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DNA testing applied to fibromyalgia syndrome analysis and management

Abstract

The Fibromyalgia syndrome (FMS) is a very complex condition with a relevant clinical heterogeneity. Considering this premise, the present paper interprets this heterogeneity as the result from differences in individual genetic makeup (genetic polymorphisms) and a constant interaction gene-gene and gene-environment. This paper proposed a method based on the detection of a genetic profile as an additional analytical tool to incorporate in a clinical protocol with the aim to individualize the FMS management.

Keywords: fibromyalgia syndrome (FMS), genetics, personalized medicine, DNA-polymorphisms

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Abbreviations: FMS, fibromyalgia syndrome; CD, crohn's disease; UC, ulcerative colitis; IBS, irritable bowel syndrome; COMT, catechol-o-methyl transferase

A genetic approach to FMS from a multifactorial point of view

We know that there is a genetic component for FM the history of a diagnosed case in a family multiplies by 8 the risk of suffering from it among first-degree family members.[1] Different population studies have been performed to identify the causal genes linked to FM,[2,3] but until now there are none which alone explain all the cases, meaning the investigations must continue.

FMS has been long considered as a psychogenic or psychosomatic disease. Most patients are suffering this stigma because they show many symptoms which are too many and too diverse to be considered as a single organic disease. For that reason, it is more appropriate to consider fibromyalgia as a syndrome with a vast heterogeneity in causes as well as in severity of symptoms and clinical evolution. It is a health problem which is very frequent in Spain having a prevalence of 2.4% of the population older than 20 years and being more frequent in women than in men, in a ratio of 21:1. Despite the high prevalence, its etiology remains unknown and no effective treatments exist.[4]

Main mechanisms

There are four mechanisms to consider for a diagnosis and management of FMS (Figure 1):

a. Neurochemistry determining the Neurotransmitter balances.

b. System of enzymatic antioxidants which determine differential vulnerability to environmental toxics.

c. Immune system mediators of Inflammation.

d. Pharmacogenetics.

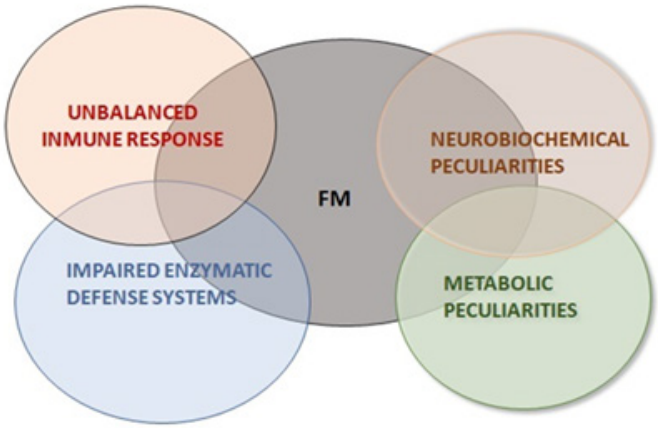

Figure 1 Four mechanisms to consider for a diagnosis and management of FMS.

Neurochemistry determining the neurotransmitter balance

There are several genetic polymorphisms in genes linked to these mechanisms.[5,6] These genetic polymorphisms determine the variability of expression of them which in turn determines the differences in functional efficiency that lead to a lower or higher probability to develop health complications related to FMS.

We have designed a genetic analysis methodology which encompasses the main genes linked to the different pathways which determine the 4 mechanisms that we proposed to consider in the process of analysis to carry out in FMS (Table 1).[7–37]

Table 1 Clinical and biochemical variables of individuals with overweight-obesity

Molecular mechanisms	Genes	Gene function
System of enzymatic antioxidants	CYP1A1,[7,8] CYP1B1,[7,8,13] SOD2[9]	Phase I Enzymes
	CAT,[10] GSTM1,[11,12] GSTT1,[11,12,14] GSTP1,[11,12] SUOX,[13] SULT1A1,[14] NAT2[11,15]	Phase II Enzymes
Mediators of Inflammation	IL6,[16] IL10,[16] TNFa[17]	Cytokines
	VDR[18]	Immunomodulatory role

Table Continued....

