RESEARCH

Mixed Motor Disorder

Essential Tremor Families With Heterogeneous Motor Phenomenology

Elan D. Louis, MD, Nora C. Hernandez, MD, Ruth Ottman, PhD, and Lorraine N. Clark, PhD

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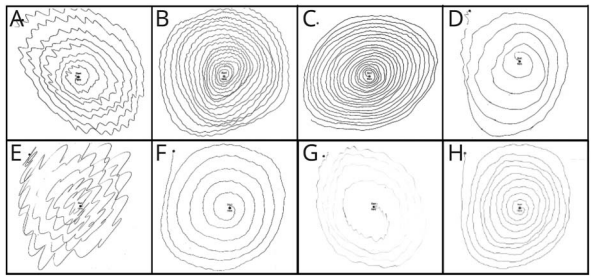
Correspondence
Dr. Louis
elan.louis@utsouthwestern.edu

Abstract



Background and Objectives

Essential tremor (ET) is one of the most prevalent movement disorders. Because ET is so common, individuals with other neurologic disorders may also have ET. There is evidence, however, that the cooccurrence of ET with Parkinson disease (PD) and/or dystonia is not merely a chance cooccurrence. We have observed combinations of these 3 movement disorders within individuals and across individuals within families containing multiple individuals with ET. This observation has a number of implications. Our objective is to present 4 ET families in whom motor phenomenology was heterogeneous and discuss the implications of this finding.

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Methods

ET cases and their relatives were enrolled in the Family Study of Essential Tremor (2015–present). Phenotyping was performed by a senior movement disorders neurologist based on neurologic examination.

Results

We present 4 families, including 14 affected individuals, among whom assigned diagnoses were ET, PD, ET + PD, and ET + dystonia. In those with ET and another movement disorder, the predominant and earliest phenotype was ET.

Discussion

There are assortments of these 3 involuntary motor disorders, ET, dystonia, and PD, both within individuals and in different individuals within ET families. This observation has mechanistic implications. Furthermore, we believe that the concept of the mixed motor disorder should enter into and inform the clinical dialogue. In assigning diagnoses, clinicians are swayed by family history information, and they should be prepared to observe a mix of different motor disorders to manifest within particular families.

Essential tremor (ET), a highly prevalent movement disorder, is commonplace across populations.[1] Given its high prevalence, it is entirely conceivable that patients with other movement disorders (e.g., Parkinson disease [PD] or dystonia) might on occasion already have a history of ET. As such, these individuals would have a combination or mix of these conditions. Along similar lines, in families containing multiple individuals with dystonia or families with multiple individuals with PD, it is conceivable that family members would on occasion manifest a highly prevalent condition such as ET, making the family one in which there is a mix of motor disorders. These are examples of what is likely to be chance cooccurrence within individuals and within families.[2]

Department of Neurology (EDL, NCH), University of Texas Southwestern, Dallas; G.H. Sergievsky Center (RO), Department of Neurology (RO), College of Physicians and Surgeons, and Department of Epidemiology (RO), Mailman School of Public Health, Columbia University; Division of Translational Epidemiology (RO), New York State Psychiatric Institute; and Taub Institute for Research on Alzheimer's Disease and the Aging Brain (LNC), College of Physicians and Surgeons, Columbia University, New York.

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Yet there is also evidence that the cooccurrence of ET with other movement disorders, specifically PD and dystonia, is not entirely due to chance. Cross-sectional studies have shown significant associations between ET and PD,[3,4] and in a longitudinal, prospective population-based study, the risk of incident PD was 4 times higher in patients with ET than in similarly aged controls.[5] Family studies also show associations between ET and PD that are not due to chance.[3,6-8] There is growing recognition that patients with ET may develop dystonia on examination.[9-11] Furthermore, within a limited number of published ET kindreds, one may find examples of family members with combinations of tremor, dystonia, or both.[12-15]

Irrespective of the interpretation, evidence suggests that these 3 motor disorders, ET, dystonia, and PD, cooccur within individuals and in different individuals within the same families. Yet this has not been the focus of concentrated scholarly attention, and such families have not been presented with detailed tremor examinations or individual-level phenotypic data. The purpose of this study was to present meticulous case-by-case phenotypic details (i.e., deep phenotyping) of 4 such families with mixed motor phenomenology and to discuss the possible mechanisms.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by Columbia University and Yale University Institutional Review Boards; participants signed written informed consent. The current analyses were approved by Columbia University, Yale University, and the University of Texas Southwestern Institutional Review Boards (respective protocol numbers: AAAQ3307, 1412015096, and STU-2020-0566).

