

High concordance for essential tremor in monozygotic twins of old age

D. Lorenz, MD; H. Frederiksen, MD, PhD; H. Moises, MD, PhD; F. Kopper, MD; G. Deuschl, MD, PhD; and K. Christensen, MD, PhD

Abstract—Objective: To assess the relative contribution of genetic and environmental factors for the etiology of essential tremor (ET) and to explore the effect of different diagnostic criteria. **Methods:** A total of 2,448 twins of the Danish twin registry aged 70 years or more were screened for ET by an interview and an Archimedes spiral test. All twin pairs ($n = 162$) with a positive screening test of at least one of the twins were recontacted and 218 individuals (109 pairs) were interviewed and examined by a movement disorder specialist. The consensus criteria of the Tremor Investigation Group were applied to diagnose ET. **Results:** Twenty-nine twins fulfilled the criteria of definite, 7 of probable, and 56 of possible ET. The probandwise concordance rate for the broadest definition of ET was 77% for monozygotic twins (MZ) and 59% for dizygotic twins (DZ). However, in an analysis restricted to cases of probable and definite ET, the concordance rates were 93% and 29%. The heritability for the liability to ET ranged from 93% to 99% using a general population prevalence of 1.2% for white 70+-year-olds. The inclusion of probable and exclusion of possible cases in the diagnosis of ET produced the highest concordance rates. **Conclusion:** The high concordance among MZ twins of very old age in this first population-based twin study of ET suggests that a disease phenotype consisting of definite and probable ET has a high heritability and hence is a good candidate for a phenotype to be used in linkage studies.

NEUROLOGY 2004;62:208–211

Essential tremor (ET) is the most prevalent adult movement disorder. The prevalence estimates in different studies worldwide range from 0.4% to 3.9% for the general population and from 1.3% to 5.1% for the age group above 60 years.¹

Family studies frequently show a pattern of aggregation corresponding to an autosomal dominant mode of inheritance of ET.^{2–4} Furthermore, unrepliated linkage findings suggest that susceptibility genes for ET are localized on chromosomes 2 and 3.^{5–11} However, the magnitude of the genetic contribution and the nature of the environmental effect is unknown.¹²

Twin studies can provide an estimate of the magnitude of the genetic effect by employing statistical models. The twin methodology is based on the fact that monozygotic (MZ) twins have identical genotypes whereas dizygotic (DZ) twins share, on average, only half of their segregating genes. The complete lack of twin investigations for ET in 2000 motivated us to carry out the first population-based twin study to estimate the magnitude of the genetic effect in the etiology of the disease and to explore the effect of different diagnostic criteria.

Subjects and methods. *Twin sample.* The sample is based on the participants in the Longitudinal Study of Aging Danish Twins (LSADT).^{13,14} It was drawn from the older cohorts of the Danish Twin Registry, which include twins born between 1870 and 1910 and like-sex twin pairs born between 1911 and 1930 in Denmark.

The 2,448 participants in the LSADT 2001 survey were investigated for signs of ET by a screening procedure.

Screening procedure. The screening procedure for signs of ET consisted of the drawing of an Archimedes spiral with the dominant hand within preprinted lines¹⁵ and an interview. The spiral of each participant was rated blindly and independently by two movement disorder specialists (D.L., F.K.) with moderate interrater agreement (kappa value 0.48).¹⁵ For interview, a shortened version of a questionnaire with good sensitivity and high specificity was employed,¹⁶ consisting of the following questions: 1) Has a doctor diagnosed you as having familial tremor or essential tremor? 2) Do you often have shaking or tremor that you cannot control anywhere in the following parts of the body: hands, arms, or voice? 3) Does your head often shake uncontrollably? 4) Do other people often tell you that you have tremor? 5) Do you have a problem because your hand trembles uncontrollably when you button your shirt? 6) Does anybody in your family have the same sort of tremor? Participants were considered to be positively screened for ET 1) if they had a spiral score of >4 or 2) if they reported positively on question 1 or 3) on two or more of the questions 2 to 6. The procedure is shown in the figure.

