Are Generalized and Localization-Related Epilepsies Genetically Distinct?

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Background: Whether the genetic influences are distinct for generalized and localization-related epilepsies or whether some susceptibility genes raise the risk for both types of epilepsy is uncertain.

Objective: To evaluate genetic heterogeneity in epilepsy.

Methods: We used Cox proportional hazards analysis to compute rate ratios (RRs) for generalized and localization-related idiopathic or cryptogenic epilepsy in the first-degree relatives of 1498 adult probands with idiopathic or cryptogenic epilepsy ascertained from voluntary organizations. The reference group comprised the first-degree relatives of 362 probands from the same study with postnatal symptomatic epilepsy in whom the genetic contributions appear to be minimal.

Results: In the parents and siblings, the risk for all idiopathic or cryptogenic epilepsy was greater if the proband's epilepsy was generalized than if it was localization-related (RR, 4.7 vs 2.4). However, in the parents and siblings of each group of probands, the increased risk was not restricted to the same type of epilepsy as in the proband. The results differed in offspring, with a greater risk for all types of epilepsy if the proband's epilepsy was localization-related than if it was generalized (RR, 4.2 vs 1.6) and a greater risk for localization-related epilepsy than for generalized epilepsy (RR, 7.8 vs 1.8) if the proband's epilepsy was localization-related.

Conclusions: These findings in parents and siblings suggest that some susceptibility genotypes raise the risk for both generalized and localization-related epilepsies but are more common in persons affected with generalized epilepsy. The different findings in offspring may reflect a different influence on susceptibility in that subgroup.

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The risk of epilepsy generally has been found to be higher in the relatives of probands with generalized epilepsy than in the relatives of probands with localization-related epilepsy. Two alternative genetic models can be proposed to explain this observation. The first model assumes that the genetic influences on risk are different for generalized and localization-related epilepsies. This model predicts that relatives of probands with specific types of epilepsy will have increased risk only for the same types of epilepsy as in the probands. The second model assumes that the genetic influences on risk are the same for both types of epilepsy, but a higher genetic susceptibility is required to cause generalized epilepsy than localization-related epilepsy. This model predicts that risk for both types of epilepsy will be higher in the relatives of probands with generalized epilepsy than in the relatives of probands with localization-related epilepsy.

Few data are available to distinguish between these alternative models. Several recent studies suggest that there is a tendency for clinical characteristics to cluster within families. Berkovic et al studied the syndrome classifications of 9 monozygotic twin pairs concordant for epilepsy and found that in every case, the syndrome classifications were concordant also. Tsuboi and Beck-Mannagetta and Janz found that the distribution of epilepsy types in affected relatives was skewed toward the same types of epilepsy as in the probands, although different types of epilepsy also were observed. In a study of 72 families of probands with idiopathic generalized epilepsy (IGE) syndromes, each of which contained 3 or more affected persons, multiple different IGE syndromes were observed in 54 families (75%), but few cases of localization-related epilepsy were found.
SUBJECTS AND METHODS

STUDY POPULATION

The study population comprised families of probands with epilepsy from the Epilepsy Family Study of Columbia University (EFSCU). The methods for data collection in this study have been described in detail. Briefly, 1957 adults (mean age 45 years old) with epilepsy (probands) were ascertained from voluntary organizations with 84% participation. We used semistructured telephone interviews to obtain detailed information on the seizure histories of the probands and their parents, full siblings, half-siblings, offspring, and spouses. Whenever possible (67% of families), we also interviewed an additional family informant (usually the mother of the proband) about the same relatives described by the proband, to improve the sensitivity of the family history data. To confirm and augment the clinical detail on the family histories, we also were able to interview 51% of living adult relatives who were reported to have had seizures when they were at least 5 years old. We obtained medical records for 60% of the probands.

Of the probands, 87% were white, 55% had at least 1 year of college education, and 60% were women. Subjects interviewed did not differ in sex or ethnicity from those who refused to be interviewed, but they were more educated. Probands ranged in age from 18 to 82 years (mean, 36 years).

CLINICAL DIAGNOSIS AND CLASSIFICATION

Probands were interviewed about the clinical symptomatology of seizures and potential causative factors for themselves and any other relative they described as having had seizures. The interviews with other family informants included the same questions about seizure type and etiology in the proband, the relative who was being interviewed, and any other relatives described by the second informant as having had seizures. Diagnoses of seizure disorders were based on a consensus review of all information collected on each proband or relative (ie, from the proband interview, the second informant interview, a direct interview, and/or the medical record). Relevant information from electroencephalograms and magnetic resonance imaging or computed tomographic scans was seldom available; hence, the diagnosis was based solely on historical information in most cases. For each subject (proband or relative), the consensus review was performed without knowledge of the information collected on other relatives. This ensured that the diagnosis and classification of epilepsy for each subject was made independently and eliminated the potential for bias in the classification of seizures.

