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Genomic Variants Associated With Cancer-Related Fatigue: A Systematic Review

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Background: Cancer-related fatigue (CRF) is the most common stressful side effect caused by cancer and cancer treatments. Although CRF causes a significant burden to quality of life, no pharmacologic interventions are available because the mechanism remains unknown.

Objectives: This systematic review analyzed the genomic variants that have been found to be associated with CRF.

Methods: A search for peer-reviewed articles through PubMed, EBSCOhost, and DePaul WorldCat Libraries Worldwide yielded 16 published studies.

Findings: The majority of genomic variants demonstrated that the inflammatory and immune response pathways, including the neuro-proinflammatory cytokine pathway, have statistically significant associations with CRF. Additional genomic studies are still needed to validate the findings in this systematic review. The exact biologic underpinnings that contribute to the development of CRF remain unknown.

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The prevalence of fatigue experienced by patients with cancer during treatment ranges from 25%–99% (Bower et al., 2013). Healthcare providers are proactive about treating pain and related acute symptoms, and cancer-related fatigue (CRF) is a symptom that has been recognized for many years. However, a biologic-based intervention remains elusive because of a lack of systematic studies examining the biologic underpinnings of CRF. Researchers believe that the cancer itself and its treatment contribute to the development of CRF (Piper & Cella, 2010). The physiologic basis of molecular-genetic etiology of CRF is still unclear, and limited research has been done (Saligan & Kim, 2012). To develop treatments for CRF, accurately assessing and analyzing biologic biomarkers related to CRF is essential. Researchers on CRF are now using advanced technologies, such as genomics or proteomics, to accurately and reliably discover biomarkers that can explain the biologic mechanisms of CRF development.

CRF is associated with negative health outcomes and decreased health-related quality of life. Some of the health issues associated with CRF include sleep disturbance, im-

paired cognitive function, and increased rates of depression (Bower & Lamkin, 2013; Piper & Cella, 2010; Saligan et al., 2015). Biomarkers are characteristics that are objectively measured and evaluated as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (News-Medical.Net, 2016). Examples of biomarkers studied in CRF include inflammatory and metabolic cytokines or chemokines (e.g., interleukin-6, tumor necrosis alpha, cortisol, serotonin), but results are conflicting. Investigators are starting to examine the role of genomics, genomic variants, and other genomic biomarker changes associated with CRF to better understand the biologic mechanisms of this symptom and overcome some of the weaknesses of conventional biomarker tests. Nurses need to understand the significance of biomarkers and their biologic impact on CRF development to help design interventions based on the biologic mechanism of symptoms. In addition, advanced genomic technologies have the potential to uncover the downstream and/or upstream mechanisms that are at the root of CRF development and eventually provide new insights into the role of inflammatory and metabolic pathways

FIGURE 1. Conceptual Map of CRF Development and Symptoms

Note. Based on information from Saligan & Kim, 2012.

vation also tends to affect other pathways, including endocrine/metabolic, transcriptional proteins, and mitochondrial pathways in the peripheral and central nervous systems, leading to the development of CRF and related cognitive and behavioral symptoms (Saligan et al., 2015; Saligan & Kim, 2012). In addition, genomic variants that are significantly associated with CRF development could elucidate several biologic pathways affected by cancer and its treatment. Saligan and Kim (2012) hypothesized that understanding these genomic damages would provide a window for better understanding of the development of CRF and its cognitive and behavioral symptoms.

A conceptual map also guided the authors in conducting this systematic review (see Figure 1). The authors have conceptualized a theoretical map that reflects the multiple biologic changes and their pathways, which may contribute to the development of CRF and its symptoms.

Literature Review

Cancer-Related Fatigue

CRF is a common, distressing, and often unrelieved symptom reported by patients diagnosed with cancer. CRF has been described as feeling tired, weak, worn-out, heavy, or slow or having no energy, and is associated with a diagnosis of cancer and its treatment (National Cancer Institute, 2016).

Studies show that fatigue occurrence ranges from 25%–99% based on the patient population studied, types of treatments that patients receive, assessments performed, and whether or not the prevalence rates for moderate to severe fatigue were reported by patients (Bower & Lamkin, 2013; Saligan et al., 2015). Although many potential mechanisms may be involved in CRF, the exact biologic underpinnings of CRF remain elusive, which explains why there is no therapeutic success reported for CRF. Reyes-Gibby et al. (2013) and other researchers (Collado-Hidalgo, Bower, Ganz, Irwin, & Cole, 2008; Saligan et al., 2015) reported that the interactions of multiple inflammatory biomarkers could play a role in CRF development. Other studies suggest that alterations associated with immune response and mitochondrial function can explain the up-regulation of certain genomic variants with corresponding CRF intensity (Hsiao, Araneta, Wang, & Saligan, 2013).

Nonpharmacologic Management

In the past, patients with cancer were encouraged to rest if they felt fatigued. However, a systematic review on nonpharmacologic management of CRF in patients with cancer found that exercise and the provision of adequate information to cope with CRF symptoms were beneficial (Cramp & Daniel, 2008). Other nonpharmacologic interventions reported to have some benefits in relieving CRF include mindfulness meditation, yoga, and self-regulatory responses to stress (Vilchvnska & Beard, 2016). One study tested mindfulness-

during the development of CRF postchemotherapy, as well as new therapeutic strategies.

