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Familial Clustering of Seizure Types within the Idiopathic Generalized Epilepsies

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Abstract

Objective: To examine the genetic relationships among epilepsies with different seizure types -- myoclonic, absence, and generalized tonic-clonic -- within the idiopathic generalized epilepsies (IGEs).

Background: Careful phenotype definition in the epilepsies may allow division into groups that share susceptibility genes. Examination of seizure type, a phenotypic characteristic less complex than IGE syndrome, may help to define more homogeneous subgroups.

Methods: Using the approach that found evidence for distinct genetic effects on myoclonic vs absence seizures in families from the Epilepsy Family Study of Columbia University, we examined an independent sample of families from Australia and Israel. We also examined the familial clustering of generalized tonic clonic seizures (GTCs) within the IGEs in our two combined datasets. Families were defined as concordant if all affected members had the same type of seizure or IGE syndrome, as appropriate for the analysis performed.

Results: The proportion of families concordant for myoclonic vs absence seizures was greater than expected by chance in the Australian families. In addition, GTCs clustered in families with IGEs to a degree greater than expected by chance.

Conclusions: These results provide additional evidence for distinct genetic effects on myoclonic vs absence seizures in an independent set of families. They also suggest that there is a genetic influence on the occurrence of GTCs within the IGEs.

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Keywords

Epilepsy; genetics; phenotype; IGE; myoclonic; absence; tonic-clonic; seizure

INTRODUCTION

Epilepsy is a collection of many different seizure disorders with different characteristics. In addition, it is etiologically complex; multiple genetic and non-genetic influences play a role in its development and clinical manifestations. Genetic heterogeneity and variable expressivity complicate the search for susceptibility genes; several epilepsy syndromes result from mutations in more than one gene, [1–10] and some genetic mutations produce multiple different epilepsy phenotypes.[11] Careful phenotype definition is essential for gene identification because it allows division of the epilepsies into groups more likely to share susceptibility genes. Substantial evidence from twin studies and studies of families with multiple affected individuals indicates that genes raise risk for specific types of seizures or epilepsy syndromes.[12–15] These results make it clear that the success of future genetic studies depends on selection of appropriate phenotypes to reduce genetic heterogeneity and improve power to find causative genes.

Phenotype definition within the idiopathic generalized epilepsies (IGEs) has posed a particularly difficult problem. The IGEs, including juvenile myoclonic epilepsy (JME), juvenile absence epilepsy (JAE), and childhood absence epilepsy (CAE), are distinguished by combinations of myoclonic, absence, and generalized tonic-clonic seizures (GTCs), and generalized spike-wave or polyspike wave patterns on EEG, with characteristic ranges of age of onset.[16] Despite extensive evidence for a strong genetic contribution to the IGEs, gene discoveries reported to date[17–20] appear to explain only a small subset of families and individuals. Allelic association studies have identified several possible risk-conferring polymorphisms, but their role in IGE etiology has yet to be confirmed.[21–27]

Phenotype definition can be difficult in the IGEs. Classification of individuals is challenging because existing International League against Epilepsy (ILAE) categories are not mutually exclusive, and subjects may have atypical features or features common to more than one syndrome. Classification of families for genetic studies is also difficult because multiple IGE syndromes often coexist within the same family.[28, 29] One useful method for approaching this problem is to examine seizure type, a phenotypic characteristic less complex than IGE syndrome. In prior work, we used a novel approach that examines the clustering of seizure types in families to study the genetic effects on myoclonic and absence seizures.[29] Our results indicated that some of the genetic influences on these two seizure types are separate. They also provided evidence for separate genetic influences on the myoclonic syndrome JME compared with either of the absence syndromes, JAE and CAE. In addition, we did not obtain evidence for different genetic influences on the two absence syndromes, CAE vs. JAE. This supports the importance of seizure type as a defining characteristic in genetic analysis. Other investigators have also identified genetic influences on seizure type within the IGEs.[30, 31] In the study described here, we sought to confirm our evidence for distinct genetic effects on myoclonic and absence seizures in an independent sample. We also examined whether the occurrence of other seizure types could help subdivide the IGEs into categories for genetic analysis, in particular, generalized tonic-clonic seizures (GTCs) within the IGEs. In the IGEs, GTCs occur commonly but not universally, and their occurrence may result from specific genetic influences.

