Current Neurology and Neuroscience Reports (2021) 21: 48
https://doi.org/10.1007/s11910-021-01135-w

MOVEMENT DISORDERS (T. SIMUNI, SECTION EDITOR)

Tremor in Primary Monogenic Dystonia

Sanjay Pandey[1] · Sonali Bhattad[1] · Shreya Dinesh[1]

Accepted: 30 June 2021 / Published online: 15 July 2021

Abstract

Purpose of Review Tremor is an important phenotypic feature of dystonia with wide variability in the reported prevalence ranging from 14 to 86.67%. This variability may be due to the types of dystonia patients reported in different studies. This article reviews research articles reporting tremor in primary monogenic dystonia.

Recent Findings We searched the MDS gene data and selected all research articles reporting tremor in primary monogenic dystonia. Tremor was reported in nine dystonia genes, namely *DYT-HPCA*, *DYT-ANO3*, *DYT-KCTD17*, *DYT-THAP1*, *DYT-PRKRA*, *DYT-GNAL*, *DYT-TOR1A*, *DYT-KMT2B*, and *DYT-SGCE* in the descending order of its frequency. HPCA gene mutation is rare, but all reported patients had tremor. Similarly, tremor was reported in eight genes associated with dystonia parkinsonism, namely *DYT-SLC6A3*, *DYT-TH*, *DYT-SPR*, *DYT-PTS*, *DYT-GCH1*, *DYT-TAF1*, *DYT-QDPR*, and *DYT-SCL30A10* in the descending order of its prevalence.

Summary *DYT-HPCA* and *DYT-ANO3* gene showed the highest prevalence of tremor in isolated dystonia, and *DYT-SLC6A3* has the highest prevalence of tremor in combined dystonia.

Keywords Dystonia · Gene · Parkinsonism · Tremor

Introduction

Dystonia is a common movement disorder, and of the different forms of dystonia, isolated idiopathic and genetic forms are more common [1]. Tremor has been generally recognized as an important manifestation of dystonia ranging in 14–86.67% of patients [2]. According to the recent consensus statement, "dystonia" is defined as "a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation" [3]. It also further classifies dystonia into two axes. The axis-I describes dystonia as isolated or combined [3]. In isolated dystonia, dystonia is the only motor feature except for tremor, whereas in combined dystonia, the dystonia is combined with other movement disorders such as myoclonus, parkinsonism, and others [3]. Tremor has been described in isolated as well as combined dystonia. The second axis (axis – II) in the new dystonia classification addresses etiology in three broad groups; inherited acquired and idiopathic. Tremor has been reported in inherited dystonia, but their exact prevalence is not known.

We reviewed tremor in genetically associated dystonia to know the prevalence and clinical characteristics of tremor in different types of primary monogenic dystonia.

Methods

We searched the MDS gene database (https://www.mdsgene.org/) (https://www.mdsgene.org/) on December 22, 2019, for the genes associated with dystonia and dystonia parkinsonism. They have described nine causal genes for dystonia (*DYT-HPCA*, *DYT-ANO3*, *DYT-KCTD17*, *DYT-THAP1*, *DYT-PRKRA*, *DYT-GNAL*, *DYT-TOR1A*, *DYT-KMT2B*, and *DYT-SGCE*) and eight genes causing dystonia-parkinsonism (*DYT-GCH1*, *DYT-QDPR*, *DYT-SLC30A10*, *DYT-SLC6A3*, *DYT-TAF1*, *DYT-TH*, *DYT-PTS*, and *DYT-SPR)*. A total of 150

This article is part of the Topical Collection on *Movement Disorders*

✉ Sanjay Pandey
sanjaysgpgi2002@yahoo.co.in

[1] Department of Neurology, Govind Ballabh Pant Postgraduate Institute of Medical Education and Research, Academic Block, Room No 501, New Delhi 110002, India

papers (Supplementary table 1) reporting genes for dystonia (Table 1) and 106 papers (Supplementary table 1) reporting genes associated with dystonia parkinsonism (Table 2) were screened for the presence of tremor in dystonia and dystonia parkinsonism patients. We read the full text of these research papers, and the percentage of patients with tremor and without tremor for each gene was calculated. The phenotypic and clinical correlation of these genes was established by a detailed review of articles.

