Temporal Discrimination Threshold: VBM evidence for an endophenotype in adult onset primary torsion dystonia

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Familial adult-onset primary torsion dystonia is an autosomal dominant disorder with markedly reduced penetrance. Most adult-onset primary torsion dystonia patients are sporadic cases. Disordered sensory processing is found in adult-onset primary torsion dystonia patients; if also present in their unaffected relatives this abnormality may indicate non-manifesting gene carriage. Temporal discrimination thresholds (TDTs) are abnormal in adult-onset primary torsion dystonia, but their utility as a possible endophenotype has not been examined. We examined 35 adult-onset primary torsion dystonia patients (17 familial, 18 sporadic), 42 unaffected first-degree relatives of both familial and sporadic adult-onset primary torsion dystonia patients, 32 unaffected second-degree relatives of familial adult-onset primary torsion dystonia (AOPTD) patients and 43 control subjects. TDT was measured using visual and tactile stimuli. In 33 unaffected relatives, voxel-based morphometry was used to compare putaminal volumes between relatives with abnormal and normal TDTs. The mean TDT in 26 control subjects under 50 years of age was 22.85 ms (SD 8.00; 95% CI: 19.62–26.09 ms). The mean TDT in 17 control subjects over 50 years was 30.87 ms (SD 5.48; 95% CI: 28.05–33.69 ms). The upper limit of normal, defined as control mean + 2.5 SD, was 42.86 ms in the under 50 years group and 44.58 ms in the over 50 years group. Thirty out of thirty-five (86%) AOPTD patients had abnormal TDTs with similar frequencies of abnormalities in sporadic and familial patients. Twenty-two out of forty-two (52%) unaffected first-degree relatives had abnormal TDTs with similar frequencies in relatives of sporadic and familial AOPTD patients, 32 unaffected second-degree relatives of familial adult-onset primary torsion dystonia (AOPTD) patients and 43 control subjects. TDT was measured using visual and tactile stimuli. In 33 unaffected relatives, voxel-based morphometry was used to compare putaminal volumes between relatives with abnormal and normal TDTs. The mean TDT in 26 control subjects under 50 years of age was 22.85 ms (SD 8.00; 95% CI: 19.62–26.09 ms). The mean TDT in 17 control subjects over 50 years was 30.87 ms (SD 5.48; 95% CI: 28.05–33.69 ms). The upper limit of normal, defined as control mean + 2.5 SD, was 42.86 ms in the under 50 years group and 44.58 ms in the over 50 years group. Thirty out of thirty-five (86%) AOPTD patients had abnormal TDTs with similar frequencies of abnormalities in sporadic and familial patients. Twenty-two out of forty-two (52%) unaffected first-degree relatives had abnormal TDTs with similar frequencies in relatives of sporadic and familial AOPTD patients. Abnormal TDTs were found in 16/32 (50%) of second-degree relatives. Voxel-based morphometry analysis comparing 13 unaffected relatives with abnormal TDTs and 20 with normal TDTs demonstrated a bilateral increase in putaminal grey matter in unaffected relatives with abnormal TDTs. The prevalence of abnormal TDTs in sporadic and familial AOPTD patients and their first-degree relatives follows the rules for a useful endophenotype. A structural correlate of abnormal TDTs in unaffected first-degree relatives was demonstrated using voxel-based morphometry. Voxel-based morphometry findings indicate that putaminal enlargement in AOPTD is a primary phenomenon. TDTs may be an effective tool in AOPTD research with particular relevance to genetic studies of the disorder.
Keywords: dystonia; endophenotype; temporal discrimination; voxel-based morphometry; putamen

Abbreviations: AOPTD = Adult-onset primary torsion dystonia; SDT = spatial discrimination threshold; TDT = temporal discrimination threshold

Introduction

Adult-onset primary torsion dystonia (AOPTD) is the most common form of dystonia; most patients appear to have sporadic AOPTD but up to 25% of these have another affected family member (Stojanovic et al., 1995; Leube et al., 1997). Familial AOPTD is inherited in an autosomal dominant fashion with a penetrance as low as 12%–15% (Waddy et al., 1991); the paucity of multiplex AOPTD families makes genetic study of the disorder difficult. The use of a sensitive endophenotype, a marker of subclinical gene carriage in unaffected relatives, is one approach to this problem.

