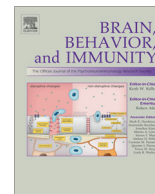




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Review Article

A systematic review of the association between fatigue and genetic polymorphisms

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ABSTRACT

Fatigue is one of the most common and distressing symptoms, leading to markedly decreased quality of life among a large subset of patients with a variety of disorders. Susceptibility to fatigue may be influenced by genetic factors including single nucleotide polymorphisms (SNPs), especially in the regulatory regions, of relevant genes. To further investigate the association of SNPs with fatigue in various patient populations, a systematic search was conducted on Pubmed, CINAHL, PsycINFO, and Sociological Abstracts Database for fatigue related-terms in combination with polymorphisms or genetic variation-related terms. Fifty papers in total met the inclusion and exclusion criteria for this analysis. These 50 papers were further classified into three subgroups for evaluation: chronic fatigue syndrome (CFS), cancer-related fatigue (CRF) and other disease-related fatigue. SNPs in regulatory pathways of immune and neurotransmitter systems were found to play important roles in the etiologies of CFS, CRF and other disease-related fatigue. Evidence for associations between elevated fatigue and specific polymorphisms in *TNFRx*, *IL1b*, *IL4* and *IL6* genes was revealed for all three subgroups of fatigue. We also found CFS shared a series of polymorphisms in *HLA*, *IFN-γ*, *5-HT* and *NR3C1* genes with other disease-related fatigue, however these SNPs (excluding *IFN-γ*) were not found to be adequately investigated in CRF. Gaps in knowledge related to fatigue etiology and recommendations for future research are further discussed.

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Contents

1. Introduction	00
2. Methods	00
3. Results	00
3.1. Chronic fatigue syndrome	00
3.1.1. Overview	00
3.1.2. Mechanisms	00
3.1.3. Predicted effect	00
3.2. Cancer-related fatigue	00
3.2.1. Overview	00
3.2.2. Mechanisms	00
3.3. Other disease-related fatigue	00
3.3.1. Overview	00
3.3.2. Mechanisms	00
4. Discussion	00
4.1. Limitations and future directions	00
4.2. Strengths	00

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5. Conclusion	00
Funding source	00
Acknowledgment	00
Appendix A. Supplementary data	00
References	00

1. Introduction

Fatigue is a common symptom whose descriptors include tiredness, weakness, lack of energy, and inability to concentrate (Landmark-Hoyvik et al., 2010). Among studies investigating symptom prevalence, fatigue consistently ranks among the top three symptoms reported by patients with a variety of diseases (Wessely, 2001). Fatigue symptoms can have a negative effect on social relationships, mental health, and daily activities, causing a marked decrease in overall quality of life both during illness and after treatment (Bower, 2014; Bower et al., 2013). For the purposes of further understanding the etiology and pathophysiology of fatigue, fatigue symptoms can be categorized into three major subgroups: chronic fatigue syndrome (CFS), cancer-related fatigue (CRF), and other disease-related fatigue.

Following standard guidelines, CFS is a chronic, disabling disorder that is defined as six months of disabling fatigue that cannot be explained by an underlying condition. A diagnosis of CFS also requires at least four of the following eight possible accompanying symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, headaches, unrefreshing sleep, or malaise after exertion (Fukuda et al., 1994; Reeves et al., 2003). Although CFS has a relatively low prevalence (0.3–2.5%) in the general population (Prins et al., 2006), disease-related fatigue is one of the most common symptoms of cancer, infectious diseases, cardiovascular diseases, and autoimmune disorders as well as their related treatments. Disease-related fatigue may be acute (such as in response to an infection) or chronic, persisting for years, even after treatment completion (such as in a chronic medical condition or ongoing fatigue after resolution of an infection) (Allen et al., 2008; Becker et al., 2015; Bower, 2014; Helbig et al., 2003). Cancer-related fatigue (CRF) is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or its treatment that is not proportional to recent activities and interferes with usual functioning (Bower, 2014). Of fatigue related to disease, CRF has been extensively investigated, perhaps due to its high prevalence (25–99%), severity, persistence, and debilitating effects (Bower et al., 2013; Reinertsen et al., 2011b).

Studies suggest that CFS, CRF, and other disease-related fatigue are complex conditions with multifactorial etiology involving multiple mechanisms (Landmark-Hoyvik et al., 2010). Although CFS, CRF, and other disease-related fatigue may be qualitatively and quantitatively different from one other, they may also share biological mechanisms of onset and exacerbation. Previous studies have shown that they all involve both the peripheral nervous system (PNS) and the central nervous system (CNS) (Rovigatti, 2012). In addition, there has been a long-standing interest in the role of the immune system in the pathogenesis and pathophysiology of CFS and CRF, especially the role of inflammatory cytokines (Blundell et al., 2015; Saligan et al., 2015). Accordingly, genetic components, such as single nucleotide polymorphisms (SNPs) in immune and neurotransmitter-related genes, have been investigated. SNPs are single base variations in DNA structure that are found in 1% of the population or more (the most common type of genetic variation). They are typically measured by genotyping techniques based on DNA extracted from peripheral blood. SNPs

found in the regulatory regions of genes (called functional SNPs), including promoters, introns and untranslated regions, can, in many cases, affect the expression of the related gene products including proteins (Albert, 2011), thereby potentially influencing mechanisms involved in fatigue susceptibility (Reyes-Gibby et al., 2013b).

Polymorphisms specific to the three subgroups of fatigue are not well-established, and no study has identified SNPs common to these subgroups. A systematic review of the available literature may help to elucidate shared etiologies by examining potential common relationships between genetic polymorphisms and the various fatigue subtypes across studies. Moreover, this information may contribute to improved clinical management of fatigue symptoms by avoiding underestimation of prevalence and under-treatment by clinicians (Saligan and Kim, 2012; Vogelzang et al., 1997).

2. Methods

A general literature search was conducted in Pubmed, CINAHL, PsycINFO, and Sociological Abstracts Database, using the following key words: fatigue AND (single nucleotide polymorphisms OR genetic variation). In order to incorporate specific concerns related to cancer-related fatigue, other key words added to the search included: (Cancer OR neoplasms OR tumor OR oncology) AND (gene OR single nucleotide polymorphisms OR genetic variation). Reference lists and bibliographies from published studies were used to find additional articles to review. The search was limited to articles written in English, but there was no limitation on publication year. The titles and abstracts of the articles identified through the search were evaluated by two reviewers (TW and JY), and articles for more extensive review were selected using the following inclusion and exclusion criteria:

Inclusion criteria: 1) clear focus on chronic fatigue syndrome, cancer-related fatigue, or other disease-related fatigue (both acute and chronic); and 2) containing data on any polymorphisms. Studies categorizing subjects as fatigued or not (case-control) and studies examining fatigue as a continuous variable were included.

Exclusion criteria: 1) general reviews, systematic reviews and meta-analysis, editorials, case studies, and non-human studies; 2) studies not focusing on the three types of fatigue; or 3) studies with no data on gene polymorphisms.

Selection of studies to be reviewed involved four steps depicted in Figs. 1 and 2. Data from studies that met inclusion criteria were independently extracted by two reviewers (TW and JY). The data extracted included descriptive information about the study authors, publication year, main goals of the study, clinical phenotype, number of participants, study design, methods of fatigue assessment, biological end point(s) (specific genes and SNPs), and main findings. Disagreements between reviewers were resolved by consensus or, when necessary, adjudicated by a third reviewer (CX). The definition of fatigue was based on the criteria of each individual study.

