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Symptom Science: Advocating for Inclusion of Functional Genetic Polymorphisms

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Abstract

Incorporating biologically based data into symptom science research can contribute substantially to understanding commonly experienced symptoms across chronic conditions. The purpose of this literature review was to identify functional polymorphisms associated with common symptoms (i.e., pain, sleep disturbance, fatigue, affective and cognitive symptoms) with the goal of identifying a parsimonious list of functional genetic polymorphisms with evidence to advocate for their inclusion in symptom science research. PubMed was searched to identify genes and functional polymorphisms associated with symptoms across chronic conditions, revealing eight functional genetic polymorphisms in seven different genes that showed evidence of association with at least three or more symptoms and/or symptom clusters: *BDNF* rs6265, *COMT* rs4680, *FKBP5* rs3800373, *IL-6* rs1800795, *NFKB2* rs1056890, *SLC6A4* 5-HTTLPR+rs25531, and *TNFA* rs1799964 and rs1800629. Of these genes, three represent protein biomarkers previously identified as common data elements for symptom science research (BDNF, IL-6, and TNFA), and the polymorphisms in these genes identified through the search are known to impact secretion or level of transcription of these protein biomarkers. Inclusion of genotype data for polymorphisms offers great potential to further advance scientific knowledge of the biological basis of individual symptoms and symptom clusters across studies. Additionally, these polymorphisms have the potential to be used as targets to optimize precision health through the identification of individuals at risk for poor symptom experiences as well as the development of symptom management interventions.

Keywords

symptom science, functional genetic polymorphism, biomarker

Symptom science focuses on characterizing symptoms and understanding associated biological and behavioral mechanisms that can support clinical applications that prevent or alleviate symptoms (Cashion & Grady, 2015). Researchers and funding agencies have made numerous calls to action to integrate omics-based approaches into symptom science research (Corwin et al., 2014; Miaskowski et al., 2017; National Institute of Nursing Research [NINR], 2016; Taylor & Barcelona de Mendoza, 2018). Notably, omics-based approaches offer the potential to aid in identifying risk factors and understanding the biological underpinnings of symptoms. Deciphering the biological underpinnings of individual symptoms or symptom clusters has the potential to optimize precision health approaches to symptom management through the identification of at-risk individuals and targets for pharmacological and nonpharmacological interventions.

Evidence supports shared biological pathways for and genomic influences on symptom development. A recent review identified common genes and biological pathways to be considered among five frequently experienced symptoms including sleep disturbance, cognitive impairment, fatigue, gastrointestinal distress, and pain (McCall et al., 2018). While this review identified candidate genes to be considered across studies of common symptoms, it did not identify specific genetic polymorphisms. Likewise, a recent position paper proposed several protein biomarkers as common data elements (CDEs) that may mediate or moderate symptom experiences (Page et al., 2018). Functional genetic polymorphisms are

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Table 1. PubMed Literature Search Terms.

Symptom	Search Terms
Anxiety	("anxiety"[MeSH Terms] OR "anxiety"[All Fields]) AND "functional"[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields])
Cognitive dysfunction	("cognitive dysfunction"[MeSH Terms] OR {"cognitive"[All Fields] AND "dysfunction"[All Fields]} OR "cognitive dysfunction"[All Fields] OR {"cognitive"[All Fields] AND "disturbance"[All Fields]} OR "cognitive disturbance"[All Fields]) AND "functional"[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphisms"[All Fields])
Depression	("depressive disorder"[MeSH Terms] OR {"depressive"[All Fields] AND "disorder"[All Fields]} OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms]) AND "functional"[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields])
Fatigue	("fatigue"[All Fields] OR "lack of energy"[All Fields]) AND "functional"[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields])
Pain	("pain"[MeSH Terms] OR "pain"[All Fields]) AND "functional"[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphisms"[All Fields])
Sleep	("sleep"[MeSH Terms] OR "sleep"[All Fields]) AND "functional"[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields]) ("dyssomnias"[MeSH Terms] OR "dyssomnias"[All Fields] OR {"sleep"[All Fields] AND "disturbance"[All Fields]} OR "sleep disturbance"[All Fields]) AND functional[All Fields] AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields])
Positive affect	("positive affect"[All Fields] OR "positive mood"[All Fields] OR "psychological wellbeing"[All Fields] OR "euthymic"[All Fields] OR {"happiness"[MeSH Terms] OR "happiness"[All Fields]}) AND ("polymorphism, genetic"[MeSH Terms] OR {"polymorphism"[All Fields] AND "genetic"[All Fields]} OR "genetic polymorphism"[All Fields] OR "polymorphism"[All Fields])

variations in DNA for which there is evidence that they impact structure, function, or level of a gene product (Albert, 2011). Functional genetic polymorphisms that are associated with multiple symptoms have the potential to provide a minimal set of stable (across tissue types and over time) targets that can be an initial step in identifying additional biological CDEs for symptom science studies. Including polymorphisms in these studies could contribute substantially to building the knowledge base and addressing limitations in symptom science research (Corwin et al., 2017; Redeker et al., 2015).

