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Segregation Analysis of Cryptogenic Epilepsy and an Empirical Test of the Validity of the Results

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Summary

We used POINTER to perform segregation analysis of cryptogenic epilepsy in 1,557 three-generation families (probands and their parents, siblings, and offspring) ascertained from voluntary organizations. Analysis of the full data set indicated that the data were most consistent with an autosomal dominant (AD) model with 61% penetrance of the susceptibility gene. However, subsequent analyses revealed that the patterns of familial aggregation differed markedly between siblings and offspring of the probands. Risks in siblings were consistent with an autosomal recessive (AR) model and inconsistent with an AD model, whereas risks in offspring were inconsistent with an AR model and more consistent with an AD model. As a further test of the validity of the AD model, we used sequential ascertainment to extend the family history information in the subset of families judged likely to carry the putative susceptibility gene because they contained at least three affected individuals. Prevalence of idiopathic/cryptogenic epilepsy was only 3.7% in newly identified relatives expected to have a 50% probability of carrying the susceptibility gene under an AD model. Approximately 30% (i.e., 50% × 61%) were expected to be affected under the AD model resulting from the segregation analysis. These results suggest that the familial distribution of cryptogenic epilepsy is inconsistent with any conventional genetic model. The differences between siblings and offspring in the patterns of familial risk are intriguing and should be investigated further.

Introduction

Epilepsy is a condition in which seizures occur repeatedly in the absence of acute structural or metabolic insults to the CNS (Hauser et al. 1991). 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 underlying complexity in the genetic contributions. In most forms of epilepsy, the familial distribution is inconsistent with a simple Mendelian model. 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 differ across some clinically defined subgroups.

Clinically, epilepsy is subclassified according to seizure type (Commission on Classification and Terminology of the International League Against Epilepsy 1981) and epilepsy syndrome (Commission on Classification and Terminology of the International League Against Epilepsy 1989). 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 epilepsies.

Approximately 25 percent of prevalent epilepsy is associated with an antecedent CNS injury (e.g., head trauma, stroke, or brain infection) and accordingly is classified as "symptomatic" (Hauser et al. 1991). The remainder without identified cause is assigned into two broad classes by the current International Classification of Epileptic Syndromes (Commission on Classification and Terminology of the International League Against Epilepsy 1989): "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

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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.

Familial aggregation of epilepsy is well established, with two- to threefold increased risks in first-degree relatives of affected individuals (Annegers et al. 1982). Genes that have a major effect on susceptibility have been localized in six human epilepsy syndromes (Greenberg et al. 1988; Leppert et al. 1989; Lehesjoki et al. 1991; Lewis et al. 1993; Tahvanainen et al. 1994; Ottman et al. 1995*c*; Phillips et al. 1995). However, the epilepsy syndromes with linkage evidence constitute only a small proportion of all epilepsy. In the remainder, the genetic mechanisms underlying familial aggregation are unclear.

In 1985, we undertook the Epilepsy Family Study of Columbia University (EFSCU), a large study designed to evaluate the relations between clinical and genetic heterogeneity in the epilepsies and to test consistency with various genetic and nongenetic models. Previous analyses of this data set have indicated that genetic susceptibility raises risk for idiopathic/cryptogenic epilepsy and for epilepsy associated with neurological deficits presumed present at birth, but not for epilepsy associated with postnatal CNS insults (Ottman et al. 1996*a*, 1996*b*). In the current study, we extended these investigations by performing complex segregation analysis of idiopathic/cryptogenic epilepsy. Very few of the probands in this series have idiopathic epilepsy syndromes. Thus, this is essentially a study of the mode of inheritance of cryptogenic epilepsy.

Subjects and Methods

Study Population

The study population consisted of families of probands with epilepsy from EFSCU. The methods for data collection in this study have been described in detail previously (Ottman and Susser 1992). In brief, 1,957 adults (≥18 years of age) with epilepsy (probands) were ascertained from voluntary organizations with 84% participation. We used semistructured telephone interviews to obtain 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 obtained family history information on the same relatives from an additional informant (usually the mother of the proband). We also interviewed 51% of living adult relatives who were reported to have had seizures when they were ≥5 years old. We obtained medical records for 60% of probands.

