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Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the *DYT1* gene mutation

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Summary

A mutation in the *DYT1* gene on chromosome 9q34 causes early-onset primary torsion dystonia with autosomal dominant inheritance but low phenotypic penetrance. The aim of the present study was to assess the functional consequences of the *DYT1* gene, by comparing the electrophysiology of cortical and spinal circuits in clinically affected and unaffected carriers of the *DYT1* gene mutation. We assessed intracortical inhibition (ICI), intracortical facilitation (ICF), the cortical silent period (SP) and spinal reciprocal inhibition (RI) in 10 manifesting *DYT1* gene carriers (MDYT1), seven non-manifesting *DYT1* gene carriers (NMDYT1) and 13 healthy controls. The MDYT1 subjects had abnormalities similar to those seen in previous studies of non-genetically characterized individuals with primary dystonia. They had reduced ICI, shorter SP and absent presynaptic phase of RI compared with the healthy controls. NMDYT1 subjects also had a significant reduction in cortical inhibition (ICI and SP), but their spinal RI was not different from controls. We conclude that clinical expression of dystonia depends on widespread electrophysiological deficits, and the presence of the *DYT1* gene mutation itself leads only to a subset of these changes. This is consistent with the hypothesis that additional environmental/genetic insults may be needed to reveal clinical symptoms in *DYT1* gene carriers.

Keywords: DYT1 dystonia; cortical excitability; penetrance

Abbreviations: BFM = Burke–Fahn–Marsden scale; ICF = intracortical facilitation; ICI = intracortical inhibition; ISI = interstimulus interval; MDYT1 = manifesting *DYT1* gene mutation carriers; MEP = motor evoked potential; NMDYT1 = non-manifesting *DYT1* gene mutation carriers; RI = reciprocal inhibition; SP = silent period

Introduction

Familial early-onset primary torsion dystonia is commonly associated with a single GAG deletion in the *DYT1* gene on chromosome 9q34 (Ozelius *et al*., 1997). The typical phenotype associated with this mutation is of limb-onset dystonia in childhood or early teens, with subsequent progression to generalized dystonia in most cases (Bressman *et al*., 1994). Despite an autosomal dominant inheritance, the phenotypic penetrance is low: only 30–40% of gene carriers go on to develop dystonia (Bressman *et al*., 1994). The penetrance is also age dependent, with the manifestation of symptoms in gene carriers mainly occurring before the age of 25 years (Bressman *et al*., 1994). Inter- and intra-familial phenotypic variability is common, with some manifesting gene carriers having only mild focal dystonia, and others being severely affected (Bressman *et al*., 1994; Opal *et al*., 2002).

The aim of the present study was to use physiological techniques to probe the underlying mechanisms responsible for this variation. The *DYT1* gene product is torsin A, an endoplasmic reticulum-bound protein (Kustedjo *et al*., 2000) with significant homology to heat shock proteins (Breakefield, 2001). It seems likely that the level of expression of abnormal torsin A or its interaction with environmental and/or genetic factors causes the variable spectrum of clinical abnormalities (Bressman *et al*., 1998). It is possible that non-manifesting carriers of the mutation have no clinical symptoms because they have no physiological consequences from the abnormal *DYT1* gene (perhaps as it is

Table 1 *Clinical features of the MDYT1 group*

Subject	Age at onset (years)	Site of onset	Current distribution of dystonia	BFM score	Medication	Experiments completed
1, Male	12	R arm	Generalized	46	None	SP, RI
2, Female	11	R hand	Segmental	12	Clonazepam, benzhexol	ICI, SP, RI
3, Female	10	L foot	Generalized	44	Benzhexol	ICI, SP, RI
4, Male	6	L foot	Generalized	74	Diazepam	SP
5, Female	3	L foot	Segmental	16	None	ICI, SP, RI
6, Male	10	R hand	Multifocal	28	None	ICI, SP, RI
7, Female	13	R arm	Segmental	18	Levodopa	ICI, SP, RI
8, Male	12	R hand	Focal	6	Benzhexol	ICI, SP, RI
9, Male	9	R arm	Segmental	6	None	ICI, SP, RI
10, Male	18	L leg	Generalized	27	None	ICI, SP

R = right; L = left.

inactivated in them). It is also possible that in these individuals, subclinical abnormalities occur, which then have to be supplemented or enhanced by other factors for clinical symptoms to become apparent.

