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Familial risk of epilepsy: a population-based study

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Almost all previous studies of familial risk of epilepsy have had potentially serious methodological limitations. Our goal was to address these limitations and provide more rigorous estimates of familial risk in a population-based study. We used the unique resources of the Rochester Epidemiology Project to identify all 660 Rochester, Minnesota residents born in 1920 or later with incidence of epilepsy from 1935–94 (probands) and their 2439 first-degree relatives who resided in Olmsted County. We assessed incidence of epilepsy in relatives by comprehensive review of the relatives' medical records, and estimated age-specific cumulative incidence and standardized incidence ratios for epilepsy in relatives compared with the general population, according to proband and relative characteristics. Among relatives of all probands, cumulative incidence of epilepsy to age 40 was 4.7%, and risk was increased 3.3-fold (95% confidence interval 2.75–5.99) compared with population incidence. Risk was increased to the greatest extent in relatives of probands with idiopathic generalized epilepsies (standardized incidence ratio 6.0) and epilepsies associated with intellectual or motor disability presumed present from birth, which we denoted 'prenatal/developmental cause' (standardized incidence ratio 4.3). Among relatives of probands with epilepsy without identified cause (including epilepsies classified as 'idiopathic' or 'unknown cause'), risk was significantly increased for epilepsy of prenatal/developmental cause (standardized incidence ratio 4.1). Similarly, among relatives of probands with prenatal/developmental cause, risk was significantly increased for epilepsies without identified cause (standardized incidence ratio 3.8). In relatives of probands with generalized epilepsy, standardized incidence ratios were 8.3 (95% confidence interval 2.93–15.31) for generalized epilepsy and 2.5 (95% confidence interval 0.92–4.00) for focal epilepsy. In relatives of probands with focal epilepsy, standardized incidence ratios were 1.0 (95% confidence interval 0.00–2.19) for generalized epilepsy and 2.6 (95% confidence interval 1.19–4.26) for focal epilepsy. Epilepsy incidence was greater in offspring of female probands than in offspring of male probands, and this maternal effect was restricted to offspring of probands with focal epilepsy. The results suggest that risks for epilepsies of unknown and prenatal/developmental cause may be influenced by shared genetic mechanisms. They also suggest that some of the genetic influences on generalized and focal epilepsies are distinct. However, the similar increase in risk for focal epilepsy among relatives of probands with either generalized (2.5-fold) or focal epilepsy (2.6-fold) may reflect some coexisting shared genetic influences.

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Abbreviations: GESDR = Genetic Epidemiology of Seizure Disorders in Rochester; IGE = idiopathic generalized epilepsy; ILAE = International League Against Epilepsy; SIR = standardized incidence ratio

Introduction

The pace of gene discovery in the epilepsies is increasing rapidly, but for most affected individuals the genetic contributions are complex and the specific genes that influence risk remain to be identified (Poduri and Lowenstein, 2011; Sisodiya and Mefford, 2011; The Epi4K Consortium, 2012). Epidemiological studies of familial aggregation play a key role in elucidating the genetic contributions to complex disorders such as the epilepsies. They provide empirical risk estimates essential for genetic counselling (Winawer and Shinnar, 2005), clues to mode of inheritance of the underlying genes (Ottman *et al.*, 1997), and critical information about phenotypic and genetic heterogeneity. Analyses of familial risk according to proband and relative phenotypes can help to identify the clinical features with the greatest genetic influences, and clarify the shared versus distinct genetic influences on different clinical features or syndromes (Winawer, 2006).

Although familial risk in the epilepsies has been studied extensively, almost all previous studies have had potentially serious methodologic limitations such as referral and reporting biases, small sample size, ambiguous disease definitions in probands and relatives, lack of controls, and failure to control adequately for age in the relatives (Lennox, 1947, 1951; Alstrom, 1950; Harvald, 1951; Ounsted, 1955; Eisner *et al.*, 1960; Metrakos and Metrakos, 1960, 1961; Doose *et al.*, 1968; Matthes and Weber, 1968; Tsuboi and Christian, 1973; Annegers *et al.*, 1976, 1982; Tsuboi and Endo, 1977; Ottman *et al.*, 1988, 1989, 1996*a*, *b*, 1998; Jain *et al.*, 1997, 2004; Bianchi *et al.*, 2003; Hemminki *et al.*, 2006). These problems can have important consequences, leading to inaccuracy in risk estimates conveyed to patients in clinical settings and incorrect assumptions in study designs aimed at gene identification.

With only three exceptions, previous studies have ascertained probands from tertiary referral settings. As many patients are not treated in specialty centres, restriction of ascertainment in this way can distort the distribution of epilepsy types included, which would be expected to influence estimates of risk in family members either directly (through selective inclusion of patients with affected relatives) or indirectly (through selective inclusion of patients with more severe epilepsies, which might differ in their genetic contributions from less severe epilepsies). Also, all but three previous studies obtained information through patient family history interviews (sometimes supplemented by interviews or examinations of some relatives). Use of patient (or parent) interviews for data collection can under-identify affected relatives, particularly among older parents or siblings who may have had epilepsy long before patients were interviewed (Ottman *et al.*, 1995, 2011). With few exceptions (Eisner *et al.*, 1960; Annegers *et al.*, 1976, 1982; Jain *et al.*, 2004; Hemminki *et al.*, 2006), controls without epilepsy have not been included. Instead, studies have compared observed rates of epilepsy in relatives with epilepsy prevalence estimates from the US World War I draft (Lennox, 1947, 1951, 1960; Alstrom, 1950), or used internal controls (patients with epilepsies other than those of primary interest) (Tsuboi and Christian, 1973; Ottman *et al.*, 1998; Bianchi *et al.*, 2003).

