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An Overview of Epigenetics in Nursing

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Synopsis

Science has evolved since the inception of the Human Genome Project to demonstrate that disease and health conditions evolve from a genetic/genomic element influenced by a multitude of factors (lifestyle, environment, etc.). Epigenetic changes to the genome are biochemical alterations to the DNA that do not change an individual's genome but do change and influence gene expression. As all nurses are trained in the biological sciences the profession is prepared to conduct and integrate epigenetic-focused nursing research into practice. The purpose of this paper is to (a) discuss current epigenetic nursing research; (b) provide an overview of how epigenetic research relates to nursing practice; (c) list recommendations; and (d) provide epigenetic online resources for nursing research. An overview of major epigenetic studies in nursing (specific to childbirth studies, preeclampsia, metabolic syndrome, immunotherapy cancer, and pain) will be provided as with recommendations on next steps.

Keywords

epigenetics; nursing; fetal; metabolic syndrome; cancer

Introduction

The last two decades of ongoing work in science has suggested that there is a genetic/genomic basis for health, illness, disease risk, and treatment response in health care. [1] Nurses have an intimate knowledge of patient, family, and community perspectives on health as well as basic science training in some cases. The profession of nursing tends to focus on health promotion and disease prevention, which are both fundamental to genetic/

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genomic health care practice. [2] Many diseases and conditions that affect the population have a genetic/genomic element influenced by environment, lifestyle, and other factors directly impacting patient care and the nursing profession. [2] Epigenetic changes include biochemical alterations to DNA molecules that do not change the sequence but does influence gene expression. [3] Epigenetic-related diseases have the following characteristics: (a) a heritability that could not be fully explained by strict genetic inheritance patterns (SNPs, mutations), (b) evidence of the influence of imprinting (maternal diet, or other *in utero* exposure to toxins, pathogens, drugs, etc.) which could influence the development of the disease in the offspring even into adulthood, and (c) an increase in prevalence with aging. [4] This last characteristic is based on an epigenetic model of complex disease. This suggests that with progressive accumulation of epimutations over the lifespan, a critical threshold is reached, this is beyond which the genome, cell, or tissue can no longer function normally, resulting in a diseased phenotype. [4–6] The two most commonly examined epigenetic mechanisms include histone modifications and methylation. [3] An epigenetic approach in research is used to examine complex, multifactorial diseases (eg., cancer, pain, cardiovascular diseases, childbirth, immunotherapy, and others) that have an environmental component associated with the condition or disease of interest. These technologies will soon becoming a driving force in patient management and care. The nursing profession bridging the interface of technology and nursing science, is prepared to conduct epigenetic-focused nursing research. [7] The purpose of this paper is to (a) discuss current epigenetic nursing research; (b) provide an overview of how epigenetic research relates to nursing in practice; (c) list recommendations; and (d) provide epigenetic online resources for nursing research. Based on the purpose stated above we will discuss major epigenetic studies in nursing currently found in the literature and provide recommendations on next steps. Topics to be covered in this overview include: childbirth studies, preeclampsia, metabolic syndrome, immunotherapy, cancer, and pain.

Epigenetics in Nursing

Epigenetic Impact of Childbirth (EPIIC)

A group of international nurses formed an interdisciplinary research collaboration investigating the state of the science concerning normal intrapartum epigenetic physiology. Their group, named the Epigenetic Impact of Childbirth has expertise in genetics, physiology, developmental biology, epidemiology, midwifery, and nursing. [8] They hypothesized based on years of research, clinical practice, and recent basic science evidence, that events during the intrapartum period of pregnancy, specifically the use of synthetic oxytocin, antibiotics, and caesarean section, affect the epigenetic remodeling processes and subsequent health of the mother and offspring. Numerous studies have linked mode of birth (particularly caesarean section) to increasing rates of asthma, eczema, type 1 diabetes, infant bronchiolitis, multiple sclerosis, and obesity. [9–20] The EPIIC hypothesis indicates that physiological labor and birth have a positive stress, known as eustress on the fetus and that this process has an epigenetic effect on particular genes, specifically those that program immune responses, genes responsible for weight regulation, and specific tumor suppressor genes. [9] Reduced or elevated levels of cortisol, adrenalin, and oxytocin produced during the labor process may lead to fetal epigenomic remodeling discrepancies which exert effects on abnormal gene expression. Effects of environmental stress on epigenetic changes and exposure to chemical and environmental toxins have been shown to disrupt epigenetic regulation of gene expression in cells by altering DNA methylation patterns [21–25] and chromatin structure, [21, 26–28] but may also have direct implications for a variety of human diseases including cancer, infertility, and neurodegenerative disorders. [29–32] The EPIIC group proposes a program of research to examine general patterns of epigenomic remodeling in neonates born after home births in the most familiar environment to the