Eighty-seven percent of probands were white, 55% had ≥1 year of college education, and 60% were women. Subjects interviewed did not differ from those who refused in term of gender or ethnicity, but participants were more educated. Probands ranged in age from 18 to 82 years, and averaged 36 years of age.

Clinical Diagnosis and Classification

Diagnoses of seizure disorders were based on a consensus review of all information collected on each proband or relative (proband interview, second informant interview, direct interview, and/or medical record). Epilepsy was defined as a lifetime history of at least two unprovoked seizures (Hauser et al. 1991). All 1,957 probands were confirmed to have epilepsy in the consensus review. The proband's report of epilepsy in parents and siblings had excellent validity (sensitivity 87%, specificity 99%), with the mother's report used as the gold standard (Ottman et al. 1993*a*).

We classified seizures according to the 1981 criteria of the International League Against Epilepsy (Commission on Classification and Terminology of the International League Against Epilepsy 1981). As we have reported elsewhere, the resulting seizure classifications were reliable (reproducible) (Ottman et al. 1993*b*) and valid, compared with the diagnoses of expert physicians (Ottman et al. 1990). Probands with generalized seizures were considered to have generalized epilepsies, and those with partial seizures were considered to have localization-related epilepsies.

For classification of etiology, we asked specific questions about illnesses and events strongly associated with risk for epilepsy in previous epidemiological studies. Seizures occurring <7 d after such events were classified as "acute symptomatic" rather than "unprovoked." For individuals with epilepsy, we used three categories of etiology: *idiopathic/cryptogenic*—epilepsy occurring in the absence of a historical insult to the CNS demonstrated to increase greatly the risk of unprovoked seizures; *neurological deficit presumed present at birth (neurodeficit from birth)*—epilepsy associated with a history of cerebral palsy (motor handicap or movement disorder) or mental retardation (IQ < 70) presumed present at birth; and *postnatal symptomatic*—epilepsy associated with a history of a postnatal CNS insult occurring ≥7 d prior to the first unprovoked seizure. The study was approved by the Columbia-Presbyterian Medical Center Institutional Review Board.

Phenotype Definition

We restricted the analysis to the families of probands with idiopathic/cryptogenic epilepsy and defined relatives as "affected" only if they had idiopathic/cryptogenic epilepsy. Relatives with postnatal symptomatic epilepsy or epilepsy associated with neurodeficit from birth were classified as "unknown," and those with only acute symptomatic seizures were classified as "unaffected."

Segregation Analysis

We performed segregation analysis under the unified mixed model, conditional on the parents' phenotypes, as

Table 1

Prevalence of a History of Idiopathic/Cryptogenic Epilepsy in First-Degree Relatives of Probands with Idiopathic/Cryptogenic and Postnatal Symptomatic Epilepsy, by Age at Last Follow-Up of Relatives

Age at Last Follow-Up[a] (years)	Relatives of Probands with Idiopathic/Cryptogenic Epilepsy			Relatives of Probands with Postnatal Symptomatic Epilepsy		
	Total No.	No. Affected	(%)	Total No.	No. Affected	(%)
<10	525	9	1.7	109	1	.9
10–19	644	29	4.5	141	2	1.4
20–29	1,402	38	2.7	324	6	1.9
30–39	1,425	41	2.9	382	4	1.0
40–49	954	29	3.9	232	1	.4
50–59	1,026	27	2.6	232	2	.9
≥60	1,730	27	1.6	433	5	1.2
Total[b]	7,706	200	2.6	1,853	21	1.1

[a] Age at the time of the proband's interview for living relatives and age at death for deceased relatives.