Only three previous studies of familial risk of epilepsy have been population-based. The most recent of these was based on all hospitalizations for epilepsy in Sweden from 1987–2001 (Hemminki *et al.*, 2006). Although it was quite large, it was limited to siblings, included only patients with epilepsy who were hospitalized, and relied on International Classification of Diseases codes rather than expert epileptologist review for classification of both probands and relatives. The other two population-based studies (Annegers *et al.*, 1976, 1982) used the resources of the unique Rochester Epidemiology Project medical record-linkage system (Melton, 1996; St Sauver *et al.*, 2011; Rocca *et al.*, 2012). One of these examined risks only in offspring of patients with epilepsy (Annegers *et al.*, 1976; Ottman *et al.*, 1988, 1989, 1991). The other, the most important predecessor to the current study, examined risks of epilepsy in all descendants of the parents of incident epilepsy patients residing in Rochester, Minnesota (Annegers *et al.*, 1982). However, proband ascertainment was restricted to epilepsy or isolated unprovoked seizures of unknown cause with onset in childhood, and hence did not allow a comprehensive analysis of familial risk for all patients with epilepsy. Also, the sample was relatively small (196 probands with epilepsy), limiting comparisons among subgroups of probands or relatives.

Our goal was to address the limitations of previous familial aggregation studies of the epilepsies and carry out a more rigorous assessment of familial risk than has previously been possible. To this end, we designed the Genetic Epidemiology of Seizure Disorders in Rochester study (GESDR) (Ottman *et al.*, 2010, 2011), a population-based investigation using the resources of the Rochester Epidemiology Project (Melton, 1996; St Sauver *et al.*, 2011; Rocca *et al.*, 2012).

Materials and methods

The GESDR probands were identified in previous epidemiologic studies (Hauser *et al.*, 1993, 1996) and comprised all 910 residents of Rochester, Minnesota who were born $\geqslant$1920 and had incidence of a single unprovoked seizure or epilepsy ($\geqslant$2 unprovoked seizures) from 1935 through 1994. In the current study, we assessed incidence of epilepsy in first-degree relatives of the 660 probands with incident epilepsy during the study period. The remaining probands either had a single unprovoked seizure ($n = 218$) or were unclassifiable ($n = 32$).

Between 2003 and 2008, we comprehensively reviewed the medical records of each proband at the Mayo Clinic and all other local health care providers to confirm study eligibility and update information on clinical diagnosis and classification. This involved initial review by trained nurse abstractors, followed by expert review by study epileptologists (J.R.B. and W.A.H.), and included all outpatient and inpatient medical visits and test results (including EEG, neuroimaging, seizure

descriptions, etc.) from date first seen to last seen by a Rochester Epidemiology Project provider, encompassing essentially all medical care delivered while individuals resided locally (Melton, 1996; St Sauver *et al.*, 2011; Rocca *et al.*, 2012).

We used information available through the Rochester Epidemiology Project to identify the probands' first-degree relatives, estimate their periods of residency in Olmsted County, and screen their Rochester Epidemiology Project medical records for diagnostic codes possibly indicative of seizure occurrence (Supplementary material). To maximize sensitivity for identification of affected relatives, we screened broadly for diagnostic codes that might have indicated seizure occurrence, using a comprehensive set of 95 codes from the three different diagnostic coding systems used during the study period. We then reviewed the complete Rochester Epidemiology Project medical records of relatives with any such code and a sample of those with none of the codes. Among the sample of 156 relatives with none of the codes whose records were reviewed, only one (0.6%) had incidence of unprovoked seizures while residing locally, suggesting the false negative rate was very low.

Study epileptologists classified unprovoked seizures in probands and affected relatives by seizure type according to the 1981 ILAE criteria (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) and by epilepsy syndrome according to the 1989 ILAE criteria (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) in place at the time data collection began in 2003. Patients were classified as having generalized epilepsy syndromes if they had generalized ictal or interictal epileptiform EEG abnormalities or seizure semiology consistent with absence, myoclonic, or atonic seizures, and were subdivided according to the 1989 ILAE criteria into idiopathic generalized epilepsies (IGEs) or other generalized epilepsies (denoted in the 1989 classification as generalized 'symptomatic' or 'cryptogenic'). Patients were classified as having focal epilepsy if they had focal epileptiform EEG abnormalities or focal seizure semiology, and were also subclassified into syndromes according to the 1989 ILAE criteria. When broad epilepsy syndrome (generalized or focal) could not be determined, the reasons were recorded (nocturnal seizures only, limited semiology information, or lack of EEG findings) and cases were categorized as 'unclassified.'

Presumed cause was assigned based on the history of structural or metabolic CNS insults occurring before the first unprovoked seizure. Patients with structural or metabolic causes (Berg *et al.*, 2010) were further subdivided into prenatal/developmental (i.e. neurological deficit presumed present at birth, as reflected by intellectual or motor deficits or CNS congenital malformations), identified genetic disorder (e.g. tuberous sclerosis or Down syndrome), or postnatal cause (e.g. stroke or traumatic brain injury). Findings on neuroimaging (CT or MRI) were used to support the diagnosis (especially if known to be associated with focal epilepsy, e.g. tumour, focal cortical dysplasia) but negative findings were not required for exclusion of structural or metabolic causes. Seizure types and aetiologies were classified independently, allowing classification of generalized seizures in some individuals with identified brain injuries. Records were reviewed in order of randomly assigned study identification numbers, minimizing potential bias related to diagnoses in affected relatives.

Statistical analysis

As the GESDR study was population-based and covered a long time interval (1935–94), families containing multiple affected individuals frequently contained multiple probands. We used the Weinberg proband method to correct for ascertainment bias resulting from proband-based sampling (Weinberg, 1928; Fisher, 1934; Morton, 1959). In this method, risks are estimated by discarding the proband and computing the proportion affected among remaining relatives, repeating the process for each proband.