Molecular mechanisms	Genes	Gene function
Neurochemistry and potential metabolic responses	COMT,[19,20] MAOA[20]	Enzymes
	HTR2A,[21,22] ADRA2,[23] DRD2,[24] OPRM1,[25] OXTR[26]	Receptors
	DAT1,[27] 5HTT[28]	Transporters
	APOE,[29–31] MTHFR[32,33]	Metabolism
Pharmacogenetics	CYP2D6,[35,36] CYPC9,[35,37] CYP2C19[35,38]	Drug metabolism

SD, standard deviation; BMI, body mass index; WC, waist circumference; AC, abdominal circumference; HC, hip circumference; RER, respiratory exchange ratio; HR, hear rate

It is important to highlight some genes as COMT and IL6 included in our study according to our personal experience.[16] The relevance of these genes has been also corroborated by other authors in different population studies.[19]

There are many other relevant genes as MAO-A[20] and HTR2A[21,22] also included in our study as well as polymorphisms at adrenergic receptor genes,[23] and special immunogenetics leading to a pro-inflammatory status,[16–18,34] among others as CYP450 enzymatic polymorphisms which are mainly related to the pain management.[35–38]

All these genes are involved in the neurotransmitters balance determining the potential to have excess or defect in any of them. A tendency to show low serotonin levels is quite significant among fibromyalgia patients.[39] Due to several genetic polymorphisms affecting the dopamine and/or serotonin pathways can take place an imbalance (excess of dopamine/ serotonin defect) inducing sensitivity to pain, sleep disorders and mood alterations. For this reason the use of anti-depressives is very frequent within the treatment of fibromyalgia, as anti-depressives usually act in a way which increases serotonin levels.[40] The problem arise from the undesirable drug effects which normally accompany most of the antidepressant drugs, something that can even turn out to be damaging in many patients. Being the slow variant of COMT enzyme the most prevalent in FMS patients, there is a tendency to have increased levels of dopamine which might induce some movement disorders (Periodic limb movement disorder and Restless leg syndrome) that have been also reported as comorbidities in some FMS patients.[41,42] The proposed methodology starts with a medical consultation, where an interview is conducted to obtain exhaustive information about the patient personal and family history. As the second step, the procedure for the genetic analysis is explained to obtain the inform consent to proceed. The genetic analysis is always carried out under inform consent guaranteeing data protection and pre-and post-test genetic counseling. Once the genetic analysis of the laboratory is finished, the entire history is analyzed together with the results of the DNA testing. Considering all the information, we design specific measures or intervention strategy and medical follow-up which are based on nutrigenomics and pharmacogenetics.

Impairment in the functioning of phase i and phase ii enzymatic detoxifying systems which determine different degree of tolerance to oxidative stress

Our organism has diverse enzymatic protection systems against toxic attacks from the environment. These mechanisms also allow us to maintain the homeostasis of endogenous metabolites. The functioning efficiency of each of the enzymes which make up these defense systems (Phase I and Phase II detoxification systems) is genetically determined so diverse genetic polymorphisms exist which codify for such enzymes.[7–15]

It has been shown that there is an association between defects in the xenobiotic metabolism gene that code for detoxifying enzymes and the risk of developing diverse human pathologies with clear environmental components, such as the FMS.[43–45]

Oxidative stress has also been involved as a primary or secondary occurrence in other diseases. Important data exists relating both to the start and the progression of Parkinson´s, demonstrating the presence of high levels of free radicals in early stages of Huntington´s disease, in renal diseases and Alzheimer´s and several other neurodegenerative diseases.[46] Also, it´s role in the worsening of symptoms in diseases such as hemolytic anemia[47] or amyotrophic lateral sclerosis has been.[48] At this point, it is also relevant its interrelation with another essential mechanism to take in consideration: the aberrant functioning of the immune system.

Increased tendency to show an unbalanced immune system functioning with pro-inflammatory preponderance

Recent studies have emphasized the role of the immune system in FM pathogenesis and its comorbidities.[16–18] On the other hand, taking back the previously mentioned mechanism (oxidative stress), It has been demonstrated that high levels of inflammation correlate to oxidative stress and mitochondrial dysfunction, at the same time, these levels of inflammation correlate to pain so that more oxidative stress induce more inflammation and at therefore, more pain.[49]

There is strong evidence making possible to support the idea that inflammatory process may be contributing to the appearance and progression of FM. Even though classic inflammatory processes were not observed in some FM patients, they display some anomalies related to inflammation. In a previous study, we have corroborated in Spanish FM patients a strong correlation with some pro-inflammatory mediators as interleukin-6 (IL6) and FM clinical severity.[16] In other studies, it has been shown that FMS patients commonly show higher levels than normal of inflammatory mediators (P substance and Corticotrophin-releasing hormone, CRH). In the same way, the serum of patients with fibromyalgia commonly contains higher levels than normal of pro-inflammatory cytokines emphasizing interleukin-6 (IL-6), while fibromyalgia patients´ skin commonly contains higher than normal quantities of mast cells, which can produce IL-6.[50]