woman without medical interventions, compared to those born after elective caesarean section for breech presentation, where there are no underlying medical complications preceding the caesareans. [9] They propose this research to include prospective longitudinal cohorts undergoing various methods of labor, diverse environments, multiple ethnic groups, gestational ages, maternal ages, socioeconomic backgrounds, and a range of interventions. This work should enhance our scientific and medical understanding of epigenetics related to the childbirth process and prolonged health of the mother and child.

Preeclampsia

Preeclampsia, a condition associated with pregnancy, is defined as an elevated blood pressure coupled with excess protein in the urine of pregnant women after 20 weeks of pregnancy, who previously had normal blood pressure. [33] If left untreated, this could lead to serious, even fatal complications for the mother or baby. Preeclampsia results from placental insufficiency leading to pregnancy-induced hypertension in the second half of the pregnancy, affecting 8–10% of women in the United States. [33] Nurse scientists have been studying the acute effects of preeclampsia and genetic origins of this disorder. [34, 35] They have begun pilot work towards examining DNA methylation patterns focusing on maternal nutrition status and placental programming through epigenetic alternations in DNA as a plausible explanation for maternal. [35] These nurses used genome-wide DNA methylation patterns, targeting genes producing proteins used specifically in vitamin D signaling. Their results suggest that vitamin D insufficiency in pregnancy is associated with increased blood pressure and risk for preeclampsia, further increasing risk for cardiovascular disease in mothers and offspring. Placental DNA hypermethylation in the genes, VDR and RXR were found to possibly reduce vitamin D binding and gene transcription, thereby reducing utilization during pregnancy and programming the fetal cardiovascular system for possible future risk of preeclampsia and hypertension. Other studies addressing immune function, endothelial function, thrombophilia variants, and other potential biomarkers for heritable risk of preeclampsia have been conducted by nurses as with examining maternal vitamin D as a determinant in gestational diabetes. [36, 37] While diet plays a role in determining gestational diabetes, nutrition also affects the genome in terms of epigenetics.

Metabolic Syndrome

Nurses are beginning to address the role of epigenetics in the development of cardiovascular disease (CVD), obesity, and diabetes. Metabolic syndrome is a clustering of these conditions or risk factors including hypertension, insulin resistance, and obesity [38, 39] In the case of CVD, although a family history of heart disease is an independent risk factor for the occurrence of heart disease, CVD does not follow a standard Mendelian pattern [40]. Nurse scientists have found that race and ethnicity, sex differences, age, and prenatal influences (such as maternal diet) point too an epigenetic role in the development of CVD [41]. While obesity is also a risk factor for CVD, the exact cause, like CVD is difficult to pinpoint. Obesity is related to an energy imbalance of too many calories consumed combined with inadequate exertion of physical activity. This relationship may also be associated with heritability, behavior, lifestyle, and genetic predisposition of obesity [38, 39, 42–45]. Roundtable discussions among basic scientists, clinicians, and researchers to address the issue of epigenetics and obesity highlights the need to work collaboratively to better understand the relationship between obesity and epigenetic changes to the genome. [46] Complications of obesity overtime lead to insulin resistance, which is associated with type 2 diabetes. Studies revealed commonality associated with gene-activated hyperglycemic events and chromatin modification as well as, miRNAs which have also been implicated in epigenetic mechanisms with insulin secretion and immune function. [4, 47] While this research has been explicated by basic scientists and researchers, the literature addresses the nursing profession as becoming aware of, interested, and active in elucidating genetic and

epigenetic mechanisms in the case of Metabolic Syndrome. A 2013 special Genomics issue of the Journal of Nursing scholarship has highlighted work on Metabolic syndrome, [38] CVD, [41] and others and have had accompanying webinars to inform the nursing community and general public about genomics in healthcare.

