Movement Disorders
CLINICAL PRACTICE
LETTER: NEW OBSERVATION

QSM-Based Evidence of Brain Iron Accumulation in *THAP1* Dystonia with Biallelic Mutation

Gullu Tarhan, MD,[1,*] Ibrahim Kamaci, MD,[2] Petr Dusek, MD, PhD,[3] Nalan Capan, MD,[4,5] Ceyhun Sayman, MD,[5,6] Cagla Turan, MD,[5] Sibel Aylin Ugur Iseri, MD,[7] and Zuhal Yapici, MD[2]

The *thanatos-associated protein domain-containing apoptosis-associated protein 1 (THAP1)* gene was initially identified in Amish–Mennonite families with craniocervical dystonia, referred to as DYT6 dystonia.[1,2] Patients often present with craniocervical or limb-onset segmental dystonia during adolescence. While conventional MRI is often unremarkable, recent studies show iron accumulation in the globus pallidus in some *THAP1* cases.[3,4] Advanced MRI techniques have enabled the quantitative assessment of brain iron levels.[5] Accordingly, this study aims to assess iron accumulation in a patient with recessive *THAP1*-related dystonia compared to healthy controls using quantitative susceptibility mapping (QSM).

A 13-year-old right-handed girl born to consanguineous parents (first cousins) was referred to assessment for treatment-refractory dystonia. Her older brother and two older sisters were neurologically unaffected. Dystonic contractions began in her left hand at age six and spread gradually over 2 years to her right foot, neck, cranial muscles, right hand, and eventually all extremities.

Neurological examination revealed dysphonic speech and impaired saccadic, pursuit, and optokinetic eye movements. She exhibited bradykinesia and generalized dystonia, predominantly affecting the cervical and cranial regions. Axial dystonia presented as rightward truncal deviation and left shoulder elevation, along with distal limb involvement. Occasional blepharospasm, jaw-opening dystonia, and risus sardonicus were noted. Due to severe dystonia, she was unable to walk even with support and had poor sitting balance. Her Burke-Fahn- Marsden Dystonia Rating scale socre (BFMDRS) was 94.5. The difficulty in sitting was therefore attributed to dystonia rather than ataxia, and no clinical signs of cerebellar dysfunction were observed.

Nerve conduction and needle EMG studies were also unremarkable. CSF neurofilament level was elevated (497.5 pg/ml; cut-off >380 for age <30 years). The cranial CT scan was normal, without signs of basal ganglia calcification. Brain MRI showed bilateral T2- and SWI-hypointensities in the globus pallidus.

Levodopa (62.5 mg/day) induced tongue dyskinesias and was discontinued. Trihexyphenidyl titrated to 15 mg/day was ineffective. Over the two-year follow-up period after implantation of combined GPi and STN DBS, STN stimulation was discontinued due to limited benefit, and only GPi DBS remained active. The patient has been more comfortable under GPi-only stimulation with a BFMDRS score of 87.5, without any stimulation-induced side effects (Table S1).

In the proband who underwent WES, a homozygous missense variant in the *THAP1* gene (ENST00000254250.7: c.149A>G; p.Tyr50Cys) was identified and classified as likely pathogenic (PM1, PM2, PP3_Moderate). Segregation analysis using Sanger sequencing confirmed heterozygosity for the variant in both parents and the elder brother. Pedigree analysis showed that the proband was homozygous for the variant, while individuals marked with a plus sign (+) were identified as heterozygous carriers (Fig. S1).

QSM revealed increased susceptibility in the globus pallidus bilaterally, corresponding to hypointensity on T2*-weighted images in the patient (Fig. 1B,D). Detailed QSM methodology is provided in the Supplementary Methods.

The susceptibility values in all the DGM regions of the patient were higher than the average of the control group; however, a statistically significant difference was only detected in the globus pallidus externus. The DGM volumes in the patient were smaller compared to the control group, particularly in the putamen; however, this difference was not statistically significant (Fig. 1E,F).

[1]*Department of Neurology, Bitlis State Hospital, Bitlis, Turkey;* [2]*Istanbul Faculty of Medicine, Department of Neurology, Istanbul University, Istanbul, Turkey;* [3]*Department of Neurology, Charles University, 1st Faculty of Medicine and General University Hospital in Prague, Prague, Czech Republic;* [4]*Istanbul Faculty of Medicine, Department of Physical Therapy and Rehabilitation, Istanbul University, Istanbul, Turkey;* [5]*Institute of Health Sciences, Department of Neurology, Translational Neurodevelopmental Medicine PhD Program, Istanbul University, Istanbul, Turkey;* [6]*Department of Neurology, Alanya Alaaddin Keykubat University, Antalya, Turkey;* [7]*Aziz Sancar Experimental Medicine Research Institute, Department of Genetics, Istanbul, Istanbul University, Turkey*

***Correspondence to:** Gullu Tarhan, Bes Minare, Selahattin Eyyubi Street No:160, 13000 Bitlis Merkez, Bitlis, Türkiye. E-mail: gllutrhan@gmail.com
Keywords: QSM (quantitative susceptibility mapping), *THAP1* mutation, DYT6 dystonia, autosomal recessive dystonia, neurodegeneration with brain iron accumulation (NBIA).
Received 5 August 2025; revised 14 October 2025; accepted 25 October 2025.
Published online 00 Month 2025 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.70432

© 2025 International Parkinson and Movement Disorder Society.