METHODS

Subjects and diagnosis

The families included in this study are drawn from two sources, the Epilepsy Family Study of Columbia University (EFSCU),[32] and a set of IGE families from Australia and Israel .[28] Methods of ascertainment and evaluation of these families have been described in detail previously.[28, 29, 33] Analyses were restricted to families containing two or more individuals with IGEs—46 families containing 121 individuals from Australia, and 35 families containing 95 individuals from EFSCU. Methods for ascertainment, inclusion, and evaluation are described for the two studies below.

EFSCU.—EFSCU began in 1985 as a familial aggregation study and evolved into an ongoing genetic linkage study of epilepsy. We screened each subject for seizure disorders through either an in-person or telephone interview. In subjects who screened positive for afebrile seizures, we carried out a complete diagnostic evaluation, including (1) a validated diagnostic interview administered by a neurologist or physician with specialized training in epilepsy,[34, 35] (2) review of medical records (frequently containing EEG reports, imaging results, and reports of neurological exams), and in a subset of cases, (3) a study EEG. We administered the diagnostic interview directly to subjects whenever possible. In those who were deceased, under age 12, or otherwise unavailable, we interviewed 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 the subject's own recall was insufficient, we interviewed additional informants to clarify the seizure history. Two senior epileptologists 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, we removed identifying information prior to this review, and reviewed subjects from different families in random order. We used findings from the neurological examination, study EEG, and medical records to supplement the clinical descriptions of seizures and possible etiologic factors. In many cases, clinical information was sufficiently detailed and clear for unambiguous classification of seizure and syndrome type; in these cases we used EEG data (from the study EEG, tracings provided by the treating physician, or reports in the medical records) to supplement and support the diagnoses. However, when clinical information was ambiguous, we required generalized epileptiform abnormalities on EEG (such as generalized spike wave or polyspike wave) for diagnosis of an idiopathic generalized seizure or syndrome type. When both clinical information and EEG data were inconclusive, we classified individuals as unknown.

AUSTRALIAN STUDY.—Families were collected by referral from neurologists or pediatricians and from the First Seizure Clinic at Austin Health, Melbourne, Australia. Six families were collected in Israel. The Israeli families were all personally evaluated by S.F.B. in Israel, using the same techniques as for the Australia cases.

All probands and their available family members underwent a detailed clinical interview by phone or in person with a validated seizure questionnaire,[36] neurological examination, and 21-channel EEG recording to allow classification of the epilepsy syndrome. Medical records and EEG reports from treating physicians were also collected to supplement clinical information. Generalized spike-wave (GSW) was required for diagnosis of CAE, JAE, and IGE with tonic-clonic seizures only (IGE-TCS); for JME clinical history was considered sufficient for the diagnosis.

Seizure type and Syndrome Classification in the Combined Study

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

League Against Epilepsy (ILAE).[37] Individuals with epilepsy were then classified as having myoclonic seizures, absence seizures, both, or neither.

We diagnosed IGE syndromes according to the ILAE definitions;[16] however, as IGE sub-syndromes do not have clear-cut clinical boundaries, we developed systematic methods to deal with "borderline" cases. JAE and JME were distinguished by the more frequent defining seizure type (absence vs. myoclonus) or, when frequency was equal, with the seizure type of earliest onset. If one defining seizure type (myoclonus vs. absence) occurred in isolation and the other always occurred only immediately preceding a GTC, then the independently occurring seizure type defined the syndrome. When absence seizures began at age eight or younger, we classified the syndrome as CAE; when absence seizures began at age 12 or older, JAE. For individuals with absence seizures beginning between nine and 11 years, CAE was differentiated from JAE by frequency of absences. The ILAE Classification describes CAE as occurring in children of "school age (peak manifestation age six to seven years)" while JAE is described as having "manifestation …around puberty". Using these definitions, individuals with absence seizures beginning at age eight or younger seemed clearly to be definable as CAE and age 12 or older as JAE. However, the range between nine and 11 was less clear. In this borderline age range, seizure frequency could be used to differentiate the two syndromes, since the ILAE definitions describe CAE absence seizure frequency as "very frequent (several to many a day)" and JAE absence seizure frequency as "…lower than in Pyknolepsy…occurring less frequently than every day, mostly sporadically". We also included categories of CAE/JAE indistinguishable, and JAE/JME indistinguishable, for cases that could not be placed confidently in either category.

