Genetic Epidemiology of Epilepsy

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Epilepsy is one of the most common neurologic disorders, affecting approximately 4 percent of individuals at some time in their lives (1). An inherited contribution to its etiology has been suspected for centuries, yet until recently, little progress has been made in understanding the genetic influences on susceptibility. This slow progress is owed in part to methodological problems in previous studies and in part to underlying complexity in the genetic contributions. In most forms of epilepsy, the familial distribution is inconsistent with a simple Mendelian model, and the mode of inheritance is uncertain. Both genetic and environmental factors may contribute to susceptibility, and it is unclear how they interact in their influence on risk. Epilepsy is clinically very heterogeneous, and the important genetic and environmental effects may differ across clinically defined subsets or syndromes. Even within narrowly defined clinical syndromes, different susceptibility genotypes or environmental factors may influence risk in different families. On the other hand, a single susceptibility locus could influence risk for different syndromes in different individuals, either through allelic heterogeneity, pleiotropic expression of a single allele, or the modifying effects of environmental factors.

Epilepsy is defined by recurrent (≥2) unprovoked seizures (2). Seizures are considered to be unprovoked when they occur in the absence of an immediate precipitating factor (although an injury to the central nervous system may have occurred at some time in the past). Epilepsy is distinguished from the two other major classes of seizure disorders: acute symptomatic seizures, in which seizures occur only in association with acute structural or metabolic insults to the central nervous system (the largest class of which is febrile convulsions), and isolated unprovoked seizures, in which only a single unprovoked seizure has occurred.

Clinically, epilepsy is subclassified according to seizure type (3) and epilepsy syndrome (4). In the seizure classification, the primary distinction is between generalized onset seizures, which are presumed to involve the entire brain from the outset, and partial onset seizures, in which seizures begin in a localized brain region. The syndrome classification combines information on seizure type, age at onset, etiology, clinical course, and electroencephalographic findings, and distinguishes between generalized epilepsies and localization-related (focal or partial) epilepsies.

Approximately 25 percent of prevalent epilepsy is associated with an antecedent central nervous system injury (e.g., head trauma, stroke, or brain infection) and, accordingly, is classified as “symptomatic” (2). The remainder, without identified cause, are assigned into two broad classes by the current International Classification of Epileptic Syndromes (4): “idiopathic,” reserved for syndromes of presumed genetic origin, and “cryptogenic,” for syndromes presumed to be nongenetic but with insufficient evidence to assign a specific etiology. For most of the syndromes currently classified as “idiopathic,” however, clear evidence of a genetic basis, either from linkage studies or demonstration of a specific mode of inheritance, is lacking. Similarly, in syndromes classified as “cryptogenic,” a genetic contribution to etiology cannot be ruled out. Thus we believe it more appropriate to use one term (“idiopathic/cryptogenic”) to describe cases in which evidence to establish etiology is lacking, and to address the question of genetic susceptibility separately.

METHODOLOGICAL ISSUES

Several problems of epidemiologic design and analysis have impeded progress in genetic research on epilepsy. Many early studies used highly selected populations, and few included comparison groups or used standardized interview methods. Age adjustments were seldom made when examining risks of seizures in relatives of epilepsy patients. Definitions of epilepsy were often ambiguous, and the disorder of in-
terest in the relatives was seldom clearly defined. Some studies included as affected only those relatives with epilepsy, while others included those with any seizure or those with only electroencephalographic abnormalities.

Accurate information about seizure occurrence in family members is essential for valid testing of genetic hypotheses about epilepsy and other seizure disorders. In most genetic studies of epilepsy, data are obtained indirectly, in “family history” interviews in which the proband with epilepsy (or the mother, if the proband is a child) is interviewed about seizures in other family members. For many disorders, family history data obtained in this way have low sensitivity, and many affected relatives are misclassified as unaffected. This problem can usually be remedied by using a family study design, in which each relative is examined or given a diagnostic interview directly. Study of the genetic epidemiology of epilepsy presents a unique problem, however, because the diagnosis in both probands and relatives cannot usually be made on the basis of physical examination or laboratory testing. It is essentially historical, based on a description of seizure events that occurred prior to visiting the physician.

