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Psychological Stress, Trauma and Epigenetic Changes in Fibromyalgia

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Abstract: Fibromyalgia is a chronic multisymptom disorder characterized by widespread pain, fatigue, sleep disturbance, cognitive dysfunction, and high comorbidity with mood disorders. Increasing evidence implicates psychological stress and trauma — particularly early-life adverse experiences — in the onset and severity of fibromyalgia. The pathways linking stress and trauma to fibromyalgia risk and expression are complex and likely involve neuroendocrine dysregulation (notably hypothalamic-pituitary-adrenal [HPA] axis and autonomic nervous system dysfunction), neuroinflammation, altered central pain processing (central sensitization), and epigenetic modifications including DNA methylation, histone modifications, and noncoding RNAs (e.g., microRNAs). Epigenetic changes offer a compelling mechanistic bridge between environmental exposures (stress/trauma) and persistent changes in gene expression relevant to pain, immune function, and stress reactivity. This paper synthesizes contemporary evidence linking psychological stress and trauma to epigenetic alterations observed in fibromyalgia, reviews candidate epigenetic biomarkers and mechanisms, discusses implications for diagnosis and treatment, and suggests priorities for future research.

Keywords: Fibromyalgia; Psychological stress; Trauma; Epigenetics; DNA methylation; Neuroinflammation.

Introduction - Fibromyalgia is a chronic pain disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, cognitive impairment, and heightened sensitivity to sensory stimuli. Although its etiology remains incompletely understood, accumulating evidence supports a multifactorial model involving genetic predisposition, environmental exposures, neuroendocrine dysregulation, and altered central pain processing. Among environmental contributors, psychological stress and trauma have emerged as significant factors influencing both disease onset and symptom severity. Epidemiological studies consistently demonstrate higher rates of adverse childhood experiences,chronic psychosocial stress, and posttraumatic stress disorder among individuals with fibromyalgia compared to healthy controls (Kaleychevaet. al., 2021).

The biological mechanisms linking psychological stress and trauma to persistent pain syndromes are complex and involve dysregulation of stress-responsive systems, including the hypothalamic–pituitary–adrenal (HPA) axis, autonomic nervous system imbalance, and neuroimmune activation (Coppens et.al., 2018). Chronic activation of these systems may contribute to central sensitization, a key feature of fibromyalgia characterized by amplified nociceptive signaling within the central nervous system. However, the persistence of these alterations beyond the immediate stress exposure suggests the involvement of long-term molecular regulatory processes (Agorastoset.al., 2018).

Epigenetic modifications such as DNA methylation, histone modifications, and noncoding RNA regulation provide a plausible mechanistic framework through which environmental stressors may exert enduring effects on gene expression without altering DNA sequence. Studies showed that stress-related epigenetic reprogramming of genes involved in stress responsivity, inflammation, and neurotransmission may predispose individuals to maladaptive pain processing and multisystem symptomatology. Therefore, examining the interplay among psychological stress, trauma, and epigenetic alterations offers critical insights into the pathophysiological mechanisms underlying fibromyalgia and may inform future biomarker development and targeted therapeutic strategies.

Psychosocial Stressors and Their Clinical Impact in Fibromyalgia: Accumulating epidemiological evidence indicates that psychological stress and trauma are significant risk factors in the development and clinical manifestation of fibromyalgia. Population-based and clinical studies consistently report a higher prevalence of adverse childhood experiences (ACEs)—including emotional, physical, and sexual abuse, as well as neglect—among individuals with fibromyalgia compared to healthy and

disease controls (Galvez-Sánchez et.al., 2019). Early-life trauma is associated with increased vulnerability to chronic pain syndromes, potentially through long-term alterations in neuroendocrine, autonomic, and immune regulation (Agorastoset.al., 2018). These findings support a stress-sensitization model in which early adversity primes biological systems for heightened reactivity to subsequent stressors. In adulthood, exposure to chronic psychosocial stress, interpersonal violence, and traumatic events has also been linked to the onset and exacerbation of fibromyalgia symptoms. Comorbid psychiatric conditions, particularly posttraumatic stress disorder (PTSD), major depressive disorder, and anxiety disorders, are observed at elevated rates in fibromyalgia populations (Chandanet.al., 2021). The presence of trauma history is associated with greater symptom severity, including intensified pain, fatigue, cognitive dysfunction, and sleep disturbances. Moreover, trauma-exposed individuals frequently demonstrate maladaptive cognitive and behavioral patterns, such as pain catastrophizing and hypervigilance, which may further amplify central sensitization mechanisms (McKernanet.al., 2019).

