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HEALTH SCIENCES

Fibromyalgia: A Review of Related Polymorphisms and Clinical Relevance

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Abstract: Fibromyalgia (FM) is a chronic pain syndrome that affects the central nervous system and generates disability, which is characterized by generalized pain, fatigue, and functional decline. In this review, we aimed to identify the polymorphisms related to the pathophysiology of FM and the clinical characteristics generated by genetic influence. Only original studies with genes related to FM were considered, totaling 27 articles. The genes found were: *MTHFR*, *RGS4*, *MYT1L*, *TACR1*, *SCN9A*, *DRD3*, *ADRB2, IL-4*, *HLA-DRB1*, *EDN1*, *CNR1*, *TAAR1*, *OPRM1*, *ADRA1A, ADRB3, BDNF*, *GRIA4*, *HTR3A*, *HTR3B*, *HTR2A*, *SERPINA 1* or *A1AT*, *NRXN3*, *GCH1*, *MEFV*, *TRPV3*, *SLC6A4*, *ACE I/D, TSPO*, *COMT*, and *MAOA*. Several genes related to different pain syndromes and altered pain thresholds have been identified and some polymorphisms were related to susceptibility to FM. It was observed that 73.33% of the genes related to FM were also associated with some psychological disorders, such as anxiety, depression, schizophrenia, and obsessive and compulsive disorder, and 40.00% with pain sensitivity and/or migraine, besides other disorders associated (drug addiction, autoimmune disorders, circulatory problems, and metabolic alterations). This review demonstrated an association of FM and genetic polymorphisms that can expand our knowledge about the pathophysiology of this disease.

Key words: fibromyalgia, gene, polymorphisms, SNPs.

INTRODUCTION

Fibromyalgia (FM) is a chronic pain syndrome that affects an estimated 3-6% of the world population (NFMCPA 2021), which represents about 230-470 million of people. It affects the central nervous system and generates disability, which is characterized by generalized pain, fatigue, and functional decline. FM is related to central sensitization processes and involves the loss of glial cells homeostasis, among other mechanisms (Deitos et al. 2018). It is more prevalent in women (2%) than in men (0.5%), greatly increasing its prevalence in women after the age of 60 (12%). FM patients frequently present other chronic pain syndromes, such as rheumatoid arthritis and endometriosis (Jameson et al. 2020).

According to the American College of Rheumatology (ACR), for research and clinical practice purposes FM can be diagnosed following a series of clinical criteria (D'Agnelli et al. 2019, Wolfe et al. 2010). The publication of the 2010/2011 ACR criteria for the diagnosis of FM syndrome superseded the traditional 1990 ACR criteria, according to the identification of the multi-symptomatic nature of FM and the difficulty of the standardization of the tender points exam, required in 1990 ACR criteria. The ACR 1990 criteria recommended anatomical tender point locations for the diagnosis of fibromyalgia with digital palpation. On physical examination, of 18 tender points, more than 11

are noticed during palpation with a 4kg pressure (Jameson et al. 2020). The new ACR criteria consider: (1) generalized pain index; (2) pain persisting for more than 3 months; and (3) there is no other pathology that accounts for such pain (Wolfe et al. 2010). Regarding clinical aspects, the main complaints presented by patients are pain, chronic muscle stiffness, fatigue, sleep disorders, cognitive dysfunctions, and psychological disorders. A recent retrospective analysis of many patients included in an FM continuum spectrum identified 4 possible classes of the disease: Class 1 presents widespread, but more regional pain; Class 2 was characterized by a greater severity of pain, a broader involvement of body regions and several associated symptoms; Class 3 was characterized by an increase in the level of pain compared to the previous classes, a strict association with sleep disorders and the possibility of chemical sensitivity; Class 4 is the highest severity of pain and of associated symptoms, which represented the "secondary FM" to other diseases such as multiple sclerosis and lupus, which had a high prevalence in this class (Atzeni et al. 2019).

The pathophysiology of FM is poorly understood, however, and many plausible hypotheses have been raised. Although specific biomarkers have not been fully identified and validated, some studies show that there is a genetic predisposition involved (D'Agnelli et al. 2019). Buskila & Neumann (1997) and Arnold et al. (2013) observed that family members of patients with FM have a higher prevalence of this disease than the general population. Several genes related to different pain syndromes and altered pain thresholds have been identified and there are indications that some Single Nucleotide Polymorphisms (SNPs) are related to susceptibility to FM (D'Agnelli et al. 2019). However, gene polymorphisms do not always account for gene expression. Also, environmental factors are considered important in the development of chronic pain (Park et al. 2016a, Xiao et al. 2012). An important hypothesis for the pathophysiology of FM is central sensitization, which occurs in patients with a genetic predisposition who suffer painful stimuli for a long period of time (Oliveira Junior & Almeida 2018).

