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Tremor and Other Hyperkinetic Movements

Articles

Genetic Testing Preferences of Individuals in Families with Essential Tremor

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Abstract

Background: The search for essential tremor (ET) genes is active, and it is only a matter of time before genetic tests become available. Genetic testing preferences in families have been studied in numerous other neurological disorders but there are no published data about ET.

Methods: We surveyed 34 ET probands and their relatives (43 affected, 28 unaffected) enrolled in our Family Study of Essential Tremor to assess their interest in genetic testing. We examined whether clinical factors influenced their interest in testing. Clinical utility ("Your physician will be able to use the information obtained to improve your care") and penetrance ("How likely an individual who carries an ET gene is to develop ET") were defined for participants.

Results: Interest in genetic testing was high in ET families (90/105 [85.7%]). There was a significant difference between affected (including probands and affected relatives) and unaffected relatives in terms of their interest in genetic testing, with the former being more interested (70/77 [90.9%] vs. 20/28 [71.4%] $p = 0.04$). Participants were more likely to want testing in the scenarios with high clinical utility; disease penetrance was not a determining factor (all $p < 0.05$). Sixteen hypothetical factors were identified that might influence a participant's decision to undergo genetic testing for ET.

Discussion: Interest in genetic testing was high in ET families. While genetic testing is not currently available for ET, the hunt for ET genes is ongoing, and this is a highly familial disorder. Understanding genetic testing preferences will greatly aid clinicians once a genetic test becomes available.

Keywords: Essential tremor, genetics, epidemiology, survey

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Introduction

Essential tremor (ET) is the most common tremor disorder and among the most common neurological disorders.[1–4] Tremor in ET typically occurs in the hands and arms during voluntary movements and may eventually affect other body regions such as the head, jaw, and voice.[5]

ET is highly familial. Familial aggregation data show that first-degree relatives of ET cases are approximately five times more likely to develop ET than are first-degree relatives of control subjects.[6] ET has traditionally been characterized as having a Mendelian (autosomal dominant) mode of inheritance.[7–10] However, recent evidence also suggests that ET could be a complex disease.[11]

The yield in genetic studies of ET has been somewhat limited, however, due to a variety of issues, including phenotypic and genotypic heterogeneity.[10] As a result, no causative mutations have been reproducible and a specific genetic test is not currently available.[8–10]

The lack of definitive clinical diagnostic criteria or a specific biomarker unique to ET has also presented obstacles in candidate gene studies.[8–10] Even so, the search for ET genes is active, and it is only a matter of time until gene discovery efforts are more successful and genetic tests become available.[8]

Genetic testing preferences in families have been studied in numerous other neurological disorders such as epilepsy, Huntington's disease, and Alzheimer's disease, with occasional unexpected results.[12–14] Despite the fact that it is highly familial, the literature available on genetic testing preferences in ET families is non-existent. Indeed, there are no published data on 1) genetic testing preferences of patients with ET or 2) how various demographic or clinical factors might influence a patient's decision to decide to undergo genetic testing.

We surveyed the preferences of individuals currently enrolled in our Family Study of Essential Tremor (FASET II) to assess their willingness to undergo genetic testing. We also examined whether clinical and demographic factors influenced this willingness.

Methods

Study sample

The study sample comprised ET probands and their first- and second-degree affected and unaffected relatives enrolled in FASET II (September 2015 to present). Families were primarily recruited with targeted advertisements posted on the International Essential Tremor Foundation (IETF) and the Tremor Action Network (TAN) websites. These families met the initial criteria of having 1) a proband whose ET diagnosis had been assigned by a doctor and whose age of tremor onset was ≤40 years (later changed to ≤50 to be more inclusive), 2) at least three reportedly affected family members and at least two reportedly unaffected family members, and 3) no family history of dystonia or Parkinson's disease.

