

Fertility in Essential Tremor

Data from Population-Based and Clinical Sources

Elan D. Louis

GH Sergievsky Center, Department of Neurology, and Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, N.Y., USA

Key Words

Essential tremor · Fertility · Epidemiology

Abstract

Background: The view of essential tremor (ET) as a degenerative disorder, which is now gaining support from post-mortem studies, is at odds with traditional views of ET as a 'super-healthy' condition characterized by increased longevity and fertility. Longevity has recently been re-examined in ET, yet fertility, measured by number of offspring, has never been critically assessed in this disease. The objective was to determine whether ET cases and controls differ in terms of number of children. **Methods:** Family history data were collected on ET cases and controls from 2 distinct sources, a population and a clinical (referred) sample. **Results:** In the population, the number of children was similar in 59 cases vs. 72 controls [mean \pm SD (median) = 2.3 \pm 2.9 (1) vs. 2.2 \pm 1.8 (2); $p = 0.26$]. In the referred sample, number of children was similar in 184 cases vs. 241 controls [2.0 \pm 1.5 (2) vs. 1.9 \pm 1.7 (2); $p = 0.33$]. In adjusted analyses, results were similar. **Conclusions:** Fertility, measured by number of children, was similar in cases and controls. With a newer understanding of the biological substrate of ET emerging from postmortem studies, it is important to critically reassess this and other fundamental biological questions about the disease.

Copyright © 2008 S. Karger AG, Basel

Introduction

Essential tremor (ET) is one of the most prevalent neurological disorders [1–5]. The central clinical feature is action tremor of the arms, although patients may exhibit other motor and non-motor features [6]. Treatment options are limited [7].

The view of ET as a degenerative disorder is not new. For example, Critchley and Greenfield [8] proposed more than a half-century ago that ET could represent an incomplete variant of olivopontocerebellar atrophy. This view of ET as degenerative is now gaining fresh support from recent postmortem studies, which demonstrate Purkinje cell loss and other degenerative changes in the cerebellum of the majority of ET cases and Lewy bodies in the brainstem of the remaining cases [9–11]. However, this view is at variance with older and perhaps more entrenched views of ET as a benign or even possibly a 'super-healthy' condition. In the 1920s, Minor [12] proposed the idea of status macrobioticus multiparus, a triad of familial tremor, longevity and fertility. This view of ET was often propagated in older literature [13, 14], but it also continues to be carried forward into more recent scientific literature on this disease [15–17].

Two longitudinal studies have examined the issue of longevity in ET [18, 19]. Rajput et al. [19] reported no case-control difference in longevity. Louis et al. [18] recently reported an increased risk of mortality in ET cases vs. controls. Therefore, the notion of increased longevity has not been supported by these studies; by contrast, decreased longevity is emerging as a distinct possibility.

Fertility may be defined as reproductive capacity, and is often measured in number of offspring. Extremely limited data on fertility in ET have been provided in several sources [12, 20–22]; however, this issue has not been examined critically. For example, other than the data presented here, there are no case-control data on fertility in ET.

The goal of this study was to determine whether ET cases and controls differed in terms of number of children. To do so, cases and controls were sampled from two distinct settings, a population and a clinical referral sample. The immediate goal of these analyses was to address a basic biological question about this disease. The overarching goal was to frame a broader conceptual question about this disease as a super-healthy condition vs. a degenerative condition.

Methods

As outlined below, two samples of participants were used. All participants signed written informed consent as approved by the Columbia University Medical Center ethics board.

Population-Based Sample

The Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) was a family study of ET conducted in the Washington Heights-Inwood community in northern Manhattan, New York [23]. Enrollment began in 1995 and was completed in 2000. There were 59 ET case probands, 72 control probands and several thousand case relatives and control relatives [23]. The design of this population-based study has been described in detail elsewhere [23]. Control probands were matched to case probands on age, gender, and race, and each case and control proband underwent a demographic and medical history and a videotaped tremor examination, from which a total tremor score (range = 0–36 maximal tremor) was determined. All probands were asked to list by name each living and deceased first- and second-degree relative, and report whether they had tremor.