The multidimensional approach to FM definition undoubtedly offers advantages in terms of current clinical practice and in relation to diagnosis. Nevertheless, considering the possible changes over time and the heterogeneity of this syndrome, it may be limiting in terms of practical management of the single FM patient. Genetic factors influence vulnerability to the FM syndrome, but no specific genes have been definitively implicated (Xiao et al. 2012). In this review, we aimed to identify the SNPs related to the pathophysiology of FM and the clinical characteristics generated by the polymorphisms.

MATERIALS AND METHODS

This systematic review follows the methodology described in the PRISMA statement (Moher 2010). A literature search of electronic databases MedLine/PubMed was carried out up to August 2020. Key search terms included "(fibromyalgia) AND (polymorphisms)". A manual search of the reference list of studies and review articles was subsequently performed. The first author (L.J.) did the initial selection based on titles and abstracts. All studies concerning genes related to fibromyalgia were eligible for inclusion in the present review. Only studies in English where the full text was available were considered. Full text articles were assessed for inclusion in the analysis independently by two reviewers (L.J.; J.S.) with all the discrepancies resolved through

a discussion. The chosen articles were analyzed with respect to their quality, including in the review only if the experimental protocol applied was adequate.

RESULTS

The results of the literature search and the stepwise exclusion process are described in Figure 1. The electronic searches identified 120 records relating fibromyalgia to polymorphism. Twenty-nine records were excluded because they were not in English or were review articles, and afterwards another 74 were excluded because the research did not include FM-related genes and clinical manifestations in patients with FM. A total of 27 full-text articles were assessed for eligibility.

Following literature review, we plotted in a table all SNPs related to genes potentially involved in the pathogenesis of fibromyalgia and associated with clinical features. In the studies, we found a total of 30 genes related to FM and influencing FM symptoms (Table I): (1) *MTHFR* (methylenetetrahydrofolate reductase); (2) *RGS4* (regulator of G protein signaling 4); (3) *MYT1L* (myelin transcription factor 1 like); (4) *TACR1* (tachykinin receptor 1); (5) *SCN9A* (sodium voltage-gated channel alpha subunit 9); (6) *DRD3* (dopamine receptor D3); (7) *ADRB2* (adrenoceptor beta 2); (8) *IL-4* (interleukin 4); (9) *HLA-DRB1* (major histocompatibility complex, class II, DR beta 1); (10) *EDN1* (endothelin 1); (11)

