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# Gene Expression Changes in Blood as a Putative Biomarker for Huntington's Disease

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***Abstract:*** **Several studies demonstrated alterations of gene expression in blood in various neurological disorders including Huntington's disease (HD). Using microarray technology, a recent study identified a large number of significantly altered mRNAs in HD blood, from which a 12-gene set was selected as classifier for discriminating controls and HD patients. The aim of our study was to validate expression changes of these 12 genes in an independent cohort of HD patients and evaluate their sensitivity and specificity. Four different subject groups were included—patients with HD, Parkinson's disease (PD), acute ischemic stroke (AS) and healthy controls. Although the previous results were successfully validated, gene expression changes in HD blood partly overlapped with those observed in blood from PD and AS patients. Predictive value of the selected biomarker set for HD group was 78%, with 82% sensitivity and 53% specificity. Further gene expression analyses in longitudinal studies are needed to validate and refine possible transcriptomic blood biomarkers in HD.** © 2009 Movement Disorder Society

**Key words:** biomarkers; gene expression; Huntington's disease; neurodegeneration; transcriptomics

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## INTRODUCTION

Transcriptomics is one of the emerging high throughput technologies with a potential to identify molecular signatures that could serve as clinically useful biomarkers of disease progression. For a biomarker to be clinically useful, noninvasive detection is desirable. This is a challenge for neurodegenerative diseases where the tissue of interest is unavailable for sampling. Peripheral blood is easily accessible tissue and gene expression patterns have been shown to exist in human blood in a wide variety of central nervous system diseases where no obvious clinical phenotype in blood is present.[1–6] However, these potential molecular signatures have not been independently validated and tested for diagnostic accuracy using different cohorts of patients analyzed at independent sites.

In this study, we focused on HD, an autosomal dominant neurodegenerative disorder characterized by progressive motor impairment, cognitive decline and various psychiatric symptoms with the typical age of onset in the third to fifth decades. The disease is fatal after 15 to 20 years of progressive neurodegeneration. So far, no effective treatment has been available to cure the disease or to slow its progression.[7] As there is a single mutation—expansion of CAG tract in the huntington gene, detection of the mutation provides an efficient diagnostic test for both symptomatic patients and presymptomatic HD mutation carriers. Although the genetic mutation defines the *trait*, it does not provide any information about the *state* of HD. Therefore, *state* markers are needed as surrogate endpoints to clinical rating scales used to monitor disease progression and response to treatment. The clinical rating scales are subject to intra- and inter-rater variability and cannot distinguish disease modification from symptom relief. There is compelling evidence that disease-modifying therapies can be developed for HD, but it will be crucial to develop biomarkers to reduce the sample size requirement for the upcoming clinical trials.

Using microarray technology, we previously detected significant alterations in expression of a large number of genes in HD blood and selected a 12-gene set for further study by PCR.[6] Here, we examined expression and diagnostic performance of the 12-gene

set in an independent cohort of HD patients as compared to normal and disease control subjects.

## PATIENTS AND METHODS

### Patients

All the patients and controls were residents of Slovenia and Caucasian. HD group consisted of 61 HD patients with confirmed genetic mutation. Average CAG repeat number of mutated allele was 44.7 ± 3.3 CAG repeats. The neurological status of the HD patients was assessed by an experienced HD neurologist using Unified Huntington's Disease Rating Scale UHDRS.[8] The HD group included a cohort of 14 presymptomatic carriers of the gene mutation, consisting of 6 females and 8 males (average age, 30.2 ± 4.2 years) and 47 symptomatic HD patients, 23 females and 24 males (average age, 49.8 ± 12.9 years). In the symptomatic group 30 patients had UHDRS motor score 5 to 50 and 17 were advanced symptomatic with the UHDRS motor score >50. Thirty-two healthy controls with no family history of HD were included.

Additionally, 20 patients with idiopathic Parkinson's disease (PD) and 10 patients with acute ischemic stroke (AS) were recruited to serve as disease controls. Patients with PD were diagnosed by a movement disorder specialist using the United Kingdom Brain Bank criteria.[9] The group consisted of 8 females and 12 males, average age 58.7 ± 5.8 years. Acute ischemic stroke was diagnosed by a neurologist based on the presence of focal neurological signs and symptoms. The AS patient group consisted of 5 females and 5 males, average age 62.8 ± 7.1 years. The blood samples were taken 72 hours after the onset of acute stroke. Exclusion criteria for all groups included the presence of any acute medical illness, use of anticoagulants, abnormal blood counts or blood disorder. All samples were obtained in accordance with the institutional review boards, and participants gave written informed consent.

### Sample Collection and Quantitative RT-PCR Analysis

Peripheral blood was drawn in PAXgene™ blood collection tubes (PreAnalytiX, Qiagen). RNA isolation, reverse transcription, QRT-PCR reactions and relative gene expression calculation were performed as previously described.[6] Beta-actin and 28S rRNA were used as reference genes.

### Statistical and Machine Learning Setup

To examine whether a series of 12 biomarkers varied as a function of the participant status (HD vs. healthy control) a one-way multivariate analysis of variance (MANOVA) was conducted. Follow-up Welch two-sample *t*-tests were then conducted on each of the 12 biomarkers, utilizing the Bonferroni procedure to guard against inflating the Type I error rate and using an $\alpha = 0.05$, resulting in a significance level of $P < 0.004$.

