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Primer in Genetics and Genomics, Article 3—Explaining Human Diversity: The Role of DNA

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Abstract

Genetic variation lays the foundation for diversity and enables humans to adapt to changing environments. The order of the nucleotides adenine, guanine, cytosine, and thymine on the deoxyribonucleic acid (DNA) molecules of the nuclear chromosomes and mitochondrial DNA (mtDNA) plays an important role in normal cell division, tissue development, and reproduction but is susceptible to alteration from a large number of random, inherited, or environmental events. Variations can range from a change in a single nucleotide to duplication of entire chromosomes. Single nucleotide polymorphisms are the major source of human heterogeneity. Other variations that can alter phenotypes and adversely impact growth, development, and health include copy number variations, aneuploidies, and structural alterations such as deletions, translocations, inversions, duplications, insertions, or mutations in mtDNA. In addition, DNA rearrangements in somatic cells underlie the uncontrolled cell growth found in cancer. This article explores the mechanisms by which variations in DNA arise and the impact those changes can have on human health.

Keywords

genomics, genetic variation, DNA, mutation, chromosome

The differences among individuals in any group are readily apparent. We look, act, and feel unique, despite the fact that, on average, about 99.5% of human deoxyribonucleic acid (DNA) is the same across all individuals. Even our ancestors, siblings, and children, with whom we share the greatest number of DNA sequences, are markedly different from us and from each other. DNA, the molecule in which genetic information is stored, comprises long strands of four nucleotide bases, adenine (A), guanine (G), cytosine (C), and thymine (T), arranged in a double helix (Figure 1). Particular stretches that contain instructions for the assembly of proteins are called genes. Our DNA sequence is referred to as our *genotype*, and the observable characteristics that result from translation of the instructions in the DNA into protein comprise our *phenotype.* Genetic variation, the tendency of individual genotypes in a population to become different from one another, lays the foundation for genetic diversity and enables human adaptation to changing environments through the process of natural selection (Jorde, Carey, & Bamshad, 2016; Kurnat-Thoma, 2015; Nussbaum, McInnes, & Willard, 2016).

The human genome has approximately 20,000 genes residing within the chromosomes in cell nuclei and 37 genes in the circular DNA molecules found in the mitochondria in the cell cytoplasm. Only about 1% of the DNA in the genome is translated into protein, but the remaining DNA may exert a regulatory influence over expression or repression of those protein-coding genes. Every nucleated cell in the body has the same chromosomal DNA, yet cells have widely different functions that vary throughout the lifespan. Explaining how approximately 20,000 genes can encode hundreds of thousands of different proteins is a current focus of genomic science. One important explanation involves alternative messenger RNA (mRNA) splicing. During the process of DNA transcription in the cell nucleus, a complementary strand of mRNA is created. Some regions of that mRNA transcript, called *introns*, are removed, and the remaining sequences, called *exons*, are spliced back together in a number of different ways. Those alternative forms of the transcript are then translated to proteins with different structures and functions (Dorman, Schmella, & Wesmiller, 2016).

Genes can also be turned on and off by epigenetic forces. *Epigenetics* is the study of changes in gene expression that do not involve variation in DNA sequences. Examples include histone modification, DNA methylation, and noncoding RNA. These phenomena will be discussed in a future article in this series.

Variation in human genotypes may result from a change in a single nucleotide of nuclear or mitochondrial DNA (mtDNA), from differences in stretches of a gene or a whole gene, or from gross rearrangements in or deletions of entire chromosomes.

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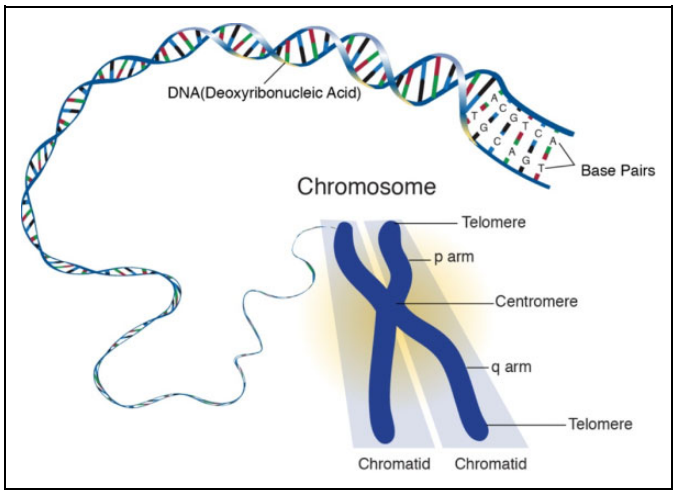