Neurologic examination. The positive twin pairs were recontacted by letter requesting their participation in a neurologic follow-up study in their homes. This letter included information about ET, the tremor project, and the duration of the visit, and indicated that a blood sample would be taken. A German neurologist specializing in movement disorders (D.L.) interviewed and examined 109 twin pairs after obtaining informed consent. The neurologist was blinded to the twin zygosity, was not informed about the twins' names or addresses, and was not involved in the route planning or the scheduling of the visits. The co-twins were examined at separate appointments. The interview as well as the neurologic examination was conducted in a standardized manner and the tremor criteria were applied uniformly. The 218 individuals were visited during a period of 5 months with short weekly breaks and a frequency of about eight twins per day. Dropouts

From the Department of Neurology and Department of Psychiatry (Drs. Lorenz, Moises, Kopper, and Deuschl), Christian-Albrechts-University Kiel, Germany; and the Danish Twin Registry (Drs. Frederiksen and Christensen), Epidemiology, Institute of Public Health, University of Southern Denmark.

Supported by the US National Institute on Aging research grant NIA-P01-AG08761I and in part by the BMBF Kompetenznetz Parkinson.

Received June 20, 2003. Accepted in final form September 18, 2003.

Address correspondence and reprint requests to Dr. Günther Deuschl, Department of Neurology, Christian-Albrechts-University Kiel, Niemannsweg 147, 24105 Kiel, Germany; e-mail: g.deuschl@neurologie.uni-kiel.de

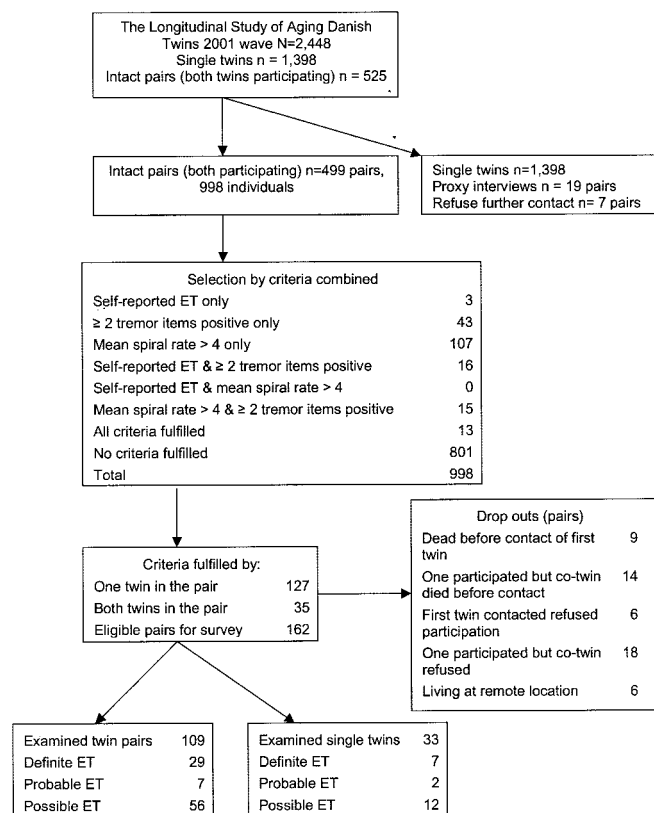


Figure. Screening procedure and diagnoses. ET = essential tremor.

were due to lack of consent, death, or living on a remote island (see the figure).