The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of non-randomized studies (Stang, 2010). The NOS recognizes quality indicators in three domains: selection of study groups, comparability of study groups, and exposure and outcome ascertainment. Using this scale, a study could be awarded a maxi-

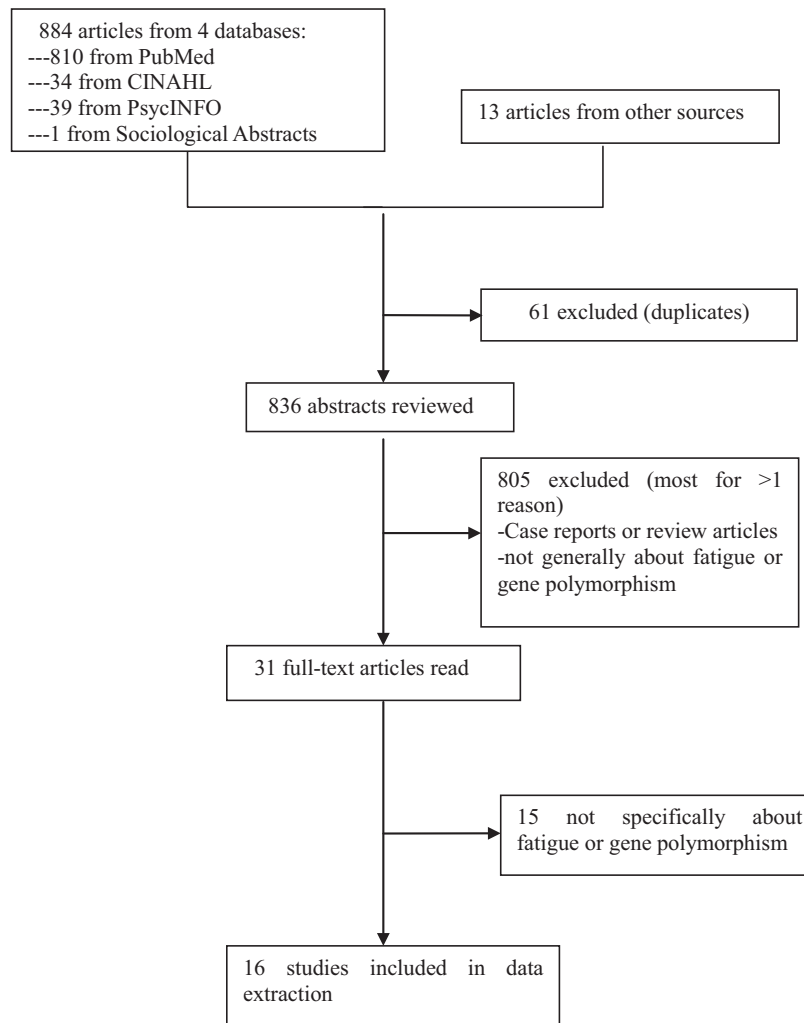


Fig. 1. Process of study selection for cancer related fatigue.

mum of one or two points for each indicator (sample size, inclusion-exclusion criteria, fatigue measurement, HWE assessment, genotype blinding, genotype assessment, statistical method, and confounder assessment) within each assessment domain (selection, comparability, and ascertainment) for a possible maximum total score of 15 points. The assessment of study quality was independently conducted by two reviewers (TW and JY), and the results were compared until a consensus was reached. The full quality assessment criteria are described in detail in the [Supplementary Appendix](#).

3. Results

Fifty articles met our inclusion and exclusion criteria and were categorized into three major subgroups including CFS, CRF, and other disease-related fatigue. For each subgroup, we provided an overview of our findings, related mechanisms, and predicted effects (if applicable).

3.1. Chronic fatigue syndrome

3.1.1. Overview

Sixteen articles on CFS, published between 2003 and 2015, were included in this systematic review based on our inclusionary and exclusionary criteria. The number of cases in these studies ranged

from 35 to 171. Two articles did not specify the number of controls (Fukuda et al., 2013; Lee et al., 2009; Smith et al., 2006). All of the studies used 1994 Fukuda criteria as the definition of CFS (Fukuda et al., 1994). Table 1 provides details on the studies related to CFS included in the analyses. The average quality score was 7.5, with scores ranging from 2 to 13. The most common reasons for lower scores were not mentioning genotyping blinding methods and insufficient description of confounders.

3.1.2. Mechanisms

Although the pathophysiological mechanisms for CFS are not clearly identified, the 12 of the 16 studies provided evidence to support gene-related mechanisms of CFS. These mechanisms primarily included neurotransmitter dysregulation (five studies) (Fukuda et al., 2013; Narita et al., 2003; Smith et al., 2008, 2011; Sommerfeldt et al., 2011), hypothalamic-pituitary adrenal (HPA) axis regulation (two studies) (Lee et al., 2009; Rajeevan et al., 2007), inflammatory/immunomodulatory responses (four studies) (Carlo-Stella et al., 2006, 2009; Rajeevan et al., 2015; Smith et al., 2005), and other mechanisms involving metabolism and endurance (one study) (Vladutiu and Natelson, 2004).

3.1.2.1. Neurotransmitter system. The most common neurotransmitter system related to CFS was the serotonergic system. A number of polymorphisms in serotonin transporters, receptors and

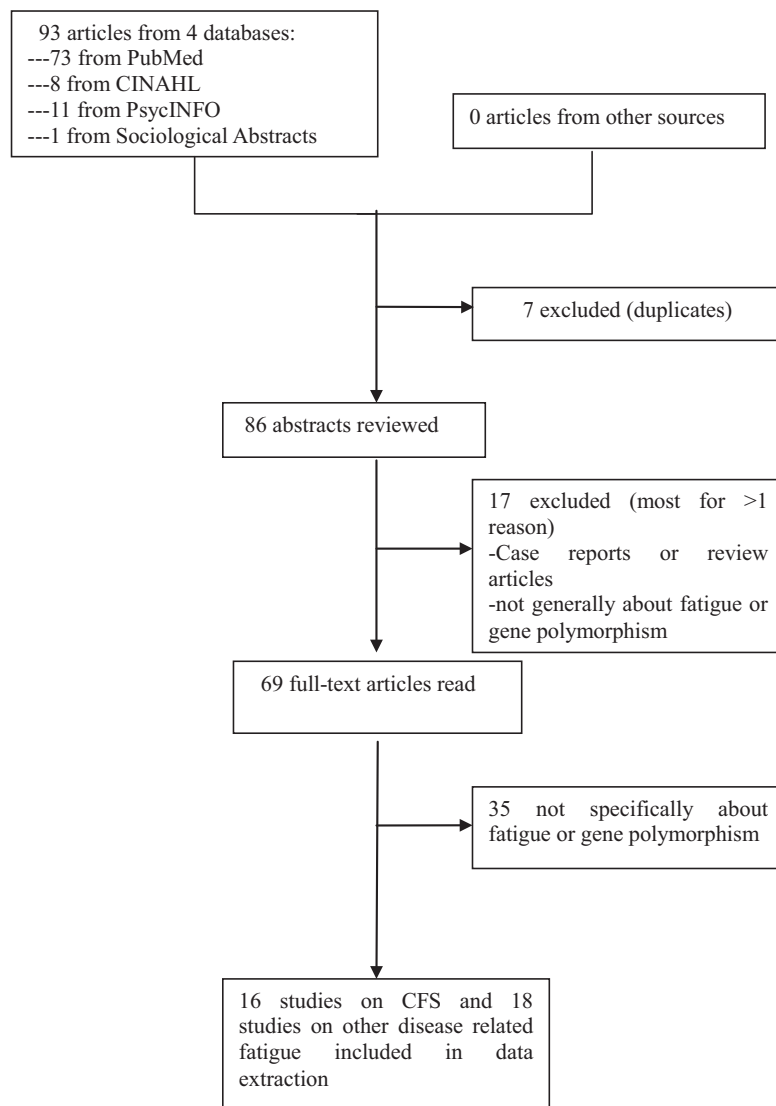


Fig. 2. Process of study selection for CFS and other specific diseases-related fatigue).

synthetic enzymes were linked to CFS. In a case-control study (Narita et al., 2003), a polymorphism in the serotonin transporter gene 5' upstream region (5-HTTLPR) (rs25531, rs25532) was identified in CFS patients, but not controls. In addition, three markers located in the 5-HT receptor subtype *HTR2A* (rs1923884, rs6311 and rs6313) were found to be associated with CFS (Smith et al., 2008).

Additionally, polymorphisms in the monoamine synthetic enzymes, tyrosine hydroxylase (*TH*) (rs10770141), which synthesizes dopamine, and GTP cyclohydrolase I (*GCH*) (rs841), which is involved in the synthetic pathway of all the monoamines, have been associated with the pathophysiology of CFS (Fukuda et al., 2013). Two polymorphisms in the adrenergic signaling pathway, including the β 2-adrenergic receptor and catechol-O-methyl transferase (*COMT*) that catabolizes noradrenaline, were found to be significantly more abundant in CFS patients than in controls; these were the GG genotype of rs1042714 and the AA genotype of rs4680, respectively (Sommerfeldt et al., 2011). Finally, two genes involved in other neurotransmission systems were found to be nominally associated with CFS (Smith et al., 2011), suggesting possible roles for genes involved in glutamatergic neurotransmission (*GRIK2* rs2247215) and circadian rhythms (*NPAS2* rs356653).

