Original Article

Mutations in *GABRG2* receptor gene are not a major factor in the pathogenesis of mesial temporal lobe epilepsy in Indian population

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Abstract

Aim: This study is focused on *GABRG2* gene sequence variations in patients with mesial temporal lobe epilepsy (mTLE). The $GABA_A$ receptor is a heteropentameric receptor and alpha-1 beta-2 gamma-2 subunits combination is most abundant and present in almost all regions of the brain. The gamma-2 subunit (*GABRG2*) gene mutations have been reported in different epilepsy pathologies. In the present study we have looked for *GABRG2* gene sequence variations in patients with mTLE. **Materials and Methods:** Twenty patients (12 females and eight males, age 4.6-38 years) with MTLE were recruited for this investigation. Patients were recommended for epilepsy surgery after all clinical investigations as per the epilepsy protocol. Ethnically matched glioma or meningioma patients were considered as nonepileptic controls. During temporal lobectomy of amygdalohippocampectomy, hippocampal brain tissue samples were resected guided by intraoperative electrocorticography (ECoG) activity. All 11 exons of *GABRG2* gene with their flanking intronic regions were amplified by polymerase chain reaction (PCR) and screened by DNA sequencing analysis for sequence variations. **Statistical Analysis Used:** Comparison of allele frequencies between patient and control groups was determined using a χ^2 test. **Results and Conclusions:** Total five DNA sequence variations were identified, three in exonic regions (c.643A > G, rs211035), (c.T > A, rs424740), and (c.C > T, rs418210) and two in intronic regions (c.751 + 41A > G, rs211034) and (c.751 + 52G > A, rs 34281163). Allele frequencies of variants identified in this study did not differ between patients and normal controls. Thus, we conclude that *GABRG2* gene may not be playing significant role in the development of epilepsy or as a susceptibility gene in patients with MTLE in Indian population.

Key Words

Epilepsy, GABRG2 receptor, mutations

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Introduction

Epilepsy is one of the most common neurological disorder which is characterized by recurrent unprovoked seizures affecting approximately 50 million people worldwide.[1] There are significant number of epilepsy cases where treatment with antiepileptic drugs is not effective. For these medically refractory epilepsy cases, surgery has been established as an effective mode of cure. About 30-40% of patients, who have undergone an adequate epilepsy surgery, still continue to have seizures.[1] Temporal lobe epilepsy (TLE) is a neurological condition characterized by recurrent seizures that originate from the temporal lobe. TLE accounts for one-third of all patients with epilepsy and can be divided into several subgroups including mesial TLE (mTLE). MTLE is the most frequent form of partial epilepsy observed in adults, accounting for 40% of cases. About 30% of MTLE cases are resistant to antiepileptic drugs.[2-4] MTLE with hippocampal sclerosis (MTLE-HS) is the most common cause of surgical and refractory epilepsy in adulthood. MTLE-HS syndrome is restricted to patients in whom hippocampal atrophy and/or abnormal signal intensity on MRI, anterior psychological assessment is demonstrated.[5] TLE is treated by a variety of surgical techniques including tailored anterior temporal lobectomy guided by intraoperative electrocorticography (ECoG) or without ECoG which provide for an extensive

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resection of mesial temporal lobe structures, particularly the hippocampus.[6] Early identification of intractability if possible could help plan better clinical management of patients by combined drug therapy and surgery to achieve an effective treatment. The pathological mechanisms underlying mTLE are poorly understood and there are no biomarkers to predict the subset of patients who develop intractable epilepsy. Familial forms of MTLE-HS have been recognized, but there are no studies reporting causal gene or linkage associated with it.[5]