This systematic review of the association of genomic variants in CRF is useful in understanding the biologic mechanisms of CRF at the genetic level to better understand the potential pathways that play a role in CRF development. The purpose of this systematic review is to identify the significant associations of inflammatory and immune, metabolic, or other biologic-related genomic variants of CRF and synthesize the findings with statistically significant correlations ($p \leq 0.05$) from the studies. The findings from this systematic review can serve as a building block for the development of genome-based biomarkers that can be tested in future studies. Ultimately, the knowledge gained from this systematic review can contribute to the development of biologic-based interventions for CRF. The research question, therefore, pertains to identifying statistically significant associations between inflammatory and immune-, mitochondrial-, metabolic-, or transcription protein-related genomic variants and CRF.

Theoretical Framework

The immunogenomic model of CRF development, postulated by Saligan and Kim (2012), was used to guide this systematic review. According to Saligan and Kim (2012), patients with cancer receiving therapies to kill cancer cells can activate the immune system, leading to the release of proinflammatory and immune system cytokines. This acti-

based stress reduction (MBSR) for CRF and related symptoms and found that the MBSR group reported large postintervention reductions of CRF as assessed by effect sizes (fatigue interference, $d = -1.43$, $p < 0.001$; fatigue severity, $d = -1.55$, $p < 0.001$) (Johns et al., 2014). In addition, accurate and age-appropriate information about CRF should be made available to all patients and their caregivers, which can lead to better CRF management.

Tools to Assess Cancer-Related Fatigue in Clinical Practice

Unidimensional measures, various subscales, and multidimensional measures are available to assess CRF. Wang and Woodruff (2015) suggested that clinicians and researchers should consider individual preference, good clinical practice, and research goals as guides for choosing the most appropriate fatigue measurement tool. A literature review by Saligan et al. (2015) revealed that the Functional Assessment of Cancer Therapy (FACT)–Fatigue (Yellen, Cella, Webster, Blendowski, & Kaplan, 1997) and Fatigue Questionnaire (Chalder et al., 1993) were the two commonly used tools to assess baseline and progressive severity of CRF during research studies. Most researchers have used cutoff scores for CRF and recommend using a five-point increment for CRF progression from mild to moderate to severe level in terms of CRF intensity (Yost, Eton, Garcia, & Cella, 2011). For practicing nurse clinicians, Figure 2 outlines various scales that can be used to assess and monitor severity or improvement in CRF during and after chemotherapy.

Covariates of Cancer-Related Fatigue

Several covariates of CRF have been reported to have statistically significant associations with genomic variants. The covariates that were investigated included age, race, depression, gender, body mass index (BMI), genotype, and marital status. One of the studies reported the IL-8-T251A gene variant to be significantly associated with depressed mood (odds ratio [OR] = 0.37, 95% confidence interval [CI] [0.14, 1], $p = 0.001$) (Reyes-Gibby et al., 2013). In relation to gender, one study reported that women were over-represented

Unidimensional

- Brief Fatigue Inventory (BFI)
- European Organisation for the Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ C30)
- Fatigue Severity Scale
- Functional Assessment of Cancer Therapy–Fatigue (FACT-F) subscale
- The Profile of Mood States (PMS) fatigue subscale

Multidimensional

- Chalder Fatigue Scale (also known as the Fatigue Questionnaire)
- Fatigue Symptom Inventory (FSI)
- Lee Fatigue Scale (or Visual Analog Scale for Fatigue [VASF])
- Multidimensional Assessment of Fatigue (MAF)
- Multidimensional Fatigue Inventory (MFI-20)
- Multidimensional Fatigue Symptom Inventory (MFSI-30) short form

FIGURE 2. Scales for Assessing and Monitoring Cancer-Related Fatigue

DePaul WorldCat Libraries Worldwide

- Initial articles yield ($n = 41$)
- Articles after removal of 11 duplicates ($n = 30$)
- Articles that met the criteria; full text reviewed ($n = 7$)
- Final articles yield for systematic review ($N = 7$)

PubMed

- Initial articles yield ($n = 81$)
- One duplicate found ($n = 80$)
- Articles that met the criteria; full text reviewed ($n = 3$)
- Final articles yield for systematic review ($N = 3$)

EBSCOhost

- Initial articles yield ($n = 203$)
- Eight duplicates found ($n = 195$)
- Articles that met the criteria; full text reviewed ($n = 3$)
- Final articles yield plus three articles yield using ancestry approach for systematic review ($N = 6$)

FIGURE 3. Systematic Computer-Based Literature Search Process and Article Selection ($N = 16$)

in the high-severity groups of CRF compared to men, and that women are more likely to report physical and physiological symptoms than men (Piraino, Vollmer-Conna, & Lloyd, 2012). In addition, younger age, female gender, and AA genotype have a significant correlation with CRF (Miaskowski et al., 2010). The regression analysis of pro-inflammatory cytokine genomic variant IL6 c.-6101 A>T (rs4719714) showed a significant association with age (6.6%, $p < 0.0001$), gender (1.7%, $p = 0.03$), and genotype (3.8%, $p = 0.001$) (Miaskowski et al., 2010). No significant correlation was found for the covariates of race, BMI, and marital status.

Methods

For this systematic review, the literature search was conducted using PubMed, Academic Search Complete through EBSCOhost, and DePaul WorldCat Libraries Worldwide. Academic Search Complete through EBSCOhost is designed for academic institutions, and it provides complete coverage of multidisciplinary academic journals with easy access to peer-reviewed journals, full-text periodicals, reports, and books. DePaul WorldCat Libraries Worldwide includes databases such as WorldCat, MEDLINE, OAlster, and PsycARTICLES. The following medical subject heading (MeSH) terms were used: *fatigue*, *cancer*, and *genomics*. The search results are illustrated in Figure 3.