Clinically, trauma-related dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system has been proposed as a biological substrate linking psychological adversity to persistent pain. Collectively, epidemiological and clinical data support a biopsychosocial framework in which psychological stress and trauma function as both predisposing and perpetuating factors in fibromyalgia, underscoring the importance of trauma-informed assessment and management strategies (Tidmarsh et.al., 2022).

Epidemiological observations alone cannot establish causality, but prospective cohort data and mechanistic findings support a contributory role of psychological stress/ trauma in disease development via long-term alterations in stress-responsive systems and gene regulatory programs.

Stress-Related Neurobiological Mechanisms in Fibromyalgia: Stress-responsive biological systems are increasingly recognized as central components in the pathophysiology of fibromyalgia. Scientific studies showed that the hypothalamic–pituitary–adrenal (HPA) axis is the primary neuroendocrine pathway mediating the stress response. Activation of the hypothalamus leads to the secretion of corticotropin-releasing hormone (CRH), which stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH), subsequently promoting cortisol secretion from the adrenal cortex. In individuals with fibromyalgia, alterations in HPA axis functioning have been documented, including blunted cortisol responses to acute stress, flattened diurnal cortisol rhythms, and relative hypocortisolism in certain subgroups (Coppens et.al., 2018). Such dysregulation may impair adaptive stress regulation and contribute to enhanced pain sensitivity, fatigue, and mood disturbances.

In parallel, dysfunction of the autonomic nervous system (ANS) has been widely reported. Fibromyalgia patients frequently exhibit sympathetic predominance and reduced parasympathetic (vagal) tone, as evidenced by decreased heart rate variability and impaired cardiovascular reactivity. Persistent sympathetic activation may facilitate nociceptive transmission and disrupt restorative sleep processes, thereby reinforcing symptom chronicity . Reduced vagal activity may further limit anti-inflammatory signaling, exacerbating systemic stress responses (Siracusaet.al., 2021).

Neuroimmune pathways provide an additional mechanistic link between stress and chronic pain. Chronic psychological stress can promote glial cell activation and increase the release of proinflammatory cytokines, leading to low-grade neuroinflammation. This inflammatory milieu may enhance central sensitization, characterized by amplified pain processing within the central nervous system. Interactions among the HPA axis, ANS, and immune mediators create a bidirectional feedback network in which stress-induced biological alterations sustain pain perception and multisystem symptom expression (Bainset.al., 2023). Collectively, dysregulation across these interconnected systems supports a stress-based neurobiological model of fibromyalgia .

Epigenetic Mechanisms in Fibromyalgia: Epigenetic mechanisms encompass molecular processes that regulate gene expression without altering the underlying DNA sequence. These modifications influence chromatin architecture and transcriptional accessibility, thereby modulating cellular phenotype in response to environmental signals. Epigenetic regulation is dynamic yet potentially stable over time, allowing environmental exposures—such as psychological stress and trauma—to produce sustained biological effects. In the context of fibromyalgia and other chronic stress-related disorders, epigenetic processes are increasingly recognized as key mediators linking environmental factors to persistent alterations in neuroendocrine, immune, and nociceptive pathways (Ovromet. al., 2023).

The most extensively studied epigenetic mechanism is **DNA methylation**, which involves the addition of a methyl group to cytosine residues, typically at CpG dinucleotides (Fig.2). Increased methylation in gene promoter regions is generally associated with transcriptional repression, whereas hypomethylation may enhance gene expression. Environmental stressors such as exposure to childhood trauma and chronic psychological stress, particularly during sensitive developmental windows, can alter DNA methylation patterns in genes regulating the hypothalamic–pituitary–adrenal (HPA) axis, inflammatory pathways, and neurotransmission, potentially leading to long-term dysregulation of stress and pain systems (Gerraet.al., 2021).