Taking back the concept of oxidative stress and its close relationship with immunity, it is relevant to mention that a high level of pro-oxidant molecules (e.g. peroxynitrite) induce the exaggerated increase in inflammatory cytokine levels (IL-1b, IL-6, TNF-a) being more intense in those patients having a genetic susceptibility to an exaggerated releasing of such cytokines. These cytokines, in turn, produce nitric oxide that combines with superoxide to form more peroxynitrite, a situation which finishes perpetuating the cycle and contributing to cellular damage, being especially negative for the

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health of mitochondria.[51] It is well known that many FMS patients have intestinal health problems. In fact, an excess of pro-inflammatory mediators as IL6 together with low levels of anti-inflammatory mediators like IL10 as we have previously reported in study carried out in FMS[16] may induce an increased intestinal permeability due to a sustained excess of intestinal inflammation. This situation would lead to a disruption of the microbiota balance in favor of an overpopulation of pathogens[52] which, in turn, might induce more inflammation falling into a vicious circle that trigger more serious inflammatory bowel disease (IBD) problems as Crohn's disease (CD), ulcerative colitis (UC) and (IBS).[53]

Conclusion

CSS encompasses a complex and heterogeneous group of syndromes whose diagnosis is still a challenge for professional health careers. Up to the present, it is only based on clinical criteria without any single confirmatory laboratory test.

Their condition as biologically based disorders have been long discussed and yet not well understood. Nevertheless, there are an increasing number of evidences pointing out to several mechanisms that might be involved in their etiology. Several genetic polymorphisms related to these pathways make possible to carry out a biological characterization by a genotyping process that we have designed as the FibromialGen.

We defined as the main representative causal mechanisms an especial neurobiochemistry and metabolic characteristics in conjunction with an extremely impaired defensive antioxidant capacity and an exaggerated pro-inflammatory tendency. Although the four mechanisms are always present in the biological profile of all CSS types; they act in a different way in each one. According to the preponderance or specific weight of one of them over the set, we might define the most likely type of CSS that we are facing in each analyzed patient.

Recognizing these differences, we might be able to design more effective therapeutic approach because we are acting on biological individualities as targets.

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Conflict of interest

The author declares that there is no conflict of interests regarding the publication of this paper.