[b] Parents ($N = 6$) and siblings ($N = 8$) in doubly ascertained families were counted twice. Relatives with missing data on history of idiopathic/cryptogenic epilepsy or age at last follow-up were excluded (relatives of probands with idiopathic/cryptogenic epilepsy: 865; relatives of probands with postnatal symptomatic epilepsy: 219).

implemented by POINTER (Lalouel and Morton 1981). The analysis included data on 1,557 pedigrees comprising 10,853 individuals (1,560 probands and their 3,114 parents, 3,979 full siblings, 1,464 offspring, and 740 spouses). Three of the families were ascertained independently through two siblings. We used SEGRAN (Morton 1969) to estimate the ascertainment probability, π, and used the resulting value of $\pi = 0.04$ in the segregation analysis. For analysis using POINTER, we broke the pedigrees into 2,297 nuclear families (1,557 incomplete ascertainment, 740 complete ascertainment).

In the analysis, we used a simple assumption of 1.0% liability in relatives of all ages. Prevalence of a history of idiopathic/cryptogenic epilepsy in this data set did not vary markedly with age and was close to 1.0% in all age strata among relatives of probands with postnatal symptomatic epilepsy, in whom genetic contributions appear to be minimal (Ottman et al. 1996*a*, 1996*b*) (table 1). This flat age distribution results from underreporting of epilepsy in older relatives, which counteracts the expected increase in prevalence with advancing age (Ottman et al. 1995*b*). We repeated the analysis, using 10 liability classes based on age- and sex-specific cumulative incidence of idiopathic/cryptogenic epilepsy in Rochester, MN (Hauser et al. 1993). The results of the two analyses were very similar; hence, only the results using the simpler model (with one liability class) are reported here.

To assess heterogeneity according to mode of ascertainment (complete vs. incomplete) and proband epilepsy type (generalized vs. localization-related), we repeated the analysis within subgroups defined by these factors. The difference between the summed likelihoods in the stratified analysis and the likelihood for the total data set (without stratification) is asymptotically distributed as a χ^2 with df equal to $p(g - 1)$, where p is the number of iterated parameters and g is the number of subgroups.

Expected Risks under Various Genetic Models

We used POINTER to compute the expected risks in siblings and offspring of probands overall, and conditional on additional affected relatives in the family, under the best-fitting autosomal dominant (AD) mixed model, autosomal recessive (AR) mixed model, and polygenic model resulting from segregation analysis. To do this, we first created a test data set of nuclear families each of which contained two parents and three offspring. The test families varied in the distribution of affected relatives (i.e., one offspring, two offspring, all three offspring, a parent only, a parent and an offspring, a parent and two offspring), with all of the remaining relatives coded as "affection status unknown" (to avoid the issue of penetrance). We used POINTER to compute $-2\ln L$ for each family in the test data set under two competing hypotheses, specifying as one hypothesis (PA control card) the parameters of the best-fitting AD mixed model, and as the other (RA control card) the parameters of the best-fitting AR mixed model. Then we repeated this procedure, specifying the parameters of the best fitting polygenic model as one of the two hypotheses.

The output from POINTER gives $-2\ln L$ for each family under each of the models specified. We divided these values by -2 and used the resulting $\ln L$ values to compute expected risks by exponentiating the difference in $\ln L$ between different test families. For example, the risk to a sibling of a proband is obtained from the likelihoods for a family with only one sibling affected (the proband), and a family with two siblings affected as shown below:

Table 2

Segregation Analysis Results for Idiopathic/Cryptogenic Epilepsy

Model	*d*	*t*	*q*	*H*	*T2*	$-2 \ln L + C$
1. No transmission	...	...	(0)[1]	(0)	...	−5,265.70
2. Polygenic, no major gene	...	...	(0)	.374	...	−5,440.76
Single major locus:						
3. Dominant	(1.0)	2.06	.0015	(0)	(.5)	−5,457.55
4. Codominant	(.5)	4.03	.0016	(0)	(.5)	−5,458.09
5. Recessive	(0)	2.79	.0418	(0)	(.5)	−5,438.77
Mixed model:						
6. Dominant	(1.0)	2.63	.0003	.219	(.5)	−5,464.44
7. Codominant	(.5)	5.24	.0003	.218	(.5)	−5,464.45
8. Recessive	(0)	9.36	.0229	.195	(.5)	−5,449.53
9. D estimated	.573	4.58	.0003	.218	(.5)	−5,464.45
10. Unrestricted	.493	4.60	.0002	.222	.17	−5,466.64

