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Importance of genetic factors in the occurrence of epilepsy syndrome type: A twin study

Linda A. Corey[1], **John M. Pellock**[2], **Marianne J. Kjeldsen**[3], and **Karl Otto Nakken**[4]

[1]Department of Human and Molecular Genetics, Virginia Commonwealth University, P.O. Box 980033, Richmond, VA. 23298-0033. corey@vcu.edu, Fax: +804 8271124

[2]Departments of Neurology and Pediatrics, Virginia Commonwealth University, P.O. Box 980599, Richmond, VA. 23298-0599 jpellock@mcvh-vcu.edu, Fax: +804 828 6690

[3]Department of Neurology, Odense University Hospital, 29 Sdr. BLVD, DK-5000, Odense C, Denmark. marianne.juel.kjeldsen@ouh.regionsyddanmark.dk, Fax; + 47 23 40 82 52

[4]National Center for Epilepsy, GF Henriksen vei 23, P.O. ox 53 N-1306 Baerum posterminal, Norway. Karl.Otto.Nakken@epilepsy.no, Fax: +47 67 54 04 96

Summary

Although there is strong evidence that genetic factors contribute to risk for epilepsy, their role in the determination of syndrome type is less clear. This study was undertaken to address this question. Information related to epilepsy was obtained from twins included in 455 monozygotic and 868 dizygotic pairs ascertained from population-based twin registries in Denmark, Norway and the United States. Syndrome type was determined based on medical record information and detailed clinical interviews and classified using the International Classification Systems for the Epilepsies and Epileptic Syndromes. Concordance rates were significantly increased in monozygotic versus dizygotic pairs for all major syndrome groups except localization-related cryptogenic epilepsy. Among generalized epilepsies, genetic factors were found to play an important role in the determination of childhood absence, juvenile absence, juvenile myoclonic, and idiopathic generalized epilepsy; and to a lesser degree for epilepsies with grand mal seizures on awakening. Among localization-related epilepsies, genetic factors contributed to risk for localization-related idiopathic and symptomatic syndromes overall, but did not appear to play an important role in determining risk for frontal, occipital or temporal lobe epilepsy. These results suggest that, while genetic factors contribute to risk for major syndrome types, determined when possible, their contribution to risk for localization-related syndrome sub-types, as defined by specific focality, may be modest.

Keywords

epilepsy syndrome type; twins; genetics

1. Introduction

Epilepsy is an etiologically heterogeneous disorder that is characterized by a wide range of clinical phenotypes. It has been recognized that risk for seizures appears to aggregate in families. Further, the identification of gene mutations that are responsible for the development of specific syndromes (summarized by Gurnett & Hedera, 2007 and Helbig et al., 2008), has provided compelling evidence that genetic factors play a major role in determining risk for seizures/epilepsy. However, the epileptic syndromes for which causal mutations have been identified have largely been those that are inherited in a Mendelian fashion. Since monogenic epilepsy syndromes appear to account for a very small proportion of cases, the degree to which genetic factors contribute to risk for the occurrence of the more common epilepsies remains to be clarified.

Twin studies provide an efficient tool for determining the degree to which genetic and environmental factors contribute to risk for the occurrence of disease. Previous twin studies have shown higher concordance rates for epilepsy in MZ compared to DZ twin pairs (Lennox, 1951, Inouye, 1960, Harvald & Hauge, 1965, Tsuboi, 1980, Corey, et al., 1991, Berkovic, 1998, Kjeldsen, et al., 2003). The results of the previous twin studies of epilepsy have been difficult to compare because of differences in methods of ascertainment, study population characteristics, epilepsy definition and the methods used in data analysis. Concordance rates for epilepsy in hospital or referral studies have generally been higher than those in population-based samples. Since most studies were performed prior to the implementation of the International Classification Systems for Epileptic Seizures (Commission on Classification, International League Against Epilepsy (ILAE), 1981) and for the Epilepsies and Epileptic Syndromes (Commission on Classification, ILAE, 1989) and involved relatively small samples, they focused upon epilepsy in general and did not examine specific epilepsy syndromes. Except for two studies, sample sizes have been too small to support the estimation of MZ and DZ concordance rates for specific epilepsy syndrome subtypes. In these two studies, (Berkovic et al., 1998, Kjeldsen et al., 2003), it was only possible to estimate concordance rates for major syndrome type.