The Rochester-Olmsted County [Minnesota] Record Linkage Project (5), is a unique exception to the usual methods for collection of familial data. The records linkage system of the Mayo Clinic includes essentially all medical, surgical, and pathologic diagnoses of residents of Olmsted County from 1922 to the present, and, therefore, provides an excellent resource for epidemiologic studies of epilepsy and other disorders (1, 2). This system was adapted for collection of genetic information using a three-step procedure that avoids the use of interviews completely. First, probands with epilepsy were identified by searching the records of the Mayo Clinic to identify all children aged <15 years with diagnoses of epilepsy while residing in Rochester after 1935. Second, the records were used to identify the parents of these probands, and all of the other descendants of the parents (i.e., the probands’ siblings, children, nieces and nephews, and grandnieces and grandnephews). Third, the medical records of these relatives at the Mayo Clinic, and all other medical facilities serving southeastern Minnesota, were reviewed for evidence of seizure disorders. The resulting data afford several unique advantages for genetic studies: the probands were ascertained without selection bias; the data on seizure disorders in relatives have high validity; and the clinical detail on seizure disorders in both probands and relatives is extensive. The only disadvantage is the limitation in sample size imposed by the population-based nature of the sample, and the relatively small population of Rochester.

The Epilepsy Family Study of Columbia University (EFSCU) (6) is another major study of the genetic epidemiology of epilepsy. This study, begun in 1985, aimed to evaluate the genetic relations among different clinically defined classes of epilepsy and seizure disorders, and to test consistency with various genetic models. Estimates of statistical power indicated that 2,000 families would be needed for the planned analyses. To ascertain this large number of families, the investigators carried out a telephone survey of the adult clients of 10 different voluntary organizations for epilepsy. Semistructured telephone interviews were used to collect clinical and family history data from 1,957 enrolled probands. Sensitivity of the family history data was improved by interviewing, in addition to the proband, an additional family informant (usually the proband’s mother) in each family where possible. Specificity was improved through direct interview of relatives reported to have had seizures. The EFSCU database is advantageous for genetic studies because of its large size. Its major disadvantage is limited generalizability arising from overrepresentation, in the proband sample, of severe epilepsies of long duration (resulting from use of adults who had contacted voluntary organizations as the source population).

The validity of the proband’s family history report of epilepsy in first-degree relatives was assessed in the EFSCU data, using as the “gold standard” either the mother’s report or self-report of a seizure history in the proband’s parents and siblings (7). The results suggest that family history data on epilepsy in parents and siblings are reasonably accurate, but isolated unprovoked seizures and acute symptomatic seizures are underreported. Sensitivity for epilepsy was 87 percent compared with the mother’s report and 3 percent compared with self-report, whereas sensitivity for other seizure disorders was only 32 percent compared with the mother’s report and 18 percent compared with self-report.

Analyses of the EFSCU data have also indicated that epilepsy is underreported in older relatives (8). A “cohort effect” in reported familial risks was observed, with a 50 percent increase in the observed cumulative incidence of epilepsy for each 20-year increase in birth year of the relatives (8). Population-based data from Rochester indicate that incidence rates of epilepsy have not increased during the age- and time-periods investigated in the study (1), thus the apparent “cohort effect” appeared to be an artifact of underreporting of epilepsy that was present at young ages in older relatives.
EVIDENCE OF A GENETIC CONTRIBUTION TO EPILEPSY

Most early studies of the genetics of epilepsy were devoted to demonstrating familial aggregation, i.e., an increased risk of epilepsy in relatives of affected persons, compared with risks in the general population (or relatives of unaffected persons). The best estimates of familial aggregation are derived from the work of Annegers et al. (5, 9), using data from the Rochester-Olmsted County Record Linkage Project. In these data, the standardized morbidity ratio for epilepsy in relatives of probands with idiopathic/cryptogenic epilepsy with onset prior to age 16 years was 2.5 in siblings (95 percent confidence interval 1.3–4.4) and 6.7 in offspring (95 percent confidence interval 1.8–17.1). The cumulative incidence of epilepsy to age 40 years was 3.6 percent in siblings and 10.6 percent in offspring of these probands, compared with 1.7 percent in the Rochester population. Risk of epilepsy was not increased in more distant relatives (e.g., nieces and nephews, grandchildren).