The purpose of the present review of literature was to identify genes and specific targets to measure (i.e., functional polymorphisms) associated with five common symptoms (pain, sleep disturbance, fatigue, and affective and cognitive symptoms) across chronic conditions. Our goal was to identify a parsimonious list of functional polymorphisms for which there is replication of evidence of association with symptoms and to advocate for their utility to the symptom science research community.

Method

We conducted a structured search of the literature to identify functional genetic polymorphisms associated with symptoms. We selected the primary symptoms of relevance to the NINR-supported centers of excellence (Redeker et al., 2015). These symptoms included pain, sleep disturbance, fatigue, and affective (i.e., anxiety, depressive symptoms, positive affect) and cognitive symptoms. Search terms were specific to the symptom of interest and availability of associated literature (see Supplemental Material 1–7 for more information about symptom-specific searches methods). In brief, we queried in PubMed by combining several search terms, including *polymorphism* or *functional polymorphism* and the symptom of interest. Table 1 includes a comprehensive list of search terms used for each symptom. We completed all searches prior to December 18, 2017. Coauthors discussed and reviewed each other's search results, and an iterative process of group discussions guided additional searches and more detailed reviews. Articles selected evaluated associations between a genetic polymorphism and a symptom of interest and stating a significant finding(s) within the context of that study. We used a standardized table to guide data abstraction across all symptoms, and a second author verified abstracted data.

While our initial queries did not specifically include symptom clusters, some articles retrieved reported on symptom clusters containing one or more of the symptoms of interest. We included these articles in our final results. We excluded articles if they were reviews, editorials, preclinical studies, or written in a language other than English. Data extracted from selected articles included the author, year, gene, polymorphism(s), symptom phenotype, context (e.g., sample details), and

Table 2. Functional Gene Polymorphisms with Multisymptom Associations.

Gene	SNP	Anxiety	Cognitive Symptoms	Depressive Symptoms	Fatigue	Pain	Sleep	Positive Affect	Symptom Cluster
BDNF	rs6265	X	X	X	X	X	X		
COMT	rs4680	X	X	X		X	X	X	
FKBP5	rs3800373	X		X		X			
IL-6	rs1800795	X		X	X	X			
NFKB2	rs1056890				X		X		X[a,b]
SLC6A4	5-HTTLPR + rs25531	X	X	X	X	X	X	X	
TNFA	rs1799964	X		X		X			
	rs1800629		X		X	X	X		

Note. SNP = single nucleotide polymorphism.
[a]Mood-cognitive symptom cluster includes difficulty concentrating, feeling sad, worrying, itching, and feeling irritable. [b]Sickness behavior symptom cluster includes pain, lack of energy, feeling drowsy, difficulty sleeping, and sweats (Miaskowski et al., 2017).

relevant findings. Details for symptom-specific search strategies, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagrams, and complete tables with extracted data from relevant articles are provided in Supplementary Material 1–7.

We synthesized the findings of the preliminary search described above in a single table displaying the associations between genetic polymorphisms and symptoms, with polymorphisms as the rows and each symptom as a column. Polymorphisms associated with two or more symptoms were then included in the second phase of our search to verify results and to identify any potential article that we had not captured in the initial search. In this phase, we searched PubMed using the specific polymorphism reference (rs) number and the symptom keywords used in the initial search. We reviewed results using the same criteria as listed above. The threshold for final inclusion was determined by evaluating all data and group discussion. As a result, polymorphisms included in the final list had evidence of association with three or more of the symptoms of interest and/or a symptom cluster that contained one or more of those symptoms. Including polymorphisms that were associated with three or more symptoms resulted in the most comprehensive yet parsimonious list.

