Fibromyalgia: A Look at Genes and Behavior

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Presentation Objectives

1. Define fibromyalgia syndrome and describe its history, diagnosis, and common treatments;

2. Present recent findings that support genetic contributions to the development of fibromyalgia;

3. Describe racial differences in pain severity, rates of depression, and levels of physical functioning among adult patients with fibromyalgia.
Fibromyalgia

Definition, History, Diagnosis, and Treatment
History of Fibromyalgia: Past to Present

Fatma Inanici, MD and Muhammad B. Yunus, MD

Fibromyalgia syndrome (FMS) is now a recognized clinical entity causing chronic and disabling pain. For several centuries, muscle pains have been known as rheumatism and then as muscular rheumatism. The term fibrositis was coined by Gowers in 1904 and was not changed to fibromyalgia until 1976. Smythe laid the foundation of modern FMS in 1972 by describing widespread pain and tender points. The first sleep electroencephalogram study was performed in 1975. The first controlled clinical study with validation of known symptoms and tender points was published in 1981. This same study also proposed the first data-based criteria. The important concept that FMS and similar conditions are interconnected was proposed in 1984. The first American College of Rheumatology criteria were published in 1990 and neurohormonal mechanisms with central sensitization were developed in the 1990s. Serotonergic/norepinephric drugs were first shown to be effective in 1986.

Fever in 1592 [1]. By the 18th century, physicians started to distinguish articular rheumatism with deforming features from painful but nondeforming soft tissue musculoskeletal disorders, which generally were called muscular rheumatism [2].

Since the 19th century, various forms of muscular rheumatism under different nomenclature have been described [1,3–6,7,8–21] (Table 1). The early definitions were vague and it is almost impossible to distinguish between generalized and regional/localized types. Important chronologic developments that have had an impact on FMS literature are shown in Table 2.

Literature on muscular rheumatism was published by German, Scandinavian, and British physicians from the beginning of 1800s. In 1815, William Balfour [22], a surgeon from Edinburgh, described nodules and suggested that inflammation in muscle connective tissue is the cause for nodules and pain. Balfour also first reported focal tenderness, referred to as tender points, in 1824 [5]. In 1827, another British physician, Scudamore [23], identified rheumatism as “pain of a peculiar kind, usually attended with inflammatory action, affecting the white fibrous textures belonging to muscles and joints, such as tendons, aponeuroses, and ligaments; the synovial membranes of the bursae and tendons; and
Most Relevant History

Fibromyalgia first published in 1976
First clinical trial validating symptoms 1981
First clinical relationship to other established disorder 1984
PNS emphasized in pathogenesis 1984
First report of efficacy of tricyclic in a controlled FMS trials 1986
Suggested overlaps with psychiatric illnesses 1989
HPA axis other CNS factors emphasized in pathogenesis 1993
First US population-based study 1995
Confirmation of temporal summation in FMS 2001

Table 2. Important chronologic developments with emphasis on the first published report that made a subsequent impact on FMS literature