3.1.2.2. *Hypothalamic-Pituitary-Adrenal axis. NR3C1*, a glucocorticoid receptor gene influential in regulating HPA axis function and blood glucocorticoid (cortisol) concentrations has garnered attention in exploration of the pathological mechanism of CFS. Supporting results were observed in a case-control study conducted by Rajeevan et al. (2007) in this study, four markers of *NR3C1* (rs1866388, rs2918419, rs860458 and rs6188) were significantly associated with CFS. Furthermore, in a study using an integrated approach to seek the association between genotype variation and disease, *NR3C1* rs1866388, rs852977 and rs258750 were shown to be highly associated with CFS (Lee et al., 2009).

3.1.2.3. *Inflammation and immune response.* Immune dysregulation and inflammatory reactions may also contribute to CFS. A study focusing on human leucocyte antigen (*HLA*) class II alleles found a significant association between *HLA-DQA1*01* and CFS (Smith et al., 2005). Another study (Carlo-Stella et al., 2009) found that the combination of *RAGE-374A* (rs1800624), *HLA-DRB1*1104* (rs1800625), *RAGE-374A*, and *HLA-DRB1*1301* was associated with CFS, whereas when singly expressed, these variants were not associated with disease. *DRB1*1104* was found to be a protective factor when expressed alone. In addition, the cytokine SNP *TNF-308* was

Table 1
Studies on the association between chronic fatigue syndrome and genetic polymorphisms.

Study	Objective	Disease	Sample	Design	Fatigue measure	Genes	SNPs	Main findings	Quality Scores
Narita et al. (2003)	To examine the difference of (5-HTT) gene promoter polymorphism in the CFS patients and the controls	CFS	ca = 78; co = 50	Case-control	1994 Fukuda Criteria	5-HTT	rs25531, rs25532	Significant differences were found between the CFS patients and the controls both by the genotype distribution and the allele frequencies; 5-HTTLPR is highly associated with the pathophysiology of CFS	4
Vladutiu and Natelson (2004)	To evaluate that the genes associated with muscle metabolism and physical endurance may contribute to the etiology of medically unexplained severe and chronic fatigue	CFS	Non-veteran: ca = 61, co = 45; Veteran: ca = 49, co = 30	Case-control	1994 Fukuda Criteria	AMPD1, CPT2, DCP1	Q12X, V368I, M647V	The I/D polymorphism in the DCP1 gene is significantly associated with CFS in Gulf War veterans	6.5
Smith et al. (2005)	To investigate the association between HLA class II antigens and CFS	CFS	ca = 49, co = 102	Case-control	1994 Fukuda Criteria	HLA-DRB1, HLA-DQA1, HLA-DQB1	Alleles on HLA-DRB1*11, HLA-DQA1*01, HLA-DQB1*06	CFS is associated with HLA-DQA1*01	8.5
Carlo-Stella et al. (2006)	To investigate the association between the gene polymorphisms of pro-inflammatory or anti-inflammatory cytokines and CFS	CFS	ca = 80, co = 224	Case-control	1994 Fukuda Criteria	IL-10, IL-6, IFN γ , TNF	IL-10-592, IL-10-819, IL-10-1082, IL-6-174, IFN γ 874, TNF-308, TNF-857	A significant increase of TNF-857 TT and CT genotypes was found along with a decrease of IFN γ 874 AA genotype among patients with respect to controls	8.5
Goertzel et al. (2006)	To investigate the accuracy of SNP profiles to predict CFS	CFS	ca = 43, co = 58	Case-control	1994 Fukuda Criteria	COMT, CRHR1, CRHR2, NR3C1, POMC, TH, TPH2, 5HTT	28 SNPs	CFS has a genetic component that may help to explain some aspects of the illness	5.5
Rajeevan et al. (2007)	To examine the association of sequence variations in the glucocorticoid receptor gene (NR3C1) with CFS	CFS	CFS = 40, ICF = 55, co = 42	Case-control	1994 Fukuda Criteria	NR3C1	rs1866388, rs2918419, rs860458, rs852977, rs6188, rs6198, rs258750, rs6196, rs6191	All associated SNPs were related to an increased risk for CFS. NR3C1 is a potential mediator of CFS	13
Smith et al. (2008)	To examine the sequence variants in 14 genes of the serotonergic system among CFS patients	CFS	CFS = 58, co = 55, ISF = 114	Case-control	1994 Fukuda Criteria	TPH2, HTR1A, HTR1E, HTR2A, HTR2B, HTR2C, HTR3A, HTR3B, HTR4, HTR5A, HTR6, HTR7, SLC6A4, MAOA	rs9534512, rs6311, rs643627, rs655888, rs1923885, rs1923884, rs1923882, rs6314	Three markers (-1438 G/A, C102T, and rs1923884) located in the 5-HT receptor subtype HTR2A were associated with CFS when compared to controls	12
Carlo-Stella et al. (2009)	To analyze the association between RAGE polymorphisms and HLA-DRB1 alleles and CFS	CFS	ca = 75, co = 141	Case-control	1994 Fukuda Criteria	RAGE, HLA-DRB1	rs1800624, rs1800625	The HLA haplotypes rather than single alleles of RAGE or of DRB1 genes are associated with CFS	6.5
Lee et al. (2009)	To characterize complex diseases by integrating genotype variation data and gene expression data	CFS	n = 171	Case-control	1994 Fukuda Criteria	NR3C1, COMT	rs1866388, rs2918419, rs860458, rs852977, rs6188, rs258750, rs6196, rs93271, rs5993882	The SNPs within NR3C1 gene were shown to differently influence the susceptibility of developing CFS and CFS-MDD/m through integrative action with gene expression levels	4.5
Lin and Hsu (2009)	To detect gene-gene and gene-environment interactions in CFS patients	CFS	ca = 55, co = 54	Case-control	1994 Fukuda Criteria	COMT, CRHR1, CRHR2, MAOA, MAOB, NR3C1, POMC, SLC6A4, TH, TPH2	42 SNPs	NR3C1 was found in the significant two-locus gene-gene effect model, as well as in the significant two-factor gene-environment effect model	2
Cifuentes and Barreto (2011)	To evaluate the efficacy in predicting CFS by using polymorphisms selected by a supervised approach	CFS	ca = 43, co = 58	Case-control	1994 Fukuda Criteria	NR3C1, 5HTT	rs11159943, rs7911132, etc.	The polymorphisms of NR3C1_11159943 major allele and the 5HTT_7911132 minor allele were associated with CFS	4
Smith et al. (2011)	To identify the associations between CFS and some novel candidate genes	CFS	ca = 35, co = 27	Case-control	1994 Fukuda Criteria	GRIK2, NPAS2	rs2247215, rs356653	Sixty-five SNPs were nominally associated with CFS ($p < 0.001$)	9

(continued on next page)

Table 1 (continued)

Study	Objective	Disease	Sample	Design	Fatigue measure	Genes	SNPs	Main findings	Quality Scores
Sommerfeldt et al. (2011)	To explore the frequency of polymorphisms in adrenergic cardiovascular control genes in CFS patients	CFS	ca = 53, co = 33	Case-control	1994 Fukuda Criteria	COMT, β_1 , β_2 -adrenergic receptor, α_2 -receptor	rs4680, rs1042713, rs1042714, rs1801253, rs1800544	CFS might be related to polymorphisms of COMT and the β_2 -adrenergic receptor	9
Fukuda et al. (2013)	To explore the genetic factors that influence CFS development and to examine the possible association between the SNPs of the TH and GCH genes and the various characteristics of CFS patients	CFS	ca = 155	Case-control	1994 Fukuda Criteria	GCH, TH	rs841, rs10770141	GCH gene with the C+243T polymorphism affected harm avoidance, while the TH gene with the C-824T polymorphism affected persistence in the CFS patients	7
Shimosako and Kerr (2014)	To identify SNP allele associations with CFS/ME and the subtypes	CFS/ME	CFS/ME: n = 108; Endogenous depression: n = 17; Normal blood donors: n = 68	Case-control	1994 Fukuda Criteria	FAM1268, TCF3, EIF3A, UBTF, METTL3, SORL1, IL6ST, PNPLA6, BMP2K, ARSD, GSN, HIF1A, PEX16	21 SNPs	21 SNPs were significantly associated with CFS/ME compared with depression and normal groups. 148 SNP alleles had a significant association with one or more CFS/ME subtypes	10
Rajeevan et al. (2015)	To explore the association of functionally important genetic variants in inflammation and immune pathways with CFS	CFS	ca = 50, co = 121	Case-control	1994 Fukuda Criteria	32 Genes	32 SNPs	CFS is associated with genetic variants, especially with rs4151667 (L9H) in CFH, rs1061170 (Y402H) in CFH, and rs11214105 in IL18	12

Abbreviation: CFS, chronic fatigue syndrome; ME, myalgic encephalomyelitis; ca, cases; co, controls.

found to be highly associated with CFS (Carlo-Stella et al., 2006). This relationship was further supported by another study that demonstrated associations between 32 inflammation and immune-related SNPs and CFS (Rajeevan et al., 2015).