[a] Parameters shown in parentheses are fixed.

$$L(\text{sibling affected} \mid \text{proband affected}) = \frac{L(\text{sibling affected and proband affected})}{L(\text{proband affected})}$$

$$= \exp \ln\left(\frac{L[\text{sibling affected and proband affected}]}{L[\text{proband affected}]}\right)$$

$$= \exp(\ln L[\text{sibling affected and proband affected}] - \ln L[\text{proband affected}]) .$$

We used analogous methods to compute risks for individuals with other constellations of affected relatives.

Validation of the AD Model

To test the validity of the AD model resulting from the segregation analysis, we assumed that the families most likely to be segregating the putative AD gene were those containing at least three first-degree relatives with idiopathic/cryptogenic epilepsy, including the proband. In these families, we extended the family history information to include first-degree relatives of previously identified relatives with idiopathic/cryptogenic epilepsy. We screened for seizure disorders in these newly ascertained relatives through telephone interviews administered either directly or to a close relative (for subjects who were deceased or otherwise unavailable) and performed in-person diagnostic evaluations in those who screened positive for seizures. Each newly ascertained relative had a 50% probability of carrying the putative susceptibility gene under the AD model. Thus, if the AD model were correct, the expected prevalence of epilepsy in newly ascertained relatives would be 50% of the estimated lifetime penetrance of the susceptibility gene.

Results

The results of the segregation analysis are shown in table 2. The model of no familial transmission was strongly rejected (model 1 vs. 10, $\chi^2 = 200.94$; df = 2–5). The polygenic model with no major gene effect was also rejected (model 2 vs. 10, $\chi^2 = 25.88$; df = 1–4). Each of the single major locus models with no polygenic influence had a significantly lower likelihood than the corresponding mixed model, providing support for a polygenic influence on susceptibility (dominant: model 3 vs. 6, $\chi^2 = 6.89$; df = 1; $P = .009$; codominant: model 4 vs. 7, $\chi^2 = 6.36$; df = 1; $P = .012$; recessive: model 5 vs. 8, $\chi^2 = 10.76$; df = 1; $P = .001$). The recessive mixed model was rejected, when compared with the unrestricted model (model 8 vs. 10, $\chi^2 = 17.11$; df = 2; $P = .0002$). Neither the dominant nor codominant mixed model was rejected. These two models gave nearly equal likelihoods and parameter estimates: mean liability of 2.6 for heterozygotes (dominant: 1.0×2.63; codominant: 0.5×5.24), $q = 0.0003$, and $H = 22\%$. (The dominant and codominant models are essentially equivalent, because, with a low frequency of the susceptibility allele, abnormal homozygotes are virtually nonexistent.) The mixed model with *d* unrestricted (model 9) also gave a similar likelihood and parameter estimates. An additional mixed model in which both *d* and *Z* (the ratio of childhood to adult heritability) were unrestricted did not have a significantly higher likelihood than model 9 (with $Z = 1.0$) ($\chi^2 = 1.09$; df = 1; $P = .30$). The parameter estimates of the unrestricted model (model 10) were also very similar to those of the dominant and codominant models. The maximum likelihood estimate of *T2*, the heterozygote transmission probability, was 0.17, but this value did not differ significantly from its Mendelian expectation of 0.5 (model 9 vs. 10, $\chi^2 = 2.19$; df = 1; $P = .14$).