As described,[16,17] ET cases (i.e., probands) and their relatives were enrolled in a genetic study of ET, the Family Study of Essential Tremor (phase 2, September 2015–present), which enrolled participants from throughout the United States. Inclusion criteria for probands were as follows: (1) diagnosis of ET assigned by a doctor, (2) age of tremor onset ≤40 years (later changed to ≤50 to be more inclusive), and (3) at least 2 living relatives in the United States who were reported to have ET diagnosed by a doctor.[16] The exclusion criterion for probands was a reported diagnosis of dystonia or PD.[16] As described,[16] during telephone interviews with probands, relatives were identified and reported by the proband to be affected or unaffected.

As detailed elsewhere,[16] trained personnel conducted in-person in-home evaluations; the evaluation included clinical questionnaires, including the Mini-Mental State Examination (0 [maximally impaired]–30),[18] the Lawton Instrumental Activities of Daily Living Scale (0 [maximally impaired]–8),[19] and a standardized videotaped neurologic examination. The latter included a detailed assessment of postural tremor, 5 tests for kinetic tremor, the motor portion of the Unified Parkinson Disease Rating Scale[20] excluding an assessment of rigidity, and a comprehensive assessment of dystonia. The assessment of dystonia was performed through review of views of the face, neck, trunk, and extremities: while seated, standing, and walking (including turning); with posture (arms extended in front of body and in "wing-beating" position); and with multiple tests of action (finger taps, hand-opening/closure, finger-to-nose, pouring/drinking/lifting water with a spoon, and alternating toe-heel taps). Handwriting was videotaped and reviewed.[21] Audio recordings of sustained phonation and speech were also reviewed to assess for spasmodic dysphonia.[21]

A senior level movement disorders neurologist (E.D.L.) reviewed all videotaped examinations, rating the severity of postural and kinetic arm tremors on 12 examination items using a reliable scale.[22] As reviewed elsewhere,[16] ratings were 0 (absent), 0.5 (very low amplitude and almost never present), 1.0 (mild = low amplitude or intermittent tremor), 1.5 (mild-to-moderate [tremor sometimes more than mild]), 2 (moderate = clearly oscillatory and > mild amplitude), 3 (severe), and 4 (extremely severe) and resulted in a total tremor score (range = 0–46 [maximum]).

As described,[16] all ET diagnoses were assigned by E.D.L. based on review of questionnaires and videotaped neurologic examination using the published diagnostic criteria.[23] The criteria include gradations of possible, probable, and definite ET.[23] At a minimum, possible ET required moderate or greater amplitude kinetic tremor during 3 or more activities in the absence of another known cause (e.g., medication-induced tremor and tremor from hyperthyroidism) (Table 1).[23] These diagnostic criteria for ET were developed for a population-based genetic study, and based on data from approximately 2,000 nondiseased controls, the criteria carefully detail the specific examination maneuvers during which tremor should be present and the severity of tremor that should be evident during these maneuvers to distinguish normal from ET.[16] These criteria have been shown to be both reliable[22] and valid[24] and have been used by tremor investigators in the United States and worldwide.[16]

The diagnosis of dystonia was made using the published diagnostic criteria (sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both) (Table 1).[21] PD was diagnosed using the published diagnostic criteria, which required the presence of at least 2 cardinal signs (Table 1).[25,26] As described,[16] some patients with ET may develop mild dystonia; ET and dystonia were the diagnostic categories used for patients with long-standing, severe ET who were developing mild dystonic movements or postures (Table 1). As described,[26] the diagnosis of ET-PD required that (1) the ET diagnosis was present for at least 5 years before the PD diagnosis, (2) the initial ET was characterized by moderate or greater amplitude kinetic tremor in the absence of any signs of PD, and (3) the initial ET diagnosis occurred in the absence of red flags for possible emerging PD (isolated postural tremor without kinetic tremor, unilateral tremor) (Table 1).