<table>
<thead>
<tr>
<th>First author [reference number]</th>
<th>Year</th>
<th>Important developments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillaume de Ballou [1]</td>
<td>1952</td>
<td>Initial naming of muscular rheumatism</td>
</tr>
<tr>
<td>Gowers [75]</td>
<td>1904</td>
<td>First use of the term fibrositis</td>
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<tr>
<td>Copeman [55]</td>
<td>1945</td>
<td>First controlled study showing that fibrotic nodules are as frequent in patients with FMS as in control subjects</td>
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<tr>
<td>Trauer [57-]</td>
<td>1968</td>
<td>First near-modern description of FMS with systemic features</td>
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<tr>
<td>Smythe [61+*]</td>
<td>1972</td>
<td>First modern description of FMS with widespread pain and multiple tender points at specified sites, along with a set of working criteria that stimulated clinical interest and research</td>
</tr>
<tr>
<td>Moldofsky [62++*]</td>
<td>1973</td>
<td>First EEG sleep study showing a disturbance of non-rapid eye movement sleep by an intrusion</td>
</tr>
<tr>
<td>Hench [21]</td>
<td>1976</td>
<td>First use of the term fibromyalgia</td>
</tr>
<tr>
<td>Smythe [63]</td>
<td>1977</td>
<td>Brought into focus the importance of sleep with sleep EEG findings and suggested a revised set of criteria for FMS that generated further interest in research</td>
</tr>
<tr>
<td>Yunus [64++*]</td>
<td>1981</td>
<td>First description of a controlled clinical study validating previous anecdotal symptoms and tender points; addition of new symptoms (eg, subjective swelling and paresthesia); first data-based suggested criteria; beginning of a new concept of FMS association with other functional syndromes (eg, irritable bowel syndrome); popularization of the term fibromyalgia</td>
</tr>
<tr>
<td>Yunus [68++*]</td>
<td>1984</td>
<td>First depiction (by a Venn diagram) of the important modern concept that FMS and other functional syndromes have overlapping features, have mutual associations, and are interconnected</td>
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<tr>
<td>Wolfe [74]</td>
<td>1984</td>
<td>First report of a high prevalence of FMS in rheumatoid arthritis</td>
</tr>
<tr>
<td>Yunus [72]</td>
<td>1985</td>
<td>First description of juvenile FMS by a controlled study</td>
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<tr>
<td>Carette [104], Goldenberg [105]</td>
<td>1986</td>
<td>First report of efficacy of amitriptyline by randomized, controlled trial</td>
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<tr>
<td>Verhey [99]</td>
<td>1988</td>
<td>First report of elevated substance P in cerebrospinal fluid of patients with FMS</td>
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<tr>
<td>Bennett [106]</td>
<td>1988</td>
<td>First report of efficacy of cyclobenzaprine by randomized control trial</td>
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<tr>
<td>Yunus [107]</td>
<td>1989</td>
<td>First blunted, controlled study of muscle biopsy showing normal results, resulting in a new focus on the central nervous system</td>
</tr>
<tr>
<td>Bennett [102]</td>
<td>1989</td>
<td>First demonstration of a lack of aerobic fitness in patients with FMS compared with normal control subjects with implications for research findings (eg, muscle studies)</td>
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<tr>
<td>Hudson [69*]</td>
<td>1989</td>
<td>Suggested overlaps between functional and psychiatric syndromes by affective spectrum mechanism</td>
</tr>
<tr>
<td>Wolfe [58++]</td>
<td>1990</td>
<td>Publication of the American College of Rheumatology criteria for classification of FMS in a well-designed, blinded study</td>
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<tr>
<td>Burkhardt [86++*]</td>
<td>1991</td>
<td>Development of a validated questionnaire (Fibromyalgia Impact Questionnaire) for assessing physical and psychiatric functions in FMS</td>
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<tr>
<td>Bennett [95]</td>
<td>1992</td>
<td>Demonstration of a low-serum somatomedin C (growth hormone)</td>
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<tr>
<td>Yunus [73++]</td>
<td>1992</td>
<td>Proposal of a new model for fibromyalgia pathogenesis with emphasis on central aberrant pain mechanisms</td>
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<tr>
<td>Granger [87], Arroyo [88]</td>
<td>1993</td>
<td>First demonstration of central sensitization on FMS</td>
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<tr>
<td>Greip [93]</td>
<td>1993</td>
<td>First demonstration of hypothalamic-pituitary-adrenal axis abnormalities in a well-designed study showing exaggerated ACTH release with relative hyporesponsiveness</td>
</tr>
<tr>
<td>Crofford [94]</td>
<td>1994</td>
<td>Important confirmation of hypothalamic-pituitary-adrenal axis dysfunction</td>
</tr>
<tr>
<td>Russell [1]</td>
<td>1994</td>
<td>Important confirmation of elevated substance P in cerebrospinal fluid of patients with FMS</td>
</tr>
<tr>
<td>Wolfe [75]</td>
<td>1995</td>
<td>First US population study showing 2% prevalence of FMS</td>
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<tr>
<td>Mountz [91]</td>
<td>1995</td>
<td>First study of brain imaging by SPECT showing decreased cerebral blood flow in thalamus and caudate nuclei</td>
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<tr>
<td>Buskila [103]</td>
<td>1997</td>
<td>Report of a controlled study showing the role of trauma (cervical spine injury) in FMS</td>
</tr>
<tr>
<td>Yunus [97]</td>
<td>1999</td>
<td>First report of genetic linkage (unlike less reliable association studies) of FMS (with HLA) with later confirmation</td>
</tr>
<tr>
<td>Yunus [71++]</td>
<td>1999</td>
<td>An important review of evidence for central sensitization in FMS and other related syndromes; coined the term central sensitization syndromes</td>
</tr>
<tr>
<td>Staud [89+]</td>
<td>2001</td>
<td>Well-designed study demonstrating temporal summation</td>
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</tbody>
</table>