To our knowledge, only one study has attempted to address these questions. Eidelberg *et al.* (1998*a*, *b*) used [^{18}F]fluoro-2-deoxy-D-glucose PET to compare the pattern of resting brain metabolism in *DYT1* gene carriers versus healthy controls. They used principal component analysis of the signal to show that there was increased coupling between the lentiform nucleus, cerebellum and supplementary motor area in both manifesting and non-manifesting carriers of the *DYT1* gene mutation, similar to the pattern previously observed in other patients with primary dystonia. This would be consistent with the idea that both groups of subjects had physiological consequences from the *DYT1* gene mutation. However, abnormalities in brain metabolism measured by PET are only one of many physiological changes that have been noted in patients with dystonia at all levels of the CNS from cortex to brainstem to spinal cord. Our aim in the present study was to extend observations on manifesting and non-manifesting gene carriers by examining a range of cortical and spinal pathways with electrophysiological methods (which are easier to quantify than principal components analysis with PET) to evaluate and compare the functional consequences of the *DYT1* gene mutation in manifesting and non-manifesting gene carriers.

Methods

Subjects

We recruited 10 *DYT1* gene carriers with manifesting clinical dystonia (MDYT1) from the movement disorder clinics at the National Hospital for Neurology and Neurosurgery. Inclusion criteria were (i) genetic analysis positive for the typical *DYT1* gene mutation; (ii) onset of limb dystonia prior to the age of 25 years with or without subsequent progression; (iii) no other cause for dystonia revealed by investigation, including MRI and blood tests; (iv) no brain, spinal or peripheral nerve surgery for dystonia or other cause in the past; (v) no history of other neurological disease; and (vi) no use of botulinum toxin in the past 4 months. Subjects were permitted to continue their other medications as normal during the study. Clinical details of these patients are given in Table 1. All patients had clinical dystonia affecting the arm and hand used for electrophysiological testing. Seven *DYT1* gene carriers without manifesting clinical symptoms (NMDYT1) were ascertained by genetic and clinical assessment of family members of the MDYT1 group. Inclusion criteria were (i) genetic analysis positive for the typical *DYT1* gene mutation; (ii) clinical absence of dystonia confirmed by personal independent assessment of each patient by two authors (Y.Z.H. and M.J.E.) as well as video assessment by K.B.; (iii) no brain, spinal or peripheral nerve surgery for any cause in the past; (iv) no history of neurological disease; and (v) age over 30 years. Thirteen healthy controls were recruited from a departmental register of volunteers. The average age of those in the MDYT1 group was 49 years (SD: 9), in the NMDYT1 group 50 years (SD: 8), and in the control group 42 years (SD: 7). The study was approved by the Joint Research Committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology. Subjects gave their written informed consent to participate.

Clinical assessment of MDYT1 subjects

The clinical severity of dystonia in the MDYT1 subjects was rated using the Burke–Fahn–Marsden scale (BFM), a validated clinical measure for patients with generalized dystonia (Burke *et al*., 1985).

Study design

Assessments of intracortical inhibition (ICI), intracortical facilitation (ICF), cortical silent period (SP) and reciprocal inhibition (RI) were attempted in all subjects. The assess-

ments were all performed on the same day, with ICI and SP in one session, and then RI in a second session.

ICI and ICF

The technique of ICI measures the influence of a subthreshold 'conditioning' pulse of transcranial magnetic stimulation (TMS) given over the hand motor area on a subsequent suprathreshold 'test' pulse given over the same area. Experiments in normal subjects have shown that at short interstimulus intervals (ISIs; 0–4 ms), there is a reduction in the size of the motor evoked potential (MEP) elicited from the contralateral first dorsal interosseous (ICI) (Kujirai *et al*., 1993). At ISIs of between 7 and 15 ms, there tends to be an increase in the size of the MEP elicited by the suprathreshold stimulus (ICF) (Kujirai *et al*., 1993).