Table 1 Diagnostic Features of the Movement Disorders Observed in Our Families

Neurologic disease	Diagnostic features
ET	• Moderate or greater amplitude kinetic tremor during 3 or more activities in the absence of another known cause (e.g., medication-induced tremor and tremor from hyperthyroidism) • Head tremor
PD	The presence of at least 2 cardinal signs of parkinsonism (bradykinesia, rigidity, rest tremor, and postural instability)
Dystonia	Sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both
ET + dystonia	Patients with ET with long-standing, severe ET who develop mild dystonic movements or postures
ET + PD	• ET diagnosis was present for at least 5 y before the PD diagnosis • The initial ET was characterized by moderate or greater amplitude kinetic tremor in the absence of any signs of PD • The initial ET diagnosis occurred in the absence of red flags for possible emerging PD (isolated postural tremor without kinetic tremor, unilateral tremor)

Abbreviations: ET = essential tremor; PD = Parkinson disease.

Data Availability

Anonymized data will be shared by request from any qualified investigator.

Results

There were 4 families, including 14 affected individuals (Table 2). Pedigrees are shown in Figure 1, A–D.

Family 1

The proband in family 1 (person 1), age 67 years, was from a White family of mixed German-English ancestry. Her deceased father and paternal grandmother were reported to have had ET. Age of tremor onset was 23 years, and a neurologist had diagnosed ET. She was taking primidone for ET. On examination, there was mild postural tremor and kinetic tremor scores (pouring, using a spoon, drinking, finger-nose-finger, and while drawing spirals) were moderate-to-severe (Table 3, Figure 2A). There was mild voice tremor but no head tremor. The total tremor score was 24.5, indicating moderate overall tremor. The diagnosis was probable ET.

Her sister (person 5), age 76 years, reported an age of tremor onset of 10 years and was diagnosed with ET later in life. In the past, she had taken medication for ET. On examination, there was mild postural tremor and moderate or severe kinetic tremor while pouring, using a spoon, drinking, and drawing spirals (Table 3, Figure 2B). There was mild voice tremor but no head tremor. The total tremor score was 21.5, indicating moderate overall tremor. The diagnosis was probable ET.

A brother (person 6), age 64 years, reported an age of tremor onset in his late 20s. He had not been diagnosed with ET yet reported having taken propranolol. On examination, there was mild postural tremor and mild-to-severe kinetic tremor on various tasks (Table 3, Figure 2C). There was mild voice tremor but no head tremor. The total tremor score was 19, indicating mild-to-moderate overall tremor. The diagnosis was probable ET.

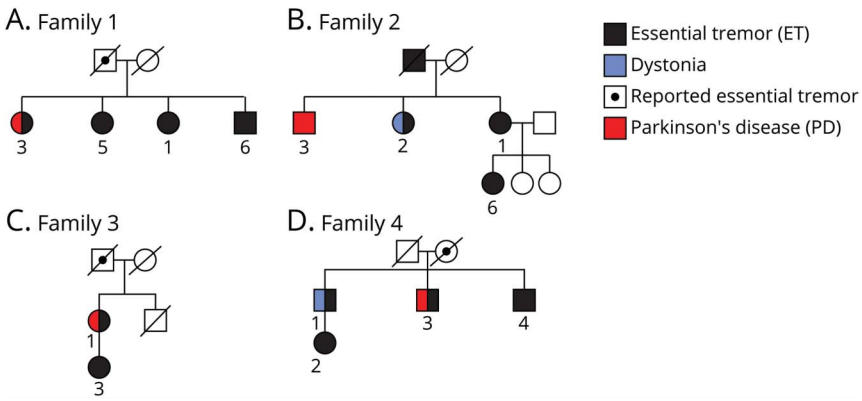
Another sister (person 3), age 80 years, did not recall her age of onset but had seen a neurologist at age 79 years and was diagnosed with ET. Given the severity of her kinetic tremor (Table 3), it is likely that she had had tremor for many years. She was taking primidone and atenolol for tremor. On examination, there were mild postural tremor and moderate kinetic tremor while pouring, using a spoon, drinking from a cup, and drawing spirals (Table 3, Figure 2D). There was a head tremor but no voice tremor. The total tremor score was 21.5, indicating moderate overall tremor. The diagnosis was probable ET. In addition, she had numerous features of early PD: rest tremor while standing (right), mild flexed posturing of her right hand during arm extension, decreased eye blink frequency and pauses, and mild decrement during rapid alternating movements. She was on no medications that could have resulted in these features. Hence, the final diagnosis was ET + PD (Video 1).

