

Predicting Age of Onset in Familial Essential Tremor: How Much Does Age of Onset Run in Families?

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Key Words

Essential tremor • Genetics • Familial • Clinical characteristics • Age of onset

Abstract

Background: The extent to which age of onset of essential tremor (ET) aggregates in families is unknown; hence, it is unclear whether information about the age of onset in one family member can be used to predict the age of onset in others. **Methods:** ET probands and relatives were enrolled in a genetic study at Columbia University. **Results:** Data from 26 probands and 52 relatives were analyzed. The probands' age of onset correlated significantly with their relatives' age of onset ($r = 0.50$, $p = 0.001$). In 57.7% of cases, the relative's age of onset was within 10 years of the proband's onset (i.e. a 20-year age range). The proportion of affected relatives with age at onset <20 years was 64.7% in the families of probands with onset younger than 20 years, but only 7.7% in the families of probands with onset ≥ 20 years ($p < 0.001$). There was little evidence for genetic anticipation; 9/18 (50.0%) children reported a younger age of onset than the proband. **Conclusions:** In families containing multiple individuals with ET, the age at onset of probands and relatives was significantly correlated. Age of onset may be most tightly linked in families in which the proband had a young age of onset.

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Introduction

Essential tremor (ET) is considered to be a very heritable disorder [1–4]. Given its high prevalence [5, 6], the familial form of ET is commonly encountered in clinical practice settings [7, 8]. Clinicians often care for patients who have multiple affected family members as well as other at-risk family members (especially children and grandchildren). Surprisingly, it is not known whether the basic clinical features of the ET in one family member (e.g. age of onset, severity) can help predict the course the disease will take in other family members. For example, the extent to which age of onset runs in ET families is not known; hence, it is unclear whether age of onset in one family member can be used to predict the expected age of onset in siblings, children and other relatives.

ET cases (probands) and their relatives were enrolled in a genetic study of ET at Columbia University Medical Center (CUMC); 100 subjects have been enrolled to date. We sought to determine whether age of onset was significantly associated among family members and whether there was evidence of genetic anticipation. To our knowledge, data to address these questions have not been published in the tremor literature. We hope that these data will be used by clinicians to provide basic prognostic and family guidance information to their patients with ET.

Methods

*Ascertainment of Proband*s

ET cases (proband) and their reportedly affected first- and second-degree relatives were enrolled in a genetic study of ET, the Family Study of Essential Tremor (FASET) at CUMC. The study was advertised on two ET society websites. The three initial inclusion criteria for probands were: (1) a diagnosis of ET had been assigned by a doctor, (2) age of tremor onset ≤ 40 years (later changed to ≤ 50 to be more inclusive), and (3) ≥ 2 living relatives in the United States who have ET that was diagnosed by a doctor; these relatives were not reported to have dystonia or Parkinson's disease (PD). The exclusion criterion for probands was a prior diagnosis of dystonia or PD. Potential ET probands contacted the FASET study coordinator. Before probands were selected for enrollment, they were asked to submit a set four Archimedes spirals (two right, two left), which were rated by a senior neurologist specializing in movement disorders (E.D.L.). Proband were included if one or more of the spirals had a Washington Heights Inwood Genetic Study of Essential Tremor rating of 2 (moderate tremor) or higher [9].

Ascertainment of Relatives

Based upon a telephone interview with the proband, relatives with ET were identified. With the proband's permission, these relatives were then contacted by telephone, and were pre-enrolled if they reported the presence of tremor in the absence of a prior diagnosis of dystonia or PD. Before final selection for enrollment, relatives also submitted four Archimedes spirals. These spirals were rated (E.D.L.), and relatives were included if one or more of the spirals had a rating ≥ 2 [9].

In-person Evaluation

An in-person evaluation was then conducted in the enrollees' homes; this included a series of questionnaires and a videotaped neurological examination. Age of onset was defined as the self-reported age at which the individual first noted tremor. Prior studies have indicated that it is reliably reported by ET patients [10]. The videotaped neurological examination included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia and other movement disorders [11]. The neurologist (E.D.L.) reviewed all videotaped examinations and rated the severity of postural and kinetic arm tremors (0–3), resulting in a total tremor score (range = 0–36 [maximum]) [11]. The study was approved by the CUMC Institutional Review Board and all participants gave written informed consent.

Diagnoses

All ET diagnoses were reconfirmed based on review of questionnaires and videotaped neurological examinations. Diagnoses of ET were assigned based on published diagnostic criteria (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD or another known cause) [9, 12].

Statistical Analyses

Analyses were performed in SPSS (version 19.0) and SAS (version 9.3). Age of onset difference (AOD) was defined as the proband's age of onset – relative's age of onset; a positive value indicated that the relative's age of onset was younger than the pro-

band's and a negative value indicated that the relative's age of onset was older than the proband's.

