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Sporadic adult onset primary torsion dystonia is a genetic disorder by the temporal discrimination test

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Adult-onset primary torsion dystonia is an autosomal dominant disorder with markedly reduced penetrance; patients with sporadic adult-onset primary torsion dystonia are much more prevalent than familial. The temporal discrimination threshold is the shortest time interval at which two stimuli are detected to be asynchronous and has been shown to be abnormal in adult-onset primary torsion dystonia. The aim was to determine the frequency of abnormal temporal discrimination thresholds in patients with sporadic adult-onset primary torsion dystonia and their first-degree relatives. We hypothesized that abnormal temporal discrimination thresholds in first relatives would be compatible with an autosomal dominant endophenotype. Temporal discrimination thresholds were examined in 61 control subjects (39 subjects <50 years of age; 22 subjects >50 years of age), 32 patients with sporadic adult-onset primary torsion dystonia (cervical dystonia $n = 30$, spasmodic dysphonia $n = 1$ and Meige's syndrome $n = 1$) and 73 unaffected first-degree relatives (36 siblings, 36 offspring and one parent) using visual and tactile stimuli. Z-scores were calculated for all subjects; a $Z > 2.5$ was considered abnormal. Abnormal temporal discrimination thresholds were found in 1/61 (2%) control subjects, 27/32 (84%) patients with adult-onset primary torsion dystonia and 32/73 (44%) unaffected relatives [siblings (20/36; 56%), offspring (11/36; 31%) and one parent]. When two or more relatives were tested in any one family, 22 of 24 families had at least one first-degree relative with an abnormal temporal discrimination threshold. The frequency of abnormal temporal discrimination thresholds in first-degree relatives of patients with sporadic adult-onset primary torsion dystonia is compatible with an autosomal dominant disorder and supports the hypothesis that apparently sporadic adult-onset primary torsion dystonia is genetic in origin.

Keywords: focal dystonia; basal ganglia; temporal discrimination; endophenotype

Abbreviations: AOPTD = adult-onset primary torsion dystonia

Introduction

Adult-onset primary torsion dystonia (AOPTD) is a hyperkinetic movement disorder associated with significant morbidity and the most common form of primary dystonia. Epidemiological studies suggest that, although most cases appear to be sporadic, the disorder is autosomal dominant with a penetrance of 12–15% (Waddy et al., 1991; Stojanovic et al., 1995; Leube et al., 1997).

Although progress in elucidating the presumed genetic basis of AOPTD has been slow, recently DYT6 dystonia, associated with some adult-onset laryngeal phenotypes, has been found to be a due to a mutation in *THAP1* (Fuchs *et al.*, 2009). About 25% of patients with AOPTD have one other family member affected (Stojanovic *et al.*, 1995), but families with sufficient numbers for linkage analysis are infrequent and most gene carriers, even in multiplex AOPTD families, are non-manifesting.

The possibility of success of linkage analysis in poorly penetrant disorders may be increased by the use of an endophenotype (Gotteman and Shields, 1973; Gotteman and Gould, 2003), and a number of potential endophenotypes have been examined in AOPTD including the temporal discrimination threshold (Hallett, 1998; Meunier *et al.*, 2001; Molloy *et al.*, 2003; Fiorio *et al.*, 2003, 2007; O'Dwyer *et al.*, 2005; Walsh *et al.*, 2007; Frima *et al.*, 2008). The temporal discrimination threshold is defined as the shortest time interval at which two stimuli can be determined to be separate in time and has recently been demonstrated to be a potentially useful endophenotype in several forms of dystonia (Fiorio *et al.*, 2003, 2007, 2008a; Scontrini *et al.*, 2009; Bradley *et al.*, 2010). However, an abnormal temporal discrimination threshold is not specific to dystonia, having also been found in other basal ganglia disorders (Artieda *et al.*, 1992; Lee *et al.*, 2005; Lyoo *et al.*, 2007; Fiorio *et al.*, 2008b) and in non-manifesting gene carriers of DYT1 dystonia (Fiorio *et al.*, 2007) and PINK1 parkinsonism (Fiorio *et al.*, 2008b). Autosomal dominant transmission of abnormal temporal discrimination thresholds has been reported in both affected and unaffected members of multiplex AOPTD families (Bradley *et al.*, 2009). We hypothesized that most individuals with sporadic AOPTD have a genetically determined disorder and the absence of other affected family members reflects reduced gene penetrance. In this study, we examined temporal discrimination thresholds in patients with sporadic AOPTD and their first-degree relatives to determine whether temporal discrimination threshold abnormalities are present at rates compatible with a highly penetrant endophenotype. We hypothesized that abnormal temporal discrimination thresholds would be found in most patients with AOPTD and approximately half of their first-degree relatives.