Table 2 Movement Disorders in 4 Families Enrolled in Genetic Study of ET

	Type of movement disorder observed in the family					
Family no.	ET	PD	Dystonia	ET + PD	ET + dystonia	ET + PD + dystonia
1	3 (including the proband)			1		
2	2 (including the proband)	1			1	
3	1			1 (the proband)		
4	2			1	1 (the proband)	

Abbreviations: ET = essential tremor; PD = Parkinson disease.
Cells show the number of individuals we enrolled in the family with each movement disorder or with each combination of movement disorders.

Figure 1 Pedigrees of 4 Families



Pedigrees are shown, demonstrating the affected individuals in each family.

Family 2

The proband in family 2 (person 1) was age 80 years and was from a White family of mixed European ancestry. Her deceased father was reported to have had ET. The Age of tremor onset was 65 years, and a neurologist had diagnosed ET. She had taken medication for ET in the past. On examination, there was moderate postural tremor. Kinetic tremor was moderate-to-severe while pouring, using a spoon, drinking, finger-nose-finger maneuver, and while drawing spirals (Table 3, Figure 2E). The total tremor score was 30, indicating moderate-to-severe overall tremor. There was moderate voice tremor but no head tremor. Diagnosis was definite ET.

Her sister (person 2), age 71 years, reported that her tremor had started at age 45 years, but she had not been diagnosed with ET or taken medication for ET. On examination, there were mild postural tremor and moderate-to-severe kinetic tremor during multiple tasks (Table 3, Figure 2F). Mild head, jaw, and voice tremors were present. The total tremor score was 23.5, indicating moderate overall tremor. The diagnosis was probable ET. There were also features of mild dystonia: (1) dystonic posturing of the left thumb during arm extension, (2) head tremor, although mild, persisted even while supine (typically a feature of dystonic head tremor rather than ET head tremor),[27] and (3) none of her spirals had a clear tremor orientation axis (also a feature aligning them with dystonic tremor rather than ET) (Video 2).[28]

The proband's daughter (person 6), age 58 years, had noted the onset of arm tremor in her mid-40s and head tremor at age 58 years. She had not sought medical attention for her tremor. She did not consent to a videotaped examination, but her spirals revealed mild-to-moderate tremor on the right and moderate tremor on the left (Table 3, Figure 2G), consistent with a diagnosis of ET, although a subcategory (possible, probable, and definite) could not be assigned.

The proband's brother (person 3), age 66 years, first noted right arm tremor at age 60 years and had been diagnosed with PD and was taking pramipexole (Table 3). On examination, there was hypomimia with reduced eye blink rate, moderately to severely slowed rapid alternating arm movements, marked tremor at rest in the left arm while seated and while standing, a severe re-emergent tremor in the right arm, no or mild kinetic tremor on numerous tasks, no head tremor, and no voice tremor, consistent with the diagnosis of PD.

Family 3

The proband (person 1), age 76 years, was from a White family of Danish and German ancestry. Her deceased father was also reported to have had ET. Age of tremor onset was 20 years, and a neurologist had diagnosed ET. She had taken medication for ET in the past. On examination, there were mild postural tremor and mild-to-moderate kinetic tremor on a range of tasks (Table 3, Figure 2H) and the total tremor score was 16.5, consistent with mild-to-moderate ET. There were a head tremor and mild voice tremor. The diagnosis was probable ET. There were several features of PD as well: rest tremor in right arm while seated and while standing, which was considered marked given the amount of kinetic tremor; reduced arm swing bilaterally; and rapid alternating movements that were moderately bradykinetic in the left arm and leg. She was on no medications that could have resulted in these features. The final diagnosis was ET + PD.

The proband's daughter (person 3), age 47 years, had noted arm tremor since the age of 14 years but had not been diagnosed with ET or taken medication for it. On examination, there were mild postural tremor and kinetic tremor scores that ranged from none-to-severe (Table 3, Figure 2I). There was no voice or head tremor. The total tremor score = 18, consistent with mild ET, and the diagnosis was possible ET.