Immunotherapy

Immunotherapy is yet another area of medicine, using epigenetic research as a basis for evidence and to guide treatment effectiveness. Sometimes referred to as biologic therapy or biotherapy, immunotherapy uses certain parts of the immune system to fight diseases, such as cancer. This process begins by stimulating the immune system to work harder and smarter to attack cancer cells, or by providing the immune system with components such as proteins to better target cancer cells while boosting the immune system. [48] In the case of acute myeloid leukemia, antigen-specific immunotherapy has been applied in elderly patients such as by allogeneic stem cell transplantation. [49,50] Nurses are at the forefront of caring for patients undergoing allogeneic stem cell transplants from delivering immunosuppressive drugs to manage risk for infection, to the use of protective isolation, particulate air filters, managing patient hygiene, oral care, keeping a close eye on clinical indicators of febrile neutropenia, and frequent vital signs (the most important indicator of infection). [51] Care of these patients without nursing would not be possible, yet a gap exists whereby nurses have not extended the profession to include bench to bedside care in this domain.

While clinical trials are being conducted on pharmacotherapy, only a small fraction of the profession is involved in this area of medicine. The drug 5-azacytidine (5-aza), a hypomethylating agent approved for use in myelodysplastic syndromes, has led to a significant epigenetic regulating of cytokine genes and transcription factors. This suggests it may have the ability to be an effective immunotherapy treatment. [52–54] While strides are being made, large prospective studies aimed at correlating the induction of an efficient immune response with clinical responses in patients are warranted with nursing helping to recruit patients and being involved in the active process of clinical trials. The profession has the training background and knowledge to bridge the gap between bench science and bedside care. By involving nurses in greater basic science pursuits, in clinical trials, and comparative effectiveness studies, nursing could extend their scope and build a foundation for enhanced translational medicine in this burgeoning field of immunotherapy. [52] Cancer has also been an area of interest for epigenetic research as abnormal gene expression leading to cancer is like immunotherapy, multifactorial in nature. [55]

Cancer

Cancer can stem from genetic, infectious, radiation, environmental, hormonal or lifestyle factors which modify the structure of DNA. Nurses are involved in many aspects of cancer treatment from tumor profiling, cancer risk assessment, pharmacogenomics, and targeted therapy. [55] In the progression of cancer, epigenetic methylation is observed in certain cancers such as the RB1 gene associated with retinoblastoma. [56] This gene which is “turned off” means that gene expression is no longer possible. In another cancers such as colon cancer, methylation testing aids the provider to differentiate between sporadic colon cancers and Lynch syndrome. [55] As nurses at the forefront of patient care, the initial step the profession can take is in evaluating an individual or family through a cancer risk assessment. This assessment provides a definition to the individual or family regarding cancer risk based on health and family history, identifies individuals who may benefit from genetic testing, assesses the psychosocial and cultural implication of risk, and provides education counseling and psychosocial support. [55, 57, 58] Tumor profiling is the evaluation of genomic, proteomic, and epigenomic expression factors. Tumors are now known to differ not only histologically requiring different treatments but also molecularly.

Tumor profiling techniques influencing clinical care include immunohistochemistry staining (IHC), microsatellite instability (MSI), and microarray analysis. [55] Each of these techniques differ from one another but all are performed using a blood sample and these results inform the direction of care, consideration of genetic counseling, treatment regimens, and risk-reduction strategies. Nurses are involved in all of these processes.