The full neurologic examination included a rating of tremor according to the Fahn tremor scale¹⁷ as well as additional task-related tremor items (using a spoon to drink water, drinking water, and finger-to-nose test)¹⁸ and the performance of an additional Archimedes spiral test for each hand, which was evaluated according to Bain et al.'s criteria.¹⁵ Parkinson's disease (PD) was excluded by examining for akinesia, rigidity, postural stability, and rest tremor as well. ET was diagnosed on the three levels of certainty as definite, probable, or possible ET by the consensus criteria of the Tremor Investigation Group (TRIG).¹⁹ Zygosity was determined by genotyping short-tandem repeats at 15 genetic loci on different chromosomes.²⁰

Statistical analysis. The sample and dropouts were tested by standard statistical methods (*t*-test/analysis of variance and the χ^2 test) for significant differences with regard to sex, screening results, age, and age at onset.

The intrapair similarity in MZ and DZ twins was assessed using probandwise concordance rates and correlations for ET. The probandwise concordance rate is defined as the proportion of affected twin partners of probands. The probandwise concordant risk is directly comparable to risk estimates for other relatives whereas the pairwise concordance rate refers to the proportion of affected pairs and not individuals.²¹ However, to compare our results to the only other existing twin study of ET, the World War II Veteran Twin study,²² we also calculated pairwise concordance rates.

The correlations for ET, expressed as the standard tetrachoric correlations used in twin studies, were estimated using the multifactorial threshold model.²³ This assumes that there is an underlying normally distributed liability (susceptibility) to a disease due to genetic and environmental factors. The manifestation of a disease appears when an individual exceeds the threshold of affection on the liability distribution. The impact of genetic and environmental effects is reflected in the similarity of the other twin's liability to the disease. According to standard biometric practice the heritability of the liability to ET can be calculated

under these assumptions.²⁴ If the prevalence of ET in the population under study is known then the heritability can be calculated based on the pairs with at least one twin affected (i.e., without having neurologic examinations of the pairs where both co-twins were negative on the ET screen test).²⁵

The study was approved by the Danish Scientific Ethical Committees (reference no. 20010177).

Results. Evaluation of screening results revealed 162 pairs where at least one twin fulfilled the screening criteria. Among these, 218 twins from 109 twin pairs were visited and examined. Overall, 29 twins fulfilled the criteria of definite, 7 of probable, and 56 of possible ET according to the TRIG criteria.¹⁹ Among the eligible, 23% did not participate for various reasons (see the figure). The non-participants did not differ with regard to age or sex in comparison to the examined group (data not shown). Furthermore, the proportion of pairs that were concordant for being positive on the screening criteria was highly comparable among the examined (21.1%) and nonparticipants (23.5%, $p = 0.8$). Additional PD was diagnosed in one twin in the possible ET group and furthermore in two twins whose siblings were positively screened and had possible ET.

Table 1 shows that the age at examination, age at onset of ET, and sex distribution were highly comparable across zygosity and different diagnostic categories. The only exception was a statistically significant difference between MZ and DZ with regard to age at onset in the subgroup of definite ET reflecting a lower mean age at onset in DZ ($p = 0.02$, see table 1).

Probandwise concordance rates and heritability estimates are displayed in table 2. In addition, pairwise concordance rates are given to enable a direct comparison with the results of the World War II Veteran Twin study.²² The concordance rates and heritability estimates depend on the definition of the phenotype (diagnostic certainty of ET). The probandwise concordance rate for ET was higher in MZ than in DZ twins for all diagnostic classes. In the highest level of diagnostic certainty, the definite ET group, the probandwise concordance rate was 0.77 for MZ and 0.25 for DZ. The inclusion of probable cases resulted in an increase of the probandwise concordance rate to 0.93 in MZ and to 0.29 in DZ as compared to the definite cases. However, the inclusion of possible ET led again to a decrease of the probandwise concordance rate to 0.77 in MZ and to 0.59 in DZ.

Using the current data, the heritability for the liability to ET was estimated to be 93% in the definite ET group, 99% in the group consisting of definite and probable ET, and 93% in all ET cases based on a general population prevalence of 1.2% for white 70+-year-olds. A prevalence of 5% gave similar results (heritabilities 87% to 99%), indicating robustness of the estimates.

