Published in final edited form as:
Epilepsia. 2001 ; 42(Suppl 5): 24–30.

Progress in the Genetics of the Partial Epilepsies

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Summary

The importance of genetic contributions to the partial epilepsies is now well established. Evidence for this genetic contribution has come from familial aggregation studies, twin studies, positional cloning of specific genes that raise risk, and clinical descriptions of families. Familial aggregation studies are consistent in showing an increased risk of epilepsy in the relatives of patients with partial epilepsies that occur in the absence of environmental insults to the central nervous system. Susceptibility genes have been localized in five syndromes: autosomal dominant nocturnal frontal lobe epilepsy (20q, 1q, and 15q), autosomal dominant partial epilepsy with auditory features (10q), familial partial epilepsy with variable foci (22q), benign epilepsy of childhood with centrotemporal spikes (15q), and benign familial infantile convulsions (19q). In nocturnal frontal lobe epilepsy, the genes on chromosome 20q and 1q have been identified as subunits of the neuronal nicotinic acetylcholine receptor.

Keywords

Epilepsy; Seizures; Genetics; Epidemiology

Until recently, partial (focal or localization-related) epilepsies were widely believed to be nongenetic. This view probably resulted from the recognition that epilepsy following an identified environmental insult (e.g., severe head injury, stroke, brain tumor) is usually partial; and hence a greater proportion of partial than of generalized epilepsies are environmental in origin. In partial epilepsies that occur in the absence of environmental insults, however, the importance of genetic contributions is now well established (1–5).

In a previous review published 12 years ago, I showed that studies were consistent in finding evidence of a genetic contribution to some partial epilepsies (1). Newer studies have provided much stronger evidence for this genetic contribution, and an important genetic influence is now known or suspected in a growing list of localization-related epilepsy syndromes (Table 1). Various study designs have been used in these investigations; and the strength of their conclusions depends on the methods used. Below I summarize the evidence derived from four study designs: familial aggregation studies, twin studies, linkage analysis, and clinical descriptions of families. Finally, I discuss some of the questions that remain to be addressed.

FAMILIAL AGGREGATION STUDIES

The evidence summarized in my previous review came entirely from familial aggregation studies. These studies use an epidemiologic approach to assess the degree of increased risk in relatives of individuals with partial epilepsies, compared with either relatives of individuals

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with generalized (or unselected) epilepsies, relatives of controls, or the general population. An important limitation of these studies is that they cannot distinguish between genetic and nongenetic causes of familial aggregation. Clustering of disease within families can sometimes result from shared exposure to environmental factors (such as air pollution) or shared behavioral patterns (such as diet), rather than from genetic susceptibility. In addition, many of the earlier studies had methodologic problems such as lack of a control group, failure to control for family size or age of the relatives, lack of specificity in the definitions of affection status (e.g., any seizure vs. epilepsy), and selection bias of the included probands.

Despite these potential problems, early studies provided evidence of a genetic contribution to partial epilepsies, albeit of lower magnitude than that to generalized epilepsies. In two studies that compared relatives of partial epilepsy cases with relatives of controls, risk did appear to be increased in the relatives of the partial cases (6,7). However, three studies that examined the prevalence of a history of seizure disorders in relatives of probands with different seizure types were consistent in finding a prevalence ~ 1.5 times as high in the relatives of generalized versus partial cases (6–8).

Early studies also provided evidence for a genetic contribution to epilepsy with complex partial seizures (most of which was probably temporal lobe epilepsy). Four studies examined the proportion affected among relatives of patients with complex partial (or “psychomotor”) seizures, compared with relatives of all patients included in the study (not selected by seizure type) (6–9). In each of the four studies, the difference between the two groups was small; and in the single study that included a control group, prevalence of a seizure history was higher in the relatives of patients with complex partial seizures than in the relatives of controls (8).

A significant limitation of the earlier studies was the failure to control for the confounding effect of the etiology of epilepsy. Partial epilepsies are more likely to be caused by identified environmental insults to the central nervous system than are generalized epilepsies, and genetic contributions are much smaller in epilepsies associated with such insults (symptomatic epilepsies) than in those without identified causes (idiopathic or cryptogenic epilepsies). This was a problem in all of the early studies except that of Lennox and Lennox (6), which was restricted to patients with idiopathic or cryptogenic epilepsy.

