Publication Packet & Brief Summaries

Publication Title:
Predicting age of onset in Familial Essential Tremor: How much does age of onset run in families?

Summary:
Columbia University enrolled 26 participants with essential tremor and relatives with essential tremor. The data was analyzed in hopes of determining whether age of onset in one relative could predict age of onset in other family members. In large families, with multiple affected individuals, the age of onset of the main participant was associated with the age of onset of relatives. 57.7% of cases were within a 20-year age range. With more analysis, it is possible that the age of onset is even more tightly linked in families in which participants had a very young age of onset.

Publication Title:
Familial Aggregation of Cranial Tremor in Familial Essential Tremor

Summary:
Cranial tremor is an important aspect of essential tremor and it includes the neck, voice, and jaw tremors. With 95 subjects in 28 families, researchers at Columbia University investigated whether or not cranial tremor is seen in various members of families with essential tremor. In other words, whether the presence of cranial tremor in one family member is associated with its presence in another affected relative. Cranial tremors are the most common tremors after upper limb tremors. After analysis, it was established that cranial tremor was associated with severity of tremors rather than its presence in other family members.

Publication Title:
Does rate of Progression Run in Essential Tremor Families? Slower vs. Faster Progressors

Summary:
Essential tremor is a progressive disorder, gradually worsening over time, and commonly occuring in families. At Columbia University, 28 families were studied to see whether or not the rate of progression of essential tremor differs between families. In other words, do some families progress more slowly than other families? After data analysis, there was a 4-fold difference in the average rate of progression amongst the participants. It was concluded that some families seemed to progress more rapidly than others. Although the rate of progression within families was not identical, family members seemed to follow a similar pattern.

Original Paper

Neuro-epidemiology

Neuroepidemiology 2013;40:269–273
DOI: 10.1159/000345253

Received: July 30, 2012
Accepted: October 16, 2012
Published online: January 24, 2013

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.

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Methods

Ascertainment of Probands

ET cases (probands) 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.). Probands 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 proband'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.

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Table 1. Demographic and clinical characteristics of study sample

	Probands (n = 26)	Relatives (n = 52)
Age, years	64.3 ± 11.2	58.5 ± 18.8
	37 – 83	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 (%).

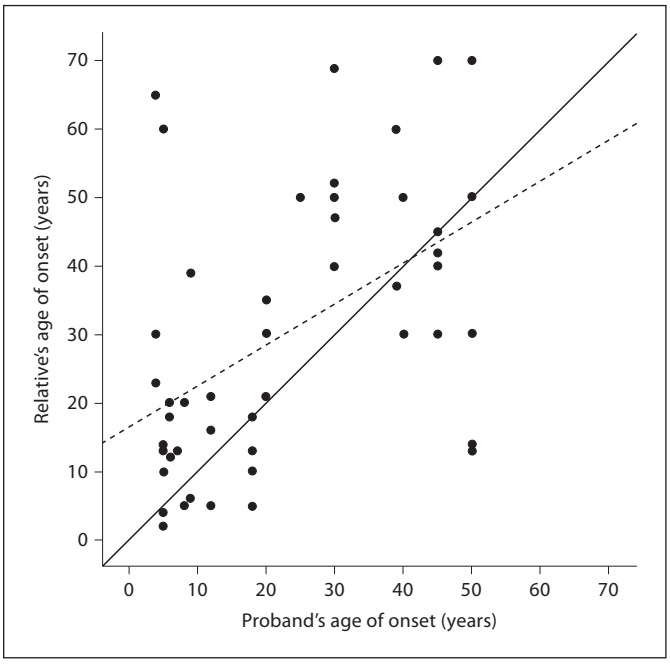

Fig. 1. Age of onset in 52 relatives who knew their age of onset. Each relative's age of onset (y-axis) is plotted against the age of onset of his/her proband (x-axis). The relatives' age of onset correlated with that of the respective proband (Pearson's r = 0.50, p = 0.001, see dotted regression line).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

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 median 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 = 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

