Published in final edited form as:
*Epilepsia*. 2003 September ; 44(9): 1176–1182.

# Evidence for Distinct Genetic Influences on Generalized and Localization-related Epilepsy

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## Summary

**Purpose—**Determining the existence of syndrome-specific genetic factors in epilepsy is essential for phenotype definition in genetic linkage studies, and informs research on basic mechanisms. Analysis of concordance of epilepsy syndromes in families has been used to assess shared versus distinct genetic influences on generalized epilepsy (GE) and localization-related epilepsy (LRE). However, it is unclear how the results should be interpreted in relation to specific genetic hypotheses.

**Methods—**To assess evidence for *distinct* genetic influences on GE and LRE, we examined concordance of GE and LRE in 63 families containing multiple individuals with idiopathic or cryptogenic epilepsy, drawn from the Epilepsy Family Study of Columbia University. To control for the number of concordant families expected by chance, we used a permutation test to compare the observed number with the number expected from the distribution of individuals with GE and LRE in the study families.

**Results—**Of the families, 62% were concordant for epilepsy type, and 38% were discordant. In all analyses, the proportion of concordant families was significantly greater than expected.

**Conclusions—**This suggests that some genetic influences predispose specifically to either GE or LRE. Because of the ascertainment bias resulting from the selection of families containing multiple individuals with epilepsy, we could not test whether there are also shared genetic influences on these two epilepsy subtypes. Population-based studies will be needed to explore these results further.

### Keywords

Epilepsy; Genetics; Concordance; Permutation test; Epidemiology

The epilepsies are etiologically and clinically heterogeneous, with genetic influences of primary importance in only a subset of patients (1). Even among epilepsies with a genetic influence, the genetic mechanisms are varied. Some involve the major effects of single genes, producing simple patterns of inheritance in families, whereas others involve the combined

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effects of multiple genes and environmental factors, each with a smaller effect on susceptibility, and producing more complex patterns of inheritance.

For most epilepsy, the relation between clinical syndrome and genetic mechanism is complex and not well understood. *Locus heterogeneity*, in which a single syndrome is caused by different genes in different families, is well documented. For example, in benign familial neonatal convulsions, two different autosomal dominant susceptibility genes (*KCNQ2* on chromosome 20q and *KCNQ3* on chromosome 8q) have been identified in different families (2,3). The converse situation, in which different syndromes are caused by a single genetic mechanism (*variable expressivity*), also is documented. One example is generalized epilepsy with febrile seizures plus (GEFS+), in which causative genes on chromosomes 19q, 2q, and 5q produce febrile seizures in some family members, generalized-onset epilepsy (GE) in some, and localization-related epilepsy (LRE) in others (4–8).

It is commonly assumed that the genetic contributions are different for GE and LRE. Despite considerable investigative effort, however, the question of whether these two broadly defined syndromes have distinct genetic contributions has not been convincingly answered.

If the genetic influences on GE and LRE were distinct, we would expect that families containing multiple affected individuals would tend to be concordant for GE or LRE, and risk in relatives of probands with a given syndrome would be increased only for the same syndrome as in the proband. In contrast to this expectation, previous results from two familial aggregation studies have demonstrated an increased risk for GE in relatives of probands with LRE and vice versa, suggesting that some genetic mechanisms increase the risk for both GE and LRE (9,10). In population-based data from Rochester, Minnesota, offspring of probands with epilepsy had significantly increased risk for LRE, regardless of whether the proband's epilepsy was GE or LRE. Similarly, in data from the Epilepsy Family Study of Columbia University (EFSCU), the increased risk for epilepsy in parents and siblings of probands with idiopathic epilepsy was not restricted to the same type of epilepsy as in the proband.

Whereas familial aggregation studies suggest that there are shared genetic mechanisms for LRE and GE, twin studies show different results. Concordance of syndrome type in monozygotic (MZ) twin pairs ranges from 75 to 94% (11,12) and is greater than the control or dizygotic (DZ) concordance rates, suggesting that distinct, syndrome-specific genetic effects exist. The reason for the different results in familial aggregation versus twin studies is not clear. One possible explanation is that diagnosis of one twin's syndrome is made with knowledge of the other twin's syndrome. In this case, bias may affect diagnostic accuracy. It also is possible that both shared and distinct genetic effects on these syndromes exist, and are being demonstrated by different study designs.

