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Genetic etiology of new forms of familial epilepsy

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1. ABSTRACT

Epilepsy is a common neurological disorder with an incidence of approximately 0.5%. In order to develop better strategies for treatment of epilepsy, more insight on the etiology and pathogenesis of epilepsy is required. In 2001, based on the diagnostic scheme of the International League Against Epilepsy, three new forms of familial epilepsy were identified. These include familial temporal lobe epilepsy, familial focal epilepsy with variable foci, and generalized epilepsy with febrile seizure plus. Mutation of a distinct set of genes has been reported in several forms of epilepsy. Mutation of *LGI1* gene has been identified in familial lateral temporal lobe epilepsy while mutations of genes which encode sodium channels and $GABA_A$ receptors have been reported in generalized epilepsy with febrile seizure plus. However, no disease-causing gene has yet been found in families with familial mesial temporal lobe epilepsy or those with familial focal epilepsy with variable foci. Here, we review the genetic background of these three familial epilepsy syndromes, and provide a better insight on their genetic etiology.

2. FAMILIAL TEMPORAL LOBE EPILEPSY (FTLE)

According to the diagnostic scheme for classification of epileptic syndromes proposed in 2001, Familial temporal lobe epilepsy is a new form of epilepsy (1). Based on clinical and molecular characteristics, FTLE is divided into mesial and lateral forms (2). Both these forms show autosomal dominant inheritance with incomplete penetrance. Patients with familial mesial temporal lobe epilepsy (FMTLE) exhibit mesial temporal onset, febrile seizures, and hippocampal sclerosis (3,4). However, the gene involved in this form of the disease has not yet been identified. Familial lateral temporal lobe epilepsy (FLTLE), is an autosomal dominant partial epilepsy with auditory features (5). This disease is associated with mutations of leucine-rich, glioma-inactivated 1 (*LGI1*) gene which resides on chromosome 10q (6,7). Based on the fact that no families with FMTLE were found to have an *LGI1* mutation, FMTLE and FLTLE are different genetic syndromes.

2.1. Clinical features

FMTLE is characterized by seizures with mesial temporal symptoms, including deja-vu, rising epigastric sensation, psychotic episodes, experiential phenomena, (8). The common manifestation is complex partial seizure with oral or manual automatism. In addition, secondary generalized tonic-clonic seizures may occur. The mean age for onset of seizure is about 10 years, with a range of 1-56 years (3). Some patients also show a history of febrile seizures. EEG recordings show unilateral or bilateral epileptiform discharges, and rhythmic activity over mesiotemporal areas. Majority of patients with FMTLE have a good prognosis, and exhibit spontaneous remissions. Refractory seizures may occur in up to 29% of patients (3). Moreover, the MRI reveals hippocampal atrophy and hyperintense T2 signals are present both in asymptomatic family members and in about 70% of affected individuals (3,6). However, hippocampal atrophy associated with abnormal T2 signal is more frequent and more severe in patients with intractable seizures (3).

FLTLE is characterized by focal seizures with auditory auras. Other manifestations include psychotic, cephalic and other sensory and motor phenomena, ictal aphasia and visual misperceptions, and secondary generalized tonic-clonic seizures. Age of onset is variable, usually in the second or third decades of life, and seizures are easily controlled with antiepileptic drugs. EEG recordings are frequently normal but occasional temporal epileptiform discharges may occur (9-15). No evidence of hippocampal atrophy is found in MRI imaging. However, 45% of affected family members have a lateral temporal malformation, such as enlargement of left temporal lobe, or global increase in the volumes of the anterior temporal lobes (14).

2.2. Genetics

Temporal lobe epilepsy has been traditionally regarded as an acquired disease, and genetic factors were thought to be of low significance in the development of the disease. Since the first familial type of mesial temporal lobe epilepsy in 1996, this view is being changed and FMTLE is gradually being recognized to be a heterogeneous disease (16).