Neuroepidemiology 2013;40:269–273
DOI: 10.1159/000345253

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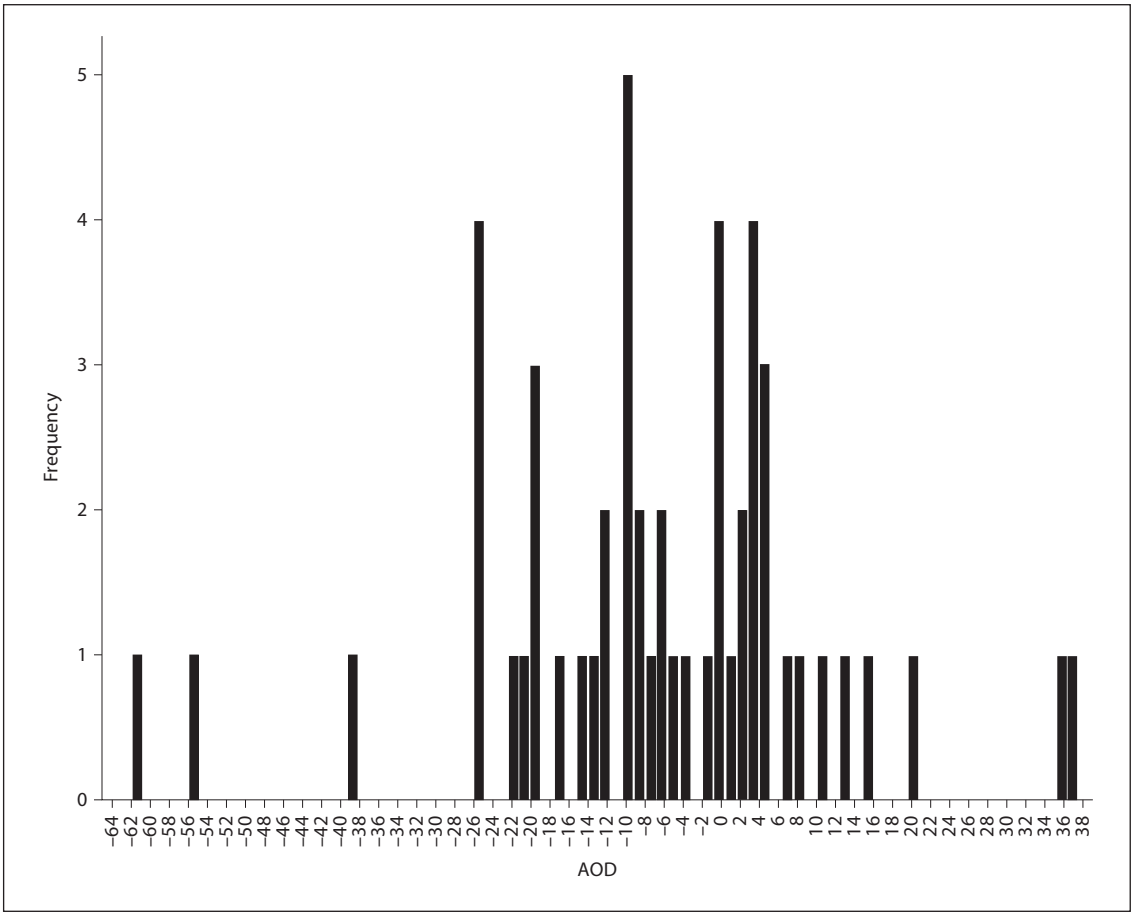

Fig. 2. The AOD (x-axis) in 52 relatives. AOD = The proband's age of onset – the relative's age of onset; a positive value indicates that the relative's age of onset was younger than the proband's and a negative value indicates that the relative's age of onset was older than the proband's. The y-axis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

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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.

Acknowledgement

This research was supported by National Institutes of Health Grant R01 NS073872 (Dr. Louis, Dr. Ottman, and Dr. Clark).

Disclosure Statement

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

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Original Paper

Neuro-epidemiology

Neuroepidemiology 2013;41:48–53
DOI: 10.1159/000348553

Received: December 19, 2012
Accepted: February 4, 2013
Published online: May 25, 2013

Familial Aggregation of Cranial Tremor in Familial Essential Tremor

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Key Words
Essential tremor · Genetics · Familial tremor · Clinical correlates · Cranial tremor · Head tremor

Abstract
Background: Essential tremor (ET) is often familial and phenotypic features may be shared within families. Cranial (neck, voice, and jaw) tremor is an important feature of ET. We examined whether cranial tremor aggregates in ET families, after controlling for other factors (age, tremor severity, and duration). ***Methods:*** Among ET probands and relatives enrolled in a genetic study at Columbia University (95 subjects in 28 families), we assessed the degree to which occurrence of cranial tremor in the proband predicted occurrence of cranial tremor in affected relatives. ***Results:*** Forty-five (47.4%) subjects had cranial tremor on neurological examination (probands 66.7%, relatives 39.7%). Among 28 families, 23 (82.1%) contained individuals with and individuals without cranial tremor, indicating a high degree of within-family heterogeneity. In comparison to subjects without cranial tremor, those with cranial tremor had higher total tremor scores ($p < 0.001$), were older ($p = 0.003$), and had tremor of longer duration ($p = 0.01$). In logistic regression models, the odds of cranial tremor in a relative were not related to occurrence of cranial tremor in the proband ($p > 0.24$). ***Conclusions:*** Cranial tremor did not aggregate in families with ET; the major predictor of this disease feature was tremor severity rather than presence of cranial tremor in another family member.

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Introduction

Cranial tremor, including neck, voice, and jaw tremor, is an important feature of essential tremor (ET). Following upper limb tremor, it stands out as the most common site of tremor in this disease [1–3]. It also has several important clinical correlates; for example, it has been found to be associated with greater gait and balance difficulty [4–6] and may be more resistant to treatment than other tremor types [7–9]. Head and jaw tremor are also visually quite apparent and of particular cosmetic concern for patients.

ET is often familial [10]. In the ongoing search for susceptibility genotypes [11], the study of its manifestations within families is currently an area of considerable research focus.