Clinical (Referred) Sample

ET patients were enrolled in an ongoing clinical study at the Neurological Institute of New York, Columbia University Medical Center [24], a tertiary referral center in northern Manhattan, New York. ET patients came from two sources: patients whose neurologist was on staff at the Institute or patients who were cared for by their local doctor in the tri-state region (New York, New Jersey, Connecticut) and, as members of the International Essential Tremor Foundation, had read advertisements for the study. Controls were recruited using random-digit telephone dialing. They were ascertained from the same source population as the cases, and were frequency-matched based on age, gender, and race. Control recruitment proceeded more rapidly than case recruitment, resulting in a larger number of controls than cases [24]. Case and control ascertainment and recruitment have been described in detail elsewhere [24]. All cases and controls under-

went demographic and medical histories and a videotaped tremor examination. Family history data were collected and all female enrollees were asked how many children they had.

Statistical Analyses

Data were analyzed in SPSS (version 15.0). The number of children was not normally distributed; therefore, nonparametric tests (Spearman's r , Mann-Whitney test, Kruskal-Wallis test) were used when assessing this variable. Also, there were zero values (i.e., participants who had no children). Therefore, in linear regression analyses, the value $\log_{10}(\text{children} + 1)$ was used as the dependent variable. In these models, diagnosis (ET = 1, control = 0) was the independent variable. In the main analyses, ET cases were stratified into those who reported an affected first- or second-degree relative (familial ET) vs. those who had not (non-familial ET). In a secondary analysis, familial ET was defined more stringently, as having an affected parent; this definition is less prone to misclassify as familial ET those sporadic ET cases who report an affected relative in the setting of a large family size. A survival analysis was also performed in which having ET was considered to be the exposure and the birth of the first child was the outcome, with the time variable being the age at evaluation (in cases or controls without children) or the age at the time of the birth of their first child (in cases or controls who had children).

Results

Population-Based Sample

ET cases and controls were similar in terms of age, gender, and race (table 1). A higher number of children was associated with non-white race [mean \pm SD (median) = 2.6 ± 2.6 (2.0) in nonwhites vs. 1.3 ± 1.3 (1.0) in whites, Mann-Whitney $z = 2.48$, $p = 0.01$]. Number of children was not associated with older age ($r = -0.12$, $p = 0.17$) or gender [mean \pm SD (median) = 2.5 ± 2.6 (2.0) in men versus 1.9 ± 1.8 (1.5) in women, Mann-Whitney $z = 1.07$, $p = 0.28$].

The proportion of ET cases and controls who had children did not differ significantly [38/59 (64.4%) cases vs. 55/72 (76.4%) controls, $p = 0.13$]. The mean and median number of children was similar in ET cases and controls (table 1; fig. 1). Five (33.3%) of 15 familial ET cases versus 9 (12.5%) of 72 controls had ≥ 5 children (Fisher's $p = 0.12$). One (6.7%) of 15 familial ET cases versus 0 (0.0%) of 72 controls had ≥ 10 children (Fisher's $p = 0.35$). The marginally higher proportion of familial ET cases versus controls with ≥ 5 children skewed the mean; however, the medians of the 2 groups were identical (both medians = 2; table 1). When familial ET was defined more stringently (i.e. probands who reported an affected parent), there were only 7 familial ET cases. One of these had ≥ 10 children, which skewed the mean (3.9) but not the median, which remained at 2.

In an unadjusted linear regression analysis, log-transformed number of children (dependent variable) was not associated with ET ($\beta = -0.05$, $p = 0.36$). In a linear regression analysis that adjusted for age, gender, and white race, log-transformed number of children was not associated with ET ($\beta = -0.06$, $p = 0.24$). In an unadjusted linear regression analysis restricted to 15 familial ET cases and 72 controls, log-transformed number of children was not associated with ET ($\beta = 0.12$, $p = 0.17$). In the same restricted model after adjusting for age, gender, and white race, there was no association ($\beta = 0.08$, $p = 0.38$).

