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Phenotypic concordance in 70 families with IGE-implications for genetic studies of epilepsy

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Summary

Introduction—A crucial issue in the genetic analysis of idiopathic generalized epilepsy (IGE) is deciding on the phenotypes that are likely to give the greatest power to detect predisposing variants. A complex inheritance pattern and unclear nature of the genotype—phenotype correlation makes this task difficult. In the absence of much definitive genetic information to clarify this correlation, we inferred the putative effects of predisposing genes by studying the clustering of various phenotypic features, both clinical and electrophysiological, within families.

Methods—We examined the distribution of clinical features among relatives of a proband in 70 French—Canadian families with a minimum of two affected individuals with a clear diagnosis of IGE and then, using concordance analysis, identified the relative genetic influences on IGE syndrome, seizure type, age-at-onset, and EEG features.

Results—The mean number of affected individuals with IGE per family was three. One-third of relatives had the same syndrome as the proband. 16—22.5% of relatives of a proband with one of the absence syndromes had juvenile myoclonic epilepsy (JME). Conversely, 27% of relatives of probands with JME had an absence syndrome. 15% of relatives displayed the exact constellation of seizure types as the proband. Concordance analysis demonstrated greater clustering within families of IGE syndrome, seizure type, and age-at-onset than would be expected by chance. Significant concordance was not evident for EEG features.

Discussion—There was a large degree of clinical heterogeneity present within families. However we found evidence for clustering of a number of clinical features. Further refinement of the phenotypes used in genetic studies of complex IGE is necessary for progress to be made.

Keywords

Concordance; IGE; Epilepsy genetics

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¹He carried out statistical analysis.

Conflict of interest

None.

Introduction

Idiopathic generalized epilepsy (IGE) is a disorder with a strong genetic component (Beck-Mannagetta and Janz, 1991; Berkovic et al., 1998). However, little is known about its genetic architecture. Like other common diseases, this architecture is likely to be quite complex, with genetic factors contributing a spectrum of predisposing effects (Goldstein et al., 2003). Highly penetrant mutations have been discovered in a few large families segregating auto-somal dominant IGE (Cossette et al., 2002; Kananura et al., 2002; Haug et al., 2003; Suzuki et al., 2004). However screening for these variants in large cohorts of unrelated individuals with IGE has been negative (Lu et al., 2002; Nakayama et al., 2003; Ito et al., 2005). In addition families with large numbers of affected individuals are rarely seen, suggesting that highly penetrant mutations are probably uncommon. Most patients with IGE present as isolated cases or as part of small multiplex families with a complex inheritance pattern. An oligogenic or polygenic disease model is commonly proposed to explain this complexity although at present there is limited genetic data to confirm this model. A large amount of recent research has thus focused on the use of both association and linkage studies to detect pre-disposing variants and loci. Although a number of positive associations (Sander et al., 1997a, 2000a, 2000b, 2002; Steinlein et al., 1997; Chioza et al., 2001, 2002; Chen et al., 2003; Pal et al., 2003; Vijai et al., 2003; Gu et al., 2004) and loci (Sander et al., 1995, 1997b, 2000c; Durner et al., 1991, 1999, 2001; Liu et al., 1996; Serratos et al., 1996; Pinto et al., 2004; Zara et al., 1995; Puranam et al., 2005; Elmslie et al., 1997; Greenberg et al., 1988, 2000, 2005) have been reported, few have been replicated with any consistency. In addition, recent work by Hempelmann et al. (2007) using 126 multiplex IGE families suggested heterogenous configurations of susceptibility loci associated with different IGE subtypes and seizure types, further highlighting the likely complexity of the situation.

However, while dissecting the genetic architecture of epilepsy is clearly complicated, the relative lack of success raises the possibility that poor understanding of the epilepsy phenotype is producing mixed and unclear genetic signals in these studies. Of particular concern is that subtle phenotypic differences may exist between replication cohorts. Currently the most commonly used phenotype is that of IGE subtype. Although concordance studies from twins suggest that inherited genetic factors predispose specifically to IGE (Berkovic et al., 1998; Kjeldsen et al., 2003; Vadlamudi et al., 2004) it is unclear if these factors predispose to the same or different IGE subtypes. If a specific variant pre-disposes to a specific IGE subtype, e.g. juvenile myoclonic epilepsy (JME), only patients with this phenotype should be included in a study to maximise the power to detect that variant. However, if a variant predisposes to a variety of IGE subtypes, the study cohort could include individuals with different subtypes of IGE. If, as may well be the case, the genotype—phenotype correlation for subtypes is extremely complicated it may be more appropriate to use an alternative phenotype such as seizure type, or an endophenotype, such as EEG pattern, if it can be demonstrated that genetic factors have stronger and more reliable correlations with these clinical features.