Figure 1. Chromosomes are comprised of genes (strands of deoxyribonucleic acid that code for proteins) that are made up of nucleotide base pairs (adenine, thymine, cytosine, and guanine) linked in a double helical molecule. Figure from the National Institutes of Health, National Human Genome Research Institute (https://www.genome.gov/), Digital Media Database. Darryl Leja/NHGRI/NIH. Retrieved from http://genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85281

The sequence of the DNA in all species is constantly changing due to random mutations that get passed on to future generations. The frequency of inherited mutations depends on the balance between the number of errors introduced and the efficacy of the DNA repair mechanisms (Ségurel, Wyman, & Przeworski, 2014). These changes may contribute to natural selection, go unnoticed, or result in fetal demise, developmental abnormalities, or diseases and disorders. Our environments change as well, and genes that were beneficial in ancient times may plague modern humans. For example, genes that allowed efficient nutrient storage in times of scarcity may increase susceptibility to obesity and diabetes today (Tishkoff & Verrelli, 2003). The purpose of this article is to explore the mechanisms by which variations in DNA arise and the impact those changes can have on human health.

Some Important Terms and Concepts

Prior to a discussion of variations in human DNA sequences, it is important to define some underlying terms and concepts. These include the terms *locus*, *allele*, *mutation*, and *polymorphism*, the distinction between *germ line* and *somatic* cells, and the characteristics of *inherited* versus *acquired* mutations.

A segment of DNA at a particular position on a chromosome is called a locus. A locus may be small, consisting only of a single nucleotide, or large, consisting of several genes. Different forms at a given locus are called alleles, and the most common allele in a population is referred to as the *wild type.* When a locus has two or more alleles that occur at a frequency of greater than 1% in a population, the locus is said to be *polymorphic.* A mutation is a permanent change in a DNA sequence compared to a reference sequence. Mutations may involve a single-nucleotide base or a much longer DNA stretch and may be unique to one individual. Mutations that occur in protein-coding regions of DNA may direct the synthesis of altered proteins, while mutations in noncoding regions may interfere with protein synthesis by altering various regulatory mechanisms. A *missense* mutation is a single-nucleotide change that alters the protein structure by changing an amino acid, and a *nonsense* mutation is a single-nucleotide change that halts the protein synthesis by creating a *stop* codon. A change that involves a single-nucleotide deletion is classified as a *frameshift* mutation because it alters the reading frame for all downstream amino acids (Jorde et al., 2016). Most mutations exert no harmful effect on the organism, and some may confer selective advantage that contributes to genetic evolution of a species (Kurnat-Thoma, 2015).

Germ line cells are cells capable of producing gametes (sperm or egg). The DNA in a germ line cell will likely be transmitted to every cell of any offspring it produces, and mutations in the DNA of germ line cells before or during conception may cause inherited mutations in the offspring. Somatic cells are all other cells. Since somatic cells do not participate in the creation of sperm or egg, there is no way for somatic-cell DNA to be transmitted to offspring. However, somatic-cell DNA is transmitted to its own daughter cells in the constant process of cell division. Mutations in DNA of somatic cells, called acquired mutations, are of significant concern when they lead to malignant transformation of cells in cancer (Jorde et al., 2016).

Single Nucleotide Polymorphisms (SNPs)

An SNP (pronounced "snip") is a difference in a single-nucleotide base pair that is found at a given locus in at least 1% of the population. Humans have more than 10 million SNPs that are responsible for much of the heterogeneity among individuals. Some SNPs are associated with phenotypic changes and others are not. SNPs usually exist in two forms, although more than two forms (alleles) are possible. For example, an adenine may be replaced by a thymine, a guanine, or a cytosine. SNPs may be located on coding or noncoding regions of the DNA molecule. Within coding regions, SNPs can directly result in an amino acid change that alters the growing protein molecule. SNPs in noncoding regions can also have an impact on protein structure if they occur in regions that participate in regulation of gene expression or alter the mRNA splicing process. Small (1 to approximately 1,000 base pairs) insertions or deletions, called *indels*, are also very common and may or may not be associated with observable phenotypic changes, as are copy number variations (CNVs; discussed in the next section; Kurnat-Thoma, 2015; Nussbaum et al., 2016).