Two recent familial aggregation studies have further elucidated the familial aggregation of partial epilepsies. First, standardized morbidity ratios (SMRs) for unprovoked seizures were examined in the offspring of individuals with idiopathic or cryptogenic epilepsy from the population-based Rochester–Olmsted County Records Linkage Project, compared with age- and sex-specific population incidence rates (Table 2) (10). The SMRs were very similar for offspring of patients with generalized (3.3) and partial epilepsies (3.2). However, risk was increased to a greater extent in offspring of parents with absence seizures (SMR = 9.2) than in offspring of parents with either partial epilepsies or generalized epilepsies without absence seizures. This suggests that the greater genetic contribution to generalized than to partial epilepsy may be restricted to specific clinically defined subgroups of generalized epilepsy.

Second, in a study that eliminated the possible confounding effect of etiology of epilepsy, the risk of idiopathic or cryptogenic epilepsy was examined in first-degree relatives of 1,498 adult probands with cryptogenic epilepsy from the Epilepsy Family Study of Columbia University (Table 3) (11). The comparison group was first-degree relatives of probands with epilepsies associated with postnatal environmental insults (postnatal symptomatic epilepsy), whose risk had been shown to be equal to that in the general population of Rochester, Minnesota (12). In parents and siblings, the relative risk (RR) was lower if the proband’s epilepsy was localization related than if generalized (RR = 2.4 vs. 4.7), but risk was significantly elevated in both groups, when compared with that in the controls. In offspring, the degree of increased risk was actually

greater if the proband's epilepsy was localization related than if generalized (RR = 4.2 vs. 1.6). The reason for this difference is not clear.

TWIN STUDIES

Twin studies have consistently found higher concordance rates of epilepsy in monozygotic (MZ) than dizygotic (DZ) twins, providing strong evidence for genetic contributions to epilepsy overall. However, very few of these studies have examined partial epilepsies specifically, or compared partial with generalized epilepsies. Berkovic et al. (13) studied concordance rates for specific epilepsy syndromes in 253 twin pairs in which one or both co-twins had epilepsy or febrile convulsions, ascertained from two Australian twin registries and by referral. Concordance rates were significantly higher in MZ than in DZ pairs in both generalized (82 vs. 26%) and partial epilepsies (36 vs. 5%), although they were higher in both types of twins with generalized epilepsies. Interestingly, all of the evidence for a genetic effect in the partial epilepsies came from 30 pairs with cryptogenic partial epilepsies, in whom the concordance rates in MZ and DZ pairs were 55% and 0 ($p < 0.001$). In the 10 pairs with idiopathic partial epilepsies, most of whom had benign rolandic epilepsy, concordance rates did not differ between MZ and DZ pairs. None of the 25 pairs with symptomatic partial epilepsy was concordant.

These findings provide strong evidence for a genetic influence on cryptogenic partial epilepsy. This is very important, because it calls attention to a problem with the current International League Against Epilepsy (ILAE) classification of epilepsy syndromes (14). In the current system, the term "idiopathic" refers to syndromes with a presumed genetic etiology; "symptomatic," to those resulting from a known or suspected disorder of the central nervous system; and "cryptogenic," to those presumed to be symptomatic but with unknown etiology. The genetic contributions have been shown to be minimal in the symptomatic epilepsies associated with identified postnatal insults to the central nervous system (12,15). Cryptogenic epilepsies clearly differ from symptomatic epilepsies in this regard.

CHROMOSOMAL LOCALIZATION AND GENE IDENTIFICATION

In a rapidly growing list of localization-related epilepsy syndromes, clear evidence has been obtained for an important genetic influence through chromosomal localization of specific genes that increase risk (Table 4). The syndromes with linkage evidence probably comprise only a minority of all localization-related epilepsies, but they hold great promise for elucidating basic mechanisms of epileptogenesis, and in particular, the genetic basis for pathology expressed in localized brain regions. It is very interesting to note that despite the widespread assumption of a greater genetic effect on generalized epilepsies, more progress has been made to date in localizing genes for partial epilepsies than for generalized epilepsies.

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)

ADNFLE was localized to chromosome 20q13.2 in one large Australian kindred with 27 affected individuals (16). The gene in that family was subsequently identified as the neuronal nicotinic acetylcholine receptor α_4 sub-unit (CHRNA4) (17). Locus heterogeneity has been demonstrated by showing that in another family, the syndrome resulted from a mutation in the gene encoding the β_2 subunit of the neuronal nicotinic acetylcholine receptor (CHRNB2) (18,19). In still other families, the syndrome was found to be linked to chromosome 15q24, in the region of a cluster of genes encoding other subunits of the nicotinic acetylcholine receptor (20).