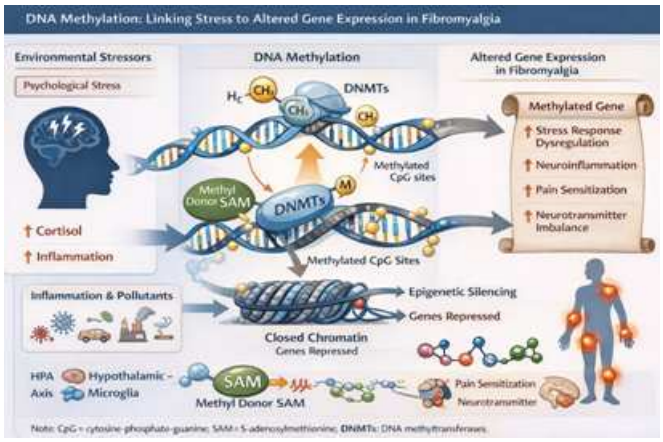

Figure 1: DNA methylation as a key epigenetic mechanism linking environmental stressors to altered gene expression in fibromyalgia.

Another critical mechanism involves **histone modifications**, including acetylation, methylation, phosphorylation, and ubiquitination of histone proteins around which DNA is wrapped. These modifications influence chromatin structure and accessibility of transcriptional machinery (Fig.3). For example, histone acetylation is typically associated with an open chromatin conformation and transcriptional activation, whereas certain methylation patterns may promote chromatin condensation and gene silencing. Stress-induced alterations in histone-modifying enzymes may lead to persistent changes in gene networks regulating neuronal plasticity and immune responses, thereby contributing to central sensitization and chronic inflammation observed in fibromyalgia (Torres-Perez et.al., 2021).

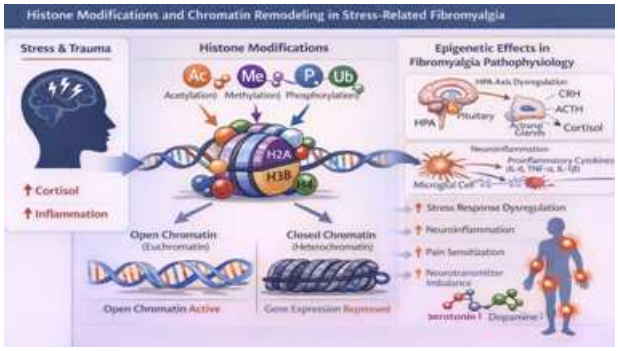

Figure 2: Histone modifications and chromatin remodeling in fibromyalgia

In addition, **noncoding RNAs**, particularly microRNAs (miRNAs), regulate gene expression post-transcriptionally by binding to target messenger RNAs and inhibiting their translation or promoting degradation. Dysregulated miRNA expression in response to psychological stress and trauma may alter inflammatory pathways and nociceptive signaling mechanisms. Such changes are implicated in central sensitization and persistent pain in fibromyalgia pathophysiology (Berg et.al., 2023).

Each mechanism is sensitive to environmental inputs, including psychosocial stress, nutritional status, inflammation, and toxins. Critically, epigenetic marks can be stable over long intervals and may therefore explain how discrete traumatic exposures — particularly during sensitive developmental windows — yield lasting alterations in stress reactivity and pain processing.

Evidences of Epigenetic Alterations in Fibromyalgia: Growing empirical evidence supports the presence of epigenetic alterations in fibromyalgia, suggesting that dysregulated gene expression may contribute to its pathophysiology. Epigenome-wide association studies (EWAS) and candidate-gene analyses have identified differential DNA methylation patterns in individuals with Fibromyalgia compared to healthy controls. Przybylowicz et al. (2023) performed an epigenome-wide screen in blood and described methylation shifts associated with fibromyalgia and chronic fatigue spectrum disorders. These methylation changes frequently involve genes related to stress regulation, immune signaling, neurotransmission, and neuronal plasticity, all of which are central to chronic pain mechanisms. Overall, while interstudy heterogeneity exists (sample size, tissue type, and analytic methods differ), the reproducible finding is that Fibromyalgiais associated with altered DNA methylation signatures that converge on stress-responsive and neuroimmune pathways.

Altered DNA methylation has been reported in genes associated with the hypothalamic–pituitary–adrenal (HPA) axis and glucocorticoid receptor pathways, potentially contributing to abnormal cortisol dynamics observed in Fibromyalgia. Additionally, differential methylation in immune-related genes, including those regulating cytokine production and inflammatory responses, supports the hypothesis of low-grade systemic and neuroinflammation (Penas and Navarro, 2018). These findings align with evidence of glial activation and elevated proinflammatory mediators in affected individuals.