A number of databases catalog SNPs. For example, the Single Nucleotide Polymorphism Database (https://www.ncbi.nlm.nih.gov/projects/SNP/) is a publicly available archive that contains SNPs as well as indels and other known short genetic variations. Since SNPs may be inherited, they can be used to track inheritance of disease genes within families. Some SNPs

can be used to predict an individual's response to certain drugs or toxins. SNPs are also used in ancestry studies to determine the probability that two persons are related and in forensics to match DNA at a crime scene with the DNA of a suspect (Kurnat-Thoma, 2015).

Sickle cell anemia is an example of a human disease caused by a change in a single nucleotide. The substitution of thymine for adenine at a particular locus on the beta globin (*HBB*) gene on Chromosome 11 results in the substitution of valine in the place of glutamic acid in the polypeptide chain. If both parents carry this autosomal recessive mutation, there is a 25% chance that their child will be affected with sickle cell anemia, a condition in which the misshapen hemoglobin molecules lead to the destruction of red blood cells (Nussbaum et al., 2016).

CNVs

A relatively new area of study in genomics is that of CNV (McCarroll & Altshuler, 2007). CNV occurs when regions of the genome repeat. The repeated sequences may be short, as in dinucleotide or trinucleotide repeats, or longer if entire genes are involved. Thus, there may be some overlap in discussions of CNV and chromosomal alterations such as duplications. CNVs contribute to diversity within the population, and the number of repeats in a CNV varies among individuals. Some CNVs are associated with disease or dysfunction, but recent research indicates that 4.8–9.5% of the human genome can be classified as CNVs (Zarrei, Macdonald, Merico, & Scherer, 2015), and many are not associated with known adverse consequences.

One well-known "short repeat" CNV is associated with the development of Huntington's disease (HD), a progressive neurological disorder that is transmitted in an autosomal dominant manner. Patients with HD have expanded numbers of the trinucleotide cytosine, adenine, and guanine (CAG) bases in part of the Huntingtin (*HTT*) gene on Chromosome 4 that codes for the HTT protein. This variation results in the production of long chains of glutamine, the amino acid translated when the CAG codon is transcribed. This mutant form of the HTT protein leads to increased destruction of the basal ganglia and other neurons in the brain that control motor function. Those pathological changes result in incoordination, unsteady gait, and jerky body movements. HD ultimately progresses to include severe motor dysfunction, impaired cognitive ability, and neuropsychiatric disturbances (Alexander, 2016).

The number of CAG repeats correlates with the age of onset and the progression of HD. A person with 27−35 repeats may never develop HD, but offspring who inherit the gene are at increased risk since the number of repeats can expand with each generation (Alexander, 2016). With repeats of 40 or more CAGs, HD is "fully penetrant," and the person may begin to show signs of the disease by the age of 20. This phenomenon of trinucleotide repeat expansion and more severe disease presentation in subsequent generations is known as *genetic anticipation.* About 10% of cases of HD are not inherited from the parents but rather are caused by spontaneous mutations (Dayalu & Albin, 2015), and only one copy of a mutant gene is needed for an autosomal dominant disease to occur.

