Indian J Med Res 145, June 2017, pp 713-714
DOI: 10.4103/ijmr.IJMR_725_17

Quick Response Code:

Commentary

An insight about genomic susceptibility & multiple sclerosis

Multiple sclerosis (MS) is an inflammatory, demyelinating disorder of the central nervous system (CNS) leading to various degrees of physical and cognitive disability[1]. The risk factors implicated in the development of MS are viral infections such as Epstein-Barr virus, human herpes virus-6, vitamin D3 deficiency and genomic susceptibility[2]. It is an immune-mediated disorder causing destruction to oligodendroglia, myelin sheath and secondary axonal damage[3].

The disease has varied manifestations, the most common being remitting relapsing type, secondary progressive MS, primary progressive MS and acute fulminant MS[4]. The genomic vulnerability has been substantiated by many studies[5,6]. The incidence of MS is found to be more in monozygotic twins as compared to dizygotic twins[6].

The immunopathogenesis is contributed by many immunological factors, which include CD4 cells, T helper type 1 (Th1) cells, antibodies, complement, CD8+ T-cells and innate immunity. These immunological factors have complex interplay, causing damage to CNS structures[7].

Haile *et al*[8] in 1980 reported that variability in human leucocyte antigen (HLA) region predisposed individuals to develop MS. The genetic vulnerability for MS has been ascertained by Class 2 risk alleles, while Class 1 alleles confer protective functions. In Class 2 risk alleles, HLA-DRB1*15.01 has been proven to be most important susceptible factor for MS, across the population throughout the world[9].

The destruction of myelin sheaths surrounding axons of CNS has been caused by dysregulated immune processes. The most widely studied are the three polymorphisms within the proximal 1.3 kb (−1085 G/A, −819 C/T and −592 C/G) region of interleukin-10 (IL-10). These variations are mainly from three different haplotypes (GCC, ATA and ACC), which regulate expression levels of IL-10. The haplotype combination GCC/GCC is associated with high IL-10 expression, whereas GCC/ATA and GCC/ACC are associated with medium expression and ATA/ATA, ATA/ACC and ACC/ACC with low expression. Significant associations of these genotypes with MS have been reported in different population with causation as well as severity of disease[10].

Genetic studies have shown implication of *HLA DRB1*15*, one among the three candidate risk genes of HLA-DR2 haplotype as the main susceptibility allele in MS[11]. Association of this allele is strongest in Northern Europeans genome-wide association study and identified almost in all population[12].

Shahbazi *et al*[13] in their study in this issue have evaluated the susceptibility of IL-10 (−1082 and −819) and HLA-DRB1*15 polymorphisms in relation to MS. The study was conducted in Iranian population in age-, sex-, ethnicity-matched MS patients and controls. IL-10 −1082 G/G and IL-10 −819 C/C genotypes were more frequent in MS patients than in healthy individuals. HLA DRB1*15 allele also showed an association with MS patients. Importantly, individuals having both G at −1082 position/C at −819 position with DR15 risk alleles showed risk for developing MS. Haplotypes [H2 (CA) and H4 (TG)] were suggested for their protective roles against MS[13].

This study emphasizes on the association of IL-10 −1082 G/G and IL-10 −819 C/C genotypes and HLA DRB1*15 allele in MS patients. However, additional functional studies related to these polymorphisms will help further understand interplay between HLA DRB and IL-10 gene.

As ethnicity plays an important role in association studies, further larger studies in different ethnic population are needed. This may further provide

evidence that both HLA DRB1*15 allele and HLA DRB1-regulated-Th-2-specific IL-10 cytokine polymorphisms may be important determinants of MS.

Future perspectives

The aetiology of MS is still not certain. MS is a complicated inflammatory neurodegenerative disease of the CNS, the aetiology and evolution both determined by environmental and genetic influences. The genetic studies have proved the role of genes regulating immunological factors. The genetic susceptibility studies have tried to establish the role of genetic polymorphisms in causation, progression, magnetic resonance imaging lesion loads, relapses and prognosis of MS. However, the results are conflicting in nature. The genetic studies are mainly related with genes governing immunopathological factors but not giving insights about natural course of the disease. Further research is required to know the genetic contribution to understand the causative factors in MS, their correlation with therapeutics and prognosis.

Rajesh Verma[1,*] & Neetu Singh[2]
Departments of [1]Neurology &
[2]Molecular Biology, Center for Advance Research,
King George's Medical University,
Lucknow 226 003, Uttar Pradesh, India
[*]*For correspondence:*
drrajeshverma32@yahoo.com

Received May 11, 2017

References

1. Compston A, Coles A. Multiple sclerosis. *Lancet* 2008; *372* : 1502-17.
2. Ramagopalan SV, Herrera BM, Bell JT, Dyment DA, Deluca GC, Lincoln MR, *et al.* Parental transmission of HLA-DRB1*15 in multiple sclerosis. *Hum Genet* 2008; *122* : 661-3.
3. Holmøy T , Vartdal F. Infectious causes of multiple sclerosis. *Lancet Neurol* 2005; *4* : 268.
4. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, *et al.* Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology* 2014; *83* : 278-86.
5. Moutsianas L, Jostins L, Beecham AH, Dilthey AT, Xifara DK, Ban M, *et al*. Class II HLA interactions modulate genetic risk for multiple sclerosis. *Nat Genet* 2015; *47* : 1107-13.
6. Hemminki K, Li X, Sundquist J, Hillert J, Sundquist K. Risk for multiple sclerosis in relatives and spouses of patients diagnosed with autoimmune and related conditions. *Neurogenetics* 2009; *10* : 5-11.
7. Sewell AK. Why must T cells be cross-reactive? *Nat Rev Immunol* 2012; *12* : 669-77.
8. Haile RW, Hodge SE, Visscher BR, Spence MA, Detels R, McAuliffe TL, *et al.* Genetic susceptibility to multiple sclerosis: A linkage analysis with age-of-onset corrections. *Clin Genet* 1980; *18* : 160-7.
9. Alcina A, Abad-Grau Mdel M, Fedetz M, Izquierdo G, Lucas M, Fernández O, *et al.* Multiple sclerosis risk variant HLA-DRB1*1501 associates with high expression of *DRB1* gene in different human populations. *PLoS One* 2012; *7* : e29819.
10. Djuric T, Zivkovic M, Stankovic A, Dincic E, Raicevic R, Alavantic D. Association of the *MMP-3* 5A/6A gene polymorphism with multiple sclerosis in patients from Serbia. *J Neurol Sci* 2008; *267* : 62-5.
11. Tuwir I, Dunne C, Crowley J, Saddik T, Murphy R, Cassidy L. The relationship between HLA-DRB1 alleles and optic neuritis in Irish patients and the risk of developing multiple sclerosis. *Br J Ophthalmol* 2007; *91* : 1288-92.
12. Mihailova S, Ivanova M, Mihaylova A, Quin L, Mikova O, Naumova E. Pro- and anti-inflammatory cytokine gene polymorphism profiles in Bulgarian multiple sclerosis patients. *J Neuroimmunol* 2005; *168* : 138-43.
13. Shahbazi M, Abadi JSA, Roshandel D, Koochaki M, Amiri H, Kohansal R, *et al*. Combination of interleukin-10 gene promoter polymorphisms with HLA-DRB1*15 allele are associated with multiple sclerosis. *Indian J Med Res* 2017; *145* : 746-52.