Subjects were seated in a comfortable chair. EMGs were recorded from the right first dorsal interosseous using Ag–AgCl electrodes. EMG activity was recorded with a gain of 1000 and 5000. Magnetic stimulation was given using a hand-held figure-of-eight coil connected though a Bistim module (Magstim Company, Whitland, UK) to two magnetic stimulators (Magstim Company, Whitland, UK).

The location of the hand motor area was defined by the location on the scalp where magnetic stimulation produced the largest MEP from the contralateral first dorsal interosseous when the subject was relaxed (the 'motor hot-spot'). We defined the resting motor threshold as the minimum stimulation intensity over the motor hot-spot that could elicit an MEP of no less than 50 μV in five out of 10 trials. We defined the active motor threshold as the minimum stimulation intensity over the motor hot-spot that could elicit an MEP of no less than 200 μV in five out of 10 trials during a voluntary contraction of the contralateral first dorsal interosseous.

The conditioning stimulus was set at 80% of active threshold. The test stimulus was set at the intensity of magnetic stimulation required to produce an MEP of 1 mV consistently.

Subjects received in a random order either the test stimulus alone, or conditioning–test stimuli at ISIs of 2, 3, 4, 5, 6, 7, 10 and 15 ms. Subjects received the stimuli in two blocks of 50 stimuli each. All trials in which EMG movement artefact occurred were rejected on-line, and that stimulus condition was repeated.

SP

The SP is a period of EMG silence that occurs in a voluntarily contracted muscle following a suprathreshold magnetic stimulation given over the contralateral representative motor area. In normal subjects, the SP is typically 120 ms, although this can be longer if the stimulation intensity is raised (Inghilleri *et al*., 1993).

EMGs were recorded as described above. A single magnetic stimulation unit (Magstim Company, Whitland, UK) was used to deliver the magnetic pulse through a standard figure-of-eight coil. Motor thresholds were obtained as described above.

Subjects were asked to squeeze a 2.5 cm block between their thumb and index finger. Visual feedback on the intensity of muscle contraction was provided to the subjects, and they were instructed to maintain a constant muscle contraction at ~30% of maximum.

Magnetic stimulation was applied over the contralateral hand motor area at 120% of rest threshold. Twelve stimulations were recorded for each subject. The SP was calculated by measuring the time from the end of the MEP to the reappearance of EMG activity in excess of 20 μV. Those trials where voluntary muscle activation exceeded or was less than 30% of maximum were rejected on-line, and the stimulus was given again.

RI

RI assesses the interaction between stimulation of the radial nerve supplying the extensor muscles of the forearm and the H reflex produced by stimulation of the median nerve. At particular ISIs, a reduction in the size of the H reflex occurs in normal subjects (Day *et al*., 1984). We grouped these ISIs into three phases of RI, one occurring at 0 ms, one at 10–20 ms and one at 70–750 ms.

We attached Ag–AgCl electrodes to extensor digitorum communis, and to flexor carpi radialis. Electric pulses were supplied by two constant current generators (Digitimer, Welwyn, UK). One electrical stimulator was used to stimulate the median nerve in the antecubital fossa. Stimulation duration was 1000 μs, and the intensity used was that which produced the maximum size of the H reflex. The second electrical stimulator was used to stimulate the radial nerve above the elbow. The duration of the stimulus was 500 μs, and the intensity used was that which produced an EMG response of >50 μV from extensor digitorum communis.

We recorded H reflex size during stimulation of the median nerve alone, and for ISIs of –1, 0, 3, 5, 10, 20, 30, 50, 70, 100, 300, 500 and 750 ms. Stimuli were given in a random order in one block of 60 trials and two blocks of 50 trials. Any trials where EMG movement artefact occurred were rejected on-line, and were repeated.

Statistical analysis

To assess ICI and ICF, repeated-measures analysis of variance (ANOVA) was used. Because inhibition and facilitation at particular ISIs have different mechanisms, we grouped means at an 'inhibitory' interval (average of 2, 3 and 4 ms ISIs), an 'intermediate' interval (average of 5 and 6 ms ISIs) and a 'facilitatory' interval (average of 7, 10 and 15 ms ISIs).