Data Evaluation Stage

Articles were reviewed carefully and texts were read line by line. The inclusion criteria include the following: the title of articles and abstract must report inflammatory, immune, metabolic, and other genomic biomarkers that are statistically associated ($p \leq 0.05$) with CRF. Reviews, commentaries,

TABLE 1. Summary of Genomic Variants Associated With CRF

Study	Sample	Population and Design	Significant Genomic Variants or SNPs	Associations With CRF	Psychosomatic Factors With CRF	CRF Covariates	Limitations
Aouizerat et al., 2009	288 patients aged 45–65 years; mean age is 61.4 years	Patients diagnosed with brain, prostate, lung, or breast cancer Longitudinal	TNFA-308G>A (rs1800629)	Controlling for TNFA genotype, for every one year increase in age, the mean morning fatigue score significantly decreased ($p \leq 0.0001$).	Sleep; carriers of the TNFA minor allele reported lower overall levels of sleep disturbance and morning fatigue.	Age and genotype	Small sample size
Bower et al., 2011	11 breast cancer survivors with persistent fatigue; control includes 10 healthy individuals; mean age not reported	Married, Caucasian, and postmenopausal women with breast cancer Longitudinal	IL1A, IL1B, and OSM, CXCL2, CXCR5, CCL20, IER3, ZNF331, NR4A2, NR4A3	Fatigue is associated with immune and inflammatory genomics ($\bar{X} = 0.45$ fold [$SD = 0.09$] across nine combinations of promoter length and scan stringency, $p \leq 0.0001$).	Major depressive disorder; fatigued women were also significantly more likely to have a current diagnosis of depression (50% versus 0%, $p = 0.01$) and marginally more likely to have a past depression diagnosis (55% versus 20%, $p = 0.1$) compared to study controls.	Depression	Small sample population; not using comprehensive assessment in HPA activity
Bower et al., 2013	171 patients aged 31–65 years; mean age is 51.5 years	Women diagnosed with early-stage breast cancer Cross-sectional	IL6-174(rs1800795) G/C or C/C, TNFA-308 (rs1800629)	Analyses of individual SNPs showed that TNFA-308 and IL6-174 were independently associated with fatigue ($p = 0.032$).	Depression and memory; the genetic risk index was also associated with depressive symptoms ($p = 0.007$) and memory complaints ($p = 0.016$).	Age, BMI, depression, and treatment; age ($p = 0.035$), BMI ($p = 0.031$), chemotherapy ($p = 0.001$)	Small sample, cross-sectional design
Collado-Hidalgo et al., 2008	44 patients; aged 50 years or older; mean age is 54.1 years	Breast cancer survivors Cross-sectional	IL1B-511, IL6-174	Predictors of fatigue included presence of at least one cytosine at IL1B-511 (95% CI [0.91, 16.6], $p = 0.007$) and homozygosity for either variant of the IL6-174 genotype (G/G or C/C; 95% CI [1.12, 17.9], $p = 0.027$).	None	Depression and genotype	Small sample size and lack of a control group
Dhruva et al., 2015	167 patients with cancer aged 18 years or older; mean age is 61.5 years	Patients with breast, prostate, lung, or brain cancer Longitudinal	IL4 (rs2243248), TNFA (rs2229094), TNFA (rs3093662), TNFA-308 (rs1800629)	For morning fatigue, TNFA (rs3093662), TNFA-308 (rs1800629) remained significant for both genomic markers ($p = 0.006$). For evening fatigue score, IL4 (rs2243248) and TNFA (rs2229094) showed significance ($p = 0.011$ and $p = 0.009$, respectively).	None	Age and performance status	Small sample size

(Continued on the next page)

ADT—androgen deprivation therapy; BMI—body mass index; CI—confidence interval; CRF—cancer-related fatigue; EBRT—external beam radiation therapy; HPA—hypothalamic-pituitary-adrenal; IL—interleukin; OR—odds ratio; SNP—single nucleotide polymorphism; TNFA—tumor necrosis factor alpha

TABLE 1. Summary of Genomic Variants Associated With CRF (Continued)

