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The Molecular Genetics of the Benign Epilepsies of Infancy

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1. Introduction

Three benign epilepsy syndromes with autosomal dominant inheritance are recognised in infancy. These are Benign Familial Neonatal Epilepsy (BFNE), Benign Familial Neonatal-Infantile Epilepsy (BFNIE) and Benign Familial Infantile Epilepsy (BFIE). These disorders were previously known as Benign Familial Neonatal Seizures, Benign Familial Neonatal-Infantile Seizures and Benign Familial Infantile Seizures, respectively (Berg et al., 2010). They were recently renamed by the International League Against Epilepsy Classification Committee. The three disorders differ in their average ages of onset but age of onset distributions overlap between the syndromes. Ages of onset vary within syndromes and within families affected with any of the syndromes.

BFNE patients have lateralised motor seizures with a mean age of onset of around 3 days of age and a mean age of seizure offset of 3 months of age. Subsequent neurological development usually proceeds normally. However, about 15% of patients have later seizures or epilepsy and occasional cases deteriorate into severe epileptic encephalopathies with intellectual disability (Dedek et al., 2003; Borgatti et al., 2004; Steinlein et al., 2007). The benign form of the disorder was originally described in an Austrian family by Rett and Teubel (1964). Since then numerous BFNE families have been described, many with potassium channel subunit mutations, to provide a well established range of presentations.

BFIE was originally described by Watanabe and colleagues in 1987, and is sometimes referred to as Watanabe syndrome. Watanabe observed that a subgroup of infants with generalised motor seizures had subsequent normal development and became seizure-free by 3 years of age. Similar families were subsequently described by Vigevano and colleagues (1992). Onset of seizures in BFIE occurs between 4 and 6 months of age with seizure offset generally occurring by 12 months of age. Seizures are generally not seen in later life. However, some cases develop paroxysmal dyskinesia or paroxysmal kinesigenic choreoathetosis in adolescence. This is known as infantile convulsions and choreoathetosis (ICCA) syndrome.

BFNIE patients have similar seizures to those seen in BFNE and BFIE, with the average age of onset intermediate between the other two. Although BFNIE differs from these disorders in the average age of seizure onset, the age of onset distribution which can range within a single family from 3 days up to 13 months of age (Herlenius et al., 2007), significantly
overlaps with BFNE and BFIE. Seizure onset in BFNE most commonly occurs at between 2 and 4 months of age. Clinically the condition was first described by Kaplan and Lacey (1983) and molecularly delineated two decades later (Heron et al., 2002). The aim of this chapter is to describe the current state of knowledge of the molecular genetics underlying these disorders and the significance that this has for patient care.

2. The molecular genetics of benign familial neonatal epilepsy

Benign familial neonatal epilepsy is most commonly caused by mutations in two related voltage-gated potassium channel subunit genes, KCNQ2 and KCNQ3. Together, these form the pore of the neuronal M-channel, which plays an important role in neuronal inhibition by acting as a “brake” on repetitive action potential discharges (Delmas & Brown, 2005). Mutations in KCNQ2 and KCNQ3 were originally described in 1998 (Biervert et al., 1998; Charlier et al., 1998; Singh et al., 1998). There are now more than 80 known mutations in KCNQ2; but only four described for KCNQ3. There may be other, rare, families with mutations in other genes.

2.1 BFNE caused by mutations in the potassium channel subunit KCNQ2

KCNQ2 (OMIM 602235) encodes one of the pore-forming subunits of the M-channel. The M-channel is a heteromultimer consisting of two KCNQ2 and two KCNQ3 proteins, as well as accessory subunits. The gene is located close to the q-arm telomere of chromosome 20, at 20q13.3. It consists of 17 exons embedded within 87kb of genomic DNA. The gene codes for an 872 amino acid protein consisting of three domains: a short N-terminal domain; a transmembrane domain; and a large C-terminal domain, which contains regions that interact with other channel subunits. The gene has five splice variants, which produce proteins that differ in the C-terminal domains. The transmembrane domain consists of six transmembrane segments (S1-S6) and the pore-loop between segments S5 and S6, which forms the lining of the ion pore. The S4 domain is the voltage sensor and contains a number of positively charged arginine or lysine residues, which are required for normal channel function. The S4 segments move within the membrane in response to a change in voltage, opening the channel.