To assess SP, one-way ANOVA was used to compare the three groups. To assess RI, repeated-measures ANOVA was used to compare the data between the three groups at each of three ISIs: 'first phase' (ISI of 0 ms), 'second phase' (average

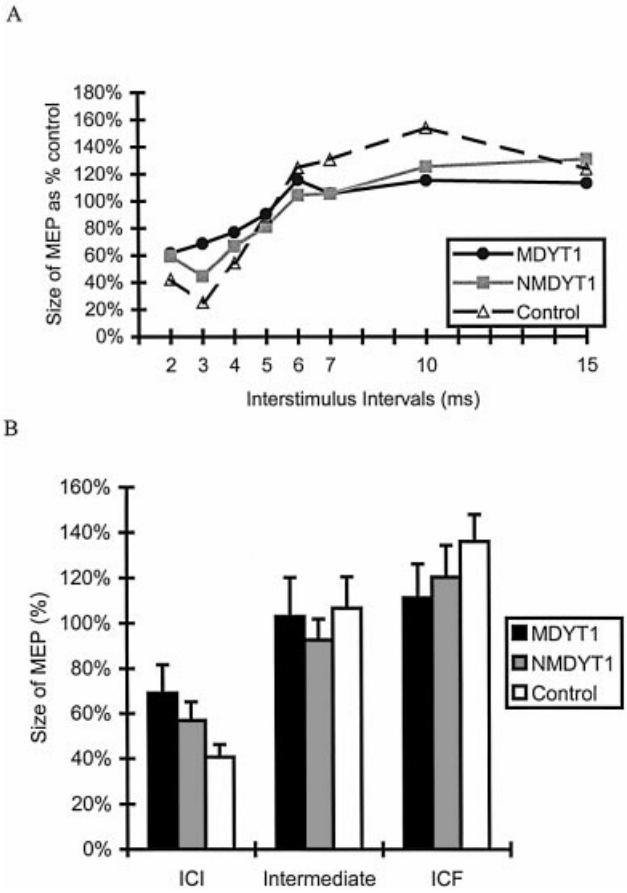

Fig. 1 ICI and ICF for MDYT1, NMDYT1 and control subjects. (**A**) The size of MEP as a percentage of the unconditioned size at all ISIs. (**B**) The mean size of MEP as a percentage of the unconditioned size at the ICI, intermediate and ICF intervals.

of ISIs 10 and 20 ms) and 'third phase' (average of ISIs 70–750 ms).

Spearman's correlation coefficient was used to assess any correlation between the clinical severity of dystonia in MDYT1 individuals measured on the BFM scale and the degree of abnormality observed on tests of ICI, SP and RI.

Not all subjects were able to participate in all the experiments. Subjects 4 and 10 had no consistent H reflex, and therefore RI could not be assessed in them. In subjects 1 and 4, assessments of ICI/ICF were confounded by movement artefact. One subject in the NMDYT1 group also did not have a consistent H reflex, and therefore could not have RI assessed. Statistics were performed using SPSS for Windows 10.0.

Results

Clinical assessment

The BFM scores of each MDYT1 subject are shown in Table 1. A higher score indicates more severe dystonia; the minimum score is zero, and the maximum score is 150.

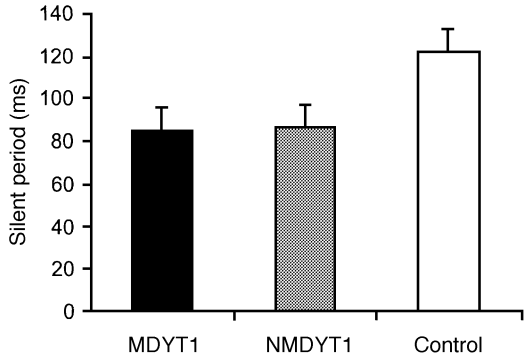

Fig. 2 SP duration for MDYT1, NMDYT1 and control subjects.

