A Twin Study of Genetic Influences on Epilepsy Outcome

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The identification of genetic factors that confer susceptibility to the epilepsies has to date been the focus of genetic efforts in this field. Few studies have assessed the genetic contribution to disease course in epilepsy, yet an understanding of the genetic influences on epilepsy outcome is key to developing new therapeutic strategies. The aim of this study was to assess the genetic contributions to epilepsy outcome in twin pairs concordant for epilepsy. We studied 37 epilepsy concordant twin pairs (27 monozygotic, 10 dizygotic) in whom there were no recognized environmental contributions (e.g., acquired brain injury) to epilepsy, and in whom the most likely cause for epilepsy was a shared genetic susceptibility. Clinical outcome was determined using the binary measure of Seizure Status (seizure remission or recurrence) and on a six-category ordinal Outcome Scale. Epilepsy outcome was independent of age of seizure onset, age at assessment and major epilepsy syndrome diagnosis. The proportion of twin pairs concordant for Seizure Status was 0.81 (22/27) for monozygous and 1.0 (10/10) for dizygous pairs, $p = 0.3$. Within-pair correlation in outcome (Outcome Scale) was 0.60 (95% CI: 0.32, 0.78) in monozygous and 0.78 (0.48, 0.92) in dizygous pairs. These data provide no evidence for genetic influences on epilepsy outcome independent of those that contribute to disease susceptibility. The observed high correlations for outcome suggest that, for epilepsy, susceptibility genes also have a major influence on outcome.

Twin studies represent a powerful method to dissect inherited contributions to disease etiology and clinical expression. To date, the focus in epilepsy has been in explaining variation in susceptibility to the disease (Anderson et al., 1989; Berkovic et al., 1993; Berkovic et al., 1996; Berkovic et al., 1998; Corey et al., 1991; Kjeldsen et al., 2001; Lennox, 1951; Miller et al., 1998; Miller et al., 1999; Sillanpaa et al., 1991). Yet for someone developing the disease, a key question is whether or not their seizures will cease. Few studies have assessed the genetic contribution to disease course in epilepsy. The purpose of our study was to evaluate the role of genetic factors on clinical outcome of epilepsy using the twin method.

Epilepsy can be caused by a wide variety of conditions, varying from the purely genetic (simple Mendelian and polygenic modes of inheritance) to environmental (secondary to brain injury from infection, trauma, stroke etc.). This heterogeneity of epilepsy etiology contributes to a varied natural history that confounds the analysis of epilepsy outcomes. We address the problems posed by the heterogeneity of epilepsy etiology using a cohort of epilepsy concordant twin pairs in whom the most likely cause for their epilepsy was their shared genetic susceptibility. Such twin pairs provide a powerful resource to study the possibility of there being a genetic component to clinical outcome in epilepsy, and to test the hypothesis that outcome is influenced by genetic factors distinct from those that contribute susceptibility to the disease.

A further challenge to the study of epilepsy outcome concerns the measures used to assess it. Epilepsy outcome is much more heterogeneous than is reflected in the dichotomous measure of seizure status (recurrent seizures or in remission). It is a complex, relative concept constructed from the interaction of many separate but interrelated factors including the clinical impact of seizures (seizure burden), response to therapy (the chance that seizures are suppressed by medication) and ultimate prognosis (the chance of terminal remission of seizures; Sander, 1993). Whilst seizure status provides an unequivocal measure of epilepsy outcome, as a binary measure it may fail to make fine distinctions among people with epilepsy, thus limiting analytical power (Hobart et al., 2000). Because of a lack of suitable measures of long-term epilepsy outcome, we therefore sought to develop a measure that might provide greater discriminative value in the evaluation of the various epilepsy outcomes.

Participants and Methods

Study Population

The sample for this study was obtained from two community-based volunteer twin registers (La Trobe Twin Register and the Australian Twin Registry) and by referral. From over 500 twin pairs in whom one or both have epilepsy, we identified adult and pediatric monozgous (MZ) and dizygous (DZ) twin pairs concordant for

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epilepsy. Ethical approval was obtained from the hospital research ethics committee.