Significant sensory processing abnormalities are found in AOPTD patients including abnormalities in spatial discrimination threshold (SDT), temporal discrimination threshold (TDT) and vibration induced illusion of movement (VIIM) (Hallett, 1998; Meunier et al., 2001; Fiorio et al., 2003, 2007; Molloy et al., 2003; O’Dwyer et al., 2005; Walsh et al., 2007; Frima et al., 2008). These sensory abnormalities may be of utility as endophenotypes. In addition, it has been proposed that abnormal sensory processing may play a primary phenomenon in AOPTD, and may play a role in the pathogenesis of AOPTD (Hallett, 1995; Tinazzi et al., 2003).

SDTs are abnormal in some unaffected relatives of AOPTD patients (O’Dwyer et al., 2005; Walsh et al., 2007) and have been investigated as an endophenotype. However, the prevalence of abnormal SDTs in AOPTD patients is low and a more sensitive marker of gene carriage is needed which might significantly aid genetic research.

The TDT is the shortest time interval at which a subject can detect that two stimuli are asynchronous; TDT testing is psycho-physiological task that is relatively easy to administer with the advantage of showing significantly less age-dependence than other candidate sensory tests in AOPTD such as SDTs (O’Dwyer et al., 2005; Walsh et al., 2007). One study by Hoshiyama and colleagues, for example, showed little effect of age on TDT up to 65 years (Hoshiyama et al., 2004). The TDT has been shown to be abnormal in DYT1 patients and non-manifesting DYT1 carriers compared with non-carrier relatives or controls (Fiorio et al., 2007). The TDT has also been shown to be abnormal in patients with writer’s cramp (Fiorio et al., 2003), blepharospasm (Fiorio et al., 2008), Parkinson’s disease (Artieda et al., 1992; Lee et al., 2005) and multiple system atrophy (Lyoo et al., 2007) and therefore may be a sensitive marker of abnormal sensory integration in the basal ganglia. An early study of temporal discrimination in subjects with focal cerebral lesions found that TDT was increased without evident sensory loss in lesions involving the putamen (Lacruz et al., 1991). fMRI studies of both spatial and temporal discrimination tasks evoked basal ganglia activation (Pastor et al., 2004), and during an auditory temporal discrimination task activation in the basal ganglia occurred early and was uniquely associated with encoding time intervals (Rao et al., 2001). Pastor and colleagues suggested that disorders affecting the basal ganglia would affect both spatial and temporal discrimination (Pastor et al., 2004).

All these studies suggest that TDT may function as an endophenotype in AOPTD by identifying subclinical basal ganglia dysfunction; however, this has not been investigated by examining both AOPTD patients and their unaffected relatives. The findings that TDT abnormalities act as a marker of non-penetrant gene carriage in unaffected relatives would be useful in performing genetic studies of the disorder. The aim of this study was to investigate the potential use of TDT as an endophenotype by measuring the prevalence of TDT abnormalities in familial and sporadic AOPTD patients, their unaffected relatives and healthy control subjects. We hypothesized that an abnormal TDT in clinically unaffected relatives of AOPTD patients is a marker of subclinical gene carriage. We further sought to validate the candidate endophenotype (TDT) by demonstrating a structural correlate associated with abnormal TDTs in unaffected relatives using voxel-based morphometry. We hypothesized that a difference in putaminal volume would be found between unaffected relatives with abnormal TDTs compared with those with normal TDTs.

