Genetic Contributions to the Development of Fibromyalgia

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Fibromyalgia (FM) is a centrally and peripherally mediated chronic pain syndrome with biological, psychological, and environmental predispositions. It is estimated that the prevalence of FM in the general population is 2%. FM is characterized by generalized chronic pain, fatigue, sleep changes, decreased cognitive function, and numerous tender points throughout the body. Diagnosing and treating FM are challenging. FM has a high comorbidity rate with rheumatologic disorders such as psoriatic arthritis and ankylosing spondylitis. Many FM individuals have psychiatric disorders.

fibromyalgia genetics Genes

1. Introduction

Fibromyalgia (FM) is a centrally and peripherally mediated chronic pain syndrome with biological, psychological, and environmental predispositions [1][2][3][4]. It is estimated that the prevalence of FM in the general population is 2% [5]. FM is characterized by generalized chronic pain, fatigue, sleep changes, decreased cognitive function, and numerous tender points throughout the body [6]. Diagnosing and treating FM are challenging. FM has a high comorbidity rate with rheumatologic disorders such as psoriatic arthritis and ankylosing spondylitis [7]. Many FM individuals have psychiatric disorders [8].

FM has a strong genetic component, and the risk of developing FM is eightfold higher among first-degree relatives, as evidenced by familial aggregation studies [9]. The discovery of decreased serum and cerebrospinal fluid levels of serotonin (5-HT) in FM patients has guided many genetic studies [10][11]. Similarly, the catabolism and anabolism of other neurotransmitters, such as dopamine, were examined [12][13]. This has expanded to genes involved in pain processing and inflammation that may amplify pain signals in the nervous system or systemically.

Multiple epigenetic mechanisms of gene regulation have been studied in the pathogenesis and symptomatology of FM, including micro-RNA and DNA methylation. Environmental factors in the development of FM are significant. At present, childhood trauma, physical abuse, and chronic psychosocial stressors are believed to amplify stress responses mediated by the hypothalamic pituitary axis, ultimately leading to higher concentrations of substance-P in the central nervous system and increased pain interference in day-to-day life [14][15][16].

2. Catechol-O-Methyltransferase (COMT) Polymorphisms and FM

COMT is one of the primary enzymes that inactivates catecholamines, including dopamine, by transferring a methyl group from S-adenosyl-L-methionine to dopamine to generate 3-methoxytyramine. Functional polymorphisms in the *COMT* gene can change the enzyme's activity to be either a fast or slow metabolizer of catecholamines [17]. The three common *COMT* genotypes are Val-158-Val, Met-158-Met, and Val-158-Met. The Val-158-Val genotype has the highest enzymatic activity. The Met-158-Met genotype has the lowest enzymatic activity [18]. Phenotypically, Met-158-Met carriers showed a higher threshold to pain and pressure stimuli [12][19][20] and fatigue levels than Met-158-Val carriers [21]. Val-158-Val carriers exhibited significantly worse working memory measures than Met-158-Val carriers [22]. Val-158-Val carriers also showed more pain catastrophizing thought and higher levels of anxiety and symptoms of depression than Met-158-Val carriers [23]. Val-158-Val carriers reported higher sensory and affective ratings of pain along with negative internal affective states [24].

In FM individuals, the *COMT* Val-158-Met genotype, also named rs4680, has been examined for its association with pain symptoms and mood disorders. Multiple studies demonstrate that rs4680 increases the risk of developing FM [12][25][26][27][28][29]. However, repeat investigations show no association between rs4680 and an increased risk of developing FM [30][31][32][33]. A possible explanation is that rs4680 may be overrepresented within the FM population. Since rs4680 is associated with increased pain symptoms [12][25][26][29][34], it is not surprising that individuals with rs4680 report an increased severity of FM-associated symptoms.

Several other single nucleotide polymorphisms (SNP) were investigated for FM association in FM individuals from different countries. SNP rs4818 of the *COMT* gene was associated with FM risk in Korean [31], Brazilian [25], and Spanish populations [29]. However, rs4818 was not associated with FM diagnosis in a large study examining diverse FM individuals [35], the Mexican population [29], or the Spanish population [12]. Similar to rs4680, rs4818 is associated with pain sensitivity [25][31]. The presence of both rs4818 and a SNP (rs1799971) in the opioid receptor mu 1 (*OPRM1*) gene is associated with pain catastrophizing [34]. Additional variants have been evaluated, with some showing an association with FM development. SNP rs2097903 of the *COMT* gene is associated with a higher risk of FM susceptibility [36]. rs6269 is associated with FM development in a Spanish population [29]. rs4633 is associated with FM development in a Korean population [31].

