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Tremor and Other Hyperkinetic Movements

Articles

Familial Aggregation of the Cerebellar Signs in Familial Essential Tremor

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Abstract

Background: Although the hallmark feature of essential tremor (ET) is kinetic tremor, patients may exhibit additional motor features (e.g., intention tremor and mild gait ataxia) that are markers of an underlying abnormality of cerebellar function. ET is also a highly familial disorder, but we do not know whether the presence and expression of cerebellar signs are similar across family members. There are simply no published data. The alternative possibility is that these features are not heritable. We tested the specific hypothesis that the presence of cerebellar signs (i.e., intention tremor, tandem gait difficulty) ran in ET families.

Methods: ET probands and relatives enrolled in a genetic study at Yale and Columbia universities underwent a detailed videotaped neurological examination.

Results: There were 187 enrollees (59 probands, 128 affected relatives). In a bivariate logistic regression model, the presence of intention tremor in the proband was not a predictor of the presence of intention tremor in the relatives (odds ratio [OR]=0.60, 95% confidence interval [CI]=0.28–1.27, p=0.18). In a similar model, the presence of greater tandem gait difficulty (i.e., a tandem gait score in the upper quartile) in the proband was not a predictor of the presence of such difficulty in the relatives (OR=1.22, 95% CI=0.41–3.66, p=0.73).

Discussion: The presence of cerebellar signs did not aggregate in families with ET. In the current dataset, these did not seem to be disease features that were heritable.

Keywords: Essential tremor, genetics, familial, clinical

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Introduction

Essential tremor (ET) is one of the most prevalent neurological diseases.[1–3] Although the hallmark feature of ET is kinetic tremor of the arms,[4,5] patients may exhibit a number of other motor features. These features, which include intention tremor[5–7] and mild gait ataxia,[8–10] are clinical markers of what is likely to be an underlying abnormality of cerebellar function.[11] Further support for the notion that the cerebellum is abnormal in this disease is derived from both neuroimaging[12,13] and postmortem studies.[14–16]

ET is also a highly familial disorder.[17–19] Treating physicians often care for patients who have affected family members and other family members who are at increased risk. Several clinical features run in ET families (e.g., age of onset of tremor,[20] rate of progression of tremor[21]) whereas other clinical features do not (e.g., presence of cranial tremor).[22] Whether the presence and expression of cerebellar signs (intention tremor and gait ataxia) is similar across family members is not known. There are simply no published data. The alternative possibility is that these features are not heritable. For example, there is

evidence that intention tremor[6] and rest tremor[23] tend to accumulate simply with the natural progression of ET. Yet data are very limited.

ET cases (probands) and their relatives were enrolled in a genetic study of ET. We tested the specific hypothesis that the presence of cerebellar signs (i.e., intention tremor, tandem gait difficulty) ran in families. These are the two cerebellar signs most commonly noted to be associated with ET.[6–10] We hope these data will be useful to clinicians in providing additional family guidance information for their patients and families with ET.

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) (2011 to present).[21] The study was approved by the Columbia University and Yale University Institutional Review Boards and all participants signed written informed consent. The study was advertised on several 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), 3) two or more 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 of 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 enrolled if one or more of the spirals had a Washington Heights–Inwood Genetic Study of Essential Tremor rating that indicated moderate or greater tremor.[24]

Ascertainment of relatives

Based upon a telephone interview with the proband, relatives with ET were identified.[21] 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 by E.D.L. Relatives were enrolled if one or more of the spirals indicated moderate or greater tremor.[24]

In-person evaluation

An in-person evaluation was then conducted in enrollees' homes; this included several questionnaires and a videotaped neurological examination.[21] The latter included a detailed assessment of postural, kinetic, intention and rest tremors, as well as dystonia, other movement disorders, and other neurological signs (e.g., cranial nerve abnormalities, weakness).[25] E.D.L. reviewed all videotaped examinations, and the severity of postural and kinetic arm tremors was rated on 12 examination items using a reliable rating scale,[26] resulting in a total tremor score (range, 0–36; maximum).[25]