Clinical Evaluation

All twin pairs underwent a detailed clinical assessment using a standardized protocol that recorded age at seizure onset, seizure types, epilepsy syndrome, date of last seizure, evolution of epilepsy, response to medication, a clinical assessment of compliance and a review of all previous clinical data including EEG, neuroimaging and hospital records. Routine electroencephalography (EEG) and clinical examination were performed on all subjects. All twin pairs were assessed within 6 months of each other. Epilepsy was classified according to the "major epilepsy syndrome" categories of idiopathic generalized, symptomatic generalized, unclassified generalized, idiopathic partial, symptomatic partial, cryptogenic partial and unclassified epilepsy according to the system of classification recognized by the International League Against Epilepsy (Commission, 1989). By convention, the diagnosis of epilepsy was made only after the second unprovoked seizure and thus twin pairs with acute symptomatic seizures, febrile seizures and all neonatal seizure disorders were excluded from this study.

First, we assessed clinical outcome of epilepsy in terms of the binary trait of seizure remission or recurrence defined by the year preceding the date of clinical assessment (Seizure Status). No distinction between seizure types was made. Second, we assessed outcome using a novel Outcome Scale. It is well recognized that treatment decisions in epilepsy reflect clinical status of epilepsy and such observations form the basis of retention study methodology whereby the continuation (retention) of an anti-epileptic drug (AED) by a patient can be regarded as a composite measure of adverse events and efficacy over time (Wong et al., 1999). Moreover, treatment decisions also include the important subjective aspect of patient and physician perceptions of epilepsy severity. Thus mild epilepsy with infrequent simple partial or absence seizures may be accepted as not requiring treatment whereas unremitting complex partial or generalized tonic clonic seizures are usually treated with trials of different AEDs or combinations of multiple AEDs in an attempt to gain control. We reasoned that a scale incorporating treatment decisions with Seizure Status might better reflect relative epilepsy outcomes. As with Seizure Status, treatment decisions were defined by the year preceeding the date of clinical assessment. We did not distinguish between different AEDs except for an assessment of clinical appropriateness of each AED in order to prevent patients sub-optimally treated being classified erroneously. Monotherapy was defined as treatment with a single, clinically appropriate AED, and polytherapy as treatment with two or more clinically appropriate AEDs or multiple trials of different, appropriate AEDs. If a subject remitted on an AED, having previously had recurrent seizures on the same AED, by definition this was considered remission on treatment although the possibility of terminal remission of seizures could not be discounted. Using these operational criteria, patients could be assigned a point on the following six-category combined item ordinal scale of epilepsy outcome (Outcome Scale):

1. Terminal remission of seizures — untreated
2. Recurrent seizures — untreated
3. Remission of seizures on monotherapy
4. Recurrent seizures on monotherapy
5. Remission of seizures on polytherapy
6. Recurrent seizures on polytherapy

Study Design

To minimize the potential effects of environmental susceptibility on clinical outcome we included only those twin pairs who were both concordant for major epilepsy syndrome, and in whom no antecedent environmental factors (such as acquired brain injury) had been identified as contributing to the cause of their epilepsy. Note also that twin birth is not a risk factor for the development of epilepsy (Berkovic, 1993). Therefore, given that genetic factors influence susceptibility to epilepsy, and that these genetic factors are major syndrome-specific (Berkovic, 1998), all twins in this study are highly likely to have a shared inherited susceptibility to their epilepsy. The potential effects of environmental factors on epilepsy etiology have therefore been discounted. If a subject's epilepsy outcome is determined by genetic factors that are independent of those that confer susceptibility to the disease, syndrome concordant MZ pairs will be more similar for clinical outcome than syndrome concordant DZ pairs. Alternatively, if genetic factors that determine clinical outcome are attributed to genes that influence susceptibility to epilepsy, and none are independent, syndrome concordant MZ and DZ pairs will be equally highly correlated for clinical outcome. However, high correlation for clinical outcome that is independent of zygosity might also result from the influence of environmental factors unrelated to epilepsy susceptibility. These factors, such as being treated by the same physician or receiving the same medication, and including measurement error, could be shared within twin pairs and were unmeasured.