Cases were not included in the syndrome analysis when the syndromes could not be reliably distinguished (e.g., because information was not available on age at onset or seizure frequency). We created an additional category, IGE not otherwise specified (NOS). This category comprises cases with idiopathic generalized seizures that for one or more reasons do not fit into conventional IGE categories. This includes: 1) atypical age-at-onset/seizure type constellations, 2) photosensitive myoclonus, 3) onset after age 30, 4) unclear age of onset, 5) atypical seizure types, and 6) isolated GTCs with GSW on EEG. Several syndrome categories were unique to the Australian cohort (see Table 1). Individuals with GTCs and non-epileptiform or unavailable EEGs were classified as "epilepsy with TCS unclassified" (ETCSU); these were excluded from all analyses. Those with absence seizures or status beginning after age 20 were classified as adult absence epilepsy (AAE); these were included in the IGE NOS category.[38] The Australian study also reported the co-occurrence of idiopathic photosensitive occipital epilepsy (IPOE) with JME in several cases.[39] In keeping with inclusion of individuals with both partial epilepsy and IGEs (described below), those with both JME and IPOE were classified as JME. For the analysis of the occurrence of GTCs in the IGEs in our combined dataset, we also classified subjects with IGEs by whether or not they had GTCs.

Inclusion/Exclusion Criteria

We included individuals in the myoclonus/absence analysis only if they had definite myoclonic seizures or absence seizures or both. Individuals with focal in addition to generalized epilepsy were included in the analysis, but individuals with only focal epilepsy or epilepsy of unknown type were excluded entirely. The analysis of concordance was based on the seizure classifications of subjects with idiopathic epilepsy only; subjects with symptomatic epilepsy, isolated unprovoked seizures, or only acute symptomatic seizures (including febrile seizures) were not considered. Relatives with abnormal EEGs but without clinical seizures were also excluded, as were married-in individuals not genetically related to the other family members.

For studies of IGE syndromes, including GTCs within the IGEs, we restricted the analysis to families with two or more individuals with the clearly defined syndromes CAE, JAE, and JME.

The seizure type analysis (myoclonus/absence) included all families with two or more individuals with the appropriate seizure types, regardless of syndrome. Because the inclusion of families containing individuals with unknown seizure types or syndromes could affect results in unpredictable ways, we performed additional analyses in a subset of families in which no individual was classified as having an unknown type of epilepsy.

Analysis

We undertook three analyses in this study: 1) assessment of familial clustering of myoclonic and absence seizures in an independent sample of IGE multiplex families from Australia and Israel, 2) assessment of familial clustering of IGE syndromes in these new families, and 3) clustering of GTCs in families with multiple affected individuals with IGEs in the combined Australian and EFSCU datasets. The method used to assess clustering of specific seizure types and syndromes in families is the concordance analysis method, which we described in detail previously, and used to investigate the genetic effects on generalized vs. localization-related epilepsy, and myoclonic vs. absence seizures.[29, 33, 40] (The computer program we have developed for concordance analysis is available on request; email Daniel Rabinowitz at dan@stat.columbia.edu.) The basic principle underlying the method is that if the genetic effects on epilepsy are type-specific, the number of families concordant for epilepsy type should exceed that expected by chance. For example, type-specific genetic effects on myoclonic and absence seizures could include genes that affect risk for myoclonus but not absence, genes that affect risk for absence but not myoclonus, or (more generally), genes that affect risk for one seizure type to a greater degree than they affect risk for the other. If none of the genes has such different effects on the two seizure types, then familial concordance of seizure type should be consistent with that expected by chance.