Autosomal dominant partial epilepsy with auditory features (ADPEAF)

ADPEAF was localized to a 10-cM region on chromosome 10q22–24, in a single family containing 11 affected individuals (21). Ten of the affected family members had clearly localization-related epilepsy, and the remaining subject had only nocturnal seizures that could not be classified. Six (55%) of those affected reported auditory auras at seizure onset. This and other features suggested a lateral temporal (neocortical) focus (21,22). Subsequently, a large Basque family was identified with clinical features similar to those of ADPEAF (23). Auditory symptoms were reported by four (36%) of 11 affected individuals, and visual symptoms by six (55%). The partial seizure manifestations suggested a lateral temporal lobe origin, near the temporooccipital junction, and EEG and single-photon emission computed tomography (SPECT) abnormalities also pointed to the temporal lobe as an area of dysfunction. The syndrome in the Basque family was named autosomal dominant lateral temporal epilepsy (ADLTE), and a susceptibility gene was localized to a 15-cM interval on chromosome 10q that overlaps with the ADPEAF region by a common 3-cM core. Two other families with ADPEAF were recently reported, with linkage evidence consistent with the same localization on 10q, but too few affected family members to reach statistical significance (24,25). Further studies will be needed to determine whether the same gene underlies both ADPEAF and ADLTE.

Familial partial epilepsy with variable foci

Familial partial epilepsy with variable foci was described in a family with mostly nocturnal seizures arising from frontal, temporal, and occasionally occipital epileptic foci (26,27). The variable focus of pathology raises interesting questions about the possible heritable mechanism for multifocal pathology. The disease locus was mapped to a 3.8-cM interval on chromosome 22q11–12 (27).

Benign epilepsy of childhood with centrotemporal spikes (BECTS)

BECTS is the only one of the partial epilepsies currently classified as idiopathic in which evidence for linkage has been obtained. This syndrome is primarily characterized by an EEG abnormality rather than by clinical seizures, and raises questions about the genetic contributions to epileptiform abnormalities and their genetic relations to the accompanying epilepsy syndrome. BECTS has been studied extensively from a genetic point of view. Bray and Wiser (28) examined EEG abnormalities and seizure disorders in the siblings and offspring of children with seizures and temporocentral spikes or sharp waves, and siblings and offspring of controls. In the relatives of the cases, they found an increased prevalence of both focal temporal spikes or sharp waves and diffuse, bilaterally synchronous discharges in the EEGs. Other investigators confirmed these findings (29,30). Several investigators suggested that the mode of inheritance of temporocentral EEG foci was autosomal dominant, but this is uncertain because of incorrect control for ascertainment bias (1). Neubauer et al. (31) recently evaluated linkage of BECTS to chromosomal regions known to contain genes coding for subunits of the neuronal nicotinic acetylcholine receptor, in an affecteds-only study of 22 families. Evidence for linkage to chromosome 15q14 was obtained, with a maximal LOD score of 3.56 under an autosomal recessive mode of inheritance. Peak scores were in the region of the gene coding for the α_7 subunit of the acetylcholine receptor, but a mutation has not been identified.

Benign familial infantile convulsions

Benign familial infantile convulsions is a syndrome characterized by onset between 3.5 and 12 months, seizures of mostly partial origin (based on clinical features with confirmation by ictal EEG recordings), and normal psychomotor development. It was originally described in families or Italian ancestry, but has subsequently been described in families from other parts of the world. Linkage to chromosome 19q was established in five families of Italian descent

with autosomal dominant inheritance (32). Interestingly, a common haplotype appeared to be present in four of the five families, suggesting the possibility of a founder effect.

CLINICAL DESCRIPTIONS OF FAMILIES

Several studies have described the clinical manifestations of epilepsy in single families, or sets of families, in some cases using the data as the basis for definition of new syndromes. These studies are interesting because they show the types of symptom constellations and families that can (and do) occur. However, this type of study cannot be used to determine mode of inheritance, or to provide information about the proportion of all epilepsy represented by a given syndrome. This is because the reported families are selected for study because they contain several individuals who are affected with a particular epilepsy syndrome. Families selected in this way will automatically contain a high proportion of affected family members, because that is why they were selected in the first place! If this ascertainment bias is not corrected, the proportion of family members who are affected, or "recurrence risk," may be so high that the families appear to be consistent with autosomal dominant inheritance. However, it would not be accurate to make this inference based on data from families selected in this way.

To make accurate inferences about mode of inheritance, unbiased estimates of recurrence risk are needed. In general, this means we need to incorporate information about the families that were *not* selected, in addition to the families that were selected. Regardless of the mode of inheritance, some families in the population will contain no, or only one, affected individual, and if these families are not counted, the estimates of recurrence risk will be inflated. However, incorporation of information about such families is usually very difficult, because the method for finding the families is unsystematic, and nothing is known about how many families were examined to find those that appeared interesting.