Study design and sample size

As part of FASET II, each participant underwent a 3-hour in-person evaluation that included signed informed consent, clinical questionnaires, a videotaped neurological examination, and phlebotomy.[15,16] These evaluations were conducted by one of four trained research personnel (K.V.N., J.P., K.P.C., N.H.). The severity of postural and kinetic tremors on videotaped neurological examination was rated (0–3) by a senior movement disorders neurologist (E.D.L.), and published diagnostic criteria for ET (moderate or greater amplitude kinetic tremor [tremor rating ⩾2] during three or more videotaped activities or a head tremor in the absence of Parkinson's disease or other known causes) were applied.[7,17]

Each enrollee was also eligible to participate in an additional genetic testing survey, which was the focus of the current analyses. The survey was posted from August 8, 2016, to January 15, 2017. From a pool of 122 enrollees, 105 (86.1%) agreed to participate. This sample size was of similar or greater magnitude to those used in prior studies of Alzheimer's disease and Huntington's disease with similar aims.[12,14] All study procedures and surveys were approved by the Yale University Institutional Review Board.

Genetic testing survey

General comments. The genetic testing survey was completed online (Qualtrics, yalesurvey.qualtrics.com) and included demographic questions, family history questions, questions about tremor, a section that assessed interest in genetic testing in four genetic testing scenarios (see below), and a section that assessed whether each of 21 hypothetical factors such as "The results could improve your health/healthcare" might affect the participant's decision to undergo genetic testing.

Demographic questions. The survey included demographic questions (age, gender, ethnicity, religion, education, marital status, and number of children) (Table 1). These could influence genetic testing preferences.

Family history, tremor history and question about genetic testing. Each participant endorsed whether they had tremor or not and how many family members were reportedly affected. If tremor was endorsed, follow-up questions on severity and duration of tremor and modes of treatment were included. To assess the level of interest in genetic testing, the survey included a question that specifically asked whether each participant would "be interested in genetic testing for ET if such a test were available" (Table 2).

Four genetic testing scenarios. Each participant was given a definition bank that defined certain terms to be used in four genetic testing scenarios that followed (Figures 1 and 2). These terms were 1) clinical utility ("Your physician or neurologist will be able to use the information obtained to improve your treatment or care") and 2) penetrance ("How likely an individual who carries an ET gene is to develop ET") alongside a graphic denoting 100% penetrance (everyone who carries the gene will develop ET) vs. 50% penetrance (only one-half of the individuals who carry the gene will develop ET).

Each of the four genetic testing scenarios comprised a different combination of clinical utility and penetrance: clinical utility and penetrance, each was 100% (Scenario 1); clinical utility and penetrance, each was 50% (Scenario 2); no clinical utility and penetrance, 100% (Scenario 3); and no clinical utility and penetrance, 50% (Scenario 4). Participants were asked to indicate whether in each scenario they would decide to undergo genetic testing. To do so, participants used a five-point Likert scale (definitely yes, probably yes, don't know, probably no, definitely no).

Twenty-one hypothetical factors that could influence decision to undergo testing. We also assessed whether each of 21 hypothetical factors might influence a participant's decision to undergo genetic testing (Table 3). For analytical purposes, we grouped these factors into four categories: 1) the factor positively impacts desire for genetic testing (e.g., "The results could improve your health or healthcare"), 2) the factor negatively impacts desire for genetic testing (e.g., "Impact on your career", "An effect on insurance coverage"), 3) beliefs, family, and future, which could have positive or negative impact (e.g., "Your religious, cultural, and/or spiritual beliefs", "Your decision about having children"), and 4) medical implications ("Having test results to share with your doctor", "Your treatment options for essential tremor").

Table 1. **Demographic and Clinical Characteristics of 105 Participants**

Characteristic	Data
Age (years)	59.3 ± 16.1
Gender	
Male	46 (43.8)
Female	59 (56.2)
Religion	
Catholic	28 (26.7)
Protestant	26 (24.8)
Jewish	15 (14.3)
Other	15 (14.3)
None	21 (20.0)
Education level	
At least a bachelor's degree	68 (64.7)
Less than a bachelor's degree	37 (35.3)
Marital status	
Married	70 (66.7)
Widowed	10 (9.5)
Divorced	14 (13.3)
Never married	11 (10.5)
Children	
None	19 (18.1)
Yes (biological, step, and/or adopted)	86 (81.9)[1]
Biological	83 (79)
Step	11 (10.5)
Adopted	9 (8.6)
Family history of ET	
"I am the only person with essential tremor"	1 (1.0)
"Yes, myself and one other person"	3 (2.9)
"Yes myself and two or more people"	73 (69.5)
"Yes my family but not me"	28 (26.7)
Tremor duration (years)	30.5 ± 20.8
Form of ET treatment	
"I do not treat it in any way"	42 (40.0)
"I take medication when needed"	5 (4.8)