3. Polymorphisms in 5-HT Processing and FM

The role of 5-HT in mood is well established. Low levels of 5-HT are associated with a low mood. Raising the level of 5-HT from low levels is associated with improved mood [37]. 5-HT also plays a role in pain modulation. Although the full relationship has not been fully elucidated, it appears that increased levels of 5-HT within the peripheral nervous system are associated with sensitization of peripheral nerves and hyperalgesia. In the central nervous system, the role of 5-HT in pain modulation is complicated. It is dependent on receptor availability and affinity, 5-HT concentration, spinal cord pathways, and associated cerebral neural networks [38]. Low 5-HT levels are associated with FM diagnosis [39][40].

To understand the associations between 5-HT and FM, a review of 5-HT biosynthesis and physiology is needed. Tryptophan hydroxylase converts tryptophan into 5-hydroxytryptaminae (5-HTP). Aromatic decarboxylase converts

5-HTP into 5-HT. 5-HT is transported to storage in the presynaptic vesicles by the vesicular monoamine transporter (SLC18A2: Solute carrier family 8A member 2). When 5-HT is released into the synaptic cleft, it interacts with post-synaptic 5-hydroxytryptamine receptors (5-HTR1, 2, 3A, 4, 6, and 7) to activate secondary messenger cascades. Simultaneously, 5-HT stimulates presynaptic 5-HTR1 in a negative feedback loop to inhibit further release of 5-HT and interacts with solute carrier family 6 member 4 (SCL6A4) to transport synaptic 5-HT back into the pre-synaptic neuron [41]. 5-HT is also transported back into the pre-synaptic neuron by the serotonin transporter (5-HTT) [42]. Inhibitory serotonergic 5-HT1A receptors in the presynaptic neurons become activated and decrease serotonergic signalling [43].

Any changes in the described pathway that affect 5-HT concentrations have been reported to increase FM susceptibility or alter FM-associated symptoms. Individuals carrying a “short allele” polymorphism (44 base pair deletion) in the 5′ regulatory region of *SLC6A4*, also known as the serotonin transporter promoter region (*5-HTTLPR*), appear to have an increased risk of developing FM [44]. This polymorphism decreases SCL6A4 transporter expression. A potential mechanism is that an impaired ability for 5-HT reuptake by SLC6A4 increases 5-HT1 receptor-mediated negative feedback to decrease 5-HT concentration in the synaptic cleft [39][45]. Individuals carrying the short allele of the *5-HTTLPR* gene also have associated depression and anxiety disorders [44]. In a study examining the association between 5-HT autoantibodies and FM in a cohort of FM individuals, 73% of FM individuals have auto-antibodies to 5-HT [46]. They have lower 5-HT concentrations. It is postulated that a lower 5-HT concentration increases the risk of developing FM.

Polymorphisms in the *5-HTR2A* (5-hydroxytryptamine receptor 2A) gene have been associated with FM and depressive symptoms. FM female individuals carrying the *5-HTR2A* polymorphism of Cytosine-Thymine (CT) genotype have lower pain thresholds than those with TT and CC genotypes [34]. FM individuals with a combined *5-HT1a* CC and *5-HTT*-high expression have the fewest depressive symptoms compared to individuals with a combined *5-HT1a* CC/G and *5-HTT*-low expression [47].

SNP rs1062613 with the CC homozygotes genotype in the *5-HTR3a* gene were found to be more frequent in individuals with FM than in healthy controls. Carriers of the CC genotype were found to have fewer dopamine receptors available when compared to TT carriers, suggesting that CC carriers may experience less reward associated with dopamine release. However, there was no association between rs1062613 and pain threshold or tolerance [48][49]. Further examination of six different *5-HTR3a* variants and eight different *5-HTR3b* variants revealed mixed results when compared to healthy controls [49]. Several variants were more frequently observed in individuals with fibromyalgia compared to healthy controls but did not reach statistical significance.

4. Polymorphisms in Pain Processing and FM

The pain pathway consists of four general processes: transduction, transmission, modulation, and perception. Polymorphisms in genes involved in the processing of noxious stimuli along this pathway confer different pain phenotypes to individuals with FM. The *ATP2C1* (ATPase Secretory Pathway Ca2+ Transporting 1) gene encodes a magnesium-dependent calcium pump protein called hSPCA1 (human secretory pathway Ca^{2+}/Mn^{2+} ATPase

