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DYT1 mutations amongst adult primary dystonia patients in Singapore with review of literature comparing East and West

Roland Dominic G. Jamora [a], Eng-King Tan [a,b], Chun-Ping Liu [c], Paramasivam Kathirvel [c], Jean-Marc Burgunder [c,d,e], Louis C.S. Tan [a,*]

[a] *Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore*
[b] *Division of Research, SingHealth, Singapore General Hospital, Singapore, Singapore*
[c] *Neurogenetics Laboratory, National Neuroscience Institute, Singapore, Singapore*
[d] *Department of Medicine, National University of Singapore, Singapore, Singapore*
[e] *Department of Neurology, University of Bern, Bern, Switzerland*

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Abstract

Background: Dystonia is a heterogenous group of movement disorders whose clinical spectrum is very wide. At least 13 different genes and gene loci have been reported. While a 3-bp deletion in the *DYT1* gene is the most frequent cause of early limb-onset, generalized dystonia, it has also been found in non-generalized forms of sporadic dystonia. An 18-bp deletion in the *DYT1* gene has also been reported.
Objectives: We screened for the 3-bp and 18-bp deletions in the *DYT1* gene among our sporadic, adult-onset primary dystonia patients in Singapore. We reviewed the literature to compare the frequency of *DYT1* mutation between the East and the West.
Methods: We screened 54 patients with primary dystonia (focal: $n=41$; segmental: $n=11$; multifocal: $n=1$; generalized: $n=1$) for the deletions in the *DYT1* gene. A careful review of all published literature on *DYT1* screening among sporadic, non-familial, non-Ashkenazi Jewish patients was done.
Results: We did not detect any mutations in the exon 5 of the *DYT1* gene in any of our patients. The frequency of *DYT1* mutation amongst Asians (1.0%) was comparable to the West (1.56%) ($p=$NS).
Conclusions: *DYT1* mutations are uncommon amongst adult primary dystonia patients in Singapore.

Keywords: Primary dystonia; Movement disorders; *DYT1*

1. Introduction

Dystonia is a movement disorder of heterogenous etiologies characterized by involuntary, sustained, patterned, and often repetitive muscle contractions of antagonistic muscles, causing twisting movements or abnormal postures that result in significant pain and functional disabilities [1]. Primary dystonia occurs either in familial or sporadic pattern with dystonia as the sole phenotypic manifestation with the exception that tremor can be present as well. Its clinical spectrum is very wide, ranging from task-specific focal forms, to segmental and generalized forms. At least 13 different genes and gene loci are associated with primary and hereditary forms of dystonia [2]. A deletion of the GAG triplet (3 bp) in the *DYT1* gene is the most frequent cause of early limb-onset, generalized dystonia, found in up to 90% of Ashkenazi Jewish populations and up to 60% of non-Jewish populations [3,4]. Moreover, the *DYT1* mutation has also been reported in non-generalized forms of early-onset, non-familial dystonia as well as in sporadic, late-onset (> 26 years old) dystonia [5–13]]. Furthermore, an 18-bp (GTTCACCAAGTTAGATTA) deletion in the *DYT1* gene has also been reported [14]. Most of the genetic studies on primary dystonia have been performed in the West with very

* Corresponding author. Tel.: +65 6357 7171; fax: +65 6357 7137.
E-mail address: louis_tan@nni.com.sg (L.C.S. Tan).

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Table 1
Baseline characteristics of patients

Variables	Number (%)
Male	32 (59.3)
Mean age at onset of disease (years ± S.D.)	47.60 ± 13.04
Mean age at diagnosis (years ± S.D.)	49.55 ± 13.25
Race – Chinese	39 (72.2)
– Indian	7 (12.9)
– Malay	5 (9.3)
– Others	3 (5.6)
Site affected at maximum severity – neck	32 (59.3)
– Hand	11 (20.4)
– Face	10 (18.5)
– Trunk	1 (1.9)
Types of dystonia	
Focal	41 (75.9)
Cervical dystonia	24 (58.5)
Task-specific dystonia	8 (19.5)
Blepharospasm	4 (9.8)
Limb dystonia	3 (7.3)
Oromandibular dystonia	2 (4.9)
Segmental	11 (20.4)
Multifocal	1 (1.9)
Generalized	1 (1.9)

few studies performed in Asia. The reported frequency of *DYT1* mutation among Asians with primary dystonia ranged from 1.5% to 3.37% [9,12,13].

To the best of our knowledge, the frequency of the 3-bp and 18-bp deletions in the *DYT1* gene have not been evaluated in Southeast Asia, an ethnically and linguistically diverse region with a population of 443 million [15]. We therefore screened for *DYT1* mutations in our patients with primary dystonia in Singapore, a multi-ethnic Southeast Asian country with a population of 4 million people comprising 76% Chinese, 14% Malays, and 8% Indians [16].

