Published in final edited form as:
Curr Opin Genet Dev. 2011 June ; 21(3): 325–332. doi:10.1016/j.gde.2011.01.005.

Epilepsy Genetics—Past, Present, and Future

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Abstract

Human epilepsy is a common and heterogeneous condition in which genetics play an important etiological role. We begin by reviewing the past history of epilepsy genetics, a field that has traditionally included studies of pedigrees with epilepsy caused by defects in ion channels and neurotransmitters. We highlight important recent discoveries that have expanded the field beyond the realm of channels and neurotransmitters and that have challenged the notion that single genes produce single disorders. Finally, we project toward an exciting future for epilepsy genetics as large-scale collaborative phenotyping studies come face to face with new technologies in genomic medicine.

Introduction

Epilepsy is a common neurological condition defined by recurrent, unprovoked seizures that affects one percent of the population, including one in 200 children [1]. Epilepsy genetics encompasses two broad categories—(1) genes and loci discovered in association with primary epilepsy syndromes, in which the epilepsy is a primary presenting feature, and (2) genes discovered in association with disorders of brain development that are associated with epilepsy. In both cases, the genes identified provide an opportunity for the study of mechanisms of brain development and epileptogenesis in the context of the developing brain.

Though the causes of epilepsy are diverse and heterogeneous, epilepsy is considered a highly genetic and in many cases heritable condition [2,3]. An inherited predisposition to seizures (called an "epileptic diathesis" by Lennox and Lennox in 1960), combined with some trigger or additional factor(s), has long been suspected as a cause of many types of epilepsy [4]. Epidemiological studies of families and twins provide compelling evidence for the heritability of epilepsy [5-9]. For example, the risk of epilepsy among first-degree

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relatives of individuals with idiopathic generalized epilepsy is eight to 12 percent; this is well above the risk (approximately 0.5 percent) in the general population, illustrating a strong genetic component but a complex one that does not always show a pattern consistent with Mendelian inheritance [5].

The clinical classification of epilepsy includes the categories of symptomatic, presumed symptomatic, and so-called idiopathic epilepsy [10,11]. Over time, idiopathic epilepsy has been understood to mean epilepsy caused at least in part by genetics, and the majority of cases in this category are likely to be influenced by genetic susceptibility. Past studies of genetic epilepsies have validated the notion that genetics play a major role in epilepsy, largely by identifying channels and neurotransmitters important in epileptogenesis. More recent studies have moved the field of epilepsy genetics beyond the channelopathies, and, with the beginning of the era of whole genome exploration, we are now at the threshold of understanding more complex genetic mechanisms that underlie many forms of epilepsy, both common and rare.

The Past: Setting the stage of epilepsy genetics

The approach to epilepsy genetics has, until relatively recently, been based on Mendelian genetics, relying on the ascertainment of large pedigrees, linkage analysis of polymorphic markers to established disease-associated loci, and positional cloning within these loci to identify the pathogenic gene mutation. Inheritance is autosomal dominant in many of the familial epilepsy syndromes in which mutations have been identified, with many of the genes encoding subunits of ion channels or neurotransmitter receptors [2,3,12]. A prototypic epilepsy gene discovery is the example of Autosomal Dominant Partial Epilepsy with Auditory Features (ADPEAF), with mapping of the gene completed in 1995 and mutations in the gene *LGI1* (leucine-rich glioma-inactivated 1) reported in 2002 [13,14]. The mechanisms by which *LGI1* mutations produce epilepsy are not fully established but are postulated to involve a potassium channel mechanism, a glutamatergic mechanism, or altered binding of the secreted neuronal protein to a transmembrane receptor (ADAM22) [15,16].

While the early discovery of genes in families with Mendelian inheritance was exciting proof of principle that epilepsy may be genetically mediated, the genes discovered thus far (listed in Table 1 and shown in the Figure) collectively do not account for the majority of idiopathic epilepsy. This is illustrated by the example of Genetic Epilepsy with Febrile Seizures Plus (GEFS+), a familial syndrome in which family members are affected with a range of phenotypes ranging from simple febrile seizures to severe myoclonic epilepsy with infancy. Between 1998 and 2004, mutations were identified in families with GEFS+ in three sodium channel subunit genes (*SCN1B*, *SCN1A*, and *SCN2A*) and two GABA receptor subunit genes (*GABRG2* and *GABRD*) [17-21], but these five GEFS+ genes explain only 10 percent of GEFS+ [22,23]. Linkage studies have identified seven additional regions associated with GEFS+ and five regions associated with familial febrile seizures [24-35]. The causative mutations in genes in these regions have not yet been uncovered, likely because of constraints of time, labor, and cost of Sanger sequencing methods, or because the mutations lie outside of the exonic regions typically targeted by the same methods. The

variable penetrance and variable expressivity seen in these syndromes suggest that in addition to a primary genetic mutation required for disease, there may be other genes involved and potentially other non-genetic factors that influence phenotype.