In the current absence of much genetic data on which to base genotype—phenotype correlations, one can infer the putative effects of predisposing genes by studying the clustering of phenotypic features within families. Affected members of the same family presumably share most of the genetic factors that predispose them to disease. Previous work by members of this group has provided some data about shared and distinct genetic influences on IGE subtype and seizure type in families. In this study we examined 70 families with IGE from a founder population in order confirm these findings in a different population cohort. In addition we performed a number of novel analyses including age-at-onset, and EEG features in order to identify the relative genetic influences on these phenotypic features. We then consider the implications of these and previous results on the best method of phenotyping for genetic studies in IGE.

Methods

Subjects and diagnosis

Families were collected by referral from neurologists or pediatricians in Quebec, Canada. All families were located in greater Montreal and Quebec City regions. Informed consent was obtained from all participants and the study was approved by the ethics committee of the CHUM-Notre Dame Hospital. The diagnosis of IGE was based on detailed clinical interview, full neurological examination and a 21 channel EEG recording. We included families with a minimum of two affected individuals with a clear diagnosis of IGE. Patients were diagnosed as having JME, CAE, JAE, or IGE-TCS according to ILAE definitions (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). In total, eight different neurologists were involved in the referral of families. However all charts and investigations were reviewed by a single physician (PC) before making a final clinical diagnosis.

All patients had at least one EEG performed. The majority of these (78%) occurred within 6 months of first seizure onset. Data was not available for all patients regarding whether they were taking AED medication at the time of the EEG. Hyperventilation and photic stimulation were performed in all patients. Photosensitivity was defined as any epileptiform discharge that was consistently triggered by photic stimulation. We did not further subdivide into the different categories of photosensitivity.

To categorise cases without clear-cut boundaries, and for atypical cases, we used methods previously described by Winawer et al. (2005) to generate the category of IGE-not otherwise specified (IGE-NOS). Individuals with GTCs and non-epileptiform or unavailable EEGs were classified as “epilepsy with TCS unclassified” (ETCSU); these were excluded from all analyses.

We firstly examined the distribution of each clinical trait within relatives of each proband to give an overall impression of the homogeneity or heterogeneity within our families. However, as the frequency of traits in the relatives of probands depends on the frequency in the data set as a whole, we then went on to perform concordance analysis to help identify specific genetic effects on each trait.

Concordance analysis

We analysed the following clinical traits for concordance within families:

- *IGE syndrome.* We analysed families for concordance for CAE, JAE, JME or IGE-TCS.
- *Seizure type.* We analysed families for concordance for myoclonic, absence or primary generalized tonic—clonic seizures.
- *Age of onset of epileptic seizures.* This was analysed by treating age-at-onset as a continuous variable.
- *EEG pattern of abnormality.* We categorised EEG results as (1) generalized spike and wave at a frequency of 2.5—3.5 Hz; (2) generalized spike and wave at a frequency of >3.5 Hz; and (3) generalized polyspike and wave. The small number of individuals with clinical JME who had normal recordings were excluded.
- *Photosensitivity.* Patients were described as photosensitive if this response was evident on at least one EEG recording. We analysed families for concordance for the presence or absence of photosensitivity on routine EEG.

Interpretation of concordance

Families are defined as concordant if all affected relatives have the same clinical feature, for example IGE subtype or seizure type. If genetic effects are specific to a particular clinical feature, then the number of families concordant for that particular feature should exceed that expected by chance. To determine if this is the case the observed number of concordant families is compared to the number of families expected to be concordant by chance, taking into account selection via probands (who might have a different probability of having the feature because of the way they were sampled) and multiple affected family members. This is done using a permutation test in which the expected number is calculated based on (1) the overall proportion of subjects with each clinical feature in all study families and (2) the number of affected subjects in each family. (For further details of this method, see Winawer et al., 2002). The concordance analyses were carried out excluding singletons (i.e., families in which only one individual has the trait of interest) and using a Monte-Carlo approximation to exact *p*-values.