The goal of this study was to examine the role of genetic and environmental factors in the occurrence of epilepsy in a large unselected sample of monozygotic and dizygotic twins who were ascertained from population-based twin registries in the United States, Norway and Denmark. It was designed to determine if the role that genetic factors play in determining risk for epilepsy differs between epilepsy syndrome types. Information of this type will be extremely useful in the search for epilepsy susceptibility genes.

2. Materials and Methods

2.1 Clinical methods

Twins included in the population-based Danish (DTR), Norwegian (NTR) and Mid-Atlantic (MATR) twin registries were screened for history of seizures by mailed questionnaire or telephone interview as part of a baseline survey carried out by each twin registry that collected information on a wide variety of health problems. None of the initial surveys focused specifically on history of seizures. Questions related to history of seizures in the Norwegian and Danish questionnaires were direct translations of those used by the MATR. Among twins identified from vital records, 34% of MATR twins, 79.9% of Norwegian and 88.6% of Danish twins could be traced. Information on health history, including history of seizures, was provided by 82,342 twins included in 47,626 twin pairs (45.6% (MATR), 80.6% (NTR), and 90.9% (DTR) of twins contacted, respectively). The results of the questionnaire survey are described in greater detail elsewhere (Kjeldsen, et al., 2005). Twins who reported a history of epilepsy, febrile seizures, other seizures or staring spells in survey

were then contacted by telephone using a standard protocol to verify the initial report of seizures. Of the 6,234 twin pairs where at least one pair member reported a history of seizures of some type, 32% were not included in this study either because they were lost to follow-up (death or additional efforts to trace the twin were required) or because the rate of false positives among those reporting a history of staring spells. A standardized telephone interview was used as an initial screen for likely seizure cases among twins who reported a history of seizures of some type in the general health history survey. In the US and Norwegian samples, twins were asked to report on the seizure history of their co-twins. In cases (US and Norway) where an unaffected twin reported a history of seizures in their co-twin, the unaffected twin was contacted to verify the information prior to contacting the affected co-twin. This procedure was followed in cases where only one twin responded to the questionnaire. In those cases where only one Danish twin completed the questionnaire survey, the co-twin who did not respond was contacted by telephone to determine their seizure history status only in those pairs where the twin completing the questionnaire reported a positive history of seizures. For 24.7% of the twins contacted, previously reported seizures were found to be a mistake, another medical condition or the twin did not wish to participate in the study. This resulted in a total of 1,606 twins included in 1,367 pairs whose medical history, based upon the results of the telephone interview, was consistent with previous seizures and were available for study. These twins underwent a standardized study protocol that included a detailed clinical interview, medical record review and the provision of a blood sample for zygosity determination. Unaffected co-twins also underwent a standardized study protocol that included verification of unaffected status, an interview to obtain detailed information pertinent to any instances where they observed seizures in their co-twin and the provision of a blood sample for zygosity determination. Upon completion of the standardized study protocol, 1,578 twins included in 1,344 pairs were found to have a verified history of seizures. The results presented herein are based upon these twin pairs.

The study protocol was approved by the Virginia Commonwealth University Institutional Review Board, the Danish National and Regional Ethics Committees and the Norwegian Regional Ethics Committee. All subjects provided informed consent before participating in the study.

