Singular DYT6 phenotypes in association with new THAP1 frameshift mutations

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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. 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,” 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.
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 tri-
hexiphenydyl 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. Standar-
dized 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 disturban-
ces. Paisan-Ruiz4 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 over-
laps 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 adoles-
cence who present cervicocranial and upper limb involvement
or generalized dystonia and cranial involvement.

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bers for participation in this study.

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).

Table 1. Clinical characteristics of carriers of THAP1 mutations

| Sex | Age at onset (y) | Age at last examination (y) | Family history | Site at onset |  |
|-----|-----------------|-----------------------------|----------------|--------------|  |
|     |                 |                             |                | Upper limb   | Lower limb | Cervical | Cranial |     |
|     |                 |                             |                | +            | +          | +        | +       |  |
|     |                 |                             |                | 11 (44%)     | 1 (4%)      | 5 (20%)  | 8 (32%) |  |
|     |                 |                             |                | 22 (88%)     | 12 (48%)    | 14 (56%) | 17 (68%) |  |
|     |                 |                             |                | 28 of 48 (58.3%) | 5 of 48 (10.4%) | 6 of 48 (12.5%) | 12 of 48 (25.0%) |  |
|     |                 |                             |                |              |            |          |         |  |
|     |                 |                             |                | 35 of 41 (85.4%) | 22 of 41 (53.7%) | 29 of 41 (70.7%) | 27 of 41 (65.8%) |  |
|     |                 |                             |                |              |            |          |         |  |
|     |                 |                             |                | 28 of 50 (56.0%) | 43 of 50 (48.0%) | 52 of 50 (76.0%) | 58 of 50 (96.0%) |  |

Sex: F, female; M, male. Dystonia distribution: G, generalized; Fo, focal; Mu, multifocal; S, segmental.

*4 Families, 25 patients.
**21 Families, 11 sporadic cases, 50 patients including our 3 patients.
+48 Patients, as data were not available for patients reported by Djarmati et al.
+41 Patients, as data were not available for patients reported by Houlden et al.
Pantothenate kinase–associated neurodegeneration: Clinical description of 10 patients and identification of new mutations in the THAP1 gene.

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