Since age-at-onset was a continuous variable with truncation issues (i.e., onset could not occur at an age older than the individual's age at the time of study) we did not use the permutation test approach. Instead we used a method based on proportional hazards regression (Rabinowitz and Betensky, 2002). This method accounts for truncation of age-at-onset by current age. The kernel function was the normal density and the smoothing parameter was half the non-parametric maximum likelihood estimate of the inter-quartile range.

Results

We identified 70 families containing at least two individuals with a clear diagnosis of an IGE syndrome. These families were divided into 22 families in which the proband had CAE, 15 families in which the proband had JAE, 20 families in which the proband had JME and 13 families in which the proband had IGE-TCS. In total there were 214 affected individuals in whom a clear diagnosis of IGE could be made. 78 individuals were first-degree relatives of the proband while 66 were more distant relatives. In 32 additional individuals a history of seizures was reported by the family but detailed diagnostic data were not available. These individuals were excluded from the study. The mean number of affected individuals with IGE per family was three (range 2–9).

Distribution of clinical forms of IGE in relatives of probands

Approximately one-third of relatives had the same syndrome as the proband (CAE probands—34%; JME probands—37%; IGE-TCS probands—36%). The only exception was JAE probands where only 10% of relatives had JAE. The frequency of alternate syndromes is shown in Table 1. 16–22.5% of relatives of a proband with one of the absence syndromes had juvenile myoclonic epilepsy. Conversely, 27% of relatives of probands with JME had an absence syndrome. Localization-related epilepsy was found in 4.9% of relatives overall. In terms of seizure types, the percentage of relatives who displayed the exact constellation of seizure types as the proband was 15%. The frequency of the various seizure types in relatives is shown in Table 2.

Concordance of IGE subtype

The results of concordance analysis for IGE subtype and seizure type are shown in Table 3 and Table 4. The number of families included in each analysis, the observed number of concordant families, the expected number of concordant families, the standard error of the difference, and the associated *p*-value are recorded. In an analysis including all IGE syndromes (CAE vs JAE vs JME vs IGE-TCS), the number of concordant families was significantly greater than expected by chance. Further analysis also showed significantly more families concordant for JME than expected, when compared to the two absence epilepsy syndromes, JAE and CAE,

combined. These results remain significant after Bonferroni correction for multiple tests. The number of families concordant for IGE-TCS (as opposed to CAE or JAE or JME combined) did not exceed that expected by chance. In an analysis restricted to families containing two or more individuals with the absence epilepsy syndromes (CAE and JAE), the number of families concordant for CAE vs JAE was greater than expected (suggesting some distinct genetic influence on these two syndromes), although the p -value ($p = 0.02$) did not survive Bonferroni correction for multiple tests.

Concordance of seizure type

The number of families concordant for either myoclonic seizures, absence seizures or both was significantly greater than expected by chance. This remained significant after excluding individuals who had both seizure types, suggesting independent genetic effects on absence and myoclonus. The number of families concordant for generalized tonic—clonic seizures approached but did not reach significance ($p = 0.07$). The borderline significant effect was restricted to the families with absence syndromes (number of concordant families: observed 12 vs expected 8.3, $p = 0.06$), suggesting that there may be independent genetic effects on absence syndromes with tonic—clonic seizures and absence syndromes without.

Concordance of EEG features

There was no evidence of significant clustering within families of either the pattern of EEG abnormality or the presence of photosensitivity (Table 5).

Concordance of age of onset

The proportional hazards regression model gave an estimated regression coefficient for the kernel function ($\beta = 0.908$) with standard error (S.E. = 0.264) and associated p -value <0.001 . This result provides highly significant evidence of familial aggregation of age-at-onset.

Discussion

Using a different population cohort we have confirmed some previous findings of concordance studies that there are independent genetic effects on the type of IGE syndrome and the seizure type. Unlike previous reports we included the syndrome of IGE-TCS in the analysis which does not appear to cluster significantly in families. We also present a number of novel findings. We examined EEG features for the first time in this type of analysis. These did not appear to cluster significantly within families. However, EEG features are susceptible to both physiological and interpreter variables, making these analyses the least reliable. Finally, concordance of age at which the disorder begins was significantly greater than expected by chance although, as syndromes are defined to a certain extent by age-at-onset this finding may be partially explained by the concordance shown for syndrome subtype. What is perhaps of most interest is that we put these findings in the context of the actual distribution of phenotypic features in the affected relatives of probands with IGE which allows us to see that despite the significant concordance findings, there is a large degree of phenotypic heterogeneity within families with IGE.

