

## Brief Reports

# Clinical Classification of Borderline Cases in the Family Study of Essential Tremor: An Analysis of Phenotypic Features

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## Abstract

**Background:** In genetic research on essential tremor (ET), certain individuals may be particularly challenging to categorize diagnostically.

**Methods:** In the Family Study of Essential Tremor (>200 enrollees), 28 participants with borderline clinical findings who did not meet strict criteria for ET were assigned final diagnoses of ET. We scrutinized the clinical features of these cases and the sensitivity/specificity of certain features that best separated them from 19 unaffected individuals.

**Results:** Borderline ET cases differed from unaffected individuals in eight features: total tremor score, at least one kinetic tremor rating  $\geq 1.5$ , at least one kinetic tremor rating  $\geq 1.5$  in the dominant arm, tremor rating during spiral drawing  $\geq 1.5$ , higher spiral axis score, head tremor, complaint of tremor, and comment on tremor by others. The combination of at least one kinetic tremor rating  $\geq 1.5$  in the dominant arm and the presence of at least three of the remaining seven features predicted the clinician-assigned diagnosis in 88.6% of borderline ET vs. unaffected individuals (sensitivity 84.6%, specificity 94.4%).

**Discussion:** In a family study, a small number of clinical features characterized borderline ET, and a particular combination of these separated the majority of these borderline cases from normals. These analyses may help researchers minimize diagnostic misclassification.

**Keywords:** Essential tremor, classification, genetic, clinical, epidemiology

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## Introduction

The search for essential tremor (ET) genes is ongoing.<sup>1,2</sup> In such research, certain individuals may be particularly challenging to diagnose because their clinical findings are borderline. Such individuals may be difficult to classify as either normal or emerging ET cases. Diagnostic misclassification reduces the likelihood of finding an ET gene.

In the Family Study of Essential Tremor (FASET), we enrolled 242 individuals (61 probands, 181 relatives). Approximately 15% had borderline clinical findings that did not meet strict diagnostic criteria for ET, but were nonetheless categorized by the study clinician as ET.

We scrutinized the clinical features of these cases as well as the sensitivity and specificity of features that best separated them from normals. These analyses may clarify issues related to diagnostic misclassification in genetic studies of ET, and are intended to help researchers minimize diagnostic misclassification.

## Methods

### Ascertainment of probands

ET cases (probands) and their reportedly affected first- and second-degree relatives were enrolled in FASET, a genetic study of ET at

Columbia University Medical Center (CUMC).<sup>3–5</sup> 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) young age of tremor onset, and 3) two or more 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.

Potential ET probands contacted the FASET study coordinator. Prior to final selection for enrollment, a set of four Archimedes 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.<sup>6</sup>

### Ascertainment of relatives

Based upon a telephone interview with the proband, relatives with ET were identified.<sup>3</sup> With the proband's permission, these relatives were then contacted by telephone, and 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 Archimedes spirals. These spirals were rated (E.D.L.), and relatives were included if one or more of the spirals had a rating  $\geq 2$ .<sup>6</sup> We also targeted a small number of reportedly unaffected relatives with normal spirals to serve as a useful comparison group in our analyses.

### Evaluation

An in-person evaluation was conducted in the enrollees' homes; this included a series of questionnaires about their tremor and their use of medications, and a videotaped neurological examination.<sup>3</sup> 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.<sup>7</sup> 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.<sup>8</sup> The neurologist (E.D.L.) reviewed all videotaped examinations and rated the severity of postural and kinetic (pouring, drinking, using spoon, drawing spirals, finger-nose-finger) arm tremors (ratings = 0–3), resulting in a total tremor score (range = 0 to 36 [maximum]).<sup>7</sup> A rating of 1 = low-amplitude oscillations, 1.5 = low-amplitude oscillations are present in multiple places and oscillations can at times reach moderate amplitude, 2 = moderate-amplitude oscillations that are present in many areas of the spiral (see visual examples in Louis et al.).<sup>9</sup> The presence of a single identifiable tremor orientation axis has been reported in ET,<sup>10</sup> and was noted as present or absent on each of four spirals (see example in Louis et al.),<sup>10</sup> and a spiral axis score (range = 0 [none of four spirals had a single identifiable tremor orientation axis] to 4 [a single axis was observed on all four spirals]) was assigned to

each person. 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 a review of the questionnaires and videotaped neurological examinations.<sup>3</sup> Diagnoses of ET were assigned based on published diagnostic criteria with demonstrated reliability and validity (moderate or greater amplitude kinetic tremor during three or more activities or a head tremor in the absence of PD, dystonia, or another known cause, including medication-induced tremor).<sup>6,11</sup> Medication-induced tremor was excluded based on clinical history (e.g., the onset of tremor preceded the use of the medication, the severity of the tremor did not change in response to reductions or increases in dose of medication), and physical examination features (e.g., the presence of severe and/or asymmetric tremor). A borderline ET category was created for enrollees who did not fully meet these strict diagnostic criteria for ET but were nonetheless considered by the study clinician to have clinical features that aligned them more with ET than normal.