Seizure cases were validated using medical records, where available, and information obtained from detailed clinical interviews of the affected twin and any family members who had directly observed an event by epileptologists at each study site (Denmark, Norway and Virginia) who were blinded to zygosity, pair membership or case status of the co-twin. Seizure and epilepsy syndrome types were classified according to the ILAE classification systems for seizures (Commission on Classification, ILAE, 1981) and syndromes (Commission on Classification, ILAE, 1989) using a protocol that was standardized across sites. The major epilepsy syndrome groups included localization-related (major subtypes: idiopathic, symptomatic, cryptogenic), generalized (major subtypes: idiopathic, cryptogenic, symptomatic-nonspecific etiology, symptomatic-specific syndromes), undetermined (with both generalized and focal features, without both generalized and focal features) and special syndromes or situation-related seizures (febrile convulsions, isolated seizures or status epilepticus, seizures occurring only when there is an acute or toxic event), Major subtypes were then further sub-divided into specific epilepsy syndromes. Epilepsy type was classified in a given individual only to the extent that the available data clearly supported a specific syndrome type. When available information was not adequate so as to permit a case to be classified as belonging to a specific epilepsy syndrome subtype, a less specific syndrome type was used, e.g. if available information was inadequate to permit a case to be diagnosed as localization-related (now proposed to be termed focal) symptomatic, but adequate to permit the case to be diagnosed as localization-related, the case was classified simply as localization-related. Where it was possible to determine that a twin definitely had had

epilepsy but it was not possible to determine the type of epilepsy that the individual had based on available information, epilepsy syndrome type was classified as undetermined and not sub-typed with regard to whether or not seizures had generalized or focal features. In cases where it was not possible to document with any certainty that a co-twin had a seizure, the co-twin was considered to be unaffected. In reviewing the total population, those who had epilepsy more recently had a better semiology of seizures along with imaging and EEG. For, those twins who had epilepsy prior to 1970, imaging was not generally available. Therefore, classification was based upon clinical history. The methods used to classify epilepsy type were reviewed on an annual basis by all involved with classification, as were cases where epilepsy syndrome type diagnosis was less than straightforward based upon available information. Information on the validation procedure used in this study is provided in greater detail elsewhere (Corey et al., 2009).

This study is limited to those twins where the epileptologists responsible for syndrome classification were confident that the affected twin did, in fact, have a history of epilepsy. In cases where one pair member could be documented as having a history of epilepsy and the co-twin had a history of something, but it was unclear whether they had ever had epileptic seizures, the co-twin was assumed to be unaffected. For the purposes of this study, twins with a history of febrile seizures but no history of afebrile seizures were included in the febrile seizure group. Twins with a verified history of both febrile and afebrile seizures were considered to have an epileptic rather than a special syndrome. A twin pair that was concordant for epilepsy but discordant for epilepsy syndrome type was treated as two discordant pairs in analyses involving epilepsy syndrome types.

Zygosity was assigned using six DNA markers, giving a probability of correct assignment of >99.9% (Derom, 1985). Where it was not possible to obtain a DNA sample, zygosity was assigned on the basis of response to a series of questions which have been shown to accurately assign zygosity in greater than 97% of cases (Magnus, 1983). In a small number of cases (31 twins included in 26 pairs), the co-twin of a case was deceased or was unwilling to provide a DNA sample. These cases were excluded from the analyses.

2.2 Statistical Methods

Pairwise concordance rates were estimated as ½ (c +w)/ (½(c + w) + d) where c equals the number of doubly ascertained concordant pairs, w, the number of singly ascertained concordant pairs and d the number of discordant pairs (Allen et al., 1967). Twin pairs were considered to be doubly ascertained if both pair members completed and returned a health survey questionnaire and both members of the pair reported that they, themselves, had a history of seizures of some type or both twins returned a health survey questionnaire and each reported their co-twin have had at least one seizure. Differences in overall rates of concordance between populations were assessed using pairwise rates.

Probandwise concordance rates, which estimate the prevalence of epilepsy among twin siblings of probands, were used to quantify the degree of concordance for epilepsy syndrome type in MZ and DZ twin pairs. This rate is estimated as $[2c_2 + c_1]/ [2c_2 + c_1 + d]$, where c_1 is the number of singly ascertained concordant twin pairs, c_2 the number of doubly ascertained twin pairs and d the number of discordant pairs (Kendler & Eaves, 1985). All concordance rates are reported with 95% confidence intervals (CI). Since ascertainment of affected twins by questionnaire was not complete, either because both pair members failed to complete the health survey or an affected pair member failed to report a history of seizures, probandwise rather than casewise concordance rates were estimated. Probandwise concordance rates were not determined for some epilepsy syndrome subtypes due to insufficient sample size.