In fact what we see is a substantial number of families who broadly share the same phenotype while others appear to have a range of different phenotypes. One possible interpretation of our findings, based on a possibly simplistic monogenic model, is that certain variants may predispose to a relatively narrow clinical phenotype while others result in a much more varied phenotype. This hypothesis is supported by previous findings on monogenic IGE syndromes in which mutations have been identified. For example, certain mutations in *GABRA1* and *EFHC1*, appear to be associated with a relatively homogenous IGE phenotype (JME) (Cossette et al., 2002; Suzuki et al., 2004). In contrast, mutations in *SCN1A* can result in a combination

of febrile seizures, generalized and focal epilepsy (Escayg et al., 2000). Similarly, linkage studies have identified loci linked with specific IGE subtypes (Greenberg et al., 1988; Liu et al., 1996) and others loci linked to cohorts with a variety of IGE syndromes (Sander et al., 2000c; Kinirons et al., 2008). Under a more complex model, these findings could reflect the possibility that individuals within some families may possess additional genetic variants which influence phenotypic expression, a hypothesis previously suggested by Durner et al. (2001).

While our concordance data was similar to previous analyses, the one possible exception was a suggestion (albeit non-significant after adjusting for multiple comparisons) that JAE and CAE clustered separately in families suggesting distinct genetic effects on the two syndromes. Previous analyses suggested a shared genetic influence on these two syndromes (Winawer et al., 2003, 2005). It should be noted in both datasets the total number of families used for this analysis was small. However a recent report suggesting a different genetic mechanism for both syndromes may be in keeping with our findings (Strug et al., 2006). We also found less significant clustering of GTCs in our families than in those of (Winawer et al. 2005). However, the clustering of GTCs in that study was most evident in the absence syndromes, in agreement with our observations. In addition, the distribution of phenotypes among relatives with IGE showed some differences from previous studies. We found a higher percentage IGE-TCS in relatives of probands with IGE-TCS (36%) than the 13% reported by (Marini et al. 2004), although our figure is similar to that reported by the Italian ILAE group (ILAE genetic collaborative group, 1993). We found a higher percentage of patients with JME among relatives of probands with absence epilepsy (19%) and vice versa (26%), than that reported by either of these groups, although our figures are similar to those reported in a German population (Beck-Mannagetta and Janz, 1991). While some of these variations between studies may be due in part to differences in syndrome classification between clinicians as well as possible ascertainment bias, they may also reflect variable prevalence of predisposing variants with different effects among distinct populations. This possibility has also been suggested by a recent large-scale association study involving different populations (Cavalleri et al., 2007).

Based on these findings, what are the implications for future genetic studies in IGE? It is possible that in a typical association study of CAE, for example, the cohort under study may include individuals with genetic variants predisposing specifically to CAE with GTCs, to CAE without GTCs as well as variants predisposing non-specifically to different IGE subtypes including CAE. If one then takes into account the likely genetic heterogeneity contributing to each of these different scenarios and the potentially modest effect of these variants, it becomes apparent why there has been relatively little success with the current approach.

Certain steps could be taken to try and improve the current situation. Given that the proportion of individuals with IGE who have affected relatives appears to be high (Marini et al., 2003; Jayalakshmi et al., 2006), one option is to concentrate on families that have phenotypic data available on more than one affected member. This would allow a greater understanding of the phenotypic effect of the pre-disposing genetic variant within that family. This effect can often be difficult to predict when faced with an isolated individual in the clinical setting. Using the CAE example again, one could then select families who appear to have a variant predisposing to 'pure' CAE. One could further refine the families of interest by selecting those with CAE with or without tonic-clonic seizures. Selection of an affected individual from each of these families could then make up the study cohort for an association study. Similarly for linkage studies using multiple small families it would be appropriate to select families in which all, or at least the majority, of individuals have the same IGE subtype and then further refine the families with similar seizure types and age-at-onset. Durner et al. attempted to do this in their IGE cohort by examining the seizure types in relatives of their probands. Although a relatively small number of affected relatives were available (53 relatives of 91 probands), this allowed them to stratify the families somewhat for the dominant seizure type. Using this method they