When the status of the genetics of epilepsy was reviewed in 1980, the strongest evidence for a genetic role in the causation of epilepsy was the existence of pedigrees with epilepsy and the presence of animal models with epilepsy [36]. It is notable that among genetic mouse models for epilepsy, only one-quarter are caused by defects in channel-related genes [37], suggesting that there are multiple classes of epilepsy genes yet to be discovered. In parallel with the discovery of "epilepsy genes" in pedigrees with epilepsy as the primary phenotype, epilepsy genetics includes the discovery of genes associated with syndromes and cerebral cortical malformations highly associated with epilepsy. These genes include *LIS1*, *DCX*, *ARX*, *FLNA*, *GPR56*, and *MECP2* [38-44]. The subject of brain malformations will be addressed in depth elsewhere in this issue, but there is a strong causal link between brain malformations and epilepsy. We have already seen some genes discovered in the setting of dramatic, radiographically evident brain malformations that are also responsible for epilepsy syndromes without brain malformations. A notable example is *ARX*, associated initially with X-linked lissencephaly but subsequently found to be associated with isolated infantile spasms without lissencephaly [45].

The Present: Recent Advances in the Genetics of Epilepsy

There have been several advances in epilepsy genetics in the past three years, including additional Mendelian genetics studies, further studies of previously discovered genes, and identification of genes encoding proteins in novel pathways not previously demonstrated to be relevant to epilepsy. Major advances in the field also include the recognition of the importance of copy number variation.

Genetically determined "interneuronopathies" associated with epilepsy

Our understanding of developmental "interneuronopathy" associated with severe epilepsy has been advanced by several recent studies of the role of *ARX* in the developing brain [46]. Refinement of the mechanisms involved in tangential neuronal migration has included the recognition that *ARX* has a cell autonomous role in proliferation as well as GABAergic interneuron migration [47,48]. In an early study of a human case of *ARX*-associated lissencephaly, the neocortical subventricular region showed cells positive for glutamic acid decarboxylase and calretinin as well as Mash-1 and nestin, suggesting a role for *ARX* in radial migration in addition to its traditional role in tangential GABAergic interneuron migration from the ganglionic eminence [49].

The translation of *ARX* genetics to a mouse model with real relevance to human epilepsy came in the form of a conditional knockout mouse in which *Arx* was deleted from neurons derived from the ganglionic eminence derived neurons; the result was a mouse with early life seizures resembling the human infantile spasms phenotype [50]. The body of work related to *ARX* provides a paradigm for epilepsy-related research with broad applicability. Stemming from the discovery of a gene for a severe form of infantile epilepsy, the *ARX* field

now includes animal models that can be used to further study infantile spasms and to develop rational treatment strategies.

New epilepsy genes revealing novel mechanisms of epileptogenesis STXBP1

Early infantile epileptic encephalopathy with suppression-burst (EIEE) is a severe form of early onset epilepsy recently associated with mutations in the gene *STXBP1* (also known as *MUNC18-1*) [51]. Importantly, the discovery of EIEE-associated sporadic heterozygous *STXBP1* mutations arose from the initial identification of a microdeletion at 9q33.3-34.11 in a single case by comparative genomic hybridization (CGH), leading to candidate gene sequencing in other index cases of the genes in that region. In contrast to the previously mentioned epilepsy genes that encode subunits of ion channels or neurotransmitter receptors, the protein encoded by this gene, synaptic binding protein 1, is involved in synaptic vesicle release. The discovery of this gene has opened a new arena for targeted rational drug design, not only for the rare syndrome of EIEE but for epilepsy generally.

As is likely to be the case for many epilepsy-associated conditions, there are broader implications for *STXBP1* that extend well beyond EIEE. There is already a report of heterozygous mutations in *STXBP1* in patients with intellectual disability and nonsyndromic focal onset epilepsy, a phenotype much milder and less specific than EIEE [52]. The overall impact of *STXBP1* in patients with epilepsy, with or without intellectual disability, is yet to be determined.