To build the prediction model, relative gene expression data were analyzed using logistic regression (LR) model with 10-fold cross-validation regime to avoid overfitting and to assure statistical validity of the computed quality indices.[10] Accuracy, sensitivity and specificity were used as diagnostic performance indicators to evaluate the effectiveness of the predictive model. Data management and computations were carried out using R language for statistical computing and graphics[11] and Weka suite of machine learning algorithms.

## RESULTS

### Expression Changes in the Group of HD Patients

Using real-time PCR we examined expression of the previously identified 12-gene set in a new cohort of 61 HD patients and 32 age- and gender-matched healthy controls. The MANOVA revealed a statistically significant multivariate effect between HD and control samples across the whole set of 12 biomarkers (Pillai's $V = 0.36$, $F(12, 78) = 3.70$, $P < 0.001$). When the 12 genes were tested individually, 10 showed statistically significant overexpression in HD samples compared to healthy controls ($P < 0.004$) with fold changes ranging from 1.41 to 1.90 (data not shown). Of the remaining two genes, SF3B1 was not significantly altered and PCNP did not show statistical significance after correction with Bonferroni adjustment ($P = 0.01$).

Next, we examined whether expression of the 12 genes changed in relation to progression of HD from presymptomatic to symptomatic (UHDRS = 6–50) and advanced symptomatic stage (UHDRS > 50).[8] Expression of individual genes increased with disease progression from the presymptomatic to advanced symptomatic stage, but the differences did not reach statistical significance (Fig. 1). Although only 6 genes, ANXA, MARCH7, CAPZA1, HIF1A, TAF7, and YPEL5, were significantly upregulated in the presymptomatic (P) group ($P < 0.05$), 10 genes were significantly upregulated in the symptomatic (S) group ($P < 0.05$) (PCNP and SF3B1 were not significant) and 11 genes were

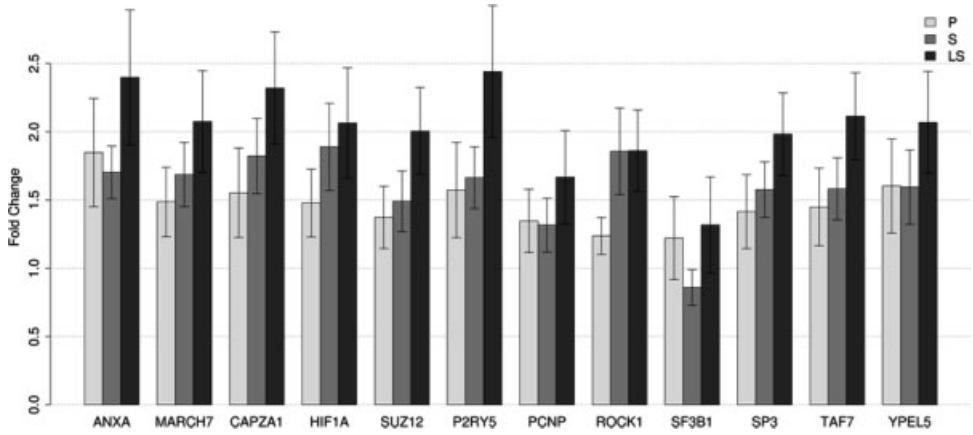


**FIG. 1.** Expression fold changes of 12 genes in different stages of HD. The upregulation of expression of the 12 previously selected genes[6] was validated in the new cohort of HD patients. Bars represent fold increase in mRNAs in HD patients relative to healthy controls. Interval lines represent the (average fold change) $\times(2^{\mathrm{SEM}} - 1)$. P-presymptomatic HD mutation carriers, S-symptomatic patients, LS-late symptomatic patients: ANXA-annexin A1; *MARCH7*-membrane-associated ring finger 7; *CAPZA1*-capping protein muscle Z-line, alpha 1; ***HIF1A***-hypoxia-inducible factor 1, alpha subunit; SUZ12-suppressor of zeste 12 homolog; P2RY5-purinergic receptor P2Y, G-protein coupled, 5; PCNP-PEST proteolytic signal containing nuclear protein; ROCK1-Rho-associated, coiled-coil containing protein kinase 1; SF3B1-splicing factor 3b, subunit 1; SP3-Sp3 transcription factor; TAF7-TAF7 RNA polymerase II, TATA box binding protein (TBP)-associated factor; YPEL5-Yippee-like 5.

significantly upregulated in the late symptomatic (LS) group ($P < 0.05$) (SF3B1 was not significant).

In order to investigate predictive performance of the gene set, we examined logistic regression machine learning algorithm on our dataset. Proposed classifier reached overall positive predictive value of 78% with 82% sensitivity and 53% specificity for HD with respect to healthy control.

In addition, the potential of gene set to discriminate between presymptomatic and symptomatic patients was evaluated using the logistic regression algorithm. The results showed overall positive predictive value of 85% with relatively high sensitivity (83%), but with low specificity (50%). A possible explanation for low specificity may be the unequal distribution of cases in our dataset (14 presymptomatic and 47 symptomatic cases) and small set of training cases.

