

## Case Report

Open Access, Volume 4

# 9-year-old girl with TUBB4A dystonia

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Received: Jun 05, 2023

Accepted: Aug 03, 2023

Published: Aug 10, 2023

Archived: www.jcimcr.org

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DOI: www.doi.org/10.52768/2766-7820/2538

### Abstract

Whispering dystonia, also known as DYT-TUBB4A, is characterized by laryngeal dystonia and is linked to upper limb dystonia, cervical dystonia, and frequent generalization. Mutations in the TUBB4 gene, which codes for a tubulin that is expressed in neurons, have been identified as the root cause of whispering dysphonia. Magnetic Resonance Imaging and genetic testing are used to diagnose diseases. Treatment options for the condition include Deep Brain Stimulation (DBS) and pharmacotherapy. We will go through the case history of a 9-year-old kid who had trouble speaking and walking. The patient was identified as having Dystonia Type 4 (DYT4) after undergoing several tests. The existence of such patients suggests that dystonia may be the result of de novo mutations, which should be considered in the differential diagnosis of other patients exhibiting the aforementioned symptoms.

**Keywords:** TUBB4A; Dystonia type 4; Acquired disease.

**Abbreviations:** DYT4: Dystonia Type 4; MRI: Magnetic Resonance Imaging; DBS: Deep Brain Stimulation; H-ABC: Hypomyelination With Atrophy of The Basal Ganglia And Cerebellum Syndrome; WES: Whole Exome Sequencing; DTR: Deep Tendon Reflex; GPi: Globus Pallidus Pars Interna.

### Introduction

Parker originally identified hereditary whispering dysphonia, subsequently known as DYT4, in an Australian family with 20 affected family members in 1985 [1]. DYT4 is an autosomal dominant leukodystrophy that manifests in the second to third decade and is characterized by segmental or generalized dystonia with prominent spasmodic dysphonia and Hypomyelination With Atrophy Of The Basal Ganglia And Cerebellum Syndrome (H-ABC) [2]. Developmental delay, a range of extrapyramidal movements, ataxia, progressive spastic tetraplegia, and seizures are all features of this uncommon, sporadic disorder [3].

In 2013, a heterozygous missense mutation, c.4C>G; p.R2G, in exon 1 of the TUBB4A gene was found to be the cause of the condition among members of the original family by two different research teams almost simultaneously [4,5]. The gene TUBB4A on chromosome 19p codes for beta-tubulin 4A, a tu-

bulin that is expressed in neurons [5], which is a crucial part of microtubules, which make up the cytoskeleton and perform a variety of biological functions [6].

Here, we describe a patient who presented with progressive gait and speech impairment, and the diagnosis of DYT4 was confirmed by the MRI and Whole Exome Sequencing (WES).

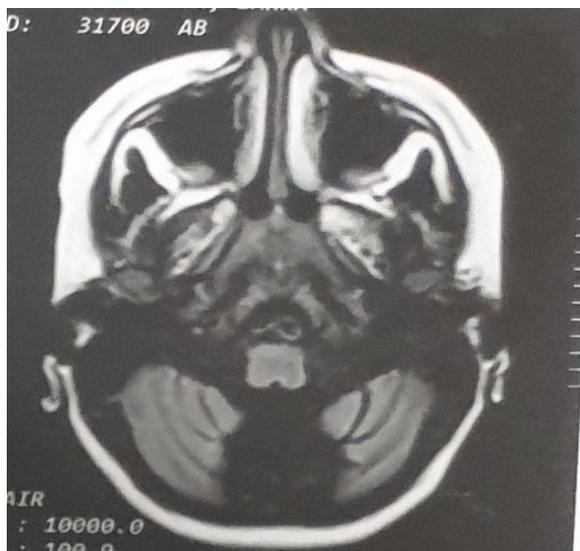
### Case presentation

Our patient is a 9-year-old girl who complains of progressive gait and speech impairments. She doesn't have any difficult labor history, familial history, or head trauma. She had normal developmental milestones until the age of 3 years.

