Genetica ed epigenetica

Piercarlo Sarzi Puttini

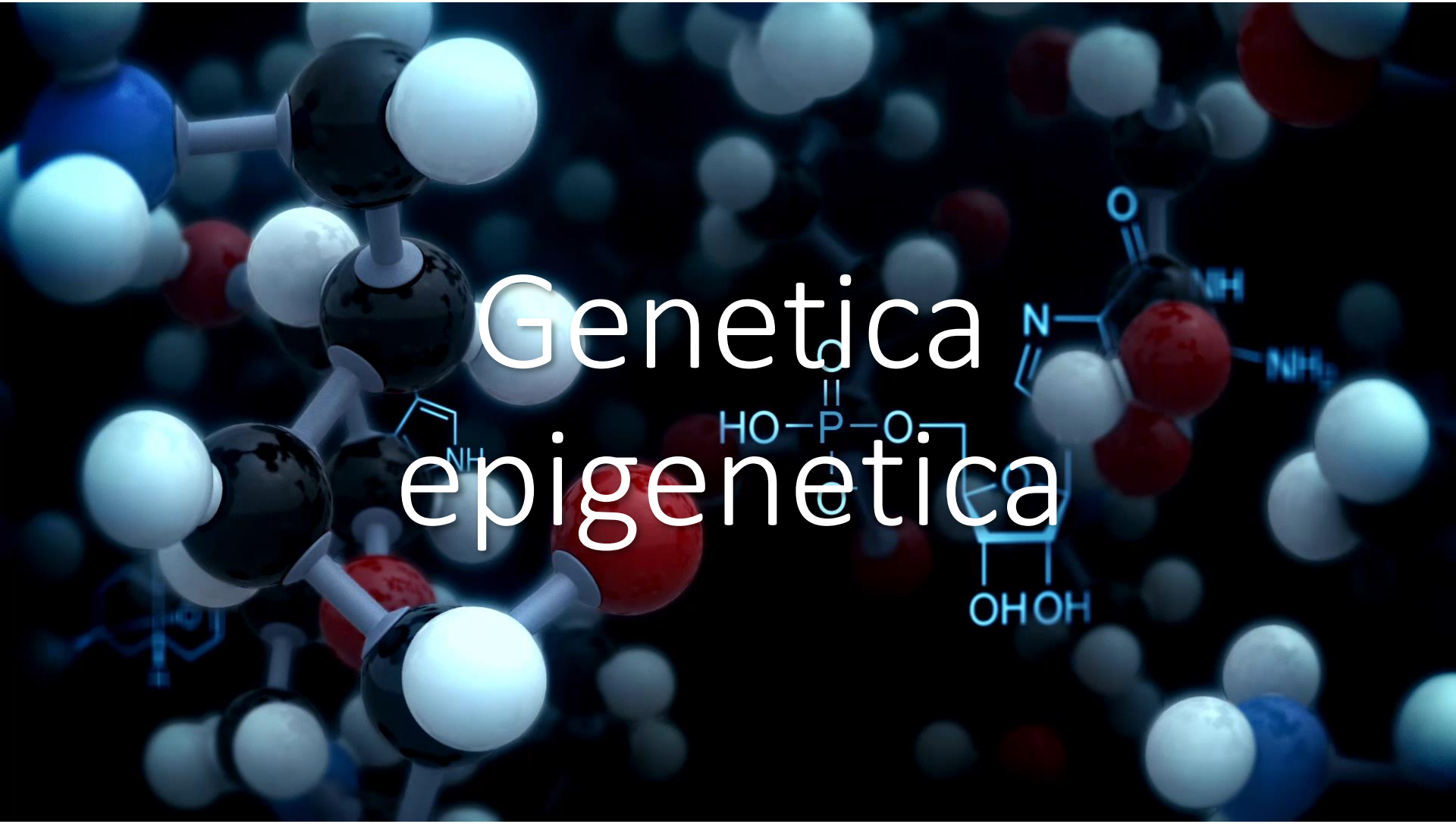
Director of Rheumatology Unit

Ospedale Galeazzi-Sant'Ambrogio IRCCS

Full Professor of Rheumatology

Dipartimento di Scienze Cliniche e Biomediche

Università Statale di Milano -Italy


Genetica
epigenetica

Predisposizione genetica e fibromialgia

Uno dei più importanti campi di interesse della moderna genetica umana è costituito dallo **studio delle malattie o disturbi ereditari per quanto riguarda i meccanismi d'insorgenza, le modalità di trasmissione, le tecniche di individuazione precoce e di prevenzione**.

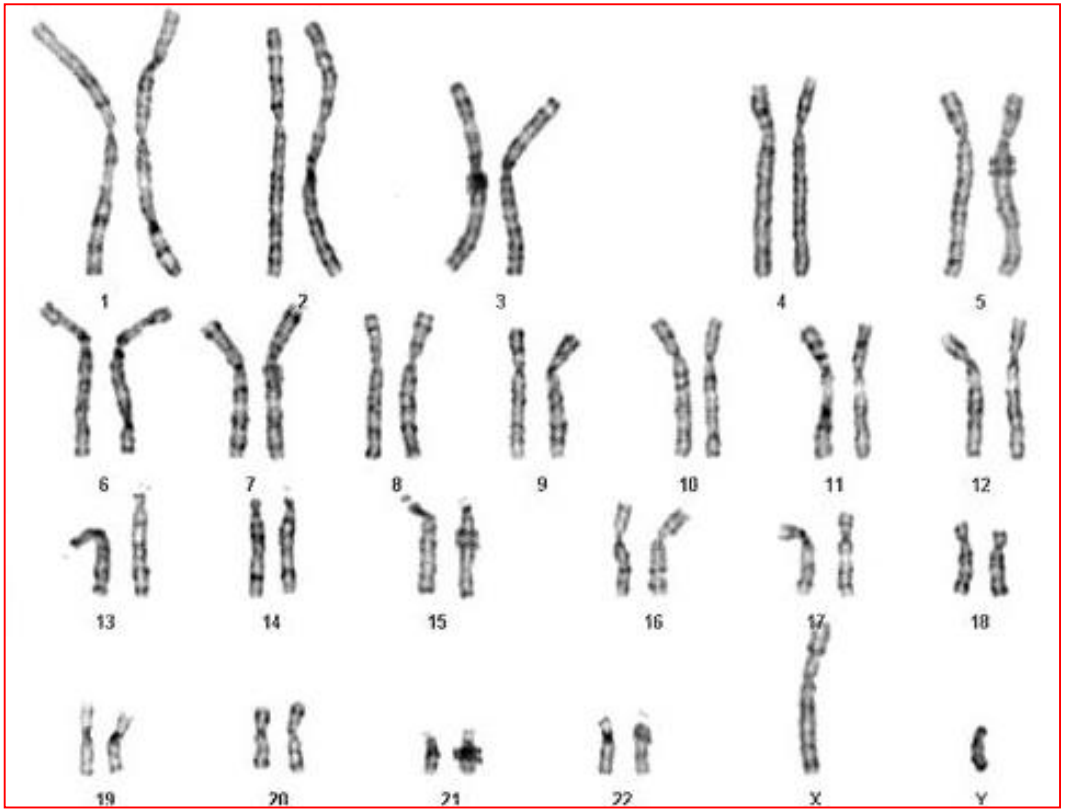
Il notevolissimo grado di **variabilità genetica, o polimorfismo**, all'interno della popolazione "normale", giustifica in larga misura le variazioni naturali che hanno luogo nelle caratteristiche somatiche e psichiche dei singoli individui, dall'altezza all'intelligenza, alla pressione arteriosa e così via.

Inoltre queste **differenze genetiche** determinano marcate diversità nella capacità di ogni singolo individuo di affrontare gli stimoli e le condizioni ambientali esterne, comprese quelle capaci di causare uno stato morboso.

Predisposizione genetica e fibromialgia

Di conseguenza, sotto questo aspetto, **ogni malattia può essere considerata come il prodotto risultante dalla interazione tra un dato corredo e assetto genetico e l'ambiente esterno.**

Mappa cromosomica



I cromosomi contengono i geni e sono trasmessi dai genitori ai figli tramite i gameti (gli spermatozoi nel maschio e le cellule uovo nella femmina).
Il genoma umano è costituito da 23 paia di cromosomi:
22 coppie formano i cosiddetti autosomi
una coppia costituisce i cromosomi sessuali (un cromosoma denominato X e un cromosoma denominato Y nel maschio e due cromosomi X nella femmina)

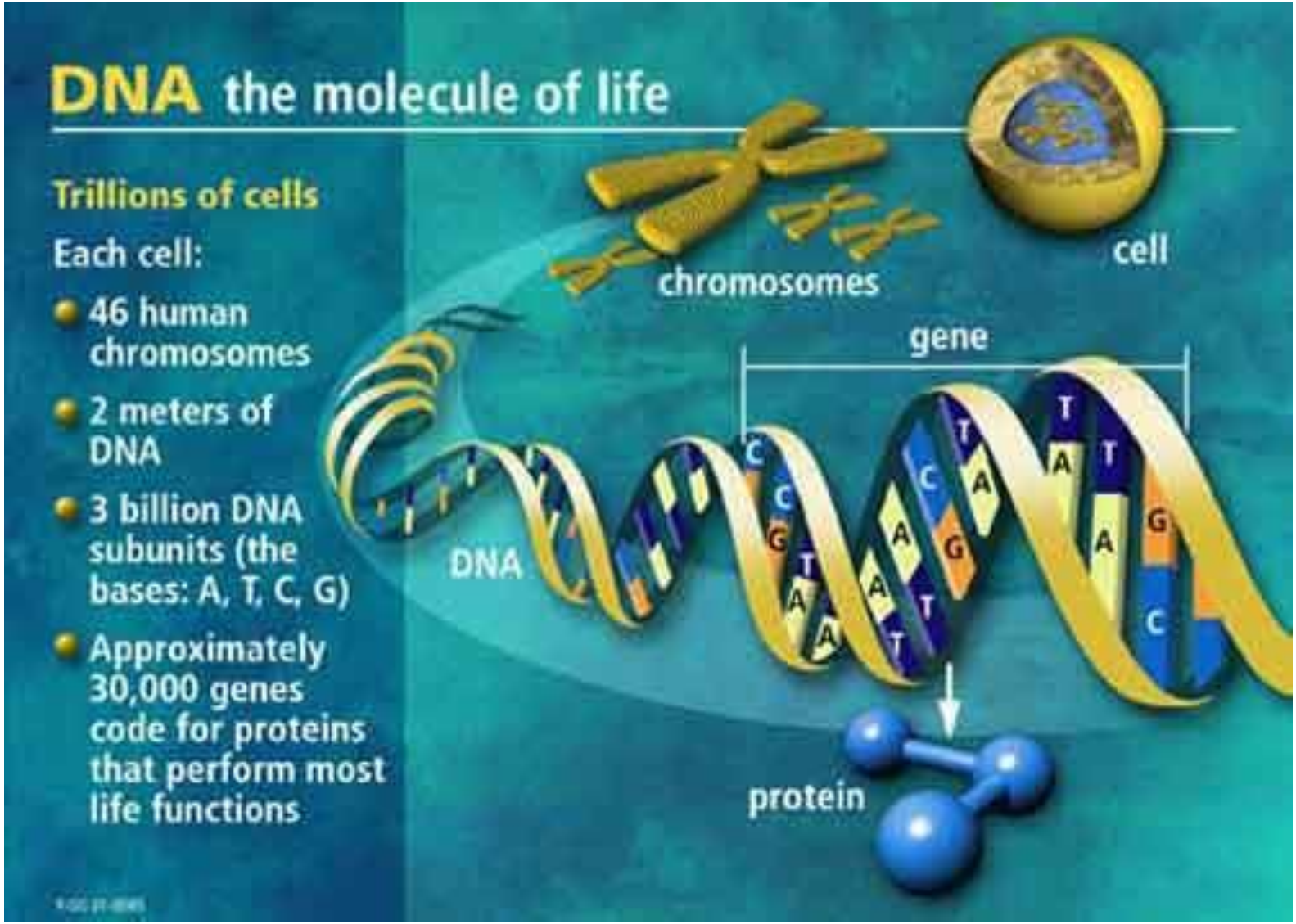
Predisposizione genetica e fibromialgia

Le malattie genetiche vengono usualmente distinte in tre gruppi:

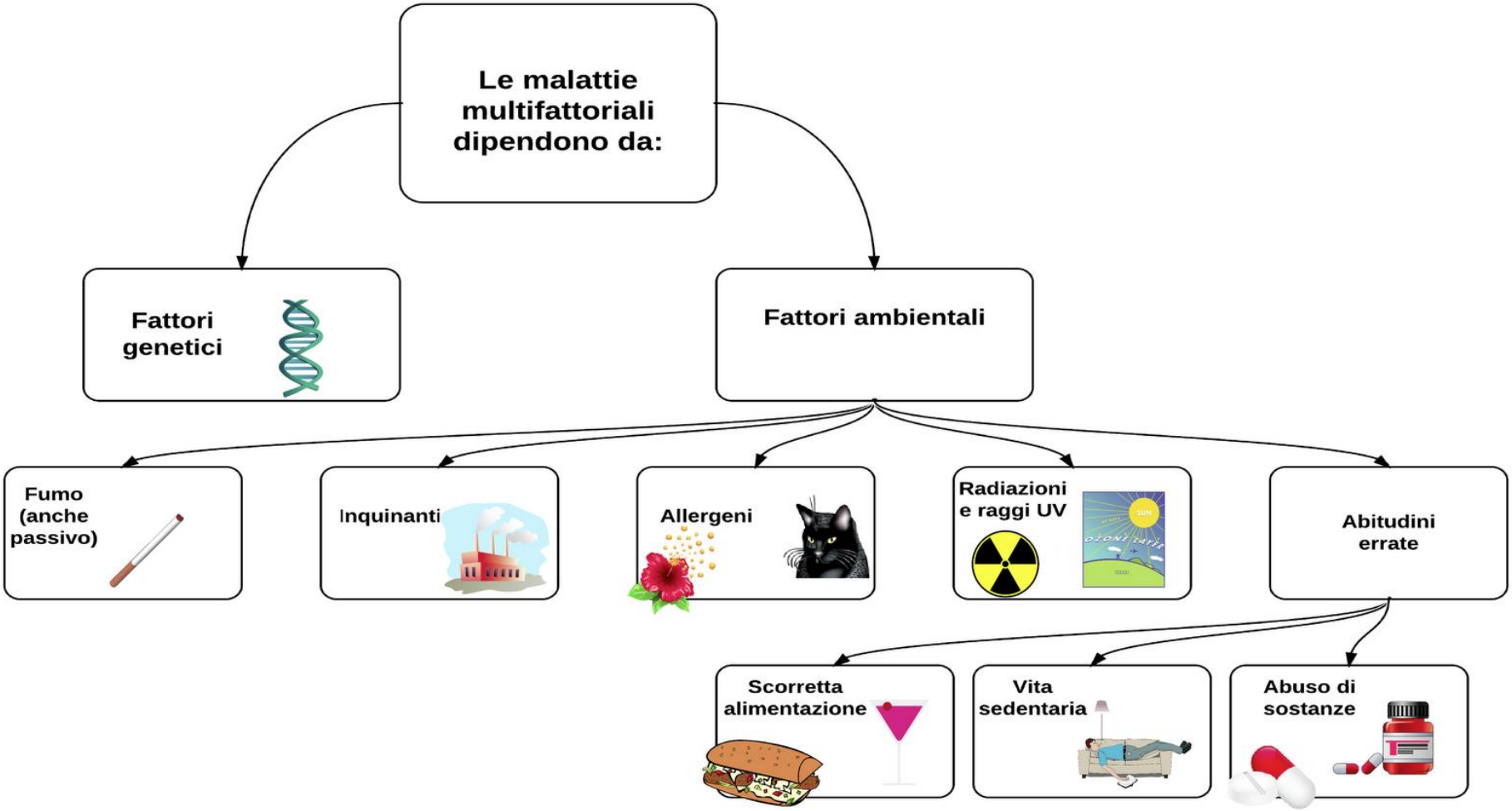
le anomalie cromosomiche, che comportano la mancanza, l'eccesso o l'assetto anomalo di uno o più cromosomi (**Trisomia 21 o sindrome di Down)**

le malattie ereditarie semplici, causate dalla presenza di un singolo gene mutante (tale caratteristica è evidenziata dal fatto che questi disturbi presentano modalità semplici di trasmissione ereditaria, classificabili come autosomiche dominanti, autosomiche recessive, o legate al sesso) **(emofilia , talassemia)**