In the analysis of familial aggregation of age at onset, current age of the family members is an important potential confounder [13]. First, estimates of anticipation can be inflated by 'age-at-interview bias': offspring are likely to have younger age of onset than parents unless the offspring are currently at least as old as the parents were when they had onset of the disease [14, 15]. Second, since individuals cannot have onset at ages older than their current age, and current age tends to be correlated within families, artifactual familial aggregation of age at onset can occur. We dealt with these issues in two ways. First, to minimize 'age-at-interview bias', it has been suggested that investigators exclude data from offspring who are currently younger than the parents were when they had onset of the disease [14]. Thus, our analyses excluded relatives ($n = 5$) whose current age was younger than the probands' age at ET onset. Second, to examine whether the findings were robust to adjustment for truncation by current age, we also performed a proportional hazards regression analysis as previously described [13], where current age was a truncation variable and the absolute value of time from proband's onset (in years) was a time-varying predictor. We assessed the effects of additional covariates by performing additional simple and multiple proportional hazards regression models.

Finally, the basic analysis treats all proband-relative pairs as independent of one another, although there may be more than one proband-relative pair in a pedigree (e.g. a proband may have multiple affected siblings or children). As previously suggested, we addressed this problem by also performing a 'pedigree-averaged analysis' in which the average of the onset ages of the relatives is examined in relation to the proband's age at onset [14].

Results

There were 100 enrollees, including 28 probands and 72 relatives (58 first-degree, 11 second-degree, and 3 third-degree). We excluded two probands and their relatives ($n = 2$) because the probands were found to have dystonia rather than ET. We also excluded 2 of the remaining 70 relatives because they had dystonia rather than ET. Eleven additional relatives did not recall their age of onset and five offspring (all children) were excluded to minimize age-at-interview bias. The final sample comprised 26 probands and 52 relatives (table 1).

The probands' age of onset correlated to a significant degree with their relatives' age of onset (Pearson's $r = 0.50$, $p = 0.001$; fig. 1). A pedigree-averaged analysis yielded similar results (Pearson's $r = 0.53$, $p = 0.001$). In the proportional hazards regression model, there was significant familial aggregation of age at onset after controlling for truncation by current age ($p = 0.032$). The proportional hazards regression model results did not change substantially after adjustment for gender and education.

Table 1. Demographic and clinical characteristics of study sample

	Probands (n = 26)	Relatives (n = 52)
Age, years	64.3 ± 11.2 37–83	58.5 ± 18.8 19–95
Female gender	14 (53.8)	25 (48.1)
White race	23 (88.5)	46 (88.5)
Relationship to proband		
Self	26 (100)	0 (0)
Child	0 (0)	18 (34.6)
Sibling	0 (0)	17 (32.7)
Parent	0 (0)	7 (13.5)
Grandchild	0 (0)	1 (1.9)
Aunt/uncle	0 (0)	3 (5.8)
Nephew/niece	0 (0)	4 (7.7)
Other (third-degree)	0 (0)	2 (3.8)
Total tremor score on neurological examination	22.6 ± 3.7	18.0 ± 5.7
Voice tremor on neurological examination	9 (34.6)	7 (13.5)
Head (neck) tremor on neurological examination	14 (53.9)	10 (19.2)
Currently taking medication to treat ET	16 (61.5)	18 (34.6)
Age of ET onset, years	24.4 ± 15.6	30.5 ± 19.4
Duration of ET, years	40.4 ± 15.0	28.5 ± 20.2

Values are mean ± SD, range or number (%).

To further consider the effects of current age, we stratified relatives by age quartile (<44, 44–57, 58–72, >72 years). Except for the second quartile (Pearson's $r = 0.13$, $p = 0.66$), the probands' age of onset correlated with their relatives' age of onset to a similar degree (Pearson's $r = 0.78$, $p = 0.003$ [first quartile], Pearson's $r = 0.70$, $p = 0.008$ [third quartile], and Pearson's $r = 0.55$, $p = 0.04$ [oldest quartile]).

The mean AOD was -6.7 ± 17.8 years (range = -61.0 to 37.0 years) (fig. 2). The value of AOD was negative in 30/52 (57.7%) relatives, positive in 18/52 (34.6%) relatives, and 0 in 4/52 (7.7%) relatives. In 17/52 (32.7%) relatives, the AOD ranged from -5 to 5 (i.e. the relative's and proband's ages of onset were within ± 5 years of one another); in 30/52 (57.7%) relatives, they were within ± 10 years of one another.