There was no correlation in ET cases between the number of children and total tremor score ($r = 0.001$, $p = 0.99$) or tremor duration ($r = -0.13$, $p = 0.45$).

A survival analysis was performed, comparing familial ET cases to controls. In the analysis, having ET was considered to be the exposure and the birth of the first child was the outcome. In these analyses, the risk of giving birth was similar in familial ET cases and controls (relative risk = 1.24, 95% CI = 0.65–2.38, $p = 0.52$; after adjusting for gender and race, relative risk = 1.12, 95% CI = 0.56–2.22, $p = 0.76$).

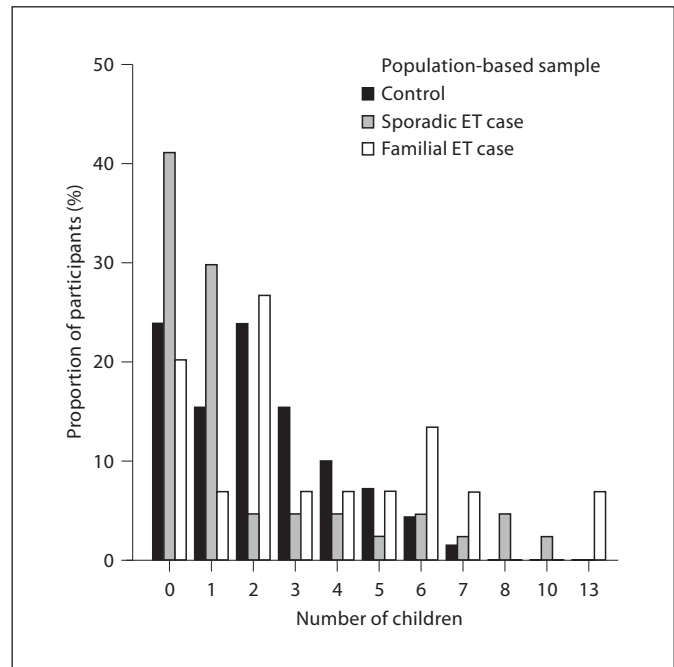


Fig. 1. Proportion of participants (controls, sporadic ET cases, and familial ET cases) with each number of children (population-based sample).

Table 1. Characteristics of ET cases and controls in population-based sample and referred sample

	Population (ET)	Population (controls)	Referred (ET)	Referred (controls)
Number of participants	59	72	184	241
Age, years	79.9 ± 6.7	79.2 ± 6.0	67.4 ± 15.0	68.2 ± 12.1
Range	70–96	70–93	18–94 ¹	18–95 ¹
Female gender	35 (59.5%)	45 (62.5%)	184 (100%) ²	241 (100%) ²
White race	16 (27.1%)	19 (26.4%)	170 (92.4%)*	203 (84.2%)
Education, years	not collected	not collected	14.7 ± 3.2	15.2 ± 3.2
Current cigarette smoker	not collected	not collected	14/164 (8.5%)	21/239 (8.8%)
Total tremor score	19.8 ± 6.9***	6.6 ± 4.4	18.1 ± 7.8***	3.2 ± 2.6
Tremor duration, years	15.8 ± 20.7	not applicable	22.9 ± 18.5	not applicable
Family history of ET or tremor	15 (25.4%)**	4 (5.6%)	114 (62.0%***)	30 (12.4%)
Number of children	2.3 ± 2.9 (1)	2.2 ± 1.8 (2)	2.0 ± 1.5 (2)	1.9 ± 1.7 (2)
(familial ET cases vs. controls)	3.5 ± 3.5 (2)	2.2 ± 1.8 (2)	2.1 ± 1.4 (2)	2.0 ± 1.7 (2)

Unless otherwise indicated, figures in parentheses are median values. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, when compared with controls.