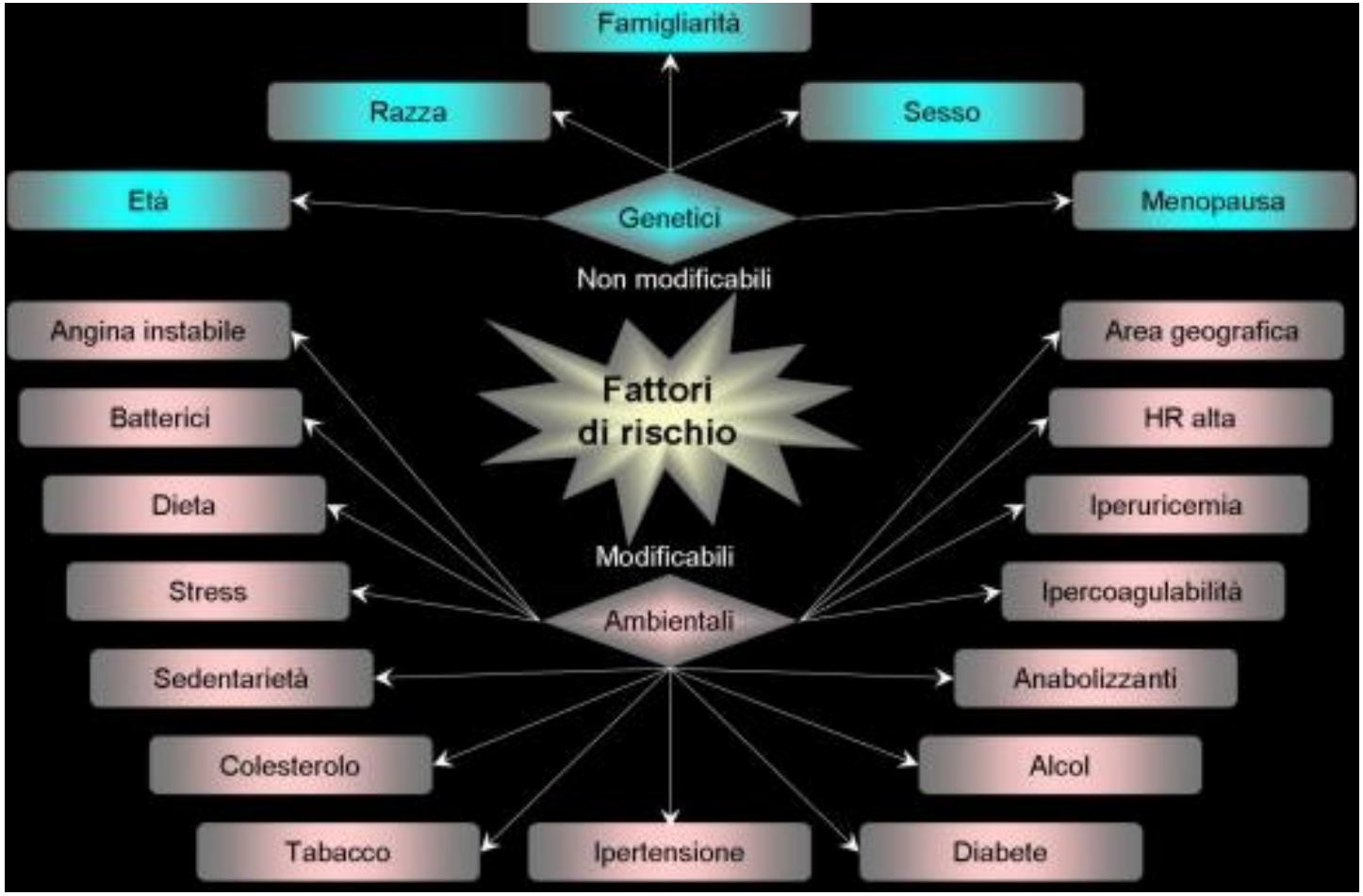
le malattie genetiche multifattoriali, causate dall'interazione tra più geni e molteplici fattori esogeni o ambientali.**(ipertensione arteriosa, aterosclerosi, diabete, sindrome fibromialgica ecc).**


DNA the molecule of life
Trillions of cells
Each cell:
46 human chromosomes
2 meters of DNA
3 billion DNA subunits (the bases: A, T, C, G)
Approximately 30,000 genes code for proteins that perform most life functions
chromosomes
cell
gene
DNA
protein

Le malattie poligeniche o multifattoriali



Le malattie poligeniche o multifattoriali



Questo modello descrive le possibili determinanti che contribuiscono al rischio di comparsa e mantenimento di condizioni dolorose croniche che si sovrappongono **common chronic overlapping pain conditions (COPCs).**

Fattori ambientali

Fisici
Trauma
Abusi sessuali
Fumo

Psicologici
Eventi stressanti

Culturali
Comportamenti appresi

Dolore cronico diffuso

Sindromi dolorose croniche persistenti

Sindromi dolorose croniche transitorie

Segni e sintomi subclinici

Elevato stress psicologico

Elevata predisposizione all'amplificazione sensoriale del dolore

Stati pro-infiammatori

Alterata regolazione del dolore

Risposta allo stress

Funzioni neuroendocrine

Funzioni autonomiche

umore

ansia

depressione

Somatizzazione

GAD 65 — MAO — Xp-11.23

Serotonin receptor — 12q11.22

Cannabinoid receptor — NMDA — 9q34.23

CREB1 — GR — 11q.23

Dopamine receptor — Adrenrgic receptor — 5q31-32

Serotonin trasporter — DREAM — 6 q24-q25

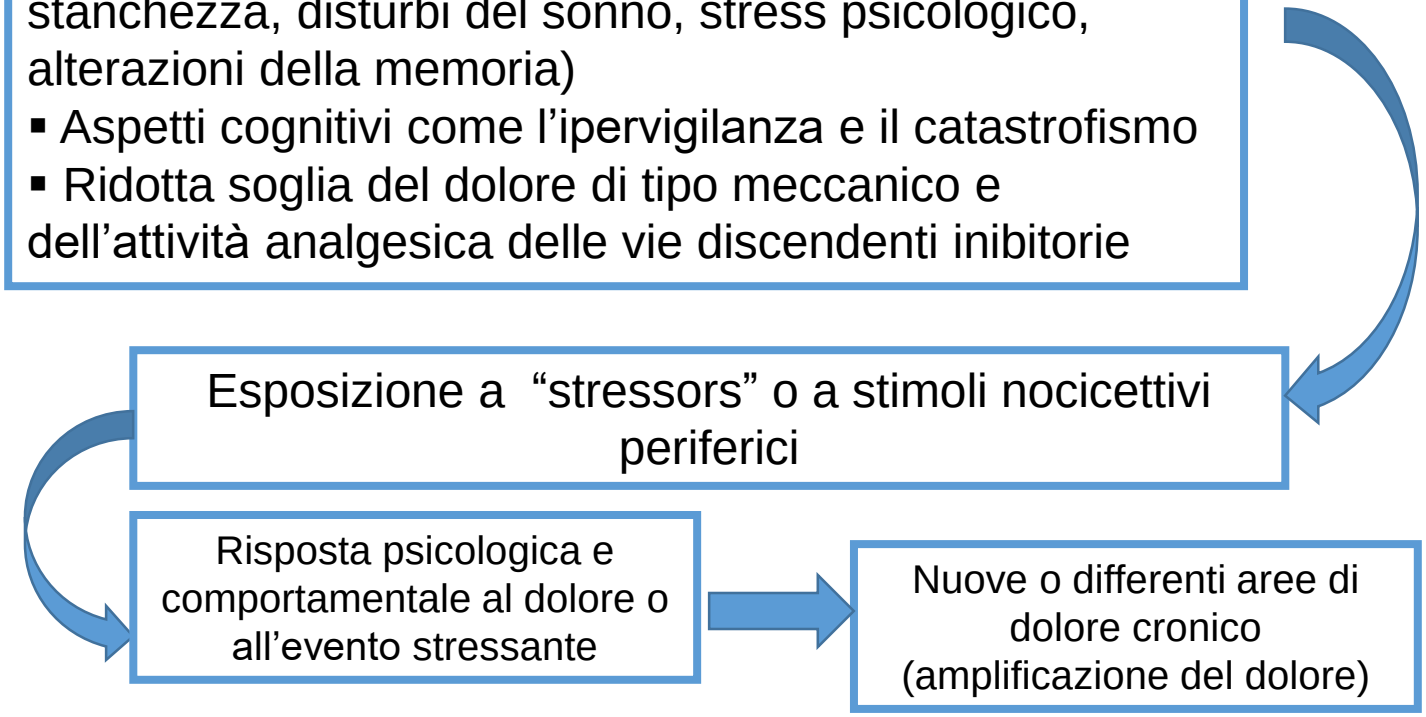
NET — POMC — NA+,K+ ATPase — Opioid receptors — 1p13.1

IKK — BDNF — COMT — prodynorfins — 22q11.21

Interleukins

“Tipologia (fenotipo) di paziente predisposto al dolore “centrale”

- Sesso femminile
- Genetica
- Traumi nell’ infanzia/adolescenza
- Storia familiare di dolore cronico e disturbi dell’umore
- Storia personale di sintomi cronici da attivazione centrale (dolore multifocale con descrittori neuropatici , stanchezza, disturbi del sonno, stress psicologico, alterazioni della memoria)
- Aspetti cognitivi come l’ipervigilanza e il catastrofismo
- Ridotta soglia del dolore di tipo meccanico e dell’attività analgesica delle vie discendenti inibitorie



“Stressors” in grado di attivare una „sindrome da sensibilizzazione centrale“ (supportato das studi caso-controllo[1,2])

- Sindromi dolorose periferiche
- Infezioni (eg, parvovirus, Epstein-Barr virus, malattia di Lyme, febbre Q; infezioni delle vie aeree respiratorie superiori)
- Traumi fisici (incidenti automobilistici)
- Stress/distress psicologici (abusi , mobbing, bullying , PTSD ecc)
- Alterazioni ormonali (eg, ipotiroidismo)
- Farmaci
- Vaccini
- Alcuni eventi catastrofici (guerra, terremoto ecc)

1. Clauw D, et al. *Neuroimmunomodulation* 1997;4:134–53.
2. McLean SA, et al. *Med Hypotheses* 2004;63:653–8.

L’espressione della Fibromialgia

- Genetica
- Fattori ambientali

Genetic factors

- Genetic factors may predispose individuals to FM
- Sibship analysis has demonstrated possible genetic linkage of FM to the HLA region
- A recent analysis of genetic polymorphism for catechol-O-methyltransferase, an enzyme that inactivates catecholamines, indicated that the LL and LH genotypes occurred more often in patients with FM than in controls. In addition, the HHgenotype was seen less often in patients with FM than in healthy patients.

J Rheumatol 2005; 32:6-21

Enviromental factors

- A number of “stressors” have been temporally correlated with the onset of the syndrome,including trauma, infections (e.g., hepatitis C virus, HIV, and Lyme disease), emotional stress, catastrophic events (e.g., war), autoimmune disease, and other pain conditions.

- FM has been reported to coexist in 25% of patients with RA, 30% of patients with lupus, and 50% of patients with Sjögren's syndrome.

J Rheumatol 2005; 32:6-21

Esposizione a fattori ambientali (Stressors)

- Traumi fisici
- Infezioni
- Stress emotivi
- Malattie endocrinologiche
- Stimolazioni immunitaria
- Solitamente è difficile valutare con certezza il ruolo di un singolo fattore in un singolo paziente.

- Aggregazione familiare

Genetica e Fibromialgia

- La prevalenza della FM nella popolazione generale e l'osservazione dei reumatologi che **questa sindrome ricorre nelle famiglie** suggerisce che fattori genetici e famigliari possono avere un ruolo nella eziopatogenesi della FM

- **Esistono alcuni lavori in letteratura** che abbiano riportato la prevalenza di sintomi fibromialgici nei famigliari di pazienti affetti da FM

Genetica e FM

- Il primo studio evidenziava che la prevalenza familiare di FM era consistente con una ereditarietà autosomica dominante con prevalenza nel sesso femminile.

Case Reports > Arch Phys Med Rehabil. 1989 Jan;70(1):61-3.

Familial occurrence of primary fibromyalgia

M J Pellegrino [1], G W Waylonis, A Sommer

Affiliations + expand

PMID: 2916922

Abstract

Seventeen families of patients with primary fibromyalgia were studied for evidence of inherited primary fibromyalgia. Fifty parents and siblings were included in the analysis. Twenty-six (52%, mean age 33.5 years) had characteristic symptoms and findings of primary fibromyalgia. Eleven (22%, mean age 28 years) were asymptomatic but had clinical evidence of abnormal muscle consistency to palpation without tender or trigger points. One person had clinical evidence of lupus. Thirteen (26%) had no evidence of fibromyalgia or abnormal muscle consistency. The mode of inheritance was autosomal dominant. Identical twins are described who developed symptoms of primary fibromyalgia within six months of each other, as are two brothers who developed abnormal palpable muscle consistency years before acquiring the characteristic findings of the fibromyalgia syndrome. Primary fibromyalgia may be an inherited condition with a variable latent stage before clinical expression of the disease.

Genetica e FM

- Descrizione di presenza stimata di FM nei famigliari basata solamente sulla descrizione da parte dei fibromialgici del proprio nucleo familiare.
- Anche questo studio suggeriva un ‘ereditarietà di tipo autosomico dominante.

Stormorken & Brosstad, Scand J Rheumatol, 1992

Familiarità e FM

- 71% delle madri di bambini fibromialgici presentava una FM non diagnosticata a differenza del 30 % delle mamme con bambini con dolore cronico e 0% delle mamme di bambini asintomatici
- Una concordanza significativa è stata osservata tra diagnosi di FM nei bambini e nelle loro mamme.

J Rheumatol. 1997 Mar;24(3):579-85.

Juvenile fibromyalgia: clinical and polysomnographic aspects

S Roizenblatt [1], S Tufik, J Goldenberg, L R Pinto, M O Hilario, D Feldman

Affiliations + expand

PMID: 9058669

Abstract

Objective: To identify the child-mother diagnostic correlation in fibromyalgia (FM), to study sleep disturbance in juvenile FM, and to compare clinical aspects and sleep disorders between these groups.

Methods: We studied 34 children with confirmed FM aged 11 +/- 1 years, 10 children with diffuse pain, and 17 age and sex matched asymptomatic controls. The respective 61 mothers were included: 34 asymptomatic and 27 with FM. All participants were subjected to clinical evaluation, a sleep questionnaire, and nocturnal polysomnography, preceded by a night of adaptation. Sleep scoring was done visually and a computerized analysis was performed for alpha, theta, and delta waves in slow wave sleep (SWS).

Results: A significant predominance of mothers with FM was observed in the group of children with FM (71%) compared to children with diffuse pain (30%) and asymptomatic children (0%). According to the sleep questionnaire, the complaints of superficial sleep and nonrestorative sleep were more prominent in mothers with FM than in children with FM, whereas motor agitation during sleep was more frequent in the children with FM. Polysomnographic anomalies were also more prominent in mothers with FM than in children with FM in terms of decrease in sleep efficiency, increase of number of arousals during sleep, and alpha intrusion in SWS. Both FM groups presented an increased alpha + theta time/delta time index during SWS compared to respective controls, and mothers with FM also showed an increase in alpha time/delta time index during SWS, compared to asymptomatic mothers. A correlation was found between alpha + theta time/delta time index during SWS and intensity of clinical manifestations of pain and sleep anomalies in children and their mothers.

Conclusion: Significant concordance was observed regarding FM diagnosis in children and their mothers. Sleep complaints and polysomnography findings were less prominent in affected children compared to mothers with FM. In addition, we observed a significant correlation between polysomnographic indexes, sleep anomalies, and pain manifestations in children and their mothers.

30 pazienti fibromialgci di sesso femminile e 117 dei loro parenti (genitori, fratelli, sorelle, figli, mariti) sono stati valutati per presenza di dolorabilità non articolare

La prevalenza di FM tra i parenti consanguinei era del 26%, e tra i mariti del 19%

I familiari di pazienti con FM presentano una maggiore prevalenza di FM e sono più dolorabili rispetto alla popolazione generale.

Questa osservazione può essere attribuita a fattori genetici e ambientali .

J Rheumatol. 1997 May;24(5):941-4.

Fibromyalgia syndrome (FM) and nonarticular tenderness in relatives of patients with FM

D Buskila [1], L Neumann

Affiliations + expand

PMID: 9150086

Abstract

Objective: To determine the prevalence of fibromyalgia (FM) and to assess nonarticular tenderness in relatives of patients with FM.

