticodon loop. A = adenine; C = cytosine; G = guanine; U = uracil. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. Author: Yikrazuul. https://commons.wikimedia.org/wiki/File: TRNA-Phe_yeast_en.svg

However, humans have many different types of cells (e.g., neurons, red blood cells) that express vastly different proteins. And each cell type expresses only a fraction of the 20,000 genes present in each of our cells. For example, neurons produce dopamine, but they don't express hemoglobin. And, developing red blood cells generate hemoglobin, but they don't make dopamine. Expression of a subset of genes allows the phenotype and function of each cell type to differ. The mechanisms by which tissue-specific genes are regulated are known as epigenetic controls of gene expression. Thus, in neurons, hemoglobin is epigenetically silent, but dopamine is epigenetically active. The reverse is true in red blood cells.

The word epigenetic means "above the genome," and epigenetic mechanisms control gene expression without changing the actual sequence of a gene. Epigenetic mechanisms are controls that cells use to turn genes on or off in specific tissue types. Although some epigenetic mechanisms are heritable and maintained across generations, others are influenced by environmental factors, such as diet and stress, and are therefore reversible. Thus, identical twins, who have identical genomes in terms of DNA sequence, can have different epigenomes, which become increasingly diverse with age. In this way, identical twins may actually express different genes and, therefore, express different proteins in their cells.

There are three general epigenetic mechanisms that control tissue-specific gene expression: (1) noncoding RNA, (2) histone modifications, and (3) DNA methylation. Many of the DNA sequences that do not code for proteins are transcribed into short fragments of RNA that control gene expression through what is known as RNA interference (RNAi). These fragments are also involved in cell cycle regulation and other cellular functions. Micro-RNAs (miRNAs) are short double-stranded RNA molecules that are 21−24 base pairs in length and are transcribed in the nucleus of a cell. They are then transported into the cytoplasm where they bind to proteins and become single-stranded molecules in search of complementary mRNA. When they find their complement, the miRNA/protein complex inactivates that mRNA transcript either by cutting or degrading it or by preventing the mRNA from interacting with ribosomes, thereby halting translation.

Histone modifications and DNA methylation are epigenetic mechanisms that change the way DNA is packaged into chromosomes, which is the focus of the next section.

What Is a Chromosome?

Chromosomes contain genes. Humans have 23 pairs of chromosomes, which are always located in the nucleus of a cell. Other species have different numbers of chromosomes. For example, cats have 19 chromosome pairs, while dogs have 39