Study	Sample	Population and Design	Significant Genomic Variants or SNPs	Associations With CRF	Psychosomatic Factors With CRF	CRF Covariates	Limitations
Fernandez-de-las-Penas et al., 2012	128 patients aged 36–65 years; mean age is 49 years	Breast cancer survivors treated with radiation therapy and chemotherapy	Val158Met (rs4680)	Total fatigue score ($p = 0.001$); post hoc comparisons revealed that breast cancer survivors with Val/Met or Met/Met genotype exhibited significantly ($p = 0.01$) higher fatigue scores than those with Val/Val genotype.	Neck pain and shoulder/axillary pain; a significant effect of genotype ($p = 0.001$) was found for neck pain intensity but not for shoulder/axillary pain ($p = 0.827$).	No covariates associated with CRF	Used only Caucasian breast cancer survivors and not diverse racial backgrounds
Hsiao et al., 2013	40 Caucasian men aged 60 years or older; mean age is 65.6 years	Caucasian men with prostate cancer with 20 controls and 20 who received EBRT	Alpha-inducible protein 27 (IFI27)	Significant IFI27 expression over time during EBRT was confirmed by qPCR ($p \leq 0.5$), which correlated with fatigue scores during EBRT ($r = -0.9$, $p = 0.006$).	None	Race, disease type, and treatment	Small sample size; control group only had one-time data collection, limiting generalizability.
Hsiao et al., 2014	50 male patients aged 49–81 years; mean age is 61.7 years	Patients with nonmetastatic prostate cancer receiving EBRT	BCL2L1, BCS1L, FIS1, SLC25A37	BCS1L (b 1/4 1.3), SLC25A37 (b 1/4 2.44), and two genomics on the outer mitochondrial membrane vital for mitochondrial integrity, BCL2L1 (b 1/4 1.68) and FIS1 (b 1/4 2.35), were significantly associated with changes in fatigue scores of study participants during EBRT.	None	None	Small sample size
Jim et al., 2012	53 patients aged 45–90 years; mean age is 67 years	Patients with prostate cancer receiving ADT	IL6-174 (rs1800795), TNFA-308 (rs1800629) G/A	Patients with the IL6-174 (rs1800795) G/C or C/C genotype displayed greater increases in fatigue intrusiveness, frequency, and duration than the G/G genotype ($p \leq 0.05$). TNFA-308 (rs1800629) G/A genotype showed greater increases in fatigue severity than the G/G genotype ($p = 0.02$).	None	Genotype	Small sample size and homogeneous race
Landmark-Hovvik et al., 2009	137 patients aged older than 75 years	Survivors treated for stage II–III breast cancer with adjuvant radiotherapy	NPCDR1 and PLOD1	Grouping A chronic fatigue; HADS6+ versus HADS ($p = 0.05$)	None	None	Shorter period of time to test the genomic variants

(Continued on the next page)

ADT—androgen deprivation therapy; BMI—body mass index; CI—confidence interval; CRF—cancer-related fatigue; EBRT—external beam radiation therapy; HPA—hypothalamic–pituitary–adrenal; IL—interleukin; OR—odds ratio; SNP—single nucleotide polymorphism; TNFA—tumor necrosis factor alpha

TABLE 1. Summary of Genomic Variants Associated With CRF (Continued)

Study	Sample	Population and Design	Significant Genomic Variants or SNPs	Associations With CRF	Psychosomatic Factors With CRF	CRF Covariates	Limitations
Light et al., 2013	91 patients aged 40–70 years; mean age is 65.1 years	Patients treated with ADT for prostate cancer Cross-sectional	ADRB2, CXCR4, LTA, NR3C1, P2RX7, SOD2, TLR4, TNF	Fatigue scores of patients with prostate cancer overlapped with the chronic fatigue syndrome group ($p \leq 0.001$).	Pain	None	Used only leukocyte genomic expression
Massaccesi et al., 2006	56 patients aged 42–78 years; mean age is 62 years	Metastatic or locally advanced carcinoma Longitudinal	UGT1A1	UGT1A1 was found to be the main predictive factor for diarrhea ($p = 0.00005$), emesis ($p = 0.0001$), and fatigue ($p = 0.007$).	Diarrhea and emesis side effects of the therapy; UGT1A1 6/6 decreased incidence of diarrhea ($p = 0.0001$) and emesis ($p = 0.0001$).	Genotype and treatment	Small sample size
Miaskowski et al., 2010	288 patients with cancer aged 18 years or older; mean age is 61.4 years	Patients diagnosed with breast, prostate, lung, or brain cancer Longitudinal	IL6 c.-6101 A>T (rs4719714)	Common allele homozygotes for the IL6 c.-6101 A>T polymorphism reported higher overall levels of evening fatigue, morning fatigue, and sleep disturbance; evening fatigue ($p = 0.003$)	Sleep disturbance; results report that common allele homozygotes (i.e., AA) reported significantly higher evening and morning fatigue scores, as well as higher total sleep disturbance scores than minor allele carriers (i.e., AT/TT).	Age, gender, and genotype	Lack of control group
Rausch et al., 2010	1,149 patients with lung cancer aged 35–89 years; mean age is 65.2 years	Mostly Caucasian patients with lung cancer who participated in lung cancer research at the Mayo Clinic Longitudinal	IL-1B (rs1143633), IL-1B (rs2853550), IL-1RN (rs397211)	IL-1B (times 1 and 2) and IL-1RN (at time 2) SNPs were associated with fatigue.	Pain, dyspnea, and coughing	Genotype	Lack of a control group; findings included only lung cancer survivors.
Reyes-Gibby et al., 2013	599 patients aged 50 years or older; mean age is 61 years	Non-Hispanic population, male and female, with early and advanced stages of lung cancer Longitudinal	IL-8-T251A	IL-8-T251A was the most relevant genetic factor for pain, depressed mood, and fatigue.	Pain, depressed mood, and fatigue in lung cancer; IL-8-T251A was the most relevant genetic factor for pain (OR = 2.18, 95% CI [1.34, 3.55], $p = 0.001$), depressed mood (OR = 0.37, 95% CI [0.14, 1]), and fatigue (OR = 2.07, 95% CI [1.16, 3.7]).	Type of disease, depression, gender, and genotype	Use of IL-8, and IL-10 only; limited inflammatory biomarkers
Saligan et al., 2013	16 patients aged 49–81 years; mean age is 63 years	Men with nonmetastatic prostate cancer Longitudinal	SNCA	Fatigue scores were significantly correlated with SNCA genomic expression on day 14 ($r = 0.55$, $p \leq 0.05$).	None	None	Small sample size; CRF covariates were not examined.