Methods: Thirty female patients with FM randomly chosen from 117 of their close relatives (parents, brothers, sisters, children, husbands) were assessed for nonarticular tenderness. A count of 18 tender points was conducted by thumb palpation, and tenderness thresholds were assessed by dolorimetry at 9 tender sites. FM was diagnosed according to the 1990 American College of Rheumatology criteria.

Results: The prevalence of FM among blood relatives of patients with FM was 26%, and among their husbands 19%. FM prevalence in male relatives was 14%, and in female relatives 41%. The mean tender point counts of male and female young relatives was significantly higher than that of controls: 6.1 vs 0.2 ($p < 0.01$), and 4.4 vs 0.4 ($p < 0.01$) respectively. Similarly, adult relatives had considerably higher mean tender point counts than controls: 4.0 vs 0.04 ($p < 0.01$) and 10.3 vs 0.28 ($p < 0.01$) respectively, for males and females.

Conclusion: Relatives of patients with FM have a higher prevalence of FM and are more tender than the general population, as recently reported and shown in a healthy control group. This finding can be attributed to genetic and environmental factors.

- 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

Available online http://arthritis-research.com/content/10/4/211

Review

Biology and therapy of fibromyalgia

Evidence-based biomarkers for fibromyalgia syndrome

Dina Dadabhoy[1], Leslie J Crofford[2], Michael Spaeth[3], I Jon Russell[4] and Daniel J Clauw[5]

[1]Northwest Rheumatology Specialists, Elk Grove Village, IL 60007, USA
[2]Department of Internal Medicine, University of Kentucky, Lexington, KY 40536, USA
[3]Center for Clinical Rheumatology Research, 82166 Graefelfing/Munich, Germany
[4]Department of Medicine, The University of Texas Health Science Center at San Antonio, San Antonio, TX 78229, USA
[5]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48105, USA

Corresponding author: Daniel J Clauw, dclauw@med.umich.edu

Published: 8 August 2008
This article is online at http://arthritis-research.com/content/10/4/211

Arthritis Research & Therapy 2008, **10**:211 (doi:10.1186/ar2443)

Abstract

Researchers studying fibromyalgia strive to identify objective, measurable biomarkers that may identify susceptible individuals, may facilitate diagnosis, or that parallel activity of the disease. Candidate objective measures range from sophisticated functional neuroimaging to office-ready measures of the pressure pain threshold. A systematic literature review was completed to assess highly investigated, objective measures used in fibromyalgia studies. To date, only experimental pain testing has been shown to coincide with improvements in clinical status in a longitudinal study. Concerted efforts to systematically evaluate additional objective measures in research trials will be vital for ongoing progress in outcome research and translation into clinical practice.

Introduction

Fibromyalgia (FM) is a chronic condition characterized by widespread pain and tenderness on examination, along with symptoms of nonrestorative sleep, fatigue, and cognitive difficulties. Recent familial studies have suggested an underlying genetic susceptibility on which environmental factors trigger the expression of symptoms [1,2]. Despite the myalgias that patients experience, no abnormality in muscle has been reliably found [3]. Instead, aberrant pain and sensory processing probably caused by alterations in the central nervous system function are being consistently recognized in FM and related syndromes. Investigations into the autonomic nervous system and the hypothalamic–pituitary–adrenal axis also suggest a role of these stress–response systems in vulnerability to FM or in symptom expression in FM.

Our improved understanding of FM has stimulated the search for biomarkers to be used to identify individuals susceptible to the syndrome, for the diagnosis of FM, for objective measures of disease activity, or as surrogate endpoints of clinical trials. Using an expert panel from the FM workshop of the Outcome Measures in Rheumatology (OMERACT), a list of potential objective measures was first developed. Studies evaluating the measures were then methodically compiled by systematic review of the literature using a search for FM and the specific objective measure of interest. The databases searched included MEDLINE (1966 to 2006), PubMed (1966 to 2006), CINAHL (1982 to 2006), EMBASE (1988 to 2006), Healthstar (1975 to 2000), Current Contents (2000 to 2006), Web of Science (1980 to 2006), PsychInfo (1887 to 2006), Science Citation Indexes (1996 to 2006), and/or Cochrane Collaboration Reviews (1993 to 2006). The resulting published studies were used as the basis for the review.

Genetics

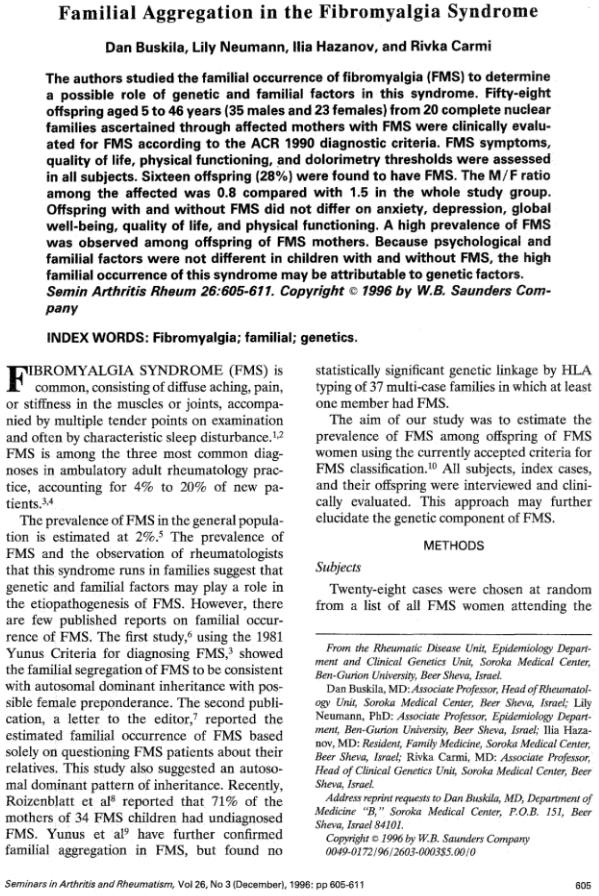
Increasing evidence supports a genetic predisposition to FM. First-degree relatives of individuals with FM display an eightfold greater risk of developing the syndrome than those in the general population [1]. As such, a genetic study using multicase families has been completed that identified an HLA linkage not yet replicated [4].

Polymorphisms in the serotonergic 5-hydroxy tryptamine 2A receptor (T/T phenotype), the serotonin transporter, the dopamine 4 receptor and the catecholamine *o*-methyl transferase enzyme have also been evaluated in patients with FM [5-10]. Notably, these polymorphisms all affect the metabolism or transport of monoamines, compounds that have a critical role in both sensory processing and the human stress response. With the exception of the catecholamine *o*-methyl transferase finding and the dopamine-4-receptor gene polymorphism, however, which have not been replicated or

DNIC = diffuse noxious inhibitory control; ERP = event-related potential; FM = fibromyalgia; fMRI = functional magnetic resonance imaging; IL = interleukin; SPECT = single-photon emission computed tomography.

Aggregazione familiare nella sindrome fibromialgica

- 58 figli di età tra i 5 e i 46 anni (35 maschi e 23 femmine) provenienti da 20 nuclei familiari completi selezionati perchè la mamma era fibromialgica (ACR 1990 criteria)
- 16 figli (28%) presentavano la FM.
- I figli di donne FM con o senza FM non differiscono tra loro per ansia, depressione, benessere globale, qualità di vita e efficienza fisica
- La elevate prevalenza di FM nei figli potrebbe essere dovuta a fattori genetici



Familial Aggregation in the Fibromyalgia Syndrome

Dan Buskila, Lily Neumann, Ilia Hazanov, and Rivka Carmi

The authors studied the familial occurrence of fibromyalgia (FMS) to determine a possible role of genetic and familial factors in this syndrome. Fifty-eight offspring aged 5 to 46 years (35 males and 23 females) from 20 complete nuclear families ascertained through affected mothers with FMS were clinically evaluated for FMS according to the ACR 1990 diagnostic criteria. FMS symptoms, quality of life, physical functioning, and dolorimetry thresholds were assessed in all subjects. Sixteen offspring (28%) were found to have FMS. The M/F ratio among the affected was 0.8 compared with 1.5 in the whole study group. Offspring with and without FMS did not differ on anxiety, depression, global well-being, quality of life, and physical functioning. A high prevalence of FMS was observed among offspring of FMS mothers. Because psychological and familial factors were not different in children with and without FMS, the high familial occurrence of this syndrome may be attributable to genetic factors.

Semin Arthritis Rheum 26:605-611.

INDEX WORDS: Fibromyalgia; familial; genetics.

FIBROMYALGIA SYNDROME (FMS) is common, consisting of diffuse aching, pain, or stiffness in the muscles or joints, accompanied by multiple tender points on examination and often by characteristic sleep disturbance.[1,2] FMS is among the three most common diagnoses in ambulatory adult rheumatology practice, accounting for 4% to 20% of new patients.[3,4]

The prevalence of FMS in the general population is estimated at 2%.[5] The prevalence of FMS and the observation of rheumatologists that this syndrome runs in families suggest that genetic and familial factors may play a role in the etiopathogenesis of FMS. However, there are few published reports on familial occurrence of FMS. The first study,[6] using the 1981 Yunus Criteria for diagnosing FMS,[3] showed the familial segregation of FMS to be consistent with autosomal dominant inheritance with possible female preponderance. The second publication, a letter to the editor,[7] reported the estimated familial occurrence of FMS based solely on questioning FMS patients about their relatives. This study also suggested an autosomal dominant pattern of inheritance. Recently, Roizenblatt et al[8] reported that 71% of the mothers of 34 FMS children had undiagnosed FMS. Yunus et al[9] have further confirmed familial aggregation in FMS, but found no statistically significant genetic linkage by HLA typing of 37 multi-case families in which at least one member had FMS.

The aim of our study was to estimate the prevalence of FMS among offspring of FMS women using the currently accepted criteria for FMS classification.[10] All subjects, index cases, and their offspring were interviewed and clinically evaluated. This approach may further elucidate the genetic component of FMS.

METHODS

Subjects

Twenty-eight cases were chosen at random from a list of all FMS women attending the

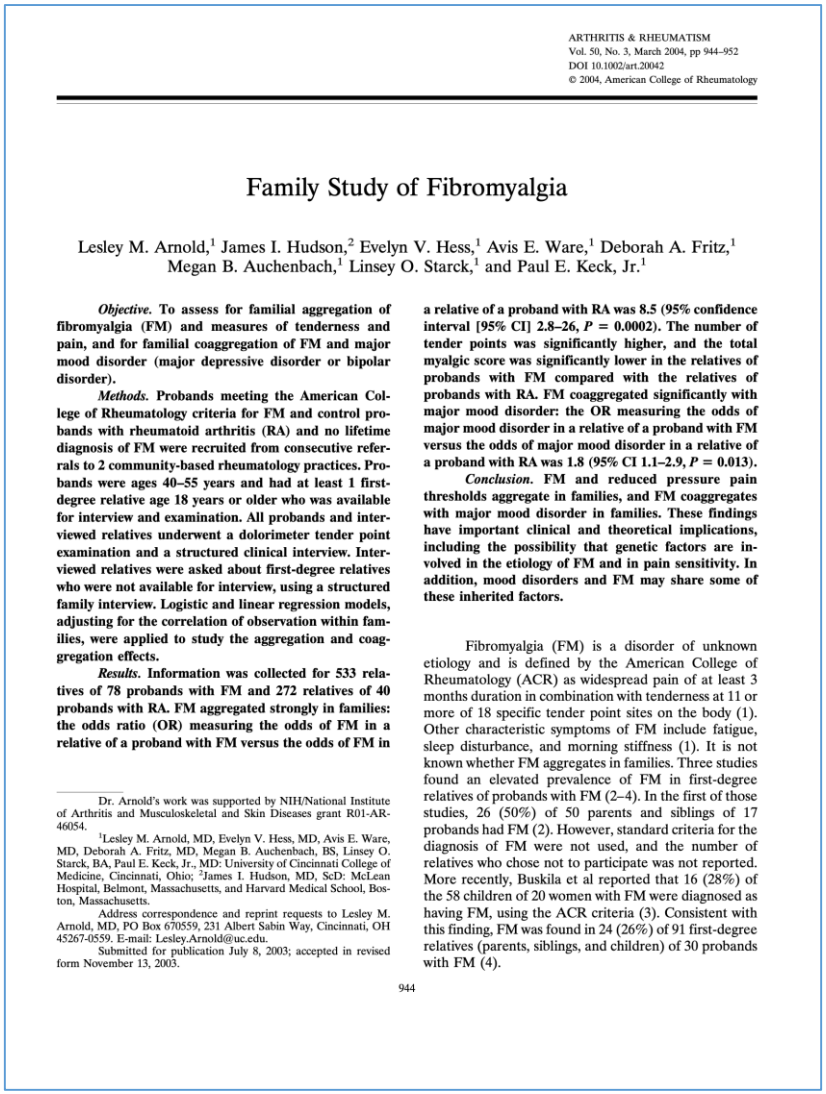
From the Rheumatic Disease Unit, Epidemiology Department and Clinical Genetics Unit, Soroka Medical Center, Ben-Gurion University, Beer Sheva, Israel.

Dan Buskila, MD: *Associate Professor, Head of Rheumatology Unit, Soroka Medical Center, Beer Sheva, Israel;* Lily Neumann, PhD: *Associate Professor, Epidemiology Department, Ben-Gurion University, Beer Sheva, Israel;* Ilia Hazanov, MD: *Resident, Family Medicine, Soroka Medical Center, Beer Sheva, Israel;* Rivka Carmi, MD: *Associate Professor, Head of Clinical Genetics Unit, Soroka Medical Center, Beer Sheva, Israel.*

Address reprint requests to Dan Buskila, MD, Department of Medicine "B," Soroka Medical Center, P.O.B. 151, Beer Sheva, Israel 84101.

0049-0172/96/2603-0003$35.00/0

- Information was collected for 533 relatives of 78 probands with FM and 272 relatives of 40 probands with RA.
- FM aggregated strongly in families: the odds ratio (OR) measuring the odds of FM in a relative of a proband with FM versus the odds of FM in a relative of a proband with RA was 8.5 (95% confidence interval [95% CI] 2.8–26, P 0.0002).
- The number of tender points was significantly higher, and the total myalgic score was significantly lower in the relatives of probands with FM compared with the relatives of probands with RA.
- FM coaggregated significantly with major mood disorder: the OR measuring the odds of major mood disorder in a relative of a proband with FM versus the odds of major mood disorder in a relative of a proband with RA was 1.8 (95% CI 1.1–2.9, P 0.013).



ARTHRITIS & RHEUMATISM
Vol. 50, No. 3, March 2004, pp 944–952
DOI 10.1002/art.20042

Family Study of Fibromyalgia

Lesley M. Arnold,[1] James I. Hudson,[2] Evelyn V. Hess,[1] Avis E. Ware,[1] Deborah A. Fritz,[1] Megan B. Auchenbach,[1] Linsey O. Starck,[1] and Paul E. Keck, Jr.[1]

Objective. **To assess for familial aggregation of fibromyalgia (FM) and measures of tenderness and pain, and for familial coaggregation of FM and major mood disorder (major depressive disorder or bipolar disorder).**

Methods. **Probands meeting the American College of Rheumatology criteria for FM and control probands with rheumatoid arthritis (RA) and no lifetime diagnosis of FM were recruited from consecutive referrals to 2 community-based rheumatology practices. Probands were ages 40–55 years and had at least 1 first-degree relative age 18 years or older who was available for interview and examination. All probands and interviewed relatives underwent a dolorimeter tender point examination and a structured clinical interview. Interviewed relatives were asked about first-degree relatives who were not available for interview, using a structured family interview. Logistic and linear regression models, adjusting for the correlation of observation within families, were applied to study the aggregation and coaggregation effects.**

Results. **Information was collected for 533 relatives of 78 probands with FM and 272 relatives of 40 probands with RA. FM aggregated strongly in families: the odds ratio (OR) measuring the odds of FM in a relative of a proband with FM versus the odds of FM in a relative of a proband with RA was 8.5 (95% confidence interval [95% CI] 2.8–26, $P = 0.0002$). The number of tender points was significantly higher, and the total myalgic score was significantly lower in the relatives of probands with FM compared with the relatives of probands with RA. FM coaggregated significantly with major mood disorder: the OR measuring the odds of major mood disorder in a relative of a proband with FM versus the odds of major mood disorder in a relative of a proband with RA was 1.8 (95% CI 1.1–2.9, $P = 0.013$).**

Conclusion. **FM and reduced pressure pain thresholds aggregate in families, and FM coaggregates with major mood disorder in families. These findings have important clinical and theoretical implications, including the possibility that genetic factors are involved in the etiology of FM and in pain sensitivity. In addition, mood disorders and FM may share some of these inherited factors.**

Fibromyalgia (FM) is a disorder of unknown etiology and is defined by the American College of Rheumatology (ACR) as widespread pain of at least 3 months duration in combination with tenderness at 11 or more of 18 specific tender point sites on the body (1). Other characteristic symptoms of FM include fatigue, sleep disturbance, and morning stiffness (1). It is not known whether FM aggregates in families. Three studies found an elevated prevalence of FM in first-degree relatives of probands with FM (2–4). In the first of those studies, 26 (50%) of 50 parents and siblings of 17 probands had FM (2). However, standard criteria for the diagnosis of FM were not used, and the number of relatives who chose not to participate was not reported. More recently, Buskila et al reported that 16 (28%) of the 58 children of 20 women with FM were diagnosed as having FM, using the ACR criteria (3). Consistent with this finding, FM was found in 24 (26%) of 91 first-degree relatives (parents, siblings, and children) of 30 probands with FM (4).