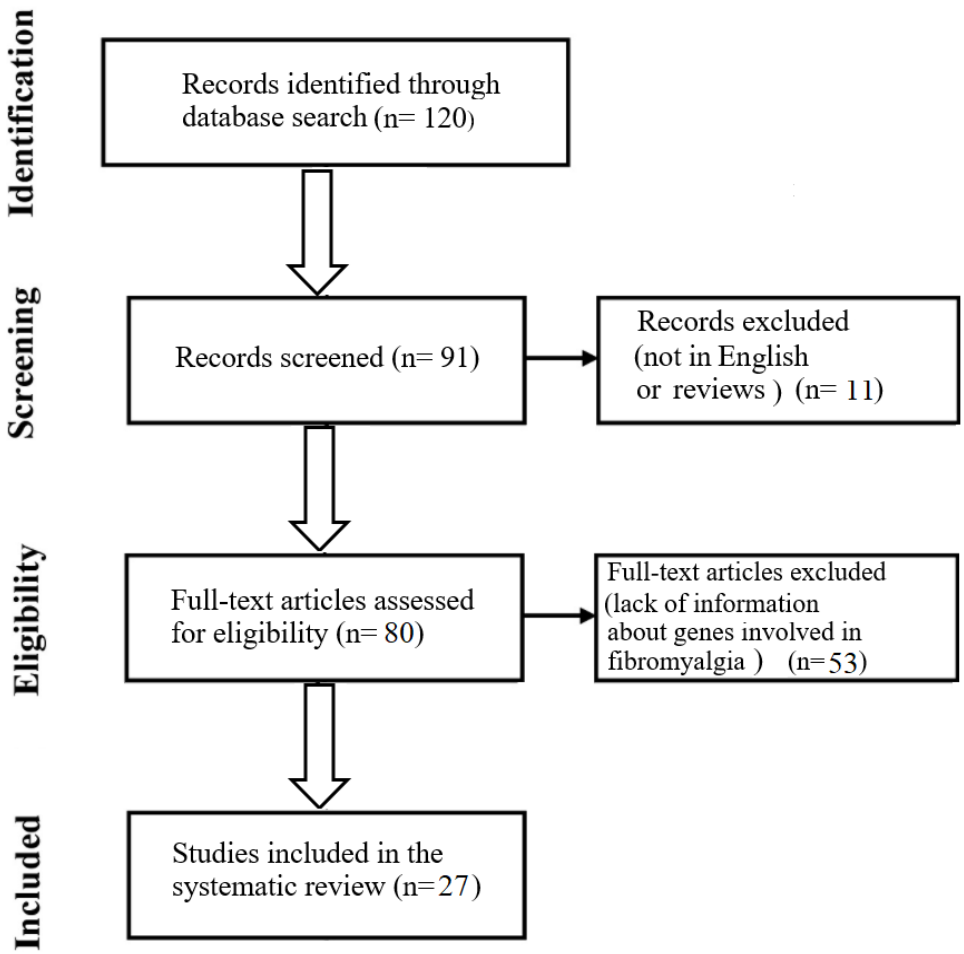

Figure 1. Fibromyalgia and polymorphisms: study selection flow chart.

CNR1 (cannabinoid receptor 1); (12) *TAAR1* (trace amine associated receptor 1); (13) *OPRM1* (Opioid Receptor mu 1); (14) *ADRA1A* (adrenoceptor alpha 1A); (15) *ADRB3;* (16) *BDNF* (brain derived neurotrophic factor); (17) *GRIA4* (glutamate ionotropic receptor AMPA type subunit 4); (18) *HTR3A* (5-hydroxytryptamine receptor 3A); (19) *HTR3B* (5-hydroxytryptamine receptor 3B); (20) *HTR2A* (5-hydroxytryptamine receptor 2A; 5HT-2A); (21) *SERPINA 1* or *A1AT* (serine protease inhibitor A1); (22) *NRXN3* (neurexin 3); (23) *GCH1* (guanosine triphosphate or GTP cyclohydrolase 1); (24) *MEFV* (Mediterranean fever gene; pyrin innate immunity regulator); (25) *TRPV3* (transient receptor potential cation channel subfamily V member); (26) *SLC6A4* (solute carrier family 6 member 4); (27) *ACE I/D* (angiotensin I converting enzyme); (28) *TSPO* (translocator protein); (29) *COMT* (catechol O-methyltransferase); and (30) *MAOA* (monoamine oxidase A). The polymorphisms associated with the pathogenesis and susceptibility of FM are listed in the table.

Our results demonstrate that, out of the total of 30 genes, 73.33% of the genes related to FM are also associated with some psychological disorders, such as anxiety, depression, schizophrenia, and obsessive and compulsive disorder, 40.00% with pain sensitivity and/or migraine, besides other disorders associated (drug addiction, autoimmune disorders, circulatory problems, and metabolic alterations). The chromosome analysis demonstrates that most genes are located at chromosome 6 (16.67%). The other genes are located at chromosome 11 (13.33%), 2 (10%), 14 (10%), 17 (10%), 1 (6.67%), 5 (6.67%), 8 (6.67%), 22 (6.67%), and only one gene at chromosome 3, 13, 16 and X (each one at 3.33%). All chromosome groups had at least one gene involved, except the "F" group, and mainly long arms (q).

DISCUSSION

FM is still poorly understood today, as described before in this review, the patient may have other family members with the same disease, individuals exhibit degrees of pain that may fluctuate throughout the course of their disease, and quality of life can also affect the variability of conditions of the pathology found. Thus, having a broad overview of how genes would be associated with the susceptibility and/or development of the disease could help in the search for a better treatment. Recent years, the genetic component of FM has received attention, and meta-analyses from observational studies and GWAS (genome-wide association study/SNP) were performed and identified some genetic variants. This review identified 30 genes related to the pathophysiology of FM and the clinical characteristics generated by the polymorphisms, which displayed important insights into the mechanisms underlying this disease development.