We define families as “concordant”if all affected relatives have the same seizure type or syndrome of interest; for example, if a family contained four individuals with IGEs, and all four had myoclonic seizures, then the family would be concordant for myoclonic seizures. The number of concordant families in the sample can be easily calculated. Concordance is meaningful only if a family contains two or more subjects with the seizure type or syndrome of interest; hence each analysis is restricted to the subset of families that meets this requirement, and the number of included families varies in the different analyses.

For interpretation, the observed number of concordant families must be compared with the number expected by chance. This is done by a permutation test, in which the expected number is calculated based on two factors: 1) the overall proportion of individuals with each seizure type in all study families, and 2) the number of affected individuals in each family. In estimating the expected proportion of concordant families, we also stratified by the proband’s seizure type or syndrome (whichever was being analyzed), because it might have influenced the probability that the family was included in the sample. For analysis of the genetic influences on GTCs within the IGEs, we examined whether, within the IGEs overall (CAE plus JAE plus JME), the occurrence of GTCs clustered in families, whether GTCs clustered within each of the three IGE subsyndromes, and whether GTCs clustered in the combined absence syndromes (JAE plus CAE).

RESULTS

Table 1 shows the distribution of seizure types and syndromes in families with two or more individuals with IGEs from the two datasets. Among all 81 families with two or more IGEs, 48 had two affected, 18 had three affected, 13 had four affected, one had six affected, and one had eight affected individuals.

Familial Concordance of Myoclonic and Absence Seizures in Australian Families

Among the 121 subjects from 46 Australian families, 29 (24%) had myoclonic seizures only, 66 (55%) had absence seizures only, and 13 (11%) had both seizure types. These percentages are comparable to the distribution of seizure types in EFSCU IGE families (Table 1). One Australian case had an unknown seizure type—this individual was excluded from the seizure type analysis, and in a sub-analysis, the entire family was excluded.

The absence/myoclonic seizure type analysis was restricted to 40 Australian families, since families were excluded if they contained fewer than two individuals whose seizure type could be classified clearly. Of these 40 families, 23 (58%) were concordant for seizure type (i.e., all individuals in the family had myoclonic seizures, all had absence seizures, or all had both myoclonic and absence seizures). The number of families expected to be concordant for seizure type (considering myoclonus alone, absence alone, and both myoclonus and absence as three different types) was 15.52, and this difference was significant (Table 2). To restrict attention to the independent genetic effects on myoclonus alone and absence seizures alone, we performed an additional analysis excluding individuals with both myoclonic and absence seizures. Concordance for these two seizure types in isolation was again significantly greater than expected by chance (Table 2). Results of the seizure type analyses confirm our prior findings in EFSCU families.

Familial Concordance of IGE Syndrome in Australian Families

Thirty-seven families were included in the analysis of IGE syndromes, because they contained two or more subjects who could be unambiguously classified as having JME, JAE, or CAE. Nineteen of these 37 families were concordant for syndrome (i.e., all individuals with IGEs within the family had the same IGE syndrome: JME, JAE or CAE). The number of families expected to be concordant was only 9.17; this difference was highly significant (Table 2). When the concordance method is applied to more than two groups, it cannot determine which groups are distinct in their familial distribution. In order to determine which specific syndromes were responsible for the overall difference, we performed several additional analyses. First, we examined concordance of JAE vs. CAE within 29 families containing two or more subjects with these syndromes. As in prior studies in EFSCU, in this analysis the number of concordant families did not exceed that expected by chance (13 observed vs. 11.3 expected, Table 2), providing no evidence for distinct genetic contributions to the two absence syndromes. In contrast, in analyses of JME vs. CAE and JME vs. JAE, concordance was significantly greater than expected.