Table 1. Continued

Characteristic	Data
"I take medication daily"	25 (23.8)
"I had surgery to treat it and take medication"	5 (4.8)
"I do not have ET" (unaffected relatives)	28 (26.7)

Abbreviation: ET, Essential Tremor.
All values are mean ± standard deviation or number (percentage).
[1]Some individuals have more than one type (e.g., biological and adopted).

Table 2. **"Would you be Interested in Genetic Testing for ET if such a Test were Available"**

		Yes	No	Not Sure	p (Chi-Square Test)
Entire sample		90 (85.7)	2 (1.9)	13 (12.4)	
Gender	Male	40 (87.0)	1 (2.2)	5 (4.8)	0.91[1]
	Female	50 (84.7)	1 (1.7)	8 (13.6)	
Participant type	Proband	32 (94.1)	1 (2.9)	1 (2.9)	0.08[2]
	Affected relative	38 (88.4)	0 (0.0)	5 (11.6)	0.04[3]
	Unaffected relative	20 (71.4)	1 (3.6)	7 (25.0)	

All values represent number (row percentage).
[1]There was no difference between gender and desire for genetic testing.
[2]Comparing probands, affected relatives, and unaffected relatives.
[3]Comparing affected (probands + affected relatives) and unaffected relatives.

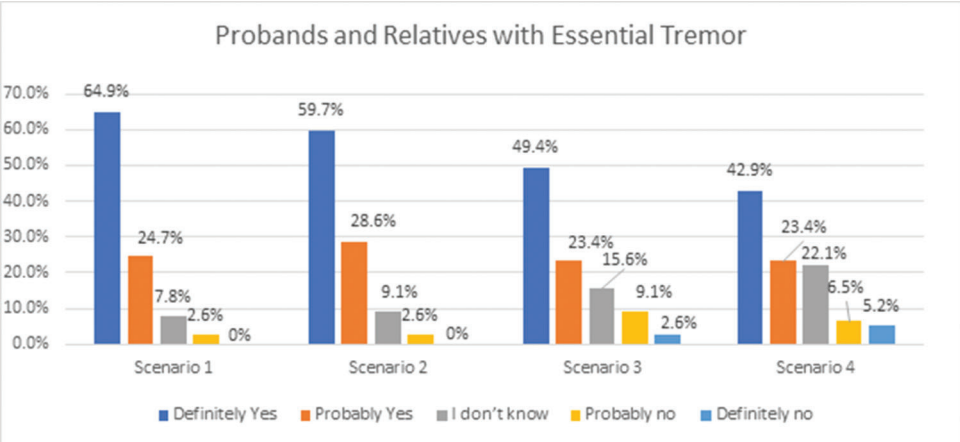

Figure 1. **Genetic Testing Preferences of Affecteds in Four Scenarios**

How each of the 21 factors would affect a participant's decision to undergo genetic testing was measured on a five-point Likert scale (much less likely to want testing, somewhat less likely to want testing, no effect on my desire for testing, somewhat more likely to want testing, much more likely to want testing).

Statistical analysis

Statistical analyses were carried out using IBM SPSS Statistics (Version 24). We used chi-square tests to compare the two genders and the three participant types (proband, affected relative, unaffected