3. Results

A total of 1,993 twins included in 1,714 pairs ascertained from the MATR, NTR or DTR reported a history of seizures. Of these, it was possible to assign twin zygosity, verify history of seizures and classify epilepsy syndrome type in 1,547 twins included in 1,323 (455 MZ, 868 DZ) pairs. Significant differences ($p<0.001$) were found between populations in the ability to assign an epilepsy syndrome type, in 2/805 (DTR), 6/356 (NTR) and 83/417 (MATR) cases of verified epilepsy, epilepsy syndrome type had to be classified as undetermined based upon available information. As shown in Table 1, 56% of twins included in this sample had situation-related seizures, but not epilepsy. Of these, 88.1% were febrile seizures. Among those having epilepsy, 53.5% had a localization-related (now proposed to be termed focal) epilepsy, 27.2% had a generalized epilepsy, and 19.3% were classified as having an undetermined syndrome type. Cryptogenic localization-related epilepsies defined by seizure type and etiologic examinations accounted for the largest number of affected pairs (135 pairs), followed by those classified as temporal lobe epilepsy (TLE) whether or not cryptogenic (70 pairs) and juvenile myoclonic epilepsy (36 pairs).

Table 2 provides the pairwise and probandwise concordance rates for all pairs in which a history of seizures could be verified in at least one pair member, along with the 95% confidence intervals for each, for MZ and DZ pairs partitioned by ascertainment source. All observed concordance rates are significantly greater than zero. While the pairwise rates observed for MZ and DZ twins do not differ significantly between populations, the probandwise rates observed for Danish twins are significantly increased compared to those observed for MATR ($p<0.01$) and Norwegian DZ pairs ($p<0.05$).

Pairwise and probandwise concordance rates with their 95% confidence intervals observed in MZ and DZ pairs partitioned by verified history of epilepsy, irrespective of epilepsy syndrome type, febrile seizures or other situation-related seizures are shown in Table 3. With the exception of situation-related seizures unrelated to fever, all MZ and DZ concordance rates are significantly greater than zero and rates observed for MZ pairs are significantly increased over those observed for DZ pairs ($p<0.0001$).

Table 4 provides the probandwise concordance rates for MZ and DZ twin pairs partitioned by major epilepsy syndrome subtype, along with the results of tests of the difference in observed concordance rates in MZ versus DZ pairs for epilepsy syndrome sub-types. Concordance rates for localization-related and generalized epilepsy syndromes, overall, were significantly greater than zero in both MZ and DZ pairs with generalized idiopathic epilepsy being characterized by the highest rates observed in this sample in both MZ and DZ twins. Although the lower bounds of the 95% confidence intervals for the concordance rates observed for the undetermined syndrome group in MZ pairs do not overlap with zero, DZ rates are low and are not significantly different from zero.

When epilepsy syndrome subtypes are further subdivided, concordance rates that were significantly greater than zero were observed for localization-related idiopathic, localization-related symptomatic and generalized cryptogenic epilepsy syndromes in MZ twins and localization-related cryptogenic epilepsy in DZ twins. While the available sample was relatively large compared to previous studies that have examined twin concordance for epilepsy subtype (Berkovic et al., 1998, Kjeldsen et al., 2003), it was not large enough to examine twin concordance for each of the epilepsy subtypes classified by more specific localization (e.g., frontal, occipital) included in the ILAE classification system (Commission on Classification, ILAE, 1989) with great precision. Further as major epilepsy syndrome types were further subdivided, the number of concordant pairs within a given sub-type decreased. Many of the cases classified as undetermined were suspected to be focal in

nature, however, adequate information was not available to permit their classification as such. As shown in Table 5, although the number of concordant pairs for localization-related syndromes was reduced compared to that observed for generalized epilepsies, concordant pairs were observed for TLE, other localization-related idiopathic, parietal, undetermined localization-related and cryptogenic defined by seizure type. There were no concordant twin pairs among those containing members with verified epilepsies classified as either symptomatic – nonspecific etiology or symptomatic – specific syndromes. Among those with undetermined epilepsies who had both generalized and focal seizures and those with undetermined epilepsies without unequivocal generalized or focal features, the single concordant twin pair observed in each case was MZ.

