



## **Singular DYT6 phenotypes in association with new THAP1 frameshift mutations**

Arnaud Blanchard, Agathe Roubertie, Marion Simonetta-Moreau, Vuthy Ea, Coline Coquart, Melissa Y. Frederic, Gael Gallouedec, Jean-Paul Adenis, Isabelle Benatru, Michel Borg, et al.

### **► To cite this version:**

Arnaud Blanchard, Agathe Roubertie, Marion Simonetta-Moreau, Vuthy Ea, Coline Coquart, et al.. Singular DYT6 phenotypes in association with new THAP1 frameshift mutations. *Movement Disorders*, 2011, 26 (9), pp.1775 - 1776. 10.1002/mds.23641 . hal-01670065

**HAL Id: hal-01670065**

**<https://hal.science/hal-01670065>**

Submitted on 21 Dec 2017

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

---

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

DYT6 dystonia is an autosomal dominant disorder with incomplete penetrance ( $\approx 60\%$ ) characterized by early-age onset (median, 13 years) and slight female predominance.<sup>1</sup> 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 dys-

tonia were included. Patients with a mean age at onset of  $20.4 \pm 16.7$  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,”<sup>2</sup> 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,

---

**\*Correspondence to:** Gwenaelle Collod-Bérout, INSERM, U827, Montpellier, France; gwenaelle.collod-beroud@inserm.fr  
Arnaud Blanchard and Agathe Roubertie contributed equally to this work.

**Relevant conflicts of interest/financial disclosures:** Nothing to report. This study was supported by grants from the French Ministry of Health (National PHRC 2007-A00614-49), AMADYS-LFCD, Alliance France Dystonie, Lions Club, French Dystonia Network, Université Montpellier 1 and INSERM. Arnaud Blanchard and Vuthy Ea are supported by a grant from the Ministère de l’Enseignement Supérieur et de la Recherche (MESR).

**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 <sup>a</sup>
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 <sup>b</sup>
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.<sup>1</sup>

\*\*21 Families, 11 sporadic cases, 50 patients including our 3 patients.<sup>2,4–8</sup>

<sup>a</sup>48 Patients, as data were not available for patients reported by Djarmati et al.<sup>6</sup>

<sup>b</sup>41 Patients, as data were not available for patients reported by Houlden et al.<sup>7</sup>

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 torticollis. 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 trihexiphenidyl treatment and botulinum toxin injections in the neck. Such transient improvement, or “honeymoon,” is not uncommon in other primary dystonias, particularly in cervical dystonia,<sup>3</sup> 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<sup>4</sup> 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.

**Acknowledgments:** We thank all patients and family members 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).

Arnaud Blanchard, MS,<sup>1,2</sup> Agathe Roubertie, MD, PhD,<sup>1,2,3</sup>  
Marion Simonetta-Moreau, MD, PhD,<sup>4</sup> Vuthy Ea, MS,<sup>1,2</sup>  
Coline Coquart,<sup>5</sup> Melissa Y. Frederic, PhD,<sup>1,2</sup>

Gael Gallouedec, MD,<sup>6</sup> Jean-Paul Adenis, MD,<sup>7</sup>  
 Isabelle Benatru, MD,<sup>8</sup> Michel Borg, MD,<sup>9</sup>  
 Pierre Burbaud, MD, PhD,<sup>10</sup> Patrick Calvas, MD, PhD,<sup>11</sup>  
 Laura Cif, MD,<sup>12</sup> Philippe Damier, MD, PhD,<sup>13</sup>  
 Alain Destee, MD, PhD,<sup>14</sup> Laurence Faivre, MD, PhD,<sup>15</sup>  
 Lucie Guyant-Marechal, MD,<sup>16</sup> Piotr Janik, MD, PhD,<sup>17</sup>  
 Samer Janoura, MD,<sup>18</sup> Alexandre Kreisler, MD, PhD,<sup>14</sup>,  
 Anna Lusakowska, MD, PhD,<sup>17</sup> Sylvie Odent, MD, PhD,<sup>19</sup>  
 Anna Potulska-Chromik, MD, PhD,<sup>17</sup>  
 Monika Rudzińska, MD, PhD,<sup>20</sup> Stephane Thobois, MD, PhD,<sup>21</sup>  
 Isabelle Vuillaume, MD, PhD,<sup>22</sup> Christine Tranchant, MD,<sup>23</sup>  
 Sylvie Tuffery-Giraud, PhD,<sup>1,2</sup> Philippe Coubes, MD, PhD,<sup>12</sup>  
 Bernard Sablonnière, MD, PhD,<sup>22</sup>  
 Mireille Claustres, MD, PhD,<sup>1,2,5</sup>,  
 Gwenaëlle Collod-Bérout, PhD,<sup>1,2\*</sup>

