Genomic Essentials *for* Graduate Level Nurses

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Preface

The purpose of this book is to improve the genomic competency of nurses prepared at the graduate level. The more informed graduate level nurses are about the rapidly evolving field of genomics, the more likely they are to apply it at the point of care, and the more prepared they will be to engage in conversations about how, when and where genomic technologies should be used in healthcare systems.

In 2009, a group of fifteen graduate nurses with genetics/genomics expertise from around the U.S. began a 2-year process to develop 'The Essential Genetic/Genomic Competencies for Nurses with Graduate Degrees," an expanded set of genetic/genomic competencies tailored to meet the needs of nurses prepared at the graduate level. The competencies have two major domains, with each divided into seven major categories. The first domain, Professional Practice, includes (1) Risk Assessment & Interpretation; (2) Genetic Education, Counseling, Testing and Results Interpretation; and (3) Clinical Management. The second domain, Professional Responsibilities, comprises: (4) Ethical, Legal and Social Implications (ELSI); (5) Professional Role; (6) Leadership; and (7) Research.

The present volume evolved from and is based on constructs found in the graduate essentials mentioned above, and many of the chapters are authored by nurses who participated in developing the competencies. A number of chapters address the competencies in a clinical setting, while others, e.g., chapters 4 and 16, are focused exclusively on a single category within the competencies. The first five chapters provide the scientific underpinnings for genomic practice, which are Basic Genetic/Genomic Concepts, Risk Assessment, Genetic Testing and Counseling, ELSI and Pharmacogenomics. The next four chapters present genomic issues across the human lifespan: Preconceptual/Prenatal, Newborn Screening, Pediatrics and Aging. The following six chapters review genetic and genomic contributions to disorders of selected body systems: Respiratory, Cardiology, Hematology, Neurology, Endocrine and Cancer. The next two chapters discuss issues unique to nursing, Genomics in Nursing Research, Practice, Administration & Education and Genomics and Symptomatology. The final chapter, Genomic Technologies, offers a glimpse of genomic advances that are being translated into clinical application. Because genomic science is evolving so quickly, new information was emerging daily as this book was being prepared. Each chapter therefore should be considered an orientation and introduction to a topic, in contrast to a comprehensive resource.

We would like to thank the talented inter-professional team of nurses, physicians, researchers, scientists, geneticists and genetic counselors who worked with us to turn an idea into reality. Inter-professional education and collaboration, endorsed by the Institute of Medicine and the American Association of Colleges of Nursing are essential to improve outcomes in today's healthcare environment. This book's collaborating authors represent a highly experienced group of health care professionals from a number of different specialties, including: advanced practice registered nurses (many who have received post-doctoral training at the National Institutes of Health or National institute of Nursing Research), board-certified advanced genetics nurses, certified genetic counselors, physicians, nurse ethicists, molecular geneticists, nurse genetic scientists, nurse academicians, nursing leaders and administrators. Working in hospitals, specialty clinics, universities, laboratories and pharmacies throughout the world, these specialists devoted many hours to researching and writing chapters, sending references we may never have found otherwise, and furnishing valuable insight and support across the entire life of this writing

project. We wholeheartedly thank each and every contributor.

We hope readers find this book useful, informative and interesting. In creating it our ultimate goal has been to produce a resource that will improve healthcare outcomes for individuals, their families and communities by moving nursing one step closer to the further goals of personalized healthcare and precision medicine.

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Introduction to Basic Genetics and Genomics

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Objectives:

- Describe the difference between "genetics" and "genomics".
- Explain the similarities and differences between mitosis and meiosis.
- Discuss normal and abnormal chromosome structure.
- Explain how DNA and RNA function in creation of gene products.
- Describe various alterations in the genetic code and their functional effects.
- Discuss details of each of the patterns of inheritance.

1.1. INTRODUCTION

Basic genetic/genomic concepts need to be understood to meet competencies outlined in the *Essential Genetic and Genomic Competencies for Nurses with Graduate Degrees* (Greco, Seibert & Tinley, 2012). This chapter provides a foundation for the remaining chapters in this book by offering a review of the basic principles of "genetics," and introduces the concept of "genomics." The traditional science of "genetics" is focused on exploring and explaining the impact of individual (or single) gene or chromosome changes, most of which are individually quite rare, on health. The broader term, "genomics," considers the interactions between and within genes, regulatory sequences, and the environment. Genomics research is improving our understanding of genetic disorders, common complex health problems such as diabetes and heart disease, and disease prevention and treatment response. The basic science of "genetics" has evolved into "genomic healthcare." For simplicity and continuity, the term genomics will be used throughout this book except when addressing specific genetic concepts or conditions. Because the genomics education of our readers may vary substantially, there are references at the end of the chapter to resources that can provide additional information. The reader is encouraged to refer back to these resources in the future, to stay current with the rapidly changing field of genomics and its impact on specific areas of nursing practice, administration, research, and education.

1.2. DNA STRUCTURE AND REPLICATION

1.2.1. Structure of DNA and Chromosomes

Deoxyribonucleic acid (DNA) is the molecule that provides the genetic instructions for the development, growth, and ongoing functioning of any human being. There are two different cellular locations for DNA, in the nucleus (nuclear DNA [nDNA]) and in the mitochondria (mitochondrial DNA [mtDNA]). The nucleus is the location for the vast majority of human DNA; except in areas where both types of DNA are being discussed, it can be assumed that DNA is used to refer to DNA in the nucleus.

DNA is composed of two strands of polynucleotides. Each nucleotide is made up of a five carbon sugar, a phosphate, and a nitrogenous base. The appearance of DNA has been compared to a ladder which is coiled around core units of eight histones to provide support and stability to the structure.

The two sides of the ladder are composed of the alternating sugar and phosphate, and each sugar phosphate unit has a base attached. Hydrogen bonding between the bases holds the two strands together, forming the rungs of the ladder. One of the bases in a pair is larger, a purine, and the other is smaller, a pyrimidine. The purines