Results

Table 2 includes a synthesis of this review highlighting eight functional genetic polymorphisms that showed evidence of association with three or more symptoms and/or with symptom clusters. The solute carrier family 6 member 4 (*SLC6A4*) 5-HTTLPR+rs25531 polymorphism was associated with all seven symptoms. Brain-derived neurotrophic factor (*BDNF*) rs6265 had evidence of association with all symptoms except positive affect. Catechol-O-methyltransferase (*COMT*) rs4680 had associations with all symptoms except fatigue. Another two polymorphisms were associated with four separate symptoms: Interleukin 6 (*IL-6*) rs1800795 was associated with anxiety and depressive symptoms, pain, and fatigue, whereas tumor necrosis factor alpha (*TNFA*) rs1800629 had associations with pain, sleep, fatigue, and cognitive symptoms.

Both FK506 binding protein 5 (*FKBP5*) rs3800373 and *TNFA* rs1799964 showed evidence of association with three separate symptoms: anxiety, depression, and pain. Furthermore, nuclear factor kappa B subunit 2 (*NFKB2*) rs1056890 had evidence of associations with both sleep disturbance and fatigue as well as two symptom clusters (i.e., mood-cognitive or sickness behavior symptom clusters). Table 3 provides a summary of the putative functional impact of each polymorphism. Symptom-specific findings and associated references are provided in the Supplementary Materials.

Discussion

This review is the first to synthesize the literature to identify associations between functional genetic polymorphisms and common symptoms experienced across chronic conditions. The review identified eight polymorphisms in seven genes that were associated with at least three symptoms or symptom clusters, providing a starting place for those contemplating the inclusion of genetic polymorphisms in their symptom research trajectories. Consistently collecting and analyzing genetic polymorphisms across studies can provide further insight into the genomic contributions to variability in patients' experiences with common symptoms and symptom clusters across disease processes.

The review independently identified three genes, *BDNF*, *IL6*, and *TNFA*, for which the resulting protein has been previously identified as a CDE for symptom science research (Page et al., 2018). Interestingly, the functional polymorphisms identified for these genes impact either the secretion of the protein or the level of transcription of the gene (Bull et al., 2009; Chen et al., 2004; Kroeger et al., 1997; Paul-Samojedny et al., 2010; Wilson et al., 1997). Independently identifying these genes that have already been implicated as CDEs at the protein level increases the evidence in support of including the polymorphisms in these genes in research focused on symptoms.

The final list of polymorphisms is consistent with several publications underscoring the putative function of inflammatory and immune processes and neuroendocrine processes

Table 3. Description and Function of Polymorphisms.

Gene	Polymorphism (Alternative Name If Applicable)	Polymorphism Function
BDNF	rs6265 (val66met)	This missense variant results in an amino acid substitution (i.e., valine to methionine) at codon 66. This change impairs the secretion of BDNF in the nervous system (Chen et al., 2004; Egan et al., 2003).
COMT	rs4680 (val158met)	This missense variant results in an amino acid substitution (i.e., valine to methionine) at position 158 of *COMT*. This alters the structure of the COMT enzyme and reduces its activity, resulting in higher dopamine levels (Stein, Newman, Savitz, & Ramesar, 2006).
FKBP5	rs3800373	This variant is located in the 3 prime untranslated region and likely alters the stability and half-life of the mRNA and modulates glucocorticoid signaling and hypothalamic–pituitary–adrenal axis function. This variant has been associated with greater *FKBP5* induction by cortisol and decreased glucocorticoid-receptor sensitivity (Fudalej et al., 2015; Tatro et al., 2009).
IL-6	rs1800795 (-174 G/C)	This variant is located in the promoter region, which is a region essential for inducing transcription of *IL-6*. rs1800795 has been associated with differential gene expression and decreased plasma levels of IL-6 during immune activation (Bull et al., 2009; Paul-Samojedny et al., 2010).
NFKB2	rs1056890	This variant is located in the 3 prime untranslated region, which is a region known to bind miRNAs and regulate protein translation (Ma, Becker Buscaglia, Barker, & Li, 2011; Tian et al., 2018).
SLC6A4	5-HTTLPR + rs25531	The HTTLPR variant is a 43-base-pair variable-number tandem repeat (VNTR) polymorphism, and rs25531 is a single nucleotide polymorphism (SNP) located in the promoter region of *SLC6A4*. The VNTR determines if the alleles are long or short, and the SNP further divides the long allele into La and Lg. The La allele produces significantly more 5-HTT mRNA and protein and results in increased expression and serotonin transporters in the cell membrane. The short allele results in lower levels of serotonin (Wendland, Martin, Kruse, Lesch, & Murphy, 2006).
TNFA	rs1799964 (-1031 T/C)	This variant is located in the promoter region and influences gene expression. The C allele is correlated with increased serum TNFA levels (Nourian et al., 2017; Sandoval-Pinto et al., 2016).
	rs1800629 (-308 G/A)	This variant is located in the promoter region. The A allele has been associated with an increase in the binding of nuclear factors and heightened transcription of the gene (Kroeger, Carville, & Abraham, 1997; Wilson, Symons, McDowell, McDevitt, & Duff, 1997).