This evidence of familial aggregation is suggestive of, but does not prove, a genetic contribution to the etiology of epilepsy. Alternative explanations include common exposures to environmental factors or shared behavior patterns in family members, in addition to genetic susceptibility. Five other lines of evidence can be cited as evidence of a genetic basis for the familial aggregation, however. First, concordance rates in monozygotic twins are consistently higher than in dizygotic twins (10–14). The observed concordance rates vary substantially across studies (table 1), probably reflecting differences in the methods used to ascertain twin-pairs or the definitions of epilepsy employed. Second, many human genetic disorders (both single gene and chromosomal) have seizures associated with them (15). Although these Mendelian disorders account for only a small proportion of epilepsy (about 1 percent), they do illustrate that genetic mechanisms can raise susceptibility to seizures. Third, in experimental animals several genes that raise seizure susceptibility have been identified, and these genes may have homology to human epilepsy susceptibility genes (16). Fourth, in six human epilepsy syndromes, genetic linkage analysis has been used to localize human epilepsy susceptibility genes to specific chromosomal regions (17–29) (table 2). Fifth, in two of the syndromes with genes localized to chromosomal regions, the causative genes have been identified (30, 31).

The epilepsy syndromes with linkage evidence comprise only a small proportion of all epilepsy. In the remainder, the genetic mechanisms underlying familial aggregation are unclear. However, linkage findings provide powerful evidence of the genetic influences on a complex disorder such as epilepsy. They are derived from analysis of statistical association, within families, between a disease phenotype and a genetic marker allele. The analysis must be performed within families, because the specific marker allele associated with the disease generally varies from family to family, in accordance with the allelic distribution of the marker in the population. Such a within-family association is unlikely to be attributable to systematic bias, because most genetic markers have no clinical manifestations or social connotations, and marker information is collected by laboratory analysis of biologic samples, independently of disease status. It provides strong evidence both that 1) disease susceptibility is influenced by a gene (otherwise the disease would not be expected to cosegregate with a genetic marker), and 2) the chromosomal location of the susceptibility gene is near that of the marker.

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<th>TABLE 1. Concordance rates for epilepsy in monozygotic and dizygotic twins</th>
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<td>Authors (reference no.)</td>
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<td>Lennox (10)</td>
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<th>TABLE 2. Localized susceptibility genes for epilepsy</th>
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<td>Epilepsy syndrome</td>
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<tr>
<td>Benign familial neonatal convulsions</td>
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<tr>
<td>Progressive myoclonus epilepsy (Unverricht-Lundborg type)</td>
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<td>Progressive epilepsy with mental retardation</td>
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<td>Juvenile myoclonic epilepsy</td>
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<td>Autosomal dominant partial epilepsy with auditory features</td>
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<td>Autosomal dominant nocturnal frontal lobe epilepsy</td>
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A locus for benign familial neonatal convulsions was originally found on chromosome 20q (17), and a second locus for the same syndrome was later found on chromosome 8q (18). One form of progressive myoclonus epilepsy (Unverricht-Lundborg type), a recessive disorder with complete penetrance, was localized to chromosome 21q (19), and the gene has recently been identified as cystatin B, a protease inhibitor (30). Another recessive form of progressive epilepsy, progressive epilepsy with mental retardation, was localized to chromosome 8p (20). Juvenile myoclonic epilepsy has an uncertain mode of inheritance, with reduced penetrance and a range of phenotypic expressions within families. Greenberg et al. found evidence for linkage of juvenile myoclonic epilepsy to the human leukocyte antigen (HLA) region of chromosome 6 (21). Two subsequent studies (22, 23) confirmed the linkage, but another two (24, 25) found evidence against it. Part of the difficulty is that if a susceptibility gene linked to HLA does exist, it is unclear what phenotype it produces, because all three of the studies reporting positive-linkage findings used several alternative schemes to define which relatives were considered affected. A recent study suggested that a juvenile myoclonic epilepsy susceptibility gene maps to chromosome 6p, but lies some distance centromeric to the HLA region (26). In that study, linkage was observed only in families in which juvenile myoclonic epilepsy was unaccompanied by childhood absence seizures (26).