It is believed that many epilepsy syndromes too have genetic basis, and vary in the severity form childhood to adult.[7] These genetic epilepsy syndromes have been associated with DNA mutations/polymorphism sequence variants in several subunits of neurotransmitter receptor ion channels.[8] Various mutations in *GABRG2* genes impair channel gating and/or reduced mRNA stability, aberration in subunit folding, and glycosylation which result in abnormal receptor assembly and trafficking.[9] Mutations in these subunits that either directly or indirectly enhance the excitatory neurotransmission or reduce inhibitory neurotransmission would cause brain hyperexcitability, and thereby predispose patients to seizures. The γ-aminobutyric acid (GABA) is the most important inhibitory neurotransmitter in the central nervous system (CNS) for fast inhibition, and its action is mediated through the GABA A- and B-type receptors. GABAA receptors are pentameric chloride ion channels formed from various combinations of proteins encoded by α (α1-α6), β (β1-β3), γ (γ1-γ3), δ, ε, π, θ, and ρ (ρ1-ρ3).[10] The major isoforms of the GABAA receptor consist α, β, and γ subunits and show a regional heterogeneity that is associated with distinct physiological effects. The α1β2γ2 subunits combination is the major subtype (60%) and most abundant in almost all regions of the brain.[11] Reduction of inhibitory neurotransmission has been proposed as one of the main factors in epileptogenesis. Because of their widespread distribution in the CNS and their ability to cause postsynaptic inhibition, the GABRs encoding genes represent high ranking candidates for epilepsy susceptibility.

Single-nucleotide polymorphisms (SNPs) are the most abundant types of DNA sequence variation in the human genome.[11,12] It is a single base pair on the DNA that varies from person to person. SNPs are markers that may provide a new way to identify complex gene-associated diseases. The *GABRG2* gene (γ2 subunit) mutations have been reported in various studies in different epilepsy pathologies. The *GABRG2* gene is located in chromosome 5q34 and is highly expressed in the brain. A > G polymorphism was observed in alcohol dependence in German population in intronic region.[13] The same A > G polymorphism was also observed in psychiatrically healthy German population.[14] The *GABRG2* missense mutation, R82Q, is located in the distal N-terminus and is associated with febrile seizures (FS).[15] The *GABRG2* missense mutation, R177G, is located in the N-terminus and has been associated with FS.[16] The *GABRG2* splice-donor site mutation, IVS6 + 2T→G, is located in intron 6 and was identified in a family with FS and childhood absence epilepsy (CAE).[17] The *GABRG2* missense mutation, K328M, is located in the short extracellular loop between transmembrane domains M2 and M3 and is associated with an autosomal dominant generalized epilepsy with FS plus (AD-GEFS +).[18] The *GABRG2* nonsense mutation, Q390X, is located in the intracellular loop between transmembrane domains M3 and M4 and was identified in a family with GEFS + and DS.[19] The two *GABRG2* nonsense mutations, Q40X and W429X, have been associated with, DS and GEFS +, respectively.[7,20] Kang *et al*., observed the *GABRG2* mutation, Q351X, associated with generalized epilepsy with FS plus, has both loss of function and dominant-negative suppression.[21] Ito *et al*., identified three different sequence variations C315T, T588C, and C1230T which do not seem to be a major genetic cause of epilepsy with typical and atypical absences in Japanese subjects.[22]

Most of the studies describing mutations in *GABRG2* gene of GABAA receptor associated with epileptogenesis are carried out with blood samples. Very few studies are reported with brain tissues. In this study we have tested the hypothesis that genetic variation in the *GABRG2* gene might be associated with intractable MTLE-HS. More specifically we have investigated the mutation of *GABRG2* gene from highly targeted tissue from hippocampus (defined electrically at surgery, from microelectrodes recording intraoperativley from these areas) in MTLE-HS patients.