Statistical Methods

For Seizure Status, we determined the proportion of MZ and DZ pairs with the same Seizure Status and compared the proportions using Fisher's Exact Test. For Outcome Scale, we fitted fixed and random effects models. The fixed effects included age at diagnosis, age at assessment, zygosity and epilepsy syndrome. The variance and covariance structure was modelled in terms of the residual variance (σ^2) and separate correlations for MZ and DZ pairs (ρ_{MZ} and ρ_{DZ}). The model assumed a bivariate normal distribution for residuals. The statistical package FISHER was used to fit all models by maximum likelihood and to identify outlier pairs and individuals (Hopper & Visscher, 2002). Nested models were tested using the Likelihood Ratio Test (χ^2) Statistic (Wilks, 1938). All quoted nominal p-values are two sided.

Results

Outcome Scale Construct Validity

Construct validity evaluates how well the results of a new scale correlate with those of a standard scale for the same domain of interest (i.e., epilepsy outcome). For Outcome

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Scale, construct validity was assessed by determining the correlation between epilepsy outcome as defined by the Outcome Scale and a subjective assessment of outcome by the patient's treating neurologist. An unrelated group of 25 non-twin subjects with a range of clinical outcomes was assessed. The patients' neurologist was asked to rank their epilepsy on a scale from 1 to 6, where 1 = terminal remission of epilepsy and 6 = severe epilepsy refractory to medical therapy, and the results compared to an assessment of clinical outcome using the Outcome Scale. A high level of correlation between the assessment of clinical outcome using the Scale and the assessment of outcome by the patient's treating neurologist was observed (χ^2 = 0.93, 95% CI: 0.83, 0.97).

Sample Characteristics

We studied the 37 syndrome concordant twin pairs (27 MZ, 10 DZ) (see Table 1). The breakdown of major epilepsy syndrome diagnoses based on the ILAE Classification were as follows: idiopathic generalized epilepsy (n = 21), unclassified generalized epilepsy (n = 7), idiopathic partial epilepsy (n = 3), cryptogenic partial epilepsy (n = 5), unclassified epilepsy (n = 1). Of the 74 individual twins, 27 had active epilepsy and 47 were in remission (on treatment or in terminal remission). The distribution of Outcome Scale scores for individual twins (n = 72) were score 1 (n = 23), score 2 (n = 8), score 3 (n = 20), score 4 (n = 10), score 5 (n = 4), score 6 (n = 9). Mean age at seizure onset was: MZ = 12.4 years (SD = 9.8), range 2 to 61; DZ = 9.8 years (SD = 7.0), range 1 to 29. Mean age at assessment: MZ = 31.1 years (SD = 12.3), range 13 to 64; DZ = 25.3 years (SD = 8.0), range 14 to 39. These variables did not differ by zygosity.

Correlation of Clinical Outcome of Epilepsy

Syndrome concordant twin pairs showed high correlation for clinical outcome of epilepsy. Assessed by Seizure Status, MZ concordance = 0.81 (22/27) and DZ concordance = 1.0 (10/10), p = 0.3. High within pair correlation was demonstrated for Seizure Status irrespective of treatment status. Thus 9 of 32 concordant pairs were discordant for treatment status and 3 of 5 pairs discordant for Seizure Status were concordant for treatment status. Assessed on the Outcome Scale, MZ correlation = 0.60 (95% CI: 0.32, 0.78), DZ correlation = 0.78 (0.48, 0.92). There was no evidence that the MZ and DZ correlations were different: $\chi^2(1)$ = 1.28, p = 0.3 and correlation for all pairs combined was 0.65 (0.42, 0.80).

Within-pair correlation in clinical outcome could be artefactually inflated if outcome is associated with age at seizure onset and age at onset is correlated within twin pairs or if outcome is associated with age at assessment and age at assessment is correlated within pairs. We addressed this analytically by fitting Outcome Scale score as a linear function of age at onset or assessment in the model. That is, we fitted the line Y = a + b X, where Y is outcome and X is age at onset or assessment. For age at onset, we found the estimate of b to be 0.01 (SE = 0.02), showing no evidence of an association (p = 0.7). The estimated correlation in age-at-onset-adjusted-outcome was 0.61 (95% CI: 0.32, 0.80) for MZ pairs and 0.79 (0.49, 0.92) for DZ pairs, similar to the unadjusted correlations. This was repeated adjusting for twin age at the time of assessment and again there was no evidence of confounding: b = 0.01 (SE = 0.02), adjusted correlations: MZ = 0.58 (0.28, 0.77), DZ = 0.78 (0.47, 0.92).