PCDH19

Epilepsy and mental retardation limited to females (EFMR) is an X-linked condition that is unusual in that it is transmitted through males and only carrier females show classic symptoms. The recognition of this unique mode of inheritance led to a study of seven families with EFMR that identified mutations in protocadherin 19 (*PCDH19*), a cadherin that is expressed in the developing brain [53]. This discovery is of particular interest on several counts: (a) the authors recognized this very unusual pattern of expression as a defining feature of an epilepsy syndrome with linkage to the X chromosome, (b) gene identification was possible due to increasing efficiency of resequencing methods and was accomplished by resequencing 737 genes on the X chromosome, and (c) the discovery of a link between cadherins and epilepsy expands the field to include still another class of proteins beyond ion channels and neurotransmitter receptors.

The implications of *PCDH19* on epilepsy have already been shown to be broader than the familial EFMR syndrome. *PCDH19* mutations have been identified by multiple groups in sporadic cases of epilepsy in females with intellectual disability as well as infantile onset epilepsy, even that resembling the severe myoclonic epilepsy of infancy phenotype of Dravet syndrome [54-57].

TBC1D24

Mutations in *TBC1D24* have recently been identified in association with focal onset epilepsy with associated intellectual disability in a consanguineous pedigree [58]. Again, a novel category of epilepsy genes has emerged as this gene has been shown to have a role in axon

specification in developing neurons [58]. While the brain imaging described in the original report includes evidence of a subtle anterior pachygyria pattern, it appears that this pattern is not a required feature of the phenotype associated with mutations in *TBC1D24*: simultaneous with the report of *TBC1D24* mutations with the fairly non-specific phenotype of focal epilepsy and intellectual disability was a report of compound heterozygous mutations in a non-consanguineous pedigree with a distinct phenotype of familial infantile myoclonic epilepsy [59]. It would not be surprising to see the discovery of other effects of mutations in this gene in the months and years to come, perhaps with still different forms of phenotypic expression.

Cortical malformation genes with implications for epilepsy

Three microcephaly genes are particularly relevant to epilepsy genetics. *ASPM*, an established primary microcephaly gene, is associated with a microcephaly phenotype that now includes epilepsy (microcephaly with seizures) [60]. *CDKL5*, a gene traditionally associated with a Rett syndrome-like phenotype, is now considered on the differential diagnosis for individuals with microcephaly and infantile spasms [61,62]. Mutations in a novel microcephaly gene involved in DNA repair, *PNKP*, are responsible for microcephaly with early-onset epilepsy and developmental delay [63].

Another category of cortical malformation genes with implications for the field of epilepsy are the “tubulinopathies.” Mutations in *TUBA1A* have been associated not only with lissencephaly but also with polymicrogyria [64,65], both of which have a high prevalence of associated epilepsy. The role of *TUBA1A* as well as *TUBB2B* in brain development is reviewed elsewhere [66].

Structural genomic variations and epilepsy

Chromosomal deletions and duplications have been found in patients with epilepsy but are frequently in the context of a recognizable genetic syndrome and have been detectable by clinical methods such as karyotyping (e.g., trisomy 21, ring chromosome 20, fragile X syndrome) [67-69]. More recently, oligonucleotide arrays have allowed for evaluation of smaller duplications and deletion across the genome. This approach has revealed associations between copy number variations and neurodevelopmental conditions such as autism and intellectual disability, as well as a number of syndromes in which children have dysmorphic features [70, 71].

In the field of epilepsy genetics, large-scale studies of copy number variation have yielded results that are somewhat surprising in that the patients studied have idiopathic epilepsies without autism, intellectual disabilities, or dysmorphic features. One group studied 1234 Northern European subjects with idiopathic generalized epilepsy by high-density single nucleotide polymorphism arrays and identified microdeletions in almost 2 percent, most notably at 15q11.2 and 16p13.11 [72]. In another report, 517 subjects with idiopathic focal or generalized onset epilepsy were analyzed by whole-genome oligonucleotide array CGH, and nearly 3 percent were found to have deletions at 15q11.2, 15q13.3, or 16p13.11, loci previously associated with autism and intellectual disability [73]. Finally, a study of 3812 cases representing a wide range of epilepsy phenotypes found 23 cases to have 16p13.11

deletions 100 kb or larger [74]. These studies have identified structural genomic variations associated with epilepsy in the absence of dysmorphic features, representing a change from the conventional wisdom that chromosome microarray analysis is useful only for patients with intellectual disability or autism and abnormal physical features. As such, they may have important implications in the clinical arena.