Lastly, single nucleotide polymorphisms (SNPs) combined with pharmacogenomics (the study of how genomic factors determine an individual's response to drugs) are important to oncology care. Genetic testing can be performed for specific variants identified as interfering with the metabolism of a drug. Nurses can educate individuals regarding drug interactions and help individuals to understand why they may be receiving a different treatment for the same disease compared to another individual. [55] Oncology has changed to include nursing care in all aspects of patient care from risk assessment and prevention, to diagnosis and management. It is more important now than ever for the profession to be aware of developments in the field of epigenetics, genetics, and genomics.

Pain

Pain management is a major concern in the area of cancer treatment as is an issue for other chronic diseases as well. Pain is a pervasive symptom aligned with nearly every health condition or disorder. The epidemic of chronic pain, not necessarily associated with an underlying condition or trait, affects more than 100 million Americans. [59, 60] When comparing this number to 25.8 million Americans suffering from diabetes, [61] 16.3 million Americans suffering from coronary heart disease, [62] 11.9 million suffering from cancer, [63] and 7 million Americans suffering from stroke, it is clear that addressing pain in nursing care is essential. The present focus of nursing epigenetic research has centered on examining current knowledge of nociceptive pathways and alterations that could lead to pathologic pain. [60] Epigenetic mechanisms have been identified in the transition to, maintenance of, and response to pain and analgesics. [60] While nurse scientists did not map out the biochemical pathways identified in the literature, nurses have begun using epigenetic applications in response to pain management from initially identifying patients at risk for pain, to pharmacogenetic tests, guiding the selection of therapeutic modalities to target pain.

Nursing

Clinical practice

The knowledge science and nursing has gained from epigenetics concerns data related to chemical modifications and structure of the DNA which impact gene regulation. [64] The clinical value of epigenetic contributions to patient care are vast. As this research encompasses chromatin structure, activities of non-coding RNAs and DNA methylation, these modifications have the potential to guide diagnostic testing. Nurses are at the pivotal edge of patient care, collaborating with a variety of healthcare providers, and managing evidence-based research. Epigenetics unlike other genomic approaches, has a dual role in which epigenetic data can allow a better understanding of biological phenomenon and thereby health conditions related to the biological phenomenon of interest. [65] For nurses, this data can aid the profession in enhanced understanding in terms of variability of patient outcomes, therapeutic responses, and patient symptomatology. While the potential for manipulating epigenetic gene regulation through the modification of environmental factors such as nutrition is gaining, nursing must be kept up to date with advancing knowledge, technologies, and understanding of disease mechanisms. [64] With all this in mind, nurses must also seek to educate patients and families on the state of the science, dealing with uncertainty, managing expectations, explaining treatment choices, and targeted treatment. Nursing is a profession fueled by a multiplicity of roles and responsibilities and they are

exactly the right group of medical professionals to take on the job of incorporating epigenetics into clinical care.

Research practice

With the National Institute for Nursing Research's (NINR) Summer Genetics Institute (SGI), [66] a competitive tuition-free one-month intensive research-training program held at the National Institute of Health, nurses are able to gain a foundation of knowledge in molecular genetics. This program is grounded in increasing nursing research capability among graduate students and faculty and seeks to develop and expand clinical practice in genetics. Most of the nurses highlighted have gone through this program or similar ones such as the 18-week Web-Based Genetics Institute, which used the SGI as a template for development, education, and research efforts. [67] Nurses are already using the tools from this program and others in biobehavioral research, to describe epigenetic trends, and identify applications in the clinical setting for continued research. A table of epigenetic resources is provided (Table 1) with various online websites to aid the practicing nurse and nurse researcher in epigenetic tools, education modalities, and current research/practice trends. Nurses can continue in this vein by recruiting patients into studies, building the evidence base for epigenetic health care in nursing practice, and by leading in the translation of new knowledge and understanding of healthcare practice and pathways in research. [64]