*Other important historic developments are described in the text.
ACTH—adrenocorticotropic hormone; EEG—electroencephalogram; FMS—fibromyalgia syndrome; SPECT—single photon emission computed tomography.
Definition of Fibromyalgia – Early 1990s

- "is a chronic and disabling condition of widespread musculoskeletal pain and tenderness, accompanied by secondary symptoms such as non-restorative sleep, morning stiffness, fatigue, and affective dysfunction, in the absence of any apparent "organic cause"

- Can be associated with IBS, dysmenorrhea, endometriosis, interstitial cystitis, fatigue, myofascial pain, lbp, tmjd, and mood disturbance

American College of Rheumatology (ACR), 1990
Definition of Fibromyalgia – More Current

- is a disorder of chronic widespread pain (CWP), and joint and muscle tenderness, affecting 2%-5% of the population, but more prevalent in adult women.
- can be accompanied by symptoms such as fatigue, sleep disturbance, cognitive dysfunction (“fibro fog”) and mood disturbances as well as headaches, and digestive problems

Feng, Zhang, Wu, Mao, Chang, Deng, Gao, Ouyang, Dery, Le, Longmate, Marek, St. Amand, Krontiris, Shively (2013). Discovery of potential new gene variants and inflammatory cytokine associations with fibromyalgia syndrome by whole exome sequencing. Plos ONE, 8(6), e65033.
American College of Rheumatology, 2013.
Etiology of FMS

Epidemiology of Musculoskeletal Pain
Including FMS and CWP

- Effects 2%-5% of the US general population, and 3%-6% of the world population
- More prevalent in women (3.4% than men .5%)
- More prevalent in adulthood than adolescence, and more in adolescence than teen years (prevalence increases with age)
  - Some evidence that adolescents from more affluent families are more likely to report musculoskeletal pains. Adolescents from lower income families were more likely to report chest pains (Rhee, 2005)
- In adults, lower education and income are associated with increased prevalence of pain (Bergman, Herrstrom, Hogstrom, 2001)
- More prevalent in individuals with existing rheumatic disease (lupus, RA, and problems with joints, muscles, and bones to include osteoarthritis)

Epidemiology of Musculoskeletal Pain
Including FMS and CWP

- Higher prevalence of recurrent musculoskeletal pains in White (29.7%) than Black adolescents (21.6%)
  Whites have a greater likelihood of developing FMS as compared to Blacks when another chronic illness exist (Friedman, Tew, Ahn, et al., 2003)
  - Not good prevalence by race in the US data
- Prevalence 3.2% in South Africa, 1.1% in New Zealand
- Black and Hispanic adults present with greater pain severity, lower pain tolerance, and an increased likelihood of seeking care for pain than their White counterparts (Edwards, Suresh, Lynch, 2001; McCraken, Palmer, Roy, 2005)
- Factors such as trust of the prescribing physician influence medication compliance in Black patients with FMS (Lempp, Hatch, Carville, Chov, 2009)
Diagnosis of FMS

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

- Widespread pain index (WPI) \( \geq 7 \) and symptom severity (SS) scale score \( \geq 5 \) or WPI \( 3 - 6 \) and SS scale score \( \geq 9 \).
- Symptoms have been present at a similar level for at least 3 months.
- The patient does not have another disorder that would otherwise explain the pain.

American College of Rheumatology, 2010
Widespread Pain Index (WPI)

- WPI: note the number areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19.
  - Shoulder girdle, left
  - Shoulder girdle, right
  - Upper arm, left
  - Upper arm, right
  - Lower arm, left
  - Lower arm, right
  - Hip (buttock, trochanter), left
  - Hip (buttock, trochanter), right
  - Upper leg, left
  - Upper leg, right
  - Lower leg, left
  - Lower leg, right
  - Jaw, left
  - Jaw, right
  - Chest
  - Abdomen
  - Upper back
  - Lower back
  - Neck
Sum of Severity (SS)

- SS scale score: Fatigue, Waking unrefreshed, Cognitive symptoms

- For each of the 3 symptoms above, indicate the level of severity over the past week using the following scale:
  0 = no problem
  1 = slight or mild problems, generally mild or intermittent
  2 = moderate, considerable problems, often present and/or at a moderate level
  3 = severe: pervasive, continuous, life-disturbing problems

- Considering somatic symptoms in general, indicate whether the patient has:*
  0 = no symptoms
  1 = few symptoms
  2 = a moderate number of symptoms
  3 = a great deal of symptoms

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score is between 0 and 12.