For each set of parameter estimates, POINTER reports both the penetrance of each genotype (i.e., *P*[affected | genotype]) and the proportion with each genotype among affected individuals (i.e., *P*[genotype | affected]). Under the

Table 3

Observed and Expected Risks of Epilepsy in Persons with Specific Constellations of Affected Relatives

Risk Group	Expected Risk, Given Parameters of Best Fitting (%)			Observed Risk	
	Autosomal Dominant Mixed Model	Autosomal Recessive Mixed Model	Polygenic Model	Affected/Total No. of Relatives	%
Siblings of probands	3.1	3.2	3.2	92/3,746	2.5
Siblings of probands with an affected parent	15.4	6.7	6.5	9/154	5.8
Third sibling, given that proband and one sibling are affected	15.4	14.3	6.5	24/205	11.7[a]
All offspring of probands	3.1	2.0	3.2	57/1,380	4.1
Second offspring, given that one offspring is affected	15.4	6.7	6.5	23/84	27.4[a]

[a] Ascertainment corrected according to the method of Davie (1979).

best-fitting AD mixed model (model 6), the estimate of penetrance was 61% for carriers of the susceptibility allele, and the estimate of the proportion of carriers among affected individuals was 3.5%.

The patterns of expected risks, computed on the basis of the parameter estimates from POINTER, were strikingly different for the polygenic, AD mixed, and AR mixed models (table 3). For all three models, the expected risk was 3% in siblings of probands with epilepsy. Under the AD model, the expected risk in siblings increased substantially (fivefold) when an additional relative (parent or sibling) was affected, and the expected risk was the same regardless of whether the additional affected relative was a parent or sibling. Under the AR model, the expected risk in siblings increased substantially (four- to fivefold) when an additional sibling was affected, but only modestly (twofold) when a parent was affected. Under the polygenic model, only a modest increase in risk to siblings (twofold) was expected when an additional relative was affected, and as in the AD model, risk did not vary depending on whether the affected relative was a parent or sibling.

The polygenic and AD models both predicted a 3% risk in offspring of probands, whereas the AR model predicted a lower risk (2%). Under the AD model, a large (fivefold) increase was expected in a second offspring, given that one offspring was affected. The polygenic and AR models predicted a smaller (two- to threefold) increase in risk to a second offspring.

Comparison of the observed risks with these expectations (table 3) shows that the data were inconsistent with the polygenic model because the observed risks were higher than expected, both in a third sibling, given that the proband and one sibling were affected (11.7% vs. 6.5%), and in a second offspring, given that one offspring was affected (27.4% vs. 6.5%). The data on siblings and offspring differed markedly in their consistency with the AD and AR models. The risks in siblings were generally consistent with the AR model (observed vs. expected risks: all siblings, 2.5% vs. 3.2%; siblings of probands with an affected parent, 5.8% vs. 6.7%; and third sibling, given a proband and one affected sibling, 11.7% vs. 14.3%) but were inconsistent with the AD model. In contrast, the risks in offspring were inconsistent with the AR model and more consistent with the AD model (observed vs. expected risks: all offspring, 4.1% vs. 3.1%; and second offspring, given that one offspring was affected, 27.4% vs. 15.4%). However, the risks in offspring were higher than predicted by any of the three models.

Consistent with the analysis of observed and expected risks (table 3), comparison of the likelihoods and parameter estimates for the mixed model revealed significant heterogeneity according to mode of ascertainment ($\chi^2 = -5{,}464.45 - [-5{,}476.61] = 12.16$; df = 4; $P = .016$) (table 4). The estimate of d, the degree of dominance, was lower in the families with incomplete ascertainment (i.e., the sibships of the probands) than in those with complete ascertainment (i.e., the offspring of the probands) (0.32 vs. 0.88), suggesting a closer fit to a recessive model in the sibling data and to a dominant model in the offspring data.

The test for heterogeneity across strata defined by the type of epilepsy in the proband was not significant ($\chi^2 = -5{,}227.32 - [-5{,}231.17] = 3.85$; df = 4; $P = .43$) (table 4). Although d was similar in the two groups of families (0.7), the estimates of penetrance and frequency of the susceptibility allele differed substantially. In the families of probands with localization-related epilepsy, the best-fitting model involved a gene with high heterozygote penetrance (84%) and very low frequency (.0001), whereas in the families of probands with generalized epilepsy it involved a gene with lower penetrance (41%) and higher frequency (.0014).