BFNE was originally mapped to the KCNQ2 locus in 1989 (Leppert et al.) by linkage analysis of a large, four-generation pedigree. Further families were reported that confirmed the chromosome 20q localisation (Ryan et al., 1991; Malafosse et al., 1992). KCNQ2 was identified as the BFNE gene at this locus when a submicroscopic deletion containing KCNQ2 was detected in a single BFNE family. Screening of additional BFNE families revealed missense, frameshift and splice-site mutations in KCNQ2 (Singh et al., 1998). A frameshift mutation was simultaneously identified in KCNQ2 when it was screened as a candidate gene in another family mapped to the 20q locus (Biervert et al., 1998).

In total, 85 mutations in KCNQ2 have been described in the scientific literature (Heron et al., 2007; Soldovieri et al., 2007; Wuttke et al., 2007; Yalcın et al., 2007; Neubauer et al. 2008; Sadewa et al., 2008; Goldberg-Stern et al., 2009; Ishii et al., 2009; Kurahashi et al. 2009; Lee et al., 2009; Miceli et al., 2009; Volkers et al. 2009; Yum et al., 2010). These include missense, nonsense, splice site and frameshift mutations as well as deletions or duplications affecting multiple exons. The latter type of mutation accounts for over 10% of the published KCNQ2 mutations and for around 20% of the KCNQ2 mutations in one BFNE cohort.
comprehensively analysed for all classes of mutation (Heron et al., 2007). Several deletions have been described which also affect the genes surrounding KCNQ2 (Kurahashi et al., 2009). Patients carrying these deletions do not exhibit different phenotypes to BFNE patients with KCNQ2 missense mutations, indicating that the loss of one copy of these contiguous genes is no more pathogenic than the loss of one copy of KCNQ2 alone. The deletions and duplications affecting KCNQ2 are shown in Figure 1.

Approximately one-third of the mutations in KCNQ2 are missense mutations. Unlike the truncating mutations, which are spread throughout the gene, most of the missense changes occur in regions of functional importance. A cluster of missense mutations is seen in the transmembrane domain, with mutations particularly frequent in the S4 segment and the pore-loop. Functional studies of some of these mutations showed that they reduce channel activity and thus reduce neuronal inhibition (Soldovieri et al., 2007). Clusters of missense mutations are also seen in two regions of the C-terminal domain involved in binding to calmodulin. This interaction is known to be required for optimal channel function and mutations affecting it can disrupt the interaction and thus the normal function of the M-channel (Wen and Levitan, 2002; Yus-Najera et al., 2002; Richards et al., 2004).

The published mutations in KCNQ2 are summarised in Table 1. More than half of the mutations in KCNQ2 are either truncating mutations or large deletions or duplications that disrupt the structure of the gene. Both of these types of mutation extinguish protein expression from the mutated allele. Haploinsufficiency is the most significant mutational mechanism affecting KCNQ2 that manifests as BFNE.

| Mutation Type                  | Number Reported |
|-------------------------------|-----------------|
| Start Codon                   | 2               |
| Missense                      | 28              |
| Nonsense                      | 9               |
| Frameshift                    | 21              |
| In-frame deletion             | 3               |
| Splice site                   | 11              |
| Large deletion or duplication | 10              |
| Other                         | 1               |
| **Total**                     | **85**          |

Table 1. Summary of mutations reported in KCNQ2

### 2.2 BFNE caused by mutations in the potassium channel subunit KCNQ3

KCNQ3 (OMIM 602232) encodes the second pore-forming subunit of the M-channel. The KCNQ3 gene is located on the long arm of chromosome 8, at 8q24, and consists of 15 exons spread across 360kb of genomic DNA. The 849 amino acid KCNQ3 protein has a structure very similar to that of the KCNQ2 protein described above. The two proteins have highly homologous sequences in the transmembrane domains, but the sequences of the N- and C-terminal domains differ markedly (GenBank accession numbers NP_742105 and NP_004510).

