

The Genetics of Fibromyalgia – Closing Osler’s Backdoor

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William Osler, arguably the greatest physician in modern times, has been famously quoted as remarking that when he noticed a patient suffering from arthritis coming in the front door he felt like escaping through the back one. Though not the most politically correct clinical conduct, one can imagine the frustration that must have been inherent in treating a patient with rheumatoid arthritis in the second half of the 19th century. Aspirin was not introduced until 1899 by Bayer [1] and steroids were over half a century away as well [2]. Understanding of the pathogenesis was also rudimentary, not to say primitive. And yet there the patient was – suffering, complaining, demanding treatment. The backdoor must have seemed irresistible at times. Over a hundred years later, fibromyalgia patients seem to raise rather similar emotions among many a noble physician. A syndrome characterized by widespread pain and tenderness over multiple “tender points,” fibromyalgia is currently considered to represent a condition where the central nervous system is unduly amplifying pain, as opposed to a pathology located in the peripheral locomotor or nervous systems [3]. The syndrome is common enough, and the patients undoubtedly suffer and demand help, yet the pathogenesis seems obscure and the therapeutic options are woefully limited. Not surprisingly, once again the backdoor maintains its allure, as many doctors attempt to dismiss fibromyalgia patients to the care of some other discipline and get on to the “really sick patients.”

A decade and a half have passed since the American College of Rheumatology published classification criteria for fibromyalgia. Although these criteria, no less than the syndrome itself, have attracted ongoing criticism and calls for revision, they have nonetheless formed a framework for a plethora of research and publications focused on fibromyalgia over this period. Insight has been gained into many aspects of the fibromyalgia syndrome, including (but not limited to) neuroendocrine aberrations [4], sympathetic nervous system dysfunction [5], immune dysregulation [6], sleep disruption [7], as well as psychological aspects related to chronic pain and fibromyalgia [8].

Entering the term “fibromyalgia” as a Medline search for the years 1990–2006 currently yields 3095 results. According to studies conducted in western countries, up to 3–4% of the population may suffer from fibromyalgia (with far more suffering from chronic pain not meeting criteria of fibromyalgia). Even so,

despite the staggering magnitude of the problem and despite the progress made, many physicians, whether in primary care or rheumatology, continue to view fibromyalgia with suspicion. Patients are constantly informed that “it’s all in your head” and that they should learn how to stop complaining and “live with it.” Some rheumatologists contend that fibromyalgia is a psychiatric disorder and should be treated as such, while no enthusiastic embrace of the issue by the psychiatric community seems imminent. Needless to say, this “ping-pong” attitude does little to alleviate the suffering of patients. In an era in which the right of patients to achieve freedom from pain is gaining increasing legitimation and recognition, to the point at which physicians in the United States are being held liable to malpractice suits due to inadequate pain control [9], it seems more constructive to try understand what makes fibromyalgia patients suffer as they do, rather than to try making them disappear.

It is against this background that the growing data on the familial and genetic basis of fibromyalgia comes forth. A number of studies published over the past 15 years have clearly demonstrated the increased incidence of fibromyalgia among family members of patients suffering from this syndrome [10–13]. This clear familial aggregation could of course potentially represent either a genetic or environmental influence, or most likely a combination of both. As a result, a significant body of data has been gathered regarding genes that may be responsible. This research endeavor, which has typically focused on candidate genes considered to play a role in the complex neurotransmitter matrix responsible for pain transmission and processing, has led to significant insight into the role of genes concerned with the serotonergic [14,15], dopaminergic [16], norepinephrine [17] systems, with a gene coding for a substance P receptor being the latest addition to the list [18]. In the case of some of these candidates, statistically significant associations have been identified between specific polymorphisms and the development of fibromyalgia [14–16], while in other cases results have been inconclusive [18]. It remains very probable that no single gene will be identified as the sole cause of fibromyalgia. Much more likely, a combination of genetic traits, coupled with a chain of environmental events such as trauma, infection, stress, etc., will gradually emerge as the explanation. In this context it is intriguing to note that both in depression [19], a disorder of

presumably “endogenous” causes, and in post-traumatic stress disorder [20], a disorder that would seem to be the epitome of an environmentally induced syndrome (both disorders being co-classified with fibromyalgia within the affective, or functional spectrum) – a combination of genetic predisposition and external events has been demonstrated to be at play.

