Abstract

Genetic and environmental factors may play a role in the etiopathology of fibromyalgia syndrome (FMS) and other related syndromes. There is a high aggregation of FMS in families of FMS patients. The mode of inheritance is unknown but it is most probably polygenic. There is evidence that polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems play a role in the etiology of FMS. These polymorphisms are not specific for FMS and are associated with other functional somatic disorders and depression. Future genetic studies in the field of FMS and related conditions should be conducted in larger cohorts of patients and ethnically matched control groups.

Introduction

Fibromyalgia is an idiopathic, chronic pain syndrome defined by widespread nonarticular musculoskeletal pain and generalized tender points [1]. Fibromyalgia syndrome (FMS) overlaps with several related syndromes, the functional somatic syndromes [2]. The pathogenesis of FMS and related conditions is not entirely understood, although the current concept views FMS as the result of central nervous system malfunction, resulting in amplification of pain transmission and interpretation [3,4]. Recent evidence suggests that FMS and related syndromes share heritable pathophysiological features [5,6]. Certain environmental factors may trigger the development of FMS and related conditions in genetically predisposed individuals [7]. The aim of this article is to review the current evidence that genetic and familial factors may play a role in the development of FMS.

Familial aggregation in fibromyalgia

The prevalence of FMS in the general population is estimated at 2% [8]. The prevalence of FMS and the observation of rheumatologists that this syndrome runs in families suggest that genetic and familial factors may play a role in its etiopathogenesis. Several studies have addressed the frequency of FMS in families of patients with FMS.

Two studies [9,10] suggested that FMS segregates within families in an autosomal dominant mode of inheritance. One of them [9], based on clinical diagnostic criteria modified from Yunus, showed female preponderance and, in addition, postulated the existence of a latent or precursor stage of the disease characterized by abnormal palpable muscle consistency. If such a latent stage exists, this study actually showed that 70% of offspring of FMS patients are affected, a rate that considerably exceeds the one expected from autosomal dominant inheritance (50%) and suggests over-diagnosis in this study. In addition, this study rejected the polygenic mode of inheritance based on data on second degree relatives, which was not presented in the article. The second study by Stormorken and colleagues [10] was based on data retrieved from questionnaires regarding FMS symptoms in family members of index patients.

According to this study, about two-thirds of the study population reported family clustering. However, the statement regarding a clear pattern of dominant inheritance was not corroborated by numerical data. A subsequent study attempted to document the mother-child correlation with regard to the occurrence of fibromyalgia, and also compared sleep disorder patterns between a group of childhood fibromyalgia patients and their mothers [11]. A significant concordance was observed between children and mothers regarding both occurrence of FMS and the sleep disorder.

Buskila and colleagues [12] analyzed the occurrence of FMS among 58 offspring of 20 affected mothers with FMS; 16 offspring (28%) were found to have FMS. The male/female ratio among those affected was 0.8 compared with 1.5 in the whole group.

Offspring with and without FMS did not differ in anxiety, depression, global well being, quality of life and physical functioning. Because psychological and familial factors were...
not different in children with and without FMS, the high familial occurrence of this syndrome was suggested to be attributed to genetic factors [12].

In another study [13], the authors further observed 30 female patients with FMS and 117 of their close relatives (parents, brothers, sisters, and children). The prevalence of FMS among the blood relatives of patients with FMS was 26%, compared to 19% among their husbands. Fibromyalgia prevalence was 14% in male relatives and 41% in female relatives. It was suggested that the higher prevalence of FMS in relatives could be attributed to genetic and environmental factors [13]. The quality of life and physical functioning of these relatives were found to be impaired, especially in female relatives and those with undiagnosed FMS [14].

Arnold and colleagues [15] tested the hypotheses that FMS and measures of pain and tenderness aggregate in families and that FMS co-aggregates with major mood disorder. They performed a family interview study of 78 probands with FMS and 40 probands with rheumatoid arthritis, assessing FMS and major mood disorder in a total of 533 first degree relatives (146 interviewed) of the probands with FMS and a total of 272 first degree relatives (72 interviewed) of the probands with rheumatoid arthritis.

Fibromyalgia aggregated strongly in families: the odds ratio measuring the odds of fibromyalgia in a relative of a proband with fibromyalgia versus the odds of fibromyalgia in a relative of a proband with rheumatoid arthritis was 8.5. Moreover, the number of tender points was significantly higher in relatives of FMS patients compared to relatives of patients with rheumatoid arthritis. Fibromyalgia was also found to co-aggregate with other forms of affective spectrum disorder (ASD). The authors concluded that genetic factors are probably involved in the etiology of fibromyalgia and pain sensitivity and that fibromyalgia and mood disorders are likely to share such inherited factors [15].

Mikkelsson and colleagues [16] examined the prevalence of widespread musculoskeletal pain among 11 year old Finish twins. The prevalence of widespread pain was 9.9% and most twin pairs were discordant. The authors concluded that genetic factors play only a minor role in widespread pain in this population and that environmental factors shared by family members accounted for a substantial proportion of the variability in widespread pain.

The strong familial aggregation reported in FMS, though not excluding a possible contribution by environmental factors, appears to point to a genetic basis as an important contributor to its etiology.