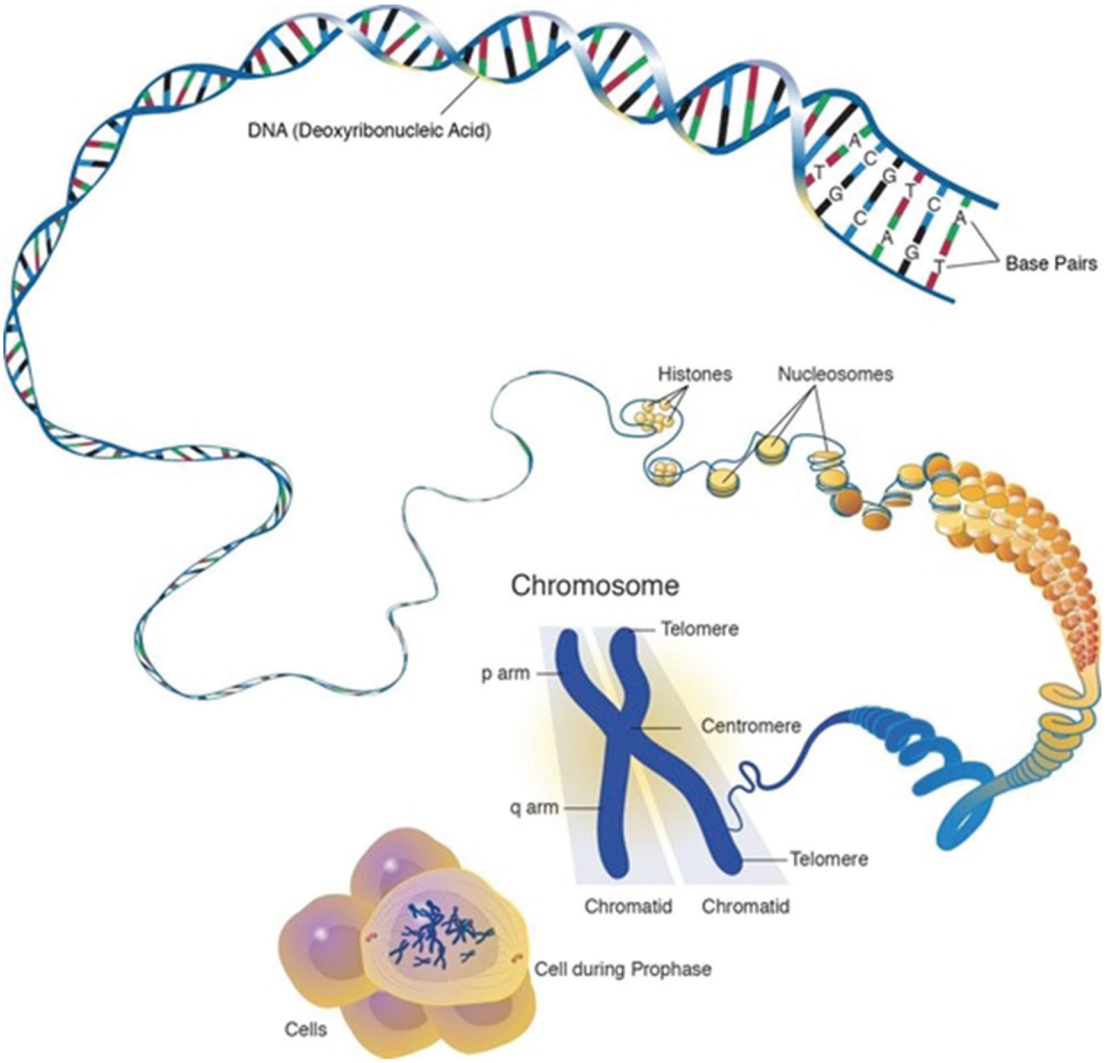

FIGURE 1.1. Chromosome. (Figure from the National Institutes of Health. National Human Genome Research Institute. Digital Media Database. Darryl Leja/NHGRI/NIH. Available at: http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85281.)

are adenine and guanine (A and G) and the pyrimidines are cytosine and thymine (C and T). The pyrimidine thymine always pairs with the purine adenine (A and T) and the pyrimidine cytosine always pairs with the purine guanine (C and G). This consistent pairing is essential when the DNA replicates itself during cell division and during transcription and translation of the DNA code into proteins. A gene is a unit of the DNA that provides the code for a protein (Figure 1.1).

The nuclear DNA, which will be the primary focus of this chapter, is packaged into 23 pairs of chromosomes. Within each pair, 1 chromosome is maternally derived and the other is paternally derived. Of the 23 pairs of chromosomes, 22 are the same for males and females and are called autosomes, numbered "1 to 22," with 1 being largest and 22 the smallest. The 23rd pair of chromosomes determines the sex of the individual: XX for females and XY for males. The Y chromosome carries approximately 50 genes (National Library of Medicine [NLM] [U.S.], 2014a), whereas the X chromosome, which is much larger, carries approximately 2,000 genes (NLM [U.S.], 2014b).

The chromosome consists of two arms joined at a constriction point called the centromere. The shorter of the two arms is the p arm (for "pe-

FIGURE 1.2. Acrocentric, Metacentric, and Submetacentric Chromosomes. (Figure adapted from U.S. Department of Energy Genomic Science Program's Biological and Environmental Research Information System (BERIS). Individual chromosome illustrations available at: https://public.ornl.gov/site/gallery/default.cfm?restsection=.)

tite") and the longer arm is the q arm. Some of the pairs of chromosomes are the same size, but the centromeres are located in different positions on the chromosome. Chromosomes with centromeres located in the center (chromosomes 1, 3, 16, 19, and 20) are called metacentric; those with off-center centromeres (chromosomes 2, 4 to 12, 17, 18, X, and Y) are called submetacentric; and those with centromeres at the tip of the chromosome (chromosomes 13, 14, 15, 21, and 22) are acrocentric (Figure 1.2).

Another way of differentiating the chromosome pairs, in addition to their size and centromere placement, is by the distinctive patterns of

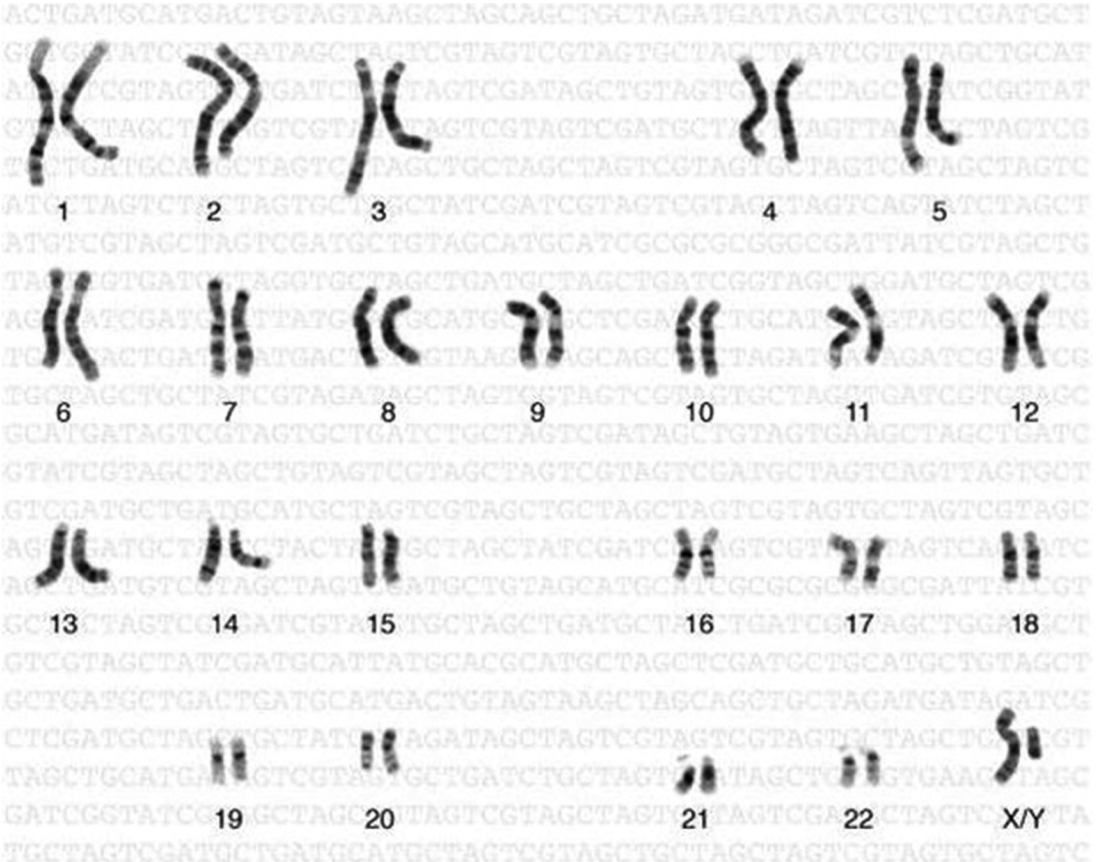

FIGURE 1.3. Chromosomes of the Human Genome. (Figure from National Human Genome Research Institute. Digital Media Database. Darryl Leja/NHGRI/NIH. Available at: http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85175.)

light and dark bands (Figure 1.3). The tips of the chromosomes (similar to shoelace tips) are called telomeres (Figure 1.1), which act as a cap to prevent the chromosome from unraveling. Telomeres are made of many repeats of the sequence "TTAGGG," and each time a cell divides, 20 to 30 of these TTAGGG repeats are lost. When all the telomere repeats are completely gone, the cell dies. Germ cells produce an enzyme called "telomerase," which restores the telomeres to their original length so that at fertilization, there are sufficient repeats for the new individual's lifetime (Read & Donnai, 2011).