### Final sample

We enrolled 242 individuals (61 probands and 181 relatives). For the current analyses, we excluded enrollees who had been diagnosed with PD, dystonia, or psychogenic movements. The final sample included 207 individuals (52 probands and 155 relatives), including 160 ET, 28 borderline ET, and 19 normal.

### Statistical analyses

Analyses were performed in SPSS (Version 20.0). Subject characteristics were compared across the three groups (ET, borderline ET, normal) using analysis of variance, chi-square tests and Jonckheere–Terpstra tests (a non-parametric test of trend). If the three group comparisons revealed a significant difference, we compared the groups two at a time using t tests, chi-square tests, and Mann–Whitney tests. We created receiver operating characteristic (ROC) curves for the clinical features, alone and in combination, in order to determine their diagnostic performance (i.e., their ability to separate borderline ET from normals).

### Results

Clinical characteristics of the final sample are shown in Table 1. The majority of the borderline ET cases were children of probands. Total tremor score is shown by age across the three groups (Figure 1); although their tremor scores were low in absolute terms, borderline ET cases had a higher mean total tremor score than individuals who had been categorized as normal (Table 1). Compared with normals, borderline ET cases also had a higher spiral axis score (i.e., they exhibited a more clearly identifiable spiral axis), and a larger proportion had at least one or more kinetic tremor rating  $\geq 1.5$  (i.e., intermediate or greater tremor), including in their dominant arm, and a larger proportion had spiral scores  $\geq 1.5$  (Table 1). A marginally

Table 1. Clinical and Demographic Characteristics of Enrollees

Characteristic	ET (N=160)	Borderline ET (N=28)	Normal (N=19)	Significance (p)
Age (years)	60.0 ± 18.0*	48.0 ± 12.5	49.3 ± 17.9	<0.001 <sup>1</sup>
Female gender	82 (51.3)*	16 (57.1)	15 (78.9)	0.07 <sup>2</sup>
Education (years)	16.3 ± 3.7	16.6 ± 2.0	16.5 ± 3.5	0.90 <sup>1</sup>
Tremor duration (years)	32.8 ± 19.3	17.8 ± 12.8	Not applicable	<0.001 <sup>1</sup>
Relationship				<0.001 <sup>2</sup>
Proband	50 (31.3)*	2 (7.1)	0 (0.0)	
Child	37 (23.1)	18 (64.3)	8 (42.1)	
Sibling	38 (23.8)	5 (17.9)	5 (26.3)	
Other	35 (21.9)	3 (10.7)	6 (31.6)	
“Other people tell me that I have tremor”	126 (78.8)**	12 (42.9)***	3 (15.8)	<0.001 <sup>2</sup>
“I sometimes have tremor that I can’t control”	154 (96.3)**	21 (75.0)***	8 (42.1)	<0.001 <sup>2</sup>
Total tremor score	20.1 ± 5.2**	11.4 ± 2.6*	7.3 ± 1.8	<0.001 <sup>1</sup>
Spiral axis score	2.2 ± 1.3 (2.0)**	1.1 ± 1.0 (1.0)***	0.4 ± 0.5 (0.0)	<0.001 <sup>3</sup>
Any kinetic tremor score ≥ 1.5	160 (100)**	27 (96.4)**	10 (52.6)	<0.001 <sup>2</sup>
Any kinetic tremor score ≥ 1.5 in dominant arm	157 (98.1)**	25 (89.3)**	7 (36.8)	<0.001 <sup>2</sup>
Spiral score ≥ 1.5	126 (78.8)**	8 (28.6)*	0 (0.0)	<0.001 <sup>2</sup>
Rest tremor	16 (10.0)	0 (0.0)	0 (0.0)	0.08 <sup>2</sup>
Head tremor	72 (45.0)**	4 (14.3)***	0 (0.0)	<0.001 <sup>2</sup>
Voice tremor	26 (16.4)***	1 (3.6)	0 (0.0)	<0.001 <sup>2</sup>
Intention tremor	62 (38.8)*	1 (3.6)	2 (10.5)	<0.001 <sup>2</sup>

Abbreviation: ET, Essential Tremor.

