Monogenic dystonia

Monogenic dystonia refers to forms of dystonia caused by a single gene mutation. These disorders often have distinct clinical features and inheritance patterns (autosomal dominant, autosomal recessive, or X-linked).

Definition

Dystonia characterized by involuntary muscle contractions, resulting in twisting, repetitive movements or abnormal postures, directly attributable to mutations in one specific gene.

Inheritance Patterns

Autosomal dominant (e.g., DYT1 dystonia due to mutations in TOR1A gene).

Autosomal recessive (e.g., dystonia associated with mutations in TH or GCH1 genes).

X-linked (rare, associated with mutations in the TAF1 gene, causing X-linked dystonia-parkinsonism or Lubag).

Monogenic Dystonias – Summary Table

Dystonia Type	Gene	Inheritance	Key Features	Treatment
DYT1	TOR1A	Autosomal dominant	Early-onset, limb onset, generalizes, Ashkenazi Jewish	DBS (GPi), anticholinergics, botulinum toxin
DYT5 (A/B)	GCH1 / TH	AD / AR	Childhood onset, diurnal fluctuation, excellent levodopa response	Levodopa (dramatic response)
DYT6	THAP1	Autosomal dominant	Variable onset, cranial/cervical involvement, speech affected	DBS, pharmacologic (limited effect)
DYT11	SGCE	AD with maternal imprinting	Myoclonus + dystonia, alcohol-responsive	Clonazepam, DBS, alcohol (transient relief)
DYT16	PRKRA	Autosomal recessive	Early-onset generalized dystonia, rapidly progressive	Limited response to meds; DBS considered
DYT3 (Lubag)	TAF1	X-linked recessive	Filipino males, adult-onset dystonia-parkinsonism	Limited; anticholinergics, levodopa
DYT-TUBB4A	TUBB4A	Autosomal dominant	Whispering dysphonia (laryngeal), adult onset	Botulinum toxin, DBS in select cases

Monogenic Dystonias and Their Treatment

Gene / Syndrome	Clinical Features	Treatment
DYT1 (TOR1A)	Childhood or adolescent-onset generalized dystonia, usually starting in limbs, no other neurological signs	**GPi-DBS** (highly effective) `Anticholinergics, benzodiazepines, baclofen (variable effect)`
DYT6 (THAP1)	Similar to DYT1 but more frequent cranio-cervical involvement; later onset possible	**GPi-DBS** (less predictable response than DYT1) `Symptomatic treatment`
DYT11 (SGCE) (Myoclonus-dystonia)	Myoclonus and dystonia, improves with alcohol, autosomal dominant with maternal imprinting	`Clonazepam, levetiracetam, other GABAergic drugs` **GPi-DBS** in severe cases
DYT5a (GCH1) (Dopa-responsive dystonia)	Childhood-onset, fluctuating dystonia, diurnal variation, excellent response to levodopa	**Low-dose levodopa** (dramatic and sustained improvement)
DYT12 (ATP1A3) (Rapid-onset dystonia-parkinsonism)	Sudden onset, fixed dystonia, ataxia, parkinsonian features	`Poor response to medications` **DBS** (variable benefit)
DYT-TUBB4A (H-ABC syndrome)	Dysarthria, dystonia, cerebellar atrophy, mixed symptoms	`Symptomatic treatment, physiotherapy` **DBS** with experimental results
DYT-PARK (PRKRA)	Dystonia-parkinsonism, often juvenile onset	`Levodopa (helpful in some cases)` **GPi-DBS** (variable outcomes)

General Principles

- **Genetic testing** is crucial – some monogenic dystonias have highly specific treatments (e.g., **levodopa in DYT5**).
- **Early diagnosis and treatment** improve functional outcomes.
- **Deep Brain Stimulation** (typically targeting **GPi**) is effective in drug-resistant dystonia, especially in **DYT1** and **DYT6**.
- Consider inclusion in **research protocols or registries** for rare or treatment-resistant cases.

Systematic review protocols

A systematic review protocol, designed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, to evaluate the efficacy and safety of Deep Brain Stimulation in patients with monogenic dystonia — a subset of rare, genetically defined dystonias caused by mutations in single genes [1)].

Strengths

- **Clear scope and methodology:** The study uses a robust systematic framework to identify, extract, and synthesize evidence related to DBS in monogenic dystonias.
- **Focus on rare diseases:** It addresses a crucial evidence gap in a neglected patient population where clinical guidance is often based on anecdotal reports or small case series.
- **Planned subgroup analyses:** If data allow, subgroup analyses will help delineate differences

across dystonia genotypes (e.g., DYT1, DYT6, DYT11).
- **Prospective risk of bias evaluation:** Includes planned bias assessment, increasing reliability of conclusions.

Limitations

- **Protocol stage only:** As a protocol, it does not yet present results. Its value depends on the actual quality and quantity of included studies.
- **Heterogeneity risk:** Variability in patient phenotypes, surgical targets, outcome scales, and follow-up durations may limit the feasibility of meta-analysis.
- **Potential publication bias:** Due to the rarity of conditions, the body of evidence may overrepresent positive outcomes (publication bias).

Relevance for Neurosurgery

This protocol is highly relevant for neurosurgeons involved in functional neurosurgery, especially those performing Deep brain stimulation for movement disorders. By focusing on genetic subtypes of dystonia, it may inform future patient selection, target choice, and timing of intervention.

1)
Carmona-Hidalgo B, Quintero J, Rodríguez-López R, Blasco-Amaro JA, Boesch S, Reinhard C. Efficacy of deep brain stimulation in treating monogenic dystonia symptoms: protocol for a systematic review. BMJ Open. 2025 Apr 9;15(4):e083127. doi: 10.1136/bmjopen-2023-083127. PMID: 40204321.