Results

Genes for Dystonia (*DYT*)

MDS gene described nine causal genes for dystonia: *DYT-HPCA*, *DYT-ANO3*, *DYT-KCTD17*, *DYT-THAP1*, *DYT-PRKRA*, *DYT-GNAL*, *DYT-TOR1A*, *DYT-KMT2B*, and *DYT-SGCE*. A single review article was reported for *DYT-HPCA* gene which had mentioned three patients, and all had tremors. *DYT-ANO3* gene was associated with tremor in 66% of dystonia patients. Mutations in *DYT-KCTD17* gene are known to cause myoclonus dystonia, and it showed tremor in 25% (2/8) of patients. Tremor was reported in 18% of patients with *DYT-THAP1*, 17% of patients with *DYT-PRKRA*, 12% of patients with *DYT-GNAL*, 11% of patients of *DYT-TOR1A*, and 6% of patients with *DYT-KMT2B* gene mutation. *DYT-SGCE* gene mutations have a similar phenotype of that of *DYT-KCTD17*, and it showed tremors in only 4% of patients.

Genes for Dystonia/Parkinsonism (*DYT-PARK*)

MDS gene database had reported 8 genes causing dystonia-parkinsonism: *DYT-GCH1*, *DYT-QDPR*, *DYT-SLC30A10*, *DYT-SLC6A3*, *DYT-TAF1*, *DYT-TH*, *DYT-PTS*, and *DYT-SPR*. *DYT-SLC6A3* gene causing dystonia parkinsonism showed the highest (64%) frequency of tremor followed by *DYT-TH* (44%) which encodes for tyrosine hydroxylase. *DYT-PTS* and *DYT-SPR* are two genes that encode for protein involved in tetrahydrobiopterin (BH4) biosynthesis, and the mutation in these genes leads to symptoms of dystonia-parkinsonism. Tremor was present in 26% and 25% of patients with *DYT-SPR* and *DYT-PTS* genes, respectively. *DYT-GCH1* gene which encodes a GTP cyclohydroxylase showed tremor in 18% patients. *DYT-TAF1* gene is reported to be causal for X-linked dystonia parkinsonism, and 4% of patients with this mutation are reported with tremors. Two genes, *DYT-QDPR* and *DYT-SLC30A10*, did not show tremor in any of the patients. In most of these studies, the cohorts were small, and the prevalence will have to be validated.

Clinical Description

DYT-HPCA gene was found to have the highest prevalence of tremor among all the genes associated with dystonia, but due to the small number of patients (only three) reported, this can be considered as non-significant. This gene is inherited in an autosomal recessive pattern, and the onset can be childhood, adolescence, or early adulthood [4, 5••]. Clinical manifestations include isolated dystonia or dystonia combined with infantile seizures, developmental delay, and cognitive decline [4]. Bilateral upper limb tremors and occasionally head tremor can also be seen [4]. Tremor was seen in 66% of dystonia patients with the *DYT-ANO3* gene, which is inherited as autosomal-dominant cranio-cervical dystonia [6, 7]. Age at onset of *DYT-ANO3* ranges from the very early childhood to 40 years. The dystonia can be focal or segmental without generalization. It can involve laryngeal, brachial, or cranio-cervical regions with tremor and/or myoclonic jerks. The tremor is dystonic with a jerky quality affecting the head, voice, or upper limbs [6]. Occasionally few patients might present only with upper limb tremor leading to misdiagnosis of essential tremor [7].

