An inherited contribution to the etiology of epilepsy has been suspected for centuries. Until recently, however, little progress has been made in identifying the specific genetic influences on susceptibility to seizures. This slow progress is partly due to underlying complexity in the genetic contributions. The epilepsies are etiologically and clinically heterogeneous, and genetic influences appear to have primary importance in only a subset of patients. Moreover, many different genetic mechanisms may influence risk for epilepsy in different families or different syndromes. Some of these mechanisms involve major effects of single genes, producing simple patterns of inheritance in families (autosomal or X-linked, dominant or recessive). Other mechanisms probably involve the combined effects of multiple genes and environmental factors, each with a smaller effect on susceptibility to seizures.

The important genetic mechanisms clearly differ across some clinically defined epilepsy syndromes, but the relationship between clinical syndrome and genetic mechanism is not straightforward. Risk for a single syndrome is sometimes influenced by different genetic mechanisms in different families; conversely, a single genetic mechanism may influence risk for different syndromes within the same family.

Approximately 25 percent of prevalent epilepsy is associated with an antecedent central nervous system (CNS) injury (e.g., head trauma, stroke, or brain infection) and accordingly is classified as “symptomatic” (1). The remainder without identified cause is assigned into two broad classes by the current International Classification of Epileptic Syndromes (2): “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. The current system of classification is problematic, however, because idiopathic and cryptogenic epilepsies are not easily distinguishable in terms of the importance of genetic susceptibility. For most of the syndromes currently classified as “idiopathic,” clear evidence of a genetic basis, either from linkage studies or from demonstration of a specific mode of inheritance, is lacking. Similarly, in syndromes classified as “cryptogenic,” a genetic contribution to etiology cannot be ruled out.

EVIDENCE OF A GENETIC CONTRIBUTION TO EPILEPSY

Most people with epilepsy do not have affected relatives, and for most of those who do have a family history, the familial distribution is inconsistent with a simple Mendelian model. When all types of epilepsy are considered together, however, the risk of developing epilepsy is clearly increased in the relatives of affected people compared with the general population. The best estimates of the extent of this familial aggregation are derived from the Rochester–Olmsted County Record Linkage Project (3,4). In that study, in the families of probands with idiopathic or cryptogenic epilepsy with onset before age 16, the risk of developing epilepsy by age 40 was 3.6 percent in siblings and 10.6 percent in offspring, compared with 1.7 percent in the Rochester population. Overall, the risk of epilepsy was increased 2.5-fold in siblings [95% confidence interval (CI) 1.3–4.4] and 6.7-fold in offspring (95% CI 1.8–17.1). The risk of epilepsy was not increased in more distant relatives, such as nieces, nephews, and grandchildren.

Familial aggregation does not necessarily indicate a genetic etiology; it could result instead from shared environmental exposures in members of the same family. However, four lines of evidence clearly indicate a genetic contribution to the familial aggregation of epilepsy. First, concordance rates in monozygotic twins are consistently higher than in dizygotic twins
The observed concordance rates vary substantially across studies, probably reflecting differences in the methods used to ascertain twin pairs or the definitions of epilepsy employed. Second, seizures are part of the phenotype of many human genetic disorders resulting from either single gene mutations or chromosomal abnormalities (10). Although these disorders account for only about 1 percent of epilepsy, they do illustrate that a wide variety of 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 (11). Fourth, positional cloning techniques have been used to chromosomally localize, and subsequently identify, genes that raise risk for a growing list of human epilepsy syndromes (Table 5-2). Research in this area is moving extremely rapidly, so that it is quite likely that by the time this chapter appears in print the list of syndromes in Table 5-2 will be out of date.