Her parents noticed difficulty in running and stuttering after a few minutes of speaking. Since the age of 6, she has not been able to stand and walk independently. She passed the first year

of school in a public school without learning problems, but in the following year, abnormal movement in the upper limb constrained her from holding a pen and writing. So she was sent to a special school, and again, the severity of her hand dystonia led to dropout. During the physical examination, she didn't have any cognitive impairment. She had generalized dystonia. The extension of dystonia to the lower limb had led to a spacial gait called the "hobby horse gait." She also had laryngeal dystonia, pes cavus deformity, and a brisk Deep Tendon Reflex (DTR). She wasn't able to stand and walk independently.

On the brain MRI, there was a Dandy Walker variant anomaly (Figure 1), an intensity change in the basal ganglia, and scattered white matter hyperintensities (Figure 2). The WES was done and revealed a TUBB4A mutation. She was prescribed levodopa, carbidopa, and occupational therapy.



**Figure 1:** Hypoplasia of the vermis with normal posterior fossa size (Dandy-Walker variant).



**Figure 2:** Intensity change in the basal ganglia with scattered white matter hyperintensities.

## Discussion

DYT4 follows an autosomal dominant mode of inheritance with seemingly high penetrance based on the lack of unaffected obligate carriers and a high number of affected individuals in large sibling groups [5]; however, there is no family history in the mentioned patient, and genetic counseling should be done again for mosaicism and de novo mutations, which the family disagree. Pizzino et al [7], in a study in 2014, describe novel de novo mutations in TUBB4A in 5 patients with hypomyelinating leukodystrophy who lack the full complement of features associated with H-ABC.

According to recent studies, the treatment of dystonia with Globus Pallidus Pars Interna (GPI) DBS has had favorable effects [8-10]. Also, few drugs, such as propranolol and tetrabenazine, as well as alcohol consumption, have been effective in the treatment of DYT4 [8]. We also suggested DBS for the raised case, but the family disagree. In conclusion TUBB4A mutations are exceedingly rare cause of dystonia. DYT4 has an autosomal dominant inheritance pattern and often presents in second to third decade of life. The best symptomatic treatment is DBS with estimated efficacy of 40%.

**Acknowledgements:** The authors received no financial or any type of support for the research, authorship, and/or publication of this article.

## References

1. N Parker. Hereditary whispering dysphonia, *Journal of Neurology, Neurosurgery & Psychiatry*. 1985; 48: 218-224.
2. C Simons, et al. A de novo mutation in the  $\beta$ -tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum, *The American Journal of Human Genetics*. 2013; 92: 767-773.
3. M van der Knaap and S Naidu, Pouwels PJ, Bonavita S, Van Coster R, Lagaffe L, et al. New syndrome characterized by hypomyelination with atrophy of the basal ganglia and cerebellum. *Am. J. Neuroradiol*. 2002; 23: 1466-1474.
4. J Hersheson, et al. Mutations in the autoregulatory domain of  $\beta$ -tubulin 4 a cause hereditary dystonia. *Annals of neurology*. 2013; 73: 546-553.
5. K Lohmann, et al. Whispering dysphonia (DYT4 dystonia) is caused by a mutation in the TUBB4 gene. *Annals of neurology*. 2013; 73: 537-545.
6. K Lohmann, C Klein. Update on the genetics of dystonia. *Current neurology and neuroscience reports*. 2017; 17: 1-12.
7. A Pizzino, et al. TUBB4A de novo mutations cause isolated hypomyelination," (in eng), *Neurology*. 2014; 83: 898-902.
8. JF Bally, et al. DYT-TUBB4A (DYT4 Dystonia): Clinical Anthology of 11 Cases and Systematized Review, (in eng), *Mov Disord Clin Pract*. 2022; 9: 659-675.
9. AMR de Moura, et al. Targets for treatment of dystonia caused by several etiologies. Meta analysis, *Rev. Chil. Neurocirugía*. 43: 8-14.
10. S Tisch, KR Kumar. Pallidal Deep Brain Stimulation for Monogenic Dystonia: The Effect of Gene on Outcome, (in English), *Frontiers in Neurology, Review*. 2021; 11.