Family 4

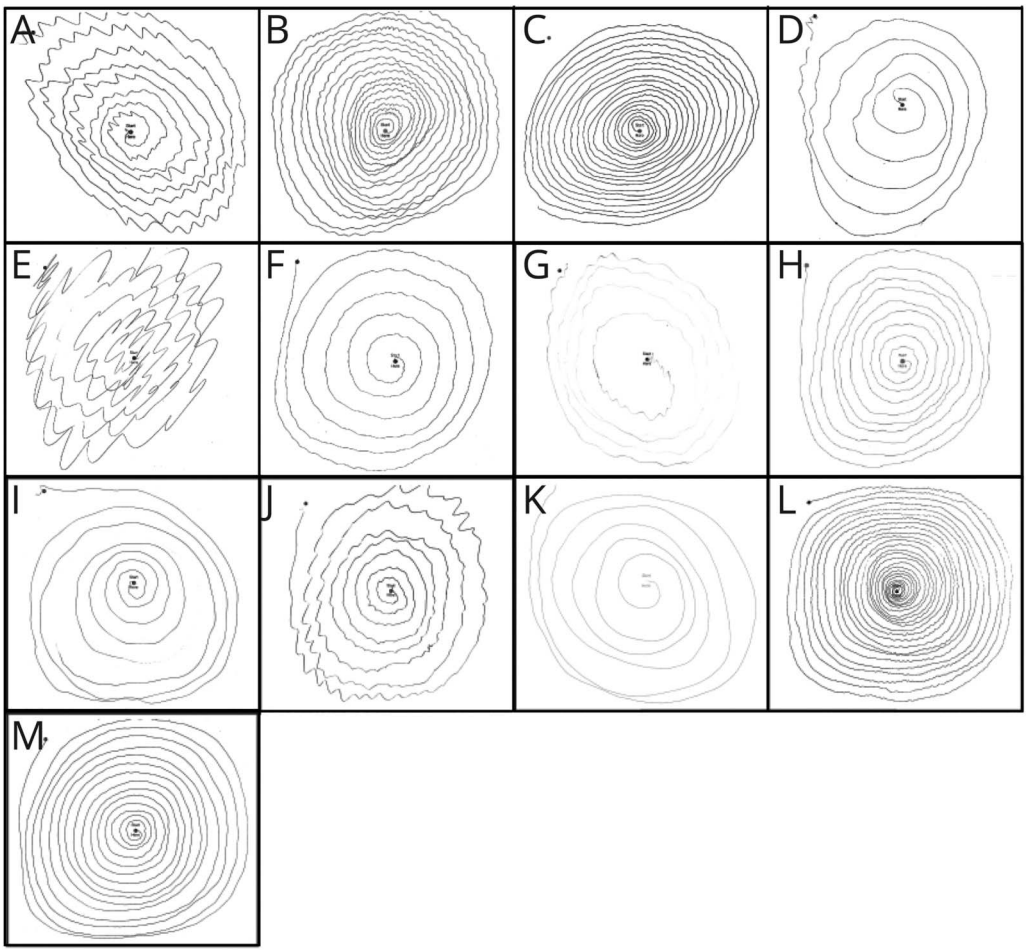
The proband (person 1), age 52 years, was from a White family of Scandinavian ancestry. His deceased mother was also reported to have had ET. Age of tremor onset was 8 years, and a neurologist had diagnosed ET. He had taken