The epilepsies with well-established genetic causes constitute only a small proportion of the total. In the majority, the genetic mechanisms underlying familial aggregation of epilepsy are unclear. However, linkage findings, even before identification of the specific causative genes, provide powerful evidence of the genetic influences on 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 disorder generally varies from family to family, in accordance with the distribution of the marker alleles in the population. Such a within-family association is unlikely to be artifactual because most genetic markers have no clinical or social effects, and marker information is based on laboratory analysis of biological samples performed independently of disease status. Thus, finding genetic linkage provides strong evidence that the disease susceptibility is influenced by a gene. Otherwise the condition would not cosegregate with a genetic marker allele. Finding genetic linkage also indicates that the susceptibility gene is located near the marker on the same chromosome.

The first locus for benign familial neonatal convulsions (BFNC), an autosomal dominant syndrome with complete penetrance, was found on chromosome 20q (12). A second locus for the same syndrome was later found on chromosome 8q (13). The gene on chromosome 20q was identified as a novel voltage-gated potassium channel, KCNQ2 (14), and the gene on chromosome 8q was identified as another member of the same family of potassium channels, KCNQ3 (15).

Juvenile myoclonic epilepsy (JME) has an uncertain mode of inheritance, with reduced penetrance.
and a range of phenotypic expressions within families. Greenberg and coworkers (16) found evidence for linkage of JME to the HLA region of chromosome 6. Two subsequent studies confirmed the linkage (17,18), but others found evidence against it (19,20) and instead found evidence for linkage to chromosome 15q (21). Another recent study suggested that a JME susceptibility gene maps to chromosome 6p but lies some distance centromeric to HLA (22). The lack of consistency in the linkage findings in JME may be partly explained by uncertainty about the phenotype that is produced by the susceptibility gene because the studies reporting positive linkage findings have used several alternative schemes to define which relatives were considered affected.

As shown in Table 5-2, evidence for linkage has also been reported in childhood absence epilepsy, benign familial infantile convulsions, familial autosomal recessive idiopathic myoclonic epilepsy of infancy, and familial adult myoclonic epilepsy (23–26). Until recently, most localization-related (partial or focal) epilepsies were presumed to be nongenetic. However, evidence for linkage has been obtained for four forms of localization-related epilepsy. First, a gene for autosomal dominant partial epilepsy with auditory features (ADPEAF) was localized to chromosome 10q in a single large pedigree (27). Subsequently, evidence for linkage was reported for an overlapping region of chromosome 10q in a large family with autosomal dominant lateral temporal epilepsy, a phenotype clinically similar to ADPEAF (28). Further molecular studies are needed to determine whether these two entities are the same. Second, autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) was localized to chromosome 20q (29). The ADNFLE gene was identified as the neuronal nicotinic acetylcholine receptor α4 subunit (CHRNA4) (30). This locus has been excluded in some families with the same syndrome, suggesting that at least one other gene causing ADNFLE remains to be identified. Evidence for linkage to chromosome 15 has been reported in one of these families (31). Third, a gene for benign epilepsy of childhood with centrotemporal spikes was localized to chromosome 15q14 in the region of the alpha 7 subunit of the neuronal nicotinic acetylcholine receptor (32). Fifth, evidence for linkage to chromosome 22q11 was reported for a family with familial partial epilepsy with variable foci (33).

Evidence for linkage has been reported on chromosomes 8q, 19q, and 5q in three different families with apparently autosomal dominant forms of febrile convulsions (34–36). In a related disorder, generalized epilepsy with febrile seizures plus (GEFS+), linkage was reported on chromosome 19q13, and the gene was identified as SCN1B, the voltage-gated sodium channel β1 subunit (37). In another family with GEFS+, the gene was localized to chromosome 2q and identified as the α1 subunit of the voltage-gated sodium channel, SCN1A (38).

Causative genes have been identified in five progressive epilepsy syndromes with mental retardation. Progressive myoclonus epilepsy of Unverricht-Lundborg type, an autosomal recessive disorder with complete penetrance, was localized to chromosome 21q (39), and the gene was subsequently identified as cystatin B, a protease inhibitor (40). The gene for Lafora’s disease, another autosomal recessive form of progressive myoclonus epilepsy, was identified as a novel protein phosphatase gene on chromosome 6q24 (41). An autosomal recessive gene for progressive epilepsy with mental retardation was localized to chromosome 8p (42), and the gene was identified as a neuronal ceroid lipofuscinase (43). Two forms of progressive epilepsy, myoclonic epilepsy with ragged red fibers (MERRF) and myoclonic epilepsy with lactic acidosis and strokelike episodes (MELAS), have been shown to be caused by mutations in mitochondrial genes (44,45).