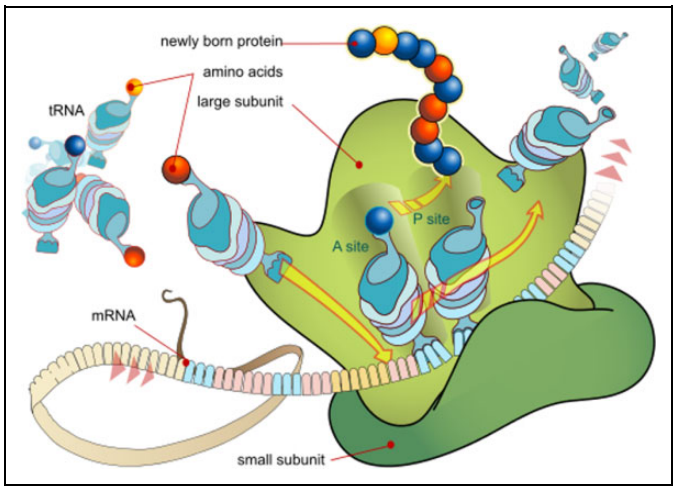

Figure 7. A ribosome conducting protein synthesis. A ribosome engaged in protein synthesis consists of a small subunit (the dark structure at the bottom of the figure) and a large subunit (the lighter structure at the top of the figure). Messenger RNA (mRNA) is between the two subunits. In this configuration, there is an A site and a P site within the ribosome where transfer RNA (tRNA) molecules dock during protein synthesis. tRNA molecules shown on the left are attached to an amino acid. The first tRNA molecule will enter the P site and await the second tRNA's entrance into the A site. When that occurs, a peptide bond will form between the two amino acids, which will now be connected to the tRNA in the A site. The tRNA in the P site now exits the ribosome, and the tRNA with two amino acids moves into the P site. A new tRNA with a third amino acid enters the A site, and the process continues until a termination codon in mRNA is present in the A site. This image was obtained from the Creative Commons and was downloaded from Wikimedia on September 6, 2016. Author: LadyofHats. https://commons.wikimedia.org/wiki/File: Ribosome_mRNA_translation_en.svg

chromosome pairs (Klug et al., 2013). One member of each pair is inherited from the biological father and the other from the biological mother. Twenty-two of the chromosome pairs in humans are called autosomes and differ from one another in terms of size and the number and function of the genes they carry. For the members of any given autosomal pair, the genes present are located in exactly the same position along the length chromosome, but the alleles present at each gene differ. The 23rd pair of chromosomes is the sex chromosomes. Females have two X chromosomes, and males have one X and one Y chromosome.

Human chromosomes are typically displayed pictorially in a karyotype, as shown in Figure 9, arranged according to length and position of the centromere (i.e., the most constricted area of a chromosome). The ends of the chromosomes are called telomeres. Most human karyotypes look identical because they are constructed from cells arrested in the phase of the cell cycle when chromosomes are most condensed. During this phase of the cell cycle, allelic differences cannot be detected.

Chromosomes consist of DNA wrapped around proteins called histones. This wrapping reduces the length of DNA by about one third (Figure 10). These nucleosomes (i.e., approximately 150 base pairs of DNA wrapped around eight histone proteins) are then coiled together to form solenoids, which are further condensed to form loop domains and finally chromatin. The degree of chromatin coiling has a direct impact on gene expression. When chromatin is relatively relaxed, it is called euchromatin and is transcriptionally active. When chromatin is highly condensed, it is transcriptionally inactive and is called heterochromatin. The degree of coiling is controlled, in part, by increasing or decreasing, respectively, the distance between the nucleosomes. A longer distance between nucleosomes provides space for transcription factors and RNA polymerase to bind to the gene's promoter and allows gene expression to proceed. When nucleosomes are very close together, these proteins no longer have access to these regulatory sequences, which prohibits gene expression.

Histone proteins have "tails," which are short sequences of amino acids that extend out of the nucleosomes. These histone tails can be modified, for example, by the addition of methyl or acetyl groups (Figure 11). Histone modifications are an epigenetic mechanism that influences gene expression by moving nucleosomes closer together or further apart. Histone acetylation (i.e., the addition of an acetyl group to one of the amino acids) allows for an open chromatin configuration, with more distance between nucleosomes, which facilitates transcription for reasons described above. Histone proteins are acetylated by enzymes known as histone acetyltransferases, while acetyl groups can be removed by histone deacetylases. Histone methylation, which is catalyzed by methyltransferases, creates a more closed chromatin structure, which inhibits transcription. These methyl groups can be removed by demethylases. Because many different amino acids make up the histone tails, the combination of possible outcomes is known as the histone code.

The third epigenetic mechanism that influences gene expression is DNA methylation, which involves the addition of a methyl group to cytosine bases that are adjacent to a guanine base in a sequence of DNA. This combination of cytosine bases that are adjacent to nucleotides containing guanine (i.e., CpG dinucleotides) are often located near promoter sequences of many genes. Unlike chromatin remodeling and histone modifications, DNA methylation is heritable. That is, when DNA is replicated, the CpG dinucleotides on the newly synthesized strand are methylated before the cell divides. Thus, the two daughter cells that are produced by mitosis have the same DNA methylation pattern as the parent cell. When CpG dinucleotides are unmethylated, the genes are transcriptionally active. Methylated CpG dinucleotides, however, are transcriptionally inactive.