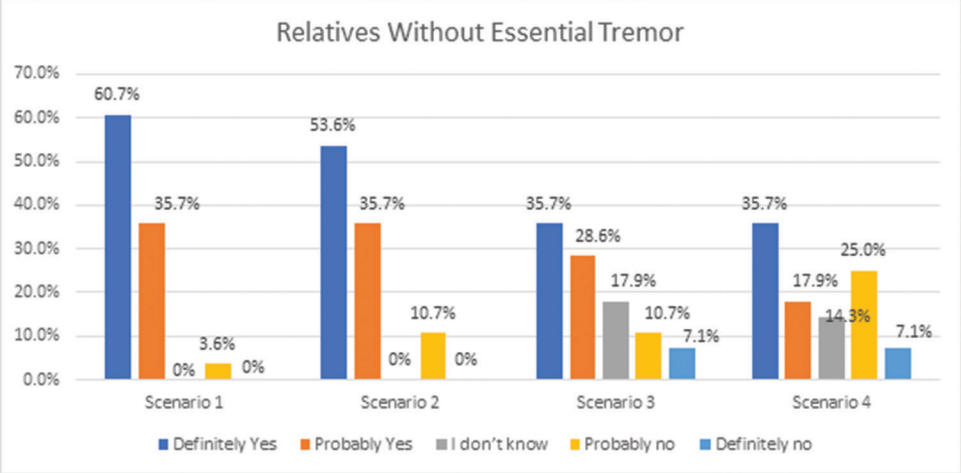

Figure 2. **Genetic Testing Preferences of Unaffecteds in Four Scenarios**

relative) in their responses to the question "Would you be interested in genetic testing for ET if such a test were available?" (Table 2). Using McNemar's tests, we compared responses across the four genetic testing scenarios. For these analyses, we collapsed the five responses into dichotomous categories (definitely yes/probably yes vs. definitely no/probably no/don't know). We first performed these analyses in affected individuals (i.e., probands and affected relatives) and then repeated these analyses in unaffected relatives (Figures 1 and 2).

In order to assess the significance of the 21 hypothetical factors that might influence a participant's decision to undergo genetic testing we coded each of the possible responses into numerical values. Negative responses were coded as –2 for "much less likely to want testing" and –1 for "somewhat less likely to want testing". "No effect on my desire for testing" was a neutral response and therefore coded as 0. The positive responses were accordingly coded as 1 for "somewhat more likely to want testing" and 2 for "much more likely to want testing". We calculated the mean value of each of the 21 responses to determine overall positive vs. negative effect (Table 3). Coding the responses in such a way allowed us to distinguish factors with a positive effect reflected by a positive mean value and factors with a negative effect reflected by a negative mean value. We then performed a one-sample t-test to detect significance from a fixed value of zero. Given the number of comparisons ($n = 21$), a Bonferroni correction was applied ($0.05/21 = 0.0024$), with significance set at $p < 0.0024$ (Table 3).

Lastly, to analyze any potential association between demographic and other clinical factors and interest in genetic testing, we used generalized estimating equations to determine whether each of these factors predicted the answer to "Would you be interested in genetic testing if such a test were available?" (Table 4). For some variables, we collapsed categories: for religion we compared "Catholic" with "non-Catholic". For marital status, we compared "ever married" (married, divorced, separated, widowed) with "never married". Lastly, for the presence of children, we included biological children only (omitting adopted and step-children) and compared with none. These analyses yielded beta and p values.

Results

Demographic and clinical characteristics

The 105 participants comprised 34 (32.4%) probands, 43 (41.0%) affected relatives, and 28 (26.6%) unaffected relatives (Table 1). Forty-six (43.8%) were male and nearly all (104 or 99.0%) were non-Hispanic white. The mean age was 59.3 ± 16.1 years (range 21–90 years). Nearly two-thirds (64.7%) had at least a bachelor's degree (Table 1).

Question about genetic testing

To assess general interest in genetic testing for ET we asked each participant: "Would you be interested in genetic testing for ET if such a test were available?" (Table 2). Interest in genetic testing was high in families (90/105 [85.7%], Table 2). There was a marginal difference between probands, affected relatives, and unaffected relatives in their interest in genetic testing (Table 2, $p = 0.08$). However, there was a significant difference between affected relatives (including probands and affected relatives) and their unaffected relatives in terms of their interest in genetic testing, with the former being more interested (70/77 [90.9%] vs. 20/28 [71.4%], $p = 0.04$, Table 2).