DYT-THAP1 gene was found to have tremor in 18% of patients. It is inherited in an autosomal dominant fashion with reduced penetrance [1]. The onset is generally at adolescence

Table 1 Tremor in primary monogenic dystonia gene

Gene	Number of papers reviewed	Patients	Tremor present	Percent	Tremor absent	Percent
DYT-HPCA	1	3	3	100%	0	0%
DYT-ANO3	7	33	22	66%	8	29%
DYT-KCTD17	1	8	2	25%	6	75%
DYT-THAP1	29	168	31	18%	137	82%
DYT-PRKRA	3	12	2	17%	10	83%
DYT-GNAL	9	48	6	12%	42	88%
DYT-TOR1A	63	403	46	11%	354	89%
DYT-KMT2B	7	56	4	7%	52	93%
DYT-SGCE	30	161	6	4%	155	96%

Table 2 Tremor in primary monogenic dystonia parkinsonism genes

Gene	Number of papers reviewed	Patients	Tremor present	Percent	Tremor absent	Percent
DYT-SLC6A3	3	14	9	64%	5	36%
DYT-TH	18	45	20	44%	25	55%
DYT-SPR	10	19	5	26%	14	74%
DYT-PTS	4	20	5	25%	15	75%
DYT-GCH1	50	245	44	18%	201	82%
DYT-TAF1	16	419	19	4%	400	96%
DYT-QDPR	2	3	0	0%	3	100%
DYT-SLC30A10	3	21	0	0%	21	100%

or adulthood with generalized or segmental dystonia, involving laryngeal, cranio-cervical, and oromandibular dystonia [8, 9], but it can also present with focal dystonia of the limbs [1]. Presentation of tremors ranges from mild, asymmetrical, rest, and postural bilateral upper limb to occasional head and lower limb tremors [10].

Tremor in *DYT-PRKRA* was observed in 17% (2/12) of patients. It is inherited as an autosomal recessive condition presenting either as pure generalized dystonia or with a dystonia-parkinsonism which is unresponsive to L-dopa [11]. In cases where both features are present, parkinsonism appears as a late feature than dystonia, although rest tremor has not been described. Mild postural tremors are most frequently reported [11]. A gradual onset of dystonia in childhood, affecting the limbs with prominent, relatively rapid onset, bulbar cranio-cervical, and striking axial dystonia, opisthotonos, hyperextension of the trunk, and tortipelvis, was the most common presentation [11].

Tremor in *DYT-GNAL* was reported in 22% of patients. *DYT-GNAL* gene is involved in dopamine signaling. D1 dopamine receptors have a known role in mediating locomotor activity; hence, there is a link between *DYT-GNAL* and dystonia [1] Tremor is reported to occur in the head and upper limbs [12]. It causes primary torsion dystonia with onset in the region of the neck and cervical region, and it may progress to other sites but rarely generalizes [1, 12].

Among the childhood, dystonia tremor was reported in 11% of patients with *DYT-TOR1A* gene. *DYT-TOR1A*-related dystonia typically presents in childhood with dystonic posturing of the foot or leg, though it may begin in any part of the body and evolves to generalized dystonia with fixed deformities [1, 13]. Clinical features range from focal, segmental, multifocal, or generalized dystonia with the initial presentation being generally the gait difficulties [13].

Tremor can manifest as jerky postural tremors and action tremors of upper limbs and lower limbs with occasional dystonic tremors [1].

Early-onset dystonia due to *DYT-KMT2B* gene mutation is inherited as an autosomal dominant complex childhood-onset movement disorder [14]. It has its onset in the form of lower-limb focal dystonia leading to toe walking and gait disturbances progressively evolving into generalized dystonia with prominent cervical, cranial, and laryngeal involvement [14, 15••]. Upper limb involvement in the form of abnormal postures and dystonic tremors, leading to reduced dexterity and handwriting difficulties, has also been reported [14]. Additional features comprise mild to moderately impaired cognition, oculomotor disturbances, spasticity, epilepsy, and other systemic comorbidities, including psychiatric or dermatological illnesses [14, 15••]. Dysmorphic features and characteristic facial appearances in the form of an elongated face and bulbous nasal tip are seen [14].