Materials and methods

Subjects

Ethical approval for this work was granted by the Ethics and Medical Research Committee, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

Control participants

Sixty-one healthy control subjects were recruited from hospital staff and visitors to the hospital. Exclusion criteria included: a history of neurological disease including neuropathy; visual disorder or a history of cerebral, cervical or brachial plexus injury; or a family history of dystonia. Control subjects were divided into two groups: <50 years of age (n = 39; mean age 31.8 years; range 21–49) and >50 years of age (n = 22; mean age 58.9 years, range 50–71). This resulted in two control groups, within which there was no correlation between age

and temporal discrimination threshold result, allowing standardized Z-scores to be calculated as described below.

Patients with adult-onset primary torsion dystonia

Thirty-three patients with sporadic AOPTD were recruited for temporal discrimination threshold testing (mean age 57 years, range 42–78) (cervical dystonia n = 31, spasmodic dysphonia n = 1 and Meige's syndrome n = 1). The diagnosis of primary dystonia was made at a dedicated dystonia clinic by two neurologists with expertise in movement disorders.

Unaffected first-degree relatives

Seventy-three unaffected first-degree relatives of the patients with sporadic AOPTD were examined for temporal discrimination threshold (mean age 42 years, range 18–77) (36 siblings, 36 offspring and 1 parent). None of the unaffected relatives had any symptoms or signs of a movement disorder. Relatives were examined by the research registrars (O.K. and D.B.) and had a full medical history and neurological examination including an examination protocol to assess for any evidence of a neurological disorder, in particular a focal dystonia. A video examination of the relatives was not performed.

Sensory testing

Temporal discrimination threshold testing was carried out as described previously (Bradley *et al.*, 2009). Briefly, testing was carried out in a single session in a sound-proof air-conditioned room. For the comparison of temporal discrimination threshold task type, subjects were tested for two modalities: (i) a visual task (two flashing light-emitting diodes); and (ii) a tactile task (non-painful electrical stimulation of the index and middle finger). Stimuli were presented at 5-s intervals and the separation between pairs of stimuli was increased in 5 ms steps. The light-emitting diodes were positioned 7° into the subject's peripheral field on the side being tested. Light-emitting diodes were illuminated for 5 ms on each presentation of the visual stimulus. Electrical stimuli were presented using square-wave stimulators (Lafayette Instruments Europe) and rectangular cloth electrodes (TD-141C1, Discount Disposables). Stimulus pulse length was set at 5 ms and stimulus current was increased (in 0.1 mA steps) until the subject could reliably detect the stimuli. Each task was performed four times on each side of the body with the median of the four trials in each condition (side × task) taken to eliminate practice effect. This resulted in a total of four conditions/16 trials. Thus, values in milliseconds for the visual, tactile and combined visual and tactile temporal discrimination thresholds were determined.

Statistical analysis

All temporal discrimination threshold results (in milliseconds) were converted to standardized Z-scores to enable easy comparison of individual results using the formula:

Z-score = Actual temporal discrimination threshold − age-related control mean temporal discrimination threshold/age-related control standard deviation

For each subject, the Z-score was calculated using the relevant (<50 or >50 years of age) control dataset. Z-scores were determined for each participant's visual, tactile and combined visual and tactile temporal discrimination threshold (three Z-scores). $Z \geqslant 2.5$ were considered abnormal. Comparison of the rates of abnormal temporal

discrimination thresholds between subgroups of relatives was carried out using Fisher's Exact Test (P < 0.05 considered statistically significant).