3.1.2.4. Other mechanisms. In a case-control study investigating the genetics of muscle metabolism and physical endurance, M647V on gene Decapping Enzyme Homolog (*DCP1*) was found to be associated with CFS among veterans of the first Persian Gulf War (Vladutiu and Natelson, 2004).

3.1.3. Predicted effect

While most studies aimed to investigate the association between SNPs and CFS, several studies explored the predictive effects of SNPs on CFS. One study (Goertzel et al., 2006) found that 28 SNPs could be used to predict CFS with 76% accuracy. The majority of relevant SNPs were located in regions of *TPH2*, *COMT* or *NR3C1*. Another study (Cifuentes and Barreto, 2011) also found a valid profile of 13 SNPs that predicted CFS with 72.8% accuracy. The majority of polymorphisms associated with CFS occurred in *5-HTT* and *NR3C1*. Moreover, a previous study (Lin and Hsu, 2009) found that a gene-gene effect involving *NR3C1* and a gene-environment effect of *NR3C1* and gender could play important roles in CFS. To seek clinical diagnostic meaning, Shimosako and Kerr (2014) observed that 21 out of 504 SNPs were significantly associated with CFS/myalgic encephalomyelitis. Most were located in the bone morphogenetic protein-2-inducible protein kinase (*BMP2K*) gene, which plays an important role in skeletal development and patterning (Liu et al., 2009), and in the *IL6ST* gene (aka. Glycoprotein 130), which encodes a transmembrane protein as part of the type I cytokine receptor in *IL-6* receptor family (thereby ensuring correct ligand binding and protein folding) (Hibi et al., 1990).

3.2. Cancer-related fatigue

3.2.1. Overview

A total of 16 articles on CRF were chosen based on our inclusionary and exclusionary criteria. Of those 16 articles, 10 were longitudinal studies (Aouizerat et al., 2009; Dhruva et al., 2015; Fernandez-de-las-Penas et al., 2012; Illi et al., 2012; Jim et al., 2012; Miaskowski et al., 2010; Reinertsen et al., 2011a; Reyes-Gibby et al., 2013a, 2013b; Vallance et al., 2010); three were cross-sectional studies (Bower et al., 2013; Collado-Hidalgo et al., 2008; Shi et al., 2015); two were cohort studies (Rausch et al., 2010; Sloan et al., 2012) and the remaining one used a case-control design (Athanasoulia et al., 2012). The studies differed in almost all clinical (e.g., cancer type, therapeutic intervention) and methodological components. More than three quarters (14/16, 87.5%) were published recently (2010–2013). The predominant cancer populations studied were breast and lung cancer. Half of the studies (8/16) enrolled solely breast cancer or lung cancer participants, and the remaining studies enrolled patients with mixed cancer diagnoses other than breast or lung. As might be expected, a wide variety of fatigue instruments was used, including the Lee Fatigue Scale (LFS) (5/16, 31%), Multidimensional Fatigue Symptom Inventory (MFSI) (2/16, 12.5%), 12-Item Short Form Health Survey (SF-12) (2/16, 12.5%), and others (7/16, 44%). All studies assessed fatigue using multi-item questionnaires. The rating scores of the two independent raters using eight quality categories together are shown in Table 2. The overall quality of the studies was moderately high, averaging 10.2. Across the 16 studies, the most common reasons for lower quality scores were not mentioning genotype blinding and insufficient control of confounding factors.

3.2.2. Mechanisms

The genetic polymorphisms under investigations from the above described studies can be grouped into 2 categories: inflammation and immune response (thirteen studies) (Aouizerat et al.,

Table 2
Studies on the association between cancer-related fatigue (CRF) and genetic polymorphisms.

Study	Objective	Disease	Sample size	Design	Fatigue measure	Genes	SNPs	Main findings	Quality scores
Collado-Hidalgo et al. (2008)	To test the hypothesis that cytokine-related fatigue is influenced by genetic polymorphisms in genes IL-1b and IL-6	Breast cancer	47	Cross-sectional	MFSI	IL1B IL6	rs16944 (-511 (C/T), rs1800795 -174 (G/C)	Prevalence of at least one cytosine at IL1B rs16944 was substantially greater among fatigued participants than non-fatigued (p = 0.007); Only 33.3% of fatigued survivors were heterozygous for IL6 174, compared to 69.2% of non-fatigued controls (p = 0.027)	9.25
Aouizerat et al. (2009)	To investigate whether genetic variation TNF α rs1800629 was associated with mean ratings of evening fatigue, morning fatigue, and sleep disturbance in oncology patients and family caregivers	Breast, prostate, lung, or brain cancer	288	Longitudinal	LFS	TNF α	rs1800629	Common allele homozygotes (GG) reported higher morning LFS scores (p = 0.02) than minor allele carriers (GA + AA)	12
Miaskowski et al. (2010)	To investigate whether genetic variation IL-6 rs4719714, was associated with mean ratings of evening fatigue, morning fatigue, and sleep disturbance in oncology patients and family caregivers	Breast, prostate, lung, or brain cancer	288	Longitudinal	LFS	IL6	rs4719714	Common allele homozygotes reported higher levels of evening fatigue than minor allele carriers	12
Rausch et al. (2010)	To evaluate the predictive value of cytokine gene SNPs on symptom burden and QOL in Caucasian lung cancer survivors	Lung cancer	1149	Longitudinal	Lung cancer symptom Scale	IL1B, IL6	rs1143633, rs2853550, rs41800795.	The odds ratio for the association between IL-1Brs1143633 is 1.00–1.02; for IL-1B was 1.01–1.06; No association was found between IL6 rs41800795 and fatigue	10.75
Vallance et al. (2010)	To explore mechanisms (pharmacokinetics, serum albumin and pharmacogenetics) through which dexamethasone may cause debilitating fatigue and disrupted sleep	Acute Lymphoblastic Leukemia (ALL)	72	Longitudinal	FSI, pediatric and parent versions	IL6, AHSG, POLDIP3	rs13447445, rs4918, rs1771889.	No association was found between these SNPs and fatigue	5
Reinertsen et al. (2011a, 2011b)	To test the hypothesis that variations in cytokine-related fatigue are influenced by genetic polymorphisms in genes IL-1b and IL-6	Breast cancer recurrence, other cancer	302	Longitudinal	Fatigue Questionnaire (Norwegian)	IL1B, IL6	rs16944, rs1800795	No association was found between these SNPs and fatigue	12
Fernandez-de-las-Penas et al. (2012)	To examine the influence of COMT Val158Met genotypes on cancer-related fatigue, post-mastectomy pain, and pressure pain hypersensitivity in breast cancer survivors	Breast cancer	128	Longitudinal	PFS	COMT	Val158Met	Val/Met or Met/Met genotype exhibited significantly (P = 0.01) higher fatigue scores	9.5
Illi et al. (2012)	To determine if genetic variations in a number of pro- and anti-inflammatory cytokines were associated with latent class membership which based on the symptom cluster of pain, fatigue, sleep disturbance, and depression	Breast, prostate, brain, lung	253	Longitudinal	LFS	IL4	rs2243248	The minor allele of IL4 rs2243248 was associated with higher level of fatigue	12.25
Jim et al. (2012)	To examine the relationship between changes in fatigue following initiation of ADT and SNPs in IL1B, IL6, and TNF α	Prostate	53	Longitudinal	FSI	IL1B, IL6, TNF α	rs16944, rs1800795, rs1800629.	Only IL1B-511 (rs16944) genotype did not significantly predict changes in fatigue	10.5

(continued on next page)

Table 2 (continued)