Recommendations

In 2012, a Genomic Nursing State of the Science Advisory Panel was convened to develop a blueprint for genomic nursing science. [68] This framework was created to further genomic nursing science and to improve health outcomes using the state of the science and the NINR strategic plan to create nursing research priority considerations. The panel suggests that research focused on the value of nursing in the delivery of effective genomics-based care for individuals, families, communities, and populations will accelerate the translation of evidence into practice and this is critical for moving health care forward. [68] Increasing the capacity of nurse scientists in genetic, genomic, and epigenetic science will promote the application of research discoveries to benefit individuals. Perhaps the most critical and greatest challenge to nursing science and research though lies in nursing education. A prepared nursing workforce is essential to effective translation of genetic/genomic and epigenetic research to benefit patient care. [69] Nurses need to be able to explain to patients and families the implications of screening and testing, while explaining risk in an individualized context, regarding treatment options. They also need to be able to appraise new developments, technologies, and research appropriate for use in the clinical setting. The profession should possess a basic understanding of molecular laboratory science and be competent to translate their knowledge of physiology into a scientific setting. The role of nursing is fundamental to improving patient care, clinically and with research, and a growing body of evidence-based epigenetic nursing is arising. Continued research though is essential to health promotion, education, and disease management in order to drive clinical relevance and improved patient outcomes.

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Key Points

- This article focuses on the emerging role of the practicing nurse and nurse researcher in epigenetics.
- Major epigenetic studies in nursing specific to childbirth, preeclampsia, metabolic syndrome, immunotherapy cancer, and pain are examined.
- Evaluation of epigenetics related to nursing, clinical practice, and research, with recommendations for future work is discussed.

Table 1

Epigenetic Resources [3, 70]

Name	Web Address	Description
Genetics Home Reference	http://ghr.nlm.nih.gov/	National Library of Medicine website containing information on genetic conditions, genes, and chromosomes
Talking Glossary of Genetic Terms	http://www.genome.gov/Glossary/	A glossary with audible function from scientists at the NIH speaking definitions of terms. Illustrations and animations of genetic/genomic processes also provided.
Understanding the Basics of Microarrays	http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html	An overview from the National Center for Biotechnology Information (NCBI) on DNA microarrays, gene expression, the technology of microarrays, the importance of microarrays, and basic epigenetic microarray experiments.
Serial Analysis of Gene Expression (SAGE)	www.sagenet.org	Allows for the analysis of overall gene expression patterns with digital analysis, also provides SAGE applications, publications, and resources.
Gene Expression Omnibus (GEO)	http://www.ncbi.nlm.nih.gov/geo	A public repository and online virtual resource center for storage and retrieval of gene expression data. This site maintains microarray and serial analysis of gene expression (SAGE) data on many model organisms.
Histone Database	http://www.research.nhgri.nih.gov/histones	National Human Genome Research Institute histone database with histone sequence information and posttranslational modifications.

Name	Web Address	Description
Chromatin Structure and Function	http://www.chromatin.us/chrom.html	A site dedicated to information on chromatin biology, histones, and epigenetics.
Database for DNA methylation and Environmental Epigenetic Effects	http://www.methdb.de/	A human DNA methylation database site, open to the public.
CpG Island Searcher	http://www.uscnorris.com/cpgislands2/cpg.aspx	A site dedicated to searching for CpG islands, searching algorithms allows for selection of percentage methylation and length of (ISLAND) and gaps between islands.
The Epigenome Network of Excellence	http://www.epigenome-noe.net/WWW/index.php	A network of epigenetic research, including protocols, an antibody database, and reference information on epigenetics.
Human Epigenome Project	http://www.epigenome.org/	The Human Epigenome Project Research Consortium, a collaborative site created to catalogue and interpret genome-wide methylation patterns of all human genes and major tissues.
The Genes, Environment, and Health Initiative	http://www.genesandenvironment.nih.gov	Site for genes, environment, and health initiative (GEI)
Functional Genomics Resources: Epigenetics	http://www.sciencemag.org/site/feature/plus/sfg/resources/res_epigenetics.xhtml#methl	An epigenetic section on the <i>Science</i> Functional Genomics site, on chromatin, methylation, imprinting, and other genetic topics with an epigenetics bend.
Epigenome Informally Informative	http://www.epigenie.com	The latest epigenetic and non- coding RNA research with special features, technology highlights, and conference information.

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