MicroRNA (miRNA) profiling studies further substantiate epigenetic involvement. Several circulating or tissue miRNAs implicated in inflammatory regulation, nociceptive signaling, and synaptic plasticity have been found to be differentially expressed in Fibromyalgia cohorts. Dysregulated miRNA expression may influence post-transcriptional control of target genes, thereby contributing to central sensitization and altered neurotransmitter balance (D'Agnelliet.al., 2019; Akaslanet.al., 2021).

Direct evidence of histone modifications and chromatin remodeling in Fibromyalgia is less numerous than DNA methylation and miRNA studies, but emerging research indicates that chromatin remodeling enzymes and histone marks may be altered in stress-related pain conditions. Preclinical models show stress or trauma can change histone acetylation in brain regions relevant to pain and mood; translational human studies in fibromyalgia are beginning to explore similar marks (Torres-Perezeet.al.,

2021, Ovromet.al., 2023).

Although most studies utilize peripheral tissues such as blood due to limited access to central nervous system samples, consistent patterns across independent cohorts suggest biological relevance. However, heterogeneity in study design, sample size, and analytic methodology necessitates cautious interpretation. Overall, current evidence indicates that epigenetic dysregulation represents a meaningful component of Fibromyalgia pathophysiology and may offer potential biomarkers for diagnosis and therapeutic monitoring (Favrettiet.al., 2023).

Linking Trauma and Stress to Epigenetic Changes: Emerging evidence supports a mechanistic framework in which psychological trauma and chronic stress contribute to persistent epigenetic alterations that influence vulnerability to fibromyalgia. Stress exposure activates neuroendocrine pathways, particularly the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system, resulting in sustained release of glucocorticoids and catecholamines (Maldonado-Bouchard and Incayawar, 2020). These stress mediators interact with intracellular signaling cascades that regulate epigenetic enzymes, including DNA methyltransferases, histone acetyltransferases, and histone deacetylases, thereby modifying chromatin structure and gene transcription.

During sensitive developmental periods—such as early childhood—epigenetic programming is especially plastic. Exposure to adversity at these stages can induce long-lasting DNA methylation changes in genes involved in stress responsivity (e.g., glucocorticoid receptor–related pathways), inflammatory regulation, and neurotransmission (Alyamani and Murgatroyd, 2018; Boyce et.al., 2021). Such modifications may recalibrate stress thresholds, alter immune signaling, and enhance neuronal excitability, thereby predisposing individuals to maladaptive pain processing later in life.

Chronic stress in adulthood may further reinforce these alterations through cumulative biological burden, often conceptualized as allostatic load. Repeated activation of stress-response systems promotes proinflammatory cytokine release and glial activation, which can interact with epigenetic regulators to sustain transcriptional changes in genes related to nociception and neuroplasticity (Guidiet.al., 2020). Although much of the current evidence is correlational, longitudinal and translational studies increasingly support a causal pathway linking stress exposure to epigenetic remodeling and subsequent symptom persistence. Collectively, trauma- and stress-induced epigenetic modifications provide a plausible biological mechanism connecting environmental adversity to enduring neurobiological dysregulation in fibromyalgia. Empirical work in humans links childhood trauma to altered methylation in stress-related genes, and in fibromyalgia cohorts trauma exposure correlates with both symptom severity and distinct methylation or miRNA profiles. While causal proof from human studies remains challenging, convergent evidence from longitudinal human cohorts and animal models supports the stress'!epigenetic'!phenotype pathway.

Candidate Genes and Pathways Identified in Fibromyalgia Epigenetic Studies: Recent epigenetic investigations in fibromyalgia have identified several candidate genes and molecular pathways that may contribute to altered pain processing, stress responsivity, and immune dysregulation. These findings primarily derive from epigenome-wide association studies (EWAS), candidate-gene methylation analyses, and microRNA (miRNA) profiling studies conducted in peripheral blood or related tissues.

One major category involves genes regulating neurotrophic signaling, particularly brain-derived neurotrophic factor (BDNF). Scientific studies show the epigenetic modifications affecting BDNF expression have been associated with altered neuronal plasticity and central sensitization, mechanisms central to chronic pain amplification (Polliet.al., 2020). Dysregulated methylation patterns in genes involved in monoaminergic neurotransmission—such as serotonergic and dopaminergic pathways—have also been reported. These alterations may contribute to abnormalities in descending pain modulation and explain the frequent coexistence of mood disorders in fibromyalgia (Janssen et.al., 2021).