1.2.2. The Cell Cycle

Each somatic cell goes through a cycle from its formation to its division into two daughter cells. There are four phases in each cell cycle: Gap1 (G1), S, Gap2 (G2), and M (Figure 1.4). During G1, the longest phase, individual chromosomes cannot be distinguished, because the DNA is unwound (extended) to allow easy access to the genetic code for protein production.

During the "S" phase, the DNA is reproduced in the process of replication (Figure 1.5) so that each daughter cell receives an exact copy of the DNA from the original cell. During replication, the hydrogen bonds between the bases break so that the two strands of the DNA can separate. The bases of each strand attract new nucleotides with complementary bases, and hydrogen bonds form between the bases to hold the new strand to the old strand. Replication does not occur at the same time in all of the chromosomes or even within any given chromosome, but by the end of the S phase, all of the chromosomes are completely reproduced. Each of the original two DNA strands have been a template for a new complete molecule of DNA that is an exact copy of the original. The two identical copies of the chromosome are called sister chromatids, and they are held together at the centromere.

In the G2 phase, any replication errors that occurred during the S phase are detected and repaired. If the errors are too numerous or severe, programmed cell death (apoptosis) occurs. Malfunction in the process of apoptosis can lead to the development of cancer, which is discussed in greater depth in Chapter 15.

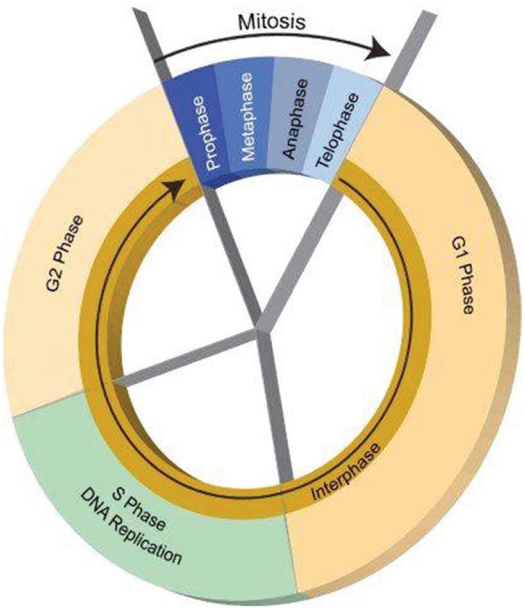

FIGURE 1.4. Cell Cycle. (Figure from National Human Genome Research Institute (NHGRI) Digital Media Database. Darryl Leja/NHGRI/NIH. Available at http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85276.)

1.2.3. Mitosis

The M phase of the cell cycle is the phase in which the cell divides, forming 2 new cells. In somatic cells, this phase is called mitosis (Figure 1.6). During the first stage of mitosis (prophase), the chromosomes become tightly coiled and visible under a microscope. The nuclear membrane disappears and spindle fibers develop at the centrioles at either side of the cell, and the free end of the spindle fibers attach to the centromeres. During the second stage (metaphase), the chromosomes are highly condensed and most easily visualized under the microscope. During metaphase, the chromosomes are arranged along the equatorial plane of the cell, and the spindle fibers begin to contract, pulling the sister chromatids apart. During the third phase (anaphase), all the centromeres divide and the spindle fibers pull one sister chromatid to one side of the cell and the other to the opposite side. At the end of anaphase, there should be 92 chromosomes, with 46 on either side of the cell. During the next phase (telophase), a nuclear membrane develops around each group of 46 chromosomes, which are beginning to extend into indistinguishable

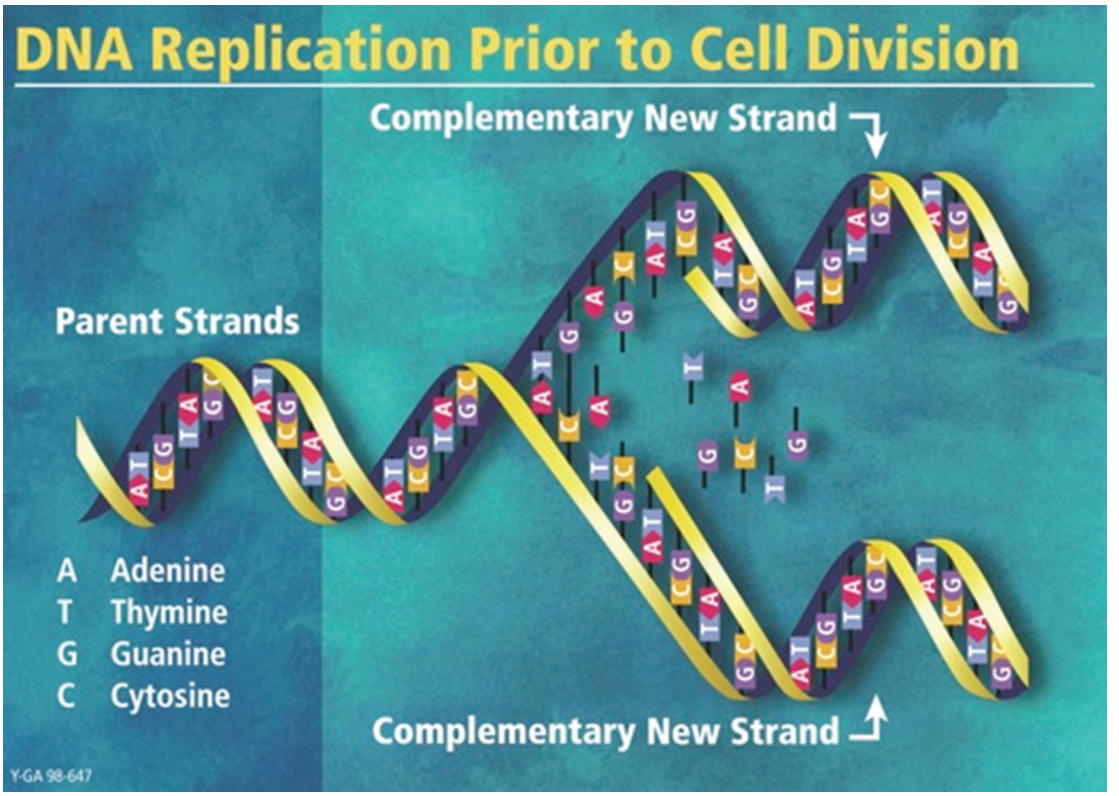

FIGURE 1.5. DNA Replication Prior to Cell Division. (Figure from Human Genome Program, U.S. Department of Energy, *Genomics and Its Impact on Science and Society: A 2008 Primer*, 2008. [Original version 1992, revised 2001 and 2008.] Available at: https://public.ornl.gov/site/gallery/detail.cfm?id=393&topic=&citation=&general=DNA%20replication&restsection=all.)

structures again. The division of the cytoplasm (cytokinesis) follows, forming two daughter cells which are identical to the original cell. These two daughter cells then enter interphase, which corresponds to G1, S, and G2 of the cell cycle.

1.2.4. Meiosis

A different series of cell division steps occurs during meiosis, ultimately reducing the number of chromosomes in germ cells (sperm and ova) from 23 pairs (46 individual chromosomes) to 23 single chromosomes (Figure 1.7). To accomplish this, two cell divisions are required. As in mitosis, during meiosis, DNA replicates during prophase I, which occurs prior to the first meiotic division. In meiosis, prophase I is divided into five periods:

Leptokene: DNA becomes condensed, but the two chromatids are so tightly associated, they cannot be distinguished.

Zygotene: Chromosomes pair up (e.g., maternal chromosome 12 pairs up with paternal chromosome 12) and are held tightly together by the synaptical complex.

Pachytene: Chromosomes condense even further and some genetic material from one chromosome trades places with genetic material of the other chromosome, creating four unique chromatids. This exchange is called crossing over or recombination.