2.3. Loci

Several Loci are associated with familial temporal lobe epilepsy. The first locus was mapped in 1995. Linkage analysis showed a 10-cM region on chromosome 10q24 with a maximum two-point LOD of 3.99 and the maximum LOD of 4.83 at marker D10S192 in a family with autosomal dominant partial epilepsy with auditory features (5). This locus was confirmed in other pedigrees. Linkage was subsequently reported to an overlapping interval in another large family (9,10,17,18). Digenic inheritance with loci on chromosomes 1q25–q31 and 18qter was suggested with significant LOD>3 for markers on 18qter and suggestive LOD>2 for markers on 1q25-q31 in a large French family with febrile seizures and subsequent temporal lobe epilepsy without hippocampal abnormality (19). In addition, a locus on chromosome 12q22-23.3 was identified in a five generation family with familial temporal lobe epilepsy and febrile seizures but without hippocampal sclerosis. A maximum two-point logarithm of odds (LOD) of 6.94 and the maximum multipoint LOD 7.87 were reached at marker D12S1706 using a genome wide scan analysis (20). More recently, a locus of FMTLE was identified in a four-generation family with several affected members with FMTLE. Significant linkage was established on chromosome 4q13.2-q21.3 with a maximum multipoint linkage LOD of 3.59. Possible candidate genes at this locus, including sodium bicarbonate cotransporter (SLC4A) gene and cyclin I (CCNI), was sequenced, but no disease-causing mutation was identified in these genes (21).

The FMTLE is characterized by a relatively benign course and without hippocampal sclerosis. However, the presence of hippocampal atrophy in both affected and unaffected family members in FMTLE suggests that a genetic heterogeneity might exist (22). On the other hand, FMTLE might be due to mutation of a gene(s) that causes hippocampal abnormalities, and is under the influence of other genetic and environmental modifying factors (23). However, linkage analysis has failed to find a significant positive LOD scores at any of the genotyped microsatellite markers in a family with FMTLE who exhibited hippocampal atrophy. Based on the available evidence, potassium channel is not thought to be the major gene responsible for the phenotype of FMTLE with hippocampal atrophy (24)

2.4. Genes

Mutations in the *LGI1* gene have been found in individuals of families who are affected with FLTLE (25,26). A study in an Italian population showed that *LGI1* is not a major gene for sporadic cases of partial epilepsy with auditory features (27). Therefore, *LGI1* seems to be a specific gene for FLTLE. However, the identification of *LGI1* mutations in only one-half of families with the phenotype suggests that FLTLE is genetically heterogenous (25,26). In contrast to FLTLE so far, no specific gene mutation has yet been found in patients with FMTLE.

LGI1 gene which is located at the 10q24 with central leucine-rich repeat region, is predominantly expressed in neural tissues. The mature 60 kD LGI1 protein shows a high degree of homology with a number of transmembrane and extracellular proteins that control cell growth, adhesion, and migration (28). In addition, *LGI1* may modulate the properties of a potassium channel through protein-protein interactions by their intracellular domains (29). In some families with lateral temporal malformation, mutation of *LGI1* gene suggests that this gene might be implicated in the development of the temporal lobe (14). In affected family members with FLTLE, several mutations of *LGI1* have been implicated in the pathogenesis of the syndrome, including: (1) a 1372A-C transversion in exon 8, resulting in a missense glu^{383}-to-ala (E383A) substitution (6); (2) a one-basepair deletion, 835delC, in exon 6 (6); (3) a single nucleotide change, from C to A, at the third base from the acceptor intron-exon boundary of exon 4 (6); (4) a cys46-to-arg substitution (C46R) in a conserved extracellular cysteine cluster region

of the *LGI1* gene (13); (5) a 1320C-T transition in exon 8, terming 1420C-T, as a *de novo* mutation. (7,30); (6) a single-basepair deletion in position 758 in exon 7 (7); (7) a heterozygous 953T-G transversion in exon 8, resulting in a phe^{318}-to-cys (F318C) substitution (31). (8) a point mutation, IVS7-2A>G, resulting in exon 8 skipping, thus producing a truncated protein (14); (9) a 598T/C substitution in exon 6, causing cysteine200-to-arginine (C200R) substitution (15); (10) a missense mutation at position 1295 (1295 T-A) in exon 8, causing valine at position 432 to be replaced by glutamic acid residue (V432E) (15); (11) a heterozygous missense T to C transition at the second base of codon 26 in exon 1, causing a leucine to arginine change (L26R) (32); (12) a missense mutation in exon 1 (348T>C), resulting in a cysteine-toarginine substitution in amino acid residue 42 (C42R) (26); (13) a missense mutation in exon 8 (1117T>C), resulting in an isoleucine-to-threonine substitution in amino acid residue 298 (I298T) (26); (14) a missense mutation in exon 3 (553C>A), resulting in an alanine-to-aspartate substitution in residue 110 (A110D) (26); (15) a heterozygous single-nucleotide deletion at position 329 (del 329C), resulting in a frameshift predicted to introduce a stop codon at the end of the exon 3 (33); (16) a heterozygous missense mutation at position 435 (C435G) in the exon 5, predicted to result in a serine-to-arginine substitution at codon 145 (33); (17) a missense mutation in exon 1 (c.124T->G), leading to the replacement of a conserved cysteine by glycine (C42G) (25); (18) a missense mutation in exon 8 (c.1418C->T), changing a serine to a leucine (S473L) (25); (19) a heterozygous c.431+1G>A substitution located in the almost invariant donor splicing site of intron 5 caused exons 3 and 4 to be skipped in the *LGI1* transcript (29); (20) a heterozygous c.695T>C substitution was detected in exon 7 causing the leucine at position 232 to be replaced by a proline (p.Leu232Pro/L232P) (29).