The regulation of gene expression is extremely complex and is a very active area of research. It is clear that controls for housekeeping and tissue-specific genes involve a range of mechanisms, some of which are impacted by the environment. Epigenetic changes are most malleable prenatally and in early life; they play a critical role in growth and development of a fetus. Epigenetic changes are also involved in the development of diseases, such as diabetes, obesity, and cancer. Therefore,

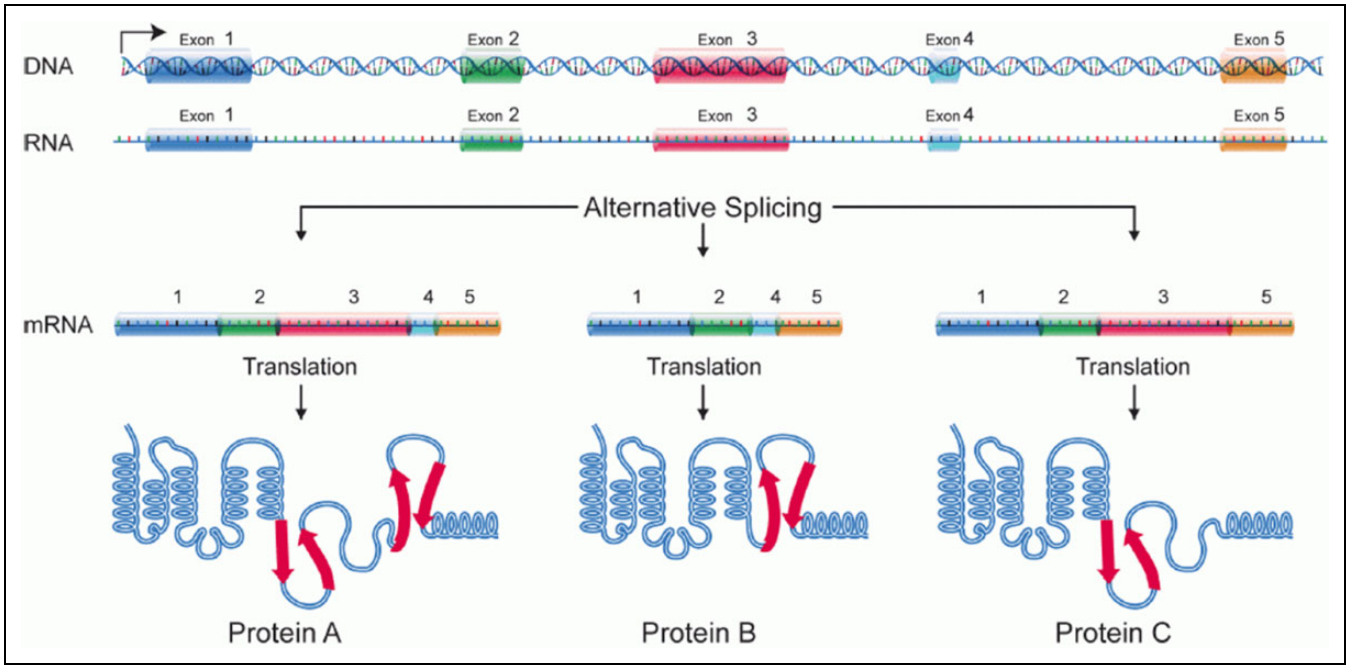

Figure 8. Alternative RNA splicing. DNA is transcribed into RNA, but not all of the transcript will be translated into protein. Sequences between exons will be spliced out and the exons will be joined together. However, different proteins can be made from one primary transcript by altering which exons are included in the mature messenger RNA (mRNA) transcript that is translated into protein. The mRNA on the left consists of Exons 1 through 5, but the mRNA in the middle includes Exons 1, 2, 4, and 5. The transcript on the right is missing Exon 4. In this way, multiple proteins can be generated from one primary transcript through the process of alternative splicing. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. Author: National Human Genome Research Institute. https://commons.wikimedia.org/wiki/File: DNA_alternative_splicing.gif