Diplotene: The synaptical complex disappears and the chromosomes in each pair start to separate. The two chromatids of each chromosome are still held together at the centromere.

Diakenesis: The chromosomes reach maximum condensation.

After prophase, the division steps proceed as in mitosis: the nuclear membrane dissolves, and the chromosome pairs align along the cells equatorial plane (metaphase I). Each pair then splits, and the individual chromosomes assort

randomly, with some paternally derived chromosomes going to one pole and others to the other side, and similarly with the maternally derived chromosomes (anaphase I). Because of random assortment of maternally and paternally derived chromosomes, there are 2^{23} or > 8 million possible chromosomal combinations. This tremendous potential for diversity is further increased by the crossing over that occurs during the pachytene period of prophase 1 (Clancy, 2008). The chromosomes group at either pole during telophase I and then the cell divides. The cell enters into a short interphase prior to beginning meiosis II.

During prophase of meiosis II, the nuclear membrane disappears and the spindle apparatus forms. In metaphase II, the chromosomes line up in the center of the cell, and in anaphase II, the centromeres of the chromosomes separate as the spindle fibers pull the sister chromatids apart toward opposite poles. In telophase II, the nuclear membrane reforms and cytokinesis occurs so that there are now four cells, each having 23 chromosomes with a single chromatid. At the time of fertilization, the nuclei of the sperm and ovum join into one nucleus with 23 pairs of chromosomes, a unique combination of genetic information from mother and father.

1.3. NUMERICAL AND STRUCTURAL CYTOGENETIC ABNORMALITIES

Cytogenetics is the field that focuses on the examination of chromosomes for correct number and structure. A basic understanding of chro-

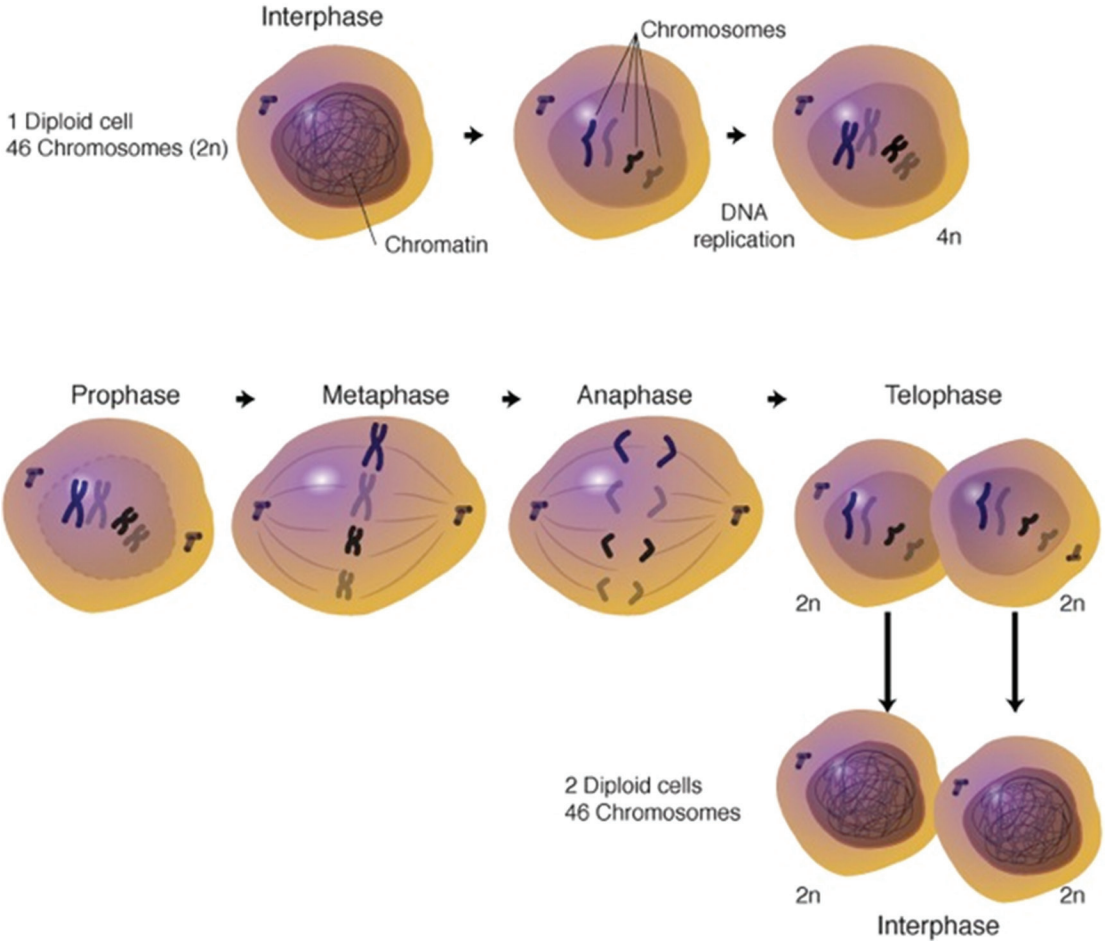

FIGURE 1.6. Mitosis. (Figure from National Institutes of Health, National Human Genome Research Institute. Digital Media Database. Darryl Leja/NHGRI/NIH. Available at: http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85204.)