Dr. Arnold's work was supported by NIH/National Institute of Arthritis and Musculoskeletal and Skin Diseases grant R01-AR-46054.

[1]Lesley M. Arnold, MD, Evelyn V. Hess, MD, Avis E. Ware, MD, Deborah A. Fritz, MD, Megan B. Auchenbach, BS, Linsey O. Starck, BA, Paul E. Keck, Jr., MD: University of Cincinnati College of Medicine, Cincinnati, Ohio; [2]James I. Hudson, MD, ScD: McLean Hospital, Belmont, Massachusetts, and Harvard Medical School, Boston, Massachusetts.

Address correspondence and reprint requests to Lesley M. Arnold, MD, PO Box 670559, 231 Albert Sabin Way, Cincinnati, OH 45267-0559. E-mail: Lesley.Arnold@uc.edu.

Submitted for publication July 8, 2003; accepted in revised form November 13, 2003.

- The estimated sibling recurrence risk ratio (λs) for fibromyalgia was 13.6 (95% CI: 10.0–18.5), based on a reported population prevalence of 2%. Genome-wide suggestive evidence of linkage was found at marker D17S2196 (Empirical P =0.00030) and D17S1294 (Empirical P =0.00035) on chromosome 17p11.2-q11.2.
- The estimated sibling recurrence risk ratio suggests a strong genetic component of fibromyalgia.
- This is the first study to report genome-wide suggestive linkage of fibromyalgia to the chromosome 17p11.2-q11.2 region.

NIH Public Access
Author Manuscript
Arthritis Rheum. Author manuscript; available in PMC 2014 April 01.

Published in final edited form as:
Arthritis Rheum. 2013 April ; 65(4): 1122–1128. doi:10.1002/art.37842.

The Fibromyalgia Family Study: A Genome-Scan Linkage Study

Lesley M. Arnold, M.D.[1,+], **Jinbo Fan, Ph.D.**[2,+], **I. Jon Russell, M.D., Ph.D.**[3], **Muhammad B. Yunus, M.D.**[4], **Muhammad Asim Khan, M.D.**[5], **Irving Kushner, M.D.**[5], **Jane M. Olson posthumous, Ph.D.**[2], and **Sudha K. Iyengar, Ph.D.**[2]

[1]Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio

[2]Department of Epidemiology and Biostatistics, Case Western Reserve University School of Medicine, Cleveland, Ohio

[3]Department of Medicine, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas

[4]Department of Medicine, University of Illinois College of Medicine, Peoria, Illinois

[5]Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, Ohio

Abstract

Objective—Familial aggregation of fibromyalgia has been increasingly recognized. The goal of the current study was to conduct a genome wide linkage scan to identify susceptibility loci for fibromyalgia.

Methods—We genotyped members of 116 families from the Fibromyalgia Family Study and performed a model-free genome-wide linkage analysis of fibromyalgia with 341 microsatellite markers, using the Haseman-Elston regression approach.

Results—The estimated sibling recurrence risk ratio (λ_s) for fibromyalgia was 13.6 (95% CI: 10.0–18.5), based on a reported population prevalence of 2%. Genome-wide suggestive evidence of linkage was found at marker D17S2196 (Empirical *P*=0.00030) and D17S1294 (Empirical *P* =0.00035) on chromosome 17p11.2-q11.2.

Conclusion—The estimated sibling recurrence risk ratio suggests a strong genetic component of fibromyalgia. This is the first study to report genome-wide suggestive linkage of fibromyalgia to the chromosome 17p11.2-q11.2 region. Further investigation of these multi-case families from the Fibromyalgia Family Study is warranted to identify potential causal risk variants for fibromyalgia.

Keywords

fibromyalgia; genome scan; linkage; sibling pairs; multi-case families

Fibromyalgia is a common, chronic pain disorder affecting an estimated 2% of the general population and defined by the American College of Rheumatology (ACR) as widespread pain of at least 3 months duration and pain on palpation in at least 11 of 18 tender point sites (1,2). Although the underlying pathophysiological mechanisms underlying fibromyalgia are not completely understood (3-5), Arnold et al. (6) reported that fibromyalgia strongly

Corresponding author: Lesley M. Arnold, M.D. 260 Stetson Street, Suite 3200 Cincinnati, Ohio 45219 Lesley.Arnold@uc.edu Phone: 513-558-4622 Fax: 513-558-4280; Or Sudha K. Iyengar, Ph.D. Department of Epidemiology and Biostatistics Case Western Reserve University Wolstein Research Building, 1315 10900 Euclid Avenue ski@case.edu Telephone: 216-368-4388 Fax: 216-368-4880 .
[+]Contributed equally

biomedicines

MDPI

Review

A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia

Erik A. Ovrom [1], Karson A. Mostert [2], Shivani Khakhkhar [3], Daniel P. McKee [3], Padao Yang [4] and Yeng F. Her [5,*]

1 Mayo Clinic Alix School of Medicine, Rochester, MN 55905, USA; ovrom.erik@mayo.edu
2 Department of Physical Medicine and Rehabilitation, Mayo Clinic Hospital, Rochester, MN 55905, USA
3 Department of Orthopedics and Rehabilitation, University of Wisconsin School of Medicine and Public Health, Madison, WI 53705, USA
4 Department of Psychiatry and Psychology, Mayo Clinic Hospital, Rochester, MN 55905, USA
5 Department of Anesthesiology and Perioperative Medicine, Mayo Clinic Hospital, Rochester, MN 55905, USA
* Correspondence: her.yeng@mayo.edu; Tel.: +1-507-284-9696

Abstract: This narrative review summarizes the current knowledge of the genetic and epigenetic contributions to the development of fibromyalgia (FM). Although there is no single gene that results in the development of FM, this study reveals that certain polymorphisms in genes involved in the catecholaminergic pathway, the serotonergic pathway, pain processing, oxidative stress, and inflammation may influence susceptibility to FM and the severity of its symptoms. Furthermore, epigenetic changes at the DNA level may lead to the development of FM. Likewise, microRNAs may impact the expression of certain proteins that lead to the worsening of FM-associated symptoms.

Keywords: fibromyalgia; genetics; epigenetics

Citation: Ovrom, E.A.; Mostert, K.A.; Khakhkhar, S.; McKee, D.P.; Yang, P.; Her, Y.F. A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia. *Biomedicines* **2023**, *11*, 1119. https://doi.org/10.3390/biomedicines11041119

Academic Editor: Rosanna Di Paola

Received: 14 March 2023
Revised: 23 March 2023
Accepted: 28 March 2023
Published: 7 April 2023

1. Introduction

Fibromyalgia (FM) is a centrally and peripherally mediated chronic pain syndrome with biological, psychological, and environmental predispositions [1–4]. 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 [14–16]. In this review, we will not examine the role of the environment in the development of FM.

In the last ten years, there have been unprecedented advances in technology to identify genetic and epigenetic contributions to the development of FM. This has led to a better understanding of disease pathogenesis. In this review, we focus on the associations of genetic and epigenetic changes with the development of FM and its related symptoms.

Future Medicine Ltd
Pharmacogenomics
Volume 8, Issue 1, January 2007, Pages 67-74
https://doi-org.pros2.lib.unimi.it/10.2217/14622416.8.1.67

Review

The genetics of fibromyalgia syndrome

Dan Buskila[1,†], Piercarlo Sarzi-Puttini[2] & Jacob N Ablin[3]
[1]Ben Gurion University, Department of Medicine H, Soroka Medical Center and Faculty of Health Sciences, Beer Sheva, Israel. dbuskila@bgumail.bgu.ac.il
[2]L Sacco University Hospital, Senior Rheumatologist, Rheumatology Unit,Via GB Grassi 74, 20157 Milano, Italy. sarzi@tiscali.it
[3]Tel-Aviv University, Departments of Rheumatology, Tel-Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel-Aviv, Israel. ajacob@post.tau.ac.il
[†] *Author for correspondence*

Fibromyalgia syndrome (FMS) is a common chronic widespread pain syndrome mainly affecting women. Although the etiology of FMS is not completely understood, varieties of neuroendocrine disturbances, as well as abnormalities of autonomic function, have been implicated in its pathogenesis. The exposure of a genetically predisposed individual to a host of environmental stressors is presumed to lead to the development of FMS. Fibromyalgia overlaps with several related syndromes, collectively compromising the spectrum of the functional somatic disorder. FMS is characterized by a strong familial aggregation. Recent evidence suggests a role for polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems in the etiopathogenesis of FMS. These polymorphisms are not specific for FMS and are similarly associated with additional comorbid conditions. The mode of inheritance in FMS is unknown, but it is most probably polygenic. Recognition of these gene polymorphisms may help to better subgroup FMS patients and to guide a more rational pharmacological approach. Future genetic studies conducted in larger cohorts of FMS patients and matched control groups may further illuminate the role of genetics in FMS.

Published online: 22 December 2006.

Keywords: familial aggregation • fibromyalgia • genetics • gene polymorphisms

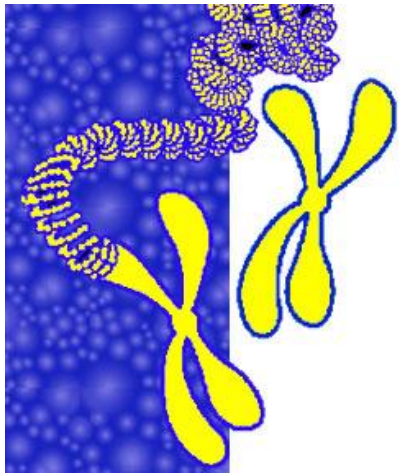
Genetica e Fibromialgia

- 77 % dei pazienti FM avevano il DR4 vs. 30% dei normali controlli. Si osservava inoltre un aumentato rischio relativo(4.5)

  Burda et al, Clin Exp Rheumatol, 1986.

- Uno studio su 40 nuclei familiari con casi ripetuti di FM confermava l'esistenza di un possibile gene per la FM collegato alla regione HLA.

  Yunus et al, J Rheumatol, 1999



Predisposizione genetica alla percezione del dolore

- Polimorfismo del Cathechol-O-methyl transferase (COMT) gene
- COMT. Via principale catabolica della catecolamine.

  ≈50% della popolazione ha il genotipo H/H .

  ≈25% ha il genotipo L/L .

- Il genotipo H/H è associato con ridotta percezione del dolore negli individui sani. ***(Zubieta. Science 2003;299:1240)***
- 26% dei pazienti FM presentano il genotipo H/H in contrasto con il 47% dei soggetti di controllo ($p<0.05$) ***(Gursoy. Rheumatol Int 2003;23:104)***

Genetica e Fibromialgia

- Possibile associazione tra FM con un polimorfismo nel serotonin transporter gene regulating region ***(Offenbaecher et al, A&R, 1999)***

- Polimorfismo T 102 C del 5-HT2A-receptor gene nei fibromialgici ***(Bondy et al, Neurobiol Dis, 1999)***

Catechol-O-Methyltransferase (COMT) Polymorphisms and FM

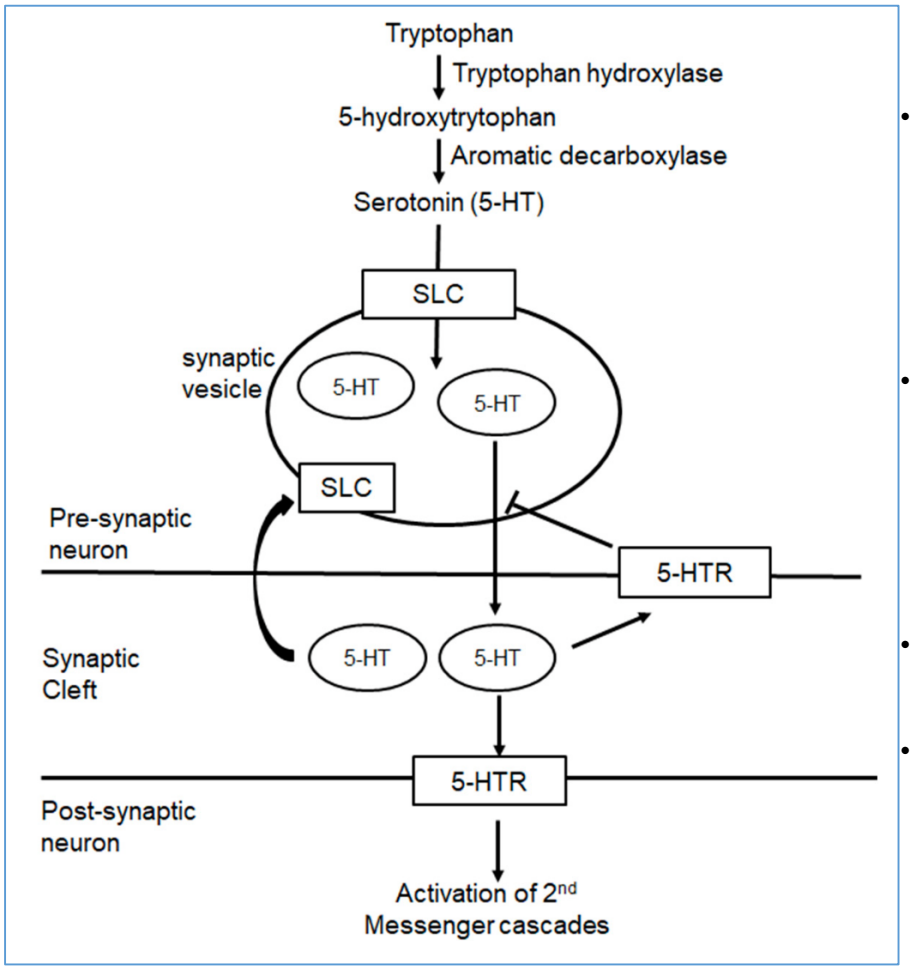
COMT is one of the primary enzymes that inactivates catecholamines, including dopamine, by transferring a methyl group from S-adenosyl-L-methionine to dopamine to generate 3-methoxytyramine.

Functional polymorphisms in the *COMT* gene can change the enzyme's activity to be either a fast or slow metabolizer of catecholamines

Genes	Effects in FM
COMT Val-158-Met (rs4680)	Increased risk of developing FM
rs4818 of the *COMT* gene	No increased risk of FM development in diverse, Mexican, or Spanish populations
rs4818 of the *COMT* gene	Increased risk of FM development in Korean, Brazilian, and Spanish populations
rs6269 of the *COMT* gene	Increased risk of FM development in the Spanish population
COMT Val-158-Met (rs4680)	No increased risk of developing FM
rs4633 of the *COMT* gene	Increased risk of FM development in the Korean population
COMT Val-158-Met (rs4680)	Increased severity of symptoms
rs2097903 of the *COMT* gene	Increased risk of FM development

COMT: Catechol-O-Methyltransferase; FM: fibromyalgia.

Polymorphisms in 5-HT Processing and FM



- 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.
- 5-HT is also transported back into the pre-synaptic neuron by the serotonin transporter.
- Inhibitory serotonergic 5-HT1A receptors in the presynaptic neurons become activated and . decrease serotonergic signalling

5-HT biosynthesis and physiology. 5-HT: serotonin; SLC: solute carrier; 5-HTR; serotonin receptor

Associations of Genes in the Serotonin Pathway and FM Development and Symptoms.

Genes (Polymorphisms)	Effects In FM
5-HTR2A, CT polymorphism genotype	Lower pain threshold
SLC6A4 "short allele"	Increased risk of FM
5-HT1a, CC/G polymorphism alone and with 5-HTT-low *5HT1a*, CC polymorphism with 5-HTT-high	Increased depressive symptoms Fewest depressive symptoms, highest response to an SSRI
5-HTR3a, SNP rs1062613 CC homozygote	Increased risk of FM
5-HTR3a, *5-HTR3b*	Unsure currently

5-HTR2A: 5-hydroxytryptamine receptor 2A; *SCL6A4*: solute carrier family 6 member 4; *5-HT1a*: serotonin 1A receptor; *5-HTR3a*: 5-hydroxytryptamine receptor 3A; *5-HTR3b*: 5-hydroxytryptamine receptor 3B; SSRI: Selective serotonin reuptake inhibitor, CT: Cytosine-Thymine.