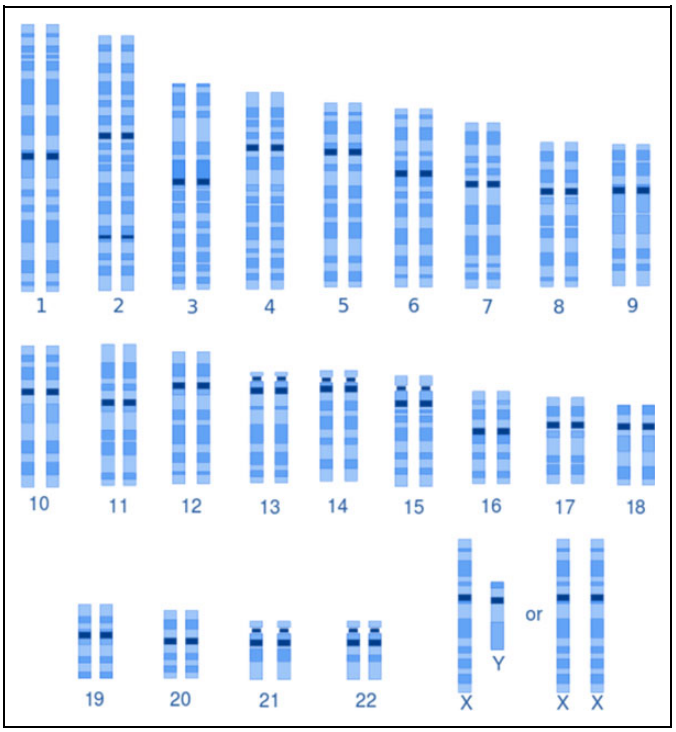

Figure 2. A human karyotype depicting nuclear chromosome pairs 1−22 with either XX (female) or XY (male). From Wikimedia Commons. Retrieved from https://commons.wikimedia.org/wiki/File:Human_karyotype.svg#/media/File:Human_karyotype.svg.

Larger Alterations in Genes and Chromosomes

The genes that code for proteins and the noncoding stretches of DNA that influence gene expression are packaged within the 23 pair of human nuclear chromosomes and the circular DNA of the mitochondria. When chromosomes undergo errors during cell division or gamete formation, DNA rearrangements can result in a variety of dysfunctions/syndromes. Larger nuclear chromosomal abnormalities such as aneuploidies may be detected with a karyotype (Danchanko & Kasper, 2015). Mutations in mtDNA are more difficult to detect and are analyzed only in patients who fit into a specific, well-described mitochondrial phenotype (United Mitochondrial Disease Foundation, 2016).

A human karyotype (shown in Figure 2) is an image of the 46 nuclear chromosomes, usually constructed from the person's white blood cells, displayed as a systematized arrangement of the pairs. A karyotype is constructed from cells at the phase of mitosis where both the original and newly copied DNA are in the form of *sister chromatids* visible under a light microscope (Figure 1). In this phase, the sister chromatids are joined together at a point called the *centromere*. Each chromosome has a short arm (labeled *p*) and a long arm (labeled *q*).

Chromosomes with very short *p* arms, such as Chromosomes 13, 14, 15, 21, and 22, are called *acrocentric*. Acrocentric chromosomes are distinguished from *metacentric* chromosomes, which have relatively central centromeres and arms of nearly equal length, and *submetacentric* chromosomes, which have an off-center centromere and arms of different lengths (Nussbaum et al., 2016).

Abnormalities of Chromosome Number: Aneuploidies

Aneuploidy refers to the state of a cell with an abnormal number of chromosomes in the nucleus. An aneuploid cell could possess a number of chromosomes greater than or less than the normal number. Aneuploidies may affect the autosomes (Chromosomes 1−22) or sex chromosomes (X or Y) and can be categorized as *monosomy*, when only one member of a chromosome pair is present, or *polysomy*, when more than two chromosomes of a pair are present. Most embryonal autosomal monosomies are lethal and lead to pregnancy loss, but monosomy of the X chromosome is less severe and results in Turner syndrome. The best-known human polysomy, Down syndrome, results from three copies of Chromosome 21 (trisomy 21) due to *nondisjunction*, wherein Chromosome 21 fails to separate from its pair during meiosis that leads to sperm or egg production. Having an extra Chromosome 21 is compatible with life, but many other aneuploidies are lethal or cause severe defects, as in trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome; Grossman, 2014).

Structural Rearrangements of Nuclear DNA

Structural alterations that rearrange DNA result when chromosomes break apart and reorganize abnormally or incompletely. These changes may result from random events, exposure to radiation or certain chemicals, extreme changes in the cellular environment, or viral infections (Grossman, 2014). Figure 3 depicts some examples of these structural abnormalities, including deletion, balanced translocation, inversion, Robertsonian translocation, isochromosome formation, and ring chromosome formation.

Deletion of part of a chromosome can occur when DNA segments are lost during cell replication or gamete formation. Large deletions that occur during gamete formation are usually fatal. Smaller deletions that affect a number of genes may cause recognizable disorders such as cri du chat syndrome, a condition caused by a deletion of the end of the short (*p*) arm of Chromosome 5. Deletions too small to observe with a microscope, called microdeletions, can be detected by molecular genetic techniques such as fluorescent in situ hybridization. Examples of microdeletion syndromes include Prader–Willi syndrome and 22q11.2 deletion syndrome. When a deletion results in fusion of the ends of the broken chromosome, a *ring chromosome* forms. Since ring chromosomes may fail to duplicate properly during cell division, ring chromosomes may only be found in some proportion of, but not all, cells (Grossman, 2014; Jorde et al., 2016; Nussbaum et al., 2016).