Because of the study inclusion criteria, which required that probands have onset ≤ 40 years (later extended to ≤ 50 years), the age at onset in the probands ranged from 5 to 50, with a median of 20 years. We examined the proportion of relatives whose age of onset fell below the me-

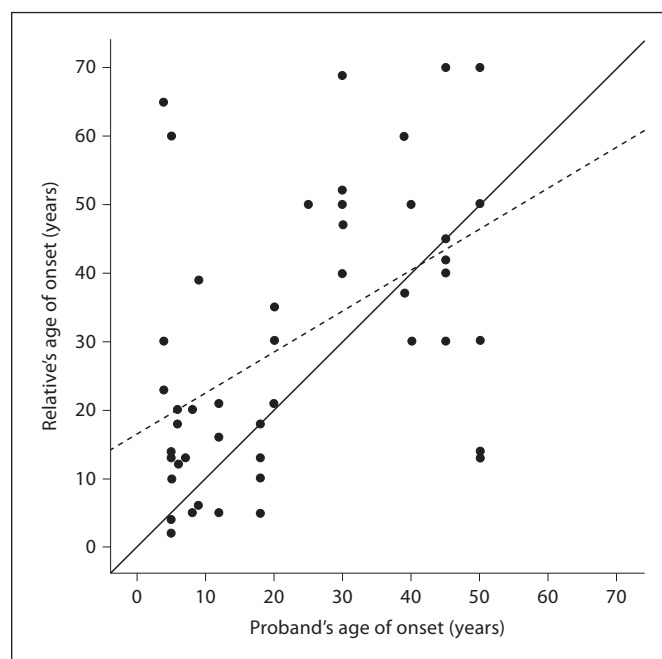


Fig. 1. Age of onset in 52 relatives who knew their age of onset. Each relative's age of onset (y-axis) is plotted against the age of onset of his/her proband (x-axis). The relatives' age of onset correlated with that of the respective proband (Pearson's $r = 0.50$, $p = 0.001$, see dotted regression line). The diagonal lines indicates a situation in which the relative's age of onset is identical to that of each respective proband.

dian age of onset in the probands (i.e. <20 years). This analysis was restricted to the 43 relatives who were currently aged ≥ 40 , to ensure that the relatives could have had older onset. The proportion of affected relatives with age at onset <20 years was 64.7% (11/17) in the families of probands with onset younger than 20 years, but only 7.7% (2/26) in the families of probands with onset ≥ 20 years ($p < 0.001$) (table 2). These analyses provide evidence that age of onset may be most tightly linked in families in which the proband had a young age of onset.

Most of the relatives were siblings or children (table 1). For children, the probands' age of onset correlated with their own age of onset (Pearson's $r = 0.51$, $p = 0.03$), and the mean AOD was 3.5 ± 15.2 years (range = -15.0 to 37.0 years), with 9 (50.0%) of 18 children reporting a younger age of onset than the proband, 1 (5.6%) reporting the same age, and 8 (44.4%) of 18 reporting an older age of onset than the proband. For siblings, the probands' age of onset correlated with their own age of onset (Pearson's $r = 0.49$, $p = 0.048$) and the mean AOD was -13.2 ± 18.2 years (range = -61.0 to 15.0 years), with 4/17 (23.5%) reporting a