Within-pair correlations in clinical outcome might also be artificially inflated if subjects with the same major epilepsy syndrome tend to have more similar clinical outcomes than subjects with different syndromes, regardless of whether or not they are genetically related. That is, if at least part of the variation in Outcome Scale score for all syndromes combined were due to an association between clinical outcome and epilepsy syndrome. We assessed this in a number of ways. Firstly, we compared models allowing the mean Outcome Scale score to depend on syndrome and found no evidence of an association: $\chi^2(4)$ = 5.74, p = 0.2. Correlation estimates were little influenced by adjustment for syndrome in mean Outcome Scale score: MZ = 0.53 (0.22, 0.75), DZ = 0.76 (0.45, 0.91). We then compared models allowing the variance of Outcome Scale score to depend on syndrome, pooling twin pairs concordant for Unclassified Epilepsy (1 twin pair only) and Unclassified Generalized Epilepsy (7 pairs), and found no evidence of an association: $\chi^2(3)$ = 1.72, p = 0.6. Finally, we tested whether the strength of the within-pair correlations differed by syndrome. MZ and DZ twins were pooled in fitting models allowing correlations between twins to vary with syndrome. Twins had identical outcome scores within all pairs concordant for three syndromes: unclassified generalized epilepsy, idiopathic partial epilepsy and unclassified epilepsy. The estimated correlation for twins with idiopathic generalized epilepsy was 0.39 (0.02, 0.66). For twins concordant for cryptogenic partial epilepsy, the estimated MZ/DZ pooled correlation (based on 5 pairs) was 0.11 (–0.85, 0.90).

Discussion

Prognosis varies considerably in the epilepsies, even between patients with seemingly the same epilepsy syndrome, and its determinants are largely unknown. The purpose of this study was to evaluate the role of genetic factors on epilepsy outcome using a twin method that controlled for the diversity of underlying epilepsy etiologies. Our analysis of epilepsy concordant pairs concordant for disease etiology demonstrated high within-pair similarities for clinical outcome, independent of zygosity. Clinical outcome was highly correlated whether assessed by Seizure Status or Outcome Scale. Further modelling showed that the high correlations in clinical outcome assessed on the Outcome Scale were consistent across the different epilepsy syndromes studied. We found no evidence that correlation of clinical outcome was artefactually inflated by within pair correlation for age of seizure onset or age at assessment, nor that syndrome concordant pairs were correlated independent of genetic relatedness (i.e., no evidence for correlation in outcome between unrelated syndrome concordant pairs).

Our study population consisted of a range of epilepsy syndrome diagnoses as defined by the system of classification acknowledged by the ILAE (Commission, 1989). In this system, epileptic seizures and epilepsy syndromes are defined by clusters of clinical and EEG features which may