¹ 25 ET cases and 16 controls were between 18 and 49 years of age.

² Only women were asked about the number of children.

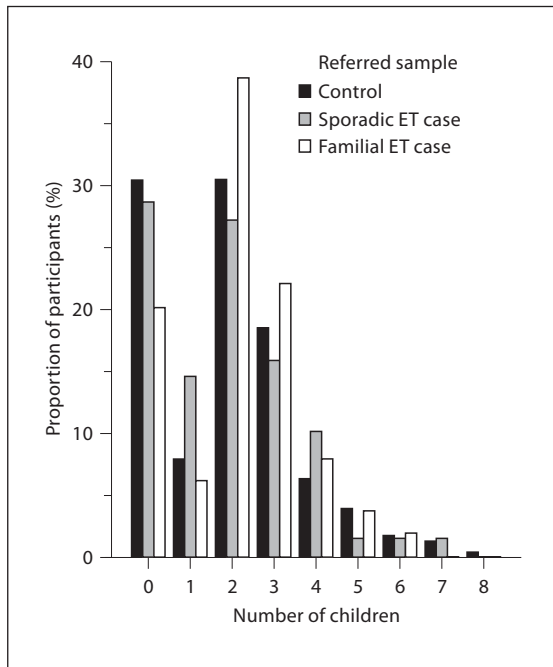


Fig. 2. Proportion of participants (controls, sporadic ET cases, and familial ET cases) with each number of children (referred sample).

Referred Sample

ET cases and controls were similar in terms of age, gender, education, and smoking status. In this sample, a slightly lower proportion of controls than cases were white (table 1). A higher number of children was associated with lower education ($r = -0.13$, $p = 0.01$) and marginally with older age ($r = 0.09$, $p = 0.07$), but not with current smoking status [mean \pm SD (median) = 1.9 ± 1.4 (2.0) in current smokers vs. 1.9 ± 1.6 (2.0) in current nonsmokers, Mann-Whitney $z = 0.13$, $p = 0.90$] or race [mean \pm SD (median) = 2.0 ± 1.6 (2.0) in whites vs. 1.6 ± 1.5 (2.0) in nonwhites, Mann-Whitney $z = 1.44$, $p = 0.15$].

The proportion of ET cases and controls who had children did not differ significantly [141/184 (76.6%) cases vs. 168/241 (69.7%) controls, $p = 0.11$]. The mean and median number of children was similar in ET cases and controls (table 1; fig. 2). Six (5.3%) of 114 familial ET cases versus 17 (7.1%) of 241 controls had ≥ 5 children ($\chi^2 = 0.41$, $p = 0.52$) and no cases or controls had ≥ 10 children. When the sample was restricted to 114 familial ET cases and 241 controls, the number of children remained similar (table 1). When one further restricted the analyses to participants who had ever been married (99 familial ET cas-

es and 202 controls), the number of children was similar [mean \pm SD (median) = 2.4 ± 1.3 (2.0) in ever-married familial ET cases vs. 2.2 ± 1.6 (2.0) in ever-married controls, Mann-Whitney $z = 1.26$, $p = 0.21$]. Also, when familial ET was defined more stringently (i.e. reporting an affected parent), the results were similar [mean \pm SD (median) number of children in 37 ET cases with more stringently defined familial ET = 2.0 ± 1.3 (2.0)]. Twenty-five ET cases and 16 controls were between the ages of 18 and 49 years; when analyses were restricted to participants who had completed their child-bearing years (age 50 and older), results were similar [mean \pm SD (median) number of children = 2.1 ± 1.4 (2.0) in 159 ET cases versus 2.0 ± 1.7 (2.0) in 225 controls, Mann-Whitney $z = 1.35$, $p = 0.18$].