What stands to be gained by understanding such genetic associations? The trivial answer is that more insight into the genetics involved could eventually lead to a better understanding of the pathophysiology of fibromyalgia and ultimately lead to novel therapeutic strategies. No less important, from the viewpoint of patients however, is the prospect that revealing fibromyalgia to be a disorder with a genetic basis will add legitimacy to the very concept and will help discredit the notion that we (or the patients) can actually wish the problem away. Then perhaps we may be more equipped to return to another maxim of Oslerian medicine: “As physicians, we should strive to cure a few, help most, but comfort all” [21]. Then perhaps, the backdoor can finally be shut for good.

References

- Hammerschmidt DE. The first commercial bottle of aspirin: March 6, 1899. *J Lab Clin Med* 1998;123(6):556.
- Hirschmann R. The cortisone era: aspects of its impact. Some contributions of the Merck Laboratories. *Steroids* 1992;57(12):579–92.
- Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 2001;91(1-2):165–75.
- Adler GK, Manfredsdottir VF, Creskoff KW. Neuroendocrine abnormalities in fibromyalgia. *Curr Pain Headache Rep* 2002;6(4):289–98.
- Martinez-Lavin M. Fibromyalgia as a sympathetically maintained pain syndrome. *Curr Pain Headache Rep* 2004;8(5):385–9.
- Staines DR. Is fibromyalgia an autoimmune disorder of endogenous vasoactive neuropeptides? *Med Hypotheses* 2004;62(5):665–9.
- Roizenblatt S, Moldofsky H, Benedito-Silva AA, Tufik S. Alpha sleep characteristics in fibromyalgia. *Arthritis Rheum* 2001;44(1):222–30.
- Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. *Arthritis Rheum* 2005;52(5):1577–84.
- Tucker KL. The debate on elder abuse for undertreated pain. *Pain Med* 2004;5(2):214–17.
- Pellegrino MJ, Waylonis GW, Sommer A. Familial occurrence of primary fibromyalgia. *Arch Phys Med Rehabil* 1989;70(1):61–3.
- Roizenblatt S, Tufik S, Goldenberg J, Pinto LR, Hilario MO, Feldman D. Juvenile fibromyalgia: clinical and polysomnographic aspects. *J Rheumatol* 1997;24(3):579–85.
- Buskila D, Neumann L, Hazanov I, Carmi R. Familial aggregation in the fibromyalgia syndrome. *Semin Arthritis Rheum* 1996;26(3):605–11.
- Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. *Arthritis Rheum* 2004;50(3):944–52.
- Offenbaeher M, Bondy B, de Jonge S, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. *Arthritis Rheum* 1999;42(11):2482–8.
- Cohen H, Buskila D, Neumann L, Ebstein RP. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5-HTTLPR) polymorphism, and relationship to anxiety-related personality traits. *Arthritis Rheum* 2002;46(3):845–7.
- Buskila D, Cohen H, Neumann L, Ebstein RP. An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. *Mol Psychiatry* 2004;9(8):730–1.
- Gursoy S, Erdal E, Herken H, Madenci E, Alasehirk B, Erdal N. Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. *Rheumatol Int* 2003;23(3):104–7.
- Ablin JN, Bar-Shira A, Yaron M, Orr-Urtreger A. Possible association between fibromyalgia and a novel 1354G>C polymorphism in the TACR1 (substance P receptor) gene in Ashkenazi patients. *Arthritis Rheum* 2005;52(9 Suppl):S269.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* 2003;301:386–9.
- Segman RH, Cooper-Kazaz R, Macciardi F, et al. Association between the dopamine transporter gene and posttraumatic stress disorder. *Mol Psychiatry* 2002;7(8):903–7.
- Gibofsky A. If I am not for myself, who will be for me? *Arthritis Rheum* 2003;48(4):869–72.

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