Results

Control participants

Because of an effect of age on temporal discrimination threshold, control subjects were divided into two groups, <50 and >50 years of age. The results of the visual, tactile and combined temporal discrimination threshold testing are summarized in Table 1. The mean temporal discrimination threshold in the 39 controls <50 years was 24.54 ms [SD 8.97 ms; 95% confidence interval (CI): 21.63–27.44 ms], (mean $Z = 0$, range -1.4 to 2.3). Of the control participants <50 years of age, one subject had an abnormal tactile temporal discrimination threshold ($Z = 3.4$) but normal visual and combined temporal discrimination threshold results. In the 22 control subjects >50 years of age, the mean temporal discrimination threshold was 31.11 ms (SD 8.69 ms; 95% CI: 27.25–34.96 ms), (mean $Z = 0$, range -1.5 to 2.9). In the older group, one control participant's visual temporal discrimination threshold Z-score was 2.9, with a tactile Z-score of 1.71 and a combined threshold of 2.96; this result fell outside the combined temporal discrimination threshold normal range of $Z < 2.5$. All the 39 control participants <50 years of age had combined temporal discrimination threshold $Z < 2.5$ (Fig. 1 and Table 1).

Patients with adult-onset primary torsion dystonia

One of the patients with AOPTD with cervical dystonia was unable to complete the temporal discrimination threshold task because of visual impairment; her relatives were examined. In the other 32 patients with AOPTD, abnormal visual temporal discrimination thresholds were found in 25/32 patients (78%). Only 29 of the 32 patients with AOPTD could complete the tactile temporal discrimination threshold task, three patients found the tactile

test difficult and could not complete it (two of these three had abnormal visual temporal discrimination thresholds); abnormal tactile temporal discrimination thresholds were found in 24/29 patients (83%). Using the combined temporal discrimination threshold, 27 of the 32 patients with AOPTD (84%) had $Z > 2.5$ (Fig. 1, Tables 1 and 2). The results of temporal discrimination threshold testing by task type are given in Table 2. The mean combined temporal discrimination threshold in the 32 patients with AOPTD was 74.35 ms (SD 25.95 ms; 95% CI 64.99–83.70 ms) (mean $Z = 4.94$, range 0.96–13.71). Because of the higher sensitivity of using combined temporal discrimination threshold results (84% abnormal) compared with either the visual (78% abnormal) or the tactile (83% abnormal) task alone, the Z-score of the combined visual and tactile temporal discrimination threshold tasks was used to ascertain the presence of abnormal thresholds in relatives.

Unaffected first-degree relatives

The mean combined temporal discrimination threshold in the 73 unaffected first-degree relatives was 47.04 ms (SD 20.41 ms; 95% CI 42.88–51.80 ms) (mean $Z = 2.35$, range -1.42 to 6.7). Abnormal temporal discrimination threshold results were found in 32/73 (44%) relatives. Only one parent was tested and had an abnormal temporal discrimination threshold, and the other abnormal temporal discrimination thresholds were in siblings [20/36 (56%)] and offspring [11/36 (31%)].

Frequency of abnormal temporal discrimination thresholds in individual families

In the 33 families, the total number of siblings and offspring >18 years of age was 250. We tested 72 (39%) of the 189 siblings/offspring available for testing. The main reason for not testing relatives was distance from the hospital laboratory. In nine families, only one relative was tested (2/9 abnormal temporal

Table 1 The raw mean temporal discrimination threshold results (in milliseconds) with SDs, mean and range of Z-scores and number and percentage abnormal of the visual, tactile and combined temporal discrimination threshold task results for the 61 control subjects divided by age, the 32 patients with AOPTD and 73 unaffected first-degree relatives