Epilepsy was defined as a lifetime history of at least 2 unprovoked seizures. All 1957 probands were confirmed to have epilepsy in the consensus review. The proband’s family history report of epilepsy in parents and siblings had excellent validity (sensitivity, 87%; specificity, 99%), using the mother’s report as the “gold standard.”

We classified seizures according to the 1981 criteria of the International League Against Epilepsy. The data for seizure classification included verbatim descriptions of seizures and closed-ended questions about relevant signs and symptoms (specific aura, unilateral signs, alteration in consciousness, etc.). As Ottman et al reported, the resulting seizure classifications were reliable (reproducible) and valid compared with the diagnoses of expert physicians. Patients with generalized onset seizures were classified as having generalized epilepsy, and patients with partial onset seizures (including patients with secondary generalization) were classified as having localization-related epilepsy.

For the classification of causes, we asked specific questions about factors demonstrated in previous epidemiologic studies to be strongly associated with the risk for

RESULTS

Among the 1957 probands in the EFSCU study population, 1560 had idiopathic or cryptogenic epilepsy. Sixty-two of the families of probands with idiopathic or cryptogenic epilepsy (4.0%) were excluded because the proband had both generalized onset and partial onset seizures (n=20) or unclassifiable epilepsy (n=42). The families of the remaining 1498 probands (generalized epilepsy, 203 [13.6%]; localization-related epilepsy, 1295 [86.4%]) included 6551 first-degree relatives who were born after 1920 (parents, 1656; siblings, 3547; offspring, 1348). We excluded 275 (4.2%) of these relatives from the study because their histories of epilepsy were unknown, leaving 6276 relatives for the present analysis. Overall, 181 (2.9%) of these relatives were classified as having idiopathic or cryptogenic epilepsy. Epilepsy was generalized in 31 (17.1%), localization-related in 102 (56.4%), and unclassifiable in the remaining 48 (26.5%) of the affected relatives. The proportion of affected relatives with unclassifiable epilepsy was similar in relatives of probands with generalized (25.0%) and localization-related epilepsy (26.8%).

The comparison group comprised the families of 362 EFSCU probands who had postnatal symptomatic epilepsy. These families included 1392 first-degree relatives born after 1920 (parents, 362; siblings, 887; offspring, 343), of whom 80 (5.0%) were excluded from the study because of missing information about epilepsy, leaving 1512 for the present analysis. Fifteen (1.0%) of these relatives were affected with idiopathic or cryptogenic epilepsy (generalized epilepsy, 4 [26.7%]; localization-related epilepsy, 9 [60.0%]; unclassifiable epilepsy, 2 [13.3%]).
epilepsy. Whenever a history of one of these factors was reported, we inquired about the age at which it occurred, whether seizures had occurred in close temporal association with the event, and how long after the event the seizures had occurred. Seizures occurring within 1 week after the event were classified as acute symptomatic rather than unprovoked. Although subjects who had had only acute symptomatic seizures were ineligible to be probands, some of the relatives included in the study had had only acute symptomatic seizures. We used 3 categories of causes of epilepsy: (1) idiopathic or cryptogenic, ie, epilepsy occurring in the absence of a historical insult to the central nervous system demonstrated to increase greatly the risk of unprovoked seizures; (2) neurologic deficit presumed present at birth (neurodeficit from birth), ie, epilepsy associated with a history of cerebral palsy (motor handicap or movement disorder) or mental retardation (IQ < 70) presumed present at birth; and (3) postnatal symptomatic, ie, epilepsy associated with a history of a postnatal central nervous system insult occurring at least 7 days before the first unprovoked seizure.

The current classification of epileptic syndromes13,14 reserves the term idiopathic to refer to a specific set of clinically described syndromes that are presumed to be genetic and cryptogenic to refer to syndromes that are presumed to be nongenetic, but with insufficient evidence to establish a specific cause. Few of the probands in our series had syndromes that would be classified as idiopathic in this context. Thus, although we refer to probands without identified causative factors as having idiopathic or cryptogenic epilepsy, this is primarily a study of epilepsies that would be classified as cryptogenic in the current classification.