4. Discussion

This study is the largest to date to have used ILAE criteria for epileptic syndromes to classify syndrome type in twin pairs containing members with a verified history of epilepsy. Although a standardized protocol was used to assign epilepsy syndrome type across populations, significant differences were observed in the proportion of verified epilepsy cases receiving a classification of undetermined between populations. Differences in the age distribution of subjects ascertained from the DTR compared to the NTR and MATR and the availability of medical record information that is afforded by nationalized medical systems that have been in existence in Norway and Denmark for decades, and are not available in the United States are a likely explanation for these discrepancies.

The pattern observed in the distribution of localization-related, generalized and undetermined epilepsies among cases in this sample is consistent with that observed in French (Picot et al., 2008), Swedish (Forsgren, 1992) and Finnish (Keränen et al., 1989) samples. Although the frequency of generalized epilepsies in this sample did not differ from that reported by Picot et al. (2008) (27.2% vs 30.8%), fewer localization-related epilepsies (53.4% vs 63.6%) were observed. The reduced frequency of localization-related epilepsies is likely to be a result of the way in which cases were ascertained and the age of the sample. It is unlikely, however, that the differences in frequency observed are due to the fact that these subjects are twins. Many of the twins included in this study have been seizure free for many years and in a number of cases, while it was possible to verify that they, in fact, had epilepsy, it was not possible to assign syndrome type on the basis of available information. This is reflected in the fact that in 19.3% of cases, it was not possible to determine epilepsy syndrome type on the basis of available information. Given that the frequency of localization-related syndromes appears to have been more greatly impacted than generalized epilepsy syndromes, it suggests that localization-related epilepsies may be more difficult to identify using what is often incomplete retrospective information.

Although there were no significant differences in the pairwise concordance rates observed for MZ and DZ twins across populations, probandwise concordance rates were increased in the Danish sample. Estimates of probandwise concordance rates are very sensitive to whether or not the members of a concordantly affected pair are ascertained independently. Therefore, rather than representing true differences in probandwise concordance rates in Danish versus US and Norwegian twins, the differences observed are more likely to be a function of differences in the questionnaire response rates and case ascertainment between populations. The US sample included the largest number of twin pairs where only one pair member responded to the survey. The Danish sample was the smallest. Further, while it was possible to include queries about history of seizures in a co-twin in the US and Norwegian surveys, the Danish Ethics Committee limited questionnaire queries about history of seizures to the respondent alone. Thus, in addition to the Danish sample containing a larger number of concordant pairs in which both pair members reported a history of seizures and

were therefore independently ascertained, it included fewer discordant pairs. This is because discordant pairs, where the responding twin was unaffected, would not have been included in the study. This was not the case for the US and Norwegian samples since affected twins who either did not return a questionnaire survey or returned a survey but did not report a history of seizures were identified through survey information provided by their co-twin.

As expected, genetic factors were found to play an important role in determining risk for seizures overall and for both epilepsy and febrile seizures as reflected in the significantly increased probandwise concordance rates observed for MZ compared to DZ twins ($p<0.0001$). Genetic factors also appear to play an important role in the occurrence of both localization-related and generalized epilepsies overall given that both MZ and DZ concordance rates are significantly greater than zero and concordance rates observed for MZ pairs are significantly greater than those observed for DZ pairs. These results are in agreement with those of Berkovic et al. (1998), both with regard to the importance of genetic factors and with regard to the large number of pairs who were concordant for major epilepsy syndrome type. However, the number of twin pairs who were concordant for type, deceased as major syndrome type was increasingly subdivided. In fact, among pairs who were concordant for epilepsy 13/59 MZ (22%) and 20/29 DZ (69%) pairs were discordant for epilepsy syndrome subtype. Further, among those who were concordant for epilepsy but discordant for epilepsy syndrome type and both members of the twin pair could be classified as having either a localization-related or generalized epilepsy syndrome, 3/10 MZ and 3/14 DZ pairs were discordant for major epilepsy syndrome type, e.g. in twin A, the epilepsy syndrome was localization-related while in twin B it was generalized. These results are consistent with those reported by Kinirons et al (2008) who examined concordance for epilepsy phenotype in families with IGE and found that only one third of relatives had the same syndrome and suggest that in some cases, genetic influences may not specifically predispose to either a localization-related or generalized epilepsy as has been suggested by Winawer, et al (2003a, 2003b, 2005) but rather could predispose to epilepsy in general with syndrome type being determined by interaction(s) with genetic background, epigenetic factors or environmental exposures. Our results, taken in the context of current understanding of the role of genetic influences on the determination of epilepsy syndrome phenotype do not negate previous findings by Winawer, et al (2003a, 2003b, 2005), but rather provide further evidence of heterogeneity with regard to the genetic determinants of epilepsy syndrome type.