During the examination, the finger-nose-finger maneuver included 10 repetitions per arm. Intention tremor was defined as present when tremor amplitude increased during visually guided movements towards the target.[6] We excluded position-specific tremor or postural tremor at the end of movement. Similar to prior work,[6] intention tremor was rated (E.D.L.) in the terminal period of the finger-nose-finger test: 0 (no intention tremor); 0.5 (probable intention tremor); 1 (definite intention tremor); 2 (incapacitating intention tremor); however, no cases received ratings of 2. The intention tremor score (both arms combined) ranged from 0 to 2. Cases with definite intention tremor in at least one arm or probable intention tremor in both arms were labeled as "ET with intention tremor."[6]

An assessment of tandem gait was performed during the study visit and was videotaped so that the number of mis-steps could be evaluated later by a senior neurologist (E.D.L.). Tandem gait was explained and demonstrated to subjects; they were carefully instructed to walk placing one foot directly in front of the other, being careful to touch toe to heel with each step. If they misunderstood the task (i.e., failed to follow directions), they were immediately re-instructed and began again. They could choose their own line (i.e., a line was not drawn or placed on the floor). The tandem gait score was the number of mis-steps (i.e., steps to the side) during a single trial of 10 steps.

Diagnoses

All ET diagnoses were reconfirmed on the basis of 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).[21,24,26]

Final sample

There were 295 enrollees. We excluded 21 enrollees who did not qualify for a diagnosis of ET. We also excluded 50 enrollees who came from families in which either the proband had not yet been enrolled or in which at least one relative had not yet been enrolled. We excluded nine probands who had had surgery for ET (seven deep brain stimulation and two thalamotomy). We also excluded the relatives of these nine probands.

The final sample (187 enrollees) included 59 probands and 128 affected relatives (105 first-degree, 16 second-degree, and seven third-degree).

Statistical analyses

Analyses were performed in SPSS (Version 21.0). Probands' vs. relatives' characteristics were compared using the Student t-test, the chi-square test, and the Fisher exact test and Mann–Whitney test (Table 1). We also assessed the clinical correlates of presence of intention tremor (definite intention tremor in at least one arm or probable intention tremor in both arms) and the presence of greater

Table 1. **Demographic and Clinical Characteristics of 187 Cases**

	Probands (N=59)	**Affected Relatives (N=128)**	**p**
Age (years)	64.1±15.0, 22–91	60.5±17.2, 20–93	0.18[1]
Female gender	38 (64.4)	64 (50.0)	0.07[2]
White race	55 (93.2)	121 (94.5)	0.74[3]
Right-handed	57 (96.6)	117 (91.4)	0.23[3]
Relationship to proband			NA
Self	59 (100)	0 (0.0)	
Child	0 (0.0)	33 (25.8)	
Sibling	0 (0.0)	57 (44.5)	
Parent	0 (0.0)	15 (11.7)	
Grandchild	0 (0.0)	3 (2.3)	
Aunt/uncle	0 (0.0)	4 (3.1)	
Nephew/niece	0 (0.0)	9 (7.0)	
Other (third-degree)	0 (0.0)	7 (5.5)	
Total tremor score (neurological examination)	23.5±5.1, 12.5–35.5	18.7±5.0, 8.0–32.0	<0.001[1]
Intention tremor score[4]	0.85±0.63 (1.0), 0.0–2.0	0.59±0.56 (0.5), 0.0–2.0	0.006[5]
Intention tremor[6]	32 (54.2)	44 (34.4)	0.01[2]
Tandem gait score	2.89±3.62 (1.0), 0–10	2.40±3.66 (0.0), 0–10	0.102[5]
Greater tandem gait difficulty[7]	13 (28.3)	32 (29.1)	0.92[2]
Currently takes daily medication for ET	38 (64.4)	33 (25.8)	<0.001[2]
Age of tremor onset (years)	22.4±14.8	30.9±19.2	0.001[1]
Duration of tremor (years)	41.7±18.3	30.2±17.9	<0.001[1]
Diabetes mellitus by history	6 (10.2)	17 (13.3)	0.55[2]
Arthritis by history	24 (40.7)	43 (33.6)	0.35[2]

ET, Essential Tremor; NA, Not Applicable.
All values are mean±standard deviation (median), range or number (%), unless otherwise specified.
[1]Student t-test.
[2]Chi-square test.
[3]Fisher exact test.
[4]The intention tremor score (both arms combined) ranged from 0 to 2.
[5]Mann–Whitney test.
[6]Definite intention tremor in at least one arm or probable intention tremor in both arms.
[7]Three or more mis-steps is the upper quartile of tandem mis-steps. Data absent for 31 study subjects.

tandem gait difficulty (three or more mis-steps, which is the upper quartile of tandem mis-steps) using the Student t-test, chi-square test, and Fisher exact test (Table 2). Neither the intention tremor score nor the tandem gait score was normally distributed, even after log transformation (Kolmogorov–Smirnov test $p<0.05$); hence these outcomes were assessed as categorical measures (presence of intention tremor and presence of greater tandem gait difficulty, as defined above) rather than continuous measures, and logistic rather than linear regression models were used.