Study subjects	TDT task	n	Mean TDT (ms)	SD	Mean Z-score	Range Z-score	Abnormal TDTs n (%)
Controls <50 years	Visual	39	24.49	9.04	0	−1.6 to 1.85	0 (0)
	Tactile	39	24.58	10.44	0	−1.6 to 3.4	1 (2.6)
	Combined	**39**	**24.54**	**8.97**	**0**	**−1.4 to 2.3**	**0 (0)**
Controls >50 years	Visual	22	31.08	9.67	0	−1.6 to 3.3	1 (4.5)
	Tactile	22	31.99	11.83	0	−2.02 to 1.7	0 (0)
	Combined	**22**	**31.11**	**8.69**	**0**	**−1.5 to 2.9**	**1 (4.5)**
Patients with AOPTD	Visual	32	73.16	25.24	3.97	0.75 to 11.53	25 (78)
	Tactile	29	73.05	27.83	5.66	1.0 to 14.69	24 (83)
	Combined	**32**	**74.35**	**25.95**	**4.94**	**0.96 to 13.71**	**27 (84)**
Unaffected first-degree relatives	Visual	73	46.49	19.78	2.05	−1.19 to 6.56	30 (41)
	Tactile	70	47.59	24.80	2.49	−1.84 to 10.43	26 (37)
	Combined	**73**	**47.04**	**20.41**	**2.35**	**−1.42 to 6.7**	**32 (44)**

TDT = temporal discrimination threshold.
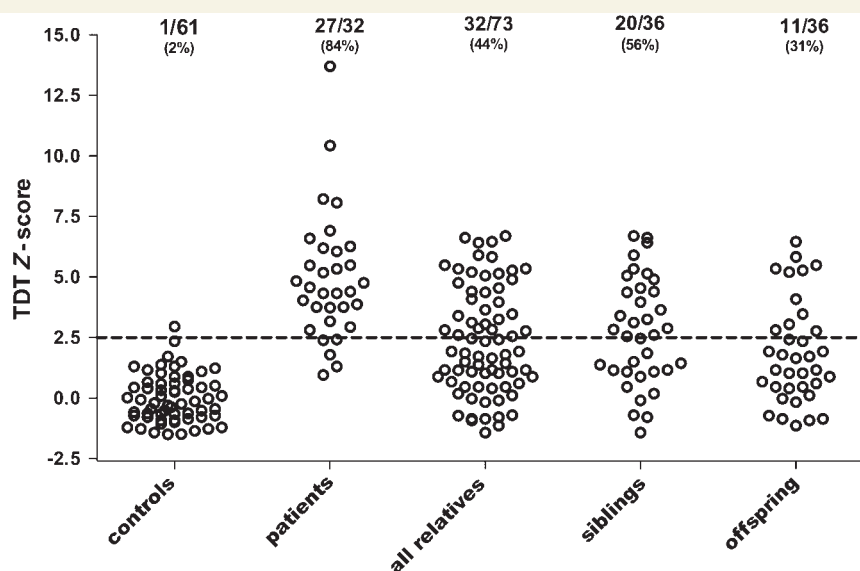
Figure 1 Temporal discrimination threshold Z-scores in 61 healthy control subjects, 32 patients with sporadic AOPTD and 73 unaffected first-degree relatives, with relatives divided by relationship to patients into siblings, offspring to the right of the graph. TDT = temporal discrimination threshold.

Table 2 Temporal discrimination threshold (TDT) results in 32 patients with AOPTD for the visual and tactile tasks

	Visual TDT task		
	Abnormal (combined)	Normal (combined)	Total (combined)
Tactile TDT task			
Abnormal	21 (21)	3 (3)	24 (24)
Normal	2 (1)	3 (0)	5 (1)
Not done	2 (2)	1 (0)	3 (2)
Total	25 (24)	7 (3)	32 (27)

An abnormal temporal discrimination threshold was defined as a $Z \geqslant 2.5$ compared with the age-related control mean. The figures in brackets indicate the number of patients with abnormal combined temporal discrimination threshold results. The combined temporal discrimination threshold had a higher sensitivity than either the visual or the tactile task alone. Because of task difficulty, three patients were unable to perform the tactile test, two of these had abnormal visual temporal discrimination thresholds and one had a normal visual temporal discrimination threshold.

Table 3 Families of patients with sporadic AOPTD divided in relation to the number of asymptomatic first-degree relatives examined by temporal discrimination threshold in each family

Relatives tested in family, n	Families, n	Total relatives tested	Relatives with abnormal TDT, n	Families with no abnormal TDT, n
Three or more relatives tested	9	34	13	0
Two relatives tested	15	30	17	2
One relative tested	9	9	2	7
All families	33	73	32	9

All families had at least one asymptomatic relative with an abnormal temporal discrimination threshold apart from seven of nine families in which only one relative was examined and 2 of 15 families in which two relatives were examined. TDT = temporal discrimination threshold.

discrimination thresholds), in 15 families two relatives were tested (17/30 abnormal temporal discrimination thresholds) and in nine families three or more relatives were tested (13/34 abnormal temporal discrimination thresholds) (Table 3). When two or more relatives were tested, only 2/24 families did not have an unaffected relative with an abnormal temporal discrimination threshold.