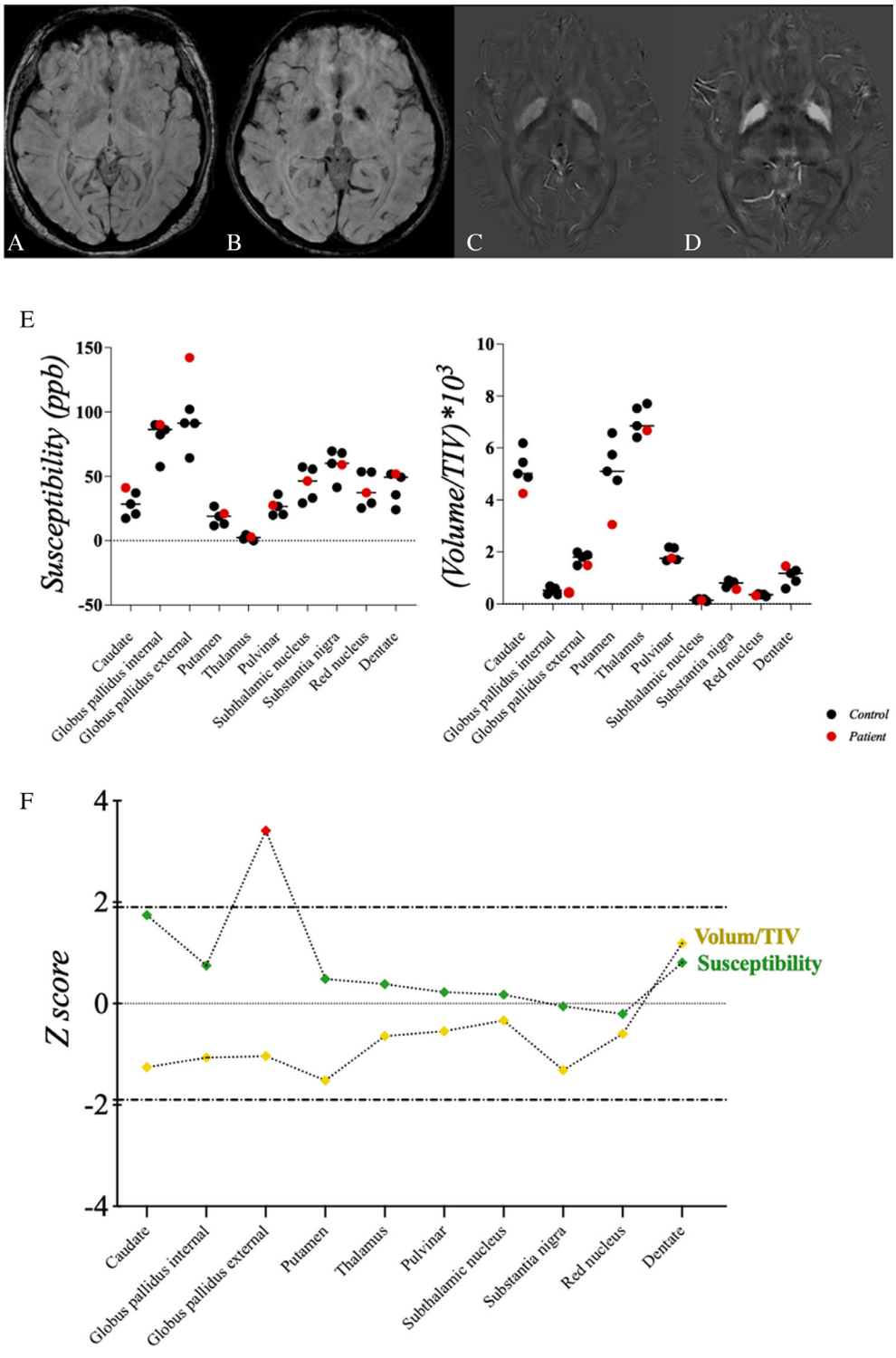


Figure 1. On the left, T2*-weighted gradient-recalled echo magnitude images are shown for (A) a control subject and (B) the patient; on the right, quantitative susceptibility maps (QSM) are displayed for (C) the control and (D) the patient. In the patient, bilateral hypointensity is observed in the globus pallidus, which is reflected as increased susceptibility on QSM.E) illustrates that susceptibility values in all deep gray matter (DGM) regions of the patient were higher than the average of the control group. (F) demonstrates that the adjusted DGM volumes of the patient were lower than the control group average. The third graph shows z-scores, indicating that only the susceptibility of the globus pallidus externus was statistically significant (z-score = 3.41).