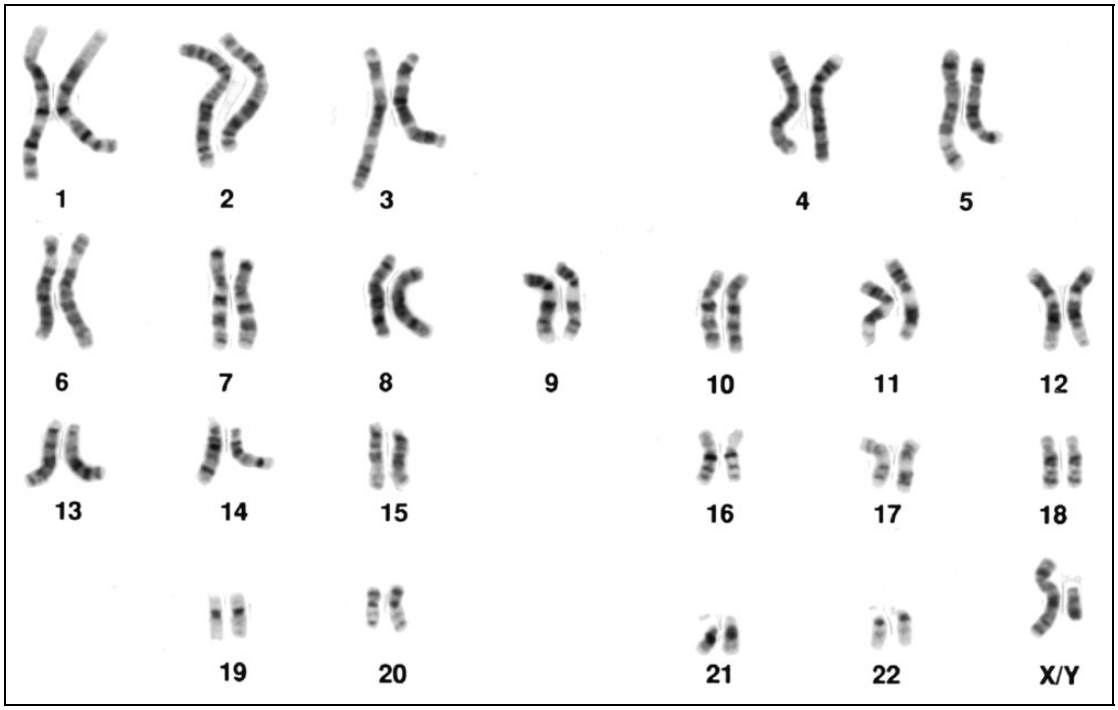

Figure 9. A normal human male karyotype. Humans have 23 pairs of chromosomes, which can be visualized in a karyotype. To construct a karyotype, cells are grown in culture for several days and are arrested in the phase of the cell cycle when the chromosomes are most condensed and can be visualized under a microscope. The cells are lyzed and the chromosomes are fixed onto a slide and photographed. The individual chromosomes are separated from one another and arrange in pictorial form from largest to smallest and according to the position of the centromere, which is the most constricted portion of the chromosome. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. Author: National Cancer Institute. https://commons.wikimedia.org/wiki/File: Karyotype_(normal).jpg