Study	Objective	Disease	Sample size	Design	Fatigue measure	Genes	SNPs	Main findings	Quality scores
Sloan et al. (2012)	To explore relationships among baseline quality of life assessments and candidate genetic variations in a large cohort of patients with lung cancer	Lung cancer	1299	Cohort	Lung cancer symptom scale or linear analog self-assessment measures	470 SNPs in 56 genes	rs10741191 etc.	Three SNPs in the MGMT gene (rs3858300, rs10741191 and rs3852507) from DNA repair pathway were associated with overall QOL. Two SNPs (rs2287396 [GSTZ1] and rs9524885 [ABCC4]) from glutathione metabolic pathway were associated with fatigue	10.75
Athanasoulia et al. (2012)	To investigate whether polymorphisms in the ABCB1 gene could predict the occurrence of central side effects in PRL adenoma patients treated with cabergoline	Prolactin adenoma	79	Case-control	Self-designed questionnaire	ABCB1	rs1045642, rs2032582, rs2032583, rs2235015.	There were significant negative associations under cabergoline for the C-carriers and heterozygous CT individuals of SNP rs1045642 with frequency of fatigue	7
Bower et al. (2013)	To test the hypothesis that expression-regulating polymorphisms in pro-inflammatory cytokine genes would predict post-treatment fatigue in breast cancer survivors	Breast cancer	171	Cross-sectional	MFSI	IL1B, IL6, TNF α	rs16944, rs1800795, rs1800629	No association was found between these SNPs and fatigue; rs1800795 and rs1800629 were significant associated with fatigue	12
Reyes-Gibby et al. (2013a, 2013b)	To determine if a panel of immune-response genes may underlie the co-occurrence of severe pain, depressed mood, and fatigue and help identify patients with severe versus non-severe symptom clusters	Lung cancer	599	Longitudinal	SF-12	55 SNPs in the 37 genes	rs1800587 etc	An additive effect of mutant alleles in endothelial nitric oxide synthase (-1474 T/A) IL1B T-31C; TNFR2 Met196Arg; PTGS2 exon 10+837T > C and IL10RB Lys47Glu were predictive for symptom clusters	9.75
Reyes-Gibby et al. (2013a, 2013b)	To assess whether variants of 37 inflammation genes may serve as biologic markers of risk for severe pain, depressed mood, and fatigue in non-Hispanic white patients with non-small cell lung cancer	Lung cancer	599	Longitudinal	SF-12	59 SNPs in the 37 inflammation genes	rs1800587 etc.	IL-8-T251A was the most relevant genetic factor for fatigue (OR = 2.07, 95% CI = 1.16–3.70). Variants in the IL-10 receptor were relevant for fatigue among women. Men with IL-1A C-889T, C/T, or T/T genotypes had a lower risk of severe fatigue compared with those with C/C genotype (OR = 0.38, 95% CI = 0.13–1.06)	9.25
Dhruva (2014)	To evaluate for differences in variations in pro- and anti-inflammatory cytokine genes between participants who were classified as having low and high levels of morning and evening fatigue	Breast, prostate, lung, or brain	252	Longitudinal	LFS	IL4, TNF α	rs2243248, rs1800629, rs3093662, rs2229094	All studied SNPs were significantly associated with fatigue	11.25
Shi et al. (2015)	To identify a subset of multiple myeloma patients with a higher risk for persistent symptom burden and to determine whether any regulatory SNP in a cytokine gene was associated with such a high symptom burden	Multiple myeloma	344	Cross-sectional	MD Anderson Symptom Inventory multiple myeloma module	IL1B, IL6, TNF α , IL10	rs16944, rs1800795, rs1800629, rs1800896.	For non-Hispanic whites, the IL1b-511 CC genotype was associated with a high over-all symptom burden (OR, 2.35; 95% CI, 1.25–4.72; P = 0.004), whereas the IL6 2174 GG genotype predicted less moderate/severe fatigue (OR, 0.53; 95% CI, 0.29–0.88; P = 0.013)	9.5

Abbreviation: Symptom Inventory (FSI), Piper fatigue scale (PFS), Lee Fatigue Scale (LFS), Multidimensional Fatigue Symptom Inventory (MFSI), 12-Item Short Form Health Survey (SF-12), Fatigue impact scale (FIS), Fatigue Assessment Scale (FAS).

2009; Bower et al., 2013; Collado-Hidalgo et al., 2008; Dhruva et al., 2015; Illi et al., 2012; Jim et al., 2012; Miaskowski et al., 2010; Rausch et al., 2010; Reinertsen et al., 2011a; Reyes-Gibby et al., 2013a; Reyes-Gibby et al., 2013b; Shi et al., 2015; Sloan et al., 2012) and other mechanisms (three studies) (Athanasoulia et al., 2012; Fernandez-de-las-Penas et al., 2012; Vallance et al.,

2010). Genotypes of the following genes were assessed in these 16 studies: interleukin (IL)-1a (*IL-1a*), *IL-1b*, *IL-4*, *IL-6*, *IL-10*, tumor necrosis factor- α (*TNF- α*), a2-Heremans-Schmid glycoprotein (*AHSG*), polymerase delta-interacting protein 3 (*POLDIP3*), *COMT*, and ATP binding cassette subfamily B member 1 (*ABCB1*).

3.2.2.1. Inflammation and immune response. The majority (13/16, 81%) of the identified articles focused on exploring potential immune and inflammatory contributors to CRF. The associations of SNPs in genes *IL-1b* (rs16944), *IL-6* (rs1800795), and *TNF- α* (rs1800629) with fatigue severity were the most frequently investigated, and these studies yielded mixed results. One study (Collado-Hidalgo et al., 2008) suggested that the prevalence of at least one cytosine mutation in *IL1b* (rs16944) was substantially greater among fatigued than non-fatigued breast cancer survivors. However, three other recent studies found that the *IL1b-511* (rs16944) genotype did not significantly predict changes in fatigue in survivorship (Bower et al., 2013; Jim et al., 2012; Reinertsen et al., 2011a). Two studies observed that GG genotypes of *TNF α -308* (rs1800629) and *IL-6-174* (rs1800795) were significantly associated with CRF in women with early breast cancer both during and after treatment (Aouizerat et al., 2009; Bower et al., 2013). Another study (Jim et al., 2012) also observed that men with prostate cancer with the *IL-6-174* (rs1800795) G/C or C/C genotype and those with the *TNF α -308* (rs1800629) genotype showed greater increases in fatigue 6 months after initiation of androgen deprivation therapy. However, after controlling for covariates such as age, race, and baseline depressive symptoms, only the *TNF- α* genotype remained significantly associated with fatigue severity.

Researchers also studied the association between other SNPs in *IL-1b* and *IL-6* genes and cancer-related fatigue. One study (Rausch et al., 2010) identified 21 SNPs in cytokine genes related to symptom burden and quality of life (QOL) outcomes among 1149 lung cancer survivors. Among the 21 SNPs, they found that *IL-1b* rs1143633 and rs2853550 were associated with fatigue symptoms. However, no association was found between *IL-6* rs41800795 and fatigue. A study on QOL in 168 oncology outpatients and 85 family caregivers (FCs) demonstrated that, along with younger age, being white and being a patient (versus a FC), the minor allele of *IL4* rs2243248 was associated with higher degrees of fatigue, pain, sleep disturbance, and depression (Illi et al., 2012). Another more recent study (Reyes-Gibby et al., 2013b) assessed whether a panel of immune-response genes may underlie the co-occurrence of fatigue, severe pain, and depressed mood in non-small-cell lung cancer patients during treatment. Among 55 SNPs in the 37 genes, the researchers found that interleukin *IL8-T251A* was the most relevant genetic factor for fatigue.

3.2.2.2. Other mechanisms. Three studies focused on SNP associations in other non-inflammatory related gene pathways (Athanasoulia et al., 2012; Fernandez-de-las-Penas et al., 2012; Vallance et al., 2010). Vallance et al. (2010) explored three mechanisms (pharmacokinetics, serum albumin and pharmacogenetics) through which dexamethasone may cause debilitating fatigue and disrupt sleep in pediatric acute lymphoblastic leukemia (ALL) patients during treatment. They found *AHSG C > G* (Thr238Ser) exon 7 genotype (rs4918) and *POLDIP3* (rs1771889) to be associated with sleep disturbance but not fatigue. Fernandez-de-las-Penas et al. (2012) examined the influence of *COMT* Val158Met genotypes on cancer-related fatigue in breast cancer survivors; their results suggested that breast cancer survivors carrying the Met/Met genotype reported higher levels of fatigue. Since 2012, the number of SNPs under investigation increased substantially. After examining 470 SNPs in 56 genes of three biologic pathways in 1299 patients with non-small-cell lung cancer, Sloan et al. (2012) found three SNPs in the *MGMT* gene (rs3858300,

rs10741191 and rs3852507) in DNA repair pathway to be associated with overall QOL. Two SNPs (rs2287396 [*GSTZ1*] and rs9524885 [*ABCC4*]) from the glutathione metabolic pathway were associated with fatigue.