We computed standardized incidence ratios (SIRs) for epilepsy in relatives, defined as the ratio of the observed number of incident cases among relatives to the number expected based on age-, sex-, and calendar year-specific population incidence rates in Rochester, Minnesota (Supplementary material). For calculation of SIRs for specific clinical categories of epilepsy in relatives (e.g. generalized or focal), expected numbers were based on population incidence rates for those specific types. We also estimated age-specific cumulative incidence of epilepsy in first-degree relatives (interpreted as the risk of developing epilepsy by the time a relative reaches a specific age), using stratified proportional hazards models. Analyses included all of the relatives' person-years of residency in Olmsted County (regardless of age) and all ages at onset of epilepsy in relatives. However, cumulative incidence is displayed only up to age 40 because sample sizes were too small at older ages to provide stable estimates.

Results

Risks in relatives by proband diagnostic category

Among all 2439 first-degree relatives, 75 had incidence of epilepsy while residing in Olmsted County from 1935–2008, with age at onset from birth to 81 years (85% with onset before 40 years). Cumulative incidence of epilepsy to age 40 was 4.7% [standard error (SE) 0.60%] in relatives of epilepsy cases, compared with 1.3% in the Rochester population (Table 1 and Fig. 1). The SIR was 3.3 [95% confidence interval (CI) 2.75–5.99]. Risk to age 40 was similar in parents (4.5%, SE 1.67%), siblings (4.8%, SE 0.87%), and offspring (3.9%, SE 0.89%).

Risk was increased to the greatest extent in relatives of probands with idiopathic epilepsy syndromes (SIR = 5.5), and was also significantly increased in relatives of probands with unknown cause of epilepsy (SIR = 2.7) or 'structural/metabolic' cause

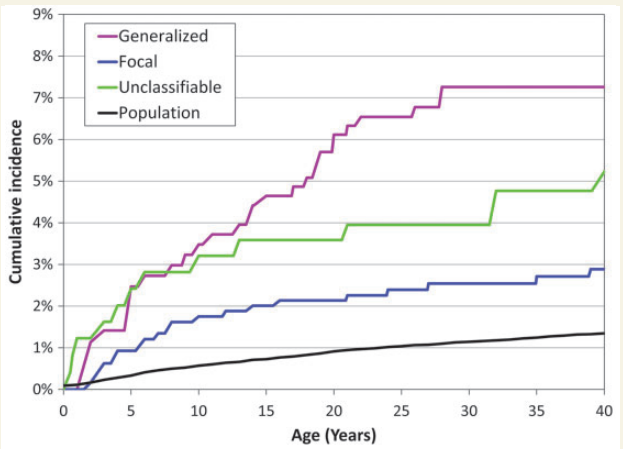

Figure 1 Age-specific cumulative incidence of epilepsy in first-degree relatives of probands with epilepsy, by proband epilepsy type.

(Berg *et al.*, 2010) (SIR = 2.6). The increased risk in relatives of probands with structural/metabolic causes was primarily restricted to relatives of probands classified as having prenatal/developmental causes (SIR = 4.3). In relatives of probands with identified postnatal causes, the degree of increased risk was lower (SIR = 1.8), and was not significant.

Risks were increased to a greater extent in relatives of probands with generalized versus focal epilepsies (SIR 5.0 versus 2.1), but were significantly increased in both groups (Table 1 and Fig. 1). In relatives of probands with generalized epilepsies, the greatest increase in risk was in relatives of probands with IGEs (SIR = 6.0). As in the analysis of all epilepsies combined, risk was also increased strongly in relatives of probands with generalized epilepsies with prenatal/developmental causes (SIR = 4.7, Table 1).

Among relatives of probands with focal epilepsy of unknown cause, risk was increased ~2-fold. The SIR for relatives of probands with idiopathic focal epilepsies was similar, but was based on small numbers (2/76 affected relatives) and was not significant. As in relatives of generalized probands, risk was particularly increased among relatives of probands with focal epilepsies of prenatal/developmental cause (SIR = 4.8). Risk was not increased in relatives of probands with focal epilepsy with postnatal causes (SIR = 1.3).

Twenty-one per cent of probands (140/660) were unclassifiable by broad epilepsy syndrome. The most frequent reason (89% of cases) was lack of identified EEG abnormalities (although 89% of cases in this group had one or more EEG) in individuals without clear evidence of focal or generalized onset seizure semiology. Among relatives of these probands, risk was increased 4.2-fold overall, and 4.7-fold among relatives of those without identified cause.

Familial relationships of epilepsies of unknown and prenatal/developmental cause

We examined the co-occurrence in families of epilepsies of prenatal/developmental cause and epilepsies in which no cause was

Table 1 Cumulative incidence of epilepsy to age 40 and SIRs for epilepsy in first-degree relatives of probands with epilepsy, by proband epilepsy syndrome[a]

Proband Epilepsy Syndrome	*n* probands	First-degree relatives		Cumulative incidence to age 40 (%) (SE)	SIR (95% CI)
		n	With epilepsy		
All epilepsy[b]	660	2439	75	4.7 (0.60)	3.3 (2.45–4.32)
Idiopathic	136	571	28	7.3 (1.52)	5.5 (3.52–7.93)
Unknown cause	279	984	25	3.8 (0.84)	2.7 (1.71–3.97)
Structural/metabolic	245	884	22	3.8 (0.94)	2.6 (1.54–3.93)
Prenatal/developmental	91	317	13	6.1 (1.88)	4.3 (2.27–7.22)
Identified genetic[c]	14	54	0	–	–
Postnatal cause[d]	140	513	9	2.7 (1.03)	1.8 (0.66–3.14)
Generalized	175	708	32	7.3 (1.40)	5.0 (3.18–7.45)
Idiopathic	116	495	26	8.1 (1.72)	6.0 (3.75–8.93)
Unknown cause[e]	10	43	0		–
Structural/metabolic	49	170	6	6.3 (2.85)	3.9 (1.01–8.20)
Prenatal/developmental	30	112	5	7.3 (3.66)	4.7 (0.93–10.29)
Identified genetic	7	21	0	–	–
Postnatal cause	12	37	1	4.9 (4.38)	2.7 (0.00–13.45)
Focal	337	1239	25	2.9 (0.65)	2.1 (1.27–3.10)
Idiopathic	20	76	2	2.0 (2.01)	2.7 (0.00–6.81)
Unknown cause	167	603	13	2.9 (0.94)	2.2 (1.07–3.48)
Structural/metabolic	150	560	10	2.9 (0.95)	1.9 (0.90–3.27)
Prenatal/developmental	39	121	5	8.5 (3.50)	4.8 (1.56–9.88)
Identified genetic	7	33	0	–	–
Postnatal cause	104	406	5	1.6 (0.76)	1.3 (0.26–2.53)
Unclassifiable	140	461	17	5.2 (1.46)	4.2 (2.37–6.31)
Unknown cause	97	322	12	6.2 (1.82)	4.7 (2.53–7.51)
Structural/metabolic	43	139	5	3.2 (2.39)	3.3 (0.67–6.66)
Prenatal/developmental	20	75	3	1.9 (1.89)	3.6 (0.00–8.01)
Postnatal cause	23	64	2	5.1 (4.85)	2.8 (0.00–8.95)