We used a bivariate logistic regression model to assess the predictors of the presence of intention tremor in relatives; this model used the presence of intention tremor in the proband as a primary predictor of interest. Because of the non-independence of proband–relative pairs within each family, for this model, we used generalized estimating

Table 2. **Clinical Correlates of IT and Tandem Gait Difficulty in 187 ET cases**

		IT[1]		Greater Tandem Gait Difficulty[2]
Age (years)	IT– IT+	58.7 ± 16.9 65.9 ± 15.4 p=0.003[3]	TD– TD+	54.3 ± 15.3 74.9 ± 9.1 p<0.001[3]
Male gender	IT– IT+	57 (51.4) 28 (36.8) p=0.05[4]	TD– TD+	52 (46.8) 18 (40.0) p=0.44[4]
White race	IT– IT+	107 (96.4) 69 (90.8) p=0.125[5]	TD– TD+	106 (95.5) 42 (93.3) p=0.69[5]
Right-handed	IT– IT+	100 (90.1) 74 (97.4) p=0.055[5]	TD– TD+	102 (91.9) 43 (95.6) p=0.51[5]
Total tremor score (neurological examination)	IT– IT+	18.48 ± 4.58 22.63 ± 5.19 p < 0.001[3]	TD– TD+	19.34 ± 5.10 20.89 ± 5.78 p=0.10[3]
IT[1]	IT– IT+	–	TD– TD+	32 (28.8) 24 (53.3) p=0.004[4]
Greater tandem gait difficulty[2]	IT– IT+	21 (21.0) 24 (42.9) p=0.004[4]	TD– TD+	–
Currently takes daily medication for ET	IT– IT+	35 (31.5) 36 (47.4) p=0.03[4]	TD– TD+	33 (29.7) 23 (51.1) p=0.01[4]
Age of tremor onset (years)	IT– IT+	28.7 ± 18.3 27.3 ± 18.3 p=0.61[3]	TD– TD+	24.8 ± 15.3 35.0 ± 21.2 p=0.006[3]
Duration of tremor (years)	IT– IT+	30.4 ± 17.3 39.1 ± 19.6 p=0.002[3]	TD– TD+	30.0 ± 15.9 40.2 ± 21.5 p=0.007[3]

ET, Essential Tremor; IT, Intention Tremor; IT–, Intention Tremor Absent; IT+, Intention Tremor Present; TD–, Tandem Gait Difficulty Absent; TD+, Tandem Gait Difficulty Present.
For IT, the table demonstrates either the mean ± standard deviation of a variable (e.g., age) by category of IT (IT– vs. IT+) or it demonstrates the number (%) with IT in each variable category (e.g., males vs. females, whites vs. non-whites). For tandem gait difficulty, the table demonstrates either the mean ± standard deviation of a variable (e.g., age) by category of tandem gait difficulty (TD– vs. TD+) or it demonstrates the number (%) with tandem gait difficulty in each variable category (e.g., males vs. females, whites vs. non-whites).
[1]Definite IT in at least one arm or probable IT in both arms.
[2]Three or more mis-steps is the upper quartile of tandem mis-steps. Data absent on 31 study subjects.
[3]Student t-test.
[4]Chi-square test.
[5]Fisher exact test.

equations (GEEs) to compute odds ratios (ORs), 95% confidence intervals (CIs), and p-values. In additional GEE analyses, we also stratified our sample into first-degree vs. second-degree relatives, and by genetic load (i.e., number of enrolled affected relatives). In multivariate logistic regression models using GEE, other predictors that we considered included the relative's current age, gender, race,

relationship to the proband, daily use of medication for ET, age of tremor onset, duration of tremor, and total tremor score.