**MATERNAL TRANSMISSION**

Risk of epilepsy is approximately twice as high in offspring of affected women as in offspring of affected men (46). This maternal effect is inconsistent with any conventional genetic model (46,47). Models involving X-linkage are rejected as an explanation because the risks are nearly the same in male and female offspring. Studies have indicated that the maternal effect cannot be explained either by (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 (48–51). The possible roles of unidentified environmental exposures, mitochondrial genes, imprinted nuclear genes, or expanded repeat mutations remain to be investigated.

**COMPLEXITY IN THE GENETIC CONTRIBUTIONS TO EPILEPSY**

**Etiologic and Genetic Heterogeneity**

Important genetic and nongenetic influences clearly differ among some epilepsy syndromes, and in some cases also among different families that have the same syndrome. For example, locus heterogeneity (i.e., a single syndrome caused by mutations at different genetic loci in different families) has been demonstrated in BFNC through identification of two different susceptibility...
bility genes (KCNQ2 on chromosome 20q and KCNQ3 on chromosome 8q) (14,15).

One approach to studying etiologic and genetic heterogeneity is to examine how different clinical characteristics of epilepsy, such as different seizure types, age at onset, and etiology, affect the risk of seizures in relatives of people with epilepsy. The results of such studies can provide important information about which patients are most likely to have a genetic susceptibility. The risk of having seizures has consistently been found to be higher in relatives of patients with idiopathic or cryptogenic epilepsy than in relatives of those with symptomatic epilepsy (52–58). In the classic twin study conducted by Lennox and Lennox (5), the difference in concordance rates between monozygotic and dizygotic twins was greater for twins with idiopathic or cryptogenic epilepsy than for those with identified etiologic factors (Table 5-1). Similarly, Ottman and coworkers (56–57) found that epilepsy following a postnatal CNS lesion caused by conditions such as head trauma, stroke, or brain infection was not associated with increased familial risk. This suggests that the genetic contributions to postnatal symptomatic epilepsy are minimal.

Relatives of patients with early age at onset of epilepsy have also been found to have a higher risk of seizures than relatives of those with later onset (52,53,58). The risks of seizures in relatives are also higher when there is a previous family history of epilepsy than when there is no such history (59,60).

Most of the epileptic syndromes classified as “idiopathic” (presumed genetic) are generalized (2), and until recently most localization-related epilepsies were believed to be nongenetic. However, in most studies the difference in familial risk for generalized versus localization-related epilepsies is small (61). Recent findings indicate that the risk of epilepsy is higher in the parents and siblings of probands with generalized epilepsy than in those of probands with localization-related epilepsy, but this is not true in offspring (56). Similarly, in an earlier study of offspring of epilepsy patients in Rochester (62), the risk of unprovoked seizures was higher in offspring of probands with generalized epilepsy only for the subset of probands who had absence seizures.

Genetic contributions are commonly assumed to be different for each clinically defined epilepsy syndrome. If this were true, we would expect that among relatives of probands with specific syndromes, risk would be increased only for the same syndromes as in the probands. Several recent studies suggest that there is a tendency for clinical characteristics to cluster within families. Berkovic and coworkers (63) studied the syndrome classifications of twin pairs concordant for epilepsy and found that in most cases the syndrome classifications were also concordant. Both Tsuboi (64) and Beck-Mannagetta and Janz (65) 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 (IGEs), each of which contained three or more affected individuals, multiple different IGEs were seen in 75 percent of families, but there were very few cases of localization-related epilepsy (66).