Two genes with myoclonus-dystonia are *DYT-KCTD17* and *DYT-SGCE* with tremor being reported in 25% and 4%, respectively. Tremor in *DYT-KCTD17* gene mutation is reported to occur in the head or jerky arm tremors, whereas in *DYT-SGCE* gene mutation, the tremor is associated with dystonia [16]. Myoclonus in *DYT-KCTD17* is the initial symptom at the onset, although mild when compared to *DYT-SGCE* gene mutation [17]. *DYT-KCTD17* gene mutation has progressive dystonia with spreading to other sites, whereas *DYT-SGCE* gene mutation has characteristic cervical dystonia and writer's cramp [16, 17].

Among the combined dystonia, *DYT-SLC6A3* was found to have the highest reported tremor. Mutations in the *DYT-SLC6A3* gene is the first inherited dopamine "transportopathy" to be described [18]. It is inherited in an autosomal recessive pattern with early infantile onset [18]. Tremor occurs as rest tremor as a part of parkinsonism features along with slowness of movement, muscle rigidity, and dystonic features [19]. Other observed features of parkinsonism-dystonia are ocular flutter and saccade initiation failure [19].

Dopa responsive dystonia can occur due to *DYT-TH* (5b), *DYT-GCH1* (5a), and *DYT-SPR* genes. The frequency of tremors in these genes was found to be 44%, 26%, and 18%, respectively. *DYT-GCH1* (5a) and *DYT-TH* (5b) were reported to have postural tremors, whereas *DYT-SPR* was found to have rest tremors [20, 21].

Tremor in *DYT-PTS* gene mutation was found to be 25%, but the details of tremor were not available. Patients with 6-PTS deficiencies typically develop neurological symptoms in infancy, such as motor developmental delay, mental retardation, neonatal hypotonia, and seizures, as a form of primary BH4 deficiency [22]. Predominant clinical features include generalized dystonia, involving the eyelids, oromandibular region, trunk, and extremities [22].

In four percent of patients with *DYT-TAF1* mutation, tremor was reported. It is an X-linked recessive syndrome of combined dystonia-parkinsonism associated with an insertional mutation within the intron of *DYT-TAF1* [23]. The frequently noted clinical phenotype consists of initial focal dystonia that spreads to multiple body regions that are seen in combination with or is replaced by parkinsonism over a period [24]. Tremors can be asymmetric resting tremor or action tremor either in the early or later stages of the disease with rest tremors being usually common. Symmetric upper-limb tremor or head tremor like essential tremor can be seen in some patients. In some rare cases, tremor might involve the trunk, craniofacial region, voice, and lower limb.

Other genes involved in combined dystonia are *DYT-SLC30A10* gene and *DYT-QDPR*, but tremor was not reported in both the genes [25, 26]. *DYT-SLC30A10* encodes a manganese [Mn] transporter which on mutation will cause Mn accumulation in basal ganglia, cerebellum, and liver [25]. It presents as an early-onset autosomal recessive disorder called hypermagnesemia with dystonia, cirrhosis, and polycythaemia [25]. Dystonia of all four limbs, toe walking, gait difficulties, and dysarthria are the major clinical manifestations [27].

Our review was based on published research papers, and it has certain limitations. Many studies did not include detailed phenotypic features including types of tremor, and additional clinical details of affected and non-affected family members were missing. Also, studies included in this review had followed the 1998 "Movement Disorder Society" (MDS)-consensus criteria of tremor leading to the inclusion of many patients with overlapping features of dystonic tremor and ET-syndromes [28]. In a recent review based on 2018 MDS criteria, Magrinelli and colleagues have highlighted that the understanding of genetically determined tremor syndrome may have been hampered due to the inclusion of heterogeneous entities including dystonic tremor in previous studies on ET [29••].

