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Genetic study of juvenile myoclonic epilepsy (JME) patients and their family members in a University Hospital in North India

MM Mehndiratta, K Bhaskar Rao, *Shweta Singh, *S Ganesh, GA Khwaja

*Department of Neurology, G.B.Pant Hospital- Maulana Azad Medical College, University of Delhi, New Delhi; *Department of Biological Sciences and Bioengineering, IIT, Kanpur, India.*

Background and Objectives: Among the 40-100 million persons with epilepsy worldwide, approximately 50% have generalized epilepsies. Juvenile myoclonic epilepsy (JME) is a common epileptic syndrome and has been classified as idiopathic generalized epilepsy by the International League Against Epilepsy.[1] JME constitutes 10-30% among all cases of epilepsy. The syndrome is characterized by myoclonic jerks, generalized tonic clonic seizures in 80-97% and absence seizures in 12-54% of patients. Age of onset is between 8-20 years with peak age at 15 years. Inheritance in JME is thought to be autosomal dominant with incomplete penetrance. Previous linkage studies on larger JME families have identified 6 different chromosomal loci being involved: 6p12-11, 6p21.3, 15q14, 6q24, 2q22-2q23, and 5q34. Of all the loci identified, only 5q34 lead to identification of a mutation in the GABRA1 gene in a single larger JME family from Quebec, Canada. Candidate gene analyses in multiplex families identified CLCN2 gene as one of the major genes involved in JME. CLCN2 is the first known gene in which both mutations and a common sequence variant confer a range of varying susceptibility effects to genetically complex epilepsies. Such genes are thought to function as genetic "risk factors" but on their own they may not cause epilepsy. These include KCNQ3, BRD2, LGI4, GABRG2 and CACNB4.[2] The objective of this study was to study the genetic association analysis for sequence polymorphisms in the BRD2, LGI4 and GABRG2 genes and the clinical, EEG characteristics in JME probands and their family members.

Methods: This study was conducted in the Department of Neurology, G.B. Pant Hospital involving 50 JME probands. All the patients were subjected to history, examination, laboratory tests, EEG, genetic analysis and imaging studies according to a structured proforma. The case-control association study design was used to test the potential involvement of BRD2, LGI4 and GABRG2 gene variations in the etiology of JME. The sequence variations tested in the present study are: SNP -198A/T located in the promoter region of the gene *BRD2;* SNP 3145G/A located in the intronic region of the gene GABRG2; and SNP 1914GC/AT located in the coding region of the gene LGI4.

Results: A significant difference was found in the genotype distribution of the -198A/T polymorphism in the BRD2 gene between JME patients and controls (χ^2=4.28, P=0.038) and a stronger difference in allele frequency was found (χ^2=8.82, P=0.004). A significant difference in the dinucleotide polymorphism 1914GC/AT of the LGI4 gene was observed in the JME cases when compared to controls (χ^2=4.32, P=0.03) and striking difference when the allele frequency was considered (χ^2=6.69, P=0.009). However, we did not observe any significant difference in the genotype or allele frequency for the SNP 3145G/A in GABARG2 gene.

Discussion and Conclusion: The present study provides evidence for a genotypic and allelic association between JME and the -198A/T polymorphism of the BRD2 gene. The evidence is predominantly based on decrease of the -198A/A homozygotes in the JME patients compared with controls. The excess of -198A/A homozygotes in the control group suggests this allele to be acting as a protective allele. We find that the SNP -198A/T affects the binding sites for two transcription factors. It is of interest to note that BRD2 protein is a nuclear transcriptional regulator and plays an important role in the development of central nervous system. Thus it is likely that the SNP -198A/T, in combination with other genetic factors, serves as a causative factor for JME. The present study also identifies a positive association for the dinucleotide polymorphism 1914GC/AT of the LGI4 gene with the JME.

LGI4 maps to 19q13.11, the chromosomal region that showed evidence for a susceptibility gene for idiopathic generalized epilepsies in a whole genome scan. It would be of interest to define the haplotype block around the 1914GC/AT locus for the Indian population and in JME. Nevertheless our results are suggestive of a genetic risk factor for JME in Indian population. Similar to BRD2, LGI4 protein might regulate neuronal cell migration, axon guidance or synaptogenesis during development. Thus sequence variations in LGI4, in combination with other genetic factors might modulate this developmental process leading to the expression of JME symptoms in concordance with other studies from India and elsewhere.

In conclusion, the present study suggests that the polymorphisms screened for the BRD2 and LGI4 could serve as a risk factor for JME in Indian population. Our study also suggests that genes associated with development and differentiations of nervous system are ideal candidates for JME. The present study may provide the basis for further survey for BRD2 and LGI4 polymorphisms in JME and underscores the need for a large-scale prospective study.

References

1. Commission on classification of terminology of International League Against Epilepsy and Epileptic Syndromes. *Epilepsia* 1985; 26: 268-78.
2. Gardiner M. Genetics of idiopathic generalized epilepsies. *Epilepsia* 2005; 46 (Suppl 9): 15-20.