ADT—androgen deprivation therapy; BMI—body mass index; CI—confidence interval; CRF—cancer-related fatigue; EBRT—external beam radiation therapy; HPA—hypothalamic–pituitary–adrenal; IL—interleukin; OR—odds ratio; SNP—single nucleotide polymorphism; TNFA—tumor necrosis factor alpha

and animal studies were excluded. Abstracts that did not discuss genomic biomarkers of CRF in the study purpose section were excluded. Studies on chronic fatigue syndrome (CFS) among patients with cancer in remission were excluded. The 41 genomic variants reported by 16 studies included in this systematic review were inputted and analyzed using SPSS®, version 23.0.

Results

A summary table outlining the studies that report genomic variants with worsening CRF scores can be found in Table 1. There are 41 genomic changes reported to have a significant correlation with CRF. Most of the studies used longitudinal research design to accurately assess the correlation of these genomic variants with CRF across a span of time postchemotherapy or postradiation therapy. Figure 4 is a synthesis of all the statistically significant genomic variants, with the majority (56%) of genomic variants demonstrating linkages to inflammatory and immune response pathways, including the neuro-proinflammatory cytokine pathway with CRF (Aouizerat et al., 2009; Bower et al., 2013; Bower, Ganz, Irwin, Arevalo, & Cole, 2011; Collado-Hidalgo et al., 2008; Dhruva et al., 2015; Jim et al., 2012; Light et al., 2013; Miaskowski et al., 2010; Rausch et al., 2010; Reyes-Gibby et al., 2013; Saligan et al., 2013). Other genomic variants associated with CRF were linked to mitochondrial (14.6%) (Hsiao et al., 2013; Hsiao, Wang, Kaushal, Chen, & Saligan, 2014; Light et al., 2013); transcription regulation (14.6%) (Bower et al., 2011; Light et al., 2013); metabolic (4.9%) (Landmark-Hoyvik et al., 2009; Massacesi et al., 2006); adrenergic, monoamines, peptides (4.9%) (Fernandez-de-las-Penas et al., 2012; Light et al., 2013); sensory ion channels (2.4%) (Light et al., 2013); apoptosis (2.4%) (Bower et al., 2011); and one unknown pathway (2.4%) (Landmark-Hoyvik et al., 2009). The genomic variants associated with CRF were significant regardless of gender; statistically significant differences were found between both genders. Most studies included patients with breast, prostate, or lung cancer, and some studies included patients who were receiving chemotherapy and radiation therapy. The sample sizes for many studies were small, and several studies used cross-sectional research design.

The frequently reported genomic variants significantly associated with CRF are TNFA-308 (rs1800629), IL-8-T251A, and IL-174 (rs1800795) G/C or C/C and IL1B-511 C>T (rs16944). In Figure 4, some of the genomic variants are reported in two or more studies; therefore, the cumulative frequency is 48, which is greater than the total number of published studies included in this systematic review (N = 16). The cumulative percentage is reported as 117% and is greater than 100% because of the report of some genomic variants by more than one published study.

Genomics Tests Used in Cancer-Related Fatigue Studies

To test the association of genomic variants with fatigue, several genomic tests were used in identifying the significant association with CRF. In most studies, genomic data were obtained through blood samples using whole plasma or peripheral-blood leukocytes. Confirmatory quantitative real time polymerase chain reaction and enzyme-linked immunosorbent assay were commonly used to verify the microarray results (Bower et al., 2013; Hsiao et al., 2013; Saligan et al., 2013). Other studies collected genomic data using the Sequenom's MassARRAY System (Piraino et al., 2012) and Qiagen's PUREGenomic DNA Isolation System and data processing using Illumina's GenomeStudio software (Dhruva et al., 2015).

Discussion

This systematic review revealed 41 genomic variants that have statistically significant associations with CRF. After analyzing the number of genomic variants that were significantly associated with CRF, they were analyzed further in terms of the number of times they were reported in all 16 published

Inflammatory and Immune Response <ul style="list-style-type: none">• TNFA-308 (rs1800629) (n = 4)• IL6-174 (rs1800795) G/C or C/C (n = 3)• L-8-T251A (n = 2)• IL1B-511 C>T (rs16944) (n = 2)• TNF (n = 1)• NLRC4 (n = 1)• LTA (n = 1)• IL6c.-6101A>T (rs4719714) (n = 1)• IL-6 (n = 1)• IL1B (n = 1)• IL1A (n = 1)• IL-10RB Lys (n = 1)• CXCR4 (n = 1)• CXCR5 (n = 1)• CXCL2 (n = 1)• CCL20 (n = 1)• TNFA (rs3093662) (n = 1)• TNFA (rs2229094) (n = 1)• IL4 (rs2243248) (n = 1)• IL-1RN (rs397211) (n = 1)• IL-1B (rs1143633; rs2853550) (n = 1)	Apoptosis <ul style="list-style-type: none">• IER3 (n = 1) Inflammatory, Immune Response, Transcription, and Growth Factor <ul style="list-style-type: none">• NR3C1 (n = 1) Inflammatory, Immune Response, and Transcription Growth Factor <ul style="list-style-type: none">• TLR4 (n = 1) Metabolic, Biological Oxidations, Tryptophan II, and Glucuronidation <ul style="list-style-type: none">• UGT1A1 (n = 1) Metabolic, Collagen Biosynthesis and Lysine Degradation <ul style="list-style-type: none">• PLOD1 (n = 1) Mitochondria and Heme Biosynthesis <ul style="list-style-type: none">• SLC25A37 (n = 1) Mitochondria and Lipid/Energy Metabolism <ul style="list-style-type: none">• SOD2 (n = 1) Mitochondrial and Respiratory Chain <ul style="list-style-type: none">• BCS1L (n = 1) Neuro-Inflammatory <ul style="list-style-type: none">• SNCA (n = 1) Sensory Ion Channels (Adenosine Triphosphate- and Metabolite-Sensing) <ul style="list-style-type: none">• P2RX7 (n = 1) Unknown Pathway: A Nasopharyngeal Carcinoma-Related Genomic Protein <ul style="list-style-type: none">• NPCDR1 (n = 1)
Mitochondria and Apoptosis <ul style="list-style-type: none">• IFI27 (n = 1)• FIS1 (n = 1)• BCL2L1 (n = 1) Adrenergic, Monoamines, and Peptides <ul style="list-style-type: none">• ADRB2 (n = 1)• Val158Met (rs4680) (n = 1) Transcription Regulation <ul style="list-style-type: none">• ZNF331 (n = 1)• NR4A2 (n = 1) Transcription and Growth Factors <ul style="list-style-type: none">• OSM (n = 1)• NR4A3 (n = 1)	

