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Singular DYT6 Phenotypes in Association with New *THAP1* Frameshift Mutations

DYT6 dystonia is an autosomal dominant disorder with incomplete penetrance (≈60%) characterized by early-age onset (median, 13 years) and slight female predominance.[1] The upper limb is a common site of onset, with progressive extension of the disease to other body parts. The cranial region is affected in almost two thirds of patients, and the functional repercussions of the disease are perceived by patients as mainly a result of disturbances in this region and particularly to the speech problems present in more than half of the patients; functional impairment is moderate overall (patients remain ambulatory). *THAP1* gene mutations have now been identified in numerous DYT6 families. Here we describe 2 new *THAP1* mutations identified in non-Amish patients with primary non-DYT1 dystonia.

Patients were selected among those followed in outpatient clinics by trained neurologists from the French Dystonia network. Eight index patients were recruited from Polish outpatient clinics through an international collaboration. A set of 178 independent index patients with primary non-DYT1 dystonia were included. Patients with a mean age at onset of 20.4 ± 16.7 years were diagnosed as having "generalized, segmental, or multifocal dystonia" (54% of patients), or "oromandibular or cervical dystonia" (21.3%). Moreover, as clinical expression of DYT6 has been redefined as "broad and overlapping with non-DYT6 dystonia subtypes,"[2] we also included patients with "blepharospasm" (7.3%) or with "other focal dystonia" such as writer's cramp (17.4%). Sixty-three percent were isolated cases, and autosomal dominant transmission with sometimes incomplete penetrance was observed in families. Informed consent and blood samples were collected and DNA extracted from peripheral lymphocytes according to standard procedures. Direct sequencing of the 3 *THAP1* coding regions and their exon boundaries was carried out. In the group of "generalized, segmental, or multifocal dystonia," we identified 2 novel *THAP1* heterozygous mutations (c.377_378delCT deletion [p.Pro126ArgFsX2] in patient 1; c.514dupA insertion [p.Arg172LysFsX7] in patient 3) (Supplementary Figure 1). The same *THAP1* deletion was identified in the dystonic sibling of patient 1 (patient 2). These new frameshift mutations result in the formation of premature STOP codons at positions 127 and 178,

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Table 1. Clinical characteristics of carriers of *THAP1* mutations

	Patient 1	Patient 2	Patient 3	Amish families* n = 25	Non-Amish patients** n = 50
Sex	F	M	M	F 15 (60%)	F 30 (60.0%)
Age at onset (y)	4	7	9	Median, 14.5 (5–38)	2–62
Age at last examination (y)	52	50	38	Median, 40 (10–66)	13–79
Family history	+	+	No	1	0.656
Site at onset					48 patients[a]
Upper limb		+	+	11 (44%)	28 of 48 (58.3%)
Lower limb	+			1 (4%)	5 of 48 (10.4%)
Cervical				5 (20%)	6 of 48 (12.5%)
Cranial				8 (32%)	12 of 48 (25.0%)
Site at examination					41 patients[b]
Upper limb	+	+	+	22 (88%)	35 of 41 (85.4%)
Lower limb	+	+	No	12 (48%)	22 of 41 (53.7%)
Cervical	++	+	+	14 (56%)	29 of 41 (70.7%)
Cranial	+	+	No	17 (68%)	27 of 41 (65.8%)
Speech	+	+	No	16 (64%)	28 of 50 (56.0%)
Distribution	G	G	S	Fo: 3 (12%) S: 10 (40%) Mu: 4 (16%) G: 8 (32%)	Fo: 10/50 (20.0%) S: 14/50 (28.0%) Mu: 2/50 (4.0%) G: 24/50 (48.0%)

Sex: F, female; M, male. Dystonia distribution: G, generalized; Fo, focal; Mu, multifocal; S, segmental.
*4 Families, 25 patients.[1]
**21 Families, 11 sporadic cases, 50 patients including our 3 patients.[2,4–8]
[a]48 Patients, as data were not available for patients reported by Djarmati et al.[6]
[b]41 Patients, as data were not available for patients reported by Houlden et al.[7]

respectively, and suggest, as previously reported, a loss-of-function mechanism by haploinsufficiency.

The clinical picture of these 3 patients (Table 1) fits with the clinical phenotype associated with *THAP1* mutations, but some clinical aspects are singular. In patient 3, dystonia initially implicated the right upper limb at the age of 9, with progressive axial involvement; at 14 years of age, the right upper limb and the cervical region were clearly dystonic, with writer's cramp and torticolis. The patient was not treated. At the age of 18 the patient reported spontaneous, complete remission (cervical and upper limb). This remission was transient, and after a free interval of 4 years, without any obvious triggering factor, dystonia rapidly recurred with right arm and cervical involvement. Afterward, dystonia did not spread to other body parts; upper limb dystonia remained moderate and stable, and disability was mainly due to cervical involvement. No worsening or remission has been reported since the age of 22, except for partial improvement after trihexiphenydyl treatment and botulinum toxin injections in the neck. Such transient improvement, or "honeymoon," is not uncommon in other primary dystonias, particularly in cervical dystonia,[3] but usually occurs within the first 5 years after onset. To our knowledge, such a honeymoon has never been observed in other known DYT6 patients.

Patient 1 is remarkable because of the lower limb onset of the disease at an early age, thus mimicking DYT1 dystonia. Nevertheless, upper limb onset is reported in more than half of DYT6 patients, and cranial onset occurs in one quarter of the cases (Table 1). In patients 1 and 2, who are siblings, dystonia became progressively generalized, with prominent cranial involvement, as described in almost half the DYT6 patients reported in the literature.

Although the 3 patients did not report any family history of motor disabilities or movement disorders (except for the sibling of patient 1), unfortunately, other family members could not be examined or tested for *THAP1* mutations. Patient 3 was thus considered a sporadic case.

The occurrence of cognitive and psychiatric disorders is an area of uncertainty in rare genetic forms of dystonia. Standardized cognitive and psychiatric assessments were not performed in our 3 patients; they were all university graduates, and their past medical histories was uneventful for psychiatric disturbances. Paisan-Ruiz[4] reported cognitive changes in 1 DYT6 patient. Cognitive or psychiatric functions among *THAP1* mutation carriers will need to be better analyzed.

In conclusion, *THAP1* implication in primary dystonia is rare in non-Amish patients (about 1.5% of tested dystonic patients reported in the literature). The DYT6 phenotype overlaps with that of other forms of primary early-onset dystonia, especially DYT1 dystonia. Good candidates for *THAP1* screening might be patients with onset in childhood or during adolescence who present cervicocranial *and* upper limb involvement or generalized dystonia *and* cranial involvement.

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Note that during the reviewing process, several new *THAP1* mutations were reported (Zittel et al, Groen et al., Söhn et al, Cheng et al, and De Carvalho et al).

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