Genetic Factors in Seizures: A Population-Based Study of 47,626 US, Norwegian and Danish Twin Pairs

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The purpose of the study was to describe a large sample of twins reporting a history of seizures, to characterize seizures in the three subpopulations, and to estimate the relative importance of genetic and environmental factors in seizure occurrence. Seizure history was determined by questionnaires completed by twins in population-based twin registries in the United States, Norway and Denmark. Concordance rates were calculated for all seizure categories within and across twin populations. Of 47,626 twin pairs evaluated, 6234 reported a history of seizures in one or both twins. Concordance rates were significantly higher for monozygotic (MZ) versus dizygotic (DZ) pairs for all seizure categories within and across populations. The results of this study involving the largest unselected, population-based sample of twins with seizures assembled to date confirm the importance of genetic factors in determining risk for epilepsy, febrile seizures, other seizures and staring spells. This sample is likely to provide an important resource for studying the genetics of epilepsy subtypes and febrile seizures.

Epilepsy, which consists of more than 40 clinical syndromes, may be associated with a variety of conditions. It can be symptomatic and secondary to a known cause (i.e., infections, trauma, stroke, tumors) or idiopathic, without a known cause, and thought to be influenced by genetic factors. Epilepsy and febrile seizures often run in families. Since families share both genes and environmental exposures, this familial aggregation can be due either to shared genes or to shared environment. Familial aggregation studies (Ottman et al., 1996), twin studies (Berkovic et al., 1994; Berkovic et al., 1998; Corey et al., 1991; Kjeldsen et al., 2001; Kjeldsen et al., 2002; Miller et al., 1998; Miller et al., 1999; Sillanpaa et al., 1991) and molecular genetic studies (Anderson, Berkovic, et al., 2002) have provided abundant evidence of a genetic contribution to the risk for epilepsy. Although the localization and identification of the genes responsible for an increasing number of epilepsy syndromes have led to major advances in understanding the etiology of epilepsy, these discoveries have been confined, for the most part, to relatively rare monogenic syndromes accounting for less than 1% of the epilepsies. Therefore the contributions of genetic and environmental factors to risk for the occurrence of more common epilepsy types continue to be poorly understood. This is particularly true since their pattern of inheritance is likely to be complex and the seizure occurrence may involve the actions of multiple genes interacting in complex ways with multiple environmental factors.

The twin study design is unique in its ability to separate and estimate the effects of shared genes from those of shared environment as the source of familial aggregation. Population-based twin samples are especially valuable for studies of this type due to the minimization of selection biases that are usually associated with volunteer or clinic-based samples. However, twin samples of sufficient magnitude to permit precise estimates of the relative contributions of genetic and environmental factors to disease etiology are unlikely to be found in any one region, particularly for diseases, like the epilepsies, that have multiple and heterogeneous phenotypes. Large population-based twin samples combined over geographic regions are therefore needed in order to provide adequate statistical power for hypothesis testing.

This paper characterizes a sample of twins with seizures who were ascertained from population-based

Received 1 September, 2004; accepted 3 February, 2005.

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https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

twin registries in the United States (US), Norway and Denmark. It represents the largest cohort of twins with seizures to be assembled to date. The purpose of the study was to characterize these individual twin populations within the larger cohort; to compare the frequencies of the seizure types examined (i.e., epilepsy, febrile seizures, other seizures and staring spells) in the three populations; and to estimate the relative contributions of genetic and environmental factors to the occurrence of each seizure type. Analyses of subsets of these data have been published previously (Corey et al., 1991; Kjeldsen et al., 2001; Kjeldsen et al., 2002; Miller et al., 1998; Miller et al., 1999).

Materials and Methods

Study Sample

Health history information was collected by questionnaire from twins included in population-based twin registries in three countries: the US (the Mid-Atlantic Twin Registry), Norway (the Norwegian Twin Panels) and Denmark (the Danish Twin Registry). These registries and their sampling methods are described below.

Mid-Atlantic Twin Registry (MATR)

The Mid-Atlantic Twin Registry (MATR), housed in the Virginia Institute for Psychiatric and Behavioral Genetics, Department of Human Genetics at Virginia Commonwealth University, is a population-based registry of twins born in Virginia, North Carolina and South Carolina. The MATR includes all same- and opposite-sex twin pairs born in Virginia (VA) between 1915 and 2000, in North Carolina (NC) between 1913 and 2000, and in South Carolina (SC) between 1915 and 2000 identified by birth records (Anderson, Beverly, et al., 2002). Since efforts to trace twins born in SC are continuing, this study is limited to twins born in VA and NC between 1915 and 1980 (adult cohort) and in VA between 1987 and 1996 (juvenile cohort; Figure 1). A total of 131,470 twin pairs were identified in these cohorts. Contact information was obtained through a variety of public and private sources. It was possible to trace at least one pair member in 48% of adult and 65% of elementary and preschool pairs in the VA component of this sample and at least one pair member in 23% of adult pairs identified thus far in NC. In all, a total of 44,729 twin pairs (34%) were traced in this sample. Seizure history information was obtained for one or both members of all adult pairs participating in the panel (57% [VA]; 23% [NC]) and from the parents of young twins who consented to a telephone interview (99%). In the MATR sample overall, seizure history information was provided by one or both members of 17,112 twin pairs (44%).