Immune and inflammatory genes (CD38, cytokine regulators)represent another prominent group of candidates. Differential methylation has been observed in genes regulating cytokine signaling, inflammatory mediators, and immune cell activation. For example, alterations in genes involved in interleukin and tumor necrosis factor pathways suggest that epigenetic modulation may contribute to low-grade systemic and neuroinflammation (Huang et.al., 2023). Such immune dysregulation is consistent with evidence of glial activation and elevated proinflammatory cytokines in fibromyalgia.

Additionally, genes associated with stress regulation, including components of the hypothalamic–pituitary–adrenal (HPA) axis and glucocorticoid signaling pathways, have demonstrated epigenetic variability. These changes may influence cortisol responsiveness and stress adaptation (Jovanovicet.al., 2023). Ion channel genes and pathways involved in nociceptor excitability have also been implicated, potentially contributing to heightened pain sensitivity (Œlêczkowskaet.al., 2023).

Collectively, these candidate genes converge on interconnected biological pathways involving neuroplasticity, immune signaling, stress regulation, and nociceptive processing. Although replication and larger cohort studies are required, current evidence supports the role of epigenetic regulation in shaping the molecular landscape underlying fibromyalgia pathophysiology.

Clinical and Translational Implications: One promise of

epigenetic research is the development of objective biomarkers to aid Fibromyalgiadiagnosis and to identify biologically distinct subgroups. Several groups have proposed methylation indices or miRNA panels that differentiate Fibromyalgia from controls with promising sensitivity in initial cohorts (Beiner et.al., 2023) However, these findings require replication in larger, diverse samples and across tissue types before clinical deployment. Nevertheless, epigenetic markers could eventually support earlier diagnosis, prognostic stratification (e.g., trauma-exposed vs non-exposed phenotypes), and personalized treatment selection (D'Agnelliet.al., 2019).

Therapeutic Opportunities: Reversing Maladaptive Epigenetic Programming: The recognition of epigenetic dysregulation as a mechanistic contributor to fibromyalgia has generated interest in therapeutic strategies aimed at reversing maladaptive epigenetic programming. Unlike genetic mutations, epigenetic modifications are dynamic and potentially reversible, rendering them attractive targets for intervention (Davies et.al., 2020). Therapeutic approaches may be broadly categorized into pharmacological, psychological, and lifestyle-based strategies, each with the potential to modulate epigenetic regulation either directly or indirectly.

Pharmacological agents that influence epigenetic machinery—such as DNA methyltransferase (DNMT) inhibitors and histone deacetylase (HDAC) inhibitors—have demonstrated efficacy in oncology and are being explored in neuropsychiatric and pain-related conditions. By altering chromatin accessibility and gene transcription, these agents may theoretically normalize dysregulated expression of genes involved in stress responsivity, inflammation, and nociceptive signaling (D'Agnelliet.al., 2019). However, systemic epigenetic drugs pose challenges related to specificity, off-target effects, and long-term safety, necessitating cautious translational application in fibromyalgia.

Psychological interventions represent a nonpharmacological avenue for epigenetic modulation. Evidence from stress-related disorders suggests that cognitive-behavioral therapy, trauma-focused psychotherapy, and mindfulness-based interventions can influence biological stress markers, including cortisol regulation and inflammatory mediators. Emerging data indicate that psychotherapy may induce measurable epigenetic changes in genes regulating the hypothalamic–pituitary–adrenal axis and immune function, suggesting a potential mechanism through which behavioral interventions exert sustained clinical benefits (Polli et.al., 2019).

Lifestyle factors such as physical activity, sleep optimization, and nutritional modulation also influence epigenetic processes, particularly DNA methylation and histone acetylation pathways. Regular exercise and anti-inflammatory dietary patterns have been associated with favorable epigenetic profiles linked to reduced inflammation and improved neuroplasticity (Ramos-Lopez et.al., 2021). Collectively, integrative therapeutic strategies targeting stress reduction and biological regulation may contribute to the reversal of maladaptive epigenetic programming in fibromyalgia.

Methodological Challenges of Epigenetics Research in Fibromyalgia: Despite growing interest in epigenetic contributions to fibromyalgia, several methodological challenges limit the interpretability and generalizability of current findings. One primary concern is tissue specificity. Most human studies rely on peripheral samples such as whole blood, peripheral blood mononuclear cells, or saliva due to limited accessibility of central nervous system tissue (Favrettiet.al., 2023). However, epigenetic patterns are highly cell-type specific, and peripheral markers may not fully reflect epigenetic alterations within brain regions implicated in pain processing and stress regulation. Advanced approaches, including cell-type deconvolution algorithms and single-cell epigenomic profiling, are necessary to enhance biological precision.

