EPILEPSY CURRENTS

Current Review
In Basic Science

Advances in Epilepsy Genetics and Genomics

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Current and emerging technologies for mutation identification are changing the landscape of genetics and accelerating the pace of discovery. Application of high throughput genomic analysis to epilepsy will advance our understanding of the genetic contribution to common forms of epilepsy and suggest novel therapeutic strategies for improved treatment.

Epilepsy is a common neurological disease that exhibits a high degree of heritability based on familial aggregation and twin studies (1–6). It is estimated that there is an underlying genetic predisposition for epilepsy in approximately half of individuals, with monogenic epilepsies accounting for less than 1 percent. The vast majority of genetic generalized epilepsies (GGE) and nonacquired focal epilepsies (NAFE) have a strong genetic basis with a complex inheritance pattern in which multiple genetic and environmental factors contribute to epilepsy risk (6–8). Considerable progress has been made in the last 15 years in identifying genes that contribute to monogenic forms of epilepsy. The genes identified are components of neuronal signaling, including voltage-gated ion channels, neurotransmitter receptors, ion channel–associated proteins and synaptic proteins (7, 9, 10). These genes have provided useful insights into the molecular basis of epileptogenesis. However, population-based studies in more common forms of epilepsy have not identified significant risk associated with those monogenic epilepsy genes. Thus, it is likely that there are many more epilepsy genes yet to be discovered. Identification of genes for more common forms of epilepsy will likely come from unbiased genome-wide surveys in large study populations.

Large-Scale Genome-Wide Association and Linkage

Success in identifying monogenic epilepsy genes relied on traditional genetic mapping in large pedigrees with Mendelian inheritance. However, these large pedigrees are rare, limiting the rate of progress. The complex etiology of GGE and NAFE, with multiple genetic and environmental factors contributing to risk, requires larger sample sizes to have sufficient power to detect the responsible genes. A frequent approach for tackling this problem in other common diseases is to perform large-scale genome-wide linkage or genome-wide association studies (GWAS) with large collections of families or cases and controls, respectively.

Epilepsy Currents, Vol. 12, No. 4 (July/August) 2012 pp. 143–146
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To date, two epilepsy GWAS have been published. The first study, reported by Kasperaviciute and colleagues in 2010, included 3,445 individuals with focal epilepsies and 6,935 controls (11). The phenotype criteria were broad and included individuals with focal epilepsy, regardless of etiology. Although the study was sufficiently powered to detect associations with modest effects, none reached genome-wide significance (11). They concluded that it is unlikely that common single nucleotide polymorphisms (SNPs) increase risk for broadly defined focal epilepsies, at least in European populations. A second GWAS, published in 2012, also focused on focal epilepsy but in the Han Chinese population (12). This study included a total 1,087 focal epilepsy patients with acquired (symptomatic) or unknown etiology and 3,444 controls. The analysis used a two-stage approach, with a discovery cohort of 504 patients and 2,947 controls and a replication cohort of 583 patients and 497 controls. In combined meta-analysis of the two stages, the authors identified a single SNP that reached genome-wide significance on chromosome 1q32.1 in the *CAMSAP1L1* gene, encoding a calmodulin-regulated spectrin-associated cytoskeletal protein (12). To date, there has not been a GWAS published for GGE.

A number of family-based genome-wide linkage studies of GGE have been performed (13–18). Failure to replicate the initial linkage in independent families has diminished the impact of those findings. However, the lack of replication is not surprising given that most studies have limited power because of relatively small sample sizes. Recently, the EPICURE Consortium attempted to overcome the power issue with a genome-wide linkage meta-analysis (19). This analysis included 379 genetic generalized epilepsy multiplex families, including 982 relatives with GGEs. Using a broad trait definition, they did not detect any significant linkage. However, stratification by epilepsy subtype revealed significant linkage at 2q34 and 13q31.3 for myoclonic and absence seizures, respectively (19). The locus at 2q34 is supported by an independent report of linkage to this region in a multigeneration family with juvenile myoclonic epilepsy (JME) (20). This study highlights the important influence of phenotype definition on the ability to detect genetic contributions.

Overall, the results from GWAS and genome-wide linkage in common forms of epilepsy have been somewhat disap-

pointing and suggest that genetic risk for epilepsy is quite complex. It may include both rare and common variants that contribute small effects, including both risk and protective alleles. This is not entirely unexpected, considering the high degree of variable expressivity and penetrance observed in monogenic epilepsies, which suggest that gene–gene and gene–environment interactions can have profound effects.

Copy Number Variants

The contribution of structural variation to epilepsy has become increasingly apparent. Structural variation encompasses deletions and duplications of genomic DNA segments larger than 1 kb. In the last several years, a number of studies have examined the contribution of copy number variants (CNVs) to epilepsy (21, 22). Rare, nonrecurrent CNVs have been implicated in several types of epilepsy. Mefford and colleagues (23) examined a cohort of 517 patients with various types of epilepsy, including GGE and NAFE, and observed that 8.9 percent carried one or more rare CNVs that were not present in controls. Another study of GGE and NAFE reported similar rates of rare CNVs as well as an increased burden of large, gene-rich CNVs in patients (24). Rare CNVs also appear to contribute to epileptic encephalopathies, with 7.9 percent of patients carrying rare CNVs not observed in controls (25). These studies suggest that rare CNVs may contribute significant genetic risk in various types of epilepsy.