FIGURE 4. Frequency of Cancer-Related Fatigue Genomic Variants Listed by Pathway

studies included in this systematic review. Of the 16 studies, 4 reported the genomic variant TNFA-308 (rs1800629) to be associated with CRF (Aouizerat et al., 2009; Bower et al., 2013; Dhruva et al., 2015; Jim et al., 2012). The second most reported genomic variant associated with CRF is IL6-174 (rs1800795) G/C or C/C, which is reported by three studies (Bower et al., 2013; Collado-Hidalgo et al., 2008; Jim et al., 2012). The genomic variants IL-8-T251A (Rausch et al., 2010; Reyes-Gibby et al., 2013) and IL1B-511 C>T (rs16944) (Collado-Hidalgo et al., 2008; Jim et al., 2012) were both reported at least by two studies. Overall, these studies provide sufficient evidence that the inflammatory and immune response pathways are likely involved in CRF development as previously reported by researchers using conventional tests (Bower & Lamkin, 2013; Saligan et al., 2015; Saligan & Kim, 2012).

This systematic review also reveals other pathways that may play a role in CRF development and its symptoms. These pathways include the mitochondrial pathways; transcription regulation pathways; adrenergic, monoamines, and peptides pathways; and sensory ion channels pathway. Of note, these pathways also have been reported as potential mechanisms for the development of CFS (Light et al., 2013), which is a debilitating and complex disorder characterized by intense fatigue that is not improved by bed rest and that may be worsened by physical activity or mental exertion in people without the diagnosis of cancer (Centers for Disease Control and Prevention, 2015). The mitochondrial pathways have been reported in the past as a major factor in fatigue development in patients with various disease types, including patients with CFS, multiple sclerosis, systemic lupus erythematosus, HIV, and cancer (Filler et al., 2014). Apoptosis and metabolic pathways have also been associated with fatigue in other prior studies involving conventional testing among healthy populations and patients with cancer, respectively (Navalta, Tibana, Fedor, Viera, & Prestes, 2014; Payne, 2004). The findings in

this systematic review provide some validation of previously reported biomarkers associated with CRF with the use of advanced genomic technologies. The diversity of genomic biomarkers found in this systematic review provides preliminary genome-based evidence that CRF may need to be sub-typed according to cancer diagnosis and cancer therapy. An index of CRF may need to be developed in the future using statistically significant genomic biomarkers in studies that have next-generation gene sequencing techniques. An interesting note in this systematic review is the types of cancers associated with inflammatory and immune response genomic variants, which include breast, prostate, lung, and brain cancer populations. However, mitochondrial, metabolic, adrenergic, monoamine, and peptides pathways have mainly been reported to be associated with CRF among patients with prostate cancer. Future studies should be conducted in specific cancer diagnosis with specific type of therapy to accurately phenotype CRF according to cancer diagnosis and treatment. Research studies with adequate sample sizes using longitudinal research design are still needed to validate the findings of this systematic review. Although evidence-based interventions for CRF have not been well established, many practice guidelines for managing CRF have been developed by professional organizations, and they are outlined in Figure 5.

The strength of this review is the summary of 41 genomic variants that have been shown to have statistically significant association with CRF from 16 published studies in peer-reviewed journals, which were retrieved through a systematic computer-based database literature search and the use of other search strategies such as citation index searching and ancestry method. Saligan et al. (2015) included only seven studies related to genomics and CRF in a literature review on this topic and did not provide a summative report of the most commonly reported genomic variants. Although the exact pathways of CRF are still unknown, this systematic review provides genome-based evidence that the inflammatory and immune pathways play a major role in CRF development, validating Saligan and Kim's (2012) immunogenomic model of CRF development.

The limitations of this systematic review include weak generalizability of the results related to a small sample size of most studies and heterogeneous samples with a variety of cancer diagnoses receiving various types of cancer therapies. More research should be focused on understanding the pathways of genomic variants specific to the type of cancer and type of chemotherapy to control these potential confounders in CRF studies. Identifying a particular pathway in targeted patient population receiving specific therapy may help in developing a tailored drug treatment for specific CRF subtype. The future discovery of genome-based and individually tailored treatment for specific CRF genotype will undoubtedly improve the quality of life of patients with cancer.