Materials and Methods

Participants

In the present study, 20 unrelated patients with MTLE-HS enrolled at our Neurosurgery Department, All India Institute of Medical Sciences (Delhi, India). Out of 20 cases 12 are females and eight are males [Table 1]. The diagnostic criteria for intractable epilepsy surgery carried out as per the institutional epilepsy protocol. After all investigation patients were admitted for the intractable epilepsy surgery. All the patients of bilateral MTLE-HS, presence of dual pathology like cortical dysplasia with MTLE-HS and any contradictions for surgery for MTLE-HS are the exclusion criteria of the study. The study protocol was approved by the institutional ethical committee, and written informed consent form was obtained from all participants. We also assessed the mutation analysis sample comprising 20 unrelated and unmatched tumor (glioma/meningioma) patients consider as controls that have no familial history of any epileptic seizures. Out of 20 controls, 11 were males and nine were females, 15 controls belong to glioma and five with meningioma tumors [Table 1].

ECoG and tissue collection

The intraoperative ECoG performed during the surgery for all MTLE-HS patients. A four single point grid electrode inserted into hippocampus (anterior, middle, and posterior), the degree of abnormality recorded and graded as per ECoG scores [Table 1].[23] Following ECoG activity, hippocampal brain tissues were collected. One normal brain tissue sample was collected from the periphery of the tumor during the resection of tumor.

Molecular analysis

Genomic DNA was extracted from brain samples using Qiagen kit. All 11 exons of *GABRG2* gene (transcript no. ENST00000414552, 3927 base, 515 amino acids, CCDS47333) including intron-exon-intron boundaries were amplified using primer sets [Table 2]. Primers were designed against flanking intronic sequence using published sequence and public genomic assemblies (http://www.ensembl.org). Polymerase

Table 1: Clinical Characteristics of the case and control group

S. No.	Age (Years)	Sex	Diagnosis
P1	14	Male	Rt MTS
P2	24	Male	Rt MTS
P3	34	Female	Lt MTS
P4	26	Female	Lt MTS
P5	26	Female	Rt MTS
P6	36	Male	Rt MTS
P7	28	Female	Lt MTS
P8	31	Male	Lt MTS
P9	38	Female	Rt MTS
P10	4.6	Female	Lt MTS
P11	37	Female	Rt MTS
P12	15	Female	Rt MTS
P13	15	Male	Rt MTS
P14	34	Male	Rt MTS
P15	29	Female	Rt MTS
P16	24	Male	Rt MTS
P17	29	Female	Rt MTS
P18	25	Female	Lt MTS
P19	18	Male	Lt MTS
P20	28	Female	MTS
C1	60	Female	Right lateral sphenoid wing meningioma
C2	45	Female	Right medial frontal sol high grade glioma
C3	35	Female	Meningiothelial cells tumor
C4	52	Female	Left frontal glioma
C5	30	Male	Posterior 3 RD Ventricular Cranial Tumor
C6	27	Male	Right frontal low grade glioma
C7	35	Female	Posterior 1/3 falcine parasagital meningioma
C8	61	Female	Residual tentorial meningioma
C9	35	Female	Frontal meningioma
C10	44	Female	Tentorila meningioma
C11	60	Male	Left frontal glioma
C12	60	Male	Frontal low grade glioma
C13	58	Male	Right frontotemporal multicentric meningioma
C14	45	Female	Interhemispheric ependymona
C15	24	Male	Left frontal parietal glioma
C16	45	Male	Glioma
C17	64	Male	Glioma
C18	2	Male	Glioma
C19	30	Male	Glioma
C20	30	Male	Glioma

P = Patient, C = Control, Rt = Right, Lt = Left, MTS = Mesial temporal lobe epilepsy

chain reactions (PCRs) were carried out in a thermal cycler (Biorad, S1000). The master mix contained a total of 25 µl volume composed of 100ng of genomic DNA, 0.25 ml of 10 pm each of forward and reverse primers, 0.5 µl of 100 mM each of dinucleotide triphosphates, 2.5 µl of ×10 Taq buffer (containing $MgCl_2$), and 0.2µl of Taq DNA polymerase prepared in sterilized water. PCR parameters were as follows: Denaturation at 95°C for 5 min followed by 35 cycles at 95°C for 30 s, annealing at 58-64°C for 30 s, and extension 72°C for 30 s. After amplification, PCR products were purified by gel extraction using Qiagen kit and following manufacturer's instruction. Purified amplicons were analyzed by gel electrophoresis and finally visualized by gel documentation system after ethidium bromide staining. Amplicons were sequence commercially (Biolinkk, India) by automated sequencing. Sequences were analyzed using Mutation@A Glance (http://rapid.rcai.riken.jp/mutation/) tool which is a highly integrated web-based analysis tool for analyzing human disease mutations.