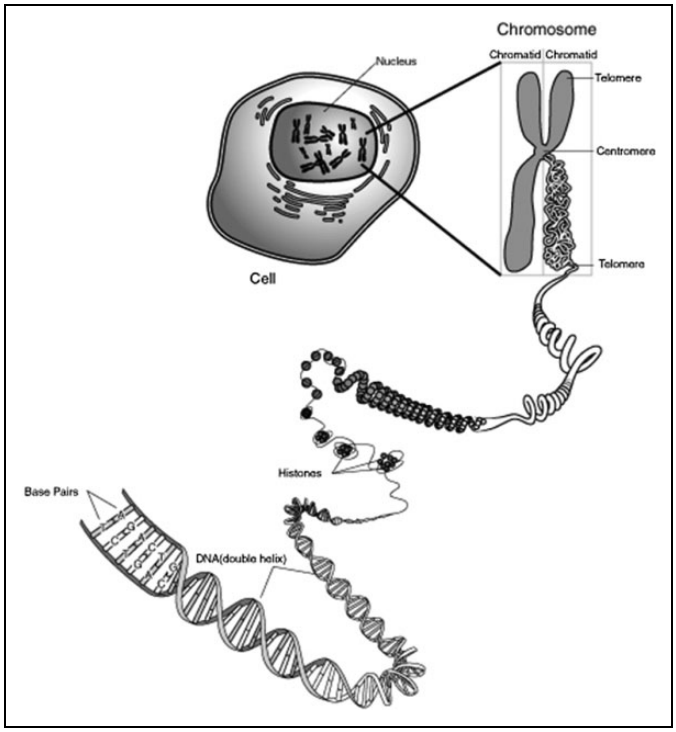

Figure 10. Chromatin coiling. Chromosomes consist of DNA and proteins. Initially a small amount of DNA is wrapped around histone proteins; these units are further condensed into solenoids and ultimately chromatin. Chromosomes are visible just before a cell is ready to divide into two daughter cells. The X-like structure reveals two chromatids, which are genetically identical and are formed just after DNA has replicated during the cell cycle. Ultimately, the chromatids will split, each going into a daughter cell to ensure that the daughter cells are genetically identical to the parent cell. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. https://commons.wikimedia.org/wiki/File: Chromosome.gif

drug developers are now focusing on epigenetics as a mechanism for treating and preventing adverse health outcomes. In order to effectively explore and utilize these novel therapies, nurses will need to have a strong understanding of the roles of genetic and epigenetic mechanisms in the development of diseases.

The Human Genome Project

In the mid-1970s, scientists developed molecular techniques that enabled them to determine the order of nucleotides in a piece of DNA in a laboratory. Initially, this was an arduous process that yielded reads of only about 200 nucleotides per experiment. However, by the late 1980s, DNA sequencing was largely automated using computers, allowing for hundreds of thousands of sequences to be generated in a single experiment.

These developments led to the Human Genome Project, an international effort based on a 15-year plan and a U.S. budget of $3 million to determine the DNA sequence of the entire human genome. One of the major goals when the project began in 1990 was to focus on improving methods for sequencing DNA in terms of increasing speed and decreasing costs. This goal was quickly achieved, allowing for the first draft of the human genome to be released ahead of schedule. Publications in 2001 included both a publicly funded (International Human Genome Sequencing Consortium, 2001) and a privately funded initiative (Venter et al., 2001). Thus, it took 11 years to generate the first sequence of an entire human genome. More information about the Human Genome Project and its rich history can be found by going to www.genome.gov and clicking on the "Education" tab.

Methods for DNA sequencing are constantly being improved, with the ultimate goal of sequencing a human genome in a single day for a cost of about US $1,000, an end that appears to be in sight (Hayden, 2014). In the very near future, whole-genome sequencing will be routinely available for clinical purposes, perhaps even beginning at birth. The major challenge ahead is the interpretation of this information. How do our genes interact with each other, and how does the environment contribute to the development of health and disease? What are the individual and societal implications of knowing our genome sequence? The answers to these and other important questions will unfold in the years ahead. Thus, we are truly in an era where precision medicine may soon become a reality.

Implications

One of the first fields in which precision medicine will likely be achieved is pharmacogenomics, or the study of how genetic variation effects a patient's response to medications. Advances in this field will give clinicians the ability to determine which patients are most likely to respond favorably to a particular medication. Many genes are involved in drug metabolism, and variation in those genes is one reason some patients require more or less of a particular drug relative to others to achieve an optimum response or experience adverse drug reactions.