Conclusion

The exact biologic underpinnings that contribute to the development of CRF remain unknown. The inflammatory and immune response pathways have significant roles in CRF development. However, several other pathways also are implicated in CRF development with limited evidential

American Society of Clinical Oncology
Patient and Survivor Care: Screening, Assessment and Management of Fatigue in Adult Survivors of Cancer

www.instituteforquality.org/screening-assessment-and-management-fatigue-adult-survivors-cancer-american-society-clinical

National Cancer Institute

Cancer-Related Fatigue Physician Data Query (CRF-PDQ®)

Patients: www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-pdq

Nurses: www.cancer.gov/about-cancer/treatment/side-effects/fatigue/fatigue-hp-pdq

National Comprehensive Cancer Network

Managing Fatigue: Patient and Caregiver Resources

www.nccn.org/patients/resources/life_with_cancer/managing_symptoms/fatigue.aspx

Oncology Nursing Society

Putting Evidence Into Practice: Fatigue

www.ons.org/practice-resources/pep/fatigue

FIGURE 5. Additional Resources for Information on Cancer-Related Fatigue

Implications for Practice

- ▶ Assess cancer-related fatigue (CRF) using well-validated tools, and provide age-appropriate education and tailored nursing interventions.
- ▶ Educate patients and their families about CRF and its genomic biomarkers.
- ▶ Guide patients toward available support and interventions for the management of CRF and stay abreast of current development in CRF management.

support. The different types of cancer and types of therapy may account for the other various pathways reported in CRF. Oncology nurses and other clinicians must continue to stay abreast of research developments related to CRF and its management. In addition, this systematic review should engender new research questions and theories that will help provide new insights into the scientific underpinnings of CRF development after chemotherapy, such as possible crosslinks of multiple biologic pathways found in this systematic review.

References

- Aouizerat, B.E., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., . . . Miaskowski, C. (2009). Preliminary evidence of a genetic association between tumor necrosis factor alpha and the severity of sleep disturbance and morning fatigue. *Biological Research for Nursing, 11*, 27–41. doi:10.1177/1099800409333871
- Bower, J.E., Ganz, P.A., Irwin, M.R., Arevalo, J.M., & Cole, S.W. (2011). Fatigue and genomic expression in human leukocytes: Increased NF-kappaB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. *Brain, Behavior, and Immunity, 25*, 147–150. doi:10.1016/j.bbi.2010.09.010
- Bower, J.E., Ganz, P.A., Irwin, M.R., Castellon, S., Arevalo, J., & Cole, S.W. (2013). Cytokine genetic variations and fatigue among patients with breast cancer. *Journal of Clinical Oncology, 31*, 1656–1661. doi:10.1200/JCO.2012.46.2143
- Bower, J.E., & Lamkin, D.M. (2013). Inflammation and cancer-related fatigue: Mechanisms, contributing factors, and treatment implications. *Brain, Behavior, and Immunity, 30*(Suppl.), S48–S57. doi:10.1016/j.bbi.2012.06.011
- Centers for Disease Control and Prevention. (2015). CFS case definition. Retrieved from <http://www.cdc.gov/cfs/case-definition>
- Chalder, T., Berelowitz, G., Pawlikowska, T., Watts, L., Wessely, S., Wright, D., . . . Wallace, E.P. (1993). Development of a fatigue scale. *Journal of Psychosomatic Research, 37*, 147–153.
- Collado-Hidalgo, A., Bower, J.E., Ganz, P.A., Irwin, M.R., & Cole, S.W. (2008). Cytokine genomic polymorphisms and fatigue in breast cancer survivors: Early findings. *Brain, Behavior, and Immunity, 22*, 1197–1200. doi:10.1016/j.bbi.2008.05.009
- Cramp, F., & Daniel, J. (2008). Exercise for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews, 11*, CD006145. doi:10.1002/14651858.CD006145.pub3
- Dhruva, A., Aouizerat, B.E., Cooper, B., Paul, S.M., Dodd, M., West, C., . . . Miaskowski, C. (2015). Cytokine genomic associations with self-report ratings of morning and evening fatigue in oncology patients and their family caregivers. *Biological Research for Nursing, 17*, 175–184. doi:10.1177/109980041453 4313
- Fernandez-de-las-Penas, C., Fernandez-Lao, C., Cantarero-Villanueva, I., Ambite-Quesada, S., Rivas-Martinez, I., del Moral-Avila, R., . . . Arroyo-Morales, M. (2012). Catechol-O-methyltransferase genotype (Val158met) modulates cancer-related fatigue and pain sensitivity in breast cancer survivors. *Breast Cancer Research and Treatment, 133*, 405–412. doi:10.1007/s10549-011-1757-y
- Filler, K., Lyon, D., Bennett, J., McCain, N., Elswick, R., Lukkahatai, N., & Saligan, L.N. (2014). Association of mitochondrial dysfunction and fatigue: A review of the literature. *BBA Clinical, 1*, 12–23.
- Hsiao, C.P., Araneta, M., Wang, X.M., & Saligan, L.N. (2013). The association of IFI27 expression and fatigue intensification during localized radiation therapy: Implication of a para-inflammatory bystander response. *International Journal of Molecular Sciences, 14*, 16943–16957. doi:10.3390/ijms140816943
- Hsiao, C.P., Wang, D., Kaushal, A., Chen, M.K., & Saligan, L. (2014). Differential expression of genes related to mitochondrial biogenesis and bioenergetics in fatigued prostate cancer men receiving external beam radiation therapy. *Journal of Pain and Symptom Management, 48*, 1080–1090. doi:10.1016/j.jpainsymman.2014.03.010
- Jim, H.S., Park, J.Y., Permuth-Wey, J., Rincon, M.A., Phillips, K.M., Small, B.J., & Jacobsen, P.B. (2012). Genetic predictors of fatigue in prostate cancer patients treated with androgen deprivation therapy: Preliminary findings. *Brain, Behavior, and Immunity, 26*, 1030–1036. doi:10.1016/j.bbi.2012.03.001
- Johns, S.A., Brown, L.F., Beck-Coon, K., Monahan, P.O., Tong, Y., & Kroenke, K. (2014). Randomized controlled pilot study of mindfulness-based stress reduction for persistently fatigued cancer survivors. *Psycho-Oncology, 24*, 885–893. doi:10.1002/pon.3648
- Landmark-Hoyvik, H., Reinertsen, K.V., Loge, J.H., Fossa, S.D., Borresen-Dale, A.L., & Dumeaux, V. (2009). Alterations of genomic expression in blood cells associated with chronic fatigue in breast cancer survivors. *Pharmacogenomics Journal, 9*, 333–340. doi:10.1038/tpj.2009.27
- Light, K.C., Agarwal, N., Iacob, E., White, A.T., Kinney, A.Y., VanHaitsma, T.A., . . . Light, A.R. (2013). Differing leukocyte genomic expression profiles associated with fatigue in patients with prostate cancer versus chronic fatigue syndrome. *Psychoneuroendocrinology, 38*, 2983–2995. doi:10.1016/j.psyneuen.2013.08.008
- Massacesi, C., Terrazzino, S., Marcucci, F., Rocchi, M.B., Lippe, P., Bisonni, R., . . . Leon, A. (2006). Uridine diphosphate glucuronosyl transferase 1A1 promoter polymorphism predicts the risk of gastrointestinal toxicity and fatigue induced by irinotecan-based chemotherapy. *Cancer, 106*, 1007–1016. doi:10.1002/cncr.21722
- Miaskowski, C., Dodd, M., Lee, K., West, C., Paul, S.M., Cooper, B.A., . . . Aouizerat, B.E. (2010). Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. *Journal of Pain and Symptom Management, 40*, 531–544. doi:10.1016/j.jpainsymman.2009.12.006
- National Cancer Institute. (2016). Fatigue PDQ®. Retrieved from <http://bit.ly/2d1C6E5>
- Navalta, J.W., Tibana, R.A., Fedor, E.A., Vieira, A., & Prestes, J. (2014). Three consecutive days of interval runs to exhaustion affects lymphocyte subset apoptosis and migration. *Biomed Research International, 2014*, 694801. doi:10.1155/2014/694801