Genome-wide association studies of epilepsy

Advances in techniques allow for genome-wide linkage analysis for familial disorders and large-scale association studies to establish allelic variants that may have broad impact in a population. These techniques present an opportunity to study a common yet heterogeneous condition such as epilepsy but present a challenge in that well-powered association studies need large numbers of affected individuals who are carefully phenotyped. A genome-wide association study (GWAS) of 3445 partial-onset epilepsy cases (and nearly 7000 controls) has been conducted but did not reveal any strong candidate genes [75].

The Future: Applying Advancing Genetic Technologies to Epilepsy Genetics

Though the results of the first large GWAS for epilepsy were disappointing in that no additional epilepsy genes or loci were identified, the study did show that a large consortium approach combined with powerful bioinformatics platforms can be successful in accruing enough samples for well-powered genetic studies in epilepsy and performing analyses on such large groups of cases. The large groups of samples already collected for this and other large studies, such as the Epilepsy Phenome/Genome Project [76], may provide a future reservoir in which to search for mutations in established and newly discovered genes.

Massively parallel sequencing strategies now allow whole exome and whole genome sequencing experiments to be performed at increasingly affordable costs and with analysis tools that allow comparison to a growing number of reference cases, such as presented in the 1000 Genomes Project [77]. In the immediate future, we should expect efforts to resolve the unanswered questions of which genes are responsible for epilepsies for which excellent linkage data are available, such as the GEFS+ and familial febrile seizures loci mentioned above. Moving forward, gene discovery will continue in pedigrees identified with epilepsy. We now face the exciting prospect of identifying mutations among large groups of individuals with specific epilepsy syndromes and then applying these discoveries to the broader epilepsy field and beyond.

We present a summary of the past, present, and future of the actively evolving field of epilepsy genetics in Table 2. Along with the ability to identify vast numbers of genetic variants potentially associated with epilepsy will come the challenges of validating genetic associations and analyzing their significance. Indeed, ongoing successes in gene discovery —whether in families with Mendelian inheritance or in large cohorts of patients with epilepsy—will unearth questions regarding the functional significance of the mutations discovered thus far. The true measure of our successes will be the ability to translate these

genetic discoveries into a deeper mechanistic understanding of epilepsy that can be translated into effective therapies.

Acknowledgments

Annapurna Poduri was supported by the NINDS (K23 NS069784). Daniel Lowenstein was supported by the NINDS (U01 NS053998, Epilepsy Phenome Genome Project).

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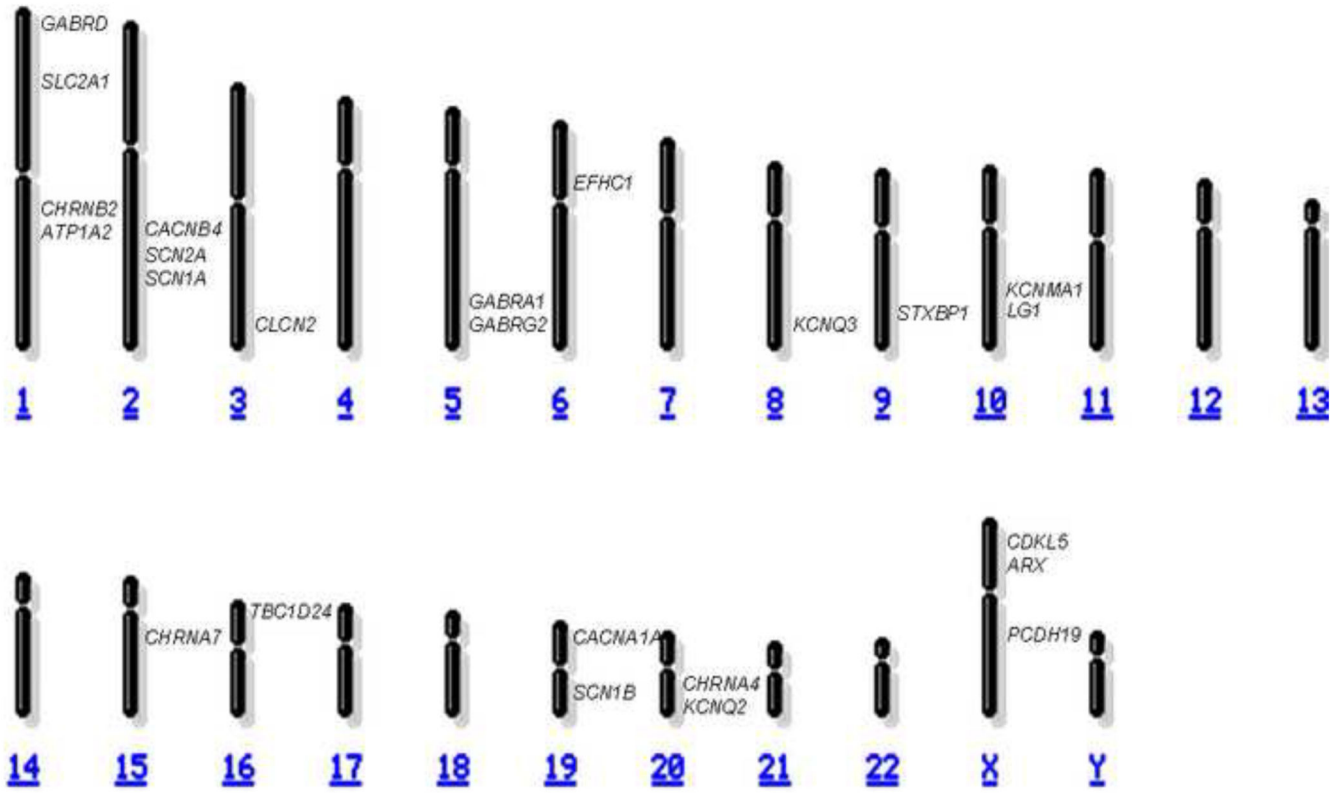