The results of the previous analyses of this data set indicated that the genetic contributions to postnatal symptomatic epilepsy are minimal.33,34 Those analyses also suggested possible shared genetic influences on epilepsy and cerebral palsy, but persons with epilepsy and cerebral palsy may be a unique subgroup. For the present analysis, therefore, we assessed the degree of increased risk of idiopathic or cryptogenic epilepsy in the relatives of probands with idiopathic or cryptogenic epilepsy. We used the relatives of probands with postnatal symptomatic epilepsy, in whom genetic contributions seemed to be minimal, as an internal control group. This ensured that the methods for classification of epilepsy were the same in the various comparison groups.

STATISTICAL METHODS

We used Cox proportional hazards analysis15 to compute rate ratios (RRs) for specific types of idiopathic or cryptogenic epilepsy in relatives, using the relatives of probands with postnatal symptomatic epilepsy as the reference group. We defined relatives as affected only if they had idiopathic or cryptogenic epilepsy. We assumed that each relative was at risk of idiopathic or cryptogenic epilepsy from birth until current age or age at death (for relatives without unprovoked seizures) or the age at which the first unprovoked seizure occurred. Thus, relatives with symptomatic epilepsy (ie, postnatal symptomatic epilepsy or epilepsy associated with neurodeficit from birth) were classified as unaffected, but their follow-up was considered to be censored at the age of their first unprovoked seizure. Similarly, in the analysis of risk of idiopathic or cryptogenic generalized or localization-related epilepsy specifically, relatives with the specific type under consideration were classified as affected, and relatives with the other type (or whose epilepsy type was unknown) were classified as unaffected, with follow-up censored at the age of their first unprovoked seizure. Relatives whose histories of epilepsy were unknown were excluded from the study.

In a previous analysis of this data set, we found that epilepsy was underreported in older relatives.16 The greatest underreporting was for relatives born in 1920 or earlier; thus, the present analysis was restricted to relatives born after 1920.

The proportions of relatives who were affected were similar in parents and siblings but differed in offspring (Table 1). Among the parents and siblings, prevalence of a history of idiopathic or cryptogenic epilepsy was higher if the proband had generalized epilepsy than if the proband had localization-related epilepsy (4.3% vs 2.2%). The RR was 4.7 for parents and siblings of probands with generalized epilepsy and 2.4 for parents and siblings of probands with localization-related epilepsy. This pattern was reversed in offspring, with a lower proportion affected if the proband’s epilepsy was generalized than if it was localization-related (1.7% vs 4.8%). The RRs were 1.6 for offspring of probands with generalized epilepsy and 4.2 for offspring of probands with localization-related epilepsy.

Because the risks were so similar in parents and siblings, we combined them in the analyses of risks of specific types of epilepsy in relatives (Table 2). Regardless of the type of epilepsy in the proband, a higher proportion of the relatives had localization-related than generalized epilepsy. For relatives of each group of probands, the RRs in parents and siblings were similar for generalized and localization-related epilepsies (relatives of probands with generalized epilepsy, 4.8 vs 4.1; relatives of probands with localization-related epilepsy, 1.8 vs 2.1).

Among the offspring of probands with generalized epilepsy, only 3 were affected, and in all 3, the type of epilepsy was unknown. Among the offspring of probands with localization-related epilepsy, the RR was greater for localization-related epilepsy (7.8) than for generalized epilepsy (1.8).

We also studied the effect on our RR estimates of excluding, from the analysis of risks of specific types of epilepsy, relatives whose epilepsies could not be classified. The proportion of relatives whose epilepsies were unclassified increased from 16% (9/58) in the parents to 25% (24/97) in the siblings and 33% (20/61) in the offspring. This was unexpected, so we rereviewed the data used for epilepsy classification in all of the relatives with unclassified epilepsy. In the parents and siblings, most of the relatives with unclassified epilepsy had reported having only tonic-clonic seizures, without preictal or postictal localizing symptoms. Many of the relatives clearly should have been classified as having generalized epilepsy. In contrast, most of the offspring whose epilepsy was unclassified experienced seizure onset during childhood and had experienced remission...
soon after onset, or they were still too young for a
detailed description of symptoms to be obtained. Many
of the offspring with unclassified epilepsy also probably
had generalized epilepsy. Childhood onset epilepsies
with early remission were probably underreported in
parents and siblings and may account for the higher
proportion of offspring with epilepsy that could not be
classified.