Following the linkage of BFNE to the KCNQ2 locus at 20q13.3, families were described that did not link to the region, indicating the presence of a second locus for the disorder. Some of these families were found to have evidence of linkage to a locus on chromosome 8q (Lewis et al., 1993; Steinlein et al., 1995) where the KCNQ3 gene, with similarities to the KCNQ2
gene, was known to map. A mutation in KCNQ3 was described at the same time as the first mutations in KCNQ2 (Charlier et al., 1998). Only four mutations in KCNQ3 associated with BFNE have been reported in the literature. All of these affect amino acid residues located in or near the pore-loop (Charlier et al., 1998; Hirose et al., 2000; Singh et al., 2003; Li et al., 2008a). These mutations have not been functionally investigated, so their precise effect on channel function is unknown. The transient occurrence of seizures in BFNE may be due to changes in the expression of KCNQ2 and KCNQ3 that occur during development (Weber et al., 2006; Geiger et al., 2006; Kanauami et al., 2008).

Fig. 1. Nine microchromosomal rearrangements described in KCNQ2. A: Intragenic deletions (red) and duplication (blue). B: Deletions extending beyond KCNQ2. A tenth deletion has been reported (Steinlein et al., 2007) but its breakpoints were not described.

2.3 BFNE with other causes

Occasional cases of BFNE have been reported with causes other than mutations in KCNQ2 or KCNQ3. A small family with a pericentricromeric inversion on chromosome 5 was reported in 2002 by Concolino and colleagues. The breakpoints for this inversion were mapped to 5p15.1 and 5q11.2. This inversion is presumed to disrupt a gene at one of these breakpoints, but this gene has not been identified. However, it is possible that further BFNE families have missense or other mutations affecting this gene on chromosome 5. It is also possible that the inversion disrupts a regulatory sequence for a gene located at some distance from the breakpoint.

Mutations have also been reported that cause BFNE with co-morbidities (Dedek et al., 2001; Dedek et al., 2003; Borgatti et al. 2004; Schmitt et al., 2005; Steinlein et al., 2007). Recently a
family with familial neonatal seizures and intellectual disability caused by a microduplication at chromosome 2q24.3 has been reported (Heron et al., 2010). The four affected members of this family all had neonatal seizures and some degree of intellectual disability ranging from borderline intelligence to an IQ score less than 40. A second patient with a similar microduplication has been described with seizures starting at 2-3 weeks of age and developmental delay (Raymond et al., 2011). This suggests that microduplications at chromosome 2q24.3, which contains a cluster of five voltage-gated sodium channel genes, could be a recurrent cause of neonatal seizures accompanied by intellectual disability. Such mutations can be easily detected and characterised using comparative genome hybridisation (CGH), therefore patients with neonatal seizures and intellectual disability should be tested for microduplications using this method. The pathogenic mechanism of these microduplications is hypothesised to be an increase in the expression of the duplicated sodium channel genes, in contrast to the haploinsufficiency cause by truncating or deletion mutations or the changes in function caused by missense mutations in KCNQ2. The two duplications described so far have slightly different breakpoints (Raymond et al., 2011), but are probably both the result of non-homologous recombination between the five sodium channel genes in the region. These reports suggest that not all cases of BFNE are caused by KCNQ2 and KCNQ3 mutations. However, these exceptions are not common as mutations in these two genes account for around 90% of cases of BFNE.

3. The molecular genetics of benign familial neonatal-infantile epilepsy

Patients with benign familial neonatal-infantile epilepsy (BFNIE) have similar seizures to those seen in BFNE and BFIE. BFNIE differs from these disorders in the age of onset, which can range within a single family from 3 days up to 13 months of age (Herlenius et al., 2007), although seizure onset in BFNIE most commonly occurs at between 2 and 4 months. BFNIE was first described as a distinct clinical entity by Kaplan and Lacey in 1983. They described an American family with 12 affected individuals who had seizures with onset ranging from 3 days to 3½ months. All these individuals had subsequent normal development. Another family was subsequently described with seizure onset also occurring between 3 days and 3½ months of age (Lewis et al., 1996). Linkage to KCNQ2 and KCNQ3 was excluded for this family, indicating the existence of an additional locus for seizures occurring in early infancy.