In an unadjusted linear regression analysis, log-transformed number of children (dependent variable) was not associated with ET ($\beta = 0.03$, $p = 0.26$). In a linear regression analysis that adjusted for age, white race, education, and current smoker, log-transformed number of children was not associated with ET ($\beta = 0.02$, $p = 0.42$). In an unadjusted linear regression analysis restricted to 114 familial ET cases and 241 controls, log-transformed number of children was only marginally associated with ET ($\beta = 0.05$, $p = 0.09$). In the same restricted model, after adjusting for age, white race, education, and current smoker, there was no association ($\beta = 0.04$, $p = 0.17$).

ET cases came from 2 sources. When compared with controls, the number of children was similar [mean \pm SD (median) = 2.1 ± 1.5 (2.0) in 120 ET patients whose neurologist was on staff at the Neurological Institute, 1.8 ± 1.5 (2.0) in 64 ET patients who were cared for by their local doctor, and 1.9 ± 1.7 (2.0) in controls, Kruskal-Wallis = 3.54, $p = 0.17$].

There was no correlation in ET cases between the number of children and total tremor score ($r = -0.06$, $p = 0.47$) or tremor duration ($r = -0.03$, $p = 0.69$).

Discussion

Fertility may be measured by the production of offspring [25, 26]. In this study, the proportion of cases and controls with offspring was similar, and the number of offspring was similar in ET cases and controls. This similarity was observed both in a population-based sample of ET cases and controls and in a referred sample of cases and controls. Furthermore, the number of children was similar in familial ET cases and sporadic ET cases.

Minor [12] and his contemporaries viewed certain disorders of the nervous system as being degenerative, not only in a limited neurological sense, but also in a broader neuropsychological and sociological sense, with families being characterized by members with a variety of neurological conditions, eccentricity, alcoholism, insanity, and epilepsy. Minor [12] promoted the idea that families with ET should not be viewed as carrying such a degenerative condition, but rather, these families were super-healthy and were characterized by members with greater longevity and fecundity. Hence, through the same genetic mechanism, certain families were characterized by individuals with benign tremor, greater reproductive health, and a longer life. Such families were seen as giving rise to lusty, virile, active, and super-healthy people [13]. In terms of fecundity, Minor [12] reported large numbers of offspring in his 9 ET families (e.g. 15 children per generation in some families). Pelnar [20] had also reported large ET pedigrees around that time. Pintus [21] reported no difference between the fertility of 1 large ET family and that of the general local population. Larsson and Sjögren [22] studied a large population-based sample of 201 ET cases from 9 ancestral families in Sweden, and came to the conclusion that there was no increase in fertility in these families, although no case-control data were presented. This issue has continued to be a subject of comment in more current literature [15–17], but has not been addressed critically, with no prior case-control comparisons. The data presented in the current set of analyses do not support the view that there is increased fertility in ET.

Longitudinal data similarly have not supported the notion that ET is associated with increased longevity [18, 19]; in fact, recent data have demonstrated the converse [18]. This finding is consistent with current postmortem studies that are showing degenerative changes in ET, with Purkinje cell loss and other changes in the cerebellum of the majority of ET cases and Lewy bodies in the brainstem of the remaining cases [9–11]. As a rule, degenerative diseases are associated with decreased rather than increased longevity [18].

This issue of fertility has been examined in several other progressive neurological disorders besides ET. In one study of males with amyotrophic lateral sclerosis, fertility was reduced, leading the authors to question whether reactive oxygen species could play a role in reduced fertility in that disease [27]. Reduced fertility, through reduced nuptiality, has been demonstrated in patients with Machado-Joseph disease [28]. However, increased fertility has not been demonstrated in progressive neuro-

logical disorders. In Alzheimer's disease, it had been hypothesized that greater fertility, and therefore lower natural estrogen exposure, might increase the risk of disease, but there has been no demonstrable association between that disease and increased fertility [25, 26].