3.3. Other disease-related fatigue

3.3.1. Overview

Eighteen articles on other disease-related fatigue were found in our systematic review. The studies were published from 2003 to 2015, including six case-control studies (Bahadir et al., 2013; Helbig et al., 2003; McLaren et al., 2008; Piraino et al., 2012; Utge et al., 2010), five cohort studies (Allen et al., 2008; Bull et al., 2009; Lotrich et al., 2010; Scotet et al., 2005; Udina et al., 2013), three cross-sectional studies (Maluchenko et al., 2009; Ragnarsson et al., 2014; Vazquez-Rey et al., 2005), two longitudinal studies (Lee et al., 2014; Sundstrom et al., 2007) and two clinical trials (Becker et al., 2015; van der Deure et al., 2008). Sample sizes ranged from 33 to 31,192. The methods for assessing or diagnosing fatigue varied widely, including LFS, FIS, FAS, SF-11, SF-36, MFI-20, Chalder Fatigue Questionnaire, Beck Depression Inventory-II, VAS, SPHERE and PSC. Table 3 shows the details of the articles reviewed on other disease-related fatigue. The overall quality of the studies was moderately low, with a mean of 7.0. The main reasons for the lower scores were relatively small sample sizes, not mentioning genotyping blinding method, and insufficient description of confounders.

3.3.2. Mechanisms

The genes under investigations from these studies can be grouped into 3 categories: neurotransmitter systems and HPA axis (five studies) (Bahadir et al., 2013; Bull et al., 2009; Maluchenko et al., 2009; Ragnarsson et al., 2014; Utge et al., 2010), inflammation (six studies) (Becker et al., 2015; Helbig et al., 2003; Lee et al., 2014; Lotrich et al., 2010; Piraino et al., 2012; Udina et al., 2013) and other mechanisms (seven studies) (Allen et al., 2008; Dlugos et al., 2010; McLaren et al., 2008; Scotet et al., 2005; Sundstrom et al., 2007; van der Deure et al., 2008; Vazquez-Rey et al., 2005).

3.3.2.1. Neurotransmitter system and HPA axis. Similar to chronic fatigue syndrome, disease-related fatigue was found to be highly associated with alterations in the serotonergic system and HPA axis. One study found *5-HTT* was associated with central fatigue (a form of fatigue linked to the central nervous system) among selected college students, and this association differed by gender (Maluchenko et al., 2009). Among migraine patients, the genotype frequency of methylene tetrahydrofolate reductase (*MTHFR*) gene, which is involved in the conversion of the active form of the vitamin folate to *5-HT*, C677T was found to be higher in patients suffering from fatigue, compression, allodynia, and sleeplessness compared to controls (Bahadir et al., 2013). However, in patients undergoing pegylated IFN- α and ribavirin treatment for chronic hepatitis C infection, *5-HTT* was not associated with symptoms of fatigue ($p = 0.5$) (Bull et al., 2009). Furthermore, a study of patients with Cushing's syndrome found that the *Bcl1* polymorphism (rs41423247) in *NR3C1* was associated with fatigue (Ragnarsson et al., 2014). In a study by Smith and colleagues, unexplained chronic fatigue was found to be associated with neurotransmitter related genes including polymorphisms in the catabolic enzymes, monoamine oxidase A and B (*MAOA*, *MAOB*) that break down monoaminergic neurotransmitters including serotonin, and four polymorphisms involved in HPA axis function (*NR3C1*-rs1866388, rs852977, rs258750, and *POMC*) (Smith et al., 2006).

3.3.2.2. Inflammation. In patients with post-Q fever fatigue syndrome (QFS), variants in *HLA-DR-11*, *NRAMP*, and *IFN γ* were associated with fatigue compared to controls (Helbig et al., 2003). Similar results were found in a study on acute sickness responses to infection, showing that *IFN γ* (rs2430561) was associated with increased fatigue (Piraino et al., 2012). In a study on side effects of IFN- α treatment, the only association observed was that *IL-6* rs1800795 was associated with fatigue at baseline (Udina et al., 2013). Furthermore, a study on hepatitis C patients treated with IFN- α showed that *TNF α* rs1800629 was associated with fatigue during treatment (Lotrich et al., 2010). In patients with HIV/AIDS, SNPs in select cytokine genes (*IL1B* rs1071676 and rs1143627, *IL4* rs2243274, and *TNFA* rs1800683 and rs1041981) were related to fatigue (Lee et al., 2014). Moreover, in patients with ischemic stroke, *IL1RN* rs4251961 was associated with self-reported fatigue, and *TLR4* rs4986790 and rs4986791 were associated with lower levels of fatigue (Becker et al., 2015). In patients with pegylated IFN- α and ribavirin treatment for chronic hepatitis C virus, *IL-6* (rs1800795) was not associated with symptoms of fatigue (Bull et al., 2009).

3.3.2.3. Other mechanisms. Various other genetic linkages have been investigated in association with fatigue. Among patients with hemochromatosis, or iron-overload-related disease, the prevalence of C282Y homozygotes in the human hemochromatosis (*HFE*) allele was investigated in three studies (Allen et al., 2008; McLaren et al., 2008; Scotet et al., 2005). *HFE* regulates iron uptake by controlling the relationship between transferrin and the transferrin receptor (Gallego et al., 2015). All three studies observed significant associations between C282Y and fatigue. In a study on patients presenting with angina and normal coronary arteriograms (ANCA), a polymorphism of the human angiotensin-converting enzyme (*ACE*) gene was associated with fatigue scores (Vazquez-Rey et al., 2005). Among patients with mild traumatic brain injury, Apolipoprotein E (*APOE*) genotype was related to post-injury fatigue (Sundstrom et al., 2007). Furthermore, in a study of patients with primary autoimmune hypothyroidism, both the *OATP1C1*-intron3C > T and the *OATP1C1*-C3035T polymorphisms were associated with symptoms of fatigue and depression (van der Deure et al., 2008). In a study (Norheim et al., 2014) that aimed to identify SNP variants in primary Sjogren's syndrome (pSS) patients with high and low chronic fatigue, variants associated with the Rho-dependent signaling pathway (rs3786654 and rs10416904 of protein kinase N1) and cell membrane transport proteins (rs10276819 of solute carrier family 25, member 40 or SLC25A40) were associated with fatigue.

4. Discussion

The goal of this systematic review was to determine patterns of associations between pathway-based genetic polymorphisms and fatigue (CFS, CRF and other disease-related fatigue), both individually and collectively. We found that functional genetic variations (100% of the SNPs investigated in the association studies were functional) in the pathways of neurotransmitter regulation, HPA axis function, and immune-mediated inflammation appear to play important roles in the etiologies of CFS, CRF and other disease-related fatigue. This review provides empirical support for the association between functional polymorphisms in *TNF- α* , *IL1b*, *IL4* and *IL6* genes and elevated fatigue for all three subgroups of fatigue. We also found CFS shared a series of polymorphisms in *HLA*, *IFN- γ* , *5-HT* and *NR3C1* genes with other disease-related fatigue, however these SNPs (excluding *IFN- γ*) were not found to be adequately investigated in CRF.

The reviewed studies demonstrate that select neurotransmitter- and HPA axis-related genes may play important roles in both chronic fatigue syndrome and other disease-related fatigue. Specifically, polymorphisms in *5-HT*, *NR3C1*, *POMC*, *MAOA*, *MAOB*, *TPH2*, *COMT*, *GRIK2* and *NPAS2* were all found to be associated with fatigue. 5-HT, a monoamine neurotransmitter known to regulate mood, appetite, and sleep, acts via interactions with 5-HT receptors, and fatigue and mood disorders may be regulated by altering the expression of these receptors (Couch et al., 2015). The glucocorticoid receptor NR3C1 mediates feedback within the HPA axis and influences concentrations of the glucocorticoid cortisol, which is known to impact metabolism, the immune system, and the brain as well as stress-related behaviors (Bao et al., 2008). As both low and high levels of circulating cortisol are related to CFS, HPA axis-related genes may affect CFS (Cleare, 2004). As discussed in our review, a variety of neurotransmitter and HPA axis-related genes, including *POMC*, *MAOA*, *MAOB*, and *TPH2*, were associated with CFS and other disease-related fatigue. Due to the fact that these polymorphisms have not been fully investigated in CRF, it is difficult to know the extent to which specific neurotransmitters may be involved. Future studies are necessary to elucidate the association between neurotransmitter and HPA-axis-related genes and CRF.