Patients and Methods

TDT testing

AOPTD patients

Thirty-five AOPTD patients (17 familial, 18 sporadic) (mean age 53; range 35–73) with focal dystonia (20 cervical dystonia, 13 focal hand dystonia, one spasmodic dysphonia, one musician’s dystonia) were recruited from our cohort at St Vincent’s University Hospital. The clinical diagnosis of these patients was assessed using a videotaped neurological examination reviewed by two neurologists with expertise in dystonia. The majority of the familial patients came from six multiplex families; the index cases of these families were DYT1 negative. The remaining patients did not have routine DYT1 screening in keeping with guidelines (Bressman et al., 2000; Albanese et al., 2006) as all had onset after the age of 26 years with no family history of early-onset dystonia. Eighteen of the thirty-five patients were receiving regular botulinum toxin injections for their dystonia. The mean (SD) time since last injection in these 18 individuals was 8.2 (14.2) weeks.

Unaffected relatives

Forty-two first-degree relatives (26 of familial cases, 16 of sporadic cases) and 32 second-degree relatives (all of familial cases) were recruited (mean age 42 years; range 19–76). All were examined clinically using a protocol for evidence of dystonia; none had any evidence of dystonia or dystonic tremor.
Control participants
From hospital staff and visitors to the hospital, 43 healthy control subjects were recruited. These were divided into two groups; under 50 years of age (n = 26; mean age 31 years; range 22–49) and over 50 years (n = 17; mean age 58 years, range 50–71). Exclusion criteria were a history of neurological disease including neuropathy, visual disorder or a history of cerebral, cervical or brachial plexus injury.

All subjects had normal cognition, normal visual acuity, absence of sensory symptoms and a normal sensory examination.

Sensory testing
TDTs were examined in a single session in a sound proof, air-conditioned room. TDTs were measured for three tasks: (i) visual—visual: two LED lights were used, horizontally orientated and placed on the table in front of the subject. The lights were seven degrees into the subject’s peripheral vision on the side of the body being tested; (ii) tactile–tactile: non-painful, above-threshold electrical stimulation was used on the second and third fingers on the side of the body being tested using square-wave stimulators (Lafayette Instruments Europe, LE12 7XT, UK). Stimulus current was progressively increased from zero in 0.1 mA steps to the lowest point at which the subject could reliably detect the impulse (tested using a paradigm with 10 trials of randomly assigned real or sham impulses requiring a response from the subject). Equality of stimulus intensity was then established between the digits if necessary. The stimulus current required ranged between 2 and 4.5 mA; and (iii) visual–tactile: a combination of one LED light and stimulation of one finger on the same side was used with the same equipment. Each of the three tasks were performed four times on each side of the body in random order, resulting in a total of 24 runs per subject. Task order was randomized to minimize practice or attention effect. Pairs of stimuli were synchronized initially and were progressively separated in 5 ms steps. When the subject reported that the pairs of stimuli were asynchronous on one side, the test was continued with the other side.

The median of the four runs for each of the six conditions (3 tasks × 2 sides) was used for each subject to allow for practice effect and these six results were averaged to obtain a summary (combined) TDT score. Results of the combined TDT (in ms) are shown with their standard deviations (SD) and 95% confidence intervals (CI).

Analysis
Using the formula:

\[ Z = \frac{\text{Actual TDT} - \text{Age-related control mean TDT}}{\text{Age-related control standard deviation}} \]

Z-scores of ≥ 2.5 were considered abnormal.

Voxel-based morphometry
Patients and methods
Structural MRI was acquired in 33 relatives (13 first-degree sporadic relatives, 11 first-degree familial relatives, 9 second-degree familial relatives, 11 first-degree familial relatives, 9 second-degree familial relatives). All MRI scans were obtained at 1.5T on the same scanner (Siemens Avanto, Erlangen, Germany). A high-resolution three-dimensional T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence was acquired (TR = 1160 ms; TE = 4.21 ms, TI = 600 ms, flip angle = 15°) with a sagittal orientation, a 256 × 256 matrix size and 0.9 mm isotropic voxels.