To complicate interpretation further, studies that assess concordance of syndromes in families are extremely variable, with concordance estimates ranging from 39 to 83% (13–17). The wide variation in concordance estimates could result from differences in study methods, definitions of concordance, and syndromes and seizure types evaluated. Furthermore, none of the previous studies used a control or comparison group or corrected for concordance rates expected by chance, making the meaning of these percentages uncertain.

In this study, we aimed to address the variability in the results of previous concordance studies, to develop valid methods for analysis of within-family concordance, and to interpret results in relation to specific genetic hypotheses. In particular, we explored the evidence for distinct genetic susceptibility to GE and LRE, by examining concordance of syndrome types in a set of families collected for genetic linkage analysis without restriction to specific syndromes.

## METHODS

The families included in this study are drawn from EFSCU, which began in 1985 as a familial aggregation study (18) and evolved into an ongoing genetic linkage study of epilepsy. EFSCU began with 1,957 adults with epilepsy (probands), who were ascertained from voluntary organizations. The present study includes 27 of the original 1,957 families. It also includes 36 additional families containing an affected sibling pair or three or more affected individuals with idiopathic or cryptogenic epilepsy subsequently collected for genetic linkage analysis, with diagnoses completed as of January 2001. The additional 36 families were ascertained through a variety of sources, including physician referrals, advertisements through voluntary organizations, and a study web site. The 63 included families contained 206 individuals with idiopathic or cryptogenic epilepsy.

An intensive protocol was used to diagnose and classify seizure disorders in these families. Each subject was screened for seizure disorders through either an in-person or a telephone interview administered directly or, if the subject was younger than 12 years, deceased, or otherwise unavailable, to a close relative. Screening interviews also were administered to either the mother or the father of each subject whenever possible, even when the subject was reached for interview. In subjects who screened positive for afebrile seizures, a complete diagnostic evaluation was carried out, including (a) a detailed semistructured diagnostic interview administered in person or over the telephone by a neurologist or physician with specialized training in epilepsy, and whenever possible; (b) review of medical records (frequently containing EEG reports, imaging results, and reports of neurologic examinations); (c) a neurologic examination performed specifically for the study; and (d) a study electroencephalogram (EEG). The diagnostic interview was administered directly to subjects whenever possible (81% of subjects; Table 1). In those who were dead, younger than 12 years, or otherwise unavailable, the diagnostic interview was administered to the relative deemed to be the best living informant regarding the subject's seizure history. Whenever the quality of information regarding seizure history was in question, or when the subject's own recall was insufficient, additional informants were contacted for diagnostic interviews to clarify the seizure history. Table 1 shows the numbers of subjects with each type of diagnostic evaluation as well as a more detailed delineation of informants contacted.

The diagnostic interview (19) obtained information on seizure semiology through both verbatim descriptions and structured questions about signs and symptoms, and on seizure etiology through questions about the history and timing of specific risk factors previously demonstrated for epilepsy. Use of a standardized interview for data collection ensured that the information needed to distinguish GE from LRE was collected in the same way for all subjects. Seizure classification based on an earlier version of the interview was found to be reliable (reproducible) and valid, compared with the clinical diagnoses of expert physicians (19,20). Based on the results of the previous validation, the diagnostic interview was revised to improve the classification of nonconvulsive seizures, particularly the distinction of focal and generalized nonconvulsive events.

Senior epileptologists (W.A.H., T.A.P., M.L.S.) reviewed all of the data collected on each subject to arrive at a final diagnosis. To ensure that diagnoses were made blindly with respect to those of other family members, identifying information was removed before this review, and subjects from different families were reviewed in random order. Findings from the neurologic examination, EEG, and neuroimaging were used to supplement the clinical descriptions of seizures and possible etiologic factors.

Epilepsy was defined as a lifetime history of two or more unprovoked seizures. In probands and relatives with epilepsy, seizures were classified according to the 1981 criteria of the

International League Against Epilepsy (21). Epilepsy was classified as LRE if there was clear clinical or electrographic evidence of focal onset of seizures. Epilepsy was classified as generalized (i.e., *generalized at onset*) if there was clear clinical or electrographic evidence of nonconvulsive primary generalized seizures, such as myoclonic, absence, and atonic seizures, or primary generalized tonic–clonic seizures (GTCs). GTCs were considered primary generalized only if clear evidence of generalized onset was obtained, either EEG (e.g., generalized spike–wave discharge) or clinical (e.g., with coexisting absence seizures or myoclonic jerks). Individuals with GTCs were classified as having epilepsy of unknown type if no clear EEG or clinical evidence of focal or generalized onset was obtained.

