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Update on the genetics of the fibromyalgia syndrome

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A B S T R A C T

Fibromyalgia syndrome (FMS), a condition characterized by chronic widespread pain and tenderness, is a complex condition considered to represent a paradigm of centralized pain. FMS has demonstrated a clear familial aggregation, and hence it is considered to have a genetic background. Multiple candidate-gene studies have been conducted in this field, focusing on target genes that play a role in the transmission and processing of pain. While many of these have focused in the past on markers related to neurotransmitter systems such as catecholamines (catechol-O-methyltransferase (COMT)) and serotonin, novel target genes have recently emerged. In addition, genome-wide sequencing scanning (genome-wide association study (GWAS)) is increasingly being harnessed for the study of chronic pain, including FMS. Micro RNAs are another novel field of research related to posttranscriptional inhibition of gene expression, which are currently regarding the pathogenesis of FMS.

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Introduction

Fibromyalgia syndrome (FMS) is a concept in evolution. Previously identified and defined as a discrete rheumatological entity responsible for widespread pain and tenderness [1], fibromyalgia has subsequently evolved conceptually; currently, this clinical syndrome is perceived of not as a discrete entity but rather as part of a continuum representing an increased and heightened processing of pain within the nervous system [2]. As such, individuals with or without other pain-related pathologies may exhibit varying degrees of "fibromyalgianess", which may also fluctuate over the course of their illness [3]. During this shift, the concept of centralized pain has been described and characterized, with FMS remaining the original "paradigmatic" centralized pain condition [4].

This evolution must be corroborated and explained in terms of incorporating genetic markers hitherto tied to the pathogenesis of FMS into the current concepts regarding the nature and taxonomy of FMS. This again poses somewhat of a challenge. Classically, medical genetics have strived to identify specific genetic markers, which could be linked to particular diagnoses. Thus, when describing an entity such as rheumatoid arthritis (RA) in textbook style, besides chapters on pathophysiology and diagnosis one would include a chapter on genetics, in which all genetic underpinnings of the nosological entity under consideration would be enumerated. A similar strategy was originally pursued by researchers who pioneered the genetics of FMS. Thus, target-gene studies explored the frequency with which it was possible to identify specific genetic polymorphisms among FMS patients, compared with healthy individuals. This strategy led to the identification of a number of targets, which will be covered in the following sections. However, as the conceptual framework of FMS continues to evolve, as described above, genetic information as well should no longer be thought of in terms such as "identifying the gene or genes responsible for FMS" but rather as incorporating genetic data relevant to the processing of pain and to pain centralization into the spectrum of centralized pain. Thus, the presence of such genetic markers might be anticipated to be increased in various conditions concerning chronic (presumably centralized) pain, such as temporal mandibular joint disorder (TMJD) [5] or chronic pelvic pain [6]. Moreover, one can easily anticipate a future in which individualized genetic data become regularly available, and in which such data will be able to aid both in the identification of centralized pain among patients suffering from other musculoskeletal disorders and in the tailoring of personalized treatment for such patients [7].

In the current review, we will attempt to cover evidence available on the genetic underpinnings of FMS, as well as demonstrating the relevance of these data to the understanding of centralized pain in general. Table 1 presents a compilation of the specific genetic markers covered in this review.

Familial aggregation in FMS

Early on in the study of FMS, it became apparent that familial aggregation plays an important role in the epidemiology of this disorder. An increased incidence of either FMS or muscle tenderness was demonstrated among parents and siblings of FMS patients [8]. In a study investigating both FMS and sleep disorders among mothers and offspring, a significant concordance was observed between children and mothers regarding both traits [9]. In other studies, 28% of offspring of FMS patients were identified as fulfilling FMS criteria [10] as well as 28% of "close relatives." [11] The quality of life and the functional level of FMS-patient relatives were found to be relatively low in another study [12].

In the family study of fibromyalgia [13], Arnold et al. collected information from 533 relatives of 78 probands suffering from FMS and 272 relatives of 40 probands suffering from RA. FMS strongly aggregated in families, and the odds ratio of FMS in a relative of a proband with FMS versus that of a relative of a proband with RA was 8.5. Tenderness was also found to be strongly aggregated, and the findings were interpreted as implying the important role of genetic factors in the pathogenesis of FMS.

Candidate-gene studies

Subsequent to the observations regarding the significant familial aggregation of FMS, candidate-gene studies originally focused on target genes, which were considered to have a link with the