A simple numeric example illustrates the problem presented by ascertainment bias. The cumulative incidence of epilepsy is ~1% by age 20 years in the general population of Rochester, Minnesota (33). Suppose a person with epilepsy comes from a family of four siblings, including the patient himself. The probability that two (50%) of the four siblings are affected (i.e., the patient and one of his three siblings) can be calculated from a standard binomial probability. In this case, assuming the siblings are older than 20 years, this probability is 0.015, implying that one of every 67 families of this type in the population will contain 50% affected siblings. This implies that if one were to search among all the patients in a clinical practice to identify "interesting" families, it would not be surprising to find one containing multiple affected siblings. In fact, the proportion of families with multiple affected siblings will be higher in a clinical practice than in the population, because the chance that *at least one* of the siblings comes to the practice is proportional to the number of affected siblings in the family. The identification of such a family would not mean that the mode of inheritance was autosomal dominant, despite its containing what seemed like a large proportion of affected siblings. The same considerations apply to extended pedigrees containing multiple affected individuals. Some of them might reflect a major genetic etiology, but others will have surely occurred by chance, and it is impossible to distinguish between these possibilities without further genetic evidence.

The co-occurrence of clinical syndromes within families selected in this way is also very difficult to interpret, because of the possible effects of ascertainment bias and concordance expected by chance. Because of these problems, syndromes defined purely on the basis of this type of study should be considered provisional, until more definitive data are obtained through linkage or gene identification.

Several of the syndromes listed in Table 1 have been described in studies of this type. Familial temporal lobe epilepsy was identified in five concordant MZ pairs in the twin study described earlier (34). The authors described the pedigrees of these twin families and seven additional families containing two or more individuals with temporal lobe epilepsy ascertained from the private and hospital practices of one of the investigators over a 4-year period. Affected individuals in these families had simple partial seizures, complex partial seizures, and tonic–clonic seizures. The simple partial seizures had psychic, autonomic, or special sensory components, and the complex partial seizures consisted of brief periods of behavioral arrest, with oral–alimentary automatisms in some (suggestive of mesial temporal onset), and minimal postictal confusion and amnesia. Although an increased prevalence of a history of seizure disorders had been demonstrated in the families of subjects with complex partial seizures, this study was the first to designate the familial occurrence of temporal lobe epilepsy as a syndrome. Although the authors concluded the families were consistent with autosomal dominant inheritance, the manner in which they were selected makes the mode of inheritance uncertain.

Cendes et al. (35) described a series of 11 families containing 36 affected individuals with temporal lobe epilepsy. Seizure types were simple partial, complex partial, and rarely generalized tonic–clonic. Clinical manifestations were quite variable, with a significant number of severely affected individuals who were not optimally controlled by medical therapy. This series provides further evidence for the clinical heterogeneity of familial temporal lobe epilepsy.

Autosomal dominant rolandic epilepsy and speech dyspraxia was first described in a family of nine affected individuals with orofaciobrachial partial seizures, secondarily generalized seizures, and centrotemporal epileptiform discharges, with associated speech and cognitive dysfunction (36). Anticipation was described, with worsening severity of the syndrome in subsequent generations. The authors postulated an expanded repeat region to explain the variable phenotype, but molecular evidence is not yet available.

Childhood epilepsy with occipital paroxysms, one of the three partial epilepsies currently classified as idiopathic, was first described by Gastaut in 1982 (37). Onset is usually between ages 4 and 8 years, and seizures involve visual symptoms followed by secondarily generalized seizures. The course is usually benign, with remission by age 20 in many cases. The EEG pattern involves unilateral or bilateral occipital sharp-wave discharges that attenuate with eye opening and have age-dependent occurrence. Kuzniecky and Rosenblatt (38) described the prevalence of epilepsy and EEG abnormalities in 25 members of an extended family ascertained through a sibship of four affected children. Only one of the family members had seizures, but 11 (57%) had EEG abnormalities, of whom five (26%) had the occipital pattern.

Primary reading epilepsy, the third of the partial syndromes classified as idiopathic, is characterized by seizures precipitated by reading (especially aloud), talking, or writing. The reading-induced seizures are mostly simple focal motor; in most patients secondarily generalized seizures occur rarely. Wolf (39) reviewed all published patients with reading epilepsy, and found that 20 (27%) of 75 had affected first-degree relatives. This may be an overestimate, because of the possibility of publication bias.