protein 1), which mediates uptake of cytosolic calcium and magnesium to the Golgi apparatus [50]. A GWAS (genome-wide association study) discovered that a SNP (single nucleotide polymorphism) at the *ATP2C1* locus (rs10490825) is associated with chronic widespread pain [51]. This finding suggests that changes in intracellular calcium concentrations may play a role in pain transduction for FM individuals. Similarly, Andolina et al. reported that the *TRPM6* (transient receptor potential cation channel subfamily M member 6) SNP (rs395357), which encodes for a calcium and magnesium channel in pain transduction, is associated with a higher risk of developing FM [52][53]. HAP1 (Huntingtin-associated protein 1) is another intracellular protein involved in pain transduction. It is enriched in neuronal cells and mediates vesicular transport between organelles. A GWAS comparing FM and healthy volunteers showed that a *HAP1* SNP (rs4796604) is associated with a lower nociceptive flexion reflex threshold—the reflex by which individuals withdraw their hand from a hot oven dish before perceiving the painful stimulus at the supratentorial level [54]. The transient receptor potential vanilloid (TRPV) family of non-selective cation channels have a well-established role in sensing and transmitting noxious stimuli via sensory afferents [55]. Park et al. showed that a polymorphism of *TRPV3* (rs395357) is associated with the severity of fatigue symptoms and mental health in FM individuals [56].

In the pain transmission process, polymorphism in the *SNAP25* (Synatposome Associated Protein 25) gene is associated with worsening FM related symptoms in FM individuals. SNAP25 regulates neurotransmitter release via vesicle docking and fusion in the presynaptic neuron [57]. Balkarli et al. showed that FM individuals with the SNAP-25 TC genotype have higher Beck depression scale and visual analogue scale scores compared to FM patients with the TT and CC genotypes [58]. Similar to *SNAP25*, *SCN9A* (Sodium voltage gated channel alpha subunit 9) plays a role in mood symptoms and pain interference in FM individuals [59]. *SCN9A* encodes the Nav1.7 sodium channel, which is highly expressed in the dorsal root ganglion and sympathetic root ganglion. Polymorphisms in *SCN9A* (rs6754031 and rs4453709) are associated with higher FM impact questionnaire scores [60] and reduced motivation and activity [61].

Polymorphisms in proteins involving pain modulation and perception are associated with FM susceptibility and FM-related symptoms. Guanosine triphosphate cyclohydrolase 1 (GCH1) is needed for tetrahydrobiopterin (BH4) production. BH4 is a cofactor in dopamine and serotonin biosynthesis, which plays a role in the passage of pain signals between interneurons in the spinal cord and brain [14]. *GCH1* polymorphisms (rs3783641, rs84, rs752688, and rs4411417) have been reported to be associated with lower pain sensitivity and susceptibility to FM [62]. A polymorphism of the mu-opioid receptor gene (*OPRM1*; rs1799971) was shown to alter frontoparietal network processing during pressure stimulation in FM individuals [63]. Smith et al. reported that *TAAR1*, *RGS4*, and *GRIA4* (trace amine-associated receptor 1, regulator of G protein signaling 4, and glutamate ionotropic receptor AMPA type subunit 4, respectively) are associated with susceptibility to FM [64]. *TAAR1* encodes for a G-protein-coupled receptor that plays a role in reward and cognitive function [65]. RGS4 is a regulatory GTPase activating molecule that can negatively regulate G protein signaling in cells [66]. GRIA4 is a glutamate receptor that mediates excitatory neurotransmission [67]. Sleep disturbances are well established in FM individuals, and it has long been disputed whether these changes are in response to living with chronic pain, comorbid mental illness, or the underlying biological aberrations. Indeed, polymorphisms in several adrenergic receptor genes have been found in FM patients who suffer from disrupted sleep. The Gly16Arg SNP at the beta-2-adrenergic receptor gene has been

found in patients with FM who suffer from sleep dysfunction [68][69]. Two SNPS in the alpha(1A)-adrenergic receptor gene (rs1048101 and rs1383914) were reported to be associated with the presence of FM and elevated FM impact questionnaires for disability [69]. The SNP rs574584 was associated with FM impact questionnaires measuring morning stiffness and tiredness upon awakening.

5. Inflammatory Genes/Proteins and FM

Inflammation is often associated with pain amplification. FM individuals appear to have higher levels of serum cytokines, chemokines, reactive oxygen species, and acute phase proteins [70], and there is increasing evidence that inflammation in FM may have a genetic underpinning.

Interleukins are a class of cytokines that facilitate communication between white blood cells during an inflammatory response [71], and serum levels of many interleukins have been found to be elevated in FM individuals. An exome sequencing of 19 probands in a nuclear family of FM showed two nonsense mutations in chromosome 11 putative open reading frame 40 (*C11orf40)* and zinc finger protein 77 (*ZNF77*) with increased transmission to affected probands. These two nonsense mutations were associated with elevated plasma levels of inflammatory cytokines compared to controls [72]. Yigit et al. showed that an interleukin-4 gene 70 bp variable number tandem repeat polymorphism is associated with increased risk for FM [73].