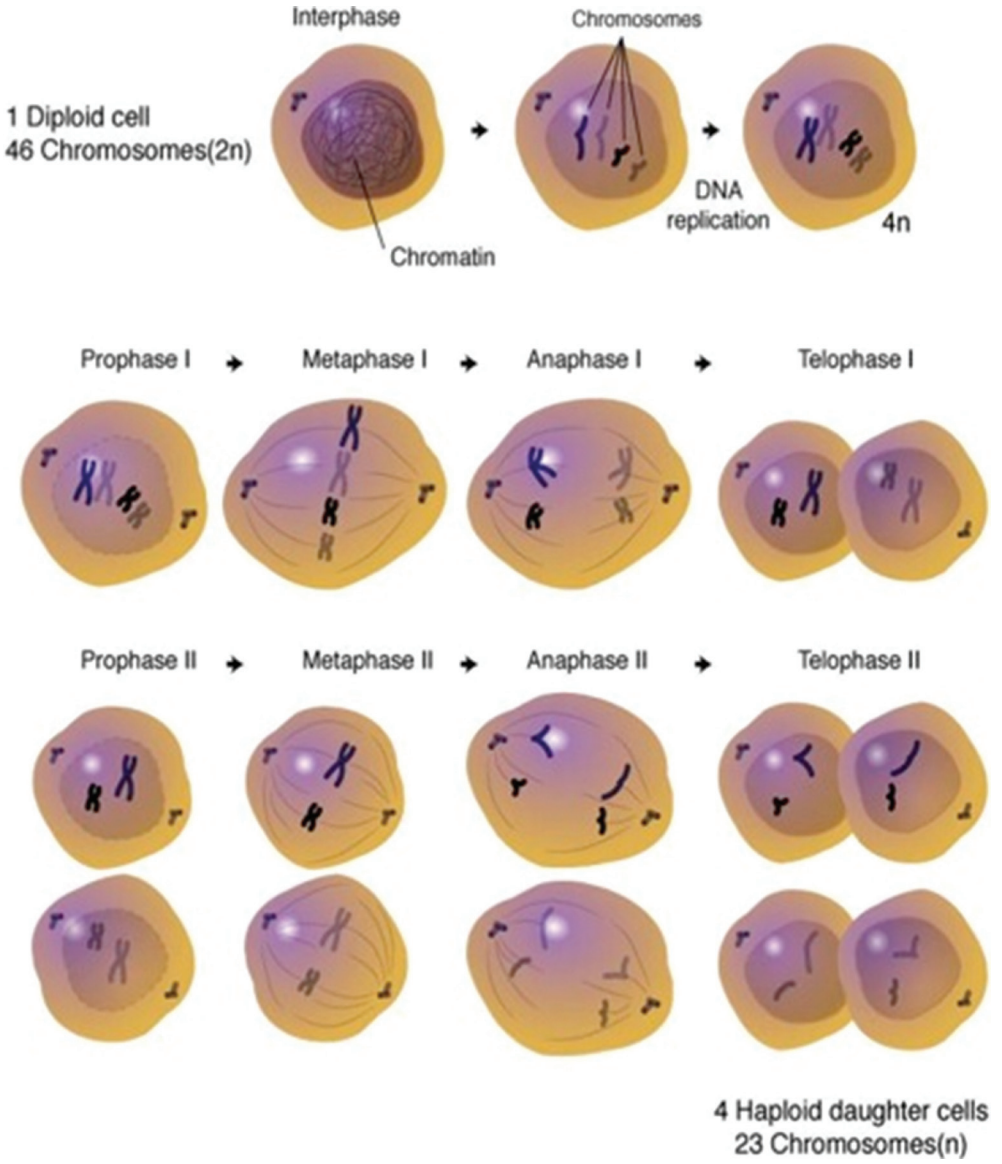

FIGURE 1.7. Meiosis. (Figure from National Institutes of Health. National Human Genome Research Institute. Digital Media Database. Darryl Leja/NHGRI/NIH. Available from; http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85196.)

mosomal abnormalities is particularly important when caring for prenatal and pediatric populations and in oncology settings, because chromosomal abnormalities occur during reproduction and may arise in malignant cells, particularly those found in leukemia, lymphoma, and some solid tumors.

1.3.1. Nondisjunction

Meiosis usually produces germ cells with 23 chromosomes ready for fertilization with another germ cell with its own 23 chromosomes. Occasionally, however, a nondisjunction error occurs and chromosomes or chromatids fail to separate. Nondisjunction errors can occur either during the first or second meiotic division. If the nondisjunction occurs in the first meiotic division, one daughter cell receives an extra chromosome and the other is missing one, and when these cells go through the second meiotic division, the error is passed on to their respective daughter cells.

If nondisjunction occurs during the second division, the chromatids of one chromosome fail to separate, and two copies go to one cell and none to the other.

If a germ cell with 24 chromosomes is fertilized, it will contain three copies of one chromosome (trisomy). Conceptuses with Trisomy 13, 18, and 21 may survive to birth, whereas trisomies of other autosomes are lethal. Chromosome 13 has approximately 300 to 400 genes that code for proteins (NLM, 2014c). chromosome 18 has approximately 200 to 300 genes (NLM, 2014d), and chromosome 21 has approximately 200 to 300 genes (NLM, 2014e), fewer than any of the other autosomes. If a germ cell with 22 chromosomes is fertilized (monosomy), the embryo rarely survives because too little genetic information is usually lethal. The one monosomy that is compatible with survival is Monosomy X (Turner syndrome [TS]), although it is estimated that up to 99% of Monosomy X conceptuses miscarry in the first or second trimester. It is theorized that those that survive to term have a mosaicism (Wolff, Van Dyke, & Powell, 2010).

1.3.2. Genetic Mosaicism

Genetic mosaicism is the result of a chromosomal nondisjunction or DNA mutation that develops during a very early mitotic division after fertilization. The individual develops with both normal and abnormal cell lines. Individuals affected with a chromosomal mosaicism usually are more mildly affected (milder phenotype) than someone with a meiotic nondisjunction, because at least some of their cells have a normal chromosomal complement. Females with TS (45 X) often have a mosaic form of the disorder.

1.3.3. Translocations

Some chromosomal abnormalities are due to translocations of which there are two major

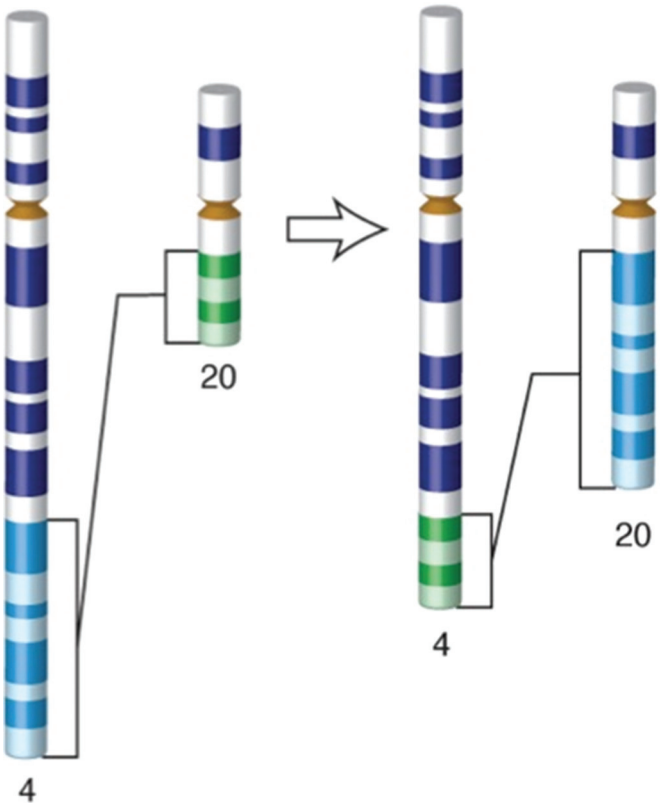

FIGURE 1.8. Reciprocal translocation. (Figure from National Institutes of Health. National Human Genome Research Institute. Digital Media Database. Daryl Leja/ NHGRI/NIH. Available at http://www.genome.gov/dmd/img.cfm?node=Photos/Graphics&id=85253.)