Until recently, the familial aggregation of the phenotypic features of ET has received little attention. We re-

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cently found that age of onset and rate of progression aggregate in ET families [12, 13]. Despite the high prevalence of cranial tremor, there are no readily available data on the concordance for such tremor within ET patients and their families. This is an issue that has research as well as clinical ramifications. ET patients whose relatives (e.g. parents) have/had head tremor often ask whether they, too, are likely to develop a similar feature. Data to guide clinicians on how to answer this question are lacking.

In the current investigation, our goal was to study the familial aggregation of cranial tremor in families containing multiple individuals with ET, enrolled in a genetic study of ET at Columbia University Medical Center (CUMC) [14]. We also considered whether several other factors (age, tremor severity, and duration) predicted occurrence of cranial tremor. Our hypothesis was that the presence of cranial tremor in one or more family members would strongly predict the presence of such tremor in their relatives, after controlling for other factors. Given the higher prevalence of cranial tremor among women with ET [15], we also expected that female gender would predict presence of cranial tremor.

Methods

Ascertainment of Probands

ET cases (probands) 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 [14]. 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 was ≤40 years (this was later changed to ≤50 years to be more inclusive), and (3) ≥2 living relatives in the United States with ET also diagnosed by a doctor and who were not reported to have dystonia or Parkinson's disease (PD). The exclusion criterion for probands was a prior diagnosis of dystonia or PD. The rationale for enrolling probands whose tremor onset was ≤40 years was to increase the likelihood of enrolling probands with underlying susceptibility genotypes of ET. ET patients with younger age of tremor onset often have the familial form of the disease. Indeed, we previously reported that a large proportion of the young-onset cases had the familial form of ET [16].

Potential ET probands contacted the FASET study coordinator. Prior to final selection for enrollment, a set of four Archimedean spirals (two right, two left) was submitted by probands and rated by a senior neurologist specializing in movement disorders (E.D.L.). Probands 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 [17].

Ascertainment of Relatives

Based upon a telephone interview with the proband, relatives with ET were identified [14]. 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. Prior to final selection for enrollment, relatives submitted four Archimedean spirals. These spirals were rated (E.D.L.), and relatives were included if one or more of the spirals had a rating ≥2 [17].

Evaluation

An in-person evaluation was then conducted in the enrollees' homes; this included a series of questionnaires and a videotaped neurological examination [14]. Age of tremor onset was by self-report and was the age at which the individual first noted tremor. Prior studies have indicated that it is reliably reported by ET patients [18]. Tremor duration was the difference between current age and age of tremor onset. The videotaped neurological examination included a detailed assessment of postural, kinetic, intention, and rest tremors in the limbs, as well as dystonia and other movement disorders [19]. Voice tremor was assessed during sustained phonation, conversational speech, and while reading a prepared passage. Neck (i.e. head) tremor was assessed while seated comfortably and facing the camera. Jaw tremor was assessed while the mouth was stationary (closed), while the patient was asked to hold their mouth slightly open, during sustained phonation, and during speech [3]. 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)] [19]. 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 [14]. 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) [17, 20].

Final Sample

There were 145 enrollees (38 probands and 107 relatives). For the current analyses, we excluded 47 enrollees for the following reasons: 26 families did not contain ≥1 relatives with ET, 22 had dystonia (mainly torticollis), and 2 had incomplete data. Hence, the final sample consisted of 27 probands and 68 relatives (95 ET total). These 95 included 1 family (family 23) in which there were 4 relatives, but the proband had dystonia, so only the data on the 4 relatives are presented here. The final sample of 95 (table 1) was similar to the initial sample of 145 in terms of age (56.3 ± 18.5 vs. 58.5 ± 18.0 years, $t = 0.92$, $p = 0.36$), gender [49 (51.6%) vs. 86 (59.3%) female, $\chi^2 = 1.39$, $p = 0.24$], tremor duration (28.3 ± 18.9 vs. 29.6 ± 20.0 years, $t = 0.50$, $p = 0.62$), total tremor score (18.5 ± 6.3 vs. 17.5 ± 7.0, $t = 1.13$, $p = 0.26$), and proportion with cranial tremor [45 (47.4%) vs. 58 (40.0%), $\chi^2 = 1.27$, $p = 0.26$].

Statistical Analyses

Analyses were performed in SPSS (version 19.0). Subject characteristics were compared using Student's t tests and χ^2 tests. Correlations between continuous variables were assessed with Pearson's correlation coefficients. Bivariate and then multivariate logistic regression models assessed the predictors of cranial tremor in relatives. We used these models to assess the predictors of cranial tremor in relatives, using the presence versus absence of cra-

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Table 1. Demographic and clinical characteristics of enrollees