The reviewed articles reveal that the development of fatigue is influenced by immune dysregulation, where specific functional SNPs and genotypes of *TNF α* , *IL1b*, *IL4*, and *IL-6* contribute to worsening or persistent fatigue (Saligan et al., 2015). Cytokine gene polymorphisms can significantly influence cytokine production levels. These findings are consistent with previous studies that have demonstrated associations between peripheral blood cytokine concentrations and fatigue occurrence or severity. A quantitative review (Schubert et al., 2007) suggested a positive correlation between fatigue and circulating concentrations of inflammatory markers. More importantly, genetic polymorphisms in these pathways may indicate a host predisposition to fatigue (Carlo-Stella et al., 2006). Among the cytokine SNPs investigated, GG genotypes of *TNF α* -308 was the only polymorphism significantly associated with all three subgroups of fatigue. *TNF α* is a pro-inflammatory cytokine involved in the regulation of a wide range of biological processes. These findings support the hypothesis that a *TNF- α* gene variation may be associated with differences in symptom frequency and severity of fatigue. This hypothesis was based on findings from clinical and experimental studies in both humans and animals suggesting that tumor and/or disease treatments can trigger increased *in vivo* concentrations of *TNF- α* , which can further influence fatigue via cytokine regulation of CNS function (Aouizerat et al., 2009; Dantzer et al., 2008). Preliminary evidence also suggests that the SNPs rs16944 in *IL1b* and rs1800795 in *IL-6* are associated with CRF during and after treatment (Bower et al., 2013; Collado-Hidalgo et al., 2008; Dhruva et al., 2015). Of note, these SNPs were not studied in CFS and other disease-related fatigue. Current studies also suggest that certain SNPs in *IL1b*, *IL1RN*, *IL4* are associated with HIV and post-stroke related fatigue symptoms (Becker et al., 2015; Lee et al., 2014). In addition, *HLA-DR* genes/gene products have been shown to play an immune-regulatory role in resistance or susceptibility to other infective agents. Relevant in this regard, *HLA-DR* polymorphisms have been related to other disease-related fatigue, such as in chronic Q fever (Helbig et al., 2003).

In addition to the neurotransmitter, HPA axis, and immune mechanisms discussed above, genes related to other mechanisms associated with CFS, CRF and other disease-related fatigue include *HFE* C282Y, *DCP1*, *ACE*, *APOE*, *OATP1C1*, *AHSG*, and *POLDIP3*. Several studies suggest that the polymorphism *HFE* C282Y may be associated with fatigue among Hereditary Hemochromatosis (HH) patients (Allen et al., 2008; McLaren et al., 2008; Scotet et al.,

Table 3
Studies on the association between other specific diseases-related fatigue and genetic polymorphisms.

Study	Objective	Disease	Sample size	Design	Fatigue measure	Genes	SNPs	Main findings	Quality scores
Helbig et al. (2003)	To explore the difference of gene variants spanning 15 genes and HLA-B and DR frequencies among QFS (post-infection fatigue syndrome) patients and controls	Chronic Q fever	186	Case-control	N.A.	HLA, NRAMP, IFN	HLA-DR11 etc.	QFS patients exhibited significant differences in frequencies of HLA-DR-11 NRAMP, and IFN γ genes, compared with controls	3
Scotet et al. (2005)	To investigate the impact of the HFE gene on the clinical presentation and epidemiology of HH	Hereditary hemochromatosis (HH)	415	Cohort	N.A.	HFE	C282Y	The frequency of fatigue was significantly increased after DNA-based testing (68.0 vs. 51.2%, OR = 2.03, p = 0.004)	4.5
Vazquez-Rey et al. (2005)	To prove that the ACE gene D allele might be associated with the presence of fatigue in angina and normal coronary arteriograms (ANCA) patients	Muscle fatigue in patients with angina and normal coronary arteriograms	33	Cross-sectional	SF-11	ACE	Insertion(I); deletion (D)	Patients with the highest fatigue scores had significantly higher D allele frequency compared to those with the lowest (64% vs. 36%; p = 0.027)	6.5
Smith et al. (2006)	To examine how genetic differences link to individual subgroups of the latent class solution for CFS	Unexplained Chronic Fatigue	140	Case-control	1994 Fukuda Criteria	POMC, NR3C1, MAOA, MAOB, TPH2	rs12473543, rs1866388, rs852977, rs258750, rs1801291, rs979606, rs979605, rs3027452, rs217363, rs4760816, rs4760750	Three classes of CFS were distinguished by gene polymorphisms involved in either HPA axis function or neurotransmitter systems, including POMC, NR3C1, MAOA, MAOB and TPH2	8.5
Sundstrom et al. (2007)	To explore the association between fatigue and APOE genotype	Fatigue for persons following a mild traumatic brain injury	93	Longitudinal	Mini-Mental State Examination	APOE	ϵ 4 allele	In the MTBI-group, post-injury fatigue was significantly associated with the APOE ϵ 4 allele	4.5
Allen et al. (2008)	To assess the risk of iron-overload-related disease in some hemochromatosis gene (HFE) C282Y homozygotes	Hereditary hemochromatosis	31,192	Cohort	Self-designed interview	HFE	C282Y	Male C282Y homozygotes with elevated serum ferritin levels had higher prevalence of iron-overload-related disease including fatigue	7.5
McLaren et al. (2008)	To compare the prevalence of symptoms and clinical conditions in persons homozygous for the HFE mutation (C282Y) and the controls	Hereditary hemochromatosis	646	Case-control	SF-36	HFE	C282Y	C282Y homozygotes with elevated serum ferritin levels had higher prevalence of certain symptoms such as chronic fatigue (OR 2.8; 95% CI 1.34 to 5.95, and OR 2.0; 95% CI 1.07 to 3.75, respectively)	7.5
van der Deure et al. (2008)	To examine whether polymorphisms in OATP1C1 were associated with well-being, neurocognitive functioning and preference for replacement therapy with levothyroxine (LT4) and liothyronine (LT3)	Hypothyroid	141	Clinical trails	MFI-20	OATP1C1	intron3C > T, Pro143Thr, C3035T	Both the OATP1C1-intron3C > T and the OATP1C1-C3035T polymorphisms were associated with fatigue and depression	8
Bull et al. (2009)	To determine the association between polymorphisms of IL-6 (rs1800795) and 5-HTTLPR and depression and fatigue during IFN- α and ribavirin treatment	Side effects of interferon- α (IFN- α) treatment	98	Cohort	Chalder Fatigue Questionnaire	IL6, 5-HTTLPR	rs1800795 (IL-6), L/S allele (serotonin deficit (LL genotype), serotonin excess (S genotype)	Neither polymorphisms were associated with symptoms of fatigue (IL-6: F = 1.2, d.f. = 430, P = 0.2; 5-HTT: F = 0.5, d.f. = 430, P = 0.5)	8.5

(continued on next page)

Table 3 (continued)