[a]Restricted to relatives born in 1920 or later and to residency periods from 1935–2008 in Olmsted County, Minnesota.
[b]Includes relatives of eight probands with both generalized and focal epilepsy (31 relatives, one affected) who are excluded from generalized, focal, and unclassifiable subgroups.
[c]Identified genetic causes such as tuberous sclerosis, phenylketonuria, and Down syndrome.
[d]Postnatal causes in probands include: traumatic brain injury (*n* = 39), stroke (*n* = 26), neoplasm (*n* = 24), CNS infection (*n* = 17), autoimmunity (*n* = 3), neurodegeneration (*n* = 5), alcoholism (*n* = 9), encephalopathy (*n* = 3), and other or multiple causes (*n* = 14).
[e]Includes West syndrome (*n* = 2), epilepsy with myoclonic-astatic seizures (*n* = 1), epilepsy with myoclonic absences (*n* = 1), and other generalized epilepsies of unknown cause other than IGEs (*n* = 6).

identified (Table 2). To maximize the sample size and separate the effects of cause from those of syndrome (generalized versus focal), for this analysis we combined epilepsies classified as idiopathic (almost all of which were generalized) with epilepsies classified as unknown cause. In relatives of probands without identified cause of epilepsy, risk was significantly increased for both epilepsy without identified cause (SIR = 4.6) and epilepsy of prenatal/developmental cause (SIR = 4.1). In relatives of probands with prenatal/developmental cause, risk was significantly increased for epilepsy without identified cause (SIR = 3.8), but the increase in risk for epilepsy of prenatal/developmental cause was not significant.

Specificity of increased risk for generalized versus focal epilepsy

In relatives of probands with generalized epilepsy, risk was increased >8-fold for generalized epilepsy (SIR = 8.3) but only 2.5-fold for focal epilepsy (95% CI 0.92–4.00) (Table 3). In relatives of probands with focal epilepsy, risk was increased 2.6-fold for focal epilepsy and was not increased for generalized epilepsy (SIR = 1.0). In relatives of probands with unclassifiable epilepsy, risk was significantly increased for both generalized (SIR = 5.5) and focal epilepsy (SIR = 3.9).

When the phenotype was restricted to IGE in both probands and relatives, the SIR was higher than that for all generalized epilepsy in relatives of probands with generalized epilepsy: 11.5 (95% CI 3.78–22.83). Similarly, when the phenotype was restricted to focal epilepsy of unknown cause in both probands and relatives, the SIR was higher than that for all focal epilepsy in relatives of probands with focal epilepsy: 4.0 (95% CI 0.81–8.16), although it was not significant with the reduction in sample size.

Risks in offspring by proband sex and epilepsy type

Incidence of epilepsy was increased 5-fold in offspring of female probands, but was not significantly increased in offspring of male probands (Table 4 and Fig. 2A). This difference appeared to be restricted to offspring of probands with focal epilepsy (Fig. 2C); risks were similar in offspring of female and male probands with generalized epilepsy (Fig. 2B).

Discussion

The design of the GESDR study addresses the limitations of previous family studies and facilitates a comprehensive analysis of familial risk of epilepsy. Among first-degree relatives of all probands, cumulative incidence of epilepsy to age 40 was 4.7%, and risk was increased 3-fold, compared with incidence rates in the general population. These estimates, based on an unselected, population-based series of patients, all classes of first-degree relatives, and comparison with incidence rates for all members of the same population, provide the most reliable indicators available of the magnitude of increased risk of epilepsy in first-degree relatives of affected individuals.

Comparison of these findings with those of previous studies is difficult because of wide variation in inclusion criteria, methods of data collection, and methods of analysis, and infrequent use of controls (Supplementary Table 1). However, the results of many previous studies do not appear to differ dramatically from ours, providing reassurance that most previous studies were not seriously biased. Most studies that included probands with all types of epilepsy found a history of epilepsy in ~3–5% of first-degree relatives, although estimates vary widely, from 1.5% (Alstrom, 1950) to 7% (Ounsted, 1955). In the few studies with a comparison group, estimates of the magnitude of increased risk in first-degree relatives have usually been in the range of 2–3-fold, with some as high as 6-fold (Jain *et al.*, 2004).

Table 3 SIRs for epilepsy in first-degree relatives, by epilepsy type in probands and relatives[a]

Epilepsy type in probands	Total relatives	Epilepsy type in relatives	With epilepsy	SIR (95% CI)
Generalized	708	Generalized	14	8.3 (2.93–15.31)
		Focal	8	2.5 (0.92–4.00)
		Unclassifiable	10	7.3 (2.82–12.98)
Focal	1239	Generalized	3	1.0 (0.00–2.19)
		Focal	16	2.6 (1.19–4.26)
		Unclassifiable	6	2.0 (0.40–3.85)
Unclassifiable	461	Generalized	6	5.5 (1.78–10.24)
		Focal	8	3.9 (1.39–6.46)
		Unclassifiable	3	3.5 (0.00–7.86)

[a]Restricted to relatives born in 1920 or later and to residency periods from 1935-2008 in Olmsted County, Minnesota.