3. FAMILIAL FOCAL EPILEPSY WITH VARIABLE FOCI (FFEVF)

ILAE recently proposed that FFEVF is a new epilepsy syndrome (1). This syndrome which involves frontal, temporal, parietal or occipital foci cannot be diagnosed in a single individual since the seizure pattern and EEG localization differ among different members of the same family. To date, at least nine families with autosomal-dominant FFEVF have been reported (34-37). FFEVF shows about 70% penetrance (23). Based on linkage analysis, FFEVF is linked to chromosome 22q (35). However, it is difficult to identify some inherited forms of FFEVF due to their low penetrance, and variability in age of onset and electroclinical features (34).

3.1. Clinical features

FFEVF is relatively rare and family members show a variety of focal seizure types. The clinical manifestation is consistent with EEG localization, mainly with simple or complex focal seizures. Secondary generalized tonic-clonic seizures occur in 60-86% patients. Each individual exhibits a single seizure pattern (4,37). The most frequent symptom is nocturnal seizures which primarily are of frontal lobe origin and occur upon awakening (37,38). However, predominant temporal seizures are reported in an Australian family (34). The mean age of the onest of seizure is variable, but mostly falls within the first three decades of life (37). The interitcal EEG recordings show that, in approximately 86% of patients with FFEVF, there are EEG abnormalities, including focal slow waves, focal spikes or sharp waves with a unilateral or bilateral distribution (36). FFEVF is considered a benign epilepsy, and most patients show a good response to traditional antiepileptic drugs, especially, carbamazepine (36).

3.2. Genetics

Based on genetic analyses, FFEVF has an autosomal dominant inheritance with an incomplete penetrance. The studies on the genetics of FFEVF have excluded the possibility of sharing the same region on chromosome 20 with autosomal dominant nocturnal frontal lobe epilepsy. In a four-generation Australian family with ten family members affected by FFEVF, an initial genome-wide analysis suggested a probable linkage on chromosome 2q (34). However, this locus has not been confirmed by other investigations. Moreover, linkage analysis has identified a new susceptibility locus on chromosome 22q11-12 in two large French-Canadian families with FFEVF (35). This was recently confirmed in Dutch (38), Spanish and French-Canadian families (37). However, no specific gene mutation contributing to the development of FFEVF has yet been identified.

4. GENERALIZED EPILEPSY WITH FEBRILE SEIZURE PLUS (GEFS+)

According to the 2001 ILAE diagnostic scheme, GEFS+ is an unidentified form of epilepsy syndrome (1). In 1997, Scheffer and Berkovic described “generalized epilepsy with febrile seizure plus” as a genetic condition with a heterogeneous clinical phenotype with febrile seizures (39). Many other studies confirmed the existence of this familial form of the disease. Usually, presence of febrile seizures plus in more than one member of the family can be considered as an exceptional feature. Four susceptibility loci and five genes were found to contribute to this genetic syndrome.

4.1. Clinical features

Patients with GEFS+ have normal neurologic exam and initially show febrile seizures, which last beyond the age of 6. Afebrile seizures occur in various forms including generalized tonic-clonic seizures, typical absences, myoclonic-astatic seizures, atonic seizures and focal seizures (40). Since the spectrum of GEFS+ encompasses both generalized and partial epilepsies, some believe that GEFS+ is better be renamed as “autosomal dominant epilepsy with febrile seizures plus (ADEFS+)” (41). The phenotype of individuals in a pedigree is variable. Some GEFS+ patients show no specific interictal EEG abnormalities. However, in most patients, EEG usually shows diffuse and irregular spike and wave complexes or multiple spike waves. In GEFS+ patients with atonic seizures, spike and wave complexes can be observed at the frequency of 2-3 Hz (40,42).