	All enrollees (n = 95)	Probands (n = 27)	Relatives (n = 68)
Age, years	56.3±18.5, 19–93	62.7±12.6, 37–83	53.7±19.9, 19–93
Female gender	49 (51.6)	16 (59.3)	33 (48.5)
White race	86 (90.5)	24 (88.9)	62 (91.2)
Relationship to proband			
Self	27 (28.5)	27 (28.5)	0
Child	28 (29.5)	0	28 (29.5)
Sibling	16 (16.8)	0	16 (16.8)
Parent	6 (6.3)	0	6 (6.3)
Grandchild	3 (3.2)	0	3 (3.2)
Aunt/uncle	4 (4.2)	0	4 (4.2)
Nephew/niece	5 (5.3)	0	5 (5.3)
Other (third-degree)	6 (6.3)	0	6 (6.3)
Total tremor score on neurological examination	18.5±6.3	23.0±4.8	16.7±5.9
Cranial tremor on neurological examination			
Neck, jaw or voice tremor	45 (47.4)	18 (66.7)	27 (39.7)
Neck tremor	31 (32.6)	15 (55.6)	16 (23.5)
Jaw tremor	18 (18.9)	7 (25.9)	11 (16.2)
Voice tremor	16 (16.8)	10 (37.0)	6 (8.8)
Currently takes medication to treat ET	44 (46.4)	20 (74.1)	24 (35.3)
Age of tremor onset, years	28.0±18.6	24.2±15.4	29.5±19.6
Duration of tremor, years	28.3±18.9	38.6±14.9	24.2±18.8

All values are means ± standard deviation, range or number (%), unless otherwise specified.

nial tremor in the proband as a primary predictor of interest. Other predictors that we considered included relative's age, total tremor score, tremor duration, and gender. Because of the non-independence of proband-relative pairs within each family, we used generalized estimating equations (GEEs) to compute odds ratios (ORs) and 95% confidence intervals (CIs).

Results

Prevalence and Correlates of Cranial Tremor

The 68 relatives included 28 (41.2%) children, 16 (23.5%) siblings, and 6 (8.8%) parents, with the remainder comprising other types of relatives (e.g. aunts/uncles).

Forty-five subjects (18 probands and 27 relatives) had cranial tremor on neurological examination (table 1). Compared with the 50 subjects without cranial tremor, the 45 with cranial tremor had higher total tremor scores (20.9 ± 6.5 vs. 16.3 ± 5.3, $t = 3.72$, $p < 0.001$), were older (62.5 ± 18.2 vs. 50.7 ± 17.1 years, $t = 3.25$, $p = 0.003$), and had tremor of longer duration (33.3 ± 17.7 vs. 23.8 ± 18.9 years, $t = 2.51$, $p = 0.01$). Cranial tremor was more prevalent in women than men [26 (53.1%) women vs. 19 (41.3%) men, but not to a significant degree, $\chi^2 = 1.32$, $p = 0.25$], and in particular, head tremor was more common in women [20 (40.8%) vs. 11 (23.9%), $\chi^2 = 3.08$, $p = 0.079$]. Total tremor score, age, and duration were collinear (all pairwise Pearson's $r > 0.51$, $p < 0.001$). The association between total tremor score and presence of cranial tremor is shown by family; in most families, the individuals with cranial tremor were those with the highest tremor scores (fig. 1). Similar relationships were seen when age and duration were plotted by presence of cranial tremor within families (data not shown).

Familial Aggregation of Cranial Tremor

Twenty-three (82.1%) of 28 families included both individuals with and without cranial tremor, indicating a high degree of within-family heterogeneity. Three families (Nos. 20, 24, 28) were completely concordant for presence of cranial tremor (i.e. each family contained 2 affected family members both of whom had cranial tremor). Two families (Nos. 21 and 23) were concordant for absence of cranial tremor. Eighteen (66.7%) of 27 probands versus 27 (39.7%) of 68 relatives had cranial tremor ($\chi^2 = 5.63$, $p = 0.018$). With regard to presence versus absence of cranial tremor, 25 (36.8%) relatives were concordant with their proband, 38 (55.9%) relatives were discordant with their proband, and 5 relatives (family 23) did not have a proband with ET.

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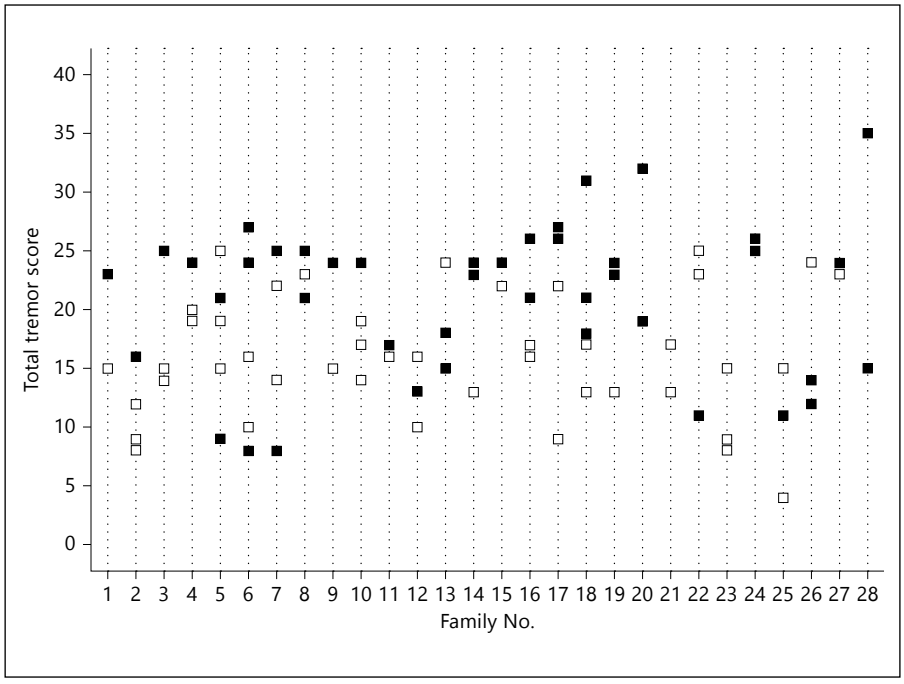