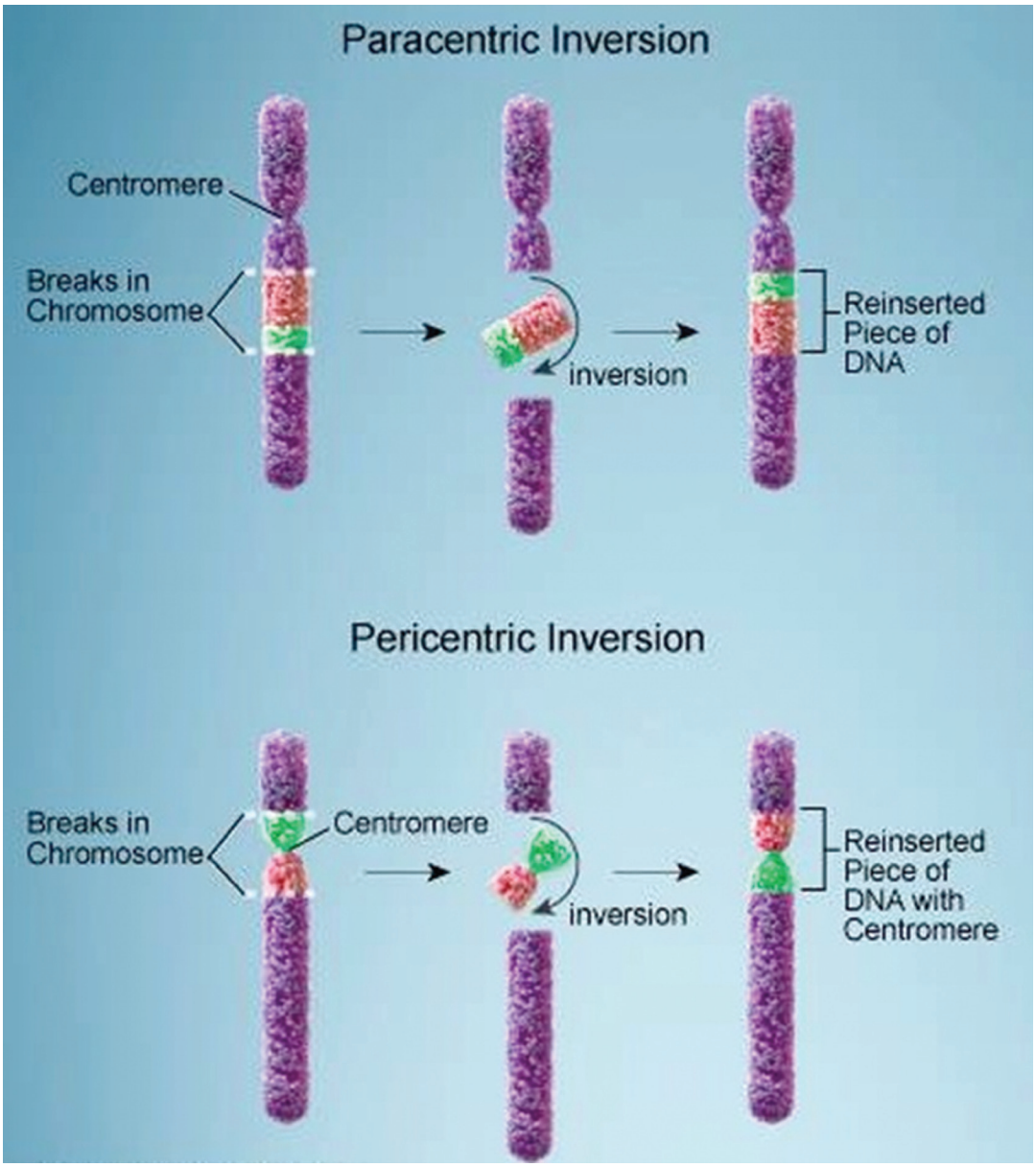

FIGURE 1.9. Chromosomal Inversion. (Figure from United States National Library of Medicine. Genetics Home Reference. Available at http://ghr.nlm.nih.gov/handbook/illustrations/inversion.)

types, Robertsonian and reciprocal. Robertsonian translocations develop when the centromere of one acrocentric chromosome fuses with the centromere of another acrocentric chromosome. The two most common types are Robertsonian and reciprocal translocations.

Robertsonian translocations should be considered when a couple has more than one child with Down syndrome (DS). Although DS is most frequently due to a nondisjunctional error, about 5% of DS is the result of an unbalanced Robertsonian translocation. In an unbalanced Robertsonian translocation of chromosomes 14 and 21, the offspring inherits the translocated chromosome as well as two normal 21s and one normal 14. The embryo has a normal number of chromosomes (46), but because of the fused 21 and 14, it inherits three copies of chromosome 21 and manifests the typical DS phenotype.

Standard nomenclature for translocation DS in

Genomics and Symptomatology

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Objectives:

- Discuss the impact of genomics on cancer related fatigue.
- Discuss the genes associated with pain.
- Explain the role of nursing regarding genomics and symptomatology.

18.1. INTRODUCTION

An individual's genome impacts the trajectory of their health and illness throughout life. Thus far, the focus of this book has been on the impact of genomics as it relates to an individual's response to drugs, their risk for developing diseases based on their family history, or as a result of shared genetic and environmental factors. Beyond health, illness, and the effectiveness of drugs, genomics also influences how an individual experiences a particular disorder—or the *symptomatology* of that condition. Research examining the genetics of common symptoms offers the promise of reducing adverse symptoms and improving quality of life, which is particularly important, because symptom management is a key function for nursing.

In this chapter, brief overviews of two common symptoms are discussed These symptoms are *cancer-related fatigue* and *pain*, as each of these symptoms have been shown to be influenced by genomic discoveries. The role of genomic variants (i.e., single nucleotide polymporphisms [SNPs]) influencing the onset, duration, or severity of symptoms, as well as how they influence therapeutic responses in preventing, alleviating, or eliminating patient's symptoms, will be discussed. Where applicable, other influences that may potentiate the effects of genomic variants in symptom manifestation and treatment will be described. Genomic advances in symptom management will help ensure that the right person receives the right therapy (personalized or precision health care), will reduce adverse effects, and will improve both quality of life and overall health outcomes.

18.2. GENOMICS AND CANCER-RELATED FATIGUE

Fatigue is a symptom manifested in patients that is associated with a wide range of diseases and syndromes that often affect individual's physical, social, and mental functioning (Landmark-Hoyvik *et al.*, 2010). It is also one of the most commonly reported symptoms in individuals diagnosed with cancer, often resulting in increased stress and anxiety and other health-related quality of life issues including, but not limited to, impaired physical performance, inactivity, helplessness, sleep disturbances, lack of appetite, and/or depression (Escalante, Kallen, Valdres, Morrow, & Manzullo, 2010; Horneber, Fischer, Dimeo, Ruffer, & Weis, 2012; Saligan & Kim, 2012). *Cancer-related fatigue* (CRF) is defined as a "distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (National Comprehensive Cancer Network (NCCN), 2015m p. MS-3). The symptoms of

CRF can occur during and after treatment of the cancer and are often attributed to treatment regimens, such as cytotoxic chemotherapy, radiation therapy, or other biological treatments. However, CRF can vary, occurring any time in the course of disease, and may be self-limiting or persisting for many years even after treatment (Bower *et al.*, 2006; Horneber *et al.*, 2012). For example, in one longitudinal study of breast cancer survivors, approximately 34% of the participants reported fatigue 5 to 10 years after diagnosis (Bower *et al.*, 2006). Similar effects regarding fatigue persistence after diagnosis and treatment have been reported (Husson *et al.*, 2013; Hwang *et al.*, 2014).

Fatigue among patients with cancer can be associated with multifactorial etiologies and manifest in a myriad of clinical features (Horneber *et al.*, 2012; NCCN, 2015). Contributing factors to fatigue include pain, emotional distress, sleep disturbances, and co-morbidities such as anemia; poor nutrition; physical inactivity; medication side effects; alcohol and/or substance abuse; therapeutic management with cytotoxic, biologic, or radiation therapy; or other medical conditions (National Cancer Institute, 2013; NCCN, 2015). However, the diagnostic criteria for CRF include fatigue, distress, or impairment due to fatigue, etiology related to cancer or cancer treatment, and the exclusion of underlying psychiatric or medical disorders. CRF is common, with studies revealing varied prevalence estimates ranging from 25% to 99% of patients with cancer experiencing this symptom, depending on the population and type of assessment (Bower, 2007). Most common clinical manifestations of CRF are focused on fatigue, lack of energy, exhaustion, or impaired physical function that can affect physical or psychosocial well-being of the individual (Horneber *et al.*, 2012).

The exact biological mechanisms of CRF are unknown; however, some proposed mechanisms associated with the symptom include 5-HT3 neurotransmitter deregulation, disturbances in hypothalamic regulation, dysregulation in circadian rhythm, skeletal muscle wasting, pro-inflammatory cytokines, or dysregulation of inflammatory cytokines (Barsevick *et al.*, 2013; Bower & Lamkin, 2013; Horneber *et al.*, 2012; NCCN, 2015; Ryan *et al.*, 2007). Genomic factors associated with inflammation have been linked to CRF prior to, during, and after treatment, particularly in the pro-inflammatory cytokine network (Bower & Lamkin, 2013). Molecular-genetics, particularly gene polymorphisms, have shown to possibly play an important role in the mechanism of CRF. One example is that of proinflammatory cytokine SNP that influences interleukin (IL) and/or tumor necrosis factor (TNF) genes (i.e., *IL1B; IL-6; TNFα*) and is associated with CRF both during and after treatment (Aouizerat *et al.*, 2009; Bower, 2007; Bower & Lamkin, 2013; Miaskowski *et al.*, 2010). Alteration in pro-inflammatory cytokine production of *IL6* and other inflammatory markers has been linked with persistent fatigue among breast cancer survivors (Bower *et al.*, 2006; Collado-Hidalgo, Bower, Ganz, Cole, & Irwin, 2006). Persistent CRF among patients with breast cancer has also been found to be associated with increased activity of pro-inflammatory transcription factors NF-κB activity and decreased expression of glucorticoid receptor anti-inflammatory transcription factors (Bower, Ganz, Irwin, Arevalo, & Cole, 2011). The association with CRF and cytokines, the proteins that mediate cell-to-cell communication, may be due to dysregulation of cytokines often attributed to cancer and cancer treatments that increase plasma levels of many cytokines, particularly the *TNF-α* and certain *IL* genes (Ahlberg, Ekmanb, Gaston-Johansson, & Mock, 2003; Ryan *et al.*, 2007). Cytokines are important for the development and functioning of the immune response, and aberrant expression from genetic polymorphisms have been associated with overall disease and functionality (Smith & Humphries, 2009). Pro-inflammatory cytokines, particularly *IL-1B, IL-6* and *TNF-α*, are thought to induce symptoms of fatigue via signaling of the central nervous system through varied somnogenic influence (Weschenfelder, Sander, Kluge, Kirkby, & Himmerich, 2012).