Norwegian Twin Panels (NTP)

The twin sample in Norway includes two population-based registries: the Norwegian Twin Panel located at the Institute of Medical Genetics at the University of Oslo, and the Norwegian Institute of Public Health Twin Panel maintained by the Norwegian Institute of Public Health. The Norwegian Twin Panel includes same-sex twins born in Norway between 1915 and 1960 (Bergem, 2002) who were identified through the Central Bureau of Statistics. The Norwegian Institute of Public Health Twin Panel includes same- and opposite-sex twin pairs born in Norway between 1967 and 1979 (Harris et al., 2002) who were identified on the basis of information about multiple births contained in the Medical Birth Registry, a national agency to which all live and stillbirths in Norway must be reported. Overall, a total of 23,917 Norwegian twin pairs were identified (Figure 1). At least one twin pair member could be traced in 79% and 83% of the pairs included in the 1915–1960 cohorts and 1967–1979 cohorts, respectively. A total of 19,101 twin pairs (80%) were traced, with information on health history being obtained from 84% of the older and 74% of the younger group. Seizure history information was provided by one or both members of 13,691 twin pairs (81%) included in the total NTP sample.

Danish Twin Registry (DTR)

The Danish Twin Registry (DTR) is a nationwide, population-based twin panel located at the University of Southern Denmark, in Odense. It includes all twins born in Denmark between 1870 and 1996 (Skytthe et al., 2002). For this study, the sample was restricted to same- and opposite-sexed pairs born between 1953 and 1982. All twins in this cohort were identified through the national Civil Registration System using the unique 10-digit personal identification number assigned to every Danish citizen at birth (Kyvik et al., 1995). Twins were identified by linking mothers with children. Individuals with the same mother who were born within 3 consecutive days were assumed to be twins. A total of 20,888 twin pairs were identified and traced in this cohort (Figure 1). Information about seizure history was obtained from one or both members of 16,823 twin pairs (91%).

Data Collection

Data were collected from twins or their parents. Seizure cases in the adult US and Norwegian samples were identified on the basis of a positive response to questions about whether the individual or their co-twin had a history of epilepsy, febrile seizures, other types of seizures/jerks/convulsions or staring spells. Telephone interviews were used to obtain information pertinent to seizure history from the parents of elementary and preschool twins (VA juveniles).

Danish cases were also selected on the basis of a positive response to questions concerning a history of epilepsy, febrile seizures, other types of seizures, convulsions, jerks or absences. The Danish survey differed from the US and Norwegian versions in that it queried twins only about themselves. No information was requested about the seizure history of the co-twin. Thus, complete health history information on a twin