Fig. 1. The association between tremor severity and presence of cranial tremor in 28 ET families. Total tremor score (y-axis) by family No. (x-axis and vertical lines). Subjects with cranial tremor are represented by closed boxes and subjects without cranial tremor are represented by open boxes. In most families, individuals with cranial tremor were those with the highest tremor scores. In 10 instances, ≥2 individuals within a family had the same total tremor score and are represented by a single data point.

Predictors of Cranial Tremor in Relatives: Regression Modeling

Presence of cranial tremor in the relative (outcome variable) was associated with the relative's age (OR = 1.03, 95% CI = 1.003–1.06, p = 0.03) and tremor duration (OR = 1.03, 95% CI = 1.00–1.06, p = 0.047). The strongest predictor of cranial tremor in the relative was the relative's total tremor score (OR = 1.1, 95% CI = 1.01–1.22, p = 0.035).

Presence of cranial tremor in relatives was not associated with presence of cranial tremor in the proband (OR = 0.7, 95% CI = 0.36–1.40, p = 0.32). This result was not substantially changed after adjusting for the relative's total tremor score (OR = 0.8, 95% CI = 0.37–1.58, p = 0.47), relative's tremor duration (OR = 0.9, 95% CI = 0.45–1.88, p = 0.82), or relative's age (OR = 0.6, 95% CI = 0.26–1.40, p = 0.24) in multivariate models. The relative's gender was not a confounder either. Total tremor score, age, and duration could not be included in the same model because they were collinear.

Additional Analyses

The large majority of individuals with cranial tremor had neck tremor. In a parallel set of analyses, we examined the predictors of neck tremor, and results were similar. Presence of neck tremor in relatives was not associated with presence of neck tremor in the proband (OR = 0.6, 95% CI = 0.23–1.63, p = 0.33). Adjusting for potential confounders (relative's total tremor score, relative's tremor duration, and relative's age) did not change the results. There was no confounding by gender.

Discussion

Head tremor is highly prevalent in ET, occurring in 30–50% of cases [15, 21]. In addition to its reported clinical correlates [4–6], imaging studies have suggested that ET patients with head tremor may form a distinct subgroup, with reductions in cerebellar volume relative to those without head tremor [22, 23]. The presence/absence of cranial tremors is also often used as a stratification point in genetic studies of ET [24, 25]. Yet, there are no readily available data on the concordance for such tremors in ET patients and their affected family members.

A large population-based family study in Sweden in the late 1950s included phenotype information on approximately 200 ET cases descended from a small number of ancestral families, and cranial tremors were reportedly present in some members of some families but not others, suggesting, as observed in our families, a high degree of within-family heterogeneity with respect to cranial tremor in ET, although the investigators did not consider the contributions of subject age, gender, duration, and other factors in their analyses [26]. Aside from that

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study, we are not aware of any prior published data on the concordance for cranial tremors in ET families.

ET patients whose relatives (e.g. parents) have/had head tremor often ask whether they, too, are likely to develop a similar head bobble. In the absence of published data, it has not been clear how to counsel these patients. The current data suggest that the development of head tremor is not strongly linked with family history, but rather, it seems to be more dependent on the extent of tremor severity and disease progression.

Eighteen (66.7%) of 27 probands versus 27 (39.7%) of 68 relatives had cranial tremor. Probands in this study may have self-selected based on the severity of their disorder, resulting in a high proportion with cranial tremor.

This study had limitations. Sample size was limited due to our restriction of the study to individuals who received in-person examination rather than including individuals with self-reported or proband-reported ET [27]. Despite the modest sample size, we were able to detect several important associations. Our restrictive inclusion criteria may also be viewed as a study strength, because they probably increased the validity of our diagnoses. Further strengths included the presence of multi-case families and a broad range of phenotypic features.

In summary, the familial aggregation of cranial tremor was low in ET. The major predictor of this disease feature was tremor severity rather than the presence of cranial tremor in another family member.

Acknowledgement

This research was supported by National Institutes of Health grant R01 NS073872 (E.D.L., L.N.C., and R.O.).

E.D.L. has received research support from the National Institutes of Health: NINDS R01 NS042859 (principal investigator; PI), NINDS R01 NS39422 (PI), NINDS T32 NS07153–24 (PI), NINDS R01 NS073872 (co-principal investigator; CoPI), NINDS R21 NS077094 (co-investigator; CoI), and NINDS R01 NS36630 (CoI), as well as the Parkinson's Disease Foundation (PI), the Arlene Bronstein Essential Tremor Research Fund (Columbia University), and the Claire O'Neil Essential Tremor Research Fund (Columbia University).