Until recently, most localization-related (partial or focal) epilepsies were presumed to be nongenetic. However, evidence for linkage has been obtained for two forms of localization-related epilepsy. First, a gene for autosomal dominant partial epilepsy with auditory features was localized to chromosome 10q (27). Second, autosomal dominant nocturnal frontal lobe epilepsy was localized to chromosome 20q, in a region very close to the benign familial neonatal convulsions locus on chromosome 20 (28). The autosomal dominant nocturnal frontal lobe epilepsy gene was identified as a mutation in the neuronal nicotinic acetylcholine receptor $\alpha_4$ subunit (CHRNA4) (31). The CHRNA4 gene has not been shown to be involved in benign familial neonatal convulsions, although it was mapped to nearly the same region of chromosome 20q.

Recently, suggestive evidence for linkage to chromosome 8q was obtained in a large pedigree with an apparently autosomal dominant form of febrile convulsions (29). Evidence for linkage was only considered suggestive, because the analysis was maximized over different values of penetrance and phenocopy rate, thus inflating the possibility of a false-positive result. A maximum LOD score of 3.4 was found at a penetrance of 60 percent and a phenocopy rate of 3 percent.

Although only two epilepsy genes have been identified in humans, significant progress has been made in identifying genes that influence seizure risk in experimental animals (16). Model systems have been developed in various species, and help to resolve some of the complexity involved in human epilepsy. For example, given that many molecular defects can give rise to a single disorder, study of a single locus mutation in an experimental animal can permit detailed examination of the effect of one gene at a time. The gene can be isolated and sequenced to predict transcription and translation products and identify the subset of cells affected, in order to predict the various phenotypic manifestations of the mutation. In the mouse, this approach has been used to study a large number of specific mutations that affect seizure susceptibility. The genes that have been identified to date include ion channel genes that affect intrinsic neuronal excitability, genes that affect neurotransmitter release mechanisms, and genes that affect synaptic receptors.

MATERNAL TRANSMISSION

Previous studies have consistently found that risks of epilepsy are approximately twice as high in offspring of affected women as in offspring of affected men (32) (figure 1). From a critical review and analysis of published data, Ottman et al. (32, 33) concluded that this maternal effect is inconsistent with any conventional genetic model. Analyses of data from Rochester indicate that it cannot be explained either by

**FIGURE 1.** Cumulative incidence of unprovoked seizures, by age, in offspring of men and women with epilepsy, and in the general population of Rochester, Minnesota, 1935-1979. Adapted from Ottman et al. (34), with permission from the University of Chicago Press (© by the American Society of Human Genetics). All rights reserved.
1) intrauterine exposure to seizures or anticonvulsants in offspring of women with epilepsy, 2) perinatal complications that occur with increased frequency in women with epilepsy, or 3) patterns of selective fertility leading to a higher proportion of affected mothers than affected fathers with familial forms of epilepsy (34–37). The possible roles of mitochondrial genes, imprinted nuclear genes, or expanded repeat mutations remain to be investigated.

COMPLEXITY IN THE GENETIC CONTRIBUTIONS TO EPILEPSY

As noted above, the genetic contributions to epilepsy are exceedingly complex. As with many familial disorders, this complexity derives essentially from an imperfect correspondence between the specific genes that affect risk (i.e., the susceptibility genotypes) and the anatomic or functional manifestations of these susceptibility genotypes (i.e., the phenotypes). Four reasons for this imperfect correspondence are discussed below, as they apply to the genetic epidemiology of epilepsy.

Reduced penetrance

Many of the relevant genotypes probably have reduced penetrance, implying that some persons with the high risk genotype are unaffected, and that nongenetic factors may be required for phenotypic expression. The implication is that in studying epilepsy in families, one cannot assume that unaffected individuals do not carry a susceptibility gene. For example, because risk of epilepsy is age-related, gene carriers may be unaffected if studied at young ages.

Etiologic/genetic heterogeneity

Different genetic and nongenetic factors influence risk in different families, or in different clinically defined subgroups of epilepsy. Discovery of clinical features that distinguish between genetic and nongenetic epilepsies, and investigation of the genetic relations among different types of epilepsy, are important research goals. Such distinctions could aid in the design of genetic linkage studies, and greatly refine classification of syndromes.