Analysis
Statistical parametric mapping software (SPM5; Wellcome Centre for Neuroimaging, London, UK), running under Matlab 7 (Mathworks, Sherborn, MA, USA), was used to pre-process and analyse the data. Pre-processing incorporated image registration and classification into a single generative model (Ashburner and Friston, 2005). Segmented grey matter data were modulated in order to preserve volume. The spatially normalized and modulated grey matter partitions were smoothed using a 12mm full-width at half maximum Gaussian kernel allowing parametric statistical analysis. Total grey matter volume, age and sex were entered as nuisance covariates in all analyses. Analyses were restricted to a predefined region of interest—the putamen—using anatomically defined masks (Wake Forest University PickAtlas) (Maldjian et al., 2003). This software employs SPM5’s small volume correction feature, reducing the number of multiple comparisons. Type I errors were controlled using false discovery rate (FDR) of 0.05, which controls the expected proportion of false positives among supra-threshold voxels for each analysis performed (Genovese et al., 2002). The locations of significant voxels were summarized by their local maxima separated by at least 8 mm, and by converting the maxima coordinates from MNI to Talairach coordinate space. These coordinates were assigned neuroanatomic labels using the Talairach Daemon brain atlas (Lancaster et al., 2000).

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

Results
TDTs
Control subjects
There was a statistically significant effect of age on the combined TDT score. Control subjects were divided into two groups under 50 years (n = 26; mean 31 years; range 22–49) and over 50 years (n = 17; mean 58 years, range 50–71) to allow age-related normal values to be calculated. The mean TDT in the under 50 control group was 22.85 ms (SD 8.00; 95% CI: 19.62–26.09 ms). The mean TDT in the over-50 control group was 30.87 ms (SD 5.48; 95% CI: 28.05–33.69 ms). The upper limit of normal, defined as control mean + 2.5 SD, was 42.86 ms in the under 50 group and 44.58 ms in the over 50 group. All of the control subjects’ Z-scores were < 2.5 (range –2.21 to +1.76).

AOPTD patients
Thirty out of thirty-five (86%) AOPTD patients had abnormal TDTs compared with controls; the frequency of abnormalities was similar in sporadic (16/18; 89%) and familial (14/17; 82%) patients (Fisher’s exact test; P = 0.658). There was also a similar frequency of abnormalities when comparing cervical dystonia (19/20; 95%) and focal hand dystonia (10/13; 77%) patients.
In the 18 patients treated with botulinum toxin, there was no statistical correlation between TDT and time since last botulinum toxin injection.

Unaffected relatives

The frequency of TDT abnormalities amongst the first-degree relatives was 52% (22/42); the frequencies in familial relatives (15/26; 57%) and sporadic relatives (7/16; 44%) were similar (Fisher’s exact test; \( P = 0.527 \)). Sixteen of thirty-two second-degree relatives had abnormal TDTs (Figs 1 and 2, Table 1).

Group differences

The mean TDT in the patient group was 70.32 ms (SD 26.87; 95% CI: 61.09–79.55 ms) and in the relatives group was 52.29 ms (SD 24.15; 95% CI: 46.69–57.88 ms). The TDTs in AOPTD patients, unaffected relatives and control subjects were statistically significantly different [one-way non-parametric ANOVA \( P < 0.0001 \); post hoc comparisons using Tukey 99% simultaneous confidence intervals showed that all three groups (patients, relatives and controls) were statistically different from each other]. When analysed as a within-subject factor, side of body was non-significant.

Individual tasks

The combined TDT results in Figs 1 and 2 and Table 1 present the mean of the measurements for the three individual tasks (visual, tactile and mixed). When analysed as a within-subject factor in the control group, task type was not significant \( F(2,84) = 2.242; \ P = 0.095 \). The combined TDT was chosen to assign TDT status as a mechanism of increasing sensitivity as it uses all of the available temporal discrimination data for each subject. However, task type was a significant within-subject factor in the patient \( F(2,64) = 5.460; \ P = 0.006 \) and relative \( F(2,144) = 18.105; \ P < 0.0001 \) groups. In keeping with similar studies (Fiorio et al., 2007, 2008), the visual task had the lowest TDT followed by the tactile and then the mixed task. Concordance (all three individual task results in a particular subject being <2.5 SD ‘normal’ or \( >2.5 \) SD ‘abnormal’) was not 100%. In using the combined TDT score, some subjects who did not reach the 2.5 SD threshold for abnormality in one task were still assigned abnormal status because the combined result for the three tasks exceeded the cutoff (i.e. some subjects categorized as having an abnormal combined TDT had a Z-score <2.5 for one of the three tasks).
and willing to undergo TDT measurement for the present study. The three remaining familial AOPTD subjects had only one other family member affected. All of the familial unaffected relatives of AOPTD patients (26 first degree and 32 second degree) belonged to the six multiplex families; 15 of 26 unaffected first-degree relatives and 16 of 32 second-degree relatives had abnormal TDTs.