## Expression Changes in Patients with Parkinson's Disease and Acute Ischemic Stroke

To further examine the specificity of gene expression changes observed in HD blood expression of the 12-gene set was analyzed in blood samples obtained from patients with Parkinson's disease (PD) and acute ischemic stroke (AS) (Fig. 2). When the 12 genes were

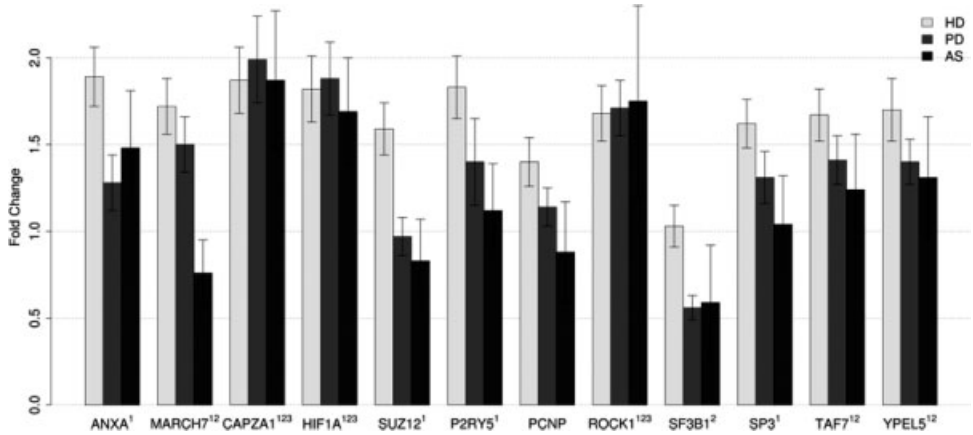


**FIG. 2.** Fold changes of 12 genes in HD, PD, and AS groups. Values represent expression fold changes in PD and AS groups relative to healthy controls. Error bars represent (average fold change) $\times(2^{\mathrm{SEM}} - 1)$. Numbers 1, 2, and 3 represent statistically significant difference in expression of the gene between HD (1), PD (2) or AS (3) in comparison to healthy controls ($P < 0.01$).

analyzed as a set, the expression was significantly higher in HD compared to PD ($P < 0.0001$) or AS ($P < 0.001$).

On the other hand, examination of individual genes revealed that 3 genes (CAPZA1, HIF1A and ROCK1) were also significantly upregulated in PD and AS when compared to healthy controls. For three additional genes, detected changes were similar in HD and PD group, but not in AS group (MARCH7, TAF7, YPEL5). These results suggest that at least some of the gene expression changes detected in HD blood may be also present in other neurological diseases.

## DISCUSSION

In this study, we provide confirmatory evidence of significant gene expression changes in freshly isolated blood samples obtained from patients with Huntington's disease. In the previous analysis of global gene expression in blood of HD patients more than 300 genes were differentially expressed in HD compared to healthy controls.[6] Moreover, it was suggested that presymptomatic carriers of HD mutation and symptomatic HD patients could be classified using gene expression in blood. Furthermore, the study identifed a subset of 12 genes that were further analyzed by real-time PCR in presymtomatic subjects and symptomatic HD patients.

In this work, we found statistically significant overexpression of 10 of 12 genes originally identified in HD blood. Expression of the 12 genes appeared higher in the advanced symptomatic group of patients compared to the presymptomatic group, but these stage-dependent differences in expression did not reach statistical significance. In order to determine whether the observed changes were specific for HD, we examined expresison in PD as a model of another chronic disease of basal ganglia, and in acute ischemic stroke as a model of an acute neurological condition. A subset of genes that were altered in all three conditions might reflect nonspecific changes in expression due to central nervous system injury. Further studies will be required to determine the significance of these overlapping expression changes.

To address the diagnostic performance of the 12-gene biomarker set, a logistics regression model was employed. This approach revealed a positive predictive value of 78% with 82% sensitivity and 53% specificity for HD compared to controls. Although high specificity and sensitivity are generally desirable for diagnostic biomarkers, these parameters are not essential in diseases such as HD where the diagnosis is already known and the intended use of biomarkers is to primarily monitor disease progression. As a potential marker of disease progression, the 12-gene set showed promising overall positive predictive value and sensitivity (85 and 83%, respectively), but with relatively low specificity (50%). Nevertheless, our results suggest that the 12-gene set may be of better clinical value compared to individual genes as a marker of disease progression in HD. Moreover, we hypothesize that including more altered genes in the gene set may further enhance its clinical applicability.

In addition, another study of global gene expression in lymphoblastic cell lines from HD patients failed to identify significant changes in gene expression[12] that were observed in freshly isolated blood samples.[6] Moreover, the 12-gene set expression was not validated in the aforementioned study.[12] It is therefore evident that multiple independent validation studies will be required to evaluate potential clinical applicability of a putative biomarker. Standard operating procedures will have to be defined in order to appropriately address the biological and methodological variability in such studies. Although development of novel hemogenomic approaches to noninvasively monitor disease progression showed promise, it remains unclear whether the observed changes in blood gene expression will be sufficiently robust to serve as biomarkers of disease. A combination of genomic, metabolomic and proteomic approaches may be required, in combination with neuroimaging, to succesfully identify biomarkers of disease progression in HD and other neurodegenerative diseases.

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# Isolated Head Tremor: Part of the Clinical Spectrum of Essential Tremor? Data from Population-Based and Clinic-Based Case Samples

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***Abstract:*** **Essential tremor (ET) still remains a clinical diagnosis. Nonetheless, it is misdiagnosed in 30 to 50% of cases. There are a number of areas of diagnostic uncertainty. One of these is isolated head tremor, on which published data are limited and at variance. We studied the prevalence of isolated head (i.e., neck) tremor in ET in two population-based studies (Turkey and New York) and a large clinical sample (New York); these 583 ET cases all received the same detailed tremor examination. Head tremor with mild arm tremor occurred in a very small percentage of cases in each sample (1.9–3.1%, overall 2.7%). Nearly all of them were women. Head tremor in the complete absence of arm tremor was not observed in any cases (0.0%). These clinical data may be of value to clinicians in practice settings and researchers in phenotyping efforts in the emerging field of ET genetics.** 