Because a disproportionate number of the relatives with
unclassified epilepsy probably had generalized epilepsy, we
repeated the analysis in Table 2, assuming that epilepsy was
generalized in all relatives with unclassified epilepsy. The
RRs for generalized epilepsy rose to 5.8 for parents and sib-
lings of probands with generalized epilepsy, 3.0 for par-
ents and siblings of probands with localization-related epi-
lepsy, 3.1 for offspring of probands with generalized
epilepsy, and 2.1 for offspring of probands with localization-
related epilepsy. The RRs for localization-related epilepsy
remained the same as in Table 2.

These results are inconsistent with a model of distinct
genetic influences on generalized and localization-
related epilepsies. Such a model would predict that in the
relatives of probands with generalized epilepsies, the risk
of localization-related epilepsy is not increased, ie, RR
of 1.0. However, our data indicate that risk is increased
for both generalized (RR, 4.8) and localization-related
epilepsy (RR, 4.1) in the parents and siblings of pro-
bands with generalized epilepsy. Our results for the par-
ents and siblings of probands with localization-related
epilepsy also are inconsistent with a model of specificity
in the genetic effects. Such a model would predict an RR
of 1.0 for generalized epilepsy in the relatives of pro-
bands with localization-related epilepsy. We found in-
stead that in the parents and siblings of probands with
localization-related epilepsy, the risk was increased
for both generalized (RR, 1.8) and localization-related
epilepsy.

### Table 1. Rate Ratios for All Idiopathic or Cryptogenic Epilepsy in the Relatives of Probands With Specific Types of Idiopathic or Cryptogenic Epilepsy

<table>
<thead>
<tr>
<th>Class of Relatives and Type of Epilepsy in the Proband</th>
<th>Total No. of Relatives</th>
<th>Type of Idiopathic or Cryptogenic Epilepsy in Relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Generalized</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. Affected</td>
</tr>
<tr>
<td>Parents and siblings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized idiopathic or cryptogenic</td>
<td>672</td>
<td>8</td>
</tr>
<tr>
<td>Localization-related idiopathic or cryptogenic</td>
<td>4306</td>
<td>19</td>
</tr>
<tr>
<td>Postnatal symptomatic</td>
<td>1182</td>
<td>3</td>
</tr>
<tr>
<td>Offspring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized idiopathic or cryptogenic</td>
<td>172</td>
<td>0</td>
</tr>
<tr>
<td>Localization-related idiopathic or cryptogenic</td>
<td>1126</td>
<td>4</td>
</tr>
<tr>
<td>Postnatal symptomatic</td>
<td>330</td>
<td>1</td>
</tr>
</tbody>
</table>

*Relatives with idiopathic or cryptogenic epilepsy of unknown type were classified as unaffected, with follow-up censored at the age of the first unprovoked seizure. CI indicates confidence interval; ellipses, rate ratio could not be calculated.
epilepsy (RR, 2.1). Thus, some genetic mechanisms may raise the risk for both generalized and localization-related epilepsies.

These findings are different from those of several other investigations,2-5 which have suggested that epilepsy types tend to be similar in affected family members. Part of this difference may be explained by a difference in methods. In our study, epilepsy in each proband or relative was classified without knowledge of the number of affected persons in the family and the epilepsy classifications in other family members. None of the previous study reports stated that this was done. The different results in other studies may also be explained by a different distribution of epilepsy types in the probands. Most of the previous studies focused on probands with IGE syndromes, whereas our study population contained few probands with IGE syndromes. The low proportion of probands with IGE syndromes in our study is a consequence of our ascertainment protocol, which involved sampling adults with epilepsy from voluntary organizations. Many IGEs have onset in childhood or adolescence and tend to remit before adulthood. Hence, among the adult probands with idiopathic or cryptogenic epilepsy in our study, only 14% had generalized epilepsies, and these generalized epilepsies were unusual because they either had late onset or long duration. Because of this selection bias, our results do not apply to the genetics of IGE syndromes. Unlike the genetic influences on other forms of idiopathic or cryptogenic epilepsy, the genetic influences on IGE syndromes may be specific for IGE syndromes (although they may be shared across different forms of IGE syndromes [juvenile myoclonic epilepsy, childhood absence epilepsy, etc]).

In a previous analysis of data from the Rochester–Olmsted County, Minnesota, record linkage project,17 the risks of unprovoked seizures were similar for the offspring of probands with generalized and localization-related epilepsies overall, but the risks in the offspring were higher for the subset of probands with absence seizures. Furthermore, in the offspring of probands with absence seizures, the degree of increased risk was greater for absence than for other seizure types. In the present study, risks were not higher in the relatives of probands with absence seizures than in the relatives of probands with generalized epilepsy without absence seizures (proportion affected among relatives of probands with absence seizures: offspring, 0/71 [0%]; parents and siblings, 11/273 [4.0%]). As noted, the different findings in our present study might be attributed to a different distribution of epilepsy types (eg, as defined by age at onset or duration of illness), among the probands with absence seizures in our study.