L.N.C. has received research support from National Institutes of Health grants R21NS050487 (PI), R01NS060113 (PI), R01NS0738072 (CoPI), P50AG008702 (CoI), P50 NS038370 (CoI), the Parkinson's Disease foundation (PI), and the Michael J. Fox foundation (CoI).

R.O. has received research support from the National Institutes of Health: NINDS R01 NS073872 (CoI), NINDS R01 NS053998 (CoI), NINDS R03 NS065346 (PI), NINDS RC2 NS070344 (PI), NHGRI P20 HG005535 (CoI), NINDS U01 NS077276 (PI), NINDS U01 NS077367 (PI), NINDS R01 NS078419 (PI), and NIA R01 AG041797 (CoI).

Disclosure Statement

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

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Parkinsonism and Related Disorders 19 (2013) 363–366

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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Short communication

Does rate of progression run in essential tremor families? Slower vs. faster progressors

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ARTICLE INFO

Article history:
Received 24 July 2012
Received in revised form
25 September 2012
Accepted 5 October 2012

Keywords:
Essential tremor
Genetics
Familial
Clinical
Rate of progression

ABSTRACT

Background: Essential tremor (ET) is a progressive disorder, worsening gradually with time in most patients. Yet there are few data on the factors that influence rate of progression. ET is a highly familial disorder, and physicians often care for patients who have other affected family members. Do ET families differ from one another with respect to rate of progression? Are some families slower progressors and other families faster progressors? We are unaware of published data.
Methods: ET probands and relatives were enrolled in a cross-sectional genetic study at Columbia University. Rate of progression was calculated as total tremor score ÷ log disease duration.
Results: There were 100 enrollees (28 probands, 72 relatives). Data from 78 enrollees (23 probands, 55 relatives) were selected for final analysis. The mean familial rate of progression ranged from as little as 8.4 to as much as 34.3, $a > 4$-fold difference. In an analysis of variance, we found significant evidence of heterogeneity in the log rate of progression across families ($p < 0.001$), with more than one-half (i.e., 55.4%) of the total variance in the log rate of progression explained by the family grouping.
Conclusions: Familial factors seem to affect rate of tremor progression in ET. There was a 4-fold difference across families in observed mean rate of progression; thus, some families seemed to be more rapid progressors than others. We hope these data may be used by clinicians to provide basic prognostic and family guidance information to their patients and families with ET.
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1. Introduction

Essential tremor (ET) is a progressive disorder, worsening gradually over time in most patients [1]. Despite previous attempts to identify factors that influence rate of progression [2,3], there are few published data.

ET is generally considered to be a highly familial disorder [4]. Treating physicians often care for patients who have multiple affected family members (e.g., siblings) as well as other at risk family members (esp., children and grandchildren). Surprisingly, it is not known whether the basic clinical features of the ET in one family member can be used to predict the course the disease will take in other family members. More specifically, the extent to which rate of progression runs in ET families is not known: are some families slower progressors and some families faster progressors? There are no published data to guide treating clinicians.

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 asked whether families differed with respect to rate of progression and whether some families were slower progressors and other families faster progressors. We hope these data will be useful to clinicians in providing a basic prognostic framework and family guidance information to their patients and families with ET.

2. Methods

2.1. Ascertainment of probands

ET cases (probands) 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 cross-sectional, and was advertised on two ET

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http://dx.doi.org/10.1016/j.parkreldis.2012.10.005

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 $\leq$ 40 years (later changed to $\leq$50 to be more inclusive), (3) $\geq$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. Prior to final selection for enrollment, a set four Archimedes spirals (two right, two left) were submitted by probands, and rated by a senior neurologist specializing in movement disorders (E.D.L.). Probands 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 [5].

2.2. 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. Prior to final selection for enrollment, four Archimedes spirals were submitted by relatives and rated. Relatives were included if one or more of the spirals had a rating $\geq$2 [5].

2.3. 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, which included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia and other movement disorders [6]. Data on age of onset of tremor were collected; prior studies have shown that this is reliably reported [7]. A senior movement disorders neurologist reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors were rated on 12 examination items using a reliable 0–3 rating scale [8], resulting in a total tremor score (range = 0–36 [maximum]) [6]. The study was approved by the CUMC Institutional Review Board and all participants signed written informed consent.

2.4. Diagnoses

All ET diagnoses were reconfirmed based on review of questionnaires and videotaped neurological examination data. 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) [5,8].

2.5. Statistical analyses

Analyses were performed in SPSS (Version 19.0). Duration of disease was the current age − age of onset. In prior publications, rate of progression was calculated as the total tremor score ÷ duration of disease [2,9,10]. To diminish the effect of the wide range of reported durations (2–90 years), we log-transformed duration of disease; hence, rate of progression was total tremor score ÷ log (duration of disease). Rate of progression was not normally distributed (Kolmogorov–Smirnov $z = 1.71$, $p = 0.006$); the log-transformed variable (log rate of progression) was normally distributed (Kolmogorov–Smirnov $z = 0.99$, $p = 0.28$). In an analysis of variance, we tested for heterogeneity across families in log rate of progression.