https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

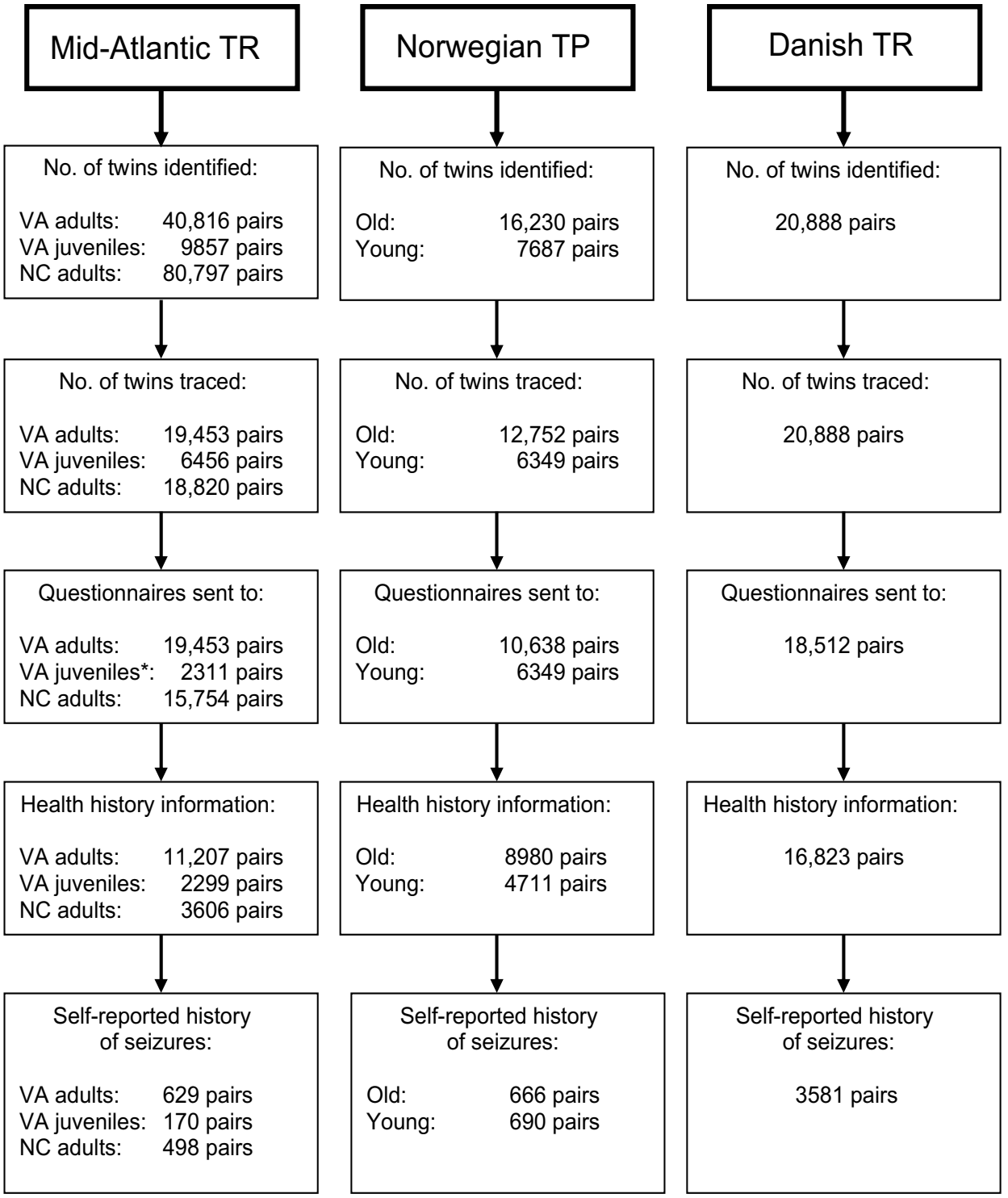

Figure 1

Flow diagram showing ascertainment of seizures in the twin populations from the US, Norway and Denmark.

Note: * VA juveniles were contacted by telephone.

https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

pair was obtained only when both pair members answered and returned the questionnaire.

The screening questions for self-reported seizures were identical in the three countries.

Data Analyses

Seizure type frequencies were calculated within each twin sample and combined over registries for epilepsy (regardless of any other seizure types reported), febrile seizures (regardless of any other seizure types reported), other seizure types (excluding those who reported either epilepsy or febrile seizures) and staring spells (excluding those who reported epilepsy, febrile seizures or other seizures). The diagnostic categories are not mutually exclusive and an affected twin can endorse more than one category (i.e., a twin can be included in both the epilepsy and the febrile seizure category if the twin reported both).

A proband was defined as an individual who reported a history of seizures independently of their co-twin. A secondary case was defined as a twin with seizures who was ascertained through a proband. Probandwise concordance rates were used to estimate the degree of similarity in epilepsy/seizure occurrence of members of monozygotic (MZ) and dizygotic (DZ) twin pairs. Probandwise concordance rates were 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 concordant twin pairs and d, the number of discordant pairs. This statistic gives disease risk for a twin given that his or her co-twin is affected and is directly comparable to disease risk rates in the background population and to recurrence risk in relatives (McGue, 1992). Probandwise concordance rates are robust in the presence of incomplete ascertainment (McGue, 1992) and are, therefore, comparable across studies. Adult US and Norwegian twin pairs were considered to be concordant if both members of the pair reported a history of seizures of the same type or if one or both members of the pair reported that they and their co-twin had a history of seizures of the same type. The elementary/preschool component of the US sample contains no secondary cases because parents provided information about both members of the twin-pair. In the Danish sample, a twin-pair was considered to be concordant when both twins reported a history of seizures of the same type. In all samples, discordant pairs were those where one twin reported seizures and the other did not. Twin-pairs concordant for seizures, but discordant for subtype (i.e., epilepsy, febrile seizures, other seizures, staring spells), were classified as discordant in both categories so as not to overestimate genetic influences.

Concordance rates were calculated for epilepsy, febrile seizures, other forms of seizures and staring spells within and across samples. Twin-pairs where seizure history information was unavailable for both pair members or zygosity could not be assigned were excluded from analyses. Significantly greater similarity within MZ compared to DZ twin-pairs indicates that genetic factors play a role in disease etiology.