- News-Medical.Net. (2016, January). What is a biomarker? Retrieved from <http://bit.ly/2dghkjg>
- Payne, J.K. (2004). A neuroendocrine-based regulatory fatigue model. *Biological Research for Nursing*, 6, 141–150.
- Piper, B.F., & Cella, D. (2010). Cancer-related fatigue: Definitions and clinical subtypes. *Journal of the National Comprehensive Cancer Network*, 8, 958–966.
- Piraino, B., Vollmer-Conna, U., & Lloyd, A.R. (2012). Genetic associations of fatigue and other symptom domains of the acute sickness response to infection. *Brain, Behavior, and Immunity*, 26, 552–558. doi:10.1016/j.bbi.2011.12.009
- Rausch, S.M., Clark, M.M., Patten, C., Liu, H., Felten, S., Li, Y., . . . Yang, P. (2010). Relationship between cytokine genomic single nucleotide polymorphisms and symptom burden and quality of life in lung cancer survivors. *Cancer*, 116, 4103–4113.
- Reyes-Gibby, C.C., Wang, J., Spitz, M., Wu, X., Yennurajalingam, S., & Shete, S. (2013). Genetic variations in interleukin-8 and interleukin-10 are associated with pain, depressed mood, and fatigue in lung cancer patients. *Journal of Pain and Symptom Management*, 46, 161–172. doi:10.1016/j.jpainsymman.2012.07.019
- Saligan, L.N., Hsiao, C.P., Wang, D., Wang, X.M., St John, L., Kaushal, A., . . . Dionne, R.A. (2013). Upregulation of alpha-synuclein during localized radiation therapy signals the association of cancer-related fatigue with the activation of inflammatory and neuroprotective pathways. *Brain, Behavior, and Immunity*, 27, 63–70. doi:10.1016/j.bbi.2012.09.009
- Saligan, L.N., & Kim, H.S. (2012). A systematic review of the association between immunogenomic markers and cancer-related fatigue. *Brain, Behavior, and Immunity*, 26, 830–848. doi:10.1016/j.bbi.2012.05.004
- Saligan, L.N., Olson, K., Filler, K., Larkin, D., Cramp, F., Yennurajalingam, S., . . . Mustian, K. (2015). The biology of cancer-related fatigue: A review of the literature. *Supportive Care in Cancer*, 23, 2461–2478. doi:10.1007/s00520-015-2763-0
- Vilchvnska, T., & Beard, B. (2016). Cancer-related fatigue in palliative care: A global perspective. *International Journal of Palliative Nursing*, 22, 244–252. doi:10.12968/ijpn.2016.22.5.244
- Wang, X.S., & Woodruff, J.F. (2015). Cancer-related and treatment-related fatigue. *Gynecologic Oncology*, 136, 446–452.
- Yellen, S.B., Cella, D.F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *Journal of Pain and Symptom Management*, 13, 63–74.
- Yost, K.J., Eton, D.T., Garcia, S.F., & Cella D. (2011). Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. *Journal of Clinical Epidemiology*, 64, 507–516.