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Multiple Sclerosis: Searching a Link between Eukaryotic Translation Initiation Factor-2B and Multiple Sclerosis

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ABSTRACT

Multiple Sclerosis (MS) is an inflammatory disease governed by demyelination of myelin sheath around the axons of brain and spinal cord. It is characterized by a broad spectrum of signs and symptoms. The exact etiology remains elusive. It appears to be a polygenic condition and is more prevalent in some ethnic groups than others. From the studies conducted so far, it has been found that it may be associated with a defect in candidate genes like: human leukocyte antigen (HLA), interleukin-7 receptor alpha (IL7RA), C type lectin domain family 16 (CLEC16-A), and eukaryotic translation initiation factor 2B (EIF2B), etc. There is a strong evidence to support the notion that MS is hereditary and therefore more attention is still needed to explore new candidate genes involved in its development. This review summarises the up-to-date knowledge on association between MS and EIF2B and also highlights the role of EIF2B as a susceptibility factor for development of MS in different populations. In conclusion, this small review provides an impetus to explore the association of MS with EIF2B.

Keywords: MS, Myelin, Demyelination, HLA, IL7RA, CLEC16-A, EIF2B, Heredity.

INTRODUCTION

Multiple Sclerosis (MS) represents an autoimmune and chronic inflammatory condition of the central nervous system (CNS) in which demyelination of the myelin

sheath occurs. It is the most common neurological disease affecting young adults especially women. It leads to neurodegeneration and scarring with wide continuum of signs and symptoms [(1)]. It has a prevalence ranging between 2 and 150 per 100, 000 [(2)].

The most frequent symptoms include hypoesthesia, paresthesia, ataxia, dysarthria, dysphagia, muscle spasms, vertigo, optic neuritis, bladder and psychological disturbances [(1)]. Although the causes for MS remain unclear, but studies have shown that there occurs interaction between genetic and environmental factors [(3-8)]. A recent study on animal model for MS has shown that leakage of blood in the brain acts as an early trigger for switching the brain's inflammatory response on; creating a neurotoxic environment that damages nerve cells [(9)].

Although there is no known cure for MS, but it can be managed by using combination of drugs and therapies [(10)]. Despite lack of evidence on its effectiveness, many people use alternative medicine like herbal medicine, helminthic therapy, etc. [(11-13)]. In a recent study on mice model of MS, it was shown that biodegradable nano-particles could be used as vehicle to deliver antigen that modulate the immune system to stop its attack on myelin [(14)].

MOLECULAR GENETICS OF MS WITH SPECIAL FOCUS ON EUKARYOTIC TRANSLATION INITIATION FACTOR 2B (EIF2B)

A large number of studies have shown that genetics plays a significant role in MS development [(1, 10, 15)]. It has been proposed that genetic heterogeneity exists in MS, meaning that particular genes have impact on susceptibility and pathogenesis in some individuals but not in others and that it varies from population to population [(7)]. MS seems to have an evident genetic backdrop with many candidate genes recognized. The strongest evidence for MS susceptibility has been linked to the Major Histocompatibility Complex (MHC) [(16, 17)], in particular that association is between MS and DR15 and DQ6 alleles of MHC [(1)]. Even increased levels of Heat Shock Proteins (HSP) that are located within the MHC have been shown to be associated with pathophysiology of MS [(18)]. Recent studies have shown that MS also results from the defects in translation initiation machinery [(19)]. EIF2B encoding the five non identical subunits of eukaryotic translation initiation factor 2B (eIF2B) complex has been shown to be involved in vanishing white matter disease (VWM) (OMIM 603896) [(20-22)]. The mutations in these candidate genes impair their function, thus disturbing the process they govern.

The eIF2B complex plays an imperative role in protein synthesis and its regulation by governing nucleotide exchange on eukaryotic initiation factor 2 (eIF2). It changes an inactive eIF2-guanosine diphosphate (GDP) into the active complex eIF2-guanosine triphosphate (GTP), thus restoring active eIF2 by exchange of GDP for GTP (Figure 1) [(23)]. This is a central point in the regulation of protein synthesis initiation under multifarious cellular conditions. In different stress conditions, various mechanisms known to regulate the activity of eIF2B involve the phosphorylation of its ε-subunit on several serine/threonine residues [(24, 25)]. EIF2B5 which encodes the largest and catalytic subunit of the complex contains most of the mutations and most

likely mutations involving this subunit would be critical [26, 27]. Therefore it appears that mutations in this gene hamper the activity of the complex.