Two types of genetic heterogeneity should be distinguished because they lead to different predictions about epilepsy risks in families. With locus heterogeneity, genes at different genetic loci raise risk for the same epilepsy syndrome, and, hence, different families with the same syndrome would be expected to carry susceptibility genes in different chromosomal locations. This type of heterogeneity has been demonstrated in benign familial neonatal convulsions, through localization of two different susceptibility genes (on chromosomes 20q and 8q) in different families with the same syndrome (17, 18). With allelic heterogeneity, alternative alleles at a single locus could raise risk for different epilepsy syndromes, and families with different epilepsy syndromes would be expected to carry susceptibility genes in the same chromosomal location. It was suspected that benign familial neonatal convulsions and autosomal dominant nocturnal frontal lobe epilepsy might be caused by alternative alleles at the same locus, since the two syndromes were localized to the same region of chromosome 20q. However, current evidence suggests that this is unlikely because the CHRNA4 gene is a strong candidate for autosomal dominant nocturnal frontal lobe epilepsy, but not for benign familial neonatal convulsions.

One approach to studying genetic/etiologic heterogeneity is to compare subjects with different clinical characteristics of epilepsy (e.g., seizure type, age at onset, and etiology of epilepsy) in terms of the risks of seizure disorders in their relatives. The results of such studies can provide important information about which patients are most likely to have a genetic susceptibility. One of the most consistent findings has been that risks are higher in relatives of patients with idiopathic/cryptogenic epilepsy than in relatives of those with remote symptomatic epilepsy (38–43). In the classic twin study by Lennox (10), the difference in concordance rates between monozygotic and dizygotic twins was greater for twins with idiopathic/cryptogenic epilepsy than for those with identified etiologic factors (table 1). In the EFSCU, epilepsy following a postnatal central nervous system lesion (e.g., head trauma, stroke, or brain infection) was not associated with increased familial risk, suggesting that the genetic contributions to postnatal symptomatic epilepsy are minimal (42, 43). Relatives of patients with early age at onset epilepsy have also been found to have higher seizure risk than relatives of those with later onset (38, 39, 44). Seizure risks in relatives are also higher when there is a previous family history than when there is no such history (45, 46).

It is widely assumed that genetic contributions are more important in generalized than in localization-related epilepsy. Most of the syndromes classified as "idiopathic" (presumed genetic) are generalized (4). However, in most studies, the difference in familial risk between generalized and localization-related epilepsies is small (47). Recent findings from the EFSCU indicate that risks in parents and siblings are higher for probands with generalized-onset versus partial-onset seizures, but this is not true in offspring (42). Similarly, in an earlier study of offspring of epilepsy pa-

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Given the extreme clinical heterogeneity of the epilepsies, many investigators currently assume that the genetic contributions are different for each clinically-defined epilepsy syndrome. If this were true, we would expect that among relatives of probands with specific types of epilepsy, risk would be increased only for the same types as in the probands. Few data are available to address this question. Several recent studies suggest that there is a tendency for clinical characteristics to cluster within families. Berkovic et al. (49) studied the syndrome classifications of nine monozygotic twin pairs concordant for epilepsy and found that in every case the syndrome classifications were concordant also. Both Tsuboi (50) and Beck-Mannagetta and Janz (51) found that the distribution of seizure types in affected relatives was skewed toward the same types of seizures as in the probands, although different seizure types were seen also. In a study of 72 families of probands with idiopathic generalized epilepsy syndromes, each of which contained three or more affected individuals, multiple different idiopathic generalized epilepsy syndromes were seen in 75 percent of families, but there were very few cases of localization-related epilepsy (52).

However, the results differed in the EFSCU (53). In the parents and siblings, risk for all epilepsy was greater if the proband had generalized versus localization-related epilepsy. However, the increased risk in parents and siblings was not restricted to the same type of epilepsy as in the proband. These results are not consistent with a model of genetic heterogeneity involving separate genetic influences on generalized and localization-related epilepsy. They suggest, instead, that some genetic mechanisms raise risk for both generalized and localization-related epilepsies.