Genomics also affords opportunities for individuals to undergo genetic testing to determine whether they carry genes that cause disease or increase disease risk. For example, women with a strong family history of breast and ovarian cancer may be tested to determine whether or not they carry mutations in their *BRCA1* or *BRCA2* genes before they develop either of these diseases. If they do, they may elect to have a prophylactic mastectomy and oophorectomy to ensure that they will remain disease free in the future. Nurses working with patients with cancer are already familiar with treatment plans based on the results of genetic testing. For example, only women who have a specific genotype for the *HER-2* gene are treated with Herceptin™ for breast cancer. Children with acute lymphoblastic leukemia are always tested for the *TPMT* gene before mercaptopurine therapy is initiated to determine doses (or the need for an alternative immunosuppressant therapy), as patients with two nonfunctional *TPMT* alleles require drastically reduced doses or an alternative drug. Nurses working with patients in pain are also familiar with the utility of genetic testing. Individuals respond differently to medication for pain based on

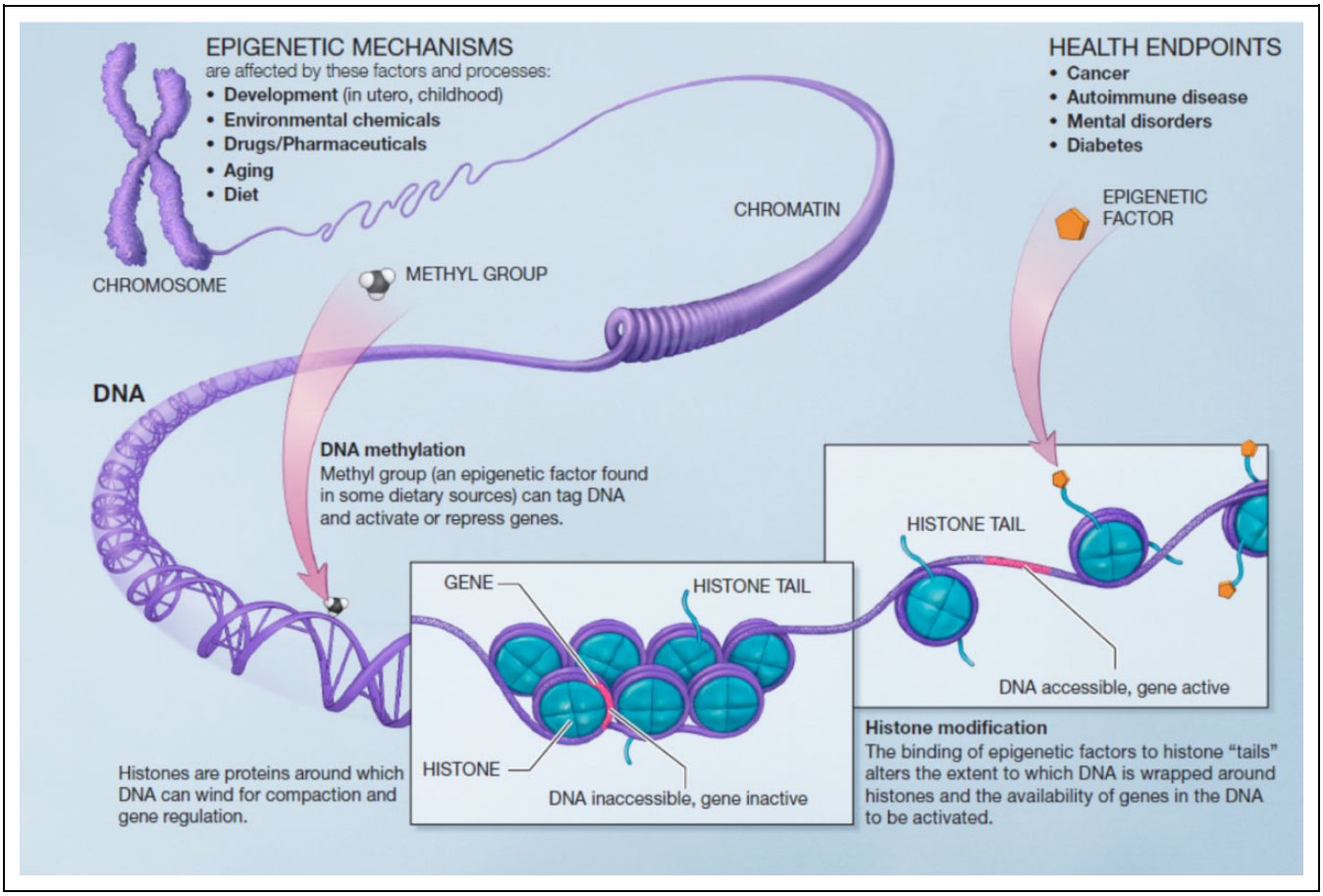

Figure 11. Epigenetic mechanisms. This figure shows DNA methylation and histone modifications. Nucleotides containing cytosine bases that are adjacent to nucleotides containing guanine (i.e., CpG dinucleotides) are often methylated. DNA methylation suppresses gene expression. Modifications to histone tails, such as the addition of an acetyl group to an amino acid of a histone tail, can relax chromatin coiling and enhance gene expression. This image was obtained from the Creative Commons and was downloaded from Wikimedia Commons on September 6, 2016. Author: National Institutes of Health. http://commonfund.nih.gov/epigenomics/figure.aspx

Table 1. Useful Online Genomics Resources.

Resource Name	URL
Genetics Home Reference	https://ghr.nlm.nih.gov/
National Human Genome Research Institute	https://www.genome.gov/education/
Talking Glossary of Genetic Terms	https://www.genome.gov/glossary/
All About the Human Genome Project	https://www.genome.gov/10001772/all-about-the–human-genome-project-hgp/
Fact Sheets	https://www.genome.gov/10000202/fact-sheets/
Online Genetics Education Resources	https://www.genome.gov/10000464/online-genetics-education-resources/
Learn.Genetics	http://learn.genetics.utah.edu/
National Cancer Institute	http://www.cancer.gov/
Centers for Disease Control and Prevention Public Health Genomics	http://www.cdc.gov/genomics/