**Key words:** essential tremor; clinical; head tremor

Head (i.e., neck) tremor is among the most commonly noted clinical features of essential tremor (ET),[1–4] in contrast to Parkinson's disease (PD), in which it is rare.[5,6] Although tremor typically spreads from the hands to the head,[2,3] patients on occasion complain of isolated head tremor. ET

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remains a clinical diagnosis. However, it is misdiagnosed in 30 to 50% of cases,[7] suggesting that it could be the most commonly misdiagnosed movement disorder. One area of diagnostic ambiguity is that of isolated head tremor. Unfortunately, published data are limited to brief comments in case series that are broadly focused on other issues.[8–17] Many of these series are small (30–40 cases)[8–11] and none[8–17] provide detailed individual level case data on the relative severity of arm vs. head tremor. Furthermore, results are discrepant. Although several series imply that isolated head tremor is not part of the phenotypic spectrum of ET (0% of cases),[8–10] others suggest that it is a feature of every 5th or 10th ET case.[12,17] Hence, clinicians are left to wonder whether isolated head tremor is part of the phenotypic spectrum of ET? In this study, we examined the prevalence of isolated head tremor in ET in two population-based studies and a large clinical series. Each study provided sufficient individual case data to evaluate whether head tremor occurred in the absence of other tremors. We also conducted a critical review of published data. It is hoped that these efforts will assist in clinical diagnosis, thereby lessening diagnostic misclassification. We also anticipate that these data will be of use in phenotyping efforts in emerging genetic studies of ET.[18]

## METHODS

### Overview

Three ET case samples were used.[19–21] In each set of cases, the same neurological examination was performed by study neurologists. A tremor examination included one test for postural tremor and five for kinetic tremor (pouring, using spoon, drinking, finger-nose-finger, and spiral) performed with each arm (12 tests total, with tremor ratings of 0 [none], 1 [mild], 2 [moderate], and 3 [severe]), along with evaluations of head (i.e., neck), voice, and jaw tremors. Neck tremor in ET was coded as present or absent and was distinguished from dystonic tremor by the absence of twisting or tilting movements of the neck, jerk-like or sustained neck deviation, or hypertrophy of neck muscles. Study neurologists assigned ET diagnoses using the same published diagnostic criteria (kinetic tremor rated ≥2 during at least three tests or head tremor, in the absence of PD or dystonia); diagnostic criteria have been published in detail for each study,[19–21] and diagnostic gradations of definite, probable and possible ET were applied in each case.[22] Cases signed written informed consent on enrollment.

### Description of Population-based Study in Turkey

A population-based study of the prevalence of ET was conducted in Mersin, Turkey.[20] As described previously,[20] the target study population consisted of 2,500 adults who represented 0.65% of the Mersin population ≥40 years. The epidemiological survey used door-to-door interviews and examinations. Study neurologists performed the evaluations, as described above. The neurologists visited the 2,500 residents in their homes between July and December 2002. There were 89 prevalent ET cases (47 [52.8%] definite ET, 17 [19.1%] probable ET, and 25 [28.1%] possible ET).[20]

### Description of Population-based Study in New York

The Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) was a family study of ET in the Washington Heights-Inwood community in Northern Manhattan, New York. WHIGET enrollment began in 1995 and was completed in 2000. The design of this population-based study has been described in detail.[21] After enrollment, each participant (age ≥ 18 years) was examined, as described above. There were 106 ET cases (59 probands with ET, 33 of their relatives with ET, and 14 affected relatives of control probands),[21] whose diagnoses were definite ET (37 [34.9%]), probable ET (44 [41.5%]), and possible ET (25 [23.6%]).

### Description of Clinical Sample in New York

ET cases are being enrolled in an ongoing study of the environmental epidemiology of ET (2000—present) at the Neurological Institute of New York, Columbia University Medical Center; the design of this study has been described in detail previously.[19] Before enrollment, all cases were diagnosed with ET by their neurologist. After enrollment, each case (age ≥ 18 years) was examined, as described above.[19] There are 388 ET cases (110 [28.4%] definite ET, 181 [46.6%] probable ET, and 97 [25.0%] possible ET).

### Statistical Analyses

Chi-square tests were use to compare proportions across ET case samples.

## RESULTS

There were 583 ET cases across the three study samples. In each of the two population-based studies, the proportion of ET cases with head tremor was approximately 18% (Table 1); in the clinical sample it was higher (37.1%, Chi-square = 22.4, $P < 0.001$). The majority (62.5–73.7%) of ET cases with head tremor were women (Table 1). A smaller proportion of cases (12.3–21.1%, Table 1) had head tremor in the absence of voice or jaw tremor.

The prevalence of isolated head tremor depended on the definition that was used (Table 1). When defined initially as head tremor in the absence of either (1) voice or jaw tremor or (2) moderate arm tremor (i.e., arm tremor of at least moderate amplitude during 1 of 12 tasks), the prevalence was 2 of 89 (2.3%) in Turkey, 2 of 106 (1.9%) in the population-based study in New York, and 12 of 388 (3.1%) in the clinical sample (overall = 16 of 583, 2.7%). These 16 cases were nearly all women (14 of 16, 87.5%). Each of the 16 cases had mild kinetic arm tremor on one or more test, with most having mild tremor on several tests (mean = 5.3, median = 5, range = 1–10 tests, Table 2). When isolated head tremor was defined more stringently as head tremor in the absence of voice, jaw, or any arm tremor (i.e., tremor score = 0 on all 12 tests), then the prevalence was 0.0% in each of the three case samples.