Statistical analysis

Statistical analysis was performed using STATA software. Allele frequencies were compared between patient and control groups using a χ^2 test.

Results

Molecular result

Mutation analysis of *GABRG2* gene did not reveal any obvious pathogenic mutations. Total five DNA sequence variations were identified [Figure 1 and Table 3]. Figure 1 shows the sequencing traces of allelic changes of five SNPs:

1. c.643A > G,
2. c.751 + 41A > G,
3. c.751 + 52G > A,
4. c.C>T, and
5. c.T > A.

The peak showing variation is marked with an arrow. These sequences were further analyzed for their locations in the genomic regions and their functional significance using Mutation@A Glance (http://rapid.rcai.riken.jp/mutation/) tool which is a highly integrated web-based analysis tool for analyzing human disease mutations. Three mutations were identified in the exonic regions c.643A > G (rs211035), c.T > A (rs424740), and c.C > T (rs418210).c.643A > G (rs211035) variant is a missense mutation and results in a conservative amino acid substitution (p.Ile215Val) causing nonsyndromic change. We found this coding polymorphism at approximately equal frequencies in both affected individuals and controls [Table 3]. c.T > A (rs424740) and c.C > T (rs418210) are silent substitutions. Two mutations were identified in intronic regions c.751 + 41A > G (rs211034) and c.751 + 52G > A (rs34281163), which were not predicted to affect RNA splicing. These mutations were present in both control as well as affected cases [Table 3].

Statistical analysis

Comparison of allele frequencies between patient and control groups was determined using a χ^2 test. Allelic frequencies of various SNPs identified in this study show no significant differences between the control and the epileptic group [Table 4]. Although the SNP (rs418210) is showing significant variation ($P = 0.011$) as seen in Table 4, however, this is due to higher frequency of the mutation in control group as compared to the epileptic group. Functional analysis of this SNP shows that it is a silent mutation, which makes this variation insignificant.

Discussion

In this study we have identified SNPs of *GABRG2* gene of GABAA receptor specifically in patients with MTLE-HS and individual without epilepsy as controls, and compared the