Table 4

Parameter Estimates and Likelihoods for Mixed Model within Strata Defined by Mode of Ascertainment, Proband Seizure Type, and Proband Gender

Subgroup (No. of Families)	d	t	q	H	$-2 \ln L + C$	Penetrance G'G'	Penetrance G'G	Penetrance GG
All families (2,297)	.57	4.58	.0003	.23	−5,464.45	.99	.61	.01
Mode of ascertainment:								
Multiple incomplete (1,557)	.32	4.99	.0024	.07	−5,897.43	1.00	.23	.01
Complete (740)	.88	7.01	.0002	.19	420.82	1.00	1.00	.01
Partitioned total	...	...	...	...	−5,476.61	...	...	...
Type of epilepsy in proband:								
Generalized or localization related (2,195)[a]	.58	4.53	.0003	.23	−5,227.32	.99	.61	.01
Localization related (1,892)	.65	5.08	.0001	.27	−4,515.56	1.00	.84	.01
Generalized (303)	.73	2.92	.0014	.00	−715.61	.72	.41	.01
Partitioned total	...	...	...	...	−5,231.17	...	...	...
Mode of ascertainment, within families of probands with localization related epilepsy:								
Multiple incomplete (1,294)	.00	3.33	.024	.09	−4,916.70	.84	.01	.01
Complete (598)	1.00	8.02	.0002	.21	382.66	1.00	1.00	.01
Partitioned total	...	...	...	...	−4,534.04	...	...	...

[a] Families of probands with unknown seizure type, or both generalized and partial onset seizures, were excluded from this analysis (102 nuclear families of 62 probands).

The observed risks in siblings and offspring are shown separately for families of probands with generalized and localization-related epilepsy in table 5. Risks were *higher* in siblings (4.1% vs. 2.3%), but *lower* in offspring (1.8% vs. 4.8%) of probands with generalized versus localization-related epilepsy.

In the families of probands with generalized epilepsy, the pattern of risks in siblings was consistent with that predicted by an AD model, i.e., similar, high risks in families with an affected parent (15.2%) or an additional affected sibling (21.9%). However, the risks in offspring were lower than expected in an AD model. There were too few families to permit valid heterogeneity testing by mode of ascertainment within this subgroup.

In the families of probands with localization-related epilepsy, the results were similar to those in the full data set. Risks in siblings were higher when an additional sibling was affected (10.0%) than when a parent was affected (3.4%), consistent with the expectation of an AR model. However, risks in offspring increased substantially when an additional offspring was affected (from 4.8% to 28.8%), consistent with the expectation of an AD model and inconsistent with that of an AR

Table 5

Observed Risks of Idiopathic/Cryptogenic Epilepsy in Families, Stratified by Type of Epilepsy in the Proband

Risk Group	Probands with Generalized Epilepsy: Affected/Total No. of Relatives	Probands with Generalized Epilepsy: %	Probands with Localization-Related Epilepsy: Affected/Total No. of Relatives	Probands with Localization-Related Epilepsy: %
Siblings of probands	19/460	4.1	72/3121	2.3
Siblings of probands with an affected parent	5/33	15.2	4/117	3.4
Third sibling, given that proband and one sibling are affected[a]	7/32	21.9	17/170	10.0
All offspring of probands	3/174	1.8	54/1135	4.8
Second offspring, given that one offspring is affected[a]	0/4	...	23/80	28.8

[a] Ascertainment corrected according to the method of Davie (1979).

Table 6

Results of Sequential Ascertainment in 29 Families Containing at Least Three Individuals with Idiopathic/Cryptogenic Epilepsy

Previously Ascertained Relatives with Idiopathic/Cryptogenic Epilepsy	Newly Ascertained Relatives	No. (%) with Epilepsy			
		Total No.	Idiopathic/Cryptogenic	Symptomatic	Total
Parents of probands (N = 14)	Parents of affected parents	28	1 (3.6)	0 (. . .)	1 (3.6)
	Siblings of affected parents	47	0	5 (10.6)	5 (10.6)
	Offspring of affected parents (half-siblings of probands)	8	3 (37.5)	1 (12.5)	4 (50.0)
Siblings of probands (N = 31)	Offspring of affected siblings	42	1 (2.3)	0 (. . .)	1 (2.3)
Offspring of probands (N = 26)	Offspring of affected offspring	11	0 (. . .)	0 (. . .)	0 (. . .)
Total (N = 71)		136	5 (3.7)	6 (4.4)[a]	11 (8.1)

[a] Etiologies of epilepsy in relatives: neurological deficit presumed present at birth (N = 2), head trauma (N = 2), CNS tumor (N = 1), and unknown (N = 1).

model. There was significant heterogeneity by mode of ascertainment within this subgroup (χ^2 = −4,515.56 − [−4,534.04] = 18.48; df = 4; P = .001) (table 4).