ICI and ICF

ICI/ICF was compared in eight MDYT1, seven NMDYT1 and eight control subjects. The complete time course at all ISIs is shown in Fig. 1A, with grouped data (inhibitory, intermediate and facilitatory ISIs) in Fig. 1B. Repeated-measures ANOVA was performed on grouped data, with group (MDYT1, NMDYT1 and controls) and ISI (inhibitory, intermediate and facilitatiory) as main factors (Fig. 1B). As expected, ANOVA showed a highly significant effect of ISI [$F(2,40) = 68$, $P < 0.001$], but there was also a significant interaction between group and ISI [$F(4,38) = 3.5$, $P < 0.05$]. *Post hoc* analysis showed that there was significantly less inhibition in MDYT1 and NMDYT1 subjects compared with controls in the inhibitory interval [$F(1,13) = 6.8$, $P < 0.05$; and $F(1,13) = 5.7$, $P < 0.05$, respectively]. There were no significant differences found at the inhibitory interval between MDYT1 and NMDYT1 subjects. No significant differences were found between controls and either group of subjects at the intermediate or facilitatory intervals.

SP

SP was assessed in 10 MDYT1, six NMDYT1 and eight control subjects. Results are shown in Fig. 2. One-way ANOVA was performed on the data, and demonstrated a significant effect of group on the length of the SP [$F(2,21) = 3.9$, $P < 0.05$]. *Post hoc* analysis using independent sample *t* tests was then performed. The SP was shorter in both groups of gene carriers compared with controls (MDYT1 subjects: $t = -2.3$, $P = 0.05$; NMDYT1 subjects: $t = -2.5$, $P = 0.05$), but no significant differences in SP were found between MDYT1 and NMDYT1 subjects.

RI

RI was assessed in eight MDYT1, six NMDYT1 and 13 control subjects. The complete time course of RI at all ISIs is shown in Fig. 3A, with grouped data in Fig. 3B. Repeated-measures

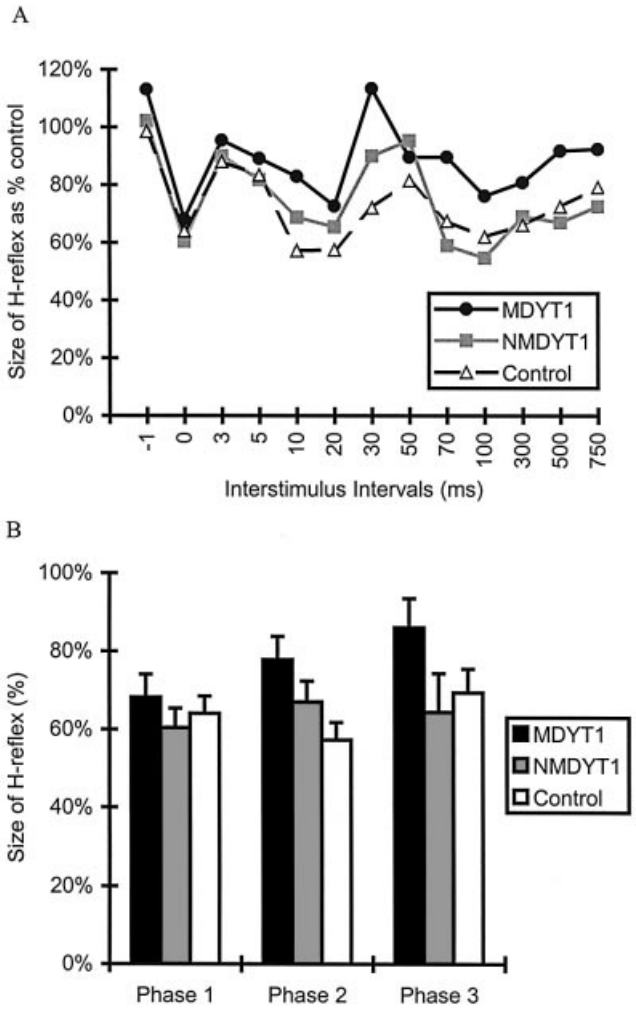

Fig. 3 RI for MDYT1, NMDYT1 and control subjects. (**A**) The H reflex size as a percentage of the unconditioned size at all ISIs. (**B**) Mean data for the H reflex size as a percentage of the unconditioned size at each of the three phases of RI.