Figure.

The major epilepsy genes, including those highlighted in this review, are shown to depict their relative chromosomal locations on this schematic karyotype (adapted from the National Center for Biotechnology Information website www.ncbi.nlm.nih.gov).

Table 1

GENE	ASSOCIATED EPILEPSY SYNDROME(S)
ARX	Infantile spasms Early infantile epileptic encephalopathy
ATP1A2	Benign familial infantile convulsions Familial hemiplegic migraine and epilepsy
CACNA1A	Absence epilepsy and episodic ataxia
CACNB4	Juvenile myoclonic epilepsy
CDKL5 (STK9)	Infantile spasms
CHRNA4	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNB2	Autosomal dominant nocturnal frontal lobe epilepsy
CHRNA7	Juvenile myoclonic epilepsy
CLCN2	Childhood absence epilepsy Juvenile absence epilepsy Juvenile myoclonic epilepsy
EFHC1	Juvenile myoclonic epilepsy
GABRD	Genetic epilepsy with febrile seizures plus
GABRA1	Juvenile myoclonic epilepsy
GABRG2	Childhood absence epilepsy Genetic epilepsy with febrile seizures plus
KCNQ2	Benign familial neonatal convulsions
KCNQ3	Benign familial neonatal convulsions
KCNMA1	Generalized epilepsy with paroxysmal dyskinesia
LGI1	Autosomal dominant partial epilepsy with auditory features
PCDH19	Epilepsy in females with mental retardation
SCN1A	Genetic epilepsy with febrile seizures plus Severe myoclonic epilepsy of infancy (Dravet syndrome)
SCN1B	Genetic epilepsy with febrile seizures plus
SCN2A	Benign familial neonatal/infantile convulsions Genetic epilepsy with febrile seizures plus
SLC2A1	Early-onset absence epilepsy Epilepsy with paroxysmal exercise-induced dyskinesia
STXBP1	Early infantile epileptic encephalopathy Partial onset epilepsy with intellectual disability
TBC1D24	Familial infantile myoclonic epilepsy Focal epilepsy with developmental disability

Table 2

The Evolution of Epilepsy Genetics

Past

- Ion channel and neurotransmitter receptor subunits dominated epilepsy genetics.

Present

- Newly discovered genes highlight the importance of novel pathways involved in epileptogenesis.
- Copy number variations associated with idiopathic epilepsy collectively explain a larger portion of epilepsy than any single gene.

Future

- Genotype-phenotype correlation is an evolving target: genes and copy number variations discovered in the context of one syndrome are often subsequently found to have broader applicability within the field of epilepsy and to other neurodevelopmental disorders.
- Modern methods will allow rapid discovery of more pathogenic gene mutations, variants in non-coding DNA, and copy number variations that encompass several genes.
- The new challenge ahead is to model these rapidly accumulating genetic changes in the laboratory so we can continue to build upon our understanding of epilepsy and move toward more rational treatment.