3.1 Identification of mutations in the sodium channel subunit gene SCN2A

SCN2A (OMIM 182390) is located at chromosome 2q24.3 and contains 26 exons spread across 150kb of genomic DNA. The gene codes for the voltage-gated sodium channel alpha subunit Na+1.2, a large protein of 2005 amino acids. Voltage-gated sodium channels consist of the large alpha subunit and two small accessory beta subunits. The alpha subunits consist of a small N-terminal domain, four transmembrane domains (DI-DIV) linked by intracellular loops, and a large C-terminal domain. The transmembrane domains all comprise six transmembrane segments (S1-S6) with a pore-loop between segments S5 and S6. The S4 domains act as voltage sensors. Overall, the structure of one of these transmembrane domains is very similar to the structure of the transmembrane domains of the voltage-gated potassium channels associated with BFNE described above. Indeed, it is thought that the voltage-gated sodium channels evolved from the assembly of four voltage-gated potassium channels (Marban et al., 1998).
SCN2A was originally suggested as a candidate gene for BFIE by Malacarne and colleagues (2001) when they mapped four BFIE families to the chromosome 2q24.3 locus. Mutations in SCN2A were then described in two families: the family described by Lewis and colleagues (1996) and a newly described family (Heron et al., 2002). Mutations have been subsequently described in another ten families and one sporadic case diagnosed clinically with neonatal seizures, who had a de novo mutation (Berkovic et al., 2004; Striano et al., 2006a; Herlenius et al., 2007; Liao et al., 2010). These families included the one originally described by Kaplan and Lacey (1983) and one of the families mapped to the SCN2A region by Malacarne and colleagues (2001). Interestingly, two of these families were originally described by clinical criteria as having BFIE (Malacarne et al., 2001; Striano et al., 2006a), highlighting the clinical overlap between BFNIE and BFIE.

The mutations in SCN2A associated with BFNIE are distributed throughout the SCN2A protein. Most of them occur either in the transmembrane segments or in intracellular loops, as shown in Figure 2. The mutations were originally predicted to increase sodium current, as increased sodium current leads to hyperexcitability (Heron et al., 2002). Functional studies done for six of the mutations supported this prediction (Scalmani et al., 2006; Xu et al., 2007; Liao et al., 2010). There have been two possible mechanisms suggested as the basis for the transient occurrence of the seizures in BFNIE. The first of these is age-dependent alternative splicing of SCN2A. The second is developmental changes in the expression of the gene. Studies showing a decrease in the expression of the SCN2A gene during development and a change in the intracellular distribution of the Na\textsubscript{+}1.2 protein suggest that the latter mechanism is the more plausible of the two (Liao et al., 2010).

![Fig. 2. Diagram showing the structure of the SCN2A protein and the locations of published mutations associated with BFNIE (red circles). The four transmembrane domains are indicated in bold.](image)

### 3.2 Clinical overlap between BFNE and BFNIE

There is considerable similarity in the phenotypes of BFNE caused by potassium channel mutations and BFNIE caused by SCN2A mutations. The epileptic seizures in BFNE and
BFNIE are similar except for a difference in average age of onset and the two disorders cannot always be distinguished on the basis of age of onset (Mulley et al., 2011). As discussed above, the age of onset in BFNIE ranges from a few days up to one year of age. While most BFNE patients have onset in the neonatal period, occasional patients are reported with later ages of onset up to around 4 months of age, which is the typical age of onset for BFNIE (Singh et al., 2003; de Haan et al., 2006; Heron et al., 2007). A Chinese family with a KCNQ2 mutation has been reported in which the entire family had seizure onset at between 2 and 4 months of age (Zhou et al., 2006). This variation in the age of seizure onset means that, especially in small families or those with limited clinical information, it is difficult to distinguish between BFNE and BFNIE in both familial and sporadic cases. This clinical overlap means that determining the genetic defect is the only certain method to distinguish between BFNE and BFNIE. Making the distinction accurately is of clinical significance as 15% of patients with KCNQ2 mutations have seizures in later life, while this is rare in patients with SCN2A mutations. Seizures in later life have also not been reported in patients with KCNQ3 mutations, although the total number of patients described with these mutations is small (Hirose et al., 2000; Singh et al., 2003; Li et al., 2008a). Genetic diagnosis therefore has prognostic value in these disorders in the context of predicting the likelihood of later seizures. Severe epileptic encephalopathies have also been reported in families with KCNQ2 mutations and this is another consideration when counselling families with KCNQ2 mutations as opposed to those with SCN2A or KCNQ3 mutations (Dedek et al., 2003; Borgatti et al., 2004; Schmitt et al., 2005; Stenlein et al., 2007). Genetic diagnosis therefore has prognostic value in these disorders in the context of predicting the likelihood of later seizures. Severe epileptic encephalopathies have also been reported in families with KCNQ2 mutations and this is another consideration when counselling families with KCNQ2 mutations as opposed to those with SCN2A or KCNQ3 mutations (Dedek et al., 2003; Borgatti et al., 2004; Schmitt et al., 2005; Stenlein et al., 2007). Extension of genetic diagnosis to BFIE awaits the discovery of the BFIE genes.