There were 192 ET cases who were taking daily antitremor medication (3 in Turkey, 5 in the population-based study in New York, and 184 in the clinical sample in New York). We repeated the analyses, excluding these 192 cases, and the results were similar in the remaining 391 cases (overall initial

**TABLE 1.** *Data from three studies of essential tremor*

| | Population-based study in Turkey | Population-based study in New York | Clinical sample in New York |
|---|---|---|---|
| Total number of ET cases | 89 | 106 | 388 |
| Age (yrs) | 57.3 ± 11.6 | 69.8 ± 18.4 | 67.4 ± 15.3 |
| Gender (%) | 42 (47.2) women | 63 (59.4) women | 200 (51.5) women |
| ET cases with head tremor | 16 (18.0% of 89) | 19 (17.9% of 106) | 144 (37.1% of 388) |
| Age (yrs) | 64.3 ± 11.3 | 69.6 ± 20.0 | 71.9 ± 12.1 |
| Gender (%) | 10 (62.5) women | 14 (73.7) women | 101 (70.1) women |
| ET cases with head tremor and no voice or jaw tremor | 11 (12.3% of 89) | 13 (12.3% of 106) | 82 (21.1% of 388) |
| Age (yrs) | 65.7 ± 12.3 | 65.4 ± 22.2 | 70.2 ± 12.8 |
| Gender (%) | 6 (54.5) women | 11 (84.6) women | 58 (70.7) women |
| ET cases with head tremor, no voice or jaw tremor, and no arm tremor of moderate or greater amplitude during at least one of 12 tests | 2 (2.3% of 89) | 2 (1.9% of 106) | 12 (3.1% of 388) |
| Age (yrs) | 52.5 ± 0.7 | 56.5 ± 26.2 | 63.3 ± 14.6 |
| Gender (%) | 1 (50.0) woman | 2 (100) women | 11 (91.7) women |
| ET cases with head tremor and no voice or arm tremor | 0 (0% of 89) | 0 (0% of 106) | 0 (0% of 388) |

In each cell, the number of cases (percentage of total cases) is provided, as well as their mean ± SD age and gender distribution.

prevalence of isolated head tremor = 11 of 391 [2.8%], and 0 of 391 [0.0%] when more stringently defined).

## DISCUSSION

When defined most stringently as head tremor in the complete absence of other clinically observable tremor, the prevalence of isolated head tremor in ET was 0.0%. Although no cases had head tremor in the complete absence of arm tremor, 2.7% had head tremor in the presence of mild arm tremor, with most of these cases having mild arm tremor on multiple tests.

Critchley[23] listed the 13 most common groupings of muscular involved in ET; isolated head tremor was not among them. He also described the typical pattern of spread of tremor (arms to head) but not the converse. Similarly, in a study on "essential tremor variants," Koller et al.[9] described isolated voice, chin, or tongue tremors but not isolated head tremor.

**TABLE 2.** *Kinetic tremor ratings in 16 ET cases who had head tremor in the absence of either (1) voice or jaw tremor or (2) moderate arm tremor*

| Case | Post D | Post ND | Pour D | Pour ND | Spoon D | Spoon ND | Drink D | Drink ND | FNF D | FNF ND | Spiral D | Spiral ND |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Population-based study in Turkey | | | | | | | | | | | | |
| 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 2 | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Population-based study in New York | | | | | | | | | | | | |
| 1 | 1 | | 1 | | | | | | 1 | | | |
| 2 | 1 | 1 | | | | | | | | 1 | | |
| Clinical sample from New York | | | | | | | | | | | | |
| 1 | | | | | | 1 | | | | 1 | 1 | 1 |
| 2 | | | | | | | | | | 1 | | |
| 3 | | | | | 1 | | | | 1 | 1 | | 1 |
| 4 | | | 1 | 1 | | | | 1 | 1 | 1 | | 1 |
| 5 | | | 1 | | | | | 1 | 1 | 1 | | |
| 6 | | | 1 | | 1 | | 1 | 1 | 1 | 1 | 1 | 1 |
| 7 | 1 | | 1 | 1 | 1 | 1 | | | 1 | 1 | | 1 |
| 8 | 1 | 1 | 1 | 1 | | 1 | 1 | 1 | | 1 | | 1 |
| 9 | | | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 10 | | | | | | | | 1 | | | | |
| 11 | | | 1 | 1 | | | | 1 | 1 | 1 | | |
| 12 | | | | 1 | | 1 | | 1 | 1 | 1 | | |

Post, postural tremor; Pour, pouring; Spoon, using spoon; Drink, drinking; FNF, finger-nose-finger; Spiral, drawing Archimedes spiral; D, dominant arm; ND, nondominant arm; 1, tremor rating of 1 (mild tremor); Blank cells have tremor rating = 0 (no tremor).

Published data are limited to brief remarks in case series that are broadly focused on other issues. In this literature, (1) isolated head tremor was either not observed at all, (2) its presence in a very small subsample of cases was likely due to torticollis, or (3) it is not clear whether head tremor occurred with complete absence of arm tremor. In treatment-based settings, the proportion of ET cases without arm tremor ranges from 0.0 to 6.9%. Thus, in a study in Benin, Nigeria, 0 of 35 (0.0%) patients had isolated head tremor.[10] Two studies in England indicated that 0 of 34 (0.0%)[8] and 0 of 20 (0.0%)[16] index cases and 0 of 135 (0.0%)[16] affected relatives had isolated head tremor. Similarly, in studies of children, isolated head tremor occurred in 0 of 39[24] and 0 of 19.[25] Another English study indicated that 1 of 42 ET cases had mild titubation without arm tremor; however, that patient also had torsion spasm (dystonia),[11] indicating that the diagnosis was dystonia rather than ET. Similarly, a study in the United States[13] noted 24 of 350 (6.9%) with isolated head tremor,[13] however, 165 (47.1%) cases also had dystonia,[13] and the overlap between the two is not indicated. In a series in Bulgaria, approximately 4 to 5% had isolated head tremor; however, no data on torticollis or mild arm tremor were provided.[14] In each of these studies, individual case data were not presented, so it is not clear whether head tremor occurred with complete absence of arm tremor.