Table 3 Clinical Characteristics of Study Subjects

	Fam 1	Fam 1	Fam 1	Fam 1	Fam 2	Fam 2	Fam 2	Fam 2	Fam 3	Fam 3	Fam 4	Fam 4	Fam 4	Fam 4
Relationship	Proband	Sibling	Sibling	Sibling	Proband	Sibling	Child	Sibling	Proband	Child	Proband	Child	Sibling	Sibling
Sex	F	F	M	F	F	F	F	M	F	F	M	F	M	M
Person no.	1	5	6	3	1	2	6	3	1	3	1	2	4	3
Handed	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Age, y	67	76	64	80	80	71	58	66	76	47	52	23	60	57
Age of tremor onset, y	23	10	Late 20s	Not known	65	45	Mid-40s	60	20	14	8	Not known	7	18
Duration ET, y	44	66	Approx 35	Not known	15	26	Approx 13	NA	56	33	44	NA	53	39
Diagnosed with ET	Yes	Yes	No	Yes	Yes	No	No	No	Yes	No	Yes	No	No	Yes
ET medication	Pri	PMU	Pro	Pri, atenolol	PMU	No	No	No	PMU	No	PMU	No	No	PMU
TTS	24.5	21.5	19	21.5	30	23.5	NV	12.5	16.5	18	30.5	14.5	17	23.5
Postural T	1/1.5	1.5/1	1/1	1.5/1	2/2	1.5/1	NV	3[a]/0.5	1/1	1/1	2/2	1/1	1/1.5	1.5/1.5
Pouring T	2/2	2/2	1.5/1.5	2/2	2/2	2/2	NV	1/0.5	2/1	2/2	2/3	1/1.5	1/2	2/2
Using spoon T	2/3	2/3	2/3	2/2	3/3	3/3	NV	2/1	2/2	1.5/3	3/3	1/1.5	3/2	2/3
Drinking T	2/3	2/2	1/2	2/2	3/3	1.5/1.5	NV	1/0	1/2	1/2	3/3	1.5/1.5	1/1	2/2
F-N-F T	2/2	1/1	1/1.5	1.5/1.5	2/2	2/2	NV	0.5/1	0.5/0.5	1.5/1.5	2/1.5	1/1.5	0.5/1	1.5/2
Spiral T	2/2	2/2	2/1.5	2/2	3/3	2/2	1.5/2	1/1	1.5/1.5–2	0/1.5	2/2	0.5/1–1.5	1/1.5–2	2/2
Head T	None	None	None	Yes	None	Yes	NV	None	Yes	None	None	None	None	None
Voice T	Mild	Mild	Mild	None	Mod	Mild	NV	None	Mild	None	None	None	None	None
Jaw T	None	None	None	None	None	Yes	NV	None	None	None	None	None	None	None
ET diagnosis	Probable ET	Probable ET	Probable ET	Probable ET	Definite ET	Probable ET	ET	No	Probable ET	Possible ET	Definite ET	ET	Possible ET	Probable ET
PD diagnosis	None	None	None	PD	None	None	None	PD	PD	None	None	None	No	PD
Dystonia	No	No	No	No	No	Yes	No	No	No	No	Yes	No	No	No
MMSE	30	30	30	29	27	28	NA	27	27	30	29	28	30	27
IADL	8	8	8	7	8	8	NA	8	8	8	8	8	8	8
Figure	2A	2B	2C	2D	2E	2F	2G	NA	2H	2I	2J	2K	2L	2M

Abbreviations: Approx = approximately; ET = essential tremor; Fam = family; F-N-F = finger-nose-finger maneuver; IADL = Instrumental Activities of Daily Living Scale; L = left handed; MMSE = Mini-Mental State Examination; Mod = moderate; NA = not applicable; NV = no videotaped neurologic examination; PD = Parkinson disease; PMU = past medication use; pri = primidone; pro = propranolol; R = right handed; T = tremor; TTS = total tremor score.
[a] Re-emergent tremor.
Tremor scores reflect right/left arm.

Figure 2 Spirals Demonstrating Kinetic Tremor



(A) Kinetic tremor rating = 2 on drawing a spiral with the left hand (family 1, person 1). (B) Kinetic tremor rating = 2 on drawing a spiral with the right hand (family 1, person 5). (C) Kinetic tremor rating = 2 on drawing a spiral with the right hand (family 1, person 6). (D) Kinetic tremor rating = 2 on drawing a spiral with the left hand (family 1, person 3). (E) Kinetic tremor rating = 3 on drawing a spiral with the right hand (family 2, person 1). (F) Kinetic tremor rating = 2 on drawing a spiral with the right hand (family 2, person 2). (G) Kinetic tremor rating = 2 on drawing a spiral with the left hand (family 2, person 6). (H) Kinetic tremor rating = 1.5–2 on drawing a spiral with the left hand (family 3, person 1). (I) Kinetic tremor rating = 1.5 while drawing a spiral with the left hand (family 3, person 3). (J) Kinetic tremor rating = 2 while drawing a spiral with the right hand (family 4, person 1). (K) Kinetic tremor rating = 1–1.5 while drawing a spiral with the left hand (family 4, person 2). (L) Kinetic tremor rating = 1.5 while drawing a spiral with the left hand (family 4, person 4). (M) Kinetic tremor rating = 2 while drawing a spiral with the right hand. Micrographia is also noticeable (family 4, person 3).

medication for ET in the past. On examination, there was moderate postural tremor bilaterally, although the middle finger on the right was dystonic (flexing involuntarily). There was moderate-to-severe kinetic tremor during multiple tasks (Table 3, Figure 2J) and the total tremor score = 28.5, consistent with severe ET. There was no head or voice tremor. The diagnosis was definite ET with mild dystonia (Video 3).