Three of the family trees with the TDT Z-scores for each family member examined are illustrated (Fig. 4A–C). It is noteworthy that in pedigree 006 (Fig. 4C) one family member (II:2) was clinically unaffected, but was regarded as an obligate carrier due to having an affected child (III:8) and an affected sibling (II:6), this obligate carrier had an abnormal TDT (Z = 9.4). Two individuals in pedigree 008 (IV:3 and IV:4) and two in pedigree 006 (II:3 and III:5) who were clinically unaffected with affected siblings were considered obligate endophenotype carriers as some of their clinically unaffected offspring had abnormal TDTs; these obligate endophenotype carriers also had abnormal TDTs.

Using TDT testing in 72 individuals in the six families, 29 had normal TDT Z-scores, one of whom had spasmodic dysphonia and 43 abnormal TDT Z-scores were identified in 12 affected individuals, one obligate carrier and 30 other unaffected relatives (14 first-degree and 16 second-degree). Thus in these six families using TDT as an endophenotype, we were able to identify more than twice as many endophenotype carriers as clinically manifesting individuals. No individual who had a normal TDT was found to have an offspring with an abnormal TDT.

### Voxel-based morphometry study

Of the 33 unaffected relatives of AOPTD patients who had MRI scanning, 13 had an abnormal TDT (Z-score > 2.5) and 20 had normal TDTs (Z-score < 2.5). The mean age in of the abnormal TDT group was 41.7 years and the mean age in the normal TDT group was 38.1 years. The age difference between the groups was not statistically significantly different \([t (21) = 1.11, P > 0.05]\). The mean TDT Z-score of the normal TDT group was 0.51 (range – 1.83 to 2.40) and the mean TDT Z-score of the abnormal TDT group was 5.9 (range 3.39–12.68). Results are reported with Z-value, 5% FDR P-value and Talairach x, y, z coordinates in parentheses. Relatives with abnormal TDTs had significantly greater putaminal grey matter volume compared with relatives with normal TDT in the left putamen \((Z = 3.75, P_{FDR} = 0.016, x = -26, y = 14, z = 2)\) and right putamen \((Z = 3.00, P_{FDR} = 0.021, x = 24, y = 16, z = -4)\), (Fig. 3).

### Discussion

In this study, we have found abnormal TDTs in 86% of patients with AOPTD with similar frequencies in sporadic (16/18; 89%) and familial (14/17; 82%) patients. In addition, 52% of unaffected first-degree relatives of AOPTD patients (familial relatives 15/26; 57% and sporadic relatives 7/16; 44%) had abnormal TDTs. Unaffected relatives with abnormal TDTs were found to have increased putaminal volume when compared with relatives with normal TDTs. An ideal endophenotype for an autosomal
dominant disorder should be abnormal in 100% of affected individuals, 50% of first-degree relatives and in no control subjects; the frequency of abnormal TDTs in this study are in line with these values. TDT scores of the control subjects were closely grouped around the mean of 22.85 ms (SD 8.00 ms) under 50 years and 30.87 ms (SD 5.48 ms) over 50 years and no control subject had a TDT Z-score > 2.5; thus the occurrence of TDT Z-scores > 2.5 in the AOPTD patients and relatives can be regarded as reliably abnormal.