References

1. Buskila D, Neumann L, Hazanov I, et al. Familial aggregation in the fibromyalgia syndrome. *Semin Arthritis Rheum*. 1996;26(3):605–611.
2. Yunus MB, Khan MA, Rawlings KK, et al. Genetic linkage analysis of multicase families with fibromyalgia syndrome. *J Rheumatol*. 1999;26(2):408–412.
3. García–Fructuoso FJ, Lao–Villadóniga JI, Santos C. Identification of differential genetic profiles in severe forms of fibromyalgia and chronic fatigue syndrome/myalgic encephalomyelitis: a population–based genetic association study. *Journal of Clinical Research*. 2008;11:1–24.
4. Jahan F, Nanji K, Qidwai W, et al. ibromyalgia Syndrome: An Overview of Pathophysiology, Diagnosis and Management. *Oman Med J*. 2013;27(3):192–195.
5. Gursoy S, Erdal E, Herken H, et al. Significance of catechol–O–methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol Int*. 2003;23(3):104–107.
6. Buskila D, Neumann L. Genetics of fibromyalgia. *Curr Pain Headache Rep*. 2005;9(5):313–315.
7. Shimada T, Guengerich PF. Inhibition of human cytochrome P450 1A1–, 1A2–, and 1B1–mediated activation of procarcinogens to genotoxic metabolites by polycyclic aromatic hydrocarbons. *Chem Res Toxicol*. 2007;19(2):288–294.
8. Jeyabalan J, Vadhanam MV, Ravoori S, et al. Sustained overexpression of CYP1A1 and 1B1 and steady accumulation of DNA adducts by low–dose, continuous exposure to benzo (a) pyrene by polymeric implants. *Chem Res Toxicol*. 2011;24(11):1937–1943.
9. Noha E Elsakka, Nigel R Webster, Helen F Galley. Polymorphism in the manganese superoxide dismutase gene. *Free Radical Research*. 2007;41(7):770–778.
10. Ren C, Park SK, Vokonas PS, et al. Air pollution and homocysteine: more evidence that oxidative stress–related genes modify effects of particulate air pollution. *Epidemiology*. 2010;21(2):198–206.
11. Schnakenberg E, Fabig KR, Stanulla M, et al. A cross–sectional study of self–reported chemical–related sensitivity is associated with gene variants of drug–metabolizing enzymes. *Environ Health*. 2007;6:6.
12. Engström KS, Strömberg U, Lundh T, et al. Genetic Variation in Glutathione–Related Genes and Body Burden of Methylmercury. *Environ Health Perspect*. 2008;116(6):734–739.
13. Kisker C, Schindelin H, Pacheco A, et al. Molecular basis of sulfite oxidase deficiency from the structure of sulfite oxidase. *Cell*. 1997;91(7):973–983.
14. Lopes BA, Emerenciano M, Gonçalves BA, et al. Polymorphisms in CYP1B1, CYP3A5, GSTT1, and SULT1A1 Are Associated with Early Age Acute Leukemia. *PLoS One*. 2015;10(5):e0127308.
15. Ladona MG, Izquierdo–Martinez M, Posada de la Paz M, et al. Pharmacogenetic profile of xenobiotic enzyme metabolism in survivors of Spanish Toxic Oil Syndrome. *Environ Health Perspect*. 2001;109(4):369–375.
16. Garcia–Fructuosa F, Beyer K, Lao–Villadoniga JI. Analysis of Val158Met genotype polymorphisms in the COMT locus and correlation with IL–6 and IL–10 expression in fibromyalgia syndrome. *J Clin Res*. 2006;9:1–10.
17. Qidwai T, Khan F. Tumour necrosis factor gene polymorphism and disease prevalence. *Scand J Immunol*. 2011;(6):522–547.
18. Valdivielso JM, Fernandez E. Vitamin D receptor polymorphisms and diseases. *Clin Chim Acta*. 2006;371(1–2):1–12.
19. Vargas–Alarcón G, Fragoso JM, Cruz–Robles D, et al. Catechol–O–methyltransferase gene haplotypes in Mexican and Spanish patients with fibromyalgia. *Arthritis Research & Therapy*. 2007;9(5):R110.
20. Su SY, Chen JJ, Lai CC, et al. The association between fibromyalgia and polymorphism of monoamine oxidase A and interleukin–4. *Clin Rheumatol*. 2007;26(1):12–16.
21. Harris SE, Fox H, Wright AF, et al. A genetic association analysis of cognitive ability and cognitive ageing using 325 markers for 109 genes associated with oxidative stress or cognition. *BMC Genet*. 2007;8:43.
22. Tander B, Gunes S, Boke O, et al. Polymorphisms of the serotonin–2A receptor and catechol–O–methyltransferase genes:a study on fibromyalgia susceptibility. *Rheumatol Int*. 2008;28(7):685–691.
23. Vargas–Alarcón G, Fragoso JM, Cruz–Robles D, et al. Association of adrenergic receptor gene polymorphisms with different fibromyalgia syndrome domains. *Arthritis Rheum*. 2009;60(7):2169–2173.

24. Hamidovic A, Dlugos A, Skol A, et al. Evaluation of genetic variability in the dopamine receptor D2 in relation to behavioral inhibition and impulsivity/sensation seeking: an exploratory study with d–amphetamine in healthy participants. *Exp Clin Psychopharmacol*. 2009;17(6):374–383.

25. Fernandez Robles CR, Degnan M, Candiotti KA. Pain and genetics. *Curr Opin Anaesthesiol*. 2014;25(4):444–449.

26. Myers AJ, Williams L, Gatt JM, et al. Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress. *J Psychiatr Res*. 2014;59:93–100.

27. Kosek E, Jensen KB, Lonsdorf TB, et al. Genetic variation in the serotonin transporter gene (5–HTTLPR, rs25531) influences the analgesic response to the short acting opioid Remifentanil in humans. *Mol Pain*. 2009;5:37.

28. Yeo A, Boyd P, Lumsden S, et al. Association between a functional polymorphism in the serotonin transporter gene and diarrhoea predominant irritable bowel syndrome in women. *Gut*. 2004;53(10):1452–1458.

29. Becker RM, da Silva VK, Machado Fda S, et al. Association between environmental quality, stress and APOE gene variation in fibromyalgia susceptibility determination. *Rev Bras Reumatol*. 2010;50:617–624.