<sup>1</sup>INSERM, U827, Montpellier, France; <sup>2</sup>Université  
 Montpellier 1, UFR Médecine, Montpellier,  
 France; <sup>3</sup>CHU Montpellier, Hôpital Gui de  
 Chauliac, Service de Neuropédiatrie, Montpellier,  
 France; <sup>4</sup>Hôpitaux de Toulouse, Pôle  
 Neurosciences, Toulouse, France;  
<sup>5</sup>CHU Montpellier, Hôpital Arnaud de Villeneuve,  
 Laboratoire de Génétique Moléculaire,  
 Montpellier, France; <sup>6</sup>CHU Dupuytren, Service de  
 Neurologie, Limoges, France; <sup>7</sup>CHU Dupuytren,  
 Service d'Ophthalmologie, Limoges, France;  
<sup>8</sup>CHU de Dijon, Hôpital Général, Service de  
 Neurologie, Dijon, France; <sup>9</sup>CHU de Nice, Service  
 de Neurologie, Nice, France; <sup>10</sup>CHU Pellegrin,  
 Service de Neurophysiologie, Clinique, Bordeaux,  
 France; <sup>11</sup>CHU Toulouse, Hôpital Purpan, Service  
 de Génétique Médicale, Toulouse, France;  
<sup>12</sup>CHU Montpellier, Hôpital Gui de Chauliac,  
 Service de Neurochirurgie, Montpellier, France;  
<sup>13</sup>CHU Nantes, CIC0004, Service de Neurologie,  
 Nantes, France; <sup>14</sup>CHU de Lille, Service de  
 Neurologie, et Pathologie du Mouvement, Lille,  
 France; <sup>15</sup>CHU de Dijon, Hôpital d'Enfants,  
 Centre de Génétique, Dijon, France; <sup>16</sup>CHU de  
 Rouen, Hôpital Charles Nicolle, Département de  
 Neurologie, Rouen, France; <sup>17</sup>Department of  
 Neurology, Medical University of Warsaw,  
 Poland; <sup>18</sup>CHG Roanne, Service de Neurologie,  
 Roanne, France; <sup>19</sup>Service de Génétique Clinique,  
 CHU de Rennes, Hôpital Sud, Rennes, France;  
<sup>20</sup>Department of Neurology, Jagiellonian  
 University Medical College, Poland;  
<sup>21</sup>Hospices Civils de Lyon, Hôpital Neurologique,  
 Service de Neurologie C, Lyon, France;  
<sup>22</sup>CHRU de Lille, Département de Biochimie, et  
 de Biologie Moléculaire, Lille, France;  
<sup>23</sup>Hôpitaux Universitaires de Strasbourg, Service  
 de Neurologie, Strasbourg, France

dystonia: a genetic screening study. *Lancet Neurol* 2009;8:  
 441–446.

3. Koukouni V, Martino D, Arabia G, Quinn NP, Bhatia KP. The entity of young onset primary cervical dystonia. *Mov Disord* 2007; 22:843–847.
4. Paisan-Ruiz C, Ruiz-Martinez J, Ruibal M, et al. Identification of a novel THAP1 mutation at R29 amino-acid residue in sporadic patients with early-onset dystonia. *Mov Disord* 2009;24: 2428–2429.
5. Bonetti M, Barzaghi C, Brancati F, et al. Mutation screening of the DYT6/THAP1 gene in Italy. *Mov Disord* 2009;24:2424–2427.
6. Djarmati A, Schneider SA, Lohmann K, et al. Mutations in THAP1 (DYT6) and generalised dystonia with prominent spasmodic dysphonia: a genetic screening study. *Lancet Neurol* 2009;8:447–452.
7. Houlden H, Schneider SA, Paudel R, et al. THAP1 mutations (DYT6) are an additional cause of early-onset dystonia. *Neurology* 2010;74:846–850.
8. Xiao J, Zhao Y, Bastian RW, et al. Novel THAP1 sequence variants in primary dystonia. *Neurology* 2010;74:229–238.

## References

1. Fuchs T, Gavarini S, Saunders-Pullman R, et al. Mutations in the THAP1 gene are responsible for DYT6 primary torsion dystonia. *Nat Genet* 2009;41:286–288.
2. Bressman SB, Raymond D, Fuchs T, Heiman GA, Ozelius LJ, Saunders-Pullman R. Mutations in THAP1 (DYT6) in early-onset