The concordance among the three individual TDT tasks was lower in AOPTD patients (76%) and unaffected relatives (77%) than in control subjects, who had 100% concordance. There was a higher frequency of abnormal results using the combined TDT compared with any individual task. Using the combined TDT, abnormal status was assigned in some subjects with abnormalities in two TDT tasks when the third TDT task was normal. For example, 52% of the group of first-degree relatives had abnormal status using combined TDT, while the proportions who had an abnormal visual and tactile TDT were 50 and 45%, respectively. In considering the use of TDT as a practical endophenotype, it is interesting to note that the frequencies of abnormalities in Cervical Dystonia and Writer’s Cramp (Table 2) were not significantly different. This suggests that the usefulness of TDT task type does not vary between phenotypes—a finding consistent with TDT being a state-independent endophenotype. In addition, the lower sensitivity of the mixed TDT task (Table 2) suggests that it could be omitted in order to produce a simpler experimental design for application as an endophenotype. Our TDT values in the healthy control subjects are in keeping with other published work; Hoshiyma and colleagues (2004) described a study of TDTs in 80 healthy volunteers and reported a mean TDT of 26.1 ms at the index finger. Tinazzi and colleagues (1999) reported a control TDT of 35.48 ms in a study of idiopathic dystonia. The mean TDT in our control subjects was lower than the range of 58–68 ms reported by Fiorio and colleagues (2003, 2007, 2008). There are some methodological differences in that we chose the median for each task-side combination to attenuate practice effects and recorded at 5 ms steps in our protocol. The protocol used to measure TDT is a major determinant of performance. For example, an auditory task generally results in better performance (Grondin et al., 2004). Using a more sophisticated technique, Giersch et al. (2008) described recording of TDTs using visual stimuli with and without distracters or priming. They found that without distracters, the mean TDT amongst controls was ~25 ms while with distracters (additional lights) or primers (pre-judgement presentation of lights), the mean amongst controls rose to between 50 and 70 ms. Therefore, the results of studies using different protocols or equipment are not directly comparable and thresholds are only precisely applicable within each individual experimental paradigm.

Our novel findings of bilaterally increased putaminal volume when comparing asymptomatic relatives with abnormal TDTs to those with normal values further supports and validates the endophenotype. Increased putaminal volume is a consistent
finding associated with manifesting AOPTD patients including those with idiopathic blepharospasm (Etgen et al., 2006), focal hand dystonia and cranial dystonia (Black et al., 1998). We have, therefore, demonstrated a disease-associated phenomenon in individuals with the candidate endophenotype. An fMRI study of temporal processing of an auditory task showed that initial activation occurs in the striatum, particularly the putamen, followed later by more diffuse activation (Rao et al., 2001), lending support to the hypothesis that the basal ganglia, and possibly dopaminergic pathways in particular (Malapani et al., 1998), act as a basic time processor in the CNS. Further fMRI studies have confirmed the central role of the putamen in temporal processing and have found activation lateralized to the right hand side (Nenadic et al., 2003; Pastor et al., 2008). Interestingly, Pastor et al. (2008) also demonstrated that activation in the putamen decreases with perceptual difficulty suggesting it is primarily involved in automatic perception of time. We postulate, therefore, that a disorder of sensory integration in the basal ganglia involving the putamen in particular is the patho-physiological basis of abnormal temporal discrimination in these individuals.

There are many outstanding questions relating to the multitude of abnormal experimental findings in AOPTD and whether these represent primary phenomena or secondary features of disease manifestation (Breakefield et al., 2008). Our novel demonstration of increased putaminal volume in asymptomatic relatives with abnormal temporal processing is helpful in this regard. This finding suggests that putaminal enlargement is a primary phenomenon in AOPTD gene carriers and is associated with abnormal temporal processing in contrast to the suggestion that putaminal enlargement in AOPTD is secondary to abnormal dystonic motor activity (Etgen et al., 2006). Further studies using TDTs in AOPTD asymptomatic relatives may prove useful in defining the primary and secondary features of AOPTD. These studies could utilize fMRI or PET to measure functional processing and diffusion tensor imaging (DTI) to examine dynamic pathways.

The mean age of the relatives with abnormal TDTs was 3.7 years older than the relatives with normal TDT, a non-significant difference. The greater putaminal volume found in the abnormal TDT relatives group cannot be attributed to this difference for two reasons: age was included as a nuisance variable in the voxel-based morphometry analysis and the human putamen has an annual rate of shrinkage of 0.73% (Raz et al., 2003).