Time to get a diagnosis - years

Diagnosis

- Total average
- Rheumatoid
- Osteoarthritis
- Fibromyalgia
- Gout
- Psoriasis
- Osteoporosis
- Polymyalgia
- Ank spond
- JRA
- SLE
- HPOA

Years

3.01 2.01 2.28 3.03 2.84 3.45 3.43 3.48 2.91 1.03 1.03 2
Depression and FMS

  - 304 adult subjects with FMS surveyed with BDI and SCL-90-R (1/3 responded)
    - 27% of subjects reported a BDI >21
    - 46% of subjects carried a current and past diagnosis of depression
    - 92% of subjects elevated SCL-90-R Somatization
    - 68% of subjects elevated SCL-90-R Depression
    - 23% has a positive family history of depression
    - 46% has positive family history of FM

  - 100 adult subjects with FMS surveyed depression with Computer Diagnostic Interview Schedule (C-DIS), Beck Depression Inventory-Adjusted (BDI-A), and Minnesota Multiphasic Personality Inventory depression scale (MMPI-d), Beck Depression Inventory (BDI):
    - C-DIS-22% MMPI-d-44%
    - BDI-A-29% BDI-55%

- Adults with fibromyalgia are 3.4 times more likely to have major depression than peers without fibromyalgia (Patten, Beck, Kassam, 2005)
Depression and FMS


- 18 individuals with FM, 18 individuals with rheumatoid arthritis (RA), and 19 healthy pain-free controls (HC) exposed to arousing pictures while NFR, skin conductance, EMG, startle modulation, and emotional reactions.
  - Patients with FM displayed deficits in arousal to a range of pleasurable and noxious stimuli
  - The normal effects of emotional modulation on pain were observed in RA and HC, but not in FM
  - NFR thresholds were not lower in FM

- Conclusions: Subjects with FM may experience a disruption of supraspinal processes that influence positive affect and the emotional modulation of pain, in the absence of differences between brain-spinal cord functioning.
Disability and FMS

- Women with FMS hospitalized for work related musculoskeletal disorders are about 10 times less likely to return to work and 4 times less likely to retain work at 1-year post hospitalization than their non-FMS counterparts (Howard, Mayer, Neblett, Perez, Cohen, Gatchel, 2010)

- Adults with FMS miss approximately 17 days of work per year while only 6 days are missed by their non-FMS counterparts (Kleinman, Harnett, Melkonian, 2009)

- Fibromyalgia has been associated with lower levels of health-related quality-of-life and less work productive (McDonald, DiBonaventura, Ullman, 2011)
Treatment of FMS

Psychosocial Treatments:
- Wicksell, Kemani, Jensen, et al. (2013) acceptance and commitment therapy
- Luciano, Sabes-Figuera, Cardenosa, et al. (2013) psychoeducation
- Segura-Jimenez, Carbonell-Baeza, Aparicio et al. (2013) pool therapy
- Onieva-Zafra, Castro-Sanchez, Matran-Penarrocha, Moreno-Lorenzo (2013) music
- Giggins, Persson, Caulfield (2013) biofeedback
- Sandstrom, Keefe (1998) self-management and coping skill
- Schanberg, Keefe, Lefebvre, Kredich, Gil (1996) coping skills
- Keefe, Caldwell (1997) CBT

Pharmacology:
- Yeephu, Suthisisang, Suttiruksa, et al. (2013) mirtazapine
- Harris, Napadow, Huggins, et al. (2013) pregabalin
- Jesus, Feder, Peres (2013) Vitamin D supplementation
- Wiffen, Derry, Lunn, Moore (2013) Topiramate
- Seidel, Aigner, Ossege, Pernicka, Wildner, Sycha (2013) review of antipsychotics
- Non-narcotic mechanism are preferred (American College of Rheumatology, 2013)
Multidisciplinary Treatment of FMS Yields Best and Most Consistent Long-Term Outcomes

- Castel, Fontova, Montull, et al. (2013). Efficacy of a multidisciplinary treatment adapted for women with low educational levels: a randomized controlled trial. Arthritis Care and Research, 65(3), 421-431.