Conclusion

Our review has provided some important data regarding tremor in dystonia patients. First, it partially explains the wide variability in studies reporting the prevalence of tremor in dystonia patients ranging from 14 to 86.67%. Second, it also explains the type of tremor (postural/kinetic/rest) reported in different studies. Third, tremor is more common in multifocal dystonia patients, suggesting the role of genetic mechanisms that might underlie both tremor and dystonia. Fourth, phenotypic heterogenicity in tremor associated with dystonia could have an underlying genetic basis and may contribute to its pathophysiology. However, our review findings are based on limited data, and future studies are necessary regarding prevalence and clinical spectrum of tremor in primary monogenic dystonia.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11910-021-01135-w.

Acknowledgements This "Point of view" article is not funded by any organization.

Author Contribution Sanjay Pandey, Sonali Bhattad, and Shreya Dinesh contributed in manuscript preparation by writing the first draft, review, and critique.

Funding The Junior research fellowship for Shreya Dinesh (co-author) was funded by a grant from the Department of Biotechnology from project # BT/PR26428/Med/12/783/2018.

Declarations

Conflict of Interest Sanjay Pandey, Sonali Bhattad, and Shreya Dinesh each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Charlesworth G, Bhatia KP, Wood NW. The genetics of dystonia: new twists in an old tale. Brain. 2013;136(Pt 7):2017–37.
2. Pandey S, Sarma N. Tremor in dystonia. Parkinsonism Relat Disord. 2016;29:3–9.
3. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013;28(7):863–73.
4. Balint B, Charlesworth G, Erro R, Wood NW, Bhatia KP. Delineating the phenotype of autosomal-recessive HPCA mutations: not only isolated dystonia! Mov Disord. 2019;34(4):589–92.
5.•• Atasu B, Hanagasi H, Bilgic B, Pak M, Erginel-Unaltuna N, Hauser AK, et al. HPCA confirmed as a genetic cause of DYT2-like dystonia phenotype. Mov Disord. 2018;33(8):1354–8. **The authors report two consanguineous Turkish DYT-HPCA families carrying the novel HPCA mutations confirming that HPCA leads to recessively inherited dystonia**.