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Table 1

Syndrome Concordant Twin Pairs Analysed for Epilepsy Outcome

Zygosity	Major Syndrome	Age at Onset	Age Studied	Seizure Status	Outcome Score
MZ T1	IGE	9	22	REM	3
MZ T2	IGE	9	22	REM	3
MZ T1	IGE	15	28	REM	3
MZ T2	IGE	10	28	REM	5
MZ T1	IGE	6	33	REC	4
MZ T2	IGE	6	33	REC	4
MZ T1	IGE	13	27	REM	5
MZ T2	IGE	15	27	REC	6
MZ T1	IGE	13	20	REM	1
MZ T2	IGE	9	20	REM	3
MZ T1	IGE	18	37	REM	1
MZ T2	IGE	16	37	REC	6
MZ T1	IGE	7	33	REM	3
MZ T2	IGE	7	33	REC	4
MZ T1	IGE	11	26	REM	5
MZ T2	IGE	10	26	REM	3
MZ T1	IGE	7	42	REM	3
MZ T2	IGE	7	42	REM	1
MZ T1	IGE	5	17	REM	1
MZ T2	IGE	7	17	REM	1
MZ T1	IGE	17	26	REC	2
MZ T2	IGE	23	26	REC	2
MZ T1	IGE	12	40	REC	4
MZ T2	IGE	14	40	REC	6
MZ T1	IGE	4	21	REM	1
MZ T2	IGE	5	21	REM	1
MZ T1	IGE	7	13	REC	2
MZ T2	IGE	8	13	REC	2
MZ T1	UGE	5	14	REC	4
MZ T2	UGE	5	14	REC	4
MZ T1	UGE	2	37	REM	3
MZ T2	UGE	6	37	REM	3
MZ T1	UGE	4	13	REC	6
MZ T2	UGE	2	13	REC	6
MZ T1	UGE	2	18	REC	6
MZ T2	UGE	2	18	REC	6
MZ T1	UGE	14	53	REM	1
MZ T2	UGE	14	53	REM	1
MZ T1	IPE	25	42	REM	1
MZ T2	IPE	19	42	REM	1
MZ T1	IPE	6	39	REM	1
MZ T2	IPE	5	39	REM	1
MZ T1	CPE	32	44	REC	2
MZ T2	CPE	32	44	REC	2
MZ T1	CPE	23	33	REC	4
MZ T2	CPE	21	33	REC	4
MZ T1	CPE	61	64	REC	4
MZ T2	CPE	21	64	REM	1
MZ T1	CPE	15	33	REC	2
MZ T2	CPE	15	33	REM	1
MZ T1	CPE	12	38	REC	4
MZ T2	CPE	14	39	REC	2
MZ T1	UE	12	26	REM	3
MZ T2	UE	11	26	REM	3
DZ T1	IGE	1	14	REM	1
DZ T2	IGE	4	14	REM	1

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Table 1 continued

Zygosity	Major Syndrome	Age at Onset	Age Studied	Seizure Status	Outcome Score
DZ T1	IGE	15	26	REM	1
DZ T2	IGE	12	26	REM	3
DZ T1	IGE	11	24	REM	3
DZ T2	IGE	7	24	REM	5
DZ T1	IGE	12	37	REM	1
DZ T2	IGE	11	37	REM	1
DZ T1	IGE	29	39	REM	3
DZ T2	IGE	13	39	REM	1
DZ T1	IGE	10	14	REM	3
DZ T2	IGE	8	14	REM	3
DZ T1	IGE	23	26	REM	3
DZ T2	IGE	8	26	REM	3
DZ T1	UGE	2	28	REC	6
DZ T2	UGE	1	28	REC	6
DZ T1	UGE	5	24	REM	1
DZ T2	UGE	5	24	REM	1
DZ T1	IPE	13	21	REM	3
DZ T2	IPE	6	21	REM	3

Note: T1 = Twin 1; T2 = Twin 2; MZ = monozygotic; DZ = dizygotic.
IGE = idiopathic generalized epilepsy; UGE = unclassified generalized epilepsy; IPE = idiopathic partial epilepsy; CPE = cryptogenic partial epilepsy; UE = unclassified epilepsy; REM = remission of seizures; REC = recurrent seizures.

represent distinct etiologies. The ILAE Classification established standardized terminology for the classification of epileptic seizures and epilepsy for use in clinical practice and research but now recognizes that too rigid a classification of epilepsy can adversely shape the manner in which clinicians and neuroscientists think about epilepsy (ILAE, 2001). Our sample consisted of pairs of twins in whom the only identified cause to their epilepsy was their shared epilepsy genetic susceptibility. In no cases were environmental factors or brain injury identified as contributing to the cause of the epilepsy (i.e., none were symptomatic). We therefore consider the term "idiopathic epilepsy" (meaning no cause other than an inherited susceptibility) adequately describes the etiology of the epilepsies we studied, regardless of the varying major syndrome diagnoses (e.g., cryptogenic partial epilepsy) provided by the ILAE Classification.