Different studies demonstrated *COMT* (rs4680, rs2097903, rs4818), *SLC6A4* (5-HTTLPR), *HTR2A* (rs6313), *ADRA1A* (rs1383914, rs1048101, rs574584, rs573542), and *ADRB2* (rs1042713, rs1042714) genes as directly related to FM. Although the other genes cited in our results are potentially involved, especially with the intensity of pain. Central sensitization is an important hypothesis for the pathophysiology of FM, and in this hypothesis, when the non-myelinated C fibers, located in the central nervous system, are frequently stimulated by intense pain, there is a hyperexcitability in which neuronal impulses are added, generating the depolarization of N-methyl-D-aspartate receptors (NMDA) (Park et al. 2018). Activation of glial cells and an increase in interleukin-8 and substance P are observed, responsible for the growth of nerve fibers that generate the symptom intensity (Park et al. 2018).

Table I. SNPs related to genes studied potentially involved in fibromyalgia's pathogenesis.

Cytogenetic Location	GENE (Polymorphisms)	Some clinical relevance and association with FM	References
1p36.22	*MTHFR* (C677T or rs1801133)	Potentially involved in FM, homocystinuria, alopecia areata, muscle stiffness, dry eyes, schizophrenia, autism, depression, dementia, and migraine.	Inanir et al. 2015
1q23.3	*RGS4* (rs10799897, rs2842003, rs2805050)	Potentially involved in FM, schizophrenia, and alteration in pain inhibition	Smith et al. 2012, D'Agnelli et al. 2019
2p25.3	*MYT1L* (rs11127292)	Associated with low comorbidities in FM, autism spectrum disorder, mental and cognitive retardation.	Docampo et al. 2014
2p12	*TACR1* (rs3771863)	Dementia, breast cancer, fatigue, and Sicca syndrome in FM.	Rodriguez-Rodriguez et al. 2015
2q24.3	*SCN9A* (rs6754031)	Risk of developing FM, congenital insensitivity to pain, erythromelalgia, paroxysmal pain disorder, small fiber neuropathy, genetic epilepsy with seasonal fever, type 2 hereditary sensory and autonomic neuropathy.	Vargas-Alarcon et al. 2012
3q13.31	*DRD3* (rs6280 or Ser9Gly)	Thermal hyperalgesia in FM, migraine, schizophrenia, opioid addiction, alcoholism, and hereditary essential tremor type 1.	Potvin et al. 2009
5q31-q32	ADRB2 (rs1042713, rs1042714)	(FM) + migraine, autoimmune disorders, musculoskeletal pain disorder, type 2 diabetes, autism, obesity and metabolic alterations.	Vargas-Alarcón et al. 2009
5q31.1	*IL-4* (Intron 3 VNTR)	Risk for developing FM, hypocortisolism resulting in the inflammatory state on patients and chronic symptoms	Yigit et al. 2013
6p21.32	*HLA-DRB1*	Low association with immune response in FM, depressive symptoms, alopecia areata, autoimmune Addison's disease, Crohn's disease, Graves' disease, Lyme disease, Hashimoto's thyroiditis, idiopathic inflammatory myopathy, idiopathic juvenile arthritis, multiple sclerosis, narcolepsy, psoriatic arthritis, rheumatoid arthritis, rosacea, type 1 diabetes, and autoimmune disorders.	Yunus et al. 1999
6p24.1	*EDN1* (rs1800541)	Susceptibility to FM, hearing loss, rheumatoid arthritis.	Nah et al. 2017
6q15	*CNR1* (rs6454674, rs1078602, rs10485171)	Potentially involved in FM, obesity, irritable bowel syndrome, migraine, and post-traumatic stress disorder.	Smith et al. 2012, D'Agnelli et al. 2019
6q23.2	*TAAR1* (rs8192619, rs4129256)	Potentially involved in FM, schizophrenia, increased pain sensitivity and low dopamine disponible.	Smith et al. 2012, D'Agnelli et al. 2019
6q25.2	*OPRM1* (rs1799971)	Risk of developing FM, pain intensity, schizophrenia, alcoholism, and drug addiction.	Estévez-López et al. 2018
8p21.2	*ADRA1A* (rs1383914, rs1048101, rs574584, rs573542)	(FM) + pain syndrome, obesity, and schizophrenia.	Vargas-Alarcón et al. 2009
8p11.23	*ADRB3* (rs4994)	Potentially involved in FM, obesity, schizophrenia, type 2 diabetes, and cardiovascular risk.	Vargas-Alarcón et al. 2009
11p14.1	*BDNF* (rs6265, rs12273539, rs11030104)	Alzheimer's disease, risk of suicidal behavior, increased BMI, opioid addiction, WAGR syndrome (disorder that affects Wilms tumor, aniridia, genitourinary anomalies, and intellectual disability) and psychiatric diseases (anxiety, bipolar disorder, schizophrenia and eating disorder).	Xiao et al. 2011, Park et al. 2018

Table I. Continuation.