were able to successfully identify several linkage signals for specific seizure types. While this strategy would cut down on the numbers from any one center, substantial cohort sizes could be achieved through collaboration between multiple centers and would have the benefit of increased power. Further success may be achieved by concentrating on founder populations, in which the degree of genetic heterogeneity is likely to be less. Most importantly detailed description of the phenotypes used when publishing results of any study on the genetics of IGE will allow better interpretation of results and clearer comparisons between replication studies.

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Table 1

Epilepsy syndromes in relatives of probands

Epilepsy syndrome in relatives	Proband Epilepsy Syndrome (no. of probands, <i>N</i> %)			
	CAE probands (<i>N</i> = 22)	JAE probands (<i>N</i> = 15)	JME probands (<i>N</i> = 20)	IGE-TCS probands (<i>N</i> = 13)
CAE	13(34.2)	5(12.5)	6(16)	6(21)
JAE	0(0)	4(10.5)	4(11)	1(4)
JME	6(16)	9(22.5)	15(39)	4(14)
IGE-TCS	12(32)	15(37.5)	11(29)	10(36)
IGE-NS	5(13)	4(10)	1(2)	4(14)
Partial epilepsy	2(5)	1(2.5)	1(2)	3(11)

CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; IGE-TCS, IGE with tonic—clonic seizures only. *N*, number of individuals.

Table 2

Seizure types in relatives of probands

Seizure types in relatives	Proband Epilepsy Syndrome (no. of probands, <i>N</i> %)			
	CAE probands (<i>N</i> = 22)	JAE probands (<i>N</i> = 15)	CAE probands (<i>N</i> = 22)	IGE-TCS probands (<i>N</i> = 13)
Absence	18(47)	13(32.5)	13(34)	9(32)
Myoclonic	6(16)	12(30)	16(42)	4(14)
Tonic—clonic	24(63)	30(75)	30(79)	17(61)

CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; IGE-TCS, IGE with tonic—clonic seizures only. *N*, number of individuals.

Table 3

Concordance analysis of IGE subtype

Analysis	N	Observed	Expected	S.D.	p-Value
CAE vs JAE vs JME vs IGE-TCS	63	22	10.7	2.8	<0.001
JME vs (JAE or CAE)	38	25	15	2.7	<0.001
CAE vs JAE	21	16	10.9	1.9	0.02
IGS-TCS vs (CAE or JAE or JME)	36	17	13.4	2.8	0.115

N, number of families included in each analysis; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; IGE-TCS, IGE with tonic clonic seizures only.

Table 4

Concordance analysis of seizure type

Analysis	N	Observed	Expected	S.D.	p-Value
MYO vs ABS vs MYO + ABS	43	21	12.6	2.6	<0.001
MYO vs ABS	43	27	20.5	2.2	0.005
GTC vs no GTC	70	36	30.4	3.7	0.07
GTC vs no GTC, JME only	16	9	8.3	1.6	0.465
GTC vs no GTC, JAE only	5	3	3.3	0.7	1
GTC vs no GTC, CAE only	16	10	7.7	1.9	0.175
GTC vs no GTC, JAE or CAE only	21	12	8.3	2.3	0.06

N, number of families included in each analysis; MYO, myoclonic seizures; ABS, absence seizures; GTC, generalized tonic-clonic seizures.

Table 5

Concordance analysis of EEG features

Analysis	N	Observed	Expected	S.D.	p-Value
3/s GSW vs >3.5/s GSW vs PSW	36	17	14.3	2.3	0.164
(3/s GSW or >3.5/s GSW vs PSW	36	24	28.9	2.1	1.000
3/s GSW vs >3.5/s GSW	33	18	14.7	2.1	0.090
3/s GSW vs PSW	25	20	18.8	0.9	0.220
Photosensitivity vs no photosensitivity	65	41	37.7	2.2	0.105

N, number of families included in each analysis 3/s GSW = 2.5—3.5 Hz generalized spike and wave; >3.5/s GSW = >3.5 Hz generalized spike and wave; PSW, generalized polyspike and wave.