Associations between Polymorphisms in Pain Pathway Processing Genes, Inflammatory Genes, Mitochondrial DNA, and Vascular Genes and the Development of FM (2).

Genes	Effects in FM
Beta2-Adrenergic Receptor gene	The Gly16Arg SNP increases the risk of FM and may cause sleep dysfunction in FM.
alpha(1A)-Adrenergic Receptor	rs1383914 and rs1048101 SNPs are associated with higher FM impact questionnaire scores; rs574584 is associated with a higher FM impact questionnaire score, increased stiffness, and increased fatigue.
CCL11	Associated with increased susceptibility to FM due to higher levels of plasma chemokines and an increased inflammatory response.
VNTR	Encodes interleukin 4. A 70 bp polymorphism at this locus is associated with a higher risk for FM.
C11orf40	Associated with higher levels of inflammatory cytokines.
ZNF77	Associated with higher levels of inflammatory cytokines.
MEFV	Encodes a protein called pyrin, which suppresses inflammation; missense mutations of this gene correlated with higher levels of plasma IL-1beta.
RNF123	Encodes E3 ubiquitin-protein-ligase, which plays a role in cell cycle progression, innate immunity, and the metabolism of proteins. rs1491985 SNP is associated with an increased risk of developing FM.
AAT	Encodes alpha-1-antitrypsin; the PI*Z polymorphism has increased prevalence in FM patients. $\frac{1}{4}$ to 1/36 of FM patients found to have AAT deficiency.
BDNF	rs12273539 SNP is associated with susceptibility and symptoms of FM; rs7124442 and rs2049046 SNPs are associated with body mass index and anxiety symptoms of FM. rs6265 polymorphism is associated with pain catastrophizing in FM. Val66Val SNP is associated with elevated plasma CRP and body mass index.

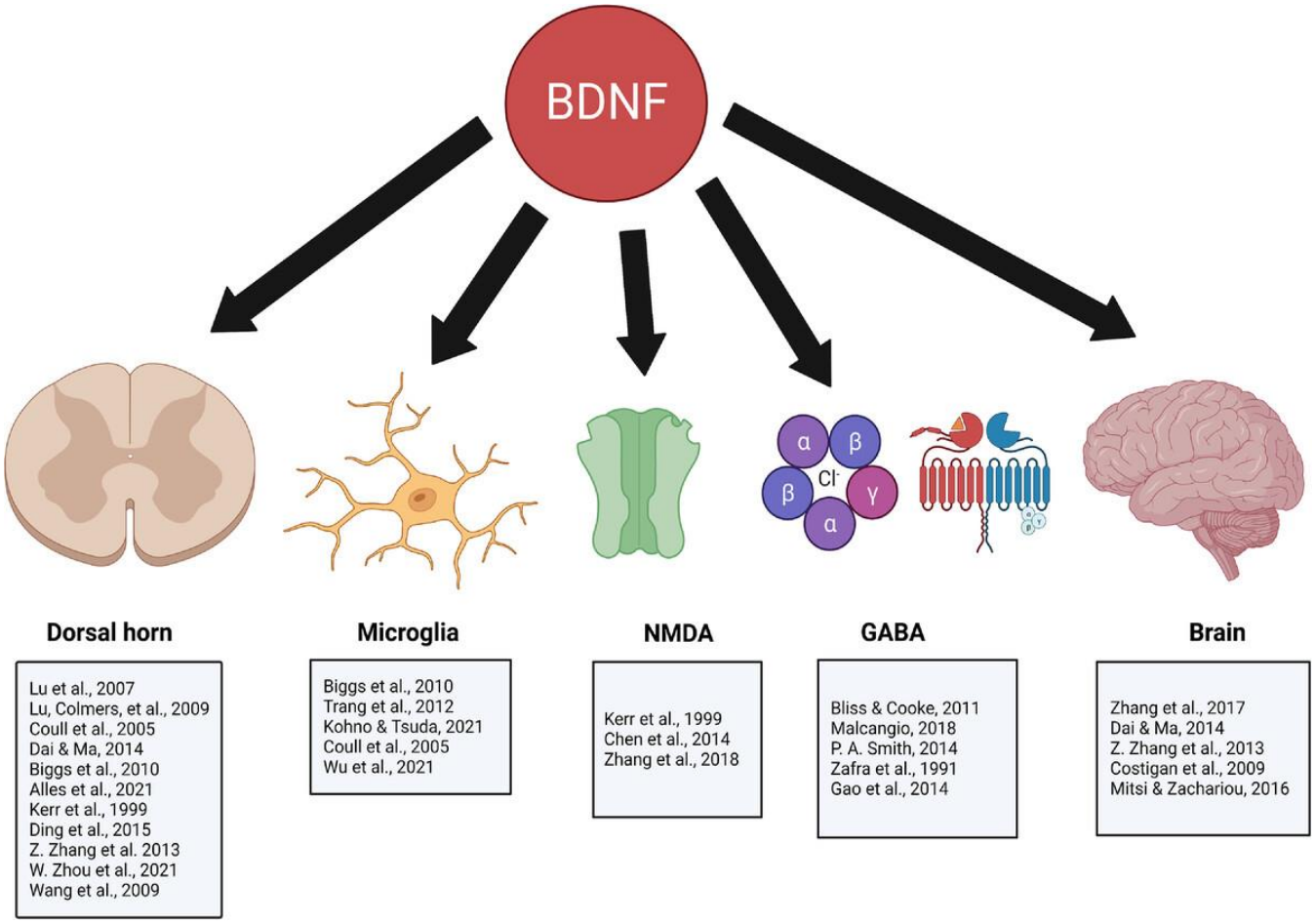
Ovrom EA, Mostert KA, Khakhkhar S, McKee DP, Yang P, Her YF. A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia. Biomedicines. 2023 Apr 7;11(4):1119.

Associations between Polymorphisms in Pain Pathway Processing Genes, Inflammatory Genes, Mitochondrial DNA, and Vascular Genes and the Development of FM (3).

Genes	Effects in FM
VDR	Encodes the vitamin D receptor; Apal polymorphism and Fokl polymorphism increase the risk of developing FM in women.
CNR1	Encodes the cannabis receptor; the rs6454674 SNP increases the risk for depression in FM.
m.2352C	Mitochondrial DNA gene, which increases the risk of developing FM.
MTHFR	Encodes a key enzyme in folate metabolism and increases the risk of developing FM.
EDN-1	Encodes endothelin-1, a potent vasoconstrictor; the rs1800541 SNP is associated with higher levels of endothelin-1 and susceptibility to FM.
ACE I/D	Encodes angiotensin-converting enzyme; the ACE I/D polymorphism increases susceptibility to FM.

Ovrom EA, Mostert KA, Khakhkhar S, McKee DP, Yang P, Her YF. A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia. Biomedicines. 2023 Apr 7;11(4):1119.

BDNF as a biomarker for neuropathic pain: Consideration of mechanisms of action and associated measurement challenges



Brain and Behavior, Volume: 13, Issue: 3, First published: 01 February 2023, DOI: (10.1002/brb3.2903)

BDNF (brain derived neurotrophic factor)

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 .

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 under- lying several anxiety and depressive disorders and is the target of several antidepressant drugs .**

Casarotto, P.C.; et al. BDNF-TRKB signaling system of the dorsal periaqueductal gray matter is implicated in the panicolytic-like effect of antidepressant drugs. *Eur. Neuropsychopharmacol.* **2015**, *25*, 913–922. Sikandar, S.; et al, J Brain-derived neurotrophic factor derived from sensory neurons plays a critical role in chronic pain. *Brain* **2018**, *141*, 1028–1039.

BDNF (brain derived neurotrophic factor)

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 .
- The rs7124442 and rs2049046 *BDNF* polymorphisms are associated with a higher body mass index and anxiety symptoms in FM individuals .
- Similarly, the *BDNF* Val66Val SNP is associated with elevated plasma levels of high-sensitivity C-reactive protein and a higher body mass index .
- 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

Casarotto, P.C.; et al. BDNF-TRKB signaling system of the dorsal periaqueductal gray matter is implicated in the panicolytic-like effect of antidepressant drugs. *Eur. Neuropsychopharmacol.* **2015**, *25*, 913–922. Sikandar, S.; et al, J Brain-derived neurotrophic factor derived from sensory neurons plays a critical role in chronic pain. *Brain* **2018**, *141*, 1028–1039.

Vitamin D and fibromyalgia

- Vitamin D plays a role in regulating nociceptive and inflammatory pain.
- 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.
- 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.

Atherton, K.; Berry, D.J.; Parsons, T.; Macfarlane, G.J.; Power, C.; Hyppönen, E. Vitamin D and chronic widespread pain in a white middle-aged British population: Evidence from a cross-sectional population survey. *Ann. Rheum. Dis.* **2009**, *68*, 817–822

Santos, S.K.F.S.; Fernandes, K.B.P.; Zicarelli, C.A.M.; Santana, A.V.; Perrucini, P.D.D.O.; Poli-Frederico, R.C. Evaluation of ApaI and FokI polymorphism of VDR gene and functional characterization in patients with fibromyalgia. *Fisioter. Mov.* **2022**, *35*, e35122.

Associations of upregulated genes/proteins and FM.

Genes/Proteins	Main Results
SNP (rs1800541) *EDN1* gene	FM patients had higher plasma levels of EDN1, a potent vasoconstrictor, compared to controls
METTL18, *IGL3-25*, *IL1RAP*, *IGHV1OR21-1*	Increased *METTL18*, *IGL3-25*, *IL1RAP*, and *IGHV1OR21-1* expression can differentiate FM individuals from healthy controls.
Th-17 related genes (14 total), *Type 1 IFN* related genes (15 total)	Genes involved in the immunologic pathway connected to interleukin-17 and type I interferon were overexpressed in FM individuals compared to controls.
421 genes exhibited differential expression in FM patient compared to healthy controls	The genes identified are involved in pain processing and axonal development.
TNF-α, interleukin-1β, interleukin-6	Significant positive correlation between TNF-α, interleukin-1β, and interleukin-6 overexpression and FM symptoms.
TNF-α, interleukin-1β, interleukin-6	TNF-α, interleukin-1β, and interleukin-6 were upregulated in the skin tissue of FM individuals.
Interleukin-17A, interleukin-2, interleukin-4, interleukin-10, TNF, interferon necrosis-gamma	IL-17A levels were significantly higher in FM individuals.
Interleukin-1Ra, interleukin-8, interleukin-6	FM individuals had lower serum Interleukin-1Ra levels and normal interleukin-8 and interleukin-6 levels.
33 genes were overexpressed	Interplay between inflammation, coagulation, and complement cascades contributes to an inflammatory state in FM individuals compared to controls.
NLR, PLR	Systemic inflammatory response marker PLP levels correlated with the number of tender points in FM individuals.
Oleoylethanolamide, palmitoylethanolamide	Plasma levels of oleoylethanolamide and palmitoylethanolamide were significantly higher in FM individuals than in controls. Both are potential indicators of systemic inflammatory state in chronic widespread pain individuals.

Ovrom EA, Mostert KA, Khakhkhar S, McKee DP, Yang P, Her YF. A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia. Biomedicines. 2023 Apr 7;11(4):1119.

Associations of upregulated genes/proteins and FM.

Genes/Proteins	Main Results
Oleoylethanolamide, palmitoylethanolamide	Plasma levels of oleoylethanolamide and palmitoylethanolamide were significantly higher in FM individuals than in controls. Both are potential indicators of systemic inflammatory state in chronic widespread pain individuals.
CGRP, CLR, RCP	CGRP, CLR, and RCP were elevated in FM versus controls.
S100A8, S100A9, VCAM, CD163, SERPINA1, ANXA1, interleukin-8, AXIN1, SIRT2, STAMBP	Overexpression of identified proteins are associated with an interferon signature in B cells and increased inflammation in FM individuals.
Abeta1-42	Abeta1-42 was significantly higher in FM individuals.
Neural cell adhesion molecule L1, complement C4-A, lysozyme C, receptor-type tyrosine-protein, phosphatase zeta, apolipoprotein D, alpha-1-antichymotrypsin granulins, calcium/calmodulin-dependent protein kinase type II subunit alpha, mast/stem cell growth factor receptor, prolow-density lipoprotein receptor-related protein 1	Identified proteins were higher in FM and rheumatoid arthritis patients than controls. These proteins are related to synaptic transmission, inflammatory responses, neuropeptide signaling, and hormonal activity.
Catecholamines, anandamide	Plasma levels of catecholamines and anandamide are higher in FM individuals.
Delta-opioid receptor, Kappa-opioid receptor, mu-opioid receptor	Upregulation of delta and kappa receptor and downregulation of mu receptors in FM individuals compared to controls.
Alpha 2-adrenergic receptors	Upregulated alpha 2-adrenergic receptors in FM individuals positively correlate with receptor number and vasospastic symptoms.

Ovrom EA, Mostert KA, Khakhkhar S, McKee DP, Yang P, Her YF. A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia. Biomedicines. 2023 Apr 7;11(4):1119.

Associations of upregulated genes/proteins and FM.

Genes/Proteins	Main Results
57 genes linked to hepatic stellate cell activation, oxidative phosphorylation, and airway pathology related to COPD	Expression of these genes can differentiate FM individuals from healthy controls with high validation accuracy.
Eotaxin, MCP-1	Elevated levels of Eotaxin and MCP-1 in FM individuals versus controls.
Eotaxin-2	Higher levels of Eotaxin-2 in FM versus controls, but no correlation between marker levels and FM disease severity.
HSP99AA1	High levels are expressed in FM individuals; higher plasma levels are associated with an increased number of pain sites, fatigue, and decreased motivation.
HSP99AA1	HSP99AA1 was significantly upregulated in FM individuals.
12 genes identified, including CENPK, HSP99AA1	CENPK and HSP99AA1 were significantly elevated in FM women.
6-SMT	6-SMT was significantly elevated in FM, but there was no correlation with disease severity.
CatS, CysC	Serum levels of CatS and CysC were higher in FM individuals than controls.

Ovrom EA, Mostert KA, Khakhkhar S, McKee DP, Yang P, Her YF. A Comprehensive Review of the Genetic and Epigenetic Contributions to the Development of Fibromyalgia. Biomedicines. 2023 Apr 7;11(4):1119.

Inflammatory state and FM

- An inflammatory state due to reduced anti-inflammatory cytokines production can contribute to the development of FM.
- Keskin et al. examined the anti-inflammatory cytokine profiles in FM individuals and healthy controls. They reported significantly **lower levels of serum IL-13 in FM patients.**
- Uceyler et al. conducted a similar study and reported **decreased expression levels of IL-4 and IL-10 in FM indivi**duals compared to healthy controls

Keskin,G.;I ̇nal,A.;Keskin,D.;Mus ̧abak,U.;S ̧engül,A.;Köse,K.Serum interleukin-13(IL-13)levels in patients with fibromyalgia. *Gulhane Med. J.* **2008**, *50*, 257–260.
Uçeyler,N.;Valenza,R.;Stock,M.;Schedel,R.;Sprotte,G.;Sommer,C.Reduced levels of antiinflammatory cytokines in patients with chronic widespread pain. *Arthritis Rheum.* **2006**, *54*, 2656–2664.

mitochondrial dysfunction and FM

Cordero et al. investigated the relationship between inflammation, oxidative stress, and mitochondrial dysfunction. They showed that TNF-alpha was elevated in FM in- dividuals compared to healthy controls. FM individuals had higher levels of mitochondrial reactive oxygen species and reduced co-enzyme Q10. **They postulated that inflammation in FM individuals could be dependent on mitochondrial dysfunction**.