## Assessment of concordance

The analysis of concordance was based on the syndrome classifications of subjects with idiopathic or cryptogenic epilepsy only; subjects with symptomatic epilepsy, isolated unprovoked seizures, or acute symptomatic seizures (including febrile seizures) were not considered. Families were considered to be concordant if all individuals with idiopathic or cryptogenic epilepsy in a family had the same type of epilepsy: either all GE or all LRE.

In the analysis of concordance, the appropriate treatment of individual subjects with idiopathic or cryptogenic epilepsy who had *both* generalized and focal seizures is not clear. When an individual has both types, he or she may harbor either one gene, increasing the risk for both types, or two genes, increasing the risk for each type individually. Including the families may actually introduce bias, because their ascertainment may have depended on the coexistence of two epilepsy subtypes and two genes. Conversely, exclusion of these families or individuals could eliminate evidence for shared genetic influences on GE and LRE. To address this problem, we analyzed the data in three ways: (a) including all families; (b) excluding families containing individuals with mixed epilepsy; and (c) including *families* containing mixed individuals but excluding the *individuals* with both types. Those with idiopathic/cryptogenic epilepsy who could not be classified were excluded in the classification of concordance for the family. We also performed an additional analysis excluding families containing individuals with unknown epilepsy type, as including them might bias results.

To limit our analyses to families that do not harbor previously identified epilepsy genes, we excluded families with autosomal dominant partial epilepsy with auditory features (22). We also identified three families with phenotypes possibly consistent with GEFS+ and performed separate analyses excluding them. To address the possibility that phone and in-person interviews might produce different results, we examined concordance in individuals with each interview type separately.

## Statistical approach

Two major issues arise in the interpretation of the crude concordance estimates. First, it is necessary to correct for concordance that would be expected by chance. Second, the influence of ascertainment strategy on observed concordance must be taken into account. To address the issue of concordance expected by chance, we formulated a formal null hypothesis that represents one extreme of the relation of genotype to phenotype: no genetic influence increases risk for *only* GE or *only* LRE, without also increasing risk for the other type to the same extent. This null hypothesis predicts that within-family concordance of GE and LRE will be no greater than expected by chance, given the overall proportion of family members with each type among relatives of probands with each type.

The method used to test this hypothesis examines clustering of type within families in a manner that adjusts for the distorted patterns of familial clustering that can be evident when inclusion in a study relies on the affection status of multiple relatives. The method is based on a

permutation-test approach in which the number of affected individuals in each family is fixed, the number of individuals affected with each type of disease in the sample is fixed, and the disease type of each proband is fixed, but the assignment of types to affected individuals is otherwise random. Fixing the numbers of affected individuals in each family adjusts for ascertainment schemes that seek families with multiple members. Fixing the disease type of probands adjusts for the possibility that disease status could influence the probability of coming to the attention of the researchers as a proband. Fixing the number of individuals affected with each disease type in the sample is done to obtain an exact test while allowing unknown frequencies of disease types in the population. The test statistic used was the number of families concordant for disease type. Thus to test for familial aggregation beyond what would be expected by chance, the observed number of concordant families was compared with the expected number computed under the null hypothesis that epilepsy type was randomly distributed within families, given the fixed factors. Further details of this analytic approach and the corresponding statistical tests are elaborated elsewhere (23).

## RESULTS

The 63 included families comprised 21 affected sibling pairs, 23 families containing three affected individuals, and 19 families containing four or more affected individuals. Table 2 shows the distribution of epilepsy types in individuals. Overall, the proportion of individuals with LRE was slightly greater than that with GE (46 vs. 33%). Three percent had both generalized and partial seizures (denoted mixed epilepsy type), and 18% had unknown epilepsy type. Seven families (four sibling pairs and three families with three affected individuals, totaling 11% of families) were excluded from the concordance analysis because only one individual in the family had epilepsy that could be classified. Of the remaining 56 families, 62% were concordant for epilepsy type, and 38% were discordant (Table 3).