Clustering of Generalized Tonic-Clonic Seizures in Combined Australian and EFSCU IGE Families

The analysis of clustering of GTCs in families was restricted to families containing two or more subjects with GTCs; 100 individuals with IGEs (52 with GTCs and 48 without GTCs) in 60 families contributed to the analysis (Table 3). When we examined all three syndromes together (JME, JAE, and CAE), familial concordance of GTCs was greater than expected by chance. In other words, GTCs clustered in families containing any combination of these three IGE syndromes. We also attempted to examine familial clustering of GTCs with each syndrome individually. Within each IGE syndrome the number of families concordant for occurrence of GTCs in individuals exceeded that expected, but no result reached statistical significance. Because our current and previous analyses provided no evidence for separate genetic effects on CAE vs. JAE, we also examined the concordance of GTCs in the combined absence epilepsies. Among 39 families containing two or more individuals with either JAE or CAE, 22 were concordant for GTCs, significantly greater than the 16.61 expected by chance.

DISCUSSION

In prior studies of EFSCU families, we used the concordance method to assess the evidence for distinct genetic effects on generalized vs. localization-related epilepsy, and on myoclonic vs. absence seizures. The results presented here confirm our previous findings of distinct genetic effects on absence and myoclonic seizures in an independent set of families. Examination of IGE syndrome concordance provides significant evidence for different genetic effects on the myoclonic syndrome JME, compared with either of the absence syndromes CAE or JAE, but not for genetic effects to distinguish CAE from JAE. Overall, the results for both seizure and syndrome concordance support our earlier findings in EFSCU—that myoclonic syndromes differ from absence syndromes in their genetic contributions.

Our analyses of the distribution of GTCs in IGE families suggest that occurrence of GTCs in families is important for classifying families for genetic analysis. Concordance results indicate that the occurrence of GTCs within the combined syndromes JME, JAE and CAE may have specific genetic determinants. The small number of individuals in each IGE subgroup (JME, JAE, and CAE,) did not allow examination of the clustering of GTCs in each subgroup separately. However, in the (JAE + CAE) group, GTCs clustered in families to a degree greater than expected by chance.

In order to address the potential effects of multiple testing on inflation of type 1 error, we used the familiar and conservative Bonferroni correction to assess significance. Using the most conservative correction possible, we corrected for all twelve tests performed in Tables 2 and 3. Most p-values are small enough that they fall under even the 0.05/12=0.004 level dictated by the Bonferroni correction. Only two sub-analyses do not retain significance after correction. In the IGE syndrome analysis, the JME vs. JAE comparison is just above the threshold (Table 2; 17 families). This analytic subgroup is based on a small subset of families, which limits power, but a trend to differentiate these two syndromes is evident even with this very stringent correction. In addition, this result confirms results from a prior study in another dataset, and therefore might be considered to be less subject to stringent significance limits than original reports. The second sub-analysis with a corrected p-value above 0.004 is the analysis of GTCs within the combined absence syndromes JAE + CAE, (Table 3; 39 families). The smaller number of families in this subset may limit our ability to conclude that GTCs constitute a genetically distinct group within the combined absence syndromes as opposed to within the IGEs overall. This does not dramatically affect the conclusions that can be drawn from the results.

Overall, our results show that IGEs with GTCs and IGEs without GTCs cluster separately in families—this suggests that some of the genetic influences differ in the development of IGEs with GTCs vs. those without GTCs. Evidence is strongest for the clustering of GTCs within the absence syndromes. Our results, derived from individuals with well-defined IGE syndromes, emphasize the importance of the use of seizure types—myoclonic, absence, and GTCs-- in phenotype definition and selection of subgroups of families more likely to be genetically homogenous for genetic analysis. Epilepsy syndromes, which are largely determined by seizure type, probably add another level of subtlety to the genetic analysis. Work from other investigators supports this hypothesis. A genome scan of 91 families ascertained through IGE probands found evidence for an oligogenic model with one locus common to most IGEs, and other loci that may influence specific seizure phenotypes--such as myoclonic jerks--rather than syndromes as they are currently defined.[30] Clinical epidemiologic evidence has shown that there are distinct prognostic subgroups of certain IGEs defined by the presence or absence of GTCs.[31] A meta-analysis of 23 study cohorts including 2,303 patients identified that half of patients with ILAE-defined absence epilepsy developed GTCs; the subgroup with

GTCs were less likely to go into remission.[41] These differences suggest a fundamental difference in neurobiology that may have an underlying genetic basis.