Not surprisingly, genetic factors were found to play an important role in the determination of risk for idiopathic generalized epilepsy overall as well as for the childhood absence, juvenile absence, juvenile myoclonic subtypes. Genetic factors also appear to play a role, but to a lesser degree, in determining risk for epilepsies with grand mal seizures on awakening and cryptogenic generalized epilepsies, overall. Sample sizes were too small to assess the contribution of genetic factors to the occurrence of West syndrome, Lennox Gastaut syndrome or symptomatic epilepsies that are either of non-specific etiology or related to a specific syndrome. However, it should be noted that, with the exception of a single MZ pair with early myoclonic encephalopathy, all twin pairs with these syndromes in this sample were dizygotic and discordant.

Risk for a localization-related epilepsy (idiopathic, symptomatic and cryptogenic) was significantly increased in MZ co-twins of affected individuals over that expected by chance ($p<0.0001$); suggesting that genetic factors play an important role in determining susceptibility for syndromes where genetic factors have generally been thought to play little role. Although it has been suggested that genetic factors contribute to risk for temporal lobe epilepsy, only two of the 70 TLE (1 of 26 MZ and 1 of 44 DZ) pairs included in this study were found to be concordant for TLE. Based upon these results, it would seem that genetic

factors do not appear to play a major role in the occurrence of TLE. Given the size of this sample; it is unlikely that this result is a function of a reduced sample size. Our finding that only 2 of 70 twin pairs where the clinical history of epilepsy was consistent with TLE were concordant was unexpected, given that the results of Berkovic et al. (1996) and Crompton et al (2010) have suggested that familial TLE is a common disorder. It should be noted that the characteristics of the samples upon which these studies were based with regard to their population based nature are quite different and therefore differences in the results obtained are not unexpected. It is possible that cases of familial TLE in this sample were missed. However, the prevalence of familial TLE in the general population is unknown and would have to be high in order to be easily detectable in a sample ascertained by our methods rather than a clinic based population. Further, although this sample is the largest assembled to date, we would be the first to admit that epilepsy is difficult to classify retrospectively. It is also possible that, because the symptoms of familial TLE may be rather subtle, pairs with this disorder fell into the group that had a symptomatic epilepsy but the specific type could not be determined based upon available information. However, the co-twins of 21/26 MZ and 39/44 DZ twins with a history of TLE, had no history of seizures of any kind. It is also possible that the two twin pairs who were concordant for TLE represent those with hippocampal sclerosis whether congenital (Moore et al., 1999), or familial (Fernandez et al., 1998) or acquired as is often seen in conjunction with TLE (Chang & Lowenstein, 2003) even though recent findings that individuals with familial hippocampal abnormalities may not present with epilepsy could argue against this explanation (Secolin et al, 2010).

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Table 1

Distribution of epilepsy syndromes in overall study sample

Localization – related	371 (23.5%)
Idiopathic	23 (6.2%)
Symptomatic	180 (48.5%)
Cryptogenic	162 (43.7%)
Undetermined	6 (1.6%)
Generalized	189 (12.0%)
Idiopathic	166 (87.7%)
Cryptogenic	17 (9.0%)
Symptomatic – Non specific etiology	2 (1.1%)
Symptomatic – Specific syndrome	2 (1.1%)
Undetermined	2 (1.1%)
Undetermined	134 (8.5%)
With both generalized/focal features	12 (9.0%)
W/o unequivocal gen/focal features	31 (23.1%)
Undetermined	91 (67.9%)
Special Syndromes	884 (56.0%)
Febrile seizures alone	779 (88.1%)
Other situation-related seizures	105 (11.9%)