In the main analyses, familial ET was defined as having 1 or more affected first- or second-degree relatives. One issue is that ET is a common disease, and having a large family is likely to increase the likelihood of having a relative with ET. In this sense, large family size might be linked with familial ET not because of a biological association between ET and larger family size, but merely because ET is a highly prevalent condition and having a large family mathematically increases the probability of having a relative with ET. Therefore, in additional analyses, familial ET was defined more stringently as having an affected parent; with this definition, one is less prone to misclassify as familial ET those sporadic ET cases with an affected relative in the setting of a large family size. The results of these analyses also demonstrated that familial ET cases and controls had similar numbers of children.

This study was presented as a case-control study, in which study subjects were identified based on diagnosis and their fertility histories were compared. However, one also could have designed it as a retrospective cohort study, in which the exposure was having the disease (ET) and the outcome was childbirth. However, a problem with this approach is that survival analyses lend themselves more to analyses of one-time life events (disease onset or death), and are not ideal for assessing repeated events (births). The hypothesis of Minor [12] centered around the number of children (i.e. repeated events) rather than birth as a one-time dichotomous outcome. Hence, the survival analyses that we present are additional secondary analyses.

The factors that influence fertility are complex and go well beyond a woman's bodily capacity to procreate. A broad array of complex social and societal factors are important, including contraceptive use, education, and social empowerment, to name only a few [29]. While a limited number of demographic factors were considered in the adjusted analyses, these broader factors could not be taken into account. The referred sample may have been prone to a variety of selection biases, making it even more difficult to assess these complex issues. Therefore, the population-based analyses were perhaps more valid.

This study had additional limitations. In the referred sample, women but not men were asked about the number of children. However, in the population-based sam-

ple, men and women did not differ in terms of number of children, so this is not likely to have influenced the results in the referred sample. Second, participants were questioned about live births but not about abortions or miscarriages, so fertility may have been underestimated. This study had several strengths. These are the only case-control data that have examined this particular issue. Furthermore, the question was addressed using ET cases from two distinct sources, one of which was a population-based sample. Finally, a number of potential confounding factors (e.g. race, education) were considered and then adjustments made in these analyses.

In summary, fertility, measured by number of children, was similar in ET cases and controls. With a newer understanding of the biological substrate of ET emerging from postmortem studies, it is important to critically address this and other fundamental biological questions about this common neurological disease.

Acknowledgments

Funding Source: R01 NS39422, RR00645 (General Clinical Research Center; NIH, Bethesda, Md., USA).