A major strength to our study was that the effect of epilepsy heterogeneity on clinical outcome was minimized by the use of twin pairs concordant for epilepsy etiology. The most likely cause for epilepsy in the affected syndrome concordant pairs we studied was their shared genetic susceptibility, given there was no evidence of an environmental cause and previous twin studies have consistently found evidence for major syndrome-specific genetic susceptibility factors. For their clinical outcome, the potential effect of environmental factors not involved in epilepsy susceptibility cannot be discounted. Cohabitation-related effects, such as being treated by the same physician or being given similar treatments because both twins had the same syndrome, could have contributed to the observed high within-pair correlation in Outcome Score. In terms of Seizure Status, however, concordant outcomes were observed even in pairs with discordant treatment (and vice versa), so the high within-pair correlation in seizure outcome cannot be explained solely in terms of shared treatment-related effects. Further support for this comes from observations in the wider population, where considerable variation in outcome is seen despite optimal medical management, even between patients with seemingly identical epilepsy syndromes (e.g., Gelisse et al., 2001). An alternative explanation for the observed high correlation of clinical outcome in etiology concordant twin pairs, given the high heritability of the epilepsies studied, is that the epilepsy genetic susceptibility shared by twins contributes substantially to clinical outcome. This model explains the observed differences in clinical outcome between phenotypically identical idiopathic epilepsies in terms of heterogeneity of epilepsy genetic susceptibility.

Referral bias is unlikely to have contributed to the high correlation between twin pairs since twin pairs were ascertained solely on the basis of a past or current history of seizures and not on the basis of clinical outcome. Moreover, neither age of seizure onset nor epilepsy outcome was a factor in major syndrome diagnosis (see Methods), and thus identified syndrome concordant twin pairs were not biased to be more alike for these measures. A further strength to the study was that its cross-sectional nature resulted in most twins being evaluated years after seizure onset (mean 16.9 years), long enough for the natural history of the epilepsy to become apparent (some age-dependent epilepsies appearing refractory in childhood, only to remit in later life).

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Epilepsy outcome was evaluated using the binary measure of Seizure Status and on a novel six-category ordinal Outcome Scale. Whilst assessment in terms of Seizure Status provides an unequivocal measure of outcome, it may fail to make the fine distinctions between the various clinical outcomes of epilepsy necessary to show an etiology-independent genetic effect on outcome. A number of seizure severity scales have been described, but these are scales of seizure burden (seizure frequency and their clinical impact) for use in drug trials and are not measures of long-term outcome (Baker et al., 1991; Cramer, 2001; Cramer et al., 1983; O'Donoghue et al., 1996). In an attempt to better discriminate between the various epilepsy outcomes, we constructed an Outcome Scale that combined items on Seizure Status with treatment decisions. Construct validity for the scale was supported by the high level of agreement between the assessment of clinical outcome using the Outcome Scale and a subjective assessment of outcome by the patient's treating neurologist, suggesting that the scale had discriminative value in the assessment of relative epilepsy outcomes. Since our study failed to identify a difference between MZ and DZ pairs, however, a structural problem with the scale cannot be excluded. The finding of high correlation in outcome in terms of Seizure Status is unaffected by this uncertainty.

In conclusion, for epilepsy whose sole apparent etiology is an inherited susceptibility (idiopathic epilepsy), our data provide no evidence to support the hypothesis that clinical outcome is determined by genetic factors distinct from those that determine susceptibility to the disease. Although there was no difference between the MZ and DZ correlations for epilepsy outcome, the DZ estimate had a wide confidence interval, suggesting that only large differences between MZ and DZ correlations would have been detectable. The potential role of outcome specific genetic factors cannot therefore be discounted. Our analysis would clearly be improved by a larger number of etiology concordant epilepsy twin pairs, perhaps via international collaboration. A major obstacle to the international ascertainment of etiology concordant epilepsy twin pairs, however, is that the assessment of epilepsy etiology and clinical outcome demonstrated in this study requires a very high level of clinical evaluation of epilepsy.

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References

Anderson, V. E., Wilcox, K. J., Leppik, L. E., & Hauser, W. A. (1989). Twin studies in epilepsy. In G. Beck-Managetta, V. E. Anderson, H. Doose, & D. Janz (Eds.), *Genetics of the epilepsies* (pp. 145–155). Heidelberg: Springer-Verlag.

Baker, G. A., Smith, D. F., Dewey, M., Morrow, J., Crawford, P. M., & Chadwick, D. W. (1991). The development of a seizure severity scale as an outcome measure in epilepsy. *Epilepsy Research, 8*, 245–251.

Berkovic, S. F., Howell, R. A., Hay, D. A., & Hopper, J. L. (1993). Twin birth is not a risk factor for seizures. *Neurology, 43*, 2515–2519

Berkovic, S. F., McIntosh, A., Howell, R. A., Mitchell, A., Sheffield, L. J., & Hopper, J. L. (1996). Familial temporal lobe epilepsy: A common disorder identified in twins. *Annals in Neurology, 40*, 227–235.