Table 2

Concordance rates for verified history of seizures in MZ and DZ pairs partitioned by ascertainment source

	MZ			DZ		
	Pairs	**Pairwise**	**Probandwise**	**Pairs**	**Pairwise**	**Probandwise**
DTR	206	0.21 0.15<cr<0.27[f]	0.46 0.40<cr<0.52	456	0.07 0.04<cr<0.09	0.18 0.15<cr<0.22
MATR	131	0.16 0.09<cr<0.23	0.36 0.29<cr<0.1144	220	0.03 0.01<cr<0.06	0.07 0.04<cr<0.10
NTR	118	0.16 0.09<cr<0.23	0.42 0.34<cr<0.50	192	0.03 0.01<cr<0.04	0.10 0.06<cr<0.14
Total	455	0.18 0.14<cr<0.22	0.43 0.39<cr<0.47	865	0.05 0.04<cr<0.06	0.14 0.12<cr<0.16

[f]Denotes the 95% confidence interval for the concordance rate

Table 3

Concordance rates for epilepsy, febrile seizures and other special syndromes combined over samples

	MZ			DZ			
	Pairs	**Pairwise**	**Probandwise**	**Pairs**	**Pairwise**	**Probandwise**	**MZ vs DZ**[ff]
Epilepsy	203	0.16 0.11<cr<0.21[f]	0.39 0.33<cr<0.45	395	0.02 0.01<cr<0.04	0.07 0.05<cr<0.10	p<0.0001
Febrile Seizures	234	0.17 0.12<cr<0.23	0.41 0.36<cr<0.47	425	0.05 0.03<cr<0.07	0.14 0.11<cr<0.17	p<0.0001
Other Situation-Related Seizures	31	0.02 −.03<cr<0.06	0.06 −.02<cr<0.15	71	0.01 −.01<cr<0.03	0.01 −.01<cr<0.04	ns

[f]Denotes the 95% confidence interval for the concordance rate (cr)

[ff]Test of difference between MZ and DZ probandwise concordance rates

Table 4

Probandwise concordance rates for epilepsy syndrome types in MZ and DZ pairs

	MZ		DZ		
Syndrome Type	**Pairs**	**Concordance Rate**	**Pairs**	**Concordance Rate**	**MZ>DZ[ff]**
Localization-related	109	0.21 0.14<cr<0.28[f]	232	0.04 0.02<cr<0.07	p<0.0001
Idiopathic	9	0.36 0.08<cr<0.65	12	0.00	p<0.02
Symptomatic	63	0.18 0.09<cr<0.27	104	0.01 −0.01<cr<0.03	p<0.0001
Temporal lobe	26	0.07 −0.03<cr<0.17	44	0.04 −0.02<cr<0.06	n.s.
Undetermined	8	0.40 0.10<cr<0.70	12	0.00	p<0.01
Cryptogenic	39	0.08 −0.01<cr<0.16	113	0.05 0.01<cr<0.09	n.s.
Defined by seizure type	35	0.08 −0.01<cr<0.17	100	0.06 0.01<cr<0.10	n.s.
Generalized	55	0.64 0.53<cr<0.74	98	0.09 0.03<cr<0.14	p<0.0001
Idiopathic	49	0.66 0.55<cr<0.77	82	0.10 0.04<cr<0.17	p<0.0001
Childhood absence	8	0.55 0.25<cr<0.84	20	0.10 −0.03<cr<0.22	p<0.01
Juvenile absence	5	0.89 0.68<cr<1.09	8	0.13 −0.10<cr<0.35	p<0.01
Juvenile myoclonic	13	0.53 0.29<cr<0.77	23	0.08 −0.03<cr<0.19	p<0.0001
Epilepsies with grand mal seizures on awakening	4	0.40 −0.03<cr<0.83	7	0.00	p<0.05
Other specific mode of action	5	0.75 0.45<cr<1.05	7	0.00	p<0.01
Undetermined	16	0.50 0.28<cr<0.72	18	0.11 −0.03<cr<0.24	p<0.01
Cryptogenic	3	0.20 −0.30<cr<0.70	12	0.00	p<0.01
Undetermined	44	0.26 0.13<cr<0.38	70	0.04 −0.00<cr<0.09	p<0.001