Interest in genetic testing in four genetic testing scenarios

Affected individuals were more likely to want testing in the scenarios with clinical utility; disease penetrance was not a determining factor, and the differences were not significant. Thus, among 77 affected persons (i.e., probands and affected relatives), 69 (89.6%) said they would definitely or probably want genetic testing in Scenario 1 (clinical utility and penetrance, each were 100%) vs. only 56 (72.7%) in Scenario 3 (no clinical utility and 100% penetrance) (McNemar's test $p < 0.001$). Similarly, in Scenario 2 (clinical utility and penetrance, each were 50%), 68 (88.3%) of 77 affected individuals said they would definitely or probably want genetic testing vs. only 51 (66.2%) in Scenario 4 (no clinical utility and penetrance, 50%) (McNemar's test $p < 0.001$) (Figure 1).

Table 3. **Twenty-one Hypothetical Factors that Might Influence a Participant's Decision to Undergo Genetic Testing**

	Significance	Mean	Category
The results could improve your health or health care	0.000*	1.67[1]	1
Learn that changing your behavior could reduce symptoms	0.000*	1.65[1]	1
Learn if ET is caused by a specific gene	0.000*	1.58[1]	1
Determine if your children are at risk	0.000*	1.54[1]	1
Learn some of your genetic information	0.000*	1.50[1]	1
The test is highly accurate	0.000*	1.43	2
Your treatment options for ET	0.000*	1.39	4
The test is affordable	0.000*	1.30	2
Having test results to share with your doctor	0.000*	1.17	4
Your decision to opt for surgery to treat ET	0.000*	0.58	4
An effect on your future plans	0.002	0.50	3
Your family's reaction to genetic testing	0.000*	0.44	3
Having your blood drawn for testing	0.000*	0.35	4
Your decision about having children	0.000*	0.25	3
Impact your career	0.042	0.23	2
Your religious, cultural, and/or spiritual beliefs	0.004	0.23	3
Your decision about marriage	0.000*	0.20	3
Affect your insurance	0.411	–0.11[2]	2
Impact your privacy	0.054	–0.22[2]	2
The test is less accurate	0.000*	–0.51[2]	2
The test is not affordable	0.000*	–1.01[2]	2

Abbreviation: ET, Essential Tremor.
*Statistically significant, $p < 0.0024$.
[1]Highest ranked positive effect factors.
[2]Negative effect factors.

Akin to their affected counterparts, the 28 unaffected relatives were more likely to want testing in the scenarios with clinical utility whereas disease penetrance was not a determining factor: 27 (96.4%) in Scenario 1 vs. 18 (64.3%) in Scenario 3 (McNemar's test $p = 0.004$), and 25 (89.3%) in Scenario 2 vs. 15 (53.6%) in Scenario 4 (McNemar's test $p = 0.002$) (Figure 2).

Twenty-one hypothetical factors that could influence decision to undergo testing

In order to assess the significance of the 21 hypothetical factors that might influence a participant's decision to undergo genetic testing we coded each of the possible responses into numerical values. We ranked the factors by the mean response such that "The results could improve your health or healthcare" was the most positive factor with a mean of 1.67 and "The test is not affordable" was the most negative factor with a mean of –1.01 (Table 3). We conducted a one-sample t-test with Bonferroni correction in order to test the statistical significance of each factor. We found a factor to be significant if the p-value was less than 0.0024. A large number of factors ($n = 16$ that were significant) were identified that might influence a participant's decision to undergo genetic testing (Table 3).

As noted above, we grouped the 21 hypothetical factors into four categories. As expected, factors in Category 1 (i.e., the factor positively impacts desire for genetic testing: "The results could improve your

Table 4. **Demographic and Clinical Predictors Influencing Desire to Undergo Genetic Testing**

Predictor Factor	beta	p
Gender	0.182	0.78
Religion	0.000	1.00
Education	0.023	0.90
Marital status	0.941	0.20
Diagnostic status (affected vs. unaffected)	–1.386	0.023[1]
Tremor duration	0.015	0.51
Biological children	–0.375	0.59
Age	0.010	0.65

[1]Statistically significant.
These analyses utilized generalized estimating equations.

health or healthcare") had higher means across all participants. For Category 2 (i.e., the factor negatively impacts desire for genetic testing: "An effect on insurance coverage"), the responses had a negative mean. Participants cared more about the affordability of a test rather than its accuracy: "The test is not affordable" had a mean of –1.01 vs. –0.51 for "The test is less accurate" (Table 3).