Berkovic, S. F., Howell, R. A., Hay, D. A., & Hopper, J. L. (1998). Epilepsy in twins: Genetics of the major epilepsy syndromes. *Annals of Neurology, 43*, 435–445.

Commission on Classification and Terminology of the International League Against Epilepsy. (1989). Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia, 30*, 389–399

Corey, L. A., Berg, K., Pellock, J. M., Solaas, M. H., Nance, W. E., & DeLorenzo, R. J. (1991). The occurrence of epilepsy and febrile seizures in Virginian and Norwegian twins. *Neurology, 41*, 1433–1436.

Cramer, J. A., Smith, D. B., Mattson, R. H., the VA Epilepsy Cooperative Study Group et al. (1983). A method of quantification for the evaluation of antiepileptic drug therapy. *Neurology, 33*(Suppl 1), 26–37.

Cramer, J. A. (2001). Assessing the severity of seizures and epilepsy: which scales are valid? [Review]. *Current Opinion in Neurology, 14*, 225–229.

Gelisse, P., Genton, P., Thomas, P., Rey, M., Samuelian, J. C., & Dravet, C. (2001). Clinical factors in juvenile myoclonic epilepsy. *Journal of Neurology, Neurosurgery, and Psychiatry, 70*, 240–244.

Hauser, W. A., & Hesdorffer, D. C. (1990). *Epilepsy: Frequency, causes and consequences*. New York: Demos Publications.

Hobart, J. C., Freeman, J. A., & Thompson, A. J. (2000) Kurtzke scales revisited: The application of psychometric methods to clinical intuition. *Brain, 123*, 1027–1040.

Hopper, J. L., & Visscher, P. M. (2002). Variance component analysis. In R. C. Elston, J. M. Olson, & L. Palmer (Eds.), *Biostatistical genetics and genetic epidemiology*. Chichester, UK: John Wiley and Sons.

ILAE Commission Report. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE Task Force on Classification and Terminology. *Epilepsia, 42*, 796–803.

Kjeldsen, M. J., Kyvik, K. O., Christensen, K., & Friis, M. L. (2001). Genetic and environmental factors in epilepsy: A population-based study of 11,900 Danish twin pairs. *Epilepsy Research, 44*, 167–178.

Lennox, W. G. (1951). The heredity of epilepsy as told by relatives and twins. *JAMA, 146*, 529–536.

Miller, L. L., Pellock, J. M., DeLorenzo, R. J., Meyer, J. M., & Corey, L. A. (1998). Univariate genetic analysis of epilepsy and seizures in a population-based twin study: The Virginian Twin Registry. *Genetic Epidemiology, 15*, 33–49.

Miller, L. L., Pellock, J. M., Boggs, J. G., DeLerenzo, R. J., Meyer, J. M., & Corey, L. A. (1999). Epilepsy and seizure occurrence in a population-based sample of Virginian twins and their families. *Epilepsy Research, 34*, 135–143.

O'Donoghue, N. F., Duncan, J. S., & Sander, J. W. A. S. (1996). The National Hospital Seizure Severity Scale: A further

https://doi.org/10.1375/twin.6.2.140 Published online by Cambridge University Press

development of the Chalfont Seizure Severity Scale. *Epilepsia, 37*, 563–571.

Sander, J. W. (1993). Some aspects of prognosis in the epilepsies: A review [Review]. *Epilepsia, 34*, 1007–1016.

Sillanpaa, M., Koskenvuo, M., Romanov, K., & Kaprio, J. (1991). Genetic factors in epileptic seizures: Evidence from a large twin population. *Acta Neurologica Scandinavica, 84*, 523–526.

Wilks, S. S. (1938). The large-sample distribution of the likelihood ratio for testing composite hypotheses. *Annals of Mathematics and Statistics, 9*, 60–62.

Wong, I. C., Chadwick, D. W., Fenwick, P. B., Mawer, G. E., & Sander, J. W. (1999). The long-term use of gapapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy. *Epilepsia, 40*, 1439–1445.

https://doi.org/10.1375/twin.6.2.140 Published online by Cambridge University Press