Note. miRNAs = microRNAs; mRNA = messenger RNA.

(e.g., regulation of the hypothalamic–pituitary–adrenal axis) in the experiences of symptoms or symptom clusters (McCall et al., 2018; Miaskowski & Aouizerat, 2012; Miaskowski et al., 2017; Page et al., 2018). Of the polymorphisms identified in this review, five are in genes that play an important role in inflammation and immune regulation. For example, *IL-6* encodes a protein that is involved in the regulation of inflammation and maturation of the lymphocytes including T cells and B cells. Likewise, *NFKB2* is integral in central activation of the inflammatory system through transcription activation and repression of several genes. *TNFA* encodes a pro-inflammatory cytokine that is involved in cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation. *FKBP5* is integral in immunoregulation (National Library of Medicine, 2018; Online Mendelian Inheritance in Man OMIM®, 2018).

The remaining polymorphisms are in genes involved in neural development and/or neurotransmission. BDNF is a nerve growth factor involved in neuroplasticity and regulation of synapse transmission. *COMT* encodes for an enzyme that is responsible for the metabolism of several neurotransmitters such as epinephrine, norepinephrine, and dopamine. Lastly, *SLC6A4* regulates serotonergic signaling and transport in the central nervous system (National Library of Medicine, 2018; Online Mendelian Inheritance in Man OMIM®, 2018). These findings further support the shared biological underpinnings of symptoms and symptom clusters.

While there are many types of biomarkers (e.g., proteins, epigenetic markers) that may be considered useful for symptom science research, genetic polymorphisms have several strengths. They are stable over time and are not impacted by factors such as age, sex, comorbidities, medication regimens, or other clinical interventions. Additionally, it does not matter what tissue type (e.g., whole blood, serum, saliva) is used for DNA extraction, and current technologies allow for the measurement of these polymorphisms with precision, sensitivity, and specificity quickly enough to have clinical utility. In contrast, other biological markers such as proteins (e.g., IL-6, TNF-α, CRP) are dynamic and can fluctuate based on a number of clinical factors, gene expression, or tissue type (Gry, Oksvold, Ponten, & Uhlen, 2010). Therefore, the use of genetic polymorphisms as biomarkers in symptom research increases the potential for their future clinical utility across populations, ages, and conditions.

While not all studies currently have relevant research questions or resources (e.g., infrastructure, finances) for genetic data collection and analyses, we encourage researchers to store biological samples. The investment involved in recruitment and phenotyping for symptom-based studies warrants securing the possibility to address genetic polymorphisms in the future. Stored samples could be used to expand current research or provide for replication of findings from other studies. Additionally, more symptom science research that includes genetic

polymorphisms would allow for the mega-analyses and meta-analyses essential to the evidence base required for translation to clinical utility.

The results of the present review should be interpreted with consideration of some limitations. It was not designed to identify all polymorphisms that could explain the complex phenotype of symptoms. Our search was limited to functional polymorphisms, and findings could be biased toward polymorphisms of candidate genes chosen in symptom-related studies. The final list of polymorphisms represents only the current literature at the time of the search. As more evidence emerges, additional polymorphisms will likely be identified and more support for the polymorphisms identified in the present review will likely come to light. Although we conducted this search in a systematic fashion, our literature search was limited to PubMed and was not exhaustive. It is possible that we excluded relevant studies outside of our search criteria. There was notable variability in phenotyping of symptoms in the included studies, which could have impacted the findings of associations between the genetic polymorphisms and symptoms of interest.

Conclusion

In the present review, we identified specific and stable functional genetic polymorphisms we recommend for inclusion in symptom science research. Using genetic polymorphisms as biomarkers has the potential to provide greater understanding of the biological basis of individual symptoms and symptom clusters and stable biomarkers related to symptom development. These genetic polymorphisms could also be used to identify individuals at risk for poor symptom experiences and target for precision health interventions.

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Author Contributions

All authors contributed to the conceptualization, data collection from the literature, interpretation of the literature, and writing of this manuscript.

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Supplemental Material

Supplemental Material for this article is available online.

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