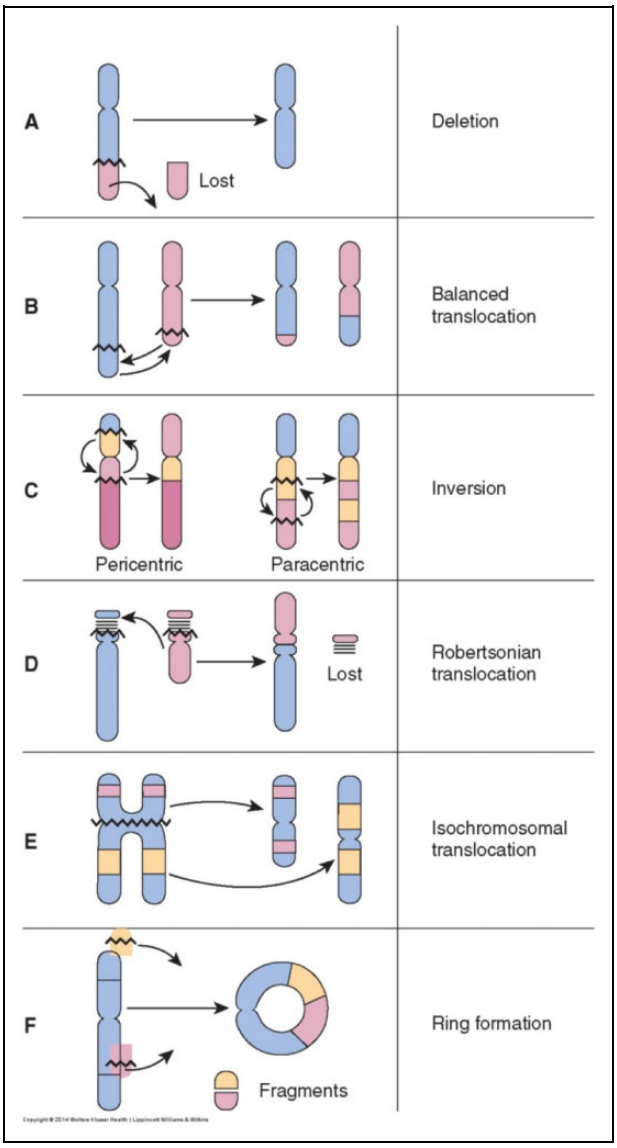

Figure 3. Structural abnormalities in the human chromosome. (A) Deletion of part of a chromosome leads to loss of genetic material and shortening of the chromosome. (B) A reciprocal translocation involves two nonhomologous chromosomes, with exchange of the acentric segment. (C) Inversion requires two breaks in a single chromosome, with inversion to the opposite side of the centromere (pericentric) or with the fragment inverting but remaining on the same arm (paracentric). (D) In Robertsonian translocation, two nonhomologous acrocentric chromosomes break near their centromeres, after which the long arms fuse to form one large metacentric chromosome. (E) Isochromosomes arise from faulty centromere division, which leads to duplication of the long arm and deletion of the short arm, or the reverse. (F) A ring chromosome forms with breaks in both telomeric portions of a chromosome, deletion of the acentric fragments, and fusion of the remaining centric portion. Adapted from Rubin and Strayer (2012, p. 223). [*Copyright 2012 by Wolters Kluwer. Reprinted with permission.*]

Duplication of a gene or a portion of a gene on a chromosome can result from a variety of errors in DNA replication or repair and may affect the phenotype by altering the amount of

protein synthesized. For example, Charcot–Marie–Tooth disease type 1A, a demyelinating peripheral neuropathy, is caused by duplication of the gene encoding peripheral myelin protein 22 on Chromosome 17 (Bird, 2015).

Isochromosome formation involves both a deletion and a duplication. Isochromosomes form when the centromere separates horizontally instead of vertically, resulting in a duplication of the long arm (*q*) and deletion of the short arm (*p*) or the reverse. Isochromosomes in a fetus are generally lethal, especially when they occur on an autosome. However, some patients with Edwards syndrome have an isochromosome 18q, and isochromosome Xq is found in some patients with Turner syndrome (Jorde et al., 2016).