11q22.3	*GRIA4* (rs642544, rs17104711, rs2510177, rs10895837)	Potentially involved in FM, neurodevelopmental disorder, and central sensitivity.	Smith et al. 2012, D'Agnelli et al. 2019
11q23.2	*HTR3A* (rs118162387)	Associated with severity of FM, irritable bowel syndrome, serotonin syndrome, schizophrenia, and social phobia.	Frank et al. 2004, Limer et al. 2008
11q23.2	*HTR3B* (rs118162387)	Drug addiction, *Gilles de la Tourette* syndrome, myasthenic congenital syndrome, schizophrenia and pigmented paravenous chorioretinal atrophy.	Frank et al. 2004, Limer et al. 2008
13q14.2	*HTR2A* or *5HT-2A* (rs6313 or T102C)	(FM) + schizophrenia, alcoholism, comorbid symptoms of pain, psychological and behavioral disorders.	Mergener et al. 2011, D'Agnelli et al. 2019, Limer et al. 2008
14q22.2	*GCH1* (rs841)	(FM) + Pain sensitivity.	Estévez-López et al. 2018, Kim et al. 2013
14q24.3-q31.1	*NRXN3* (intronic CNVs/copy number variants)	Associated with low comorbidities in FM, schizophrenia, alcoholism, and autism spectrum disorder.	Docampo et al. 2014
14q32.13	*SERPINA 1* or *A1AT*	Potentially involved in FM, anxiety disorder, type 1 and 2 bipolar disorder, post-traumatic stress disorder and alpha 1 antitrypsin deficiency.	Schmechel & Edwards 2012
16p13.3	*MEFV* (rs224222)	Potentially involved in FM, fatigue, irritable bowel syndrome and immunity regulator.	Karakus et al. 2012
17p13.2	*TRPV3* (rs395357)	Potentially involved in FM, fatigue, palmoplantar keratoderma, and Olmsted syndrome.	Vargas-Alarcon et al. 2012, Park et al. 2016a, b
17q11.2	*SLC6A4* (rs25531, 5-HTTLPR or rs4795541)	(FM) + depression, migraine, psychological stress, obsessive and compulsive disorder, alcoholism, anxiety, suicide, and temporomandibular joint disorder.	Arnold et al. 2013, Kosek et al. 2016, D'Agnelli et al. 2019
17q23.3	*ACE* (rs1799752)	Potentially involved in FM, migraine, cardiovascular disorder, and psychiatric conditions.	Inanir et al. 2015
22q13.2	*TSPO* (rs6971)	Potentially involved in FM, bipolar disorder, and pain severity.	Kosek et al. 2016
22q11.21	*COMT* (rs4680, rs2097903, rs4818, rs4633, rs6269)	(FM) + increase of pain severity, fatigue, headaches, schizophrenia, 22q11.2 deletion syndrome, alcoholism, opioid addiction, mental disorders, disability, depression, bipolar disorder, panic disorder, anxiety, obsessive, and compulsive disorder, eating disorder and attention deficit.	Inanir et al. 2014, Cohen et al. 2009, Estévez-López et al. 2018, Desmeules et al. 2014, Fernández-de-las-Peñas et al. 2014, Fernández-de-las-Peñas et al. 2012, Barbosa et al. 2012, Desmeules et al. 2012, Lee et al. 2015, Vargas-Alarcón et al. 2007, Gürsoy et al. 2003, Park at al. 2016a, b
Xp11.3	*MAOA* (rs6323)	Potentially involved in FM, neuropsychiatric conditions such as alcoholism, antisocial personality and impulsivity.	Gürsoy at al. 2008, Limer et al. 2008

NMDA is related to the BDNF, responsible for the neuroceptive articulation in the human body. *BDNF* gene could be related to hyperalgesia caused by chronic FM pain and its deregulation is responsible for the patient's hypersensitivity (Park et al. 2018). These observations lead to hypothesize a decreased serotonergic and noradrenergic activities (D'Agnelli et al. 2019).