The different findings in the EFSCU compared with other studies may be partly explained by a difference in the types of epilepsy in the probands. Very few of the EFSCU probands had idiopathic generalized epilepsy syndromes, whereas most of the previous studies focused on the families of probands with these syndromes. Methodological differences may have also contributed to the different findings. In the EFSCU, diagnosis and classification of epilepsy in each individual was performed blindly with respect to the diagnoses of other family members. None of the other studies stated that this was done.

Pleiotropy

Some "epilepsy susceptibility genotypes" may have multiple phenotypic manifestations affecting several different disorders, and even different organ systems. The implication is that when we study epilepsy in families, we might be leaving out other disorders that result from the same genotypes. There is a strong basis for assuming a common genetic basis for epilepsy and febrile convulsions. Hauser et al. (54) found that the risk of epilepsy was increased to the same extent in the relatives of probands with febrile convulsions as in relatives of probands with epilepsy. Similarly, the risk of febrile convulsions was increased to the same extent in the relatives of probands with epilepsy as in the relatives of probands with febrile convulsions. When the proband had both epilepsy and febrile convulsions, however, risk of epilepsy was increased to a greater extent, suggesting that a higher genetic liability is required to manifest both disorders.

Previous studies also support the possibility of a shared genetic susceptibility to epilepsy and cerebral palsy. In the National Collaborative Perinatal Project, incidence of cerebral palsy in offspring was associated with the mother's history of epilepsy (55), and incidence of nonfebrile seizure disorders in offspring without cerebral palsy was associated with a history of motor deficits in siblings (56). Similarly, Rimoin and Metrakos (57) reported an increased prevalence of convulsions and epileptiform electroencephalographic abnormalities in relatives of children with hemiplegia, a specific form of cerebral palsy. In the EFSCU, risk of idiopathic/cryptogenic epilepsy was increased in the relatives of probands with epilepsy associated with cerebral palsy, and conversely, risk of epilepsy associated with cerebral palsy was increased in the relatives of probands with idiopathic/cryptogenic epilepsy (43).

Gene-environment interaction

The effects of some genotypes on risk for epilepsy may involve interaction with specific environmental exposures (58, 59). For example, a genotype might not affect risk directly, but might operate by increasing susceptibility to the effect of an environmental factor. Thus, although it might be expected that idiopathic/cryptogenic epilepsy is more likely to be genetic than is remote symptomatic epilepsy, some susceptibility genes might contribute to remote symptomatic epilepsy and even to acute symptomatic seizures, as well as to idiopathic/cryptogenic epilepsy. In the EFSCU, risk for idiopathic/cryptogenic epilepsy was not increased in the relatives of probands with postnatal symptomatic epilepsy, suggesting that the genetic contributions are minimal for epilepsy occurring in the context of an identified postnatal environmental insult (43). Similarly, in a recent study by Schaumann et al.
(60), seizure risk was not increased in relatives of probands with posttraumatic epilepsy.

These findings provide clues about the relations between genetic susceptibility and environmental risk factors in their influence on epilepsy risk (59). Models of gene-environment interaction, like those of interaction generally, are scale dependent. If risks are measured on an additive scale, then genetic and environmental factors are considered to be independent (i.e., no interaction) if the risk difference due to an environmental exposure is the same regardless of genetic susceptibility. Such a model predicts that probands who develop epilepsy in the absence of an environmental insult (i.e., those with idiopathic/cryptogenic epilepsy) would be more likely to be genetically susceptible than those with identified insults. The higher risk of epilepsy in the relatives of probands with idiopathic/cryptogenic epilepsy than in the relatives of those with postnatal symptomatic epilepsy is consistent with this prediction.

On the other hand, if risks are measured on a multiplicative scale, then genetic and environmental factors are considered to be independent if the relative risk of an environmental exposure is the same regardless of genetic susceptibility. Such a model predicts that exposed and unexposed probands have the same likelihood of being genetically susceptible, and can, therefore, be rejected based on the findings in epilepsy.