Translocations occur when a portion of one chromosome is transferred to another chromosome. If genetic material is transferred from one chromosome to another with no exchange, the translocation is labeled *nonreciprocal.* In *reciprocal* translocation, chromosomal material is exchanged between two nonhomologous chromosomes. If a reciprocal translocation occurs during gamete formation and no genetic material is lost, the translocation is said to be *balanced.* If the translocation is inherited from a healthy parent, the fetus will likely be healthy. However, gametes formed by persons carrying a balanced translocation are at risk of having offspring with *unbalanced* translocations that may cause abnormalities or result in early pregnancy loss (Grossman, 2014).

A *Robertsonian translocation* is a special case of nonreciprocal translocation that can have clinical significance. In a Robertsonian translocation, two long arms of different chromosomes fuse, and their short arms, having little genetic material, may be lost without consequence. Robertsonian translocation carriers, despite having only 45 chromosomes, are typically unaffected because they have all of the necessary protein-coding DNA. However, gametes of carriers have an atypical number of chromosomes, so their offspring may inherit too little or too much genetic material, which is the scenario in about 5% of Down syndrome cases. A child with translocation Down syndrome has the normal number of chromosomes (46), but three copies of the long arm of Chromosome 21. One parent of a child with translocation Down syndrome is a carrier of the translocation and has a higher recurrence risk of Down syndrome in subsequent pregnancies than parents of children with Down syndrome caused by nondisjunction (Grossman, 2014).

An *insertion* is another type of nonreciprocal translocation, which results when a segment from one chromosome is deleted from its normal place and inserted into another chromosome. Like all rearrangements, insertions can cause disease by disrupting a gene or altering gene regulation. Insertions may also cause disease in the offspring of an otherwise healthy insertion carrier (Nussbaum et al., 2016).

Inversions occur when two breaks in a single chromosome allow a reversed DNA strand to reincorporate back into the same chromosome. In a *pericentric* inversion, the inverted fragment goes to the opposite side of the centromere. In a *paracentric* inversion, the centromere is not involved and the inverted fragment remains on the same arm of the chromosome

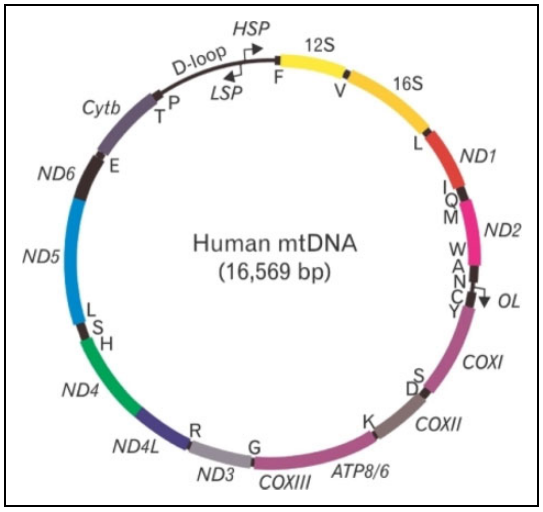

Figure 4. Schematic representation of the human mitochondrial genome. The genome encodes two ribosomal RNAs (12S and 16S), 22 transfer RNAs (indicated by single-letter abbreviation) between the coding genes, and 13 essential genes that encode subunits of the oxidative phosphorylation enzyme complexes. From Open-i Biomedical Images https://openi.nlm.nih.gov/detailedresult.php?img=PMC2998782_acb-43-97-g001&req=4#.WFlF_NxEXsg.email

(Grossman, 2014). Inversions may go unnoticed, especially if they are balanced, or cause no extra or missing DNA. However, inversions may have a role in disease, either directly or as a result of abnormal DNA arrangements in the offspring of inversion carriers (Puig, Casillas, Villatoro, & Cáceres, 2015).