The proband's daughter (person 2), age 23 years, did not endorse tremor, had not been diagnosed with ET, and was taking no medications for ET. On examination, there were mild postural tremor and kinetic tremor ratings that were mild (rating = 1) to mild-to-moderate (rating = 1–1.5) in nearly all tasks (Table 3, Figure 2K). Total tremor score = 14.5. There was no head of voice tremor. Here, although tremor did not reach the threshold severity for possible ET, given her age and family history, it was considered abnormal and a diagnosis of ET was assigned.

The proband's brother (person 4) was 60 years old. He had noticed arm tremor at age 7 years but had not been diagnosed with ET or taken medication to treat tremor. On examination, there were mild postural tremor and kinetic tremor that ranged from mild-to-severe (Table 3, Figure 2L). The total tremor score = 17, consistent with mild ET. There was no voice or head tremor. The diagnosis was possible ET.

The proband's brother (person 3), enrolled at age 57 years, had first noted tremor at age 18 years and had been diagnosed with ET. He had not been diagnosed with PD. He had taken medication for tremor in the past. On examination, there were mild to mild-to-moderate postural tremor and kinetic tremor that ranged from mild-to-moderate to

severe (Table 3, Figure 2M). There was no head or voice tremor. The total tremor score = 23.5, consistent with moderate ET. The diagnosis was probable ET. In addition, there were numerous signs of PD: mild hypomimia, decreased eye blink rate, rest tremor in right arm while walking, decreased arm swing, and loss of amplitude and decrement during finger taps on the right. The final diagnosis was ET + PD (Video 4).

Discussion

Ours is not the first study to report the presence of mixed motor disorder in ET families, although there are only a few other reports and none presented detailed tremor examinations with individual-level phenotypic data. A study published in 1997 reported 4 ET kindreds containing 55 persons with ET, numerous individuals with ET + dystonia or ET + PD, and several with ET + dystonia + PD.[14] A study published in 2003 reported a family that included 13 members with ET included 3 with ET + PD and 1 with ET and focal hand dystonia.[15] A study published in 2006 reported 4 ET kindreds containing 65 individuals diagnosed with ET.[13] In that study, several women from Pedigree A had mild cervical dystonia, but their arm tremor was without any dystonic features, and they were classified as ET.[13] In addition, there was 1 ET case in Pedigree B with a 30-year history of action tremor; 4 years before death, he also developed PD.[13] As noted above, this small number of other reports either did not provide detailed and meticulous data on the phenotypic features of tremor in the ET cases (e.g., description of the physical examination limited to "definite ET"),[13,15] restricted their detailed characterization of movement disorders only to the probrand,[14] were limited to a single family,[15] did not provide visual examples of handwriting samples or spirals,[13-15] did not provide videotaped examination material,[13-15] or did not include dystonia cases.[13]

ET is a very common neurologic disease and based on this, it is likely to cooccur within the same individual or within families with other movement disorders.[2] This being said, there is abundant evidence in cross-sectional, longitudinal, and family studies of an association between ET and PD[3-8] and data indicating that dystonia occurs in the setting of ET,[9-11] and these suggest that the cooccurrence is not entirely due to chance. In addition, there is not a comparable literature linking ET to other highly prevalent movement disorders (e.g., tics, restless legs syndrome), arguing that the association is specific and thus less likely to be due to chance. A single gene or genes raising risk of ET could also affect risk of dystonia or PD (pleiotropy), or conversely, multiple disease-specific genes could cooccur within some families. On a pathophysiologic level, both ET and dystonia are linked to cerebellar dysfunction,[29-32] and there are patients with ET with Lewy bodies,[33] the hallmark feature of PD. Hence, commonalities exist in this regard.