Support for the concept that an abnormal TDT represents an endophenotype comes from study of DYT1 families in which non-manifesting carriers of the gene had abnormal TDTs whereas the non-carrier relatives had normal TDT (Fiorio et al., 2007). Thus sensory abnormalities as an endophenotype can be present in carriers of a dystonia gene without clinical manifestation of the disorder. In our study, the similar frequencies of TDT abnormalities in unaffected relatives of both sporadic and familial AOPTD patients, suggest that apparently sporadic AOPTD patients are the only manifesting carrier of poorly penetrant familial AOPTD. The finding that an obligate carrier examined by TDT had an abnormal Z-score is strong supportive evidence that an abnormal TDT represents an endophenotype. Autosomal dominant transmission of abnormal TDTs was demonstrated in the multiplex

Figure 4 Examples of the TDT testing in three of the six familial AOPTD pedigrees. Affected individuals are represented by filled icons and obligate carriers by half-filled icons. All individuals tested for TDT have a coloured central dot (green = normal TDT, Z < 2.5; red = abnormal TDT, Z > 2.5) with individual TDT Z-scores shown. Subjects who have been examined clinically (some of whom were not available for TDT testing) have a horizontal line above their icon. (A) In a sub-pedigree of pedigree 008, the autosomal dominant transmission of the endophenotype is illustrated; IV:3 and IV:4 have abnormal TDTs and have transmitted the TDT endophenotype to their children V:5, V:7 and V:8- V:11, V:13. (B) In pedigree 010, the usefulness of TDT is illustrated. In addition to the four clinically affected individuals (II:3, II:5, II:6:13), five unaffected relatives with abnormal TDTs (II:2, II:4, III:6, III:7, III:17) are identified along with six unaffected relatives with normal TDTs who may be included in a genetic analysis. (C) In pedigree 006, an unaffected obligate carrier (II:2) with an affected sibling (II:6) and offspring (III:8) has an abnormal TDT (Z = 9.4). Both II:6 and III:8 have cervical dystonia. In this pedigree, one individual with spasmodic dysphonia (III:22) has a normal TDT (Z-score 1.9). Autosomal dominant transmission of abnormal TDTs is demonstrated from II:3 to three of five offspring (III:10, III:11 and III:14) and from II:5 to 1 of 4 examined offspring (III:21).
pedigrees and no parent with a normal TDT had an offspring with an abnormal TDT. Heretofore, the lack of informative families has hampered genetic research in AOPTD; the TDT endophenotype may strengthen the power of linkage analysis studies (Fig. 4). TDT could be used to define two groups in AOPTD families; gene carriers (AOPTD patients and unaffected relatives with abnormal TDTs) and non-carriers (unaffected relatives with normal TDTs). In this way, the power of a genetic study may be significantly improved. Alternatively, TDT could increase the numbers available for a transmission disequilibrium study (Defazio et al., 2006) by assigning gene carrier status based on TDT rather than disease manifestation alone.

Conclusion

The high prevalence of TDT abnormalities in both familial and sporadic AOPTD patients and their unaffected relatives, the finding of abnormal TDTs in obligate heterozygotes and the autosomal dominant pattern of transmission suggest that TDT is a sensitive endophenotypic marker for AOPTD. Voxel-based morphometry further validates the hypothesis that TDT can effectively fulfil the role of a sensitive marker of subclinical gene carriage in AOPTD. The presence of increased putaminal volume in clinically unaffected relatives with abnormal TDT in this study supports the hypothesis that increased putaminal volume in AOPTD is a primary phenomenon. The similar frequency of abnormal TDTs in relatives of sporadic and familial AOPTD patients suggests that in sporadic AOPTD patients the affected individual is the only manifesting carrier of a poorly-penetrant genetic disorder. TDT testing is likely to be a useful tool in AOPTD genetic research.

Supplementary material

Supplementary material is available at Brain online.

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References