Zygosity

Twin zygosity was determined on the basis of each twin's responses to a series of standard questions about physical similarity in childhood and the degree to which pair members were mistaken for each other by relatives and other individuals. This method of zygosity determination is reliable in large twin surveys and has been found to correctly assign zygosity with a greater than 95% probability (Hauge, 1981; Magnus et al., 1983; Peeters et al., 1998). Parents of young twins were asked a similar set of questions, which were adapted for use in children. Those classified as MZ indicated that they were frequently confused by teachers and strangers, had the same eye color, and were as alike as 'two peas in a pod' or 'two drops of water'. With the exception of the procedures used at the Norwegian Institute of Public Health Twin Panel, inconsistent answers or pairs for which there was disagreement between pair members were classified as being of unknown zygosity (UZ). The procedure used there applied discriminant function coefficients to the answers provided by the pair if both twins answered, or by the single responding twin (Harris et al., 1995). These scores were derived from a previous Norwegian twin study which verified the classification based upon discriminant function analysis in a subgroup classified using serological markers (Magnus et al., 1983).

Results

Seizure Prevalence

Seizure history information was provided from a total of 47,626 twin pairs included in the US (29,789 twins included in 17,112 pairs), Norwegian (22,830 twins included in 13,391 pairs) and Danish (29,179 twins included in 16,823 pairs) samples. The distribution of cases partitioned by country is provided in Table 1. Overall, one or both members of 13.1% of twin pairs responded positively to at least one seizure question.

Table 1

Pairs with One or Both Twins Reporting Seizures in Each Twin Sample and the Combined Total, Split Up on Responses to Screening Questions

	Number of twin pairs in:			
	MATR	NTP	DTR	Combined
No. of pairs screened:	17,112 (%)	13,691 (%)	16,823 (%)	47,626 (%)
Positive response to:				
Epilepsy	371 (2.2)	408 (3.0)	473 (2.8)	1252 (2.6)
Febrile seizures	328 (1.9)	465 (3.4)	677 (4.0)	1470 (3.1)
Other seizures	358 (2.1)	244 (1.8)	1976 (11.7)	2578 (5.4)
Staring spells	240 (1.4)	239 (1.7)	455 (2.7)	934 (2.0)
Total no. with seizures:	1297 (7.6)	1356 (9.7)	3581 (21.3)	6234 (13.1)

Note: MATR: Mid-Atlantic Twin Registry; NTP: Norwegian Twin Panels; DTR: Danish Twin Registry. Percentages are given in parenthesis.

https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

Table 2

Frequency of Epilepsy by Sex and Zygosity in Each Country and Combined Across Registries

	MATR		NTP		DTR		MATR + NTP + DTR	
Zygosity group	Total no. of twins	Epilepsy no. (%)	Total no. of twins	Epilepsy no. (%)	Total no. of twins	Epilepsy no. (%)	Total no. of twins	Epilepsy no. (%)
MZ-F	4421	59 (1.3)	5236	81 (1.5)	4569	64 (1.4)	14,226	204 (1.4)
MZ-M	3904	44 (1.1)	4089	62 (1.5)	3977	48 (1.2)	11,970	154 (1.3)
DZ-F	4065	46 (1.1)	5965	125 (2.1)	5232	123 (2.4)	15,262	294 (1.9)
DZ-M	3920	52 (1.3)	5034	115 (2.3)	5295	96 (1.8)	14,249	263 (1.8)
DZ-OS	9420	127 (1.3)	2506	29 (1.2)	9280	149 (1.6)	21,206	305 (1.4)
UZ	4059	66 (1.6)	–	–	826	24 (2.9)	4885	90 (1.8)
ALL	29,789	394 (1.3)	22,830	412 (1.8)	29,179	504 (1.7)	81,798	1310 (1.6)

Note: MZ-F: Monozygotic female twins; MZ-M: Monozygotic male twins; DZ-F: Dizygotic female twins; DZ-M: Dizygotic male twins; DZ-OS: Dizygotic opposite-sex pairs. MATR: Mid-Atlantic twin registry; NTP: Norwegian twin panels; DTR: Danish twin registry.

The increased number of pairs in DTR reporting a seizure history as compared to the MATR and NTP is primarily due to the large number of Danish pairs reporting a history of other seizures (DTR: 11.7%; MATR: 2.1%; NTP: 1.8%). When Danish twin pairs reporting other seizures are excluded, the overall frequency of cases in the combined sample is reduced to 8.9% (4258/47,626) and the frequency of cases in the DTR no longer differs significantly from that observed in the NTP (9.5%, $p = .07$), even though it continues to be significantly higher than in the MATR (7.6%, $p < .05$).