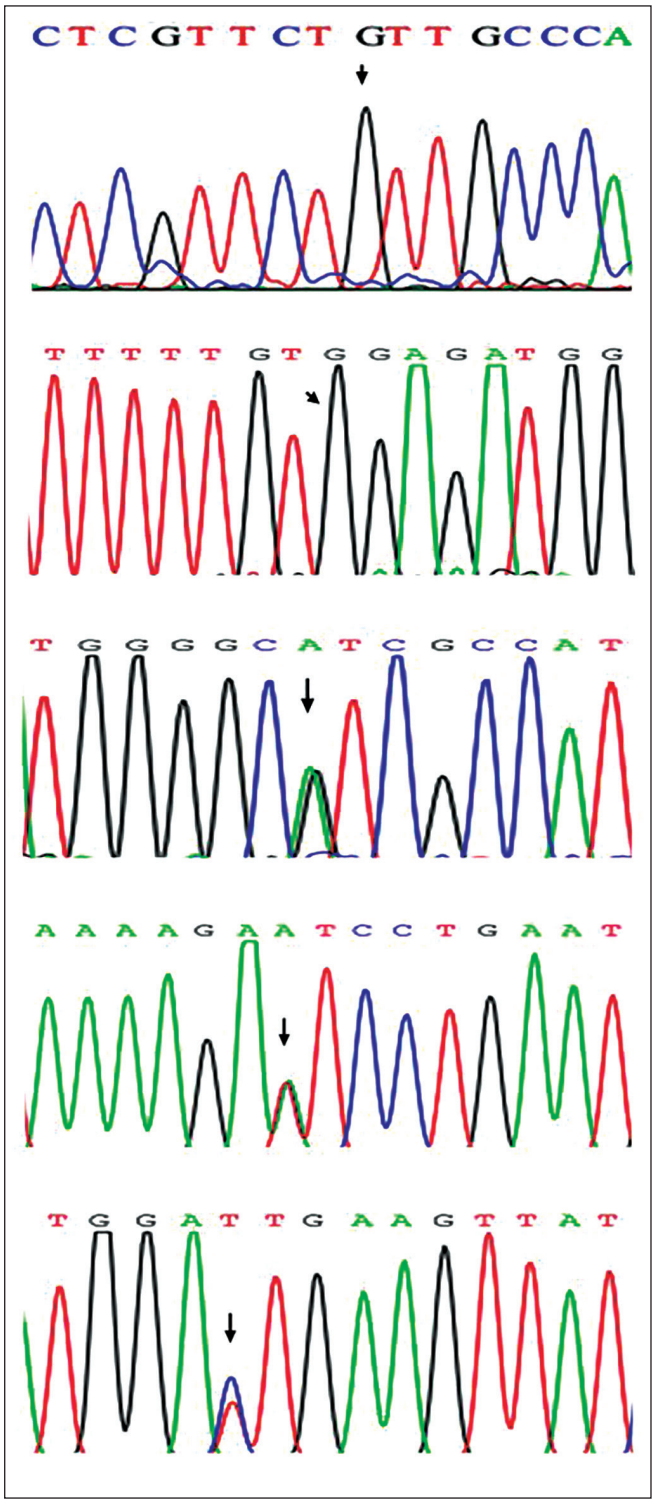

Figure 1: The sequencing traces of allelic change of five single nucleotide polymorphisms: (i) c.643A > G (ii) c.751 + 41A > G (iii) c.751 + 52G > A (iv) c.C > T (v) c.T > A

association of these variations with intractable MTLE-HS. All of these are sporadic cases predominant in Indian population [Table 1]. All 11 exons of *GABRG2* gene (transcript no. ENST00000414552) including intron-exon-intron boundaries were screened in 20 unrelated MTLE-HS patients. We have compared allelic frequencies of various SNPs identified in this study between the control and the epileptic group and this analysis shows no significant variations [Table 4]. One SNP (rs418210) which appears to be significant as its frequency is higher in control group as compared to the epileptic group is actually a silent mutation causing no functional variation, so this SNP is also considered to be insignificant in this study. We could not detect any pathogenic mutations in this study. To some extent these results suggest that the *GABRG2* subunit variations are not associated with susceptibility to MTLE-HS in this population. Although several single-nucleotide amplified polymorphisms in the *GABRG2* gene (γ2 subunit) have been reported in various studies in different epilepsy pathologies, only a few polymorphisms are found to have functional significance in different epilepsies. Not many such studies are reported from Indian population. One report shows involvement of GABRA1 IVS11 + 15 A > G polymorphism in increasing risk for developing epilepsy as well as in modulating drug response in pharmacotherapy, while *GABRG2* 588C > T was not found to be associated either with epilepsy susceptibility or with drug resistance in north Indian epilepsy subjects. In our study we found five SNPs in the *GABRG2* gene, but none of them seem to be specific to the epileptic group and of functional significance. These observations raise the question of whether genetic variation of the *GABRG2* gene confers susceptibility to MTLE-HS in this population. Although many common*GABRG2* receptor gene missense mutations like R43Q, R138G, and K289Mcausing trafficking and/or channel gating defects are reported in literature; however, to our surprise we could not find these SNPs in our studies.[24] Numerous studies have shown that the allelic and genotype frequencies of various SNPs of *GABRG2* gene 588C > T and rs211037 polymorphism show wide variations across different world populations which is attributed to ethnic and phenotypic differences.[17,20,22] Hence in order to get significant findings, it is essential to do such studies in different populations followed by correlation of these findings. Although various studies support the fact that different subunits of GABRG2 receptor subtypes play differential roles in epilepsy; however, there are very few reports showing the role of genetic variants of *GABRG2* in epilepsy and multiple drug resistance. Therefore, in this respect our study contributes towards the investigation of various SNPs in *GABRG2* gene and their functional significance in Indian population. Even though the current study was on small number of patients; our preliminary data shows lack of significant differences between found polymorphisms in cases and controls in *GABRG2* receptor genes and does not support association of this gene with the development or as a susceptibility gene in MTLE-HS patients in this particular population. Although our study and several other genetic association studies did not identify many SNPs in *GABRG2* gene showing association of this polymorphism either with epilepsy susceptibility or drug resistance, still the genetic contribution of *GABRG2*cannotbeentirelyexcludedatthispoint. Our preliminary study not only provides a basis but also makes it all the more important to do future studies in a bigger cohort of patients to analyze more SNPs in the *GABRG2* gene in order to exclude some rare variants as susceptibility alleles in MTLE-HS patients. Also it will be important to look for other possible regulatory mechanisms like the copy number variations (CNVs), gene expression alterations, and/or epigenetic modulations such as modifications in DNA methylation