2. Methodology

The patients were recruited from two adult movement disorders (MD) clinics (Departments of Neurology of the National Neuroscience Institute at Tan Tock Seng Hospital and Singapore General Hospital) between October 2004 and March 2005. After a complete neurological examination performed by MD specialists (EKT and LCST), the clinical diagnosis of primary dystonia was made according to current criteria [2]. The demographic and clinical data were collected using a standardized and structured questionnaire. All patients underwent routine laboratory testing and/or neuroimaging to exclude secondary causes of dystonia. This study has been approved by the respective Institutional Review Boards of both participating hospitals.

After obtaining informed consent, venous blood samples were drawn and DNA was extracted from peripheral blood leukocytes using the salting out DNA extraction method [17]. To screen for the mutations in exon 5, polymerase chain reaction (PCR) amplification was performed using 6419 forward and 6418 reverse primers as previously described and sequenced [14].The BLAST program (http://www.ncbi.nlm.nih.gov/BLAST/) was used to analyse for the presence of mutations in exon 5 sequence.

We did a review of literature of studies which screened for *DYT1*. We included studies which screened for the mutation among sporadic, non-familial, non-Ashkenazi Jews with primary dystonia in a clinic-based setting. Studies that included familial and Ashkenazi Jews were included if the number of non-familial and/or non-Ashkenazi Jewish population was indicated.

Quantitative variables were expressed as means ± S.D. while qualitative variables were expressed as percentages. The χ^2 test was used in comparing qualitative variables. The data were analyzed using SPSS ver. 11.5 (SPSS Inc.).

3. Results

A total of 60 patients with primary dystonia were approached and 54 (90%) agreed to be tested for the two known mutations in the *DYT1* gene. The patients consisted of 32 males (59.3%, M/F ratio = 1.5:1). The racial composition of Chinese, Malays and Indians in our study was comparable to that found in Singapore ($\chi^2 = 2.82$, $p = 0.244$). None of our patients had a family history of dystonia. The mean age at onset of dystonia was 47.60 ± 13.04 years

Table 2
Summary of selected literature on *DYT1* (GAG deletion) screening amongst sporadic, non-familial, non-Ashkenazi Jewish primary dystonia patients

Population	Total *DYT1* (+) patients[a]	Total patients screened[a]	%
Asians	4	402	1.0[b]
Japanese (Matsumoto et al., 2001) [9]	1	159	0.62
Taiwanese (Lin et al., 2006) [13]	3	189	1.5
Singaporeans (This paper)	0	54	0
Europeans	10	639	1.56
Serbian (Major et al., 2001) [8]	1	34	2.94
Danish (Hjermind et al., 2002) [19]	1	103	0.97
Italian (Zorzi et al., 2002)[10]	2	27	7.41
Germans	6	371	1.62
(Maniak et al., 2003) [20]	(0)	(89)	(0)
(Grundmann et al., 2003) [11]	(3)	(200)	(1.5)
(Kamm et al., 2000) [21]	(0)	(37)	(0)
(Kamm et al., 1999) [6]	(3)	(45)	(6.67)
French (Dhaenens et al., 2005) [22]	0	104	0

[a] The total number of patients reflected excluded familial and/or Ashkenazi Jewish population from the original cohort.
[b] No significant difference between Asians and Europeans ($\chi^2 = 0.604$, p = NS).

(range, 20–90). Focal dystonia accounted for 75.9% of primary dystonia while segmental (20.4%), multifocal dystonia (1.9%) and generalized dystonia (1.9%) accounted for the rest (Table 1). We could not detect any mutation in the exon 5 of the *DYT1* gene in any of our patients.

We found 10 studies fulfilling our inclusion criteria. The frequency of *DYT1* mutation among Asians with sporadic primary dystonia (1.0%) was comparable to the West (1.56%) (p=NS) (Table 2).

4. Discussion

We report the screening of our 54 patients with different subtypes of sporadic primary dystonia for the 3-bp and the 18-bp deletions. The distribution of our patients according to the subtypes of dystonia and the male predominance was in agreement with our previous paper on dystonia in Singapore [18]. We did not find either the 3-bp or the 18-bp deletions in any of our patients.

To compare the prevalence of the *DYT1* mutations in sporadic primary dystonia between Eastern and Western countries, a careful review of the available literature on studies amongst clinic-based, non-familial, non-Ashkenazi Jewish populations was performed. We managed to find only two studies from Asia and eight from Europe. The difference in the prevalence rates between East and West was found not to be significant between these populations with sporadic primary dystonia (Table 2).

The small number of patients screened for the *DYT1* mutations is a limitation of this study. While we did not find any patient with the 3-bp and 18-bp mutations in the *DYT1* gene, this was the first paper to report on the screening for these mutations among Chinese, Indians and Malay Singaporeans. Our analysis revealed a comparable frequency of *DYT1* mutation amongst Asians and Europeans.

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