References

- 1 Dogu O, Sevim S, Camdeviren H, Sasmaz T, Bugdayci R, Aral M, Kaleagasi H, Un S, Louis ED: Prevalence of essential tremor: door-to-door neurologic exams in Mersin province, Turkey. *Neurology* 2003;61:1804–1806.
- 2 Benito-Leon J, Bermejo-Pareja F, Morales JM, Vega S, Molina JA: Prevalence of essential tremor in three elderly populations of central Spain. *Mov Disord* 2003;18:389–394.
- 3 Louis ED, Dogu O: Does age of onset in essential tremor have a bimodal distribution? Data from a tertiary referral setting and a population-based study. *Neuroepidemiology* 2007;29:208–212.
- 4 Bergareche A, De La Puente E, Lopez De Munain A, Sarasqueta C, De Arce A, Poza JJ, Marti-Masso JF: Prevalence of essential tremor: a door-to-door survey in Bidasoa, Spain. *Neuroepidemiology* 2001;20:125–128.
- 5 Rautakorpi I, Marttila RJ, Takala J, Rinne UK: Occurrence and causes of tremors: a population-based investigation. *Neuroepidemiology* 1982;1:209–215.
- 6 Benito-Leon J, Louis ED: Clinical update: diagnosis and treatment of essential tremor. *Lancet* 2007;369:1152–1154.
- 7 Zesiewicz TA, Elble R, Louis ED, Hauser RA, Sullivan KL, Dewey RB Jr, Ondo WG, Gronseth GS, Weiner WJ: Practice parameter: therapies for essential tremor: report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2005;64:2008–2020.
- 8 Critchley M, Greenfield JG: Olivo-pontocerebellar atrophy. *Brain* 1948;71:343–364.
- 9 Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, Pahwa R, Lyons KE, Ross GW, Borden S, Moskowitz CB, Lawton A, Hernandez N: Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain* 2007;130:3297–3307.
- 10 Louis ED, Vonsattel JP: The emerging neuropathology of essential tremor. *Mov Disord* 2007;23:174–182.
- 11 Shill HA, Adler CH, Sabbagh MN, Connor DJ, Caviness JN, Hentz JG, Beach TG: Pathologic findings in prospectively ascertained essential tremor subjects. *Neurology* 2008;70:1452–1455.
- 12 Minor L: Neue Beobachtungen über das erbliche Zittern. *Russk Klin* 1929;12:713–725.
- 13 Critchley M: Observations of essential (heredofamilial) tremor. *Brain* 1949;72:113–139.
- 14 Davis CH Jr, Kunkle EC: Benign essential (heredofamilial) tremor. *AMA Arch Intern Med* 1951;87:808–816.
- 15 Koller WC, Busenbark, KL: Essential tremor; in Watts RL, Koller WC (eds): *Movement Disorders: Neurologic Principles and Practice*. New York, McGraw-Hill, 1997, pp 365–385.
- 16 Lambert D, Waters CH: Essential tremor. *Curr Treat Options Neurol* 1999;1:6–13.
- 17 Jankovic J, Beach J, Schwartz K, Contant C: Tremor and longevity in relatives of patients with Parkinson's disease, essential tremor, and control subjects. *Neurology* 1995;45:645–648.
- 18 Louis ED, Benito-Leon J, Ottman R, Bermejo-Pareja F: A population-based study of mortality in essential tremor. *Neurology* 2007;69:1982–1989.
- 19 Rajput AH, Offord KP, Beard CM, Kurland LT: Essential tremor in Rochester, Minnesota: a 45-year study. *J Neurol Neurosurg Psychiatry* 1984;47:466–470.
- 20 Pelnar J: *Das Zittern*. Berlin, Springer, 1913.
- 21 Pintus G: Sulla trasmissione ereditaria del tremore essenziale. *Riv Patol Nerv Ment* 1931;39:1–32.
- 22 Larsson T, Sjögren T: Essential tremor: a clinical and genetic population study. *Acta Psychiatr Scand Suppl* 1960;36:1–176.
- 23 Louis ED, Ford B, Frucht S, Barnes LF, X-Tang M, Ottman R: Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. *Ann Neurol* 2001;49:761–769.
- 24 Louis ED, Zheng W, Applegate L, Shi L, Factor-Litvak P: Blood harmaline concentrations and dietary protein consumption in essential tremor. *Neurology* 2005;65:391–396.
- 25 Ptok U, Barkow K, Heun R: Fertility and number of children in patients with Alzheimer's disease. *Arch Womens Ment Health* 2002;5:83–86.
- 26 White JA, McGue M, Heston LL: Fertility and parental age in Alzheimer disease. *J Gerontol* 1986;41:40–43.
- 27 Johnson WG, Lucek PR, Chatkupt S, Furman Y, Lustenberger A, Lazzarini A: Reduced fecundity in male ALS gene-carriers. *Am J Med Genet* 1995;59:149–153.
- 28 Lima M, Smith MT, Silva C, Abade A, Mayer FM, Coutinho P: Natural selection at the MJD locus: phenotypic diversity, survival and fertility among Machado-Joseph disease patients from the Azores. *J Biosoc Sci* 2001;33:361–373.
- 29 Greenhalgh S: *Situating Fertility: Anthropology and Demographic Inquiry*. Cambridge, Cambridge University Press, 1995.