Among the 36 individuals with unknown epilepsy type, 17 (47%) had only GTCs with no distinct aura or prodrome, no other clearly generalized seizure types, and no EEG abnormalities that would contribute to the diagnosis. Six (17%) had only nocturnal GTCs. Six individuals (17%) had insufficient information to allow diagnosis of seizure type—because the subject was deceased, refused to participate, did not have an adequate witness, was too young to describe any aura or prodrome, or because a diagnostic interview could not be obtained for other reasons. Seven individuals (19%) had nonconvulsive seizures in which the distinction between primary generalized and partial seizures could not be made (e.g., absence vs. complex partial seizures).

Most individuals with GE had a recognizable idiopathic generalized epilepsy (IGE) syndrome: juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), childhood absence epilepsy (CAE), or grand mal seizures on awakening. Only one individual had benign childhood epilepsy with centrotemporal spikes.

Using the permutation analysis, we found that the proportion of concordant families was significantly greater than expected by chance for all analyses: including all families, excluding families with mixed individuals, excluding individuals with mixed epilepsy, treating mixed as a third type, and excluding families with phenotypes consistent with GEFS+. We repeated the analyses after excluding families containing individuals with unknown epilepsy type and again found greater than expected concordance of seizure type. We also found significantly increased concordance when examining subjects with in-person and telephone interviews separately (Table 4).

## DISCUSSION

Our results indicate that some of the genetic influences on GE and LRE are distinct. This finding is important because it affects syndrome definition in genetic linkage studies and informs research on basic mechanisms.

Despite previous research on this question, it has not been answered definitively. Previous epidemiologic studies and twin studies have conflicting results, within-family concordance studies have wide variation in methods, and both designs may be prone to bias by failure to blind diagnosticians to family history. In addition, family concordance studies to date all fail to provide an inferential statistical method that allows assessment of whether the concordance rate differs from the rate expected by chance in the population studied; therefore the percentages reported are of limited value in supporting or rejecting any underlying genetic hypothesis.

Much of the variability in previous results may be the result of differences in study design, inclusion criteria, and definitions of concordance. For example, twin-study concordance and family-study concordance are not directly comparable because monozygous twins, who share 100% of their genes, might be expected to show greater syndrome or seizure-type concordance than other types of relative pairs.

Selection criteria for probands, such as age or syndrome type, also can influence concordance rates. A series ascertained through children, like that of Callenbach et al. (16), would be expected to comprise a greater proportion with IGEs, and therefore might have higher concordance rates. The twin study by Berkovic et al. (12) included both symptomatic and idiopathic/cryptogenic epilepsies, whereas we limited inclusion of affected individuals to those with idiopathic/cryptogenic epilepsy. Studies by the Italian League Against Epilepsy (17) included febrile seizures and benign familial neonatal convulsions—a syndrome with two identified causative genes—and excluded cryptogenic epilepsies entirely.

The number of affected individuals in each included family can also affect concordance estimates. Concordance might be expected to be greatest in families containing many affected individuals, because such families are more likely to carry a major gene with high penetrance, affecting both susceptibility to epilepsy and its clinical features. Conversely, increasing the overall family size or number of affected individuals in the family could increase the chance of discordance by chance alone.

Finally, failure to perform epilepsy diagnoses blind to family history could bias concordance estimates significantly. To our knowledge, no other twin or family studies diagnose and classify epilepsy type without knowledge of the diagnoses of other family members.

Most clinical information collected for epilepsy classification—whether in clinical or research settings—is historical, and such information can be obtained adequately over the telephone. To assess whether any error might have been introduced by the use of telephone interviews to collect clinical information in our study, we analyzed the data in subjects with telephone interviews and in-person interviews separately. We found significant evidence for concordance in both groups, providing reassurance that the results were not explained by bias resulting from using telephone interviews.

EEG data were available in only 52% of patients, and imaging data, in only 24% of patients. However, the limited availability of these data is unlikely to have affected the validity of the results. In an earlier phase of our study in which EEGs were obtained systematically, abnormalities were identified in only 10 (22%) of 82 individuals tested. This low yield may be partly explained by the characteristics of our study population; many of our subjects were adults at the time of the study and were evaluated years after the onset of their epilepsy.