Mosaicism

Errors in mitosis after fertilization can lead to a situation called *somatic mosaicism*. These errors happen sometime after the first zygotic division and only affect descendants of the cell line that experienced the error. An individual with a mosaicism will have different karyotypes in different cells. When this happens in disorders such as Down syndrome or Turner syndrome, the affected individual, with some unaffected cells and some affected cells, may have a milder phenotype (Grossman, 2014; Tinley, 2016). Increasing evidence suggests that genetic mosaicism is a common phenomenon that helps to explain diversity in healthy persons but is also a typical characteristic of malignant tumors (Fernández, Torres, & Real, 2016). *Germ line mosaicism* occurs when a mutation arises in the cells that form the sperm or egg of the parent. The parent will not have the disease, but all the cells that descend from the affected sperm or egg will carry the mutation. Although rare, germ line mosaicism has been identified in some diseases, including the lethal perinatal form of osteogenesis imperfecta (Jorde et al., 2016).

Mutations in mtDNA

Mitochondria reside in the cytoplasm outside the cell nucleus and contain their own DNA (mtDNA), a double-stranded closed circle containing only 37 genes (Figure 4). Many of the

mtDNA genes participate in oxidative phosphorylation, the process that uses oxygen and simple sugars to create adenosine triphosphate, the body's primary energy source. Cells may contain over 1,000 mitochondria, each with more than one genome. mtDNA is inherited from the mother, since sperm contain only a small number of mtDNA molecules. mtDNA, which does not segregate equally during cell division, differs in each cell and contributes to differences between monozygotic twins. Mutations in mtDNA are scattered randomly across the mitochondria and result in disease only when the amount of mutant mtDNA sufficiently outweighs the amount of normal mtDNA (Nussbaum et al., 2016).

Disorders of mtDNA, although rare, commonly affect tissues with a high energy requirement such as those of the neuromuscular system. For example, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes result from one of several mtDNA mutations and cause muscle weakness, stroke-like signs, sensorineural hearing loss, headaches, loss of appetite, vomiting, and seizures. Mitochondrial diseases typically exhibit a wide variability of clinical manifestations (Alexander, 2016).

Mitochondrial disease is not limited to conditions inherited at birth. Because mtDNA possesses a relative lack of DNA repair mechanisms and is exposed to damage from free-oxygen radicals generated during oxidative phosphorylation, it has a mutation rate that is 10 times higher than that of nuclear DNA. Much recent attention has been given to the role of mtDNA mutations in late-onset conditions, such as Alzheimer's disease, cancer, Parkinsonism, and even the normal aging process (Grossman, 2014; Jorde et al., 2016; Kurnat-Thoma, 2015).

Cancer Genetics

Cancer results from uncontrolled cell growth caused by genetic alterations in cell regulatory mechanisms. Many of the types of DNA alterations I have discussed in this article can also lead to malignant cell transformation. For example, aneuploidy occurs in the cells of virtually all cancers (Harith & Lengauer, 2004). When aneuploidies occur during somatic cell division (mitosis), malignancy can result as the daughter cells lose the characteristics of the parent over many cell divisions. Rearrangements and translocations that occur from errors during mitosis are associated with cancer development. A well-known example is translocation between Chromosomes 9 and 22, called the Philadelphia chromosome, found in chronic myelogenous leukemia (Zheng, 2013). Somatic mutations in mtDNA have been found in a broad range of primary human cancers, although the causal mechanisms remain largely unknown (Santos et al., 2008). Although 75% of cancers are sporadic and occur from malignant transformations in somatic cells, some mutations associated with cancer are inherited via the germ line. Well-known examples of inherited, cancer-related single-gene disorders include hereditary breast and ovarian cancer and hereditary colon cancer (Edwards, Maradiegue, & Jasperon, 2016). Our expanding understanding of genomics is having a significant impact on cancer detection and treatment and underlies the precision medicine initiative of the National Institutes of Health (2016).

Summary and Conclusion

Humans are diverse and evolving. Our understanding of the genetic mechanisms that make us similar to and different from one another and the implications these mechanisms have for health is progressing at a rapid pace. The order of nucleotides on the DNA molecule plays an important role in normal cell division, tissue development, and reproduction but is also susceptible to alteration from a large number of random, inherited, or environmental events. Knowledge of human genetic variation holds promise, not only for advancing health care but also for increasing our understanding of evolution, population migration, and human relationships. Practicing nurses need a solid background in genomics in order to assist patients to make informed decisions in an era of personalized health care and precision medicine, and nurse researchers on multidisciplinary teams are key to ensuring the relevance of translational genomic science.

Author's Contribution

Catherine Y. Read contributed to conception, design, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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