Table 2: Primers and product size of each amplicon

	Forward	Reverse	Size (bp)
Exon 1	TGTTAATTCGTGCTGCAGCA	CTGGGTGGTCTCCCGAGT	755
Exon 2	TCCATCTGTGGACTCCTTG	GGAGACAAATACCTGAACAGCT	316
Exon 3	TGGTCTGTGGATAAAAGTCAACT	GTAGACATGTTTATGTGCTCCTATC	274
Exon 4	AGCAAGCTGGAGCTGCTTA	GTCCTAACTCACTGTGGTGGAC	309
Exon 5	ATCTTGCACCTCTCTATGTGCA	TCCATGACATCACATTTTCTCTC	183
Exon 6	CTTTGCTTCATATTGGCAA	CAATTACTCCTTTCCTTTTGC	355
Exon 7	AGTCACCAGCACATTCTCTGC	AGTGATAATATCCAGCTTGGGC	283
Exon 8	CCTCAGTGTCATGTTCATAGAAG	CCTCAGTGTCATGTTCATAGAAG	279
Exon 9	GTGTGTGCATAACCATTAAATAC	AGCAGATCAACATAGAAATGGAC	363
Exon 10	GTAGTCTCACGAGTGACTCAGTT	TTAGCCTGCAGATAGGCTAAT	109
Exon 11	ATGCAATTCTCTTTTCTGTCTAC	AGTTAAATTTAGCAGTTGCATG	752

Table 3: SNPs detected in patients with MTLE-HS

	Nucleotide change	Amino acid change		Known Variation	
		Type	HGVS Nomenclature	Mutation	dbSNP
Exon 6	c. 643A>G	missense	p.Ile215Val	Unknown	rs211035
Intron 6	c. 751+41A>G	-	-	Unknown	rs211034
Intron 6	c. 751+52G>A	-	-	Unknown	rs34281163
Exon 11	c.T>A	-	-	Unknown	rs424740
Exon11	c.C>T	-	-	Unknown	rs418210

Table 4: Allelic frequencies detected in GABRG2 gene polymorphisms in patients and controls

Polymorphisms	Genotype	Allelic frequency in cases	Allelic frequency in controls	*P*-value
rs211035	GG	0.75	0.8	0.705
rs211034	GG	1	0.9	0.147
rs34281163	AG	0.25	0.1	0.212
rs424740	AT	0.4	0.6	0.206
rs418210	TC	0.35	0.75	0.011

patterns of the *GABRG2* gene that may be responsible for the modulation of the function of the *GABRG2* subunit in MTLE-HS patients.

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