All values represent mean ± standard deviation (median) or number (percentage).

<sup>1</sup>Analysis of variance test comparing all three groups or the Student t test comparing two groups.

<sup>2</sup>Chi-square test comparing all three groups.

<sup>3</sup>Jonckheere–Terpstra test comparing all three groups.

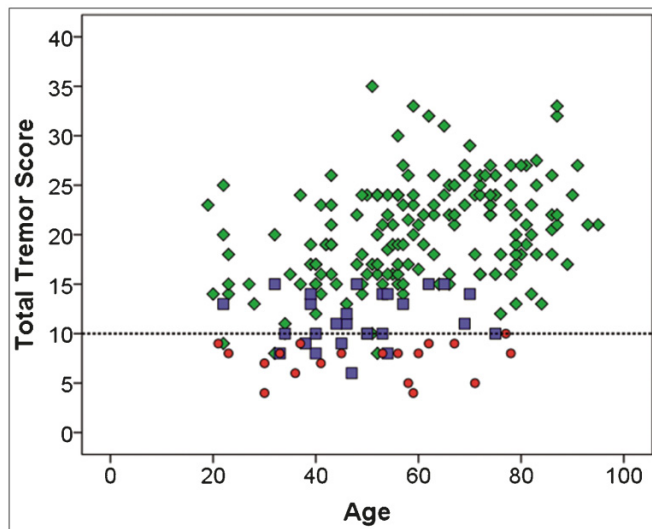
\*p<0.05 compared with normals; \*\*p<0.01 compared with normals; \*\*\*p=0.05–0.09, compared with normals.

Note: For some items, data were available on <207 enrollees.

larger proportion also had head tremor (Table 1). When compared with normals, borderline ET cases were more likely to have complained of tremor that they could not control and were more likely to have had other people tell them that they had tremor (Table 1).

We combined these eight clinical features into an index. On this index, ET cases averaged 6.6 ± 1.0 (median=7), compared with 4.7 ± 1.4 (median=5) for borderline ET cases and only 1.7 ± 1.7 (median=2) for normals (Jonckheere–Terpstra test p<0.001).

With ROC modeling, we found that a total tremor score ≥ 10 did a satisfactory job of separating those who were categorized as borderline ET from those who were categorized as normal (sensitivity=77.8%, specificity=94.7%, correct classification=84.7%). Further ROC modeling revealed that the combination of one or more kinetic tremor rating ≥ 1.5 in the dominant arm and the presence of three or more of the remaining seven features predicted the clinician-assigned diagnosis (borderline ET vs. normals) with 88.6% accuracy (sensitivity=84.6%, specificity=94.4%).



**Figure 1. Total Tremor Score (y-Axis) by Age (x-Axis) Across the Three Diagnostic Groups.** Essential tremor (ET), green diamonds; borderline ET, blue squares, and normals, red circles. A total tremor score  $\geq 10$  (horizontal line) separated the borderline ET cases from normals with a sensitivity of 77.8% and a specificity of 94.7% (correct classification, 84.7%). One borderline ET did not have a total tremor score and two others had identical total tremor scores and ages.

### Discussion

In a family study of ET, a small and definable number of clinical features differentiated borderline ET from normals, and a combination of these features separated the majority of these borderline cases from those who were considered normal. The search for ET genes is currently ongoing and intensive. Attention to these features may help lessen diagnostic misclassification.

The clinical features that best aligned with the clinician-assigned diagnosis were both historical and examination based. Historical features included patient reports that tremor was at times difficult to control and that others were aware of the tremor. Examination features that differentiated borderline ET from normals included a total tremor score  $\geq 10$ , at least one kinetic tremor score  $\geq 1.5$ , the clearer presence of a tremor axis score, and the presence of head tremor. Most borderline cases had scores that were 1.5 rather than 2 or higher.

This study had limitations. Although we enrolled several hundred individuals from across the country, additional studies with other cohorts would be valuable for confirming our findings. In addition, the study used accepted clinical methods to assess tremor, including detailed neurological examinations, but it did not incorporate tremor analysis or other instrumentation, which would have added to the precision with which we assessed tremor amplitude. Strengths of the study included the uniform method of evaluating all enrollees and the standardized approach to the history and physical examination.

There is an ongoing and difficult search for ET genes;<sup>1,2,12</sup> rigorous phenotype classification is central to gene discovery efforts in ET as in

other disorders. These analyses may clarify issues related to diagnostic misclassification in genetic studies of ET. Inclusion of borderline cases should proceed with caution, with one option being to perform parallel analyses, one of which includes these cases with ET cases, and another that excludes them altogether rather than including them with unaffected normals.

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