The postnatal environmental risk factors for epilepsy evaluated in EFSCU and other genetic studies (i.e., head trauma involving ≥30 minutes of unconsciousness, stroke, brain tumor, brain surgery, and brain infection) have strong effects, each raising risk for epilepsy at least 10-fold (61). Other risk factors with milder effects may show different patterns of gene-environment interaction. For example, in the study by Schaumann et al. (60), seizure risk was increased in the relatives of probands with alcohol-related seizures. The increased familial risk was observed for probands with either unprovoked seizures associated with chronic alcohol abuse, or acute symptomatic seizures associated with alcohol intoxication. The possibility of interaction between alcohol exposure and genetic susceptibility to epilepsy would be interesting to explore.

OTHER SYNDROMES OF INTEREST FOR GENETIC STUDIES

In the following syndromes, family studies have indicated an important genetic influence on susceptibility, and additional research is underway.

Childhood absence (pyknolepsy)

In the 1960s, Metrakos and Metrakos (46) examined the distribution of seizures and electroencephalographic abnormalities in families of children with "centrencephalic epilepsy," most of whom would be classified today as having idiopathic childhood absence epilepsy. They concluded that this type of epilepsy and its associated 3/second generalized spike-wave electroencephalographic trait were caused by an autosomal dominant gene with reduced and age-dependent penetrance. In contrast, Borecki et al. (62) used data collected by Doose and Baier (63) to perform segregation analysis of epilepsy in families of probands with "primary generalized minor motor epilepsies," many of which probably would also be classified today as childhood absence. They concluded that the data were most consistent with an autosomal recessive susceptibility allele which, however, accounted for only 9.3 percent of the variability. Linkage studies of this syndrome are underway, but susceptibility genes have yet to be localized.

Benign rolandic epilepsy with centrotemporal spikes

Several investigators have suggested an autosomal dominant etiology for benign rolandic epilepsy, with associated central temporal spikes or sharp waves in the electroencephalogram (64–66). While it is clear that this syndrome is highly familial, its mode of inheritance remains to be determined. No evidence for linkage has been reported to date.

Febrile convulsions

Febrile convulsions have been studied extensively from a genetic point of view (54, 67–70). In a segregation analysis of susceptibility to febrile convulsions, Rich et al. (70) found significant genetic heterogeneity. In the families of probands with only a single febrile convolution, the data were most consistent with a polygenic mode of inheritance, whereas in families of probands with multiple febrile convulsions, the data were consistent with an autosomal dominant mode of inheritance. As noted above, suggestive evidence has been obtained for linkage to chromosome 8q in a single family with apparently autosomal dominant inheritance (29). In families with idiopathic epilepsy syndromes, it would be of great interest to determine whether susceptibility genes raise risk for febrile convulsions, in addition to epilepsy.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

Although evidence is strong for an important genetic influence on susceptibility to epilepsy, for the
majority of patients the specific genetic influences remain to be identified. Identification of genes influencing susceptibility to epilepsy holds great promise for future studies. It could facilitate early identification of susceptible individuals, early treatment, and, perhaps, prevention of the disorder in some individuals. It is also a first step in investigating the physiologic effects of susceptibility genes, leading to better understanding of pathogenesis and to development of new strategies for treatment and prevention.

Progress in gene mapping and gene identification to date have been limited to epilepsy syndromes with relatively simple, single gene inheritance. The results of linkage studies in juvenile myoclonic epilepsy, which appears to have more complex inheritance, have been conflicting. Families with apparently single gene inheritance of epilepsy are quite rare, and most of the familial aggregation of this disorder is attributable to families containing few affected individuals, with unclear patterns of inheritance. Identification of genes that raise risk in these small families is a daunting prospect. Given the overall modest level of familial aggregation of epilepsy (two- to fourfold increased risks in relatives) and the likelihood that multiple genes are involved in raising risk in these families, nonparametric designs with very large sample sizes will be required. From a public health point of view, however, these studies are potentially important because they could influence risk in a large proportion of families.

Future studies should also be aimed at resolving several key issues in the genetic epidemiology of epilepsy. First, the explanation for the maternal effect remains a mystery. A related finding that the patterns of familial risk appear to differ between offspring and other relatives is also unexplained. Second, the genetic relations between alcohol-related seizures, febrile convulsions, and epilepsy should be explored. Third, the genetic influences on specific electroencephalographic abnormalities, and their relations to the genetics of epilepsy, should be investigated.

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