A recent study by Picard et al. (40) illustrated the difficulties in using clinical information for syndrome classification in the partial epilepsies. They examined 19 families containing multiple affected individuals with partial epilepsies, and attempted to classify them as having familial temporal lobe epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, or familial partial epilepsy with variable foci. They noted considerable clinical variability both within and among families, and found that classification was difficult in at least five of the families. They concluded that the current system of classification, which is based on brain localization, is

difficult to apply because of extensive overlap in ictal symptoms and scalp EEG data for the different syndromes.

UNRESOLVED QUESTIONS

Although substantial progress has been made in research on the genetics of the partial epilepsies, several unresolved questions remain. First, it is unknown what proportion of patients with partial epilepsy have a genetic susceptibility. This question applies not only to partial epilepsies analyzed as a group, but also to specific syndromes such as temporal lobe epilepsy.

Second, many of the syndromes currently considered to have an important genetic influence were defined on the basis of highly selected families. Data are needed regarding the risks of epilepsy in the families of patients with these syndromes from a population-based series. Further, the designation of a certain type of epilepsy as a genetic “syndrome” implies that the effect of a genetic susceptibility is to increase risk for that type of epilepsy specifically, rather than to increase risk for that type in addition to other types. The extent to which the different forms of partial epilepsy assort independently within families is uncertain. Some susceptibility genes may even increase the risk for both partial and generalized epilepsies (10,11).

Third, it is unclear how the various forms of partial epilepsy should be classified. Currently, brain localization is used as the basis for classification, but as noted by Picard et al. (40), this can be difficult to apply in many cases. In addition, substantial genetic heterogeneity may be present within epilepsies originating from a given brain region (e.g., temporal lobe, or even mesial or lateral temporal lobe specifically). An alternative approach, which we have used, is to define syndromes based on symptoms (e.g., auditory auras) (21,22).

In summary, significant progress has been made in recent years in understanding the genetics of the partial epilepsies. Research in this area is moving rapidly, and genes that increase risk for new syndromes will undoubtedly be discovered soon. This information will be crucial for elucidating pathogenesis, and also for clarifying the definition of syndromes with a major genetic contribution.

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TABLE 1

Partial epilepsy syndromes with a known or suspected major genetic contribution to their etiology

Syndromes currently classified as idiopathic:
Benign childhood epilepsy with centrotemporal spikes
Childhood epilepsy with occipital paroxysms
Primary reading epilepsy
Syndromes currently classified as cryptogenic:
Autosomal dominant nocturnal frontal lobe epilepsy
Autosomal dominant partial epilepsy with auditory features
Familial partial epilepsy with variable foci
Benign familial infantile convulsions
Familial temporal lobe epilepsy
Autosomal dominant rolandic epilepsy with speech dyspraxia

TABLE 2

Standardized morbidity ratios for unprovoked seizures in offspring of parents with partial epilepsy, generalized epilepsy, and generalized epilepsy with absence seizures[a]

Proband seizure type	No. of offspring	No. affected		
		Observed	Expected	SMR (95% CI)
All partial	393	14	4.35	3.2 (1.8–5.4)
All generalized onset	294	9	2.77	3.3 (1.5–6.2)
Generalized with absence seizures	42	3	0.32	9.2 (1.9–27.0)

[a]Modified from (10).

TABLE 3

Rate ratios for idiopathic or cryptogenic epilepsy in relatives of probands with generalized or localization-related idiopathic or cryptogenic epilepsy[a]

Class of relatives and type of epilepsy in the proband	No. of relatives	Affected (%)	RR (95% CI)
Parents and siblings			
Generalized idiopathic/cryptogenic	672	29 (4.3)	4.7 (2.35–9.41)
Localization-related idiopathic/cryptogenic	4,306	95 (2.2)	2.4 (1.29–4.48)
Postnatal symptomatic	1,182	11 (0.9)	1.0 (reference)
Offspring			
Generalized idiopathic/cryptogenic	172	3 (1.7)	1.6 (0.35–6.96)
Localization-related idiopathic/cryptogenic	1,126	54 (4.8)	4.2 (1.50–11.46)
Postnatal symptomatic	330	4 (1.2)	1.0 (reference)

[a]Data from (11).

TABLE 4

Chromosomal localization and gene identification in idiopathic and cryptogenic partial epilepsies

Syndrome	Chromosomal localization	Gene
Autosomal dominant nocturnal frontal lobe epilepsy	20q13	CHRNA4
	1q	?
	15q24	?
Autosomal dominant partial epilepsy with auditory features	10q22–24	?
Familial partial epilepsy with variable foci	22q11–12	?
Benign epilepsy of childhood with centrotemporal spikes	15q14	?
Benign familial infantile convulsions	19q	?