Table 2 Familial relationships of epilepsies of unknown cause and prenatal/developmental cause[a]

Predisposing cause of epilepsy in probands	No. relatives	Predisposing cause of epilepsy in relatives	With epilepsy	SIR (95% CI)
Idiopathic or unknown	1555	Idiopathic or unknown	40	4.6 (2.97–6.27)
	1140	Prenatal/developmental[b]	6	4.1 (1.24–7.54)
Prenatal/developmental	317	Idiopathic or unknown	7	3.8 (1.02–7.29)
	189	Prenatal/developmental[b]	2	7.6 (0.00–18.63)

[a]Restricted to relatives born in 1920 or later and to residency periods from 1935–2008 in Olmsted County, Minnesota.
[b]Restricted to siblings and offspring because individuals with intellectual disability are unlikely to become parents.

Table 4 Cumulative incidence and SIRs for epilepsy in offspring of probands with epilepsy, by proband sex and proband epilepsy type[a]

Proband sex and epilepsy type	No. offspring		Cumulative incidence to age 40 (SE)	SIR (95% CI)
	Total	With epilepsy		
Female probands				
All epilepsies	355	14	5.39 (1.38)	5.0 (2.70–7.60)
Generalized	82	5	8.36 (3.64)	8.7 (1.92–18.87)
Focal	210	7	4.43 (1.61)	4.0 (3.92–7.10)
Unclassifiable	63	2	5.00 (3.33)	4.2 (0.00–11.11)
Male probands				
All epilepsies	279	4	1.94 (0.96)	1.8 (0.40–3.78)
Generalized	60	3	6.90 (3.52)	7.2 (0.00–16.34)
Focal	152	1	0.85 (0.85)	0.8 (0.00–2.81)
Unclassifiable	67	0	-	-

[a]Restricted to relatives born in 1920 or later and to residency periods from 1935–2008 in Olmsted County, Minnesota.

One of the most consistent observations in previous studies is a higher risk of epilepsy among relatives of individuals with unknown cause of epilepsy than among relatives of those with an identified antecedent cause. In Lennox's classical study of the family histories of 4231 patients, the proportions of first-degree relatives with epilepsy were 3.6% for patients with epilepsy of unknown cause and 1.8% for patients with epilepsies associated with identified causes (Lennox, 1947, 1951, 1960). Findings in other studies have been similar (Harvald, 1951; Tsuboi and Endo, 1977; Ottman *et al.*, 1996*a*; Bianchi *et al.*, 2003; Hemminki *et al.*, 2006).

In the current study, we extended this finding by examining separately postnatal causes of epilepsy (e.g. severe head trauma and stroke) and prenatal causes associated with motor or intellectual deficit presumed present at birth. In relatives of probands with postnatal causes, the SIR was lower than that in other aetiological categories (SIR = 1.8, Table 1), and was not significant. Most of the probands with postnatal causes had focal epilepsy (104/140; 74%) and the SIR in their relatives was only 1.3 (Table 1). This is consistent with our previous findings from the Epilepsy Family Study of Columbia University, in which ~84% of the probands had focal epilepsy, and the SIR among relatives of those with postnatal causes was 1.0 (Ottman *et al.*, 1996*a*). In the current study, an increase in risk among relatives of probands with postnatal causes, if present, might have been restricted to relatives of probands with generalized (or unclassifiable) epilepsies, although the numbers of probands in those groups (12 generalized and 23 unclassifiable) are too small for separate analysis.

Risk was increased 4.3-fold among relatives of probands classified as having prenatal/developmental causes of epilepsy, which is nearly as high as the increased risk among relatives of probands with idiopathic epilepsies (5.5-fold, Table 1). This subgroup is highly heterogeneous, containing multiple disorders associated with intellectual disability. As proband ascertainment ranged from 1935–94, most of these disorders were unexplained; with current diagnostic methods specific causes could be identified for some of them. However, we found that risk for epilepsy of unknown cause was significantly increased in relatives of probands with prenatal/developmental cause (Table 2), and conversely, risk for epilepsy of prenatal/developmental cause was increased in relatives of probands with unknown cause. These findings are also similar to those in the Epilepsy Family Study of Columbia University (Ottman *et al.*, 1996*a*), and suggest that shared genetic mechanisms may influence risk for some epilepsies of unknown cause and those associated with intellectual disability. This interpretation is consistent with evidence of the overlap of copy number variants associated with epilepsy and intellectual disability (Pescosolido *et al.*, 2013), and a recent report that individuals with IGE who also have intellectual disability (and would be excluded from the usual definition of IGE) have an increased frequency of these associated copy number variants (Mullen *et al.*, 2013).

Important findings are emerging regarding the genetics of epileptic encephalopathies (Carvill *et al.*, 2013; Epi4K Consortium and Epilepsy Phenome/Genome Project, 2013), which are frequently associated with intellectual disability. Thus we explored the overlap between epileptic encephalopathies and cases we classified as having prenatal/developmental cause. Among all 660 incident epilepsy probands, only 12 were classified as having a specific infantile epileptic encephalopathy included in the syndrome classification in place when we began data collection in 2003 (Commission on Classification and Terminology of the International League Against Epilepsy, 1989): West syndrome ($n = 8$), Lennox-Gastaut syndrome ($n = 1$), epilepsy with myoclonic absences ($n = 1$), or epilepsy with myoclonic-astatic seizures ($n = 2$). We classified these cases according to presumed cause as prenatal/developmental ($n = 7$), unknown ($n = 4$), or genetic (a single case with trisomy 21 and West syndrome). None of them had any affected relatives. Although other probands probably had epileptic encephalopathies that could not be recognized based on the available information, the increased risk in relatives of cases in the prenatal/developmental subgroup is probably primarily associated with other syndromes involving motor or intellectual disability.