Similarly, evaluating the correlations of oxidative and antioxidative parameters and FM symptoms severity, Fatima et al. reported reduced enzymatic activity of catalase, glutathione peroxidase, and glutathione reductase in FM individuals compared to controls. **Individuals with increased oxidative stress had more severe FM-related symptoms**

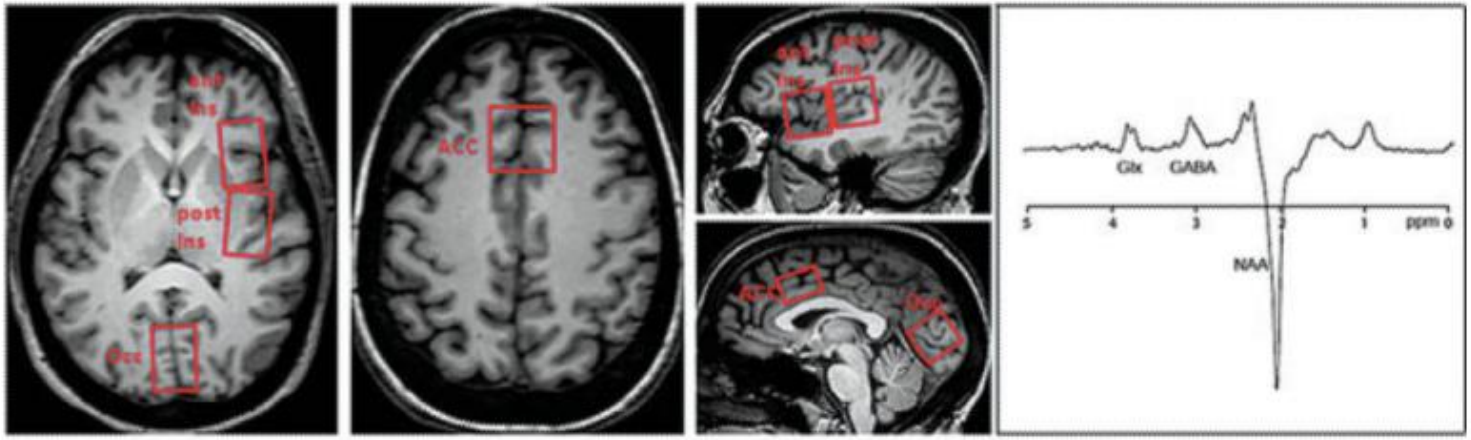
Cordero, M.D.; Díaz-Parrado, E.; Carrión, Á.M.; Alfonsi, S.; Sánchez Alcázar, J.A.; Miguel Rodríguez, M.D.; Battino, M. is inflammation a mitochondrial dysfunction-dependent event in fibromyalgia? *Antioxid. Redox Signal.* **2013**, *18*, 800–807.

Fatima,G.;Das,S.K.;Mahdi,A.A.Some oxidative and antioxidative parameters and their relationship with clinical symptoms in women with fibromyalgia syndrome. *Int. J. Rheum. Dis.* **2017**, *20*, 39–45.

Associations of downregulated genes/proteins and FM.

Genes/Proteins	Main Results
TNF-alpha	Elevated TNF-alpha levels in FM individuals are associated with higher levels of mitochondrial reactive oxygen species and reduced coenzyme Q10 activity.
GABA	FM individuals had reduced GABA levels in the right anterior insula compared to controls. This is positively correlated with lower pressure pain thresholds.
Interleukin-13	FM individuals had lower interleukin-13 levels than controls.
Interleukin-4, Interleukin-10	FM individuals had decreased expressions of interleukin-4 and interleukin-10 compared to controls.
EGR1	FM individuals had lower serum EGR1 compared to controls.
HSP99AA1	Gender and race may alter levels of HSP99AA1in FM individuals; HSP99AA1 levels lower in non-Caucasian FM individuals; and HSP99AA1 levels lower in Caucasian men with FM compared to controls
Interleukin-4, Interleukin-10, Opioid receptor	FM individuals had reduced opioid receptor binding to F-18-fluoro-ethyl-diprenorphine in the mid cingulate cortex compared to controls. FM individuals had low interleukin-4, interleukin-10 gene expression levels.
Natural killer cells	FM individuals had less natural killer cells than controls, but it was more responsive when exposed to human leukocyte antigen null target cells.
Catalase, glutathione peroxidase, glutathione reductase	Identified enzymes were significantly lower in FM; expression levels correlated with higher oxidative stress parameters compared to controls; and correlated with severity of FM related symptoms.

GABA: ɤ-aminobutyric acid; EGR1: Early Growth Response 1.



- gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter of the central nervous system.
- It has been proposed that decreased GABA levels may result in chronic pain conditions.
- Foerster et al. demonstrated that GABA levels were reduced in the right anterior insula of FM individuals using 3T proton magnetic resonance spectroscopy during pressure-pain testing.
- Reduced GABA levels positively correlated with lower pressure-pain thresholds in the FM individuals

Foerster, B.R.; Petrou, M.; Edden, R.A.; Sundgren, P.C.; Schmidt-Wilcke, T.; Lowe, S.E.; Harte, S.E.; Clauw, D.J.; Harris, R.E. Reduced insular γ-aminobutyric acid in fibromyalgia. *Arthritis Rheum.* **2012**, *64*, 579–583.

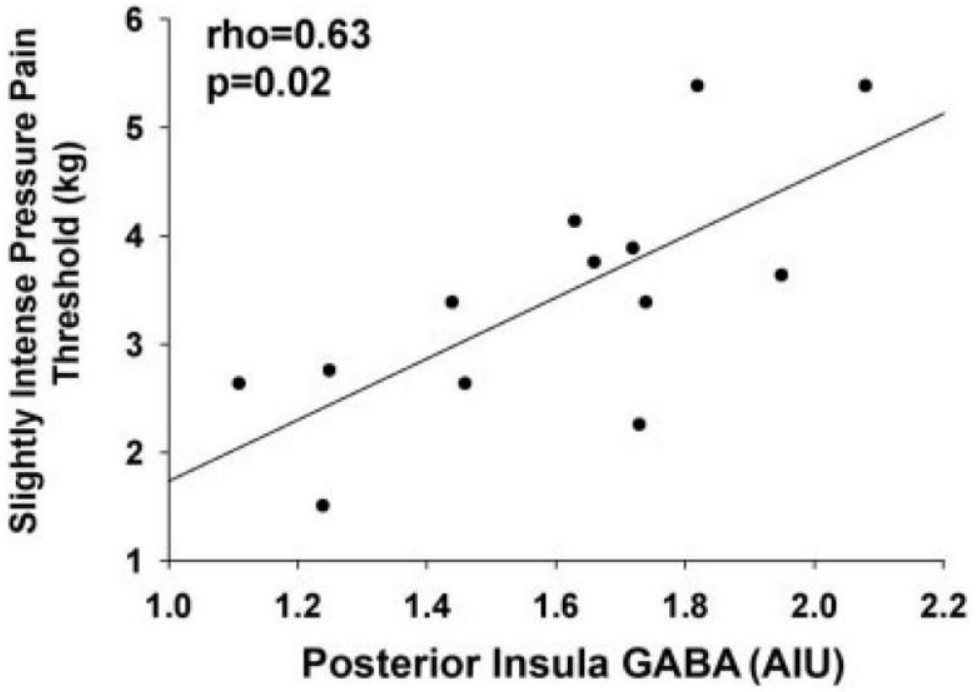


Figure 3.
Levels of γ-aminobutyric acid (GABA) within the right posterior insula are positively correlated with pressure–pain thresholds in patients with fibromyalgia. Results are shown as a scatterplot of GABA concentrations in relation to slightly intense pressure–pain thresholds in individual patients (solid circles); the regression line is also shown. Correlations were assessed using Spearman's rho. AIU = arbitrary institutional units.

Foerster, B.R.; Petrou, M.; Edden, R.A.; Sundgren, P.C.; Schmidt-Wilcke, T.; Lowe, S.E.; Harte, S.E.; Clauw, D.J.; Harris, R.E. Reduced insular γ-aminobutyric acid in fibromyalgia. *Arthritis Rheum.* **2012**, *64*, 579–583.

Gli studi hanno dimostrato il coinvolgimento di fattori genetici nell'insorgenza della fibromialgia

- Circa 100 geni che regolano il dolore sono rilevanti per la sensibilità al dolore o l'analgesia.
- I geni principali sono quelli che codificano per i canali del sodio voltaggio-dipendenti, le proteine della via GABAergica, i recettori mu-oppioidi, la catecol-O-metiltransferasi e la GTP cicloidrolasi 1
- Il gene del trasportatore della serotonina (SLC64A4)
- il gene del potenziale canale vanillico del recettore transitorio 2 (TRPV2) sono i principali geni responsabili della suscettibilità al dolore nella fibromialgia.
- Altri polimorfismi genetici che sono stati identificati e associati alla suscettibilità alla fibromialgia sono nei geni del trasportatore della serotonina (5-HTT), della catecol-O-metiltransferasi (COMT) e della serotonina 2A (5-HT2A).
- Uno studio sull'associazione dell'intero genoma e sulla variante del numero di copie in 952 casi di fibromialgia e 644 controlli ha rivelato l'esistenza di due variabili associate alla fibromialgia: il polimorfismo a singolo nucleotide rs11127292 e un numero di copie introniche variabile nel gene neurexin 3 (NRXN3).

Epigenoma, un compagno di vita “flessibile”

- Accanto al genoma, l’insieme dei geni che compone il nostro DNA, i ricercatori studiano oggi anche **l’epigenoma**, ovvero l’insieme di tutte le molecole che rendono possibili i cambiamenti epigenetici presenti nell’organismo.
- Una prima grande differenza tra genoma ed epigenoma risiede nel fatto che, mentre il primo si mantiene piuttosto costante per tutta la vita e in tutte le cellule, il secondo **cambia nel corso della nostra esistenza** ed è diverso anche tra cellula e cellula.

EPIGENETICA

L’epigenetica studia come l’età e l’esposizione a fattori ambientali possono modificare l’espressione dei geni.

AGENTI FISICI E CHIMICI

DIETA

STRESSOR

ATTIVITÀ FISICA

In passato, si pensava che la sequenza di DNA dei geni fosse l'unica responsabile dell'espressione dei geni stessi.

Oggi sappiamo che ci sono molti altri meccanismi e molecole che possono attivare o disattivare l'espressione dei geni. Questi meccanismi sono chiamati "epigenetici" e si trovano sopra la sequenza di DNA, con sistema di attacco e stacco

Questo rende alcune parti del DNA più o meno accessibili e può influire sull'espressione dei geni.

Questo può causare cambiamenti nel modo in cui una cellula, un tessuto o un organismo si comportano, senza cambiare la sequenza di DNA dei geni stessi.

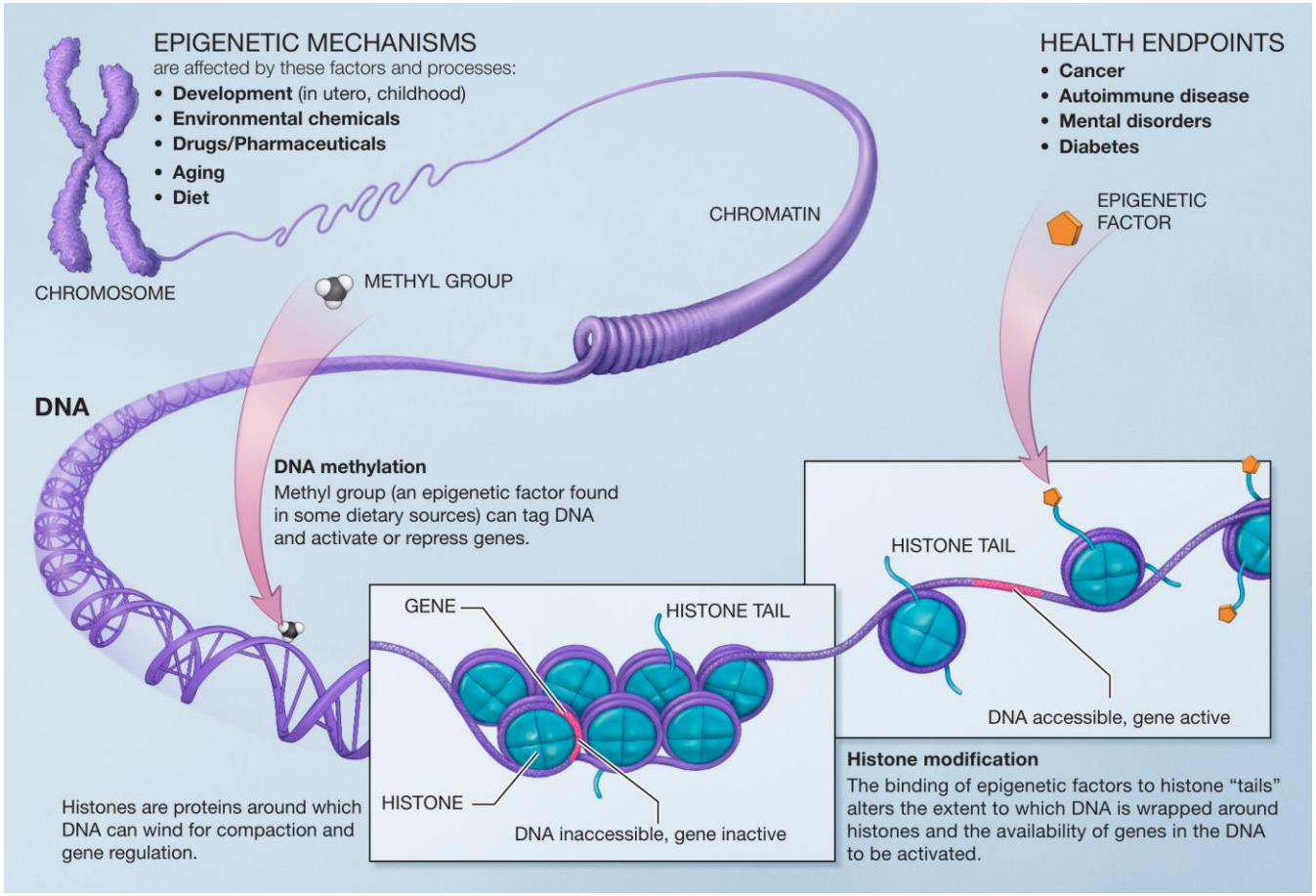
Un modo per pensare alle modifiche epigenetiche è come gli accenti posti sulle parole nella lingua scritta.

Gli accenti non cambiano la sequenza di lettere di una parola, ma possono influire sul modo in cui la parola viene pronunciata e compresa.

Come l’epigenetica può influenzare la regolazione dell’espressione genica?

Sono tre i meccanismi principali: la metilazione del DNA, la modificazione degli istoni e l’azione degli RNA non codificanti.

- **La metilazione del DNA** inibisce l'espressione genica, mentre la demetilazione può riattivare un gene.
- **La modifica degli istoni (**L’acetilazione , metilazione ,fosforilazione ed ubiquitinazione) consiste nell'aggiunta di gruppi chimici a queste proteine, che si trovano sulle quali il lungo filamento di DNA si avvolge.
- **Gli RNA non codificanti** possono silenziare l'espressione dei geni associandosi agli RNA codificanti.



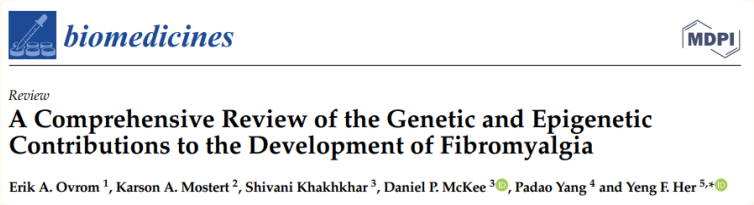
La **metilazione del DNA** consiste nell'aggiunta di un gruppo chimico (metile, formula - CH_3) in punti specifici del DNA. In genere la metilazione blocca l'espressione del gene e di fatto lo inattiva, per esempio impedendo ad apposite proteine di trascrivere il DNA. Il processo opposto, ovvero la rimozione del gruppo metile, è detto **demetilazione** e, in genere, può portare a riattivare un gene, permettendone l'espressione.

Stress ed epigenetica ?

- Prima si pensava che il genoma subisse importanti cambiamenti solo durante lo sviluppo embrionale, regolando l'attivazione o la repressione di classi di geni specifici nella differenziazione cellulare. Studi recenti dimostrano che la **metilazione del DNA può cambiare anche nei neuroni maturi in risposta a segnali ambientali.**
- I piccoli ratti che ricevono alti livelli di stimolazione materna subiscono una demetilazione del gene del recettore dei glicocorticoidi nell'ippocampo, con un aumento a lungo termine dei livelli di trascrizione.
- ***Questo si traduce in maggiori quantità del recettore e in un fenotipo caratterizzato da ridotti livelli di stress.***
- Cambiamenti epigenetici cruciali sono implicati anche nella regolazione dei processi di apprendimento e memoria.

I fattori genetici sono probabilmente responsabili fino al 50% della suscettibilità alla malattia. (geni candidati sono SLC64A4, TRPV2, MYT1L e NRXN3)

I parametri di eccitabilità corticale sono alterati in parallelo con le variazioni del livello di metilazione nel sangue periferico dei pazienti di fibromialgia.



