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Fibromyalgia

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Abstract

Fibromyalgia is a neuromuscular disease affecting nearly 3% of US population. It is characterized by persistent pain, sleep disturbances, severe fatigue, parasthesias, prolonged muscle spasms, functional bowel disturbances. The cause for this disease is yet to be unraveled. Various groups in different parts of the world are working to find the etiology of this disease. This article is an attempt to present a review on some of the articles published on the work carried out in this direction in the last two decades. Genes involved in dysfunction of the CNS sensory processing are being studied. Genetic predisposition was confirmed by the familial studies carried out by several groups. Identification of mechanisms of polymorphism-dependent gene expression, such as regulation of translation by interacting alleles in the catechol-O-methyl transferase(COMT) gene locus can contribute to our further understanding of the genotypic structure[7] of pain-related genes and thus very soon can the etiology of Fibromyalgia be unraveled.

Pain perception is one of the most complicated measurable traits because it is an aggregate of several phenotypes associated with peripheral and central nervous system dynamics, stress responsiveness and inflammatory state[7].Pain is an adaptive response

that signals the presence of damaging and life-threatening events. It promotes escape behaviours and thus contributes to survival advantage. By contrast, persistent pain is mal-adaptive and it evokes human suffering. Fibromyalgia is one such condition of persistent pain in the muscles. It is characterized by chronic pain, allodynia (pain perception evoked by a stimulus that under normal conditions evokes non-painful sensation), high levels of distress, fatigue, frequent health care seeking behavior, needle-like tingling of the skin, morning stiffness, anxiety. Women in the age-range of 30-50 are predominantly affected[6]. Patients with fibromyalgia feel greater pain even to a gentle stimulus. This is due to the pain-amplification by the central nervous system. This is why it is also referred as Pain Amplification Syndrome. Since pain is processed by Central Nervous System, studies were carried out to unravel the mechanisms in CNS sensory processing.Aricle [10] claims that abnormalities in CNS sensory processing as well as peripheral tissue cause Fibromyalgia. Central Sesitization is proposed as a mechanism for pain amplification. Central Sensitization is a process in which the entire Central Nervous System becomes sensitized to a stimulus. Substance P, a nuero-peptide is found in high levels in the muscles and skin of fibromyalgia patients. Substance P functions as a neurotransmitter and nueromodulator which alters the excitability of dorsal horn ganglion (pain responsive neurons). It belongs to tachykinin nueropeptide family. Its amino acid sequence was found out to be 'Arg Pro Lys Pro Gln Gln Phe Gly Leu Met'. It is involved in nociception (the nueral process of encoding and processing noxious stimuli). Central Sesitization can occur as an immediate or delayed phenomenon resulting in increased sensitivity of wide dynamic range and nociception specific neurons of the spinal cord. Immediate central sensitization relies mainly on dorsal horn receptor mechanisms of those like N-methyl-D-asparatate(NMDA) and neurokinin-1 receptor. Delayed central sensitization depends mostly on transcriptional and translational neuronal changes during afferent barrage[10]. Hyperexcitability of dorsal horn neurons that transmit nociceptive input to the brain, results in high levels

of noiceptive input to the brain even to a low intensity stimuli delivered to the skin or deep muscle, and thus amplifies the pain. Specifically, intense or prolonged impulse input from myelinated and unmyelinated afferents sufficiently depolarizes the dorsal horn neurons and results in the removal of Mg2+ block of NMDA-gated ion channels. This is followed by influx of extracellular Ca2+ and production of nitric oxide(NO). NO promotes release of substance P from pre-synaptic afferent terminals and causes dorsal-horn neurons to become hyperexcitable.

There is no particular biomarker yet for Fibromyalgia. Objective markers that were worked on are Pressure pain threshold, sleep logs and polysomnography, Hypothalamus pituitary adrenal axis, functional nueral imaging, muscle abnormalities. In all these cases longitudinal studies are needed for them to be accepted as biomarkers[6].

Higher levels of IL-8, IL-10 were found in the serum levels of patients with Fibromyalgia. But as the reports on immunological markers were not concordant and as there is no evidence for inflammatory mechanisms in this syndrome, it is not considered an autoimmune disorder.[2]

Recent research studies have been carried out to identify the cause of fibromyalgia at the genetic level. It has been found that Fibromyalgia Syndrome segregates within families in an autosomal dominant mode of inheritance. Higher prevalence of fibromyalgia in relatives could be attributed to genetic and environmental factors [3]. Serotonins, Dopamine are the nuerotransmitters involved in conducting the information or pain through neurons. Polymorphisms of genes in the serotoninergic dopominergic and cathecholaminergic systems were studied to find if they are involved in the etiology of Fibromyalgia. Serotonin (5Hydroxy-Tryptamine) receptors HTR3A (GeneId: 15561), HTR3B (Geneid: 9177), HTR2A (Geneid: 3356) were the genes arrived at. Genotype distributions of these receptors in Fibromyalgia patients were found to be

different than normal[3].But recent Mutational analysis studies on HTR3A, HTR3B [1] reported that the mutations observed in these genes were not statistically significant to accept a hypothesis that these mutations could be the cause of Fibromyalgia. FM patients score high on anxiety related traits and another group reported that decrease in frequency of 7 repeat allele in exon III of Dopamine4 (D4) receptor gene(Geneid:25432) could be attributed to this .COMT (Cathecol-O-Methyl Transferase) is an enzyme involved in inactivation of cathecolamine neurotransmitters. *COMT* is the gene that codes COMT.It is located on long(q) arm of Chromosome 22.One of the research groups reported that the COMT Val158Met polymorphism influences the human experience of pain and may underlie inter-individual differences in the adaption and responses to pain and other stressful stimuli.Substitution of Val to Met at codon 158 of COMT results in threefold reduction in thermostability and activity of the enzyme.*COMT* consists of atleast five functional polymorphisms that imapct its biologic activity and associated phenotypes.The overall functional state of the gene is thus difficult to understand from genotypic information alone[7].

Because of the polymorphisms in the pain related genes it is difficult to attribute pain to a particular loci on a chromosome. Variations are observed in individuals and thus techniques like high throughput screening can be used to study the genotype of an individual and analyze the results for pain phenotypes[7]. Thus studies on the genes involved in pain perception,can reveal the etiology of fibromyalgia and other chronic pain related syndromes.

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