Table 2 provides the number and frequency of twins reporting a history of epilepsy stratified by zygosity and sex. The frequency of twins with a history of epilepsy varied from 1.3% to 1.8% across samples, with an overall frequency 1.6%. This frequency was very similar in the Danish and Norwegian samples (1.7% vs. 1.8%, $p = .5$), but significantly increased compared to the US ($p < .05$). The frequency of epilepsy was significantly increased in DZ compared to MZ twins (1.7% [DZ] vs. 1.4% [MZ], $p < .05$). However, no differences attributable to gender were found (females: 1.7%; males: 1.6%; $p = .4$).

The distribution of febrile seizures stratified by zygosity and sex within and across populations is provided in Table 3. The frequency of febrile seizures ranged from 1.5% to 2.8%, with an overall frequency of 2.1% in the combined sample. The frequency of febrile seizures was significantly lower in the MATR sample compared to the NTP and DTR samples (1.4%, $p < .05$); with febrile seizures being more prevalent in Danish compared to Norwegian twins (2.8% vs. 2.1%, $p < .05$). Neither zygosity (MZ: 2.3%; DZ: 2.1%, $p = .09$) nor sex (females: 2.1%; males: 2.2%, $p = .7$) appear to influence risk for febrile seizures.

The number and frequency of twin individuals reporting a history of other seizures stratified by zygosity and sex within each country and combined across registries are given in Table 4. The frequency of other seizures is quite variable and ranges from 1.0% to 7.2%. Overall, 3.4% of twins reported a history of other seizures, with the Danish samples accounting for the majority of these reports (7.2%, $p < .001$). The frequency of other seizures reported by Norwegian twins is significantly more than in the US sample even though the observed frequencies fall within a similar range (NTP: 1.4%; MATR: 1.0%, $p < .001$). Significantly

Table 3

Frequency of Febrile Seizures (FS) by Sex and Zygosity in Each Country and Combined Across Countries

	MATR		NTP		DTR		MATR + NTP + DTR	
Zygosity group	Total no. of twins	FS no. (%)	Total no. of twins	FS no. (%)	Total no. of twins	FS no. (%)	Total no. of twins	FS no. (%)
MZ-F	4421	69 (1.6)	5236	98 (1.9)	4569	144 (3.2)	14,226	311 (2.2)
MZ-M	3904	71 (1.8)	4089	93 (2.3)	3977	119 (3.0)	11,970	283 (2.4)
DZ-F	4065	60 (1.5)	5965	132 (2.2)	5232	122 (2.3)	15,262	314 (2.1)
DZ-M	3920	47 (1.2)	5034	88 (1.7)	5295	150 (2.8)	14,249	285 (2.0)
DZ-OS	9420	130 (1.4)	2506	77 (3.1)	9280	250 (2.7)	21,206	457 (2.2)
UZ	4059	67 (1.7)	–	–	826	20 (2.4)	4885	87 (1.8)
ALL	29,789	444 (1.5)	22,830	488 (2.1)	29,179	805 (2.8)	81,798	1737 (2.1)

Note: MZ-F: Monozygotic female twins; MZ-M: Monozygotic male twins; DZ-F: Dizygotic female twins; DZ-M: Dizygotic male twins; DZ-OS: Dizygotic opposite-sex pairs. MATR: Mid-Atlantic twin registry; NTP: Norwegian twin panels; DTR: Danish twin registry.

https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

Table 4

Frequency of Other Seizures by Sex and Zygosity in Each Country and Combined Across Registries

	MATR		NTP		DTR		MATR + NTP + DTR	
Zygosity Group	Total no. of twins	Other no. (%)	Total no. of twins	Other no. (%)	Total no. of twins	Other no. (%)	Total no. of twins	Other no. (%)
MZ-F	4421	64 (1.4)	5236	52 (1.0)	4569	348 (7.6)	14,226	464 (3.3)
MZ-M	3904	42 (1.1)	4089	44 (1.0)	3977	237 (5.9)	11,970	323 (2.7)
DZ-F	4065	56(1.4)	5965	66 (1.1)	5232	371 (7.1)	15,262	493 (3.2)
DZ-M	3920	44 (1.1)	5034	46 (0.9)	5295	405 (7.6)	14,249	495 (3.5)
DZ-OS	9420	128 (1.4)	2506	28 (1.1)	9280	719 (7.7)	21,206	875 (4.1)
UZ	4059	82 (2.0)	–	–	826	73 (8.8)	4885	155 (3.2)
ALL	29,789	416 (1.4)	22,830	236 (1.0)	29,179	2153 (7.2)	81,798	2805 (3.4)

Note: MZ-F: Monozygotic female twins; MZ-M: Monozygotic male twins; DZ-F: Dizygotic female pairs; DZ-M: Dizygotic male twins; DZ-OS: Dizygotic opposite-sex pairs. MATR: Mid-Atlantic twin registry; NTP: Norwegian twin panels; DTR: Danish twin registry.

more DZ twins reported a history of other seizures (MZ: 3.0%; DZ: 3.7%, $p < .001$). No differences attributable to gender were observed (females: 3.2%; males 3.1%, $p = .4$).