- Lee et al. hanno studiato l'associazione epigenetica tra esperienze infantili avverse come stupro, abuso fisico e abuso emotivo e lo sviluppo di FM.
- DAP3 e miR2100 erano ipermetilati in individui FM con esperienze infantili avverse DAP3 è una proteina che svolge un ruolo chiave nella respirazione cellulare e nell'apoptosi.
- **Gerra et al. hanno riferito che gli individui con FM hanno ipermetilazione del gene del recettore metabotropico del glutammato 2 (GRM2), che porta ad un'alterata elaborazione del dolore.**

Association of DNA methylation changes and FM.

Genes	Main Results
Sp1 *C/EBPalpha*	DNA methylation at Sp1 and C/EBPalpha correlated with widespread pain syndrome and decreased leptin expression and serum leptin levels in FM individuals.
GRM2	Hypermethylation of *GRM2* in FM individuals compared to healthy controls.
BDNF	Hypomethylation at exon 9 of the *BDNF* gene. BDNF levels are increased in FM individuals.
BDNF, *NAT15*, *HDAC4*, *PRKCA*, *RTN1*, *PRKG1*	Differentially methylated in these genes in women with FM compared to healthy controls. These genes are involved in neuron differentiation/nervous system development, skeletal/organ system development, and chromatin compaction.
DAP3 miR2100	Hypermethylation at these sites in FM individuals with adverse childhood experiences compared to FM individuals without adverse childhood experiences.
69% of the differentially methylated genes are in the MAPK signaling pathway, regulation of the actin cytoskeleton, endocytosis, and neuroactive ligand receptor pathways.	FM individuals had 1610 differentially methylated positions compared to healthy controls.
MDH2, *CLEC3B*, *HSPB6*	In a 281-twin individual epigenome-wide analysis of DNA methylation, CpG loci with significant *p*-values were MDH2, tetranectin, and heat shock protein beta-6.

GRM2: metabotropic glutamate receptor 2; *BDNF*: brain derived neurotrophic factor; *NAT15*: N-acetyltransferase 15; *HDAC4*: histone deacetylase 4; *PRKCA*: protein kinase C alpha; *RTN1*: reticulon 1a; *PRKG1*: protein kinase cGMP-dependent 1a; *DAP3*: death associated protein 3; MAPK: mitogen-activated protein kinase 1; *MDH2*: malate dehydrogenase 2; *CLEC3B*: C-type lectin domain family 3 member B; *HSPB6*: heat shock protein B6.

Studies on DNA methylation and FM

- The first study investigating epigenetic changes in FM women compared to controls was a genome-wide methylation pattern analysis that **highlights 69 differentially methylated sites in cases against controls**, and 91% of these sites were responsible of **an increased micronuclei frequency in FM women.**
- This correlation should be further investigate as useful tool evaluation and/or diagnosis.

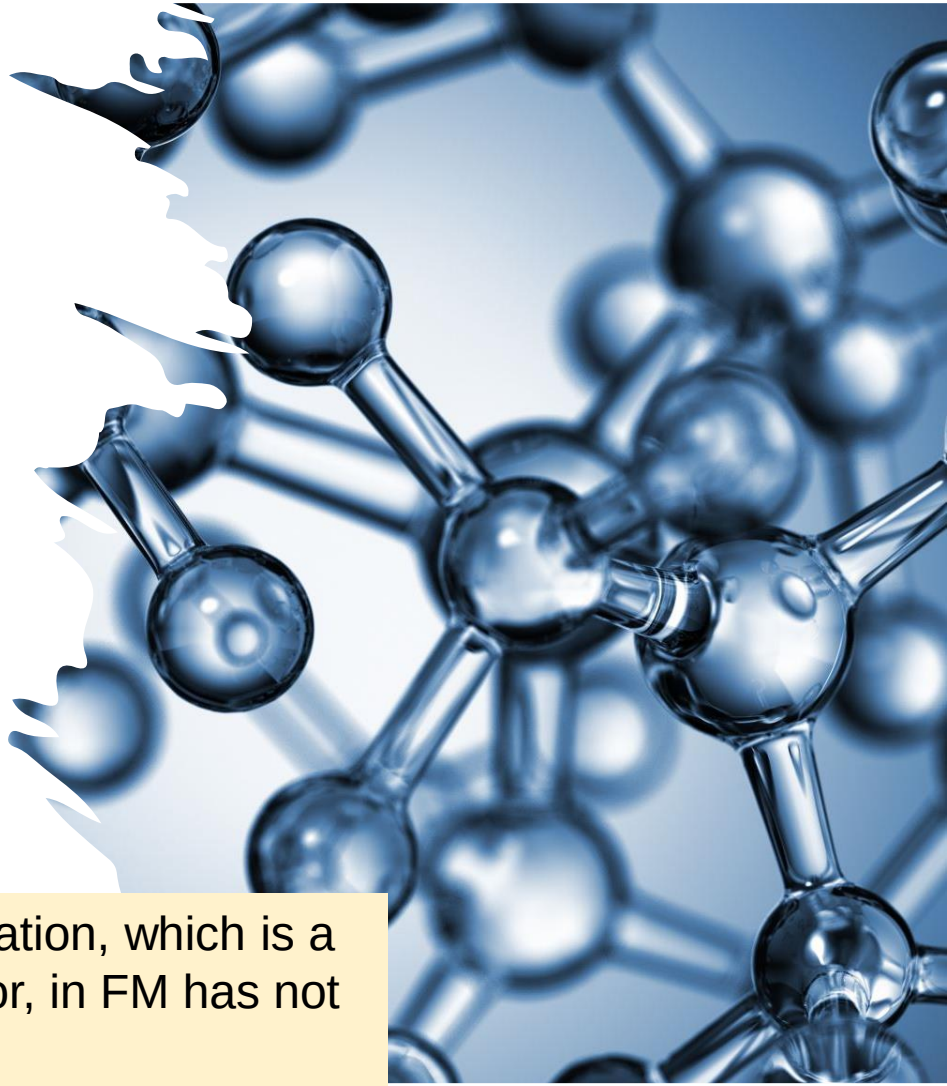
Menzies V, Lyon DE, Archer KJ, Zhou Q, Brumelle J, Jones KH, Gao G, York TP, and Jackson-Cook C. Epigenetic alterations and an increased frequency of micronuclei in women with fibromyalgia. Nurs Res Pract 2013; 2013: 795784

Studies on DNA methylation and FM

- Ciampi de Andrade et al.74 have investigated DNA methylation state in blood samples from a cohort of 24 FM cases and 24 healthy controls.
- **The results identified 1610 differentially methylated positions**: **1042 (65%) were found hypomethylated and 568 (35%) hypermethylated in cases compared to controls**.
- Most of the differentially methylated genes were related to signal transduction and calcium signaling, MAPK signaling pathway, regulation of actin cytoskeleton endocytosis, and neuroactive ligand-receptor interaction pathways.
- In general, the differentially methylated sites identified associated with FM map on genes involved in biological processes as DNA repair, immune system, and membrane transport genes

Ciampi de Andrade D, Maschietto M, Galhardoni R, Gouveia G, Chile T, Victorino Krepischi AC, Dale CS, Brunoni AR, Parravano DC, Cueva Moscoso AS, Raicher I, Kaziyama HHS, Teixeira MJ, and Brentani HP. Epigenetics insights into chronic pain: DNA hypo- methylation in fibromyalgia-a controlled pilot-study. Pain 2017; 158: 1473–1480.

Come l'epigenetica può influenzare la regolazione dell'espressione genica?



Sono tre i meccanismi principali: la metilazione del DNA, la modificazione degli istoni e l'azione degli RNA non codificanti.

- **La metilazione del DNA** inibisce l'espressione genica, mentre la demetilazione può riattivare un gene.
- **La modifica degli istoni (**L'acetilazione , metilazione ,fosforilazione ed ubiquitinazione) consiste nell'aggiunta di gruppi chimici a queste proteine, che si trovano sulle quali il lungo filamento di DNA si avvolge.
- **Gli RNA non codificanti** possono silenziare l'espressione dei geni associandosi agli RNA codificanti.

Moreover, histone modification, which is a major epigenetic modulator, in FM has not been reported

Come l’epigenetica può influenzare la regolazione dell’espressione genica?

Sono tre i meccanismi principali: la metilazione del DNA, la modificazione degli istoni e l’azione degli RNA non codificanti.

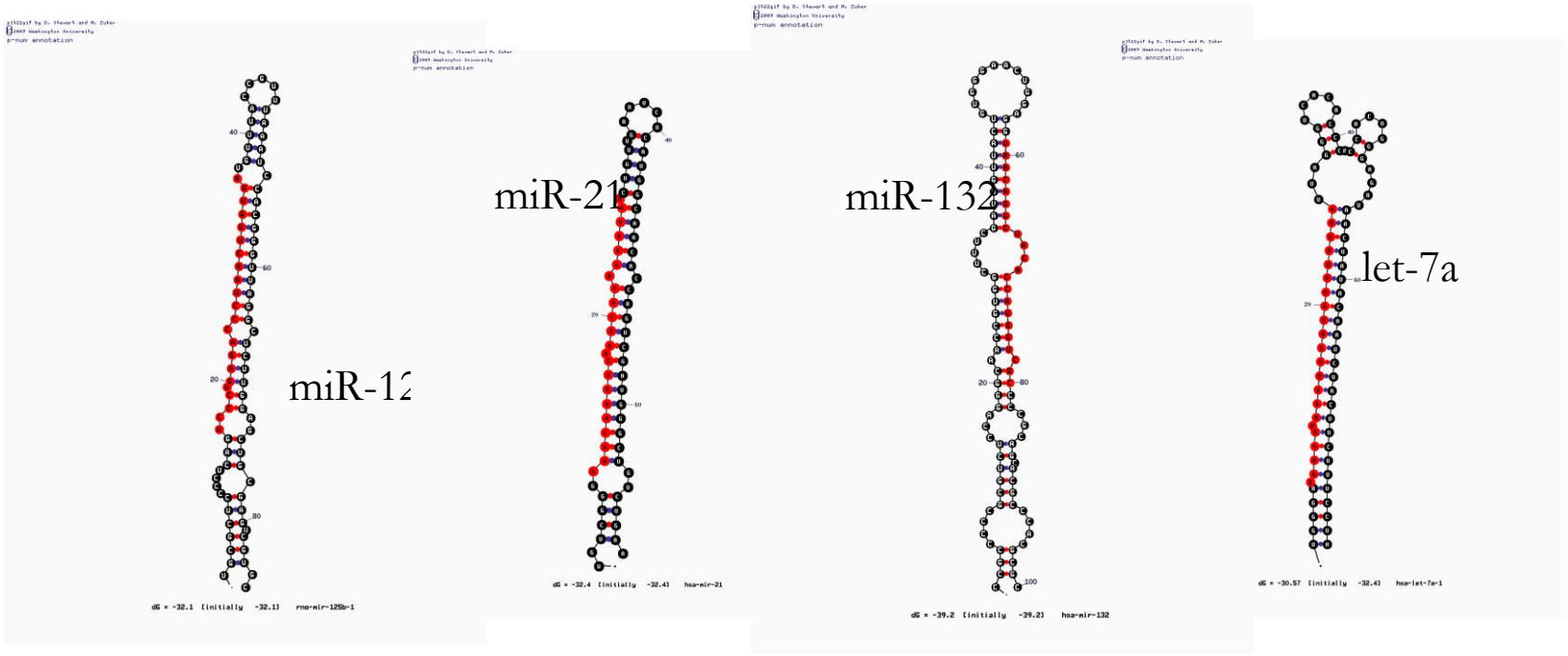
- **La metilazione del DNA** inibisce l'espressione genica, mentre la demetilazione può riattivare un gene.
- **La modifica degli istoni (**L’acetilazione , metilazione ,fosforilazione ed ubiquitinazione) consiste nell'aggiunta di gruppi chimici a queste proteine, che si trovano sulle quali il lungo filamento di DNA si avvolge.
- **Gli RNA non codificanti** possono silenziare l'espressione dei geni associandosi agli RNA codificanti.

MicroRNA profiles

- MicroRNAs are short non-coding RNA molecules approximately 20 to 22 nucleotides in length, highly evolutionary conserved; **these factors have a fundamental role in the regulation of gene expression** in disease processes and physiological pathways, since they are involved in cell growth, differentiation, stress response, and tissue remodeling;
- they exert **several regulatory functions** as mRNA cleavage, translational repression, or mRNAs deadenylation within cells where they were initially transcribed.
- **MicroRNAs regulate at least 30% of human genes, and each microRNAs can repress hundreds of genes**.

Cos'è un microRNA?

–> breve sequenza di RNA non codificante (circa 22 nucleotidi)

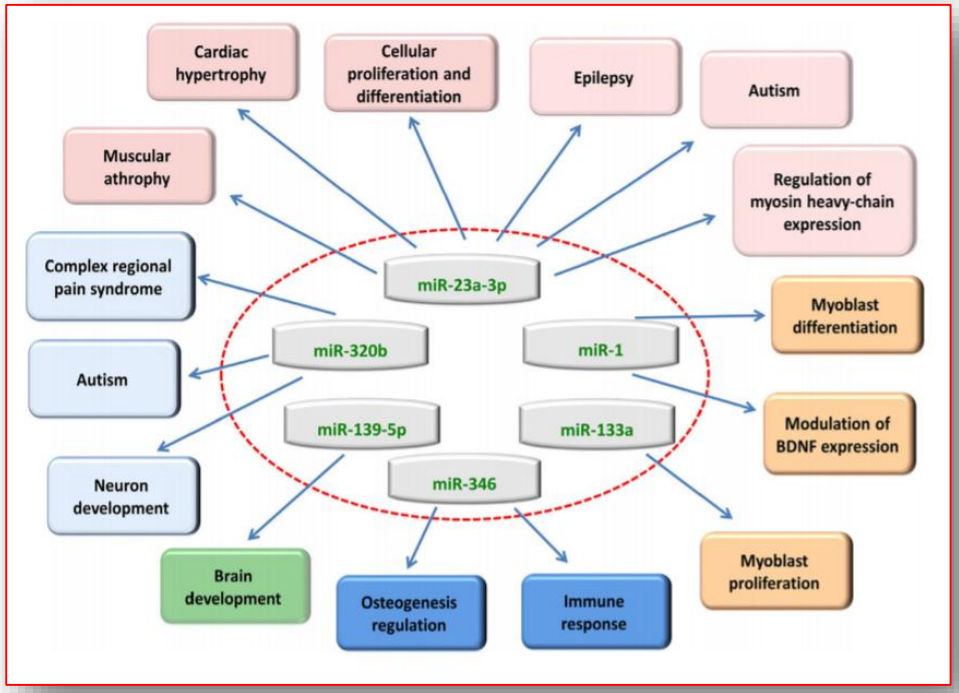


miRNA expression in FM

- Masotti et al.[90] conducted a study on accurately selected FM patients, excluding drugs' use and thus avoiding variations of miRNA expression arising from analgesics.
- The expression of **six miRNAs has proved to be downregulated** (miR-23a-3p, miR-1, miR- 133a, miR-346, miR-139-5p, and miR-320b) in FM patients compared to controls and, interestingly, miR-23a was downregulated in both CSF[82] and serum of FM patients, although not significantly associated with FM symptoms

Masotti A, Baldassarre B, Guzzo MP, Iannuccelli C, Barbato C, and Di Franco M. Circulating microRNA profiles as liquid biopsies for the characterization and diagnosis of fibromyalgia syndrome. Mol Neurobiol 2017; 54: 7129–7136.

Questo lavoro mirava a studiare i profili circolanti di microRNA (miRNA) nel siero e nella saliva di pazienti affetti da sindrome fibromialgica (FM), correlando i loro valori di espressione con parametri clinici e clinimetrici e suggerendo un modello matematico per la diagnosi di FM.



Mol Neurobiol
DOI 10.1007/s12035-016-0235-2

Circulating microRNA Profiles as Liquid Biopsies for the Characterization and Diagnosis of Fibromyalgia Syndrome

Andrea Masotti[1] · Antonella Baldassarre[1] · Maria Paola Guzzo[2] · Cristina Iannuccelli[2] · Christian Barbato[3] · Manuela Di Franco[2]

179 miRNA analizzati

Cinque di questi miRNA sono stati inclusi in un modello predittivo lineare . Sei miRNA sono stati trovati downregolati che ha raggiunto una sensibilità molto elevata (100%) e un'elevata specificità (83,3%).