Discussion. The probandwise concordance rate for the broadest definition of ET (i.e., including cases possibly affected) was 77% for MZ twins and 59% for DZ twins. However, in an analysis restricted to cases with a higher degree of certainty of being affected by ET (probable and definite ET), the concordance rates were 93% and 29%. The estimate of heritability, a term denoting the magnitude of the genetic effect, was in this group 99% (95% CI 90 to 100%). In the only discordant MZ twin pair the nonaffected twin

Table 1 Age at examination, sex, and age at onset of ET for different zygosity and diagnostic categories

Characteristics	Definite ET		Probable ET		Possible ET	
	MZ, n = 13	DZ, n = 16	MZ, n = 2	DZ, n = 5	MZ, n = 23	DZ, n = 33
Age at examination, y, mean ± SD	75.7 ± 4.3	74.5 ± 4.2	79.8 ± 4.8	72.9 ± 1.2	76.3 ± 3.6	75.9 ± 4.7
Age at ET onset, y, mean ± SD	49.8 ± 23.3	22.3 ± 21.3	70.0 ± 2.8	68.4 ± 1.1	73.3 ± 4.4	73.0 ± 6.1
Males, %	92	62.5	50	80	56.5	57.6

ET = essential tremor; MZ = monozygotic; DZ = dizygotic.

had clinical ET but only for 2.5 years and hence will meet the diagnostic criteria for probable ET in about half a year, meaning a 100% concordance for this. The finding was so unexpected that we tried to find possible biases in our study without avail.

First, although an observer bias with regard to zygosity cannot be excluded, it is rather unlikely to have influenced our findings because the examiner was blind in regard to the results of the zygosity determination. Furthermore, she was blind in regard to the diagnostic status of the co-twin during her visits. Because of the high number and the high daily frequency of visits of twins over a period of 5 months, even similar appearances of twins escaped the examiner's perception. Furthermore, the interview and neurologic examination was conducted in a standardized manner and the tremor criteria were applied uniformly. The strict classification criteria prevented a substantial influence of observer biases on the findings of the current study.

Second, any study on the epidemiology and genetics of ET is limited by the uncertainties about the inclusion criteria for ET. We have employed the TRIG criteria, which were defined as a consensus statement by several movement disorder specialists,

although their reliability has not been investigated so far.

Third, a selection bias toward the familial form of ET appears to be unlikely because the number of self-reported ET in the family was low. Only three individuals who reported other cases of tremor in the family were included solely on basis of the tremor item criteria (>1 tremor item positive), but such a report was not a sufficient criterion for inclusion in the study (see the figure). There might be a selection bias toward more severely affected ET cases because the original form of the modified screening questionnaire employed in the current investigation has shown a tendency to miss milder tremor cases.¹⁶ On the other hand, the Veteran Twin study did not use this screening questionnaire and obtained results that are in agreement with the findings of the current study if the same diagnostic threshold (inclusion of possible ET) and statistical method (pairwise concordance rate) are applied to our material (see table 2).

The observed statistically significant difference in age at onset between MZ and DZ twins in the subgroup of definite ET cases is caused by a higher number of DZ twins reporting an onset of tremor in

Table 2 Probandwise and pairwise concordance rates and tetrachoric correlations for essential tremor (ET) among Danish twins aged 70+ years

Zygosity	Concordant pairs (both ET)	Discordant pairs (one with ET and one without ET)	Probandwise concordance rate (95% CI)	Pairwise concordance rate (95% CI)	Tetrachoric correlation (95% CI)
TRIG diagnostic criteria—definite only					
Monozygotic	5	3	0.77 (0.55–1.00)*	0.63 (0.25–1.00)*	0.93 (0.71–0.99)
Dizygotic	2	12	0.25 (0.13–0.60)	0.14 (0.00–0.38)	0.50 (0.11–0.79)
TRIG diagnostic criteria—probable included					
Monozygotic	7	1	0.93 (0.86–1.00)*	0.88 (0.57–1.00)†	0.99 (0.90–1.00)
Dizygotic	3	15	0.29 (0.11–0.62)	0.17 (0.00–0.39)	0.55 (0.22–0.79)
TRIG diagnostic criteria—possible included					
Monozygotic	15	9	0.77 (0.63–0.91)	0.63 (0.43–0.83)*	0.93 (0.83–0.98)
Dizygotic	15	21	0.59 (0.43–0.76)	0.42 (0.26–0.58)	0.82 (0.68–0.91)