Chemokines are a similar class of inflammatory mediators that transduce signals through G-protein-coupled receptors. The *CCL11* (C-C motif chemokine ligand 11) gene on chromosome 17 encodes a chemokine that can dampen the body's response to inflammatory triggers. In a GWAS involving the FM family, Zhang et al. found that a SNP at *CCL11* (rs1129844) is associated with increased susceptibility to the development of FM [74]. Further, about 36% of the SNP was transmitted from parents to children, both of whom developed FM, and individuals with the SNP were found to have compensatory increases in the expression of CCL11. This suggests an underlying immune connection to FM. The *RNF123* (Ring Finger Protein 123) gene on chromosome 3 encodes E3 ubiquitin-protein ligase [75], which plays a role in cell cycle progression, innate immunity, and metabolism. In a GWAS, a *RNF123* (ring finger protein 123) SNP (rs1491985) was associated with developing FM [51]. Lastly, lower levels of the anti-inflammatory agent alpha-one antitrypsin [76] were found in a survey of FM individuals in 10 countries [77]. Blanco et al. reported that a polymorphism in the *AAT* (Alpha-1-antitrypsin) gene (PI*X) is found at higher frequencies in FM cohorts compared to the general population [77].

BDNF (brain derived neurotrophic factor) is a protein that regulates neuronal excitability and plasticity at multiple levels of the nervous system and has been shown in mouse models to play a key role in inflammatory pain and the development of chronic pain [78]. When released from the dorsal root ganglia, it acts on TrkB (tropomyosin receptor kinase B) receptors on primary afferent nerve endings and post-synaptic tracts in the spinal cord to amplify and potentiate ascending sensory signals. At the level of the periaqueductal grey matter, the BDNF-TRKB system is involved in the pathophysiologic mechanisms underlying several anxiety and depressive disorders and is the target of several antidepressant drugs [79]. Altered BDNF levels in the blood and cerebrospinal fluid are thought to play a role in the pathophysiology of FM, and these altered levels are largely genetically determined. A *BDNF*

polymorphism (rs12273539) is associated with susceptibility to FM and symptoms of FM [80]. The rs7124442 and rs2049046 *BDNF* polymorphisms are associated with a higher body mass index and anxiety symptoms in FM individuals [81]. Similarly, the *BDNF* Val66Val SNP is associated with elevated plasma levels of high-sensitivity C-reactive protein and a higher body mass index [82]. Lastly, a *BDNF* polymorphism (rs6265) likely modulates pain signals at the level of the periaqueductal grey matter and is associated with pain catastrophizing in FM individuals [23].

Vitamin D plays a role in regulating nociceptive and inflammatory pain [83]. Vitamin D expression and regulation differs in patients with FM. The ApaI and FokI polymorphisms of the Vitamin D receptor (VDR) gene are associated with the development of FM [84]. Specifically, women with the C allele for ApaI polymorphism are 3.33 times more likely to have FM, and women with the T allele for FokI polymorphism are 10.9 times more likely to have FM. Further, Balkarli et al. showed that haplotypes of VDR gene polymorphisms are risky (ATC and TTT) and protective (TTC) for FM [85]. In addition, cannabinoid receptors in the body are implicated in the mood symptoms of FM. A FM family carrying the rs6454674 SNP in the cannabinoid receptor gene (CNR1) is associated with the development of depression [86].

6. Polymorphisms in Mitochondrial DNA and Vascular Genes and FM

In terms of metabolic changes and FM, Tilburg et al. reported that the C allele at the SNP m.2352T>C (rs28358579) in the mitochondrial DNA is associated with increased risk for FM with an odd ratio of 4.6 [87]. In their cellular study, they demonstrated that the SNP decreased mitochondrial membrane potential under conditions that required oxidative phosphorylation. Polymorphism in the gene encoding methylenetetrahydrofolate reductase (MTHFR) may also play a role in the development of FM. Deveci et al. reported that the *MTHFR* C677T genotype may be associated with increased FM risk and symptoms of stiffness and dry eyes [88].

As for vascular changes and FM, two mediators of vascular tone, endothelin-1 (EDN-1) and angiotensin-converting enzyme (ACE), are associated with FM. EDN-1 is a potent vasoconstrictor, and a polymorphism of *EDN1* (rs1800541) is associated with higher plasma levels of EDN1 in FM patients compared to control and may increase risk of developing FM [89]. Individuals with ACE I/D polymorphisms have been more susceptible to the development of FM [90].

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