  - Biopsychosocial model is relevant in conceptualizing and treating fibromyalgia (genetic, biological, psychological, and social factors are all relevant)
  - Effective “treatment of fibromyalgia requires a comprehensive and multidimensional approach with patient education, cognitive behavior therapy, exercise, physical therapy and pharmacological therapy”
Genetics and FMS/CWP
Association between fibromyalgia syndrome and polymorphism of the IL-4 gene in a Turkish population

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ABSTRACT

Purpose: Fibromyalgia (FM) syndrome is a form of non-articular rheumatism characterized by long term and widespread musculoskeletal pain, morning stiffness, sleep disturbance, paresthesia, and pressure hyperalgesia at characteristic sites, called soft tissue tender points. The etiology of FM is still obscure. Genetic factors may predispose individuals to FM. Cytokines may play a role in the pathophysiology of FM. The aim of this study was to investigate the interleukin-4 (IL-4) 70 bp VNTR variations in Turkish patients with FM and evaluate if there was an association with clinical features, especially between these polymorphisms.

Methods: The study included 300 patients with FM and 270 healthy controls. Genomic DNA was isolated and genotyped using polymerase chain reaction (PCR) for the IL-4 gene 70 bp VNTR polymorphisms.

Results: There was statistically significant difference between the groups with respect to IL-4 genotype distribution and allele frequencies (p < 0.0001). The homozygous P,P genotype and P allele were significantly higher in FM patients than in healthy controls (p = 0.04; OR: 3.25, 95% CI: 1–10, p < 0.0001; OR: 4.84, 95% CI: 3–7.7). There was not any difference between the groups respect to IL-4 genotype distribution and allele frequencies (p > 0.05) and clinical characteristics.

Conclusion: Our findings suggest that there is an association of IL-4 gene 70 bp VNTR polymorphism with susceptibility of a person for development of FM. As a result, further studies are necessary to determine whether IL-4 may be a genetic marker for FM in the Turkish population.

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The Big Wednesday Evening Conversation
Being at The Right Place and at The Right Time
Alpha-1-Antitrypsin (A1AT)

- Protease inhibitor
  - Protects tissues in the body from enzymes associated with inflammation
  - Naturally found in humans at a reference range of 1.5-3.5 gram/liter
    - Levels can rise substantially during periods of inflammatory response
  - In its absence, (alpha-1-antitrypsin deficiency), immune cells, like neutrophils, attack connective tissues and render them inflexible (lungs) or dysfunctional
    - Produces stiff lung tissue cells consistent with emphysema
    - Mutations can occur in the gene encoding and produce dysfunctional protein secretions
  - The A1AT gene is located on the 14th chromosome and there are over 100 variants known
    - All humans have 2 copies of the gene
    - The “M” copy is the normal functioning state of the gene
    - Other less functional copies are known as A-L and N-Z
      - PiMM: 100% (normal)
      - PiMS: 80% of normal serum level of A1AT
      - PiSS: 60% of normal serum level of A1AT
      - PiMZ: 60% of normal serum level of A1AT
      - PiSZ: 40% of normal serum level of A1AT
      - PiZZ: 10-15% (severe A1AT deficiency)
        - PiZ is caused by a glutamate to lysine mutation at position 342
        - PiS is caused by a glutamate to valine mutation at position 264
    - Other rarer forms have been described; in all there are over 80 variants.

(Pi= Protease Inhibitor; MM is the pattern of the gene on each chromosome)
Fibromyalgia, mood disorders, and intense creative energy: A1AT polymorphisms are not always silent

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d Duke Pain and Palliative Care Center, Duke University Medical Center, United States

A B S T R A C T

Persons with single copies of common alpha-1-antitrypsin polymorphisms such as S and Z are often considered “silent carriers”. Published evidence however supports a complex behavioral phenotype or trait – intense creative energy (“ICE”)– associated with A1AT polymorphisms. We now confirm that phenotype and present an association of fibromyalgia syndrome (FMS) and A1AT in a consecutive series of neurological patients.