4. The molecular genetics of benign familial infantile epilepsy

Benign familial infantile epilepsy (BFIE) has a later average age of onset than BFNE and BFNIE (Berkovic et al., 2004). The disorder was originally described by Watanabe and colleagues (1987), who observed that a subgroup of infants with generalised motor seizures had subsequent normal development and later became seizure-free. Additional families were described by Vigevano and colleagues (1992) several years later. The disorder was demonstrated to be genetically distinct from BFNE in 1994 when Malafosse and colleagues excluded BFIE families from linkage to the BFNE region containing KCNQ2. A subset of BFIE patients also have paroxysmal movement disorders with onset in adolescence: either paroxysmal kinesogenic choreoathetosis or paroxysmal dyskinesia. The co-occurrence of these disorders is referred to as infantile convulsions and choreoathetosis (ICCA) syndrome. None of the genes associated with BFIE have been identified. The disorder has been mapped to loci on chromosomes 1, 16 and 19 (Guipponi et al., 1997; Szepetowski et al., 1997; Li et al., 2008b). A single family has been described with partial co-segregation of BFIE and familial hemiplegic migraine (FHM) and a mutation in ATP1A2 (Vanmolkot et al., 2003).

4.1 Rare BFIE loci

The first locus for BFIE was described in 1997. Five Italian families were mapped to a locus on chromosome 19q. The five families shared partial marker haplotypes for the region, possibly suggesting a founder effect – that is, that the five families were descended from a common ancestor and had the same mutation. No further families have been described which map to this locus and the mutation in the region has not been identified. Study of a further seven
Italian BFIE families showed that they were not linked to the locus (Gennaro et al., 1999). This suggests that the putative mutation at the chromosome 19 locus is a rare cause of BFIE restricted to a localised geographic region. Indeed, given the possible founder effect in the five families originally linked to the locus, it may harbour a single BFIE founder mutation.

Another single BFIE family has been mapped to a locus on chromosome 1. This was a large Chinese family containing eight affected individuals. The family was mapped to a 12.4 centiMorgan region on chromosome 1p36.12-p35.1 (Li et al., 2008b) with a maximum LOD score of 3.14. Analysis of 45 candidate genes selected from the 315 genes in the region on the basis of function or neuronal expression did not identify any causative mutations in the family (Li et al., 2010).

### 4.2 BFIE associated with ATP1A2

A single family has been described in which BFIE partially co-segregates with familial hemiplegic migraine (FHM) (Vanmolkot et al., 2003). FHM has been associated with several genes, including ATP1A2, the gene mutated in the family with BFIE. No further families have been described with BFIE and mutations in ATP1A2. However, several families have been described with mutations in the gene and other epileptic phenotypes (Haan et al., 2007). It appears that mutations in ATP1A2 can cause a predisposition to seizures, without being associated with any particular seizure type. Given that there was only partial co-segregation of BFIE and the ATP1A2 mutation in the family described by Vanmolkot and colleagues (2003), it is possible that additional mechanisms are contributing to the seizures in the family.

### 4.3 The chromosome 16p11.2-q12.1 BFIE locus

By far the most common locus for BFIE is located in the pericentromeric region of chromosome 16, between 16p11.2 and 16q12.1. This locus was originally described by Szepetowski and colleagues (1997), who mapped four French families with co-occurrence of BFIE and paroxysmal kinesigenic choreoathetosis (PKC) to the region. Numerous other families have subsequently been mapped to the region for similar conditions. Numerous additional smaller families are consistent with mapping to the region, showing no recombination, although they are of insufficient size to demonstrate linkage. Families mapping to the region include those with BFIE or PKC and PKD alone as well as those with both disorders (ICCA). The intervals for ICCA, BFIE and PKC/PKD from 13 published studies are shown in Figure 3. Two of these localisations (Valente et al., 2000; Callenbach et al., 2005) are small and do not overlap, suggesting that there may be more than one causative gene in the region. However, most of the localisations are large and span the centromere, a region of greatly reduced recombination on chromosome 16, especially in female meioses.