U.S. National Library of Medicine Genetics Resources	https://www.nlm.nih.gov/services/genetics_resources.html
International Society of Nurses in Genetics	http://www.isong.org/
The American Society of Human Genetics	http://www.ashg.org/
DNA Learning Center	https://www.dnalc.org/

how quickly or slowly they metabolize the drugs. Individuals who are ultrarapid metabolizers may suffer from a life-threatening event if given codeine. These are just a few examples of the use of genetic testing to individualize care, but as our understanding of the human genome increases, there will be many more.

Precision medicine will soon be a part of the daily routine for nurses. As highlighted in *Essentials of Genetic and*

Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators (Consensus Panel on Genetic/Genomic Nursing Competencies, 2009), genetics and genomics impact essentially all human diseases and conditions, and the public is increasingly looking to health-care providers to incorporate this information into their practice. As such, all nurses, regardless of academic preparation or practice setting, must possess the ability to provide competent genetic- and genomic-based nursing care (e.g., elicit a minimum three-generation family history and construct a minimum three-generation pedigree). Thus, it is imperative for nurses to have a strong foundation in genetics and genomics, to understand the response differences in culturally diverse populations, and to be ready to provide excellent patient and family education regarding treatment and testing decisions.

We hope that this review has helped you explore genomics and proteomics and that you will be inspired to learn about how new discoveries are changing patient care. For additional information, please consult the resources we have included in Table 1. In addition, the document *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators* (Consensus Panel on Genetic/Genomic Nursing Competencies, 2009) includes a glossary as well as other information to increase nurses' understanding of the exciting fields of genetics and genomics and can be freely downloaded from the following website: http://www.aacn.nche.edu/education-resources/Genetics__Genomics_Nursing_Competencies_09-22-06.pdf

Author Contribution

Janice S. Dorman contributed to conception and design, drafted the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Mandy J. Schmella contributed to conception and design, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Susan W. Wesmiller contributed to conception and design, critically revised the manuscript, gave final approval, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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