

Deletion of the *THAP1* Gene Is Responsible for Typical DYT-THAP1

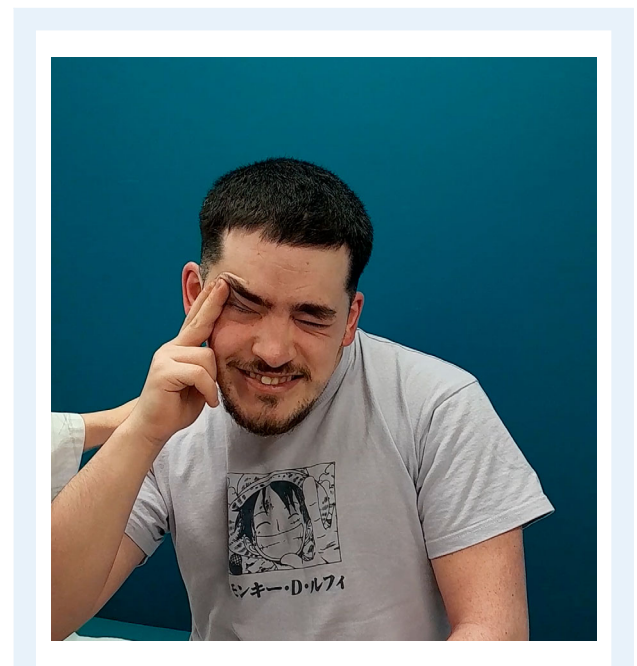
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DYT-THAP1, formerly dystonia type 6 (DYT-6), is a monogenic isolated dystonia associated with pathogenic variants in the *THAP1* gene.¹ The *THAP1* gene encodes the THAP domain-containing protein 1, which is a zinc-finger transcription factor. Missense variants are the most frequent abnormalities identified in patients, followed by truncating variants (ie, nonsense, frame shift, and splice site variants).² To date, no structural variant (ie, large deletion, duplication, or insertion) has been reliably associated with DYT-THAP1. We first report a patient who presents a typical DYT-THAP1 associated with a deletion involving the *THAP1* gene.

Our patient first developed focal hand dystonia at the age of 6 years that spread to the axial muscles after 2 years. Five years later, he developed cervical dystonia. Severe spasmodic dysphonia was observed at the age of 16 years. At this time, deep brain stimulation (DBS) electrodes were implanted in the globi pallidi interni, which partially improved his symptoms. Eventually, 3 years after the surgery, he developed a severe blepharospasm responsible for functional blindness. His neurological examination is illustrated in Video 1. Besides, his brain magnetic resonance imaging was normal, and he did not present brain calcifications nor white matter abnormalities. His neurological symptoms impacted his educational path, but he did not present intellectual disability nor neurodevelopmental disorders. He had no family history of movement disorders.

Neither missense nor truncating variants were identified by a next-generation sequencing panel targeting the analysis of 426 genes associated with movement disorders, including *THAP1* gene, from whole exome sequencing (WES) data. However, a deletion of the *THAP1* gene was suspected as the number of reads was lower in this region of the genome (Fig. 1). This deletion was confirmed using shallow whole genome sequencing (BIOOS–Illumina NextSeq–Novaseq kit, Liège, Belgium). The patient presented a heterozygous deletion of 145.6 kb on the chromosome 8p11.21 (arr[GRCh37] 8p11.21(42552677_42698251)x1), which contains the *THAP1* gene and 2 other genes not associated with human disease (ie, *CHRNA6* and *CHRNA3*). This copy number variant (CNV) was classified as pathogenic based on the American College

of Medical Genetics and Genomics guidelines.³ This variant has never been described in healthy population databases such as the Genome Aggregation Database (gnomAD).⁴ This deletion contains



Video 1. Neurological examination of our patient's severe generalized dystonia. Segment 1: gait examination highlights the contrast between the gait—relatively well preserved—and the severity of the dystonic features affecting the craniocervical segment, left upper limb and trunk. Segment 2: left upper-limb dystonia and bilateral blepharospasm. A sensory trick (ie, lifting his left eyelid with his index finger) can be observed. Segment 3: craniocervical features that include cervical dystonia, severe blepharospasm, and oromandibular dystonia. Segment 4: spasmodic dysphonia triggered when the vowel “A” is maintained. All videos have been recorded in the DBS ON state. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14350>