As observed in previous studies, risk for epilepsy was greater in relatives of probands with generalized epilepsy than in relatives of probands with focal epilepsy (Ottman *et al.*, 1996*a*, *b*; Bianchi *et al.*, 2003; Jain *et al.*, 2004; Hemminki *et al.*, 2006). Also, in relatives of probands with generalized epilepsy, risk was increased to a greater extent for generalized (SIR = 8.3) than focal epilepsy

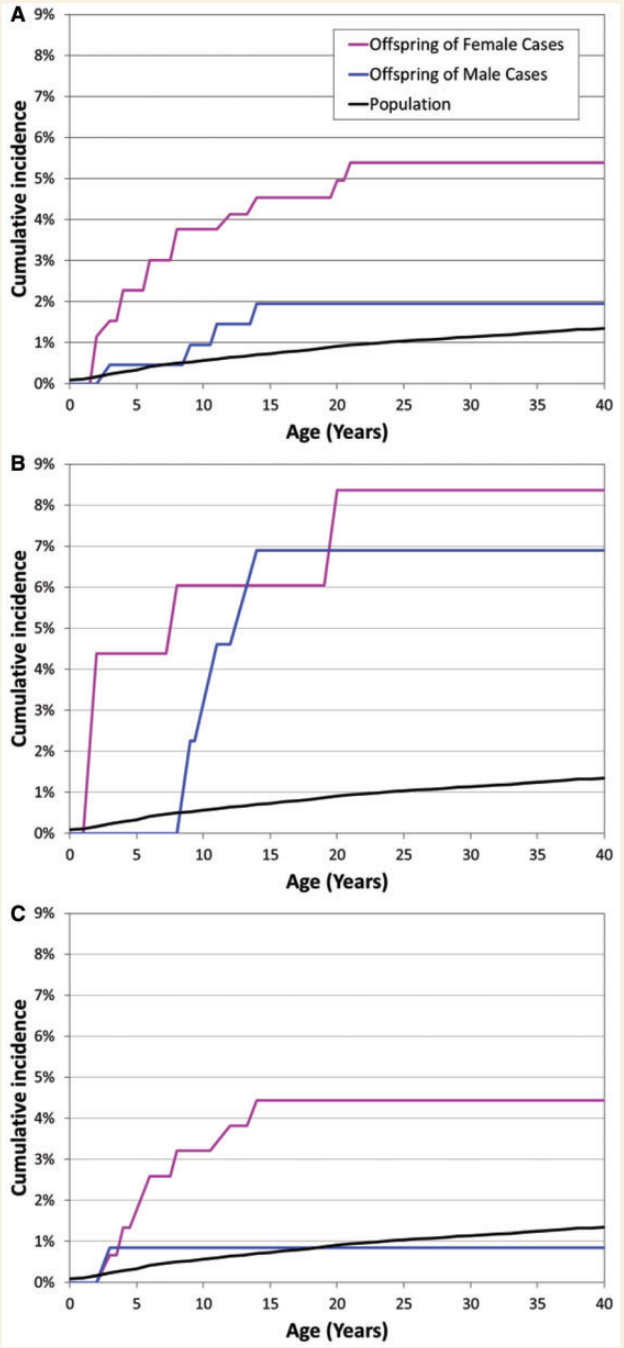

Figure 2 Age-specific cumulative incidence of epilepsy in offspring, by sex of the proband. (**A**) Offspring of all probands. (**B**) Offspring of probands with generalized epilepsy. (**C**) Offspring of probands with focal epilepsy.

(SIR = 2.5), and similarly, in relatives of probands with focal epilepsy, risk was increased to a greater extent for focal (SIR = 2.6) than generalized epilepsy (SIR = 1.0). The SIR for generalized epilepsy in relatives is significantly greater in relatives of probands with generalized (8.5) versus focal epilepsy (1.0), as shown by their non-overlapping confidence intervals. However, within strata defined by proband epilepsy type, the SIRs for generalized and focal epilepsy in relatives do not differ significantly with our sample size (generalized probands: 8.3 versus 2.5, focal probands: 1.0 versus 2.6). Nevertheless, the overall pattern of results suggests that some of the genetic influences on these two broad epilepsy syndromes are distinct. This is consistent with previous results in twin (Berkovic *et al.*, 1998; Kjeldsen *et al.*, 2003; Vadlamudi *et al.*, 2004) and family studies (Bianchi *et al.*, 2003; Winawer *et al.*, 2003; Jain *et al.*, 2004; Hemminki *et al.*, 2006), although no previous study has estimated the magnitude of increased risk for specific epilepsy types in first-degree relatives of probands with the same types, compared with incidence rates in the general population.

The observed pattern of increased risk for specific epilepsy types in relatives (Table 3) also shows an inconsistency that is difficult to explain. Although risk for generalized epilepsy is not increased among relatives of probands with focal epilepsy (SIR = 1.0), risk for focal epilepsy is increased (though not significantly so) among relatives of probands with generalized epilepsy (SIR = 2.5). This difference appears to depend only on whether shared familial risk is viewed from the perspective of the proband or relative. Moreover, our estimate of the magnitude of increased risk for focal epilepsy in relatives is the same, regardless of whether the proband had generalized (SIR = 2.5) or focal epilepsy (SIR = 2.6). This inconsistency may be explained by Type 1 statistical error in the estimate of the SIR for focal epilepsy in relatives of generalized probands, or may reflect some coexisting shared genetic influences on the two types of epilepsy.