4.2. Genetics

It is known that a GEFS+ syndrome has a genetic component. Four susceptibility loci of GEFS+ syndrome reside on chromosomes 19q (*GEFSP1*) (43), 2q (*GEFSP2*) (44), 5q (*GEFSP3*) (45), and 2p (*GEFSP4*) (46). The existence of multiple loci suggests that GEFS+ is genetically heterogeneous. Furthermore, recent studies have demonstrated that patients with GEFS+ may have mutations in one of several genes that encode sodium channels and $GABA_A$ receptors, including three voltage-gated sodium channel genes, *SCN1A*, *SCN2A*, and *SCN1B*, and two $GABA_A$ receptor subunit genes, *GABRG2* and *GABRD*. The mutation of channel genes leads to distinct changes in sodium and activity or in GABAergic currents, and contributes to the development of seizures. These mutations suggest that GEFS+ syndrome is a channelopathy. However, since Bonanni and colleagues have found, in seven Italian families, mutations in genes which are unrelated to *SCN1A*, *SCN1B*, and *GABRG2*, GEFS+ might be a heteregenous group of diseases (47).

4.3. Loci

The first locus of GEFS+ was mapped in 1998 in a large Anglo-Australian family that showed presence of a linkage to chromosome 19q13.1 with multipoint LOD score of 3.85 (43). The second locus was identified in 1999 in 13 members of a French family affected over three generations (44). In this study, a genome wide scan was performed which identified a new locus on chromosome 2q21-q33 with an autosomal dominant mode of inheritance and an incomplete penetrance at 85%. The maximum pairwise LOD score was 3.00 for marker D2S2330. Other studies provided hints to the existence of a chromosome 2q locus, including at 2q24-33 in a French family (48) and at 2q23-31 in an Australian family (49). In 2001, another GEFS+ susceptibility locus was identified on chromosome 5q34 in a large three-generation French family with 17 affected members: 13 had histories of febrile seizures and 7 developed generalized tonic-clonic seizures (45). In addition, genome wide linkage analysis identified the fourth candidate region on chromosome 2p24 in a four-generation Belgian family with a maximum two-point LOD score of 4.22 at marker D2S305 (46).

4.4. Genes

4.4.1. Sodium channel neural type 1 alpha subunit gene (*SCN1A*)

SCN1A gene resides on chromosome 2q24 and has 26 exons. *SCN1A* mutations change persistent sodium current, and change activation, inactivation or recovery from inactivation. These changes lead to neuronal hyperexcitability and epileptic seizures (50). GEFS+-associated *SCN1A* mutations include: (1) a G-to-A transition at nucleotide 4943 in exon 26, resulting in an arg-to-his substitution at codon 1648 (R1648H) (51); (2) a C-to-T transition at nucleotide 2624, resulting in an amino acid substitution thr 875 to met (T875M) (51); (3) a 563A-to-T variant in exon 4, resulting in an asp188-to-val (D188V) missense mutation (50,52); (4) a 4057G-to-C change in exon 21, resulting in a val1353-to-leu (V1353L) missense mutation (52); (5) a 4968C-to-G change, resulting in an ile1656-to-met (I1656M) missense mutation (52); (6) a T-to-C transition in exon 18, resulting in a trp1204-to-arg (W1204R) missense mutation (53); (7) an A-to-C transversion at nucleotide 3809, resulting in a lys1270-to-thr (K1270T) substitution (54); (8) a 4283T-C missense mutation at the pore-forming region, resulting in a val1428-to-ala substitution (Val1428Ala) (55); (9) a heterozygous point mutation c.5054C->T in the transmembrane helix, resulting in ala1685-to-val change (Ala1685Val) (55); (10) a missense mutation (ala1674-to-val substitution in the transmembrane region) (41); (11) a C-to-T transition at nucleotide 4969, resulting in the replacement of arginine-1657 with cysteine in the S4 segment of domain IV (R1657C) (56); (12) a heterozygous mutation (A2336G) in exon 13, resulting in a tyr779-to-cys amino acid substitution (57) (13) a heterozygous single-basepair mutation (T5522C), resulting in a met1841-to-thr amino acid substitution (57); (14) a heterozygous G-to-T substitution, causing an aspartate residue to tyrosine (D1866Y) (58); (15) an aspartic acid for glycine substitution at position 1742 of this sodium channel subunit. The amino-acid replacement lies in the pore-forming region of domain IV (59); (16) a 5569G-to-T substitution in exon 26, causing an amino acid substitution of Nav1.1, val1857-to-leu (V1857L) (60); (17) a 2575C-to-T substitution in exon 14, resulting in the amino acid substitution (R859C) (61); (18) a missense 4096G-to-A mutation, resulting in the alteration of valine residue at the position of 1366 into isoleucine (V1366I) (62).

