

Lighting Up the Genetic Understanding of Fibromyalgia



This year's Nobel Prize in Chemistry recognized the groundbreaking discovery of an important family of cellular receptors. It was Robert Lefkowitz and Brian Kobilka's decades-long molecular dissections that deciphered the exciting mystery of how cells sense their environment¹. Along their journey was a crucial milestone: the pinpointing of architectural parallels between the beta-adrenergic receptor and rhodopsin, the light-detecting receptor in the retina. That same revelation literally opened the scientific community's eyes to a group of proteins that mediate innumerable functions in the human body. The pathobiological understanding of a plethora of medical conditions has greatly advanced since these receptors, the G-protein coupled receptors (GPCR), were identified. Now, it might be time for a common albeit historically underappreciated disorder to gain some benefits.

Fibromyalgia syndrome (FM), an often-debilitating chronic pain syndrome, remains largely idiopathic. With its widespread nonarticular musculoskeletal pain and generalized tenderness, it is a diagnosis made when no tracing of structural or inflammatory process is present². While FM has eluded clear etiological understanding for decades, its hallmark alteration in sensitivity to painful stimuli has been the target of meticulous investigation^{3,4}. Enhanced central processing of pain has been implicated as the predominant mechanism, with correlations at the functional imaging level⁵. The relative contribution of heightened pain perception and psychological elements to the pathogenesis of FM is a matter of continuing investigation⁶. Hypervigilance and anticipation have been demonstrated to increase activity in the secondary somatosensory cortex⁶, reinforcing the already augmented cortical and subcortical processing of pain. Biologic and cognitive factors have also been shown to influence the expression of pain symptoms. Moreover, the relative weight of each pathology — cognitive, biologic, and psychological — has been hypothesized to affect the symptom profile. Accordingly, distinct FM subgroups have been postulated, based on degree of tenderness, mood assessment, and level of perceived control over pain⁷. Such a classification was created to accommodate the extensive variability of this chronic multi-

symptom illness. In the attempt to confer practical significance to the FM subgroups described, researchers have turned to both bench and bedside to explore several conundrums: Do patients from different FM clusters have distinct neurobiologic profiles? Would specific treatments show differential effectiveness in the individual patient from a particular cluster? The symptomatic heterogeneity of FM has been partially ascribed to varying degrees of neurotransmitter dysfunction found among patients⁸. Of interest, 5-HT₃ receptor antagonists have proven to be efficacious in FM patients with a predominant pain phenotype (without depression), but less so in those with depression⁹. Similarly, naltrexone has been shown to improve fatigue and perceived stress in FM patients, an observation that potentially stems from its disinhibition of the hypothalamus-pituitary-adrenal axis¹⁰. Interestingly, the endogenous μ -opiate system has recently been implicated as a contributor to the hyperalgesia/allodynia of FM, thus implying additional potential roles for opiate antagonists¹¹. A therapeutic approach to FM tailor-made for the individual patient is the desired goal.

Deciphering the genetic underpinning for the hyperalgesia in FM would constitute a major advance in solving this puzzle. In this issue of *The Journal*, Kim, *et al* analyze gene polymorphisms that might influence susceptibility and pain sensitivity in FM¹². They focus on the *GCH1* gene, a key modulator of pain sensitivity¹³. The corresponding enzyme of that gene interacts with various regulatory molecules involved in GPCR signaling. More relevant, the *GCH1* enzyme catalyzes the rate-limiting step in the synthesis of tetrahydrobiopterin (BH₄), a cofactor for synthesis of several pain modulators. The authors hypothesized that polymorphisms in the *GCH1* gene would alter the balance of nitrous oxide (NO) production and thus change the susceptibility to pain in patients with FM. To that aim, they scrutinized the presence and intensity of tender points, as well as different clinical markers of disease severity, in 409 patients with FM. They then genotyped 4 single-nucleotide polymorphisms (SNP) in the *GCH1* gene, in both patients and controls. They were not able to show any association between any SNP and FM susceptibility or

See SNP in *GCH1* gene affect pain sensitivity in FM, page 316

severity. However, one particular haplotype (CCTA) was found to be significantly more frequent among healthy individuals compared with FM patients. That same haplotype also correlated with fewer tender points on examination and decreased intensity of pain perception. The authors ascribe this haplotype a protective function possibly mediating diminished sensitivity to pain.

The pain-protective effect conferred by the CCTA haplotype is in accordance with other studies of pain disorders that explored variants of the *GCH1* gene¹⁴. The authors use their findings to argue that alterations in pain perception in FM are NO-dependent. Notably, this argument needs further scientific corroboration, as the GCH1 enzyme is central to production not only of NO but of other pain-related mediators as well, for example, serotonin and biogenic amines.

In light of the well known and significant familial association of FM¹⁵, multiple research endeavors have previously been made to elucidate the genetic basis of this syndrome. While investigators originally used the candidate gene approach, and focused on genetic markers with a plausible pathogenetic link to FM (e.g., polymorphisms related to the metabolism of serotonin, noradrenaline, dopamine, etc.^{16,17,18}), it has become apparent that FM is most likely a polygenic disorder. Thus, the implementation of genome-wide association techniques, exploited in other complex and heterogeneous disorders like Parkinson's disease and Alzheimer's disease^{19,20}, is likely to pave the road to future advances in the understanding of FM genetics. Viewed in this perspective, the elegant work of Kim, *et al*, based on a clear mechanistic hypothesis, is something of a throwback to the classical candidate gene approach. While one must keep in mind the inherent limitations of this strategy, the convincing results of this study demonstrate its continuing merit and may indeed lead to the acquisition of further insight into the role that the GCH1 system plays in FM and in the general field of pain.

The current study puts more flesh on the bones of FM. It implicates a gene, postulates a pain hypothesis, and exposes a wealth of potential new gene haplotypes in FM. Sprouting from a prestigious family of membrane receptors, GCH1 may strike our rhodopsins and bring about a more refined understanding of FM, a complex pain syndrome.

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Correction

Lighting up the Genetic Understanding of Fibromyalgia

Oren H, Ablin JN. Lighting up the genetic understanding of fibromyalgia [editorial]. *J Rheumatol* 2013;40:214-5. Mr. Oren's academic degree should correctly be BSc. We regret the error.

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