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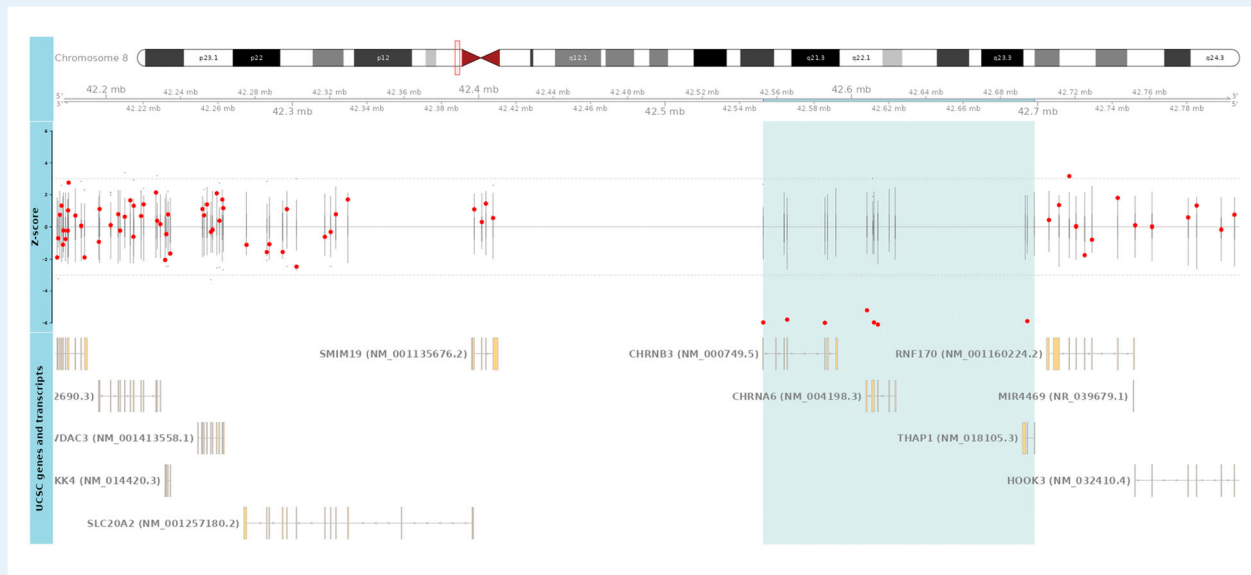


FIG. 1. WES (whole exome sequencing) data from our patient, showing the heterozygous deletion of 145.6 kb on the chromosome 8p11.2 (ie, blue box), which contains *THAP1*, *CHRNA6*, and *CHRNA3* genes. This image was obtained by an in-house CNV (copy number variant) analysis script that calculates z-scores by exon in CANOES comparing the number of reads in 30 reference samples (ie, box plots) to the number of reads in our patient (ie, red dots). Annotations are extracted from UCSC (NCBI RefSeq genes and transcripts track).

the entire *THAP1* gene that is sensitive to haploinsufficiency due to the number of loss-of-function pathogenic variants (ie, missense and truncating variants) previously reported in DYT-THAP1 patients.² Moreover, conditional *THAP1* knockout mice (ie, *THAP1* specifically deleted in glial and neuronal precursors) show locomotor impairment reflecting disturbance in the cerebellar and basal ganglia circuitry.⁵ Finally, no other variant linked to the phenotype was identified in WES data.

This deletion of the *THAP1* gene seems to be responsible for his severe dystonic features. Indeed, he presents the typical generalized dystonia associated with DYT-THAP1, with a focal onset affecting predominantly the hand, neck, or laryngeal muscles but no lower-limb involvement.² The median age of onset is ~15 years, with most patients having onset in childhood,² as our patient who presented the first signs at the age of 6 years. The absence of clear family history is frequent in DYT-THAP1 due to the incomplete penetrance (ie, ~50%) and the variable expressivity even in the same family.²

Regarding the type of variant, no deletion encompassing exclusively the *THAP1* gene (ie, in terms of human disease genes) has ever been described, neither in the healthy population nor in patients. Three publications reported large heterozygous deletions of chromosome 8p11.2 encompassing *SLC20A2* and *THAP1* genes in 13 individuals.^{6–8} All patients presented brain calcifications and dystonia. As dystonia can be present in familial idiopathic basal ganglia calcification associated with *SLC20A2* gene,⁹ the link between the phenotype of these patients and the deletion of *THAP1* gene remains undetermined. However, we identified the first patient with a deletion restricted to the *THAP1* gene (ie, which does not include other human disease genes) who presented dystonia

without brain calcification. Therefore, we hypothesize that the heterozygous absence of *THAP1* is responsible for the dystonic features of our patient and those previously reported.

The identification of the genetic cause of dystonia allows treatment adaptation. For DYT-THAP1, botulinum toxin and anticholinergic medications represent the current therapeutic recommendations.² By contrast, DBS is associated with poorer outcomes especially on dysarthria.¹⁰ Our patient underwent DBS surgery before he had a genetic diagnosis. These therapeutic implications illustrate the importance of establishing a proper genetic diagnosis and especially detecting CNVs on exome data as targeted gene panels are the most frequent analysis performed when monogenic isolated dystonia is suspected.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

C.M.: 1A, 1B, 1C, 3A

D.A.: 1A, 1B, 1C, 3B

F.D.: 1A, 1B, 1C, 3B

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in-house script from which the image of the *THAP1* deletion was derived.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institution review board was not required for this work. The patient provided written informed consent for the use of his photograph and video for the purpose of this scientific work. The authors confirm that they have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Financial Disclosures for the Previous 12 Months: Frédérique Depierreux is on the advisory board of Merz, Teva, and Ipsen Adboards. She is also responsible for various workshops organized by Merz and Ipsen.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. ■

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