Our work, however, suggests that some genetic mechanisms raise the risk for both generalized and localization-related epilepsies (67). Risk for all epilepsy in parents and siblings was greater if the proband had generalized epilepsy than if the proband had localization-related epilepsy, but the increased familial risk was not restricted to the same type of epilepsy as in the proband. The difference between these results and those found earlier may be attributed to a different distribution of epilepsy syndromes in the probands. In our study, very few of the probands had IGEs, whereas in the others, many or all of the probands had IGEs. The genetic influences on IGEs do appear to raise risk for IGEs specifically (although they may be shared across different IGEs such as JME, pyknolespys, etc.). The genetic influences on other forms of epilepsy may have less specific effects than those on IGEs, raising the risk for multiple different syndromes.

Pleiotropy

Some of the genetic influences on idiopathic or cryptogenic epilepsy may have broad phenotypic effects, raising risk for other disorders as well. Evidence is strong for a shared genetic influence on epilepsy and febrile convulsions. Hauser and coworkers (68) 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 probands with febrile convulsions.

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 was associated with the mother’s history of epilepsy (69), and incidence of nonfebrile seizure disorders in children without cerebral palsy was associated with a history of motor deficits in siblings (70). Similarly, Rimoin and Metrakos reported an increased prevalence of convulsions and epileptiform electroencephalogram (EEG) abnormalities in the relatives of children with hemiplegia (71).
Ottman and coworkers (57) found that the risk for idiopathic or cryptogenic epilepsy was increased in the relatives of probands with epilepsy associated with cerebral palsy, and, conversely, the risk of epilepsy associated with cerebral palsy was increased in the relatives of probands with idiopathic or cryptogenic epilepsy.

Gene–Environment Interaction

The effects of some genotypes on the risk for epilepsy may involve interaction with specific environmental exposures (72–73). For example, a genotype that raises the risk for epilepsy might increase susceptibility to the effect of an environmental risk factor such as head injury. In this case, the influence of the genotype on risk would be greater in persons who were exposed to the environmental factor than in those who were unexposed. Recent results do not appear to support this possibility because they suggest that the genetic contributions are minimal for epilepsy occurring in the context of an identified postnatal environmental insult (57,74). However, the postnatal environmental risk factors for epilepsy that have been evaluated in many previous studies (i.e., severe head trauma, stroke, brain tumor, brain surgery, and brain infection) have strong effects, each raising the risk for epilepsy at least 10-fold (75). Other risk factors with milder effects may show different patterns of gene–environment interaction. For example, in a study by Schaumann and coworkers (74), seizure risk was increased in the relatives of probands with alcohol-related seizures. The possibility of interaction between alcohol exposure and genetic susceptibility on risk for 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 under way.

Childhood Absence (Pyknolepsy)

In the 1960s, Metrakos and Metrakos (60) examined the distribution of seizures and EEG 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 three per second generalized spike-wave EEG trait were caused by an autosomal dominant gene with reduced and age-dependent penetrance. In contrast, Boreki and coworkers (76) used data collected by Doose and coworkers (77) 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. Susceptibility genes have not yet been identified in this syndrome, although linkage was reported (23).

Benign Rolandoic Epilepsy with Centrotcentral Spikes

Several investigators have suggested an autosomal dominant etiology for benign rolandic epilepsy with associated central temporal spikes or sharp waves in the EEG (78–80). While this syndrome is clearly highly familial, its mode of inheritance remains to be determined.

Febrile Convulsions

Febrile convulsions have been studied extensively from a genetic point of view (81–84). In a segregation analysis of susceptibility to febrile convulsions, Rich and coworkers found significant genetic heterogeneity (84). In the families of probands with only a single febrile convulsion, 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 previously noted, evidence has been obtained for linkage to three different chromosomes in families with apparently autosomal dominant inheritance (34–36). In families with idiopathic epilepsy syndromes, it is of great interest to determine whether susceptibility genes raise risk for febrile convulsions in addition to epilepsy.

CONCLUSIONS

Although evidence is mounting 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.
REFERENCES