Inheritance of the abnormal temporal discrimination threshold endophenotype

Two families illustrative of temporal discrimination threshold transmission in sporadic AOPTD are illustrated in Fig. 2.

The frequencies of abnormal temporal discrimination threshold in patients stratified by gender, relationship and number of relatives examined are displayed in Table 4 and Fig. 3. We examined the pattern of inheritance in the 24 families with at least two unaffected first-degree relatives examined (total of 64 relatives; 30 siblings, 33 offspring, one parent). In those families, there was a significantly higher frequency of abnormal temporal discrimination thresholds in siblings (18/30; 60%) compared with offspring (11/33; 33%) (Fisher's Exact Test $P = 0.0447$) (Fig. 3). In all the 73 unaffected relatives, there was a trend for abnormal temporal discrimination thresholds to be more common with age; the frequency of abnormal thresholds in relatives <45 years was 16/44 (36%) and in relatives >45 years was 16/29 (55%) (Fisher's exact test $P = 0.1496$).
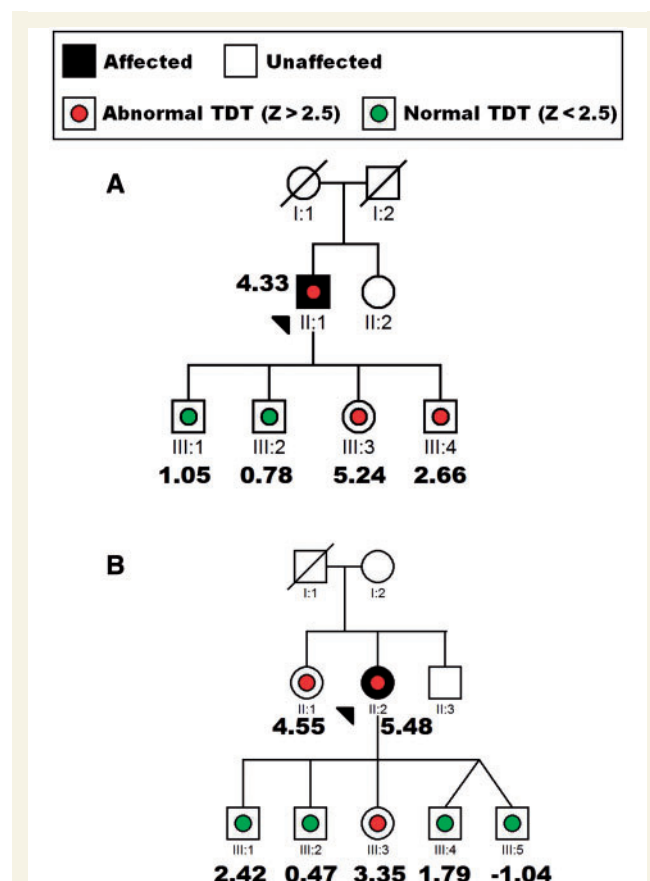
Figure 2 Illustrative family trees of sporadic AOPTD. Temporal discrimination threshold Z-scores are positioned, in bold, beside each family member examined. Clinically affected individuals have filled icons. Individuals tested for temporal discrimination threshold have a central dot; red for abnormal temporal discrimination threshold (Z > 2.5) and green for normal temporal discrimination threshold (Z < 2.5). (**A**) Temporal discrimination thresholds were examined in five family members including the propositus. The proband (II:1), a 63-year-old male had cervical dystonia for 19 years at the time of examination. He had an abnormal temporal discrimination threshold Z-score of 4.33. All four of his asymptomatic offspring were tested for temporal discrimination threshold, two with normal results (Z-scores 1.05 and 0.78) and two with abnormal results (Z-scores 5.24 and 2.66). (**B**) Temporal discrimination thresholds were examined in seven family members including the propositus. The proband (II:2), aged 64 years, had oromandibular dystonia and blepharospasm (Meige's syndrome) present for 12 years at the time of testing. She had an abnormal temporal discrimination threshold with a Z-score of 5.48. Her older female sibling (II:1) and one female offspring (III:3) were asymptomatic with abnormal Z-scores consistent with autosomal dominant transmission of abnormal temporal discrimination thresholds. Four other offspring, all male, all had normal temporal discrimination threshold Z-scores. TDT = temporal discrimination threshold. The black triangles indicate the propositus in each family.