* $p < 0.05$,

† $p < 0.01$.

p Values for monozygotic ≤ dizygotic concordance rates.

childhood and probably reflects random variation due to the small numbers in each group. The exclusion of the early onset cases from the analysis gave similar concordance rates and did not change the conclusions of our study. Moreover, the lower mean age among DZ twins at diagnosis would lead to a bias toward finding no genetic effect, and thus we cannot rule out that our estimate of a genetic influence is conservative.

Splitting or lumping is an unsolved controversy in the nosologic research of many common disorders. Lumping has the advantage intellectually of avoiding unnecessary complexity and statistically of providing large sample sizes.²⁶ Historically, many disease entities had to be split in smaller etiologic categories (e.g., the epilepsies) with the former disease entity sometimes remaining as a syndrome caused by a common final pathway. In genetic research, many problems have to be overcome before one can expect a reasonable chance of success in mapping genes underlying a complex disease such as ET.²⁷ A major problem is the lumping of nongenetic (phenocopies) and genetic cases originating from different mutations and different genes (locus and allelic heterogeneity). Locus heterogeneity in familial ET has already been found by linkage analyses of multiplex families.^{5,6} Splitting and analyses of subgroups are generally expected to enhance gene finding.²⁶ ET can be subdivided by electrophysiologic and pharmacologic measures.²⁸ Measures of the genetic effect are sometimes employed to obtain genetically more homogeneous subgroups.²⁹ In the current study, the effect of differences in diagnostic certainty was explored by observing the effect on concordance rates and heritability estimates. The highest concordance rate (93%) and heritability estimate (99%) was found by including probable cases and by excluding possible ET. This finding suggests that a disease phenotype consisting of definite and probable ET according to the TRIG criteria should be the most suitable for the identification of genes involved in the development of ET by approaches based on candidate genes,³⁰ screening of single nucleotide polymorphisms,³¹ or sequencing,³² because this restricted phenotype appears to increase etiologic homogeneity and sample size. This would also fit with the spirit of the TRIG criteria, which have introduced the term possible ET even for cases that nowadays are considered to be clearly different from ET, such as myoclonic or dystonic tremors.¹⁹

Acknowledgment

The authors thank Berit Bents, technician at the Odense University Hospital, for commitment to this study, and Prof. Oehmichen and Dr. von Wurmb-Schwark of the Institute of Legal Medicine, Kiel, for determination of zygosity in the patients.