Furthermore, even when abnormal EEG findings were present, they were often non-specific or nonepileptiform, and thus did not contribute to seizure classification. Among the 36 individuals classified as “unknown type” in the current study, nine had EEGs that did not help to clarify the diagnosis.

In EFSCU, we rely primarily on semiology to classify seizure type and are therefore careful to obtain detailed descriptions of each type of event, through both structured diagnostic interviews and review of medical records. In many cases, the clinical description alone is sufficient to distinguish between GE and LRE. When a distinction between GE and LRE was not possible with semiology and history alone, we made every effort to obtain medical records, EEGs, and imaging study reports. However, even when EEGs were obtained in this situation, they were helpful for classification in only three of eight cases. When the clinical information collected through our diagnostic interview and medical record review could not support a definite distinction between generalized-onset and focal-onset seizures, we classified subjects as unknown. We then excluded individuals (and/or families) with unknown type from the analysis. This conservative approach should avoid any serious misclassification.

The approach presented here examines the underlying genetic contributions to GE and LRE by testing an extreme null hypothesis that all genetic influences increase the risk for both GE and LRE to the same extent. We applied this approach to examine the distinction between LRE and GE, and found evidence sufficient to reject the null hypothesis, suggesting that some of the genetic influences on these two broadly defined syndromes are distinct.

In theory, one would be able to test the opposite null hypothesis, that all of the genetic influences on GE and LRE are distinct (which, if rejected, would provide evidence for shared genetic effects). This method is discussed in detail separately (24). Applicability of this method to test the second null hypothesis requires that a family’s likelihood of being ascertained does not depend on the number of affected individuals it contains or the types of epilepsy they have. This requirement was not met in our study because, as in most genetic linkage studies, we aimed to collect families with as many affected individuals as possible.

As mentioned earlier, two previous familial aggregation studies showed evidence for shared genetic effects on GE and LRE, whereas our present study reveals distinct genetic influences on these two broadly defined syndromes. The two epidemiologic studies were performed in samples that were not selected with respect to family history, whereas the sample used in our present study was collected for linkage analysis, targeting families with multiple affected individuals. This is the essential difference that underlies not only the different results observed, but also which hypotheses could be tested; we could not test for shared effects in the current sample because of ascertainment bias. In addition, shared genetic effects, even if they could be tested for, might not be as apparent in samples of families collected for linkage as in data sets collected for epidemiologic studies, without regard to the number of affected individuals per family. In samples collected for linkage analysis, mixing of seizure types within families might be expected, and would not necessarily provide evidence for shared genetic influences. This is because selection through multiple affected individuals might lead to oversampling of families containing multiple type-specific genes.

In any case, both shared and distinct genetic influences probably do coexist; the two findings are actually complementary, rather than contradictory. Some genes may increase risk for both types, and other genes may be type specific. These two types of genetic effects could be acting simultaneously, but have been revealed by different analytic models in different populations.

The nature of the sampling scheme, which specifically targets families containing multiple affected individuals, is likely to affect the types of epilepsies ascertained, and would similarly be selecting *a priori* for genes with stronger effects. Proband-based sampling also can affect

the characteristics of disease brought into a sample. This is the typical sampling scheme used in other genetic linkage studies. Because we are examining the genetic effects at work in a sample selected in this way, we cannot draw conclusions about what proportion of epilepsy in the general population is influenced by these distinct genetic effects on type. Results from this study are particularly useful for directing phenotype definition in other linkage studies of epilepsy, as many of these studies use similar criteria for inclusion.

The investigation of a shared genetic cause for the two types of epilepsy merits further attention; future studies must address the problem of ascertainment bias. Population-based designs will therefore be particularly powerful in unraveling the complexity of the genetic contributions to GE and LRE, as well as other clinical forms of epilepsy.

The methods described here have many applications. They could be applied to other epilepsy subtypes such as specific focal epilepsies (e.g., mesial vs. lateral temporal), specific seizure types (e.g., absence or myoclonic), or to selected electrophysiologic abnormalities (e.g., the presence or absence of a photoparoxysmal response). The results of this study and future studies using these methods can be used to help guide linkage analysis by allowing rational subdivision of epilepsy syndromes into groups that are likely to share susceptibility genes. In the future, application of these methods might even allow reclassification of epilepsy syndromes and seizure types by genetic etiology.