3. Results

There were 100 enrollees, including 28 probands and 72 relatives (58 first-degree, 11 second-degree, and 3 third-degree) (Table 1). We excluded 10 enrollees who did not recall their age of onset, one with incomplete data, three others because they were probands with no enrolled family members, 4 with dystonia rather than ET, and 4 who were normal. The final sample comprised 78 enrollees (23 probands and 55 relatives); these were similar to the base sample of 100 (Table 1).

In the 78 enrollees, the mean ± SD rate of progression was 15.4 ± 6.5 (range = 5.4–43.2), median = 14.4 (Fig. 1a). As expected, rate of progression was associated with total tremor score (Spearman's $r = 0.53$, $p < 0.001$) and disease duration (Spearman's $r = -0.41$, $p < 0.001$). Rate of progression was also associated with age of onset (Spearman's $r = 0.45$, $p < 0.001$), but not age at evaluation (Spearman's $r = 0.02$, $p = 0.88$). Rate of progression was not associated with gender ($p = 0.68$), white race ($p = 0.44$), daily use of ET medication ($p = 0.92$), presence vs. absence of head tremor ($p = 0.36$) or subject type (i.e., proband vs. relative, $p = 0.68$).

Table 1
Demographic and clinical characteristics of enrollees.

	All enrollees ($N = 100$)	Enrollees in final sample ($N = 78$)
Age (years)	59.0 ± 17.4, 19–95	59.2 ± 17.6, 19–95
Female gender	55 (55.0)	41 (52.6)
White race	88 (88.0)	68 (87.2)
Ashkenazi Jewish Ancestry	12 (12.0)	10 (12.8)
Relationship to proband		
Self	28 (28.0)	23 (29.5)
Child	27 (27.0)	20 (25.6)
Sibling	24 (24.0)	17 (21.8)
Parent	7 (7.0)	7 (9.0)
Grandchild	1 (1.0)	1 (1.3)
Aunt/uncle	3 (3.0)	3 (3.8)
Nephew/niece	7 (7.0)	5 (6.4)
Other (third-degree)	3 (3.0)	2 (2.6)
Total tremor score on neurological examination	17.6 ± 6.5	19.4 ± 5.5
Voice tremor on neurological examination	16 (16.0)	16 (20.5)
Head (neck) tremor on neurological examination	24 (24.0)	22 (28.2)
Currently takes daily medication for ET	39 (39.0)	33 (42.3)
Age of tremor onset (years), median	28.1 ± 18.3, 22	28.6 ± 18.3, 27.5
Duration of tremor (years), median	30.8 ± 19.4, 29.5	30.6 ± 19.3, 29

All values are mean ± standard deviation, range or number (%), unless otherwise specified.

Each family's mean rate of progression is plotted (Fig. 1b) as are individual data points within and across families (Fig. 1a). The mean familial rate of progression ranged from as little as 8.4 (Family 1) to as much as 34.3 (Family 23, Fig. 1b), $a > 4$-fold difference.

In an analysis of variance, we found significant evidence of heterogeneity in the log rate of progression across families (ANOVA $F = 3.11$, $p < 0.001$), with more than one-half (i.e., 55.4%) of the total variance in the log rate of progression explained by the family grouping. Adjusting for age of onset, which was associated with rate of progression, did not change the results ($p < 0.001$). While rate of progression was not identical in different members of the same family, members of the same family seemed to follow a similar pattern (Fig. 1a).

The use of ET medications could reduce observed tremor severity. To assess the impact of medication usage on our results, we excluded 33 participants who were taking ET medications. The results did not change: the mean familial rate of progression ranged from as little as 8.4 to as much as 34.3. As the diagnosis of ET in some individuals was based primarily on the presence of head tremor, which would not have been reflected in the total tremor scores, we also performed an analysis in which we excluded 22 individuals with head tremor. The results did not change: the mean familial rate of progression ranged from as little as 8.4 to as much as 34.3.

Because disease duration was the denominator in the index that was used to assess rate of progression, a very short duration could magnify the rate of progression. We therefore performed an analysis in which we excluded 12 cases with short disease duration ($\leq$10 years). The results were similar: the mean familial rate of progression ranged from as little as 8.4 to as much as 29.8. We also performed an analysis in which we stratified the sample based on median age of onset (27.5 years) into two groups (younger vs. older age of onset). The results were similar in the two strata.