There are few population-based data. In Papua, New Guinea, isolated head tremor occurred in as many as 1 in 10 ET cases (16 of 175, 9.1%).[12] However, these cases had sustained contractions of the "sternomastoid and neck muscles" and head displacement (i.e., "simulated very closely the appearance of ... spasmodic torticollis"), indicating that the diagnosis was likely dystonia rather than ET.[12] In a study in rural Sweden, 3 of 210 (1.4%) cases had isolated head tremor, but none of these three were examined (i.e., examinations were reported by affected relatives).[15] A study in rural Tanzania reported 13 of 65 (20.0%) had isolated head tremor; however, individual case data were not presented and it is not clear whether head tremor occurred with complete absence of mild arm tremor.[17] In the population-based study in New York, we previously reported head tremor in 37 ET cases,[26] but included jaw tremor in our estimate of head tremor and did not report separately the proportion with isolated head tremor.

In the current study, a nearly identical proportion of cases in the two population-based studies had head tremor (18.0% in Turkey and 17.9% in New York), whereas the proportion of ET cases with head tremor in the clinical sample was approximately double that (37.1%). As can be seen from the data in Table 1, this difference is not due to age or gender. Rather, it is likely due to the fact that clinical samples tend to ascertain a more self-selected group of cases with more severe and widespread tremor. Indeed, in some highly self-selected samples, the proportion of cases with head tremor can exceed 60%.[27]

This study had limitations. We did not assess children,[19–21] and one of our samples did not assess cases aged younger than 40 years.[20] A limitation of this study is that data on the severity and direction of tremor were not collected uniformly across studies and were not presented here. However, strengths of this study are the use of both population-based and clinical data. Arm tremor in ET cases was assessed in detail in each study and individual level data were provided, thereby allowing us to both estimate the prevalence of isolated head tremor and examine the effects of using different definitions of arm tremor (e.g., none vs. mild) on this prevalence. Furthermore, patients with neck dystonia were systematically excluded.

In summary, head tremor with mild arm tremor occurred in a very small percentage of ET cases (1.9–3.1%, overall 2.7%), with most of these having mild arm tremor on multiple tests. Nearly all of these were women. However, head tremor in the complete absence of arm tremor was not observed in any of these cases (0.0%). Head tremor in the complete absence of clinically observable arm tremor was not part of the clinical spectrum of ET in these three broadly ascertained ET case samples nor is there compelling support for the presence of such patients in the published ET literature.

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# Positive Family History of Essential Tremor Influences the Motor Phenotype of Parkinson's Disease

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***Abstract:*** **Previous reports have suggested that essential tremor (ET) represents a risk factor for the development of Parkinson's disease (PD). Patients with long-standing ET who develop PD tend to have a tremor-dominant subtype. To further clarify this association, we examined patients from kindreds with autosomal dominant ET who had signs of isolated PD but did not meet criteria for overlapping ET. We identified 22 patients with PD meeting these diagnostic criteria, and 90% (20 of 22) had tremor-predominant subtype of PD. Unilateral rest tremor was the presenting symptom in 15 of 22 patients, bradykinesia or rigidity in 5 of 22, and gait problems in 2 of 22. Postural tremor was relatively mild, and the severity of kinetic tremor tightly correlated with rest tremor ($r = 0.83$, $P < 0.001$). Tremor-dominant subtype of PD in patients with a positive family history of ET suggests that these patients have inherited a genetic susceptibility factor for tremor, which affects the motor phenotype of PD.** © 2009 Movement Disorder Society

**Key words:** Parkinson's disease; essential tremor; genetics; autosomal dominant inheritance

The prevailing opinion about a possible causal relationship between essential tremor (ET) and Parkinson's disease (PD) has recently undergone a significant shift.[1] Previously, their association was primarily attributed to a random coexistence of two common disorders.[2,3] However, several studies reported a higher than expected occurrence of ET and PD.[4–7] This link has been further strengthened by findings of Lewy bodies in brainstem structures of some patients with ET.[8,9]

Patients who present with signs of ET and later developed probable PD usually display the tremor-predominant subtype of PD.[1,10] The possible relationship between ET and PD is

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less certain in patients with probable PD who developed kinetic tremor or have a prominent postural tremor that is distinct from a re-emergent rest tremor.[11] To further clarify the association between ET and PD, we analyzed the motor phenotype in a cohort of patients who met the diagnostic criteria for probable PD but not for ET and whose first degree relatives were affected with ET without any of the other cardinal features of PD. We hypothesized that the presence of a positive family history of ET would affect the degree of tremor in these PD patients, suggesting that genetic susceptibility factors to ET may influence the motor presentation of PD.