Associations of micro-RNA and FM.

micro-RNA103a, micro-RNA107		Positive association between micro-RNA103a and micro-RNA-107 expressions and adaptive coping in FM individuals.
micro-RNA-23a-3p, micro-RNA-1, micro-RNA-133a, micro-RNA-346, micro-RNA-139-5p, and micro-RNA-320b		micro-RNA-23a-3p, micro-RNA-1, micro-RNA-133a, micro-RNA-346, micro-RNA-139-5p, and micro-RNA-320b were downregulated in FM individuals.
micro-RNA-let-7d	Insulin-like growth factor-1	Higher levels of micro-RNA-let-07d correlated with reduced small nerve fiber density in FM individuals. Insulin-like growth factor-1 is a downstream target of micro-RNA-let-07d that may lead to small nerve fiber impairment.
hsa-micro-RNA223-3p, hsa-micro-R451a, hsa-micro-RNA338-3p, hsa-micro-RNA143-3p, hsa-micro-RNA145-5p, and hsa-micro-RNA-21-5p		hsa-micro-RNA223-3p, hsa-micro-R451a, hsa-micro-RNA338-3p, hsa-micro-RNA143-3p, hsa-micro-RNA145-5p, and hsa-micro-RNA-21-5p are significantly downregulated in FM individuals.
micro-RNA-21-5p, micro-RNA-145-5p, micro-RNA-29a-3p, micro-RNA-99b-5p, micro-RNA-125b-5p, micro-RNA-23a-3p, 23b-3p, micro-RNA-195-5p, and micro-RNA-223-3p		Expressions of micro-RNA-21-5p, micro-RNA-145-5p, micro-RNA-29a-3p, micro-RNA-99b-5p, micro-RNA-125b-5p, micro-RNA-23a-3p, 23b-3p, micro-RNA-195-5p, and micro-RNA-223-3p are significantly lower in FM individuals compared with healthy controls. MiR-145 is associated with pain and fatigue.

MiRNA differenzialmente espressi nelle donne FM rispetto ai controlli sani.

miRNA	Regolamento in FM	Campione biologico	Sintomi clinici
miR-145-5p [82]	Giù	CSF	Dolore e stanchezza
miR-21-5p [82]	Giù	CSF	Alterazione dei circuiti centrali
miR-195-5p [82]	Giù	CSF	Alterazione del metabolismo energetico e della crescitaDemenza
miR-223-3p [82]	Giù	CSF	Dolore infiammatorio
miR-23a-3p [82]	Giù	CSF	Nessuna correlazione trovata
miR-23b [82]	Giù	CSF	Alterazione dell'espressione del recettore μ-oppioide Alterazione dell'esito del trattamento a lungo termine con morfina
miR-320a [82]	Su	Siero	Soglia del dolore
miR-107 miR-151a-5p miR-142-3p [86]	Giù	Siero	Nessuna correlazione trovata
miR-30b-5p [86]	Giù	Siero	Quantità di sonno
miR-374b-5p [86]	Giù	Siero	Soglia del dolore
miR-103a-3p let-7a-5p [86]	Giù	Siero	Quantità di sonno Dolore
miR-451a miR-338-3p miR-143-3p miR-145-5p miR-223-3p [89]	Giù	PBMC	Nessuna correlazione trovata
miR-23a-3p [90]	Giù	Siero	Mantenimento dell'integrità del muscolo scheletrico
miR-1 miR-133a miR-346 miR-139-5p miR-320b [90]	Giù	SerumSaliva	Nessuna correlazione trovata

Alcuni miRNA (evidenziati) sono ugualmente deregolati in diversi tessuti come ***miR223-3p*** e ***miRNA-145-5p*** che sono stati trovati inibiti sia nelle PBMC che nel liquido cerebrospinale dei pazienti affetti da FM, e ***miR-23a-3p*** che è stato trovato downregolato in entrambi siero e CSF. CSF: liquido cerebrospinale; FM: fibromialgia; PBMC: cellule mononucleate del sangue periferico.

Conclusions

- The genetic and epigenetic etiologies of FM remain elusive.
- **There is no direct genetic variant or epigenetic modification that results in the development of FM**.
- Genetic studies focusing on polymorphisms in genes involved in the catecholaminergic and serotonergic pathways reveal mixed outcomes.
- Depending on the population studied, the genes involved may either be associated with an increased risk of developing FM or no risk.
- Similarly, it is unclear whether these gene polymorphisms are associated with the severity of FM symptoms.
- Meanwhile, genetic studies of polymorphisms in genes involved in pain processing, inflammation, and oxidative stress suggest an underlying connection to the severity of FM symptoms.

Table 1. SNPs related to genes potentially involved in fibromyalgia's pathogenesis.

SNPs	Gene	Clinical relevance
5-HTTLPR[24]	*SLC6A4*	Temporal mandibular joint disorder Depression Psychological disorders
rs4680[28]	*COMT*	Depression Anxiety Disability
rs1048101[29]	*HTR2A*	FIQ disability
rs6313[30,31]	*HTR2A*	Fibromyalgia onset
rs11127292[32]	*MYT1L*	Cognitive disability
Intronic CNV[32]	*NRXN3*	Autism
rs819219, rs4129256[33]	*TAAR1*	Impaired dopamine availability Enhanced pain sensitivity
rs10799897, rs2842003, rs2805050[33]	*RGS4*	Alteration in the descending inhibition of pain perception
rs6454674, rs1078602, rs10485171[33]	*CNR1*	Migraine Irritable bowel syndrome Post-traumatic stress disorder
rs642544, rs17104711, rs2510177, rs10895837[33]	*GRIA4*	Central sensitization

SNP: Single Nucleuotide Polymorphism; CNV: copy number variant.

Table 2. Genes differentially methylated in FM women.

Gene	Biological samples	Physiological function	Associations
BDNF[73]	Blood	Neuron Differentiation/nervous system development	Mood disorders Alzheimer Parkinson Huntington's disease
NAT15[73]	Blood	Histone acetyltransferase Chromatin compaction	Acetylation process Facilitation of transcription process
HDAC4[73]	Blood	Deacetylation of the core histones Muscle maturation	Deacetylation's process Gene silencing
PRKCA[73]	Blood	Cell signaling pathways	Post-traumatic stress syndrome Emotional memory formation Cancer
RTN1[73]	Blood	Secretion or membrane trafficking in neuroendocrine cells	Neurological diseases Cancer
PRKG1[73]	Blood	Regulation cardiovascular and neuronal functions Relax smooth muscle tone Prevent platelet aggregation Modulate cell growth	Aortic aneurysm Phosphoglycerate kinase deficiency
SLC17A9[74]	Blood	Regulation neuronal differentiation	Neuronal plasticity
TFAP2A[74]	Blood	Survival functions of sympathetic progenitors and noradrenergic neurons	Neuronal circuits

A general hypomethylated pattern in FM patients compared to healthy subjects seem to be revealed, considering the first studies on DNA methylation and FM.

Review Article

MOLECULAR PAIN

Molecular Pain
Volume 15: 1–12

DOI: 10.1177/1744806918819944
journals.sagepub.com/home/mpx
SAGE

Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers

Simona D'Agnelli[1], Lars Arendt-Nielsen[2], Maria C Gerra[2], Katia Zatorri[1], Lorenzo Boggiani[3], Marco Baciarello[1], and Elena Bignami[1]

Abstract

Fibromyalgia is a disease characterized by chronic widespread pain with additional symptoms, such as joint stiffness, fatigue, sleep disturbance, cognitive dysfunction, and depression. Currently, fibromyalgia diagnosis is based exclusively on a comprehensive clinical assessment, according to 2016 ACR criteria, but validated biological biomarkers associated with fibromyalgia have not yet been identified. Genome-wide association studies investigated genes potentially involved in fibromyalgia pathogenesis highlighting that genetic factors are possibly responsible for up to 50% of the disease susceptibility. Potential candidate genes found associated to fibromyalgia are *SLC64A4*, *TRPV2*, *MYT1L*, and *NRXN3*. Furthermore, a gene-environmental interaction has been proposed as triggering mechanism, through epigenetic alterations: In particular, fibromyalgia appears to be characterized by a hypomethylated DNA pattern, in genes implicated in stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities. Differences in the genome-wide expression profile of microRNAs were found among multiple tissues, indicating the involvement of distinct processes in fibromyalgia pathogenesis. Further studies should be dedicated to strength these preliminary findings, in larger multicenter cohorts, to identify reliable directions for biomarker research and clinical practice.

Keywords

Fibromyalgia, genetics, epigenetics, biomarkers, genome-wide association study, DNA methylation, miRNAs

Date Received: 11 September 2018; revised 3 November 2018; accepted: 21 November 2018

Introduction

Fibromyalgia (FM) is a common and complex chronic pain syndrome, affecting 1% to 5% of the population,[1] characterized by chronic widespread pain persisting for more than three months without any obvious organic lesion. Joint stiffness, fatigue, sleep disturbance, cognitive dysfunction, and depression are additional symptoms found associated with FM.[2,3]

The disease is more common in female than male,[4] with a ratio of 2:1 similarly to other chronic pain conditions, and it can occur at any age.[5] Since women show lower pain threshold and more severe symptoms than men,[6] the majority of researches focused on female subjects. However, the pathogenesis of FM is not fully understood, especially because compared to neuropathic conditions in FM, the source of sensory inputs is unknown;[7] some hypothesis on peripheral and central pathophysiological mechanisms have been proposed. Evidence support a central sensitization and a central dysregulation at a spinal and supra-spinal levels in FM patients compared to controls: FM patients showed an exaggerated pain response after sensory stimulation and

[1]Anesthesiology, Critical Care and Pain Medicine Division, Department of Medicine and Surgery, University of Parma, Parma, Italy
[2]Department of Health Science and Technology, Aalborg University, Denmark
[3]Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

Corresponding Author:
Simona D'Agnelli, Department of Medicine and Surgery, University of Parma, Via Gramsci 14 Road, 43126 Parma, Italy.
Email: simona.dagnelli@studenti.unipr.it

Table 3. MiRNAs differentially expressed in FM women compared with healthy controls.

miRNAs	Regulation in FM	Biological sample	Clinical symptoms
miR-145-5p[82]	Down	CSF	Pain and fatigue
miR-21-5p[82]	Down	CSF	Alteration of central circuits
miR-195-5p[82]	Down	CSF	Alteration in energy metabolism and growth Dementia
miR-223-3p[82]	Down	CSF	Inflammatory pain
miR-23a-3p[82]	Down	CSF	No correlation found
miR-23b[82]	Down	CSF	Alteration of μ-opioid receptor expression Alteration of outcome to long-term morphine treatment
miR-320a[82]	Up	Serum	Pain threshold
miR- 107	Down	Serum	No correlation found
miR-151a-5p			
miR-142-3p[86]			
miR-30b-5p[86]	Down	Serum	Sleep quantity
miR-374b-5p[86]	Down	Serum	Pain threshold
miR-103a-3p	Down	Serum	Sleep quantity
let-7a-5p[86]			Pain
miR-451a	Down	PBMCs	No correlation found
miR-338-3p			
miR-143-3p			
miR-145-5p			
miR-223-3p[89]			
miR-23a-3p[90]	Down	Serum	Maintenance of skeletal muscle integrity
miR-1	Down	Serum	No correlation found
miR-133a		Saliva	
miR-346			
miR-139-5p			
miR-320b[90]			

Some miRNAs (highlighted) are equally deregulated across different tissue like ***miR223-3p*** and ***miRNA-145-5p*** that have been found to be inhibited in both PBMCs and CSF of FM patients, and ***miR-23a-3p*** that has been found downregulated in both serum and CSF. CSF: cerebro spinal fluid; FM: fibromyalgia; PBMC: peripheral blood mononuclear cells.

Review Article

MOLECULAR PAIN

Molecular Pain
Volume 15: 1–12

DOI: 10.1177/1744806918819944
journals.sagepub.com/home/mpx
SAGE

Fibromyalgia: Genetics and epigenetics insights may provide the basis for the development of diagnostic biomarkers

Simona D'Agnelli[1], Lars Arendt-Nielsen[2], Maria C Gerra[2], Katia Zatorri[1], Lorenzo Boggiani[3], Marco Baciarello[1], and Elena Bignami[1]

Abstract

Fibromyalgia is a disease characterized by chronic widespread pain with additional symptoms, such as joint stiffness, fatigue, sleep disturbance, cognitive dysfunction, and depression. Currently, fibromyalgia diagnosis is based exclusively on a comprehensive clinical assessment, according to 2016 ACR criteria, but validated biological biomarkers associated with fibromyalgia have not yet been identified. Genome-wide association studies investigated genes potentially involved in fibromyalgia pathogenesis highlighting that genetic factors are possibly responsible for up to 50% of the disease susceptibility. Potential candidate genes found associated to fibromyalgia are *SLC64A4*, *TRPV2*, *MYT1L*, and *NRXN3*. Furthermore, a gene-environmental interaction has been proposed as triggering mechanism, through epigenetic alterations: In particular, fibromyalgia appears to be characterized by a hypomethylated DNA pattern, in genes implicated in stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities. Differences in the genome-wide expression profile of microRNAs were found among multiple tissues, indicating the involvement of distinct processes in fibromyalgia pathogenesis. Further studies should be dedicated to strength these preliminary findings, in larger multicenter cohorts, to identify reliable directions for biomarker research and clinical practice.

Keywords

Fibromyalgia, genetics, epigenetics, biomarkers, genome-wide association study, DNA methylation, miRNAs

Date Received: 11 September 2018; revised 3 November 2018; accepted: 21 November 2018

Introduction

Fibromyalgia (FM) is a common and complex chronic pain syndrome, affecting 1% to 5% of the population,[1] characterized by chronic widespread pain persisting for more than three months without any obvious organic lesion. Joint stiffness, fatigue, sleep disturbance, cognitive dysfunction, and depression are additional symptoms found associated with FM.[2,3]

The disease is more common in female than male,[4] with a ratio of 2:1 similarly to other chronic pain conditions, and it can occur at any age.[5] Since women show lower pain threshold and more severe symptoms than men,[6] the majority of researches focused on female subjects. However, the pathogenesis of FM is not fully understood, especially because compared to neuropathic conditions in FM, the source of sensory inputs is unknown;[7] some hypothesis on peripheral and central pathophysiological mechanisms have been proposed. Evidence support a central sensitization and a central dysregulation at a spinal and supra-spinal levels in FM patients compared to controls: FM patients showed an exaggerated pain response after sensory stimulation and

[1]Anesthesiology, Critical Care and Pain Medicine Division, Department of Medicine and Surgery, University of Parma, Parma, Italy
[2]Department of Health Science and Technology, Aalborg University, Denmark
[3]Department of Chemistry, Life Sciences and Environmental Sustainability, University of Parma, Parma, Italy

Corresponding Author:
Simona D'Agnelli, Department of Medicine and Surgery, University of Parma, Via Gramsci 14 Road, 43126 Parma, Italy.
Email: simona.dagnelli@studenti.unipr.it

Conclusions

- DNA methylation studies comparing FM individuals to healthy controls or in twins have suggested that **certain methylated genes may be associated with the development of FM**.
- However, there are **no molecular explanations of how this leads to FM susceptibility.**
- Likewise, many microRNAs have been found in FM individuals compared to controls, but their targets and effects are still unknown

Future Directions

- The mechanism underlying **fatigue in FM** is still poorly understood.
- There is discord in the current literature as to **whether fatigue is a centrally mediated process or the result of differences in the percentage of type 1 muscle fibers** .
- It is worth noting that fatigue in **FM occurs more frequently in women**, and gender differences may be a good area for future research.
- Indeed, **sexually dimorphic dorsal root ganglia** have been discovered between genders, and research is ongoing as to whether **differences in the nervous system explain the increased prevalence of FM in women** .

Martínez-Lavín, M. Fibromyalgia in women: Somatisation or stress-evoked, sex-dimorphic neuropathic pain? *Clin. Exp. Rheumatol.* **2021**, *39*, 422–425

Future Directions

.

- The role of **increased glutamatergic tone in centrally mediated pain** and drugs that modulate NMDA receptor activation are another area of research that should be further explored.
- Furthermore, **genome wide association studies** thus far have identified several FM-associated genetic variants the rs11127292 SNP at the MYT1L locus involved in neuronal differentiation and **a copy number variation in the NRXN3 locus involved in cell adhesion.**
- Despite these variants not being statistically significant, further studies may consider using **FM individuals from different ethnic backgrounds**

Conclusions

- Regarding the differential gene expressions found in FM individuals, a possible molecular and cellular explanation may be related to the **factors that influence epigenetic modifications, such as diet, medical comorbidities, psychological stressors, physical activity, environmental pollutants, and sleep**.
- **Depending on the temporal relationships** between FM and these factors, the gene expression profile may vary

Kubota,T.;Miyake,K.;Hirasawa,T.Epigenetic understanding of gene-environment interactions in psychiatric disorders: A new concept of clinical genetics. *Clin. Epigenet.* **2012**, *4*, 1