As noted above, greater tandem gait difficulty was defined as a tandem gait score that was in the upper quartile for probands and relatives (three or more mis-steps). We used a bivariate logistic regression model to assess the predictors of the presence of greater tandem gait difficulty in relatives; this model used the presence of greater tandem gait difficulty in the proband as a primary predictor of interest. Because of the non-independence of proband–relative pairs within each family, for this model we used GEEs to compute ORs, 95% CIs, and p-values. In additional GEE analyses, we also stratified our sample into first-degree vs. second-degree relatives, and by genetic load (i.e., number of enrolled affected relatives). In multivariate logistic regression models using GEE, other predictors that we considered included the relative's current age, gender, race, relationship to the proband, daily use of medication for ET, age of tremor onset, duration of tremor, total tremor score, history of diabetes mellitus, and history of arthritis.

Results

General

The characteristics of enrollees are shown (Table 1); all enrollees had bilateral arm tremor. Probands differed from their affected relatives in a number of respects (total tremor score, use of daily medication for ET, age of tremor onset, duration of tremor) and marginally in other respects (gender). A larger proportion of probands had intention tremor and their intention tremor score was higher than that of their relatives (Table 1). Of 59 probands, 15 (25.4%) had at least one other enrolled affected relative, 28 (47.5%) had two, eight (23.6%) had three, and eight (23.6%) had four or more.

Intention tremor

We examined the clinical correlates of intention tremor (Table 2). When compared with their counterparts without intention tremor, cases with intention tremor were older, had a higher total tremor score, and had a longer disease duration; they were more likely to have greater tandem gait difficulty and to take daily medication for ET and less likely to be male.

We made a graph showing the intention tremor score in probands and their relatives (Figure 1); there seemed to be no pattern of the relatives' intention tremor score based on that of the probands.

In a bivariate logistic regression model, the presence of intention tremor in the proband was not a predictor of the presence of intention tremor in the relatives (OR=0.60, 95% CI=0.28–1.27, p=0.18). We also stratified our sample into first-degree and second-degree relatives. In these models, the presence of intention tremor in the proband was not a predictor of the presence of intention tremor in the first-degree relatives (OR=0.67, 95% CI=0.30–1.50, p=0.33) or in the second-degree relatives (OR=0.20, 95% CI=0.03–1.24, p=0.084). We then stratified our sample by genetic load (i.e., number of enrolled affected relatives). In these models, we did not find that increasing genetic load affected the relationship between the presence of intention tremor in the proband and the presence of intention tremor in the relatives.

In a series of multivariate logistic regression models, other predictors that we considered, one by one, included the relative's current age, gender, race, relationship to the proband, daily use of medication for ET, age of tremor onset, duration of tremor, and total tremor score. Current age (OR=1.02, 95% CI=1.002–1.041, p=0.03), tremor duration (OR=1.03, 95% CI=1.004–1.047, p=0.018), and total tremor score (OR=1.15, 95% CI=1.05–1.25, p=0.003) were each associated with the presence of intention tremor in the relatives when it was included in a two-variable model along with the presence of