Validation of the AD Model

Among the 1,557 pedigrees included in the study, 32 (2.0%) contained at least three individuals classified as having idiopathic/cryptogenic epilepsy (the proband and at least two of his or her parents, siblings, or offspring). Three of these families were excluded from the validation study because they either refused to participate (N = 2) or were lost to follow-up (N = 1). In the remaining 29 families, we used sequential ascertainment to extend the family history information (table 6). These families contained 71 previously ascertained relatives (parents, siblings, and offspring of the probands) with idiopathic/cryptogenic epilepsy. Among 136 newly ascertained first-degree relatives of these affected relatives, 11 (8.1%) had epilepsy of any etiology. In 5 of those affected, epilepsy was idiopathic/cryptogenic, and in the remaining 6, the etiology was neurological deficit (N = 2), head trauma (N = 2), CNS tumor (N = 1), or unknown (N = 1). Twenty-nine of the newly ascertained relatives were <10 years of age (age at study or at death) and hence had not passed through most of the age periods at risk of epilepsy. If we exclude these relatives from the calculations, the proportion affected increases slightly, to 9.2% for all epilepsy and 4.6% for idiopathic/cryptogenic epilepsy.

Under the AD model resulting from the segregation analysis, 50% of the sequentially ascertained relatives were expected to be gene carriers, and penetrance in carriers was estimated to be 61%; thus, the expected proportion affected is 50% × 61% = 30.5%. The observed proportion affected is much lower than this expectation.

Discussion

We performed segregation analysis to assess the most likely mode of inheritance of cryptogenic epilepsy. Although the AD mixed model provided the best overall fit to the data, our subsequent analyses indicated that the familial distribution is inconsistent with any conventional genetic model. The major reason for this inconsistency is the large difference between siblings and offspring in the patterns of familial aggregation. Risk was much lower in siblings of probands with an affected parent (5.8%) than in a second offspring, given that one offspring was affected (27.4%). Regardless of mode of inheritance, these two risks are expected to be the same, because these two family constellations are essentially equivalent. They differ only in terms of the position occupied by the proband.

Many investigators currently assume that the genetic contributions are different for each clinically defined epilepsy syndrome. However, our previous analyses of this data set suggest that the genetic influences are common to generalized and localization-related epilepsies. Although risk was higher in the relatives of probands with generalized epilepsy than in relatives of probands with localization-related epilepsy (Ottman et al. 1996*b*), the increased risk in the relatives was not restricted to the same type of epilepsy as in the probands (Ottman et al. 1995*a*). Thus, in our segregation analysis, we stratified on the clinical type of epilepsy in the probands but not in the relatives.

The results for the full data set are strongly influenced by the excess of probands with localization-related epilepsy in our series (84%, vs. 60% in prevalent cases of all ages in the general population) (Hauser et al. 1991). The proportion with localization-related epilepsy in our series is similar to that in other series of adults ascertained from clinical care settings. As we have described elsewhere (Ottman et al. 1996*a*, 1996*b*), the excess is due to the greater tendency for patients with localization-related than generalized epilepsy to continue having seizures until they are adults and to seek clinical care or contact voluntary organizations.

The reasons for the difference between siblings and

offspring are unclear. The difference does not appear to be explained by the tendency for epilepsy to be underreported in older relatives (Ottman et al. 1995*b*), because the patterns of risk differed according to the type of epilepsy in the proband. In the families of probands with generalized epilepsy, we observed high risks in siblings and low risks in offspring, whereas, in the families of probands with localization-related epilepsy, we observed low risks in siblings and high risks in offspring. The effects of underreporting would be expected to be similar in the families of probands with generalized and localization-related epilepsies.