The concordance method and the results we describe here help clarify the role of genes in determining the specific manifestations of the epilepsies. This has clear implications for genetic studies, because it allows *a priori* identification of disease subtypes that are more likely to share susceptibility genes. Reducing genetic heterogeneity by careful, informed phenotype definition improves power to find linkage or association in a sample of patients or families. Examination of the clustering of disease types or characteristics in families can be applied to any disorder to guide future genetic studies.

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Table 1

Distribution of IGE syndrome and seizure types in families containing at least two individuals with idiopathic generalized epilepsy, in EFSCU and Australian/Israeli families

Syndrome	No. with syndrome	Myoclonic and/or Absence Seizures*			
		Myoclonic seizures only	Absence seizures only	Both	Neither
EFSCU					
JME	23	20	0	3	0
JAE	16	0	13	3	0
CAE	28	0	24	4	0
JME/JAE#	13	0	3	10	0
JAE/CAE#	1	0	1	0	0
IGE NOS#	14	11	0	3	0
EFSCU Total	95	31	41	23	0
Australia/Israel					
JME	31	26	0	5	0
JAE	25	0	23	2	0
CAE	44	0	40	4	0
IGE-TCS#	12	0	0	0	12
AAE#	3	0	3	0	0
JME/IPOE#	4	2	0	2	0
TCS/IPOE#	1	0	0	0	1
IGE NOS#	1	1	0	0	0
Australia Total	121	29	66	13	13
Overall Total	**216**	**60**	**107**	**36**	**13**

*For ease of presentation in this table, individuals with unknown or uncertain myoclonus or absence seizures were classified as not having these types, however, these individuals were excluded from the myoclonus/absence analyses.

#See methods section for definitions

Table 2

Observed vs. Expected Concordance of **Myoclonic versus Absence Seizure Types** and **IGE Syndromes** in Australian & Israeli Families

	Number of Concordant Families		Variance	p-value (2-tailed)*
	Observed	Expected		
Seizure Type Analysis				
All individuals with myoclonic or absence seizures (40 families)	23	15.52	5.63	**0.0008**
Excluding individuals with both myoclonic and absence seizures (34 families)	27	17.71	4.66	**<0.0001**
IGE Syndrome Analysis				
JME vs. JAE vs. CAE (37 families)	19	9.17	5.93	**<0.0001**
JAE vs. CAE (24 families)	13	11.28	3.67	0.1847
JME vs. CAE (29 families)	23	11.98	6.53	**<0.0001**
JME vs. JAE (17 families)	12	7.90	2.63	**0.0061**

* P-values less than 0.05 are highlighted in boldface type. Please see Results for discussion of multiple testing and Bonferroni correction.

Table 3

Familial Concordance of **Generalized Tonic-Clonic Seizures** among Individuals with IGE (Australia/Israel and EFSCU Families Combined)

IGE syndrome	Number of Families Concordant for GTCs Observed	Expected	Variance	p-value (2-tailed)*
Total IGEs (JME + JAE + CAE) (60 families)	35	23.36	12.4	**0.0005**
Total IGEs excluding families with individuals who have unknown GTC status (59 families)	34	23	12.05	**0.0008**
JME only (16 families)	10	8.05	1.88	0.0776
JAE only (9 families)	6	4.36	2.05	0.1265
CAE only (23 families)	16	13.41	3.66	0.0878
JAE + CAE (39 families)	22	16.61	8.80	**0.0346**

*P-values less than 0.05 are highlighted in boldface type. Please see Results for discussion of multiple testing and Bonferroni correction.