## PATIENTS AND METHODS

We recruited 621 individuals, including married-in, who were members of kindreds where at least two individuals met diagnostic criteria for definite ET.[12,13] Each of these pedigrees had to have had evidence of vertical transmission of tremor, consistent with an autosomal dominant (AD) inheritance. Probable PD was diagnosed based on the presence of at least three of the four diagnostic criteria—rest tremor, rigidity, bradykinesia, and asymmetric onset—and the absence of features suggesting an alternative diagnosis, including the absence of dystonic tremor.[14] Furthermore, patients with PD were excluded if they had any history of postural or kinetic tremor preceding the onset of the cardinal parkinsonian features defined above.

Postural and kinetic tremor was quantified using the rating scale from the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET).[15,16] Postural tremor was defined as tremor without delay in its appearance. The onset of a postural tremor after a delay of more than 3 seconds following the assumption of an outstretched posture was considered a re-emergent tremor.[17] We used only WHIGET subscores for postural and kinetic tremor, whereas rest of the tremor was evaluated using the Unified Parkinson's disease rating scale (UPDRS-III); thus, the maximum score for an upper extremity is 23.

UPDRS-III scoring using 0 to 4 scale was used to assess the severity of motor signs.[18] Tremor-predominant subtype of PD was defined as previously described with the ratio of tremor subscore/gait and postural instability subscore greater than or equal to 1.5.[19] The assessments were performed in a practical "off" state, requiring the patient to hold at least two doses of dopaminergic or anticholinergic medications before examination, and in "on" state. Tremor subcores were analyzed using the Spearman rank order correlation test.

## RESULTS

The studied cohort consisted of 543 individuals affected by definite ET or probable PD from 158 kindreds, in which at least two individuals were classified as having definite ET. We identified 22 patients (see Table 1) with probable PD without ET from 21 different ET kindreds. The most common presenting symptom was unilateral rest tremor (15 of 22), followed by bradykinesia or rigidity (5 of 22), and gait problems but without significant postural abnormalities (2 of 22; Table 1). Only two PD patients did not meet the criteria for the tremor-predominant subtype of PD, and their ratio values were 0.41 and 0.83 (Patients 1 and 2, Table 1), respectively. The other PD patients had a tremor-predominant motor phenotype with the ratio values from 1.77 to 3.44 (average 2.45 $\pm$ 0.54). Postural tremor was mostly mild when present. Contrary to this, kinetic tremor varied from a moderate WHIGET score of 9 of 23 on more symptomatic side to severe with the worst score of 19 of 23 on more affected upper extremity. Kinetic tremor was unilateral in four patients and significantly asymmetric with WHIGET score differences between the upper extremities higher than 70% in eight patients. Within individuals, there was a high correlation between the severity of kinetic and rest tremor ($r = 0.83$, $P < 0.001$). There was no significant relationship between the tremor subscores. Patients with tremor-predominant PD also developed additional cardinal signs of PD, and bradykinesia was present in 20 patients, rigidity in 21, gait disturbance in 6, postural instability in 4, and motor fluctuations in 12.

## DISCUSSION

Asymmetric rest tremor, one of the cardinal diagnostic features of PD, is a typical tremor manifestation of patients with idiopathic PD.[14] However, many patients with PD also exhibit significant postural and kinetic tremors, the diagnostic hallmark of ET. One possible explanation for the concurrent tremor phenotypes is an overlap of these two common movement disorders. Familial aggregation of PD and ET has also been demonstrated by several studies, suggesting shared pathophysiologic processes.[1,4,5] Twin studies have shown that two thirds of individuals with postural or kinetic tremor also had PD or a twin with PD. Relatives of patients with PD have double the risk of the general population of having kinetic tremor, especially in families where the PD was considered to be the tremor-predominant subtype.[20]

Patients with PD have significantly a higher chance to also suffer from ET, with the relative risk increased to 5-fold when compared to age-matched control subjects.[7] Similarly, estimates vary from 6% to 19% of patients with a long-standing ET later developing parkinsonism.[4,6] Even though our study was not designed as an epidemiologic survey, the results from our cohort of patients are comparable with those studies, and we found the rate of PD conversion to be 8% in patients with ET (43 of 521) and overall frequency of PD at 12% (64 of 543).

We found tremor-predominant PD in 90% (20 of 22) of our patients who met the criteria for idiopathic PD. This is significantly higher than the expected occurrence of this subtype of PD that typically comprise about one third of all PD patients.[19] Tremor-predominant PD has also been associated with a relatively slower progression and milder deficits from the other aspects of parkinsonism, prompting the suggested designation "benign tremulous parkinsonism."[21–23] However, this collection of patients with a benign course may represent an ascertainment bias because of selection criteria. The patients in our cohort exhibited a more typical progression of PD. It is likely that a subset of patients with significant tremor may indeed show a slower than normal progression of axial symptoms, but it is unlikely to be a universal feature in tremor-predominant PD patients.

The tremor phenotype was recently studied in patients with a previous diagnosis of ET who later developed a hypo-