This is a retrospective case control series of 3176 consecutive patients presenting to Duke University Memory Clinic (747 patients) and to regional community-based Caldwell Hospital Neurology and Memory center (2429 patients). Work-up included medical history and examination, psychological evaluation, and genetic analysis. Chronic widespread pain (CWP) or FMS were diagnosed according to clinical guidelines, mostly as secondary diagnoses. Neurological patients carrying A1AT polymorphisms were common (ca 16% prevalence) and carriers had significantly higher use of inhaler and anxiolytic medications. Patients with ICE phenotype had a significantly higher proportion of A1AT polymorphisms (42%) compared to non-ICE patients (13%). Presence of CWP or FMS was common (14–22%) with average age at presentation of 56 years old and mostly female gender (82%). Patients with CWP/FMS had again significantly higher proportion of A1AT polymorphisms (38%) compared to other neurological patients (13%). Patients with anxiety disorders, bipolar I or bipolar II disorders or PTSD also had increased proportion of A1AT polymorphisms and significant overlap with ICE and FMS phenotype. Significant reductions in CWP/FMS prevalence are seen in apolipoprotein E4 carriers and methylene
Materials and Methods

- 3176 consecutive patients (~70% White) collected from Duke (747) and Caldwell Memory Disorders Clinic (2429; 58% female)
- Neurological disorders of memory, concentration, behavior (mean age=62.6 ± 17.9 years; mean education=13.2 ± 3.3 years)
- Ascertained ADD, FMS, PTSD, affective disorders
- Genotyping: A1AT, APOE
Fibromyalgia Results

- 14% prevalence rate of FMS in neurology sample
- 82% of FMS were women,
- 10% rate of FMS in PiMM, normal A1AT
- 40% rate of FMS in A1AT mutations (PiMZ, PiSZ, etc.)
- 46% rate of FMS in homozygous A1AT and deficiency state (PiZZ, PiSS)
- A1AT mutation found at high rates also for JRA, PTSD, mood disorder
  - 63% JRA are carriers of A1AT mutation
  - 35% Bipolar II are carriers of A1AT mutation
  - 40% PTSD are carriers of A1AT mutation
Fibromyalgia Results

Patients with FMS compared to those without presented with:
- Lower MMSE scores
- Greater likelihood of a hx of migraine controlling for gender
- Greater BMI
- Greater prevalence of sleep disorder
- Greater prevalence of antibiotic allergy
- Greater likelihood of being on a psychotropc
- Greater likelihood of being on a narcotic
- Greater likelihood of a mood disorder
- Greater likelihood of an anxiety disorder
- Greater prevalence of RA or JRA

- Altered copper, iron, and ferritin metabolism consistent with acute phase inflammatory response
- APOE 3/4, 4/4 were associated with reduced risk of FMS; No effects of alleles 2/2, 2/3, and 3/3 on FMS
Summary

- The etiology and manifestation of FMS is most likely a multifactorial product of genetic, biological, psychological, and social factors.

- FMS may be the result of autoimmune dysregulations that exert PNS (pain) and CNS effects (dementia).

- Consistent with this notion, effective treatments of FMS will likely include a multidisciplinary approach.

- There is no cure for FMS although there are many viable pharmacological and non-pharmacological management strategies.

- The future of FMS research will likely continue to identify and understand etiological contributors to FMS in gene x gene, gene x environment, and pure environmental influences.
Future of A1AT in FMS: How Relevant is Race?
Topical review

Race, ethnicity and pain

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Abstract

The current paper provides a brief overview of research on the effects of race and ethnicity on pain. More specifically, the article reviews the utility of the concepts of race and ethnicity for pain research, suggests operational definitions of race and ethnicity, reviews the literature on the effects of race and ethnicity on laboratory and clinical pain, and provides suggestions for future research. © 2001 International Association for the Study of Pain. Published by Elsevier Science B.V. All rights reserved.

\textit{Keywords:} Pain; Race and ethnicity; Culture; Differences in pain perception in African--Americans and Caucasians; Definitions of race and ethnicity
Presence of A1AT Mutation by Race/ Ethnicity

- What is the prevalence rate by race of FMS in Blacks?
- Is the prevalence of the A1AT mutations by race similar to that of other US populations?
- Are psychosocial factors that characterize Blacks with pain in other disease states (lower pain tolerance, lower pain threshold, greater disability, greater pain ratings, years to diagnosis, etc.) consistent in Black patients with FMS?
- Are there other relevant gene x A1AT interactions that influence FMS onset and manifestations?
Questions