Abnormal temporal discrimination thresholds were found more frequently in female than male siblings and offspring. In families where two or more relatives were assessed, of the 30 siblings examined, 11/17 (65%) females and 7/13 (53%) males had abnormal temporal discrimination thresholds. Of the 33 offspring examined, 7/16 (44%) females and 4/17 (24%) males had abnormal temporal discrimination thresholds. Thus, abnormal temporal discrimination thresholds were found in 18/33 (51%) of female siblings and offspring and 11/30 (33%) of male siblings and offspring (Fisher's exact test P = 0.208) (Fig. 3). There was no effect of gender of the propositus on transmission of abnormal temporal discrimination thresholds. Male parents with AOPTD passed the abnormal temporal discrimination threshold to 5/10 offspring (2/7 males and 2/4 females) while female parents with AOPTD passed an abnormal temporal discrimination threshold to 6/22 children (3/10 males and to 5/12 females) (Fisher's exact test P = 0.415). Five of the patients with sporadic AOPTD had normal temporal discrimination thresholds; two had only one relative tested and both these relatives had normal thresholds. Three of the five patients with AOPTD with normal temporal discrimination thresholds, who had two or more relatives tested, had relatives with abnormal temporal discrimination thresholds (three female siblings, one female offspring and one parent).
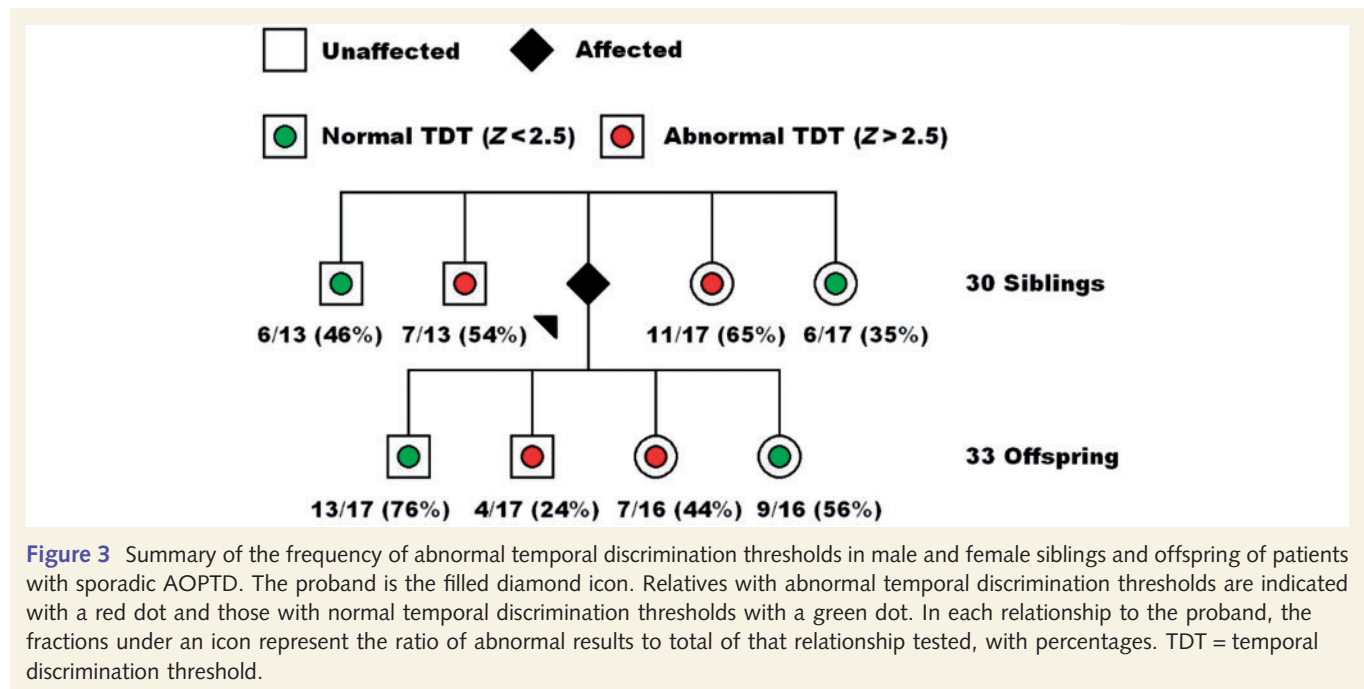
Discussion