The nuclear factor NF-κB, pro-inflammatory transcription factor, for example, is activated by the cancerous tumor microenvironment (Aggarwal, 2004) and, thus, pretreatment CRF may be due to tumorigenesis (Bower & Lamkin, 2013). Fatigue often occurs also during treatment, particularly due to chemotherapy or radiation therapy; this effect has been associated with elevations in inflammatory markers secondary to the therapeutic intervention. For example, in one

study, changes in inflammatory markers, including C-reactive protein and IL1 receptor antagonist, were found to be associated with fatigue symptoms among certain individuals with breast and ovarian cancer (Bower *et al.*, 2009). CRF has been found to occur years after completion of therapy in breast cancer survivors and alterations in proinflammatory markers also have been found among these individuals (Collado-Hidalgo *et al.*, 2006; Orre *et al.*, 2009).

Besides pro-inflammatory genes, other genomic factors are currently being studied to determine their impact on fatigue among cancer patients. For example, the relationship between dysfunction in certain mitochondrial genes has been found among prostate cancer patients receiving external beam radiation (Hsiao, Wang, Kaushal, & Saligan, 2013). Advances in genomic technologies will certainly change the face of understanding the molecular impact of genetics and CRF that will enhance predicting and managing the symptoms and improving outcomes.

18.2.1. Future Implications—Cancer Related Fatigue and Genomics

Although many studies have shown an association with varied inflammatory markers and CRF among patients with cancer, causality has not been established and gaps in knowledge continue, warranting further research in this area (Saligan & Kim, 2012). Specifically, problems exist regarding measurement of CRF, exact understanding of the underlying biology of the symptom, and clinical trials targeted towards CRF (Barsevick *et al.*, 2013). However, future links between CRF and inflammatory markers may be a means to provide personalized/precision medicine as a prognostic biomarker for fatigue among cancer patients or genetic predictors of fatigue for therapeutic management (Collado-Hidalgo *et al.*, 2006; Jim *et al.*, 2012), as well as future development of effective treatments such as cytokine antagonists targeting CRF (Bower & Lamkin, 2013). Further, because fatigue is a complex symptom with phenotypic heterogeneity, the inclusion of biobehavioral research of fatigue may provide clarity and contribute to the understanding of CRF and to future development of genetic/genomic interventions (Lyon, McCain, Pickler, Munro, & Elswick, 2011). The international and interdisciplinary *GeneQoL Consortium* is one means to improve patient outcomes regarding issues that impact quality of life, including that of fatigue (GeneQol Consortium, 2015; Sprangers *et al.*, 2009). This consortium was established to investigate genetic disposition of patient-reported quality-of-life outcomes in order to gain insight on the impact of disease and treatment on patient outcomes (GeneQol Consortium, 2015). Clinical implications of the consortium are based on obtaining genetic knowledge, including understanding biological pathways that may impact quality of life (GeneQol Consortium, 2015), and incorporating understanding of the biological and genetic mechanisms of CRF (Barsevick, Frost, Zwinderman, Hall, & Halyard, 2010).

18.3. GENOMICS AND PAIN

Pain is universal and has been described since antiquity, and yet the biochemical pathways and pathophysiologic underpinnings of pain are only now beginning to be unraveled. An excellent review of the history of pain and pain management can be found in the article by Meldrum (2003). Despite the lack of understanding and effective therapies to manage pain, helping patients and families cope with the manifestations of pain has been a central feature and core mission area for nurses since at least the 19th century, when Florence Nightingale discussed pain management in "Notes on Nursing" (Nightingale, 1860). Since then, many resources have been developed to improve nursing competency in pain management, including a pain management nursing certification awarded by the American Nurses Credentialing Center; establishment of the American Society for Pain Management Nursing (ASPMN) in 1991, which publishes a journal dedicated entirely to nursing management of pain; and nursing competencies focused on pain management (http://mbon.maryland.gov/Documents/pain_management.pdf).

Over 100 million Americans suffer from pain every year (Institute of Medicine ([U.S.] Committee on Advancing Pain Research, 2011), and a recent study estimates that chronic pain is more expensive than cancer, heart disease, and diabetes, costing up to $635 billion a year (i.e., up to $300 billion in direct costs and $334 billion

in lost productivity) (Gaskin & Richard, 2012). Pain, a very important signaling mechanism in animals, plays a significant role in survival, because it forces the animal to protect an injury until it heals. Pain becomes chronic when the noxious stimuli persists after healing is complete, evolving into pain without a purpose. The *experience* of pain is highly variable; some people who experience acute pain from a noxious agent will develop chronic pain whereas others, exposed to the same causative agent, will not (Mogil, 2012). The *perception* of pain is highly individualized and subjective as well, as indicated by pain rating scores used in research and clinical settings. Finally, there is marked individualized variability in *response to analgesics*, with some people responding to very small doses and others requiring much larger doses to feel an effect (Aubrun, Langeron, Quesnel, Coriat, & Riou, 2003). All of this variability raises questions about the possibility that genetic factors could influence the experience of pain. More than 350 candidate genes have been associated with variability in pain sensitivity, and twin studies have clarified the heritability of pain in several specific conditions; however, to date, there are still many unanswered questions related to the basic genetic underpinnings of pain (Smith & Muralidharan, 2012).

Several classification systems have been developed to guide pain assessment and management. Some of the most common categorization systems include stratifying pain as acute or chronic, based on the length of time it has been present, or by intensity (mild to moderate, or severe). Numeric pain scales were developed to attempt to capture pain intensity. Physiologic changes (nociceptive, neuropathic, and inflammatory) and manifestations based on the affected tissue types (skin, muscles, viscera, joints, tendons, and bones) have also been used to categorize pain. Some diseases have classic pain characteristics; therefore, pain has been clustered by syndrome (cancer, fibromyalgia, migraine, etc.) (University of Wisconsin, 2014). This chapter reviews just a few of the areas being explored in the genomics of pain.

A few rare single gene disorders are associated with alterations in pain sensation, such as paroxysmal pain or a complete inability to feel pain. Although at first glance the genes appear to involve seemingly unrelated functional protein classes, on closer inspection, almost all the pathways involve the *SCN9A* gene in one way or another (Mogil, 2012). *SCN9A* encodes for the alpha subunit of the NaV1.7 sodium channel, expressed primarily in peripheral sensory nerves that transmit pain, touch, and smell signals to the central nervous system (Mogil, 2012). The role that *SCN9A* plays in more common pain responses is less clear (Young, Lariviere, & Belfer, 2012). Some studies have shown that variations in *SCN9A* alter pain responses (e.g., individuals with a G allele on *SCN9A* report lower pain scores compared with individuals having the less common A allele); other studies have been unable to consistently replicate those findings (Starkweather & Pair, 2013)

Genome wide association studies (GWAS) are changing the landscape of genomic research. GWAS tools such as computerized databases containing the reference human genome sequence, a map of human genetic variation, and new analytic technologies that can cheaply, rapidly, and accurately analyze whole-genome are making it possible to locate the genes associated with common diseases, such as asthma, diabetes, and heart disease. Once a new gene has been located, new strategies to detect, prevent, and/or treat a particular disorder can be developed.