Despite the large number of families that have been mapped to the locus (approximately 50 have been described in the literature), no causative mutation has been identified at the chromosome 16 BFIE locus. A recent analysis of copy number variants in the region did not reveal any pathogenic copy number changes in the region, although low copy numbers of a particular variant were observed with increased frequency in a small cohort of BFIE patients (Roll et al., 2010). This suggests that the BFIE mutation on chromosome 16 has an unusual mechanism or is in an unannotated gene. Such unusual mutational mechanisms include: mutations in regulatory regions; balanced inversions; small copy number changes, which would not be detected by standard CGH arrays; and repeat expansions or contractions as in unstable triplet repeats.
Fig. 3. Physical map showing the positions of microsatellite markers in the pericentromeric region of chromosome 16 and the linkage intervals for ICCA (red), BFIE (blue) and PKC/PKD (green) determined by analysis using the markers. These intervals are derived from the following 13 publications: aSzepetowski et al., 1997; bLee et al., 1998; cSwoboda et al., 2000; dCaraballo et al., 2001; eWeber et al., 2004; fCallenbach et al., 2005; gStriano et al., 2006b; hWeber et al., 2008; iTomita et al., 1999; jBennet et al., 2000; kValente et al., 2000; lCuenca-Leon et al., 2002; mKikuchi et al., 2007.
The identification of the mutation in the chromosome 16 BFIE locus will potentially require the application of techniques for the detection of alterations in gene expression, analysis of the non-coding sequence or the identification of small copy number changes. These techniques have not traditionally been applied for mutation detection. However, they may be required for the identification of the mutation or mutations causing BFIE linked to the pericentromeric region of chromosome 16.

5. Conclusions

The molecular genetic basis of the benign epilepsies of infancy has not been fully determined. The molecular basis for BFIE remains elusive. However, striking progress has been made in determining the mutations underlying BFNE, of which around 90% are in the potassium channel subunit gene KCNQ2. A significant proportion of these are exonic deletions or duplications, so in addition to DNA sequencing comprehensive screening for mutations in this gene requires the application of a technique such as multiplex ligation dependent probe amplification (MLPA) for detecting copy number mutations. A small number of BFNE mutations have also been found in the KCNQ3 subunit, which appears to be far less mutable than KCNQ2. It is apparent from the report of a BFNE family with a pericentromeric inversion of chromosome 5 that other, rare, BFNE loci exist. Some cases of BFNE associated with developmental delay or intellectual disability are caused by duplications of chromosome 2q24.3. This region contains a cluster of voltage-gated sodium channels and the overexpression of these and perhaps other contiguous genes within the microduplication is hypothesised to cause the seizures and other phenotypes associated with the duplications. Only two cases with these duplications have been described so far, but it is likely that more will emerge with the increased routine application of array comparative genome hybridisation in cases that do not fit within conventional syndrome parameters. Mutations in the voltage-gated sodium channel SCN2A have been identified as a cause of BFNIE. There is considerable phenotypic overlap between BFNE and BFNIE, which in some cases can only be resolved by identifying a genetic defect in either SCN2A or KCNQ2/KCNQ3. This is of clinical significance as patients with neonatal or infantile seizures caused by KCNQ2 mutations have a significantly higher risk of later seizures than patients with SCN2A or KCNQ3 mutations, based on current observations of families that have been studied in detail. Several loci have been mapped for BFIE, but no genes have been identified at any of these loci. The most important locus located in the pericentromeric region of chromosome 16 has been the focus of considerable research, but no causative gene has been identified as yet. The identification of the BFIE gene on chromosome 16 remains a major challenge for completing the molecular picture for the benign epilepsies of infancy.

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This book on Epilepsy was conceived and produced as a source of information on wide range of issues in epilepsy. We hope that it will help health care providers in daily practices and increase their understanding on diagnosis and treatment of epilepsies. The book was designed as an update for neuroscientists who are interested in epilepsy, primary care physicians and students in health care professions.

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