We have demonstrated that the temporal discrimination threshold is a relatively sensitive measure of abnormal temporal processing in patients with sporadic AOPTD. The frequencies of abnormal temporal discrimination thresholds in patients (84%) and their first-degree relatives (44%) are consistent with an autosomal dominant endophenotype. When there was relatively complete temporal discrimination threshold assessment of the majority of the members of any one family, there was evident autosomal dominant transmission of the abnormal threshold (Fig. 2), similar to that found in familial AOPTD (Bradley *et al.*, 2009). We thus propose that the presence of an abnormal temporal discrimination threshold in unaffected relatives of patients with AOPTD, both sporadic and familial, is a marker of gene carriage. In support of this, we had previously noted an abnormal temporal discrimination threshold in an unaffected obligate heterozygote in familial AOPTD (Bradley *et al.*, 2009). Further support for the proposition comes from the evidence of abnormal temporal discrimination thresholds in both affected and unaffected gene carriers of PINK1 (Fiorio *et al.*, 2008b) and DYT1 (Fiorio *et al.*, 2007). In order to prove that an abnormal temporal discrimination threshold indicates an asymptomatic heterozygote, in the absence of gene identification, it would be necessary to demonstrate that an asymptomatic relative with an abnormal temporal discrimination threshold subsequently developed AOPTD. Given the low penetrance of the phenotype, this is an unlikely event.

In comparison with the spatial discrimination threshold, which we previously examined in sporadic AOPTD, abnormal temporal discrimination thresholds are significantly more frequent than abnormal spatial discrimination thresholds in patients (temporal: 86% versus spatial: 25%) and first-degree relatives (temporal: 44% versus spatial: 25%) (Bradley *et al.*, 2010). While temporal discrimination threshold is a sensitive endophenotype, it is imperfect in that it was abnormal in only 84% of this group of affected patients; in other AOPTD cohorts, we found a higher rate

Table 4 The number and per cent of abnormal temporal discrimination threshold tests in all of the control participants, patients with sporadic AOPTD and their first-degree relatives by gender and relationship in the study

Group	Control subjects	Patients with AOPTD			First-degree relatives				
		All	Male	Female	All	Male	Female	Siblings	Offspring
Number tested	61	32	12	20	73	34	39	36	36
Number abnormal TDTs	1	27	10	17	32	12	20	20	11
% abnormal	2	84	83	85	44	35	51	56	31

TDT = temporal discrimination threshold.

Figure 3 Summary of the frequency of abnormal temporal discrimination thresholds in male and female siblings and offspring of patients with sporadic AOPTD. The proband is the filled diamond icon. Relatives with abnormal temporal discrimination thresholds are indicated with a red dot and those with normal temporal discrimination thresholds with a green dot. In each relationship to the proband, the fractions under an icon represent the ratio of abnormal results to total of that relationship tested, with percentages. TDT = temporal discrimination threshold.

(97%) of abnormal temporal discrimination thresholds in cervical dystonia (Bradley et al., 2011). Also specificity is <100%, with an abnormal combined temporal discrimination threshold ($Z = 2.96$) found in 1 (2%) of our 61 control participants who was 64 years of age. Abnormal temporal discrimination thresholds are found in parkinsonism and when studying temporal discrimination thresholds in subjects >60 years of age, there is the risk of detecting a subclinical basal ganglia disorder, an endophenocopy. In order to ensure 100% specificity, it might be better to confine temporal discrimination threshold testing as a marker of gene carriage to individuals <50 years of age.