Genes involved in FMS

HLA antigen class I and II were determined in a small group of FMS patients and normal controls [17]; 67% of FMS patients had DR4 versus 30% of normal controls. Yunus and colleagues [18] confirmed in a 40 multicase families study the existence of a possible gene for FMS that is linked with the HLA region (a weak association). It was emphasized that these results should be confirmed independently by other studies [18].

Research done in recent years has demonstrated a role for polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems in the etiology of FMS.

Offenbaecher and colleagues [19] analyzed the genotypes of the promoter region of the serotonin transporter gene (5-HTT) in 62 patients with FMS and 110 healthy controls. A significantly higher frequency of the S/S genotype of the serotonin transporter promoter region was found in FMS patients (31%) compared with healthy controls (16%). The S/S subgroup exhibited higher mean levels of depression and psychological distress. It was suggested that the results support the notion of altered serotonin metabolism in at least a subgroup of patients with FMS.

These researches have further investigated the silent T102C polymorphism of the 5-HT2A receptor gene in 168 FMS patients and 115 healthy controls [20]. Their results show a significantly different genotype distribution in FMS patients, with a decrease in T/T and an increase in both T/C and C/C genotypes compared to the control population. However, the increase in allele C102 frequency fell short of significance. Correlation of genotypes to clinical parameters revealed no influences on age of onset, duration of disease or psychopathological syndromes, measured with the Beck Depression Inventory and the symptom check list SCL-90-R. In contrast, the pain score was significantly higher for patients with the T/T genotype. It was suggested that the T102 allele might be involved in the complex circuits of nociception.

It was concluded that the T102C polymorphism is not directly involved in the etiology of FMS, but might be in linkage disequilibrium with the true functional variant, which has to be unraveled [20].

To verify and extend these findings, Cohen and colleagues [21] performed genotyping in a group of 99 female FMS patients from two Israeli ethnic groups. Additionally, each patient was assessed with the Tridimensional Personality Questionnaire, a self report instrument consisting of 100 yes/no questions. The results of this study confirm the association between FMS and the serotonin transporter promoter region (5-HTTLPR) polymorphism in two ethnic groups in Israel, Jewish and Bedouins.

A significant association between the 5-HTTLPR polymorphism and anxiety related personality traits was found as well [21]. Gursoy could not find an association between the serotonin transporter (5-HT) nor its polymorphism with FMS [22].
forms of ASD. Collectively and familial co-aggregation of FMS with other conditions 
including generalized pain sensitivity, it is postulated that they share common pathogenetic mechanisms. Indeed, Hudson and colleagues [28] reported on familial aggregation of ASD [28]. These syndromes include FMS, chronic fatigue syndrome (CFS), irritable bowel syndrome, gulf war fatigue syndrome (CFS), irritable bowel syndrome, gulf war

Fibromyalgia is one member of a group of medical disorders collectively termed functional somatic syndromes [2] or, alternatively, ASD [28]. These syndromes include FMS, chronic fatigue syndrome (CFS), irritable bowel syndrome, gulf war syndrome and more [2]. Since these syndromes share many clinical features, including generalized pain sensitivity, it is postulated that they share common pathogenetic mechanisms. Indeed, Hudson and colleagues [28] reported on familial aggregation of ASD collectively and familial co-aggregation of FMS with other forms of ASD.

Another study [29] evaluated 178 relatives of 64 probands suffering from major depressive disorder and 152 relatives of 58 probands without major depressive disorder.

A family history study was conducted among patients with CFS [30]; 25 patients with CFS were compared to 36 control individuals, assessing for symptoms of fatigue as well as psychiatric symptoms. Information was collected regarding similar symptoms among first degree relatives of patients and controls. Significantly higher rates of chronic fatigue were identified among relatives of CFS patients compared to relatives of healthy controls, suggesting a significant role for familial factors in CFS. Familial aggregation of irritable bowel syndrome also has been recently reported, supporting a genetic or interfamilial environmental component [31].

A high prevalence of FMS was found among female migraine patients [32]. It was shown that migraine, as well as other co-morbid conditions, aggregates in families [29]. A significant overlap exists between FMS and post-traumatic stress disorder according to the currently accepted diagnostic criteria for each [33]. A twin study of Vietnam veterans has shown significant genetic contribution to post-traumatic stress disorder [34].

Similar to the findings in FMS, polymorphism of genes in the serotoninergic and dopaminergic systems have been reported for other functional somatic syndromes. A study conducted in 78 CFS patients showed a significant increase of longer allelic variants of the serotonin transporter (5-HTT) gene promoter polymorphism, which affects the transcriptional efficiency of 5-HTT [35].

It was concluded that attenuated concentration of extracellular serotonin due to longer variants may cause higher susceptibility to CFS. Serotonin transporter polymorphism was shown to influence response to the 5-HT antagonist in diarrhea predominant irritable bowel syndrome and influence the benefit/risk ratio with this class of compounds [36].

Juhász and colleagues [37] have suggested that the genetic susceptibility of migraine may be associated with a locus at or near the 5-HT transporter gene. Segman and colleagues [38] reported on an association between the dopamine transporter gene and post-traumatic stress disorder. It was suggested that genetically determined changes in dopa-
The mode of inheritance of FMS is unknown, but it is most likely polygenic. Environmental factors (mechanical trauma, emotional trauma) may trigger the development of FMS in genetically predisposed individuals.

More prospective studies, conducted in larger numbers of patients and matched controls, are needed to better clarify the role of genetics in FMS and related conditions.

Competing interests

The authors declare that they have no competing interests.

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