4.4.2. Voltage-gated sodium channel beta-1 subunit gene (*SCN1B*)

SCN1B gene which resides on chromosome 19q13.1 and spans approximately a 9.0 kb of genomic DNA has 5 exons and 4 introns. It is thought that *SCN1B* increases the density of sodium channels on the cell surface and modulates the inactivation of the sodium current. It also hastens the recovery from inactivation (63), and causes a hyperpolarizing shift in the voltage-dependent inactivation. It also modulates the alpha subunit by increasing the fraction of channels which operate in the fast-gating mode (64). To date, four *SCN1B* mutations have been reported. The C121W mutation (C-to-G transversion of nucleotide 387, resulting in a cys121-to-trp amino acid substitution) has been confirmed in several families (43,65,66). A second mutation which involves a heterozygous A-to-C transversion in the splice acceptor site of exon 3 of the *SCN1B* gene leads to the deletion of 5 amino acids within the extracellular immunoglobulin-like fold of the protein (67). R85H and R85C mutations have been recently described (66).

4.4.3. Sodium channel neural type 2 alpha subunit gene (*SCN2A*)

SCN2A gene is located on chromosome 2q23-24.3 and has 4 internal homology repeats, each of which contains 8 potential transmembrane segments, and multiple glycosylation and phosphorylation sites. CHO cells with transient expression of the *SCN2A* gene displayed voltage-dependent, sodium-selective, and tetrodotoxin-sensitive currents, biophysical and pharmacologic properties characteristic of sodium channels. Thus, this gene plays a fundamental role in controlling electrical excitability during

development and plasticity (68). So far, only one mutation of the *SCN2A* gene has been described in a patient with febrile seizures associated with afebrile seizures. This R187W mutation is due to a c.562C-to-T change, and causes an arg^{187}-to-trp substitution (69).

4.4.4. Gamma-aminobutyric acid (GABA) receptor gamma 2 subunit gene (*GABRG2*)

GABRG2 gene is located on chromosome 5q31.1-q33.1. The first *GABRG2* mutation involved in the pathogenesis of GEFS+ was reported by Baulac *et al* who identified an A/T variant in exon 8, which caused substitution of a positively charged lysine residue by a neutral methionine (K289M). This mutation may decrease the amplitude of GABA-activated currents, but does not change benzodiazepine sensitivity (45).

4.4.5. Gamma-aminobutyric acid receptor delta gene (*GABRD*)

GABRD gene is located on chromosome 5q31.1-q33.1, has nine exons, and encodes a subunit of the ligand-gated chloride channel for gamma-aminobutyric acid, the major inhibitory neurotransmitter in the mammalian brain (70). Two mutations in *GABRD* were identified recently, including a glu^{177}-to-ala mutation (E177A) and a heterozygous arg^{220}-to-his substitution (R220H). Both variants result in decreased $GABA_A$ receptor current amplitudes and therefore are associated with increased neuronal excitability and may contribute to the common generalized epilepsies (71).

5. CONCLUSION

In conclusion, genetic factors play an important role in these three new epilepsy syndromes. *LGI1* mutation contributes to familial lateral temporal lobe epilepsy, and mutation of five genes (*SCN1A*, *SCN2A*, *SCN1B*, *GABRG2* and *GABRD*) are involved in generalized epilepsy with febrile seizure plus. Functional analysis of the mutant genes should provide new strategies for treatment of these forms of epilepsy. Further studies including determination of genetic pedigree, however, are required in familial mesial temporal lobe or familial focal epilepsy to identify the etiology of these forms of epilepsy.

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