Our findings are in keeping with the hypothesis that most, if not all, patients with sporadic AOPTD are the only manifesting individuals of an autosomal dominant disorder, because of the low penetrance of the gene or genes causing AOPTD. In this study, 22 of the 24 families in which two or more family members were examined by temporal discrimination threshold had at least one unaffected family member with an abnormal threshold. The only families in which there was no relative with an abnormal temporal discrimination threshold were seven of the nine in which only one first-degree relative was examined and 2 of 15 in which two

relatives were tested. As a result of the low penetrance of the gene(s) causing AOPTD, one reason for sporadic AOPTD presentation may be a relatively lower number of first-degree relatives in sporadic than in familial AOPTD patients; this needs to be examined further. In addition, the ages of siblings and children may be a factor in a disorder that does not become manifest until the fourth decade or later (O'Riordan et al., 2004).

In this study, although not reaching statistical significance, there is evidence of a trend in the difference of the prevalence of abnormal temporal discrimination thresholds in unaffected first-degree relatives between males and females and also in the frequency of abnormal temporal discrimination thresholds with age. Cervical dystonia is more common in females than males (Leube et al., 1997) and this gender effect in the penetrance of the phenotype may also affect the endophenotype, an abnormal temporal discrimination threshold. Similarly in relation to age, the mean age of onset of cervical dystonia is 41 years (O'Riordan et al., 2004) and there was a trend for greater prevalence of abnormal temporal discrimination thresholds with age; abnormal temporal discrimination thresholds were found in 55% of those >45 years of age and in 36% of those <45 years of age.

Defazio *et al.* (2006) have examined the feasibility of using affected sib-pair analysis to search for dystonia genes; because of low penetrance, the resources of a cooperative international study using multiple dystonia cohorts would be needed (Defazio *et al.*, 2006). However, such a study using patients with sporadic AOPTD and unaffected siblings, <50 years of age, with abnormal temporal discrimination thresholds would be possible in one centre.

Normal temporal discrimination, as determined by the temporal discrimination threshold, is a reflection of effective putaminal processing of sensory stimuli. In one functional MRI study, subjects were tested with both auditory stimuli, separated by intervals of from 1 to 20 ms, and tactile stimuli to the left forearm, separated by intervals of from 5 to 110 ms. When subjects were perceptually certain that the stimuli were either single or double, there was activation in the right putamen, at different sites, for auditory and tactile stimuli (Pastor *et al.*, 2008). The authors concluded that the putamen has a central role in the automatic processing of temporally distinct stimuli. Temporal discrimination in the normal putamen occurs with remarkable definition; individuals can process and recognize tactile and visual stimuli separated by <1/20 of a second. Such accuracy mediated by subcortical–basal ganglia circuits may be of evolutionary significance alerting the individual to environmental stimuli of potential danger (Redgrave *et al.*, 2010). Abnormal temporal discrimination may be a marker of disrupted putaminal function, whether primary or secondary to disordered cortical input (Tamura *et al.*, 2008). Given the presence of abnormal temporal discrimination in Parkinsonism and its improvement with dopamine supplementation (Malapani *et al.*, 1998), a mechanism involving a disorder of dopaminergic transmission seems probable. Abnormal temporal discrimination thresholds in AOPTD, DYT1 dystonia, multiple system atrophy, Parkinson's disease and PINK1 parkinsonism may reflect an abnormality in dopamine transmission at differing points of the nigrostriatal–pallidal–thalamic pathway. Abnormal temporal discrimination in non-penetrant AOPTD family members represents a primary subclinical trait which may require other factors, including possibly age and gender, to become clinically manifest as AOPTD.

Conclusion

Abnormal temporal discrimination thresholds in patients with sporadic AOPTD and their unaffected first-degree relatives are compatible with an autosomal dominant endophenotype. Most patients with AOPTD have a genetic cause with sporadic cases representing the only manifesting carrier in that family. The temporal discrimination threshold appears to be a sensitive marker in both manifesting and non-manifesting AOPTD gene carriers and therefore of use in genetic studies of this disorder.

Funding

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