4. Discussion

In terms of rate of progression in ET, family matters. In this family study of ET, there was a 4-fold difference across families in

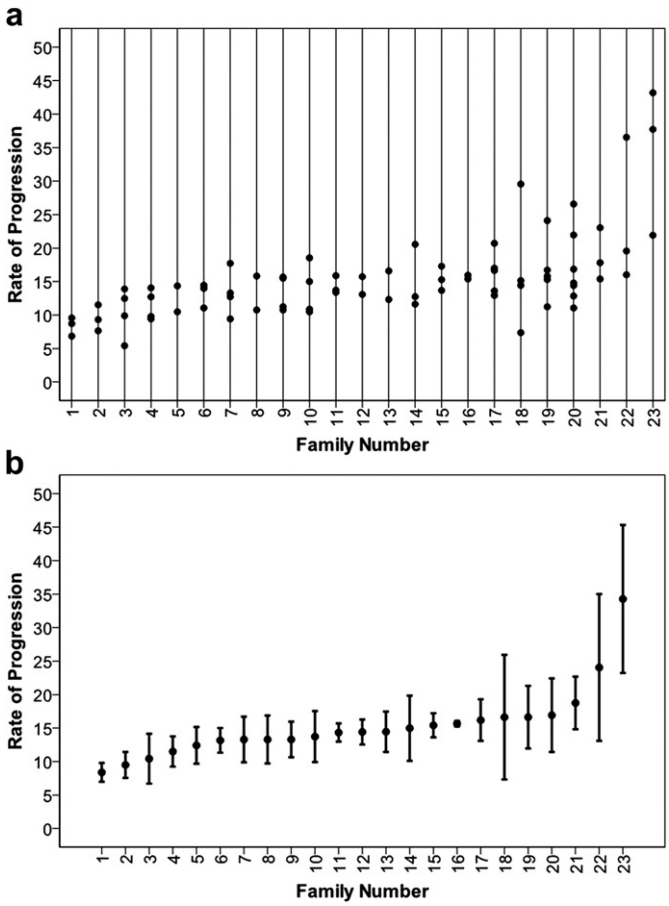

Fig. 1. a. Rate of progression by family number. Each family was assigned a unique family number (1, 2, 3, 4…n) based on increasing value of rate of progression. Thus, the family with the smallest value (i.e., slowest rate of progression) was assigned the family number of 1. Each data point represents one individual. Vertical grid lines run through the data points in each family. Rate of progression was calculated as the total tremor score ÷ log (duration of disease). b. Rate of progression by family number. Each family was assigned a unique family number (1, 2, 3, 4…n) based on increasing value of rate of progression. Thus, the family with the smallest value (i.e., slowest rate of progression) was assigned the family number of 1. Circles represent the mean (all family members within than family) and bars represent ± 1 standard error. Rate of progression was calculated as the total tremor score ÷ log (duration of disease).

observed mean rate of progression; some ET families seemed to be more rapid progressors than others. Family membership explained more than one-half of the total variance in the rate of progression. Furthermore, while rate of progression was not identical in different members of the same family, family members seemed to follow a similar pattern.

Thus, at least in the context of familial ET, family membership seems to be an important contributor/predictor of rate of progression. There are few other data on factors that contribute to rate of progression in ET. We have previously demonstrated in both a community-based and clinic-based sample of ET cases that older age of onset was associated with faster rate of progression [2,10]. Here too, in the context of familial ET, we showed that the rate of progression was also associated with age of onset (Spearman's $r = 0.45$, $p < 0.001$). The faster rate of tremor progression in older onset ET is similar to that reported in patients with several neurodegenerative disorders. As discussed elsewhere [10], in PD patients, age at disease onset was the main predictor of motor decline, indicating a faster and less restricted pathologic disease process in patients with older onset PD. Postmortem studies in PD also support the notion that in advanced age, brain pathology advances more rapidly. Similar findings have been reported in patients with multiple system atrophy and motor neuron disease [10].

In complex diseases, rate of progression is probably determined by both genetic and environmental factors. Good examples of this can be found in the PD literature. For example, *parkin* mutation carriers have an earlier age of onset than other PD [11]. LRRK2-linked PD displays high variability in age at onset [12].

This study had limitations. We utilized data on reported age of onset. Prior studies have shown that these data are reliably reported [7], yet the validity of reported age of onset is not fully known. Second, rate of progression was assessed with a cross-sectional measure (tremor severity ÷ log duration) rather than a longitudinal measure (change in tremor severity across two or more time points), and future studies could improve on our methods by using such an approach. Third, the mix of families that we studied may not be representative of all ET families, so that studies will larger sample sizes would be valuable. Finally, the study did not attempt to assess specific patterns in the disease progression (e.g., the hand tremor followed by head tremor vs. the converse).

With these new data, what can we counsel ET patients? First, we can identify some factors that influence rate of tremor progression. More specifically, familial factors do seem to affect rate of tremor progression. Thus, ET families differ with regards to rate of tremor progression; some families are slower progressors and some families are faster progressors. Indeed, we observed a four-fold difference in rate of tremor progression across families. Second, while rate of progression is not identical in different members of the same family, family members seem to follow a similar pattern. Future study of these familial factors and how they may translate into biologically-meaningful factors of mechanistic importance would be important.

Conflict of interest statement

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

Statistical analyses

The statistical analyses were conducted by Dr. Louis.

Acknowledgments

This research was supported by National Institutes of Health Grant R01 NS073872 (Dr. Louis, Dr. Ottman, Ionita-Laza, and Dr. Clark).

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