6. Charlesworth G, Plagnol V, Holmström KM, Bras J, Sheerin UM, Preza E, et al. Mutations in ANO3 cause dominant craniocervical dystonia: ion channel implicated in pathogenesis. Am J Hum Genet. 2012;91(6):1041–50.
7. Stamelou M, Charlesworth G, Cordivari C, Schneider SA, Kägi G, Sheerin UM, et al. The phenotypic spectrum of DYT24 due to ANO3 mutations. Mov Disord. 2014;29(7):928–34.
8. Lohmann K, Uflacker N, Erogullari A, Lohnau T, Winkler S, Dendorfer A, et al. Identification and functional analysis of novel THAP1 mutations. Eur J Hum Genet. 2012;20(2):171–5.
9. Xiromerisiou G, Houlden H, Scarmeas N, Stamelou M, Kara E, Hardy J, et al. THAP1 mutations and dystonia phenotypes: genotype phenotype correlations. Mov Disord. 2012;27(10):1290–4.
10. LeDoux MS, Xiao J, Rudzińska M, Bastian RW, Wszolek ZK, Van Gerpen JA, et al. Genotype-phenotype correlations in THAP1 dystonia: molecular foundations and description of new cases. Parkinsonism Relat Disord. 2012;18(5):414–25.
11. Camargos S, Scholz S, Simón-Sánchez J, Paisán-Ruiz C, Lewis P, Hernandez D, et al. DYT16, a novel young-onset dystonia-parkinsonism disorder: identification of a segregating mutation in the stress-response protein PRKRA. Lancet Neurol. 2008;7(3):207–15.
12. Carecchio M, Panteghini C, Reale C, Barzaghi C, Monti V, Romito L, et al. Novel GNAL mutation with intra-familial clinical heterogeneity: expanding the phenotype. Parkinsonism Relat Disord. 2016;23:66–71.
13. Magrinelli F, Bacchin R, Tinazzi M, Gambarin M. Twelve-year follow-up of a large Italian family with atypical phenotypes of DYT1-dystonia. Mov Disord Clin Pract. 2018;6(2):166–70.
14. Zech M, Boesch S, Maier EM, Borggraefe I, Vill K, Laccone F, et al. Haploinsufficiency of KMT2B, encoding the lysine-specific histone methyltransferase 2B, results in early-onset generalized dystonia. Am J Hum Genet. 2016;99(6):1377–87.
15.•• Meyer E, Carss KJ, Rankin J, Nichols JM, Grozeva D, Joseph AP, et al. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet. 2017;49(2):223–37. **The authors report heterozygous variants in the gene KMT2B in 27 unrelated individuals with a complex progressive childhood-onset dystonia with a typical facial appearance and characteristic brain magnetic resonance imaging finding.**
16. Mencacci NE, Rubio-Agusti I, Zdebik A, Asmus F, Ludtmann MH, Ryten M, et al. A missense mutation in KCTD17 causes autosomal dominant myoclonus-dystonia. Am J Hum Genet. 2015;96(6):938–47.
17. Kübler D, Borngräber F, Lohmann K, Kühn AA. Novel SGCE mutation in a patient with myoclonus-dystonia syndrome - diagnostic delay of more than 40 years. J Clin Neurosci. 2018;50:131–2.
18. Kurian MA, Li Y, Zhen J, Meyer E, Hai N, Christen HJ, et al. Clinical and molecular characterisation of hereditary dopamine transporter deficiency syndrome: an observational cohort and experimental study. Lancet Neurol. 2011;10(1):54–62.
19. Blackstone C. Infantile parkinsonism-dystonia: a dopamine "transportopathy". J Clin Invest. 2009;119(6):1455–8.
20. Hoffmann GF, Assmann B, Bräutigam C, Dionisi-Vici C, Häussler M, de Klerk JB, et al. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. Ann Neurol. 2003;54(Suppl 6):S56–65.
21. Lohmann E, Köroğlu Ç, Hanagasi HA, Dursun B, Taşan E, Tolun A. A homozygous frameshift mutation of sepiapterin reductase gene causing parkinsonism with onset in childhood. Parkinsonism Relat Disord. 2012;18(2):191–3.
22. Hanihara T, Inoue K, Kawanishi C, Sugiyama N, Miyakawa T, Onishi H, et al. 6-Pyruvoyl-tetrahydropterin synthase deficiency with generalized dystonia and diurnal fluctuation of symptoms: a clinical and molecular study. Mov Disord. 1997;12:408–11.
23. Domingo A, Westenberger A, Lee LV, Brænne I, Liu T, Vater I, et al. New insights into the genetics of X-linked dystonia-parkinsonism (XDP, DYT3). Eur J Hum Genet. 2015;23(10):1334–40.
24. Rosales RL. X-linked dystonia parkinsonism: clinical phenotype, genetics and therapeutics. J Mov Disord. 2010;3(2):32–8.
25. Tuschl K, Mills PB, Parsons H, Malone M, Fowler D, Bitner-Glindzicz M, et al. Hepatic cirrhosis, dystonia, polycythaemia and hypermanganesaemia–a new metabolic disorder. J Inherit Metab Dis. 2008;31(2):151–63.
26. Lu DY, Ye J, Han LS, Qiu WJ, Zhang HW, Zhou JD, et al. QDPR gene mutation and clinical follow-up in Chinese patients with dihydropteridine reductase deficiency. World J Pediatr : WJP. 2014;10(3):219–26.
27. Au C, Benedetto A, Aschner M. Manganese transport in eukaryotes: the role of DMT1. Neurotoxicology. 2008;29(4):569–76.
28. Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. Mov Disord. 1998;13(Suppl 3):2–23.
29.•• Magrinelli F, Latorre A, Balint B, Mackenzie M, Mulroy E, Stamelou M, et al. Isolated and combined genetic tremor syndromes: a critical appraisal based on the 2018 MDS criteria [published online ahead of print, 2020 Jun 15]. Parkinsonism Relat Disord. 2020;77:121–40. **This review discusses the wide range of tremor disorders with defined or presumed genetic etiology, both isolated and combined focusing mainly on essential tremor-like phenotypes.**