All *SLC6A4*, *HTR3A*, *HTR3B*, *HTR2A* genes are associated with serotonergic regulation. The *SLC6A4* gene is responsible for the transport of serotonin to presynaptic neurons and is associated with chronic pain conditions (Kosek et al. 2016, D'Agnelli et al. 2019). The SNP rs25531 is related to psychological distress in FM patients and the 5-HTTLPR (or rs4795541) polymorphism is associated with pain modulation in FM patients (Kosek et al. 2016). *HTR3A* and *HTR3B* genes are receptors of serotonin expressed in amygdala, caudate nucleus and hippocampus, and cause fast and depolarizing responses in neurons. These genes revealed different genotypes in patients with putative impact on nociception circuits, a characteristic present in FM patients (Frank et al. 2004). The *HTR2A* gene encodes a receptor for serotonin and plays a role in anxiogenic situations. All of them are highly associated with psychological disorders and/or psychiatric symptoms (Offenbaecher et al. 1999, Frank et al. 2004, Tander et al. 2008, Heddini et al. 2014).

Decreased levels of serotonin in the serum and cerebrospinal fluid (catecholamine metabolites) were an early finding in FM. The sympathetic nervous system plays an incompletely understood role in the pathogenesis of chronic and acute pain. The *COMT* gene is an important gene related to FM risk and increase of pain severity (Inanir et al. 2014, Park et al. 2016b, Estévez-López et al. 2018). It is responsible for the production of catechol-O-methyltransferase (COMT) enzymes in nerve cells and in other tissues, such as liver and blood. This enzyme breaks down neurotransmitters in the prefrontal cortex area, which is responsible for human emotions, personality, and ensures that there are proper amounts of both dopamine and norepinephrine. The *COMT* gene (rs4680-Val158Met), is associated with painful symptoms in FM patients (Cohen et al. 2009, Park et al. 2018) and they are strongly related to other clinical manifestations, showing psychological disorders, such as depression, anxiety and schizophrenia, alcoholism, opioid addiction and eating disorders. The SNP rs2097903 is also associated with FM susceptibility (Estévez-López et al. 2018) and rs4818 and rs4633 are both related to a higher risk of FM development and worse symptoms (Park et al. 2016b).

The androgen receptor gene is involved in the metabolism of steroid-hormone since it stimulates the transcription of androgen responsive genes (Davey & Grossmann 2016). It is divided into alpha-AR (for example: *ADRA1A*), responsible for vasoconstriction, and beta-AR (*ADRB2* and *ADRB3*), activated by catecholamines and responsible for vasodilation, resulting in homeostasis and regulation factors (Xiao et al. 2011). Mutations in this gene are also associated with complete androgen insensitivity. *AR* gene is related to the development of FM and different symptoms, SNPs rs1042713 and rs1042714 (*ADRB2)* are associated with chronic pain condition, SNP rs1383914 (*ADRA1A*) is related to FM susceptibility, SNP rs1048101 (*ADRA1A*) is linked to disability, and SNP rs574584 (*ADRA1A*) is associated with tiredness upon awakening and morning stiffness (Vargas-Alarcón et al. 2009). In view of the finding of the elevated cerebrospinal fluid levels of substance P among FM patients, a polymorphism in the *TACR1* gene has been studied in patients. The *TACR1* gene is from the tachykinin receptors family, and it is responsible for neurokinin 1, which is involved

in the phosphatidylinositol metabolism. These tachykinin receptors are characterized by interactions with G proteins and contain seven hydrophobic transmembrane regions. This gene encodes the receptor for the tachykinin substance P, also referred to as neurokinin 1. In clinical manifestations of FM, *TACR1* gene is related to dementia, and fatigue, and SNP rs3771863 associated with Sicca syndrome, an autoimmune syndrome prevalent in FM patients (Rodriguez-Rodriguez et al. 2015).