One of the most intriguing findings of the present study is that the patterns of familial risk are different in offspring than in parents and siblings. In the parents and siblings, risk is higher if the proband had generalized epilepsy, whereas in the offspring, risk is higher if the proband had localization-related epilepsy. Furthermore, the increased risk in the offspring of probands with localization-related epilepsy is greater for localization-related than for generalized epilepsy. This is true even if all of the offspring whose epilepsy could not be classified are assumed to have generalized epilepsy.

The validity of our results hinges on the validity of the classification of seizure type in probands and affected relatives. Although our seizure classifications had adequate validity when compared with diagnoses of physicians who used the same criteria for classification,3,11 errors in classification were almost always in the direction of misclassifying truly generalized seizures as partial onset (sensitivity and specificity for generalized onset seizures, 60% and 100%; for partial onset seizures, 100% and 75%, respectively). Thus, the classifications for most of the probands and relatives classified as having generalized epilepsy were probably correct, whereas some of those classified as having localization-related epilepsy probably actually had generalized epilepsy.

This type of misclassification would be expected to have 2 effects on the RRs estimated in this study. First, misclassification of epilepsy in the probands would inflate the estimate of the RR for generalized epilepsy in the relatives of probands with localization-related epilepsy. This is expected because a proportion of the probands classified as having localization-related epilepsy actually had generalized epilepsy, and familial risk is greater for those with generalized epilepsy than for those with localization-related epilepsy. Second, misclassification of epilepsy in the relatives would inflate the estimate of the RR for localization-related epilepsy in the relatives of probands with generalized epilepsy. This is expected because a proportion of the relatives classified as having localization-related epilepsy actually had generalized epilepsy. No bias is expected in the RR of generalized epilepsy in the relatives of probands with generalized epilepsy because few of the probands or relatives in that analysis had epilepsy that was misclassified.

We evaluated the magnitude of the bias in our RR estimates due to misclassification by developing a statistical model with the following assumptions: (1) the risk of all idiopathic or cryptogenic epilepsy in relatives was 4% for probands with generalized idiopathic or cryptogenic epilepsy, 2% for probands with localization-related idiopathic or cryptogenic epilepsy, and 1% for control probands (based on the results in Table 1 for parents and siblings); and (2) among the affected relatives of control probands, 50% had localization-related and 50% had generalized epilepsy (based on the distribution of incident idiopathic or cryptogenic epilepsy in Rochester, Minn [W.A.H., unpublished data, 1997]). We then evaluated the effects on the RRs estimated in Table 2 of varying degrees of misclassification of epilepsy in the probands and relatives.

Although our observed RR of 4.1 for localization-related epilepsy in the parents and siblings of probands with generalized epilepsy (Table 2) is inflated because of misclassification, the true RR is unlikely to be as low as 1.0. Under the assumptions described in the previous paragraph, if the RR for generalized epilepsy in the relatives of probands with generalized epilepsy is 5.0 (based
on our estimate of 4.8 in parents and siblings from Table 2, which should be unbiased), then the true RR (with no misclassification) for localization-related epilepsy in the relatives of probands with generalized epilepsy would be 3.0. If the true RR for generalized epilepsy in the relatives of probands with generalized epilepsy were 5.8, as estimated from our analysis assuming that epilepsy was generalized in all of those with unclassified epilepsy, then the true RR for localization-related epilepsy in the relatives of probands with generalized epilepsy would be 2.0. Conversely, if the true RR for localization-related epilepsy in relatives of probands with generalized epilepsy were 1.0, the observed RR would not be as high as our observed value of 4.1 unless the epilepsy in more than 90% of the relatives were misclassified, which is unlikely. Similarly, an RR of 3.0 for generalized epilepsy in the relatives of probands with localization-related epilepsy (as estimated in parents and siblings, assuming that epilepsy was generalized in all with unclassified epilepsy) would be observed only if the epilepsy in 60% to 70% of the probands with generalized epilepsy were misclassified, which is unlikely.11

Our results indicate that some of the genetic influences on epilepsy are common to generalized and localization-related epilepsies. In the offspring of probands with localization-related epilepsy, an additional influence may raise the risk for localization-related epilepsy specifically. This difference between offspring and other relatives in the patterns of familial risk is unexplained and should be investigated further.

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