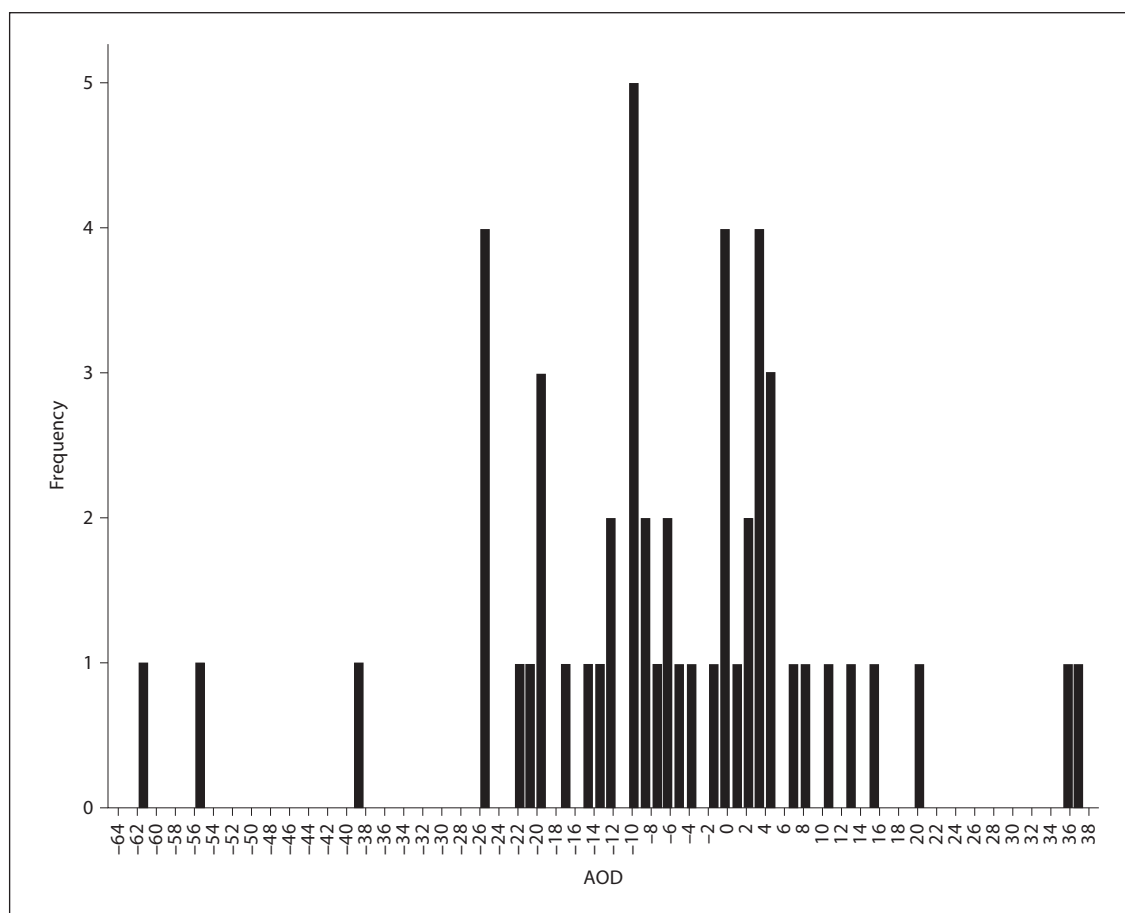


Fig. 2. The AOD (x-axis) in 52 relatives. AOD = The proband's age of onset – the relative's age of onset; a positive value indicates that the relative's age of onset was younger than the proband's and a negative value indicates that the relative's age of onset was older than the proband's. The y-axis indicates the number of relatives with each AOD.

Table 2. Age of onset in relatives versus probands^a

Proband's age of onset	Relative's age of onset	
	<20 years	≥20 years
<20 years	11 (64.7)	6 (35.3)
≥20 years	2 (7.7)	24 (92.3)

Values are numbers (row percentage). $\chi^2 = 15.84$, $p < 0.001$.

^a Restricted to 43 relatives whose current age was ≥40 years.

younger age of onset than the proband. We also stratified relatives into first-degree versus others; the probands' age of onset correlated with their relatives' age of onset in each stratum (Pearson's $r = 0.51$, $p = 0.001$, in first-degree relatives, and Pearson's $r = 0.63$, $p = 0.05$, in other relatives).

Discussion

The degree to which age of onset runs in ET families has not yet been studied. Thus, the extent to which information about the age of onset in one family member can be used as a guide to predict the expected age of onset in siblings, children and other relatives is not known. Given the high prevalence of ET as well as the extent to which it is considered to be genetic, this is surprising. In the current study, we found a significant correlation between the relative's age of onset and the proband's age of onset; the magnitude of the correlation was moderate ($r = 0.50$). Approximately 60% of the time, the relative's age of onset was within ± 10 years of the proband's (i.e. a 20-year age range).

In a subanalysis, we found that the proportion of affected relatives with age at onset <20 years was 64.7% in

the families of probands with onset younger than 20 years, but only 7.7% in the families of probands with onset ≥ 20 years ($p < 0.001$). Hence, age of onset may be most tightly linked in families in which the proband had a very young age of onset.

The possibility of genetic anticipation has been raised previously in ET families [16]. Yet we found that only 9 (50.0%) of 18 children reporting a younger age of onset than the proband, and a similar proportion reported an older age of onset, suggesting that genetic anticipation was not likely to be occurring in these families.

One-half of the children reported a younger age of onset than the proband; for siblings, this value was only 23.5%. Furthermore, for siblings, the mean AOD was -13.2 ± 18.2 (i.e. on average, age of onset was 13 years older in siblings than in probands). One explanation for these findings is that probands were selected for this study based on younger age of onset, yet no such selection criterion was operative for siblings.

One limitation is that the sample size was modest, with 26 probands and 52 relatives. Despite this, we were

able to detect a number of important associations that were statistically significant. Nonetheless, future studies with larger sample sizes would also add to the literature.

While age of onset was moderately correlated within families, approximately 40% of the time, the discrepancy between the proband's and the relative's age of onset was greater than ± 10 years. Whether environmental factors or other genetic factors modify age of onset is not known, but the possibility of such is raised by our data.

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Disclosure Statement

The authors declare that there are no conflicts of interest and no competing financial interests.

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