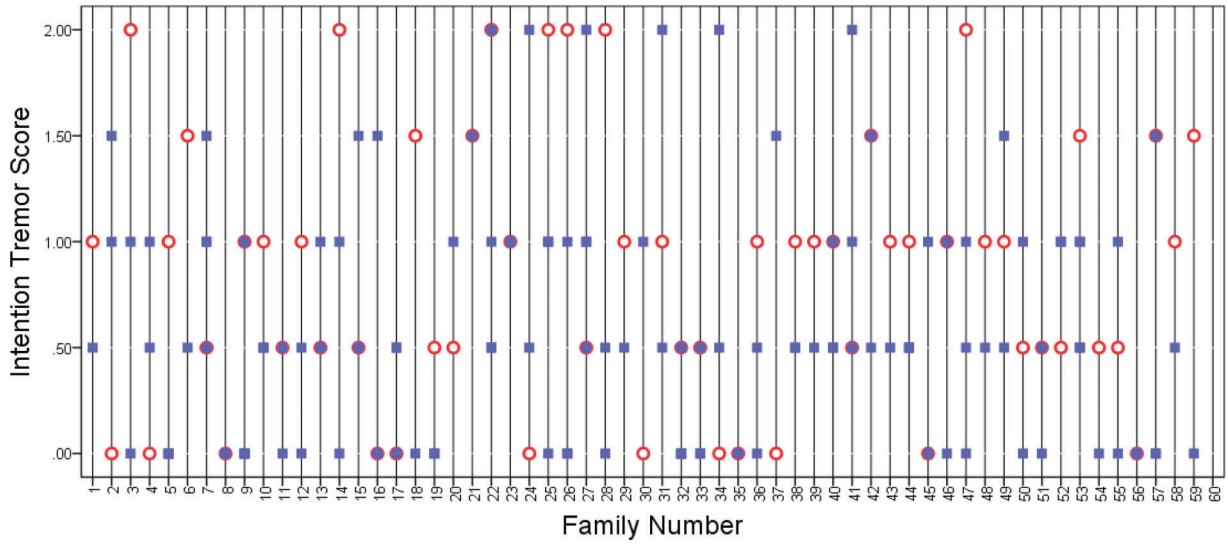

Figure 1. **Intention tremor score (both arms) in probands (open red circles) and relatives (closed blue squares)**. Vertical grid lines run through the data points in each family. Data points were identical for some individuals in the same family and in these instances would appear as a single data point.

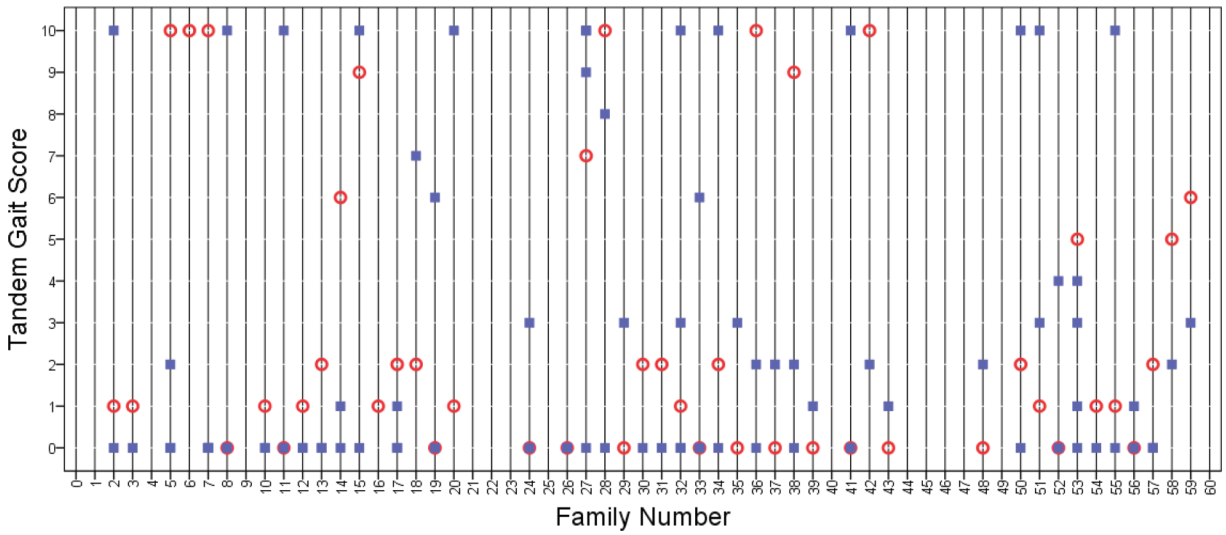

Figure 2. **Tandem gait score in probands (open red circles) and relatives (closed blue squares)**. Vertical grid lines run through the data points in each family. For some families, tandem gait score were incomplete; hence, data for that family were not graphed. Data points were identical for some individuals in the same family and in these instances would appear as a single data point.

intention tremor in the proband; however, the presence of intention tremor in the proband was not associated with the presence of intention tremor in the relatives in any model (all $p>0.05$).

Tandem gait

We examined the clinical correlates of greater tandem gait difficulty (Table 2). Greater tandem gait difficulty was associated with older age, older age of tremor onset, a longer tremor duration, use of daily medication for ET, and the presence of intention tremor.

The tandem gait score in probands and their relatives are shown in a graph (Figure 2); there seemed to be no pattern of the relatives' tandem gait score based on that of the probands'.