One issue is that PD may in its earliest stages begin as an action tremor, raising the question as to whether the ET + PD cases we report had only PD. This is unlikely because they manifested typical bilateral kinetic predominant action tremor, a feature of ET, rather than the unilateral postural tremor that is typically seen in early cases of PD who present with action tremor.[34] Second, among those with clear age of onset data, ET symptoms and diagnoses preceded PD by decades. Third, these cases were embedded in families with a clear stamp of ET.

As seen in Table 2, we note the presence of several movement disorders within a single ET family and within a single individual. In another report of ET kindreds, some family members had isolated dystonia and others had ET + PD + dystonia[14] (Table 2, not seen in our 4 families). Hence, the motor phenomenology in these families can involve all combinations of these 3 disorders.

All tested individuals had a Mini-Mental State Examination score of 27 or higher and all of them had Lawton Instrumental Activities of Daily Living Scores of 7 or 8, indicating that these individuals likely did not have dementia or significant cognitive impairment.

We no longer include questions about response to ethanol in our epidemiologic or genetics studies of ET because this question has limited utility. First, many ET cases are elderly, and they do not use ethanol. Studies show that as few of 19%[35] to 42.9%[36] to 67%[37] use ethanol. Second, response to ethanol is not specific to ET, being a feature of many tremor disorders (e.g., primary writing tremor, orthostatic tremor, isolated vocal tremor, and Parkinson disease) and a large number of other movement disorders (e.g., torticollis, spasmodic dysphonia, and generalized dystonia),[38,39] both because of its calming effects and likely also because of direct effects. Therefore, whether response to ethanol differs in these families in comparison with families with pure ET could not be assessed, although it is not likely.

Only 8 of these 14 patients had ever used medication for their ET. During the course of the study, we added a question on pharmacologic response phenotype, and this was administered to 2 of the 8, one of whom reported no response to atenolol and the other who did not recall his response to medication. More complete data would have been of interest.

Our observations have several implications. First, they underscore challenges for studies that attempt to identify candidate genes for ET. Second, they point to what could be common genetic etiologies for these varied movement disorders. An example of this would be DYT24, because of mutations in the anoctamin 3 gene, resulting in a range of movement disorders, including tremor, dystonia, and myoclonus.[40] Third, they suggest mechanistic or pathophysiologic commonalities among these disorders, whether it is mutual involvement of the cerebellum or deposition of Lewy bodies. For example, neuroanatomical studies in nonhuman

primates demonstrate that cerebellar and basal ganglia outputs converge at the level of the cerebral motor cortex.[31] Furthermore, cerebellar and basal ganglia circuits with the cerebral cortex seem to be interconnected at several subcortical levels as well.[31] Such evidence is used to support the notion that the cerebellum, a region that plays a central role in the pathophysiology of ET,[29] and plays a role in the pathophysiology of dystonia.[31] Fourth, we believe the concept of the "mixed motor disorder" should on multiple levels enter into and inform the clinical dialogue and clinical decision making of providers. In assigning diagnoses, clinicians are influenced or swayed by family history information; in doing so, they should be prepared to accept the possibility of a significant mix of motor disorders within the same family rather than feeling constrained to assign a homogeneous diagnosis to every family member. This will serve to lessen the likelihood of diagnostic misclassification (i.e., assigning the incorrect diagnosis to a patient) and reduce the possibility of treating patients for the wrong condition. Furthermore, the discussion with families who seem to have mixed conditions will be informed by understanding that similar families with heterogeneous conditions have been observed and presented in the literature and that their family has a described and documented situation.

In summary, there are "mixes" of these 3 involuntary motor disorders: ET, dystonia, and PD, within individuals and across family members within a family. The recognition of this has implications in both the clinical and research realms and might serve to guide those who are studying disease etiology and pathogenesis.

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Appendix Authors

Name	Location	Contribution
Elan D. Louis, MD	University of Texas Southwestern, Dallas	Obtaining funding, study conception, study design, interpretation of data, writing first draft of article, and revision of drafts of article
Nora C. Hernandez, MD	University of Texas Southwestern, Dallas	Interpretation of data, collection of data, and critical revision of drafts of article
Ruth Ottman, PhD	Columbia University, New York	Obtaining funding, study conception, study design, interpretation of data, and critical revision of drafts of article
Lorraine N. Clark, PhD	Columbia University, New York	Obtaining funding, study conception, study design, interpretation of data, and critical revision of drafts of article

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