In addition to rare CNVs, there are a number of CNV hotspots that have been associated with a variety of neuropsychiatric disorders, including autism, intellectual disability, and schizophrenia (26). Examination of CNV hotspots in epilepsy patient cohorts revealed association of recurrent deletions at 15q13.3, 15q11.2, and 16p13.11 with epilepsies (21, 22). The 16p13.11 deletion was associated with both GGE and NAFE, while the 15q11.2 and 15q13.3 deletions were primarily associated with GGE (23, 27–30). The pleiotropic effects of these recurrent CNVs suggest that they may be involved in fundamental neurodevelopmental processes and that the clinical manifestation depends on other genetic and environmental risk factors.

Next-Generation Epilepsy Genetics

With the rapid advances in sequencing technology, whole exome and whole genome sequencing can be accomplished rapidly at an ever-decreasing cost. Whole exome sequencing is an efficient strategy that involves targeted capture and sequencing of the protein coding regions, which constitute approximately 1 percent of the genome. These technological advances will likely accelerate the pace of epilepsy gene discovery.

Application of next-generation sequencing recently implicated two new epilepsy genes. Corbett and colleagues reported mapping of focal epilepsy and intellectual disability with autosomal recessive inheritance to 16p13.3 in a large family (31). To identify the responsible genome, they performed targeted capture and sequencing of the mapped interval (>3 Mb) and identified a pathogenic mutation in *TBC1D24*, a gene of unknown function (31). Veeramah and colleagues applied whole-genome sequencing in a case of sporadic epileptic encephalopathy with autistic features, intellectual disability, ataxia, and SUDEP (32). They performed whole-genome sequencing of the affected patient and her unaffected parents and sibling. Initial sequence analysis revealed 114 potential de novo mutations, 48 of which were novel and not present in any SNP databases. Of the novel variants, 47 were determined to be false positives by Sanger sequencing. The single novel de novo mutation resulted in a missense mutation in *SCN8A*, encoding the voltage-gated sodium channel Nav1.6 (32). Although other voltage-gated sodium channel genes had previously been implicated in epilepsy, this was the first reported association of *SCN8A* with epilepsy.

Large-scale application of next-generation sequencing is likely to reveal additional epilepsy genes in the next 5 years. A large-scale international collaborative effort to sequence epilepsy genomes was recently announced. Epi4k is an NIH-funded National Institute of Neurological Disorders & Stroke Center without Walls that aims to sequence the genomes of approximately 4,000 epilepsy patients (33). The Center without Walls consists of three core facilities (Administrative; Phenotyping Clinical Informatics; and Sequencing, Biostatistics & Bioinformatics) and will initially focus on three projects. The first project will perform whole-exome sequencing of approximately 500 patients with Lennox-Gastaut syndrome or Infantile spasms and their parents, with the underlying hypothesis that these severe epileptic encephalopathies are likely due to de novo mutation in the patient. (34). The second project will examine the genetic basis of GGE and NAFE by whole-genome sequencing of 1,500 pairs of affected first-degree relatives and 300 multiplex families with three or more affected individuals (35). The third project will focus on developing bioinformatic tools for CNV discovery and applying them to the Epi4K whole-exome and whole-genome sequence data to better understand the contribution of CNVs to epilepsy risk (36). The Epi4K project should be sufficiently large to survey the genetic landscape and assess the contribution of rare and common variants to epilepsy.

Next-Generation Diagnostics

Next-generation sequencing technology has already debuted in the molecular diagnostics arena. There is a commercially available genetic test that uses next-generation sequencing along with array comparative genomic hybridization (CGH) analysis to interrogate a panel of 53 epilepsy genes (37). Single nucleotide variants and small insertions/deletions are detected by sequencing, while array CGH evaluates duplications and deletions >150 bp. The panel consists of genes that have been implicated in monogenic forms of epilepsy. Although this panel has clinical utility for patients with epilepsy types that warrant genetic testing (38, 39), it has limited utility for more common forms of epilepsy.

Personalized whole-exome sequencing is already available through clinical diagnostic laboratories and whole-genome sequencing is likely to be routinely available within 10 years. However, the utility of this type of screening will depend heavily on our ability to provide sophisticated interpretation of the sequence. Results from the Baylor Ion Channel Sequencing Project highlight the bioinformatic challenge of sequence-based analysis in sporadic epilepsy patients. The authors recently reported on sequencing of 237 ion channel genes in individuals with sporadic epilepsy and unaffected controls and found that

both groups had similar numbers of rare missense variants in epilepsy-associated ion channel genes (40). This demonstrates that single variants in epilepsy genes alone have poor predictive value. It is likely that combinations of alleles in multiple genes contribute to disease status. Therefore, advances in systems biology and bioinformatics will need to keep pace with technology in order to better understand gene networks and to leverage fully the clinical utility of genomic profiling.

Conclusions

Advances in genetic and genomic technologies are generating unprecedented amounts of information. Integration of these powerful techniques with functional biology and sophisticated bioinformatics will improve our understanding of the genetic contribution to epilepsy. This knowledge will suggest novel therapeutic strategies and enhance the clinical utility of genetic testing for risk assessment and personalized treatment.

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13. Other (err on the side of full disclosure)	☒				

* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

☐ No other relationships/conditions/circumstances that present a potential conflict of interest.
☐ Yes, the following relationships/conditions/circumstances are present:

Thank you for your assistance.