The distribution of twins reporting staring spells without a concomitant history of any other seizure type stratified by zygosity and sex within and combined across populations, is given in Table 5. The frequency of staring spells varied from 1.0% to 1.6% across samples, with an overall frequency of 1.2%. Significantly higher frequency of staring spells was found in the DTR compared to the US and Norwegian samples (DTR: 1.6 %; MATR, NTR: 1.0%, $p < .001$). Although no significant differences due to zygosity were observed in the combined sample (MZ: 1.1%; DZ: 1.2%, $p = .08$), significantly more female members of same-sex pairs reported a history of staring spells than males (females: 1.4%; males: 0.6%, $p < .001$). This preponderance of females with staring spells was found in all three twin samples and was further substantiated in opposite-sex pairs (DZ-OS) where significantly more affected pair members than expected were female (66%, $p < .001$).

The probandwise concordance rates for epilepsy, febrile seizures, other seizures and staring spells within and across populations are provided in Table 6. Twin pairs where disease status of both pair members was unknown were excluded from these analyses. MZ twins were significantly more concordant for epilepsy than were DZ twins both within and across samples. MZ co-twins of epilepsy probands had a 28% risk of being affected in the combined sample. This risk is significantly reduced for co-twins of DZ proband (7%, $p < .001$). Significantly higher concordance rates were also seen for febrile seizures in MZ as compared to DZ twins both within and across registries. MZ co-twin of a febrile seizure proband had a 33% probability of being affected whereas this risk is significantly reduced for co-twins of DZ probands (11%, $p < .001$). A similar pattern was seen for other seizures and staring spells in the Norwegian and Danish samples.

Discussion

The contribution of genetic and environmental factors to risk for seizures was examined using data provided by twins ascertained from three large, unselected, population-based twin registries from the US, Norway

Table 5

Frequency of Staring Spells by Sex and Zygosity in Each Country and Combined Across Registries

	MATR		NTP		DTR		MATR + NTP + DTR	
Zygosity group	Total no. of twins	Staring no. (%)	Total no. of twins	Staring no. (%)	Total no. of twins	Staring no. (%)	Total no. of twins	Staring no. (%)
MZ-F	4421	38 (0.9)	5236	69 (1.3)	4569	95 (2.1)	14,226	202 (1.4)
MZ-M	3904	14 (0.4)	4089	25 (0.6)	3977	39 (1.0)	11,970	78 (0.7)
DZ-F	4065	39 (1.0)	5965	64 (1.1)	5232	104 (2.0)	15,262	207 (1.4)
DZ-M	3920	14 (0.4)	5034	18 (0.4)	5295	50 (0.9)	14,249	82 (0.6)
DZ-OS	9420	96 (1.0)	2506	58 (2.3)	9280	172 (1.8)	21,206	326 (1.5)
UZ	4059	97 (2.3)	–	–	826	17 (2.1)	4885	114 (2.3)
ALL	29,789	298 (1.0)	22,830	234 (1.0)	29,179	477 (1.6)	81,798	1009 (1.2)

Note: MZ-F: Monozygotic female twins; MZ-M: Monozygotic male twins; DZ-F: Dizygotic female twins; DZ-M: Dizygotic male twins; DZ-OS: Dizygotic opposite-sex pairs. MATR: Mid-Atlantic twin registry; NTP: Norwegian twin panels; DTR: Danish twin registry.

https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

Table 6

Number of Affected Twin Pairs and Concordance Rates by Country and Combined Across Registries