**Acknowledgements**

This work was supported by NIH grants R01 NS20656 and K23 NS02211.

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## TABLE 1

Number of subjects with each type of diagnostic evaluation

| Type of evaluation | No. of subjects (N = 206) | %[a] |
|---|---|---|
| Method of interview | | |
| By phone | 119 | 58% |
| In person | 87 | 42% |
| Informants contributing | | |
| Self interview | 166 | 81% |
| Self only | 50 | 24% |
| Self + parent(s) | 60 | 29% |
| Self + parent + other relatives | 34 | 17% |
| Self + one other nonparent relative[b] | 16 | 8% |
| Self + multiple (≥2) other relatives | 6 | 3% |
| Nonself interview | 40 | 20% |
| Parent(s) | 20 | 10% |
| Parent + other relatives | 4 | 2% |
| One other nonparent relative[b] | 12 | 6% |
| Multiple (≥2) other nonparent relatives | 4 | 2% |
| Imaging | | |
| CT | 35 | 17% |
| MRI | 31 | 15% |
| Neither | 157 | 76% |
| EEG | 108 | 52% |
| Neurologic examination | 102 | 50% |

MRI, magnetic resonance imaging; CT, computed tomography.

[a] Percentages rounded to nearest integer.

[b] Sibling/spouse/offspring/other.

**TABLE 2**

Distribution of epilepsy types in EFSCU families[a]

| No. of affected family members | No. of families | No. of individuals with each epilepsy type | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Generalized | | Focal | | Mixed | | Unclassifiable | | Total | |
| | | No. | (%) | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| 2 | 21 | 17 | (41) | 20 | (48) | 1 | (2) | 4 | (10) | 42 | (100) |
| 3 | 23 | 20 | (29) | 35 | (51) | 1 | (2) | 13 | (19) | 69 | (100) |
| ≥4 | 19 | 31 | (33) | 40 | (42) | 5 | (5) | 19 | (20) | 95 | (100) |
| Total | 63 | 68 | (33) | 95 | (46) | 7 | (3) | 36 | (18) | 206 | (100) |

EFSCU, Epilepsy Family Study of Columbia University.

[a]Percentages do not always add up to 100 because of rounding.

**TABLE 3**

Concordance of epilepsy syndromes in families containing multiple individuals with idiopathic or cryptogenic epilepsy[a]

| | Number of concordant or discordant families | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Discordant | | Concordant generalized | | Concordant focal | | Total no. of classifiable families | |
| No. of affected individuals per family | No. | (%) | No. | (%) | No. | (%) | No. | (%) |
| 2 | 10 | (59) | 3 | (18) | 4 | (24) | 17 | (100) |
| 3 | 6 | (30) | 4 | (20) | 10 | (50) | 20 | (100) |
| ≥4 | 5 | (26) | 5 | (26) | 9 | (47) | 19 | (100) |
| Total | 21 | (38) | 12 | (22) | 23 | (41) | 56 | (100) |

[a]Percentages do not always add up to 100 because of rounding.

*Epilepsia*. Author manuscript; available in PMC 2006 October 27.

**TABLE 4**

Concordance analysis results

| Restriction | No. of families contributing | Number of concordant families | | | | |
|---|---|---|---|---|---|---|
| | | Observed | Expected | Standard deviation | Z statistic | p Value |
| None | 56 | 35 | 17.8 | 3.2 | 5.38 | <0.0001 |
| Excluding GEFS+ | 53 | 34 | 17.8 | 3.1 | 5.23 | <0.0001 |
| Excluding families with mixed | 52 | 35 | 19.2 | 3.3 | 4.79 | <0.0001 |
| Excluding individuals with mixed | 55 | 36 | 19.3 | 3.5 | 4.91 | <0.0001 |
| Excluding phone interviews | 21 | 16 | 8.3 | 1.7 | 8.41 | <0.0001 |
| Excluding in-person interviews | 34 | 19 | 13.5 | 2.6 | 2.12 | 0.034 |

GEFS+, generalized epilepsy with febrile seizures plus.

*Epilepsia*. Author manuscript; available in PMC 2006 October 27.