In a bivariate logistic regression model, the presence of greater tandem gait difficulty (i.e., a tandem gait score that was in the upper quartile) in the proband was not a predictor of the presence of greater tandem gait difficulty in the relatives (OR=1.22, 95% CI=0.41–3.66, p=0.73). We also stratified our sample into first-degree and second-degree relatives. In these models, the presence of greater tandem gait difficulty in the proband was not a predictor of the presence of greater tandem gait difficulty in either first-degree or second-degree relatives (data not shown). We then stratified our sample by genetic load. In these models, we did not find that increasing genetic load affected the relationship between greater tandem gait difficulty in the proband and greater tandem gait difficulty in the relatives.

In a series of multivariate logistic regression models, other predictors that we considered, one by one, included the relative's current age, gender, race, relationship to the proband, daily use of medication for ET, age of tremor onset, duration of tremor, and total tremor score. Current age (OR=1.17, 95% CI=1.09–1.25, $p<0.001$), duration (OR=1.04, 95% CI=1.003–1.067, p=0.03), age of tremor onset (OR=1.037, 95% CI=1.01–1.07, p=0.007), history of diabetes mellitus (OR=5.46, 95% CI=1.90–15.69, p=0.002), and history of arthritis (OR=5.40, 95% CI=2.19–13.32, $p<0.001$) were each associated with the presence of greater tandem gait difficulty in the relatives when it was included in a two-variable model along with the presence of greater tandem gait difficulty in the proband; however, presence of greater tandem gait difficulty in the proband was not associated with the presence of greater tandem gait difficulty in the relatives in any model (all $p>0.05$).

Discussion

Cerebellar signs are known to occur in patients with ET, a disease that is highly familial. Whether the presence and expression of these cerebellar signs is similar across family members with ET has not been studied previously. An alternative possibility is that these features are not heritable. Although this question is an elementary one, there are no published data on this topic. In the current study, we found that family membership did not seem to be an important contributor/predictor of the presence of cerebellar signs. Whatever the pathophysiological factors are that are contributing to the presence of such signs, in the current dataset, familial factors do not seem to be underlying them.

The major predictor of cerebellar signs in this study was the duration and severity of the underlying disease. That is, these signs tended to accumulate with time. Based on data from prior patient cohorts, there is some evidence that the prevalence of intention tremor increases with increasing disease duration in ET.[6] Yet other cerebellar signs (e.g., saccadic abnormalities) seem to be independent of tremor duration or severity in ET.[27]

How will the data we present here allow us to better counsel ET patients? ET patients are often seeking predictors of the course their disease will take and, in familial ET, this means making direct clinical comparisons with their affected relatives. Several of the features of

their relative's tremor can be predictive of their own, as is the case with rate of progression of tremor[21] whereas others are not (e.g., in the case of presence of cranial tremor).[22] With specific regards to cerebellar signs, the current data suggest that there seems to be no familial pattern and ET cases should not look towards their relatives for predictive information.

A sizable number of our enrollees took five or more tandem mis-steps, which indicates significant problems with balance. When considering this, it is important to be mindful of the fact that our enrollees were as old as 93 years of age. Indeed, 66 of 197 (35.3%) enrollees were ⩾70 years of age, and the large majority (28 of 35; 80.0%) of our enrollees who took five or more tandem mis-steps were age 70 and older.

This study had limitations. We collected and presented data on two cerebellar signs that were relatively easy to elicit in field settings; future studies may wish to collect data on a broader array of cerebellar signs (e.g., eye motion abnormalities). However, these examinations may require more sophisticated equipment that is not available in the field and may therefore not be feasible for family studies. Despite this limitation, we collected data on the two cerebellar signs most commonly noted to be associated with ET.[6–10] Second, the mix of families that we studied may not be representative of all ET families, so that studies with larger sample sizes would be valuable. The study also had strengths. First, the question we ask has not been addressed before so that there are no available data other than our own. Second, ET cases were carefully phenotyped and diagnosed by a senior neurologist with a particular expertise in tremor disorders. Third, the sample size was large, with data from more than 50 ET families. Fourth, we were able to examine a broad range of demographic and disease-linked factors that could have contributed to the presence of cerebellar signs. Finally, the data generated will provide added value to the clinical dialogue, giving patients one more piece of information about the way the disease manifests within families.

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