30. Stewart WF, Schwartz BS, Simon D, et al. ApoE genotype, past adult lead exposure, and neurobehavioral function. *Environ Health Perspect*. 2002;110(5):501–505.

31. Pedersen WA, Chan SL, Mattson MP. A mechanism for the neuroprotective effect of apolipoprotein E:isoform–specific modification by the lipid peroxidation product 4–hydroxynonenal. *J Neurochem*. 2000;74(4):1426–1433.

32. Lao JI. The homocysteine pathway: A new target for Alzheimer disease treatment? *Drug Development Research*. 2004;62(3):221–230.

33. Inanir A, Yigit S, Tekcan A, et al. Angiotensin converting enzyme and methylenetetrahydrofolate reductase gene variations in fibromyalgia syndrome. *Gene*. 2015;564(2):188–192.

34. Bote ME, Garcia JJ, Hinchado MD, et al. Inflammatory/stress feedback dysregulation in women with fibromyalgia. *Neuroimmunomodulation*. 2012;19(6):343–351.

35. Webster LR, Belfer I. Pharmacogenetics and Personalized Medicine in Pain Management. *Clin Lab Med*. 2016;36(3):493 – 506.

36. Zhou SF. Polymorphism of Human Cytochrome P450 2D6 and its Clinical Significance: Part II. *Clin Pharmacokinetic*. 2009;48(12):761–804.

37. Ali Z, Kim RJ, Ysla FM. CYP2C9 polymorphisms: considerations in NSAID therapy. *Curr Opin Drug Discov Devel*. 2009;12(1):108–114.

38. Desta Z, Zhao X, Shin GJ, et al. Clinical Significance of the Cytochrome P450 2C19 Genetic Polymorphism. *Clin Pharmacokinet*. 2002;41(12):913–958.

39. Juhl JH. Fibromyalgia and the serotonin pathway. *Altern Med Rev*. 1998;3(5):367–375.

40. Moret C, Briley M. Antidepressants in the treatment of fibromyalgia. *Neuropsychiatr Dis Treat*. 2006;2(4):537–548.

41. Yunus MB, Aldag JC. Restless legs syndrome and leg cramps in fibromyalgia syndrome: a controlled study. *BMJ*. 1996;312(7042):1339.

42. Viola–Saltzman M, Watson NF, Bogart A, et al. High prevalence of restless legs syndrome among patients with fibromyalgia: a controlled cross–sectional study. *J Clin Sleep Med*. 2010;6(5):423–427.

43. National Research Council (US). *Multiple Chemical Sensitivities: A Workshop*. Washington (DC): National Academies Press (US); 1992.

44. Maixner W, Fillingim RB, Sanders AE, et al. Initial findings from the OPPERA study: implications for translational pain Medicine. *Pain Clinical Updates*. 2014;22(5):1–6.

45. Korkina L, Scordo G, Deeva I, et al. The Chemical Defensive System in the Pathobiology of Idiopathic Environment–Associated Diseases. *Curr Drug Metab*. 2009;10(8):914–931.

46. Manoharan S, Guillemin GJ, Abiramasundari RS, et al. The Role of Reactive Oxygen Species in the Pathogenesis of Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease: A Mini Review. *Oxid Med Cell Longev*. 2016;2016:8590578.

47. Fibach E, Rachmilewitz E. The role of oxidative stress in hemolytic anemia. *Curr Mol Med*. 2008;8(7):609–619.

48. Zarei S, Carr K, Reiley L, et al. A comprehensive review of amyotrophic lateral sclerosis. *Surg Neurol Int*. 2015;6:171.

49. Sturgeon JA, Darnall BD, Zwickey HL, et al. Proinflammatory cytokines and DHEA–S in women with fibromyalgia: impact of psychological distress and menopausal status. *J Pain Res*. 2014;7:707–716.

50. Geiss A, Rohleder N, Anton F. Evidence for an association between an enhanced reactivity of interleukin–6 levels and reduced glucocorticoid sensitivity in patients with fibromyalgia. *Psychoneuroendocrinology*. 2012;37(5):671–684.

51. Pacher P, Beckman JS, Liaudet L. Nitric Oxide and Peroxynitrite in Health and Disease. *Physiol Rev*. 2007;87(1):315–424.

52. Miyoshi J, Chang EB. The gut microbiota and inflammatory bowel diseases. *Translational Research*. 2017;179:38–48.

53. Yang TY, Chen CS, Lin CL, et al. Risk for irritable bowel syndrome in fibromyalgia patients: a national database study. *Medicine (Baltimore)*. 2015;94(10):e616.

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