23301619, 0, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mdc3.70432 by Zuhal Y APICI - Istanbul University , Wiley Online Library on [09/01/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

In our study, we provide the first confirmation of iron accumulation in recessive *THAP1* mutations using QSM, thereby validating this association through a novel imaging method. However, it remains unclear whether iron accumulation differs between homozygous and heterozygous *THAP1* mutations. Within the NBIA spectrum, the patterns and extent of iron accumulation are not yet clearly defined. While this study confirms brain iron accumulation in recessive *THAP1* mutation cases, it also highlights the value of QSM as a diagnostic tool in the NBIA group. Additional interpretation and clinical implications of these findings are discussed in detail in the Supplementary Discussion.

Ethics Statement

Approved by the Ethics Committee of Istanbul University, Istanbul Faculty of Medicine (Meeting No: 24, Date: December 1, 2023), for the study titled "Laboratory Evaluation of Findings and Genetic Biomarker Determination in Neurodegenerative Diseases with Brain Iron Accumulation (NBIA)" (File number: 2023/513). Consent for publication was obtained from the patient's family.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Conflict of Interest Statement

The authors declare no conflict of interest.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution.

(2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique.

(3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

ZY: 1A, 1B, 1C, 3A, 3B, 4.

PD: 1A, 1B, 2A, 2C, 3B, 4.

GT: 2A, 2B, 3A, 3B.

IK: 1C, 3A.

NC: 1C.

CS: 1C.

CT: 1C.

SAUI: 3A, 3B.

Acknowledgments

We would also like to extend our sincere thanks to Dr. Pınar Topaloğlu, Dr. Semih Taşdelen, Dr. Zeynep Karakuş, Dr. Pınar Elkoca, Dr. Özgür Öztop Çakmak, Dr. Selçuk Peker, Dr. Yavuz Samancı, and Dr. Erdi Şahin for their valuable contributions.

Funding Sources and Conflict of Interest

This study was supported in part by the İstanbul University Scientific Research Projects Coordination Unit (Project ID: 40651; Project Code: TSA-2024-40651).

The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the previous 12 months

GT has received financial support in the form of an educational scholarship from the Turkish Neurology Society. ZY, PD, İK, NÇ, CS, ÇT, SAUİ: The authors declare that there are no additional disclosures to report.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions. ■

References

1. Almasy L, Bressman S, Raymond D, Kramer P, Greene P, Heiman G. Idiopathic torsion dystonia linked to chromosome 8 in two Mennonite families. *Ann Neurol* 1997;42(4):670–673.
2. Fuchs T, Gavarini S, Saunders-Pullman R, Raymond D, Ehrlich ME, Bressman SB. Mutations in the T*HAP1* gene are responsible for DYT6 primary torsion dystonia. *Nat Genet* 2009;41(3):286–288.
3. Zorzi G, Danti FR, Reale C, Panteghini C, Invernizzi F, Moroni I. *THAP1* dystonia with Globus Pallidus T2 Hypointensity: a report of two cases. *Mov Disord* 2021;36(6):1463–1464.
4. Agarwal A, Garg D, Rajan R, Garg A, Srivastava AK. *THAP1* associated dystonia: an NBIA mimic. *Mov Disord Clin Pract* 2023;10(12):1815–1817.
5. Acosta-Cabronero J, Milovic C, Mattern H, Tejos C, Speck O, Callaghan MF. A robust multi-scale approach to quantitative susceptibility mapping. *Neuroimage* 2018;183:7–24.

Supporting Information

Supporting information may be found in the online version of this article.

Data S1. Supplementary Discussion: Extended discussion of the clinical and imaging findings with reference to relevant literature.

Data S2. Supplementary Methods: Detailed description of the QSM methodology used in this study.

TABLE S1. Functional and motor scores before and after deep brain stimulation (DBS) are presented. Following the

23301619, 0, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mdc3.70432 by Zuhal YAPICI - Istanbul University , Wiley Online Library on [09/01/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

implantation of combined GPi and STN DBS, STN stimulation was discontinued due to limited benefit, and only GPi DBS remained active during the two-year follow-up. The patient was more comfortable under GPi-only stimulation, with a BFMDRS score of 87.5 (improved from 94.5), and without any stimulation-induced side effects. Arrows (↑/↓) indicate worsening or improvement, respectively.

Figure S1. Pedigree of the family. The proband, indicated by an arrow, is homozygous for the THAP1 variant (ENST00000254250.7:c.149A>G; p.Tyr50Cys). Individuals marked with a plus sign (+) underwent targeted variant analysis and were all found to be heterozygous carriers of this variant. Individuals IV-5 and IV-6 died at 7 and 8 months of age, respectively, before genetic testing could be performed.

23301619, 0, Downloaded from https://movementdisorders.onlinelibrary.wiley.com/doi/10.1002/mdc3.70432 by Zuhal Y APICI - Istanbul University , Wiley Online Library on [09/01/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License