**TABLE 1.** *Clinical characteristics of analyzed patients with PD from AD ET kindreds*

| | Gender | Age (yr) | Disease duration | Motor Fluctuations* | HY | UPDRS-III total score | | UPDRS-III rest tremor R/L | | WHIGET postural tremor R/L | | WHIGET kinetic tremor R/L | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Off | On | Off | On | Off | On | Off | On |
| 1 | M | 62 | 4 | Y | III | 34 | 17 | 1/1 | 1/1 | 0/0 | 0/0 | 3/0 | 2/0 |
| 2 | M | 66 | 7 | N | II | 10 | 6 | 1/0 | 1/0 | 1/0 | 1/0 | 0/0 | 0/0 |
| 3 | F | 66 | 5 | Y | II | 15 | 7 | 4/3 | 3/2 | 1/0 | 0/0 | 16/4 | 14/2 |
| 4 | M | 55 | 5 | N | II | 13 | 8 | 3/1 | 1/0 | 1/0 | 1/0 | 17/3 | 17/2 |
| 5 | M | 60 | 5 | N | II | 16 | 9 | 1/4 | 0/2 | 0/1 | 0/1 | 0/14 | 0/11 |
| 6 | F | 58 | 3 | N | I | 8 | 5 | 0/3 | 0/2 | 0/0 | 0/0 | 0/10 | 0/10 |
| 7 | M | 67 | 7 | Y | III | 18 | 6 | 4/2 | 3/2 | 1/1 | 0/1 | 9/3 | 6/2 |
| 8 | M | 62 | 5 | Y | II | 19 | 6 | 3/1 | 2/1 | 0/1 | 0/0 | 15/3 | 5/0 |
| 9 | F | 55 | 2 | N | I | 8 | 3 | 0/3 | 0/1 | 0/0 | 0/0 | 0/11 | 0/4 |
| 10 | M | 60 | 8 | Y | III | 29 | 11 | 4/4 | 2/2 | 1/2 | 0/1 | 17/15 | 9/4 |
| 11 | F | 59 | 7 | Y | III | 28 | 7 | 3/4 | 2/2 | 1/1 | 1/1 | 15/19 | 10/16 |
| 12 | F | 58 | 3 | N | I | 9 | 7 | 3/0 | 1/0 | 0/0 | 0/0 | 13/2 | 6/0 |
| 13 | M | 57 | 5 | N | II | 17 | 8 | 2/3 | 0/2 | 1/1 | 1/0 | 5/14 | 2/4 |
| 14 | M | 62 | 5 | Y | II | 22 | 10 | 3/4 | 2/2 | 1/2 | 1/1 | 9/16 | 5/11 |
| 15 | M | 72 | 8 | Y | III | 22 | 12 | 4/3 | 3/2 | 2/2 | 1/1 | 15/10 | 7/4 |
| 16 | M | 66 | 6 | Y | III | 21 | 9 | 2/4 | 1/3 | 1/1 | 0/1 | 6/14 | 4/14 |
| 17 | M | 49 | 3 | Y | II | 15 | 10 | 2/4 | 0/2 | 0/0 | 0/0 | 4/13 | 4/14 |
| 18 | M | 58 | 5 | N | I | 10 | 5 | 0/3 | 0/1 | 0/1 | 0/0 | 0/11 | 0/11 |
| 19 | M | 71 | 6 | Y | II | 14 | 4 | 3/1 | 1/0 | 0/0 | 0/0 | 14/1 | 14/0 |
| 20 | F | 59 | 6 | Y | III | 21 | 6 | 4/3 | 3/1 | 2/1 | 1/1 | 17/13 | 18/8 |
| 21 | F | 63 | 7 | Y | III | 23 | 11 | 3/3 | 1/0 | 1/0 | 0/0 | 15/14 | 8/4 |
| 22 | M | 63 | 6 | N | II | 18 | 9 | 4/2 | 2/1 | 1/1 | 1/1 | 16/11 | 13/6 |

*All motor fluctuations are considered.

HY, Hoehn/Yahr stage; UPDRS-III, unified Parkinson's disease rating scale; WHIGET, Washington Heights-Inwood Genetic Study of Essential Tremor scale; R, right; L, left; M, male; F, female.

kinetic-rigid syndrome consistent with idiopathic PD.[1,10] These patients developed tremor-predominant PD, and a new rest tremor was the heralding symptom of PD in 71% of these patients. Similarly, the tremor-predominant subtype was also noted in a cohort of 55 patients with ET who later developed PD with a mean latency of 14 years.[10]

We approached the question of whether the presence of ET modifies the motor phenotype of PD from a different angle. We examined patients with isolated PD from families with AD ET. The diagnosis of PD was reached only on clinical basis without any assessment of dopaminergic deficit by neuroimaging studies[24]; however, we observed a good response to dopaminergic challenge and the appearance of motor fluctuations in 60% of all patients, further supporting the diagnosis of probable PD. Similar to studies analyzing the transformation of ET to PD, we found tremor-predominant subtype of PD in 90% (20 of 22) of patients whose first-degree relatives have isolated definite ET.[1,10] One possible explanation of these nearly identical findings is that our patients had simply an overlap of both the tremor-causing conditions, and PD was the initial presentation of both movement disorders. This is less likely because there were considerable differences in tremor manifestation from the typical phenotype of ET. Most of the tremor-predominant PD patients had relatively minor postural tremor, which was defined as postural tremor without any delay in its appearance, while advanced ET is typically associated with pronounced postural tremor. Kinetic tremor was unilateral or asymmetric with WHIGET score differences between both upper extremities larger than 70% in 12 patients, and ET tremor is characteristically symmetrical.[25] The side of more-affected extremity highly correlated with severity of rest tremor, whereas no similar correlation was identified for postural tremor. Thus, our patients did not meet formal diagnostic criteria for definitive ET.

Each of these PD patients was from a pedigree with AD ET and, therefore, had *a priori* 50% risk of inheriting ET, assuming a single-gene Mendelian model of ET inheritance. However, this model has been recently questioned, and ET may not be a classic single-gene AD disorder.[26] Thus, one possible explanation is that the patients who developed PD inherited a partial genetic susceptibility factor, which influenced their motor hypokinetic-rigid phenotype. The elucidation of genetic factors causing ET will determine whether this hypothesis is correct. In summary, our data further strengthen the connection of ET and PD, and support the influence of ET risk factors on the motor phenotype of PD.

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