We also considered the possibility that the high risk in a second offspring might be related to ascertainment bias resulting from our sampling strategy. If persons with epilepsy who had more than one affected offspring were more likely to contact voluntary organizations than other persons with epilepsy, this might explain the high risk we observed in a second offspring. This explanation also appears unlikely, however, because this effect would also be expected to be similar in persons with generalized and localization-related epilepsies, and the risks in offspring differed markedly between these two groups.

Previous studies have consistently found higher risks of epilepsy in offspring of affected women than in offspring of affected men (Ottman et al. 1985, 1988). This maternal effect cannot be explained by any conventional genetic model (Ottman et al. 1985, 1988; Ottman 1987). Our previous analyses indicate that it cannot be explained, either, by intrauterine exposure to seizures or anticonvulsants in offspring of women with epilepsy, perinatal complications that occur with increased frequency in women with epilepsy, or patterns of selective fertility leading to a higher proportion of affected mothers than affected fathers with familial forms of epilepsy (Ottman et al. 1988; Schupf and Ottman 1994 , 1996). We considered the possibility that the higher-than-expected risk in a second offspring, given that one was affected, might be attributed to the maternal effect. This explanation can be rejected, however, because risk to a second offspring was the same in offspring of female and male probands (28.0% and 28.6%, respectively). In the families of probands with localization-related epilepsy, one possible explanation for the higher risk in offspring than in siblings is an increase in heterozygote penetrance with advancing generations, such as would be expected in a model of "anticipation."

The comparison of observed risks with those expected from various sets of parameter estimates provides a useful method for validating the results of segregation analysis. We also attempted to validate the results empirically, by selecting families likely to be segregating the putative AD susceptibility gene (those containing at least three affected individuals) and investigating the prevalence of epilepsy in newly ascertained relatives with a 50% chance of being gene carriers in these families. The results indicate a poor fit of the AD model to our data. Prevalence of a history of epilepsy in newly ascertained relatives was much lower than predicted by the AD model. The low prevalence was not explained by young age of the newly ascertained relatives, because it increased very little when relatives <10 years of age were excluded. Underreporting of epilepsy in older relatives (Ottman et al. 1995*b*) probably partly explains the low prevalence in the parents and siblings of the probands' affected parents. However, it cannot explain the low prevalence in offspring of the probands' affected siblings (2.3%). (If offspring <10 of age are excluded, prevalence increases to 3.6% (1/28), still much lower than expected.)

The low prevalence in offspring of the probands' affected siblings is also inconsistent with any conventional genetic model. In the families of probands who have affected siblings, prevalence of idiopathic/cryptogenic epilepsy in the offspring of the *probands* is 20.8% (103/496). Regardless of mode of inheritance, the same prevalence is expected in offspring of the affected siblings in these families. The low prevalence in offspring of affected siblings in the families included in our validation study is even more striking, because these families were selected to contain at least *three* affected individuals.

We suggest three possible contributing explanations for the low prevalence of epilepsy in newly ascertained relatives in the validation study: (1) AD susceptibility is present in only a small subset of families containing at least three affecteds; (2) penetrance of the AD gene is much lower than estimated; or (3) susceptibility is due to genes at multiple loci (an additive or epistatic model).

We have documented evidence in favor of the first alternative. In one of the families included in the validation study, we were able to localize an AD susceptibility gene to chromosome 10q (Ottman et al. 1995*c*). Among the remaining 28 included families, however, very few appear consistent with an AD model. Three of the five relatives with idiopathic/cryptogenic epilepsy, and three of the six relatives with symptomatic epilepsy in table 6, were in the family in which we found linkage.

Our results indicate that, in most families containing multiple individuals affected with cryptogenic epilepsy, the mode of inheritance is unclear and may involve a multigenic (additive or epistatic) model. In these families, nonparametric approaches may be the optimal strategy for localizing susceptibility genes. The differences between siblings and offspring in the patterns of familial risk are intriguing and should be investigated further.

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