References

- Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. *Mov Disord* 1998;13:5–10.
- Larsson T. Essential tremor. *Acta Psychiatr Neurol Scand* 1960;36(suppl):3–176.
- Rajput AH, Offord KP, Beard CM, et al. Essential tremor in Rochester, Minnesota: a 45-year study. *J Neurol Neurosurg Psychiatry* 1984;47:466–470.
- Rautakorpi I, Takala J, Marttila RJ, et al. Essential tremor in a Finnish population. *Acta Neurol Scand* 1982;66:58–67.
- Gulcher JR, Jonsson P, Kong A, et al. Mapping of a familial essential tremor gene, FET1, to chromosome 3q13. *Nat Genet* 1997;17:84–87.
- Higgins JJ, Pho LT, Nee LE. A gene (ETM) for essential tremor maps to chromosome 2p22-p25. *Mov Disord* 1997;12:859–864.
- Higgins JJ, Jankovic J, Lombardi RQ, et al. Haplotype analysis of the ETM2 locus in familial essential tremor. *Neurogenetics* 2003 (in press).
- Illarioshkin SN, Rakhmonov RA, Ivanova-Smolenskaia IA, et al. [Molecular genetic analysis of essential tremor.] *Genetika* 2002;38:1704–1709.
- Abbruzzese G, Pigullo S, Di Maria E, et al. Clinical and genetic study of essential tremor in the Italian population. *Neurol Sci* 2001;22:39–40.
- Kovach MJ, Ruiz J, Kimonis K, et al. Genetic heterogeneity in autosomal dominant essential tremor. *Genet Med* 2001;3:197–199.
- Illarioshkin SN, Ivanova-Smolenskaya IA, Rahmonov RA, et al. Clinical and genetic study of familial essential tremor in an isolate of Northern Tajikistan. *Mov Disord* 2000;15:1020–1023.
- Louis ED, Ottman R. How familial is familial tremor? The genetic epidemiology of essential tremor. *Neurology* 1996;46:1200–1205.
- Christensen K, Holm NV, McGue M, et al. A Danish population-based twin study on general health in the elderly. *J Aging Health* 1999;11:49–64.
- Christensen K, Gaist D, Vaupel JW, et al. Genetic contribution to rate of change in functional abilities among Danish twins aged 75 years or more. *Am J Epidemiol* 2002;155:132–139.
- Bain PG, Findley LJ, Atchison P, et al. Assessing tremor severity. *J Neurol Neurosurg Psychiatry* 1993;56:868–873.
- Louis ED, Ford B, Lee H, et al. Does a screening questionnaire for essential tremor agree with the physician's examination? *Neurology* 1998;50:1351–1357.
- Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. *Parkinson's disease and movement disorders*. Baltimore: Williams & Wilkins, 1993;271–280.
- Louis ED, Ford B, Lee H, et al. Diagnostic criteria for essential tremor: a population perspective. *Arch Neurol* 1998;55:823–828.
- Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. *Ad Hoc Scientific Committee. Mov Disord* 1998;13(suppl 3):2–23.
- PAK AI. User's manual. Foster City, CA: Applied Biosystems.
- McGue M. When assessing twin concordance, use the probandwise not the pairwise rate. *Schizophr Bull* 1992;18:171–176.
- Tanner CM, Goldman SM, Lyons KE, et al. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. *Neurology* 2001;57:1389–1391.
- Falconer D. Inheritance of liability to certain diseases estimated from incidence among relatives. *Ann Hum Genet* 1965;29:51–76.
- Neale M, Cardon L. *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publishers, 1992.
- Kendler KS, Heath AC, Neale MC, et al. A population-based twin study of alcoholism in women. *JAMA* 1992;268:1877–1882.
- Rao DC. Genetic dissection of complex traits: an overview. *Adv Genet* 2001;42:13–34.
- Rannala B. Finding genes influencing susceptibility to complex diseases in the post-genome era. *Am J Pharmacogenomics* 2001;1:203–221.
- Deuschl G, Lucking CH, Schenck E. Essential tremor: electrophysiological and pharmacological evidence for a subdivision. *J Neurol Neurosurg Psychiatry* 1987;50:1435–1441.
- Perris CA. A study of bipolar (manic-depressive) and unipolar recurrent depressive psychoses. I. Genetic investigation. *Acta Psychiatr Scand Suppl* 1966;194:15–44.
- Tabor HK, Risch NJ, Myers RM. Opinion. Candidate-gene approaches for studying complex genetic traits: practical considerations. *Nat Rev Genet* 2002;3:391–397.
- Emahazion T, Feuk L, Jobs M, et al. SNP association studies in Alzheimer's disease highlight problems for complex disease analysis. *Trends Genet* 2001;17:407–413.
- Botstein D, Risch N. Discovering genotypes underlying human phenotypes: past successes for mendelian disease, future approaches for complex disease. *Nat Genet* 2003;33(suppl):228–237.