Despite the rapid advances made in fields such as cardiology, oncology and hematology using GWAS, research into the genes associated with pain has lagged for several reasons. Reasons include the subjective nature of pain, relatively low funding levels, and associated lack of interest from researchers (Mogil, 2012). More recently, however, more research has been done to examine the genetic underpinnings of pain associated with diseases such as migraine headaches, osteoarthritis, endometriosis, Crohn's disease, and temporomandibular disorder (TMD) (Young *et al.*, 2012). Some of the genes found in these studies include a mutation in *ZNF429* and a gene upstream of the *RHBDF2* gene, whose function is currently unknown. Although no polymorphisms have been found in any of the known opioid receptor genes, ethnic differences appear to play an important role, because the strongest effect in one study was country of origin (Mogil, 2012). Despite the progress that has recently been made in understanding the genes associated with pain response, significant hurdles remain,

such as technology and data analysis limitations, explaining phenotypic heterogeneity, and the costs associated with conducting GWAS, which typically involve genotyping large numbers of people (Young *et al.*, 2012).

18.3.1. Epigenetics and Pain

As scientific understanding of epigenetic processes has increased over the past decade, there has been a concurrent surge of research exploring epigenetic mechanisms involved in regulating the nervous system, particularly the epigenetic processes associated with memory and synaptic plasticity (Denk & McMahon, 2012). Recent studies have found that epigenetic control is particularly important in three distinct areas: peripheral inflammation, pain processing, and plasticity.

When the body is exposed to a physical, chemical, or biologic insult, an inflammatory response develops rapidly to remove or destroy the injurious material, setting the stage for tissue repair and healing. Inflammation is commonly associated with pain, redness, heat, and swelling, which have been shown to increase healing, either because the injured person protects that area or because inflammatory cells, such as macrophages, produce high levels of insulin-like growth factor-1 (IGF-1), which increases the rate of healing and muscle regeneration (Lu *et al.*, 2011). The inflammatory response is highly complex, involving genes involved in a number of different processes, such as antimicrobial defense, immune response, tissue repair, and remodeling. Epigenetic changes in genes regulating macrophage function may play a particularly important role in inflammatory response, because they help macrophages change in response to different infectious organisms (Bayarsaihan, 2011). Epigenetic changes in T cells and monocytes, transcription factors found in several protein families (NF-κB, FOXP3, IRF, STAT), RE1silencing transcription factors (REST), and histones (i.e., histone H4 hyperacetylation) have all been shown to regulate inflammatory response (Bayarsaihan, 2011; Selvi, Mohankrishna, Ostwal, & Kundu, 2010).

Inflammation persisting beyond the normal healing period is considered "chronic inflammation" characterized by chronic infiltration of mononuclear immune cells and low antioxidant and high free radicals levels, creating an environment in which tissue healing is occurring at the same time tissue is being damaged, become a self-perpetuating cycle of injury, repair and usually, pain (Khansari, Shakiba, & Mahmoudi, 2009). Identifying the epigenetic mechanisms associated with the development of chronic pain may open the door to much needed advances in pain management (Denk & McMahon, 2012; Mogil, 2012). Epigenetic regulation of tissues in the nervous system is of particular interest, because these are the cells that generate and transmit pain signals, but also because the regeneration rate of individual neurons in the nervous system is very slow. The same neuron is likely to survive for decades, and because DNA is very resistant to change, epigenetic adjustments that occur over the life of the cell may be critical as they continually adapt to environmental stressors (Seo *et al.*, 2013). A neuron's use of epigenetics to adapt to the environment is particularly important because such changes are reversible; therefore, if pain develops because of an epigenetic change, a drug that chemically "resets" the neuron to its normal state might be a powerful therapeutic tool (Seo *et al.*, 2013). Although there is evidence from animal studies to demonstrate that it is possible to modify epigenetic mechanisms with drugs (Geranton, 2012), more research needs to be done before human studies can begin to ensure that the drugs do not alter epigenetic mechanisms in other tissues (Crow, Denk, & McMahon, 2013).

Reinforcing the idea that epigenetics plays an important role in the development and perception of pain, data from genomic studies examining pain response is often contradictory. For example, *ORPM1*, a common m-opioid receptor variant, has been shown to increase bendorphin binding and activation of g-proteins in some studies, but this effect is not found in all studies on a consistent basis. Similarly, in some studies, individuals with *COMT* variations were found to have greater sensitivity to pain, but the same association has not been seen in other studies (Bond *et al.*, 1998; Kim *et al.*, 2004; Zubieta *et al.*, 2003). These inconsistencies suggest that factors, such as epigenetics, may play an important role in pain phenotypes (Seo *et al.*, 2013)

Opioids are used to treat pain on a routine ba-

sis, and many opioids are now approved for use, each of which has different efficacy and adverse response profiles based on the individual. If an individual has a poor response to one opioid, another is usually tried in a trial and error fashion until the most effective drug is found. Because this random approach exposes individuals to adverse effects and decreases quality of life, as the search for an effective analgesic agent continues, there has been considerable interest in finding the genetic factors that explain the variability in response to opioids (Branford, Droney, & Ross, 2012).

Several studies have found an association between the *A118G* SNP in *OPRM1* and opioid dosing (Chou *et al.*, 2006a; Chou *et al.*, 2006b; Reyes-Gibby *et al.*, 2007), but similar to the issues with *OPRM1* mentioned above, a meta-analysis of genetic association studies concluded that the *A118G* SNP is inconsistently associated with pain-related phenotypes (Walter & Lotsch, 2009). It is becoming clear that the genes associated with pain relief are not the same genes that influence the development of adverse effects, highlighting the need to carefully choose and define the phenotype being studied. It is also very likely that interactions among multiple genetic and environmental factors are playing important roles in the phenotype (Branford *et al.*, 2012).

Acute pain transforms into chronic pain in a complex series of discrete pathophysiologic and histopathologic steps involving more than 2000 gene changes in over 400 candidate genes. Broadly, the process involves neurons that abandon the normal "modulated" response to pain (reversible activation of intracellular signal-transduction cascades) and adopt a more persistent "modified" response involving relatively permanent changes to neuron activation (Voscopoulos & Lema, 2010). A growing body of evidence suggests that nociceptor modifications can occur in response to psychological triggers, further complicating research efforts (Diatchenko, Fillingim, Smith, & Maixner, 2013).

Understanding the genomics of individual variability in pain sensitivity, analgesic response, adverse reactions, and triggers that transform acute to chronic pain is still in its infancy. Once the genomic roadmap has been created, the highly complex interactions between the environment and the human genes that regulate the pain response can then be explored, leading to a more effective and safe personalized approach to pain management.

18.4. NURSING ROLE AND SYMPTOMATOLOGY

Symptom management applies to nurses prepared at every level and practicing in virtually every setting—from nurses providing direct care to patients in inpatient and outpatient settings to conducting genomic research and to nursing faculty and nurses leading the largest health care systems. Nurses working at the point of care should be familiar with the emerging genetic information that helps support decisions that can improve the care of an individual patient, the goal of precision and personalized care. Nurses in faculty roles are responsible for ensuring that students entering nursing are well informed about genetics and are prepared to use emerging genomic information to improve patient outcomes. Nurse researchers might want to focus their scientific efforts on exploring the biological and behavioral aspects of symptoms such as pain and fatigue, with the goal of developing new knowledge and new strategies for improving patient health and quality of life (National Institute of Nursing Research, nd). Nurse administrators play a critical role, because they serve in key leadership roles as systems begin to integrate genomic discoveries into clinical settings in a meaningful way. Their support can accelerate nurses' use of genomic information as it continues to emerge from large population based studies.

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