Study	Objective	Disease	Sample size	Design	Fatigue measure	Genes	SNPs	Main findings	Quality scores
Maluchenko et al. (2009)	To test the “serotonin” hypothesis of central fatigue genesis using the 5HTT as an example	Central fatigue	143	Cross-sectional	AMF	5-HTTLPR	L/S allele (serotonin deficit (LL genotype), serotonin excess (S genotype))	Young men with serotonin deficit (LL genotype) and girls with serotonin excess (S genotype) experienced more fatigue	1.5
Lotrich et al. (2010)	To investigate the impact of TNF- α polymorphism on the susceptibility to psychiatric symptoms during IFN- α therapy	Side effects of interferon- α (IFN- α) treatment	105	Cohort	Question 20 in Beck Depression Inventory-II	TNF- α	rs1800629	The TNF- α A allele was associated with anger (F = 2.5; p < 0.05) and fatigue (F = 2.9; p < 0.05) during treatment	7.5
Piraino et al. (2012)	To evaluate the association between acute sickness response to infection and functional single nucleotide polymorphisms (SNPs) in interleukin (IL)-6, tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and IL-10	Acute sickness response to infection	296	Case-control	SPHERE and PSC	IL-6, (TNF)- α , IFN- γ , and IL-10	IL-6-174 G/C, IFN- γ -874 T/A, IL-10-592 C/A	The SNP IFN- γ + 874 T/A was associated with fatigue (p = 0.0003; OR: 3.3)	9.5
Bahadir et al. (2013)	To investigate the relationship between biochemical and clinical parameters of migraine and methylenetetrahydrofolate reductase (MTHFR) gene C677T polymorphism	Compression, allodynia, fatigue, and sleeplessness	257	Case-control	N.A.	MTHFR	C677T	The polymorphism of MTHFR C677T was associated with compression, allodynia, fatigue, and sleeplessness (p = 0.027, 0.023, 0.006, and 0.05, respectively)	6
Udina et al. (2013)	To investigate the association between interferon (IFN)-induced depression, anxiety and fatigue and genetic variants of interleukin-6 gene (IL-6) and serotonin transporter gene (SERT)	Side effects of interferon- α (IFN- α) treatment	385	Prospective cohort	VAS	IL6, 5-HTTLPR	rs1800795 (IL-6), L/S allele (serotonin deficit (LL genotype), serotonin excess (S genotype))	At baseline, a significant effect of IL-6 polymorphism on fatigue symptoms was found	10.5
Lee et al. (2014)	To investigate the relationship between different fatigue patterns in adults with HIV and cytokine plasma concentrations and gene polymorphisms	HIV/AIDS	224	Longitudinal	LFS	15 genes	IL1B rs1071676, rs1143627; IL4 rs2243274; TNFA rs1800683 and rs1041981, etc	High fatigue pattern was associated with five single nucleotide polymorphisms (SNPs): IL1B rs1071676 and rs1143627, IL4 rs2243274, and TNFA rs1800683 and rs1041981	9.5
Norheim et al. (2014)	To investigate single nucleotide polymorphism (SNP) variations in pSS patients with high and low fatigue.	Primary Sjögren's syndrome (pSS)	569	Case-control	VAS	SLC25A40 PKN1	rs10276819 rs3786654, rs10416904, rs2241362	Significant associations with pSS were found for one SNP in SLC25A40 (unadjusted p = 0.007) and two SNPs in PKN1 (both p = 0.03)	9.5
Ragnarsson et al. (2014)	To explore the impact of polymorphisms in glucocorticoid (GC) sensitivity related genes on cognitive function in patients with Cushing's syndrome (CS)	Cushing's syndrome	106	Cross-sectional	FIS	NR3C1	Bcl1	The Bcl1 polymorphism was associated with fatigue, worse visual attention and working memory	10
Becker et al. (2015)	To evaluate the association between Poststroke fatigue (PSF) and the polymorphisms in 2 genes that affect the immune response	Poststroke fatigue (PSF)	39	A substudy of a larger trial	FAS	IL-1RN, TLR4	IL-1RN (rs4251961), TLR4 (rs4986790, rs4986791)	SNPs in IL-1RN, TLR4 were significantly associated with PSF	8

Abbreviations: Fatigue Symptom Inventory (FSI), Piper fatigue scale (PFS), Lee Fatigue Scale (LFS), Multidimensional Fatigue Symptom Inventory (MFSI), 12-Item Short Form Health Survey (SF-12), Acute Mental Fatigue (AMF) questionnaire, Visual Analogue Scale (VAS), Fatigue impact scale (FIS), Fatigue Assessment Scale (FAS); N.A.: not available.

2005). Hereditary Hemochromatosis is a hereditary disease, known as iron overload, characterized by dysregulated iron absorption resulting in total body iron overload (Siezenga et al., 2004). It is known that the mutation of C282Y in the *HFE* gene is very common in patients with HH (Feder et al., 1996) and one of the most common clinical manifestations of HH is fatigue (Gasser et al., 2014). However, more work needs to be done to confirm the association between *HFE* C282Y and fatigue.

4.1. Limitations and future directions

We are limited in our ability to draw strong conclusions from the above discussed work due to limitations in the individual studies and general gaps of knowledge in our understanding of fatigue.

The first caveat to the discussed is that sample sizes for all the studies included in this review were relatively small. Across a total of the 50 articles, only seven (14%) have a sample size larger than 500. Additional studies with larger sample sizes are needed to ensure statistical power, especially considering that individual SNPs are likely only weakly associated with risk. With larger samples, more subgroup (stratification) analyses can also be conducted to further explore fatigue and health disparities across age, race, gender, and other groups.

The second caveat of the discussed work is that many of the studies lack an accurate case-definition, especially for CRF and other disease-related fatigue. For example, of the 50 studies described, only 20 conceptually defined fatigue. It may be that incongruities between studies in the described associations between fatigue and genetic polymorphisms are related to alternate definitions of fatigue, as well as varied requisite duration of symptoms (Saligan and Kim, 2012). Moreover, unlike CFS, clear definitions of fatigue with respect to duration and severity for cancer-related and other disease-related fatigue are lacking in the current state of knowledge. In addition, because most of the studies on CRF and other disease-related fatigue did not include a control group (i.e. lacking a cancer diagnosis or a disease history), we cannot determine whether the association between these polymorphisms and fatigue was specific to disease diagnosis and/or treatment (Collado-Hidalgo et al., 2008). Fatigue may also be applicable to individuals in the general population that experience symptoms as a result for example of stressful circumstances (Aouizerat et al., 2009). Finally, because of differences in the study designs (e.g. case-control or not), the results of this review should be interpreted with caution. For instance, studies using case-control designs that categorized participants as fatigued or not may generate biased effect estimates of SNP-fatigue association (disease misclassification bias) compared to studies that used severity of fatigue as a continuous variable as the primary outcome.

The third caveat is that, only 28% of the studies used a longitudinal design to examine the associations between genetic variations and fatigue. More longitudinal studies are necessary to assess the roles of disease progression and treatment in the experience of fatigue across groups of patients (Saligan and Kim, 2012). It is possible that other genetic associations with fatigue will emerge if the same analyses are conducted at different points in the patient's disease or treatment, as classification of disease severity can change over time (Dodd et al., 2011).

Fourth, most of these studies used a candidate gene approach (all genes and SNPs were selected based on existing empirical literature and were thus hypothesis-driven), and therefore, there may be some influential polymorphisms that were not identified. It is notable that no genome-wide studies (GWAS) were found, thus there is a reasonable likelihood of biased findings from these 50 articles. Additionally, there was not a uniform statistical model used across the cited studies to assess SNPs-fatigue associations,

and thus our original plan for a meta-analysis was impeded. Moreover, the use of statistical methods to address multiple comparisons across studies was limited.

Finally, despite all the limitation identified above, our review had three additional limitations. First, we may have missed studies that are ongoing but not yet published. Second, although we searched among four public databases, some relevant studies might have been found using other databases or different key words. Third, we could not conduct any statistical analysis, as there was no uniform genetic statistical model across the studies, and no information outlining the distribution of each genotype or allele that would allow us to assess/calculate the SNPs-fatigue association.

4.2. Strengths

Selection bias is a common concern in observational studies when subject participation depends jointly on exposure and disease status. However, the assessment of polymorphism prevalence is not subject to selection bias under the assumption that genotype does not influence subject participation that is dependent upon exposure and disease status as outlined by Morimoto and colleagues (Morimoto et al., 2003). This is a strength of these SNPs-fatigue association studies. In addition, more than half of these studies collected information on major covariates, thereby decreasing unmeasured confounding issues.

5. Conclusion

We found several potentially important associations of SNPs related to neurotransmitter systems, the HPA axis, and immune-mediated inflammation with fatigue, including CFS, CRF, and other disease-related fatigue. Our review suggests a major role for cytokine SNPs in all the three subgroups of fatigue. Additionally, the review supports the continued use of genetic and epigenetic perspectives in assessing the role neurotransmitters play in persistent fatigue among cancer survivors. We consider that new knowledge gained from these studies could help CFS, cancer, and other disease-affected patients and survivors, their healthcare providers, and their caregivers by identifying specific genes of risk for fatigue, targeting subgroups of people who would most greatly benefit from supportive management of symptoms, as well as identifying pathways and mechanisms that might serve as targets for the development of cognitive behavioral interventions and novel medical therapies.

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Appendix A. Supplementary data

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