[f]Denotes the 95% confidence limits

[ff]Test of difference in probandwise concordant rates in MZ vs DZ twins

Table 5

Distribution of Concordant and Discordant Pairs by Epilepsy Syndrome Types

SYNDROME TYPE	MZ		DZ		
	Con	Dis	Con	Dis	Total
LOCALIZATION-RELATED					
Idiopathic (Primary)					
Benign childhood epilepsy with centro-temp spike	0	4	0	7	11
Childhood epilepsy with occipital paroxysms	0	1	0	1	2
Other localization related idiopathic	2	2	0	3	7
Idiopathic - undetermined	0	0	0	1	1
Symptomatic (Secondary)					
Temporal lobe epilepsies	1	25	1	43	70
Frontal lobe epilepsies	0	6	0	12	18
Parietal lobe epilepsies	1	0	0	5	6
Occipital lobe epilepsies	0	2	0	1	3
Other localization-related symptomatic	0	2	0	2	4
Localization-related symptomatic - type undetermined	2	6	0	12	20
Symptomatic - head trauma	0	4	0	8	12
Symptomatic - tumor	0	3	0	2	5
Symptomatic - infection	0	0	0	1	1
Symptomatic - stroke	0	2	0	3	5
Symptomatic - neurocutaneous disorder	1	0	0	0	1
Symptomatic - perinatal	1	7	0	13	21
Symptomatic - inherited metabolic disorder	0	1	0	1	2
Cryptogenic					
Cryptogenic defined by seizure type	2	33	4	96	135
Cryptogenic defined by clinical features	0	3	0	4	7
Cryptogenic defined by etiology	0	0	0	2	2
Cryptogenic defined by other	0	1	0	1	2
Cryptogenic - undefined	0	0	0	6	6
Localization- related - undetermined	0	2	0	4	6
GENERALIZED					

SYNDROME TYPE	MZ		DZ		
	Con	Dis	Con	Dis	Total
Idiopathic					
Benign neonatal familial convulsions	1	0	0	0	1
Benign neonatal convulsions	0	1	0	0	1
Childhood absence epilepsy (pyknolepsy)	3	5	1	19	28
Juvenile absence epilepsy	4	1	1	7	13
Juvenile myoclonic epilepsy (impulsive petit mal)	5	8	1	22	36
Epilepsies with grand mal seizures on awakening	1	3	0	7	11
Idiopathic other- specific mode of activation	3	2	0	7	12
Idiopathic undetermined	6	10	1	17	34
Cryptogenic					
West syndrome	0	0	0	4	4
Lennox Gastaut syndrome	0	0	0	6	6
Cryptogenic epilepsy with myoclonic-astatic seizures	0	0	0	2	2
Cryptogenic or symptomatic other	0	1	0	0	1
Cryptogenic or symptomatic - undetermined	1	1	0	0	2
SYMPTOMATIC - NONSPECIFIC ETIOLOGY					
Early myoclonic encephalopathy	0	1	0	0	1
Undetermined	0	0	0	1	1
SYMTOMATIC - SPECIFIC SYNDROMES					
Symptomatic - epileptic seizures with specific disease	0	0	0	2	2
UNDETERMINED EPILEPSIES					
With Both Generalized and Focal Seizures					
Neonatal seizures	0	1	0	0	1
Epilepsy w/continuous spike-waves during slow wave sleep	0	1	0	0	1
With both generalized and focal seizures - other	1	2	0	4	7
With both generalized and focal seizures - undetermined	0	1	0	1	2
Without Unequivocal General or Focal Features	1	14	0	15	30
Undetermined	7	16	2	49	74
SPECIAL SYNDROMES					
Febrile convulsions	69	166	40	385	660

SYNDROME TYPE	MZ		DZ		
	Con	Dis	Con	Dis	Total
Isolated seizures or isolated status epilepticus	1	17	0	39	57
Seizures occurring only when there is an acute or toxic event	0	13	0	29	42
Other special syndromes	0	0	0	5	5
TOTAL	113	368	51	849	1381