ANOVA was performed with group (MDYT1, NMDYT1 and controls) and ISI as main factors. A significant interaction between group and ISI was found [$F(2,20) = 4$, $P = 0.05$]. *Post hoc* analysis on grouped data showed no significant differences between the three groups in the first phase of RI [$F(2,24) = 0.441$, NS]. However, a significant difference was found between MDYT1 and controls in the second phase [$F(1,15) = 6$, $P = 0.05$] and in the third phase [$F = (1,15) = 4.6$, $P = 0.05$]. NMDYT1 subjects were not significantly different from controls in any of the three phases of RI.

Correlations wih clinical assessment

No correlation was found between BFM score and ICI, ICF, SP or any phase of RI in MDYT1 subjects.

Discussion

We have demonstrated for the first time (to date) that electrophysiological abnormalities of cortical excitability exist in both manifesting and non-manifesting carriers of the *DYT1* gene. Manifesting and non-manifesting carriers had reduced ICI, and shorter cortical SPs, but the second and third phases of RI were only abnormal in manifesting gene carriers. We conclude that the *DYT1* gene mutation produces subclinical physiological deficits in non-manifesting carriers, which are not as widespread as those seen in manifesting patients. This would be consistent with the hypothesis that additional genetic/environmental insults are necessary to produce clinical dystonia in gene carriers.

Changes in manifesting carriers of the DYT1 mutation

Previous physiological studies of non-genetically characterized individuals with dystonia have revealed a variety of abnormalities in inhibitory mechanisms at many levels of the CNS (Berardelli *et al*., 1998). These changes are thought to be the result of a functional disturbance in basal ganglia function that causes altered thalamic control of cortical motor areas and abnormal regulation of brainstem and spinal cord inhibitory mechanisms. The present experiments examined a selection of cortical and spinal circuits in manifesting carriers of the *DYT1* gene mutation, and found a similar pattern of abnormalities. The reduced ICI is likely to reflect a decrease in the excitability of intrinsic, probably GABAa, circuits in the motor cortex (Cowan *et al*., 1986; Day *et al*., 1989; Ziemann *et al*., 1996*a*; Levy and Hallett, 2002), whilst the shorter SP is likely to be due to changes in a different cortical inhibitory circuit that may involve GABAb mechanisms (Ziemann *et al*., 1996*b*). Spinal RI depends in its first part on disynaptic postsynaptic inhibition, whereas presynaptic inhibition of Ia terminal is important in its second part. The nature of the third phase of RI is unresolved. The present data showing a normal first phase of RI and reduced later phases are compatible with the original description of Nakashima *et al*. (1989) in non-genetically characterized dystonia. One criticism of our data in MDYT1 subjects is that some of them (5/10) were taking medication at the time of the study. Two were receiving benzhexol, one clonazepam and benzhexol, one diazepam and one levodopa. However, it is likely that, if such medication has any effect at all on the parameters measured in our experiments, it would have the effect of reducing cortical excitability, not of causing the excessive cortical excitability revealed in our experiments. Our results in these medicated subjects did not differ systematically from those not taking medication, and our results overall fit in with established patterns of electrophysiological abnormality found in non-medicated patients with primary dystonia.

Changes in non-manifesting carriers of the DYT1 mutation

Clinically, movement control in the non-manifesting carriers of the mutation was indistinguishable from that of the normal

controls. Despite this, electrophysiological tests revealed subclinical abnormalities: two GABAergic circuits in the motor cortex were hypoexitable to the same extent as in manifesting individuals, as measured by ICI and SP. Spinal RI appeared normal.