As in other population-based studies, a substantial number of probands in our current study could not be classified (Manford *et al.*, 1992; Hemminki *et al.*, 2006). The SIR for relatives of unclassifiable cases was 4.2 (Table 1)—higher than a simple 50% weighted average of the SIRs in relatives of probands with generalized and focal epilepsy, and closer to what would be expected if ~72% of the probands in this group were generalized (i.e. $4.2 = 5.0 \times 72\% + 2.1 \times 28\%$). An excess of generalized cases in this group is likely also because the primary difficulty with classification was lack of EEG findings, which were required for diagnosis of generalized epilepsy in the absence of clear generalized seizure semiology. Assuming most of the unclassifiable relatives had generalized epilepsy, we may have underestimated the SIRs for generalized epilepsy in relatives, implying that the true difference between the SIRs for generalized and focal epilepsy may have been larger than we estimated in relatives of generalized probands, but smaller than we estimated in relatives of focal probands.

We also considered the potential impact of misclassification on our findings. The direction and magnitude of misclassification are difficult to assess because all available information was used for classification of probands and relatives. If misclassification was non-differential by family history, it would be expected to diminish, rather than exacerbate, differences among epilepsy syndromes in the SIR estimates. Differential misclassification was unlikely during the review process because study epileptologists were unaware of relatives' diagnoses, but could have affected the seizure descriptions in the medical records if, for example, treating physicians assumed related patients had the same type of epilepsy.

To assess the impact of misclassification, we explored differences according to the time frame of diagnosis in the probands.

Diagnoses were likely to be more accurate during more recent time periods, when EEG and imaging data were more readily available. For example, among cases diagnosed from 1960–94, the diagnosis of generalized epilepsy was supported by generalized epileptiform EEG abnormalities in 82% of cases (versus 43% of those diagnosed from 1935–59); and similarly, the diagnosis of focal epilepsy was supported by focal epileptiform EEG abnormalities in 62% of cases (versus 49% of those diagnosed earlier). We therefore re-evaluated the SIRs for specific epilepsy types in probands and relatives, after restricting the data to relatives of probands diagnosed in 1960 or later (Supplementary Table 2). The results were quite similar to those in all probands, providing reassurance that misclassification did not have a serious impact on our results.

Our current findings with regard to shared and distinct genetic influences differ from those in our previous work in the Epilepsy Family Study of Columbia University (Ottman *et al*., 1998). In the previous study, risk in parents and siblings was increased to the same extent for focal and generalized epilepsy, among relatives of probands with each epilepsy type (4-fold in relatives of probands with generalized epilepsy, and 2-fold in relatives of probands with focal epilepsy). However, our previous study had limitations that need to be considered. We had no control group, and instead used the relatives of probands with postnatal symptomatic epilepsy as control subjects. Also, diagnosis and classification were based largely on our validated semistructured interview (Ottman *et al*., 1990), which tended to lead to misclassification of individuals with generalized epilepsy as having focal epilepsy. As discussed in (Ottman *et al.*, 1998), this type of differential misclassification would be expected to diminish the estimate of increased risk for generalized epilepsy in relatives of probands with generalized epilepsy. These methodological issues left us with some doubt about the findings, and were a major motivation for carrying out this new study. In the current study, diagnoses were less subject to misclassification because they were based on detailed and comprehensive data abstracted from Mayo Clinic medical records. Because of this and other methodological strengths, we have more confidence in our current results than in our previous ones.

The ILAE Commission on Classification and Terminology has recommended that the IGEs instead be called 'genetic generalized epilepsies' (Berg *et al.*, 2010). We elected not to use this term for two reasons. First, we wanted to distinguish these epilepsies from those in which a specific genetic cause had been identified (e.g. tuberous sclerosis). Second, we were concerned that this term does not reflect the heterogeneity or complexity of cause within the IGEs.

The ILAE Commission describes 'appropriate family studies' as one form of evidence for a genetic basis of these syndromes (Berg *et al.*, 2010). However, few previous family studies provide relevant information about the extent or nature of a genetic contribution to the IGEs. In four major twin studies that examined IGEs specifically, concordance rates in monozygotic twins ranged from 64–82%, implying IGEs are not exclusively genetic (Berkovic *et al.*, 1998; Kjeldsen *et al.*, 2003; Vadlamudi *et al.*, 2004; Corey *et al.*, 2011). The Commission stated that use of the term 'genetic' 'does not exclude the possibility that environmental factors (outside the individual) may contribute to the expression of disease' (Berg *et al.*, 2010). However, incorporating the term 'genetic' into the name of a disorder gives such primacy to the genetic effects that it implies an exclusively genetic cause. This can easily lead to misunderstanding by both physicians and patients, and discourage research to identify non-genetic effects.

Our results show a 6-fold increased risk for all epilepsies (Table 1) and an 11.5-fold increased risk for IGE specifically, in first-degree relatives of individuals with IGEs. This high level of familial aggregation is consistent with a range of different genetic models, including Mendelian effects in a proportion of families and non-genetic effects in others (although no environmental risk factors have yet been identified), or the additive effects of small or moderate genetic and non-genetic effects as assumed in a 'genetically complex' disorder. Although rare monogenic forms of IGE have been identified (Cossette *et al.*, 2002; Suzuki *et al.*, 2004), the pattern of occurrence of IGEs in families is seldom consistent with a Mendelian mode of inheritance. Hence, like most forms of epilepsy, IGEs are widely considered to be genetically complex.