Another critical limitation is clinical heterogeneity. Fibromyalgia is characterized by variable symptom severity, comorbid psychiatric conditions, medication use, and differing trauma histories. Failure to adequately stratify participants may obscure subgroup-specific epigenetic signatures. Standardized diagnostic criteria and detailed phenotyping—including stress exposure assessments—are essential for reproducibility and meaningful subgroup analyses (Sarzi-Puttiniet.al., 2020).

Confounding variables also pose significant challenges. Age, sex, body mass index, smoking status, pharmacotherapy, and circadian influences can independently affect DNA methylation and noncoding RNA expression. Rigorous statistical control and replication in independent cohorts are therefore necessary to reduce bias. Additionally, many existing studies employ cross-sectional designs, limiting causal inference regarding whether epigenetic alterations precede disease onset or arise secondary to chronic pain and stress exposure.

Finally, sample sizes in epigenome-wide association studies (EWAS) are often modest, reducing statistical power and increasing the risk of false-positive findings. Large, longitudinal, multi-omics investigations integrating epigenetics with transcriptomic, proteomic, and clinical data will be critical for clarifying the mechanistic role of epigenetic regulation in fibromyalgia and advancing translational applications.

Future Research Priorities: Advancing the understanding of epigenetic contributions to fibromyalgia requires strategically designed, methodologically rigorous investigations. A primary priority is the implementation of large-scale, longitudinal cohort studies that integrate detailed phenotyping with repeated biological sampling. Such designs would enable examination of temporal relationships between psychological stress, trauma

exposure, epigenetic alterations, and symptom trajectories, thereby improving causal inference. Prospective studies beginning prior to disease onset or during early symptom development would be particularly informative in distinguishing primary epigenetic vulnerabilities from secondary adaptations to chronic pain.

Integration of multi-omics methodologies represents another critical direction. Combining epigenomic data (e.g., DNA methylation, histone modification profiling, microRNA expression) with transcriptomic, proteomic, metabolomic, and neuroimaging datasets may provide a systems-level understanding of fibromyalgia pathophysiology. This integrative approach could identify convergent molecular pathways linking stress biology, immune dysregulation, and central sensitization. Advanced computational modeling and machine learning techniques may further enhance biomarker discovery and patient stratification.

Greater attention to biological heterogeneity is also warranted. Stratification based on trauma history, sex differences, comorbid psychiatric conditions, and autonomic or endocrine phenotypes may reveal biologically distinct fibromyalgia subtypes with unique epigenetic signatures. Additionally, single-cell epigenomic analyses and tissue-specific investigations, when feasible, would refine understanding of cell-type–specific regulatory mechanisms. Finally, translational research evaluating epigenetic changes as treatment-responsive biomarkers should be prioritized. Randomized controlled trials incorporating epigenetic endpoints could determine whether psychological, pharmacological, or lifestyle interventions modify maladaptive epigenetic patterns and whether such modifications correlate with clinical improvement. Collectively, these research priorities aim to bridge mechanistic insight with precision medicine approaches in fibromyalgia. Addressing these priorities will require interdisciplinary collaborations bridging clinical rheumatology, psychiatry, molecular biology, and computational biology.

Conclusion: Fibromyalgia is a multifactorial chronic pain disorder characterized by complex interactions among psychological, neuroendocrine, immune, and molecular mechanisms. Accumulating evidence supports a model in which psychological stress and trauma contribute to dysregulation of the hypothalamic–pituitary–adrenal axis, autonomic imbalance, and neuroimmune activation. Epigenetic mechanisms, including DNA methylation, histone modifications, and microRNA regulation, provide a plausible biological interface linking environmental exposures to sustained alterations in gene expression. Emerging studies demonstrate differential epigenetic signatures in pathways related to stress responsivity, inflammation, neuro-transmission, and neuronal plasticity in individuals with fibromyalgia. Although methodological limitations persist, these findings suggest that maladaptive epigenetic programming may contribute to central sensitization and chronic symptom persistence. Continued integration of longitudinal, multi-omics, and translational research approaches is essential to clarify causal pathways and identify clinically relevant biomarkers. A deeper understanding of stress-related epigenetic regulation may ultimately support the development of mechanism-based, personalized therapeutic strategies for fibromyalgia.a

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