Responses to Category 3 (i.e., beliefs, family, and future: "Your religious, cultural, and/or spiritual beliefs", "Your decision about having children") and Category 4 (i.e., medical implications: "Having test results to share with your doctor", "Your treatment options for essential tremor") showed positive averages overall. It should be noted that "Your treatment options for ET" could have been ranked high among factors because our sample contained more affected than unaffected relatives. Alternatively, it might be the case that all family members are equally interested in viable treatment options.

Demographic and clinical predictors influencing desire to undergo genetic testing

We were interested in learning whether demographic and other clinical factors were predictors for desire to undergo genetic testing. We evaluated the answers to "Would you be interested in genetic testing if such a test were available?" in a dichotomous manner such that the responses were analyzed as "yes" vs. "no"/"unsure". Factors we considered were gender, religion, education, marital status, diagnosis status (affected vs. unaffected), tremor duration, presence of biological children, and age as possible predictors. Only diagnostic status (affected vs. unaffected) was statistically significant (Table 4).

Discussion

Currently, the only tool for diagnosing and phenotyping ET is clinical. There are no serum or imaging biomarkers for ET, and clinical overlap with Parkinson's disease and dystonia further complicates diagnosis.[18] Therefore gene identification could aid considerably in ET diagnosis in ET families. Furthermore, gene identification will eventually be an issue for ET families, among whose members may wish to determine their gene status, especially if ET is regarded as a risk factor for dementia or Parkinson's disease and if it is viewed as associated with an increased risk of mortality.[19–22] We surveyed the preferences of individuals currently enrolled in our family study of ET to assess their willingness to undergo genetic testing.

Genetic testing survey responses from patients at risk for Huntington's disease showed, before genetic testing was available, a high interest in future genetic testing to verify status. However, once a test became available, the interest was far lower than expected (~15%).[12,22] These data can partly be explained by the fact that a positive Huntington's disease genetic testing result has dire prognostic implications. Our data also show that, before genetic testing is available, individuals with a family history of ET were highly interested in genetic testing. Indeed, 90.9% of affected individuals (probands and affected relatives) and 71.4% unaffected relatives expressed interest in genetic testing with the information currently available to them.

Affected individuals were more interested in genetic testing than were unaffected individuals (90.9% vs. 71.4%, p = 0.04). This could relate to the fact that these individuals are searching for knowledge or interventions that could impact on their disease either at present or in the foreseeable future.

We also demonstrated that individuals, whether affected or unaffected, were more likely to want testing in the scenarios with clinical utility; disease penetrance was not a determining factor. This was similar to the findings in a survey of epilepsy.[13] In diseases with symptomatic treatments, clinical utility may be translated to better treatment or clinical management options.

A number of hypothetical factors negatively impact desire for genetic testing: both affected and unaffected relatives cared quite a bit about the affordability of a test. In a time of expensive and increasingly sophisticated testing and treatment options, this is not unexpected. As would be expected, all the hypothetical factors in Category 1 ("The results could improve your health/ healthcare", "Knowing ET is caused by a specific gene", "Changing your behavior could reduce symptoms", "Knowing if your children are at risk", and "Learn some of your genetic information"), positively impacted desire for genetic testing.

This study had several limitations. First, the sample size was modest; despite this, the sample size was of similar or greater magnitude to those used in prior studies of Alzheimer's disease and Huntington's disease with similar aims.[12,14] Indeed, we detected significant effects across analyses. Despite this, future studies with larger samples would be beneficial. Second, ours was a very educated cohort (64.7% of participants had a bachelor's degree or higher). Our study heavily recruited patients from patient-centered organizations (IETF and TAN) and patients with long-standing disease; hence, our findings of this study might not be generalizable to cohorts with different characteristics recruited through different means. Third, we asked our

study subjects about hypothetical testing situations. Their responses, when actually confronted with a testing situation, could differ. Furthermore, we did not elicit their desire to undergo genetic testing to enhance science and research.

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