Smith et al. (2012) investigated a large candidate gene association for pain treatment in FM, suggesting involvement of TAAR1, RGS4, CNR1, and GRIA4. About clinical manifestations, gene *TAAR1* was associated in neurological systems and in the immunological functions, *RGS4*, inhibits pain perception in the spinal, *CNR1*, encodes one of the cannabinoid receptors, and *GRIA4* are associated with the increasing of pain sensitivity in FM patients (D'Agnelli et al. 2019). The gene *ACE I/D*, associated with renin-angiotensin system and hypothalamic-pituitary-adrenal axis regulation during stress (Inanir et al. 2015), *SERPINA 1*, responsible for producing the alpha-1 antitrypsin protein (Schmechel & Edwards 2012), *HLA-DRB1*, play a role in the immune system with human leukocyte antigen (Yunus 1998), *MEFV*, produce pyrin protein that control in the inflammatory process with white blood cells and signaling molecules (Karakus et al. 2012), *NRXN3*, important for nervous system receptors and transmission by synaptic and cell adhesion molecules (Docampo et al. 2014), and *GRIA4*, associated with glutamate receptors (D'Agnelli et al. 2019, NIH 2020), were all associated with the susceptibility of development FM syndrome, however the mechanisms are not well known.

DRD3 and *DRD4* genes are related to the dopaminergic system. The *DRD3* gene encodes the D3 subtype of dopamine receptors, which are mediated by G proteins. D3 is in a limbic area that is responsible for cognitive, emotional, and endocrine mechanisms. Studies show that dopamine is related to pain inhibition and the dopamine activity of FM patients is interrupted by painful stimuli and they have a decreased thermal pain threshold, causing hyperalgesia in patients with Ser9Gly and difficulties in endogenous pain inhibition (Potvin et al. 2009, Park et al. 2016a, Park & Lee 2017). The *OPRM1* gene is responsible for the mu (μ) opioid receptor, an endogenous system that regulates pain in neurons (Estévez-López et al. 2018). When opioids (endogenous or exogenous) bind to the receptor, the interaction triggers a cascade of chemical signals in the nervous system. When there is a reduction of activity, the pain is replaced by pleasure, and the production of euphoria and dopamine also increases. The SNP rs1799971 is related to alcoholism and opioid addiction and was associated with FM susceptibility and genetic risk of FM development (Estévez-López et al. 2018). The *BDNF* gene is associated with higher sensitivity on C-reactive proteins and opioid addiction in patients with FM (Xiao et al. 2012). Val66Met polymorphism is associated with higher body mass index in FM patients, SNP rs11030104 is related to fatigue and anxiety symptoms, and SNP rs12273539 is associated with FM susceptibility (Park et al. 2018).

The *GCH1* and *TRPV3* genes are associated with the nitric oxide metabolism and higher risk for the development of FM, as well as pain sensitivity. The *GCH1* gene is important to produce GTP cyclohydrolase 1 enzyme, which produces tetrahydrobiopterin (BH4) molecules. BH4 is involved in the amino acids metabolism and is a cofactor to produce nitric oxide, which in excess is associated with increased pain sensitivity and hyperalgesia in neuropathic pain (Park et al. 2016b, Kim et al. 2013). The *GCH1* gene is important for the synthesis of

serotonin and dopamine neurotransmitters. The SNP rs841 showed FM susceptibility in 76.8% of cases with a GG genotype in relation to 66.7% of the control group (Estévez-López et al. 2018). The *TRPV3* gene is present in the TRP group of transient receptor potential channels which mediate pain perception and activate neurons and neurotransmitters. The SNP rs395357 was associated with fatigue symptoms usually common in FM patients, causing disability (Park et al. 2016a). The fatigue seems to occur due to interaction between environmental and biological factors and disability on TRP ion channels (Park et al. 2016a). Sodium channels are responsible for providing electrical signals in the cells and they work under instructions from *SCN9A* gene. The sensation of pain is the result of the transmission of sodium channels in nociceptors when there is hyperexcitability, that are in peripheral nervous systems and sympathetic ganglia neurons (Vargas-Alarcon et al. 2012). Mutations in this gene have been associated with primary erythermalgia, channelopathy-associated insensitivity to pain, and paroxysmal extreme pain disorder. SNP rs6754031 was associated with severe symptoms of FM and studies demonstrate that FM patients have dorsal root ganglia sodium channelopathy, leading to a persistent pain state (Vargas-Alarcon et al. 2012).