Previously, it has not been clear why non-manifesting gene carriers do not manifest dystonia. One potential hypothesis is that the *DYT1* gene has no physiological consequences in non-manifesting individuals, perhaps through inactivation of the gene. Our results would indicate that this is not the case. Clinically non-manifesting carriers of the *DYT1* gene had clear electrophysiological abnormalities. In this respect, our data confirm those of Eidelberg *et al*. (1998*a*, *b*) who used PET to reveal subclinical metabolic abnormalities in the brains of non-manifesting individuals. However, our results also show that the abnormalities in non-manifesting individuals are not as widespread as in manifesting carriers.

It is interesting that the abnormalities in non-manifesting subjects lay in two cortical pathways known to be influenced by basal ganglia input: ICI and SP. This may indicate that the primary defect caused by the *DYT1* gene is in basal ganglia function, and that this then leads to secondary changes in connected structures. Whatever the mechanism, the lack of clinical symptoms in non-manifesting individuals suggests that there are other factors, perhaps not even tested in these experiments, which determine the expression of clinical dystonia. These factors could be at the level of the sensory system, which has been implicated in the genesis of dystonia, or possibly in the direct connections between the basal ganglia and the brainstem. Regardless of the nature of the additional abnormalities necessary for dystonia to develop, we suggest that genetic and/or environmental modifying factors are likely to play a part in determining the clinical phenotype. There has certainly been considerable debate about the role of environmental factors (particularly trauma) in triggering symptoms in primary dystonia. A recent report of monozygotic twins with familial adult-onset craniocervical dystonia suggested that trauma might have played a role in the greater severity of dystonia in one of the twins (Albanese *et al*., 2000). Epidemiological studies of patients with blepharospasm have implicated facial trauma as a risk factor for the development of the condition (Defazio *et al*., 1999). However, little is known about the role of such factors in the onset of dystonia in *DYT1* gene carriers. A case–control study (published in abstract form only) implicated measles infection and high fever in early childhood as possible predisposing factors to the development of dystonia in *DYT1* gene carriers (Sanders-Pullman *et al*., 2000). Interestingly, torsin A, the protein product of the *DYT1* gene, bears significant homology to heat shock proteins (Breakefield *et al*., 2001).

The idea that electrophysiological abnormalities may exist without clinical signs of dystonia is not new. Subclinical abnormalities in the unaffected body parts of those with non-genetically characterized primary dystonia have been observed in previous electrophysiological studies. Examples of these abnormalities include abnormal reciprocal inhibition in the forearms of those with cervical dystonia (Deuschl *et al*., 1992), abnormal intracortical excitability in the hand motor area in those with blepharospasm (Sommer *et al*., 2002) or in the unaffected arm of patients with writer's cramp (Ridding *et al*., 1995), and abnormal temporal discrimination of sensory inputs in the unaffected hand of those with writer's cramp (Fiorio *et al*., 2003). The implication is that additional abnormalities must occur to prompt the appearance of symptoms. In such cases, additional reorganization of central pathways produced by overuse or injury may be one trigger for dystonia. Thus, in these dystonic conditions, as we suspect in *DYT1* gene carriers, there also is an interplay between intrinsic and environmental modifying factors that modulates the clinical expression of underlying electrophysiological abnormalities.

In conclusion, we have shown that non-manifesting carriers of the *DYT1* gene, although they are clinically unaffected by dystonia, demonstrate some, but not all of the electrophysiological abnormalities found in *DYT1* gene carriers with dystonia. This has two implications: first, that the electrophysiological changes previously found in those with other forms of dystonia are not merely an artefact of dystonic movements themselves, as they can occur independently of clinical dystonia. Secondly, it implies that additional abnormalities are needed to cause clinical dystonia, perhaps in sensorimotor integration or basal ganglia–brainstem outflow. Our findings underline the importance of looking outside cortical motor abnormalities in dystonia to other aspects of the motor system for the clues to the genesis of dystonia in *DYT1* gene carriers, and those with other forms of primary dystonia. In addition, it is also important to identify potential environmental and genetic modifying factors that could influence penetrance of the *DYT1* phenotype. If these could be identified, it is feasible that *DYT1* gene carriers could be protected from, or at least counselled about, such factors. From a wider point of view, such factors might give significant insights into the pathogenesis of primary dystonias, and have the potential to provide novel treatment strategies to correct these pathophysiological abnormalities.

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