As the relative contributions of genetic and environmental factors to the IGEs are unknown, we estimated the proportion of interindividual variability in risk for IGE that can be attributed to additive genetic variability under a theoretical model for a complex genetic disorder (i.e. narrow sense heritability; Visscher *et al.*, 2008). For this purpose we used an on-line calculator available at http://gump.qimr.edu.au/genroc, which is based on the approach described in Wray *et al.* (2010). Calculations are based on the magnitude of increased risk in first-degree relatives (our SIR of 11.5) and the risk for IGE in the general population, which we estimated as a cumulative incidence of 0.27% up to age 40. Under these assumptions, the resulting estimate of heritability of IGE was 66%. This estimate clearly has some imprecision associated with it—the true value could be higher (or lower) than we estimated. We could find no heritability estimates from twin studies for IGE specifically; in three twin studies that estimated heritability for all epilepsies, estimates were 27% (Sillanpaa *et al.*, 1991), 69% (Miller *et al.*, 1998), and 80% (Kjeldsen *et al.*, 2003). For comparison, we estimate a heritability of all epilepsies of 43%, based on the same method described above. Although these heritability estimates should be interpreted with caution because of their underlying assumptions (e.g. no dominance genetic effects, epistasis, or gene-environment interaction; Visscher *et al.*, 2008), our estimate of 66% does not support the idea that these syndromes should be called 'genetic generalized epilepsies,' despite their high level of familial aggregation.

Risks were substantially higher in offspring of female probands than in offspring of males. As we noted previously (Ottman *et al.*, 1985), this 'maternal effect' has been observed consistently, in almost every study that has ever considered epilepsy risk in offspring in relation to the sex of the affected parent (Ottman *et al.*, 1988; Greenberg *et al.*, 2000). We extended this finding in two ways. First, we found that risks in offspring of female probands were comparable to risks in first-degree relatives overall, whereas risks in offspring of male probands were lower, and not significantly increased compared to the general population. These results suggest that in this population, the maternal effect is more consistent with a lack of increased risk among offspring of men with epilepsy than a greater increase in risk among offspring of

women with epilepsy. Second, in contrast to previous reports (Tsuboi and Christian, 1973; Greenberg *et al.*, 2000), we found that the maternal effect was essentially restricted to offspring of probands with focal epilepsy.

Several biological and methodological explanations have been proposed to explain this finding, but none has proven satisfactory thus far (Ottman *et al.*, 1985, 1988). The design of GESDR allows us to exclude an effect of reporting bias since affected relatives were identified through medical record review rather than interview. Although identification of biological offspring was easier for female than male probands in our study, this would not be expected to lead to reduced rates of epilepsy in offspring who were identified. If we are correct in interpreting the phenomenon as lack of increased risk in offspring of male probands (rather than inflated risk in offspring of females), one possible explanation is 'selective fertility,' i.e. greater reproductive loss or reduced fertility for males with genetic versus non-genetic forms of epilepsy. Some previous studies have found reproductive disadvantage in individuals with epilepsy that may be greater in males than in females (Webber *et al.*, 1986; Schupf and Ottman, 1994, 1996, 1997; Wallace *et al.*, 1998), but findings are inconsistent (Olafsson *et al.*, 1998; Lofgren *et al.*, 2009). We are currently performing additional analyses to address these questions.

The GESDR study has several important strengths. Ascertainment was population-based and included all diagnostic categories of probands, minimizing selection bias in estimating overall risk in relatives. Identification and classification of affected relatives were based on screening and comprehensive review of the relatives' medical records, rather than potentially biased family history interviews. Medical record review for each individual (proband or relative) was carried out independently of that of other affected family members, minimizing the potential for bias in classification according to family history.

Analyses were restricted to relatives' residency periods in Olmsted County, leading to exclusion of some family members; however, this was unlikely to have introduced selection bias because only relatives known to be unaffected at the time of first residency were included and incidence of epilepsy would not be expected to differ between relatives who did and did not live in Olmsted County. Our search of Rochester Epidemiology Project resources may have resulted in incomplete identification of first-degree relatives, but comparison with data from interviews suggests that few were missed. Similarly, the false negative rate for identification of relatives with seizure disorders through screening diagnostic codes was very low (0.6%). Screening of medical records can only capture seizure disorders that are medically attended, but in developed countries, epilepsy prevalence estimates using door-to-door surveys have been similar to those from medical record-based studies (Banerjee *et al.*, 2009), suggesting that nearly all incident cases of epilepsy among relatives residing in Olmsted County were captured.

The Olmsted County population differs from other USA populations in that it is predominantly white non-Hispanic, better educated, and has better access to medical care. Epidemiological studies of the epilepsies in this population have produced many findings that have been confirmed in other settings (Annegers *et al.*, 1996; Hauser *et al.*, 1996), suggesting that generalizability of our findings may not be seriously compromised. Estimates of the magnitude of increased risk in relatives might be expected to differ in populations with substantially different distributions of epilepsy susceptibility alleles or environmental factors, as is well known in the assessment of heritability (Visscher *et al.*, 2008; Wray *et al.*, 2010). However, the consistency of our findings with previous studies (Supplementary Table 1) suggests differences are likely to be small, at least in developed countries where most of this work has been done.

Our estimates of cumulative incidence of epilepsy in relatives may be useful for genetic counseling. For application to clinical settings, statistical uncertainty should be taken into account, and we recommend use of a range of risks derived from the estimates' 95% CIs. These are easily obtained by first computing $1.96 \times SE$, and then subtracting (for the lower limit) or adding (for the upper limit) the result to the risk estimate. For example, the risk of epilepsy to age 40 is 3.5–5.9% for a first-degree relative of an individual with epilepsy overall, and 4.7–11.5% for a first-degree relative of an individual with IGE.

Our results also have implications for phenotype definition in molecular genetic research. The evidence for distinct genetic influences on generalized and focal epilepsy suggests these two broad syndromes should be studied separately. However, because we cannot rule out some coexisting shared genetic influences, in family-based research (linkage analysis or sequencing studies) focused on one of the two broad epilepsy types, it would be prudent to define individuals with the other type as 'unknown' rather than 'unaffected.' The familial aggregation of epilepsies of unknown cause (whether called 'idiopathic,' 'genetic,' or 'unknown') with those associated with intellectual or motor disability (i.e. our 'prenatal/developmental' subgroup) suggests they may be alternative expressions of some shared genetic mechanisms, and should be studied together in the search for susceptibility genes.

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Supplementary material

Supplementary material is available at *Brain* online.

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