The *EDN1* gene plays an important role in peptide and muscle cells with vasoconstrictor action and is produced by endothelial cells. It is associated with G-protein and glomerular mesangial cells cascade. The *EDN1* gene is associated with pain and inflammation of nerve fibers, causing hyperalgesia and contributing to FM symptoms. The FM susceptibility was influenced by SNP rs1800541 (Nah et al. 2017). The *TSPO* gene is present mainly in the mitochondrial compartment of peripheral tissues. The protein encoded by this gene interacts with some benzodiazepines and has different affinities from its endogenous counterpart. It is important for the synthesis of steroid hormone with the cholesterol molecule and modulates the energy metabolism during oxidative stress (Kosek et al. 2016). It is activated in microglia and its expression is altered in neuroinflammatory and neurodegenerative diseases, causing psychiatric disorders (Kosek et al. 2016, Milenkovic et al. 2018). The *TSPO* (rs6971) in FM patients was associated with the elevation of IL-8 that is expressed together with TSPO in glial cells, resulting in severe pain and stronger symptoms (Kosek et al. 2016). The methylenetetrahydrofolate reductase enzyme (MRE) is made from instructions of the *MTHFR* gene. MRE is important for the folate and methionine metabolism, and both substances play a role in protein metabolism. Genetic variation in this gene influences susceptibility to occlusive vascular disease, neural tube defects, colon cancer and acute leukemia, and mutations in this gene are associated with methylenetetrahydrofolate reductase deficiency. It is also implicated in acid-B12-B6 metabolism and mutations on the *MTHFR* gene can cause cytokine activation, interfering in inflammatory symptoms in FM patients (Inanir et al. 2015). The *IL-4* gene is important for immune regulatory signals of a pleiotropic cytokine produced by activated T cells. The protein encoded by this gene is a pleiotropic cytokine produced by activated T cells. This cytokine is a ligand for interleukin 4 receptor. It plays a role in tissue repair with proinflammatory type 1 cytokines, but type 2 cytokines are responsible for allergic reactions and acute inflammation. In FM, cytokines on cerebrospinal fluid are responsible for hypocortisolism resulting in the inflammatory state of patients and chronic symptoms. Also, FM patients demonstrate a decreased level of IL-4, however, in autoimmune diseases, such as rheumatoid arthritis, the induced increase

of IL-4 seems to be an important intervention (Pernambuco et al. 2018).

CONCLUSIONS AND FUTURE APPROACHES

In conclusion, our results demonstrated a total of 30 genes, many of which are associated with psychological disorders, such as anxiety, depression, schizophrenia, and obsessive and compulsive disorder, and with pain sensitivity and/or migraine, besides other disorders associated (drug addiction, autoimmune disorders, circulatory problems, and metabolic alterations). Related polymorphisms in pain transmission pathways, such as catecholamine-O-methyltransferase (*COMT*), monoamine oxidase (*MAOA*), serotonin (*SLC6A4, HTR2A, HTR3A, HTR3B*), and μ1 opioid receptor (*OPRM1*), are believed to be involved in the genetic predisposition to FM, through serotonergic, dopaminergic and catecholaminergic pathways (Foulkes & Wood 2008, Park et al. 2016a, Solak et al. 2014). In addition, androgen receptor gene is related to the development of FM and susceptibility (*ADRB2* and *ADRA1A*). Chromosomal analysis showed no association.

Environment and genetic predisposition may be involved in the development of FM. Early-life events, including both physical trauma and psychosocial stressors could influence gene expression and thus contribute to the occurrence of FM (Polli et al. 2019). Studies suggested that down-regulation in peripheral blood and cerebrospinal fluid with hypermethylated status in peripheral blood induce neuron differentiation, nervous, skeletal and organ system development and chromatin compaction. This mechanism demonstrates that DNA methylation is strongly involved in FM pathogenesis (Ciampi-De Andrade et al. 2017). Epigenetic expression with stressful events (exposure to cumulative environmental risk factors) in FM patients induces an expanding frequency of somatic chromosomal changes (Menzies et al. 2013). Epigenetics may be responsible for the induction and maintenance of chronic pain (Liang et al. 2015). Thus, FM and epigenetic should be investigate in further studies since epigenetics may influence the FM physiopathology and the course of the disease.

The pathophysiology of FM is not fully understood, but we know that genetic, physical, environmental, and psychological factors are involved. This review demonstrated that genetic factors in FM and polymorphism strongly affects symptom severity and susceptibility to disease, so should be studies about the polymorphisms found in this research and possible pharmacological treatment. More studies with larger populations and association between polymorphisms and other diseases are needed to expand our knowledge in the field of FM pathophysiology.

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