	MATR	NTP	DTR	Combined
Epilepsy				
MZ pairs	89	132	79	300
DZ pairs	217	274	267	758
MZ-CR	.23 (.15–.32)	.27 (.20–.34)	.37 (.28–.48)	.28 (.24–.34)
DZ-CR	.04 (.02–.08)	.07 (.04–.11)	.08 (.05–.12)	.07 (.05–.09)
	$p < .001$	$p < .001$	$p < .001$	$p < .001$
Febrile seizures:				
MZ pairs	98	163	180	441
DZ pairs	196	284	361	841
MZ-CR	.39 (.30–.48)	.27 (.21–.34)	.36 (.29–.42)	.33 (.29–.38)
DZ-CR	.10 (.06–.15)	.11 (.08–.15)	.11 (.08–.15)	.11 (.09–.13)
	$p < .001$	$p < .001$	$p < .001$	$p < .001$
Other seizures				
MZ pairs	90	47	390	527
DZ pairs	212	74	996	1,282
MZ-CR	.27 (.18–.37)	.16 (.09–.25)	.30 (.25–.33)	.26 (.23–.30)
DZ-CR	.10 (.06–.15)	.07 (.03–.12)	.18 (.16–.20)	.16 (.14–.18)
	$p < .001$	$p < .05$	$p < .001$	$p < .001$
Staring spells				
MZ pairs	45	90	90	225
DZ pairs	136	149	217	502
MZ-CR	.17 (.08–.31)	.27 (.18–.37)	.29 (.20–.38)	.26 (.20–.32)
DZ-CR	.12 (.07–.19)	.09 (.05–.15)	.05 (.02–.08)	.08 (.06–.11)
	ns	$p < .001$	$p < .001$	$p < .001$

Note: 95% confidence interval in parenthesis; MZ: Monozygotic; DZ: Dizygotic; CR: Concordance rate.
Data analysis is done on complete pairs, where disease status is known in both twin members of the pair.
MATR: Mid-Atlantic Twin Registry; NTP: Norwegian Twin Panels; DTR: Danish Twin Registry; *ns*: nonsignificant.

and Denmark. This sample of 47,626 pairs included more than 6000 pairs containing at least one member reporting seizures. It represents the largest sample of this type to be studied to date.

Significant differences were observed in the frequency of cases within seizure categories across populations. However, these differences are more likely to be a result of large sample size rather than a reflection of true differences in seizure risk between populations. Across populations, 1.6% of twins reported a history of epilepsy and is well within the range reported by others (Hauser et al., 1993; Hauser & Kurland, 1975; Sander, 2003). The frequency of seizures did not differ between the two Scandinavian countries and the lower frequency in the US twin sample could be due to differences in recall bias, level of stigmatization or differences in the medical care systems in the US and Scandinavia.

The frequency of febrile seizures in the combined sample is lower than expected, with the observed frequency approaching 3% in Denmark alone. Differences in the age distribution of the three registries could explain this discrepancy as the Danish cohort is younger. These twins are more likely to be aware of their own febrile seizure history and more likely to have parents available to provide relevant information.

The frequency of 'other seizures' varied widely across populations with estimates ranging from 1.0% in NTR to 7.2% in DTR. The Danish sample might include a high frequency of false positives since the phrasing in Danish for 'other forms of seizures, convulsions or jerks', is unspecific. The Danish word for seizure ('anfald') includes everything from an epileptic seizure to an anxiety attack, panic attack, fit, or burst of anger, and jerks could be anything from epileptic jerks to leg cramps or hygnagogic myoclonias.

Staring spells were reported by 1.2% of the total sample with frequencies being fairly similar in the three countries. Staring spells were consistently found to be more frequent in females than males, both in same- and opposite-sex pairs. Absences are more frequent in girls (Loiseau, 1992) and if some cases of staring spells reported actually represent absence seizures, a female preponderance is to be expected.

The significantly increased concordance of MZ compared to DZ twins for all seizure categories in the combined sample suggest that genetic factors play a major role in seizure occurrence and confirm the results of previous studies that emphasize the important contribution of genes to seizure risk (Berkovic et al., 1998; Corey et al., 1991; Harvald & Hauge, 1965; Kjeldsen et al., 2001; Kjeldsen et al., 2002; Lennox, 1951; Lennox-Buchthal, 1971; Lennox-Buchthal, 1973; Miller et al., 1998; Schiøttz-Christensen, 1972; Sillanpaa et al., 1991; Tsuboi, 1989; Tsuboi & Endo, 1991).

In the majority of cases, the occurrence of febrile seizures does not appear to be associated with later risk for epilepsy. This is consistent with previous studies that have suggested that the genes that influence isolated febrile seizures are different from those that influence afebrile seizures (Annegers et al., 1987; Knudsen et al., 1996; Verity & Golding, 1991). With the exception of generalized epilepsy with febrile seizures plus (GEFS+), the loci that are responsible for determining risk for isolated febrile seizures are different from those responsible for epilepsy (Anderson, Berkovic et al., 2002). Although the comorbidity of febrile seizures and epilepsy has not been examined in this study, the differences observed in the variance structures of each are consistent with the existence of different etiologies.

The degree to which the results of twin studies can be generalized to singletons may be of concern. Twins do differ from singletons in both intrauterine environment and upbringing. However, a comprehensive Australian study conducted by Berkovic et al. (1993), has shown that twin birth is not a major risk factor

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for seizures, suggesting that the results obtained in this study can be applied to the general population. Further, since the frequency of epilepsy and febrile seizures observed in this sample was within the expected range for singletons, twin birth does not appear to be a risk factor for these disorders.