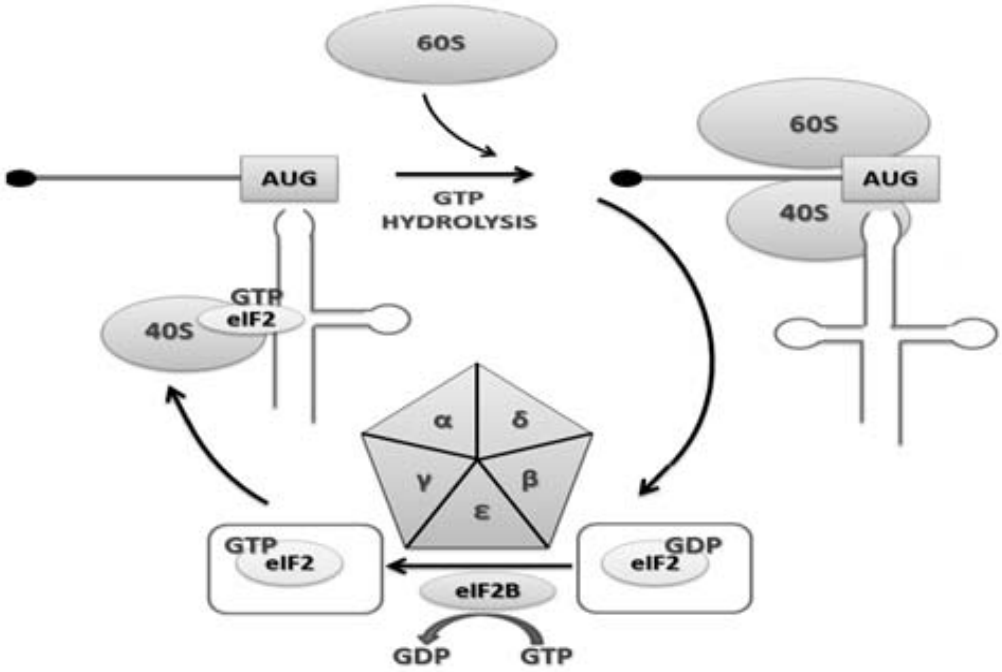

Figure 1: Role of eIF2B in translation initiation. eIF2-bound GTP binds initiator Met-tRNA and mediates binding to the small 40S ribosomal subunit. Upon binding to the mRNA, the large 60S ribosomal subunit joins leading to GTP hydrolysis. For another round of initiation, eIF2 is reactivated by eIF2B by promoting exchange of GDP for GTP on eIF2. In this way, eIF2B regenerates active eIF2 and enables it to carry out next round of initiation along with other components (not shown) of translation initiation.

Although previous studies have not shown any relationship between EIF2B5 variations and MS, but majority of mutations in this gene not only cause VWM but also VWM with milder phenotype [19, 28-30], thus making EIF2B5 gene more crucial among the other EIF2B genes.

One of the recent studies strongly suggests a possible involvement of Ile587Val polymorphism of EIF2B5 gene in the development of MS [19]. A recent study on gene's impact on a signaling pathway in white matter disease development has identified Sox17 gene as a regulator of the Wnt/beta-catenin pathway during myelination [31]. Most of the published studies have been carried out on the Caucasian population. A recent study carried out on the Chinese population has shown that the mutations in EIF2B5 gene impair the activity of eIF2B protein in diverse ways [32]. Despite some major differences between MS and VWM, there are certain similarities between the two which justifies looking for association between EIF2B polymorphism and MS susceptibility [21, 33-35]. Since both MS and VWM are sensitive

to stress by heat, therefore variation in EIF2B gene might be a susceptibility factor increasing the risk of developing MS by promoting/provoking the disease. Furthermore, earlier studies have reported cases in which the genetic and biochemical data of MS patient along with MRI data was similar to that seen in VWM [21]. Thus variations in EIF2B gene draw strong attention as a possible cause of MS. Thus, it is evident that further research is needed to determine any significant association between EIF2B and MS. Preliminary work from our lab also suggests an association between EIF2B and MS, but because of the small number of patients involved, we could not publish the same.

The understanding of molecular genetics behind MS is critical for developing efficient treatment. MS is regarded as a complex and multigenic condition linking many pathways, each one mediated by a group of distinct genetic profiles. Unveiling the molecular mechanisms and genetics of such a complex disorder remains a great challenge in human genetics. Therefore, studying the genetic variations of MS-related genes can further elucidate the link between molecular genetics of MS and its development.

CONCLUSIONS

For the better management and cure of MS, newer and promising strategies are needed. New collaborative efforts among researchers could help establish the molecular pathophysiology of MS. This short review has been written with the intention that polymorphism present in individuals suffering from MS strongly depends on environmental factors and it varies from population to population. The mutations and/or single nucleotide polymorphisms (SNPs) in EIF2B5 gene might predispose carriers to MS and might lead to an earlier MS manifestation. Most of the Indian patients have not been studied vis-a-vis EIF2B. In conclusion, there is a need to search for new MS candidate genes and more variations in EIF2B genes in different populations to identify possible allelic association of these genes with the development of the disease. This will help to a larger extent to comprehend the exact role of EIF2B in MS development.

COMPETING INTERESTS

The authors declare that no competing interests exist.

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WEBSITE AND DATABASE INFORMATION

URLs for data presented in this paper are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for human EIF2B5 gene [OMIM 603945] and for VWM [OMIM 603896]).

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