Despite the population-based nature of this sample, the information obtained is based upon self- and, in some cases, co-twin reports. Potential biases could therefore exist in estimates of seizure frequency in this group. A history of seizures may be underreported due to recall bias or lack of knowledge of seizures during childhood. It is likely that different types of biases may be operating in each of the populations as a result of their unique characteristics. In the Danish sample, twins provided information about seizure history for themselves alone. The true frequency of seizures in the Danish sample could be underestimated since those discordant pairs where the affected twin did not respond or denied ever having had a seizure would not be included in the analysis. In the older Norwegian and US samples the loss of affected twins due to recall bias may well equal the loss of affected twins in the Danish sample due to the lack of information on both pair members. Although the ability to trace and contact twins was not an issue with regard to the Danish and Norwegian samples because of the registration system, it was an issue for the MATR.

While it was possible to ascertain all twin pairs born in the MATR catchment area from birth records, current addresses of the twins identified were not readily available. Twins were traced largely by matching names and dates of birth with the Virginia or North Carolina Departments of Motor Vehicles or by matching names and dates of birth with credit header files maintained by commercial data warehouses. This approach may have introduced a bias against the inclusion of those with more severe forms of epilepsy since these individuals are likely to be unable to obtain and maintain a driver's license. This bias is reduced to some degree, however, because twins were asked to provide information on their co-twin, and only those pairs where both members were so severely affected as to be unable to drive or obtain credit cards would be missed. This could reduce the number of concordant pairs and thereby estimates of concordance rates.

As is the case for all results based upon self-reported information, the validity of the data on seizures is of concern. Affected cases are based on the twins' own perception of having epilepsy, febrile seizures or other types of seizures. Since it is self-reported data that has not been neurologically verified, the diagnostic criteria of epilepsy may in some cases not be fulfilled. The category 'other types of seizures' may also be very broad and may encompass syncope and isolated epilepsy seizures. For this reason, all twins who reported a history of seizures are currently being clinically evaluated by neurologists, and seizures and syndromes are being classified according to criteria of the International League Against Epilepsy (ILAE; 1981, 1989). As part of this ongoing study, the families of twins in whom seizures have been verified are also being screened, evaluated and classified using the same procedure.

This cohort, which represents the largest population-based sample of twins with seizures identified to date, provides an important resource for assessing the genetic bases of seizures that extends well beyond the classical twin study paradigm. Although twin studies alone will not permit the identification of the specific genes involved in determining seizure risk, their use in analyses of epilepsy syndrome subgroups will facilitate the identification of syndromes in which the search for epilepsy susceptibility genes might be most successful. An examination of twin pairs who are discordant for 'idiopathic or genetic epilepsy' could lead to the identification of acquired factors that cause epilepsy (Briellmann et al., 2001; Jackson et al., 1998). The relatively large number of MZ pairs included in this sample may permit an assessment of the extent to which the importance of the environmental exposures in the occurrence of seizures differs across epilepsy types, as well as provide insight about the specific epilepsy types most affected by environmental exposures. This information will be valuable in the identification of those subtypes where susceptibility rather than syndrome specific genes are important. For those epilepsy types where occurrence is dependent upon the presence of less specific susceptibility alleles in conjunction with the existence of specific environmental exposures, concordance rates for MZ twins would be reduced and the number of discordant MZ pairs increased.

Extending the twin study to include other family members makes it possible to identify multiplex families for more extensive genetic analyses. Twins, as ideally matched sib-pairs, provide a powerful tool for identifying genes. Studying epilepsy in DZ twins can enhance the power of conventional strategies to detect genetic influence through linkage and association as a result of their precise matching for age, shared environmental factors and background environmental variation (MacGregor et al., 2000).

Acknowledgments

This study was supported in part by the following grants: NINDS grant (NS-31564); The Clinical Research Institute, University of Southern Denmark, Odense University; The grant committee of Consultancy Counsel, Odense University Hospital; The Danish Epilepsy Society Research Foundation; The Hede Nielsen Foundation; The K. A. Rohdes Foundation, The Hørslev Foundation, The Jacob and Olga Madsen Foundation and The Novo Nordic Foundation. The Norwegian Institute of Public Health twin research program is supported by grants from The Norwegian Research Council, The Norwegian Foundation for Health and Rehabilitation, and the European Commission under the program 'Quality of Life and

https://doi.org/10.1375/twin.8.2.138 Published online by Cambridge University Press

Management of the Living Resources' of 5th Framework Programme (no. QLG2-CT-2002-01254).

We especially would like to thank all of the twins who participated in the study in the US, Norway and Denmark, and without whom this study would not have been possible.

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